

Urological Oncology

Significance of Predicted Tumor Volume as a Predictor of Pathologic Stage in Patients Undergoing Radical Prostatectomy

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Purpose: The purpose of this study was to evaluate whether predicted tumor volume could predict pathologic stage in patients undergoing radical prostatectomy.

Materials and Methods: The clinical and pathologic data of 236 patients who underwent a 12-core needle biopsy followed by radical prostatectomy were obtained from our database and reviewed retrospectively.

Results: Observed tumor volume correlated best with serum prostate-specific antigen (PSA) level ($r=0.677$, $p<0.001$) and the number of positive biopsy cores ($r=0.489$, $p<0.001$). Stepwise multiple linear regression analysis was used to develop a model for predicting tumor volume before radical prostatectomy. All explanatory variables except PSA and the number of positive biopsy cores were eliminated, yielding the equation ($[\text{predicted tumor volume}] = 0.381 \times [\text{PSA}] + 0.921 \times [\text{No. of positive biopsy cores}] - 0.992$). Tumor volume predicted by this equation correlated strongly with observed tumor volume ($r=0.722$, $p<0.001$). This was also true when a different cohort of 159 patients was analyzed ($r=0.638$, $p<0.001$). The areas under the receiver operating characteristic curves of predicted tumor volume were 68.5% for extracapsular extension, 75.7% for seminal vesicle invasion, and 70.4% for positive surgical margin. Kaplan-Meier curves revealed that predicted tumor volume correlated significantly with biochemical recurrence-free survival ($p<0.001$; log-rank test).

Conclusions: Our findings suggest that tumor volume predicted on the basis of PSA levels and number of positive biopsy cores may predict pathologic stage with reasonable accuracy.

Key Words: Prostatectomy; Prostatic neoplasms; Treatment outcome; Tumor burden

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INTRODUCTION

It has been suggested previously that the malignant potential of prostate cancer correlates strongly with the size of the primary cancer [1]. Reflecting this, all definitions of clinically significant vs. potentially insignificant prostatic carcinoma incorporate tumor size measurements [2,3]. Numerous studies have also shown that prostate cancer volume correlates with other prognostic indicators and with progression after radical prostatectomy [4,5]. These observations suggest that obtaining an accurate estimation of tumor volume preoperatively might aid the treatment decision. However, it remains difficult to estimate tu-

mor volume preoperatively on the basis of clinical parameters such as preoperative biopsy data. Indeed, there is often significant discord between the extent of cancer detected on biopsy and the tumor volume in the final surgical specimen [6,7]. Moreover, although prostate-specific antigen (PSA) is the most widely used tumor marker in clinical practice for the diagnosis, staging, and monitoring of prostate cancer, PSA associates only weakly with prostate cancer volume in men treated by radical prostatectomy [8].

The aim of this study was to determine whether it is possible to estimate tumor volume on the basis of preoperative clinical variables and whether such predicted tumor volumes could predict pathologic stage in patients who under-

go radical prostatectomy. For this purpose, we developed a regression model composed of several preoperative variables to predict total tumor volume.

MATERIALS AND METHODS

1. Patient population

Approval of the study was obtained from the Institutional Review Board of our institution. Between 2000 and 2004, 260 radical retropubic prostatectomies for the treatment of prostate cancer were performed at a single institution. The clinical and pathologic data of these patients were obtained from our surgical database and were reviewed retrospectively. Patients with positive lymph nodes and who had received neoadjuvant or immediate adjuvant androgen ablation or radiotherapy were excluded from the study. A total of 236 patients were included in the study. Individuals who visited our department for a variety of reasons, such as prostate cancer screening or because of voiding symptoms, were enrolled regardless of whether the visit was primary or referred. Patients with high serum PSA levels or abnormal digital rectal examination (DRE) findings underwent a 12-core needle biopsy; all biopsies were performed by a single radiologist. The DRE was performed by senior urologists at our institution. The patients' median age at the time of surgery was 67.2 years (range, 41.8-80.7 years). The median preoperative PSA level was 8.1 ng/ml (range, 0.7-98.0 ng/ml). None of the patients had evidence of nodal disease or distant metastasis on either contrast-enhanced computed tomography or bone scans.

2. Histologic analysis

The presence of carcinoma in needle biopsy tissue was assessed by a single pathologist (K.C.M). Gleason primary and secondary grades with sum scores were assigned, and the number of core biopsy specimens that contained carcinoma was quantified. The radical prostatectomy specimens were handled and processed in a standard manner, in which all prostatic tissue was embedded as previously described [9]. The total tumor volume and the tumor volume of each cancer focus were calculated by using the formula $0.4 \times \text{length} \times \text{width} \times \text{cross-sectional thickness}$, i.e., number of cross sections \times section thickness [10]. All specimens were scored according to the Gleason grading system. The pathologic stages were determined on the basis of the 2002 TNM classification, and a positive surgical margin was defined as the presence of cancer cells in the inked surface of the prostate specimen.

3. Follow-up

Follow-up information was collected from the medical records. All patients were followed up by measuring their PSA levels every 3 months. The median follow-up period was 17.9 months (range, 1.0-75.3 months). The endpoint of this study was biochemical recurrence. Biochemical recurrence was defined as detectable PSA levels (greater than 0.2 ng/ml on least two occasions), and the time of bio-

chemical recurrence was taken to be the first time PSA became detectable.

4. Statistical analysis

Pearson correlation coefficients for the relations between clinical parameters and total tumor volume were generated. Stepwise multivariate linear regression was performed to develop a model for predicting tumor volume before radical retropubic prostatectomy. The regression model in this study included age, body mass index, serum PSA, biopsy Gleason score, number of positive biopsy cores, and clinical stage. Clinical stage was categorized according to organ confinement. Differences in tumor volume (ΔV) were calculated by subtracting observed tumor volume (V_1) from predicted tumor volume (V_2). These differences were plotted against the mean volume by using the approach described by Bland and Altman [11]: $\Delta V = (V_2 - V_1) \times 2 / (V_2 + V_1)$. The receiver operating characteristic (ROC) curve was used to indicate the ability of the predicted tumor volume to predict several pathologic parameters, namely, extracapsular extension, seminal vesicle invasion, and positive surgical margin. For this, areas under the ROC curves were estimated. Determining the area under the curve is a suitable way to summarize the overall discriminatory or diagnostic value of a model: the area can range from 0.5 (equivalent to flipping a coin, namely, a useless model) to 1.0 (perfect discrimination). The more the area under the ROC curve approached 100% (i.e., the more the ROC curve approached the upper left corner), the greater the predictive power. The Kaplan-Meier method was used to calculate the biochemical recurrence-free survival by predicted tumor volume. The differences were tested with the log-rank test. All p-values were two-sided and $p < 0.05$ was significant. All statistical analyses were performed with SPSS ver. 17.0 (SPSS Inc., Chicago, IL, USA) programs.

RESULTS

The patient characteristics are listed in Table 1. Of the 236 patients, 200 (84.7%) were deemed to have clinically localized prostate cancer (T1-T2, N0) on the basis of the initial physical and radiographic evaluation. However, after surgery, extracapsular extension was detected in 74 (31.4%), seminal vesicle involvement was observed in 26 (11.0%), and 75 (31.8%) had positive surgical margins.

Correlation coefficients between the tumor volume that was determined after radical prostatectomy and various clinical parameters were obtained. The correlations between observed tumor volume and body mass index or biopsy Gleason score were low (0.153 and 0.283, respectively). The number of positive biopsy cores correlated more strongly with observed tumor volume ($r=0.489$, $p < 0.001$). The highest correlation ($r=0.677$, $p < 0.001$) was found between serum PSA and observed tumor volume (Table 2). Moreover, when the patients were divided into two groups on the basis of clinical stage, the two groups differed sig-

TABLE 1. Patient characteristics

	No. (%)	Mean±SE	Median (range)
Age (yr)		66.3±0.4	67.2 (41.8-80.7)
Body mass index (kg/cm ²)		23.8±0.2	23.9 (15.3-31.1)
Serum PSA (ng/ml)		12.3±0.9	8.1 (0.7-98.0)
Biopsy Gleason score			
≤6	106 (44.9)		
7	73 (30.9)		
≥8	57 (24.1)		
No. of positive biopsy cores		3.8±0.2	3.0 (1.0-12.0)
Clinical stage			
<cT3a	200 (84.7)		
≥cT3a	36 (15.3)		
Surgical Gleason score			
≤6	67 (28.3)		
7	133 (56.4)		
≥8	36 (15.2)		
Surgical margin			
Negative	161 (68.2)		
Positive	75 (31.8)		
Extracapsular extension			
Negative	162 (68.6)		
Positive	74 (31.4)		
Seminal vesicle invasion			
Negative	210 (89.0)		
Positive	26 (11.0)		
Observed tumor volume (ml)		7.2±0.6	3.7 (0.3-59.9)

SE: standard error, PSA: prostate-specific antigen

nificantly in terms of observed tumor volume (6.4±0.6 for patients with <cT3a vs. 11.3±1.9 for those with ≥cT3a, p=0.020).

The relation between these clinical parameters and observed tumor volume was explored by multiple linear regression analysis. By using the stepwise method described earlier, all explanatory variables were eliminated except for PSA and the number of positive biopsy cores. This resulted in the equation: [Predicted tumor volume]=0.381x [PSA] + 0.921x[No. of positive biopsy cores] - 0.992. There was a strong correlation between predicted tumor volume and observed tumor volume (r=0.722, p<0.001) (Fig. 1A). The mean difference in volume measurements was 0.3 ml (range, -1.4-1.7 ml; 95% confidence interval: -0.9-1.5 ml) (Fig. 1B).

Fig. 2 presents the areas under the ROC curves, which indicate the ability of predicted tumor volume to predict pathologic stage. The areas under the ROC curves of predicted tumor volume were 68.5% for extracapsular extension, 75.7% for seminal vesicle invasion, and 70.4% for positive surgical margin. Thus, overall, predicted tumor volume predicted the pathologic results reasonably well.

TABLE 2. Correlation between clinical parameters and observed tumor volume

	r	p-value
Age (yr)	-0.28	0.671
Body mass index (kg/cm ²)	0.153	0.019
Serum PSA (ng/ml)	0.677	<0.001
Biopsy Gleason score	0.283	<0.001
No. of positive biopsy cores	0.489	<0.001

PSA: prostate-specific antigen

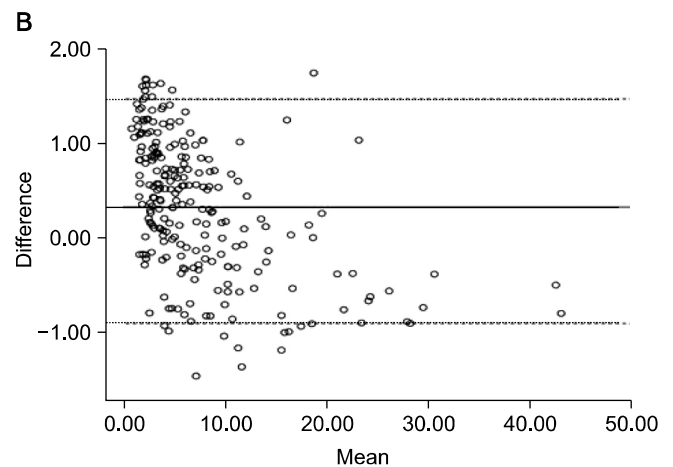
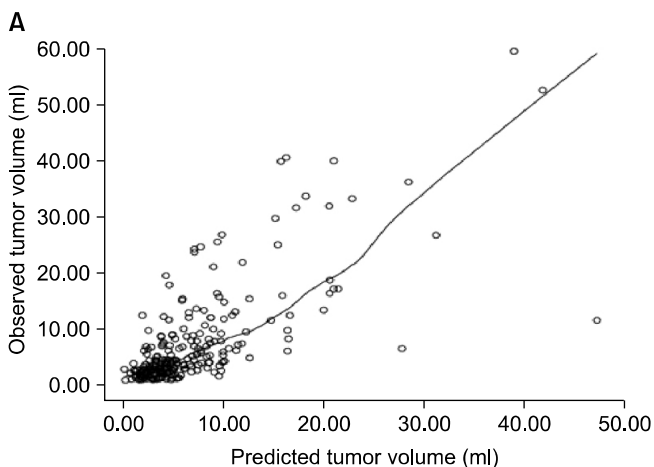
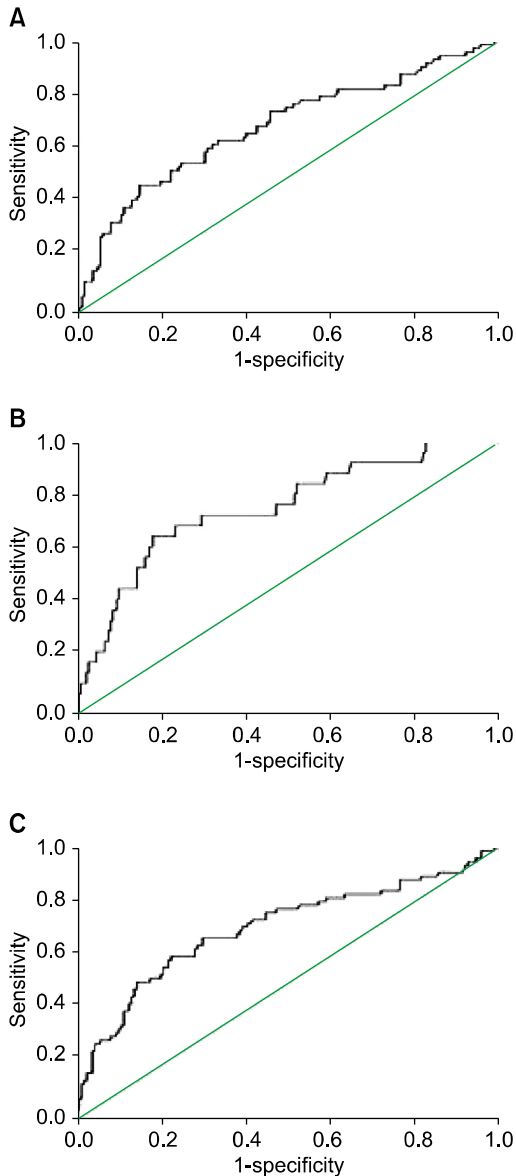


FIG. 1. (A) Regression analysis showing the correlation between observed tumor volume and predicted tumor volume (r=0.722, p<0.001), for which predicted tumor volume was calculated by using the following equation: [Predicted tumor volume]=0.381x[prostate-specific antigen] + 0.921x[No. of positive biopsy cores] - 0.992. (B) Bland-Altman analysis of the agreement between observed tumor volume and predicted tumor volume. The linear line indicates the mean difference. Dotted lines represent 95% confidence intervals from the mean of the two volumes.



Cutoffs (ml)	Sensitivity	Specificity	AUC (95% CI)
Extracapsular extension			0.685 (0.609-0.762)
1 (%)	98.6	1.2	
2 (%)	94.6	10.5	
3 (%)	83.8	24.1	
4 (%)	79.7	41.4	
5 (%)	68.9	57.4	
6 (%)	62.2	66.7	
7 (%)	55.4	72.2	
8 (%)	48.6	79.6	
9 (%)	43.2	85.2	
10 (%)	35.1	89.5	
Seminal vesicle invasion			0.757 (0.655-0.858)
1 (%)	100.0	1.4	
2 (%)	100.0	10.0	
3 (%)	92.3	23.3	
4 (%)	88.5	37.6	
5 (%)	76.9	52.4	
6 (%)	73.1	61.4	
7 (%)	73.1	68.1	
8 (%)	69.2	75.7	
9 (%)	65.4	81.4	
10 (%)	50.0	85.7	
Positive surgical margin			0.704 (0.627-0.781)
1 (%)	98.7	1.2	
2 (%)	90.7	8.7	
3 (%)	84.0	24.2	
4 (%)	80.0	41.6	
5 (%)	72.0	59.0	
6 (%)	66.7	68.9	
7 (%)	60.0	74.5	
8 (%)	52.0	81.4	
9 (%)	45.3	86.3	
10 (%)	34.7	89.4	

AUC: area under the curve, CI: confidence interval

FIG. 2. Ability of predicted tumor volume to predict pathologic outcomes. (A) Extracapsular extension. (B) Seminal vesicle invasion. (C) Positive surgical margin.

The sensitivity and specificity with which various predicted tumor volume levels predicted pathologic stage are also shown in Fig. 2.

Fig. 3 shows the Kaplan-Meier curves of patients categorized according to predicted tumor volume. The curves revealed that predicted tumor volume correlated significantly with biochemical recurrence-free survival ($p < 0.001$; log-rank test) when the patients were stratified into two groups according to the median value (i.e., less than 5 ml or 5 ml or greater).

To validate the above formula, the data for another cohort of patients who underwent radical retropubic prostatectomy ($n=284$), this time between 2005 and 2006, were obtained and reviewed. Of these patients, data for 159 were available. There was a significant correlation between the predicted tumor volume calculated by using the above for-

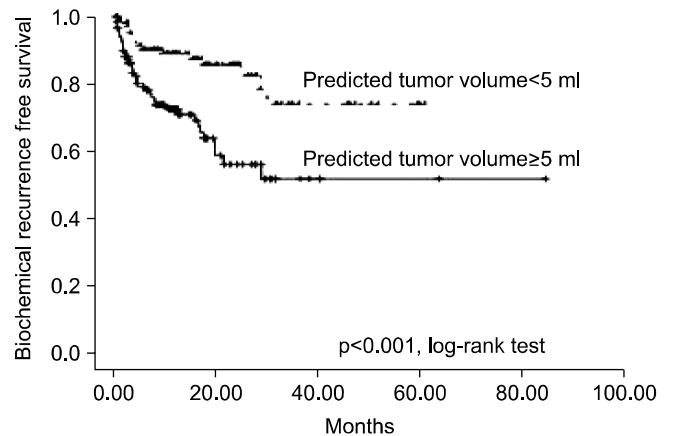


FIG. 3. Biochemical recurrence-free survivals of patients according to median predicted tumor volume ($p < 0.001$; log-rank test).

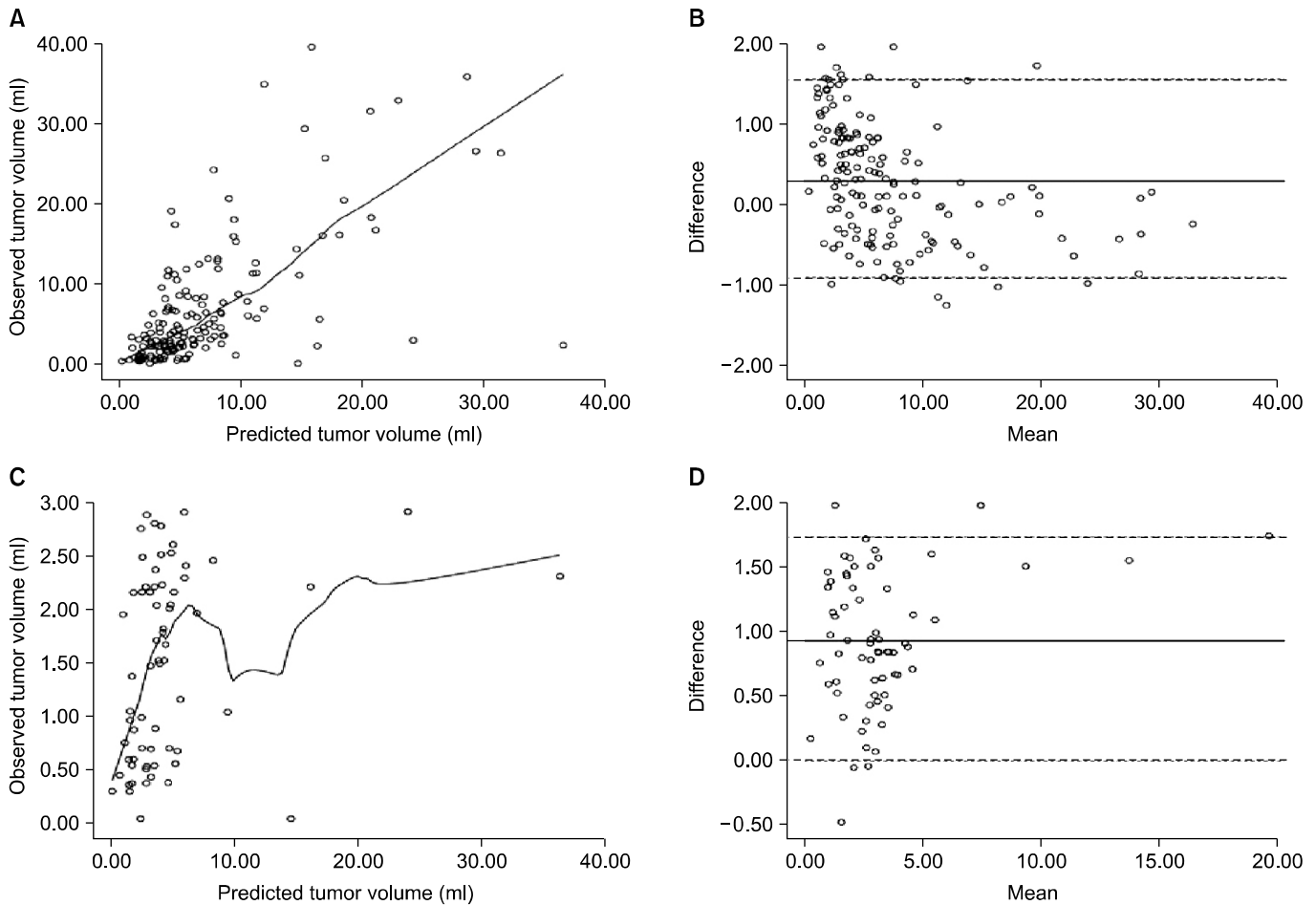


FIG. 4. Observed and predicted tumor volumes of a second cohort of patients who underwent radical retropubic prostatectomy between 2005 and 2006. (A) Regression analysis of all 159 patients ($r=0.638$, $p<0.001$). (B) Bland-Altman analysis of all 159 patients. (C) Regression analysis of the 66 patients whose observed tumor volume was <3 ml ($r=0.277$, $p=0.024$). (D) Bland-Altman analysis of the 66 patients whose observed tumor volume was <3 ml.

mula and the observed tumor volume ($r=0.638$, $p<0.001$) (Fig. 4A). The mean differences in volume measurements amounted to 0.3 ml (range, -1.3 - 2.0 ml; 95% confidence interval: -0.9 - 1.6 ml) (Fig. 4B).

The patients in our series are not representative of most patients seen today in North America and Western Europe, where 75% of those who receive a diagnosis of prostate cancer have nonpalpable disease and tumor volumes that are smaller than those observed in our series. Consequently, we performed subgroup analysis by using 66 of the 159 patients whose observed tumor volume was <3 ml. There was a weak correlation between predicted tumor volume and observed tumor volume ($r=0.277$, $p=0.024$) (Fig. 4C). The mean difference in volume measurements was 0.9 ml (range, -0.5 - 2.0 ml; 95% confidence interval: 0.9 - 1.8 ml) (Fig. 4D).

DISCUSSION

The size of a tumor is an important reflection of its biology, which is why tumor size has been reported to correlate di-

rectly with disease extent and to be an important prognostic indicator for prostate cancer. For example, Bostwick et al found that progression from capsular invasion to seminal vesicle invasion and finally metastasis was linked to increasing tumor volume [5]. Others have also noted that small-volume tumors rarely progress, whereas large-volume tumors progress more frequently [3,12,13].

However, a method for accurately estimating the tumor volume of prostate cancer before radical prostatectomy is still lacking. Although serum PSA correlates with cancer volume, its ability to predict tumor size on its own is poor [14]. Radiologic imaging techniques often underestimate the tumor volume or even fail to detect the tumor [15]. Although histologic grade has been shown to correlate with actual tumor volume [16], we found that the Gleason score derived from preoperative biopsies correlated poorly with the actual tumor volume. Furthermore, the needle biopsy-based Gleason score was not an independent explanatory variable for tumor volume in this study.

Because the total tumor volume in the radical prostatectomy specimen correlates with disease extent and may help

to predict tumor aggressiveness, we asked whether preoperative parameters could serve collectively to predict preoperative tumor volume. Two variables, namely, serum PSA and the number of positive needle biopsy cores, were found to be most highly predictive of observed tumor volume. These observations are similar to those made in other studies that investigated the predictive power of tumor extent on needle biopsies. For example, Ogawa et al found that the number of cancer-positive biopsy cores and serum PSA were independently predictive of organ-confined disease [17]. Moreover, Egawa et al reported that the number of cores with cancer is jointly predictive of extraprostatic extension in a model that incorporates PSA, clinical stage, and Gleason score [18]. In addition, Wills et al showed that Gleason score and the number of cancer-positive cores were the two best predictors of pathologic stage [19]. Recently, Ochiai et al found that the number of positive cores obtained during extended biopsy may be a tool for predicting the biological significance of prostate cancer [20].

Although actual tumor volume helps to predict tumor aggressiveness, its calculation is time consuming and requires much effort. There are several different ways of estimating the size of tumors in radical prostatectomy specimens, but these methods are not suitable for routine clinical practice. Therefore, an alternative method of estimating tumor size is desirable. When we established a regression model in which tumor volume was the dependent variable and the predicted tumor volume was the explanatory variable, the regression coefficient was significant at the 5% level with an adjusted $R^2=0.521$. We also found that predicted tumor volume was a reasonable predictor of pathologic stage.

This study suffered from several limitations. First, because this study was conducted retrospectively, it may suffer from the typical biases of such research, including referral, selection, and inclusion biases. Second, at the time of analysis, the median follow-up period of the cohort was only 17.9 months, which hampered our ability to analyze the associations of predicted tumor volume with progression variables. Third, the percentage of needle biopsy core length that involved tumor was not reported consistently in our series, which meant that we could not analyze the relationship between this variable and predicted tumor volume. It may be that the percentage of cores with adenocarcinoma is useful for predicting the outcomes of pathologic or biochemical recurrence. However, this limitation may be less serious because the number of positive cores may indicate tumor extent in needle biopsy specimens more quantitatively and reproducibly than visual inspection estimates of the percentages of prostate needle biopsy tissue that contains carcinoma [21]. Furthermore, the prostate gland was typically sampled by 12-core biopsies in the present study. Increased sampling may improve the ability of tumor extent in needle biopsy specimens to accurately reflect whole-gland tumor volume [22].

CONCLUSIONS

The prediction of pathologic stage is a key element in prostate cancer treatment decision-making. We found that tumor volume predicted on the basis of PSA levels and the number of positive biopsy cores predicted pathologic stage with reasonable accuracy. Thus, this method of preoperatively predicting tumor volume may improve the decision-making regarding patients with prostate cancer.

Conflicts of Interest

The authors have nothing to disclose.

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