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Original Research Article

Active surveillance: transperineal biopsies and evaluation of multi-parametric magnetic resonance imaging

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ABSTRACT

Background: Active surveillance has emerged as an acceptable choice for low-risk prostate cancer patients and is defined as a treatment strategy of close monitoring through PSA, digital rectal examination, imaging and prostate biopsy, with conversion to curative treatment if progression occurs. An ideal tool for risk-stratification would detect aggressive cancers and exclude such men from taking up active surveillance in the first place.
Methods: We retrospectively reviewed patients who underwent transperineal template biopsies from January 2016 till December 2018. All the patients had been classified as low grade prostate cancer after conventional trans-rectal ultrasound guided biopsy and enrolled in AS after discussion in hospital MDM. As per NICE guidelines all patients underwent multi-parametric magnetic resonance imaging (MRI). All suspicious lesions were assigned a PIRAD score; this was followed by Trans-perineal prostate biopsy. 142 patients were on active surveillance and underwent mapping transperineal template biopsies and cognitive target biopsies. 130 of them had multi-parametric MRI prior to the biopsies.
Results: In 52% of cases the histology was upgraded. In 34 (24%) the cancer was upgraded to Gleason 3+4 and 39 (28%) it was upgraded to scores higher than Gleason 3+4. Only 64 (45%) patients continued on active surveillance post-template biopsies due to significant upgrading of histology.
Conclusions: We advocate combination of MRI and an early transperineal template guided prostatic biopsies for intermediate risk prostate cancer, multiple core involvement, higher PIRAD grades and suspicious prostate on digital rectal examination in order to re-stage the initial disease and provide better safety for this cohort of patients.

Keywords: Prostate cancer, Active surveillance, Transperineal biopsy

INTRODUCTION

The European randomised study of screening for prostate cancer trial (ERSPC) and Prostate cancer intervention versus observation trial (PIVOT) indicate that overtreatment of the low risk prostate cancer is quite common.[1,2] The radical prostatectomy doesn't lead to any improvement in cancer specific survival compared to active surveillance even after prolonged follow-up and the majority of deaths in these patients are due to non-prostate cancer related causes.[2-4] Active surveillance is thus an ideal option for low-risk prostate cancer patients but the potential risk with the active surveillance strategy is that the cancer may be initially under staged or progress beyond the stage of cure. Studies have shown that almost up to 29-34% of candidates enrolled for

active surveillance are under staged and wouldn't meet the inclusion criteria if they have immediate re-biopsy or radical prostatectomy.[5-7] This is thought to be largely due to shortcomings of the traditional 12-core random biopsy technique in adequately sampling the entire prostate gland resulting in under-detection of aggressive cancer. Efforts to address the weaknesses of conventional biopsy and better stratify patients for AS or treatment have now led to a proliferation of imaging, imaging-guided biopsy, mapping biopsy and biomarker tests.

Hence repeat prostate biopsy, employed for restaging, is the cornerstone in the management of patients according to the active surveillance protocol. Bott et al developed the innovative brachytherapy template-guided transperineal technique for prostatic biopsies and now it has acquired a definitive place along with multi-parametric MRI in the management of active surveillance patients.[8,9] This retrospective longitudinal study was carried out to determine the role of multi-parametric MRI and template prostatic biopsies in the reclassification of low risk prostate cancer patients placed on active surveillance post transrectal ultrasound guided biopsies. The study also aims to determine the reliability of the transrectal prostatic biopsies in recruiting patients on the active surveillance pathway.

METHODS

The study was carried out as an audit within the trust and and registered with the audit and research department (Reference number 1920.016N). 142 patients on active surveillance were included in the study. This included 127 patients who were diagnosed on 12 core transrectal ultrasound guided biopsies. 9 patients were put on active surveillance post-transperineal template guided biopsies and 6 patients post-transurethral resection of prostate for lower urinary tract symptoms or retention of urine. 124 patients had Gleason 3+3 prostate cancer disease, 18 patients were having with low volume Gleason 3+4 prostate cancer disease. All patients were monitored according to the UK Nice protocol.[10] They were followed by PSA measurements, clinical examination, multi-parametric MRI and template guided transperineal prostatic biopsies. Patients on active surveillance who were already planned for surgery were excluded from the study.

These patients underwent transperineal template guided prostatic biopsies (5 mm grid reference mapping biopsies) from January 2016 till December 2018 and multi-parametric prostatic MRI. Systematic mapping biopsies were taken from both the lobes of prostate and 4 target biopsies in 42 patients who had definite lesions on MRI. All men received perioperative antibiotics which were continued postoperatively for 3 days, according to the local microbiology protocol. Using transrectal ultrasound probe the prostate gland was examined and prostate volume was determined.

Most of the patients underwent MRI prior to the transperineal template prostatic biopsies unless there were contraindications. MRI scans were done using 3-tesla scanner and two dedicated specialist uro-radiologists reported all the scans. Radiologist's evaluated suspicious lesions using T2-weighted imaging, diffusion-weighted imaging and lately dynamic contrast-enhanced MRI. The MRI prostate scans were reported as Tx i.e., Prostate imaging–reporting and data system (PIRAD 1-2), PIRAD 3, 4 and 5. The template biopsies were performed by only one experienced urologist.

Descriptive statistical data are expressed as the mean±standard deviation or median with range. Most of the data analysis was done using percentages.

RESULTS

142 patients on active surveillance were included in the study. This included 124 patients who had Gleason 3+3 prostate cancer disease, 18 patients with low volume Gleason 3+4 prostate cancer diseases. 9 patients were put on active surveillance post-transperineal template guided biopsies and 6 post-transurethral resection of prostate for lower urinary tract symptoms or retention of urine.

Table 1: Demographics of patients enrolled in study.

Total patients	142
Median age	68 (42-79)
Median PSA for TRUS cohort	6.1 (0.8-24)
Median PSA template cohort	6.7 (0.2-38)
Low risk prostate cancer (Gleason 3+3)	124
Intermediate risk prostate cancer (Gleason 3+4)	18
Mean PSA density	0.1035 (0.0076-0.58)

130 patients had MRI prior to the transperineal template guided biopsies. 21 (16.15%) MRI scans were reported as PIRAD 1-2 (Tx), 109 (83.84%) as PIRAD 3-5 and 12 patients couldn't have MRI. 74.31% of PIRAD 3-5 revealed prostate cancer whereas the cancer detection rate was only 42.85% for PIRAD 1-2 areas.

Out of 142 patients on active surveillance in 52% the histology was upgraded. In 34 patients (24%) the cancer was upgraded to Gleason 3+4 and 39 (28%) it was upgraded to >Gleason 3+4. 69 patients (48%) had either benign disease (30%) or low risk prostate cancer (18%). This implies considerable differences and upgrading of histology compared to 12 cores transrectal ultrasound guided biopsies.

The patients with PIRAD 1-2 MRI scans, post template biopsies didn't show any significant prostate cancers. However histology post template biopsies for PIRAD 3, 4 and 5 on MRI revealed 17.50%, 28.84% and 58.82%

significant prostate cancers respectively. The overall cancer detection rate post transperineal template guided prostatic biopsies with PIRAD 1-2, 3, 4 and 5 scores were 42.85%, 67.50%, 75% and 88.23% respectively. The mean PSA density was 0.14 ng/ml for PIRAD 3 cases and 0.19-0.20 ng/ml for higher PIRAD scores. The sensitivity of PSA density for prostate cancer diagnosis across the PIRAD groups was highest (61.54%) for PIRAD 4 cases and specificity was 100% for PIRAD 5 group.

Table 2: Correlation between PIRAD, Gleason score and PSAD along with Gleason scores.

	PIRAD 3 (n=40)	PIRAD 4 (n=52)	PIRAD 5 (n=17)
Benign	13	13	2
Gleason 3+3	12	7	-
Gleason 3+4	8	17	5
Gleason 4+3	5	9	5
Gleason 4+4	1	3	-
Gleason 3+5	-	2	2
Gleason 4+5	-	1	2
Gleason 5+4	1	-	-
Gleason 5+5	-	-	1
Cancer (%)	67.50	75	88.23
Gleason 3+4 (%)	17.50	28.84	58.82
Mean PSAD	0.14 (0.01-0.58)	0.20 (0.01-0.58)	0.19 (0.01-0.71)
Sensitivity	59.26% (38-77)	61.54% (44-76)	46.67% (21-73)
Specificity	46.15%(19-75)	46.15% (19-75)	100%

42 patients had targeted template biopsies, out of which 32 (76.19%) were positive for the diagnosis of prostate cancer. However only 4 (12.5%) patients were diagnosed entirely on target biopsies when their systematic biopsies showed no cancer and further 4 (12.5%) patients had higher grade cancer on target biopsies. 24 (75%) patients had same grade on target as well as systemic biopsies.

Although only 18 patients were Gleason 3+4 low volume on transrectal ultrasound guided biopsies, all higher Gleason grades were found post template biopses. Its alarming that 11 patients had Gleason 5 disease post template guided biopsies.

Table 3: Description of template histology for active surveillance patients (n=142).

Histology	No. of patients (n)
Benign histology	43
Gleason 3+3	26
Gleason 3+4	34
Gleason 4+3	22
Gleason 4+4	6
Gleason 3+5	4
Gleason 4+5	5
Gleason 5+4	1
Gleason 5+5	1

Table 4: Patients with abnormal DRE with their outcome.

	N	Active surveillance	Radical prostatectomy	Radical radiotherapy	Antiandrogens
Benign	11	-	-	-	-
Gleason 3+3	4	3	1	-	-
Gleason 3+4	7	-	4	2	1
Gleason 4+3	8	-	-	8	-
Gleason 4+4	1	-	1	-	-
Gleason 3+5	1	-	1	-	-
Gleason 4+5	2	-	-	1	1

Out of 142 patients only 64 (45%) patients continued on active surveillance, 29 (20%) patients underwent laparoscopic or robotic prostatectomy, 40 (28%) patients had external beam radiotherpay, 4 (3%) were treated with antiandrogens, 4 changed to watchful waiting and 1 patient received brachytherapy.

18 patients with low grade Gleason 3+4 prostate cancer were enrolled on active surveillance, out of these 7 were upgraded to >Gleason 3+4, 8 remained Gleason 3+4 and 3 were found to have benign histology on transperineal template guided biopsies. 11 patients were treated with radical radiotherapy and 4 had radical prostatectomy. 1, 6, 9 and 2 patients had PIRAD 1-2, 3, 4 and 5 scores respectively on multi-parametric MRI.

Abnormal suspicious prostate was found on digital rectal examination in 34/142 (24%) patients and was associated with prostate cancer in 23/34 (67.64%) patients. Out of the cancers diagnosed 12/23 (53.17%) were clinically significant cancers. 23/34 (67.64%) patients with suspicious prostate on examination underwent treatment.

DISCUSSION

The aim of active surveillance is to delay or avoid curative treatment in order to avoid side effects of the radical treatment and any compromise in long-term cancer-specific survival.[11,12] The delayed radical curative treatment if required even up to years from initial prostate cancer diagnosis seems not to have any negative impact on morbidity and disease specific mortality.[13] Prospective studies have also shown that 60-80% of such men will avoid the need for radical treatment and that 96-100% prostate cancer-specific survival at 10 years is achievable both for low and intermediate-risk prostate cancer patients.[14-16]

There is a general agreement on which patients to enrol for active surveillance but with certain variations depending on various groups and guidelines. The European association of Urology suggests active surveillance as a favourite option for ISUP grade 1, when specified <2-3 positive cores with <50% cancer involvement in every positive core, a clinical T1c or T2a, a PSA <10 ng/mL and a PSA density <0.15 ng/mL/cc.[17-20] The UK NICE advocates active surveillance also in low-volume intermediate-risk prostate cancer patients i.e., PSA up to 15 ng/ml, Gleason score of 3+4 and up to 10mm core length in Gleason 6 prostate cancer.[10]

Multi-parametric magnetic resonance imaging can differentiate between Gleason 6 and 7 prostate cancers and also between organ confined and extracapsular spread.[21-23] This study demonstrated that higher PIRAD grades are associated with increased risk of cancer diagnosis and higher Gleason scores (significant prostate cancer) post transperineal template guided biopsies. PIRAD 1-2 were not found to be associated with any cases of significant prostate cancer. Two-thirds of PIRAD 3 cases were associated with prostate cancer but only less than one-fifth had clinically significant prostate cancer on mapping template biopsies. Almost three-fourths of PIRAD 4 cases revealed prostate cancer but only less than one-third were clinically significant. 90% of PIRAD 5 cases were associated with prostate cancer diagnosis, out of which approximately two-thirds were clinically significant. These findings and also other studies indicate that MRI prostate has a definite role in counselling, enrolling, monitoring and deciding about definitive management in low or intermediate prostate cancer patients eligible for active surveillance.

PIRAD 4 and 5 cases were associated with higher PSA densities. The sensitivity of PSA density for prostate cancer diagnosis across the PIRAD groups was highest (61.54%) for PIRAD 4 cases and specificity was 100% for PIRAD 5 group. We didn't found any significant correlation between PSA density and cancer detection rate across various PIRAD groups perhaps because of small number of patients. UK NICE recommends repeat biopsy after at one year of active surveillance no matter whether PSA is stable or not. PSA velocity can correlate with upgrading on prostatic re-biopsies and prostatectomy but the correlation with PSA doubling time is poor.[24-28] Active surveillance patients had 3-4 monthly PSA checks in our study. Similar to previous studies, PSA velocity has been used as a trigger, intentionally or unintentionally, for template biopsies in our study as the median PSA for initial transrectal ultrasound guided prostatic biopsies is 6.1 ng/ml and template biopsies is 6.7 ng/ml.[15,29]

Most of the MRI scans (84%) did show PIRAD 3-5 abnormalities. 76% of the target biopsies were positive for cancer diagnosis. 12.5% patients were diagnosed entirely on target biopsies when their systematic biopsies showed no cancer and further 12.5% patients had higher grade cancer on target biopsies. 75% patients had same grade on target as well as systemic biopsies. These reflect similar findings as reported previously.[30,31]

In our study, 8 out 18 patients with initial Gleason 3+4 prostate cancers (diagnosed on TRUS biopsies) that were enrolled on active surveillance were upgraded and 15 patients were treated with radical treatment options post template biopsies. Although most of these patients had higher PIRAD grades on MRI but were still enrolled for active surveillance. Out of 142 patients on active surveillance the histology was upgraded in 52% post template biopsies. 24% of the cancers were upgraded to Gleason 3+4 and 28% to higher than Gleason 3+4. This implies that these patients were significantly under staged on initial transrectal ultrasound guided prostatic biopsies and indicate considerable unreliability of TRUS biopsies for recuriting patients on active surveillance. Also 30% patient's had benign histology post template which is higher than reported in literature.[32]

In our series, abnormal suspicious prostate was reported in one fourth of the cases and was associated with clinically significant prostate cancer in almost up to 50% of the cases. Two-thirds of the patients with suspicious prostate on examination underwent radical treatment. Abnormal prostate on digital rectal examination is bad prognostic factor for patients placed on active surveillance.

The protocol for discontinuation of active surveillance in our series was based on histology from repeat biopsy. Following template biopsies 55% of the patients discontinued active surveillance mostly due to upgrading of gleason scores. The discontinuation rate in our series is much higher than the previously reported studies and can be attributed to multiple factors. Our active surveillance cohort included patients with higher PSA ranges, multiple core involvement and higher PIRAD MRI grades. This reflects common routine UK practice of active surveillance, which commonly outstretches the recommendations for surveillance. We also observed that repeat biopsies were not done routinely at the end of year one. According to a previous UK based study merely 40% of patients have repeat biopsy at the end of one year and only 60 % have MRI routinely.[33]

Limitation

The important limitation of the study is the small sample size. Also the transperineal template biopsies in our experience were performed in the operating theatre with general anaesthesia which is expensive and has anaesthetic risks and may be logistically infeasible in settings where operating theatre time is extremely limited and needed for larger cases. However increasingly the template biopsies are now performed under regional anaesthesia in most of the centres. The other limitation of the study is that the post-template biopsy complications were not included.

CONCLUSION

This retrospective review underlines the importance of transperineal biopsy and MRI scanning in assessing a patient's suitability for active surveillance. It also provides real world evidence for template biopsies in patients being considered for active surveillance in the UK and it clearly demonstrates that we cannot rely on TRUS biopsy and the MRI alone to make the decision on suitability of patients for active surveillance and how bad reliance upon TRUS biopsies outcomes are.

Targeted template biopsies change outcome only in 25% of cases according to our study and in 75% the results are same as the systematic biopsies. We recommend targeted biopsies if there is a definite lesion on MRI which is important especially with the introduction of MRI fusion biopsies. We do not recommend target only biopsies to avoid the chances of missing prostate cancer. When there is no lesion on MRI, PSA density may indicate the risk of prostate cancer, however we couldn't evaluate that due to small number of cases.

In the patients enrolled for active surveillance, we advocate an early transperineal template guided prostatic biopsies for intermediate risk prostate cancer, multiple core involvement, higher PIRAD grades and suspicious prostate on digital rectal examination. Patients with these characteristics should be selectively and very cautiously offered active surveillance. All the low risk active surveillance should be re-biopsied at one year. Active surveillance patients should be discussed in multidisciplinary team meetings in presence of radiologists and pathologists. These patients should have follow up in dedicated active surveillance clinics by dedicated urologists and cancer specialist's nurses who have specific interest and experience in the management of such patients. There should be provision for continuous audits and re-audits in the centres managing active surveillance patients and be updated with ever changing practice and guidance.

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