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The Role of Radical Cystectomy in Patients with Clinical T4b Bladder Cancer

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SUMMARY

Objectives—Patients with clinical T4b bladder cancer (extension to pelvic wall and/or adjacent organs other than prostate, vagina or uterus) are commonly considered unresectable. We hypothesized that select patients might achieve durable benefit from multiagent chemotherapy and extirpative surgery.

Methods—We identified patients with clinical T4bN0 bladder cancer from our IRB-approved database of patients undergoing radical cystectomy (n = 1194). Relevant demographic, clinical and pathologic data were compiled. Overall (OS), disease-specific (DSS) and recurrence-free survival (RFS) were analyzed by Kaplan-Meier estimation. Cox proportional hazards regression modeling was used to evaluate the influence of several potential prognostic factors.

Results—Twenty-three patients (16 male) with a median age of 65 years met study criteria. Chemotherapy was administered pre-operatively to 19 (83%) and post-operatively to 8 (35%) patients. Eight patients died of disease and one of other causes. The 1-, 2- and 5-year DSS was 91% (95% C.I. 70–98%), 66% (95% C.I. 42–83%) and 60% (95% C.I. 34–78%), respectively. Eight of 17 patients with pT2–4 tumors succumbed to disease compared to none of 6 who were ≤ pT1 (p = 0.04). Other predictors of decreased DSS included positive surgical margins (HR = 5.34, 95% C.I. 1.25–22.83) and presence of pathologic nodal metastasis (HR = 29.33, 95% C.I. 3.13–275.19). Variant histology was more common in this cohort than in the overall cystectomy database (43% vs. 11%).

Conclusions—Long-term survival can be achieved in a proportion of patients with cT4b bladder cancer undergoing chemotherapy and extirpative surgery. Careful selection of patients and meticulous surgical technique to avoid positive margins are critical.

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Keywords

bladder cancer; cystectomy; chemotherapy

INTRODUCTION

Radical cystectomy is the mainstay of therapy for invasive bladder cancer and is often combined with multi-agent chemotherapy for high-risk resectable disease to improve patient outcome. Disease considered unresectable is usually primarily treated with chemotherapy, and surgical consolidation is not performed because the disease is thought to be incurable. Clinical T4b disease is considered unresectable because tumor extends to the abdominal/pelvic wall or into adjacent organs other than those amenable to resection at the time of radical cystectomy (cT4a; prostate, vagina or uterus). This cT4b stage determination is made primarily with a combination of examination under anesthesia (EUA), which reveals an immobile, fixed mass, and cross-sectional imaging studies, which reveal extent of local spread.

The response rate to cisplatin-based multiagent chemotherapy for locoregionally advanced bladder cancer is as high as 60%^{1,2}. Thus tumors that are initially unresectable may become technically resectable, and the rationale for consolidative surgery in these patients is the observation that many patients with a clinical complete response still recur locoregionally, along with the finding that residual viable disease is often present in the radical cystectomy specimen^{3,4}. Furthermore, a subset of patients undergoing radical cystectomy are helped by palliation of current or future symptoms.

In order to evaluate the efficacy of consolidative surgery in cT4b bladder cancer, we retrospectively evaluated our experience with radical cystectomy in this cohort of patients.

MATERIALS AND METHODS

Study population

After obtaining approval from our institutional review board, we reviewed our cystectomy database to identify patients with cT4b urothelial carcinoma of the urinary bladder who underwent radical cystectomy at our institution between January 1990 and June 2006.

Patients were considered to have cT4b disease according to the 2002 TNM classification⁵ if the tumor was fixed and immobile on bimanual examination under anesthesia after transurethral resection of the tumor and/or there was direct invasion of an adjacent organ (other than prostate, vagina or uterus) on cross sectional imaging (CT or MRI). In this study all patients had a fixed mass on EUA.

Twenty-three patients underwent radical cystectomy, pelvic lymph node dissection and urinary diversion with curative intent for cT4b urothelial carcinoma of the bladder. No prospective criteria for proceeding with cystectomy were defined, but in general we considered cystectomy in patients who had a major response to chemotherapy as determined by EUA. Of note, our surgical database did not capture patients who presented with cT4b cancer but did not undergo cystectomy. Also, four additional cT4b patients with pre-treatment clinical evidence of lymph node metastasis (N+) were excluded from the study. No patient had distant metastasis. All cystectomy specimens were reviewed and classified by a genitourinary pathologist⁵.

Statistical analysis

The date of diagnosis of cT4b bladder cancer was used for all survival analyses. The date of death from any cause, death from bladder cancer and recurrence of bladder cancer was used for calculating overall (OS), disease-specific (DSS), and recurrence-free survival (RFS), respectively. Patients were censored at the date of last follow-up or, for DSS and RFS, at the date of death from causes other than bladder cancer.

The median OS, DSS and RFS were determined using the method of Kaplan and Meier.⁶ Cox's proportional hazards regression model was used to assess the predictive value of several potential risk factors for each clinical outcome (OS, DSS or RFS)⁷. This modeling was done in a univariate fashion and multivariate analysis was not performed due to the low numbers of events.

All statistical analyses were performed using SAS 9.1 for Windows (Copyright © 2002–2003 by SAS Institute Inc., Cary, NC). A p-value <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Twenty three patients with cT4bN0 bladder cancer underwent radical cystectomy (total n=1194) at M.D. Anderson Cancer Center between January 1990 and June 2006. Sixteen patients were male and the mean age was 65 years (range 41–89). The clinical and pathologic features are summarized in Table 1. Only 6 patients had conventional transitional cell carcinoma (TCC) without a secondary component; 7 had TCC with a component of glandular or squamous differentiation. Ten patients (43%) had a variant histologic pattern, which compared to 11% of patients in the overall cystectomy cohort.

Six patients were found to have $\leq$ pT1 disease, while 17 had residual muscle invasive disease at cystectomy. Three patients had positive margins and five had lymph node involvement. Overall 21 received chemotherapy (19 pre-operatively and 8 post-operatively). Different regimens of pre-operative chemotherapy were given, including MVAC (methotrexate/vinblastine/adriamycin/cisplatin) in 3, gemcitabine/cisplatin or gemcitabine/cisplatin/ifosfamide in 6, a Taxol-containing regimen in 9 and combinations of these agents in the others. Some of the variability was related to variant histologic subtypes. Post-operative chemotherapy was administered within 6 months of cystectomy in all 8 patients who received it, including all 3 patients with positive margins, 3 patients with pathologic nodal metastasis and 6 patients with pT4 disease. All three patients who received radiation therapy were treated with palliative intent at outside institutions prior to presentation at our institution. The patients who did not receive pre-operative chemotherapy were considered unlikely to tolerate both chemotherapy and surgery, and were treated with cystectomy with the intention of maximal potential palliation. Two of these chose also not to receive adjuvant chemotherapy. One of these was without evidence of disease at last follow-up (3.3 years) and one died of other causes at 14.9 years.

Survival Analysis

The median follow-up for the entire cohort was 1.6 years (range 0.5–14.9); 3.6 years (range 0.8–10.5) for 14 patients who remained alive, and 1.5 years (range 0.5–14.9) for 9 patients who died. Kaplan-Meier estimates for OS, DSS and RFS are shown in Figure 1. OS and DSS are identical up to 14.9 years, at which time one patient died from causes other than bladder cancer. One patient died in the post-operative period. The median OS was 14.9 years and the median DSS was not reached. The OS and DSS rates were equal at 1, 2 and 5 years:

91% (95% C.I. 70–98%), 66% (95% C.I. 42–83%) and 60% (95% C.I. 34–78%), respectively.

Two patients were alive with disease at last follow-up, and a total of 10 patients recurred. One patient died without recurrent disease. The median RFS was 4.0 years. The RFS rate was 78% (95% C.I. 55–90%), 63% (95% C.I. 39–80%) and 50% (95% C.I. 26–70%) at 1, 2 and 5 years, respectively. Recurrences were local in one, systemic in seven and in unknown location in two cases.

Risk factors

The results of univariate analysis using Cox proportional hazards modeling are summarized in Table 2 for DSS. The analysis for OS was identical. None of the pre-treatment factors predicted DSS or OS. Of the post-treatment factors, pathologic stage, positive surgical margins and the presence of lymph node metastasis at the time of cystectomy correlated significantly with DSS. As is shown in Figure 2, none of 6 patients with pT0/Tis/Ta/T1 carcinoma died of disease, compared to 8 of 17 with pT2/T3/T4 disease ($p=0.04$, log rank test). All three patients with positive margins died of disease, including one after isolated local recurrence. Four of five patients with lymph node metastasis, but only 2 of 15 without, died of disease ($p=0.003$). Patients receiving adjuvant chemotherapy had significantly worse DSS ($p=0.028$), likely a reflection of selection bias of patients with adverse pathologic features. A similar trend was observed when this analysis was restricted to the 17 patients with residual muscle-invasive disease at the time of cystectomy, but was not statistically significant ($p=0.177$). RFS was predicted only by pathologic node status ($p=0.010$; HR 9.72, 95% C.I. 1.72–55.1) and adjuvant chemotherapy ($p=0.016$; HR 5.52, 95% C.I. 1.38–22.1), with a trend observed with pathologic stage ($p=0.116$; HR 5.39, 95% C.I. 0.66–44.0) and margin status ($p=0.069$; HR 3.68, 95% C.I. 0.91–14.9). Multivariate analysis was not performed due to the low number of events.

DISCUSSION

Our results suggest that surgical extirpation can be efficacious in a select group of patients with cT4b urothelial carcinoma of the bladder. Radical cystectomy is not usually considered by most practicing urologists for patients with cT4b tumors and, at M.D. Anderson Cancer Center, we receive referrals of these patients to consider ‘palliative therapy’. We have taken an aggressive approach to treating such patients with pre-surgical chemotherapy and radical cystectomy, and our results here demonstrate that a durable response rate as high as 60% can be achieved in some.

It bears emphasizing that the patients reported here are a highly select group. Not all patients presenting with clinical T4b bladder cancer will be candidates for cystectomy. Furthermore, we consider only those who respond well to chemotherapy for surgery, along with some patients in whom surgery is deemed necessary for palliation of local symptoms. Since our database only includes patients who undergo cystectomy, we do not know what proportion of patients presented with cT4b bladder carcinoma but did not respond adequately to chemotherapy to permit surgical consolidation.

Response to chemotherapy is reflected most directly in the pathologic T stage. In our series, patients with down-staging to pT0/Tis/Ta/T1 cancer had prolonged long-term survival despite presenting with cT4b disease. This echoes the findings of studies evaluating neoadjuvant chemotherapy for resectable disease^{1,2} and is also similar to reports on post-chemotherapy surgery⁸.

Not surprisingly, the presence of pathologic nodal metastasis and the presence of positive surgical margins predicted poor survival in this cohort of patients. Both of these factors have been demonstrated to be highly predictive in other studies^{2,4,9}, and reinforce the knowledge that adjuvant chemotherapy cannot compensate for an inadequate surgical resection of urothelial carcinoma. Proper patient selection and meticulous surgical technique are essential factors contributing to surgical margin status. One of three patients with a positive margin recurred locally, compared to none without positive margins.

Our report is not unique. A multicenter international review of advanced urothelial carcinoma treated with cisplatin-based chemotherapy included 53 patients with cT4b disease without nodal or distant metastasis¹⁰. An undefined fraction of these patients underwent cystectomy. A complete response was seen in 28% and a partial response in 35% of patients. Median survival was 13.4 months and the five year survival was 25%. The difference between our results and these is likely due to patient selection, since we have included only patients who proceeded to cystectomy. Herr et al. reported on 32 patients who underwent radical cystectomy with cT4bNx and 48 with cT3N2-3 bladder cancer⁴. Eighty patients received combination chemotherapy. While many patients in this cohort had more advanced disease than in our study, the general conclusions were similar. Despite a clinical complete response to chemotherapy, many patients had viable disease in the bladder, supporting the rationale for surgical consolidation. Patients with a pathologic complete response had the best outcome and patients with persistent unresectable disease after chemotherapy had a dismal outcome. Notably, 12 patients in this series, including 10 with a complete response to chemotherapy, refused surgery, and only one of these survived to 3 years (8%).

One limitation of our current study is that we used EUA plus imaging for clinical staging. In in-experienced hands, a 'fixed mass' on EUA may not always translate into pathologic T4 disease^{11,12}, but this potential for 'over-staging' provided an even stronger rationale to consider such patients for radical cystectomy after chemotherapy.

CONCLUSIONS

Advances in multimodal therapy of urothelial carcinoma of the bladder have enabled us to expand the indication for extirpative surgery beyond the traditional indication of clinically localized disease at the time of presentation. Our results suggest that radical cystectomy can be efficacious in a select group of patients with cT4b bladder cancer. Thus, rather than offer only palliative therapy (as we have found to be the case among community practices), these patients should be considered to be potentially candidates for surgery with curative intent. However, Careful patient selection is paramount, and we suggest using response to pre-operative chemotherapy as the primary criterion for proceeding with surgery.

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ABBREVIATIONS

cT4b	clinical T4b
OS	overall survival
DSS	disease-specific survival
RFS	recurrence-free survival

C.I.	confidence interval
EUA	examination under anesthesia
CT	computed tomography
MRI	magnetic resonance imaging
N+	presence of lymph node metastasis
N–	absence of lymph node metastasis
TURBT	transurethral resection of bladder tumor
LVI	lymphovascular invasion
TCC	transitional cell carcinoma
TCC/mix	TCC with component of glandular or squamous differentiation
MVAC	methotrexate/vinblastine/adriamycin/cisplatin
XRT	radiation therapy

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Figure 1. Kaplan-Meier estimates of overall (OS), disease-specific (DSS) and recurrence free (RFS) survival for 23 patients with clinical stage T4b bladder carcinoma. Note that OS and DSS are identical up to the end time-point (14.9 years), at which time one patient died of other causes.

Figure 2. Kaplan-Meier estimate of disease-specific survival stratified by pathologic stage (residual muscle invasive disease pT2/T3/T4 versus no residual muscle invasive disease pTa/Tis/T0/T1). P-value from log rank test.

Table 1

Clinicopathologic patient characteristics (n=23)

Characteristic	No. of Patients (%)
Race	
Caucasian	17 (74)
Hispanic	4 (17)
African American	2 (9)
Histology	
TCC	6 (26)
TCC/mix	7 (30)
Adenocarcinoma	3 (13)
Sarcomatoid	1 (4)
Small cell	2 (9)
Micropapillary	4 (17)
Hydronephrosis	
Present	16 (70)
LVI at TURBT	
Present	4 (17)
Absent	11 (48)
Not noted	8 (35)
Pathologic T stage	
T0	4 (17)
Ta	1 (4)
Tis	1 (4)
T1	0
T2	2 (9)
T3	8 (35)
T4	7 (30)
Pathologic nodal status	
Negative	15 (65)
Positive	5 (22)
Not noted	3 (13)
LVI at cystectomy	
Present	9 (39)
Absent	8 (35)
Not noted	6 (26)
Surgical margins	
Negative	20 (87)
Positive	3 (13)
XRT	
Yes	3 (13)
Pre-operative chemotherapy	

Characteristic	No. of Patients (%)
Yes	19 (83)
Adjuvant chemotherapy	
Yes	8 (35)

TCC = transitional cell carcinoma; TCC/mix = TCC with component of glandular or squamous differentiation; LVI = lymphovascular invasion; TURBT = transurethral resection of bladder tumor; XRT = radiation therapy

Factors associated with disease-specific survival

Table 2

Characteristic	Referent	Comparison	Hazard Ratio	95% CI for HR	P-value
Gender	Male	Female	0.95	0.19–4.8	0.95
Age	≤65	>65	1.28	0.32–5.2	0.73
Histology	TCC	Other	1.22	0.30–4.9	0.78
Hydronephrosis	No	Yes	1.50	0.30–7.5	0.62
cLVI	Absent	Present	1.39	0.25–7.7	0.71
pT stage	T0/Tis/Ta/T1	T2/T3/T4	*	*	0.044
pN status	N–	N+	29.33	3.1–275	0.003
pLVI	Absent	Present	2.30	0.42–12.7	0.34
Surgical margins	Negative	Positive	5.34	1.25–22.8	0.024
XRT	No	Yes	0.95	0.12–7.8	0.97
Pre-op. chemo	No	Yes	2.04	0.25–16.8	0.51
Adj. chemo	No	Yes	6.10	1.21–30.7	0.028

* Since there were no deaths in patients with pT0/Tis/Ta/T1 disease, a Cox proportional hazard model could not be used; the p-value reflects the results of a log rank test.
TCC = transitional cell carcinoma; N– = lymph node metastasis absent; N+ = lymph node metastasis present; pLVI = lymphovascular invasion in cystectomy specimen; XRT = radiation therapy; pre-op = pre-operative; adj = adjuvant