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Original Article

Outcome of patients with clinically node-positive bladder cancer undergoing consolidative surgery after preoperative chemotherapy: The M.D. Anderson Cancer Center Experience

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Abstract

Purpose: Patients with urothelial cancer with nodal metastasis have a poor prognosis, with many deemed incurable. We report outcomes of a prospective clinical protocol of patients with clinically node-positive disease treated via a multimodality treatment approach.

Patients and methods: A total of 55 patients with bladder urothelial carcinoma with concurrent node-positive disease including pelvic nodal and retroperitoneal lymph node (RPLN) involvement underwent preoperative chemotherapy followed by consolidative surgery between 1995 and 2010. Associations between clinicopathologic factors and outcomes were analyzed using log-rank test and Cox regression analysis.

Results: Median cancer-specific survival (CSS) was 26 months (95% CI: 12.9–not applicable) for all patients. A total of 30 (55%) patients had pN0 category disease at the time of surgical extirpation. Despite radiologic complete response after chemotherapy, 6 of 21 patients (29%) had pN+ category disease. The 5-year CSS rate was 66% for pN0 category disease vs. 12% for pN+ category disease ($P < 0.001$). Radiologic complete response to chemotherapy was associated with a 5-year CSS rate of 60% vs. 33% for a partial response ($P = 0.038$). Although no recurrences occurred within the lymphadenectomy template, 2 (14%) patients with cM1 RPLN disease who did not undergo RPLN dissection had recurrences in the RPLN basin and died within 6 months.

Conclusion: Multimodality treatment approach with upfront chemotherapy followed by surgery can result in a 66% 5-year CSS rate for patients rendered as having pN0 category disease despite initially presenting with node-positive disease. However, as those with residual disease do so poorly, further efforts in refining selection of patients for surgical consolidation are needed.

Keywords: Bladder cancer; Node-positive disease; Surgical consolidation; Preoperative chemotherapy; Multimodality treatment approach

1. Introduction

Although patients with localized bladder cancer are treated with radical surgery with an intent to cure, patients with either nodal or visceral metastases have historically been deemed surgically incurable. With a poor prognosis and limited benefit from surgical extirpation, these patients are oftentimes limited to undergo chemotherapy as the primary and sole treatment modality. However, studies have

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shown that patients with regional metastasis to the lymph nodes, as compared with that to visceral organs, appear to have an improved response to chemotherapy [1–3].

A multimodality approach with chemotherapy and surgery has been used to treat patients with locally advanced disease. Grossman et al. [4] demonstrated improved survival outcomes in patients with localized muscle-invasive disease after neoadjuvant chemotherapy followed by radical cystectomy, with benefit most pronounced in those with advanced stages of tumor. In addition, some studies have demonstrated a beneficial role of consolidative surgery after preoperative cisplatin-based chemotherapy for patients with node-positive disease [1,3,5–7].

We previously published results from our prospective phase II study examining the role of surgical consolidation in patients with metastatic urothelial cancer of the bladder to the retroperitoneal lymph nodes after response to chemotherapy [5]. In this study, we expand our previous cohort to include all patients with clinically node-positive disease, including disease in either pelvic or retroperitoneal sites, to report outcomes after preoperative chemotherapy followed by surgical extirpation.

2. Methods

1. We identified all patients at the University of Texas M.D. Anderson Cancer Center diagnosed with bladder urothelial carcinoma with concurrent clinically lymph node–positive disease, defined radiographically as the presence of lymph nodes $\geq$10 mm. The site of lymphadenopathy included both the pelvis alone (N1, N2, and N3) and pelvic with retroperitoneal lymph node disease (M1). (The American Joint Committee on Cancer 2010 TNM Staging System was used to define extent of primary tumor and nodal disease; i.e., N1—single regional lymph node in the true pelvis, N2—multiple regional lymph nodes, N3—common iliac lymph node involvement, and M1—distant lymph nodes [restricted to retroperitoneal].) Any patient with the presence of visceral metastases or predominantly nonurothelial carcinoma (squamous cell carcinoma, adenocarcinoma, small cell carcinoma, and micropapillary) was excluded from the study.

2. After approval from our Institutional Review Board, we collected data from patients in our protocol and also performed a retrospective medical record review of all patients with clinically node-positive disease who underwent preoperative chemotherapy followed by consolidate extirpative surgery. We restricted our cohort to patients treated from 1995 to 2010.

3. Patient demographic information including sex and age at treatment initiation was recorded. The clinical tumor category was based on both a pathologic review from transurethral resection of bladder tumor and findings from examination under anesthesia. Computed tomography cross-sectional imaging was used to determine the clinical nodal category and clinical response to chemotherapy. All tumors were high-grade based on the 2004 World Health Organization grading system. At surgical consolidation, all patients underwent a pelvic lymph node dissection, with retroperitoneal lymph node dissection reserved for those with clinical retroperitoneal lymph node disease. Operative and pathology reports were used to determine the lymphadenectomy templates with careful determination of the most proximal limit of dissection. The presence, number, density, and location of positive lymph nodes were reviewed.

4. Various different preoperative chemotherapeutic regimens were used, as the selection of combination agents was left to the discretion of the medical oncologist. Most of the patients received cisplatin-based chemotherapy. The predominant reason for using a non–platinum-based regimen was poor renal function. As a rule, chemotherapy was given with the goal of achieving either a complete radiologic response or as maximal response as possible, which oftentimes involved changing chemotherapeutic regimens. In general, patients were restaged after 2 cycles of chemotherapy to assess for response. If a clinical response was not seen, the chemotherapy regimen was often altered. Patients were once again restaged with cross-sectional imaging on completion of their course of chemotherapy. Nodal response to chemotherapy was based on the Response Evaluation Criteria in Solid Tumors (RECIST criteria) and was considered complete response (CR), partial response (PR), stable disease (SD), or progressive disease [8]. Adjuvant chemotherapy was only reserved for patients with progressive or recurrent disease after surgery and was not given in the setting of pathologic nodal disease alone. Radiotherapy was not used in our cohort of patients.

5. The primary end points of the study were cancer-specific survival (CSS) and recurrence-free survival (RFS). Cause of death was determined by reviewing patients' clinical notes and follow-up reports. In cases where a definitive cause of death was not evident, we based it on patients' most recent clinical status and time from last follow-up to death. The CSS was calculated as the period from the date of consolidative surgery to the date of death or date of last follow-up, if patients were alive at the time of last follow-up. Patients who were alive or died due to reasons other than cancer were censored. The RFS was calculated as the time from the date of surgery to the date of death, the date of disease recurrence, or the date of last follow-up. Patients who were alive without disease recurrence at the last follow-up were censored. The Kaplan-Meier method was used to estimate CSS and RFS probabilities. The log-rank test and the univariable and the multivariable Cox proportional hazards regression analyses were used to evaluate the association between clinicopathologic factors and outcomes factoring in variables of age, time from chemotherapy to surgery, pathologic category, presence of lymphovascular invasion, clinical nodal response to chemotherapy, extent of lymphadenectomy,