Preoperative Prostate Specific Antigen and Prostate Volume Are Significant Predictors of Seminal Vesicle Invasion in Patients with Prostate Cancer

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Abstract: To evaluate the potential role of several clinical and pathological parameters in prediction of seminal vesicle invasion in patients with clinically localized prostate cancer undergoing radical prostatectomy. We retrospectively analyzed the medical records of patients who undergone radical prostatectomy from January 2005 until November 2010. Patients age, prostate volume, PSA, PSA density, percent of cancer in prostate biopsy material, Gleason summary, 1st Gleason pattern, 2nd Gleason pattern and the presence of high grade prostatic intraepithelial neoplasia were studied for their predictive ability. Two hundred and seventeen patients analyzed and 13.8% of them had seminal vesicle invasion in the final histopathological examination of the surgical specimen. A significant difference in PSA values, PSA density, percentage of cancer in biopsy material, biopsy Gleason score and 1st Gleason pattern was noticed between patients with and without seminal vesicle invasion. In univariate analysis, PSA, PSA density, prostate volume, percentage of cancer in biopsy material, biopsy Gleason score and 1st Gleason pattern found significant. However, in multivariate analysis, only PSA (p=0.008) and prostate volume (p=0.027) were found to be significant predictors. PSA ≥10 ng/ml and prostate volume ≤41 ml was shown to be the optimal cut-off values for seminal vesicle invasion in receiver operating curve analysis. PSA and prostate volume should be considered significant predictors for adverse pathology of the seminal vesicles in patients planned for surgical treatment of prostate cancer. This is of great concern especially in cases that a seminal vesicle sparing technique is planned.

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Introduction

Seminal vesicle invasion (SVI) represents an adverse pathologic and prognostic factor and increases the rates of prostate cancer (PCa) specific mortality (Han et al., 2001; Eggener et al., 2011). Consequently, the complete removal of seminal vesicles (SV) is included in radical prostatectomy (RP) standard technique.

In the pre-prostatic specific antigen (PSA) and in early PSA era, when screening and diagnosis of PCa was based solely on digital rectal examination, the incidence of SVI was reported in 19–26% of RP specimens (Mukamel et al., 1987; Villers et al., 1990). However, stage migration has decreased the rates of SVI and this has resulted in the suggestion that SV may be safely left untouched during RP without compromising prognosis and cure (Korman et al., 1996). Furthermore, because of the close relationship of SV and bladder base arterial supply, trigonal nerves and proximal neurovascular bundle, sparing techniques may decrease the rates of post surgical impotence and incontinence by avoiding damage in these close neighbour structures (John and Hauri, 2000; Colombo et al., 2001; Walz et al., 2010).

Although SV sparing RP can be a potential surgical modification, even though the benefits on continence and erectile function have not been well established yet, patients' selection for such treatment modifications is of great concern, in order not to harbour the oncological outcome. Preoperative clinical and pathological data should be used for clarifying the appropriate candidates that will mostly benefit by SV spare during RP, in terms of functional results, without influencing the oncological parameters (biochemical recurrence, survival). Based on this concept, the aim of our study was to analyze several preoperative factors and evaluate their predictive potential for SVI in patients undergoing RP for clinically localized PCa.

Material and Methods

A retrospective analysis of the medical records of patients who underwent a RP with the diagnosis of clinically localized PCa was conducted. Our study included patients who operated between January 2005 and November of 2010. Any preoperative therapies, in terms of active surveillance, hormone therapy or radiation were exclusion criteria. Patients diagnosed after transurethral resection of the prostate and patients with incomplete records were excluded as well.

Preoperative PSA was measured before any prostate manipulation (digital rectal examination, transrectal ultrasound, biopsy). In all patients, the PCa diagnosis was made after transrectal ultrasound biopsy and positive for malignancy histological examination of the obtained cores. The preoperative value of 1st and 2nd pattern and concomitant Gleason summary, the percentage of cancer found in the biopsy cores material (% CM) and the presence of high grade prostatic intraepithelial neoplasia (HGPIN) were recorded from histological examination report, as well. An open or laparoscopic extraperitoneal RP was performed in all patients by 4 experienced surgeons. The surgical specimen was then sent for pathological

examination and a report concerning prostate dimensions, pathological stage and Gleason grade of cell atypia was obtained. Based on the information of the prostate dimensions, the pathological volume was calculated. A formula ($D1 \times D2 \times D3 \times \pi/6$) based on the prostate ellipse dimension theory was used, where D1 is the maximum transverse diameter, D2 is the maximum anteroposterior diameter, D3 is the maximum longitudinal diameter and π is a mathematical constant with a value of 3.14. Consecutively, the value of PSA density was estimated by dividing preoperative PSA and pathological volume of prostate gland.

The preoperative parameters which analyzed for their predictive ability for SVI were comprised of preoperative 1st and 2nd Gleason pattern and Gleason summary, age, preoperative value of PSA, prostate volume, PSA density, % CM and the presence of HGPIN.

Statistical analysis was performed by using SPSS version 17 (SPSS Inc., Chicago, IL, USA). The descriptive statistics are presented as the mean ± standard deviation (SD) and interquartile range (IQR) for continuous variables and as the absolute and percent frequency for categorical variables.

The normality condition of the numerical variables was studied by means of the Kolmogorov-Smirnov test. None of them had normal distribution. For this reason, the Mann-Whitney test was used to compare means between numerical groups. The chi-square $\chi 2$ test was used for categorical variables. A univariate analysis was performed to identify the predictive significance of age, preoperative PSA, prostate volume, PSA density, preoperative 1st and 2nd Gleason pattern, Gleason summary, % CM and the presence of HGPIN in biopsy cores in prediction of SVI.
A multivariate analysis was performed then for the variables identified as statistically important in univariate analysis, using logistic regression.

The optimal cut-off values, sensitivity and specificity for quantitative variables, found to be significant predictors for SVI in multivariate analysis, were estimated by using receiver operating curve (ROC) analysis. Furthermore, ROC curve was used for determination of accuracy for predicting SVI for significant variables found in multivariate analysis. Positive [true positive/(true positive + false positive)] and negative predictive value [true negative/(true negative + false negative)] were estimated as well.

All tests were 2-tailed with $p<0.05$ to be considered as statistically significant.

Results

The data from 217 patients who underwent RP for the treatment of localized PCa were analyzed. Patients' age was ranged from 46–79 (66.94 ± 6.30, 9). Preoperative median PSA value was 8.50 ng/ml (10.89 ± 8.31, 5.50) and median PSA density was 0.23 ng/ml2 (0.32 ± 0.36, 0.19). Prostate volume, measured based on prostate dimensions obtained by the pathologoanatomic report, had a median value of 40 ml (43.49 ± 21.35, 24.85). Prostate biopsy data analysis revealed that the median % CM was 20.00 (28.78 ± 25.11, 33.00), while in 121 cases (55.8%) the presence

of HGPIN was noticed. Atypical small acinar proliferation was noticed in 7 patients (3.2%) and due to the limited number did not enter the analysis.

SV pathologic analysis after RP has shown that there was cancer invasion in 30 patients (13.8%). The clinical and pathological characteristics of the patients found to have or not SVI are shown in Table 1. A statistically significant correlation

Table 1 – Clinical and pathological characteristics of patients according to seminal vesicle invasion

Characteristics	SVI –	SVI +	P
no. of patients (%)	187 (86.2%)	30 (13.8%)	
age (years)			0.821*
mean ± SD (IQR)	66.96 ± 6.26 (8)	66.77 ± 6.65 (11)	
prostate volume (ml)			0.055*
mean ± SD (IQR)	44.75 ± 22.26 (27)	35.69 ± 11.92 (16)	
PSA (ng/ml)			<0.001*
mean ± SD (IQR)	9.92 ± 5.81 (5.33)	16.91 ± 15.96 (9.21)	
PSA density (ng/ml2)			<0.001*
mean ± SD (IQR)	0.29 ± 0.29 (0.17)	0.54 ± 0.63 (0.32)	
% CM			0.015*
mean ± SD (IQR)	26.86 ± 23.64 (31)	40.87 ± 30.59 (56)	
GS, n (%)			0.050**
2	2 (100.0)	0 (0.0)	
3	6 (85.7)	1 (14.3)	
4	8 (88.9)	1 (11.1)	
5	21 (95.5)	1 (4.5)	
6	68 (90.7)	7 (9.3)	
7	67 (84.8)	12 (15.2)	
8	10 (58.8)	7 (41.2)	
9	5 (83.3)	1 (16.7)	
1st pattern, n (%)			0.001**
1	3 (100.0)	0 (0.0)	
2	25 (89.3)	3 (10.7)	
3	116 (92.8)	9 (7.2)	
4	40 (70.2)	17 (29.8)	
5	3 (75.0)	1 (25.0)	
2nd pattern, n (%)			0.960**
1	8 (88.8)	1 (11.2)	
2	17 (89.5)	2 (10.5)	
3	111 (86.7)	17 (13.3)	
4	45 (83.3)	9 (16.7)	
5	6 (85.7)	1 (14.3)	
HGPIN, n (%)			0.773**
no	82 (85.4)	14 (14.6)	
yes	105 (86.8)	16 (13.2)	

*Mann-Whitney U test; **chi-square $\chi 2$ test; SD – standard deviation; IQR – interquartile range; CM – cancerous material; GS – Gleason score; HGPIN – high grade prostatic intraepithelial neoplasia; SVI – seminal vesicle invasion

was found between PSA, PSA density, % CM and presence of SVI while these patients had significantly higher biopsy Gleason summary and 1st Gleason pattern.

Based on the results of the univariate analysis, prostate volume, preoperative PSA, PSA density, % CM, biopsy Gleason score and 1st Gleason pattern were found significant (Table 2). The multivariate analysis of the parameters, that were found to be significant in univariate analysis, has shown that smaller prostate volume and higher preoperative PSA value are significant predictors for SVI (Table 3).

The optimal cut-off values of PSA and prostate volume for prediction of SVI were ≥10 ng/ml and ≤41 ml respectively, obtained by using ROC analysis. Area

Table 2 – Univariate analysis

			95% CI for Exp(B)	
	Significance	Exp(B)	Lower	Upper
Age	0.874	0.995	0.936	1.058
Prostate volume	0.032*	0.974	0.951	0.998
PSA	0.001*	1.083	1.032	1.136
PSA density	0.005*	3.819	1.500	9.725
% cancer material	0.006*	1.020	1.006	1.034
Gleason score	0.023*	1.525	1.059	2.196
1st pattern	0.001*	2.653	1.454	4.838
2nd pattern	0.495	1.192	0.720	1.971
High grade PIN	0.773	0.893	0.412	1.934

*statistically significant; CI – confidence interval; PIN – prostatic intraepithelial neoplasia

Table 3 – Multivariate analysis

			95% CI for Exp(B)	
	Significance	Exp(B)	Lower	Upper
Prostate volume	0.027*	0.951	0.909	0.994
PSA	0.008*	1.177	1.042	1.328
PSA density	0.071	0.052	0.002	1.295
% cancer material	0.206	1.011	0.994	1.028
Gleason score	0.361	0.749	0.403	1.392
1st pattern	0.089	2.395	0.876	6.547

*statistically significant; CI – confidence interval

Table 4 – Sensitivity, specificity, positive and negative predictive value of PSA ≥10 ng/ml and prostate volume ≤41 ml for seminal vesicle invasion

	Sensitivity	Specificity	ppv	npv
PSA	70.0%	65.8%	24.7%	93.2%
Prostate volume	76.7%	43.9%	18.0%	92.1%

ppv – positive predictive value; npv – negative predictive value

under the curve for PSA was 0.716 and 0.609 for prostate volume. The predictive parameters are seen in Table 4.

Discussion

SV are in close anatomical relationship with structures like neurovascular bundle and trigonal nerves and this feature has stimulating research in recent years for the potential benefit of SV sparing RP in continence and erectile function outcomes after surgery (Korman et al., 1996; John and Hauri, 2000). Direct lesion during surgery or postoperative fibrotic changes may harm both the nerve and blood supply. Interestingly, it has reported that in 71 consecutive patients underwent RP, no tumor was found in the distal 1 cm of the SV, including 12 with SVI (Korman et al., 1996). Given the fact that utilization of PSA in PCa screening has led to early diagnosis, an increased incidence of insignificant cancer detection has been notified with younger patients to undergo surgery. Consequently, this has resulted in a great concern of the postoperative functional results of RP. However, since SVI by PCa cannot be identified with secure by the standard preoperative staging tools (digital rectal examination, transrectal ultrasound, computer tomography), the danger of leaving back cancer material if SV left in place during RP is high. Furthermore, SVI is a bad prognostic factor for survival and most of the patients will present early biochemical relapse and will need an adjuvant treatment protocol (radiotherapy, hormone manipulations). For the above reasons the preoperative estimation of SVI by using clinical and pathological factors is mandatory for the appropriate and correct patients selection.

Several factors have been proposed as potential predictors for SVI. The Partin tables represent one of the most widely used PCa staging tools for adverse pathology features including SVI (Makarov et al., 2007). These nomograms are utilizing preoperative PSA value, biopsy Gleason score and clinical stage and can predict SVI with an accuracy rate of 78%. The predictive accuracy of this standard model was maximally enhanced by including the percent of cancer found at the prostate base during biopsy (Koh et al., 2003). Recently, another nomogram has been developed using stage, grade and PSA plus the percentage of positive for malignancy cores obtained during transrectal ultrasound prostate biopsy (Gallina et al., 2007). An external validation of this nomogram has reported that the predictive accuracy of SVI is increased compared to Partin tables, reaching 81% (Zorn et al., 2009).

A multi-institutional study of 6,740 patients reported that by utilizing PSA, grade, stage and patients' age, the patients with an increased risk for SVI can be identified (Baccala et al., 2007). In another analysis conducted in a large cohort of 1,283 patients, authors reported that SV involvement is lower than 5% in all patients with a preoperative PSA level <10 ng/ml, except when Gleason score is ≥7 or when more than 50% of prostate biopsy cores show cancer involvement. Thus, removal of the SV may not be oncologically necessary and might spare complete

resection (Zlotta et al., 2004). Other authors suggest that PSA <4 ng/ml, Gleason score <7 and less than 12% of biopsy cores involved with cancer are criteria that can be used preoperatively for vesiculectomy decision during RP, since SV complete removal would not benefit almost 99% of patients (Reis et al., 2010).

Results from our analysis demonstrate and confirm the value of preoperative PSA in predicting SVI. We found that patients having PSA ≥10 ng/ml have an increased likehood of local metastasis in SV and consequently such patients should not be considered as candidates for SV sparing RP. Statistical analysis showed that PSA values were significantly higher in patients with SVI and similarly a statistical significance was noticed in multivariate analysis. Actually, PSA was the strongest predictor among those who analyzed. With a sensitivity of 70% and a negative predictive value of 93.2%, preoperative PSA values ≥10 ng/ml should be considered when counselling patients and deciding extend of surgery.

Even though a large number of studies have reported that Gleason score can predict SVI, this was not the case of our study. Although Gleason summary between patients with and without SVI after pathological specimen examination was significant different, the multivariate analysis revealed that this preoperative parameter was not statistically significant in SVI prediction. Similar results obtained when 1st and 2nd Gleason pattern analyzed for their predictive potential.

Except of PSA, our analysis results demonstrated that the volume of prostate is significant correlated with the presence of SVI. Actually, in multivariate analysis of the various parameters, prostate volume was the second and last predictor following PSA. ROC analysis defined that patients with prostate volume ≤41 ml, have an increased likehood for SVI and this parameter should be accounted when surgery modifications regarding SV removal are planned. This is the first study to demonstrate the predictive significance of prostate volume for SVI. Although prostate volume was calculated postoperatively according to the dimensions of prostate, reported by the histopathology examination of the specimen, there is a great positive correlation between preoperative (during transrectal ultrasound) and postoperative prostate volume calculation (Wolff et al., 1995).

We evaluated a number of preoperative clinical and pathological parameters. Some of them, like PSA density and % CM, were found statistically significant in univariate analysis. However, this was not confirmed by the multivariate analysis.

Reviewing the literature, a number of parameters, including preoperative Gleason score and stage, have been found to be significant predictors of SVI. In contrast, our results revealed that PSA and prostate volume are the ones that can predict seminal vesicle metastasis. In our opinion, relying on preoperative PSA and prostate volume alone can be both impractical and misleading and it would be safer and more efficient to be used not as single parameters but in addition with other significant prognostic factors.

Preoperative identification of seminal vesicle involvement in patients with PCa is limited based on the current imaging tools. Therefore, a number of patients

undergoing a RP for clinically localized PCa will harbor SVI and worse prognosis. On the other hand, patients with insignificant, low volume and grade disease, who are interesting to preserve sexual function, might be benefited by intraoperative preservation of seminal vesicle tips, since it can minimize neurovascular bundle trauma. Consequently, preoperative prediction of SVI may assist appropriate treatment selection, either for the preservation of seminal vesicles in low risk patients and either for the identification of these patients at risk of advanced disease that might be offered less burdening therapy, like radiotherapy and androgen deprivation. We have to state that none of the present or earlier reported predictors for seminal vesicles involvement are absolutely safe and are just indicating the possibilities. Therefore, the risk for SVI involvement always exists despite of the presence of favourite or unfavourable predictors. Patients have to be fully informed about this in all cases a SV sparing technique is planned or discussed with the patient.

Our study has some important limitations that we should report. Apart of the retrospective design, the analysis used the results of pathological analysis of biopsy cores made by different anatomists. Therefore, we believe that inter-observer variability in obtaining tumor grade might be built into the study results. The assessment of preoperative Gleason score was determined according to an older fashion grading system. The results of the present study, even significant, might alter if the conclusions of the ISUP 2005 conference (Epstein et al., 2005) are used. Prostate dimensions were estimated based on the surgical specimen which was fixed in formalin solution. As already documented, formalin may alter tissue structure and size and this should also be taken in account. For this reason, prospective studies using preoperative estimation of prostate volume, using transrectal ultrasound, are mandatory to confirm the present results.

Conclusion

Our findings may help to further define a selected group of patients that could be offered a SV sparing RP. Especially, our findings regarding the predictive role of prostate volume bring new data in the current scientific knowledge and this parameter should be used when decisions, regarding the SV removal, are taken.

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