ORIGINAL ARTICLE

Pathological Outcome in Men with Prostate Cancer Suitable for Active Surveillance After Radical Prostatectomy

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ABSTRACT

Background: Active surveillance (AS) as a treatment option for low risk prostate cancer is gaining recognition. We evaluate the validity of the AS protocol in our patient population, by defining the risk of undergrading and understaging in their pathology. We also aim to determine more accurate inclusion criteria, in order to improve the prediction of early low risk prostate cancer.

Materials and Methods: Data was taken from our institutional prostate cancer registry for all men who underwent radical prostatectomy (RP) between Jan 2000 and June 2009. We determined if any of the patients would have met the University of Toronto's (UoT) AS inclusion criteria and examined their post-operative pathology. The primary end-point was pathological upgrading and upstaging. The individual inclusion factors i.e. preoperative PSA, were tested for statistical significance and better cutoffs. Univariate, multivariate and ROC curves were used in the statistical analysis.

Results: 216 RPs were performed between January 2000 and June 2009. We identified 79 men who fulfilled the UoT AS criteria. 35% of patients had a Gleason score upgrade from biopsy to surgery, and 21.5% of patients had an upstage to T3 disease. Overall, 34 (43%) patients had an unfavourable change in the grade and/or stage of their prostate cancer.

Conclusions: There is a significant risk of undergrading and understaging with the current criteria used for AS. There is a need to identify more discriminative AS criteria before it can be offered as an option to patients with clinically early prostate cancer.

Keywords: active surveillance, low risk prostate cancer, radical prostatectomy

INTRODUCTION

Since the use of serum prostate specific antigen (PSA) as a cancer marker in the 1980s, an increasing number of small, non-palpable, early stage cancers are being diagnosed. These low risk cancers have been shown to pose minimal risk of cancer progression and metastasis[1], and the treatment of these patients have raised concerns of over-treatment.

As a modification of watchful waiting, active surveillance (AS) as a treatment option for low risk prostate cancer is gaining recognition. There have been several prospective cohort studies on AS[2-6]. These studies, performed at western institutions, have varying inclusion criteria, which were mainly based on the Epstein criteria[7]. These inclusion criteria consist of PSA, PSA density, Gleason score, number of positive biopsy cores, percentage of positive cores, and percentage of single core involvement. The surveillance methods were also different between the studies, however repeat PSA, DRE and re-biopsy at a range of intervals were generally applied. Results showed that 14%-35% of these western patients progressed from AS to definitive treatment, and deferring treatment, did not seem to alter the natural history[8,9]. The drawback is that these studies have limited follow-

Table 1. Pre and postoperative descriptive statistics.

Patient Variable	Mean±SD	Median	Range	No of patients (%)
Age at diagnosis (years old)	61.0±6.4	61.0	42.0–73.0	79
Pre-op PSA (ng/ml)	6.7±1.6	6.7	3.0–10.0	79
Biopsy Gleason score		6	4–6	79 (100)
<6	-	-	-	3 (4)
6	-	-	-	76 (96)
No. of positive cores	2±1	2	1–3	79
% positive biopsy cores	16.4±8.2	14.0	3.0–33.0	79
% single core involvement	22.4±14.1	20.0	3.0–50.0	79
No. of cores taken at biopsy	11.7±4.0	10.0	10.0–34.0	79
Time between biopsy and RP (days)	88.0±41.4	89.0	16.0–195.0	79
Clinical T stage				79 (100)
T1	-	-	-	59 (75)
T2	-	-	-	20 (25)
Prostate Volume (g)	45.0±16.0	40.8	20.0–114.0	54

up. Furthermore, these studies did not include statistical analysis of the individual inclusion criteria. These wide-ranging results, the use of varied inclusion criteria and surveillance protocols, and our clinical experience has led us to believe that at present, AS may pose significant risk for the patient with clinically early stage prostate cancer.

The aim of this study is to validate the AS protocol in an Asian population, by defining the risk of pathological undergrading and understaging. We adopted the University of Toronto's AS criteria[10] as the control protocol. To our knowledge, there is no formal validation of this criteria in Asian men. We also aim to determine more accurate inclusion criteria, in order to improve prediction of upgrading and upstaging.

MATERIALS AND METHODS

Data was taken from our institutional prostate cancer registry, for all Asian men who underwent radical prostatectomy (RP) between January 2000 and June 2009. Approval for the study was obtained from the Institutional Review Board. Patients were included in the study if they underwent RP for primary treatment of prostate cancer of clinical stage T2 and less, and had the RP within 180 days of initial diagnosis. In addition, patients were only included if they had at least 10 cores taken during prostate biopsy, and complete clinical data including PSA, Gleason score, number of positive biopsy cores, and percentage single core involvement.

For the study, we adopted the University of Toronto's inclusion criteria[10], which includes PSA<10, Gleason≤6, ≤3 positive cores and <50% single core involvement. The University of Toronto's criteria was chosen, as it is one of the more stringent and commonly adopted criteria worldwide. The data that it required was also readily available in our population. We further determined if any of our RP patients would have met the above AS inclusion criteria, and examined if there was any change between their pre-operative and postoperative pathologies.

We defined upgrading as any increase in Gleason score from biopsy to surgery, and upstaging as any change in the T stage to T3, without differentiating between T3a–T3c disease. This definition was used as the changes would increase the patient's risk profile, and make them unsuitable for AS.

In terms of statistical analyses, the factors analysed were preoperative PSA, number of positive cores, percentage positive cores, percentage single core involvement, number of cores taken, prostate volume, and the time between biopsy and RP in days. Data normality and homogeneity were checked

Table 2. Pathological findings at RP.

Variable	No of patients (%)
Pathological gleason score	
No tumour	1(1)
5	7(9)
6	48 (60)
7	22 (28)
8	1(1)
Gleason changes	
No change*	52 (65)
Upgrade**	27 (35)
Pathological T stage	
No tumour	1 (1)
T2	15 (77)
T3a	16 (20)
T3b	1 (1)
T stage changes	
No change	62 (78.5)
Upstage***	17 (21.5)
Overall Grade and Stage changes	
No change	45 (57)
Upgrade and/or Upstage	34 (43)

* Includes 8 downgrade cases
** Upgrade: increase in Gleason score
*** Upstage: T1/2 to T3

for skewness, kurtosis, and with histograms. These were satisfied for all, except 'number of cores taken' and 'prostate volume'. Hence, these two factors were analysed by the Mann-Whitney test. The rest of the data were analysed with one-way ANOVA. Multivariate analysis was also carried out for the variables tested, and p less than 0.05 was considered significant. To determine if there were better limits for the inclusion criteria, ROC curves were used.

All statistical analyses were performed using SPSS Statistics 18.

RESULTS

216 RPs were performed between January 2000 and June 2009. Out of these 216 men, 24 men had less than 10 cores taken at biopsy, 19 men had RP more than 180 days after initial diagnosis, 35 patients had a preoperative PSA>10ng/ml , 55 patients had a Gleason score>6, and 83 patients had incomplete data. Ultimately, 79 men fulfilled the University of Toronto's AS inclusion criteria[10] and were recruited into the study.

The pre-operative and post-operative characteristics of the 79 patients included in the study were summarised in Table 1. Prostate volume data was only available for 54 (68%) patients and this was used in a sub-analysis. Table 2 summarised the pathological findings on RP specimens. Overall, 34 (43%) patients had an unfavourable change in the grade and/or stage of their prostate cancer.

Upon analysis of the individual inclusion factors, "number of positive cores", "percentage positive cores", and "percentage single core involvement" were statistically significant on univariate analysis. "Pre-operative PSA", "number of cores taken", and "time between biopsy and RP" did not show any statistical significance. None of the variables were statistically significant on multivariate analysis (Table 3). When the number of positive cores was further analysed, there was a striking increase

Table 3. Statistical analysis of inclusion factors.

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Pre-op PSA (ng/ml)	1.170	0.272	1.386	0.161
No. of positive cores	2.272	0.004	11.833	0.220
% positive cores	1.070	0.018	0.842	0.407
% single core involvement	1.041	0.018	1.016	0.547
No. of cores taken	1.011	0.665	0.921	0.637
Time between bx and RP (days)	1.008	0.162	1.007	0.366
Prostate volume (g) N=54	0.971	0.061	0.980	0.352

Table 4. Sub-analysis of "number of positive cores".

No. of positive cores	Change in grade and stage		Logistic regression			
	No. of No change (%)	No. of Upgrade and Upstage (%)	OR (95% CI)*	p value	95% Confidence Interval	
					Lower Bound	Upper Bound
1	26 (72.2)	10(27.8)	5.2	0.006	1.624	16.655
2	12 (54.5)	10 (45.5)	2.4	0.165	0.697	8.259
3	7 (33.3)	14 (66.7)	-	-	-	-

* the reference category is "3 positive cores"

Table 5. New limits tested with ROC curve.

Variable	New limits tested
No. of positive cores	1, 2, 3
% single core involvement	10%, 20%, 30%, 40%
% positive cores	10%, 20%, 30%

(66.7%) in the number of upgrade and upstage cases in patients who had three positive cores, compared with patients who had fewer than three positive cores (Table 4).

Secondary analysis of the 54 patients whose prostate volume data were available revealed that there was no correlation between prostate volume and the other tested variables. Additionally, in this subset, there was no significant difference between the patients who had pathological upgrading and upstaging vs. those who had no change.

With the ROC curve analysis, we were unable to find better cutoffs for number of positive cores, percentage single core involvement and percentage positive cores. For number of positive cores, the limits tested were 1, 2 and 3; for percentage single core involvement, the limits tested were 10%, 20%, 30% and 40%; and for percentage positive cores, the limits tested were 10%, 20% and 30%. The area under the curves were all less than 0.7 (Table 5).

DISCUSSION

The AS criteria relies heavily on pathological information from the prostate biopsy, in order to

Table 6. Prospective studies enrolling patients in active surveillance programs.[14]

References	Institution	No. Pts	Mean Age	Inclusion Criteria	Surveillance Protocol	Mean Yrs Followup	% Treated
Loblaw et al.	University of Toronto	423	67	Gleason 3+4 or less, PSA 15ng/ml or less, stage T1–T2, 3 or less pos biopsy cores, 50% or less single core involvement	PSA, re-biopsy after 1 yr then every 3 yrs	4.6	35
Hardie et al.	Royal Marsden	80	71	Gleason 7 or less, stage T1–T2, PSA 20ng/ml or less	DRE, PSA every 3–6 mos then every 6 mos	3.5	14
Carter et al.	John Hopkins Medical Institution	407	66	Gleason 6 or less, no pattern 4 or 5, PSAD 0.15 or less, stage T1, 2 or less pos biopsy cores, 50% or less single core involvement	DRE, PSA every 6 mos biopsy every 12 mos	3.4	25
Dall'Era et al.	UCSF	312	63	Gleason 6 or less, PSA 10 ng/ml or less, stage T1–T2, 1/3 or less pos biopsy cores, 50% or less single core involvement	DRE, PSA every 3 mos TRUS every 9–12 mos, biopsy after 1 yr then every 1–2 yrs	3	21
Patel et al.	Memorial Sloan-Kettering Cancer Centre	88	65.3	Gleason 7 or less, stage T1–T2	DRE, PSA every 3 mos for 1 yr then every 6 mos, re-biopsy at 6 mos	4.6	35

predict the final pathology. This poses an issue, as histological information from the biopsy has its own intrinsic inadequacies. In the first instance, differences have been reported between the biopsy and final pathology Gleason score by Steinberg et al, because of sampling error, and error in the pathologist's interpretation of the specimens[11]. Under-sampling during the prostate biopsy remains a large issue with the AS criteria. Approaches aimed at improving the harmony of biopsy and RP Gleason scores have been widely reported, and perhaps the most promising is that of saturation biopsies[12]. Another possible approach is to eliminate inter-observer variability, and ensure that the same pathologist is responsible for reporting both the biopsy and RP histology.

A low PSA is associated with organ confined tumour and is part of most AS criteria. However, there is also sufficient data to show that a lower PSA is not always associated with low risk prostate cancer. Geary et al found positive surgical margins in 13% of non-palpable tumours with PSA between 4–10ng/ml[13].

We found in this study that 35% of patients experienced upgrading and 21.5% experienced upstaging. Overall, 43% of these patients had upgrading and/or upstaging. This finding indicated that if practised, AS protocols might place a substantial number of men with higher risk disease in a low risk group.

We also attempted to refine the existing criteria, and identify new inclusion criteria. However, further analysis of the individual inclusion criteria did not yield any meaningful results. In addition, no better cutoffs for other parameters, such as number of positive cores, percentage single core involvement and percentage positive cores could be found. This finding again demonstrates the limitations of the current AS inclusion criteria. It does not provide patients sufficient safety and assurance in choosing AS, as their treatment of choice.

Our study bears similar results to that of a recent evaluation on five common AS protocols by Conti et. al.[14] The study reported a 23–35% upgrade, and a 7–19% upstage in groups of low risk prostate cancer patients. It is noteworthy that the men who qualified for the more stringent AS criteria (University of Toronto, UCSF and Johns Hopkins) had a lower incidence of adverse pathology. These stringent criteria all included estimates of tumour volume. The various AS criteria are summarised

in Table 6. Conversely, our study considered the "upgraders" and/or "upstagers" as a single group. We felt that this would be more accurate in defining the risk of undergrading and understaging in AS. Apart from this, our study also included statistical analysis of the individual inclusion criteria, in an attempt to improve prediction upgrading and upstaging.

Sang and colleagues recently tested the Epstein criteria in a group of 131 Korean men.[15] They reported a 40% risk of upgrading and 3.1% risk of upstaging. This is similar to our study of Asian men, and further emphasises the risk of upgrading and upstaging, when common AS protocols are applied to Asian men.

The limitations of this study are those inherent to retrospective studies. Data collection posed some difficulties, resulting in a smaller sample size, and limited the choice of AS criteria that we could use. The choice of the inclusion criteria used in this study was largely based on the data that was available. In the strictest sense, the John Hopkins criteria is likely the most stringent and would have been the ideal criteria to use in this study. Also, the lack of a full set of prostate volumes (PV) restricted our data analysis; we were unable to correlate PV with the other variables, and hence could not ascertain if the " number of cores taken" had any correlation to the size of the prostate. This may explain why there was a higher incidence of upgrading and/or upstaging in patients who had three positive cores at biopsy. Another weakness of our study is that multiple pathologists examined the biopsy and surgical specimens, which may raise concerns of consistency of the reported Gleason scores. In addition, because of the grade migration in recent years, current patients may be considered incomparable to earlier candidates.[16] Lastly, it has to be mentioned that the issue with AS, is mainly that of the timing of treatment, rather than a question of whether to treat or not. Hence, it is hard to illustrate the effect a delay in treatment would have in patients who are undergraded or understaged.

Despite these limitations, our results clearly show that the common AS criteria (UoT AS inclusion criteria), is fairly inaccurate when used for surveillance of the Asian men with presumably low risk prostate cancer. Such limitations should be considered when treatment options are contemplated based upon the use of the common AS criteria among Asian patients. Increasing the sample size in this study will possibly allow more meaningful results to determine new cutoffs for the AS criteria. This may well allow us to better predict upgrading and upstaging.

CONCLUSION

Based on the UoT AS criteria, there is a significant risk of undergrading and understaging in patients presumably suitable for AS. There is a need to identify more discriminative AS criteria before it can be offered as an option to patients with clinically early prostate cancer.

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