Residual Pathological Stage at Radical Cystectomy Significantly Impacts Outcomes for Initial T2N0 Bladder Cancer

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Purpose: We hypothesized that in patients with T2N0 stage disease at transurethral bladder tumor resection a lower residual cancer stage (P1N0 or less) at radical cystectomy may correlate with improved outcomes relative to those with residual P2N0 disease.

Materials and Methods: We analyzed 208 patients with T2N0 stage disease at transurethral bladder tumor resection whose tumors were organ confined at radical cystectomy (P2 or lower, pN0). None received perioperative chemotherapy. Kaplan-Meier as well as univariable and multivariable Cox regression models addressed the effect of residual pT stage at radical cystectomy on recurrence and cancer specific mortality rates. Covariates consisted of age, gender, grade, lymphovascular invasion, carcinoma in situ, number of lymph nodes removed and year of surgery.

Results: Residual pT stage at radical cystectomy was P0 in 24 (11.5%) patients, Pa in 9 (4.3%), PCIS in 22 (10.6%), P1 in 35 (16.8%) and P2 in 118 (56.7%). Median followup of censored patients was 55.7 months for recurrence and 52.1 months for cancer specific mortality analyses. The 5-year recurrence-free survival rates of patients with P0/Pa/PCIS, P1 and P2 stage disease were 100%, 85% and 75%, respectively. The 5-year cancer specific survival rates for the same cohorts were 100%, 93% and 81%, respectively. On multivariable analysis the effect of residual stage P1 or lower at radical cystectomy achieved independent predictor status for recurrence (adjusted HR 0.20, $p = 0.002$) and cancer specific mortality (adjusted HR 0.24, $p = 0.02$).

Conclusions: Down staging from initial T2N0 bladder cancer at transurethral bladder tumor resection to lower stage at radical cystectomy significantly reduces recurrence and cancer specific mortality. Further validation of this finding is warranted.

Key Words: carcinoma, transitional cell; cystectomy, urinary bladder neoplasms, neoplasm staging

Abbreviations and Acronyms

CIS = carcinoma in situ

LVI = lymphovascular invasion

RC = radical cystectomy

TCC = transitional cell carcinoma

TURBT = transurethral resection of bladder tumor

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EVIDENCE of muscle invasive transitional cell carcinoma at transurethral bladder tumor resection is an established indication for radical cystectomy.[1,2] Patients with histologically proven muscle invasion at TURBT may demonstrate various cancer control outcomes after RC. Some experience rapid progression while others may enjoy long-term remissions or cures. The effect of down staging

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between TURBT and RC may contribute to the observed heterogeneity of cancer control outcomes in patients with muscle invasive bladder TCC. Specifically stage reduction to residual P0 from TURBT to RC with or without neoadjuvant chemotherapy was associated with reduced recurrence and/or cancer specific mortality rates.[3–5]

Up to 30% of patients with muscle invasive TCC at TURBT have disease down staged to nonmuscle invasive disease at RC.[3] Moreover as many as 20% of patients with muscle invasive bladder TCC at TURBT have no evidence of residual tumor at RC.[3,4,6,7] Studies addressing the effect of down staging from muscle invasive disease at TURBT to nonmuscle invasive disease at RC have provided conflicting results. Some reported virtually perfect long-term survival rates[4,6,7] while others did not corroborate this finding.[8] However, several of the currently available analyses that examined the effect of down staging from muscle invasive bladder cancer at TURBT to nonmuscle invasive disease at RC have potential biases. For example, the inclusion of patients treated with neoadjuvant systemic chemotherapy and/or radiation therapy limits the ability to accurately diagnose disease stage and grade at RC.[7–10] The inclusion of patients with clinical T3 TCC at TURBT[3,7,9] also introduces a potential bias because such tumors are unlikely to be down staged and may confound the analysis. Finally the inclusion of patients with lymph node metastases at RC also undermines the ability to assess the effect of pathological T stage on recurrence and cancer specific mortality rates since the predominant effect on these end points originates from the N stage.[4,6,11,12]

Thus, we decided to evaluate the impact of down staging between TURBT and RC on recurrence and cancer specific mortality rates. Specifically we focused on patients with clinical T2 stage at TURBT and pathological stage T2 or lower at RC without clinical or pathological evidence of lymph node metastases, and who were unexposed to any form of neoadjuvant or adjuvant therapy. We hypothesized that the extent of residual disease at RC may be related to cancer control outcomes. Lower disease stage at RC may be associated with lower recurrence and cancer specific mortality rates owing to superior TURBT and/or biologically favorable disease. Such data may also assist in the improved risk stratification of patients with muscle invasive and bladder confined disease undergoing RC, and enable the selection of appropriate high risk patients for trials of adjuvant therapy. Most recent trials of adjuvant chemotherapy have only included patients with pathological extravesical disease greater than T2 and have been unable to complete the target accrual. While trials demonstrating improved outcomes with neoadjuvant chemotherapy have included patients with T2-T4a disease,[5] patients with T2N0 disease may be treated with initial RC for complete pathological staging to enable better risk stratification. This approach will enable the avoidance of chemotherapy in low risk patients as well as the selection of high risk patients for potential trials of adjuvant chemotherapy.

MATERIALS AND METHODS

Patient Population

The study was performed with the approval and institutional oversight of the institutional review board for the protection of human subjects at each institution. A total of 530 consecutive patients with baseline clinical T2N0 bladder TCC treated with RC with curative intent at the University of Texas Southwestern (Dallas, Texas), Johns Hopkins Hospital (Baltimore, Maryland) and the Baylor College of Medicine (Houston, Texas) between March 1984 and October 2003 were potential candidates for this analysis. All patients underwent RC and bilateral pelvic lymphadenectomy with the common iliac bifurcation as the minimum proximal limit of dissection.

In this analysis we exclusively focused on patients with muscle invasive, yet organ confined TCC of the bladder at TURBT (clinical T2). None of the patients received perioperative radiation therapy or systemic chemotherapy. Of the overall 530 patients 250 were excluded from study due to pathological extravesical disease at RC, 11 due to neoadjuvant chemotherapy, 41 due to the presence of lymph node metastasis at RC and 20 due to the use of postoperative chemotherapy. Eventually 208 patients were assessable for this retrospective analysis.

Pathological Examination

Staff pathologists with expertise in genitourinary pathology examined all the RC specimens according to institutional protocols. Multiple, well oriented quadrant sections from the tumor, adjacent and distal bladder wall, ureters and urethra were processed. Pelvic lymph node dissections were examined grossly and all lymphoid tissues were submitted for histological examination. Tumors were staged according to the 5th edition of the American Joint Committee on Cancer staging manual and graded according to the 1973 WHO classification.[13] LVI was defined as the unequivocal presence of tumor cells within an endothelium lined space without underlying muscular walls.[14,15] Equivocal cases and tumor cells that merely encroached on a vascular lumen were considered negative and a perivascular reaction was not required. In males the prostate and seminal vesicles were evaluated in accordance with the Guidelines of the College of American Pathologists.[16] In females the ovaries, uterus and vagina were evaluated when included in the surgical specimen.

Followup

For each patient comprehensive clinical and pathological information was collected, and entered into an institutional review board approved database. Multiple internal and external data checks were done to ensure the accuracy and completeness of data elements. Clinical followup was performed according to institutional protocols. Patients generally were seen postoperatively at least every 3 to 4