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Original Article

Surgery Section

Validation of Selection Criteria for Active Surveillance in Prostate Cancer

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ABSTRACT

Introduction: Considerable Proportion of Prostate Cancer (PCa) patients suitable for Active Surveillance (AS) harbour aggressive disease at surgical histopathology. Identification of truly indolent prostate cancer at diagnosis is difficult.

Aim: Of this study was to evaluate the accuracy of current AS protocols in identifying low risk PCa by comparing the histopathology at biopsy and surgery.

Materials and Methods: A retrospective study was performed on all patients who underwent Radical Prostatectomy (RP) between 2008 and 2012. We identified patients who fulfilled inclusion criteria of five different established AS protocols. Histopathology at biopsy was compared with final surgical histopathology to identify upgrading or upstaging of disease. The biochemical recurrence rate in the cohort was also determined.

Results: A total of 59 patients (24%) met criteria of at least one protocol. Sixteen patients (28%) were eligible for AS based on all studied criteria. Overall 24 patients (40.6%) were upgraded in their final histopathology while 12 patients (20%) upstaged from their original TRUS biopsy. Two patients (3%) had PSA failure, both had salvage radiotherapy

Conclusion: There is considerable discrepency in current AS selection criteria which makes it necessary to introduce novel markers to identify indolent disease as a part of AS protocol for PCa.

Keywords: Histopathology, Low risk, Upgrading, Upstaging

INTRODUCTION

Prostate cancer (PCa) can be defined as Low Risk (LR) if the Gleason score is 6 or less, PSA is less than 10 mg/ml and a tumor is either non-palpable or only palpable in less than half of one lobe of the prostate (clinical stage T1c or T2a) [1]. Very Low Risk (VLR) prostate cancer can be defined as all LR prostate cancers with one or two positive cores, less than 50% involvement of any one core and PSA density less than 0.15. Men with LR prostate cancer have a marginal risk of dying from prostate cancer after20 years of follow-up [2]. This is relevant because overtreatment of low-risk prostate cancer is associated with significant morbidity including urinary in continence and erectile dysfunction.

Some low risk (LR) and very low risk (VLR) prostate cancer patients are managed by active surveillance (AS). This strategy is based on identifying tumours which have a low risk of progression. The aim of AS is to "avoid or delay radical treatment and its associated morbidity without compromising survival" [3]. This method differs from the "watchful waiting" as patients undergo more intensive monitoring with repeat biopsies and PSA kinetics at various intervals. Ultimately treatment is offered if there is disease progression; however there is a lack of consesus on the point at which curative treatment should be offered. Previous studies have shown that depending on the criteria used for AS, varying number of eligible patients could have more advanced disease on the final surgical histopathology at Radical Prostatectomy (RP) [4].

In a study on nearly 3000 men with PCa who met the criteria for AS but underwent RP, it was found that 16–19% had positive surgical margins, 3–4% had a Gleason score (GS) of 8–10,15–18% had extracapsular tumour extension, 3–5% had seminal vesicle invasion and 0.4–1% had lymph node metastasis [4]. Another study found that patients with low risk prostate cancer had extracapsular disease in 10%, 15% understaging for Gleason score in 15% and biochemical recurrence in 25% [5]. Hence, accurate identification of patients with truly indolent cancer at the time of diagnosis remains challenging. [Table/Fig-1] outlines the currently available criteria for AS of low grade prostate cancer.

AIM

The objective of the study was to evaluate pathological outcomes of patients undergoing RP but eligible for AS (according to five published AS selection criteria) based on upgrading and upstaging of their surgical histopathology compared to the biopsy report. We also investigated the incidence of biochemical recurrence based on postoperative PSA density.

MATERIALS AND METHODS

A total of 245 radical prostatectomies were performed in our tertiary centre over a three-year period from January 2008 to December 2012. Inclusion criteria were, patients that met active surveillance (AS) criteria (for low grade disease) as determined by the parameters listed in [Table/Fig-1]. No patient received neoadjuvant hormonal or radiation therapy. The primary endpoint between was to evaluate accuracy of current AS protocols in identification of low risk prostate cancer by comparing the histopathology at biopsy and surgery as well as biochemical recurrence.

Pre-operative investigations included clinical examintation (Digital Rectal Exam) and PSA level. Patients with abnormal DRE or high PSA level underwent high standard Trans Rectal Ultrasound Guided (TRUS) biopsy.

All surgeries were performed through an open retropubic approach by a single surgeon. Lymph node dissection was performed if the chance of lymph node involvement was ≥5% according to Partin's tables. Histopathological evaluation of biopsy and surgical specimens was performed independently by 2 different histopathologists according to the Gleason grading system [6] and pathological stage was graded based on the 2002 TNM.

Upstaging was defined as any occurrence of extraprostatic extension or seminal vesicle involvement. Extraprostatic extension was defined as carcinoma mixed with periprostatic adipose tissue, or bulging out beyond the contours of the prostate gland or Bladder neck invasion [7] (EUA Guidelines 2013). Upgrading was defined as GS 3+4 or greater in the surgical specimen [8].

Criteria	T Stage	PSA	Gleason score	No Of Core	PSAD	% Core involvement
Johns Hopkins [9]	T1	-	6 OR LESS	MAX 2	0.15ng/ml/ml	Less than 50%
PRIAS [10]	T1 –T2	10ng/ml	6 OR LESS	MAX 2	Less than 0.2	-
Eastham (MSKCC) [11]	T1-T2a	10ng/ml	6 OR LESS	Max 3	-	Less than 50%
Soloway [12]	T1 –T2	15ng/ml	6 OR LESS	MAX 2	-	Less than 20%
University of California [13]	T1 –T2a	10ng/ml	6 OR LESS	-	-	Less than 33%

[Table/Fig-1]: Active surveillance criteria.

Serum PSA levels were measured 3, 6, 12, 18, 24, 30, and 36 months postoperatively, and annually thereafter. The duration to biochemical failure was measured as the time to a postoperative serum PSA level was >0.2 ng/mL.

RESULTS

Out of 245 patients who underwent RP in our institute over a three-year period, 59 patients met the criteria for AS according to at least one of the criteria presented in [Table/Fig-1]. [Table/Fig-2] demonstrates the relevant patient demographics and clinicopathological characteristics.

The median follow up was 39.9 months (range 10 - 66 months). Overall two patients (3%) had PSA failure and both had salvage radiotherapy. The eligibility for AS according to one of the criteria in [Table/Fig-1] is demonstrated in [Table/Fig-3]. A total of 24 (40.6%) specimens upgraded and 12 (20%) upstaged based on their final histopathology specimen. Among the patients eligible for PRIAS criteria, 28% upgraded and 6% upstaged; from the MSK criteria 42% upgraded and 15% upstaged, 44% upgraded and 20% upstgaed from the eligible patients according to Soloway criteria. From the patients eligible for the University of California criteria and John Hopkins critera 46% and 17% upgraded respectively while 23% and 11% upstaged respectively. The details of the same are highlighted in [Table/Fig-3,4].

Parameter	Median	Standard Deviation (SD)
Age (years)	56	6.037
PSA (ng/ml)	6.78	2.652
Transrectal Ultrasound (TRUS) Volume ml	30	13.0079
PSA Density ng/nl/ml	0.21	0.1319
Gleason Grade (TRUS Biopsy)	3+3	N/A
Number of positive cores on TRUS biopsy	1.7	N/A
Length of follow up (months)	39	N/A
PSA after radical Prostatectomy	0.00	N/A
Disease recurrence (n,%)	2 (3%)	

[Table/Fig-2]: Characteristics of patients included on the study.

	PRIAS	MSK	Soloway	University of California	Johns Hopkins
Number of patients who met AS criteria	32(54%)	45(76%)	50(84%)	52(88%)	17(28%)
Upgrade (n,%)	9(28%)	19(42%)	22(44%)	24(46%)	3(17%)
Upstage (n,%)	2(6%)	7(15%)	10(20%)	12(23%)	2(11%)
PSA failure (n,%)	1(3%)	2(4%)	2(4%)	2(3%)	1(5%)

[Table/Fig-3]: The differences different protocols in predicting the outcome of radical prostatectomy.

PSA density at diagnosis	Upgrade (n,%)	Upstage (n, %)
< = 0.20 (n=29)	8 (27%)	4 (14%)
>0.20 (n=24)	14 (58%)	6 (25%)

[Table/Fig-4]: Upgrading and Upsatging according to PSA density at diagnosis.

DISCUSSION

There is considerable controversy around selection criteria for AS in LR prostate cancer as different institutions apply different eligibility criteria. In our study, the PRIAS criteria was relatively broad as it identified very low-risk patients and this was reflected on the final outcome as 28% patients upgraded while only 6% upstaged. These results were comparable to previously published data [8]. John Hopkins criteria for AS have a narrower spectrum which is why there was less disease progression in the form of upgrading (17%) and upstaging (11%) in the final surgical histopathology specimen of patients selected based on this criteria. This criteria has been reported at the strictest among other published AS criteria [5,14,15]. Even so PSA failure was seen in one patient eligible for the criteria.

Soloway (University of Miami) criteria for AS and University of California criteria were both comparitively broad. This was evident in the fact that most patients in our cohort were eligible for AS in accordance to these criteria: 86% and 88% respectively. Conversely the outcome was not as favourable for these selection criterias: 44% upgraded and 20% upstaged for Soloway protocol while 46% upgraded and 23% upstaged for university of California protocol. For both protocols, two patients had PSA failure and both of them required adjuvant radiotherapy. Conti et al., reported that overall 28% of men who met AS criteria had GS upgrading, 21% had extracapsular extension and 11% had seminal vesicle involvement at RP [14]. The upgrading proportion varied from 23-35% based on the criteria applied. Louie Johnsun et al., reported that in 23% of 549 patients who received laparoscopic RP with low-risk disease GS upgrading was evident while 5% had extracapsular extension, and 0.9% had seminal vesicle invasion [15]. In a large study on 1,375 patients with prostate cancer, 125 met the University of California-San Francisco and Johns Hopkins criteria and they were followed for 36 months. At the end of this period, 20% patients for University of California and 27% patients for John Hopkins protocol upgraded at the surgical histopathology. The rate of upstage was 6% and 8% respectively which was lesser than our study (23% and 11% respectively) [16]. Another retrospective study by Norman et al., from Santiago, Chile included patients who underwent RP and met the following criteria for AS: Gleason score (GS) ≤ 3+3 = 6, PSA ≤ 10ng/mL, T1c - T2a, < 1/3 of positive cores, < 50% of involvement in any core and PSA density < 0.15.(11) The total number of patients was 167 and their result showed 31% patients had a GS > 6 in the surgical specimen. Extracapsular extension, seminal vesicle and lymph node involvement was found in 6.1%, 3.1% and 1.2% of the specimens, respectively [17].

Several studies have reported the correlation between PSA density and the aggressiveness of the final histopathology. In a study by Corcoran et al., PSAD was the strongest single predictor of Gleason score upgrading in patients with a Gleason score 6 and 3+4=7 cancer on biopsy, but it was less effective in higher grade tumours [18]. This is comparable to the findings of our study: PSAD higher than 0.2 was associated with a higher risk of tumour upstaging and upgrading (58% and 25% respectively), while PSAD less or equal to 0.2 was associated with less tumour upgrading and upstaging (27% and 13% respectively).

A recent systematic review attempted to identify novel markers for AS selection, Magnetic Resonance Imaging and PSA isoforms showed promise among different new markers [19]. MRI has been included in the recent 2014 AS recommendations by National

Institute of Health and Care (NICE), UK [20]. MRI can be offered both at the enrolment stage and to inform rebiopsy decisions. Patients with a negative MRI do not need further biopsies according to NICE, unless their biopsy showed atypical/insitu disease, the risk of prostate cancer is still present or if the DRE is abnormal. The inclusion of novel isoforms of PSA or other serum markers in routine AS protocols is still not recommended. Cost effectiveness of these novel imaging and serum markers and their utility with respect to long term end points of metastasis or disease specific mortality need to be studied [19].

LIMITATIONS

The limitations of this retrospective study lie in the small sample size and short follow-up period. The patient population had less ethnical variation as majority were caucasians.

CONCLUSION

It can be surmised that current AS criteria are not balanced in identifying patients with low-risk disease. Some of these criteria like the John Hopkins criteria may be too strict thus excluding candidates in whom expectant management would be safe; while othes like Solway criteria may be very broad. Even with the strictest of selection criteria, it is observed that varying proportion of patients with LR disease could harbour unfavourable diasease on account of inaccuracy in the currently used biopsy protocols. Hence current array of selection criteria for AS even though focus on similar factors of low grade-low volume cancer; subtle discrepencies exist between different protocols which affect clinical decision making. These current markers used for selection of patients for AS thus may not be sufficient to consistently identify patients with LR disease and there is a need for new markers. Prospective studies assessing the utility of novel markers to allow for accurate and uniform selection of patients with LR prostate cancer for AS are the need of the hour.

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