Role of Maximal Endoscopic Resection Before Cystectomy for Invasive Urothelial Bladder Cancer

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Abstract

Transurethral resection of all endophytic tumors in patients with invasive urothelial cell carcinoma before neoadjuvant chemotherapy (NC) is associated with complete pathologic tumor response at time of radical cystectomy (RC). These patients should undergo complete transurethral resection (TUR) of all endophytic tumors before cystectomy when feasible.

Introduction/Background: The aim of this study was to examine whether TUR of all visible endophytic tumors performed before RC, with or without NC, affects final pathologic staging. **Patients and Methods:** We retrospectively reviewed data from patients with clinical T2-T4N0-1 urothelial carcinoma of the bladder who underwent RC at our institution between July 2005 and November 2011. Degree of TUR was derived from review of operative reports. We used multivariate logistic regression to assess the association of maximal TUR on pT0 status at time of RC. **Results:** Of 165 eligible RC patients, 81 received NC. Reported TUR of all visible tumors was performed in 38% of patients who did not receive NC and 48% of NC patients ($P = .19$). Nine percent of patients who underwent maximal TUR and did not receive NC were pT0, whereas among NC patients, pT0 was seen in 39% and 19% of those with and without maximal TUR, respectively ($P = .05$). On multivariate analysis in all patients, maximal TUR was associated with a nonsignificant increased likelihood of pT0 status (odds ratio [OR], 2.03; 95% confidence interval [CI], 0.84-4.94), which was significant when we restricted the analysis to NC patients (OR, 3.17; 95% CI, 1.02-9.83). **Conclusion:** Maximal TUR of all endophytic tumors before NC is associated with complete pathologic tumor response at RC. Candidates for NC before RC should undergo resection of all endophytic tumors when feasible. Larger series are warranted to see if maximal TUR leads to improved overall and disease-specific survival.

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Introduction

Radical cystectomy (RC) with pelvic lymphadenectomy can provide excellent local control and confer long-term survival in patients with muscle invasive bladder cancer.[1] Neoadjuvant chemotherapy (NC) before cystectomy has been shown to be beneficial in this population.[2] The role of NC traditionally has been to treat known and occult metastatic disease and the goal of RC to provide local control of disease via extirpation of the primary tumor. However, in addition to providing a survival benefit compared with RC alone, NC affords patients a higher rate of pathologic T0 (pT0) stage at the time of RC.[3,4] Although the benefits of NC have been well described, the role of maximal endoscopic resection before RC and particularly before NC is uncertain. Herr examined a population of patients with muscle invasive bladder cancer who received NC and subsequently declined RC. Factors contributing to improved survival included the number and size of invasive tumors and completeness of endoscopic resection, suggesting a role for aggressive endoscopic resection.[5] We sought to examine the potential benefit of maximal transurethral resection (TUR) before RC on final pathologic staging in patients who did and did not receive NC before undergoing RC for muscle invasive bladder cancer.

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Patients and Methods

Study Population and Data Collection

We conducted a retrospective analysis of patients with clinical T2-T4aN0-1 urothelial cell carcinoma of the bladder who underwent RC at our institution between July 2005 and November 2011. Included were patients who had a predominant pathology of urothelial cell carcinoma; patients with predominant squamous, micropapillary, and neuroendocrine tumors were excluded. Information gathered from patient medical records included demographic characteristics, comorbid conditions, and the clinical and final pathologic stages of their bladder cancers. We further abstracted receipt of NC. NC regimens included gemcitabine/cisplatin, methotrexate/vinblastine/doxorubicin/cisplatin, or gemcitabine/carboplatin. Administration of NC was patient- and provider-dependent.

A detailed review of the surgical and clinical notes was conducted to determine the subjective completeness of TUR immediately preceding NC and RC. We included patients that underwent preceding TUR at outside hospitals if we could abstract information on the completeness of endoscopic resection from the surgical report. Patients were classified as having a maximal resection if there was no evidence of residual endophytic disease visualized cystoscopically as clearly stated in the operative report. Only patients with a definitive statement in the medical record regarding the presence or absence of residual visible, endophytic tumor within the bladder after TUR were included in our analysis.

We further excluded female patients with cT4 disease and men with cT4b disease because it was considered not feasible to endoscopically resect all visible tumor burden; men with cT4a disease due to prostatic stromal invasion were included. Other exclusion criteria included salvage cystectomy after chemotherapy/radiation and unknown chemotherapy status.

Statistical Analysis

Baseline differences between patients grouped by whether or not a maximal resection was completed were compared with χ^2 tests. We further stratified use of maximal resection among only patients who underwent NC. Multivariate logistic regression was performed to determine the association of complete TUR on pT0 status at cystectomy. We constructed a model that included all patients (adjusting for age, sex, race, NC, and completeness of TUR) and a multivariate model including only those who received NC. Finally, we performed an analysis in which the outcome of interest was clinical downstaging, with the final pathology $\leq$ pT1. We tested for effect modification between clinical stage and maximal TUR comparing a full model with an interaction term with the reduced model with the likelihood ratio test. Odds ratios (ORs) and 95% confidence intervals (95% CIs) are reported. Approval of the institutional review board at the University of Washington was obtained for this study. All analyses were performed using Stata 12.1 (StataCorp LP, College Station, TX).

Results

The charts of 178 patients who underwent RC were reviewed for this analysis. Extent of endoscopic debulking could not be ascertained in 11 patients and 2 women with clinical T4 disease were excluded, leaving a total of 165 patients who were included for this analysis. Eighty-one patients (49%) received NC. Table 1 includes the demographic and clinical factors of patients that did and did not undergo maximal TUR. Maximal TUR was not associated with receipt of NC. Maximal TUR was performed in 32 patients (38%) who did not receive NC and in 39 patients (48%) who received NC ($P = .17$). Additionally, there was no association with age, sex, race, and pathologic stage and extent of TUR; however, clinical stage was associated with maximal TUR ($P < .001$). Receipt of NC was associated with a higher proportion of pT0 compared with those who received NC alone; 23 patients (28%) who received NC were pT0 as compared to 8 patients (9%) who did not receive NC.

The results of the multivariate analyses are shown in Table 2. In the model including all patients, maximal resection was associated with a greater than 2-fold increase in the likelihood of pT0, a finding that trended toward statistical significance (OR, 2.03; 95% CI, 0.84-4.94). In the multivariate model limited to patients who received NC, maximal resection was significantly associated with achieving pT0 (OR, 3.17; 95% CI, 1.02-9.83). There was no evidence for effect modification between clinical stage and maximal TUR (likelihood $P = .66$). Maximal TUR was also associated with partial pathologic response ($\leq$ pT1) in the model including all patients and in the model limited to those who received NC.

Discussion

Our results indicate that maximal TUR of bladder tumors before the administration of NC is strongly associated with complete pathologic response at time of RC. The introduction of NC to complement RC for the treatment of muscle-invasive urothelial cell carcinoma of the bladder has improved survival. The rationale for use of NC is that patients benefit from the treatment of micrometastatic disease present at diagnosis and local control with RC. Grossman et al demonstrated an improvement in median survival in patients treated with NC before RC compared with RC alone (77 months vs. 46 months). Additionally, this report noted that those receiving NC had a higher rate of pT0 at time of RC compared with those who underwent RC alone (38% vs. 15%).[2] A large metaanalysis also showed a 5% absolute improvement in 5-year survival in patients who received combination cisplatin-based NC compared with local therapy alone.[6] Splinter et al demonstrated an improvement in 5-year survival in patients downstaged to pT1 or less after NC (75% vs. 20%), further illustrating the potential positive effect on survival of downstaging in those who respond to NC.[7]

The effect of maximal TUR on final pathology after RC is less clear, particularly in the setting of NC, but there are many theoretical reasons to consider a complete TUR before NC. Although the bladder will eventually be resected in patients undergoing NC, there is a delay for surgery because of initiation of chemotherapy. Although it is clear that NC offers an overall survival benefit, this benefit occurred in a trial population. There are patients who do not respond to chemotherapy, as evidenced by advanced disease trials in which significant response rates approximate 50%.[8] It is theoretically possible that patients who have chemotherapy-insensitive disease might progress locally and/or shed metastases during the period of time that NC is administered while waiting for RC. Performing a complete TUR before embarking on NC might eliminate some of the risk and eventually further improve multimodality outcomes in patients with muscle-invasive urothelial bladder cancer.