The Use of Transperineal Sector Biopsy as A First-Line Biopsy Strategy: A Multi-Institutional Analysis of Clinical Outcomes and Complications

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Purpose: Systematic transrectal ultrasound biopsies have been the first-line biopsy strategy in men with suspected prostate cancer for over 30 years. Transperineal biopsy is an alternative approach but has been predominately reserved as a repeat biopsy strategy and not widely used as a first-line approach. This study evaluates the diagnostic and clinical outcomes of transperineal sector biopsy (TPSB) as a first-line biopsy strategy in the diagnosis and management of prostate cancer.

Materials and Methods: A multi-institutional review of 402 consecutive patients who underwent primary transperineal sector biopsy. All patients had no prior history of prostate biopsy. TPSB was carried out as a day-case procedure under general or regional anaesthesia. The cancer detection rate, location and complications for all cases were evaluated.

Results: Prostate cancer was identified in 249 patients (61.9%) and was comparably sited across anterior, middle and posterior sectors. The disease was clinically significant (Gleason 3+4 or > 4mm maximum cancer length) in 187 patients (47%). Post biopsy urinary retention occurred in 6 patients (1.5%). Hematuria requiring overnight hospital admission occurred in 4 patients (1.0%). There were no cases of urosepsis.

Conclusions: As a primary diagnostic strategy, TPSB is a safe and effective technique with high cancer detection rates. It also offers an attractive compromise to more extensive transperineal protocols, which can be more time-consuming and associated with higher morbidity.

Keywords: biopsy; disease management; prostate cancer; transperineal; needle biopsy

INTRODUCTION

Systematic transrectal ultrasound biopsies have been the gold standard first-line biopsy strategy in men with suspected prostate cancer for over 30 years. The original sextant technique was described by Hodge et al[1]. and was extended to include 10 to 12 core biopsy schemes directed towards the lateral peripheral zones[2]. These extended biopsy schemes improved cancer detection rates but a significant proportion of tumours are missed[3,4] and disease is mischaracterised[5,6]. Approximately a third of patients with low risk disease on transrectal biopsies are found to have intermediate or high risk disease on subsequent transperineal biopsy[7-9]. This leads to diagnostic uncertainty and as a consequence risks both over and under treatment. There are further concerns regarding increasing rates of transrectal biopsy sepsis with the emergence of fluroquinolone resistant bowel flora[10,11]. Transperineal template biopsy developed as a more comprehensive biopsy to improve the sampling of the anterior and apical regions which are not easily biopsied transrectally, particularly in the larger gland[12]. Initially thought to be rare, these anterior tumours when large (pT3) increase the likelihood substantially of a positive surgical margin[13] and a recent study demonstrated anterior tumours accounted for 80% of cancer on saturation biopsy[14]. Drawbacks are associated with cost of equipment, general anesthesia and extended pathological processing. To offset these, benefits are a painless procedure, reduced risk of sepsis13 and improved pathological information, which would improve the stratification of disease and selection of patients for active surveillance or radical treatment options. Previous studies on transperineal biopsy have focused on its use as a repeat biopsy strategy. There have been limited reports on its use as an initial primary diagnostic procedure. With the increasing use of pre-biopsy MRI, targeted biopsies may become the norm[15]. For the time being, however, it is necessary to systematically sample the normal appearing peripheral zone to avoid missing disease not visible on MRI[16]. This paper evaluates our transperineal sector biopsy (TPSB) approach in the primary biopsy setting between 2007 and 2013. The biopsies were a systematic sampling

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Table 1: Criteria for Primary TPSB

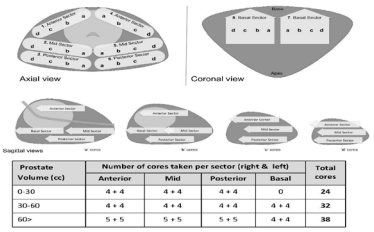
Immunocompromise inferring increased risk of sepsis e.g. Diabetes, immunosuppressant drugs
Increased risk of fluoroqinolone resistant bowel flora e.g. recent treatment with fluoroquinolone antibiotics or travel to South-East Asia.
Anterior/ apical anomaly on MRI
Enlarged prostate (> 40cm^3)
Patient preference for general anaesthetic

of the peripheral zone and were not directly informed by pre biopsy MRI findings. We report the cancer detection rate, clinical outcomes and morbidity of TPSB in patients undergoing their first set of prostate biopsies.

PATIENTS AND METHODS

Databases at three institutions were interrogated for information on patients who underwent primary transperineal sector biopsy (TPSB) between January 2007 and August 2013. The inclusion criteria were all patients referred with an elevated age-adjusted PSA and/or abnormal DRE. Men who had a previous biopsy were excluded. All patients were provided with information on standard transrectal biopsy under local anaesthetic and TPSB under general anaesthetic. At two institutions, TPSB was offered as the optimal approach for patients fulfilling the criteria in **Table 1**. In the third institution within the private sector, TPSB was as the first-line approach for the majority of patients. Four hundred and one patients underwent the procedure as a day-case under regional or general anaesthesia. Pre-operative administration of alpha-blockers or catheterisation was not carried out. At induction an intravenous aminoglycoside (usually gentamicin) was administered as prophylaxis. All patients were positioned in the extended dorsal lithotomy position and a rectal examination was done. The technical setup was similar to that for brachytherapy. A biplanar transrectal ultrasound probe machine attached to a stepping unit with a standard 5mm brachytherapy template grid was positioned over the perineum. Volumetric ultrasonographic evaluation of the prostate was performed to determine prostate size by ellipsoid approximation. An 18-gauge biopsy needle with a 22mm sampling depth was directed through the brachytherapy template grid traversing the perineum to the apical prostate in the sagittal plane. Real time transrectal ultrasonography aided differentiation of transition-peripheral zone interface to facilitate preferential sampling of the peripheral zone according to our standardised sector biopsy protocol[17]. The procedure time is approximately 15 minutes per patient. Patients were discharged after successful voiding, usually within four hours, and patients were discharged with 3 to 5 days of an oral fluoroquinolone (usually ciprocloxacin). All patients were reviewed 7 to 14 days post biopsy and any complications recorded. Our TPSB protocol is standardised biopsy scheme in which the prostate is divided into sectors (**Figure 1**). Biopsies were taken from anterior, middle and posterior sectors with additional basal sectors in prostates larger than 30cc. The exact number of biopsies was determined by the volume of the prostate and ranged from a minimum of 24 to a maximum of 38 cores (**Figure 1**). Cores were placed into separate pots by sector distribution (i.e. one pot per sector). All cores were analysed by dedicated uro-pathologists. The primary outcome measures were the detection rate of any prostate cancer as well as detection rate of clinically significant cancer. Clinically significant disease was defined as maximum cancer core length

Figure 1. Transperineal Sector Biopsy Core number protocol



Prostate Volume (cc)	Number of cores taken per sector (right & left)				Total cores
	Anterior	Mid	Posterior	Basal	
0-30	4 + 4	4 + 4	4 + 4	0	24
30-60	4 + 4	4 + 4	4 + 4	4 + 4	32
60>	5 + 5	5 + 5	5 + 5	4 + 4	38

Table 2: Baseline patient characteristics, stratified by TPSB biopsy diagnosis

Characteristic	All patients	Prostate Cancer	No Prostate Cancer	P value
No of patients (%)	402	249 (61.9)	153 (38.1)	
Mean (SD, median)				
Age at biopsy, years	61.1 (8.73, 61)	62.0 (8.6, 62)	59.0 (8.4, 60)	0.02[a]
Prebiopsy PSA, ng/mL	12.8 (31.2, 6.9)	15.9 (29.0, 7.5)	7.7 (6.1, 6.3)	<0.01[a]
Free/total PSA ratio	15.3 (9.38, 14.0)	16.0 (0.1, 14.0)	14.0 (0.05, 12.0)	0.77[b]
Prostate volume, mL	47.0 (25.2, 40.0)	41.3 (19.2, 39.5)	56.4 (30.5, 50.0)	<0.01[a]
PSA density, ng/mL/mL	0.27 (5.4, 0.15)	0.38 (6.4, 0.19)	0.14 (3.1, 0.12)	<0.01[a]
No. biopsy cores	28.6 (6.2, 29)	27.7 (6.2, 27.5)	29.9 (5.9, 31) 0.35b	
DRE (%)				0.02[c]
Normal prostate	281 (70)	95 (38)	26 (83)	
Abnormal finding	121 (30)	154 (62)	127 (17)	

[a]Student's *t*-test, [b]Mann-Whitney *U*-test,[c] Pearson's chi-square test

Table 3: Pathological features

	N (%)
Clinically significant cancer(18)	
Significant	187 (75.1)
Insignificant	62 (24.9)
Gleason score	
3 + 3	120 (48.2)
3 + 4	73 (29.3)
4 + 3	23 (9.2)
≥ 8	33 (13.3)
positive cores	
1 – 4	106 (42.6)
5 – 12	110 (44.2)
> 12	33 (13.3)
Sector location	
Anterior only	43 (17.3)
Mid only	13 (5.2)
Posterior only	26 (10.4)
Anterior & mid	27 (10.8)
Mid & posterior	22 (8.8)
Posterior & anterior	12 (4.8)
Anterior, mid & posterior	106 (42.6)

(mccl) greater than 4mm and/or Gleason score 3+4 or greater[18]. Secondary outcome measures included tumour location and adverse events. Statistical analysis was performed using the Statistical Package for Social Sciences software (Version 20.0; SPSS Inc., Chicago. IL). The Mann-Whitney U-test, Student's t-test and Pearson's chi square test were used to compare continuous and categorical variables as appropriate. All p-values were two sided and statistical significance was set at $P < .05$. This study was approved by the local ethics and governance boards as a prospective audit.

Table 4: Detection rates by age, PSA & volume

Variable	Prostate Cancer	No prostate cancer	Detection rate
PSA, ng/mL			
0 – 4.0	36	30	55%
4.1 – 10.0	117	92	56%
10.1 – 20.0	58	25	70%
20.1 – 50.0	31	5	86%
> 50.0	7	1	87%
Volume, mL			
0 – 40	151	64	70%
40 – 60	65	39	63%
> 60.0	33	50	40%
Age, year			
< 50	21	25	46%
50 – 60	86	62	58%
60 – 70	94	56	63%
> 70	48	10	83%

RESULTS

Prostate cancer was diagnosed in 249 patients giving a cancer detection rate of 61.9%. High grade PIN was found in 31 patients (7.7%), and ASAP in 7 patients (1.7%). Entirely benign pathology was found in 115 patients (29%). The baseline characteristics of the study population are summarised in Table 2. The mean age at TPSB was 61.1 years and the median pre-biopsy PSA was 6.9 ng/mL. A mean of 28.6 biopsy cores was obtained per patient. Table 3 summarises the pathological features of the patients diagnosed with prostate cancer. Clinically significant disease was identified in 75.1% of those with cancer (187/249). Cancer was located in the anterior sectors in a similar frequency to the mid and posterior sectors. There were 43 patients (17.3%) where the cancer was located exclusively in the anterior sector and this was clinically significant in 27 (10.8%). The cancer detection rate stratified by PSA level, prostate volume and age is shown in **Table 4**. In the 209 patients with PSA level 4-10.0 ng/mL, the cancer detection rate was 56%. In patients with PSA >10.1 ng/mL, this increased to over 70%. Low prostate volume, high PSA density and increasing age were predictors of cancer detection. The free/total PSA ratio was available for 130 patients and was not found to be predictive of prostate cancer in this series. There were few complications reported following TPSB (**Table 5**). Six patients (1.4%) developed acute urinary retention requiring short-term catheterisation. The mean prostate volume in these patients was 85.6 cc. All these patients were able to void following a successful trial without catheter. Two were subsequently treated with HoLEP. Four patients (1.0%) required overnight hospitalisation for haematuria and were successfully managed by bladder irrigation. **Table 6** shows the management outcomes of the patients diagnosed with prostate cancer. Prostatectomy specimens were available for 55 patients and all had cancer volumes greater than 0.5mL and/or Gleason score 3+4 or above. There was exact concordance between Gleason score at prostatectomy and the diagnostic TPSB in 47 patients (85.3%). There were no episodes of Gleason downgrading following pathological examination of the specimen. 8 patients (14.6%) were upgraded from Gleason 3+3 to 3+4.

Table 5: Complications after biopsy

Variable	N (%)
Acute urinary retention	6 (1.5)
Haematuria requiring irrigation	4 (1.0)
Sepsis	0 (0)
Transfusion	0 (0)

Table 6: Treatment decisions

Variable	N (%)
Active Surveillance	67 (26.9)
Dynamic prostate brachytherapy	53 (21.3)
Radical Prostatectomy	67 (26.9)
Hormones and/or EBRT	62 (24.9)

DISCUSSION

We report the results of TPSB protocol developed at our institution in the primary biopsy setting. To our knowledge this is currently the largest reported primary transperineal biopsy series. The overall cancer detection rate was 61.9%. Of those with cancer, clinically significant disease was identified in 75.1% and 17.3% had disease exclusively in the anterior sector. At present there is no standardised transperineal biopsy protocol and approaches have varied widely in the anatomical distributions sampled and number of biopsies obtained[19]. Table 7 summarises cancer detection rates across primary series using different approaches.

Transrectal biopsy has detection rates of approximately 40% to 44% in cohorts of men with similar risk to our study. The higher detection rate achieved by TPSB might be interpreted as a consequence of the higher number of cores taken. However, attempts to improve diagnostic yields of transrectal biopsy by increasing prostatic sampling density have not been successful in the primary biopsy setting[20]. Lane et al.[21] reported a cohort of 257 men who underwent transrectal saturation biopsy with a median of 24 cores and achieved a cancer detection rate of 43% comparable to the yield from non-saturation transrectal biopsies. The difference in detection rates is most likely due to better sampling of the peripheral zones, which are preferentially targeted by TPSB. There are two factors, firstly transperineal biopsies are taken along the length of the peripheral zone (PZ) in the sagittal plane whereas transrectal biopsies tend to be fired across the PZ towards the transition zone (apart from the most laterally directed cores, as in the Presti protocol). As a consequence three areas are consistently undersampled by transrectal biopsies. The anterior apical to middle gland peripheral zone, the posterior basal region in the midline which corresponds to McNeal's central zone surrounding the ejaculatory ducts and the midline apical region of the peripheral zone, which is avoided in transrectal biopsy because of the urethra and patient discomfort. Transperineal midline biopsies pass below the urethra. In our cohort, 17% were identified as having isolated anterior tumours that may have been missed by transrectal biopsy. This is consistent with studies of prostatectomy specimens where anterior tumours are found to account for 21% of prostate cancers[22]. Transperineal template-guided mapping biopsy (TTMB), as reported by Taira et al.[23], involves taking biopsies at a higher sampling density with the prostate sampled every 5 mm on a brachytherapy grid[24]. Using TTMB, a median of 55 cores were taken from 79 patients with a high cancer detection rate of 76% but associated with significant procedure-related morbidity. The rate of acute urinary retention rate was reported as 29% despite the routine use of alpha blockers prior and for two weeks post TTMB. This retention rate is consistent with other TTMB series[3,25] and probably reflects the additional trauma from multiple biopsy needles sampling the transition zone leading to intra-prostatic oedema. The key difference between our sector biopsy approach and other transperineal template guided approaches is that it preferentially targets the peripheral zones and avoids unnecessary sampling of the transition zone. The transition zone has a low incidence of isolated can-

Table 7: Primary Biopsy Literature Review

Biopsy	No. of Patients	PSA (ng/mL)	Cores (median)	Detection Rate
Transperineal template-guided				
Current Study	402	6.9[a]	29	62%
Furuno et al (28)	86	6.2[b]	18	49%
Taira et al (23)	79	4.8[a]	55	76%
Transperineal freehand				
Hara et al (32)	126	8.3[b]	12	42%
Ficarra et al (35)	480	7.6[b]	14	44%
Kawakami et al (36)	289	10.7[b]	14	36%
Kojima et al (37)	541	5.3[a]	12	24%
Transrectal				
Presti et al (2)	2229	6.1[a]	12	44%
Gore et al (38)	264	5.9[a]	12	42%
Presti et al (39)	483	-	10	42%
Eskew et al (40)	119	8.9[b]	13	40%
Lane et al(21)	257	5.5[a]	24	43%

[a]Median, [b]Mean

cer as shown on both TP mapping biopsy studies[26] and on radical prostatectomy series where 83% of tumours were located predominately in the peripheral zone[27]. Other techniques distribute their cores evenly through the prostate without differentiating transition zone and peripheral zone. This may explain the higher detection rates of our series compared to Furuno et al.[28]

This TPSB protocol limits the maximum number of cores taken even in larger prostates. The preferential targeting of the peripheral zone results means it achieves comparable cancer detection rates with reduced morbidity to other TTMB series. Our retention rate was 1.3% and alpha blockers were not routinely prescribed. Given the high detection rates with minimal morbidity, TPSB may be a practical compromise to the drawbacks associated with more extensive biopsy schemes. MRI-targeted biopsy may further improve detection rates[16] though this was not investigated in this series. However, if the MRI does not identify a targetable lesion a systematic biopsy is still required and TPSB would provide a means of doing this. Following the introduction of multi-parametric MRI, our centre has reported that despite having no targetable lesion on MRI, 36.6% of patients had intermediate risk prostate cancer with TPSB[29]. Even in the event of an MRI lesion, there is significant debate whether systematic biopsy can be omitted and it has been argued that the remaining prostate should still be systematically biopsied to avoid missing significant disease[30]. The randomised controlled trial frequently cited in national guidelines[31] to justify the use of transrectal biopsy as a primary biopsy strategy found no significant difference in detection rates between transrectal and transperineal biopsy[32]. However, it was based on a freehand transperineal approach, which is a vastly different approach to the template-guided techniques described above. Fewer cores are taken and no template is used to guide the biopsy needle through the relatively long transperineal needle path. This freehand needle placement increases the probability of inaccurate biopsy and several studies have shown it achieves cancer detection rate ranging from 24% to 44% (**Table 7**). Transrectal biopsy has the advantage of requiring fewer cores and can be performed in an outpatient setting. However, it is known to underestimate the presence of cancer and is estimated to miss approximately a third of clinically significant disease[7-9]. Bittner et al. reported a series of 485 patients with a previous negative transrectal biopsy. Following transperineal biopsy, 40% were identified as having clinically significant prostate cancer[25]. Resources allocated to prostate cancer diagnostics have been built around delivering transrectal biopsy as the default technique. This paper provides some evidence that there are a number of advantages to be gained from transperineal biopsies in terms of safety and detection of significant disease. Whilst there is a place for transrectal biopsy (e.g. the patient with obvious palpable abnormality who simply needs histological confirmation prior to treatment), it is likely that transperineal biopsy will become more popular in conjunction with MRI, particularly in an era of increasing infection rates. TPSB may reduce the need for repeat biopsy and facilitate the confident discharge of those with negative biopsies. It allows accurate risk stratification of patients at low risk and suitable for active surveillance. In addition, in our TPSB cohort there were no instances of post-biopsy sepsis requiring hospitalisation. Hospital admissions for transrectal biopsy complications have risen from 0.6% to 3.6% over the last decade[33]. This reflects a higher rate of post-biopsy sepsis due to the growth of fluroquinolone resistant Escherichia coli(11,34). In TPSB, biopsy needles pass through prepared skin rather than bowel reducing infection risk. However, our results may also be influenced by an extensive antibiotic prophylaxis protocol. These benefits need to be weighed against the costs of introducing TPSB as a primary biopsy strategy. TPSB is well tolerated as a day case but may not be feasible for some centres due to financial constraints and pressures on operative time. We acknowledge that there are resource implications due to the requirements of general anaesthesia, operative time and increased pathology analysis. Further studies providing detail on cost effectiveness are required. A further limitation of this case series is that it is not possible to make a direct comparison with alternative biopsy techniques.

CONCLUSIONS

TP sector biopsy is a safe technique, which offers a high cancer detection rate in the primary setting. As a primary biopsy technique it has advantages over transrectal biopsy in reducing sepsis and better characterisation of cancer thus allowing accurate treatment decisions to be made. It also offers an attractive compromise to more extensive transperineal protocols, which can be more time-consuming and associated with higher morbidity.

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CONFLICTS OF INTEREST

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