Visual-estimation (cognitive), image-fusion (software) and in-bore targeted prostate biopsy: is there an optimal approach?

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The diagnostic superiority of multiparametric magnetic resonance imaging (mpMRI) prior to targeted and systematic prostate biopsy over systematic transrectal ultrasound-guided (TRUS) biopsy alone in the detection of clinically significant prostate cancer (csPCa) has been proven by multiple level 1 studies [1]. When this is combined with the high reported negative predictor value (NPV) of prostate mpMRI it has resulted in a revolution in the established prostate cancer diagnostic pathway [2]. Routine pre-biopsy mpMRI in biopsy naïve men is now recommended in the most recent iterations of the European Association of Urology (EAU) and National Institute for Health and Care Excellence (NICE) prostate cancer diagnosis guidelines [3,4].

Research focus has now shifted to evaluate the clinical utility of various mpMRI targeted biopsy approaches. The three commonly used techniques are visual-estimation (cognitive), image-fusion (software) and in-bore (in-gantry) biopsy. Visual-estimation registration relies on the operator's skill in interpreting mpMR imaging prior to biopsy and then manually targeting the lesion using TRUS guidance. Image-fusion (software) registration utilises a computer platform to overlay the contoured mpMRI lesion onto real-time TRUS imaging in either a rigid or elastic (deformable) manner, thereby guiding the operator's biopsy needle (Figure 1). Platforms are expensive, can malfunction, and use may lengthen procedural duration. However, their use standardises technique, and allows biopsy information to be electronically recorded and reviewed at a later date should there be diagnostic doubt. In-bore biopsy (performed within the MRI scanner) involves fusion of the

Figure 1: Image-fusion targeted transperineal prostate biopsy (Hitachi Ultrasound and MedCom BiopSee fusion system).

Table 1. Comparison of targeted prostate biopsy methods.

	Visual-estimation	Image-fusion	In-bore
Cost	Low	Moderate	High
Procedure duration	Low	Moderate	High
Complexity	Easy	Moderate	Difficult
Operator dependency	High	Moderate	Low
Documentation	No	Yes	Yes
Capability to target small lesions (<10mm)	No	Moderate	Yes

diagnostic mpMRI with real-time MR imaging to ensure accurate needle deployment. Although this is resource heavy and time-consuming, in-bore might offer greater accuracy (Table 1).

Whether any single targeting route yields superior cancer detection above the others remains contentious, and there are multiple aspects to consider. In this article, we contextualise current practice, discuss the available evidence in image-guided targeted prostate biopsy approaches and evaluate potential differences dependant on patient, prostate and procedural factors.

The evolution of MRI-guided prostate biopsy

Prior to evaluating MRI targeted biopsy approaches, it is useful to briefly consider its origin. Magnetic resonance imaging of the prostate was first introduced in the 1980s. This major advance allowed the substructure of the prostate (peripheral and central zones) to be reliably visualised on T2 weighted images. Unfortunately, images were limited in spatial resolution (due to larger fields of view and thicker slices) and so therapeutic application was limited [5]. It was not until the early 2000s that MRI was utilised to guide prostate biopsy. Cormack and colleagues described an in-bore biopsy of a 74-year-old patient who had previously undergone a proctocolectomy – despite having a raised PSA, four separate transurethral prostate biopsies were all negative. In a 0.5T MR scanner, eight transperineal samples were taken, two of which yielded cancer [6]. However, widespread uptake of in-bore biopsy was limited by patient discomfort, long duration, cost, and lack of specialist equipment and skillset. When prostate cancer was suspected, 'blind' TRUS prostate biopsies remained the standard.

Subsequent advances in MR imaging and interpretation have galvanised its use in the prostate cancer diagnostic pathway. First developed by consensus in the late 2000s, the Prostate Imaging Reporting And Data System (PI-RADS) aims to standardise prostate MRI acquisition and reporting. By combining various imaging

findings, PI-RADS risk stratifies mpMRI lesions from 1 (very low risk) to 5 (very high risk). Meta-analysis yields pooled csPCa detection rates for PI-RADS version 2 of 4% for score 1-2, 17% for score 3, 46% for score 4 and 75% for score 5 [7].

The PROMIS study heralded a sea-change in biopsy approach. 576 men underwent mpMRI (as an index test) followed by both standard 10-12 core TRUS biopsies and transperineal template mapping biopsies. mpMRI sensitivity and negative predictive value was 93% and 89%, respectively; in this cohort, if mpMRI had been used as a triage tool, 27% could have safely avoided biopsy [8]. Building on this, the PRECISION study randomised men to either 10-12 core TRUS biopsy, or mpMRI with or without targeted prostate biopsy (using either visual-estimation or image-fusion depending on local expertise). MRI-targeted biopsy resulted in detection of more csPCa (38% vs. 26%, p=0.005) and less clinically insignificant (9% vs. 22%, p<0.001) cancer [9]. As the superiority of the mpMRI directed diagnostic pathway became apparent, image-fusion software platforms (which track movement of the probe to fuse TRUS and MR imaging) were developed. Initial models used electromagnetic trackers to detect the TRUS probe's position. Subsequent iterations used a mechanical arm, and then spatially combined imaging only; biopsy accuracy and cancer detection rates of image-fusion platforms have gradually improved [10].

Is greater accuracy really needed?

Comparisons of radiological and histopathological lesion volumes have shown that mpMRI underestimates the size and extent of malignant lesions. Priester et al. examined mpMRI and whole-mount pathology specimens of 114 men who underwent radical prostatectomy. The mean tumour volume was three-times greater than the corresponding mpMRI region of interest (p=0.01) [11]. In a similar study of 37 men, Le Nobin et al. report volume underestimations of 32% and 47% on T2 weighted imaging and apparent diffusion coefficient respectively compared to histology [12]. As prostate cancer lesions lie on a spectrum from dense malignancy to a few abnormal cells in normal tissue, it can be very hard to differentiate the latter on mpMRI [13]. Consequently, mpMRI lesions may have surrounding 'MRI invisible' disease. This means that, even if the biopsy needle does not quite hit the target, it may still detect the cancer.

Current evidence: comparative image-guided targeted prostate biopsy trials

So, what does the comparative evidence show? Unfortunately, there is a lot of heterogeneity in the design of studies to date. Baseline populations include biopsy naïve men, those with prior negative biopsy, or both. Men may have been biopsied using visual-estimation, image-fusion, or in-bore; systematic biopsy may or may not have been used as the standard. Biopsy routes differ – transrectal might be compared to transperineal outcomes. A wide variety of image-fusion platforms utilising rigid or elastic registration have been used. Individual operator expertise is rarely reported. The number of cores taken may vary, as might the anaesthetic route. To further complicate the presentation of results, multiple definitions of what constitutes csPCa have been used. Finally, analyses have been conducted and results reported on patient and lesion-based levels.

Without discussion of such variations in protocols it is, perhaps, unsurprising that the majority of studies report no significant differences in overall cancer or csPCa (subsequently defined as any Gleason ≥3+4 unless otherwise stated) detection rates between visual-estimation, image-fusion and in-bore biopsy. Comparisons of pooled estimates from a systematic meta-analysis suggested that no one technique is superior in detecting clinically significant cancer [14]. This is supported by the subsequent FUTURE trial, which randomised 655 men with suspicion of prostate cancer to visual-

estimation, image-fusion or in-bore targeted biopsy. There were no significant differences in cancer detection rates between techniques not only overall but also on various subgroup comparisons (PI-RADS score, lesion location and prostate volume) [15]. However, the literature is not entirely unanimous, and there are some hints that techniques are not completely equivocal.

Visual-estimation versus image-fusion

Lesion location and size may matter. In the PROFUS study, 125 men underwent two transrectal targeted cores. A blinded second operator then took two visually-estimated targeted cores before further systematic biopsies. Although there were no differences in overall cancer or csPCa detection rates multivariate analysis of positive image-fusion and negative visual-estimation targeted biopsies noted that image-fusion had a significantly higher detection rate in anterior lesions (OR 3.84, p=0.05) and those of smaller diameter (OR 0.83, p=0.005) [16]. The converse was reported in a study of 200 men undergoing repeat biopsy; transperineal visual-estimation missed less csPCa (Gleason ≥3+4 and/or >2 positive cores) in the anterior zone compared to transrectal image-fusion biopsy (1 vs. 12, p=0.001) [17]. A study of 396 regions-of-interest in 286 men undergoing transrectal visual-estimation and image-fusion biopsies again found no overall difference in csPCa detection. However, image-fusion found significantly more cancer in the transition zone (p=0.046) [18].

What about when comparisons are made by mpMRI PI-RADS score? Kam et al. indirectly compared men undergoing either transrectal visual-estimation or transperineal image-fusion registration biopsies with systematic cores as the standard. Of 121 men included, there was no difference in csPCa detection rate (p=0.084). However, when considering just those with mpMRI lesions scored PI-RADS 4 or 5, visual-estimation biopsy was superior (91% vs. 71%, p=0.03) [19]. The opposite was seen by Oderda et al. in their study of 50 men – in those with PI-RADS 4 target lesions, image-fusion provided superior overall cancer detection (16.7% vs. 57.9%, p=0.05) [20].

Urologists conventionally use 'centroid' targeting (i.e. aiming towards the centre of the lesion). However, simulation evidence suggests that image-fusion 'ring' targeting may provide a superior cancer yield compared to visual-estimated 'centroid' targeting, as it mitigates for guidance system, image registration and random errors, although this has not been evaluated in a trial setting (Figure 2) [21].

Whether there are any true differences between visual-estimation and image-fusion by other factors remains to be seen. For example, image-fusion registration is known to have a long learning curve [22-24], so does operator experience play a role? What if there is more than one mpMRI target lesion? Is there a difference by anaesthetic route (local vs. sedation vs. general)? Preliminary analysis of the Rapid Assessment and Prostate Imaging
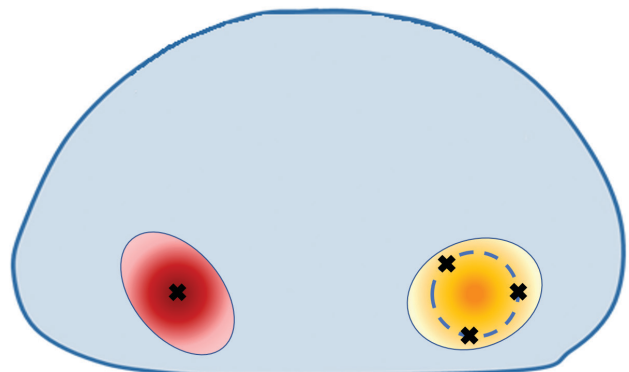

Figure 2: Centroid (red lesion) vs. ring (orange lesion) targeting.

for Diagnosis (RAPID) registry suggests image-fusion may well be advantageous in certain subgroups [25].

Visual-estimation versus in-bore

Osses et al. compared 64 men biopsied using visual-estimation to 155 who underwent in-bore biopsies. csPCa detection rates were similar, and no differences were seen based on PI-RADS score or lesion area. However, in lesions <1.5ml, in-bore was more accurate (39% (9/23) vs. 69% (69/92), p=0.009) [26]. A retrospective Australian study comparing biopsy outcomes in 482 patients with 595 mpMRI target lesions had similar findings. Two hundred and ninety-eight lesions were biopsied in-bore, with the remainder biopsied using visual estimation (either transperineal or transrectal). Again, there were no differences in csPCa (>4 mm Gleason ≥3+4 or >6 mm Gleason ≥3+3) detection overall, by PI-RADS score or by anatomical area. In this study, there was no difference by lesion volume [27]. Finally, Zhang et al. compared 85 men biopsied using visual estimation with 88 undergoing in-bore biopsy. Although in-bore had a superior overall cancer detection rate (36.5% vs. 52.3%, p=0.037), there was no difference in csPCa detection (23.5% vs. 29.5%, p=0.371); in-bore detected more insignificant cancers [28].

Image-fusion versus in-bore

Studies comparing image-fusion and in-bore biopsy are sparse. One RCT allocated 110 men to image-fusion plus systematic 12-core TRUS biopsy and 104 to in-bore. There was no difference in overall cancer or csPCa detection [29]. Similarly, Venderink et al. retrospectively compared 278 men undergoing image-fusion or in-bore biopsy, with no difference in overall csPCa detection noted. However, although in-bore biopsy showed clinically relevant improved detection at all lesion sizes, this was greatest in smaller lesions (8mm: 49% vs 61.2%) [30].

What might the future hold?

Over the last 20 years, the importance of MRI in prostate cancer diagnosis has been established. But will other imaging modalities come to the fore? Radiotracers targeting prostate specific membrane antigen (PSMA) have increasingly been used for early detection of recurrent prostate cancer but may yet have a role in initial diagnosis [31]. Donato et al. evaluated concordance of preoperative PSMA PET/CT and mpMRI with biopsy histopathology and radical prostatectomy specimens (when available) in 144 men.

Although both imaging modalities had high rates of csPCa detection, PSMA PET/CT was superior in detecting secondary cancer foci and smaller lesions [32]. In 31 men with persistently elevated prostate specific antigen but previous negative biopsies, PSMA PET-ultrasound targeted image-fusion biopsy yielded clinically significant disease in 12 (38.7%) [33]. As radiotracers become more readily available and use less restricted, PSMA PET/CT, or PET/MRI to mitigate radiation dose, may be used alongside or even instead of mpMRI in identifying prostate biopsy targets.

Will there come a point at which the reporting radiologist or the biopsying urologist is rendered superfluous? Recent years have seen machine learning techniques applied to prostate diagnostics. Rather than rigidly matching outputs to inputs, machine learning utilises statistical tools to enable improvement in output through experience; the algorithm can change [34]. This technique has been applied to prostate cancer diagnosis. For example, on prostate mpMRI, there are multiple radiomic features unappreciable by the naked eye that may indicate malignancy [35]. Several high accuracy machine learning diagnostic algorithms exist. Litjens et al. developed a machine learning algorithm which can segment and interpret prostate mpMRI. When evaluated in 347 consecutive patients using MR-guided biopsy as the reference standard, area under the curve was 0.889 [36]. Machine learning has also been used to increase accuracy of real-time deformable registration of mpMRI and TRUS imaging, with excellent concordance with human expertly labelled imaging [37]. One could foresee such a time when such advances are implemented in an image-fusion or in-bore robotic device to automate prostate biopsy [38,39].

Conclusion

"The machine is only a tool after all, which can help humanity progress faster by taking some of the burdens of calculations and interpretations off its back" – Isaac Asimov, *The Evitable Conflict*.

At present, the available evidence suggests equivalence between visual-estimation registration, image-fusion registration and in-bore targeting. However, newer iterations of image-fusion platforms may offer the greatest balance of accuracy, cost-effectiveness and ease of use. Visual-estimation may be the most straightforward choice for larger, diffuse lesions, with in-bore used in selected cases for men with ongoing suspicion of cancer despite negative visual-estimation

or image-fusion biopsy. Urologists have traditionally been quick to embrace new technologies and if image-fusion platforms providing diagnostic advantages in certain situations (dependant on anatomical, mpMRI and operator factors) are developed, to offer the best to our patients, we are likely to embrace such change.

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