

**Novel cytoreductive treatments for
de novo synchronous metastatic
hormone-sensitive prostate cancer**

A thesis presented for the degree of
Doctor of Philosophy (PhD)

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Abstract

Survival in patients with metastatic hormone-sensitive prostate cancer (mHSPC) has increased following the use of contemporary systemic therapy with traditional androgen deprivation therapy (ADT). However, systemic therapy in isolation does not target the primary tumour and typically results in the development of a castrate resistant state which restricts overall survival. In my thesis, I will assess the feasibility of performing novel local cytoreductive and metastasis directed treatment strategies in patients with *de novo* synchronous mHSPC to confer additional survival benefits.

The first part of my thesis I provide the pathobiological and clinical rationale of primary tumour cytoreduction, including an evaluation of introducing cytoreductive radical prostatectomy (cRP) and cytoreductive minimally invasive ablative therapies (MIAT). In addition, I systematically review the current evidence for both metastasis-directed therapy (surgery or stereotactic ablative radiation therapy [SABR]) and patient preferences' for such innovative treatments in this disease setting. We explore how to identify suitable patients with non-curative disease, in a contemporary prostate cancer referral pathway.

This leads to the design and development of a phase II, randomised controlled trial, entitled "IP2-ATLANTA", in the second part of this thesis. The completion of IP2-ATLANTA internal multicentre pilot enables us to report the acceptability, compliance and safety of using our novel cytoreductive interventions. By utilising serial research prostate biopsies and multi-parametric magnetic resonance imaging (mpMRI) of the prostate we report a detailed histopathological and radiological characterisation of the primary tumour and its response to ADT, with chemotherapy or androgen receptor signalling inhibitors (ARSI). A dedicated embedded exploratory prospective, blinded, imaging response sub-study assess whether sequential [⁶⁸Ga] PSMA-11 PET imaging can predict the presence or absence of residual prostate cancer in the prostate compared to paired mpMRI prostate imaging and prostate biopsy. In the final section, I confirm the safe technical surgical performance of cytoreductive MIAT (with or without metastasectomy), and report acceptable genitourinary and gastrointestinal toxicity in patient-reported outcome measures (PROMS) from the internal pilot RCT patients.

We confirm that most patients have a viable residual prostate tumour on which local cytoreduction can be targeted despite contemporary systemic therapy intensification. It is both safe and feasible to allocate patients with *de novo* synchronous mHSPC to cytoreductive MIAT, cRP or cytoreductive radiotherapy, with or without metastasis-directed interventions. The main stage component of IP2-ATLANTA will confirm treatment efficacy and superiority of any trial interventions against current standard of care.

Declaration of Originality

I hereby declare that the work presented in this thesis was undertaken by me. Furthermore, this thesis and the work described therein was planned and carried out over a three year period as a Clinical Research Fellow at Imperial Prostate, Division of Surgery, Department of Surgery and Cancer, Imperial College London. Where collaboration and expert input occurred it is referenced explicitly within the respective thesis chapters. Where work has already been published the author has confirmed the right to reuse their own article's version of record from the publisher, in whole or in part, as cited in these relevant sections.

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The academic opinions that are presented in this thesis are those of the thesis candidate and do not reflect those of Imperial College London, Imperial College Healthcare NHS Trust, Royal Marsden Hospital NHS Foundation Trust, NHS England, RM Partners, the NIHR, BRC, Imperial Health Charity, UCLH Charity, or indeed the Wellcome Trust.

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- Regional newspapers
 - Various regional newspapers also covered the launch of IP2-ATLANTA trial including the: Express and Star, The Belfast Telegraph, The Argus, Jersey Evening Post, The Northern Echo, News and Star, In Cumbria.

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Chapter 1 - Introduction

1.1 Rationale for thesis

Overall, 47,000 patients are diagnosed with prostate cancer each year in the United Kingdom (UK) (1). Approximately, 4,500 of these patients will be diagnosed with *de novo* synchronous metastatic hormone-sensitive disease (mHSPC) at first presentation (1). As with the United States, where just under 8% present with metastatic disease and where the annual burden is predicted to reach approximately 15,000 cases by 2025, so the prediction for the same magnitude is likely for the UK as rates of community based PSA testing start to increase through increased awareness (2,3) .

Historically, metastatic prostate cancer was managed with androgen deprivation therapy (ADT) alone, via medical or surgical castration (4). Unfortunately this restricted the median time to the emergence of a castrate resistant state in the order of 11 to 18 months, limiting overall survival (OS) to 3.5 years (5). Promisingly, the reported OS in this group has now risen to a median 4.8 years with the addition of upfront systemic agents, such as docetaxel chemotherapy and androgen receptor signalling inhibitors (ARSI). ARSIs include enzalutamide, abiraterone acetate and apalutamide (6-10).

Moving beyond combinations of systemic therapy intensification there has been an increased focus on the role of local cytoreductive prostate and metastasis-directed interventions (surgery and stereotactic ablative radiation [SABR]) to gain additive oncological benefit (4).

This is in part based upon the emergence of the 'oligo-metastatic state' hypothesis in prostate cancer. This posits that different biological characteristics may arise in a clinically-defined favourable metastatic burden, and such patients may occupy an intermediate state between 'locally advanced' and 'poly-metastatic' disease (11,12). It has thus been postulated, but not proven, that patients exhibiting such disease patterns gain most benefit in progression-free survival (PFS) and overall survival resulting from attempts to control localised and distant metastases, via cytoreductive interventions.

Against this landscape of change, there is an urgent need to re-evaluate whether existing approved local surgical interventions for non-metastatic prostate cancer can be introduced in novel combinations in mHSPC. Such interventions include radical prostatectomy, pelvic lymph node dissection and minimally invasive-ablative therapies (MIAT). In parallel, there is also a need to consider if metastatic lesion-directed therapy, in the form of surgical metastasectomy or SABR, could reduce our reliance on aggressive lines of systemic anti-cancer agents.

1.2 Aims of thesis

When this thesis was conceived, there was no randomised evidence to support any local cytoreductive prostate or metastasis-directed intervention in patients with *de novo* synchronous mHSPC. However, retrospective cohort studies and population-based studies had been performed suggestive of a potential survival benefit from interventions (13-17).

The first objectives were to appraise the evidence for primary tumour cytoreduction and metastasis-directed interventions. Subsequent objectives were driven around the design of a robust randomised study to evaluate novel cytoreductive treatments. Firstly, we aimed to understand patients' preferences for treatment in mHSPC. Secondly, we aimed to identify patients with mHSPC from our tertiary prostate cancer referral pathway, and finally we considered the suitability of patients for novel cytoreductive surgical treatments against various applied hypothetical eligibility criteria.

The subsequent objectives in this thesis were to demonstrate the feasibility of performing a randomised study using novel cytoreductive and metastasis-directed interventions. This was performed by designing a prospective, multicentre, randomised controlled trial, the Imperial Prostate 2 ATLANTA study (IP2-ATLANTA). Trial participants were allocated to either standard of care treatment alone, addition of cytoreductive MIAT or addition of radical therapy (cRP or cytoreductive radiotherapy). Metastases-directed interventions were combined with intervention arm treatments only. The design included an initial recruiting internal pilot, which was the focus of the major objectives presented in this thesis.

Ensuing internal pilot objectives evaluated trial recruitment, compliance, patient acceptability and safety. Further objectives focussed on prostate tumour response assessments to contemporary systemic therapy, via serial research prostate biopsy and serial research multi-parametric magnetic resonance imaging (mpMRI) of the prostate. In addition, using a blinded analysis of trial specimens we aimed to detail histologic changes in the primary prostate tumour and provide hypothesis generating clinical translations. Furthermore, an imaging response sub-study aimed to evaluate intraprostatic PSMA expression response and its relationship with prostate histology pre- and post-systemic therapy, detectable by ⁶⁸Ga-Prostate Specific Membrane Antigen (PSMA)-11 Positron Emission Tomography/Computed Tomography (PET/CT). We also aimed to report the technical performance of cytoreductive MIAT and surgical metastasectomy and analyse patient-reported outcome measures (PROMS) from all arms of the internal randomised pilot study.

Final objectives of this study were to consider our findings in the context of the mandated study protocols in the ongoing main stage component of IP2-ATLANTA study, and the wider feasibility of incorporating trial interventions into routine clinical practice.

1.3 Thesis outline

This thesis can be divided into three broad parts, which contain 12 separate chapters. Each chapter opens with an overview contextualising and summarising the contents of the forthcoming chapter. In this overview section we will assign clearly where the chapter, or its constituent parts, have undergone prior presentation or peer-reviewed publication.

Part 1, Chapters 1 to 5, comprises the evidence base and the vital building blocks for the design of a robust randomised study evaluating novel cytoreductive treatments in the *de novo* synchronous mHSPC disease setting. I provide a narrative review of the pathobiological and clinical rationale of primary tumour cytoreduction. Furthermore, we systematically evaluate both the current evidence for using both surgery and SABR as a metastasis-directed therapy and the literature pertaining to patients' values, preferences and expectations for the treatment of metastatic prostate cancer. Finally, using a prospective multicentre study we report the clinical, histopathological and multiparametric MRI features of patients with mHSPC who present within a modern pre-biopsy MRI prostate cancer referral pathway.

Part 2, Chapters 6 and 7, in collaboration with my supervisors, I designed and delivered a prospective, unblinded, multicentre, randomised controlled trial, IP2-ATLANTA. I explain the granular detail of trial development which uniquely brought together multiple healthcare professionals, in many cases at a national level, to input into the trial design, novel treatments and delivery of quality assurance. We present the results of the primary endpoints from the internal pilot RCT. Concluding it is both feasible and safe to allocate patients with *de novo* synchronous mHSPC to cytoreductive MIAT, or cRP or cytoreductive radiotherapy, with or without metastasis-directed treatments. Furthermore, following the contemporary combination of ADT with systemic anticancer therapies, the majority of patients appear to have a viable residual prostate tumour on which local cytoreduction can be targeted.

Part 3, Chapters 8 to 12, provide a granular assessment of the primary tumour response using further blinded histopathological evaluation and radiological response from a dedicated embedded prospective, blinded, [⁶⁸Ga] PSMA-11 PET/CT and mpMRI imaging response sub-study. We report the final primary outcome of the internal pilot RCT, confirming the safe surgical performance of novel cytoreductive treatments and metastasis-directed surgery, and acceptable patient-reported outcome measures. I conclude my thesis by providing a summary overview of the key findings and discuss our contributions to the literature. I deliver a recommendation and framework, to be considered by the ongoing main study of IP2-ATLANTA and to direct future studies exploring this research hypothesis.

Chapter 2 - Background to local cytoreduction

2.1 Overview

This chapter sets the context of this thesis by outlining the current landscape of treatment for *de novo* synchronous metastatic hormone-sensitive prostate cancer (mHSPC). Particular focus is given to explaining the oligometastatic state, the pathobiological and clinical basis of cytoreduction rationale for primary tumour. Further the current reported. A large section of this chapter was published in *Nature Reviews Clinical Oncology* and has been reproduced under the *Springer Nature* author reuse for an academic thesis guidance¹.

2.2 Introduction

The global burden of prostate cancer is considerable. Metastatic prostate cancer has a limited median overall survival (OS) duration of 3.5 years (8,18,19). The widespread use of serum prostate-specific antigen (PSA) testing has been linked to a reduction in the proportion of men presenting with metastatic prostate cancer (2); however, following the US Preventive Services Task Force's decision in 2012 to recommend against routine serum PSA-based screening, the frequency of *de novo* metastatic prostate cancer seems to have risen, accounting for 4.9% of prostate cancers diagnosed in 2011 versus 7.7% of those diagnosed in 2014 ($P = 0.08$) (20,21). Accordingly, the annual burden of metastatic prostate cancer in the USA is expected to increase by 42% between 2015 and 2025, from 10,615 to 15,097 cases (2).

Metastatic prostate cancer is currently managed with systemic therapy alone (22). Specific to metastatic prostate cancer, exposure to androgen-deprivation therapy (ADT) for a period of 18 to 24 months typically results in the development of a castration-resistant state, whereby tumour cell proliferation occurs via androgen-independent pathways leading to progression of metastatic disease (23). In addition to systemic therapy, men may receive an array of interventions based on the appearance of troublesome symptoms (24). Such interventions commonly include, but are not limited to, palliative radiotherapy to the prostate and bony metastasis, transurethral resection of the prostate (TURP), ureteric stenting and suprapubic catheter insertion (24).

Emerging evidence suggests, however, that local treatment of the primary prostate tumour in those who present with oligometastatic disease can delay disease progression and may lead to improved overall survival (17,22,25). Oligometastatic disease is a highly favourable

¹ Connor, M.J., *et al.* Cytoreductive treatment strategies in *de novo* metastatic prostate cancer. *Nature Reviews Clinical Oncology*. 2020 Mar;17(3):168-82.

restricted clinical state where, dependent on the definition employed, between one and five metastasis are present on imaging (**Table 1**) (11). Indeed, findings of preclinical studies indicate that the primary tumour cells often secrete interleukins, growth factors and endocrine factors, including testosterone and/or dihydrotestosterone, which promote the proliferation and growth of malignant cells at metastatic sites (26-30). Removal of the primary tumour might, therefore, disrupt these interactions and slow the growth of metastases or even induce regression of these lesions (**Figure 1**).

Together, these observations suggest that the paradigm of systemic therapy alone needs to be challenged in order to make additional gains in survival. This paradigm shift might be particularly pertinent in light of the lineage crisis hypothesis, which posits that potent and highly active systemic anticancer therapies drive cancer cells to evolve to form resistant cell lineages (31). This phenomenon has been likened to the mechanism by which multidrug resistance arises in bacteria following exposure to antibiotics (31).

Importantly, surgical or ablative local treatment that disrupts the crosstalk between the primary prostate tumour and metastatic lesions, as well as reducing the actual volume of cancer cells in the body, would be expected to reduce the likelihood of lineage adaptation and might, therefore, improve time to castration resistance, progression-free survival (PFS) and OS. Clinical evidence of survival benefits derived from such cytoreductive therapy can be drawn from patients with other metastatic non-urological malignancies, such as colorectal and ovarian cancer (32,33), in addition to mixed results in patients with metastatic renal cell carcinoma (34-36).

Table 1. Definitions of oligometastatic prostate cancer

Study	Study Design	n	Radiological imaging	Definition
<i>Clinical trials</i>				
STAMPEDE; Parker et al. (2018)(16)	RCT	2,061	Bone scan + CT	<4 metastases confined to vertebral bodies and pelvis, with no visceral metastases
CHAARTED; Sweeney et al. (2015)(10)	RCT	790	Bone scan	<4 metastases confined to vertebral bodies and pelvis, with no visceral metastases
Heidenreich et al.(2015)(37)	Prospective case-control study	23	Bone scan + CT	<4 metastases with no visceral or extensive lymph node metastases plus decrease in serum PSA level to <1.0 ng/ml after neoadjuvant ADT
<i>Retrospective studies</i>				
Ost et al. (2016)(38)	Retrospective case series	119	¹⁸ F-FDG PET-CT (n = 24) or ¹¹ C-choline PET-CT (n = 92)	≤3 metastases (any)
Schick et al. (2013)(39)	Prospective case series	50	Bone scan + either ¹⁸ F-choline PET-CT or ¹¹ C-acetate PET-CT	≤4 metastases (NS)
Berkovic et al. (2013)(40)	Prospective case series	24	Bone scan + either ¹⁸ F-FDG (n = 20) or ¹¹ C-choline PET-CT (n = 4)	<3 metastases (bone or lymph node)
Tabata et al. (2012)(41)	Retrospective case series	35	Bone scan	≤5 metastases, each <50% the size of a vertebral body
Soloway et al. (1988)(42)	Prospective case series	166	Bone scan	≤5 metastases, each <50% the size of a vertebral body ^a

Legend: ADT, androgen-deprivation therapy; FDG, 2-deoxy-2-fluoroglucose; n, number of patients; PSA, prostate-specific antigen; RCT, randomized controlled trial. ^aReferred to by authors as extent of disease level 1.

2.3 Pathobiological basis of cytoreduction

2.3.1 Preclinical evidence

The pathobiological basis for cytoreductive treatment of metastatic cancer is not fully understood; however, many theories exist regarding the role of the primary tumour and its relationship with metastatic deposits, with a growing body of supporting in vivo and ex vivo evidence (26-29,35,43-45).

Circulating tumour cells (CTCs) and disseminated tumour cells (DTCs) can commonly be detected in the blood and bone marrow, respectively, of men with metastatic prostate cancer (46-48). In addition to directly seeding new metastases, CTCs and DTCs have also been

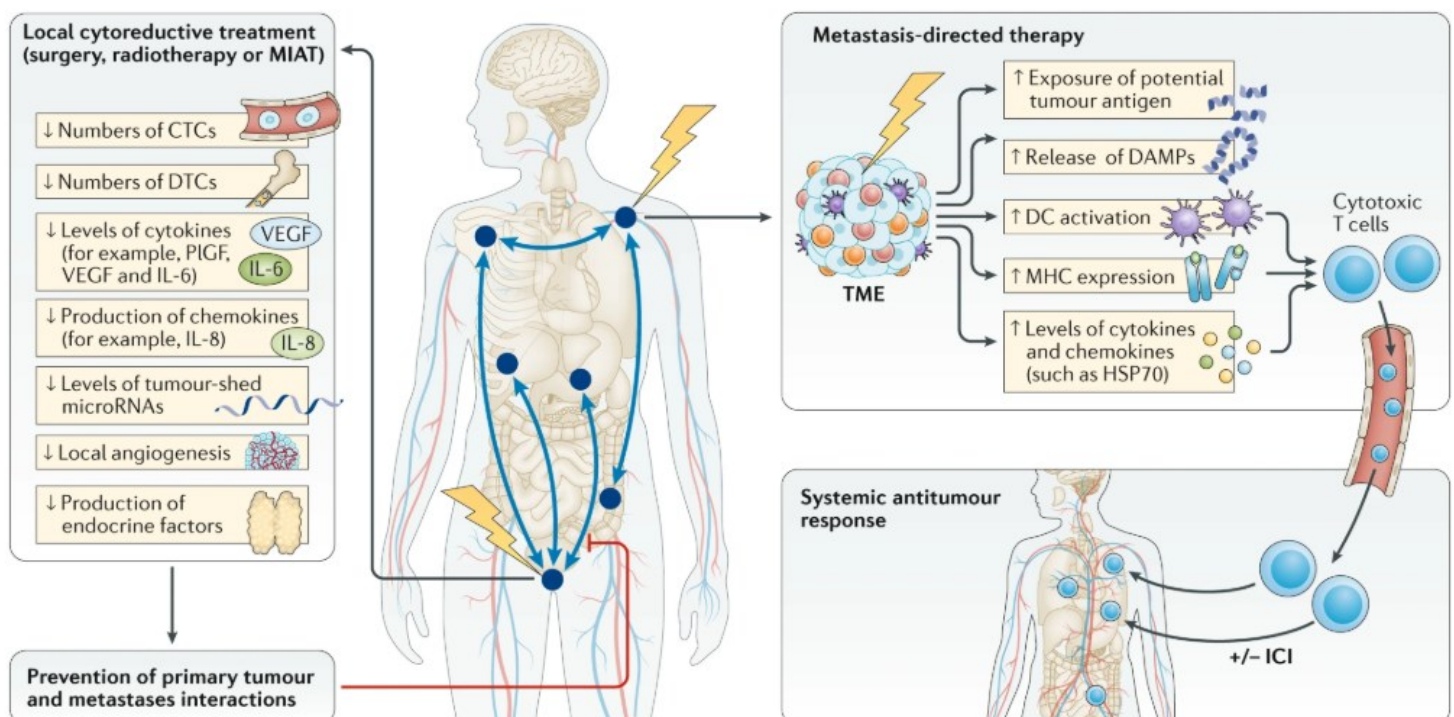
implicated in remodelling of the pre-metastatic niche, thus priming these sites for subsequent invasion and colonization by other cancer cells (49,50). Reducing the tumour burden by cytoreduction may hypothetically prevent and/or delay the development of new metastasis (50). Moreover, multifocal sequencing approaches have revealed that both primary tumour to metastasis and metastasis to metastasis transfer of clonal tumour cells can occur in patients with prostate cancer (51-53). Consequently, a tumour 'self-seeding' hypothesis has been proposed in a number of other cancers, including melanoma, breast and colon cancers (43,45). This model is supported by the finding in preclinical models that primary tumour-derived CTCs or DTCs from secondary distant sites (for example, bone) can return to their tumour of origin. Following self-seeding of their tumour of origin, these cells can alter the tumour microenvironment (TME) through the release of cytokines and matrix metalloproteinases (MMP) (such as CXCL1 and MMP1). The primary tumour also releases inflammatory interleukins (such as IL-6 and IL-8) that attract further CTC's. The results are aggressive local tumour growth and promotion of primary tumour angiogenesis (45). Further, DTCs at point of dissemination have been shown to release paracrine mediators (such as IL-6). These result in Stat3-mediate MYC activation which drives metastatic proliferation (54). Thus, the presence of a primary tumour can result in the persistence of multidirectional interactions and transfer of tumour cells between primary tumour and metastatic sites (43,45). These findings provide a rationale to study the mechanisms and effects of primary–metastasis and metastasis–metastasis communication via physical and paracrine interactions between cancer cells and neighbouring cells, as well as circulating secreted factors (51). En bloc, these observations also underscore the therapeutic benefits that could potentially be achieved by reducing primary tumour–metastasis crosstalk through cytoreductive treatment strategies.

The metastatic niche hypothesis is, arguably, a natural extension of Paget's soil and seed hypothesis, whereby focus is on the microenvironment changes required to create a distant metastasis (50). Cancer dissemination also posits that bone marrow-derived haematopoietic cells localize to pre-metastatic sites, where they contribute to establishing a supportive local environment for metastatic colonization (48); bone marrow-derived endothelial and mesenchymal cells have also been implicated in the outgrowth of micrometastases to form macrometastases (50). The mobilization of these cells results largely from the secretion of VEGF and PlGF by the primary prostate tumour (48).

Although understanding is in its infancy, differences in outcome associated with metastatic location may be influenced by interactions between the primary tumour and the metastatic niche, or tumour microenvironment itself (55-57). In particular, immunohistochemical

analysis of tissue microarray, examining antiapoptotic pathways in bone and visceral metastasis, has demonstrated significant increase expression of nuclear survivin in visceral metastasis when compared to bone (57). Further, ctDNA analysis of genes associated with promotion of fibrin and clot formation (such as F13A1 (Factor XIIIa)) were found to be significantly increased in bone versus liver and lymph node metastasis (56). These findings may help to underpin the poorer clinical survival outcomes observed in men with visceral prostate metastasis (55). Although, clear evidence is yet to emerge on the ability of systemic factors (such as cytokines) in discerning the probable anatomical location of prostate metastasis (55). The TME consists of a dynamic milieu of diverse cells (including mesenchymal, smooth muscle and endothelial cells, fibroblasts and various types of immune cells), proteins and other factors that normally constitute the nonmalignant tissue or organ or that accumulate in the neoplastic tissue during the course of tumorigenesis; thus, the TME is unique to different tumours. A variety of factors in the TME are able to influence tumorigenesis through a combination of paracrine signalling (including chemokines and cytokines) and physical interactions (for example, between immune cells and cancer cells) (58).

Figure 1. Mechanisms underlying the potential clinical benefits of local cytoreductive treatment and metastasis directed therapy of prostate cancer



Legend: Local cytoreduction of a primary prostate cancer (and/or metastases thereof) has various effects on tumour-derived factors that are likely to translate into survival benefits for patients, predominantly by removing a source of circulating tumour cells (CTCs) and disseminated tumour cells (DTCs) and by abrogating the supportive interactions between the primary tumour and metastases, which involve

*cytokines, chemokines and microRNAs. These effects would be expected to limit the growth of existing lesions and/or delay or prevent the outgrowth of new metastases and might be enhanced by the suppression of angiogenesis in the tumour microenvironment (TME) as a result of radiotherapy or ablative therapy. Metastasis-directed therapy with ionizing radiation (primarily stereotactic ablative radiotherapy) or other ablative therapies can be associated with abscopal effects on lesions located outside the field of treatment. These effects on distant tumours reflect the release of tumour antigens and damage-associated molecular patterns (DAMPs) as well as the upregulation of MHC presentation in the treated lesion that can result in local activation of immune cells, including dendritic cells (DCs) and cytotoxic T cells, which can subsequently mediate a systemic antitumour immune response. These abscopal responses could potentially be promoted through enhancement of T cell activity, for example, through immune-checkpoint inhibition (ICI), and might also occur with irradiation or ablation of the primary tumour (not shown). HSP70, heat shock protein 70; MIAT, minimally invasive ablative therapy. [*Reproduced with permissions (Appendix A) from Springer Nature: Connor MJ, Shah T, Horan G, Bevan C, Winkler M, Ahmed HU. Cytoreductive treatment strategies in de novo metastatic prostate cancer. Nature Reviews Clinical Oncology. 2019.]*

A role for cancer cells themselves, whether from the primary tumour or another metastatic lesion, in priming the metastatic niche for tumour seeding is widely accepted; however, other circulating tumour-derived factors have also been hypothesized to contribute to metastatic spread by similarly facilitating the priming of metastatic sites and perhaps the subsequent cancer cell colonization of and/or proliferation within these niches. For example, tumour cells can secrete endocrine factors, such as testosterone and dihydrotestosterone in the case of prostate cancer, which can promote the growth of metastases and also compete with endocrine therapies (including agents used for ADT), thus reducing the effectiveness of treatment (26,28,29). Furthermore, tumour shedding of high levels of DNA and microRNAs (miRNAs), either unencapsulated or encapsulated in exosomal vesicles, provides compelling mechanisms for communication between cancerous lesions (59-61). Indeed, the seemingly active release of miRNAs with hormone-like properties has resulted in coining the term 'hormomirs' to describe these factors. Hormomirs have the potential to act locally or distantly to influence the development and progression of cancer or other diseases (62). The levels of epithelial cell-derived microRNAs (for example, miR-375, miR-141 and miR-200b) are particularly elevated in metastatic prostate cancer. The levels of these miRNAs have been hypothesized to be indicative of either the presence of CTCs or mesenchymal-to-epithelial transition (MET) of CTCs or metastases (63-65). Notably, the MET phenotype has been associated with enhanced tumour cell proliferation and accelerated metastasis in preclinical models (63). Furthermore, extracellular vesicles have been recently recognised as an important method for cell-to-cell communication between primary prostate tumour and its environment. When applied to metastatic disease, proof-of-concept studies now support the hypothesis that prostate cancer derived miRNA, carried by extracellular vesicles communication, result in the promotion of osteoblast viability and supportive growth

environments within bone stroma (66). This is a novel primary-metastasis route, which leads to the production of bone metastasis (66). These findings suggest that, by virtue of reducing the levels of circulating tumour-derived factors, cytoreduction using local treatments might delay disease progression and thus prolong patient survival.

The first preclinical evidence supporting a cytoreduction strategy for metastatic prostate cancer was reported in 1982 by Kadmon and colleagues' (67). In rats implanted ectopically with R3327-MAT-Lu prostate adenocarcinoma cells, lung metastases, this group found that the number of lung colonies continued to increase the longer the primary prostate tumour was left in situ (67). Moreover, although tumour resection or chemotherapy alone substantially decreased the number of metastases compared with those observed in untreated rats, only the combination of primary tumour excision with postoperative chemotherapy prolonged survival and resulted in cure in some rats(67). In a similar rat model, Grinis et al.(68) confirmed that cytoreductive surgery of the primary R3327-MAT-LyLu flank tumours results in a statistically significant reduction in metastatic burden in the lungs ($P < 0.05$). In addition, increased T helper to regulatory T cell ratios were observed in the blood of these rats after cytoreductive surgery suggesting a beneficial host immune response to tumour excision (68).

2.3.2 Clinical evidence

In a comparison of prostatectomy specimens from patients with locally advanced or lymph-node metastatic prostate cancer who received a year of treatment with ADT plus three cycles docetaxel and archived specimens from patients with untreated high-grade prostate cancer, Tzelepi et al.(44) found no statistically significant difference in the expression of proteins associated with proliferation and apoptosis. Moreover, the expression of certain factors implicated in tumorigenesis, including proteins involved in androgen synthesis, Hedgehog signalling and angiogenesis, were increased after systemic therapy. Thus, the authors concluded that potentially lethal cancer cells persist in the primary tumour even after chemohormonal therapy and might contribute to disease progression (44). The clinical implications of such findings are that even in patients who appear to have an effective cancer control with systemic agents alone, the persistence of the primary tumour maybe an uncontrolled source of continued seeding of new distant metastasis.

Weckermann et al. performed bone marrow aspirates on 384 men with clinically localised disease prior to radical prostatectomy (69). Unsurprisingly, the level of DTCs (specifically,

Cytokeratin-positive cells) prior to prostatectomy was an independent predictor of development of distant metastasis post-operatively. Interestingly, DTC level post-operatively had no effect on metastatic disease risk. The authors' hypothesised that these findings support the theory that persistence of a primary tumour-DTC interplay was thus required to stimulate DTCs to colonise and form prostate metastasis (69).

2.4 Abscopal effects of local therapies

2.4.1 Radiobiological mechanisms.

The direct cytotoxic effects of local prostate radiotherapy are well established and have been widely reported (70). Furthermore, indirect effects on distant metastatic tumours have been described and associated with clinical benefits. The term 'abscopal' is derived from the Latin prefix 'ab' (meaning away) and 'scopus' (target) and was coined by R. Mole in 1953 (71). The descriptor 'abscopal effect' can be used broadly to define a therapeutic response of lesions located distant to the primary anatomical site of local treatment (71).

Findings in mouse models indicate that the abscopal effect of radiotherapy is dose-dependent and have revealed an interplay between *TP53* status and responsiveness of the non-irradiated tumours (72,73). Specifically, abscopal effects have been observed in *TP53*-wild-type but not *TP53*-null CT116 colon cancer xenograft tumours, with pro-apoptotic signalling via p53 being implicated in these effects (73). Additionally, effects on the TME of the irradiated lesion, systemic cytokine-mediated inflammatory signalling and activation of the immune system are key components of the abscopal effect (74).

A number of case reports of rapid distant tumour regression following irradiation of a single metastatic lesion and systemic immune-checkpoint inhibition (ICI) have led to heightened research interest in exploiting this strategy more broadly in the clinic (72,75,76). The radiobiological mechanisms of these clinical responses involve tumour cell death and alterations of the TME induced by ionizing radiation (77). Briefly, radiation results in direct damage to components of the TME, which triggers the release of chemokines (such as HSP70) that attract immune cells to the tumour (78,79). Concurrently, ionizing radiation leads to the release of danger-associated molecular patterns (DAMPs) in the TME, which are detected by Toll-like receptors (such as TLR4) on the surface of dendritic cells (DCs), among other cell types, and activate these cells. Furthermore, irradiation of the tumour leads

to a dose-dependent increase in expression of major histocompatibility complex class I (MHC I) proteins on the surface of tumour cell (78). Ultimately, the release of chemokines, activation of DCs and increased MHC I-mediated antigen presentation by tumour cells can all promote immune recognition of tumour-associated antigens (TAAs), resulting in the priming of antitumour T cells (80-82). Subsequently, the TAA-specific cytotoxic T cells can attack not only tumour cells in the local, irradiated tumour, but also those of distant metastasis provided that the relevant antigen is also present therein (83) (**FIG. 1**).

Clinical studies demonstrating such responses specifically in the context of prostate cancer are very rare. Low-dose ^{125}I -based prostate brachytherapy has, however, been demonstrated to increase the proportion of circulating activated T cells and the ratio of activated T cell to regulatory T (T_{reg}) cells, despite an increase in the proportion of T_{reg} cells, in patients with this disease (84), indicating the potential for abscopal responses. Irrespective of this evidence gap, a shift in the focus of research has occurred, with initiation of a large number of trials designed to evaluate the role of ICI in combination with metastasis-directed radiotherapy (85,86). Initial results from 799 patients with metastatic castration-resistant prostate cancer (mCRPC) that had progressed after docetaxel therapy were mixed, with receipt of the anti-cytotoxic lymphocyte protein 4 (CTLA-4) antibody ipilimumab following bone-directed radiotherapy resulting in a PFS benefit (median 4.0 months versus 3.1 months with placebo; HR 0.70, 95% CI 0.61–0.82; $P < 0.0001$) but no statistically significant OS benefit (median 11.2 months versus 10.0 months; HR 0.85, 95% CI 0.72–1.00; $P = 0.053$)(86). These disappointing results are thought to reflect, in part, a limited capacity for a successful systemic antitumour response at such a late stage of the disease. Indeed, an OS benefit was observed in a subgroup of patients with favourable prognostic features, including an absence of visceral metastases (median 22.7 months with ipilimumab versus 15.8 months with placebo; HR 0.62, 95% CI 0.45–0.86; $P = 0.0038$). Notwithstanding, some investigators have argued that consistently generating a systemic antitumour immune response is likely to require irradiation of more than one lesion (77), contrary to the single-lesion hypothesis widely promulgated on the basis of the early reports of abscopal responses.

2.4.2 Immune effects of ablative therapies

Similar to radiotherapy, minimally invasive ablative therapies (MIATs) for the local treatment of prostate cancer might have additional, beneficial, systemic immunological effects (87). The two most widely used MIATs for prostate cancer are cryotherapy and high-intensity

focused ultrasound (HIFU). During cryotherapy, a real-time transrectal ultrasonography (TRUS) probe is used to visualize and guide the transperineal insertion of thermosensors and cryoprobes into the prostate. TRUS also enables visualization of 'ice ball' formation during the alternating freeze and thaw cycles, which leads to cell death in the treated prostate tissues (87,88); cryotherapy can be focal or encompass the whole gland, including seminal vesicles. Histologically, freezing of the tissues results in a central zone of coagulative necrosis and a gradient of devitalisation extending from the core of the ice ball (87). HIFU involves the application of ultra-high-frequency sound waves to prostatic tissues via a transrectal transducer probe in order to generate heat that ablates cells located in the treatment zone. TRUS, often via a separate imaging transducer on the same probe, is used for treatment planning and although there is no direct temperature measurement, indirect feedback can be quantified from the USS images and often echogenic changes are also seen in real time (89). Like cryotherapy, HIFU leads to extensive coagulative necrosis, followed by tissue fibrosis seen histologically from 6 months onwards (87,90).

The cellular destruction caused by MIATs results in the release of TAAs that can ultimately stimulate an acquired humoral or cellular antitumour immune response. Cell and tissue damage also results in stimulation of cells of the innate immune system, including antigen-presenting cells, which promote the acquired immune response through activation of TAA-specific T cells (87,91,92). This response is augmented by interactions of co-stimulatory molecules such as DNA, RNA, heat shock protein 70 (HSP70), uric acid and high mobility group protein B1 (HMGB1) which are released during the process of necrosis and by the presence of danger signals (93). Thus, tissue necrosis is the underlying driver of the immunological response orchestrated by the release of proinflammatory cytokines and presentation of antigens, predominantly by DCs, to T cells. Different key populations of T cells are involved in the acquired immune response, some with opposing effects: CD4⁺ T helper cells and CD8⁺ cytotoxic T cells are effectors of antitumour immune responses, whereas CD4⁺ T_{reg} cells typically have immunosuppressive effects (91). Apoptosis does not routinely lead to an immunostimulatory reaction and, therefore, the balance between necrosis and apoptosis induced within any treated lesion might explain why not all studies of ablative therapies have provided promising evidence of productive antitumour immune responses (91,94).

The effects of cryotherapy in experimental animal models, including the generation of autoantibody against the targeted tissue, were originally demonstrated in the 1960s (95-97). In 1972, Ablin reported a series of five patients, all of whom had regression of distant

metastases following local prostate cryotherapy (98); however, other groups have been unable to replicate such responses, with some reporting that, paradoxically, cryotherapy leads to an immunosuppressive state in animal models (99,100).

HIFU has also been reported to induce an immune response against non-prostate cancers, in both mouse models and patients. For example, in mouse models where neuroblastoma cells were injected subcutaneously and allowed to develop, a significantly reduced tumour volume (mm³) at 10 days was demonstrated after a tumour rechallenge with injected neuroblastoma cells occurred only in those who had had an initial successful HIFU treatment (101). This finding was replicated in studies involving mouse models of hepatocellular carcinoma, which included the use of vaccines containing tumour antigens generated from repeated mincing and homogenizing treated tumours resulting in an overall reduction in tumour growth and improved survival (102). Clinical studies across a wide range of malignancies have revealed increases in the CD4:CD8 ratio and reductions in the serum levels of immunosuppressive cytokines (such as VEGF and TGF β) with concurrent increases in the levels of type 2 T helper cell cytokines (including IL-6 and IL-10) following HIFU treatment, which might be indicative of an enhanced antitumour response (103).

2.5 Local cytoreductive treatments

2.5.1 Clinical trial endpoints in mHSPC

Prior to an appraisal of the clinical trial evidence it is important to briefly consider meaningful clinical trial endpoints in patients with mHSPC. Randomised controlled studies with a primary endpoint of overall survival, commonly defined as time from randomisation to death, have been historically considered the gold standard for patients with mHSPC (10). However, such an approach can result in protracted follow-up for novel therapies, an increased sample size and associated costs (104). Collectively, this may delay dissemination of new findings. In addition, there are an emerging number of therapies which may be provided to patients at point of progression, these therapies may act as confounders adding uncertainty to the true magnitude of effect of the trial intervention under evaluation.

In non-metastatic prostate cancer there has been a recent exploration of possible intermediate clinical endpoints for overall survival. Metastasis-free survival (MFS) is commonly defined as time from randomisation to first evidence of recorded distant metastases, confirmed by conventional imaging or histologic evidence, or death from any cause. MFS has emerged as the most robust intermediate clinical endpoint in this setting

(105). Clearly MFS cannot be applied to patients with established metastatic disease at trial entry.

In mHSPC a number of intermediate clinical endpoints have been considered over the years, with radiographic progression-free survival (rPFS) and clinical progression free survival (cPFS) both supported by randomised evidence as valid intermediate clinical endpoints (104,106). rPFS is commonly defined as time from randomisation to radiographic progression (on CT or bone scintigraphy) or death from any cause, whichever occurred first (106). Clinical progression free survival (cPFS) is commonly defined as time from randomization to date of radiographic progression, disease symptoms, initiation of new treatment, or death from any cause, whichever occurred first.

The STOPCAP M1 collaborative applied these definitions to individual patient data from 8,612 patients with mHSPC in 9 randomised controlled trials that compared treatment regimens of ADT or ADT with docetaxel in the control or research arms (106). The collaborative calculated the surrogate threshold effect (STE), defined as the minimum intermediate clinical endpoint treatment effect necessary to estimate a non-zero effect on overall survival. Median overall survival was reported as 4.1 years, median rPFS 2.3 years, and median cPFS 2.1 years, respectively. Correlation at a patient level revealed an STE of 0.83 (95% CI 0.82-0.84) for rPFS and 0.84 (95% CI 0.83-0.85) for cPFS, respectively. The collaborative concluded that the observed STE of ≥ 0.82 made it viable for either endpoint (rPFS or cPFS) to be considered as a valid surrogate primary endpoint for overall survival in phase III randomised controlled trials in this setting (106).

2.5.2 Cytoreductive radiotherapy

Early evidence of survival benefits derived from local cytoreductive radiotherapy of the primary tumour in patients with metastatic prostate cancer comes from large population-based retrospective analyses as well as smaller prospective case-control studies (13-17) (**Table 2**). Using data from the US National Cancer Database, Rusthoven et al. (17) performed a retrospective analysis encompassing 6,382 men with newly diagnosed metastatic prostate cancer. These investigators reported that 538 (8.4%) of these men received prostate radiotherapy in addition to ADT and that this group had a statistically significant absolute OS benefit of 16% (5-year OS 49% compared with 33% in those who received ADT alone; HR 0.62, 95% CI 0.55–0.70; $P < 0.0001$). Culp et al. (13) analysed the outcomes of 8,185 men diagnosed with metastatic prostate cancer recorded in the Surveillance, Epidemiology, and End Results (SEER) database between the 2004 and 2010. These investigators found that 129 men who received prostate brachytherapy had a 12.6%

absolute benefit in terms of 5-year disease-specific survival (DSS) compared with 7,811 men who did not undergo definitive local therapy of the primary tumour (61.3% versus 48.7%; $P < 0.001$); receipt of brachytherapy was also associated with a 5-year OS benefit of 30.1% (**Table 2**). In addition, the results of a pilot prospective case–control study conducted by Cho and colleagues (14) demonstrated superior 3-year OS in 38 patients with metastatic disease who received local prostate radiotherapy versus 101 patients who did not (69% versus 43%; $P = 0.004$).

In 2018, data from two large-cohort randomized controlled trials (RCTs) of cytoreductive prostate radiotherapy were published and provide the first level 1 evidence supporting this approach (15,16). In the phase II HORRAD trial (15), 432 men with de novo bone-metastatic prostate cancer and a serum PSA level >20 ng/ml received ADT with or without local external beam radiotherapy of the primary tumour (**Table 2**). No clinically relevant difference in OS was observed between the two groups (median 45 months with ADT plus EBRT versus 43 months with ADT alone; HR 0.90, 95% CI 0.70–1.14; $P = 0.40$); however, a subgroup analysis of data from those with low-volume disease (<5 bone metastasis) did reveal a nonsignificant trend towards improved OS favouring the EBRT group (HR 0.68, 95% CI 0.42–1.10)(15). Moreover, the median time to biochemical progression of disease was found to be significantly prolonged to 15 months with local prostate radiotherapy, from 12 months with ADT alone (crude HR 0.78, 95% CI 0.63–0.97; $P = 0.02$). However, the authors did not formally stratify patients according to metastatic burden and were unaware of the presence or absence of visceral metastasis at randomisation (15).

In the phase III STAMPEDE trial by Parker et al. (16), 2,061 men with newly diagnosed metastatic prostate cancer received standard-of-care systemic therapy (ADT with or without docetaxel) plus or minus local EBRT delivered to the prostate (**Table 2**). Similar to the HORRAD results (15), cytoreductive prostate radiotherapy did not provide a significant OS advantage (HR 0.92, 95% CI 0.80–1.06; $P = 0.27$)(16). In a pre-specified subgroup analysis, however, men with a low metastatic burden (according to the CHAARTED definition; **Table 1**), were found to derive a statistically significant survival advantage from prostate EBRT (3-year OS 81% versus 73% in the standard-of-care alone group; HR 0.68, 95% CI 0.52–0.90; $P = 0.007$) (16). In addition, cytoreduction was associated with a 3-year failure-free survival (FFS) benefit, not only in the subgroup with a low disease burden (50% versus 33%; HR 0.59, 95% CI 0.49–0.72; $P < 0.0001$), but also in the overall population (32% versus 23%; HR 0.76, 95% CI 0.68–0.84; $P < 0.0001$) (16). Importantly, radiotherapy was well tolerated with only 5% of patients having grade 3–4 adverse events during the course of radiotherapy (16). However, no data on locoregional symptoms - haematuria, urinary retention (with or

with a clot), urinary tract obstruction or pelvic pain - were presented in the reports of either RCTs (15,16).

The demonstration of a statistically significant OS benefit for patients with a low metastatic burden in STAMPEDE but not HORRAD has been suggested to be attributable to the underpowered size of this patient subgroup in the latter trial (15). Nevertheless, STAMPEDE had several key limitations relating to classification of metastatic burden and imaging, radiotherapy dosage and the nature of the 'standard-of-care' treatment. The definition of low burden (oligometastatic) disease was prespecified according to the CHAARTED definition (**Table 1**), although no attempts were made to perform analysis using alternative definitions. As such, men at the extremities of the definition (that is, those with <5 bone metastases) are likely to be considered ineligible for local treatment of the primary tumour, despite the potential for clinical benefit. In addition, the STAMPEDE eligibility criteria did not require the use of PET-CT, which has higher sensitivity for the detection of metastatic deposits than conventional imaging (16). Thus, the general accuracy of the categorization of metastatic burden in this trial could be questioned (16). Finally, the use of systemic therapy in STAMPEDE did not reflect current clinical practice, with only 18% of men in the trial receiving docetaxel (16).

In summary, local cytoreductive radiotherapy seems to benefit some men with low-burden metastatic prostate cancer; however, the most appropriate definition of low burden or oligometastatic disease, the optimal radiotherapy schedule and the absolute OS benefit in the context of contemporary upfront chemohormonal therapy all remain to be determined.

Table 2. Key studies utilising cytoreductive radiotherapy

Study	Study design (n)	Radiotherapy schedule	Median follow-up duration	Extent of metastatic disease	Study arms (n)	OS (HR, 95% CI ^a)	FFS (HR, 95% CI ^a)
STAMP EDE; Parker et al. (2018) (16)	Phase III RCT (2,061)	36 Gy in 6 fractions over 6 weeks or 55 Gy in 20 fractions over 4 weeks	37 months (IQR 24–48)	Any	ADT ^b + EBRT: (1,032) vs ADT ^b (1,029)	At 3 years: 65% vs 62% (0.92, 0.80–1.06; <i>P</i> = 0.27)	At 3 years: 32% vs 23% (0.76, 0.68–0.84; <i>P</i> <0.0001)
				<4 metastases with no visceral, vertebral body or pelvis metastases	ADT ^b + EBRT (408) vs ADT ^b (410)	At 3 years: 81% vs 73% (0.68, 0.52–0.90; <i>P</i> = 0.007)	At 3 years: 50% vs 33% (0.59, 0.49–0.72; <i>P</i> <0.0001)
HORR AD; Boeve et al. (2018) (15)	Phase II RCT (432)	70 Gy in 35 fractions of 2 Gy, during an overall treatment time of 7 weeks	47 months (IQR 46–68)	Any	ADT + EBRT (216) vs ADT (216)	Median: 45 months vs 43 months (0.90, 0.70–1.14; <i>P</i> = 0.40)	Median 15 months vs 12 months (0.86, 0.69–1.08; <i>P</i> = 0.20)
				<5 metastases bone metastases	ADT + EBRT (71) vs ADT (89)	Median: NR] (0.68, 0.42–1.10; <i>P</i> >0.05)	NR
Rusthoven et al. (2016) (17)	Population-based retrospective study (6,382)	Not specified	61 (IQR NR)	Any	EBRT + ADT (538) vs ADT (5,844)	Median: 55 months vs 37 months At 5 years: 49% vs 33% (0.62, 0.55–0.71; <i>P</i> <0.001)	NR

Cho et al. (2016) (14)	Prospective case-control study (140)	Median 60 Gy in 24 fractions	34 months (IQR 1.7–108)	Any Disease extent subgroups Solitary bone (n = 25) 2 - 4 bone (n = 41) ≥5 bone (n = 66) Visceral (n = 8)	EBRT (38) vs SoC ^c (102)	Overall at 3 years: 69% vs 43% (HR 0.43, NR; <i>P</i> = 0.015) Disease extent subgroups UVA OS 3 years: Solitary Bone 57%; 2-4 bone 41%; ≥ 5 28%; Visceral 0% (<i>P</i> = 0.007)	3-year biochemical FFS: 52% vs 16% (NR, NR; <i>P</i> = 0.002)
Culp et al. (2013) (13)	Population-based retrospective study (8,185)	Brachytherapy	16 months (IQR 7–31)	Any [	Brachytherapy (129) or RP (245) vs NSR (7,811)	At 5 years: 52.6% with brachytherapy and 67.4% with RP vs 22.5% with NSR (NR, NR; <i>P</i> <0.001 for both comparisons)	NR

Legend: ADT, androgen-deprivation therapy; CI, confidence interval; EBRT, external beam radiotherapy, FFS, failure-free survival, HR, hazard ratio; IQR, interquartile range; n, number of patients; NR, not reported; NSR, no prostate surgery or radiotherapy; OS, overall survival; RCT, randomized controlled trial; RP, radical prostatectomy; RT, radiotherapy; SoC, standard of care (as defined in cited references); UVA, Univariate analysis. ^aOn multivariate analysis. ^bWith or without upfront docetaxel. ^cIncluded radiotherapy to lesions other than the primary tumour.

2.5.3 Cytoreductive prostatectomy

The benefits of a cytoreductive surgical strategy were hypothesized as long ago as 2002, following a post-hoc analysis of data from the Southwest Oncology Group (SWOG) 8894 trial involving 1,286 men with metastatic prostate cancer who were randomly assigned to receive bilateral orchidectomy plus either placebo or the antiandrogen flutamide (107). This analysis revealed that, surprisingly, men who had previously undergone radical prostatectomy had a significantly reduced risk of death than those who had not (HR 0.77, 95% CI 0.53–0.8) (107). Interestingly, prior prostate radiotherapy was associated with a greater risk of death than prostatectomy or no definitive local treatment (HR 1.22, 95% CI 0.93–1.59).

In 2013, the aforementioned retrospective analysis of the SEER database provided more direct evidence supporting a cytoreductive prostatectomy strategy (13). In this study, 245 men who received radical prostatectomy had a 27.1% increase in 5-year absolute DSS compared with the 7,811 men who did not received definitive local treatment (75.8% versus 48.7%; $P < 0.001$) (13). Cytoreductive surgery was also associated with a 44.9% absolute OS benefit at 5 years (**Table 3**). These findings were mirrored by those of an analysis of the Munich Cancer Registry (1998–2010), in which 74 men with de novo metastatic disease who had undergone cytoreductive prostatectomy were found to have a 30% absolute improvement in 5-year OS benefit relative to 1,464 how did not undergo surgery (108) (**Table 3**). Neither of these major retrospective population-based studies provide any insight into subgroup stratification or clinical characteristics that might be predictive of OS outcomes (13).

Sooriakumaran et al.(109) have reported a retrospective case series of 106 men with de novo cTxM1a-b prostate cancer who received cytoreductive prostatectomy and extended pelvic lymphadenectomy, demonstrating 88.7% DSS after a median follow-up duration of 22.8 months. The authors stated that the feasibility of the approach and the complication rate (20.4%), rather than oncological outcomes, were the primary focus of their analysis, concluding that these aspects are acceptable when the procedure is performed by experienced surgeons (109).

In a retrospective case–control study involving 79 men with oligometastatic prostate cancer (defined in this study as ≤ 5 bone-only metastases), 38 of whom underwent robotic-assisted cytoreductive prostatectomy with or without ePLND, the investigators observed an absolute PFS advantage of 47 months compared with the 41 patients who received ADT alone (median PFS 75 months versus 28 months; $P = 0.008$); the median DSS was not reached versus 40 months ($P = 0.002$) (110). However, this study is inherently limited by differences in surrogates of disease status, such as Gleason score, serum PSA level and clinical stage, between the treatment groups at baseline, owing to the lack of randomization (110).

Evidence supporting a local cytoreductive strategy can also be drawn from studies involving patients with lymph node-limited metastasis (that is, locally advanced disease). For example, in a matched-cohort study, the outcomes of 79 men with de novo pTxN+cM0 prostate cancer who had undergone radical retropubic prostatectomy and lymphadenectomy plus orchidectomy were compared with those of 79 men who had undergone lymphadenectomy plus orchidectomy alone (111). The prostatectomy group had absolute 10-year DSS and OS benefits of 40% (79% versus 39%; RR 0.28, 95% CI 0.13–0.59; $P < 0.001$) and 38% (66% versus 28%; RR 0.36, 95% CI 0.20–0.66; $P < 0.001$), respectively.

Prospective evidence to support a role for cytoreductive prostatectomy in men with oligometastatic disease is also emerging, although of low quality. For example, Heidenreich et al. have performed a prospective case–control study involving 23 men with investigator-defined oligometastatic prostate cancer (**Table 3**) who received neoadjuvant ADT followed by cytoreductive prostatectomy and extended pelvic lymph node dissection (ePLND) (37). After a median follow-up duration of 34.5 months, this group had a 12.1-month improvement in median PFS (38.6 months compared with 26.5 months in 38 men treated with ADT alone; $P = 0.032$); cytoreductive surgery was also associated with an 11.4% improvement in DSS and a 12.4% improvement in OS at this time point (**Table 3**). The complication rate was reported as 21.7%, with no grade 4–5 adverse events according to the Clavien–Dindo classification (37), in keeping with the findings of other retrospective case series (109,110). Beyond oncological outcomes and surgical complications, Heidenreich et al.(37) reported no locoregional symptoms among the 23 men in the cytoreductive prostatectomy arm, with a urinary continence (requirement of ≤ 1 pads per day) rate of 91.3%. Nevertheless, the small number of patients and probable selection bias limit the generalizability of the findings of this study.

Several RCTs designed to evaluate the addition of cytoreductive prostatectomy to standard-of-care therapy are current ongoing. For example, a phase II trial of best systemic therapy (BST) plus radical prostatectomy (or prostate radiotherapy) versus BST alone is being is underway (NCT01751438), with planned enrolment of a selected group of 180 men with clinically favourable extracranial metastatic disease (112). The g-RAMPP trial (NCT02454543) is being performed to explore the combination of cytoreductive prostatectomy and ePLND with BST in men with oligometastatic disease (≤ 5 bone metastasis and no visceral metastases), with an enrolment target of 452 patients (113). Similarly, in the UK, the TRoMbone trial (ISRCTN15704862) is enrolling men <75 years of age with 1–3 skeletal metastases and no visceral metastases ($n = 50$) in order to explore the feasibility of randomized assignment to receive either BST alone or with cytoreductive prostatectomy and ePLND (114).

Table 3. Key studies utilising cytoreductive prostatectomy

Study	Study design (n)	Extent of metastatic disease	Median follow-up duration	Study arms (n)	OS ^a (HR, 95% CI)	CSS ^a (HR, 95% CI)
Jang et al. (2017) (110)	Retrospective case-control study (79)	≤5 hot spots on bone scan and no visceral metastases	40 months (IQR 28–58)	RARP (38) vs ADT alone (41)	NR	Median: not reached vs 40 months (NR, NR; $P = 0.002$)
Sooriakumaran et al. (2016) (109)	Retrospective case series (106)	Any	22.8 months (IQR NR)	RP + ePLND (106) Subgroups: ePLND (92.1%), adjuvant ADT (73.7%), neoadjuvant ADT (57.9%)	NR	At median follow-up: 88.7% (NR)
Heidenreich et al. (2015) (37)	Prospective case-control study (61)	<4 metastases with no visceral or extensive lymph node metastases in patients with a serum PSA level <1.0 ng/ml after neoadjuvant ADT	34.5 months (range 7–75) in RP group and 47 months (range 28–96) in ADT alone group	RP (23) vs ADT alone (38)	At median follow-up: 91.3% vs 78.9% ($P = 0.048$)	At median follow-up: 95.6% vs 84.2% (NR, NR; $P = 0.043$)
Gratzke et al. (2014) (108)	Retrospective population-based study (1,538)	Any	NR	RP (74) vs no RP (1,464)	At 5 years: 55% vs 21% ($P < 0.01$)	NR

Culp et al. (2013) (13)	Retrospective population-based study (8,185)	Any	16 months (IQR 7–31)	RP (245) or brachytherapy (129) vs NSR (7,811)	At 5 years: 67.4% with RP and 52.6% with brachytherapy vs 22.5% with NSR (NR, NR; $P < 0.001$ for both comparisons)	NR
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ADT, androgen-deprivation therapy; BST, best systemic therapy; CI, confidence interval; CSS, cancer-specific survival; ePLND, extended pelvic lymph node dissection; HR, hazard ratio, NA, not applicable; NR, not reported; NSR, no prostate surgery or radiotherapy; OS, overall survival; PSA, prostate-specific antigen; RARP, robot-assisted radical prostatectomy; RCT, randomized controlled trial; RP, radical prostatectomy; RT, radiotherapy. ^aOn multivariate analysis. ^bExpected number of trial participants.

2.5.4 Cyto-reductive minimally-invasive ablative therapy

Minimally-invasive ablative therapy (MIAT) is emerging as a novel treatment modality for prostate cancer, typically for men with low to intermediate risk non-metastatic disease (87,115); scant clinical evidence is available for use of these ablative therapies in the metastatic setting, with the most promising data relating to cryotherapy. However, cryoablation has been proven to provide local disease control and improve the oncological outcomes of patients with metastatic renal cell carcinoma (116,117). Importantly, this form of therapy can avoid the need for surgical metastasectomy and can be used safely alongside systemic agents (116,118,119).

Specifically relating to primary prostate tumour cryoablation, Sheng et al. performed a retrospective case–control study involving 46 men with $\leq$ cT3a disease, bone metastasis, no visceral metastasis and a decrease in serum PSA level to <1.0 ng/ml after 6 months of neoadjuvant ADT (120). A total of 23 men underwent cyto-reductive cryotherapy followed by adjuvant ADT, while 26 received ADT alone (120). The authors reported an absolute median PFS advantage of 10 months with cyto-reductive cryotherapy (35 months versus 25 months; HR 0.21, 95% CI 0.09–0.45; $P = 0.0027$); thus, cryotherapy reduced the risk of disease progression by 79% (120). These investigators should be credited for selecting patient groups that were well matched in terms of metastatic burden, Gleason score and age; however, the small size of the study cohort, the inherent limitations of retrospective studies and, crucially, the exclusion of patients with T3b–T4 disease restricts the clinical applicability of the findings. With regard to locoregional symptoms, the men who underwent cyto-reductive cryotherapy were less likely to require palliative urological interventions than those who received ADT alone (19.2% versus 4.3%) (120). Moreover, the safety of cryotherapy in this series of patients was favourable, with no reported cases of rectal injury or fistulae (120). Three patients had temporary urinary incontinence, which self-resolved within 12 months

(120). These findings are in keeping with the cryotherapy complication rates reported in other series that included patients with non-metastatic stage T3b prostate cancer (115,121). Indeed, MIAT in the non-metastatic disease setting results in fewer adverse effects than radical therapies, which might be beneficial when applied to the group of men with metastatic disease who are at a high risk of complications (115,121).

Finally, a recent propensity-scored matched analysis of alone cytoreductive whole-gland cryotherapy ($n=54$) against ADT alone ($n=54$) has reported a median failure-free survival advantage of 18 months (39 versus 21 months; $p = 0.005$) (122). There was no difference in CSS or OS between the two groups. Again an acceptable side effect profile was reported with no recto-urethral fistula and no urinary incontinence in the intervention group. Patients in the intervention groups had a greater relief of their urinary symptoms when compared to those on ADT alone (79.1 vs. 59.1%; $p = 0.044$).

Considering the potential of immunotherapy to augment these immunological effects, the results of a clinical trial (NCT02489357) of pembrolizumab in combination with cytoreductive cryotherapy performed by Ross and colleagues are of interest (123). In this small 12-patient study low burden (≤ 5 extra-pelvic metastases) patients underwent ADT (8 months) with pembrolizumab (200 mg every 3 weeks for six doses). Cytoreductive whole-gland cryotherapy was performed within 3 days of the first dose of pembrolizumab. Co-primary endpoints were <0.6 ng/mL at 1 year and adverse events, other endpoints included PFS. Five patients achieved (5/12; 42%) the PSA endpoint at one-year. In addition, 14 months median PFS, and 17.5 months median systemic therapy-free survival as reported, respectively. Reassuringly in the majority of patients (83.3%; 10/12) there was no evidence of disease on post-cryotherapy prostate biopsy. Furthermore, all adverse events were ≤ 2 , grade 1 urinary incontinence and haematuria were reported in 2 (16.7%) and 2 (16.7%) participants, respectively. This pilot study provides the first prospective evidence on the technical feasibility and safety of delivering cytoreductive cryotherapy with immunotherapy in a small number of patients (124).

In summary, the current evidence base for MIAT in the local cytoreductive therapy paradigm is extremely limited compared with the body of evidence supporting prostate radiotherapy and prostatectomy. Clearly, further high-quality prospective evidence is urgently needed in order to establish the potential clinical utility of these ablative therapies in men with metastatic prostate cancer. Nevertheless, MIATs — in particular, cryoablation — have the potential to induce a beneficial immunogenic response (125).

Chapter 3 – Metastasis-directed therapy: a systematic review

3.1 Overview

This chapter sets out the current evidence for metastasis-directed therapy targeted towards oligometastasis arising in patients with mHSPC. This systematic review focussed on stereotactic ablative radiation therapy (SABR) or surgery and was limited to prospective clinical trials for *de novo* synchronous metastatic hormone-sensitive prostate cancer (mHSPC). The majority of this chapter was published in *European Urology Oncology*², and one aspect appeared in *JAMA Oncology*³.

3.2 Introduction

Research focus has shifted to evaluate the role of metastasis directed therapy (MDT), in the form of stereotactic ablative radiation therapy (SABR), surgical metastasectomy, or in combination, to provide men with additional survival benefit or delay progression to subsequent systemic agents (4).

The oligo-metastatic hypothesis postulates that an intermediate metastatic state exists which could potentially be fully controlled or even cured through local prostate gland primary treatment combined with therapy directed to the limited areas of metastases using surgical metastasectomy or ionising radiation, such as stereotactic ablative radiation (SABR)(11). This challenges the established oncological narrative that metastases secondary to solid organ malignancy are widespread, incurable and lead to a chronic state.

Definitions oligo-metastatic (or low burden) disease are not universally accepted(126). Local cytoreductive trials have adopted the CHARTED definition of high (≥ 4 bone metastasis with ≥ 1 beyond the vertebral bodies/pelvis, or visceral metastasis) and low burden(10,16). However, it has been proposed the state should be further classified into: *de novo* or synchronous, metachronous, oligo-recurrent and oligo-progressive disease (11). In particular, the role of MDT in *de novo* or synchronous disease is in its infancy and is currently experimental.

By utilizing lesion directed therapy men may avoid progressing through aggressive lines of anti-cancer systemic agents. This is important since in some men such systemic therapy

² Connor, M.J., *et al.* Targeting oligometastasis with stereotactic ablative radiation therapy or surgery in metastatic hormone-sensitive prostate cancer: a systematic review of prospective clinical trials. *European Urology Oncology*. 2020. 3(5), pp.582-593.

³ Connor, M.J., *et al.* Survival in Oligometastatic Prostate Cancer - A New Dawn or the Will Rogers Phenomenon? *JAMA Oncology*. 2020; 6 (2): 185-186.

leads to cell lineage crisis and further when combined with androgen deprivation therapy (ADT) promotes development of a castrate resistant state, whereby metastatic progression is driven by androgen independent pathways (23,31).

This systematic review synthesises the evidence on MDT, in the form of SABR and/or surgical metastasectomy, in men with mHSPC in whom the primary cancer in the prostate gland has been treated.

3.3 Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines (127) and prospectively registered on PROSPERO [CRD42019127071] (128).

3.3.1 Search Strategy

A systematic search of the literature was performed using Medline, Embase, Cochrane Review Database, and Clinicaltrials.gov databases. The search was performed from individual database inception to 28th March 2020 for articles that met our inclusion and exclusion criteria (**Appendix B**). Review articles, cost-analysis studies, letters, bulletins, comments and conference abstracts were also excluded. Further relevant articles were identified by manual review of bibliographies of candidate articles. Title and abstracts were reviewed by two authors independently (Mr. Martin J. Connor [MJC] & Ailbe Smith [AS]) and adjudicated by a third author (Mr. Saiful Miah [SM]). Eligibility criteria were applied. Disparities were discussed with co-authors until agreement was reached. Agreement was verified by third author (S.M.). The full text of remaining articles were reviewed independently by (M.J.C & A.S.).

3.3.2 Inclusion and exclusion criteria

We included articles reporting on oncological outcomes (progression free survival (PFS), overall survival (OS), and ADT-free survival), complications of surgical metastasectomy, toxicity of SABR in men with metastatic (M1a-c) prostate cancer in whom primary prostate gland treatment had occurred. Both recurrent (metachronous) and synchronous oligometastatic disease were included, with a burden up to 10 metastasis (**Table 2**). Surgical metastasectomy was defined as any surgery excision of M1 (a-c) disease. Radiotherapy was considered SABR if radiotherapy delivery fell within American Association of Physicists in Medicine (AAPM) Task Group 101 and UK SABR Consortium (version 6.1) guidelines(129,130) .

A number of prior systematic reviews have addressed the heterogeneous retrospective and prospective non-clinical trial evidence on this topic (131). For this reason, in this systematic review we aimed to present to the readership the current highest level of evidence within this field. Studies were excluded if studies were i) non-clinical trials, ii) exclusively castrate resistant disease, iii) where the primary tumour was not treated (absence of radical prostatectomy, prostate radiotherapy or brachytherapy), iv) there was no separate analysis of outcomes in mixed primary studies, v) non-SABR radiotherapy.

3.3.3 Data extraction

The following data was extracted from all included manuscripts: author, reference, publications year, patient population, number of patients, age, study design, diagnostic imaging performed (Abdominopelvic computed-tomography (CT-AP), positron-emission tomography/CT (PET/CT), Magnetic-resonance imaging (MRI)) form of treatment to metastases, local treatment of primary tumour, dose and fractionation of SABR, oncological outcomes (PFS, ADT-Free survival, LC), complications of surgical metastatectomy, toxicity of SABR and clinical trial design.

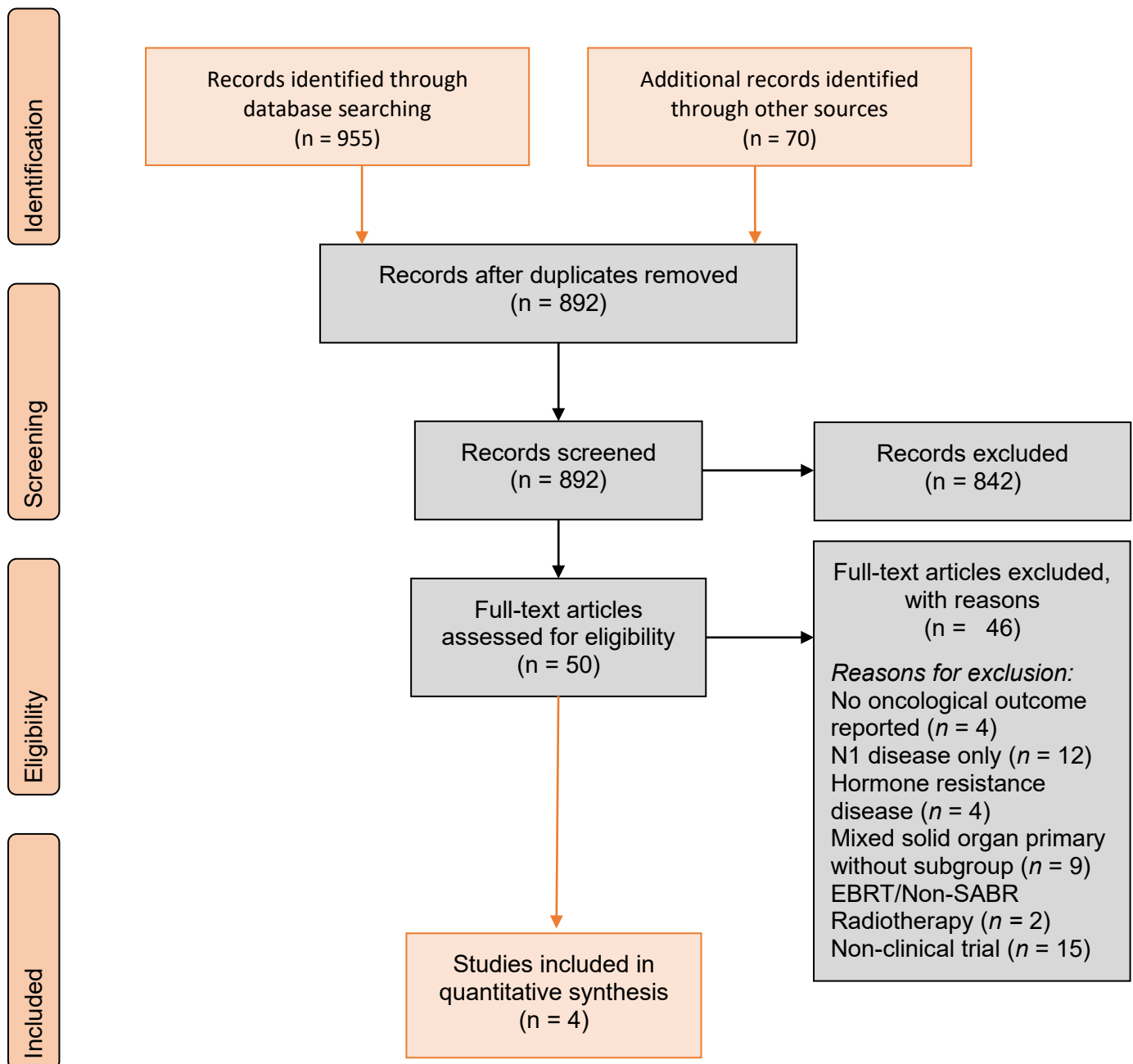
3.3.4 Risk of Bias & GRADE assessment

Risk of bias and quality assessment for randomised studies was carried out independently by two authors (M.J.C & S.M.) using the Cochrane handbook risk-of-bias 2.0 tool for randomised studies and ROBINS-I for non-randomised studies (132,133). Certainty of evidence was assessed using the GRADE assessment, independently by two authors (M.J.C & S.M.)(134).

3.3.5 Statistical analysis

All collected data points were analysed using SPSS database (SPSS statistics version 25). A meta-analysis of this data was not performed given the small patient study sizes, absence of multiple randomised controlled trials and heterogeneous pool of reported oncological outcomes.

Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flowchart



3.4 Results

We identified four separate clinical trials that met eligibility for inclusion in this systematic review, as outlined in the PRISMA flow diagram (**Figure 2**) (135-138). Three studies reporting on hormone sensitive recurrent (metachronous) disease and one reporting *de novo* (synchronous) disease met eligibility criteria (**Figure 3**).

Study design of included articles: randomised controlled trials ($n = 2$), single arm clinical trials ($n = 2$). The form of MDT delivered in included studies was: SABR ($n = 2$) or a combination of surgical metastasectomy with or without SABR ($n = 2$)(135-138) .

3.4.1 Patient demographics, PSA level, metastatic sites and burden

A total of 169 patients were eligible for inclusion from the identified studies. In included articles: median age at baseline ranged from 43 to 75 years, baseline PSA ranged from 2.0 – 17.0 ng/ml (**Table 4**).

The number of metastasis per patient ranged from 1 to 7. Nodal, bone, nodal and bone, visceral metastases were present in 49.7% (84/169), 33.7% (57/169), 15.9% (27/169), and 0.5% (1/169), respectively (**Table 4**). Maximum metastatic burden permissible, when conventional diagnostic imaging was utilised, ranged from up to three (ORIOLE) or up to 10 (O'Shaughnessy *et al.*), respectively (137,138). Maximum metastatic burden when PET/CT diagnostic imaging was utilised was up to three (STOMP, POPSTAR) (135,136). Three studies restricted site of metastasis to nodal or bone (135,137,138). STOMP also permitted visceral metastasis (136).

3.4.2 Staging imaging modalities

Staging with positron-emission (PET)/CT in 56.2% (95/169) (**Table 4**). Choline and sodium fluoride (NaF) were used in 36.6% (62/169), 19.5% (33/169), respectively. Diagnostic conventional cross-sectional imaging (CT/MRI), with or without bone scintigraphy, accounted for the remaining 43.7% (74/169) of staging imaging.

3.4.3 Type of treatment

In total, (120/169) underwent treatment in investigational arms of included studies. Treatment comprised of SABR alone to 78.3% (94/120) underwent, 21.6% (26/120) SABR with surgical metastasectomy.

3.4.4 SABR delivery

Of the 78.3% (94/120) patients who underwent SABR the dose (Gy) and fractionation (Fr) schedules varied dependent on anatomical site and study design. SABR to bone and nodal metastasis regimes included: 19.5-48.0Gy / 3-5Fr (ORIOLE), 30Gy / 3Fr (STOMP), 20Gy /

1Fr (POPSTAR) and 20-30Gy / 1-5Fr (O'Shaughnessy *et al.*)(135-138). Further details are presented in the **Appendix B**.

3.4.5 Surgical metastasectomy approach

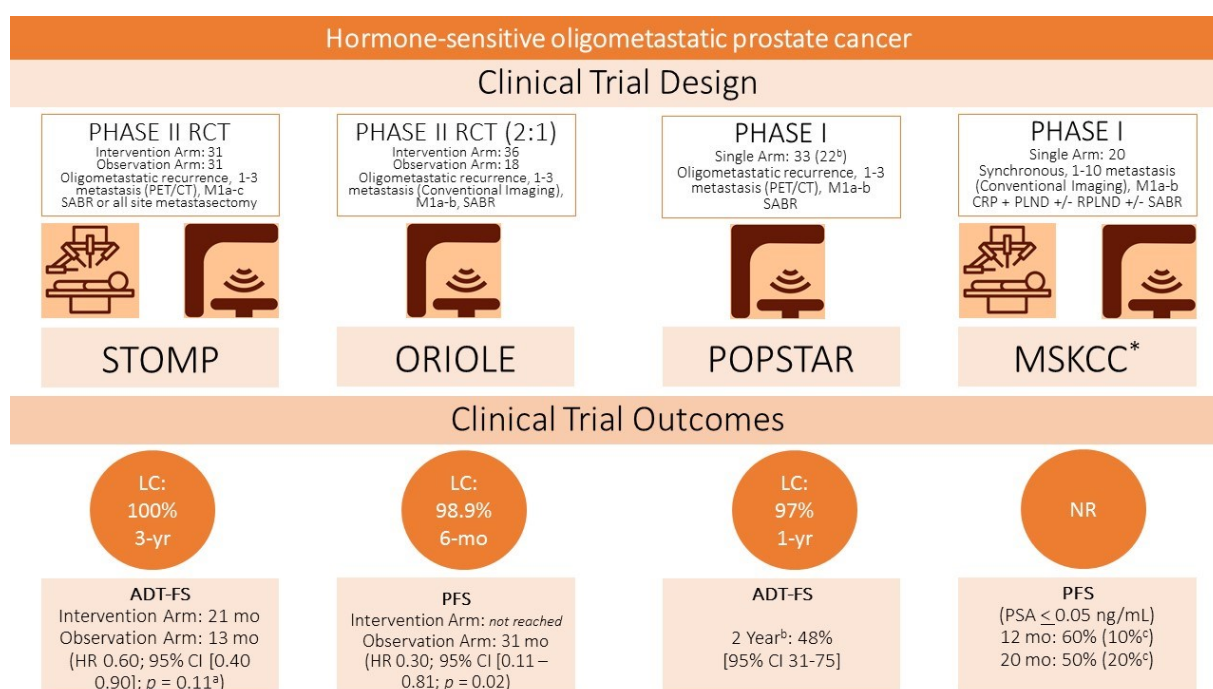
Surgical MDT included 20.83% (25/120) retroperitoneal lymph node dissection (RPLND) and a further 0.8% (1/120) surgical metastasectomy to alternative sites (136,137). In all studies RPLND was performed against a pre-set template and using pre-operative imaging (e.g. PET/CT) to guide extent of dissection. Where not performed during the primary tumour resection, some men underwent simultaneous extended pelvic lymph node dissection (136). In O'Shaughnessy and colleagues study, men underwent a cytoreductive radical prostatectomy followed by bilateral PLND and with or without RPLND in the same operative sitting (137).

3.4.6 Oncological outcomes

Studies reported on progression-free survival (PFS), ADT free survival (ADT-FS) and local control (LC) (**Table 4**). Definitions of each outcome were heterogonous and are presented by study in full in the **Appendix B**.

Summary of oncological outcomes should be viewed with respect to the quality of included studies and aforementioned lack of uniformity in individual study definitions. Early progression-free survival (PFS) at ≤ 1 -year was, reported in two studies and ranged from 19% to 60%. Local control (LC) at ≤ 3 years was reported in three studies and ranged from 93% to 100% (**Figure 3**).

Figure 3. Summary of clinical trial design and outcomes



Legend: ^a80% confidence interval. ^bHormone sensitive cohort only. ^cPSA $\leq$ 0.05 ng/ml and testosterone recovery defined as $\geq$ 150 mg/dL. NR – Not reported; LC – Local Control; ADT-FS – Androgen Deprivation-Free Survival; PFS – Progression Free Survival; MSKCC – Memorial Sloan Kettering Cancer Centre (O'Shaughnessy et al.(17)); CRP - cytoreductive radical prostatectomy; PLND – Pelvic lymph node dissection; RPLND – Retroperitoneal lymph node dissection. STOMP men underwent stereotactic ablation radiotherapy (SABR) or surgical metastasectomy (including PLND). ORIOLE men underwent SABR to metastasis. POSTAR men underwent SABR to metastasis. MSKCC men commenced ADT, underwent a followed by bilateral PLND with or without RPLND, consolidatory prostate bed radiotherapy and SABR to visible bone metastasis. Reproduced with permissions (Appendix A) from European Urology [Elsevier]. Connor, Martin J., Ailbe Smith, Saiful Miah, Taimur T. Shah, Mathias Winkler, Vincent Khoo, and Hashim U. Ahmed. "Targeting oligometastasis with stereotactic ablative radiation therapy or surgery in metastatic hormone-sensitive prostate cancer: a systematic review of prospective clinical trials." 2021. European Urology Oncology]

3.4.7 SABR outcomes

A total of two studies (ORIOLE, POPSTAR), including 94 patients, reported SABR monotherapy (**Table 4**). Median follow-up in these studies ranged from 18.8 to 24 months.

The ORIOLE study, performed by Johns Hopkins University School of Medicine, randomised 54 men 2:1, with one to three visible metastasis on conventional imaging, to SABR ($n = 36$) or observation only ($n = 18$)(138). Median follow-up was relatively short at 18.8 months (IQR 5.8-35). The authors' reported a median-PFS as not reached in the investigational arm compared to 5.8 months in observation arm (HR 0.30; [95% CI 0.11 - 0.81]; $p = 0.002$). Early PFS at 6-months occurred in 19% [IQR 9.6 – 35.4] of men undergoing SABR compared to 61% [IQR 38.5 – 79.6] in the control arm. Local control at 6-months was 98.9% in men undergoing SABR. There were no on-study deaths.

Siva and colleagues POPSTAR study also reported on SABR targeted at metastasis alone (single-fraction SABR dose of 20 Gy). The single arm prospective non-comparator study of 33 patients with 1 to 3 nodal or bone metastasis, staged with sodium fluoride (NaF) PET/CT, had a median follow-up of 24 months (135). Of the 33, 22 men had hormone sensitive disease in this study. This subgroup reported a 48% (95% CI 31-75) 2-year ADT free survival. All cohort local control at 1-year was observed in 97% (95% CI: 91–100). Furthermore, no men died during the study and all men who relapsed had M1b disease at time of trial inclusion (135).

3.4.8 Multi-modal surgical metastasectomy and SABR

A further two clinical trials explored the role of SABR and surgical metastasectomy in combination, inclusive of 51 patients (**Table 4**). Median follow-up in these studies ranged from 36 to 40 months.

Ost *et al.* reported on the only RCT in the oligorecurrent setting where both SABR or all site surgical metastasectomy were performed as determined case-by-case. This phase II study reported median ADT-FS of 13 months (80% CI, 12-17 months) for the surveillance group compared to a 21 months (80% CI, 14-29 months) for the MDT group (HR, 0.60 [80% CI, 0.40- 0.90]; log-rank $p = 0.11$). It should be noted the trial sought to assess feasibility as a primary outcome, with an alpha of 0.20. Further, ADT-FS was used as the clinical end-point which is novel in the setting (136). There were no reported treatment related deaths. However, four patients died during follow-up period, three from other malignancies and one from cardiac failure(136).

Recently, mature data has been presented by the group in abstract form, confirming persistent significant ADT-FS at 5-years, 8% for the surveillance group versus 34% for MDT group (HR 0.57 [80% CI: 0.38-0.84], log-rank $p = 0.06$)(139). Of note, the 5-year overall survival was 85%, with 6 out of 14 deaths attributed to prostate cancer(139).

O'Shaughnessy *et al.* (2017) reported a single arm study in 20 men with *de novo* disease who underwent sequential systemic therapy (ADT), surgery (cytoreductive prostatectomy + Bilateral PLND +/- RPLND), and consolidation SABR to bone metastasis (137). On review of surgical pathology, two men also underwent conventional intensity modulated radiotherapy (66-72 Gy) to prostate bed with or without nodal irradiation. Men were eligible based on conventional imaging with a maximum (nodal, bone or combined) metastatic burden of up to 10. In M1a and M1b men the median RPLND, nodal yield to nodal positive ratio (IQR) was

reported as: 40 (22-48):21 (0-30) and 25 (23-27):7 (0-14), respectively. Of note, 93% ($n = 13$) men were continent at 12-month follow-up.

A novel end-point of PFS defined by achieving “undetectable PSA” (defined as ≤ 0.05 ng/ml) following testosterone recovery was used and met by 20% ($n = 4$) of patients in this study. In total, 95% ($n = 19$) of men achieved an undetectable PSA this after all three multimodal treatments. When analysed separately systemic therapy and surgery resulted in 75% ($n = 15$) of men achieving undetectable PSA and a further 20% ($n = 4$) of men following the addition of SABR treatment. All patients who met the primary end point had M1b disease at presentation (137). At 12-months 60% ($n = 12$) of men had PSA ≤ 0.5 ng/ml, although testosterone recovery was seen in only 10% ($n = 2$). No treatment related deaths. However, two prostate cancer attributable deaths occurred on follow-up at 24 and 59 months, respectively.

Table 4. Overview of included studies, patient demographics, diagnostic imaging, site of metastasis and PSA at treatment

N o	Author, (Year)	Design	Patients, <i>n</i>	Staging imaging, <i>n</i>	Mean metastatic lesions, <i>n</i> [SD]	Primary tumour treatment, <i>n</i> (%)	M D T	Anatomical sites of metastasis per- patient (<i>n</i>) [Nodal/Bone/N odal & Bone/Visceral]	Median PSA at baseline (ng/mL) [IQR]	Median age years [IQR]
<i>Oligo-recurrent (metachronous) disease</i>										
1.	Phillips <i>et al.</i> (2020) (138)	Prospective Randomised Controlled Trial (Phase II)	Intervention Arm: 36 Control Arm: 18	CTCAP, MRI and/or Radionuclide bone scan (54)	Intervention Arm: 2.03 [NR] Control: 1.66 [NR]	RP: 45 (83.3) EBRT: 9 (16.6)	S A B R	Intervention Arm: 21/0/15/0 Control Arm: 12/0/6/0	Intervention Arm: 6.0 [2- 13] Control Arm: 7.0 [3-17]	Intervention Arm: 68 [61- 70] Control Arm: 68 [64 - 76]
2.	Ost <i>et al.</i> (2018) (136)	Prospective Randomised Controlled Trial (Phase II)	Intervention Arm: 31 Control Arm: 31	Choline PET/CT (62)	Intervention Arm: 2.09 [0.83] Control Arm: 1.64 [0.84]	RP = 2 (6.5) RP + EBRT = 22 (70.9) EBRT = 7 (22.5)	S u r g e r y +/ - S A B R	Intervention Arm: 17/13/0/1 Control Arm: 17/11/3/0	Intervention Arm: 5.30 [2.8-12] Control Arm: 3.8 [0.8–9.6]	Intervention Arm: 68 [61- 70] Control Arm: 68 [64 - 76]
3.	Siva <i>et al.</i> (2018) (135)	Prospective Single arm clinical trial (Phase II)	Single arm: 33 (22 ^a)	NaF PET/CT (33)	1.52 [0.80]	RP = 18 (54) EBRT = 15 (45)	S A B R	12/20/1/0	6.40 [1.1 – 12.5]	70 [67-75]

<i>De novo (synchronous) disease</i>										
4	O'Shaughnessy et al. (2017) (137)	Prospective Single arm clinical trial (Phase II)	Single Arm: 20	CTCAP, Radionuclide bone scan (20)	NR	RP = 20 (100)	Surgery +/- SABR	5/13/2/0	NR	59 [44 - 74]

NR – not reported, IQR – Interquartile Range, FCH – Fluoromethylcholine, RP – Radical Prostatectomy, EBRT – External Beam Radiotherapy, BT – Brachytherapy, WB – Whole Body, FDG – fluorodeoxyglucose, NaF – Sodium Fluoride. : *80% confidence interval. ^aHormone sensitive cohort only, ⁱIntervention arm only.

3.4.9 Toxicity and complications

Grade II and III SABR toxicity were reported in 8% (8/100), 1% (1/100), respectively. This used a variety of definitions (**Appendix B**). Notably, grade III SABR related toxicity did not occur in any patients in either of the included randomised studies (STOMP) (136). No treatment related deaths were reported.

Clavien-dindo classified surgical complications were as follows: 15.4% (4/26) grade IIIa, Grade II 0% (0/26), Grade IIIa 7.69% (2/26), Grade IIIb 0% (0/26), Grade IV 0% (0/26) (**Table 4**). Sporadically reported grade IIIa complications included: anastomotic leak ($n = 1$), pelvic abscess requiring drainage ($n = 1$). No post-operative deaths were reported in the included studies.

3.4.10 Ongoing clinical trials

Two ongoing clinical trials were identified as treating men with metachronous disease. NCT02192788 is a single arm prospective study of 68 men treating up to four (distant nodal or bone) metastasis with SABR, the primary end point is local disease progression(140). The CORE trial (NCT02759783) is a phase II, non-blinded, parallel group RCT in patients with breast, prostate or non-small cell lung cancer. In which patients are randomised 1:1 to standard of care or standard care with SBRT for extra-cranial metastases, with a primary focus on feasibility of treatment and secondarily on PFS. The trial completed recruitment ahead of planned time in February 2019, with the largest expected SABR metastatic prostate cohort to date ($n = 180$). Trial results due to be published in 2024 (141).

In the *de novo* synchronous setting, four clinical trials were identified(142-145). Firstly, PLATON (NCT03784755) is two arm phase II RCT exploring sequential treatment with ADT +/- chemotherapy followed by cytoreductive prostatectomy or external beam radiotherapy (EBRT) and then SABR to oligo-metastasis in 410 men. The comparator arm is systemic therapy alone, although low volume men are allowed conventional local prostate radiotherapy (142).

Second, IP2-ATLANTA (NCT03763253) is a phase II three arm RCT exploring sequential systemic, local physical cytoreductive therapy and finally SABR versus standard of care in 918 men with all volume metastatic disease, as described in **Chapter 6**. Similar to PLATON, experimental arms will have post-primary treatment SABR to oligo-metastasis, access to upfront systemic chemotherapy and low volume men in standard of care comparator arm will be able to have local prostate radiotherapy (3).

Thirdly, NCT02716974 is a phase II single arm trial evaluating sequential treatment with ADT +/- chemotherapy followed by cytoreductive prostatectomy or EBRT and then SABR to oligo-metastasis in 33 men (144). Finally, NCT03298087 is another phase II veterans study of M1a-b (1-5 distant metastasis) in which men undergo systemic (leuprolide, abiraterone acetate with prednisone, and apalutamide), cytoreductive prostatectomy and SABR to all sites of metastases(145).

Of note two trials are evaluating mixed cohorts of *de novo* synchronous and metachronous hormone-sensitive oligometastasis (146,147). Firstly, SABR in combination with radium Ra 223 dichloride IV is being trialled in a group of 24 men with (NCT03361735). Men undergo leuprolide followed by SABR (up to 4 lesions) and radium Ra 223 dichloride IV which may be repeated over time. Investigators are primarily concerned with time to treatment failure and radiological response. Secondly, the phase II PRESTO (NCT04115007) randomised study of 350 men to systemic therapy or systemic therapy with SABR to up to 5 lesions(147). Men with *de novo* synchronous disease undergo primary control with prostate EBRT. The primary outcome is time to castration-resistance.

3.4.11 Risk of Bias Assessment & GRADE Assessment

Risk of bias and quality assessment of the studies is available in **Table 5**. The included RCT had some concerns in two of four domains, respectively, with no concerns in all remaining domains (136,138). Both included non-randomised studies with single arms were found to be of moderate risk and serious risk of bias, respectively (135,137). The GRADE 'certainty of evidence' per outcome was: PFS (*Very Low*), LC (*Low*), ADT-FS (*Low*), SABR toxicity (*Low*) and surgical complications (*Very Low*), respectively (**Table 5**).

Table 5. Risk of Bias & GRADE Assessment

Quality assessment							Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Progression-free survival								
4	Phase I/II, RCT, Single Arm	Serious ^a	Not serious	Serious ^a	Serious ^a	Strong association	⊕○○○ Very Low	CRITICAL
Local control								
4	Phase I/II, RCT, Single Arm	Not serious	Not serious	Serious ^b	Not serious	Strong association	⊕⊕○○ Low	IMPORTANT
ADT-free survival								
4	Phase I/II, RCT, Single Arm	Not serious	Serious ^b	Serious ^a	Not serious	Strong association, suspected selection bias	⊕⊕○○ Low	CRITICAL
SABR toxicity								
4	Phase I/II, RCT, Single Arm	Not serious	Not serious	Not serious	Not serious	Strong association.	⊕⊕○○ Low	IMPORTANT
Surgical complications								
4	Phase I/II, RCT, Single Arm	Serious ^c	Serious ^c	Serious ^c	Serious ^c	Strong association.	⊕○○○ Very Low	IMPORTANT

^aNot all endpoints are consistent, early outcome data, lack of comparator group. ^bMedium term data not available, imaging used varied across studies i.e. conventional versus metabolic. ^cLack of uniformity of the surgical approach and anatomical site for surgical metastasectomy performed.

3.5 Discussion

In summary, our systematic review shows that men with hormone sensitive oligometastatic prostate cancer, who undergo treatment to the primary cancer within the prostate gland, appear to gain oncological benefit, in terms of local control and distant progression, from metastasis directed therapy. However, this evidence is predominantly derived from small cohort clinical studies with heterogeneous approaches, and without confirmatory phase III randomised validation.

Further, there is now comparative RCT evidence, that SABR or surgical metastatectomy performed in men who develop distant oligometastasis, following primary treatment, confer early benefit in disease progression (136). In men with *de novo* synchronous metastatic disease, pilot clinical trial data demonstrates that there may be a role for MDT as part of a sequential multi-modal approach (137).

The premise for MDT is that it leads to alterations in the tumour microenvironment (TME) secondary to radiation induced cytotoxicity or surgical excision. As described in detail in **Chapter 2**, this treats the primary metastasis but may also promote an “abscopal effect” (148-150). The term ‘abscopal’ is formed from the Latin prefix ‘ab’ (*away*) and ‘scopus’ (*target*) and is used to describe destruction of tumours distant to the primary site of treatment (out-of-field) through a systemic anti-tumour response (72,78,151).

Promisingly, T-cell receptor expansion was identified in men undergoing SABR in the ORIOLE study. Further, 4 (8.2%) ¹⁸F-DCFPyL-PSMA PET/CT avid lesions at baseline demonstrated complete radiological response despite not receiving direct irradiation. Both are supportive of the presence of an in-situ vaccine response (138). However, the overall clinical magnitude of this effect is unknown, and it may in fact be small, particularly when applied to larger cohorts.

Our systematic review provides specific focus on the outcomes of MDT in men who have hormone sensitive metastatic disease. Men who reach a castrate resistant disease may have exhausted multiple systemic anti-cancer therapy lines with disease progression occurring, in part, via androgen independent pathways (23,31).

This bears importance on the timing of lesion directed therapy within this evolving paradigm. The promising oncological outcomes presented in this systematic review promote the notion that MDT ought to be seen as a treatment to be used to delay ADT and/or prevent a castrate resistant state emerging. Such a move is supported by recent multifocal sequencing evidence that demonstrate for the first time metastasis-to-metastasis seeding occurs in prostate cancer (51,53). This contradicts the previous notion that spread results from solely

primary-to-metastasis seeding, raising the importance of treatment to macro-metastases even in a man with a controlled primary (51).

As such there has been the emergence of ADT-FS as a novel primary endpoint, particularly in MDT metachronous and local oligorecurrent trials (N1, M0), which offer appeal to men in terms of potential quality-of-life and lower toxicity benefits(135,136,152). However, ADT-FS utility is unclear in *de novo* synchronous presentations where ADT in combination with systemic therapy intensification has provided clear survival advantage(6-8,153).

The distant oligometastatic recurrent disease studies (STOMP, POPSTAR and ORIOLE) included this review confirm previous retrospective evidence of excellent local control and significant PFS or ADT-FS advantage(131,135,136,138). However, all trials were of small cohorts and in the case of POPSTAR some castrate resistant men were also treated in the trial, thus the subgroup analysis of hormone sensitive men is only relevant for presentation in our review.

All these studies demonstrated SABR has an acceptable safety profile, with no SABR related deaths. Nevertheless, the single 20 Gy fraction used in POPSTAR was associated with 15% more grade II complications when compared to STOMP 30 Gy in 3 fraction (135,136). Although the heterogenous nature in anatomical sites (nodal vs bone) targeted within these studies and an absence of significant grade III-V complications makes meaningful comparisons limited.

The SABR-COMET randomised clinical trial firmly supported a SABR approach (154). Palma and colleagues reported an impressive 13 month absolute overall survival increase (41 vs 28 months [HR 0.57; 95% CI 0.30 - 1.10; $p=0.90$]) following SABR in patients with a low metastatic burden following post-primary tumour treatment (154). The study was not included in this systematic review as it contained patients with mixed solid organ malignancies, of which prostate was a minority ($n = 14$; 21%) (154). Notably, the trial reported a toxicity profile ($\geq$ Grade II 29%; $n = 19$) that was higher than the prostate primary only clinical trials included in this systematic review. Further, there were 3 (5%) SABR-arm deaths. On further evaluation only one of these death (radiation pneumonitis post-centrally located SABR) appears to be a typical sequelae of the experimental arm(155). Finally, long-term OS benefit appears to be durable (156).

With regard to surgical metastasectomy, the pilot study by O'Shaughnessy and colleagues has demonstrated three in every four men can achieve an undetectable PSA with systemic therapy and surgical metastasectomy alone(137). This supports the benefits that were obtained in STOMP utilizing RPLND, guided by pre-operative novel targeted imaging. As with SABR, the safety profile in this limited dataset appears to be acceptable.

Radiological identification of disease and its implication on attributing men to different disease risk groups also requires further prospective investigation. The higher sensitivity and specificity for the identification of bone metastasis of novel imaging tracers such as Gallium⁶⁸ combined with PSMA-PET/CT when compared to conventional imaging (i.e. CT-AP) have a significant impact (157). Almost 50% of men in this systematic review had diagnostic PET-CT as the sole imaging for eligibility for study entry prior to MDT. We have previously published a hypothesis paper describing the risk of a Will Roger's phenomenon in interpreting oncological outcomes when such men are re-classified with "micro" oligometastatic disease, in whom this would be previously radiologically invisible (12).

Briefly, this is likely to lead to a rise in the cohort of men diagnosed with local pelvic nodal oligorecurrent disease (i.e. N1, M0). In this cohort MDT trials such as PEACE V:STORM and OLIGOPELVIS: GETUG P07 will be crucial in determining optimal management(152,158).

In the ORIOLE study SABR was directed at up to three "macro" metastasis on conventional imaging at enrollment (138). This is despite an additional 49 PSMA PET/CT avid lesions identified in the investigational arm, which were not disclosed to trialists and thus not included within the radiation treatment fields. Therefore, some men had a higher enrollment disease burden when defined by metastatic avidity on concomitant PSMA PET/CT(138). It could be assumed that these men would not have been eligible for treatment in other included studies (i.e. STOMP, POPSTAR) due to perceived polymetastatic state (135,136). Perhaps, the oligometastatic definition should be explored to include parameters on lesion size, volume (e.g. total metabolic tumour volume), anatomical site and liquid biomarkers.

Another priority is to further understand those men who might benefit most from MDT. The ORIOLE study explored the role of novel-targeted imaging as a predictor of PFS. The study performed a blinded pre- and post-treatment PSMA-PET/CT in men in the investigational arm. This reported that ≥ 4 PET-avid lesions at enrolment were a relative adverse predictor on early PFS (6-month PFS; 46.7% vs 0%; [$p = 0.001$]). Although, it is unclear if this would remain prognostic for medium and late-stage PFS.

Beyond radiomic predictors, it is vital to understand the molecular phenotyping in oligometastatic prostate cancer (159,160). The presence or absence of baseline unfavourable mutations (e.g. *TP52*, *ATM*, *BRCA1*, *BRCA2*, *RB1*) or subgrouping microRNAs may be predictive of disease progression (138,161). Such phenotyping has provided a significant breakthrough in the prognostication of favourable and unfavourable liver metastasis in oligometastatic colorectal cancer (162).

Despite the inclusion of four clinical trials, most were small cohorts and lacked comparative primary end-points preventing meta-analysis. Further, there was significant heterogeneity in

the dose/fractionation and surgical approaches (i.e. not all men who were entered into studies using combined MDT underwent treatment with both modalities), and a lack of standardised definitions of treatment failure. Importantly, a selection of men with minimal disease burden were entered into studies using ADT-FS as an outcome, producing a potential selection bias. Two trials (STOMP, ORIOLE) included patients who had treatment to nodal oligorecurrent disease that was confined to the pelvis only, limiting the generalizability of the overall finding to the distant oligometastatic state (136,138). Finally, MDT in *de novo* synchronous disease is experimental and findings presented are based on a single non-randomised pilot study.

3.6 Conclusion

Metastasis-directed therapy is a promising therapeutic approach in men with hormone sensitive oligometastatic prostate cancer. Further randomized comparative trials are required to ascertain role and optimal timing of MDT in oligometastatic recurrent disease and to determine efficacy and toxicity in *de novo* synchronous disease.

Chapter 4 - Patients' values, preferences and expectations for the treatment of metastatic prostate cancer: a systematic review

4.1 Overview

This chapter sets out the current understanding of patients' values and treatment preferences in the treatment of metastatic prostate cancer. This was an important for our in developing a trial that would be acceptable to patients and align with the currently known patient preference and expectation in metastatic disease states. In its simplest form the re-introduction of radical treatment options to the non-curative setting, confers toxicity, but may offer incremental survival benefits. Understanding if survival benefits drive decision making for patients' is a vital step. The majority of this chapter also appears in was publications in *European Urology*⁴ and *European Urology Open Science*⁵ (163).

4.2 Introduction

Unlike localised prostate cancer, patients with metastatic prostate cancer have a distant spread of disease that is not curative(4). Novel interventions offer significant oncological promise to patients with metastatic prostate cancer(4). Furthermore, secondary benefits may also arise from the avoidance or delay of second- and third-line systemic agents as well as their associated toxicity(164,165).

However, each specific treatment is not without its own treatment-related risk (e.g. death) and significant side-effects may develop (e.g. urinary incontinence, fatigue) (165). Thus, an understanding of patients' values and preferences for management is important for patient counselling, decision-making and guideline development.

This systematic review synthesises the evidence from both quantitative preference elicitation studies and qualitative studies, reporting on patients' values, preferences and expectations in the treatment of metastatic prostate cancer.

⁴ Connor M.J., *et al.* Radical Treatment Without Cure: Decision-making in Oligometastatic Prostate Cancer. *European Urology*. 2021 Apr 1;79(4):558-60.

⁵ Connor, M.J., *et al.* A Systematic Review of Patients' Values, Preferences, and Expectations for the Treatment of Metastatic Prostate Cancer. *European Urology Open Science* 36 (2022): 9-18.

4.3 Methods

This prospectively registered PROSPERO [CRD42020201420] systematic review was performed according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA-P) guidelines(127,166).

4.3.1 Search strategy

A systematic search of MEDLINE, CINAHL, and Embase and searching of reference lists of eligible studies was performed to capture additional relevant articles that met our inclusion and exclusion criteria. Briefly, search key terms included “*Prostate neoplasm/adenocarcinoma*” and “*Metastasis/oligmetastasis/advanced/stage IV/metastatic*” and “*Preference elicitation/discrete choice experiment/stated preference/part-worth utility/functional measurement/paired comparison/pairwise choice/conjoint analysis/conjoint measurement/best-worst scale/contingent valuation/standard gable/time-tradeoff/willingness-to-pay/willingness-to-accept*”. A detailed search strategy is available in the **Appendix B**. Search results were limited to the English language and from database inception until 1st November 2020. Review articles, letters and conference abstracts were excluded at this stage. The title and abstracts were reviewed independently by three authors (DB, MGG, VW) and adjudicated by a fourth author (MJC). Eligibility criteria were then applied. Any disparities that arose were discussed with co-authors until an agreement was reached. Agreement was verified by fifth author (HUA), where required. The full text of the remaining articles were reviewed independently by four authors (DB, MGG, VW, MJC).

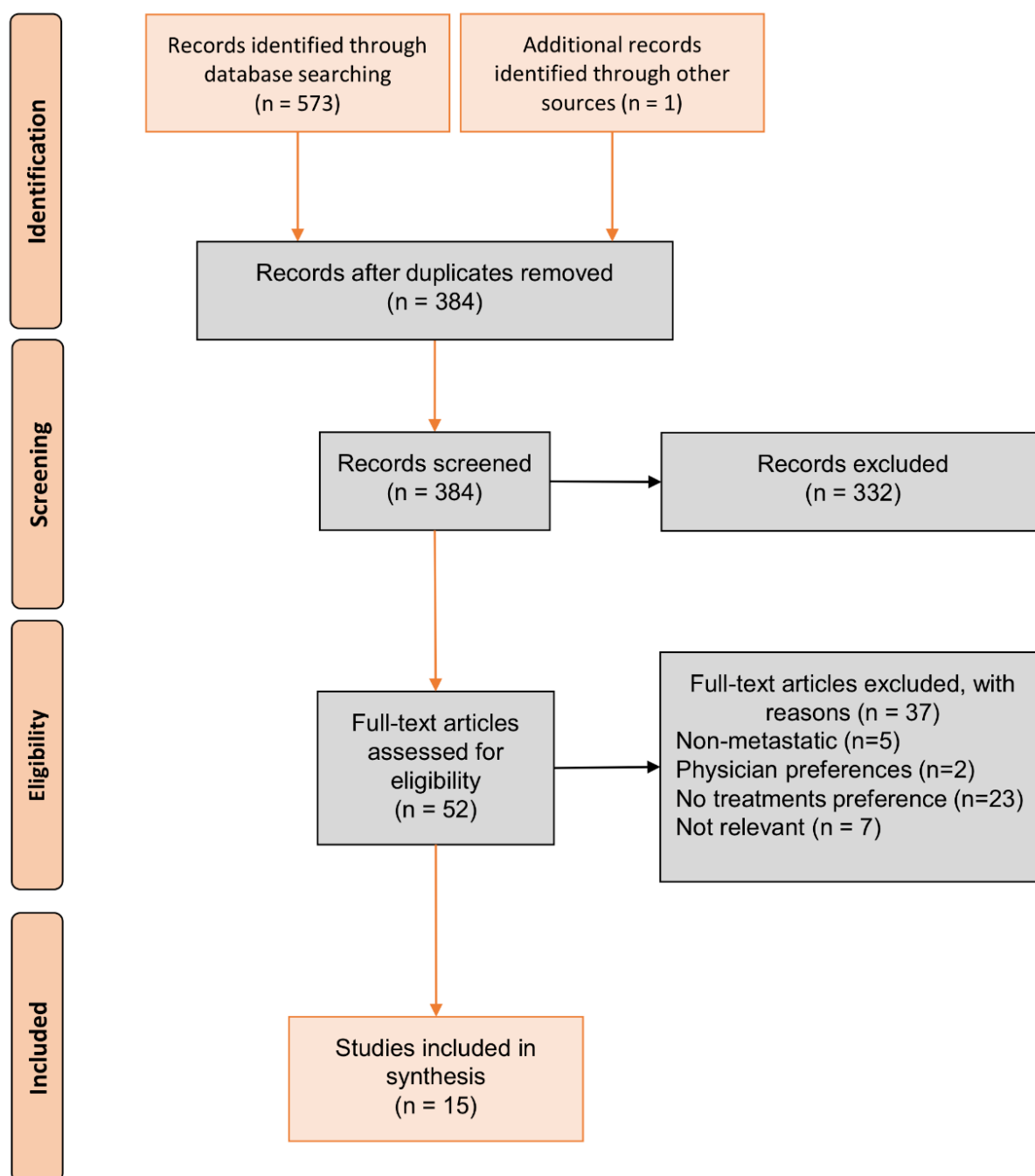
4.3.2 Inclusion and exclusion criteria

We included quantitative preference elicitation studies (i.e., discrete choice experiments, time trade-off (TTO) and standard gamble), and qualitative studies (i.e. interviews, focus groups) which reported on patients’ preference in the treatment of metastatic prostate cancer. Studies were excluded if they were concerned with: i) non-metastatic disease ii) mixed cohort of disease states (i.e. localised and metastatic) or mixed primary cancers, if the presentation of separate study outcomes by disease states was absent.

4.3.3 Data extraction

The following data were extracted from all included studies: reference, author, publishing journal, year of publication, the disease state of the patient population, study size, age, study design or methodology, evaluated treatment, the main topic in relation to the study's purpose, primary results and conclusions.

Figure 4. Preferred reporting items for systematic reviews flowchart on Patients' values, preferences and expectations for the treatment of metastatic prostate cancer.



4.3.4 Assessment of Methodological Quality

For quantitative studies, this was assessed using the Purpose, Respondents, Explanation, Findings, and Significance (PREFS) quality assessment checklist, which was developed to assess the quality of studies in systematic reviews of patient preference literature (**Appendix B**) (167). For qualitative studies, this was assessed using the Standards for Reporting Qualitative Research (SRQR) criteria (**Appendix B**) (168).

4.3.5 Risk of bias

For quantitative studies Risk of Bias (RoB) was assessed using a RoB tool. This contained the subgroups: (1) sample selection, (2) response (or attrition) rate (3) choice and administration of the methodology, (4) outcome (or health state) presentation, and (5) respondent understanding & data analysis (**Appendix B**). As per previous systematic reviews, “high” RoB was assigned where the measurement instrument was not valid. If the measurement instrument was valid, RoB was assigned “low” if there were no individual items marked high RoB and “moderate” if not more than two items at moderate RoB(169). For qualitative studies, this was assessed using the Standards for Reporting Qualitative Research (SRQR) criteria (**Appendix B**) (168). Studies with a total score of less than 20 were deemed of “high” methodological limitation (RoB).

4.3.6 Assessment of Certainty of Evidence

Certainty of evidence presented was assessed using Grading of Recommendation, Assessment, Development and Evaluation (GRADE) and GRADE Confidence in the Evidence from Reviews of Qualitative Research (CERQual), respectively (**Appendix B**) (170,171).

4.3.7 Data analysis

A narrative synthesis (quantitative studies) and thematic analysis (qualitative studies) of the collected data were undertaken, with the presentation of interpretation of major findings in the context of the current field (172). All discrete data points were analysed using SPSS v.27.0 (IBM Statistics). A meta-analysis of quantitative studies was not performed given the heterogeneous pool of study populations, designs and reported outcomes.

4.4 Results

4.4.1 Quantity of evidence and characteristics of included studies

Of the 573 articles identified, 15 studies with a total of 1,488 participants met pre-specified eligibility for inclusion in this systematic review, as outlined in the PRISMA-P flow diagram (**Figure 4**) (173-187). The mean number of participants per study was 101 (SD 58.7). Study design of the included articles were reported as: discrete choice experiments ($n = 5$), mixed methods ($n = 3$), qualitative methods ($n = 7$) (**Table 6**). The reported mean age of participants ranged from 69.1 to 75.4 years. Disease states of participants per study were: mCRPC 9 (60.0%), mHSPC 2 (13.3%) and mixed (mCRPC/mHSPC) cohort 4 (26.6%), respectively.

Treatments evaluated in the studies were chemotherapy (n=5; 41.6%), Abiraterone Acetate (n=3; 25.0%), Enzalutamide (n=1; 8.3%), Radium-223 (n=1; 8.3%), radiotherapy (n=1; 8.3%), any systemic therapy (n=1; 8.3%), any hormonal therapy (n=1; 8.3%) and any bone-targeted agents (n=12; 25%), respectively. In total, 8 out of 12 (66.6%) studies were commercially funded (**Table 6**). The largest single contributors (37%) were authors from the United Kingdom (UK) (**Appendix B**).

Table 6. Characteristics and design of included studies

N o	Author , (Year)	Analy sis	Desig n	Setting	Sam ple Size, <i>n</i>	Mea n Age (yr); (SD)	Disease State	Primary Focus	Treatment(s) evaluated	Funders (A/C)		(P) PREFS / (S) SRQR Scores
1	De Freitas <i>et al.</i> (2019)(173)	Quanti tative	DCE	Hospital	152 (*45)	69.1 (7.7)	mHSPC	Patient perceptions of the risks and benefits of systemic treatments	Docetaxel or Abiraterone Acetate	C	Janssen	(P) 4
2	Eliasso <i>n et al.</i> (2017) (174)	Quanti tative	DCE	Hospital	285	70.7 (NR)	mCRPC	Patient perceptions of the risks and benefits of chemotherapy	Chemotherapy	C	Janssen	(P) 4
3	Nakaya <i>ma et al.</i> (175) (2018)	Quanti tative	DCE	Hospital	103 (*37)	NR	mCRPC	Investigating the concordance of treatment preferences between patients and physicians	All treatment options	C	Janssen	(P) 4
4	Uemur <i>a</i> (2016) <i>et al.</i> (176)	Quanti tative	DCE	Hospital	133	75.4 (7.4)	mCRPC	Patients preferences for treatments, sub-analysis of symptomatic and asymptomatic patients	Docetaxel, RA-223, Abiraterone Acetate	C	Bayer Yakuhin, Ltd	(P) 4
5	Hauber	Quanti	DCE &	Hospital	401	(UK)	Mixed	Quantify how patients value	Bone-targeted	C	Amgen	(P) 4

.	et al. (177)(2014)	tative	TTO			= 71.6 (NR) (Sweden) = 71.5 (NR)		hypothetical treatments that may delay bone metastasis versus specific bone-targeted treatment risks (e.g. ONJ).	agents		Inc.	
6	Clark et al.(178) (1997)	Qualitative & Qualitative	Mixed-methods study	Hospital	201	NR	Mixed	Identifying and measuring dimensions of quality of life following the initiation of treatment for advanced prostate cancer.	Hormone therapy	A	Veterans Affairs Health Services Research	(S) - 15
7	Ito et al.(180) (2018)	Qualitative & Qualitative	Mixed-methods study	Community	31	NR	mHSPC	Exploring the perspectives of men and carers of men with mHSPC who had received docetaxel	Docetaxel	C	Janssen	(S) - 17
8	Clark et al. (179)(2001)	Qualitative & Qualitative	Mixed-methods study	Hospital	201	NR	Mixed	Understanding patients' experiences of regret of their treatment choices and closely examining factors associated with regret	Bone-targeted agents	A	Veterans Affairs Health Services Research	(S) - 13
9	Burbridge et	Qualitative	Semi-Structu	Hospital	22	72.2 (7.01	mCRPC	Exploring the symptomatic experience of diagnosis of mCRPC,	Bone-targeted agent	C	Janssen	(S) – 22

	al.(181) (2020)		red Intervi ew			)		and the emotional response to this diagnosis.				
1 0 .	Catt et al.(182) (2019)	Qualita tive	Structu red Intervi ews	Hospital	37	70.8 (6.81)	mCRPC	Exploring experiences of treatment decisions, information provision, perceived benefits and harms of treatment on patients' and partners'	Systemic therapy, Radiotherapy	A	Brighton & Sussex Medical School	(S) – 19
1 1 .	Dearde n et al. (183)(2 019)	Qualita tive	Semi- Structu red Intervi ew	Commu nity	38	NR	mCRPC	Understanding and quantifying the experience of living with in patients receiving Abiraterone Acetate or Enzalutamide either pre-chemotherapy or post-chemo- therapy settings.	Abiraterone Acetate or Enzalutamide	C	Janssen	(S) - 14
1 2 .	Grunfel d et al.(184) (2012)	Qualita tive	Semi- Structu red Intervi ew	Hospital	21	78 (NR)	Mixed	Interviews exploring the experience and impact of andropause symptoms.	Hormone therapy	-	Unfunded	(S) - 20
1 3 .	Iacoros sia et al.(185) (2019)	Qualita tive	Semi- Structu red Intervi ew	Hospital	13	NR	mCRPC	Exploring the phenomenon of adherence to oral hormone treatment in patients with mCRPC and the factors that may influence their adherence.	Hormone therapy	-	Unfunded	(S) - 22

14	Jones et al. (186)(2018)	Qualitative	Semi-Structured Interview	Hospital	35	NR	mCRPC	Examining the experiences of patients with advanced prostate cancer and their decision partners.	Chemotherapy	A	National cancer institute & the Robert Wood Johnson Foundation	(S) - 22
15	Doveson et al. (187) (2020)	Qualitative	Semi-Structured Interview	Hospital	16	NR	mCRPC	Exploring the perspectives of men when facing life-prolonging treatment of metastatic castration-resistant prostate cancer	Chemotherapy , Enzalutamide, Abiraterone Acetate, Hormone Therapy	A	Spphiahe mmet Foundatio n & the Kamprad Family Foundatio n	(S) – 20

mHSPC	mCRPC	Mixed
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Legend: NR – not reported; IQR – Interquartile Range; SD – Standard Deviation; DES – diethylstilbestrol; RAI - Relative Attribute Importance; A – Academic; C – Commercial; M – Mixed; TTO – Time trade-off; DCE – Discrete Choice Experiment; SRQR - Standards for Reporting Qualitative Research; PREFS - Preference and qualitative studies the Purpose, Respondents, Explanation, Findings, and Significance. *Metastatic subgroup cohort.

4.4.2 Methodological quality and RoB

Methodological validity assessments for each study are listed in **Appendix B**. Of the five quantitative studies, n=4 (80%) reported a high response rate, n=1 (20%) tested participant understanding, and all studies analysed the data correctly (**Appendix B**). For the quantitative studies, the mean PREFS quality score was 4 (SD=0). In terms of validity assessment, none of the studies justified their forced-choice study design; n=3 (60%) of studies did not report details of their experimental design. All studies piloted the data collection tool with the target population before implementing the main survey. N=2 (40%) met most of the analysis criteria. The mean SRQR quality score for the included qualitative studies was 18.4 (SD=3.4) (**Appendix B**). A single quantitative preference study was deemed “high” RoB (n=1; 20%). Five qualitative studies were deemed “high” risk of bias (n=5; 50%).

4.4.3 Quantitative treatment preference studies

A summary of the demographics and study design of included quantitative preference studies ($n = 5$) is presented in **Table 7** (173-177). In all studies, participants were asked to choose between two treatment alternatives, and were not given the option to report that they would not be treated. None of the studies justified this study design. The number of evaluated treatment attributes ranged from two to seven (Mean 5 [SD 2]). Overall, “*treatment effectiveness*”, “*delay in time to symptoms*”, and “*fatigue*” emerged as the predominant treatment-related preferences that patients valued (**Table 7**).

mHSPC

de Freitas and colleagues explored how 152 patients with mHSPC perceived the risks and benefits of hypothetical Abiraterone Acetate and Docetaxel treatment in three European countries (173). The study included six treatment attributes: mode of administration, tiredness and fatigue, treatment effectiveness, bone pain, nausea and vomiting, and risk of infection. They reported treatment effectiveness was the main objective for patients, and that patients wanted to avoid uncontrolled pain. In terms of relative attribute importance (RAI) the treatment attribute ranking was: treatment effectiveness (RAI=7.25); pain (RAI=6.26); risk of nausea (RAI=4.12); vomiting (RAI=3.17); risk of fatigue (RAI=2.24); and mode of administration (RAI=2.09) (173).

mCRPC

In the mCRPC setting, Eliasson and colleagues explored hypothetical treatment options for 285 patients across the UK and Europe (174). The study included seven treatment attributes: effectiveness (delay in months before chemotherapy), steroid use, possible drug interactions (additional hospital visits for monitoring), cognitive impairment described as

“fogginess” (effects on cognition and memory), fatigue, food restrictions, and bone pain. Findings were presented in terms of odds ratios (OR), and results suggested that patients preferred treatments that fully control bone pain (OR = 12.06; [95% CI 10.55–13.80]) and those that delay chemotherapy (OR = 1.72; [95% CI 1.54–1.92]). Findings suggested patients preferred treatments with a lower risk of “fogginess” (OR = 2.11; 95% CI 1.84–2.42]), a lower risk of fatigue (OR = 1.36; [95% CI 1.21-1.52]), and fewer additional hospital visits (OR = 1.24; [95%CI 1.11-1.39]) (174).

The concordance of treatment preferences between patients and physicians in mCRPC was explored in a study of 102 patients in Japan (175). The study included four attributes: quality of life, effectiveness, side effects, and accessibility. In terms of the relative importance (RI) of attributes, patients’ preference ranking was: effectiveness (RI=32%); accessibility of treatment (RI=26%); quality of life (RI=23%); and side effects (RI=19%).

With regard to bone-targeted and systemic agents in the mCRPC setting, Uemura et al explored preferences associated with various treatments (Radium-223, Abiraterone Acetate, Docetaxel) (176) for 134 patients in Japan. The study included six attributes: length of Overall Survival, time to a symptomatic skeletal event (SSE), administration method, reduction in the risk of bone pain, treatment-associated risk of fatigue and lost workdays. In terms of the relative importance (RI) of attributes, patients’ preference ranking was: fatigue (RI=24.9%), reduction in the risk of bone pain (RI=23.2%) and OS (RI=19.2%). The authors compared preferences across symptomatic and asymptomatic patients, and found symptomatic patients placed significantly more importance on delaying an SSE. The authors concluded that patients with CRPC were more concerned about reduced quality of life from side effects of treatment than an extension of survival.

Hauber *et al.* also explored preferences for bone-targeted agents in 243 patients with a mixed disease states in the UK and Sweden (177). The study used two TTO questions to assess patients’ trade-offs between avoiding metastases-induced bone complications and increased survival. Results found that patients were willing to trade-off up to 5 months of survival to prevent bone complications (177).

Table 7. Summary of major findings of patient preferences and values (quantitative) studies

Patient preference (categories of values and preferences)	Estimates of outcome importance (range across studies)	n	Included Study No.	Certainty of evidence	Interpretation of findings
Treatment effectiveness (forced choice)	▪ Two studies ranked treatment effectiveness as most important attribute ○ RAI = 7.25 (de Freitas <i>et al.</i>(173)). ○ RI = 32% (Nakayama <i>et al.</i>²⁶). ▪ One study used terminology of treatment impact on overall survival reporting a RI = 19.2%. (Uemura <i>et al.</i>³¹).	768	1,2,3,5	⊕⊕○○ Low	Patients consistently consider the effectiveness of a treatment above other treatment related attributes
Delay in time to symptoms (forced choice / proportions)	▪ Four studies reporting on time to symptoms appearing: ○ One study reported pain as the second most important attribute (RAI = 6.26; de Freitas <i>et al.</i>(173)). ○ Study using odds ratio for choosing treatment had strong preference for treatment that fully control bone pain (OR = 12.069; Eliasson <i>et al.</i>²⁹). ○ One study 80% of the patients would trade-off at least 3 months of survival to avoid bone complications (Hauber <i>et al.</i>³²).	864	1,2,4,5	⊕⊕○○ Low	Patients consistently consider a treatment impact on the time until they may develop symptoms of metastatic prostate cancer above other treatment related attributes

Fatigue (forced choice)	▪ Three studies reporting fatigue as a major patient preference ○ Fatigue reported as the most important attribute (RI = 24.9%; Uemura <i>et al.</i>³¹) ○ Odd ratio for treatment that lower risk of fatigue (OR = 1.365; Eliasson <i>et al.</i>²⁹). ○ Fourth important attribute (RAI 3.17; de Freitas <i>et al.</i>(173)).	178	1,2,4	⊕○○○ Very Low	Relationship between fatigue and the treatment choice may be important
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Legend: RAI - Relative Attribute Importance, RI – Relative Importance, OR – Odd Ratio

4.4.4 Qualitative studies

A summary of the demographics and study design of included qualitative studies is presented in **Table 8** (178-187). A complete list of all findings per study is available in the **Appendix B**. Thematic analysis revealed the following key themes: cancer progression and/or survival; pain; fatigue; other symptoms (sexual dysfunction, bothersome lower urinary tract symptoms [LUTS]) (**Table 8**) (172).

“*Cancer progression and/or overall survival*” benefits related to treatment were a key theme extracted from five included studies (181-185). Dearden *et al* undertook semi-structured interviews with 152 patients with mCRPC who were receiving novel anti-androgen therapies (Abiraterone Acetate or Enzalutamide) (183). Patients were satisfied with these therapies, specifically with reductions in prostate-specific antigen levels and the extended survival quality.

Burbridge *et al* undertook semi-structured interviews with 25 patients diagnosed with mCRPC (181). 83.3% of patients said they would have taken a medication to delay (metastasis) progression, if one had been available, irrespective of side effects (181). Ito *et al* conducted semi-structured interviews with 31 patients with mHSPC across Europe and

the UK receiving Docetaxel. They found that at the beginning of therapy, men were willing to take Docetaxel to prolong their life, despite being fearful of the potential side effects and impacts on their daily lives.

“*Fatigue*” was a key theme related to treatments identified in five included studies (178,180-182,184). Catt et al undertook structured interviews with 37 patients with mCRPC, exploring experiences of treatment decisions, perceived benefits and harms of treatment, and their effects on their lives (182). At 3 months since starting a systemic therapy, 42% of patients said fatigue was the worst treatment-related side effect. Burbridge *et al.* also found that more than 75% of men with mCRPC reported fatigue or extreme tiredness (“*Whatever [I do] is exhausting*”)(181). In Ito *et al.*, fatigue was a significant treatment-related side-effect reported in up to 60.9% of patients interviewed (180).

“*Pain*”, was identified as a theme in two studies (181,182). Burbridge *et al.* found pain as one of the most frequent symptoms reported by more than 75% of patients (“*I had a lot of pain*”, “*The pain comes and goes and I usually feel it somewhere in my back*”) (181). Catt et al also found that pain was the worst symptom reported by most patients (46%) although nearly a fifth (19%) made comments attributing the pain to causes other than prostate cancer (“*I think the pain in my hip could be rheumatic*”, “*My pain in the lower back and shoulder are due to degeneration*”)(182).

“*Other symptoms*” related to treatments and local disease were sexual dysfunction and bothersome LUTS reported in four studies (178,181,184,187). It is known from earlier work in the pre-Docetaxel era that andropause symptoms (including sexual dysfunction) relating to ADT administration were a significant consideration for patients in deciding upon commencing treatment and a source of treatment regret (178,179,184). Burbridge *et al.* found that bothersome LUTS were reported in more than 75% of men (181). Patients were willing to consider supportive treatment to alleviate these symptoms, likely due to the progression of an untreated local tumour.

Grunfeld *et al.* found that most patients reported hot flashes and night sweats, gynecomastia, cognitive decline, and changes in sexual dysfunction (“*That the erection is rather painful is somewhat of a disincentive to trying it too often*”) as the most frequent adverse effects, affecting everyday functioning³⁹. Some patients felt that there was no need for treatment as they were older and single, whereas others reported a belief that the negative aspects outweighed the benefits.

Table 8. Summary of major findings of patient preferences and values (qualitative) studies

Patient preference/values	Key themes defined	n	Study No.	Confidence of evidence	Interpretation of key themes
Cancer progression or survival	Patients reported that they were willing to accept a range of side effects for potential benefits in cancer progression and/or survival.	145	9,10,11, 13, 14	⊕⊕○ ○ Low	Patients with metastatic disease may be willing to trade-off side effects for potential oncological benefits.
Fatigue	Fatigue emerged as a prominent treatment related symptom, significantly impacting on patients quality of life.	281	6,9,10, 12	⊕⊕○ ○ Low	Fatigue has a large impact on this group of patients quality of life and risks of fatigue should be considered in relation to any treatment proposed.
Pain	In patients with symptomatic metastatic prostate cancer pain was consistently a the most troublesome symptom.	59	9,10	⊕○ ○○ Very Low	In the presence of symptomatic metastatic disease, avoidance or relief of pain appears to be paramount.
Other symptoms: Sexual dysfunction, Bothersome LUTS	Erectile dysfunction and bothersome LUTS were both frequently reported in patients, impacting negatively on their quality of life and relationships.	260	6,9,12, 15	⊕○ ○○ Very Low	Local symptoms may have a significant negative impact on patients quality of life. Treatments that alleviate local symptoms may lead to secondary benefits.

Legend: LUTS – Lower urinary tract symptoms.

4.5 Discussion

4.5.1 Principal findings

This systematic review addresses the evidence from both quantitative and qualitative studies reporting on patients' values, preferences and expectations in the relations to their treatment of metastatic prostate cancer. In quantitative preference elicitation studies, patients consistently valued "*treatment effectiveness*" and "*delay in time to symptoms*" as the two predominant ranked treatment attributes (low to very-low certainty; **Table 7**). Patients were willing to trade-off treatment-related toxicity for potential oncological benefits (low certainty). With a rapidly emerging field of local tumour treatments and metastasis-directed therapies now available to patients, these findings are of important consideration to patients and their clinicians (**Figure 5**).

When qualitative thematic analysis was performed "*cancer progression or survival*", "*pain*" and "*fatigue*" emerged as key to treatment decisions (low to very-low certainty; **Table 8**). Patients continue to value oncological benefits in making decisions for treatments. However, in the subgroup of symptomatic patients, treatments that could alleviate pain were highly valued even at the expense of survival benefits (very low certainty).

Furthermore, treatment inducing fatigue had a significant negative impact on the remaining quality of life (very low certainty). Given that ionising radiation directed to metastasis may secondarily exacerbate or induce fatigue highlights just one example of the difficult decision-making balance patients and clinicians face (188).

4.5.2 Comparison with prior reviews and guidelines

To our knowledge, this is the first systematic review to evaluate patients' preference and values for treatments following a diagnosis of metastatic prostate cancer. Prior systematic reviews of patients' preferences have been completed in patients with localised prostate cancer where the marginal gains in absolute survival advantage (up to 5% over 10 to 15 years) and side effects associated with radical prostate treatment remain the predominate issue (189,190). In the non-curative setting, it can be assumed that patients' treatment preferences are entirely different.

The landmark STAMPEDE (arm-H) study of 2,061 men with newly diagnosed metastatic prostate cancer receiving additional local prostate radiotherapy compared to those receiving systemic therapy alone demonstrated a significant OS advantage in patients with low volume disease in the radiotherapy arm (3-year OS 81% vs 73%; HR 0.68, [95% CI: 0.52–0.90]; $p = 0.007$) (16).

On this background, international prostate cancer guidelines have incorporated radiotherapy into the standard of care (191,192). However, some guidelines chose dose/fractionation schedules (e.g. 36Gy/6F) that specifically reduce hospital attendances on the basis that patients would value such an approach in the decision-making process (191). There is, however, no robust evidence detailing how patients trade-off the risks and benefits of applying new treatments to this setting to support such an implementation (165).

4.5.3 Strength and limitations

This is the first study to use an expert panel of urologists, oncologists and health economists to develop a priori for conducting a systematic review on this topic. This methodological rigour has enabled us to summarise the key findings and rate the certainty of the evidence presented using the GRADE and GRADE CERQual criteria, respectively.

Unfortunately, the varied study design and reported outcomes in the quantitative preference studies prevented a meta-analysis from being performed. Furthermore, the diverse qualitative studies reported likely reflect the heterogeneous pool of patients included in interviews (i.e., varied disease states, metastatic burdens, asymptomatic versus symptomatic).

Finally, although bone-targeted agents were evaluated in this systematic review, the majority of studies were focused upon existing systemic therapy. No studies specifically reported on cytoreductive radical prostatectomy, minimally-invasive ablative therapies, metastasectomy or SABR. We are thus unable to report upon patient preferences' and values with regard to these treatments.

4.5.4 Unanswered questions and future research

This systematic review has predominantly highlighted patients' preferences in the context of being offered established systemic therapy options and a limited number of bone-targeted agents. Our overall understanding of how novel surgical and radiotherapy treatment options are valued by patients, therefore, remains limited.

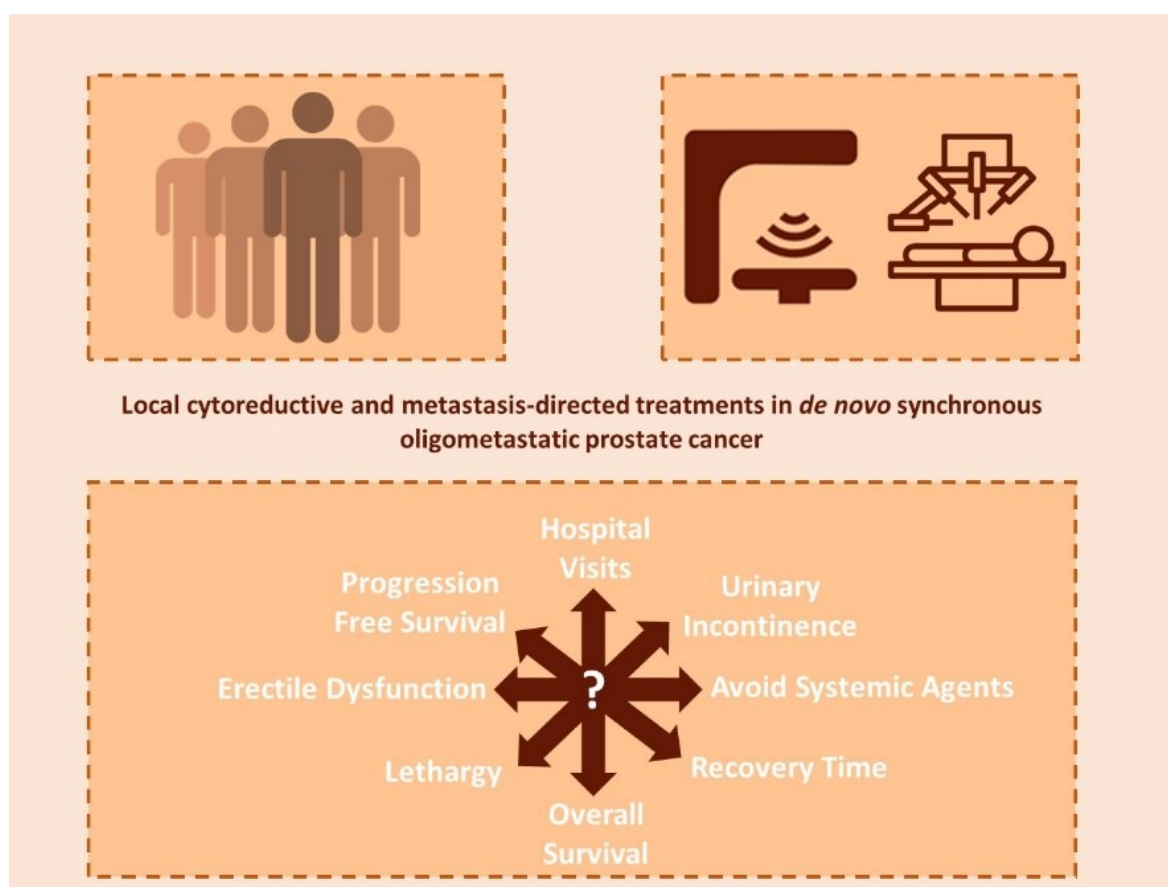
However, results continue to be published, following robust trial evaluation, supporting a number of these treatment options (164,193,194). We therefore propose that a reappraisal of patient preferences is now required to permit new treatment integration into the existing standard of care pathways. this may take the form of a prospective stand-alone study or indeed could be integrated into those studies in longitudinal follow-up (e.g. NCT01751438; NCT03456843; NCT02454543; NCT03988686; NCT02742675; ISRCTN15704862; NCT03655886; NCT03678025; NCT03763253).

The IP5-MATTER study is a multicentre (NCT04590976) discrete choice experiment, currently in its accrual phase, evaluating 300 patients with *de novo* synchronous mHSPC(195). This trial is designed to evaluate novel treatments (cytoreductive radical prostatectomy, external beam radiotherapy, minimally-invasive ablative therapy and SABR) in addition to systemic therapy for the first time. This study is collecting data on patient characteristics (e.g. age, co-morbidities) and will offer an insight into whether this also impacts upon patient preference (196).

It can be hypothesised that the results from studies, can then be combined with the effect sizes from future reported interventional randomised trials to determine if, on average, patients are willing to accept the potential effect sizes that are reported in these studies (3,197).

Finally, research on patients' values, preferences and expectations for treatment should be cognizant of an emerging theme of "treatment regret" that has been reported in localised disease (198) . One option to mitigate such levels of treatment regret is to assist in the informed decision making process. It is possible that once novel treatment pathways are established for metastatic prostate cancer the findings from patient preference elucidation studies (such as DCE's) may be integrated into further work towards the creation of a decision treatment aids (DAT). Whilst residual uncertainty in the role of DCE's in the development of such DATs remains, the methodology is currently being validated in localised prostate cancer and other benign surgical studies. If proven it may offer utility in the development in any future decision treatment aid for this specific cohort of patients (199-201).

Figure 5. Hypothetical representation of patients' preferences for, and trade-offs between, the attributes (survival and side effects) associated with different treatment options



Legend: Central graphic represents the various attributes (e.g. urinary incontinence, lethargy, overall survival) which may for part of patients' preferences for, and trade-offs between, different treatment options available to them in mHSPC. Reproduced with permissions (Appendix A) from *European Urology* [Elsevier]. Connor, MJ, Khoo V, Watson V, Ahmed, HU. Radical treatment without cure: decision making in oligometastatic prostate cancer. 2021. *European Urology*. 79(4), pp.558-560.

4.6 Conclusion

Currently, a limited understanding of patients' preferences for treatment, and thus trade-off decisions, exists following a new diagnosis of metastatic prostate cancer. In order to appropriately invest in emerging cytoreductive prostate and metastasis-directed treatments options that are most acceptable to such patients, attempts to formalise our understanding of the trade-offs between oncological benefits and risks in this cohort of patients should be performed.

Chapter 5 – Identifying suitable patients with mHSPC in a contemporary pre-biopsy MRI prostate biopsy referral pathway and implications for cytoreductive surgery

5.1 Overview

In this chapter I addressed a number of basic unknowns for urologists (i) how do we identify patients with mHSPC? (ii) What is the prevalence of patients with mHSPC in a modern pre-biopsy MRI prostate cancer referral pathway (iii) What does mpMRI tell us about the prostate and pelvis in mHSPC (iv) Is transperineal prostate biopsy safe in patients with mHSPC? (v) What are the histological features of the primary tumour in patients with established mHSPC.

Finally, I evaluate the implications on the potential performance of minimally invasive ablative therapy, cytoreductive radical prostatectomy and lymph node dissection in this group of patients particularly with respect to the IP2-ATLANTA RCT. Building on the cohort of patients in the pathway I was able to analyze suitability for surgical resection, patterns of nodal metastasis at presentation, MRI tumour volume, tumour staging and suitability for ablative therapy.

Such a characterization is an important step for our group to understand the numbers of suitable patients and in developing a pathway to identify patients who may be suitable for a subsequent novel surgical randomised controlled trial. A section of this chapter was presented at the *American Urology Association (AUA) 2021* conference and key arguments have been published in *Urology News* and *Prostate Cancer and Prostatic Diseases*^{6,7,8}.

5.2 Introduction

Historically, patients with presumed locally-advanced and/or metastatic prostate cancer, identified either by concerning surrogate markers of disease burden (e.g. absolute serum PSA > 100 ng/ml) or clinical examination, did not routinely undergo primary tumour biopsy or mpMRI prostate evaluation (202-204). Indeed, such patients were frequently streamed away

⁶ Connor, M.J., *et al.* MRI findings in *de novo* synchronous metastatic prostate cancer and implications for cytoreductive surgery. 2021. *The Journal of Urology*, 206(Supplement 3), pp.e587-e587.

⁷ Connor, M.J., *et al.* Cytoreductive cryotherapy for newly diagnosed oligometastatic hormone-sensitive prostate cancer. *Prostate Cancer and Prostatic Diseases* 23, no. 3 (2020): 537-538.

⁸ Connor, M.J., *et al.* Trials offering cytoreductive surgery for men with *de novo* synchronous metastatic prostate cancer. 2021. *Urology News*, 12, p.19.

from local tumour characterization. This was in part due to the higher risk of sepsis following transrectal ultrasound prostate biopsy approaches, weighed against the utility of primary tumour characterization in an era of restricted systemic treatment options (202). This has limited urologists' understanding of patients with mHSPC.

The emergence of evidence supporting local treatment to the prostate in patients with 'oligometastatic' disease has heightened interest in the deeper characterisation of the primary prostate tumour (16,22). This research has coincided with the routine integration of pre-biopsy multi-parametric magnetic resonance imaging (mpMRI) into the diagnostic pathway for biopsy naïve patients, of good performance status, referred with a suspicion of prostate cancer (205-207). Thus, I am able to describe the baseline MRI features of the prostate and pelvis in patients with mHSPC with greater accuracy.

Following a mpMRI, patients undergo an MRI-targeted and systematic prostate biopsy to complete their diagnostic evaluation (208). Primary tissue diagnosis may identify distinct subtypes (e.g. neuroendocrine differentiation) or aggressive variants of prostate cancer offering the ability to personalise choice of treatments (124,209).

Collectively, the modern prostate cancer referral pathway offers the opportunity to routinely visualise the primary prostate tumour and associated pelvic changes with mpMRI imaging, in patients with *de novo* synchronous mHSPC for the first time. The subsequent clinical information has implications for planning and developing approaches to local cytoreductive surgery (including metastasis directed lymph node dissection, cytoreductive radical prostatectomy and ablative therapy) (193).

MRI findings of the prostate and pelvis are an uncharted territory as a planning tool for cytoreductive surgery. To our knowledge, no studies to date on local cytoreductive treatments, including those exploring local prostate radiotherapy, have reported on prostate MRI findings for planning of post-systemic therapy local treatment to the primary and lymph nodes. Furthermore, there is no evidence available on patterns of intraprostatic and nodal disease on mpMRI prostate among patients presenting with mHSPC in the literature. Evidence available to date has focused on whole-body MRI in combination with molecular imaging (e.g. ⁶⁸Ga PSMA PET/MRI) performance in whole body staging of metastatic disease (210).

Whilst cytoreductive prostatectomy with pelvic lymph node dissection has been performed in locally-advanced disease previously, the performance of minimally invasive ablative

therapy in this setting is relatively unknown (123,124,211). Currently ablative therapies, such as cryotherapy and high-intensity focused ultrasound (HIFU) are recommended in patients with a good life expectancy, with low- and intermediate-risk (Gleason 3 + 4 = 7 or 4 + 3 = 7) that is localized and of discrete small volume (212). Application towards higher volume and grade disease has been restricted to the radio-recurrent non-metastatic salvage setting (213). Finally, performing lymph node dissection at the time of simultaneous MIAT has not been reported beyond the cadaveric setting (214).

The principal objectives of this study were to report the clinical, histopathological and multiparametric MRI features of patients with mHSPC who present within a modern pre-biopsy MRI prostate cancer referral pathway. Furthermore, we aimed to contextualise these findings in relation to the potential performance of cytoreductive surgical treatments.

5.3 Methods

5.3.1 Study Design

We performed a prospective multicentre study of patients referred with suspicion of prostate cancer. The study uses data from the Rapid Assessment for Prostate Imaging for Diagnosis (RAPID) prospective registry (215). Patients presenting between April 2017 and March 2021 were consecutively identified from the RAPID registry. All patients entering this referral pathway had a suspicion of prostate cancer and were of restricted Performance Status 0 or 1. Patients underwent a pre-biopsy mpMRI assessed using PI-RADS (version 2.0). An overview of the clinical pathway is presented in **Figure 6**.

5.3.2 Outcome measures

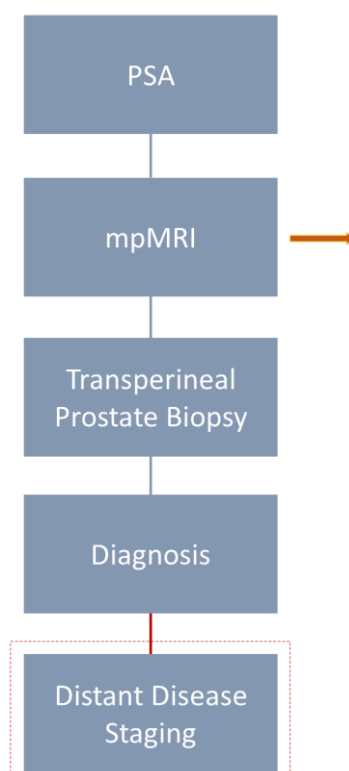
The primary outcome was the proportion of patients diagnosed with *de novo* synchronous mHSPC within the RAPID prostate cancer referral pathway. This was reported as the proportion (%) of patients with a histological diagnosis of prostate cancer from primary tumour biopsy and radiological or histological diagnosis of metastatic (any M1a-c) disease, compared to all patients referred with a suspicion of prostate cancer in the RAPID pathway.

Secondary outcomes were: i) evaluating the clinical and pathological features of patients with mHSPC ii) safety and adverse events analysis of transperineal prostate biopsy in patients with mHSPC iii) baseline mpMRI features in patients with mHSPC (including MRI-tumour volume and patterns of MRI-nodal disease), and iv) suitability for cytoreductive surgery and ablation (analysed from baseline mpMRI imaging).

5.3.3 Ethical Approval

This study was reviewed and prospectively approved by the local service evaluation board (Imperial College Healthcare NHS Trust, London, United Kingdom; Reference Number: SPS028). Following review, patient specific consent for this study was not deemed necessary.

Figure 6. Flowchart for the Rapid Assessment for Prostate Imaging and Diagnosis (RAPID) prostate cancer diagnostic pathway



Legend: Orange arrow demonstrates recommendation of immediate biopsy avoidance for patients were absence of clinical risk factors, mpMRI PI-RADS Score ≤ 3 and PSAD < 0.12 ng/ml. Red line/box demonstrates patient with confirmed prostate cancer on transperineal prostate biopsy and/or suspicion of nodal disease and/or metastasis on mpMRI, or deemed high-risk based on PSA (> 20 ng/ml), underwent a computed tomography thorax, abdomen & pelvis (CT-TAP) and bone scintigraphy (BS). PSA – Prostate Specific Antigen, mpMRI – Multiparametric Magnetic Resonance Imaging, RAPID - Rapid Assessment and Prostate Imaging for Diagnosis, PI-RADS - Prostate Imaging-Reporting and Data System [Version 2.0], PSAD – Prostate Specific Antigen Density.

5.3.4 Multiparametric MRI Acquisition and Reporting

An mpMRI was performed using a 1.5-T scanner. mpMRI was performed and reported in accordance with the technical requirements in PIRADSV2. The sequences included T1-weighted, T2-weighted, dynamic contrast-enhanced (DCE) and multi b-values (for derivation of apparent diffusion coefficient (ADC) maps) and a high b-value of 1500. Reporting was

performed exclusively by uro-radiologists, with a minimum 3 years of reporting experience with the reporter having access to baseline clinical information, including PSA, age, and DRE findings.

5.3.5 MRI-tumour volume assessment

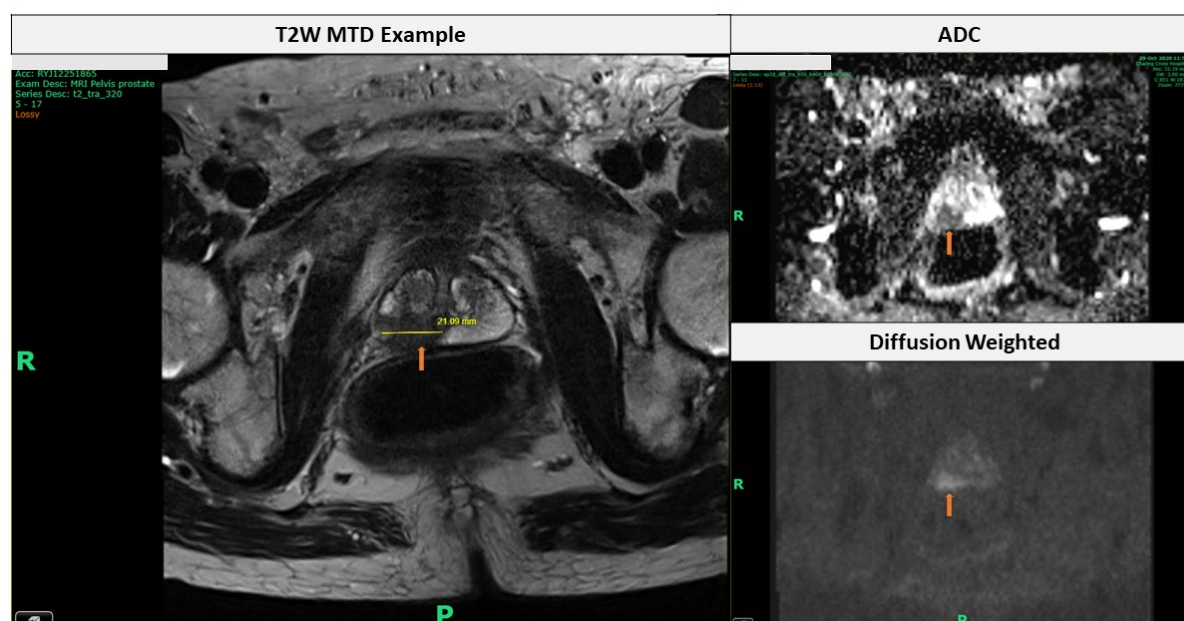
Presently there is no agreement on the optimal method of measuring MRI-tumour volume on mpMRI, with maximum tumour diameter (MTD), ellipsoid formula and planimetry all being proposed in the literature (211,216-218). Of these options, MTD is an established simple measurement which is feasible to obtain in clinical practice as part of the PI-RADS v2.1 classification, and is a recognised inexpensive surrogate for tumour volume in radical prostatectomy specimens (217). In addition, MTD has been shown to be associated with distant metastasis development in the high-risk localised and salvage setting, respectively (216,219). Specifically, in the high-risk localised cohort a MTD > 24 mm has been independently associated with increased risk of distant metastasis with unfavourable post treatment outcomes (HR 10.13, $p = 0.04$, [95% CI 1.13-91.12]) (216).

All mpMRI sequences were reviewed by myself to assess MRI-tumour volume of the index lesion (or the largest lesion if multifocal lesions), using the single measurement of the largest dimension in the axial plane described previously described in the literature as “maximum tumour diameter” (**Figure 7**) (216,218). For the purposes of this study, an exploratory subgroup analysis comparing Gleason Grade Groups, MRI-Tumour and MRI-Nodal staging with MTD was planned. In the absence of known MTD prognostic groups for mHSPC patients in the literature, MTD prognostic groups identified in high-risk localised disease studies were applied to the results (“favourable” defined as ≤ 24 mm; “unfavourable” defined as > 24 mm) (216).

5.3.6 MRI-anatomical pattern of pathological lymph nodes

MRI anatomical patterns of pathological lymph nodes were collated and mapped onto established surgical templates. Reporting of nodal disease “arising within extended pelvic lymph node dissection (ePLND) template” assumed that dissection were to include external iliac, obturator, internal iliac nodes as initially described by Mattei and colleagues (220).

Figure 7. Example of MRI Tumour Volume Assessment with Maximum Tumour Diameter



Legend: mpMRI images of a 69 year old patient with a presenting PSA 6.9 ng/ml. Right Peripheral Zone Tumour; PI-RADS 5, Likert 5; PVol 29 cc; PSAD 0.21 ng/ml; MRI-staged T3b N0. Orange arrow demonstrates prostate tumour on T2W, Diffusion Weighted ($b=1400\text{sec/mm}^2$) and ADC. Measurement of maximum tumour diameter was completed using the T2 weighted image in the axial plane (Yellow Line; 21.09 mm/2.10 cm) due to the increased resolution and reduced susceptibility to geometric distortion this provides, when compared to the diffusion restriction images. This was in all cases except where diffusion restriction imaging more clearly depicted the tumour. MTD approach as previously described by Parson and colleagues (2022) (216). ADC – apparent diffusion coefficient, mpMRI – Multiparametric Magnetic Resonance Imaging, PVol – Prostate Volume; PSAD – Prostate Specific Antigen Density.

5.3.7 Suitability of surgical resection

Baseline MRI images were reviewed by myself (MJC) commented upon suitability for primary tumour resection at baseline. Reasons for irresectable disease included the following:

- Invasion of adjacent structures (e.g., direct rectal invasion).
- Irresectable pelvic lymph nodal disease
- Presence of distant non-regional (M1a) nodal disease (i.e. retroperitoneal)

Radiological T3b disease was permitted. This is in keeping with the TRoMbone (ISRCTN15704862) cytoreductive radical prostatectomy studies inclusion criteria (221).

5.3.8 Suitability for minimally invasive ablative therapy

Baseline MRI scans were reviewed by myself (MJC) to comment upon suitability for primary tumour cytoreductive cryotherapy or HIFU. Reasons for non-suitable ablative disease included any of the following:

- Invasion of adjacent structures in keeping with T4 (e.g. direct rectal invasion, levator sling).

Radiological T3b disease was permitted. Whole gland ablation was recommended when a diffuse lesion was present, whilst focal ablation was suitable for unifocal or bilateral lesions which permitted tissue preservation of more than 40%.

5.3.9 Distant disease imaging & definition of metastatic disease

For this study metastatic prostate cancer required a composite of histological confirmation of primary tumour on biopsy and distant radiological evidence of metastasis (i.e M1a-c). In all men with nodal disease on mpMRI, suspicion of metastasis and/or high-risk prostate cancer on biopsy underwent a computed tomography thorax, abdomen & pelvis (CT-TAP) and bone scintigraphy (BS). Bone metastases were confirmed on best available comparator (CT-TAP/BS/MRI). Patients with equivocal conventional imaging underwent confirmatory positron-emission tomography (PET)/CT imaging. In cases of persistent radiological uncertainty of metastasis or primary origin, a radiologically guided biopsy of amenable metastasis was performed. Such cases were discussed at the tumour board meeting and evaluated on a case-by-case basis.

5.3.10 Prostate Biopsy Technique

PI-RADS score 4 or 5 identified on mpMRI results in a biopsy. Where PI-RADS score of 3 was present a PSA density $\geq 0.12\text{ng/mL}$ was required to initiate a biopsy. Furthermore, some patients within this pathway were evaluated to be at high-risk of prostate cancer, predominantly due to presence of family history, concerning PSA kinetics, or ethnicity. Such biopsies were at the discretion of treating clinician and evaluated on a case-by-case basis.

All biopsies were performed transperineal and in accordance with a pre-determined standard operating procedure, used by all study centres. MRI-targeted prostate biopsies were performed either using visual-estimation (i.e. cognitive) or with image-fusion software. This was at the discretion of the treating clinician. When image-fusion was utilised, mpMRI scans were imported onto the registration system (Biopsee, Medcom®) and subsequent images were manually fused with on-table acquired TRUS images. Lesions of suspicion were then marked and targeted stereotactically using real-time TRUS guidance.

Sampling of targeted lesions occurred first (minimum of 3 cores per lesion; no maximum). Secondly, non-targeted ipsilateral and contralateral peripheral zone cores were performed in all cases. This was except where bilateral PI-RADS 4 lesions, bilateral PI-RADS 5 lesions or “diffuse lesions” were reported.

5.3.11 Histopathology

Gleason Grade Group (International Society of Urological Pathology [ISUP]) and cribriform pattern were reported in all specimens. Where neuro-endocrine features were suspected a further immunohistochemical panel, including chromogranin A, neurospecific enolase and synaptophysin, was performed. Senior uro-pathologists reported all cases, and these were subsequently discussed in a specialist central prostate cancer tumour board meeting.

5.3.12 Metastatic burden

Metastatic burden was defined by the CHAARTED criteria as 'low' or 'high'. High burden disease was the presence of visceral metastasis or four or more bone metastases with one or more located outside the vertebral bodies or pelvis(10,16).

5.3.13 Statistical analysis

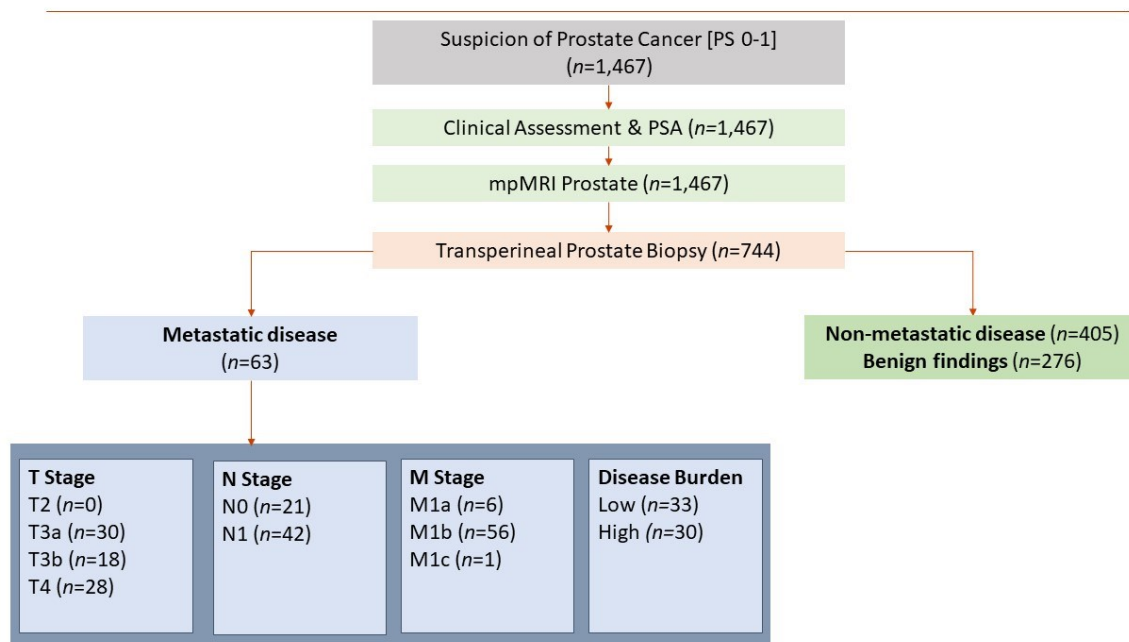
Descriptive statistics presented summarise patient demographics, clinical, radiological and biopsy characteristics. Normally distributed data are presented as mean +/- standard deviation and compared by Student' s t-test between group performed, using SPSS (IBM Corp., IBM SPSS Statistics for Windows, Armonk, USA, v.28.0), some tables and graphs were recreated in Excel (Microsoft, v.2019).

5.4 Results

5.4.1 Patient demographics

Overall, 1,467 consecutive patients were referred during the study period (**Figure 8**). The median age was 67.0 years (Interquartile Range [IQR] 12.0), median baseline PSA 6.9 ng/ml (IQR 5.4) and median prostate volume 50.0 (IQR 41.75), respectively (**Table 9**).

Figure 8. Overview of patients from the RAPID pathway



Legend: T- Tumour, N – Nodes, M – Metastatic (M1a – Distant Nodal Metastasis, M1b – Bone Metastasis, M1c – Visceral Metastasis), Disease Burden – Metastatic Disease as per CHAARTED definition “high” vs “Low” (10), mpMRI – Multiparametric Magnetic Resonance Imaging, PSA – Prostate Specific Antigen, PS – Performance Status as per ECOG, Non-metastatic disease – Any T, Any N combined with an M0 status.

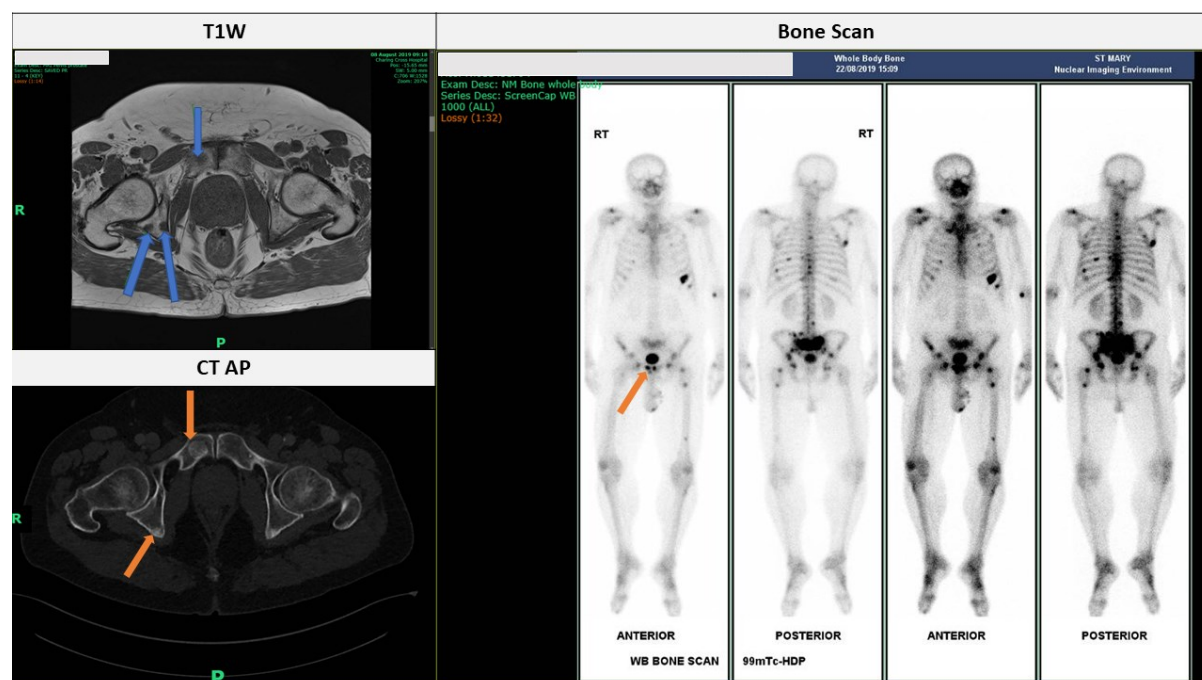
5.4.2 Primary outcome

The proportion of patients with a diagnosis of *de novo* synchronous mHPSC was 4.29% (63/1467). Within this mHSPC sub-group, the median age was 70.5 years (IQR 8.6) and median baseline PSA was 83.6 ng/ml (IQR 234.0) (**Table 9**). Performance status was reported as “PS=0” in 95.2% (60/63) of patients.

Distant disease was confirmed using conventional imaging alone in 62/63 (98.4%). One patient required a PET/CT to confirm metastatic disease 1/63 (1.6%) (**Figure 9**). In addition, a further patient underwent an ultrasound-guided liver biopsy for suspicious hepatic lesion, without complication. This was confirmatory of a prostate adenocarcinoma. The overall metastatic staging of patients within this sub-group was as follows: M1a 6/63 (9.5%), M1b

56/63 (88.9%), M1c 1/63 (1.6%), respectively. High burden disease was present in 30/63 (47.6%) and low burden in 33/63 (52.4%) of patients, respectively (**Figure 8**).

Figure 9. Example of mHSPC bone metastases visualised on mpMRI, computed tomography abdomen & bone scan and bone scan.



Legend: Distant disease staging imaging of previously described patient in **Figure 10**. [T1W] (Blue Arrow) Three hypointense bone lesions suggestive of bone metastasis. [CT AP (Axial Bone Window) & Bone Scan] (Orange Arrow) Confirm two hypointense bone lesions visualise on mpMRI demonstrate features of sclerotic osteoblastic bone metastasis. Bone scan further confirms multiple other distant osteoblastic bone metastases with uptake in the pelvis, spine, ribs, scapulae and femoral shafts. Confirming polymetastatic prostate cancer (M1b). CT AP – Computed Tomography Abdomen and Pelvis; Bone Scan - Whole Body Bone Scintigraphy with hydroxydiphosphonate labelled with technetium (99mTc-HDP).

5.4.3 Pre-biopsy mpMRI prostate results

In patients with mHSPC confirmed, the median prostate volume was 50.0 cc (IQR 30.3) (**Table 9**). In all patients (63/63) PI-RADS 5 lesions were identified, with an “index lesion” in 20/63 (38.1%) and a “diffuse lesion” in a further 42/63 (68.3%). Reported primary tumour stage was: T2 0/63 (0%), T3a 4/63 (10.8%), T3b 18/63 (35.1%), T4 28 (48.6%), respectively. Suspicious nodal disease (N1) was reported on mpMRI in 42/63 (66.7%). Overall, 56/63 (88.9%) had bone metastasis visible on their pre-biopsy prostate mpMRI.

Table 9. Baseline demographics and pre-biopsy mpMRI feature of patients with mHSPC

	mHSPC (n = 63)	Overall (n = 1,467)
Age, median (IQR), years	70.5 (9.6)	67 (12)
Baseline PSA, median (IQR), ng/ml	83.6 (234.0)	6.9 (5.4)
Prostate Volume, median, (cc)	50.0 (30.3)	50.0 (41.75)
MRI T Stage		
T2 (%)	0 (0.0)	534 (46.4)
T3a (%)	4 (10.8)	83 (9.7)
T3b (%)	18 (35.1)	43 (5.0)
T4 (%)	28 (48.6)	37 (4.3)
Unknown	0 (0)	770 (52.4)
PI-RADS Score		
<3	0 (0)	350 (23.5)
3	0 (0)	121 (8.2)
4	0 (0)	212 (14.4)
5	63 (100)	150 (9.5)
Unknown	0	634 (43.2)

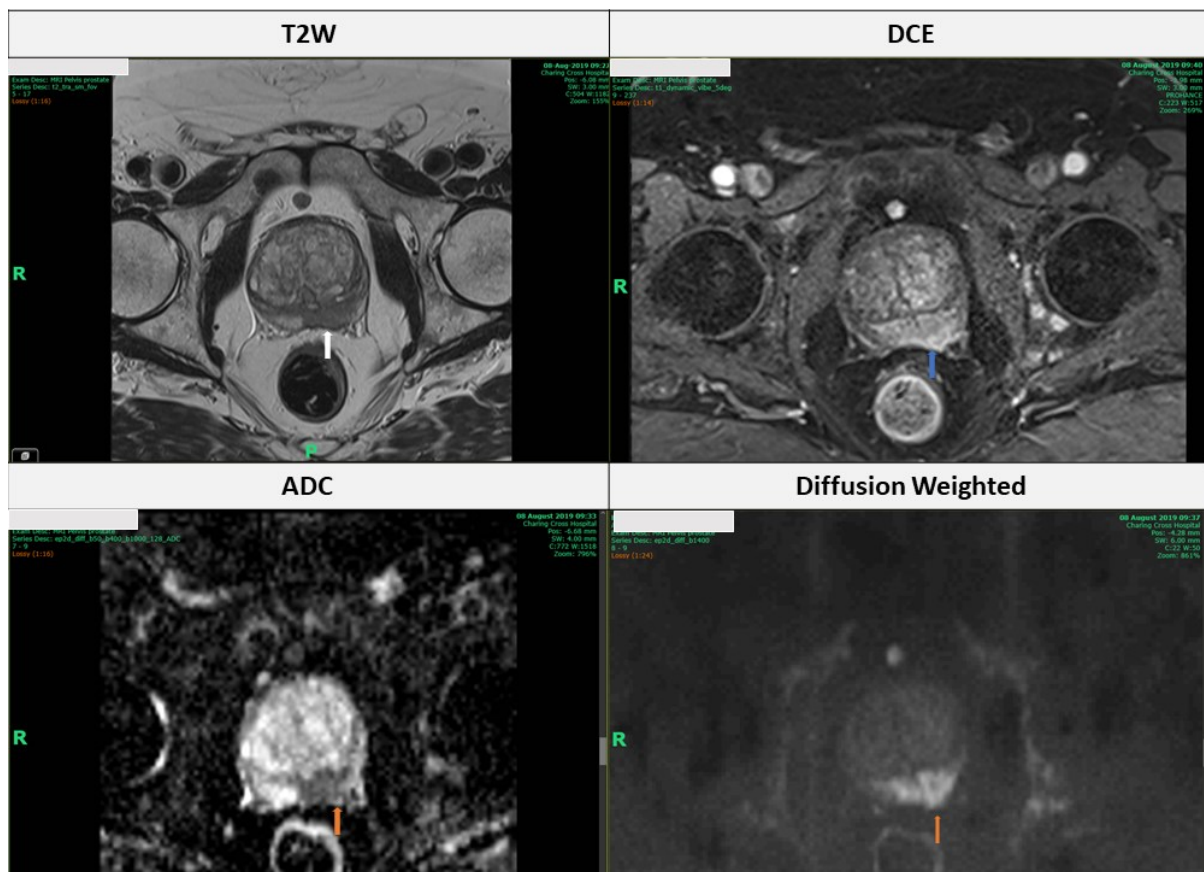
Legend: SD – Standard Deviation; IQR: Interquartile Range. PI-RADS – Prostate Imaging Reporting & Data System; BS – Bone Scintigraphy; CT-TAP – CT Thorax, Abdomen & Pelvis. Highest PI-RADS Score used.

5.4.4 MRI-tumour volume results

MRI-tumour volume assessment revealed a mean MRI-tumour volume of 36.88 mm (SD 11.76) and median 36.4 mm (IQR 16.47), respectively (**Table 10; Figure 10**). There was a significant trend towards larger MRI-tumour volume in higher Gleason Grade / ISUP Groups and ascending MRI-reported tumour stage, respectively. Statistically significant differences in MRI-tumour volumes of Gleason > 8 [ISUP > 5] were observed when compared to Gleason < 8 [ISUP < 5] (40.1 mm vs 29.4 mm; $p = 0.001$). In addition, statistically significant differences in MRI-tumour volumes in MRI reported T3 disease were observed when compared to MRI reported T4 disease (33.7 mm vs 39.8 mm; $p = 0.03$).

Furthermore, there was also a non-significant trend towards larger MRI-tumour volumes in MRI-Nodal positive (N1) disease compared to MRI-Nodal negative (N0) disease (37.7 mm vs 33.7 mm; $p = 0.14$). When prognostic thresholds of MRI-tumour volumes from high-risk localised studies were applied to our mHSPC sub-group, 84.2% (53/63) of patients were classed as having “unfavourable” MRI-tumour volumes.

Figure 10. Example of primary tumour in patient with mHSPC identified on pre-biopsy mpMRI



Legend: 71 year-old patient, asymptomatic, presenting Prostate Specific Antigen (PSA) 11.0 ng/ml, Prostate Volume 141.0 cc (56 mm x 81 mm x 60 mm), PSA Density 0.08 ng/ml. MRI: PI-RADS 5; Likert 5; T3b N0 M1b. [T2W] (White Arrow) 29 mm of the left peripheral zone is replaced by low T2 signal; [ADC & DCE] (Orange Arrows) corresponding area of low signal intensity left peripheral zone; [DCE] (Blue arrow) Relative early contrast enhancement. Suspected right superior pubic rami bone metastasis visible (T2W). ADC – apparent diffusion coefficient, DCE – dynamic contrast enhancement, mpMRI – Multiparametric Magnetic Resonance Imaging.

Table 10. mHSPC MRI-Tumour Volume Results

	mHSPC MRI-Tumour Volume*
Overall	
Mean (SD)	36.8 mm (11.76)
Median (IQR)	36.4 mm (16.47)
Pathology	
Gleason 7 / ISUP 2-3	
Mean (SD)	27.9 mm (14.96)
Median (IQR)	25.6 mm (6.06)
Gleason 8 / ISUP 4	
Mean (SD)	29.6 mm (4.31)
Median (IQR)	32.4 mm (4.51)
Gleason >8 / ISUP 5	
Mean (SD)	40.1 mm (11.02) ^a
Median (IQR)	39.7 mm (12.97)
High grade with treatment effect	
Mean (SD)	42.3 mm (4.17)
Median (IQR)	44.0 mm (3.92)
MRI T-Stage	
T3	
Mean (SD)	33.7 mm (10.43)
Median (IQR)	36.3 mm (17.31)
T4	
Mean (SD)	39.8 mm (12.45) ^b
Median (IQR)	37.7 mm (16.69)
MRI N-Stage	
N0	
Mean (SD)	34.7 mm (11.15)
Median (IQR)	34.2 mm (15.75)
N1	
Mean (SD)	39.3 mm (11.90)
Median (IQR)	40.0 mm (13.19)
MTD Prognostic Risk Groups	
Favourable ≤ 24 mm (%)	10 / 63 (15.8%)
Unfavourable > 24 mm (%)	53 / 63 (84.2%)

Legend: *MRI-Tumour Volume presented as Maximum Tumour Diameter in mm. ^aComparison between Gleason >8 [ISUP > 5] and Gleason <8 [ISUP < 5] (40.1 mm vs 29.4 mm; $p = 0.001$) with Students t-test.

^bComparison between MRI-Tumour stage T3 and T4 (33.7 mm vs 39.8 mm; $p = 0.03$) with Students t-test.

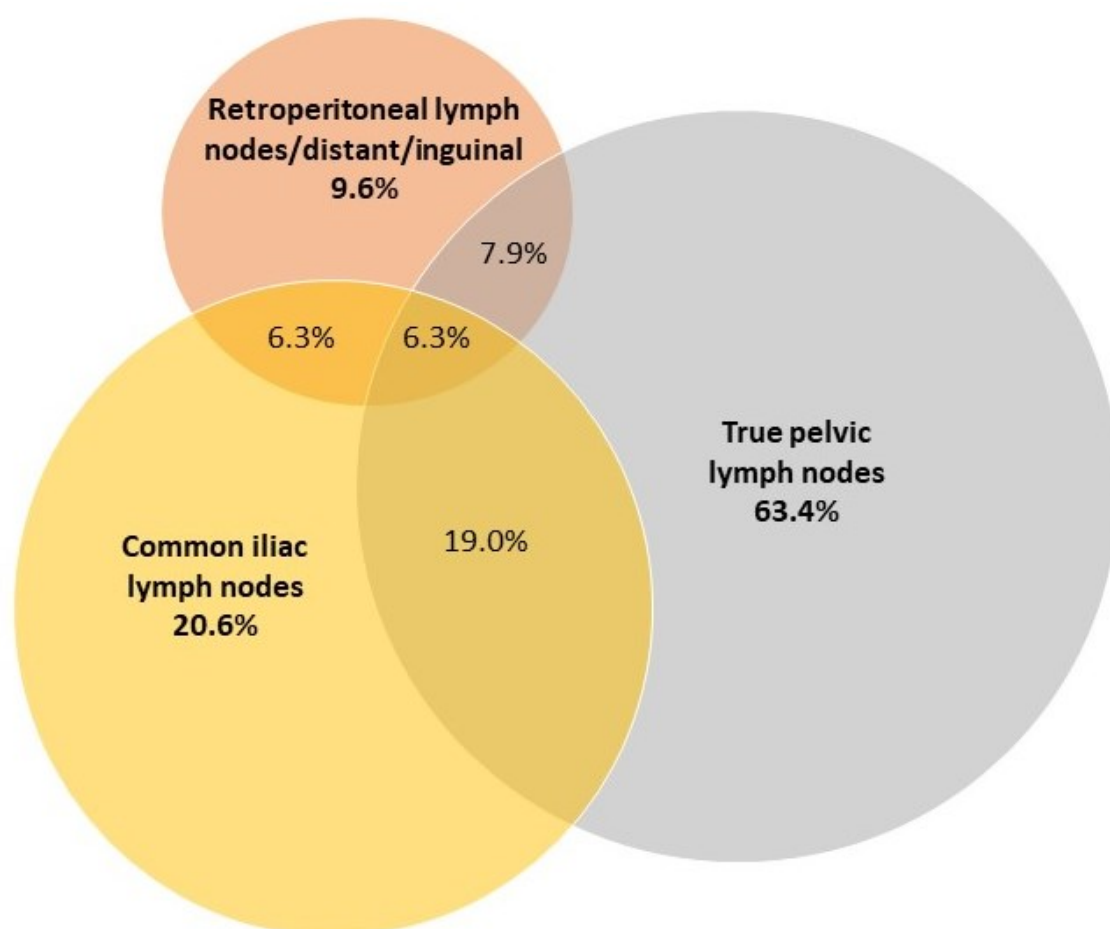
Risks group (MTD > 24mm vs ≤ 24 mm) as classified by Parson and colleagues (2022) (216).SD –

Standard Deviation; IQR: Interquartile Range; ISUP - International Society of Urological Pathology. Tumour, N – Nodes, M – Metastatic (M1a – Distant Nodal Metastasis , M1b – Bone Metastasis M1c – Visceral Metastasis).

5.4.5 MRI-anatomical pattern of pathological lymph nodes

At baseline MRI reported pelvic sidewall mass was present in 11/63 (17.4%), para-rectal or pre-sacral nodes in 20/63 (31.7%), nodes within extended-pelvic lymph node dissection template in 39/63 (61.9%), common iliac nodes 13/63 (20.6%), extra-pelvic (M1a) nodal metastasis in 6/63 (9.6%) patients (**Figure 11; Figure 12**).

Figure 11. Venn diagram presenting anatomical mapping of MRI lymphatic nodal metastasis per patient



Legend: At baseline MRI reported pelvic sidewall mass was present in common iliac nodes 13/63 (20.6%), extra-pelvic (M1a) nodal metastasis in 6/63 (9.6%) patients.

5.4.6 Transperineal prostate biopsy & histopathology

The median number of cores and maximum cancer core length (MCCL) were reported as 12 (IQR 7.8) and 14.0 (4.0), respectively (**Table 11**). Overall Gleason Grade Group was reported as: 3+4 1/62 (1.6%), 4+3 8/63 (12.7%), 4+4 9/63 (14.3%), >8 42 (66.6). No Gleason Grade Group 3+3 disease was reported. Due to biopsy delays, secondary to the Covid-19 pandemic, ADT was commenced prior to biopsy in three patients. Therefore

‘adenocarcinoma of the prostate without Gleason grade due to treatment effect’ was reported in three patients (3/63; 4.8%). Cribriform pattern was present in 39/63 (61.9%). Three patients (3/63; 4.8%) without ADT exposure, demonstrated adenocarcinoma with neuroendocrine differentiation on biopsy.

5.4.7 Transperineal prostate biopsy safety and adverse events

Clavien-dindo grade I acute urinary retention and haematuria (requiring urinary catheterization) was not reported in the metastatic sub-group (0/63). However, Clavien-dindo grade II post-biopsy sepsis was reported in a single patient (1.6%, 1/63) (**Table 11**). By comparison, in our overall RAPID case series, there were 0.1% cases of reported sepsis(215). There were no reported Clavien-dindo grade >II complications in this subgroup, or the overall study.

Table 11. Transperineal prostate biopsy histology, safety and adverse events

	mHPSC (n = 63)	Overall (n = 1,467)
Prostate biopsy (%)		
Transperineal prostate biopsy	63 (100)	744 (50.7)
Gleason grade group (%)		
Benign	N/A	276 (37)
3+3 (ISUP 1)	0 (0.0)	71 (9.5)
3+4 (ISUP 2)	1 (1.6)	169 (23)
4+3 (ISUP 3)	8 (12.7)	117 (16)
4+4 (ISUP 4)	9 (14.3)	32 (4.3)
>8 (ISUP 5)	42 (66.6)	74 (9.9)
High grade with treatment effect	3 (4.8)	3 (0.4)
Unknown	0 (0)	2 (0.2)
Number of cores		
Median (IQR)	12 (7.8)	13 (6.0)
Maximum Cancer Core Length (MCCL)		
Median (IQR)	14 (4.0)	9.0 (7.0)
Safety and adverse events (Clavien-Dindo >= II)		
Acute urinary retention (%)	0 (0)	7 (0.9)
Sepsis (culture-proven) (%)	1 (1.6)	3 (0.4)
Haematuria requiring irrigation (%)	0 (0)	4 (0.5)

Legend: SD – Standard Deviation; IQR: Interquartile Range; LHRHa - Luteinizing Hormone-Releasing Hormone analogue; ISUP - International Society of Urological Pathology; MCCL – Maximum Cancer Core Length. Hormone analogue; ISUP - International Society of Urological Pathology; MCCL – Maximum Cancer Core Length.

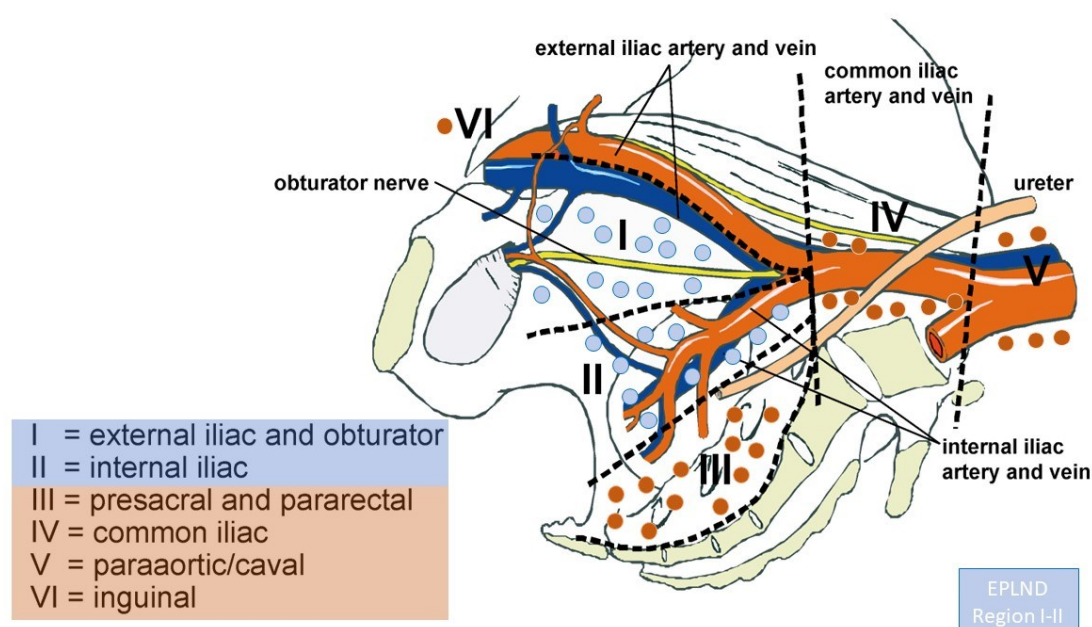
5.4.8 Systemic therapy

Luteinizing hormone-releasing hormone analogue (LHRHa) were commenced in 63/63 (100%) of patients. A single patient (1/63; 1.6%) commenced maximum androgen blockade. In the remaining patients, additional systemic therapy was as follows: docetaxel 34/63 (53.9%), enzalutamide 19/63 (30.2%), and abiraterone acetate 1/63 (1.6), respectively.

5.4.9 Suitability for surgical resection

Surgical irresectable disease was present in 28/63 (48.6%) patients. Overall, 42/63 (66.7%) with suspicious nodal (N1) disease on pre-biopsy.

Figure 12. Anatomical mapping of MRI lymphatic nodal metastasis per patient, presented by PLND surgical template



Legend: Graphic circles represent each individual patient with nodal metastasis displayed per anatomical region I-VI. ePLND coverage region I-II. Number of patients with nodal metastasis per region: I-II (n=22); III (n=12), IV (n=8), V (n=5), VI (n=1). Patients may appear in more than one region to present extent of disease patterns. Inter-region graphic location of nodal metastasis is representative. Reproduced with permissions (Appendix A) from European Urology [Elsevier]. Mattei, A., et al. 2008. The template of the primary lymphatic landing sites of the prostate should be revisited: results of a multimodality mapping study. European Urology, 53(1), pp.118-125.

5.4.10 Suitability for minimally invasive ablative therapy

Following review disease not amenable to ablation therapy due to direct invasion of surrounding structures was present in 28/63 (48.6%) patients. Furthermore, based on MRI features alone 20/63 (38.1%) would be planned for focal MIAT and 42/63 (68.3%) would require whole gland MIAT approaches.

5.5 Discussion

This is the first study, to our knowledge, to report on the clinical and histological outcomes of patients presenting with *de novo* mHSPC who arise in a modern pre-biopsy mpMRI prostate cancer diagnostic pathway, with a restricted favourable performance status. The key findings of this study are that patients with *de novo* synchronous mHSPC are infrequently diagnosed within such a pathway (4.3%). However, when present, MRI T4-stage disease (48.6%), surgically irresectable (48.6%), diffuse high volume intraprostatic lesions (Median MTD 36.4 mm [IQR 16.47]), Gleason >8 disease (66.6%) are commonplace prior to systemic therapy being commenced. Despite concerns of higher complication rates in patients with mHSPC, transperineal MRI targeted biopsy of the primary appears safe in this sub-group (Clavien-Dindo $\geq$ II; 1.6%) and the single case of sepsis one of the rare cases seen overall in the RAPID series of 1,042 cases biopsied transperineally (215).

The routine integration of pre-biopsy MRI has occurred in recent years, limiting directly comparable literature. However, MRI has been previously validated in the detection of bone metastasis prior to radical treatment (222,223). In Woo and colleagues retrospective series of 308 patients with newly-diagnosed prostate cancer, marginally higher rates of *de novo* synchronous metastatic disease were observed (21/308; 6.8%) (223). The study's primary focus was to report upon the sensitivity (95.2%), specificity (99-100%), positive predictive value (86.9-100%), and negative predictive value (99.7%) of MRI for bone metastasis detection. Similar to our study, isolated bone metastasis in an anatomical location not covered by the MRI prostate protocol was extremely rare (1/308; 0.32%) (223).

Furthermore, Vargas and colleagues performed a retrospective study of 3,765 patients undergoing an MRI for newly-diagnosed prostate cancer, reporting the incidence of *de novo* synchronous metastatic disease to be lower at 1.5% (57/3765) (222). As with our study, no metastatic disease was seen in patients with Gleason < 7 and/or cT2 disease.

In patients with established metastatic disease baseline MRI-tumour volume was larger than previously reported in non-metastatic studies (216,218,224). For example, our reported study median MTD was 36.4 mm (IQR 16.47), this compares to a median MTD of 18.0 mm (IQR 11.0) reported in a study of patients with high-risk localised disease (216). Our reported findings that a significant trend towards larger MRI-tumour volumes in higher Gleason Grade / ISUP Groups and ascending MRI-Tumour stage is in keeping with previous findings reported in high-risk non-metastatic disease (216,218). Whether such MRI-derived tumour volumes retain a similar negative oncological impact in patients who have already developed distant disease at baseline a current unknown.

In previous non-metastatic studies, absolute MTD ≥ 20 mm has been reported as a significant risk factor for the presence of lymph nodal metastasis (68.4% N0 vs 31.6% N1; $p = 0.02$) (224). In our study, all patients had distant disease at baseline. There was a non-significant trend towards larger MRI-tumour volumes in MRI node positive disease when compared to MRI node negative disease, the clinical significance of this however is unclear (37.7 mm vs 33.7 mm; $p = 0.14$).

In high-risk non-metastatic disease sequential MRI and derived MRI-tumour volume response, when performed as part of analysis of neoadjuvant systemic therapy to radical prostatectomy, has been shown to have prognostic value (225). It is plausible to consider that in the mHSPC setting, where all patients primarily undergo systemic therapy, that using sequential MRI to monitor tumour volume changes in a similar fashion may have prognostic value in determining which patients may benefit most from additional local cytoreductive approaches.

The proposal of both cRP and MIATs as alternatives to cytoreductive local prostate radiotherapy have led us to evaluate the feasibility of performing these interventions routinely (3,16,37,114,123,124,226). Firstly, if we consider cRP, in this study almost half of all patients (28/63; 48.6%) had surgically irresectable disease when their baseline mpMRI prostate was reviewed. Furthermore, irresectable pelvic sidewall disease was present in 11/63 (17.4%) and distant (M1a) nodal metastasis in 6/63 (9.6%). This raises the question of the size of the cohort of patients who would be routinely eligible for cRP and ePLND clearance.

However, this of course does not account for the debulking effect of ADT, contemporary ARSI's and chemotherapy, respectively. Comparisons can be drawn from Hajili and colleagues observational study of 116 patients with cT4 disease at baseline who underwent neoadjuvant ADT prior to radical prostatectomy (227). In this study direct rectal lesions at surgery were only encountered in 2.5% ($n=3$) and no cases were abandoned intraoperatively due to irresectable disease (227).

Such historical studies utilised digital rectal examination and diagnostic transrectal ultrasound (227). We therefore will need to wait for the contemporary randomised cRP studies, such as the IP2-ATLANTA internal pilot, where baseline and pre-operative but post-systemic therapy MRI were mandated (228). The results of this are presented in **Chapter 7** of this thesis. This will allow us to ascertain whether adverse baseline MRI features of the primary prostate and pelvis remain consistent and are indeed predictive of inoperability following contemporary systemic therapy.

Furthermore, if we consider minimally-invasive ablative therapies (122-124). Cyto-reductive whole-gland cryotherapy is the most extensively evaluated MIAT to date, demonstrating a median failure-free survival advantage of 18 months, in a recent propensity-scored matched analysis against ADT alone (39 versus 21 months; $p = 0.005$) (122). In our study, mpMRI reported only a third of patients (20/63; 31.7%) had an “MRI index” lesion at baseline (229). Notwithstanding, the aforementioned intraprostatic debulking effect of systemic therapy, it is clear that the vast majority of patients would require whole-gland prostate ablation if cyto-reductive MIAT were to be routinely considered as a routine treatment option.

The residual post-systemic therapy gland size would also impact upon the most suitable and safe energy modality permissible. In addition, as with cRP, the persistence of rectal invasion post-systemic therapy would likely preclude most MIAT approaches due to higher operative risks, albeit the size of this subgroup is currently unknown.

However, the results of this study suggest that, if either novel approach is proven a viable alternative to cyto-reductive local prostate radiotherapy, then routine integration would likely have to be alongside, rather than in replacement of cyto-reductive local prostate radiotherapy, given the restricted pool of suitable patients at baseline presentation. This has an impact on the trial design of any randomised studies attempting to evaluate such approaches.

Tissue diagnosis of the primary tumour may have a role in prognostication and systemic agent choice in this cohort of patients (209). Gleason Grade Group >8 disease was present in the majority of patients (42/63; 66.6%). This is in keeping with baseline biopsy findings reported in prior cRP studies (16,37). In addition, cribriform pattern was present in the majority of patients (39/63; 61.9%) and adenocarcinoma with neuroendocrine differentiation in a minority (3/63; 4.8%). Previous high-risk locally-advanced prostate cancer studies, evaluating neoadjuvant Docetaxel followed by radical prostatectomy, have reported the adverse impact of certain baseline biopsy histology (such as cribriform pattern) on relapse free survival and development of nodal metastases (230). It is yet to be delineated whether such baseline histologic findings remain of prognostic value in the setting of established metastatic disease, although this should be considered a focus of evaluation in contemporary cyto-reductive treatment trials.

5.6 Limitations

Although we report on a prospective study, it was not performed within the remit of a clinical trial. Whilst guidance and standard operating procedure were issued for mpMRI acquisition these offered a range of options and thus there was some variation in clinical practice. For the purposes of the research question whole gland ablation or focal ablation recommendations were based on appearance of mpMRI in isolation and did not include an evaluation of biopsy results of areas outside the MRI region of interest. Thus, some patients with MRI index lesions may have bilateral clinically significant disease proven on prostate biopsy that would need to be managed with whole gland ablation, thus number of whole gland ablations is likely to have been underestimated. MRI-tumour volume measurements were performed by a single researcher (MJC) who is a urology registrar, and these did not undergo interobserver variability evaluation. Finally, metastases and nodal disease were confirmed on best available comparator imaging and did not undergo routine molecular PET/CT imaging and/or histological confirmation. This was a pragmatic approach to distant staging and reflects current standard of care in the NHS.

5.7 Conclusion

Patients with *de novo* synchronous metastatic disease uncommonly present within routine pathways. When present, contemporary MRI-targeted transperineal prostate biopsy has a low morbidity and primary tissue diagnosis may have a role in choice of systemic therapy and prognostication. Baseline MRI features suggest a minority of patients are suitable for surgical resection prior to initiation of systemic therapy although further work needs to be performed (see **Chapter 7**).

Those involved in future trial design need to consider whether interval imaging post systemic therapy induction should be considered to facilitate the wider recruitment of patients. The integration of interval imaging may have secondary utility in identifying baseline clinical and radiological predictors in those patients who are most likely to subsequently qualify for cytoreductive surgery and/or minimally invasive ablative therapy at baseline.

Chapter 6 – Designing a randomised controlled trial with novel cytoreductive surgery and metastasis-directed treatments: IP2-ATLANTA

6.1 Overview

In order to ascertain the performance of novel local and metastasis-directed treatments in patients with metastatic hormone-sensitive prostate cancer I designed, in collaboration with my supervisors, a prospective, unblinded, multicentre, randomised controlled trial ($n=918$). The study title was “Additional treatments to the local tumour for metastatic prostate cancer- Assessment of novel treatment algorithms”; acronym “IP2-ATLANTA”. This phase II study included an internal pilot ($n=80$) that forms the basis of my thesis. The study includes multiple specialities (e.g. urological surgeons, clinical oncologists, medical oncologists, radiologists) and their unique inputs into the trial design components were made via the trial protocol development group and intervention arm quality assurance boards, respectively.

This is the first randomised controlled study to evaluate minimally invasive ablative therapy (i.e. cryotherapy, HIFU) and metastasis-directed therapy (i.e. SABR or surgery) in patients with newly diagnosed mHSPC who have commenced contemporary systemic therapy. Sections of this chapter are published in *BMJ Open*⁹ and have been presented at the *American Society of Clinical Oncology (ASCO) Annual Conference* in 2020¹⁰.

6.2 Introduction

Overall, 47,000 men are diagnosed with prostate cancer each year in the United Kingdom (UK) (1). Approximately, 4,500 of these men will be diagnosed with *de novo* synchronous metastatic disease at presentation (1). As with the United States, where just under 8% present with metastatic disease and where the annual burden is predicted to reach approximately 15,000 cases by 2025, so the prediction for the same magnitude is likely for the UK [2].

⁹ Connor, M.J., *et al.* Additional treatments to the local tumour for metastatic prostate cancer- Assessment of novel treatment algorithms (IP2-ATLANTA): protocol for a multicentre, phase II randomised controlled trial. *BMJ Open*. 2021. 1;11(2):e042953.

¹⁰ Connor, M.J., *et al.* Initial experience of the adjuvant treatments to the local tumour for metastatic prostate cancer: Assessment of novel treatment algorithms, a multicentre, phase II randomized controlled trial (IP2-ATLANTA). *Journal of Clinical Oncology*. 2020. 38(15), Supplement TPS5600.

Traditionally, such men were managed with androgen deprivation therapy (ADT) alone, via medical or surgical castration (4). Unfortunately the median time to the emergence of a castrate resistant state is in the order of 11 to 18 months, limiting overall survival (OS) to 3.5 years (5,19). Promisingly, the reported OS in this group has now risen to a median 4.8 years with the addition of upfront systemic agents, such as Docetaxel, Enzalutamide, Abiraterone Acetate or Apalutamide (6-10).

Moving beyond early systemic therapy escalation there has been an increased focus on the role of local cytoreductive and metastasis-directed interventions (primarily stereotactic ablative radiotherapy [SABR]) to gain additional oncological benefit (4). This is in part based upon the emergence of the 'oligo-metastatic state', which may exhibit different biological characteristics to poly-metastatic prostate cancer (11).

Such men present with a clinically-defined favourable metastatic burden, and are hypothesised to occupy an intermediate state between 'locally advanced' and 'poly-metastatic' disease (11,12). It is postulated, but not proven, that men exhibiting such disease patterns gain most benefit in progression-free survival (PFS) and OS resulting from localised cancer control achieved via cytoreductive interventions (4,11). The arguments to support the individual proposed trial interventions have been presented at length in the preceding parts of this thesis (**Chapters 1 & 2**) and are thus not reproduced here for brevity.

In this chapter we present a detailed overview of the design of the IP2-ATLANTA randomised controlled trial, and the internal pilot, detailing the rationale and events that supported the delivery of the successful multicentre randomised pilot study on which this thesis is based.

6.3 Study hypothesis

We hypothesised that patients with metastatic hormone-sensitive prostate cancer who undergo treatment of the local tumour in the form of either radical therapy (cytoreductive radical prostatectomy (CRP) or external-beam radiotherapy (EBRT)), or minimally invasive ablative therapy (MIAT), combined with metastases-directed therapy (MDT), will improve progression-free survival in comparison to patients who receive standard of care treatment alone.

6.4 Methods Part A: Study Population, Patient Involvement and Eligibility

6.4.1 Study population

Patients who were willing to undergo local therapy to the prostate and selective metastases-directed therapy for newly diagnosed metastatic prostate cancer in addition to standard of care systemic treatment.

6.4.2 Patient and public involvement

A patient-involvement focus group was held with six patients who had advanced or metastatic prostate cancer, to determine initial patient acceptability and gauge important opinions on the proposed study design. Four patients had previously received radiotherapy as either their primary or secondary treatment. Comments from the group discussion were recorded along with anonymous questionnaires, which the patients returned, by post after the meeting. Two patient and public involvement (PPI) representatives were present during the HRA REC assessment. These patients continue to be involved throughout the IP2-ATLANTA trial, within the Trial Management Group. Finally, additional patients are involved in the direct management of the study via their respective roles in the independent Trials Steering Committee.

6.4.3 Patient identification of patients & consent

There was broad agreement from the trial protocol development group that patients should be selected from the multidisciplinary team meeting (MDT). As described in **Chapter 5** of this thesis, reliance on community prostate cancer referral pathways alone was unlikely to yield a high level of recruitment. The MDT meeting offers the ability for direct referral from oncology, incidental findings on radiology (e.g. sclerotic bone metastasis of unknown primary) and linked MDT discussions with haematology to broaden the number of patients identified for trial consideration through screening.

Members of the MDT identified patients suitable for IP2-ATLANTA. Treating clinicians mentioned the study at the time or shortly following diagnosis. Then the local research nurses/fellows, clinical trial coordinators, clinical trial practitioners or the treating clinicians approached interested patients. In the case of Imperial College Healthcare NHS Trust (Site A1), West Middlesex University Hospital (Site A4), Chelsea and Westminster NHS Foundation Trust (Site A9) patients in the pilot study were recruited directly by the national trial research fellow Mr Martin Connor.

A Patient Information Sheet (PIS) was provided (**Appendix D**) or if agreed, emailed or posted out to the patient. Those patients already aware of their diagnosis were approached by telephone to enquire as to their interest in the study so that a PIS could be sent out by email or post prior to a clinical visit. Patients were given as much time as they needed to read the PIS before consenting to participate, with a minimum of 24 hours stipulated.

6.4.4 Agreement on eligibility criteria

Table 12 presents the eligibility criteria for the IP2-ATLANTA study. Incorporating surgical cytoreduction and minimally invasive ablative therapy into metastatic disease is highly novel. Thus a point-by-point explanation of the final eligibility criteria follows.

Table 12. Eligibility Criteria IP2-ATLANTA

Inclusion Criteria	
(i)	Diagnosed with prostate cancer within 6 months of screening visit
(ii)	Metastatic disease (Any T, Any N, M1+) of any grade, stage or Prostate Specific Antigen (PSA) level
(iii)	Fit to undergo standard of care systemic treatment for metastatic disease and both minimally invasive therapy and prostate EBRT/cytoreductive radical prostatectomy
(iv)	Performance status 0-2
(v)	Histologically-proven local tumour
Exclusion Criteria	
(i)	Patient did not undergo and/or is unable to undergo standard of care baseline imaging tests for confirmation of metastatic status (CT abdomen/pelvis AND chest X-ray (or CT chest) AND radioisotope bone scan (or whole body imaging such as MRI or PET imaging as alternative to all preceding scans mentioned here) AND prostate MRI
(ii)	Prior exposure to long-term androgen deprivation therapy or hormonal therapy for the treatment of prostate cancer unless started within 6 months of screening visit
(iii)	Prior chemotherapy or local or systemic therapy for treatment of prostate cancer (apart from ADT or hormonal therapy as outlined above)

Legend: T – Tumour, N – Nodes, M – Metastasis (M1a-c); PSA – Prostate specific antigen; EBRT – External beam radiotherapy; MRI – Magnetic Resonance Imaging; PET – Positron Emission Tomography; CT – Computed Tomography; ADT – Androgen Deprivation Therapy.

6.4.4.1 Inclusion Criteria

(i) Diagnosed with prostate cancer within 6 months of screening visit

This enabled patients to be recruited prior to castrate resistance and provided a pragmatic window of opportunity to complete all baseline investigations (including MRI and prostate biopsy) for study entry. Both of these may not have been routinely performed in this cohort of patients, depending on their local NHS site. Furthermore, this enabled comparability to prior studies in the literature using cytoreductive EBRT, which have also adopted this threshold (15,16).

(ii) Metastatic disease (Any T, Any N, M1a-c) of any grade, stage or Prostate Specific Antigen (PSA) level

We have decided not to apply limitations on Tumour or Nodal staging in our trial design, allowing the full range of patients to enter the study. This was in part due to the acknowledgment that ADT with Docetaxel or ARSI's is likely to have a significant change on both of these characteristics prior to any proposed local treatments, as discussed in **Chapter 5** of this thesis.

Distant disease staging (M1a-c) is a rapidly evolving space with conventional imaging (such as CT and Bone Scintigraphy) being augmented by Prostate-Specific Membrane Antigen (PSMA)-targeted imaging in some academic centres (231). This is particularly apparent in high-risk, presumed localised, prostate cancer following the results of the proPSMA study demonstrating superior diagnostic accuracy of first line Ga⁶⁸ PSMA-PET/CT over conventional imaging (231). PSMA PET/CT imaging can identify “micro-” or “early-” oligometastatic disease, in the same vein “oligometastatic” may also appear as “poly-metastatic” (232). This has a downstream impact on the accurate assignment of metastatic burden definitions, used in prior oncology studies. Therefore, generating robust distant staging criteria for a trial that also takes account of the changing landscape and potential risk of a ‘Will Rogers’ effect of stage specific migration is a significant challenge to clinical trialists (12,232).

In the current literature, SWOG 1802, NCT03988686, NCT01751438 and FUSCC-OMPCa are limited to disease identified on conventional imaging and MRI (228). The g-RAMPP and TRoMbone protocols allowed for both conventional imaging and PET/CT. We designed IP2-ATLANTA to permit, both modalities, but derives metastatic burden from conventional components of the imaging performed to mitigate against this stage migration effect. Similar to prior oncology trials, this trial has a pre-specified low-burden subgroup (CHAARTED definition) that will ensure equal low and high disease burden representation across all trial

arms through our randomisation approach (10). As described, in the subsequent section on stratified randomisation.

(iii) Fit to undergo standard of care systemic treatment for metastatic disease and both minimally invasive therapy and prostate EBRT/cytoreductive radical prostatectomy & (iv) Performance status 0-2.

The application of these eligibility criteria protect patients who would not be medically fit for, and likely not benefit from, the subsequent trial intervention from being recruited into the study. As detailed in the later stages of this chapter the radical trial design (cRP or EBRT), uniquely provided the opportunity to recruit patients into this arm who are no fit for cRP in isolation.

(v) Histologically-proven local tumour

As discussed in **Chapter 5**, transperineal prostate biopsy appears safe in these patients. Prostate biopsy confirms prostate cancer as the primary and may have a role in prognostication in future. Finally, in the internal pilot of this trial sequential biopsy data was compared to ascertain the persistence of a primary tumour following initiation of systemic therapy.

6.4.4.2 Exclusion Criteria

(i) Patient did not undergo and/or is unable to undergo standard of care baseline imaging tests for confirmation of metastatic status (CT abdomen/pelvis AND chest X-ray (or CT chest) AND radioisotope bone scan (or whole body imaging such as MRI or PET imaging as alternative to all preceding scans mentioned here) AND prostate MRI

All patients underwent staging imaging to confirm there is distant (M1+) metastatic disease. Pre-biopsy mpMRI prostate has an important role in the new prostate cancer diagnostic pathway (**Chapter 5**). In our study all patients in the experimental treatment arms underwent a second prostate MRI post systemic therapy. This post-systemic therapy prostate MRI was converted to optional in the main study. To enable reporting on the radiological changes observed in the local tumour and pelvis following contemporary systemic therapy and their correlation to repeat histological evaluation of the prostate. Our study will also provide data on the role of serial prostate MRI in planning for cytoreductive surgery and ablative therapies (233).

(ii) Prior exposure to long-term androgen deprivation therapy or hormonal therapy for the treatment of prostate cancer unless started within 6 months of screening visit & (iii) Prior chemotherapy or local or systemic therapy for treatment of prostate cancer (apart from ADT or hormonal therapy as outlined above)

Long-term exposure to androgen deprivation therapy or hormonal therapy risked the development of a castrate resistant state in some patients prior to local intervention. This would also reduce the standardisation of the study population to be investigated

Table 13. Summary of standard operative procedures written for the IP2-ATLANTA trial

Standard Operating Procedure	Relevant Trial Arm	Authors
<i>Systemic Therapy</i>	All trial arms	Mr. M.J. Connor Dr. N. Sarwar Prof. H.U. Ahmed
<i>Metastasis Directed Therapy</i>	Intervention Arm 1* Intervention Arm 2*	Mr. M.J. Connor Mr. V. Khoo Mr. T. Dudderidge Mr. M. Winkler
<i>Cytoreductive Local Radiotherapy</i>	Intervention Arm 1 Control Arm*	Mr. M.J. Connor Ms. O. Naismith Prof. J. Staffurth
<i>Cytoreductive Radical Prostatectomy +/- (Extended) Pelvic Lymph Node Dissection</i>	Intervention Arm 2	Mr. M.J. Connor Mr. T. Dudderidge Mr. M. Winkler
<i>Cytoreductive Minimally Invasive Ablative Therapy (MIAT)</i>	Intervention Arm 1	Mr. M.J. Connor Mr. T. Shah Prof. H. Ahmed
<i>Laparoscopic or Robotic-Assisted Laparoscopic (Extended) Pelvic Lymph Node Dissection following MIAT</i>	Intervention Arm 1 ⁺	Mr. M.J. Connor Mr. T. Dudderidge Mr. M. Winkler Prof. H.U. Ahmed
<i>Post systemic therapy biopsy</i>	Intervention Arm 1 Intervention Arm 2	Mr. M.J. Connor Prof. H.U. Ahmed
<i>Central Histopathology Review</i>	Intervention Arm 1 Intervention Arm 2	Mr. M.J. Connor Dr. M. Yeung Dr. A. Smith Dr. H. Markham Prof. H.U. Ahmed

*Legend: *Patients with low burden only, declared prior at randomisation for metastasis directed treatment at study entry. *Patients with clinical pelvic nodal metastatic disease (N1) at study entry declared for*

*treatment prior at randomisation at study entry. All standard operative procedures (SOP) are presented in full in **Appendix F** of this thesis.*

6.5 Methods Part B: Trial Design, Interventions, Statistical Analysis and Endpoints

6.5.1 Control arm: agreement on standard systemic therapy (SST)

Historically, most patients have undergone at least six cycles of docetaxel, thus requiring a 6 to 8-month period post-diagnosis to complete this treatment (10). Recent advances in systemic agents have led to a wider landscape of drug therapies which include anti-androgen compounds (such as Enzalutamide, Abiraterone Acetate and Apalutamide) (4,31,37,193). What truly constitutes ‘standard systemic therapy’ (SST) is thus constantly debated. For trialists in this space, restricting men to historical agents with higher risks or greater side-effects may impact on acceptability of the study by patients and clinicians. This was the case in TroMbone, where the study was designed with ADT monotherapy and required a major amendment to permit additional systemic agents to enable accrual (114). As such, all recruiting RCTs in this space permit oncologists to use ADT with or without any systemic agent. However, the minimum duration of time on other antiandrogen agents required prior to local treatment, is not known.

As trialists we had a difficult choice between a narrow prescription of SST that would risk limitation on future recruitment and managing a heterogenous pool of SST that may have an impact on components (i.e. radiological, biochemical) of chosen progression-free survival composite. Comparatively, in SWOG 1802 all SST agents that are permitted by the National Comprehensive Cancer Network (NCCN) guidelines are permissible for use upfront in the trial. SWOG 1802 study requires 22 to 28 weeks of SST prior to local treatment (cRP or EBRT). Finally, in the TroMbone study patients underwent cRP within 12-months from initiation of SST.

Following consensus within our trial development protocol group, we decided that SST in IP2-ATLANTA was to be determined by the treating clinician and would be declared upfront prior to randomisation. This gave us the ability to incorporate such decision making into the stratified randomisation, as described in subsequent sections, and introduced an element of control into the proportion of SST agents present in each trial arm.

Our trial schedule for local treatment was design to standardise the length of exposure of ADT +/- ARS’I/Docetaxel across all arms (32 [+/-12] weeks), as set out in the SOP on standard systemic therapy (**Table 13; Appendix F** [M. Connor, N. Sarwar , H.U. Ahmed. Systemic Therapy SOP]). Chosen STT was made with reference to the current National

Institute Health and Care Excellence (NICE) guidelines and with respect to the regional NHS clinically commissioned (206). Prior to COVID-19, Docetaxel was recommended for use in all patients in England and Wales with newly diagnosed metastatic prostate cancer who did not have significant co-morbidities (206,234). However, the perceived risks of Docetaxel based chemotherapy during the pandemic resulted in the emergency licensing of Abiraterone Acetate and Enzalutamide as alternative first-line options in England and Wales. As we had designed IP2-ATLANTA to accommodate such changes, there was no requirement to change the trial design. It should be noted that NHS Scotland had approved Abiraterone Acetate prior to the pandemic via NHS Scotland clinically commissioned guidelines on metastatic prostate cancer (206,235). Although, no Scottish trial sites were opened during the internal pilot.

6.5.2 Control arm: interventions beyond SST

Another challenge we faced was how to manage prostate EBRT for low volume patients in any SOC comparator arm, following the results of STAMPEDE Arm-H (16). The IP2-ATLANTA trial was submitted to the HRA/REC at the time of the STAMPEDE Arm-H publication arising, this publication specifically supported the additional benefit of EBRT to the prostate at reduced dose/fractionation in a low burden subgroup of patients. The IP2-ATLANTA trial protocol development group was cognisant of this evolving change in future standard of care practice in the UK.

As such we designed IP2-ATLANTA so if local prostate radiotherapy was planned for local disease patients with low burden metastases in the event they should be randomised to the control arm, then this treatment intent would need to be declared prior to randomisation by the treating clinician. For patients with low burden disease, EBRT prostate radiotherapy was permitted and defined by the Local Radiotherapy SOP (**Appendix F** [M. Connor, O. Naismith, J. Staffurth]), which reflected the current NHS clinically commissioned guidelines (191).

The use of pelvic lymph node radiotherapy, whole pelvis radiotherapy and/or metastasis directed radiotherapy or SABR was not be permitted in the control arm. Palliative prostate radiotherapy for locoregional symptom control (e.g. refractory haematuria) in patients with high burden metastases was permitted as per local clinical practice. Palliative bone radiotherapy for symptoms (e.g. bone pain) and prevention of fracture was also permitted in all patients as per local clinical practice.

The adoption of this approach was pragmatic, as we recognised that offering patients a ‘no local treatment’ versus ‘EBRT/cRP/MIAT’ study was unlikely to be accepted by patients, who could regard this as risk of losing access to the current standard of care treatments offered by the NHS. European experiences from the g-RAMPP trials early closure, which adopted such a design, suggests this design is not broadly accepted by patients or clinicians(228).

Finally, we recognised that there were a list of commonly occurring locoregional complications of metastatic prostate cancer (e.g. refractory haematuria, malignant ureteric obstruction, malignant bladder outflow obstruction, urinary incontinence) that may require intervention in all trial arms (e.g. suprapubic catheter insertion, channel transurethral resection of the prostate, ureteric stent insertion, nephrostomy insertion)(236). In addition, emergency complications include malignant spinal cord compression and cauda equina syndrome. Our trial did not seek to re-iterate the well-established standard of care approaches to the management of these. In keeping with prior large oncology trials, such cases were left to the local treating trial clinicians, but were recorded via the adverse events and serious adverse events data collection mechanism (8).

6.5.3 Experimental Treatment Arms

6.5.3.1 Experimental treatment development groups & quality assurance boards

The introduction of IP2-ATLANTA into the management of mHSPC patients in the United Kingdom represented a significant change in clinical practice for such patients. Notably, the introduction of urological surgeons and sub-specialty clinical oncologists (i.e. for SABR delivery) into this disease space required close collaboration and careful oversight.

With my supervisors, we therefore decided at time of submission to REC and HRA that all experimental treatment arms would have a dedicated development group to assist in the generation of SOPs for the treatment options (**Figure 13**; **Table 14**). In addition, it was important to have a reciprocal quality assurance mechanism for each trial treatment arms (**Table 14**). Some naturally fell into existing national bodies e.g. radiotherapy oversight by the UK Radiotherapy Trials Quality Assurance (RTTQA). Whilst others would require us to generate our own in-house quality assurance structures.

Table 14. Experimental trial treatment development groups and associate quality assurance (IP2-ATLANTA)

Trial Treatment Development Groups	Members	Quality Assurance
<i>Cytoreductive Local Radiotherapy</i>	Prof. J. Staffurth (Co-lead) Dr. A. Falconer (Co-lead) Dr. S. Mangar Dr. V. Khoo Mr. M. Connor Ms. O. Naismith (RTTQA)	UK Radiotherapy Trials Quality Assurance (RTTQA): EBRT Section
<i>Stereotactic Ablative Radiotherapy (SABR)</i>	Dr. V. Khoo (Lead) Prof. H. U. Ahmed Mr. M. Connor	UK Radiotherapy Trials Quality Assurance (RTTQA): SABR Section
<i>Cytoreductive Surgery (incl. MDT approaches)</i>	Mr. M. Winkler (Co-lead) Mr. T. Dudderidge (Co-lead) Prof. N. Soomro Mr. P. Cathcart Mr. M. Connor	ATLANTA Surgeons Quality Assurance Board (members as per development group)
<i>Cytoreductive Minimally Invasive Ablative Therapy (MIAT)</i>	Prof. H. U. Ahmed (Lead) Prof. I. Shergill Mr. S. McCracken Mr. T. Dudderidge M. T. Shah Mr. M. Connor	ATLANTA MIAT Quality Assurance Board (members as per development group)

Legend: All standard operative procedures (SOP) are presented in full in **Appendix F** of this thesis.
SABR – Stereotactic ablative radiotherapy; RTTQA - Radiotherapy Trials Quality Assurance.

6.5.3.2 Intervention Arm 1: Cytoreductive MIAT with or without PLND

Cytoreductive MIAT to the prostate involved a number of considerations and these are discussed in greater detail in **Chapter 10** of this thesis. Firstly, we were required to consider which ablative techniques should be used and who to approach with simultaneous PLND.

It was unknown what effect contemporary systemic agents would have on the tumour volume and local invasion of patients with mHPSC a various disease burdens. The cytoreductive MIAT trial treatment developments group met and considered the current literature. Prior studies are extremely limited but those exploring cytoreductive cryotherapy had excluded T4 disease (120,123,124). However, such studies had utilised ADT without

contemporary systemic therapy, which was hypothesised to provide greater tumour debulking. The consensus suggested that rather than altering the entire trial inclusion criteria, T4 disease could be included and this reviewed at the pilot stage.

Finally as the extent of total prostate volume cytorreduction was unknown. We permitted the use of cytorreductive cryotherapy or high-intensity focused ultrasound [HIFU], as detailed in **Chapter 10**. Briefly, it was agreed that patients with peripheral zone tumours in glands with an anterior-posterior (AP) height of ≤ 3 cm may undergo either cytorreductive cryotherapy or HIFU. Patients with peripheral zone tumours in glands with an AP height of ≤ 3 cm underwent either cytorreductive cryotherapy or HIFU.

Clearly, one of the benefits of MIAT is the ability to minimise tissue ablative and thus potentially local treatment side effects, as such focal approaches were adopted where baseline histology and mpMRI suggested areas without csPCa were present. In cases of bilateral clinically significant disease either of the following treatment plans were utilised: Anterior or Posterior Extension, Hockey stick, subtotal with either anterior or posterior sparing or a whole-gland treatment. Seminal vesical treatment for T3b disease was permitted to both SVs if deemed feasible by the treating clinician and either HIFU or cryotherapy may be used. It was agreed that seminal vesical disease of >10 mm is better treated with cryotherapy.

Clearly, there was a need to target lymph nodes to ensure there was comparable treatments across trial arms (i.e. cRP + PLND or EBRT + PLNRT). However, this had never been performed outside of cadaveric studies. This was the most experimental SOP and the group took guidance from the ATLANTA surgical co-leads (Mr Winkler & Mr Dudderidge) to develop an approach where minimally invasive (Robotic-Assisted Laparoscopic or Laparoscopic) PLND was performed based on presence of resectable nodal disease, patient fitness and consent/discussion with operating surgeon, as set out in the trials MIAT with PLND SOP (**Appendix F** [M. Connor, M. Winkler, T. Dudderidge]).

Patients who are underwent cytorreductive MIAT, were not permitted to have local prostate radiotherapy. However, radiotherapy could be administered for palliative reasons (e.g. refractory haematuria, pain) in progressive disease. We adopted an open door policy in the internal pilot of this study, actively encouraging cases to be referred for multidisciplinary discussion to the IP2-ATLANTA MIAT Quality Assurance Board.

6.5.3.3 Intervention Arm 2: Radical therapy (cytorreductive radical prostatectomy or EBRT)

It was agreed within the IP2-ATLANTA protocol development that radical therapy treatment arm should involve either: i) cytorreductive radical prostatectomy, with or without PLND, or ii) prostate EBRT, with or without simultaneous PLNRT. This permitted the entry of all patients,

irrespective of the need to confirm ability to perform surgical resection. Furthermore, such a design now reflects that of the other multi-modal treatment RCT, SWOG 1802 recruiting in the United States (NCT03678025) (237). The actual modality chosen in this arm was based on physician and patient preference as well as patient co-morbidities and performance status.

The surgical technique used was at the discretion and expertise of the surgical team but had to reflect current UK surgical practice, laid down in the cytoreductive radical prostatectomy SOP (**Appendix F**; [M. Connor, M. Winkler, T. Dudderidge]). Trial surgeons must have met minimum case volume and optimal complication outcomes prior to operating in the trial. This was achieved by signing a self-declaration form. These were peer-approved by the IP2-ATLANTA Surgeons Quality Assurance Board. Those patients who underwent cRP, could not have prostate radiotherapy as part of the intervention. However, it was agreed that radiotherapy can be given subsequently for palliative reasons, as previously discussed in cytoreductive MIAT arm.

Following consensus discussions in the cytoreductive local radiotherapy trial arm development group, we agreed that the broad principles of pelvic nodal treatment within the study will follow those of the PIVOTALboost study (nodal arm-B), with variation to allow both dose and fractionation regimes (238). Two local prostate radiotherapy dose and fractionation options were available:

- **60Gy in 20 fractions.** Treating the prostate to 60Gy and the seminal vesicles to 47Gy using a simultaneous integrated boost administered over 27 days. If the pelvic lymph nodes were to be treated then this was performed simultaneously to a dose of 47Gy in 20 fractions (if treated).
- **74-78Gy in 37-39 fractions.** Treating the prostate to 74-78Gy and the seminal vesicles to 60Gy, using a simultaneous integrated boost. If the pelvic lymph nodes were to be treated then this was performed simultaneously to a dose of 55Gy in 37-39 fractions (in accordance to same fractions employed for treating the prostate and seminal vesicles).

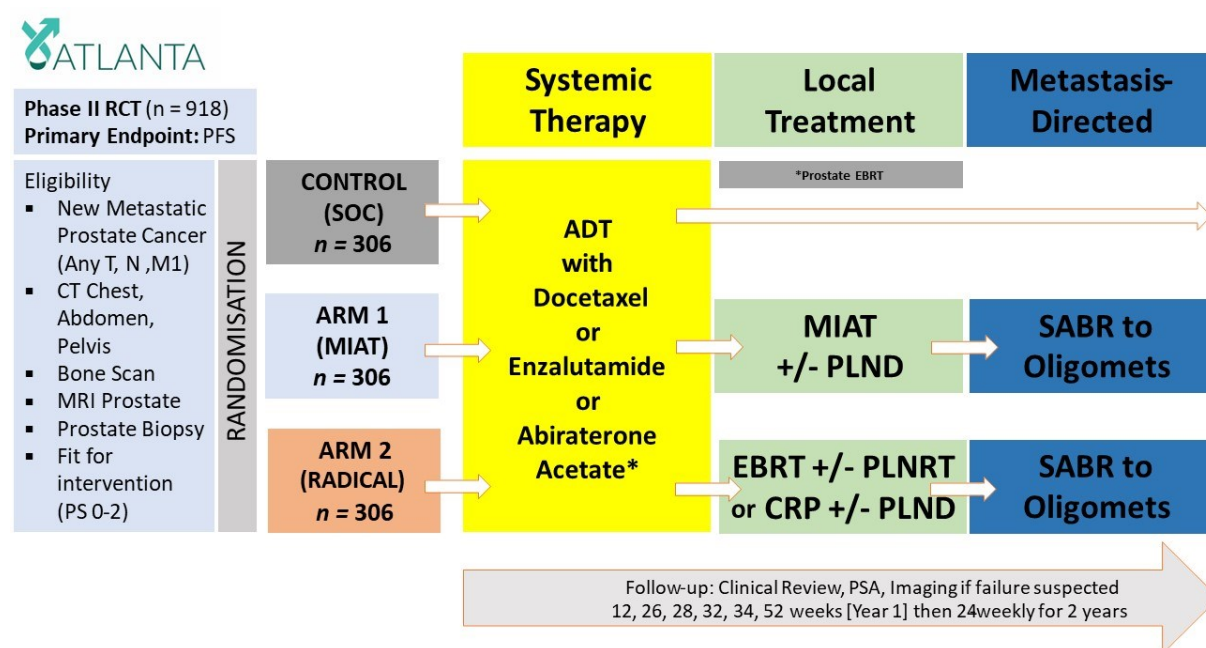
We were able to utilise the Staffurth and colleagues' (2017) "PIVOTALboost Trial Lymph Node Contouring Instructions & Atlas" with the kind agreement from the PIVOTALboost trial steering committee (238). Quality assurance for radiotherapy was completed by the RTTQA.

6.5.3.4 Intervention arm 1 & 2: Metastasis-directed therapy

In men with low-burden disease in both intervention arms 1 and 2, MDT, was permitted but intent-to-use MDT had to be declared prior to randomisation. In the case of a metastatic recurrence after MDT, a re-treatment with MDT was allowed if there were new metastatic areas/locations. The imaging reporting of metastases as well as doses and protocol for MDT was pre-defined and determined by the Imaging Reporting SOP and Metastases-Directed Therapy SOP (**Appendix F** [M. Connor, V. Khoo, T. Dudderidge, M. Winkler]).

SABR was prohibited whilst concurrent chemotherapy was being delivered. Concurrent hormonal therapy was acceptable. SABR delivered to metastases had to be completed within 3 months of allocated local treatment: prostate radiotherapy +/- PLNRT OR cytoreductive radical prostatectomy +/- PLND OR MIAT +/- PLND. Constraints on the dose and fractionations by anatomical site mirrored those defined in the established SABR UK consortium guidelines v.6.1 guidelines (2019) or, if absent, in the open CORE Trial Radiotherapy, Planning & Delivery guidelines v.2.0 (2018) (141,239). The quality assurance for SABR was completed by the RTTQA body in a similar fashion to cytoreductive radiotherapy in this study.

Figure 13. Study overview for IP2-ATLANTA, a phase II, randomised controlled trial



*Legend: CRP, cytoreductive radical prostatectomy; EBRT, external beam radiotherapy; MIAT, minimally invasive ablative therapy; PLND, pelvic lymph node dissection; PLNRT, pelvic lymph node radiotherapy; RCT, randomised controlled trial; SOC, standard of care. *Systemic therapy is not limited to listed agents. *Prostate only EBRT may be performed in selected men with low-burden disease, if declared prior to randomisation and local SOC. [Reproduced from: Connor, M.J. et al. Additional Treatments to the Local tumour for metastatic prostate cancer-Assessment of Novel Treatment Algorithms (IP2-ATLANTA): protocol for a multicentre, phase II randomised controlled trial. *BMJ Open*, 11(2). 2021]*

6.5.4 Revisiting the primary tumour prior to local treatment

There is residual uncertainty of the impact that SOC systemic treatment may have on down-staging the local tumour. As the SOC systemic treatment was administered prior to any local MIAT or CRP/EBRT in intervention arms 1 and 2, an attempt at reclassifying the residual disease with a prostate MRI and biopsies was a pragmatic approach. This aimed to prevent patients from developing adverse events from unnecessary local treatment when they have no evidence of “residual intraprostatic disease”. We had planned patients with positive post-SOC biopsies would then receive the local treatment as outlined below. Gleason Grade Group and PI-RADS scoring systems were not developed for post systemic therapy classification, with many now not allocating these in this setting.

As we do not know the biological significance of volume of residual disease after SOC systemic therapy, even if determined to be low-volume, local treatment was performed as per allocated randomisation. Re-classification prostate biopsy and MRI at 6-9 months from initiation of SOC systemic therapy were mandated as part of the protocol during the internal pilot RCT.

Unfortunately, COVID-19 pandemic resulted in the inability to perform additional hospital visits and research interventions in these patients. This was due to the complete cessation of all additional investigations within the NHS and in particular the group of patients were deemed at highest risk due active immunosuppressant chemotherapy. These patients were advised to shield under government guidance as extremely vulnerable.

Rather than removal from the study, it was agreed that patients could receive a research biopsy on table immediately prior to delivery of cytoreductive MIAT. In the radical arm, whole mount prostatectomy specimens could replace repeat biopsy histology. Patients undergoing radical radiotherapy were still offered a prostate biopsy where COVID-19 clinical restrictions permitted. To a lesser extent there were restrictions on research imaging (including a second MRI) in some centres. The absence of post systemic therapy prostate biopsy and/or MRI were added to a list of expected Covid-19 Related Protocol Deviations, and are reported separately in **Chapter 7**.

These changes still allowed us to obtain a point estimate of the magnitude of this intraprostatic response and also a degree of patient acceptability of a post-systemic therapy prostate biopsy in the pilot RCT patients (240-243). Taken collectively the results will assist us in determining their ongoing utility in the main study component, where they are were not planned to be mandated.

6.5.5 Statistical considerations and sample size calculations

6.5.5.1 Randomisation approach

During the development of the trial we recognised that a number of patient factors could significantly impact upon the primary endpoint of Progression-Free Survival. As simple chance randomisation does not lead to representative balance of such variables we employed “stratified randomisation” (244,245).

Briefly, stratified randomisation is a two-stage procedure in which trial participants are first grouped into “strata” according to “clinical features (or variables)” that may influence outcome risk (244). Within each stratum, patients are then assigned to a trial arm according to separate randomization schedules. The total number of strata is the product of the number of levels of each factor in the process (244).

In this study, we performed permuted block randomisation, as described by Mats and Lachin (245), allocating the three treatment arms at a 1:1:1 ratio to random block sizes of 3,6,9,12 and 15. Variables were drawn from discussions held with my supervisor (Prof. Hashim Ahmed) and our co-investigators, with evidence drawn from non-systematic and systematic literature searches completed in **Chapter 2** and **Chapter 3** of this thesis. In total, 16 strata were established from 4 stratification factors:

- I. Intent to treat pelvic lymph nodes?: yes versus no*
- II. Metastatic burden: low versus high (CHAARTED definition) (10).*
- III. Intent to use systemic agent (i.e. Chemotherapy/ARSI)?: yes versus no*
- IV. Intent to use metastases directed therapy?: yes versus no*

6.5.5.2 Internal pilot

We were seeking to determine whether the randomisation of men with metastatic disease is feasible and whether men are compliant to the therapy following randomisation. We aimed to approach 80 patients from up to 17 centres in the UK over a 6-month period to allow us to estimate a 33% recruitment rate with 95% confidence interval width of approximately ± 10 percentage points.

6.5.5.3 Main stage

The study will have 80% power to detect a treatment difference with a hazard ratio 0.7 in favour of any of the intervention arms compared to the control at a two-sided 5.0% significance level. This is based on the assumption that the accrual period will be uniform over 24 months, that the follow-up period will be 24 months, and that the median progression-free survival is 37 months. This calculation may be adjusted depending on the

compliance rate assessed during the internal pilot study. The overall sample size will be 918 participants considering a 5% loss to follow-up (291 participants per group, 873 participants for three arms). This will allow the detection of an effect size of 9.2% increase in progression free survival at 24 months. This effect size is keeping with that reported in STAMPEDE Arm-H (16).

6.5.6 Study endpoints and outcome measure

Primary and secondary endpoints for the internal pilot and main study are presented in **Table 15**. Study outcome measures for the internal pilot study and main study are presented in **Table 16**.

The internal pilot study, which is the predominant focus of this thesis, primary endpoints were grouped into: i) evaluation of trial design (recruitment, compliance, patient acceptability) ii) safety (adverse event and patient reported outcome measures), and iii) local tumour response (complete pathological response and response on serial MRI imaging). Given the novel extent of the treatments employed in the trial design we believed that on balance this above evaluation was warranted prior to moving into the main study.

The adoption of progression free-survival (PFS) was a natural primary endpoint as it has been used extensively in prior large radiotherapy and medical oncology trials in this metastatic setting (16,19,246). To allow direct comparison the STAMPEDE randomised study definition was adopted using the composite outcome of biochemical failure; local progression; lymph node progression or bone metastases progression (new sites); or progression or development of new distant metastases, defined as lymph nodes outside the pelvis, bone or organ involvement or skeletal-related events confirmed as progression (16).

Table 15. Study primary and secondary endpoints

PRIMARY ENDPOINT: Internal Pilot	a) Recruitment, randomisation and compliance to allocation b) Adverse events and side effects of cytoreductive treatments c) Proportion of patients with complete pathological response on post systemic therapy prostate biopsy at 6-9 months.
PRIMARY ENDPOINT: Main Stage	a) Progression-free survival (PFS) <i>confirmed as progression as in the STAMPEDE randomised study [42].</i>
SECONDARY ENDPOINT: Main Stage	a) Adverse events and side-effect profile b) Predictive factors for PFS and OS in each arm. c) Effect on PFS or OS from varying radiotherapy dosage and schedules d) Effect on PFS and OS stratified by volume and site for local and metastatic disease e) Effect on PFS and OS stratified by the use of metastases directed therapy. f) Effect on PFS using an alternative definition of failure, defined as a PSA increase of $\geq 25\%$ and $\geq 2\text{ng/mL}$ if PSA was $\geq 2\text{ng/mL}$ from baseline, or a PSA increase of $\geq 25\%$ if PSA was $< 2\text{ng/mL}$ at random assignment. g) Effect on PFS using an alternative definition of local progression of a soft tissue metastatic lesion: defined as an increase of $\geq 20\%$ in the largest tumour dimension with a minimum absolute increase of 5mm. Local progression of bone metastases to be assessed using MD Anderson Cancer Center–criteria with a $\geq 25\%$ increase in the size of a measurable lesion on CT or a $\geq 25\%$ increase in the size of ill-defined lesions on CT considered to be progression (1, 2). h) Costs and resource utilisation for future cost-effectiveness analyses i) In those men undergoing repeat biopsies after 6-9 months of standard of care systemic therapy, the proportion of patients with negative biopsies. j) In those men undergoing repeat prostate/pelvic MRI after 6-9 months of standard of care systemic therapy, the proportion of patients with a negative prostate MRI for local tumour. k) In those men undergoing repeat imaging (local prostate/pelvic and / or other body areas) after 6-9 months of standard of care systemic therapy, the proportion of patients with reduction on imaging of metastatic tumour deposits.

Table 16. Study outcome measures

PRIMARY OUTCOMES: Internal Pilot	a) Compliance to randomised arm b) Recruitment and randomisation rate c) Safety (adverse events and patient reported outcome measures) d) Proportion of patients with complete pathological response on post SOC systemic therapy prostate biopsies at 6-9 months.
PRIMARY OUTCOMES: Main Stage	a) Progression-free survival (PFS)
SECONDARY OUTCOMES: Main Stage	a) Urinary, sexual and rectal side-effects b) Patient-reported outcomes using validated questionnaires c) Progression on PSA and imaging and impact of clinical features on progression d) Health-related quality-of-life e) Data on costs and resource utilisation for future cost-effectiveness analysis

6.5.7 Study follow-up

It was important to design a follow-up schedule that reduced patient and clinician burden, thus we adopted a follow-up that would mirror NHS standard practice, as presented in **Table 17**. This included a 12-weekly serum PSA tests in the first year. Further clinical reviews occurred as SOC visits at 12, 26, 28, 32, 34 and 52 weeks in the 1st year which is the extend of the analysis for the internal pilot follow-up.

In the intervention arms, of the internal feasibility pilot only, a prostate MRI, systematic and targeted prostate biopsy was performed at 6-9 months following the initiation of the SST. In the main study, these procedures could be carried out by local centres at the discretion of local clinicians and when they are, data we plan to collect their outcomes.

For those randomised to MIAT or CRP/EBRT, the date for treatment were booked in accordance with the local hospital waiting lists. Removal of the urethral catheter after cytoreductive MIAT or CRP will occur after a minimum period of 7-days during a hospital visit or it was removed either at the GP surgery or at a local hospital to the patient if traveling for treatment out of region.

The main study will continue at 24-weekly intervals thereafter until mortality or 2 years after enrolment (whichever is first), and 2-weekly thereafter, until mortality or 4 years after initial randomisation (whichever is first). Follow-up imaging to determine response from treatment on primary and metastatic disease will not be protocolled but we recommend imaging to take place when there is suspicion of progression, such as patients with a rising PSA (i.e. biochemical failure). The appropriate imaging will be chosen as per the local hospital resources and policies. We envisage that the majority will perform a combination of a prostate MRI, bone scintigraphy, PET-CT, whole body MRI or CT chest/abdomen/pelvis.

For long-term outcomes, patients were consented for their details to be linked to national registries for survival information such as NHS Information Centre/Office of National Statistics (ONS) in England/Wales and General Register Office in Scotland, Hospital Episode Statistics (HES). This ONS-HES linkage however was an optional consent.

Overall, the minimum follow-up for each patient was set at 2 years. However, yearly follow-up will continue long term for the entirety of the study alongside linkage to appropriate national database.

Table 17. IP2-ATLANT study visit schedule

	Screening	Treatment					Post-treatment	Main Study
Visit	1	2	3	4	5	6	7	8 onwards
Week (+/-)	0	12 (+/- 4)	26 (+/-12)	28 (+/- 12)	32 (+/- 12)	34 (+/- 12)	52 (+/- 4)	Every 24 weeks (+/- 4) (year 2-4)
Informed consent	X							
Inclusion & exclusion criteria	X							
Demography	X							
Medical history	X							
Vital signs/physical examination/clinical or subject assessment	X		X				As deemed necessary	As deemed necessary
PSA Blood Test	X	X	X			X	X	X
PROMS Questionnaires	X		X				X	X (24 months)
Review/reporting of patient AEs/SAEs								
(may be performed via a face to face or telephone or email consultation)		X	X	X	X	X	X	X
Blood and urine tests including those for biobanking	X		X			X	At time of failure	Failure or at 24, 36, 48 months
Randomisation	X ¹							
Standard of Care Therapy	X	X	X	X	X	X	X	X
Imaging Tests (Combination of but not limited to CT, X-rays, PET, MRI, Bone Scan)	x		Recommended but not protocolled				As deemed necessary	As deemed necessary
Prostate MRI	x		X				As deemed necessary	As deemed necessary
Biopsy			X				As deemed necessary	
Testosterone blood test	X (if available)		X (recommended)				As deemed necessary	
Treatment in intervention arms					X			
Removal of catheter						X		

Legend: ¹Randomisation should be performed within 7 days from screening visit. Green = Mandatory in Pilot only, during Main study these can be conducted at clinician discretion within standard of care process. Yellow = Main study.

6.5.8 Safety, adverse events and Patient-reported outcome measures (PROMS)

Safety was assessed using adverse event and patient-reported outcome measures (PROMS). The Common Terminology Criteria for Adverse Events (CTCAEv5.0) domain was used to report adverse events, in keeping with prior major oncology trials (247).

The rationale for the choice of specific PROMS in this trial is discussed extensively in **Chapter 11** of this thesis. Briefly, PROMS were collected every 6-months in the first year and annually thereafter, until mortality or 4 years after initial randomisation (whichever is first).

These PROMS included: The European Organisation for the Research and Treatment of Cancer (EORTC); Core Quality of Life Questionnaire-C30 (QLQ-C30), with prostate-specific, fatigue, elderly, general and bone metastases modules; International Prostatic Symptoms Score (IPSS); The Expanded Prostate Cancer Index Composite Bowel and Bladder (EPIC) and International Index of Erectile Function 15 (IIEF15). The EuroQol (EQ-5D-5L) was used in the study as a generic measure of health-related quality-of-life which can be linked to public preferences.

For the main study component the data will be used to calculate quality-adjusted life-years as part of a future health economic evaluation. Patients agreeing to return questionnaires on quality-of-life will continue to complete quality of life data beyond the internal pilot, up to 4 years after enrolment.

6.5.9 Trial funding, organisation and administration

IP2-ATLANTA was funded by the Wellcome Trust (204998/Z/16/Z). I was able to present this trial in person, alongside my supervisor Prof Hashim U. Ahmed, to the Health Research Authority (HRA) Research Ethics Committee Wales (REC5) in Bangor, November 2019. The IP2-ATLANTA trial was subsequently approved by the HRA (19/WA0005; **Appendix C**).

The study was conducted by Imperial College Clinical Trials Unit (ICTU). Monitoring teams from ICTU assessed the progress of the study, verify adherence to the protocol, ICH GCP E6 guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data.

The principal means of data collection from participant visits were via Electronic Data Capture (EDC) using the web-based InForm database. All study data was entered into electronic Case Report Forms (eCRFs) in a database provided by the Sponsor. All eCRFs were completed using de-identified data.

A combined independent data monitoring and trial steering committee met twice a year, of which I was a member of the open forum.

6.6 Discussion

IP2-ATLANTA is a multicentre, phase II, randomised controlled trial. The internal pilot will confirm patient acceptability, compliance and safety of novel cytoreductive interventions. In addition, this trial component will provide deeper radiological and histological characterisation of the primary tumour in the contemporary upfront systemic therapy setting.

The main study component will provide Level I evidence on oncological outcomes from prostate minimally invasive ablative therapy or radical therapy, in combination with metastasis-directed therapy, against standard of care treatment alone, in patients with newly-diagnosed hormone sensitive metastatic prostate cancer. If either intervention arm is proven to provide significant oncological benefit this will have wide-reaching implications on the current standard of care paradigm.

6.7 Conclusion

IP2-ATLANTA addresses an important research gap in the role of sequential systemic, local cytoreductive and metastasis-directed interventions in men with newly-diagnosed metastatic prostate cancer.

Chapter 7 – Additional treatments to the local tumour: assessment of novel treatment algorithms (IP2-ATLANTA), a phase II multicentre randomised controlled trial, internal pilot study results

7.1 Overview

This chapter will report on the primary outcomes for the internal pilot study of IP2-ATLANTA, a phase II multicentre randomised controlled trial exploring additional treatments to the local tumour in patients with *de novo* synchronous hormone-sensitive metastatic prostate cancer. The design of IP2-ATLANTA has been extensively described in the preceding **Chapter 6**. In this chapter I will report on i) evaluation of trial design (recruitment, compliance, patient acceptability) ii) safety (adverse event and patient reported outcome measures), and iii) local tumour response (complete pathological response and response on serial MRI imaging). A further blinded central histopathology analysis of trial local tumour pathology is presented in **Chapter 8**. Finally, patient-reported outcome measures (PROMS) that contribute to the “Safety” internal pilot study endpoint is presented in detail in **Chapter 11**. Sections of this chapter have been published in *BMJ Open*¹¹ and early recruitment rate figures were presented at the *American Society of Clinical Oncology (ASCO) Annual Conference* in 2020 as part of a trials-in-progress abstract¹².

7.2 Introduction

The IP2-ATLANTA trial reports on the performance of additional novel local cytoreductive and metastasis-directed treatments in patients with *de novo* synchronous metastatic hormone-sensitive prostate cancer (mHSPC). The rationale and background for this study have been described at length in this thesis in the preceding chapters (**Chapter 1 to 4; Chapter 6**).

This is the first randomised controlled trial to evaluate minimally-invasive ablative therapy (e.g. cryotherapy, high-intensity ultrasound) and metastasis-directed therapy (i.e. SABR or surgery) in patients with newly diagnosed mHSPC who have commenced contemporary systemic therapy as well as radical therapy in the form of surgery or high-dose radiotherapy.

¹¹ Connor, M.J., *et al.* Additional treatments to the local tumour for metastatic prostate cancer- Assessment of novel treatment algorithms (IP2-ATLANTA): protocol for a multicentre, phase II randomised controlled trial. *BMJ Open*. 2021. 1;11(2):e042953.

¹² Connor, M.J., *et al.* Initial experience of the adjuvant treatments to the local tumour for metastatic prostate cancer: Assessment of novel treatment algorithms, a multicentre, phase II randomized controlled trial (IP2-ATLANTA). *Journal of Clinical Oncology*. 2020. 38(15), Supplement TPS5600.

We hypothesised that patients with mHSPC who undergo treatment of the local tumour in the form of either radical therapy (cytoreductive radical prostatectomy (CRP) or external-beam radiotherapy (EBRT)), or MIAT, combined with metastases-directed therapy (MDT), will improve progression-free survival in comparison to patients who receive standard of care treatment alone.

Here-in we present the internal pilot study results on the feasibility of trial design, novel surgical and metastasis-directed interventions; safety and PROMS; and local primary tumour response to systemic therapy intensification with docetaxel or ARSI's (pathological and mpMRI response imaging). The outcomes described are set out as predefined analyses in the protocol and a completed and signed off Statistical Analysis Plan specific for the pilot. Given the novel nature of the treatments employed in IP2-ATLANTA we believe that evaluation of these internal pilot endpoints was required prior to moving into the main stage of the study.

7.3 Methods

7.3.1 Study design, recruitment, randomisation and trial interventions

The study design, recruitment strategy, randomisation methodology and trial interventions of IP2-ATLANTA has been extensively described in the preceding **Chapter 6** and thus have not been duplicated here for brevity.

7.3.2 Internal pilot outcomes

The internal pilot study primary endpoints can be broadly grouped in: i) evaluation of trial design (recruitment, randomisation, compliance, patient acceptability), ii) safety (adverse event and patient-reported outcome measures), and iii) local tumour response (complete pathological response and response on serial MRI imaging) (**Chapter 6**).

7.3.2.1 Internal pilot population

All participants that consented before the cut-off date of 6th February 2021 were part of the pilot population for analysis. All participants underwent follow-up for at least 12 months to enable visit 7 (Week 52+/-4) to be completed. Given this was an actively recruiting multicentre study this date was chosen as the trial recruitment approached the 80th patient. As we were required to provide sufficient notice to recruiting sites for change of study procedures for entering the main stage of the study, specifically to alter the consent process to remove discussion of a pilot mandated post-SOC repeat MRI and prostate biopsy, we recognised that there may be a small overshoot in 80 patients in the final analysis if patients were consented simultaneously within this 24-hour period.

7.3.2.2 Definition of Compliance

Compliance was measured by attendance at visits (screening and follow-up). SOC treatment was given at visits 1 to 7. Intervention treatment to which patients were randomly allocated was given at visit 5.

7.3.2.3 Definition of Recruitment & Randomisation Rate

Recruitment rate is calculated as the number of participants recruited out of the total number approached. Randomisation is calculated as the number of participants randomised out of the total number approached. For the purposes of analysis, two rates were calculated for randomisation and recruitment rate, respectively. These were: (*Rate A*) total number of patients approached which includes all patients who were given the patient information leaflet (PIS) and “ELIGIBLE” but declined and patients who were given PIS but “non-Eligible” (following distant disease imaging); (*Rate B*) total number of patients approached which included patients who were given PIS and “ELIGIBLE” but subsequently declined the study.

7.3.2.4 Definition of Attendance

The proportions of patients, in each treatment arm, who attended their visit “on time” is presented. An “on time” visit is a visit which is within the visit window defined in the Visit Schedule (**Chapter 6**). The proportions of patients, in each treatment arm, with a missing, early, delayed or not applicable visit will also be presented. A missed visit is a visit at which no information was collected and recorded as not done, but for which the patient has not been withdrawn. Early visits and delayed visits are visits which are outside of the visit window (before or after, respectively) defined in the Visit Schedule (**Chapter 6**).

7.3.2.5 Safety (adverse event and patient reported outcome measures)

Safety was assessed using adverse event and patient reported outcome measures (PROMS). The Common Terminology Criteria for Adverse Events (CTCAEv5.0) domain was used to report adverse events (247). All adverse events were reported from first patient enrolled to completion of pilot enrolment and analysis (“soft-lock”; July 2022) of the live trial database.

All pilot PROMS are reported in full in **Chapter 11**. For the purposed of this main results chapter the following were reported: International Prostatic Symptoms Score (IPSS); The Expanded Prostate Cancer Index Composite Bladder (EPIC-Bladder) and International Index of Erectile Function 5 (IIEF15).

The IPSS is based on the answers to seven questions concerning urinary symptoms and one question concerning quality of life (248,249). The responses to the questions concerning urinary symptoms range from 0 to 5, indicating increasing severity of the particular symptom.

Thus, the overall score can range from 0 (asymptomatic) to 35 (very symptomatic). IPSS Quality of life (IPSS QoL), range 0 “delighted”; 3 “mixed equally satisfied/dissatisfied”; 6 “terrible”.

IIEF-15 questionnaire is a validated, multi-dimensional, self-administered investigation that is useful in the clinical assessment of erectile dysfunction and treatment outcomes in clinical trials. A score of 0-5 is awarded to each of the 15 questions that examine the 4 main domains of male sexual function: erectile function, orgasmic function, sexual desire, and intercourse satisfaction. Here-in we will reported on the overall satisfaction score (Q13,Q14) where maximum score is 10. Previously reported studies define sexual dysfunction mean score at 4.4; control mean score of 8.6 (250).

The EPIC-Urinary is a comprehensive instrument designed to evaluate patient function and bother after prostate cancer treatment (251). EPIC assesses the disease-specific aspects of prostate cancer and its therapies and comprises of four summary domains (Urinary, Bowel, Sexual and Hormonal). Here-in we will report on the Urinary Domain Summary Score and Urinary Pad use changes per trial arm. The Urinary Domain Summary which is split into two distinct “Incontinence” and “Irritative/Obstructive” subscales. In addition, the Domain Score has measurable “Function” and “Bother” subscale components. Response options for each EPIC item form a Likert scale, and multi-item scale scores are transformed to a 0 to 100 scale. Higher scores represent higher Health-Related Quality of Life (HRQOL).

The EQ-5D-5L comprises of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression (252). EQ-5D-5L health scale is a visual-analogue scale range from 0 to 100. Higher scores indicate better health.

7.3.2.6 Local tumour response

All results reported in this chapter are those of the local trial histopathologist. We report on Gleason Grade Group and Maximum Cancer Core Length (MCCL) changes in the intervention arms 1 and 2. Gleason Grade Group may not be reported, in line with current guidelines following treatment due to the effect of ADT on tissue (**Chapter 6**) (243). Features of high-grade prostatic intraepithelial neoplasia (HGPIN) and atypical small acinar proliferation (ASAP) were considered as benign tissue.

Complete pathological response on post-systemic therapy prostate biopsy was defined as the presence of benign tissue or grade pT0 (prostate cancer not identified) AND/OR the absence of “post-hormone therapy adenocarcinoma” and/or “chemotherapy post-treatment effects” (240-243).

An mpMRI was performed using a 1.5-T or 3.0 T scanner at baseline (SCR Visit 1; Week 0) and prior to trial interventions in arm 1 or 2 being performed (Visit 3 or 4; Week 26 or Week 28) in keeping with trial protocol (**Chapter 6**). Initial mpMRI was performed and reported in accordance with the technical requirements in PIRADSv2. MRI tumour and nodal stage, MRI lesion changes (mm) and baseline PI-RADS score were all reported.

A second post-systemic therapy mpMRI was performed in accordance with the technical requirements in PIRADSv2, but a PI-RADS score could not be assigned due to systemic therapy treatment effects, as per the PI-RADSv2 guidelines (253). Both mpMRI sequences included T1-weighted, T2-weighted, dynamic contrast-enhanced (DCE) and multi b-values (for derivation of apparent diffusion coefficient (ADC) maps) and a high b-value of 1500.

All mpMRI prostate results reported in this chapter are those by the local reporting uro-radiologist. Reporters had access to prior imaging, clinical and trial treatment information, current PSA at the at time of report.

7.3.3 Statistical analysis

Analysis was performed according to the pre-specified IP2-ATLANTA statistical analysis plan (SAP) [v3.0; July/2022]. We aimed to approach 80 patients from up to 17 centres in the UK over a 6-month period to allow us to estimate a 33% recruitment rate with 95% confidence interval width of approximately ± 10 percentage points (**Chapter 6**).

During the development of the trial, we recognised that a number of patient factors could significantly impact upon the primary endpoint of Progression-Free Survival. Thus in this study, we performed permuted block randomisation, as described by Mats and Lachin (245), allocating the three treatment arms at a 1:1:1 ratio to random block sizes of 3,6,9,12 and 15. Variables were drawn from discussion held with my supervisor (Prof. Hashim Ahmed) and co-investigators, with evidence drawn from non-systematic and systematic literature searches completed in **Chapter 2** and **Chapter 3** of this thesis. In total, 16 strata were established from 4 stratification factors:.

- I. Intent to treat pelvic lymph nodes?: yes versus no*
- II. Metastatic burden: low versus high (CHAARTED definition) (10).*
- III. Intent to use systemic agent (i.e. Chemotherapy/ARSI)?: yes versus no*
- IV. Intent to use metastases directed therapy?: yes versus no*

For the purposes of the internal pilot study these are presented to demonstrate equal distribution across all study arms.

For completeness a Covid-19 impact analysis of baseline demographics, recruitment and randomisation rate, compliance to study visits, safety and adverse events is provided for patients recruited to the trial “before” and “during/after” the Covid-19 pandemic, separately. On 05/03/2020, Covid-19 was added to Public Health England’s list of notifiable diseases in England and Wales (254). Patients recruited to the trial after this date were assigned as recruited “during/after” the Covid-19 pandemic for purposes of analysis.

All outcomes are analysed using all randomised patients according to the intention-to-treat (ITT-) principle. All other analysis presented in this Chapter and subsequent chapters is exploratory, including the COVID-19 trial impact analysis. The study statistician, senior statistician and I performed the initial analysis. The final analysis was reviewed by an independent third statistician and the report signed off by the trial’s Chief Investigator and my primary supervisor (H.U. Ahmed). All analysis were performed using STATA (StataCorp LLC, College Station, T, v.17.0) or SPSS (IBM Corp., IBM SPSS Statistics for Windows, Armonk, USA, v.28.0), some tables and graphs were recreated in Excel (Microsoft, v.2019).

7.3.4 Funding, ethical approval and trial registration

IP2-ATLANTA was funded by the Wellcome Trust charity (204998/Z/16/Z) and research ethics committee approval granted by the UK Health Research Authority (Ref: Wales REC5; 19/WA0005). The study was prospectively registered at ClinicalTrials.gov (NCT03763253) and ISRCTN.com (ISRCTN58401737).

7.4 Results

7.4.1 Overview

Between 26th April 2019, and 6th February 2021, 121 patients were assessed for eligibility from eleven active trial sites in England and Wales (**Figure 14**). All participants’ follow-up reached Visit 7 (Week 52 +/-4) on study, with median follow-up of 25 (IQR 20-30) months. Of these 81 patients were randomly allocated to Control Arm: SOC (34.6%; 28/81), Intervention Arm 1: MIAT (33.3%; 27/81) and Intervention Arm 2: Radical (32.1%; 26/81).

Groups were well balanced with respect to trial participants baseline characteristics (**Table 17**). Overall, mean and median age were 68.23 (SD 7.64) and 69.0 (IQR 62.00 – 74.00) years, respectively. Overall, ethnicity was reported as “White (any)” 64.2% (52/81), “Black (any)” 6.2% (6/81), “Asian (any)” 1.2% (1/81) and “Not Reported/Disclosed” in 28.4% (23/81), respectively. There was patient representation across all Index of Multiple Deprivation Deciles ([IMD]; 1 = “most deprived” to 10 = “least deprived”), with 44.4% (36/81) from IMD 1 to 5 and 53.1% (43/81) from IMD 6 to 10. Overall, 2.5% (2/81) were in IMD 1

and 14.8% (12/81) were in IMD 10. Similarly, Body Mass Index (BMI) was equally represented across all arms with an overall median BMI of 26.90 (IQR 24.20 – 29.10).

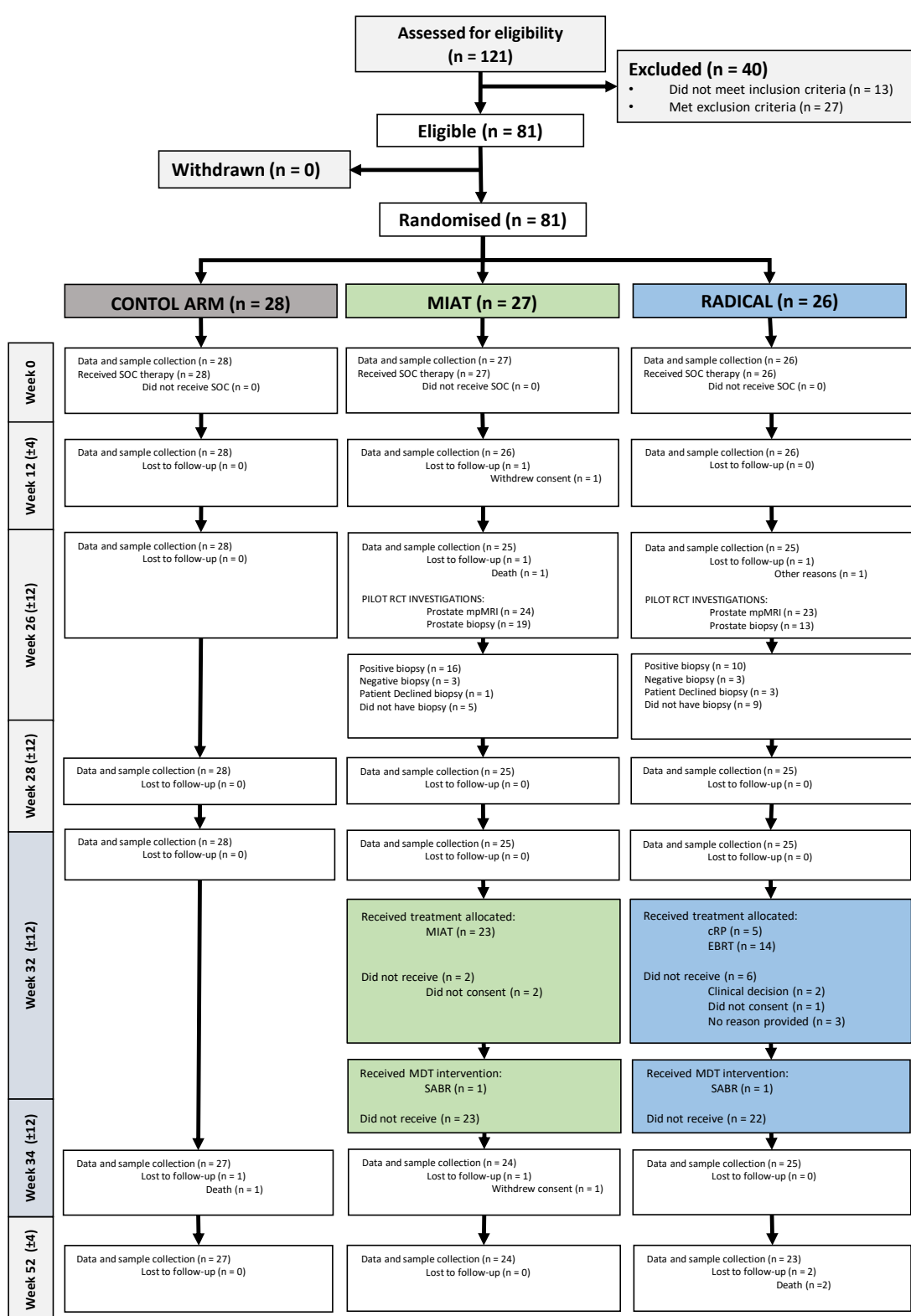
Performance Status (PS) was reported as PS 0 in 91.4% (74/81) and PS 1 in 7.4% (6/81). Highest tumour(T)-stage at randomisation was equal across all trial arms, with no cases of T0-T2 disease, T3 49.4% (40/81), T4 38.3% (31/81) and Tx 2.5% (2/81) (**Table 18**). Overall T-stage at randomisation was equal across all trial arms, with no cases of T0-T2 disease, T3 49.4% (40/81), T4 38.3% (31/81). Highest nodal(N)-stage at randomisation was also well balanced across all trial arms, with a predominance towards pelvic lymph node metastases in the majority of the pilot RCT patients: N0 29.6% (24/81), N1/N+ 58.0% (47/81) and Nx 2.5% (2/81).

Highest metastasis(M)-stage at randomisation was predominantly M1b (bone metastasis) in all trial arms, representing over half the pilot RCT patients 56.8% (46/81). M1a (non-regional/distant nodal metastasis) and M1c (visceral metastasis) were present in 12.3% (10/81) and 3.6% (1/81) of the study patients, respectively. CHAARTED defined metastatic burden was also well balanced across all trial arms, as expected following its inclusion as a separate randomisation strata; 50.6% (41/81) were low burden and 49.4% (41/81) were high burden (**Table 18**).

The mean and median PSA at diagnosis of mHSPC were reported as 278.4 ng/ml (489.80 SD) and 80.50 ng/ml (20.25 – 261.78 IQR), respectively. There was variation across trial arms with mean PSA reported as 266.9 ng/ml (458.1 SD) in the Control Arm, 386.6 ng/ml (653.1 SD) Intervention Arm 1: MIAT, and 143.5 ng/ml (202.4 SD) (**Table 18**).

All participants in the internal pilot underwent a prostate biopsy prior to randomisation, in adherence with the trial eligibility criteria (**Chapter 6**). All cases were confirmed prostate adenocarcinoma (100%; 81/81) without presence of variant pathology (e.g., small cell, neuroendocrine differentiation). ISUP Grade Group ≥ 5 (Gleason Sum Score ≥ 9) predominated across all trial arms, representing almost two thirds of the pilot RCT patients (65.4%; 53/81) (**Table 18**). ISUP Grade Group 2-3 (Gleason Sum Score 7) was present in 4.9% (4/81) and 4.9% (4/81), respectively. A single case of ISUP 1 or Gleason = 6 disease was present in the pilot RCT patients (1.2%; 1/81), randomised to the control arm. In a single participant “adenocarcinoma with treatment effect” was reported due to the effect of initiation of androgen deprivation therapy on the tissue, prior to prostate biopsy, preventing accurate Gleason Grade Group assignment (1.2%; 1/81).

Figure 14. IP2-ATLANTA Pilot Trial Profile



Legend: CONSORT diagram for the IP2-ATLANTA internal pilot RCT patients. Week 32 = local cytoreductive treatment; Week 34 = MDT. mpMRI – Multiparametric Magnetic Resonance Imaging; cRP – cytoreductive Radical Prostatectomy; EBRT – External Beam Radiotherapy; MIAT – Minimally Invasive Ablative Therapy; SOC – Standard of Care; SABR – Stereotactic ablative body radiotherapy;

Table 18. Baseline characteristics of IP2-ATLANTA internal pilot RCT patients, by trial arm

Variable	Statistics	Control Arm: SOC	Intervention Arm 1: MIAT	Intervention Arm 2: Radical	Total
Age	<i>n</i>	28	27	26	81
	Mean (SD)	68.50 (7.24)	67.59 (7.74)	68.62 (8.20)	68.23 (7.64)
	Median (IQR)	69.50 (61.00-74.00)	67.00 (61.00-75.00)	71.50 (65.00-74.00)	69.00 (62.00-74.00)
Ethnicity (n (%))	White	22 (78.6%)	15 (55.6%)	15 (57.7%)	52 (64.2%)
	Mixed	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Asian	1 (3.6%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
	Black	1 (3.6%)	1 (3.7%)	3 (11.5%)	5 (6.2%)
	Not Disclosed	4 (14.3%)	11 (40.7%)	8 (30.8%)	23 (28.4%)
IMD Decile (n (%))	1	0 (0.0%)	1 (3.7%)	1 (3.8%)	2 (2.5%)
	2	1 (3.6%)	4 (14.8%)	0 (0.0%)	5 (6.2%)
	3	1 (3.6%)	1 (3.7%)	5 (19.2%)	7 (8.6%)
	4	4 (14.3%)	3 (11.1%)	5 (19.2%)	12 (14.8%)
	5	4 (14.3%)	3 (11.1%)	3 (11.5%)	10 (12.3%)
	6	2 (7.1%)	2 (7.4%)	3 (11.5%)	7 (8.6%)
	7	2 (7.1%)	1 (3.7%)	3 (11.5%)	6 (7.4%)
	8	3 (10.7%)	4 (14.8%)	2 (7.7%)	9 (11.1%)
	9	6 (21.4%)	2 (7.4%)	1 (3.8%)	9 (11.1%)
	10	3 (10.7%)	6 (22.2%)	3 (11.5%)	12 (14.8%)
	Missing from eCRF (n (%))	2 (7.1%)	0 (0.0%)	0 (0.0%)	2 (2.5%)
BMI	<i>n</i>	25	20	22	67
	Mean (SD)	26.26 (3.33)	26.96 (4.77)	27.30 (3.00)	26.81 (3.70)
	Median (IQR)	26.20 (23.90-28.00)	25.75 (24.20-28.85)	27.50 (25.30-29.40)	26.90 (24.20-29.10)
	Missing from eCRF (n (%))	3 (10.7%)	7 (25.9%)	4 (15.4%)	14 (17.3%)
Performance status (n (%))	Grade 0	26 (92.9%)	23 (85.2%)	25 (96.2%)	74 (91.4%)
	Grade 1	2 (7.1%)	3 (11.1%)	1 (3.8%)	6 (7.4%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing from eCRF (n (%))	0 (0.0%)	1 (3.7%)	0 (0.0%)	1 (1.2%)
T category at randomi- sation	T0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	T1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	T2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	T3	13 (46.4%)	15 (55.6%)	12 (46.2%)	40 (49.4%)
	T4	10 (35.7%)	10 (37.0%)	11 (42.3%)	31 (38.3%)
	Tx	2 (7.1%)	0 (0.0%)	0 (0.0%)	2 (2.5%)
	Missing from eCRF (n (%))	3 (10.7%)	2 (7.4%)	3 (11.5%)	8 (9.9%)
N category	N0	9 (32.1%)	7 (25.9%)	8 (30.8%)	24 (29.6%)
	N1/N+	16 (57.1%)	16 (59.3%)	15 (57.7%)	47 (58.0%)

at randomisation	Nx	1 (3.6%)	1 (3.7%)	0 (0.0%)	2 (2.5%)
	Missing from eCRF (n (%))	2 (7.14%)	3 (11.1%)	3 (11.5%)	8 (9.9%)
M category at randomisation	M1a	4 (14.2%)	3 (11.1%)	3 (11.5%)	10 (12.3%)
	M1b	18 (64.3%)	16 (59.3%)	12 (46.2%)	46 (56.8%)
	M1c	1 (3.6%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
	M1 (any) – not specified	5 (17.9%)	8 (29.6%)	11 (42.3%)	24 (29.6%)
Metastatic burden	High	13 (46.4%)	14 (51.9%)	13 (50.0%)	40 (49.4%)
	Low	15 (53.6%)	13 (48.1%)	13 (50.0%)	41 (50.6%)
Gleason Grade Group / ISUP	<= 3+3 / ISUP 1	1 (3.6%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
	3+4 / ISUP 2	1 (3.6%)	0 (0.0%)	3 (11.5%)	4 (4.9%)
	4+3 / ISUP 3	1 (3.6%)	0 (0.0%)	3 (11.5%)	4 (4.9%)
	4+4, 3+5, 5+3 / ISUP 4	4 (14.3%)	7 (26.0%)	7 (26.9%)	18 (22.2%)
	4+5, 5+4, 5+5 / ISUP 5	20 (71.4%)	20 (74.1%)	13 (50.0%)	53 (65.4%)
	Adenocarcinoma with treatment effect	1 (3.6%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
Maximum Cancer Core Length (mm)	Mean (SD)	4.1 (5.3)	3.0 (4.1)	2.4 (2.8)	3.7 (4.6)
	Median (IQR)	13.0 (6.0 – 9.0)	14.0 (10.5 – 15.0)	14.0 (10.5 – 15.6)	14 (10.0 – 15.0)
	Mean (SD)	4.1 (5.3)	3.0 (4.1)	2.4 (2.8)	3.7 (4.6)
	Unknown	1 (3.6%)	1 (3.7%)	2 (7.7%)	4 (4.9%)
PSA at diagnosis (ng/ml)	Mean (SD)	266.9 (458.1)	386.6 (653.1)	153.5 (202.4)	278.40 (489.80)
	Median (IQR)	47.4 (15.4 – 176.0)	386.6 (38.0 – 384.8)	60.4 (18.1 – 253.9)	80.50 (20.25 – 261.78)
	Missing from eCRF (n (%))	3 (10.7%)	0 (0.0%)	4 (15.4%)	7 (8.6%)
Significant past medical history					
Type 2 Diabetes (n (%))	Yes	3 (10.7%)	4 (14.8%)	3 (11.5%)	10 (12.3%)
	No	25 (89.3%)	23 (85.2%)	23 (88.5%)	71 (87.7%)
Ischaemic Heart Disease (n (%))	Yes	4 (14.3%)	3 (11.1%)	4 (15.4%)	11 (13.6%)
	No	24 (85.7%)	24 (88.9%)	22 (84.6%)	70 (86.4%)
Stroke (n (%))	Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	No	28 (100.0%)	27 (100.0%)	26 (100.0%)	81 (100.0%)
Peripheral	Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	No	28 (100.0%)	27 (100.0%)	26 (100.0%)	81 (100.0%)

Vascular Disease (n (%))					
Benign Prostatic Enlargement (n (%))	Yes	2 (7.1%)	1 (3.7%)	3 (11.5%)	6 (7.4%)
	No	26 (92.9%)	26 (96.3%)	23 (88.5%)	75 (92.6%)
COPD (n (%))	Yes	0 (0.0%)	0 (0.0%)	1 (3.8%)	1 (1.2%)
	No	28 (100.0%)	27 (100.0%)	25 (96.2%)	80 (98.8%)
Systemic therapy use					
Androgen deprivation treatment (n (%))	Anti-androgen	1 (3.6%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
	LHRH agonist (n (%))	27 (96.4)	25 (92.60%)	26 (100.0%)	78 (96.3)
	LHRH antagonist (n (%))	0 (0.0%)	1 (3.6%)	0 (0.0%)	1 (1.2%)
	Missing from eCRF (n (%))	0 (0.0%)	1 (3.6%)	0 (0.0%)	1 (1.2%)
Escalation Agent (n (%))	Docetaxel (n (%))	19 (67.9%)	8 (29.7%)	13 (50.0%)	40 (49.4%)
	Enzalutamide (n (%))	6 (21.4%)	18 (66.7%)	8 (30.8%)	32 (39.5)
	Abiraterone Acetate (n (%))	1 (3.6%)	0 (0.0%)	2 (7.7%)	3 (3.7%)
	None (n (%))	2 (7.1%)	0 (0.0%)	3 (11.5%)	5 (6.1%)
	Missing from eCRF (n (%))	0 (0.0%)	1 (3.6%)	0 (0.0%)	1 (1.2%)

Legend: SOC – Standard of care; BMI – Body Mass Index; PS – Performance Status as per ECOG; IMD - Index of Multiple Deprivation Decile (England & Wales); Disease Burden – Metastatic Disease as per CHAARTED definition “High” versus “Low” (255); N – Nodes; M – Metastasis; T – Tumour; MCCL - Maximum Cancer Core Length; ISUP - International Society of Urological Pathology.

7.4.2 Primary Outcome II: Evaluation of trial design (recruitment, randomisation, compliance and patient acceptability)

Overall, 121 patients were assessed for eligibility, with 40/121 (33.1%) excluded, and 81/121 (66.9%) eligible for recruitment (**Figure 14**). When “Rate A” was applied recruitment and randomisation rate was 66.9% (81/121) and 66.9% (81/121), respectively. When “Rate B” was applied, recruitment and randomisation rate was 75.0% (81/108) and 75.0% (81/108), respectively (**Table 19**).

Table 19. Recruitment and Randomisation Rates

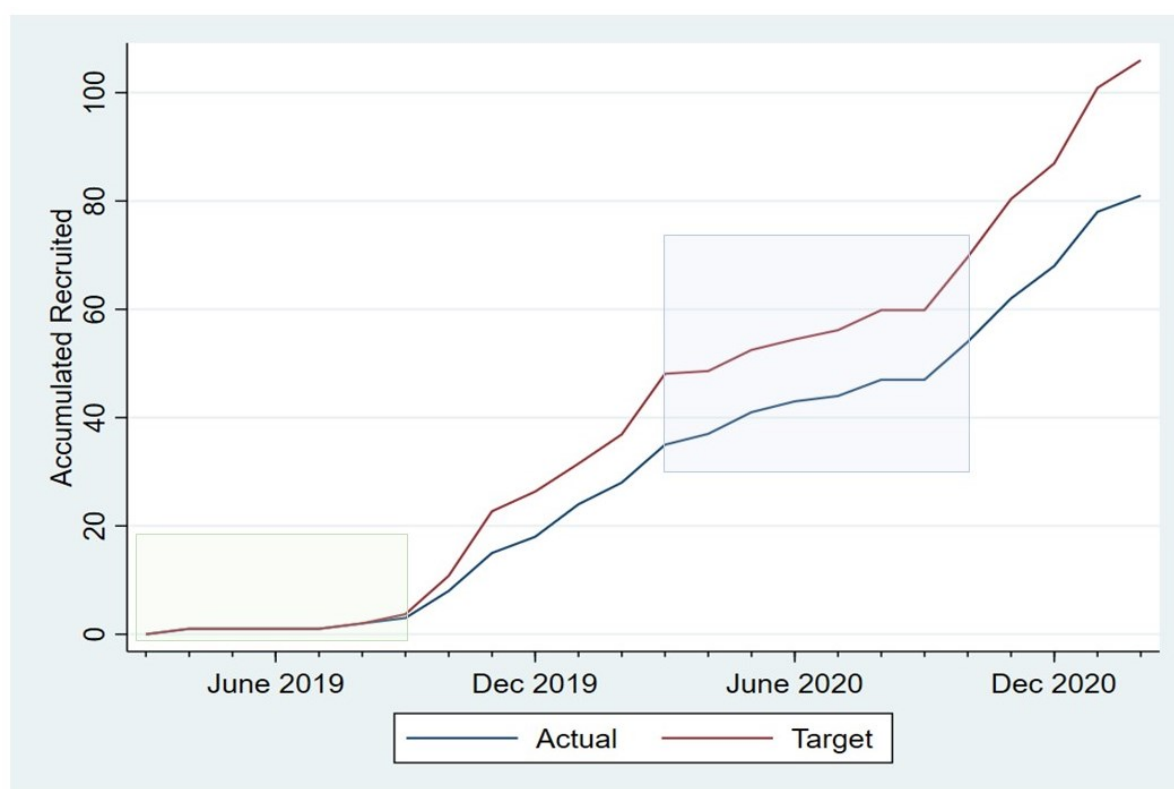
		Rate A	Rate B
Recruitment Rate	% (n)	66.9% (81/121)	75.0% (81/108)
	SD	8.5	8.2
	95% CI	58.5 - 75.3	66.8 - 83.2
Randomisation Rate	% (n)	66.9% (81/121)	75.0% (81/108)
	SD	8.5	8.2
	95% CI	58.5 - 75.3	66.8 - 83.2

Legend: Rate A - calculated out of total number of people all approached which include patient who were given PIS and ELIGIBLE but declined and patients who were given PIS but non-Eligible (following distant disease imaging). Rate B - calculated out of total number of people approached which include patient who were given PIS and ELIGIBLE but declined. CI – Confidence Interval; SD – Standard Deviation.

As demonstrated by **Figure 15**, using recruitment “Rate B”, the IP2-ATLANTA internal pilot recruitment rate remained lower than predicted throughout the pilot accrual period. As a result, the pilot period spanned 22 months, this was 16 months longer than anticipated. This was due to a six-month delay in multiple sites opening between April 2019 and September 2019. Unfortunately, this was then followed by the COVID-19 pandemic, which led to temporary but prolonged suspension of recruitment across various trial centres between March 2020, and October 2021 as well as a halt in opening up new sites (**Figure 15**).

In relation to the original sample size calculations, when the 95% confidence interval reported the difference in expected recruitment rate (33% of 80) compared to actual (66.9% of 121) did not increase the width of the confidence interval beyond the planned +/- 10% estimate.

Figure 15. Graph displaying actual vs target recruitment rate over time



Legend: Graph displaying actual versus target recruitment rate (using recruitment rate B) over time for the IP2-ATLANTA internal pilot RCT. Accumulated recruitment rate affected by six-month delay in multicentre opening between April/19 and Sept/19 [Light Green Square Shading], followed by COVID-19 pandemic impact of temporary multisite new recruitment suspensions across various sites between March/20 and Oct/2020 [Light Blue Square Shading].

The mean number of patients recruited per month varied per geographical regions, with the host site (A1, Imperial College Healthcare NHS Trust) recruiting 1.94 patients per month compared with the lowest recruiting site (A7, City Hospitals Sunderland NHS Foundation Trust) recruiting just 0.08 patients per month (**Table 20**). When sub-group analysis was performed “central (regional) cancer trial network centres” had a mean recruitment of 0.91 patients per month compared to 0.24 patients per month for “local cancer network trial centres”.

The mean time (days) between patient consent and randomisation was: SOC arm 5.93 (SD 6.31); Intervention Arm 1: MIAT 4.93 (SD 4.72); Intervention Arm 2: Radical 3.0 (3.65). Overall, the mean and median time (days) between patient consent and randomisation was 4.65 (SD 5.1) and 4.0 (IQR 0 to 7), respectively.

Table 20. Mean number of patients recruited and randomised per month per centre

Trial Site ID	Centre	Recruited	Randomised
A1	Imperial College Healthcare NHS Trust	1.94	1.94
A2	Northwick Park, London Northwest Healthcare NHS Trust	0.11	0.11
A3	Queen Elizabeth Hospital Kings Lynn	0.28	0.28
A4	West Middlesex University Hospital	0.69	0.69
A6	Royal Marsden NHS Foundation Trust	0.33	0.33
A7	University Hospital Southampton NHS Trust	1.73	1.73
A8	City Hospitals Sunderland NHS Foundation Trust	0.08	0.08
A9	Freeman Hospital, The Newcastle upon Tyne Hospitals NHS Trust	0.25	0.25
A10	Wirral University Teaching Hospital	0.12	0.12
A13	Royal Devon & Exeter Hospital NHS Trust	0.33	0.33
A16	Chelsea & Westminster Hospital	0.19	0.19
A1, A7, A9, A6, A13	Central (Regional) Cancer Network Trial Centre	0.91	0.91
A2, A3, A4, A8, A10, A16	Local Cancer Network Trial Centre	0.24	0.24

Legend: Central (Regional) Network Trial Centre defined as a centre that has a central multi-disciplinary team meeting that routinely discussed prostate cancer referrals from surrounding local centres. All remaining trial centres analysed as local cancer network trial centres.

Stratified randomisation was completed correctly for 80/81 (98.7%) of patients in the pilot. This error in assignment of “metastatic burden” definition was corrected for the purposes of this analysis. Stratified randomisation led to equal representation across all trial arms of variables that may impact upon the progression-free survival primary endpoint in the main study component of IP2-ATLANTA study (**Table 21**).

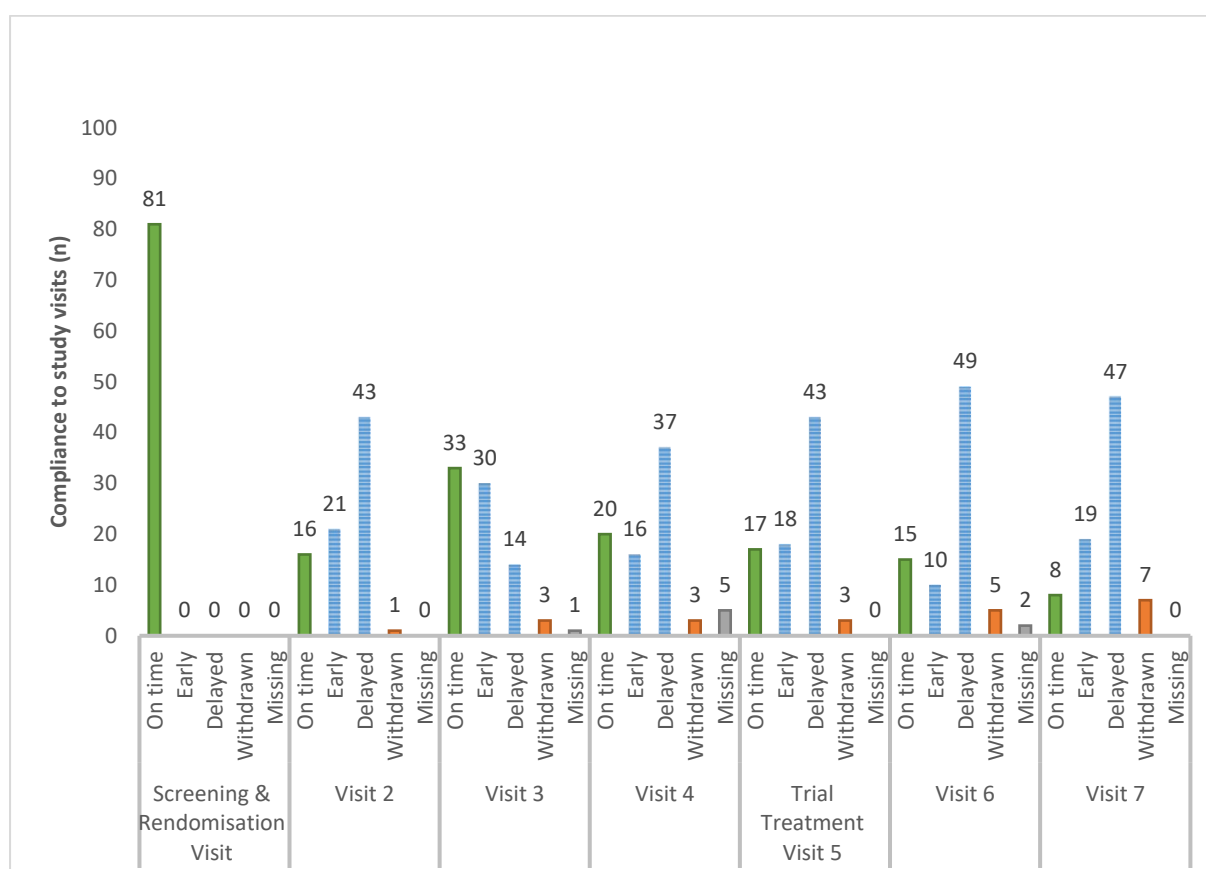
Compliance and attendance to study visit remained balanced across all trial arms (**Figure 16**). When all arms were analysed withdrawal rates remained low across all internal pilot visits. These ranged between 1.2-3.8% prior to experimental trial interventions (Visit 2 to 4), increasing to 3.8% at experimental trial intervention visit (Visit 5), following experimental trial interventions withdrawal increased further to 6.2%-8.6% (Visit 6 to 7).

Table 21. Performance of stratified randomisation in internal pilot RCT

Stratified Randomisation Variables		Control Arm: SOC	Intervention Arm 1: MIAT	Intervention Arm 2: Radical	Total
Intent to treat pelvic lymph nodes (n (%))	Yes	14 (50.0%)	15 (55.6%)	12 (46.2%)	41 (50.6%)
	No	14 (50.0%)	12 (44.4%)	14 (53.8%)	40 (49.4%)
Metastatic burden (n (%))	High	13 (46.4%)	14 (51.9%)	13 (50.0%)	40 (49.4%)
	Low	15 (53.6%)	13 (48.1%)	13 (50.0%)	41 (50.6%)
Intent to use systemic chemotherapy or ARSI (n (%))	Yes	28 (100.0%)	25 (92.6%)	23 (88.5%)	76 (93.8%)
	No	0 (0.0%)	2 (7.4%)	3 (11.5%)	5 (6.2%)
Intent to use metastases directed therapy (n (%))	Yes	10 (35.7%)	11 (40.7%)	10 (38.5%)	31 (38.3%)
	No	18 (64.3%)	16 (59.3%)	16 (61.5%)	50 (61.7%)

Legend: ARSI – Androgen receptor signalling inhibitor; Metastatic burden – Metastatic Disease as per CHAARTED definition “High” versus “Low” (255).

Figure 16. Compliance to study visits (all arms)



Legend: Overall compliance (n) to study visits for all trial arms across the IP2-ATLANTA pilot RCT. Visit schedule as per Chapter 6. Visits beyond visit 7 no represented as follow-up limited to one-year for pilot analysis (Feb/2021 – Feb/2022). Compliance by randomised arm and long-term follow-up beyond one year available in supplementary material and in some instances “not applicable” maybe assigned as patients have not met visit date. Green – “on-time”; Blue – “Early/Delayed”; Orange – “Withdrawal”; Grey – “Missing data”.

When analysed by trial arm all study withdrawals prior to trial intervention visit occurred exclusively in the intervention arms and these were highest in Intervention Arm 1: MIAT. The withdrawal rate for Intervention Arm 1: MIAT were as follows: 3.7-7.4% (Visit 2 to 4); 7.4% (Visit 5); 11.1% (Visit 6 to 7). The withdrawal rate for Intervention Arm 2: Radical were as follows: 0-3.8% (Visit 2 to 4); 3.8% (Visit 5); 3.8-11.1% (Visit 6 to 7).

As demonstrated in the CONSORT diagram in **Figure 14**, in Intervention Arm 1: MIAT, 23 of 27 (85.2%) participants received their allocated randomised trial intervention, one (3.7%) participant died prior to MIAT being performed and a further three (3/27; 11.1%) participants withdrew consent for allocated trial intervention. This is explained in greater detail in **Chapter 10**. Briefly, treatments performed were: cytoreductive (whole gland) cryotherapy + robotic bilateral PLND 6/27 (22.2%); cytoreductive cryotherapy 11/27 (40.7%) and cytoreductive HIFU 6/27 (22.2%), respectively. Metastasis-directed therapy (MDT) in the form of SABR was performed in one patient (1/27; 3.7%) (**Table 22**). Median operating time (IQR) and length of stay (IQR) for all MIAT procedures was 110.8 (90.5 – 188.5) minutes and 1.0 (0.5 - 1.0) days, respectively. All patients requiring PLND were admitted overnight. “Day case” cytoreductive MIAT was achieved in 7/23 (30.4%) of patients. There were no intraoperative complications, abandoned procedures or blood transfusions (0/23; 0.0%). Furthermore, there were no reported post operative blood transfusions (0/23; 0.0%).

In Intervention Arm 2: Radical 19 of 26 (73.1%) participants received trial interventions, two (2/26; 7.7%) participants were deemed not fit for radical treatment at time of planned intervention, a further participant (1/26; 3.8%) withdrew consent, no reason was provided for three patients (3/26; 11.5%) (**Figure 14**). Overall, treatments performed were cytoreductive Radical Prostatectomy (cRP) in 5/26 (19.2%) and Cytoreductive EBRT in 14/26 (53.8%). All cytoreductive radiotherapy to the prostate used 60 Gy / 20 fractions, with prostate only treatment in 6/26 (23.1%) and prostate with PLNRT in 8/26 (30.1%), respectively. MDT in the form of SABR was performed in one patient, in whom a cRP was also performed (1/26; 3.8%) (**Table 22**).

All five (19.2%) participants who underwent a cRP, had a robotic-assisted laparoscopic approach. In two (7.7%) a concomitant robotic bilateral PLND was performed. Median (IQR) operating time and blood loss were reported as 126 mins (118 – 156) and 150 ml (87.5 – 250.0), respectively. Median (IQR) post operative length of stay was 1.0 day (1.0 – 1.5). In those who concomitant robotic bilateral PLND median (IQR) nodes retrieval was 15.5 (9.8 – 21.3). There were no intraoperative complications, abandoned surgical procedures or blood

transfusions (0/26; 0.0%). Furthermore, there were no reported post operative blood transfusions (0/26; 0.0%).

Table 22. Trial interventions in internal pilot RCT

Intervention Arm 1: MIAT (n)	27
Cytoreductive MIAT (n; %)	23 (85.2%)
<i>Cytoreductive Cryotherapy (n (%))</i>	11 (40.7%)
<i>Cytoreductive Cryotherapy + PLND (n (%))</i>	6 (22.2%)
<i>Cytoreductive HIFU (n (%))</i>	6 (22.2%)
Metastasis-directed therapy (n; %)	1 (3.7%)
<i>SABR (n (%))</i>	1 (3.7%)
Did not receive planned trial arm intervention* (n; %)	4 (14.8%)
<i>Death prior to planned trial arm intervention (n (%))</i>	1 (3.7%)
<i>Did not consent to trial arm intervention (n (%))</i>	3 (11.1%)
<i>Withdrew from study prior to visit 5 (n (%))</i>	1 (3.7%)
Intervention Arm 2: Radical (n)	26
Cytoreductive radiotherapy (n; %)	14 (53.8%)
<i>Cytoreductive EBRT (n (%))</i>	6 (23.1%)
<i>Cytoreductive EBRT + PLNRT (n (%))</i>	8 (30.8%)
Cytoreductive radical prostatectomy (n; %)	5 (19.2%)
<i>cRP (n (%))</i>	3 (11.5%)
<i>cRP + PLND (n (%))</i>	2 (7.7%)
Metastasis-directed therapy (n; %)	1 (3.8%)
<i>SABR (n (%))</i>	1 (3.8%)
Did not receive planned trial arm interventions* (n; %)	7 (26.9%)
<i>Clinically unfit for trial arm interventions (n (%))</i>	2 (3.7%)
<i>Did not consent to trial arm interventions (n (%))</i>	1 (3.7%)
<i>Withdrew from study prior to visit 5 (n (%))</i>	1 (3.7%)
<i>No reason provided (n (%))</i>	3 (11.5%)

Legend: *Reasons for not receiving trial arm 1 intervention cytotoreductive MIAT were: death prior to intervention = 1 (3.7%); withdrew from study prior to intervention = 1 (3.7%); did not consent to trial arm intervention = 3 (11.1%). *Reasons for not receiving trial arm 1 intervention RADICAL were: clinically unfit for intervention = 2 (3.7%); did not consent to trial arm intervention = 1 (3.7%). No reason provided = 3 (11.5%). HIFU - High-intensity focused ultrasound, EBRT – External Beam Radiotherapy; SABR – Stereotactic ablative body radiotherapy; PLNRT – Pelvic lymph node radiotherapy.

7.4.2 Primary Outcome II: Safety (adverse events and PROMS)

Overall, CTAE (version 5.0) defined Grade 2 adverse events occurred in 17.9% (5/28) of trial arm participants in the control arm; 33.3% (9/26) of Intervention Arm 1: MIAT; and in 15.4% (4/26) of Intervention Arm 2: Radical, respectively. Grade 3 adverse events occurred in 10.7% (3/28) of trial arm participants in the control arm; 7.4% (2/26) of Intervention Arm 1: MIAT; and in 15.4% (4/26) of Intervention Arm 2: Radical, respectively. Grade 4 adverse events occurred exclusively in the control arm in 17.9% (5/28) of trial arm participants. There were no Grade 5 adverse events reported.

The incidence of symptomatic locoregional adverse events is presented in **Table 23**. The most common were bothersome lower urinary tract symptoms (Grade ≥ 1). These were present in 16.0% (13/81) of the pilot RCT patients and were most commonly reported in Intervention Arm 2: Radical (6/26; 23.1%). Urinary retention requiring urethral catheters were common in all arms and present in 4.9% (4/81) of the pilot RCT patients. Emergency suprapubic catheter insertion and transurethral resection of the prostate occurred infrequently and events were confined to the control arm, in 3.6% (1/28) and 3.6% (1/28) of control arm participants, respectively. Genital oedema occurred exclusively in Intervention Arm 1: MIAT and Intervention Arm 2: Radical, in 7.4% (2/27) and 3.81% (1/27) of trial arm participants, respectively. Urinary tract infections were reported in 3.7% (3/81) of the pilot RCT patients and exclusively reported in participants in Intervention Arm 2: Radical (11.5%; 3/26).

Serious adverse events (SAE) deemed life threatening occurred in a single patient in Intervention Arm 2: Radical (3.8%; 1/26) due to pulmonary embolism 10 months post-EBRT. SAE's requiring inpatient hospitalisation occurred in 14.8% (12/81) of the pilot RCT patients, with 17.9% (5/28) in the control arm, 7.4% (2/26) in Intervention Arm 1: MIAT; and 19.2% (5/26) arising in Intervention Arm 2: Radical, respectively. There were no SAE's reported that resulted in death of a trial participant.

Death on study occurred in 14.8% (12/81) of trial participants during the pilot follow-up, and in 13.6% (11/81) this was reported as due to prostate cancer (**Table 23**). This was highest in the control arm 21.4% (6/28), followed by Intervention Arm 2: Radical 11.5% (3/26) and Intervention Arm 1: MIAT 7.4% (2/27). It should be noted that two participants and a further participant died on study prior to being able to receive their allocated trial treatment in Intervention Arm 2: Radical and Intervention ARM 1: MIAT, respectively.

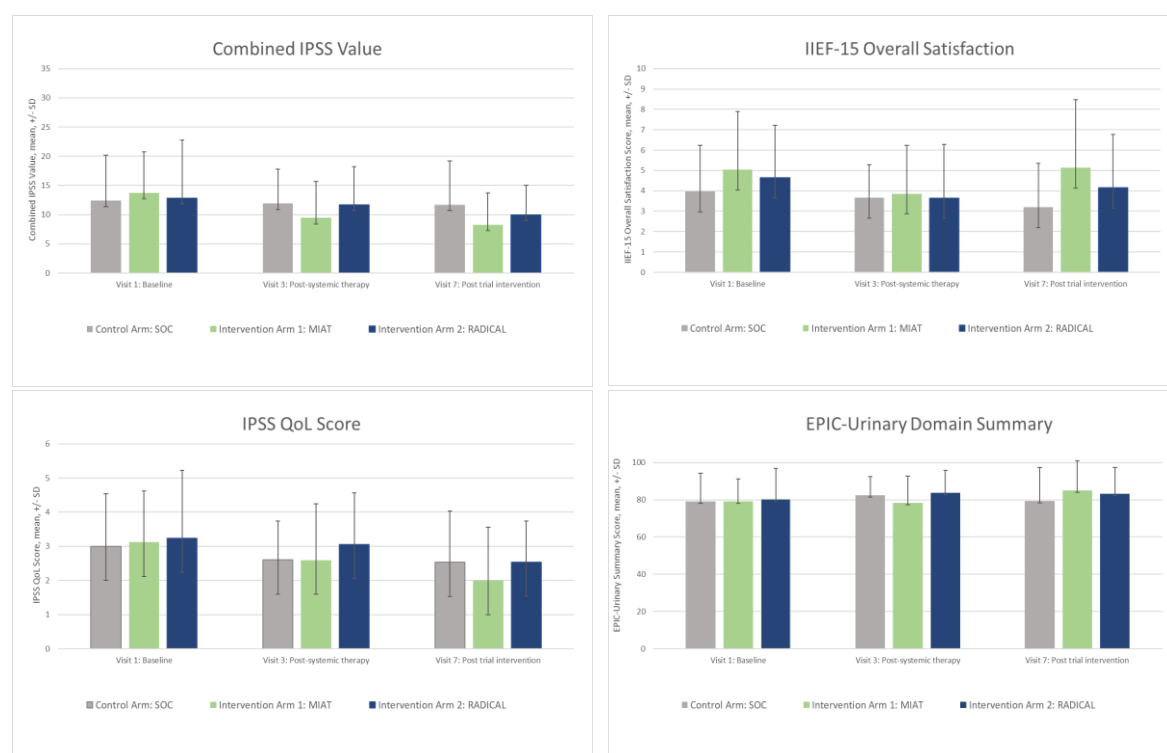
Table 23. Incidence of symptomatic locoregional adverse events and death by trial arm

Variable	Control Arm: SOC	Intervention Arm 1: MIAT	Intervention Arm 2: Radical	Total
<i>n</i>	28	27	26	81
Urinary retention requiring insertion of indwelling urethral catheter or CISC, <i>n</i> (%)	1 (3.6%)	2 (7.4%)	1 (3.8%)	4 (4.9%)
Emergency suprapubic catheter insertion, <i>n</i> (%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
Transurethral Resection of the Prostate (TURP), <i>n</i> (%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
Drainage of lymphocele, <i>n</i> (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Rectal injury or recto-urethral fistula formation <i>n</i> (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Genital oedema, <i>n</i> (%)	0 (0.0%)	2 (7.4%)	1 (3.8%)	3 (3.7%)
Nephrostomy insertion, <i>n</i> (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Haematuria requiring intervention, <i>n</i> (%)	0 (0.0%)	1 (3.7%)	0 (0.0%)	1 (1.2%)
Urinary tract infection, <i>n</i> (%)	0 (0.0%)	0 (0.0%)	3 (11.5%)	3 (3.7%)
Any (Grade ≥ 1) lower urinary tract symptoms, <i>n</i> (%)	4 (14.3%)	3 (11.1%)	6 (23.1%)	13 (16.0%)
Death from prostate cancer				
All pilot participants, <i>n</i> (%)	6 (21.4%)	2* (7.4%)	3* (11.5%)	11 (13.6%)
Visit 1 to Visit 7 [Week 0 to Week 52], <i>n</i> (%)	1 (3.6%)	1* (3.7%)	2* (7.7%)	4 (4.9%)

Legend: *In a single patient trial intervention not performed due to death from prostate cancer prior to planned MIAT. †In two patients trial intervention not performed due to clinical deterioration from prostate cancer, both patients died prior to Visit 7. cRP/EBRT. MIAT – Minimally invasive ablative therapy; TURP – transurethral resection of the prostate; CISC – clean intermittent self-catheterisation; SPC – suprapubic catheter insertion, cRP – Cytoreductive Radical Prostatectomy, EBRT – External beam radiotherapy.

Overall, IPSS combined scores were well balanced at baseline (**Figure 17**). Most patients had bothersome lower urinary tract symptoms scored as “moderate” (IPSS = 8 to 19) at baseline with mean (SD) combined IPSS values reported as: 12.39 (7.81) Control Arm: SOC; 13.76 (7) Intervention Arm 1: MIAT; and 12.82 (9.98) Intervention Arm 2, respectively. Similarly, IPSS Quality-of-Life (IPSS QoL) scores were well balanced with most participants reporting “mixed satisfaction/dissatisfaction” (IPSS QoL = 3) at baseline, with mean IPSS QoL values reported as: 3 (SD 1.54) Control Arm: SOC; 3.12 (SD 1.56) Intervention Arm 1: MIAT; and 3.24 (SD 1.98) Intervention Arm 2, respectively.

Figure 17. Summary of PROMS by trial arm at baseline, post-systemic therapy and post-trial intervention



Legend: The Expanded Prostate Cancer Index Composite Bowel and Bladder (EPIC) urinary domain summary score comprises several urinary items. These are formed by linear transformation of raw scores, ranging from “0” to “100” i.e. “worse” to “better”. IIEF-15 - International Index of Erectile Function 15-question, overall satisfaction domain (Q13,Q14): maximum score 10. Previously reported studies define sexual dysfunction mean score 4.4; control mean score 8.6 (250). The International prostate symptom score (IPPS) combined score: 0-7 “mildly symptomatic”; 8-19 “moderately symptomatic”; 20-35 “severely symptomatic”. IPSS Quality of life (IPSS QoL), range 0 “delighted”; 3 “mixed equally satisfied/dissatisfied”; 6 “terrible”. All presented mean (SD) scores are unpaired and as per ITT-analysis. PROMs – Patient-reported outcome measures. SD – Standard Deviation.

In all treatment arms mean IPSS combined scores improved following visit 3 and the induction of systemic therapy (**Figure 17**). Further improvements in mean IPSS combined scores were reported in all trial arms by visit 7. When Visit 7 was compared to baseline (Visit 1), the maximum improvements in mean combined IPSS scores were observed in participants in Intervention Arm 1: MIAT -6.41 (SD 9.46) (**Table 24**). When Visit 7 was compared to baseline, the lowest improvements in mean combined IPSS paired-scores were reported in participants in Control Arm: SOC -1.58 (SD 6.87).

In all treatment arms mean IPSS-QoL scores improved following Visit 3 and the induction of systemic therapy (**Table 24**). Further improvements in mean IPSS-QoL scores were reported all trial arms by Visit 7. When Visit 7 was compared to baseline (Visit 1), the maximum improvements in mean combined IPSS QoL scores were reported in participants in Intervention Arm 1: MIAT -1.11 (SD 1.49). Most participants in Visit 7 of Intervention Arm 1: MIAT were reported to be “mostly satisfied” with current urinary symptoms (mean 2.0 [SD 1.56]). When Visit 7 was compared to baseline (Visit 1), the lowest improvements in mean IPSS QoL scores were reported in participants in Intervention Arm 2: Radical -0.33 (SD 1.87).

In all treatment arms mean EPIC-Urinary Domain summary score improved following Visit 3 and the induction of systemic therapy (**Table 24**). When Visit 7 was compared to baseline (Visit 1), the maximum improvements in mean EPIC-Urinary Domain summary scores were reported in participants in Intervention Arm 1: MIAT +6.85 (SD 13.69). When Visit 7 was compared to baseline, the mean EPIC-Urinary Domain summary score reduced only in participants in Intervention Arm 2: Radical -1.53 (SD 15.22). A similar pattern was observed in mean EQ-5D-5L Health (VAS) scores (Visit 7 vs Visit 1; -10.17 [SD 21.24]).

At baseline “no urinary pad usage per day” was reported in 92.9% of the control arm, 88.5% of Intervention Arm 1: MIAT, and 76.9% of Intervention Arm 2: Radical, respectively. At Visit 7 “no urinary pad usage per day” was reported in 73.1% of the control arm, 72.7% Intervention Arm 1: MIAT, and 52.6% of Intervention Arm 2: Radical, respectively. When Visit 7 was compared to baseline (Visit 1), “any increase in pad usage” was reported in +3.8% of the control arm, +9.1% of Intervention Arm 1: MIAT, and +10.5% of Intervention Arm 2: Radical, respectively. When Visit 7 was compared to baseline (Visit 1), “any decrease pad usage” was reported in -3.8% of the control arm and -4.5% of Intervention Arm 1: MIAT, respectively. No participants reported any reductions in urinary pad usage in Intervention Arm 2: Radical.

At baseline IIEF-15 overall satisfaction scores were globally low against prior reported control values (≤ 8.6), suggesting elements of sexual dysfunction on average in all trial arms (**Table 24**) (250). However, only patients in the Control Arm: SOC had clinically significant low overall satisfaction scores that were suggestive of sexual dysfunction at baseline (≤ 4.4) with a mean value of 3.96 (SD 2.27). In all treatment arms mean overall satisfaction scores reduced following the induction of ADT, and further reductions were observed in both the Control Arm: SOC (3.2; [SD 2.14]) and Intervention Arm 2: Radical (4.15; [SD 2.61]) by visit 7, respectively. When Intervention Arm 1: MIAT visit 7 score (5.23; [SD 3.34]) was compared to baseline, the mean IIEF-15 overall satisfaction score was only

marginally impacted at -0.79 (SD 3.09) suggestive of preservation of elements of sexual function in participants of this trial arm.

Table 24. Key Patient-Reported Outcome Measures (PROMS) by trial arm and visit

PROMS Domain	Visit Schedule			
	Visit 1: Baseline	Visit 3: Post Systemic Therapy	Visit 3: Post-Trial Intervention	Visit 7 vs Visit 1
Control Arm: SOC (n=28)				
<i>IPSS Combined Score</i>				
Mean (SD)	12.39 (7.81)	11.9 (5.92)	11.68 (7.52)	-1.58 (6.87)
Missing (n, (%))	0 (0.0%)	6 (22.2%)	7 (26.9%)	7 (29.6%)
<i>IPSS-Quality of Life Score</i>				
Mean (SD)	3 (1.54)	2.6 (1.14)	2.53 (1.5)	-0.42 (2.04)
Ungradable (n, (%))	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)
Missing (n, (%))	0 (0.0%)	6 (22.2%)	7 (26.9%)	-
<i>EPIC-Urinary Domain Summary Score</i>				
Mean (SD)	79.17 (14.98)	82.52 (9.88)	79.36 (18.01)	+1.47 (21.74)
Ungradable (n, (%))	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)
Missing (n, (%))	0 (0.0%)	9 (34.6%)	6 (23.1%)	6 (23.1%)
<i>EPIC Pad Usage Score</i>				
None (n, (%))	26 (92.9%)	17 (65.4%)	19 (73.1%)	-
1 per day (n, (%))	1 (3.6%)	0 (0.0%)	0 (0.0%)	-
2 per day (n, (%))	0 (0.0%)	0 (0.0%)	1 (3.8%)	-
>= 3 per day (n, (%))	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Increase (% , (n))	-	-	-	+3.8% (1)
No change (% , (n))	-	-	-	65.4% (17)
Decrease (% , (n))	-	-	-	-3.8% (1)
Missing (n, (%))	1 (3.6%)	9 (34.6%)	6 (23.1%)	7 (26.9%)
<i>IIEF-15 Overall Satisfaction Score</i>				
Mean (SD)	3.96 (2.27)	3.67 (1.61)	3.2 (2.14)	-1.43 (2.24)
Ungradable (n, (%))	4 (14.3%)	2 (7.4%)	5 (19.2%)	6 (23.1%)
Missing (n, (%))	1 (3.6%)	7 (25.9%)	6 (23.1%)	6 (23.1%)
<i>EQ-5D-5L VAS score</i>				
Mean (SD)	76.86 (17.7)	73.57 (11.53)	73.82 (16.44)	+0.47 (20.06)
Ungradable (n, (%))	0 (0.0%)	0 (0.0%)	3 (14.3%)	3 (14.3%)
Missing (n, (%))	0 (0.0%)	0 (0.0%)	1 (4.8%)	1 (4.8%)

Intervention Arm 1: MIAT (n=27)				
<i>IPSS Combined Score</i>				
Mean (SD)	13.76 (7)	9.44 (6.24)	8.28 (5.44)	-6.41 (9.46)
Ungradable (n, (%))	1 (3.8%)	1 (5.3%)	1 (4.5%)	2 (9.1%)
Missing (n, (%))	0 (0.0%)	2 (10.5%)	3 (13.6%)	3 (13.6%)
<i>IPSS-Quality of Life Score</i>				
Mean (SD)	3.12 (1.56)	2.59 (1.66)	2 (1.56)	-1.11 (1.49)
Missing (n, (%))	0 (0.0%)	2 (10.5%)	3 (13.6%)	3 (13.6%)
<i>EPIC-Urinary Domain Summary Score</i>				
Mean (SD)	79.13 (12.01)	78.44 (14.17)	84.9 (16.06)	+6.85 (13.69)
Ungradable (n, (%))	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing (n, (%))	0 (0.0%)	4 (21.1%)	3 (13.6%)	5 (20.8%)
<i>EPIC Pad Usage Score</i>				
None (n, (%))	23 (88.5%)	13 (68.4%)	16 (72.7%)	-
1 per day (n, (%))	2 (7.7%)	1 (5.3%)	3 (13.6%)	-
2 per day (n, (%))	1 (3.8%)	0 (0.0%)	0 (0.0%)	
>= 3 per day (n, (%))	0 (0.0%)	1 (5.3%)	0 (0.0%)	
Increase (% , (n))	-	-	-	+9.1% (2)
No change (% , (n))	-	-	-	72.7% (16)
Decrease (% , (n))	-	-	-	-4.5% (1)
Missing (n, (%))	0 (0.0%)	4 (21.1%)	3 (13.6%)	3 (13.6%)
<i>IIEF-15 Overall Satisfaction Score</i>				
Mean (SD)	5.05(2.84)	3.86(2.38)	5.13(3.34)	-0.79 (3.09)
Ungradable (n, (%))	4 (15.4%)	3 (15.8%)	4 (18.2%)	5 (22.7%)
Missing (n, (%))	0 (0.0%)	2 (10.5%)	3 (13.6%)	3 (13.6%)
<i>EQ-5D-5L Health (VAS) score</i>				
Mean (SD)	69.38 (20.03)	66.12 (18.81)	72.58 (13.89)	+5.26 (21.96)
Missing (n, (%))	0 (0.0%)	0 (0.0%)	1 (5.0%)	1 (5.0%)
Intervention Arm 2: Radical (n=26)				
<i>IPSS Combined Score</i>				
Mean (SD)	12.82 (9.98)	11.72 (6.49)	10 (5.02)	-2.33 (8.34)
Ungradable (n, (%))	3 (11.5%)	1 (4.2%)	2 (10.5%)	4 (21.1%)
Missing (n, (%))	1 (3.8%)	5 (20.8%)	6 (31.6%)	6 (31.6%)
<i>IPSS-Quality of Life Score</i>				
Mean (SD)	3.24 (1.98)	3.06 (1.51)	2.54 (1.2)	-0.33 (1.87)
Ungradable (n, (%))	0 (0.0%)	1 (4.2%)	0 (0.0%)	1 (5.3%)
Missing (n, (%))	1 (3.8%)	5 (20.8%)	6 (31.6%)	6 (31.6%)

<i>EPIC-Urinary Domain Summary Score</i>				
Mean (SD)	80.41 (16.46)	83.65 (12.08)	83.29 (13.96)	-1.53 (15.22)
Ungradable (n, (%))	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing (n, (%))	3 (11.5%)	6 (25.0%)	6 (31.6%)	9 (47.4%)
<i>EPIC Pad Usage Score</i>				
None (n, (%))	20 (76.9%)	17 (70.8%)	10 (52.6%)	-
1 per day (n, (%))	0 (0.0%)	0 (0.0%)	1 (5.3%)	-
2 per day (n, (%))	2 (7.7%)	1 (4.2%)	1 (5.3%)	-
>= 3 per day (n, (%))	0 (0.0%)	0 (0.0%)	1 (5.3%)	-
Increase (% (n))	-	-	-	+10.5% (2)
No change (% (n))	-	-	-	42.1% (8)
Decrease (% (n))	-	-	-	-0.0% (0)
Missing (n, (%))	4 (15.4%)	6 (25.0%)	6 (31.6%)	9 (47.7%)
<i>IIEF-15 Overall Satisfaction Score</i>				
Mean (SD)	4.65 (2.57)	3.65 (2.64)	4.15 (2.61)	-1.0 (2.32)
Ungradable (n, (%))	2 (7.7%)	3 (12.5%)	1 (5.3%)	2 (10.5%)
Missing (n, (%))	1 (3.8%)	4 (16.7%)	5 (26.3%)	6 (31.6%)
<i>EQ-5D-5L Health (VAS) score</i>				
Mean (SD)	76.68 (18.57)	73.68 (18.77)	71.77 (20)	-10.17 (21.24)
Ungradable (n, (%))	0 (0.0%)	1 (4.8%)	1 (6.7%)	1 (6.7%)
Missing (n, (%))	1 (3.8%)	1 (4.8%)	1 (6.7%)	2 (13.3%)

Legend: Individual visit data as per ITT-analysis, without pairing. Paired-PROMs presented for comparison of Visit 7 versus Visit 1. The Expanded Prostate Cancer Index Composite Bowel and Bladder (EPIC) urinary domain summary score comprises several urinary items. These are formed by linear transformation of raw scores, ranging from "0" to "100" i.e. "worse" to "better". IIEF-15 - International Index of Erectile Function 15-question, overall satisfaction domain (Q13,Q14): maximum score 10. Previously reported studies define sexual dysfunction mean score 4.4; control mean score 8.6 (250). The International prostate symptom score (IPSS) combined score: 0-7 "mildly symptomatic"; 8-19 "moderately symptomatic"; 20-35 "severely symptomatic". IPSS Quality of life (IPSS QoL), range 0 "delighted"; 3 "mixed equally satisfied/dissatisfied"; 6 "terrible". All presented mean (SD) scores are unpaired and as per ITT-analysis. PROMs – Patient-reported outcome measures, SD – Standard Deviation, VAS – Visual Analogue Score.

7.4.4 Primary Outcome II: Local tumour response

Overall, 49/53 (92.4%) of intervention arm trial participants underwent the protocolled repeat mpMRI following systemic therapy but prior to trial treatment (**Chapter 6**). The reasons for not performing repeat mpMRI prostate were as follows 1/53 (1.9%) death from prostate cancer prior to mpMRI and 3/27 (5.6%) withdrawal from study. In 47 / 49 (95.9%) complete paired data was available for analysis.

MRI prostate volume reduced from a mean of 47.49 cc (SD 20.16) to 26.06 cc (SD 13.86) post systemic therapy ($p < 0.0001$; [95% CI -15.04 to -30.1]) (**Table 25**). There was a significant reduction in MRI-T4 stage reported pre- and post-systemic therapy (44.9% vs

55.1%; $p=0.0184^*$). In addition, Tx disease was reported in 8.5% of post-systemic therapy mpMRI prostate.

There was a significant downstaging in MRI-N1 stage reported pre- and post- systemic therapy (72.3% vs 40.4%; $p=0.0184^*$). MRI-reported lesion diameter (mm) was available 13/49 (26.5%) of patients at baseline and post-systemic therapy. There was a significant reduction in mean MRI reported lesion diameter (mm) pre- and post- systemic therapy in this subgroup (33.19 [SD 16.54] vs 21 [8.39]; $p=0.0262$; [95% CI -1.6 to -22.8]).

Table 25. Summary statistics for mpMRI prostate measurements at baseline and post-systemic therapy

	Statistics	Pre-systemic therapy	Post-systemic therapy	<i>p-value / % change</i>
MRI-Prostate Volume (PVol)	Mean (SD)	47.49 (20.16)	26.06 (13.86)	$p<0.0001^*$
MRI Tumour (T-) Stage	Tx	0 (0.0%)	4 (8.5%)	-
	T2	1 (2.1%)	6 (12.8%)	+500.0%
	T3	3 (6.4%)	0 (0.0%)	-100.0%
	T3a	3 (6.4%)	7 (14.9%)	+133.3%
	T3b	18 (38.3%)	18 (38.3%)	0.0%
	T4	21 (44.7%)	10 (21.3%)	-52.4%
	$\leq$ T3b	25 (53.2%)	35 (74.5%)	-
	T4	21 (44.7%)	10 (21.3%)	$p=0.0184^*$
MRI Nodal (N-) Stage	Missing from eCRF – n (%)	0 (0.0%)	2 (4.1%)	-
	Nx	0 (0.0%)	2 (4.3%)	-
	N0	12 (25.5%)	24 (51.1%)	+100.0%
	N1	34 (72.3%)	19 (40.4%)	-20.83%
	N0/Nx	12 (25.5%)	26 (55.4%)	-
	N1	34 (72.3%)	19 (40.4%)	$*p=0.0022$
MRI Nodal (N-) Stage	Missing from eCRF – n (%)	1 (2.1%)	2 (4.3%)	-

Legend: *Chi-square analysis were used to assess differences MRI-nodal status (N1 versus N0/Nx) and MRI T4 Status (T4 versus $\leq$ T3b) in comparison to baseline MRI. *Paired t-test was used to assess the significance of the change in mean MRI prostate volume and MRI lesion length compared to baseline. MRI – Magnetic Resonance Imaging. PI-RADS version 2.0, post systemic therapy lesions are not issued a score.

Overall, 32 of 53 (60.4%; [95%CI 46.00–73.55]) second prostate biopsies were performed following systemic therapy for 6-9 months (**Table 26**). A further central review of histology samples in this trial is available in **Chapter 8**.

Table 26. Post SOC repeat prostate biopsy results

	Intervention Arm 1: MIAT		Intervention Arm 2; Radical		Total	
	<i>n</i> (%)	95% CI	<i>n</i> (%)	95% CI	<i>n</i> (%)	95% CI
Second prostate biopsies following systemic therapy						
Biopsy performed, <i>n</i> (%)	19 (70.4%)	(49.82% to 86.25%)	13 (50.0%)	(29.93% to 70.07%)	32 (60.4%)	(46.00% to 73.55%)
Patient Declined Biopsy, <i>n</i> (%)	1 (3.7%)	-	3 (11.5%)	-	4 (7.5%)	-
Complete pathological response						
Total cases, <i>n</i> (%)	3 (11.1%)	(2.35% to 29.16%)	3 (11.5%)	(2.45% to 30.15%)	6 (11.3%)	(4.27% to 23.03%)
Prostate cancer not identified (pT0), <i>n</i> (%)	3 (11.1%)	(2.35% to 29.16%)	3 (11.5%)	(2.45% to 30.15%)	6 (11.3%)	(4.27% to 23.03%)
Benign	1 (3.7%)	(0.09% to 18.97%)	1 (3.8%)	(0.1% to 19.64%)	2 (3.8%)	(0.46% to 12.98%)
Atrophy, <i>n</i> (%)	1 (3.7%)	-	1 (3.8%)	-	2 (3.8%)	-
Inflammation, <i>n</i> (%)	0 (0.0%)	-	1 (3.8%)	-	1 (1.9%)	-

Legend: Only includes patients who were randomised to intervention arms 1 and 2 (MIAT and Radical). The SOC group (control arm) does not receive a post-SOC biopsy at 6-9 months. All histology in Intervention Arm 1: was acquired via transperineal prostate biopsy 13/13 (100%). In intervention arm 2: radical repeat biopsy histology was acquired via a transperineal prostate biopsy in 8/13 (61.5%) and via review of whole mount prostatectomy samples in 5/13 (38.7%), respectively.

In Intervention Arm 1: MIAT, 19 of 27 (70.4%; [95%CI 49.82–86.25]) participant underwent a second prostate biopsy (**Table 26**). Reasons for not performing biopsy were as follows: 1/27 (3.7%) death from prostate cancer prior to biopsy, 1/27 (3.7%) withdrew consent for second biopsy, 3/27 (11.1%) withdrawal from study, and 1/27 (3.7%) due to protocol deviation.

In Intervention Arm 2: Radical, 13 of 26 (50.0%; [95%CI 29.93–70.07]) participants underwent a second biopsy. Reasons for not performing second biopsy were as follows:

3/26 (11.5%) withdrew consent for second biopsy, 8/26 (30.1%) withdrawal of consent for trial intervention, 2/26 (7.7%) unfit for repeat biopsy/trial treatment.

Overall, complete pathological response rate was reported as 11.3% (6/53; [95%CI 4.27-23.03]). Complete pathological response rate was equal in both trial arms at 11.1% (3/27) in Intervention Arm 1: MIAT and 11.5% (3/26) in Intervention Arm 2: Radical, respectively. Entirely benign features were reported in a minority of the overall pilot RCT patients (2/53; 3.8% [95%CI 0.46-12.98]).

Thus, 26 of 32 (81.2%) of trial participants had evidence of residual prostate adenocarcinoma on second prostate biopsy. Within this pilot RCT patients mean MCCL reduced by -2.24 mm (12.56 [SD 4.03] vs 10.32 [SD 8.70]; $p=0.24$ [95% -1.62 to 6.10]). Maximum residual MCCL following systemic therapy was reported as 45 mm.

7.4.5 Covid-19 related impact

For completeness, presented in **Appendix E** are the results of the Covid-19 related impact analysis. A complete list of Covid-19 related protocol deviations accompanies this, of which 10 were reported. Of these, one affected the pilot RCT outcome as a single trial participant was unable to undergo a repeat prostate biopsy due to recent coronavirus (Covid-19) infection and proceeded to trial intervention of cytoreductive radiotherapy. No other protocol deviations impacted pilot outcomes.

7.5 Discussion

In this multicentre randomised controlled trial, we were able to demonstrate the feasibility of allocating patients with *de novo* synchronous mHSPC to systemic therapy intensification with cytoreductive minimally invasive ablative therapy, cytoreductive radical prostatectomy or cytoreductive radiotherapy, against an active comparator of standard of care alone. We confirmed satisfactory recruitment, randomisation, and compliance of this trial design. All trial intervention arm treatments had an acceptable safety and adverse event profile, inclusive of the novel cytoreductive MIAT. Furthermore, we reported low rates of complete pathological response of the primary tumour. This confirms, for the first time, the presence of a viable primary tumour in the majority of patients with mHSPC following contemporary systemic therapy intensification. Providing weight to the narrative that the destruction of a highly prevalent persistent residual viable primary tumour and its crosstalk with established metastatic lesions, may reduce the likelihood of lineage adaptation and thus lead to progression-free survival benefits.

To our knowledge, IP2-ATLANTA is the first study to randomise patients with *de novo* synchronous mHSPC to systemic therapy intensification and cytoreductive MIAT+/- PLND or

cytoreductive radical therapy (cRP+/-PLND or cytoreductive EBRT+/-PLNRT), with or without metastasis-directed therapy, against an active comparator arm. Our study recruitment rate was 66.9% (SD 8.5; [95%CI 58.5-75.3] and this exceeded the expected planned recruitment rate of 33% (95%CI +/-10%). Our reported recruitment rate is also in keeping with the TRoMBone randomised study (cRP+PLND versus no local treatment), reported at 71.8% (51/71) (221). Similar to TRoMBone, we found the number of patients eligible were lower than expected per month, with our central cancer trial network centres recruiting an average of less than 1 patient per month. Combined with the impact of the COVID-19 pandemic on trial site capabilities, the IP2-ATLANTA accrual remained constant but below that of predicted throughout the internal pilot study, leading to an extended period of accrual.

In our study, 3.7% of patients in the radical therapy arm, which included the option of cytoreductive radical prostatectomy, withdrew consent for allocated trial treatment at point of planned delivery. This is comparable to a 4.0% (1/25) rate reported in the recent TRoMBone (221). However, our rate was higher than the 2.0% (2/100) rate reported in Dai and colleagues randomised study of ADT with cRP versus ADT alone (256). Following IP2-ATLANTA commencing, the SWOG 1802 (Southwest Oncology Group; Texas; USA) randomised study opened and is currently recruiting over 1200 patients with all burden disease to either standard systemic therapy (SST) or SST + radical therapy (cRP or EBRT), utilising our radical trial arm design (237). The results of our randomised study demonstrate the acceptable feasibility of this pragmatic trial design, that integrate cRP alongside EBRT as a radical treatment option in mHSPC.

The acceptability of randomisation to cytoreductive MIAT+/-PLND has not been reported previously. Withdrawal of consent for allocated trial treatment at point of expected delivery in this arm was higher at 11.1%. However, indirect comparisons can be drawn from randomised studies in the localised disease setting, such as PART which allocated patients to focal HIFU or radical prostatectomy (257). In this study withdrawal rates of 2.4% and 21.9% were reported at point of allocated treatment, respectively. In addition, 22.2% underwent lymph node treatment, compared to 38.4% in Intervention Arm 1: Radical, this is despite declarations of intention to treat pelvic lymph nodes being similar in both arms 55% and 46%, respectively. It is unclear whether patient factors, surgeon factors or a combination results in the reduced compliance to pelvic lymph node treatment in this trial arm.

The relative uncertainty on the complication profile associated with MIAT in *de novo* synchronous mHSPC may have increased the observed withdrawal rate in the internal pilot.

Thus, the publication of these promising results and the associated technical performance data (**Chapter 10**), may reduce the withdrawal rates in this intervention arm reported in the main study component of IP2-ATLANTA.

Baseline characteristics, Gleason/ISUP Grade Group, tumour and nodal staging, PSA, and metastatic burden were all comparable in our study to the STAMPEDE (arm-H) randomised study which explored cytoreductive prostate radiotherapy against systemic therapy alone (16). The accurate reporting of adverse events was particularly important in this study given the introduction of novel cytoreductive MIAT as a new treatment. In our study, CTAE Grade 4 adverse events were limited to the control arm. Grade 3 adverse events occurred in 7% of those undergoing cytoreductive MIAT and 15% in the radical arm.

Despite the inclusion of MRI-T4 disease in 45% of patients at baseline, we did not report any intraoperative rectal injury or recto-urethral fistula formation. This is in comparison to prior cRP randomised trials where rectal injury rate has been reported to be between 1.2% to 4.0% (221,256). In these studies the use of docetaxel or ARSI's in addition to ADT was highly limited (0.0% to 45.8%) (221,256). This is compared to 100% in Intervention Arm 1: MIAT and 88.5% in Intervention Arm 2: Radical, in this study. We also performed serial mpMRI prostate in the intervention arms and this enabled us to report on the radiological response to contemporary systemic treatment. Our findings confirm large volume reductions of a mean of 21 cc and a 50% (baseline 21/47 [44.7%] versus 10/47 [21.3%] post-systemic therapy) downstaging of MRI-reported T4 disease compared to baseline imaging. It could be postulated that the impact of such significant cytoreduction was protective against risk of rectal injury from cRP and recto-urethral fistula following cytoreductive MIAT and radiotherapy. In addition, patients with persistent T4 disease may have been directed towards non-surgical trial treatments utilising our radical trial arm design where cytoreductive radiotherapy was an alternative option.

Urinary incontinence following cytoreductive intervention in mHSPC is an ongoing key concern for patients' and clinicians (**Chapter 4**) (163). In our pilot of IP2-ATLANTA, reported incontinence rates that were similar to those observed in patients undergoing our trial treatments for localised prostate cancer (212,258,259). At 52 weeks follow-up, approximately 10% patients reported an increase in urinary pad usage in both intervention arms compared to an increase of only 4% in the control arm. More than one pad usage per day was not reported in patients undergoing cytoreductive MIAT, but occurred in 10% of patients in the radical arm. This compares to rates ranging between 8.2% - 16.7% in randomised studies utilising cRP (221,256,260).

In the internal pilot RCT only 9.6% (2/21) of patients eligible for SABR, in whom there was also a declared intent perform SABR at baseline, underwent the treatment. These are marginally lower than predicted and a number of reasons as to the limited use of SABR in the pilot RCT patients. Firstly, in 50% the radical intervention arm, cytoreductive radiotherapy was used. As per the trials MDT SOP, cytoreductive radiotherapy may have included simultaneous radiotherapy directed to pelvic bone metastasis within reach of planned radiotherapy fields (e.g. pubic ramus), removing the need for further SABR (**Appendix F**). Secondly, SABR could only be delivered to a an anatomical site if the target lesion could be reliably identified (irrespective of functional activity) or accurately localised (irrespective of identification). In a number of common clinical scenarios, such as rib lesions or central iliac bone lesions, these criteria are unlikely to have been met post-systemic therapy. The larger sample size of main study will be able to explore the use of SABR post-systemic therapy and accurately report on the adverse event rates related to this intervention.

Bothersome lower urinary tract symptoms, assessed by IPSS, showed maximal improvements in the cytoreductive MIAT arm and were lowest in the control arm. Quality of life (EQ-5D-5L Health Visual Analogue Score) improvements were highest in the cytoreductive MIAT arm. Marginal reductions in QoL were reported in Intervention Arm 2: Radical Therapy. However, such changes were in keeping with those reported in prior cRP randomised studies (221).

To our knowledge, multi-parametric MRI prostate response assessment of the primary tumour in mHSPC has not been reported previously in the literature. However, response to neoadjuvant Enzalutamide prior to radical prostatectomy in localised prostate cancer ($n=36$), has been reported by Karzai and colleagues' (225). Similar to our study, significant reductions in intraprostatic tumour volumes ($>50\%$ reduction in 55 / 59 tumours) and MRI-prostate volume (median PVol 39.5 cc [IQR NR] to 20.0 cc [IQR NR]) were reported.

In our study almost two thirds of patients underwent their planned re-classification transperineal prostate biopsy, or had whole-mount specimens available, following contemporary systemic therapy. There has been highly limited reporting of complete pathological response in mHSPC using ADT with Docetaxel or ARSI's. In 11.3% of patients in this study complete pathological response occurred. Our rate was higher than the previously reported 2.3% (2/85) on cRP whole-mount specimens following ADT monotherapy. Our rate was also higher than the 4.3% (1/23) rate reported on radical prostatectomy whole-mount specimens following 6-months of Enzalutamide with ADT in the high-risk non-metastatic setting (261).

Our findings confirm that most patients with *de novo* synchronous mHSPC have a persistent viable residual primary tumour despite contemporary systemic therapy escalation. Concerns regarding exposure of the majority of patients to unnecessary invasive cytoreductive local treatments are not supported by this evidence. The biological significance of residual intraprostatic disease following such systemic therapy is relatively unknown (44). However, it has been reported that highly active systemic anticancer therapies drive cancer cells to evolve to form resistant cell lineages, thus primary tumour cytoreduction can restrict this opportunity (31,44). The main study component of IP2-ATLANTA will confirm if such cytoreductive interventions directed at residual intraprostatic tumour burden will translate to additional oncological benefits.

7.6 Limitations

Although we report on a multicentre randomised controlled trial there are a number of limitations. At baseline in 29.6% (24/81) the exact distant site of metastatic disease was not available (M1 (any) – not specified). However, metastatic burden classification has been previously predictive of oncological outcome in mHPSC, and this was available in all patients (16). Complete pathological response was analysed on transperineal prostate biopsy or on whole mount prostatectomy specimens following a repeat mpMRI. Whilst transperineal targeted and systematic prostate biopsy combined with mpMRI has been proven to demonstrate high concordance in Gleason Grade ≥ 7 disease, it is possible that residual foci of treated prostate adenocarcinoma may have been missed when compared to evaluation of a whole mount prostatectomy specimens or a template mapping prostate biopsy, impacting the response rate reported (262). Given the nature of the alternative trial arm interventions (i.e., radiotherapy or MIAT), this prostate biopsy approach was the only viable method of histological reclassification of disease post-systemic therapy in this study. In three patients in the radical arm, LHRHa without Docetaxel or ARSI's was used at the treating trial oncologist's discretion. Finally, we were unable to comment on the root cause of reduce compliance for pelvic lymph node treatment in Intervention Arm 1: cytoreductive MIAT.

7.7 Conclusion

The internal pilot of this randomised controlled trial confirms it is both feasible and safe to allocate patients with *de novo* synchronous mHSPC to cytoreductive minimally invasive ablative therapy, or cytoreductive radical prostatectomy or cytoreductive radiotherapy, with or without metastasis-directed treatments. Furthermore, we report that despite the contemporary combination of ADT with systemic anticancer therapies, the majority of patients have a viable residual prostate tumour on which local cytoreduction can be targeted. The main study component of the IP2-ATLANTA randomised study will confirm treatment efficacy and superiority of any trial interventions against current standard of care.

Chapter 8 – Histopathological behaviour of the primary tumour in response to contemporary systemic therapy

8.1 Overview

In this chapter we have performed an in-depth morphologic characterisation of the primary prostate tumour in patients with *de novo* synchronous mHSPC, at baseline diagnosis and post-systemic therapy. The analysis is within the internal pilot RCT patients of the IP2-ATLANTA randomised study, “Primary Pilot Endpoint C” (**Chapter 6**) (3). Providing a deeper histopathological characterisation of the primary in the setting of established metastatic disease is novel. We chart the morphological changes to the primary in response to androgen deprivation therapy in combination with docetaxel or enzalutamide. We provide a particular focus on exploring patients who had reported complete pathological response on post-systemic therapy prostate biopsy or whole-mount specimen at 6-9 months within the internal pilot RCT study.

8.2 Introduction

Clinical trials evaluating local cytoreductive surgical treatments have provided us with the opportunity to perform a deeper characterisation of the primary prostate tumour in response to systemic therapy intensification in patients with *de novo* synchronous mHSPC. As previously described in this thesis (**Chapter 2**), the persistence of a primary tumour and potential for primary-to-metastasis communication remains a cornerstone in support of local cytoreductive treatment for metastatic prostate cancer (51,263).

Furthermore, as eluded too in **Chapter 5**, there has been a historical movement against performing primary tumour biopsy in patients with presumed metastatic prostate cancer, identified either by concerning surrogate markers of disease burden (e.g. absolute serum PSA > 100 ng/ml), radiological evidence or clinical examination findings (202-204). As such little is known about the impact of chemotherapy and androgen receptor signalling inhibitors (ARSI's) on tumour histopathologic features in patients with established metastatic disease. Furthermore, we do not understand if such features retain clinical or prognostic value in this setting (230).

There have been numerous studies on the role of “neoadjuvant” ADT and taxane based chemotherapy in patients with “high-risk localised” or “locally-advanced” prostate cancer planned for radical prostatectomy with curative intent (264-267). These studies had primarily focused on the goal of “downstaging” the primary and thus converting this into a significant

additional oncological benefit. Unfortunately, to date no studies have been able to report a significant additive survival benefit of any neoadjuvant therapy in this setting (268).

However, in addition to the primary endpoints, such studies also reported on morphologic changes, for example intraprostatic tumor volume, high-grade prostatic intra-epithelial neoplasia (HGPIN), margin positivity and residual tumour rates (*ypT0*) in these cohorts. This has provided us with a unique insight into the behavior of adenocarcinoma and non-neoplastic prostate tissue when exposed to such agents, when they are used as short-term neoadjuvant therapies in the curative setting. The primary findings are pre-dominantly drawn from baseline T1-T3a disease, and it should be noted that intraprostatic changes were most distinct in those with $\leq$ T2 disease when compared to T3 disease (243,264,265,267-269). A summary of the current literature on prostate neoplasia and nonneoplastic changes in response to neoadjuvant ADT, Docetaxel and ARSI's is provided in **Table 27**.

Table 27. Summary of reported histopathologic features of prostate neoplasia following neoadjuvant ADT, chemohormonal and androgen receptor signalling inhibitors

Histopathologic Feature	ADT	Chemotherapy with ADT	ARSI's with ADT
<i>Tumour Volume</i> (211,269,270)	Up to 40% reduction after 4 months, up to 60% reduction after 6 months.	3.3% minimal residual disease with a tumour volume of <5%.	Tumour volume significant reduction when AA + ADT compared to ADT alone
<i>Margin Positivity/Status</i> (211,242,261,264-269,271)	Up to 25% reduction in positive margin rates	Persistent positive margin status in 0-33.3% of patients	Persistent positive margin status in 5-21.7% of patients
<i>High-Grade Prostatic intra-epithelial neoplasia (HGPIN)</i> (269,272)	Nucleolar prominence should be disregarded to distinguish high-grade PIN from normal glands When removed from definition, HGPIN is present in: Present in 72% of cases after 3 months, and in 59% of cases at 6 months.	NR	NR
<i>Complete pathological response / ypT0</i> (242,261,264-268)	Reported between 2-8% of patients	Randomised study data failed to report ypT0 (0%)	Reported in 4-13%
<i>Gleason Grade</i> (264,269)	False apparent increase in Gleason score due to either: Resistant high-grade cancer cell number	As per ADT	As per ADT

	Reduction in mass leaving residual single cancer Gleason scoring not recommended for use following ADT		
<i>Intraductal carcinoma (IDC) and invasive carcinoma with cribriform architecture (230,273)</i>	Consider the presence of cribriform pattern or intraductal spread as a stronger predictor of biochemical relapse than pathologic stage, tumour volume, PSA level at diagnosis, and biopsy Gleason score. Consider using Efstathiou <i>et al.</i> Post-ADT Therapy Histologic Classification: Group A,B,C	IDC and cribriform architecture were identified in 20% and 14% of cases, respectively Consider using the following criteria for IDC in Docetaxel exposed tissue: 2-fold expansion of prostate gland lumina - neoplastic cells span, in a solid or - cribriform architecture, the lumen of glands in which a basal cell layer is retained - nuclear atypia	NR
<i>Neuroendocrine Differentiation (NE) (274-276)</i>	NE is common following prolonged ADT exposure. NE is present in up to 10% of patients with castrate-resistant disease. NE expression is typically AR-negative	NR	NR
<i>Other observed changes in benign prostate tissue (243)</i>	Marked glandular atrophy within the peripheral zone with prominent basal cells and rupture of atrophic acini. Prominent basal cell hyperplasia within the transition zone.	NR	NR

Legend: When referring to Androgen Deprivation Therapy, this includes maximum androgen blockade (MAB), combining luteinizing hormone releasing hormone (LHRH) agonist and a pure anti-androgen (e.g. Bicalutamide). HGPIN - High-Grade Prostatic intra-epithelial neoplasia; ADT – Androgen Deprivation Therapy; NE – Neuroendocrine Differentiation; IDC – Intraductal Carcinoma; AA – Abiraterone Acetate; ARSI - Androgen receptor signalling inhibitors; NR – Not reported.

8.3 Study objectives

The aim of this descriptive histopathological study was to perform a blinded assessment of local histopathological reporting of trial arm specimens further provide a detailed morphologic characterisation of the primary prostate tumour in patients with *de novo* synchronous mHSPC within the pilot RCT patients of the IP2-ATLANTA study.

8.4 Methods

8.4.1 Study design and ethical approval

This study is a post-hoc analysis of “Primary Pilot Endpoint C” (**Chapter 6**) referring to serial prostate histology performed in the internal pilot RCT patients of the IP2-ATLANTA study. The phase II, multicentre randomised controlled trial has been described in detail in **Chapter 6 & 7** of this thesis, and thus for brevity is not replicated here. This study is applicable to patients who were allocated to the interventions arms of the trials internal pilot ($n=81$).

8.4.2 Multicentre consensus meeting for central histopathology review

We performed a non-systematic review of the literature, which is summarised in the introduction and discussion sections of this thesis chapter. A trial consensus board of interested consultant histopathologists from the IP2-ATLANTA trial was assembled from the following members (in addition to myself and Prof. Hashim U. Ahmed):

- Dr. Andrew Smith (AS), Consultant Histopathologist, Imperial College Healthcare NHS Trust [*ATLANTA Lead Histopathologist*]
- Dr. Hannah Markham (HM), Consultant Histopathologist, University Hospitals Southampton
- Dr. Maidie Yeung (MY), Consultant Histopathologist, Imperial College Healthcare NHS Trust

On the 1st April 2021 I chaired a central trial histopathology consensus meeting where we established the central review process for histopathology specimens in the IP2-ATLANTA trial. We were able to generate the “**Central Histopathology Review SOP**” (A. Smith, M.J. Connor, H. Markham, M. Yeung, H.U. Ahmed), available in full in **Appendix F**.

Given the uncertainty in the clinical translation of the reclassification biopsies in the post-systemic therapy setting in mHSPC, it was agreed by all parties that central histopathology review was for “research purposes only”. Furthermore, trial sites would not be re-issued with a new report, even in the instance that discordance emerged. Central reader reports were thus not added to the patients’ clinical notes. Furthermore, central histopathology reports

would not be used to alter or decide upon patients' planned, current or indeed future clinical care.

It was agreed that all available samples should undergo a blinded central reader report by a trial Consultant Histopathologist (AS) in accordance with the International Society of Urological Pathology guidelines on prostate reporting (version 2019) (277). Additional parameters outlined in the central review a priori for research purposes only (i.e., minimal residual disease) would also be collected as part of this process. Samples suitable for review included prostate biopsies and/or whole-mount prostatectomy specimens. The reporting histopathologist was blinded to systemic agent used, clinical details and the trial arm. The trial arm blinding was as much as practical (i.e., whole-mount prostatectomy specimens clearly indicated radical arm allocation although the pre-operative biopsy review was carried out blind to arm allocation).

8.4.3 Variable to be considered at central review

Following the trial's histopathology consensus meeting we prospectively agreed upon a set of variables for consideration at central review, which are summarised in **Table 28**.

Table 28. Summary of variables for consideration at central review

Specimen	Variables
Baseline Prostate Biopsy	▪ Gleason Grade / International Society of Urological Pathology (ISUP) Grade Group (277) ▪ Maximum cancer core length (MCCL) ▪ Percentage of pattern 4 ▪ Cribriform Pattern ▪ Intraductal Carcinoma of the Prostate (IDC-P) ▪ High grade prostate intraepithelial neoplasia (HGPIN) ▪ Perineural invasion (PNI) ▪ Extra-prostatic extension (EPE) ▪ Neuroendocrine Differentiation (NED)
Second Prostate Biopsy OR Whole-mount prostatectomy specimens	▪ Complete pathological response (CPR) ▪ Minimal residual disease (MRD) ▪ IDC-P ▪ Cytoplasmic loss and/or cytoplasmic ratio changes ▪ Prominence of nucleoli ▪ Cell size reduction ▪ Cribriform glands with central necrosis ▪ Clear cell changes ▪ NED ▪ PNI ▪ EPE ▪ <i>Whole-mount only:</i> ○ Tumour volume ○ Margin status ▪ <i>Benign changes:</i> ○ prominent basal cells ○ urothelial metaplasia

Legend: NED – Neuroendocrine differentiation; IDC – Intraductal Carcinoma; HGPIN – High grade prostate intraepithelial neoplasia; PNI – Perineural invasion; EPE – Extra-prostatic extension; NED – neuroendocrine differentiation.

Intraductal Carcinoma of the Prostate (IDC-P) was defined at baseline (Guo and Epstein criteria) and following systemic therapy (O'Brein *et al.*) as (1) 2-fold expansion of prostate gland lumina (2) neoplastic cells span, in a solid or cribriform architecture the lumen of glands in which a basal cell layer is retained (3) nuclear atypia (230,278).

8.4.4 Assessing pathological response

Complete pathological response (CPR) on post-systemic therapy prostate biopsy was defined as (240-243):

- Presence of benign tissue or grade pT0 (prostate cancer not identified)
AND/OR
- Absence of “post-hormone therapy adenocarcinoma” and/or “chemotherapy post-treatment effects”.

In keeping with prior literature, minimal residual disease (MRD) was defined as a tumour < 5 mm in overall diameter at final pathology (242). In all cases where CPR or MRD were not met then residual cancer (RC) was assigned as a response.

8.4.5 Assessing concordance between readers

Concordance analysis between with central reader and local histopathology reader was performed on baseline biopsy and for CPR/RC rates on repeat biopsy and is presented using contingency tables. Formal inter-observer agreement analysis was performed in all specimens in terms of baseline ISUP Grade Group and pathological response assessment. Inter-observer agreement analysis was calculate using both percentage agreement and Cohen's kappa index. As MRD was a research response and is not utilised in clinical practice agreement with local reader could not be performed.

8.4.6 Statistical analysis

Descriptive statistics presented summarise patient demographics, clinical, radiological and biopsy characteristics. Inter-observer agreement analysis was calculated using both percentage agreement and Cohen's kappa index (279). Two overall complete pathological response rates were calculated from local and secondary histopathology reads. All statistics were performed using SPSS (IBM Corp., IBM SPSS Statistics for Windows, Armonk, USA, v.28.0) with some graphs re-created in Excel (Microsoft, version 2019).

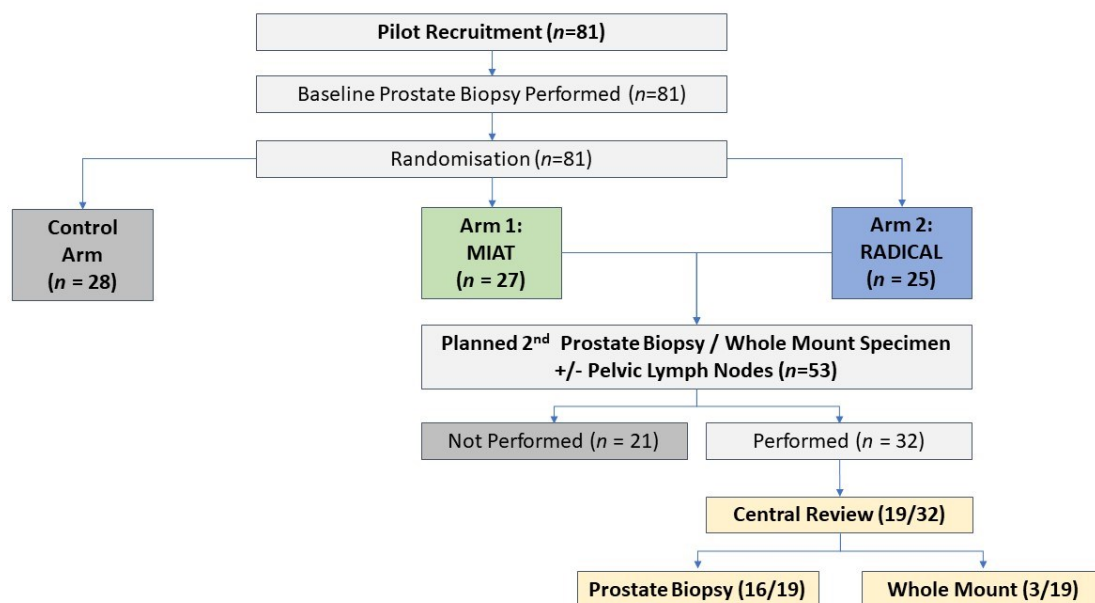
8.5 Results

8.5.1 Overview

81 patients were randomly allocated to Control Arm (34.6%; 28/81), Intervention Arm 1: MIAT (33.3%; 27/81) and Intervention Arm 2: Radical (32.1%; 26/81), respectively (**Figure 18**; 26th April 2019- 6th February 2021). Key demographics for the intervention arms have been presented in detail in **Chapter 7** of this thesis. Baseline prostate biopsy was performed in all patients (81/81) and repeat histology acquisition was planned following systemic therapy in patient allocated to the trial intervention arms 1 and 2 ($n=53$). In 32 of 53 (60.4%) a second prostate biopsy, or cytoreductive radical prostatectomy, was performed following systemic therapy at 6 to 9 months (**Chapter 7**).

We received 19 of 32 (59.3%) of requested paired specimens for central blinded pathology review. In 84.2% (16/19) post-systemic therapy pathology specimen available was a second prostate biopsy. In the remaining 15.7% (3/19) whole mount prostatectomy specimen was available. This represented a review of all performed cytoreductive radical prostatectomy specimens in the internal pilot RCT (3/81).

Figure 18. Histopathology available for central review by trial arm



Legend: Overview of planned histopathology available for central review by trial arm dated 1st April 2021, at time of multicentre consensus meeting to define the SOP for central histopathological management and reporting in the IP2-ATLANTA Internal Pilot RCT. Valid as per September 2022.

8.5.2 Pathological response assessments and inter-observer agreement

All patients with specimens available for paired analysis had $\geq$ ISUP 2 (Gleason 3+4) disease reported on local and secondary read of baseline prostate biopsy (**Table 29**). The overall percentage agreement for ISUP Grade Group for local reader and central blinded secondary reader was 89.5%. Cohen's kappa agreement was “near perfect” ($\kappa = 0.812$; [95%CI 0.6 – 1.0]) (279).

Table 29. Agreement between ISUP grading on baseline prostate biopsy readers

		Central Blinded (Secondary) Reader					
		ISUP 1 [$\leq$ 3+3]	ISUP 2 [3+4]	ISUP 3 [4+3]	ISUP 4 [4+4, 3+5, 5+3]	ISUP 5 [4+5, 5+4, 5+5]	Total
Local (Primary) Reader	ISUP 1 [$\leq$ 3+3]	0	0	0	0	0	0
	ISUP 2 [3+4]	0	1	0	0	0	1
	ISUP 3 [4+3]	0	0	1	0	0	1
	ISUP 4 [4+4, 3+5, 5+3]	0	0	1	4	1	6
	ISUP 5 [4+5, 5+4, 5+5]	0	0	0	0	11	11
	Total	0	1	2	4	12	19
Overall percentage agreement: 89.5%.							
Cohen's kappa agreement: ($\kappa = 0.812$; [95%CI 0.6 – 1.0])							

Legend: Green Shading = Downstaging on Central Blinded Read; Orange Shading = Upstaging on Central Blinded Read; Blue Shading = No change on Central Blinded Read.

In **Chapter 7**, we reported the complete pathological response rate using local reader only was equal in both trial arms at 11.1% (3/27) in Intervention Arm 1: MIAT and 11.5% (3/26) in Intervention Arm 2: Radical, respectively. Providing and overall complete pathological response rate of 11.3% (6/53; [95%CI 4.27-23.03]) (**Table 30**).

There was complete agreement for pathological response (complete pathological response versus residual cancer) between local reader and central blinded secondary readers (overall percentage agreement 100%; $\kappa = 1.00$). Thus, the overall complete pathological response rate of both local and secondary readers was also unchanged and reported at 15.8% (3/19;

[95%CI 3.4-39.6]) in our blinded study (**Table 31**). In a single patient, CPR was present on whole-mount specimen following cRP.

Minimal residual disease was reported in 26.3% (5/19; [95%CI 0.9-51.2]) of patients and in all cases, this was following review of second prostate biopsy specimens. In the three whole-mount specimens, tumour volume was 0 ml (i.e., CPR), 0.1 ml and 16 ml, respectively. Margins were clear in both cases where residual cancer was found.

Table 30. Central blinded pathological response assessments

Pathological response on Central Blinded (Secondary) Reader	Rate % (n)	95% CI
Minimal Residual Disease (MRD)	26.3% (5/19)	0.9 - 51.2
Complete Pathological Response (CPR)	15.8% (3/19)	3.4 - 39.6

Table 31. Interobserver agreement between pathological response assessment between primary and secondary reader(s)

		Central Blinded (Secondary) Reader		
		Residual Cancer	Complete Pathological Response	Total
Local (Primary) Reader(s)	Residual Cancer	16	0	16
	Complete Pathological Response	0	3	3
	Total	16	3	19
Overall percentage agreement: 100%.				
Cohen's kappa agreement: (κ = 1.0; [95%CI NR])				

Legend: Blue Shading = No change on Central Blinded Read.

8.5.3 Histologic patterns on central review

In **Table 32** all morphological changes reported by the central blinded reviewer are presented and categorised by specimen and systemic agent used. Overall, systemic agents were ADT with Docetaxel 52.6% (10/19), ADT with enzalutamide 42.1% (8/19), and LHRHa alone 5.2% (1/19), respectively. Given the small sample size histologic patterns are discussed collectively.

Cribriform pattern was present in 94.7% (18/19) of baseline prostate biopsies, but reduced by -88.9% (10.5%; 2/19) following systemic therapy. Perineural invasion was present in 78.9% (15/19) of baseline prostate biopsies, but reduced by -33.3% (52.6%; 10/19) following systemic therapy. Extra-prostatic extension reduced by -50.0% (4/19 [21.1%] versus 2/19 [10.5%]) following systemic therapy intensification. However, a +25% increase in intraductal carcinoma of the prostate was observed, reported in 42.1% (8/19) of baseline prostate biopsies and 52.6% (10/19) following systemic therapy, respectively.

In over 60% of post-systemic therapy specimens there was cytoplasmic loss and cell size reductions (12/19; 62.1%). Clear cell changes (9/19; 47.4%) and prominence of nucleoli (8/19; 42.1%) were also commonplace post-systemic therapy. Of note a neuroendocrine differentiation was present in specimens at baseline (1/19; 5.2%) and specimens post-systemic therapy (1/19; 5.2%). This was attributed to two separate patients, managed with ADT with enzalutamide, in whom resolution of- and *de novo* neuroendocrine differentiation occurred.

Common benign prostate morphology on post-systemic biopsy was the presence of basal cells and urothelial neoplasia present in 78.9% (15/19) and 57.9% (11/19) of specimens, respectively.

Table 32. Morphological changes on central review

Specimen Available	ADT + Agent	No (%)	Baseline Pre-Systemic Therapy						Post-Systemic Therapy								
			Cribriform <i>n</i> (%)	IDC <i>n</i> (%)	HGPIN <i>n</i> (%)	PNI <i>n</i> (%)	EPE <i>n</i> (%)	NED <i>n</i> (%)	IDC <i>n</i> (%)	PNI <i>n</i> (%)	EPE <i>n</i> (%)	Cribriform <i>n</i> (%)	Prominent nucleoli <i>n</i> (%)	Cell size reduction <i>n</i> (%)	Cytoplasmic loss <i>n</i> (%)	Clear cell change <i>n</i> (%)	NED <i>n</i> (%)
All	All	19 (100)	18 (94.7)	8 (42.1)	6 (31.6)	15 (78.9)	4 (21.1)	1 (5.2)	10 (52.6)	10 (52.6)	2 (10.5)	2 (10.5)	8 (42.1)	12 (62.1)	12 (62.1)	9 (47.4)	1 (5.2)
									+25.0	-33.3	-50.0	-88.9					
(Baseline) Prostate biopsy + 2 nd Prostate biopsy	Docet axel	8 (42.1)	7 (36.8)	4 (21.0)	2 (10.5)	6 (31.6)	2 (10.5)	0 (0.0)	1 (5.2)	6 (31.6)	1 (5.2)	1 (5.2)	3 (15.8)	6 (31.6)	6 (31.6)	3 (15.8)	0 (0.0)
	Enzalu tamide	8 (42.1)	8 (42.1)	4 (21.0)	4 (21.0)	7 (36.8)	2 (10.5)	1 (5.2)	1 (5.2)	3 (15.8)	0 (0.0)	1 (5.2)	6 (31.6)	5 (26.3)	6 (31.6)	5 (26.3)	1 (5.2)
(Baseline) Prostate biopsy + Whole- mount specimen	Docet axel	2 (10.5)	2 (10.5)	0 (0.0)	0 (0.0)	1 (5.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.2)	1 (5.2)	0 (0.0)	2 (10.5)	1 (5.2)	0 (0.0)	0 (0.0)	0 (0.0)
	None	1 (5.2)	1 (5.2)	0 (0.0)	0 (0.0)	1 (5.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Legend: NED – Neuroendocrine differentiation; IDC - Intraductal Carcinoma (of the prostate); HGPIN - High grade prostate intraepithelial neoplasia; PNI - Perineural invasion; EPE - Extra-prostatic extension; NED - neuroendocrine differentiation. All patients were administered LHRHa with either docetaxel, enzalutamide. A single patient had no additional agent.

8.6 Discussion

8.6.1 *Principle findings*

In this study we were able to perform a blinded central review of almost 60% of all pilot histology specimens in the IP2-ATLANTA randomised controlled trial. We reported strong agreement between baseline ISUP Grade Group and pathological response assessments following systemic therapy between local and central trial histopathologists. These findings support the accuracy of the results we have previously reported in the overall internal pilot RCT (**Chapter 7**).

To our knowledge, serial primary prostate tumour histology acquisition in patients with distant synchronous metastasis at baseline (mHSPC) pre- and post- contemporary systemic therapy intensification has not been reported previously in the literature. We reported hypothesis generating, key histologic features in the primary tumour (e.g. IDC-P, Cribriform) and their associated responses to contemporary systemic treatment in a paired blinded prospective manner.

In a similar fashion to non-metastatic disease, the prevalence of such baseline features and the nature of their responses may have a role in prognostication of mHSPC. Furthermore, the persistent visualisation of histologic features post-systemic therapy, may impact upon systemic agent choice and outcomes from any local cytoreductive intervention.

8.6.2 *Comparison with prior studies*

In the pilot specimens that underwent a secondary blinded central read, we confirmed complete agreement with the local CPR rates presented in **Chapter 7**. The established literature on CPR in this setting has been discussed in **Chapter 7** and thus is not replicated here for brevity.

In central review we applied an accepted minimal residual disease definition, that is not reported in routine clinical practice. In our study the MRD rate was 26.3% (5/19; [95%CI 0.9-51.2]). There is limited MRD response data in the literature for mHSPC. However, indirect evidence from the high-risk localised setting is available. In a small prospective study using a more stringent MRD definition of <3 mm, a MRD rate of 13.0% (3/23) was achieved on whole-mount radical prostatectomy specimens following 6-months of neoadjuvant Enzalutamide with ADT (261). In a similarly designed study, using 6-months of neoadjuvant Enzalutamide with ADT prior to radical prostatectomy in high-risk localised prostate cancer, 36% (13/36) of patients demonstrated MRD (defined as < 0.05 cc) on whole-mount specimens. It is unclear if MRD following contemporary systemic therapy is a surrogate

marker of disease progression in the non-metastatic setting. When MRD (defined as ≤ 0.5 cm) was applied to historical cohorts using neoadjuvant ADT alone prior to radical prostatectomy, MRD was predictive of a very low risk of post-operative biochemical failure (242).

It is entirely uncertain regarding the clinical translation of the presence of minimal residual disease in patients with mHSPC following 6-months of systemic therapy. It could be hypothesised that those with MRD are most likely to benefit from additive local cytoreductive treatment as such patients have had a favourable response to systemic therapy and MRD suggests that removal of all residual primary tumour foci maybe a realistic goal. However, such a hypothesis ignores the presence of other histologic features that have been proven to be highly prognostic in the non-metastatic setting (280).

There are a number of histologic features that may be biomarkers of prostate tumour biology in the metastatic setting. In 2021, ISUP issued a consensus definition of cribriform pattern prostate cancer, and confirmed the pattern as an independent adverse prognostic indicator for prostate cancer thus recommending its inclusion in routine reporting (280-282). A retrospective study evaluating 48 patients in whom a radical prostatectomy and pelvic lymph node dissection was performed, reported lymphovascular invasion (LVI) and pN1 disease was present in 93.7% of patients (283). Small cribriform architecture prostate adenocarcinoma was present in all of these patients (100%), and was also present in 70% (7/10) of the subgroup of “pN1 disease without LVI”, suggestive of a strong correlation between small cribriform architecture and lymph node metastasis.

In **Chapter 5** of this thesis, we previously reported rates of cribriform pattern in the majority of patients with mHSPC referred with a suspicion of prostate cancer (39/63; 61.9%) in whom a biopsy was performed following mpMRI prostate triage. In this study, almost all patients had cribriform pattern on second central blinded reporting of their baseline prostate biopsy (94.7%). However, cribriform disease reduced by -88.9% following systemic therapy (2/10; 10.5%).

The clinical translation of persistent cribriform pattern adenocarcinoma following systemic therapy in mHSPC is not known. In a prior phase II study of neoadjuvant docetaxel, prior to radical prostatectomy for localise prostate cancer ($n=50$), the persistent presence of cribriform pattern architecture (14%) on whole-mount specimen was an independent predictor (HR 2.3; [95% CI 1.3 - 4.0]; $p=.003$) of likelihood of nodal metastases. In the salvage setting, a study of 53 patients with localised prostate cancer who failed primary radiotherapy and underwent salvage prostatectomy, reported the presence of cribriform morphologies in 81% of whole-mount prostatectomy specimens.

Returning to the mHSPC setting, it is plausible to conceive that persistence of cribriform architecture following systemic therapy may correlate with an increased risk of disease progression. This is supported by an emergent range of oncogenic alterations (e.g. PTEN-loss) that can impact upon the tumour microenvironment of this histologic pattern and may thus confer selective advantage for cribriform architecture (284).

Intra-ductal carcinoma and cribriform architecture may be identified in the same gland (285). Intra-ductal carcinoma of the prostate is a unique histologic pattern that has been recognised to be a morphological manifestation of aggressive prostate adenocarcinoma (230,278,286-288). In previous studies in localised prostate cancer, IDC-P has been reported as an independent adverse pathological risk factor for disease progression (230,286-288).

In our study we reported IDC-P at baseline and following systemic therapy. In 4 in 10 patients at baseline (42.1%; 8/19) IDC-P was present, this rose to 5 in 10 (52.6%; 10/19) post-systemic therapy. Our rate of IDC-P was in keeping with that reported in prior retrospective studies (20.5% to 67.0%) (287-289). In a retrospective study of 278 patients who underwent transperineal prostate biopsy at baseline diagnosis of synchronous mHSPC, 20.5% (57/278) of patients had IDC-P (289). In this study patients received maximum androgen blockade only, and in this setting the group reported IDC-P as a negative prognostic factor for castration resistant prostate cancer-free survival (HR = 4.88; $p=0.011$) and overall survival (HR = 1.94; $p=0.020$), respectively. Another group retrospectively reviewed the baseline prostate biopsies of 150 patients who presented with synchronous mHSPC (288). IDC-P was reported in 67.0% (100/150) in this study and was associated with cancer-specific survival ($p=0.018$), but not with progression-free survival (288).

When attempting to understand the impact of IDC-P on the risk of evasion from androgen deprivation therapy, Porter and colleagues' performed a retrospective review of 38 patients who developed metastatic prostate cancer (287). The group reviewed either their baseline biopsy, or where radical prostatectomy was performed, whole-mount specimens. IDC-P was present in 63% (24/38) and contrary to the prior retrospective studies no correlation between IDC-P and overall survival was reported. In addition, this group utilised patient-derived xenografts to demonstrate that some IDC-P can exhibit therapeutic resistance to androgen deprivation therapy (287).

In a similar fashion to cribriform architecture, oncogenic alterations have been reported to be associated with IDC-P (e.g., BRCA2 mutations) (290). It has been suggested that whilst such persistent tumour cells in IDC-P are not yet proliferating via androgen independent pathways, their survival and persistent presence offers the opportunity for these cells to be precursors towards castrate resistance (291). One could hypothesise that patients with

persistent IDC-P may benefit from local cytoreductive treatments directed towards tumour cells that have remained resistant to systemic approaches. This would provide further clinical utility to re-classification prostate biopsies post-systemic therapy in those patients with known IDC-P reported at baseline. Such a hypothesis would need examining once oncological outcomes are available from the main phase component of the IP2-ATLANTA trial.

As prostate cancer is a neurotropic malignancy, there is a predilection towards invasion of the perineuronal space in some cancers (292). In localised cancer there is conflicting evidence as to whether PNI predicts biochemical recurrence rates (292). However, there is some retrospective evidence that PNI may predict mortality (293,294). For example in a study of 849 patients with prostate cancer on watchful waiting, 7% had PNI, and the presence of PNI was associated with lethal prostate cancer (OR 7.4; [95% CI 3.6-16.6]; $p<0.001$) (293). In our study PNI was present in the majority of patients at baseline (78.9%; 15/19) but reduced by -33% following systemic therapy. Further research is required to understand the role, if any, of PNI in patients with mHSPC.

In this chapter we have focussed on the histopathological changes to the primary in response to contemporary systemic therapy. As described in **Chapter 2** of this thesis there are numerous proposed tumour microenvironment changes, immune mediated responses and ontogenetic mutations that maybe important in delineating treatment response and fall beyond the scope of this sub-study. Our data set allows for both future immunohistochemical analysis to ascertain the presence of different T cell populations (e.g. CD8+) that maybe implicated in anti-tumour responses when cytoreduction is applied (92). Furthermore, the data set also allows for genomics sequencing to identify known oncogenic alterations in metastatic prostate cancer and their frequencies in response to systemic therapy (53). Should future funding become available such approaches would have utility in both our understanding of primary tumour response and in the predictions of response of applied cytoreduction.

In summary, we have presented the results of our secondary blinded reporting study on pathological response rates and common histologic features of prostate tumours in patients with *de novo* synchronous mHSPC, in paired specimens at baseline and post-systemic therapy, in the IP2-ATLANTA pilot study. The oncological outcomes of the main phase component of the IP2-ATLANTA study may establish whether these sub-groups of pathological entities and response categories are linked to resistance of therapeutic and local cytoreductive treatment strategies through hypothesis generating analyses.

8.7 Limitations

Although all patients had reached Visit 7 (Week 52) of the IP2-ATLANTA pilot, prior to analysis, central site delays in receiving and reporting of specimens may result in the presented analysis being updated in the future to include further specimens that become available to the trials team during the lifespan of this study. As such this analysis is presented for purposes of this research thesis only.

Furthermore, of the 11 open and recruiting pilot sites the 19 returned samples arose from four trial sites. This was due in part to the randomised nature of the study where some sites had recruited and randomised only control arm patients during the pilot accrual period. This narrow spectrum impacts upon the generalisability of the interobserver variability rates reported to the wider open trial sites in IP2-ATLANTA. However, as reclassification prostate biopsy is not mandated beyond the internal pilot RCT, this has no material impact on the main phase study endpoints.

Clearly, more tissue is histologically evaluated in patients in whom a cytoreductive radical prostatectomy has been performed than those where a second prostate biopsy has been acquired. This is an inherent limitation in the design of IP2-ATLANTA due to the alternative non-excisional treatments (i.e., cytoreductive radiotherapy or cytoreductive MIAT). Furthermore, morphological changes maybe more apparent in the whole-mount specimens.

8.8 Conclusion

There was strong agreement between local reader and secondary central blinded reader in the allocation of baseline ISUP Grade Group and complete pathological response assessment. These findings support the high accuracy of the results we have previously reported in the overall internal pilot RCT (**Chapter 7**). We also reported key histologic features in the primary tumour (i.e. IDC-P, Cribriform) and their associated responses to contemporary systemic treatment in a paired blinded prospective manner. A number of these responses are entirely novel and hypothesis generating. In a similar fashion to non-metastatic disease, the presence sub-pathologies, and the nature of their responses, may have a role in prognostication.

Chapter 9 – Sequential ⁶⁸Ga-PSMA-11 PET/CT and MRI imaging in predicting intraprostatic response to systemic therapy

9.1 Overview

Serial ⁶⁸Ga-PSMA-11 PET/CT and multi-parametric MRI imaging of the prostate may have a role in predicting residual prostate adenocarcinoma in the primary tumour in patients with *de novo* synchronous mHSPC managed with androgen deprivation therapy (ADT) and upfront systemic therapy intensification. ⁶⁸Ga-PSMA-11 PET/CT imaging, with or without mpMRI prostate, has potential utility in predicting disease responders who might benefit most from additional local cytoreductive treatments and non-responders who are unlikely to derive further additive benefits from such interventions but maybe exposed to unnecessary morbidity.

Utilising results from the IP2-ATLANTA main study and its embedded proof-of-concept “sub-study” I investigated intraprostatic pre- and post-systemic therapy PSMA expression detectable by ⁶⁸Ga-PSMA-11 PET/CT and its relationship with prostate histology findings. In addition, I explored the concordance between serial research mpMRI prostate, serial ⁶⁸Ga-PSMA-11 PET/CT and serial prostate histology. As repeat research prostate biopsy and mpMRI prostate imaging were restricted to participants allocated to the intervention arms of the main study, this chapter limits its analysis to this group of patients in the sub-study. The rationale and background for this chapter was presented as part of a review published in *European Urology Focus*¹³.

9.2 Introduction

⁶⁸Ga-PSMA-11 PET-derived functional assessments have the potential to provide granular detail on active intraprostatic lesions, that currently not provided by existing response assessments with either prostate specific antigen (PSA) or conventional imaging (295). At present radiological response (RR) assessments in the monitoring of *de novo* synchronous mHSPC are based on whole-body evaluation of computed tomography (CT) or magnetic resonance imaging (MRI) using the Response Evaluation Criteria in Solid Tumors (RECIST) currently in version 1.1 (296). Against the background of emerging evidence for cytoreductive local prostate treatments, there is no ability to routinely perform response

¹³ Connor, M.J., *et al.* Clinical Translation of Positive Metastases Identified on Prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography Imaging in the Management of De Novo Synchronous Oligometastatic Prostate Cancer. *European Urology Focus*. 2021

assessments of the local tumour to systemic therapy in the metastatic treatment setting (263).

We hypothesized that serial ^{68}Ga -PSMA-11 PET/CT imaging, with or without multi-parametric prostate MRI (mpMRI), for intraprostatic disease monitoring may have a role in predicting patients with *de novo* synchronous mHSPC who harbour residual adenocarcinoma of the prostate following ADT with upfront contemporary systemic therapy (e.g. docetaxel, enzalutamide).

Should ^{68}Ga -PSMA-11, with or without mpMRI, be able to accurately predict residual intraprostatic cancer burden, this would have clinical utility in identifying patients that may benefit most from additive local cytoreductive interventions and defer the toxicity of further anticancer systemic agents. Conversely, such imaging maybe able to show non-responders who are unlikely to gain oncological benefit from such interventions but maybe exposed to unnecessary morbidity.

There is currently limited evidence for the use of ^{68}Ga -PSMA-11 PET/CT in response assessments, and it is confined to small retrospective series evaluating whole-body response only, predominantly in the metastatic castrate-resistant disease setting (297-303).

We are able to draw some parallels from the recent use of a combination of pre-biopsy pelvic-only ^{68}Ga -PSMA-11 PET/CT with mpMRI prostate in the detection of clinically significant prostate cancer (csPCa) (304). In Emmett and colleagues' phase II imaging trial, of 296 biopsy naïve patients who underwent both imaging and a systematic +/- targeted prostate biopsy, a ^{68}Ga -PSMA-11 prostate tumour SUVmax of ≥ 12 , predicted csPCa (defined as any $\geq$ ISUP GG2) in all participants independent of their pre-biopsy mpMRI findings (304). How such ^{68}Ga -PSMA-11 derived intraprostatic tumour parameters behave after ADT and contemporary systemic therapy in the mHSPC setting is unknown.

Here-in we utilise the IP2-ATLANTA randomised study internal pilot RCT patients, in which serial mpMRI prostate and research biopsy were mandated in the intervention arms, with analysis from its dedicated ^{68}Ga -PSMA-11 PET/CT imaging response sub-study to help answer these research questions.

9.3 Methods

9.3.1 Study Overview & Design

In prior chapters of my thesis, I have extensively described the process for serial paired mpMRI and prostate biopsy in the Intervention arms of the IP2-ATLANTA pilot (**Chapters 6 to 7**). For brevity this has not been replicated here, and for clarity I will refer to the "main study" as the pilot of the IP2-ATLANTA randomised study and this analysis as the PSMA

PET/CT “sub-study” in the chapter. The PSMA PET/CT sub-study ($n=25$) was designed as a prospective single blinded exploratory ^{68}Ga PSMA-11 PET/CT imaging response study, which was submitted for ethical approval alongside the main study (**Appendix F**).

In the sub-study a blinded research ^{68}Ga -PSMA-11 PET/CT was performed at baseline and repeated following completion of either docetaxel chemotherapy (up to 6 cycles) or at Visit 3 to 4 study timepoint if the participant was commenced on enzalutamide (**Figure 19**). This was compared to the results of mpMRI prostate, CT Chest, Abdomen and Pelvis (CT CAP) and prostate biopsy which were performed at baseline and repeated following completion of docetaxel chemotherapy) or at Visit 3 to 4 study timepoint if on enzalutamide.

The primary objective for the sub-study was to investigate whether PSMA expression detectable by ^{68}Ga -PSMA-11 PET/CT was associated with intraprostatic residual disease post-systemic therapy (**Appendix F**). A secondary objective was to investigate the relationship between changes in PSA and changes in ^{68}Ga -PSMA-11 PET-CT. A post-hoc analysis was performed to explore the concordance between response assessment of serial research mpMRI prostate, serial ^{68}Ga -PSMA-11 PET/CT imaging and serial prostate biopsy histology. As serial mpMRI prostate and research prostate biopsies were restricted to participants allocated to the intervention arms of the main study, this chapter restricts its analysis to this specific group of the sub-study.

All trial participants from hospitals which were recruiting IP2-ATLANTA centres in the North West London Cancer Network were offered the chance to enrol patients into the “sub-study”. Patients were introduced to the sub-study by myself and were issued with the sub-study patient information sheet (PIS) (**Appendix D**). Patients were made aware that the sub-study was entirely voluntary and they could withdraw at any time without the need to provide a reason. Enrolment into the sub-study did not impact on the main study and/or any standard of care treatment options available to them.

A dedicated sub-study Oncologist (Dr Suraiya Dubash, Consultant Clinical Oncologist and Dr Preetha Aravind, Oncology Research Fellow, Imperial College Healthcare NHS Trust) then completed the informed consent process for the sub-study for trial participants who wished to take part.

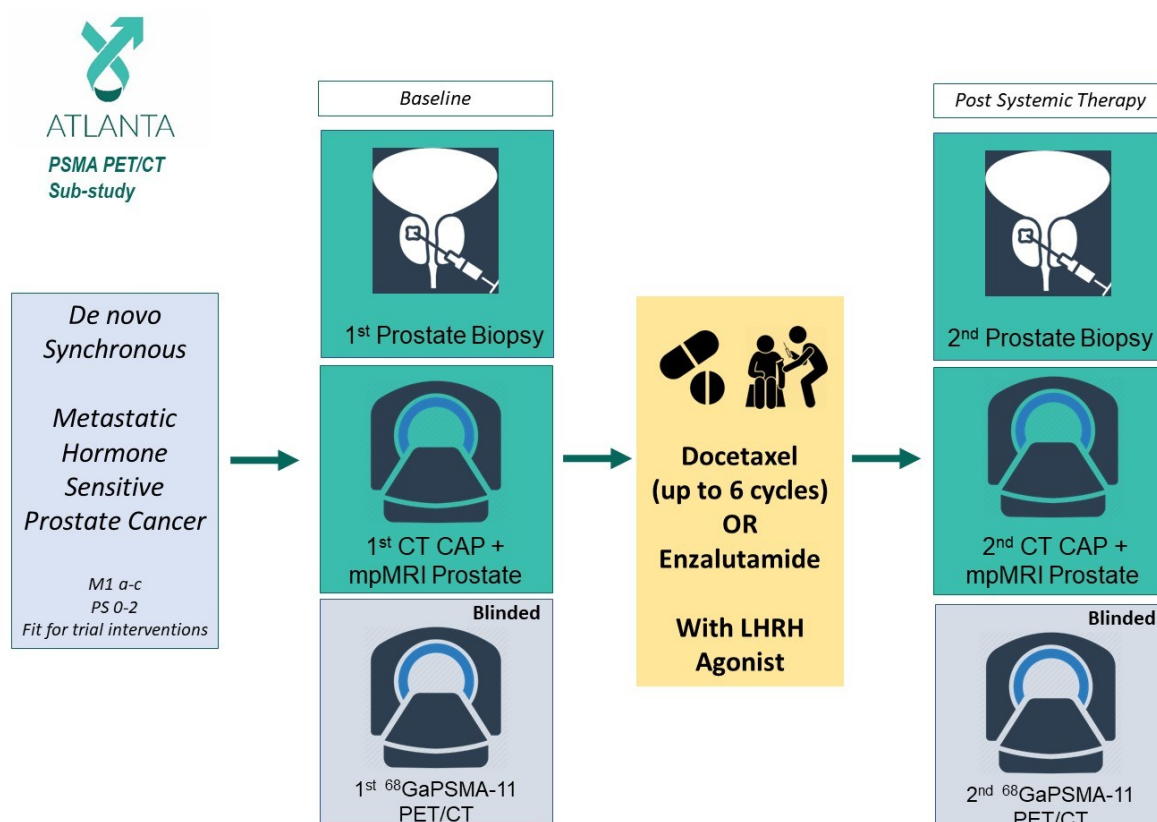
It was permitted to commence ADT prior to baseline ^{68}Ga -PSMA-11 PET/CT. The length of ADT exposure prior to baseline ^{68}Ga -PSMA-11 PET/CT was recorded. However, patients were deemed ineligible if other systemic therapy (e.g. docetaxel, enzalutamide) had been administered. This was a pragmatic decision reflecting the NHS standard of care practice to immediately initiate ADT in established or clinically suspected metastatic disease at time of diagnosis.

All sub-study imaging and results were blinded to the clinical team, main-study trials teams and the patient. Dr Dubash was not involved in the management of patients with metastatic prostate cancer at Imperial College Healthcare NHS Trust. Specifically, I remained blinded to all sub-study results and analysis until completion of the IP2-ATLANTA internal pilot study.

9.3.2 Sample Size and Power Calculations

As this was an exploratory (proof-of-concept) study there were no power calculations involved to generate an estimate of sample size. The original sample size was set at 25 participants, and based on estimating a likely residual disease detection rate of 25-50%. This was based on best available retrospective and small prospective series evidence, at the time of study conception, on the published sensitivity of ^{68}Ga PSMA-11 PET at PSA levels consistent with most treatment of metastatic prostate cancer patients (305). This sample size was subsequently reduced to 15 following the impact of closure of the sub-study during the COVID-19 pandemic.

Figure 19. PSMA PET/CT Sub-study Design



Legend: Blinded research ⁶⁸Ga-PSMA-11 PET/CT was performed at baseline and repeated following completion of docetaxel chemotherapy (Visit 3-4) or at Visit 3 to 4 timepoint if on enzalutamide. All prostate biopsies performed transperineal. M1a – distant (non-regional) nodal disease; M1b – bone metastasis; M1c – visceral metastasis; PS – Performance Status; CT CAP – Computed Tomography with contrast of Chest, Abdomen and Pelvis; LHRH – ; ⁶⁸Ga – Gallium-68; PSMA – prostate-specific membrane antigen; PET/CT – Positron emission tomography / computed tomography; LHRH – luteinizing hormone-releasing hormone; mpMRI – multi-parametric magnetic resonance imaging.

9.3.3 Imaging Protocol

9.3.3.1 PSMA Imaging Acquisition

⁶⁸Ga PSMA-11 PET/CT images were acquired on a Siemens Biograph 6 TruePoint with true V PET/CT scanner (21.6 cm axial and 60.5 cm transaxial fields of view). Trial patients were administered with ⁶⁸Ga-PSMA-L (maximum dose 250MBq; mean 192MBq, range 118-249 MBq). Following a uptake period of 60 minutes, a non-contrast attenuation CT (mid-thigh to vertex; 110 kV; 50 effective mAs; pitch, 0.8; slice thickness, 5 mm; rotation time, 0.6 s) was performed immediately followed by a PET emission scan (4min per bed position, mid-thigh to vertex);. All PET/CT were reconstructed using ordered-subsets expectation maximization algorithm (OSEM- 4 iterations and 8 subsets) with corrections for dead time, scatter, attenuation and radioactive decay.

9.3.3.2 MRI and CT Imaging Methods

An mpMRI prostate was performed using a 1.5-T or 3.0T scanner. mpMRI was performed and reported in accordance with the technical requirements in PIRADSV2. The sequences included T1-weighted, T2-weighted, dynamic contrast-enhanced (DCE) and multi b-values (for derivation of apparent diffusion coefficient [ADC] maps) and a high b-value of 1500. CT Chest, Abdomen and Pelvis (CT CAP) with contrast as per standard of care pre- and post-systemic therapy.

9.3.4 Imaging Reporting, Analysis and Radiological Response (RR)

⁶⁸Ga PSMA-11 PET/CT imaging analysis was performed on a dedicated PET/CT workstation (Hermes Diagnostics, Stockholm, Sweden) by a Clinical Research Fellow (Dr Preetha Aravind, Imperial College London) under direct supervision of an experienced PET/CT Consultant Radiologist (Prof. Tara Barwick, Imperial College Healthcare NHS Trust, > 20 years' experience). Reporters were blinded to baseline clinical information (including PSA, DRE, systemic therapy and trial arm), standard of care imaging (CT, MRI and bone scintigraphy). However, in cases where no intra-prostate residual tumour could be identified against background ⁶⁸Ga-PSMA-11, PET visual score was documented and then the corresponding mpMRI prostate was unblinded to permit outlining on PET at the site of any tumour on MRI so that quantitative PET analysis could be performed.

Scans were assessed both visually and quantitatively. Criteria to define a PET positive lesion included focal areas of increased tracer uptake with or without any underlying lesions on CT, deviating from normal physiological distribution (306). For visual scoring, standardized reporting European Association of Nuclear Medicine (EANM) guidelines for PSMA-PET (v1.0) were utilised, with a PSMA expression visual score (0 = Below blood pool; 1 = Equal to or above blood pool and lower than liver; 2 = Equal to or above liver and lower than parotid gland; 3 = Equal to or above parotid gland) assigned to the prostate.

⁶⁸Ga PSMA-11 PET-derived parameters underwent semi-quantitative analysis. For each scan, volumes of interest (VOIs) were generated around tumour index lesions (intraprostate and extra-prostatic using a metabolic tumour volume (MTV) 50% threshold) (307,308). Organs (2 cm fixed sphere iliac crest bone not involved by tumour; 3 cm fixed sphere gluteal muscle; 3 cm fixed sphere liver; 2 cm fixed sphere mediastinal blood pool at level of main pulmonary artery and 2cm fixed sphere parotid gland). For each VOI Standardized Uptake Value (SUV) max and SUVmean was documented.

For the follow-up visits the same index lesions were outlined. In the one case where the index prostate lesion was no longer visible, the response assessment mpMRI prostate was unblinded to guide outlining on PET at the site of residual signal abnormality on MRI.

A per patient response analysis was performed assessing the %-change of each PET-derived parameter (Tumour SUVmax, Tumour SUVmean), for prostate this used the index lesion. Tumour response assessment was visually defined as complete response (CR) where there was no PSMA uptake visible above background activity at sites of all target lesions (297). A decrease in tumour SUVmean change of $\geq 30\%$ was considered a partial response (PR) (297). New PMSA positive lesions on post-systemic therapy imaging or an absolute increase in SUVmean of $\geq 30\%$ was considered progressive disease (PD). Where change in SUVmean was between -30% and $+30\%$ and there were no new target lesions, this was considered stable disease (SD).

CT CAP and mpMRI prostate sequences were reported by a single main IP2-ATLANTA central study uro-radiologist with over 10 years' experience (Dr Henry Tam, Consultant Radiologist, Imperial Healthcare NHS Trust). A Response Evaluation Criteria in Solid Tumors (RECIST) was completed as per RECIST version 1.1 (296). This was performed using the prospectively created IP2-ATLANTA "Baseline & Response Worksheet" (**Appendix F**; [H. Tam, M. Connor, H. Ahmed]).

In addition, a per patient analysis of MRI-tumour volume of the index lesion (or maximum of three largest lesions in cases of multifocal disease), using the single measurement of the largest dimension in the axial plane described previously in the literature as "maximum tumour diameter (MTD)", as described in **Chapter 5** of this thesis (216,218). PI-RADS version 2.0 score (1-5) and LIKERT score (1-5) was applied to all baseline imaging. PI-RADS score was not applied to post-systemic therapy mpMRI in accordance with current reporting guidelines (PI-RADS, v2.0). On the post-systemic therapy mpMRI a visual assessment of viable tumour was performed using multiparametric parameters to guide probable activity in the form of a unique study defined "ATLANTA MRI Score" (residual viable lesion score: 1=no residual viable lesion; 2=probable residual viable lesion; and 3=residual viable lesion, respectively). In addition, a score of likely extraprostatic extension (EPE) was provided, as defined by Mehravivand and colleagues' (1=no evidence of EPE; 2=large lesion-capsule contact length or capsular bulge; and 3=frank EPE) (309). The reporter had access to baseline clinical information, including PSA, age, DRE findings at time of report. The reporter was blinded to the research ^{68}Ga -PSMA-11 PET/CT imaging.

9.3.5 Prostate biopsy technique, reporting and Complete Pathological Response (CPR)

At baseline, all biopsies were performed transperineal and accordance with a pre-determined standard operating procedure, used by all RAPID study centres (**Chapter 5**). All repeat biopsies were performed in accordance with the IP2-ATLANTA post systemic therapy biopsy (**Appendix F** [M. Connor, H.U. Ahmed]).

All baseline prostate biopsies were reported by a blinded central histopathologist (Dr Andrew Smith, Consultant Histopathologist, Imperial College Healthcare NHS Trust) according to the agreed SOP (**Appendix F** [Central Histopathology; A. Smith, M. Connor, M. Yeung, H. Markham, H.U. Ahmed]); this process is described in detail in **Chapter 8**.

Complete pathological response (CPR) on post-systemic therapy prostate biopsy was defined as (240-243):

- Presence of benign tissue or grade pT0 (prostate cancer not identified)
AND/OR
- Absence of “post-hormone therapy adenocarcinoma” and/or “chemotherapy post-treatment effects”.

In keeping with prior literature, minimal residual disease (MRD) was defined as a tumour < 5 mm in overall diameter at final pathology (242). In all cases where CPR or MRD were not met then residual cancer (RC) was assigned as response.

9.3.6 Biochemical response

Biochemical response mirrored that of the IP2-ATLANTA main study definition (**Chapter 6**).

Biochemical failure (BF) was calculated in one of three ways:

1. If the lowest recorded PSA value in the 24 weeks following randomisation is more than 4ng/ml and more than 50% of the pre-treatment PSA level then the patient fulfils the criteria for immediate treatment failure.
2. For patients whose PSA nadir in the 24 weeks following randomisation is less than or equal to 50% of the pre-treatment PSA level but remains above 4ng/ml, biochemical failure will be defined as a rise of 50% above the nadir level.
3. For patient whose PSA nadir is less than or equal to 4ng/ml, biochemical failure is defined as at least a 50% rise above the nadir value that is also above 4ng/ml.

Complete biochemical response (C-BR) was assigned if serum PSA <0.01 ng/ml. Biochemical response (BR) was assigned in the absence of any of the above definitions of BF being met.

9.3.7 Ethical Approval & Funding

The IP2-ATLANTA main study was funded by the Wellcome Trust (204998/Z/16/Z). The PSMA PET/CT sub-study was funded by the National Institute of Health Research (NIHR) Imperial Biomedical Research centre (BRC) (P70225). Research Ethics Committee approval was granted by the UK Health Research Authority (Wales REC5; 19/WA0005) simultaneously for the main-study and sub-study (**Appendix F**). IP2-ATLANTA was

prospectively registered at ClinicalTrials.gov (NCT03763253) and ISRCTN.com (ISRCTN58401737).

9.3.8 Statistical analysis

Descriptive statistics presented summarise patient demographics, clinical, radiological and histopathological characteristics and response analysis were performed by myself using SPSS (version v.28.0).

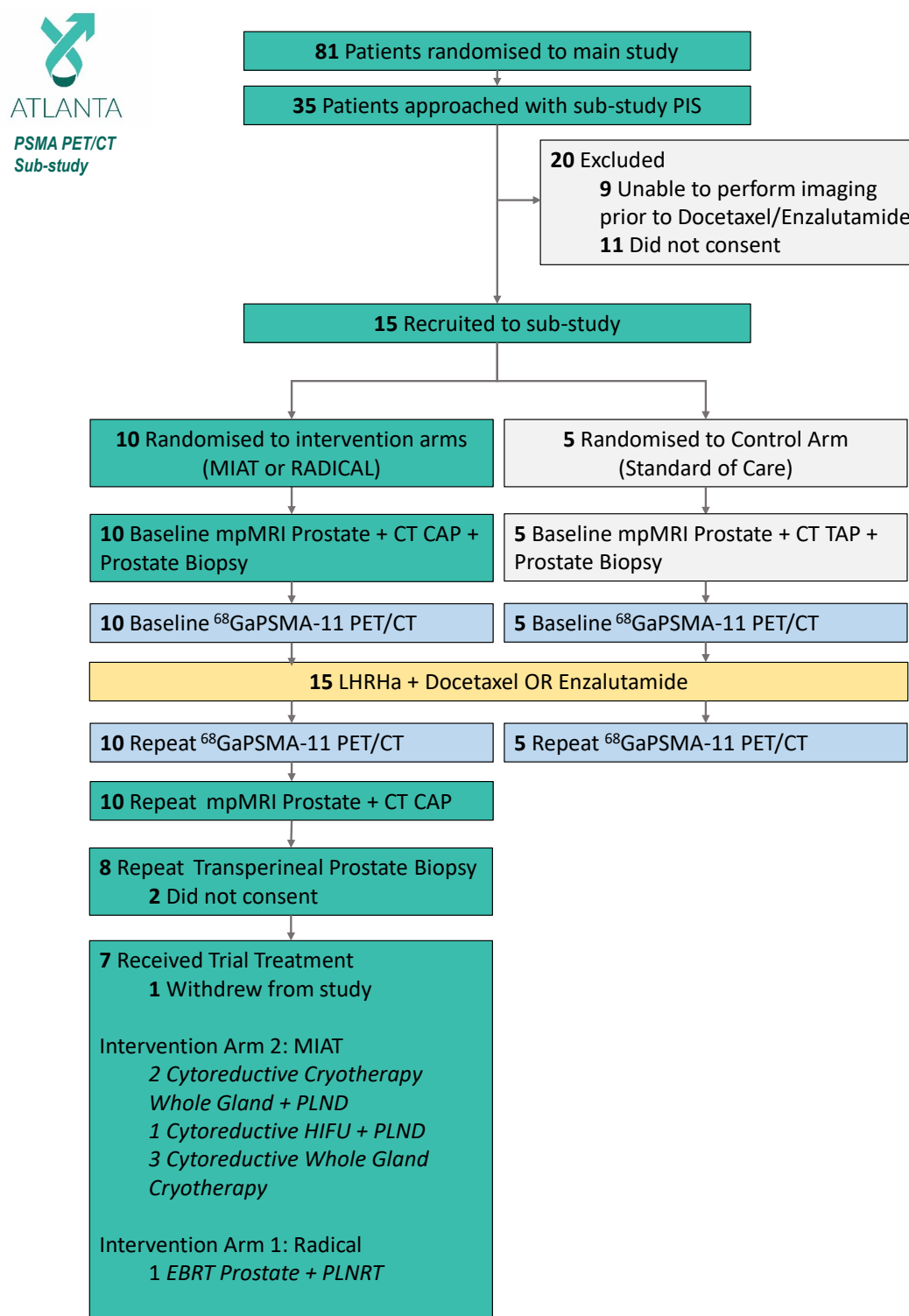
9.4 Results

9.4.1 Patient demographics

Between 26th April 2019, and 6th February 2021, 81 patients were assessed and randomised in the IP2-ATLANTA trial from 11 active trial sites in England and Wales (**Chapter 7**). Overall, the COVID-19 adjusted recruitment target for the sub-study of 15 patients was met; 35 (35/81; 43.2%) patients were offered the sub-study PIS, with a 42.8% (15/35) recruitment rate (**Figure 20**). In 9/35 (25.1%) patients, the trials team were unable to provide access to a PSMA PET/CT prior to initiation of systemic therapy, this was particularly problematic during the COVID-19 pandemic, where the sub-study imaging centre was heavily affected. Overall, 12 patients (11/35; 31.4%) did not consent for the sub-study following receiving and reviewing the sub-study PIS. In the 15 sub-study participants, 10 (66.7%) were randomly allocated to Intervention arms 1 and 2, respectively. Of these 8 (53.3%) underwent an mpMRI prostate, prostate biopsy and ⁶⁸PSMA-11 PET/CT pre- and post-systemic therapy. This group is the focus of the analysis presented in this Chapter of my thesis.

Within this group the median age and mean PSA was 66 years (IQR 13) and 203.67 ng/ml (SD 193.68), respectively (**Table 33**). All patients had a performance status of 0 (8/8; 100.0%) at baseline. Metastatic burden on conventional imaging, by CHAARTED defined, was “High” in three (3/8; 37.5%) and “Low” in three participants (5/8; 62.5%), respectively (10). All participants were commenced on LHRH analogues and this was combined with systemic agents of Docetaxel in two participants (2/8; 25.0%) and Enzalutamide in four participants (6/8; 75.0%), respectively.

Figure 20. Consort flow chart for PSMA PET/CT sub-study



Legend: Green shaded area denotes sub-study participants analysed in this chapter. Patients were deemed ineligible if systemic therapy (e.g. Docetaxel, Enzalutamide) had been administered prior to baseline PSMA PET/CT. EBRT - external beam radiotherapy; MIAT - minimally invasive ablative therapy; PLND - pelvic lymph node dissection; PLNRT - pelvic lymph node radiotherapy; ⁶⁸Ga - Gallium-68; PSMA - prostate-specific membrane antigen; PET/CT - Positron emission tomography / computed tomography.

Table 33. Baseline characteristics of sub-study participants for analysis

Trial ID	Age (years)	PS	Ethnicity	Serum PSA at diagnosis (ng/ml)	Baseline Prostate Biopsy		Maximum TMN stage at randomisation ^a				Standard of Care Treatment			2 nd Research Prostate Biopsy		Serum PSA post-systemic therapy (ng/ml)	Time (days) between 1 st & 2 nd PSMA PET/CT
					Gleason Grade Group / ISUP	MCCL (mm)	T	N	M	Metastatic Burden	ADT	ADT prior to 1 st PSMA PET/CT (days)	Systemic Therapy Agent	Pathological Response	MCCL (mm)		
A4-008 CIF3252	74	0	NR	48.5	4+5 / ISUP5	12	T3b	N1	M1a	Low	LHRHa	35	E	RC	12	0.2	196
A1-005 CIF3103	72	0	White British	18.71	5+4 / ISUP5	15	T3b	N1	M1b	High	LHRHa	43	D	RC	15	0.13	152
A1-008 CIF3116	66	0	White British	419.62	4+4 / ISUP4	9	T4	N1	M1a	Low	LHRHa	49	D	RC	14	8.6	184
A1-024 CIF3233	61	0	NR	90.00	4+4 / ISUP4	9	T3a	N1	M1a	Low	LHRHa	31	E	CPR	N/A	<0.01	196
A1-026 CIF3253	73	0	White British	313.54	4+5 / ISUP5	12	T4	N1	M1b	High	LHRHa	28	E	MRD	4	0.16	212
A1-029 CIF3268	56	0	White British	177.00	4+5 / ISUP5	16	T3b	N0	M1a	Low	LHRHa	17	E	MRD	4	0.05	212
A1-030 CIF3275	64	0	NR	36.00	4+4 / ISUP4	12	T4	N0	M1b	Low	LHRHa	24	E	RC	7	<0.01	215
A1-031 CIF3276	60	0	NR	526.00	4+5 / ISUP5	17	T4	N1	M1b	High	LHRHa	46	E	RC ^b	- ^b	6.68	258
Mean (SD)	65.9 (6.9)	-	-	203.67 (193.69)	-	12.8 (3.0)	-			-	-	43.19 (22.5)	-	-	9.33 (4.9)	2.26 (3.7)	195.3 (22.2)
Median (IQR)	65 (13)	-	-	133.5 (353.98)	-	12.0 (6.0)	-			-	-	44.50 (24.0)	-	-	9.5 (8.1)	0.16 (6.67)	196 (28)

Legend: ^aTMN and Metastatic Burden derived from conventional imaging components, as per CHARTED definition. ^bProtocol deviation, intraprostatic tissue not acquired at time, residual cancer present in pelvic lymph nodes at simultaneous PLND. PSA – Prostate Specific Antigen; PS – Performance Status as per WHO; MCCL – Maximum Cancer Core Length; T – Tumour; N- Nodes; M- Metastasis; NR – Not reported; D – Docetaxel chemotherapy (up to 6 cycles); E – Enzalutamide; LHRH – Luteinizing Hormone-Releasing Hormone Analogue; ⁶⁸Ga – Gallium-68; PSMA – prostate-specific membrane antigen; PET/CT – Positron emission tomography / computed tomography

Table 34. Serial changes in mpMRI and PSMA PET/CT imaging

Trial ID	Serial ⁶⁸ Ga PSMA-11 PET/CT Intraprostatic					Serial mpMRI Prostate											
	Baseline			Post-systemic therapy		Baseline							Post-systemic therapy				
	VES	Tumour SUVmean	Tumour SUVmax	Tumour SUVmean	Tumour SUVmax	PVol (cc)	PI- RADS / LIKERT	F/ D	MTD ^a (mm)	EPE	S/ B/ R	MRI T-stage	PVol (cc)	F/D	MTD ^a (mm)	EPE	S/ B/ R
A4-008 CIF3252	1	4.0	6.5	1.9	2.5	44.9	P5 / L5	D	45.0	3	S	T3a	22.0	F	20.0	3	-
A1-005 CIF3103	2	(i)12.9	(ii)20.3	(i)5.1	(i)7.3	71.2	P5 / L5	D	40.0	3	-	T3b	40.0	F	11.0	3	-
		(ii)8.7	(ii)13.6	(ii)3.7	(ii)5.6												
A1-008 CIF3116	3	25.3	40.3	13.6	20.0	54.0	P5 / L5	D	58.0	3	S	T4	30.0	F	8.0	3	-
A1-024 CIF3233	3	7.07	12.02	1.43	2.08	31.6	P5 / L5	F	23.0	3	-	T3a	11.0	N/A	N/A	N/A	-
A1-026 CIF3253	2	8.3	13.4	2.2	3.3	81.3	P5 / L5	D	60.0	3	SB	T4	3.0	F	14.0	3	B
		11.8	19.9														
A1-029 CIF3268	3	8.7	14.2	2.0	2.8	24.5	P5 / L5	D	33.0	3	SB	T4	12.0	F	18.0	1	-
A1-030 CIF3275	2	29.1	44.3	2.1	3.0	26.1	P5 / L5	F	26.0	3	-	T3b	23.0	F	15.0	3	-
A1-031 CIF3276	3	22.6	34.8	12.2	18.7	66.6	P5 / L5	D	55.0	3	SB	T4	16.6	F	14.0	1	-

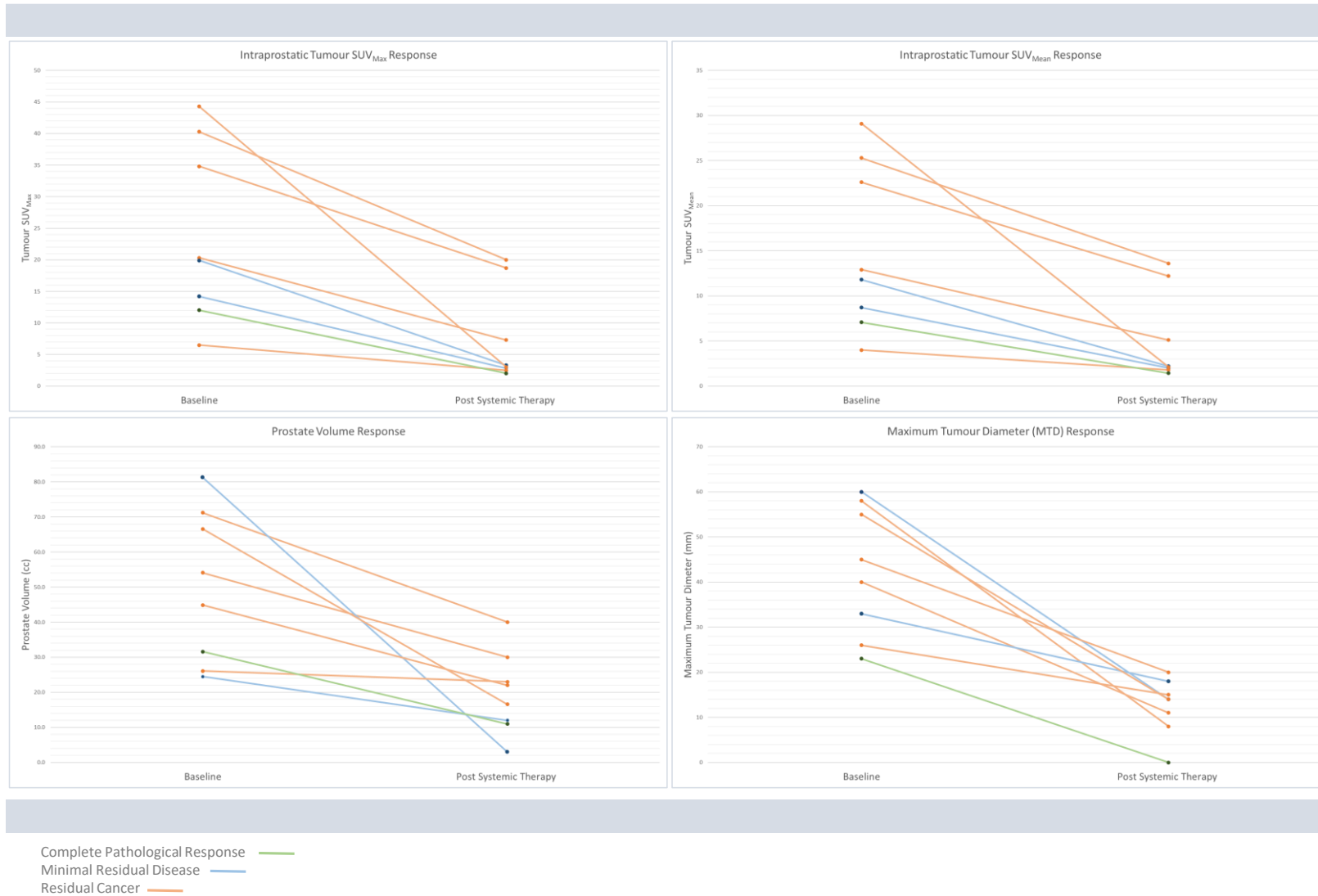
Legend: (i) – (ii) In cases of whole prostate MTV50 underestimating SUVmax, the MTV50 per visible tumour is provided resulting in a range, in the case of A1-026 tumour response resulted in single value post-systemic therapy. ^aMaximum Tumour Diameter (MTD) of largest MTD lesion at baseline mpMRI prostate in cases of multifocal disease. CR – Complete Response, PR – Partial Response; BR – Biochemical Response; F – Focal lesion; D – Diffuse Lesion; S – MRI suggestive of (Urinary) Sphincter invasion of tumour; B – MRI suggestive of bladder invasion of tumour; R – MRI suggestive of rectal invasion of tumour; PVol – Prostate Volume (cc); EPE – Extra-prostatic extension score; ⁶⁸Ga - Gallium-68; PSMA - prostate-specific membrane antigen; PET/CT – Positron emission tomography / computed tomography; SUV - Standardized Uptake Value.

Table 35. Response assessments

Trial ID	Intraprostatic response									Whole body response			
	⁶⁸ Ga PSMA-11 PET/CT Response			mpMRI Prostate Response				Prostate Histology		⁶⁸ Ga PSMA-11 PET/CT Overall Response	RECIST Evaluation		Biochemical Response (PSA)
	%-change Tumour SUVmax	%-change Tumour SUVmean	Tumour Response Category	%-change PVol	Residual tumour visible	Tumour Viable Score ^b	%-change MTD ^a	Pathological Response	%-change MCCL		%-change Target Lesion	RECIST Response	
A4-008 CIF3252	-64.5%	-55.0%	PR	-51.0%	Y	2	-55.6%	RC	0.0%	PR	-56.0%	PR	BR
A1-005 CIF3103	-58.8% (i) to -64.0% (ii)	-57.5% (i) to -60.5% (ii)	PR	-43.8%	Y	3	-72.5%	RC	0.0%	PR	-69.0%	PR	BR
A1-008 CIF3116	-50.4%	-46.3%	PR	-44.6%	Y	3	-86.21%	RC	+56.6%	PR	-67.0%	PR	BR ^d
A1-024 CIF3233	-83.2%	-79.7%	PR	-65.2%	N	N/A	N/A	CPR	N/A	CR	-100.0%	CR	C-BR
A1-026 CIF3253	-75.4%	-73.5%	PR	-96.1%	Y	2	-76.7%	MRD	-66.7%	PR	-67.0%	PR	BR
A1-029 CIF3268	-80.3%	-77.0%	PR	-51.0%	Y	1	-42.3%	MRD	-75.0%	PR	-42.0%	PR	BR
A1-030 CIF3275	-93.2%	-92.8%	CR	-11.9%	Y	2	-45.5%	RC	-41.7%	CR	-56.0%	PR	C-BR
A1-031 CIF3276	-46.3%	-46.2%	PR	-75.1%	Y	3	-74.5%	RC ^b	-	PR	-55.0%	PR	BR ^d

Legend: (i) – (ii) In cases of whole prostate MTV50 underestimated tumour SUVmax, the MTV50 per visible tumour is provided resulting in a range, in the case of A1-026 tumour response resulted in single value post-systemic therapy. ^aMaximum Tumour Diameter (MTD) %-change of largest MTD lesion at baseline mpMRI prostate in cases of multifocal disease. ^bProtocol deviation, intraprostatic tissue not acquired at time, residual cancer present in pelvic lymph nodes at simultaneous PLND. ^cHighest post-systemic therapy viable score. ^dPSA nadir in the 24 weeks following randomisation was less than 50% of the pre-treatment PSA level but remains above 4ng/ml, PSA did not meet biochemical failure level definition in scenario (rise of 50% above the PSA nadir value). C-BR – Complete Biochemical Response [Dark Green]; CR – Complete Response [Dark Green]; PR – Partial (Radiological) Response [Orange]; BR – Biochemical Response [Blue]; PVol – Prostate Volume (cc); MRD – Minimal Residual Disease [Blue]; EPE – Extra-prostatic extension score; ⁶⁸Ga - Gallium-68; PSMA - prostate-specific membrane antigen; PET/CT – Positron emission tomography / computed tomography; SUV - Standardized Uptake Value.

Figure 21. Graph plotting serial intraprostatic imaging response against pathological response (per-patient-analysis)



9.4.2 Adherence to research imaging protocol and biopsy

All patients underwent the planned baselines and post-systemic therapy ^{68}Ga PSMA-11 PET/CT, mpMRI Prostate and CT CAP at planned trial intervals. All patients commenced a form of ADT prior to baseline ^{68}Ga -PSMA-11 PET/CT imaging, with median exposure reported to be 43.19 days (IQR 22.5) (**Table 33 & 34**). The median time between 1st and 2nd ^{68}Ga -PSMA-11 PET/CT imaging was 195.3 days (IQR 22.2), this was within the study window. All patients underwent a transperineal prostate biopsy at baseline. All patients underwent a transperineal prostate biopsy following systemic therapy, with the exception of A1-031 (CIF3276) where nodal tissue but prostate tissues absent for review. We were thus unable to comment on the intraprostatic persistence of residual cancer in this patient, although this remained present in adjacent lymph nodes from simultaneous PLND.

9.4.3 ^{68}Ga -PSMA-11 intraprostatic tumour response

At baseline, ^{68}Ga -PSMA-11 intraprostatic mean intraprostatic Tumour SUVmax was 24.0 (SD 13.9; range 6.5 – 44.3). Post-systemic therapy, ^{68}Ga -PSMA-11 intraprostatic mean intraprostatic Tumour SUVmax was 5.1 (SD 1.0; range 2.0 – 20.0). ^{68}Ga -PSMA-11 intraprostatic tumour response was reported as PR in 7/8 (87.5%). ^{68}Ga -PSMA-11 intraprostatic tumour response was reported to be CR in 1/8 (12.5%) patient, this was not concordant with a complete biochemical response (**Table 35**).

There were no patients who had PD or SD responses reported on ^{68}Ga -PSMA-11, with the lowest %-change Tumour SUVmax and %-change Tumour SUVmean reported as -46.3% and -46.2%, respectively (**Figure 21**).

9.4.4 MRI intraprostatic tumour response

All patients had PI-RADS 5 / LIKERT 5 MRI-visible lesions at baseline (8/8; 100.0%). At baseline all patients had $\geq$ MRI T3 disease; with 12.5% (1/8) T3a, with 12.5% (1/8) T3b, and 50.0% (4/8) T4 (**Table 35**). At baseline median MTD was 42.5 (IQR 29.5), and all patients had extraprostatic extension score of 3 (8/8; 100.0%). Probable urinary sphincter and bladder involvement were reported in 5/8 (62.5%) and 3/8 (37.5%). No patients had direct rectal invasion.

Post-systemic therapy cytorreduction resulted in a fall in all MRI calculated prostate volumes, with %-change in PVol ranging from -11.9% to -96.1% (**Table 35**). Median MTD reduced to 14.0 (IQR 8.5). Significant cytorreduction occurred in three patients with repeat prostate volumes of less than 15 cc (3.0 - 12 cc). No patients had residual urinary sphincter tumour invasion on MRI, with bladder invasion persisting in just one patient (1/8; 12.5%). Furthermore, no patients developed MRI reported rectal invasion. Post-systemic therapy

MTD reduced for all patients, ranging from -42.3% to -86.21%. In five (5/8; 62.%) patients an EPE score of 3 persisted post-systemic therapy.

In a single patient (1/8; 12.5%), mpMRI was reported as T0 with no visible residual tumour, this was concordant with serial prostate biopsy reporting of complete pathological response and indeed complete biochemical response, respectively (**Table 35**)

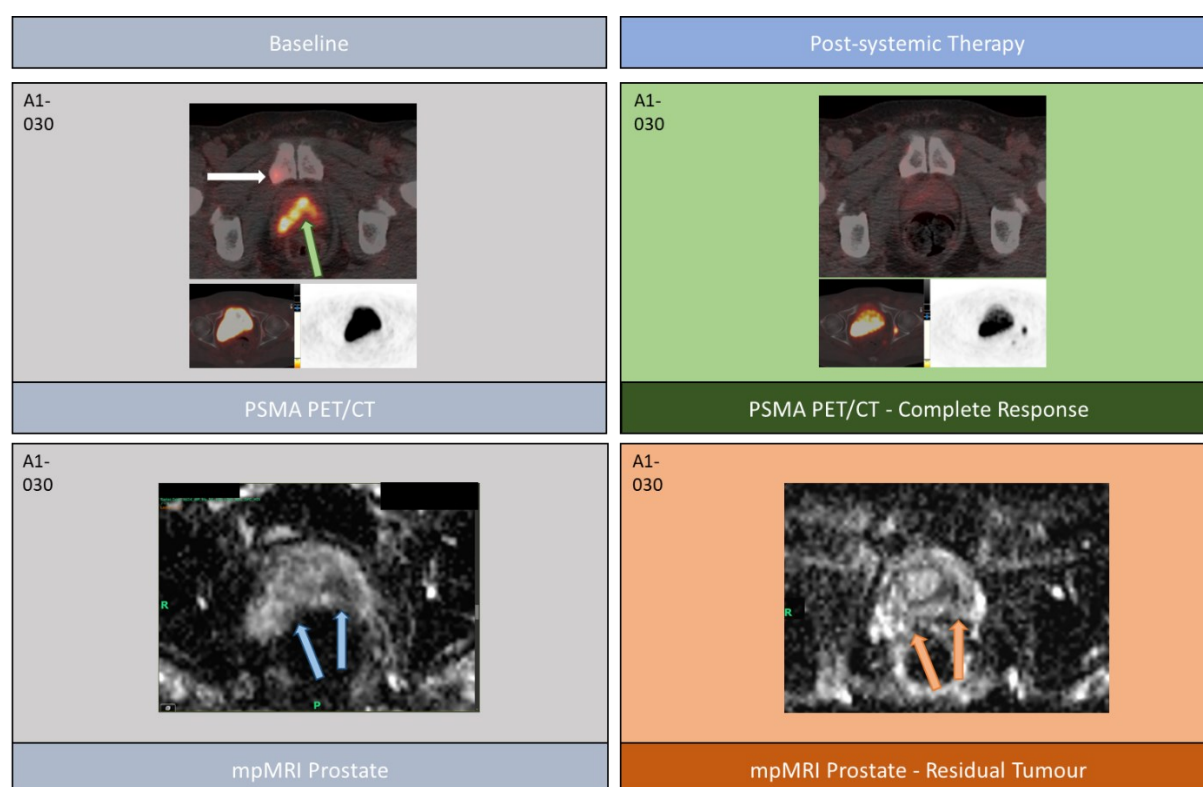
9.4.5 ⁶⁸Ga-PSMA-11 in comparison to MRI intraprostatic tumour response

When ⁶⁸Ga-PSMA-11 PET/CT and mpMRI intraprostatic tumour responses were compared, in isolation from histological response, there was discordance between the response assessments. In the single patient (1/8; 12.5%) where complete response on ⁶⁸Ga-PSMA-11 PET/CT was reported, mpMRI reported a residual visible tumour with an ATLANTA MRI tumour viability score of 2. This case was subsequently confirmed as a residual adenocarcinoma with treatment effect with MCCL 7.0 mm on prostate biopsy (**Figure 22**).

Furthermore, in the single patient (1/8; 12.5%) where mpMRI reported no residual visible tumour, ⁶⁸Ga-PSMA-11 PET/CT reported a partial response only. This case was subsequently confirmed as a complete pathological response on prostate biopsy.

In the 7 patients where (7/8; 87.5%) ⁶⁸Ga-PSMA-11 intraprostatic tumour response was reported as a partial response, mpMRI reported a residual visible tumour in 6/8 (75.0%). In those patients with a ⁶⁸Ga-PSMA-11 partial response reported and where mpMRI reported a residual visible tumour there were a range of ATLANTA MRI tumour viability scores: “= 1” (16.7%; 1/6); “= 2” (33.3%; 2/6) and “= 3” (50.0%; 3/6), respectively (**Table 35**).

Figure 22. Example of discordant intraprostatic tumour response on serial 68Ga-PSMA-11 PET/CT and MRI



Legend: Discordance between PSMA PET/CT and mpMRI response for A1-A1-030 (CIF3275). %-mean Tumour SUVmax of -93.2% from baseline tumour (light green tumour), prostate no longer visible against background signifying radiological complete response. Serial diffusion weight imaging from mpMRI prostate, at baseline demonstrating PI-RADS 5 / LIKERT 5 lesion (light blue arrows) with MTD of 26.0 mm extending into seminal vesicle from base. Post-systemic therapy (light orange arrows), this demonstrates residual patchy diffusion restriction with lesion of 15 mm MTD and residual tumour viable score of 2. Baseline transperineal prostate biopsy histology Gleason 4+4 / ISUP4, MCCL 12.0 mm Post-systemic therapy transperineal prostate biopsy histology residual adenocarcinoma with treatment effect, MCCL 7.0 mm. Note: white arrow demonstrates PSMA positive right pubic tubercle bone metastasis on baseline imaging, no longer visible on post-systemic therapy imaging.

9.4.6 Biochemical and histological response prostate

At baseline, median PSA was 133.50 ng/ml (IQR 353.98) and in all patients PSA responded to systemic therapy. No patients met the definition of biochemical failure at the point of second PSMA PET/CT imaging. In two patients there was a complete biochemical response (2/8; 25.0%). Median PSA following systemic therapy was 0.16 ng/ml (IQR 6.67).

All baseline prostate biopsy histology were reported to be $\geq$ ISUP 4, with a median MCCL of 12.8 mm (IQR 3.0). The median MCCL post-systemic therapy was 7.0 (IQR 9) and %-change in MCCL ranged from 0.0% to -68.8%. Complete pathological response was reported in a single patient (1/8; 12.5%) and was concordant with MRI and biochemical response reporting. Minimal residual disease was reported in a single patient (2/8; 25.0%). All remaining cases demonstrated residual adenocarcinoma (5/8; 62.5%).

9.5 Discussion

To our knowledge, this is the first prospective study to investigate imaging response of the primary prostate tumour, on ^{68}Ga -PSMA-11 PET/CT and mpMRI, following initiation of upfront ADT with Enzalutamide or Docetaxel in patients with metastatic hormone-sensitive prostate cancer. The results of this blinded paired proof-of-concept imaging study suggest that ^{68}Ga -PSMA-11 PET/CT in combination with mpMRI prostate imaging is a promising method to predict residual intraprostatic tumour burden following contemporary systemic therapy in mHSPC, and furthermore this may have a role in identifying patients who may benefit from additional local cytoreductive prostate interventions.

We were unable to find comparable literature on intraprostatic primary tumour PSMA PET/CT or mpMRI responses in the mHSPC setting. In metastatic castrate-resistant prostate cancer (mCRPC) Caffo and colleagues' presented a case series of 12 patients, who received LHRHa and Enzalutamide for 7 months (310). Of these, 10 patients underwent a ^{18}F -fluorocholine-PET/CT (^{18}F -FCH PET/CT) at months 3 and 7, respectively. Baseline median intraprostatic tumour SUVmax was reported as 7.25 and this reduced by -43% ($p=0.009$) after 7 months. These results demonstrate, similar to our study, the significant cytoreductive impact of such contemporary systemic anticancer agents on intraprostatic tumours. The use of ^{18}F -fluorocholine-PET/CT, which is reliant on metabolic activity, and the non-comparable advanced CRPC disease state limits further comparisons.

When compared to patients with intermediate- and high-risk localised prostate cancer who have undergone ^{68}Ga -PSMA-11 PET/CT intraprostatic tumour evaluation, as part of a pre-biopsy mpMRI diagnostic pathway, our study reported the SUVmax of all but one patient's tumours exceeded the prior published SUVmax ≥ 12 that has been recently proposed as a threshold for csPCa (SUVmax 24.0 [SD13.9]) (304). Such findings are perhaps expected, given our knowledge of the large intraprostatic MTD commonly present in patients with mHSPC arising within such diagnostic pathways (**Chapter 5**).

In our exploratory study %-change in intraprostatic ^{68}Ga -PSMA-11 tumour parameters or assigned response categories did not correlate with the final pathological response demonstrated on biopsy. However, all patients with CRD and MRD had absolute initial Tumour SUVmean values ≤ 12.0 and Tumour SUVmax values ≤ 20.0 , respectively. It has been previously reported that SUVmax closely correlates with PSMA tissue expression, and further that more aggressive prostate tumours (i.e. increasing ISUP GG, cribriform morphology) express higher PSMA (63,311-313). It could be postulated in the same manner, that the absolute baseline Tumour SUVmax and SUVmean values in mHSPC may have a role in predicting tumours that may reach complete pathological response with systemic

therapy intensification alone. Thus, providing a non-invasive approach to selecting patients who can avoid the potential morbidity associated with additive local cytoreductive interventions. This hypothesis would need to be tested in a larger prospective imaging study. However, the increasing use of PSMA PET/CT in the baseline distant staging of high-risk prostate cancer may allow for multi-institutional registry studies to answer this question indirectly, in the absence of a dedicated trial.

The impact of ADT in combination with taxane-based chemotherapy and androgen receptor signalling inhibitors (ARSI) on the primary tumour in patients with mHSPC is poorly understood (314). It has been postulated previously that loss of AR expression, may lead to a concomitant fall in expression of related proteins, such as PSMA. This can result in a scenario in mHSPC where PSMA-negative and positive lesions arise on PSMA PET/CT imaging (315). This is in a similar fashion to the hypothesis that prolonged exposure of prostate cancer cells to ADT may lead to the evolution of resistant cell lineages and androgen independent pathways (**Chapter 2**) (31).

On first evaluation of the results of this study, one could take the position that ^{68}Ga -PSMA-11 PET/CT does not predict patients with complete pathological response, which was accurately identified by mpMRI imaging alone (A1-030 / CIF3275). There are two reasons to be sceptical, first the low event rate ($n=1$) and sample size cannot support such a conclusion, second there maybe clinical usefulness in discordance between imaging modalities as this may indicate a change intraprostatic tumour biology. If we return to the CRPC setting we have seen that patients who have discordant imaging, in the form of avid ^{18}F -fluorodeoxyglucose (FDG) PET/CT imaging and negative ^{68}Ga -PSMA-11 PET/CT lesions, have a poor prognosis and worse survival than those patients with concordant imaging (316,317).

As such, I would rather hypothesize that such intraprostatic tumour imaging phenotype discordance may have meaningful value as it could be an early indication of AR-independent resistance. In the mHSPC setting identification of discordance in the primary tumour with ^{68}Ga -PSMA-11 PET/CT and mpMRI imaging could lead to the exploration of initiating alternative anti-cancer therapy (e.g. immunotherapy, alternative lines of chemotherapy, Poly (ADP-ribose) polymerase (PARP) inhibitors) (318). In addition, it is entirely unknown whether local cytoreductive prostate treatments in mHSPC would retain additive oncological benefit in such patients with loss of AR expression (metabolically inactive tumours) but persistent MRI-visible tumours. One could postulate that such patients could have dose escalation via local cytoreductive interventions to achieve localised control, as loss of expression may suggest growing resistance to ARSI's (317).

The role of mpMRI response assessment of the primary tumour in mHSPC has not been reported previously in the literature, to our knowledge. However, response assessment to neoadjuvant enzalutamide, prior to radical prostatectomy in localised prostate cancer, has been explored by Karzai and colleagues' (225). In this imaging response study of 36 patients who underwent mpMRI at baseline and following Enzalutamide, paired with baseline biopsy and whole-mount specimens, the group reported significant reductions in intraprostatic tumour volumes (>50% reduction in 55 / 59 tumours) and MRI-prostate volume (median PVol 39.5 cc [IQR NR] to 20.0 cc [IQR NR]). In addition, improvements in EPE scores were reported (EPE=0; 17% [6/36] to 58% [21/36]). Such findings share similarities to those reported in our study. Finally, the group calculated MRI "relative tumour burden" (relative tumour burden = combined volumes of each MRI-lesions / PVol), and reported that low relative tumour burden at baseline mpMRI was the strongest predictor of complete pathologic response with an optimal cut-off of 8.1%. In our study of patients with mHSPC relative tumour volume was not available, and as all patients had bulky tumours at baseline (median MRI-MTD 42.5 mm [IQR 29]), it is uncertain if this would retain prognostic value in the distant disease setting. Of note in our study there appeared to be no correlation between baseline PVol or MRI-MTD with reported pathological response to systemic therapy.

In the absence of specific scoring systems for intraprostatic mpMRI tumour response in the literature, we developed and utilised a study specific score for residual tumour viability (1 to 3). This permitted our experienced blinded reader to assign the probability of underlying residual viable tumour where it was persistently visible lesion on mpMRI. The ATLANTA MRI Score fared well in this small study and the reporter was able to predict the single case of complete pathological response, and furthermore assigned scores of 3 in those with residual cancer on biopsy and 1-2 in those with minimal residual disease, respectively. Should mpMRI response imaging be introduced, further large-scale validation of this scoring system should be performed to confirm these findings. If confirmed this may have use in patient selection for additional local cytoreductive treatments.

Finally, in our study all patients had a biochemical response following 6-9 months of systemic therapy, with a complete BR associated with both CPR and RC on repeat prostate biopsy. This suggests, similar to its limited role in predicting whole-body response, PSA kinetics alone are inadequate in classifying intraprostatic primary tumour responses post-systemic therapy in mHSPC (319).

9.6 Limitations

This was a proof-of-concept study that was limited by its small sample size, which was insufficient to define the optimal ⁶⁸Ga PSMA PET-derived parameters that would predict

residual prostate adenocarcinoma following systemic therapy. The clinical significance of residual prostate adenocarcinoma in patients with mHSPC post-systemic therapy is unknown. Some patients allocated to the intervention arms declined a repeat prostate biopsy as part of the main study, and as such were excluded from the subsequent per-patient analysis. Whilst all patients underwent ADT in the form of LHRHa, upfront systemic agent varied between Docetaxel and Enzalutamide as per current standard of care practice. Furthermore, the impact of different systemic agents on the primary tumour in mHSPC is unknown. It was permitted to commence ADT, but not Docetaxel or Enzalutamide prior to baseline ^{68}Ga -PSMA-11 PET/CT, this could have led to an underestimation of the absolute tumour SUVmax and SUVmean in some patients. This was partially mitigated by removing absolute values from response reporting criteria in favour of %-change alone. This was a pragmatic decision reflecting the NHS standard of care practice to immediately initiate ADT in established or clinically suspected unknown burden metastatic disease at the time of diagnosis, in part to avert life-threatening complications arising (e.g., metastatic spinal cord compression). The low event rate of complete pathological response following systemic therapy ($n=1$), combined with a COVID-19 reduced sample size ($n=15/25$), prevented an analysis of predictors of such a response.

9.7 Conclusion

Serial ^{68}Ga -PSMA-11 PET/CT imaging, when combined with mpMRI prostate, is a promising method to monitor residual intraprostatic tumour burden following contemporary systemic therapy in patients with *de novo* synchronous mHSPc. These findings provide information on the functional behaviour of the post-systemic therapy primary tumour against paired prostate histology for the first time in the literature. Such findings may have future clinical utility in the appropriate assignment of patients to emerging local cytoreductive treatments options in this setting.

Chapter 10 – Performance of novel cytoreductive minimally-invasive ablative therapy and surgical metastasectomy

10.1 Overview

In this chapter, I report on the technical performance, safety and feasibility of delivering cytoreductive minimally invasive ablative therapy, with or without simultaneous, surgical metastasectomy (in the form of pelvic lymph node dissection) in the IP2 -ATLANTA multicentre randomised controlled trial, pilot study.

This was the first randomised study to utilise cytoreductive MIAT in mHPSC. The use of cytoreductive MIAT with simultaneous surgical metastasectomy has not been reported beyond the cadaveric setting. Here-in, using both the ITT-analysis and a granular per-protocol (PP-) analysis, I report the feasibility and safety profile of this approach and found that cytoreductive MIAT's feasibility and safety profile is comparable to cytoreductive radiotherapy and cytoreductive radical prostatectomy in this setting. In addition, I was able to document the intraprostatic tumour response to cytoreductive MIAT utilising serial mpMRI and histology at “pre-systemic”, “pre-operative” and “post-operative” time points, respectively.

I conclude that cytoreductive minimally invasive ablative therapy, with or without simultaneous surgical metastasectomy (in the form of pelvic lymph node dissection), is a feasible and safe alternative approach to treating the primary tumour and local pelvic metastases in patients with mHSPC who have received pre-operative systemic therapy intensification.

10.2 Introduction

We have previously extensively discussed the current body of retrospective evidence supporting cytoreductive minimally invasive ablative therapy in **Chapter 2** and **Chapter 5**, respectively. At present, ablative therapies such as cryotherapy and high-intensity focused ultrasound (HIFU) in prostate cancer are recommended in selected patients with a good life expectancy, with low- and intermediate-risk (e.g. Gleason 3 + 4 = 7 or 4 + 3 = 7) that is localized and of discrete small volume (212). The application of MIAT for high volume and high grade localised disease has been largely restricted to the radio-recurrent non-metastatic salvage setting (213).

Briefly, there is no randomised evidence supporting cytoreductive MIAT currently available (120,122-124,320). Of the available ablative modalities, cytoreductive whole-gland cryotherapy is the most extensively evaluated to date. In a recent retrospective study using propensity-scored matched analysis against ADT alone, cytoreductive whole-gland cryotherapy demonstrated an absolute median failure-free survival advantage of 18 months (39 versus 21 months; $p = 0.005$) (122). Finally, performing surgical metastasectomy in the form of pelvic lymph node dissection (PLND) at the time of simultaneous MIAT has never been reported, to the author's knowledge, beyond the cadaveric setting (214).

The aim of this thesis chapter was to report on the performance of the novel surgical approach of cytoreductive minimally invasive ablative therapy, with or without surgical metastasectomy in the form of PLND, in patients with *de novo* synchronous mHSPC allocated to Intervention Arm 1 of the IP2-ATLANTA multicentre randomised controlled trial, internal pilot (**Chapter 7**).

10.3 Methods

10.3.1 Study design

In **Chapter 5** of this thesis, we have described the overall trial design of IP2-ATLANTA and cytoreductive MIAT (Intervention Arm 1) with or without PLND in detail. The full SOP for both trial treatments in this intervention arm are available in **Appendix F**, respectively.

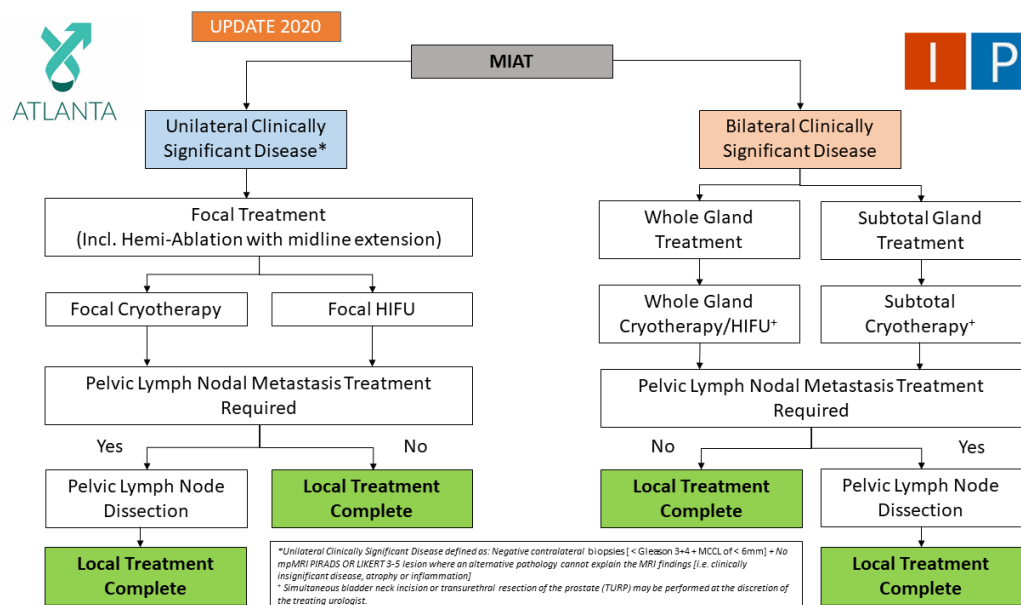
10.3.2 Ablation treatment plan

Cytoreductive ablation treatment plan was based on tumour location and volume, determined by mpMRI and prostate biopsy findings at study entry (**Figure 22**) (212,217). An mpMRI was performed using a 1.5-T or 3.0-T scanner and the report was available at trial visit 1 (SCR, week 0). A repeat mpMRI was acquired following systemic therapy, but prior to cytoreductive MIAT, being performed (Visit 3 or 4; Week 26 or Week 28) in keeping with the trial protocol (**Chapter 5**). The initial mpMRI and repeat mpMRI were performed and reported in accordance with the technical requirements of PI-RADS (version 2.0). However, a PI-RADS score could not be assigned due to treatment effect on the second mpMRI. Both mpMRI sequences included T1-weighted, T2-weighted, dynamic contrast-enhanced (DCE) and multi b-values (for derivation of apparent diffusion coefficient [ADC] maps) and a high b-value of at least 1500. All mpMRI were reported by uro-radiologists, with a minimum of 3 years reporting experience.

In total, three trial sites performed cytoreductive MIAT, these were: A1-Imperial College Healthcare NHS Trust; A7-University Hospital Southampton NHS Trust; and A8-City

Hospitals Sunderland NHS Foundation Trust. Where a trial patient's baseline mpMRI was reported outside of these trials sites it underwent a secondary report at the relevant trial site assigned to performing cytoreductive MIAT, linked cancer multidisciplinary meeting.

Figure 23. Intervention Arm 1 MIAT: Ablative treatment plan and modality flowchart



Legend: Flowchart of MIAT treatment options created by M. Connor (2020). MIAT – Minimally Invasive Ablative Therapy; MRI – Magnetic Resonance Imaging; HIFU – High Intensity Focused Ultrasound; MCCL – Maximum Cancer Core Length. Clinically insignificant disease was defined as $\leq$ Gleason 3+3 and Maximum Cancer Core Length (MCCL) of <6mm.

An overview of the decision making for cytoreductive ablative energy modality and ablative field is presented in **Figure 23**. Clinically insignificant prostate cancer (cisPCa) was defined as $\leq$ Gleason 3+3 and Maximum Cancer Core Length (MCCL) of <6mm.

In cases of bilateral clinically significant prostate cancer (csPCa) either of the following treatment plans were utilised: “anterior or posterior extension”, “hockey stick (hemi-ablation with midline extension either anteriorly or posteriorly), “subtotal” (with either anterior or posterior sparing) or “whole-gland” ablation (212). Where whole-gland treatment was performed, rectal protection procedures, such as (but not limited to) gel or balloon spacers or hydro-dissection use depending on ablative energy modality. In all cases, if deemed clinically necessary and in particular for whole-gland treatment, a simultaneous bladder neck incision (BNI) or transurethral resection of the prostate (TURP) was performed at the discretion of the treating urologist. Seminal vesical (SV) treatment for T3b disease was permitted to both SVs if deemed feasible by the treating urologist.

Unilateral csPCa disease was confirmed by negative contralateral biopsies and no mpMRI PI-RADS lesion score 3-5 where an alternative pathology could not explain the MRI

findings (i.e. cisPCa, atrophy, inflammation). In such cases a quadrant ablation approach to the treatment plan was adopted. Treatment fields could extend across the midline or were performed as a hemi-ablation to ensure an adequate margin of 5-10mm was achieved. A hockey stick was also permitted. In cases of unilateral csPCa with cisPCa in the contralateral biopsies and a mpMRI PI-RADS tumour lesions 3-5 at baseline, the decision to treat the contralateral lobe was at the discretion of the treating urologist or central multi-disciplinary team meeting (MDTM).

Due to the cytoreductive nature of the treatment in this trial it was recognised, that while maximal ablation of involved tissue was the aim, complete primary tumour ablation may not be possible or safe in all cases.

10.3.3 Energy modality selection

The energy modality was selected based on the chosen treatment plan, detailed in the prior section, with the following additional guidance (**Table 36**).

Table 36. Cytoreductive energy modality selection guidance

Specific Scenarios	Energy modality selection	
	Cytoreductive Cryotherapy	Cytoreductive HIFU
PZ tumours in glands with an AP height of ≤ 3 cm	Y	Y
PZ tumour in glands with an AP height >3 cm who need a hemi-ablation	Y	N
Anterior or TZ tumour (of any gland size)	Y	N
Subtotal or Whole-gland Treatment	Y	Y* [*permitted only if small gland size post-systemic therapy prevents safe cryotherapy]
SV treatment < 10 mm	Y	Y
SV treatment > 10 mm	Y	N
Widespread intraprostatic calcification and/or anal canal stenosis	Y	N
Require spinal anaesthesia	Y	N

Legend: HIFU – High Intensity Focused Ultrasound; PZ – Peripheral Zone; TZ – Transition Zone; SV – Seminal Vesical ; AP – Anterior posterior.

10.3.4 Trial procedure: Cytoreductive Cryotherapy

All patients underwent cytoreductive cryotherapy using either the SeedNet or Visual ICE cryotherapy device (Boston Scientific, Marlborough, MA, USA). Patient were placed in the lithotomy position with transrectal ultrasound (TRUS) probe inserted to allow for treatment planning. Using a standard brachytherapy grid, transperineal cryoprobe needles were placed 5 mm to 15 mm apart TRUS guidance. Needle location was according to treatment plan, needles type and ablation strategy. Thermocouples were placed as close to the centre of the lesion. In addition, they were placed in either Denonvilliers' fascia (for posterior ablations), or in the peripheral zone (for anterior ablations). Either an open-ended urethral catheter was placed prior to cryoprobes insertion to ensure these did not traverse the urethra or a flexible cystoscopy was performed after cryoprobe insertion to confirm that no needles had inadvertently migrated into the bladder neck or the urethra. A urethral warmer was inserted over a guide-wire placed at the time of the flexible cystoscopy or through the open tip urethral; catheter.

During the procedure, TRUS was used to visualise the ice-ball. The duty-cycle or gas flow settings were adjusted to control the ice-ball dimension. All patients underwent an initial freeze-thaw cycle with a target temperature for the cancer lesion thermocouple of -40°C or lower. This was held for at least 3 minutes and subsequently a 3-minute passive and 3-minute active thaw was performed followed by a second freeze-thaw cycle of similar parameters, times and temperature targets. Following the second cycle an active thaw was performed only until it was possible to remove the needles which allowed for a slow passive thaw to occur naturally. A third freeze-thaw cycle was permitted at the treating urologist's discretion.

The margin of the focal cryotherapy was determined by visualisation of the hypoechoic ice-ball edge and the temperature changes in the thermocouples. We recommended extension to at least 5 mm beyond the intra-prostatic tumour margin. For extra-prostatic tumour margins the ice-ball edge was moved to 1-2 mm beyond the tumour margin, if this was safe and possible or if the thermocouple within Denonvilliers' fascia reached 0 degrees centigrade. Treatment of the SV extended as far cranially as it was safe, given the likely proximity of the distal ureters (</= 10-15mm).

All patients had a urethral or suprapubic catheter placed post-operatively for a minimum of 7 days. Antibiotics peri- and post-operatively were given as per local antimicrobial policies along with an alpha blocker (e.g., tamsulosin, laxatives and analgesics).

10.3.5 Trial procedure: Cytoreductive HIFU

Cytoreductive HIFU (Sonablate, Sonacare, Charlotte, NC, USA) was performed under a general anaesthetic. Given the availability of HIFU, local operative procedure and manufacturer's guidance were followed, with the following taken into consideration: i) treatment using three blocks ii) dose escalation (i.e. layering) iii) longer duty cycle.

All patients had a urethral or suprapubic catheter placed post-operatively for a minimum of 7 days. Antibiotics peri- and post-operatively were given as per local antimicrobial policies along with an alpha blocker (e.g., tamsulosin, laxatives and analgesics).

10.3.6 Trial procedure: Surgical Metastasectomy (PLND)

Surgical metastasectomy in the form of pelvic lymph node dissection was set out in the "Laparoscopic or Robotic-Assisted Laparoscopic (Extended) Pelvic Lymph Node Dissection following Minimally Invasive Ablative Therapy SOP" (**Appendix F** [Connor M., Dudderidge, T., Ahmed, H.]). Unlike the cytoreductive prostatectomy arm, an open approach was not permitted, given the minimally invasive nature of the primary treatment delivered.

General anaesthesia achieved was per anaesthetist, patient specific factors and in accordance with local protocol. The patient underwent cytoreductive MIAT and then was repositioned in a Trendelenburg or similar position as determined by patient specific factors and the operating surgeon. Pneumoperitoneum was created by any means (Veress needle insufflation/open Hasson technique) determined by operating surgeon.

We did not mandate a specific PLND template in this study, in keeping with prior cytoreductive prostatectomy studies, but performed as per the operating surgeon, in accordance with accepted surgical practice and local departmental protocol (221,237). As there is no evidence to the extent of PLND in this setting, we permitted ePLND (i.e., dissection up to the common iliac arteries with or without the presacral areas) where pathological nodes were present on baseline imaging, where this was deemed a safe approach. The extent of lymphadenectomy was recorded as "ePLND" or "PLND" in the trial electronic data capture form post-operatively.

Individual operating surgeon submitted declaration to the "IP2-ATLANTA Surgeon Quality Assurance Board", confirming they have met minimum standards expected of an operating surgeon: (1) > 200 recorded cases in logbook; (2) <4% complication rate defined as Clavien Dindo III and above, and (3) <3% post-operative transfusion rate (**Chapter 6**).

10.3.7 Study outcomes

Here-in, using both the ITT-analysis and a granular per-protocol (PP-) analysis, we report the feasibility and safety profile of cytoreductive MIAT in mHSPC

Using PP-analysis, feasibility and safety were reported using the Common Terminology Criteria for Adverse Events (CTCAEv5.0) domain were used to report adverse events as per the IP2-ATLANTA protocol described in **Chapter 6** of this thesis. In addition, we were able to document the intraprostatic tumour response to cytoreductive MIAT in mHSPC, using serial mpMRI and histology at “pre-systemic”, “pre-operative” and “post-operative” time points. Intraoperative imaging was collected of cytoreductive cryotherapy and pelvic lymph nodal dissection, given the approach has not been previously described in the literature.

Using ITT-analysis, for the purposes of this chapter, the International Prostatic Symptoms Score (IPSS), The Expanded Prostate Cancer Index Composite Bowel and Bladder (EPIC) and International Index of Erectile Function 15 (IIEF-15) were reported pre-operatively at “baseline” (SCR Visit 1; Week 0) and “post-operatively” (Visit 7; Week 52), as per the IP2-ATLANTA protocol described in **Chapter 6** of this thesis.

10.3.8 Statistical analysis

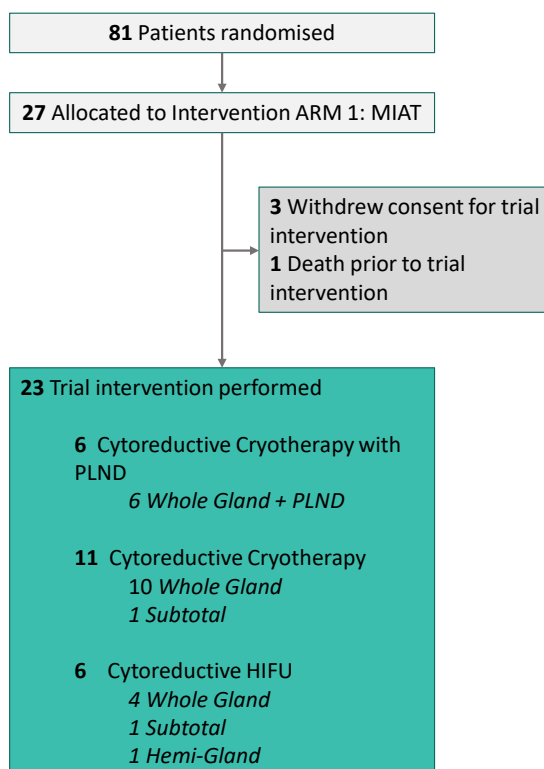
Descriptive statistics presented summarise patient demographics, clinical, radiological and biopsy characteristics. To determine outcomes of individual constructs of the relevant PROMS these were reported in associated domains as per published PROMS analysis guidance. With respect to the EPIC urinary domains these comprise several urinary items. These are formed by linear transformation of raw scores, ranging from “0” to “100” i.e. “worse” to “better”. A paired t-test was used for parametric data and Mann-Whitney U test for non-parametric data, respectively. All data points were analysed by myself using SPSS (IBM Corp., IBM SPSS Statistics for Windows, Armonk, USA, v.28.0).

10.4 Results

Overall, 81 patients consented and were randomised in the IP2-ATLANTA internal pilot (**Figure 24**) during March 2019 to February 2021. 27 (33.3%) trial participants were allocated to receive cytoreductive MIAT, with or without surgical metastasectomy (PNLD). Of these 27, 23 (85.2%) received their planned trial intervention, with 6/23 (26%) receiving cytoreductive MIAT with PLND and 17/23 (74%) receiving cytoreductive MIAT alone.

Of these, 4 of 27 (14.8%) who did not receive their planned trial intervention: three (3/27; 11.1%) did not consent for cytoreductive MIAT following clinical consultation and a further patient (1/27; 3.7%) died from progressive metastatic disease prior to the planned intervention occurring.

Figure 24. Consort diagram for of Intervention Arm 1: MIAT



Legend: A single patient died of progressive disease prior to allocated trial treatment. Three patients did not consent to their allocated trial treatment and continued under standard of care follow-up. MIAT - Minimally Invasive Ablative Therapy; HIFU – High Intensity Focused Ultrasound.

10.4.1 Baseline demographics

Baseline demographics, have been previously presented in **Chapter 7** using the ITT-analysis. Here-in we present the PP-analysis of patients who went onto receive the allocated treatment in Intervention Arm 1 (**Table 37**). All patients reached the minimum follow-up visit 7 (52 weeks), the overall median (IQR) follow-up for the treatment arm was 21 (18- 28) months. The median age (IQR) and baseline PSA (IQR) was 67.0 (64-75) years and 102.00 (35.43 – 264.93), respectively. At baseline, M stage classification was predominantly M1b (bone metastasis; 20/23 [86.9%]), with a minority of M1a (non-regional lymph nodes; 3/23; 13.0%). There were no patients with visceral metastases.

At study entry 100.0% (23/23) of patients had a performance status of “0” and furthermore CHAARTED defined metastatic burden was even (Low - 12/23 [52.2%]; High – 11/23 [47.8%]). Classification by metastasis groups was as follows: “1 to 3” 47.8% (11/23), “4 to 7” 0.0% (0/23), “8 to 10” 8.7% (2/23); and >10 in 43.5% (10/23), respectively. Regional nodal metastasis (N1+) on imaging predominated at baseline in 65.2% (15/23) of the study cohort.

Table 37. Baseline demographics of patients who received the allocated intervention in arm 1

Variable	Intervention Arm 1: MIAT +/- PLND n=23 (PP-analysis)
Age at randomisation (years)	
Median, years (IQR)	67.0 (64 – 75)
Mean, years (SD)	68.5 (7.3)
WHO Performance Status	
0 (%)	23 (100.0%)
1 (%)	0 (0.0%)
Body mass index (BMI)	
Mean, kg/m ² (SD)	27.4 (4.7)
Median, kg/m ² (IQR)	27.0 (24.9 – 29.3)
Racial/Ethnic Group	
White British (%)	10 (43.5%)
White Other (%)	2 (8.7%)
Black Caribbean (%)	1 (4.3%)
Not reported (%)	10 (43.5%)
Overall T Stage at randomisation	
T2 (%)	0 (0.0%)
T3a (%)	3 (13.0%)
T3b (%)	10 (43.5%)
T4 (%)	10 (43.5%)
Overall N Stage at randomisation	
N0 (%)	8 (34.8%)
N1 (%)	15 (65.2%)
Overall M Stage at randomisation	
M1a [Non-regional lymph nodes] (%)	3 (13.0%)
M1b [Bone] (%)	20 (86.9%)
M1c [Visceral] (%)	0 (0.0%)
Number of metastases at randomisation using conventional imaging	
1-3 (%)	11 (47.8%)
4-7 (%)	0 (0.0%)
8-10 (%)	2 (8.7%)
>10 (%)	10 (43.5%)
Metastatic burden at randomisation using conventional imaging	
Low (%)	12 (52.2%)
High (%)	11 (47.8%)

Systemic treatment prior to cytoreductive MIAT +/- PLND	
LHRH Agonist (%)	23 (100.0%)
Docetaxel (%)	10 (43.5%)
Enzalutamide (%)	11 (47.8%)
Abiraterone (%)	1 (4.3%)
MAB (%)	1 (4.3%)
Baseline Gleason Score and pattern / ISUP grade group	
<= 4+3 / ISUP 3 (%)	0 (0.0%)
4+4 / ISUP 4 (%)	7 (30.4%)
4+5 / ISUP 5 (%)	10 (43.5%)
5+3 / ISUP 4 (%)	0 (0.0%)
5+4 / ISUP 5 (%)	5 (21.7%)
5+5 / ISUP 5 (%)	1 (4.3%)
Baseline Maximum Cancer Core Length (MCCL)	
Median, mm (IQR)	14.0 (10.0 – 15.0)
Mean, mm (SD)	12.3 (4.3)
Pre-operative second biopsy finding	
Biopsy performed, <i>n</i> (%)	19 (82.6%)
Complete pathological response, <i>n</i> (%)	3 (15.8%)
Residual adenocarcinoma, <i>n</i> (%)	16 (84.2%)
Pre-operative Second Biopsy MCCL	
Median, mm (IQR)	7.5 (5.0 – 11.0)
Mean, mm (SD)	7.9 (4.3)
PSA baseline prior to systemic therapy	
Median, ng/ml (IQR)	102.00 (35.42 – 264.93)
Range, ng/ml	2.57 – 3200.00
PSA prior to MIAT “pre-operative”	
Median, ng/ml (IQR)	1.00 (0.22 – 1.45)
Range, ng/ml	0.01 – 24.00
PSA post MIAT “post-operative”	
Median, ng/ml (IQR)	0.10 (0.01 – 0.82)
Range, ng/ml	0.01 – 30.00
Intervention Arm 1: pre-randomisation treatment declarations	
Intention to treat pelvic lymph nodes, <i>n</i> (%)	10 (43.5%)
Treatment delivered to pelvic lymph nodes, <i>n</i> (%)	6 (26.0%)

Legend: Highest PI-RADS Score was used. SD – Standard Deviation; IQR - Interquartile Range; PI-RADS – Prostate Imaging Reporting & Data System; BS – Bone Scintigraphy; CT-TAP – CT Thorax, Abdomen & Pelvis; N – Nodes; M – Metastasis; T – Tumour; MCCL - Maximum Cancer Core Length; ISUP - International Society of Urological Pathology; BMI – Body Mass Index; WHO – World Health Organisation; PP – Per protocol analysis.

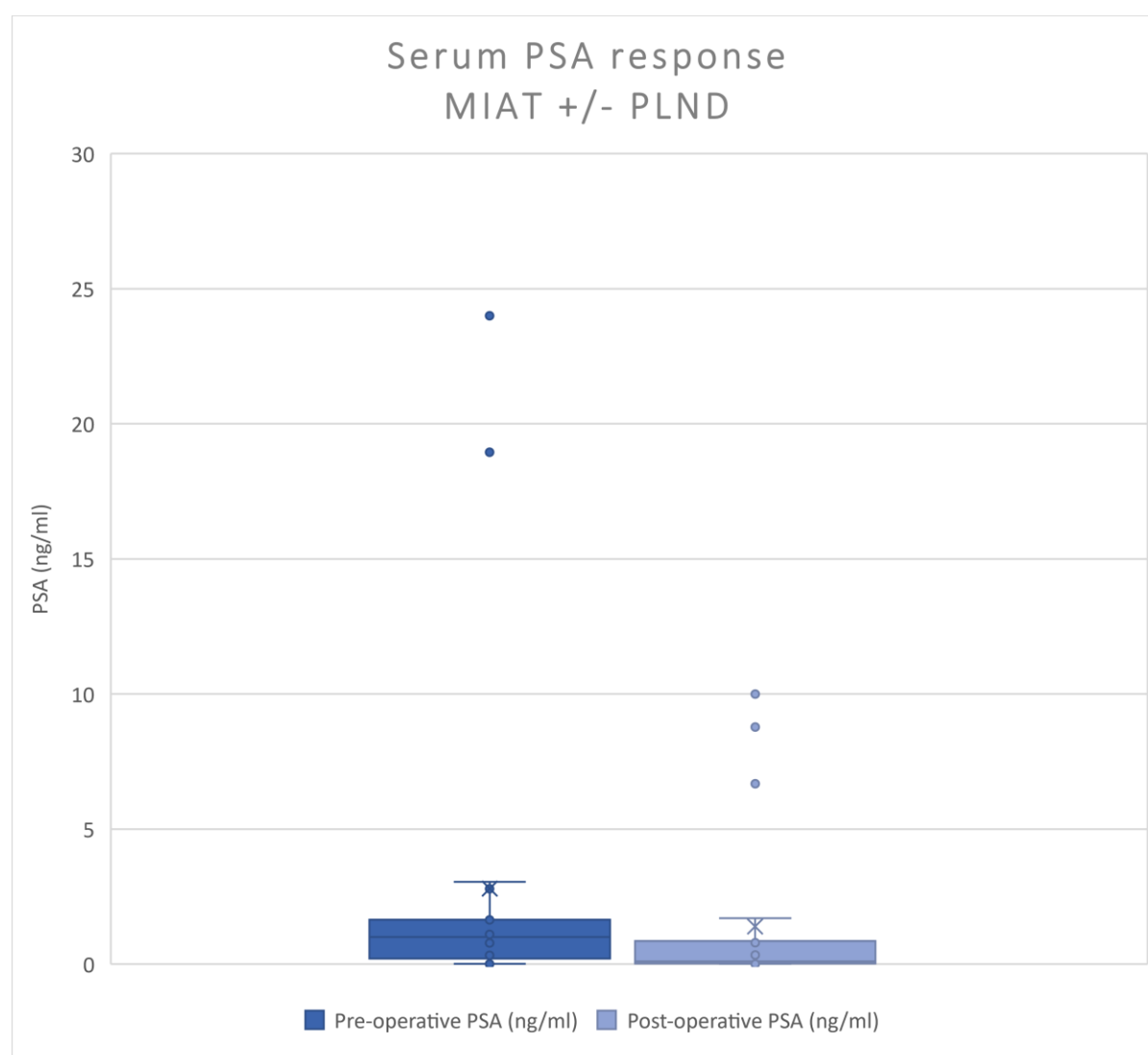
10.4.2 Sequential prostate biopsy and PSA response

The overall ITT-analysis sequential prostate biopsy results have been presented in prior **Chapter 7** and **Chapter 8**. Here-in we provide granular detail on the cohort of patient who received their allocated trial protocol treatment in Intervention Arm 1: MIAT (**Table 37**). Baseline biopsy reported only $\geq$ ISUP 4 & 5 disease, with the most common Gleason Grade Groups: 4+4 (7/23; 30.4%), 4+5 (10/23; 43.5%) and 5+4 (5/23; 21.7%), respectively. As per current guidelines repeat Gleason reporting following ADT is not recommended as there may be a false apparent increase, due to either resistant high-grade cancer cell number or reduction in mass, leaving a residual single cancer of higher grade (264,269).

Repeat transperineal prostate biopsy was performed in 19 of 27 (82.6%) of the cohort. Residual prostate adenocarcinoma was identified in the majority of patients 84.2% (16/19) who underwent a pre-operative repeat biopsy, following 6 to 9 months of systemic therapy. In three patients (3/19; 15.8%) complete pathological response was reported. Furthermore, there were significant reductions in mean Maximum Cancer Core Length (MCCL) following systemic therapy (12.3 [SD 4.3] versus 7.9 [SD 4.3] mm; 95%CI 1.45-7.32; $p < 0.0046$).

The IP2-ATLANTA embedded pilot study ($n=81$) was not designed to report on oncological outcomes, which will be derived from the main phase sample size using a composite definition of progression-free survival. In this exploratory analysis, median serum PSA was reported to be at: “baseline” 102.00 (IQR 35.43 – 264.93) ng/ml, “pre-operatively” 1.00 (IQR 0.22 – 1.45) ng/ml, and “post-operatively” 0.1 (IQR 0.02 – 0.82) ng/ml, respectively (**Figure 25**).

Figure 25. Serum PSA response of patients treated with cytoreductive MIAT +/- PLND (Intervention Arm 1)



Legend: Box-whisker plot of serum PSA response in patients who received cytoreductive minimally invasive ablative therapy with or without pelvic lymph node dissection. "X" indicates the mean value; "-" indicates median value; "●" indicates individual values; Interquartile range presented. (Dark Blue) Pre-operative PSA was derived from Visit 3 (Week 26 [+/-12]) and (Light Blue) post-operative PSA derived from Visit 7 (Week [52+/-4]), respectively. MIAT – Minimally Invasive Ablative Therapy; PSA – Prostate Specific Antigen; PLND – Pelvic Lymph Node Dissection.

10.4.3 Baseline and pre-operative MRI changes

All patients underwent a pre-operative mpMRI ($n=23$; **Table 38**). Mean prostate volume reduced from 45.6 (SD 19.4) cc at baseline to 25.2 (SD 11.8) cc pre-operatively ($p=0.0002$). Maximal MRI-PVol reduction was reported in LHRHa with Docetaxel compared to LHRHa Enzalutamide (42.9% versus 22.5%). Mean prostate-specific antigen density (PSAD) reduced from 10.2 (SD 16.4) ng/ml to 0.09 (SD 0.162) ng/ml ($p<0.0001$).

Intraprostatic diffuse lesions increased by +40.0% between MRI imaging timepoints (10/23 versus 14/23). MRI T4 stage disease predominated in 10/23 (43.5%) of the cohort at

baseline. There were no cases of <T3a reported at baseline MRI. Following systemic therapy MRI T4 stage disease was reported in 7/23 (30.4%), representing a -30.0% decrease. In addition, Tx and T2 disease were reported in 1/23 (4.3%) and 2/23 (8.7%), respectively. Similarly, MRI N1 disease was reported in 15/23 (65.2%) at baseline, this reduced to 10/23 (-33.3%) following systemic therapy. At baseline PI-RADS 5/5 lesions were reported in all patients (23/23; 100.0%).

Table 38. PP-analysis of sequential MRI reporting changes in patients receiving cytoreductive MIAT

Baseline MRI (n=23)		Pre-operative MRI (n=23)		p-value / % change
Prostate Volume, cc, mean (SD)	45.6 (19.4)	Prostate Volume, cc, mean (SD)	25.2 (11.8)	p=0.0002 ⁺ / -44.7%
<i>i) Docetaxel, cc, mean (SD)</i>	52.2 (22.4)	<i>i) Docetaxel, cc, mean (SD)</i>	25.5 (12.8)	-42.9%
<i>ii) Enzalutamide, cc, mean (SD)</i>	41.9 (16.4)	<i>ii) Enzalutamide, cc, mean (SD)</i>	26.63 (12.7)	-22.5%
PSA-Density (PSAD) ng/ml, mean (SD)	10.2 (16.4)	PSA-Density (PSAD) ng/ml, mean (SD)	0.09 (0.16)	p<0.0001 ⁺
Intraprostatic Lesion Characteristics		Intraprostatic Lesion Characteristics		
<i>Distinct, n (%)</i>	13 (56.2%)	<i>Distinct, n (%)</i>	9 (39.1%)	-30.4%
<i>Diffuse, n (%)</i>	10 (43.5%)	<i>Diffuse, n (%)</i>	14 (60.9%)	+40.0%
MRI T-Stage		MRI T-Stage		
<i>Tx, n (%)</i>	0 (0)	<i>Tx, n (%)</i>	1 (4.3%)	-
<i>T2, n (%)</i>	0 (0)	<i>T2, n (%)</i>	2 (8.7%)	-
<i>T3a, n (%)</i>	3 (13.0%)	<i>T3a, n (%)</i>	1 (4.3%)	-66.7%
<i>T3b, n (%)</i>	10 (43.5%)	<i>T3b, n (%)</i>	12 (52.2%)	+20.0%
<i>T4, n (%)</i>	10 (43.5%)	<i>T4, n (%)</i>	7 (30.4%)	-30.0%
MRI N-Stage		MRI N-Stage		
<i>N0, n (%)</i>	8 (24.8%)	<i>N0, n (%)</i>	13 (56.2%)	+62.5%
<i>N1, n (%)</i>	15 (65.2%)	<i>N1, n (%)</i>	10 (43.5%)	-33.3%
PI-RADS Score		PI-RADS Score		
3, n (%)	0 (0.0%)	N/A		N/A
4, n (%)	0 (0.0%)			
5, n (%)	23 (100.0%)			

Legend: *Mann-Whitney U test. SD – Standard Deviation; IQR: Interquartile Range. PI-RADS – Prostate Imaging Reporting & Data System (version 2); BS – Bone Scintigraphy; CT-TAP – CT Thorax, Abdomen & Pelvis. Highest PI-RADS Score used.

10.4.4 Peri-operative data

Treatments performed were: Cytoreductive (Whole Gland) Cryotherapy + PLND 6/23 (26.0%); Cytoreductive Cryotherapy 17/23 (43.5%) and Cytoreductive HIFU 6/23 (26.1%), respectively (**Table 39**). Median operating time (IQR) and length of stay (IQR) for all MIAT procedures was 110.8 (90.5 – 188.5) minutes and 1.0 (0.5 - 1.0) days, respectively. All patients requiring PLND were admitted overnight. “Day case” cytoreductive MIAT was achieved in 7/23 (30.4%) of patients.

Cytoreductive cryotherapy ablation pattern was predominantly whole gland in 69.5% (16/23) and a further 4.35% (1/23) were subtotal. All cases of PLND were associated with use of cryotherapy energy to the primary tumour and all were whole gland ablation pattern. Focal cryotherapy was not used in the trial cohort. Median (IQR) operating time for cytoreductive cryotherapy and cytoreductive cryotherapy with PLND were 90.8 (84.8 – 104.8) minutes and 226 (219.5 – 228.8) minutes, respectively. Median (IQR) length of stay for cytoreductive cryotherapy and cytoreductive cryotherapy with PLND was 1.0 (0.5 – 1.0) days and 1.5 (1.1 - 1.9) days, respectively. Median lymph node retrieval was 14.5 (IQR 8.25 – 22.5).

Cytoreductive HIFU ablation pattern were whole gland, sub-total and hemi-gland in 17.4% (4/23), 4.3% (1/23) and 4.3% (1/23) of patients, respectively. Focal HIFU, excluding hemi-gland ablation, was not used in the trial cohort. Median (IQR) operating time and length of stay (IQR) for cytoreductive HIFU was 124.5 (105.0 – 153.5) minutes and 1.0 (0.5 -1.0) days, respectively.

There were no major peri-operative complications. Specifically, there were no intraoperative or post-operative blood transfusions. Trial without catheter was successful in 91.3% (21/23) of patients treated.

Table 39. Perioperative data in patients treated in intervention arm 1: MIAT

Variable	Intervention Arm 1: MIAT +/- PLND n=23 (PP-analysis)
Overview of Intervention Arm 1 treatments	
Cytoreductive (Whole Gland) Cryotherapy + PLND, <i>n</i> (%)	6 (26.0%)
Cytoreductive Cryotherapy, <i>n</i> (%)	17 (73.9%)
Cytoreductive HIFU, <i>n</i> (%)	6 (26.1%)
Metastasis-directed therapy - SABR, <i>n</i> (%)	1 (4.3%)
Cytoreductive Cryotherapy	
Whole Gland + PLND, <i>n</i> (%)	6 (26.0%)
Whole Gland, <i>n</i> (%)	10 (43.5%)
Subtotal, <i>n</i> (%)	1 (4.3%)
Cytoreductive HIFU	
Whole Gland, <i>n</i> (%)	4 (17.4%)
Subtotal, <i>n</i> (%)	1 (4.3%)
Hemi-gland, <i>n</i> (%)	1 (4.3%)
Operating Time	
All procedures, median, mins (IQR)	110.8 (90.5 – 188.5)
All procedures, mean, mins (SD)	140.8 (73.3)
Cytoreductive (Whole Gland) Cryotherapy + PLND, median, mins (IQR)	226 (219.5 – 228.8)
Cytoreductive Cryotherapy, median, mins (IQR)	90.8 (84.8 – 104.8)
Cytoreductive HIFU, median, mins (IQR)	125.50 (105.0 – 153.5)
Intraoperative complications	
Procedure abandoned, <i>n</i> (%)	0 (0.0%)
Intraoperative blood transfusion, <i>n</i> (%)	0 (0.0%)
Intraoperative complications, <i>n</i> (any) (%)	0 (0.0%)
Cytoreductive pelvic lymph node dissection (n=6/23)	
Approach: Robotic-assisted laparoscopic, <i>n</i> (%)	6 (100.0%)
PLND	6 (100.0%)

ePLND	0 (0.0%)
Lymph nodes removed, <i>n</i> , median (IQR)	14.5 (8.2 -22.3)
Lymph nodes positive, <i>n</i> , median (IQR)	2.0 (2.0 – 3.5)
Post operative care	
Post-operative blood transfusion, <i>n</i> (%)	0 (0.0%)
Return to theatre during hospital stay, <i>n</i> (%)	0 (0.0%)
Length of stay overall, days, median (IQR)	1.0 (0.5 – 1.0)
Day-case Cytorreductive MIAT (excl. PLND) (%)	7 (30.4%)
Length of stay Cytorreductive Cryotherapy + PLND, days, median (IQR)	1.5 (1.1 – 1.9)
Length of stay Cytorreductive Cryotherapy, days, median (IQR)	1.0 (0.5 – 1.0)
Length of stay Cytorreductive HIFU, days, median (IQR)	1.0 (0.5 – 1.0)
Failed trial without catheter, <i>n</i> (%)	2 (8.7%)
Erections sufficient for intercourse without invasive aids at Visit 7, <i>n</i> (%)	1 (4.3%)

Legend: SD – Standard Deviation; IQR: Interquartile Range. PI-RADS – Prostate Imaging Reporting & Data System; BS – Bone Scintigraphy; CT-TAP – CT Thorax, Abdomen & Pelvis; AE – Adverse Event; SAE – Serious Adverse Event; CTAE – Common Terminology for Adverse Events (Version 5.0). Highest PI-RADS Score used. Grade 1 Urinary Retention able to void with some residual and no requirement for urethral/suprapubic/intermittent catheterisation.

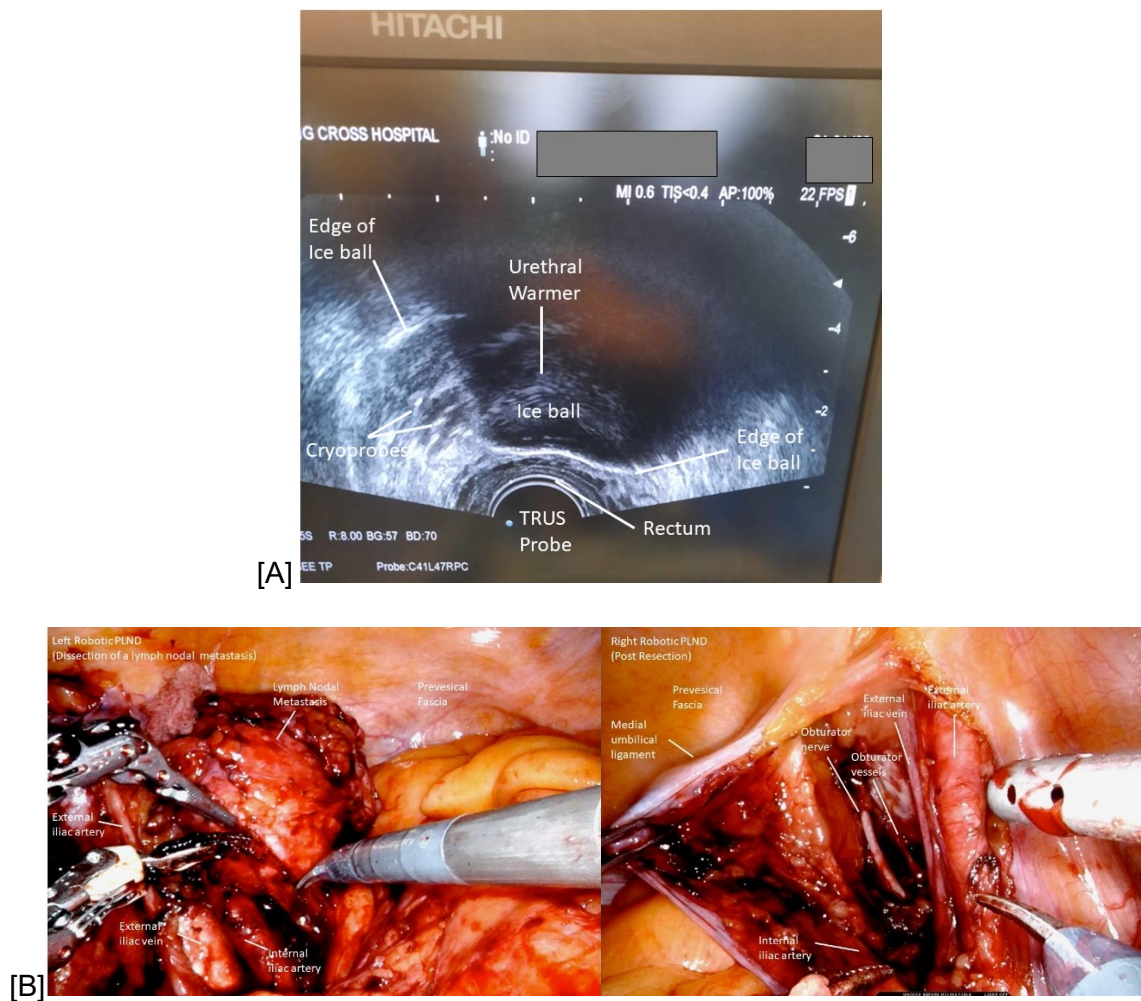
10.4.5 Intraoperative imaging of cytorreductive MIAT with PLND

In **Figure 26**, we present a case of cytorreductive whole gland cryotherapy with pelvic lymph node dissection. Intraoperative transrectal ultrasound images of cryotherapy and images of simultaneous robotic bilateral pelvic lymph node dissection.

10.4.6 Serial mpMRI and prostate histology changes during cytorreductive MIAT

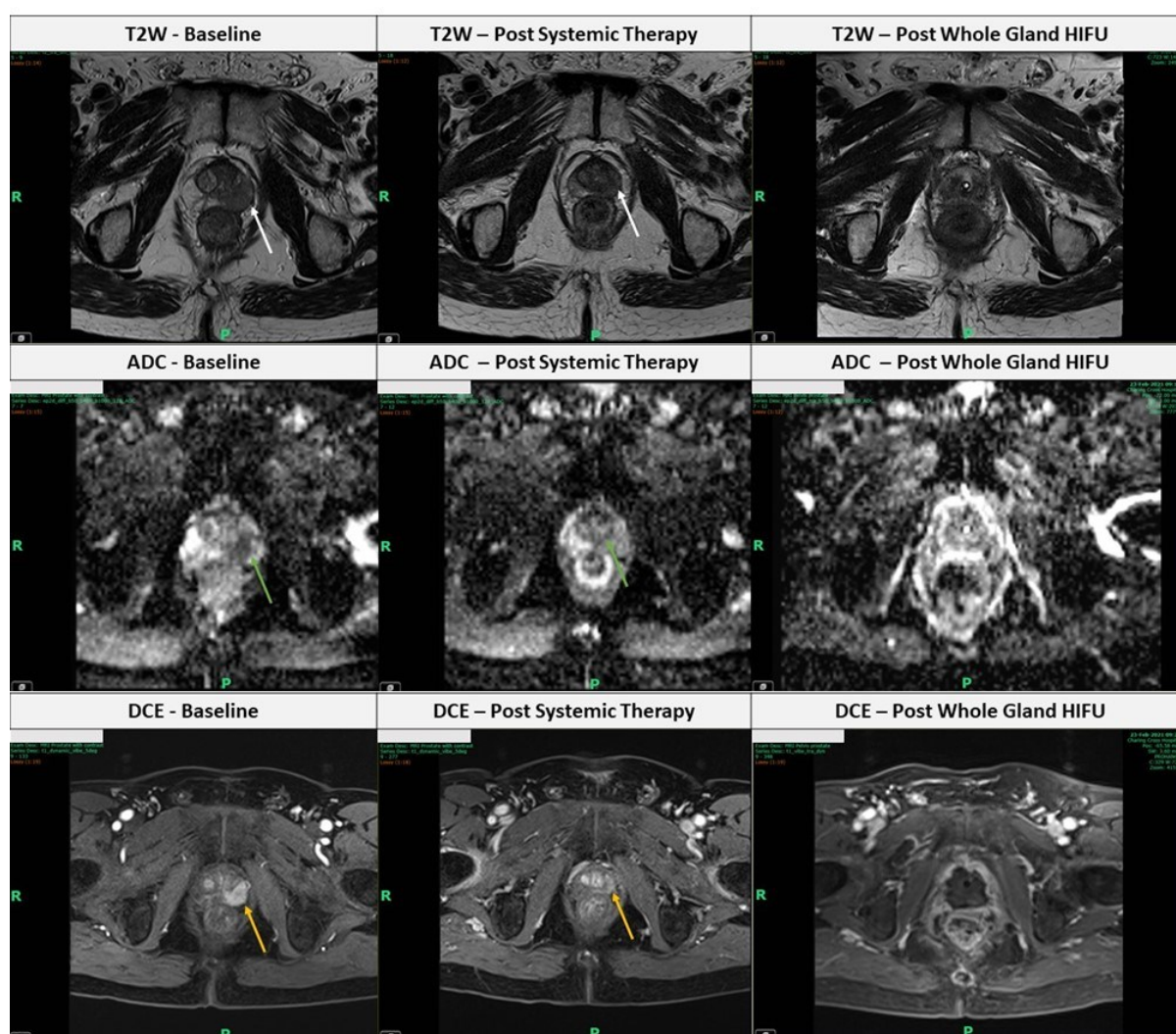
In **Figure 27** to **Figure 28**, we present the intraprostatic tumour response to cytorreductive MIAT in mHSPC, using serial mpMRI and histology at “pre-systemic”, “pre-operative” and “post-operative” time points. This case series documents i) cytorreductive whole gland HIFU ii) cytorreductive subtotal cryotherapy, iii) lymph node mpMRI and histology changes in a case of cytorreductive whole gland cryotherapy with bilateral PLND. MRI imaging is accompanied by a complete case report, in both HIFU and cryotherapy cases no evidence of residual or recurrent disease is noted in the ablated region on MRI post-operatively, at 3 weeks and 11 months, respectively.

Figure 26. Intraoperative images of cytoreductive cryotherapy with bilateral robotic lymph nodal metastasectomy



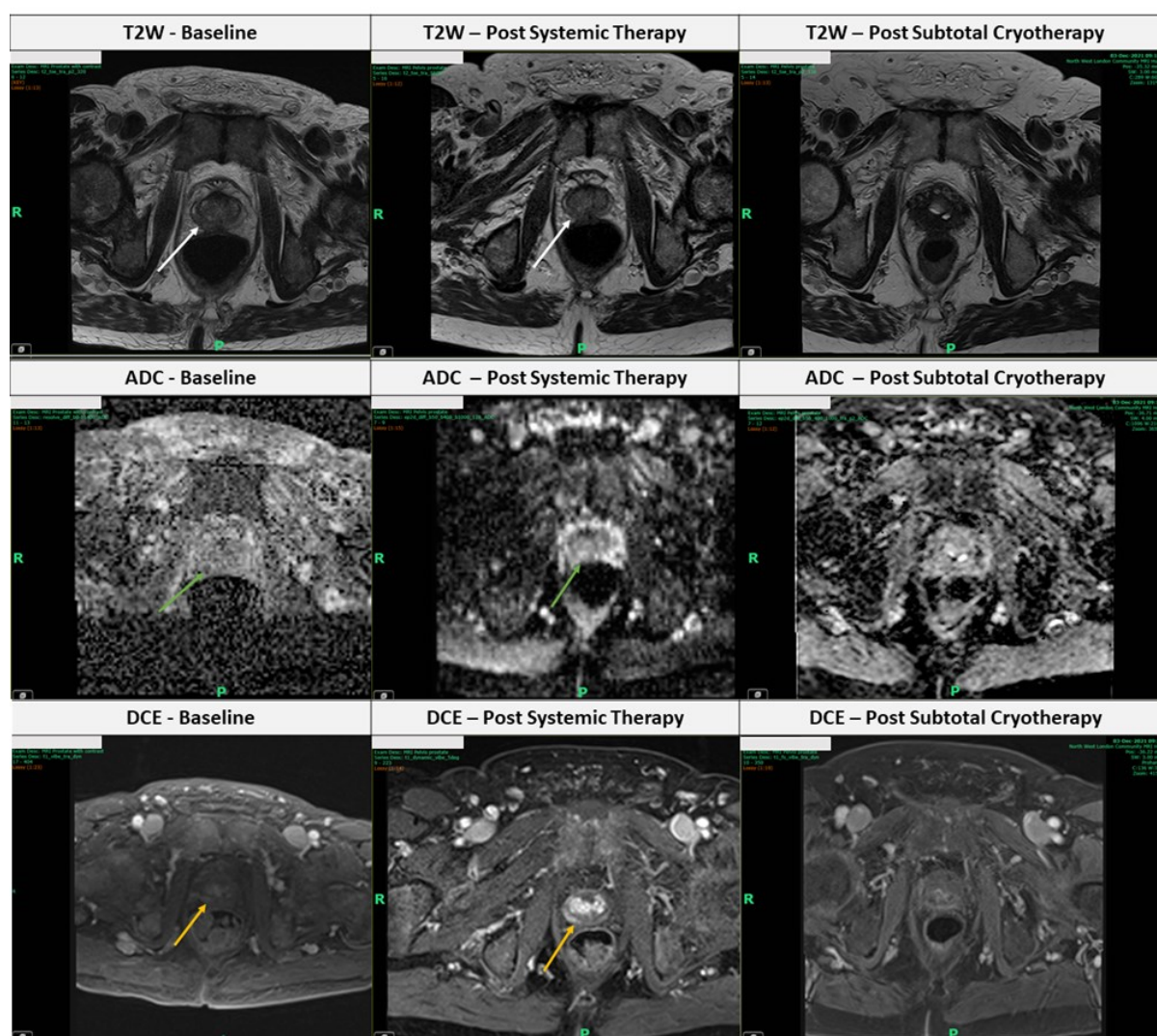
Legend: Cytoreductive whole-gland cryotherapy performed alongside robotic pelvic lymph node dissection. [A] Biplanar TRUS of prostate (axial) demonstrating partial ice ball formation as part of cytoreductive whole gland cryotherapy. Extent of the edge of ice ball is visible as enhancing signal on imaging superiorly and inferiorly, separate to rectal wall. Relative sparing of right peripheral zone of ice ball at time of capture, allowing one to visualise underlying cryoprobes placement in this region. Urethral warmer provide protection for urethral tissue from cryotherapy. [B] Bilateral robotic lymph nodal metastasectomy, as labelled. TRUS – Transrectal Ultrasound Probe.

Figure 27. Cytoreductive Whole Gland HIFU Serial MRI



Legend: 72 year-old male, asymptomatic, presenting Prostate Specific Antigen (PSA) 6.40 ng/ml, Prostate Volume 32.0 cc (43 mm x 46 mm x 31 mm), PSA Density 0.2 ng/ml. 1.5 Tesla mpMRI. Overall baseline MRI: PI-RADS 5; Likert 5; T3b N0 M1b. Histology: Gleason 4+4 = 8, MCCL 12 mm. Metastatic Burden = "Low". IP2-ATLANTA randomisation outcome: Arm 1: Minimally invasive ablative therapy. Commenced on androgen deprivation therapy and Enzalutamide. **(1) Baseline imaging:** [T2W] (White Arrow) majority of the left peripheral zone is replaced by low T2 signal; [ADC] (Green Arrow) area of low signal intensity 26 mm left peripheral zone mid gland; [DCE] (Orange arrow) Large left peripheral zone lesion with early contrast enhancement. **(2) Post Systemic Therapy:** Prostate volume 18 cc (34 mm x 37 mm x 27 mm); [T2W] (White Arrow) Significant reduction in left peripheral zone lesion; [ADC] (Green Arrow) Persistent area of subtle low intensity at the left peripheral zone; [DCE] (Orange arrow) Ongoing mild increase contrast enhancement. Repeat Histology: Adenocarcinoma with treatment effect, MCCL 2 mm. **(3) Post Whole Gland HIFU:** Prostate volume 18 cc (34 mm x 37 mm x 27 mm); [T2/ADC/DCE] at 3 weeks post HIFU changes within the prostate, No evidence of residual or recurrent disease is noted in the ablated region. Residual rim of peripheral enhancement only. ADC – apparent diffusion coefficient, DCE – dynamic contrast enhancement, mpMRI – Multiparametric Magnetic Resonance Imaging, HIFU - High-intensity focused ultrasound, MCCL – Maximum Cancer Core Length.

Figure 28. Cyto-reductive Subtotal Cryotherapy Serial MRI features



Legend: 76 year-old male, asymptomatic, presenting Prostate Specific Antigen (PSA) 1200.0 ng/ml, Prostate Volume 31.0 cc (38 mm x 34 mm x 46 mm), PSA Density 38.7 ng/ml. 1.5 Tesla mpMRI. Overall baseline MRI: PI-RADS 5; Likert 4; T3b N0 M1b. Histology 5+4 = 9, MCCL 1 mm. Metastatic Burden = "Low"; IP2-ATLANTA randomisation outcome= "Arm 1: Minimally invasive ablative therapy". Commenced on androgen deprivation therapy and Enzalutamide. (1) **Baseline imaging:** [T2W] (White Arrow) generalised reduced T2 signal in the right peripheral zone; [ADC] (Green Arrow) area of restricted diffusion at the right peripheral zone mid gland; [DCE] (Orange arrow) Six to ten o'clock position, measuring 19 mm early contrast enhancement. (2) **Post Systemic imaging:** Prostate Volume 31.0 (38 mm x 34 mm x 46 mm) [T2W] (White Arrow) Loss of zonal differentiation, persistent reduced T2 signal in the right peripheral zone; [ADC] (Green Arrow) Persistent area of restricted diffusion at the right peripheral zone mid gland; [DCE] (Orange arrow) Persistent six to ten o'clock position, measuring 19 mm contrast enhancement. Repeat Histology adenocarcinoma with treatment effect, MCCL 5 mm (3) **Post Subtotal Cryotherapy** [T2/ADC/DCE] at 11 months post cryotherapy changes within the prostate, no definite evidence of residual or recurrent disease is noted in the ablated region. ADC – apparent diffusion coefficient, DCE – dynamic contrast enhancement, mpMRI – Multiparametric Magnetic Resonance Imaging.

Figure 29. Serial MRI image and histology of pelvic lymph nodal metastasis



Legend: 56 year-old male, asymptomatic, presenting Prostate Specific Antigen (PSA) 177.0 ng/ml, Prostate Volume 44.0 cc, PSA Density 4.2 ng/ml. 1.5 Tesla mpMRI. Overall baseline MRI: PI-RADS 5; Likert 5 T4 N1 M1a. Histology 4+5 = 9; MCCL 16. Metastatic Burden = "Low". IP2-ATLANTA randomisation outcome: Arm 1: Minimally invasive ablative therapy with planned PLND. Commenced on androgen deprivation therapy and Enzalutamide. (1) Baseline imaging: [T1] (White Arrow) Bilateral pelvic lymph nodes measure up to 2.2 cm short axis in the right obturator region. (2) Post Systemic imaging [T1] (Orange Arrows) significant reduction in size of the bilateral pelvic lymphadenopathy. The largest left pelvic sidewall lymph node has reduced from 14 to 4 mm and the largest right pelvic sidewall lymph node has reduced from 22 to 9 mm. Repeat histology demonstrated adenocarcinoma with treatment effect, MCCL 5 mm. Whole gland cryotherapy to primary with robotic pelvic lymph node metastasis was performed. Total lymph nodes removed = 8, total positive lymph nodes = 4/8 (50%). Example of Lymph nodal metastasis demonstrating adenocarcinoma with treatment effect shown (H&E, original magnification 25x). ADC – apparent diffusion coefficient, DCE – dynamic contrast enhancement, mpMRI – Multiparametric Magnetic Resonance Imaging.

10.4.7 Adverse events

The overall adverse event rate by ITT-analysis and PP-analysis is presented in **Table 40**. The most common adverse events (PP-analysis) were: 8.7% (2/23) urinary retention requiring insertion of indwelling urethral catheter or clean intermittent self-catheterisation (CISC), 8.7% (2/23) genital oedema, and haematuria requiring intervention 4.3% (1/23). There were no serious complications related to pelvic lymph node dissection. There were no cases of recto-urethral fistula.

Table 40. Incidence of symptomatic locoregional adverse events by participant

Variable	Intervention Arm 1: MIAT	Intervention Arm 1: MIAT
Analysis (n)	PP-analysis (n=23)	ITT-analysis (n=27)
Urinary Retention requiring insertion of indwelling urethral catheter or CISC, n (%)	2 (8.7%)	2 (7.4%)
Emergency SPC Insertion, n (%)	0 (0.0%)	0 (0.0%)
TURP, n (%)	0 (0.0%)	0 (0.0%)
Surgery for bowel obstruction, n (%)	0 (0.0%)	0 (0.0%)
Recto-urethral fistula n (%)	0 (0.0%)	0 (0.0%)
Genital oedema, n (%)	2 (8.7%)	2 (7.4%)
Nephrostomy insertion, n (%)	0 (0.0%)	0 (0.0%)
Haematuria requiring intervention, n (%)	1 (4.3%)	1 (3.7%)
Urinary Tract Infection, n (%)	0 (0.0%)	0 (0.0%)
Any (Grade ≥ 1) lower urinary tract symptoms, n (%)	3 (13.0%)	3 (11.1%)

Legend: CTAE – Common Terminology for Adverse Events (Version 5.0). Highest PI-RADS Score used. Grade 1 Urinary Retention able to void with some residual and no requirement for urethral/suprapubic/intermittent catheterisation. TURP – transurethral resection of the prostate; CISC – clean intermittent self-catheterisation; SPC – suprapubic catheter insertion, cRP – Cytoreductive Radical Prostatectomy, EBRT – External beam radiotherapy.

5.4.8 Functional and quality of life changes

Presented in **Table 41**. are the IPPS, IPPS-QoL, EPIC Urinary Domain Summary Score, respectively. These are paired from post-operative (Visit 7) compared to baseline, as per the ITT-analysis.

At baseline median (IQR) IPSS was 13 (9 - 19) suggestive of “moderate symptoms”. At baseline median (IQR) IPSS-QoL was 3 (2 - 5) suggestive of “mixed” feeling towards urinary symptoms. Paired-median (IQR) IPSS and IPPS-QoL improved from baseline by -4 points (-13.0 – 0.0) and -1 (-2.0 – 0.0), respectively. The EPIC urinary domain summary scores,

which is focussed on incontinence and irritative/obstructive subscales, these reported a median (IQR) reduction of -8.33 percentage points (0-100; Higher scores associated with higher related Quality of Life).

Overall satisfaction at baseline median IIEF15 was 4.5 (IQR 2-7). Overall satisfaction paired-IIEF-15 changes were marginal following induction of androgen deprivation therapy and cytoreductive MIAT, with overall median satisfaction change of -0.5 (-2 to 1) compared to baseline. However, all domains of IIEF-15 reduced, in particular erectile function (max score 30) reduced by a median (IQR) of -4.33 (8.19) post-operatively.

Table 41. Functional and quality of life changes in intervention arm 1: MIAT (PP-analysis)

Variable	Post-operative versus Baseline
IPSS, n	17
Mean total, (SD)	-6.41 (9.46)
Median total, (IQR)	-4 (-13 to 0)
Ungradable, n (%)	2 (9.1)
Missing, n (%)	3 (13.6)
IPSS-QoL, n	19
Mean total, (SD)	-1.11 (1.49)
Median total, (IQR)	-1 (-2.0 to 0)
Ungradable, n (%)	0 (0.0)
Missing, n (%)	3 (13.6)
IIEF-15, n	14
Satisfaction Overall Mean total, (SD)	-0.79 (3.09)
Satisfaction Overall Median total, (IQR)	-0.5 (-2 to 1)
Ungradable, n (%)	5 (22.7)
Missing, n (%)	3 (13.6)
Erectile Function, (SD)	-4.33 (8.19)
Orgasmic Function, (SD)	-1.37 (2.95)
Sexual Desire, (SD)	-0.94 (1.83)
Intercourse Satisfaction, (SD)	-1.26 (3.59)
EPIC Urinary Domain Summary	19
Mean total, (SD)	-6.85 (13.69)
Median total, (IQR)	-8.33 (-4.83 to 18.75)
Ungradable, n (%)	0 (0)
Missing, n (%)	3 (13.6)

Legend: Functional and quality of life changes in intervention arm 1: MIAT of all patients in this arm n = 27, using ITT-Analysis. Note "baseline" was considered as Visit 1/SCR (Week 0), "pre-operative" was derived from Visit 3 (Week 26 [+/-12]) and "post-operative PSA" derived from Visit 7 (Week [52+/-4]), respectively. IPSS - International Prostatic Symptoms Score; EPIC - The Expanded Prostate Cancer Index Composite Bowel and Bladder; IIEF-15 - International Index of Erectile Function.

Presented in **Table 42.** are EPIC urinary pad usage changes from baseline, pre-operative and post-operative, using a PP-analysis. No patients reported > 1 pad usage per day post-operatively. Furthermore, using the PP-analysis, the number of patients pad free per day post-operatively was 69.6% (16/23).

Table 42. Urinary pad usage changes in intervention arm 1: MIAT (PP-analysis)

EPIC Urinary Pad Usage (Q5) (n=23)	Baseline	Pre-operative	Post-operative
0 pads per day, n (%)	20 (86.9)	13 (56.5)	16 (69.6)
1 pads per day, n (%)	2 (8.7)	0 (0.0)	2 (8.7)
2 pads per day, n (%)	1 (4.3)	0 (0.0)	0 (0.0)
>= 3 pads per day, n (%)	0 (0.0)	1 (4.3)	0 (0.0)
Missing, n (%)	0 (0.0)	9 (39.1)	5 (21.7)

Legend: Note that EPIC Urinary Pad Usage contains only those patients who underwent trial treatment (n=23). "baseline" was considered as Visit 1/SCR (Week 0), "pre-operative" was derived from Visit 3 (Week 26 [+/-12]) and "post-operative PSA" derived from Visit 7 (Week [52+/-4]), respectively. EPIC - The Expanded Prostate Cancer Index Composite Bowel and Bladder;

10.5 Discussion

This is the first randomised study, to our knowledge, to report on cytoreductive minimally invasive ablative therapy. The main findings are that cytoreductive minimally invasive ablative therapy, with or without simultaneous surgical metastasectomy (in the form of pelvic lymph node dissection), is a feasible and safe alternative approach to treating the primary tumour and local pelvic metastasis in patients with mHSPC who have received pre-operative systemic therapy intensification. Furthermore, the results of this study suggest that, if additive oncological benefit from cytoreductive MIAT approach is proven, this is a viable alternative to cytoreductive external beam radiotherapy or radical prostatectomy in the management of patients with *de novo* synchronous mHSPC.

Cytoreductive MIAT in the form of whole gland cryotherapy has been reported previously in retrospective studies (120,320). The only prospective study of cytoreductive cryotherapy was a small (n=12) single arm pilot focused on exploring the used of simultaneous programmed cell death protein 1 (PD-1) receptor blockade, in the form of Pembroluzimab. In this study 11 of 12 patients had benign or Gleason 3+3=6 reported on post cytoreductive whole gland cryotherapy prostate biopsies, suggestive of adequate local pathological response (123). In Wang and colleagues' propensity score-based study, 54 patients with mHSPC underwent whole gland cryotherapy following ADT. The study was limited to <= cT3 disease but with a comparable baseline metastatic burden distribution and high Gleason Grade (>= Gleason 8; 30/54; 55.6%). Similar to our study, cytoreductive cryotherapy was well tolerated and there

were no reported cases of recto-urethral fistula formation. Scrotal oedema rates were slightly higher at 14.8% (8/54) when compared to our findings of 8.7% (2/23). This could be accounted for by the use of HIFU energy in 26.1% (6/23) of our patients, where oedema is less commonly reported (257,321). Urinary retention rates of 3.7% (2/54) were marginally lower than reported in our study (8.7%; 2/23).

We were unable to find reports of cytoreductive HIFU for patients with *de novo* synchronous mHSPC in the literature. Cytoreductive HIFU was incorporated in our initial cytoreductive MIAT SOP in the expectation of cases of large prostate volume reductions arising, and tumours confined to the peripheral zone where the residual anterior-posterior height was $\leq$ 3cm, post systemic therapy. Such expectations were observed following contemporary systemic therapy in our study, with a mean MRI Pvol reduction of -42.9% (45.6 versus 25.2 cc; $p=0.0002$) between baseline and repeat imaging, and residual gland sizes as small as 8 cc. Thus, cytoreduction with whole gland HIFU was utilised in 4/23 (17.4%) of patients. Overall, cytoreductive HIFU was performed in a minority of our study (6/23) but was well tolerated without any significant adverse events.

Indirect comparisons can be drawn from salvage HIFU setting in radio-recurrent disease, where some patients have been treated with established and occult metachronous metastatic disease (322,323). Reassuringly, complication rates appear greatly reduced in our *de novo* synchronous mHSPC setting than are reported in these prior salvage trials, where CTAE Grade 3 adverse events occurred in up to 5% (323). It could be postulated, that despite similar high grade and high volume intraprostatic disease in mHSPC, the untreated nature of the prostate tissue and surrounding anatomical structures may account for the more favourable complication profile we observed.

We were unable to locate any prior comparable literature, beyond the cadaveric setting, of cytoreductive MIAT with simultaneous surgical metastasectomy in the form of PLND (214). In our randomised study there were no major complications of incorporating the PLND component. Median positive lymph node removal was 14.5 (IQR 8.2 -22.3) nodes, and this was similar to the median lymph node removal rate in the recent TRoMBone randomised study on cRP with PLND (11.0 nodes; IQR 7-14) (221). Median operating time in our study was 226 (IQR 219.5 – 228.8) minutes, which was marginally longer than median operating time for cRP + PLND performed in TRoMBone (185 minutes; IQR 165 – 217).

There was some discordance between planned PLND (10/23; 43.5%) and performed PLND (6/23; 26.1%). In these patients PLND was not performed ($n=4$) due to clinical fitness and

suspicion of surgically irresectable disease. However, local cytoreductive MIAT was performed in all patients who consented to the trial treatment. Whilst a degree of discordance was expected, and may decrease with increasing experience of this procedure, this highlights the introduction of PLND in to the cytoreductive MIAT pathway results in the application of surgical fitness criteria to a heterogeneous nature of pool of patients with mHSPC. This may limit treatment delivery. Nevertheless, we are cognisant that such limitations also exist in performing PLND alongside cRP, and indeed arise in the delivery of pelvic lymph nodal radiotherapy in some circumstances (e.g., inflammatory bowel disease). The main study of IP2-ATLANTA will be able to explore the additive benefit of PLND to cytoreductive MIAT alone.

In almost 70% (16/23) of our cytoreductive MIAT patients reported no post-operative urinary pad usage per day, this compared to an unpaired 86.9% (20/23) patients at baseline. In 8.7% of patients (2/23) one post-operative urinary pad per day was reported, this was unchanged on the baseline incontinence reported at 8.7% (1 pad per day; 2/23). No patients reported more than 1 urinary pad per day following cytoreductive MIAT. This compares a 56% of patients who were pad free following cRP or cytoreductive radiotherapy in the pilot RCT (**Chapter 7**). This also compares favourably to cRP studies where median pad usage per day is reported to be 2 (1.0 – 2.0) (221). Our results also compared favourably to prospective studies on primary localised prostate cancer managed with whole-gland HIFU and cryotherapy. Whole-gland HIFU and cryotherapy have been reported to have a urinary pad free post operative rates of 56% (105/189) and 94.6% (6/108), respectively (324,325) .

In addition, moderate improvements in paired-IPSS in this study were reported post-operatively at visit 7 (Week 52+/-4) when compared to baseline (Week 0; mean IPSS -6.41 [SD 9.46]). Comparative data is limited, a prior retrospective study of 110 predominantly metastatic (81%) patients who were administered ADT alone reported a mean IPSS change of -7.27 (SD 0.72) in the first year, falling to -5.23 (SD 0.58) in those with more than one year follow-up (326). However, the low participant return rate in the first year of this study ($n=21$) is a likely source of significant selection bias. Longer term follow-up of our RCT patients, beyond visit 7 of the study, will ascertain if cytoreductive MIAT may lead to a more sustained improvement IPSS that has not been achievable by systemic therapy alone.

The use of serial mpMRI at baseline and post operatively is unique in the local treatment of mHSPC. This research imaging was mandated in our study and enabled us to include T4 disease at baseline, with an opportunity for repeat classification post systemic therapy and pre-operatively. Such an approach is a significant divergence from prior retrospective studies

that have all used restricted eligibility criteria for cytoreductive MIAT (e.g., $\leq$ T3a). We were able to report -30.0% decrease (43.5% versus 30.4%) in MRI T4 disease compared to baseline. Despite the persistence of MRI T4 disease in seven (30.4%) patients we were able to safely perform cytoreductive MIAT all patients using our pre-planned treatment SOP which favoured safety over maximal tissue ablation. The findings of this study suggest that patients with MRI T4 disease at baseline can be routinely considered for cytoreductive MIAT using such a treatment SOP. mpMRI also allows us to determine the ablation pattern, the presence of diffuse lesions at baseline in 43.5% (10/23) increasing to 60.9% (14/23) was evidence to support the predominantly whole-gland or subtotal pattern used in 95.7% (22/23) of patients.

Post operative mpMR-imaging following cytoreductive MIAT was performed in a minority of patients in a non-protocolled manner, for exploratory purposes in this study. In the post-operative monitoring of HIFU and cryotherapy following treatments of primary localised prostate cancer the reported negative predictive value (NPV) for clinically significant disease within the zone of ablation of mpMRI is high at 82% to 97% (327-329). We could assume that similar NPV exists in the mHSPC primary tumour setting, although this would require a further repeat biopsy, which is challenging to mandate in patients with mHSPC. Our initial series of post-operative imaging has shown clear ablation zones without recurrence in up to 11 months post cytoreductive MIAT.

Overall, we were able to perform “day-case” cytoreductive MIAT without PLND in 30.4% of patients with median overall length of stay reported as 1.0 days (IQR 0.5 – 1.0). This compares to a median (IQR) post operative length of stay of 1.0 day (IQR 1.0 – 1.5) for patients who underwent cRP in the pilot RCT (**Chapter 7**). This also similar to the median length of stay of 1.0 (IQR 1.0 – 2.0) days in TRoMBone for cRP + PLND. Practically both surgical approaches are shorter than established radiotherapy schedules in this setting that typically exceed 27 days. Should cytoreductive MIAT be proven to derive at least equivalent additive oncological benefit as cytoreductive radiotherapy, a formal economic analysis will be performed.

10.6 Limitations

Although we report on a prospective randomised pilot study this was not powered to report on oncological outcomes. We protocolled a repeat mpMRI and prostate biopsy in patients in this study, but post operative mpMRI was as per treating clinician and for illustrative purposes, a standardised post operative radiological assessment of the primary tumour was not mandated and does not form part of accepted PFS composite definitions in mHSPC. Repeat prostate biopsy was protocolled following systemic therapy but was not protocolled following treatment, we are thus unable to report upon concordance between MRI and pathological intraprostatic response to prostate to cytoreductive MIAT. Although, cytoreductive cryotherapy ablation has been reported as adequate in generating complete pathological response previously by Ross *et al.* (123). Although adverse event follow-up was a median 21 months, the small sample size ($n=23$) may impact upon the adverse event rate reported in this study. A large number of these limitations will be overcome by the main study of IP2-ATLANTA, which is currently in its final phase of accrual.

10.7 Conclusion

Cytoreductive minimally invasive ablative therapy, with or without simultaneous surgical metastasectomy (in the form of pelvic lymph node dissection), is a feasible and safe approach to treating the primary tumour and local pelvic metastasis in patients with mHSPC who have received pre-operative systemic therapy intensification. If additive oncological benefit from cytoreductive MIAT approach is proven, this is a viable alternative to the currently available cytoreductive external beam local prostate radiotherapy in the management of patients with *de novo* synchronous mHSPC.

11.0 Patient-reported outcome measures from the internal pilot randomised controlled trial (IP2-ATLANTA)

11.1 Overview

This chapter will report on patient-reported outcome measures (PROMS) collected during the internal pilot of IP2-ATLANTA, a phase II multicentre randomised controlled trial exploring additional treatments to the local tumour in patients with *de novo* synchronous metastatic hormone-sensitive prostate cancer (mHSPC). This completes the reporting of the primary outcome (Pilot Study: Primary Outcome C) on safety that includes adverse events and patient-reported outcome measures. The design of IP2-ATLANTA has been extensively described in the preceding **Chapter 6** and the results of a limited number of PROMS were included in **Chapter 7** in the reporting of the internal pilot RCT patients. In this section we report on the PROMS collected every 6-months in the first year.

The following PROMS available for review at the time of writing this thesis were: The International Prostatic Symptoms Score (IPSS); The Expanded Prostate Cancer Index Composite Bowel and Bladder (EPIC) and International Index of Erectile Function-15 (IIEF-15). The EuroQol (EQ-5D-5L) was used in the study as a generic measure of health-related quality-of-life (HRQOL).

11.2 Introduction

The internal pilot RCT of IP2-ATLANTA reported on the performance of a number of novel local cytoreductive and metastasis-directed treatments in the management of patients with *de novo* synchronous metastatic hormone-sensitive prostate cancer (**Chapter 7**). As we have described previously, in this thesis, the introduction of radical treatment options into a metastatic disease state is a careful balance of oncological benefit and potential impact of treatment related toxicity (**Chapter 3**) (165).

When assessing whether the patient-reported outcome measures (PROMS), and overall health-related quality of life (HRQOL), are compromised by the addition of such novel cytoreductive treatments is of increasing importance that is considered a key assessment parameter by regulatory decision makers who approve integration into standard of care, such as the National Institute for Health and Care Excellence (NICE) (330-332).

Furthermore, the broad set of patient-reported outcome measures presented in this chapter allow us to complete the reporting of the safety primary outcome (Pilot Study: Primary Outcome C; **Chapter 6**). Here-in we present the internal pilot RCT results of patient-reported

outcome measures of trial participants in all arms of IP2-ATLANTA, restricted to outcomes arising between Visit 1 (Week 0) and Visit 7 (Week 52).

11.3 Methods

11.3.1 IP2-ATLANTA pilot RCT overview

The study design, recruitment strategy, randomisation methodology and trial interventions of IP2-ATLANTA has been extensively described in the preceding **Chapter 6** and thus have not been duplicated here for brevity.

The internal pilot RCT primary outcome included “ii) safety”, of which adverse event and patient-reported outcome measures were reported. A condensed version of these PROMS were reported in **Chapter 7**.

As described in the **Chapter 7**, the results from PROMS presented in this Chapter are from those participants that consented before the cut-off date of 6th February 2021, as part of the pilot population. All participants underwent follow-up for at least 12 months to enable visit 7 (Week 52+/-4) to be completed. Further details on the design, ethical approvals, and results of IP2-ATLANTA are detail in **Chapter 6** and **Chapter 7** of this thesis.

11.3.2 Patient-reported outcome measures

A details in **Chapter 6**, PROMS in this study were collected every 6-months in the first year and annually thereafter, until mortality or 4 years after initial randomisation (whichever was first).

The following PROMS completed by IP2-ATLANTA pilot RCT patients are included for analysis:

- International Prostatic Symptoms Score (IPSS)
- The Expanded Prostate Cancer Index Composite Bowel and Bladder (EPIC)
- International Index of Erectile Function 15 (IIEF-15)
- EuroQol (EQ-5D-5L)

The IPSS is based on the answers to seven questions concerning urinary symptoms and one question concerning quality of life. The responses to the questions concerning urinary symptoms range from 0 to 5, indicating increasing severity of the particular symptom. Thus, the overall score can range from 0 (asymptomatic) to 35 (very symptomatic). IPSS Quality of life (IPSS QoL), ranges from 0 “delighted”, 3 “mixed equally satisfied/dissatisfied”, to 6 “terrible”.

IIEF-15 questionnaire is a validated, multi-dimensional, self-administered investigation that is useful in the clinical assessment of erectile dysfunction and treatment outcomes in clinical trials (248,249). A score of 0 to 5 is awarded to each of the 15 questions that examine the 4 main domains of male sexual function: erectile function, orgasmic function, sexual desire, and intercourse satisfaction.

The Expanded Prostate Cancer Index Composite is a comprehensive instrument designed to evaluate patient function and bother after prostate cancer treatment (251). EPIC assesses the disease-specific aspects of prostate cancer and its therapies. This comprises of four summary domains (Urinary, Bowel, Sexual and Hormonal). We will report on EPIC Urinary and Bowel in this chapter. Response options for each EPIC item form a Likert scale, and multi-item scale scores are transformed to a 0 to 100 scale. Higher scores represent higher Health-Related Quality of Life (HRQoL).

The EPIC-Urinary domain summary score is split into two distinct incontinence and irritative/obstructive subscales. The EPIC-Bowel has a domain summary score. In addition, both, EPIC-Urinary and EPIC-Bowel, domain scores have measurable “Function” and “Bother” subscale components.

The EQ-5D-5L comprises of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression (252). EQ-5D-5L health scale is a visual-analogue scale range from 0 to 100. Higher scores indicate better health. Score on the EQ-5D-5L health index range from 0 to 1, with higher scores indicating better health.

11.3.3 Statistical analysis

In able to facilitate the results and discussion, the PROMS have been grouped as either i) genito-urinary ii) bowel/gastrointestinal iii) sexual function or iv) health-related quality of life. These are presented in unpaired form by trial arm and by visit. Visit 1 (baseline), visit 3 (post-systemic therapy) and Visit 7 (post-intervention). A paired analysis of patients who completed both Visit 7 (post-intervention) and Visit 1 (baseline) is provided.

All PROMS are analysed using all randomised patients according to the intention-to-treat (ITT-) principle. All analysis were performed using STATA (StataCorp LLC, College Station, T, v.17.0) or SPSS (IBM Corp., IBM SPSS Statistics for Windows, Armonk, USA, v.28.0), some tables and graphs were recreated in Excel (Microsoft, v.2019). The EQ-5D-5L health index was calculated with the value set for England using the computing EQ-5D-5L index values with STATA using the English (ENG) Devlin value set version 1.1 (updated 01/12/2020).

The study statistician, senior statistician and I performed the initial analysis. The final analysis was reviewed by an independent third statistician and the report signed off by the trial's Chief Investigator and my primary supervisor (H.U. Ahmed).

11.4 Results

11.4.1 Overview of pilot RCT results

The internal pilot study RCT results have been reported extensively in **Chapter 7**, and are thus are not replicated in this chapter for brevity. Overall, 121 patients were assessed for eligibility from eleven active trial sites in England and Wales (April/2019 to Feb/2021) (**Figure 14**). Of these 81 patients were randomly allocated to Control Arm: SOC (34.6%; 28/81), Intervention Arm 1: MIAT (33.3%; 27/81) and Intervention Arm 2: Radical (32.1%; 26/81). All participants' follow-up reached Visit 7 (Week 52 +/-4) on study, with median follow-up of 25 (IQR 20-30) months.

Groups were well balanced with respect to trial participants baseline characteristics (**Table 17**). Overall, mean and median age were 68.23 (SD 7.64) and 69.0 (IQR 62.00 – 74.00) years, respectively. Performance Status (PS) was restricted to 0-1 in this study and overall PS 0 was reported in 91.4% (74/81) and PS 1 in 7.4% (6/81), respectively. PS 1 was highest in Intervention Arm 1: MIAT (11.1%; 3/27). PS 1 was reported in the Control Arm: SOC in 7.1% (2/28) and in the Intervention Arm 2: Radical in 3.8% (1/28), respectively.

11.4.2 Genito-urinary PROMS

The genito-urinary function results are presented in **Table 43**. This encompasses the following PROMS: IPSS and EPIC Urinary Function. The IPPS changes have been discussed in detail in **Chapter 7**, and are thus not replicated here.

In all treatment arms mean EPIC-Urinary Domain summary score improved following Visit 3 and the induction of systemic therapy (**Table 43**). The EPIC-Domain Summary score and urinary-pad usage change have also been discussed in detail in **Chapter 7**, and is thus not replicated here. However, we were able to present the EPIC-Urinary Domain subscales (**Figure 30**). There was reduction in both EPIC-Urinary: "Function" and "Incontinence" subscales across both interventions arms when Visit 7 was compared to Visit 1, these were highest in Intervention Arm 2: Radical. Conversely, large improvements in EPIC-Urinary: "Bother" and "Irritative/Obstructive" symptoms were reported in the intervention arms, that were not observed in the control arm. These were highest in Intervention Arm 2: MIAT where "Bother" and "Irritative/Obstructive" symptoms improved by +12.31 (SD 18.79) and +10.56 (SD 15.66), respectively.

11.4.3 Gastrointestinal PROMS

In all treatment arms mean EPIC-Bowel Domain summary score reduced following Visit 3 and the induction of systemic therapy (**Table 43**). When Visit 7 was compared to baseline (Visit 1), the maximum improvements in mean EPIC-Bowel Domain summary scores were reported in participants in Intervention Arm 1: MIAT +3.3 (SD 10.38). When Visit 7 was compared to baseline, the mean EPIC-Bowel Domain summary score reduced on Intervention Arm 2: Radical -4.06 (SD 11.13) (**Figure 31**).

11.4.4 Sexual function PROMS

The sexual function results are presented in **Table 43**. This encompasses the following only results from the IIEF-15 questionnaire.

In all IIEF-15 questionnaire functional domains (“Erectile Function”, “Orgasmic Function”, “Sexual Desire”, “Intercourse Satisfaction”, “Overall Satisfaction”) there was reported large reductions, in all trial arms at Visit 7 when compared to Visit 1 (baseline). In particular there was almost no preservation of IIEF-15 “Orgasmic Function” (max score 10; control mean 9.8). The mean scores at Visit 7 were 0.14 (SD 0.36) in Intervention Arm 2: Radical; 0.47 (SD 0.9) in Intervention Arm 1: MIAT; and 0.68 (SD 1.45) in the Control Arm, respectively.

11.4.5 Health-related quality of life PROMS

The results for health-related quality of life are presented in detail in **Table 44**. This encompasses the following PROMS: IPSS (QoL), EQ-5D-5L VAS score and EQ-5D index value, respectively.

In all treatment arms mean IPSS-QoL scores improved at Visit 7, when compared to baseline. When Visit 7 was compared to baseline, “clinically meaningful change” in mean combined IPSS QoL scores was observed in participants in Intervention Arm 1: MIAT of -1.11 (SD 1.49). At Visit 7 the average trial participant was “mostly satisfied” with current urinary symptoms (mean 2.0 [SD 1.56]), when compared to baseline where in “mixed” feeling were reported (mean 3.12 [SD 1.56]).

In all treatment arms there was a reduction in EQ-5D-5L VAS HRQoL scores, when Visit 7 was compared to Visit 1 (baseline). The reported highest reductions were seen in Intervention Arm: Radical where a -10.17 (SD 21.24) was reported. Changes in mean EQ-5D index value ≥ 0.1 were not reported in any trial arms. There was a minor improvement in the EQ-5D index value reported in Intervention Arm 1: MIAT at +0.06 (SD 0.19), this is unlikely to be clinically meaningful.

Table 43. IPPS and EPIC Domains by trial arm, by visit

PROMS Domain		Visit Schedule			
		Visit 1: Baseline	Visit 3: Post Systemic Therapy	Visit 7: Post-Trial Intervention	Visit 7 vs Visit 1
Control Arm: SOC (n=28)					
IPPS	<i>IPSS Combined Score</i>				
	Mean (SD)	12.39 (7.81)	11.9 (5.92)	11.68 (7.52)	-1.58 (6.87)
	Missing (n, (%))	0 (0.0%)	6 (22.2%)	7 (26.9%)	7 (29.6%)
EPIC-Urinary	<i>Summary Score</i>				
	Mean (SD)	79.17 (14.98)	82.52 (9.88)	79.36 (18.01)	+1.47 (21.74)
	<i>Function</i>				
	Mean (SD)	89.19 (15.84)	92.87 (7.26)	88.53 (15.95)	+0.26 (21.69)
	<i>Bother</i>				
	Mean (SD)	71.96 (17.17)	75.45 (14.22)	72.86 (20.58)	+2.47 (25.08)
	<i>Incontinence</i>				
	Mean (SD)	88.76 (15.23)	89.75 (13.41)	86.88 (15.96)	+0.47 (14.88)
	<i>Irritative/Obstructive</i>				
	Mean (SD)	77.04 (16.99)	82.14 (12.58)	76.61 (22.36)	+1.25 (25.55)
	<i>EPIC Pad Usage Score</i>				
	None (n, (%))	26 (92.9%)	17 (65.4%)	19 (73.1%)	-
	1 per day (n, (%))	1 (3.6%)	0 (0.0%)	0 (0.0%)	-
	2 per day (n, (%))	0 (0.0%)	0 (0.0%)	1 (3.8%)	-
	>= 3 per day (n, (%))	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
	Increase (% , (n))	-	-	-	+3.8% (1)
	No change (% , (n))	-	-	-	65.4% (17)
	Decrease (% , (n))	-	-	-	-3.8% (1)
	Missing (n, (%))	1 (3.6%)	9 (34.6%)	6 (23.1%)	7 (26.9%)
EPIC-Bowel	<i>Summary Score</i>				
	Mean (SD)	90.2 (10.91)	88.76 (12.58)	90.88 (8.91)	-1.44 (10.8)
	<i>Function</i>				
	Mean (SD)	92.22 (8.96)	89.23 (12.06)	89.55 (12.83)	-2.23 (14.48)
	<i>Bother</i>				
	Mean (SD)	88.32 (19.84)	88.24 (15.1)	90.79 (11.62)	-3.11 (13.69)
IIEF-15	<i>Erectile Function</i>				
	Mean (SD)	5.96 (8.93)	3.67 (7.09)	2.35 (4.15)	-4.54 (9.75)
	<i>Orgasmic Function</i>				
	Mean (SD)	1.78 (3.4)	0.84 (1.92)	0.68 (1.45)	-1.22 (3)
	<i>Sexual Desire</i>				
	Mean (SD)	3.37 (1.69)	2.8 (1.32)	2.79 (1.4)	-0.94 (1.51)
	<i>Intercourse Satisfaction</i>				
	Mean (SD)	1.41 (3.48)	0.74 (2.23)	0.47 (1.84)	-1.28 (3.63)

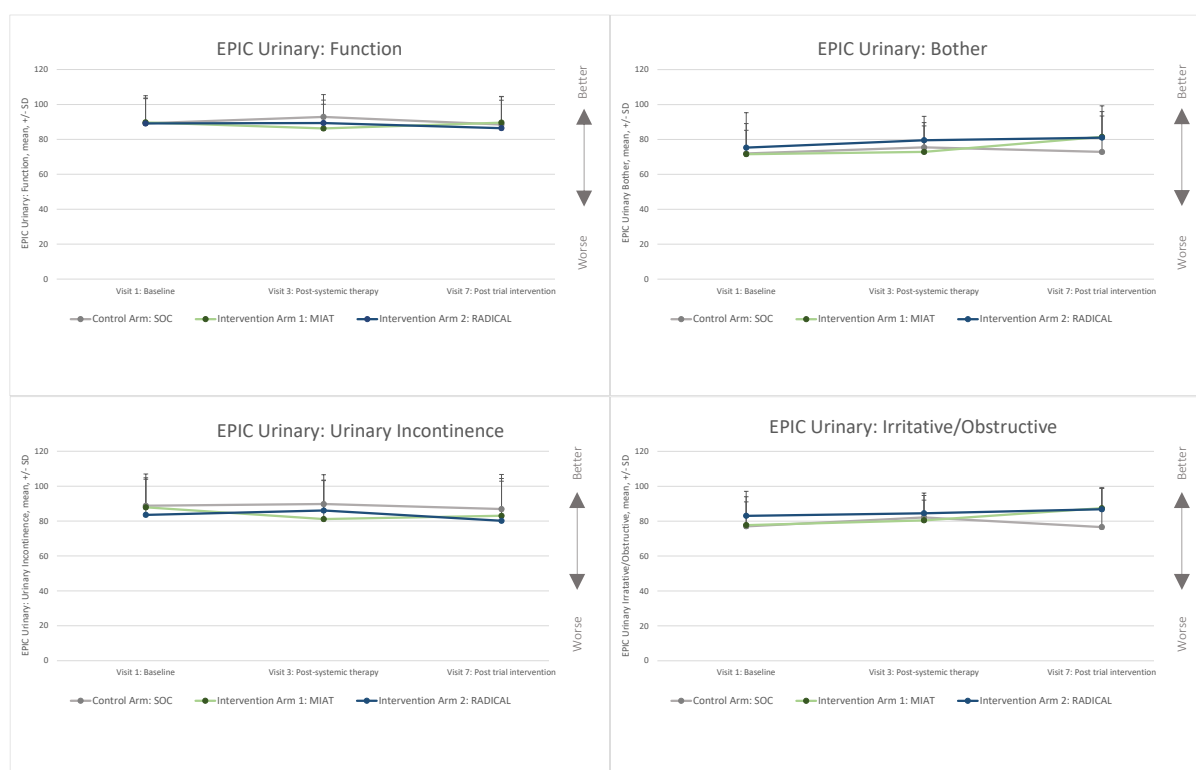
	<i>Overall Satisfaction Score</i> Mean (SD)	3.96 (2.27)	3.67 (1.61)	3.2 (2.14)	-1.43 (2.24)
Intervention Arm 1: MIAT (n=27)					
IPSS	<i>IPSS Combined Score</i>				
	Mean (SD)	13.76 (7)	9.44 (6.24)	8.28 (5.44)	-6.41 (9.46)
	Ungradable (n, (%))	1 (3.8%)	1 (5.3%)	1 (4.5%)	2 (9.1%)
	Missing (n, (%))	0 (0.0%)	2 (10.5%)	3 (13.6%)	3 (13.6%)
EPIC-Urinary	<i>Summary Score</i>				
	Mean (SD)	79.13 (12.01)	78.44 (14.17)	84.9 (16.06)	+6.85 (13.69)
	<i>Function</i>				
	Mean (SD)	89.71 (13.62)	86.25 (19.42)	89.59 (14.98)	-0.88 (9.5)
	<i>Bother</i>				
	Mean (SD)	71.57 (13.68)	72.86 (14.9)	81.48 (17.81)	+12.31 (18.79)
	<i>Incontinence</i>				
	Mean (SD)	87.86 (19.08)	81.15 (25.43)	83.04 (23.62)	-4.72 (10.15)
	<i>Irritative/Obstructive</i>				
	Mean (SD)	77.75 (13.3)	80.48 (11.6)	87.44 (11.35)	+10.56 (15.66)
	<i>EPIC Pad Usage Score</i>				
	Ungradable (n, (%))	23 (88.5%)	13 (68.4%)	16 (72.7%)	-
	Missing (n, (%))	2 (7.7%)	1 (5.3%)	3 (13.6%)	-
	2 per day (n, (%))	1 (3.8%)	0 (0.0%)	0 (0.0%)	
	>= 3 per day (n, (%))	0 (0.0%)	1 (5.3%)	0 (0.0%)	
	Increase (% (n))	-	-	-	+9.1% (2)
	No change (% (n))	-	-	-	72.7% (16)
	Decrease (% (n))	-	-	-	-4.5% (1)
	Missing (n, (%))	0 (0.0%)	4 (21.1%)	3 (13.6%)	3 (13.6%)
EPIC-Bowel	<i>Summary Score</i>				
	Mean (SD)	88.06 (14.44)	87.81 (9.27)	92.56 (8.05)	+3.3 (10.38)
	<i>Function</i>				
	Mean (SD)	89.54 (10.9)	88.03(12.37)	92.83 (7.51)	+2.07 (7.42)
	<i>Bother</i>				
	Mean (SD)	88.54 (16.55)	87.61(11.72)	92.29 (9.09)	+4.56 (14.89)
IIEF-15	<i>Erectile Function</i>				
	Mean (SD)	5.43 (7.53)	1.31 (0.6)	1.28 (0.57)	-4.33 (8.19)
	<i>Orgasmic Function</i>				
	Mean (SD)	1.65 (3.15)	0.63 (1.54)	0.47 (0.9)	-1.37 (2.95)
	<i>Sexual Desire</i>				
	Mean (SD)	3.48 (1.85)	2.81 (1.76)	2.63 (1.21)	-0.94 (1.83)
	<i>Intercourse Satisfaction</i>				
	Mean (SD)	1.15 (3.17)	0.06 (0.24)	0.32 (1.0)	-1.26 (3.59)
	<i>Overall Satisfaction Score</i>				
	Mean (SD)	5.05 (2.84)	3.86 (2.38)	5.13 (3.34)	-0.79 (3.09)

Intervention Arm 2: Radical (n=26)					
IPSS	<i>IPSS Combined Score</i>				
	Mean (SD)	12.82 (9.98)	11.72 (6.49)	10 (5.02)	-2.33 (8.34)
	Ungradable (n, (%))	3 (11.5%)	1 (4.2%)	2 (10.5%)	4 (21.1%)
	Missing (n, (%))	1 (3.8%)	5 (20.8%)	6 (31.6%)	6 (31.6%)
EPIC-Urinary	<i>Summary Score</i>				
	Mean (SD)	80.41 (16.46)	83.65 (12.08)	83.29 (13.96)	-1.53 (15.22)
	<i>Function</i>				
	Mean (SD)	89.11 (14.54)	89.38 (13.11)	86.43 (15.99)	-5.68 (14.93)
	<i>Bother</i>				
	Mean (SD)	75.31 (20.03)	79.56 (13.69)	81.04 (14.9)	+1.43 (17.35)
	<i>Incontinence</i>				
	Mean (SD)	83.55 (21.25)	86.03 (17.47)	80.15 (24.22)	-10.85 (30.56)
	<i>Irritative/Obstructive</i>				
	Mean (SD)	83.07 (14.05)	84.52 (11.62)	86.81 (12.32)	+3.21 (9.59)
	<i>EPIC Pad Usage Score</i>				
	None (n, (%))	20 (76.9%)	17 (70.8%)	10 (52.6%)	-
	1 per day (n, (%))	0 (0.0%)	0 (0.0%)	1 (5.3%)	-
	2 per day (n, (%))	2 (7.7%)	1 (4.2%)	1 (5.3%)	-
	>= 3 per day (n, (%))	0 (0.0%)	0 (0.0%)	1 (5.3%)	-
	Increase (% , (n))	-	-	-	+10.5% (2)
	No change (% , (n))	-	-	-	42.1% (8)
	Decrease (% , (n))	-	-	-	-0.0% (0)
	Missing (n, (%))	4 (15.4%)	6 (25.0%)	6 (31.6%)	9 (47.7%)
EPIC-Bowel	<i>Summary Score</i>				
	Mean (SD)	90.14 (14.31)	88.57(16.7)	88.92 (11.57)	-4.06 (11.13)
	<i>Function</i>				
	Mean (SD)	90.62 (12)	88.04(16.23)	90.8 (8.5)	-1.3 (10.01)
IIEF-15	<i>Bother</i>				
	Mean (SD)	89.73 (17.54)	89.11(19.13)	87.76 (15.52)	-6.55 (14.91)
	<i>Erectile Function</i>				
	Mean (SD)	4.91 (8.18)	2.8 (3.98)	1.08 (0.28)	-1.18 (3.03)
IIEF-15	<i>Orgasmic Function</i>				
	Mean (SD)	1.39 (2.92)	0.8 (1.91)	0.14 (0.36)	-0.17 (1.27)
	<i>Sexual Desire</i>				
	Mean (SD)	3.48 (2.02)	3.2 (2.12)	2.36 (0.93)	-0.23 (1.48)
	<i>Intercourse Satisfaction</i>				
	Mean (SD)	1.52 (3.72)	0.75 (2.57)	0 (0.0)	-0.46 (1.66)
IIEF-15	<i>Overall Satisfaction Score</i>				
	Mean (SD)	4.65 (2.57)	3.65 (2.64)	4.15 (2.61)	-1.0 (2.32)

Legend: Individual visit data as per ITT-analysis, without pairing. Paired-PROMs presented for comparison of Visit 7 versus Visit 1. The Expanded Prostate Cancer Index Composite Bowel and Bladder (EPIC) urinary domain summary score comprises several urinary items. These are formed by linear transformation of raw scores, ranging from "0" to "100" i.e. "worse" to "better". IIEF-15 - International Index of Erectile Function 15-question, overall satisfaction domain (Q13,Q14): maximum score 10. Previously reported studies define sexual dysfunction

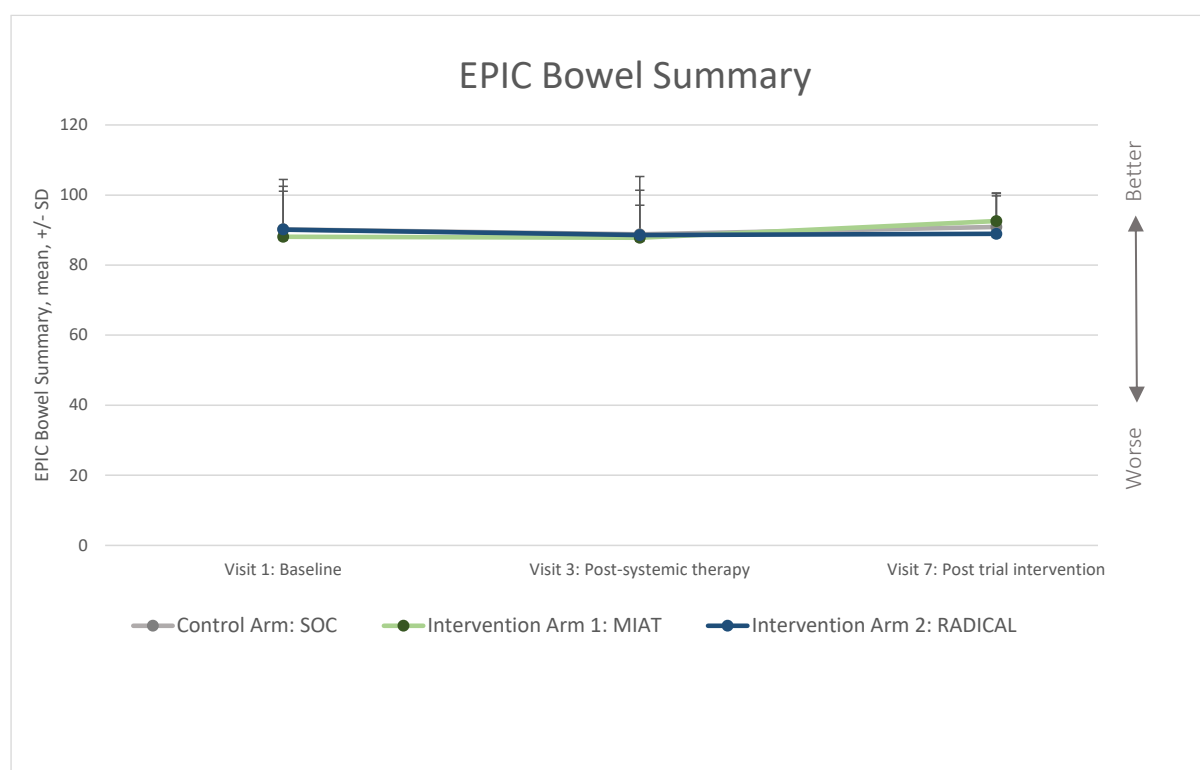
mean score 4.4; control mean score 8.6 (250). The International prostate symptom score (IPPS) combined score: 0-7 “mildly symptomatic”; 8-19 “moderately symptomatic”; 20-35 “severely symptomatic”. All presented mean (SD) scores are unpaired and as per ITT-analysis. PROMs – Patient-reported outcome measures, SD – Standard Deviation, VAS – Visual Analogue Score.

Figure 30. EPIC Urinary sub-domains during longitudinal follow-up on study (Visit 1 to Visit 7), by trial arm



Legend: The Expanded Prostate Cancer Index Composite Bowel and Bladder (EPIC) urinary domain, the four “sub-domains”, on longitudinal follow-up. These are formed by linear transformation of raw scores, ranging from “0” to “100” i.e. “worse” to “better”. Mean scores +/- SD shown by error bars, at each visit data as per ITT-analysis, without pairing. PROMs – Patient-reported outcome measures. SD – Standard Deviation

Figure 31. EPIC Bowel summary scores during longitudinal follow-up on study (Visit 1 to Visit 7), by trial arm



Legend: The Expanded Prostate Cancer Index Composite Bowel and Bladder (EPIC) Bowel domain. Summary Score, on longitudinal follow-up. These are formed by linear transformation of raw scores, ranging from “0” to “100” i.e. “worse” to “better”. Mean scores +/- SD shown by error bars, at each visit data as per ITT-analysis, without pairing. PROMs – Patient-reported outcome measures. SD – Standard Deviation

Table 44. Health-related quality of life of PROMS by trial arm, by visit

PROMS Domain	Visit Schedule			
	Visit 1: Baseline	Visit 3: Post Systemic Therapy	Visit : 7 Post-Trial Intervention	Visit 7 vs Visit 1
Control Arm: SOC (n=28)				
IPSS-Quality of Life Score				
Mean (SD)	3 (1.54)	2.6 (1.14)	2.53 (1.5)	-0.42 (2.04)
Ungradable (n, (%))	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)
Missing (n, (%))	0 (0.0%)	6 (22.2%)	7 (26.9%)	N/A
EQ-5D-5L VAS score				
Mean (SD)	76.86 (17.7)	73.57 (11.53)	73.82 (16.44)	+0.47 (20.06)
Ungradable (n, (%))	0 (0.0%)	0 (0.0%)	3 (14.3%)	3 (14.3%)
Missing (n, (%))	0 (0.0%)	0 (0.0%)	1 (4.8%)	1 (4.8%)
EQ-5D index value				
Mean (SD)	0.89 (0.1)	0.83 (0.16)	0.81 (0.15)	-0.07 (0.09)
Missing (n, (%))	0 (0.0%)	0 (0.0%)	1 (4.8%)	1 (4.8%)
Intervention Arm 1: MIAT (n=27)				
IPSS-Quality of Life Score				
Mean (SD)	3.12 (1.56)	2.59 (1.66)	2 (1.56)	-1.11 (1.49)
Missing (n, (%))	0 (0.0%)	2 (10.5%)	3 (13.6%)	3 (13.6%)
EQ-5D-5L VAS score				
Mean (SD)	69.38 (20.03)	66.12 (18.81)	72.58 (13.89)	+5.26 (21.96)
Missing (n, (%))	0 (0.0%)	0 (0.0%)	1 (5.0%)	1 (5.0%)
EQ-5D index value				
Mean (SD)	0.76 (0.28)	0.78 (0.21)	0.8 (0.21)	+0.06 (0.19)
Missing (n, (%))	0 (0.0%)	0 (0.0%)	1 (5%)	1 (5%)
Intervention Arm 2: Radical (n=26)				
IPSS-Quality of Life Score				
Mean (SD)	3.24 (1.98)	3.06 (1.51)	2.54 (1.2)	-0.33 (1.87)
Ungradable (n, (%))	0 (0.0%)	1 (4.2%)	0 (0.0%)	1 (5.3%)
Missing (n, (%))	1 (3.8%)	5 (20.8%)	6 (31.6%)	6 (31.6%)
EQ-5D-5L VAS score				
Mean (SD)	76.68 (18.57)	73.68 (18.77)	71.77 (20)	-10.17 (21.24)
Ungradable (n, (%))	0 (0.0%)	1 (4.8%)	1 (6.7%)	1 (6.7%)
Missing (n, (%))	1 (3.8%)	1 (4.8%)	1 (6.7%)	2 (13.3%)
EQ-5D index value				
Mean (SD)	0.87 (0.15)	0.84 (0.13)	0.87 (0.11)	-0.07 (0.09)
Missing (n, (%))	1 (3.8%)	1 (4.8%)	1 (6.7%)	2 (13.3%)

Legend: Individual visit data as per ITT-analysis, without pairing. Paired-PROMs presented for comparison of Visit 7 versus Visit 1. EuroQol (EQ-5D-5L) VAS score and EQ-5D index value. IPSS Quality of life (IPSS QoL), range 0 “delighted”; 3 “mixed equally satisfied/dissatisfied”; 6 “terrible”. All presented mean (SD) scores are unpaired and as per ITT-analysis. *Missing data prevented accurate analysis. PROMs – Patient-reported outcome measures, SD – Standard Deviation, VAS – Visual Analogue Score.

11.5 Discussion

Patient-reported outcome measures from this study of internal pilot RCT patients demonstrates acceptable genitourinary and gastrointestinal toxicity, with preservation of health-reported quality of life in all trial intervention arms.

Given the innovative nature of a number of our trial interventions in this setting, there was limited comparative literature (221,260). This is also particularly compounded by the largely retrospective literature body, where validated PROMS are not often reported (**Chapter 1**). Regarding genitourinary function, our trial intervention arm incontinence rates were similar to those that have been observed in patients undergoing our trial treatments for localised prostate cancer (210,253,254). At Visit 7 (Week 52) follow-up, approximately 10% of all patients reported an increase in their urinary pad usage in both trial intervention arms, this compared to an increase of only 4% in the control arm. In 7 in every 10 patients in Intervention Arm 1: MIAT there was no pad usage per day, this was the same as patients in the Control Arm. There was no pad usage per day in 5 in every 10 patients in Intervention Arm 2: Radical. In prior cytoreductive radical prostatectomy studies mean pad-usage has been reported between 1.6 to 1.9 per day (3 months – 25 months post-operatively) (221,260).

Despite the advanced nature of the disease state of patients in this RCT, there was a surprising preservation of most subscales of the EPIC-Urinary domain post-operatively. EPIC-Urinary domain mean subscales reported at Visit 7 (Week 52) in the Intervention Arms were all within a 10-point difference, compared to those reported at 12-months post-radical prostatectomy or external beam prostate radiotherapy performed in patients with localised disease (333).

The EPIC-Bowel domain subscales reported at Visit 7 (Week 52) were preserved compared to baseline in the Intervention Arms. These mean subscales scores were also all within a 5-point difference, compared to those reported at 12-months post-radical prostatectomy or external beam prostate radiotherapy performed in patients with localised disease (333).

In our internal pilot RCT, there were profound reductions in all IIEF-15 questionnaire functional domains suggestive of severe erectile and sexual dysfunction. This was observed in all trial arms and across all trial visits after systemic therapy initiation. Similar reductions have been reported in those studies utilising cRP in mHPSPC, with post-operative mean IIEF-5 questionnaire scores ranging from 7.7 to 8.5 (“moderate” to “severe” erectile dysfunction) (221,260). It is well documented that hormonal manipulation (i.e. ADT) and systemic anti-cancer agents (e.g. docetaxel, ARSI’s) have a significant impact on sexual and erectile function (221,334). The findings of this study are therefore in keeping with those

published in the literature. In future, trialists designing cytoreductive local treatment studies can use these findings to support reducing the burden of sexual function PROMs. This could be achieved by reducing these to short form assessments (e.g. IIEF-5).

There is limited comparative outcomes data for HRQoL in this setting. In this study, the mean EQ-5D index value at Visit 7: post trial intervention was 0.87 (SD 0.11) in Intervention Arm: 2 Radical Arm and 0.8 (SD 0.21) in Intervention Arm 1: MIAT. This compares to 0.9 (SD 0.2) in the cRP arm of the recent TRoMBone randomised study (221).

The preservation of EQ-5D index value in mHSPC over time has been reported previously in studies evaluating the impact of ADT with ARSI's compared to ADT in isolation. For quality of life related specifically to urinary function, a small retrospective study of 14 patients who had cRP with metastatic castrate-resistant prostate cancer (mCRPC), reported small reductions in preoperative and postoperative (<3-month) EPIC-Urinary function QoL scores (median 84 [IQR 70–95] versus 78 [IQR 62–81]) (335).

Health-related quality of life is an increasingly common focus for those involved in the clinical commissioning of new interventions for cancer (330). In the mCRPC setting, The Prostate Cancer Clinical Trials Working Group 3 trial design and objective document lists the importance of reporting HRQOL parameters and in particular performing serial meaningful assessments of global changes in HRQOL (336).

Precision gains in HRQOL outcomes require significant longitudinal follow-up (i.e. years). This presents a challenge to clinical trialists involved in advanced prostate cancer, where the meaningful time points for HRQOL may be well beyond that of the chosen appropriate oncological endpoint adopted by study investigators (e.g. progression-free survival, failure-free survival) (337). In future, it could be conceivable that as HRQOL becomes an important study outcome for regulators and funders, trialists involved in mHSPC study designs may choose to adopt a prospective threshold to define “clinically meaningful deterioration” in HRQOL score during the trial development phase.

In this climate, the main study of the IP2-ATLANTA trial will retain a focus on reporting longitudinal follow-up of HRQOL instruments (**Chapter 6**). This will predominantly be achieved via the EuroQoL (EQ-5D-5L), which has been reported in this internal pilot RCT study. Such detail in reporting will be vital to the presentation, of any of proven novel cytoreductive trial treatments, to NICE regulatory boards and NHS clinical commissioning panels to support changes to standard of care (330-332).

11.6 Limitations

The IP2-ATLANTA pilot RCT was designed to assess feasibility and thus its analysis was restricted to Visit 7, at week 52. Given this restriction we are unable to comment upon the long-term patient-reported outcome measures from trial interventions. The main IP2-ATLANTA RCT is ongoing and will be used to calculate quality-adjusted life-years as part of a future health economic evaluation (**Chapter 6**). Patients agreeing to return questionnaires on quality of life will continue to complete quality of life data beyond the internal pilot, and up to 4 years after enrolment. This is important as a group of patients in localised prostate cancer appear to experience toxicity from radiotherapy at a later stage, years after their initial treatment (338). The EORTC QLQ-C30, Prostate-specific module (QLQ-PR25), Cancer-related fatigue module (QLQ-FA12), Elderly cancer patients module (QLQ-ELD14), Bone metastases module (QLQ-BM22) assessments reported by pilot RCT patients were not available for inclusion in this chapter at the time of thesis submission (339,340). QLQ-BM22 assessments will be particularly important in the assessment of SABR, as the total number of patients undergoing this treatment is predicted to increase significantly in the main study of IP2-ATLANTA. Collectively, the EORTC series may have provided further granular detail to the HRQOL assessments already reported in this chapter.

11.7 Conclusion

Patient-reported outcome measures from the internal pilot RCT of IP2-ATLANTA demonstrate acceptable genitourinary and gastrointestinal toxicity relating to all novel cytoreductive trial interventions. Health-reported quality of life appears to be preserved in this early period of longitudinal follow-up.

Chapter 12 – Discussion

12.1 Overview

In this discussion chapter I provide an overview and evaluation of my thesis. This includes a summary of my research, key findings, impact statement and limitations of this thesis. Furthermore, I provide context for the proposed future body of work within a future research needs section. This chapter concludes with final remarks.

12.2 Summary of my research

The overall purpose of my thesis was to assess the feasibility of performing novel local cytoreductive and metastasis directed treatment strategies in patients with *de novo* synchronous metastatic hormone-sensitive prostate cancer (mHSPC) to confer additional survival benefits. With reference to the thesis outline (**Chapter 1.3**), I have presented the summary of my research in this thesis into three parts:

12.2.1 Part 1: Evidence and rationale for cytoreductive treatments

In the first part of the thesis I performed a narrative review of the pathobiological and clinical rationale of primary tumour cytoreduction (**Chapter 2**). This confirmed the pathobiological evidence supporting local cytoreduction of a primary prostate cancer (and/or metastases thereof). I was able to report the various effects of tumour-derived factors that are likely to translate into direct survival benefits for patients with mHSPC. This was in keeping with the proposed “oligo-metastatic” hypothesis that has been described in other malignancies (e.g. lung) (11). Furthermore, the presented data suggests that metastasis-directed therapy can be associated with “abscopal effects” on lesions located outside the field of treatment, hypothesised to mediate systemic antitumour immune responses.

Finally, I appraised the clinical rationale for cytoreduction. Importantly, the first randomised evidence for primary tumour cytoreduction, from the STAMPEDE (Arm-H) study was published in my first year as a doctoral clinical research fellow. These results supported survival (OS) benefit from cytoreductive prostate radiotherapy compared to systemic therapy (16). I concluded the chapter by presenting the remaining early evidence for alternative surgical approaches, such as, cytoreductive radical prostatectomy, pelvic lymph node dissection and cytoreductive minimally invasive ablative therapies, respectively (4). The paucity of available evidence became a major focus for exploration in this part of the thesis.

In the next project I performed (**Chapter 3**) a systematic review of prospective clinical trials in patients with mHSPC where oligometastasis had been targeted by using surgery or SABR (193). These metastasis-directed therapies reported good early progression-free survival

(19% to 60%) and excellent local control (93% to 100%) benefits. The chapter concluded that MDT was a promising and safe experimental therapeutic approach in mHSPC. This allowed us to move forward and support MDT inclusion in the IP2-ATLANTA RCT design.

In **Chapter 4** I performed a second systematic review evaluating patients' values, preferences and expectations for the treatment of metastatic prostate cancer (163). In quantitative preference elicitation studies patients consistently valued "treatment effectiveness" and "delay in time to symptoms" as the two top-ranked treatment attributes. The chapter concluded that there was a limited understanding of how patients make treatment and trade-off decisions following a diagnosis of metastatic prostate cancer. However, there was evidence that patients were willing to trade off treatment-related toxicity for potential oncological benefits, supporting the notion that a cytoreductive interventions study offering potential oncological benefits may be accepted by patients with mHSPC.

In **Chapter 5** I performed a prospective study on the clinical and histological outcomes of patients presenting with *de novo* mHSPC who arise in a modern pre-biopsy mpMRI prostate cancer diagnostic pathway (RAPID) with a restricted favourable performance status. Patients with mHSPC were infrequently diagnosed within such a pathway (4.3%). However, prior to systemic therapy being commenced MRI T4-stage disease, surgically irresectable, diffuse high volume intraprostatic lesions, and Gleason >8 disease were prevalent. I concluded that interval imaging post-systemic therapy induction should be considered to facilitate the wider recruitment of patients at baseline into novel cytoreductive surgical trials. This had key implications when we developed eligibility criteria of IP2-ATLANTA (233). Unlike previous studies using cRP or cytoreductive MIAT, the inclusion of serial imaging in the pilot RCT allowed us to permit and review the changes in T4 disease from baseline or pre-operative stage. Our approach was unique compared to currently recruiting surgical trials, where radiological stage criteria are a key barrier to inclusion (228).

Despite clinician concerns of higher complication rates in patients with mHSPC, I could confirm that transperineal MRI-targeted biopsy of the primary appeared safe in this study. This allowed us to integrate serial transperineal research prostate biopsy into our internal pilot RCT of IP2-ATLANTA. Collectively, the work presented in the first part of this thesis provided the vital building blocks for the design of a robust randomised study incorporating novel cytoreductive treatments.

12.2.2 Part 2: Novel cytoreductive treatments: a randomised controlled trial

In the second part of this thesis I designed, together with my supervisors, a prospective, unblinded, multicentre, randomised controlled trial, IP2-ATLANTA (3). **Chapter 6** details the trial development and design which uniquely brought together multiple healthcare

professionals in prostate cancer research (e.g. urological surgeons, clinical oncologists, medical oncologists). In many cases this was at a national level (e.g. NHS England for SABR commissioning) to input into the trial design, novel treatments and deliver trial quality assurance. We developed a number of standard operating procedures that had not been performed previously in the literature beyond the pre-clinical setting, such as cytoreductive MIAT with or without metastasectomy. The chapter also reported the internal pilot and main study endpoints we would use.

In our internal pilot RCT we opened eleven active trial sites in England and Wales and we randomly allocated 81 patients to our trial arms. I was able to visit all these trial sites in person and I recruited 60% (49/81) of all patients in the internal pilot RCT across three London trial sites. My dual role as a London Urology Trainee enabled me to perform or assist in a number of these local cytoreductive procedures and baseline/re-classification prostate biopsies. To the best of our knowledge, this included assisting in the first ever (in-human) cytoreductive whole gland cryotherapy with robotic bilateral PLND at Charing Cross Hospital, Imperial College Healthcare NHS Trust (Prof Hashim U. Ahmed and Mr Mathias Winkler).

The results from the internal pilot RCT patients of IP2-ATLANTA were presented in **Chapter 7**. In this multicentre randomised controlled trial we were able to confirm the acceptable feasibility of allocating patients with *de novo* synchronous mHSPC to systemic therapy intensification with cytoreductive MIAT +/- PLND or cytoreductive radical therapy (cRP +/- PLND or cytoreductive EBRT +/- PLNRT), with or without metastasis-directed therapy, against an active comparator arm. We reported a satisfactory recruitment, randomisation rate, and compliance for local cytoreduction, respectively. Furthermore, we reported all trial intervention treatments had an acceptable safety and adverse event profile.

Importantly, the results presented in **Chapter 7** confirmed, for the first time in the literature, the presence of a viable primary tumour in the majority of patients with mHSPC despite contemporary systemic therapy intensification with ADT and docetaxel/ARSI's.

12.2.3 Part 3: Primary tumour responses and novel cytoreductive treatments

The third part of this thesis commenced with a blinded second central histopathology review of 60% of internal pilot RCT patient specimens (**Chapter 8**). Having complete reported ISUP Grade Group assignment and pathological response assessment at a local trial site level, the next step was consider the accuracy of this against a central review. In this chapter I confirmed strong inter-observer agreement between baseline ISUP Grade Group and pathological response assessments following systemic therapy between local and central trial histopathologists. Such findings support the validity of the results we have previously

reported in the overall internal pilot. To our knowledge, serial primary prostate tumour histology acquisition in patients with distant synchronous metastasis at baseline (mHSPC) pre- and post- contemporary systemic therapy intensification had not been reported previously in the literature.

In **Chapter 9** we performed a dedicated embedded exploratory prospective, blinded imaging response sub-study alongside the IP2-ATLANTA internal pilot RCT (**Chapter 9**). This reported early promise on the role of sequential [⁶⁸Ga] PSMA-11 PET imaging in prediction of residual intraprostatic tumour foci following systemic therapy, when compared to paired serial mpMRI prostate imaging and prostate biopsy.

I confirmed the safe technical surgical performance of cytoreductive MIAT, with or without metastasectomy, using the per-protocol analysis from the internal pilot RCT patients in IP2-ATLANTA (**Chapter 10**). Finally, I presented a wide variety of relevant PROMS from all trial arms reported in the IP2-ATLANTA internal pilot study. **Chapter 11** concluded there was acceptable genitourinary and gastrointestinal toxicity derived from PROMS in the intervention arms of this study.

12.3 Key findings and impact statements

12.3.1. Randomising patients with mHSPC to novel cytoreductive treatments

To our knowledge, IP2-ATLANTA was the first study in the literature to perform cytoreductive MIAT, cRP and SABR interventions for mHSPC in a randomised design, against an active comparator arm.

We were able to confirm the acceptable feasibility of allocating patients with *de novo* synchronous mHSPC to systemic therapy intensification with cytoreductive MIAT +/- PLND or cytoreductive radical therapy (cRP +/- PLND or cytoreductive prostate radiotherapy +/- PLNRT), with or without metastasis-directed therapy, against standard of care alone. This was a novel trial design in which sequential systemic therapy, local cytoreduction and then metastasis-directed intervention were performed in mHPSC. In addition, SABR for low burden metastasis in *de novo* synchronous mHSPC had never been attempted in a randomised study. The feasibility results enabled IP2-ATLANTA to move to its main study component and work towards reporting on progression-free survival (PFS).

These results also have external implications that support a number of ongoing surgical trials that have chosen to integrate “cRP” alongside “cytoreductive radiotherapy” as a “radical treatment” arm design (228).

As we have explained in **Chapter 6**, there were a large number of considerations in the debate surrounding a radical trial arm design. It is plausible to suggest that given the inherent patient eligibility restrictions that cytoreductive radical prostatectomy has (e.g. irresectable disease), should cRP be proven to offer similar additive oncological benefits as cytoreductive radiotherapy, its routine integration into patient care would likely be alongside cytoreductive radiotherapy and would mirror our trial arm design.

We reported a satisfactory recruitment, randomisation, and compliance rates for local cytoreduction, respectively. This chapter also reported acceptable compliance for all local cytoreductive treatments. However, there was reduced compliance for simultaneous pelvic lymph node directed treatments in all arms at the time of planned local cytoreductive treatment. There is a number of possible reasons for this, including patient and surgeon factors and it is unknown if this compliance rate would still be observed if a larger sample size were analysed. “Within study implications” for these findings has led to a central trials team review of the current rates of PLND in comparison to those declared at baseline in all trial arms. This will insure adherence to this aspect of the protocol is maintained in the main phase component.

Furthermore, we reported all trial intervention treatments had an acceptable safety and adverse event profile. Grade 4 adverse events occurred exclusively in the control arm and no Grade 5 adverse events were reported. Locoregional symptomatic events were also reported to be confined to the control arm (e.g. SPC insertion, TURP) only. The presence of locoregional symptomatic events relating to the unchecked progression of the primary tumour is in keeping with prior studies that have demonstrated the benefits of local cytoreduction on reducing these events and their negative impact on survival (236). Clearly, the safety and adverse event profile is also reassuring for clinicians and patients involved in the main study component of IP2-ATLANTA.

12.3.2 Behaviour of the primary tumour in response to contemporary systemic therapy

Metastasis remains the leading cause of cancer-associated death (341). However, the rapid advances in systemic agents has led some to question the need and value of treating the primary tumour as part of the “oligometastatic hypothesis” when advanced anti-cancer therapies are now available to most patients (341,342).

In this thesis, for the first time in the literature, we report on post-systemic primary tumour pathology patients with mHSPC in whom over 90% had ADT with docetaxel or an ARSI's. In our RCT the complete pathological response rate was low (11.3%) and remained unchanged on blinded central review. We can thus conclude that most patients with mHSPC have residual adenocarcinoma of the prostate despite best contemporary systemic therapy escalation. This provides weight to the narrative that the destruction of a highly prevalent persistent residual viable primary tumour, and its crosstalk with established metastatic lesions, may reduce the likelihood of lineage adaptation and thus lead to progression-free survival benefits (4).

Of course, there are also implications of these findings for patients and clinicians who can be reassured that for the majority of patients with mHSPC, the provision of local cytoreduction would be targeted towards a viable residual tumour. Assuming such local cytoreductive treatments are proven to have progression-free survival benefits in the main stage, such interaction would not represent “unnecessary overtreatment” in these patients.

We also reported key histologic features in the primary tumour (i.e. IDC-P, Cribriform architecture) and their associated responses to contemporary systemic treatment in a paired blinded prospective manner (287-289). A number of these responses are entirely novel and hypothesis generating. In a similar fashion to non-metastatic disease, the presence of sub-pathologies, and the nature of their responses, may have a role in prognostication (209).

Finally, in our imaging response study, serial ⁶⁸Ga-PSMA-11 PET/CT when combined with mpMRI prostate was a promising method to monitor residual intraprostatic tumour burden. In particular, our newly developed “ATLANTA MRI Score” fared well in its ability to predict complete pathological response. In the main study of IP2-ATLANTA these radiological and pathological response assessments can be re-evaluated with a larger sample size and an exploratory post-hoc analysis linked to PFS should be considered.

12.3.3. Novel cytoreductive minimally-invasive ablative therapies

This is the first randomised study, to our knowledge, to report on cytoreductive minimally invasive ablative therapy. The main findings were that cytoreductive minimally invasive ablative therapy, with or without simultaneous surgical metastasectomy (in the form of pelvic lymph node dissection), was feasible and a safe alternative approach to treating the primary tumour and local pelvic metastasis in patients with mHSPC who have received pre-operative systemic therapy intensification. This is an innovative and novel approach to surgical cytoreduction.

As eluded to previously, we had to develop the cytoreductive MIAT SOP to predict prostate gland and stage changes to systemic therapy. This included managing pelvic lymph nodal metastasis in a similar dose escalated fashion as available in radical treatment arm SOPs. Cytoreductive cryotherapy and cytoreductive HIFU was well tolerated and there were no reported cases of recto-urethral fistula formation. In 9 in every 10 patients trial without catheter was successful. The benefit of such intervention in the localised setting is the greatly reduced genitourinary toxicity profile compared to surgery or radiotherapy (212). In our study, 7 in every 10 patients were pad-free following cytoreductive MIAT and no patients required more than one pad per day. This compared to 5 in every 10 patients in the radical arm undergoing cRP or cytoreductive radiotherapy.

Cytoreductive MIAT with simultaneous surgical metastasectomy, in the form of pelvic lymph node dissection, was reported for the first time in the clinical setting in this study. We were thus unable to locate any prior comparable literature beyond the cadaveric setting (214). There were no major complications of incorporating the PLND component of this novel procedure. Our positive lymph node removal rates were in keeping with other randomised studies that utilised cRP with PLND (221).

Collectively, these highly promising results of this pilot RCT suggest that, if additive oncological benefit from cytoreductive MIAT approach is proven, this is a viable alternative to cytoreductive radiotherapy in the management of patients with *de novo* synchronous mHSPC.

12.4 Limitations of this thesis

In each of the chapters presented in this thesis, a detailed limitations section has been provided. The overall purpose of this thesis was to report on feasibility, and the pilot RCT that supported this purpose was not powered to report on progression-free survival benefits from any of the proposed novel cytoreductive treatments. As such, the individual analysis presented on technical performance of cytoreductive MIAT is linked to the assumption that progression-free survival benefits of this approach will be reported in the main study.

With regard to our feasibility study, although this was a multicentre randomised controlled trial, there were a number of expressed key limitations. Particularly there was absent data on the exact distant site of metastatic disease (M1 (any) – not specified). Although we were able to assign a correct metastatic burden classification, we could not contextualise our findings accurately by exact metastatic stage. This limited some discussion elements and comparison with the literature in the subsequent trial chapters.

With regard to the complete pathological response reported, we analysed specimens acquired from transperineal prostate biopsy or whole mount prostatectomy specimens following a repeat mpMRI. It is possible that residual foci of treated prostate adenocarcinoma may have been missed, when compared to evaluation of whole mount prostatectomy specimens, impacting the response rate reported (262). Given the nature of the alternative trial arm interventions (i.e., radiotherapy or MIAT), repeat prostate biopsy was the only viable method of histological reclassification of disease post-systemic therapy in this study.

We were unable to comment on the root cause of reduced compliance issues for simultaneous pelvic lymph node treatment in Intervention Arm 1: cytoreductive MIAT. Finally, SABR to metastasis was performed in only two patients in this internal pilot study. As such we were unable to accurately comment on the adverse event rate of this trial intervention, which will become clear in the main study.

12.5 Future research needs

12.5.1. Oncological outcomes from novel cytoreductive treatments

The IP2-ATLANTA internal pilot has demonstrated the clear feasibility of performing novel cytoreductive treatments in a randomised controlled trial design for patients with mHSPC. The next step is for the main study component to provide Level I evidence on oncological outcomes from prostate minimally invasive ablative therapy or radical therapy, in combination with metastasis-directed therapy, against standard of care treatment alone. If either intervention arm is proven to provide significant oncological benefit this will have wide-reaching implications on the current standard of care paradigm.

This study is in its accrual phase and at the time of this thesis submission had 238 patients recruited and randomised, from 19 open trial sites in England and Wales. This main phase component has been issued with a funded extension by the Wellcome Trust to cover the recruitment time lost during the Covid-19 pandemic and enable the trial to continue until 2026.

12.5.2 Patient preferences' for cytoreductive treatments

Novel local cytoreductive treatments and metastasis-directed therapy may provide added survival benefit or delay the requirement for further systemic agents and associated toxicity but can confer additional harm. Understanding patients' preferences for treatment options, particularly where radical treatment options have been introduced into an advanced disease state, is crucial for patients, clinicians, carers and future healthcare service providers (165).

Thus as a lead co-principal investigator, together with my supervisor Prof. Hashim U. Ahmed (Imperial College London) and Dr. Verity Watson from the Health Economics Research Unit (University of Aberdeen), I designed a prospective, multicentre discrete choice experiment study to answer this research question alongside my time as a doctoral clinical research fellow. The Imperial Prostate 5 - Metastatic prostate cancer patients' Attitudes towards Treatment of the local Tumour and metastasis Evaluative Research (IP5 – MATTER) (343). This study was funded by the Wellcome Trust (204998/Z/16/Z) & University College London Hospitals (UCLH) Charity (P83624/1348). IP5-MATTER was approved by the HRA (East of England, Cambridgeshire and Hertfordshire Research Ethics Committee (Reference: 20/EE/0194) and registered on ClinicalTrials.gov (NCT04590976).

We aim to determine the attributes associated with treatment that are most important to patients with mHSPC. Furthermore, we plan to determine patients' preferences for, and trade-offs between, the attributes (survival and side-effects) of different treatment options including systemic therapy, local cytoreductive approaches (external beam radiotherapy, cytoreductive radical prostatectomy or minimally-invasive ablative therapy) and metastases-directed therapies (metastasectomy or stereotactic ablative body radiotherapy). All patients with newly-diagnosed mHSPC within four months of commencing ADT and WHO performance status 0 to 2 are eligible. Patients who have previously consented to a cytoreductive treatment or have developed castrate-resistant disease will be excluded. This study includes a qualitative analysis component, with patients ($n=15$) and healthcare professionals ($n=5$), to identify and define the key attributes associated with treatment options that would warrant trade-off evaluation in a DCE. The main phase component planned recruitment is 300 patients. At time of submission of this thesis, the first two phases have been completed in this study and the final phase of recruitment is ongoing. We were

able to open 30 UK trial sites and recruitment to date is 287 patients, with results due in early 2023.

Once completed, IP5-MATTER will be the first multi-centre discrete choice experiment conducted to evaluate patients' treatment preferences for local cytoreductive and metastasis-directed therapy in mHSPC. This study will explore preference heterogeneity according to the patients' personal characteristics. This is also the first study to determine if patients with mHSPC are willing to accept the potential effect sizes that are reported in randomised studies (343).

12.5.3 PSMA PET/CT role in staging disease and monitoring response

The staging of distant disease (M1a-c) is facing rapid changes following the introduction of PSMA-targeted imaging in some academic centres (231). This has increased following the results of the proPSMA study demonstrating superior diagnostic accuracy of first line Ga⁶⁸ PSMA-PET/CT over conventional imaging (231).

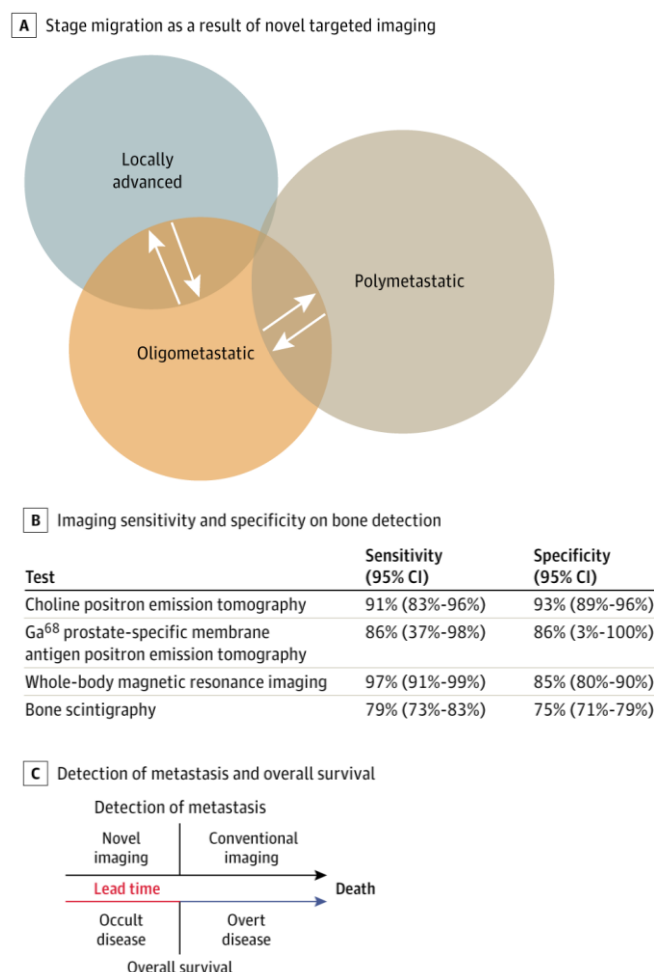
The unchecked introduction of PSMA PET/CT imaging presents a challenge to clinical trialists evaluating cytoreductive treatments based on patients stratified on conventional imaging. PSMA PET/CT can identify “micro-” or “early-” oligometastatic disease, in the same vein “oligometastatic” may also appear as “poly-metastatic” (232). This has a downstream impact on the accurate assignment of metastatic burden definitions used in prior oncology studies (344).

Prior to the results of proPSMA, I previously published a hypothesis paper with my supervisors in *JAMA Oncology* describing the risk of such a Will Roger's phenomenon in interpreting oncological outcomes when such patients are re-classified with “micro” oligometastatic disease, in whom this would be previously radiologically invisible (**Figure 32**) (12).

In IP2-ATLANTA we decided to permit PSMA PET/CT and conventional imaging modalities, but derived metastatic burden from the conventional components. This allowed us to mitigate against this stage migration effect and utilise pre-specified low-burden subgroup (CHAARTED definition) that has been used elsewhere in the literature.

The widespread adoption of PSMA PET/CT in the high risk presumed localised prostate cancer setting, based on clinical validity studies (such as proPSMA), may have unexpected consequences to those undertaking research in the cytoreductive metastatic setting. All current and proposed trials should develop mechanisms to prevent or appropriately control stage migration that results from such next generation imaging, to enable the wider clinical community to interpret their findings.

Figure 32. Outcomes of Novel Targeted Imaging on Detection of Metastasis, Disease Classification, and Reported Overall Survival



Legend: [A], Stage migration as the result of novel targeted imaging with its subsequent association with disease course in terms of time from detection of metastasis and overall survival. [B], Choline positron emission tomography, prostate-specific membrane antigen positron emission tomography, and whole-body magnetic resonance imaging sensitivity and specificity (per patient) on bone detection. [C], Detection of metastasis and overall survival time. [Reproduced with permissions (Appendix A) from JAMA Oncology [American Medical Association]. Connor MJ, Winkler M, Ahmed HU. Survival in oligometastatic prostate cancer—a new dawn or the Will Rogers phenomenon?. JAMA Oncology. 2020 Feb 1;6(2):185-6.]

However, there may be a promising role for PSMA PET/CT in response assessments and disease monitoring in patients with mHSPC. This thesis in particular highlighted the potential role for ⁶⁸Ga-PSMA-11 PET/CT PSMA PET/CT imaging in the assessment of intraprostatic tumour response.

Our pilot RCT embedded PSMA PET/CT sub-study cohort will be analysed and published by the dedicated sub-study team in order to answer the remaining secondary objectives, not reported in this thesis, which include: (a) to investigate whether PSMA expression detectable by ⁶⁸Ga-PSMA-11 PET/CT is associated with extraprostatic residual disease; (b) to correlate, where available, tissue PSMA expression with ⁶⁸Ga-PSMA-11 PET/CT uptake (c)

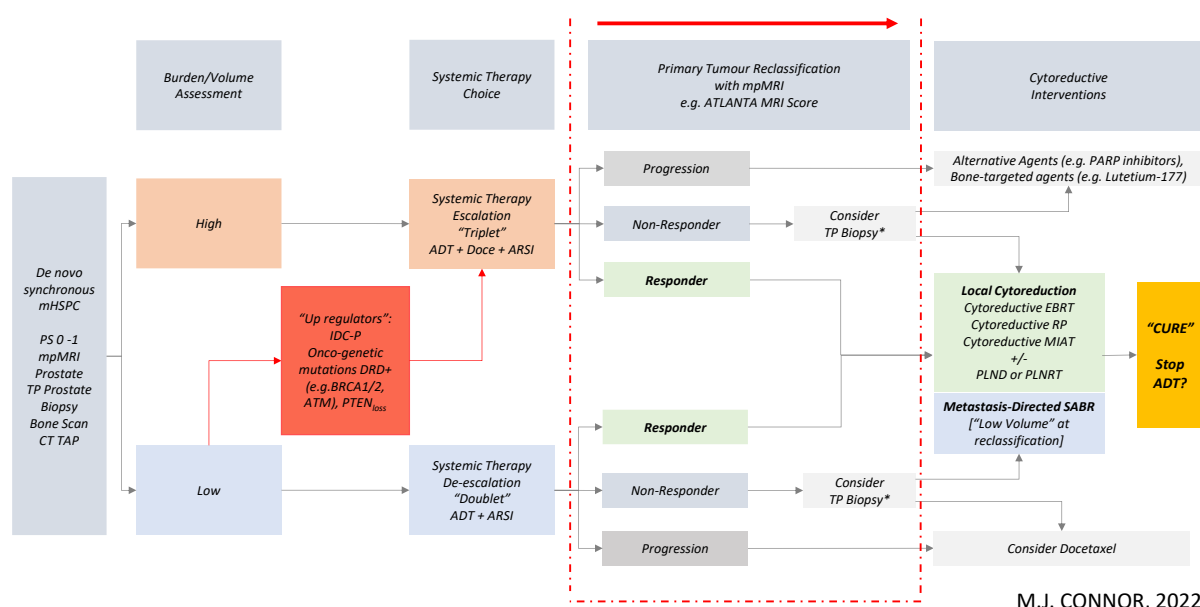
to verify a set of biomarkers (miRNA or cfDNA) in blood and urine that are differentially altered in relation to radiological response to systemic therapy.

12.5.4 Next generation treatment pathway

How do my thesis findings translate into the development of a next generation treatment pathway? How and when should we identify and stratify patients who are most likely to benefit from cytoreductive interventions?

In **Figure 33** we present a hypothetical treatment pathway, integrating stratification and primary tumour response assessments from the results of this thesis. It should be noted that there is a principal assumption that all our novel trial interventions demonstrate superiority against current standard of care.

Figure 33. Hypothetical future treatment pathway including risk stratification, systemic therapy alterations and novel cytoreductive treatments



Legend: Hypothetical presentation of future treatment pathways, encompassing baseline tumour risk stratification with histopathological factors (IDC-P) and onco-genetic mutations (BRCA1/2, ATM, PTEN_{loss}, p53, RB1), tumour reclassification of patients post systemic therapy (Red line). Systemic therapy escalation to "triple" upfront therapy in those with unfavourable risk factors and high burden disease. Low burden disease patients can be de-escalated to "doublet" therapy of ADT+ARSI, without taxane based chemotherapy. mpMRI tumour reclassification with mpMRI prostate to identify responders for local cytoreduction, this should include the ATLANTA MRI Score to provide tumour viability. *Consider transperineal prostate biopsy in those without local response as underlying concerning histologic features such as neuroendocrine differentiation or IDC-P. In such cases discussion regarding unclear benefits of further systemic agent versus attempt at local cytoreduction. ADT – Androgen Deprivation Therapy; CT TAP – Computed Tomography Thorax, Abdomen and Pelvis; TP Prostate – Transperineal Prostate Biopsy; mHSPC – metastatic hormone sensitive prostate cancer; Bone scan – bone scintigraphy; Doce – Docetaxel; ARSI – Androgen receptor signalling inhibitor; SABR – Stereotactic ablative radiation; MIAT – Minimally invasive ablative therapy; RP – Radical prostatectomy; PLND – Pelvic Lymph Node

Firstly, we consider the level of systemic therapy required upfront. There are now a number of studies suggesting that systemic therapy escalation with “triplet” therapy (docetaxel + ARSI + ADT) provide greater overall survival benefits in those patients with high volume disease (345). In the same manner there is evidence that those with homogenous low burden disease respond better to “dual” androgen directed interventions (ARSI + ADT), omitting the risk of toxicity from taxane based chemotherapy (346).

It is clear to me from my research that there is certainly more to the prediction of outcomes from cytoreductive treatment in mHSPC, than can be explained by calculating the number and pattern of metastasis seen on baseline imaging (**Chapter 1**). The treatment naïve primary prostate tumour microenvironment, and the interaction with any onco-genetic mutations (BRCA1/2, ATM, PTEN_{loss}, p53, RB1), are likely to play a role in predicting response to systemic therapy (**Chapter 8**) (347). In this thesis we found that certain histopathologic features that have been reported as independent adverse pathological risk factor for disease progression in localised disease were present and persistent in the primary tumour of some patients with mHSPC at baseline and post-therapy (230,286-288). As demonstrated in this thesis, we can safely perform routine transperineal prostate biopsy in patients with mHSPC (**Chapter 7**). Therefore, we can start to routinely identify and those expressing adverse features and arguably consider whether dose escalation to triple therapy is required, despite their original baseline assignment of “low burden disease”.

This leads us to a wider question as to whether we should in fact be deciding upon cytoreduction at the time of reclassification post-systemic therapy? The early findings from this thesis support the potential utility of mpMRI prostate in the accurate reclassification of the primary tumour following systemic therapy. Such a move to reclassify patients with mHSPC following systemic therapy is at odds with all current studies evaluating cytoreductive treatments, including IP2-ATLANTA, where point of decision for allocation to cytoreductive intervention is almost always performed in the baseline and treatment naïve state. I would argue that selection for cytoreductive treatments in mHSPC is best placed at this moment of tumour reclassification.

Tumour reclassification with mpMRI offers clinicians the option of i) identifying progression, offering an alternative systemic agent (e.g. second line taxane chemotherapy, PARP inhibitor) and deferring the possible toxicity of local cytoreductive treatments; ii) identifying responders who may achieve control from cytoreduction and benefit most; and iii) identifying the non-responder/stable cohort, who can have safe re-evaluation of their primary tumour

with transperineal prostate biopsy, to recognise the presence of persistent precursors that maybe lead to a castrate resistance emerging (e.g. persistence of IDC-P). In this final scenario, it remains unclear as to whether a further systemic agent would be beneficial versus dose escalation of treatment to the primary tumour and surrounding regional metastasis with cytoreductive interventions. At present this decision would need to be on a per-patient basis.

Irrespective of the finding of the main study of IP2-ATLANTA, it is clear that the next steps in identifying ideal candidates for cytoreduction in mHSPC requires a deeper understanding of both the baseline primary tumour phenotypes and primary tumour response patterns once exposed to contemporary systemic therapy intensification (348).

12.6 Final remarks

In this thesis, the complete pathological response rate in our pilot RCT was low and remained unchanged on blinded central review. These findings confirm that most patients with mHSPC have residual adenocarcinoma of the prostate despite contemporary systemic therapy escalation. This finding, and the various sub-pathologies identified in the primary tumour, are a platform for future research into the radiological and pathological behaviour of the primary in response to systemic therapy. The clinical translation of such a response is expected to be particularly relevant to the identification and stratification of patients with mHSPC who may be considered for cytoreductive treatments. This is a key future research objective if we continue to report oncological benefits from additive cytoreductive interventions.

Overall, we confirmed the acceptable feasibility of allocating patients with *de novo* synchronous mHSPC to systemic therapy intensification with cytoreductive MIAT +/- PLND or cytoreductive radical therapy (cRP +/- PLND or cytoreductive prostate radiotherapy +/- PLNRT), with or without metastasis-directed therapy, against standard of care alone. This was a novel trial design and these feasibility results have enabled IP2-ATLANTA to move to its main study and to report its main primary endpoint of progression-free survival.

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Appendices

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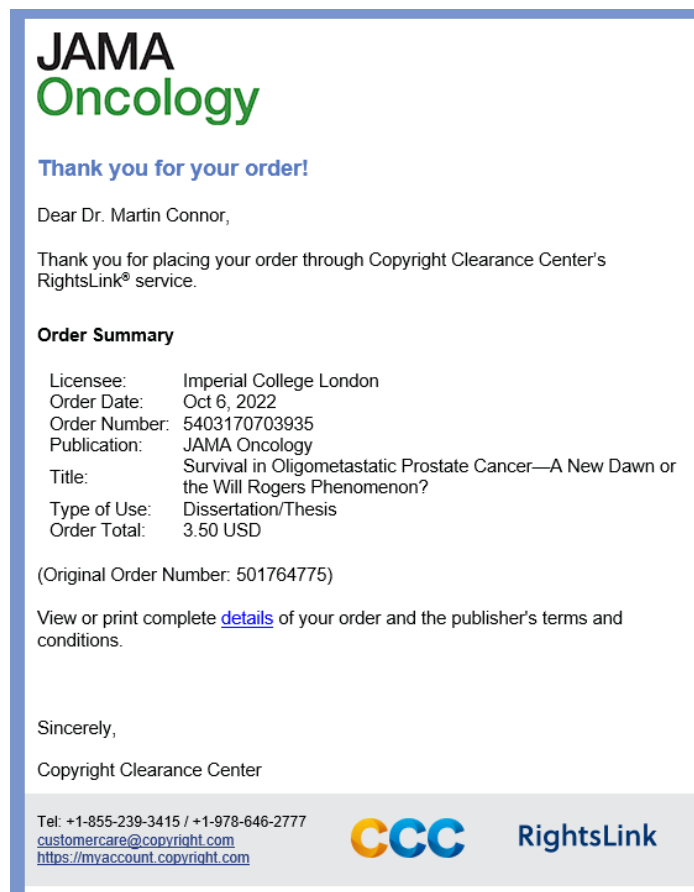
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Radical Treatment Without Cure: Decision-making in Oligometastatic Prostate Cancer

Author: Martin J. Connor, Vincent Khoo, Verity Watson, Hashim U. Ahmed

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Appendix B: Supplementary material for systematic review chapters

Chapter 3 Supplementary Material

Search Strategy

A systematic search of the literature was performed using Medline, Embase, Cochrane Review Database, and Clinicaltrials.gov databases. The search was performed from individual database inception to 28th March 2020 for articles that met our inclusion and exclusion criteria. Only clinical trials that were published by the 28th March 2020 were included.

The following combinations of search terms was used for MEDLINE: *prostat* adj3 adenocarcinoma* OR prostat* adj3 cancer* OR prostat* adj3 neoplas* OR prostatic neoplasms (MeSH) AND oligo recurren* OR oligorecurren* OR oligo metasta* OR oligometasta* OR oligoprogress* OR neoplasm metastasis (MeSH) AND SBRT OR SABR OR stereotactic ablative radiotherapy OR stereotactic body radiotherapy OR stereotactic body radiation therapy OR lymphadenectom* OR lymph node* adj3 dissection OR lymph node* adj3 resection OR lymph node* adj3 excision OR RPLND OR LND OR lymph node excision (MeSH) OR metastasectom* OR metasta* adj3 dissection OR metasta* adj3 excision OR metasta* adj3 resection OR metasta* adj3 removal OR metasta* adj3 surg* OR metasta* directed therapy OR metasta* targeted therapy OR metasta* directed treatment OR metasta* targeted treatment OR metastasectomy (MeSH) OR radiosurgery (MeSH).*

The following combination of search terms was used for EMBASE: *prostat* adj3 adenocarcinoma* OR prostat* adj3 cancer* OR prostat* adj3 neoplas* OR prostate tumor (MeSH) OR prostate cancer (MeSH) OR prostate adenocarcinoma (MeSH) AND oligo recurren* OR oligorecurren* OR oligo metasta* OR oligometasta* OR oligoprogress* OR metastasis (MeSH) AND SBRT OR SABR OR stereotactic ablative radiotherapy OR*

stereotactic body radiotherapy OR stereotactic body radiation therapy OR stereotactic body radiation therapy (MeSH) OR lymphadenectom OR lymph node* adj3 dissection OR lymph node* adj3 resection OR lymph node* adj3 excision OR RPLND OR LND OR lymph node dissection (MeSH) OR metastasectom* OR metasta* adj3 dissection OR metasta* adj3 excision OR metasta* adj3 resection OR metasta* adj3 removal OR metasta* adj3 surg* OR metasta* directed therapy OR metasta* targeted therapy OR metasta* directed treatment OR metasta* targeted treatment OR metastasis resection (MeSH) OR radiosurgery (MeSH)*

PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4,5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5, Suppl.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7

RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-14
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-14
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	14
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	14, Table 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7-14

DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19-20

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

GRADE “Certainty of Evidence”

Quality assessment							Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Progression-free survival								
4	Phase I/II, RCT, Single Arm	Serious ^a	Not serious	Serious ^a	Serious ^a	Strong association	⊕○○○ Very Low	CRITICAL
Local control								
4	Phase I/II, RCT, Single Arm	Not serious	Not serious	Serious ^b	Not serious	Strong association	⊕⊕○○ Low	IMPORTANT
ADT-free survival								
4	Phase I/II, RCT, Single Arm	Not serious	Serious ^b	Serious ^a	Not serious	Strong association, suspected selection bias	⊕⊕○○ Low	CRITICAL
SABR toxicity								
4	Phase I/II, RCT, Single Arm	Not serious	Not serious	Not serious	Not serious	Strong association.	⊕⊕○○ Low	IMPORTANT
Surgical complications								
4	Phase I/II, RCT, Single Arm	Serious ^c	Serious ^c	Serious ^c	Serious ^c	Strong association.	⊕○○○ Very Low	IMPORTANT

^a Not all endpoints are consistent, early outcome data, lack of comparator group. ^bMedium term data not available, imaging used varied across studies i.e. conventional versus metabolic. ^c Lack of uniformity of the surgical approach and anatomical site for surgical metastatectomy performed.

SABR dose and fractionation and delivery of included studies

No	Author (Year)	Patients <i>n</i>	Anatomical Sites	Total dose (Gy)	Fractionation	Frequency	Full SABR site-specific dose/fractionation schedule published
1.	Phillips <i>et al.</i> (2020) (138)	54 (36 ^a)	i) Overview ii) Isolated osseous ii) bone lesions	i) 19.5 – 48 Gy ii) 19.5-24 Gy iii) 50-60 Gy	i) 3-5 Fr ii) 3-5 Fr iii) 5 Fr	Completed within 3-weeks	Yes
2.	Ost <i>et al.</i> (2018) (136)	62 (31 ^a)	i) Bone ii) Nodal	i) 30 Gy ii) 30 Gy	i) 3 Fr ii) 3 Fr	i-iii) Split by >48 but <96 hours	Yes
3.	Siva <i>et al.</i> POPSTAR (2018) (135)	32 (22 ^b)	i) Bone ii) Nodal	i) 20 Gy ii) 20 Gy	i) 1 Fr ii) 1 Fr	Single fraction	Yes
4.	O'Shaughnessy <i>et al.</i> (2017) (137)	20	i) Bone or Nodal	i) 20 – 30 Gy	i) 1 – 5 fr	Single fraction - Not reported	No

Fr – Fraction, NR – not reported. ^aIntervention arm only. Hormone-sensitive patients cohort only.

Study Progression-Free Survival, Local Control, ADT-Free Survival, Toxicity and/or Complication Criteria

No	Study	Progression-Free Survival (PFS)	Local Control (LC)	ADT-Free Survival (ADT-FS)	Toxicity and/or Complications
1.	Phillips <i>et al.</i> (2020) (138)	PSA rise of at least 2 ng/dL (to convert to micrograms per liter, multiply by 0.01) and 25% above nadir; concern for radiologic progression by CT, magnetic resonance imaging, or bone scan as determined by the reading radiologist; symptomatic progression of disease; initiation of ADT for any reason; death or withdrawal from the study after randomization	Any evidence of progression by size.	-	CTCAE v.4.0
2.	Ost <i>et al.</i> (2018) (136)	-	>= 25% increase in the size of a measurable lesion on CT or a >= 25% increase in the size of ill-defined lesions on CT.	The time between random assignment and the start of palliative ADT	CTCAE v.4.0. OR Clavien-Dindo Classification
3.	Siva <i>et al.</i> (2018) (135)	Development of distant metastases	An increase of >20% in the largest tumour dimension with a minimum	The time to starting ADT treatment	CTCAE v.4.0.

			absolute increase of 5 mm		
4.	O'Shaughnessy <i>et al.</i> (2017) (137)	Detectable PSA (PSA $\geq$ 0.05 ng/ml)	-	-	Clavien-Dindo Classification

ADT – Androgen Deprivation Therapy, PSA – Prostate Specific Antigen, SBRT – Stereotactic Body Radiotherapy, PTV – Planning Target Volume, PET/CT – Positron Emission Tomography/Computerised Tomography, MRI – Magnetic Resonance Imaging, LN – Lymph Node, RTOG/EORTC – Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer, CTCAE – Common Terminology Criteria for Adverse Events.

Chapter 4 Supplementary Material

Search Strategies

1. exp Prostatic Neoplasms/
2. (prostat\$ adj3 (adenocarcinoma* or cancer\$ or carcinoma\$ or malignan\$ or tumo?r\$ or neoplas\$)).ti,ab,kw.
3. 1 or 2
4. exp Neoplasm Metastasis/
5. (metasta* or stage 4 or stage IV or oligo* or advanced).tw.
6. 4 or 5
7. 3 and 6
8. (preference* adj2 elicit*).tw.
9. discrete choice*.tw.
10. stated preference*.tw.
11. part-worth utilit*.tw.
12. functional measurement.tw.
13. paired comparison*.tw.
14. pairwise choice*.tw.
15. conjoint analys*.tw.
16. conjoint measurement.tw.
17. conjoint stud*.tw.
18. conjoint choice.tw.
19. best-worst scal*.tw.
20. contingent valuation.tw.
21. standard gamble.tw.
22. time trade off.tw.
23. (willing* to pay or WTP).tw.
24. willing* to accept.tw.
25. (willing* adj2 wait*).tw.
26. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27. 7 and 26
28. exp animals/ not humans/
29. 27 not 28
30. (editorial or letter or news).pt.

31. 29 not 30

32. limit 31 to english language

33. (((("semi-structured" or semistructured or unstructured or informal or "in-depth" or indepth or "face-to-face" or structured or guide) adj2 (interview* or discussion* or questionnaire*)) or (focus group* or qualitative or ethnograph* or fieldwork or "field work" or "key informant")).tw,kw. or interviews as topic/ or focus groups/ or narration/ or qualitative research/

34. 7 and 33

35. exp animals/ not humans/

36. 34 not 35

37. (editorial or letter or news).pt.

38. 36 not 37

39. limit 38 to english language

Supplementary Table 1 DCE PREFS quality checklist

Authors	de Freitas et al. (2019)		Eliasson et al. (2017)		Nakayama et al. (2018)		Uemura et al. (2016)		Hauber et al. (2014)		% studies that fulfill the criteria
Standards for PREFS	No/unclear	Yes	No/unclear	Yes	No/unclear	Yes	No/unclear	Yes	No/unclear	Yes	
Purpose: Is the purpose of the study in relation to preferences clearly stated?		1		1		1		1		1	100
Respondents: Are the responders similar to the non-responders?	0		0		0		0		0		0
Explanation: Are methods of assessing preferences clearly explained?		1		1		1		1		1	100
Findings: Were all respondents included in the reported findings and analysis of preference results?		1		1		1		1		1	100
Significance: Were significance tests used to assess the preference results?		1		1		1		1		1	100
Total Score	4		4		4		4		4		

Supplementary Table 2 Risk of bias (RoB) tool for DCE studies

Subdomains	Study population Subdomain 1: Sample selection	Study population Subdomain 2: Response rate	Measurement accuracy Subdomain 1: Choice of the methodology	Measurement accuracy Subdomain 2: Administration of the methodology	Measurement accuracy Subdomain 3: Outcome presentation	Measurement accuracy & data analysis Subdomain 4: Understanding of the methodology		Overall Risk of Bias
Questions	Was the study sample selected in a manner to ensure the representativeness to the target population? • Yes • Probably yes • Probably no • No	Was the attrition sufficiently low to minimise the risk of bias? • Yes • Probably yes • Probably no • No	Was the choice of the methodology for eliciting values and preferences appropriate? • Yes • Probably yes • Probably no • No	Was the instrument administered in the intended way? • Yes • Probably yes • Probably no • No	Was the health state presentation a good representation of the health state assessed? • Yes • Probably yes • Probably no • No	Did the researchers check the understanding to the measurement techniques? • The investigator tested the understanding, and understanding was adequate. • The investigators did not formally test the understanding, but there was evidence suggesting adequate understanding. • The investigator tested the understanding, and the understanding was inadequate. • The investigators did not formally test the understanding, but there was evidence suggesting inadequate understanding.	Were the results analysed appropriately? • Yes • Probably yes • Probably no • No	
de Freitas et al. (2019)	Probably no	Probably yes	Yes	Yes	Not relevant	The investigators did not formally test the understanding	Yes	Moderate
Eliasson et al. (2017)	Probably no	Probably yes	Yes	Probably yes	Not relevant	The investigators did not formally test the understanding	Yes	Moderate
Nakayama et al. (2018)	No	Probably no	Probably yes	Probably yes	Not relevant	The investigators did not formally test the understanding	Probably yes	High
Hauber et al. (2014)	Probably no	Probably yes	Probably yes	Probably yes	Probably yes	The investigator tested the understanding	Probably yes	Moderate
Uemura et al. (2016)	Probably no	Yes	Yes	Yes	Not relevant	The investigator tested the understanding, and understanding was adequate.	Yes	Moderate

Supplementary Table 3 Validity assessment of methods used in DCEs

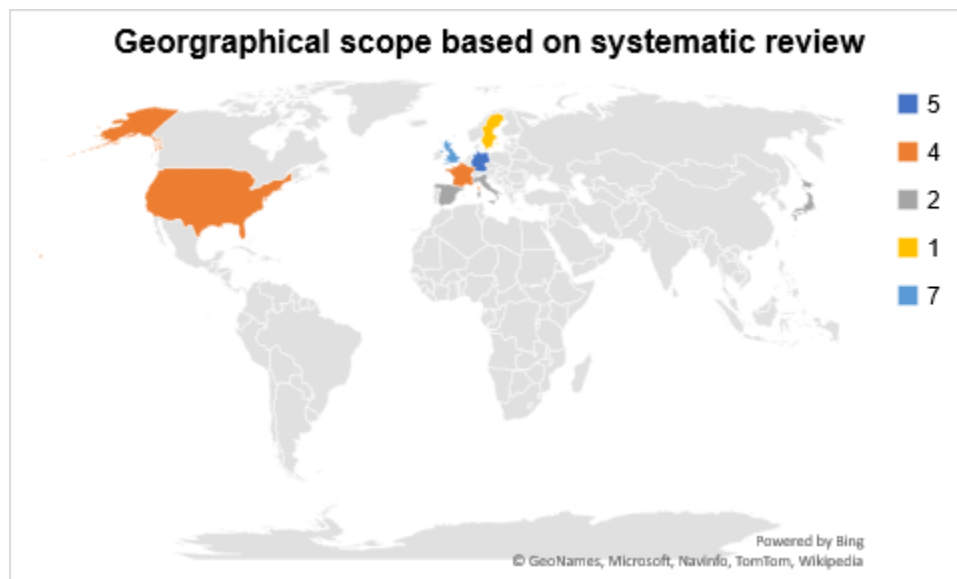
	Choice task design			Experiment al design	Conduct				Analysis			
	Attributes and levels based in qualitative work with target population	No conceptual overlap between attributes	Opt- out/status- quo option or justification of forced choice	Experimental design optimal or statistically efficient	Piloting conducted amongst target population	Target population appropriate for research objective	Sampling frame representativ e of target population	Response rate sufficient to minimise response bias	Econometri c model appropriate for choice task design	Relative attribute effects compared using common metric	Any pooled analysis from difference subgroups appropriate	Econometric model accounts for serial correlation of choice
de Freitas et al. (2019)	Green	Red	Red	Green	Green	Green	Red	Green	Green	Green	Green	Red
Eliasson et al. (2017)	Red	Red	Red	Red	Green	Green	Red	Green	Green	Red	Red	Red
Nakayama et al. (2018)	Green	Red	Red	Red	Green	Green	Red	Red	Green	Red	Red	Red
Uemura et al. (2016)	Red	Red	Red	Green	Green	Green	Red	Green	Green	Green	Green	Red
Hauber et al. (2014)	Red	Red	Red	Red	Green	Green	Red	Green	Green	Red	Red	Red

Red = criteria not met (no evidence or not enough evidence to justify the criteria in the text); Green = criteria met (the text sufficiently confirmed the criteria).

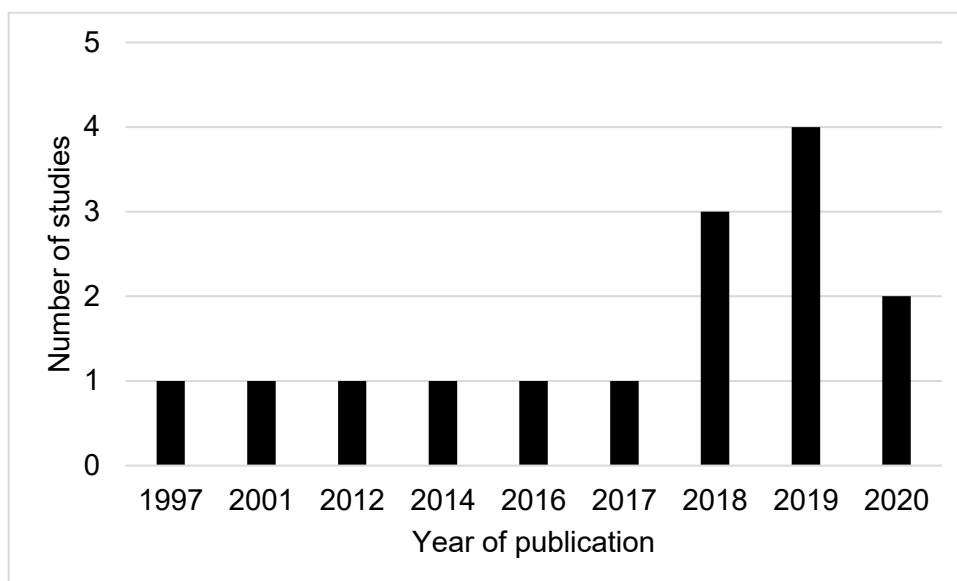
Supplementary Table 4 Standards for Reporting Qualitative Research (SRQR) criteria

Authors	Burbridge et al. (2019)	Catt et al. (2019)	Clark et al. (1997)	Clark et al. (2001)	Dearden et al. (2016)	Grunfeld et al. (2012)	Iacrossia et al. (2019)	Ito et al. (2018)	Jones et al. (2018)	Doveson et al. (2020)	
Standards for SRQR	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	% studies that fulfill the criteria
(1) Title and abstract											
Title indicate qualitative or the approach	1	0	0	0	0	1	1	1	1	1	64%
Abstract quality	1	1	0	1	1	1	1	1	1	1	92.9%
(2) Introduction											
Problem formulation	1	1	1	1	1	1	1	1	1	1	100%
Purpose or research question	1	1	1	1	1	1	1	1	1	1	100%
(3) Methods											
Qualitative approach	1	1	1	0	1	1	1	1	1	1	92.9%
Research paradigm	1	0	0	0	0	0	0	0	1	0	28.6%
Researcher characteristics and reflexivity	1	0	0	0	0	1	1	0	0	0	42.9%
Context	1	1	0	1	0	1	1	0	1	1	78.6%
Sampling strategy	0	1	0	0	0	0	1	0	0	1	
Ethical issues pertaining to human subjects	1	1	0	0	1	0	1	1	1	1	78.6%
Data collection methods	1	1	1	0	1	1	1	1	1	1	92.9%
Data collection instruments and technologies	1	1	1	0	0	1	1	0	1	1	78.6%
Units of study	1	1	1	1	1	1	1	1	1	1	100%
Data processing	1	1	1	0	0	1	1	0	1	1	78.6%

Data analysis	1	0	1	0	0	1	1	1	1	1	78.6%
Techniques to enhance trustworthiness and credibility of data	1	1	0	1	0	1	1	1	1	1	78.6%
(4) Results/Findings											
Synthesis and interpretation	1	1	1	1	1	1	1	1	1	1	100%
Links to empirical data	1	1	1	1	0	1	1	1	1	1	85.7%
Integration with prior work	1	1	1	1	1	1	1	1	1	1	100%
Implications and transferability	0	0	1	1	1	1	1	1	1	1	85.7%
Contribution(s) to the field	1	1	1	1	1	1	1	1	1	1	100%
Limitations	1	1	1	1	1	0	1	1	1	0	85.7%
(5) Other											
Conflicts of interest	1	1	0	0	1	1	1	0	1	0	64.3%
Funding	1	1	1	1	1	1	1	1	1	1	100%
Total (max 24)	22	19	15	13	14	20	22	17	22	20	
Risk of Bias	Low	High	High	High	High	Low	Low	High	Low	Low	



Supplementary Figure 1 Geographical scope based on systematic review (15 articles)



Supplementary Figure 2 The number of studies included per publication year among the final 15 articles

Quality assessment									Certainty of evidence
Outcome Assessed	Included study No.	No. patients	Studies design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	
Treatment effectiveness	27,29,30	388	Discrete Choice Experiment	Not serious	Not serious	Serious	Serious	-	⊕⊕○○ Low
Delay in time to symptoms	27,28,31	838	Discrete Choice Experiment. Time-Trade Off	Not serious	Not serious	Serious	Serious	-	⊕○○○ Very Low
Fatigue	27,28,30	570	Discrete Choice Experiment	Not serious	Serious	Serious	Serious	-	⊕○○○ Very Low

Supplementary Table 5 GRADE Criteria (Quantitative Preference Elicitation Studies)

Certainty of evidence								Confidence/ Certainty of evidence
Review Finding	No. studies	of patient s	Studies design	Methodological Limitation	Coherence	Adequacy	Relevance	
Cancer progression or survival	35-37,39,40	148	Semi-structure interviews / mixed methods	Moderate	Minor Concern	Minor Concern	Minor Concern	⊕⊕○○ Low
Fatigue	32,34-36,38	315	Semi-structure interviews / mixed methods	Moderate	Minor Concern	Minor Concern	Minor Concern	⊕⊕○○ Low
Pain	35,36	62	Semi-structure interviews / mixed methods	Moderate	Minor Concern	Serious Concern	Serious Concern	⊕○○○ Very Low
Other Symptoms	32,35,38,41	263	Semi-structure interviews / mixed methods	Moderate	Minor Concern	Serious Concern	Serious Concern	⊕○○○ Very Low

Supplementary Table 6 GRADE-CERQual (Qualitative Studies)

Supplementary Table 7 Major findings presented in each of the articles included in the review – Qualitative studies

References	Aims	Main findings/themes/policy implication
Burbridge et al. (2019)	Exploring the symptomatic experience of men who are told their castration-resistant prostate cancer has metastasised, the impact of mCRPC, and the emotional response to this diagnosis.	Most patients were willing to take medication to delay metastasis, and the most frequent symptoms were fatigue/tiredness, sexual dysfunction, and pain.
Catt et al. (2019)	Exploring experiences of treatment decisions, information provision, perceived benefits and harms of treatment and the effects of these on lives among patients with mCRPC.	Most men reported pain was their worst symptom. At 3 months, most men reported fatigue was the worst treatment-related side effect. Patients believed the treatment would delay progression, improve wellbeing, alleviate pain and extend life. As pain and other symptom management are not optimal, increased specialist nurse provision and earlier palliative care links are needed.
Clark et al. (1997)	Identifying and measuring dimensions of quality of life following the initiation of treatment for advanced prostate cancer.	Focus group and survey to develop a QoL measure - disruption of bodily integrity resulting from treatment may disrupt the maintenance of valued social identity and personal integrity. Living with a chronic illness means living with diminished personal capabilities and the potential for a spoiled social identity
Clark et al. (2001)	Understanding patients' experiences of regret of their treatment choices and closely examining factors associated with regret.	23% men expressed regret about treatment choice - those that did had worse QoL scores but not worse treatment side effects - regret associated with cancer distress. Better communication with clinicians needed.
Dearden et al. (2019)	Understanding and quantifying the experience of living with mCRPC in patients receiving AAP or ENZ in either pre-chemotherapy or post-chemo- therapy settings.	Patients in both treatment groups were largely satisfied with their treatment and reported high health status and quality of life. Self-reported fatigue severity and fatigue-related impairment were significantly lower in patients receiving AAP than patients receiving ENZ.
Grunfeld et al. (2012)	Exploring the experience and impact of andropause symptoms, particularly hot flashes, among men undergoing ADT for metastatic prostate cancer.	The occurrence of andropause symptoms, including hot flashes and night sweats, was common among the participants
Iacorossia et al. (2019)	Exploring the phenomenon of adherence to oral hormone treatment in patients with mCRPC and the factors that may influence their adherence.	Patients expressed an optimal level of adherence, which resulted from the extensive, easily understandable information received from the healthcare staff, the support of the family members as a presence and as a reminder and the few side effects related to treatment.
Ito et al. (2018)	Exploring the perspectives of men and carers of men with mHSPC who had received docetaxel	Real-world experience of docetaxel may differ from that observed in clinical trials, and that care must be taken to ensure that treatment options are tailored to the needs of individual patients to enhance not only how long patients survive but also the quality of that survival
Jones et al. (2018)	Examining the experiences of patients with advanced prostate cancer and their decision partners.	Participants believed a decision aid helped them, become more aware of their personal values, assisted in their treatment decision making, and facilitated an interactive patient - healthcare provider relationship
Doveson et al. (2020)	Exploring the perspectives of men when facing life-prolonging treatment of metastatic castration-resistant prostate cancer	When facing life-prolonging treatment of mCRPC, men's perspectives concern not only the treatment outcome but their entire lives in relation to the treatment. The importance of encouraging men at this stage to express expectations, hopes and fears regarding the treatment and the future when considering life-prolonging treatments is highlighted. Nurses working with these patients are important in the decision-making process and in evaluating treatments to detect needs for interventions.

PRISMA-P Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2,3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2,5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5-6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5-6, Suppl.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6, Suppl.
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6, Suppl.

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6, Suppl.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5-6, Suppl
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-6, Suppl
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5-6, Suppl.

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5-6, Suppl.
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5-6, Suppl.

RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8-11, Suppl
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-11, Suppl
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8-11, Suppl
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-11, Suppl
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-11, Suppl
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8-11, Suppl

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-11, Suppl
DISCUSSION			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11-13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendix C: Research Approvals for the IP2-ATLANTA study

Full Set of Project Data

IRAS Version 5.9.1

Integrated Research Application System Application Form for Other clinical trial or investigation

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting [Help](#).

Please define any terms or acronyms that might not be familiar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
IP2 - ATLANTA

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

ATLANTA - Adjuvant Treatments to the Local tumour for metastatic prostate cancer: Assessment of Novel Treatment Algorithms

A2-1. Educational projects

Name and contact details of student(s):

Student 1

	Title	Forename/Initials	Surname
	Dr	Martin John	Connor

Address 5th Floor East, Laboratory Block
Charing Cross Hospital
Fulham Palace Road

Post Code W8 8RF

E-mail m.connor@imperial.ac.uk

Telephone

Fax

Give details of the educational course or degree for which this research is being undertaken:

Name and level of course/ degree:

MBBS, BSc (Hons), MSc, MRCS

Name of educational establishment:

Imperial College London

Name and contact details of academic supervisor(s):

Academic supervisor 1

	Title	Forename/Initials	Surname
	Professor	Hashim U.	Ahmed

Address Imperial College London



Ymchwil Iechyd
a Gofal Cymru
Health and Care
Research Wales



Professor Hashim U. Ahmed
Imperial College London
5th Floor East, Laboratory Block
Fulham Palace Road
W6 8RF

Email: hra.approval@nhs.net
Research-permissions@wales.nhs.uk

14 March 2019

Dear Professor Ahmed

**HRA and Health and Care
Research Wales (HCRW)
Approval Letter**

Study title:	ATLANTA - Adjuvant Treatments to the Local tumour for metastatic prostate cancer: Assessment of Novel Treatment Algorithms
IRAS project ID:	246081
Protocol number:	18HH4804
REC reference:	19/WA/0005
Sponsor	Imperial College London

I am pleased to confirm that [HRA and Health and Care Research Wales \(HCRW\) Approval](#) has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?
You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

Following the arranging of capacity and capability, participating NHS organisations should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "*summary of assessment*" section towards the end of this letter.

You should provide, if you have not already done so, detailed instructions to each organisation as to how you will notify them that research activities may commence at site following their confirmation of capacity and capability (e.g. provision by you of a 'green light' email, formal notification following a site initiation visit, activities may commence immediately following confirmation by participating organisation, etc.).

Dr Hashim Ahmed

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england.speccommetcs@nhs.net

12 January 2021

Dear Dr Ahmed,

IRAS 246081 – ATLANTA: Adjuvant treatments to the local tumour for metastatic prostate cancer: assessment of novel treatment algorithms

Under national assurance arrangements established in October 2018, it has been agreed that when potential excess treatment costs or savings relating to specialised care are identified in a study proposal, NHS England will have the opportunity to assure the costs proposed, consider whether expenditure might fall differentially across the country to inform regional budget setting and forecasting, and identify any issues or risks to be mitigated.

NHS England has now completed its review, based on the information received in the research proposal and the SoECAT submitted, of the proposed excess treatment savings of -£7,445,469.

The completion of the financial assurance undertaken confirms the net impact of the trial has a net saving of -£6,424,500 to the NHS. The main differences to the original estimate provided in the SoECAT are:

- Omission of SABR costs from the SoECAT: increase of £819k
- Cost of Abiraterone/Enzalutamide based on 13 weeks per quarter rather than 12: reduction of £693k
- Cost of Docetaxel based on Pharmex data file (generic) rather than BNF: reduction of £481k
- Difference in radiotherapy pricing: increase of £439k
- Adjustments to standard of care costing: increase of £382k

The gross ETCs for the NHS will therefore be noted as a saving of -£6,424,500. There are therefore no (£0) net payable excess costs per patient recruited. This is because the additional costs, relating only to the provision of radiotherapy treatment, are covered by the national tariff. The gross figure effectively takes into account

NHS England and NHS Improvement



Appendix D: Copy of patient information leaflets for internal pilot RCT & embedded sub-study for IP2-ATLANTA



Version: 2.0 29 JAN 2019
Protocol Number: 18HH4804
IRAS Number: 246081
REC Reference: 19/WA/0005
Sponsor: Imperial College London
Principal Investigator: Professor Hashim Ahmed

Affix patient sticker here

ATLANTA

Additional Treatments to the Local tumour for metastatic prostate cancer:

PARTICIPANT INFORMATION SHEET

We would like to invite you to take part in a study called **ATLANTA**. Before you decide whether you would like to join the study, it is important for you to understand why the research is being done and what it will involve. We will go through this participant information leaflet with you and answer any questions you might have. You do not have to decide straight away.

Before you decide whether to take part in this study, it is important for you to understand why the study is being done and what it will involve. Please take time to read the following information carefully and if you wish to, with your GP, family or other people.

PART 1 tells you the purpose of this study and what will happen if you choose to take part

PART 2 gives you more detailed information about the conduct of the study

Please ask us if there is anything that is not clear or if you would like more information. You have as long as you need to decide whether you want to take part.

PART 1

1. WHAT IS THE PURPOSE OF THE ATLANTA STUDY?

You have been diagnosed with prostate cancer that has spread into other areas of the body outside the prostate gland. This is called advanced or metastatic prostate cancer. Your doctor has discussed your treatment options with you and it has been agreed that you would normally be started on **standard treatment** that usually involves **medical therapy**. Medical therapy involves hormone therapy and sometimes chemotherapy as well. As part of their standard treatment some men may also receive additional treatments such as radiotherapy to the prostate. The main cancer in the prostate is not normally treated in most cases because it is believed that there is no benefit from doing this. Recently there is some evidence that treating this main cancer might be beneficial to men. This is because by treating the main cancer inside the prostate we might reduce the amount of cancer cells in the rest of the body and remove the cells that can grow despite **standard treatment**. Some studies have shown that the main cancer in the prostate can send growth signals to the areas of cancer outside the prostate. Recent studies have also shown that some men might benefit from having the areas of cancer outside of the prostate as well.

We do not know if treating the main cancer inside the prostate, or whether treating areas of spread in some men, really does benefit men. We want to test this idea in the **ATLANTA** study. We can treat the prostate with traditional **radical therapy** (like surgery or radiotherapy) even if the cancer has spread. We can also use treatments that heat or freeze the prostate - this is called **ablation**. All these treatments are effective in treating prostate cancer that has not spread but we do not know if they have any benefit for men in whom the cancer has spread outside the prostate gland. We are also not sure about the side-effects that might happen when we use radical therapy or ablation therapy on men who have advanced prostate cancer. In this study, we are trying to find out if local treatment using radical therapy or ablation therapy is safe compared to standard treatment. We also want to see how effective local therapy, plus treatment to metastases in some men, is compared to standard therapy.

ATLANTA aims to find the best treatment for the type of prostate cancer you have. We are comparing standard treatment to standard treatment with either additional radical therapy (radiotherapy or prostatectomy) or with ablation therapy (heat or freeze). Some men in the radical therapy and ablation therapy groups will also get treatment to metastases. We want to find out what differences there are between these three approaches in terms of treating the cancer as well as the side effects and quality of life impact between the three approaches.

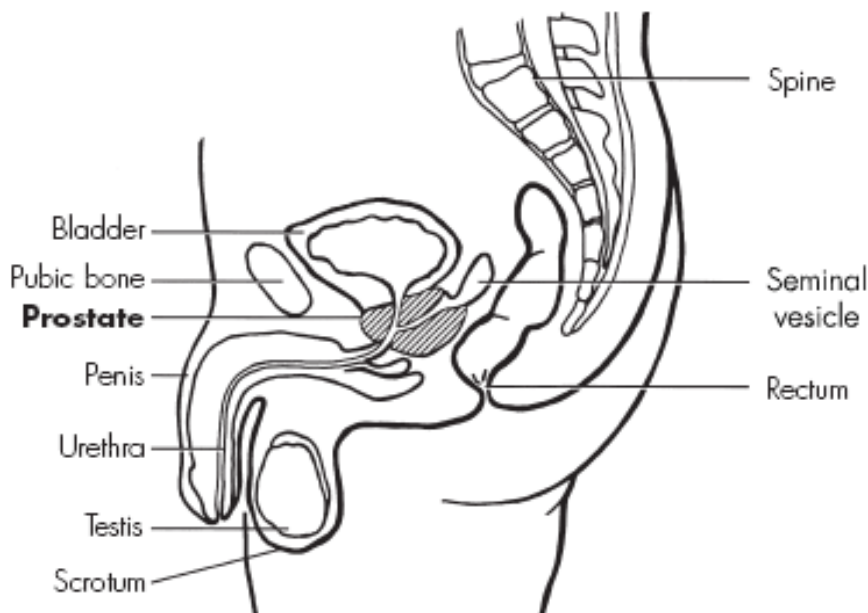
There will be two stages to the **ATLANTA** study. The initial pilot stage aims to see if men with advanced prostate cancer are willing to participate in the study to make sure that a bigger study can be carried out comparing these treatments. We will aim to recruit 80 patients for the pilot and then 918 patients for the bigger study. Your doctor or research nurse will let you know which stage of the study you would be in. If you take part in the pilot, your results and data will still be included in the same way as those patients who take part later and you will receive the same treatments as patients in stage 2 of the study.

2. WHAT IS THE PROSTATE?

The prostate is an organ that forms part of the male reproductive system. It is located immediately below the bladder, just in front of the bowel. Its main function is to produce fluid that makes up part

of the semen and may help enrich sperm. In younger men the prostate is about the size of a walnut. It surrounds the beginning of the urethra, the tube that carries urine from the bladder to the penis. The nerves that control erections surround the prostate.

Figure 1: Location of the prostate



3. WHY HAVE I BEEN ASKED TO JOIN THE ATLANTA STUDY?

You have been asked to consider joining the study because you have had a diagnosis of prostate cancer that has unfortunately spread into other areas of the body. Looking at your results, the research team think that you may be suitable for the new treatments that we are testing in the study.

4. DO I HAVE TO TAKE PART?

No. It is completely up to you to decide whether or not to join the **ATLANTA** study. If you decide to take part, you are still free to withdraw at any time without giving a reason. Whether you take part or not it will not affect the standard of care you receive.

5. WHAT WILL HAPPEN TO ME IF I DECIDE TO TAKE PART?

Normally men would receive standard treatment for their prostate cancer. This is drug therapy and in some cases radiotherapy to prostate. In this study, we need to compare men who have this standard therapy with those who have standard drug treatment with either radical therapy (radiotherapy or surgery to the prostate) or with ablation therapy (usually either heating or freezing the prostate). These will be combined with treatment to the areas of cancer spread in some cases. These other approaches are not available outside of a clinical trial as they remain unproven. All men as a minimum will get the standard drug treatment. You will have been given this information leaflet

about ATLANTA when you visited your doctor at your routine clinic visit in the hospital. You can take the information leaflet away with you, to think more about joining the study.

If after routine blood tests, scans (imaging) and prostate biopsies, you are considered eligible to take part in the study, you will be invited to attend an information appointment to discuss the **ATLANTA** study further. We have summarised what taking part in this study would involve in section 7 onwards. If you are not eligible for the **ATLANTA** study, you will be informed by your doctor and continue with standard treatment.

6. WHAT ARE THE DIFFERENT TREATMENTS IN ATLANTA?

There are three different treatments in **ATLANTA** and if you take part, the chance of receiving one of these 3 treatment approaches will be through a process called randomisation. Randomisation is explained in section 7 of this information sheet:

STANDARD TREATMENT ALONE

This usually involves taking tablets or injections or the combination of the tablets and injections. This is a type of hormone therapy. These medications lower the testosterone hormone levels in your body. As prostate cancer relies on testosterone to grow, drug therapy like this can shrink the tumours in the body and keep them under control. Some men might also be suitable for, and choose to have additional chemotherapy. Some men may be suitable for radiotherapy to the prostate. Your doctor will discuss exactly what type of standard treatment you are eligible for. Some prostate cancer cells can, after a time, grow despite this treatment. Usually, other drug therapies can be used at this time.

Advantages

- Can be easily taken or given as they do not involve procedures or operations
- Can keep the cancer in control with no risk of incontinence or back passage symptoms, such as bleeding, and changes in normal bowel habits in those men who do not have local radiotherapy

Disadvantages

- Hormone therapy has side-effects like tiredness, weight gain, breast swelling and breast tenderness. Prolonged use can sometimes lead to diabetes, heart disease and bone-thinning
- Chemotherapy, if given, can carry risk of tiredness and a greater susceptibility to infections
- Some cancer cells can start to grow even with hormone and chemotherapy
- Some men who have radiotherapy to the prostate can have urinary symptoms and bowel symptoms

STANDARD TREATMENT FOLLOWED BY RADICAL THERAPY

The radical treatment is either surgery or radiotherapy and in some cases both. The whole prostate is treated. Radiotherapy involves using x-rays to treat the prostate over several visits in hospital. Surgery involves open or keyhole removal of the prostate completely, under general anaesthetic.

Advantages

- The whole prostate is treated using traditional treatments that are known to work in cancer that has not spread to other areas of the body

Disadvantages

- Side-effects can happen. After radiotherapy and surgery these can include incontinence and erectile dysfunction. After radiotherapy, back passage symptoms like bleeding, diarrhoea or discomfort can also occur. Surgery carries some risk of the operation itself.
- Side-effects of drug therapy can still occur
- Cancer cells can sometimes be left behind after surgery or some cells might be resistant to radiotherapy

STANDARD TREATMENT FOLLOWED BY ABLATION THERAPY

Ablation works by using sound waves (high-intensity focused ultrasound, HIFU) to heat or using ice (cryotherapy) to freeze areas of tissue where the cancer has been located. It is a day procedure and does not involve cuts to skin. The procedure is performed under general anaesthetic. HIFU treatment involves a probe that will be introduced in your rectum, similar to the one you had during your prostate biopsies. HIFU raises the temperature of the prostate to 70 to 90 degrees centigrade. Cryotherapy involves inserting an ultrasound probe into the rectum followed by needles placed through the skin above the rectum into the prostate. The needles are hollow and a gas is passed down to freeze and kill the cells. Since you will be under the general anaesthetic, you will not feel anything. The treatment lasts between 1-3 hours and can often be repeated once, if necessary.

Advantages

- Quicker recovery than radical therapy
- Has fewer urinary, erectile and bowel side-effects when used in men with prostate cancer that has not spread to other areas of the body
- Is effective in treating prostate cancer and can be targeted to either the whole prostate or certain areas affected by cancer depending on each patient.

Disadvantages

- Can cause side-effects such as urinary leakage requiring pads or erectile dysfunction in some men. Rarely it can cause back passage side-effects.
- Cancer cells can sometimes be left behind and further ablation therapy might be needed
- Is a newer form of treatment compared to radical therapy so less is known about how effective it is in the long-term

7. WHAT WILL HAPPEN TO ME IN THE STUDY?

PRE-SCREENING:

Prior to enrolment you must have undergone standard of care (SOC) investigations which include imaging tests such as a MRI, Computer Tomography (CT), X-rays or any other whole body imaging scans. Any tissue, blood and urine samples, and imaging that have been taken prior to you taking part may be used in the study also, and may be used for bio-banking (bio banking is an optional consent – please see section 11 for further details on optional consent) . Additional biopsies taken are decided by your doctors at the multidisciplinary team meeting and will be discussed with you. Some imaging tests can also be performed within the study at your first study visit, or soon after, if these imaging tests have not been done already.

Standard of care drug therapy may have been started up to 3 months before you sign the consent form to take part. This includes but is not limited to hormone therapy or chemotherapy. The decision

for which drug therapy will be used will be by your treating doctors and yourself. You will receive standard of care drug therapy regardless of whether or not you decide to join this study.

CONSENT AND SCREENING TESTS:

Once you have discussed the study with the research team and after you have signed the ATLANTA consent form, we may need to do a medical and physical examination, if required. You will then be randomised to a treatment arm. Your research nurse or your doctor will tell you which treatment arm you have been assigned to.

Once randomised your research nurse or your doctor will take some detail about you and the prostate cancer. Blood tests may be taken to measure PSA and testosterone hormone levels.

In addition to questions related to the prostate cancer you will also be asked questions regarding your general health. This means you will be asked to fill in questionnaires that tell us what your urinary, sexual and bowel function is like as well as your general quality of life. These will include the following:

- The International Prostate Symptom Score (IPSS)
- International Index of Erectile Function (IIEF15)
- EPIC The Expanded Prostate Cancer Index Composite Bowel and Bladder (EPIC)
- EQ-5D-5L (quality of life and the European Organisation for the Research and Treatment of Cancer (EORTC) questionnaires.

These questionnaires may also be sent to you via post or electronically via email if you wish. You can take as much time as possible to complete these questionnaires. You should continue to complete these for up to 4 years after randomisation

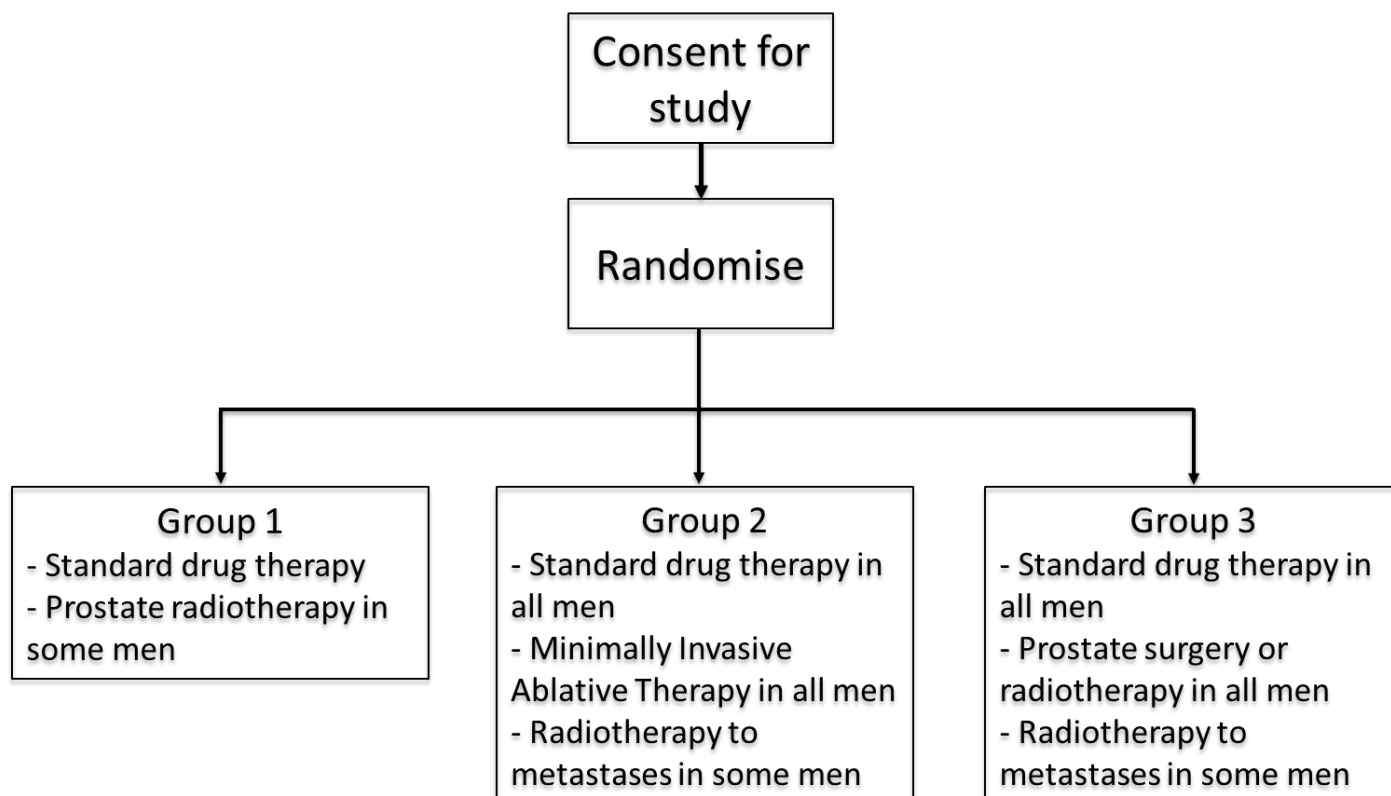
If you have agreed on the optional consent form for additional blood (3 table spoons) and urine (1 complete voided) samples to be taken, these will be taken at this visit also.

RANDOMISATION:

The best way to compare the three treatment approaches in a research study is to have similar groups of patients allocated to either i) standard drug treatment and some men getting prostate radiotherapy, or ii) standard drug treatment plus radical prostate therapy and some men getting metastases therapy or iii) standard drug treatment plus prostate ablation therapy and some men getting metastases therapy.

The only way to make sure that the groups of patients are as similar as possible is to have the allocation decided by chance: this is called randomisation. This means that you will have an equal chance of having of the above three treatment approaches. Randomisation ensures that the treatments are compared fairly and is carried out using a study database software known as InForm. It is important for the study that you only agree to take part if you believe you would be prepared to accept any of the three treatments. Whichever treatment you are allocated to, doctors experienced in treating prostate cancer will treat you with the best possible care.

Figure 2: Randomisation



CONSENT AND SCREENING VISIT

If you are interested in taking part in this study we will invite you to attend a consent and screening visit with your local hospital research team. This will start with a consultation with one of the clinical research team. You will have the opportunity to raise any questions again, which you may have about the study and if you wish you may sign the consent form if you are happy to take part.

A prostate MRI will be performed during this visit 1 or soon after on another day if not already performed previously.

Once you consent, we will also randomise you to a treatment arm. Once randomised we will record some details about you and take a medical history and may need to examine you. A blood test will be taken to measure PSA and testosterone levels. A record of other relevant medications will also be taken.

During this visit, we will also ask you to fill out the patient questionnaires that have been detailed above.

Finally, we will ask you if you would like to consider optional Consent for exploratory research. Please see section 11 for further details.

In order to reduce the burden of visits for you we will perform all these screening tests/consent and assessments in a single visit. The MRI, if it needs to be repeated, might need to be on a different day.

TREATMENT:

For up to 6 months at the start of the study you will have standard of care treatment and so you will not be denied any drug treatment that has already proven beneficial. This treatment will normally be either hormone therapy and in some cases additional chemotherapy. What therapy will be most beneficial to you will be decided and discussed with you by your treating clinical team.

After this initial period of standard drug treatment you will then move onto your randomised therapy. If you are randomised to group 2 or 3, 6 to 9 months after the drug treatment you will have another prostate MRI and prostate biopsy to see if there is still cancer left in the prostate. Men who do not have any local cancer left inside the prostate can avoid having radical or ablation therapy to the prostate. One of the aims of the pilot stage will be to find out if MRI and biopsies should continue to the main stage.

If your biopsies do not show any cancer inside the prostate we will then continue with your standard of care drug treatment (even if you were randomised to an ablative or radical therapy) and you will have regular visits with your doctor. If are eligible for metastases therapy, you will have continue to have this in groups 2 and 3.

If at this stage your biopsies show cancer is still present inside the prostate you will undergo the local intervention that you have been randomly allocated to. This will vary dependent on the type of intervention:

- Radical therapy (surgery or radiotherapy). Your doctor and you will decide the most appropriate radical therapy for you, whether it be surgery or radiotherapy. Radiotherapy involves a number of weekday visits over 4 to 6 weeks to deliver fractions of the total radiation dose. It may include radiotherapy to the lymph node as well as to the prostate. Surgery involves keyhole or open surgery under general anaesthetic with admission to hospital for a few days. In men undergoing prostatectomy, the lymph nodes may be removed during the operation itself. Surgery may need to be done at an expert centre and not at your normal hospital although other visits will be at your normal hospital.

- Ablation therapy involves treatment under general anaesthetic with most men able to go home the same day. In men undergoing ablation, the lymph nodes may be treated with radiotherapy. Ablation therapy may need to be done at an expert centre elsewhere and not at your normal hospital, although other visits will be at your normal hospital. Some travel costs can be reimbursed for this so ask your research team for details.

A date for the local treatment will be booked in accordance with the local hospitals waiting lists. Removal of the urethral catheter after minimally invasive therapy or radical prostatectomy will happen after a minimum period of 7-days during a hospital visit or it can also be removed either at your local GP surgery.

If you have been randomised to the standard of care group 1, we will continue your drug therapy, and some men in this group may be eligible for local radiotherapy. You will have follow-up within the study but you will not receive any additional treatments unless at some point in the future your cancer is found to be progressing.

Please see figure 3, which shows the tests performed at each visit.

Figure 3: Tests taken at each study visit



8. WHAT HAPPENS IF I WANT TO CHOOSE WHICH TREATMENT I GET?

At the end of the discussion, you may feel that you want to choose your treatment. Radical therapy or ablation therapy, with metastases therapy in some men, can only be offered to men where prostate cancer has spread to others areas of the body within a clinical trial. They are not approved for routine use in the NHS unless they show benefit in studies like **ATLANTA**. You will still get the standard treatment in all three groups so you will not be denied any treatment that is already approved in standard clinical care.

9. WHAT HAPPENS DURING FOLLOW UP?

Whatever group you are in, you will be under the care of your medical team and you will have follow up regularly. As part of the study you will be asked to complete several questionnaires over the course of the study.

Follow-up will consist of 3 monthly serum Prostate Specific Antigen (PSA) tests, clinical reviews, and patient reported outcome measures (PROMS) questionnaires in the first year, and 6-monthly thereafter for a maximum of 4 years. Further imaging tests may be performed by your treating doctors.

If the study does not proceed to the bigger stage following the analysis of the initial pilot stage, you will be followed up for a period of 6 months after which you will then receive standard follow-up by your treating doctors.

10. WHAT IF THE CANCER GETS WORSE DURING THE STUDY?

You will be monitored carefully by the medical and research team, but you should always contact your GP or a member of the study team if you have any concerns. If your PSA blood test results suggest that your disease might have got worse, the doctors might organise new tests, x-rays or scans to assess things further. Your medical team will consider other treatments that they will discuss with you.

11. WHAT ELSE WILL I HAVE TO DO?

THERE ARE SOME ADDITIONAL OPTIONAL RESEARCH REQUESTS.

PSMA PET Scan

- We will also ask men in the pilot stage of **ATLANTA** if they are willing to undergo a new whole body scan called a PSMA PET scan. We want to see if this new scan might be as accurate as prostate biopsies and normal body scans like MRI, CT or bone-scans. This is optional and you do not need to agree to do this to take part in the study. If you agree for this PSMA PET scan you will have one soon after consent and another scan will be done before your prostate biopsies at 6-9 months after consent. This involves two extra visits for the two scans. Exactly what the PSMA PET scan involves will be discussed with you in detail, and a separate participant information leaflet and consent form will be provided

for you if you decide to take part in this sub-study. Some travel costs can be reimbursed for these two extra visits so ask your research team about this.

Extra blood and urine samples

- We will ask you to provide extra blood and urine samples to be collected and stored for research (up to 50ml of blood and up to 250 ml of urine (one cup)). If you take part in **ATLANTA**, we would like your permission to use these stored blood and urine samples for prostate cancer research. These research studies are not expected to benefit you, but may help to improve the diagnosis and/or the treatment of prostate cancer for future patients.

Bio banking

- The laboratories for these tests may be based in the UK or abroad which would require us to transport your samples outside of your local hospital. Any extra blood and urine samples that you give us for these research studies will be stored securely in Imperial College Healthcare Biobanks or another biobank in the UK for a period of up to 10 years (or as per local policy) so that we can repeat any tests on them if necessary, and use them to look at new tests for prostate cancer. These samples will be identified using a special study number assigned to you, in such a way that the scientists analysing them will not be able to find out your identity. This research would be carried out only after approval from an independent research ethics committee and would involve extracting DNA or other chemicals from the samples to see whether the tests make it is easier to detect or monitor the effect of treatment for prostate cancer. These samples would be considered a gift from you and no personal results from these tests or studies could be provided to you.

Biopsy samples

- We would also like your approval to store any biopsy samples that have been taken as part of your care. We may use these samples in a similar way to the blood and urine to look at new tests for prostate cancer.

This research would be carried out only after approval from an independent research ethics committee and would involve extracting DNA and non- DNA or other chemicals from the samples to see whether the tests make it is easier to detect or monitor the effect of treatment for prostate cancer. These samples would be considered a gift from you and no personal results from these tests or studies could be provided to you.

Bio banking

The laboratories for these tests may be based in the UK or abroad which would require us to transport your samples outside of your local hospital therefore all samples taken will be transferred to the Imperial College Healthcare Tissue Bank, Institute of Cancer Research London or any other biobank in the UK and will be used for histological, genomic and epigenetic analysis and for ethically approved future studies by our team or other scientists interested in prostate cancer research. Samples will not have any personal identifiable information written on them,

but will have your study number only. Therefore, no delegated member of staff at the central study team will be able to identify you from your samples

Imaging Scan Data

- Imaging scans are performed as part of this study. We would also like to know if you are willing for us to store and use your scan data to see if new ways of looking at these scans can detect cancer better in the future.

Health Status

- We will also ask you if you are happy to give consent for your health status to be followed up over time. This will be done by linking your name and NHS number with records held by the NHS and maintained by the NHS Information Centre and the NHS Central Register or any applicable NHS information system. This will allow us to track what happens after the study finishes to see if anyone gets other cancer in future and about the type of cancer and the treatment they have had. Results of your optional health status check will also help us in any future upcoming studies. This does not mean that that you will need to make any follow up visits.

Partial Postcode

- We would also like to know if you are willing for us to record and store your partial postcode. This part of the study is also optional. The postcode will be used to study socioeconomic status and performance of the recruitment across different areas of **ATLANTA** participants. Your postcode will be collected at study registration and kept confidential in a secure and password protected database.

Future Contact

- As prostate cancer is often a slow-growing disease which may not present for many years we will also ask if you are happy to keep personal data be stored or accessed on the NHSCR- see section 14 for more detail.

All of the above in section 11 are optional and you do not need to consent to them. If you do not wish to give this permission, you can still participate in the ATLANTA study.

12. WHAT ARE THE POTENTIAL BENEFITS OF TAKING PART IN ATLANTA?

We cannot guarantee that participating in this study will be of direct benefit to you. The main benefit of you taking part will be the information that we can gather. This may help us improve treatment options for men with prostate cancer like you in the future.

13. WHAT ARE THE POSSIBLE DISADVANTAGES AND RISKS IN TAKING PART?

The potential risks and disadvantages for each treatment are listed above, in Section 6. Please read through them carefully, and ask as many questions as you wish at your next appointment.

14. WHAT HAPPENS WHEN THE STUDY STOPS?

Once the study is completed, you will continue to be looked after by the clinical team in hospital. It would also be great for us to know how you are doing even after your participation in the study has stopped so we can follow up on your health status to help future related research. For this reason, we will ask for your consent for your name to be used to gather information from records held by the NHS and maintained by the NHS Information Centre and the NHS Central Register or any applicable NHS information system (including linkage to routine hospital admission data). In order for us to do this we provide identifiable information for us to trace you on the National Health Service Care Register (NHSCR) for up to 10 years (this is an optional part of the study) after study end date.

15. CAN I CHANGE MY MIND?

Yes, you can decide not to have any of the procedures at any time. Depending on when you change your mind your doctor will recommend that you continue with standard treatment.

This completes Part 1 of the information sheet. If you are considering participating in the study, please continue to read the additional information in Part 2 before making your decision.

PART 2

1. WHAT HAPPENS IF RELEVANT NEW INFORMATION BECOMES AVAILABLE?

Data from this study will be monitored regularly by scientists who are independent of the study. Sometimes, during the course of a research project, new information becomes available about the procedures that are being studied. If you are in the study and this happens, your study doctor will tell you about it and discuss with you whether you want to, or should, continue in the study. If you decide not to carry on, your study doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign a consent form that includes new information. Also, on receiving new information your study doctor might consider it to be in your best interests to stop the medical procedures in the study. If so, they will explain the reasons and arrange for your care to continue another way. If the study is stopped for any other reason, you will be told why and your doctor will arrange for your continuing care. If any relevant new information becomes available after you have had all of your procedures and you have received your results, it will not affect you as you will no longer be in the study.

As described earlier, you can stop taking part in the study at any time without giving a reason and without your rights or care being affected in any way. If you do decide to withdraw then you should inform your doctor of your decision so that appropriate follow up can be arranged.

2. WHAT IF SOMETHING GOES WRONG?

Every care will be taken in the course of this study. However, in the unlikely event that you are injured by taking part.

Imperial College London holds insurance policies which apply to this study. If you experience harm or injury as a result of taking part in this study, you will be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator (Professor Hashim Ahmed on 0203 311 1673 or via email Atlanta@imperial.ac.uk). The normal National Health Service mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial College, Joint Research Compliance Office

If you have any concerns about any aspect of the way you have been approached or treated by members of staff or about any side effects (adverse events) you may have experienced due to your participation in the clinical trial, the normal National Health Service complaints mechanisms are available to you including your local hospitals' Patient Advice and Liaison Service (PALS) who can be contacted on **020 3313 0088**. Please ask your study doctor if you would like more information on this. Details can also be obtained from the Department of Health website (<http://www.dh.gov.uk>).

3. WHAT WILL HAPPEN IF I LOSE THE CAPACITY TO CONSENT DURING THE STUDY?

In the unlikely event that you lose capacity to consent during your participation in the study, you would be withdrawn from the study. Any data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected.

4. WILL MY PARTICIPATION IN THE STUDY BE KEPT CONFIDENTIAL?

Imperial College London is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Imperial College London will keep identifiable information about you for the purpose of the study for 10 years after the study has finished in relation to data subject consent forms.

Further information on Imperial College London's retention periods may be found at <https://www.imperial.ac.uk/media/imperial-college/administration-and-supportservices/records-and-archives/public/RetentionSchedule.pdf>.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. You can find out more about how we use your information by contacting Professor Hashim Ahmed on 0203 311 1673 or via e-mail at Hashim.ahmed@nhs.net.

LEGAL BASIS

As a university we use personally-identifiable information to conduct research to improve health, care and services. As a publicly-funded organisation, we have to ensure that it is in the public interest when we use personally-identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use your data in the ways needed to conduct and analyse the research study. Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research.

INTERNATIONAL TRANSFERS

There may be a requirement to transfer information to countries outside the European Economic Area (for example, to a research partner). Where this information contains your personal data, Imperial College London will ensure that it is transferred in accordance with data protection legislation. If the data is transferred to a country which is not subject to a European Commission (EC) adequacy decision in respect of its data protection standards, Imperial College London will enter into a data sharing agreement with the recipient organisation that incorporates EC approved standard contractual clauses that safeguard how your personal data is processed.

CONTACT US

If you wish to raise a complaint on how we have handled your personal data or if you want to find out more about how we use your information, please contact Imperial College London's Data Protection Officer via email at dpo@imperial.ac.uk, via telephone on 020 7594 3502 and via post at Imperial College London, Data Protection Officer, Faculty Building Level 4, London SW7 2AZ. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO). The ICO does recommend that you seek to resolve matters with the data controller (us) first before involving the regulator.

As it is standard practice to inform your GP about your participation in a research study, we will ask your permission to do this. If you do not give this permission, you cannot participate in **ATLANTA**.

Imperial College Healthcare NHS Trust will keep your name, NHS number and contact details confidential and will not pass this information to Imperial College London. **Imperial College Healthcare NHS Trust** will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Certain individuals from Imperial College London and regulatory organisations may look at your medical and research records to check the accuracy of the research study. Imperial College London will only receive information without any identifying information. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

Imperial College Healthcare NHS Trust will keep identifiable information about you from this study for 10 years after the study has finished.

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

Your information could be used for research in any aspect of health or care, and could be combined with information about you from other sources held by researchers, the NHS or government. Where this information could identify you, the information will be held securely with strict arrangements about who can access the information. The information will only be used for the purpose of health and care research, or to contact you about future opportunities to participate in research. It will not be used to make decisions about future services available to you, such as insurance. Where there is a risk that you can be identified your data will only be used in research that has been independently reviewed by an ethics committee.

All data will be identified by a study number which can link to your other details. This link will be held separately from all other data collected on you. If you consent to take part in this study, we will collect information on you and your test results, and we will enter it onto a study database held at Imperial College Trials Unit, London. This is for the purposes of analysing the results. Employees of the Imperial Clinical Trials Unit (ICTU) and staff from Imperial College London Joint Research Compliance Office may need to examine your medical records to ensure the study is being run properly, but your confidentiality will be protected at all times, and your name will not be disclosed outside the study. Your information may also be looked at by an independent quality control agency to check that the study is being carried out correctly.

5. WHO IS ORGANISING AND FUNDING THE STUDY?

ATLANTA is funded by a Wellcome Trust Senior Clinical Research Fellowship awarded to Professor Ahmed and Imperial College London (grant code: 204998/Z/16/Z). The study is being carried out by Imperial College London. In addition to this the PSMA PET scan is being funded by a National

Institute of Health Research (NIHR) Imperial College London Biomedical Research Centre (BRC) Grant. The researchers include a team of specialised doctors, scientists, technical staff and nurses. Our team is experienced and has conducted similar research in this field.

6. WHO HAS REVIEWED THE STUDY?

Patients and expert reviewers have looked at the study both before the funding was awarded and after.

This study was given a favourable ethical opinion for conduct in the NHS by the WALES REC5 Ethics Committee. This committee is responsible for making sure that research takes place in a way that protects the patients' rights and welfare.

7. WILL I GET PAID FOR TAKING PART?

There is no payment for taking part in this study. Some visits might have some travel costs reimburse which your research team will explain.

8. WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

When the study is completed the results will be analysed and presented at international meetings before being published in a medical journal. Large studies such as this take many years to complete and for the final results to appear. When the study results are concluded, they will be presented by clinicians and patient groups, and posted on our website for patients to access. Our website is: <http://imperialprostate.org.uk/atlanta>

A newsletter presenting the salient findings will be written, and circulated to all consenting participants by email or letter depending on their preferences. Findings will be presented through the websites and newsletter of a number of supporting organisations of which our team members have links including Prostate Cancer UK, Maggie's support group, Pelican Cancer Foundation and CRUK. The social media presence of organisations involved will be used to highlight news about the trial also.

9. WHAT DO I HAVE TO DO NOW?

You will be given as much time as you feel you need to discuss any issues or questions involving this research during your appointment with the researchers and study nurses. If you have any concerns or wish to discuss the study further, please contact:

Study Manager

Ms Johanna Sukumar
Imperial College London
Charing Cross Hospital
Fulham Palace Road, London
W6 8RP
London
Tel: 0203 311 5473

Sub-Investigator & National CRF

Mr Martin Connor
Imperial College London
Charing Cross Hospital
Fulham Palace Road, London
W6 8RP
London
Tel: 0203 311 5473

Chief/Principal Investigator

Professor Hashim U. Ahmed,
Imperial College London,
Charing Cross Hospital
Fulham Palace Road, London
W6 8RP
London
Tel: 0203 311 5473

Email: Atlanta@imperial.ac.uk

Email: Atlanta@imperial.ac.uk

Email: Atlanta@imperial.ac.uk

WE WILL GIVE YOU A COPY OF THIS INFORMATION AND A COPY OF THE SIGNED CONSENT FORM TO KEEP.

THANK YOU FOR TAKING THE TIME TO READ THIS INFORMATION SHEET

PARTICIPANT INFORMATION SHEET

Short title: ⁶⁸[Ga] PSMA in MPC (Sub-study to ATLANTA)

Invitation

We would like to invite you to take part in an imaging research study in prostate cancer sponsored by Imperial College London. Before you decide, it is important for you to understand why this research is being carried out and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives, and your GP if you wish. Please ask us if there is anything that is not clear or if you would like more information. Please take time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of the Study?

We are looking to see how prostate cancer cells respond/react to treatment. We would do this by looking at the information obtained from a special scan & from a blood and urine sample, done on 2 separate visits at the Clinical Imaging Facility at Hammersmith Hospital. This study uses a PET/CT (Positron Emission/ Computerized Tomography) scanner along with a very small amount of an injected, radioactive substance called a “tracer”. These tracers can detect different processes occurring in the body. This type of scan may help in detecting tumour in the prostate gland and in the surrounding tissues. In this study, a tracer called ⁶⁸Gallium-PSMA (prostate specific membrane antigen ligand) will be used. We believe that as the prostate cancer tumour cells express a protein Prostate Specific membrane Antigen (PSMA), they will take up more of this tracer. The PET/CT scanner can detect the tracer in your body and produce images from the radioactivity taken in by the tumour cells. We believe that as the prostate cancer cells respond to treatment, we will see a change in the amount of tracer that cancer cells take in and we may therefore be able to get more information about the tumour and if it has spread elsewhere. Some patients with prostate cancer have specific markers in their cell DNA (deoxyribonucleic acid). DNA helps cells to make substances called proteins, which the cells need to live. The blood and urine samples will help us look for this marker.

Why have I been asked to join the ⁶⁸[Ga] PSMA in MPC Sub-Study?

You have already agreed to participate in the ATLANTA study. When you consented to ATLANTA you were also informed of this sub-study looking at the role of PSMA PET imaging following treatment. We are hoping to recruit about 25 men to take part in this sub-study. This patient information sheet includes more detailed information about this sub-study. Even though you indicated in the ATLANTA consent form that you may be willing to participate in this PSMA PET sub-study, you do not have to. Refusing to take part in this PSMA PET sub-study does not impact in any way your participation in the main ATLANTA study.

You have been invited for this study because you need to undergo treatment for your prostate cancer. Your participation in this study will not affect your treatment or delay your treatment. The results of this scan would not be used to alter the course of treatment your doctor has planned for you.

Do I have to take part?

No. Taking part in the study is voluntary and you are free to withdraw at any time without giving a reason. Not taking part, or stopping at any time if you have started the study, will not affect the care you receive.

If you decide that you would like to take part, you will be given this information sheet to keep and be asked to sign a consent form after you have discussed any questions you may still have with one of the research doctors. With your permission, we will inform your General Practitioner that you are taking part in the study.

What will happen to me if I take part and what will I need to do?

After you have agreed to take part and signed a consent form, we will arrange for you to have a PET-CT scan session at the Clinical Imaging Facility at Hammersmith Hospital. For this study you will be asked to have two PET-CT scans. One before you start your treatment and one after you finish your treatment.

We will arrange the dates of the scan with you in advance. At each of the two PET/CT scan visits, we will take a blood and a urine sample. We will take in total 60mls of blood (4 tablespoons) and 50-100mls (3-7 tablespoons) of urine over both scans. These samples will be anonymised using a unique subject identifier so that they can be used for analysis of specific markers of prostate cancer. Samples may be stored for future research if required according to Imperial College Healthcare Tissue Bank regulations for a period of up to 10 years. Sample analysis will take place at Imperial College London and the Institute of Cancer Research London. This research would only be carried out after approval from an independent research ethics committee.

Before the PET-CT scan, we will insert a very fine plastic needle (cannula) into the vein of the arm, which will be used for injecting the radioactive tracer, ⁶⁸[Ga]PSMA. The PET/CT scan involves injecting the tracer (via cannula in the arm) and waiting for 20-30 minutes. After this time, you will be asked to lie flat on the PET/CT scanner bed. The bed will move into a short tunnel and then we will start scanning. The scan will last about 24-30 minutes. You will be asked to lie still during the scan, as movement may cause a blurred picture. You are free to fall asleep during the scan if you wish. You will be able to listen to music during the scan and can bring your own CDs/ mp3 player.

There is no PET scan related follow up and after each scan, you should keep the appointment you have with your clinical team to proceed with your treatment as planned. We will compare the PET-CT scan results with your other imaging and the results of any biopsy you have after your treatment has finished. The results of the scan **will not be revealed to the clinical team or you**, and will not influence the treatment you will receive. This is because we do not know whether the PSMA PET scans are useful in making decisions about your prostate cancer treatment. This study is trying to work that out.

What do I have to do?

You must be willing to attend the two scheduled scan visits at Hammersmith Hospital, London. Please continue with any normal medication as usual. We will provide a taxi for you and a friend/ relative to and from the study visits, or will pay your travel expenses as needed.

What are the possible disadvantages and risks of taking part?

The total amount of radiation given in this study is about the same as receiving approximately 9 years of the natural levels of background radioactivity in the UK. Naturally occurring background radiation comes from sources, which we are surrounded by such as rays from the sun and the ground. It is similar to a routine PET-CT scan and represents very little additional risk to someone like you. Some discomfort may occur when the cannula is inserted into your arm. Mild bruising may occur around this site but should resolve within a few days. We will ensure you are comfortable before we start scanning you.

You should be aware that if we find anything unexpected during your clinical examination or scans which may have relevance to your health, we will discuss this with you and your G.P, as well as your treating doctor and, if necessary, provide any support that you may require, such as arranging follow-up tests and/or treatment.

What are the possible benefits of taking part?

Your participation in this study will not benefit you directly; however, the information we get from this study may help improve the treatment of people with prostate cancer in the future. This is an investigational study of these scans and it will not be clear until the end of the study if these scans will be of benefit to patients in the future.

What if something goes wrong?

Imperial College London holds insurance policies which apply to this study. If you experience harm or injury as a result of taking part in this study, you will be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during

the course of this study then you should immediately inform the Investigator (Dr Suraiya Dubash on 0203 313 3720). The normal National Health Service mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial College, Joint Research Compliance Office

Will my taking part in the study be kept confidential?

Imperial College Healthcare NHS Trust and Imperial College London will use your name, NHS number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from Imperial College London and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The only people in Imperial College London who will have access to information that identifies you will be people who need to contact you to check willingness to participate in the study or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

Imperial College Healthcare NHS Trust and Imperial College London will keep identifiable information about you from this study [for up to 10 years after the study has finished.

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

Your identifiable information will be collected and held by Imperial College Healthcare NHS Trust and Imperial College London. Your information could be used for research in any aspect of health or care, and could be combined with information about you from other sources held by researchers, the NHS or government. Where this information could identify you, the information will be held securely with strict arrangements about who can access the information. The information will only be used for the purpose of health and care research, or to contact you about future opportunities to participate in research. It will not be used to make decisions about future services available to you, such as insurance. Where there is a risk that you can be identified your data will only be used in research that has been independently reviewed by an ethics committee.

Your Rights

Your usual statutory rights to access, change or move your information are limited, because of exceptions applicable to some types of research, and also because we need to manage your information in specific, lawful ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already

obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. You can find out more about how we use your information from Dr Suraiya Dubash.

Legal Basis

As a university we use personally-identifiable information to conduct research to improve health, care and services. As a publicly-funded organisation, we have to ensure that it is in the public interest when we use personally-identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use your data in the ways needed to conduct and analyse the research study. Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research.

International Transfers

There may be a requirement to transfer information to countries outside the European Economic Area (for example, to a research partner). Where this information contains your personal data, Imperial College London will ensure that it is transferred in accordance with data protection legislation. If the data is transferred to a country which is not subject to a European Commission (EC) adequacy decision in respect of its data protection standards, Imperial College London will enter into a data sharing agreement with the

recipient organisation that incorporates EC approved standard contractual clauses that safeguard how your personal data is processed.

Contact Us

If you wish to raise a complaint on how we have handled your personal data or if you want to find out more about how we use your information, please contact Imperial College London's Data Protection Officer via email at dpo@imperial.ac.uk, via telephone on 020 7594 3502 and via post at Imperial College London, Data Protection Officer, Faculty Building Level 4, London SW7 2AZ. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO). The ICO does recommend that you seek to resolve matters with the data controller (us) first before involving the regulator.

What will happen to the results of the research study?

After completion of the study the results may be presented at national/international scientific meetings or published in a leading medical journal. You will not be identified in any report/publication, and some of the tests done as a part of this research may not be available to you individually. Data and images obtained from the

scans may be used in an anonymous form for future research, including that carried out by commercial healthcare companies. You will not be contacted by any companies carrying out such research and the companies will not be given access to your medical records.

research, including that carried out by commercial healthcare companies. You will not be contacted by any companies carrying out such research and they will not be given access to your medical records. Please note that if any inventions resulting in commercial gain emerge from any of the above research, you will not be eligible to benefit financially from these discoveries.

Who is organising and funding the research?

This study is funded by NIHR Imperial Biomedical Research Centre (BRC). The study is being organised by Imperial College London.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee to protect your safety, rights, well-being and dignity. This study has been approved by the North of Scotland Research Ethics Committee. This committee is responsible for making sure that research takes place in a way that protects the patients' rights and welfare.

CONTACT DETAILS

EMERGENCY CONTACT NUMBERS (0900-1700)		OUT OF HOURS (AFTER 1700)
2. Dr Suraiya Dubash	0203 313 3720	1. Dr Suraiya Dubash
3. Ms Kasia Kozlowski	0203 313 3720	Via switchboard 0203 313 1000

If you
have any

questions about the study, please contact Dr Suraiya Dubash or Ms Kasia Kozlowski on 02033133720, who will be happy to answer your questions. This information sheet is for you to keep. Thank you for taking the time to read this information and for considering taking part in this study.

**PLEASE GIVE ONE COPY OF THE PATIENT INFORMATION SHEET TO THE PATIENT, FILE ONE COPY IN THE
PATIENT'S MEDICAL RECORDS,**

AND RETAIN THE ORIGINAL IN THE INVESTIGATOR SITE FILE

Appendix E: Internal pilot IP2-ATLANTA impact of the Covid-19 pandemic analysis

1. Analysis Populations

Each of the respective analyses are presented for patients recruited to the trial before the Covid-19 pandemic, and during/after the Covid-19 pandemic, separately. On 05/03/2020, Covid-19 was added to Public Health England's list of notifiable diseases in England and Wales (9). Patients recruited to the trial before this date were recruited prior to the Covid-19 pandemic, and patients recruited to the trial after this date were recruited during/after the Covid-19 pandemic.

2. Tables to Present

3. *Baseline Characteristics*

Table 4. 1: Baseline characteristics, by treatment arm, for patients recruited to the trial before¹ the Covid-19 pandemic

Variable	Statistics	SOC	MIAT	Radical	Total
Age	N	12	8	10	30
	Mean (SD)	68.50 (6.63)	63.63 (6.41)	67.60 (8.00)	66.90 (7.12)
	Median (IQR)	70.00 (62.00-73.50)	65.50 (59.50-67.00)	68.00 (65.00-73.00)	67.00 (64.00-73.00)
	Missing from eCRF (n (%))	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ethnicity (n(%))	White	10 (83.3%)	7 (87.5%)	8 (80.0%)	25 (83.3%)
	Mixed	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Black	1 (8.3%)	1 (12.5%)	2 (20.0%)	4 (13.3%)
	Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not reported	1 (8.3%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
	Missing from eCRF	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
IMD Decile (n (%))	1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	2	0 (0.0%)	4 (50.0%)	0 (0.0%)	4 (13.3%)
	3	1 (8.3%)	0 (0.0%)	3 (30.0%)	4 (13.3%)
	4	1 (8.3%)	1 (12.5%)	2 (20.0%)	4 (13.3%)
	5	0 (0.0%)	1 (12.5%)	0 (0.0%)	1 (3.3%)
	6	1 (8.3%)	2 (25.0%)	2 (20.0%)	5 (16.7%)
	7	1 (8.3%)	0 (0.0%)	2 (20.0%)	3 (10.0%)
	8	1 (8.3%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
	9	4 (33.3%)	0 (0.0%)	0 (0.0%)	4 (13.3%)

	10	2 (16.7%)	0 (0.0%)	1 (10.0%)	3 (10.0%)
	Missing from eCRF	1 (8.3%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
Height	N	12	8	9	29
	Mean (SD)	179.42 (9.34)	176.50 (10.66)	176.56 (8.03)	177.72 (9.12)
	Median (IQR)	179.00 (172.00-183.00)	178.50 (173.50-183.00)	178.00 (171.00-182.00)	178.00 (171.00-183.00)
	Missing from eCRF (n (%))	0 (0%)	0 (0%)	1 (10%)	1 (3.3%)
Weight	N	12	8	9	29
	Mean (SD)	86.93 (14.96)	89.45 (22.15)	85.81 (13.66)	87.28 (16.31)
	Median (IQR)	88.05 (76.75-94.40)	89.50 (74.80-97.75)	90.30 (76.20-97.00)	88.20 (76.20-97.00)
	Missing from eCRF (n (%))	0 (0%)	0 (0%)	1 (10%)	1 (3.3%)
BMI	N	12	8	9	29
	Mean (SD)	26.88 (3.15)	28.66 (6.48)	27.39 (2.80)	27.53 (4.15)
	Median (IQR)	26.75 (25.00-30.10)	28.70 (25.60-29.85)	27.80 (24.80-28.50)	27.20 (25.30-30.10)
	Missing from eCRF (n (%))	0 (0%)	0 (0%)	1 (10%)	1 (3.3%)
Performance status (n (%))	Grade 0	11 (91.7%)	6 (75.0%)	9 (90.0%)	26 (86.7%)
	Grade 1	1 (8.3%)	2 (25.0%)	1 (10.0%)	4 (13.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing from eCRF (n (%))	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Type 2 Diabetes (n (%))	Yes	2 (16.7%)	2 (25.0%)	1 (10.0%)	5 (16.7%)
	No	10 (83.3%)	6 (75.0%)	9 (90.0%)	25 (83.3%)
	Missing from eCRF (n (%))	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ischaemic Heart Disease (n (%))	Yes	2 (16.7%)	0 (0.0%)	2 (20.0%)	4 (13.3%)
	No	10 (83.3%)	8 (100.0%)	8 (80.0%)	26 (86.7%)
	Missing from eCRF (n (%))	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Stroke (n (%))	Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	No	12 (100.0%)	8 (100.0%)	10 (100.0%)	30 (100.0%)
	Missing from eCRF (n (%))	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Peripheral Vascular Disease (n (%))	Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	No	12 (100.0%)	8 (100.0%)	10 (100.0%)	30 (100.0%)
	Missing from eCRF (n (%))	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Benign Prostatic Enlargement (n (%))	Yes	0 (0.0%)	1 (12.5%)	2 (20.0%)	3 (10.0%)
	No	12 (100.0%)	7 (87.5%)	8 (80.0%)	27 (90.0%)
	Missing from eCRF (n (%))	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
COPD (n (%))	Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	No	12 (100.0%)	8 (100.0%)	10 (100.0%)	30 (100.0%)
	Missing from eCRF (n (%))	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Stratification Factors					
Intent to treat pelvic lymph nodes (n (%))	Yes	4 (33.3%)	4 (50.0%)	4 (40.0%)	12 (40.0%)
	No	8 (66.7%)	4 (50.0%)	6 (60.0%)	18 (60.0%)
Metastatic burden (n (%))	High	5 (41.7%)	5 (62.5%)	6 (60.0%)	16 (53.3%)
	Low	7 (58.3%)	3 (37.5%)	4 (40.0%)	14 (46.7%)
Intent to use systemic chemotherapy (n (%))	Yes	12 (100.0%)	8 (100.0%)	9 (90.0%)	29 (96.7%)
	No	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (3.3%)
Intent to use metastases directed therapy (n (%))	Yes	4 (33.3%)	3 (37.5%)	3 (30.0%)	10 (33.3%)
	No	8 (66.7%)	5 (62.5%)	7 (70.0%)	20 (66.7%)

¹Patients were recruited before the Covid-19 pandemic if they were recruited to the trial before 05/03/2020 (see Section 1)

Table 4. 2: Baseline characteristics, by treatment arm, for patients recruited to the trial during/after¹ the Covid-19 pandemic

Variable	Statistics	SOC	MIAT	Radical	Total
Age	N	16	19	16	51
	Mean (SD)	68.50 (7.88)	69.26 (7.78)	69.25 (8.52)	69.02 (7.90)
	Median (IQR)	69.50 (61.00-74.50)	72.00 (61.00-76.00)	72.00 (65.00-75.50)	72.00 (62.00-76.00)
	Missing from eCRF (n (%))	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ethnicity (n (%))	White	12 (75.0%)	8 (42.1%)	7 (43.8%)	27 (52.9%)
	Mixed	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Asian	1 (6.3%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
	Black	0 (0.0%)	0 (0.0%)	1 (6.3%)	1 (2.0%)
	Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not reported	3 (18.8%)	11 (57.9%)	8 (50.0%)	22 (43.1%)
	Missing from eCRF	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
IMD Decile (n (%))	1	0 (0.0%)	1 (5.3%)	1 (6.3%)	2 (3.9%)
	2	1 (6.3%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
	3	0 (0.0%)	1 (5.3%)	2 (12.5%)	3 (5.9%)
	4	3 (18.8%)	2 (10.5%)	3 (18.8%)	8 (15.7%)
	5	4 (25.0%)	2 (10.5%)	3 (18.8%)	9 (17.6%)
	6	1 (6.3%)	0 (0.0%)	1 (6.3%)	2 (3.9%)
	7	1 (6.3%)	1 (5.3%)	1 (6.3%)	3 (5.9%)
	8	2 (12.5%)	4 (21.1%)	2 (12.5%)	8 (15.7%)
	9	2 (12.5%)	2 (10.5%)	1 (6.3%)	5 (9.8%)
	10	1 (6.3%)	6 (31.6%)	2 (12.5%)	9 (17.6%)
	Missing from eCRF	1 (6.3%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
Height	N	13	12	14	39
	Mean (SD)	175.31 (7.17)	178.25 (4.43)	181.07 (8.05)	178.28 (7.07)
	Median (IQR)	177.00 (175.00-180.00)	178.50 (174.50-181.00)	180.00 (175.00-186.00)	178.00 (175.00-182.00)
	Missing from eCRF (n (%))	3 (18.8%)	7 (36.8%)	2 (12.5%)	12 (23.5%)
Weight	N	14	14	14	42
	Mean (SD)	77.87 (13.98)	82.73 (9.73)	89.82 (12.99)	83.47 (13.04)
	Median (IQR)	76.40 (67.70-90.00)	81.60 (76.20-85.00)	92.00 (79.80-99.40)	81.65 (74.60-92.60)

	Missing from eCRF (n (%))	2 (12.5%)	5 (26.3%)	2 (12.5%)	9 (17.6%)
BMI	N	13	12	13	38
	Mean (SD)	25.68 (3.51)	25.83 (3.00)	27.25 (3.25)	26.26 (3.26)
	Median (IQR)	24.70 (23.80-27.70)	24.85 (24.00-27.35)	27.30 (25.80-29.40)	25.70 (24.10-28.00)
	Missing from eCRF (n (%))	3 (18.8%)	7 (36.8%)	3 (18.8%)	13 (25.5%)
Performance status (n (%))	Grade 0	15 (93.8%)	17 (89.5%)	16 (100.0%)	48 (94.1%)
	Grade 1	1 (6.3%)	1 (5.3%)	0 (0.0%)	2 (3.9%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing from eCRF (n (%))	0 (0.0%)	1 (5.3%)	0 (0.0%)	1 (2.0%)
Type 2 Diabetes (n (%))	Yes	1 (6.3%)	2 (10.5%)	2 (12.5%)	5 (9.8%)
	No	15 (93.8%)	17 (89.5%)	14 (87.5%)	46 (90.2%)
	Missing from eCRF (n (%))	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ischaemic Heart Disease (n (%))	Yes	2 (12.5%)	3 (15.8%)	2 (12.5%)	7 (13.7%)
	No	14 (87.5%)	16 (84.2%)	14 (87.5%)	44 (86.3%)
	Missing from eCRF (n (%))	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Stroke (n (%))	Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	No	16 (100.0%)	19 (100.0%)	16 (100.0%)	51 (100.0%)
	Missing from eCRF (n (%))	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Peripheral Vascular Disease (n (%))	Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	No	16 (100.0%)	19 (100.0%)	16 (100.0%)	51 (100.0%)
	Missing from eCRF (n (%))	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Benign Prostatic Enlargement (n (%))	Yes	2 (12.5%)	0 (0.0%)	1 (6.3%)	3 (5.9%)
	No	14 (87.5%)	19 (100.0%)	15 (93.8%)	48 (94.1%)
	Missing from eCRF (n (%))	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

COPD (n (%))	Yes	0 (0.0%)	0 (0.0%)	1 (6.3%)	1 (2.0%)
	No	16 (100.0%)	19 (100.0%)	15 (93.8%)	50 (98.0%)
	Missing from eCRF (n (%))	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Stratification Factors					
Intent to treat pelvic lymph nodes (n (%))	Yes	10 (62.5%)	11 (57.9%)	8 (50.0%)	29 (56.9%)
	No	6 (37.5%)	8 (42.1%)	8 (50.0%)	22 (43.1%)
Metastatic burden (n (%))	High	8 (50.0%)	9 (47.4%)	7 (43.8%)	24 (47.1%)
	Low	8 (50.0%)	10 (52.6%)	9 (56.3%)	27 (52.9%)
Intent to use systemic chemotherapy (n (%))	Yes	16 (100.0%)	17 (89.5%)	14 (87.5%)	47 (92.2%)
	No	0 (0.0%)	2 (10.5%)	2 (12.5%)	4 (7.8%)
Intent to use metastases directed therapy (n (%))	Yes	6 (37.5%)	8 (42.1%)	7 (43.8%)	21 (41.2%)
	No	10 (62.5%)	11 (57.9%)	9 (56.3%)	30 (58.8%)

¹Patients were recruited during/after the Covid-19 pandemic if they were recruited to the trial after 05/03/2020 (see Section 1)

4. Analysis of Objectives

Table 5. 1: Summary statistics of time between consent and randomisation (Days), by treatment arm, for patients recruited to the trial before¹ the Covid-19 pandemic

Statistics	SOC	MIAT	Radical	Total
N	12	8	10	30
Min	0	0	0	0
Mean (SD)	5.42 (7.04)	3.13 (4.45)	2.7 (4.19)	3.9 (5.54)
Median (IQR)	3.5 (0 to 7.5)	0.5 (0 to 6)	0.5 (0 to 6)	1 (0 to 7)
Max	24	12	12	24
Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

¹Patients were recruited before the Covid-19 pandemic if they were recruited to the trial before 05/03/2020 (see Section 1)

Table 5. 2: Summary statistics of time between consent and randomisation (Days), by treatment arm, for patients recruited to the trial during/after¹ the Covid-19 pandemic

Statistics	SOC	MIAT	Radical	Total
N	16	19	16	51
Min	0	0	0	0
Mean (SD)	6.31 (5.91)	5.68 (4.74)	3.19 (3.15)	5.1 (4.83)
Median (IQR)	5.5 (1.5 to 9)	6 (2 to 7)	2 (0.5 to 5.5)	4 (1 to 7)
Max	21	18	9	21
Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

¹Patients were recruited during/after the Covid-19 pandemic if they were recruited to the trial after 05/03/2020 (see Section 1)

Table 5. 3: Mean number of patients recruited and randomised per month per centre, for patients recruited to the trial before¹ the Covid-19 pandemic

Id	Centre	Recruited	Randomised
A1	Imperial College London Healthcare NHS Trust	0.69	0.69
A2	Northwick Park, London Northwest Healthcare NHS Trust	0.11	0.11
A3	Queen Elizabeth Hospital Kings Lynn	0.17	0.17
A4	West Middlesex University Hospital	0.25	0.25
A6	Royal Marsden NHS Foundation Trust		
A7	University Hospital Southampton NHS Trust	0.64	0.64
A8	City Hospitals Sunderland NHS Foundation Trust	0.08	0.08
A9	Freeman Hospital, The Newcastle upon Tyne Hospitals NHS Trust		
A10	Wirral University Teaching Hospital	0.12	0.12
A13	Royal Devon & Exeter Hospital NHS Trust	0.08	0.08
A16	Chelsea & Westminster Hospital		
	Total	30	30

¹Patients were recruited before the Covid-19 pandemic if they were recruited to the trial before 05/03/2020 (see Section 1)

Table 5. 4: Mean number of patients recruited and randomised per month per centre, for patients recruited to the trial during/after¹ the Covid-19 pandemic

Id	Centre	Recruited	Randomised
A1	Imperial College London Healthcare NHS Trust	1.25	1.25
A2	Northwick Park, London Northwest Healthcare NHS Trust		
A3	Queen Elizabeth Hospital Kings Lynn	0.11	0.11
A4	West Middlesex University Hospital	0.44	0.44
A6	Royal Marsden NHS Foundation Trust	0.33	0.33
A7	University Hospital Southampton NHS Trust	1.09	1.09

A8	City Hospitals Sunderland NHS Foundation Trust		
A9	Freeman Hospital, The Newcastle upon Tyne Hospitals NHS Trust	0.25	0.25
A10	Wirral University Teaching Hospital		
A13	Royal Devon & Exeter Hospital NHS Trust	0.25	0.25
A16	Chelsea & Westminster Hospital	0.19	0.19
	Total	51	51

¹Patients were recruited during/after the Covid-19 pandemic if they were recruited to the trial after 05/03/2020 (see Section 1)

Table 5. 5: Recruitment and randomisation rates, for patients recruited to the trial before¹ the Covid-19 pandemic

	Rate¹	*95% CI for Rate¹	Rate²	*95% CI for Rate²
Recruitment	85.7% (30/35)	(69.7% to 95.2%)	93.8% (30/32)	(79.2% to 99.2%)
Randomisation	85.7% (30/35)	(69.7% to 95.2%)	93.8% (30/32)	(79.2% to 99.2%)

¹Patients were recruited before the Covid-19 pandemic if they were recruited to the trial before 05/03/2020 (see Section 1)

²Rate calculated out of total number of people all approached which include patient who were given PIS and ELIGIBLE but declined and patients who were given PIS but non-Eligible (after scans)

³Rate calculated out of total number of people approached which include patient who were given PIS and ELIGIBLE but declined

*95% Confidence interval obtained using Binomial exact in Stata

Table 5. 6: Recruitment and randomisation rates, for patients recruited to the trial during/after¹ the Covid-19 pandemic

	Rate¹	*95% CI for Rate¹	Rate²	*95% CI for Rate²
Recruitment	59.3% (51/86)	(48.2% to 69.8%)	67.1% (51/76)	(55.4% to 77.5%)
Randomisation	59.3% (51/86)	(48.2% to 69.8%)	67.1% (51/76)	(55.4% to 77.5%)

¹Patients were recruited during/after the Covid-19 pandemic if they were recruited to the trial after 05/03/2020 (see Section 1)

²Rate calculated out of total number of people all approached which include patient who were given PIS and ELIGIBLE but declined and patients who were given PIS but non-Eligible (after scans)

³Rate calculated out of total number of people approached which include patient who were given PIS and ELIGIBLE but declined

*95% Confidence interval obtained using Binomial exact in Stata

Table 5. 7: Summary statistics of time between consecutive visits (Days) from screening visit to final follow-up visit, by treatment arm, for patients recruited to the trial before¹ the Covid-19 pandemic

Visits ²	Statistics	SOC	MIAT	Radical	Total
Screening Visit 1 – Visit 2	N	12	8	10	30
	Min	70	77	77	70
	Mean (SD)	88.17 (13.02)	97.63 (16.43)	92.9 (12.11)	92.27 (13.79)
	Median (IQR)	89.5 (76.5 to 98)	98 (88.5 to 99)	94.5 (83 to 103)	92 (81 to 98)
	Max	111	133	112	133
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 2 – Visit 3	N	12	7	10	29
	Min	25	28	33	25
	Mean (SD)	84.67 (26.99)	64.57 (30.81)	87.8 (31.73)	80.9 (30.05)
	Median (IQR)	89 (70.5 to 104)	75 (34 to 91)	94.5 (70 to 105)	87 (57 to 103)
	Max	119	103	133	133
	Missing from eCRF – n (%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	1 (3.3%)
Visit 3 – Visit 4	N	12	7	10	29
	Min	14	14	7	7
	Mean (SD)	46.75 (22.41)	42.14 (30.96)	28.5 (15.94)	39.34 (23.49)
	Median (IQR)	48.5 (28 to 61.5)	30 (15 to 69)	24.5 (15 to 37)	30 (21 to 56)
	Max	84	96	57	96
	Missing from eCRF – n (%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	1 (3.3%)
Visit 4 – Visit 5	N	12	7	10	29
	Min	7	-29	0	-29
	Mean (SD)	64.67 (63.25)	32.29 (61.2)	27.9 (24.18)	44.17 (53.59)
	Median (IQR)	50.5 (28 to 77)	15 (0 to 35)	29 (5 to 50)	34 (7 to 57)
	Max	238	162	64	238
	Missing from eCRF – n (%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	1 (3.3%)
Visit 5 – Visit 6	N	11	8	10	29
	Min	0	-15	-136	-136
	Mean (SD)	40.18 (39.15)	71.5 (39.13)	35.3 (66.25)	47.14 (50.79)
	Median (IQR)	17 (8 to 83)	74.5 (65 to 97.5)	48 (22 to 83)	61 (14 to 83)
	Max	98	113	95	113
	Missing from eCRF – n (%)	1 (8.3%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
Visit 6 –	N	11	8	9	28

Visit 7	Min	35	34	64	34
	Mean (SD)	106.55 (51.98)	72.75 (20.7)	111.89 (71.87)	98.61 (54.08)
	Median (IQR)	87 (78 to 154)	80 (60.5 to 86.5)	89 (77 to 91)	85.5 (76 to 95.5)
	Max	217	94	296	296
	Missing from eCRF – n (%)	1 (8.3%)	0 (0.0%)	1 (10%)	2 (6.7%)
Visit 7 – Visit 8	N	9	4	7	20
	Min	131	126	53	53
	Mean (SD)	161.67 (21.96)	228.25 (104.57)	157 (54.34)	173.35 (60.5)
	Median (IQR)	161 (150 to 175)	208 (155 to 301.5)	175 (126 to 194)	171.5 (142 to 191)
	Max	194	371	219	371
Visit 8 – Visit 9	Missing from eCRF – n (%)	3 (25%)	4 (50%)	3 (30%)	10 (33.3%)
	N	6	2	6	14
	Min	168	173	107	107
	Mean (SD)	191.67 (26.52)	182.5 (13.44)	168.33 (43.01)	180.36 (33.5)
	Median (IQR)	181.5 (170 to 220)	182.5 (173 to 192)	174 (135 to 196)	181.5 (168 to 196)
Visit 9 – Visit 10	Max	229	192	224	229
	Missing from eCRF – n (%)	6 (50%)	6 (75%)	4 (40%)	16 (53.3%)
	N	3	0	1 ³	4
	Min	175	-	138	138
	Mean (SD)	184.67 (15.89)	-	-	173 (26.7)
Visit 9 – Visit 10	Median (IQR)	176 (175 to 203)	-	-	175.5 (156.5 to 189.5)
	Max	203	-	138	203
	Missing from eCRF – n (%)	9 (75%)	8 (100%)	9 (90%)	26 (86.7%)

¹Patients were recruited before the Covid-19 pandemic if they were recruited to the trial before 05/03/2020 (see Section 1)

²Follow-up visits are from Visit 8 onwards. This table can be extended to accommodate more follow-up visits

³Due to having only one value at visit9-visit10, Mean (SD) and Median [IQR] are omitted

Table 5. 8: Summary statistics of time between consecutive visits (Days) from screening visit to final follow-up visit, by treatment arm, for patients recruited to the trial during/after¹ the Covid-19 pandemic

Visits ²	Statistics	SOC	MIAT	Radical	Total
Screening Visit 1 – Visit 2	N	16	18	16	50
	Min	13	28	57	13
	Mean (SD)	81.63 (31.74)	89.22 (20.16)	86.5 (16.26)	85.92 (23.25)
	Median (IQR)	84 (67.5 to 98)	91.5 (84 to 102)	85.5 (77 to 99.5)	88.5 (72 to 101)
	Max	152	119	109	152
	Missing from eCRF – n (%)	0 (0.0%)	1 (5.3%)	0 (0.0%)	1 (2%)
Visit 2 – Visit 3	N	16	17	15	48
	Min	35	9	49	9
	Mean (SD)	92.56 (39.25)	75 (31.03)	89.87 (31.78)	85.5 (34.4)
	Median (IQR)	91.5 (64.5 to 107)	75 (63 to 93)	87 (62 to 105)	84 (62.5 to 105)
	Max	183	127	167	183
	Missing from eCRF – n (%)	0 (0.0%)	2 (10.5%)	1 (6.3%)	3 (5.9%)
Visit 3 – Visit 4	N	16	13	15	44
	Min	11	6	-37	-37
	Mean (SD)	31.63 (23.62)	32.15 (15.16)	30.87 (37.79)	31.52 (26.91)
	Median (IQR)	19.5 (14 to 48.5)	36 (21 to 44)	14 (11 to 56)	23.5 (14 to 48)
	Max	84	56	119	119
	Missing from eCRF – n (%)	0 (0.0%)	6 (31.6%)	1 (6.3%)	7 (13.7%)
Visit 4 – Visit 5	N	16	13	15	44
	Min	2	-68	-71	-71
	Mean (SD)	37.63 (32.96)	45.08 (69.86)	38.8 (55.7)	40.23 (52.55)
	Median (IQR)	26 (13.5 to 56)	44 (0 to 99)	23 (12 to 52)	28 (11.5 to 67)
	Max	105	152	188	188
	Missing from eCRF – n (%)	0 (0.0%)	6 (31.6%)	1 (6.3%)	7 (13.7%)
Visit 5 – Visit 6	N	15	15	15	45
	Min	-2	-91	-134	-134
	Mean (SD)	27.87 (25.28)	29.53 (52.66)	33.33 (62.85)	30.24 (48.46)
	Median (IQR)	21 (9 to 41)	27 (12 to 56)	38 (4 to 58)	28 (12 to 56)
	Max	91	110	177	177
	Missing from eCRF – n (%)	1 (6.3%)	4 (21.1%)	1 (6.3%)	6 (11.8%)
Visit 6 –	N	15	15	14	44

Visit 7	Min	27	0	0	0
	Mean (SD)	90.8 (55.05)	113.13 (52.8)	102.14 (34.72)	102.02 (48.44)
	Median (IQR)	82 (40 to 140)	131 (77 to 147)	107.5 (93 to 119)	110.5 (66.5 to 140)
	Max	175	175	147	175
	Missing from eCRF – n (%)	1 (6.3%)	4 (21.1%)	2 (12.5%)	7 (13.7%)
Visit 7 – Visit 8	N	4	7	4	15
	Min	169	81	182	81
	Mean (SD)	187.25 (15.24)	150.71 (35.8)	188.5 (6.61)	170.53 (31.26)
	Median (IQR)	188.5 (175 to 199.5)	168 (135 to 177)	188 (183 to 194)	181 (168 to 192)
	Max	203	184	196	203
	Missing from eCRF – n (%)	12 (75%)	12 (63.2%)	12 (75%)	36 (70.6%)
Visit 8 – Visit 9	N	0	2	1 ³	3
	Min	-	161	172	161
	Mean (SD)	-	165.5 (6.36)		167.67 (5.86)
	Median (IQR)	-	165.5 (161 to 170)		170 (161 to 172)
	Max	-	170	172	172
	Missing from eCRF – n (%)	16 (100%)	17 (89.5%)	15 (93.8%)	48 (94.1%)
Visit 9 – Visit 10	N	-	-	-	-
	Min	-	-	-	-
	Mean (SD)	-	-	-	-
	Median (IQR)	-	-	-	-
	Max	-	-	-	-
	Missing from eCRF – n (%)	16 (100%)	19 (100%)	16 (100%)	51 (100%)

¹Patients were recruited during/after the Covid-19 pandemic if they were recruited to the trial after 05/03/2020 (see Section 1)

²Follow-up visits are from Visit 8 onwards. This table can be extended to accommodate more follow-up visits.

³Due to having only one value for visit8-visit9, Mean (SD) and Median [IQR] are omitted

Table 5. 9: Attendance at visits (measure of compliance), reporting proportions of participants who attended the visit on time, whose visit was delayed and whose visit was missing, for patients recruited to the trial before¹ the Covid-19 pandemic

Visit*	n (%)	SOC	MIAT	Radical	Total
Screening visit	On time	12 (100.0%)	8 (100.0%)	10 (100.0%)	30 (100.0%)
	Early	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Delayed	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Withdrawn	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 2	On time	2 (16.7%)	1 (12.5%)	2 (20.0%)	5 (16.7%)
	Early	4 (33.3%)	1 (12.5%)	2 (20.0%)	7 (23.3%)
	Delayed	6 (50.0%)	6 (75.0%)	6 (60.0%)	18 (60.0%)
	Withdrawn	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 3	On time	4 (33.3%)	4 (50.0%)	6 (60.0%)	14 (46.7%)
	Early	6 (50.0%)	2 (25.0%)	2 (20.0%)	10 (33.3%)
	Delayed	2 (16.7%)	1 (12.5%)	2 (20.0%)	5 (16.7%)
	Withdrawn	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	1 (12.5%)	0 (0.0%)	1 (3.3%)
	Not Applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 4	On time	5 (41.7%)	1 (12.5%)	3 (30.0%)	9 (30.0%)
	Early	0 (0.0%)	2 (25.0%)	2 (20.0%)	4 (13.3%)
	Delayed	7 (58.3%)	4 (50.0%)	5 (50.0%)	16 (53.3%)
	Withdrawn	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	1 (12.5%)	0 (0.0%)	1 (3.3%)
	Not Applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 5	On time	2 (16.7%)	1 (12.5%)	3 (30.0%)	6 (20.0%)
	Early	0 (0.0%)	4 (50.0%)	2 (20.0%)	6 (20.0%)
	Delayed	10 (83.3%)	3 (37.5%)	5 (50.0%)	18 (60.0%)
	Withdrawn	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 6	On time	2 (16.7%)	0 (0.0%)	2 (20.0%)	4 (13.3%)
	Early	0 (0.0%)	2 (25.0%)	1 (10.0%)	3 (10.0%)
	Delayed	9 (75.0%)	6 (75.0%)	7 (70.0%)	22 (73.3%)
	Withdrawn	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	1 (8.3%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
	Not Applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 7	On time	1 (8.3%)	2 (25.0%)	1 (10.0%)	4 (13.3%)

	Early	0 (0.0%)	3 (37.5%)	1 (10.0%)	4 (13.3%)
	Delayed	11 (91.7%)	3 (37.5%)	7 (70.0%)	21 (70.0%)
	Withdrawn	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (3.3%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 8 (follow-up)²	On time	3 (25.0%)	0 (0.0%)	0 (0.0%)	3 (10.0%)
	Early	1 (8.3%)	1 (12.5%)	1 (10.0%)	3 (10.0%)
	Delayed	5 (41.7%)	3 (37.5%)	6 (60.0%)	14 (46.7%)
	Withdrawn	1 (8.3%)	1 (12.5%)	1 (10.0%)	3 (10.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	2 (16.7%)	3 (37.5%)	2 (20.0%)	7 (23.3%)
Visit 9 (follow-up)²	On time	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (3.3%)
	Early	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (3.3%)
	Delayed	6 (50.0%)	2 (25.0%)	4 (40.0%)	12 (40.0%)
	Withdrawn	3 (25.0%)	2 (25.0%)	1 (10.0%)	6 (20.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	3 (25.0%)	4 (50.0%)	3 (30.0%)	10 (33.3%)
Visit 10 (follow-up)²	On time	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Early	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Delayed	3 (25.0%)	0 (0.0%)	1 (10.0%)	4 (13.3%)
	Withdrawn	3 (25.0%)	2 (25.0%)	1 (10.0%)	6 (20.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	6 (50.0%)	6 (75.0%)	8 (80.0%)	20 (66.7%)

¹Patients were recruited before the Covid-19 pandemic if they were recruited to the trial before 05/03/2020 (see Section 1)

²Follow-up visits are from Visit 8 onwards. This table can be extended to accommodate more follow-up visits.

*Visits 1 – 7: SOC treatment given

*Visit 5: Randomised intervention treatment given

Table 5. 10: Attendance at visits (measure of compliance), reporting proportions of participants who attended the visit on time, whose visit was delayed and whose visit was missing, for patients recruited to the trial during/after¹ the Covid-19 pandemic

Visit*	n (%)	SOC	MIAT	Radical	Total
Screening visit	On time	16 (100.0%)	19 (100.0%)	16 (100.0%)	51 (100.0%)
	Early	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Delayed	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Withdrawn	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 2	On time	3 (18.8%)	3 (15.8%)	5 (31.3%)	11 (21.6%)
	Early	7 (43.8%)	3 (15.8%)	4 (25.0%)	14 (27.5%)
	Delayed	6 (37.5%)	12 (63.2%)	7 (43.8%)	25 (49.0%)
	Withdrawn	0 (0.0%)	1 (5.3%)	0 (0.0%)	1 (2.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 3	On time	6 (37.5%)	7 (36.8%)	6 (37.5%)	19 (37.3%)
	Early	6 (37.5%)	9 (47.4%)	5 (31.3%)	20 (39.2%)
	Delayed	4 (25.0%)	1 (5.3%)	4 (25.0%)	9 (17.6%)
	Withdrawn	0 (0.0%)	2 (10.5%)	1 (6.3%)	3 (5.9%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 4	On time	4 (25.0%)	3 (15.8%)	4 (25.0%)	11 (21.6%)
	Early	3 (18.8%)	5 (26.3%)	4 (25.0%)	12 (23.5%)
	Delayed	9 (56.3%)	5 (26.3%)	7 (43.8%)	21 (41.2%)
	Withdrawn	0 (0.0%)	2 (10.5%)	1 (6.3%)	3 (5.9%)
	Missing	0 (0.0%)	4 (21.1%)	0 (0.0%)	4 (7.8%)
	Not Applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 5	On time	5 (31.3%)	3 (15.8%)	3 (18.8%)	11 (21.6%)
	Early	1 (6.3%)	7 (36.8%)	4 (25.0%)	12 (23.5%)
	Delayed	10 (62.5%)	7 (36.8%)	8 (50.0%)	25 (49.0%)
	Withdrawn	0 (0.0%)	2 (10.5%)	1 (6.3%)	3 (5.9%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 6	On time	3 (18.8%)	5 (26.3%)	3 (18.8%)	11 (21.6%)
	Early	2 (12.5%)	4 (21.1%)	1 (6.3%)	7 (13.7%)
	Delayed	10 (62.5%)	6 (31.6%)	11 (68.8%)	27 (52.9%)
	Withdrawn	1 (6.3%)	3 (15.8%)	1 (6.3%)	5 (9.8%)
	Missing	0 (0.0%)	1 (5.3%)	0 (0.0%)	1 (2.0%)
	Not Applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 7	On time	1 (6.3%)	0 (0.0%)	3 (18.8%)	4 (7.8%)

	Early	6 (37.5%)	6 (31.6%)	3 (18.8%)	15 (29.4%)
	Delayed	8 (50.0%)	10 (52.6%)	8 (50.0%)	26 (51.0%)
	Withdrawn	1 (6.3%)	3 (15.8%)	2 (12.5%)	6 (11.8%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 8 (follow-up)²	On time	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Early	0 (0.0%)	3 (15.8%)	0 (0.0%)	3 (5.9%)
	Delayed	4 (25.0%)	4 (21.1%)	4 (25.0%)	12 (23.5%)
	Withdrawn	3 (18.8%)	3 (15.8%)	2 (12.5%)	8 (15.7%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	9 (56.3%)	9 (47.4%)	10 (62.5%)	28 (54.9%)
Visit 9 (follow-up)²	On time	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Early	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Delayed	0 (0.0%)	2 (10.5%)	1 (6.3%)	3 (5.9%)
	Withdrawn	3 (18.8%)	3 (15.8%)	3 (18.8%)	9 (17.6%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	13 (81.3%)	14 (73.7%)	12 (75.0%)	39 (76.5%)
Visit 10 (follow-up)²	On time	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Early	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Delayed	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Withdrawn	3 (18.8%)	3 (15.8%)	3 (18.8%)	9 (17.6%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	13 (81.3%)	16 (84.2%)	13 (81.3%)	42 (82.4%)

¹Patients were recruited during/after the Covid-19 pandemic if they were recruited to the trial after 05/03/2020 (see Section 1)

²Follow-up visits are from Visit 8 onwards. This table can be extended to accommodate more follow-up visits.

*Visits 1 – 7: SOC treatment given

*Visit 5: Randomised intervention treatment given

5. Covid-19 Related Protocol Deviations

The following Covid-19 related protocol deviations were collected:

- No post SOC biopsy or MRI
- Early termination of chemotherapy agent
- Information not recorded
- Visit not attended (e.g. self-isolating)
- Other (specify details)

Please refer to 5.11 and 5.12 for a full listing and frequency tables of Covid-19 related protocol deviations.

Table 5. 11: Listing of Covid-19 Related Protocol Deviations

Subject ID	Treatment Arm	Site	Date reported	Deviation or violation	Description	Date of deviation /violation	Response
A1-002	MIAT	A1	21/04/2020	Protocol Deviation	Chemo prematurely stopped (completed 5/6 cycles) / Reason: COVID-19 risk	06/04/2020	N/A
A1-003	MIAT	A1	28/10/2020	Protocol Deviation	Due to COVID delay treatment outside maximum visit window. Due 13th August 2020. Planned 29th October 2020.	28/10/2020	Treatment planned for 29th October 2020
A1-005	MIAT	A1	21/04/2020	Protocol Deviation	Chemo prematurely stopped (completed 5/6 cycles) / Reason: COVID-19 risk	20/03/2020	N/A
A1-006	Radical	A1	21/04/2020	Protocol Deviation	Chemo prematurely stopped (completed 5/6 cycles) / Reason: COVID-19 risk	27/03/2020	N/A
A1-007	SOC	A1	21/04/2020	Protocol Deviation	Chemo prematurely stopped (completed 5/6 cycles) / Reason: COVID-19 risk	16/04/2020	N/A
A1-008	MIAT	A1	21/04/2020	Protocol Deviation	Chemo prematurely stopped (completed 4/6 cycles) / Reason: COVID-19 risk	26/03/2020	N/A
A3-001	SOC	A3	15/06/2020	Protocol Deviation	QOL did not get completed at visit 7 due to covid	20/04/2020	Study team informed and agreed action required which has been performed
A7-003	Radical	A7	04/06/2020	Protocol Deviation	chemo prematurely stopped at 5/6 cycles due to COVID-19 risk	02/04/2020	n/a
A8-001	Radical	A8	18/05/2020	Protocol Deviation	Patient was self-isolating during COVID19 due to a chest problem. Therefore, PSA was not tested at this visit. Study team contacted and	18/05/2020	Hopefully if circumstances allow, PSA will be tested at visit 3 as per protocol

					advised to complete protocol deviation form.		
A16-001	Radical	A16	09/02/2021	Protocol Deviation	Patient did not undergo second prostate biopsy. Repeated infections post docetaxel, suspected covid. Proceeded to radiotherapy.	09/02/2021	No material impact on primary outcome PFS.

Table 5. 12: Number of Covid-19 Related Protocol Deviations and Violations

Type of Deviation/Violation	SOC	MIAT	Radical	Total
Sampling/laboratory measurements	0 (0.0%)	0 (0.0%)	1 (25.0%)	1 (10.0%)
Study visit windows	0 (0.0%)	1 (25.0%)	0 (0.0%)	1 (10.0%)
Compliance	0 (0.0%)	0 (0.0%)	1 (25.0%)	1 (10.0%)
Dose interruptions/modifications not specified in protocol	1 (50.0%)	3 (75.0%)	2 (50.0%)	6 (60.0%)
Other:	1 (50.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)
QOL did not get done at visit 7 due to covid	1 (100.0%)			1 (100.0%)
Total	2 (20.0)%	4 (40.0)%	4 (40.0)%	10 (100.0)%

Appendix F: Copy of Standard Operating Procedures & Publications

Below is a summary of standard operative procedures written for the IP2-ATLANTA trial and reproduced in this Appendix.



Standard Operating Procedure	Relevant Trial Arm	Authors
<i>Systemic Therapy</i>	All trial arms	M. Connor N. Sarwar H. Ahmed
<i>Post systemic therapy biopsy</i>	Intervention Arm 1 Intervention Arm 2	M. Connor H. Ahmed
<i>Cytoreductive Radiotherapy</i>	Intervention Arm 1 Control Arm*	M. Connor O. Naismith J. Staffurth
<i>(Open Retropubic/Standard laparoscopic/Robotic-Assisted Laparoscopic) Cytoreductive Radical Prostatectomy +/- (Extended) Pelvic Lymph Node Dissection</i>	Intervention Arm 2	M. Connor T. Dudderidge M. Winkler
<i>Cytoreductive Minimally Invasive Ablative Therapy (MIAT)</i>	Intervention Arm 1	M. Connor T. Shah H. Ahmed
<i>Laparoscopic or Robotic-Assisted Laparoscopic (Extended) Pelvic Lymph Node Dissection following MIAT</i>	Intervention Arm 1*	M. Connor T. Dudderidge M. Winkler H. U. Ahmed
<i>Metastasis Directed Therapy</i>	Intervention Arm 1* Intervention Arm 2*	M. Connor V. Khoo T. Dudderidge M. Winkler
<i>Central Histopathology Review</i>	Intervention Arm 1 Intervention Arm 2	M. Connor M. Yeung A. Smith H. Ahmed

<i>ATLANTA Post Systemic Therapy MRI CRF</i>	Intervention Arm 1 Intervention Arm 2	M. Connor H. Tam
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Legend: Low burden patient only, who met pre-specified eligibility criteria.

STUDY GUIDANCE



Use of Upfront Systemic Therapy

IP2 - ATLANTA:

Adjuvant Treatments to the Local tumour for metastatic prostate cancer:
Assessment of Novel Treatment Algorithms

Protocol Number: 18HH4804

Version 3.0 07-July-2020

Authors: Dr Martin J. Connor, Prof. Hashim U. Ahmed

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Introduction

The purpose of this document is to describe the systemic therapy that may be applied in all men as part of their standard of care up front treatment as part of the IP2-ATLANTA trial.

1. Scope

This guidance is applicable to all patients with metastatic prostate cancer who have chosen to undergo systemic therapy offered following discussion with a named trial clinical oncologist or urological surgeon.

2. Abbreviations

ICTU	Imperial Clinical Trials Unit
ADT	Androgen Deprivation Therapy

3. References

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4. Androgen Deprivation Therapy

4.1. Overview

- ADT can involve LHRH agonists, and gonadotrophin-releasing hormone (GnRH) antagonists, orchidectomy and anti-androgens.

4.2. ADT

- ADT should follow local departmental protocol and will be determined by the treating trial clinician.
- ADT advise as per NICE guidelines CG175 (2014):

For men with metastatic prostate cancer who are willing to accept the adverse impact on overall survival and gynaecomastia in the hope of retaining sexual function, offer anti-androgen monotherapy with bicalutamide (150 mg).

All men should be offered bilateral orchidectomy cancer as an alternative to continuous luteinising hormone-releasing hormone agonist therapy.

4.2.1. Timing of ADT with local treatment

- We recommend that ADT should continue for a minimum of 20 weeks from randomisation in all arms. Although, we recognise for the majority patients ADT will be continued long-term as per local treating oncologist/trial clinician.
- This allows for local treatment to occur at a 32 +/- 12 weeks in all intervention arms.
- In the majority of men within this trial ADT will be used in addition to either Docetaxel chemotherapy or Abiraterone. Timing of local treatment should be planned with respect to these additional agents.

5. Chemotherapy

5.1. Docetaxel

5.1.1. Overview

- Evidence suggests that docetaxel improves overall survival and time to disease progression in men with hormone-sensitive metastatic prostate cancer.
- STAMPEDE and CHAARTED RCTs found that, versus androgen deprivation therapy (ADT) alone, Docetaxel combined with ADT statistically significantly improved overall survival by around 10 to 15 months in this population.
- NHS England reviewed the evidence in 2016 and concluded that was sufficient evidence to permit Docetaxel to be routinely funded for the treatment of newly-diagnosed hormone naïve metastatic prostate cancer, where treatment with Docetaxel is started within 12 weeks of commencing treatment with ADT.

5.1.2. Treatment

- Intent to use Docetaxel must be declared prior to randomisation of the patient.
- The use of Docetaxel in as part of systemic therapy in the ATLANTA trial is at the discretion of the treating trial clinician and can be used in any trial arm.

5.1.3. Indications and contra-indications

- Absolute:
 - Severe prior hypersensitivity reaction to taxanes
- Relative
 - Pre-existing significant peripheral neuropathy
 - Poor bone marrow function due to extensive disease or other prior haematological problems

- Significant co-morbidity (e.g. cardio-vascular or respiratory disease) such that prostate cancer is not likely to be the life limiting illness for the patient

5.1.4. Dose

- 75 mg/ m² of Docetaxel should be administered every 3 weeks for 6 cycles, in conjunction with prednisolone 5mg twice daily for 3 weeks.
- If patient develop febrile neutropenia as a result of treatment with Docetaxel, treating clinicians should manage the condition with dose reduction protocols and/or (depending on the treating Trust's policy on the use of granulocyte colony stimulating factors [GCSF]).
- The summary of product characteristics for Docetaxel outlines the following general dose requirements and adjustments.
- Treatment should be discontinued where reactions persist at the 60 mg/ m² dose.

5.1.5. Timing of Docetaxel with local treatment

- Docetaxel should continue for a minimum of 20 weeks from randomisation in all arms.
- This allows for local treatment can occur at a 32 +/- 12 weeks in all intervention arms.

5.2. Abiraterone Acetate

5.2.1. Overview

- NICE appraisal consultation document (2018) for Abiraterone Acetate in hormone naïve metastatic prostate cancer concluded that whilst the clinical trial results found that compared with ADT alone, abiraterone plus ADT increases the time until the progression, overall survival is not improved.
- This committee decided that Abiraterone Acetate plus androgen deprivation therapy (ADT) is not recommended, within its marketing

authorisation, for untreated high-risk hormone-sensitive metastatic prostate cancer in adult in England and Wales

- The *Scottish Medicines Consortium* has since published its own advice (January 2020) that Abiraterone Acetate (*Zytiga*®), in combination with prednisolone and ADT, is now accepted for use within NHS Scotland for the treatment of newly diagnosed high-risk metastatic hormone-sensitive prostate cancer in adults.

5.2.2. Use in the ATLANTA Trial (Scotland ONLY)

- In keeping with the *Scottish Medicines Consortium* guidance Abiraterone Acetate may be commenced as an alternative upfront systemic agent in ATLANTA in combination with ADT.
- Intent to use Abiraterone Acetate must be declared prior to randomisation of the patient.
- The use of Abiraterone Acetate as part of systemic therapy in the ATLANTA trial is at the discretion of the treating trial clinician and can be used in any trial arm.

5.2.3. Dose (Scotland ONLY)

- The recommended dose is 1,000mg (two 500mg tablets) as a single daily dose that must not be taken with food. The tablets should be taken at least one hour before or at least two hours after eating. For men with high risk mHSPC, abiraterone is to be taken with 5mg prednisone or prednisolone orally once daily. Medical castration with luteinising hormone releasing hormone (LHRH) analogue should be continued during treatment in patients not surgically castrated.
- Centres should follow local protocol for follow-up and monitoring of abiraterone.

5.2.4. Timing Abiraterone Acetate with local treatment (Scotland ONLY)

- Abiraterone should continue for a minimum of 20 weeks from randomisation in all arms. However, extended Abiraterone may be used at the discretion of local treating oncologist or surgeon. The

length of treatment should be documented on Inform “standard of care form”.

- This will allow for local treatment can occur at a 32 +/- 12 weeks in all intervention arms.
- Previous clinical studies evaluating the role of neoadjuvant abiraterone in high risk localised prostate cancer have reported no increased complications from prostatectomy after neoadjuvant abiraterone at 24 weeks.
- Restarting Abiraterone Acetate post-operatively is not recommended in this trial. If abiraterone is to be restarted post-local treatment, it should only be prescribed when deemed clinically safe and at the discretion of the treating local oncologist or surgeon in line with post-operative recovery period.

5.2.5. Future guidance and potential use in England & Wales

- NICE are awaiting confirmation from the company of the price Abiraterone Acetate will be available to the NHS for this indication. Once they have this then the appraisal process for abiraterone will re-start.
- Please note that Abiraterone Acetate is temporarily approved for use in men who are unable to tolerate Enzalutamide in NICE/NHS England “*Interim treatment change options for the COVID-19 pandemic*”.

5.3. Enzalutamide

5.3.1. Overview

- NICE and NHS England has temporarily decided to use Enzalutamide due to the COVID-19 pandemic.
- As such this is considered standard of care therapy within the ATLANTA trial.

- This gives men in England and Wales the option to give enzalutamide with androgen deprivation therapy for patients with newly diagnosed metastatic disease instead of Docetaxel to reduce toxicity and potential for admission
- For patients who are intolerant of Enzalutamide, there is also the option of switching treatment to Abiraterone Acetate. Abiraterone Acetate to be used as per advice above.

5.3.2. Use in the ATLANTA Trial

- In keeping with the guidance Enzalutamide may be commenced as an alternative upfront systemic agent in ATLANTA in combination with ADT.
- Intent to use Enzalutamide must be declared prior to randomisation of the patient.
- The use of Enzalutamide in as part of systemic therapy in the ATLANTA trial is at the discretion of the treating trial clinician and can be used in any trial arm.

5.3.3. Dose

- The recommended dose is 160 mg as a single daily dose. Medical castration with luteinising hormone releasing hormone (LHRH) analogue should be continued during treatment in patients not surgically castrated.
- Centres should follow local protocol for follow-up and monitoring of abiraterone.

5.3.4. Timing Enzalutamide with local treatment

- Enzalutamide should continue for a minimum of 20 weeks from randomisation in all arms. However, extended Enzalutamide may be used at the discretion of local treating oncologist or surgeon. The length of treatment must be documented on Inform “standard of care form”.
- This will allow for local treatment can occur at a 32 +/- 12 weeks in all intervention arms.

- Restarting Enzalutamide post-local treatment is not recommended in this trial. If Enzalutamide is to be restarted post-local treatment, it should only be prescribed when deemed clinically safe and at the discretion of the treating local oncologist or surgeon in line with post-operative recovery period.

STUDY SPECIFIC PROCEDURE MANUAL**Post Systemic Therapy Prostate Biopsy**

IP2 - ATLANTA:

Adjuvant Treatments to the Local tumour for metastatic prostate cancer:
Assessment of Novel Treatment Algorithms

Protocol Number: 18HH4804

Effective Date: 26th June 2020

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Introduction

The purpose of this document is to describe the prostate biopsy performed in men who have completed systemic therapy but have not undergone local treatment as part of the IP2-ATLANTA trial.

1. Scope

This procedure is applicable to all patients, in the interventions arms of the IP2-ATLANTA trial, with metastatic prostate cancer who have chosen to undergo systemic therapy offered following discussion with a named trial clinical oncologist or urological surgeon.

2. Abbreviations

SOP	Standard Operating Procedure
ICTU	Imperial Clinical Trials Unit
ADT	Androgen Deprivation Therapy

3. Responsibilities

Chief Investigator (CI)	• Overall responsibility for the trial • Overall responsibility for your trial at the site • Ensure facilities, staff resources and education are appropriate to carry out the trial • Delegate responsibility and ensure they are documented on the delegation log
Principal investigator (PI)	• Be available to give advice, support and to sign off documents as required • Responsibilities for carrying out study procedures or delegating these to appropriately trained staff where necessary
Surgeon	• Ensure the standard operating procedure is in accordance with trial intervention, based on safe and accepted radiotherapy practice. • Aware of SOP and mechanism to report deviation from SOP
Oncology Lead/Co-lead	• Ensure the standard operating procedure is in accordance with trial intervention, based on safe and accepted radiotherapy practice. • Aware of SOP and mechanism to report deviation from SOP.
Radiotherapist/ Clinical Oncologist	• Deliver radiotherapy intervention as per standard of practice. • Record deviations from SOP via trial electronic database and in correspondence with main trial site (via research nurse or direct contact).
Research Nurse	• Assist in sample handling including collection, labelling, processing, storage and transportation of biobanking samples. • Ensure consent is taken for additional biobanking samples.
Trial Manager	• Liaise with local study team to ensure study procedures are carried out in accordance with trial protocol and procedural manuals • Support and advice trial team and respond to queries as needed.

4. References

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5. Post-systemic therapy prostate biopsy

5.1. Overview

- Systemic therapy refers to ADT with or without docetaxel chemotherapy or abiraterone as set out in the **Systemic Therapy SOP**.
- A protocolled prostate biopsy (targeted and systematic cores) should be performed in all men in the intervention arms of IP2-ATLANTA following systemic therapy but prior to local treatment as per protocol.
- All men must undergo a repeat prostate MRI prior to biopsy.
- This should occur at trial **visit 3** (i.e. 26 +/- 12 weeks post randomisation) as per ATLANTA protocol visit schedule.
- Beyond the pilot phase men may undergo a post-systemic therapy prostate biopsy at the discretion of the treating clinician.
- Prostate biopsy performed approach should mirror local protocol. A transrectal ultrasound and / or transperineal approach is acceptable.

6. Procedures

6.1. Anaesthesia & Patient Positioning

6.1.1. Anaesthesia

- General anaesthesia achieved as per anaesthetist, patient specific factors and in accordance to local protocol.
- Sedation as per patient specific factors, surgeon and anaesthetist discretion and in accordance to local protocol.
- Local or regional anaesthesia as per patient specific factors, surgeon and anaesthetist discretion and in accordance to local protocol. Suggested protocol includes:
 - Topical peri-anal and rectal lidocaine gel (Instillagel® (20ml)
 - Infiltration into skin and peri-prostatic block:
 - Bupivacaine & Adrenaline Injection (10ml) B.P. 0.25% w/v 1 in 200,000 mixed with Lidocaine & Adrenaline Injection (10ml) L. 1% w/v 1 in 200,000

- Bupivacaine 0.25% (10ml) mixed with 1% Lidocaine (10ml) with black spinal needle

6.1.2. Pre-operative Antibiotics

- As per local biopsy protocol, patient specific factors, surgeon and microbiology discretion.
- Suggested antibiotics prophylaxis includes:
 - Intramuscular gentamicin 160mg stat

6.1.3. Pre-operative Analgesia

- As per local biopsy protocol, patient specific factors, surgeon and microbiology discretion.
- Suggested analgesia includes:
 - Codeine Phosphate 60mg or dihydrocodeine 30mg PO stat pre-procedure
 - Ibuprofen PRN and paracetamol PRN post-procedure for 5 days only
 - Alternatively, codeine/paracetamol combinations post-procedure when NSAIDS contraindicated for 5 days only

6.1.4. Patient Positioning

- Patient positioned in left lateral / lithotomy / Trendelenburg or similar position as determined by patient specific factors and operating surgeon

6.1.5. Skin preparation & hair removal

- As per local biopsy protocol, patient specific factors, surgeon.
- Suggested:
 - Hair removal carried out if necessary
 - Skin cleaned with Chlorhexidine prep

6.2. Operative Steps

Operative steps are to be **determined by the operating surgeon, in accordance with accepted surgical practice and local biopsy protocol.**

However, below describes a suggested approach to transperineal targeted and systematic prostate biopsy which can be utilised in this trial.

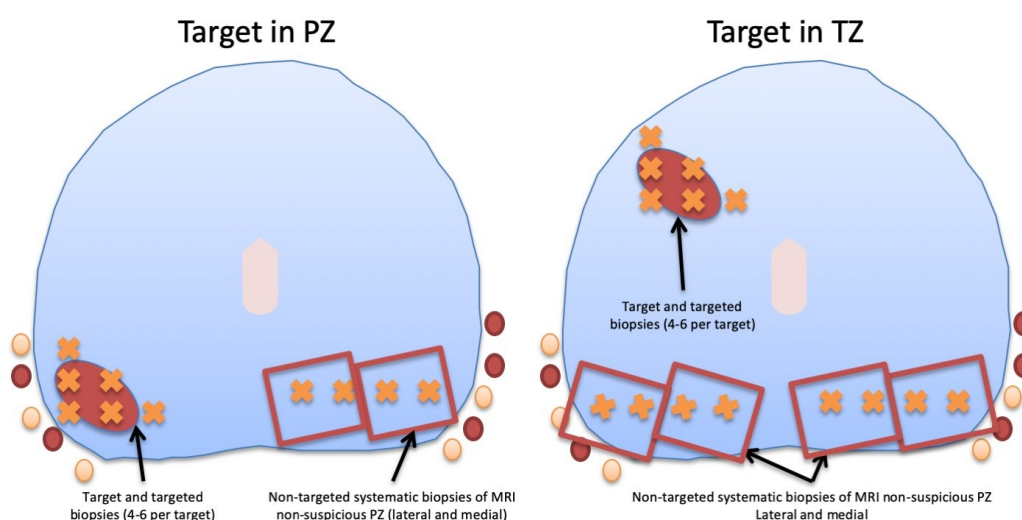
- Bupivacaine 0.5% with adrenaline 20ml infiltrated into skin and around the upper part of the anal verge.

- Allow to work for 2 minutes (by the clock - to be timed by nurse or HCA in room and operator prevented from moving on until this time has elapsed)

- Transrectal ultrasound probe with endocavity balloon attached is placed into rectum and positioned appropriately

- Bupivacaine 0.5% and lidocaine 1% mixture used as peri-prostatic block under ultrasound guidance with black spinal needle into anticipated track of targeted biopsies (if 2-3 sites).

- Allow to work for 2 minutes (by the clock - to be timed by nurse or healthcare assistant in room and operator prevented from moving on until this time has elapsed).



- Biopsies taken. 4-6 targeted cores for each suspicious site scored 3, 4, or 5. Smaller areas might require more biopsies as greater chance of missing these.

- Contralateral PZ sampling if MRI non-suspicious. Pot each site of biopsies separately. Use following nomenclature:

- Target 1/2/3: Right/Left PZ/TZ Medial/Lateral
- Sampling: Right/Left PZ/TZ Medial/Lateral

- In case of “diffuse lesions” on mpMRI, where no clear target exists (i.e. no reported PIRADS 3-5 lesion). We would recommend targeted biopsies to the areas that were previously positive pre-systemic therapy at time of diagnosis as well as 10-12-core systematic sampling.

- In cases of significant lesions on mpMRI, where it is clear visible tumour remains, and the patient is due to undergo MIAT, we would recommend targeted biopsies to the areas that were previously positive pre-systemic therapy at time of diagnosis are taken immediately prior to ablation.

- In cases of significant lesions on mpMRI, where it is clear visible tumour remains, and the patient is due to undergo cytoreductive radical prostatectomy and has declined a post-SOC biopsy we would recommend either targeted biopsies to the areas that were previously positive pre-systemic therapy at time of diagnosis are taken immediately prior to surgery or alternatively use of whole-mount histology findings to confirm presence of residual tumour. Decision remains at the discretion of operating surgeon. In both cases such findings should be reported on eCRF Post-SOC biopsy.

- Remove probe.

- Apply pressure dressing (Blue gauze and Mefix).

- Legs re-positioned to supine position.

- Patient asked to sit up slowly and then to stand slowly in case feels dizzy

6.2.1. Biobanking

- **Depending on individual consent.** Biobanking of pathological tissue or retrieval of tissue of operative pathology and biopsy of recurrent disease from prostatic and extra prostatic sites.

6.3. Specimen Delivery, Drain Insertion & Closure

6.3.1. Surgical Documentation

- Biopsy operator taking biopsies to ensure pots and pathology form are all correctly labelled with site and side location, patient details and the form has the correct history (PSA, previous biopsy grade and number/side if positive or if negative, MRI score).

Surgical procedure performed should be documented on InForm (electronic) trial database

6.4. Postoperative Care

6.4.1. Urinary Catheter

- Urinary catheter not routinely performed. Consider in those high risk of urinary retention or post-operative retention. As per local protocol.

6.4.2. Deep Vein Thrombosis (DVT) Prophylaxis

- Not routinely performed. Please refer to your local protocol.

7. Interpreting histopathology post systemic therapy

“Complete pathological response” on post-systemic therapy prostate biopsy is defined as:

- **Presence** of benign tissue only or grade pT0
AND/OR
- **Absence** of “post-hormone therapy adenocarcinoma” and/or “chemotherapy post-treatment effects”

A Gleason pattern may not be reported, in line with current guidelines. Although if it is reported it should be documented by on the Post SOC Biopsy eCRF

Features of high-grade prostatic intraepithelial neoplasia (HGPIN) and atypical small acinar proliferation (ASAP) will be considered as benign tissue.

This will be collected using the Post SOC Biopsy eCRF, in all cases where complete pathological response is met it will be recorded as a “Benign” pathology result.

8. Trial impact of a Negative / Benign Post Systemic Therapy Biopsy

In cases where men have a reported negative or benign post systemic therapy biopsy they do not have evidence of a residual primary prostate tumour. These men should not proceed to allocated trial local treatment.

This should be clearly documented on Inform. Such cases are likely to account for < / = 5% of men. They should be discussed individually with the central trial team via nhs.net email (imperial.atlanta@nhs.net cc: martin.connor2@nhs.net)

9. Revision History

SSPM Ref.	Date Effective	Reason for update (page and section of change)
Version 1.1	28 APR 2020	Section 6.2 updated
Version 2.0	26 JUN 2020	Update to allow for on-table biopsy and/or information from whole mount histology to be utilized in pilot men who are in the radical arm but decline a biopsy.

STUDY SPECIFIC PROCEDURE MANUAL**Local Prostate Radiotherapy
+/- Pelvic Lymph Nodes**

IP2 - ATLANTA:

Adjuvant Treatments to the Local tumour for metastatic prostate cancer:
Assessment of Novel Treatment Algorithms

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Foreword

This document describes the radiotherapy outlining, planning and QA processes for the ATLANTA trial. When used in conjunction with the main trial protocol it provides all the information necessary for entering patients into the trial. This document should not be used as a guide for the treatment of patients outside of the trial.

Every care has been taken in drafting these guidelines but corrections or amendments may be necessary. These will be circulated to investigators in the trial, but centres entering patients for the first time are advised to contact atlanta.qa@nhs.net to ensure they have the most recent and approved version.

If you have any queries in regards to these guidelines please submit by email to the following address: atlanta.qa@nhs.net or your local RT QA contact.

Introduction

The purpose of this document is to describe the standard radiotherapy procedures (SOP) involved in:

- A. **Intervention Arm 2:** Local prostate radiotherapy using a dose of external beam radiotherapy of 60Gy/20Fr over 27 days OR 74-78Gy in 2Gy per fraction in the intervention arm 2 of ATLANTA.
- B. **Control Arm:** Local prostate radiotherapy using a dose of external beam radiotherapy of 36Gy/6Fr OR 55Gy/20Fr OR 60Gy/20Fr over at least 27 days for low metastatic burden men only in the control arm of ATLANTA.

1. Scope

- A. This procedure is applicable to all patients with metastatic prostate cancer randomised to intervention arm 2 in the ATLANTA trial who have chosen to undergo the offered radiotherapy treatment following discussion with a named trial clinical oncologist.

Radiotherapy treatment will consist of local prostate and seminal vesicle radiotherapy with or without pelvic lymph node irradiation. Pelvic lymph node irradiation is at the discretion of the treating clinical oncologist and intent to treat is declared prior to randomisation. SABR to metastasis will be permitted in this arm, with reference to the SABR UK consortium guidelines (2018), as described in full in the **MDT SOP**.

- B. This procedure is applicable to all patients in with metastatic prostate cancer randomised to the control arm in the ATLANTA trial who have low burden metastatic disease, as defined by CHARTED definition (Sweeney *et al.*, 2016), and have chosen to undergo the local radiotherapy treatment following discussion with a named trial clinical oncologist. Radiotherapy treatment to patients in Control Arm will be limited to the local prostate with or without seminal vesicle treatment.

Treatment directed to pelvic lymph nodes will not be permitted. SABR to metastasis will also not be permitted in this arm. Men with a high metastatic burden should not receive radiotherapy, except for palliative or symptom control (as per usual local departmental practice).

2. Abbreviations

SOP	Standard Operating/Radiotherapy Procedure
ICTU	Imperial Clinical Trials Unit
SSPM	Study Specific Procedure Manual
RT	Radiotherapy
SV	Seminal Vesicle
CTV	Clinical Target Volume (CTV)
PTV	Planning Treatment Volume (PTV)

3. Responsibilities

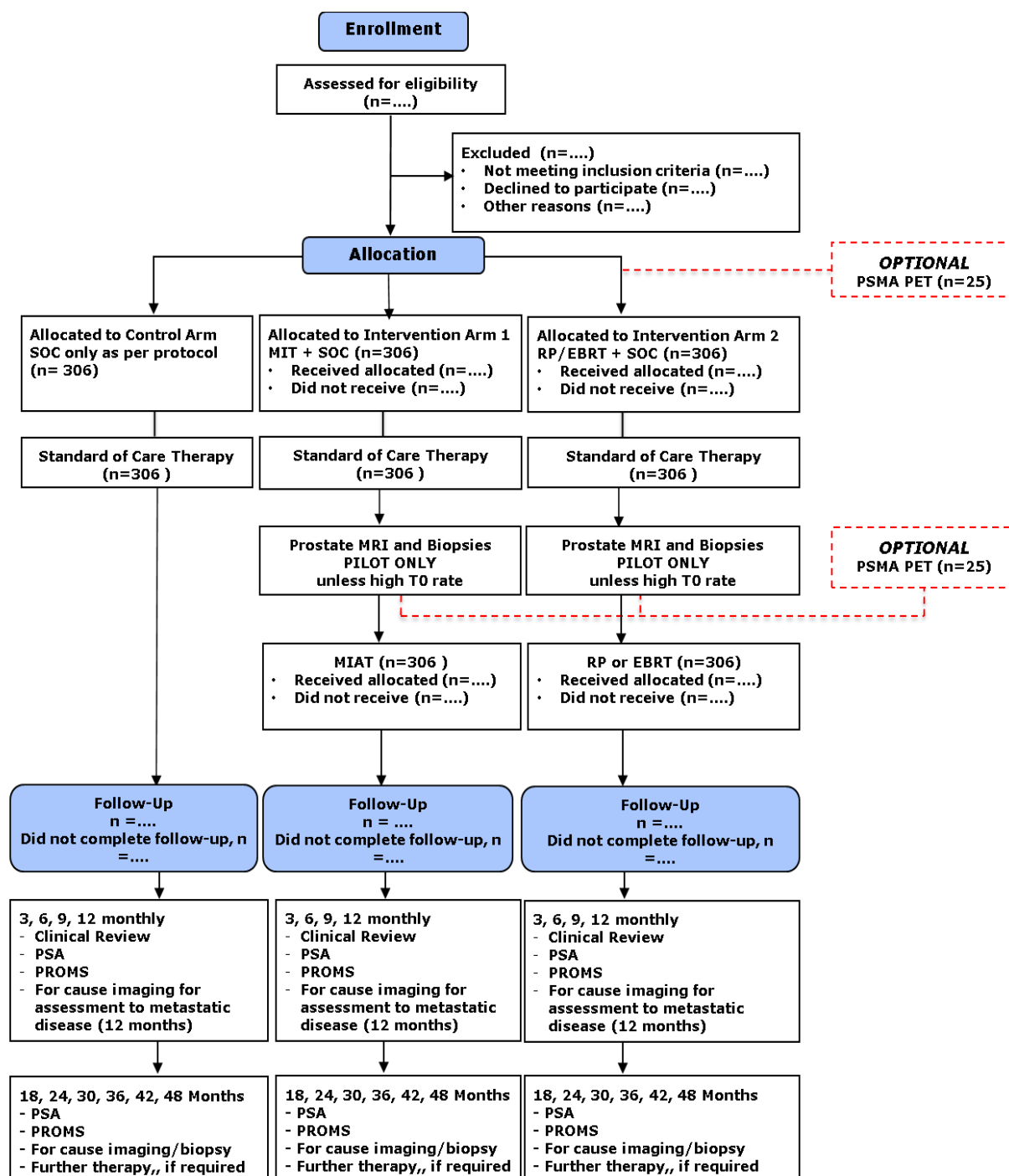
Chief Investigator (CI)	• Overall responsibility for the trial • Overall responsibility for your trial at the site • Ensure facilities, staff resources and education are appropriate to carry out the trial • Delegate responsibility and ensure they are documented on the delegation log
Principal investigator (PI) /Clinical Oncologist	• Be available to give advice, support and to sign off documents as required • Responsibilities for carrying out study procedures or delegating these to appropriately trained staff where necessary
Oncology Lead/Co-lead	• Ensure the standard operating procedure is in accordance with trial intervention, based on safe and accepted radiotherapy practice. • Aware of SOP and mechanism to report deviation from SOP.

Clinical Oncologist Lead Clinical Oncologist	• Deliver radiotherapy intervention as per standard of practice. • Record deviations from SOP via trial electronic database and in correspondence with main trial site (via research nurse or direct contact).
Research Nurse	• Assist in sample handling including collection, labelling, processing, storage and transportation of biobanking samples. • Ensure consent is taken for additional biobanking samples.
Trial Manager	• Liaise with local study team to ensure study procedures are carried out in accordance with trial protocol and procedural manuals • Support and advice trial team and respond to queries as needed.

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Pilot will be 80 patients in total with aim for 1-2 patients per month per centre on average
 Minimum follow up is 24 months (2 years) and maximum is 48 months (4 years) as patients recruited early on could be followed up for up to 48 months.

5. SECTION A (Intervention Arm 2 – Radical Radiotherapy)

6. Procedures

6.1. Pre-Planning Procedures

6.1.1. Fiducial Marker Insertion

Use of fiducials:

- Fiducial markers are mandatory if daily planar online image verification and correction is being used.
- Fiducial markers are recommended (but not mandatory) if daily imaging and online correction is with cross-sectional imaging e.g. CBCT, US, CT on rails, tomotherapy or MR-guided RT. Soft tissue matching is permitted if this is the standard technique and sufficient experience exists in the trial centre.

Fiducial Placement:

- A minimum of 3 markers (measuring 3-5mm) should be placed with transrectal ultrasound guidance, separated by 2 cm or more.
- The markers may be placed via a transrectal or transperineal method; if performed with a transrectal approach the appropriate antibiotic prophylaxis should be used. Fiducial marker placement is recognised as an outpatient procedure, the aim of which should result in a minimum of three trackable seeds, used to assess rotation and movement during treatment.
- To allow fiducial stabilisation and resolution of swelling, planning studies will be imaged at least 7 days after fiducial placement.

- If only one fiducial can be seen at planning, either use daily CBCT or insert additional fiducials and re-plan the patient.

6.2. Patient Preparation

6.2.1. Bladder Preparation

- We recommend that patients have a comfortably filled bladder (150-250ml) during imaging and treatment delivery: patients should be asked to empty their bladder and then drink enough water (e.g. 325ml or equivalent to 2 cups of water) to ensure a reasonably filled bladder on the planning scan and before each fraction of radiotherapy. If the bladder volume is <150ml, proceed with planning, check the bladder volume with CBCT during treatment and encourage good hydration.

6.2.2. Bowel Preparation

- We recommend the use of bowel preparation to reduce rectal diameter for all patients receiving radiotherapy, with an aim of maximum rectal AP diameter of 4cm (measured at the midpoint of the prostate).
- It is suggested, but not mandatory, to use daily mini-enemas for 2 days prior to, and on the day of, CT planning. In addition, it is suggested patients should restart enemas 2 days prior to starting radiotherapy, and continue with daily enemas for the first 2 weeks of treatment, to be suspended if they develop diarrhoea.

6.3. Planning Scans

6.3.1. Planning CT

- CT scans will be taken for treatment planning. CT scans will be taken at ≤ 3 mm intervals (≤ 3 mm slice thickness). The CT scan range must encompass the PTVs and OARs with a margin for dose fall off. As a guide, go from the top of L4 vertebra to the

penile urethra (usually 1cm below ischial tuberosities will be adequate).

- Support devices may be used to improve patients comfort dependent on the tumour localisation.
- It is recommended, but not mandated, that patients who are to undergo pelvic node radiotherapy should be scanned with IV contrast to aid delineation. IV and oral contrast should be used according to local departmental protocol.

6.3.2. Planning MRI

- It is recommended that all patients undergo MRI imaging within 6 weeks of treatment, if this is part of current departmental practice, for radiotherapy planning purposes to determine the anatomical borders of the prostate, and if possible, the urethra. The MRI will be fused to the treatment planning CT. It is recommended that MRI/CT fusion be done on implanted fiducials. No endorectal coil is allowed. If CT and MRI are to be performed on the same day then we recommend performing the MRI scan first.

6.4. Evaluated Structures

6.4.1. Target Volumes

- Volumes will be defined according to ICRU reports 50, 62 and 83.

6.4.2. Clinical Target Volume (CTV)

- When using MRI-fusion images, voluming accuracy declines in the more superior aspects of the prostate, particularly at the level of the seminal vesicles. We therefore recommend using MRI fusion for voluming the prostate and prostate/rectum interface, but where there is a discrepancy the CT anatomy should be used. All other structures should be outlined on CT.
- CTV volumes are defined in the table below

Volume	Structure	Definition
--------	-----------	------------

CTVp1	Prostate	Prostate, plus proximal 1cm of seminal vesicles from insertion point in the superior-inferior plane. Include any extraprostatic extension (periprostatic fat, seminal vesicle or base of bladder). The proximal seminal vesicles will be defined by creating a 1cm isotropic expansion margin around the prostate, and including the portion of seminal vesicle within this region.
CTVp2	Prostate and seminal vesicles	CTVp1 plus any remaining seminal vesicle
CTVn1	Uninvolved pelvic nodes	Pelvic nodal volume (if treated)
GTVn2 ^{inv}	Involved pelvic nodes	Radiologically involved node(s)
CTVn2 ^{inv}		GTVn2 ^{inv} plus 3-5mm; this should be fully enclosed within CTVn1

6.4.3. Planning Target Volumes (PTV)

- PTV volumes and margins are defined in the table below.

Site	Structure name	Definition
Prostate	CTVp1 PTVp1_xxxx	Prostate, base of seminal vesicles CTVp1 plus 3 mm
Prostate SV	CTVp2 PTVp2_xxxx	Prostate and seminal vesicles CTVp2 plus 6 mm
PPN	CTVn1 PTVn1_xxxx	Pelvic lymph nodes (if treated) CTVn1 plus 5 mm
Involved nodes	CTVn2 ^{inv} PTVn2 ^{inv} _xxxx	Involved lymph node(s) (if treated) CTVn2 ^{inv} plus 5 mm; PTVn2 ^{inv} should be fully within PTVn1_xxxx

Where “xxxx” to be replaced by the prescribed dose in cGy to the relevant

PTV (see section 6.6).

6.5. Organs at Risk (OAR)

6.5.1. OAR naming convention

OAR structures and naming convention for ATLANTA to be outlined include:

Volume	Naming convention
Rectum	Rectum
Bladder	Bladder
Urethra	Urethra
Right femoral head	FemoralHead_R
Left femoral head	FemoralHead_L
Penile bulb	PenileBulb
Bowel	Bowel

6.5.2. OAR Definitions

Rectum

- Defined as a solid structure, including the lumen and rectal wall, extending from the bottom of the ischial tuberosities or the anal margin (whichever is inferior) to the recto-sigmoid junction.

Bladder

- The outside of the bladder wall should be outlined. The entire bladder should be included.

Penile Bulb

- The portion of the bulbous spongiosum that lies inferior to the urogenital diaphragm. The volume is normally 9-10mm in superior-inferior direction. Use the MRI (preferred) or CT planning scan as guidance to outline the structure.

Bowel

- The individual bowel loops visible on relevant levels of the planning scan will be outlined and will be used for the 'bowel' dose-volume constraint. The outlining will include the small bowel, the large bowel and the sigmoid colon, down to the level of the recto-sigmoid junction. The superior extent of outlining should be 2cm beyond the superior extent of CTVp2 or CTVn1 as appropriate.

Right and Left femoral heads:

- The femoral heads are outlined to the bottom of the curvature of their heads (femoral necks are not included).

Urethra

- Outline the structure only if it is visible on the planning scan.
Outline the urethra or catheter from the inferior to superior end of the prostate PTV using planning MRI, if available, to assist.

6.6. Dose Specifications

6.6.1. Prescribed Dose and Fractionation

- **60Gy in 20 fractions.** Treat the prostate to 60Gy and the seminal vesicles to 47Gy over at least 27 days, also simultaneously treating the pelvic lymph nodes to 47Gy in 20 fractions (if treated).
- **74-78Gy in 2Gy fractions.** Treat the prostate to 74-78Gy and the seminal vesicles to 60Gy, also simultaneously treating the pelvic lymph nodes to 55Gy in 37-39 fractions (if treated).
- We recommend following the pelvic node dose schedules specified in the PIVOTALboost and PIVOTAL protocols for

60Gy/20 fractions and 74Gy/2Gy per fraction respectively;
however other fractionation schedules are permitted.

6.6.2. PTV dose constraints

The prescription dose shall be the dose to the PTV and the following dose objectives will be met: $D_{98\%} \geq 95\%$, $D_{50\%} = 100\% \pm 1\%$, $D_{2\%} \leq 107\%$ (aim for $D_{2\%} < 105\%$).

The minimum dose constraint ($D_{98\%}$) may be relaxed where necessary in order to meet the rectum high dose constraint, with limited undercoverage permitted posteriorly where PTV overlaps rectum.

60Gy in 20 fractions.

Planning Target Volumes	Dose to PTV
Prostate-only PTV	Report dose to PTVp1_6000 $D_{50\%} = 60\text{Gy} \pm 1\%$ (median); $D_{98\%} \geq 57.0\text{Gy}$ (95%), $D_{2\%} \leq 64.2\text{Gy}$ (107%)
Prostate + SVs PTV	Report dose to PTVp2_4700–PTVp1_6000 $D_{50\%} \geq 47.0\text{Gy}$ (median); $D_{98\%} \geq 44.65\text{Gy}$ (95%)
Pelvic Nodes PTV (if treated)	Report dose to PTVn1_4700–PTVp2_4700 $D_{50\%} = 47\text{Gy} \pm 1\%$ (median); $D_{98\%} \geq 44.65\text{Gy}$ (95%), $D_{2\%} \leq 50.3\text{Gy}$ (107%) *
Nodal Boost PTV	Report dose to PTVn2^inv_5000 $D_{50\%} = 50\text{Gy} \pm 1\%$ (median); $D_{98\%} \geq 47.5\text{Gy}$ (95%), $D_{2\%} \leq 53.5\text{Gy}$ (107%)

* May not be achievable if there is nodal boost

74-78Gy in 2Gy fractions.

Planning Target Volumes	Dose to PTV
	"xxxx" is 7400, 7600 or 7800 (prescribed dose in cGy)
Prostate-only PTV	Report dose to PTVp1_xxxx $D_{50\%} = 100\% \pm 1\%$ (median); $D_{98\%} \geq 95\%$, $D_{2\%} \leq 107\%$ (percentage of prescription dose)
Prostate + SVs PTV	Report dose to PTVp2_6000–PTVp1_xxxx $D_{50\%} \geq 60.0\text{Gy}$ (median**); $D_{98\%} \geq 57.0\text{Gy}$ (95%)

Pelvic Nodes PTV (if treated)	Report dose to PTVn1_5500–PTVp2_6000 $D_{50\%} = 55\text{Gy} \pm 1\%$ (median); $D_{98\%} \geq 52.3\text{Gy}$ (95%), $D_{2\%} \leq 58.9\text{Gy}$ (107%) *
Nodal Boost PTV	Report dose to PTVn2^inv_6000 $D_{50\%} = 60\text{Gy} \pm 1\%$ (median); $D_{98\%} \geq 57\text{Gy}$ (95%), $D_{2\%} \leq 64.2\text{Gy}$ (107%)

* May not be achievable if there is nodal boost

6.6.3. Normal tissue dose constraints for organs at risk

The nomenclature used in Section 6.5.1 should be used for planning all cases.

Note: OARs have both optimal dose constraints that should be the aim in planning and mandatory constraints that must be achieved for the plan to be acceptable. When reporting, ensure that the entire OAR volume including any overlap with the PTVs has been included.

Organ	Dose volume constraint			
	Dose (Gy) for 2Gy/# 74-78Gy	Dose (Gy) for 60Gy/20 fractions	Maximum Volume (% or cc)	
			Mandatory	Optimal
Rectum	30	24	-	80%
	40	32	-	65%
	50	40	60%	50%
	60	48	50%	35%
	65	52	30%	-
	70	56	15%	-
	74	60	5%	3%
Bladder	50	40	-	50%
	60	48	50%	25%
	74	60	35%	5%
Bowel *	44	36	158cc	78cc
	50	40	70cc	17cc
	54	44	28cc	14cc
	60	48	6cc	0.5cc
	64	52	0cc	-
Penile Bulb	50	40	-	50%

	60	48	-	10%
Left / Right Femoral head	50	40	50%	5%

*** If the mandatory dose constraints are not achieved and the plan is optimal, the coverage of PTVn1 and PTVn2^{inv} should be reduced to achieve the dose constraints.**

6.7. Radiotherapy Delivery

6.7.1. Radiotherapy Technique

Multiple dose-level PTV structures are treated simultaneously in a single phase. Therefore, an IMRT or VMAT planning technique must be used to obtain the prescription doses for adjacent PTVs.

6.7.2. IGRT

All patients will have daily image-guided radiotherapy, as defined by local protocol. It is recommended, but not mandated, that this is done with fiducial marker guidance. It is recommended that all patients be set up prior to treatment and if a significant shift is required (>10mm) the patient should be re-imaged after that shift. CBCT, Tomotherapy, and ultrasound are acceptable if this is a standard protocol in the centre.

6.7.3. Fiducial Markers and kV Imaging

Patients should be imaged daily using planar kV images and a 2 mm tolerance. At least two fiducials should be identified for each treatment. If only one fiducial can be tracked, CBCT should be used. Where the ability exists, rotational corrections should be made. If there are shifts >10mm, CBCT imaging pre-treatment is recommended to rule out any significant changes in rectal position or prostate deformation. The markers should be checked for positioning errors.

6.7.4. Cross Sectional Imaging (CBCT, CT on Rails, Tomotherapy)

Patients should be imaged daily using CBCT. The fiducial markers (if available) will be used as the reference for prostate position and all shifts should be applied.

If at fraction 1, any one shift value is greater than 10mm do not treat until the images can be reviewed. Check the bone match, rectal and bladder filling, if necessary re-position or re-plan. If during treatment, shifts of >10mm are observed in any direction, arrange a review by the clinician.

6.7.5. Cross Sectional Imaging (Ultrasound)

The use of daily ultrasound image guidance needs to be discussed with the RTQA team before treating any patient in the trial with the RTQA team

6.8. Pelvic Lymph Nodal Metastasis Radiotherapy

6.8.1. Pelvic Lymph Nodes

- Radiotherapy to pelvic lymph nodes is as per treating clinical oncologist and as declared in “intent to treat pelvic lymph nodes” on an individual patient basis, prior to randomisation.
- ATLANTA suggests treatment of pelvic lymph nodal metastasis demonstrated on PET imaging or those >10mm on CT should be considered for treatment.
- Centres with no experience of radically irradiating patients with involved pelvic nodes are required to develop a departmental protocol before treating patients within ATLANTA.
- The principles of pelvic nodal treatment within ATLANTA will follow those of PIVOTALboost nodal arm (Arm B) with important variations including 1) review of sites of nodal disease to assess suitability for PIVOTALboost template and extension to L3/4 interspace, 2) boost to involved nodes, 3) lower dose to uninvolved nodes and 4) different fractionation schedule options

6.8.2. Review of sites of nodal disease

- The majority of data used to define nodal volumes and safety of higher dose nodal IMRT/ VMAT are from patients with node-negative disease. Safety data in the multi-centre setting includes the PIVOTAL trial (Dearnaley *et al.*, 2018) which did not include boosts to involved nodes; there is little published data on safety of nodal boost with a 20 fractionation schedule, although it is used in some centres. It is known that some patients have unusual patterns of disease and the following factors should be considered when outlining:
- Are involved nodes beyond 1st station nodes or extend beyond the PIVOTALboost CTVn1 i.e. mesorectal / pararectal then consider whether patient has M1a disease. Conformal avoidance of IMRT/ VMAT may not be sensible and omission of pelvic radiotherapy or lower doses of 3dCRT (44-46Gy/ 23# equivalent) could be considered.
- Is there any evidence of involved nodes beyond true pelvis e.g. lower paraortic and M1a disease. Omission of pelvic radiotherapy or an extended volume to the L3/4 interspace and with lower doses (44-46Gy/ 23# equivalent) could be considered.
- PIVOTAL used a 37# schedule and PIVOTALboost a 20# schedule. ATLANTA allows (but does not recommend) PTVp1 doses up to 78Gy/39# if this the standard departmental protocol. There are no UK guidelines on nodal doses with this schedule, but we recommend

using the same nodal doses as the 37# schedule, accepting a small reduction in Biological Effective Dose.

- OAR avoidance within PIVOTALboost mandatory constraints (replicated for ATLANTA) take priority over PTVn1 or PTVn2^{inv} coverage for safety reasons.

6.8.3. Outlining for node positive patients

- Use all available diagnostic, follow-up and planning imaging.
- Involved nodes should be outlined on each slice that they appear and labelled as GTVn2^{inv}. GTVn2^{inv} should be expanded to CTVn2^{inv} by an isotropic 3-5mm margin, which should be fully enclosed within CTVn1 (see above). CTVn2^{inv} should be expanded to create PTVn2^{inv} using an isotropic 5mm margin. PTVn2^{inv} should be fully contained within PTVn1.

6.8.4. Doses for node positive patients

Dose schedule	PTVp1	PTVn1	PTVn2 ^{inv}
60Gy / 20#	60Gy	47Gy	50Gy
74Gy / 37#	74Gy	55Gy	60Gy
78Gy / 39#	78Gy	55Gy	60Gy

7. SECTION B (Control Arm - Standard of Care Radiotherapy)

8. Procedures

8.1. Radiotherapy

8.1.1. Radiotherapy

- Radiotherapy should be given as per local documented standard of care.

8.1.2. Fiducial Markers

- No use of fiducial markers required.

8.1.3. Bladder Preparation

- Refer to section 6.1.2

8.1.4. Bowel Preparation

- We recommend the use of bowel preparation to reduce rectal diameter for all patients receiving radiotherapy, with an aim of maximum rectal AP diameter of 4cm (measured at the midpoint of the prostate).
- Bowel preparation will be at the discretion of the treating clinician following usual local protocol of the unit.

8.1.5. Planning CT

- CT scans will be taken for treatment planning. CT scans will be taken at $\leq 3\text{mm}$ intervals ($\leq 3\text{mm}$ slice thickness) centred approximately at the prostate.
- Support devices may be used to improve patients comfort dependent on the tumour localisation.

8.1.6. Planning MRI

- It is not recommended for patients to undergo a planning MRI imaging for radiotherapy, unless this is standard local practice.

8.2. Evaluated Structures

8.2.1. Clinical Target Volume (CTV)

- The CTV should consist of the prostate gland alone. The base of seminal vesicles should also be included if they are involved in the primary tumour.

8.2.2. Planning Treatment Volume (PTV)

- $PTV = CTV + 10 \text{ mm}$, except 8 mm posteriorly, or following a written departmental protocol.

8.3. Organs at risk (OAR)

8.3.1. OAR Summary

Please see section (A), 6.5.

8.4. Dose Specifications

8.4.1. Delivered Dose

- Dose in 36Gy in 6 fractions over at least 27 days
OR
- Dose in 55Gy in 20 fractions over at least 27 days
OR
- Dose in 60Gy in 20 fractions over at least 27 days

8.4.2. Normal tissue dose constraints for organs at risk

Note that OARs have both optimal dose constraints that should be the aim in planning and mandatory constraints that must be achieved for the plan to be acceptable.

Organ	Dose volume constraint				
	Dose (Gy) for 36Gy/6#	Dose (Gy) for 55Gy/20#	Dose (Gy) for 60Gy/20#	Maximum Volume (% or cc)	
				Mandatory	Optimal
Rectum	14.8	22.6	24.6	-	80%
	19.4	29.7	32.4	-	65%
	24.5	37.4	40.8	60%	50%
	29.2	44.6	48.6	50%	35%
	31.7	48.4	52.8	30%	-
	34.2	52.3	57	15%	-
	36	55	60	5%	3%
Bladder	24.5	37.4	40.8	-	50%
	29.2	44.6	48.6	50%	25%
	36	55	60	35%	5%
Bowel	24.5	37.4	40.8	17cc	-
Penile Bulb	24.5	37.4	40.8	-	50%
	29.2	44.6	48.6	-	10%
Left / Right Femoral head	24.5	37.4	40.8	50%	5%

8.5. Pelvic Lymph Nodal Radiotherapy

8.5.1. Pelvic Lymph Nodes

- Radiotherapy must not be delivered to pelvic lymph nodes.

9. Radiotherapy Quality Assurance

9.1. Radiotherapy Quality Assurance Overview

The radiotherapy quality assurance (RT QA) programme for the ATLANTA trial will be co-ordinated by the National Radiotherapy Trials Quality Assurance (RTTQA) group.

This will include pre-accrual and during accrual QA processes.

Details of the QA programme, all required documentation and data submission can be found via the ATLANTA link on the RTTQA group website at www.rtrialsqa.org.uk.

Please submit all data for review, and address all correspondence related to RT QA, to atlanta.qa@nhs.net.

9.2. QA streamlining

The QA processes for the ATLANTA trial will be streamlined, where possible, with previous prostate trial QA based on both centre and Principal Investigator (PI) trial participation.

- Outlining: Principal Investigators who have already successfully completed the outlining QA for PACE and/or PIVOTALboost will be streamlined.
- Planning: Centres who have already successfully completed the benchmark planning case for PACE and/or PIVOTALboost will be streamlined.

Please contact the RTTQA group on the ATLANTA QA email atlanta.qa@nhs.net for clarification.

9.3. Pre-accrual QA

9.3.1. Facility Questionnaire

If prostate facility questionnaire (FQ) been completed previously for PACE-A/C or PIVOTALboost then update for ATLANTA trial; otherwise complete FQ.

9.3.2. Clinical outlining

- If treating prostate-only:
 - IF PI is QA-approved for PACE/PIVOTALboost then no pre-trial QA required;
 - Otherwise submit EITHER benchmark case OR recent plan for outlining review
- If treating pelvic nodes:
 - IF PI is QA-approved for PIVOTALboost then no pre-trial QA required;

Otherwise submit EITHER benchmark case OR recent plan for outlining review

- If treating nodal boost:
 - Must be departmental protocol
 - EITHER submit recent case for outlining and plan review OR **prospective** review required for 1st nodal boost patient

9.3.3. Treatment planning

If radiotherapy centre is QA-approved for PACE/PIVOTALboost then no pre-trial QA required.

Otherwise IF trial treatment is centre's standard then submit a patient plan for review; ELSE **prospective** plan review required for 1st patient in each arm

9.4. During Accrual QA

9.4.1. Treatment Planning

- The 1st patient recruited to EACH trial arm will undergo a timely retrospective review of clinical outlining and treatment planning, unless a prospective review has been requested by the RTTQA team.
- In addition a retrospective review of the 1st involved nodes case will be performed, unless a prospective review has been requested by the RTTQA team.

9.4.2. Data collection

DICOM treatment plan data (including CT, structures, plan and dose cube) for all ATLANTA trial patients should be exported, anonymised and sent to the RTTQA team at atlanta.qa@nhs.net electronically.

9.4.3. Dosimetry site visit

A dosimetry site visit will be conducted, subject to prior RTTQA dosimetry accreditation.

10. Revision History

SSPM Ref.	Date Effective	Reason for update (page and section of change)
XX000.00	DD MMM YYYY	

<Insert section break if adding any Attachments>

STUDY SPECIFIC PROCEDURE MANUAL

**(Open Retropubic/Standard Laparoscopic/Robotic-Assisted
Laparoscopic)**

Radical Prostatectomy +/-

(Extended) Pelvic Lymph Node Dissection

IP2 - ATLANTA:

Adjuvant Treatments to the Local tumour for metastatic prostate cancer:
Assessment of Novel Treatment Algorithms

Protocol Number: 18HH4804

Effective Date: 8th March 2019 **Draft:** 22nd February 2019

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Introduction

The purpose of this document is to describe the standard operating procedures (SOP) involved in cytoreductive radical prostatectomy with or without extended pelvic lymph node dissection by any surgical approach.

1. Scope

This procedure is applicable to all patients with metastatic prostate cancer randomised to intervention arm 2 in the ATLANTA study who have a surgically resectable tumour and have chosen to undergo the offered surgical treatment following discussion with a named trial urological surgeon.

Surgical treatment will consist of cytoreductive radical prostatectomy with or without extended lymph node dissection (eLND). Lymph node dissection should be determined prior to patient randomisation. We strongly recommend, but do not limit, eLND to men with a suspicious/positive lymph node(s) on PET Scan or ≥ 10 mm lymph node on a CT AP.

The operating trial surgeon (OS) must have meet ATLANTA surgeon quality control measures as described in **Appendix A**. A signed and completed quality assurance declaration must be submitted to the ATLANTA trial team prior to performing surgery within the ATLANTA study.

2. Abbreviations

SOP	Standard Operating Procedure
ICTU	Imperial Clinical Trials Unit
SSPM	Study Specific Procedure Manual
RALP	Robotic-assisted laparoscopic radical prostatectomy
LRP	Standard laparoscopic radical prostatectomy
ELND	Extended lymph node dissection

3. Responsibilities

Chief Investigator (CI)	• Overall responsibility for the trial • Overall responsibility for your trial at the site • Ensure facilities, staff resources and education are appropriate to carry out the trial • Delegate responsibility and ensure they are documented on the delegation log
Principal investigator (PI)	• Be available to give advice, support and to sign off documents as required • Responsibilities for carrying out study procedures or delegating these to appropriately trained staff where necessary
Surgical Lead/Co-lead	• Ensure the standard operating procedure is in accordance with trial intervention, based on safe and accepted surgical practice. • Ensure operating surgeon is aware of SOP and mechanism to report deviation from SOP.
Operating Surgeon (OS)	• Perform surgical intervention as per standard of practice. • Record deviations from SOP via trial electronic database and in correspondence with main trial site (via research nurse or direct contact).
Research Nurse	• Assist in sample handling including collection, labelling, processing, storage and transportation of biobanking samples. • Ensure consent is taken for additional biobanking samples.
Trial Manager	• Liaise with local study team to ensure study procedures are carried out in accordance with trial protocol and procedural manuals • Support and advice trial team and respond to queries as needed.

4. References

- Poelaert F, C Verbaeys, B Rappe, B Kimpe, *et al.* 2017. Cytoreductive Prostatectomy for Metastatic Prostate Cancer: First Lessons Learned From the Multicentric Prospective Local Treatment of Metastatic Prostate Cancer (LoMP) Trial. *Urology*. 106: 146-152.
- Barré C. 2007. Open radical retropubic prostatectomy. *European Urology*. 52 (1): 71-80.
- Montorsi, F, Timothy W, Raymond, E., Walter A *et al.* 2012. "Best Practices in Robot-assisted Radical Prostatectomy: Recommendations of the Pasadena Consensus Panel". *European Urology*. 62 (3): 368-381.

5. Procedures

5.1. Anaesthesia, Patient Positioning, Access to Abdominal Cavity

5.1.1. Anaesthesia

- General anaesthesia achieved as per anaesthetist, patient specific factors and in accordance to local protocol.
- Local or regional anaesthesia as per patient specific factors, surgeon and anaesthetist discretion and in accordance to local protocol.

5.1.2. Patient Positioning

- Patient positioned in Trendelenburg or similar position as determined by patient specific factors and operating surgeon

5.1.3. Pneumoperitoneum (LRP/RALP)

- Access to abdominal cavity by any reasonable means determined by operating surgeon
- Pneumoperitoneum (Laparoscopic/Robotic Assisted) created by any means (Veress needle insufflation/open Hasson technique) determined by operating surgeon

5.1.4. Incision (Open Retropubic)

- Access to abdominal cavity by any reasonable means including lower midline incision, determined by operating surgeon

5.2. Operative Steps

The below operative steps are to be **determined by the operating surgeon**, in accordance with accepted surgical practice and local departmental protocol:

5.2.1. Bladder Release

5.2.2. Endopelvic Fascia Incision

5.2.3. Anterior and Posterior Bladder Neck Transection

5.2.4. Seminal Vesicles Mobilisation & Excision

5.2.5. Dorsal Venous Complex and Urethral Transection

5.2.6. Urethrovesical Anastomosis

The below additional operative steps may also be performed. These are to be determined by the operating surgeon, in accordance with accepted surgical practice, consent of patient and must be documented post-operatively:

5.2.7. eLND

There is no mandated extent of eLND. If performed this should be in keeping with accepted surgical practice and in relation to local

departmental protocol. eLND must be recorded in trial documentation post-operatively.

5.2.8. Unilateral Nerve Sparing

5.2.9. Continence Suture (Rocco or alternative)

5.2.10. Suprapubic Catheter Insertion

5.2.11. Mesh Repair of Inguinal Hernia

- Mesh repair of inguinal hernia if noted intra-operatively.

5.2.12. Biobanking

- **Depending on individual consent.** Biobanking of pathological tissue or retrieval of tissue of operative pathology and biopsy of recurrent disease from prostatic and extra prostatic sites.

5.3. Specimen Delivery, Drain Insertion & Closure

5.3.1. Specimen Delivery

- Delivery by any incision at surgeons discretion

5.3.2. Drain insertion

- Pelvic drain insertion at surgeons discretion

5.3.3. Closure

- Fascia/port-site and skin closure as determined by operating surgeon

5.3.4. Surgical Documentation

- Surgical procedure performed should be documented on InForm (electronic) trial database

5.4. Postoperative Care

5.4.1. Urinary Catheter

- Urinary catheter to remain inserted for period of 7-14 days as determined by operating surgeon
- Removal of catheter documented in trial visit 6 (34 +/- 12 weeks)

5.4.2. Deep Vein Thrombosis (DVT) Prophylaxis

- Mechanical and chemical DVT prophylaxis should be given whilst patient has reduced mobility in accordance with local protocol up to 28 days post-operative procedure.

6. Revision History

SSPM Ref.	Date Effective	Reason for update (page and section of change)
XX000.00	DD MMM YYYY	

<Insert section break if adding any Attachments>

7. Appendix A

Quality Assurance Panel will meet to decide upon operating surgeon inclusion in ATLANTA trial.

Outcome will be guided by individual operating surgeon declaration [ATLANTA Surgeon Quality Assurance Declaration] confirming they have met minimum standards expected of an operating surgeon in ATLANTA as listed below:

1. > 200 recorded cases in logbook
2. <4% Complication Rate*
*(Clavien Dindo III and above)
3. <3% Post-operative transfusion rate

STUDY SPECIFIC PROCEDURE MANUAL**Minimally Invasive Ablative Therapy (MIAT)**

IP2 - ATLANTA:

Adjuvant Treatments to the Local tumour for metastatic prostate cancer:
Assessment of Novel Treatment Algorithms

Protocol Number: 18HH4804

Effective Date: 8th March 2019 **Draft:** 21st February 2019

Prepared by: Name:	Title:	Signature:	Date:
Mr T. T. Shah	Urology Clinical Research Fellow & Trial Co-ordinator		21.02.2019
Mr M. J. Connor	Urology Clinical Research Fellow & Trial Co-ordinator		21.02.2019
Approved by: Name:	Title:	Signature:	Date:
Prof. H. U. Ahmed	Professor of Urology & CI ATLANTA		21.02.2019

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Abbreviations

SOP	Standard Operating Procedure
ICTU	Imperial Clinical Trials Unit
SSPM	Study Specific Procedure Manual
MIAT	Minimally Invasive Ablative Treatment
SV	Seminal Vesicle
HIFU	High Intensity Focused Ultrasound
mpMRI	Multi-Parametric Magnetic Resonance Imaging
MDTM	Multi-Disciplinary Team Meeting
MCCL	Maximum Cancer Core Length
PZ	Peripheral Zone
TZ	Transition Zone
SV	Seminal Vesical
RT	Radiotherapy

1. Introduction

The purpose of this document is to describe the standard operating procedures (SOP) involved for the Minimally Invasive Ablative Treatment Procedures (MIAT), cryotherapy and High Intensity Focused Ultrasound (HIFU).

2. Scope

This procedure is applicable to all patients with metastatic prostate cancer randomised to the MIAT, Intervention arm 2 in the ATLANTA study.

Depending on the tumour location and volume, treatment may be given focally or in a whole-gland/subtotal manner.

3. Responsibilities

Chief Investigator (CI)	• Overall responsibility for the trial • Overall responsibility for your trial at the site • Ensure facilities, staff resources and education are appropriate to carry out the trial • Delegate responsibility and ensure they are documented on the delegation log
Principal investigator (PI)	• Be available to give advice, support and to sign off documents as required • Responsibilities for carrying out study procedures or delegating these to appropriately trained staff where necessary
MIAT-lead	• Ensure the standard operating procedure is in accordance with trial intervention, based on safe and accepted MIAT practice. • Aware of SOP and mechanism to report deviation from SOP.
Research Nurse or Trial Coordinator or Trial Practitioner	• Assist in sample handling including collection, labelling, processing, storage and transportation of biobanking samples. • Ensure consent is taken for additional biobanking samples.

Trial Manager	• Liaise with local study team to ensure study procedures are carried out in accordance with trial protocol and procedural manuals • Support and advice trial team and respond to queries as needed.
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4. MIAT Quality Assurance

All MIAT surgeons and centres will need to be approved via the ATLANTA MIAT Board. At site set-up all centres and surgeons will need to give estimated total number of procedures performed to date and also number performed per year.

5. Treatment Planning

Tumour location and volume will be determined by a combination of multiparametric MRI (mpMRI).

In cases of unilateral clinically significant disease confirmed by negative contralateral biopsies and no mpMRI PIRADS or LIKERT 3-5 lesion where an alternative pathology cannot explain the MRI findings i.e. clinically insignificant disease, atrophy or inflammation, a quadrant ablation approach to the treatment plan may be adopted.

Treatment fields may extend across the midline or performed as a hemi-ablation to ensure an adequate margin of 5-10mm is achieved. A hockey stick (hemi-ablation with midline extension either anteriorly or posteriorly) will be permitted.

In cases of unilateral clinically significant disease with negative or clinically insignificant prostate cancer in the contralateral biopsies and a mpMRI PIRADS or LIKERT lesion 3-5 but in whom the pre-randomisation biopsies showed significant cancer, treatment should incorporate a quadrant or the entire contralateral lobe

In cases of unilateral clinically significant disease with clinically insignificant prostate cancer in the contralateral biopsies and a mpMRI PIRADS or LIKERT lesion 3-5 at baseline and at post systemic therapy biopsies, the decision to treat the contralateral lobe will be at the discretion of the treating clinician or central multi-disciplinary team meeting (MDTM).

Clinically insignificant disease is defined as $\leq$ Gleason 3+3 and Maximum Cancer Core Length (MCCL) of <6 mm.

In cases of bilateral clinically significant disease either of the following treatment plans may be utilised: Anterior or Posterior Extension, Hockey stick, subtotal with either anterior or posterior sparing or a whole-gland treatment.

In cases of whole-gland treatment, rectal protection procedures such as but not limited to gel or balloon spacers or hydro-dissection may be utilised but are dependent on energy modality used.

In all cases if deemed clinically necessary or in particular for whole-gland treatment a simultaneous bladder neck incision or transurethral resection of the prostate (TURP) may be performed at the discretion of the treating clinician.

Seminal Vesical (SV) treatment for T3b disease is permitted to both SVs if deemed feasible by the treating clinician and either HIFU or cryotherapy may be used. It should be noted that SV disease of >10mm is better treated with cryotherapy.

6. Energy Modality Selection

The energy modality must be selected based on the chosen treatment plan with the following guidance applying:

Patients with peripheral zone (PZ) tumours in glands with an AP height of ≤ 3 cm may undergo either cryotherapy or HIFU.

Patients with anterior or transition zone (TZ) disease (of any gland size) or those needing subtotal or whole-gland treatment should undergo Cryotherapy as the urethral warmer protects the urethra against stricture formation as well as protects the external sphincter.

Patients with PZ tumour in glands with an AP height > 3 cm who need a hemi ablation should undergo Cryotherapy.

Patients with widespread calcification that may impede delivery of HIFU to the target area or a tight anus/rectum or those that require spinal anaesthesia should undergo Cryotherapy.

7. Procedures

7.1. Cryotherapy

Procedure may be performed under either a general anaesthetic or a spinal anaesthetic with sedation.

Local operative procedure and manufacturer guidance should be followed with the following taken into consideration:

All patients should undergo an initial freeze-thaw cycle with a target temperature for the cancer lesion thermocouple of -40°C or lower held for at least 3 minutes. Subsequently a 3-minute passive and 3-minutes active thaw should be performed followed by a second freeze-thaw cycle of similar parameters, times and temperature targets. Following the second cycle an active thaw should be performed only until it is possible to remove the needles which will allow for a slow passive thaw to occur naturally. A third freeze-thaw cycle is allowed and can be used at the clinician's discretion.

The margin of the focal cryotherapy should be determined by visualisation of the hypoechoic ice-ball edge and must ideally extend at least 5mm beyond the intra-prostatic tumour margin. Extraprostatic tumour margins should have the ice-ball edge to 1-2mm beyond the tumour margin if possible or as wide as is safely deemed possible by the treating clinician. Due to the cytoreductive nature of the treatment in this study complete tumour ablation may not be possible in all men.

Treatment of the SV should extend as much cranially as is safe but the clinician should be aware of the likely proximity of the ureters.

All patients should have a urethral catheter placed post-operatively for a minimum of 7 days.

Antibiotics peri- and post-operatively should be given as per local policies.

7.2. High Intensity Focussed Ultrasound (HIFU)

Procedure should be performed under a general anaesthetic.

Local operative procedure and manufacturer guidance should be followed with the following taken into consideration:

- Treatment using three blocks
- Dose escalation i.e. layering
- Longer duty cycle

All patients should have a urethral catheter placed post-operatively for a minimum of 7 days.

Antibiotics peri- and post- operatively should be given as per local policies.

7.3. Pelvic Nodal Treatment

Pelvic nodal treatment will be given in accordance with the trial protocol. This may take the form of radiotherapy or surgery. This should be booked, if necessary, after 6 weeks following the ablation to allow for recovery of LUTS.

8. Revision History

SSPM Ref.	Date Effective	Reason for update (page and section of change)
XX000.00	DD MMM YYYY	

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STUDY SPECIFIC PROCEDURE MANUAL

**Laparoscopic or Robotic-Assisted Laparoscopic
(Extended) Pelvic Lymph Node Dissection
following Minimally Invasive Ablative Therapy (MIAT)**

IP2 - ATLANTA:

Adjuvant Treatments to the Local tumour for metastatic prostate cancer:
Assessment of Novel Treatment Algorithms

Protocol Number: 18HH4804

Effective Date: 8th March 2019 **Draft:** 22nd February 2019

Prepared by: Name:	Title:	Signature:	Date:
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Approved by: Name:	Title:	Signature:	Date:
Mr T. Dudderidge	Consultant Urological Surgeon		
Approved by: Name:	Title:	Signature:	Date:
Prof. Hashim U. Ahmed	Chief Investigator, Professor of Urology		

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Introduction

The purpose of this document is to describe the standard operating procedures (SOP) involved in (extended) pelvic lymph node dissection following minimally invasive ablative therapy (MIAT).

1. Scope

This procedure is applicable to all patients with metastatic prostate cancer randomised to intervention arm 1 in the ATLANTA study who have been selected prior to randomisation to have lymph node treatment following MIAT and subsequently chosen to undergo the offered surgical treatment following discussion with a named trial urological surgeon.

Surgical treatment will consist of extended pelvic lymph node dissection (ePLND), as per treating surgeon in accordance with accepted local surgical practice. Pelvic lymph node dissection should be determined prior to patient randomisation. We strongly recommend, but do not limit, ePLND to men with a suspicious/avid lymph node(s) on PET Scan or ≥ 10 mm lymph node on a CT AP.

Extended pelvic lymph node dissection maybe performed synchronous with MIAT (see MIAT SOP) or at a suitable delay (recommended four weeks). This is at the discretion of the treating trial surgeon.

The operating trial surgeon (OS) must have meet ATLANTA surgeon quality control measures as described in **Appendix A**. A signed and completed quality assurance declaration must be submitted to the ATLANTA trial team prior to performing surgery within the ATLANTA study.

2. Abbreviations

SOP	Standard Operating Procedure
ICTU	Imperial Clinical Trials Unit
SSPM	Study Specific Procedure Manual
RALP	Robotic-assisted laparoscopic radical prostatectomy
LRP	Standard laparoscopic radical prostatectomy
ELND	Extended lymph node dissection

3. Responsibilities

Chief Investigator (CI)	• Overall responsibility for the trial • Overall responsibility for your trial at the site • Ensure facilities, staff resources and education are appropriate to carry out the trial • Delegate responsibility and ensure they are documented on the delegation log
Principal investigator (PI)	• Be available to give advice, support and to sign off documents as required • Responsibilities for carrying out study procedures or delegating these to appropriately trained staff where necessary
Surgical Lead/Co-lead	• Ensure the standard operating procedure is in accordance with trial intervention, based on safe and accepted surgical practice. • Ensure operating surgeon is aware of SOP and mechanism to report deviation from SOP.
Operating Surgeon (OS)	• Perform surgical intervention as per standard of practice. • Record deviations from SOP via trial electronic database and in correspondence with main trial site (via research nurse or direct contact).
Research Nurse	• Assist in sample handling including collection, labelling, processing, storage and transportation of biobanking samples. • Ensure consent is taken for additional biobanking samples.
Trial Manager	• Liaise with local study team to ensure study procedures are carried out in accordance with trial protocol and procedural manuals • Support and advice trial team and respond to queries as needed.

4. References

- Poelaert F, C Verbaeys, B Rappe, B Kimpe, *et al.* 2017. Cyto-reductive Prostatectomy for Metastatic Prostate Cancer: First Lessons Learned From the Multicentric Prospective Local Treatment of Metastatic Prostate Cancer (LoMP) Trial. *Urology*. 106: 146-152.
- Montorsi, F, Timothy W, Raymond, E., Walter A *et al.* 2012. "Best Practices in Robot-assisted Radical Prostatectomy: Recommendations of the Pasadena Consensus Panel". *European Urology*. 62 (3): 368-381.
- Ukimura O, De Castro Abreu Al, Matsugasumi T, Shoji S, Ma Y, & Gill Is. (2014). Robot-assisted laparoscopic high-intensity focused ultrasound for focal therapy of prostate: novel approach. *International Journal of Urology : Official Journal of the Japanese Urological Association*. 21, 1289-90.

5. Procedures

5.1. Anaesthesia, Patient Positioning, Access to Abdominal Cavity

5.1.1. Anaesthesia

- General anaesthesia achieved as per anaesthetist, patient specific factors and in accordance to local protocol.
- Local or regional anaesthesia as per patient specific factors, surgeon and anaesthetist discretion and in accordance to local protocol.

5.1.2. Patient Positioning

- Patient positioned in Trendelenburg or similar position as determined by patient specific factors and operating surgeon

5.1.3. Pneumoperitoneum (LRP/RALP)

- Access to abdominal cavity by any reasonable means determined by operating surgeon
- Pneumoperitoneum (Laparoscopic/Robotic Assisted) created by any means (Veress needle insufflation/open Hasson technique) determined by operating surgeon

5.2. Operative Steps

The below operative steps are to be **determined by the operating surgeon**, in accordance with accepted surgical practice and local departmental protocol:

5.2.1. ePLND

There is no mandated extent of ePLND or templating provided in this study. ePLND should be in keeping with accepted surgical practice and in relation to local departmental protocol. ePLND must be recorded in trial documentation post-operatively.

5.2.2. Biobanking

- **Depending on individual consent.** Biobanking of pathological tissue or retrieval of tissue of operative pathology and biopsy of recurrent disease from prostatic and extra prostatic sites.

5.3. Specimen Delivery, Drain Insertion & Closure

5.3.1. Specimen Delivery

- Delivery by any incision at surgeons discretion

5.3.2. Drain insertion

- Pelvic drain insertion at surgeons discretion

5.3.3. Closure

- Fascia/port-site and skin closure as determined by operating surgeon

5.3.4. Surgical Documentation

- Surgical procedure performed should be documented on InForm (electronic) trial database

5.4. Postoperative Care

5.4.1. Urinary Catheter

- At discretion of treating surgeon. If synchronous with MIAT then catheter to remain in situ.

5.4.2. Deep Vein Thrombosis (DVT) Prophylaxis

- Mechanical and chemical DVT prophylaxis should be given whilst patient has reduce mobility in accordance with local protocol up to 28 days post-operative procedure.

6. Revision History

SSPM Ref.	Date Effective	Reason for update (page and section of change)
XX000.00	DD MMM YYYY	

<Insert section break if adding any Attachments>

7. Appendix A

Quality Assurance Panel will meet to decide upon operating surgeon inclusion in ATLANTA trial.

Outcome will be guided by individual operating surgeon declaration [ATLANTA Surgeon Quality Assurance Declaration] confirming they have met minimum standards expected of an operating surgeon in ATLANTA as listed below:

1. > 200 recorded cases in logbook
2. <4% Complication Rate*
*(Clavien Dindo III and above)
3. <3% Post-operative transfusion rate

STUDY SPECIFIC PROCEDURE MANUAL



Metastasis-Directed Therapy (MDT), [SABR & Surgical Metastasectomy]

IP2 - ATLANTA:

Additional Treatments to the Local tumour for metastatic prostate cancer:
Assessment of Novel Treatment Algorithms

Protocol Number: 18HH4804

Effective Date: 24th February 2021

Draft: 29th March 2019

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1. Foreword

This document describes the metastasis directed therapy (MDT) in the form of SABR and surgery.

SECTION A: SABR

The SABR outlining, planning and QA processes for the ATLANTA trial will be managed by the RTTQA Group. When used in conjunction with the main trial protocol it provides all the information necessary for management of patients to be treated with SABR. The clinicians undertaking SABR treatments within the ATLANTA trial will need to have met the RTTQA quality control measures as described in Appendix A. Selected trial centres may be eligible for streamlined quality assurance, based on prior RTTQA Group SABR QA programmes (Appendix A). This document should not be used as a guide for the treatment of patients outside of this trial.

Every care has been taken in drafting these guidelines but corrections or amendments may be necessary. These will be circulated to investigators in the trial, but centres entering patients for the first time are advised to contact RTTQA via atlanta.qa@nhs.net. If you have any queries in regards to the SABR guidelines please submit by email to the following address: atlanta.qa@nhs.net or your local RT QA contact.

SECTION B: Surgery

Surgery performed to metastasis in the ATLANTA trial will be overseen by the ATLANTA Surgeons Quality Assurance Board. The operating trial surgeons (OS) must have met ATLANTA surgeon quality control measures as described in **Appendix B**.

A signed and completed quality assurance declaration must be submitted to the ATLANTA trial team prior to performing surgery within the ATLANTA study. Every care has been taken in drafting these guidelines but corrections or amendments may be necessary. These will be circulated to investigators in the trial, but centres entering patients for the first time are advised to contact the trial team via atlanta@imperial.ac.uk.

2. Introduction

The purpose of this document is to describe the standard procedures (SOP) involved in:

- A. **SABR:** SABR to extracranial synchronous prostate oligometastasis. This is available to men in Intervention Arm 1 (MIAT) or 2 (Radical Radiotherapy or Cytoreductive Radical Prostatectomy).
- B. **Surgery:** Surgical metastasectomy focused on, but not limited to, retroperitoneal lymph node dissection (RPLND). This is available to men in Intervention Arm 1 (MIAT) or 2 (Cytoreductive Radical Prostatectomy Only).

3. Scope

- A. This procedure is applicable to patients with *de novo* metastatic prostate cancer with CHAARTED defined “**Low Volume**” disease randomised to either intervention arm 1 (**MIAT**) or intervention arm 2 (**Radical Radiotherapy or Radical Prostatectomy**) in the ATLANTA trial, who have chosen to undergo the offered extracranial SABR treatment to following discussion with a named trial clinical oncologist.

If the target lesion can be reliably identified* following systemic therapy (irrespective of functional activity) or accurately localised (irrespective of identification) then SABR can be delivered to the site.

*Sites that may be reliably identified include, but are not limited to vertebral body, pubic ramus, femoral head. Sites that may be challenging to localise without sclerosis include, but are not limited to the lateral aspect of rib and the central iliac bone.

Some worked out examples below:

Target Lesion at	Imaging Post-Systemic Therapy	Trial Recommended Action
Diagnosis		
Iliac bone	Visible	Consider SABR
Vertebral body	Sclerosis or no longer visible	Consider SABR
Femoral head	Sclerosis or no longer visible	Consider SABR

Pubic ramus	Sclerosis or no longer visible	Consider SABR
Lateral rib	No longer visible	Consider omission of SABR
Central iliac bone	No longer visible	Consider omission of SABR
Para-aortic lymph node	No longer visible	Omit SABR

All SABR treatment within this trial is made with reference to the SABR UK consortium guidelines version 6.1 (January 2019). However, these guidelines are currently under revision, therefore the ATLANTA SABR guidelines have been brought in line with the HALT radiotherapy and quality assurance guidelines v3.1 20201005, the TRAP radiotherapy and quality assurance guidelines v2.0 20210218 and the SARON Radiotherapy & QA Guidelines v3.0 Final. This will ensure consistency across SABR clinical trials.

SABR will be performed a minimum of two weeks after local prostate +/- SV +/- pelvic lymph node treatments in the trial, but within 3 months. This is set out in the ATLANTA **Local Radiotherapy SOP**.

Prior EBRT directed to pelvic metastasis

It is recognised that some patients who are of low volume disease and randomised to radical radiotherapy with MDT, may under simultaneous EBRT directed to pelvic bone metastasis which are within reach of planned radiotherapy fields (e.g. pubic ramus) at the time of their allocated local treatment. This is set out in the ATLANTA **Local Radiotherapy SOP**.

These patients thus only require lesion-directed SABR if metastasis were either: not treated simultaneously with EBRT and/or are anatomically outside these radiotherapy fields.

- B. This procedure is applicable to all patients with de novo metastatic prostate cancer randomised to Intervention Arm 1 (MIAT) or 2 (Cytoreductive radical prostatectomy Only). Surgical metastasectomy focused on, but not limited to, retroperitoneal lymph node dissection (RPLND). Surgical approach includes open/standard laparoscopic/robotic assisted. Surgical MDT in both intervention arms maybe performed at the time of surgical treatment to the primary tumour or within 12 weeks of primary procedure.

Surgical treatment of nodal stations below the common iliac artery bifurcation/true pelvis should be managed as per pelvic lymph node dissection, as set out in the ATLANTA **Radical Prostatectomy SOP**.

4. Abbreviations

SOP	Standard Operating Procedure
ICTU	Imperial Clinical Trials Unit
SSPM	Study Specific Procedure Manual
RT	Radiotherapy
SABR	Stereotactic Ablative Body Radiotherapy
SBRT	Stereotactic Body Radiotherapy
MIAT	Minimally Invasive Ablative Therapy
MDT	Metastasis Directed Therapy
VMAT	Volumetric Modulated Arc Radiotherapy
IMAT	Intensity Modulated Radiotherapy
CORE	COnventional care versus Radioablation (stereotactic body radiotherapy) for Extracranial oligometastases
RPLND	Retroperitoneal Lymph Node Dissection
CRP	Cytoreductive Radical Prostatectomy
EBRT	External Beam Radiotherapy

5. Responsibilities

Chief Investigator (CI)	• Overall responsibility for the trial • Overall responsibility for your trial at the site • Ensure facilities, staff resources and education are appropriate to carry out the trial • Delegate responsibility and ensure they are documented on the delegation log
Principal investigator (PI)	• Be available to give advice, support and to sign off documents as required • Responsibilities for carrying out study procedures or delegating these to appropriately trained staff where necessary
Surgeon	• Ensure the standard operating procedure is in accordance with trial intervention, based on safe and accepted radiotherapy practice. • Aware of SOP and mechanism to report deviation from SOP
Oncology Lead/Co-lead	• Ensure the standard operating procedure is in accordance with trial intervention, based on safe and accepted radiotherapy practice. • Aware of SOP and mechanism to report deviation from SOP.
Radiotherapist / Clinical Oncologist	• Deliver radiotherapy intervention as per standard of practice. • Record deviations from SOP via trial electronic database and in correspondence with main trial site (via research nurse or direct contact).

Research Nurse	• Assist in sample handling including collection, labelling, processing, storage and transportation of biobanking samples. • Ensure consent is taken for additional biobanking samples.
Trial Manager	• Liaise with local study team to ensure study procedures are carried out in accordance with trial protocol and procedural manuals • Support and advice trial team and respond to queries as needed.

6. References

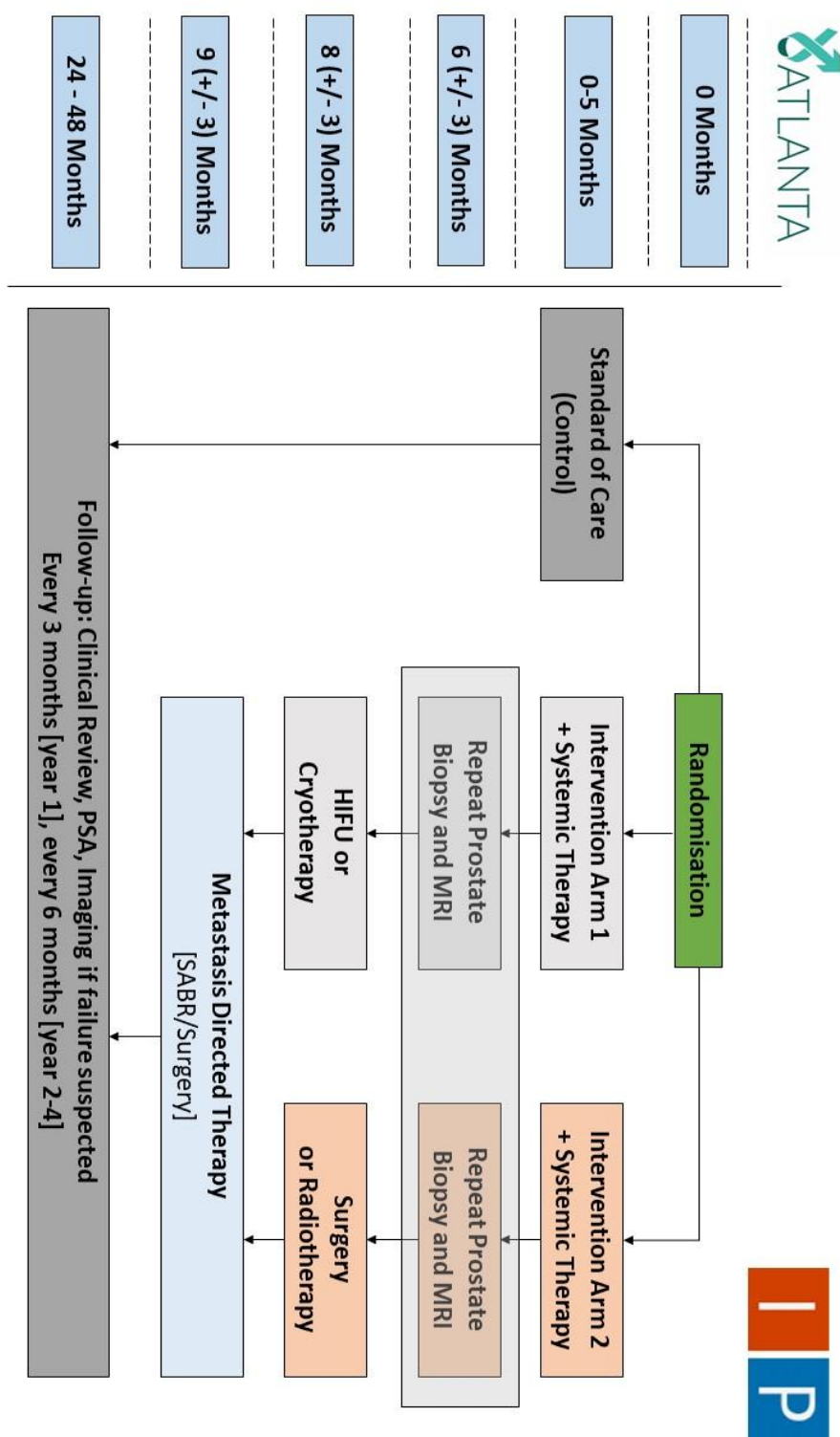
SECTION A: SABR

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SECTION A: Surgical Metastasectomy

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*Repeat Prostate Biopsy and MRI in Pilot Phase Only.

Note: SABR offered to men categorised as low burden at entry trial only.

7. SECTION A: SABR

7.1. Time interval

- SABR should not be delivered whilst concurrent chemotherapy is being delivered. Concurrent hormonal therapy is acceptable.
- SABR delivered to metastasis must be completed within 3 months of: Local prostate radiotherapy +/- SV +/- lymph nodes OR cytoreductive radical prostatectomy (CRP) OR MIAT. The ATLANTA trial should be contacted if treatment exceeds this time at atlanta@imperial.ac.uk.

7.2. Preparation

Radiation can be given on a Cyberknife or a gantry-based linac.

- Where considered appropriate e.g. for tracking delivery or to aid pre-treatment verification 3-5 fiducial markers will be placed around the lesion, into stable structures where possible, under CT guidance. This is as per usual standard of care. A single fiducial centrally located within a lesion may suffice for small, circular lesions. Clotting screen and ECG should be performed pre-insertion.
- For patients who have had fiducial markers inserted, the localisation scan will be done no earlier than 7 days after insertion to account for potential fiducial marker migration.
- For patients receiving intravenous contrast (see below), they should be advised not to eat or drink anything other than clear fluids for 2 hours prior to the localisation scan.
- For patients with pelvic lesions, interventions to reduce rectal gas artefacts (e.g. Microlet enemas 2 days before and day of CT planning, then 2 days before first treatment and on the day of each 5 treatments) should be considered where clinically appropriate. For most pelvic targets the bladder should usually be moderately full at the time of

simulation and treatment (e.g. empty bladder, drink 325ml and hold bladder for one hour).

- Patients with treated lesions close to the stomach/duodenum will be prescribed anti-emetics (5HT3 antagonists are preferred) and prophylactic proton pump inhibitors (to be continued for at least 3 months following treatment).
- Patients with pelvic lesions may be prescribed anti-diarrhoeal medication to take on an as required basis.

Co-morbidities considered to preclude safe use of SBRT:

Depending on the location of the lesions to be treated with SBRT, certain co-morbidities are relative contraindications to SBRT and usually considered as exclusion criteria for trial entry.

If the treating clinician is concerned about any co-morbid condition, they should contact the ATLANTA Trial CI/ SABR Lead (hashim.ahmed@nhs.net / imperial.atlanta@nhs.net / Vincent.khoo@rmh.nhs.uk) prior to the patient being entered into the trial.

As examples:

- A history of or radiological evidence of idiopathic pulmonary fibrosis
- A history of inflammatory bowel disease
- A history of significant systemic connective tissue disorder

7.3. Patient positioning and immobilisation

- Patients will be supine and positioned to aid comfort, stability and setup reproducibility. Knee and/or ankle supports will be used.
- For the majority of patients treated on a linac, the arms will be positioned above the head using a chest board and consideration will be given to using a vacuum bag to aid comfort and stability, particularly for treatment of vertebral lesions. For lower pelvic targets, arms may be across chest.

- For patients treated on a CyberKnife, the arms will be positioned by their sides and consideration will be given to using a vacuum bag to aid comfort and stability.
- For patients treated on a linac or CyberKnife with vertebral metastases at T4 or higher, or high anterior rib or sternal lesions, the arms will be positioned by their sides and the patient will be immobilised in a 5-point shell and consideration will be given to using a vacuum bag to aid comfort and stability.

7.4. Localisation Imaging

7.4.1. CT Slice Thickness

- For SBRT on a linac, maximum slice thickness will be 3 mm (2mm for spine).
- For SBRT on a CyberKnife, maximum slice thickness will be 1.5 mm.

7.4.2. CT Scanning levels

- The extent of the scan will depend on location of the lesion(s) being treated and the planning technique (non-co-planar planning technique with CyberKnife requires consideration of a greater cranial/caudal extent of dose assessment for normal tissues).
- All organs at risk for delineation need to be considered prior to scanning, for example, lesions in the upper abdomen may need dosimetric information from the entire lung and both kidneys and scan length should account for this.

7.4.3. Respiratory Motion Management in Localisation Imaging Acquisition

For intra-thoracic lesions which exhibit intra-fraction motion due to normal respiration e.g. anterior rib or sternal lesions, motion management techniques will be mandatory. Options include:

- Respiratory correlated 4DCT for intra-thoracic lesions (for highly mobile lesions, this alone may not be the most appropriate technique – consider one of those listed below).
- Breath-hold CT using Active Breathing Control (ABC) with breath-hold (in moderate deep inspiration for lung lesions and in exhale for liver and adrenal lesions).
- Free breathing CT using abdominal compression.
- Free-breathing CT for CyberKnife tracking of intra-fraction lesion motion via fiducials or X-sight lung (respiratory gating using an external marker is not permitted).

7.4.4. Use of Intravenous (IV) and/or Oral Contrast

- IV contrast will be considered, unless medically contraindicated, where it will aid target delineation e.g. lymph node targets to differentiate from vessels and where it will aid normal tissue delineation e.g. contouring of brachial plexus avoidance structure using vessels as a surrogate.
- The technique for IV contrast scan will depend on the method of respiratory motion management and individual centre practice. Where respiratory correlated 4DCT for linac delivery or CyberKnife tracking is being used for motion management, IV contrast may be given during an additional reference scan and the images fused with the 4DCT scan.
- Oral contrast or water (100-150 cc) will be considered up to 30 minutes prior to scanning if optimal visualization of duodenum is required, particularly for treatment of liver and right sided adrenal lesions.

7.4.5. Image Registration

- Repeat whole body imaging following local treatment, prior to SABR is strongly recommended, although not mandated. This should be performed according to local protocols following discussion with treating

trial clinician. Whole body imaging may take the form of: PET-CT, MRI, CT or Bone Scan

- **Repeat whole body imaging requested must mirror initial imaging modality at diagnosis.**
- All patients having vertebral metastases treated will additionally have an MRI (T1 and T2 sequences) of the involved vertebral level(s) plus at least two vertebral levels above and below to aid delineation. This should be performed on the same day as the CT scan with the same set up/immobilisation as the CT scan to optimise accuracy of image registration.
- Additional PET and/or MRI imaging will be used to aid target delineation where appropriate, for example, some bone metastases other than vertebral and for some lymph node targets.

7.5. Targeted Delineation

7.5.1. Target Volume Nomenclature

Consistent naming of contoured structures used in radiotherapy treatment planning is essential to facilitate the comparison of dose-volume statistics across patients for quality assurance and outcomes analysis. Maintaining consistency in nomenclature is particularly important (and challenging) in multi-institutional clinical trials, in which treatment planning data are collected from many participating institutions. A scheme for uniform naming of the structures for ATLANTA is provided, in line with AAPM TG-263 recommendations [1]. The nomenclature must be applied for treatment planning in all trial patients.

Please use the proposed naming convention in Table 1 for all target volumes (OAR nomenclature is given in Table 3). Lesions will be labelled 1 for the most cranial and increasing in number as they appear caudally.

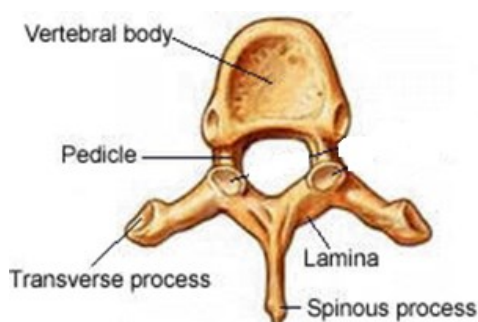
Table 1: Examples of target volume nomenclature

ICRU Name	Number	Prescription Dose (Gy)	Proposed Name
GTV	1	30	GTV1_3000
CTV	1	30	CTV1_3000
ITV	1	30	ITV1_3000
PTV	1	30	PTV1_3000
PTV	2	30	PTV2_2700

- **The total number of targeted metastasis should not exceed 3.**
- Metastases should not individually exceed a longest diameter of 7 cm, calculated on imaging prior to systemic therapy.

7.5.2. Vertebral Bony Lesions

- GTV = Visible disease as defined on CT and registered MRI.
- CTV is defined on CT and registered MRI following the International Spine Radiosurgery Consortium (ISRC) Guidelines (Figures 1 and 2, and Table 1 below) [2]

**Figure 1:** Anatomical parts of a vertebra

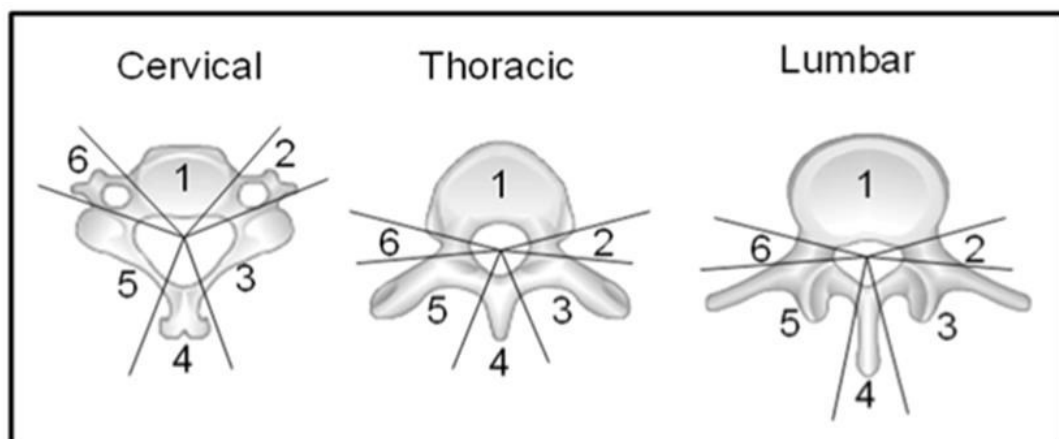


Figure 2: Vertebral lesion CTV schematic

Table 2: ISRC Consensus Guidelines for Target Volume Definition in Spinal Stereotactic Radiotherapy.

GTV Involvement	GTV Anatomic Classification	ISRC Bony CTV Recommendation	CTV Description
GTV in any portion of the vertebral body	1	1	Include the entire vertebral body
GTV lateralised within the vertebral body	1	1,2	Include the entire vertebral body and the ipsilateral pedicle/transverse process
GTV diffusely involves the vertebral body	1	1,2,6	Include the entire vertebral body and the bilateral pedicle/transverse processes
GTV involves vertebral body and unilateral pedicle/transverse process	1,2	1,2,3	Include the entire vertebral body, ipsilateral pedicle, transverse process and lamina
GTV involves vertebral body and bilateral pedicles/transverse processes	1,2,3	1,2,3,5,6*	Include the entire vertebral body, bilateral pedicles/transverse processes and laminae
GTV involves unilateral pedicle	2	2,3, +/- 1	Include ipsilateral pedicle/transverse process, lamina +/- entire vertebral body
GTV involves unilateral lamina	3	2,3,4	Include ipsilateral pedicle/transverse process, lamina and spinous process
GTV involves spinous process	4	3,4,5	Include entire spinous process and bilateral laminae

*corrected from original paper as some sections were missing

- PTV margin is dependent on technique and should be decided by individual centres following internal audit of immobilization device and delivery technique. A **minimum** PTV margin will be 1 mm for CyberKnife and 2mm for linac based delivery. If a margin > 3mm is needed to meet local set-up requirements then vertebral SBRT should not be delivered. Please discuss with RTTQA contact.

7.5.3. Non-Vertebral Bony Lesions (including Sacrum)

The GTV should be outlined, with a CTV margin applied as clinically required to cover microscopic spread.

- GTV = Visible disease as defined on CT/MRI, aided by PET if available.

- CTV = a minimum of 3 mm is suggested, constrained to anatomical boundaries (i.e. constrained to bone). However, along the bone, unless constrained by OAR tolerances, a larger margin up to 5 mm should be considered where this does not conflict with OARs.
- PTV margin is dependent on technique and should be decided by individual centres following internal audit of immobilization device and delivery technique. A minimum margin of 2 mm for CyberKnife and 3 mm for linac-based treatments will be considered, however if spine tracking is being used for lesions of the bony pelvis >10 cm from the spine, an additional margin should be applied.

7.5.4. Lymph Nodes

- GTV = Visible disease as defined on CT/MRI, aided by PET if available.
- CTV = GTV. No additional margin is added for microscopic disease.
- PTV margin is dependent on technique and should be decided by individual centres following internal audit of immobilization device and delivery technique. Minimum margins of 3 mm for both CyberKnife and linac based treatments will be considered, however if spine tracking is being used for lesions of the bony pelvis >10 cm from the spine, an additional margin should be applied.

7.6. Organ at Risk Delineation

Guidance on delineation, including organs not listed below, can be found in Organ at risk delineation for radiation therapy clinical trials: Global Harmonization Group consensus guidelines by Mir et al [3]. Please refer to this document for any OARs not listed in **Appendix B**.

In general, any OARs which are traversed by a treatment beam should be contoured. The whole structure should be contoured where OAR constraints are based on the dose received by a whole organ (e.g. lung, liver, kidneys). Otherwise, a volume of OAR should be outlined, sufficient to show that the OAR constraints have been met, with particular care paid to the volume receiving the highest doses. This will be technique/treatment platform dependent.

OARs should be contoured ≥ 2 cm superiorly and inferiorly to the PTV for coplanar techniques and within 10 cm of the PTV if non-coplanar techniques are used. For vertebral lesions, contouring will be at least a whole vertebra above and below the PTV for coplanar techniques.

Appropriate CT windowing and information from other imaging modalities should be used.

The **body contour** should always be created and the skin should be inspected to ensure that beams do not overlap, producing excessive skin dose, especially where there is a skin fold.

7.7. Dose Fractionation Schedules

Table 4 summarises the dose and fractionation schedules that will be used. A dose range is provided where dose deliverable will be dependent on proximity to normal tissues and hence organ at risk (OAR) doses at treatment planning. The aim is to deliver *the highest possible prescription dose* to the PTV allowable within this range, whilst ensuring all *mandatory* OAR dose constraints are met. Dose to PTV should NOT be further reduced to meet *optimal* OAR dose constraints. All normal tissue **mandatory** constraints will be respected.

If the mandatory dose constraint for an OAR cannot be achieved, the dose in the PTV will be reduced in order to meet the mandatory OAR constraint. Plans will be otherwise rejected. Two approaches are possible:

- Reduced prescription dose: Prescribed dose can be reduced to no less than 90% of the BED.
- Inhomogeneous PTV dose: In case of overlap of the PTV with OAR, the dose to the CTV (or ITV if applicable) can be maintained and the dose within the PTV may be reduced until the planned dose to the OAR meets the acceptable variation criteria for the OAR. The dose in 95% of the PTV should still at least be 80%.

The achieved dose to PTV should be discussed with the ATLANTA Trial SABR Lead.

Table 4: Summary of dose and fractionation schedules (all doses in Gy)

Anatomical Location		Dose (Gy)	Estimated Treatment Time*
Bone	Spine	27 in 3#	3-8 days
	Other	30-40 in 3#**	3-8 days
Lymph Nodes		30-40 in 3#**	3-8 days

**Will be delivered on alternate or consecutive days, depending on local protocol. If there is a gap in treatment >4 days this will need to be reported to the ATLANTA CTU*

***From CORE Radiotherapy Planning & Delivery Guidelines v2.0 (2018) [5]*

7.8. General Planning Principles

- Type B or Monte Carlo algorithms are mandatory for thoracic lesions and preferred for all other indications.
- Where metalwork is present, the Hounsfield Unit conversion table must extend sufficiently high to accurately account for heterogeneity. The use of beam entry avoidance and appropriate density overrides should be considered where necessary.
- Dose grid resolution on the final dose calculation must be ≤ 2 mm. Please ensure the dose grid encompasses the **whole patient** for the final calculation (a pre-requisite for the review platform used in RTTQA). Figure 3 shows an unacceptable dose grid placement.

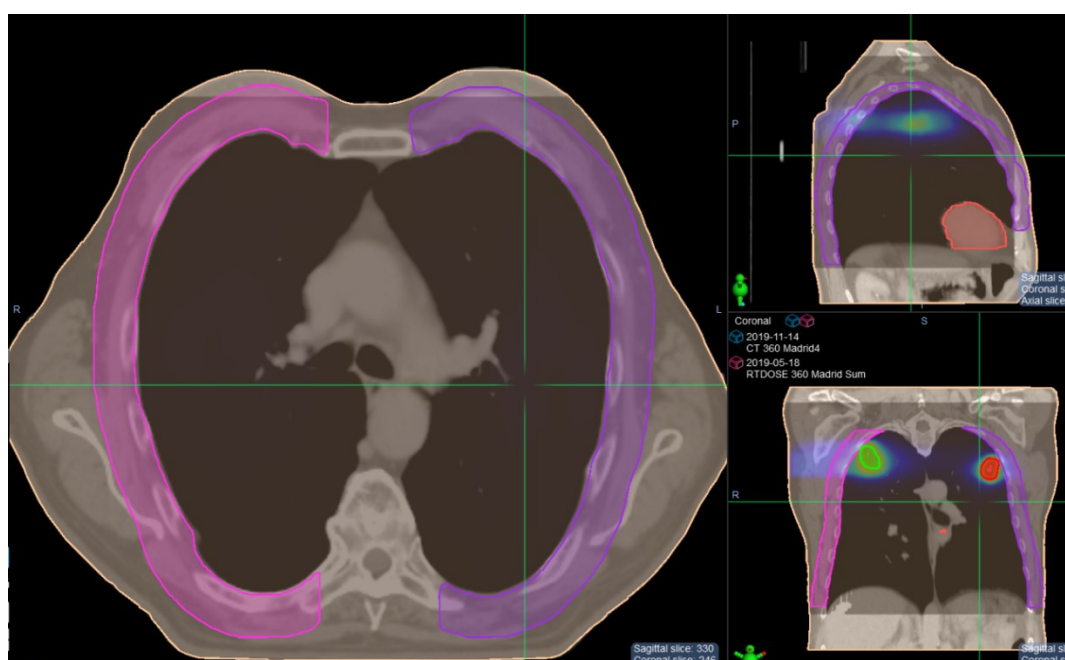


Figure 3: Part of the patient is not included anteriorly, inadequately covering OARs and causing an error in dose calculation

- An end-to-end test of the co-incidence of radiation delivery to a rigid static phantom using image guidance and couch correction should be shown to be ≤ 2 mm

7.9. Target Coverage, Maximum Dose and Conformity Parameters

- **Target Coverage:** Aim for the dose received by 95% of the PTV to be greater than 100% of the prescription dose ($D_{95} \geq 100\%$). It is expected that the PTV is mostly encompassed by the 100% isodose and that this does not break up within the PTV. However, PTV coverage should be compromised where needed to remain within OAR tolerance, generally around the cord or upper abdominal viscera. See examples on Figures 4, 5 & 6. Hotspots should always be contained within the PTV.
- **Maximum Dose:** This should ideally be within 120-140% of the prescribed dose (110-145% mandatory), and be located within the GTV (never outside the PTV). This is equivalent to prescribing to approximately the 71-83% isodose, relative to the maximum (69-91% mandatory). For CyberKnife planning, prescribing to around the 80% covering isodose is typical.
- **Target Dose Conformity:** This should be as detailed in Tables 5.1 and 5.3. Expectations are that the 100% isodose conforms closely around the shape of the PTV and that the 50% is contained within 2cm of the PTV. See examples on Figures 4, 5 & 6. There should be no more than one slice above and below the PTV with 100% isodose on it.

Legend for Figures 4 to 6: Green-PTV; orange-130% isodose; red-100% isodose; yellow-80% isodose; light blue-50% isodose; dark blue-30% isodose

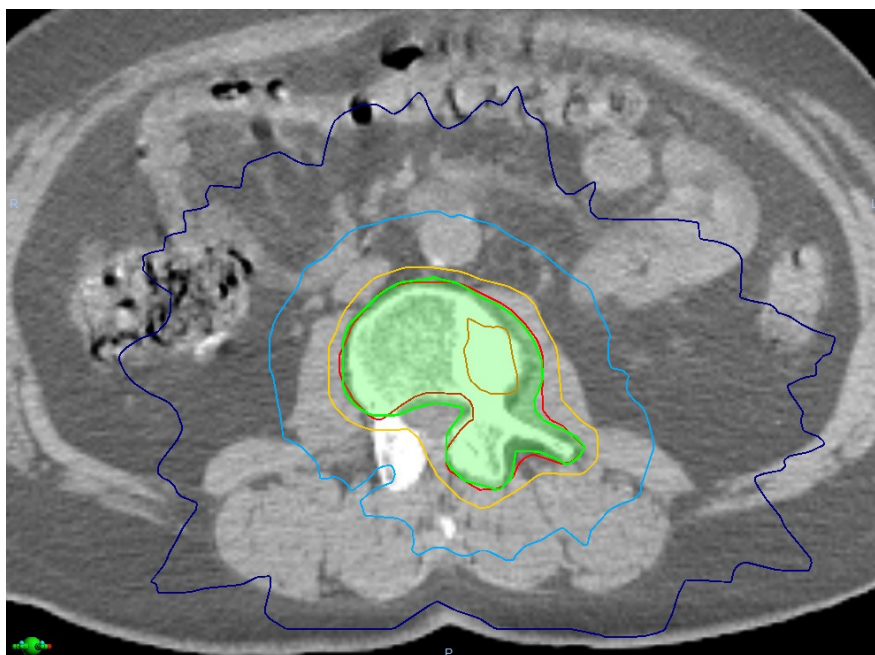


Figure 4: Good spine coverage and highly conformal, especially around transverse process. Plan as per protocol

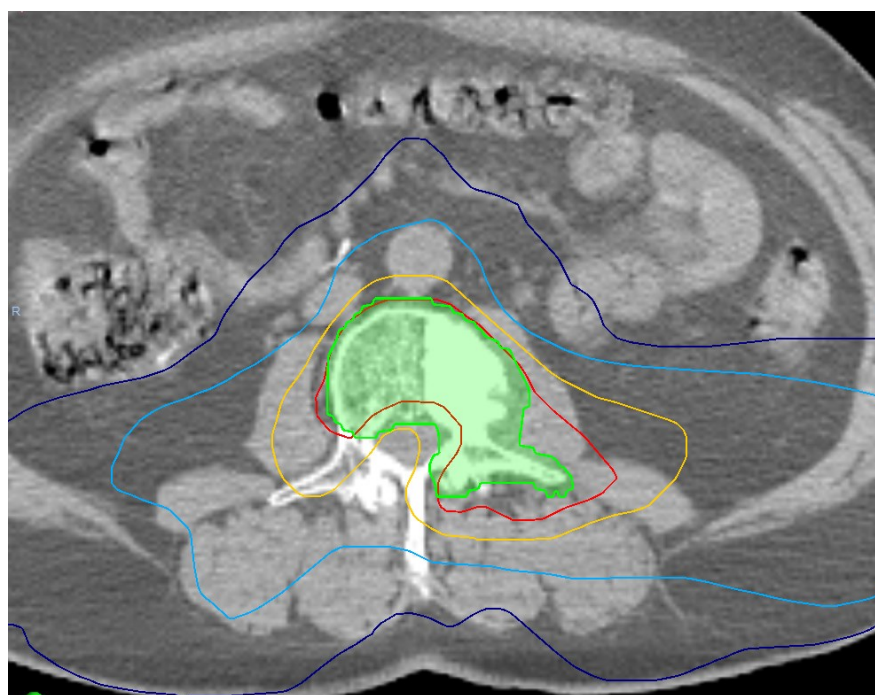


Figure 5: Coverage far too generous and not conforming to PTV. 50% is far beyond 2cm from PTV. Unacceptable plan

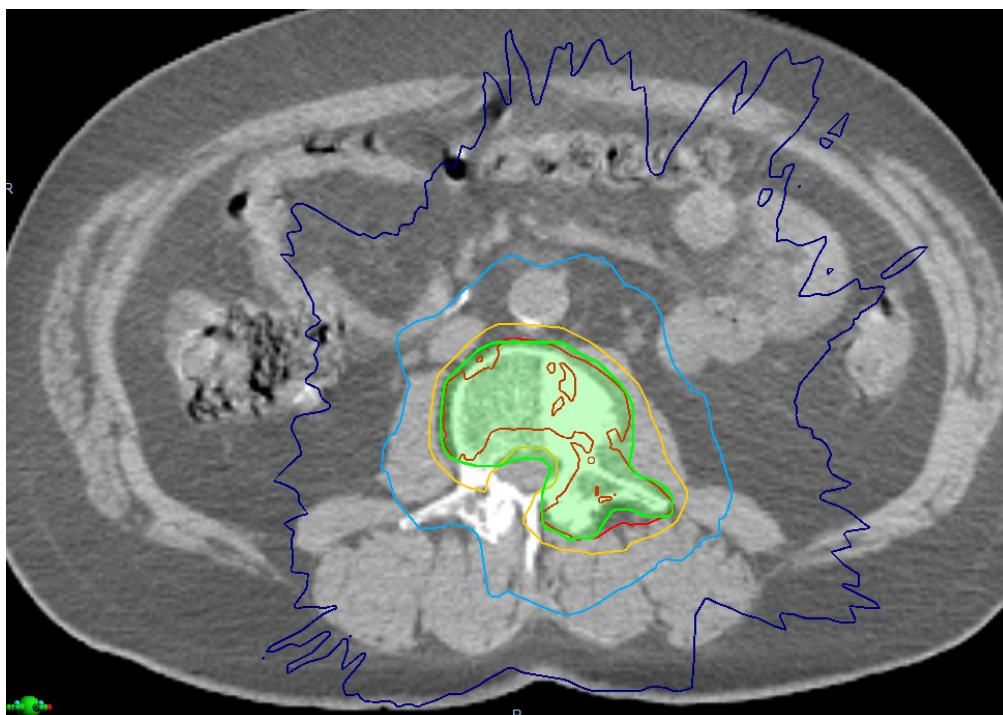


Figure 6: Although a conformal plan, PTV coverage is not good. The 100% isodose does not cover the PTV adequately and breaks up throughout the volume. Unacceptable plan

Evaluation of dose conformity was recently updated in the UK SABR Consortium Guidelines v6.1 [6]. The R100% and R50% metrics lose sensitivity to detect poor conformity with decreasing PTV coverage, so modified metrics are suggested:

$$R100\% = \frac{\text{Vol (100\%)}}{\text{Vol (PTV)}} \rightarrow \text{Prescription dose spillage} = \frac{\text{Body V100\%}}{\text{PTV V100\%}}$$

$$R50\% = \frac{\text{Vol (50\%)}}{\text{Vol (PTV)}} \rightarrow \text{Modified Gradient Index} = \frac{\text{Body V50\%}}{\text{PTV V100\%}}$$

Where “Body V_{100%}” and “Body V_{50%}” are the volumes of the patient receiving at least 100% and at least 50% of the prescription dose (in cc), respectively and “PTV V_{100%}” is the volume of PTV receiving at least 100%

of the prescription dose (in cc). When PTV coverage is 100%, “PTV $V_{100\%}$ ” will equal “Vol (PTV)” and each pair of metrics becomes equivalent.

These new metrics will be used to report conformity for the TRAP trial. Tables 4.1, 4.2 and 4.3 below describe the new dose conformity requirements for both lung and non-lung lesions. “Target” values are based on the median data recorded in the SABR CtE QA Programme. Tolerance and Minor Deviation levels are from the ROSEL Study [7] unless updated with values based on the median +1 S.D. and median +2 S.D. from the SABR CtE QA Programme (denoted by *), or based on Yaparpalvi *et al* [8] (denoted by **).

Table 4.1: Prescription dose spillage (PDS) requirements for both lung and non-lung lesions

PTV (cc)	Body V_{100} (cc)/PTV V_{100} (cc)		
	Target	Toleran	Minor
<20	≤ 1.20	<1.25	1.25-1.40
20-40	≤ 1.10	<1.20	1.20-1.30*
>40	≤ 1.10	<1.15	1.15-1.20*

Table 4.3: Modified Gradient Index (MGI) requirements for non-lung lesions

PTV (cc)	Body V_{50} (cc)/PTV V_{100} (cc)		
	Target	Toleran	Minor
<20	≤ 5.5	<7.5	7.5 - 9.5
20-40	≤ 4.5	<6.0	6.0 - 7.5
>40	≤ 4.5	<5.5	5.5 – 6.5

7.10. Organ at Risk Dose-Volume Constraints

Constraints are taken from UK SABR working group publications [6, 9], with the exception of the heart. Please refer to these documents for any OARs not listed in Table 5 below. The heart constraints are derived from AAPM-101 [10] and the SABR-COMET trial [11], and are a recent consensus reached between the TMG and UK thoracic SABR experts.

- For serial organs, constraints are described as the **maximum volume** of the organ that can receive a threshold dose or more. For parallel organs, the constraints may be described as a **maximum percentage volume** of the organ receiving a threshold dose or more. Alternatively, the constraint may be described as a **minimum critical volume of the organ which must be spared** from receiving a threshold dose or more.
- For patients with two or more sites for SABR treatment whose dosimetry impacts on the same organ, the total combined dose to the organ(s) must be within the constraints. The assessment will often require that a single planning CT for all the SABR treatments involved.
- **Multiple lesions:** lesions in close proximity yet not within the same organ, should be treated ideally on alternate days, however sequentially is also accepted. If the lesions are far apart, they should be treated concurrently to minimise patient visits and overall treatment time.

These dose constraints need to be considered carefully when treating multiple sites with SBRT and when patients have previously been treated with radiotherapy in the past prior to trial entry. The trial does not allow direct re-irradiation of an area of the body.

Please discuss any concerns on eligibility and feasibility with the ATLANTA trial SABR Lead (imperial.atlanta@nhs.net / Vincent.khoo@rmh.nhs.uk)

Table 6: OAR Constraints (for 3 fractions)

Structure	Parameter	Optimal (Gy)	Mandatory (Gy)
BileDuct_Common	D _{0.5 cc}	<50	-
Bladder	D _{0.5 cc}	-	28.2
	D _{15 cc}	-	16.8
Bowel_Large	D _{0.5 cc}	-	28.2
Bowel_Small	D _{0.5 cc}	-	< 25.2
	D _{5 cc}	-	< 17.7
BrachialPlex	D _{0.5 cc}	< 24	< 26
Bronchus_Prox	D _{0.5 cc}	< 30	< 32
CaudaEquina PRV & SpinalCanal^CE	D _{0.1 cc}	-	< 24
	D _{5 cc}	-	< 22
Chestwall	D _{0.5 cc}	< 37	-
	D _{30 cc}	< 30	-
Duodenum	D _{0.5 cc}	-	< 22.2
	D _{5 cc}	-	< 16.5
	D _{10 cc}	-	< 11.4
Esophagus	D _{0.5 cc}	-	< 25.2
FemurHeadNeck	D _{10 cc}	< 21.9	-
GreatVes	D _{0.5 cc}	-	< 45
Heart+A_Pulm*	D _{0.5 cc}	< 26	< 30
Kidney_Cortex (individual/combined)	D _{mean}	-	-
	D _{VTOT -200cc} **	-	< 16
Liver	D _{50%}	< 15	-
	D _{VTOT -700cc}	< 15	< 19.2
LumbSacPlex [†]	D _{0.1 cc}	-	< 24
	D _{5 cc}		< 22
Lungs ^{\$\$}	V _{20 Gy}	-	< 10%
Rectum	D _{0.5 cc}	-	< 28.2
Skin	D _{0.5 cc}	< 33	-
	D _{10 cc}	< 30	-
SpinalCord_PRV & SpinalCanal^SC	D _{0.1 cc}	< 18	< 21.9
	D _{1 cc}	< 12.3	-
Stomach	D _{0.5 cc}	-	< 22.2
	D _{10 cc}	-	< 16.5

Trachea	D _{0.5 cc}	< 30	< 32
Ureter	D _{0.5 cc}	-	< 40

*Heart 3 and 5 fraction constraints are taken from AAPM-101 [10]; 8 fraction constraints are from the SABR-COMET trial [11]

**If total kidney volume <200cc, or treating renal or adrenal lesions, then contralateral kidney D_{0.1cc} <16Gy and minimise spillage into ipsilateral kidney if possible.

7.11. Image Guidance for Treatment Verification and Delivery

Image guidance is mandatory for all fractions with on-line correction with pre-treatment CBCT (+/-fiducials) for linac based treatment delivery or kV-kV imaging during treatment if tracking for CyberKnife based treatment delivery.

- Linac: CBCT (or orthogonal imaging of implanted fiducials) and on-line correction prior to each fraction will be performed with manual adjustment under direct visualization of the tumour if required. The position of critical OAR will be checked. Where intra-fraction target tracking is not available, consideration must be given to intra-fractional motion monitoring or use of fast dose delivery, for example using flattening filter free (FFF) delivery. Repeat CBCT scans will be considered after correction prior to treatment delivery and again after treatment delivery if clinically indicated for additional verification. Image guidance using the ExacTrac system (KV imaging) is allowed.
- CyberKnife: The patient will have the tumour tracked using spine tracking or Synchrony and kV-kV images will be taken intermittently to ensure that the model is robust.
- MR image guidance, where available, may be used.

Appendix A

8. Radiotherapy Quality Assurance

8.1. Overview

The QA programme for the study will be co-ordinated by the National Radiotherapy Trials QA (RTTQA) Group). The ATLANTA QA programme for treatment of metastases is streamlined through the SABR QA programme (CtE and the SABR Expansion Programme, SEP) and the CORE, HALT, SARON and TRAP trials. Any previous QA (benchmark or prospective review) completed for CtE, SEP or the aforementioned trials will count towards the ATLANTA trial. For further details please contact the ATLANTA QA team (atlanta.qa@nhs.net).

Please contact RTTQA for all relevant documentation and datasets necessary for completion of the RT QA programme. All RT QA data will be submitted according to “2019-10-24 RTTQA central secure transfer service vs1.0”, which can also be requested from RTTQA.

8.2. Pre-accrual QA

a) Facility Questionnaire

The SABR Facility Questionnaire (FQ) will be completed and submitted online.

b) Basic Dosimetry Audit

Beam output measurements will be performed during centre visit or remote audit.

c) Complex Dosimetry Audit

An appropriate RTTQA audit must be completed on the relevant equipment and for the appropriate technique and energy prior to patient recruitment. Audits may include:

- RTTQA ArcCHECK® Audit
- UK SABR Consortium Lung Audit (covering lung, non-vertebral bone and nodal lesions)
- RTTQA Spine SABR Audit (covering spine, liver and adrenal lesions)
- National SRS Audit

d) Benchmark Cases: Outlining

Centres participating in SABR trials will have two clinical oncologists credentialed per anatomical site of metastasis to provide clinical cover at trial participating centres. This will include benchmarking and prospective review as established in the SABR QA programme. Situations may arise that require additional QA, these will be assessed on an individual trial/centre basis.

In order to streamline QA for clinical trials clinicians who are benchmark approved through RTTQA may mentor additional clinicians within their department. Clinical oncologists undergoing the mentorship programme should complete two clinical cases for each anatomical site they wish to treat under the supervision of a mentor (these can be trial or non-trial patients). Mentoring must be documented by a credentialed clinician using the RTTQA SABR QA Contouring Form and submitted to the relevant RTTQA contact for a named trial. Please label each submission with "Centre name_anatomical site_clinician initials" (with 1 or 2 at the end when cases are being submitted separately). The form will be

reviewed by the RTTQA Group and the clinician added to the list of benchmarked clinicians for that anatomical site.

Benchmarked clinicians may recruit into clinical trials, however at least their first trial patient treated for each anatomical site will be prospectively reviewed by RTTQA. This is a requirement for all clinicians in order to attain RT QA credentialing within clinical trials, and will be used to streamline contouring for future trials.

There is a requirement that the designated trial Principal Investigator (PI) at a participating centre is credentialed through the RTTQA Group in order to recruit and treat patients within a trial. PIs should have the appropriate expertise to become the SABR lead for that trial clinical indication. Evidence of this should be provided through completion of the RTTQA SABR QA Contouring Form, as outlined above, unless already credentialed through the RTTQA Group. It is recommended that more complex indications such as liver, adrenal or spinal metastases are referred to local experts at a centre.

Contouring cases are available for lung, bone (non-vertebral), nodes and spine metastases. All relevant documentation for each case will be provided with the datasets. One anatomical site must be completed and QA approved prior to opening the trial at a centre. For other anatomical sites, contouring benchmarks must be completed and approved prior to recruitment.

e) Benchmark Cases: Planning

A planning benchmark must be completed per treatment modality for each anatomical site. Planning cases are available for lung, bone (non-vertebral), nodes and spine metastases. All relevant documentation for each case will be provided with the datasets. Please do not edit any of the structures supplied with each case. One anatomical site must be

completed and QA approved prior to opening the trial at a centre. For other anatomical sites, planning benchmarks must be completed and approved prior to recruitment.

8.3. During Accrual QA

8.3.1. Prospective review

A full prospective Individual Case review will be performed for the first patient for each metastatic site. The review will assess outlining and planning protocol compliance and must be completed before the patient commences treatment. All data must be appropriately *anonymised* and the following submitted:

- Radiotherapy planning imaging, including 4DCT data where appropriate (CT files) in DICOM format
- Structure set (RS file) in DICOM format
- Plan (RP file) in DICOM format
- Total dose cube (RD file) in DICOM format
- Any additional information used for contouring (e.g. patient history, diagnostic MR and PET imaging [DICOM], any imaging reports and planning MRI for vertebral lesions)

8.3.2. Data collection

Treatment planning data for all ATLANTA patients will be collected. All data must be appropriately *anonymised* and the following submitted to the RTTQA team:

- Radiotherapy planning imaging, including 4DCT data where appropriate (CT files) in DICOM format
- Structure set (RS file) in DICOM format

- Plan (RP file) in DICOM format
- Total dose cube (RD file) in DICOM format
- Any additional information used for contouring (e.g. patient history, diagnostic MR and PET imaging [DICOM], any imaging reports and planning MRI for vertebral lesions)

Appendix B

9. OAR nomenclature and contouring consensus Quality Assurance

Table 3: Contouring of normal tissue structures

OAR	Standardised Nomenclature	Consensus Contouring Guidance
Bladder	Bladder	The bladder should be contoured in entirety from base to dome. The lateral extent is the outer bladder wall.
Bowel	Bowel	The bowel encompasses the small (duodenum, jejunum and ileum) and large bowel (caecum, ascending, transverse, descending, and sigmoid colon) structures in one contour. Bowel loops do not need to be joined up. Delineate from the pylorus to the recto-sigmoid junction adhering closely to the outer boundary of the external bowel wall, including bowel contents. Ensure small bowel in the lower pelvis caudal to the recto-sigmoid junction is included. This structure should only be used when small and large bowel are indistinguishable. Otherwise, <i>Bowel_Large</i> and <i>Bowel_Small</i> should be defined. The tighter dose constraints between <i>Bowel_Large</i> and <i>Bowel_Small</i> for the selected fractionation should be applied.
	Bowel_Large	The large bowel encompasses the caecum, ascending colon, transverse colon, descending colon, and sigmoid colon in one contour. Bowel loops do not need to be joined up. Contour from the ileocecal junction to the recto-sigmoid junction. The large bowel can be discriminated from the small bowel by the appearance of bowel contents, presence of haustra, sacculations, and appendices epiploicae. The contour adheres closely to the outer boundary of the external wall and includes large bowel contents. This, rather than <i>Bowel</i>, should be contoured unless large and small bowel are indistinguishable.

	Bowel_Small	The small bowel encompasses the duodenum (unless contoured separately), jejunum, and ileum in one contour. Bowel loops do not need to be joined up. Contour from the pylorus to the ileocaecal junction. Ensure small bowel in the lower pelvis caudal to the recto-sigmoid junction is included. The small bowel can be discriminated from the large bowel by the appearance of bowel contents and the presence of valvulae conniventes. The contour adheres closely to the outer boundary of the external wall and includes small bowel contents. This, rather than <i>Bowel</i>, should be contoured unless large and small bowel are indistinguishable.
Brachial Plexus	BrachialPlex_L BrachialPlex_R	Each brachial plexus should be contoured separately. The brachial plexus originates at the spinal nerve root foraminae C5, C6, C7, and T1 and terminates at the medial limit of the second rib. Begin contouring with a 5mm diameter tool at the C5, C6, C7, and T1 neural foramina and continue caudally, contouring the region from the lateral aspect of the spinal canal laterally, to the small space between the anterior and middle scalene muscles. At the levels where no neural foramina are present, contour the space or soft tissue between the anterior and middle scalene muscles. The middle scalene muscle, and therefore brachial plexus structure, will terminate in the region of the subclavian neurovascular bundle. The first and second ribs serve as the medial limit of the brachial plexus contour. Co-registration with MRI and/or the use of intravenous contrast can help distinguish between nerves and vessels. Be aware that patient positioning may influence the position of the underlying anatomy and the brachial plexus.
Anal Canal (prostatic lesions)	Canal_Anal	The anal canal originates at the anorectal junction where the perirectal fat can no longer be seen, coinciding with the insertion of the levator muscles and the pubo-rectalis sling; these structures are best visualized on coronal viewing planes. The anal canal continues caudally to the anal verge. A radio-opaque marker may be used to define the external limit of the anal canal. The contour adheres closely to the outer boundary of the external anal wall, and includes sphincter muscles and anal contents
Cauda Equina (vertebral lesions)	CaudaEquina	The cauda equina is defined by the thecal sac within the spinal canal. It will be contoured using the registered T1 and T2 weighted MR scans acquired in the treatment position and, ideally, on a flat couch, where available. If MR is contra-indicated, a CT myelogram will be performed. This will not only improve registration accuracy

		(crucial with such steep gradients in SABR) but also ensure cord position is consistent. Changes in patient position will cause significant positional differences of the cord within the canal. The PRV only accounts for set-up variation and not cord position. The cranial border of the cauda equina is located at the caudal limit of the spinal cord, usually at the level of L1-2 vertebral bodies. The spinal cord thickens into the conus medullaris at this level and can be used as a landmark. The caudal limit is at the termination of the thecal sac usually at the caudal limit of the S1 vertebral body; however, extension to the caudal limit of the S2 vertebral body or beyond is not unusual. A PRV margin equivalent to the vertebral PTV margin will be generated to create CaudaEquina_XX (where XX is the size of the margin in mm, e.g. a 2 mm margin will be labelled CaudaEquina_02). This margin is for set-up error alone.
Chestwall	Chestwall_L Chestwall_R	Each chest wall should be contoured separately. The chest wall is a 2cm rind of the hemi-thorax outside of the thoracic cavity. The structure includes intercostal ribs, nerves and muscles and excludes vertebral bodies, sternum, and skin. The anterior-medial border is at the lateral edge of the sternum; the posterior-medial border is the lateral aspect of the vertebral body.
Common bile duct	BileDuct_Common	The common bile duct is usually 8-10cm in length and 5-6mm in diameter. The contour begins at the union of the common hepatic duct and the cystic duct and extends caudally to the second section of the duodenum. The common bile duct passes posterior and medial to the duodenum and joins with the pancreatic duct to form the ampulla of Vater.
Duodenum	Duodenum	The duodenum should be defined separately from the bowel whenever possible and, in particular, when in close proximity to the tumour. The duodenum should be contoured from the pylorus to the duodenojejunal junction/ligament of Treitz. The majority of the structure is fixed to the retroperitoneum and follows a C-shaped course around the head of the pancreas. The contour follows four anatomical sections: 1) 5cm in length and anterolateral to the body of the L1 vertebra 2) 7-10cm descending adjacent to the L1-3 vertebral bodies 3) 6-8cm in length, turning medially and crossing the L3 vertebral body. The aorta and inferior vena cava are posterior; the superior mesenteric artery and vein lie anteriorly 4) 5cm in length and ascending from the L3 vertebral body to the cranial border of the L2 vertebral body

		The contour adheres closely to the outer boundary of the external wall and includes duodenal contents. Take care to distinguish the duodenum from the head of the pancreas as the structures are in close proximity. Consider using a PRV if target abuts duodenum.
Femoral Head and Neck	FemurHeadNeck_L FemurHeadNeck_R	Each femoral head and neck should be contoured separately. The structure includes the ball of the femur, femoral neck, greater trochanter, and proximal shaft to the caudal limit of the lesser trochanter. Contour on bone windowing.
Great Vessels	GreatVes	The great vessels are contoured on mediastinal windowing to include the vascular wall and muscle layers out to the fatty adventitia. The structure abuts the <i>Heart+A_Pulm</i> contour. Intravenous contrast may be helpful in distinguishing the great vessels from adjacent structures. Contour the aorta, superior vena cava and inferior vena cava. The cranial aspect of the inferior vena cava is where it is clearly separate from the right atrium of the heart. For right sided lesions, the vena cava will be contoured, and for left sided lesions, the aorta will be contoured.
Heart	Heart+A_Pulm	The heart is contoured on mediastinal windows to include the pericardial sac. The cranial border is at the cranial aspect of the pulmonary artery. The caudal extent is at the apex of the heart where the left ventricle blends with the diaphragm. Major vessels, including the inferior vena cava should be excluded. The pulmonary arteries are excluded below the main bronchi.
Kidneys	Kidney_Cortex_L Kidney_Cortex_R Kidney_Cortex	Each kidney cortex should be contoured separately from the upper to the lower pole. The kidney cortex structure is the kidney parenchyma and includes the fibrous capsule surrounding the kidney, the kidney cortex, and the kidney medulla. The structure excludes cysts, the kidney pelvis, pararenal fat, and the adrenal gland. <i>Kidney_Cortex</i> is a summation of the right and left kidney cortex and may be used for dose reporting purposes.
Liver (normal)	Liver	The liver should be contoured in its entirety from the cranial diaphragmatic aspect to the caudal tip of the right lobe, using soft tissue windowing. The liver contour should exclude the GTV. The inferior vena cava should be excluded from the liver contour when it is clearly separate from the liver. The gall bladder should be excluded.

		Intravenous contrast may be helpful in distinguishing the left border of the liver from adjacent structures.
Lumbo-sacral plexus	LumbSacPlex_L LumbSacPlex_R	<i>LumbSacPlex</i> is the entire lumbo-sacral plexus including bilateral nerve roots. Each side of the lumbo-sacral plexus should be contoured separately. The lumbosacral plexus should be contoured from the L4 nerve root to the cranial most portion of the femoral neck. The L4 nerve root should be contoured by including the space defined by the psoas muscle anterior and laterally, and the facet joint/posterior vertebral body elements posteriorly. The L5 nerve root is contoured using the common iliac vein and psoas muscle anteriorly, the iliacus muscle laterally, and the vertebral body, and sacrum posteriorly. Below the level of the L5 foramen, the sacroiliac joint should serve as the lateral border. Beginning at the level of the S1 foramen, the lumbosacral plexus and S1 lie in the area bounded by the iliac vessels anteriorly, the iliacus muscle/iliac wing laterally, and piriformis muscle posteriorly. At the caudal margin of the greater sciatic foramen, contour the space bounded by the obturator internus muscle/ischial spine anteriorly, piriformis muscle laterally, and gluteus maximus muscle posteriorly. The medial portion of the obturator internus muscle should serve as the medial extent. Below the piriformis muscle, contour the space between the obturator internus muscle anteriorly and the gluteus maximus muscle posteriorly. The medial and lateral extent should be 1-2 cm in length. If a planning MR is used, and the plexus can be clearly seen, this may alternatively be contoured under direct vision. Where not clearly seen, please revert to the method above, as per Yi <i>et al</i> [4].
Lungs (normal)	Lung_L Lung_R Lungs	Each lung should be contoured separately on lung windowing. The lung contour should include all lung parenchyma and exclude hilar structures and the GTV (or ITV). Contour the whole lung, from the apex to the diaphragm including all inflated and collapsed lung. Small vessels less than 10mm in diameter and vessels beyond the hilar region are included. Exclude the proximal bronchial tree and the trachea. <i>Lungs</i> is a summation of the right and left lung and may be used for dose reporting purposes.
Oesophagus	Esophagus	The oesophagus is contoured on mediastinal windowing to include all muscle layers out to the fatty adventitia. Contour from the lower edge of the cricoid cartilage to the gastro-oesophageal junction.

Penile bulb	PenileBulb	The penile bulb is the portion of the bulbous spongiosum of the penis immediately caudal to the genito-urinary diaphragm. The structure is bright on T2 weighted MRI. On CT, the structure is posterior to the urethra, has a round shape. The structure is normally 9-10mm in the cranial-caudal direction and should not continue in to the shaft of the penis.
Proximal bronchial tree	Bronchus_Prox	The proximal bronchial tree is contoured using mediastinal windowing and includes the external aspect of the cartilage rings. The cranial border is 2cm cranial to the carina. Caudally, the proximal bronchial tree includes the bilateral proximal airways: the carina, right and left mainstem bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus, and the right and left lower lobe bronchi. Contouring of the lobar bronchi should end immediately at the site of a segmental bifurcation. Lung windowing may assist in identification of the segmental bifurcations.
Rectum	Rectum Anorectum	The rectum should be contoured to the outer boundary of the external rectal wall, including rectal contents. Contour from the rectosigmoid flexure, approximately at the level of the S3 vertebral body, the rectosigmoid flexure is best visualized on sagittal viewing planes. The caudal border is at the anorectal junction where the perirectal fat can no longer be seen, coinciding with the insertion of the levator muscles and the pubo-rectalis sling; these structures are best visualised on coronal viewing planes. For prostate radiotherapy, please contour as Anorectum: this will consist of rectum and Canal_Anal (described above). Please apply the "Rectum" constraint to this combined structure.
Skin	Skin	The skin is the 5mm inner rind of the external body contour. Please note actual skin thickness will vary dependent on region of interest.
Spinal Canal (non-vertebral lesions)	SpinalCanal SpinalCanal^ASC SpinalCanal^CE	The spinal canal is contoured according to the inner limits of the spinal canal using bone windows. The cranial border is at the level of the tip of the dens of the C2 vertebra. The caudal border is the most caudal slice where the spinal canal is visualized, usually at the level of the L5-S1 vertebral bodies. This structure is used to assess either spinal cord or cauda equina dose constraints. No PRV is required. In the region of the lower abdomen and pelvis, the spinal canal may be required for reporting dose constraints for both spinal cord and cauda equina. In this instance, use SpinalCanal^ASC and SpinalCanal^CE, respectively, to ensure the correct constraints are

		applied to each region. The boundary between these two structures is at the level of L1-2 vertebral bodies.
Spinal Cord & Spinal Cord PRV (vertebral lesions)	SpinalCord SpinalCord_XX	The spinal cord is contoured as the true spinal cord, not the spinal canal. This will be done using the registered T1 and T2 weighted MR scans acquired in the treatment position and, ideally, on a flat couch, where available. If MR is contra-indicated, a CT myelogram will be performed. This will not only improve registration accuracy (crucial with such steep gradients in SABR) but also ensure cord position is consistent. Changes in patient position will cause significant positional differences of the cord within the canal. The PRV only accounts for set-up variation and not cord position. The cranial border is at the level of the tip of the dens of the C2 vertebra, where the structure meets the brainstem. The caudal border is where the spinal cord thickens into the conus medullaris at the level of L1-2 vertebral bodies i.e. the cranial border of the cauda equina. A PRV margin equivalent to the vertebral PTV margin will be generated to create SpinalCord_XX (where XX is the size of the margin in mm, e.g. a 2 mm margin will be labelled SpinalCord_02). This margin is for set-up error alone.
Stomach	Stomach	The stomach should be contoured from the gastro-oesophageal junction to the pylorus. Contour to the outer extent of the external wall, including stomach contents.
Trachea	Trachea	The trachea should be contoured on mediastinal windows (however, lung windowing may help identify the extent of the cartilage). Contour from the caudal edge of the cricoid cartilage, continuing to 2cm cranial to the carina. Contour to the outer boundary of the cartilage, including the lumen, and trachealis muscle. The oesophagus lies posteriorly and should be excluded.
Ureters	Ureter_L Ureter_R	Each ureter should be contoured separately. The cranial border is at the medial aspect of the kidney. The abdominal parts of the ureter are retroperitoneal and lie anterior to the psoas muscle. The ureters continue to run caudally over the pelvic brim at the bifurcation of the common iliac arteries. At the level of the ischial spine, the ureter turns anterior and medial to enter the postero-lateral wall of the urinary bladder, before opening into the urinary bladder at the ureteric orifice. The structure should be contoured to include all fibromuscular layers.

10. Acknowledgements

We would like to thank the RTTQA team for their assistance in the development of this guidelines, in particular Elizabeth Miles, Patty Diez and Rush Patel.

Acknowledgement is also due to Dr Fiona McDonald and Dr Alison Tree for allowing the radiotherapy and QA guidelines to synergise with the HALT, SARON and TRAP trials.

In addition, we would like to thank the CORE trial steering committee for allowing cross-referencing and distribution of their protocol to assist in SABR lesion directed therapy where no UK consensus has been agreed.

11. SABR Revision History

SSPM Ref.	Date Effective	Reason for update (page and section of change)
XX000.00	DD MMM YYYY	

SECTION B: SURGERY

11.1. Procedures

11.1.1. Surgical Metastasectomy (12,13)

- RPLND
- All other anatomical sites

Anaesthesia, Patient Positioning, Access to Abdominal Cavity

11.1.2. Anaesthesia

- General anaesthesia achieved as per anaesthetist, patient specific factors and in accordance to local protocol.
- Local or regional anaesthesia as per patient specific factors, surgeon and anaesthetist discretion and in accordance to local protocol.

11.1.3. Patient Positioning

- Patient positioned in Trendelenburg or similar position as determined by patient specific factors and operating surgeon

11.1.4. Pneumoperitoneum (LRP/RALP)

- Access to abdominal cavity by any reasonable means determined by operating surgeon
- Pneumoperitoneum (Laparoscopic/Robotic Assisted) created by any means (Veress needle insufflation/open Hasson technique) determined by operating surgeon

11.2. Operative Steps

The below operative steps are to be **determined by the operating surgeon**, in accordance with accepted surgical practice and local departmental protocol:

11.2.1. Pelvic Lymph Node

- Pelvic lymph node dissection (PLND) may occur at the time of cytoreductive radical prostatectomy and can be seen in the **Radical Prostatectomy SOP**.
- Pelvic lymph node metastasis is not regarded as MDT for the purposes of total targeted metastasis.

11.2.2. Retoperitoneal Lymph Node Dissection (RPLND)

- RPLND (including para-aortic, preaortic, retroaortic, inter-aortocaval, paracaval, precaval, retrocaval, common iliac, and pre-sacral) by any accepted approach will be permitted for metastasis at the discretion of the treating trial centre.
- Advice can be sort from the ATLANTA trial team regarding surgical metastasis directed therapy (excluding PLN dissection see **10.2.1**).

11.2.3. Surgical Excision

- Surgical excision by any accepted approach will be permitted for metastasis at the discretion of the treating trial centre.
- Advice should be sort from ATLANTA trial team regarding metastasis directed therapy (excluding PLN dissection see **5.6.1**).

11.2.4. Biobanking

- **Depending on individual consent.** Biobanking of pathological tissue or retrieval of tissue of operative pathology and biopsy of recurrent disease from prostatic and extra prostatic sites.

11.3. Specimen Delivery, Drain Insertion & Closure

11.3.1. Specimen Delivery

- Delivery by any incision at surgeons discretion

11.3.2. Drain insertion

- Drain insertion at surgeons discretion

11.3.3. Closure

- Fascia/port-site and skin closure as determined by operating surgeon

11.3.4. Surgical Documentation

- Surgical procedure performed should be documented on InForm (electronic) trial database

11.4. Postoperative Care

11.4.1. Urinary Catheter

- At discretion of treating surgeon. If synchronous with MIAT then catheter to remain in situ.

11.4.2. Deep Vein Thrombosis (DVT) Prophylaxis

- Mechanical and chemical DVT prophylaxis should be given whilst patient has reduce mobility in accordance with local protocol up to 28 days post-operative procedure.

12. Surgical Metastasectomy Revision History

SSPM Ref.	Date Effective	Reason for update (page and section of change)
XX000.00	DD MMM YYYY	

<Insert section break if adding any Attachments>

13. Appendix B

Quality Assurance Panel will meet to decide upon operating surgeon inclusion in ATLANTA trial.

Outcome will be guided by individual operating surgeon declaration [ATLANTA Surgeon Quality Assurance Declaration] confirming they have met minimum standards expected of an operating surgeon in ATLANTA as listed below:

1.> 200 recorded cases in logbook

2.<4% Complication Rate*

*(Clavien Dindo III and above)

3.<3% Post-operative transfusion rate

STUDY SPECIFIC PROCEDURE MANUAL**Central Histopathology Review SOP v2.0**

IP2 - ATLANTA: Additional Treatments to the Local tumour for metastatic prostate cancer-Assessment of Novel Treatment Algorithms

Protocol Number: 18HH4804

Effective Date: 1st July 2022 Draft: 1st July 2022

Prepared by: Name:	Title:	Signature:	Date:
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Introduction

The purpose of this document is to describe the central pathology review procedure for patients in the embedded pilot cohort of the IP2-ATLANTA trial.

The SOP is designed to permit the reporting of the trials primary endpoint of the embedded feasibility pilot:

“c) Proportion of patients with pathological complete response on post systemic therapy prostate biopsy at 6-9 months.”

This SOP was developed following the IP2-ATLANTA trials central histopathology consensus meeting held 1st April 2021.

1. Scope

This procedure is applicable to patients, in the interventions arms of the IP2-ATLANTA trial embedded feasibility cohort (n=80).

Abbreviations

SOP	Standard Operating Procedure
ICTU	Imperial Clinical Trials Unit
ADT	Androgen Deprivation Therapy
NED	Neuroendocrine Differentiation
IDC	Intraductal Carcinoma
PIN	Prostate Intraepithelial Neoplasia
HGPIN	High-Grade Prostate Intraepithelial Neoplasia
EPE	Extraprostatic Extension
PNI	Perineural Invasion

2. Responsibilities

Chief Investigator (CI)	• Overall responsibility for the trial • Overall responsibility for your trial at the site • Ensure facilities, staff resources and education are appropriate to carry out the trial • Delegate responsibility and ensure they are documented on the delegation log
Principal investigator (PI)	• Be available to give advice, support and to sign off documents as required • Responsibilities for carrying out study procedures or delegating these to appropriately trained staff where necessary
Histopathologist	• Ensure the standard operating procedure is in accordance with trial intervention, based on safe and accepted reporting practice. • Aware of SOP and mechanism to report deviation from SOP
Research Nurse	• Assist in sample handling including collection, labelling, processing, storage and transportation of biobanking samples. • Ensure consent is taken for additional biobanking samples.
Trial Manager	• Liaise with local study team to ensure study procedures are carried out in accordance with trial protocol and procedural manuals • Support and advice trial team and respond to queries as needed.

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4. Central Histopathology

4.1. Overview

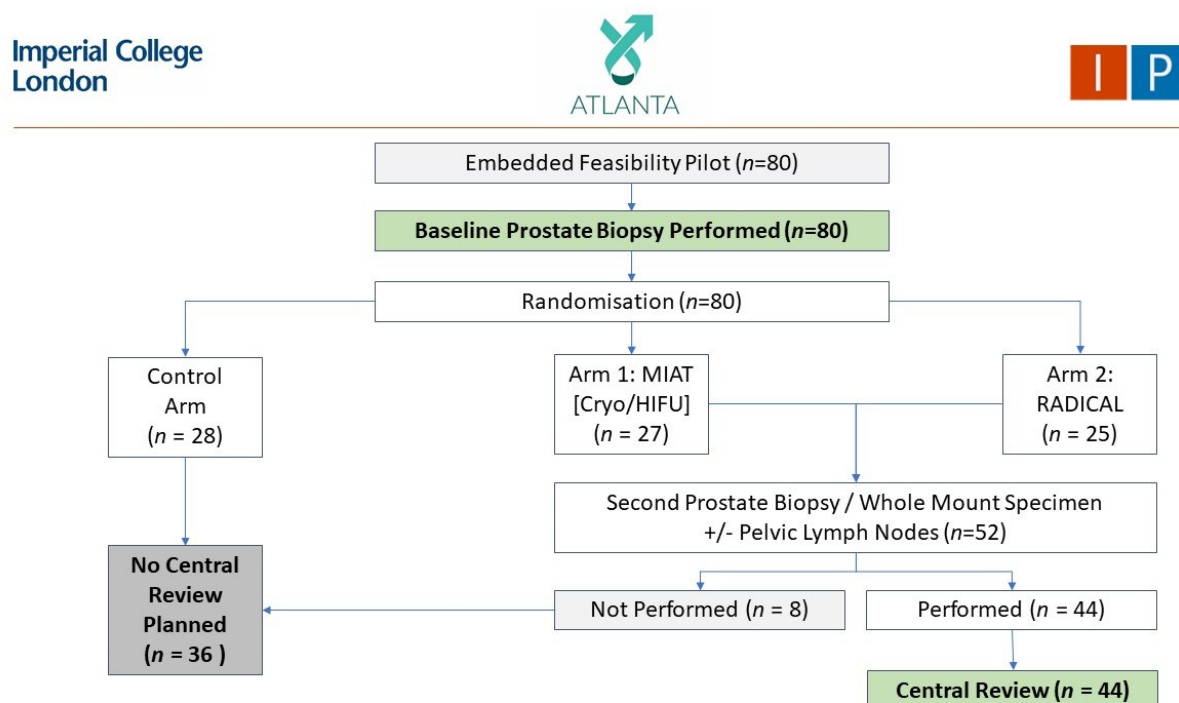


Figure 1. Overview of planned histopathology available for central review by trial arm (n=patients) dated 1st April 2021.

- Systemic therapy refers to ADT with or without Docetaxel, Enzalutamide or Abiraterone Acetate as set out in the **Systemic Therapy SOP**
- A baseline prostate biopsy (targeted and systematic cores) was performed in all patients.
- A protocolled prostate biopsy (targeted and systematic cores) should be performed in all patients at in the intervention arms of IP2-ATLANTA following systemic therapy but prior to local treatment as per protocol.
- All patients must undergo a repeat prostate MRI prior to biopsy.
- This should occur at trial **visit 3** (i.e. 26 +/- 12 weeks post randomisation) as per ATLANTA protocol visit schedule.

- Prostate biopsy performed approach should mirror local protocol. A transrectal ultrasound and / or transperineal approach is acceptable.

Beyond the pilot phase patients may undergo a post-systemic therapy prostate biopsy at the discretion of the treating clinician and these specimens are no currently planned for central review.

Randomised in the embedded feasibility pilot	80
Baseline prostate biopsy performed	80
Allocated to experimental treatment arms	52
Second biopsy/whole mount planned	52
Did not have allocated biopsy/whole mount (e.g. no consent/other)	8
Second biopsy/whole performed	44
Second Biopsy / Whole Mount	36
Whole Mount	8
Pelvic Lymph Node Dissection planned	(max.) 8
Lymph node sample available	2
Number of patients requiring central review	44

Table 1. Current overview of histopathology available for central review (1st April 2021).

5. Workflow for central review

5.1.1. Workflow

- Following trials histopathology consensus meeting held 1st April 2021, the following workflow for review was agreed upon.
- A central histopathologist will be blinded and patients specimens for central review.
- In all cases where apparent ypT0, IDC or PIN is reported specimens may undergo a cross-over second blinded review.
- All cases can be discussed in a final consensus meeting to issue a central report.

5.2. Central Review Priori

5.2.1. Central Review Priori

- Following trials histopathology consensus meeting held 1st April 2021, the following priori for review was agreed upon.

- Planned parameter for collection on central review are outlined in the priori data collection tool and appear in list form below:
 - Baseline Biopsy
 - Gleason Grade
 - MCCL
 - Pattern 4 %
 - Cribriform Pattern
 - IDC
 - HGPIN
 - PNI
 - EPE
 - NED
 - Second Biopsy
 - Apparent pT0
 - Intraductal Carcinoma [IDC] [Defined as: (1) 2-fold expansion of prostate gland lumina; (2) neoplastic cells span, in a solid or cribriform architecture, the lumen of glands in which a basal cell layer is retained; and (3) nuclear atypia]
 - Cytoplasmic loss / cytoplasmic ratio changes
 - Prominence of nucleoli
 - Cell size reduction
 - Cribriform glands with central necrosis
 - Multifocal periprostatic fibrosis
 - Clear cell changes
 - Needle-like, crystalloid structures
 - NED
 - PNI
 - EPE
 - Other comments
 - Benign Tissue: prominent basal cells
 - Benign Tissue: urothelial metaplasia
 - Whole Mount Prostatectomy
 - Apparent ypT0
 - Prostate Volume
 - Tumour Volume

- Margin status
- Intraductal Carcinoma [IDC] [Defined as: (1) 2-fold expansion of prostate gland lumina; (2) neoplastic cells span, in a solid or cribriform architecture, the lumen of glands in which a basal cell layer is retained; and (3) nuclear atypia]
- Cytoplasmic loss / cytoplasmic ratio changes
- Prominence of nucleoli
- Cell size reduction
- Cribriform glands with central necrosis
- Multifocal periprostatic fibrosis
- Clear cell changes
- Needle-like, crystalloid structures
- NED
- PNI
- EPE
- Other neoplasia comments
 - Benign Tissue: prominent basal cells
 - Benign Tissue: urothelial metaplasia

5.3. Reporting Disagreement Steps

Where reporting disagreement remain following second review and central histopathology consensus a blinded third second reviewer can review scanned slides to permit the final trial report (**Figure 2.**).

6. Trial of central histopathology report

The purpose of central histopathology review is for **research purposes only**.

Trials sites will not be issued with a new report.

Central reports should not be added to patients notes.

Central histopathology reports should not be used to alter or decide upon the patients planned or future clinical care.

7. Revision History

SSPM Ref.	Date Effective	Reason for update (page and section of change)
XX000.00	DD MMM YYYY	

<Insert section break if adding any Attachments>



ATLANTA

BASELINE MRI Report Worksheet

Subject ID Number:

A -

Size of Prostate

Transverse

AP

Cranio-Caudal

cm

cm

cm

Scan
Date

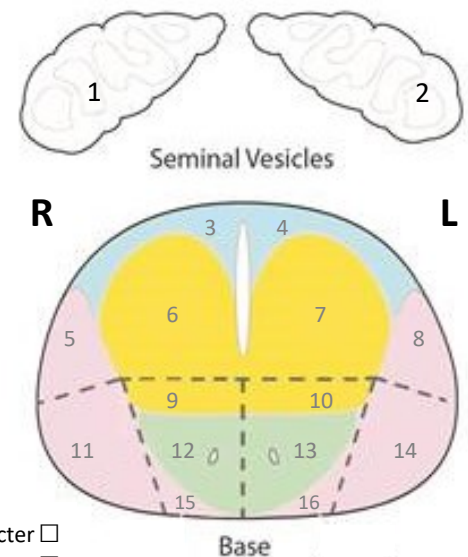
cc

Individual Lesions

Are there any lesions with an MRI^a score ≥ 3 ? Yes ☐ No ☐

(Please draw & number lesions on diagram and complete table)

Target Lesion	Max Tumour Diameter ^b (mm)	Modified PIRADS Score	LIKERT Score	EPE Score ^c (0-3)	Focal or Diffuse
MRI Lesion					Focal ☐ Diffuse ☐
MRI Lesion					Focal ☐ Diffuse ☐
MRI Lesion					Focal ☐ Diffuse ☐
MRI Lesion					Focal ☐ Diffuse ☐



Radiological stage

$\leq T2$ ☐ T2a ☐ T2b ☐ T2c ☐ T3a ☐ T3b ☐ T4 ☐ Sphincter ☐

Rectum ☐
Bladder ☐

N0 ☐ N1 ☐ — Internal Iliac N1 mm ☐
External Iliac N1 mm ☐
Common Iliac N1 mm ☐ Bulky Nodes ☐
Presacral N1 mm ☐ No Bulky Nodes ☐
Obturator N1 mm ☐
Mesorectal N1 mm ☐

M1a ☐ M1b ☐ Mx ☐ Retroperitoneal M1a mm ☐ M1b Target 1 mm ☐
Mesenteric M1a mm ☐ M1b Target 2 mm ☐
Inguinal M1a mm ☐ M1b Target 3 mm ☐
M1b Target 4 mm ☐
M1b Target 5 mm ☐

Any incidental findings? None ☐ Bladder Tumour ☐ Rectal Tumour ☐

Other: _____

Sum of target measurements for Recist: _____ mm

I Sum of non-target measurement _____ mm

Signature:

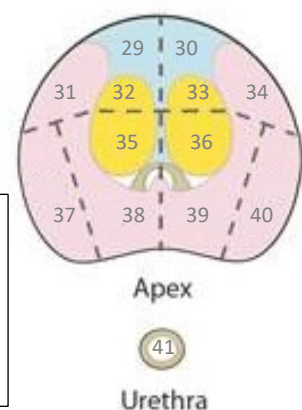
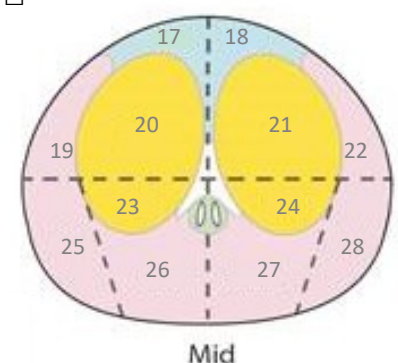
Reporter Name:

Notes:

^aPI-RADS version 2.1

^bMaximum tumour diameter using the T2 weighted image in the axial plane due to the increased resolution and reduced susceptibility to geometric distortion this provides, when compared to the diffusion restriction images. This was except in cases where diffusion restriction imaging more clearly depicted the tumour.

^cNo evidence of EPE; 1, large lesion-capsule contact length or capsular bulge; 2, large lesion-capsule contact length and capsular bulge; and 3, frank EPE.



RESPONSE (2nd) MRI Report Worksheet

Subject ID Number:

A -

Size of Prostate

Transverse cm AP cm Cranio-Caudal cm

cc

Scan
Date

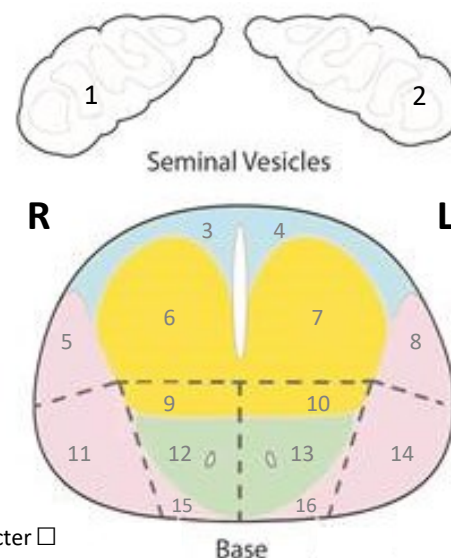
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Individual Lesions

Are there any residual visible intraprostatic lesions? Yes ☐ No ☐

(Please draw & number lesions on diagram and complete table)

Target Lesion	Max Tumour Diameter ^b (mm)	EPE Score ^c (0-3)	Focal or Diffuse
MRI Lesion			Focal ☐ Diffuse ☐
MRI Lesion			Focal ☐ Diffuse ☐
MRI Lesion			Focal ☐ Diffuse ☐
MRI Lesion			Focal ☐ Diffuse ☐



Radiological stage

≤T2 ☐ T2a ☐ T2b ☐ T2c ☐ T3a ☐ T3b ☐ T4 ☐ Sphincter ☐
Rectum ☐
Bladder ☐

Internal Iliac N1 mm ☐
External Iliac N1 mm ☐
Common Iliac N1 mm ☐
Presacral N1 mm ☐
Obturator N1 mm ☐
Mesorectal N1 mm ☐
M1a^d ☐ M1b ☐ Mx ☐ Retroperitoneal M1a mm ☐
Mesenteric M1a mm ☐
Inguinal M1a mm ☐
M1b Target 1 mm ☐
M1b Target 2 mm ☐
M1b Target 3 mm ☐
M1b Target 4 mm ☐
M1b Target 4 mm ☐

Any incidental findings? None ☐ Bladder Tumour ☐ Rectal Tumour ☐

Sum of target measurements for Recist: mm | Sum of non-target measurements for Recist: mm

Overall Recist 1.1 Criteria ^a

Target Lesions [CR / PR / SD / PD]	Non-Target Lesions [CR / PR / SD / PD]	New Lesions [Yes / No]	Overall Response Recist 1.1 ^a [CR / PR / SD / PD]

Signature:

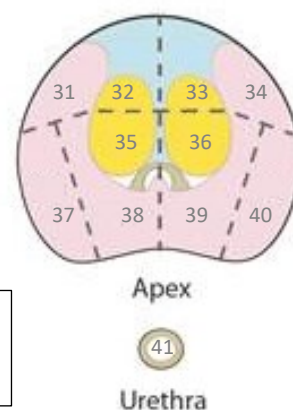
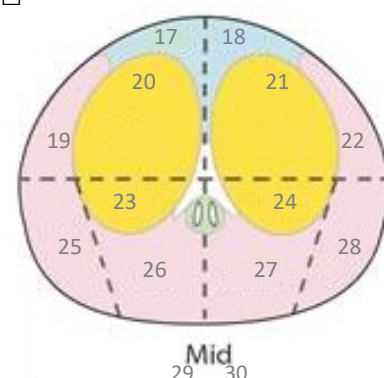
Reporter Name:

Notes:

^aRECIST version 1.1 / PCWG3. CR – Complete response / PR – Partial Response / SD – Stable Disease / PD – Progressive Disease
^bMaximum tumour diameter using the T2 weighted image in the axial plane due to the increased resolution and reduced susceptibility to geometric distortion this provides, when compared to the diffusion restriction images. This was except in cases where diffusion restriction imaging more clearly depicted the tumour.

^cNo evidence of EPE; 1, large lesion-capsule contact length or capsular bulge; 2, large lesion-capsule contact length and capsular bulge; and 3, frank EPE.

^dPCWG3 advise as per RECIST 1.1, lymph nodes that are ≥ 1.0 cm but less than 1.5 cm in the short axis may be pathologic and can be considered nonmeasurable/nontarget lesion



Urethra