PSA Nadir and Outcome in 100 Patients with pT3b Prostate Cancer

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Abstract. *Aim: The prostate-specific antigen (PSA) nadir and long-term outcome in patients with pT3b prostate cancer were evaluated. Patients and Methods: From July 2000 to December 2012, in 100 patients (median age=62 years) with pT3b prostate cancer following radical retropubic prostatectomy (RRP) preoperative and pathological findings predictive of PSA nadir (≤0.2 vs. >0.2 ng/ml) were retrospectively evaluated; moreover, biochemical recurrence-free survival (bRFS), cancer specific survival (CSS) and overall survival (OS) in patients who underwent watchful waiting (16 cases), adjuvant (84 cases) and salvage (10 cases) therapy were recorded. Results: A PSA nadir >0.2 ng/ml was correlated with node involvement, Gleason score ≥9, cT2, PSA >20 ng/ml, positive surgical margins and total cancer percentage >20%. At a median follow-up of 90 months (range=10-155 months) bRFS, OS and CSS were 92%, 96% and 80%, respectively. Conclusion: Radical retropubic prostatectomy combined with adjuvant and salvage treatments demonstrated a satisfactory outcome for pT3b prostate cancer.*

Although the great majority of patients with newly-diagnosed prostate cancer (PCa) have clinically localized disease, a percentage of 25% of these patients are classified as high risk based on either Gleason score (GS) 8 to 10, a PSA >20 ng/ml or an advanced clinical stage (1). The Surveillance Epidemiology End Results data indicate that the incidence of pathological stage T3 disease has remained relatively constant over the past two decades (2). In recent years, the high detection rate of insignificant PCa in screening protocols (up to 50% of cases) (3) has led to reconsider action of the role of definitive treatment (surgery or radiotherapy) for localized disease and the results of active surveillance protocols support the present trend of limiting surgery to selected cases and postponing active treatment in case of disease progression. On the other hand, the role of radical retropubic prostatectomy (RRP) with extended bilateral pelvic lymph node dissection (eLND) and multimodal adjuvant therapy has been found to improve cancer-specific survival (CSS) in patients with high-risk tumors (4, 5).

Among advanced PCa stages, pT3b (*i.e.* cancer involving the seminal vesicles) is considered to be associated with occult micrometastatic disease and earlier biochemical and clinical progression; in patients with disease at this stage, the 10-year CSS is greater than 80% when radical surgery is followed by adjuvant or salvage therapy (6).

In the present study, preoperative and pathological parameters predictive of poor prognosis or persistence of cancer after surgery were recorded; moreover, long-term outcome in patients with pT3b disease who underwent surgery followed by adjuvant radiotherapy or androgen-deprivation therapy (ADT) or salvage treatment was retrospectively evaluated.

Patients and Methods

From July 2000 to December 2012, 625 patients (median age=65 years; range=43-75 years) underwent RRP and eLND as primary treatment for PCa. The patients were enrolled in a case-finding protocol for early diagnosis for PCa, whose results have been published elsewhere (7). The indications for biopsy were: abnormal digital rectal examination, PSA >10 ng/ml, PSA included between 4.1-10 ng/ml, 2.6-4 ng/ml and <2.5 ng/ml with PSA free/total ratio ≤25%, ≤20% and ≤15%, respectively. Prostate biopsy was performed transperineally (8) using a freehand technique, under local anesthesia or sedation, and antibiotic prophylaxis; a median of

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18 (range=15-20 cores) and 26 cores (range=24-29 cores) were taken in case of first biopsy or repeated procedure, respectively. Among all men who underwent RRP, at pathological examination, pT3b stage was found in 100 (16%) cases that constitute the subject of this report. Their preoperative clinical and biopsy findings are listed in Table I.

Eighty-three patients were classified as having high-risk PCa (1) and underwent a preoperative lung-abdominal CT-plus-bone scan, which was negative for distant metastases in all cases.

Surgical specimens were processed as follows: after inking the specimen, the apical and basal parts were removed by a trasversal cut at 4-mm from the distal and proximal margins, respectively. The apical and proximal parts were sectioned parasagittally at 4-mm intervals and perpendicularly to the inked surface. The specimen was step-sectioned at 4-mm intervals perpendicularly to the apical-basal axis of the gland. Presence of extraprostatic extension, seminal vesicle invasion (SVI) and surgical margin status were recorded. Each case was analyzed by a dedicated pathologist (FF).

Preoperative (9) and pathological findings predictive of a PSA nadir >0.2 ng/ml 30 days after surgery, a result that is highly suspicious for persistence of cancer, were retrospectively evaluated; moreover, the incidence of biochemical recurrence-free survival (bRFS), CSS and overall survival (OS) in patients submitted to watchful waiting after surgery *vs*. adjuvant and salvage therapy was retrospectively evaluated. The patients underwent ADT (bicalutamide at 150 mg daily or LHRH agonist) or radiotherapy according to institutional protocols.

Continuous variables were analyzed as medians and range, and categorical variables are reported as percentages. Simple and multiple logistic regression was used to estimate the independent relationship between PSA nadir (≤0.2 *vs*. >0.2 ng/ml) and each pre- or postoperative variable. Unadjusted and adjusted odds ratio (OR) and their 95% confidence intervals are provided. We used forest plot to graphically report logistic regression. Statistical significance was defined as $p<0.05$; STATA package version 11.0 (Stata Corp, College Station, Texas, USA) was used to perform statistical analyses.

Results

Thirty-eight patients (38%) with pT3b stage PCa had positive nodes; overall, a median of 13.8 nodes (range=10-29) were removed: 15 (range=13-29) and 12.5 (range=10-24) in the groups with positive and negative nodes, respectively. Median pathologic GS was 7.8 (GS 6 in four cases; GS 7 in 42 cases; GS 8 in 30 cases; GS 9 in 22 cases; GS 10 in two cases); only in six cases was the definitive GS upgraded in comparison to biopsy GS. Overall, 71 (71%) patients had positive surgical margins (pSM) (53 multifocal and 18 monofocal). In pT3bN0 *vs*. pT3bN1 cases, the pSM rate was superimposable, multifocal and monofocal in 75% and 25% *vs*. 74% and 26% of the cases, respectively ($p>0.05$). At univariate analysis, a PSA nadir >0.2 ng/ml was correlated with node involvement, especially in the presence of more than two disease-positive nodes, GS ≥9, clinical stage T2, PSA >20 ng/ml, pSM and TPC >20% (Figure 1); whereas, after multivariate analysis only clinical stage, pSM and TPC were predictive for persistence of PCa after surgery (Figure 1).

Table I. *Preoperative parameters and biopsy findings in 100 patients with pT3b prostate cancer.*

Clinical and biopsy findings	Number of patients
Median age (range), years	62 (43-73)
GS=6	6
GS=7	46
GS=8	29
GS=9	19
Median PSA (range), ng/ml	18. (2.8-126)
≤4 ng/ml	3
4.1-20 ng/ml	69
>20 ng/ml	28
Clinical T1c	
Clinical T2	32
68	
Median TPC (range)	39 (15-72)
≤20%	59
21-50%	35
>50%	6
Initial biopsy	92
Repeat biopsy	8
GPC=100%	100

GS: Gleason score; TPC: total percentage of cancer; GPC: greatest percentage of cancer.

Only 16 patients (16%) with pT3bN0 and GS <8 underwent watchful waiting with a quarterly PSA evaluation; the remaining 84 (84%) underwent adjuvant therapy (24 and 10 patients were submitted to radiotherapy and ADT alone, 50 underwent radiotherapy combined with ADT).

PSA relapse was defined as two subsequent rises in PSA values >0.2 ng/ml. Median follow-up was 90 (range=10-155) months; bRFS, OS and CSS were 92%, 96% and 86%, respectively (Table II). A PSA failure occurred in 10 (10%) patients: eight with local recurrence 36 (median) months after surgery and two with systemic relapse 18 (median) months after surgery who underwent salvage radiotherapy and ADT, respectively.

Discussion

RRP reduces all-causes mortality among men with intermediate-or-high risk PCa at a median follow-up of 10 years (10); a good bRFS, CSS and OS were reported even in very high-risk patients with preoperative PSA values >100 ng/ml (11), GS 8-10 (12) or advanced clinical stage (10). Urakami *et al*. in a study of 18 patients with median PSA values of 159 ng/ml reported an estimated 10-year bRFS and OS equal to 25% and 92.9%, respectively (11). Gontero *et al*. in 12 of 26 men with PSA values >100 ng/ml and positive nodes, reported a 10-year projected bRFS, CSS and OS of 11.3%, 88.7% and 54.1%, respectively (13). In 254 patients with PSA >50 ng/ml submitted to RRP, at a

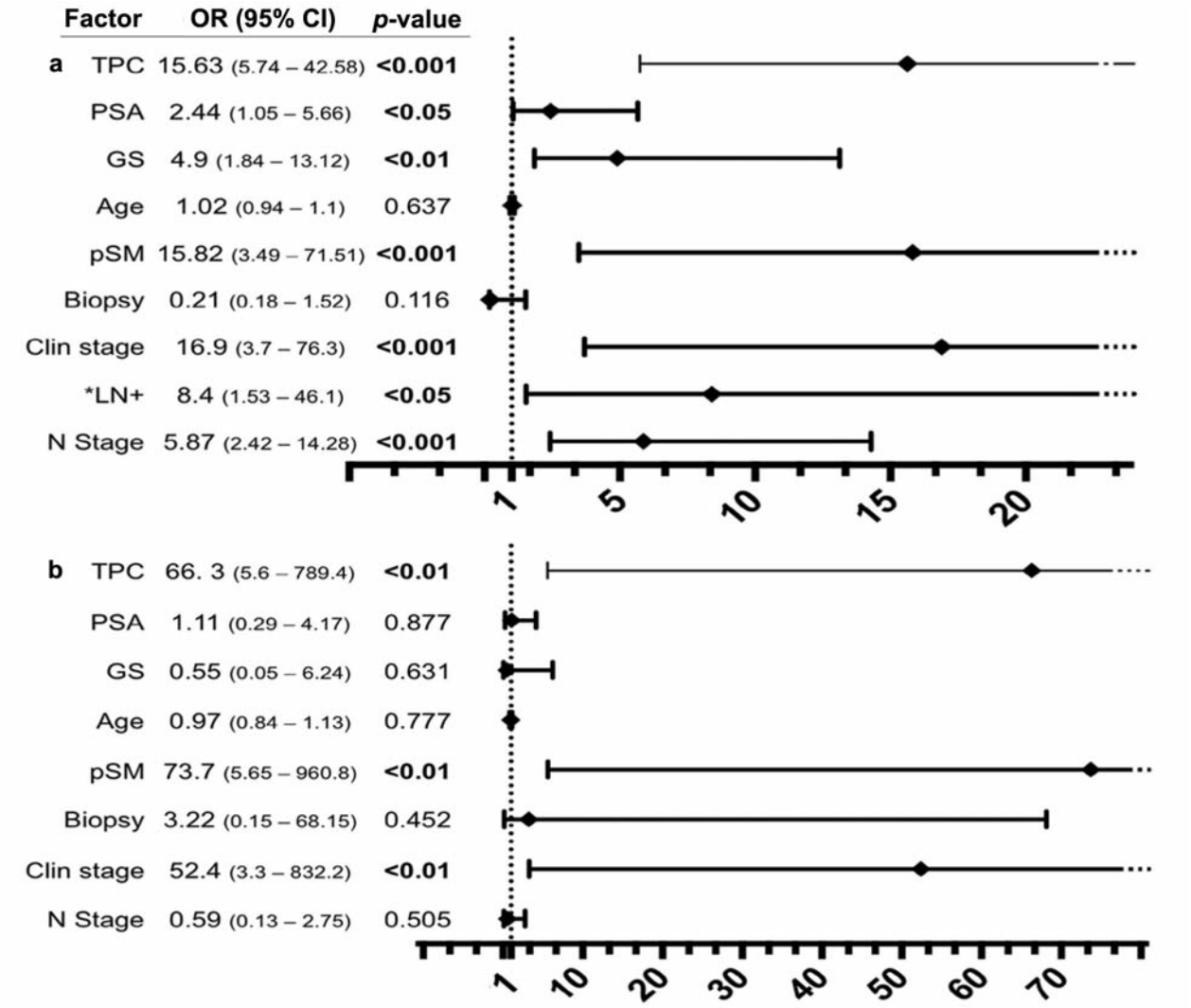

Figure 1. *Logistic regression for PSA nadir ≤0.2 vs. >0.2 ng/ml. Forest plot of logistic regression. Predictive analysis for persistence of prostate cancer following surgery (PSA nadir >0.2 ng/ml). Odds ratio (OR) shows the unadjusted results for simple logistic regression (a) and adjusted results for the multivariate model (b). N Stage: Nodal involvement (N1 vs. N0); LN+: positive lymph nodes (>2 vs. ≤2), *this analysis was performed only on N1 patients; Clin stage: clinical stage (T2 vs. T1c); biopsy: initial vs. repeat procedure; GS, Gleason score (≥9 vs. ≤8); PSA: pre-operative PSA ng/ml (≥20 vs. <20); TPC: total percentage of cancer (>20% vs. ≤20%); pSM: positive surgical margins (yes vs. no); Age: per years increment.*

median follow-up of 12.6 years, Inman *et al*. reported PSA failure and CSS of 52.7% and 89%, emphasizing that nodal involvement trebles the risk of dying from PCa (14). In 56 men with PSA >40 ng/ml, Rausch *et al*. reported a 10-year CSS, OS and bRFS following RRP plus adjuvant therapy of 83%, 81% and 11%, respectively; moreover, 75% of the patients self-estimated their general health state as good or very good (15). In a literature review, Oderda *et al*. reported that debulking surgery with eLND might have a survival benefit for patients with aggressive cancer and nodal involvement, except in the presence of metastatic or hormone-refractory PCa (10).

In the PSA era, as an effect of stage migration because of earlier detection, incidence of pT3b has decreased to approximately 6% of all RRP specimens (16); however SVI still remains a strong predictor of biochemical recurrence and cancer-specific mortality (16), and approximately 40% of men with pT3b disease have a definitive GS of 8-10. Secin *et al*. reported a PSA recurrence rate >80% in 300 patients with pT3b stage (16); Eggener *et al*. (17) demonstrated a recurrence rate equal to 54% in 220 men and no benefit from adjuvant and salvage therapy (17). Pierorazio *et al*., in 732 patients with pT3bN0 stage, reported 10-year bRFS and CSS of 80.4% and 83.8%, respectively; moreover, on multivariate

Table II. *Clinical treatment and outcomes in 100 patients with pT3b stage prostate cancer at median follow-up of 90 months (range=10-155 months).*

pTN (N. of patients)	PSA nadir ≤0.2 ng/ml	WW, n	Adjuvant Therapy, n	Salvage therapy, n	BRFS, n	CSS, n	OS, n
pT3bN0 (62)	77	26	RT=43	RT=13	90	100	90
pT3b N1 (38)	37	0	ADT=90	2nd-Line ADT=5	95	90	79
			ADT + RT=10	Chemo=15			
GS 6 (4)	100	100	0	0	100	100	100
GS 7 (42)	71	28	71	14	100	100	88
GS 8 (30)	66	0	100	13	100	100	90
GS 9 (22)	26	0	100	22	91	91	82
GS 10 (2)	0	0	100	50	100	100	0
Overall (100)	62	16	84	16	92	96	86
			ADT=50				
			RT=24	2nd-Line ADT=10			
			RT + ADT=10	Chemo=6			

GS: Gleason score; RT: radiotherapy; ADT: androgen deprivation therapy; bRFS: biochemical recurrence-free survival; CSS: cancer-specific survival; OS: overall survival; Chemo: chemotherapy; WW: watchful waiting.

analysis, PSA, clinical stage, pSM and GS were significant predictors of bRFS, whereas clinical stage T2c or GS 8-10 were predictors of metastasis-free and CSS (6). Among pT3bN0 cases, Spahn *et al*. found a poor prognosis in patients with pSM involving the bladder neck, with a 5-year CSS and OS equal to 60% and 52.3%, respectively (18).

In conclusion, although RRP combined with multimodal adjuvant and salvage therapy could improve survival in patients with pT3b, many parameters should be considered for screening men with a poor prognosis. In fact, PSA values >20 ng/ml or clinical stage ≥T2 do not always diagnose aggressive cancers; on the contrary, the presence of lower PSA values (11) and unpalpable disease are not always predictive of organ-confined PCa.

In our series, a PSA nadir >0.2 ng/ml was correlated with node involvement (OR=5.8), especially in the presence of more than two disease-positive nodes (OR=8.4), GS≥9 (OR=4.9), clinical stage T2 (OR=16.85), PSA >20 ng/ml (OR=2.44), pSM (OR=15.82) and TPC >20% (OR=17.4); whereas, after multivariate analysis only clinical stage, pSM and TPC were predictive for persistence of PCa after surgery. Finally, after a median follow-up of 90 months (range=9-155 months), RRP combined with multimodal adjuvant and salvage therapy demonstrated a bRFS rate of 92%, with a CSS and OS of 96% and 86%, respectively.

Some limitations of our study deserve mentioning. Firstly, a longer follow-up would have afforded definitive data regarding bRFS, CSS and OS rates; secondly, long-term efficacy of surgery alone in the treatment of pT3b stage was not evaluated as 86% of the patients underwent adjuvant therapy; thirdly, this is a retrospective study and adjuvant radiotherapy was routinely administered, irrespective of surgical margin status, only from 2008, thus results may be biased due to a non-homogenous standard of treatment.

In conclusion, RRP combined with adjuvant and salvage treatments demonstrated a satisfactory outcome for stage pT3b PCa. Although nodal involvement (>2), GS ≥9, T2 clinical stage, pSM and TPC >20% worsened the clinical prognosis, overall bRFS, CSS and OS, at a median follow-up of 90 months, were 92%, 96% and 86%, respectively.

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