Original Article

The Integration of Chemotherapy and Surgery for Bladder Cancer

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Key Words

Bladder cancer, lymphadenectomy, neoadjuvant chemotherapy, adjuvant chemotherapy

Abstract

Despite surgery with curative intent, approximately 50% of patients with muscle-invasive transitional cell carcinoma of the bladder will develop distant metastases and succumb to their disease. Attempts to improve outcomes have focused on refining surgical techniques and integrating perioperative chemotherapy. This review summarizes the available literature addressing the role of pelvic lymphadenectomy, neoadjuvant chemotherapy, and adjuvant chemotherapy in the management of patients with muscle-invasive transitional cell carcinoma of bladder. (*JNCCN* 2005;3:45–51)

Transitional cell carcinoma (TCC) of the bladder exists as a spectrum of clinical states ranging from superficial to invasive to metastatic disease. Each clinical state is associated with a unique prognosis, approach to treatment, and tumor biology. Although patients with superficial and muscle-invasive disease are often curable, the vast majority of patients with distant metastases will succumb to their disease. Clearly, the goal of treatment at each disease state is to prevent progression to more advanced states and, ultimately, death. For patients with muscle-invasive disease, the integration of chemotherapy and surgery has been the focus of much investigation in an effort to optimally achieve this goal.

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Surgical Management of Muscle-Invasive TCC

Radical Cystectomy

For patients with muscle-invasive disease found on a transurethral resection of bladder tumor (TURBT) specimen, the standard approach in the United States is a radical cystectomy with pelvic lymph node dissection, although organ-sparing programs may be appropriate in a select subgroup of patients. A radical cystectomy involves a wide resection of all the perivesical fat and tissue to achieve a negative margin. In men, the procedure is performed in conjunction with a prostatectomy, and in women the urethra, uterus, fallopian tubes, ovaries, anterior vaginal wall, and surrounding fascia are also removed.

The prognosis after surgery with curative intent depends on the pathologic stage. In a recent report on 1,054 patients with TCC undergoing radical cystectomy and pelvic lymph node dissection, the 5-year disease-free survival for patients with node-negative organ-confined disease exceeded 80%. This number dropped to 62% to 78% for patients with extravesical disease (pT3) and to 50% for patients with invasion of local organs (pT4).[1] Lymph node involvement generally portends an even worse prognosis. Five-year survival rates of up to 57% have been reported for patients with N1 disease compared with 0% to 27% for those with N2 to N3 disease.[2,3]

Impact of Surgical Factors on Outcome

The importance of an "adequate" pelvic lymph node dissection and pathologic assessment should not be overlooked. A standard pelvic lymph node dissection includes removal of all of the distal common iliac, external iliac, obturator, and hypogastric nodes. This approach typically yields 10 to 14 lymph nodes.[4] Several retrospective studies have correlated improved survival with the ex-

tent of lymphadenectomy. An analysis of 637 cases of invasive bladder TCC treated using radical cystectomy and pelvic lymph node dissection explored the association between surgical and pathological variables and survival.[5] Improved survival and decreased local recurrence was associated with an increased number of lymph nodes removed (and examined by the pathologist) in patients with node-negative and node-positive disease. The 5-year survival rate for patients with 0 to 6, 6 to 10, 11 to 14, and more than 14 lymph nodes examined was 33%, 44%, 73%, and 79%, respectively. This conclusion was corroborated by a report in which Surveillance, Epidemiology and End Results (SEER) data on 1,923 patients who underwent radical cystectomy were analyzed and yielded similar results.[6]

The influence of surgical factors on outcome has been shown to be independent of the impact of perioperative chemotherapy. In a recent analysis of a randomized cooperative group study exploring neoadjuvant chemotherapy, a multivariate model adjusted for perioperative chemotherapy, age, pathologic stage, and nodal status showed that negative margins and 10 or more nodes removed were significantly associated with longer post-cystectomy survival.[7] These same surgical factors were significant predictors of local recurrence.

Historically, no standard definition of an "adequate" cystectomy and lymphadenectomy has been outlined. To address this issue, the consecutive cystectomy experience of 16 surgeons from four tertiary referral centers was reviewed.[8] Based on the results achieved in 1,091 cases of cystectomy, a positive margin rate on fewer than 10% of all cases was felt to be acceptable. A standard lymphadenectomy was advised for all reasonably fit candidates. Specifically, retrieval and examination of at least 10 to 14 lymph nodes was recommended, acknowledging that some interindividual variation will exist.

Integrating Perioperative Chemotherapy

A significant proportion of patients undergoing cystectomy with curative intent will have micrometastases and ultimately die of the disease. Given the chemosensitivity of TCC in patients with overt metastases, several clinical trials have sought to administer chemotherapy in the perioperative setting to try to eradicate subclinical disease. These trials have used a variety of chemotherapeutic regimens administered before (neoadjuvant) or after (adjuvant) surgery.

Trial Design and Statistical Considerations

Well-designed, interpretable trials exploring the role of perioperative chemotherapy in TCC should include the following elements: randomization between chemotherapy plus definitive local therapy versus local therapy alone, use of cisplatin-based chemotherapy, and adequate sample size. Regarding sample size, considering that up to 50% of patients will be cured with cystectomy alone, the potential benefit of chemotherapy is limited to the remaining 50% who have micrometastatic disease. If the proportion of patients who experience complete response in the perioperative setting is the same as that for patients with overt metastases (approximately 20%), then a survival benefit may be restricted to only 10% of the entire population. A trial with adequate power to detect an absolute survival difference of 10% would require randomization of 1,000 patients.[9] A smaller sample size would be required if the benefit from chemotherapy were greater.

Neoadjuvant Chemotherapy

Administering chemotherapy before surgery has several advantages. Patients may be better able to tolerate chemotherapy in the preoperative setting. Systemic therapy is initiated sooner, theoretically against a smaller volume of micrometastases. In addition, this approach allows a response evaluation of the primary tumor, which is of prognostic significance. In a study of patients treated with neoadjuvant cisplatin-based therapy followed by definitive surgery, at a median follow-up of 25 months, 91% of patients who experienced a response to chemotherapy (defined as pathologic stage T1 or less) were alive compared with 37% of those with no response.[10]

A potential disadvantage of the neoadjuvant approach is a result of the marked discordance between clinical response (based on repeat staging cystoscopy/TURBT) and pathologic response (based on pathologic review of the cystectomy specimen). In a study exploring neoadjuvant MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) 57% of patients achieved a clinical complete response while only 30% had a pathologic complete response.[11] Although neoadjuvant therapy may afford the consideration of organ preservation in a select subgroup of patients, the majority will still require cystectomy.

Hence, cystectomy refusal in patients experiencing a complete clinical response becomes problematic. Another theoretical disadvantage of neoadjuvant chemotherapy is the risk of delaying potentially curative surgery during administration of possibly ineffective chemotherapy.

Randomized trials have explored the role of neoadjuvant chemotherapy in TCC (Table 1). Many of these trials failed to show a survival benefit in the combined modality arm; however, these studies suffered from inadequate sample size,[12] suboptimal chemotherapy,[13,14] premature closure,[15] or inadequate follow-up time.[16,17] Recently, the results of large, well-designed trials and a meta-analysis have been reported, and these have shifted the treatment paradigm in muscle-invasive disease toward the routine use of neoadjuvant chemotherapy.[17–19]

The largest trial of neoadjuvant chemotherapy in TCC was conducted by the MRC/EORTC.[17] In this trial, 976 patients with T2-T4aNx disease were randomized to receive neoadjuvant CMV (cisplatin, methotrexate, and vinblastine) or no chemotherapy. Definitive management of the primary tumor included cystectomy, radiation therapy, or both. In the initial report, the 5.5% difference in the absolute 3-year survival (hazard ratio [HR] = 0.85; 95% confidence interval [CI], 0.71–1.02) favoring the chemotherapy arm did not reach statistical significance. However, updated results, at a median follow-up of 7 years, showed a statically significant improvement in survival for patients receiving neoadjuvant chemotherapy (P = .048; HR, 0.85; 95% CI, 0.72–1.0).[17]

A U.S. intergroup trial has confirmed the benefits of neoadjuvant chemotherapy.[18] Intergroup 0080 randomized 317 patients with T2 to T4a TCC of the bladder to receive three cycles of neoadjuvant MVAC followed by radical cystectomy versus radical cystectomy alone. A complete pathologic response rate of 38% was achieved with neoadjuvant chemotherapy compared with 15% for cystectomy alone (P < .001). At a median follow-up time of 8.7 years, both median survival (77 vs. 46 months; P = .06) and 5-year survival (57% vs. 43%; P = .06) favored the neoadjuvant chemotherapy arm. Importantly, no treatment-related deaths occurred, and the use of neoadjuvant MVAC did not impair the ability to proceed with surgery or increase the rate of postoperative complications.

A recent meta-analysis that includes data from 2,688 patients treated in 10 randomized trials further supports the use of neoadjuvant chemotherapy for muscle-invasive TCC.[20] Notably, this analysis did not include data from Intergroup 0080. Compared with local therapy alone, the use of neoadjuvant platinum-based combination chemotherapy was associated with a significant improvement in overall survival (HR, 0.87; 95% CI, 0.78–0.98; P = .016) with a 5% absolute survival benefit at 5 years (overall survival increased from 45%–50%). The survival benefit did not achieve statistical significance when trials using single-agent

Table 1 Randomized Trials of Neoadjuvant Chemotherapy

Trial Organization or Country	Patients, *N*	Chemotherapy	Primary Treatment	Survival Benefit
MRC/EORTC[17]	975	CMV	RT/Cyst/Both	Yes
INT-0080[19]	317	MVAC	Cyst	Yes
Nordic-1[20]	325	C + A	RT/Cyst	*Yes
Nordic-2[34]	317	M + C	Cyst	No
Spain (CUETO)[14]	122	C	Cyst	No
Australia/UK[13]	255	C	RT	No
MGH/RTOG[15]	123	CMV	C + RT/Cyst	No
GISTV[16]	171	MVEC	Cyst	No
Egypt[27]	194	CarboplatinMV	Cyst	No

Abbreviations are: MRC, Medical Research Council; EORTC, European Organization for Research and Treatment; INT, United States Intergroup; GUONE, Gruppo Uro-Oncologico del Nord Est; CUETO, Club Urologico Espagnol de Tratiemneto Oncologico; MGH, Massachussetts General Hospital; RTOG, Radiation Therapy Oncology Group; GITSV, Gruppo Italiano per lo Studio dei Tumori de la Vesicula; M, methotrexate; C, cisplatin; V, vinblastine; A, doxorubicin; 5-FU, 5-flourouracil; E, epirubicin; Cyst, cystectomy; RT, radiation therapy.

* Benefit for subset with T3-T4

cisplatin were included (HR, 0.91; 95% CI, 0.83–1.01; P = .084).

Adjuvant Chemotherapy

Delivery of chemotherapy postoperatively also has potential advantages and disadvantages. An adjuvant approach allows the team to base the decision on administering chemotherapy on information obtained from pathologic review of the cystectomy specimen rather than the TURBT specimen. Given the inaccuracies of the latter, this may avoid "over-treating" patients who are estimated to have a reasonable outcome from surgery alone (patients with disease confined to the bladder). Disadvantages include the potential difficulties tolerating chemotherapy postoperatively and the lack of objective means of assessing treatment response after the primary tumor is removed.

At least five randomized trials have evaluated the role of adjuvant chemotherapy after cystectomy (Table 2).[21–25] All of these trials were relatively small, enrolling only 49 to 91 patients. Nonetheless, two trials did suggest a survival benefit with adjuvant chemotherapy. In a trial reported by Skinner et al.,[23] patients with pT3 or pT4 or node-positive TCC were randomized to receive CISCA (cisplatin, doxorubicin, and cyclophosphamide) for four cycles versus no further treatment after cystectomy. The median survival was 4.3 years in the adjuvant chemotherapy group versus 2.4 years in the observation group (P = .006). Criticisms of this trial include potential selection bias. Of the 498 patients deemed eligible, only 91 were enrolled.

A trial conducted by Stockle et al.[22] randomized patients with pT3b to T4a or N+ TCC to receive either three cycles of MVA(E)C (methotrexate, vinblastine, doxorubicin/epirubicin, cisplatin) or no further treatment after cystectomy. This trial was designed to detect a 35% improvement in disease-free survival and to enroll 100 patients. The study was terminated early, after 49 patients were enrolled, when an interim analysis showed a significant improvement in 3-year disease-free survival (63% vs. 13%; P = .0015).

The remaining three trials did not show a survival advantage with the use of adjuvant chemotherapy. However, these results must be interpreted cautiously. As stated, all of these trials suffered from an inadequate sample size. Two trials primarily evaluated patients with bladder-confined disease, a population with a reasonably good outcome from surgery alone, making an incremental benefit from chemotherapy even more difficult to detect.[21,24] One trial used single-agent cisplatin, known to be inferior to cisplatin-based combinations in advanced disease.[24]

As a consequence of the limitations of these trials, the data supporting adjuvant chemotherapy are less compelling than the data supporting neoadjuvant chemotherapy. Divergent opinions exist regarding a standard approach as reflected by the two large cooperative group trials currently exploring treatment in the adjuvant setting. In an effort to definitively answer this question, the European Organization for Research and Treatment of Cancer (EORTC) is randomizing patients with pT3 to T4 or node-positive disease to immediate cisplatin-based chemotherapy (MVAC or gemcitabine-cisplatin) or similar chemotherapy at the time of relapse. Already convinced of the benefit of adjuvant chemotherapy, the Cancer and Leukemia Group B/Clinical Trial Support Unit (CALGB/CTSU) is attempting to define an optimal regimen by

Table 2 Randomized Trials of Adjuvant Chemotherapy

Trial Organization/Country	Patients, *N*	Chemotherapy	Primary Therapy	Survival Benefit
University of Southern California[23]	91	CAP	Cyst (CAP Cyst	Yes
University of Mainz[22]	49	MVA(E)C	Cyst	Yes
Swiss Group for Clinical Cancer Reasearch[24]	77	C	Cyst (C Cyst	No
Italian Uro-Oncologic Cooperative Group[21]	83	CM	Cyst (CMCystCyst	No
Stanford University[20]	50	CMV	Cyst	No

Abbreviations are: M, methotrexate; C, cisplatin; V, vinblastine; A, doxorubicin; 5-FU, 5-flourouracil; E, epirubicin; Cyst, cystectomy.

randomizing patients to receive either the sequential doublet of AG-TP (doxorubicin plus gemcitabine followed by paclitaxel plus cisplatin) or gemcitabine-cisplatin.

Neoadjuvant Versus Adjuvant Chemotherapy

No randomized trials have directly compared pre-cystectomy versus post-cystectomy chemotherapy in patients with locally advanced TCC. However, a study conducted by Millikan et al.[26] randomized 140 patients to receive two cycles of neoadjuvant MVAC followed by cystectomy plus three additional cycles of adjuvant MVAC versus initial cystectomy followed by five cycles of adjuvant MVAC. No significant differences in outcome were seen between the two groups.

Choice of Chemotherapeutic Regimen in the Perioperative Setting

For patients with advanced/metastatic TCC, the combination of gemcitabine plus cisplatin has been shown to result in comparable response proportions and overall survival when compared with MVAC, but with less toxicity.[27] Although randomized trials exploring perioperative gemcitabine-cisplatin have not been performed, most have extrapolated the results from the advanced disease trial and adopted this regimen for use in the perioperative setting. Indeed, the EORTC adjuvant trial allows treatment with either gemcitabine-cisplatin or MVAC on the experimental arm and the CALGB trial includes gemcitabine-cisplatin as the control arm. No data are available to support the use of single-agent cisplatin or carboplatin-based regimens in the perioperative setting.

Post-Chemotherapy Surgery

An often-overlooked aspect of multimodality therapy in TCC is the potential role for resection of residual disease in patients who initially present with unresectable/metastatic disease and achieve an optimal response to chemotherapy. The importance of post-chemotherapy surgery in this setting has been highlighted in several studies.[28–33] In an analysis of 203 patients treated in five trials using MVAC, 50 patients underwent post-chemotherapy surgery for suspected or known residual disease.[28] Seventeen of these 50 patients had no viable tumor found at the time of surgery. Three patients had residual disease that was unresectable. In the remaining 30 patients, residual TCC was completely resected, resulting in a complete response to chemotherapy plus surgery. Of these 30 patients, 33% were alive at 5 years, a result similar to results attained for patients achieving a complete pathologic response to chemotherapy alone. Optimal candidates for post-chemotherapy resection of residual disease were patients who experienced a major response to chemotherapy and those with pre-chemotherapy disease limited to the primary site or lymph nodes.

Recommendations for Management

1. Surgical factors influence bladder cancer outcomes independent of the use of perioperative chemotherapy. An increased number of lymph nodes retrieved at the time of pelvic lymphadenectomy has been correlated with improved survival. Patients undergoing radical cystectomy for invasive TCC should undergo retrieval and examination of at least 10 to 14 pelvic lymph nodes.
2. Neoadjuvant cisplatin-based combination chemotherapy has been shown to improve survival in patients with invasive TCC. MVAC may be the most effective regimen; however, gemcitabine-cisplatin is a reasonable alternative. Enrollment on a clinical trial should always be considered.
3. Given the limitations of several completed trials, the data are less compelling for adjuvant chemotherapy. Two large cooperative group trials are underway to further define the role of chemotherapy in this setting, and enrollment should be encouraged. Outside of a clinical trial, physicians must make individual treatment decisions based on interpretation of the available data.
4. Carboplatin-based combination chemotherapy currently has no role in the perioperative setting. Therefore, in patients with relative or absolute contraindications to cisplatin (eg, inadequate creatinine clearance, status post nephrectomy for upper tract TCC), perioperative chemotherapy should be administered in the setting of a clinical trial.
5. Post-chemotherapy surgery should be considered in patients who have shown a response and who have minimal residual disease after chemotherapy.

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