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The Role of Multi-Parametric MRI and Fusion Biopsy for the Diagnosis of Prostate Cancer – A Systematic Review

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Abstract

Introduction: The use of multiparametric MRI (MpMRI) guided fusion biopsy is becoming an increasingly popular investigation in an aid to increase diagnostic yield in those suspected of having prostate cancer (PCa). Before adopting this technology, it is necessary to confirm the accuracy, so that PCa can be reliably diagnosed with characterization.

Materials and Methods: This review analyses the evidences, which varied from well-designed randomized controlled trials to case series to detect the accuracy of MpMRI comparing with biopsy/histology.

Results: MpMRI incorporating T2 and diffusion weighted imaging only detects tumor in around 92% cases. When dynamic contrast enhancement is added, cancer diagnosis is significantly improved. Fusion biopsy increases the detection of high-risk PCa by 32% over conventional biopsy alone.

Conclusion: This review also revealed that fusion biopsy did not increase cancer detection rate but combined biopsy (systematic and fusion) provide the highest detection rate for the diagnosis of PCa.

Keywords: Magnetic resonance imaging; Pathology; Prostate biopsy; Prostate cancer

Abbreviations: MpMRI: Multiparametric MRI; TRUS Biopsy: Transrectal Ultrasound Guided Biopsy; TPSB: Transperineal Saturation Biopsy; TB: Targeted Biopsy; DW MRI: Diffusion Weighted MRI; DCE MRI: Dynamic Contrast Enhanced MRI

Introduction

Prostate cancer accounts for a quarter of all new cancer cases in men in the UK and in 2011 a total of 41,700 men were diagnosed with this condition. It is the second commonest cause of cancer death in men (Prostate Cancer Research, UK). Over the last 35 years, prostate incidence rates in Great Britain have more than tripled, however much of this is attributed to increased detection with widespread use of serum prostate specific antigen (PSA) testing [1]. In Europe, around 417,000 new cases of prostate cancer were estimated to have diagnosed in 2012 [1].

The patient's history, physical examination including digital rectal examination (DRE) and serum PSA are the triggering factors for trans-rectal ultrasound guided biopsy (TRUS). DRE is a crude tool with variability from clinician to clinician and has a low predictive value [2]. Sensitivity and specificity of PSA is controversial. The conventional TRUS guided (10 cores to 12 cores) systematic biopsy also fails to detect PCa in up to 25% of cases [3]. Therefore, suspicion of malignancy remains in a significant number of men, especially if PSA is persistently raised, DRE is abnormal or a typical small cell acinar proliferation (ASAP)/high-grade PIN is seen on initial biopsy. Some patients undergo numerous repeat negative conventional biopsies over several years, subjecting them to anxiety and discomfort, with an associated added cost. The optimum management of this group is unclear. Transperineal saturation (>20 cores) prostate biopsy (TPSB) prostate has been reported to detect and map out cancer in 23% to 47% of men requiring repeat biopsy, but with a complication rate of urinary retention in 11% to 39% [4,5].

In recent years, use of multiparametric MRI (MpMRI) and fusion prostate biopsy has become an increasingly popular choice of investigation, as few targeted cores are needed to confirm the diagnosis. MpMRI has been used since 2005 to better identify and characterize PCa [6]. Many prostate cancers that are missed by conventional biopsy are detectable by MRI-guided fusion biopsy [7,8]. MRI-USS fusion biopsy uses software that fuses stored MRI with real-time ultrasound (MRI-US). The correlation between biopsy and final prostate pathology has been improved by MRI-guided biopsy as compared to TRUS guided biopsy alone [9].

For these reasons, multiparametric MRI is marketed as an emerging tool in prostate cancer diagnosis, as many patients don't wish to undergo a repeat conventional biopsy or saturation biopsy to confirm a possible diagnosis.

Aims of the Review

In patients with a negative conventional TRUSB but on-going suspicion of prostate cancer the next line of investigation requires definitive diagnosis or exclusion of malignancy, in order to prevent further uncertainty.

A negative MpMRI has been proposed as reasonable exclusion criteria for performing a repeat TRUSB/TPSB in many studies and a positive MpMRI can act as a trigger for repeat biopsy and in this way many repeat biopsies can be prevented. The patient with a positive lesion on MRI can undergo MRI-USS fusion biopsy to increase the diagnostic yield.

The aim of this review is to examine the evidence comparing the accuracy of multiparametric MRI with standard systematic prostate biopsy (10 cores to 12 cores), fusion biopsy (1 core to 4 cores) and final prostate pathology for either initial diagnosis or in those who have had one or more sets of negative conventional prostate biopsy, but in whom PCa is still suspected.

Systematic Literature Search Strategy

Introduction: The aim of this literature search is to obtain as many relevant current citations as possible in order to make a reasoned and unbiased judgment regarding the accuracy of multiparametric MRI.

Search methodology: The first part of this methodology is the formulation of this systematic review question in detail, which will aid the formulation of the search strategy undertaken to facilitate the retrieval of most current evidence. This will then be followed with use of diagrams of various keywords and combinations of keywords, derived from the dissertation question, to commence the literature search. Electronic databases to obtain current and relevant evidence, which is detailed later in this chapter, were used in a structured manner to enable reproducibility of the literature search.

In order to facilitate the literature search, the mnemonic PICO format was used to help formulate a question, which in turn would aid developing a search strategy and therefore retrieval of relevant clinical evidence [10]. A "well-built" question consists of four parts; patient problem/population, intervention, comparison and outcome. By expanding each component, appropriate search terms will be determined which would help develop an efficient approach to the question (Table1).

Patient problem/population of interest	**Repeat prostate biopsy due to ongoing high PSA or abnormal DRE or negative conventional biopsy.**
Intervention	Multi-parametric MRI
Comparison of interest	Compare with prostate biopsy/histology
Outcome of interest	To prevent many repeat biopsies

Table 1: Acronym PICO to formulate a clinical question.

The search interval was 2010 to 2016, limited to articles published in English and on humans. A literature search was then conducted using Ovid Medline, PubMed and the Cochrane Database for Systematic Reviews for the key words used "multi-parametric MRI" AND "prostate cancer" AND "efficacy of MRI" AND "prostate biopsy". Only papers investigating the efficacy of MpMRI were included. The literature search revealed a large number of studies including randomized controlled trials (RCT), case series and review articles. Ideally meta-analysis and systematic reviews would have been ideal as these are all high levels of evidence, however only two suitable were identified. This may be due to the relatively new development of MpMRI resulting in being an inadequate number of RCT's or the RCT may not be necessary for investigating the efficacy of this investigation.

Not all the studies included in this review were published in journals that had a high impact factor; however, those that did had their impact factors interpreted with caution as a large number of citations may not indicate that work is of high quality. Studies may be highly cited due to a large number of other authors refuting a study's findings. Impact factors risk citation bias as authors may cite their own work. Newer journals tend to have lower impact factors despite the standard of the studies published, as time needs to elapse before a meaningful citation analysis can be made.

Initially it seemed ideal to consider UK based studies only to analyze national practice. However, on further reflection the author felt it appropriate to include non-UK based studies, as this would allow a global comparison of attitudes and trends in prostatic cancer investigation and diagnostic methods. Total 16 studies (2 RCT's and 1 systematic review and 1 meta-analysis included) selected for this review (Table 2).

#	Searches	Results
1	Prostate cancer and biopsy	8,483
2	Prostate cancer and multi parametric MRI	15
3	1 or 2	8,488
4	Control and trial	172,748
5	Randomized and Controlled and Trial	43,173
6	4 or 5	204,570
7	3 and 6	224
8	Limit 7 to (English language, humans, year="2010 -Current")	103

Table 2: Search strategy.

Results

MpMRI with T2W images and diffusion weighted images (DWI) can detect PCa in 92% cases and when dynamic contrast enhancement (DCE) was added the efficacy of improved further. One study revealed that the speed of the contrast uptake by DCE MRI allows differentiating cancer from normal areas. There were wide variations in specificity in different studies but sensitivity and NPV was high consistently. Fusion biopsy detected more clinical significant cancer than conventional systematic biopsy. One study with contrast enhanced TRUSB (on positive MRI) confirmed excellent sensitivity. MRI guided biopsy through transperineal route also improved clinically significant cancer detection but combined fusion and systematic biopsy had the highest detection rate. Fusion biopsy detects

higher grade PCa than conventional biopsy. However, one of the studies found that fusion biopsy did not increase cancer detection rate and another one confirmed no added advantage of fusion biopsy over conventional biopsy if overall outcome is cancer detection rate.

Study	Aim	Study Type	(n)	Key Findings	(l)
[2]	Usefulness of MpMRI in detecting higher grade cancer compare with fusion biopsy	Prospective	583	MpMRI is useful in high grade PCa	2-
[7]	MpMRI for accurate localization of tumor compared with histology	Prospective	75	T2W, DCE and DW MRI significantly detect PCa	2-
[11]	To examine the performance of T2W and DW MRI after compare with histology	Prospective	199	T2W and DW MRI detects tumor in 92% cases	2-
[12]	The role of DCE MRI and MRSI for to detect PCa in biopsy negative men.	RCT	180	Combination of both this MRI offer 92% cancer detection rate	1-
[13]	Localization of PCa by the speed of contrast uptake by DCE MRI	Prospective	30	Allows differentiate cancer and from remote areas	2-
[14]	To measure the diagnostic accuracy of MpMRI	Meta analysis	7 study	High specificity variable but high sensitivity and NPV	1-
[15]	MRI guided biopsy can predict the aggressiveness of PCa	Prospective	518	DWI-Dbs had superior performance than MRS-Dbs in PZ	2-
[16]	Compare MRI guided biopsy and TRUS guided systemic biopsy	Prospective	132	Improves clinically significant cancer detection	2-
[17]	Accuracy of USS guided CE biopsy on +ve MRI but -ve biopsy patients.	Prospective	158	CE US targeted transrectal biopsy offers excellent sensitivity.	2-
[18]	Compare MRI guided biopsy and systemic biopsy through transperineal route	Prospective	182	Improves clinically significant cancer detection	2-
[19]	Compare MR-USS fusion biopsy with USS guided systemic biopsy	Prospective	1,003	Increased detection of high risk PCa	2-
[20]	MR-USS fusion biopsy may better sample the true gland pathology	Prospective	582	32% higher detection of high risk PCa	2-
[21]	Compare MR-USS fusion biopsy with USS guided biopsy	Prospective	95	Improves detection of clinically significant cancer	2-
[22]	Compare MR-USS fusion biopsy with visual targeting biopsy	Prospective	125	Fusion biopsy did not increase cancer detection	2-
[23]	Compare MR-USS fusion biopsy with final prostate pathology	Prospective	54	Fusion biopsy detects more cancer	2-
[24]	Comparison MpMRI guided TB V systematic biopsies in the detection of PCa: a systematic literature review.	Systemic review	15	No advantage of TB but combined biopsy provides highest detection rate	1-

Table 3: Result of the studies.

Discussions

The aim of this review was to examine the evidence that compares the accuracy of MpMRI with systematic (10 cores to 12 cores) prostate biopsy, fusion biopsy (1 core to 4 cores), and final prostate pathology for prostate cancer diagnosis.

Sixteen papers in total were reviewed and categorized into three groups:

– Accuracy of MpMRI (Paper 1 to 4)

– MpMRI compared with TRUS biopsy/ TPSB/ final histology (Paper 5 to 9)

– MpMRI compared with fusion biopsy (Paper 10 to 16).

Limitations of the Review

These reviews also had some limitations:

– Most of the studies did not perform power calculation prior to the study design which raised the question for external validities for these studies.

– In some studies [1,5], MpMRI was performed within 12 weeks of post biopsy; it is known that hemorrhage after biopsy/scarring can provide false positives on MRI and resolve within 12 weeks.

– No study had performed cost analysis.

– The PI-RADS scoring system was also not used by most of the studies for lesion characterization.

– Only three studies [7,9,11] included positive lesions on MpMRI but ignored negative scans.

– In two studies [8,15], authors confirmed a financial interest.

Despite limitations, this review has significant implications in clinical practice. Overall, MpMRI has a high efficacy in almost all studies and fusion biopsy is convenient for patients as fewer cores are taken to confirm the diagnosis. However, well designed controlled studies do not demonstrate a clear advantage of fusion biopsies over standard systematic biopsies in the primary setting as far as overall detection PCa is considered. However, fusion biopsy can detect more clinically significant cancer. Therefore, fusion biopsy cannot replace systematic biopsies for the diagnosis of prostate cancer. However, it can be helpful to prevent over diagnosis and over treatment for PCa. For repeat biopsies, fusion biopsy is superior to standard systematic biopsies. MpMRI and subsequent fusion biopsy could therefore be a possible solution to detect PCa in these scenarios of previous negative biopsies but ongoing suspicion of PCa.

Conclusions

This review reveals that MpMRI is a useful tool for PCa diagnosis. In the repeat biopsy setting, image-targeted biopsies can detect more clinically significant prostate cancer compared to standard systematic biopsies. However, few studies have compared the results with saturation biopsies or with final histology.

In patients with a negative conventional TRUSB but ongoing suspicion of PCa, MpMRI can be a good guide for further management planning. A negative MpMRI can't entirely exclude PCa. Fusion biopsy with fewer cores can detect more clinical significant cancer but can also miss some degree of clinically significant cancer and overall cancer detection rate was not higher than systemic biopsy, in many studies. In all studies, combined techniques detected most cancer (standard and fusion biopsy) and with all the parameters of MpMRI, PCa detection rate was highest.

The advantages to recommend combined biopsy are: it can detect more cancers and safe, patient convenient, less biopsy, less anxiety for diagnosis and early treatment decision. But the main disadvantage is as the technology for fusion biopsy is expensive and no study has performed cost analysis to recommend in clinical practice. Additional larger randomized studies are required to compare two biopsy modalities to each other with the final prostatectomy specimen. Based on the findings of these studies, future prospective PCa screening protocols are needed to evaluate the benefit of MpMRI as an independent modality, as well as MRI coupled with other screening parameters including tumor markers and measures of PSA dynamics in detecting clinically significant cancers.

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