Original Study

Comparison of Different Treatment Modalities Outcomes in Clinically Node-positive Bladder Cancer: Analysis of a Population-based Cancer Registry

Michal Staník,[1] Alexandr Poprach,[2] Michaela Zapletalová,[3,4] Denisa Krejčí,[3,4] Daniel Macík,[1] Ivo Čapák,[1] Jiří Jarkovský,[3,4] Radek Lakomý,[2] Jan Doležel[1]

Abstract

Recently, a few retrospective studies demonstrated a potential benefit of multimodal therapy in patients with clinically node-positive bladder cancer. We assessed the efficacy of different treatment modalities in 661 patients (cTanyN1-3M0) identified from the Czech National Cancer Registry. When compared with chemotherapy, combined treatment integrating cystectomy and perioperative chemotherapy reduced the risk of overall mortality by 21% and may lead to a long-term survival in one-quarter of patients.

Introduction: Patients with clinically node-positive bladder cancer were historically considered to have uniformly poor prognosis and were frequently treated with palliative chemotherapy (CHT) only. Although retrospective data show that long-term survival with combined treatment (surgery + CHT) is possible in one-third of these patients, consensus on a treatment algorithm is still lacking. The aim of the study is to compare the efficacy of different treatment modalities based on data from a population-based cancer registry. **Patients and Methods:** The study comprises 661 patients identified from the Czech National Cancer Registry (1996-2015) with cTanyN1-3M0 bladder cancer; 195 were treated with CHT alone, 234 underwent radical cystectomy alone (RC), and 232 received a combination of RC and perioperative CHT (RC + CHT). Multivariate Cox proportional hazard regression analyses were used to evaluate the effectiveness of various treatments. **Results:** The 5-year OS for CHT alone, RC alone, and RC + CHT were 21.7% (95% confidence interval [CI], 15.4%-28.0%), 12.1% (95% CI, 7.4%-16.7%), and 25.4% (95% CI, 18.9%-31.9%), respectively ($P < .001$). The median survivals were 17, 10, and 23 months, respectively. In multivariate analysis, age > 60 years (hazard ratio, 1.29; 95% CI, 1.06-1.56; $P = .011$) and clinical stage cT3-4 (hazard ratio, 1.39; 95% CI, 1.12-1.71; $P = .002$) were negative predictors of survival. When compared with CHT, RC + CHT reduced the risk of overall mortality by 21% ($P = .044$). **Conclusion:** Approximately one-quarter of clinically node-positive patients may achieve long-term survival with combined treatment integrating RC and perioperative CHT. The overall survival of patients is significantly improved with a multimodal approach in comparison to CHT alone.

Clinical Genitourinary Cancer, Vol. ■, No. ■, ■-■

Keywords: Chemotherapy, Combined modality therapy, Cystectomy, Lymphadenopathy, Urinary bladder neoplasms

Introduction

Lymph node metastases in bladder cancer are associated with poor prognosis.[1-3] Historically, patients with clinically node-positive disease were considered to be incurable and were frequently treated with palliative chemotherapy (CHT) only. They were grouped with other patients with metastatic disease and recruited in CHT-only trials, and such an approach in well-selected patients led to an overall survival (OS) of 20% within 5 years.[1]

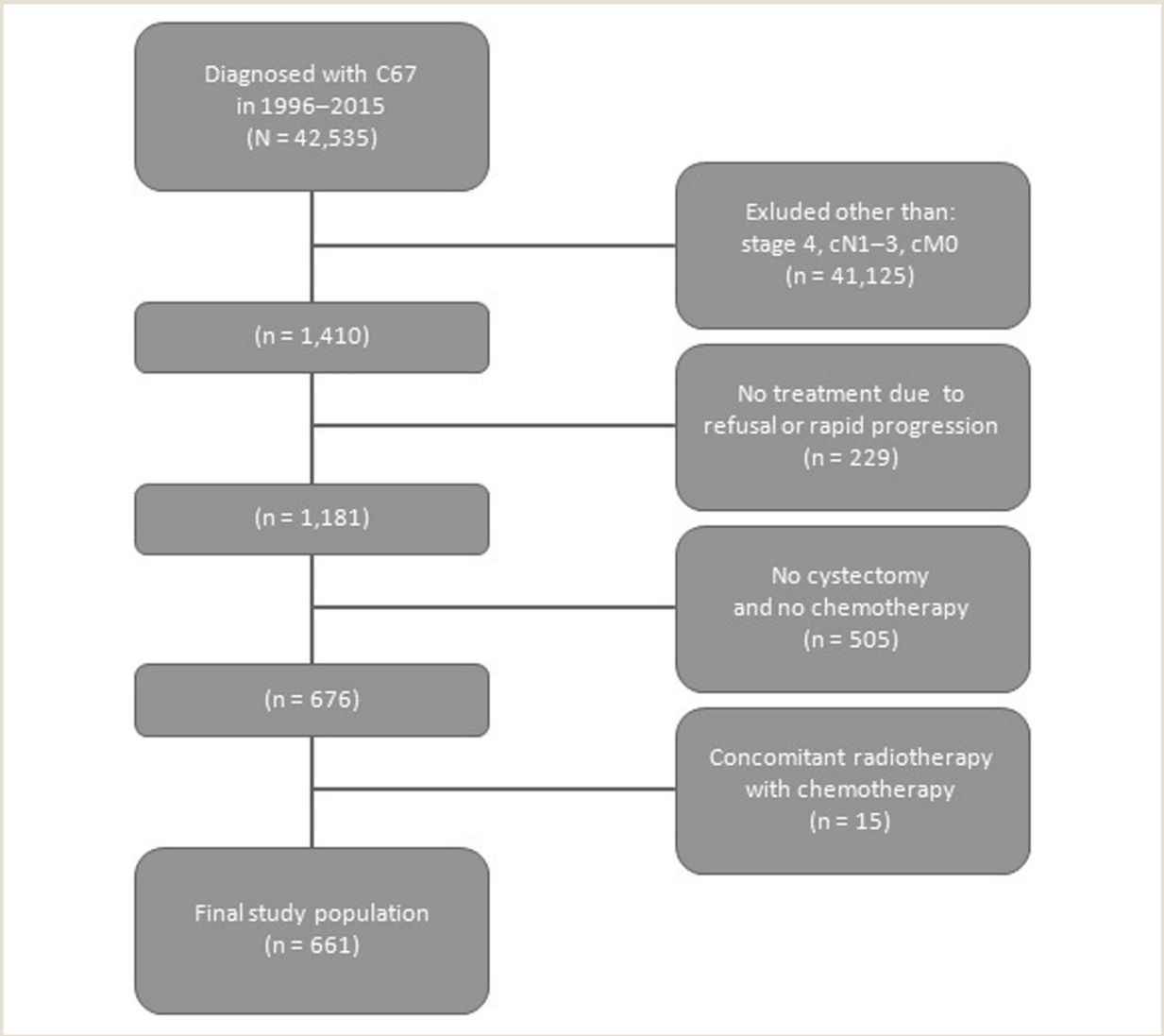
[1]Department of Urologic Oncology, Clinic of Surgical Oncology
[2]Department of Comprehensive Cancer Care, Masaryk Memorial Cancer Institute, Brno, Czech Republic
[3]Institute of Biostatistics and Analyses, Faculty of Medicine, Masaryk University, Brno, Czech Republic
[4]Institute of Health Information and Statistics of the Czech Republic, Prague, Czech Republic

Submitted: Nov 11, 2018; Revised: Mar 25, 2019; Accepted: Apr 9, 2019

Address for correspondence: Michal Staník, PhD, Department of Urologic Oncology, Clinic of Surgical Oncology, Masaryk Memorial Cancer Institute, Žlutý Kopec 7, 65653 Brno, Czech Republic
E-mail contact: stanik@mou.cz

1558-7673/$ - see frontmatter
https://doi.org/10.1016/j.clgc.2019.04.007

Figure 1 Flowchart of the Study



In contrast, a combination of radical cystectomy (RC) and platinum-based systemic CHT is the standard of care in muscle-invasive bladder cancer without lymphadenopathy (cN0), and, although still controversial, this multimodal approach is being increasingly used even in patients with limited nodal metastases, similar to other solid tumors.[4-9] The rationale for adding surgery to systemic treatment is to provide excellent local control of primary tumor and nodal metastases, which may hypothetically lead also to improved systemic control and prolonged survival.[10] There are several factors supporting this approach. First, CHT alone is rarely curative. Moreover, the pattern of relapse in patients with regional nodal metastases shows that the disease frequently recurs at the sites of previous response to CHT.[11]

There is a striking lack of randomized trials that would provide strong evidence-based treatment recommendations and potentially establish the role of surgical extirpation of the primary tumor in the setting of nodal metastases. Although the cumulative evidence points towards improved survival with a multimodal approach, at the present time, our clinical decision-making relies on retrospective uncontrolled studies and cancer registries. Cancer registries, although being heterogeneous in terms of treatment protocols and with many confounding factors, provide hypothesis-generating results based on large patient cohorts and real-world data. One recent analysis demonstrated superior outcomes with combination therapy in comparison to CHT alone, with 5-year OS up to 31%.[2]

We present our analysis of patients with clinically node-positive bladder cancer from the Czech national cancer registry and outcomes associated with different treatment modalities.

Material and Methods

Data Source

The Czech National Cancer Registry (CNCR) is a population-based cancer registry established in 1976 and is a member of the International Association of Cancer Registries. The CNCR is an

Table 1 Patient Demographic and Clinico-pathologic Characteristics

Characteristic[a]	Cystectomy Only N = 234	Chemotherapy Only N = 195	Cystectomy + Chemotherapy N = 232	*P*[b]
Age, y (range)	67 (61-73)	64 (57-70)	62 (55-67)	**<.001**
Gender				
Male	180 (76.9)	154 (79.0)	182 (78.4)	.864
Female	54 (23.1)	41 (21.0)	50 (21.6)	
Period of diagnosis				
1996-2000	43 (18.4)	38 (19.5)	22 (9.5)	<.001
2001-2005	32 (13.7)	40 (20.5)	28 (12.1)	
2006-2010	75 (32.1)	59 (30.3)	69 (29.7)	
2011-2015	84 (35.9)	58 (29.7)	113 (48.7)	
Clinical T stage				
T0	0 (0.0)	0 (0.0)	1 (0.4)	**<.001**
T1	3 (1.3)	12 (6.2)	2 (0.9)	
T2	34 (14.5)	58 (29.7)	52 (22.4)	
T3	105 (44.9)	64 (32.8)	109 (47.0)	
T4	92 (39.3)	61 (31.3)	68 (29.3)	
Clinical N stage				
N1	138 (59.0)	104 (53.3)	98 (42.2)	**<.001**
N2	91 (38.9)	75 (38.5)	120 (51.7)	
N3	5 (2.1)	16 (8.2)	14 (6.0)	
Pathologic T stage				
T0	0 (0.0)	0 (0.0)	1 (0.4)	**<.001**
T1	3 (1.3)	6 (3.1)	2 (0.9)	
T2	34 (14.5)	40 (20.5)	47 (20.3)	
T3	101 (43.2)	47 (24.1)	107 (46.1)	
T4	90 (38.5)	42 (21.5)	68 (29.3)	
Tx	2 (0.9)	41 (21.0)	6 (2.6)	
Unknown	4 (1.7)	19 (9.7)	1 (0.4)	
Pathologic N stage				
N1	132 (56.4)	pN+ in 19 (9.7)	93 (40.1)	**<.001**
N2	90 (38.5)		117 (50.4)	
N3	5 (2.1)		14 (6.0)	
Nx	3 (1.3)	176 (90.3)	7 (3.0)	
Unknown	4 (1.7)		1 (0.4)	
Resection margin status				
Negative	143 (61.1)	53 (27.2)	139 (59.9)	**<.001**
Positive	35 (15.0)	57 (29.2)	37 (15.9)	
Unknown	56 (23.9)	85 (43.6)	56 (24.1)	
Number of examined nodes				
0	140 (59.8)	176 (90.3)	121 (52.2)	**<.001**
1+	94 (40.2)	19 (9.7)	111 (47.8)	
Median (percentile); mean	12 (6-18); 13	10 (4-14); 11	12 (7-18); 13	.630
Number of positive nodes	n = 94	n = 19	n = 111	
0	1 (1.1)	1 (5.3)	1 (0.9)	.427
1+	93 (98.9)	18 (94.7)	110 (99.1)	
Median (percentile); mean	2 (1-3); 3	2 (1-4); 3	3 (1-5); 4	.066
Radiotherapy				
No	197 (84.2)	157 (80.5)	193 (83.2)	.591
Yes	37 (15.8)	38 (19.5)	39 (16.8)	

Table 1 Continued

Characteristic[a]	Cystectomy Only N = 234	Chemotherapy Only N = 195	Cystectomy + Chemotherapy N = 232	P[b]
Cancer-specific death				
No	35 (17.3)	34 (22.5)	17 (11.0)	**.028**
Yes	167 (82.7)	117 (77.5)	137 (89.0)	

Bold values indicate statistically significant ($P < .05$).
[a]Absolute and relative frequencies (%) for categorical data; median with 25th to 75th percentile (and mean, where it is specified) for continuous data.
[b]Pearson χ^2 test for categorical data; Kruskal-Wallis test for continuous data.

independent government-funded organization, and its purpose is registration of all new cases of oncologic diseases, periodic monitoring of their evolution, and processing the data for further interpretation. The compulsory data entry for all healthcare providers is legally implemented, so the outcomes should reflect nationwide patterns of care. The data are collected by independent and trained data managers and are based on individual patient files. The study comprised the data from 81 hospitals, of which 15 (19%) were academic centers.

Study Population

The Czech Republic has a population of approximately 10 million. During the reference period of 1996 to 2015, 1410 patients were identified from CNCR with a diagnosis of clinically node-positive bladder cancer (cTany cN1-3 cM0). Tumor stage was coded according to the Tumor-Node-Metastasis (TNM) classification of malignant tumors. Its 4th, 5th, 6th, and 7th editions were used in the Czech Republic since 1994, 2000, 2004, and 2011, respectively. In the 7th edition, cN1-2 comprises all nodal metastases that were classified in previous editions as cN1-3.[12]

After excluding patients owing to incomplete data, contraindications to CHT, no treatment provided, or concurrent radiotherapy, the final cohort included 661 cases (Figure 1). They were grouped into 3 arms: RC alone (RC arm), palliative CHT alone (CHT arm), and a combination of RC and perioperative CHT (RC + CHT arm). The subgroup RC + CHT was composed mainly of patients with adjuvant CHT after RC (92%). Only 19 (8%) patients had preoperative CHT; therefore, we chose not to evaluate them separately. Adjuvant CHT was defined as CHT that started within 3 months after RC. Lymph node dissection (LND) should be an essential part of RC; however, in our cohort, only approximately 50% of patients that underwent RC had LND. We assessed the outcomes in subgroups with and without LND. Radiotherapy was not an exclusion criterium for analysis. We specifically excluded only 15 patients with concomitant radiotherapy from the CHT group as it represents an alternative local treatment to surgery, and our primary focus was to compare CHT alone to its combination with local treatment. In the final analysis, 15% to 20% in each arm of the study were patients that had radiotherapy during the course of the disease. It was not possible from the CNCR data to address the indication of radiotherapy, whether it was adjuvant or palliative; only the timing of radiotherapy was available. In one-half of the patients, radiotherapy started more than 3 months after the previous surgery or CHT, and we can deduce that it was frequently a part of palliative treatment.

Statistics

Patient characteristics were evaluated using the Pearson χ^2 test and Kruskal-Wallis test for discrete and continuous data, respectively. Kaplan-Meier curves were used to estimate 5-year OS and cancer-specific survival (CSS) and were compared using the log rank test. CSS was calculated as the time from initiation of therapy (surgery or CHT) to the date of bladder cancer-related death. Patients who were alive or died of other causes were censored.

Univariate and multivariate Cox proportional hazards regression analyses were used to evaluate associations between clinicopathologic parameters and oncologic outcomes. We included age, gender, clinical T and N stage, pathologic T and N stage, resection margin status, and treatment modality in univariate analysis. All variables used in univariate analysis entered the multivariate model with the exception of redundant variables (pT vs. cT, pN vs. cN), and the final model was computed using the backward stepwise approach. In multivariate analysis, the effect of RC alone or combination of RC + CHT on OS were assessed with CHT as the reference. Results were considered significant if P value $< .05$ was achieved. Statistical analyses and tests were performed using SPSS software (version 22).

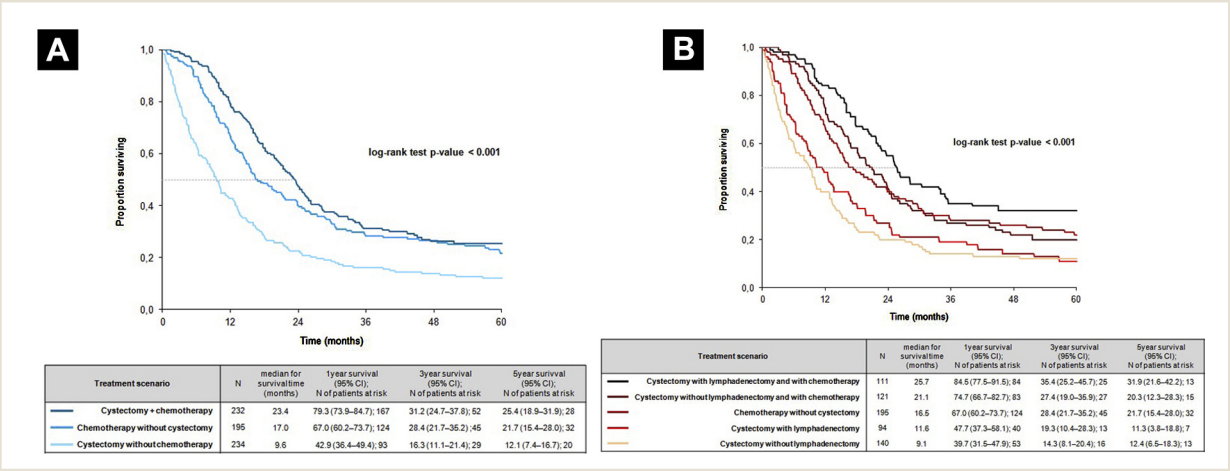
Results

In total, 661 patients were included in the analysis. Their demographic and clinical data are shown in Table 1; 195 (29.5%) were treated with CHT alone, 234 (35.4%) underwent RC alone, and 232 (35.1%) received a combination of RC and perioperative CHT. The median follow-up was 15 months (interquartile range, 7-28 months).

Of the whole cohort, 31% and 69% of patients were treated in the periods 1996 to 2005 and 2006 to 2015, respectively. Combination therapy was more frequent in recent years, as 49% of patients in the RC + CHT group were treated in the period 2011 to 2015. A decrease of palliative CHT alone was noticed in the same period, with only 23% treated without extirpative surgery.

Clinical stages cN1, cN2, and cN3 were diagnosed in 340 (51.4%), 286 (43.3%), and 35 (5.3%) patients, respectively. There was a significantly higher rate of cN2-3 cases treated with combined treatment (RC + CHT; 57.8%) when compared with CHT alone (46.7%) and RC alone (41.0%) ($P = .001$).

Figure 2 Overall Survival According to Treatment Scenario (A) and Lymphadenectomy Performed (B)



Treatment scenario	N	median for survival time (months)	1 year survival (95% CI); N of patients at risk	3 year survival (95% CI); N of patients at risk	5 year survival (95% CI); N of patients at risk
Cystectomy + chemotherapy	232	23.4	79.3 (73.9–84.7); 167	31.2 (24.7–37.8); 52	25.4 (18.9–31.9); 28
Chemotherapy without cystectomy	195	17.0	67.0 (60.2–73.7); 124	28.4 (21.7–35.2) ;45	21.7 (15.4–28.0); 32
Cystectomy without chemotherapy	234	9.6	42.9 (36.4–49.4); 93	16.3 (11.1–21.4); 29	12.1 (7.4–16.7); 20

Treatment scenario	N	median for survival time (months)	1 year survival (95% CI); N of patients at risk	3 year survival (95% CI); N of patients at risk	5 year survival (95% CI); N of patients at risk
Cystectomy with lymphadenectomy and with chemotherapy	111	25.7	84.5 (77.5–91.5); 84	35.4 (25.2–45.7); 25	31.9 (21.6–42.2); 13
Cystectomy without lymphadenectomy and with chemotherapy	121	21.1	74.7 (66.7–82.7); 83	27.4 (19.0–35.9); 27	20.3 (12.3–28.3); 15
Chemotherapy without cystectomy	195	16.5	67.0 (60.2–73.7); 124	28.4 (21.7–35.2); 45	21.7 (15.4–28.0); 32
Cystectomy with lymphadenectomy	94	11.6	47.7 (37.3–58.1); 40	19.3 (10.4–28.3); 13	11.3 (3.8–18.8); 7
Cystectomy without lymphadenectomy	140	9.1	39.7 (31.5–47.9); 53	14.3 (8.1–20.4); 16	12.4 (6.5–18.3); 13

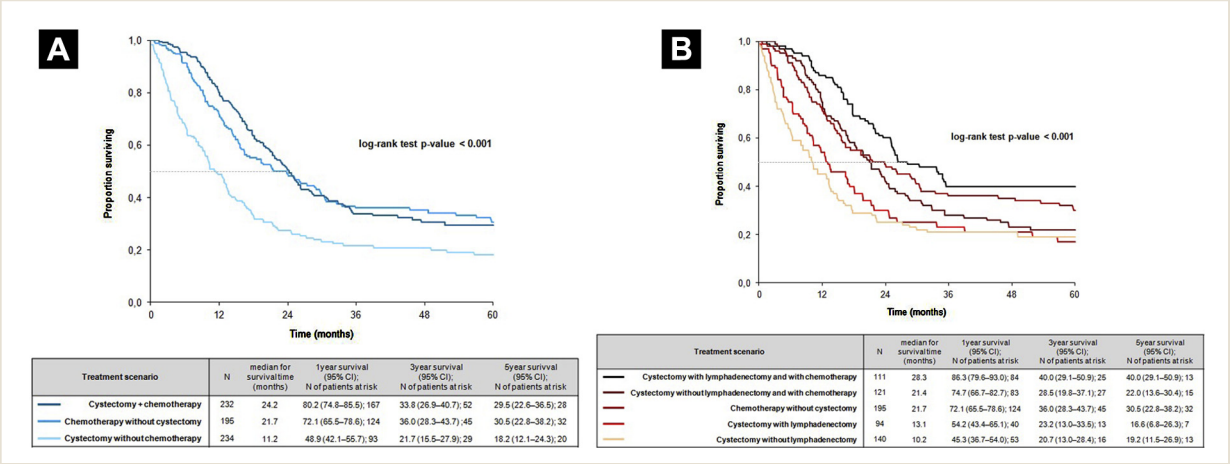
Abbreviation: CI = confidence interval.

In total, 507 (76.7%) patients died during follow-up, of which 83% were owing to bladder cancer. The 5-year OS for CHT alone, RC alone, and RC + CHT were 21.7% (95% confidence interval [CI], 15.4%-28.0%), 12.1% (95% CI, 7.4%-16.7%), and 25.4% (95% CI, 18.9%-31.9%), respectively ($P < .001$). The median survivals were 17, 10, and 23 months, respectively (Figure 2A). Owing to the low number of cases (n = 19), preoperative CHT was incorporated into the RC + CHT group. When evaluated separately, the 5-year OS of 25.1% (95% CI, 1.0%-49.2%) and the median survival of 24 months were similar to the group with adjuvant CHT after surgery.

The 5-year CSS for CHT alone, RC alone, and RC + CHT were 30.5% (95% CI, 22.8%-38.2%), 18.2% (95% CI, 12.1%-24.3%), and 29.5% (95% CI, 22.6%-36.5%), respectively ($P < .001$), with respective median survivals of 22, 11, and 24 months (Figure 3A).

LND was performed in only approximately one-half of the patients undergoing surgery. The rates of LND were 40% and 48% of patients in groups RC and RC + CHT, respectively, with a median number of 12 nodes removed in both groups (interquartile range, 6-18 nodes). When compared with patients without LND, those with LND in RC + CHT group had a better 5-year OS of 31.9% (95% CI, 21.6%-42.2%) versus 20.3% (95% CI, 12.3%-28.3%) ($P = .038$) (Figure 2B) and 5-year CSS of 40.0% (95% CI, 29.1%-50.9%) versus 22.0% (95% CI, 13.6%-30.4%) (Figure 3B). Moreover, the 5-year OS of 31.9% in the subgroup RC + CHT with completed LND was significantly higher than CHT alone (21.7%; $P = .009$); for 5-year CSS, the corresponding numbers for both groups were 40.0% and 30.5%. In univariate analysis, patients with RC + CHT with completed LND had reduced risks of overall

Figure 3 Cancer-specific Survival According to Treatment Scenario (A) and Lymphadenectomy Performed (B)



Treatment scenario	N	median for survival time (months)	1 year survival (95% CI); N of patients at risk	3 year survival (95% CI); N of patients at risk	5 year survival (95% CI); N of patients at risk
Cystectomy + chemotherapy	232	24.2	80.2 (74.8–85.5); 167	33.8 (26.9–40.7); 52	29.5 (22.6–36.5); 28
Chemotherapy without cystectomy	195	21.7	72.1 (65.5–78.6); 124	36.0 (28.3–43.7) ;45	30.5 (22.8–38.2); 32
Cystectomy without chemotherapy	234	11.2	48.9 (42.1–55.7); 93	21.7 (15.5–27.9); 29	18.2 (12.1–24.3); 20

Treatment scenario	N	median for survival time (months)	1 year survival (95% CI); N of patients at risk	3 year survival (95% CI); N of patients at risk	5 year survival (95% CI); N of patients at risk
Cystectomy with lymphadenectomy and with chemotherapy	111	28.3	86.3 (79.6–93.0); 84	40.0 (29.1–50.9); 25	40.0 (29.1–50.9); 13
Cystectomy without lymphadenectomy and with chemotherapy	121	21.4	74.7 (66.7–82.7); 83	28.5 (19.8–37.1); 27	22.0 (13.6–30.4); 15
Chemotherapy without cystectomy	195	21.7	72.1 (65.5–78.6); 124	36.0 (28.3–43.7); 45	30.5 (22.8–38.2); 32
Cystectomy with lymphadenectomy	94	13.1	54.2 (43.4–65.1); 40	23.2 (13.0–33.5); 13	16.6 (6.8–26.3); 7
Cystectomy without lymphadenectomy	140	10.2	45.3 (36.7–54.0); 53	20.7 (13.0–28.4); 16	19.2 (11.5–26.9); 13

Abbreviation: CI = confidence interval.

Table 2 Cox Model (Overall Survival), Univariate Analysis (With Chemotherapy Alone as Reference)

Treatment	Univariate Analysis	
	HR (95% CI)	*P* Value
Chemotherapy alone	Reference	
Cystectomy with chemotherapy and with lymphadenectomy	0.685 (0.511-0.919)	.012
Cystectomy with chemotherapy and without lymphadenectomy	0.936 (0.720-1.215)	.618
Cystectomy with lymphadenectomy	1.585 (1.198-2.096)	.001
Cystectomy without lymphadenectomy	1.960 (1.548-2.483)	<.001

Abbreviations: CI = confidence interval; HR = hazard ratio.

mortality (Table 2) and cancer-specific mortality (Table 3) by 31% (hazard ratio [HR], 0.69; $P = .012$) and 30% (HR, 0.70; $P = .035$), respectively, when compared with the CHT alone group as reference.

In multivariate analysis, age > 60 years (HR, 1.29; 95% CI, 1.06-1.56; $P = .011$) and clinical stage cT3-4 (HR, 1.39; 95% CI, 1.12-1.71; $P = .002$) were negative predictors of survival (Table 4 and Supplemental Figure 1). When compared with CHT, RC + CHT reduced the risk of overall mortality by 21% (HR, 0.79; $P = .044$). On the contrary, RC alone increased mortality by 69% ($P < .001$).

Discussion

Our analysis of a population-based cancer registry showed that patterns of care provided to patients with clinically node-positive bladder cancer are heterogenous, which reflects the absence of clear clinical recommendations and the underlying lack of high-level evidence data. We demonstrated that survival is not uniformly dismal in these patients. Although being at high risk of developing distant metastases, a substantial proportion are potentially curable. Our results add to the growing body of evidence based on other retrospective studies that combination therapy integrating surgery and perioperative CHT outperforms CHT alone.[2,7-9,13] In our study, 5-year OS rates for both groups differed significantly, favoring the combined treatment with 31% versus 22% in the CHT-alone group. We also analyzed cancer-specific mortality data, which were not available in previous registry studies.[2,13] The best outcomes were for RC + CHT with completed lymphadenectomy, which had a 5-year CSS of 40%, and this type of treatment reduced the risk of dying of bladder cancer by 30% in comparison to CHT alone. On the other hand, surgery without systemic treatment only infrequently leads to long-term survival (5-year OS 10%-20%) owing to the high risk of synchronous distant micrometastases.[2,13] Therefore, the selection of patients for surgical treatment is crucial; if patients are not eligible for platinum-based CHT, the prognosis is poor. Selecting patients to surgery according to response to induction CHT is an attractive option and is further discussed below.

Table 3 Cox Model (Cancer-specific Survival), Univariate Analysis (With Chemotherapy Alone as Reference)

Treatment	Univariate Analysis	
	HR (95% CI)	*P* Value
Chemotherapy alone	Reference	
Cystectomy with chemotherapy and with lymphadenectomy	0.704 (0.509-0.975)	.035
Cystectomy with chemotherapy and without lymphadenectomy	1.101 (0.831-1.457)	.503
Cystectomy with lymphadenectomy	1.617 (1.186-2.205)	.002
Cystectomy without lymphadenectomy	2.065 (1.587-2.688)	<.001

Abbreviations: CI = confidence interval; HR = hazard ratio.

In the largest retrospective study, Galsky et al analyzed 1739 cN1-3 cases from the National Cancer Database treated in 2003 to 2012 and demonstrated superior outcomes with a combination of RC and perioperative CHT.[2] The 5-year OS for CHT alone, RC alone, RC + adjuvant CHT, and preoperative CHT followed by RC was 14%, 19%, 26%, and 31%, respectively. When compared with our study, the 5-year OS rates for combined therapy were similar (31% vs. 32%). Interestingly, the outcomes of CHT alone were much better in our study (22% vs. 14%), which may be caused by selection bias, as in our study, a higher rate of patients were left out without any treatment, potentially including those with worse performance status or prognosis. We confirmed that combination therapy involving RC and adjuvant CHT results in improved survival in multivariate analysis in comparison to CHT alone or RC alone.

The timing of perioperative CHT generates some controversy, with arguments similar to neoadjuvant versus adjuvant CHT dilemma in cN0 patients. The proponents of preoperative or induction CHT (IC) argue that patients are more fit to undergo systemic treatment before surgery and that the response to IC may select them for consolidative surgery, especially in cases with gross lymphadenopathy.[3,7,13] Several studies demonstrated that pathologic downstaging is associated with excellent survival.[7,13] In contrast, non-responders have poor prognosis. In our study, we could not address this issue as there were only 19 cases with preoperative CHT. In this small cohort, the median survival of 24 months was similar to the group with adjuvant CHT.

Recently, excellent results were published using data from the Netherlands cancer registry in patients with bladder cancer with nodal metastases that underwent IC followed by consolidative surgery.[13] Of 659 patients, 210 (32%) had such therapy, and the rest underwent upfront cystectomy, with only 8% receiving adjuvant CHT. The 5-year OS rates were 58% and 29% (cN1) and 36% and 18% (cN2-3) for combined therapy and upfront RC, respectively. However, the results must be interpreted with caution because the authors acknowledge potential selection bias as more fit patients could undergo combined treatment. Moreover, they could not identify the number of patients undergoing IC and not proceeding to RC, further confounding the results. Finally, 31% of the cN1 cases proved to be pN0 at the time of surgery in upfront RC group,

Table 4 Univariate and Multivariate Cox Regression Analysis Evaluating Associations Between Clinicopathologic Parameters and Overall Survival

Characteristic	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, y				
<60 y	Reference		Reference	
≥ 60 y	1.431 (1.182-1.732)	**<.001**	1.286 (1.059-1.561)	**.011**
Gender				
Male	Reference		—	
Female	0.965 (0.779-1.195)	.744		
Clinical T stage				
cT0-cT2	Reference		Reference	
cT3, cT4	1.408 (1.144-1.732)	**.001**	1.386 (1.124-1.710)	**.002**
Clinical N stage				
cN1	Reference		—	
cN2, cN3	1.068 (0.897-1.272)	.458		
Pathologic T stage[a]				
pT0-pT2	Reference		—	
pT3, pT4	1.387 (1.103-1.744)	**.005**		
Pathologic N stage				
pN1	Reference		—	
pN2, pN3	1.094 (0.907-1.320)	.347		
Resection margin status				
Negative	Reference		—	
Positive	1.070 (0.844-1.357)	.574		
Treatment				
Chemotherapy alone	Reference		Reference	
Cystectomy without chemotherapy	1.805 (1.460-2.232)	**<.001**	1.688 (1.362-2.092)	**<.001**
Cystectomy and chemotherapy	0.813 (0.649-1.019)	.072	0.792 (0.630-0.994)	**.044**

Abbreviations: CI = confidence interval; HR = hazard ratio.
Bold values indicate statistically significant ($P < .05$).
[a]Owing to high correlation of pathologic T stage with clinical T stage, pathologic T stage was omitted in multivariate analysis.

which suggests that a substantial number of patients could be overstaged even in the arm with combination treatment. Still, this study underlines the feasibility of such an approach with promising oncologic outcomes. In our study, clinical N stage (cN1/cN2-3) was not predictor of OS (Supplemental Figure 2), which is counterintuitive; however, conflicting data were reported on this topic in literature previously. Zargar-Shoshtari et al showed no difference in OS between cN1 and cN2-3 in cohort of 304 clinically node-positive patients undergoing induction CHT and RC.[7] In contrast, in aforementioned study by Hermans et al, the authors reported an increased risk of mortality in cN2-3 patients in multivariate analysis (HR, 1.6).[13]

If combination treatment is being considered, the quality of surgery has to be guaranteed, with meticulous pelvic LND as a fundamental requirement, reducing the risk of local recurrence and further spread of the tumor.[14] In the cN+ stage, there is a lack of data regarding the optimal extent of LND, which is in contrast to the cN0 stage, where a randomized trial has been recently published.[15] In clinically node-positive patients, the usual extent of LND comprises the regional nodal landings up to aortic bifurcation. In our study, one-half of the patients had suboptimal surgery without lymphadenectomy, and we evaluated these subgroups separately. Those patients with combined treatment and LND did significantly better than those without LND, with 5-year OS rates 32% versus 20% ($P = .038$). Interestingly, there was no difference in outcome of patients between CHT alone and combined treatment if LND was not performed (5-year OS, 20% vs. 22%; $P = .615$).

There are several limitations to our study. First, it is a retrospective study with all the attendant drawbacks. Selection of optimum patients for combined therapy is a possible inherent bias that may lead to overestimating the success of such a treatment. Second, we could not account for different CHT protocols, comorbidities, extent of LND, or case volume as this type of data was not available in the cancer registry, all potentially confounding the outcomes.[16,17] Third, initial clinical lymphadenopathy was not histologically verified before treatment. Nevertheless, radiologic suspicion for nodal metastases correlates well with pathologic findings.[2] In patients with upfront cystectomy, we confirmed the nodal metastases in 98% of cases.

Collaborative efforts are urgently needed to initiate randomized trials that would potentially establish the role of combined treatment in this patient population and address issues such as the timing of perioperative CHT. Moreover, improvements in the molecular definition of bladder cancer, recent advances in immunotherapy, and emerging therapeutic targets may cause dramatic changes to how we approach this cancer in the near future and further modify our therapeutic pathways.[18,19]

Conclusion

In patients with clinically node-positive bladder cancer, combination therapy integrating RC, lymphadenectomy, and perioperative CHT provides the best oncologic outcomes, with long-term survival in approximately 30% of patients. The quality of surgery is of utmost importance when combined treatment is being considered, with meticulous pelvic LND playing the major role. If patients are not eligible for systemic treatment, their probability of cure drops significantly, despite surgery. There is a clear need for randomized trials that would establish the role of a multimodal approach and provide strong evidence for treatment recommendations in this patient group.

Clinical Practice Points

- Patients with clinically node-positive bladder cancer were historically treated with palliative CHT only.
- Recently, a few retrospective studies demonstrated potential benefit of multimodal therapy, but we still lack a strong evidence-based treatment recommendations in this group of patients.
- We assessed the outcomes in 661 patients grouped into 3 arms: RC, CHT, and RC + CHT.
- When compared with CHT, RC + CHT reduced the risk of overall mortality by 21%, and one-quarter of patients may achieve long-term survival.
- Five-year OS 31.9% in the group RC + CHT with completed LND was significantly higher than CHT alone (21.7%; $P = .009$).
- Patients who underwent RC without systemic treatment had the worst survival rate (5-year OS, 12.1%).
- Patients eligible for systemic treatment should be offered RC and perioperative CHT; the timing of CHT (induction vs. adjuvant) remains to be defined; currently, induction CHT is the preferred option.

Acknowledgment

This study was supported by the Ministry of Health of the Czech Republic MH CZ - DRO (MMCI, 00209805).

Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

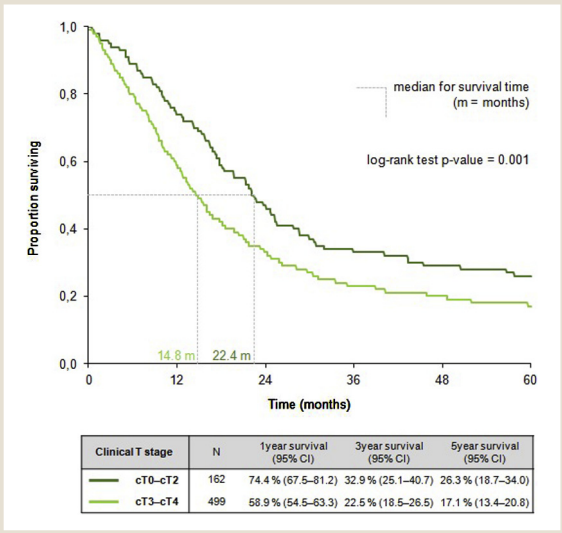
Supplemental figures accompanying this article can be found in the online version at https://doi.org/10.1016/j.clgc.2019.04.007.

References

1. Von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. *J Clin Oncol* 2005; 23:4602-8.
2. Galsky MD, Stensland K, Sfakianos JP, et al. Comparative effectiveness of treatment strategies for bladder cancer with clinical evidence of regional lymph node involvement. *J Clin Oncol* 2016; 34:2627-35.
3. Abufaraj M, Dalbagni G, Daneshmand S, et al. The role of surgery in metastatic bladder cancer: a systematic review. *Eur Urol* 2018; 73:543-57.
4. Advanced Bladder Cancer (ABC) Meta-Analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data: advanced bladder cancer (ABC) meta-analysis collaboration. *Eur Urol* 2005; 48:202-5.
5. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med* 2003; 349:859-66.
6. Witjes AJ, Lebret T, Compérat EM, et al. Updated 2016 EAU guidelines on muscle-invasive and metastatic bladder cancer. *Eur Urol* 2017; 71:462-75.
7. Zargar-Shoshtari K, Zargar H, Lotan Y, et al. A multi-institutional analysis of outcomes of patients with clinically node positive urothelial bladder cancer treated with induction chemotherapy and radical cystectomy. *J Urol* 2016; 195:53-9.
8. Meijer RP, Mertens LS, van Rhijn BW, et al. Induction chemotherapy followed by surgery in node-positive bladder cancer. *Urology* 2014; 83:134-9.
9. Ho PL, Willis DL, Patil J, et al. Outcome of patients with clinically node-positive bladder cancer undergoing consolidative surgery after preoperative chemotherapy: the M.D. Anderson Cancer Center Experience. *Urol Oncol* 2016; 34:59.e1-8.
10. Reyes DK, Pienta KJ. The biology and treatment of oligometastatic cancer. *Oncotarget* 2015; 6:8491-524.
11. Dimopoulos MA, Finn L, Logothetis CJ. Pattern of failure and survival of patients with metastatic urothelial tumors relapsing after cis-platinum-based chemotherapy. *J Urol* 1994; 151:598-600.
12. Sobin LH, Gospodarowicz GM, Wittekind C, eds. *TNM atlas*. 7th ed. Hoboken, NJ: Wiley-Blackwell; 2009.
13. Hermans TJ, Fransen van de Putte EE, Horenblas S, et al. Pathological downstaging and survival after induction chemotherapy and radical cystectomy for clinically node-positive bladder cancer-results of a nationwide population-based study. *Eur J Cancer* 2016; 69:1-8.
14. Bruins HM, Veskimae E, Hernandez V, et al. The impact of the extent of lymphadenectomy on oncologic outcomes in patients undergoing radical cystectomy for bladder cancer: a systematic review. *Eur Urol* 2014; 66:1065-77.
15. Gschwend JE, Heck MM, Lehmann J, et al. Extended versus limited lymph node dissection in bladder cancer patients undergoing radical cystectomy: survival results from a prospective, randomized trial. *Eur Urol* 2019; 75:604-11.
16. Hinata N, Miyake H, Miyazaki A, Nishikawa M, Tei H, Fujisawa M. Performance status as a significant prognostic predictor in patients with urothelial carcinoma of the bladder who underwent radical cystectomy. *Int J Urol* 2015; 22:742-6.
17. Waingankar N, Mallin K, Smaldone M, et al. Assessing the relative influence of hospital and surgeon volume on short-term mortality after radical cystectomy. *BJU Int* 2017; 120:239-45.
18. Robertson AG, Kim J, Al-Ahmadie H, et al. Comprehensive molecular characterization of muscle-invasive bladder cancer. *Cell* 2017; 171:540-56.
19. Siefker-Radtke AO, Apolo AB, Bivalacqua TJ, Spiess PE, Black PC. Immunotherapy with checkpoint blockade in the treatment of urothelial carcinoma. *J Urol* 2018; 199:1129-42.

Supplemental Data

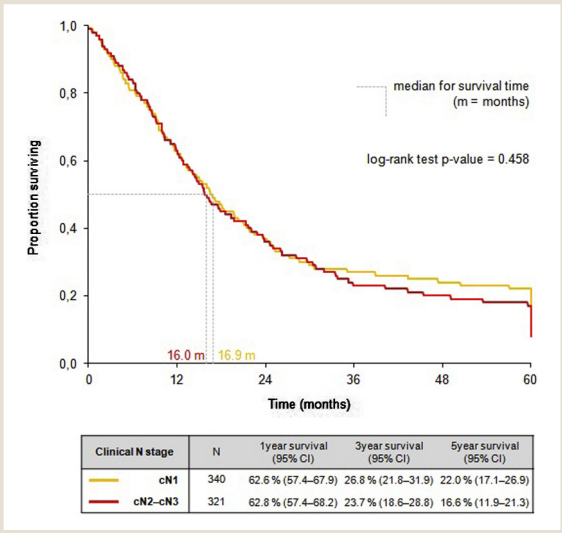
Supplemental Figure 1 Overall Survival According to Clinical T Stage



Clinical T stage	N	1year survival (95% CI)	3year survival (95% CI)	5year survival (95% CI)
cT0–cT2	162	74.4 % (67.5–81.2)	32.9 % (25.1–40.7)	26.3 % (18.7–34.0)
cT3–cT4	499	58.9 % (54.5–63.3)	22.5 % (18.5–26.5)	17.1 % (13.4–20.8)

Abbreviation: CI = confidence interval.

Supplemental Figure 2 Overall Survival According to Clinical N Stage



Clinical N stage	N	1year survival (95% CI)	3year survival (95% CI)	5year survival (95% CI)
cN1	340	62.6 % (57.4–67.9)	26.8 % (21.8–31.9)	22.0 % (17.1–26.9)
cN2–cN3	321	62.8 % (57.4–68.2)	23.7 % (18.6–28.8)	16.6 % (11.9–21.3)

Abbreviation: CI = confidence interval.