New standards in prostate biopsy

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Introduction
Prostate cancer diagnosis is undergoing a significant change in recent years. The concern about prostate cancer overtreatment as well as technological developments that allow for better visualization of prostate cancer lesions are the main drivers for this change.

Methods
This was a narrative review of the literature on prostate cancer diagnosis

Results
The diagnostic pathway of prostate cancer based on PSA screening and systematic TRUS has remained unaltered for many years. This is not free of error and many men with insignificant prostate cancer will be diagnosed. Secondly, men with significant prostate cancer will be missed. Moreover, TRUS approach is associated with a non-negligible rate of sepsis. With the introduction of prostate multiparametric MRI, it seems that we are moving towards a less invasive method of triaging men for prostate biopsy and adopting a biopsy technique which aims to target specific areas within the prostate rather than randomly sampling it. There are a number of other imaging modalities that have attracted attention such as Elastography, histoscanning and contrast enhanced ultrasound. A targeted-only biopsy approach is a feasible option for prostate cancer diagnosis that can improve significant cancer detection and reduce insignificant cancer detection when compared to TRUS biopsy.

Conclusion
The introduction of multiparametric prostate MRI has the potential to change the way that we diagnose men with prostate cancer.

Key words: Prostate cancer diagnosis, prostate biopsy, multiparametric MRI.

Introduction

Prostate cancer diagnosis has significantly changed in recent years. Traditional management consists of serum prostatic specific antigen (PSA) and digital rectal examination with systematic transrectal biopsy for men presenting with high PSA or abnormal digital rectal examination. This approach exposes many men without prostate cancer to an invasive and unnecessary procedure. Moreover, significant cancer is missed in more than half of cases, as demonstrated by clinical trial PROMIS where patients underwent transperineal template after systematic 12 core TRUS[1]. Further, this approach leads to the diagnosis of more insignificant prostate cancer, which may not benefit from treatment[2]. The use of MRI pre-biopsy helps to detect and direct biopsies to areas that might harbour significant prostate cancer, reducing unnecessary biopsies and increasing diagnostic accuracy.

Evolution of prostate biopsy

TRUS biopsy

In 1937, Astraldi described the transrectal finger guided core approach as an alternative to open transperineal prostate biopsy. This approach was then described as safe, accurate and direct. In the early nineties the frequency of carrying out prostate biopsy rose with the introduction of PSA test[3]. Alongside this discovery, ultrasound guidance was described to direct the biopsy needles[4]. In 1989, Hodge described the process of sextant biopsy[5], consisting of performing 3 biopsies on the midline of each prostatic lobe to represent base, mid-prostate and apex. That approach led to a great increase in the detection rates of cancer and became a state-of-the-art approach for many years. The zonal description of the prostate by McNeal in 1988 allowed for a better understanding of the areas where prostate cancer was more likely to arise and therefore, it was suggested that the prostate should be sampled more laterally to cover a greater portion of the peripheral zone[6].

Large prostates yielded a lower cancer detection rate so to try and compensate for this, other systematic biopsy schemes included sampling of the transition zone in prostates over 50ml or adjusted the number of cores to the prostatic volume, inflating this number for large prostates[7]. The diagnostic value of TRUS systematic biopsies varies according to different series and patient selection[8], but still with the standard 12 core approach for TRUS biopsy that we use today, this fails to diagnose 52% of significant prostate cancer as demonstrated by the clinical trial PROMIS where 12 core TRUS biopsy was compared to transperineal template mapping biopsy as reference test[1].

Transperineal biopsy

In an attempt to improve diagnostic performance of TRUS biopsies, many authors recommend using a more extended transperineal template mapping. Potential advantages of this technique lie in better sampling of the apical and

anterior part of the prostate (which can systematically be missed on TRUS biopsy), increased accuracy due to the use of a fixed grid, a decrease in infective complications and improved grading that can allow for a more appropriate patient selection for different treatments[9]. On the other hand, the increase in the diagnosis of clinically insignificant prostate cancer and the increased cost due to the need of anaesthesia represent two of the main downsides. Different transperineal biopsy schemas have been described, with the most detailed sampling every 5mm on the biopsy grid, 5mm transperineal template mapping biopsy (TTMB). Although many centres use general anaesthesia or deep sedation for this approach, satisfactory reports have been reported under local anaesthetic only; especially when the number of cores is reduced in the context of limited transperineal biopsy[11]. In an attempt to minimise some of the morbidity and burden associated with full TTMB, but optimise the amount of clinically significant cancer identified, alternative biopsy approaches such as the Ginsburg approach were developed. These approaches spare the transition zone and focus on sampling the peripheral zone, but with less intensity than a TTMB[10]

Complications of prostate biopsy

Complications of transrectal approach

The most frequent adverse events will be presence of blood in the urine, semen or back passage, which will rarely be severe or require further management and will resolve on its own. Thus, in a recent questionnaire, 65.2% of men reported some degree of haematuria following TRUS biopsy but only one in ten reported that this caused any discomfort[12]. Moreover, rates of readmission due to profuse bleeding are generally low, under 1%[13]. Rectal bleeding can be present in around one in 50 men undergoing this procedure. For the rare event of profuse rectal bleeding, men can be managed with balloon tamponade[14], endoscopically with adrenaline injection, vessel clipping or ligation[15] or with selective arterial embolization and with particularly troublesome bleeding surgical suturing of the bleeding point using an anal retractor[16-22]. The rate and severity of infective complications has risen in the last years due to antimicrobial resistance, especially to quinolones, which is widely used as prophylactic agent. Infective complications represent the most common cause for readmission, with variable incidence according to different series (0.6%-5.5%). Rates of post TRUS biopsy deaths are low (0.09-1.2%)[23,24] and generally caused by septic shock.

Complications of transperineal approach

It seems logical that comparing this rather more detailed sampling approach to a systematic 12 cores TRUS biopsy will inevitably result in more morbid outcomes for TP approach. The increase in complication rates primarily arises from the number of cores taken rather than the difference in access route. For example, trials comparing a TP versus TRUS approach where a similar number of cores are taken show a similar frequency in adverse events [25,26]. However, TTMB, where up to 1 biopsy is carried out per ml of tissue, can carry a significant rate of adverse events. For instance, in the PICTURE study, whilst

no change from baseline was noted on the EPIC-Urinary scores, the rate of urinary retention has been reported as 24%, and the rate of erectile function decline on IIEF-15 score as 23%. However, infective complications are rare (no sepsis event were registered in this serie) because unlike transrectal biopsy where faecal matter is carried into the prostate, in transperineal biopsy, this is not an issue since the needles do not cross the rectum[27]. The side effects of less intensive transperineal prostate schemas such as the Ginsburg approach are more tolerable with a much lower rate of urinary retention at 1.5%[28],.

Use of imaging in the diagnosis of prostate cancer

Prostate cancer is the only solid organ cancer where diagnosis is typically made with "blind" biopsies, taken without knowing where suspicious areas are. In the last decade, different imaging techniques have been developed to identify suspicious areas within the prostate that could harbour significant prostate cancer. These imaging approaches are primarily based on multiparametric MRI (mpMRI) or means that improve the diagnostic utility of transrectal ultrasound (TRUS) such as contrast enhanced ultrasound (CE-TRUS), Histoscanning or elastography. Image guided biopsies are typically added to systematic biopsy regimes. To assess the diagnostic utility of the image guided biopsies, the ideal scenario is a comparison of diagnostic efficacy between a systematic and a targeted biopsy with biopsy cores potted separately for each. Ideally, different operators should perform the systematic biopsies and targeted biopsies and the operator performing the systematic scheme should be blinded to the image guided targets. These methods reduce bias and allow a fairer comparison of the role of image-targeted biopsies to be made.

Contrast enhanced ultrasound TRUS (CE-TRUS)

Use of contrast ultrasound involves the use of microbubbles that enter the blood vessels and reflect the vascularization of a certain region. Different agents have been tested, and there is extensive experience in the use of this imaging technique for investigation of cardiac perfusion or liver malignancies[29]. In theory, this approach will be advantageous in terms that is relatively harmless, allows for real time visualization of the prostate anatomy, as well as allows to identify areas of increased vascularization; which ultimately can spot areas suspicious to harbour prostate cancer.
Many trials have evaluated the efficacy of CE-TRUS in detecting prostate cancer, Mitterberger et al.[30], randomised 100 patients to have either systematic TRUS biopsy (SB) or contrast ultrasound targeted biopsies. They found that the sensitivity rose from 26% to 32% whilst halving the number of cores from 10 to 5.

Frauscher[31] compared CE-TRUS vs SB and found a detection rate of 30% and 22.6% respectively. Cancer was detected solely by CE-TRUS or SB in 7.4% and 5.6% of cases respectively Furthermore, Pelzer[32] evaluated the results of combining both CE-TRUS and SB on 380 men. The cancer detection rate of combined approach increased to 37.6% compared with SB and CE-TRUS alone (27.6% and 27.4% respectively).

Ultrasound elastography

Ophir first described Sonoelastography in 1991[33], this technology evaluates tissue elasticity and prostate reaction to compression. The rationale behind elastography is that areas of solid malignancies might alter the elastic properties of the organ. Elasticity changes can be represented in a qualitative (different colours) or quantitative manner on ultrasound. Pallwein et al.[34] analysed 492 patients with sonoelastography (SE) grading the areas in the peripheral zone as soft, intermediate or hard. The "hard" areas were biopsied and subsequently all patients received a 10 cores systematic biopsy. They reported a sensitivity of 86% and specificity of 72% for the diagnosis of any cancer compared with a systematic biopsy sensitivity of 25.4%. Salomon et al.[35] retrospectively analysed 1024 patients undergoing a 4 core SE-targeted biopsy in addition to a 10 core systematic biopsy. They reported that targeted cores increased diagnostic rate of any cancer by 7.1% over systematic 10 cores only. Furthermore, 34 patients with significant Pca Gleason 4 or higher were diagnosed exclusively on the SE-targeted biopsy.

Histoscanning

Histoscanning is an ultrasound based scan of the prostate which uses back-scattered ultrasound and specific computer aided software to identify suspicious areas of malignancy. Echoes originating from the microenvironment in the prostate are different between benign and malignant tissue. These differences can be highlighted on the ultrasound screen with colour coded areas marking areas of suspicion. Early reports with analysis of radical prostatectomy specimens showed promising results, with sensitivity and specificity as high as 100% and 82% respectively[36]. Unfortunately, these results were not confirmed in a prostate biopsy setting. Schiffmann et al.[37] retrospectively compared 1188 sextant biopsies in 198 men and reported a sensitivity for diagnosis of any cancer of 84.1%, 60.9%, 40.1% and specificity of 27.7%, 60.9% and 73.3% for a signal cut-off of >0ml, >0.2ml and 0.5ml respectively. The authors conclude that Histoscanning is a poor predictor of a positive prostate biopsy and therefore should not change the systematic TRUS diagnostic approach.

Role of MRI in prostate cancer diagnosis

Magnetic resonance is an imaging technology based on the use of magnetic fields that allow for a detailed visualization of soft tissues. Multiparametric MRI can yield different information on different sequences. In basic terms, T2-sequences give anatomical information and diffusion sequences give information on the diffusion of water molecules, where areas with restricted diffusion of water molecules are more likely to harbour prostate cancer. Dynamic contrast enhanced sequences, which involve taking images at different points in time after contrast administration, can also identify suspicious areas as cancerous lesions, which can demonstrate early vascularization and early wash out pattern.

The use of magnetic resonance in evaluation of prostate cancer is a conceptual change as we move from an approach of TRUS biopsy where suspicious areas cannot be seen to an imaging modality of MRI, that allows for visualisation of the cancer, which can influence where prostate biopsies are taken from. MRI mainly identifies aggressive prostate cancer whereas clinically insignificant prostate cancer is often not identified and can be avoided. Mp-MRI can be used with two intentions, the first is to discriminate which men might benefit from a prostate biopsy. Secondly, MRI findings can serve to direct prostate biopsies should these be deemed indicated.

Use of MRI as a triage test for prostate cancer evaluation

The aim of the clinical trial PROMIS was to evaluate the utility of MRI as a triage test for prostate biopsy. Patients underwent mp-MRI and subsequent TRUS and TTMB. The operator performing the prostate biopsies was blinded to the MRI findings. The ability of both TRUS and mp-MRI to diagnose men with prostate cancer was evaluated with TTMB as a reference standard. The negative predictive value of MRI for ruling out significant prostate cancer was 76% for any Gleason ≥3+4 and 89% for UCL definition 1 (Gleason score ≥4+3 or cancer core length ≥6 mm), compared to 63% and 74% for TRUS biopsy respectively. The authors proposed that a negative MRI be used to avoid a biopsy and highlighted that over a quarter of men in this position would have avoided a prostate biopsy. Of note, the positive predictive value of MRI for significant prostate cancer detection was 65% for any Gleason ≥3+4, highlighting that a biopsy is still necessary to distinguish between cancer and other benign conditions mimicking prostate cancer such as prostatic inflammation[38].

Further to this, Panebianco et al. randomised 1140 biopsy naïve men with suspicion of prostate cancer to have TRUS biopsy or mp-MRI and subsequent TRUS biopsy plus MRI TB. Results of this trial showed superiority of MRI-TB to identify prostate cancer (73 vs 38%). All 355 patients with a negative initial TRUS underwent mpMRI, of these 208 with a positive MRI underwent further TRUS and TB which found 186 prostate cancers. MpMRI demonstrated and accuracy of 97% for diagnosis of prostate cancer. Moreover, ADC value was significantly correlated with Gleason score[39].

Systematic vs targeted biopsies

The recent improvement in reporting and conducting of mp-MRI allow for a better visualization and detection of prostate cancer. Therefore, the need to perform systematic biopsies or rather target only areas deemed to be suspicious on MRI is unclear.

To address this dilemma, the clinical trial PRECISION randomised 500 men to a diagnostic pathway of standard 10-12 cores TRUS biopsy versus an approach of MRI first as a triage test[40]; excluding men with negative MRI findings (PI-RADS v2 score ≤2) from having a biopsy and performing MRI targeted biopsy on those with PI-RADS v2 score ≥3. Clinically significant prostate cancer (defined as one or more core presenting a Gleason score of 3+4 or higher) was

diagnosed in 38% of men in the MRI arm as opposed to 26% in the TRUS biopsy arm. The 95% confidence interval showed superiority of MRI over TRUS approach, this was the case for intention-to-treat, modified intention-to-treat and per-protocol analysis. Moreover, the rate of low grade prostate cancer was significantly higher in the TRUS group (9 vs 22% in the MRI-targeted group). The conclusions of this trial justify an image-based pathway that reduces the number of men needing a prostate biopsy and the complication rate on those who do. The rate of clinically significant prostate cancer is increased with this approach whilst the rate of insignificant prostate cancer is reduced.

Integration of MRI findings to direct biopsies

Registration of mp-MRI targets to direct biopsy cores can be performed by different means. These can entail performing biopsies directly under the real-time guidance of an MRI scan (In-bore), acknowledging the MRI targets and using one's own judgment to direct the needles into these areas on realtime ultrasound (cognitive biopsy) or using software to overlay the MRI targets on a real time US scan (fusion biopsy).

One important question is whether any of the aforementioned MRI registration strategies has a greater diagnostic rate. Wegelin et al.[41] failed to demonstrate statistical difference in the pooled sensitivities of In-bore, Fusion or cognitive approaches (0.92, 0.89 and 0.86 respectively); concluding that there was no significant advantage in the use of any of these integration methods over the other.

In-bore biopsy

In-bore biopsy is performed within the MRI scanner. This approach entails fusing a prior MRI, where the targets were seen, with a contemporaneous MRI scan used by the radiologist to direct the needles. After each key positioning of the needle, the patient is re-scanned to ensure it is in the intended location. This strategy carries some disadvantages, namely the need for MRI compatible biopsy equipment, the increased in-scan time and the additional training required by the radiologist. On top of these, this approach can increase economic burden; On the other hand, this approach allows for a precise recording of the needles placement and reduced the number of biopsy cores as well as reducing rates of insignificant prostate cancer diagnosis.

Cognitive biopsy

In the cognitive approach, the biopsy operator visually registers the MRI targets on the TRUS scan to guide the biopsy needles. The information on the target locations can be given to the biopsy operator as a prose or visual report. Anatomical landmarks (such as urethra, prostatic cysts or relation with seminal vesicles) will usually be used as reference to locate the suspicious areas. This approach requires training in both transferring the visual information from one scan to the other and interpretation of MRI scans (as a MRI scan review by the operator is usually recommended before the procedure). The disadvantage of this procedure is the potential human error when registering the MRI targets onto the US scan

Fusion biopsy

Software based fusion biopsy integrates MRI targets on the US live scan used while performing a prostate biopsy. There are a number of steps in this procedure which vary from one system to another. The basic process will include performing an mpMRI and delineating the targets, this plan is then transferred to the fusion device where it is combined with the real-time US image.

Different techniques may be used to map the MRI data to the US. In the rigid fusion approach the MRI plan remains static and does not alter in shape despite deformation of the prostate during the procedure. The elastic and deformable techniques alter the MRI plan to match the surface of the prostate in the US image taking into account changes in its shape due to the position of the patient and the presence of the ultrasound probe in the rectum.

This strategy is gaining popularity and a number of different platforms have been developed. There are differences in the methods of registration of the targets, operator input, learning curves, costs and possibility to perform transperineal, transrectal approach or both (Table 1). The clinical trials that led to their commercialisation are heterogeneous in inclusion criteria and definition of significant prostate cancer, thus comparing diagnostic accuracy between devices is difficult.

Summary

The diagnosis of prostate cancer is experiencing a major change in recent years. The incorporation of imaging techniques, particularly multiparametric MRI, can allow for better selection of prostate biopsy candidates, whilst improving diagnostic yield and reducing the over diagnosis of clinically insignificant cancer that can lead to overtreatment. Prostate MRI can be used either as a triage test or a means to direct biopsies. There are different means to register MRI targets on the ultrasound scan, though the benefit of one over another is not clear. There seems to be a shift trend towards transperineal biopsy approach as it allows for an easier registration of MRI targets and it reduces infection risks. More selective targeted biopsy reducing number of cores, allows performing the procedure under local anaesthetic and is a viable diagnostic strategy. Efforts in training both urologists and radiologists in prostate MRI are warranted in order for them to make best use of this technology.

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	US scan characteristics and tracking mechanism	Image registration	Other comments
Uronav (Invivo/Philips)	Freehand swap, 2D scan. Electromagnetic tracking	Rigid	Easier learning curve “software based”
Urostation (Koelis)	Built in ultrasound Automated US probe scan, 3 volumes visually registered	Elastic	Image based registration Automatic contour of the prostate
Biopsee	US probe attached to arm fixed to operating table. Virtual needle insertion recording	Rigid	Training required with device and software. Allows for other modalities of US scan such as Histoscanning or elastography
Artemis	US scan probe rotates on a fixed axis using an articulated arm. Needle tracking recorded based on encoders at joints of mechanical arm	Elastic	Training required not only on software but also on fixed rotation of TRUS probe as opposed to freehand.
Virtual navigator/Esoate	MRI targets uploaded into software. Rigid registration performed to integrate targets with free hand moving us scan	Rigid	Allows for integration of different imaging, CT, PET, MRI.
Real-Time Sonography (HITACHI)	Freehand swap, 2D scan. Electromagnetic tracking	Rigid	Allows for integration of different imaging, CT, PET, MRI
SmartTarget	US probe attached to third party stepper device with arm fixed to operating table.	Deformable	Machine learning fusion technique realistically compensates for prostate deformation.

Table 1: Differences in the methods of registration of the targets, operator input, learning curves, costs and possibility to perform transperineal, transrectal approach or both for different fusion biopsy systems