Clinical outcomes of a cohort of patients with bulky, clinically node-positive bladder cancer undergoing radical cystectomy in the contemporary era

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Introduction

Metastasis to regional lymph nodes is recognized as a poor prognostic factor in urothelial bladder cancer. Outcomes of patients with pathologically node-positive (pN+) disease following radical cystectomy are well-characterized, with five-year overall survival (OS) rates of only 20–30%.[1,2] Studies of patients with clinically node-positive (cN+) disease based on preoperative imaging have much more variable outcomes. For example, one recent series reported five-year OS of over 50% in patients with cN+ bladder cancer; whereas two other series based on cancer registry data reported five-year OS rates of only 12–30% depending on treatment modality.[3-5] These variations are due, in part, to criteria used to stage patients as cN+. In one series, which used short-axis diameter ≥8 mm to define cN+ status, over 50% of patients staged as cN+ were found to be node-negative at surgery.[4] Induction chemotherapy (ICT) prior to surgery improves outcomes in cN+ disease. Failure to respond to ICT is an especially poor prognostic factor, with five-year OS rates as low as 12–16%.[6,7] We have felt that patients with cN+ disease and bulky (large or multiple) pelvic lymph nodes fare especially poorly. We sought to identify such a population within our practice and define their outcomes.

Methods

With IRB approval, we reviewed preoperative imaging reports of all patients undergoing radical cystectomy for bladder cancer at our institution from January 1, 2016 to December 31, 2019 to identify patients with cN+M0 disease. This period was selected to coincide with the availability of immuno-oncology (IO) treatments as salvage therapy. Patients were defined as cN+ if they had a single pelvic lymph node ≥1.5 cm in diameter or multiple pelvic lymph nodes ≥1.0 cm in diameter. These criteria were chosen based on our clinical experience, with a goal of identifying a subset of patients with bulky disease and a high probability of true N+ status. Patients with distant metastatic disease, including those with lymph nodes ≥1.0 cm above the aortic bifurcation, were excluded. Our primary outcome was two-year recurrence-free survival (RFS), starting from the date of surgery. RFS and OS were estimated using Kaplan-Meier curves. The log-rank test was used to compare survival between subgroups, with a two-sided p-value ≤0.05 deemed significant. Analyses were conducted using IBM SPSS Statistics version 27 (IBM, Armonk, NY, U.S.).

Results

A total of 612 patients underwent radical cystectomy during the study period, of whom 32 met our criteria for cN+M0 disease. Demographic factors and medical history are summarized in Table 1, and clinical staging factors in Table 2. Patients had bulky pelvic lymph nodes with a median largest node size of 2.0 cm (interquartile range [IQR] 2.4–2.7). Most patients were staged as cN2-3. High rates of hydronephrosis (66%) and variant histology (63%) were noted. Most patients (84%) initiated ICT, of whom, 89% completed three or more cycles. Reasons for not receiving ICT included patient refusal in three cases and treating clinican's discretion in two cases; no patients were excluded from receiving chemotherapy on the basis of ineligibility. Two patients with disease progression after ICT received salvage IO before proceeding to cystectomy. All patients receiving ICT were re-staged prior to surgery; nodal response to treatment is summarized in Table 2. Clinical complete response, defined as reduction in all pathological nodes to <1 cm diameter, occurred in 41% of cases. Perioperative parameters, pathological outcomes, and 90-day complications are summarized in Table 3.

Table 1. Patient demographics and history

Characteristic	n (%) or median (25th–75th)
Total patients	32
Sex	
Male	23 (72%)
Female	9 (28%)
Age	62 (58–69)
Race	
White	20 (63%)
Black	6 (19%)
Hispanic	5 (16%)
Asian/Pacific Islander	1 (3%)
Body mass index (BMI)	27 (23–31)
ECOG performance status	
0	15 (47%)
1	17 (53%)
Charlson comorbidity index (CCI)	
0	2 (6%)
1	5 (16%)
2	9 (28%)
3	9 (28%)
4	4 (13%)
5	1 (3%)
7	2 (6%)
Smoking history	
Current	9 (28%)
Prior	15 (47%)
Never	8 (25%)
Prior history of bladder cancer	8 (25%)
Interval since diagnosis (months)	12.5 (9–48)

Charlson comorbidity index calculations excluded the adjustment for concurrent malignancy.

Table 2. Clinical staging and treatment factors

Characteristic	n (%) or median (25th–75th)
Clinical tumor stage (TURBT)	
cT1	7 (21%)
≥cT2	25 (78%)
Clinical node stage (imaging)	
cN1	9 (28%)
cN2	18 (56%)
cN3	5 (16%)
Number of ≥1 cm pelvic nodes	
1	10 (31%)
2	9 (28%)
≥3	12 (38%)
Size of largest pelvic node (cm)	2.0 (2.4–2.7)
Confirmatory lymph node biopsy	2 (6%)
Hydronephrosis (imaging)	21 (66%)
Lymphovascular invasion	10 (34%)
Variant histology	
Any	20 (63%)
Squamous	8 (25%)
Micropapillary	4 (13%)
Sarcomatoid	3 (9%)
Glandular	2 (6%)
Plasmacytoid	2 (6%)
Neuroendocrine	1 (3%)
Microcystic	1 (3%)
Induction systemic treatment	
Any	27 (84%)
≥3 cycles	24 (75%)
MVAC	13 (48%)
Gem/cis	11 (41%)
Gem/carbo	3 (11%)
Immuno-oncology	2 (1%)
Clinical lymph node response to induction treatment	
Complete response (all nodes decreased to <1 cm)	12 (44%)
Partial response (≥30% reduction in node size)	2 (7%)
Stable disease	9 (33%)
Progressive disease (≥20% increase in node size)	4 (15%)

Node counts and clinical stage are discordant in some cases, as the latter may have incorporated additional staging information, such as positron emission tomography scan. Data on lymphovascular invasion was not reported for three patients, resulting in a denominator of 29. Presence of variant histology is based on consensus between pathology at transurethral resection of bladder tumor (TURBT) and radical cystectomy (RC). Two patients with variant histology had mixed patterns (micropapillary/glandular and squamous/plasmacytoid) and were counted in two categories. Both patients who received immuno-oncology therapy had previously received chemotherapy. Definitions of complete response, partial response, and progressive disease were based on RECISTv1.1 criteria. MVAC: methotrexate, vinblastine sulfate, doxorubicin hydrochloride (adriamycin), and cisplatin.

With regard to pathological outcomes, complete pathological response (pT0N0) was achieved in 5/32 (16%) patients, all of whom had received ≥3 cycles of ICT. Negative lymph nodes (pN0) were found in 11/32 (34%) patients, of whom all but one had received ICT. More than half (56%) of patients received additional treatment after surgery. Consistent with the patients' aggressive underlying disease, oncological outcomes were poor (Fig. 1). The two-year RFS and OS rates were 37% and 42%, respectively. Patients with negative lymph nodes (pN0) or complete pathological response (pT0N0) at surgery had significantly better outcomes (two-year RFS 72% for pN0 vs. 18% for pN+, log-rank p=0.005; 80% for pT0N0 vs. 28% for pT+/N+, log-rank p=0.042). All observed recurrences occurred within the first 12 months of surgery.

Discussion

Studies of patients with clinically node-positive bladder cancer have had widely varying outcomes. We sought to define the outcomes of a subset of patients with bulky cN+ disease undergoing radical cystectomy in our practice. Our cohort was notable for a high proportion of variant histol-

Table 3. Operative and pathological outcomes

Characteristic	n (%) or median (25th–75th)
Surgical approach	
Open	17 (53%)
Robotic	15 (47%)
Operative time (min)	324 (290–379)
Estimated blood loss (mL)	300 (250–575)
Postoperative length of stay (days)	6 (5–12)
Total red blood cell transfused (units)	0.5 (0–2)
Followup (months)	17 (9–24)
90-day complications	
Minor (Clavien-Dindo grade 1–2)	16 (90%)
Major (Clavien-Dindo grade 3–5)	8 (25%)
Emergency room visit	12 (38%)
Re-admission	8 (25%)
Re-operation	1 (3%)
Death	2 (6%)
Pathological stage	
pT0	5 (16%)
pTis	1 (3%)
pT1	1 (3%)
pT2	7 (22%)
pT3	12 (38%)
pT4	6 (19%)
≤pT1	7 (22%)
≥pT2	25 (78%)
pNx	2 (6%)
pN0	11 (34%)
pN1	5 (16%)
pN2	12 (38%)
pN3	2 (6%)
≥pN1	21 (66%)
pT0N0 (pathological complete response)	5 (16%)
Lymph node dissection	
Total nodes	13.5 (8–20)
Positive nodes	1 (0–2.8)
Residual disease at surgery	
Any	9 (28%)
Gross residual disease (R2)	7 (22%)
Positive soft tissue margin (R1)	4 (13%)
Adjuvant treatment	
Any	9 (29%)
Chemotherapy	1 (3%)
Immuno-oncology	7 (23%)
Radiation	2 (6%)
Salvage treatment	
Any	13 (42%)
Chemotherapy	6 (19%)
Immuno-oncology	9 (29%)
Radiation	8 (26%)

Of note, both patients staged as pNx had bulky, grossly unresectable nodal disease and were included in the calculation as ≥pN1. Data on subsequent treatment was not available for one patient. Adjuvant/salvage modalities do not sum to 100% because some patients received multiple treatments.

ogy and by high levels of adverse prognostic factors. We used two-year RFS as a primary endpoint, which has been shown to be a good proxy for longer-term outcomes.[8] We noted a high rate of early recurrence, with a two-year RFS rate of only 37%. OS at two years was similarly poor (42%), despite a large proportion of patients receiving additional treatment. Consistent with prior reports, pathological N0 status and complete response to ICT were strong predictors of improved outcomes.[4,6,9]

Our study is limited by its retrospective nature and small number of patients. Our analysis was confined to patients undergoing radical cystectomy, and it does not capture the outcomes of patients who presented as cN+ and did not undergo surgery. Most patients (84%) received ICT, and all of those who did not were clinically eligible for ICT. In light of reports that 25–50% of bladder cancer patients are chemo-ineligible,[10] this observation suggests that our cohort represents a select subset of cN+ patients and implies that chemo-ineligible patients who present with cN+ disease are not being offered curative treatment.

Conclusions

In highlighting the outcomes of this cohort of patients with bulky cN+M0 bladder cancer, we hope to draw attention to a population of patients who have limited treatment options and who suffer early, rapid recurrence of disease. It is possible that more aggressive initial treatment of these patients may improve outcomes. We anticipate clinical trials in this space in the years to come.

Competing interests: Dr. Howard co-authored a publication of a clinical trial involving enhanced cystoscopy in NMIBC sponsored by Karl Storz. The remaining authors report no competing personal or financial interests related to this work.

This paper has been peer-reviewed.

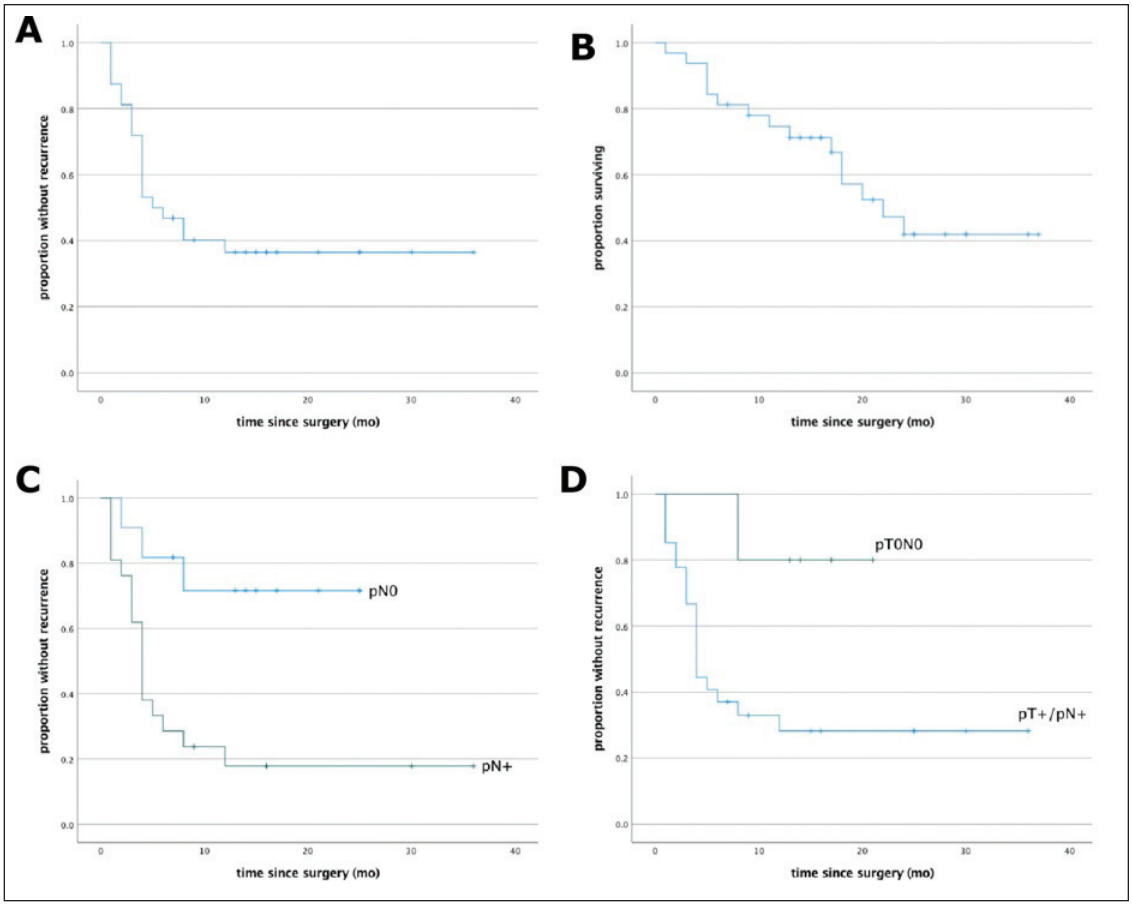

Fig. 1. Oncological outcomes.

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