

Regional lymph node status in patients with bladder cancer found to be pathological stage T0 at radical cystectomy following systemic chemotherapy

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OBJECTIVE

- To evaluate the effect of preoperative cisplatin-based chemotherapy on the regional lymph nodes of patients with bladder cancer who attain pathological T0 status in the bladder after chemotherapy followed by radical cystectomy.

PATIENTS AND METHODS

- Patients who underwent radical cystectomy at MSKCC for urothelial carcinoma of the bladder were retrospectively reviewed.
- Those patients achieving pT0 status after preoperative chemotherapy were identified and classified into two groups, those rendered pT0: (i) after receiving neoadjuvant

chemotherapy and (ii) after receiving definitive chemotherapy (defined in this case as chemotherapy given for unresectable or regionally metastatic disease).

- These two groups were analyzed separately for lymph node status at cystectomy and regional lymph node recurrence.

RESULTS

- Of 169 pT0 patients, 24 patients (14%) had received neoadjuvant chemotherapy, whereas 17 patients (10%) had received definitive chemotherapy for unresectable or regionally metastatic disease.
- No patient rendered pT0 after neoadjuvant chemotherapy had lymph node involvement at radical cystectomy or recurrence within the regional lymph node template.
- Among patients with advanced disease rendered pT0 by definitive chemotherapy,

35% had lymph node involvement at radical cystectomy or subsequent recurrence within the dissection template.

CONCLUSIONS

- Patients achieving pT0 status after receiving neoadjuvant chemotherapy had no evidence of lymph node involvement at cystectomy.
- Patients undergoing definitive chemotherapy for advanced disease followed by cystectomy experienced reduced rates of nodal involvement compared to the lymph node-positive rates predicted by preoperative clinical staging. However, there remains a risk of regional lymph node involvement in this group.

KEYWORDS

carcinoma, transitional cell, bladder, lymph nodes, cystectomy, neoadjuvant

INTRODUCTION

Radical cystectomy with pelvic lymph node dissection (RC/PLND) remains the gold-standard therapy in the setting of urothelial carcinoma (UC) invading bladder muscle. However, an overall 50% 5-year survival is observed for patients with invasive disease treated by surgery alone. Micrometastatic disease present at the time of presentation is largely responsible for disease recurrence and death. Randomized prospective studies have demonstrated that receiving neoadjuvant

chemotherapy before RC/PLND for patients with disease invading bladder muscle results in an improved overall survival and an increased proportion (30–40%) of patients whose bladders are free of disease at cystectomy (pT0) [1,2]. pT0 status at RC/PLND after receiving neoadjuvant chemotherapy is associated with an 85% overall survival rate [2]. Such outcomes have prompted some investigators to explore bladder preservation in select patients exhibiting a complete response to neoadjuvant chemotherapy [3–5]. Several concerns for such a strategy exist,

including inaccurate staging of the bladder and limited information on the status of the regional lymph nodes (LN). Even in patients who demonstrate a good response to chemotherapy in the bladder, clinical evaluation of the pelvic LNs is based on modalities that have known limitations [6]. Therefore, the present study aimed to investigate LN status in patients with bladder cancer that was pretreated with systemic chemotherapy before RC/PLND. The RC population was examined to assess the pathological status of the regional LNs in

patients found to be pT0 at RC/PLND. A strict pathological definition of pT0 status was used based on information obtained from the bladder and regional LNs at RC. The analysis focused on two separate groups of patients who achieved pT0 status: (i) patients with localized disease and no evidence of LN involvement (clinical stage \leq T4aN0, stage III) and (ii) patients with locally extensive unresectable disease or evidence of regional LN involvement (T4b, N0 or N+, stage IV). Both groups received systemic chemotherapy before RC/PLND. Group 1 received true neoadjuvant chemotherapy and group 2 received definitive chemotherapy, which, for the purposes of the present study, was defined as chemotherapy aimed at downstaging unresectable or regionally metastatic disease. Because the two groups differ greatly with respect to their clinical course and pathological features, no attempt was made to directly compare their outcomes.

MATERIALS AND METHODS

SUBJECTS AND PROCEDURES

Following Institutional Review Board approval, we queried our institutional bladder cancer database to identify patients who had undergone RC for UC at our institution. We eliminated those who had undergone a previous PLND or pelvic radiotherapy, those requiring nephroureterectomy for invasive upper tract UC before RC, and those with distant metastases (i.e. beyond the regional nodes) at presentation. From this subset, patients were selected who had no residual carcinoma within the bladder at RC, as determined by pathological evaluation of the surgical specimen (pT0). Our definition of pT0 excluded all patients with carcinoma *in situ* within the specimen (bladder or prostate). Data related to preoperative clinical staging, preoperative therapy, operative findings and oncological outcome were recorded.

Within our pT0 population, and based on their clinical presentation, two separate groups were identified that had undergone chemotherapy before RC/PLND: (i) those patients with localized, resectable disease receiving true neoadjuvant chemotherapy (clinical stage \leq T4aN0, stage III) and (ii) patients with locally extensive unresectable disease or regionally metastatic disease to the pelvic LNs (T4b, N0 or N+, stage IV) receiving definitive systemic chemotherapy before RC/PLND. We strictly defined neoadjuvant

chemotherapy to include only stage cT2–cT4a, N0 and M0 patients for whom cisplatin-based, multidrug regimens were administered preoperatively as a standard of care [7]. The group of patients receiving definitive chemotherapy included all patients receiving any systemic chemotherapy regimen given preoperatively for surgically unresectable or regionally metastatic disease (stage IV), whose multimodality treatment approach included RC/PLND. Patients receiving definitive chemotherapy for advanced disease were generally prescribed six cycles of therapy, as opposed to the three cycles of methotrexate, vinblastine, doxorubicin, cisplatin (MVAC) or four cycles of gemcitabine/cisplatin used for neoadjuvant treatment based on the standards at our institution. In both groups, patients were included in the analysis if they had successfully completed a minimum of two cycles of systemic therapy. These groups were analyzed separately to report the outcomes in these clinically distinct patient populations with no attempt to directly compare the groups.

We defined regional LN involvement as either pathologically evident disease in the surgical specimen or a radiographical recurrence within the template of the regional LND. We define the regional nodes as those located in the obturator, hypogastric, presacral and common iliac packets, as well as the lower paraaortic nodes below the inferior mesenteric artery included in our standard extended PLND [8]. Local pelvic recurrences not associated with these LNs, such as vaginal cuff or anterior rectal wall disease, were not coded as pelvic LN recurrences for this analysis.

PATHOLOGICAL EXAMINATION

RC specimens were processed according to institutional protocol. All pathological evaluations were performed by a genitourinary pathologist. Briefly, each specimen was visually inspected and prosected before formalin fixation. In the absence of grossly evident tumour, all tissue from the region of the transurethral resection (TUR) scar, as well as any other suspicious lesions, was sampled. Specimens were also taken from randomly selected normal-appearing areas of mucosa, as well as the cut edge of each surgical margin. In the event that no UC could be identified during such an evaluation, the patient was considered to be pT0. The LN specimens were prosected either

fresh or, less commonly, after fixation in 10% formaldehyde for 24 h. The LNs were then manually counted, sectioned and submitted for processing. Slides stained with haematoxylin and eosin were examined microscopically.

STATISTICAL ANALYSIS

Descriptive statistics were summarized separately for the two subgroups. We identified those patients with LN metastases at RC and those with subsequent recurrences within the template of the PLND as described above. Assuming that recurrent regional LN disease represents undetected micrometastases present at RC, the combination of the two groups should estimate the risk of nodal metastasis at the time of RC in our pT0 patients. CIs were calculated using Stata, version 8.2 (Stata Corp., College Station, TX, USA).

RESULTS

Of the 1905 patients who underwent RC for UC at our institution between 1989 and 2008, 210 patients had no residual carcinoma in the bladder at surgery (11%). We excluded 12 patients who had undergone previous PLND or pelvic radiotherapy, 11 who had been surgically treated for previous invasive upper tract disease, six with distant metastases and three patients with inadequate follow-up. Because the present study aimed to evaluate the rate of LN involvement in patients with chemo-responsive primary lesions, we excluded five patients who received substandard (carboplatin-based) neoadjuvant chemotherapy and four patients who received preoperative chemotherapy but required further TUR of viable disease to render them pT0 at RC (i.e. not complete chemotherapy responders).

Of the 169 evaluable pT0 patients remaining, 116 (69%) were male and 53 (31%) were female. The median (interquartile range) age of the entire group was 67 (60–73) years. In total, 24 (14%) received neoadjuvant chemotherapy. Seventeen patients (10%) received definitive chemotherapy for unresectable or regionally metastatic disease. These patients served as the focus of the analysis. Demographic and staging information for these distinct groups is reported in Table 1. The chemotherapy regimens utilized and number of cycles received are summarized in Table 2.

REGIONAL LN STATUS FOLLOWING SYSTEMIC CHEMOTHERAPY

All patients (24/24) achieving pT0 status in the bladder after neoadjuvant chemotherapy underwent PLND at the time of RC. Median LN counts and LN-positive rates are reported in Table 3. No patient (0/24) who received neoadjuvant chemotherapy and had a pT0 response in the bladder had pathological evidence of regional LN involvement. Additionally, no patient developed recurrent disease within the regional LN template over a median (range) follow-up of 27 (4–197) months. The overall 100% LN-negative rate in this population is associated with a one-sided 97.5% CI of 86–100%.

DEFINITIVE CHEMOTHERAPY FOR LOCALLY UNRESECTABLE OR REGIONALLY METASTATIC DISEASE

All 17 patients in the group receiving definitive chemotherapy for unresectable or regionally metastatic disease underwent PLND at the time of post-chemotherapy surgery. Median LN counts and LN-positive rates are reported in Table 3. Of 17 patients, four (24%) had involved LNs at post-chemotherapy RC/PLND, and an additional two patients had subsequent recurrences within the regional LN template (two patients with positive LNs at RC later recurred within the template as well). The median (range) follow-up for those without recurrence in this

population was 44 (5–148) months. In total, six of the 17 patients (35%) rendered pT0 in the bladder after definitive chemotherapy for advanced disease had LN involvement at RC/PLND and/or subsequent recurrence within the dissection template, whereas 11 patients (65%) have remained free of nodal involvement (95% CI 38–86%).

Of the 17 patients treated with definitive preoperative chemotherapy, 12 had clinical evidence of regional nodal metastasis (radiographic diameter ≥1 cm, positron emission tomography-positive or biopsy-proven) before chemotherapy. After chemotherapy, seven of those 12 patients (58%) were found to be pN0 at RC and remained free of regional LN disease over the follow-up period, whereas five (42%) demonstrated persistent regional LN disease. Although no formal survival analysis was performed as a result of the small size of the study population, six of the seven pN0 patients were alive without evidence of disease at the time of last follow-up. The seventh patient died of unknown causes 6 years after surgery. The median (range) follow-up for survivors in this subgroup was 39 (18–93) months.

TABLE 1 Patient demographics and clinical staging at the time of radical cystectomy

| Variable | Neoadjuvant chemotherapy | Therapeutic chemotherapy |
|--|--------------------------|--------------------------|
| pT0 patients, <i>n</i> | 24 | 17 |
| Age at surgery (years), median (IQR) | 60 (58–67) | 66 (58–72) |
| Gender, <i>n</i> (%) | | |
| Male | 16 (67) | 12 (71) |
| Female | 8 (33) | 5 (29) |
| Highest clinical stage before definitive therapy, <i>n</i> (%) | | |
| cTa | 0 (0) | 0 (0) |
| cTis | 0 (0) | 0 (0) |
| cT1 | 0 (0) | 3 (18) |
| cT2 | 13 (54) | 7 (41) |
| cT3 | 9 (38) | 1 (6) |
| cT4a | 2 (8) | 0 (0) |
| cT4b | 0 (0) | 6 (35) |
| Regionally metastatic disease, <i>n</i> (%) | 0 (0) | 12 (71) |

IQR, interquartile range.

DISCUSSION

The present study quantifies the pathological status of the regional pelvic LNs in patients who demonstrate a complete pathological response to systemic chemotherapy given before RC/PLND. We used the strict definition of complete response to indicate pathological T0 status within the bladder at RC/PLND. These data provide confirmation that, in the

TABLE 2 Chemotherapeutic regimens

| Regimen | Neoadjuvant chemotherapy (<i>n</i> = 24) | | Therapeutic chemotherapy (<i>n</i> = 17) | |
|---|---|-----------------------|---|-----------------------|
| | Receiving, <i>n</i> (%) | Median cycles (range) | Receiving, <i>n</i> (%) | Median cycles (range) |
| Methotrexate, vinblastine, doxorubicin, cisplatin | 5 (19) | 4 (2–4) | 3 (18) | 4 (4–6) |
| Gemcitabine, cisplatin | 19 (79) | 4 (2–6) | 4 (24) | 5 (2–5) |
| Ifosfamide, paclitaxel, cisplatin | 0 (0) | -- | 2 (12) | 4.5 (4–5) |
| Doxorubicin, gemcitabine, ifosfamide, paclitaxel, cisplatin | 0 (0) | -- | 3 (18) | 4 (4–4) |
| Gemcitabine, cisplatin, paclitaxel | 0 (0) | -- | 2 (12) | 5.5 (5–6) |
| Gemcitabine, carboplatin, paclitaxel | 0 (0) | -- | 2 (12) | 5.5 (5–6) |
| Cyclophosphamide, docetaxel, doxorubicin | 0 (0) | -- | 1 (6) | 6 NA |

NA, not available.

setting of neoadjuvant chemotherapy for resectable disease, patients experiencing a confirmed pT0 response within the bladder are likely to demonstrate similar chemoresponsiveness within the regional LNs. By contrast, in the setting of a pT0 response in the bladder after definitive systemic chemotherapy for more advanced disease, there remains a high likelihood that pelvic LN disease persists.

Several prospective randomized trials demonstrate a survival advantage for patients with UC invading bladder muscle using the combined treatment of neoadjuvant cisplatin-based chemotherapy followed by RC/PLND compared to RC/PLND alone.

Although ≈15% of patients will have no identifiable disease in the bladder at RC as a result of TUR alone [2], the rate of pT0 will increase to 30–40% in patients receiving neoadjuvant platin-based chemotherapy [1,2]. The Southwestern Oncology Group reported an 85% overall survival rate for patients found to be pT0 at RC after TUR and neoadjuvant MVAC [2]. Although post-chemotherapy RC/PLND remains the standard of care in this setting, the excellent outcomes associated with pT0 status after receiving neoadjuvant chemotherapy have prompted the proposal of bladder preservation in patients with a complete local response to neoadjuvant chemotherapy. The decision for bladder preservation after chemotherapy would be based on clinical staging (radiographical evaluation, repeat TUR and examination under anaesthesia) rather than a complete pathological evaluation of the bladder. In this setting, pelvic imaging (anatomic or functional) is the only modality used to stage the regional LNs following chemotherapy if no gross adenopathy is identified. Transurethral assessment of the bladder and cross-sectional imaging of the regional LN (including CT alone and fludeoxyglucose-positron emission tomography/CT) have associated rates of understaging [6,9–11]. Either the bladder or LNs, if understaged as having achieved a complete response, comprise a potential source of disease recurrence and disease dissemination if not resected.

In the present series, no patient found to be pT0 following cisplatin-based, multi-agent neoadjuvant chemotherapy had LN metastases at RC/PLND, or relapsed within the LND template. We may estimate the predicted node-positive rate for the neoadjuvantly

TABLE 3 Lymphadenectomy data and lymph node involvement

| Variable | Neoadjuvant chemotherapy (n = 24) | Therapeutic chemotherapy (n = 17) |
|--|-----------------------------------|-----------------------------------|
| Patients undergoing LND, n (%) | 24 (100) | 17 (100) |
| LNs resected, median (IQR) | 14 (10–24) | 11 (2–17) |
| Patients with +LNs at RC, n (%) | 0 (0) | 4 (24) |
| Patients with recurrent TCC in LND template, n (%) | 0 (0) | 4 (24) |
| Patients with any LN disease, n (%)* | 0 (0) | 6 (35) |

*Combination of groups with lymph node (LN) at radical cystectomy (RC) and those recurring subsequently, taking into account overlap between groups. LND, lymph node dissection.

managed patients based on the outcomes of a similar clinically staged group of patients with bladder cancer. Half of our pT0 neoadjuvantly-treated patients were cT2 and half were cT3–4a. On the basis of a previously reported series with a similar staging characteristic, we would anticipate that ≈20% of such patients would have pathological node-positive disease [12]. Even in the pT0 population that received no pre-treatment before RC/PLND (no preoperative chemotherapy, pT0 at RC/PLND following TUR alone), node-positive disease would be anticipated in a small percentage of patients. Included within the pT0 population in our cystectomy database were 128 patients rendered pT0 at RC/PLND after TUR alone who were not included in the initial analysis. This group included 44 patients who were eligible for neoadjuvant chemotherapy based on clinical stage (35 patients staged cT2, 80%; five patients staged cT3, 11%; four patients staged cT4a, 9%) and those who underwent RC/PLND. On the basis of clinical staging, the pT0 patients treated with RC/PLND alone were at lower risk for LN involvement compared to our neoadjuvantly-treated study group (clinical stage cT2 in 54%; cT3 in 38%; cT4a in 8%). However, the LN-positive rate at RC for the 44 patients treated with surgery alone was 14% (6/44) and an additional three (7%) patients developed LN involvement postoperatively, over a median (range) follow-up time of 40 (4–184) months. Although we have no pathological confirmation of LN status before systemic chemotherapy, our 0% LN-positive rate among our neoadjuvantly-treated pT0 patients supports the chemoresponsiveness of the regional LNs in these patients. It is unlikely that the lack of LN involvement was simply a result of the selection of lower risk patients.

It is important to stress that the entirety of the present study is based on patients who were pathologically staged following RC/PLND. Current clinical staging modalities will understage the bladder in up to 30% of cases [9,13] and the LNs in up to 21% [6]. Therefore, the data obtained in the present study cannot be used to accurately predict outcome in a clinically staged population, such as those being considered for bladder preservation after neoadjuvant chemotherapy. Rather, the information from the present study provides the baseline risk of regional LN involvement in patients found to be pathological stage T0 after receiving neoadjuvant chemotherapy. Until the accuracy of clinical staging improves, we continue to strongly recommend RC/PLND following neoadjuvant chemotherapy.

The present data also show that only 65% of the patients achieving pT0 status following definitive chemotherapy for unresectable or regionally metastatic disease were free of LN disease at RC/PLND or follow-up. Indeed, seven of the 12 patients with clinical evidence of LN involvement before therapy demonstrated an apparent resolution of LN disease (pN0). However, overall, there remains a 35% risk of LN involvement. This is consistent with the reported pattern of recurrence in patients who achieve a good response to systemic chemotherapy for advanced bladder cancer and subsequent recurrence. Patients with nodal involvement at presentation who recur after a clinical complete response to chemotherapy are most likely to recur at those LN sites that demonstrated initial involvement [14]. The importance of a complete LN dissection in this setting was previously demonstrated in a retrospective study of 60 patients who had received MVAC for regionally metastatic or

unresectable disease followed by RC with a minimum of 5 years of follow-up [15]. Nineteen patients had no residual disease at cystectomy, with a 5-year overall survival of 32%. Thirty-four patients underwent complete resection of residual cancer, of whom 29% survived after 5 years. This is in contrast to the 12 patients who refused RC after a major response to chemotherapy, of whom only one survived after 3 years. The data reported in the present study support the use of post-chemotherapy surgery for achieving a complete response to therapy in patients responding to chemotherapy delivered for regionally metastatic or unresectable disease.

The present study is intended to highlight the distinction that must be drawn between patients receiving chemotherapy with neoadjuvant versus definitive therapeutic intent, as well as the need for an evaluation with respect to post-chemotherapy surgery after a major response in each setting. As a retrospective review, the present study is subject to the biases inherent in that type of study. Follow-up in the the present study is limited at a median of 27 months for the group receiving neoadjuvant chemotherapy; 79% of these patients were treated after 1 January 2000. However, local relapse following chemotherapy has been shown to occur at a median of 12 months after treatment [14], which is well within our reported follow-up window. In addition, we included patients receiving gemcitabine/ cisplatin in the neoadjuvantly treated group. This regimen has not yet been validated by large, randomized controlled trials for use in the neoadjuvant setting, although it has shown efficacy when evaluated retrospectively [16]. Finally, the reported LNDs are not standardized. Although our current practice is to perform extended dissections proceeding proximally to include the entire common iliac node packets, over the course of the present study, some limited dissections were still being performed based on surgeon preference.

In conclusion, a pT0 response within the primary bladder tumour following neoadjuvant cisplatin-based chemotherapy is associated with a similar complete response within the regional LNs. By contrast, patients receiving definitive preoperative chemotherapy for locally unresectable or regionally metastatic UC are much more likely to have persistent disease within the regional

LNs despite a pathological complete response within the bladder. However, until more accurate clinically staging methods are available, we continue to advocate radical cystectomy and regional LN dissection in all patients receiving neoadjuvant chemotherapy. We also support the use of RC with regional LN dissection in patients demonstrating a major response to definitive chemotherapy for advanced disease, when safe and feasible.

CONFLICT OF INTEREST

None declared.

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Abbreviations: LN, lymph node; MVAC, methotrexate, vinblastine, doxorubicin, cisplatin; PLND, pelvic lymph node dissection; RC, radical cystectomy; TUR, transurethral resection; UC, urothelial carcinoma.