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Clinically node-positive bladder cancer: oncological results of induction chemotherapy and consolidative surgery

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Patients with clinically node-positive bladder cancer have a poor prognosis, with many receiving only palliative chemotherapy. We evaluated oncological results in bladder cancer patients with clinically regional and supraregional lymphadenopathy treated with induction chemotherapy (IC) and consolidative cystectomy. Twenty-five patients with clinically node-positive bladder cancer (including pelvic and retroperitoneal nodes) were treated with 2–4 cycles of IC followed by consolidative cystectomy between 2010 and 2016. Pathologic complete response (pCR) was defined as no residual tumor in the final specimen (ypT0N0).

The 3-year cancer-specific (CSS) and recurrence-free survival (RFS) for the whole cohort were 52% and 39%, respectively. The 3-year RFS differed according to volume of nodal metastases, the rates were 56% for minimal nodal disease (cN1) versus 33% for cN2-3 and 0% for cM1 disease ($p<0.001$). pCR was seen in 7 (28%) patients; 50% in cN1 versus 13% in cN3-M1. pCR associated with 3-year CSS of 80% versus 45% in patients with persistent disease after IC. In conclusion, a multimodal approach to patients with clinically node-positive bladder cancer, consisting of IC followed by consolidative surgery, may achieve long-term survival in selected patients. Better results may be expected in patients with initially minimal nodal burden and complete pathologic response to chemotherapy. Further studies are warranted to improve patient selection for consolidative surgery, especially with supra-regional metastases.

Key words: urinary bladder neoplasms, lymphadenopathy, combined modality therapy, induction chemotherapy, cystectomy

Patients with clinically node-positive bladder cancer do poorly, with many undergoing only palliative chemotherapy [1]. Recently, there has been interest in the concept of oligometastatic disease, which suggests that with a limited number of clinically detectable metastases, the local control of primary tumor and metastases has potential to improve systemic control and prolong survival [2]. In many solid cancers, surgical removal of the residual tumor after systemic therapy is part of the treatment strategy and survival benefit has been reported in recent series [3–5].

Similarly, in urothelial bladder cancer with clinically nodal metastases, retrospective studies showed long-term survival in selected patients treated by a multimodal approach with upfront chemotherapy followed by consolidative surgery [6–8]. Even in selected patients with supra-regional nodal metastases in the retroperitoneum (above aortic bifurcation), this approach may lead to reasonable outcomes, with 5-year cancer-specific survival reaching 24–38% [7–8].

In node-negative bladder cancer, a meta-analysis indicated that neoadjuvant chemotherapy improves survival and the greatest benefit was seen in more advanced disease [9]. Also, it was demonstrated that pathological complete response (pCR) after neoadjuvant chemotherapy is a strong predictor of survival [10]. Similarly, patients with pCR after induction chemotherapy (IC) fare better than those without [6–7].

The multimodal approach to clinically node-positive bladder cancer is appropriate only for selected patients. First, they have to be fit for cisplatin-based chemotherapy. Second, after assessment of response to IC, consolidative surgery is only performed if clinical progression is excluded and third, complete resection must be technically feasible with negative surgical margins.

In the near future, improved molecular biomarkers and imaging are needed to better define the response to chemotherapy and determine which patients with oligometastatic disease will benefit from consolidative surgery. In this study,

we report oncological results of the multimodal approach in patients with clinically node-positive bladder cancer.

Patients and methods

Patients. A total of 25 patients with clinically node-positive urothelial bladder cancer restricted to the pelvis and retroperitoneum underwent IC and consolidative cystectomy between 2010 and 2016. This cohort of patients was identified from the institutional bladder cancer registry. The study has been approved by the Ethical committee of Masaryk Memorial Cancer Institute.

The 2009 TNM classification was used for clinical staging: N1 – single regional lymph node metastasis in the true pelvis, N2 – multiple lymph node metastasis in the true pelvis, N3 – metastasis to common iliac lymph nodes, M1 – distant metastasis (restricted to retroperitoneal nodes only). Imaging with at least iliac lymph nodes computed tomography (CT) and chest x-ray was performed before and after chemotherapy. Radiographic definition of suspicious nodal metastasis was nodal short axis >10 mm on CT.

Chemotherapy. All patients fit for cisplatin were administered 2–4 cycles of gemcitabine with cisplatin (Gem/Cis). Carboplatin (Gem/Carbo) was used instead of Gem/Cis for patients with renal impairment. The patients were restaged after 2 cycles with abdominal CT scan and they proceeded to surgery if there was no response to chemotherapy. For patients exhibiting response to chemotherapy or with stable disease, a further 2 cycles were added. Imaging was repeated after 4 cycles, followed by consolidative surgery.

Response to chemotherapy was characterized according to RECIST criteria. Clinical complete response (CR) was defined as no radiologic evidence of disease, partial response (PR) as at least a 30% reduction in nodal size without increase in any other lesion, stable disease (SD) as qualifying for neither response nor progression, and progressive disease as at least a 20% increase in the size or appearance of new lesions.

Surgical procedure. After induction chemotherapy, patients with at least stable disease were scheduled for consolidative surgery, consisting of radical cystectomy and lymph node dissection. In cN1-3 disease the borders of dissection were genitofemoral nerve laterally, Cooper ligament distally and aortic bifurcation proximally. Surgery included removal of lymphatic tissue along the internal iliac vessel and presacrally. If retroperitoneal nodes above aortic bifurcation were initially enlarged (cM1), consolidative extirpation followed only if at least partial response was demonstrated on CT. For those specific patients, dissection continued cranially up to the renal hilum. pCR was evaluated after surgery and was defined as no residual tumor in the specimen (ypT0N0).

Statistics. Kaplan-Meier curves were used to estimate 3-year RFS and CSS and were compared using log rank test. Recurrence was defined as first relapse on imaging. RFS was calculated as the time from initiation of IC to the date of recurrence or bladder cancer related death. Patients who were alive without recurrence were censored at the time of last follow-up. CSS was calculated as the time from initiation of IC to the date of bladder cancer related death. Patients who were alive or died of other causes were censored.

Univariable Cox proportional hazards regression analyses were used to evaluate associations between clinicopathological parameters and oncological outcomes. The following variables were assessed: age, gender, clinical stage, radiologic and pathologic response to chemotherapy, pathologic stage, lymphovascular invasion and number of positive nodes after chemotherapy. Results were considered significant if p-value <0.05 was achieved. Statistical analyses and tests were performed using SPSS software (version 22).

Table 1. Patient characteristics.

Characteristic		N=25
Age (median, range)		65 (44–74)
Gender:	Male	19 (76%)
	Female	6 (24%)
Chemotherapy:	Gemcitabine + Cisplatin	84%
	Gemcitabine + Carboplatin	16%
Clinical T category:	cT2	11 (44%)
	cT3-4	14 (56%)
Clinical N category:	cN1	12 (48%)
	cN2	5 (20%)
	cN3	3 (12%)
	cM1	5 (20%)
Pathologic N category	ypN0	10 (40%)
	ypN1	1 (3%)
	ypN2	5 (20%)
	ypN3	6 (24%)
	ypM1	3 (12%)

Results

Twenty-five patients with clinically node-positive bladder cancer underwent IC followed by consolidative surgery. Patient characteristics are shown in Table 1. Median age was 65 (44–74).

In total, 21 (84%) patients received Gem/Cis and 4 (16%) received Gem/Carbo with a median number of 3 cycles of chemotherapy (range 2–4). Overall, radiologic CR, PR and SD after chemotherapy were found in 26%, 52% and 22%, respectively. Three-year CSS was 68% and 34% for CR and PR/SD, respectively. Nodal CR occurred in 48%. All 8 patients with cN3-M1 category had at least partial response after IC (3×CR, 5×PR).

Pelvic lymph node dissection (PLND) was performed in 20 patients and dissection up to the renal hilum (retroperitoneal lymph node dissection; RPLND) was added in 5 patients with cM1 disease. Median lymph node yield was 23 (13–39) in PLND and 36 (21–40) in RPLND. The overall lymph node count was 24 (13–40) for the whole cohort.

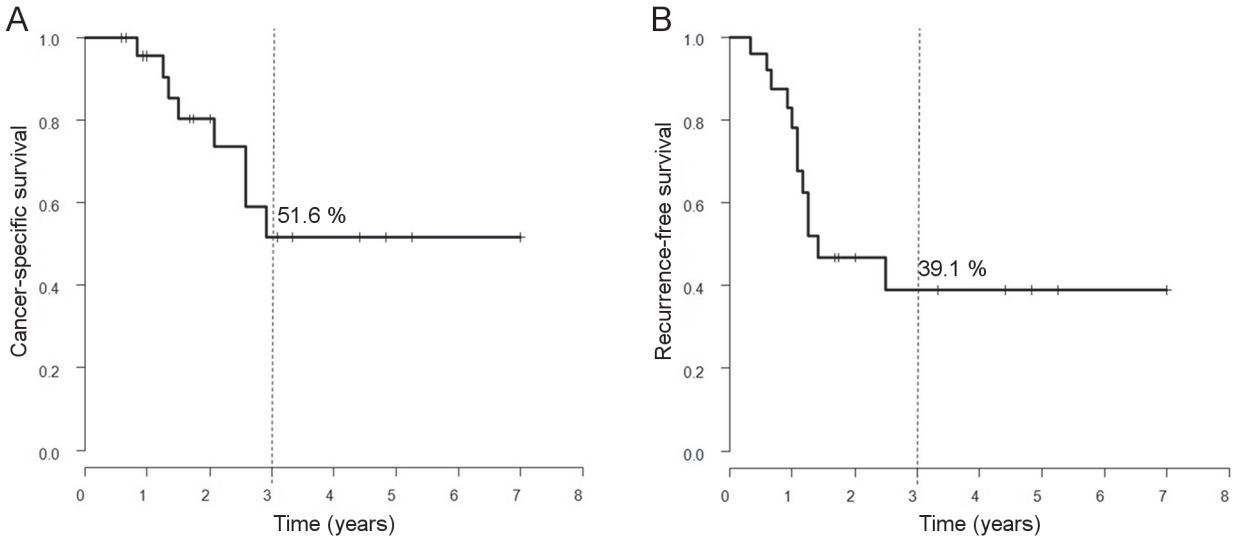

Figure 1. A) Cancer-specific and B) recurrence-free survival for the whole cohort of patients.

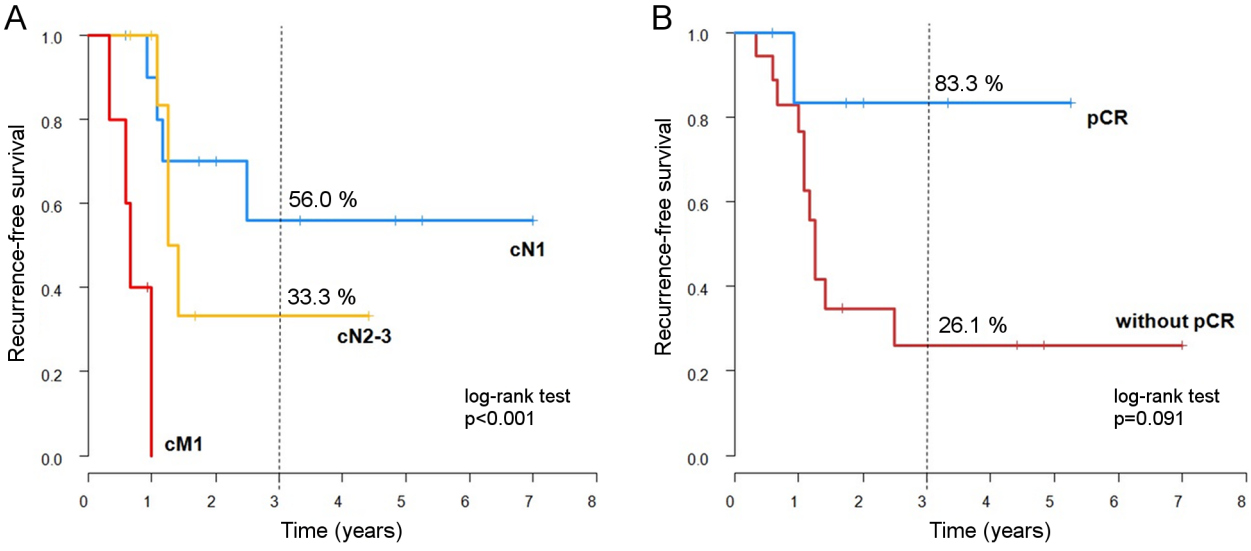

Figure 2. A) Recurrence-free survival according to clinical extent of nodal metastasis and B) response to chemotherapy.

Pathologic complete response (ypT0N0) was seen in 7 (28%) patients. The highest rate of pCR (50%) occurred in cN1 patients. It was scarce in initially bulky disease, as only one patient (13%) with cN3-M1 experienced pCR. A total of 10 (40%) patients had pN0 category after IC. Despite radiologic CR, a residual tumor was found in 33% of the patients. Persistent nodal metastases were present in 27% of patients with radiologic nodal CR.

With a median follow-up of 24 months (11–84), 3-year CSS for the entire cohort was 52% (95% CI 26–77) (Figure 1). It differed according to initial nodal extent and response to chemotherapy. Patients with cN1, cN2-3 and cM1 disease had 3-year CSS of 53%, 56% and 40%, respectively (p=0.732) (Figure 2). Patients with pCR experienced a better 3-year CSS rate of 80% versus 45% in patients with persistent disease after IC (p=0.487). It is noteworthy that 90-day mortality in our study was 0%.

Recurrence was seen in 8 out of 20 patients with cN1-3 and in 4 out of 5 patients with cM1. Median time from start of chemotherapy to relapse was 13 months (IQR 10–15), in cM1 only 8 months. A 3-year RFS rate of 39% (95% CI 16–62) was achieved (Figure 1) and again differed according to initial nodal extent: 56% in cN1, 33% in cN2-3 and 0% in cM1, respectively (p<0.001) (Figure 2). Three-year RFS was higher in patients with pCR (83%) than in those without (26%), but this was not statistically significant (p=0.091). Out

of 5 patients with cM1, 4 had recurrences after 7, 8, and 12 months, two died after 10 and 25 months, and 2 are alive after 18 and 37 months. One patient with pathologic complete response is without recurrence after 11 months.

Data from univariate analyses are listed in Table 2. Clinical stage cT3-4 was the only significant predictor of RFS (hazard ratio HR 0.27; 95% CI 0.08–0.88, p=0.031).

Discussion

Clinically node-positive bladder cancer is frequently treated with palliative chemotherapy only, as the majority of these patients were historically considered incurable. However, previous studies have shown that patients with metastatic disease form a heterogenous group and those with metastasis limited to pelvic or retroperitoneal nodes do significantly better in terms of response to chemotherapy and survival than those with visceral disease [1, 11].

Interestingly, a concept of oligometastatic disease was recently proposed, describing a state between localized and widespread metastatic disease. It presumes that there are differences in metastatic competence of malignant tumors which depend on tumor phenotype and the degree of clonal evolution [2]. Recent reports support the thesis that local control of primary tumor and metastases may improve systemic control and prolong survival of patients with a limited number of clinically detectable metastases [2].

In our study, we demonstrated that cure is possible in a subset of patients using a multimodal approach consisting of IC and consolidative surgery in clinically node-positive bladder cancer. Three-year CSS and RFS rates were 52% and 39%, respectively, comparable to other reports [6, 7, 12].

The prognosis of clinically node-positive bladder cancer correlates well with the initial extent of nodal disease and the presence of viable tumor after chemotherapy. In our cohort, 3-year RFS differed according to clinical nodal stage (56% in cN1, 33% in cN2-3 and 0% in cM1). Median RFS was 15 and 8 months in cN2-3 and cM1, respectively, which is similar to the study of Meijer et al, where median RFS was 14 and 13 months, respectively [6]. Considering the relatively small cohort of patients, the only significant predictor of RFS in univariate analysis was clinical stage cT3-4 (p=0.031). The fact that high clinical stage reduced the risk of progression may seem counter-intuitive, but can be explained by the higher rate of cT2 in bulky cN3-M1 tumors in our group of patients. Trends toward significance were notable in initially larger lymphadenopathy cN2-3/M1 disease (HR 2.97; p=0.087) and in female patients (HR 2.88; p=0.075).

Pathologic complete response is a strong predictor of CSS in published series. In our study, 28% of patients had a pCR, which is comparable to 15–30% in other studies [6, 7, 13]. Complete nodal response was present in 40% of our patients. In the study by Ho et al, this rate was even higher at 55% [7]. Patients who achieved pCR had a more favorable prognosis, with 3-year CSS rate of 80% in comparison with 45% in patients with ypT+ and/or pN+. This corroborates earlier publications, where 5-year CSS rates were 64–83% in the case of pCR, 17% and 0% for patients with persistent nodal disease in the pelvis and retroperitoneum, respectively [6, 7].

Patients with supra-regional retroperitoneal lymph node metastases are usually denied post-chemotherapy surgery, even if they show clinically complete response after IC. In our study, only one out of 5 such patients had pCR and 3-year CSS was 40%. Although still a controversial concept in this group of patients, there are several published studies that support consolidative surgery, however, only if complete or at least partial clinical response was achieved. Sweeney et al reported on 11 patients with CR or PR after IC. Residual nodal disease was present in 82% and 4-year RFS was 27% [14]. De Vries et al published results of 14 patients with CR or PR after chemotherapy. Three-year CSS was 36%, however 9 patients died within 12 months. If pCR was achieved, 3-year CSS rate was 42% [8].

The rationale for consolidative surgery is removal of residual tumor. Optimal imaging would help us to detect even minimal residual disease and potentially select those who could be spared consolidative surgery. However, clinical staging after IC is not reliable. Interestingly, a recent small study by Mertens et al showed that FDG-PET can distinguish nodal responders from non-responders to IC with 95% accuracy, which is much higher than with standard imaging but has to be confirmed in further studies [15]. Although the radiologic complete response is associated with favorable prognosis, at the present time these patients still cannot be spared consolidative surgery, because residual tumor will be present in the definitive specimen in 26–39% of patients (33% in our study) [6, 7, 13]. In addition, if not surgically removed, most recurrences will occur at a previous site of metastases [11, 13]. On the other hand, in the case of clinically stable or progressive disease after IC, only a small subset of patients will benefit from consolidative surgery and poor results are to be expected with median CSS of 6–12 months [6, 7]. In the study by Donat et al, only 2 of 27 clinical non-responders were long-term survivors [16]. Selection of patients is therefore crucial.

Table 2. Univariable analysis for clinicopathological factors associated with recurrence-free survival.

Variable		HR	95% CI	p-value
Age		0.99	0.91–1.07	0.777
Gender	Female / Male	2.88	0.90–9.22	0.075
cT category	cT3-4 / cT2	0.27	0.08–0.88	0.031
cN category	cN2-3, cM1 / cN1	2.97	0.87–10.17	0.083
Clinical CR	Yes / No	1.58	0.46–5.45	0.465
Pathologic CR	Yes / No	0.21	0.03–1.60	0.131
ypN category	ypN1-3 / ypN0	2.94	0.79–11.03	0.109
ypT category	ypT1-4 / ypT0	1.51	0.41–5.61	0.537
LVI	Yes / No	1.42	0.45–4.49	0.554

CR – complete response, LVI – lymphovascular invasion

The added value of multimodal treatment with consolidative surgery in comparison with palliative chemotherapy alone is unclear, as we lack randomized studies. Von der Maase showed that in patients with pelvic or retroperitoneal lymphadenopathy without visceral metastases (cT4 N2-3 or cM1) treated with chemotherapy alone, 5-year CSS rates around 20% may be achieved [1]. Interestingly, there is a recent study comparing multimodal treatment with palliative chemotherapy with or without radiotherapy in a heterogeneous cohort of 59 patients comprising both bladder and upper urinary tract tumors and also both primary tumors and nodal recurrences. Out of 59 patients with pelvic or retroperitoneal nodal metastases, 28 underwent post-chemotherapy surgery, whereas 31 did not. The median overall survival was 37 and 19 months for these groups and post-chemotherapy surgery was a predictor of OS in multivariate analysis (HR 0.30) [12].

Our study is limited by its retrospective nature and relatively small cohort of patients, therefore the results should be interpreted with caution. Nodal metastases were not proven by biopsy before chemotherapy, however, previous studies showed that radiologic suspicion of nodal metastases correlates well with pathologic findings [7].

In conclusion, in clinically node-positive bladder cancer, a multimodal approach consisting of induction chemotherapy and consolidative cystectomy can cure a subset of patients and survival may be prolonged even in those with retroperitoneal disease. The best results can be expected in patients with limited nodal burden at the time of diagnosis and pathologic complete response to chemotherapy. Further studies in biomarkers and imaging are warranted to better define which patients harbor residual tumor after chemotherapy and who will benefit from consolidative surgery.

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