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Analysis of different tumor volume thresholds of insignificant prostate cancer and their implications for active surveillance patient selection and monitoring

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Purpose: We compared oncological outcomes according to tumor volume (TV) thresholds defining both classical and updated insignificant prostate cancer (IPC), since the TV threshold can be used as clinical parameter for active surveillance.

Methods: Between 2001 and 2012, we retrospectively analyzed 331 organ-confined prostate cancer patients who had preoperative Gleason score 6, preoperative PSA under 10 ng/mL and pathologic TV less than 1.3 mL. Among them, 81 of 331 (24.5%) had Gleason grade 4/5 disease postoperatively. Patients were stratified into two groups: (1) TV less than 0.5 mL, using the classical definition; and (2) TV between 0.5 mL and 1.3 mL, using the range of updated definition. We compared biochemical recurrence (BCR)-free survival and identified independent predictors of BCR in each group.

Results: Group 2 had more Gleason grade 4/5 disease than group 1 ($P<0.001$). On multivariate analysis, Gleason grade 4/5 disease was not associated with BCR in group 1 ($P=0.132$). However, it was an independent predictor for BCR in group 2 ($P=0.042$). BCR-free survival were not significantly different according to the presence of Gleason grade 4/5 disease in group 1 ($P=0.115$). However, in group 2, it was significantly different according to the presence of Gleason grade 4/5 disease ($P=0.041$).

Conclusions: Although the TV thresholds of the two definitions of IPC vary only slightly, this difference was enough to result in different clinical course if Gleason grade 4/5 disease was present. Therefore, the updated IPC TV threshold should be carefully applied as clinical parameter for active surveillance.

Keywords: Insignificant prostate cancer, Tumor volume, Active surveillance

INTRODUCTION

Urologists commonly use the classical definition of insignificant prostate cancer (IPC), which describes cases as organ-confined, Gleason 6 disease with tumor volume (TV) <0.5 mL [1]. The TV threshold of this definition was suggested by Stamey et al. [2], who used a cystoprostatectomy study. This definition has also been used to select ideal active surveillance (AS) candidates [3]. Recently, Wolters et al. [4] introduced an updated TV threshold for IPC based on their own study cohort using a method similar to that of Stamey et al. [2]. This study concluded that the TV threshold of IPC may be increased up to 1.3 mL in cases of organ-confined prostate cancer without Gleason grade 4/5 disease. Using this updated definition of IPC, the rate of misclassification for AS selection according to TV could be decreased [5].

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However, whether the updated TV threshold can be used as a clinical parameter for selection of AS candidates remains unclear. According to recent reports, clinical TV analysis for selection of AS candidate using multiparameteric magnetic resonance imaging (MP-MRI) has become important and reliable as MP-MRI techniques have advanced [6-9]. Thus, determining whether the TV threshold of the classical definition or that of the updated definition of IPC for AS is more safe is a key goal, considering the window of curability. The possibility of misclassification by Gleason upgrading in radical prostatectomy (RP) specimens always exists among AS candidates [5,10,11]. We reasoned that the clinical TV parameters of the two IPC definitions should be evaluated in the context of AS, even if pathologists reported the presence of Gleason grade 4/5 disease in RP specimens after urologists decided the intervention during AS.

The aim of the present study was to identify which TV threshold, the classical or the updated, is the most desirable clinical TV parameter for AS selection and monitoring. To this end, we compared oncologic outcomes using RP specimens according to TV and the presence of Gleason grade 4/5 disease in organ-confined prostate cancer patients having the following characteristics: (1) preoperative Gleason score (GS) 6,(2) preoperative prostate-specific antigen (PSA) levels lower than 10 ng/mL, and (3) pathologic TVs less than 1.3 mL.

MATERIALS AND METHODS

We retrospectively analyzed 2,399 prostate cancer patients who underwent RP between 2001 and 2012. Of these patients, we selected those with preoperative GS 6 and preoperative PSA level under 10 ng/mL. Among this population, we identified 779 pathologically organ-confined prostate cancer patients who had no residual tumor. We also included patients with TV lower than 1.3 mL, leaving 362 patients in the final analysis. Among them, 31 patients with incomplete data were excluded. Therefore, the final study cohort consisted of 331 patients. Of these patients, 81 (24.5%) had Gleason grade 4/5 disease according to RP pathology. We hypothesized that these 81 patients would be misclassified AS candidates who had the possibility of Gleason upgrading in their RP specimens, even though they had preoperative GS 6 and preoperative PSA level under 10 ng/mL.

We corrected clinical and pathological variables including age, preoperative PSA level, prostate volume, pathologic stage, postoperative GS and TV. Postoperative GS and TV were determined from pathological evaluation. All RP specimens were analyzed by an experienced genitourinary pathologist. Transverse whole-mount step section specimens were obtained at 3–4 mm intervals on a parallel plane, and the genitourinary pathologist reported results according to a standardized processing and reporting protocol. TV was determined as part of the routine pathological assessment by visual estimation, as follows: The tumor area was outlined and x and y diameters were measured. The tumor area was then multiplied by its depth, based on the presence of the tumor in subsequent sections and the thickness of the sections. The total sum of all foci of tumor was the estimated TV. After surgery, a serum PSA assay was performed in the first 2 months and then every 3–4 months before biochemical recurrence (BCR). BCR was defined as a sustained increase in total serum PSA levels to ≥0.2 ng/mL after RP.

We divided the study cohort into two groups according to the two TV thresholds used for the definition of IPC: (1) The TV threshold of the classical definition, 0.5 mL; and (2) The TV threshold for the updated definition, 1.3 mL. To compare clinicopathologic outcomes, chi-square tests and independent *t*-tests were used for categorical and continuous variables, respectively. We compared BCR-free survival rates, and calculated the actual risk of BCR, between the two groups using the Kaplan-Meier method. We also independently identified risk factors for BCR using the Cox proportional hazards model in each group. All statistical analyses were performed using PASW Statistics 18.0 (SPSS Inc., Chicago, IL, USA). A *P*-value ≤0.05 was considered statistically significant.

RESULTS

Baseline patient characteristics are shown in Table 1. The mean patient age was 62.6 years, and the mean preoperative PSA level was 5.53 ng/mL. The mean TV was 0.49±0.40 mL. The number of patients with TV less than 0.5 mL or between 0.5 mL and 1.3 mL was 195 (58.9%) and 136 (41.1%), respectively. A total of 250 (75.5%), 76 (23.0%), and 5 patients (1.5%) had a postoperative GS ≤6, 7, and 8–10, respectively. At the time of analysis, 24 patients (7.3%) had experienced BCR during the mean follow-up period of 38 months. Comparing the two TV groups, preoperative PSA levels were not significantly different ($P=0.073$). The group with TV less than 0.5 mL had significantly larger prostate volumes compared with the other group ($P=0.005$). Postoperative GS was also significantly different according to TV ($P<0.001$). The proportion of patients with postoperative GS ≤6, 7, and 8–10 was 85.1%, 13.8%, and 1.0% in the group with TV less than 0.5 mL, while these proportions were 61.8%, 36.0%, and 2.2% in the group with TV between 0.5 mL and 1.3 mL. Patients with TV less than 0.5 mL

Table 1. Clinical and pathological characteristics

Characteristic	TV≤0.5 mL	0.5 mL< TV≤1.3 mL	*P*-value
No. of patients	195	136	
Age (yr)	62.6±7.0	62.7±97.3	0.882
Preoperative PSA level (ng/mL)	5.40±1.83	5.77±1.79	0.073
Prostate volume (mL)	39.9±17.1	34.8±14.9	0.005
Pathologic stage			0.001
pT2a/b	203 (74.1)	104 (43.7)	
pT2c	71 (25.9)	134 (56.3)	
Postoperative Gleason score			<0.001
≤6	166 (85.1)	84 (61.8)	
7	27 (13.8)	49 (36.0)	
8-10	2 (1.0)	3 (2.2)	
Presence of Gleason grade 4/5	29 (24.5)	52 (38.2)	<0.001
Tumor volume (mL)	0.20±0.16	0.91±0.22	<0.001
Total follow-up period (mo)	37.6±24.5	38.6±26.3	0.745
Biochemical recurrence	13 (6.7)	11 (8.1)	0.670

Values are presented as mean±standard deviation or number (%).
TV, tumor volume; PSA, prostate-specific antigen.

were more likely to have a postoperative GS ≤6 than those who had TV between 0.5 mL and 1.3 mL.

Table 2 shows the Cox proportional hazards model for predicting BCR in each group. Multivariate analysis of patients with TV less than 0.5 mL revealed that age, preoperative PSA level, prostate volume, pathologic stage and the presence of high Gleason grade disease were not associated with BCR. However, in the patients with TV between 0.5 mL and 1.3 mL, the presence of Gleason grade 4/5 disease was determined to significantly increase the risk of BCR compared with other risk factors; the hazard ratio was 3.85 folds (P=0.042).

Kaplan-Meier analysis is shown in Fig. 1. In patients with TV less than 0.5 mL, BCR-free survival was not significantly different regardless of the presence of Gleason grade 4/5 disease (P=0.115) (Fig. 1A). However, in patients with TV between 0.5 mL and 1.3 mL, BCR-free survival varied significantly according to the presence of Gleason grade 4/5 disease (P=0.041) (Fig. 1B). Prostate cancer patients with TV

Table 2. Multivariate analysis of factors predictive of biochemical recurrence according to tumor volume

Variable	TV≤0.5 mL			0.5 mL<TV≤1.3 mL		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age	0.98	0.90–1.08	0.725	0.97	0.89–1.06	0.479
Preoperative PSA level (ng/mL)	0.93	0.66–1.29	0.652	0.99	0.69–1.45	0.994
Prostate volume (mL)	1.01	0.98–1.05	0.374	0.99	0.96–1.04	0.883
Pathologic stage						
pT2a/b	Ref.	-	-	Ref.	-	-
pT2c	1.28	0.36–4.53	0.698	0.58	0.17–1.95	0.377
Presence of Gleason grade 4/5	2.53	0.76–8.44	0.132	3.85	1.05–14.15	0.042

TV, tumor volume; HR, hazard ratio; CI, confidence interval; PSA, prostate-specific antigen.

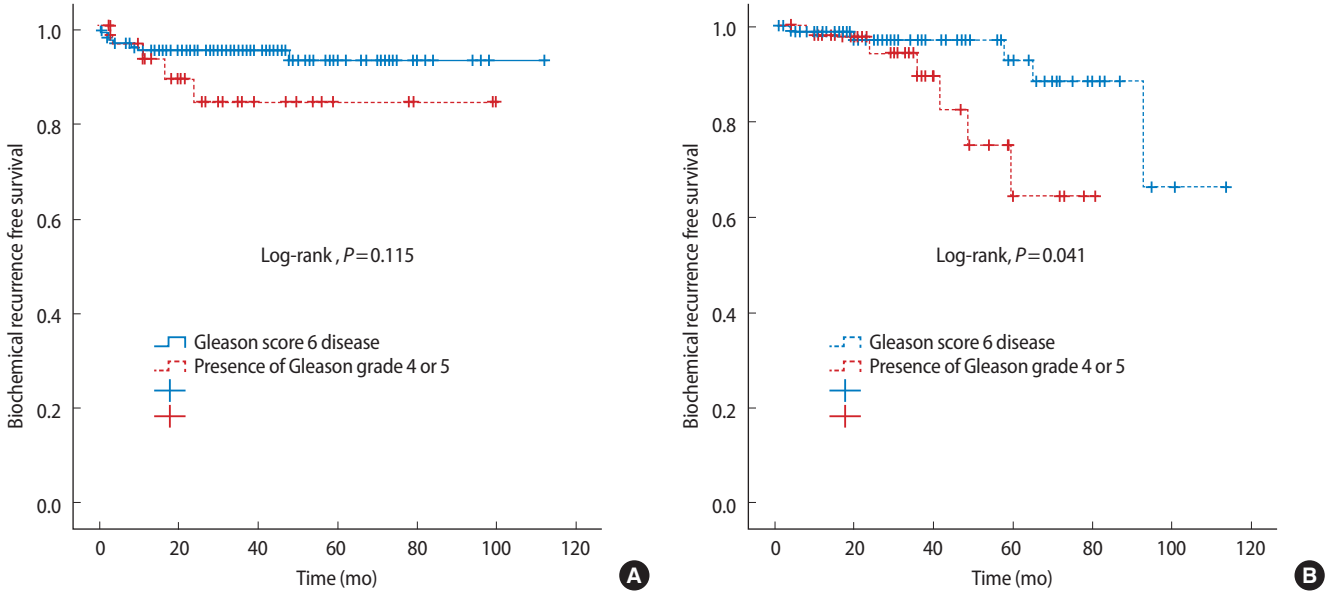

Fig. 1. Kaplan-Meier curve for biochemical recurrence-free survival according to tumor volume and the presence of high Gleason grade disease after radical prostatectomy. (A) Tumor volume less than 0.5 mL. (B) Tumor volume between 0.5 mL and 1.3 mL.

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between 0.5 mL and 1.3 mL showed an increased risk of BCR if they had Gleason grade 4/5 disease, even if the patient was an organ-confined prostate cancer patient with a preoperative PSA level lower than 10 ng/mL.

DISCUSSION

AS has become a reasonable treatment option for low-risk prostate cancer patients; furthermore, the number of low-risk prostate cancer patients has increased. Klotz et al. [12] demonstrated that AS can be a treatment option for low-risk prostate cancer patients in a prospective study. Prostate cancer patients with IPC could also be ideal AS candidates, considering the indolent nature of IPC. Thus, urologists have attempted to select appropriate IPC patients for AS using the classical definition of IPC as organ-confined, Gleason 6 disease with TV <0.5 mL [13]. TV is one of the most important criteria in the definition of IPC.

To select ideal AS candidates with IPC, several AS protocols have used clinical stage, preoperative PSA level, and the prostate biopsy profile as inclusion criteria [14-18]. However, it is difficult to precisely select ideal AS candidates using the current inclusion criteria because the possibility of misclassification always exists for RP specimens. Moreover, Gleason upgrading and pathologic upstaging can occur frequently, even when stringent AS selection criteria are used. Furthermore, misclassification by TV also occurs frequently, since predicting pathologic TV is difficult using the current AS inclusion criteria, which only include prostate biopsy profiles, and this misclassification could affect AS monitoring. Also, the detection of prostate cancer progression during AS monitoring is as important as AS selection. However, the best parameter for the identification of prostate cancer progression is still unclear. Several authors have suggested follow-up criteria including digital rectal examination, PSA follow-up and repeated prostate biopsy that should be used to decide whether intervention should be performed during AS [19-22]. Regarding imaging parameters, most of the literature does not recommend transrectal ultrasound (TRUS), since their efficacy has not been proven as a measure of progression during AS [23,24]. However, we reasoned that MP-MRI could play a role in selecting AS candidates and in monitoring the progression of prostate cancer.

In our previous study [6], we found that the prediction of AS candidates could be improved by MP-MRI. Moreover, recent studies have also concluded that MP-MRI can help predict TV and bilateral tumor rates in unilateral low-risk prostate cancer patients; furthermore, MP-MRI is useful in assessing the clinical significance of prostate cancer in men at risk prior to biopsy [7,8]. Furthermore, Turkbey et al. [9] reported that MP-MRI was better for estimating index TV and was more accurate in predicting prostate TV larger than 0.5 cm^3 than other clinical variables. We hypothesized that these advantages of MP-MRI could apply to AS follow-up, as a useful image parameter. In other words, if urologists could calculate clinical TV using MP-MRI, this measurement would be a useful parameter in deciding whether a patient should be selected for AS, and also for deciding whether intervention is required during AS. However, it is still unclear which clinical TV threshold is the best parameter to be used for AS selection and monitoring; therefore, many investigators simply use the TV threshold in the classical definition of IPC for AS-correlated studies.

Meanwhile, Wolters et al. [4] introduced the idea that the TV threshold of IPC could be increased to at least 1.3 mL. Using this definition as the clinical TV parameter, the number of AS candidates would be increased. Urologists could use the updated definition for the prostate cancer patients who met AS protocols to analysis clinical TV using MP-MRI. However, an important issue should also be discussed. The safety of the updated definition of IPC did not validate for AS candidate considering the possibility of Gleason upgrading. Even if an AS candidate who met the stringent AS protocol had a suspicious tumor lesion according to MP-MRI analysis, urologists would be unable to guarantee that the suspicious tumor lesion detected by MP-MRI was GS 6 disease. The possibility of the presence of Gleason grade 4/5 disease always exists due to sampling bias, variations in needle biopsy and pathologist-dependent variation in Gleason grading. Even though the difference between TV measurements used for defining classical and updated IPC appears small, this difference could lead to large differences in oncological outcomes, depending on the presence of Gleason grade 4/5 disease.

In the present study, the presence of Gleason grade 4/5 disease was not associated with BCR among prostate cancer patients with TV less than 0.5 mL. This TV threshold defines classical IPC. However, among patients with TV between 0.5 and 1.3 mL, a range below the threshold of the updated definition of IPC, the presence of Gleason grade 4/5 disease was an independent predictor of BCR. These patients showed different clinical courses according to their postoperative GS even though they were all organ-confined prostate cancer patients with preoperative PSA levels under 10 ng/mL. We reasoned that this observation could be relevant to AS selection and monitoring. If AS candidates exhibit clinical TV between 0.5 and 1.3 mL according to MP-MRI, even under the range of TV threshold of updated IPC, urologists should carefully

re-evaluate and reconfirm their suitability as AS candidates, since they could miss their windows of curability if they exhibit unexpected Gleason grade 4/5 disease. Also, if patients receiving AS show progression to clinical TV larger than 0.5 mL, urologists must consider either intervention or stringent reclassification using a repeat biopsy to rule out the presence of Gleason grade 4/5 disease.

Our study has several limitations. For instance, it is a small retrospective study using RP specimens, and we have no data regarding the oncological outcomes of AS patients according to the two clinical TV thresholds. Rather, we compared oncologic outcomes according to the pathologic definition of TV used in the classical definition and the updated definition of IPC. However, we found that the small difference between the two TVs used in the different definitions of IPC could be associated with quite different clinical courses if Gleason grade 4/5 disease existed in the AS candidate. We validated the oncologic safety of TV threshold of updated definition of IPC, even though this definition was not usually used in clinical practice [25], because urologists may apply the updated definition for AS more often to low-risk prostate cancer patients considering only the beneficiaries of AS. Because of this, we thought that AS candidates who had clinical TV larger than 0.5 mL are carefully reconfirmed or reclassified not to miss the window of curability.

Another limitation is the reliability of clinical TV analysis for determining the application of AS in clinical practice. In fact, the present study assumes that MP-MRI contributes to the decision-making process regarding AS selection and monitoring. This issue is still debated by urologists; Several studies have suggested that MP-MRI may be a more precise imaging tool for localizing prostate cancer and predicting TV in low-risk prostate cancer patients including AS candidates [26-28]. However, another study demonstrated that clinical TV measurement using MP-MRI could under-estimate in comparison with pathologic TV after RP [29]. Nevertheless, as MP-MRI techniques advance, we believe that this tool will become more useful in both selecting and monitoring AS candidates. Therefore, it is important to establish accurate criteria, including a clinical TV threshold, for the use of MP-MRI data in selecting candidates for AS. From this point of view, the present study may contribute to future efforts in AS selection and monitoring.

In conclusion, although the difference between the TV thresholds in the two definitions of IPC is relatively small, this difference could account for varying clinical course if Gleason grade 4/5 disease exists in organ-confined prostate cancer patients with a preoperative PSA level lower than 10 ng/mL. Therefore, considering the possibility of Gleason upgrading in AS candidates, the TV threshold in the updated definition of IPC should be carefully applied as a clinical TV threshold used for AS selection and monitoring. To further validate the use of this clinical TV parameter for AS selection and monitoring, larger patient studies and further long-term prospective studies will be required.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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