Bilateral Cancer in Prostate Biopsy Associates with the Presence of Extracapsular Disease and Positive Surgical Margins in Low Risk Patients:

A Consideration for Bilateral Nerve Sparing Radical Prostatectomy Decision

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Purpose: To evaluate the epidemiological, clinical and pathological parameters that may predict the presence of positive surgical margins and extraprostatic disease in patients with low risk [prostate specific antigen (PSA) < 10, and Gleason score ≤ 6, stage T1c)] prostate cancer.

Materials and Methods: We retrospectively analyzed the medical records of patients who had undergone radical prostatectomy from January 2005 until January 2011. The analysis comprised patients' age, preoperative serum prostate specific antigen (PSA) level, prostate volume, PSA density, biopsy Gleason score, the presence of bilateral disease according to the results of biopsy cores analysis, the percentage of cancer in biopsy material and the presence of high grade prostatic intraepithelial neoplasia.

Results: A total of 117 patients were included in the study. Positive surgical margins were found in 37 (31.6%) patients and 23 (19.7%) had advanced disease. The results of the multivariate analysis showed that bilateral disease was the single significant predictor for advanced disease prediction ($P = .04$). Same results was obtained by the univariate analysis of the variables for prediction of positive surgical margins, where bilateral disease after biopsy cores analysis was the only factor to be statistical significant ($P = .018$).

Conclusion: Bilateral prostate cancer in prostate biopsy is significantly associated with positive surgical margins and advanced disease in patients that are operated for prostate cancer of low risk. This observation may assist the selection of patients in whom a bilateral nerve sparing radical prostatectomy is planned to be performed.

Keywords: prostatic neoplasms; risk assessment; prostate-specific antigen; prostatectomy; risk

INTRODUCTION

Since the first retropubic radical prostatectomy (RP), described by Millin in 1948,[1] a number of surgical modifications have been made to offer a better cancer control and, additionally, to minimize morbidity by decreasing postoperative functional complications, mainly incontinence and sexual dysfunction. In 1982, Walsh and Donker[2] described the neurovascular bundles and their relations to the, and they proposed technical modifications of the RP. Actually, they reported that preservation of the neurovascular bundles (NVB) can be performed with safety in previously potent patients with prostate cancer, without affecting the oncological outcome, while this modification can preserve erectile function. The addition of prostate specific antigen (PSA) in everyday practice have increased the number of patients diagnosed with low volume and organ confined prostate cancer. Since most of the patients are young in age and interesting in preserving their potency, the implementation of NVB-sparing RP has become imperative.

Several studies have evaluated the criteria that should be used for identifying the appropriate candidates for bilateral NVB-sparing RP. The most used nomograms for decision-making, nowadays, are Partin tables.[3] Clinical stage T1c, preoperative Gleason score ≤ 6 and serum PSA< 10 ng/ml are the recommended criteria for bilateral nerve sparing RP (BNSRP) of the European Association of Urology latest guidelines.[4] Based on the same guidelines, clear contraindications for BNSRP are those patients with preoperative extracapsular disease, such as any clinical stage T3 or T2c, any Gleason score > 7 on biopsy, or more than one biopsy with Gleason score > 6 at the ipsilateral side. In patients with T2a or T2b clinical disease, a unilateral nerve sparing procedure may be performed.

The optimal scenario for patients with prostate cancer would be the preoperative estimation of tumor status, mainly cancer extension, in order cancer control not to be harmed, especially in patients in whom low risk characteristics might hide a more aggressive malignancy. Unfortunately, since now, no imaging technique or clinical algorithm can definitive exclude the presence of extracapsular disease even in patients with low risk characteristics.

The aim of the present study was to evaluate several preoperative epidemiological, clinical and pathological characteristics and to analyze their association with the presence of extended prostate cancer in patients with preoperative low risk cancer whom are planned to be treated with BNSRP.

MATERIALS AND METHODS

A retrospective analysis of the medical records from 144 patients who had undergone radical prostatectomy for low risk prostate cancer between January 2005 and January 2011 in our institution was performed. As low risk patient was defined the one with preoperative serum PSA < 10ng/ml, biopsy Gleason score ≤ 6 and clinically T1c disease. Twenty seven patients were excluded from the analysis due to incomplete or missing data. An open or laparoscopic radical prostatectomy was performed in all cases. The procedure included the removal of the prostate gland and the seminal vesicles. A pelvic lymph node dissection was performed in 54 (46.2%) of studied patients. Prostate cancer was diagnosed by a previous transrectal ultrasound biopsy. During the procedure, a minimum of 3 cores from each lobe were obtained.

The surgical specimen of radical prostatectomy was examined by our institution pathologists and a histological report concerning the prostate dimensions, the tumor extend, the presence of positive surgical margins (PSM), and the pathological grade and stage was obtained. Any extend of tumor outside of the prostatic capsule in the periprostatic fat was considered as advanced disease (AD) while the infiltration of the capsule without penetration was considered as localized disease. Invasion of the seminal vesicles and/or of the dissected lymph nodes was considered as AD, as well.

The 2009 TNM (tumor node metastasis) classification for prostate cancer was used to classify the pathological stage. According to the information of prostate's maximum transverse diameter (D1), maximum anteroposterior diameter (D2) and maximum longitudinal diameter (D3), reported by the pathologists, the pathological prostate volume was calculated by using the prostate ellipse dimension theory formula ($D1 \times D2 \times D3 \times \pi/6$). PSA density was calculated by dividing the preoperative PSA value and prostate volume. Even though prostate volume was calculated postoperatively according to the pathological prostate dimensions, there is a

Table 1. Characteristics of patients with organ confined and extraprostatic disease after radical prostatectomy

Characteristics	Confined disease	Advanced disease	*P* value
No. of patients, n (%)	94 (80.3)	23 (19.7)	
Age (years)			.912†
Mean ± STD, IQR	65.7 ± 6.9, 11	66.0 ± 6.2, 10	
Prostate volume (ml)			.001†*
Mean ± STD, IQR	49.9 ± 25.3, 35	32.5 ± 12.3, 11	
Serum PSA (ng/ml)			.428‡
Mean ± STD, IQR	7.2 ± 1.6, 2.2	7.5 ± 1.3, 1.5	
Serum PSAD (ng/ml2)			< .001†*
Mean ± STD, IQR	0.18 ± 0.11, 0.11	0.26 ± 0.08, 0.08	
Bilateral disease, n (%)			.015§*
No	51 (89.5)	6 (10.5)	
Yes	43 (71.7)	17 (28.3)	
PCBM (%)			.076†
Mean ± STD, IQR	18.4 ± 16.9, 19	24.5 ± 17.6, 27	
Biopsy GS, n (%)			.522§
2	1 (100.0)	0 (0.0)	
3	7 (87.5)	1 (12.5)	
4	10 (90.9)	1 (9.1)	
5	21 (87.5)	3 (12.5)	
6	55 (75.3)	18 (24.7)	
HGPIN, n (%)			.718§
No	37 (78.7)	10 (21.3)	
yes	57 (81.4)	13 (18.6)	

*statistically significant, †Mann-Whitney *U* test, ‡Student's t test, §Chi-square test,
Keys: STD = standard deviation, IQR = interquartile range, PSA = prostate specific antigen, PSAD = PSA density, PCBM = percentage of cancer in biopsy material, GS = Gleason score, HGPIN = high grade prostatic intraepithelial neoplasia

Table 2. Characteristics of patients regarding the presence of positive surgical margins after radical prostatectomy

Characteristics	no PSM	PSM	*P* value
No. of patients, n (%)	80 (68.4)	37 (31.6)	
age (years)			.547†
Mean ± STD, IQR	65.5 ± 7.0, 11	66.4 ± 6.1, 10	
Prostate volume (ml)			.803†
Mean ± STD, IQR	47.1 ± 25.1, 33	45.3 ± 22.8, 25	
Serum PSA (ng/ml)			.059‡
Mean ± STD, IQR	7.1 ± 1.6, 2.2	7.7 ± 1.3, 1.8	
PSAD (ng/ml2)			< .207†
Mean ± STD, IQR	0.19 ± 0.12, 0.17	0.20 ± 0.08, 0.11	
Bilateral disease, n (%)			.017§*
No	45 (78.9)	12 (21.1)	
Yes	35 (58.3)	25 (41.7)	
PCBM (%)			.130†
Mean ± STD, IQR	17.7 ± 15.8, 14	23.8 ± 19.3, 31	
Biopsy GS, n (%)			.558§
2	1 (100.0)	0 (0.0)	
3	6 (75.0)	2 (25.0)	
4	9 (81.8)	2 (18.2)	
5	18 (75.0)	6 (25.0)	
6	46 (63.0)	27 (37.0)	
HGPIN, n (%)			.645§
No	31 (66.0)	16 (34.0)	
yes	49 (70.0)	21 (30.0)	

*statistically significant, †Mann-Whitney U test, ‡Student's t test, §Chi-square test,
Keys: PSM=positive surgical margins, other abbreviations like in table 1.

great positive correlation between preoperative (during transrectal ultrasound) and postoperative calculation of prostate volume, reaching 90%.[5]

The analysis of the present study comprised patients' age, preoperative serum PSA, prostate volume, PSA density, biopsy Gleason score, the presence of bilateral disease according to the results of biopsy cores analysis, the percentage of cancer in biopsy material (PCBM) and the presence of high grade prostatic intraepithelial neoplasia (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 (STD) 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. Preoperative serum PSA was the only variable with normal distribution. Student's t test was used to compare PSA means between groups and Mann-Whitney *U* test was used to compare means between groups for the not-normally distributed numerical variables. 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 Gleason score, bilateral

Table 3. Univariate and multivariate analysis for advanced disease prediction

			95% C.I. for Exp (B)	
	Significance	**Exp (B)**	**Lower**	**Upper**
Univariate analysis				
Age	.821	1.008	.941	1.080
Prostate volume	.004*	.952	.921	.984
PSA	.425	1.130	.837	1.525
PSA density	.013*	311.227	3.347	28943.627
PCBM	.135	1.019	.994	1.044
Bilateral disease	.019*	3.360	1.217	9.276
Gleason score	.127	1.625	.872	3.029
HGPIN	.718	.844	.335	2.123
Multivariate analysis				
Prostate volume	.083	.959	.914	1.006
PSA density	.691	3.494	.007	1669.111
Bilateral disease	.040*	3.123	1.056	9.237

Keys: CI=confidence interval, other abbreviations like in table 1

Table 4. Univariate analysis for prediction of positive surgical margins

			95% C.I. for Exp (B)	
	Significance	**Exp (B)**	**Lower**	**Upper**
Age	.461	1.023	.963	1.086
Prostate volume	.717	.997	.981	1.013
PSA	.061	1.289	.988	1.682
PSA density	.676	2.107	.064	69.668
Bilateral disease	.018*	2.679	1.182	6.069
PCBM	.076	1.021	.998	1.044
Gleason score	.135	1.426	.896	2.270
HGPIN	.645	.830	.377	1.831

Keys: CI=confidence interval, other abbreviations like in table 1

disease, PCBM and HGPIN in biopsy cores in prediction of AD and PSM. A multivariate logistic regression analysis was performed then for the variables identified as statistically important in univariate analysis, using logistic regression. All tests were 2-tailed with $P < .05$ to be considered as statistically significant value.

RESULTS

A total of 117 patients found to have clinically T1c disease with low risk characteristics (PSA < 10 ng/ml and preoperative Gleason score ≤ 6). The median age was 67 years (65.8 ± 6.7, 11) and median preoperative PSA was 7.3 ng/ml (7.3 ± 1.6). Based on the pathological evaluation of the biopsy material, invasion of cores from both prostatic lobes was observed in 60 (51.3%) patients. From those, 17 (28.3%) patients had extracapsular disease, 25 patients (41.7%) had PSM, while 1 patient (1.7%) had lymph node and seminal vesicle invasion.

After pathological analysis of the radical prostatectomy specimen, 37 (31.6%) patients had PSM and 80 (68.4%) had complete cancer removal, while 94 (80.3%) patients had pathological confined disease and 23 (19.7%) had cancer extended outside of the prostatic capsule border. In specific, 14 (12%) patients found to have pT2a disease, 5 (4.3%) pT2b, 75 (64.1%) had pT2c, 19 (16.2%) had pT3a and 4 (3.4%) patients had pT3b disease. Fifty four patients undergone a pelvic lymph node dissection and positive nodes found in 2 of them (both patients had pT3b disease). In the 63 (53.8%) remained patients a lymph node sparing radical prostatectomy was performed. Patients' characteristics regarding the presence or not of organ confined prostate cancer and PSM are seen in Tables 1 and 2, respectively.

Prostate volume, PSA density and biopsy-based bilateral disease were the variables found to be significant in univariate analysis for advanced disease prediction, with P values to reach .04, .013, .019, respectively (Table 3). In the multivariate analysis, bilateral disease was the single significant predictor with $P = .04$ (Table 3). Same results was obtained by the univariate analysis of the variables for prediction of PSM (Table 4), where bilateral disease in biopsy cores analysis was the only factor to be statistical significant ($P = .018$).

DISCUSSION

The main concern, when a BNSRP is performed, is complete eradication of prostate tumor and preservation of sexual function. Since the surgical boundaries are closer to the prostatic capsule by preserving the NVB, this may increase the rates of incomplete tumor removal and PSM. Moreover, it has been shown that postero-lateral prostate surface, which is the region of the NVB, is the most common site of PSM.[6,7] That means that in patients with AD, and mainly extraprostatic extension, the preservation of the bundles may lead to PSM and limited cancer control. Catalona and Bigg[8] have

Table 5. Summary of indications for not performing a bilateral nerve sparing radical prostatectomy

	Clinical stage	PSA	GS	PT	PSM (%)
Zorn et al. [18]	≥ T2b		> 7		20.4
Bianco et al. [19]	> T2			+	5
Tsuzuki et al. [20]		≥ 10	≥ 7		> 10
Shah et al. [21]	> T2				8
Sofer et al. [22]	> T2	> 10	> 7		24
Graefen et al. [23]	> T2	> 10	> 7		15.9
Walsh [24]	> T2			+	5
Scardino and Kim [25]	> T2			+	5
Alsikafi and Brendler [26]	> T2		≥ 7		11

Keys: PSA = prostate specific antigen, GS = Gleason score, PT = Partin tables, PSM = positive surgical margins.

reported that, when a nerve sparing RP was performed, PSM were identified in all cases that an extracapsular disease was present in at the NVB region. Adverse prognostic events, like biochemical failure and systemic relapse, have been found to be associated with positive surgical margins.[9-11] In a series of 377 patients who had RP for localized prostate cancer, a decreased 5-year progression free survival was associated with positive surgical margins (90% vs. 78%), irrespective of the presence of extracapsular disease.[11] Another study reported a 10-year progression-free survival of 79% and 55% for patients with negative and positive surgical margins, respectively. Better prognosis was found even after the exclusion of patients with seminal vesicles invasion.[12] The prognostic value of surgical margin status appeals clinically important in planning treatment especially for those patients who are considered to undergone a nerve-sparing procedure, a subgroup with a continuously increasing number members nowadays.

Despite the wide use of nerve sparing RP, the overall rate of PSM is declined. This may be explained by a shift in early prostate cancer diagnosis and consequently the increase in organ confined disease and the improvements in the surgical expertise.[13] Several studies have evaluated the rates of cancer presence at the level of the surgical margins who underwent a RP with or without an excision of the NVB.[14-18] Actually, positive surgical margins rates and biochemical free survival are not influenced by nerve-sparing technique. Based on the reported results, in most of the cases the rates of PSM are higher when a wide excision of the bundles was performed.

Taken together these results, someone may conclude that the preservation of the NVB does not affect the prostate cancer control, in terms of complete eradication of the disease. The main problem seems to be the preoperative identification of an advanced cancers that harbor the danger of incomplete control when bundles preservation is performed. In the absence of specific and reliable imaging techniques that can define the tumor extend preoperatively, patients selection is mainly supported by preoperative and intraoperative criteria. Several parameters have been proposed for the selection of the appropriate candidates for BNSRP. Most of the reports are agreed that preoperative PSA, biopsy Gleason score and clinical stage are the most reliable criteria for patients stratification.[19-27] As seen in table 5, the majority of the investigators have reported that patients with clinical stage > T2, PSA >10ng/ml and preoperative Gleason score > 7 are of increased risk for advanced disease and therefore a BNSRP should omitted. Kamat and associates,[28] and Naya and associates[29] have tried to further refine the criteria for a non-nerve sparing RP. They reported that the presence of a prostate biopsy core with a tumor length of at least 7mm plus a positive biopsy core of at the prostate base, irrespective of the length and tumor grade, is predictive of extraprostatic disease.

In the contemporary practice, Partin tables are the most used nomograms to predict the risk of adverse events, including extracapsular cancer, by using preoperative PSA, grade and clinical stage.[3] Based on these nomograms, a patient with preoperative characteristics like the ones our study group fulfils (stage ≤T1c, PSA < 10, Gleason score ≤ 6), have 81% possibilities to have an organ confine prostate cancer, 18% to have extraprostatic disease and 1% to have seminal vesicle invasion. In our series, 19 patients (16.2%) had capsule penetration and 4 patients (3.4%) had seminal vesicles metastasis. A simple analysis of these statistics is showing us that approximately 1 to 5 or 6 patients that will undergo a RP for a low risk prostate cancer will have AD. If we consider that in the vast majority of these patients, a BNSRP will be performed, the danger for PSM is high. Since this scenario will affect the oncological outcome and the prognosis, some-

one can easily conclude that the present criteria for BNSRP decision-making might not be sufficient and should be supported with new ones.

In the current study, we focused on the presence of advanced prostate cancer and positive margins after RP, irrespective of location, in patients with low risk cancer. Our data showed that extraprostatic disease was found in 16.2% and PSM in 31.6% of the studied cases. The incidence of capsular penetration is consistent with that reported in the literature. However, an increased incidence of positive margins was identified in our series of patients. This may be explained by the fact that not all patients operated by one surgeon and therefore the learning curves are different among them. The aim of the present study was to identify potential association between several factors and the presence of AD in low risk patients in order to assist patients' selection for BNSRP. Our analysis results showed that the presence of malignancy in biopsy cores from both lobes was the only significant parameter, among several clinical and pathological factors, that can predict was associated with both PSM and AD. These data may be used as an auxiliary tool to the standard criteria used so far, like preoperative risk assessment, for the selection of patients who may be candidates for bilateral nerve sparing radical prostatectomy. However, these results should further defined in contemporary series.

The value of positive biopsy laterality in prediction of the surgical outcome has been studied in 2 other studies. Buyyounouski and associates[30] studied1038 patients with clinical T1-T3Nx-0M0 prostate cancer who were treated with radiotherapy alone. In contrast to our results, the authors reported that positive biopsy results from both prostate lobes should not be used for clinical staging, since it can cause stage migration without reflecting a change in outcome. Similar results were revealed by Bulbul and associates[31] who aim to evaluate the accuracy of prostate biopsies in predicting pathological grading and tumor distribution in the final pathological specimen. They reported that 66% of patients with unilateral disease on needle biopsy had bilateral disease on final pathology, but this did not increase their rate of having positive margins. We have to notice that both previous studies were conducted in patients with patients with localized or locally advanced disease without limitations in inclusion criteria. In contrast, we specifically studied patients who were preoperatively stratified as low risk in whom the surgical modifications and oncological expectations are different from these of the rest prostate cancer patients.

Our study has a number of limitations that we should report. Apart of the retrospective nature of the study, the main limitation is that operations have been made by more than one surgeon and these this may significantly affect the outcome concerning the rates of PSM. Furthermore, prostate biopsy procedures were made by several different operators. Therefore, different methods and experience may influence the biopsy results and consequently the presence of unilateral or bilateral disease. The way of PSA density calculation is another limitation. Officially, PSA density is calculated during transrectal ultrasound but due to the retrospective fashion of the study, we used postoperative prostate volume to estimate it. Another significant limitation of the study was the absence of data regarding vascular and/or peri-neural invasion.

CONCLUSIONS

The presence of bilateral prostate cancer, based on the results of pathological analysis of biopsy cores, is a significant predictor for positive surgical margins and advanced disease in patients that are operated for prostate cancer of low risk.

CONFLICT OF INTEREST

None declared.

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