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Active Surveillance Following Modified Transperineal Template Guided Saturation Biopsy Demonstrates a Low Rate of Progression and Conversion to Radical Treatment, with Age and PSA Associated with Upgrading, Upstaging and Treatment

Debashis Sarkar*, **Kinsley Ekwueme and Nigel J Parr**

Department of Urology, Wirral University Teaching Hospital, Upton, Wirral, United Kingdom

***Corresponding author:** Debashis Sarkar, Department of Urology, Wirral University Teaching Hospital, Upton, Wirral, United Kingdom, Tel: 0044-07791454741; E-mail: debu4726@yahoo.co.uk

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Abstract

Objectives: To evaluate outcomes in patients embarking upon active surveillance for Prostate cancer (Pca) following tumour characterisation by modified transperineal template guided saturation biopsy.

Materials and Methods: Of 500 patients with initial negative conventional transrectal ultrasound guided prostate biopsy underwent transperineal template guided saturation biopsy, detected cancer in 276 (55%). Of these, 30 (11%) elected for active surveillance. Another 158 patients considering active surveillance after initial positive transrectal ultrasound guided biopsy underwent confirmatory transperineal template guided saturation biopsy, with 43 (27%) subsequently electing for active surveillance. A total of 73 patients from these two groups (median age 63 years) were, thus, enrolled for active surveillance. Follow up consisted of 3 monthly PSA and DRE, offering repeat Multi-parametric MRI and repeat transperineal template Guided Saturation Biopsy, at 24 months, or on suspicion of progression.

Results: At a median follow up of 58 months, 59 patients have undergone repeat Multi-parametric MRI. Radiological progression was identified in 6 (8%), Gleason upgrading on repeat transperineal template guided saturation biopsy, in 14 (19%). Six (8%) have undergone radical treatments. Age >60 yrs and PSA >5 ng/mL were associated with upgrading and upstaging ($p<0.05$).

Conclusion: A large proportion of patients initially considering active surveillance dropped out following confirmatory transperineal template Guided saturation biopsy, however, in those electing for active surveillance after transperineal template guided saturation biopsy, progression rates are low and related to age and presenting PSA.

Keywords: Prostate cancer; Active surveillance; Progression rate

Introduction

Due to increasing number of patients diagnosed with potentially indolent PCa as a result of more widespread PSA testing, AS is of growing interest to both patients and physicians, offering an alternative to immediate radical treatments for the management of low risk disease. Eligibility criteria and surveillance protocols differ between institutions [1-7], but most concur with PSA <10-15, clinical stage <2a, either Gleason grade 3+3 or <3+4, single core positivity <50% and some also set an upper entry limit for PSA density (Table 1). There remains debate as to the necessity for an early confirmatory biopsy [8]. Patients under AS are followed up regularly with prostate-specific antigen (PSA) testing, digital rectal examination (DRE) and offered repeat conventional TRUS biopsies, the frequency of follow up investigations again varying across reported series. The role of mpMRI in follow up is uncertain at present.

We believe that a deterrent to both recommendation and patient acceptance of AS is the high reported rate of 'progression', leading to radical treatment by 2 years in around 30% [9].

Institution	Clinical Stage	PSA	Gleason Grade	Total positive cores	Single core positivity	Others
NICE [1]	≤ T2a	≤ 10	≤ 3+3	≤ 2	≤ 50%	
EAU Guideline [2]	≤ T2a	≤ 10	≤ 3+3	≤ 2	≤ 50%	
Royal Marsden [3]	≤ T2a	≤ 15	≤ 3+4	≤ 50%	NR	
John Hopkins [4]	≤ T2a	≤ 10	≤ 3+3	≤ 2	≤ 50%	PSADT ≤ 0.15
University of California [5]	≤ T2a	≤10	≤ 3+3	≤ 33%	≤ 50%	
University of Miami [6]	≤ T2a	≤ 10	≤ 3+3	≤ 2	≤ 20%	
PRIAS criteria [7]	≤ T2a	≤ 10	≤ 3+3	≤ 2	NR	PSADT ≤ 0.20

Table 1: Criteria for active surveillance in different institutions.

This is somewhat surprising when viewed against the natural history of low risk prostate cancer. Furthermore, many previous studies have shown disparity between both TRUS biopsy Gleason score and initial clinical stage, against the final histopathology following radical prostatectomy [10-15], suggesting current practice is inadequately sensitive and specific for accurate tumour characterisation either in the initial diagnostic or in the confirmatory biopsy setting.

TPSB provides reliable sampling to the entire prostate gland including the anterior/apical areas, when compared to conventional TRUS biopsy [16]. Thus, accurate tumour characterisation is more likely. To date no study has compared the conversion rate on AS to radical treatment following this procedure We, therefore, reviewed the outcome of patients electing for AS following TPSB, hypothesizing that the 'progression rate' should be less. We also attempted to identify factors predicting upstaging and upgrading in those patients embarking upon AS.

Materials and Methods

A total of 658 patients underwent TPSB from August 2007 to July 2015 at our institute. Of 500 patients with initial negative conventional extended TRUS biopsy (>10 cores), cancer was detected in 276 (55%). Thirty of these (11%) elected for AS. Another 158 patients considering AS underwent confirmatory TPSB, with 43 (27%) subsequently electing for AS. Therefore, a total of 73 (30+43) patients were enrolled for AS with median age of 63 (range 47-75) years and median PSA of 8 (range 4-15) ng/ml. Gleason grades were 3+3 (n=60) and 3+4 (n=13) on TPSB, with radiological stage T1c (n=58) and T2a (n=14), pre TPSB mpMRI having been performed in all, except one with claustrophobia. Follow up consisted of 3 monthly PSA and DRE, offering repeat mpMRI and repeat TPSB at 24 months, or on suspicion of progression.

Our methodology and outcomes for TPSB have previously been described [16]. Patient reported experience also demonstrates that the procedure is well tolerated and caries acceptable postoperative symptom rates [17]. Briefly, all procedures were performed under GA, with a side viewing, biplanar implant probe (BK Medical, Herlev, Denmark) attached to a brachytherapy stepping unit (DK Technologies®, Barum,Germany). A Magnum biopsy gun (BARD, Covington, GA, USA) was set on 22-mm pass. Biopsy cores were taken in rows systematically, from right to left using an 18-G needle. Each biopsy core was placed in a separate fixation pot, numbered and the site recorded, so as to allow construction of a detailed tumour map. The interval between biopsy cores on a row was 10 mm, with 5 mm between rows. The number of biopsies within a row was dictated by the width of the prostate, while ensuring that the most lateral cores were near the capsule. A median (range) of 28 (13-43) cores were taken from a median of 7 (3–9) rows. The cohort also included 51 patients who were initially referred for TTSB with prostatic volume >60 mL and who were placed on dutasteride 0.5 mg daily for 3–6 months to reduce their prostate size in order to minimise pubic arch interference. TRUS was performed to confirm prostatic volume <60 mL before offering TTSB. Follow-up outcomes were recorded prospectively on a database for all TPSB patients at our unit.

Statistical Analysis

Upgrading was defined as pathological change from Gleason 3+3 to either 3+4 or 4+3, or from Gleason 3+4 to 4+3 or more, and upstaging as on mpMRI. Our primary outcome was the percentage of patients converting to radical treatment from AS series, with a secondary outcome of identification of demographic characteristics associated with upgrading or upstaging.

Age and PSA were treated as continuous variables in our initial models. Age and PSA were dichotomized near the median, with age 60 years or younger vs. older than 60, PSA 5.0 ng/ml or less vs. greater than 5. Finally, we used 2 factors associated with upgrading and up staging to create a stratified risk table. All p values reported were 2-sided with significance at $p < 0.05$. We used STATA (version 11.1) for statistical analysis and also used the Chi-square test.

Results

At median follow up of 58 (2-78) months, 59/73 (81%) have undergone repeat mpMRI, but only 22 (30%) accepted repeat TPSB. Radiological progression was identified in 6 (8%), Gleason upgrading on TPSB was identified in 14 (19%) patients, with 9 of them upgraded from Gleason 3+3 to 3+4, 4 upgraded to Gleason 4+3 and 1 upgraded from Gleason 3+4 to Gleason 4+5. Age >60 years and PSA >5 ng/mL were associated with upgrading and radiological upstaging ($p<0.05$) (Tables 2 and 3).

Age	n (%)	PSA	Upgraded	Upstaged	Radical treatment received
46-55	7 (10%)	5.10	0	0	1(no +ve cores rose)
56-65	37(50%)	6.34	7	2	2
66-75	29(40%)	7.79	7	4	3

Table 2: Gleason upgrading and mpMRI upstaging related to age (yrs) and median PSA (ng/ml).

Age Group	PSA	p Value
>60	>5	<0.05
<60	<5	>0.05

Table 3: Age and PSA significance.

Six patients (8%) have undergone radical treatment, either due to a significant increase in core involvement by Gleason 3+3 cancer on repeat TPSB (n=1), or Gleason upgrading, or MRI progression, or a combination of these factors (Table 4). No patients have developed metastatic disease.

Age	PSA	TRUS Biopsy	mp MRI	TPSB	Repeat mpMRI	Repeat TPSB	Time on AS	Radical treatment
49	3.8	3+3	T1c	3+3	T1c	3+3	24 months	Robotic

				5 core		10 core		Prostatectomy
56	4.6	-ve	T2a	3+4 1 core	T2a	4+3 4 core	36 months	Robotic Prostatectomy
59	4.3	-ve	T1c	3+3 3 core	T1c	3+3 10 core	37 months	Brachytherapy
67	4.5	3+4, tiny	T1c	3+3 1 core	T2a	4+5 2 core	24 months	Brachytherapy
69	8.5	-ve	T1c	3+4 5 core	T2a	3+4 7 core	31 months	Robotic Prostatectomy
73	6.5	3+3	T2c	3+3 7 core	T2c	NA, PSA rising	12 months	Radiotherapy

Table 4: Details of patients proceeding to radical treatment.

Discussion

Active surveillance is an attractive concept for low or possibly intermediate risk PCa, in order to reduce the morbidity of radical treatments. Nevertheless, there are numerous potential reasons why physicians and patients may wish to avoid this option. One of these it is the unreliability of prognostic information gained from the initial TRUS biopsy. For example, Pinthus et al. performed a retrospective database analysis from 1989 to 2004 comparing pre-prostatectomy characteristics after TRUS biopsy with final histology [10]. They reported that almost half 50% of the patients with Gleason sum score 6 were upgraded to 7 and concluded that clinicians should consider the possible impact of upgrading when discussing therapeutic options with patients. A similar study by Epstein and Feng, in 2012, on 1455 patients who underwent radical prostatectomy for low Gleason grade tumour, reported a final histology Gleason sum score of 7-10 in 30% of cases [12]. The authors concluded that this is even more critical as patients increasingly opt for nonsurgical therapies such as active surveillance or radiotherapy.

The performance of annual TRUS biopsy on AS, performed by Duffield et al. in 470 patients, revealed rates for extraprostatic extension of 35% and 6% for seminal vesicle and LN involvement, with most tumor progression occurring 1-2 years after diagnosis [18]. An alternative explanation is of under sampling for more aggressive tumor, rather than progression of indolent tumors.

TPSB is reported to more accurately detect and characterise the extent and grade of PCa [16,19]. We, therefore, decided to offer this as an option to those considering AS after conventional TRUS biopsy. We expected that in patients electing for a confirmatory TPSB, a proportion would subsequently choose radical treatment options in the event of detection of worse prognostic biopsy information. However, the magnitude of drop out at this stage was surprising with almost three quarters preferring surgery or radiotherapy following TPSB.

We also accumulated a further group of patients first diagnosed with PCa by TPSB. The combination of these two groups produced a cohort of 73 patients followed up for a median of almost 5 years. Their conversion rate to radical treatment at 8% is significantly less than in series following tumour characterization only by conventional TRUS biopsy.

Isariyawongse et al. reported significant discrepancies between diagnostic and pathologic Gleason sum scores in PCa and noted the predictive role of age and prostate-specific antigen [20]. A more recent study by Dinh et al. into the incidence and predictors of upgrading and upstaging among 10,000 contemporary patients with low risk PCa found that following prostatectomy, 44% of cases was upgraded and 9.7% were up staged. Multivariable analysis of 5,581 patients showed age, PSA and percent positive cores, but not race, were each associated with occult, advanced disease. With these variables dichotomized at the median, age >60 years (AOR 1.39), PSA >5.0 ng/ml (AOR 1.28) and more than 25% positive cores (AOR 1.76) were significantly associated with upgrading (all $p<0.001$) [21]. Our results demonstrate that both age >60 years and PSA >5 ng/ml prior to AS are also associated with upgrading and radiological upstaging during AS even in those who have initially undergone TPSB. Some clinicians are reluctant to recommend AS in the younger age group believing it is associated with greater risk. However, the results of all three studies are important, pointing towards the contrary.

The exact role of mpMRI in AS protocols needs to be further explored, but clearly patients prefer this noninvasive investigation to repeat TPSB. Furthermore, there is increasing interest in MRI/TRUS fusion biopsy in this setting. Pepe et al. in a small study investigated whether MRI/TRUS fusion targeted biopsy can replace confirmatory TPSB before AS [22]. Although mpMRI had a high diagnostic accuracy for PCa (about 95%), MRI/TRUS fusion biopsy missed 30% significant PCa characterized by the presence of a single positive core of Gleason score >7 or greatest proportion cancer within a core of >50%. They concluded that TPSB should be the investigation of choice for confirmation, rather than mpMRI/TRUS fusion targeted biopsy.

Conclusions

In summary we report the first series of AS following either diagnostic or confirmatory TPSB in conjunction with mpMRI and conclude that this is a useful tool for characterization of low risk cancer, being associated with a low rate of progression to radical treatment in the medium term. Younger age and PSA <5ng/mL are associated with the lowest risk of progression. As such TPSB should be offered more widely as an option to those considering AS following cancer detection by conventional TRUS biopsy. The downside is that confirmatory TPSB excludes or deters a large proportion of patients

from AS. Further research is required to determine whether the accurate tumor mapping provided by TPSB can be supplemented by other parameters, such as cancer biopsy volume, PSA doubling time, genetic, proteomic or other molecular signatures so as to improve future predictive modeling.

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