



Controversial predictors of biochemical recurrence after radical prostatectomy: a study from a Latin American (Brazilian) Institution

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ABSTRACT

Purpose: To analyze controversial clinicopathologic predictors of biochemical recurrence after surgery: age, race, tumor extent on surgical specimen, tumor extent on needle biopsy, Gleason score 3 + 4 vs 4 + 3, and amount of extent of extraprostatic extension and positive surgical margins.

Materials and Methods: The needle biopsies and the correspondent surgical specimens were analyzed from 400 patients. Time to recurrence was analyzed with the Kaplan-Meier curves and risk of shorter time to recurrence using Cox univariate and multivariate analysis.

Results: Except for age, race, maximum percentage of cancer per core, and number of cores with cancer, all other variables studied were significantly predictive of time to biochemical recurrence using the Kaplan-Meier curves. In univariate analysis, except for focal extraprostatic extension, age, race, focal positive surgical margins, and maximum extent and percentage of cancer per core, all other variables were significantly predictive of shorter time to recurrence. On multivariate analysis, diffuse positive surgical margins and preoperative PSA were independent predictors.

Conclusions: Young patients and non-whites were not significantly associated with time to biochemical recurrence. The time consuming tumor extent evaluation in surgical specimens seems not to add additional information to other well established predictive findings. The higher predictive value of Gleason score 4 + 3 = 7 vs 3 + 4 = 7 discloses the importance of grade 4 as the predominant pattern. Extent and not simply presence or absent of extraprostatic extension should be informed. Most tumor extent evaluations on needle biopsies are predictive of time to biochemical recurrence, however, maximum percentage of cancer in all cores was the strongest predictor.

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INTRODUCTION

While the overall survival of surgically treated prostate cancer patients remains excellent, nearly

30% of patients treated definitively will have biochemical recurrence (BR), defined as prostate-specific antigen (PSA) ≥ 0.2 ng/ml according to recommendation of the American Urological Association (1).

There are well established clinical and pathological predictors of BR after radical prostatectomy (RP), including preoperative serum PSA, pathological tumor stage, Gleason histological grade, and positive surgical margins (2). However, other features are controversial predictors, which are the aim of our study.

The influence of age in the biological aggressiveness of prostate cancer is controversial (3-6). Some studies suggest that prostatic carcinoma has worse outcome with increasing age while others suggest that young age is an adverse prognostic factor.

Prostate cancer may be biologically more aggressive among Black men though controversial (7-11). The prevalence of prostate cancer in Brazil is higher in Black men compared to White men (12-15). We studied the influence of race in regard to biochemical recurrence after radical prostatectomy.

Extent of tumor on needle biopsy may be useful to predict extent of cancer in RP, surgical margin status, pathological stage, and tumor recurrence. There are several ways to evaluate tumor extent on biopsy: number and percentage of positive cores, total linear length and percentage of carcinoma in all cores, length and percentage of carcinoma in a single core, and others. The controversy is related to which is the best predictor method (16-18).

One of the most controversial aspects of the pathological assessment of RP specimens is the measurement of tumor volume or extent. There is consensus that tumor volume or extent by itself correlates with adverse findings at RP (19). The critical and controversial question concerns whether tumor volume or extent in RP is an independent prognostic parameter for BR after RP once other routinely variables are accounted for (20).

Tumors with a Gleason score of 7 have significantly worse prognosis than those with a Gleason score ≤ 6 . Given the adverse prognosis associated with Gleason pattern 4, one would expect whether a tumor Gleason score $3 + 4 = 7$ or $4 + 3 = 7$ would influence prognosis, however this issue is controversial (21-23).

Extraprostatic extension (EPE) and positive surgical margins (PSM) have prognostic importance in most studies (24-26) and may influence

therapeutic options after surgery. However, the amount of EPE and PSM seems to be more important than a simple report of presence or absence of these pathological findings. An additional concern is the absence of consensus among pathologists how to evaluate the amount of EPE and PSM (27,28).

MATERIALS AND METHODS

This retrospective study was based on needle biopsies and correspondent surgical specimens of 400 consecutive patients submitted to retropubic RP from 1997 to 2011 at an institution located in the southeast region of Brazil. The clinical variables studied included age, race, and preoperative serum PSA; the pathological variables included tumor extent on needle biopsy; and, in surgical specimens tumor extent, Gleason score, seminal vesicle invasion, extraprostatic extension and positive surgical margins. According to race, patients were considered Whites and African-Brazilians. In Brazil African-Brazilians include Mulattos (White and African-Brazilian admixture). Five patients of oriental ancestry were excluded. Some other missing data are not included in the tables. Age was categorized as ≤ 55 years and > 55 years. All other continuous data were categorized by the median value.

Linear carcinoma extent in mm on needle prostatic biopsy was measured using a single Olympus (Olympus Optical Co., Ltd., Tokyo, Japan) micrometer eyepiece with a linear array. In cases of discontinuous foci 1 mm apart, the tumor was considered as continuous and the measure included 1 mm. In discontinuous foci more than 1 mm apart, the final extent was the sum of the measures. Tumor extent on biopsies was evaluated as: number and percentage of cores with carcinoma, total length and percentage of carcinoma in all cores, and maximum length and percentage of cancer per core.

After RP, serum PSA was measured every 3 months during year 1, every 6 months during year 2 and annually thereafter. No patient in this series received radiotherapy or androgen manipulation before or after surgery. Total serum PSA was measured using the previously validated Immulite® PSA kit. Postoperative biochemical recurrence (BR) was considered PSA 0.2 ng/mL or greater according to the American Urological Association

recommendation (1). Patients without BR were censored at last follow-up. The study was approved by our institutional committee of ethics.

Surgical specimens were step sectioned at 3 to 5 mm intervals and embedded in paraffin. A mean of 32 paraffin blocks was processed. Sections (6 μ m) of each block were stained with hematoxylin and eosin. Each transverse section of the prostate was subdivided into 2 anterolateral and 2 posterolateral quadrants. Using the cone method, 8 sections from the bladder neck and 8 from the apex were obtained.

PSM was defined as cancer cells in contact with the inked specimen surface. PSM was considered focal whenever present up to 1 quadrant and/or sections from the bladder neck or apex and diffuse in more than 1 quadrant or sections.

EPE was diagnosed when cancer was seen in adipose tissue, and in case of a desmoplastic response when a protuberance corresponding to tumor extension into periprostatic tissue was observed. EPE was considered focal whenever present up to 1 quadrant of the transverse sections and/or sections from the bladder neck or apex and diffuse in more than 1 quadrant or sections. Seminal vesicle invasion occurred when there was involvement of the muscular coat.

Tumor extent at RP was evaluated by a previously described semiquantitative point count method (29). Briefly, each quadrant of the transverse sections was drawn on paper and contained 8 equidistant points. During microscopic examination of the slides, the tumor area was drawn on the correspondent quadrant on the paper. At the end of examination, the number of positive points represented an estimate of the tumor extent.

Histological tumor grading was performed according to the revised Gleason grading system (30). Gleason score was categorized as ≤ 6 , $3 + 4 = 7$, $4 + 3 = 7$, ≥ 8 . All cases were reviewed by a senior uropathologist (AB).

Statistical analysis

Time to biochemical recurrence (TBR) was analyzed with the Kaplan-Meier product-limit analysis using the log-rank test for comparison between the groups. Univariate and multivariate Cox

stepwise logistic regression models were used to identify significant predictors of shorter TBR. Two-sided P value < 0.05 was considered statistically significant. All statistical analyses were performed using PASW® Statistics 18.0.

RESULTS

Table-1 shows the clinicopathologic characteristics of 400 studied patients submitted to radical prostatectomy.

After RP 128 of the 400 men (32.0%) experienced BR at a mean follow-up of 21 months (median 10, range 3 to 129). Of the remaining patients 253 (63.2%) who were censored remained at risk at a mean follow-up of 53 months (median 48, range 3 to 155), while 19 (4.8%) had no serum PSA data available.

Table-2 shows the Kaplan-Meier product-limit analysis for TBR following RP according to several clinicopathologic characteristics. There was no statistical significant difference for age (log-rank, $p = 0.997$), race (log-rank, $p = 0.547$), maximum percentage of cancer per core (log-rank, $p = 0.313$), number of cores with cancer (log-rank, $p = 0.138$), absent vs focal EPE (log-rank, $p = 0.892$), and absent vs focal PSM (log-rank, $p = 0.069$).

Percentage extent in mm of cancer in all cores was the strongest predictor of TBR (log-rank, $p = 0.001$) (Figure-1). Tumor extent of tumor in RP evaluated as positive points was significantly associated with TBR (log-rank, $p = 0.017$) (Figure-2). Gleason score in RP categorized as ≤ 6 , $3 + 4 = 7$, $4 + 3 = 7$, and ≥ 8 was significantly associated with TBR (Figure-3). There is almost an overlap comparing the curves of Gleason score $4 + 3 = 7$ and Gleason score ≥ 8 . Diffuse EPE (log-rank, $p < 0.001$) and diffuse PSM (log-rank, $p < 0.001$) were significantly associated with shorter TBR.

Table-3 shows the Cox univariate and multivariate proportional hazard analysis of several clinicopathologic characteristics predicting TBR after RP. Except for focal EPE ($p = 0.893$), age ($p = 0.796$), race ($p = 0.550$), focal PSM ($p = 0.445$), maximum extent of cancer per core ($p = 0.133$) and maximum percentage extent of cancer per core ($p = 0.065$), all other characteristics had a significantly risk for shorter TBR.

For multivariate analysis, we included only the statistically significant characteristics of univariate analysis using the backward stepwise logistic regression method. For tumor extent evaluation on needle biopsy, we included the strongest predictor (percentage of cancer extent in all cores). Only diffuse PSM ($p < 0.001$) and preoperative PSA ($p = 0.034$) were independent predictors of shorter TBR. Seminal vesicle invasion showed a trend toward significance ($p = 0.060$).

DISCUSSION

Age

The influence of age in the biological aggressiveness of prostate cancer is controversial. Carter et al. (3) and Herold et al. (4) suggest that prostatic carcinoma is higher grade and has worse outcome with increasing age. However, the data are conflicting on this issue. Bauer et al. (5) and Catalona and Smith (6) have not found age to be related to outcome. Parker et al. (31) in a meta-analysis of 34 studies which included a total of 27551 patients concluded that evidence suggests that young age was an adverse prognostic factor in some series of radiation therapy before the advent of PSA assays, when men typically presented clinically with locally advanced disease, but that age has no significant prognostic effect in contemporary series of localized prostate cancer. In our study, TBR was not statistically different comparing patients ≤ 55 -year-old vs > 55 -year-old.

Race

Prostate cancer may be biologically more aggressive among Black men though controversial (7-9). In a study by Cross et al. (10), even though African-American men presented at a younger age and with more advanced disease compared with White men with prostate cancer, PSA outcome after RP when controlled for known clinical predictive factors was not statistically different. Freedland et al. (11) described no differences between Black and White men in the preoperative clinical factors or the pathologic features of the RP specimens and race was not an independent predictor of biochemical recurrence.

The existence of racial differences in prostate carcinoma treatment outcomes remains controversial and although Latino patients/Hispanic race were included in one report (32), our study is unique dealing with this issue in a Latin American (Brazilian) country. The frequency of non-Whites in our study (19.7%) is similar to this population in the southeast region of Brazil. The results of our cohort of patients showed that race is not significantly associated with TBR following surgery.

In contrast to the bifurcated United States model, where Blacks and Whites are clearly separate groups, with Blacks defined as those with any African ancestry, racial classification in Brazil is far more complex, ambiguous, and fluid. Non-Whites in Brazil includes an intermediate Brown (pardo) category along a white-to-black color continuum, often used as a proxy for mulattos or persons with White and Black admixture (14).

Tumor extent in radical prostatectomy

One of the most controversial aspects of the pathological assessment of radical prostatectomy specimens is the measurement of tumor volume or extent. Some institutions have accurately calculated the tumor volume through computer-assisted image analysis systems (33). As this method is not feasible for routine clinical practice, there are alternative simpler means for measuring tumor extent. We applied a practical method for estimating tumor extent in RP, which can be used by any general pathologist in the laboratory (29).

There is consensus that tumor volume or extent by itself correlates with adverse findings at RP, such as Gleason score, clinicopathological stage, seminal vesicle invasion, extraprostatic extension and margins of resection (19). The critical and controversial question concerns whether tumor volume is an independent prognostic parameter once other routinely assessed variables are accounted for (20). In our study, tumor extent in radical prostatectomy was significantly associated with TBR in univariate analysis ($p = 0.004$), however in multivariate analysis was not significant ($p = 0.633$). The result favors that this time consuming report in surgical specimens seems not to add additional information to other well established predictive findings.

Table 1 - Clinicopathologic characteristics of 400 study patients submitted to radical prostatectomy for prostate cancer. SD, standard deviation.

Characteristic	n (%)
Age (years)	
mean ± SD	63 ± 6.62
median	64
range	43 - 76
Race	
Whites	317 (80.3)
Non-whites	78 (19.7)
Preoperative PSA (ng/mL)	
mean ± SD	9.84 ± 6.80
median	8.00
range	0.28-51
Number of cores	
mean ± SD	10 ± 3.71
median	11
range	2-20
Number of cores with cancer	
mean ± SD	3 ± 2.03
median	2
range	1 - 13
Percentage of cores with cancer	
mean ± SD	36.15 ± 24.44
median	31
range	5-100
Extent of cancer in all cores	
mean ± SD	9 ± 9.49
median	6
range	1 - 62
Percentage of cancer in all cores	

continuation

mean ± SD	18.5 ± 18.28
median	12
range	0.4 - 100

Maximum extent of cancer per core

mean ± SD	4 ± 3.31
median	3.5
range	1 - 20

Maximum percentage of cancer per core

mean ± SD	51.58 ± 30.14
median	47
range	1 - 100

Gleason score in RP

≤ 6	134 (33.8)
3 + 4 = 7	186 (46.9)
4 + 3 = 7	53 (13.4)
≥ 8	24 (6.0)

Tumor extent in RP (positive points)

mean ± SD	35.80
median	27
range	1 - 225

Seminal vesicle invasion

absent	353 (89.6)
present	41 (10.4)

Extraprostatic extension

absent	254 (64.0)
focal	40 (10.1)
diffuse	103 (25.9)

Positive surgical margins

absent	213 (53.5)
focal	49 (12.3)
diffuse	136 (34.2)

Table 2 - Kaplan-Meier product-limit analysis for time to biochemical recurrence following radical prostatectomy according to several clinicopathologic characteristics.

Characteristic	X ²	Log-rank, p
Age (years)		
≤ 55 vs > 55	< 0.001	0.997
Race		
Whites vs non-Whites	0.363	0.547
Maximum percentage of cancer per core		
≤ 47% vs. > 47%	1.017	0.313
Number of cores with cancer		
≤ 2 vs. > 2	2.195	0.138
Tumor extent in RP		
≤ 27 positive points vs > 27 positive points	5.726	0.017
Maximum extent of cancer per core		
≤ 3.5 mm vs. > 3.5 mm	5.745	0.017
Percentage of cores with cancer		
≤ 31% vs. > 31%	5.768	0.016
Extent of cancer in all cores		
≤ 6 mm vs. > 6 mm	7.424	0.006
Percentage of cancer in all cores		
≤ 12% vs > 12%	10.785	0.001
Extraprostatic extension		
absent vs diffuse	12.430	< 0.001
absent vs focal	0.018	0.892

c o n t i n u a t i o n

Gleason score in RP

≤ 6 vs 3 + 4 = 7 vs 4 + 3 = 7 vs ≥ 8 13.477 0.004

Preoperative PSA (ng/mL)

≤ 10 vs >10 25.800 < 0.001

Seminal vesicle invasion

absent vs present 26.071 < 0.001

Positive surgical margins

absent vs focal vs. diffuse 33.562 < 0.001

absent vs focal 5.350 0.069

Figure 1 - Kaplan-Meier product-limit analysis shows time to PSA biochemical progression-free outcome by the median value of percentage of cancer extent in mm in all cores. *Cum*, cumulative.

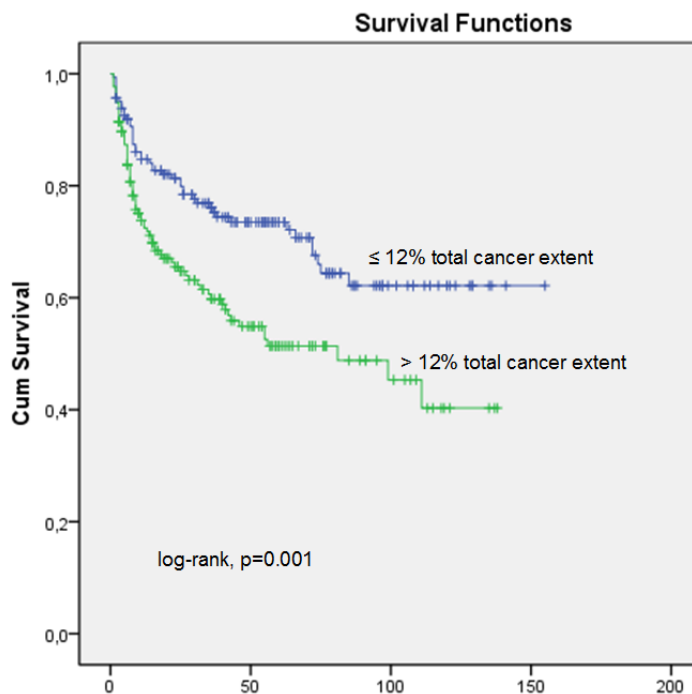


Figure 2 - Kaplan-Meier product-limit analysis shows time to PSA biochemical progression-free outcome by the median value of tumor extent evaluated as positive points in surgical specimens. *Cum*, cumulative.

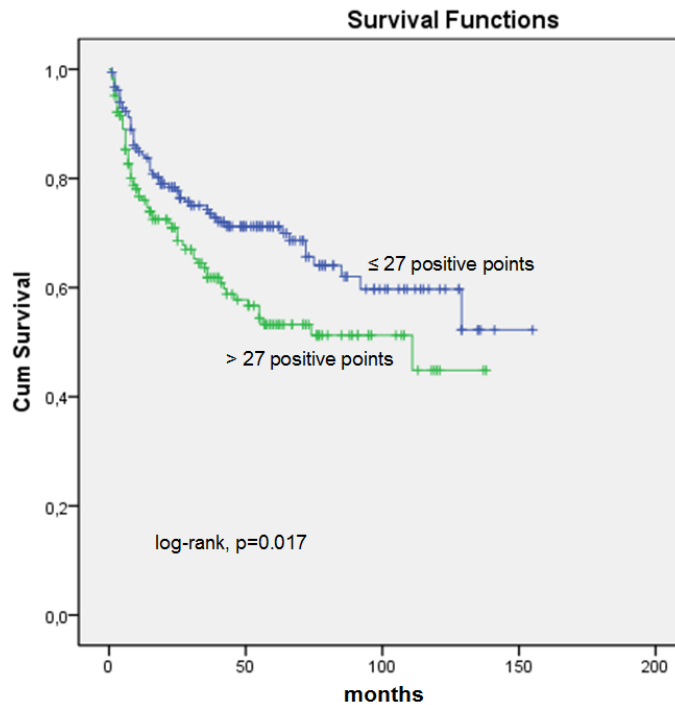


Figure 3 - Kaplan-Meier product-limit analysis shows time to PSA biochemical progression-free outcome by Gleason score ≤ 6 , $3+4=7$, $4+3=7$, and ≥ 8 in surgical specimens. *Cum*, cumulative.

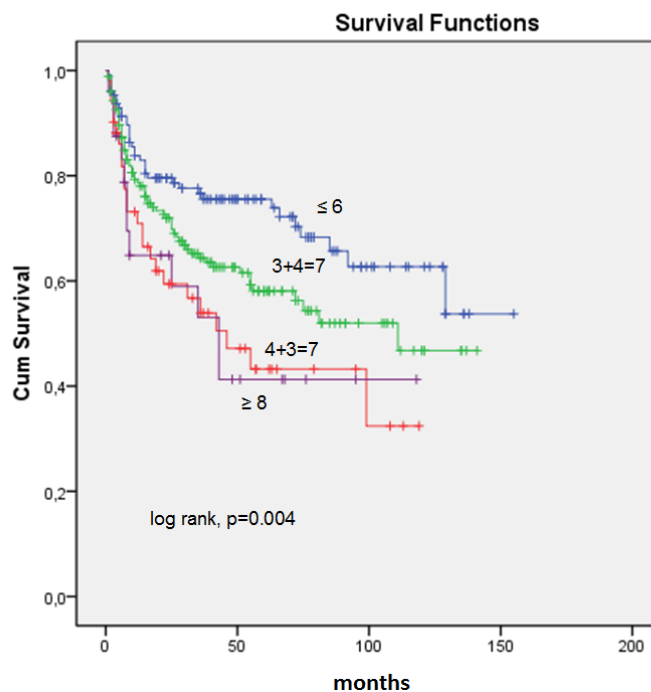


Table 3 - Cox univariate and multivariate proportional hazard analysis of several clinicopathologic characteristics predicting shorter time to biochemical recurrence following radical prostatectomy. CI, confidence interval.

Characteristic	Hazard ratio (95% CI)	Wald test	p
Univariate analysis			
Focal EPE	1.040 (0.588 - 1.841)	0.018	0.893
Age	0.997 (0.972 - 1.022)	0.067	0.796
Race	0.876 (0.567 - 1.352)	0.358	0.550
Focal PSM	1.258 (0.698 - 2.270)	0.583	0.445
Maximum extent of cancer per core	1.035 (0.990 - 1.082)	2.259	0.133
Maximum percentage of cancer per core	1.006 (1.000 - 1.011)	3.417	0.065
Extent of cancer in all cores	1.018 (1.003 - 1.034)	5.323	0.021
Number of cores with cancer	1.092 (1.014 - 1.176)	5.395	0.020
Percentage of cores with cancer	1.009 (1.002 - 1.016)	7.089	0.008
Tumor extent in RP	1.006 (1.002 - 1.011)	8.299	0.004
Gleason score in RP	1.394 (1.130 - 1.721)	9.581	0.002
Percentage of cancer in all cores	1.014 (1.005 - 1.022)	10.381	0.001
Diffuse EPE	1.375 (1.147 - 1.649)	11.843	0.001
Preoperative PSA	1.042 (1.025 - 1.060)	22.672	< 0.001
Seminal vesicle invasion	2.888 (1.880 - 4.437)	23.431	< 0.001
Diffuse PSM	1.651 (1.382 - 1.972)	30.523	< 0.001
Multivariate analysis			
Gleason score in RP	1.143 (0.653-2.001)	0.220	0.639
Tumor extent in RP	0.882 (0.526-1.478)	0.228	0.633
Diffuse EPE	0.874 (0.672-1.137)	1.011	0.315
Percentage of cancer in all cores	1.293 (0.822-2.035)	1.238	0.266
Seminal vesicle invasion	1.730 (0.978-3.061)	3.544	0.060
Preoperative PSA	1.601 (1.035-2.474)	4.477	0.034
Diffuse PSM	1.734 (1.371-2.192)	21.128	< 0.001

Gleason score in radical prostatectomy

Tumors with a Gleason score of 7 have significantly worse prognosis than those with a Gleason score ≤ 6 . Given the adverse prognosis associated with Gleason pattern 4, one would expect whether a tumor Gleason score $3 + 4 = 7$ or $4 + 3 = 7$ would influence prognosis. No significant survival advantage was reported for Gleason score $3 + 4 = 7$ over $4 + 3 = 7$ by Oefelein et al. (21). Other investigators have shown that Gleason score $4 + 3 = 7$ has a worse prognosis than Gleason score $3 + 4 = 7$ (18,19). Due to this controversy, the prognostic Gleason grouping according to score may be either ≤ 6 , 7 , ≥ 8 or ≤ 6 , $3 + 4 = 7$, $4 + 3 = 7$, ≥ 8 . In our cohort of patients the Kaplan-Meier curve showed that the Gleason score $4 + 3 = 7$ behaved similarly to score ≥ 8 and different to score $3 + 4 = 7$. This result discloses the importance of grade 4 as the predominant pattern and favors a 4 score prognostic grouping: ≤ 6 , $3 + 4 = 7$, $4 + 3 = 7$, and ≥ 8 . Gleason score in our study was significantly predictive of TBR in univariate analysis but not in multivariate analysis probably due to fewer cases in the prognostic groups $4 + 3 = 7$ and ≥ 8 . Another limitation could be the relatively short mean follow-up time.

Extraprostatic extension and positive surgical margins

Extraprostatic extension and positive surgical margins have prognostic importance and may influence therapeutic options after surgery. However, the amount of EPE and PSM seems to be more important than a simple report of presence or absence of these pathological findings (24-26).

During the International Society of Urological Pathology (ISUP) consensus conference on handling and staging of radical prostatectomy specimens held in Boston during the 98th meeting of the United States and Canadian Academy of Pathology (USCAP), no consensus could be reached as to how evaluate extent of EPE and PSM (27,28). In this study we evaluated the influence of focal and diffuse EPE and PSM on TBR using a simple method for EPE and PSM extent quantitation that can be used in the daily practice of all pathologists who step section and totally process the surgical specimen. Considering that in the 2009 version of

the TNM Classification of Malignant Tumors microscopic involvement of the bladder neck is pT3a, in our study this finding was included as EPE.

Our study is in accordance with authors that consider extent of EPE or PSM an important information in the pathology report. Diffuse EPE or PSM were significantly associated with shorter time of TBR in univariate analysis, however, only diffuse PSM was significantly associated with TBR in univariate ($p < 0.001$) and multivariate analysis ($p < 0.001$). Diffuse PSM was the strongest and an independent predictor of TBR in our cohort of patients. The incidence of PSM in the literature ranges from 16% to 50% (34). In our study the incidence was 46.5%. One of the largest potential sources of discrepancy for incidence of PSM is the different methods used to process the radical prostatectomy specimens. It is also worth mention that positive surgical margins result of surgical factors more than biology of disease.

Tumor extent on needle prostatic biopsies

Recent efforts have focused on incorporating prostate needle biopsy measurements as an adjunct to improve pretreatment risk stratification (35-38). However, it is controversial which is the best predictor method (16-18). Bismar et al. (18) studied the prediction of pathologic stage in a screening population of multiple measures of carcinoma on prostate needle biopsy tissue. In univariate analysis all measures were significantly associated with pathologic stage $> T2$ but in multivariate analysis the percentage of positive cores was the strongest predictor.

Brimo's et al. (16) study is the only one that compared different methods of measurement of carcinoma on prostate needle biopsy. In univariate analysis, the percentage of cores with carcinoma was found to be the pathological preoperative variable that was most significantly associated with pathologic stage $> pT2$. In multivariate analysis, the greatest length and percentage of cancer in a single core, and the total percentage of cancer in all cores were most significant. Length and percentage of carcinoma in all cores, and percentage of number of cores with carcinoma were significantly associated to biochemical recurrence in univariate analysis. Multivariate analysis could not be conducted.

In our study, except for maximum percentage of cancer per core and number of cores with cancer all other methods were significantly predictive of TBR using the curves of Kaplan-Meier. Using the Cox univariate analysis, all measures were statistically predictive of risk to TBR except maximum extent and percentage of cancer per core. The strongest predictor was percentage of cancer in all cores, however was not an independent predictor of shorter time of TBR in multivariate analysis.

All methods for measurement are simple and may be done in the daily practice of the surgical pathologist. However, they are not equivalent in application because measuring with an ocular micrometer foci of carcinoma can be time consuming. Total number and percentage of positive cores are the easiest way of evaluation accessible to all pathologists, and in our study were statistically significant in univariate analysis.

In summary, age and race were not significantly associated with TBR after surgery, however other more powered studies could show significance. Tumor extent evaluation in the surgical specimen was predictive of TBR in univariate analysis but not in multivariate analysis favoring that this time consuming report does not add additional information to other well established predictive findings. The higher predictive value of Gleason score $4 + 3 = 7$ vs $3 + 4 = 7$ disclosed the importance of grade 4 as the predominant pattern and favors a 4 score prognostic grouping: ≤ 6 , $3 + 4 = 7$, $4 + 3 = 7$, and ≥ 8 . Extent of EPE or PSM is an important information in the pathology report. Diffuse EPE or PSM were significantly associated with TBR in univariate analysis and diffuse PSM was independent and the strongest predictor of shorter time to BR in multivariate analysis. Most tumor extent evaluations on needle biopsies were predictive of TBR, however, maximum percentage of cancer in all cores was the strongest predictor. While shedding light to important and controversial predictors of biochemical recurrence after radical prostatectomy among Latin Americans, limitations of this study are the relatively short follow-up and the retrospective design, even in a prospectively collected database.

ABBREVIATIONS

PSA = prostate specific antigen;
SD = standard deviation;
CI = confidence interval;
RP = radical prostatectomy;
BR = biochemical recurrence;
TBR = time to biochemical recurrence;
EPE = extraprostatic extension;
PSM = positive surgical margin

CONFLICT OF INTEREST

None declared.

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