Tumor Volume in Insignificant Prostate Cancer: Increasing the Threshold is a Safe Approach to Reduce Over-Treatment

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BACKGROUND. There are conflicting results in the literature regarding the tumor volume (TV) threshold that defines insignificant prostate cancer (PCa). In this study, we retrospectively evaluate the association of an increasing TV with biochemical recurrence (BCR) following radical prostatectomy (RP) in order to provide further clarification surrounding the TV threshold definition for insignificant PCa.

METHODS. RP patients were recruited from January 2004 to December 2009. Inclusion criteria were localized (stage ≤pT2c, negative surgical margins) Gleason 6 PCa with a total TV of ≤2.50 cm^3. BCR was the primary outcome and defined as a PSA of ≥0.1. All cases with BCR were re-evaluated by the pathologist with reassessment of tumor grade, pathological stage and surgical margin status.

RESULTS. From 1,636 patients, 178 men (10.9%) met all inclusion criteria. Ninety-six patients (53.9%) had a TV <0.5 cm^3 and 82 patients (46.1%) had a TV 0.5–2.5 cm^3. Three out of 178 patients (1.7%) presented with BCR during follow-up. One of these had TV <0.5 cm^3 and two had TV 0.5–2.5 cm^3. These three cases of BCR underwent re-review of pathology; one patient was found to have a positive surgical margin and one patient was upgraded to Gleason 3 + 4 = 7. The third patient was re-reported as having positive margins for a benign hyperplastic nodule (incomplete RP specimen). Subsequently, these three cases were excluded from final analysis as they did not fit inclusion criteria. Median follow-up duration was 84 months (IQR 70–102 months). On final analysis, there were no patients with BCR, corresponding with a final BCR rate of 0% for both patients with a TV of <0.5 cm^3 and 0.5–2.5 cm^3.

CONCLUSIONS. Our results have shown that, with a median follow-up of 84 (IQR 70–102) months, patients in our cohort with localized Gleason 6 PCa with a total TV 0.5–2.5 cm^3 have a BCR rate of 0%. We would support a more liberal total TV threshold of 2.5 cm^3 for the further development of algorithms to identify patients suitable for active surveillance. *Prostate 75:1768–1773, 2015.* © 2015 Wiley Periodicals, Inc.

KEY WORDS: **prostate-specific antigen; prostatic neoplasms; tumor burden**

INTRODUCTION

The uptake of prostate specific antigen (PSA) testing in population based screening for prostate cancer (PCa) has led to a stage and grade migration towards clinically insignificant PCa [1]. Correctly identifying which of these patients have clinically insignificant PCa has become increasingly important in order to avoid over-treatment of PCa [2].

Each tumor cell in low-grade PCa is at risk of transformation to high-grade cancer; as a consequence

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the volume of cancer determines the risk of a subsequent clinical high-grade cancer [3]. As a result, definitions of insignificant PCa have incorporated tumor volume (TV) as a key parameter. The classical Epstein definition included organ confined PCa with Gleason score $\leq 3+3=6$ and a tumor volume $\leq 0.5\,cm^3$ and has been considered insignificant for many years [4].

However, this established $0.5\,cm^3$ PCa TV threshold for the index tumor in insignificant PCa may have been too restrictive. In line with this, an updated histopathological definition of insignificant PCa has recently been proposed with an increase in the TV threshold to $<1.3\,cm^3$ for the index tumor and $<2.5\,cm^3$ for the total TV in men with Gleason $3+3=6$ PCa [5]. Conversely, Schiffman et al. [6] recently questioned this increased TV threshold with data showing that patients with organ confined Gleason 6 PCa with TV 0.5–$2.49\,cm^3$ were at higher risk of biochemical recurrence (BCR) after radical prostatectomy (RP) compared to those with a TV $<0.5\,cm^3$.

In this study, we retrospectively evaluate the association of an increasing TV with BCR following RP in order to re-evaluate the hypothesis by Wolters et al. and Schiffman et al. We have analysed patients with organ-confined, Gleason score $3+3=6$ PCa with the aim of providing further clarification surrounding the TV definition of insignificant PCa.

METHODS

Patient Selection

From January 2004 to December 2009, 1,636 radical prostatectomies (RP) were performed by two urologists (PS and PB) at St. Vincent's Prostate Cancer Centre, Sydney, Australia. All patients included for final analysis were age >40 years with localized (stage $\leq$ pT2c, negative surgical margins), Gleason $3+3=6$ PCa, had a complete RP specimen available for analysis and a total TV of $\leq 2.50\,cm^3$ as measured by a single experienced pathologist (WD).

Pathologic Examination

RP specimens were processed following a standardized protocol. After fixing the specimens, they were inked and cut at 3-mm intervals perpendicular to the rectal surface. The apical slice was cut parasagittally at 2–3-mm intervals, and the sections were then divided in halves or quadrants to fit routinely used cassettes for paraffin embedding. The whole prostate was sampled. Pathologic tumor stage, Gleason score, surgical margin status, and the presence of seminal vesicle invasion (SVI) were assessed. Tumor areas were marked at each slide and measured using computerized morphometric analysis. The total TVs were then calculated by multiplying the area by the slice thickness. Staging was performed according to the 1992 TNM classification system. All specimens examined after 2005 were analysed using ISUP 2005 grading criteria. RP specimens requiring re-review were submitted to a single pathologist (WD) for analysis using ISUP 2005 grading criteria.

Follow-Up

Patients were followed up after RP by serial PSA measurements at 3, 6, and 12 months, then every 6 months until 3 years and yearly after this. Biochemical recurrence (BCR) was defined as a PSA $\geq 0.1\,ng/ml$.

Total follow-up time was defined as the time from RP to death or the last visit date. Time to recurrence was defined as the time from RP to the time of the first signs of recurrence. When no signs of recurrence were registered, cases were censored at the time of the last follow-up visit or the date of death.

All cases with BCR were re-evaluated by the pathologist (WD) with reassessment of tumor grade, pathological stage, and the status of surgical margins.

Statistical Analysis

Statistical analysis was performed using SPSS version 21.0 (IBM, Armonk, NY). Continuous variables were summarized using median and interquartile range (IQR) values. Patients were divided into two groups: patients with $TV < 0.5\,cm^3$, based on the Epstein criteria [7], and patients with TV 0.5–$2.5\,cm^3$, based on the Wolters et al. [5] criteria, for the purposes of sub-group analysis.

RESULTS

Patient Population and Primary Outcome

A total of 328 men with localized ($\leq$pT2c and negative surgical margins), Gleason 6 PCa were identified between January 2004 and December 2009. Of these, 178 men (53.3%) had a valid three-dimensional estimate of total TV $\leq 2.5\,cm^3$.

Among these men, three patients (1.7%) presented with BCR during follow-up, one with TV $<0.5\,cm^3$ and two with TV 0.5–$2.5\,cm^3$.

The pathology for these three patients was then re-reviewed. The first patient had a positive surgical margin at the right apex. The second patient was upgraded to Gleason $3+4=7$ and was also found to

have focal extra-prostatic extension in association with the index tumor. The third patient was re-reported as having positive margins for a benign hyperplastic nodule (incomplete RP specimen).

These three cases were subsequently excluded, as they did not fit into our inclusion criteria. Consequently, a total of 175 patients were included in the final analysis (Fig. 1).

In total, 95 patients (53.9%) had a TV $<0.5\,cm^3$ and 80 patients (46.1%) had a TV 0.5–2.5 cm^3. Patient demographic, pathologic, and follow-up data are summarized in Table I. Median overall age was 59 years and median overall pre-operative PSA was 5.3 ng/ml. There were two patients (1.1%) in the cohort with tertiary Gleason Grade 4.

Tumor Volume, PSA, and Pathological Stage

There was no statistically significant difference in age, median pre-operative PSA, D'Amico risk grading or follow-up duration between the two groups of TV. 14.6% of patients with TV $<0.5\,cm^3$ and 4.9% of patients with TV 0.5–2.5 cm^3 had a pre-operative PSA of 10–20 ng/ml.

Increasing TV correlated with increasing pathological stage. Patients with a larger TV (0.5–2.5 cm^3) had a relatively greater proportion of pT2c tumors (83.7% vs. 62.1%, $P = 0.001$) and conversely patients with a smaller TV ($<0.5\,cm^3$) had a relatively greater proportion of pT2a tumors (25.3% vs. 10%, $P = 0.01$).

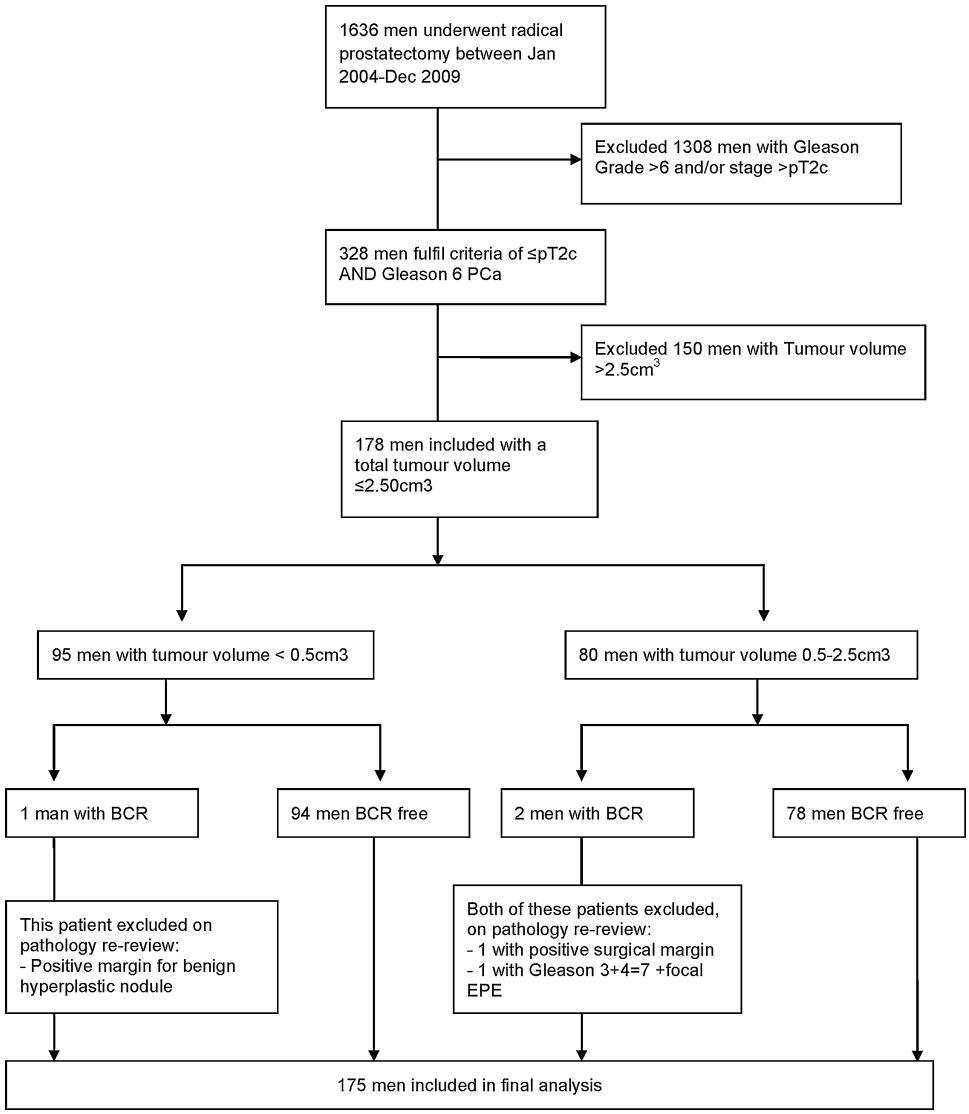

Fig. 1. Flowchart of patient selection for final analysis.

TABLE I. Demographic, Pathologic, and Follow-Up Data With Subgroup Comparison of Patients With Total TV $<0.5\,cm^3$ Versus Patients With Total TV 0.5–2.5 cm^3

	Overall	$<0.5\,cm^3$ (n = 95)	0.5–2.5 cm^3 (n = 80)	*P* value
Number of patients	175	95 (54.3%)	80 (45.7%)	
Age at RP, median (IQR)	59 (54–62)	59 (54–62)	58 (54–62)	0.79
Clinical stage				
cT1a	1 (0.5%)	0 (0.0%)	1 (1.2%)	0.27
cT1b	2 (1.1%)	1 (1.1%)	1 (1.2%)	0.90
cT1c	117 (66.9%)	71 (74.7%)	46 (57.5%)	0.02
cT2a	35 (20.0%)	15 (15.8%)	20 (25.0%)	0.13
cT2b	7 (4.0%)	2 (2.1%)	5 (6.3%)	0.16
cT2c	8 (4.6%)	4 (4.2%)	4 (5.0%)	0.80
Unknown	5 (2.9%)	2 (2.1%)	3 (3.8%)	0.52
PSA at RP, median (IQR)	5.2 (4.0–7.3) ng/ml	5.1 (3.3–8.5)	5.4 (4.3–6.9)	0.33
PSA at RP				
≤10	156 (89.7%)	81 (85.3%)	75 (95.0%)	0.07
10–20	18 (10.3%)	14 (14.7%)	4 (5.0%)	0.03
PSA unknown	1	0	1	
D'Amico risk				
Low	137 (78.3%)	74 (77.9%)	63 (78.8%)	0.89
Medium	24 (13.7%)	15 (15.8%)	9 (11.2%)	0.38
High	8 (4.6%)	4 (4.2%)	4 (5.0%)	0.80
Unknown	6 (3.4%)	2 (2.1%)	4 (5.0%)	0.29
Path stage RP				
pT2A	32 (18.3%)	24 (25.3%)	8 (10.0%)	0.01
pT2B	17 (9.7%)	12 (12.6%)	5 (6.3%)	0.16
pT2C	126 (72.0%)	59 (62.1%)	67 (83.7%)	0.001
pNx	132 (75.4%)	70 (73.7%)	62 (77.5%)	0.56
pN0	43 (24.6%)	25 (26.3%)	18 (22.5%)	0.56
pN1	0	0	0	
Path grade RP				
Gleason score 3 + 3 = 6	175 (100%)	95 (100%)	80 (100%)	
Tertiary Gleason grade 4 present	2 (1.1%)	1 (1.1%)	1 (1.3%)	
Tumor volume				
Median (IQR)	0.40 cm^3 (0.20–1.20)	0.2 (0.15–0.36)	1.23 (0.73–1.90)	
Mean (range)	0.74 cm^3 (0.02–2.5)	0.24 (0.02–0.45)	1.34 (0.5–2.5)	
Follow up in months, median (IQR)	84 (70–102)	85 (71–105)	82 (68–99)	0.98
Biochemical recurrence	0 (0%)	0 (0%)	0 (0%)	
Cancer specific mortality	0 (0%)	0 (0%)	0 (0%)	

Follow-Up and Biochemical Recurrence

Median follow-up duration was 84 months (IQR 70–102 months). There were zero patients with BCR in the final cohort, corresponding with a final BCR rate of 0% for patients with TV of $<0.5\,cm^3$ and also patients with TV 0.5–2.5 cm^3.

DISCUSSION

Insignificant PCa is an epidemiological term, which is defined as harmless PCa based on lifetime risk estimates of the occurrence of symptomatic or clinical PCa [4]. For many years, the definition of pathologically insignificant PCa was based on the pathological Epstein criteria, including a TV $<0.5\,cm^3$, Gleason score ≤6 and stage pT2 on prostatectomy [7]. More recent epidemiological data have shown that a TV of $<0.5\,cm^3$ is a considerable underestimation of the threshold for pathologically insignificant PCa [8]. Obviously, use of this definition of pathologically insignificant PCa requires pathological examination of the entire prostate. Non-invasive measurement of PCa volume has been investigated with a recent software-assisted, co-registration analysis comparing PCa lesion boundaries on MRI to histology specimens. It showed that MRI underestimates TV, with a mean TV of 0.71 cm^3 on T2 weighted imaging compared to a mean TV of 1.05 cm^3 on whole mount

histopathology [9]. However, for PCa detection, a recent meta-analysis has shown that multi parametric MRI (mp-MRI) has a sensitivity of 66–81% and specificity of 82–92% [10]. If mp-MRI continues to improve, non-invasive accurate measurement of PCa TV can potentially be used in the future as a key factor for appropriate treatment selection. Since over--treatment of patients with low-grade PCa continues to be of concern in relation to early detection, any increase in the TV threshold for insignificant PCa will have significant impacts on the treatment patterns of PCa in the coming years.

The present study showed no BCR among patients with stage $\leq$pT2c, Gleason 6 PCa and a TV $\leq$ 2.50 cm^3. This indicates that these cancers were harmless at the time of RP; however, it does not inform us of the lifetime risk of symptomatic or clinical PCa in the absence of curative treatment. The ideal study design to determine the TV threshold would prospectively include all men with low-grade disease with an accurate non-invasive measurement of their PCa TV and follow them up until death while they remain untreated. However, currently there is no accurate non-invasive method of measuring TV and more importantly this study design has major ethical issues. Thus, we have taken a more feasible approach and presented the data obtained to help establish the TV threshold for insignificant PCa.

The initial evidence for moving towards a larger TV threshold for identification of clinically insignificant PCa came from analysis of the screening arm of the Rotterdam ERSPC dataset [5]. Clinical data applied to a micro-simulation model was used to calculate the proportion of screen-detected cancers that would have been clinically detected. Applying this to their subgroup of 174 patients with organ-confined $\leq$Gleason 6 PCa, an index TV threshold of 1.3 ml and a total TV threshold of 2.5 ml for clinically significant disease was calculated.

A recent series by Schiffman et al. has challenged this by analysing 351 patients with Gleason 6, localized (negative margin, negative SVI, <pT2c) PCa [6]. Converse to our findings, their results indicate that patients with larger TV 0.5–2.5 cm^3 have higher rates of BCR compared with patients of smaller TV $<$0.5 cm^3 (5.5% vs. 0.7%). Furthermore, they found a 10-year cancer specific mortality rate of 0.5% in the larger TV group compared with 0% in the smaller TV group. However, the ISUP 2005 grading system was not applied in this study so a number of Gleason 7 tumors may have been under-graded as Gleason 6 tumors and then included in their study cohort. Pathology re-review in our series with ISUP 2005 criteria resulted in all cases of BCR being excluded. This limitation might be the main explanation for the relatively high BCR rate in the study by Schiffman et al., since several studies have shown that in cases originally diagnosed as a Gleason 6 PCa with lymph node or distant metastases, pathological re-review of the samples consistently demonstrated the presence of a Gleason grade 4 component, mostly with cribriform architecture [11]. Furthermore, it was not specified whether Schiffman et al. were referring to index or total TV, if the entire prostate specimen was included in analysis, and what methodology was used to measure TV in their study. In our opinion, due to these important limitations, and the findings from our current data, it is appropriate to continue to endorse the larger TV threshold for insignificant PCa.

Overall, most of the tumors (78.3%) in our cohort were low-risk (D'Amico criteria). Of interest, there was no statistically significant difference in low, intermediate or high-risk disease between subjects with TV $<$0.5 cm^3 and 0.5–2.5 cm^3. This may be due to the higher proportion of patients with PSA 10–20 in those with TV $<$0.5 cm^3 (14.7% vs. 5.0%) despite the generally more advanced clinical stage of those subjects in the 0.5–2.5 cm^3 TV group. Compared to the Schiffman et al. cohort, the current study had a higher proportion of medium-high risk tumors (18.3% vs. 11.5%).

With over-diagnosis, and the stage and grade migration leading to an increase in the diagnosis of insignificant PCa, the importance of being able to correctly identify patients suitable for active surveillance continues to increase. The concept of indolent PCa implies the existence of a group of small-volume low-grade PCa, which persist indefinitely, without evolving into cancers of larger volume or higher grade. Another hypothesis is that each tumor cell in low-grade PCa is at risk of transformation to high--grade cancer and, as a consequence, the volume of low-grade cancer determines the risk of a subsequent clinical high-grade cancer. In other words, PCa may be subject to a progression model of carcinogenesis, with cancers gradually evolving from a low-volume low-grade cancer to a large-volume high-grade cancer, which is able to metastasize. However, our finding that localized Gleason 6 PCa with TV $<$2.5 cm^3 has a BCR rate of 0% supports the current pool of evidence showing that low volume Gleason 6 PCa should be considered insignificant [4]. Extrapolation of this pathological definition into active surveillance criteria would decrease the morbidity and cost associated with over treatment of PCa. One study has shown that the application of more liberal criteria would enable 50% more men to participate in an active surveillance program, with the trade off of a 5% increased risk of underestimating a significant PCa [12].

The present study has a number of limitations. Firstly, sample size was moderate at 175 cases and smaller than the cohort used in Schiffman et al. Secondly, follow-up duration was also moderate with a median duration of 84 months. However, there is evidence showing that it takes approximately 7 years for a low-grade latent cancer to transform into a clinical high-grade cancer [3], and thus our follow-up period, should have been able to capture most of these cancers which were going to manifest as a BCR since >50% of the men had >7 years follow-up. Finally, this study did not analyse BCR rates post RP for subjects with TV >2.5 cm^3 and localized Gleason 6 PCa. We would suggest this as a possible direction for future study.

CONCLUSION

Our results have shown that, with a median follow-up of 84 (IQR 70–102) months, patients in our cohort with localized Gleason 6 PCa and a total TV 0.5–2.5 cm^3 have a BCR rate of 0%. We would support a more liberal total TV threshold of 2.5 cm^3 for the further development of algorithms to identify patients suitable for active surveillance.

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