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ORIGINAL ARTICLE

Invasion of bladder neck after radical prostatectomy: one definition for different outcomes

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The aim of the study was to evaluate factors of progression after radical prostatectomy in patients with bladder neck invasion (BNI). From 1988 to 2006, 1395 patients underwent radical prostatectomy, 120 (8.6%) had microscopic BNI (pT4 N0, TNM 2002). Group 1 was defined as BNI alone, group 2 as BNI plus extracapsular extension and group 3 as BNI plus seminal vesicle invasion (SVI). Postoperative follow-up data were obtained through routine serum prostate-specific antigen (PSA) and digital rectal examination. Biochemical progression was defined as a single detectable PSA level postoperatively ($>0.2\,ng\,ml^{-1}$). Groups 1, 2 and 3 included 38 (31%), 35 (30%) and 47 (39%) patients, respectively. Preoperative PSA (11.1 vs 24.7 and 23.3 $ng\,ml^{-1}$, $P=0.01$), biopsy Gleason score (5 vs 6 and 6, $P=0.003$) and specimen Gleason score (6 vs 7 and 7, $P=0.02$) were statistically different between three groups. None of the patients had a specimen Gleason score $\geqslant 8$ in group 1. After a mean follow-up of 27 months, 51 (42.5%) patients had biochemical progression. The 5-year progression-free survival was 87, 53 and 17% for groups 1, 2 and 3, respectively ($P<0.001$). Within pT4 prostate cancer, those tumors with isolated microscopic BNI appear to have better prognosis than those with associated extracapsular extension and/or seminal vesicle invasion, and should be distinguished in TNM classification.
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Introduction

Radical prostatectomy (RP) is the treatment of choice in patients with clinically localized prostate cancer (PCa). However, some patients still harbor a risk of progression after curative treatment. Among the most important predictors of progression are the final Gleason score, pathological stage and surgical margin status.[1] Furthermore, extracapsular extension (ECE) and seminal vesicle invasion (SVI) are associated with a poor prognosis.[2] According to the American Joint Committee on Cancer TNM 2002 staging system,[3] pT4 category includes tumors invading adjacent organs. Thus, bladder neck invasion (BNI) by PCa is considered within this category. However, the prognosis of men with clinically localized PCa and isolated microscopic BNI seems to be different from that of patients with invasion to the rectum or striated sphincter. Moreover, patients with PCa invading the bladder neck and associated ECE and/or SVI may have a worse prognosis when compared to those with PCa and BNI alone.

To date, the actual role of microscopic BNI on the outcome of patients with otherwise clinically localized PCa remains controversial and an adequate definition for the pT4 category is still lacking. In the current study, we analyzed a cohort of patients with PCa invading the bladder neck, with or without associated ECE or SVI to assess the prognostic influence of these factors in PCa outcome after RP.

Methods

From 1988 to 2006, 1395 patients underwent RP for clinically localized PCa at Henri Mondor University Hospital. Of these, 120 (8.6%) patients had BNI without positive lymph nodes (stage pT4N0M0 according to the TNM 2002 classification).[3] Microscopic BNI was defined as microscopic involvement of the muscular wall of the bladder neck by PCa cells in the absence of benign prostatic glandular tissue on the corresponding slide.

All patients had preoperative physical examination and serum prostate-specific antigen (PSA) determination (normal level $<4\,ng\,ml^{-1}$). None of the patients received neoadjuvant therapy. Prostatectomy specimens were analyzed according to the Stanford protocol.[4] Whole-mount step sections at 2–3 mm interval were used and separate sections of the bladder neck at the junction with the prostate were also performed. The Gleason score of the specimen, presence of ECE and surgical margin

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status were noted. Postoperative follow-up data were obtained through routine serum PSA assays and digital rectal examination at months 1 and 3 and every 6 months thereafter. Biochemical recurrence was defined as a postoperative serum PSA level of 0.2 ng ml^{-1} or higher, or the need to start either radiotherapy or hormonal therapy. According to pathological analysis, three groups were defined: group 1, BNI alone; group 2, BNI plus ECE; and group 3, BNI plus SVI.

Kaplan–Meier analysis was performed to determine the actuarial biochemical progression-free survival, and the log-rank test was used to compare these results. Univariate and multivariate analyses were performed using logistical regression. Multivariate analysis was performed using statistically significant variables in univariate analysis. To compare differences between groups, analysis of variance test was used for parametric variables and Kruskal–Wallis for the other ones. χ^2 test was used to compare percentages between groups. The computer software StatView, version 5.0, was used for these tests. Differences were considered statistically significant with a P-value <0.05.

Results

Patient and tumor characteristics are reported in Table 1. Patients in group 1 had lower PSA levels at diagnosis ($P=0.001$), lower Gleason score on prostate biopsy ($P=0.003$) and prostatectomy specimen ($P=0.02$). None of the patients in group 1 had PCa Gleason 8 or higher.

After a mean follow-up of 27 months (range 0.3–156, median 19), 51 patients had biochemical progression (42.5%). There was a statistically significant difference in biochemical progression-free survival between groups ($P<0.001$) (Figure 1).

Biological 5-year biochemical progression-free survival was 87, 53 and 17% for groups 1, 2 and 3, respectively ($P<0.001$). In the univariate analysis, PSA $\geqslant$10 ng ml^{-1} at diagnosis, prostatectomy specimen Gleason score $\geqslant$7 (4 + 3), SVI and positive surgical margins were associated with statistically significant biochemical progression. However, in multivariate analysis, only SVI was still associated to biochemical progression in this cohort of patients (Table 2). Nonetheless, while using PSA $\geqslant$20 ng ml^{-1} in multivariate analysis, surgical margins (OR = 3.5 (1.03–12.3) $P=0.046$) and PSA (OR = 3.1 (1.2–8.4), $P=0.02$) were also associated to a higher risk of biochemical recurrence.

Discussion

Radical prostatectomy remains the treatment of choice in patients with clinically localized PCa. However, some patients still have a high risk of progression depending on clinical and pathological features. Some factors identified as predictors of disease recurrence include Gleason score, surgical margin status and pathological stage.[1] Furthermore, ECE and SVI (stages pT3a and pT3b, respectively) are associated with a poor prognosis.[2] According to the 2002 TNM staging system,[3] BNI is classified currently as stage pT4 disease; nevertheless, the outcome of subjects with microscopic BNI and otherwise organ-confined disease does not appear to be similar to that of patients with PCa involving the rectum or the external sphincter.[5–7]

To our knowledge, this is the largest cohort of patients with clinically localized PCa and BNI (stage pT4) demonstrated on pathological analysis. We found that of the 120 subjects with BNI, those without associated adverse pathological features (group 1, $n=38$) had better survival than patients with cancer involving the bladder neck and either associated ECE (group 2, $n=35$) or SVI (group 3, $n=47$) ($P<0.001$). Moreover, 45% of men in group 3 had an initial PSA $>$20 ng dl^{-1}. At pathological

Table 1 Patient and tumor characteristics

	Total n = *120*	*Group 1* n = *38*	*Group 2* n = *35*	*Group 3* n = *47*	P-*value*
Age (years)	63.6	62.1	63.9	63.1	0.36[a]
Mean PSA level (ng ml^{-1})	19.9	11.1	24.7	23.3	0.001[b]
Clinical stage					
T1 a–b	3 (2.5)	2 (5.2)	1 (2.8)	—	
T1c	82 (68.5)	30 (78.9)	24 (68.5)	28 (59.6)	
T2a	20 (16.7)	4 (10.5)	6 (17.1)	10 (21.3)	
T2b	6 (5)	—	1 (2.8)	5 (10.7)	
T2c	6 (5)	2 (5.2)	2 (5.6)	2 (4.2)	
T3a	3 (2.5)	—	1 (2.6)	2 (4.2)	
Biopsies Gleason score					
2–6	73 (61.2)	34 (89.5)	19 (54.3)	20 (42.5)	0.003[c]
7	37 (30.8)	4 (10.5)	11 (31.4)	22 (46.8)	
8–10	9 (7.6)	—	4 (11.4)	5 (10.6)	
Prostate weight (g)	52.1	53.7	47.8	54.1	0.34[a]
Specimen Gleason score					
2–6	23 (19.1)	13 (34.2)	5 (14.2)	5 (10.6)	0.02[c]
7	65 (54.1)	25 (65.8)	22 (62.8)	18 (38.2)	
8–10	32 (26.6)	—	8 (22.8)	24 (51)	
Positive margins	89 (74.1)	24 (63.1)	25 (71.1)	40 (85.1)	0.01[c]

Abbreviation: PSA, prostate-specific antigen.
Values within parentheses are expressed in percentage.
[a]ANOVA.
[b]Kruskal–Wallis test.
[c]χ^2 test.

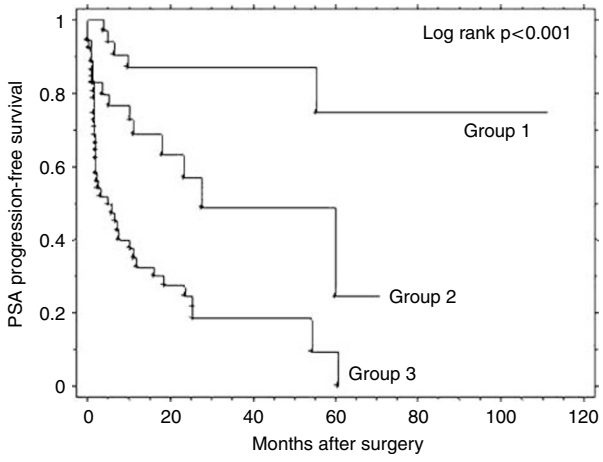

Figure 1 Comparison of biochemical recurrence-free survival between patients with bladder neck invasion (BNI) stratified in three groups: group 1, isolated BNI; group 2, bladder neck involvement with concomitant extracapsular extension; and group 3, BNI with concomitant seminal vesicle involvement (group 3). There was a statistically significant difference between groups ($P<0.001$, log-rank test).

Table 2 Univariate and multivariate analysis for biochemical recurrence risk in our population of 120 patients with bladder neck involvement

Factor	*Univariate analysis*			*Multivariate analysis*		
	P	*OR*	*95% CI*	P	*OR*	*95% CI*
Positive margin[a]	0.005	4.1	1.5–11	0.08[a]	2.9	0.9–9.3
Seminal vesicle involvement	<0.0001	11.3	4.7–27.2	<0.0001	7.2	2.8–19
Extracapsular extension	0.0005	4.7	2.0–11.1	0.32	1.7	0.6–5.2
Gleason score >3+4	0.006	2.9	1.4–6.3	0.75	1.2	0.4–3.2
PSA > 10 ng ml^{-1}[a]	0.001	3.7	1.7–8.2	0.15[a]	2.0	0.8–5.4

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio; PSA, prostate-specific antigen.
Multivariate analysis included all variables from the univariate analysis. In multivariate analysis, seminal vesicle involvement was the only factor associated with biochemical progression.
[a]When using PSA ⩾ 20 ng ml^{-1} instead of PSA ⩾ 10 ng ml^{-1} in multivariate analysis, surgical margins (OR = 3.5 (1.03–12.3) $P = 0.046$) and PSA (OR = 3.1 (1.2–8.4), $P = 0.02$) were also associated with a higher risk of biochemical recurrence.

analysis, none of the patients in group 1 had specimen Gleason score 8 or higher. On the other hand, group 3 patients also had higher biopsy Gleason grade ($P = 0.02$) and more than 50% had Gleason score 8 or higher at prostatectomy specimen ($P = 0.003$), suggesting more aggressive disease in this subset of patients. The multivariate analysis, which included only the patients of the present cohort, showed that only SVI was statistically associated with the risk of biochemical progression. The poor association with other well-known predictors could be explained by the number of patients included in the study, and by the fact that this cohort is not representative of all men who have had a prostatectomy. Preoperative PSA levels in groups 2 and 3, and surgical margin status in the entire cohort, may be related to more aggressive disease, specially in groups 2 and 3, as well as to the increasing trend in our hospital to offer surgical treatment to high-risk patients (that is PSA >20, biopsy Gleason score 8 or higher).

Our findings support those of other investigators regarding the impact of BNI after RP. Yossepowitch *et al*.[5] found that subjects with PCa involving the bladder neck classified as stage pT4 had better prognosis than those with SVI (stage pT3b). However, this study had a small number of patients and short follow-up. In a subsequent study[6] with a larger number of patients and longer follow-up (median 53 months), they found 72 subjects in stage pT4. Of these, individuals with coexisting adverse pathological characteristics such as high Gleason score (19%), ECE (53%) or SVI (33%) had poorer prognosis when compared to those with BNI alone (36%). On the basis of their findings, the authors suggested a modification of the current TNM system proposing that microscopic BNI should not be part of stage pT4. In line with these findings, Dash and colleagues[7] evaluated 60 patients with BNI after RP. They found better survival in patients with focal invasion compared to those with extensive invasion. The PSA recurrence relative risk was 1.52 ($P = 0.003$) in the former group and 2.79 for the group with extensive involvement ($P < 0.0001$). They also found that when all pathologic features are taken together, BNI confers a lower recurrence risk when compared to either ECE or SVI. These investigators also recommended a modification of the current American Joint Committee on Cancer TNM staging system.

Recently, Aydin and colleagues[8] evaluated the prognostic significance of a sole positive bladder neck margin on biochemical progression compared with positive margins at locations other than the bladder neck after RP. They evaluated 38 patients with BNI alone and 126 with positive margins at other sites and negative bladder neck. They found a higher risk of progression in the former group, with a 5-year actuarial risk of progression of 69.8 and 33.0% in men with positive and negative bladder neck margin, respectively. However, patients with capsular incision and SVI were excluded from analysis. The authors suggested that when adverse prognostic factors are absent, a positive bladder neck margin indicates a high risk of progression, but not to the level reported for stage pT4.

A study from Indiana University[9] concluded that BNI is an independent predictor of early PSA recurrence in patients undergoing RP. Of the 364 subjects, only 8 (36%) had BNI, with PSA recurrence being three times likely in this subset of patients. However, a comparison between BNI alone and that associated with other pathological features was not made.

Our study had some limitations including the retrospective nature of our investigation, which could allow some biases in patient selection. Although follow-up is similar to that of other reports, it still remains brief (mean 27 months, median 19 months) and longer follow-up is needed to confirm our results.

Conclusions

The pT4 category (TNM 2002) comprises a heterogeneous group of tumors with different clinical behaviors. Patients with PCa and isolated microscopic BNI have lower risk of progression when compared to similar pT4 tumors with associated adverse features such as ECE or SVI. Since pT4 tumors should have a worse prognosis than pT3b tumors, BNI-alone tumors may be classified at a lower level than those with BNI associated to SVI or ECE. The exact level to consider BNI-alone tumors needs to be defined better, and modification of TNM classification might be considered.

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Conflict of interest

None.

TNM classification for prostate cancer according to the AJCC 6th edition (2002) and UICC 6th edition

Evaluation of the (primary) tumor ('T')
TX: cannot evaluate the primary tumor
T0: no evidence of tumor
T1: tumor present, but not detectable clinically or with imaging
T1a: tumor was incidentally found in less than 5% of prostate tissue resected (for other reasons)
T1b: tumor was incidentally found in greater than 5% of prostate tissue resected
T1c: tumor was found in a needle biopsy performed due to an elevated serum PSA
T2: the tumor can be felt (palpated) on examination, but has not spread outside the prostate
T2a: the tumor is in half or less than half of one of the prostate gland's two Lobes
T2b: the tumor is in more than half of one lobe, but not both
T2c: the tumor is in both lobes
T3: the tumor has spread through the prostatic capsule (if it is only part-way through, it is still T2)
T3a: the tumor has spread through the capsule on one or both sides
T3b: the tumor has invaded one or both seminal vesicles
T4: the tumor has invaded other nearby structures

Evaluation of the regional lymph nodes ('N')
NX: cannot evaluate the regional lymph nodes
N0: there has been no spread to the regional lymph nodes
N1: there has been spread to the regional lymph nodes

Evaluation of distant metastasis ('M')
MX: cannot evaluate distant metastasis
M0: there is no distant metastasis
M1: there is distant metastasis
M1a: the cancer has spread to lymph nodes beyond the regional ones
M1b: the cancer has spread to bone
M1c: the cancer has spread to other sites (regardless of bone involvement)

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