**A systematic review and meta-analysis of the diagnostic accuracy of biparametric prostate MRI for prostate cancer in men at risk**

**Running title: Diagnostic accuracy of non-contrast prostate MRI.**

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**INTRODUCTION**

Prostate cancer (PCa) was previously diagnosed by digital rectal examination (DRE) and prostate-specific antigen (PSA) test findings followed by a systematic transrectal, ultrasound guided (TRUS) prostate biopsy. We have understood for a long time that this biopsy approach suffers a double affliction of a high false negative rate for significant cancer[1] as well as an overdetection rate of insignificant cancer[2]. Clinically speaking, this led to both overtreatment of men with low-risk disease, with some estimating this effect to be as high as 10% for radical prostatectomy, and 45% for radical radiotherapy[3]. Moreover, when one additionally considers the appreciable sepsis rate after TRUS biopsy in an increasingly antimicrobial resistant world, improvements clearly had to be made.

Significant improvements came with the introduction of multiparametric magnetic resonance imaging (mpMRI). Multiparametric means the use of three multiple imaging sequences. Typically these include T2, diffusion weighted (DWI) and dynamic contrast enhanced (DCE) images. The test’s high sensitivity and specificity for detecting significant cancer has been confirmed in several studies, by using a variety of reference standards[1, 4-6]. Current guidance now recommends the use of mpMRI prior to biopsy[7-9].

 Given the demonstrable accuracy of mpMRI in diagnosing prostate cancer[1], it is unsurprising that demand for it is increasing. Alongside this however, is a subsequent increase in the need for both human and material resources in order to meet this demand. As things stand currently, it is unclear how to meet clinical needs in terms of the volume of examinations, without compromising high diagnostic standards. It is of crucial importance therefore that solutions which allow for this are found. One possible solution is the removal of DCE from mpMRI sequences, in particular for biopsy naïve men.

Currently, the impact of DCE in mpMRI is currently under debate. Biparametric MRI (bpMRI), using only multiplanar T2 and axial DWI, is proposed as an alternative. Some studies have demonstrated a benefit to including DCE [10-12], others have suggested it adds little to overall cancer detection[13, 14]. It is important to determine whether or not DCE is required and if so, what the extent of the benefit. What is not in question is that the addition of DCE sequences to mpMRI increases the time utilization per scan and consequently the costs per patient [15]. Additionally, there is a small risk of gadolinium-related anaphylaxis as well as concerns over the long-term effects of gadolinium exposure[16]. As a result of these challenges, some have suggested it needn’t be used in men who have not undergone treatment for prostate cancer.

A previous systematic review found that bpMRI was significantly less sensitive in diagnosing any PCa compared to mpMRI with no concurrent difference in specificity[17]. However, since that publication, several studies have been added to the literature. Thus, we conducted an update systematic review and meta-analysis to further examine the diagnostic performance of bpMRI in the diagnosis of PCa with three objectives. First, to examine the diagnostic performance of bpMRI in the diagnosis of any and clinically significant prostate cancer. Second, to perform a subgroup and sensitivity analysis assessing for the impact of covariates on diagnostic accuracy. Finally, to perform a head-to-head analysis of the diagnostic performance of mpMRI and bpMRI.

**PATIENTS AND METHODS**

**Literature Search**

The current meta-analysis was performed with the aim to update the results on the diagnostic accuracy of bpMRI, published by Niu et al 2018[17], and followed the guidelines suggested by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[18]; We performed a systematic search of 4 electronic databases: PubMed, Embase, Cochrane electronic databases and Web of Science. The search included only articles published from 01/01/2017 to 06/07/2019 in English language. Since this was an updated search of the published systematic review, we applied the same search strategy based on the following keywords: (prostate cancer OR prostatic cancer OR prostate neoplasm OR prostatic neoplasm OR prostate tumor OR prostatic tumor OR prostate carcinoma OR prostatic carcinoma OR PCa) AND (magnetic resonance imaging OR MRI OR MR) AND (biparametric OR bp OR T2-weighted image and DWI OR T2-weighted imaging and DWI). The full details of this were registered on the PROSPERO database (CRD42020184676). We first performed the review of the titles and abstracts of the retrieved studies, after which we further evaluated the full-texts of the relevant studies.

**Study selection**

The articles were considered eligible if they met all of the following inclusion criteria: the study population were patients with suspected or diagnosed PCa; the index test was prostate bpMRI (at least including T2-weighted imaging and DWI); the reference standard was prostatectomy or prostate biopsy; it reported sufficient data to construct 2 × 2 contingency tables with at least 10 patients; it was an original article (conference abstracts, short communications, letters to the editor and reviews were excluded).

**Data Extraction and Quality Assessment**

The study data included the following information: the first author and the year of publication, the characteristics of the study, the sample size, the characteristics of the study population, the specifications regarding the methodology, the numbers of true/false positives and true/false negatives. When the results were reported from multiple readers, we included those reported from the most experienced one. The assessment of the study quality was performed according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool to determine whether there were concerns regarding the likelihood of bias and applicability to the review questions[19]. Two authors (AP and HUA) were involved in data extraction and quality assessment of studies.

**Study Quality**

Regarding the study quality, we focused our sensitivity analysis by including only those graded as having low risk of bias and low concerns regarding applicability to the current review question. According to the QUADAS-2 guidelines, a study should be judged as having overall “low risk of bias” and “low concern regarding applicability” if all domains related to bias or applicability are graded as “low”. In contrast, a study should be judged as having “risk of bias” or as having “concerns regarding applicability” if a study is graded as “high” or “unclear” in 1 or more domains[20]. As evaluation of publication bias is not usually recommended in the meta-analysis for diagnostic test accuracy, we did not perform them[20].

**Statistical Analysis**

The extracted diagnostic accuracy data from the studies (true/false positives and true/false negatives) were combined in order to compute the sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV) and diagnostic odds ratios (DOR) along with 95% CIs across all individual studies and their corresponding summary measures, by employing the random intercept logistic regression model with the function “*metaprop*” from “*meta*” package[21]. We generated a summary receiver operating characteristic (ROC) curve and obtained the area under the ROC curve (AUC) values by the use of the bivariate model with the package “*mada*” after fitting the model with the “*reitsma*” function. Heterogeneity between the studies was explored with I2 statistics and visually through inspect of forest plots and SROC curves.

We further explored the potential influence of several (categorical) covariates when we observed considerable heterogeneity among the studies by performing meta-regression analysis with the function “*metareg*” from the “*meta*” package. The covariates included: design (prospective vs retrospective), patient enrollment (consecutive vs non-consecutive), MRI–reference standard interval (reported vs not reported), blinding to histologic findings (blinded vs not blinded), b value (high vs low), MRI field strength (3.0 vs 1.5 T), localization analyzed (whole prostate vs peripheral or transitional zone), analysis type (per patient vs per lesion). In addition, we compared the pooled estimates between the levels of the covariates by performing subgroup analyses.

New studies were merged with the 11 studies from the previously published systematic review[16] to evaluate diagnostic accuracy. To ensure inadvertent exclusion of studies in this systematic review, the eligibility criteria for included studies for this systematic review were the same as for that of Niu et al[17]. We compared their pooled estimates by performing meta-regression analysis (by adding the type of MRI technique as a covariate) and subgroup analysis. In addition, a head-to-head analysis of bpMRI and mpMRI was performed by way of summary ROC curves. These were generated by employing the bivariate random model by plotting sensitivity and specificity of individual studies. All statistical analyses were performed in R studio Version 1.2.1335 (Boston, MA, USA).

**Code availability**

Example r code used for this analysis is found in a statistical methodology paper by Shim et al[22]

**RESULTS**

**Evidence Acquisition**

**Study Selection**

The whole study selection process is presented with a PRISMA flow diagram (Figure 1). The search of electronic databases yielded a total of 234 articles. After removing the duplicates, title and abstract review was performed in the remaining 147 articles, after which 18 underwent full text assessment. Seven studies were excluded because they either reported no outcome of interest or it was not possible to extract the data in a 2x2 contingency table. Finally, the remaining 11 studies including 3672 patients were included in the qualitative and quantitative synthesis, which yielded a total of 44 independent studies after merging with the studies included by Niu et al[17].

**Study and Patients’ Characteristics**

Detailed patients’ characteristics are presented in table 1. The sample size varied considerably between the studies, from 23 to 1020 patients, who were aged from 58 to 71 years. There were a total of 6055 included patients in the meta-analysis. The majority of studies (n=29) included patients with a mean PSA level lower than 10 ng/mL. Twelve studies were of biopsy-naive men, 11 included men who had undergone at least one biopsy and 21 studies did not report this either way. Twenty studies included men on active surveillance or in whom there was already a diagnosis of prostate cancer. Thresholds for clinically significant prostate cancer, subjected to sensitivity analysis (csPCa) were reported in 16 studies. Whilst a single study used a Gleason score of 3+3 as the threshold for significance, 12 used a Gleason score of >/=3+4.

Most of the studies were retrospective (n=28), and 24 enrolled patients consecutively. Seventeen studies reported using 3.0 T and 20 reported using 1.5T MRI. For diffusion scans, high b-values (b≥1400 s/mm2) were used in 14, while lower b-values (< 1400 s/mm2) were used in 27 studies. The majority of studies reported that the readers were blinded to histologic results (n=36). The results on diagnostic accuracy were reported either on per patient basis (n=20) or per lesion basis (n=24). Twenty-three studies used radical prostatectomy, 21 studies used transrectal ultrasound (TRUS)–guided biopsy, 4 studies used MRI-TRUS fusion–guided biopsy, and 2 studies applied standardized transperineal template saturation biopsy (Table 2).

**Assessment of Study Quality**

A total of 23 studies are graded as having low risk of bias and low concerns regarding the applicability to the review question[15, 23, 26, 31, 36, 37, 41, 46, 51, 53-65]. Sixteen studies were graded as having high risk of bias regarding patient selection process[24, 25, 27-30, 31-35, 39, 40, 42-45, 47]. Four studies were judged that might pose concerns regarding the applicability of the index tests[28, 47-49], while 8 studies were graded to have high risk of bias regarding the reference standard that was employed[25, 27, 30, 32, 38, 40, 50, 52]. All other domains were graded as having low risk of bias or low concerns regarding the applicability to the review question. A pictorial representation of the QUADAS-2 risk assessment is presented in Figure 2.

**Diagnostic Accuracy of bpMRI in detecting any PCa and csPCa**

For all cancers, the sensitivity ranged from 0.559 to 1.000 in individual studies (Figure 3), while specificity ranged from 0.12 to 0.98 (Figure 4). The pooled sensitivity of all studies (n=44) was 0.84 (95%CI, 0.80-0.88, I2=95.2%), specificity 0.75 (95%CI, 0.68-0.82, I2=97.7%), PPV 0.74 (95%CI, 0.68-0.79, I2=96.4%), NPV 0.85 (95%CI, 0.80-0.89, I2=96.2%) and DOR 14.6 (95%CI, 11.2-19.2, I2=88.0%). The summary ROC curve yielded a high AUC value (AUC=0.86)(Figure 5). The values of the pooled sensitivity, specificity and DOR in this updated meta-analysis are similar to those found by Niu et al (0.81, 0.77 and 14, respectively)[17]. Diagnostic accuracy of detecting csPCa was evaluated in 15 studies in total[15, 23, 38, 40, 45, 48, 50, 52, 53, 55, 58-60, 62, 63]. The pooled relative sensitivity was 0.87 (95%CI, 0.78-0.93; I2=93.2%), specificity 0.72 (95%CI, 0.56-0.84; I2=98.3%) and the AUC value was 0.87 (figure 6). These values are again similar to those reported by Niu et al (sensitivity was 0.81, specificity 0.74 and AUC value was 0.85)[17].

**Subgroup and Sensitivity Analysis**

We explored the effect of eight potential covariates (Table 3). The subgroup analysis showed that five of them (patient enrollment, reporting of MRI-reference standard interval, whether the readers were blinded to histologic findings, b value and the analysis type (per patient or per lesion)) were significantly associated with sensitivity (p <0.05 for all). Higher pooled sensitivity was observed when the patients were not consecutively enrolled, when MRI-reference standard interval was not reported, when reader’s blinding to histologic results was not reported, in case of high b-values, and when the analysis was reported on a per patient basis. In the case of specificity, a conventionally significant difference was only observed with respect to whether the MRI reference standard was reported, indicating a much higher specificity when the standard was reported.

When we focused our analysis only on studies judged to have low risk of bias and low concerns regarding applicability to the current review question, it included a total of 23 studies. The pooled sensitivity was somewhat higher compared with the value obtained after pooling the data from all 44 studies - 0.88 (95%CI, 0.82-0.92. I2=92.8%) while the pooled specificity was somewhat lower - 0.72 (95%CI, 0.62-0.80, I2=96.9%).

**Head to head comparison between bpMRI and mpMRI**

There were 17 studies included in this analysis[26, 28, 31-33, 37, 47, 50, 53-57, 62-65]. The pooled sensitivity for bpMRI was 0.84 (95%CI, 0.73-0.91), while for mpMRI it was 0.89 (95%CI, 0.80-0.94). Pooled specificity for bpMRI was 0.79 (95%CI, 0.70-0.85) and for mpMRI it was 0.74 (95%CI, 0.56-0.87). Meta-regression analysis revealed no statistically significant difference in the pooled diagnostic estimates between these two protocols (p=0.39 and p=0.53 for sensitivity and specificity, respectively). The summary ROC curves of bpMRI and mpMRI are presented in figures 7a & b.

**Discussion**

BpMRI involves removing DCE sequences from the imaging study and relies on T2 and DWI. This meta-analysis of 6055 men demonstrates that bpMRI detects PCa with a high degree of accuracy. The pooled sensitivity is 84% and specificity 79%. Further, the head-to-head analysis suggests that any historical benefit of mpMRI in cancer detection decreased with the addition of more contemporary studies. Whilst the previous review by Niu et al[17] reported an improved sensitivity of mpMRI compared to bpMRI (bpMRI, 0.80 (95%CI, 0.71–0.90); mpMRI, 0.85 (95%CI, 0.78–0.93); p=0.01), our updated analysis, containing seven more recent studies found no significant difference (bpMRI, 0.84 (95%CI, 0.73-0.91); mpMRI, 0.89 (95%CI, 0.80-0.94); p=0.39). This may either be due to a collective increase in user experience, or to incremental technological improvements and future analyses are needed to confirm this trend.

The results of this meta-analysis are also pertinent, considering the wider debate over whether or not there should be organised screening programmes for PCa as using mpMRI for large scale, population wise testing is unfeasible. Until recently, in the context of traditional TRUS biopsy for all with raised PSA, it was thought that organised screening was harmful as it led to needless overdiagnosis and overtreatment of men with cancer that would never have reduced their life expectancy[66]. In the UK, the CAP study follow up to date supported the position that ‘one-off’ PSA screening offered no benefit[67]. However, observations over the last decade, where PSA screening fell out of favour, has shown an increase in high-grade and high-risk disease[68]. While there are numerous potential reasons, one argument is a continued increase in men being tested with PSA combined with the traditional TRUS biopsy approach which offers a high false negative rate for significant cancer[1] as well as an overdetection rate of insignificant cancer[2]. The use of TRUS biopsy, based only on elevated PSA leads to overtreatment of low-risk disease in up to 45% of men biopsied[3]. Transperineal template mapping biopsy will miss less significant cancer[69], but will also over diagnose low-risk disease[69] as well as hugely increasing healthcare costs[71].

MpMRI –using T2, DWI and DCE sequences - has increasingly been integrated into mainstream diagnostic practice[7-9]. The addition of mpMRI has significant advantages when added to existing diagnostic prostate cancer pathways. Numerous studies using either whole-mount prostatectomy specimens[72] or template mapping biopsies[1], have demonstrated the sensitivity of mpMRI in detecting csPCa and that mpMRI might also effectively ‘rule out’ csPCa by nature of its high negative predictive value (NPV). For example, the PROMIS trial found mpMRI had an NPV of 0.72 – 0.89, depending on the threshold for significant disease[1].The pooled NPV of the included studies in this meta-analysis was 0.85 suggesting a similar ability to rule out a diagnosis of all prostate cancers. Further, MRI allows for image-guided biopsies of the prostate. A number of studies recently evaluated within a meta-analysis[73] of seven robust trials containing 2583 pooled men found that MRI with or without a targeted biopsy offered a 57% increase in csPCa detection, a 33% decrease in the total number of biopsies, a 77% reduction in cores per biopsy procedure with little to no benefit in adding systematic cores.

Several disadvantages to universal uptake of mpMRI have been raised. First, there is controversy over the cost effectiveness of mpMRI. However, some of this may be explained by assumption due to its relative novelty. For example, cost effective analyses have suggested an mpMRI first approach, followed by to TRUS MRI-targeted biopsies was more cost effective in detecting significant disease than a systematic TRUS biopsy first strategy[74].Second, DCE increases the time to acquire and interpret each set of images. Each patient must have their renal function checked and all must be checked for prior gadolinium reactions. Intravenous access must be achieved for contrast delivery, which requires on-site medical support. These factors increase the image acquisition and reporting times as well as healthcare resource utilisation. Third, although acute gadolinium reactions are extremely rare[16], studies have shown gadolinium retention in body tissues for months or years, particularly the brain[16]. The effects of this are not yet known however forward caution is warranted, a fact noted by the United States Food and Drug Administration, who now mandate counseling of patients in regard to potential risks before a gadolinium contrast agent is administered. A bpMRI approach has potential advantages by reducing resource utilisation and cost and gadolinium related risks.

Most bpMRI protocols also do not require an endorectal coil (ERC). ERCs also add significant time to scan protocols due to more lengthy patient preparation[75]. ERCs are useful in 1.5-Tesla machines as they improve cancer detection at lower magnet strengths[76]. As 3-Tesla machines are increasingly utilized this effect is much less pronounced, in particular for diagnostic studies[77]. Many centres do not use ERCs routinely for diagnostic protocols. They may offer greater accuracy in local staging especially with 1.5-Tesla machines[78]. The European Society of Urogenital Radiology still recommends ERC use for this purpose[79]. This review found 14 studies[24, 25, 29, 31, 32, 24, 36-38, 40, 41, 45, 47, 53] reporting use of an ERC, the most recent reported on patients who underwent MRIs between 2013 and 2015[53].

Whilst this meta-analysis suggests that bpMRI might offer these advantages whilst not sacrificing diagnostic accuracy, it does so in the context of a dearth of randomised evidence comparing bpMRI with mpMRI. A large pivotal randomized comparative study powered to show non-inferiority will be required to impact changes in practice.

There are some limitations to the study. First, like any systematic review the results of this study are inherently dependent on those included within it. In the case of bpMRI as a diagnostic test for PCa level-one evidence is lacking. However, the inclusion of a sufficient number of trials (and participants) in the analysis mitigated this issue. Second, this analysis focused on primary PCa. Thus, the findings are not applicable to the investigation of post treatment residual or recurrent disease where DCE sequences have shown value[80, 81] nor in active surveillance sequential scans. Third, there was significant heterogeneity between the studies with both sensitivity and specificity being affected. However, this is not unusual in meta-analyses of diagnostic studies due to variability in both thresholds for clinical significance, and of reference standard. The type of patient enrollment, analysis type, reporting of MRI reference standard, blinding to histological findings and the b-values of diffusion sequences all caused a significant effect on reported sensitivity. For specificity, only the reporting of MRI reference standard caused a significant effect. In general, this was due to studies with elements of high risk of bias tending to overestimate their sensitivity and specificity. Such elements include a non-consecutive enrollment, non-reporting MRI reference standard and blinding of histological findings. By comparison, higher quality (high b value) DWI images probably genuinely increase sensitivity, whilst a per lesion analysis underestimates it. Fourth, 22 studies were rated as having a high risk of overall bias. When a pooled analysis of studies with only a low risk of bias was performed, the sensitivity increased to 88% though specificity decreased to 72%. Finally, the utility of bpMRI in detecting extracapsular extension, seminal vesical invasion and lymph node metastasis is unproven and beyond the scope of this study. A more detailed meta-analysis designed to determine this is welcome.

**CONCLUSION**

This meta-analysis shows that bpMRI offers comparable sensitivity and specificity to mpMRI in detecting prostate cancer. However, there is significant heterogeneity between studies and in particular, there is a lack of randomised, comparative data in a biopsy naïve population.. An appropriately powered study, designed to confirm the ability of bpMRI to address the disadvantages of mpMRI without sacrificing diagnostic efficacy, with embedded cost-effectiveness analyses would be welcome.

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**Conflict of Interest Statement**

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**FIGURE CAPTIONS**

**Figure1:** PRISMA flow diagram of the study selection process.

**Figures 2a & b:** Summary tables of the QUADAS-2 bias assessment.

**Figure 3:** Forest plot representing the pooled and individual sensitivity estimates of the included studies.

**Figure 4:** Forest plot representing the pooled and individual specificity estimates of the included studies.

**Figure 5:** Summary ROC curve (bivariate model) for diagnostic test accuracy of all PCa.

**Figure 6:** Summary ROC curve (bivariate model) for diagnostic test accuracy of csPCa.

**Figure 7:** Summary ROC curve (bivariate model) for diagnostic test accuracy of all PCa for: **a)** bpMRI and mpMRI & **b)** of all PCa with linked data points. BpMRI : mpMRI Sensitivity = 0.84 : 0.89 (p=0.39), Specificity = 0.79 : 0.74 (p=0.53).