Assessment of safety and efficacy of Transanal Total Mesorectal Excision by Observational Clinical Human Reliability Analysis and analysis of international registry data

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DECLARATION

I hereby declare that I am the sole author of this thesis and that all work within it is my own. All else and any individuals who carried out any collaborative work are appropriately credited and referenced.

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ABSTRACT

The introduction of any new surgical technique should undergo a vigorous process of development and implementation, that ensures a safe and controlled clinical adoption. Transanal Total Mesorectal Excision (TaTME) for rectal cancer attracted great interest and enthusiasm amongst the colorectal community following its first live case in 2009; postulating numerous advantages over conventional abdominal rectal cancer surgery. The aim of this PhD thesis was to evaluate the safety and efficacy of TaTME by analyzing outcomes recorded on the international TaTME registry and assessing the actual technique itself in detail by performing Observational Clinical Human Reliability Analysis (OCHRA).

Three main aspects were explored through data recorded on the TaTME registry by surgeons worldwide: 1) Histopathological outcomes during the initial stage of TaTME experience, 2) Clinical outcomes following TaTME with particular focus on anastomotic failure rates; 3) Proficiency-gain curve of TaTME. Overall outcomes have been very encouraging with a low R1 resection rate of 2.7% and acceptable overall 30-day morbidity of 32.6%. The early anastomotic leak rate from a cohort of 1594 was 7.8% and overall anastomotic-related problems (anastomotic failure) was 15.7%. The occurrence of an unexpected intra-operative complication, namely urethral injury, was also highlighted with an incidence of 0.8%. Proficiency-gain curve analysis using the risk adjusted cumulative sum (CUSUM) method applied to 2751 TaTME cases from 154 surgical units, revealed that intra-operative adverse events showed a change point with improvement in performance after the initial 10 restorative procedures. Histological outcomes and overall post-operative 30-day complications did not produce a meaningful learning curve, whereas anastomotic failure had a clearer picture with a

peak or change point reached after the initial 15 cases, followed by a “slow transition” period between cases 15 and 49, after which improvements were seen more clearly.

Systematic analysis of the technique by OCHRA provided a greater understanding of what types of errors occur and the ‘error-pathways’ that lead to an adverse intra-operative event, as well as what constitutes an optimal technical performance. A clinical categorisation of technical errors was devised including errors of set up/exposure, and executional errors divided into tissue-instrument interface errors and instrument-handling errors. Overall 5101 errors and 904 adverse consequences were logged in 100 transanal operations, with a mean of 51 ±32.4 errors and 9 ±6.6 adverse consequences per case. A technical accuracy scoring system was developed for the transanal operation with higher scores indicating a poorer technical performance with more errors committed. An accuracy score above 24 was found to significantly increase the risk of post-operative complications (15.8% vs 42.9%, Odds ratio 4.00, 95% CI 1.415–11.310, p 0.007). Semi-structured interviews and face-to-face workshop with international TaTME experts lead to the development of error-reducing mechanisms and technical recommendations to help guide future training and as a useful resource for all TaTME surgeons. An OCHRA feedback form incorporating the learning points and recommendations has been developed during the national TaTME training programme in the UK.

In conclusion, TaTME is a technically demanding operation which has the potential to allow optimal oncological resections especially in more challenging cases. However, thorough structured training in the technique is essential and its true benefits over conventional approaches remain to be determined.

PEER-REVIEWED PUBLICATIONS & PRESENTATIONS

Publications

1. Penna M, Hompes R, Arnold S, Wynn G, Austin R, Warusavitarne J, Moran B, Hanna GB, Mortensen NJ, Tekkis PP; TaTME Registry Collaborative. Transanal Total Mesorectal Excision: International Registry Results of the First 720 Cases. Ann Surg. 2017;266(1):111-117.

2. Penna M, Hompes R, Arnold S, Wynn G, Austin R, Warusavitarne J, Moran B, Hanna GB, Mortensen NJ, Tekkis PP; International TaTME Registry Collaborative. Incidence and Risk Factors for Anastomotic Failure in 1594 Patients Treated by Transanal Total Mesorectal Excision: Results from the International TaTME Registry. Ann Surg. 2019;269(4):700-711.

Presentations

1. Global Uptake and Audit of TaTME. American College of Surgeons (ACS) Clinical Congress, San Francisco, 2019.

2. Latest data from the International TaTME Registry. TaTME Congress, St. Gallen, 2019.

3. TaTME International Registry: Updates on Global Outcomes, Complications and Functional Data. American Society of Colon and Rectal Surgeons (ASCRS) Annual Scientific Meeting, Cleveland, 2019.

4. Observational Clinical Human Reliability Analysis of Transanal Total Mesorectal Excision: Results from 100 clinical cases. European Association of Endoscopic Surgeons (EAES), Seville, 2019.

5. Observational Clinical Human Reliability Analysis: The UK TaTME Experience. Pelvicare Colorectal masterclass, Bordeaux, 2018.

6. Observational Clinical Human Reliability Analysis of TaTME. The Belgian Group for Endoscopic Surgery (BGES) Congress, Antwerp, 2018.

7. International TaTME Registry. Chinese TaTME Conference, Shenyang, 2018.

8. Transanal Total Mesorectal Excision: Fingerprinting the technique. TaTME Congress, Netherlands, 2017.

9. International TaTME Registry: Update and initial results. TaTME summit. Los Angeles, 2016

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ABBREVIATIONS

95% C.I.	95% Confidence Interval
ACPGBI	Association of Coloproctology of Great Britain and Ireland
AL	Anastomotic Leak
APE	Abdomino-Perineal Excision
ARJ	Anorectal Junction
ASA	American Society of Anaesthesiologists
ASCRS	American Society of Colon and Rectum Surgeons
AV	Anal Verge
BMI	Body Mass Index
BORIS	Behavioural Observation Research Interactive Software
CAT	Competency Assessment Tool
CRM	Circumferential Resection Margin
CSSANZ	Colorectal Surgical Society of Australia and New Zealand
CUSUM	Cumulative Sum method (RA-CUSUM is risk-adjusted)
DRM	Distal Resection Margin
EAES	European Association of Endoscopic Surgeons
EMVI	ExtraMural Venous Invasion
ETAP	Endoscopic Transanal Proctectomy
EUA	Examination Under Anaesthesia
GAS	Global Assessment Scoring
IBD	Inflammatory Bowel Disease
IDEAL	Innovation, Development, Exploration, Assessment, Long-term study
IHD	Ischaemic Heart Disease

IPAA	Ileal Pouch-Anal Anastomosis
IRAS	Integrated Research Application System
LAPCO	LAParoscopic COlorectal training programme
LOREC	Low Rectal Cancer Development
MRI	Magnetic Resonance Imaging
N+	Positive nodal status (N1 or N2)
NICE	National Institute for Health and Care Excellence
NOTES	Natural Orifice Transluminal Endoscopic Surgery
OCHRA	Observational Clinical Human Reliability Analysis
OR	Odds Ratio
OSATS	Objective Structured Assessment of Technical Skill
PS	Pursestring
REC	Research Ethical Committee
RCS	Royal College of Surgeons
RCT	Randomised Controlled Trial
ROLARR	RObotic versus LAparoscopic Resection for Rectal cancer
SAGES	Society of American Gastrointestinal and Endoscopic Surgeons
SD	Standard Deviation
SHERPA	Systematic Human Error Reduction and Prediction Approach
SILS	Single Incision Laparoscopic Surgery
TAMIS	TransAnal Minimally Invasive Surgery
TaTME	Transanal Total Mesorectal Excision
TEM	Transanal Endoscopic Microsurgery
TEO	Transanal Endoscopic Operation
TME	Total Mesorectal Excision

TNM	Tumour, Nodes, Metastases
TRG	Tumour Regression Grade

CHAPTER I

LITERATURE REVIEW

What is Transanal Total Mesorectal Excision and its evolution to date?

1. Introduction

With over 1.8 million new cases diagnosed annually, colorectal cancer remains the third most common malignancy worldwide.[1] Approximately one-third of cases affect the rectum for which surgery currently remains the mainstay of curative treatment in primary tumours. Total mesorectal excision (TME) was a pivotal milestone in the history of rectal cancer surgery, as the first en bloc excision for cancer whose boundaries were conceptually and practically founded in embryology.[2] Following the introduction of TME, the rate of sphincter-saving procedures increased, and local recurrence rates significantly decreased from 16% to less than 5%.[3]

Achieving an intact mesorectal excision without injuring important surrounding structures can be very challenging regardless of the abdominal technique performed. This is particularly true when dealing with bulky low advanced rectal tumours in obese males, whose clinical, oncological and functional outcomes are likely to be poor.[4] Hence, the need and drive to develop a new surgical approach to tackle these more difficult features, bringing rise to Transanal Total Mesorectal Excision (TaTME). Although most commonly known as TaTME, various acronyms have been used in the literature describing the same procedure, including 'bottom up TME, hybrid natural orifice transluminal endoscopic surgery (NOTES), transanal proctectomy and transanal minimally invasive surgery (TAMIS) TME.

The development and introduction of any new surgical technique is an exciting process, but also one that carries many unknowns as well as the need and opportunity to undertake plenty of thorough research. As stated by the Royal College of Surgeons' guide to good practice "Surgical innovation, new techniques and technologies",[5] surgical innovations can be risky, especially if they occur without following a clear guiding framework. Three well published sources that provide methodologies to identify what constitutes surgical innovation and critically appraise new technologies include the Macquarie Surgical Innovation Identification Tool,[6] the Medical Research Council (MRC) recommendations,[7] and the IDEAL framework.[8] The Macquarie and MRC guidance start by asking key questions that aim to clarify the degree of change from current interventions, potential benefits and risks of the new procedure and whether it can be implemented in a research setting.[6,7] The MRC then categorises five stages of evaluation of the complex intervention from an initial pre-clinical theoretical stage, to phase I modelling, phase II exploratory trial, phase III definitive randomised controlled trial (RCT) and phase IV long-term implementation of the new intervention.[7] The objectives must be met at each stage before moving to the next. The IDEAL framework adapts these MRC recommendations and tailors them to the surgical setting with a similar five step process progressing from the initial idea, to its development and exploration by increasing numbers of adopters, to its assessment with RCTs and long-term studies.[8] IDEAL encourages evaluation alongside innovation in an ordered, transparent and monitored manner in order to promote safe introduction of a new technique. There are however two important aspects that are not fully explored within these frameworks including the optimal training pathway novice surgeons should undertake and the need for robust data collection which should be mandatory for outcomes of new interventions. By making data collection obligatory and the surgeons' expectations of being audited, a more vigorous and reliable validation process of the data can subsequently be carried out. Further guidance specific to a certain intervention can also be provided by surgical associations/societies and for example, in the UK, by the National Institute for Health and Care Excellence (NICE). NICE published guidelines on TaTME in March 2015 which are outlined in chapter II section 1.1 and include recommendations on who and how TaTME should be implemented, and the importance of ongoing data collection and research.[9]

Research into a new surgical technique should include a thorough evaluation of how the technique is being performed by practicing surgeons. This can create a deeper understanding of the technical benefits and risks of the procedure, identify areas for improvement, as well as set a standard of performance. Various assessment methods of technical performance have been reported in the literature for simulated, direct observational, and video-based procedures.[10,11] The systematic review by Ahmed *et al.*[10] identified three main categories of assessment methods including global assessment scales evaluating generic skills, task-specific methods assessing procedure-specific skills, and combinations of the former two. The most well-known global assessment scale is the OSATS (Objective Structured Assessment of Technical Skill) tool, which was originally designed for simulated procedures on bench-top models.[12] Hence, a modified OSATS is more commonly used; for example, in Birkmeyer's New England Journal of Medicine paper,[13] the tool included five domains for the rater to assess gentleness, tissue exposure, instrument handling, time and motion, and flow of operation, of gastric bypass surgery. Other global rating scales that have been studied, particularly in laparoscopic surgery, include the Global Operative Assessment of Laparoscopic Skills (GOALS) and visual analog scales.[14-15] The advantages of using such global scales are their simplicity, ease of use, application to various procedures and overall holistic view of the operation. However, the major disadvantage is the lack of specificity in being able to provide more detailed, individualised or operation specific feedback for skill improvement.[16]

Procedure-specific rating tools are better equipped at providing more specific information on technical performance and start by breaking down the procedure into tasks (task analysis). Some of these tools outline a simple checklist of tasks,[10] whilst others adopt a more sophisticated method that defines a formal task analysis and a detailed error categorization system.[17] Observational Clinical Human Reliability Analysis (OCHRA) is one of the most studied and validated of these more complex tools, adapted from human reliability methods, and used to assess technical performance.[18,19] OCHRA can provide very detailed feedback and identify specific high-risk areas of technical difficulty that require focused attention. An element of subjectivity does exist and OCHRA is the most labour-intensive process compared to other rating systems. However, in order to gain as much information and insight into the TaTME technique as possible, together with my main supervisor's expertise in this area, OCHRA was chosen as the method of assessment of technical performance in this project.

This thesis aims to evaluate the safety and efficacy of TaTME by assessing its outcomes based on the international TaTME registry data and obtaining a deeper understanding of the technique through Observational Clinical Human Reliability Analysis (OCHRA).

2. Transanal Total Mesorectal Excision

2.1 The Rationale for TaTME

Optimal rectal cancer surgery requires an accurate oncological resection with clear resection margins (proximal, distal and circumferential) and a complete mesorectal specimen, as well as preservation of important surrounding pelvic structures that control bowel, urinary and sexual function. The surgical approach to rectal cancer has undergone numerous changes over the last few decades encompassing a wide spectrum of techniques from traditional open surgery to more minimally invasive approaches including laparoscopy, robotics and, most recently, transanal. Although change can represent continuous improvement and modernisation of techniques, it can also imply an inherent complexity or difficulty in performing the operation and a 'mission' to overcome the technical challenges encountered.

Laparoscopic surgery has been associated with several advantages over open surgery, including less post-operative pain, fewer wound infections and shorter hospital stay.[20] However, to date, results from randomized controlled trials comparing laparoscopic to open surgery for rectal surgery have shown a wide range of histopathological outcomes. In the COLOR II trial, a positive circumferential resection margin (CRM) was seen in 10% of cases overall but reached 22% in the open surgery group for low rectal tumours.[21] A complete TME specimen was achieved in 91.5% of open and 88.4% of laparoscopic cases, which did not reach statistical significance. Positive CRM rates of 16% and 18% were also found in the CLASSIC trial[22] and Professor Rullier's French randomized trial,[23] respectively. Long-term results of the CLASICC trial reported a slightly better median overall survival in the laparoscopic group (82.7 vs. 78.3 months) but found no difference in recurrence rate or disease-free survival, and once again results were not statistically different between the two groups.[24] Long-term 3-year rates of cancer recurrence, disease-free survival and overall survival from the COLOR II trial also did not show any statistically significant difference between open and laparoscopic surgery in rectal cancer patients.[25]

Two of the most recent randomized clinical trials, ALaCaRT[26] and ACOSOG Z6051[27] were unable to demonstrate non-inferiority of laparoscopic compared to open surgery for rectal cancer in terms of histopathological outcomes and morbidity. Both trials used a new trichotomous composite outcome based on the completeness of the mesorectal excision as well as the negativity of resection margins. In ACOSOG Z6051 trial[27] a successful primary outcome was achieved in 81.7% of laparoscopic resection cases (95%CI, 76.8%-86.6%) and 86.9% of open resection cases (95%CI, 82.5%-91.4%), which did not support noninferiority (difference, −5.3%; 1-sided 95%CI, −10.8%to ∞; P for noninferiority = .41). Similarly, in the ALaCart trial,[26] a successful resection was achieved in 194 patients (82%) in the laparoscopic surgery group and 208 patients (89%) in the open surgery group (risk difference of −7.0% [95%CI, −12.4%to ∞]; P = .38 for noninferiority). The positive CRM rate for laparoscopic versus open TME surgery in these trials was 7.0%–12.1% versus 3.0%–7.7%, respectively. A meta-analysis including 10,861 patients from 27 studies comparing laparoscopic and open TME found no difference in terms of rate of complete resection, quality of the mesorectal specimen and rate of local recurrence.[28]

Furthermore, high conversion rates from laparoscopic to open surgery, which is known to increase postoperative morbidity and lead to a poorer oncological outcome,[21,29] have also been reported in the COLOR II[21] and ACOSOG Z6051[27] trials, 16% and 11.3% respectively.

An interesting study by Bondeven et al.[30] assessed the quality of surgery by reviewing resected specimens and performing MRI scans on 136 patients who had undergone rectal cancer surgery. The study found almost 40% of patients still had residual mesorectum even after supposed “TME” surgery. Such mesorectal residues are a principal source of local recurrence in most countries.

Robotic TME surgery was the great hope to facilitate achieving the optimal rectal cancer resection. However, to date, superiority of the robot over laparoscopic surgery in terms of oncological outcomes has yet to be demonstrated. The recent ROLARR (Robotic versus Laparoscopic Resection for Rectal Cancer) trial[31] reported similar CRM rates in the laparoscopic and robotic groups of 6.3% and 5.1% (Odds ratio, OR = 0.78, 95% CI=0.35 to 1.76, p=0.56), respectively. Conversion rates were also comparable between the two groups, with 8.1% in the robotic arm (OR = 0.61,95% CI 0.31-1.21, p=0.16). No statistical difference was seen for any of the other 8 reported pre-specified secondary endpoints, including intraoperative complications, postoperative complications, plane of surgery, 30-day mortality, bladder dysfunction, and sexual dysfunction.

A meta-analysis including 1,676 patients from six studies (two randomised controlled trials and four propensity matched studies) comparing robotic to conventional laparoscopic surgery for rectal cancer showed that robotic TME was associated with significantly lower rates of post-operative morbidity (24.2% vs 34.4%; OR= 1.67; 95% CI= 1.24–2.25; p= 0.007) and less conversion to open surgery (2.7% vs 4.8%; OR= 0.55; 95% CI= 0.33–0.93; *p*= 0.003) compared to the laparoscopic group.[32] However, robotic surgery also resulted in longer operative time (Mean difference, MD= 54.15; 95% CI= 13.02–95.29; *p*= 0.01) and a lower lymph node yield (MD= –0.90; 95% CI= –1.82 to 0.02; *p*=0.05). No statistical difference was found between the two groups in terms of intra-operative blood loss, CRM positivity and length of hospital stay.

The key problems with approaching rectal cancer from the abdomen descending downwards into the pelvis ("top-down" approach) are firstly, the increased narrowing of the available space needed to obtain optimal exposure and adequate visualisation of the mesorectal plane and, secondly, difficulty with introducing rigid instruments within a fixed bony pelvic diameter that makes the TME dissection and accurate rectal transection clearing the distal margin very challenging. Risk factors that increase the level of difficulty and likelihood of achieving a poor histological outcome have been identified through several studies. These include male gender, high body mass index (BMI), visceral obesity, narrow pelvis, and bulky, low, fixed tumours.[4] Furthermore, the fixed dimensions of the bony pelvis can prevent achieving sufficient angulation of laparoscopic stapling devices during distal transection of low tumours. Augmented reality reconstruction has demonstrated that a stapler inclination of a minimum of 65° is required in order to obtain optimal, perpendicular firing.[33] Reduced angulation of the stapler will result in multiple firings, usually two or three, producing a "zig-zag" staple line. Ito et al.[34] showed that the risk of anastomotic leak increases five-fold if more than two firings are used.

For completeness, the negative effects that long operating hours standing up and concentrating on a complex anatomical part of the body can have on the surgical team should also be mentioned, in particular, musculoskeletal pain (especially of the neck, back and arms) and visual strain, as well as mental fatigue.[35–37]

The transanal approach to TME, TaTME, was specifically pioneered to overcome the technical difficulties encountered by the "top-down" approach with the added bonus of allowing the surgeon to sit comfortably throughout the procedure. TaTME is a "bottom-up" approach whereby the rectal transection and TME dissection are performed with standard laparoscopic instruments via the anus, explained in more detail in Section 2.4 'TaTME Technique'. The proposed benefits of TaTME include intraluminal confirmation of tumour position allowing an optimal level of transection of the distal rectum, clearer visualisation of the dissection plane even in a narrow pelvis, avoidance of excessive manipulation of the specimen to obtain exposure thus allowing a more precise and trauma–free dissection. Subsequently, TaTME has the potential to produce superior oncological resections as well as preserve the pelvic autonomic nerves maintaining bowel, urinary and sexual function.

2.2 The Origins of TaTME

The evolution of TaTME is an excellent example of the process and steps required to initially develop a new surgical technique, as recommended by the IDEAL (Innovation, Development, Exploration, Assessment, Long-term study) framework.[38] The first two stages of innovation and development started with extensive work in animal laboratories[39,40] and on human cadaveric models.[41,42] This 'secure' setting that poses no risk to live patients, permitted the initial 'trial and error' phase to take place, demonstrating feasibility of the concept and establishing the critical steps of the operation. TaTME however is not a completely new concept, but rather an amalgamation of numerous other techniques including transanal endoscopic microsurgery (TEM),[43] transanal transabdominal approach,[44] natural orifice transluminal endoscopic surgery (NOTES),[45] and transanal minimally invasive surgery (TAMIS).[46] The initial procedures performed did in fact utilise equipment and instruments already used in routine surgical practice, including the TEM rigid platform, conventional laparoscopic instruments and standard insufflation.

In 2007, Whiteford et al.[41] were the first to perform a natural orifice transanal endoscopic rectosigmoid resection using a rigid TEM platform in three human cadavers. Subsequent studies by the same group confirmed that a purely transanal approach for rectosigmoidectomy is feasible, however, current conventional rigid TEM instrumentation is inadequate for colonic mobilisation and further innovation of instrument design is required.[47] Sylla and colleagues,[39] on the other hand, undertook a hybrid approach combining the NOTES transanal rectosigmoid resection with transgastric endoscopic assistance in order to achieve a more extensive left colonic mobilization. These initial studies suggested that, until improved instrumentation is available, the recommended technique should consist of a hybrid transanal approach with laparoscopic assistance, which allows a more efficient splenic flexure mobilization and secure proximal vascular control.

The first human clinical case was soon performed in 2009 by Antonio Lacy and Patricia Sylla in Barcelona.[48] The procedure, named 'NOTES rectal cancer resection using transanal endoscopic microsurgery and laparoscopic assistance', was accomplished in a 76-year-old woman with a T2 N2 anterior rectal cancer 8 cm from the anal verge on staging MRI treated with preoperative chemoradiation. The operation was completed within 4 hours 30 minutes with endoscopic dissection of the rectum and mesorectum achieved entirely transanally through the TEM platform up to the level of the rectosigmoid junction above the peritoneal reflection. Intra-operatively, a small tear of the rectal wall was noted anteriorly during early mobilisation from the posterior vaginal wall, which was immediately sutured closed. The postoperative course was uneventful with a length of hospital stay of 4 days. The final pathology demonstrated a pT1N0 tumour with 23 negative lymph nodes, negative resection margins and a complete mesorectal specimen. The surgeons concluded that this clinical case demonstrated the feasibility and safety of NOTES transanal rectal cancer resection with laparoscopic assistance. Concluding that the procedure was “safe” is questionable given the occurrence of a tear in the anterior rectal wall during TME dissection for an anteriorly located rectal tumour; thus, potentially increasing the risk of tumour cell spread and local recurrence. Rightly so, the authors caution that the long-term oncological outcomes need to be closely monitored and that such an approach should only be performed by surgeons with extensive expertise in rectal cancer and NOTES. A huge surge in the interest and adoption of this new technique soon followed, with numerous published studies by early adopters describing their technique and short-term outcomes increasing rapidly.

2.3 Selection for TaTME

“Selection” usually refers to the selection of patients with certain characteristics that indicate their suitability for a particular procedure. Defining the criteria for such patient selection, including both indications and contraindications, is an important milestone in the understanding of the true benefits that a certain approach can provide. However, “selection” can also refer to the surgeon performing the operation, and the necessary skills and training they require. TaTME is not a simple procedure and as stated by its pioneer, Antonio Lacy, “this technique is a high-stakes procedure with multiple potential pitfalls and complications, both functionally and oncologically”.[49] The introduction of TaTME has really highlighted and brought into discussion the responsibility and role surgeons have in ensuring that they, and their team, are appropriately trained to safely deliver this technique.

Patient selection

Varying opinion on the criteria for patient selection exists among surgeons performing TaTME. A systematic review including 20 papers of TaTME series and comparative studies demonstrated this variability with 8 studies only selecting cases with low rectal tumours <5cm from the anal verge, while another 3 studies accepted a tumour height of up to 12cm.[50] T4 tumours were included in most studies, while one study only performed TaTME on cases with anteriorly located tumours. Such variation is not uncommon at the beginning of the adoption of a new technique when indications tend to be much broader; in addition, each surgeon may select certain cases for which he/she believes the approach will provide most benefit. As well as surgeon choice and experience, local resources and familiarity of the technique by the whole multidisciplinary team are other possible reasons for differences in practice.[51]

A handful of consensus papers have been published so far outlining specific patient characteristics and pathological features for which TaTME is likely to provide added benefits with improved outcomes compared to conventional abdominal surgery.[52–54] One of the first consensus statements published in 2016 followed the second international TaTME conference held in Paris in July 2014,[52] which included the opinion and experience of surgeons performing TaTME with a mean caseload of 35 cases, ranging from 8 to 121 (combined caseload 492 cases). Two years later, the St Gallen Colorectal Consensus Expert Group published their consensus on safe implementation of TaTME including a section on patient selection and surgical indications.[53] A total of 37 colorectal surgeons from 20 different international countries contributed to the work, all of whom had performed a minimum of 20 TaTME procedures, published their results in peer-reviewed journals and together had a total caseload of over 1000 cases. The consensus panel also included three additional experts in the fields of clinical histopathology, radiology and medical oncology, bringing the group to a total of 40 participants. The most recent consensus process on TaTME involved 58 international surgeons regularly practicing the technique in 19 countries worldwide and was endorsed by numerous affiliated societies including ASCRS (American Society of Colon and Rectum Surgeons), SAGES (Society of American Gastrointestinal and Endoscopic Surgeons), EAES (European Association of Endoscopic Surgeons), CSSANZ (Colorectal Surgical Society of Australia and New Zealand), Chinese Society of TaTME Surgeons, Chinese Society of Surgeons, Japanese Society of Endoscopic Surgery, Brazilian Society of Coloproctology, Argentinian Society of Coloproctology.[54] For this latest expert consensus study, an adapted Delphi process and focus group discussion approach facilitated by an expert in guideline development and led by Mr Danilo Miskovic and Dr Roel Hompes, was employed. The group recognised that at present there is a lack of high-quality evidence to support or confirm any potential 'guidelines' developed from the study. The term 'guidelines' may also provoke undesired legal implications especially in some countries such as the United States of America. Furthermore, research in this field is continuously evolving with new evidence frequently emerging. Hence, the decision to provide "dynamic guidance" instead with the aim of publishing guidance statements and recommendations that will regularly be reviewed, discussed and updated as new evidence becomes available. Table 1.1 lists the selection criteria for TaTME recommended by the three consensus documents mentioned above.

Table 1.1 Indications for TaTME surgery recommended by group consensus publications.

	Second International TaTME Consensus Conference 2014 Motson et al.[52]	**St. Gallen Colorectal Consensus Expert Group, 2018** Adamina et al.[53]	**Dynamic Guidance 2019** Hompes et al.[54]
Patient characteristics	• Male gender • Narrow ± deep pelvis • Visceral obesity ± BMI >30kg/m^2 • Prostatic hypertrophy	• Both genders • Narrow pelvis • Visceral obesity with a fatty mesorectum • Previous pelvic surgery, especially prostatectomy and mesh rectopexy.	• Previous prostatectomy, pelvic radiation, complex pelvic surgery*
Tumour characteristics	• Rectal cancer <12cm from anal verge • Tumour diameter >4cm • Neoadjuvant therapy distorting tissue planes • Impalpable, low primary tumours	• Bulky, mid/distal tumours • Best for lower tumours needing TME, although PME for higher tumours can be performed	• Any malignant rectal resection where there is anticipated technical difficulty in pelvic dissection • Only when total mesorectal excision is indicated • When a clear distal margin cannot be guaranteed by a pure abdominal approach. • cT4 and Rullier Type 3 juxtasphincteric rectal cancers can be considered for a transanal approach* • Following previous full thickness local excision
Benign conditions	• Inflammatory bowel disease (IBD) requiring proctectomy • Rectal strictures • Complex fistulae • Faecal incontinence • Familial adenomatous polyposis (FAP) • Radiation proctitis • Removal of the orphaned rectum following colectomy	• Inflammatory bowel disease requiring proctectomy or proctocolectomy • Rectovaginal fistulae • Pouch advancement procedures • Removal of a neorectum in cases of chronic anastomotic sinus/leak	• Any benign rectal resection where there is anticipated technical difficulty in pelvic dissection • Inflammatory bowel disease requiring proctectomy • In IBD and FAP, for an ileoanal pouch procedure where there is anticipated difficulty in judging

			the level of distal transection • Revision of an ileoanal pouch* • Revision of refractory anastomosis-related sepsis*
Contraindications	• Obstructing rectal tumours • Emergency presentation • T4 tumours	*Not stated*	*Not stated*

* Procedure recommended to take place in an expert centre for these cases.

Over the five-year period of these three consensus studies, it is interesting to note, that the indications have remained fairly consistent, and recognise the role of the transanal approach for both malignant and benign conditions. However, three key differences are apparent and are likely to represent the increased experience and understanding of the technique as well as more available up-to-date outcomes in larger cohorts. Firstly, the recognition that both genders may benefit from the approach rather than solely concentrating on male patients as initially recommended in 2014. The fundamental factor that determines the suitability of the approach is the anticipated technical difficulty in pelvic dissection, which results from features that limit the exposure of the operating field and prevent clear visualisation of the dissection plane. These features can be present in either gender, and are usually a combination of factors, such as increased visceral obesity, a narrow pelvis, and/or a low bulky tumour. Previous pelvic surgery or radiation are also important as the dissection plane may be obscured with scarring and/or oedema, making the surgery more challenging.

Secondly, the latest dynamic guidance only recommends the transanal approach for rectal cancer when a total mesorectal excision is required.[54] This follows concerns of inappropriately low rectal transections with unnecessarily long distal resection margins for proximal third rectal tumours removed by TaTME.[55] In such cases, the complete excision of the mesorectum is not indicated and the risk of worse post-operative functional outcomes due to a deeper pelvic dissection are therefore preventable.

Lastly, the recommendation that TaTME for certain conditions should only be performed in "expert centres" was suggested in the latest guidance report.[54] A definition of expert centres was provided including specific criteria relating to the surgeon's operative and training experience, centre specifications with recommended unit resources and annual case volume, as well as performance metrics to meet. This is a clear call for "pseudo-centralisation" of TaTME, especially for the more complex cases, recognising that such surgery is challenging and will only achieve the best possible result in well-resourced, trained and experienced centres with a high case volume.

The eligibility criteria for patients entered into randomised controlled trials (RCT) assessing TaTME is another important source of information regarding patient selection for this technique. The multicentre international RCT comparing TaTME to laparoscopic TME (LapTME) called COLOR III trial aims to recruit 1104 patients in total (2 TaTME vs 1 LapTME randomisation) to demonstrate a non-inferiority effect on local recurrence of 4% after 3 years.[56] The inclusion criteria include mid or low biopsy proven rectal adenocarcinoma with a distance of up to 10cm from anal verge on staging MRI, undergoing surgery with a curative intent and planned to have a primary anastomosis. The trial excludes cases with T4 tumours and T3 with involved resection margins seen on staging MRI after neoadjuvant therapy, previous rectal resections or prostatectomy and cases with tumour ingrowth into the anal sphincter complex or levator muscles that require abdominoperineal resection.

A multicentre prospective RCT initiated in Spain is also comparing TaTME to laparoscopic TME with primary endpoints of 30-day morbidity and functional outcomes 6 months after stoma reversal.[57] They have selected similar inclusion criteria to COLOR III but also specified that included patients must have a BMI between 18 and 35 kg/m^2 and also excluded patients with liver cirrhosis and chronic renal impairment on dialysis.

Lelong et al.[58] have published the French RCT comparing endoscopic transanal proctectomy (ETAP) versus standard transabdominal laparoscopic proctectomy for rectal cancer (ETAP-GRECCAR 11). They aim to recruit 226 patients with a primary endpoint of R1 resection rate. The inclusion criteria specify non-metastatic T3 rectal adenocarcinoma suitable for a sphincter-sparing procedure with a tumour location or local condition that permits a manual coloanal anastomosis. It is important to note the difference in surgical technique allowed for ETAP in this French trial compared to the other RCTs on TaTME which predominantly start the transanal phase with placement of the pursestring. The ETAP procedure can be commenced with a mucosal incision and internal sphincter dissection according to tumour extension and primary conventional dissection performed until circumferential exposure of the fascia recti is achieved. Only then, will secondary implantation of the transanal endoscopic device be placed and mesorectal endoscopic dissection performed. It will be interesting to see the difference in post-operative function and quality of life as well as local recurrence rate in these patients who receive a very low anastomosis.

A multicentre phase II study of TaTME is also being run in the USA led by Dr Patricia Sylla.[59] The aim is to recruit 100 patients into the single arm undergoing TaTME with the primary endpoint being quality of mesorectal excision. The eligibility criteria are very similar to that of COLOR III but also excludes patients with faecal incontinence at baseline, history of inflammatory bowel disease and severely symptomatic rectal tumours.

Results from these trials should be available in the next few years and are eagerly awaited.

Surgeon selection

Standards of 'Good Surgical Practice' set out by the Royal College of Surgeons of England (RCS) state that "the introduction of new surgical techniques…must be under-pinned by rigorous clinical governance processes, having the patients' interests as the paramount consideration".[60] Furthermore, the RCS document "From Innovation to Adoption",[61] states that discussion about the technique with colleagues and approval from the medical director, as well as relevant training, mentorship and assessment of all clinical staff involved are recommended steps to be undertaken.

Before embarking on the adoption of a new technique, especially of a complex one such as TaTME, a surgeon needs to reflect on three main aspects: 1) Themselves as operating surgeon, 2) the clinical need for the operation, and 3) the whole clinical team.

<u>The surgeon</u>

The two principal factors regarding the surgeon include their present level of surgical skill prior to learning TaTME and receiving appropriate training in the new technique. The UK National Institute for Health and Care Excellence guidelines published in 2015 recommend that ''TaTME should only be done by surgeons who are experienced in laparoscopic and transanal rectal resection and who have had specific training in this procedure''.[9] All consensus papers on TaTME published to date advise that TaTME should be taken on by surgeons with prior experience in laparoscopic oncological rectal surgery as well as transanal surgery using minimally invasive transanal devices.[52–54] The consensus papers also highly recommend attending a TaTME course which should include didactic lectures, mentored cadaveric dissection, live surgery and review of unedited operative videos. A big emphasis is made, especially in the latest dynamic guidance,[54] on the availability of mentors for clinical cases undertaken as soon as possible following the training course. The guidance also states that "proctorship training should continue until safe independent performance is achieved". No estimated number of cases is provided, most likely because this will vary amongst surgeons and the learning curve for this procedure remains to be established. Furthermore, the regular availability of proctors travelling to different sites may be logistically difficult and costly. Dedicated fellowships in TaTME in experienced centres may become available and facilitate this mentorship period.

Clinical need for the operation

A certain annual case volume is required in order to allow the surgeon to overcome their learning curve and reach operative proficiency in a reasonable period of time, and for resources, especially any new equipment specific to the procedure, to be used in a cost-effective manner. Given the relatively narrow selection criteria for TaTME, each individual colorectal unit contemplating starting this technique, should evaluate whether there is a reasonable number of patients who would benefit from TaTME, i.e. is there a clinical need to adopt this new approach. In the St. Gallen consensus a minimal annual volume of 10 complete TME dissections for cancer was agreed on in order to start a TaTME practice.[53] The authors did recognise that individual variability may influence the length and steepness of the learning curve and, although low, the figure of 10 cases per year would be an absolute minimum. The latest dynamic guidance[54] increased the requirements before undertaking TaTME further recommending that surgeons should have established experience in minimally invasive TME and an annual institutional volume of more than 30 rectal resections and that at least two surgeons per institution who have completed structured training should perform TaTME. If the clinical need is low, then it would be inappropriate to adopt this new technique and rather, the occasional patient that is likely to benefit from TaTME could be referred to an "expert TaTME centre" as described in the dynamic guidance statements.

The whole clinical team

Prior to the adoption of a new technique, a vigorous clinical governance process should be adhered to as recommended by the National Institute for Health and Care Excellence (NICE).[9] To facilitate the acceptance and smooth implementation of TaTME, it is important for the whole multidisciplinary team to know the particulars of TaTME.[52] St. Gallen recommendations advise that case observation and hospital visit, involving the complete theatre team, are very useful prior to starting TaTME. This is also echoed in the dynamic guidance[54] stating that TaTME should be implemented within a multidisciplinary dedicated operative theatre team. This is likely to promote a more productive working environment with greater understanding and efficient team working.

2.4 TaTME technique and instrumentation

Various studies in the literature have described the TaTME technique but the most standardised version that underwent a robust Delphi consensus process was developed for the COLOR III randomised trial[56] and used for the video analysis study in this PhD.[62] TaTME is most commonly performed as a hybrid approach with an abdominal phase (robotic, laparoscopic or open) and transanal phase. The phases can be performed synchronously by two teams or consecutively by one team.

Standard instrumentation for laparoscopic, open or robotic surgery is used to perform the abdominal component. Transanally, the main new equipment required for TaTME includes the transanal platform and insufflation system. Numerous transanal platforms are available and broadly divided into rigid and flexible designs. The first live TaTME case was performed using the rigid TEO® platform (Karl Storz, Tuttlin-gen, Germany) with its accompanying instrumentation.[48] Variations to this platform have been developed by Karl Storz collaborating with TaTME surgeons to produce the rigid D-port and B-port platforms, specifically for TaTME. The TEM proctoscope by Wolf (Richard Wolf Medical Instruments Corp, Vernon Hills, Ill) has also been used. However, the flexible platforms appear to be more commonly adopted for TaTME, in particular the GelPoint Path Transanal Access Platform (Applied Medical, Inc., Rancho Santa Maragarita, CA). Numerous flexible alternatives exist such as the SILS Port (Covidien, Minneapolis, MN, USA), and GelPOINT Mini (Applied Medical, Inc., Rancho Santa Maragarita, CA). Limited evidence so far has shown no difference in histological outcomes between the use of rigid or flexible platforms.[63]

At the start, standard carbon dioxide insufflation typically used for laparoscopy was utilised. However, this produced an unstable working field with excessive bellowing and poor smoke evacuation. Hence the valveless trocar system, AIRSEAL Intelligent Flow System® (ConMed; Utica, New York, USA) was developed for flexible platforms with an integrated three-lumen insufflation system that provides high-flow insufflation, stable pneumoperitoneum, valveless trocar access, and constant smoke evacuation.[64] Rigid platforms tend to utilise their own high-pressure insufflation system. The rest of the instrumentation used transanally is typically the same as for standard laparoscopy such as graspers, hook diathermy and energy devices. Laparoscopes with either 30- or 45-degrees angle or with articulating tips tend to be preferred in order to be able to capture the whole field whilst avoiding too much clashing with the working instruments.

Although TaTME has been adapted for benign conditions, the technique was primarily pioneered for rectal cancer, which is also the cohort that the thesis focuses on. The following section will therefore summarise the operative steps involved in a low rectal cancer TaTME resection. Initial transanal dissection will vary depending on the location of the tumour and the operation to be performed, i.e. TME, partial mesorectal excision, abdominoperineal excision or intersphincteric resection. For tumours encroaching on the anorectal junction, ARJ, (<1.5cm), partial intersphincteric open dissection is performed prior to luminal occlusion with a pursestring when the level of the pelvic floor is reached.[52] In more proximal tumours (>1.5cm from ARJ), a circumferential pursestring is placed leaving a safe distal margin from the tumour edge. The transanal phase can be divided into the five key steps (Figure 1.1): (i) Rectal pursestring placement, (ii) Full thickness rectotomy, (iii) TME dissection, (iv) Specimen extraction, and (v) Anastomosis.

(i) Rectal pursestring placement

A pursestring suture, either 2/0 or 0 monofilament, is placed under direct vision or endoscopically through a transanal platform. Ideally, at least 1cm distance from the tumour is maintained to avoid a positive distal margin. Small equal bites starting at 5 or 7 o'clock and circumferentially without spirally up or down the lumen are required to fully occlude the lumen without leaving defects and achieving an airtight seal. This will avoid spillage of stool and potential tumour cells and prevent excessive colonic insufflation. Generous washout using a tumouricidal solution further helps prevent implantation of free tumour cells and bacterial contamination. With the transanal platform in place a 'pneumorectum' is created, usually with an initial pressure of 8-10 mmHg and standard laparoscopic instruments are used with either a 0º, 30º or 45º high-definition or 0º three-dimensional laparoscope.

(ii) Full thickness rectotomy

The mucosa is scored using monopolar diathermy at the extremities of the radial folds created by the pursestring to outline the circle of dissection for the rectotomy. A circumferential full thickness dissection through the muscular rectal wall and into the mesorectal plane must be obtained prior to proceeding to the next step. The rectotomy must be created in a tangential plane in order to avoid intramural dissection with the increased risk of causing rectal ± tumour perforation. The insufflation pressure can be increased to15-20 mmHg in order to achieve a good wall tension that will facilitate the full thickness rectotomy further.

(iii) TME dissection

It is recommended to start the dissection of the mesorectal 'holy' plane posteriorly at the 5 or 7 o'clock position, thus avoiding the central thicker raphe. Care should be taken to enter the avascular presacral plane between the parietal endopelvic fascia and mesorectal envelope, identified by the 'angel hair' that appears when sufficient retraction is applied and insufflation gas opens up the tissue planes. Bleeding from presacral veins occurs if the dissection is too far posterior. However, the steep sacral angle must be acknowledged and followed in order to avoid dissecting too horizontally and injuring the mesorectum or the rectum itself.

Anterior dissection is carried out next with identification of the lower border of the prostate in men. A plane either side of Denonvilliers' fascia can be selected depending on the position of the tumour. The membranous urethra in males is vulnerable to injury if dissection is too anterior as well as significant bleeding from the prostate and seminal vesicles. Cylindrical or 'sleeve-like' dissection should progress cephalad leaving the lateral pillars last, when the dissection plane becomes clearer by following a line between the anterior and posterior openings. This 'posterior-anterior-lateral' sequence of dissection helps to avoid dissecting too widely on the pelvic sidewall which runs the risk of injuring the lateral neurovascular bundles, pelvic sidewall vessels and subsequently mobilising the prostate and causing injury to the urethra. Connection between the abdominal and transanal teams should only occur once the anterior and posterior dissections are almost complete, as early connection can de-stabilise the pneumoperitoneum and obscure the transanal team's view. The abdominal and transanal teams can work together providing traction and counter-traction to obtain better views for dissection.

(iv) Specimen extraction

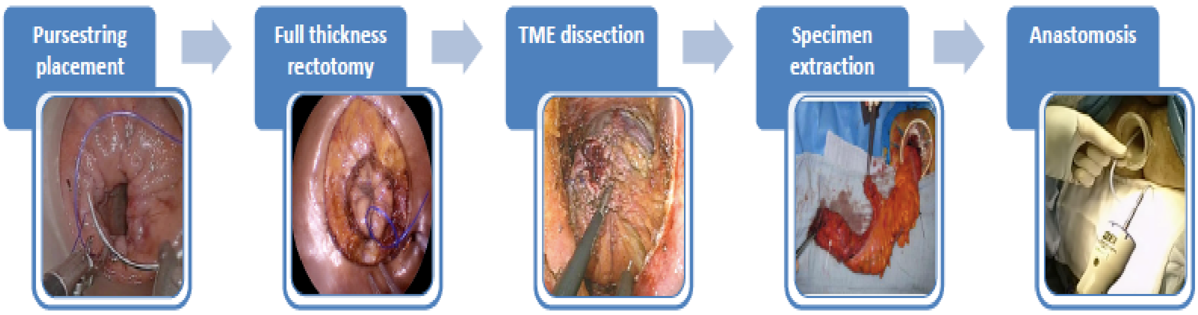
Once the rectal tube is fully mobilised, extraction of the specimen can take place either transanally or transabdominally. Extraction must be performed cautiously and gently without exerting too much tension on the specimen in order to prevent damaging the specimen as well as compromising the blood supply to the remaining colon. Thus, bulky specimens that are unlikely to fit through the transanal opening or have a short mesentery are best removed transabdominally.

(v) Anastomosis

An open distal rectal stump is left behind following specimen extraction. A handsewn coloanal or stapled colorectal/coloanal technique can then be selected for the anastomosis.[65] Three stapling approaches have been described to date using either an EEA™ Haemorrhoid Stapler (AutoSuture; Covidien, Dublin, Ireland),[66] a standard diameter circular stapler either in combination with a guiding 10Fr redivac drain[67] or a pull through method.[65] Very low coloanal anastomoses will tend to be performed manually, as there may be insufficient stump length to place the second pursestring for a stapled anastomosis. Stapled anastomosis requires a double pursestring: one on the open distal rectal stump and the second on the proximal colon or small bowel. Each technique offers unique advantages and disadvantages and may be more suited for anastomoses at different heights from the anal verge and customised to the patient characteristics, as described in our technical note.[65]

The TaTME technique is continuously being explored and modified with the addition of advancing technology, such as robotic TaTME[68–70] and stereotactic navigation.[71,72] The basic principles and steps however are likely to remain the same.

Figure 1.1 Key operative steps of transanal total mesorectal excision.



2.5 TaTME Outcomes

At the start of my PhD, TaTME was still a relatively new procedure with growing numbers of early adopters and only starting to be explored by the wider colorectal community. Below is a summary of the published literature that was available prior to embarking on the PhD research project.

2.5.1 Clinical outcomes

Early adopters of TaTME were sharing their experience through case reports, small cohorts and a few comparative studies. Two main systematic reviews captured the available data showing promising results.[73,74] The first by Similis et al.,[73] reported on 510 participants from 37 studies (9 case reports, 24 case series and 4 comparative studies). The overall peri-operative morbidity rate was 35% with no 30-day mortality. Intra-operatively, the mean blood loss ranged from 22 to 225mls, operative time ranged from 143 to 450 minutes and 12 (2.3%) conversions to open surgery occurred. The causes for conversion were posterior fixity of the tumour, intra-abdominal adhesions after previous laparotomy, a bulky high tumour, technical difficulties in obese patients and a urethral injury. Three intra-operative urethral injuries were reported, two of which were sutured transanally with no further consequences.[75,76] The anastomotic leak and reintervention rates were 6.1% and 3.7% respectively. Emergency re-operation was required due to presacral abscesses requiring drainage, small bowel obstruction, anastomotic leaks, and ischaemic colon. The mean length of hospital stay was 4.3 to 16.6 days. Arunachalam et al.[74] also conducted a systematic review of TaTME outcomes and included the largest cohort of 140 cases from the pioneer Professor Lacy. The total number of patients included was 449 from 15 different studies. Similar morbidity and mortality rates were found at 35.5% and 0.4% respectively. Both anastomotic leak rate and reoperation rate were 9.1%. Blood loss averaged 150mls and median length of stay was 7.3 days.

2.5.2 Oncological outcomes

One of the pioneers of TaTME, Professor Antonio Lacy, published results on his initial cohort of 140 consecutive cases.[77] He achieved a complete TME specimen in over 97% of cases with a positive CRM rate of 6.4%. The early local recurrence rate was 2.3% over a mean follow up period of 15 months. In the systematic review by Similis et al.[73] that included 510 patients the mesorectum was described as complete or nearly complete in 88% and 6% respectively, whilst the CRM and DRM were negative in 95% and 99.7% respectively. The systematic review by Arunachalam et al.[74] also showed similar promising results. Such outcomes compare favourably to those reported for open and laparoscopic TME, with an overall positive CRM rate of 16% in the CLASSIC trial[22] and 10% in COLOR II.[21] Even the two most recent randomised controlled trials (RCT) comparing laparoscopic to open surgery for rectal cancer, ACOSOG Z6051[27] and ALaCaRT,[26] could not demonstrate non-inferiority of laparoscopic TME over open TME for histopathological outcomes and morbidity. The positive CRM rate for laparoscopic versus open TME surgery in these trials was 7 – 12.1% vs. 3 – 7.7%, respectively.

Tuech et al.[78] published recurrence rates and survival for one of the longest follow up periods, with a median of 29 (18–52) months. He reported an overall survival rate of 96.4%, disease-free survival rate of 94.2% and local recurrence rate of 1.7%. Metastatic disease was diagnosed after surgery in two out of 52 patients (3.8%).

2.5.3 Functional outcomes

The systematic review by Similis et al.[73] found that one of the most common complications post-operatively was urinary retention and transient urinary dysfunction at a rate of 5%. Sylla et al.[79] used urodynamic testing and found minimal detrusor activity secondary to parasympathetic nerve injury on their two cases of urinary dysfunction.

Four studies recorded postoperative Wexner scores for bowel function over a follow up period between 3 to 12 months and found a mean score of 4.3 (good function).[70,78,80,81] Further studies on more detailed bowel and urinary function as well as sexual function and overall quality of life were pending.

3. Questions, Aim & Hypothesis

3.1 Research Questions

1. What is Transanal Total Mesorectal Excision (TaTME)? What is the rationale, origins and initial outcomes of this new procedure?
2. What is the current TaTME practice and short-term outcomes based on the international TaTME registry data? What is the proficiency gain curve of TaTME?
3. Which technical errors are committed during a TaTME procedure identified by Observational Clinical Human Reliability Analysis? What are the error pathways that lead to adverse events?
4. Is there a correlation between OCHRA findings and histological outcomes?
5. What are the error-reducing mechanisms and technical recommendations that can be implemented into training and practice to improve technical performance?

3.2 Aim of thesis

The aim of this thesis is to assess the safety and efficacy of Transanal Total Mesorectal Excision by Observational Clinical Human Reliability Analysis and analysis of international registry data.

3.3 Hypothesis

Transanal total mesorectal excision will provide equivalent, if not superior, short-term intra-operative (technical), clinical and histopathological outcomes for rectal cancer patients compared to conventional TME surgery, even during its early adoptive phase.

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CHAPTER II

REGISTRY-BASED OUTCOMES

What is the current TaTME practice and short-term clinical and oncological outcomes based on the international TaTME registry data? What is the proficiency-gain curve for TaTME?

1. Short-term oncological outcomes

Transanal Total Mesorectal Excision: International Registry Results of the First 720 Cases

Publication reference

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1.1 Introduction

The driving purpose for seeking an alternative approach via the transanal route was to achieve better oncological outcomes for the most challenging rectal cancer cases. Similarly, clinical and functional outcomes were also expected to improve as the transanal technique could provide better visualisation of the anatomy in a deep narrow pelvis facilitating more accurate dissection. At the time of this study, short-term outcomes following TaTME were predominantly reported in small cohorts primarily from single units of the pioneers and early adopters of the technique. Outcomes from these studies showed encouraging initial results and have been described in section 2.5 of chapter one. Randomised controlled trials were in the process of being designed or just recently started and hence their results wouldn't be available for at least another three to five years.

The use of online databases has become an increasingly popular method for data collection and conducting registry-based research, both at a national and international level.[1,2] The TaTME registry was developed in the UK,[3] funded by the Pelican Cancer Foundation and accessed via the Low Rectal Cancer Development (LOREC) website (http://www.lorec.nhs.uk). It has been available since July 2014 via a secure encrypted online server behind a firewall and protected by anti-virus software; designed by PAM Internet Ltd, a web design company experienced with securely hosting patient data in line with the general data protection regulations. Registration is voluntary, free of charge and open to all colorectal surgeons performing TaTME worldwide. In the UK, the National Institute for Health and Care Excellence (NICE) published guidelines on TaTME in March 2015 stating that "Clinicians should enter details about all patients undergoing TaTME (for malignancy or a benign indication) onto the TaTME registry".[4] The guidelines also proceed to specifying outcomes that should be recorded for cases of malignancy, as well as encouraging the reporting of all complications and highlighting the need for further research into TaTME. The dataset recorded on the TaTME registry covers all NICE recommended outcomes and is divided into nine sections that follow the patient's 'journey' through their treatment: patient demographics, tumour staging and neoadjuvant therapy, operative details, post-operative clinical and histological outcomes, readmissions and reinterventions, late morbidity, long-term oncological follow up and both quality of life and functional questionnaires. Definitions of outcomes, such as anastomotic leak and resection margin positivity, have been described on the registry; abbreviations explained in full and standard medical language in the published literature has been used throughout the database in order to achieve a mutual understanding amongst all of the international surgeons collaborating with the registry.

This study was the first analysis performed using the TaTME registry data and was published in print in Annals of Surgery in July 2017.[5] The aim of the study was to report short-term clinical and histological outcomes following TaTME surgery by TaTME registry collaborators worldwide.

1.2 Methods

Cases recorded on the TaTME registry between July 2014 and December 2015 for both malignant and benign indications were included in the analysis. Ethical approval for the TaTME registry and publication of its results was previously obtained from the UK Health Research Authority (REC reference 15/LO/0499, IRAS project ID 156930). Collaborating surgeons were informed of the upcoming data analysis three months prior to the data download and encouraged to review all of their cases, with two reminder emails, aiming to minimize missing data and obtain up-to-date results. Data entry was checked for any unexpected or possibly erroneously entered results and surgeons contacted individually to clarify these findings. Two collaborators from each contributing unit were requested to add on the manuscript as part of the international TaTME registry collaborative acknowledging their valuable contribution and strengthening the collaborative bond.

Study endpoints

The primary endpoint of the study was “good-quality TME surgery” defined as a composite of TME specimens with clear resection margins (R0 resection), no rectal perforations and an intact or nearly intact mesorectal specimen. The well-known and published Quirke et al.’s[6] categorization of the TME specimen was used describing the excised mesorectum as either intact (smooth, regular mesorectum with no defect deeper than 5 mm and no coning), nearly intact with only minor defects (moderate mesorectal bulk with moderate coning), or major defects reaching the muscularis propria (little mesorectal bulk and irregular circumferential resection margin). Rectal perforations present along any length of the specimen were included in the “bad-quality TME” or poor histological composite group as this represents a technical error with incorrect plane surgery that has the potential to shed tumour cells (especially if the perforation occurs at or close to the tumour) into the abdomen or pelvis leading to the risk of tumour regrowth. Positive resection margins, both circumferential and distal, were defined as the presence of tumour cells directly at the margin or a minimal distance between the tumour and the margin of 1mm or less. Risk factors for a poor histological composite outcome were identified.

Secondary endpoints included short-term clinical and histological outcomes. Technical details and intra-operative outcomes, such as operative time and intra-operative adverse events, were also described.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) of IBM Statistics, version 20. Categorical data are reported as number of cases and percentages, whereas continuous data are presented as either median with range or mean ± standard deviation (range). Possible risk factors associated with poor histological features (composite of R1 resection, poor TME quality and/or perforated specimen) were identified by univariate and multivariate analysis. For univariate analysis, Pearson χ^2 test was used to compare the categorical variables, whilst continuous variables were analysed using Mann-Whitney U test. All variables that achieved a p-value ≤0.100 on univariate analysis proceeded to a subsequent multivariate analysis using logistic binary regression. A p-value <0.05 was considered statistically significant for the multivariate analysis results.

1.3 Results

Sixty-six surgical centres in 23 different countries worldwide contributed a total of 720 cases during the 18-month study period. Case volume was 0–5, 6–10, 11–20 and >20 cases in 33 (50%), 12 (18%), 8 (12%) and 13 (20%) centres respectively. Most cases, 634 (88.1%), were performed for rectal cancer.

Patient and tumour characteristics

The majority of patients were male (489/720, 67.9%), with a mean age of 62 years and mean body mass index (BMI) of 26.5 kg/m^2 (Table 2.1). Nineteen percent had previous abdominal non-cancer related abdominal and/or pelvic surgery; in particular, 23 (3.2%) patients had a previous hysterectomy and 12 (1.7%) had a previous prostatectomy. These operations are specifically requested on the registry as they are likely to affect the level of difficulty of the case depending on the amount of residual scarring and potential distortion of the anatomy following such procedures.

Surgery was performed for rectal cancer in 88.1% of cases (n=634), whilst 86 patients (11·9%) had benign pathology, predominantly inflammatory bowel disease. Low rectal cancer, ≤6cm from anal verge as defined by the LOREC group,[7] accounted for 62% of cases. Mid (7 to 10cm) or high (>10cm) rectal cancer was present in 37% and 1% respectively. The median tumour height from anorectal junction on staging MRI was 3.0cm (range 0–11cm), with 43.3% of tumours being predominantly located anteriorly. Baseline MRI staged 185 (33·1%), 343 (61·4%) and 31 (5·5%) cases as T1–T2, T3 and T4 rectal cancer, respectively. Nodal status was reported as N0 in 232 (41.8%) cases, and nodal positive in 58.2% (N1: 221, 29·8%; N2: 102, 18·4%). Synchronous metastatic disease was present in 40 (6.6%) patients. A threatened

CRM, present in 115 (21.1%) cases, was due to nodal involvement in 8.3%, tumour involvement in 11% and both nodal and tumour involvement in 1.8%. Table 2.1 outlines patient and tumour characteristics in more detail.

Table 2.1 Patient and tumour staging characteristics

Factor ▪ Category	**TaTME registry data results** Total: 720 patients
Gender, n (%)	
▪ Male	489 (67.9)
▪ Female	231 (32.1)
Age in years, mean ± SD (range)	62·4 ± 13·0 (18–91)
ASA score III and IV, n (%)	136 (19.7)
BMI in kg/m2, mean ± SD (range)	26·5 ± 4·3 (16·5–42·7)
Smoker, n (%)	90 (12.5)
Presence of co-morbidities, n (%)	
Diabetes mellitus	85 (11.8)
Ischaemic heart disease	97 (13.5)
Active inflammatory bowel disease	42 (5.8)
Steroid use at time of surgery	13 (1.8)
Previous abdominal/pelvic surgery, n (%)	134 (19.0)
Previous pelvic radiation therapy, n (%)	15 (2.1)
CANCER CASES, n (%)	**634 (88.1)**
Clinical tumour height from anal verge on rigid sigmoidoscopy in cm, median (range)	6·0 (0–13)
Tumour height from anorectal junction on MRI in cm, median (range)	3·0 (0–11)
Predominant tumour location, n (%)	
▪ Anterior	243 (43·3)
▪ Posterior	233 (41·5)
▪ Lateral	85 (15·2)
▪ *Missing*	*73 (11.5)*
Circumferential extent of tumour, n (%)	
▪ 1 to 2 quadrants	399 (70·1)
▪ 3 to 4 quadrants	170 (29·9)
▪ *Missing*	*65 (10.3)*

Pre-operative MRI staging, n (%)	
▪ ≥ T3	374 (66.9)
▪ N+	323 (58·2)
Pre-operative CRM involvement on MRI, n (%)	115 (21·1)
NEOADJUVANT THERAPY	
Received neoadjuvant therapy, n (%)	355 (57·1)
▪ Short course radiotherapy	56 (15·8)
▪ Long course chemoradiotherapy	255 (71·8)
▪ Long course radiotherapy alone	27 (7·6)
▪ Chemotherapy alone	48(13·5)
▪ Contact radiotherapy	1 (0·3)
TRG response post neoadjuvant therapy, n (%)	
▪ mTRG 1 & 2 (No or small residual tumour)	136 (38·3)
▪ mTRG 3 (Mixed fibrosis and tumour)	103 (29·0)
▪ mTRG 4 & 5 (Mainly or only tumour)	116 (32·7)

SD: standard deviation. ASA: American Society of Anaesthesiologists. BMI: Body Mass Index. MRI: Magnetic Resonance Imaging. CRM: Circumferential Resection Margin. N+: Positive nodal status (N1 or N2). TRG: Tumour regression grading on MRI
Percentages for *Missing* values use the total number of cancer cases as the denominator (i.e. 634). Percentages for the variables are calculated out of the total number of actual results available excluding the missing values.

Operative details

The TaTME operation comprised of two components: an abdominal and a perineal phase. 32.3% (227 cases) of these involved synchronous operating by two teams. Table 2.2 outlines operative features.

During the abdominal phase, a minimally invasive technique, predominantly by laparoscopy, was implemented in 96.9% (650 cases), with splenic flexure mobilisation in 72.0% and a defunctioning stoma in 91.0% of restorative cases. In cancer cases, the limit of TME dissection by the abdominal team posteriorly reached 8–10cm, 5–7cm and <5cm from the anal verge in 56%, 31%, and 13%, respectively. Anteriorly, dissection stopped at the Pouch of Douglas (POD), seminal vesicles and prostate in 53%, 38% and 9% of males, respectively. In females, 7.1% of surgeons reached the mid-vagina, however, most (67%) terminated at the POD. The level of dissection was continued further down in benign cases, reaching the POD, seminal vesicles and prostate in 42%, 53% and 5.6%, respectively. Female figures were similar to cancer cases, but posterior dissection continued to <5cm from anal verge in 20%, with 44% stopping at 8–10cm.

During the perineal phase, the operation started with rectal pursestring placement in 62.5% of cancer and 52.6% of benign cases. This was via a rigid or flexible transanal platform in 14.4% and 85.6% respectively. The median height of the pursestring from the anorectal junction was 4.0cm (range 0–9). The insufflation systems used during the perineal phase were not initially recorded on the registry and only subsequently added following this study. Bowel anastomosis was created manually in 252 cases (43.6%) and stapled in 327 cases (56.5%). The configuration fashioned in cancer cases comprised of side-to-end, end-to-end, colonic-J-pouch and ileal pouch-anal anastomosis (IPAA) in 49·2%, 46·9%, 3·3% and 0·7% of cases respectively. The stapler diameters used were 28/29mm in 30·6%, 31mm in 12·4% and 33mm in 57% of cases. Manual anastomoses in cancer patients included end-to-end, side-to-end, colonic-J-pouch and IPAA in 67·9%, 27·3%, 4·4% and 0·4% respectively. In benign cases, stapled joins were made as side-to-end (10.5%) or IPAA (89·5%); with three different stapler diameters used: 28mm (5·3% cases), 29mm (73·7%) and 31mm (21·1%). Manual anastomosis configurations recorded for three benign cases were one end-to-end and two IPAA.

Table 2.2 Operative details.

OPERATIVE CHARACTERISITC Factor ▪ Category	**TaTME registry data results** n (%)	
Operations performed		
Cancer cases:		
▪ High anterior resection	30 (4·8)	
▪ Low anterior resection	537 (86·2)	
▪ Abdominoperineal excision	14 (2·2)	
▪ Intersphincteric APE	42 (6·8)	
▪ *Missing*	*11 (1.7)*	
Benign cases:		
▪ Low anterior resection	3 (3·7)	
▪ Standard APE	4 (4·9)	
▪ Intersphincteric APE	48 (58·5)	
▪ Proctectomy (close rectal) + IPAA	3 (3·7)	
▪ Proctectomy (TME plane) + IPAA	24 (29·2)	
▪ *Missing*	*4 (4.7)*	
Simultaneous abdominoperineal operating	227 (32·3)	
Surgical approach		
Abdominal phase:		
▪ Open	21 (3·1)	
▪ Laparoscopic	553 (82·4)	
▪ SILS	93 (13·9)	
▪ Robotic	4 (0·6)	
▪ *Missing*	*49 (6.8)*	
Transanal phase:	Benign	Cancer
▪ Mucosectomy	3 (3·9)	49 (8·2)
▪ Total intersphincteric	29 (28·2)	37 (6·2)
▪ Partial intersphincteric	2 (2·6)	120 (20·0)
▪ Pursestring	40 (52·6)	375 (62·5)
▪ Other*	2 (2·6)	19 (3·2)
▪ *Missing*	*10 (11.6)*	*34 (5.4)*
Stoma		
▪ No stoma	51 (7·3)	
▪ Ileostomy	580 (83·3)	
▪ Colostomy	65 (9·3)	
▪ *Missing*	*24 (3.3)*	

Specimen extraction site		
▪ Pfannenstiel	99 (14·7)	
▪ Umbilical	61 (9·0)	
▪ Right or Left Iliac Fossa	75 (11·1)	
▪ Transanal	340 (50·4)	
▪ Other**	92 (13·6)	
▪ *Missing*	*53 (7.4)*	
Anastomotic technique	Benign	Cancer
▪ Manual	3 (13·6)	249 (44·7)
▪ Stapled	19 (86·4)	308 (55·3)
▪ *Missing*	*8 (26.7)*	*10 (1.8)*
Height of anastomosis from anal verge in cm, median (range)	Benign	Cancer
▪ Manual	2 (1–4)	3 (0–5)
▪ Stapled	4 (2–6)	4 (0–10)
Operative time in minutes, mean ± SD (range)		
▪ Total operative time	277 ± 83 (62–685)	
▪ Perineal phase time	128 ± 70 (15–467)	

APE: Abdomino-perineal excision. IPAA: Ileal Pouch-Anal Anastomosis. TME: Total mesorectal excision. SILS: Single incision laparoscopic surgery. SD: Standard Deviation

*Other transanal phase surgical approaches include extra-levator dissection and abdomino-perineal excision.

**Other sites of specimen extraction: Single port incision (n=44, 6.1%), midline laparotomy incision (n=40, 5.6%), and previous stoma site (n=8, 1.1%).

Percentages for *Missing* values use the total number of cases as the denominator (i.e. 720). Percentages for the variables are calculated out of the total number of actual results available excluding the missing values.

Intra-operative adverse events

Table 2.3 outlines the technical difficulties and complications encountered during surgery. Abdominal conversion from a minimally invasive approach to open surgery occurred in 40 cases (6·3%) with a strategic conversion in 31 cases and reactive in 9 cases. Significant adverse events reported during the abdominal phase included two ureteric transections, iatrogenic enterotomy on insertion of a laparoscopic instrument, splenic injury, and bladder injury during simultaneous laparoscopic hysterectomy for myomatosis. Perineal conversion to a more extensive abdominal dissection than initially planned was required in 20 cases (2·8%): strategic and reactive conversions in 11 and 9 cases respectively. In total 11 (1.5%)

visceral injuries occurred during perineal dissection including five urethral injuries (0·7%); a complication rarely seen abdominally.

Table 2.3 Intraoperative difficulties and complications.

INTRA-OPERATIVE OUTCOMES Factor ▪ Category	TaTME registry data results Total: 720 cases n (%)
Conversion	
▪ Abdominal	40 (6·0)
▪ Perineal	20 (2·8)
Technical/equipment problems	
▪ Poor platform seal	13 (1.8)
▪ Unstable pneumopelvis	112 (15.6)
▪ Poor smoke evacuation	158 (21.9)
Failed pursestring with leakage	4 (0.6)
Incorrect dissection plane	56 (7.8)
Pelvic bleeding difficult to control	50 (6.9)
Visceral injury (perineal phase)	
▪ Urethral injuries	5 (0.7)
▪ Bladder perforation	2 (0.3)
▪ Vaginal perforation	1 (0.1)
▪ Resection of hypogastric nerves	1 (0.1)
▪ Rectal tube perforations	2 (0.3)
Intra-operative estimated blood loss	
▪ <100mls	390 (61.2)
▪ ≥500mls	21 (3.3)

Post-operative clinical outcomes

The 30-day post-operative morbidity and mortality rates were 32·6% (n=213) and 0.5% (n=3), respectively (Table 2.4). Fortunately, out of 213 patients who experienced a post-operative complication, 66.7% (n=142) did not require re-intervention (Clavien-Dindo I & II). Anastomotic leaks were recorded in 40 cases (6·7%); 32 (5.4%) were identified early, the remaining eight identified >30 days post-operatively. Surgical or radiological re-intervention was required in 14 (44%) of the 32 patients, and 10 (31%) of these patients required unplanned re-admission. An additional 17 patients were diagnosed with a pelvic abscess without evidence of anastomotic leak.

Unplanned re-interventions were required in 66 (10·1%) patients. Re-operations during the index admission included three laparotomies for ischemic left colon, one laparotomy for faecal peritonitis, three examinations under anaesthesia for anastomotic leak, two evacuations of hematoma, one negative laparotomy for severe sepsis on day 1 post resection, one incarcerated hernia repair and one case requiring bilateral fasciotomies for compartment syndrome.

Fifty patients (6·9%) required an emergency re-admission into hospital. Thirty (60%) of these readmitted patients were treated conservatively or medically for general malaise, abdominal pain, high stoma output with acute kidney injury, pulmonary embolism, prolonged ileus and delayed anastomotic leak diagnosed during chemotherapy. Fifteen patients underwent a surgical intervention during their re-admission: one laparotomy for small bowel obstruction requiring small bowel resection, one laparotomy for a coloplasty leak, one parastomal hernia repair, one drainage of a perineal abscess, one abdominal wound debridement, one pull-through procedure for anastomotic leak and nine examinations under anaesthesia; with re-suturing of partial anastomotic dehiscence (3 cases), re-do of coloanal anastomosis (1 case), dilatation of a strictured handsewn anastomosis (1 case), placement of endo-VAC therapy (2 cases) for pelvic abscess and chronic presacral sinus, transanal lavage of the presacral collection following anastomotic dehiscence (1 case) or no further action (1 case). The remaining five re-admitted patients underwent radiologically guided drainage of pelvic collections.

All deaths occurred in cancer patients; with three occurring during index admission. Deaths were categorised as cancer-related (n=6), not cancer related (n=5), post-operative (n=3) or unknown (n=1), with 2 missing results. Median time of death following surgery was 248 days (range 4–1857).

Table 2.4 Post-operative short-term clinical outcomes.

POST-OPERATIVE CLINICAL OUTCOMES Factor ▪ Category	TaTME registry data results Total: 720 cases
Length of hospital stay in days, median (range)	8·00 (2–97)
Post-operative morbidity at 30 days, n (%)	213 (32·6)
Clavien-Dindo classification at 30 days, n (%)	
▪ I or II	142 (21·7)
▪ III	66 (10·1)
▪ IV	5 (0·8)
▪ V	3 (0·5)
▪ *Missing*	*68 (9.4)*
Overall Mortality Rate*, n (%)	17 (2·4)
Pelvic sepsis, n (%)	
Anastomotic leak:	
▪ Early	32 (5·4)
▪ Delayed (>30 days)	8 (1·3)
Intra-abdominal / pelvic abscess	17 (2·4)
Surgical re-interventions	44 (6·1)
Unplanned hospital readmissions	50 (6·9)

* Overall mortality rate refers to reported deaths occurring at any time point during the study period.

Histopathological outcomes

The study cohort included 634 (88%) cancer cases (Table 2.5). Histopathological results revealed 9 cases (1.6%) of T4 disease, whilst the majority were T3 tumours. Nodal positive status was present in 30.8% of specimens. The primary endpoint of this study involving a composite outcome of poor histology that combines R1 resections with poor TME specimens and rectal perforations was found to occur at a rate of 7.4% (44 cases). R0 resection was obtained in 97·3% of cases. Sixteen cases (2·7%) were reported as R1. These were due to positive DRM, positive CRM by tumour and positive CRM by an adjacent malignant lymph node in 2 (0·3%), 10 (1·7%) and 4 (0·7%) cases respectively. A poor TME specimen with major defects in the mesorectum was reported in 24 (4·1%) cases. Twelve specimens were found to have a rectal tube perforation but only 6 of these were recorded as poor TME specimens. Although the perforation was not necessarily at the tumour site or through the mesorectum, we have included all rectal perforations into the 'poor TME specimen' category for further analysis, as any perforation of the rectal tube poses the risk of tumour cell spillage.

Table 2.5 Histopathological data.

HISTOPATHOLOGICAL DATA Factor ▪ Category	**TaTME registry data results** n=634
Pathological T stage, n (%)	
▪ T0	82 (14·1)
▪ T1	70 (12·1)
▪ T2	197 (34·0)
▪ T3	222 (38·3)
▪ T4	9 (1·6)
▪ *Missing*	*54 (8.5)*
Pathological N stage, n (%)	
▪ N0	406 (69·2)
▪ N1	122 (20·8)
▪ N2	59 (10·1)
▪ *Missing*	*47 (7.4)*
Quality of TME specimen, n (%)	
▪ Intact	503 (85·0)
▪ Minor defects	65 (11·0)
▪ Major defects	24 (4·1)
▪ Rectal perforation	12 (2·0)
▪ *Missing*	*42 (6.6)*
Number of lymph nodes harvested	
▪ Mean ± SD	16·5 ± 9·2
▪ Median (range)	15 (0–70)
Maximum tumour size in mm	
▪ Mean ± SD	27·6 ± 16·7
▪ Median (range)	25 (0–95)

Distal margin in mm	
▪ Mean ± SD	19·0 ± 14·3
▪ Median (range)	15 (0–97)
▪ Positive DRM, n (%)	2 (0·3)
▪ *Missing*	*45 (7.1)*
Circumferential resection margin in mm	
▪ Mean ± SD	9·19 ± 8·6
▪ Median (range)	8 (0–90)
▪ Positive CRM, n (%)	14 (2·4)
▪ *Missing*	*45 (7.1)*
Composite poor histological outcome:	
▪ R1 + poor TME specimen	44 (7·4)
▪ *Missing*	*42 (6.6)*

TME: Total mesorectal excision. SD: Standard Deviation. DRM: Distal resection margin. CRM: Circumferential resection margin.
Percentages for *Missing* values use the total number of cancer cases as the denominator (i.e. 634). Percentages for the variables are calculated out of the total number of actual results available excluding the missing values.

Risk factors for a poor histological composite outcome

The study revealed a poor histological composite outcome rate of 7.4% (44 cases). Possible risk factors for poor histology were explored and categorised into patient–related, tumour–related and technical variables. On univariate analysis factors that achieved a p-value ≤ 0·100 included: Tumour–related factors: (1) tumour height from anorectal junction, (2) tumour location, (3) pre-operative T-staging on MRI, (4) positive CRM on pre-operative MRI, (5) metastatic disease on staging CT, (6) neoadjuvant long course radiotherapy; Technical factors: (1) simultaneous abdomino-perineal operating, (2) anterior resection vs. abdomino-perineal excision (APE), (3) abdominal and perineal conversion, (4) blood loss over 1L, (5) extent of posterior pelvic dissection abdominally, (6) total transanal operative time (Table 2.6). No patient-related factor reached a p-value of ≤ 0·100.

Multivariate analysis identified three statistically significant risk factors (Table 2.6). Poor histological features are more likely to occur when the posterior pelvic dissection performed by the abdominal 'top-down' approach extends to less than 4cm from the anal verge. Lower tumours, with a tumour height of ≤2cm from the anorectal junction, and pre-operative positive CRM on staging MRI significantly increase the risk of obtaining a poor histological outcome.

Table 2.6: Univariate and multivariate analyses of risk factors for composite of poor histological features (R1 resection + poor TME specimen + rectal perforations)

		UNIVARIATE ANALYSIS			**MULTIVARIATE ANALYSIS**		
Factor ▪ Category	Event Rate %	Adjusted Odds ratio	95% Confidence Interval	P value	Adjusted Odds ratio	95% Confidence Interval	P value
PATIENT–RELATED FACTORS							
▪ Gender	Male 6.8	1					
	Female 8.9	1.350	0.711 – 2.562	0.358	-	-	ns
▪ BMI	<30kg/m^2 8.2	1					
	≥30 kg/m^2 8.0	0.980	0.453 – 2.120	0.960	-	-	ns
▪ ASA	I&II 7.6	1					
	III&IV 7.4	0.973	0.455 – 2.085	0.945	-	-	ns
▪ Smoker	Non-smoker 7.5	1					
	Smoker 7.3	0.981	0.401 – 2.399	0.966	-	-	ns
▪ Diabetic	Non-diabetic 7.4	1					
	Diabetic 7.7	1.044	0.426 – 2.557	0.925	-	-	ns
▪ IHD	No 7.6	1					
	Yes 6.5	0.848	0.348 – 2.068	0.717	-	-	ns
▪ Active IBD at time of surgery	No 7.3	1					
	Yes 20.0	3.163	0.346–28.923	0.282	-	-	ns
▪ Previous abdominal/pelvic surgery	No 7.5	1					
	Yes 6.9	0.914	0.395 – 2.112	0.833	-	-	ns

TUMOUR-RELATED FACTORS							
▪ Tumour height on MRI from ARJ	>2cm 3.8	1			1		
	0–2cm 11.6	3.299	1.675 – 6.496	<0.001	4.561	1.167 – 17.826	0.029
▪ Positive CRM on staging MRI	Clear 4.4	1			1		
	Positive 12.3	3.018	1.451 – 6.276	0.002	4.930	1.364 – 17.816	0.015
▪ T stage on MRI	T0-T2 6.2	1					
	T3-T4 19.4	3.654	1.396 – 9.565	0.005			
▪ Tumour location	Not anterior 5.3	1					
	Anterior 10.7	2.156	1.123 – 4.140	0.019			
▪ Metastatic disease	No 6.9	1					
	Yes 15.4	2.462	0.970 – 6.251	0.051			
▪ Neoadjuvant long course radiotherapy	No 7.1	1					
	Yes 15.4	2.391	0.786 – 7.275	0.100			
TECHINCAL FACTORS							
▪ Abdominal extent of posterior pelvic dissection	>4cm 3.1	1			1		
	0–4cm 10.4	3.630	1.162–11.344	0.019	5.849	1.424 – 24.024	0.014
▪ Type of procedure	Restorative 6.7	1					
	APE14.9	2.431	1.017 – 5.809	0.400			
▪ Synchronous operating	No 5.6	1					
	Yes 12.3	2.383	1.277 – 4.444	0.005			
▪ Conversion	No 5.6	1					
	Yes 18.2	3.724	1.425 – 9.733	0.004			
▪ Estimated blood loss	<1000mls 7.1	1					
	≥1000mls 33.3	6.566	1.165–37.003	0.014			
▪ Transanal operative time	≤ 2 hrs 8.2	1					
	> 2 hrs 3.2	0.375	0.137 – 1.028	0.048			

BMI: Body Mass Index. ASA: American Society of Anaesthesiologists. IHD: Ischaemic heart disease, IBD: Inflammatory bowel disease, MRI: Magnetic Resonance Imaging. ARJ: Anorectal junction. APE: Abdominoperineal excision.

1.4 Discussion

The present study reports the initial experience with 720 TaTME cases across 66 surgical units in 23 different countries. At the time of publication, it provided results from the largest international patient cohort undergoing the new transanal technique, with valuable insight into its clinical practice in the wider surgical community. TaTME was adopted primarily to perform low anterior resections (77%) for rectal cancer. Most surgeons undertook a minimally invasive approach for the abdominal phase, predominantly by laparoscopy (82%). This is encouraging, although not that unexpected, given the characteristics of the cases selected amenable to minimally invasive surgery and that many surgeons undertaking TaTME, especially the early adopters, are likely to already be experienced laparoscopic TME surgeons. These are most probably contributing factors to the two most promising findings from this study: low R1 resection rate (2.7%) and low conversion rates (6.3% from laparoscopic to open or transanal, and an even lower perineal conversion rate of 2.8%). Nonetheless, the three commonest reasons for conversion in the COLOR II trial[8] were a narrow pelvis (22%), obesity (10%) and tumour fixation (9%). Robotic surgery does not appear to overcome these challenging features, as similar risk factors for conversion were also found in the more recently published ROLARR (RObotic versus LAparoscopic Resection for Rectal Cancer) trial[9] with 471 patients randomised to either laparoscopy (234) or robotic (237) TME. The overall conversion rates were 12·2% and 8·1% for laparoscopic and robotic TME surgery respectively. However, subset analysis of obese patients revealed higher conversion rates of 27·8% following laparoscopic TME and 18·9% in the robotic arm. Lower rectal cancer and male gender were also associated with increased conversion rates. TaTME has the potential to overcome such risk factors as constraints and challenges posed by anatomical features are reduced when approached from below. In smaller TaTME cohorts, Veltcamp–Helbach et al. [10] reported a conversion rate of 5% on 80 taTME cases, whereas Lacy's group had no conversions in his initial 140 cases.[11]

Histopathological results are comparable to the best published literature, with an incomplete specimen in only 4·1% and R1 resection in 2·7% (16 cases). R1 was secondary to a positive CRM in 14 cases. In TaTME series by Lacy,[11] Burke[12] and Veltcamp–Helbach[10] CRM positivity was 6·4%, 4% and 2·5% respectively. In COLOR II,[8] using the limit of 1 mm for comparison, positive margins were seen in 7% of laparoscopic and 9% of open resections; most of which were cases with more proximal tumours. No statistically significant oncological or clinical advantage to robotic over laparoscopic TME surgery was seen in the ROLARR trial, with positive CRM rates of 5·1% and 6·3% respectively.[9] Patient and tumour-related factors that predict intraoperative difficulty and increase the risk of positive resection margins have been identified in similar previous studies on abdominal TME surgery, and include male gender, high BMI, visceral obesity, narrow pelvis, bulky tumours and advanced T-stage.[13–14]

Interestingly, none of the patient characteristics were significant risk factors for the composite of poor histological outcome following TaTME. This suggests that the transanal approach may overcome such features that traditionally created a difficult pelvic dissection from the abdominal approach. This also holds true in terms of the only technical risk factor for poor quality specimens identified on multivariate analysis, as the risk of obtaining a worse specimen by performing extensive trans-abdominal dissection is six times greater than if the dissection is performed transanally. The extent of transanal dissection did not increase the risk of poor histological outcome, suggesting that a better oncological resection is likely to be achieved for low rectal tumours via the transanal approach.

The two other significant risk factors for poor histological features were a positive CRM identified on staging MRI and a tumour height less than 2cm from the anorectal junction. These findings support results from the observational, multicentre MERCURY II study that predicted a positive pathological CRM by anteriorly located tumours, presence of extra-mural venous invasion (EMVI), tumours either within 4 cm of anal verge or 1 mm from the CRM.[15–16] Although an anteriorly located tumour was a statistically significant risk factor on univariate analysis in the registry cohort, the study is likely to have been underpowered for it to achieve significance on multivariate analysis. EMVI, on the other hand, was not initially recorded on the registry and so it was not possible to include this variable in the analysis.

Similarly, the type of insufflator used during the transanal phase did not appear as a datapoint on the original TaTME registry. It became apparent that insufflator type together with transanal platform are important variables to record given that almost 40% of cases encountered difficulties with inadequate pneumopelvic tension, poor platform seal and inefficient smoke evacuation. Thanks to growing experience with TaTME, the invention of alternative insufflation mechanisms and review of this registry data, the registry was updated with the addition of such important datapoints as well as a whole new quality of life and functional questionnaires module.

Concerning results highlighted by this TaTME study include the unknown risks posed by failed rectal pursestrings, rates of urethral injury and rectal perforation. Failure of the pursestring with subsequent spillage was reported in 4 cases (0.6%), although the true rate of pursestring failure is likely to be higher even if no spillage occurred. Long term follow-up following this complication is needed, evaluating the rates of pelvic sepsis and local regrowth from tumour implantation. Eleven visceral injuries, including three urethral injuries during TaTME alone and two occurring during combined rectal and prostatic resections were recorded. Urethral injury is very rarely seen from the abdominal approach to rectal resections. Furthermore, 12 (2%) rectal perforations were documented on histological analysis, of which only two were identified intra-operatively. These are clearly serious adverse events that require thorough assessment of the technique, as well as ensuring that surgeons receive appropriate education and training on TaTME. No surgery is risk free. Just as ureteric injury can occur during abdominal anterior resections, urethral injury has been identified as an important risk during TaTME. Analysis of registry data facilitates the identification of such outcomes and provides a focus for further investigation and research.

This study does have limitations related to the use of registry data. Namely, the potential for selection and reporting bias, with numerous international collaborators that may interpret datapoints differently and are under no obligation to report all cases. Recording data is time consuming and needs to be inputted on several occasions as the patient progresses through their treatment. Post-operative outcomes, such as late morbidity in particular, may therefore be under-reported. External validation of the data recorded in 23 different countries, both in terms of its accuracy and completeness, would be logistically difficult and extensive work, but nonetheless, an important process. Nevertheless, the registry does provide the largest data source available and its results contribute to establishing an identity for this new procedure. Furthermore, it assesses the therapeutic effectiveness and safety of TaTME in the 'real world', with surgeons at different stages in their learning curve, offering a rapid evaluation of a new technology. An open and transparent collaborative has also been formed amongst contributing centres that are able to share experiences and both seek and give advice.

It is important to note that during this study most surgeons performing TaTME were still at the early stage of their learning curve and despite this, histopathological results were very promising. The next registry analysis will explore the clinical outcomes, with particular focus on the most feared post-operative complication: anastomotic failure. Until results from the randomised controlled trials become available in the next few years, the TaTME database remains a unique source of information that is only possible thanks to the invaluable co-operation and dedication of the registry collaborators.

1.5 Conclusion

In conclusion, the international TaTME registry has provided some encouraging results from the initial cohort of 720 cases. The low R1 rate of 2.7% with overall composite rate for poor histology of 7.4%, as well as a low conversion rate and comparable morbidity rates are very promising. However, the data has also highlighted three main areas of concern that require further critical evaluation of the technique and it's training: failed rectal pursestrings, urethral injury and rectal perforations. An established method, such as Observational Clinical Human Reliability Analysis (OCHRA), can provide the detailed and systematic evaluation of the technique needed. Structured training, standardization of the technique and determining the proficiency-gain curve are also all necessary next steps.

2. Clinical outcomes: Focus on anastomotic failure

Incidence and Risk Factors for Anastomotic Failure in 1594 Patients Treated by Transanal Total Mesorectal Excision: Results from the International TaTME Registry

Publication reference

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2.1 Introduction

Anastomotic leakage (AL) is the most dreaded complication of a colorectal anastomosis that can lead to severe morbidity and mortality, as well as impaired anorectal function and poor long-term quality of life.[17] AL has also been associated with an increased risk of local cancer recurrence,[18] reducing overall and disease-free survival.[19–21] Furthermore, the doctor-patient relationship can be negatively impacted,[22] particularly as AL can develop into prolonged sequelae including anastomotic fistulae, chronic sinuses and anastomotic strictures, which can require further interventions and hospitalisation. The incidence of AL after colorectal surgery greatly varies in the literature from 2% to 24%[23–26] with the lower anterior resections posing the most risk.[27,28]

Over the last decade, the rate of sphincter-preserving surgery with low anastomoses has significantly risen. This is secondary to more advanced technical developments, particularly stapling instruments, but also minimal access techniques, in combination with widespread adoption of total mesorectal excision as the standard treatment for rectal cancer. Technical drawbacks of minimal access intracorporal anastomosis include the lack of direct tactile sensation, inadequate exposure, and a suboptimal cutting angle of the endo-linear stapler. Crossing staple lines by repeated firings, or incorrect staple height in relation to tissue thickness, increase the risk of AL.[29–30] Transanal total mesorectal excision (TaTME) adopts a different technique to create the anastomosis without the need for transabdominal rectal transection that is particularly difficult down a deep narrow pelvis. The standard TaTME technique forms an open rectal stump at the start and then restores continuity by a coloanal handsewn or double pursestring stapled anastomosis.[31] Identification of risk factors for AL and overall anastomotic failure may guide preoperative optimization and intra-operative surgical decision-making, adopting measures to reduce risk and consequences of AL, such as selective defunctioning stomas. This is particularly important when a novel anastomotic technique is being implemented into clinical practice.

The primary aim of this study was to report rates of anastomotic related morbidity, termed 'anastomotic failure', in patients who underwent TaTME surgery and recorded on the international TaTME registry. The secondary aim was to identify potential risk factors associated with anastomotic failure.

2.2 Methods

All TaTME cases recorded on the international TaTME registry[3] between July 2014 and December 2016 were reviewed. Cases that underwent a restorative procedure for cancer or benign disease were included in the analysis. Prior to data download, collaborating surgeons were electronically invited to update their records with two subsequent reminders with the aim of obtaining up-to-date data with minimal missing fields. Any unexpected or ambiguous datapoints were checked and discussed with the contributing surgeon.

Study endpoints

The primary endpoint of the study was "anastomotic failure" rate following primary rectal resection, defined as the overall incidence of anastomotic-related morbidity, including early and late AL, pelvic abscess, anastomotic-related fistula, chronic sinus and persistent anastomotic stricture. 'Early' anastomotic leak was defined as a symptomatic leak diagnosed and managed within 30-days of the primary resection. Anastomotic leaks were classified according to the 'International Study Group of Rectal Cancer' definition and severity grading system.[32] Secondary endpoints included intra-operative adverse events and post-operative morbidity and length of hospital stay.

Statistical analysis

All categorical data are presented as number of cases and percentages and compared by the Pearson Chi-squared test. Continuous data are shown as either mean ± standard deviation (range) or median with range and analysed by the two-sample t-test or Mann Whitney U test where appropriate. Risk factors for anastomotic failure were divided into patient-related, tumour-related and technical intraoperative factors. Continuous variables were dichotomized using the median or the value at which a significant change occurred as a cut-off point. Multivariate analysis to identify independent predictors of anastomotic failure and early AL included variables that achieved a p-value of $\leq 0{\cdot}100$ on univariate analysis. Median and mean imputation was used to adjust for missing values where appropriate and first order interactions tested in the multivariate model. Odds ratios (OR) and their 95% confidence intervals (CI) are reported and the ß coefficients (log odds ratios) derived from the multivariate analysis were used as weights in the derivation of the anastomotic failure observed risk score. Multilevel logistic regression model was used to adjust for possible clustering of anastomotic failure within centres. A p-value <0·05 was considered statistically significant. The Statistical Package for Social Sciences (SPSS) of IBM Statistics, version 24, was used for the analysis.

2.3 Results

A total of 107 surgical centres from 29 different countries contributed 1836 cases to the TaTME registry over a 29-month period. Rectal cancer was the primary indication in 1663 (90.6%) patients, whilst benign pathology contributed to the remaining 173 (9.4%). Overall, 1594 (86.8%) had a restorative procedure with an anastomosis formed and were included in the analysis.

Patient and tumour characteristics

The majority of included cases were male patients with a median age of 65 years and BMI of 26.0 kg/m^2 (Table 2.7). Previous unrelated abdominal surgery had been performed in 275 patients (17.3%), including 21 (1.3%) prior prostatectomies. Twelve patients (0.8%) had already received pelvic radiotherapy for another reason prior to the diagnosis of rectal cancer. The median tumour height from the anorectal junction was 4.0cm (range 0–17cm) with 23.4% CRM involvement on staging MRI and 56.1% received neo-adjuvant therapy.

Table 2.7 Patient and tumour characteristics

Factor ▪ Category	**TaTME registry data results** Total: 1594 cases
Gender, n (%)	
▪ Male	1080 (67.8)
▪ Female	514 (32.2)
Age in years, mean ± SD (range)	63.7 ± 12.4 (19 – 93)
ASA score, n (%)	
I + II	1271 (80.7)
III + IV	303 (19.3)
Missing	*20 (1.3)*
BMI in kg/m^2, mean ± SD (range)	26.3 ± 4.4 (15.6 – 44.2)
Smoking, n (%)	
▪ Smoker	230 (14.4)
▪ Non-smoker	1364 (85.6)
Presence of co-morbidities, n (%)	
▪ Diabetes mellitus	178 (11.2)
▪ Ischemic Heart Disease	222 (13.9)
▪ Active Inflammatory bowel disease	30 (1.9)
▪ Steroid use at time of surgery	16 (1.0)
Previous unrelated abdominal surgery, n (%)	275 (17.3)
Clinical tumour height from anal verge on rigid sigmoidoscopy in cm, median (range)	6.0 (0–17)
Tumour height from anorectal junction on MRI in cm, median (range)	4.0 (0–14)
Pre-operative MRI staging, n (%)	
▪ ≥mrT3	930 (69.0)
▪ mrN+	764 (57.3)
Pre-operative CRM involvement on MRI*, n (%)	274 (23.4)
Received neoadjuvant therapy, n (%)	895 (56.1)
TRG response post neoadjuvant therapy, n (%)	
▪ mrTRG 1 & 2 (No or small residual tumour)	446 (52.0)
▪ mrTRG 3 (Mixed fibrosis and tumour)	220 (25.6)
▪ mrTRG 4 & 5 (Mainly or only tumour)	192 (22.4)

SD: standard deviation. ASA: American Society of Anesthesiologists. BMI: Body Mass Index. MRI: Magnetic Resonance Imaging. CRM: Circumferential Resection Margin. N+: Positive nodal status (N1 or N2). TRG: Tumor regression grading on MRI.

*CRM involvement on MRI is defined as involved if the distance of tumor or malignant lymph node to the mesorectal fascia was less than 1 mm on MRI. Percentages for *Missing* values use the total number of cancer cases as the denominator (i.e. 1594). Percentages for the variables are calculated out of the total number of actual results available excluding the missing values.

Intraoperative details

Table 2.8 outlines the operative details including the intra-operative adverse events. Low anterior resection was the most commonly performed procedure in 89% of cases overall. The abdominal phase was performed laparoscopically, by SILS, open surgery and robotic approaches in 1350 (86.3%), 179 (11.4%), 26 (1.7%) and 10 (0.6%) respectively. The TME specimen was extracted transanally in 43.9%, whilst abdominal extraction was utilized in the remainder either via Pfannenstiel incision (26.6%), iliac fossa/stoma site (14.8%), umbilical opening (6.7%) or the laparotomy incision (8.0%). A pelvic drain was placed in 1134 patients (71.1%).

The anastomosis was performed by mechanical stapling in 66% with an end-to-end or side-to-end configuration in 94% of cases. The stapler diameters used included 25-28mm, 29mm, 31-32mm and33mm in 14.5%, 22.3%, 17.4% and 45.8% respectively. The mean total operative time was 4 hours 12 minutes ± 1:42 (0:30 – 12:13), whilst the mean transanal phase time was 2 hours 3 minutes ± 1:03 (0:14 – 7:47).

Intraoperative adverse events occurred in 487/1594 (30.6%). The recorded estimated blood loss was 0-99mls in 42.3% and 100-499mls in 21.1%. In 32 (2.1%) cases blood loss > 500mls was reported, mainly due to pelvic bleeding and splenic haemorrhage following splenic flexure mobilization. Conversion to an alternative technique was required in 90 patients (5.6%). Abdominal access conversion was primarily required due to limited visualization secondary to excessive adhesions and obesity, whilst perineal conversions occurred after incorrect plane dissection that led to bleeding and/or visceral injuries. Twelve cases underwent both perineal to abdominal, and minimal access to open abdominal conversions, and were predominantly men (11/12) with a higher BMI (mean 27.1 ±3.9 kg/m^2).

A total of 41 visceral injuries were recorded; 12 (0.8%) urethral injuries, 7 (0.4%) rectal tube perforation, 5 (0.3%) vaginal perforations, 5 (0.3%) ureteric injuries, 5 (0.3%) enterotomies, 3 (0.2%) bladder perforations, 2 (0.1%) hypogastric nerve divisions, 1 (0.06%) splenic injury with significant haemorrhage, and 1 (0.06%) diaphragmatic perforation during splenic flexure mobilization. Anastomosis-related technical difficulties included anastomotic defects requiring additional handsewn sutures (n=12), complete re-do of the anastomosis due to ischemia (2) or rectal tear (1). Further intraoperative complications included injury to the mesenteric vascular arcade during attempted transanal specimen extraction, carbon dioxide embolism with hemodynamic instability and intraoperative myocardial infarction.

Table 2.8 Operative details.

OPERATIVE CHARACTERISTICS Factor ▪ Category	**TaTME registry data results** Total = 1594 cases n (%)
Indication	
▪ Benign	54 (3.4)
▪ Cancer	1540 (96.6)
Operations performed	
Cancer cases:	
▪ High anterior resection	122 (7.9)
▪ Low anterior resection	1411 (91.6)
▪ Total & subtotal colectomies	7 (0.5)
Benign cases:	
▪ Low anterior resection	9 (16.6)
▪ Proctectomy (close rectal) + IPAA	6 (11.1)
▪ Proctectomy (TME plane) + IPAA	37 (68.5)
▪ Completion proctectomy	1 (1.9)
▪ Total colectomy	1 (1.9)
Synchronous 2 team operating	665 (41.7)
Transanal initial dissection:	
▪ Mucosectomy	83 (5.8)
▪ Total intersphincteric	78 (5.5)
▪ Partial intersphincteric	208 (14.7)
▪ Pursestring	1027 (72.5)

▪ Other*	21 (1.5)
▪ *Missing*	*177 (11.1)*
Conversion	
▪ Abdominal	69 (4.3)
▪ Perineal	21 (1.3)
▪ Both abdominal and perineal	12 (0.8)
Stoma	
▪ No defunctioning stoma	177 (11.7)
▪ Ileostomy	1282 (85.0)
▪ Colostomy	50 (3.3)
▪ *Missing*	*85 (5.3)*
Anastomotic technique	
▪ Manual	512 (34.0)
▪ Stapled	996 (66.0)
▪ *Missing*	*86 (5.4)*
Stapled configuration	
▪ End-to-end	485 (49.6)
▪ Side-to-end	433 (44.3)
▪ Colonic J pouch	24 (2.5)
▪ Ileal pouch-anal anastomosis	36 (3.6)
▪ *Missing*	*18 (1.8)*
MANUAL ANASTOMOSES	
Manual configuration	
▪ End-to-end	334 (65.2)
▪ Side-to-end	136 (26.6)
▪ Colo-anal J pouch	30 (5.9)
▪ Ileal pouch-anal anastomosis	12 (2.3)
Height of anastomosis from anal verge in cm, median (range)	
▪ Manual	2.0 (0-9.0)
▪ Stapled	4.0 (0-11.0)
Intraoperative adverse events	
▪ Technical problems during transanal phase	330 (18.0)
▪ Incorrect dissection plane	91 (5.7)
▪ Pelvic bleeding >100mls	67 (4.2)
▪ Visceral injuries during transanal phase, total	28 (1.8)
▪ Urethral injury	12 (0.8)
▪ Rectal tube perforation	7 (0.4)
▪ Vaginal perforation	5 (0.3)
▪ Hypogastric nerve divisions	2 (0.1)
▪ Bladder perforation	2 (0.1)

APE: Abdomino-perineal excision. IPAA: Ileal Pouch-Anal Anastomosis. TME: Total mesorectal excision. SILS: Single incision laparoscopic surgery. SD: Standard Deviation

*Other transanal phase surgical approaches include extra-levator dissection and abdomino-perineal excision.

Percentages for *Missing* values use the total number of cases as the denominator (i.e. 1594). Percentages for the variables are calculated out of the total number of actual results available excluding the missing values.

Post-operative and histopathological outcomes

The overall morbidity and mortality rates within 30-days of the primary resection was 35.4% and 0.6% respectively. Overall, 44 deaths (2.8%) occurred during a mean follow up period of 14 months (range 3–68). Post-operative complications within 30-days were classified as Clavien-Dindo[33] I/II, III, IV and V in 354 (22.2%), 188 (11.8%), 13 (0.8%) and 9 (0.6%) patients respectively. Emergency surgical re-intervention was required in 128 (8.0%), of which 10 (7.8%) treated ischaemic left bowel, and the others mostly involved management of anastomotic leak or small bowel obstruction. The median length of hospital stay was 8 days (range 2 to 94).

Histopathological results for the 1540 cancer cases showed a curative R0 resection rate in 95.7%. A positive CRM or distal resection margin (DRM) was reported in 60 (3.9%) and 10 (0.6%) cases respectively. Major defects in the TME specimen and rectal perforations were noted in 75 (4.9%) specimens.

Anastomosis-related morbidity

The overall anastomotic failure rate in this cohort was 15.7% (Table 2.9). Early AL occurred in 124 (7.8%) patients; most of whom, 68 (61.3%), were managed by active therapeutic intervention without the need for a re-laparotomy (Grade B). Re-interventions for anastomotic failure in 108/141 (76.6%) predominantly involved surgery under a general anaesthetic, with either examination under anaesthesia and washout ± vacuum therapy or re-suturing for anastomotic dehiscence, or as a later re-operation with dilatation or anastomotic re-fashioning for anastomotic stricturing.

Table 2.9 Anastomosis-related morbidity

POST-OPERATIVE COMPLICATIONS Factor ▪ Category	**TaTME registry data results** Total: 1594 cases n (%)
Anastomotic leak:	
▪ Early*	124 (7.8)
▪ Delayed^	32 (2.0)
Pelvic abscess	75 (4.7)
Anastomotic fistula	12 (0.8)
Anastomotic sinus	15 (0.9)
Anastomotic stricture	58 (3.6)
ANASTOMOTIC FAILURE§	
Number of events diagnosed	316
Number of patients affected	250 (15.7)
Management of anastomotic failure:	
Early anastomotic leak score	
A – Conservative management	23 (20.7)
B – Re-intervention without laparotomy	68 (61.3)
C – Laparotomy required	20 (18.0)
Missing	*13 (10.5)*
Total number of patients requiring re-interventions due to anastomotic failure / total number of patients undergoing a re-intervention at any time point	135 /311 (43.4)
Total number of re-interventions for anastomotic failure at any time point	141
Type of re-interventions for anastomotic failure	
Surgical	108 /141 (76.6)
Radiological	27 (19.1)
Endoscopic	6 (4.3)

*Early anastomotic leaks were diagnosed within 30-days of the primary colorectal resection.
^Delayed anastomotic leaks were diagnosed after 30-days of the primary colorectal resection.
§Anastomotic failure is defined as the defined as the overall incidence of anastomotic-related morbidity, including early and late AL, pelvic abscess, anastomotic-related fistula, chronic sinus and persistent anastomotic stricture following primary rectal resection.

Risk factors for early anastomotic leak

Univariate analysis identified eight patient–related and five technical risk factors for early AL that were included in the multivariate analysis (Table 2.10). Seven of these factors remained statistically significant on the multivariate analysis. Patient–related risk factors included male gender, obesity, smoking (borderline significance), diabetes, larger tumours (>25mm maximum diameter), and tumour height >4 cm from anorectal junction on MRI. Excessive intraoperative blood loss of >500mls was the only technical risk factor identified. Significantly more cases without a defunctioning stoma suffered an early AL compared to those that were defunctioned (12.4% vs. 7.2%, OR 0.547, 95% CI 0.334–0.895, P=0.015). Although univariate results suggested that patients who did not receive neoadjuvant therapy were at higher risk of AL and failure (Tables 2.10 & 2.11), these findings were not significant on multivariate analysis and outcomes are confounded by significantly more patients who had neoadjuvant treatment had defunctioning stomas (32.8% vs 58.1%, OR 2.846, 95% CI 2.042–3.967, P<0.001). Defunctioning stoma was not included in multivariate analysis as previous studies have shown that the presence of a defunctioning stoma may not prevent AL, but rather reduces the consequences should an AL occur.[34] Hence, a defunctioning stoma is proposed as a strategy to reduce the adverse effects of AL and is recommended in patients at high risk.

Table 2.10 Univariate and multivariate analyses of patient-related and technical risk factors for early anastomotic leak.

		UNIVARIATE ANALYSIS			**MULTIVARIATE ANALYSIS**		
Factor ▪ Category	Event Rate %	Adjusted Odds ratio	95% Confidence Interval	P value	Adjusted Odds ratio	95% Confidence Interval	P value
PATIENT–RELATED FACTORS							
▪ Gender	Female 4.1	1			1		
	Male 9.5	2.475	1.529–4.006	<0.001	2.173	1.331 – 3.548	0.002
▪ BMI	$<30 kg/m^2$ 6.9	1			1		
	$\geq 30 kg/m^2$ 12.4	1.901	1.238–2.918	0.003	1.589	1.012 – 2.494	0.044
▪ Smoker	Non-smoker 7.0	1			1		
	Smoker 12.2	1.831	1.172–2.861	0.007	1.576	0.991 – 2.506	0.055
▪ Diabetic	Non-diabetic 6.5	1			1		
	Diabetic 18.0	3.154	2.037–4.883	<0.001	2.700	1.702 – 4.282	<0.001
▪ Tumor height on MRI from ARJ	≤4cm 6.9	1			1		
	>4cm 9.8	1.466	1.010–2.127	0.043	0.607	0.401 – 0.920	0.019
▪ Tumor size	≤25mm 5.5	1			1		
	>25mm 10.4	1.997	1.291–3.088	0.002	1.883	1.212 – 2.926	0.005
▪ ASA	I-II 6.8	1					
	III-IV 12.2	1.917	1.275–2.881	0.002			
▪ Neoadjuvant therapy	No 9.2	1					
	Yes 6.7	0.713	0.494–1.029	0.070			

TECHNICAL FACTORS							
▪ Perineal dissection	Open dissection^4.9	1					
	Endoscopic PS* 8.9	1.896	1.127–3.190	0.014			
▪ Anastomotic height from AV	≤3cm 6.1	1					
	>3cm 10.4	1.779	1.194–2.651	0.004			
▪ Pelvic bleeding	Negligible 7.5	1					
	Noticeable[β] 13.4	1.905	0.920–3.943	0.078			
▪ Estimated blood loss	<500mls 6.8	1			1		
	≥500mls 25.0	4.551	1.971–10.506	<0.001	4.334	1.900–9.888	<0.001
▪ Specimen extraction	Transanal 6.2	1					
	Abdominal 9.5	1.601	1.073–2.389	0.020			

BMI: Body Mass Index. ASA: American Society of Anesthesiologists. MRI: Magnetic Resonance Imaging. ARJ: Anorectal junction. AV: Anal verge.
^Open dissection includes total and partial intersphincteric and mucosectomy dissections performed open. *PS: Pursestring suture placed endoscopically. [β]Noticeable pelvic bleeding was >100 mls with 9% of cases with pelvic bleeding having >500 mls blood loss.

Risk factors for anastomotic failure

Univariate analysis identified fourteen potential risk factors associated with anastomotic failure (Table 2.11). Five patient-related and three technical factors remained statistically significant on multivariate analysis. These included male gender, obesity, smoking, diabetes, larger tumour size over 25 mm, manual anastomoses, excessive blood loss of $\geq$500 millilitres, and longer perineal phase operative time of >1.5 hours. Manual anastomoses significantly increased the risk of late stricturing compared to stapled (5.9% vs. 2.7%, OR 0.448, 95% CI 0.263–0.762, $p=0.002$). A defunctioning stoma did not appear to significantly influence the incidence of anastomotic failure (no stoma 17.5% vs. stoma 15.6% OR 0.872, 95% CI 0.576–1.320, $p=0.516$). Multilevel regression analysis did not demonstrate any significant clustering between hospitals for anastomotic failure rates, nor alter the risk factors. The anastomotic failure observed risk score is shown in Figure 2.1 linking the five patient-related factors to their associated percentage risk of developing anastomotic failure based on this cohort of 1594 patients.

1

Table 2.11 Univariate and multivariate analyses of patient-related and technical risk factors for overall anastomotic failure.

		UNIVARIATE ANALYSIS			**MULTIVARIATE ANALYSIS**		
Factor ▪ Category	Event Rate %	Adjusted Odds ratio	95% Confidence Interval	P value	Adjusted Odds ratio	95% Confidence Interval	P value
PATIENT–RELATED FACTORS							
▪ Gender	Female 12.1	1			1		
	Male 17.4	1.537	1.129–2.092	0.006	1.419	1.030–1.955	0.032
▪ BMI	<30kg/m^2 14.6	1			1		
	≥30 kg/m^2 22.6	1.698	1.221–2.362	0.002	1.484	1.049–2.102	0.026
▪ Smoker	Non-smoker 14.7	1			1		
	Smoker 21.7	1.617	1.142–2.288	0.006	1.506	1.054–2.153	0.025
▪ Diabetic	Non-diabetic 14.2	1			1		
	Diabetic 27.5	2.296	1.600–3.295	<0.001	1.873	1.282–2.738	<0.001
▪ Tumor size	≤25mm 11.5	1			1		
	>25mm 19.1	1.813	1.313–2.504	<0.001	1.648	1.198–2.268	0.002
▪ ASA	I-II 13.7	1					
	III-IV 23.8	1.965	1.443–2.677	<0.001			
▪ Ischemic heart disease, IHD	No IHD 14.7	1					
	IHD 22.1	1.650	1.162–2.343	0.005			
▪ Neoadjuvant therapy	No 17.5	1					
	Yes 14.3	0.789	0.602–1.034	0.086			
TECHNICAL FACTORS							
▪ Anastomotic technique	Manual 18.9	1			1		
	Stapled 14.7	0.735	0.554–0.975	0.032	0.745	0.559–0.993	0.045
▪ Estimated blood loss	<500mls 13.9	1			1		
	≥500mls 34.4	3.232	1.525–6.848	<0.001	3.020	1.431–6.376	0.004

▪ Perineal operative time	≤1.5hrs 12.1	1			1		
	>1.5hrs 17.9	1.576	1.033–2.404	0.034	1.554	1.031–2.343	0.035
▪ Intraoperative problem	No 14.6	1					
	Yes 18.1	1.287	0.968–1.710	0.082			
▪ Pelvic bleeding	Negligible 15.3	1					
	Noticeable[β] 23.9	1.734	0.972–3.092	0.059			
▪ Conversion	No 15.2	1					
	Yes 23.3	1.695	1.019–2.817	0.040			

BMI: Body Mass Index. ASA: American Society of Anesthesiologists. [β]Noticeable pelvic bleeding was >100 mls with 9% of cases with pelvic bleeding having >500 mls blood loss.

Figure 2.1 Anastomotic Failure Observed Risk Score

PRE-OPERATIVE RISK SCORING				
RISK FACTOR	**SCORE**			
GENDER	**0**	Female	**1**	Male
BODY MASS INDEX	**0**	<30 kg/m^2	**1**	≥30 kg/m^2
SMOKING	**0**	No	**1**	Yes
DIABETES	**0**	No	**2**	Yes
TUMOUR SIZE	**0**	≤25mm	**1**	>25mm
	Cumulative Score: ___________________			

Cumulative Score:	0	1	2	3	4	5	6
Observed risk of anastomotic failure:	6.3%	10.7%	17.8%	23.3%	26.2%	33.3%	50.0%

2.4 Discussion

A total of 1594 TaTME cases with primary anastomosis were analysed in this study; the largest cohort in the current literature. Results focus primarily on anastomotic related morbidity as anastomotic leak and its sequelae can have a huge negative impact on patients' recovery and quality of life, as well as financial implications. The early leak rate in this cohort was 7.8%; higher than 5.4% seen in the initial 720 registry cases. Possible reasons behind this increase include a wider adoption of TaTME by surgeons at the early stages of their learning curve, exploring the transanal approach in more complex cases or more accurate recording and reporting of adverse events on the registry. The number of surgical centres joining the registry almost doubled to 107 during the course of a year with 35% of centres only having performed a maximum of five TaTME cases. Although higher leak rates have been associated with low surgical volume,[34,35] Hyman et al,[36] actually found that leak rates still ranged from 1.6–9.9% even for the more experienced high-volume surgeons. The likely explanation for this finding is that the underlying aetiology and risk factors are multifactorial and include both non-modifiable and modifiable patient and tumour–related risk factors. Hence the occurrence of an anastomotic leak is not solely due to the surgeon's technical skill.

Regardless, the leak rate of 7.8% remains within an acceptable range closely comparable to that seen from the abdominal approach of TME surgery.[23–26] Similarly, the overall morbidity rate of 35.4% is within recognized rates reported in colorectal surgery, especially when patient selection involves the more difficult low rectal cancer cases.

Interestingly, lower rectal tumours are usually considered the more difficult to operate on with low anastomoses having a higher risk of leak. In this cohort, anastomotic height appeared to be associated with AL only on univariate analysis (but not overall anastomotic failure) and a higher rate of AL occurred in anastomoses at a level of >3 cm from anal verge. Similarly, higher tumours located >4 cm from the anorectal junction on MRI were found to pose a greater risk of leakage than lower tumours, remaining significant on multivariate analysis. In contrast to abdominal rectal resections that tend to involve a stapled distal transection, TaTME results in an open rectal stump following the full thickness rectotomy. Colorectal surgeons may be less experienced in performing a transanal pursestring on an open rectal stump, especially at a further distance from the anal verge where obtaining good exposure may be more difficult. It is also easier to assess the anastomosis and place additional handsewn interrupted sutures lower down for reinforcement if needed. Furthermore, any leakage from a lower anastomosis is more likely to discharge transanally rather than accumulating intra-abdominally and causing symptomatic sepsis.

The two principal techniques for creating an anastomosis are manual and stapled approaches, with conflicting evidence in the literature as to which produces better outcomes. Our study suggests that the odds of developing anastomotic failure, in particular anastomotic stricture, is 30% less likely if a stapled anastomosis is performed; although no association was noted with early AL. Cong et al.[37] also found significantly lower rates of stricture formation following stapled compared with handsewn coloanal anastomoses after intersphincteric resection, as well as lower rates of AL. Conversely, a recent meta-analysis and Cochrane review[38,39] reported no significant differences in AL rates, stricture and mortality in colorectal anastomoses.

Management of anastomotic related problems can require multiple interventions with long-term morbidity and increased healthcare costs. Reassuringly, 82% of the patients who suffered an early AL successfully avoided a laparotomy with 20.7% being managed conservatively 61.3% undergoing a minimally invasive procedure. Kim et al.[40] also reported similar re-intervention strategies in patients with AL following minimally invasive anterior resection. Whilst 19.7% required a second open operation, 69% and 11.3% were successfully managed with laparoscopic re-intervention and transanal surgery respectively. The benefits of a less invasive approach to manage AL, where feasible, were highlighted in two retrospective cohort studies showing shorter intensive care stay, shorter time to first diet and earlier stoma functioning.[41–42]

Since prevention is better than cure, pre-operative optimisation and reduction strategies are vitally important to provide a better chance of obtaining good peri-operative outcomes. Our study identified male obese diabetic smokers with large tumours as the highest risk group for anastomotic failure, with up to 50% risk if all five factors are present. Smoking impairs tissue healing through nicotine-induced vasoconstriction, reduced perfusion, and carbon-monoxide induced cellular hypoxia, leading to reduced tissue oxygen and collagen deposition.[43] Diabetes also delays wound healing as vascular damage results from uncontrolled hyperglycaemia, leading to decreased blood flow and cellular accumulation of toxic glucose-derived metabolites.[44] Hence, pre-operative optimization with tighter glycaemic control for diabetics, weight loss for the obese and active smoking cessation programs are very important components of the whole cancer treatment regime. Operative strategies, such as the formation of a defunctioning stoma, pelvic drain placement, and use of fluorescence angiography to assess bowel perfusion, should be considered intra-operatively especially if the risk score is high. Although accurately predicting risk can be difficult, acknowledging and discussing the risk factors with the patient may aid the decision-making as to whether an anastomosis should even be attempted, especially in the context of poor pre-existing bowel function and/or poor physiological reserve to cope with anastomotic failure.

This study does have limitations which include the potential for selection and reporting bias in recording registry data, which requires formal external validation. Post-operative complications may be under-reported, especially if patients attend a different hospital or are treated in the community. Investigative methods to diagnose anastomosis-related pathology may also differ between units and under-report the true incidence. Any occult or subclinical leaks are likely to have been missed as the diagnosis was primarily based on clinical symptoms and signs. However, the main intention was to determine the incidence of symptomatic leaks and to identify potential risk factors. Other factors that may influence anastomotic healing, such as perioperative fluid management, are not recorded on the registry and hence could not be included in the risk factor analysis. Nonetheless, valuable information on anastomotic failure following TaTME was gathered from the largest surgical community performing the technique worldwide which is an important addition to the limited body of evidence currently in the published literature.

2.5 Conclusion

In conclusion, a failed colorectal anastomosis can lead to significant morbidity both short- and long-term. New and modified anastomotic techniques have been developed for TaTME which appear to have acceptable success rates. Risk factors for AL and longer–term anastomotic failure were identified in this study and an observed risk score created that can aid decision making and perioperative management of the individual patient. Further research is required to understand the various anastomotic techniques in more detail, and which produces the lowest rate of anastomotic-related problems. The learning curve for TaTME, in particular anastomotic leak and failure remains to be determined too.

3. Proficiency Gain Curve Analysis

Proficiency gain curve analysis of TaTME

3.1 Introduction

Following the first clinical TaTME case performed in 2009,[45] the technique was rapidly adopted worldwide despite limited availability of structured training courses. According to the initial analysis of the international TaTME registry,[5] technical difficulties were experienced in up to 40% of 720 cases and specific intra-operative complications that were seldom seen during the conventional abdominal approaches, specifically urethral injury and gas embolus, raised concerns.[5,46,47] The performance of a new surgical technique changes over time, with surgeons usually improving as their case volume increases, until they reach a level of competency. This change in performance during their 'learning' phase can be assessed and represented as a "proficiency-gain curve", indicating the average number of cases required in order to become proficient in performing the operation with lower complication rates.

The cumulative sum (CUSUM) technique is a commonly used statistical method to determine the number of cases required to reach proficiency.[48] CUSUM is a sequential analysis technique originally developed as a quality control test for ammunition production lines during World War II.[49] It has subsequently been applied to the medical setting to monitor and credential surgical practice. CUSUM can be risk-adjusted through a multivariate analysis in order to take into account risk factors that influence the case difficult. The majority of studies regarding proficiency-gain curve report results from individual surgeons or single institutions, which may not fully reflect the real clinical picture for the implementation of a new technique at an international level.

The aim of this study was to determine the proficiency-gain curves associated with the introduction of TaTME for the treatment of rectal cancer patients based on an international cohort.

3.2 Methods

Study design and patient population

Patients undergoing TaTME surgery for rectal adenocarcinoma with curative intent, consecutively recorded on the international TaTME registry[3] between July 2014 and January 2018, were assessed for eligibility. Collaborating surgeons were invited to review and update their entries with multiple reminders in order to ensure up-to-date records and reduce missing data. Any unexpected or ambiguous results were clarified by contacting the surgeon directly. Cases are recorded per unit rather than per surgeon. Patients were excluded if surgery was performed for a benign condition, a cancer other than adenocarcinoma (e.g. squamous cell carcinoma, neuroendocrine tumour), multi-organ resection / debulking surgery, or a palliative procedure. Eligible cases were divided into restorative procedures (i.e. those in which an anastomosis was formed) and abdominoperineal excision (APE), in which the anus is removed and a permanent stoma formed. This subdivision was deemed necessary given the different additional operative steps required to perform an APE, which adds further technical complexity to the case.

Study outcomes

The primary outcome was intra-operative adverse events, defined as any intra-operative complication that required corrective surgical actions that prolonged operative time. This included visceral injuries, ischaemic bowel, conversions, failed rectal pursestring, incomplete anastomosis requiring additional sutures or complete re-do, significant bleeding (≥500mL estimated blood loss) and gas embolus. Conversions involved a change in the operative approach to achieve the final goal, including conversion from a minimally invasive abdominal approach (laparoscopic/robotic) to open surgery and/or early termination of the transanal procedure to a more extensive than planned abdominal approach. Secondary outcomes included anastomotic failure, post-operative complications and poor histological outcome. Anastomotic failure was defined as the overall incidence of anastomotic-related morbidity, including early and late anastomotic leak, pelvic abscess, anastomotic-related fistula, chronic sinus and persistent anastomotic stricture following primary rectal resection. Post-operative complications include all undesired adverse events occurring during the recovery period up to 30-days following surgery or during the index admission if longer than 30 days. Poor histological outcome was defined as a TME dissection that resulted in a poor mesorectal specimen with major defects and/or positive resection margins (i.e. R1 resection) and/or rectal perforation. The quality of the TME specimens was categorised according to the classification by Quirke et al.[6] describing the mesorectum as either intact, nearly complete with minor defects or incomplete with major defects.

Statistical analysis

All categorical data are presented as number of cases and percentages, whilst continuous data are shown as either mean ± standard deviation (range) or median with range. Univariate and multivariate analyses were performed to identify possible risk factors associated with the primary and secondary outcomes. Univariate analysis comparing categorical variables was performed using the Pearson Chi^2 test, and continuous variables were analysed using Mann Whitney U test. Fisher's Exact test was used for counts less than 5. Continuous variables were dichotomized using the median or the value at which a significant change occurred as a cut-off point. Median and mean imputation was used to adjust for missing values where appropriate and multivariate analysis was subsequently performed using random-effects logistic binary regression for variables that achieved a p-value of $\leq 0{\cdot}100$ on univariate analysis. Risk prediction models for binary outcomes derived from the multivariate analysis provided the expected event rate used in the risk-adjusted cumulative sum (RA-CUSUM) analysis. On multivariate analysis, a p-value $<0{\cdot}05$ was considered statistically significant. The Statistical Package for Social Sciences (SPSS) of IBM Statistics, version 24 (IBM, Armonk, New York, USA) was used for the statistical analysis and Microsoft® Excel with XLSTAT for Mac version 16.21.1 (Microsoft Corporation, Redmond, Washington, USA) for the CUSUM analysis.

Proficiency-gain curve analysis

The cumulative sum (CUSUM) technique was performed to determine the number of cases required to reach proficiency.[48] To generate the CUSUM curve, the sum of all observed events was compared to the expected sum of events, using the following equation: $S_i = S_{i-1} + (\sum_i - \sum_R)$; $S_0 = 0$ as the starting point, S_i is the cumulative sum, $\sum_i$ is the sum of events observed at procedure number *i*, and $\sum_R$ and the sum of expected events predicted for procedure number *i*. The risk-adjusted CUSUM is an extension of the original CUSUM method, which takes into account risk factors that influence the case difficult and the expected event rate is adjusted in the multivariate analysis. The resulting RA-CUSUM plot provides a visual representation of how far a unit's cumulative event rate is above or below the predicted cumulative rate (y-axis), with the horizontal axis showing the consecutive cases plotted from left to right. The line moves up if the adverse event was observed more often than expected and moves down if better outcomes were achieved with less observed events than expected.

Further evaluation of the proficiency-gain curve to ascertain the reliability of an observed change was carried out by two methods: a change-point analysis using bootstrapping and a splitting model analysis. Each curve was bootstrapped with 5000 iterations in order to determine a confidence level of the change point. A confidence level of >95% was defined as providing strong evidence that a real change had occurred. The splitting model involved comparing outcomes before and after the change point.

3.3 Results

A total of 3240 cases were recorded on the TaTME registry over the 3.5-year study period. Of these, 2751 met the eligibility criteria and were included in the analysis. The cases were performed in 154 surgical units in 36 different countries worldwide with a case volume of 0–9, 10–29, 30–59, 60–89 and >90 cases in 81 (52.6%), 47 (30.5%), 14 (9.1%), 8(5.2%) and 4 (2.6%) units respectively. 2524 (91.7%) patients underwent a restorative procedure, whilst 227 (8.3%) patients received an abdominoperineal procedure (APE). Patient and tumour characteristics are outlined in table 2.12, showing a preponderance of male patients (69.8%) with mean body mass index (BMI) of 26 kg/m2. Patients undergoing APE were significantly older (69.4 vs 63.6 years, p <0.001) and with higher ASA scores compared to those undergoing restorative surgery. Significantly more patients in the APE cohort had a history of previous abdominal/pelvic surgery and pelvic radiation. The rate of previous local tumour excision prior to completion surgery was similar between the two groups.

As expected, the tumour height for APE patients was on average approximately 2cm lower than those who had restorative surgery; however, a higher rate of T4 disease and CRM involvement on staging MRI was also noted in the APE group. Nodal disease was significantly more prevalent in the restorative group, a greater proportion of whom received neo-adjuvant therapy (59.4% vs 47.1%, p <0.001).

Operative details

Restorative cases included 2494 (98.8%) anterior resections and 30 (1.2%) proctocolectomies. APE procedures included 150 (66.1%) intersphincteric APEs, 50 (22.0%) standard APEs, 20 (8.8%) extralevator APEs, and 7 (3.1%) non-restorative pan-proctocolectomies. No more than 20% of cases were proctored by an experienced mentor in each group, whilst 43.1% and 36.1% (p 0.042) of restorative and APE cases respectively involved synchronous operating by two teams (abdominal and transanal). The abdominal component of the operation was predominantly performed using laparoscopic (keyhole) surgery in 2337 (87.6%) cases overall with robotic surgery accounting for only 21 (0.8%) cases. Open abdominal surgery was performed in 40 (1.6%) and 7 (3.3%, p 0.075) of restorative and APE procedures respectively.

For the transanal component, a rigid platform was used in 11.4% (n=270) of restorative and 1.0% (n=2) APE cases (p <0.001), as opposed to the more commonly used flexible transanal platform. Overall standard insufflation was used in 570 (29.5%) cases rather than high pressure ventilation. Significantly more TME specimens were extracted transanally in the APE group (72.7% vs 43.4%, p <0.001) compared to the restorative group in which abdominal extraction was preferred. In restorative cases, the anastomosis was performed manually or stapled in 704 (29.5%) and 1686 (70.5%), respectively, with the following configurations: End-to-end 56.9%, Side-to-end 39.8%, Colonic J pouch 2.8%, and ileal pouch anal anastomosis (IPAA) 0.6%.

Intra-operative outcomes are outlined in table 2.13 showing an intra-operative adverse event rate of 12.0% (n=304) and 19.8% (n=45) [p 0.001] in the restorative and APE groups respectively. Of note, APE procedures had a significantly longer overall operating time although the transanal component was shorter. The APE group had significantly higher rates of transanal conversion, blood loss >500mls, and visceral injuries. In particular, the rate of urethral injury (2.2% vs 0.7%, p 0.030) and rectal tube perforations (2.6% vs 0.4%, p <0.001) was significantly greater in the APE group.

Table 2.12 Patient and tumour characteristics

Factor ▪ Category	**Restorative procedures** 2524 cases	**APE procedures** 227 cases	**p value**
Gender, n (%)			
▪ Male	1755 (69.5)	164 (72.2)	0.394
▪ Female	769 (30.5)	63 (27.8)	
Age in years, mean ± SD (range)	63.6 ±11.6 (20–94)	69.4 ±11.5 (24–92)	<0.001
BMI in kg/m^2, mean ± SD (range)	26.5 ±4.6 (13.5–55.9)	26.3 ±4.6 (15.6–42.7)	0.747
ASA score III + IV, n (%)	514 (21.1)	67 (31.5)	<0.001
Smokers, n (%)	330 (13.1)	24 (10.6)	0.281
Presence of co-morbidities, n (%)			
▪ Diabetes mellitus	293 (11.6)	21 (9.3)	0.285
▪ Ischaemic Heart Disease	333 (13.2)	34 (15.0)	0.449
▪ Active Inflammatory bowel disease	7 (0.3)	4 (1.8)	0.009
▪ Steroid use at time of surgery	14 (0.6)	2 (0.1)	0.536
Previous unrelated abdominal surgery, n(%)	364 (14.4)	53 (23.3)	<0.001
Previous pelvic radiation, n (%)	18 (0.7)	13 (6.2)	<0.001
Previous local tumour excision, n (%)	129 (5.1)	11 (4.8)	0.862
Clinical tumour height from anal verge on rigid sigmoidoscopy in cm, median (range)	7.0 (0–17)	5.0 (0–12)	<0.001
Tumour height from anorectal junction on MRI in cm, median (range)	4.0 (0–14)	2.0 (0–10)	<0.001
Pre-operative MRI staging, n (%)			
▪ mrT3	1432 (64.0)	100 (49.8)	<0.001
▪ mrT4 disease	118 (5.2)	24 (11.9)	<0.001
▪ mrN+	1276 (57.0)	81 (40.3)	<0.001
Pre-operative CRM involvement on MRI*, n (%)	447 (24.5)	45 (32.1)	0.044
Received neoadjuvant therapy, n (%)	1498 (59.4)	107 (47.1)	<0.001
TRG response post neoadjuvant therapy, n (%)			
▪ mrTRG 1 & 2 (No or small residual tumour)	469 (44.0)	29 (37.6)	
▪ mrTRG 3 (Mixed fibrosis and tumour)	346 (32.5)	29 (37.7)	
▪ mrTRG 4 & 5 (Mainly or only tumour)	250 (23.5)	19 (24.7)	

APE: Abdominoperineal excision. SD: standard deviation. ASA: American Society of Anesthesiologists. BMI: Body Mass Index. MRI: Magnetic Resonance Imaging. CRM: Circumferential Resection Margin. N+: Positive nodal status (N1 or N2). TRG: Tumour regression grading on MRI.
*CRM involvement on MRI is defined as involved if the distance of tumour or malignant lymph node to the mesorectal fascia was less than 1 mm on MRI.

Table 2.13 Intra-operative outcomes

Factor ▪ Category	**Restorative procedures** 2524 cases	**APE procedures** 227 cases	**p value**
Operative time, mean ± SD (range)			
▪ Total operative time, hours:minutes	4:36 ±1:35 (0:55–11:41)	5:06 ±1:44 (1:25–11:25)	0.001
▪ Transanal phase time, hours:minutes	2:20 ±1:17 (0:15–8:32)	2:04 ±1:11 (0:40–7:25)	0.010
Conversions, n (%)			
▪ Abdominal	108 (4.3)	11 (4.8)	0.688
▪ Transanal	43 (1.7)	12 (5.3)	<0.001
Intra-operative adverse events, n (%)*	304 (12.0)	45 (19.8)	0.001
Intra-operative problems			
▪ Technical problems during transanal phase^	382 (15.1)	29 (12.8)	0.340
▪ Incorrect dissection plane	114 (4.5)	10 (4.4)	0.938
▪ Rectal pursestring failure	57 (2.3)	3 (1.3)	0.355
▪ Blood loss >500mls	55 (2.9)	12 (6.2)	0.014
▪ Ischaemic bowel	13 (0.5)	3 (1.3)	0.140
▪ Incomplete anastomosis requiring re-do or additional sutures	25 (1.0)	0 (0.0)	-
▪ Gas embolus	1 (0.04)	0 (0.0)	1.000
▪ Visceral injuries during transanal phase, total patients affected	36 (1.4)	12 (5.3)	<0.001
▪ Urethral injury	17 (0.7)	5 (2.2)	0.030
▪ Rectal tube perforation	9 (0.4)	6 (2.6)	<0.001
▪ Vaginal perforation	3 (0.1)	2 (0.9)	0.057
▪ Bladder perforation	5 (0.2)	0 (0.0)	1.000
▪ Hypogastric nerve division	2 (0.1)	0 (0.0)	1.000

APE: Abdomino-perineal excision. IPAA: Ileal Pouch-Anal Anastomosis. TME: Total mesorectal excision. SILS: Single incision laparoscopic surgery. SD: Standard Deviation
*Intra-operative adverse events are defined as any intra-operative complication that required corrective surgical actions.
^Technical problems include difficulty obtaining a stable pneumopelvis or seal, and inadequate smoke evacuation.

Post-operative outcomes

Clinical outcomes: Post-operative 30-day morbidity was greater in the APE group compared to the restorative group, 48% vs 38% p 0.003, respectively. Categorisation of post-operative complications is shown in table 2.14. Significantly more patients suffered with wound break down and infection in the APE group (15.4% vs 4.6%, p <0.001) due to the perineal wound that is notoriously more difficulty to heal compared to abdominal wounds. More medical complications (pulmonary/ cardiac/ renal/ urological and thromboembolic) were also recorded in the APE group, which corresponds to the older age and higher ASA scores noted pre-operatively.

Histopathological outcomes: Table 2.15 outlines the histopathological outcomes. Overall, better results were achieved in the restorative group compared to the APE group with more intact TME specimens (85.5% vs 74.5%, p 0.001) and fewer positive circumferential resection margins (3.2% vs 6.7%, p 0.009). Subsequently the composite for poor histological outcome is significantly worse for the APE group (13.5% vs 7.8%, p 0.005) However, the higher incidence of T4 disease amongst APE patients (4.7% vs 1.8%, p 0.017) must be taken into account.

Table 2.14 Post-operative complications

Factor ▪ Category	**Restorative procedures** 2524 cases n (%)	**APE procedures** 227 cases n (%)	**p value**
30-day morbidity	959 (38.0)	109 (48.0)	0.003
Clavien-Dindo classification, n (%)			
I	168 (6.7)	12 (5.3)	
II	421 (16.7)	55 (24.2)	
III	328 (13.0)	39 (17.2)	
IV	21 (0.8)	1 (0.4)	
V (death)	21 (0.8)	2 (0.9)	
Wound complications	117 (4.6)	35 (15.4)	<0.001
Medical complications within 30 days$^{\varphi}$	318 (12.6)	44 (19.4)	0.004
Emergency surgery within 30-days	219 (8.7)	23 (10.1)	0.458
Unplanned hospital re-admissions	388 (15.4)	32 (14.1)	0.609
Anastomotic leak			
▪ Early*	218 (8.6)	-	
▪ Delayed^	55 (2.2)	-	
Pelvic abscess	114 (4.5)	15 (6.6)	0.153
Anastomotic fistula	29 (1.1)	-	
Anastomotic sinus	27 (1.1)	-	
Anastomotic stricture	81 (3.2)	-	
Overall Anastomotic Failure§	416 (16.5)	-	
Early anastomotic leak score:			
A – Conservative management	40 (19.8)	-	
B – Re-intervention without laparotomy	126 (62.4)	-	
C – Laparotomy required	36 (17.8)	-	
Length of hospital stay, median (range)	8.0 (1–167)	7.0 (2–65)	0.596

$^{\varphi}$ Medical complications include pneumonia, cardiac arrhythmias/failure, renal failure, urinary tract infections/retention, and thromboembolic events.
*Early anastomotic leaks were diagnosed within 30-days of the primary colorectal resection.
^Delayed anastomotic leaks were diagnosed after 30-days of the primary colorectal resection.
§Anastomotic failure is defined as the defined as the overall incidence of anastomotic-related morbidity, including early and late AL, pelvic abscess, anastomotic-related fistula, chronic sinus and persistent anastomotic stricture following primary rectal resection.

Table 2.15 Histopathological outcomes

Factor ▪ Category	**Restorative procedures** 2524 cases n (%)	**APE procedures** 227 cases n (%)	**p value**
Pathological T stage, n (%)			
▪ T0	300 (12.7)	17 (8.1)	0.017
▪ T1	286 (12.1)	24 (11.4)	
▪ T2	745 (31.5)	69 (32.7)	
▪ T3	994 (42.0)	91 (43.1)	
▪ T4	42 (1.8)	10 (4.7)	
▪ *Missing*	*157 (6.3)*	*16 (7.0)*	
Pathological N stage, n (%)			
▪ N0	1676 (70.4)	143 (67.8)	0.475
▪ N1	481 (20.2)	43 (20.4)	
▪ N2	222 (9.3)	25 (11.8)	
▪ *Missing*	*145 (5.7)*	*16 (7.0)*	
Quality of TME specimen, n (%)			
▪ Intact	1955 (85.5)	140 (74.5)	0.001
▪ Minor defects	250 (10.9)	37 (19.7)	
▪ Major defects	81 (3.5)	11 (5.9)	
▪ Rectal perforation	42 (1.9)	9 (4.9)	0.007
▪ *Missing*	238 (9.4)	39 (17.2)	
Number of lymph nodes harvested			
▪ Mean ± SD	17.6 ±10.0	19.1 ±12.6	0.340
▪ Median (range)	16.0 (0–110)	16.0 (1–92)	
Maximum tumour size in mm			
▪ Mean ± SD	25.0 ±19.3	30.4 ±20.2	<0.001
▪ Median (range)	25.0 (0–188)	30.0 (0–120)	
Distal margin in mm			
▪ Mean ± SD	21.0 ±16.3	28.8 ±7.5	<0.001
▪ Positive DRM, n (%)	23 (1.0)	0 (0.0)	0.252
▪ *Missing*	*153 (7.0)*	*19 (8.4)*	
Circumferential resection margin in mm			
▪ Mean ± SD	11.4 ±9.4	8.3 ±7.5	<0.001
▪ Positive CRM, n (%)	77 (3.2)	14 (6.7)	0.009
▪ *Missing*	*153 (6.0)*	*19 (8.4)*	
Composite poor histological outcome			
▪ R1 + poor TME specimen	186 (7.8)	28 (13.5)	0.005
▪ *Missing*			

TME: Total mesorectal excision. SD: Standard Deviation. DRM: Distal resection margin. CRM: Circumferential resection margin. Percentages for Missing values use the total number of cancer cases as the denominator (i.e. 634). Percentages for the variables are calculated out of the total number of actual results available excluding the missing values.

Proficiency gain curve analysis

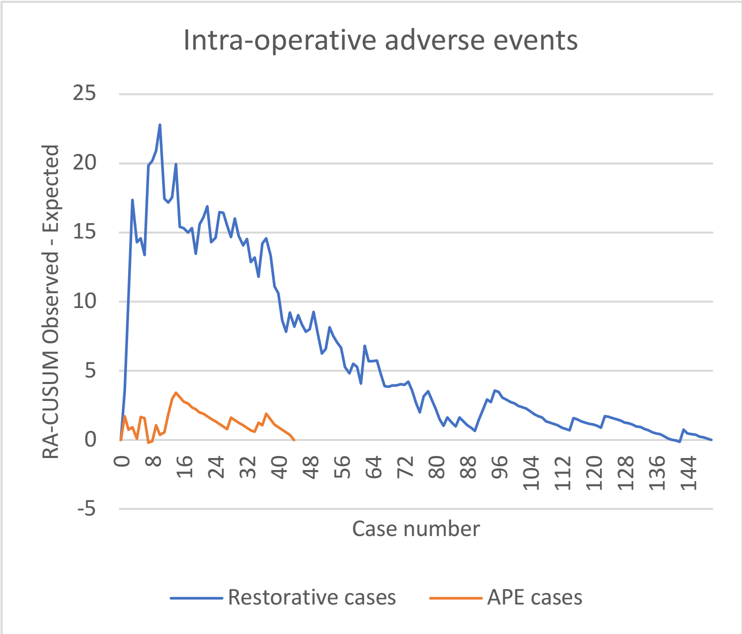
The RA-CUSUM curve for the primary outcome intra-operative adverse events showed a change point with improvement in performance after the initial 10 restorative procedures (Figure 2.2a). The confidence level at this change point was significant at 98.1% on bootstrapping (Appendix 1). For the APE cohort, the curve was less distinct, with a peak at case 15, however the confidence level only reached 82.3%. Risk factors for intra-operative adverse events identified on multivariate analysis included male gender, BMI ≥30kg/m2 and ASA grade III & IV for restorative cases (Suppl. table 2.1a) and BMI ≥30kg/m2, tumour size >25mm and standard insufflation for APE cases (Suppl. table 2.1b).

Composite for poor histological outcome showed an unexpected proficiency-gain curve with good results (observed better than expected rate) for the initial 6 restorative cases and 10 APE cases followed by a rise in the curve (Figure 2.2b). For restorative cases there is a relatively "stable" central period between cases 20 and 79 before the curve rises again. Risk factors identified for poor histological outcome included a BMI ≥30kg/m2, T4 tumours, tumour size >25mm, tumour height 0-2cm from anorectal junction, and positive nodal status on staging MRI (Suppl. Table 2.2a).

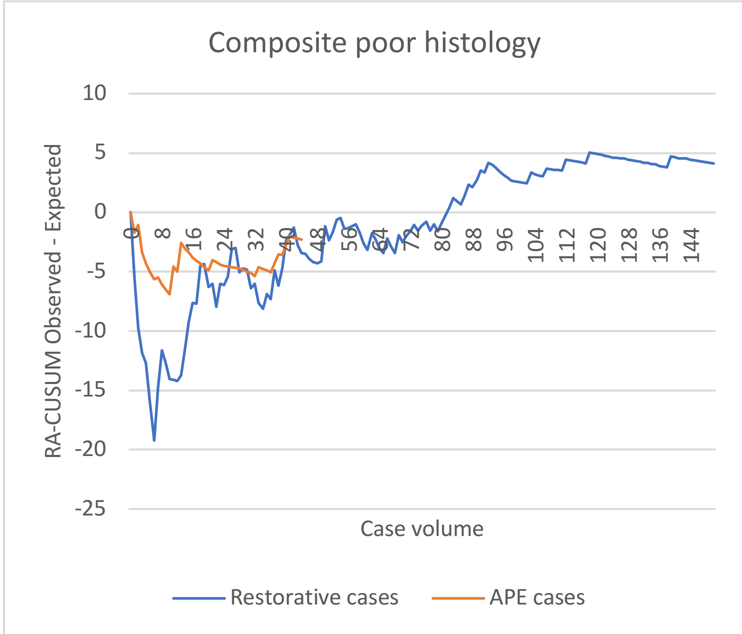
The proficiency-gain curve for overall post-operative 30-day complications showed wide variation with no sustained improvement. Anastomotic failure, however, had a clearer learning curve with a peak or change point reached after the initial 15 cases, followed by a "slow transition" period between cases 15 and 49, after which improvements are seen more clearly. The confidence level for this change point reached significance on bootstrapping at 95.2%. Risk factors included in the multivariate analysis for post-operative complications and anastomotic failure are reported in supplementary tables 2.3 and 2.4.

Figure 2.2a-d. Risk-adjusted Cumulative Sum (CUSUM) Analysis for restorative and APE procedures. a. Intra-operative adverse events; b. Composite of poor histology; c. Post-operative 30-day complications; d. Anastomotic failure.

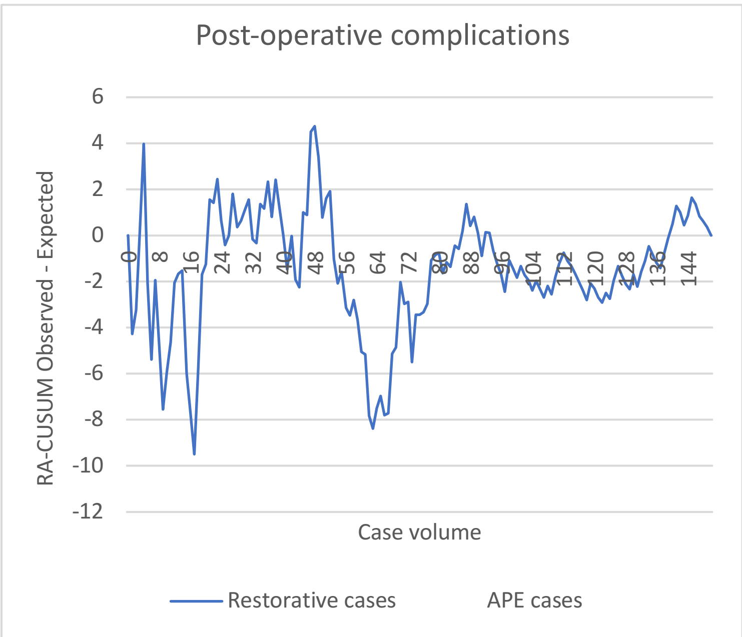
a.



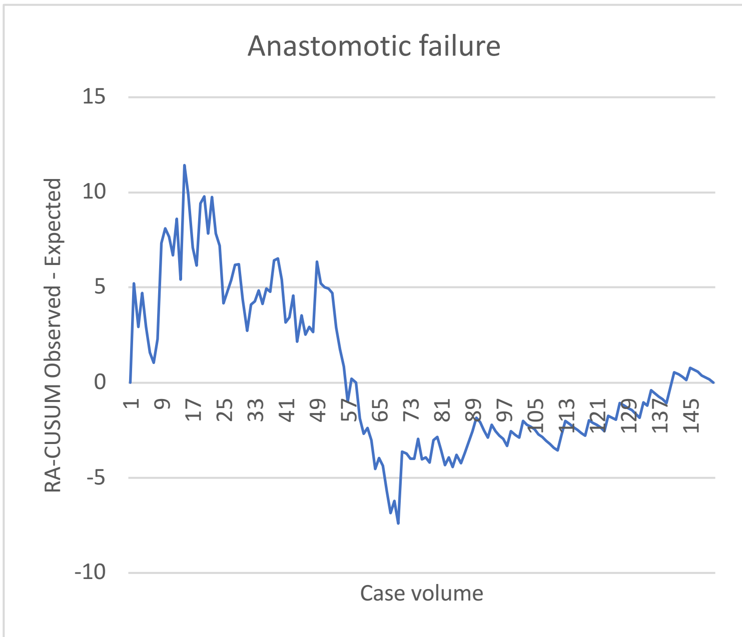
b.



c.



d.



Since the change point for the above outcomes ranged from case 6 to 15 for restorative procedures, case 10 was selected for the splitting method analysis. Results are reported in table 2.16 showing significantly fewer intra-operative adverse events after the case 10 change point (10.4% vs 14.5%, p 0.002), as well as a shorter operative time by 39 minutes on average. Conversion rate also significantly reduced from 7.0% to 4.2% (p 0.003) with both abdominal (5.7% to 3.4%) and transanal (2.1% to 1.0%) conversion improving. No difference was noted for overall post-operative complications or anastomotic failure. However, histological outcomes showed worsening results after case 10 for R1 resection (positive margins) rate (2.3% increased to 3.8%) and composite of poor histological outcome (5.8% increased to 9.2%, p 0.003).

Table 2.16 Splitting method analysis for restorative procedures
Case characteristics and outcomes before and after the change point of case 10.

Factor ▪ Category	**BEFORE** Cases 1 to 10	**AFTER** Cases 11 to 150	**p value**
Total number of cases	990	1534	
Male gender, n (%)	683 (69.0)	1072 (69.9)	0.634
Age in years, mean ± SD (range)	64.3 ±11.3 (29–92))	63.1 ±11.7 (20–94))	0.012
BMI in kg/m^2, mean ± SD (range)	26.8 ±4.8 (13.5–55.9)	26.3 ±4.4 (15.9–50.0)	0.042
ASA score III + IV, n (%)	222 (23.0)	292 (19.8)	0.060
Previous unrelated abdominal surgery, n(%)	115 (11.6)	249 (16.2)	0.001
Previous local tumour excision, n (%)	45 (4.5)	84 (5.5)	0.300
Tumour height from anorectal junction on MRI in cm, median (range)	3.00 (0–14)	4.00 (0–14)	0.188
Pre-operative MRI staging, n (%)			
▪ mrT3	571 (64.5)	861 (63.6)	0.670
▪ mrT4 disease	43 (4.8)	75 (5.5)	0.469
▪ mrN+	506 (57.0)	770 (56.9)	0.949
Pre-operative CRM involvement on MRI*, n (%)	183 (23.5)	264 (25.3)	0.370
Received neoadjuvant therapy, n (%)	591 (59.7)	907 (59.1)	0.776
Proctored cases, n (%)	139 (19.0)	257 (19.7)	0.683
Operative time, mean ± SD (range)	4:58 ±1:38 (1:07–10:02)	4:19 ±1:29 (0:55–11:41)	<0.001
Conversions, n (%)	69 (7.0)	65 (4.2)	0.003
Intra-operative adverse events, n (%)*	144 (14.5)	160 (10.4)	0.002
Post-operative 30-day complications, n (%)	375 (37.9)	584 (38.1)	0.923
Early anastomotic leak, n (%)	80 (8.1)	138 (9.0)	0.424
Overall Anastomotic Failure§, n (%)	175 (17.7)	241 (15.7)	0.194
Composite poor histological outcome, n (%)	53 (5.8)	133 (9.2)	0.003
▪ R1 resection (positive margins)	21 (2.3)	69 (4.8)	0.002
▪ Major defects in TME specimen	28 (3.1)	53 (3.8)	0.351
▪ Rectal perforations	16 (1.8)	26 (1.9)	0.778

SUPPLEMENATRY TABLES

Supplementary table 2.1a Intra-operative adverse events

Univariate and multivariate analyses of patient-related, tumour-related and technical risk factors for **INTRA-OPERATIVE ADVERSE EVENTS – RESTORATIVE CASES.**

		UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS		
Factor ▪ Category	Event Rate %	Adjusted Odds ratio	95% Confidence Interval	P value	Adjusted Odds ratio	95% Confidence Interval	P value
PATIENT–RELATED FACTORS							
▪ Gender	Female 8.1	1			1		
	Male 13.8	1.824	1.361–2.445	<0.001	1.730	1.287–2.326	<0.001
▪ Body Mass Index	<30 kg/m^2 10.6	1			1		
	≥30 kg/m^2 18.9	1.960	1.478–2.599	<0.001	1.831	1.372–2.444	<0.001
▪ ASA grade	I&II 10.4	1			1		
	III&IV 18.3	1.921	1.470–2.509	<0.001	1.688	1.285–2.218	<0.001
▪ Diabetic	Non-diabetic 11.4	1					
	Diabetic 17.1	1.602	1.150–2.230	0.005			
TUMOUR-RELATED FACTORS							
▪ Anterior tumour location	Not anterior 11.4	1					
	Anterior 14.6	1.330	1.011–1.750	0.041			
▪ N stage	N0 10.6	1					
	N+ 12.9	1.246	0.958–1.621	0.100			
TECHNICAL FACTORS							
▪ Transanal platform	Rigid 8.9	1					
	Flexible 12.6	0.679	0.438–1.053	0.082			
▪ Type of anastomosis	Stapled 11.0	1					
	Manual 13.8	0.776	0.597–1.009	0.058			

Supplementary table 2.1b Intra-operative adverse events

Univariate and multivariate analyses of patient-related, tumour-related and technical risk factors for **INTRA-OPERATIVE ADVERSE EVENTS – APE CASES.**

		UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS		
Factor ▪ Category	Event Rate %	Adjusted Odds ratio	95% Confidence Interval	P value	Adjusted Odds ratio	95% Confidence Interval	P value
PATIENT–RELATED FACTORS							
▪ Gender	Female 9.5	1					
	Male 23.8	2.964	1.187–7.399	0.016			
▪ Body Mass Index	<30 kg/m^2 16.7	1			1		
	≥30 kg/m^2 36.8	2.917	1.340–6.349	0.006	2.517	1.108–5.716	0.027
TUMOUR-RELATED FACTORS							
▪ Tumour size	25mm 13.3	1			1		
	>25mm 24.8	2.141	0.971–4.722	0.056	2.436	1.018–5.831	0.046
TECHNICAL FACTORS							
▪ Splenic flexure mobilisation	No 16.5	1					
	Yes 27.5	1.929	0.982–3.790	0.054			
▪ Type of insufflator	High pressure 16.8	1			1		
	Standard 42.1	3.605	1.306–9.946	0.010	5.818	1.874–18.066	0.002

Supplementary table 2.2a Composite poor histological outcome

Univariate and multivariate analyses of patient-related, tumour-related and technical risk factors **COMPOSITE POOR HISTOLOGY–RESTORATIVE CASES.**

		UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS		
Factor ▪ Category	Event Rate %	Adjusted Odds ratio	95% Confidence Interval	P value	Adjusted Odds ratio	95% Confidence Interval	P value
PATIENT–RELATED FACTORS							
▪ Body mass index	<30 kg/m^2 7.5	1			1		
	≥30 kg/m^2 10.0	1.376	0.952–1.989	0.088	1.464	1.003–2.139	0.048
▪ Previous prostatectomy	No 7.6	1					
	Yes 16.7	2.441	1.002–5.945	0.043			
TUMOUR-RELATED FACTORS							
▪ Anterior tumour location	Not anterior 6.5	1					
	Anterior 9.9	1.574	1.110–2.230	0.010			
▪ T4 tumour	T1-T3 7.0	1			1		
	T4 18.0	2.912	1.743–4.865	<0.001	2.561	1.452–4.520	0.001
▪ Tumour size	0–25mm 5.1	1			1		
	>25mm 10.0	2.075	1.474–2.923	<0.001	2.123	1.503–2.999	<0.001
▪ CRM status on staging MRI	Negative 5.1	1					
	Positive 10.3	2.137	1.435–3.182	<0.001			
▪ Staging tumour height from ARJ	>2cm 6.1	1			1		
	0–2cm 11.3	1.977	1.455–2.685	<0.001	2.168	1.567–2.999	<0.001
▪ N stage	N0 6.1	1			1		
	N+ 8.8	1.489	1.064–2.085	0.020	1.452	1.018–2.070	0.039
▪ EMVI status	Negative 6.0	1					
	Positive 10.3	1.795	0.927–3.477	0.079			

▪ Neoadjuvant SCRT + delay	No 7.7	1		
	Yes 14.1	1.975	0.994–3.922	0.048
TECHNICAL FACTORS				
▪ Type of insufflation	High pressure 7.2	1		
	Standard 10.1	21.457	1.017–	0.040
▪ Perineal cautery device	Monopolar 7.1	1		
	Energy device 10.3	1.501	1.044–2.158	0.027

Supplementary table 2.2b Composite poor histology

Univariate and multivariate analyses of patient-related, tumour-related and technical risk factors for **COMPOSITE POOR HISTOLOGY EVENTS – APE CASES.**

		UNIVARIATE ANALYSIS			**MULTIVARIATE ANALYSIS**		
Factor ▪ Category	Event Rate %	Adjusted Odds ratio	95% Confidence Interval	P value	Adjusted Odds ratio	95% Confidence Interval	P value
TUMOUR-RELATED FACTORS							
▪ Anterior tumour	Not anterior 9.1	1			1		
	Anterior 19.5	2.424	0.938–6.267	0.062	2.480	0.949–6.478	0.064
▪ Nodal status	N0 9.2	1			1		
	N+ 19.0	2.320	0.982–5.482	0.050	2.240	0.945–5.308	0.067
▪ CRM status on staging MRI	Negative 7.1	1					
	Positive 18.6	3.010	0.971–9.324	0.048			

Supplementary table 2.3a Post-operative 30-day complications

Univariate and multivariate analyses of patient-related, tumour-related and technical risk factors for 30-day **POST-OPERATIVE COMPLICATIONS – RESTORATIVE CASES.**

		UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS		
Factor ▪ Category	Event Rate %	Adjusted Odds ratio	95% Confidence Interval	P value	Adjusted Odds ratio	95% Confidence Interval	P value
PATIENT–RELATED FACTORS							
▪ Gender	Female 26.7	1			1		
	Male 43.0	2.072	1.721–2.495	<0.001	1.963	1.627–2.370	<0.001
▪ ASA grade	I&II 10.4	1			1		
	III&IV 18.3	1.583	1.300–1.927	<0.001	1.330	1.081–1.638	0.007
▪ Diabetic	No 36.3	1			1		
	Yes 51.2	1.844	1.443–2.355	<0.001	1.619	1.252–2.094	<0.001
▪ Smoker	No 37.1	1					
	Yes 43.9	1.329	1.052–1.679	0.017			
▪ IHD	No 36.7	1					
	Yes 46.5	1.502	1.191–1.895	0.001			
TUMOUR-RELATED FACTORS							
▪ Neoadjuvant therapy	No 40.2	1			1		
	Yes 36.5	0.857	00.728–1.009	0.064	0.811	0.686–0.959	0.014
TECHNICAL FACTORS							
▪ Intra-operative adverse event	No 36.0	1			1		
	Yes 52.3	1.946	1.529–2.477	<0.001	5.818	1.874–18.066	0.002
▪ Total operative time	≤4 hours 34.0	1					
	>4 hours 39.5	1.266	1.027–1.559	0.027			

Supplementary table 2.3b Post-operative 30-day complications

Univariate and multivariate analyses of patient-related, tumour-related and technical risk factors for **POST-OPERATIVE COMPLICATIONS – APE CASES.**

		UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS		
Factor ▪ Category	Event Rate %	Adjusted Odds ratio	95% Confidence Interval	P value	Adjusted Odds ratio	95% Confidence Interval	P value
▪ Intra-operative adverse event	No 44.5	1			-	-	-
	Yes 62.2	2.054	1.051–4.013	0.033			

Supplementary table 2.4 Anastomotic failure

Univariate and multivariate analyses of patient-related, tumour-related and technical risk factors for **ANASTOMOTIC FAILURE– RESTORATIVE CASES.**

		UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS		
Factor ▪ Category	Event Rate %	Adjusted Odds ratio	95% Confidence Interval	P value	Adjusted Odds ratio	95% Confidence Interval	P value
PATIENT–RELATED FACTORS							
▪ Gender	Female 12.5	1			1		
	Male 18.2	1.563	1.223–1.999	<0.001	1.438	1.120–1.847	0.004
▪ Body mass index	<30 kg/m^2 15.6	1			1		
	≥30 kg/m^2 22.8	1.598	1.236–2.066	<0.001	1.479	1.131–1.935	0.004
▪ ASA grade	I & II 15.3	1					
	II & IV 21.8	1.547	1.212–1.973	<0.001			
▪ Smoker	No 15.6	1			1		
	Yes 22.4	1.565	1.179–2.078	0.002	1.413	1.058–1.889	0.019
▪ Diabetic	No 15.5	1			1		
	Yes 24.2	1.748	1.307–2.338	<0.001	1.428	1.048–1.945	0.024
▪ IHD	No 15.8	1					
	Yes 21.0	1.419	1.065–1.892	0.017			
TUMOUR-RELATED FACTORS							
▪ Tumour size	0–25mm 15.1	1					
	>25mm 18.5	1.278	1.012–1.614	0.039			
TECHNICAL FACTORS							
▪ Type of anastomosis	Manual 20.5	1			1		
	Stapled 15.2	0.699	0.558–0.877	0.002	0.675	0.536–0.851	0.001

3.4 Discussion

This is the largest cohort of TaTME cases currently in the literature used to evaluate the proficiency gain curve of the procedure. With 154 surgical units from 36 different countries collaborating with the registry, the dataset represents the practice of TaTME worldwide and highlights important aspects of its current state. Firstly, the majority of centres (53%) were still at the beginning of their operative experience with TaTME having performed less than ten cases, followed by another 30.5% of centres who'd reached a maximum of 30 cases. TaTME was primarily performed for restorative cases with only 8.3% (227 cases) adopting the technique to complete an APE. By analysing the two operations separately, it shows that APE patients were older, with higher ASA grades and more likely to have a history of abdominal surgery and/or pelvic radiation. There was also more T4 disease with CRM involvement and lower tumours compared to the restorative cases. These less favourable features, at least in part, help explain the poorer results obtained in APE cases with a significantly higher rate of intra-operative adverse events including more transanal conversions, blood loss and visceral injuries (urethral and rectal tube perforations). Subsequently, post-operative morbidity was also greater post APE at 48% compared to 38% for restorative cases with more medical and wound complications. The histopathological outcomes were also worse for APE in terms of a higher positive CRM rate (6.7% versus 3.2%) and poorer TME quality (Intact 74.5% versus 85.5%). The patient and tumour-related factors that are selected for APE procedures do tend to pose a more difficult case to operate on which may well have a high-risk profile regardless of the technique used. However, it's important to consider whether the "TaTME-approach" to APE is still in its infancy and not quite ready yet to tackle these more challenging cases. Further animal and cadaveric "experimenting" with the technique may be required to establish a more standardised and safer APE approach which may employ more advanced technology such as the use of fluorescence or augmented reality.

The influence of APE was also noted by Lee et al.[50] who reported their single institution learning curve analysis on 87 consecutive patients. They showed that the good quality TME (composite of R0 and no major mesorectal defects) rate improved after 51 cases overall, and 45 cases if APE were excluded. In our dataset we were not able to produce such a clear learning curve for poor histological outcome but rather the curve appeared to suggest good histological results for the initial six cases followed by a more stable period between cases 20 to 79 before slightly worsening. Possible explanations include surgeons starting with 'easier' lower risk cases and later taking on the more advanced cases. Alternatively, some surgeons received proctorship during their initial cases, although this only accounted for a maximum of 20% of cases. The limitations of this study discussed later may act as confounding factors influencing the results. Statistically, analyzing a potential learning curve based on low rates may not be possible; a finding shared by Koedam et al.[51] when evaluating their units learning curve for TaTME.

From a cohort of 138 patients, Koedam et al.[51] found a clear improvement in post-operative outcomes after the first 40 patients with fewer major post-operative complications (47.5 to 17.5%) and lower leakage rate (27.5 to 5%). Mean operative time and conversion rates reduced following transition to a two-team approach. Our results did not provide a clear change point for overall post-operative complications but an initial improvement in rates of anastomotic failure were seen after case 15 with a more significant change following case 49.

Similarly, intra-operative adverse events appeared to initially reduce after case 10 followed by a more prominent improvement after case 38. The splitting model confirmed reduced intra-operative adverse events, fewer conversions and shorter operative time after case 10.

A proficiency-gain curve of 40-50 cases may appear as a substantial number to achieve and raise concerns for the initial 40 patients at higher risk of complications. However, comparing these figures to those for laparoscopic colorectal surgery published in the literature helps put things into perspective. Miskovic et al.[52] performed a systematic review and international multicentre analysis of 4852 laparoscopic colorectal cases demonstrating the length of the learning curves to be 152 cases for conversions, 143 for complications, 96 for operative time, 87 for blood loss, and 103 for length of stay. Pelvic dissection and BMI especially in male patients independently increased the risk of complications and conversion. The case-mix included in this analysis however was very wide. Tekkis et al.[53] showed a difference between right colonic and left colorectal resections with a learning curve of 55 and 62 cases respectively. Focusing on rectal cancer, Mackenzie et al.[54] analysed 15,008 rectal resections by 650 surgeons recorded on the Hospital Episode Statistics database. This paper reported a change point in the proficiency-gain curve for 30-day mortality, conversion, reintervention and length of stay of 20, 24, 32 and 11 respectively.

Regardless of the technique performed, undoubtedly undergoing appropriate surgical training, especially with proctorship will have a positive influence on the proficiency-gain curve. A clear example of this was the national laparoscopic colorectal training programme in the UK, LAPCO.[55] Compared to a self-taught surgeon, supervised operating by a mentor reduced the training surgeons learning curve from 150 to 30 cases, enabling them to achieve technical competence in the procedure and providing a 'safety-net' that avoided unnecessary intra-operative complications to the patient.[56]

There are limitations to this study, in that the proficiency-gain curves plotted are derived from data for the whole surgical unit rather than individual surgeons. Multiple surgeons from the same unit may be contributing data each at a different stage of their learning curve which may explain the variability seen within the curves. However, almost 40% of cases were performed synchronously by a two-team approach, and so certain outcomes such as post-operative complications and anastomotic failure should actually reflect the whole team's effort. Although the international TaTME registry does provide one of the largest cohorts of TaTME worldwide, it is a voluntary database which requires external validation of its data, and hence cases may not be consecutively entered reliably. Further, there was a large range of number of cases performed per centre with the majority (80%) recording a maximum of 30 cases and only seven centres achieving a case load of >80. This appears to have an impact on the amplitude of the CUSUM curve which may make identifying the change point less obvious. However, bootstrapping was performed to confirm the significance of any change point. As experience in the technique grows and data continues to be collected, further proficiency-gain curve analyses can be carried out especially for the longer-term endpoints such as functional and oncological outcomes.

3.5 Conclusion

In conclusion, TaTME appears to require between 40-50 cases in order to show a greater improvement in the rate of intra-operative complications and anastomotic failure. APE cases pose a greater challenge than restorative procedures with significantly higher rates of intra- and post-operative complications, bringing into question the suitability of the transanal approach for these cases as it currently stands. Supervised training and continuous monitoring of outcomes should be implemented when adopting this promising but complex technique.

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CHAPTER III

OBSERVATIONAL CLINICAL HUMAN RELIABILITY ANALYSIS

Which technical errors are committed during a TaTME procedure identified by OCHRA? What are the error pathways that lead to adverse events?
Is there a correlation between OCHRA findings and clinico-histological outcomes?

1. Introduction

Observational Clinical Human Reliability Analysis (OCHRA) is a systematic method that assesses human-machine systems for their potential to be affected by human error. Identification and analysis of these technical errors can form the basis for error-reduction mechanisms that will lead to improved operative performance and subsequently better clinical outcomes. OCHRA techniques have been used to analyse and categorise surgical errors in a number of laparoscopic procedures, including laparoscopic cholecystectomy,[1–3] pyloromyotomy,[4] laparoscopic colorectal resections[5] and palliative bypass surgery.[6] Results from these studies allowed the identification of high-risk areas with important procedural and execution errors and performance-shaping factors that could be addressed in more detail in skills training. The OCHRA method systematically divides the procedure into key operative tasks and subtasks, known as a hierarchical task analysis.[1] Technical errors are also clearly categorised using an error classification system with ten external error modes dividing interstep (procedural) and intrastep (execution) errors as described in the 'Systematic Human Error Reduction and Prediction Approach' (SHERPA).[7]

The detailed analysis that OCHRA provides is particularly useful for novel techniques such as TaTME, with a large scope for technical refinement and improvement. The aims of this study are:

1. To describe the technical errors and adverse consequences committed during transanal total mesorectal excision (TaTME).
2. To identify the high-risk zones during the procedure and the error pathways that lead to adverse consequences.
3. To determine error-reducing mechanisms and technical recommendations, for implementation into TaTME training.

4. To establish whether there is a correlation between OCHRA findings and clinico-histological outcomes.
5. To develop an OCHRA reporting form for training surgeons that can be implemented into the national pilot TaTME training initiative in the UK.

2. Methods

2.1 Study Design

This is a prospective, multicentre study composed of two parts:

Part A. Observational Phase: Observational Clinical Human Reliability Analysis (OCHRA) of at least 100 unedited videos of TaTME for rectal cancer performed by colorectal surgeons with inter-rater and test-retest reliability analyses.

Part B. Interventional Phase Identification of error-reducing mechanisms and determining technical recommendations through semi-qualitative interviews (interim stage) and an educational seminar with experts in TaTME surgery (final stage). Implementation of findings, recommendations and OCHRA into the national TaTME training initiative.

2.2 Study participants and data collection

Colorectal surgeons performing TaTME were identified through the international TaTME registry collaborative and/or as senior authors of publications in the literature for this procedure. Eligible surgeons were invited to participate via electronic mail that contained a surgeon information sheet detailing the purpose of the study and its requirements (Version 1.1, 22.03.2016). Surgeons were reassured that the study was being carried out for its educational value and contribution to improving TaTME training and is not a validation process of the surgeon's skill. Participating surgeons were required to complete the "Participating Surgeon's consent form" (Version 1.0, 10.03.2016), thus agreeing to submit at least four complete unedited videos of TaTME procedures they had performed, including both abdominal and transanal components. In order to allow the assessment of a range of intra-operative difficulties and to minimise potential selection bias, surgeons were encouraged to submit two videos of their best performed procedures and two of the most problematic operations with intra-operative adverse events.

The eligibility criteria for TaTME cases was:

Inclusion Criteria

- Participating surgeons have completed and submitted their surgeon consent forms.
- Patients who underwent TaTME surgery have given consent to the use of their anonymised video recording and data for research.
- TaTME procedures performed for rectal cancer.
- The procedure involves placement of a pursestring and full rectotomy endoscopically at the start of the operation.
- The abdominal phase is performed either laparoscopically, single-port or robotically and video recorded.

Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Surgeons who do not perform TaTME.
- Patients who are not adults (<18 years of age).
- Patients who lack capacity to consent.
- The patient does not give consent for the use of their anonymised videos for research.

- Unedited videos cannot be delivered anonymously using the secure Imperial College group space weblink.
- Procedures performed for benign disease.
- TaTME procedures that do not require a pursestring prior to the initial rectotomy and dissection, i.e. abdominoperineal excision, intersphincteric dissections.

Unedited videos were transferred accompanied by a case reporting form (Version 1.0, 10.03.2016) needed for the correlation between OCHRA findings and clinico-histological outcomes (section 5.3.5). The case reporting form is divided into five sections collating the following data points:

1. Patient characteristics: Age, gender, BMI, previous abdominal/pelvic surgery, previous rectal cancer surgery.
2. Tumour characteristics: TNM staging, tumour height from anorectal junction on MRI, circumferential resection margin (CRM) status on MRI, tumour location, circumferential extent of tumour and neoadjuvant therapy status.
3. Intra-operative details: Presence of any intra-operative complications.
4. Post-operative outcomes: Presence of any post-operative complications categorized using the Clavien-Dindo score[8] and specifying any anastomotic leaks and unplanned re-interventions.
5. Pathological results: Pathological TNM staging, tumour size, distance of circumferential and distal margins, presence of rectal wall perforation and quality of the TME specimen.

A patient information sheet (Version 1.2, 02.06.2016) and patient informed consent form (Version 1.2, 02.06.2016) were made available to all participating centres. A lay representative reviewed the patient information sheet and consent form during the development stage of the study in order to ensure clarity and the inclusion of all relevant and essential information. Anonymised unedited TaTME videos and associated paperwork were transferred from the hospital of origin to Imperial College London via a secure encrypted college weblink. All data was anonymised and kept confidential. No patient identifiable data was present, and cases were assigned a random numerical code. Based on the supervisor and department's experience in OCHRA and previous publications in this field, the planned sample size was 100 videos, which is a good representative sample for this type of analysis.

Ethical approval from the Research Ethics Committee, NRES committee East of England, Cambridge Central Research Ethics Committee, was gained on 8th June 2016 (REC reference 16/EE/0242, Protocol number 16SM3335, IRAS project ID 199881). Approval for NHS hospitals was obtained by the Health Research Authority on 1st July 2016 with Imperial College London, St Mary's Hospital as sponsor. Participating centres were assisted in obtaining local approval for the study.

2.3 Hierarchical Task Analysis

A hierarchical task analysis of the transanal phase of the TaTME procedure was constructed based on the standardized approach agreed upon through the Delphi process for the COLOR III trial,[9] by reviewing video recorded procedures and through discussion of technical steps with experienced TaTME surgeons. The task analysis divides the procedure into seven principle tasks with specific start and end points defined (Table 3.1). For each principle task, specific steps or subtasks that need to be achieved are outlined, giving a total of 24 components. Dividing the operation into separate tasks created a systematic and clear way of comparing error rates between different phases of the procedure and allowed identification of high-risk zones. High-risk zones were categorised as such based on the number of errors that occur during a particular step of the operation.

Table 3.1 Transanal Total Mesorectal Excision Hierarchical Task Analysis

Cod e	Task Subtask	Start and End points
A B C D E	**Pursestring placement** Identification of tumour Placement of rectal pursestring Closure of rectal pursestring Washout	START: Pursestring needle introduced endoscopically. END: Closed pursestring viewed endoscopically with insufflation.
F G	**Marking and Full thickness rectotomy** Completeness of rectotomy	START: Energy device introduced endoscopically. END: Full thickness rectotomy prior to proceeding cranially.
H I J K L	**TME dissection: posterior plane** Initiation point of posterior TME dissection Identification of pelvic floor Presence of angel hair aiding correct TME dissection Posterior TME dissection direction and plane	START: Posterior dissection between 4 to 8 o'clock proceeding cranially. END: Complete posterior detachment from underlying tissue.
M N O P Q	**TME dissection: anterior plane** Identification of Denonvilliers' fascia In females: Identification and protection of vagina In males: Identification and protection of prostate and seminal vesicles. Mostly in males: Identification and protection of the anterolateral neurovascular bundles	START: Anterior dissection between 10 to 2 o'clock proceeding cranially. END: Complete anterior detachment from overlying tissue.
R S T U	**TME dissection: lateral plane** Identification and protection of two lateral pillars with neurovascular bundles. Dissection plane between the posterior and anterior TME followed. Sequence of TME dissection	START: Right (8-10 o'clock) and left (2-4 o'clock) lateral dissection proceeding cranially. END: Complete lateral detachment from lateral tissue.
V W	**Connection to full rectal mobilisation** Connection between the abdominal and perineal teams	START: Initial point of connection into the abdomen from the transanal view. END: Rectal specimen fully mobilized from surrounding tissue.
X	**Final haemostatic check and irrigation**	-

2.4 Error modes and pathways

The 'Systematic Human Error Reduction and Prediction Approach' (SHERPA) system[7] for error classification mentioned above, was modified and adapted specific to TaTME (Appendix 2) by the research fellow MP and supervisor RH (colorectal surgeon experienced in TaTME). The adapted classification was constructed to allow annotation of every possible technical error and event encountered during TaTME surgery. Executional errors are coded based on the instrument used (grasper, energy device, camera) describing the exact type of error committed (e.g. excessive movement or force used). Errors of retraction and dissection are also specified, as well as adequacy of exposure of the visual field. Technical errors were further divided into consequential and inconsequential errors. A consequential error was defined as any action that led to a negative effect or increased the time of the procedure because of the required corrective action, such as bleeding or visceral injury. An inconsequential error was defined as an action that increased the likelihood of causing a negative effect but did not lead to that adverse event, i.e. a technical inaccuracy with no subsequent harm. For example, clashing of instruments in the lumen of the platform is an inconsequential technical error or inaccuracy with no adverse event. However, clashing of instruments that accidentally pushes the diathermy hook into a blood vessel that then starts bleeding is a consequential error with an adverse outcome. This modified classification of errors for TaTME was tested on five initial cases before the study cohort to confirm that all possible errors and adverse events could be recorded in a systematic and clear way.

The scientific rating software called 'Behavioural Observation Research Interactive Software' (BORIS, Turin, Italy)[10] was used to carry out the video analysis. The TaTME error classification was inputted into BORIS which also allows annotation of 'point events' and 'time periods' while streaming the video file. 'Point events' include the technical errors and adverse events that occur at a specific point in time, whilst the 'time periods' permit timing of the different phases of the operation. The software is therefore able to map the surgeon's performance, by graphically showing the time spent executing each operative step and both the number and type of errors occurring during each section. We have named this graphical representation of surgical performance "Surgeon specific procedure mapping".

Error Pathways

Similar to the well-known "Swiss cheese model" of accident causation used in risk analysis and management,[11] intra-operative adverse events appear to occur as a consequence of multiple technical errors, rather than just one single error alone. A new concept called "Error Pathways" has been developed in which sequences of events and errors that lead to adverse consequences are identified and studied. By understanding and discussing these pathways, strategies and mechanisms were devised during the intervention phase of the study in order to prevent the occurrence of technical errors; i.e. interrupting the chain of errors leading to adverse events.

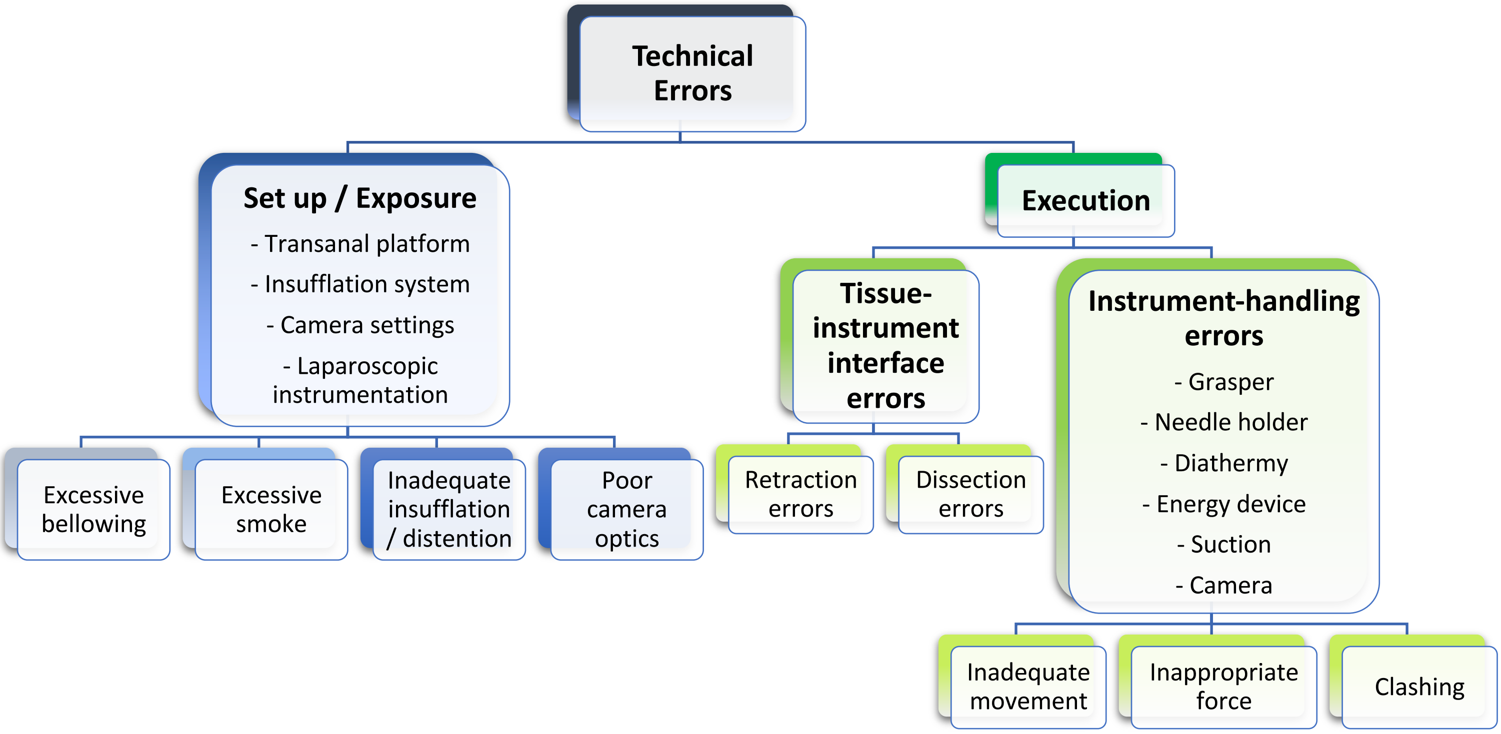
2.5 Clinical categorization of errors

An interim review of OCHRA results was carried out after analysis of the initial 50 consecutive cases. The findings, including error pathways identified, were shared with ten international surgeons selected for their experience in TaTME surgery. These ten surgeons had performed over 30 TaTME cases, were regular faculty members on TaTME cadaver courses and had been involved in consensus guideline meetings for this technique. Semi-structured interviews were conducted to explore the surgeons' thoughts and opinions about the OCHRA results and suggest possible strategies or mechanisms that they would advise or have performed in order to prevent such errors from occurring. The interviews were structured into three sections starting with three background questions to ascertain that each surgeon met the required experience needed to take part in the study. The surgeons were then asked about which phase of the operation they would expect the most errors to occur and why, followed by what they consider to be the optimal equipment set up for TaTME. The OCHRA findings were then shared with the surgeons and asked how they would prevent such errors from happening. The third part involved reviewing five short video clips of consequential errors analysed from the study cohort, identifying the errors committed and suggesting possible mechanisms to prevent such errors. All interviews were transcribed, and transcripts analysed.

The interim review and expert interviews led to the realisation that technical errors related to TaTME fall into two main categories: 1) errors related to equipment set up or exposure (e.g. poor insufflation with inadequate smoke evacuation and excessive bellowing), and 2) errors of execution (Figure 3.1). Executive errors are further divided into "instrument-handling errors" and "tissue-instrument interface errors", similar to those described by Miskovic et al.[5] Instrument-handling errors are defined as inaccurate use of a laparoscopic tool (grasper, needle holder, energy device, suction) or the laparoscopic camera; whilst, tissue errors are defined as inappropriate interactions with the tissue, namely retraction or dissection errors (Figure 3.1). Results will be reported using this clinical categorisation of errors.

The findings of this interim analysis together with the proposed strategies and technical recommendations were presented at the national TaTME training cadaver workshop in October 2017 (section 4: National TaTME Training Programme).

Figure 3.1 Clinical categorisation of errors



2.6 Task Accuracy Scoring

Performance of the main operative tasks and their associated subtasks outlined in the hierarchical task analysis can vary from an optimal execution with no negative consequences to a poor surgical performance with the worse possible adverse event for that particular step. An accuracy score from 1 to 4 was created for each subtask, describing the possible outcomes that can occur during that component (Appendix 3). A score of 1 represents the best possible outcome, whereas 4 indicates a severe adverse event. The sum of the scores produces a composite objective rating with a worse performance leading to a higher score. The task accuracy scoring also captures any interstep (procedural) errors, specifically the completion of each main task before starting the next, the sequence of TME dissection and cylindrical "sleeve-like" dissection progressing cranially.

2.7 Study Validity

OCHRA is a well-recognized and validated method of video analysis previously applied to numerous operations and published in the literature.[1-6] The TaTME cases included in this study were received from a range of hospitals in different countries including both district general hospitals as well as tertiary teaching institutes; thus, providing a good representative sample of 'real-life' operating. Furthermore, participating surgeons were specifically asked to submit two of their best performances of TaTME and two cases in which they experienced intra-operative difficulties; once again, by doing so, the aim was to evaluate a whole range of intra-operative difficulties and experiences in performing this procedure so that most, if not all, possible technical errors and adverse events could be assessed.

Each case was anonymized and allocated a random numerical code to facilitate blinding of the raters. The only information disclosed to the raters (PhD research fellow, MP, and expert rater, RH) was the case number and pre-operative patient and tumour characteristics including patient age, gender, BMI, previous abdominal and/or pelvic surgery, tumour staging on MRI, tumour location and any neoadjuvant therapy received. These features were considered important for the rater to know prior to viewing the video in order to be able to accurately assess the quality and extent of the dissection and allocate the correct accuracy score depending on the patient's gender and tumour characteristics. The surgical team performing the case and any reported intra-operative or post-operative complications recorded on the case reporting form were not disclosed to the raters to avoid potential reporting bias.

2.8 Study Reliability

All unedited TaTME videos were analysed following OCHRA principles by the PhD research fellow (MP). MP is a specialty registrar in general surgery and was trained by an expert, her supervisor GH, in ergonomics and human reliability analysis techniques. Prior to analysing the study videos, MP assisted in over 50 TaTME cases, co-organised seven TaTME cadaver workshops, discussed unedited videos with senior surgeons and performed TaTME on cadavers mentored by the clinical lead for the national TaTME training programme in the UK (RH), who is also her supervisor. To ensure stable and consistent results, the following reliability analyses relevant to this study were conducted:

1. **Inter-rater reliability**: The supervisor RH, a colorectal surgeon experienced in TaTME and clinical lead for the UK TaTME training programme, independently performed OCHRA on 20% (n=20) of randomly selected videos (computer generated random numbers) from the study cohort. The inter-rater reliability between the expert (RH) and PhD research fellow (MP) were analysed in order to ensure that the fellow understands the procedure in depth and is able to accurately and consistently identify technical errors during TaTME. Both raters were blinded to the surgical team performing the operation and the post-operative outcomes.
2. **Test-retest reliability**: The PhD research fellow (MP) repeated OCHRA on 20% (n=20) of randomly selected cases, at least 4 weeks apart. The results from Time 1 and Time 2 were correlated in order to evaluate the analysis for stability over time and to minimize the risk of observer error and bias.

2.9 Construction of error-reducing mechanisms

OCHRA results for the whole study cohort were presented and discussed at an educational seminar with an international panel of TaTME expert surgeons. The TaTME expert group consisted of 17 colorectal surgeons identified through the international TaTME registry, publications and by peer-nomination, who had performed some of the highest number of TaTME cases worldwide. The seminar was facilitated by a chairman independent to the work and also attended by the educational lead for the national TaTME training programme in the UK. Following introductions by each participant, the research fellow MP presented the aims of the session including an explanation of OCHRA, it's adaption to TaTME, the OCRHA findings and the objectives of the subsequent small group work. The experts were divided into four smaller groups and each assigned a different phase of the operation: 1) pursestring, 2) rectotomy, 3) anterior and posterior TME dissections, and 4) lateral TME dissection and connected phase. Each group was provided with a worksheet and asked to comment on the OCHRA findings described for their allocated phase. The next stage involved watching two TaTME video clips of adverse events occurring during their phase and asked to identify technical errors and the consequential adverse events. The final task requested the expert surgeons to make suggestions and technical recommendations of ways to prevent such errors from occurring, i.e. error-reducing mechanisms. Following the small group work, the findings and recommendations were shared with the whole group for further discussion and agreement. The whole seminar was audio recorded and transcribed, ensuring that no discussion points were missed, and all suggested error-reducing mechanisms noted.

2.10 Statistical analysis

The description and frequency of technical errors and any adverse consequences were annotated for each TaTME operation and extracted from the BORIS software. Results were tabulated and analysed using the Statistical Package for the Social Sciences software version 26 (SPSS, Inc., Chicago, IL, USA). Frequencies are presented per operative task and divided into the categories outlined in figure 3.1, allowing identification of high-risk zones and common technical pitfalls.

The composite objective rating derived from the accuracy scores is presented as the mean, median and range, and analysed to assess whether there is any correlation between the accuracy score and: 1) frequency of errors, 2) frequency of adverse consequences by ANOVA test and, 3) post-operative outcomes using the Chi-squared test. Data with normal distribution (Shapiro-Wilk and Kolmogorov-Smirnov tests) was analysed by the independent sample T-test, whereas abnormally distributed data was analysed using nonparametric tests (Mann-Whitney U test or Kruskal Wallis test as appropriate). Inter-rater and test-retest reliabilities were calculated using the interclass correlation coefficient (ICC). Statistical significance is set at the 5% level.

3. Results

3.1 Data characteristics

A total of 118 unedited operative videos were received during the study period. Of these, 100 videos met the eligibility criteria and were complete showing each step of the transanal operation, thus included in the analysis. The videos originated from 31 collaborating surgeons working in 20 colorectal units in ten different countries worldwide (Belgium, Canada, England, Germany, Ireland, Italy, Netherlands, Portugal, Spain, Wales). A total of 3600 data points on the 100 included cases were requested via the case reporting form, of which 88.0% were recorded. Table 3.2 describes the patient and tumour characteristics of the analysed cases. Case selection shows a predominantly male, overweight elderly patient with a virgin abdomen in 80% of cases. The median tumour height is 5.0 cm from anorectal junction measured on pre-operative baseline MRI, with the majority of tumours being staged as T3, N0, M0. Predominantly anteriorly located tumours were present in 49.5% of cases, with CRM involvement seen in 27.0% on staging MRI. 48.9% received neoadjuvant therapy.

Table 3.2 Patient and tumour characteristics

Factor ▪ Category	Total: 100 cases
Gender, n (%)	
▪ Male	77 (77.0)
▪ Female	23 (23.0)
Age in years, mean ± SD (range)	63 ± 11.3 (30–87)
BMI in kg/m^2, mean ± SD (range)	26.8 ± 4.8 (17–42)
Previous unrelated abdominal/pelvic surgery, n (%)	18 (20.2)
Previous rectal cancer related surgery, n(%)	7 (7.9)
▪ TEM	3 (3.4)
▪ Stoma	4 (4.5)
Tumour height from anorectal junction on MRI in cm, median (range)	5.0 (0–12)
Pre-operative MRI staging, n (%)	
▪ T1	1 (1.1)
▪ T2	19 (21.3)
▪ T3	64 (71.9)
▪ T4	5 (5.6)
▪ N0	42 (47.2)
▪ N1	30 (33.7)
▪ N2	16 (18.0)
▪ M0	84 (94.4)
▪ M1	5 (5.6)

Predominant tumour location	
▪ Anterior	45 (49.5)
▪ Posterior	34 (37.4)
▪ Lateral	12 (13.2)
Number of luminal quadrants covered by tumour	
▪ 1-2	65 (70.7)
▪ 3-4	27 (29.3)
Pre-operative CRM involvement on MRI, n (%)	24 (27.0)
Received neoadjuvant therapy, n (%)	43 (48.9)

Intra-operative adverse events were reported to have occurred in 23 cases (25.8%). These are listed in table 3.3 where clinical and oncological outcomes are shown. Amongst the eight cases of failed pursestring in which the suture was too loose and a hole was visible, two resulted in spillage of bowel content and contamination of the dissection field. Neither of these cases had post-operative pelvic sepsis. One case was converted from a laparoscopic abdominal approach to a laparotomy due to difficulties in identifying the anterior TME plane and occurrence of a posterior rectal tube perforation during the transanal phase. This converted case involved a 70-year-old male with a BMI of 33 kg/m^2. He had a T3 N1 M0 postero-lateral tumour located 1.5cm from the anorectal junction and had received neoadjuvant chemoradiotherapy.

The overall post-operative morbidity was 30.3% with a re-operation rate of 5.6% and anastomotic leak rate of 7.9% (7 cases). Management of anastomotic leaks involved an emergency operation in three cases (42.9%) [Table 3.3 re-operations], one CT-guided drainage (14.3%), and three cases of conservative management with antibiotics (42.9%). Other post-operative complications encountered included prolonged ileus, urinary tract infections +/- urinary retention, cardiac arrhythmias, wound infections and temporary delirium post-operatively.

With regards to histological outcomes, complete excision of the tumour with negative resection margins occurred in 97.6%. Two R1 resections were due to a positive malignant lymph node within 1mm of the resection margin and a positive distal resection margin; although the donuts excised with a circular stapler were negative. A complete, near complete and incomplete TME specimen was obtained in 92.9%, 5.9% and 1.2% respectively.

Table 3.3 Clinical and oncological outcomes

Factor ▪ Category	n (%)
Intraoperative adverse event, n (%)	23 (25.8)
Abdominal/general:	
▪ Anaphylaxis to rocuronium	1 (1.1)
▪ Bleeding from inferior mesenteric vein	1 (1.1)
▪ Bleeding from omental wrapping	1 (1.1)
Transanal:	
▪ Failed pursestring requiring repeat placement	8 (9.0)
▪ Pursestring haematoma	1 (1.1)
▪ Bleeding from presacral vessels	2 (2.2)
▪ Bleeding from lateral pillar neurovascular bundle	2 (2.2)
▪ Mesorectal injury	1 (1.1)
▪ Anterior rectal tube perforation	1 (1.1)
▪ Conversion from laparoscopic to open as difficult to identify anterior plane and posterior rectal tube perforation occurred transanally	1 (1.1)
▪ Gas embolus following venous bleeding transanally	1 (1.1)
▪ Anterior anastomotic defect requiring suturing	1 (1.1)
▪ Stapler malfunction leading to APER	2 (2.2)
Conversion rate, n (%)	1 (1.1)
Postoperative adverse event, n (%)	27 (30.3)
▪ Anastomotic leak	7 (7.9)
▪ Re-operation	5 (5.6)
Re-operations	
▪ Day 2 Ileal enterotomy repair	1 (1.1)
▪ Day 18 & 20 Laparoscopic adhesiolysis and repair of internal hernia causing small bowel obstruction	1 (1.1)
▪ EUA & stitches for anastomotic leak	1 (1.1)
▪ EUA & endosponge for anastomotic leak	1 (1.1)
▪ Laparoscopic ileostomy, washout + EUA for anastomotic leak	1 (1.1)
Clavien-Dindo Classification, n (%)	
▪ I	5 (18.5)
▪ II	14 (51.9)
▪ IIIa	3 (11.1)
▪ IIIb	5 (18.5)
▪ IV	0 (0.0)
Tumour size, mm, mean ±SD (range)	30.5 ±16.7 (0–70)
CRM distance, mm, mean ±SD (range)	9.6 ± 6.3 (1–35)
DRM distance, mm, mean ±SD (range)	22.5 ±20.3 (0–140)

Pathological staging, n (%)	
▪ T0	5 (5.9)
▪ T1	8 (9.4)
▪ T2	23 (27.1)
▪ T3	49 (57.6)
▪ N0	64 (75.3)
▪ N1	12 (14.1)
▪ N2	9 (10.6)
▪ L1	14 (16.5)
▪ V1	18 (21.2)
▪ R1	2 (2.4)
Lymph nodes harvested, mean ±SD (range)	22.0 ±13.3 (3-110)
Perforated rectal wall, n (%)	2 (2.4)
Quality of TME specimen, n (%)	
▪ Complete	79 (92.9)
▪ Nearly complete	5 (5.9)
▪ Incomplete	1 (1.2)

Table 3.4 outlines intra-operative technical features and equipment used. Majority of cases were performed using the flexible transanal platform called GelPOINT Path (Applied Medical, Santa Margarita, CA, USA) (90.0%) and AirSeal™ System (CONMED, Utica, NY, USA) as the insufflation system (83.0%). Camera position was recorded and corresponding position of the working ports as either working horizontally (hands side by side) or vertically (one hand on top of the other). The mean number of technical errors encountered appears to be higher when working ports are positioned horizontally compared to vertically (58.7 ±24.4 vs 49.1 ±34.2, p 0.035). However, no statistical difference was seen in terms of the rate of intra-operative adverse events (p 0.359) or the accuracy score (p 0.163) for camera position.

Table 3.4 Intra-operative technical features

Factor ▪ Category	Total: 100 cases
Transanal platforms, n (%)	
▪ GelPOINT Path	90 (90.0)
▪ SILS port	2 (2.0)
▪ TEM	6 (6.0)
▪ TEO	1 (1.0)
▪ B-port	1 (1.0)
Insufflation system, n (%)	
▪ Airseal	83 (83.0)
▪ High pressure insufflation	7 (7.0)
▪ Standard insufflation system	10 (10.0)
Camera position	
▪ Top left – vertical*	13 (13.0)
▪ Top right - vertical	66 (66.0)
▪ Bottom – horizontal*	10 (10.0)
▪ Top central - horizontal	1 (1.0)
▪ TEM/TEO – horizontal	7 (7.0)
▪ 12 o'clock with 4 trocars – horizontal & vertical	1 (1.0)
Synchronous operating, n (%)	
▪ Yes	70 (70.0)
▪ No	30 (30.0)

*Horizontal and vertical relate to the position of the working ports.

3.2 Technical errors during TaTME

A total of 5,101 technical errors and 904 adverse consequences were annotated during the analysis of the transanal phase of the 100 TaTME included cases (Table 3.5). The mean number of errors and consequences per case was 51 ±32.4 and 9 ±6.6 respectively. An increasing rate of technical errors was associated with an increased risk of having an adverse consequence intra-operatively (Effect size 0.109, 95% CI 0.075–0.143, p <0.001). The majority of errors and their consequences were noted during the TME dissection phase, which also took the longest operating time. Mean operating times for each phase of the procedure were 14 ±7.5, 18 ±11.5, 38 ±26.2, 20 ±13.3 minutes for pursestring, rectotomy, TME dissection and connected phases respectively.

Tables 3.6a-c present the number of technical errors identified following the clinical categorisation system shown in figure 3.1. For errors relating to set up, inadequate insufflation with excessive bellowing and poor smoke evacuation were primarily seen in cases using a standard insufflation system (10%), with 7 out of 10 of these cases experiencing adverse events and task accuracy scores ranging between 33-45 (section 3.6). However, inadequate insufflation was also noted using the AirSeal™ System (CONMED, Utica, NY, USA) when the pressure may not have been set high enough to achieve adequate tissue tension making it more difficult to identify the correct plane of dissection. Other reasons for experiencing a limited view included operating with a dirty camera, poor camera positioning and reduced circumferential view due to an ovoid-shaped flexible platform or use of the rigid platform.

Instrument handling errors (table 3.6b) were predominantly due to excessive movement, either repeated or disorganized, with all instrumentation, contributing to frequent instrument clashes. Forceful movements with graspers and energy devices followed, increasing the risk of an adverse consequence especially bleeding.

Tissue-instrument interface errors (table 3.6c) are mostly due to too little retraction occurring during the rectotomy and TME phase, which can make identifying the correct dissection plane more difficult as the anatomy is less clear and adequate wall tension for efficient dissection is not obtained. Unsurprisingly, dissection errors with new incorrect planes being created mostly occurred during the TME phase.

Table 3.5 OCHRA results of the transanal phase of TaTME

Results for 100 cases	Pursestring phase	Rectotomy phase	TME dissection phase	Connected phase	Procedure OVERALL
For total cohort:					
▪ Total number errors	900	1190	2068	941	5101
▪ Total number consequences	251	196	319	137	904
Events per case:					
▪ Errors, mean ±SD (range)	9 ±6.8 (0–43)	12 ±9.4 (0–58)	21 ±19.2 (1–124)	10 ±8.1 (0–41)	51 ±32.4 (6–194)
▪ Consequences, mean ±SD (range)	3 ±3.3 (0–29)	2 ±2.4 (0–10)	3 ±3.6 (0–21)	1 ±1.6 (0–7)	9 ±6.6 (1–45)

Table 3.6 Types of technical errors: **3.6a** Set up errors; **3.6b** Instrument handling errors; **3.6c** Tissue-instrument interface errors

3.6a Set up errors ▪ Category	Pursestring n	Rectotomy n	TME n	Connected n	Total number of errors, n (%)
▪ Excessive smoke	0	24	22	18	64 (11.6)
▪ Excessive bellowing	5	8	18	14	45 (8.2)
▪ Inadequate insufflation	49	59	32	26	166 (30.2)
▪ Limited view – other reason	38	44	124	69	275 (50.0)

3.6b Instrument handling errors ▪ Category	Pursestring n	Rectotomy n	TME n	Connected n	Total number of errors, n (%)
Grasper / Needle holder					
▪ Inadequate movement:					
⇒ Too much	372	84	126	58	640 (20.3)
⇒ Too little	1	2	0	0	3 (0.1)
⇒ Wrong position/direction	37	3	0	1	41 (1.3)
▪ Inappropriate force	56	30	64	34	184 (5.8)
Energy device					
▪ Inadequate movement					
⇒ Too much	0	92	145	45	282 (9.0)
⇒ Too little	0	1	3	0	4 (0.1)
⇒ Wrong position/direction	0	7	19	7	33 (1.0)
▪ Inappropriate force	0	83	103	47	233 (7.4)

Camera					
▪ Inadequate movement					
⇒ Too much	44	133	237	142	556 (17.7)
⇒ Too little	0	0	0	0	0 (0.0)
⇒ Wrong position/direction	46	73	186	77	382 (12.1)
Clashing of instruments/camera	123	178	337	153	791 (25.1)

3.6c Tissue-instrument interface errors ▪ Category	Pursestring n	Rectotomy n	TME n	Connected n	Total number of errors, n (%)
Retraction errors					
▪ Too much	1	4	26	20	51 (9.5)
▪ Too little	2	166	136	63	367 (68.6)
▪ Wrong direction	0	63	37	17	117 (21.9)
Dissection errors					
▪ New incorrect plane created	0	43	269	81	393 (83.3)
▪ Dissecting along wrong plane	0	15	53	8	76 (16.2)

3.2 Technical errors during TaTME continued

A total of 190 intra-operative adverse consequences were identified by OCHRA during the transanal phase of TaTME (Table 3.7). Pursestring failure occurred 23 times during the initial pursestring placement as either the suture was inadvertently torn (2 cases), or the lumen was not fully closed and a second pursestring placed (16 cases) or the lumen was not fully closed but a second pursestring wasn't placed and the operation continued (5 cases). Three further episodes of pursestring failure with the lumen opening and spillage of luminal contents occurred during the TME dissection phase and once during the connected phase. Interestingly, only 8 failed pursestrings were reported by the operating team on the case reporting forms. Prior to starting the rectotomy phase, 5% and 18% performed minimal (<50mls) or no washout of the rectum, respectively.

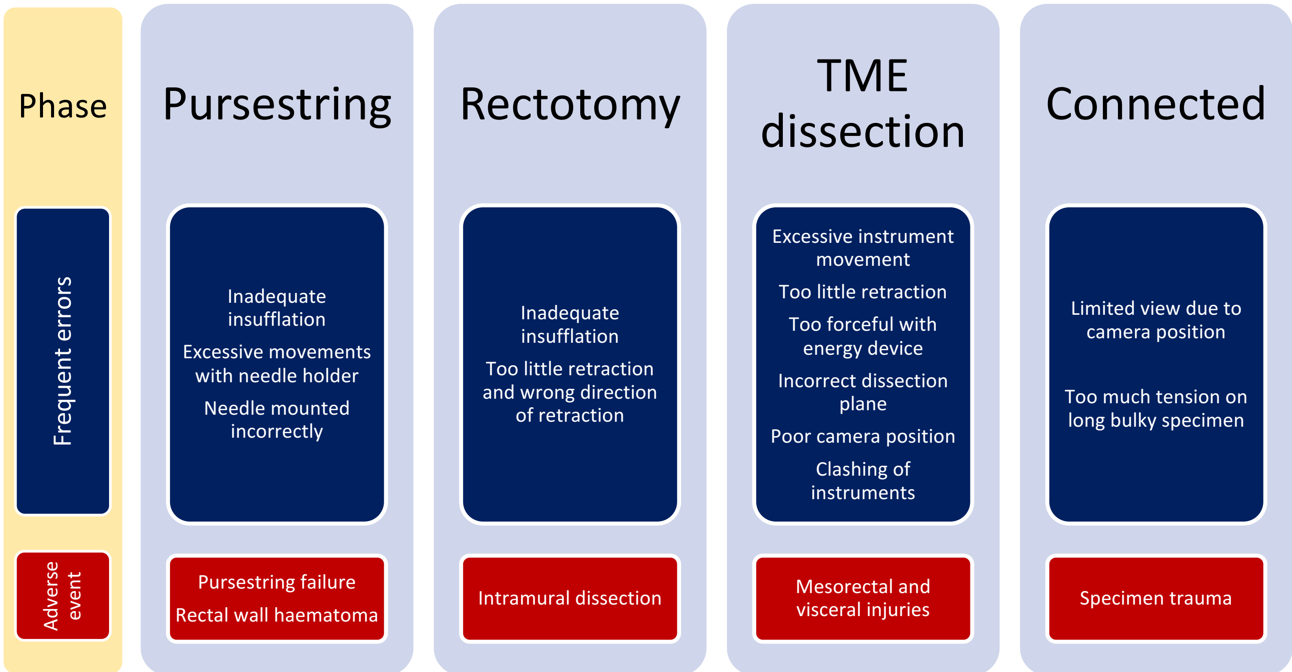
Table 3.7 Intra-operative adverse consequences identified by OCHRA

Factor ▪ Category	Number of cases, n (%)
Adverse consequences	
▪ Pursestring failure	26 (26.0)
▪ Rectal wall haematoma	12 (12.0)
▪ Intramural dissection	21 (21.0)
▪ Pelvic floor nerve injury	8 (8.0)
▪ Pelvic floor severe bleeding	7 (7.0)
▪ Posterior TME: mesorectal defect	15 (15.0)
▪ Anterior TME: mesorectal defect	10 (10.0)
▪ Lateral TME: mesorectal defect	6 (6.0)
▪ Rectal wall perforation	6 (6.0)
▪ Prostatic or seminal vesicle injury	6 (6.0)
▪ Vaginal perforation	1 (1.0)
▪ Anterolateral NVB injury	37 (37.0)
▪ Lateral pillar injury	35 (35.0)

Rectal wall perforation was identified in 6 cases (6.0%), occurring four times during the posterior TME dissection, once during the rectotomy anteriorly and once during the rectotomy laterally. Further visceral injuries included one vaginal perforation and six cases of prostatic and/or seminal vesicle injury, with one case of substantial mobilisation of the prostate. However, no urethral injuries were identified in this cohort. The most frequently injured structures during TME dissection were the anterolateral and lateral pillar neurovascular bundles (37.0% and 35.0%), causing bleeding that usually had to be controlled with an energy device. During the connected phase, the risk of causing trauma to the specimen itself was noted, especially when the specimen was long, bulky and heavy, making it difficult to lift or retract in order to obtain an adequate view for dissection.

In summary, the most frequently encountered errors and significant adverse consequences during each operative phase are shown in figure 3.2 below.

Figure 3.2 Most frequent errors and significant adverse consequences during each operative phase



3.3 Surgeon specific procedure mapping

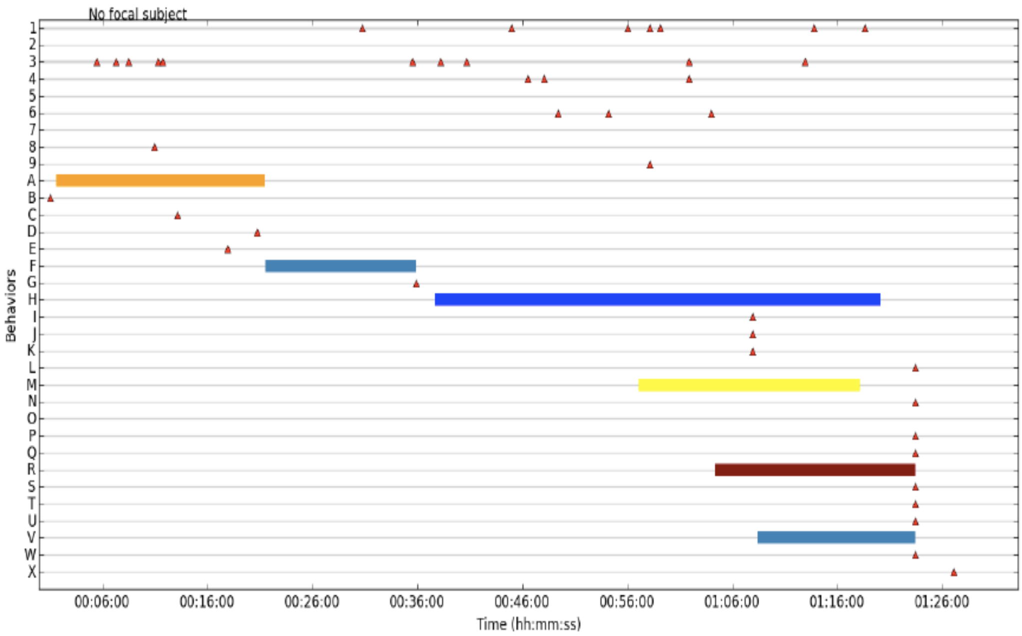
For each case, the surgeon's technical performance can be graphically represented, as shown in figures 3.3a and 3.3b. We have termed this "surgeon specific procedure mapping", and it provides a visual summary of the operation. Each coloured horizontal bar represents one of the six principle tasks or operative steps required to complete the operation as outlined in the hierarchical task analysis (see 'Figure 3.3 key' below). The red triangles at the top of the graph between lines 1 to 9 represent the technical errors committed using the error coding constructed specific for TaTME and described in appendix 2. The red triangles scattered between lines B to Z represent the task accuracy scores (Appendix 3).

A clear difference is easily seen between the performance represented in figure 3.3a compared to figure 3.3b. Figure 3.3a shows a clear consecutive sequence of operative steps with few technical errors and consequences being committed (Total number of errors = 19; Total number of consequences = 1; Task accuracy score = 17). In contrast, the case performed in figure 3.3b encountered more difficulties with a failed pursestring that required re-do (x2 orange horizontal bars) and significantly more technical errors and consequences (Total number of errors = 144; Total number of consequences = 13; Task accuracy score = 38).

It is important to acknowledge that the graphs per se do not give any information about the level of difficulty of the case or the surgeon's stage in their learning curve. Hence, these may be consecutive cases performed by the same surgeon with an easy case for figure 3.3a and a much harder case in 3.3b. Although such graphs can be helpful to the operating surgeon and their proctor to identify which operative step they are encountering most difficulties in, a further valuable use of surgeon specific procedure mapping is observing operative trends and progress over a series of cases of similar or increasing difficulty.

Figure 3.3a&b Surgeon specific procedure mapping of a (**3.3a**) well performed TaTME, and (**3.3b**) TaTME with high number of technical errors and consequences

(a)



(b)

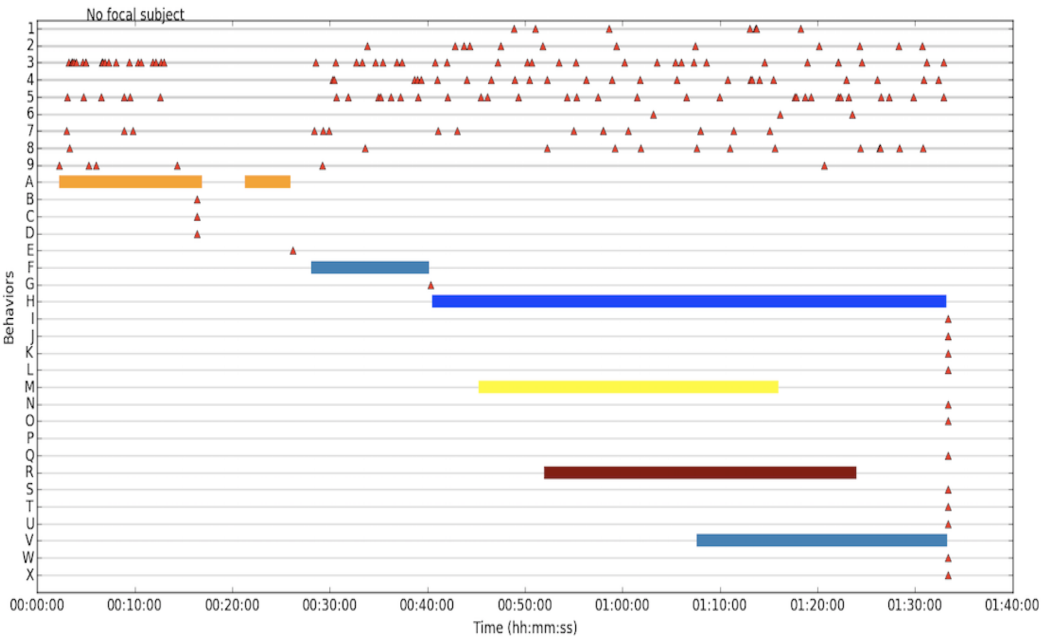


Figure 3.3 Key

Lines 1 to 9: Technical errors and consequences (Appendix Z)

Operative steps: A. Pursestring placement
F. Marking and full thickness rectotomy
H. Posterior TME dissection
M. Anterior TME dissection
R. Lateral TME dissection
V. Connection to full rectal mobilisation

Lines B–E, G, I–L, N–Q, S–U: Task accuracy scoring

3.4 Error pathways

By performing OCHRA of multiple TaTME cases, it soon became apparent that many adverse consequences are not solely due to a single preceding technical error. Although this can occur, in many cases an "error pathway" develops in which one technical error leads to another, predisposing the surgeon to committing an intra-operative complication. The chain of errors tends to include factors from at least two of the three clinical categories of errors described in figure 3.1 (Set up, Instrument handling, Tissue-instrument interface errors). Figure 3.4 shows examples of error pathways during TaTME. Early recognition and correction of such errors can interrupt the negative chain and potentially prevent the adverse consequence from happening.

Figure 3.4 Error Pathways leading to adverse events

Case	Error pathways	Adverse Events
1	Conventional CO_2 insufflation → Excessive bellowing, limited view → Too forceful with suture → Tearing of the suture	Mucosal injury, prolonged operative time
2	Inadequate insufflation → Narrow working space → Clashing of instruments and excessive movements → Inadequate retraction and poor view of dissection plane	Tumour and mucosal injury, incorrect plane surgery with excessive bleeding
3	Spiralling of initial rectal pursestring → Distortion of specimen due to tightened spiralled pursestring → Intramural dissection during rectotomy → Continued intramural dissection close to anterior tumour	Excessive bleeding, mucous spillage, risk of tumour perforation
4	Incomplete circumferential rectotomy → Distortion of the specimen held down at 5 o'clock → Forceful retraction of specimen towards 3 o'cock overexposing the lateral bundle → Incorrect lateral dissection plane (too wide)	Bleeding from lateral bundle
5	Poor view from glaring camera light and wrong camera position → Excessive instrument movements with clashing → Incorrect dissection plane identification → Bleeding obscuring view and plane	Vaginal wall perforation

3.5 OCHRA findings and clinico-histological outcomes

OCHRA identified at least one intra-operative adverse consequence in 85 out of the 100 TaTME cases analysed. The adverse events are outlined in table 3.7 and would either have posed additional difficulties with subsequent dissection, prolonged operative time and/or required extra intervention to correct the problem. Not surprisingly, an increased number of technical errors committed during the procedure was associated with a higher risk of having an adverse event (p 0.031). No specific patient or tumour-related risk factor contributing to the intra-operative adverse events overall was identified. However, if focusing on the visceral injuries encountered (mesorectal, rectal tube, prostate, vagina and neurovascular bundles) the single statistically significant risk factor in this dataset was male gender; 75.3% men vs. 47.8% women sustained a visceral injury, majority being neurovascular bundle injuries (OR 0.300, 95% CI 0.114–0.791, p 0.012). Similarly, male gender was also a risk factor for overall post-operative morbidity (37.3% men vs 10.0% women, OR 0.187, 95% CI 0.040–0.873, p 0.027), together with one-team operating (50.0% one team vs 23.0% two-team, OR 0.298, 95% CI 0.113–0.788, p 0.013) and closely associated with a low tumour height of <2cm from anorectal junction (35.6% for low tumour height 0–2cm vs 7.7% for tumour height >2cm, OR 0.151, 95% CI 0.019–1.225, p 0.055). There was no statistical difference in the rate of intra-operative adverse events between one- or two-team procedures.

A higher frequency of intra-operative technical errors was found to be significantly associated with an increased rate of post-operative morbidity, especially for more severe complications as Clavien-Dindo IIIa and above (Table 3.8). The number of intra-operative adverse consequences did not reach statistical significance in terms of post-operative morbidity; however, this may be due to a type II error with too low a rate of adverse events occurring to statistically show a difference. A cut off of 50 technical errors per case can be used as a guide to the likelihood of incurring a post-operative complication. In this cohort, the rate of post-operative complications was 23.1% and 42.9% for cases with up to 50 and more than 50 technical errors, respectively (OR 2.500, 95% CI 0.987–6.334, p 0.051).

There was insufficient evidence to support a correlation between the number of errors or adverse consequences and histological features, in particular R1 resections and a composite of poorer histological features. Similarly, this may be due to a type II error given the low R1 rate of 2%.

Table 3.8 OCHRA errors and consequences association with clinico-histological outcomes

Complication	Technical errors, Mean ±SD	P value	Adverse consequences Mean ±SD	P value
Post-operative morbidity				
▪ Yes	63.4 ±40.0	0.033	9.9 ±5.2	0.137
▪ No	45.4 ±27.4		8.9 ±7.5	
Clavien-Dindo IIIa-IV				
▪ 0 – II	50.8 ±33.1	0.049	8.8 ±6.9	0.528
▪ IIIa – IV	53.5 ±29.6		12.3 ±6.6	
Emergency re-operation				
▪ Yes	67.4 ±29.4	0.115	13.2 ±8.3	0.245
▪ No	50.0 ±32.7		9.0 ±6.8	
Anastomotic leak				
▪ Yes	76.6 ±60.5	0.242	10.0 ±7.0	0.814
▪ No	48.8 ±28.6		9.1 ±6.9	
R1 resection				
▪ R0	51.0 ±33.0	0.439	9.3 ±7.0	0.667
▪ R1	32.0 ±18.4		9.0 ±0.0	
Poorer histological outcome§				
▪ Yes	48.4 ±39.4	0.683	11.2 ±2.2	0.095
▪ No	50.7 ±32.6		9.2 ±7.1	

3.6 Accuracy Scoring of TaTME

The mean accuracy score was 28 ±7.0, with similar scores seen regardless of whether a surgeon reported intra-operative problems or not (Table 3.9a). The mean accuracy score for cases that did experience an adverse consequence detected by OCHRA was 29 ±6.7 (range 18–46), compared to those that didn't with a score of 20 ±2.9 (17–26), p-value <0.001.

The occurrence of any post-operative complication was associated with a higher accuracy score (mean 30 ±6.8 vs 26 ±6.6; table 3.9b), with a cut off accuracy score of 24 showing significant differences in terms of post-operative outcome (table 3.10). There is also a trend towards an increased likelihood of requiring an emergency re-operation for cases that obtain a score >24 (p value 0.065). No difference in accuracy score was seen in relation to the composite of poor histological features.

Table 3.9 Task accuracy scoring: **3.9a** Overall & reporting of intra-operative problem, **3.9b** Presence of post-operative complication

Table 3.9a ▪ Category	Overall	Reported intra-operative problem	No reported intraoperative problem
Overall score			
▪ Mean ±SD	28 ±7.0	27 ±7.1	27 ±6.8
▪ Median (range)	26 (17–46)	25 (17–46)	26 (17–45)

Table 3.9b ▪ Category	Post-operative complication	No post-operative complication
Overall score		
▪ Mean ±SD	30 ±6.8	26 ±6.6
▪ Median (range)	28 (23–46)	24 (17–43)

Table 3.10 Association between task accuracy score and peri-operative complications

Complication ▪ Category of accuracy score	Event rate %	Adjusted Odds ratio	95% Confidence Interval	P value
Reported intra-operative adverse event*				
▪ 0 to 24	25.6	1		
▪ 25 and above	26.5	1.047	0.402–2.731	0.925
Intra-operative adverse event detected by OCHRA				
▪ 0 to 24	32.9	1		
▪ 25 and above	67.1	28.500	3.566–227.801	<0.001
Post-operative morbidity				
▪ 0 to 24	15.8	1		
▪ 25 and above	42.9	4.000	1.415–11.310	0.007
Severe post-operative complication, Clavien-Dindo III+				
▪ 0 to 24	0.0	1		
▪ 25 and above	16.3	1.195	1.056–1.352	0.009
Emergency re-operation				
▪ 0 to 24	0.0	1		
▪ 25 and above	10.2	1.114	1.013–1.224	0.065
Poorer histological outcome§				
▪ 0 to 24	5.4	1		
▪ 25 and above	6.3	1.167	1.185–7.367	1.000

*Surgeon reported intraoperative adverse event on the case reporting form. §Poorer histological outcome refers to the composite outcome of R1 resection, major TME defects and/or rectal perforation.

The accuracy score correlated well with the number of errors and adverse consequences identified during the procedure: Effect size 2.995 (95% CI 2.278–3.711, p <0.001) for error frequency; Effect size 0.528 (95% CI 0.371–0.685, p <0.001) for adverse consequences. The greater number of technical errors and adverse events corresponds to a higher accuracy score. Interestingly, two-team synchronous operating was more likely to achieve a lower accuracy score of <25 with fewer technical errors compared to one-team procedures (lower accuracy score 52.9% vs 16.7%, OR 0.178, 95% CI 0.061–0.519, p 0.001; Mean number of technical errors 43.1 ±25.6 vs 69.5 ±39.9).

3.7 Technical recommendations

The standardised approach to the TaTME procedure published following the international Delphi consensus process for the COLOR III trial[9] outlined the key agreed steps for the operation. The evaluation of OCHRA findings from this study through semi-qualitative interviews and an educational seminar involving an international group of TaTME expert surgeons provides further in-depth review of the technique and more specific error-reducing mechanisms. Technical recommendations have been divided for each phase of the operation.

<u>Pursestring phase</u>

Based on the expert group's own experience and through training others, challenging aspects and how to overcome them during the pursestring phase include:

Challenging aspects	Solutions / technical tips
Set up / Exposure • Inadequate insufflation to create enough wall tension • Access to the upper lateral quadrant	*Set up / Exposure* • Use a high ventilation system, in particular the AirSeal™ System. • The transanal platform needs to be positioned correctly obtaining a round (not oval) aperture if using a flexible platform. A Lonestar will aid exposure and positioning of the platform. • Increase the rectal pressure if necessary, even up to 20 mmHg. • Reduce the abdominal pressure. • Clamp the bowel from above and place a gauze in the rectal lumen to avoid distending the rest of the colon and losing pressure. • Liaise with the anaesthetist to ensure the patient is fully relaxed.

Execution – Instrument handling • Excessive movements with needle holder and mounted incorrectly • Avoiding gaps between stitches • Avoiding spiralling • Ensuring an airtight closure	*Execution – Instrument handling* • Pursestring simulator training • Place diathermy dots to plan accurate stitch placement that avoids spiralling • Pause and check stitch placement after each quadrant is completed • Use a 0-monofilament suture, ideally a smaller 26mm needle. • Do not hesitate to place a second pursestring if necessary, to ensure an airtight closure
Execution – Tissue-instrument interface • Assessing depth for each pursestring bite	*Execution – Tissue-instrument interface* • Sufficient wall tension will lift the tissue while the needle is in the tissue and help prevent catching deeper tissues

For very low tumours, some surgeons perform the rectotomy before closing the rectum with a pursestring. The TaTME expert group recommends:

- Endoluminal pursestring placement before rectotomy will not be feasible for any tumour extending below the puborectal sling
- If feasible always do the pursestring before the rectotomy to avoid pelvic contamination.
- Ensure abundant washout after the rectal lumen is closed if the rectotomy has to be performed before the pursestring.
- Avoid performing such difficult cases early in the learning curve.
- No data currently available to suggest whether this practice should be abandoned.

<u>Rectotomy phase</u>

Based on the expert group's own experience and through training others, challenging aspects and how to overcome them during the rectotomy phase include:

Challenging aspects	Solutions / technical tips
Set up / Exposure • Bleeding can obscure the tissue plane making it difficult to see whether a full thickness rectotomy has been performed.	*Set up / Exposure* • Adequate insufflation needed to obtain good wall tension. • Start the rectotomy at the inferior aspect (5 or 7 o'clock). • Hook tissues towards you rather than pushing them away. • Allow sufficient contact time with the diathermy hook to stop any bleeding.
Execution – Instrument handling • Direction of instrument movements.	*Execution – Instrument handling* • Hook tissues towards you rather than pushing them away to avoid bleeding and obtain full thickness dissection.
Execution – Tissue-instrument interface • Intramural dissection that can lead to rectal tube perforation ± positive tumour margin. • Too little retraction preventing adequate exposure. • Wrong direction of retraction preventing adequate exposure.	*Execution – Tissue-instrument interface* • Avoid starting the rectotomy at the 6 o'clock position where the rectococcygeal ligament is thicker and connected posteriorly; start at either 5 or 7 o'clock. • Always identify full thickness dissection before proceeding circumferentially by identifying fat or striated muscle posteriorly. • Dissect at 90 degrees to the tissue plane. • Initial retraction can be provided by holding on to the knotted suture. However, once an opening is created retraction of the full thickness bowel close to the dissection line can create more tension and expose the underlying tissue better. • Two handed operating: use a grasper to retract the tissue and the hook to dissect. • Re-do the pursestring if it's distorting the tissues, e.g. if spiralled.

TME dissection phase

Based on the expert group's own experience and through training others, challenging aspects and how to overcome them during the TME phase include:

Challenging aspects	Solutions / technical tips
Set up / Exposure • Identification of the correct plane	*Set up / Exposure* • Facilitate the optimal exposure by ensuring a full thickness circumferential rectotomy before starting TME dissection. • Identify landmarks: Pelvic fascia/sling and rectococcygeal ligament posteriorly, rectourethral muscle in males anteriorly. • Limit any bleeding as much as possible as this will obscure the planes.
Execution – Instrument handling • Excessive and forceful movements with the cautery device. • Poor camera positioning. • Clashing of instruments.	*Execution – Instrument handling* • Use of monopolar cautery (hook or spatula) recommended rather than an energy device • Hook small bites of tissue with short bursts • Perform mainly sharp dissection with gentle blunt dissection to guide and identify the plane • Regularly clean the hook to ensure proper cautery. • Avoid using a 0-degree laparoscope as the scope needs to remain on the opposite side (out of the way) to the working instruments and use the tilting lens/articulation to focus on the point of interest. • Frequent communication between operating surgeon and camera assistant to work more efficiently together.
Execution – Tissue-instrument interface • Dissecting along the correct plane	*Execution – Tissue-instrument interface* • Allow a degree of penumodissection by the

• Too little retraction • Wrong direction of retraction • Uneven cylindrical dissection	insufflation to filter through the plane and expose angel hair. • Accurate anterior and posterior delineation of the dissection planes will help identify the correct lateral plane. • To obtain adequate traction with the grasper the insufflation pressure needs to maintain a good wall tension to provide counter-traction. • Grasping the tissue closer to the line of dissection can also improve retraction. • Ensure that the direction of traction by the grasper is opposite to the counter-traction created by the insufflation pressure. • Regularly pause, pull back the camera and get an overview of the anatomy to ensure the correct dissection plane is being followed. • Progress with dissection in a cylindrical circumferential manner to avoid distorting the specimen and anatomy.

Connected phase

Based on the expert group's own experience and through training others, challenging aspects and how to overcome them during the connected phase include:

Challenging aspects	**Solutions / technical tips**
Set up / Exposure • Limited view due to camera position – usually too far away from point of interest • Uneven pressures between abdominal and transanal teams causing bellowing.	*Set up / Exposure* • Approach the dissection from whichever end has the optimal exposure, abdominally or transanally, or together if feasible. • Stop the abdominal insufflation which will be supported by the transanal insufflation system.

Execution – Instrument handling
- Excessive and forceful tissue handling leading to specimen trauma, especially if a bulky mobile specimen

Execution – Instrument handling
- Review the MRI scan before starting the procedure and estimate the most feasible point of connection between the two teams.
- A gauze placed transanally can help retract a heavy specimen protecting it from traumatic handling.
- If the specimen becomes too long and heavy to handle transanally aim to complete the dissection from above.

Execution – Tissue-instrument interface
- Avoid conflicting directions of traction between the abdominal and transanal team.
- Specimen tilted, distorting the anatomy leading to dissection along the incorrect plane.

Execution – Tissue-instrument interface
- Frequent communication between the abdominal and transanal teams to work efficiently and safely together.
- Approach the dissection from whichever end has the optimal exposure, abdominally or transanally, or together if feasible. One team can help retract for the other facilitating more accurate dissection.
- Regularly re-assess the plane and direction of dissection both abdominally and transanally to meet along the same plane.
- Continue to maintain a cylindrical circumferential dissection even once connected.

3.8 Study Reliability

The inter-rater reliability between the TaTME expert (RH) and PhD research fellow (MP) was determined for the overall error scoring, consequence (adverse event) scoring and the task accuracy scoring. Results showed an excellent level of agreement with the following interclass correlation coefficients (ICC):

- Scoring errors 0.841 (95% CI 0.598–0.937, p <0.001),
- Scoring adverse consequences 0.923 (95% CI 0.808–0.970, p<0.001),
- Task accuracy scoring 0.908 (95% CI 0.725–0.966, p<0.001).

The test-retest reliability also showed a high level of agreement with the following interclass correlation coefficients (ICC):

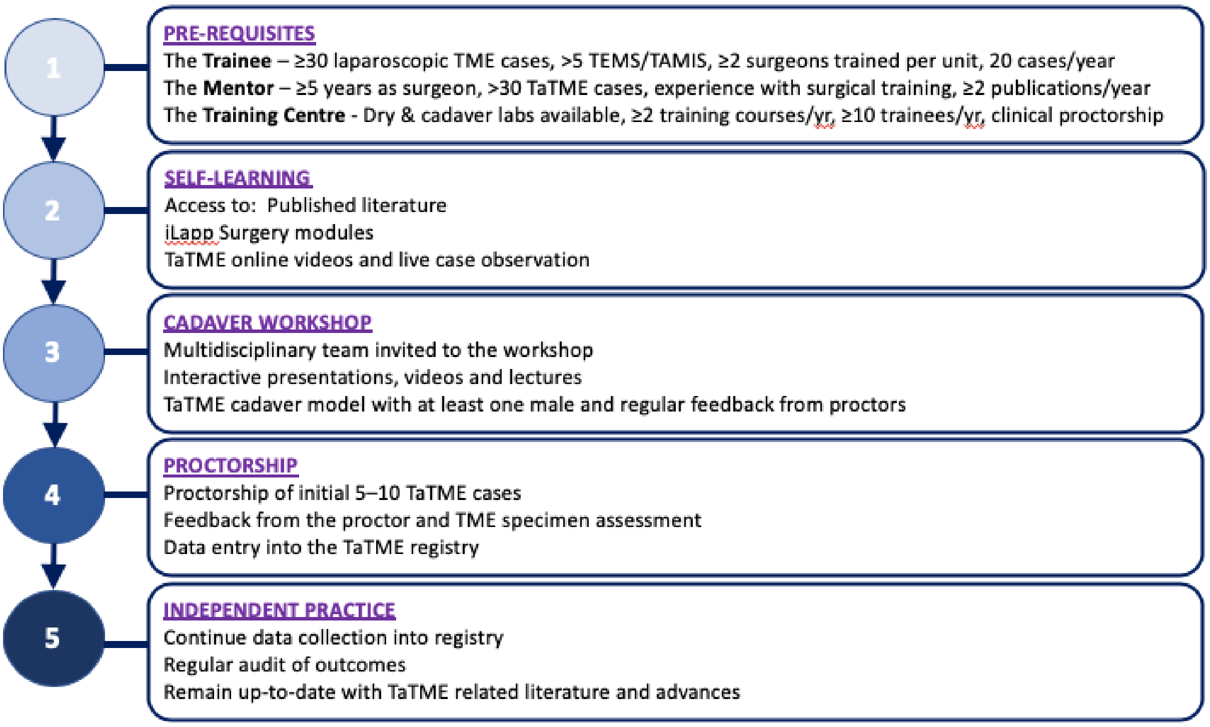
- Scoring errors 0.991 (95% CI 0.978–0.997, p <0.001),
- Scoring adverse consequences 0.994 (95% CI 0.980–0.998, p<0.001),
- Task accuracy scoring 0.995 (95% CI 0.989–0.998, p<0.001).

4. National TaTME Training Programme

4.1 Introduction

The launch of a national pilot TaTME training programme was announced in the UK in May 2017; endorsed by the Association of Coloproctology of Great Britain and Ireland (ACPGBI). Its development involved a three-phase consensus process involving overall 207 surgeons across 18 different countries with a core working group of 52 international experts in TaTME and education.[12,13] This background work and planning generated an agreed structured training pathway that provides the acquisition of both cognitive knowledge (e.g. pelvic anatomy, equipment used, procedural steps) and technical proficiency in TaTME. The pathway involves five distinct steps outlined in figure 3.5: (1) Recommended pre-requisites to learning TaTME, (2) Self-learning by online educational resources, TaTME apps and case observation, (3) Cadaver workshop, (4) Proctorship phase of initial live cases, and (5) Independent practice with continuous data collection on the international TaTME registry[14] and auditing of outcomes. Global Assessment Scoring (GAS) forms[12] adapted from validated forms used for the national laparoscopic colorectal training programme (LAPCO)[15] were used to monitor the trainee's progress during their proctored cases. Final sign off for approved independent practice was assessed using a Competency Assessment Tool (CAT)[9] specifically designed for TaTME and used to determine surgeon eligibility to take part in the COLOR III randomized controlled trial. With the aim of enhancing individual learning and feedback even further which could then improve subsequent technical performance, we planned to develop a method to incorporate OCHRA into the training programme.

Figure 3.5 Five steps of the national TaTME training programme



4.2 Methods

Proctors and trainees recruited for the first national TaTME training programme involving five UK hospitals were introduced to OCHRA during the cadaver workshop in October 2017. The rationale and principles of OCHRA were explained as well as the interim results from the initial 50 TATME videos analysis. Practice video clips during which trainees were asked to identify any errors were discussed and error-reducing mechanisms recommended by the interviewed TaTME experts were presented. This provided the participants with an understanding of the OCHRA process and how the error-reducing mechanisms were derived.

During the proctorship phase, we planned to collect TaTME videos of consecutive cases from each participating surgeon, perform OCHRA and develop an OCHRA reporting form to feedback to the individual surgeons prior to their next proctored case. The OCHRA reporting form would highlight any key technical inaccuracies/errors and adverse events that occurred during the operation, followed by recommended error-reducing mechanisms and technical tips to improve and overcome these errors (Figure 3.6a&b). The reports would be provided in between each case in order to allow the training surgeon time to reflect on the advice given and, if possible, practice any relevant steps on the bench-top simulated model. Regular feedback from the trainee and mentor regarding the OCHRA report was sought in order to further improve the layout and content of the form. This feedback was discussed during research meetings with my PhD supervisors and amendments to the OCHRA reporting forms made.

4.3 Results

The OCHRA reporting form (Figure 3.6a) was initially designed by the PhD student with input by the supervisors and a clinical psychologist with experience in education and feedback methodology. Feedback from trainees and mentors was very positive as they found it easy to follow and containing useful detailed tips on how to improve their technique (Figure 3.7a&b). The form underwent two modifications following feedback from the TaTME programme participants. Modifications involved the addition of the GAS scoring and time intervals on the videos during which the technical error/adverse event occurred. This could then enable the trainee to review the specific section on the video clip in question, to further understand and enhance their learning as well as discuss the technique in more detail. Figure 3.6b gives an example of the form completed following a trainee's first proctored case.

The main difficulty encountered involved logistically setting up the video transfer system from the surgeons' local hospital to the Imperial College online safe weblink. Due to NHS security and privacy policies, the information technology teams had to grant access and download the "Filezilla" programme on the NHS computer in order to allow the upload and transfer of videos. If a direct link between the laparoscopic stack system and the NHS computer was not available, surgeons had to download the video files from the stack onto an external hard drive and then upload them onto the computer. All of which took considerable time and organisation, leading to delays in video transfer and subsequent OCHRA feedback. Only three videos from two hospitals were actually received at the optimal time allowing OCHRA to be performed and a completed OCHRA reporting form returned to the surgeon prior to their next case. The remainder of the TaTME videos were received in blocks of two or more together, thus feedback was provided for the set of cases.

Figure 3.6a Observational Clinical Human Reliability Analysis reporting form
OCHRA: Observational Clinical Human Reliability Analysis, GAS: Global Assessment Score, TME: Total Mesorectal Excision

Transanal Total Mesorectal Excision
Observational Clinical Human Reliability Analysis

A. CASE DETAILS

A.1. Case number:
A.2. Date of operation:
A.3. Hospital:
A.4. Lead Transanal surgeon:
A.5. Name of mentor:

B. OCHRA findings:

		OPERATIVE PHASE			
		Pursestring	**Rectotomy**	**TME dissection**	**Connected phase**
GAS	**Overall GAS score** Trainee: Mentor:				
OCHRA	**Most frequently occurring technical inaccuracy**				
	Number of consequences / adverse events				
	Most frequent and serious consequences encountered				

C. Suggested Error-Reduction Mechanisms:

1.
2.
3.

Figure 3.6b Example of completed Observational Clinical Human Reliability Analysis reporting form following a TaTME proctored case

OCHRA: Observational Clinical Human Reliability Analysis, GAS: Global Assessment Score, TME: Total Mesorectal Excision

Transanal Total Mesorectal Excision
Observational Clinical Human Reliability Analysis

A. CASE DETAILS

A.1. Case number: **1**
A.2. Date of operation: XX / 11/ 2017
A.3. Hospital: XXX
A.4. Lead Transanal surgeon: XXX
A.5. Name of mentor: XXX

B. OCHRA findings:

		OPERATIVE PHASE			
		Pursestring	**Rectotomy**	**TME dissection**	**Connected phase**
GAS	**Overall GAS score** Trainee: Mentor:	2 3	4 4	2 2	2 2
OCHRA	**Most frequently occurring technical inaccuracy**	- Excessive repeated movements, in particular, with regards to mounting the needle. - Too much suture pulled through, getting caught up in needle. - Deep bite, 7 o'clock, pulling in pelvic floor. - Subsequent clashing between instruments and camera.	- Inadequate insufflation and bowel distention. - Dirty diathermy hook leading to inadequate haemostasis. - Full thickness plane obtained but not continued circumferentially.	- Too little retraction or in the wrong direction. - New incorrect planes created, mostly too wide, particularly lateral pillars and anteriorly. - Dark view due to camera position	- Too forceful retraction of the specimen. - Inaccurate 'dabbing' with the hook diathermy slowing down progress and creating new incorrect planes.
	N. of adverse events	1	8	8	2
	Most frequent and serious consequences encountered	Second pursestring required as gap left in first. Bite size and intervals appeared adequate, but likely to have become loose whilst tying.	Bleeding from rectotomy edge due to dirty diathermy hook and insufficient wall tension.	Bleeding from left lateral pillar and anteriorly due to incorrect dissection plane (too wide).	Specimen trauma by forceful retraction.

C. Suggested Error-Reduction Mechanisms:

1. Regular practice on pursestring simulator to improve efficiency of needle positioning and manoeuvrability in a tight space.

2. Increase the Airseal pressure (even up to 20mmHg) until adequate tension is obtained before the rectotomy, which can then be reduced to

12-15mmHg for the TME dissection. Do not start any TME dissection until full thickness rectotomy completely circumferentially.

3. Aim for a more structured sequence of dissection (posterior-anterior-lateral) cylindrically. Review published TaTME videos to improve

pattern recognition and identification of the correct dissection plane.

4. Make use of a small gauze (or mastoid swab) to help obtain a broader retraction and protect the specimen during TME dissection.

Figure 3.7a Trainee feedback on OCHRA reporting form
OCHRA: Observational Clinical Human Reliability Analysis, TaTME: Transanal Total Mesorectal Excision

Transanal Total Mesorectal Excision
OCHRA Report TRAINEE Feedback Form

A. CASE DETAILS
A.1. Case number:
A.2. Date of operation:
A.3. Hospital:
A.4. Lead Transanal surgeon:
A.5. Name of mentor:

B. OCHRA FEEDBACK

B.1. **Were the findings of the OCHRA report in a format that was easy to follow?**

No, not at all easy to follow		Fairly easy		Yes, very easy to follow
1	2	3	4	5

B.2. **Were the error-reducing mechanisms clearly explained?**

No, not at all clear		Fairly clear		Yes, very clear
1	2	3	4	5

B.3. **Did the OCHRA report reflect your own opinion of how the case went, including any adverse events that occurred?**

No, completely disagree		Fairly agree		Yes, completely agree
1	2	3	4	5

B.4. **Did the suggested error-reducing mechanisms influence the performance of your subsequent TaTME case?**

Yes **No**

If yes, in what way?

____

____

B.5. **Any suggestions to improve the content and/or format of the OCHRA report?**

____

Figure 3.7b Mentor feedback on OCHRA reporting form
OCHRA: Observational Clinical Human Reliability Analysis, TaTME: Transanal Total Mesorectal Excision

Transanal Total Mesorectal Excision
OCHRA Report MENTOR Feedback Form

A. CASE DETAILS
A.1. Case number:
A.2. Date of operation:
A.3. Hospital:
A.4. Lead Transanal surgeon:
A.5. Name of mentor:

B. OCHRA FEEDBACK

B.1. **Were the findings of the OCHRA report in a format that was easy to follow?**

No, not at all easy to follow		Fairly easy		Yes, very easy to follow
1	2	3	4	5

B.2. **Were the error-reducing mechanisms clearly explained?**

No, not at all clear		Fairly clear		Yes, very clear
1	2	3	4	5

B.3. **Did the OCHRA report reflect your own opinion of how the case went, including any adverse events that occurred?**

No, completely disagree		Fairly agree		Yes, completely agree
1	2	3	4	5

B.4. **Did the OCHRA report form influence your way of proctoring? If yes, please describe how?**

____

____

____

____

B.5. **Any suggestions to improve the content and/or format of the OCHRA report?**

____

____

4.4 Discussion and future work

A survey conducted by the ACPGBI identified TaTME as the top-educational need priority desired by consultant surgeon members.[16] This stimulated and encouraged the development of the national TaTME training programme in the UK, which was the first published project to provide a cohesive and internationally agreed training pathway for this technique.[12,13] The understanding that gaining surgical competence is a complex and multifactorial process has been demonstrated in the past, in particular with regards to the introduction of laparoscopic surgery in the 1990s.[17] Initial poor attempts by ill-prepared surgeons lacking appropriate training soon became apparent with rates of intra-operative complications rising to unacceptable levels; such as the fivefold increase in common bile duct injuries during laparoscopic cholecystectomy.[18] Raising serious concerns, acknowledged by the British government, led to the funding and development of the mandatory national laparoscopic training programme, LAPCO.[19] The benefits of simulation-based training with models and cadavers, as well as the vital role of proctorship during live cases soon became apparent enabling a safer and more controlled introduction of a new technique.[20]

Similarly, the national TaTME training programme adopted a multi-faceted approach to training recognising the value of each component and placing a big emphasis on proctorship. Experience and lessons learnt from members of the steering group who had organised TaTME cadaveric workshops and other training courses were also implemented, such as the importance of team training of two surgeons together with their scrub team, the preferential use of male cadavers, use of bench-top pursestring models for repeated practice prior to the cadaveric sessions and the immediate expert feedback on technique and TME specimen quality.

The potential use of OCHRA within the national TaTME training programme was explored and an OCHRA reporting form designed. The plan envisaged in order to implement OCHRA into training involved analysing and providing feedback with error-reducing mechanisms in between each consecutive proctored case. This was perceived to be the most effective way of providing detailed bespoke feedback to enhance the surgeons training experience and potentially improving their learning curve. The feedback received from the trainees and mentors regarding the OCHRA reporting form was very positive. However, due to primarily logistical problems with installing computer software and transfer of videos in a timely manner the proposed plan did not occur for most of the cases. Subsequently, feedback on the contents and format of the OCHRA reporting form was not obtained from all participants.

Moving forward, during future TaTME training programmes the video transfer system must be established prior to commencing the live proctored cases in order to avoid delays. More constructive feedback from the whole group of trainees and mentors can then also be obtained to improve the OCHRA reporting form further. Potential correlations between OCHRA findings and both GAS results and CAT outcomes may be possible with a full set of analysed cases. The individual surgeon's proficiency-gain curve can also be plotted using the OCHRA results.

At present OCHRA remains very much a research tool rather than an easy quick method accessible to a busy clinical practice. It necessitates considerable time to complete the analysis and a certain level of understanding and experience in both the procedure being analysed and how to conduct OCHRA. Future work is needed on automation of OCHRA with the use of artificial intelligence and machine learning. This will allow the implementation of OCHRA into routine clinical practice as a detailed, useful and reproducible method of individualised case feedback that can lead to more effective learning and enhance surgical performance.

5. Discussion

OCHRA methodology provided a detailed and systematic manner in which to analyse the new TaTME technique. The findings led to the categorisation of technical errors into three distinct groups including set up, instrument handling and tissue-instrument interface errors. They also generated the new concepts of error pathways and surgeon specific procedure mapping. The patient and tumour characteristics of the cohort studied included a majority of male overweight patients with low rectal tumours and approximately 50% having received neo-adjuvant therapy. These features closely reflect patient selection and the indications for TaTME adopted in current practice and in the published literature, suggesting external validity to the population studied.[21–23]

In total, 5,101 technical errors and 904 adverse consequences were annotated in 100 TaTME cases, with a mean of 51 technical errors and 9 adverse consequences per case. For comparison, Foster et al.[24] identified a total of 335 execution errors with a median of 15 per operation in 20 laparoscopic rectal cancer resections. The commonest error described was dissection in the wrong tissue plane, with 299 of the execution errors leading to a directly observed consequence, especially mesorectal injury into fat. More errors were observed during the pelvic phase of the procedure compared to the abdominal. The transanal phase of TaTME is all performed in the pelvis and perineal region which are known to be the more complex areas to operate on, due to its intricate anatomy and spatial restraint limiting exposure and working space.

The set-up of the transanal platform and insufflation system are critically important to ensuring good exposure and optimal visualisation of the operating field. In this transanal procedure, standard insufflation does not appear to achieve a safe working field with adequate exposure, and consequently leads to an increased risk of intra-operative complications. However, it's important to note that even with the newer insufflation systems, such as AirSeal™ System (CONMED, Utica, NY, USA), surgeons still need to understand and know how to create the optimal settings in order to achieve the desired wall tension and visual field needed. Subsequently, interpretation of the anatomy and identification of the correct dissection plane should become clearer. The most frequently encountered tissue-instrument interface error was wrong dissection plane surgery. Too little retraction of the tissues to help reveal the dissection line is likely to have been a leading cause to the inability of identifying the correct plane. Furthermore, the surgeon's level of experience in TaTME and familiarity of the anatomy "bottom-up" are important contributing factors to knowing how to create the optimal exposure and recognising the correct plane.

Increased operative experience has also been shown to improve the economy of movements as well as operative time and frequency of technical errors.[25] Excessive movement of instruments was the most frequent instrument handling error identified in this TaTME cohort. This was noted for both the operating surgeon and the assistant holding the laparoscope and may be due to surgeons operating during the earlier phase of their learning curve. Unfortunately, the surgeon's case volume and which case number they submitted for the study was not recorded. The team approach, as either one single team moving between abdominal and transanal phases or two teams operating synchronously, was noted and the OCHRA findings appear to support the two-team approach showing that it results in fewer visceral injuries and an overall lower accuracy score (i.e. better technical performance). Likely reasons for this are the increased fatigue and reduced concentration when having to perform the whole procedure solo, as opposed to the collaboration and co-ordination of two teams that can help each other through the procedure and each surgeon primarily concentrate on the 'top' or 'bottom' parts.

The surgeons were also asked to report on the case reporting form whether they had encountered any intra-operative adverse event. It is interesting to see that the participants only recorded intra-operative complications for 23 cases, whereas OCHRA identified an adverse consequence in 85 cases. Such a discrepancy may be due to the surgeon not recalling the event at the time of completing the form or not considering it as a serious enough event to report. Alternatively, the surgeon may not actually have recognised the error and adverse event committed. This potentially highlights how much information and learning points can be gained by watching and closely reviewing an operative video rather than relying on memory and recall at the end of the case. Such benefits of video-analysis have been shown in other types of surgery too and is an important component of training.[26] A good example from this cohort of videos is the incidence of pursestring failure: 8 events reported by the surgeons compared to 26 identified during OCHRA. In 18 cases the pursestring failed at the beginning of the procedure during or immediately after its placement and was replaced, thus unlikely to have any major consequence other than increasing the operative time. However, in 5 cases the pursestring was placed but left a central hole which was not closed off before proceeding to the rectotomy and in 3 cases the pursestring failed during TME dissection. In all 8 cases there is a substantial risk of spillage of luminal contents with both bacteria and tumour cells that increase the risk of subsequent pelvic sepsis and, potentially of local recurrence. Furthermore, in 23% of procedures an adequate washout before performing the rectotomy was not carried out, again increasing the risk of tumour cell and bacterial contamination. The operating surgeons may not have been aware of leaving a hole or were happy to accept it without knowing the potential negative consequences. Hence, initial appropriate training and then review of operative videos ideally with a more experienced TaTME surgeon are likely to promote improved and safe operative performance. Further, these technical factors or steps may appear small but actually become very important when concerns over high local recurrence rates are raised and the technique is brought into question.[27] Correlation between pursestring failure and inadequate washout with local recurrence would be an interesting future aspect to investigate.

The study did identify an association between increased number of technical errors and post-operative morbidity, especially of more serious complications (Clavien-Dindo III+). Similarly, an accuracy score above 24 significantly increased the likelihood of having a post-operative complication, as well as an intra-operative adverse event. Thus, implying that a technically well performed operation with minimum errors gives the patient a better chance of making a good uneventful post-operative recovery.

Albeit being a very detailed and informative piece of work, there are limitations to this OCHRA study. These include the termination of the video recording once the rectum was fully mobilised and not assessing the anastomotic technique. This could have provided important technical details of how best to create an anastomosis. However, this would have required an additional person to record externally and may not have captured the procedure closely enough, making the analysis incomplete and an under-estimation of the actual error count. OCHRA was also not performed for the abdominal component of TaTME which can also contribute to overall intra- and post-operative morbidity. However, the abdominal component derives from an established TME practice as opposed to the new transanal approach. The main aim of this project was to gain a better understanding of the transanal technique and how to achieve the best technical performance in the ‘bottom-up’ approach. Additional datapoints could have been collected such as the case volume for each surgeon to appreciate at which stage of the learning curve they have reached. However, this can form part of a future study as well as investigating potential technical risk factors that may contribute to local recurrence.

6. Conclusions

In conclusion, this OCHRA study of TaTME has provided valuable insight and a deeper understanding of how this latest technique for rectal resection is being performed. It has identified a vast range of technical errors and adverse consequences that can occur as well as developing an accuracy score specific to TaTME and the new concepts of error pathways and surgeon specific procedure mapping. A higher rate of technical errors and overall accuracy score of >24 were significantly associated with post-operative morbidity, especially the more severe Clavien-Dindo III+ complications. Review of the OCHRA findings with an expert panel of TaTME surgeons has generated detailed error-reducing mechanisms and technical recommendations that can be a valuable resource for any surgeon training in and performing TaTME.

7. References

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CHAPTER IV

CONCLUSIONS & FUTURE WORK

What are the next steps to undertake following this work?

1. Conclusions and future work

A surgical mentor and superb colorectal surgeon once told me that "surgical innovation is born out of necessity or boredom". The poor outcomes seen in low rectal cancer surgery drove the motivation and eagerness to find an alternative approach to tackle the problem. TaTME therefore arose from a necessity with the aim of improving both oncological and functional outcomes in rectal cancer surgery. The pioneers and early adopters spent several years strategizing, trialling and refining the technique in the laboratory prior to the first clinical live case in 2009.[1] The initial idea and development phase of TaTME closely follows the recommendations set out by the IDEAL framework on how best to develop and implement a new technique.[2] At the time when the number of early adopters was increasing, the international TaTME registry was set up with the aim of capturing the rapidly evolving TaTME practice and monitoring its outcomes.[3] A wave of enthusiasm, interest and possibly fear of missing out on the latest surgical technique, led to a fairly uncontrolled rapid uptake of the new approach worldwide with fairly limited regulation by governing bodies. The availability of appropriate training and proctorship, especially in the form of a structured training programme, lagged behind.

Initial outcomes from early adopters and the international TaTME registry were very promising from a clinical and histological point of view.[4-6] However, over time several concerns have arisen shedding a more cautious light on the technique. Namely, the occurrence of urethral injuries[7] and carbon dioxide embolus[8]; both of which appear to have an incidence of <1% but is still greater than that seen from the abdominal approach. Most recently, the alarmingly high rate and multi-focal pattern of local recurrence reported in Norway has led to the suspension of the technique in the country.[9]

Although valuable information can be gathered from analysing surgical outcomes, an in-depth understanding of the actual technique, why technical errors occur and how they can lead to the outcomes seen is of even greater value, especially when the technique is new. OCHRA was able to provide a detailed analysis of TaTME following a systematic and validated methodology. The OCHRA study brought together a panel of TaTME experts to generate precise error-reducing mechanisms and technical recommendations which will hopefully be a valuable resource to surgeons learning the procedure.

The registry-based outcomes and OCHRA findings have also highlighted future areas of research as well as a possible way of incorporating OCHRA into a national TaTME training programme. The next study planned using registry data will investigate the two-year oncological outcomes including local recurrence rate, disease free survival and overall survival following TaTME for primary rectal cancer resections with curative intent. Performing OCHRA on videos of cases that have developed local recurrence may provide further guidance and evidence as to the underlying contributing technical causes, such as pursestring failure or inadequate rectal washout currently hypothesized.

Another aspect requiring further assessment is the functional outcome and quality of life of patients undergoing TaTME. This is particularly important given that, according to the OCHRA findings, the most common visceral injury affected the neurovascular bundles especially in male patients. The TaTME registry does have a whole section dedicated to quality of life and functional data using well established and validated questionnaires. Results from which still need to be explored.

The OCHRA method currently is very much a research tool being a very labour intensive and time-consuming process. Automation of OCHRA by artificial intelligence would greatly increase its usability and implementation into the clinical and educational setting. It can also be applied to any surgical technique from different specialties as well as incorporated into surgical trainees' (residents) training programme.

The aim of this PhD thesis was to assess the safety and efficacy of TaTME. Since all procedures pose a degree of risk, "safety" can be defined as a level of harm/morbidity associated with a new technique that is acceptable when compared to its traditional approaches, whilst "efficacy" is the ability to produce a desired or intended result. Based on the rationale for developing TaTME, the extensive pre-clinical laboratory work-up and the findings from both the registry and OCHRA data presented in this thesis, I do believe that TaTME can be safely and effectively performed in rectal cancer patients. However, the two biggest factors that will influence the technique's success are appropriate patient selection and an experienced well-trained surgical team. TaTME is not an easy technique, which is then also being applied to some of the most challenging cases of rectal cancer that are already historically associated with poorer outcomes. Therefore, the risk of error is high. For these reasons, TaTME requires significant training, dedication and experience; it is therefore more likely to produce favourable outcomes if centralised to a few specialised centres that can build their experience with a greater case volume and ensure appropriate resources are available.

Although the registry-based studies described in chapter two shed some light on the current worldwide practice and outcomes of TaTME, the main limitation that brings caution when interpreting the results is the lack of data validation. This was not possible due to the international level of participation and the voluntary nature of the data collection. The sense of being "policed" may well have lost many participants. In the UK, NICE guidelines recommend adding data to the international registry,[10] however, this is not necessarily seen as a compulsory requirement and does not always happen in practice. To overcome these problems with data validation and interpretation, I believe that tighter control and monitoring of the introduction of any new technique into clinical practice is crucial, with mandatory data collection. An established colorectal association or royal college should undertake the responsibility of overseeing the whole process and regularly reviewing the data outcomes to provide insight and recommendations on various aspects related to the technique. Surgeons adopting the new procedure must inform the responsible body, undergo training, collect accurate data on all consecutive cases and expect to be externally audited at regular intervals. This process will achieve more robust data that will allow better interpretation of reliable results and a greater understanding of the true benefits and risks of a technique.

In conclusion, the development and safe implementation of a new technique such as TaTME requires extensive work, regular monitoring and structured early training. Greater understanding of the technique and how it can influence outcomes is very valuable information that can strengthen the training of the technique. TaTME, in well trained hands, does have the potential to overcome barriers encountered abdominally in TME surgery and results from severely RCTs are eagerly awaited.

2. References

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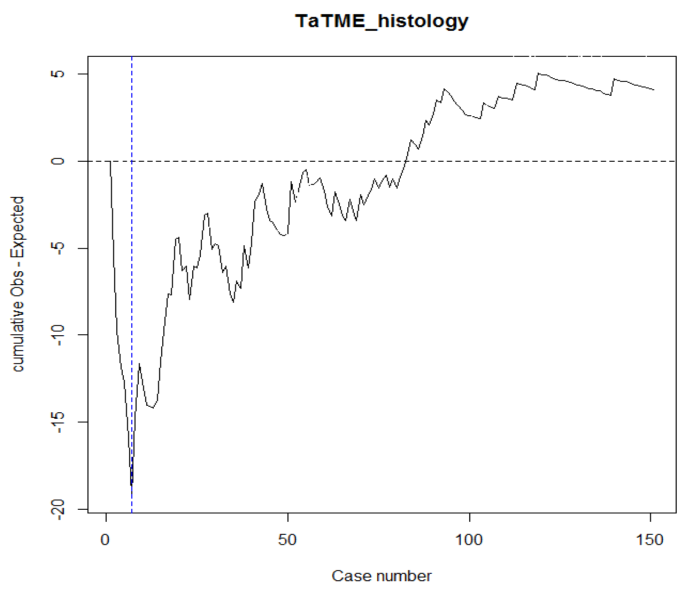
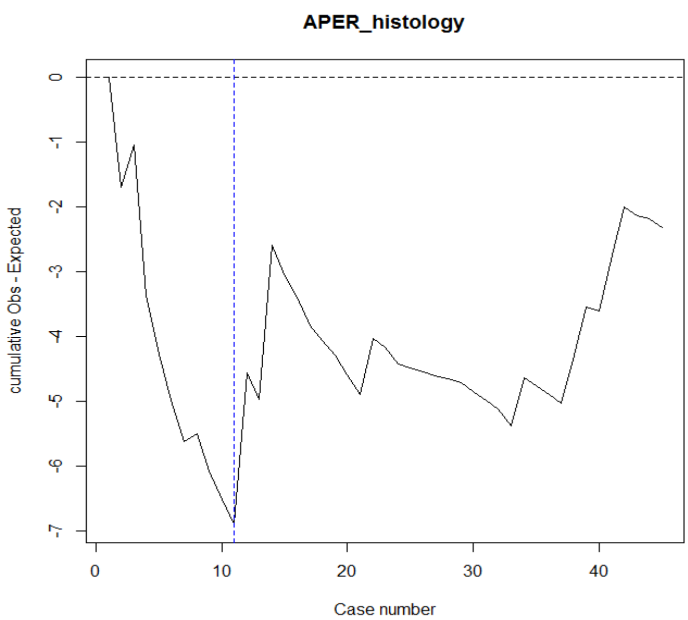
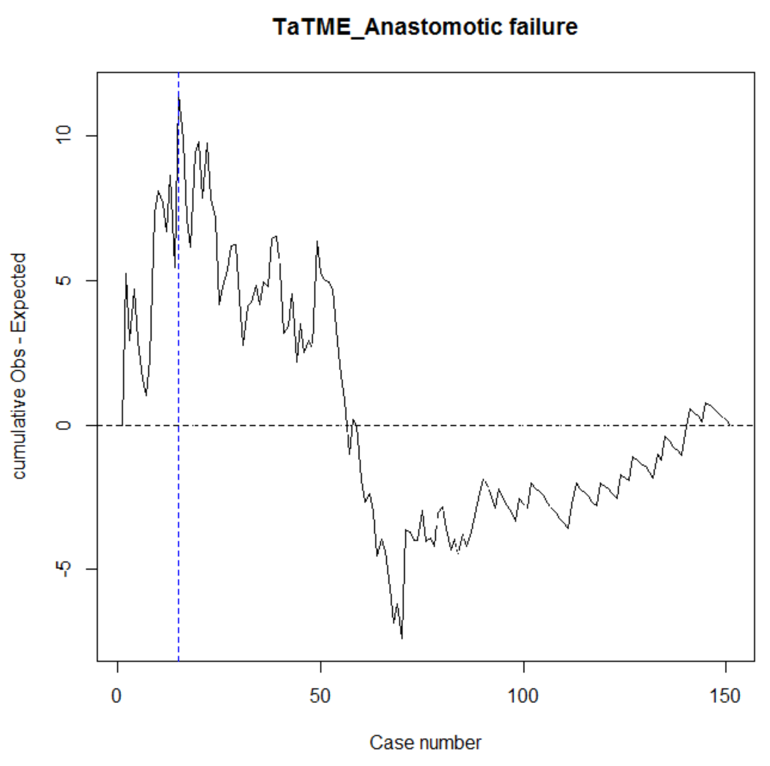
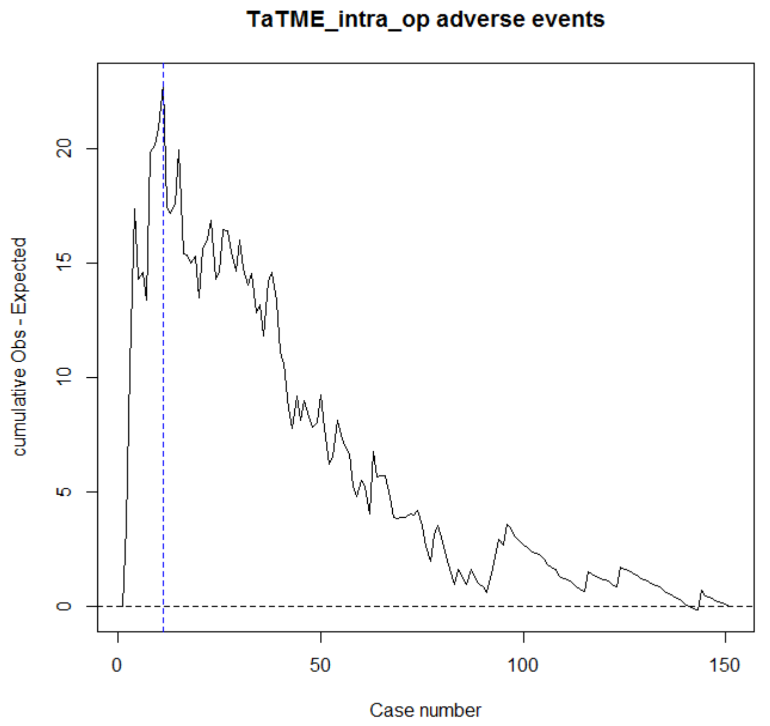
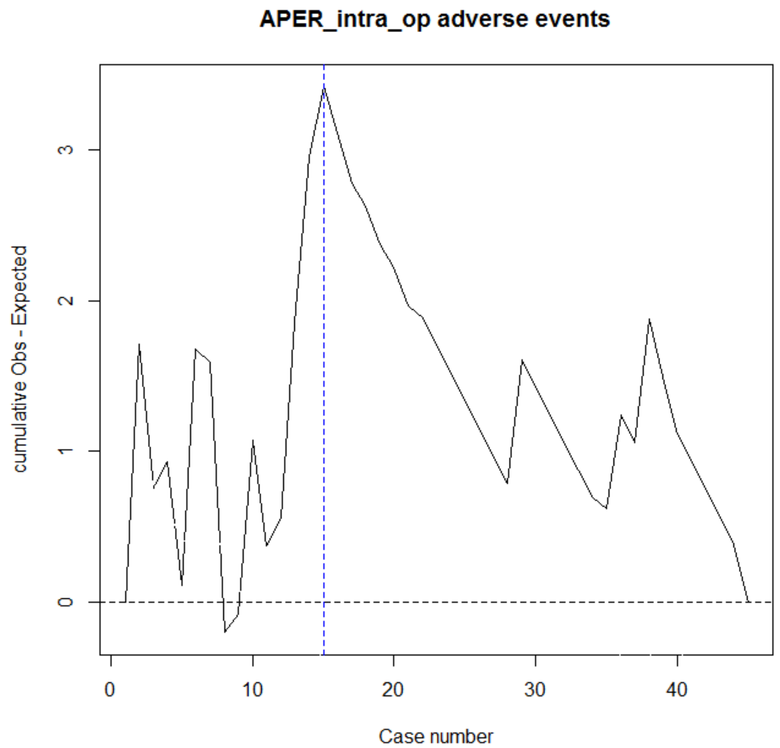
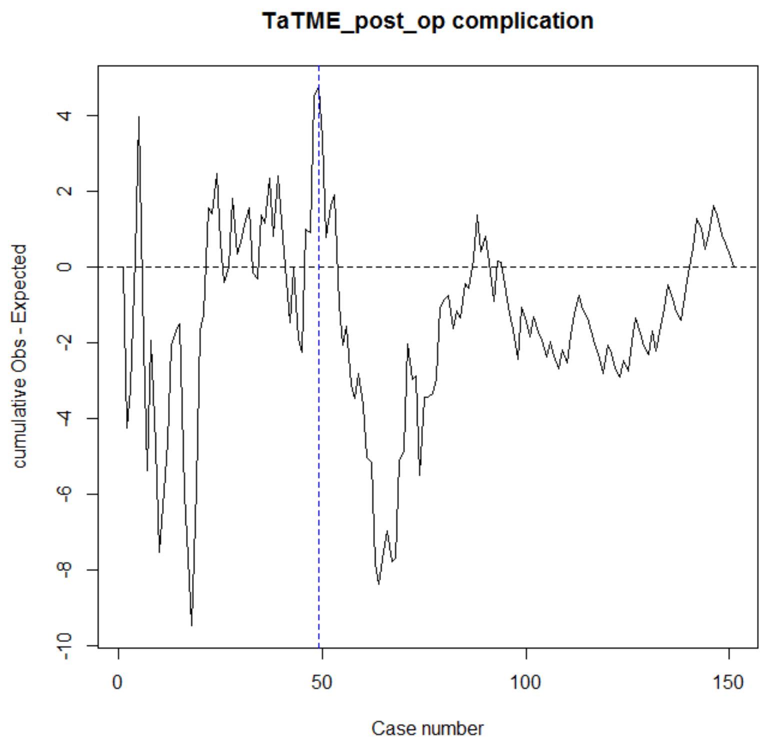
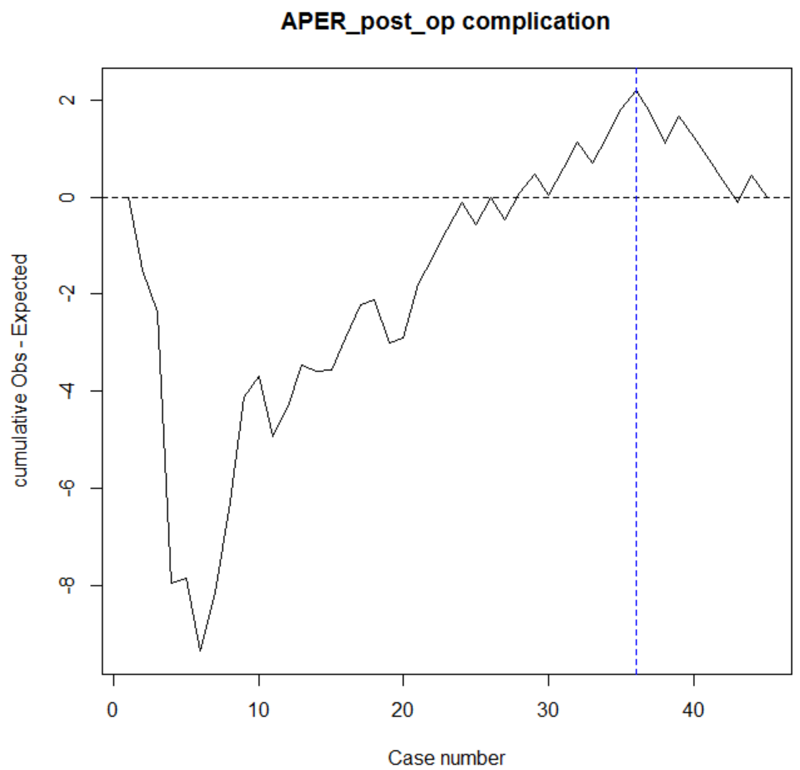
Appendices

Appendix 1. Bootstrapping results for proficiency gain curves (Chapter II)
Bootstrapping 5000 times to determine whether the change identified is random, threshold level set at 95%
Confidence level > 95% => significant change is real.

	**Poor histological outcome – Restorative cases** Change point = Case 7 Confidence level from bootstrapping 5000 times 99.9%
	**Poor histological outcome – APE cases** Change point = Case 11 Confidence level from bootstrapping 5000 times 99.9%

	**Anastomotic failure – Restorative cases** Change point = Case 15 Confidence level from bootstrapping 5000 times 95.2%

	**Intra-operative adverse event – Restorative cases** Change point = Case 11 Confidence level from bootstrapping 5000 times 98.1%
	**Intra-operative adverse event – APE cases** Change point = Case 15 Confidence level from bootstrapping 5000 times 82.3%

	**Post-operative complications – Restorative cases** Change point = Case 49 Confidence level from bootstrapping 5000 times 74.2%
	**Post-operative complications – APE cases** Change point = Case 36 Confidence level from bootstrapping 5000 times 99.8%

Appendix 2. Classification of errors and adverse events

Code	Error / Event
1	**Retraction error**
1.1	Too much retraction
1.2	Too little retraction
1.3	Wrong direction of retraction
2	**Dissecting plane error**
2.1	New incorrect plane created across planes
2.2	Dissection along a wrong plane
3	**Grasper movement**
3.1	Excessive, disorganized movement
3.2	Excessive repeated movement
3.3	Too little movement
3.4	Too forceful
3.5	Too far/overshot
3.6	Wrong direction
3.7	Wrong point in space
3.8	Clashing of instruments/camera
3.9	Other
4	**Energy device movement**
4.1	Excessive, disorganized movement
4.2	Excessive repeated movement
4.3	Too little movement
4.4	Too forceful
4.5	Too far/overshot
4.6	Wrong direction
4.7	Wrong point in space
4.8	Other
5	**Camera movement**
5.1	Excessive, disorganized movement
5.2	Excessive repeated movement
5.3	Too little movement
5.4	Too forceful
5.5	Too far/overshot
5.6	Wrong direction
5.7	Wrong point in space
5.8	Other
6	**Instrument Change**
6.1	Different graspers
6.2	Different energy device

6.3	Other
7	**Visual Field**
7.1	Excessive smoke
7.2	Excessive bellowing
7.3	Inadequate insufflation/bowel distention
7.4	Limited view for other reason – specify
8	**Consequence**
8.1a	Bleeding – no action
8.1b	Bleeding – action required
8.2	Rectal wall haematoma
8.3	Intramural dissection
8.4	Rectal perforation
8.5	Failure of pursestring during procedure
8.6	Tumour manipulation/trauma
8.7	Mucosal trauma
8.8	Specimen trauma
8.9	Other
9	**Other event**

Appendix 3. Task Accuracy Scoring

Code	Task	Task Outcome
A B	**Pursestring placement** Identification of tumour	1. Tumour is clearly visualised or is too proximal to visualise and the pursestring is placed ≥1cm distally. 2. The pursestring is placed less than 1cm distal to the tumour. 3. The pursestring is placed through the tumour. 4. The pursestring is placed proximal to the level of the tumour.
C	Placement of rectal pursestring	1. Similar sized small bites taken circumferentially without spiralling 2. Too large bites taken circumferentially. 3. Uneven and irregular sized bites taken. 4. The pursestring has spiralled up or down the bowel wall.
D	Closure of rectal pursestring	1. The rectum is closed off fully with multiple secure knots. 2. The pursestring suture tears and the pursestring is re-done. 3. The rectum is not fully closed, leaving a gap in the lumen, requiring a second pursestring. 4. The rectum is not fully closed, leaving a gap in the lumen but a second pursestring is not done.
E	Washout per rectum	1. More than one 50mls syringe of washout used 2. One 50mls syringe used for washout 3. Less than 50mls washout used 4. Washout not performed
F G	**Marking and Full thickness rectotomy** Completeness of rectotomy	1. Circumferential, full thickness rectotomy performed. 2. Full thickness rectotomy almost complete (>3/4) prior to proceeding with dissection cranially. 3. Cranial dissection commenced with only half of full thickness rectotomy complete. 4. Cranial dissection commenced with less than half of full thickness rectotomy complete.
H I	**TME dissection: posterior plane** Initiation point of posterior TME dissection	1. TME dissection is started posteriorly at 5 or 7 o'clock. 2. TME dissection is started anteriorly 3. TME dissection is started laterally 4. TME dissection is started in the centre of the pursestring.
J	Identification of pelvic floor	1. The pelvic floor is identified and kept intact. 2. The pelvic floor is breached with little consequence. 3. The pelvic floor is breached with injury to nerves. 4. Dissection is too deep through the pelvic floor causing significant bleeding.

K	Presence of angel hair aiding correct TME dissection	1. The correct TME plane is identified by the presence of angel hair with adequate traction. 2. Angel hair is apparent <50% of the time due to inadequate traction. 3. Angel hair is apparent <50% of the time due to bleeding. 4. Angel hair is not seen at any point.
L	Posterior TME dissection direction and plane	1. Dissection is performed in the correct plane with steep angulation to follow the sacral curvature but close to the mesorectal plane. 2. Dissection is performed too deep and far away from the mesorectal plane. 3. Dissection is performed too close to the mesorectum causing defects in the mesorectum. 4. Dissection is performed too close to the rectal wall causing a rectal perforation or creating a subserosal plane.
M N	**TME dissection: anterior plane** Identification of Denonvilliers fascia	1. Denonvilliers fascia is identified and dissection continued in the appropriate plane. 2. Dissection posterior to Denonvillier's fascia is performed for anterior tumours. 3. Dissection is too close to the mesorectum anteriorly causing defects in the mesorectum. 4. Dissection is too close to the rectum causing an anterior rectal perforation.
O	In females: Identification and protection of vagina	1. The vagina is identified and protected. 2. The vagina is not identified. 3. The vagina is injured or bleeding occurs but no vaginal perforation. 4. A vaginal perforation is made.
P	In males: Identification and protection of prostate and seminal vesicles.	1. The prostate and seminal vesicles are identified and protected. 2. The prostate and seminal vesicles are not identified. 3. The prostate and/or seminal vesicles are injured including causing significant bleeding. 4. Anterior dissection causes a urethral injury.
Q	Identification and protection of the anterolateral neurovascular bundles	1. The anterolateral neurovascular bundles are identified and protected. 2. The neurovascular bundles are not identified. 3. Dissection too close to the neurovascular bundles causes nerve injury. 4. Dissection too close to the neurovascular bundles causes significant bleeding.
R S	**TME dissection: lateral plane** Identification and protection of two lateral pillars with neurovascular bundles.	1. The two lateral pillars containing the neurovascular bundles are identified and protected. 2. The neurovascular bundles are not identified. 3. Dissection too close to the neurovascular bundles causes nerve injury. 4. Dissection too close to the neurovascular bundles causes significant bleeding.

T	Dissection plane between the posterior and anterior TME followed.	1. Lateral dissection follows the plane between the posterior and anterior TME. 2. Lateral dissection is too wide. 3. Lateral dissection is too close to the mesorectum causing defects in the mesorectum. 4. Lateral dissection is too close to the rectum causing rectal perforation.
U	Sequence of TME dissection	1. TME dissection follows a cylindrical "sleeve-like" dissection. 2. Uneven TME dissection with no consequence. 3. Uneven TME dissection causing difficulty proceeding with further dissection. 4. Uneven TME dissection leading to injury of surrounding structures or the mesorectum/rectum.
V **W**	**Connection to full rectal mobilisation** Connection between the abdominal and perineal teams	1. Connection between the two teams occurs when most of the dissection is complete. 2. Connection between the two teams occurs too early. 3. Connection between the two teams occurs too early leading to difficulty with the stability of pneumopelvis and/or dissection view. 4. Connection between the two teams occurs too early leading to injury to surrounding structures or the mesorectum/rectum.
X	**Final check and irrigation**	1. Checks and coagulation of any bleeding areas is performed effectively and a thorough washout. 2. Either washout or haemostasis are performed. 3. Bleeding is not controlled adequately prior to terminating the procedure and inadequate washout. 4. No attempt is made to check and control bleeding points or perform a washout.