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Biochemical recurrence risk factors in surgically treated high and very high-risk prostate tumors

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Introduction High and very high-risk prostate cancers are tumors that display great variation in their progression, making their behaviour and consequent prognosis difficult to predict. We analyse preoperative and postoperative risk factors that could influence biochemical recurrence of these tumors.

Material and methods We carried out univariate and multivariate analyses in an attempt to establish statistically significant preoperative (age, rectal examination, PSA, biopsy Gleason score, uni/bilateral tumor, affected cylinder percentage) and postoperative (pT stage, pN lymph node affectation, Gleason score, positive surgical margins, percentage of tumor affectation, perineural infiltration) risk factors, as well as their relationship with biochemical recurrence (PSA >0.2 ng/mL).

Results We analysed 276 patients with high and very high-risk prostate cancer that were treated with laparoscopic radical prostatectomy (LRP) between 2003-2007, with a mean follow-up of 84 months. Incidence of biochemical recurrence is 37.3%. Preoperative factors with the greatest impact on recurrence are suspicious rectal exam (OR 2.2) and the bilateralism of the tumor in the biopsy (OR 1.8). Among the postoperative factors, the presence of a LRP positive surgical margins (OR 3.4) showed the greatest impact, followed by the first grade of the Gleason score (OR 3.3).

Conclusions The factor with the greatest influence on biochemical recurrence when it comes to surgery and high and very high-risk prostate cancer is the presence of a positive margin, followed by the Gleason score. Preoperative factors (PSA, biopsy Gleason score, rectal examination, number of affected cylinders) offered no guidance concerning the incidence of BCR.

Key Words: biochemical recurrence ‹› risk factors ‹› prostate cancer

INTRODUCTION

Prostate cancer is a malignant tumor that is more prevalent in developed countries, and it is the third leading cause of death by cancer in men in the European Union [1, 2]. Traditionally considered as a tumor that develops over the long term, its high and very high-risk variants have been shown to behave in a very variable manner [3, 4], with an irregular prognosis, which normally leads to the need for a multiple treatment approach to achieve appropriate cancer control [5, 6].

This situation has spawned numerous works attempting to analyse the different preoperative (PSA, digital rectal examination, age, prostate Gleason score, uni/bilateral tumor involvement, percentage of affected cylinder, etc.) or postoperative (positive surgical margins, final Gleason score, disease stage, tumor volume etc.) factors that could influence such variable behaviour and help us to derive the best treatment for each case [7–10]. Some of the studies conclude that the presence of positive surgical margins is an independent predictive factor in the development of the BR, but does not affect the specific cancer mortality [11].

In this study, we analyse the different preoperative and postoperative risk factors that could influence the biochemical recurrence (BCR)

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of surgically treated, high and very high-risk, prostate tumors.

MATERIAL AND METHODS

We retrospectively analysed the clinical records of patients who underwent laparoscopic radical prostatectomy (LRP) from 2003-2007, who fulfilled one of the criteria for high and very high-risk tumors according to the 2010 European Association of Urology Clinical Guidelines (PSA >20, T3a stage or higher, Gleason score 8-10 or pN1). Patients who had received any type of neoadjuvant treatment (11 patients) were excluded, as well as patients who had not been followed up for at least 24 months (21 patients). We collected the following preoperative data: age, suspicious digital rectal exam (induration, suspicious nodule), preoperative PSA, biopsy Gleason score, percentage of positive cylinder, tumor laterality and the likelihood of an organ-confined tumor, or lymph node affectation according to the modified Partin nomogram [12]. The postoperative data are disease stage (TNM, UICC 2002), the radical prostatectomy specimen Gleason score, lymph node affectation and positive node count, perineural infiltration, prostate volume, percentage of tumor affectation positive margins (presence of tumor cells in contact with the India ink), BCR (PSA >0.20 ng/mL) and the time of appearance after LRP.

Cases lacking data on the length of the margin or the Gleason score of the surgical margins were not analysed.

The patients were followed up every 3 months during the first year, evaluated for PSA concentration at each consultation; thereafter, every 6 months until a total of 5 years, and then annually, if biochemical progression had not occured.

The data was processed using a Microsoft Excel database, imported into SPSS version 11.5 program for statistical interpretation.

The mean and the standard deviation were used to describe the continuous quantitative variables. The qualitative variables were described using absolute frequencies and relative frequencies expressed as percentages.

The continuous quantitative variables were mainly compared for the individual groups by parametric tests, using the Student's t test when two groups were compared, or the ANOVA test when three or more groups required analysis. When the work involved sample sizes under 30 individuals, due to stratification or sub-sample selection, statistical significance in this type of analysis was obtained using either the Kruskal-Wallis or Mann-Whitney U non-parametric tests.

The analysis of qualitative variable frequencies was undertaken using the χ^2 test or Fisher's exact test when required (if N <20, or if any values in the expected table of values was under 5). When the χ^2 test was used, the Yates' correction was applied in all cases. The multivariate study was carried out using a forward stepwise Logistical Regression model. The goodness of fit was evaluated using the area under the curve ROC with the confidence interval set at 95%.

RESULTS

We analysed the clinical reports of 276 patients who underwent LRP and fulfilled the previously established characteristics for high and very high-risk tumors over a total period of 5 years. The average age of these patients was 64 years (46-76) and the mean preoperative PSA was 9.3 ng/mL (2.2-38.8). The rectal exam was suspicious in 93 cases (33%) and the biopsy Gleason score was 8 in 18 cases (6.5%). According to the modified Partin tables, 51% of patients had preoperative organ-confined disease, and were free of lymph node affectation. The mean follow-up within the set is 84 months (23-123). Neurovascular preservation was performed on 87 cases (31.5%) in which a high-grade tumor at the time was not suspected.

The anatomopathological analysis of the LRP specimens showed that 8% (22 cases) had stage pT2b, 74% (204) pT3a, 17% (47) pT3b, and 1% (3) pT4. The most common Gleason score for the specimen was 4+3 (41% of cases), and was equal to, or above 8 in 54 cases (19.6%). Perineural infiltration was found in 83% of cases (230 occasions). Table 1 shows the relationship between tumor stage and the Gleason score for the LRP specimen with the biochemical recurrence rates.

Guided by the Partin nomogram, lymphadenectomy was performed on 66 cases (24%), with tumor affectation in 6 cases (9%), 3 of which presented affectation in 2 or more lymph nodes.

The overall positive surgical margins were observed in 47.8% (132 patients). Stages pT3b and pT4 were the most frequent (60% and 66%, respectively).

Biochemical recurrence (PSA >0.2 ng/dL) appears in 37.3% of cases (103 patients).

We found statistical significance ($p < 0.05$) in the PSA prior to the operation. Patients with BCR had a mean PSA of 10.5 ng/mL (9.3–11.7) compared to a mean PSA of 8.7 ng/mL (7.7–9.6) for those who did not relapse. The digital rectal examination also showed a statistically significant difference ($p < 0.05$) for those with a suspicious exam; their recurrence rate was 52.7% compared to 30% for those with no suspicious exam. When we analysed the percentage of affected cylinders, if over 45%, the recurrence

rate was also statistically significant 35% *vs.* 25% (p <0.05).
Bilateral tumor in the biopsies showed statistical significance for BCR (48% *vs.* 31%, p<0.05).

Table 1. *Postoperative data. Biochemical recurrence*

	Patients n (%)	BCR n (%)
pT2b	22 (8)	8 (37)
pT3a	204 (74)	65 (32)
pT3b	47 (17)	28 (60)
pT4	3 (1)	2 (66)
Gleason 3+3	27 (10)	6 (22)
Gleason 3+4	80 (29)	17 (21)
Gleason 4+3	115 (41)	48 (41)
Gleason ≥8	54 (20)	32 (60)
(+) Margins overall	132 (47.8)	68 (51)
pT2b (+) margins	9 (41)	3 (33)
pT3a (+) margins	93 (45.8)	41 (44)
pT3b (+) margins	28 (60)	23 (82)
pT4 (+) margins	2 (66)	1 (50)
pN0	58 (90)	21 (36)
pN1	6 (10)	5 (83)
pNx	210 (76)	77 (36)

Table 2. *Preoperative factor multivariate analysis for the BCR variable*

	Beta	SEB	OR	CI 95%	P
DRE	0.795	0.274	2.2	1.29-3.7	0.004
Gleason C2	0.596	0.231	1.81	1.15-2.85	0.01
Uni/bilateral	0.622	0.271	1.86	1.09-3.16	0.022
Constant	-3.047	0.792			0.047

DRE – digital rectal examination, SEB – standard error of Beta, OR – odds ratio, CI – confidence interval of the OR, Gleason C2 – second grade of the Gleason score

Table 3. *Postoperative factor multivariate analysis for the BCR variable*

	Beta	SEB	OR	CI 95%	P
+ Margins	1.236	0.283	3.4	1.97-5.99	0.001
Gleason C1	1.210	0.283	3.3	1.92-5.84	0.001
Gleason C2	0.472	0.206	1.6	1.07-2.4	0.02
Constant	-7.512	1.490			0.01

SEB – standard error of Beta, OR – odds ratio, CI – confidence interval of the OR Gleason C1 – first grade of the Gleason score, Gleason C2 – second grade of the Gleason score

Univariate analysis of the post LRP anatomopathological factors involved in BCR showed that the higher the disease stage is, the higher risk of recurrence (p <0.05), with up to 60% BCR in the pT3b stage, compared to 32% in the pT3a stage. There were only 3 pT4 cases, with a recurrence rate of 66%. The Gleason score for the specimen had a statistically significant relationship with BCR (p <0.01). Tumors with Gleason scores ≥8 relapsed in 59.3% patients (32 cases), compared to 32% BCR for those with a score under 8. The perineural infiltration did not affect BCR (36% *vs.* 42%). The presence of affected lymph nodes after lymphadenectomy leads to higher risk of BCR (36% *vs.* 83%, p <0.01), particularly when the number of affected lymph nodes was greater or equal to 2 (66% *vs.* 100%, p <0.05). There was a statistically significant relationship between the positive margins and BCR, 24.5% *vs.* 51.5% (p <0.001). On examination of BCR distribution by margins and pT stage (Table 1), pT3b and pT4 were the stages with a higher rate of positive margins (60 and 66% respectively), and they also showed the highest BCR rate (82 and 50% respectively, p <0.05).
When we carried out a multivariate study using logistical regression of the statistically significant preoperative factors for BCR, we found that suspicious digital rectal examination (DRE) was the predictive factor with the highest odds ratio (OR), with a 2.2 OR and p <0.004, followed by the uni/bilateralism of the biopsy tumor (1.86 OR, p <0.022) and the second grade of the Gleason score (1.81 OR, p <0.01) (Table 2). When the discriminatory capacity of these three factors for variable biochemical recurrence was analysed, they did not perform particularly well, with an area under the curve ROC of 0.67 (0.607-0.741 CI 95%).
In the multivariate analysis using logistical regression of the postoperative factors that showed statistical significance in the correlation with biochemical recurrence, the highest OR occured with the presence of positive surgical margins (3.4 OR), followed by the first Gleason grade value (3.3 OR), and finally the second Gleason grade value (1.6 OR) (Table 3). In this second group of variables studied, the discriminatory capacity of the relapse was higher than the preoperative variables, with an area under the curve ROC of 0.75 (0.698-0.818 CI 95%).

DISCUSSION

High and very high-risk prostate cancers currently comprise around 15-20% of diagnosed cases [7, 13]. This is a tumor that displays more variable and aggressive behaviour than the norm. For this reason, we believe there is an increased need to analyse the

possible factors that may lead to poor cancer control, which could guide us towards a more appropriate treatment and follow-up.

Biochemical recurrence from evaluation of PSA can be considered as the first indication of a lack of complete cancer control, although it does not necessarily affect the specific cancer mortality of the patient, as indicated by a large body of literature [14, 15, 16]. Several PSA levels can also be used to define the BCR [17].

From univariate analysis of preoperative factors obtained at diagnosis, which often form part of the most regularly used nomograms, we conclude that the following are significant predictive factors of BCR: PSA on diagnosis, suspicious digital rectal examination, the Gleason score, the percentage of affected cylinders, and bilateral tumors on biopsy. On carrying out a multivariate analysis using logistical regression, suspicious digital rectal examination is found to have the greatest effect on BCR, with an OR of 2.2. Initially, it may appear odd that something as subjective as the digital rectal examination, which can only discriminate 33% of the tumors, correlates with the relapse of the PSA. However, it is a fact that in the disease stage analysis, the highest number of suspicious rectal examinations (49%) was detected for pT3b, and this was also the stage with the highest incidence of BCR, at 60%. The fact is that pT4 stage shows a higher recurrence, in 66% of the cases, but only 3 patients were included in the study. We can conclude from this data that although the rectal examination is not particularly reliable for the diagnosis of the disease in the earlier stages, a more advanced level of the disease is usually described (disease stage) if cancer is suspected, and there is consequently a closer correlation with BCR.

The next preoperative element with a strong impact on BCR in the multivariate study is the bilateralism of the biopsy tumor, ahead of the Gleason score (OR 1.86 *vs.* 1.81). The bilateralism of the tumor can be taken as an indicator of tumor volume and its role in recurrence is controversial. There are studies that consider it a significant risk factor for recurrence [18], whereas others that reject that possibility [19]. In our study, the three factors that could be related to tumor volume (tumour bilateralism in the biopsy, number of affected cylinders, and the tumor volume in the prostatectomy specimen) were found to be statistically significant for BCR in the univariate analysis, with only bilateralism remaining in the multivariate study. As has already been indicated by other investigations, there is no relationship between tumor volume and BCR for low Gleason score tumors [19], which fits our results, given that we only analysed high-risk tumors.

Notwithstanding, the statistical study indicates that the preoperative variables group is a poor predictor of BCR, given that the receiver operating characteristic (ROC) curves and the area under the curves are below 70%, which is equivalent to low discriminatory capacity.

With respect to postoperative factors, several arose in the univariate study with significant association to BCR: disease stage, the Gleason score for the LRP specimen, lymph node affectation, tumor volume, and the presence of positive surgical margins. After the multivariate regression analysis, positive surgical margin was the independent factor with greatest impact on BCR (3.4 OR, 1.97-5.99 CI 95%). This fact coincides with the results of most of the work in the literature [20-23]. A higher OR value does occur in our case, but it is likely to be due to our analysis involving high and very high-risk tumors. Budäus et al. [24] studied 4490 patients and compared disease stages. On studying a lower disease stage with a positive margin compared to the following higher stage with a negative margin, they reach the conclusion that the presence of the positive margin has a greater effect on BCR rate than the disease stage, with the effect mainly noted in stage pT2. We have also carried out this analysis, but we did not find this trend (33% risk of BCR in stage pT2b positive margin *vs.* 21.8% risk of BCR in stage pT3a positive margin). We consider it a derivative of our smaller sample set. In the multivariate analysis of the postoperative factors, positive surgical margin is still an independent factor, and in fact, shows the strongest relationship with the disease stage. The other independent factors for recurrence are the two Gleason score values, with the first grade clearly more significant than the second (OR 3.3 *vs.* 1.6). This result also concurs with the literature, which show the total Gleason score figures as an independent predictive factor for BCR [25, 26].

Compared to the preoperative factors, we find a higher discriminatory capacity for BCR in the postoperative factors, specifically in the positive surgical margins and the total Gleason score, with an area under the curve ROC of over 70% (0.75 CI 95% 0.698–0.818).

We believe there are several limitations in our work: (1) it is a retrospective study, (2) the small sample size (only 3 cases in the pT4 stage) makes certain comparisons and interpretations of the statistical results difficult, (3) The limited number of lymphadenectomies, undertaken on very selective patients (possibly given because the cases were from the period 2003–2007 and mainly decided by surgeon criteria), implying a large number of patients with a pNx lymph node status, and (4) the lack of information

about the size and multifocal nature of the positive margins.
Currently, there are studies that analyse the importance of the size of the margin, and also the Gleason score at that point, although they do not appear conclusive for the time being [27, 28].
It is our understanding that more extended follow-up (over 10 years) may provide different results, or stronger support for these outcomes, given that the BCR is the main variable under study.

CONCLUSIONS

Patients with high or very high-risk prostate cancer (stage T3a or higher, Gleason 8-10 or PSA >20 ng/mL, pN1) may display very variable tumor behaviour, but they are generally at high risk of biochemical progression. We conclude that the preoperative factors (PSA, biopsy Gleason score, rectal examination, number of affected cylinders) offer no satisfying guidance as to the incidence of BCR. A clear correlation between BCR and postoperative factors does exist, however, specifically the presence of positive surgical margins or the Gleason score (mainly the first grade), and to a lesser extent, the disease stage. The presence of these factors may lead to the suspicion of a higher risk of biochemical recurrence, and therefore, follow-up can be personalised for those cases.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clinic. 2011; 61: 69-90.
2. Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol. 2007; 18: 581-592.
3. Walz J, Joniau S, Chun FK, et al. Pathological results and rates of treatment failure in high risk prostate cancer patients after radical prostatectomy. BJU Int. 2011; 107: 765-770.
4. Shikanov S, Marchetti P, Desai V, et al. Short (≤1 mm) positive surgical margin and risk of biochemical recurrence after radical prostatectomy. BJU Int. 2013; 111: 559-563.
5. Cao D, Kibel AS, Gao F, Tao Y, Humphrey PA. The Gleason score of tumour at the margin in radical prostatectomy is predictive of biochemical recurrence. Am J Surg Pathol 2010; 34: 994-1001.
6. Savdie R, Horvath LG. Benito RP et al. High Gleason grade carcinoma at a positive surgical margin predicts biochemical failure after radical prostatectomy and may guide adjuvant radiotherapy. BJU Int. 2012; 109: 1794-1800.
7. Briganti A, Joniau S, Gontero P, et al. Identifying the Best Candidate for Radical Prostatectomy Among Patients with High-Risk Prostate Cancer. Eur Urol. 2012; 61: 584-592.
8. Ploussard G, Agamy MA, Alenda O, et al. Impact of positive surgical margins on prostate-specific antigen failure after radical prostatectomy in adjuvant treatment-naive patients. BJU Int. 2011; 107: 1748-1754.
9. Karakiewicz PI, Eastham JA, Graefen M, et al. Prognostic impact ofpositive surgical margins in surgically treated prostate cancer: multi-institutional assessment of 5831 patients. Urology. 2005; 66: 1245-1250.
10. Swindle P, Eastham JA, Ohori M, et al. Do margins matter? the prognostic significance of positive surgical margins in radical prostatectomy specimens. J Urol. 2005; 174: 903-907.
11. Joniau S, Tosco L, Briganti A, et al. Results of surgery for high risk prostate cáncer. Curr Opin Urol. 2013. 23: 342-348.
12. Partin AW, Mangold LA, Lamm DM, Walsh PC, Epstein JI, Pearson JD. Con-temporary update of prostate cancer staging nomograms (Partin Tables) for the new millennium. Urology. 2001; 58: 843-848.
13. Cooperberg MR, Broering JM, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. J Clin Oncol. 2010; 28: 1117-1123.
14. Collette L. Prostate-specific antigen (PSA) as a surrogate end point for survival in prostate cancer clinical trials. Eur Urol. 2008; 53: 6.
15. Stephenson AJ, Kattan MW, Eastham JA, et al. Defining biochemical recurrence of prostate cancer after radical prostatectomy: a proposal for a standardized definition. J Clin Oncol. 2006; 24: 3973-3978.
16. D'Amico AV, Moul J, Carroll PR, Sun L, Lubeck D, Chen MH. Surrogate end point for prostate cancer specific mortality in patients with nonmetastatic hormone re-fractory prostate cancer. J Urol. 2005; 173: 1572.
17. Amling CL, Bergstralh EJ, Blute ML, Slezak JM, Zincke H. Defining prostate specific antigen progression after radical prostatectomy: what is the most appropriate cut point? J Urol. 2001; 65: 1146-1151.
18. Vollmer RT. Percentage of tumour in prostatectomy specimens. Am J Clin Pathol. 2009; 131: 86-91.
19. Kikuchi E, Scardino PT, Wheeler TM, Slawin KM, Ohori M. Is tumour volume an independent prognostic factor in clinically localized prostate cancer? J Urol. 2004; 172: 508-511.
20. Boorjian SA, Karnes RJ, Crispen PL, et al. The impact of positive surgical margins on mortality following radical prostatectomy during the prostate specific antigen era. J Urol. 2010; 183: 1003-1009.
21. Chalfin HJ, Dinizo M, Trock BJ, et al. Impact of surgical margin status on prostate-cancer-specific mortality. BJU Int. 2012; 110: 1684-1689.
22. Pfitzenmaier J, Pahernik S, Tremmel T, Haferkamp A, Buse S, Hohenfellner M. Positive surgical margins after radical

prostatectomy: do they have an impact on bio-chemical or clinical progression? BJU Int. 2008; 102: 1413-1418.

23. Wright JL, Dalkin BL, True LD, et al. Positive surgical margins at radical prosta-tectomy predict prostate cancer specific mortality. J Urol. 2010; 183: 2213-2218.

24. Budäus L, Isbarn H, Eichelberg C, et al. Biochemical Recurrence After Radical Prostatectomy: Multiplicative Interaction Between Surgical Margin Status and Pathological Stage. J Urol. 2010; 184: 1341-1346.

25. D'Amico AV, Whittington R, Malkowicz SB. The combination of preoperative prostate specific antigen and postoperative pathological findings to predict prostate specific antigen outcome in clinically localized prostate cancer. J Urol. 1998; 160: 2096-2101.

26. Bauer JJ, Connelly RR, Sesterhenn IA, et al. Biostatistical modeling using traditional preoperative and pathological prognostic variables in the selection of men at high risk for disease recurrence after radical prostatectomy for prostate cancer. J Urol. 1998; 159: 929-933.

27. Brimo F, Partin A, and Epstein J. Tumour grade at margins of resection in radical prostatectomy specimens is an Independent predictor of prognosis. Urology. 2010; 76: 1206-1209.

28. Mauermann J, Fradet V, Lacombe L, et al. The impact of solitary and multiple positive surgical margins on hard clinical end points in 1712 adjuvant treatment–naive pT2–4 N0 radical prostatectomy patients. Eur Urol. 2013; 65; 19-25.