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BLADDER NECK INVOLVEMENT IN PATHOLOGICAL STAGE pT4 RADICAL PROSTATECTOMY SPECIMENS IS NOT AN INDEPENDENT PROGNOSTIC FACTOR

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ABSTRACT

Purpose: Bladder neck invasion by prostate cancer in radical prostatectomy specimens is uncommon and, thus, its influence on disease recurrence has not been well defined. Consequently the classification of bladder neck invasion in the TNM staging system is controversial. We studied our cohort of patients with stage pT4 disease and bladder neck invasion to clarify the true clinical behavior and prognostic significance of bladder neck invasion in radical prostatectomy specimens.

Materials and Methods: The study group consisted of 4,090 consecutive patients treated with radical prostatectomy at one of our institutions between 1983 and 2001. Median followup was 53.1 months (range 1 to 189). After excluding from analysis patients treated with neoadjuvant androgen withdrawal or preoperative irradiation 72 of the remaining 2,571 (2.8%) with bladder neck invasion were classified with stage pT4 disease and their specimens were reviewed. Progression-free probability was determined by Kaplan-Meier analysis. Using the Cox proportional hazards model the independent prognostic significance of bladder neck invasion was assessed after controlling for pretreatment prostate specific antigen, final Gleason sum, extracapsular extension, surgical margins status, seminal vesicle invasion and lymph node involvement.

Results: Of the 72 patients categorized with stage pT4 disease 14 (19%) had poorly differentiated Gleason sum 8 to 10 cancer, 38 (53%) had established extracapsular extension, 24 (33%) had seminal vesicle invasion and 8 (11%) had lymph node involvement. However, 26 patients (36%) had cancer confined to the prostate and 28 (39%) had negative surgical margins except for the bladder neck site. The mean 5-year progression-free probability plus or minus SD in all stage pT4 cases was 68% ± 7%, which was better than in cases of seminal vesicle invasion (52% ± 5%, log rank test $p = 0.0156$) but worse than in those of extracapsular extension (84% ± 4.1%). Univariate analysis of the stage pT4 cohort revealed that higher prostatectomy Gleason sum, more extensive extracapsular extension and seminal vesicle invasion were significantly associated with an adverse prognosis. However, in a multivariate model that included all radical prostatectomy cases the finding of bladder neck invasion or stage pT4 disease did not independently predict prostate specific antigen recurrence.

Conclusions: Stage pT4 disease comprises a heterogeneous group of tumors with various pathological features and inconsistent outcomes. Assigning the pT4 stage to cases of microscopic bladder neck invasion provides no independent ability for predicting disease progression after adjusting for other adverse disease features. Due to this and previously reported data the definition of stage pT4 disease should be modified in the next version of the TNM staging system.

KEY WORDS: prostate, prostatic neoplasms, bladder, neoplasm staging, prostatectomy

The TNM classification system for prostate cancer established by the American Joint Committee on Cancer and International Union Against Cancer provides a way to describe the extent of a given tumor at a certain time point. This staging system, which gained international acceptance for clinical staging in 1992, has been widely adopted for the clinical and pathological classification of prostate cancer.[1–3] The pathological equivalent of a given clinical T category is based on histological assessment of the radical prostatectomy specimen. To be clinically meaningful accurate pathological T staging should reflect the natural history of the cancer, stratifying patients into differing prognostic groups.

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Within the TNM system the T4 category was initially intended for tumors noted on clinical assessment to invade adjacent organs, such as the rectum or bladder. Such tumors were thought to be aggressive with a high propensity to recur and metastasize after local therapy. However, clinical stage T4 cancer is rarely treated surgically and, therefore, the corresponding pathological definition of stage pT4 disease has come to refer almost exclusively to the incidental microscopic finding of cancer cells among smooth muscle bundles of the bladder neck. Moreover, the single pT4 category in the 1997 revision of the TNM staging system rendered involvement of the bladder neck, previously defined as stage pT4a, equivalent to invasion into the pelvic wall musculature, previously defined as stage pT4b.

Further confusion arises from applying the pathological definition of stage T4 to various clinical investigations. In previous studies the impact of bladder neck involvement in radical prostatectomy specimens on prognosis was considered equivalent to an involved surgical margin at the bladder neck site.[4–7] Others who analyzed the impact of bladder neck preservation techniques on continence and cancer control likewise defined bladder neck invasion as a positive surgical margin but did not designate such cancer as stage pT4.[8–10] To our knowledge the actual influence of microscopic bladder neck invasion on prognosis and the appropriate definition of the pT4 category in the TNM staging system have not been adequately delineated. Therefore, we studied our cohort of patients with bladder neck invasion, classified as stage pT4 disease, to clarify the true clinical behavior and prognostic significance of bladder neck invasion in radical prostatectomy specimens.

MATERIALS AND METHODS

From January 1, 1983 to August 31, 2001, 4,090 patients were treated with radical retropubic prostatectomy at our 2 institutions. All patients receiving neoadjuvant androgen ablation or preoperative radiation therapy were excluded, leaving 2,571 for the current analysis. Median patient age at diagnosis was 62 years (range 40.2 to 78.9). Median followup was 53 months (range 1 to 189).

Radical prostatectomy specimens were fixed in formalin with the external surface of the right and left sides inked in 2 colors. The apical prostate was truncated perpendicular to the prostatic urethra and subsequently sectioned as slices parallel to the prostatic urethra. The bladder neck margin was obtained by sampling portions of soft tissue at the junction of the rough prostatic capsule and smooth bladder neck or most proximal portion of the submitted specimen corresponding to the anatomical bladder neck. The remaining prostate was completely transected at 3 to 5 mm. intervals in a plane perpendicular to the urethra.

Pathological features were recorded for each specimen and reported in accordance with the 1992 version of the TNM staging system, including Gleason score (sum of the primary and secondary grades), surgical margin status (tumor cells touching ink and positive surgical margin sites), extracapsular extension (subdivided for various analyses as unilateral stage pT3a, bilateral stage pT3b, focal with a few neoplastic glands immediately outside of the capsule in 1 or 2 sections, established with more than a few glands traversing the capsule or doing so in more than 2 histological sections, and extracapsular extension sites), seminal vesicle invasion (stage pT3c with tumor cell invasion into the muscular layer of the seminal vesicle), bladder neck invasion (stage pT4 with neoplastic cells involving the smooth muscle bundles of the surgical bladder neck when there was no accompanying prostatic glandular tissue on the corresponding slide) and lymph node involvement.

We identified 72 patients with bladder neck involvement classified as stage pT4. Their specimens were reviewed by 1 of the 3 study pathologists. Median followup in the stage pT4 cohort was 49 months (range 1 to 189).

Progression was defined as failure of surgery to achieve cancer control (increase in serum prostate specific antigen [PSA] to 0.4 ng./ml. or higher, as confirmed by a second PSA measurement higher than the first by any amount), evidence of local recurrence in patients with undetectable PSA (positive biopsy result) or evidence of distant recurrence in patients in whom no PSA result was available. Time to progression was defined as the first recorded progression event. Adjuvant hormonal or radiation therapy was not initiated unless PSA progression had occurred.

Progression-free probability was calculated using the Kaplan-Meier methodology and curves were compared with the log rank test. The Cox proportional hazards model was used to test the independent ability of bladder neck invasion to predict progression after controlling for pretreatment PSA, Gleason sum in the prostatectomy specimen, level of extracapsular extension, surgical margins status, seminal vesicle invasion and lymph node involvement. In addition, with the intent of isolating the effect of bladder neck invasion as an independent predictor patients with a positive surgical margin at the bladder neck (that is stage pT4) but with negative margins elsewhere were considered to have negative surgical margins in our model. Variables were uniformly assessed as categorical except for preoperative PSA and pathological Gleason sum, which were incorporated as continuous. Statistical significance was considered at $p < 0.05$. Statistical analysis was performed with commercially available computer software.

TABLE 1. *Clinicopathological characteristics in 72 patients treated with radical prostatectomy for stage pT4 prostate cancer*

Variable	No. Pts. (%)
Clinical stage:	
T1a/b	3 (4)
T1c	26 (36)
T2	38 (53)
T3	5 (7)
Preop. PSA (ng./ml.):	
0–4	6 (8)
4.1–10	27 (38)
10.1–20	21 (29)
20.1–50	16 (22)
Greater than 50	2 (3)
Pathological Gleason sum:	
2–6	17 (24)
7	41 (57)
8–10	14 (19)
Extracapsular extension:	
None	26 (36)
Focal	8 (11)
Established	38 (53)
Seminal vesicle invasion:	
Neg.	48 (67)
Pos.	24 (33)
Lymph node involvement:	
Neg.	64 (89)
Pos.	8 (11)
Pos. surgical margin status:	
Bladder neck only	28 (39)
Bladder neck + elsewhere	44 (61)

RESULTS

Of the 72 patients with bladder neck invasion available for analysis only 5 (7%) were thought to have an extraprostatic

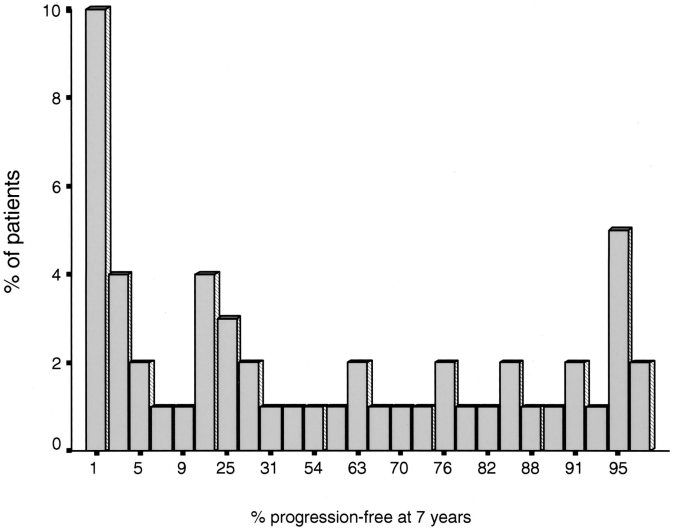

FIG. 1. Estimates of progression-free probability at 7 years in patients with stage pT4 prostate cancer calculated by postoperative nomogram.[11]