ABSTRACT

Objectives
To determine whether modified transperineal template prostate mapping (TTPM) biopsy protocols, altering the template or the biopsy density, have sensitivity and negative predictive value equal to full 5mm TTPM.

Materials and Methods
Retrospective analysis of an institutional registry including treatment-naïve men undergoing 5mm TTPM analysed in 20 zones fashion. The value of three modified strategies was assessed by comparing the information provided by selected zones against full 5mm TTPM. Strategy 1 did not consider the findings of anterior areas; strategies 2 and 3 simulated a reduced biopsy density by excluding intervening zones. A bootstrapping technique was employed to calculate reliable estimates of sensitivity and negative predictive value of these three strategies with respect to detection of clinically significant disease (maximum cancer core length >/= 4mm and/or Gleason score >/= 3+4).

Results
391 men with median age 62 years (IQR 58-67) were included. Median PSA and PSA density were 6.9 ng/ml (IQR 4.8-10) and 0.17 (IQR 0.12-0.25), respectively. A median of 6 cores (IQR 2-9) out of 48 taken per man (IQR 33-63) were positive for prostate cancer. No cancer was detected in 67 men (17%), whilst low, intermediate and high risk disease was identified in 78 (20%), 80 (21%) and 166 (42%), respectively. Strategy 1, 2 and 3 had sensitivities of 78% (95% CI 73-84%), 85% (95% CI 80-90%) and 84% (95% CI 79-89%), respectively. The negative predictive values of the three strategies was at 73% (95% CI 67-80%), 80% (95% CI 74-86%) and 79% (95% CI 72-84%), respectively.
Conclusion

Altering the template or decreasing sampling density has a substantial negative impact on the ability of TTPM to rule out clinically significant disease. This should be considered when modified TTPM strategies are performed to select men for tissue-preserving approaches, and when modified TTPM are employed to validate new diagnostic tests.
Introduction

The management of localised prostate cancer has been fraught with errors in attributing cancer risk due to the inaccuracies of the transrectal ultrasound guided (TRUS) biopsy [1]. A number of studies have shown that in around half of men undergoing radical prostatectomy, the prediction of grade and/or stage is wrong [2-4]. The true degree of diagnostic error is difficult to ascertain as those men with a negative TRUS biopsy do not usually undergo a more accurate verification test.

There have been attempts to increase the diagnostic value of sampling techniques other than the standard 10-12 core TRUS biopsy. Increasing the sampling density of transrectal biopsy using pre-established templates – so-called saturation biopsy – have met with variable results [5, 6]. For instance, despite initial encouraging results, a recent large multi-centre randomized controlled trial has shown that there was no increased detection of disease using this approach compared to a standard one [7].

Yet others have proposed that the sampling strategy should switch to incorporate a transperineal route as this allows a more systematic approach to the whole prostate including apex and anterior regions which are often missed on TRUS biopsy. However, transperineal biopsies can be performed in a number of different ways with varying biopsy densities. These can generally be categorised into those that first, map the prostate by taking biopsies every 5mm [8-11] or second, those that sample regions of the prostate but with reduced density of cores [12-15]. Whilst computer simulation studies demonstrate less sensitivity in detecting lesions that are >0.5cc or >0.2cc in volume when using a 10mm sampling frame compared to taking biopsies every 5mm [16], it is not known whether this is the case in patients. The aim of our study was to test whether diagnostic accuracy vary, and if so to what extent, when using different transperineal biopsy strategies.
Materials and Methods

Ethics committee exemption was granted for our study which involved evaluating our template transperineal prostate mapping (TTPM) biopsy institutional registry. The TTPM biopsy registry includes all patients undergoing this procedure from 05/2006 till the 01/2012. Men having TTPM biopsy after local or systemic prostate cancer treatment were excluded; 5-alpha reductase inhibitors were permitted.

TTPM biopsies were performed following a modified-Barzell template with a 5mm density as previously reported [11]. The procedure was carried out under general anaesthesia with single dose intravenous antibiotics. After positioning a urethral catheter, the urethra was aligned in the ‘D3’ or ‘D2.5’ grid position at the largest axial part of the prostate, and using a 5mm frame, at each coordinate one to two cores were taken in order to sample the whole prostate in the cranio-caudal axis. The prostate was divided in 20 zones and each core taken was potted and analysed within the respective area (figure 1). Histopathology results were given per zone, and included number of total cores taken, number of positive cores, Gleason score, maximum cancer core length and total cancer length.

For the purpose of the study, clinically significant disease was defined using the UCL risk classification, previously developed for TTPM biopsy findings (figure 1) [11]. We considered the sum of UCL intermediate- (Gleason >/=3+4 and/or maximum cancer core length >/=4mm) and high-risk disease (Gleason >/=4+3 and/or maximum cancer core length >/=6mm) as clinically significant.

The detailed manner in which the TTPM biopsy data was collected, with a high spatial resolution of risk attribution, permitted us to determine the impact of changing our template transperineal biopsy strategies. In effect, we excluded certain zones from contributing diagnostic information to the overall risk attribution to evaluate the effect of removing these
zones. We evaluated three strategies in total. Strategy 1 involved excluding the anterior areas of the prostate representing the transition area, but not the anterior horns which were sampled within the lateral zones. Strategy 2 and strategy 3 involved a reduced sampling density from 5mm to 10mm by taking out intervening areas. The difference between these latter two strategies was related to which zones were excluded from contributing diagnostic information, as shown in figure 2. These three strategies were then compared to what we deemed the reference standard, the full 5mm TTPM biopsy result.

Statistics

Standard evaluation of diagnostic tests includes the determination of four parameters: sensitivity, specificity, positive predictive value and negative predictive value. In this case, since the index tests (the three sampling strategies) were not independent of the reference test (5mm TTPM) the calculation might have wrongly led to over-estimation of specificity and positive predictive value; therefore, we determined only sensitivity and negative predictive value with respect to clinically significant disease. To calculate reliable estimates, a bootstrapping technique was employed to mimic the sampling distribution. We used 500 repeat simulations for each dataset to estimate proportions and calculate 95% confidence intervals (CI). The statistical analysis was performed using the STATA® software version 11.1 (Stata Corp. 2009, Stata Statistical Software: Release 11, College Station, TX, USA).

Results

Of 485 cases present in the TTPM biopsy registry, 94 were excluded (89 had previous treatment; five had incomplete data), leaving 391 evaluable cases for this study. Median age was 62 years (IQR 58-67). Median PSA, PSA density and prostate volume were 6.9 ng/ml (IQR 4.8-10.0), 0.17 (0.12-0.25) and 39.5 ml (30-52) respectively.
Most of these patients (69%; 269/391) underwent TTPM biopsy in order to be considered for tissue-preserving approaches after an initial diagnosis of prostate cancer based on TRUS biopsy, but some of them had previous negative biopsy (19%; 75/391) and a minority had TTPM biopsy as the first-line sampling technique (12%; 75/391) (table 1). When a cancer diagnosis was already given by prior TRUS biopsy (n=269), the majority were D’Amico low or intermediate risk (Table 1).

TTPM biopsy results are displayed in table 2. No cancer was found in 17% (67/391); of these, 22% (15/67) and 10% (7/67) had a previous diagnosis of low and intermediate risk disease, respectively—and 20% (78/391) were considered to harbour low-risk disease by UCL criteria (Gleason $\leq 3+3$ and cancer core length $\leq 3$mm). Clinically significant disease was present in 63% (246/391) with 21% (80/391) and 42% (166/391) harbouring intermediate- and high-risk disease, respectively. For each Barzell-modified zone, we calculated the percentage of men harbouring no cancer, UCL low risk, intermediate and high risk prostate cancer. Figure 3 shows risk stratification in a per zone fashion.

With respect to diagnosis of clinically significant disease, strategy 1, 2 and 3 had sensitivities of 78% (95% CI 73-84%), 85% (95% CI 80-90%) and 84% (95% CI 79-89%), respectively (table 3). The negative predictive values were lower at 73% (95% CI 67-80%), 80% (95% CI 74-86%) and 79% (95% CI 72-84%), respectively.

Discussion

Our study shows that altering the template transperineal sampling strategy by preferential sampling of certain locations or reducing the sampling density leads to significant reductions in the ability of the test to rule-out clinically significant prostate cancer when compared to full 5mm mapping biopsies.

Limitations
Prior to considering the clinical implications of our study, we would like to acknowledge its limitations. First, the study population was heterogeneous. This population reflects the practice in our tertiary referral hospital, but might not represent the same population undergoing template transperineal biopsies in other centres. Second, the alternative template biopsy strategies were artificially simulated and may not fully represent true clinical practice. However, we believe our design is an efficient one that allows the derivation of important information on clinical validity and utility without having to resort to a randomised design. Third, it may be argued that TTPM biopsies using a 5mm sampling density cannot be considered a reference test at the same level as radical prostatectomy. While we agree that TTPM has a diagnostic inaccuracy of approximately 5%, it should be noted that it can be applied to all men, including those with no previous biopsy or negative TRUS findings, or those considering treatment options (active surveillance, focal therapy, radiation therapy) other than radical prostatectomy. As a consequence, it overcomes the considerable selection bias that is inherent in comparing new diagnostic tests that are inherent to whole-mount prostatectomy sections. Further, TTPM biopsies have recently been shown to be highly accurate in ruling-in and ruling-out clinically significant disease in clinical series in which TTPM biopsies were followed by radical prostatectomy [4, 8].

Clinical implications
In our study, we sought to evaluate a number of other template transperineal biopsy strategies in terms of diagnostic accuracy. There have been various differing reports and recommendations for how transperineal biopsies are or should be conducted. One group proposed the use of a protocol that included 22 cores from 12 biopsy locations. In a cohort of 414 men undergoing transperineal biopsy using this strategy, Gleason score upgrading occurred in about 25.6% when the results of biopsy were compared to radical prostatectomy specimen [15]. Although the template covered the whole prostate, the sampling density was likely to be set around 10mm as the median number of cores was 22 and the mean prostate volume was around 50cc. In addition, this study clearly showed that the biopsy density
matters, as the agreement between biopsy and whole-mount histology results was significantly lower in the larger prostate, in which the biopsy density was lower. Other groups use protocols that preferentially sample the peripheral area while performing limited sampling of the anterior part of the prostate [12, 13]. In our study, avoiding the sampling of the transition zone led to a decrease in sensitivity and negative predictive value for clinically significant disease of over 20%. This means that in at least one man out of five who has a negative template biopsy, such as the one we describe in strategy 1, clinically significant disease would be missed. This may have important consequences as transperineal biopsy are usually offered to men seeking correct risk stratification, and inaccurate results may lead to incorrect management.

Recently, experts in the field of prostate diagnosis attempted to define a standardized approach to perform transperineal template biopsy in the setting of a consensus meeting using validated methodology (UCLA-RAND) [14]. The panellists suggested a variable number of cores ranging from 24 to 38, according to prostate volume. Although the outcomes of this protocol were not compared to a reference test, we believe that these suggestions should be questioned based on our findings. Indeed, this consensus recommendation leads to fluctuating biopsy density with low- and mid-volume prostates being sampled with around 5mm density, and large-volume prostates being less intensively sampled. As a result, in the latter group of men, there might be significantly decreased detection rates compared to a 5mm sampling frame.

The use of TTPM biopsies has some problems. It requires general anaesthesia both because of pain issues and because patient movements would affect the template precision. This means that the systematic use of TTPM has cost and resource implications. Reducing the biopsy density might have a positive impact on this, and indeed a recent series has shown the feasibility of performing an alternative TTPM strategy under local anaesthesia.
However, in light of our findings, the reduced cost should be balanced against the reduced diagnostic performance and its clinical implications.

In addition, the high biopsy density of TTPM can lead to hematuria (50%), erectile dysfunction (26%) and acute urinary retention (3%), although the morbidity is temporary [18]. This has to be weighed against another important advantage of the transperineal approach which is the negligible risk (<0.5%) of sepsis compared to the transrectal route (2-4%) [19]. It is not clear in the literature, and this is a question we were clearly unable to answer, as to whether decreasing the biopsy density or avoiding sampling certain zones might reduce the complication rates.

We fully acknowledge that the future strategy might involve the use of targeted biopsy directed to MRI suspicious areas of the prostate. This imaging-guided strategy would aim to maximise the efficiency and diagnostic accuracy of limited sampling and relies on what seems to be a high negative predictive value of a well conducted expertly read multi-parametric MRI [20]. Some studies have shown similar detection rates of targeted biopsy against template mapping biopsy [21, 22]; however, none of these studies compared targeted biopsy to systematic 5mm sampling.

As well as being used for accurate risk stratification of disease, template transperineal biopsies have also been proposed as the reference test to validate novel imaging tests such as multi-parametric MRI (mpMRI). One recent study by Thompson JE et al. attempted to determine the accuracy of mpMRI to detect clinically significant prostate cancer using transperineal 30-core template biopsy and targeted biopsy as the reference test. mpMRI provided excellent (>90%) sensitivity and negative predictive value, whereas the performance in terms of specificity and positive predictive value was moderate (~50%) [23]. Based on our own findings, the accuracy of mpMRI may actually be over-estimated as the reference test in the report by Thompson JE et al. might not be reliable in all men, especially in those with large volume glands as it is very similar to strategies 2 and 3. Two ongoing
multicentre UK trials are assessing the diagnostic value of mpMRI in biopsy-naïve men (PROMIS) [24] and in men with prior TRUS biopsy (PICTURE) [25] against 5mm TTPM. This design aims to overcome the inaccuracy linked to misclassification and to selection bias when using TRUS biopsy or radical prostatectomy specimens, respectively.

In conclusion, transperineal template biopsies that use reduced sampling densities seem to reduce diagnostic accuracy compared to a full template transperineal mapping strategy in which biopsies are taken every 5mm. If systematic sampling of the whole prostate is to be used using a transperineal approach, men and their physicians should aware of the impact of different strategies has on the ability of the test to rule-out clinically significant disease both on an individual level but also for the purpose of validating novel imaging tests.

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Conflict of Interest
M. Valerio has received funding for conference attendance from Geoscan Medical. M. Emberton and H.U. Ahmed receive funding from USHIFU, GSK, AngioDynamics and Advanced Medical Diagnostics for clinical trials. M. Emberton is a paid consultant to
AngioDynamics, Steba Biotech and SonaCare Medical (previously called USHIFU). Both have previously received consultancy payments from Oncura/GE Healthcare and Steba Biotech. None of these sources had any input whatsoever into this article.

Legends

Table 1
Patients’ characteristics.

Table 2
Overall 5mm transperineal template prostate mapping biopsies findings.

Table 3
Sensitivity and negative predictive value of the three TTPM strategies with respect to identification of clinically significant prostate cancer.

Figure 1
Modified Barzell-template biopsy report. Briefly, for readers unfamiliar with this template, zones 1-4 and 7-10 include the anterior prostate, 11-12 include the lateral horns, 5-6 and 13-20 include the posterior prostate.

Figure 2
Visual representation of the three strategies simulating reported variations of 5mm TTPM.

Figure 3
Risk stratification in a per zone fashion.
REFERENCES


