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ORIGINAL ARTICLE

Hospital variation in treatment patterns and oncological outcomes for patients with muscle-invasive and metastatic bladder cancer in the Netherlands

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Abstract

Purpose Population-based studies on treatment patterns in oncology and corresponding clinical outcomes can help identify strategies towards optimal value for patients. This study was performed to describe the variation in treatment patterns and major oncological outcomes for muscle-invasive or metastatic bladder cancer (MIBC/mBC) patients in the Netherlands.

Methods Patients diagnosed with cT2-4aN0-3M0-1 disease between 2008 and 2016 in seven large teaching hospitals in the Netherlands were included. Baseline characteristics, disease stage, intended and definitive treatment, and oncological outcomes were collected. Patients were categorized based on cTNM-stage: (1) cT2-4aN0M0, (2) cT2-4aN1-3M0 and (3) cT4b and/or M1.

Results The total study population comprised 1853 patients, of which 1303 patients were diagnosed with cT2-4aN0M0 disease. Overall, curative treatment was intended in 81% (range 74–85%, P value = 0.132). Radical cystectomy (RC) and curative radiotherapy (RTx) ranged between hospitals from 42 to 66% and 13 to 27%, respectively (P value < 0.001). For 334 patients staged cT4b and/or M1, frequencies for palliative therapy and best supportive care (no anti-cancer therapy) ranged between hospitals from 20 to 54% and 44 to 71%, respectively (P value < 0.001). There was no association between hospital site and overall survival (OS) in a univariable and multivariable Cox regression for survival analysis (after adjusting for age and cT-stage), for all three cTNM-groups. Neoadjuvant or induction chemotherapy (NAIC) utilization rates before RC ranged from 8 to 38% (P value < 0.001).

Conclusions There is large inter-hospital variation in treatment intent in MIBC/mBC patients. This variation does not seem to translate to differences in overall survival rates. There is an ongoing trend of increased use of RC. Utilisation of NAIC is relatively low considering European guideline recommendations.

Keywords Bladder cancer · Metastatic · Muscle invasive · Outcomes · Treatment patterns

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Introduction

Radical cystectomy (RC) with extended pelvic lymph node dissection (PLND) is the gold standard treatment for muscle-invasive bladder cancer (MIBC). Frail or elderly patients undergoing RC are at higher risk of postoperative adverse outcomes [1] and can, therefore, be offered bladder-sparing treatment, such as radiotherapy (RTx) or chemoradiotherapy (CRTx) [2]. Pre-operative neoadjuvant or induction chemotherapy (NAIC) extends survival in select candidates [3–7]. Patients with metastatic bladder cancer (mBC) have a poor prognosis and guidelines recommend first-line (1L) treatment with cisplatin-based chemotherapy or immunotherapy [8]. Response rates are reported to be 40–60% to first-line chemotherapy [9, 10].

To decide on appropriate treatment strategies and guide patients in expected oncological outcomes, guidelines led by data from clinical trials are used. However, clinical trials are characterized by strict in- and exclusion criteria [11]. For example, in the ABC Collaboration analysis on which guidelines rely, only 4% of patients had a Performance Status (PS) of 2–3, and 3% had a renal function (glomerular filtration rate) of < 60 mL/min [4]. It is estimated that 28–59% of urothelial carcinoma (UC) patients are ineligible for cisplatin-based chemotherapy [11, 12]. It is up to the physician and patient to choose the appropriate treatment, taking into account oncological outcomes and patients' characteristics, such as frailty. With no clear definition of 'frail' or 'elderly', it is, therefore, conceivable that choice of treatment and oncological outcomes differ between hospital sites.

There is a large international variability in bladder cancer treatment [13–16]. Literature shows major differences between abstaining from curative-intended treatment (CIT) in cT2-4aN0M0 patients from Sweden (59% no CIT) [15], the UK (47% no CIT) [16], and the USA (37% no CIT) [14]. Possibly, survival of both all cT2-4aN0M0 patients as well as the fraction that were treated with a curative treatment modality were hereby affected.

As a result, treatment received by a patient with MIBC/mBC is dependent on the country and hospital of diagnosis. Understanding of both national as international differences is important when oncological outcomes are compared. In the present study, we assessed variations in treatment strategies and oncological outcomes for MIBC/mBC patients in seven large teaching hospitals in the Netherlands.

Methods

Study design, patient population, and data collection

This non-interventional, retrospective study was performed within a network of seven large (non-university) teaching hospitals in the Netherlands, named Santeon, which is a cooperative association of hospitals that work together. These hospitals are responsible for covering approximately 15% of the Dutch population within their catchment area. The study was approved by the local research ethics committee of the St. Antonius Hospital Utrecht/Nieuwegein (W17.087), by the Institutional Review Board at each participating hospital, and was conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki.

Eligible patients included adults aged ≥ 18 years and diagnosed with cT2-4aN0-3M0-1. The study selection period covered January 1, 2008–December 31, 2016, with follow-up through July 2020. All patients newly diagnosed with bladder cancer in the seven hospitals, were retrospectively extracted from the Netherlands Cancer Registry (NCR) database. Subsequently, data were checked and supplemented by manual chart review. Excluded from analyses were non-urothelial carcinoma bladder tumours, cancer of the upper urinary tract, and patients with missing outcome data.

Topography and morphology were classified according to the International Classification of Diseases of Oncology (ICD-O) and tumour stage according to the 7th TNM-classification system [17].

Patients were stratified according to the following clinical TNM-stage: (1) cT2-4aN0M0, (2) cT2-4aN1-3M0 and (3) cT4b and/or M1. The majority of patients were staged with CT-thorax/abdomen, only a few underwent a PET/CT for staging.

Outcomes and definitions

To analyse the intention-to-treat, patients were grouped based on the intended treatment after diagnosis. For analyses on oncological outcomes, patients were grouped based on definitive treatment. Outcome variables were collected according to the Santeon Bladder cancer outcome set [18]. Under RTx, external beam radiation therapy (EBRT), brachytherapy or a combination of both was grouped. Best supportive care (BSC) was defined as appropriate palliative care without any other anticancer therapies. Palliative care was defined as systemic or radiation (or in combination) anti-cancer therapy without the intend to cure. For

patients with CIT, overall survival (OS), cancer-specific survival (CSS) time (in months) was calculated using start of treatment and date of death. For patients receiving palliative treatment or BSC, date of diagnosis was used for the calculation of survival times. Progression-free survival (PFS) was similarly calculated as time (in months) between either start of treatment or date of diagnosis and first radiological evidence of recurrence or progression. Evaluation of response to chemotherapy by imaging was performed according to the Response Evaluation Criteria in Solid Tumours (RECIST) criteria v1.1 [19].

Statistical analyses

Descriptive statistics were used to characterize the cohort. In case of continuous data, mean (± standard deviation (SD)) are presented, or when data was skewed, median with interquartile range (IQR). Continuous data was compared across hospital sites using one-way ANOVA, otherwise *t* tests were used. Categorical data are presented as frequencies with percentage, and compared across hospital sites using the chi-square tests.

The Kaplan–Meier method with 95% confidence intervals [95% CI] was used to determine survival and compared using the log-rank test, after stratification for hospital site or disease stage. Patients alive at the end of the study were censored at the last available date known to be alive. Kaplan–Meier curves were produced using R (version 4.0.2, R Core Team). The reverse Kaplan–Meier method was used to determine median follow-up.

A Cox proportional-hazards model was used to examine whether hospital site was independently associated with mortality, after adjusting for age and cT-stage.

All reported *P* values were two-sided and *P* value of < 0.05 was considered statistically significant. Statistical analyses were performed with SPSS (v24.0, IBM).

Results

Patient characteristics

Between 2008 and 2016, we identified 7531 patients with BCa, of which 2123 (28.2%) patients were diagnosed stage cT2-4aN0-3M0-1 (Online Resource 1). Lost-to follow-up were 93 patients (4.4%), and 177 patients (8.3%) had a histological variant (non-UC) and were excluded from analyses. The final cohort included 1853 patients, of which 1303 (70.3%) staged cT2-4aN0M0, 216 (11.7%) staged cT2-4aN1-3M0, and 334 (18.0%) staged cT4b and/or M1.

Between hospital sites, patients did not differ in mean age at diagnosis, or sex at birth. Clinical stage differed statistically significant (cTNM-stage *P* value = 0.003, cN-stage *P* value < 0.001 and cM-stage *P* value < 0.001), with hospital C having more patients with low-stage disease.

Intent of treatment for stage groups

An overview of intended treatment, stratified by each disease cTNM-stage can be found in Online Resource 2. Figure 1a–c shows grouped differences for each hospital site.

For patients with cT2-4aN0M0 disease, 81.0% of patients had CIT, with differences between hospital sites ranging from 74.3 to 85.2% (*P* value = 0.132). Choice of treatment modality after diagnosis was different (*P* value < 0.001). Hospital sites A through F intended RC

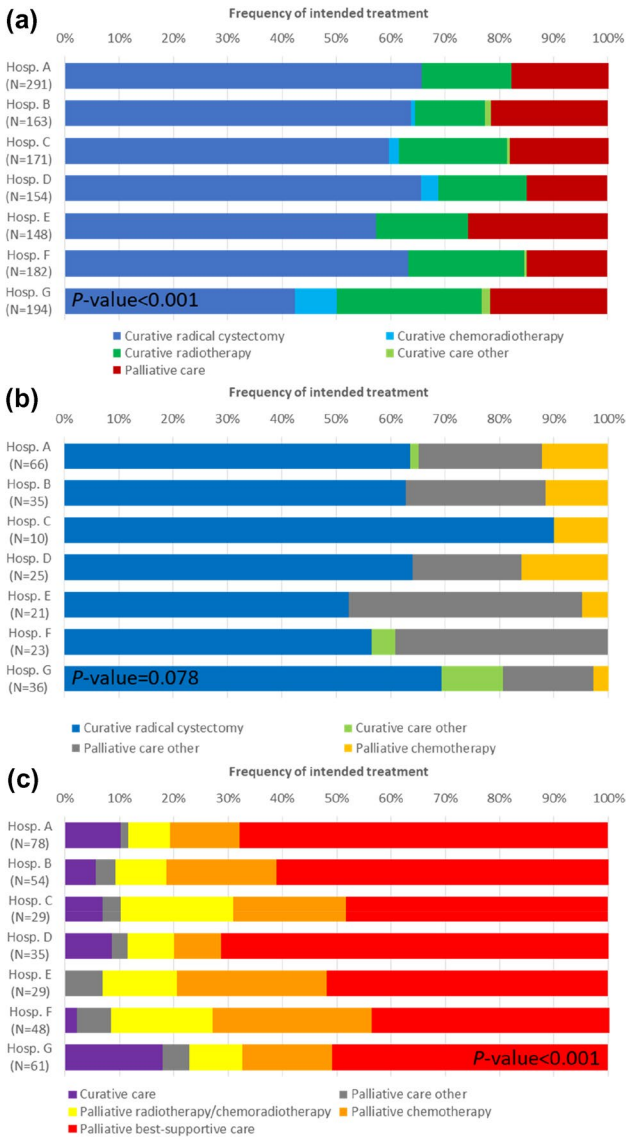

Fig. 1 **a–c** Intended treatment rates for patients with **a** cT2-4aN0M0, **b** cT2-4aN1-3M0, **c** cT4b and/or cM1 urothelial carcinoma of the bladder, according to hospital site

(with or without NAC) in 57.4–65.7% of patients. Hospital G, however, only intended RC in 42.3% of patients. Instead, bladder sparing treatment was intended more often, such as CRTx (7.7%) and RTx (26.8%).

Patients with cT2-4aN1-3M0 disease did not have different intent of treatment between hospital sites (curative vs. palliative, *P* value = 0.222), nor choice of treatment modality (*P* value = 0.078), but large differences were present. In hospital C, 90.0% of patients had CIT, whereas in hospital E only 52.3% of patients had CIT. Treatment of preference was RC (with or without NAIC) in all hospital sites, but hospital G more often intended other forms of curative treatment in 11.2% of patients.

Patients with cT4b and/or M1 disease had statistically significant different intent of treatment between hospital sites (curative vs. palliative, *P* value = 0.035). Curative treatment was intended in 0% of patients in hospital E, whereas hospital G had CIT in 18.0% of patients. Similarly, hospital D intended BSC in 71.4% of patients, and other palliative treatment in 20.1% of patients. This is in contrast with hospital F with 43.8%, and 54.3%, respectively.

Intent of treatment for age groups

When patients were divided into age groups (< 75 and ≥ 75 years of age), there were varying treatment preferences which are shown in Fig. 2a, b. Curative treatment was intended in 50.7% (range 44.9–58.2%, *P* value = 0.141) of all 816 patients aged ≥ 75 with all disease stages (cT2-4aN0-3M0-1).

Between hospital sites, CIT ranged from 58 to 72% for patients with cT2-4aN0M0 disease aged ≥ 75 (*P* value = 0.335). Only 0–8% of patients staged cT4b and/or M1 disease had CIT (*P* value = 0.616). Only 0–19% of patients with cT4b and/or M1 disease and aged ≥ 75 years received first-line chemotherapy.

Oncological outcomes

A univariable Cox regression for survival analysis for each hospital site, stratified by cTNM disease stage, can be found in Table 1. None of the three cTNM stages, had statistically significant different mOS between hospital sites, but differences were present (cT2-4aN0M0 range

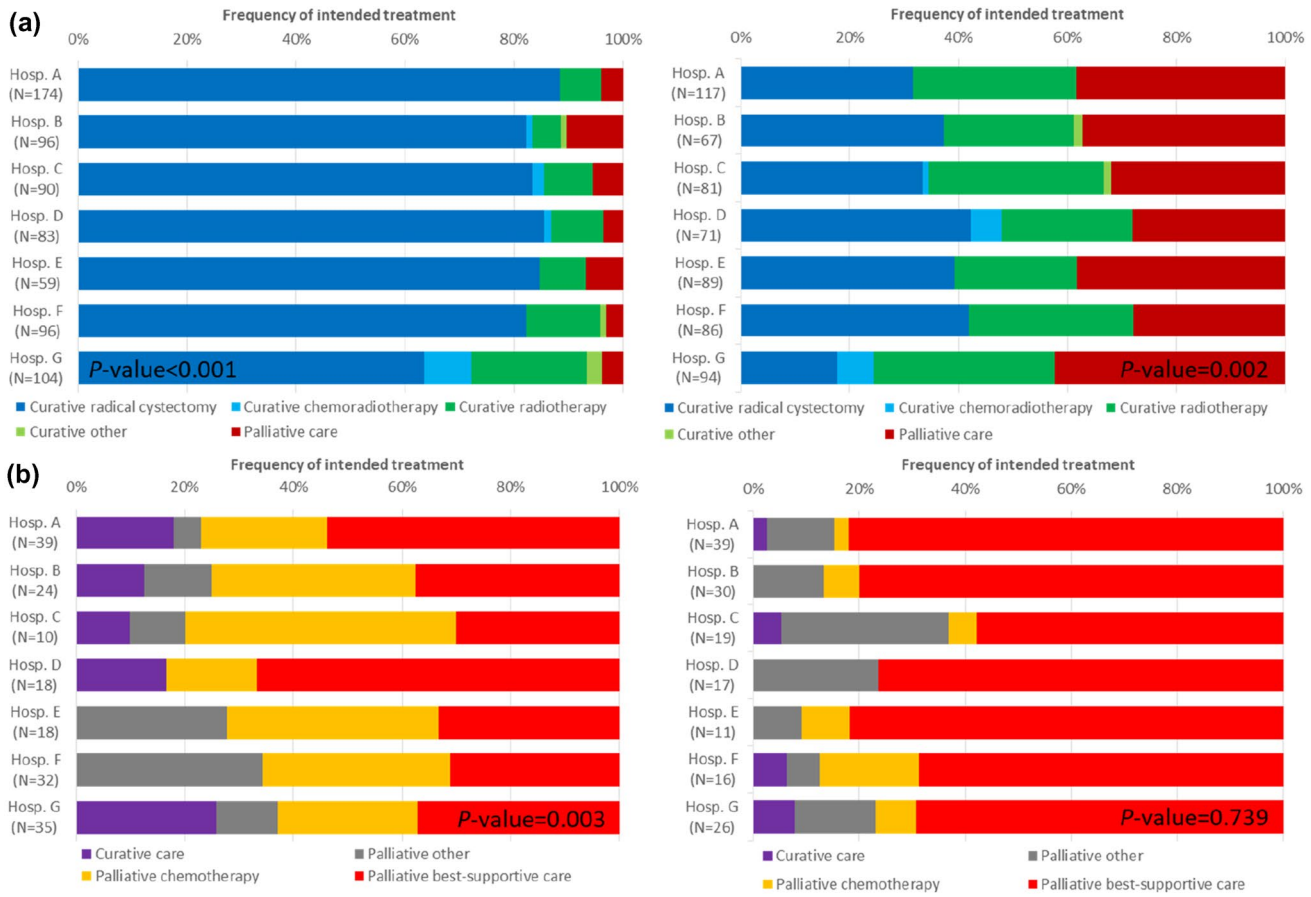

Fig. 2 **a**, **b** Intended treatment rates for patients with **a** cT2-4aN0M0 and **b** cT4b and/or cM1 urothelial carcinoma of the bladder, stratified by age category < 75 (left) and ≥ 75 (right), according to hospital site

Table 1 Survival analysis for patients with cT2-4N0-3M0-1 urothelial carcinoma of the bladder stratified by clinical stage, according to hospital site

	cT2-4aN0M0			cT2-4aN1-3M0			cT4b and/or M1		
	Median	[95% CI]	*P* value	Median	[95% CI]	*P* value	Median	[95% CI]	*P* value
Overall survival (months)	24.0	[20.7–27.2]	0.452	14.5	[11.6–17.3]	0.550	3.9	[3.2–4.7]	0.246
Hosp. A	22.8	[15.9–29.8]		16.2	[11.2–21.2]		2.9	[1.7–4.2]	
Hosp. B	21.1	[14.8–27.4]		12.5	[4.0–20.9]		4.4	[2.9–5.9]	
Hosp. C	36.8	[24.7–49.0]		13.2	[8.7–17.6]		4.1	[0.6–7.7]	
Hosp. D	23.7	[11.2–36.1]		14.5	[11.1–17.8]		1.9	[0.0–4.2]	
Hosp. E	28.9	[19.8–38.1]		11.1	[4.7–17.6]		3.2	[2.0–4.4]	
Hosp. F	27.7	[17.4–38.1]		10.7	[0.0–23.3]		4.4	[3.0–5.8]	
Hosp. G	19.5	[15.5–23.5]		14.8	[7.3–22.2]		5.7	[2.5–8.8]	

95% CI 95% confidence interval

21.1–36.8 months (*P* value = 0.452), cT2-4aN1-3M0 range 10.7–16.2 months (*P* value = 0.550), and cT4b and/or M1 range 1.9–5.7 months (*P* value = 0.246)). Kaplan–Meier OS-curves are shown in Fig. 3a–c, for all three cTNM disease stages, according to hospital site.

A multivariable Cox regression for survival analysis on hospital of treatment on the prediction of all-cause mortality, adjusted for age at diagnosis and cT-stage, was not statistically significant for all three disease stages (Online Resource 3).

Curative radical cystectomy

When analysing all curative intended treatments for all stage diseases between 2008 and 2016, the total annual number of curative RCs (without NAIC) remained stable (68–67%). The number of RCs with NAIC pre-operative increased from 9 to 15%. Treatment with curative radiotherapy decreased from 21 to 12% (Online Resource 4).

For all 944 patients of all disease stages who were intended to undergo RC, pre-operative treatment with NAIC was the largest in hospital D and G compared to the other hospital sites (36.7–38.1% vs. 7.8–15.6%, *P* value < 0.001).

In total, 780 patients with stage cT2-4aN0M0 were intended for RC (with or without neoadjuvant chemotherapy), of which 39 eventually did not underwent treatment (5.0%), due to progression of disease during neoadjuvant treatment, or unexpected inoperable disease during RC (Table 2). Occult lymph node metastases differed between hospital sites, with the largest difference between hospital D and F (22.4% vs. 28.9%, *P* value = 0.012). There was no statistically significant difference in 3-year PFS, 5-year OS and 5-year CSS between hospital sites, but large differences were present.

Curative radiotherapy

Patients with stage cT2-4aN0M0 who were treated with curative RTx, differed in median (m)PFS. Largest difference was between hospital B and F (8.4 months vs. 67.4 months, *P* value = 0.018) (Table 3). In concordance, hospital B had a lower mOS (10.2 months), compared to other hospital sites (*P* value = 0.032). In addition, median (m)CSS differed statistically significant, with the largest difference 10.6 months vs. 113.5 months (*P* value = 0.017).

Curative brachytherapy alone was intended in 26 select patients (all cT2N0M0), in mainly three hospitals (hospital C (*N* = 8), hospital E (*N* = 6) and hospital G (*N* = 10)). Nine patients (34.9%) had recurrent disease and eventually died.

Discussion

We analysed variations in treatment patterns and oncological outcomes in seven large teaching hospitals treating patients with muscle invasive or metastatic bladder cancer. In the current study, there were six major findings.

First, curative treatment was intended more often in patients with cT2-4aN0M0 disease, and as a result non-curative treatment was performed less often, compared to both past studies in the Netherlands, as to retrospective studies from other countries [13–16]. Goossens et al. studied variations in treatment patterns in the Netherlands (2001–2006) [13]. The study showed that of all stage-II or III patients, respectively, 25% and 26% were not treated with curative intent, but the frequency decreased during subsequent study years. The current study shows this decreasing trend continues, with 19% of cT2-4aN0M0 patients who did not receive CIT (11% BSC) and 21% of cT2-4aN0-3M0 patients (13% BSC). Results are lower compared to a study from the UK on cT2-4aN0M0 patients [16], where despite having been

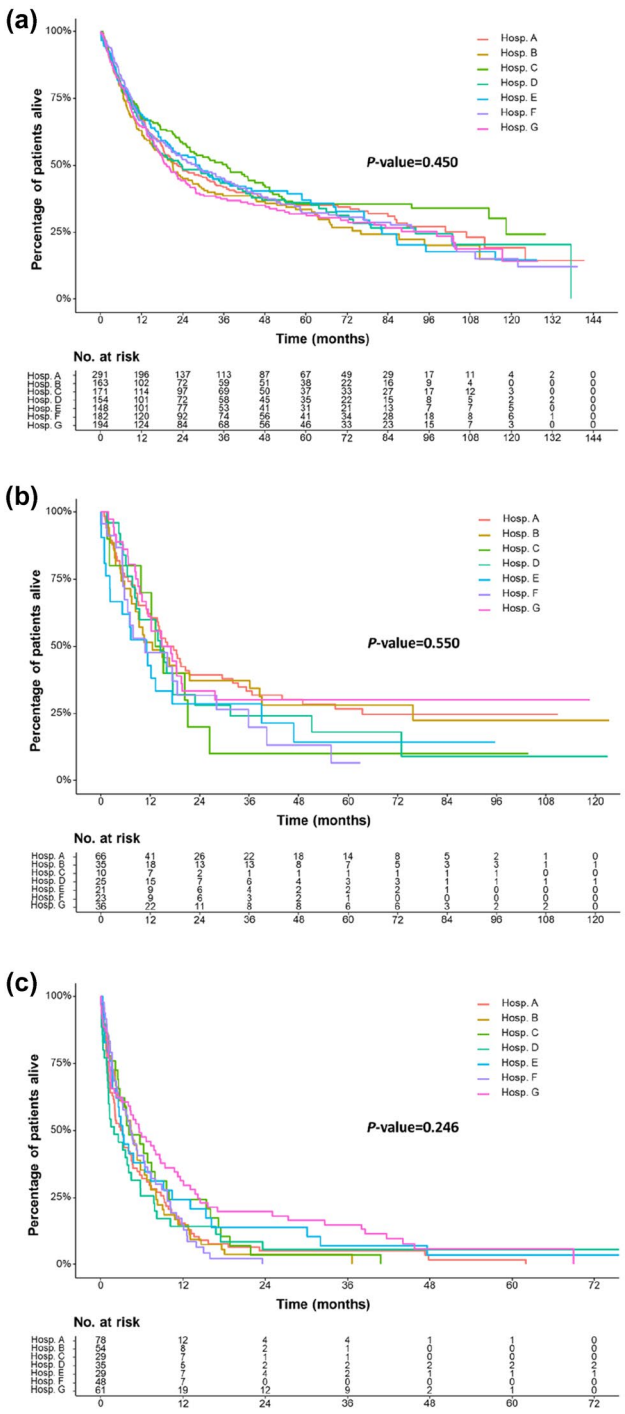

Fig. 3 **a–c** Overall survival for patients with **a** cT2-4aN0M0, **b** cT2-4aN1-3M0, and **c** cT4b and/or M1 urothelial carcinoma of the bladder, according to hospital site

diagnosed with possible curable disease, 47% of patients did not receive CIT (26% BSC). Similarly, a study from the National Cancer Database from the USA showed 37% of cT2-4aN0-3M0 patients not receiving CIT (26% BSC) [14]. A study from the Swedish Bladder Cancer Register showed that 59% of cT2-4aN0M0 patients received no CIT [15]. This Dutch study shows that in the present, an increased number of patients with cT2-4aN0-3M0 disease are considered for curative treatment compared to the past and other western countries.

Second, there was a higher preference for RC compared to earlier studies in the Netherlands [13]. RC is considered the gold standard for stage-II and III BCa in the European and Dutch Guidelines [8]. The study from Goossens et al. showed a trend of increased RC and decreased curative RTx during their study years [13]. In all stage-II and III patients, 43% and 44% were treated with RC, and 31% and 31% were treated with curative RTx, respectively. Our study also shows a continuation of both trends, as patients underwent a RC (both upfront RC as NAIC + RC) more often (60% for both cT2-4aN0M0 and cT2-4aN0-3M0 disease), than curative RTx (19% cT2-4aN0M0, 16% cT2-4aN0-3M0). This frequency slightly increased over current study years. These results were higher compared to other countries, i.e., UK (24% RC, 29% RTx in cT2-4aN0M0 patients) [16]; USA (41% RC, 8% CRTx or RTx in cT2-4aN0-3M0 patients) [14], and Sweden (33% RC, 8% RTx in cT2-4aN0-3M0 patients) [15]. Our hypothesis is that physicians have become more confident in treating a wider group of patients with RC when diagnosed with cT2-4aN0-3M0 disease.

The current study also shows different regional preferences towards certain treatment modalities. Curative RTx (with or without concomitant chemotherapy) is viewed as an alternative to RC for carefully selected patients in patients staged cT2-4aN0M0 [20, 21]. As current study shows, it is often reserved for elderly patients (median age RC vs. curative RTx patients: 68.4 vs. 77.2 years). One hospital intended more curative bladder-sparing treatment. This was not the results of treating more elder, inoperable patients with bladder-sparing treatments which otherwise would have no curative options. In contrary, the frequency of palliative treated patients staged cT2-4aN0M0 aged > 75 years was highest in this hospital. However, this hospital more often carefully selected patients (all cT2N0M0) for curative CRTx and RTx (EBRT, brachytherapy or a combination of both) compared to other hospitals. For example, all brachytherapy patients were aged < 70 years. Thus, even though BCa patient care in the Netherlands is expected to be evidence-based and not to be dependent on regional preference, experience or availability of bladder-sparing treatment modalities, this study did find these factors to be of influence.

There are various differences in oncological outcomes for patients treated with RC and RTx, between hospitals. In patients treated with RC, there were apparent differences in the utilization of neoadjuvant chemotherapy, (positive) lymph nodes removed and occult nodal metastasis. However, this did not lead to statistically significant differences in oncological outcomes, such as OS, PFS and

Table 2 Treatment characteristics of patients with cT2-4aN0M0 urothelial carcinoma of the bladder, treated with curative radical cystectomy, according to hospital site

	Total (*N* = 741)	Hosp. A (*N* = 185)	Hosp. B (*N* = 95)	Hosp. C (*N* = 98)	Hosp. D (*N* = 98)	Hosp. E (*N* = 80)	Hosp. F (*N* = 114)	Hosp. G (*N* = 71)	*P* value
Age at radical cystectomy, mean years (SD)	68.4 (9.2)	67.4 (8.5)	69.2 (8.7)	66.8 (10.4)	69.2 (8.8)	70.7 (9.4)	69.9 (8.7)	65.9 (10.3)	**0.027**
NAC before radical cystectomy, No. (%)	59 (8.0)	3 (1.6)	0 (0.0)	8 (8.2)	28 (28.6)	5 (6.3)	2 (1.8)	13 (18.3)	**< 0.001**
Lymph nodes removed, mean (SD)	14.5 (13.8)	14.1 (15.1)	12.6 (14.0)	15.0 (13.8)	16.6 (14.5)	9.6 (5.6)	15.2 (11.1)	18.4 (17.2)	**0.027**
Positive lymph nodes removed, mean (SD)	0.8 (4.1)	0.6 (1.8)	0.3 (0.7)	0.8 (2.0)	0.7 (2.1)	0.6 (1.2)	0.7 (1.7)	2.2 (12.1)	**0.014**
Occult nodal metastases, No. (%)	195 (26.3)	49 (26.5)	22 (23.2)	28 (28.6)	22 (22.4)	22 (27.5)	33 (28.9)	19 (26.8)	**0.012**
Positive surgical margin status (R1), No. (%)	48 (6.5)	9 (4.9)	8 (8.4)	7 (7.1)	4 (4.1)	5 (6.3)	8 (7.0)	7 (9.9)	0.617
3-year Progression-free survival (PFS), No. (%)	421 (58.3)	101 (56.7)	48 (53.3)	58 (59.8)	64 (65.3)	52 (66.7)	62 (55.4)	36 (52.2)	0.291
Treatment for recurrent disease, No. (%)	140 (42.2)	36 (42.4)	16 (34.8)	22 (51.2)	8 (21.6)	18 (58.1)	24 (46.2)	16 (42.1)	0.053
Overall survival (OS), median months [95% CI]	51.5 [39.9–63.1]	45.9 [18.6–73.1]	44.6 [22.8–66.3]	56.0 [16.5–95.6]	63.8 [31.9–95.7]	68.8 [45.1–92.5]	42.5 [21.7–63.3]	49.4 [0.0–99.7]	0.444
5-year Overall survival (OS), No. (%)	370 (49.9)	89 (48.1)	43 (45.3)	53 (54.1)	52 (53.1)	47 (58.8)	50 (43.9)	36 (50.7)	
5-year Cancer-specific survival (CSS), No. (%)	410 (55.2)	99 (53.5)	46 (50.0)	55 (56.7)	61 (62.2)	51 (63.8)	59 (52.2)	39 (56.5)	

P values < 0.05 are written in bold, to emphasize statistical significance

NAC neoadjuvant chemotherapy, *SD* standard deviation, *95% CI* 95% confidence interval

Table 3 Treatment characteristics of patients with cT2-4aN0M0 urothelial carcinoma of the bladder, treated with curative radiotherapy, according to hospital site

	Total (*N* = 239)	Hosp. A (*N* = 48)	Hosp. B (*N* = 21)	Hosp. C (*N* = 33)	Hosp. D (*N* = 22)	Hosp. E (*N* = 24)	Hosp. F (*N* = 39)	Hosp. G (*N* = 52)	*P* value
Age at radiotherapy, mean years (SD)	77.2 (9.0)	78.3 (9.5)	78.6 (5.5)	78.4 (5.6)	77.6 (10.6)	78.1 (10.0)	76.5 (8.3)	74.8 (10.6)	0.424
Progression-free survival (PFS), median months [95% CI]	40.2 [22.7–57.7]	23.9 [0.0–58.2]	8.4 [4.5–12.4]	59.6 [34.1–85.1]	16.4 [0.2–41.4]	42.4 [2.2–82.5]	67.4 [24.4–110.3]	29.3 NR	**0.018**
3-year Progression-free survival (PFS), No. (%)	129 (55.4)	22 (46.8)	7 (35.0)	24 (72.7)	9 (45.0)	13 (54.2)	26 (70.3)	28 (53.8)	
Treatment for recurrent disease, No. (%)	20 (16.8)	4 (15.4)	2 (14.3)	4 (28.6)	0 (0.0)	1 (7.1)	3 (21.4)	6 (24.0)	0.425
Overall survival (OS), median months [95% CI]	28.7 [22.6–34.7]	28.7 [16.2–41.1]	10.2 [6.2–14.2]	48.0 [37.1–58.9]	19.3 [3.4–35.2]	27.9 [11.0–44.7]	28.4 [21.0–35.9]	23.4 [5.1–41.6]	**0.032**
5-year Overall survival (OS), No. (%)	72 (30.1)	16 (33.3)	4 (19.0)	14 (42.4)	4 (18.2)	8 (33.3)	9 (23.1)	17 (32.7)	
Cancer-specific survival (CSS), median months [95% CI]	40.8 [25.2–56.4]	33.4 [15.6–51.3]	10.6 [5.2–15.9]	113.5 [0.3–226.7]	24.0 [3.0–44.9]	54.7 [1.7–107.6]	NR	35.1 [0.2–70.1]	**0.017**
5-year Cancer-specific survival (CSS), No. (%)	127 (53.1)	22 (45.8)	8 (38.1)	23 (69.7)	9 (40.9)	13 (54.2)	26 (66.7)	26 (50.0)	

P values < 0.05 are written in bold, to emphasize statistical significance

SD standard deviation, *95% CI* 95% confidence interval, *NR* not reached

CSS. In contrary, patients treated with curative RTx had very different oncological outcomes. Median PFS ranged from 8.4 to 67.4 months, and mOS ranging from 10.2 to 48.0 months. Undoubtedly, there is selection bias present in these groups. In addition, Bajaj et al. showed that academic facility type was associated with improved OS (HR 0.88, *P* value = 0.020) in patients treated with curative RTx, but higher case volume was not associated with improved OS (HR 0.97, *P* value = 0.150) [22]. None of the hospitals in the current study are academic hospitals, but there was a difference in the availability of an in-hospital radiotherapy department. With large disparities in oncological outcomes of cT2-4aN0M0 patients treated with curative RTx, adjustments in treatment strategy could potentially improve oncological outcomes of these patients. Further evaluation of differences in treatment characteristics between hospital sites is feasible, and future studies can aid in identification of best treatment approach and best practices.

Also, results of this study show a large variation between hospitals in use of NAIC prior to RC, and a persistent low overall utilization, compared to literature. A meta-analysis of seven randomized controlled trials showed that NAIC was associated with an absolute OS benefit of 5% after 5 years [4]. In concordance, Hermans et al. showed an increase of average NAIC utilization of 0.6% to 21% between 1995 and 2013 in the Netherlands [23]. Comparison of results of this study with literature is difficult, since patients with cT2N0M0 disease are rarely treated with neoadjuvant chemotherapy. A superior OS after NAIC + RC compared to upfront RC was not shown in cT2N0M0 patients [24]. There are multiple reasons for having a reserved attitude towards NAIC, such as patient's wishes, age, kidney function and comorbidities. First, the motivation is that delayed cystectomy might compromise outcome in patients not responsive to chemotherapy. Second, the presence of micro metastases is postulated to be lower in lower T-stage disease (cT2) compared to extensive tumours (cT3–4). However, it is apparent that NAIC utilization can be increased in patients. The reason for abstaining from NAIC before RC was not tabulated in this study. Future studies should give insight in the reasons for underutilization.

The last finding is the difference in intent of treatment between young and elderly patients, and the trend towards more palliative treatment or BSC as age increases. Curative treatment for elderly patients with MIBC is not precluded in existing guidelines. Screening on frailty after 70 years of age is recommended [25]. The decision to treat should not be based solely on age, but life expectancy based on comorbidities should be considered. Differences between hospital sites for treatment of elderly patients would, therefore, be expected. However, there was no statistically significant difference in treatment intent for elderly patients (≥ 75 years), for both cT2-4aN0M0 as cT4b and/or M1 stage disease. Frequency of CIT in elderly patients varies in literature. A systematic review on treatment of elderly patients with non-metastatic MIBC showed that 12% of patients aged > 80 received curative treatment [20]. Our results are in concordance with those findings. Fear of severe therapy-induced morbidity and estimated short life-expectancy are suggested to be the reason why elderly patients are less often treated curative. However, it should be recognized that for patients deemed unsuitable for surgical treatment, less aggressive therapies such as CRTx or RTx can be regarded. A major limitation of all literature regarding oncological outcomes in elderly patients is that these studies compare the best elderly patients with the average younger patients, since elderly patients with poorer functional status are often denied curative treatment. A knowledge gap on which elderly patient would benefit from curative treatment remains.

This study, like most retrospective studies, is limited by the absence of reliable and consistent data on patient and physician preference. The reason for previously mentioned differences in frequencies of intended treatment between this study and literature and between the hospitals in the current study, as well as the differences in oncological outcomes, and differences between age-groups, remain unexplained. Decisions on treatment have undoubtedly been influenced by unregistered confounding baseline characteristics.

Strengths of this study are high resolution data, the inclusion of all treatment modalities including BSC, and long follow-up duration. This study has several limitations. First, the study is retrospective in nature. As previously mentioned, baseline characteristics such as performance or comorbidity data could not be taken into considerations, since it could not be collected in a conformable manner. In addition, patients were grouped based on primary treatment intent. Treatment for recurrent or progressive disease were not taken into consideration. Even though large differences in treatment intent and oncological outcomes were present, the overall survival of patients between hospital sites was not statistically significant different for all three clinical disease stages. This study reports on a large cohort, but is prone to be lacking statistical power for some sub analyses, resulting in less stable survival estimates and wide CIs.

The value of large real-world retrospective studies, such as the current study, is providing evidence of differences in treatment effectiveness between hospitals. Outcomes observed in clinical trials (efficacy) might differ from outcomes observed in real-world circumstances (effectiveness); the so called efficacy-effectiveness gap. In a similar way, as current study shows, there are differences in effectiveness between hospital sites as well. In order for any physician, hospital, or country to compare their own outcome results to clinical trials or other real-world retrospective studies, complementary data on variation in treatment trends is needed to gain a more complete picture of differences found.

Conclusions

This retrospective study on treatment patterns and oncological outcomes for patients with both MIBC as mBC in the Netherlands, shows that compared to literature, more patients with local disease are intended for curative treatment. For a patient, treatment intent was dependent on the hospital of diagnosis. In addition, an ongoing trend of increased use of RC (with and without prior NAIC) was seen, whereas the use of curative RTx is decreasing. There was no difference in treatment intent for patients older than 75 years. Although utilization of NAIC prior to RC increased over years, it is still underutilized. Major differences in treatment intent and oncological outcomes were present between hospital sites, yet the overall survival of patients was not statistically significant different.

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Author contributions DJR had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. DJR: protocol/project development, Data collection or management, Data analysis, Manuscript writing/editing. EMWVG: Protocol/project development, Data collection or management, Data analysis, Manuscript writing/editing. PVN: Protocol/project development, Data collection or management, Data analysis, Manuscript writing/editing. DMS: Manuscript writing/editing. ML: Protocol/project development, Data collection or management, Data analysis, Manuscript writing/editing. SH: Protocol/project development, Manuscript writing/editing. HHEVM: Protocol/project development, Data collection or management, Data analysis, Manuscript writing/editing. MIBC Study Group: Data collection or management, Manuscript writing/editing.

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Declarations

Conflicts of interest The authors declare that they have no conflict of interest.

Ethics approval The study has been approved by the local research ethics committee of the St. Antonius Hospital Utrecht/Nieuwegein (W17.087) and was conducted in accordance with Good Clinical Practice Guidelines.

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