Original Paper

Urologia Internationalis

Urol Int 2005;75:354–359
DOI: 10.1159/000089174

Received: May 26, 2005
Accepted: August 4, 2005

Prostate Cancer Volume – Can It Be Predicted Preoperatively?

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Key Words
Prostate cancer volume · Predictive parameters, prostate cancer · Radical prostatectomy, prostate cancer

Abstract
Introduction: The prostate cancer volume (PCvol) is described as a significant predictor for tumor progression after radical prostatectomy, but its determination has not become a routine procedure yet due to high demands on technical standards, labor intensity, and costs. The objective of this study is to predict the PCvol by using common preoperative variables. ***Material and Methods:*** Between 1996 and 2001, 365 whole-mounted prostatectomy specimens, processed according to the Stanford protocol, were used for computerized reconstruction of the total PCvol. Widely accepted preoperative variables such as prostate-specific antigen (PSA), digital rectal examination findings, and Gleason score and grading (WHO) of the biopsy cores were correlated and analyzed for a relation to the PCvol by Spearman rho method and Mann-Whitney U test. Integrating these parameters in a multiple linear regression model, independent variables predicting the PCvol were determined, multiplied by their risk factors, and used for calculation of the estimated PCvol. In order to evaluate the precision of our results, we correlated measured and estimated tumor volumes. A nomogram was constructed, in order to visualize our results. ***Results:*** Multiple linear regression analysis revealed categorized PSA, grading (WHO), and Gleason score to be independent predictors for the PCvol. The estimated PCvol ranged from 0.5 to 9.8 cm^3 and the measured PCvol from 0.02 to 53 cm^3. An identical mean value of 4.1 cm^3 was observed. The Spearman rho method showed a highly significant correlation (coefficient = 0.5) between estimated and measured PCvol ($p < 0.001$). ***Conclusions:*** The PCvol is regarded as a significant predictive parameter of tumor progression after radical prostatectomy, but due to its time-consuming determination, it has not become a routine procedure yet. Currently used preoperative parameters such as PSA and grading (WHO) and Gleason score of the biopsy cores do predict the total tumor volume. These results were reconfirmed by correlation analysis. Consequently, by use of our nomogram, the labor-intensive measurement of the PCvol becomes unnecessary.

Introduction

In order to gain prognostic informations for patients who underwent radical prostatectomy, a lot of histopathological features were evaluated. Besides cytological criteria (grading), growth pattern (Gleason score), lymph node involvement, and tumor extension with special focus on surgical margins and seminal vesicles,

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the tumor volume was investigated and found to be a predictive parameter. Accurate assessment of the tumor volume requires serial sectioning of the specimen and detailed planimetric measurement of all cancer areas which cannot be performed in all pathological institutes.

In order to avoid labor-intensive volumetry, we evaluated the possibilities to predict the prostate cancer volume (PCvol) by using widely accepted preoperative parameters.

Materials and Methods

Patient Population

Between 1996 and 2001, a total of 365 men, having undergone radical retropubic prostatectomy for prostate cancer, were included. None of the patients underwent preoperative treatment, such as neoadjuvant hormonal therapy or transurethral resection. The mean age was 63 (range 41–79) years. Preoperative prostate-specific antigen (PSA) showed an average of 10.6 (range 0.9–78) ng/ml. Knowing the biopsy results, a palpable tumor was found in 86% of the patients through digital rectal examination (DRE). Positive (suspicious of cancer) transrectal ultrasound (TRUS) was observed in 63% of the patients (known biopsy results). The mean volume of the prostate was 53 (range 22–183) ml. An average of 3 (range 1–13) positive biopsy cores with an average Gleason score of 6 (range 2–9) and a grading according to the WHO of 2 (range 1–3) was found (for exact distribution see table 1).

Postoperatively, 72% of the tumors were categorized as ≤ pT2c, 16% as pT3a, and 12% as ≥ pT3b according to the 2002 TNM staging system. Positive lymph nodes were present in 5% and positive surgical margins in 21% of the patients. The distribution of categorized postoperative Gleason scores ≤ 6 and ≥ 7 was 53 and 47%, respectively. 77% of the patients had G1 + G2 tumors; 23% were documented to have G3 tumors.

Radical Prostatectomy Specimens

Radical prostatectomy was performed consecutively by a single surgeon. The specimens were processed according to the Stanford protocol [1], using serial transversal sections.

Microscopic Procedures and Measurement of the Tumor Volume

Besides evaluation of pathological features, such as tumor stage (TNM classification, UICC 2002) and grading (WHO), Gleason Score, and surgical margins, the tumor volume was calculated. Therefore, the prostate capsular surface, the urethra, and both extra- and intraprostatic cancer areas were ink dotted during microscopic study by one pathologist (J.M.).

After computerized scanning of all specimen slices, the ink-dotted cancer areas were evaluated, using PicEd Cora 7.0 software, by planimetry (fig. 1). In order to calculate the tumor volume, we multiplied the measured cancer areas (cm^2) by the mean thickness (approximately 3 mm) of the specimens:

Sum of prostatic cancer areas (cm^2) × mean thickness of specimen slices = *incomplete* PCvol (cm^3)

Table 1. Distribution of pre- and postoperative variables

Preoperative variables	
Mean age, years (range)	63 (41–79)
Mean PSA level, ng/ml (range)	10.6 (0.9–78)
DRE suspicious of cancer, %	86
TRUS suspicious of cancer, %	63
Prostate volume, ml (range)	53 (22–183)
Number of positive biopsy cores (range)	3 (1–13)
Mean grading (WHO)	2
G1+G2, %	91
G3, %	9
Mean Gleason score	6
≤ 6, %	65
≥ 7, %	35
Postoperative variables	
pT stage, %	
≤ pT2c	72
pT3a	16
≥ pT3b	12
Lymph nodes positive, %	5
Surgical margins positive, %	21
Mean grading (WHO)	2
G1+G2, %	77
G3, %	23
Mean Gleason score	6
≤ 6, %	53
≥ 7, %	47

The mean thickness of the specimens was recalculated using the quotient of the apicobasal diameter of the not processed, but fixed specimens, including apex, over the number of slices. The (incomplete) tumor volume (cm^3) was then multiplied by our laboratory-specific shrinking factor of 1.5:

Incomplete PCvol × 1.5 (shrinking factor) = *measured* PCvol (cm^3)

This shrinking factor, previously described by McNeal and Haillot [2], was used to compensate the natural shrinking of the prostate during the different de- and rehydration processes of the preparation phase. The results reported by these authors were reconfirmed by our own accurate measurements of 29 prostatectomy specimens before and after all laboratory procedures (data not shown).

Calculation of the Estimated PCvol

Currently used preoperative variables were correlated with the tumor volume by Spearman rho method and Mann-Whitney U test. Significant parameters were integrated into a multiple linear regression model, in order to detect independent predictors for tumor volume. The unstandarized coefficients B of the multiple linear regression model multiplied by their corresponding predictor value were added up to the constant value and used for the calculation of the estimated PCvol (example):

$-6.753 + 2.1 \times 2$ (= PSA 4–10 ng/ml) + 3.3×1 (= G1/2) + 1.8×2 (= Gl-Sc ≥ 7) = 4.4 cm^3

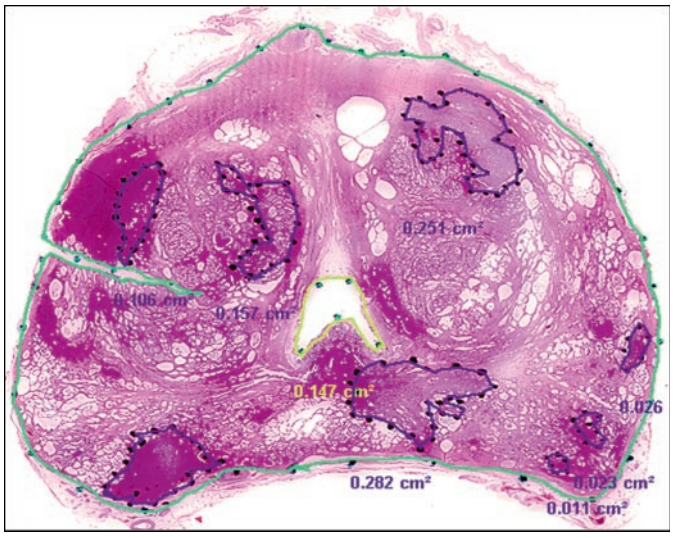

Fig. 1. Transversely sectioned specimen with ink-dotted cancer areas and planimetry.

Table 2. Univariate analysis: correlation for PCvol measured

Preoperative variables	Correlation coefficient (Spearman rho)
PSA preoperative	0.43 (p = 0.00)
Gleason score (biopsy)	0.35 (p = 0.00)
WHO grading (biopsy)	0.28 (p = 0.00)
DRE (suspicious of cancer +/–)	0.19 (p = 0.01)

To evaluate the precision of our results, values of the measured and estimated PCvol were compared by correlation analysis (Spearman rho method). Statistical analysis was performed by the software package SPSS 11.5. The significance level was determined at 0.05.

Results

The mean PCvol of the 365 patients was 4.1 (range 0.02–33) cm^3. In order to calculate the estimated PCvol, we focused on currently used preoperative parameters. Therefore, the preoperative PSA, the DRE results, the Gleason score, and the grading (WHO) of the biopsy specimens were correlated with the measured PCvol. According to the Spearman rho method, all these parameters were significantly associated with the tumor volume (table 2).

Integrating the preoperative parameters of the univariate analysis into a multiple linear regression model, only PSA (<4, 4–10, and >10 ng/ml), grading (G1/G2, G3), and Gleason score (≤ 6, ≥ 7) were found to be independent predictors of the PCvol (table 3).

The estimated tumor volumes, calculated in the way described above, ranged from 0.5 to 9.8 cm^3, with a mean value of 4.1 cm^3. The correlation analysis, done by the Spearman rho method, between estimated and measured PCvol was highly significant with a coefficient of 0.5 (table 4).

In order to visualize our results, we constructed a nomogram which is suitable to estimate the PCvol according to the corresponding preoperative values (fig. 2).

Table 3. Multivariate analysis: multiple linear regression model for preoperative variables and PCvol (dependent variable)

Model		Unstandardized coefficients		Standardized coefficients B values	t	Significance
		B values	SE			
1	Constant	–1.902	0.894		–2.127	0.034
	PSA preoperative (<4/4–10/>10 ng/ml)	2.636	0.376	0.356	7.005	0.000
2	Constant	–6.216	1.162		–5.351	0.000
	PSA preoperative (<4/4–10/>10 ng/ml)	2.365	0.364	0.319	6.491	0.000
	Grading (WHO) of biopsy (G1–2/G3)	4.534	0.824	0.271	5.506	0.000
3	Constant	–6.753	1.156		–5.842	0.000
	PSA preoperative (<4/4–10/>10 ng/ml)	–2.100	0.368	0.284	5.714	0.000
	Grading (WHO) of biopsy (G1–2/G3)	3.347	0.886	0.200	3.779	0.000
	Gleason score of biopsy (<6/>7)	1.794	0.537	0.181	3.342	0.001

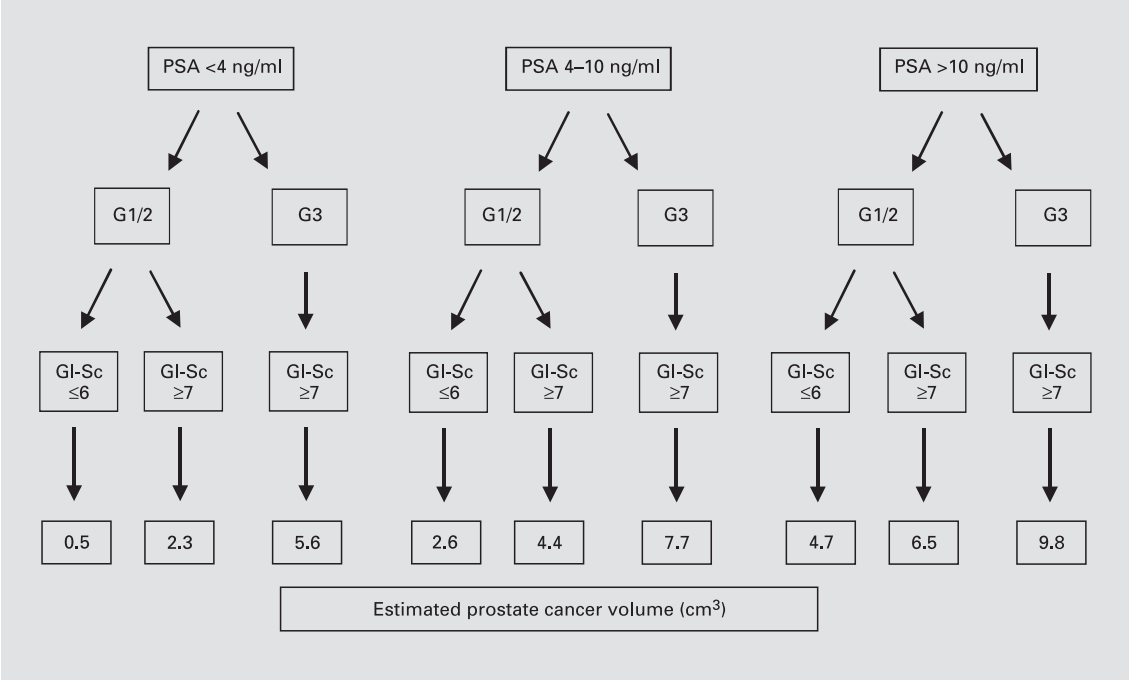

Fig. 2. Nomogram to estimate the PCvol by using prostate-specific antigen (PSA), WHO grading (G), and Gleason score (Gl-Sc).

Table 4. Comparative analysis of measured and estimated PCvol

	Measured PCvol, cm^3	Estimated PCvol, cm^3
Minimum	0.02	0.5
Maximum	33	9.8
Mean	4.1	4.1
Correlation between measured and estimated PCvol		
Correlation coefficient	0.5	
Significance (Spearman rho)	p = 0.00	

Discussion

In order to optimize therapy strategies, many studies investigated the significant predictors for tumor progression after radical prostatectomy. Besides widely accepted pathological features, such as the TNM classification, the margin status, and the different grading systems, the tumor volume was included.

The tumor volume is described as a significant predictor of PSA failure after radical prostatectomy by authors such as McNeal et al. [3], Noguchi et al. [4], Stamey et al. [5], and Partin et al. [6]. Due to high demands on technical standards, labor intensity, time effort, and costs, its measurement has not become a routine procedure yet [7, 8]. Furthermore, its definition is not clear. Since prostate cancer appears mostly multifocally [9], its volume can be measured as a sum of all tumor foci ('total' tumor volume) or as volume of only the largest (index/primary) cancer. Some of the quoted authors use the volume of the primary cancer to predict the disease outcome. The idea of this approach is that secondary cancers are unlikely to be clinically significant and should not be part of the volumetry.

In our opinion, it is necessary to measure the 'total' tumor volume. Noguchi et al. [10] could demonstrate that only 39% of the prostate cancers consist of a predominant index tumor with secondary tumors <0.5 cm^3 which is the accepted volume limit for potentially insignificant tumors. Besides this, we think that an appropriate identification of the index tumor is not always possible. According to the Stanford protocol, prostatectomy specimens are processed in serial transversal sections. Tumor foci appear two-dimensional and must be multiplied by the thickness of the specimen slide to be finally three-dimensional. Therefore, tumor growth through different speci-

men slides would be interpreted as different tumor foci, and the identification of the real primary tumor could be incorrect. Interestingly, the study by McNeal and Haillot [2] could be the proof for our doubts. They found smaller prostate cancers to grow first transversally, but then getting larger to grow mainly vertically towards the base of the prostate. These findings encouraged us to investigate the total tumor volume instead of the index tumor volume.

In 1987, Stamey et al. [11] reported a correlation coefficient of 0.70 between preoperative PSA and total tumor volume. Their results were questioned by Noldus and Stamey [12] who observed correlation coefficients ranging from 0.36 to 0.43 in a larger group of patients (n = 259) and concluded that PSA alone cannot reliably predict the total tumor volume of individual patients. Terris et al. [13] predicted volumes of the primary tumor of 92 men by using preoperative PSA, the step section planimetry volume of the tumor measured by TRUS, and the total length of cancer on biopsy cores. This method reveals an impressive correlation coefficient of 0.76, but its volume estimation depends on accurate TRUS measurements which as we know extremely vary by different investigators [14]. Similar parameters were evaluated by D'Amico et al. [15]. These authors utilized ultrasound prostate volume, PSA, and biopsy Gleason score to predict the total cancer volume in 104 patients, with correlation coefficients ranging from 0.71 to 0.96.

Sebo et al. [16] found the PSA, the percentage of positive biopsy cores, the percentage of tumor surface area, and the DNA ploidy of the biopsy specimens to be significant predictors of the postoperative total tumor volume. Dietrick et al. [17] found the biopsy core cancer length to differ between significant and insignificant tumor volumes (</>0.5 cm^3). Other authors, such as Renshaw et al. [7] and Eichelberger et al. [18], estimated the tumor volume by measuring the maximum tumor diameter of the prostatectomy specimen postoperatively, in order to avoid labor-intensive volumetry.

In our study, we focused on currently used preoperative parameters to predict the total PCvol. To make our results transferable to others, we constructed a nomogram by choosing variables that are widely accepted, as less investigator dependent as possible, and in general already available for patients who had a positive biopsy for prostate cancer.

PSA, Gleason score, and the grading according to the WHO of the biopsy cores were analyzed by uni- and multivariate analysis. Each of these parameters was significantly associated with tumor volume with correlation coefficients of 0.43, 0.35, and 0.28, respectively. Correlating the estimated PCvol with the measured cancer volume reveals a highly significant correlation (coefficient 0.5). These results are based on data of a large cohort of patients (n = 365), evaluated accurately with high clinical and laboratory standards. Our results did not confirm the same correlation coefficients as reported in some previous studies, but the use of our nomogram may help to categorize patients with certain preoperative clinical findings in order to simplify therapy decisions. Further follow-up will show to what extent different volume categories influence survival and tumor recurrence rates.

Conclusions

The PCvol is known as a significant predictor of tumor progression after radical prostatectomy and should be defined as 'total' tumor volume rather than 'primary' tumor volume. In this study, we used preoperative PSA, grading according to the WHO, and the Gleason score of the biopsy cores to predict the postoperatively measured PCvol. By performing accurate evaluation techniques, a highly significant correlation between estimated and measured tumor volumes was observed in a large cohort of patients. In order to make our results transferable to others, we constructed a nomogram which is suitable to estimate the PCvol preoperatively, without measuring it labor and cost intensively.

Acknowledgment

We thank Dr. M. Praetorius (Urologische Klinik München-Planegg, Planegg, Germany) for providing the clinical data of the patients investigated in this study.

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