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A nationwide cohort study

BlaZIB study group

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Original Article

Chemoradiation for muscle-invasive bladder cancer using 5-fluorouracil versus capecitabine: A nationwide cohort study

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ABSTRACT

Background and purpose: Oral capecitabine and intravenous 5-fluorouracil (5-FU) are both used as a radiosensitizer in chemoradiotherapy (CRT). A capecitabine-based regimen is more convenient for both patients and healthcare professionals. Since large comparative studies are lacking, we compared toxicity, overall survival (OS) and disease-free survival (DFS) between both CRT-regimens in patients with muscle-invasive bladder cancer (MIBC).

Materials and methods: All patients diagnosed with non-metastatic MIBC between November 2017-November 2019 were consecutively included in the BlaZIB study. Data on patient, tumor, treatment characteristics and toxicity were prospectively collected from the medical files. From this cohort, all patients with cT2-4aN0-2/xM0/x, treated with capecitabine or 5-FU-based CRT were included in the current study. Toxicity in both groups was compared using Fisher-exact tests. Propensity score-based inverse probability treatment weighting (IPTW) was applied to correct for baseline differences between groups. IPTW-adjusted Kaplan-Meier OS and DFS curves were compared using log-rank tests.

Results: Of the 222 included patients, 111 (50%) were treated with 5-FU and 111 (50%) with capecitabine. Curative CRT was completed according to treatment plan in 77% of patients in the capecitabine-based group and 62% of the 5-FU group (p = 0.06). Adverse events (14 vs 21%, p = 0.29), 2-year OS (73% vs 61%, p = 0.07) and 2-year DFS (56% vs 50%, p = 0.50) did not differ significantly between groups.

Conclusions: Chemoradiotherapy with capecitabine and MMC is associated with a similar toxicity profile compared to 5-FU plus MMC and no difference in survival was found. Capecitabine-based CRT, as a more patient-friendly schedule, may be considered as an alternative to a 5-FU-based regimen.

Although radical cystectomy remains the cornerstone of curative treatment for muscle-invasive bladder cancer (MIBC), bladder-preserving therapy by chemoradiotherapy (CRT) as an alternative to radical cystectomy is gaining popularity[1–3]. Several recent studies have reported survival outcomes after bladder-preserving therapy comparable to those seen in radical cystectomy series[1]. The BC2001 trial showed that CRT improves survival compared to radiotherapy alone in MIBC[4,5]. In addition, patients who received CRT had superior quality of life scores compared to those who received a radical cystectomy[6]. The ideal CRT regimen has not yet been determined. International guidelines recommend the use of either cisplatin, gemcitabine, or mitomycin C plus 5-fluorouracil (5-FU) as radiosensitizers, as most evidence exists for these regimens[2,4,6].

Capecitabine is an oral 5-FU prodrug that generates 5-FU preferentially within the tumor[7]. Both 5-FU and capecitabine, combined with Mitomycin C, are the most commonly used radiosensitizers in the Netherlands. Unlike 5-FU, which is continuously infused, capecitabine avoids the necessity of indwelling central venous devices and associated risks, such as infection,

Abbreviations: 5-FU, 5-Fluorouracil; CRT, chemoradiotherapy; OS, overall survival; DFS, disease-free survival; MIBC, muscle-invasive bladder cancer; MMC, mitomycin C; IPTW, inverse probability treatment weighting; NCR, Netherlands Cancer Registry.

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bleeding, thrombosis, and pneumothorax [8]. Furthermore, since capecitabine requires fewer hospital visits for drug administration than 5-FU and fewer fractions of radiotherapy, patients treated with capecitabine spend fewer days in the hospital. Taken together, compared to 5-FU, a capecitabine-based CRT regimen is more convenient for both patients and healthcare professionals, and needs fewer medical resources and costs[9–11].

The equivalence of CRT with 5-FU versus capecitabine-based CRT with respect to oncological outcome and decrease in tumor volume has been established in rectal cancer[12–14], and with respect to toxicity and oncological outcome in anal cancer [15,16]. However, studies directly comparing 5-FU and capecitabine-based CRT regimens are lacking for MIBC. Therefore, we evaluated the toxicity and oncological outcomes in patients with MIBC treated with 5-FU versus capecitabine-based CRT. We also provided some insight into the health-related quality of life (HRQoL).

Materials and methods

Data collection and study population

This observational cohort study is part of the nationwide, prospective BlaZIB study, aiming to provide insight and eventually improve the quality of bladder cancer care in the Netherlands. Details of the BlaZIB protocol were described previously [17]. The data collection of BlaZIB is embedded in the Netherlands Cancer Registry (NCR). We selected all adult patients, diagnosed with primary or secondary (i.e., after T1-disease) cT2-4aN0-2/xM0/x urothelial MIBC in Dutch hospitals between 1 November 2017 and 31 October 2019, treated with a 5-FU or capecitabine-based CRT regimen, combined with mitomycin C (MMC) (Fig. 1). All patients who received at least one cycle of chemotherapy were included. To evaluate HRQoL, we used data collected from a subset of patients included in the BlaZIB study at baseline (approximately 6 weeks after diagnosis) (T0), 6 months (T6), 12 months (T12) and 24 months (T24) after diagnosis. A detailed description of the variables included can be found in Supplementary Fig. 1.

Definitions

Patients were categorized into two CRT groups by type of chemotherapeutic agent used during CRT treatment, i.e., 5-FU + MMC, or capecitabine + MMC. The capecitabine-containing CRT regimen usually consists of capecitabine tablets taken twice daily at a dose of 825 per square meter per day on the days of radiotherapy. Radiotherapy and capecitabine are initiated on the same day. 5-FU is administered as a continuous infusion of 500 mg per square meter per day during fractions 1 to 5 and 16 to 20 of radiotherapy. In both regimens, MMC is administered as an intravenous bolus dose of 12 mg per square meter with a maximum dose of 20 mg on day 1. For descriptive purposes, RT treatment was categorized into the mainly used schedules: 66 Gy administered in 33 fractions, 64 Gy in 32 fractions, 60 Gy in 25 fractions, 55 Gy in 20 fractions, and other. Information on the scheduled median number of fractions and dose (Gy), and whether patients completed the intended RT-schedule was collected. Complications related to radiotherapy of CTCAE grade 3 or higher were documented. Chemotherapy schedule adjustments (a maximum of two per patient) were counted as a complication related to chemotherapy. Use of medication for side effects and first hospital (re)admission due to CRT were documented as well. CRT-related toxicity included patients with at least one chemotherapy- or radiotherapy-related complication or hospital readmission, without time constraints.

Statistical analyses

Descriptive analyses were performed to provide insight in the patient, tumor and treatment characteristics of the total cohort and by CRT-regimen. Missing data (Supplementary Table 1) were imputed using single imputation. Treatment details and toxicity were compared between groups using Fisher-exact tests and independent sample t-tests. Overall survival (OS) and disease-free survival (DFS) were evaluated using Kaplan-Meier curves and Log-Rank testing. To correct for baseline differences between groups, inverse probability treatment weighting (IPTW) based on a

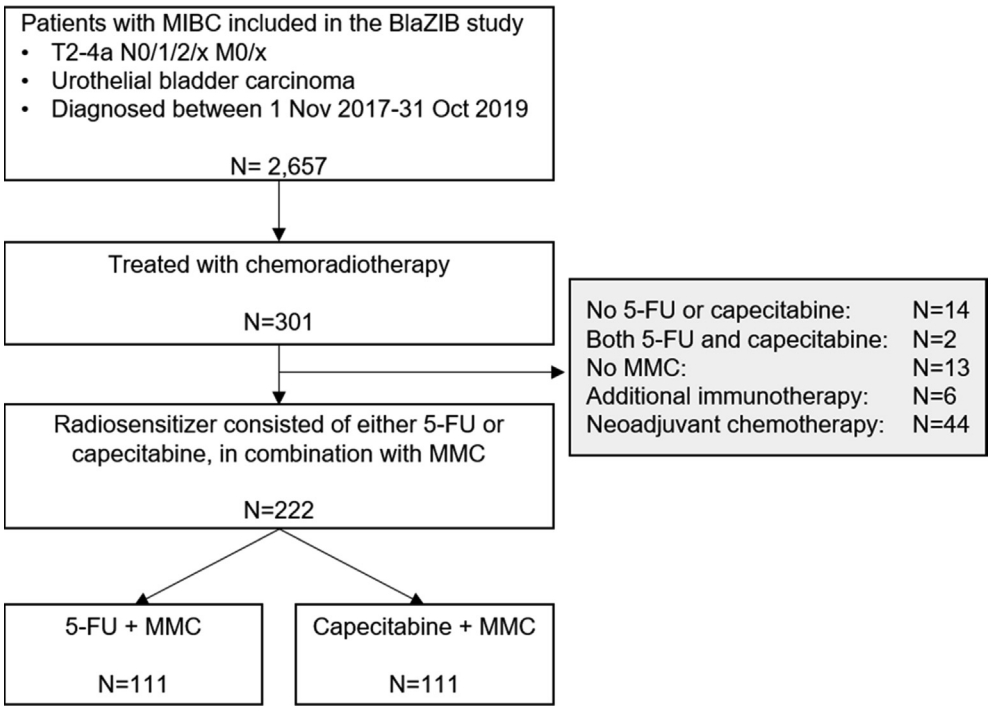

Fig. 1. Flowchart describing the inclusion of patients in the study cohort.

Table 1
Patient and tumor characteristics of patients with cT2-T4a N0/1/2/x M0/x bladder cancer treated with chemoradiotherapy, stratified by type of chemotherapeutic agent after single imputation.

	Total		5-FU + MMC		Capecitabine + MMC		Standardized difference	
	N	(%)	N	(%)	N	(%)	Before IPTW	After IPTW
Gender							0.02	0.07
Male	169	(76.1%)	85	(76.6%)	84	(75.7%)		
Female	53	(23.9%)	26	(23.4%)	27	(24.3%)		
Age at diagnosis (median, IQR)	74.0	(68.0–79.0)	74.0	(68.0–80.0)	74.0	(67.0–79.0)	−0.09	0.02
Age at diagnosis							0.15	0.03
<60 years	17	(7.7%)	7	(6.3%)	10	(9.0%)		
60–70 years	48	(21.6%)	24	(21.6%)	24	(21.6%)		
70–80 years	104	(46.8%)	51	(45.9%)	53	(47.7%)		
≥ 80 years	53	(23.9%)	29	(26.1%)	24	(21.6%)		
Performance status (ECOG)							0.29	0.03
ECOG 0	116	(52.3%)	50	(45.0%)	66	(59.5%)		
ECOG 1	80	(36.0%)	45	(40.5%)	35	(31.5%)		
ECOG 2 or higher	26	(11.7%)	16	(14.4%)	10	(9.0%)		
Weighted Charlson Comorbidity Index							0.14	0.04
0	87	(39.2%)	40	(36.0%)	47	(42.3%)		
1	58	(26.1%)	29	(26.1%)	29	(26.1%)		
2 or more	77	(34.7%)	42	(37.8%)	35	(31.5%)		
Body Mass Index (BMI) (median, IQR)	26.5	(24.1–30.0)	26.6	(24.1–30.0)	26.3	(23.8–30.1)	0.03	0.00
Body Mass Index (BMI)							0.13	0.28
< 8.5	3	(1.4%)	1	(0.9%)	2	(1.8%)		
18.5–25	79	(35.6%)	38	(34.2%)	41	(36.9%)		
25–30	85	(38.3%)	45	(40.5%)	40	(36.0%)		
≥ 30	55	(24.8%)	27	(24.3%)	28	(25.2%)		
Socioeconomic status							0.46	0.00
Low	56	(25.2%)	36	(32.4%)	20	(18.0%)		
Middle	87	(39.2%)	47	(42.3%)	40	(36.0%)		
High	79	(35.6%)	28	(25.2%)	51	(45.9%)		
Disease stage (cTNM)							0.43	0.02
cT2N0M0	161	(72.5%)	71	(64.0%)	90	(81.1%)		
cT3-T4aN0M0	54	(24.3%)	37	(33.3%)	17	(15.3%)		
cTxN + M0	7	(3.2%)	3	(2.7%)	4	(3.6%)		
Type of MIBC							0.00	−0.02
Primary	204	(91.9%)	102	(91.9%)	102	(91.9%)		
Secondary (following T1)	18	(8.1%)	9	(8.1%)	9	(8.1%)		
Focality of the tumor							−0.12	−0.12
Unifocal	158	(71.2%)	76	(68.5%)	82	(73.9%)		
Multifocal	64	(28.8%)	35	(31.5%)	29	(26.1%)		
Geographical region							1.14	1.17
North	5	(2.3%)	4	(3.6%)	1	(0.9%)		
East	10	(4.5%)	9	(8.1%)	1	(0.9%)		
Middle	37	(16.7%)	1	(0.9%)	36	(32.4%)		
South	45	(20.3%)	35	(31.5%)	10	(9.0%)		
West	125	(56.3%)	62	(55.9%)	63	(56.8%)		
Type of hospital (diagnosis)							0.30	0.28
Community hospital	87	(39.2%)	49	(44.1%)	38	(34.2%)		
Non-university referral hospital	122	(55.0%)	59	(53.2%)	63	(56.8%)		
University hospital	13	(5.9%)	3	(2.7%)	10	(9.0%)		

5-FU: 5-Fluorouracil; MMC: Mitomycin C; IQR: Interquartile Range; ECOG: Eastern Cooperative Oncology Group; MIBC: Muscle-Invasive Bladder Cancer.

propensity score was applied. The propensity score was constructed based on a logistic regression model including relevant covariates. Standardized differences were calculated to assess covariate balance before and after IPTW, with a value < 0.1 indicating adequate balance [18]. Date of start CRT was taken as start of follow-up. End of follow-up was defined as last date of follow-up or death, whichever came first. In case of DFS, date of muscle-invasive loco-regional recurrence or progression was also considered as end of follow-up. Follow-up was censored at two years. HRQoL over time was evaluated by calculating the mean (±standard deviation (SD)) EORTC-QLQ-C30 global health status score at T0 to T6, T12 and T24 per treatment group. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA). P < 0.05 was considered statistically significant.

This study was approved by the Privacy Review Board of the NCR (reference number K22.029). According to the Central Committee on Research involving Human Subjects (CCMO), this type of study does not require approval from an ethics committee in the Netherlands. The requirement for informed consent was waived due to the observational design of the study.

Results

In total, 222 patients were identified from the NCR, of whom 111 (50%) received CRT with 5-FU + MMC and 111 (50%) with capecitabine + MMC (Fig. 1). Patient characteristics were largely similar, although socioeconomic status was higher and performance status appeared to be better in the capecitabine group (Table 1). Compared to the capecitabine group, patients in the 5-FU group more often had T3 instead of T2 disease. Treatment with 5-FU or capecitabine-based CRT differed per geographical region in the Netherlands, with capecitabine being preferentially used in the mid regions of the country and 5-FU in the south part of the coun-

try. There was no clear preference for either regimen in other parts of the country.

Overall, 69 patients (62%) in the 5-FU group and 85 patients (77%) in the capecitabine group completed a curative CRT protocol according to treatment plan (p = 0.06, Table 2). Chemotherapy dose adjustment was necessary in 19 and 11 patients, respectively, and this was mostly toxicity-related. Regarding radiotherapy, 102 patients in the 5-FU group and 105 in the capecitabine group were scheduled for curative radiotherapy, of which eventually 82 (80%) and 95 (91%) patients, respectively, completed all fractions (p = 0.01). The RT schedules used for CRT differ between CRT-regimens. This was also observed in our data: the majority of patients treated with 5-FU based CRT received 66 Gy in 33 fractions (60%), the majority of patients treated with capecitabine-based CRT received 60 Gy in 25 fractions (51%).

Although not statistically significant, adverse events rates appeared to be lower in the capecitabine-based CRT group, i.e., 14% versus 21% (p = 0.29, Table 3). These adverse events were primarily hematological with 8 events (7%) in the 5-FU based CRT group versus 6 events (5%) in the capecitabine-based CRT group (p = 0.78), and gastro-intestinal with 8 (7%) versus 5 events (5%) (p = 0.57). Overall, the number of patients readmitted to the hospital did not differ significantly between groups (12% versus 8%, p = 0.50). Notably, if readmission was necessary, it occurred sooner after the start of CRT in the 5-FU based group than in the capecitabine-based group; median time from start treatment to

Table 2
Detailed description of the treatment and treatment adjustments of patients with cT2-T4a N0/1/2/x M0/x bladder cancer treated with chemoradiotherapy, stratified by chemotherapeutic agent.

	All patients (N = 222)		**5-FU + MMC (N = 111)**		**Capecitabine + MMC (N = 111)**		**P-value**
Chemoradiotherapy							
Curative CRT protocol completed							0.0602
Yes	154	(69.4%)	69	(62.2%)	85	(76.6%)	
No	36	(16.2%)	23	(20.7%)	13	(11.7%)	
Not documented	32	(14.4%)	19	(17.1%)	13	(11.7%)	
Chemotherapy (sensitizer)							
Adjustment of chemotherapy schedule							0.1686
Yes	30	(13.5%)	19	(17.1%)	11	(9.9%)	
No	192	(86.5%)	92	(82.9%)	100	(90.1%)	
Type of adjustment (n = 30, multiple adjustments possible)							
Dose reduction	10	(4.5%)	5	(4.5%)	5	(4.5%)	1.0000
Cycle reduction	13	(5.9%)	8	(7.2%)	5	(4.5%)	0.5693
Cycle interruption/postponement	8	(3.6%)	6	(5.4%)	2	(1.8%)	0.2801
Other	1	(0.5%)	1	(0.9%)	0	(0.0%)	1.0000
Reasons for adjustment/termination (n = 30*, multiple reasons possible)							
Hematological toxicity	14	(6.3%)	8	(7.2%)	6	(5.4%)	0.7836
Gastro-intestinal toxicity	8	(3.6%)	4	(3.6%)	4	(3.6%)	1.0000
Dermatological toxicity	1	(0.5%)	0	(0.0%)	1	(0.9%)	1.0000
Other, physical	2	(0.9%)	2	(1.8%)	0	(0.0%)	0.4977
Bladder cancer-related (progression/non-response)	1	(0.5%)	1	(0.9%)	0	(0.0%)	1.0000
Patients' condition/preference	5	(2.3%)	5	(4.5%)	0	(0.0%)	0.0597
Other**	2	(0.9%)	2	(1.8%)	0	(0.0%)	0.4977
Use of medication for side effects							1.0000
Yes (e.g., for nausea, diarrhea)	9	(4.1%)	5	(4.5%)	4	(3.6%)	
No	213	(95.9%)	106	(95.5%)	107	(96.4%)	
Radiotherapy							
Curative RT treatment scheduled**							0.6007
Yes (BED $\alpha/\beta_{10} \geq 70$)	207	(93.2%)	102	(91.9%)	105	(94.6%)	
No (BED $\alpha/\beta_{10} < 70$)	7	(3.2%)	5	(4.5%)	2	(1.8%)	
Unknown	8	(3.6%)	4	(3.6%)	4	(3.6%)	
BED $\alpha/\beta_{10} < 70$: Dose actually administered?						-	
Yes	7	(100.0%)	5	(100.0%)	2	(100.0%)	
Not documented	0		0		0		
BED $\alpha/\beta_{10} \geq 70$: Dose actually administered?							**0.0115**
Yes	177	(85.5%)	82	(80.4%)	95	(90.5%)	
Not documented	30	(14.5%)	20	(19.6%)	10	(9.5%)	
RT schedule							**<0.0001**
BED α/β_{10} = 79.2 (33/66)	76	(34.2%)	67	(60.4%)	9	(8.1%)	
BED α/β_{10} = 76.8 (32/64)	24	(10.8%)	23	(20.7%)	1	(0.9%)	
BED α/β_{10} = 74.4 (25/60)	56	(25.2%)	0	(0.0%)	56	(50.5%)	
BED α/β_{10} = 70.125 (20/55)	28	(12.6%)	6	(5.4%)	22	(19.8%)	
Other	38	(17.1%)	15	(13.5%)	23	(20.7%)	
Number of fractions (median, IQR)	30.0	(25.0–33.0)	33.0	(32.0–33.0)	25.0	(23.0–25.0)	**<0.0001**
Missing (n, %)	5	(2.3%)	2	(1.8%)	3	(2.7%)	
Dose in Gy (median, IQR)	62.9	(60.0–66.0)	66.0	(64.0–66.0)	60.0	(59.8–60.0)	**<0.0001**
Missing (n, %)	8	(3.6%)	4	(3.6%)	4	(3.6%)	

5-FU: 5-Fluorouracil; MMC: Mitomycin C; IQR: Interquartile Range; RT: Radiotherapy; BED: Biologically Effective Dose; α/β_{10}: alpha/beta ratio of 10 (for early-responding tissues and tumors).

* For one patient, revision of the histopathological specimen caused a change in treatment schedule. For another patient, treatment was adjusted due to a scheduling error.

** A curative RT schedule was defined as a BED α/β_{10} of $\geq$ 70.

P-value was calculated using Fisher-exact tests for categorical variables and independent sample t-tests for continuous variables. P-values in **bold** are statistically significant (p < 0.05).

Table 3
Detailed description of toxicity of patients with cT2-T4a N0/1/2/x M0/x bladder cancer treated with chemoradiotherapy, stratified by chemotherapeutic agent.

	All patients (N=222)		5-FU + MMC (N=111)		Capecitabine + MMC (N=111)		P-value
	N	%	N	%	N	%	
Toxicity							
Toxicity due to CRT							0.2899
Yes	39	(17.6%)	23	(20.7%)	16	(14.4%)	
No	183	(82.4%)	88	(79.3%)	95	(85.6%)	
Type of toxicity							
Genitourinary	5	(2.3%)	3	(2.7%)	2	(1.8%)	1.0000
Hematological	14	(6.3%)	8	(7.2%)	6	(5.4%)	0.7836
Gastro-intestinal	13	(5.9%)	8	(7.2%)	5	(4.5%)	0.5693
Dermatological	1	(0.5%)	0	(0.0%)	1	(0.9%)	1.0000
Other, physical	5	(2.3%)	3	(2.7%)	2	(1.8%)	1.0000
Malignancy-related	1	(0.5%)	1	(0.9%)	0	(0.0%)	1.0000
Patients' condition/preference	5	(2.3%)	5	(4.5%)	0	(0.0%)	0.0597
Other	1	(0.5%)	1	(0.9%)	0	(0.0%)	1.0000
Readmission							
Readmission to hospital (any time due to CRT)	22	(9.9%)	13	(11.7%)	9	(8.1%)	0.5012
Readmission < 90 days since start treatment	20	(9.0%)	13	(11.7%)	7	(6.3%)	0.2407
Readmission < 30 days since start treatment	14	(6.3%)	10	(9.0%)	4	(3.6%)	0.1656
Time from start treatment to readmission (median, IQR)	27.5	(16.0–60.0)	16.0	(14.0–29.0)	46.0	(26.0–88.0)	**0.0160**

5-FU: 5-Fluorouracil; MMC: Mitomycin C; CRT: Chemoradiotherapy; IQR: Interquartile Range.
P-value was calculated using Fisher-exact tests for categorical variables and independent sample t-tests for continuous variables. P-values in **bold** are statistically significant

readmission was 16 days (IQR 14–29) for 5-FU and 46 days (IQR 26–88) for capecitabine (Table 3).

Propensity scores were calculated based on a logistic regression model including performance status, socio-economic status and disease stage. The scores largely overlapped between the two groups. After IPTW-adjustment, the standardized differences decreased to < 0.1 (Table 1), indicating sufficient covariate balance. At 2-year follow-up, 45 deaths occurred in the 5-FU based group and 25 in the capecitabine-based group. Two-year OS did not differ significantly between both groups; 2-year OS was 61% in the 5-FU based group and 73% in the capecitabine-based group (p = 0.07, Fig. 2a). Likewise, no significant difference in DFS was observed (50% versus 56%, p = 0.50, Fig. 2b). After CRT treatment, 4 patients from the 5-FU based group (4%) and 8 from the capecitabine-based group (7%) eventually proceeded to radical cystectomy. Also, 9 patients (8%) from both groups received systemic chemo- or immunotherapy after CRT. Two (2%) and one (1%) patient(s) from the 5-FU based versus capecitabine- based group received radiotherapy after CRT due to progression of the disease, respectively.

In total, only 47 of the 222 (21%) included patients with CRT participated in the HRQoL data collection of the BlaZIB study and completed at least the baseline questionnaire. Response rates on the HRQoL questionnaires were similar: 23% (n = 25) in the 5-FU based group and 20% (n = 22) in the capecitabine-based group. For both CRT-regimens, the global health score appeared to improve a little after start of treatment. HRQoL was 75.8 at T0 and 79.9 at T24 in the capecitabine-based CRT group, and 76.0 at T0 and 83.3 at T24 in the 5-FU based group, but the standard deviations were large (Fig. 3).

Discussion

In this population-based observational study, we compared two commonly used bladder-sparing CRT regimens with 5-FU and capecitabine as radiosensitizers in patients with MIBC, in a prospectively collected database. Our study demonstrates no significant differences between both regimens in terms of toxicity, health-related quality of life, overall survival and disease-free survival. As we cannot distinguish between individual effects of either the radiosensitizer or radiotherapy, it is important to consider CRT treatment as a whole.

There was no evidence of differences in toxicity between the 5-FU and capecitabine-based CRT group; toxicity rates were 21% and 14% (p = 0.28), respectively. A larger proportion of patients completed curative treatment in the capecitabine-based group compared to the 5-FU based group. This may be partly caused by the minor differences in patient characteristics, i.e., slightly better socio-economic status and performance status in the capecitabine-based group. In the Netherlands, capecitabine-based CRT usually consists of fewer RT fractions (i.e., a hypofractionated schedule) compared to a 5-FU based regimen, therefore requiring less hospital visits and being more convenient for patients. In addition, 5-FU is administered intravenously in the hospital or through an IV pump that can be taken home but has to be disconnected by a medical professional later in time (differing per hospital guideline), whereas capecitabine can be taken orally which does not require hospital admission, therefore, lessening the burden for patients to undergo CRT treatment. The completion rate of 5-FU based CRT was also lower compared to other studies. Possible explanations could be the real-world setting of our study, evaluating an unselected patient population in both academic and non-academic hospitals in the Netherlands. Also, it should be noted that for some patients it could not be determined whether a curative CRT protocol was completed since this information was lacking in the electronic medical files.

As mentioned before, most patients in the capecitabine-based CRT group of our study received a hypofractionated RT schedule. A recent meta-analysis of the BC2001 and BCON trial showed that a hypofractionated radiotherapy schedule of 55 Gy in 20 fractions was non-inferior to 64 Gy in 32 fractions regarding toxicity and superior regarding invasive locoregional control [19]. Based on this study, the authors recommend adopting this hypofractionated radiotherapy schedule as a standard of care for bladder preservation in patients with locally advanced bladder cancer.

We reported a lower percentage of patients with toxicity than other CRT studies with either 5-FU or capecitabine in MIBC(4, 20–22). The BC2001 trial randomized 360 patients with MIBC between radiotherapy with or without 5-FU + MMC and reported grade 3–4 adverse events in 36% of the 5-FU + MMC based CRT arm(4). Patel et al. retrospectively examined treatment-related toxicity in a cohort of 14 elderly patients treated with CRT with capecitabine + MMC and reported grade 2–3 toxicities in at least 43% of patients [20]. With a similar study design, Leng et al.

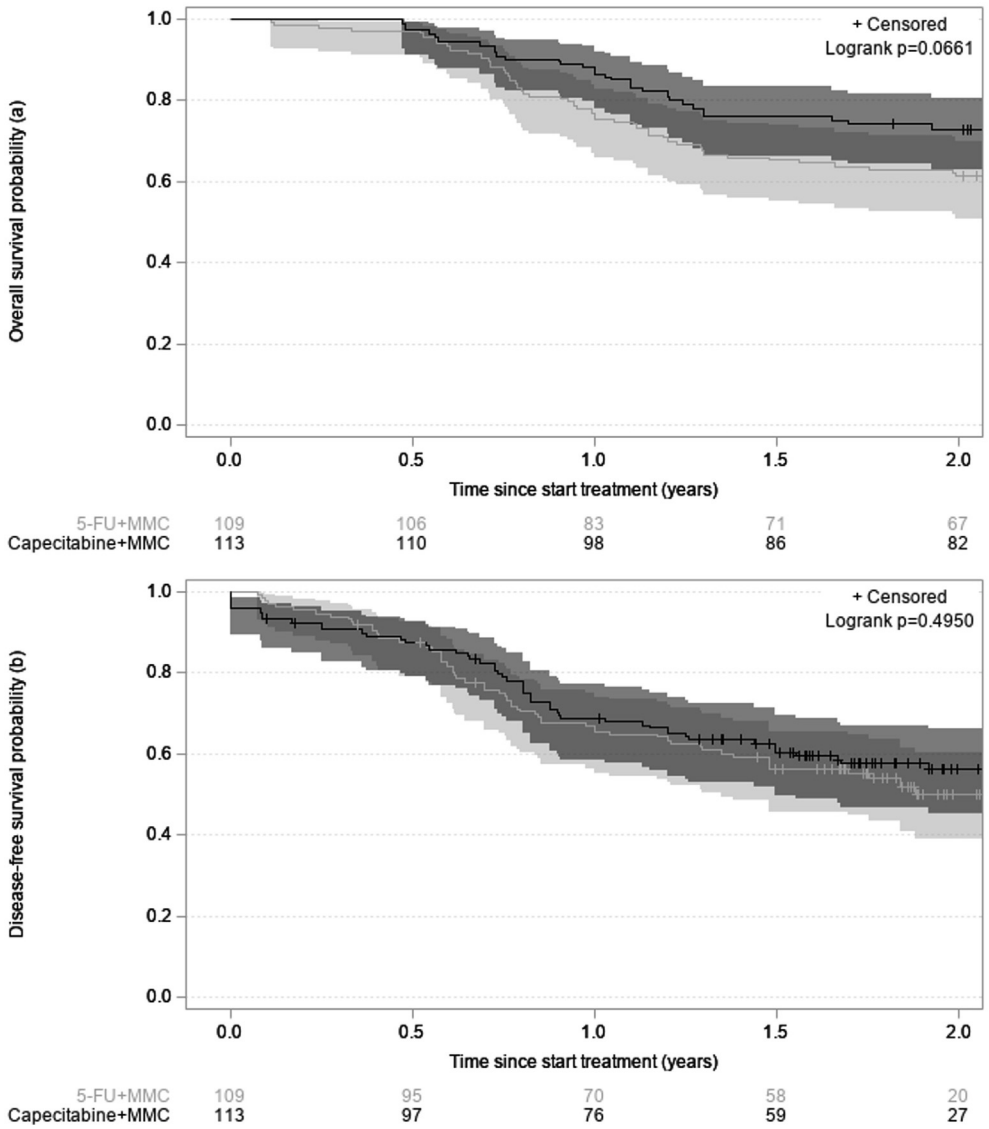

Fig. 2. IPTW-adjusted overall survival (a) and locoregional disease free survival (b) since start of chemoradiotherapy treatment of patients with cT2-T4a N0/1/2/x M0/x bladder cancer.

reported grade 3 toxicity in at least 55% of 11 elderly patients [22]. Voskuilen et al. included 75 MIBC patients treated with definitive CRT with capecitabine + MMC and reported acute toxicities of grade 1–2 in 70%, grade 3 in 9% and grade 4 toxicity in 1% of patients(21). The observed differences may be partly attributed to the use of older radiotherapy techniques in some of these studies as current radiotherapy techniques result in reduced doses in surrounding organs, leading to improved radiation-induced toxicity in contemporary cohorts [23]. In addition, differences in trial design, underreporting of toxicity in observational studies, definitions of toxicity, patient population or the period in which toxicity was documented may have also contributed to the observed differences.

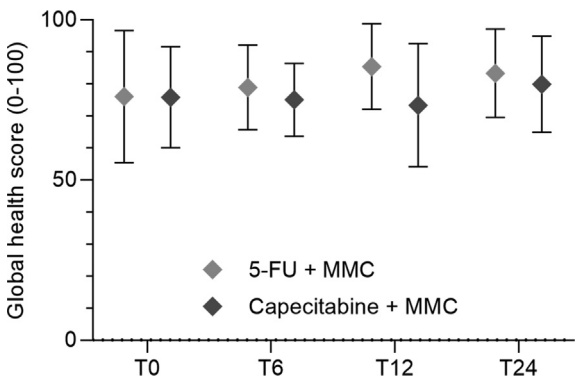

Fig. 3. EORTC-QLQ-C30 global health score (mean +/- SD) over time of patients with cT2-T4a N0/1/2/x M0/x bladder cancer treated with chemoradiotherapy, stratified by type of chemotherapeutic agent.

We report a 2-year IPTW-adjusted OS of 61% for patients receiving 5-FU based CRT and 73% for capecitabine-based CRT (p = 0.07). Two-year IPTW-adjusted DFS was 50% and 56% for the 5-FU and capecitabine-based regimen, respectively (p = 0.50). Although differences in cancer type, treatment protocol, patient selection and study design limit direct comparison between trials, our data are in line with the conclusions of CRT trials comparing 5-FU and capecitabine-based CRT in other malignancies. A large randomized German trial comparing capecitabine-based CRT with fluorouracil-based CRT in stage II-III locally advanced rectal cancer showed non-inferiority of capecitabine-based CRT with respect to OS and DFS [12]. Similarly, a small prospective cohort study in anal cancer

showed equivalent OS, cancer-specific survival and incidence of recurrence between 5-FU and capecitabine-based CRT [15].

Since 5-FU versus capecitabine-based CRT was not previously compared in patients with MIBC, our survival data can only be compared to studies examining one of the two drugs. We reported a 2-year OS of 75% with capecitabine-based CRT. This is superior to the 2-year OS of 61% reported in the study by Leng et al. [22]. This difference can be explained by the study population of this trial, which was composed of elderly patients with MIBC with a median age of 80 years ineligible for radical cystectomy or high-intensity CRT. On the other hand, our 2-year OS for capecitabine-based CRT is lower than the 2-year OS of 85% reported by Voskuilen et al. [21]. They reported a more favorable 2-year DFS, i.e., 79% versus 56%. An explanation for the improved oncological outcome in this study may be that 30% of patients was pretreated with neoadjuvant or induction chemotherapy. In addition, the study population was largely composed of very fit patients (76% WHO 0) compared to 60% of patients with ECOG 0 in our study. The higher percentage of patients with WHO > 0 in our study more accurately reflects daily clinical practice. The 2-year DFS of 50% for 5-FU based CRT in our study is worse compared to the 2-year DFS reported in the BC2001 trial [4]. In general, patients included in RCTs tend to have a superior outcome compared to patients in daily clinical practice, due to patient selection and the controlled circumstances of a RCT. Although the inclusion criteria of the BC2001 trial were quite broad, use of neoadjuvant chemotherapy was given to almost one in four included patients, which could have improved results.

Despite all recent advances, there is still a lot of room for improvement in the treatment of MIBC, which has a 5-year overall survival of approximately 50–60% for patients with a radical cystectomy or bladder-preserving therapy [24]. Current clinical research aimed at improving the systemic treatment part of CRT largely focuses on the integration of immune checkpoint inhibitors in CRT protocols. Multiple studies investigating different combinations are currently ongoing [25]. Efforts aimed at optimizing the radiotherapy part of CRT in MIBC are focusing on irradiation techniques under image guidance and proton therapy [26]. The BCON trial evaluated enrichment of radiotherapy with carbogen and nicotinamide [27] and found that even after a follow-up of 10 years, survival was better for patients treated with carbogen and nicotinamide than for patients treated with RT alone [28]. Although this finding was not statistically significant, this treatment might be considered as an alternative low toxicity protocol for bladder preservation.

To our knowledge, our study is the first to compare the toxicity and survival of CRT with 5-FU + MMC and capecitabine + MMC in an unselected, nationwide group of patients with non-metastatic MIBC using real world data. Nevertheless, our study has some limitations. Although this is the largest population-based cohort so far to compare patient outcomes of 5-FU and capecitabine-based CRT, the actual number of included patients was still limited. Therefore, the results of our analyses should be interpreted with caution, since the analyses may be underpowered. Missing values arising from poor documentation in the electronic medical files are inherent to the observational design. Missing data on baseline characteristics were addressed by employing single imputation, as it was not possible to extract survival curves after multiple imputation. We checked the robustness of the single imputation method by comparing the baseline characteristics with those after multiple (N = 20) imputation and this indeed showed to be robust (Supplementary Table 2). Less diligent documentation of side effects outside the context of a clinical trial could have led to underreporting of treatment toxicity in our observational study, especially concerning less severe side effects (i.e., grade 1 and 2). As this problem is most likely to occur on the same scale in both treatment groups, the similar toxicity rates in both groups is reassuring. Patients were not randomized to one of the CRT regimens. To minimize bias due to imbalance between the groups, we employed an IPTW-analysis based on a propensity score for treatment conditional on baseline characteristics. As we could only adjust for measured covariates, confounding by unmeasured factors cannot be ruled out.

In summary, our data show that compared to 5-FU based CRT, capecitabine-based CRT is equally tolerated and performs equally in terms of survival in patients with MIBC. Given the better convenience, capecitabine-based CRT rather than 5-FU-based CRT may be considered for patients with MIBC in whom CRT is indicated.

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Data availability

All data used for this study can be requested from the NCR. All data requests are reviewed by the supervisory committee of the NCR for compliance with the NCR objectives and (inter)national (privacy) regulation and legislation (https://iknl.nl/en/ncr/apply-for-data).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2023.109584.

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