Bladder cancer care in the Netherlands

Guidelines and practice: are they in harmony?

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Lisa Maria Catharina van Hoogstraten
geboren op 1 mei 1995
te Oss

Promotoren:
Prof. dr. L.A.L.M. Kiemeney
Prof. dr. J.A. Witjes

Copromotoren:
Dr. K.K.H. Aben
Dr. R.P. Meijer (UMC Utrecht)

Manuscriptcommissie:
Prof. dr. M.M. Rovers
Prof. dr. H. Van Poppel (KU Leuven, België)
Dr. H.M. Westgeest (Amphia Ziekenhuis)

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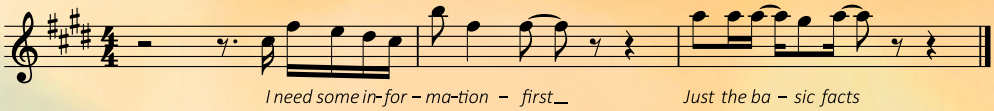

Comfortably Numb - Pink Floyd (1979)

1

General introduction and thesis outline

Adapted from:

Lisa M.C. van Hoogstraten, Alina Vrieling, Antoine G. van der Heijden, Manolis Kogevinas, Anke Richters, Lambertus A. Kiemeney. Global trends in the epidemiology of bladder cancer: challenges for public health and clinical practice

Nature Reviews Clinical Oncology (2023)

Theodora M. Ripping, Lambertus A. Kiemeney, Lisa M.C. van Hoogstraten, J. Alfred Witjes, Katja K.H. Aben. Insight into bladder cancer care: study protocol of a large nationwide prospective cohort study (BlaZIB)

BMC Cancer (2020)

Bladder cancer in numbers

Bladder cancer ranks among the top ten most common malignancies worldwide[1]. In 2020, approximately 573,000 new patients were diagnosed with bladder cancer and 213,000 patients died of the disease[1]. In the Netherlands, in recent years approximately 6,900 patients are newly diagnosed with bladder cancer and 1,900 patients die of bladder cancer each year[2]. Urothelial carcinoma is the predominant morphology in more than 90% of all bladder cancers[3]. Being the most common histological subtype, it is also the most studied one. Other histological subtypes include squamous cell carcinoma, adenocarcinoma and neuroendocrine tumors. Bladder cancer is typically a disease of the elderly, and more specifically, of elderly men; at diagnosis, more than half of all patients is over 70 years of age and more than three-quarters of all bladder cancers are diagnosed in men, in whom it is the 6th most common cancer[1].

Risk factors for bladder cancer

Smoking is the most important risk factor for bladder cancer[4]. Ever smokers have a two-to-three-fold risk of the disease compared with never smokers, increasing up to a five-fold relative risk in heavy smokers[5]. A 1.5-fold increased risk is still present even after more than 25 years of smoking cessation prior to a bladder cancer diagnosis[6]. Smoking is not only an important risk factor for developing bladder cancer but has also been associated with increased risk of recurrence and bladder cancer-specific mortality[7]. The use of electronic cigarettes ('vaping') is gaining popularity in recent years, but there are no sufficient data yet on the association between vaping and bladder cancer risk. Given that electronic cigarette smoke also contains a variety of carcinogens[8], the association between vaping and bladder cancer is plausible. Given the long latency period, these effects can only become apparent in 20 to 30 years.

Next to smoking, specific occupational exposures are important risk factors for bladder cancer. Industry workers, for instance in the tobacco, dye and rubber industry, are found to be at increased risk of bladder cancer[9]. Although occupational exposure is of less relevance in Western countries such as the Netherlands due to substantial improvement of occupational hygiene, it is still a relevant risk factor in other parts of the world.

Also, sex plays an important role. Men have a much higher lifetime risk of bladder cancer than women[10]. This can largely be related to the higher historical prevalence of smoking among men. On the other hand, women are more often diagnosed at a somewhat higher disease stage, which is associated with a worse prognosis[11]. This

is partially due to a delay in the diagnostic work-up among women presenting with hematuria[12] who, compared to men, are more likely to be (incorrectly) diagnosed with urinary tract infections and less likely to be referred to a urologist[13]. After correction for this delay, women still have a worse prognosis compared to men, especially in the first two years after diagnosis[14].

Other factors associated with an increased risk of bladder cancer include specific medical conditions such as diabetes type 2[15], or medical interventions such as radiotherapy to the lower pelvis[16]. Genetic susceptibility, arsenic in drinking water[18] and family history[19] are proven risk factors as well. There might be an association between bladder cancer risk or outcome and for instance fluid intake, diet, body weight or body mass index, physical activity, environmental factors, but the evidence for- and the anticipated impact of these factors is either scarce, weak or inconclusive[20].

Bladder cancer trends

Due to population growth and population aging, the global incidence of bladder cancer is expected to increase in the upcoming decades. In the Netherlands, the ESR (European Standardized Rate, the number of new bladder cancer diagnoses or deaths per 100,000 persons per year corrected for the age distribution of the standard European population, 1976) of bladder cancer incidence is decreasing over time, reflecting the decreasing number of smokers in the Dutch male population due to effective tobacco control policies[21]. The ESR of bladder cancer mortality remains similar for woman and is slightly decreasing in men.

Despite the discouragement of smoking and the associated decrease in standardized incidence rates and stabilization of mortality rates, the absolute incidence and mortality numbers are expected to increase. In 2032, approximately 8,100 patients will be newly diagnosed with bladder cancer (Figure 1a), and 2,600 people will die of the disease (Figure 1b)[21]. This is mainly due to the so-called double aging of the Dutch population; due to aging people will live for a longer amount of time, and more people will live for a longer amount of time.

The burden on health care and society

Due to the intensive treatment and monitoring bladder cancer requires, it is one of the most expensive cancer types per patient and it is associated with a considerable burden on patients, society and health care[22]. This burden will further increase due to the anticipated higher incidence of bladder cancer, as this will lead to a larger number of (ex)patients living with or after bladder cancer. Furthermore, in countries

with a large proportion of elderly, the population's age distribution causes a lack of health care staff due to an increasingly lower ratio of working age to older people[23]. As health care systems are already under pressure in the Netherlands[24] and abroad[25], this underlines the necessity for more efficient strategies for diagnosis, treatment and follow-up of bladder cancer.

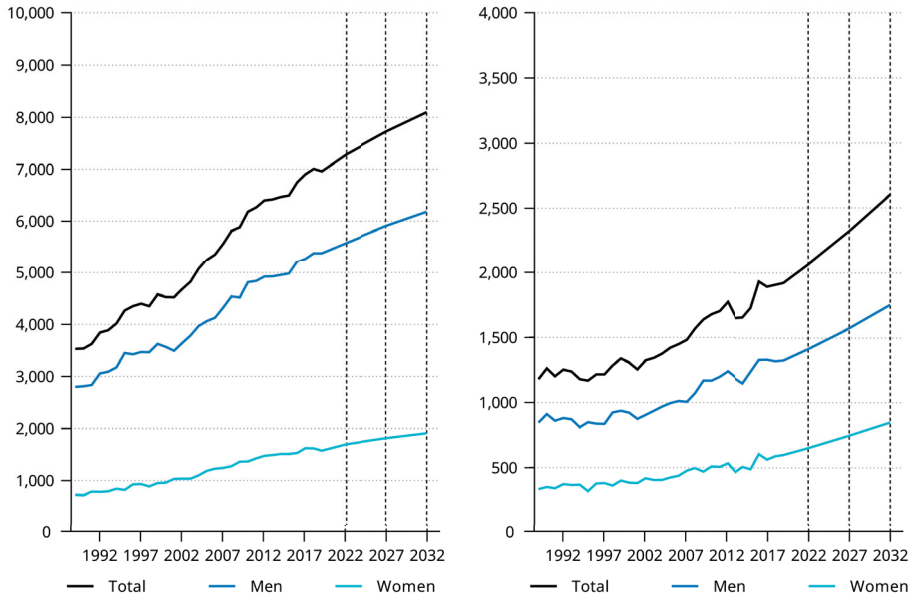

Figure 1. Absolute incidence (a) and mortality* (b) of bladder cancer in the Netherlands over time.

Source Figure 1: adapted from the IKNL report 'Kanker in Nederland - trends & prognoses tot en met 2032'.
**For mortality estimates, urinary tract tumors were included as well.*

Bladder cancer management

Bladder cancer is typically categorized into non-muscle invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC), with different behavior and treatment of these disease stages. In NMIBC (stage Ta, Tis, T1), the bladder tumor is confined to the mucosal or submucosal layer (Figure 2). In case of MIBC (stage T2 and higher), the tumor has invaded the muscle layers of the bladder or has even spread to the lymph nodes (N+) or distant sites (M+).

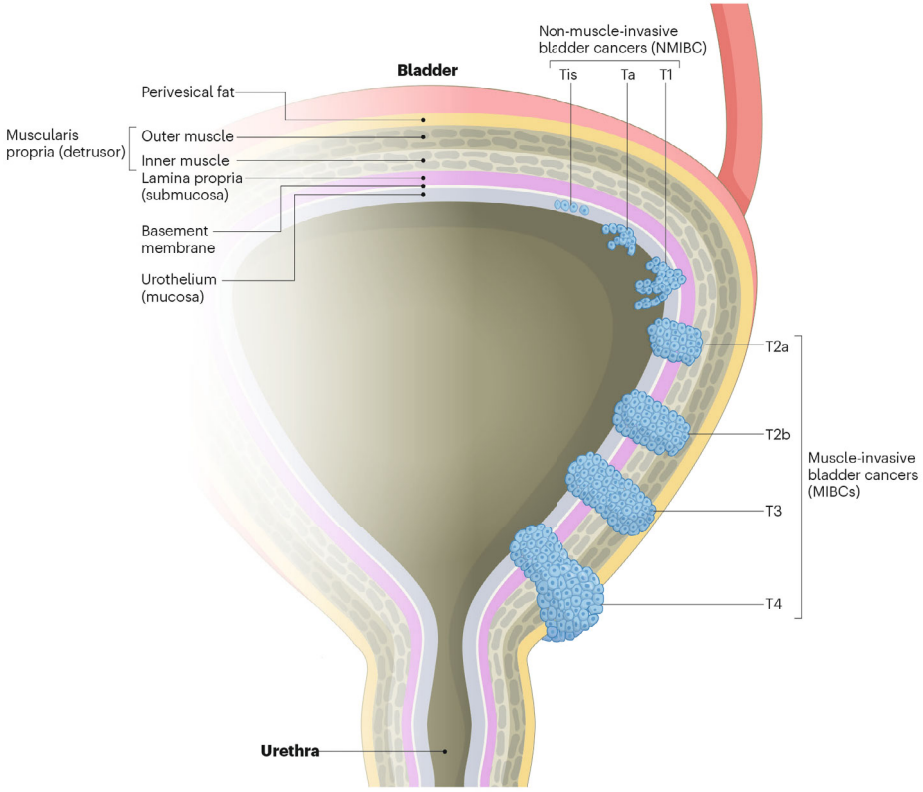

Figure 2. Anatomy of the bladder and T-staging of bladder cancer.

Source figure 2: van Hoogstraten et al., 2023. Global trends in the epidemiology of bladder cancer: challenges for public health and clinical practice.

Evidence-based guidelines for NMIBC and MIBC are formulated by the European Association of Urology (EAU) and provide guidance for daily practice regarding the diagnosis, treatment, follow-up and counselling of patients[26,27]. The Dutch association of urology (NVU) adheres to these EAU guidelines for bladder cancer management in the Netherlands[28].

NMIBC is usually locally managed by a transurethral resection of the bladder tumor (TURBT), serving both diagnostic and treatment purposes, followed by one or more intravesical chemotherapy instillations or bacillus Calmette-Guérin (BCG) immunotherapy instillations. Survival rates are generally good, i.e., the 5-year survival rate is >90%[29]. However, NMIBC has a high recurrence rate of up to 50%[29], necessitating thorough follow-up with regular cystoscopies, placing a high burden

on the patient as well as on the health care system. Also, approximately 20% of all patients with a T1-tumor will eventually progress to MIBC[30].

MIBC requires more radical treatment, due to the aggressive nature of the disease. MIBC can be subdivided into localized (T2-T4a, N0, M0) and advanced (T4b/N+/M+) disease. Localized MIBC is generally treated with a radical cystectomy (RC), preceded by neoadjuvant chemotherapy (NAC) in eligible patients. RC is an extensive surgical procedure where the whole bladder is removed. Surrounding organs such as the prostate in males and the uterus in females are often removed as well. Bladder sparing treatments such as trimodality therapy, a combination of a maximal TURBT and chemoradiotherapy, are increasingly adopted in clinical practice. Other treatment options such as brachytherapy can be considered a curative treatment option in a minority of highly selected patients. Other possible treatment options (without curative intent) are external beam radiotherapy, chemotherapy and immunotherapy. For advanced MIBC, systemic therapy is required but treatment options are often limited due to cisplatin-ineligibility, for example because of suboptimal kidney function[31]. Survival of patients with MIBC is significantly worse compared to patients with NMIBC, and depends largely on the disease stage and treatment given. If left untreated, patients with localized MIBC are at high risk of progression to metastatic disease and death: within 5 years of diagnosis, over 85% of untreated patients with MIBC succumbs to their disease[32].

Although new developments in the field of bladder cancer, for example in immunotherapy, are intensively studied, survival rates for bladder cancer have barely improved over the last decades. Thirty years ago, the 5-year relative survival bladder cancer was 54% while it is 55% now[33].

Insight into bladder cancer care

Patient outcomes such as survival can be improved by reducing variation in (the quality of) bladder cancer care, as was shown by previous research[34-36]. In order to do so, we need more insight in bladder cancer care and evaluate in which aspects of bladder cancer care variation is present. Except for the volume criterion for radical cystectomies as defined by the Dutch association of Urology (Nederlandse Vereniging voor Urologie, NVU), and the NVU cystectomy quality registration (resulting in an incomplete and underutilized database), there was no set of bladder cancer indicators available to evaluate bladder cancer care. More comprehensive, detailed clinical data are needed to evaluate (variation in) bladder cancer care in order to ultimately formulate specific recommendations for bladder cancer care improvement. Therefore, the BlaZIB study was initiated.

The BlaZIB study

BlaZIB is a Dutch acronym for *BlaaskankerZorg In Beeld*, translating to *Insight into bladder cancer care* in English. BlaZIB was inspired by the success of ProZIB (*ProstaatkankerZorg In Beeld*, *Insight into prostate cancer care*), which has set the prostate cancer field in motion and already contributed to several evidence-based improvements in prostate cancer care. For example, insights provided on the proportion of patients with urinary incontinence after radical prostatectomy[37], which was much higher than estimated by urologists, contributed to the increase of the volume criterion of 20 to 100 prostatectomies annually per hospital[38]. BlaZIB aims to provide insight in (the variation in) and improve the quality of bladder cancer care in the Netherlands.

The BlaZIB study is a nationwide, prospective cohort study including bladder cancer patients diagnosed with high-risk NMIBC (cTis or cT1(i), N0/x, M0/x) or non-metastasized MIBC (cT2-T4a, N0/x/any, M0/x) in a Dutch hospital between November 2017 and November 2019. The data collection of BlaZIB is embedded in the Netherlands Cancer Registry (NCR). The NCR is a nationwide, population-based registry serving the total Dutch population of over 17 million inhabitants. Data managers of the NCR extract information on patient, tumor and treatment characteristics from the electronic patient files in the hospitals[39]. These data include date of birth, gender, postal code, date of diagnosis, topography, histology, tumor differentiation grade, focality of the tumor, clinical and pathological stage, initial treatment, number of lymph nodes removed and number of positive lymph nodes. Vital status is obtained through annual linkage with the Personal Records Database (BRP), which contains information on emigration and vital status of all Dutch inhabitants.

The standard dataset for bladder cancer was extended for the BlaZIB study. Additional, more detailed information was collected regarding patient, tumor and hospital characteristics, diagnostics, imaging, treatment details, outcomes, recurrences and progression for at least two years after diagnosis (i.e., length and weight, performance status, comorbidity, lymphovascular invasion, multidisciplinary consultation, cytology, cystoscopy, blood values, date and type of imaging, completeness of resection, number of bladder instillations, dose and fractions of radiotherapy, reason for change or discontinuation of chemotherapy/immunotherapy, cystectomy/radiotherapy-related complications, readmissions)[40]. Data on health-related quality of life (HRQoL) were collected from patients diagnosed in hospitals participating in the HRQoL measurements. HRQoL was measured through general and (bladder) cancer-specific questionnaires administered online

or on paper at four different time points: at baseline (i.e., 6 weeks after diagnosis) and 6, 12 and 24 months after diagnosis. A comprehensive protocol of the BlaZIB study was published previously[41].

BlaZIB was funded by the Dutch Cancer Society (KWF) and was set up in collaboration with the Netherlands Comprehensive Cancer Organisation (IKNL), the Dutch association of urology (NVU), radiotherapy and oncology (NVRO), pathology (NVVP) and medical oncology (NVMO) and the patient association 'Leven met blaas- of nierkanker' (LMBNK). Based on the experiences and expertise of the BlaZIB study group, consisting of representatives of all medical disciplines involved in bladder cancer care and representatives from the patient association, it was decided on which relevant aspects of bladder cancer care we should focus. Results following from several BlaZIB-initiated studies were discussed and interpreted. The BlaZIB study group contributes to the implementation of the recommendations following from the BlaZIB study.

AIMS AND OUTLINE OF THIS THESIS

The aim of this thesis was to create a solid foundation for evidence-based recommendations to improve bladder cancer care. By assessing the variation between hospitals in the Netherlands, identifying underlying factors, and/or assessing the effect of this variation on the patients' clinical outcomes and/or health-related quality of life, we evaluated several specific aspects of bladder cancer care in the Netherlands:

In **Chapter 2**, we discuss the guideline adherence and risks of the recommended single, post-operative instillation of intravesical chemotherapy in patients with low risk bladder cancer. The chapters thereafter focus on the group of patients with non-metastatic muscle-invasive disease. In **Chapter 3**, we evaluated the uptake of and factors associated with the recommended use of neoadjuvant chemotherapy prior to radical cystectomy, and we evaluated the effect of interhospital variation on the patients' survival. In **Chapter 4**, we compared two commonly used chemoradiotherapy regimens regarding treatment completion, toxicity and survival. In **Chapter 5**, we estimated the prevalence of occult lymph node metastases after tumor downstaging. In **Chapter 6**, we investigated the characteristics and survival of the understudied group of untreated patients. During the making of this thesis, the COVID-19 pandemic emerged and disrupted health care worldwide. We addressed the general impact of the first COVID-19 wave on bladder cancer care

in the Netherlands in **Chapter 7**. Finally, in **Chapter 8**, we conclude with a general discussion of all of the studies described above, and we discuss the strengths and limitations of the BlaZIB study, and future challenges and opportunities.

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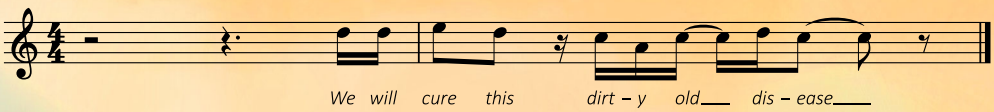

The Remedy - Jason Mraz (2002)

2

Low risk of severe complications after a single, post-operative instillation of intravesical chemotherapy in patients with TaG1G2 urothelial bladder carcinoma

Lisa M.C. van Hoogstraten, J. Alfred Witjes, Theodora M. Ripping, Ronald I. Nooter, Lambertus A. Kiemeney, Katja K.H. Aben, on behalf of the BlaZIB study group

Bladder Cancer (2021)

ABSTRACT

Background

EAU guidelines recommend a single instillation (SI) of intravesical chemotherapy (e.g. Mitomycin C) within 24 hours after transurethral resection of a bladder tumour (TURBT) in patients with low- to intermediate risk non-muscle invasive bladder cancer without (suspected) bladder perforation or bleeding requiring bladder irrigation. However, remarkable variation exists in the use of SI. The risk of severe complications is likely to contribute to this variation, but evidence is limited.

Objective

To investigate the absolute severe complication and mortality risk after SI in low- and intermediate risk bladder cancer.

Methods

In this observational, historic cohort study, data on 25,567 patients diagnosed with TaG1G2 urothelial bladder carcinoma (UBC) between 2009 and 2018 who underwent TURBT were collected from the Netherlands Cancer Registry. Data were supplemented with information on cause of death and severe complications after cancer treatment by re-examining the electronic health records and the 14-day complication risk and the 30-day mortality risk were evaluated.

Results

On average, 55% of patients had a SI after TURBT, varying from 0->80% between hospitals. The 30-day mortality risk was 0.02% and the 14-day risk of severe complications was 1.6%.

Conclusions

As the absolute risk of mortality and severe complications is very low, SI after TURBT can be considered a safe treatment in patients with low- to intermediate UBC without contraindications for SI. These results imply that a part of eligible patients is denied effective treatment.

INTRODUCTION

Patients with non-muscle invasive bladder cancer (NMIBC) are usually diagnosed and treated with a transurethral resection of the bladder tumour (TURBT) possibly followed by intravesical instillations with chemotherapy or BCG depending on stage. NMIBC often recurs[1,2] and thereby places a major (economic) burden on the patients themselves as well as on the healthcare system[3]. Previous studies have investigated the effect of a single instillation (SI) of intravesical chemotherapy (e.g. Mitomycin C) within 24 hours after TURBT, and reported a reduced recurrence risk[4-7]. The most recent meta-analysis published in 2016 showed an absolute difference of 14% in the 5-year recurrence rate in patients with Ta-T1 urothelial bladder carcinoma (UBC) with SI versus TURBT only[2]. However, SI was not effective in high-risk patients. Therefore, the use of a SI is recommended in low- to intermediate risk patients by both the European Association of Urology (EAU) Guidelines and the American Urological Association (AUA) Guidelines, assuming that the bladder was not perforated during TURBT and no bladder irrigation was required for bleeding[8,9].

Even though the beneficial effect of a SI has been extensively shown[2,4-7] and despite the recommendations in the guidelines[8,9], several studies reported remarkable variation in the use of this SI in both European countries and the USA[10-15]. A recent study evaluating European practice patterns of SI revealed substantial variation: the proportion of patients with low- or intermediate risk NMIBC receiving SI ranged from 28% to 88%[10]. Although based on fairly old data, a study from the USA evaluating national practice patterns showed that 67% of the interviewed urologists never applied SI in daily clinical practice. Overall, 58% of patients with low risk disease and 28% of patients with intermediate risk disease received a SI[13].

Besides logistic difficulties encountered by applying SI of intravesical chemotherapy and the fact that some urologists question its efficacy[13,16,17], another explanation for the low adherence to the guideline recommendation is the risk of severe and potential lethal complications such as extravasation, caused by administering SI after unobserved perforation of the bladder[13,18-21]. Even though multiple studies, including trials, evaluated the efficacy and safety of a SI and concluded that in patients without contraindications, use of SI is safe[4,6,7,18], "real world" population data on the risks are scarce and controversy regarding the use of a SI remains.

As data on the risks of SI of intravesical chemotherapy are limited, we evaluated the absolute risk of death and severe complications in patients considered eligible for a single instillation and subsequently treated with TURBT followed by SI in a Dutch

nationwide cohort of patients diagnosed with TaG1G2 urothelial carcinoma of the bladder between 2009 and 2018.

MATERIALS AND METHODS

For this historic cohort study, data from the Netherlands Cancer Registry (NCR) were used. The NCR is a nationwide, population-based registry serving the total Dutch population of approximately 17 million inhabitants. Data managers of the NCR extract information on patient and tumour characteristics, staging and treatment from the electronic patient files in the hospitals. Vital status is recorded as well in the NCR and is obtained through annual linkage with the Personal Records Database (BRP), which contains information on emigration and vital status of all Dutch inhabitants.

All patients newly diagnosed with a low- or intermediate risk non-invasive papillary (Ta) UBC between 2009 and 2018 were identified in the NCR. Patients with a history of bladder cancer were excluded. Only patients who underwent at least one TURBT were included. Low- or intermediate risk urothelial bladder cancer was defined as a grade 1 or grade 2 tumour according to the 1973 WHO grading system[22]. SI was defined as an intravesical instillation of chemotherapy administered on the day of TURBT or within 1 day after TURBT (as in the NCR only the date of TURBT and date of chemotherapy instillation are recorded). Data concerning patient- and tumour characteristics, i.e. age, gender, tumour histology, stage, grade and focality of the tumour, were retrieved from the NCR. Also information on type of chemotherapeutic agent used for SI and subsequent treatments after SI was retrieved from the NCR as this might have affected the risk of complications and death.

The electronic health records of patients deceased within 30 days after SI were re-examined by data managers of the NCR to retrieve the cause of death. Based on this information, the risk of mortality within 30 days associated with SI was calculated. In addition, we assessed the risk of severe complications, defined as complications necessitating readmission within 14 days after SI or a prolonged hospital stay (i.e. a hospital stay of 3 days or more after SI). This definition was chosen instead of the Clavien-Dindo classification because these data are not recorded as standard data items in the registry. As information on severe complications and readmissions is not readily available in the NCR, data from the Dutch Hospital Data (DHD) register, including all hospital admissions from 2017 and 2018, were linked to the cancer registry. Patients in both registries were linked on patient medical record number, date of birth, gender and 6-digit postal code. Ninety-five percent of all records in

the NCR could be linked to records in the DHD and patients with a readmission within 14 days after SI were identified. The time window of 14 days was chosen based on the assumption that severe SI-related complications will be present shortly after the chemotherapy instillation. The electronic health records of all readmitted patients and patients with a prolonged hospital stay were re-examined to evaluate the reason of readmission or prolonged hospital stay and presence of complications related to SI. All reported complications were divided into "possibly related to SI" and "unlikely to be related to SI" and were stratified by chemotherapeutic agent used. Complications possibly related to SI included irritative complaints, pain and voiding dysfunction. Other complications like bleeding and infection were considered as "unlikely to be related to SI". Based on this information the risk of severe complications possibly related to SI was calculated. We also evaluated the worst case scenario taking into account all reported complications as "possibly related to SI".

Descriptive analyses were performed to characterize the patient cohort treated with SI after TURBT by age, gender, tumour grade, and focality of the tumour. Variation in use of SI over time and in different geographic regions was assessed with the proportion of patients treated with SI as the outcome variable. Variation between hospitals was assessed using a funnel plot, plotting the proportion of patients treated with SI against the total number of patients with TaG1G2 treated with TURBT per hospital. Hospitals treating less than 10 patients between 2017-2018 and outliers were excluded from the hospital-specific analyses. The benchmark was set at the mean proportion of patients treated with SI between 2017-2018 and 95% confidence intervals were calculated. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA). 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 of the retrospective design of the study. This study was approved by the Netherlands Cancer Registry's Supervisory Committee (reference number K20.009).

RESULTS

In total, 25,567 patients with TaG1G2 UBC were included in this study (Figure 1). Of these patients, 55% (n=14,177) received a SI. The proportion of patients who had a SI after TURBT decreased from 56% in 2009 to 48% in 2018, with the highest proportion in 2011 (66%) (Supplementary Figure 1). The increase from 56% in 2009 to 66% in 2011 might reflect the period during which SI was listed as a quality indicator

in the Netherlands. In Figure 2 geographical variation in the use of SI in the period 2017-2018 is presented. In some regions SI was used in less than 40% of patients versus more than 70% in other regions. Variation between hospitals is large as well, ranging from 0% of patients with SI to over 80% (period 2017-2018). The median was 53% and the mean was 48%. The proportion of patients who had a SI after TURBT varies between hospitals and within different hospital volumes of TaG1G2 patients treated with TURBT (Figure 3).

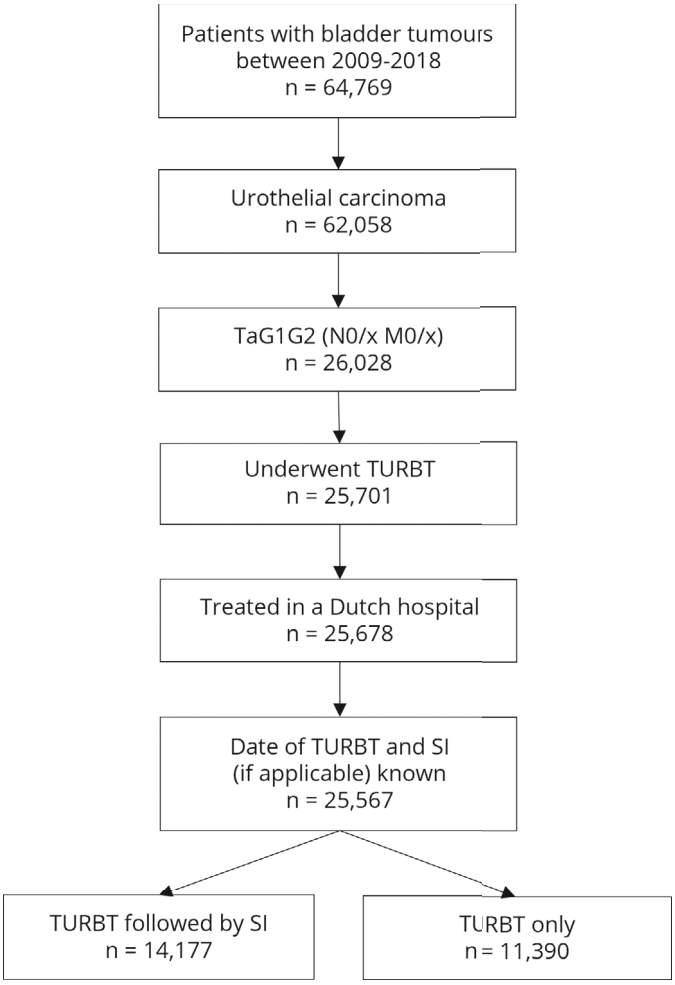

Figure 1. Flowchart describing the inclusion of patients in the study cohort.

TURBT: Transurethral Resection of the Bladder Tumour; SI: Single Instillation

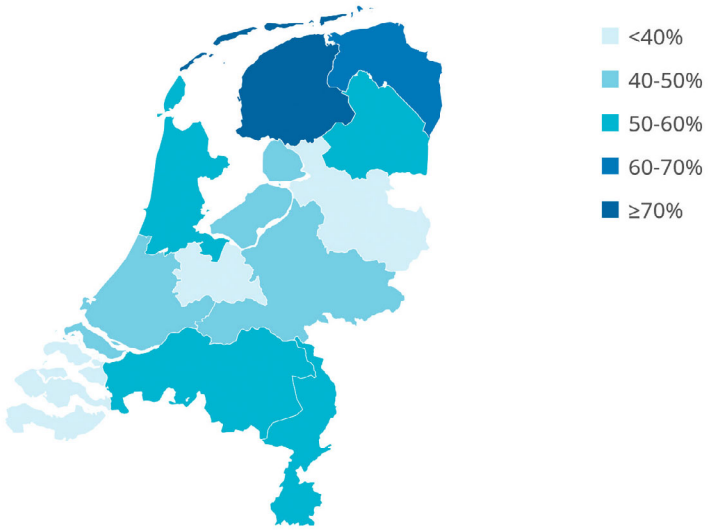

Figure 2. Percentage of patients diagnosed in 2017-2018 with TaG1G2 urothelial carcinoma receiving a SI per province in the Netherlands.

SI: Single Instillation

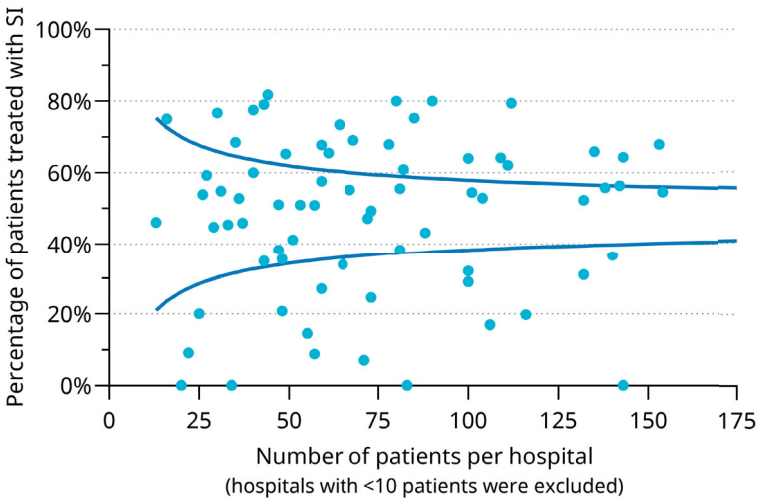

Figure 3. Percentage of patients diagnosed in 2017-2018 with TaG1G2 urothelial carcinoma receiving a SI by hospital volume in 2017-2018 in the Netherlands.

SI: Single Instillation
**Hospital volume was based on the number of patients with TaG1G2 treated with transurethral resection of the bladder tumour (TURBT). Hospitals with <10 patients were excluded from the analysis.*

The baseline characteristics of all patients treated with SI are shown in Table 1. Within 30 days after SI, one patient (0.01%) underwent partial cystectomy and 237 patients (1.7%) received BCG instillations, of which one patient died within 30 days. In total, 18 patients died within 30 days after SI. In Table 2 several characteristics like age, details regarding TURBT and cause of death of these deceased patients are presented. One death appeared to be linked directly to SI. In one patient, re-examination of the medical file remained inconclusive and therefore we considered this death as possibly associated with SI. For one other patient, no information regarding cause of death could be retrieved. Assuming the worst case scenario and considering the inconclusive deaths as associated with SI, three of 18 deaths were considered associated with SI. The absolute 30-day mortality risk due to SI is therefore 0.02% (3 out of 14,177 patients).

Out of 2,634 patients who had a SI after TURBT in 2017 and 2018, 60.9% of patients (n=1,604) received Mitomycin C, 11.1% (n=292) received epirubicin and in 28.0% (n=738) the type of chemotherapeutic agent used was not documented (data not shown). In total, 41 patients were readmitted within 14 days, 39 patients had a prolonged hospital stay and 5 patients had both because of one or more complications related to TURBT or SI. The reason for prolonged hospital stay could not be retrieved for four patients. In Table 3 the reported complications are described. The most frequently documented complications were bleeding (n=44, 1.67%), voiding dysfunction (n=22, 0.84%) and infection (n=19, 0.72%). Assuming a worst case scenario resulted in a 14-day complication risk of 3.00% (79 of 2,634 patients). The worst case scenario included all patients with reported complications and the 4 patients with unknown reason of prolonged hospital stay. However, if only the complications “possibly related to SI”, including only irritative complaints, pain and voiding dysfunction, and the patients with unknown reason of prolonged hospital stay are taken into account, this risk decreased to 1.59% (42 of 2,634 patients).

Table 1. Patient, tumour, and treatment characteristics of patients with TaG1G2 urothelial carcinoma treated with TURBT followed by a SI between 2009-2018.

	Total		Deceased	
	n	**(%)**	**n**	**(%)**
Total	14,177	(100.0)	18	(0.1)
Age (mean, SD)	68.1	11.3	78.9	7.8
Gender				
Male	10,941	(77.2)	18	(100.0)
Female	3,236	(22.8)	0	(0.0)
Tumour grade (WHO 1973)				
Grade 1	6,244	(44.0)	13	(72.2)
Grade 2	7,933	(56.0)	5	(27.8)
Focality of the tumour				
Unifocal	10,679	(75.3)	16	(88.9)
Multifocal	3,058	(21.6)	2	(11.1)
Not documented	440	(3.1)	0	(0.0)
BCG instillation within 30 days after SI				
Yes	237	(1.7)	1	(5.6)
Partial cystectomy within 30 days after SI				
Yes	1	(0.01)	0	(0.0)

TURBT: Transurethral Resection of the Bladder Tumour; SI: Single Instillation; SD: Standard Deviation; WHO: World Health Organization; BCG: Bacille Calmette-Guérin

Table 2. Overview of patients deceased within 30 days after TURBT followed by a SI between 2009-2018.

Pt. No.	Age (years)	Gender	Year of TURBT	Tumour stage	Readmission n days after SI	Deceased n days after SI	Details regarding TURBT	Comorbidities	Cause of death
1	80	Male	2014	TaG2	0	22	Bladder perforation for which laparotomy was performed		Complications (multiple organ failure) caused by extravasation of SI after bladder perforation
2	78	Male	2010	TaG2	2	4	Fausse route urethra	Myocardial infarction, CABG, mitral valve replacement	Myocardial infarction followed by cardiogenic shock
3	72	Male	2011	TaG1	22	28	Uncomplicated	Myocardial infarction, diabetes mellitus	Ventricular tachycardia
4	85	Male	2018	TaG2	2	8	Nothing reported		Possibly related to SI: upper abdominal pain during the day after TURBT and SI, and collapsed in the night (asystole/ myocardial ischemia/hypovolemia)
5	71	Male	2017	TaG2	4	7	Uncomplicated		Respiratory insufficiency (COPD), deteriorating renal function, heart disease
6	79	Male	2009	TaG1	/	28	Uncomplicated	Decompensated heart failure, cardiac arrhythmia, diabetes mellitus	Pleural carcinomatosis (colon cancer)
7	69	Male	2009	TaG1	9	11	Uncomplicated	Myocardial infarction	CVA
8	78	Male	2009	TaG2	11	21	Uncomplicated	Liver cirrhosis, diabetes mellitus, venous insufficiency	Decompensated heart failure
9	92	Male	2009	TaG1	24	27	Nothing reported	Cardiac arrhythmia	Pulmonary embolism
10	71	Male	2012	TaG2	10	12	Nothing reported		Abdominal aortic aneurysm
11	65	Male	2012	TaG2	/	2	Uncomplicated		Suicide

Table 2. Continued.

Pt. No.	Age (years)	Gender	Year of TURBT	Tumour stage	Readmission n days after SI	Deceased n days after SI	Details regarding TURBT	Comorbidities	Cause of death
12	93	Male	2013	TaG2	-13	12	Readmission for decompensated heart failure, during which bladder tumour was discovered. Thin bladder wall but no mentioning of perforation in TURBT report	Coronary artery disease	Pneumonia, complicated by decompensated heart failure
13	74	Male	2014	TaG1	8	17	Uncomplicated	Peripheral artery disease, hypertension, atrial fibrillation, thyroid disorder	CVA
14	86	Male	2015	TaG2	/	29	Uncomplicated		Hypovolemia, chronic heart failure
15	87	Male	2016	TaG2	8	29	Post-operative bleeding	Diabetes mellitus, atrial fibrillation, peripheral artery disease, CABG, CVA	Metastasized bladder cancer
16	81	Male	2018	TaG2	10	11	Uncomplicated		Pulmonary embolism
17	83	Male	2012	TaG2	/	23	Uncomplicated		Unknown
18	77	Male	2015	TaG2	/	20	Nothing reported		Unknown, however not related to SI. The patient visited the urologist two weeks after TURBT and SI

TURBT: Transurethral Resection of the Bladder Tumour; SI: Single Instillation; CABG: Coronary Artery Bypass Grafting; CVA: Cerebrovascular Accident

Table 3. Complications possibly related to treatment experienced by patients treated with TURBT followed by a SI between 2017-2018, necessitating a prolonged hospital stay or readmission within 14 days.

			Readmission (n=41)		Prolonged hospital stay (n=39)		Total** (n=75)	
Chemotherapeutic agent		**Complication***	**n**	**%**	**n**	**%**	**n**	**%**
Epirubicin (n=10)	Possibly related to SI	Pain	3	(0.11)	1	(0.04)	4	(0.15)
		Voiding dysfunction	3	(0.11)	0	(0.00)	3	(0.11)
	Unlikely to be related to SI	Bleeding	2	(0.08)	3	(0.11)	5	(0.19)
		Infection	3	(0.11)	0	(0.00)	3	(0.11)
		Kidney obstruction (consequences)	1	(0.04)	0	(0.00)	1	(0.04)
		Perforation (suspected)	1	(0.04)	0	(0.00)	1	(0.04)
Mitomycin C (n=65)	Possibly related to SI	Irritative complaints	2	(0.08)	0	(0.00)	2	(0.08)
		Pain	6	(0.23)	8	(0.30)	14	(0.53)
		Voiding dysfunction	12	(0.46)	7	(0.27)	19	(0.72)
	Unlikely to be related to SI	Bleeding	14	(0.53)	25	(0.95)	39	(1.48)
		Delirium	0	(0.00)	3	(0.11)	3	(0.11)
		Infection	8	(0.30)	8	(0.30)	16	(0.61)
		Kidney obstruction (consequences)	5	(0.19)	2	(0.08)	7	(0.27)
		Nausea	1	(0.04)	1	(0.04)	2	(0.08)
		Obstipation	2	(0.08)	0	(0.00)	2	(0.08)
		Perforation (suspected)	1	(0.04)	3	(0.11)	4	(0.15)
		Pneumonia	1	(0.04)	0	(0.00)	1	(0.04)

TURBT: Transurethral Resection of the Bladder Tumour; SI: Single Instillation; Bleeding: hematuria, clots, clogged catheter; Infection: genitourinary infection, fever, elevated inflammatory values; Kidney obstruction (consequences): dilated bladder or kidney, hydronephrosis, phylum blowout, renal dysfunction; Voiding dysfunction: all complications related to micturition, such as inability to urinate (urinary retention) or completely empty the bladder and polyuria

** Patients could have had more than one complication. To calculate the risk of complications, the number of patients with complications was divided by 2,634, the number of patients treated with TURBT and SI in 2017-2018. ** Five patients necessitated both a prolonged hospital stay and readmission.*

DISCUSSION

In this large population-based study reflecting daily practice, we can conclude that the 30-day mortality risk due to SI in patients judged to be eligible is very low (0.02%). Furthermore, the risk of severe complications within 14 days associated with SI requiring hospital readmission or prolonged hospital stay was low (1.6%), even assuming a worst case scenario (including all complications as "possibly related to SI") (3.0%). In line with previous studies, we observed substantial variation in the proportion of patients with a SI[10,11,13], depending on geographical location and between individual hospitals.

EAU guidelines recommend a SI in patients with low to intermediate risk urothelial bladder cancer. Patients with a primary, solitary, or small (≤ 3 cm) tumour, without carcinoma in situ and no perforation, extensive resection, or bleeding requiring irrigation during TURBT are considered eligible[7]. As not all patients will meet these eligibility criteria, the instillation rate will never reach one hundred percent. Assuming a more or less similar patient population in the Netherlands with regard to geographic region and hospital, case-mix will only explain a small part of the observed variation. Next to case-mix, other factors might contribute to the variation in use of SI. For instance, different perceptions of the risk of complications, e.g. depth of the resection and suspicion of possible perforation of the bladder, will likely play a role[23]. Logistic issues, such as the impossibility of administering SI in the operating room immediately after TURBT or at the ward, might also be a factor[11,13,24]. However, in the Netherlands this is rarely the case. Also, part of the urologists doubt the efficacy of SI[12,13,24] although a meta-analysis by Sylvester et al. reported a recurrence rate of 44.8% in the SI group versus 58.8% in the TURBT only group[2]. But the most important factor seems to be the risk of severe or even deadly complications caused by administering SI after unobserved perforation of the bladder[25]. This concern is based on studies showing a high risk of extravasation, as for example shown by a prospective study of Balbay et al. from 2005. In this study the perforation rates after TURBT were evaluated in 36 patients with a Ta-T2 bladder tumour and showed that without any evidence of perforation as examined by the surgeon, extravasation of a contrast agent was observed in 58% of TURBTs using a cystogram post-operatively[23]. A similar study from 2009 reported extravasation of a contrast agent in 50% of the 34 patients included[26]. However, in both studies all cases of perforation appeared to be asymptomatic except for one, and none of these patients required surgery or any other medical intervention except for catheterization. Several trials have shown that serious adverse events due to SI after TURBT are rare[4,6,18,27]. Messing et al. reported no severe adverse events of grade 4

or 5 in their trial on intravesical gemcitabine versus saline, and grade 1-3 adverse events were similar between groups[6]. Even in case of suspected extravasation, as for example reported by Bosschieter et al. in 6 out of 1,048 included patients (0.57%) surgical intervention was not necessary[18]. As our definition of complications was different, we cannot directly compare our results. Still, we found a low complication rate which is in line with the studies previously mentioned.

In order to get some insight into the reasons for not administering SI, co-author JAW performed an unstructured telephone survey among Dutch urologists (1 urologist per hospital) in a sample of 10 hospitals (13%) with low administration rates of SI. The telephone survey indicated that both risk of complications (8 out of 10 urologists) and disbelief in the efficacy of a SI (7 out of 10 urologists) were important factors when considering administering a SI. A very recent study by Dunsmore et al. (2021) investigated the barriers and facilitators concerning SI in Scotland and England, and found that barriers for administering SI were present on both professional (e.g. urologists, nurses) and organizational (hospital) level. Amongst those barriers, concern about side effects and (non-)belief in efficacy were also mentioned, confirming our findings[24].

With this large Dutch population-based study in which we re-examined the electronic health records, we have provided insight in the adherence to SI in low- and intermediate-risk NMIBC and the absolute mortality and complication risks after TURBT followed by SI. It is good to keep in mind that the reported absolute complication and mortality rate is evaluated in patients already judged to be eligible for SI after TURBT, reflecting the risk that is present in current practice. The overall 30-day mortality rate was very low in these patients, indicating that the assessment of eligibility by urologists was done well. This study has some limitations. We evaluated complications severe enough to require readmission within 14 days or a prolonged hospital stay. Mild complications not resulting in a hospital admission within 14 days could, therefore, not be taken into account. We might have missed severe complications as a result of incomplete documentation in the electronic health records. But considering the severity of complications and the good documentation of the reason of readmission or prolonged hospital stay, we assume that reporting of complications was nearly complete. Since 5% of the NCR records could not be linked to the DHD registry, it is possible that we may have missed some readmissions. In this study we could not evaluate how instillation rates could be improved as not all information on eligibility for SI (e.g. tumour size, specific TURBT details and (possible) perforation) was available or was not documented in the NCR due to rather poor documentation in the medical files. However, from the

substantial variation between individual hospitals we observed, we can conclude that instillation rates are indeed suboptimal.

Although in the majority of patients Mitomycin C was used as intravesical chemotherapy this might change in upcoming years. A meta-analysis including five randomized controlled trials showed superior efficacy of gemcitabine in preventing recurrences compared to Mitomycin C[28]. Also Messing and colleagues reported a reduced risk of recurrence after a single instillation of intravesical gemcitabine, compared to saline[6]. Therefore, use of gemcitabine as single postoperative instillation might increase over time, possibly necessitating reconsideration of the complication risk and mortality risk of SI.

CONCLUSIONS

Given the very low absolute mortality and low severe complication risk, a single, post-operative instillation of intravesical chemotherapy after TURBT can be considered a safe treatment for eligible patients with low- to intermediate risk bladder cancer who underwent TURBT without suspected perforation or extensive resection or bleeding requiring bladder irrigation. When indicated, a single instillation should therefore be administered in order to reduce risk of recurrence. Given that many urologists might be guided by the risk of complications due to SI and considering the substantial variation in use of SI we observed, it can be assumed that part of these patients are wrongfully denied a recommended and effective treatment.

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AUTHOR CONTRIBUTIONS

LMCH: conception, data collection, data analysis, data interpretation, writing the article. JAW: conception, data collection, data interpretation, writing the article. TMR: writing the article. RIN: writing the article. BlaZIB study group: writing the

article. LAK: conception, data collection, data interpretation, writing the article. KKHA: conception, data collection, data interpretation, writing the article.

The members of the BlaZIB study group (next to the authors) are: Joost Boormans, MD, PhD (Erasmus Medical Centre), Theo M. de Reijke, MD, PhD (Amsterdam University Medical Centres, location AMC), Catharina A. Goossens-Laan, MD, PhD (Alrijne hospital), Sipke Helder (Patient association 'Leven met blaas- of nierkanker'), Maarten C.C.M. Hulshof, MD, PhD (Amsterdam University Medical Centres, location AMC), Geert J.L.H. van Leenders, MD, PhD (Erasmus Medical Centre), Anna M. Leliveld, MD, PhD (University Medical Centre Groningen), Richard P. Meijer, MD, PhD (University Medical Centre Utrecht), Sasja F. Mulder, MD, PhD (Radboud University Medical Centre), Juus L. Noteboom, MD, PhD (University Medical Centre Utrecht), Jorg R. Oddens, MD, PhD (Amsterdam University Medical Centres, location AMC), Tineke J. Smilde, MD, PhD (Jeroen Bosch ziekenhuis), Guus W.J. Vanderbosch (Patient association 'Leven met blaas- of nierkanker'), Antoine G. van der Heijden, MD, PhD (Radboud University Medical Centre), Michiel S. van der Heijden, MD, PhD (Netherlands Cancer Institute), Reindert J.A. van Moorselaar, MD, PhD, Prof (Amsterdam University Medical Centres, location VUmc), Bas W.G. van Rhijn, MD, PhD, FEBU (Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital), Joep G.H. van Roermund, MD, PhD (Maastricht University Medical Centre), Bart P. Wijsman, MD, PhD (Elisabeth-TweeSteden Ziekenhuis).

CONFLICTS OF INTEREST

Lisa M.C. van Hoogstraten, J. Alfred Witjes, Theodora M. Ripping, Ronald I. Nooter, Lambertus A. Kiemeney, Katja K.H. Aben and the BlaZIB study group have no conflicts of interest to declare.

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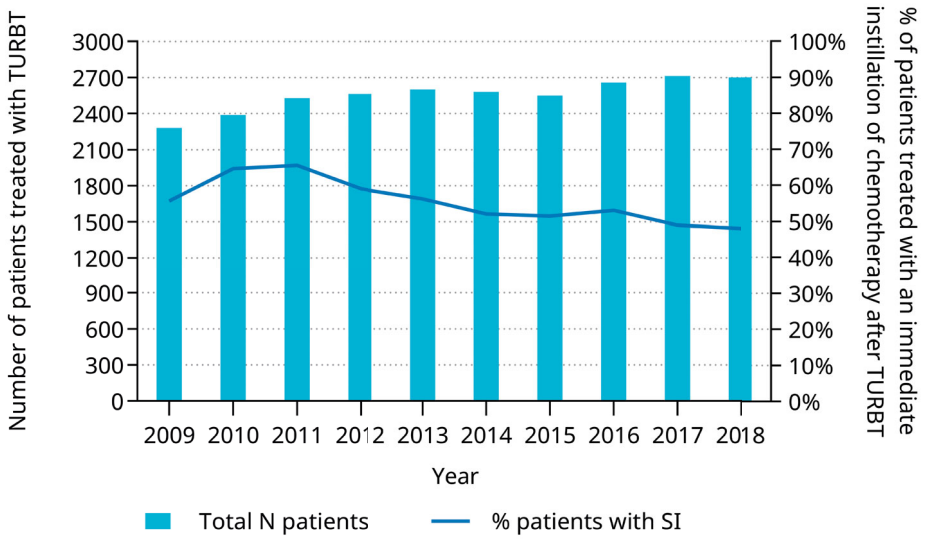
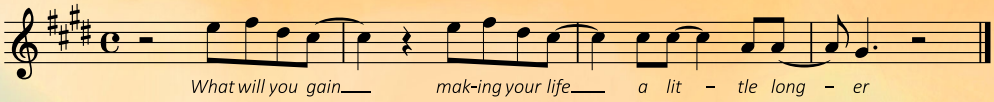
SUPPLEMENTARY MATERIAL



Supplementary Figure 1. Total number of patients with TaG1G2 urothelial carcinoma and percentage of patients receiving a SI over time between 2009-2018 in the Netherlands.

SI: Single Instillation; TURBT: Transurethral Resection of the Bladder Tumour



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3

Low guideline adherence to recommended use of neoadjuvant chemotherapy in patients with non metastatic muscle-invasive bladder cancer

Lisa M.C. van Hoogstraten, Calvin C.O. Man, J. Alfred Witjes, Richard P. Meijer, Sasja F. Mulder, Tineke J. Smilde, Theodora M. Ripping, BlaZIB study group, Lambertus A. Kiemeney, Katja K.H. Aben

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ABSTRACT

Purpose

To evaluate guideline adherence and variation in the recommended use of neoadjuvant chemotherapy (NAC) and the effects of this variation on survival in patients with non-metastatic muscle-invasive bladder cancer (MIBC).

Methods

In this nationwide, Netherlands Cancer Registry-based study, we identified 1025 patients newly diagnosed with non-metastatic MIBC between November 2017 and November 2019 who underwent radical cystectomy. Patients with ECOG performance status 0-1 and creatinine clearance ≥50 mL/min/1.73 m^2 were considered NAC-eligible. Interhospital variation was assessed using case-mix adjusted multilevel analysis. A Cox proportional hazards model was used to evaluate the association between hospital specific probability of using NAC and survival. All analyses were stratified by disease stage (cT2 versus cT3-4a).

Results

In total, of 809 NAC-eligible patients, only 34% (n = 277) received NAC. Guideline adherence for NAC in cT2 was 26% versus 55% in cT3-4a disease. Interhospital variation was 7-57% and 31-62%, respectively. A higher hospital specific probability of NAC might be associated with a better survival, but results were not statistically significant (HR_{cT2} = 0.59, 95% CI 0.33-1.05 and HR_{cT3-4a} = 0.71, 95% CI 0.25-2.04).

Conclusion

Guideline adherence regarding NAC use is low and interhospital variation is large, especially for patients with cT2-disease. Although not significant, our data suggest that survival of patients diagnosed in hospitals more inclined to give NAC might be better. Further research is warranted to elucidate the underlying mechanism. As literature clearly shows the potential survival benefit of NAC in patients with cT3-4a disease, better guideline adherence might be pursued.

INTRODUCTION

European guidelines recommend cisplatin-based neoadjuvant chemotherapy (NAC) preceding radical cystectomy (RC) in cisplatin-eligible patients with non-metastatic muscle-invasive bladder cancer (MIBC)[1]. This recommendation is based on meta-analyses showing a significant absolute 5-year survival benefit of 5–9% in favor of NAC compared to upfront RC[2–5]. Despite this recommendation, NAC administration rates vary largely in clinical practice[6–8]. This variation might, in part, be explained by more recent studies and meta-analyses showing contradicting results regarding the benefit of NAC[9,10]. The meta-analysis by Hamid et al. evaluated overall survival (OS) in 17 randomized controlled trials (RCTs) and retrospective studies up to 2020, and found a significant survival benefit in favor of NAC; the pooled hazard ratio (HR) for OS was 0.82 (95% CI 0.71–0.95). In contrast, the RCT-based meta-analysis by Li et al. showed no convincing evidence in favor of NAC: HR for OS was 0.92 (95% CI 0.84–1.00) and HR = 0.95 (95% CI 0.69–1.29) for progression-free survival, although the latter endpoint was only evaluated in 6 of the 14 included studies. A recent population-based observational study performed in the Netherlands including 5,517 patients showed no significant survival benefit of NAC in patients with cT2N0M0 bladder cancer in contrast with cT3-4aN0M0 bladder cancer[11], suggesting to reevaluate the use of NAC in patients with cT2-disease.

In the Netherlands, the NAC utilization rate for MIBC increased from 0.6% in 1995 to 21% in 2013[7] and is still increasing[12]. Variation in NAC use in current clinical practice is expected but underlying factors are largely unknown, as is the effect on outcome. This study aims to evaluate guideline adherence and variation in NAC use and to gain insight in the factors associated with use of NAC, taking patient eligibility into account, and to assess the effect of interhospital variation in use of NAC on survival.

PATIENTS AND METHODS

This 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[13]. The data collection of BlaZIB is embedded in the Netherlands Cancer Registry (NCR), hosted by the Netherlands Comprehensive Cancer Organisation. We selected all patients ≥18 years newly diagnosed with cT2–4aN0/xM0/x MIBC between 1 November 2017 and 31 October 2019 who underwent RC. A detailed description of all variables included is given in Supplementary Table 1.

Definitions

Patients were categorized into two treatment groups: NAC + RC or upfront RC. Platinum-eligibility was based on renal function and performance status. Patients were considered platinum-eligible if they had an estimated glomerular filtration rate (eGFR) ≥50 mL/min/1.73 m^2 and ECOG performance score 0-1, allowing eligibility for different chemotherapeutic agents and schedules[1]. Patients were considered platinum-ineligible if eGFR <30 mL/min/1.73 m^2 and/or ECOG ≥3. The remaining patients with an eGFR between 30 and 50 mL/min/1.73 m^2 and ECOG 0-2 were considered potentially eligible.

Statistical analyses

Descriptive analyses were performed to evaluate guideline adherence and provide insight into patient and tumor characteristics of eligible patients, including ANOVA and Chi-square tests to evaluate differences between treatment groups. Uni- and multivariable logistic regression analyses were performed to identify factors associated with receiving NAC. Hospital-specific probabilities for eligible patients to have NAC were evaluated using multilevel logistic regression analysis, both unadjusted (i.e., observed probability) and adjusted for relevant case-mix factors. Hospitals with less than 5 observations were excluded from multilevel modelling. Two-year overall survival (OS) of patients diagnosed in hospitals with the 15% lowest and 15% highest hospital-specific probabilities of administering NAC regardless of whether patients actually received NAC was evaluated using the Kaplan Meier method and Log-Rank test. This way we gain insight in whether patients diagnosed in hospitals which were more inclined to give NAC have better outcomes compared to patients diagnosed in hospitals which were much more hesitant. Start of follow-up was defined as date of diagnosis. End of follow-up was defined as last date of follow-up or death, whatever came first. Follow-up was censored at 2 years. A Cox proportional hazards model was constructed to evaluate the effect of interhospital variation on survival, adjusted for relevant case-mix factors. All analyses were stratified by disease stage (cT2 versus cT3-4a). As a sensitivity analysis, we repeated all analyses, now including potentially NAC-eligible patients as well. Missing data were imputed using single and multiple (n = 20) imputation, assuming data being missing at random. Single imputed data were used to perform survival and Cox regression analyses, multiple imputed data were used for all other analyses.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA). $P < 0.05$ was considered statistically significant.

RESULTS

Seventy-nine percent (n = 809) of all included patients were considered NAC-eligible, but only 34% (n = 277) received NAC. Of the 180 patients considered potentially eligible, 13% (n = 23) received NAC. None of the 36 ineligible patients received NAC. Patient and tumor characteristics of eligible patients are presented in Table 1. Relatively more patients with cT3-4a disease received NAC compared to patients with cT2-disease: 55% (128 out of 233) versus 26% (149 out of 576), respectively. Most patients receiving NAC started with a multiagent, cisplatin-based regimen (95%) and had 2-4 cycles (90%). All were under 80 years of age at diagnosis. A detailed description of all 1,025 patients included in this study is given in Supplementary Table 2.

Multivariable regression analysis showed that increasing age (OR = 0.93, 95% CI 0.91-0.95) and presence of comorbidity (CCI ≥2 versus 0: OR = 0.52, 95% CI 0.31–0.88) significantly decreased the odds of having NAC in eligible patients (Table 2). Higher disease stage (cT3-4a versus cT2: OR = 3.33, 95% CI 2.36-4.71) increased the odds. Better renal function (OR = 1.02, 95% CI 1.01-1.03) and female gender (OR = 1.44, 95% CI 1.05-1.98) were univariably associated with having NAC, but these effects became non-significant in multivariable analyses. No significant associations were found for BMI, performance status, SES, tumor histology and hospital of MDTM. After stratification by disease stage, higher BMI became positively associated whereas CCI was no longer significantly associated with having NAC in patients with cT2-disease. The sensitivity analysis including both eligible and potentially eligible patients yielded similar results, except that renal function remained statistically significant in multivariable analysis (Supplementary Table 3).

Large variation was observed in hospital-specific probabilities to administer NAC in platinum-eligible patients, which was 14-62% after correction for case-mix factors, i.e., age at diagnosis, comorbidity and disease stage (Figure 1). Stratification by disease stage revealed considerable differences in NAC administration probabilities; 7-57% for patients with cT2-stage and 31-62% for patients with cT3-4a stage.

Unadjusted 2-year OS was 79% for patients diagnosed in hospitals with high probability of administering NAC and 68% for patients diagnosed in hospitals with low probability (Log-Rank test p = 0.07, Supplementary Figure 1a). This is regardless of whether patients actually received NAC or not. Stratified analysis by disease stage showed a 2-year OS of 81% versus 64% in cT2-disease (p = 0.03, Supplementary Figure 1b), and 66% versus 62% in cT3-4a disease (p = 0.53, Supplementary Figure

1c). Cox regression analysis in patients with T2-disease, adjusted for age at diagnosis and BMI resulted in a hazard ratio of HR_{cT2} = 0.59 (95% CI 0.33-1.05) and HR_{cT3-4a} was 0.71 (95% CI 0.25-2.04) in patients with T3-4a disease, adjusted for age at diagnosis and comorbidity (Supplementary Table 4).

Table 1. Patient and tumor characteristics of platinum-eligible patients, diagnosed with non-metastatic muscle-invasive bladder cancer who underwent radical cystectomy, stratified by use of neoadjuvant chemotherapy (imputed data).

	All patients (n=809)		**Upfront RC (n=532)**		**NAC + RC (n=277)**		**P-value***
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	
Number of administered cycles							
1	-		-		22	(7.9%)	
2	-		-		34	(12.3%)	
3	-		-		78	(28.2%)	
4	-		-		137	(49.5%)	
5 or more	-		-		3	(1.1%)	
Unknown	-		-		3	(1.1%)	
Surgical approach							0.0553
Open	428	(52.9%)	288	(54.1%)	140	(50.5%)	
Robot-assisted	349	(43.2%)	217	(40.8%)	132	(47.7%)	
Laparoscopic, not specified	30	(3.7%)	25	(4.7%)	5	(1.8%)	
Unknown	2	(0.2%)	2	(0.4%)	0	(0.0%)	
Gender							0.0286
Male	582	(72.0%)	396	(74.5%)	186	(67.2%)	
Female	227	(28.0%)	136	(25.5%)	91	(32.8%)	
Age at diagnosis (median, IQR)	69.0	(63.0-74.0)	71.0	(65.0-76.0)	65.0	(58.0-70.0)	<.0001
Age at diagnosis							<.0001
<60 years	143	(17.6%)	60	(11.2%)	83	(29.9%)	
60-70 years	263	(32.5%)	145	(27.3%)	118	(42.5%)	
70-80 years	349	(43.1%)	272	(51.2%)	76	(27.6%)	
≥80 years	55	(6.8%)	55	(10.3%)	0	(0.0%)	
Body Mass Index (BMI)							
(median, IQR)	26.0	(23.6-29.0)	25.9	(23.6-28.7)	26.0	(23.6-29.1)	0.1694
Body Mass Index (BMI)							0.1624
Underweight (<18.5)	13	(1.7%)	10	(1.9%)	3	(1.2%)	
Normal weight (18.5-24.9)	308	(38.1%)	200	(37.6%)	108	(39.0%)	
Overweight (25.0-29.9)	357	(44.1%)	245	(46.1%)	111	(40.2%)	
Obese (≥30.0)	131	(16.1%)	77	(14.4%)	54	(19.5%)	
Weighted Charlson Comorbidity Index (CCI)							<.0001
0	432	(53.5%)	252	(47.4%)	180	(65.0%)	
1	233	(28.8%)	166	(31.2%)	67	(24.2%)	
2 or more	143	(17.7%)	114	(21.3%)	30	(10.8%)	
Performance status (ECOG)							0.8020
ECOG 0	575	(71.0%)	379	(71.3%)	195	(70.5%)	
ECOG 1	234	(29.0%)	153	(28.7%)	82	(29.5%)	

Table 1. Continued.

	All patients (n=809)		Upfront RC (n=532)		NAC + RC (n=277)		P-value*
	n	(%)	n	(%)	n	(%)	
Renal function (eGFR)							
(median, IQR)	74.0	(62.1-88.0)	72.0	(61.0-86.0)	77.0	(66.0-89.3)	<.0001
Socioeconomic status (SES)							0.4580
Low	213	(26.3%)	143	(27.0%)	70	(25.1%)	
Middle	348	(43.0%)	233	(43.9%)	115	(41.4%)	
High	248	(30.6%)	155	(29.1%)	93	(33.5%)	
Disease stage (cTNM)							<.0001
cT2N0/xM0/x	576	(71.2%)	426	(80.2%)	149	(54.0%)	
cT3N0/xM0/x	205	(25.3%)	99	(18.7%)	106	(38.1%)	
cT4aN0/xM0/x	28	(3.5%)	6	(1.1%)	22	(7.9%)	
Tumor histology							0.0948
Urothelial carcinoma	788	(97.4%)	516	(97.0%)	272	(98.2%)	
Squamous cell carcinoma	6	(0.7%)	6	(1.0%)	0	(0.0%)	
Adenocarcinoma	11	(1.3%)	6	(1.1%)	5	(1.8%)	
Other	5	(0.6%)	5	(0.9%)	0	(0.0%)	
Hospital of MDTM							0.9656
Community hospital	252	(31.1%)	167	(31.4%)	85	(30.5%)	
Non-university referral hospital	420	(51.9%)	275	(51.8%)	144	(52.1%)	
University hospital	137	(17.0%)	89	(16.8%)	48	(17.3%)	

RC: radical cystectomy; NAC: neoadjuvant chemotherapy; IQR: interquartile range; ECOG: Eastern Cooperative Oncology Group; eGFR: estimated glomerular filtration rate; MDTM: multidisciplinary team meeting

** P-value was calculated using Chi-square for categorical variables and ANOVA for continuous variables.*

Table 2. Uni- and multivariable logistic regression analysis on the association between patient, tumor and hospital characteristics and receiving NAC, in platinum-eligible patients diagnosed with non-metastatic muscle-invasive bladder cancer who underwent radical cystectomy.

	All disease stages (cT2-4a)				cT2-disease only				cT3-4a disease only			
	Univariable model		Multivariable model		Univariable model		Multivariable model		Univariable model		Multivariable model	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Gender												
Male	ref.		ref.		ref.				ref.			
Female	1.44	(1.05 - 1.98)	1.27	(0.89 - 1.82)	1.42	(0.95 - 2.12)			1.68	(0.93 - 3.04)		
Age at diagnosis Z												
(per year increase)	0.92	(0.90 - 0.94)	0.93	(0.91 - 0.95)	0.91	(0.89 - 0.93)	0.91	(0.89 - 0.93)	0.94	(0.91 - 0.97)	0.95	(0.92 - 0.99)
Body Mass Index												
(per kg/m^2 increase)	1.01	(0.98 - 1.05)			1.06	(1.01 - 1.11)	1.07	(1.01 - 1.12)	0.98	(0.92 - 1.04)		
Weighted Charlson Comorbidity Index												
0	ref.		ref.		ref.		ref.		ref.		ref.	
1	0.56	(0.40 - 0.80)	0.71	(0.48 - 1.04)	0.65	(0.41 - 1.01)	0.74	(0.45 - 1.20)	0.51	(0.27 - 0.96)	0.55	(0.29 - 1.07)
2 or more	0.37	(0.23 - 0.60)	0.52	(0.31 - 0.88)	0.49	(0.27 - 0.90)	0.62	(0.32 - 1.19)	0.24	(0.10 - 0.56)	0.32	(0.13 - 0.77)
Performance status												
ECOG 0	ref.				ref.				ref.			
ECOG 1	1.04	(0.70 - 1.56)			1.22	(0.74 - 1.98)			0.86	(0.45 - 1.66)		
Renal function (eGFR)												
(per mL/min/1.73 m^2 increase)	1.02	(1.01 - 1.03)	1.00	(0.99 - 1.02)	1.01	(1.00 - 1.03)	1.00	(0.98 - 1.01)	1.03	(1.01 - 1.05)	1.02	(0.99 - 1.04)
Socio-economic status (SES)												
Low	ref.				ref.				ref.			
Middle	1.02	(0.71 - 1.47)			1.00	(0.62 - 1.60)			1.30	(0.69 - 2.45)		
High	1.23	(0.84 - 1.80)			1.24	(0.75 - 2.03)			1.35	(0.69 - 2.65)		
Disease stage (cTNM)												
cT2N0/xM0/x	ref.		ref.									
cT3-4aN0/xM0/x	3.49	(2.54 - 4.80)	3.33	(2.36 - 4.71)								

Table 2. Continued.

	All disease stages (cT2-4a)		cT2-disease only		cT3-4a disease only	
	Univariable model	Multivariable model	Univariable model	Multivariable model	Univariable model	Multivariable model
Tumor histology						
Urothelial carcinoma	ref.		ref.		ref.	
Squamous cell carcinoma	-		-		-	
Adenocarcinoma	-		-		-	
Small cell carcinoma	1.58 (0.48 - 5.24)		1.92 (0.53 - 6.89)		-	
Other	-		-		-	
Hospital of MDTM						
Community hospital	ref.		ref.		ref.	
Non-university referral hospital	1.04 (0.75 - 1.45)		1.01 (0.67 - 1.52)		0.96 (0.50 - 1.85)	
University hospital	1.06 (0.68 - 1.64)		1.01 (0.55 - 1.87)		0.54 (0.27 - 1.12)	

NAC: neoadjuvant chemotherapy; ECOG: Eastern Cooperative Oncology Group; eGFR: estimated glomerular filtration rate; MDTM: multidisciplinary team meeting The multivariable model for all disease stages included gender, age at diagnosis, weighted Charlson Comorbidity Index, renal function and disease stage. The multivariable model for cT2-stage included age, BMI, weighted Charlson Comorbidity Index and renal function. The multivariable model for cT3-4a stage included age, weighted Charlson Comorbidity Index and renal function.

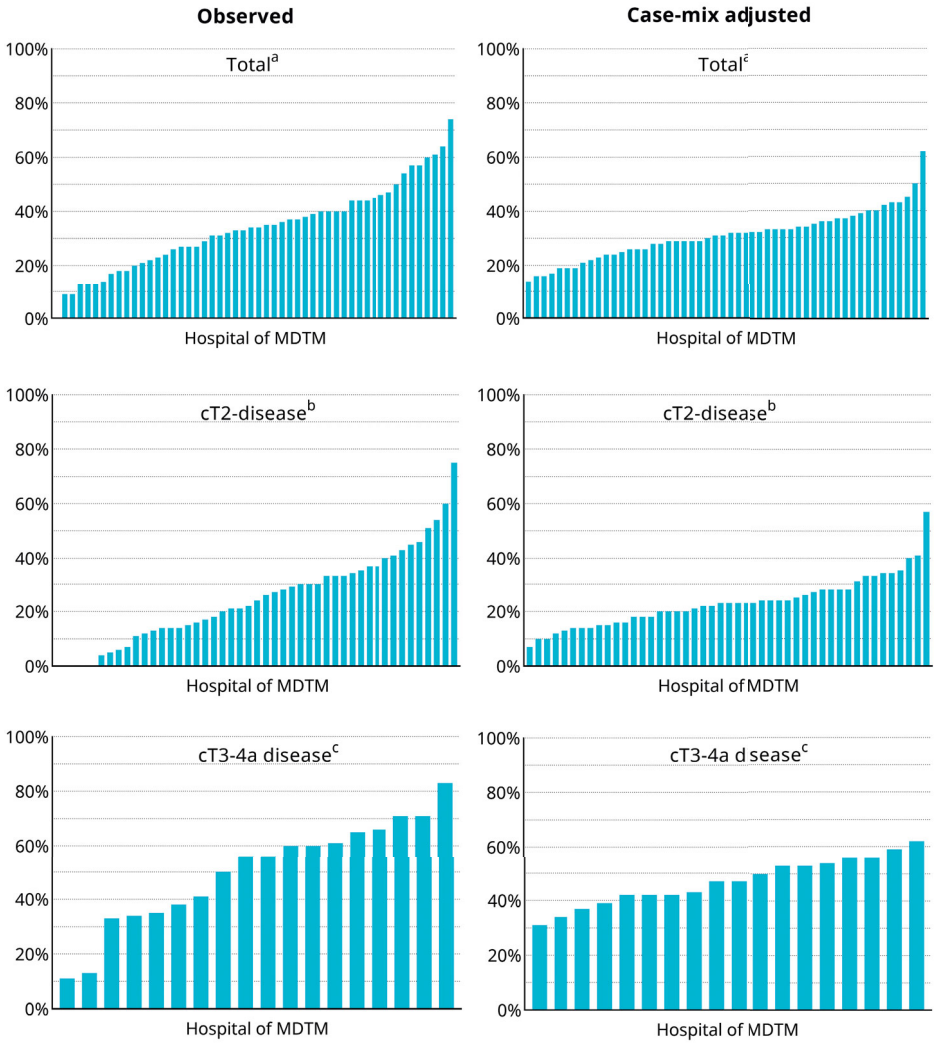

Figure 1. The probability of platinum-eligible patients to receive NAC per hospital* overall, for cT2-disease only and for cT3-4a disease only, observed and adjusted for case-mix factors.

NAC: neoadjuvant chemotherapy; MDTM: multidisciplinary team meeting
**Hospitals with <5 cases were excluded from analysis.*
a: the multilevel model for all disease stages (cT2-4a) included: age at diagnosis, comorbidity and disease stage, based on 52 hospitals;
b: the multilevel model for cT2-disease only included: age at diagnosis and BMI, based on 47 hospitals;
c: the multilevel model for cT3-4a disease only included: age at diagnosis and comorbidity, based on 18 hospitals.

DISCUSSION

In this nationwide, population-based study, we evaluated guideline adherence and variation in the recommended use of neoadjuvant chemotherapy preceding radical cystectomy as curative treatment for MIBC. We found that guideline adherence was fairly low, i.e., only 26% for cT2- and 55% for cT3-4a disease. Factors associated with NAC were age at diagnosis, comorbidity and disease stage. Large interhospital variation in NAC use was observed, especially for patients with cT2-disease, for whom 2-year overall survival appeared to be better for those diagnosed in hospitals with high probability of administering NAC compared to hospitals with a low probability.

This study showed that the minority of platinum-eligible patients actually received NAC. Reasons to abstain from NAC, as noted in the medical files, were among others the patients' preference, limited expected survival gain, patients' age and functional status, and presence of hearing loss. These patients, except for ten, also did not receive any adjuvant chemotherapy (data not shown). Although for two-thirds of patients no reason was documented for not receiving NAC, these results indicate there are more factors in play than those considered in the eligibility criteria alone.

Patients with younger age, no comorbid conditions and/or cT3/cT4a bladder cancer received NAC more often, which was expected and is in line with previous studies[6,14]. Patients who underwent upfront RC had lower renal function compared to patients treated with NAC + RC, but we anticipated an even lower mean renal function for patients undergoing upfront RC. It is likely that patients with pre-existing renal insufficiency also suffer from (higher) comorbidity, and were, therefore, precluded from NAC and did not even undergo RC at all. Despite being eligible, age remained statistically significant in our multivariable regression analysis after correction for renal function, comorbidity and disease stage, indicating that older patients are less often offered NAC or may decline NAC more often compared to younger patients. Multiple studies, reviews and even international guidelines state that, next to patient preferences, not chronological but biological age (i.e., organ function, comorbidity, frailty and functional status) should be taken into account in treatment decision-making[1,15,16].Therefore, it might be unjustified that chronological age plays such a prominent role in clinical practice.

We observed low and varying guideline adherence between hospitals. This is in agreement with previous studies demonstrating low NAC utilization rates in cisplatin-eligible patients, varying from 12 to 31%[8,17,18]. Substantial variation remained after

case-mix adjustment, especially for patients with cT2-disease (7-57%), indicating that hospital/doctor factors likely play a role in the use of NAC. An explanation would be that hospitals follow their own institutional and/or regional guideline agreements in addition to the European guidelines. Within our BlaZIB study, a survey was conducted among urologists regarding institutional NAC-practice patterns. The survey revealed that, although recommended in international guidelines, 9 out of 70 included hospitals do not offer NAC to patients with cT2-disease by default, possibly due to the limited survival benefit of NAC for cT2-disease shown in several studies. In fact, the meta-analyses on which the recommendation concerning NAC was based, included two large RCTs, i.e. the Nordic Cystectomy Trials I and II[19,20], that failed to show survival benefit in favor of NAC for cT2N0M0 compared to cT3-4aN0M0 bladder cancer. Two other trials, i.e., the MRC/EORTC trial and trial BA06-30894, did not perform stage-specific analyses[21,22]. A US study comparing real-world data of 8,732 patients with cT2-4aN0M0 bladder cancer who underwent RC between 2004 and 2012 to the results of the SWOG-8710 trial found no survival advantage of NAC either[23]. The authors attributed their findings to important differences between baseline characteristics of patients in clinical studies and those treated in general clinical practice. It is likely that utilization and efficacy of NAC are lower in real life compared to clinical studies. In that case, patients might experience no beneficial or even worse outcomes compared to patients undergoing upfront RC, since time to RC is prolonged when administering NAC. Further research is recommended to address the real-life efficacy of NAC in patients with cT2-disease.

For patients with cT3-4a disease, case-mix adjusted interhospital variation was slightly smaller. Nevertheless, our results suggest there is room for improvement regarding the use and guideline adherence of NAC in these patients. The attitude of physicians towards NAC is fundamental for its use, as believers in NAC are more likely to recommend NAC[24], and patients tend to follow recommendations from their doctor[25].

The large interhospital variation in NAC use did not significantly impact overall survival. However, there appears to be a trend in favor of hospitals with higher probability of administering NAC. For both cT2 and cT3-4a disease, these hospitals appeared to perform better regarding survival compared to hospitals with low probability, regardless of whether patients actually received NAC. This finding suggests factors other than NAC itself are important. Hospitals with higher NAC probability might have higher patient volumes, more surgical experience and more expertise on bladder cancer, resulting in better patient selection for specific treatment and better surgical outcomes affecting survival. Hospitals with the

highest probability of administering NAC indeed appear to have a slightly higher patient volume (data not shown), but more research is needed to elucidate the underlying mechanisms.

In this study, we provided detailed insight into the variation in NAC use, the factors associated with receiving NAC, and whether patient outcomes were better if patients were diagnosed in hospitals that are more inclined to give NAC compared to more hesitant hospitals, taking eligibility into account. However, the observational study design has to be recognized as a limitation. Missing values, often arising from poor documentation in the electronic medical files, are inherent to this design and were addressed by employing imputation. To check the robustness of our results after imputation on performance status, we performed a sensitivity analyses repeating our analyses; once assuming that all patients with missing performance status have an ECOG score of 0 and once assuming they have an ECOG score of 3 as this will affect the number of patients considered eligible. Our results remained fairly similar, indicating that our analysis were likely to be robust (data not shown). If patients abstained from NAC, underlying reasons were poorly documented. Eligible patients who did not undergo NAC may have declined NAC owing to poor quality of life or other personal reasons, but we would not expect such a large difference in patients' preferences between hospitals to fully explain the variation remaining after case-mix adjustment. We selected all patients who underwent RC, which might have led to underestimation of current guideline adherence since we could have missed patients who received NAC, but did not continue to RC. Our survival analyses might be prone to immortal time bias, but since patients planning to undergo RC are generally quite fit, we estimate the effect to be minimal. Also, using date of RC instead of date of diagnosis did not alter our results significantly (data not shown). Shortly after the end of the inclusion period of our study the COVID-19 pandemic emerged, disrupting regular health care. The COVID-pandemic might have affected NAC use, since use of (neoadjuvant) chemotherapy was temporarily discouraged due to potential immunosuppressive effects. To evaluate the use of NAC in more recent years post-COVID, the current study may be repeated in a few years.

In conclusion, guideline adherence regarding the recommended use of NAC is low and interhospital variation is large, especially in cT2 bladder cancer. Patients diagnosed in hospitals more likely to give NAC appear to have better case-mix adjusted survival compared to patients in hospitals with low probability, although the reported associations were not statistically significant. The underlying mechanism for this is currently unknown, further research is warranted to provide more insight. Guideline adherence in cT3-4a disease is better, but could be improved, especially

as for these patients literature is consistent concerning the beneficial effect of NAC. Raising awareness amongst physicians may lead to more consistent NAC utilization between hospitals, prevent over- and undertreatment with NAC, and potentially enhance quality of life and oncological outcomes such as survival.

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The members of the BlaZIB study group are: Katja K.H. Aben, PhD (PI, Netherlands Comprehensive Cancer Organisation); Lambertus A. Kiemeney, PhD, Prof (PI, Radboud University Medical Centre); J. Alfred Witjes, MD, PhD, Prof (PI, Radboud University Medical Centre); Lisa M.C. van Hoogstraten, MSc (project coordinator, Netherlands Comprehensive Cancer Organisation); Theodora M. Ripping, PhD (researcher, Netherlands Comprehensive Cancer Organisation); Joost L. Boormans, MD, PhD (Erasmus Medical Centre); Catharina A. Goossens-Laan, MD, PhD (Alrijne Hospital); Antoine G. van der Heijden, MD, PhD (Radboud University Medical Centre); Michiel S. van der Heijden, MD, PhD (Netherlands Cancer Institute); Sipke Helder (Patient association 'Leven met blaas- of nierkanker'); Tom J.N. Hermans, MD, PhD (VieCuri Medical Centre); Maarten C.C.M. Hulshof, MD, PhD (Amsterdam University Medical Centres, location AMC); Anna M. Leliveld, MD, PhD (University Medical Centre Groningen); Geert J.L.H. van Leenders, MD, PhD, Prof (Erasmus Medical Centre); Richard P. Meijer, MD, PhD, FEBU (University Medical Centre Utrecht); Reindert J.A. van Moorselaar, MD, PhD, Prof (Amsterdam University Medical Centres, location VUmc); Sasja F. Mulder, MD, PhD (Radboud University Medical Centre); Juus L. Noteboom, MD, PhD (University Medical Centre Utrecht); Jorg R. Oddens, MD, PhD (Amsterdam University Medical Centres, location AMC); Theo M. de Reijke, MD, PhD (Amsterdam University Medical Centres, location University of Amsterdam, department of Urology); Bas W.G. van Rhijn, MD, PhD, FEBU (Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital); Joep G.H. van Roermund, MD, PhD (Maastricht University Medical Centre); Tineke J. Smilde, MD, PhD (Jeroen Bosch Hospital); Guus W.J. Venderbosch (Patient association 'Leven met blaas- of nierkanker'); Bart P. Wijsman, MD, PhD (Elisabeth-TweeSteden Ziekenhuis).

AUTHOR CONTRIBUTION

LMCvH: conceptualization, data analysis, data curation, manuscript writing/editing; CCOM: data analysis, manuscript writing/editing; JAW: conceptualization, manuscript writing/editing, funding acquisition; RPM: manuscript writing/editing; SFM: manuscript writing/editing; TJS: manuscript writing/editing; TMR: conceptualization, manuscript writing/editing; BlaZIB study group: manuscript writing/editing; LAK: conceptualization, manuscript writing/editing, funding acquisition; KKHA: conceptualization, manuscript writing/editing, funding acquisition.

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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).

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose

ETHICAL APPROVAL

This study was approved by the Privacy Review Board of the NCR (reference number K20.212). The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

CONSENT

The requirement for informed consent was waived due to the retrospective study design.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Detailed description of the variables included in this study.

Variables in the Netherlands Cancer Registry (NCR)	
Gender	Male or female
Age at diagnosis	Categorized into <60 years, 60-70 years, 70-80 years and ≥80 years
Socio-economic status	Derived from statistics Netherlands (CBS) based on the patients' full six-digit postal code and categorized into low, middle and high
Disease stage	Defined according to the 8th edition of the tumour, node and metastasis (TNM) classification[1]. Clinical staging was based on physical examination, findings at cystoscopy and TURBT, computed tomography (CT-)scan of the abdomen/pelvis and chest imaging (at least a chest X-ray)
Tumor histology	Defined according to the International Classification of Diseases for Oncology[2] and categorized into urothelial carcinoma, squamous cell carcinoma, adenocarcinoma and other
Treatment type, start and end date	Categorized into neoadjuvant chemotherapy (NAC) + radical cystectomy (RC) or upfront RC. NAC was defined as any systemic chemotherapy administered after bladder cancer diagnosis and before RC
Type of hospital	Categorized into community, non-university referral and university hospital
Vital status and date of death	Obtained through annual linkage with the Personal Records Database
Additional variables in the BlaZIB study	
Performance status	Defined according to the Eastern Cooperative Oncology Group (ECOG) performance score[3]
Comorbidity	Defined according to the 1987 weighted Charlson Comorbidity Index (CCI) score[4] and categorized into 0, 1 and 2 or more
Renal function	Presented as the estimated glomerular filtration rate (eGFR) in mL/min/1.73 m^2, measured before first systemic treatment
Body mass index	Defined as kg/m^2, categorized into underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2) and obese (≥30.0 kg/m^2)

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Supplementary Table 2. Patient and tumor characteristics of all patients diagnosed with non-metastatic muscle-invasive bladder cancer who underwent radical cystectomy, stratified by use of neoadjuvant chemotherapy.

	All patients (n=1025)		Upfront RC (n=725)		NAC + RC (n=300)	
	n	(%)	n	(%)	n	(%)
Gender						
Male	738	(72.0%)	534	(73.7%)	204	(68.0%)
Female	287	(28.0%)	191	(26.3%)	96	(32.0%)
Age at diagnosis (median, IQR)	70.0	(63.0-75.0)	71.0	(66.0-76.0)	65.0	(58.0-70.0)
Age at diagnosis						
<60 years	164	(16.0%)	76	(10.5%)	88	(29.3%)
60-70 years	326	(31.8%)	199	(27.4%)	127	(42.3%)
70-80 years	457	(44.6%)	372	(51.3%)	85	(28.3%)
≥80 years	78	(7.6%)	78	(10.8%)	0	(0.0%)
Body Mass Index (BMI) (median, IQR)	26.2	(23.7-29.1)	26.2	(23.7-29.0)	26.0	(23.7-29.1)
(Missing %)		(5.0%)		(4.4%)		(6.3%)
Body Mass Index (BMI)						
Underweight (<18.5)	15	(1.5%)	12	(1.7%)	3	(1.0%)
Normal weight (18.5-24.9)	366	(35.7%)	254	(35.0%)	112	(37.3%)
Overweight (25.0-29.9)	424	(41.4%)	313	(43.2%)	111	(37.0%)
Obese (≥30.0)	169	(16.5%)	114	(15.7%)	55	(18.3%)
Unknown	51	(5.0%)	32	(4.4%)	19	(6.3%)
Weighted Charlson Comorbidity Index (CCI)						
0	474	(46.2%)	295	(40.7%)	179	(59.7%)
1	271	(26.4%)	205	(28.3%)	66	(22.0%)
2 or more	215	(21.0%)	186	(25.7%)	29	(9.7%)
Unknown	65	(6.3%)	39	(5.4%)	26	(8.7%)
Performance status (ECOG)						
ECOG 0	439	(42.8%)	265	(36.6%)	174	(58.0%)
ECOG 1	192	(18.7%)	117	(16.1%)	75	(25.0%)
ECOG 2	16	(1.6%)	13	(1.8%)	3	(1.0%)
ECOG 3 or higher	4	(0.4%)	4	(0.6%)	0	(0.0%)
Unknown	374	(36.5%)	326	(45.0%)	48	(16.0%)
Renal function (eGFR) (median, IQR)	69.0	(56.0-85.0)	67.0	(51.0-83.0)	76.0	(62.0-89.0)
(Missing %)		(10.3%)		(13.8%)		(2.0%)
Renal function (eGFR)						
≥50 mL/min/1.73 m^2	760	(74.1%)	485	(66.9%)	275	(91.7%)
30-50 mL/min/1.73 m^2	137	(13.4%)	118	(16.3%)	19	(6.3%)
<30 mL/min/1.73 m^2	22	(2.1%)	22	(3.0%)	0	(0.0%)
Unknown	106	(10.3%)	100	(13.8%)	6	(2.0%)
Socioeconomic status (SES)						
Low	275	(26.8%)	201	(27.7%)	74	(24.7%)
Middle	434	(42.3%)	310	(42.8%)	124	(41.3%)
High	316	(30.8%)	214	(29.5%)	102	(34.0%)

Supplementary Table 2. Continued.

	All patients (n=1025)		Upfront RC (n=725)		NAC + RC (n=300)	
	n	(%)	n	(%)	n	(%)
Disease stage (cTNM)						
cT2N0/xM0/x	709	(69.2%)	552	(76.1%)	157	(52.3%)
cT3N0/xM0/x	263	(25.7%)	148	(20.4%)	115	(38.3%)
cT4aN0/xM0/x	53	(5.2%)	25	(3.4%)	28	(9.3%)
Tumor histology						
Urothelial carcinoma	988	(96.4%)	694	(95.7%)	294	(98.0%)
Squamous cell carcinoma	15	(1.5%)	14	(1.9%)	1	(0.3%)
Adenocarcinoma	1	(0.1%)	1	(0.1%)	0	(0.0%)
Small cell carcinoma	15	(1.5%)	10	(1.4%)	5	(1.7%)
Other	6	(0.6%)	6	(0.8%)	0	(0.0%)
Platinum-eligibility*						
Not eligible	26	(2.5%)	26	(3.6%)	0	(0.0%)
Eligible	484	(47.2%)	254	(35.0%)	230	(76.7%)
Potentially eligible	97	(9.5%)	81	(11.2%)	16	(5.3%)
Unknown	418	(40.8%)	364	(50.2%)	54	(18.0%)
Chemotherapeutic agent NAC						
Cisplatin-based**	-		-		277	(92.3%)
Carboplatin-based	-		-		21	(7.0%)
Other	-		-		2	(0.7%)
Hospital of MDTM						
Community hospital	309	(30.1%)	217	(29.9%)	92	(30.7%)
Non-university referral hospital	543	(53.0%)	385	(53.1%)	158	(52.7%)
University hospital	173	(16.9%)	123	(17.0%)	50	(16.7%)

RC: radical cystectomy; NAC: neoadjuvant chemotherapy; IQR: interquartile range; ECOG: Eastern Cooperative Oncology Group; eGFR: estimated glomerular filtration rate; MDTM: multidisciplinary team meeting

** Patients were considered platinum-ineligible if they had eGFR <30 mL/min/1.73 m^2 and/or ECOG ≥3. Patients were considered platinum-eligible in case of eGFR ≥50 mL/min/1.73 m^2 and ECOG 0-1. We considered patients with eGFR 30-50 mL/min/1.73 m^2 and ECOG 0-2 potentially eligible.*

***n=13 patients later switched from cisplatin to carboplatin.*

Supplementary Table 3. Uni- and multivariable logistic regression analysis on the association between patient, tumor and hospital characteristics and receiving NAC, in platinum-eligible patients and patients with potential eligibility* diagnosed with non-metastatic muscle-invasive bladder cancer who underwent radical cystectomy.

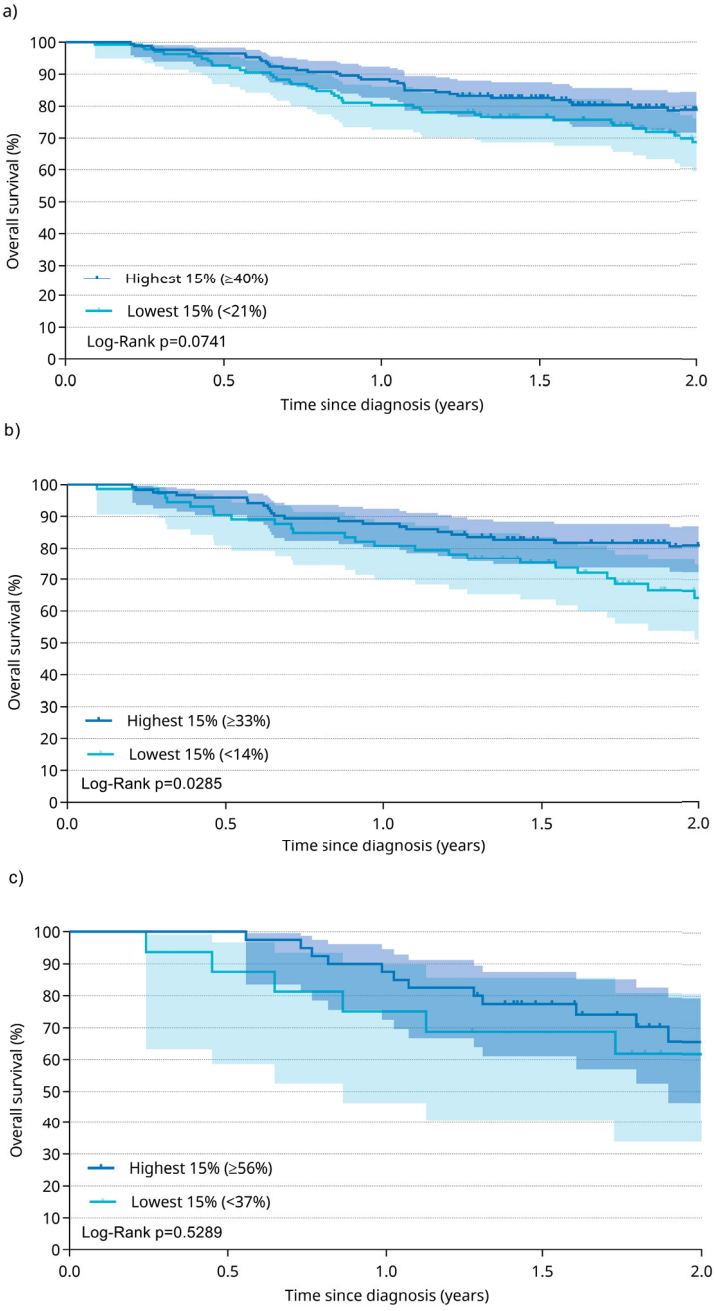
	Total				cT2-disease only				cT3-4a disease only			
	Univariable model		Multivariable model		Univariable model		Multivariable model		Univariable model		Multivariable model	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Gender												
Male	ref.		ref.		ref.		ref.		ref.			
Female	1.39	(1.03 - 1.87)	1.19	(0.85 - 1.66)	1.49	(1.01 - 2.20)	1.43	(0.94 - 2.18)	1.16	(0.71 - 1.91)		
Age at diagnosis												
(per year increase)	0.92	(0.90 - 0.93)	0.93	(0.91 - 0.95)	0.91	(0.89 - 0.93)	0.92	(0.90 - 0.94)	0.93	(0.91 - 0.96)	0.96	(0.93 - 0.99)
Body Mass Index												
(per kg/m^2 increase)	1.01	(0.97 - 1.04)			1.05	(1.00 - 1.10)	1.07	(1.01 - 1.12)	0.97	(0.92 - 1.03)		
Weighted Charlson Comorbidity Index												
0	ref.		ref.		ref.		ref.		ref.		ref.	
1	0.54	(0.39 - 0.75)	0.66	(0.46 - 0.94)	0.64	(0.41 - 0.98)	0.72	(0.45 - 1.15)	0.42	(0.24 - 0.74)	0.51	
2 or more	0.28	(0.18 - 0.44)	0.42	(0.26 - 0.68)	0.37	(0.21 - 0.65)	0.50	(0.27 - 0.90)	0.19	(0.09 - 0.41)	0.28	(0.12 - 0.62)
Performance status												
ECOG 0	ref.				ref.				ref.			
ECOG 1	0.99	(0.68 - 1.42)			1.14	(0.72 - 1.81)			0.81	(0.46 - 1.40)		
ECOG 2	0.33	(0.10 - 1.11)			0.46	(0.10 - 2.08)			0.19	(0.02 - 1.70)		
Renal function (eGFR)												
per mL/min/1.73 m^2 increase)	1.03	(1.02 - 1.03)	1.02	(1.01 - 1.03)	1.02	(1.01 - 1.03)	1.01	(1.00 - 1.02)	1.03	(1.02 - 1.05)	1.03	(1.01 - 1.04)
Socio-economic status (SES)												
Low	ref.				ref.				ref.			
Middle	1.12	(0.80 - 1.58)			1.09	(0.69 - 1.71)			1.36	(0.79 - 2.36)		
High	1.31	(0.92 - 1.88)			1.31	(0.82 - 2.10)			1.53	(0.85 - 2.75)		
Disease stage (cTNM)												
cT2N0/xM0/x	ref.		ref.									
cT3-4aN0/xM0/x	3.03	(2.27 - 4.04)	3.10	(2.26 - 4.26)								

Supplementary Table 3. Continued.

	Total				cT2-disease only				cT3-4a disease only			
	Univariable model		Multivariable model		Univariable model		Multivariable model		Univariable model		Multivariable model	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Tumor histology												
Urothelial carcinoma	ref.				ref.				ref.			
Squamous cell carcinoma	0.38	(0.05 - 3.16)			-				0.35	(0.04 - 3.43)		
Adenocarcinoma	-				-				-			
Small cell carcinoma	1.62	(0.51 - 5.16)			2.26	(0.63 - 8.12)			1.06	(0.07 - 17.06)		
Other	-				-				-			
Hospital of MDTM												
Community hospital	ref.				ref.				ref.			
Non-university referral hospital	0.96	(0.71 - 1.31)			0.92	(0.62 - 1.35)			0.90	(0.52 - 1.57)		
University hospital	0.97	(0.64 - 1.47)			0.85	(0.47 - 1.55)			0.65	(0.34 - 1.24)		

OR: odds ratio; 95% CI: 95% confidence interval; NAC: neoadjuvant chemotherapy; ECOG: Eastern Cooperative Oncology Group; eGFR: estimated glomerular filtration rate; MDTM: multidisciplinary team meeting

** Patients were considered platinum-eligible in case of eGFR ≥50 mL/min/1.73 m^2 and ECOG 0-1. We considered patients with eGFR 30-50 mL/min/1.73 m^2 and ECOG 0-2 potentially eligible.*



Supplementary Figure 1. Unadjusted overall survival of platinum-eligible patients with non-metastatic MIBC who underwent radical cystectomy, diagnosed in hospitals with a high versus low hospital-specific probability to receive NAC overall (a), for cT2-stage only (b) and for cT3-4a stage only (c).

Supplementary Table 4. Case-mix adjusted Cox Proportional Hazards regression analyses on the association between the hospital-specific probabilities of administering NAC and overall survival, in platinum-eligible patients and patients with potential eligibility* diagnosed with non-metastatic muscle-invasive bladder cancer who underwent radical cystectomy.

		Eligible patients		Eligible and potentially eligible patients	
		HR	95% CI	HR	95% CI
Total[1]	**Hospital-specific probability to administer NAC** (continuous)	0.99	(0.98 - 1.00)	0.99	(0.98 - 1.00)
	Hospital-specific probability to administer NAC Lowest 15% (<21%)	Ref.		Ref.	
	Highest 15% (≥40%)	0.69	(0.44 - 1.09)	0.71	(0.48 - 1.07)
cT2-disease[2]	**Hospital-specific probability to administer NAC** (continuous)	0.99	(0.97 - 1.00)	0.99	(0.98 - 1.01)
	Hospital-specific probability to administer NAC Lowest 15% (<14%)	Ref.		Ref.	
	Highest 15% (≥33%)	0.59	(0.33 - 1.05)	0.70	(0.42 - 1.17)
cT3-4a disease[3]	**Hospital-specific probability to administer NAC** (continuous)	1.00	(0.96 - 1.03)	0.99	(0.96 - 1.02)
	Hospital-specific probability to administer NAC Lowest 15% (<37%)	Ref.		Ref.	
	Highest 15% (≥56%)	0.71	(0.25 - 2.04)	0.52	(0.24 - 1.15)

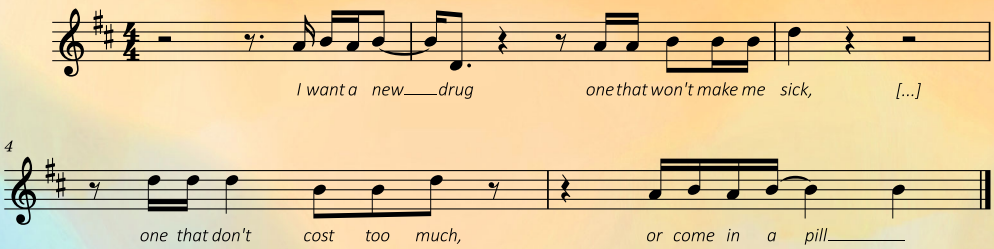
HR: hazard ratio; 95% CI: 95% confidence interval

** Patients were considered platinum-eligible in case of eGFR ≥50 mL/min/1.73 m² and ECOG 0-1. We considered patients with eGFR 30-50 mL/min/1.73 m² and ECOG 0-2 potentially eligible.*

[1] Adjusted for age at diagnosis, comorbidity and disease stage

[2] Adjusted for age at diagnosis and BMI

[3] Adjusted for age at diagnosis and comorbidity



Adapted from: I want a new drug - Huey Lewis & the News (1983)

4

Concurrent chemoradiation for muscle-invasive bladder cancer using 5-fluorouracil versus capecitabine: a nationwide cohort study

Amy de Haar-Holleman*, Lisa M.C. van Hoogstraten*, Maarten C.C.M. Hulshof, Metin Tascilar, Katharina Brück, BlaZIB study group, Richard P. Meijer, J. Alfred Witjes, Lambertus A. Kiemeney, Katja K.H. Aben

*Shared first authorship

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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.

Conclusion

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.

INTRODUCTION

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, 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) (Figure 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 Figure 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 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 (Figure 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 country. 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%).

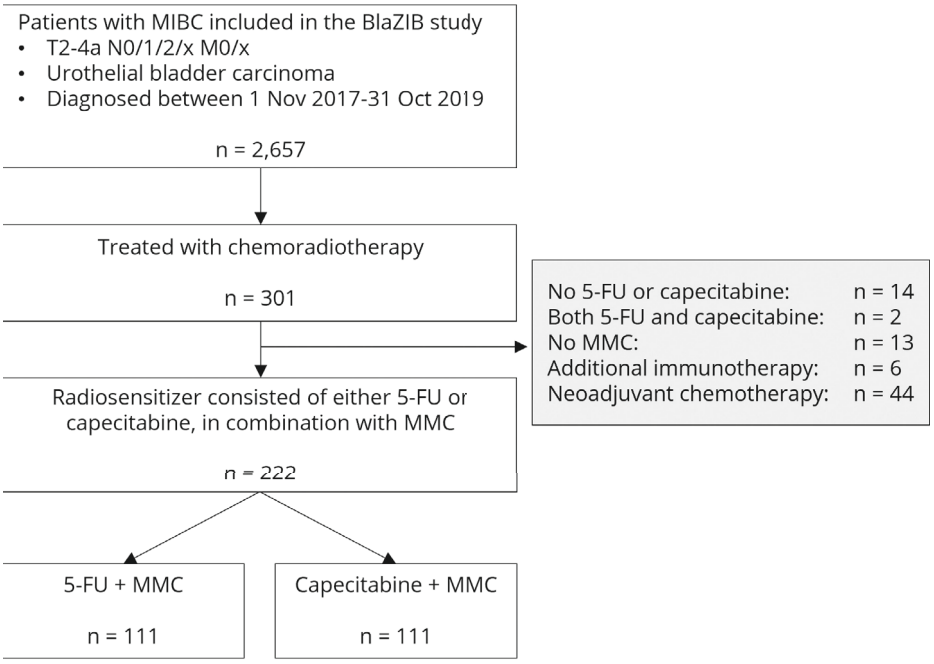


Figure 1. Flowchart describing the inclusion of patients in the study cohort.

5-FU: 5-Fluorouracil; MMC: Mitomycin C

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%)		

Table 1. Continued.

	Total		5-FU+MMC		Capecitabine+MMC		Standardized difference	
	n	(%)	n	(%)	n	(%)	Before IPTW	After IPTW
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
<18.5	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

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
	n	(%)	n	(%)	n	(%)	
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 α/β_{10} ≥70)	207	(93.2%)	102	(91.9%)	105	(94.6%)	
No (BED α/β_{10} <70)	7	(3.2%)	5	(4.5%)	2	(1.8%)	
Unknown	8	(3.6%)	4	(3.6%)	4	(3.6%)	
BED α/β_{10} <70: Dose actually administered?							-
Yes	7	(100.0%)	5	(100.0%)	2	(100.0%)	
Not documented	0		0		0		
BED α/β_{10} ≥ 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							**<.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%)	

Table 2. Continued.

	All patients (n=222)		5-FU + MMC (n=111)		Capecitabine + MMC (n=111)		P-value
	n	(%)	n	(%)	n	(%)	
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)	**<.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)	**<.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 ≥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).*

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 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, Figure 2a). Likewise, no significant difference in DFS was observed (50% versus 56%, p = 0.50, Figure 2b). After CRT treatment, 4 patients from the 5-FU based group (4%) and 8 from the capecitabine-based group (7%) eventually

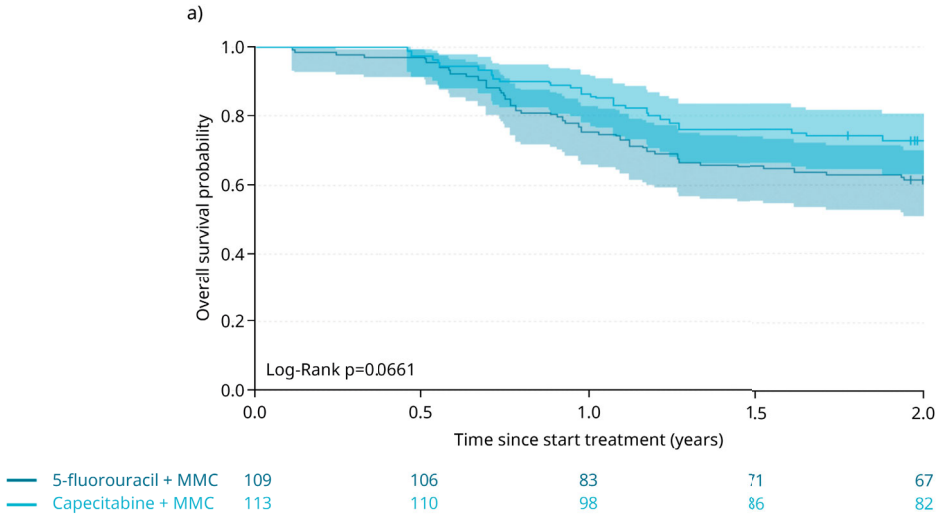
proceeded to radical cystectomy. Also, 9 patients (8%) from both groups received systemic chemo- or immunotherapy after CRT. Two (2%) and one (1%) patient(s) from the 5-FU based versus capecitabine- based group received radiotherapy after CRT due to progression of the disease, respectively.

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 (Figure 3).

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 (p<0.05).*



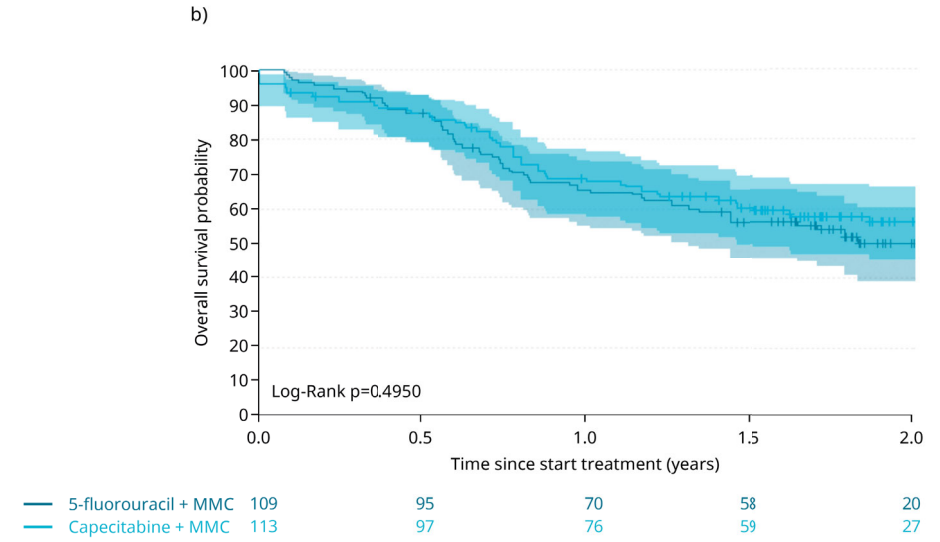


Figure 2. IPTW-adjusted overall survival (a) and locoregional disease free survival (b) since start of chemoradiotherapy treatment of patients with cT2-T4a N0/1/2/x M0/x bladder cancer.

IPTW: Inverse Probability Treatment Weighting; MMC: Mitomycin C

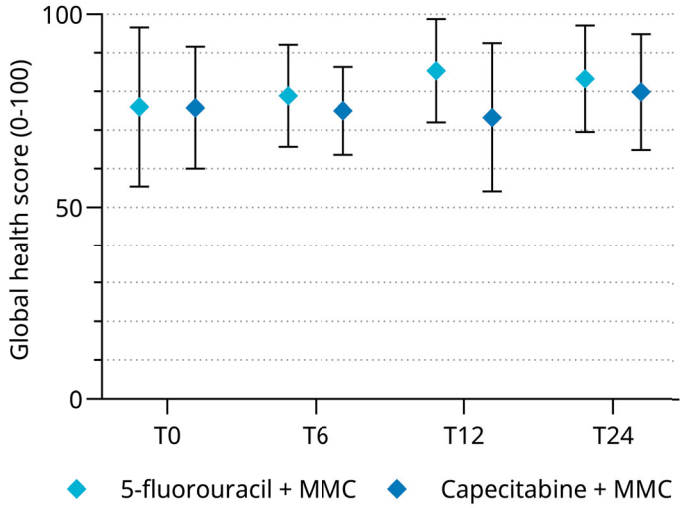


Figure 3. EORTC-QLQ-C30 global health score (mean +/- SD) over time of patients with cT2-T4a N0/1/2/x M0/x bladder cancer treated with chemoradiotherapy, stratified by type of chemotherapeutic agent.

MMC: Mitomycin C; SD: Standard Deviation

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. 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.

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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The members of the BlaZIB study group are: Katja K.H. Aben, PhD (PI, Netherlands Comprehensive Cancer Organisation); Lambertus A. Kiemeney, PhD, Prof (PI, Radboud University Medical Centre); J. Alfred Witjes, MD, PhD, Prof (PI, Radboud University Medical Centre); Lisa M.C. van Hoogstraten, MSc (project coordinator, Netherlands Comprehensive Cancer Organisation); Theodora M. Ripping, PhD (researcher, Netherlands Comprehensive Cancer Organisation); Joost Boormans, MD, PhD (Erasmus Medical Centre); Catharina A. Goossens-Laan, MD, PhD (Alrijne Hospital); Antoine G. van der Heijden, MD, PhD (Radboud University Medical Centre); Michiel S. van der Heijden, MD, PhD (Netherlands Cancer Institute); Sipke Helder (Patient association 'Leven met blaas- of nierkanker'); Tom J.N. Hermans, MD, PhD (VieCuri Medical Centre); Maarten C.C.M. Hulshof, MD, PhD (Amsterdam University Medical Centres, location AMC); Anna M. Leliveld, MD, PhD (University Medical Centre Groningen); Geert J.L.H. van Leenders, MD, PhD (Erasmus Medical Centre); Richard P. Meijer, MD, PhD, FEBU (University Medical Centre Utrecht); Reindert J.A. van Moorselaar, MD, PhD, Prof (Amsterdam University Medical Centres, location VUmc); Sasja F. Mulder, MD, PhD (Radboud University Medical Centre); Juus L.

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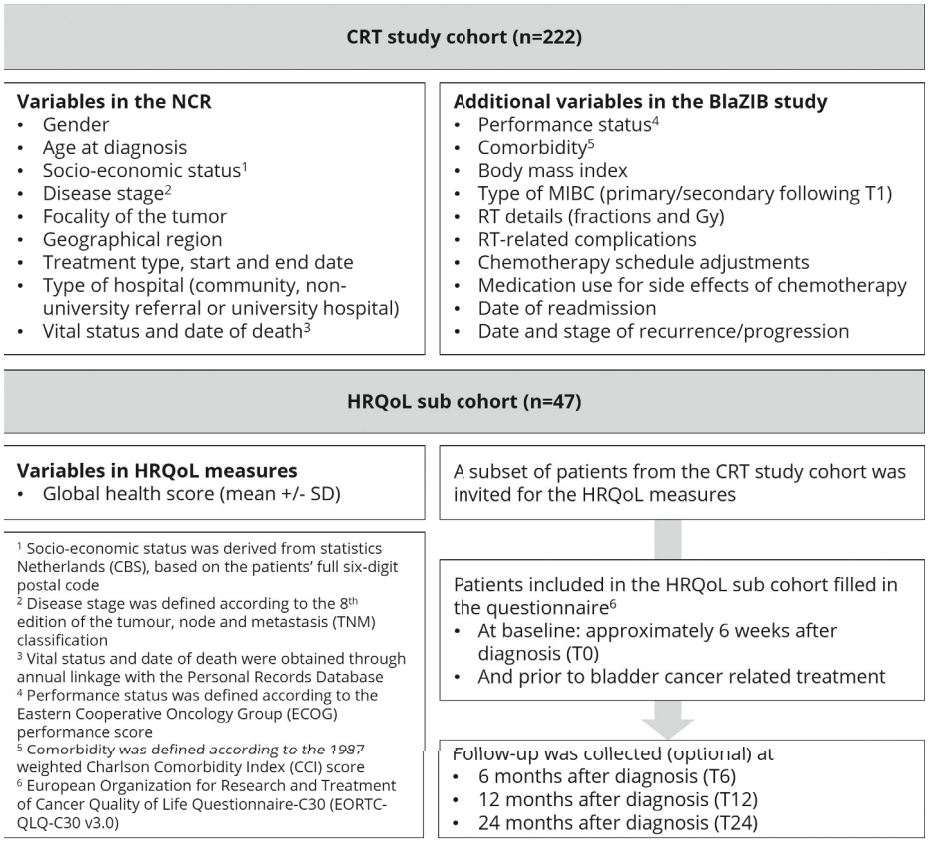
SUPPLEMENTARY MATERIAL



Supplementary Figure 1. Variables available per cohort.

Supplementary 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 (not imputed).

	All patients (n=222)		5-FU + MMC (n=111)		Capecitabine + MMC (n=111)	
	n	(%)	n	(%)	n	(%)
Gender						
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)
Age at diagnosis						
<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)						
ECOG 0	97	(43.7%)	43	(38.7%)	54	(48.6%)
ECOG 1	72	(32.4%)	39	(35.1%)	33	(29.7%)
ECOG 2 or higher	18	(8.1%)	10	(9.0%)	8	(7.2%)
Unknown	35	(15.8%)	19	(17.1%)	16	(14.4%)
Weighted Charlson Comorbidity Index						
0	80	(36.0%)	38	(34.2%)	42	(37.8%)
1	57	(25.7%)	29	(26.1%)	28	(25.2%)
2 or more	72	(32.4%)	41	(36.9%)	31	(27.9%)
Unknown	13	(5.9%)	3	(2.7%)	10	(9.0%)
Body Mass Index (BMI) (median, IQR)	26.5	(24.0-29.7)	26.6	(24.1-30.0)	26.3	(23.8-29.7)
Body Mass Index (BMI)						
<18.5 (underweight)	2	(0.9%)	0	(0.0%)	2	(1.8%)
18.5-25 (normal weight)	78	(35.1%)	38	(34.2%)	40	(36.0%)
25-30 (overweight)	83	(37.4%)	43	(38.7%)	40	(36.0%)
≥30 (obesity)	51	(23.0%)	26	(23.4%)	25	(22.5%)
Unknown	8	(3.6%)	4	(3.6%)	4	(3.6%)
Socio Economic Status (SES)						
Low	56	(25.2%)	36	(32.4%)	20	(18.0%)
Middle	87	(39.2%)	47	(42.3%)	40	(36.0%)
High	78	(35.1%)	28	(25.2%)	50	(45.0%)
Unknown	1	(0.5%)	0	(0.0%)	1	(0.9%)
Disease stage (cTNM)						
cT2N0M0	161	(72.5%)	71	(64.0%)	90	(81.1%)
cT3-T4aN0M0	54	(24.3%)	37	(33.3%)	17	(15.3%)
cN+M0	7	(3.2%)	3	(2.7%)	4	(3.6%)
Type of MIBC						
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						
Unifocal	156	(70.3%)	74	(66.7%)	82	(73.9%)
Multifocal	61	(27.5%)	32	(28.8%)	29	(26.1%)
Unknown	5	(2.3%)	5	(4.5%)	0	(0.0%)

Supplementary Table 1. Continued.

	All patients (n=222)		5-FU + MMC (n=111)		Capecitabine + MMC (n=111)	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Geographical region						
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)						
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

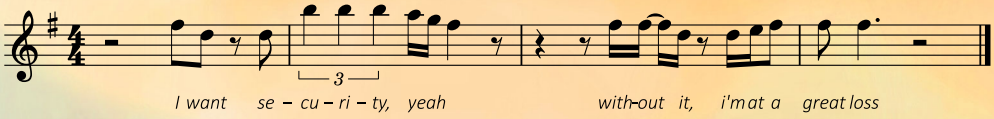
Supplementary Table 2. Patient and tumor characteristics of patients with cT2-T4a N0/1/2/x M0/x bladder cancer treated with chemoradiotherapy, stratified by type of chemotherapeutic agent (multiple imputation).

	All patients (n=222)		5-FU + MMC (n=111)		Capecitabine + MMC (n=111)	
	n	(%)	n	(%)	n	(%)
Gender						
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)
Age at diagnosis						
<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)						
ECOG 0	114	(51.1%)	50	(45.4%)	63	(56.8%)
ECOG 1	85	(38.4%)	48	(42.8%)	38	(34.1%)
ECOG 2 or higher	23	(10.5%)	13	(11.8%)	10	(9.1%)
Weighted Charlson Comorbidity Index						
0	85	(38.3%)	39	(35.2%)	46	(41.4%)
1	61	(27.7%)	30	(26.9%)	32	(28.4%)
2 or more	76	(34.0%)	42	(37.8%)	33	(30.1%)
Body Mass Index (BMI) (median, IQR)	26.5	(24.0-30.0)	26.6	(24.1-30.0)	26.3	(23.8-29.7)
Body Mass Index (BMI)						
<18.5	3	(1.4%)	0	(0.0%)	3	(2.3%)
18.5-25	80	(35.9%)	39	(35.2%)	41	(36.9%)
25-30	85	(38.4%)	44	(39.6%)	41	(36.8%)
≥30	54	(24.4%)	28	(25.2%)	26	(23.9%)
Socioeconomic status						
Low	56	(25.2%)	36	(32.4%)	20	(18.1%)
Middle	87	(39.3%)	47	(42.3%)	40	(36.4%)
High	79	(35.4%)	28	(25.2%)	51	(45.6%)
Disease stage (cTNM)						
cT2 N0M0	161	(72.5%)	71	(64.0%)	90	(81.1%)
cT3-4a N0M0	54	(24.3%)	37	(33.3%)	17	(15.3%)
cN+M0	7	(3.2%)	3	(2.7%)	4	(3.6%)
Type of MIBC						
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						
Unifocal	160	(72.0%)	78	(70.1%)	82	(73.9%)
Multifocal	62	(28.0%)	33	(29.9%)	29	(26.1%)
Geographical region						
East	5	(2.3%)	4	(3.6%)	1	(0.9%)
Middle	10	(4.5%)	9	(8.1%)	1	(0.9%)
North	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%)

Supplementary Table 2. Continued.

	All patients (n=222)		5-FU + MMC (n=111)		Capecitabine + MMC (n=111)	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Type of hospital (diagnosis)						
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: Fluorouracil; MMC: Mitomycin C; IQR: Interquartile Range; ECOG: Eastern Cooperative Oncology Group; MIBC: Muscle-Invasive Bladder Cancer



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Occult lymph node metastases in patients without residual muscle-invasive bladder cancer at radical cystectomy with or without neoadjuvant chemotherapy: a nationwide study of 5417 patients

Lisa M.C. van Hoogstraten*, Eric J. van Gennep*, Lambertus A. Kiemeney, J. Alfred Witjes, Charlotte S. Voskuilen, Marc Deelen, Laura S. Mertens, Richard P. Meijer, Joost L. Boormans, Debbie G.J. Robbrecht, Laurens V. Beerepoot, Rob H.A. Verhoeven, Theodora M. Ripping, BlaZIB Study Group, Bas W.G. van Rhijn, Katja K.H. Aben**, Tom J.N. Hermans**

*Shared first authorship, ** Shared last authorship

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ABSTRACT

Purpose

Little is known about the prevalence of occult lymph node metastases (LNM) in muscle-invasive bladder cancer (MIBC) patients with pathological downstaging of the primary tumor. We aimed to estimate the prevalence of occult LNM in patients without residual MIBC at radical cystectomy (RC) with or without neoadjuvant chemotherapy (NAC) or neoadjuvant radiotherapy (NAR), and to assess overall survival (OS).

Methods

Patients with cT2-T4aN0M0 urothelial MIBC who underwent RC plus pelvic lymph node dissection (PLND) with curative intent between January 1995–December 2013 (retrospective Netherlands Cancer Registry (NCR) cohort) and November 2017–October 2019 (prospective NCR-BlaZIB cohort (acronym in Dutch: BlaaskankerZorg In Beeld; in English: Insight into bladder cancer care)) were identified from the nationwide NCR. The prevalence of occult LNM was calculated and OS of patients with <(y)pT2N0 vs. <(y)pT2N+ disease was estimated by the Kaplan–Meier method.

Results

In total, 4,657 patients from the NCR cohort and 760 patients from the NCR-BlaZIB cohort were included. Of 1,374 patients downstaged to <(y)pT2, 4.3% (n = 59) had occult LNM 4.1% (n = 49) of patients with cT2-disease and 5.6% (n = 10) with cT3-4a-disease. This was 4.0% (n = 44) in patients without NAC or NAR, 4.5% (n = 10) in patients with NAC, and 13.5% (n = 5) in patients with NAR but number of patients treated with NAR and downstaged disease was small. The prevalence of <(y)pT2N+ disease was 4.2% (n = 48) in the NCR cohort and 4.6% (n = 11) in the NCR-BlaZIB cohort. For patients with <(y)pT2N+ and <(y)pT2N0, median OS was 3.5 years (95% CI 2.5–8.9) versus 12.9 years (95% CI 11.7–14.0), respectively.

Conclusion

Occult LNM were found in 4.3% of patients with cT2-4aN0M0 MIBC with (near-) complete downstaging of the primary tumor following RC plus PLND. This was regardless of NAC or clinical T-stage. Patients with occult LNM showed considerable worse survival. These results can help in counseling patients for bladder-sparing treatments.

INTRODUCTION

The standard treatment for clinically node-negative muscle-invasive bladder cancer (MIBC) is radical cystectomy (RC) and pelvic lymph node dissection (PLND) with cisplatin-based neoadjuvant chemotherapy (NAC) in fit patients[1]. An alternative for RC is trimodality therapy (TMT) [1]. Transurethral resection (TUR) with or without external beam radiation therapy (EBRT) is considered inferior to RC or TMT[1,2], whereas TUR with or without systemic chemotherapy has the potential to be curative in selected cases[3-5]. The prevalence of occult lymph node metastases (LNM) at RC plus PLND is approximately 25% and as such, PLND is associated with improved survival in these patients[6,7]. In contrast, PLND or treatment of the lymph nodes is not part of the TMT protocol[2].

A recent Dutch population-based study including 4,508 patients with cT2N0M0 urothelial MIBC showed that downstaging to non-MIBC was present in 25% after upfront RC and in 43 and 33% after NAC and neoadjuvant radiation (NAR), respectively[8]. In general, it is still not possible to accurately predict downstaging by TUR. Therefore, RC with PLND remains the standard of care. In selected cases or due to patient refusal, one might not always proceed to RC, CMR or EBRT[3,4]. A clinical complete response after TUR-only or TUR combined with systemic chemotherapy cannot reliably be concluded based on a combination of Re-TUR, negative cytology and cross-sectional imaging. However, these diagnostics are often performed in daily practice in attempting to confirm a so called “pT0-status” in patients who prefer bladder preservation[3,4,9,10]. In these patients, PLND for the assessment of nodal invasion is not routinely performed and the prevalence of occult metastatic disease and the potential role of PLND in this particular group has not been clearly demonstrated[11].

In a recent retrospective cohort of patients treated with NAC plus RC, 4.9 and 5.4% of patients with ypT0 and ypTa/is/1 disease had occult LNM[11]. This was irrespective of NAC or initial clinical T-stage. To our knowledge, other studies on this subject are not available. Therefore, the aim of this population-based study is to estimate the prevalence of occult LNM in patients without residual MIBC at RC, stratified by treatment with or without NAC and to assess OS in patients with and without occult LNM.

MATERIALS AND METHODS

Patients

Patients diagnosed with cT2-4aN0M0 urothelial bladder carcinoma (BC) who underwent RC plus PLND with or without NAC or neoadjuvant radiotherapy (NAR), between January 1st 1995 and December 31st 2013 (retrospective NCR cohort, data already available from Hermans et al.[8]) and between November 1st 2017 and October 31st 2019 (prospective NCR-BlaZIB cohort) were selected from the Netherlands Cancer Registry (NCR). The NCR-BlaZIB cohort consisted of patients included in the ongoing Dutch nationwide population-based prospective BlaZIB study (BlaaskankerZorg In Beeld, translation: Insight into Bladder Cancer Care)[12], which is embedded in the NCR. Patients who underwent a partial cystectomy or salvage cystectomy, or in whom PLND was not performed were excluded. Patients with histology other than UC as the main component were also excluded (Supplementary Figure 1).

The Netherlands Cancer Registry

The NCR is a nationwide population-based registry collecting data on all newly diagnosed malignancies in the Netherlands. Identification is mainly based on notification from the nationwide network and registry of histopathology and cytopathology in the Netherlands (PALGA)[13]. Well-trained data managers of the NCR collect clinical data on predefined patient, tumor, and treatment characteristics from the individual patient files at each hospital. In the NCR, topography and morphology are classified according to the International Classification of Diseases for Oncology (ICD-O)[14]. Tumor stage is classified according to the TNM system[15]. Clinical staging was based on physical examination, findings at cystoscopy and TUR, computed tomography (CT-) scan of the abdomen/pelvis and chest imaging (at least a chest X-ray).

In a previous study, all pathology reports of patients from the NCR cohort 1995–2013 were reviewed (TH, MD, CV, LM) after linkage with PALGA since pathological downstaging at RC to non-MIBC was not registered in the NCR as a standard item before 2017[8]. For the NCR-BlaZIB cohort, information on pathological downstaging was prospectively collected. Changes in TNM classifications over time (e.g., changes within pT2-stage) were irrelevant for our study outcomes[15]. Due to changes in the classification for nodal disease, it was only possible to categorize patients into node-negative (pN0) and node-positive disease (pN+).

Statistical analyses

The numbers and percentages of occult LNM in patients without and with (y) NAC and complete [(y)pT0] or partial downstaged [(y)pTa/is/1] primary tumors were calculated. The Kaplan–Meier method was applied to calculate median overall survival (OS) in patients with (y)pT0N0 vs. (y)pT0N+ disease and <(y)pT2N0 vs. <(y)pT2N+ disease. Due to the limited number of patients, it was not possible to further stratify results by NAC or NAR. Date of RC was taken as start of follow-up. End of follow-up was defined as last date of follow-up or death, whatever came first. Log-rank tests were used to compare survival distributions. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina, USA). P-values < 0.05 were considered statistically significant.

RESULTS

In total 5,417 patients with cT2-4aN0M0 urothelial MIBC who underwent RC and PLND were analyzed. From the retrospective NCR cohort, 4,657 patients were included and from the prospective NCR-BlaZIB cohort, 760 patients were included (Supplementary Figure 1). Compared to the NCR cohort, patients in the NCR-BlaZIB cohort were older (70 versus 67 years) and more often had locally advanced disease (cT3/4a in 29.7% versus 18.2%) (Supplementary Table 1). In the earlier NCR cohort, NAC and NAR were applied in 6.4% (n = 298) and 2.2% (n = 104) of patients, respectively. This was 28.3% (n = 215) and 0.5% (n = 4) in the NCR-BlaZIB cohort.

In 18.7% (n = 1,013) of all PLND specimens LNM were found. In 1,374 patients downstaged to <(y)pT2, 4.3% (n = 59) had occult LNM. In patients downstaged to (y)pT0 or (y)pTa/is/1, LNM were present in 4.1% (n = 33) and 4.6% (n = 26), respectively (Table 1). In patients with cT2 and cT3-4a disease downstaged to <(y)pT2, LNM were present in 4.1% (n = 49) and 5.6% (n = 10) (p = 0.3705), respectively. Stratification by NAC (upfront RC vs. NAC + RC) resulted in comparable percentages of <ypT2N+ and <pT2N+ disease in 4.5% (n = 10) and 4.0% (n = 44) of patients (p = 0.7093). In 108 patients who received NAR, 5 out of 37 (13.5%) had LNM with <ypT2 at RC. The prevalence of <(y)pT2N+ disease was similar over time, 4.2% (n = 48) in the NCR cohort and 4.6% (n = 11) in the NCR-BlaZIB cohort.

Patients with LNM following complete downstaging of the primary tumor [(y)pT0N+] showed inferior OS versus patients with complete downstaging without LNM [(y)pT0N0] (p < 0.001). Median OS was 3.4 (95% CI 1.7–7.0) vs. 14.1 years (95% CI 12.9–17.1) (Figure 1a). This association was also seen in patients with downstaging to non-MIBC [<(y)pT2] (p < 0.001). The median OS was 3.5 (95% CI 2.5–8.9) vs. 12.9 (95% CI

11.7–14.0) years (Figure 1b). Groups were too small to stratify by use of neoadjuvant treatment (only 10 patients with <pT2N+ after NAC). For the NCR cohort, median follow-up was 3.6 years with follow-up censored at 1 February 2017. For the NCR-BlaZIB cohort, median follow-up was 0.9 years with follow-up censored at 1 February 2020.

Table 1. The prevalence of occult lymph node metastases in patients with cT2-4aN0M0 urothelial bladder cancer without evidence of residual muscle-invasive disease at radical cystectomy.

		pN0	pN1-3	Total
All patients				
	pT0	781	33 (4.1%)	814
	pTa/is/1	534	26 (4.6%)	560
	<pT2	1315	59 (4.3%)	1374
cT2 (n=4,342)				
	pT0	673	25 (3.6%)	698
	pTa/is/1	472	24 (4.8%)	496
	<pT2	1145	49 (4.1%)	1194
cT3-4a (n=1,075)				
	pT0	108	8 (6.9%)	116
	pTa/is/1	62	2 (3.1%)	64
	<pT2	170	10 (5.6%)	180
No NAC or NAR (n=4,798)				
	pT0	585	20 (3.3%)	605
	pTa/is/1	486	24 (4.7%)	510
	<pT2	1071	44 (4.0%)	1115
NAC* (n=513)				
	ypT0	171	8 (4.5%)	179
	ypTa/is/1	42	2 (4.6%)	44
	<ypT2	213	10 (4.5%)	223
NAR* (n=108)				
	ypT0	25	5 (16.7%)	30
	ypTa/is/1	7	0 (0%)	7
	<ypT2	32	5 (13.5%)	37

NAC: Neoadjuvant chemotherapy; NAR: Neoadjuvant radiotherapy
** Two patients received both NAC and NAR.*

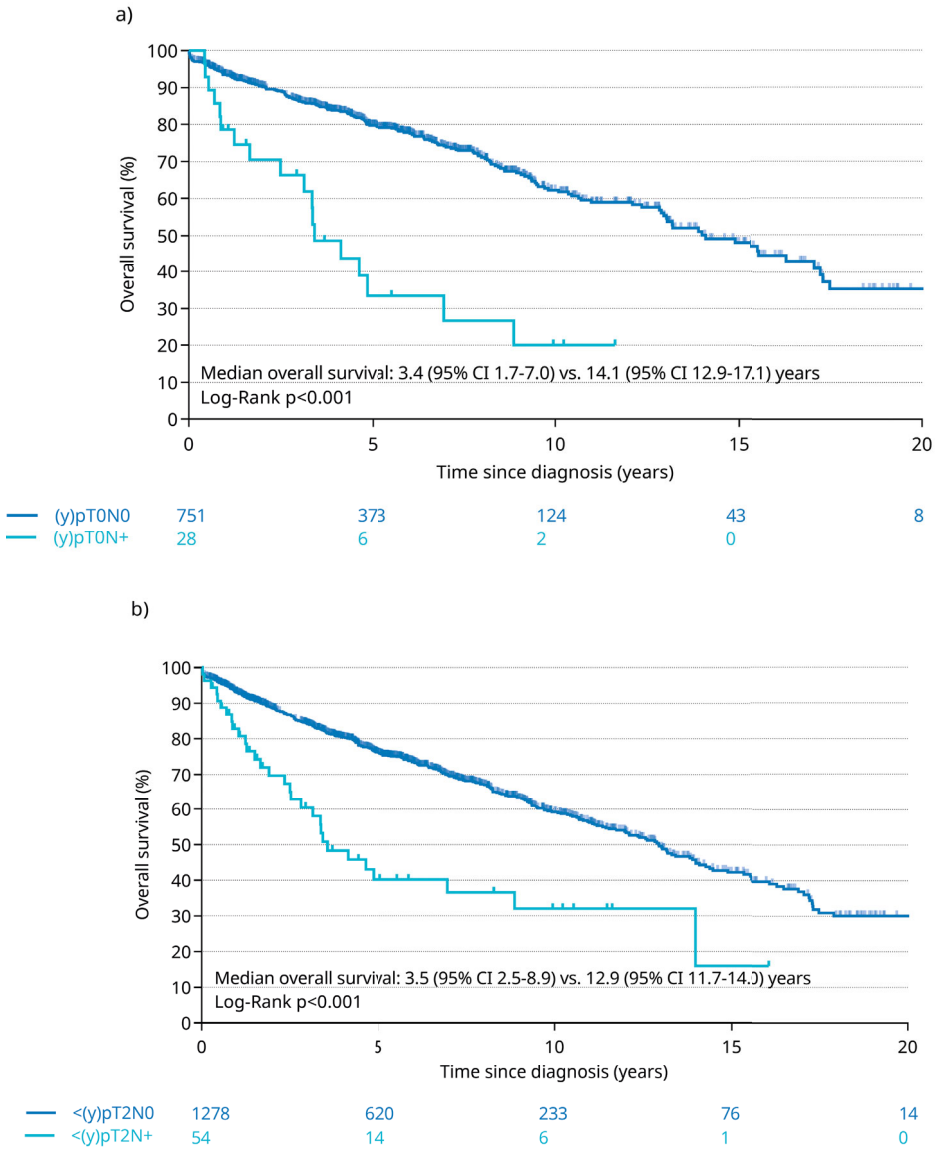

Figure 1. Overall survival of patients with and without occult lymph node metastases in cT2-4aN0M0 urothelial bladder cancer without evidence of residual bladder cancer ((y)pT0) at radical cystectomy (a) or residual muscle-invasive disease ((y)pT0/a/is/1) at radical cystectomy (b).

DISCUSSION

Pathological downstaging to non-MIBC or pT0 at RC is a favorable prognostic factor. Nevertheless, we showed that LNM are present in 4.1 and 4.6% of patients with a complete downstaging [(y)pT0] or near-complete downstaging [(y)pTa/is/1] of the primary tumor. This was regardless of the use of NAC. Moreover, these LNM were significantly associated with worse OS.

A systematic review by Bruins et al. indicated that any kind of PLND at RC is associated with beneficial OS versus no PLND[7]. Despite the low level of evidence, current guidelines recommend PLND as standard practice in combination with RC[1]. In patients who are not fit enough for RC, refuse RC or prefer a bladder-sparing approach, treatment of the pelvic lymph nodes is usually not performed. In the 2019 EAU-ESMO Consensus Statements on the management of advanced and variant BC, 64% of the experts agreed that in cN0-disease, PLND in case of bladder preservation is not recommended[16]. In contrast, a similar percentage of experts agreed on radiation of the pelvic lymph nodes in case of trimodality treatment[16]. However, given the limited evidence available in current literature no definitive consensus could be reached for both statements.

In the randomized BC2001 trial[2], disease-free survival (DFS) was compared between patients with cT2-4aN0M0 BC who underwent chemoradiotherapy (CMR) versus ERBT alone (radiation was confined to the bladder in both groups). The rate of lymph node relapses was not as high as might have been expected from surgical staging in RC cohorts, e.g., 4.9% (n = 9) in the CMR group and 6.7% (n = 12) in the ERBT-only group[2]. In another randomized chemoradiotherapy trial (cT2-4N0M0), in which radiation of the whole pelvis was compared to radiation of the bladder alone, pelvic lymph node recurrences occurred in 15.8% (15/95) and 17.6% (16/91) of patients, respectively[17]. With a median follow-up of 5 years, OS and DFS did not significantly differ between groups. In the bladder only group the first draining lymph nodes might also have been irradiated since in general a 2 cm margin around the bladder is taken. Of note, differences in pelvic lymph node recurrences between the above mentioned trials might be due to the higher percentage of T2 patients at baseline in the BC2001 trail (83 vs. 46%)[2,17]. Several other, mostly retrospective studies on bladder-preserving strategies without EBRT or TMT following TUR (e.g., regimens of TUR-NAC-Re-TUR) did not report on the prevalence of LNM during follow-up and thereby do not address the potential role of PLND or treatment of the pelvic lymph nodes in such cases[18]. Since data on the survival effect of PLND in bladder-sparing approaches are not available, it would be interesting to compare morbidity and

oncological outcomes for no treatment versus radiation versus minimal-invasive surgery for the pelvic lymph nodes in patients with MIBC undergoing bladder-preserving therapies with and without chemotherapy.

In the context of our study, it is important to note that the prevalence of LNM cannot simply be translated to the clinical scenario of selected patients with a presumed 'pT0 status' after a TUR with or without NAC and Re-TUR. Given significant discrepancies in residual tumor and LNM rates between a presumed '(y)pT0 status' and a confirmed pT0-disease in RC specimens[9,10], our results might indicate an underestimation of the prevalence of LNM in patients who are treated with TUR and/or NAC only. For example, in our RC cohort, occult LNM were present in 13% of patients with pT2-disease. Moreover, in our study PLND templates were not available, which might further underestimate the true prevalence of LNM. An earlier published NCR study indicated evidence of PLND template extension in more recent study years, as was shown by a higher number of LNM in patients with comparable clinical disease characteristics over time[19]. In line with these findings, pelvic and sentinel lymph node mapping studies in BC confirm that a limited versus an extended PLND does not capture all draining lymph nodes and thus might lead to a false negative 'pN0 status'[20,21]. It is, therefore, likely that the true prevalence of LNM in patients with a presumed 'pT0 status' before RC is higher than the 5% which was found in both the study of Nassiri et al.[11] and our study. This assumption might favor the harm to benefit ratio to perform a diagnostic PLND. Although the survival benefit of PLND in this particular group of patients is unknown, the outcome may guide adjuvant treatment. The CheckMate 274 study showed improved DFS in patients with lymph node-positive disease after NAC plus RC and PLND treated with adjuvant nivolumab[22].

It can be questioned if there are viable alternatives to a PLND or tools to select patients for whom a PLND is appropriate. The vast majority of patients in our database was staged with a contrast enhanced CT of the abdomen and a CT or conventional X-ray of the chest. Mertens et al. recently showed that by use of a FDG-PET-CT, 21% of patients were upstaged to non-localized disease[23]. Half of this group was upstaged due to regional nodal metastases. The other half had supraregional nodal or distant metastases. Clinical management changed in 13.5% of patients as a result of upstaging defined by FDG-PET-CT[23]. More sensitive imaging modalities, like FDG-PET-CT, might better select patients for PLND treated within a bladder-sparing treatment protocol. Still, according to a systematic review and meta-analysis by Ha et al. the pooled sensitivity for the detection of LNM by FDG-PET-CT was only 57%[24]. One could also argue if a sentinel node (SN) procedure could have a role in

whether or not to proceed with PLND, thereby minimizing surgical risks. In BC, the reported SN detection rates range from 81 to 92%. However, in initial validation studies false negative rates up to 19% were reported[25]. In a recent single center study, Zarifmahmoudi et al. reported a SN detection rate of 85% and a false negative rate as high as 42%[26]. However, another MIBC study concluded that SN detection played no role in staging of nodal disease since the vast majority of LNM were detected in the non-sentinel lymph nodes[27]. The high number of false negatives would, therefore, lead to understaging if one does not proceed with PLND if the outcome of the SN is negative. Altogether, prospective research in promising imaging modalities and minimally invasive diagnostics is needed to further clarify the role of PLND in bladder-sparing treatment protocols in which PLND is not standard of care.

The presence of circulating tumor cells (CTCs) in patients with muscle-invasive bladder cancer is another promising area of research. A recently presented abstract from the CirGuidance study, evaluating the role of CTCs in relation to response to NAC, showed promising results: CTC-positive patients had better overall survival when they received NAC[29]. However, the full content of this study is not yet published. It would be of interest to know whether the presence of CTCs is also predictive for occult LNM in patient with and without NAC.

Our study is subject to several limitations. In the earlier cohort, data were retrospectively collected in contrast with the more recent prospective NCR-BlaZIB cohort. Despite the high number of RCs, the group of patients with (near) complete downstaging and the presence of LNM remained low. Also, information on neoadjuvant treatment was limited. In case of NAC, exact regimens and the number of cycles were unknown. This was the same for radiation schemes in the NAR-group. Recent changes in preoperative diagnostic modalities, e.g., the use of more sensitive imaging like FDG-PET scans might result in a Will Rogers phenomenon[28]. Unfortunately, our databases had no information available regarding the use of FDG-PET scans versus conventional CT scans. Therefore, we could not assess the primary study outcome stratified by different preoperative imaging modalities. However, since the prevalence of occult LNM was similar between cohorts (NCR cohort: 4.2%, NCR-BlaZIB cohort: 4.6%) we expect the impact of such stage migration to be minimal. No information was available on the extent of the PLND templates. Since a limited PLND was often performed in the past, it is likely that we underestimated the true prevalence of occult nodal metastasis in this study. This may, however, further strengthen the potential role of PLND in selected patients who do not undergo RC. In addition, this emphasizes the need for future research to evaluate, for example, the extent of the PLND template, lymph node density in

positive cases and extracapsular extension in lymph nodes and their effects on prognosis and adjuvant treatments. Also, it will be important to identify risk factors predicting the presence of occult LNM after downstaging of the primary tumor (e.g., lymphovascular invasion, perineural spread, Ki-67 index on TURBT), as this might influence treatment decision-making as well. Despite these limitations, this is the second large nationwide database study to report on the prevalence of LNM in the patients with bladder cancer that were downstaged to (y)pT0 or (y)pTa/is/1 disease in the RC specimen.

CONCLUSION

After RC and PLND for cT2-4aN0M0 urothelial BC, occult LNM occur in 4.3% of patients with a (near)-complete downstaging of the primary tumor. This was regardless of NAC or initial clinical T-stage. Patients with occult LNM showed considerable worse survival. The risk of occult LNM should be considered and discussed with patients opting for bladder-sparing treatment. Future research, therefore, should address the diagnostic and therapeutic value of PLND in patients with MIBC undergoing bladder-sparing treatment protocols (e.g., TUR-only ± NAC, EBRT or TMT). Consequently, the outcome of PLND may have implications for radiation field extension, adjuvant treatment with chemotherapy or immune checkpoint inhibitors.

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The members of the BlaZIB study group are: Katja K.H. Aben (PI), PhD (Netherlands Comprehensive Cancer Organisation, Radboud University Medical Center); Lambertus A.L.M. Kiemeney (PI), PhD, Prof (Radboud University Medical Center); J. Alfred Witjes (PI), MD, PhD, Prof (Radboud University Medical Center); Lisa M.C. van Hoogstraten, MSc (Netherlands Comprehensive Cancer Organisation); Theodora M. Ripping, PhD (Netherlands Comprehensive Cancer Organisation); Joost Boormans,

MD, PhD (Erasmus Medical Center); Catharina A. Goossens-Laan, MD, PhD (Alrijne hospital); Sipke Helder (Patient association 'Leven met blaas- of nierkanker); Maarten C.C.M. Hulshof, MD, PhD (Amsterdam University Medical Centers, University of Amsterdam); Geert J.L.H. van Leenders, MD, PhD (Erasmus Medical Center); Anna M. Leliveld, MD, PhD (University Medical Center Groningen); Richard P. Meijer, MD, PhD (University Medical Center Utrecht); Sasja F. Mulder, MD, PhD (Radboud University Medical Center); Ronald I. Nooter (Franciscus Gasthuis & Vlietland hospital); Juus L. Noteboom, MD, PhD (University Medical Center Utrecht); Jorg R. Oddens, MD, PhD (Amsterdam University Medical Centers, University of Amsterdam); Theo M. de Reijke, MD, PhD (Amsterdam University Medical Centers, University of Amsterdam); Tineke J. Smilde, MD, PhD (Jeroen Bosch ziekenhuis); Guus W.J. Venderbosch (Patient association 'Leven met blaas- of nierkanker'); Antoine G. van der Heijden, MD, PhD (Radboud University Medical Center); Michiel S. van der Heijden, MD, PhD (Netherlands Cancer Institute); Reindert J.A. van Moorselaar, MD, PhD, Prof (Amsterdam University Medical Centers, Vrije Universiteit Amsterdam); Bas W.G. van Rhijn, MD, PhD, FEBU (Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital); Joep G.H. van Roermund, MD, PhD (Maastricht University Medical Center); Bart P. Wijsman, MD, PhD (Elisabeth-TweeSteden Ziekenhuis).

AUTHOR CONTRIBUTIONS

TJN Hermans, BWG van Rhijn, KKH Aben, and LMC van Hoogstraten contributed to the study conception and design. Material preparation and data collection were performed by LMC van Hoogstraten, LALM Kiemeney, JA Witjes, CS Voskuilen, M Deelen, LS Mertens, TM Ripping, BWG van Rhijn, KKH Aben, and TJN Hermans. Analysis was performed by TJN Hermans and LMC van Hoogstraten. The first draft of the manuscript was written by TJN Hermans, LMC van Hoogstraten, and EJ van Gennep and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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AVAILABILITY OF DATA AND MATERIAL

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.

CODE AVAILABILITY

Code used for this study can be made available post publication by the authors upon request.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

ETHICAL APPROVAL

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 of the retrospective design of the study. This study was approved by the Netherlands Cancer Registry's Supervisory Committee.

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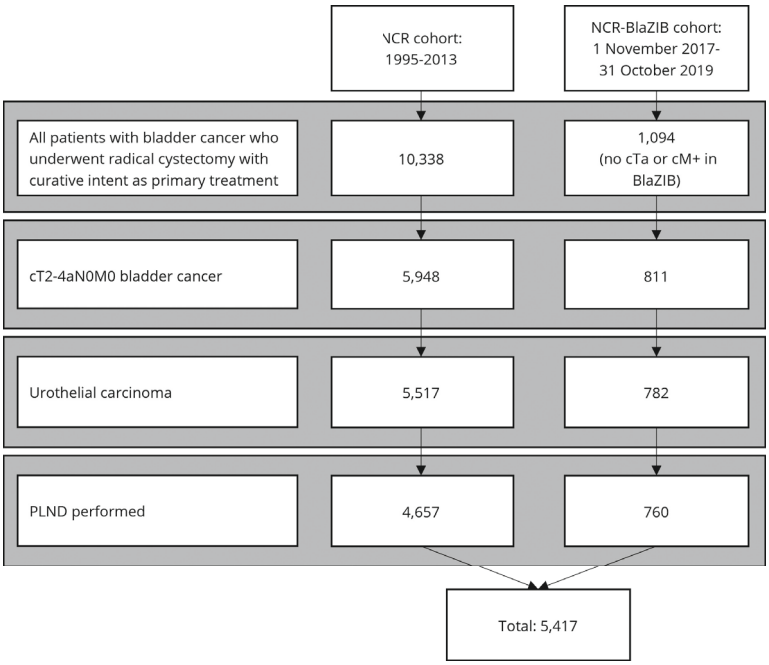
SUPPLEMENTARY MATERIAL

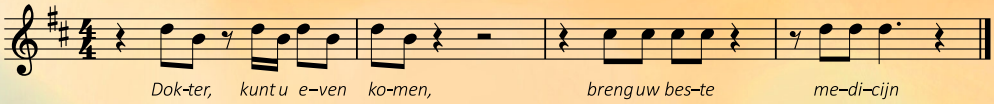


Supplementary Figure 1. Inclusion of patients with cT2-T4aN0M0 urothelial bladder carcinoma who underwent radical cystectomy followed by pelvic lymph node dissection in the Netherlands, stratified per cohort (NCR: 1995-2013, and NCR-BlaZIB: November 2017-October 2019).

Supplementary Table 1. Baseline characteristics of patients with cT2-4aN0M0 urothelial bladder cancer without evidence of residual muscle-invasive disease at radical cystectomy.

	Total		**NCR (1995-2013)**		**NCR-BlaZIB (2017-2019)**	
	n	(%)	n	(%)	n	(%)
Total	5417	(100.0)	4657	(86.0)	760	(14.0)
Gender						
Male	4116	(76.0)	3565	(76.6)	551	(72.5)
Female	1301	(24.0)	1092	(23.4)	209	(27.5)
Age at diagnosis (median, IQR)	67.0	(60.0-73.0)	67.0	(60.0-73.0)	70.0	(63.0-75.0)
Age at diagnosis						
<60 years	1244	(23.0)	1125	(24.2)	119	(15.7)
60-70 years	2003	(37.0)	1757	(37.7)	246	(32.4)
70-80 years	1882	(34.7)	1533	(32.9)	349	(45.9)
80+ years	288	(5.3)	242	(5.2)	46	(6.1)
Clinical T-stage						
cT2	4342	(80.2)	3808	(81.8)	534	(70.3)
cT3-4a	1075	(19.8)	849	(18.2)	226	(29.7)
Neo-adjuvant chemotherapy						
Yes	513	(9.5)	298	(6.4)	215	(28.3)
No	4904	(90.5)	4359	(93.6)	545	(71.7)
Neo-adjuvant radiotherapy						
Yes	108	(2.0)	104	(2.2)	4	(0.5)
No	5309	(98.0)	4553	(97.8)	756	(99.5)

Abbreviations: IQR, Interquartile range



Groot Hart - De Dijk (1985)

6

Non-metastatic muscle-invasive bladder cancer: the role of age in receiving treatment with curative intent

Lisa M.C. van Hoogstraten, J. Alfred Witjes, Richard P. Meijer, Theodora M. Ripping, BlaZIB study group, Lambertus A. Kiemeney, Katja K.H. Aben

BJU International (2022)

ABSTRACT

Objectives

To evaluate which patient and tumour characteristics are associated with remaining untreated in patients with potentially curable, non-metastatic muscle-invasive bladder cancer (MIBC), and to compare survival of untreated vs treated patients with similar characteristics.

Patients and methods

For this cohort study, 15 047 patients diagnosed with cT2–T4aN0/xM0/x urothelial MIBC between 2005 and 2019 were identified in the Netherlands Cancer Registry. Factors associated with remaining untreated were identified using logistic regression analyses. Interhospital variation was assessed using multilevel analysis. Using a propensity score, the median overall survival (mOS) of untreated and treated patients was evaluated. Analyses were stratified by age (<75 vs ≥75 years).

Results

One-third of patients aged ≥75 years remained untreated; increasing age, worse performance status, worse renal function, cT4a stage and previous radiotherapy in the abdomen/pelvic area increased the odds of remaining untreated. One in 10 patients aged <75 years remained untreated; significant associations were only found for performance status, renal function and cT4a stage. Interhospital variation for remaining untreated was largest for patients aged ≥75 years, ranging from 37% to 69% (case-mix-adjusted). Irrespective of age, mOS was significantly worse for untreated patients: 6.4 months (95% confidence interval [CI] 5.1–7.3) vs 16.0 months (95% CI 13.5–19.1) for treated patients.

Conclusion

On average, one in five patients with non-metastatic MIBC remained untreated. Untreated patients were generally older and had a more unfavourable prognostic profile. Untreated patients had significantly worse overall survival, regardless of age. Age alone should therefore not affect treatment decision-making. Considering the large interhospital variation, a proportion of untreated patients might be wrongfully denied life-prolonging treatment.

INTRODUCTION

Non-metastatic muscle-invasive bladder cancer (MIBC) is an aggressive disease with high risk of progression and death if left untreated[1]. The guideline-recommended treatment is radical cystectomy (RC), preferably preceded by neoadjuvant chemotherapy in cisplatin-eligible patients[2,3]. Less aggressive treatment options for patients unfit or reluctant to undergo surgery are multimodality treatment, external beam radiotherapy, brachytherapy and chemotherapy. In recent years, only multimodality treatment has been considered to be a full alternative for RC in a selected patient group[4–8]. Despite these treatment options, clinical practice shows that a substantial proportion of potentially curable patients remains untreated.

This group of untreated patients with non-metastatic MIBC is understudied. The same holds for the underlying factors and their effect on patient outcomes. In the few studies that included untreated patients, the proportion of untreated patients ranged between 13% and 34%[9–14]. A recent UK cohort study reported that up to 47% of patients with localized MIBC did not receive treatment with curative intent[12]. This was associated with poor 1-year survival: 55% for patients receiving palliative treatment and 32% for patients receiving no treatment. These studies did not elaborate on explanatory factors.

It is known that younger patients and patients with a more advanced disease stage are more likely to receive aggressive therapy[11]. Age, comorbidity[13,15–19], performance status[13,17], renal function[20], risk of treatment-related morbidity/mortality[15], quality of life[15,16] and patient preferences[20] are factors known to affect treatment decision-making. It has not yet been studied whether these factors also play a role in deciding not to treat patients with non-metastatic MIBC. More insight into the untreated patient population and underlying factors associated with being untreated is needed, as these insights may provide leads to improve bladder cancer care. The aims of this study were to provide insight into the characteristics of the untreated patient population with non-metastatic MIBC, to assess which patient and tumour characteristics are associated with remaining untreated, and to compare survival of untreated and treated patients with similar patient and tumour characteristics.

MATERIALS AND METHODS

For this historic cohort study, data from the nationwide Netherlands Cancer Registry (NCR) were used. All patients diagnosed with primary non-metastatic urothelial MIBC (cT2–T4aN0/xM0/x) between 2005 and 2019 were identified. Mixed

histologies with urothelial carcinoma as the main component were classified as urothelial carcinoma[21]. Tumours with predominant non-urothelial carcinoma were excluded. Patient and tumour characteristics and vital status were retrieved from the NCR. More detailed information is available from a subset of patients diagnosed between November 2017 and November 2019. These patients were included in the nationwide, prospective BlaZIB study, aiming to improve and provide insight into bladder cancer care in the Netherlands[22]. A detailed description of the patients and variables included can be found in Supplementary Figure 1.

Definitions

Patients were categorized into treatment groups: treated or untreated. Treatment consisted of upfront RC, neoadjuvant chemotherapy followed by RC, chemoradiotherapy, brachytherapy, external radiotherapy, or other (including partial cystectomy, systemic chemotherapy, immunotherapy and combination therapy). Patients with only transurethral resection of bladder tumour (TURBT) and/or bladder instillations were considered to be untreated. Age was dichotomized as <75 and ≥75 years. Body mass index (BMI) was categorized into <18.5 kg/m2 (underweight), 18.5–25 kg/m2 (normal weight), 25–30 kg/m2 (overweight) and ≥30 kg/m2 (obesity). Comorbidity was defined according to the 1987 weighted Charlson Comorbidity Index (CCI)[23] and categorized into a CCI score of 0, 1, 2 or ≥3. Performance status was defined according to the Eastern Cooperative Oncology Group (ECOG) performance score and categorized into 0, 1 and ≥2. Renal function was defined according to estimated GFR (eGFR) in mL/min/1.73 m^2, which was measured before the first treatment. Socioeconomic status (SES) was derived from Statistics Netherlands (CBS), based on the patients' full six-digit postal code.

Statistical analyses

Trends in treatment over time were evaluated stratified by age because, after the age of 75 years, the proportion of untreated patients showed a steep increase (Supplementary Figure 2). Descriptive analyses were performed to describe the untreated patient group over time, including P-value for trend, and compared to treated patients, including ANOVA and chi-squared tests. Missing data were imputed using single and multiple (n=50) imputation[24]. Single imputed data were used to perform survival analyses and multilevel analyses, multiple imputed data were used for all other analyses. Uni- and multivariable logistic regression analyses were performed in the BlaZIB subcohort stratified by age, to identify factors associated with not receiving bladder cancer-related treatment. All variables univariably associated with remaining untreated were included in a multivariable model. To take into account the prognostic differences between untreated and treated patients due

to different patient and tumour characteristics, a propensity score was calculated based on the multivariable logistic model, reflecting the patients' propensity for remaining untreated. Based on this propensity score, untreated and treated patients were matched on a 1:1 ratio in order to compare median overall survival (mOS) between treatment groups using the Kaplan–Meier method and the log-rank test. A sensitivity analysis was performed excluding patients who died within 90 days after diagnosis to account for the unfavourable prognosis at diagnosis that would result in an anticipated timely death, logically depriving the patient of any chance of being treated. A Cox proportional hazards model including the propensity score was constructed to evaluate the effect of remaining untreated. Hospital variation in the proportion of untreated patients was evaluated using multilevel logistic regression analysis stratified by age, both unadjusted (i.e. observed probability) and adjusted for relevant case-mix factors. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). P-values <0.05 were taken to indicate statistical significance. This study was approved by the Supervisory Committee of the NCR.

RESULTS

In total, 15 047 patients diagnosed with non-metastatic urothelial MIBC between 2005 and 2019 were identified from the NCR. On average, 9.9% (n=777) of patients aged <75 years remained untreated vs 34.0% (n=2459) in patients aged ≥75 years (Figure 1). The proportion of untreated patients appears to decrease slightly over time. Use of neoadjuvant chemotherapy strongly increased over time and use of upfront RC decreased in patients aged <75 years. In the more recent years, use of chemoradiotherapy increased.

Table 1 shows patient and tumour characteristics of the 3236 (21.5%) untreated patients over time. An increase in the median age at diagnosis was observed, from 81 years in 2005–2007 to 83 years in 2017–2019 (P-trend <0.05). Other trends were not as evident, although untreated patients appear to have become more fragile, i.e. they had a higher CCI score over time.

The BlaZIB subcohort (November 2017–November 2019) included 2116 patients, of whom 19.4% (n=410) were not treated. Table 2 presents the patient, tumour and hospital characteristics for this subcohort, overall and stratified by treatment. The subcohort was comparable to the entire cohort of 2005–2019 (Supplementary Table 1). Untreated patients were older, and had a lower BMI and SES, worse renal function and performance status, higher CCI score, and more often stage cT4a bladder

carcinoma. Also, untreated patients were less often discussed in a multidisciplinary team meeting (MDTM) compared to treated patients. The most important reasons for remaining untreated, as noted in the medical files, were poor functional status (46.1%, n=189) and patients' own preference (27.8%, n=114), followed by expected fast progression of the disease or expected timely death (13.9%, n=57) and no complaints or low tumour load (1.7%, n=7). Of 33 patients (10.5%), the reason for remaining untreated was not documented.

Multivariable logistic regression analysis (Table 3) showed that in both age groups (<75 and ≥75 years), ECOG performance status ≥2 vs 0 and cT4a vs cT2 stage were associated with an increased odds of remaining untreated. After stratification by age group, increasing age still increased the odds of being untreated in patients aged ≥75 years. In these patients, previous radiation in the abdomen/pelvic area was also associated with being untreated. These latter associations were not found in patients aged <75 years. With regard to hospital characteristics, being diagnosed in a university hospital decreased the odds of being untreated for patients aged ≥75 years. In case no MDTM was documented, increased odds were observed in both age groups.

The proportion of untreated patients ranged between hospitals, from 0–27% for patients aged <75 years and 0–72% for patients aged ≥75 years (Supplementary Figure 3a–e). After adjustment for case-mix factors, namely, age at diagnosis, BMI, performance status, renal function, disease stage and previous radiation, interhospital variation decreased to 37–69% for patients aged ≥75 years. For patients aged <75 years, multilevel analysis was not performed due to limited variation within this patient group (Supplementary Figure 3e).

To compare the overall survival of treated and untreated patients, 337 untreated patients (82%) were matched to treated patients by age at diagnosis, BMI, renal function, performance status, disease stage, and previous radiation in the abdomen/pelvic area, thereby reducing the imbalance regarding these variables between treatment groups (Supplementary Table 1). The mOS of untreated patients was 6.4 months vs 16.0 months for treated patients ($p<0.0001$; Figure 2a). After excluding patients who died <90 days after diagnosis, the mOS of untreated patients improved to 10.4 months but was still significantly worse compared to treated patients, whose mOS was then 17.5 months ($p<0.0001$; Figure 2b). After stratification by age, mOS remained worse for untreated patients (Figure 2c). Multivariable Cox regression analyses showed a fourfold increased risk for untreated patients aged <75 years and an over twofold increased risk for untreated patients aged ≥75 years (Supplementary Table 1).

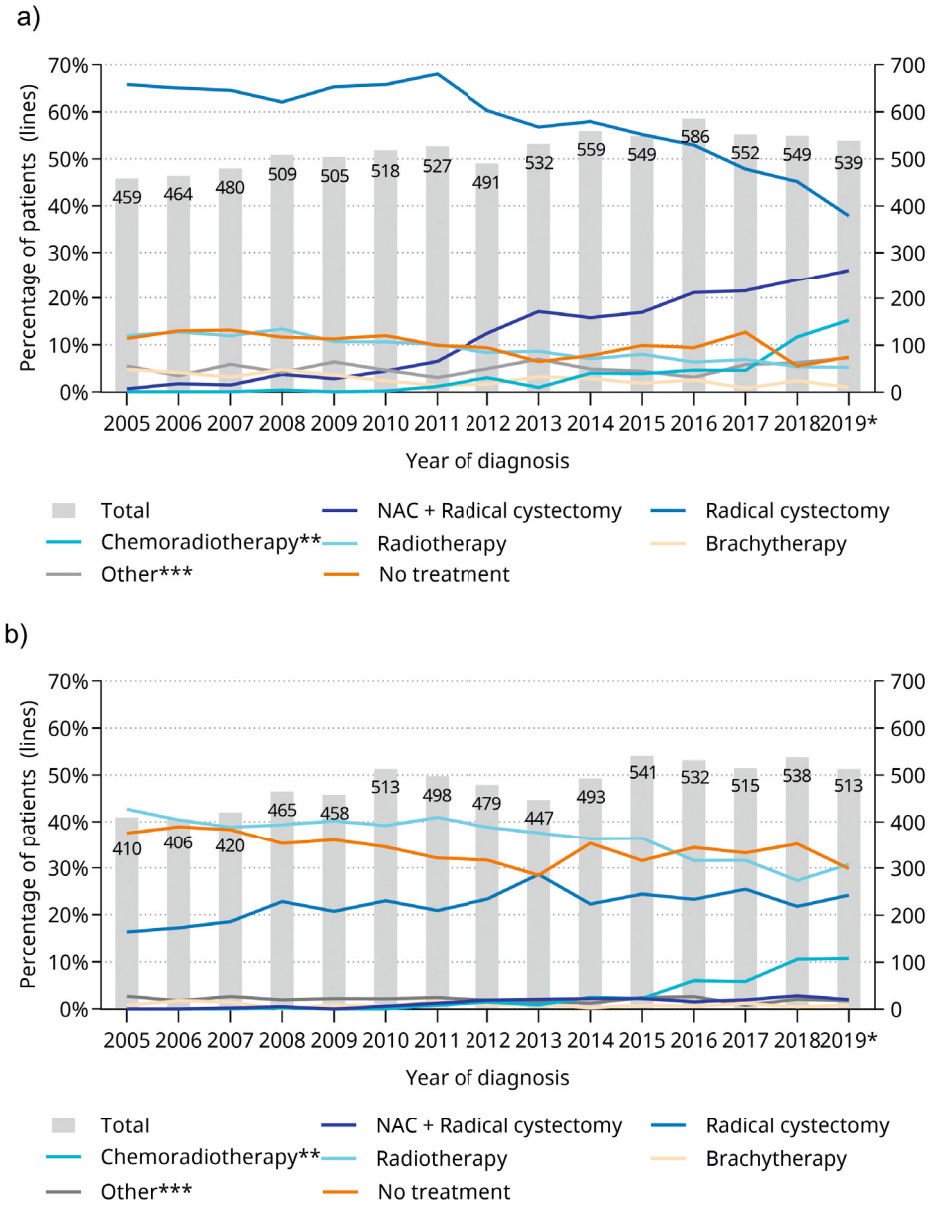


Figure 1. Treatment of patients younger than 75 years (a) and 75 years and older (b) diagnosed with non-metastatic MIBC over time (2005-2019).

NAC: neoadjuvant chemotherapy
** Data from 2019 are provisional (97% complete).*
*** Chemoradiotherapy was defined as concurrent treatment with chemotherapy and radiotherapy, e.g.: both treatments should start at the same date or show overlap between treatment periods.*
**** Other includes: partial cystectomy, systemic chemotherapy, immunotherapy, combination therapy.*

Table 1. Patient, tumour and hospital characteristics of untreated patients diagnosed with non-metastatic muscle-invasive bladder cancer over time (2005–2019).

			Year of diagnosis										
	Total		2005-2007		2008-2010		2011-2013		2014-2016		2017-2019		
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	p-value for trend*
	3236	(100.0)	648	(20.0)	684	(21.1)	571	(17.6)	680	(21.0)	653	(20.2)	
Patient characteristics													
Gender													0.5378
Male	2282	(70.5)	446	(68.8)	491	(71.8)	393	(68.8)	494	(72.6)	458	(70.1)	
Female	954	(29.5)	202	(31.2)	193	(28.2)	178	(31.2)	186	(27.4)	195	(29.9)	
Age at diagnosis (median, IQR)	82.0	75.0-86.0	81.0	74.0-85.0	81.0	74.0-86.0	82.0	75.0-86.0	83.0	76.0-87.0	83.0	76.0-87.0	<.0001
Age at diagnosis													0.0986
<60 years	138	(4.3)	31	(4.8)	35	(5.1)	20	(3.5)	32	(4.7)	20	(3.1)	
60-70 years	319	(9.9)	74	(11.4)	70	(10.2)	61	(10.7)	58	(8.5)	56	(8.6)	
70-80 years	842	(26.0)	183	(28.2)	191	(27.9)	139	(24.3)	169	(24.9)	160	(24.5)	
≥80 years	1937	(59.9)	360	(55.6)	388	(56.7)	351	(61.5)	421	(61.9)	417	(63.9)	
Age at diagnosis (dichotomous)													0.0049
<75 years	777	(24.0)	175	(27.0)	178	(26.0)	132	(23.1)	152	(22.4)	140	(21.4)	
≥75 years	2459	(76.0)	473	(73.0)	506	(74.0)	439	(76.9)	528	(77.6)	513	(78.6)	
Socio-economic status (SES)													0.1222
Low	469	(14.5)	136	(21.0)	83	(12.1)	77	(13.5)	97	(14.3)	76	(11.6)	
Middle	1291	(39.9)	253	(39.0)	299	(43.7)	237	(41.5)	263	(38.7)	239	(36.6)	
High	888	(27.4)	149	(23.0)	180	(26.3)	161	(28.2)	196	(28.8)	202	(30.9)	
Unknown	588	(18.2)	110	(17.0)	122	(17.8)	96	(16.8)	124	(18.2)	136	(20.8)	
Weighted Charlson Comorbidity Index**													0.0056
0	184	(23.7)	33	(36.3)	24	(31.6)	13	(18.8)	21	(23.1)	93	(20.6)	
1	213	(27.4)	27	(29.7)	19	(25.0)	19	(27.5)	26	(28.6)	122	(27.1)	
2	153	(19.7)	17	(18.7)	12	(15.8)	17	(24.6)	19	(20.9)	88	(19.5)	
3 or more	166	(21.3)	13	(14.3)	20	(26.3)	18	(26.1)	16	(17.6)	99	(22.0)	
Unknown	62	(8.0)	1	(1.1)	1	(1.3)	2	(2.9)	9	(9.9)	49	(10.9)	

Table 1. Continued.

	Total		Year of diagnosis										
			2005-2007		2008-2010		2011-2013		2014-2016		2017-2019		
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	p-value for trend*
Tumour characteristics													
cT stage (TNM)													0.0007
cT2	2525	(78.0)	507	(78.2)	566	(82.7)	453	(79.3)	520	(76.5)	479	(73.4)	
cT3	402	(12.4)	75	(11.6)	58	(8.5)	69	(12.1)	88	(12.9)	112	(17.2)	
cT4a	309	(9.5)	66	(10.2)	60	(8.8)	49	(8.6)	72	(10.6)	62	(9.5)	
Focality of the tumour													<.0001
Multifocal	667	(20.6)	116	(17.9)	132	(19.3)	112	(19.6)	156	(22.9)	151	(23.1)	
Unifocal	2240	(69.2)	423	(65.3)	481	(70.3)	415	(72.7)	463	(68.1)	458	(70.1)	
Unknown	329	(10.2)	109	(16.8)	71	(10.4)	44	(7.7)	61	(9.0)	44	(6.7)	
Localisation of the tumour													0.0063
Trigone	256	(7.9)	39	(6.0)	61	(8.9)	42	(7.4)	47	(6.9)	67	(10.3)	
Dome	113	(3.5)	19	(2.9)	25	(3.7)	23	(4.0)	23	(3.4)	23	(3.5)	
Right or left wall	693	(21.4)	140	(21.6)	146	(21.3)	120	(21.0)	135	(19.9)	152	(23.3)	
Anterior wall	85	(2.6)	22	(3.4)	18	(2.6)	13	(2.3)	12	(1.8)	20	(3.1)	
Posterior wall	191	(5.9)	57	(8.8)	25	(3.7)	35	(6.1)	42	(6.2)	32	(4.9)	
Bladder neck	134	(4.1)	27	(4.2)	20	(2.9)	19	(3.3)	39	(5.7)	29	(4.4)	
Left or right ureteral orifice	167	(5.2)	34	(5.2)	41	(6.0)	31	(5.4)	27	(4.0)	34	(5.2)	
Overlapping localisations	1161	(35.9)	227	(35.0)	268	(39.2)	215	(37.7)	249	(36.6)	202	(30.9)	
Unknown	436	(13.5)	83	(12.8)	80	(11.7)	73	(12.8)	106	(15.6)	94	(14.4)	
Hospital characteristics													
Type of hospital (diagnosis)													0.4210
Community hospital	1408	(43.5)	269	(41.5)	294	(43.0)	264	(46.2)	286	(42.1)	295	(45.2)	
Non-university referral hospital	1688	(52.2)	354	(54.6)	357	(52.2)	277	(48.5)	364	(53.5)	336	(51.5)	
University hospital	140	(4.3)	25	(3.9)	33	(4.8)	30	(5.3)	30	(4.4)	22	(3.4)	

IQR: Interquartile range

** P-value for trend (two-sided) was calculated using linear regression for parametric continuous variables, Cochran-Armitage trend test for binary variables and Cochran-Mantel Haenszel test for categorical variables with more than two categories.*

*** Before November 2017, the Charlson Comorbidity Index score was only available for the southern region of the Netherlands.*

Table 2. Patient, tumour and hospital characteristics of patients diagnosed with non-metastatic muscle-invasive bladder cancer between 1 November 2017 and 31 October 2019 included in the BlaZIB study, by treatment.

			Treatment				
	Total		Untreated		Treated		
	n	(%)	n	(%)	n	(%)	p-value*
Total	2116	(100.0)	410	(19.4)	1706	(80.6)	
Patient characteristics							
Gender							0.1895
Male	1506	(71.2)	281	(68.5)	1225	(71.8)	
Female	610	(28.8)	129	(31.5)	481	(28.2)	
Age at diagnosis (median, IQR)	74.0	67.0-81.0	83.0	77.0-87.0	72.0	65.0-78.0	<.0001
Age at diagnosis							<.0001
<75 years	1089	(51.5)	73	(17.8)	1016	(59.6)	
≥75 years	1027	(48.5)	337	(82.2)	690	(40.4)	
Body Mass Index (median, IQR)	25.7	23.2-28.7	24.6	22.2-27.2	25.9	23.5-29.0	
(missing %)		(8.3%)		(17.8%)		(6.0%)	0.0002
Body Mass Index							<.0001
<18.5, underweight	41	(1.9)	10	(2.4)	31	(1.8)	
18.5-25, normal weight	810	(38.3)	174	(42.4)	636	(37.3)	
25-30, overweight	775	(36.6)	109	(26.6)	666	(39.0)	
≥30, obesity	315	(14.9)	44	(10.7)	271	(15.9)	
Unknown	175	(8.3)	73	(17.8)	102	(6.0)	
Weighted Charlson Comorbidity Index							<.0001
0	766	(36.2)	89	(21.7)	677	(39.7)	
1	594	(28.1)	120	(29.3)	474	(27.8)	
2	335	(15.8)	84	(20.5)	251	(14.7)	
3 or more	299	(14.1)	94	(22.9)	205	(12.0)	
Unknown	122	(5.8)	23	(5.6)	99	(5.8)	
Type of comorbidity**							
Diabetes	383	(31.2)	99	(33.2)	284	(30.5)	0.3841
Chronic pulmonary disease	345	(28.1)	82	(27.5)	263	(28.3)	0.7988
Myocardial infarct	197	(16.0)	36	(12.1)	161	(17.3)	0.0322
Peripheral vascular disease	218	(17.8)	57	(19.1)	161	(17.3)	0.4753
Any tumour	200	(16.3)	55	(18.5)	145	(15.6)	0.2438
Cerebrovascular disease	237	(19.3)	71	(23.8)	166	(17.8)	0.0229
Moderate or severe renal disease	208	(16.9)	60	(20.1)	148	(15.9)	0.0910
Congestive heart failure	93	(7.6)	35	(11.7)	58	(6.2)	0.0018
Ulcer disease	41	(3.3)	11	(3.7)	30	(3.2)	0.6971
Connective tissue disease	55	(4.5)	14	(4.7)	41	(4.4)	0.8335
Dementia	34	(2.8)	22	(7.4)	12	(1.3)	<.0001
Metastatic solid tumour (other than bladder cancer)	24	(2.0)	11	(3.7)	13	(1.4)	0.0128
Mild liver disease	19	(1.5)	3	(1.0)	16	(1.7)	0.3850
Diabetes with end organ damage	27	(2.2)	10	(3.4)	17	(1.8)	0.1176
Hemiplegia or paraplegia	11	(0.9)	4	(1.3)	7	(0.8)	0.3472

Table 2. Continued.

			Treatment				
	Total		Untreated		Treated		
	n	(%)	n	(%)	n	(%)	p-value*
Total	2116	(100.0)	410	(19.4)	1706	(80.6)	
HIV	3	(0.2)	-	-	3	(0.3)	0.3263
Performance status							<.0001
ECOG 0	654	(30.9)	32	(7.8)	622	(36.5)	
ECOG 1	438	(20.7)	53	(12.9)	385	(22.6)	
ECOG 2 or higher	231	(10.9)	78	(19.0)	153	(9.0)	
Unknown	793	(37.5)	247	(60.2)	546	(32.0)	
Renal function (eGFR)							<.0001
mL/min/1.73 m^2	63.0	47.0-81.0	48.0	32.0-65.0	67.8	52.0-83.0	
(missing %)		(25.1%)		(18.3%)		(26.7%)	
Socio-economic status (SES)							0.0087
Low	634	(30.0)	147	(35.9)	487	(28.5)	
Middle	729	(34.5)	128	(31.2)	601	(35.2)	
High	537	(25.4)	91	(22.2)	446	(26.1)	
Unknown	216	(10.2)	44	(10.7)	172	(10.1)	
Previous surgery							0.0531
Yes	545	(25.8)	108	(26.3)	437	(25.6)	
No	1514	(71.6)	284	(69.3)	1230	(72.1)	
Unknown	57	(2.7)	18	(4.4)	39	(2.3)	
Previous radiation							0.0221
Yes	84	(4.0)	26	(6.3)	58	(3.4)	
No	1979	(93.5)	373	(91.0)	1606	(94.1)	
Unknown	53	(2.5)	11	(2.7)	42	(2.5)	
Tumour characteristics							
cT stage (TNM)							0.0286
cT2	1477	(69.8)	292	(71.2)	1185	(69.5)	
cT3	506	(23.9)	83	(20.2)	423	(24.8)	
cT4a	133	(6.3)	35	(8.5)	98	(5.7)	
Focality of the tumour							0.0016
Multifocal	508	(24.0)	104	(25.4)	404	(23.7)	
Unifocal	1533	(72.4)	280	(68.3)	1253	(73.4)	
Unknown	75	(3.5)	26	(6.3)	49	(2.9)	
Localisation of the tumour							0.4045
Trigone	173	(8.2)	39	(9.5)	134	(7.9)	
Dome	91	(4.3)	12	(2.9)	79	(4.6)	
Right or left wall	566	(26.7)	100	(24.4)	466	(27.3)	
Anterior wall	59	(2.8)	12	(2.9)	47	(2.8)	
Posterior wall	109	(5.2)	21	(5.1)	88	(5.2)	
Bladder neck	78	(3.7)	14	(3.4)	64	(3.8)	
Left or right ureteral orifice	103	(4.9)	22	(5.4)	81	(4.7)	
Overlapping localisations	724	(34.2)	138	(33.7)	586	(34.3)	
Unknown	213	(10.1)	52	(12.7)	161	(9.4)	

Table 2. Continued.

			Treatment				
	Total		Untreated		Treated		
	n	(%)	n	(%)	n	(%)	p-value*
Total	2116	(100.0)	410	(19.4)	1706	(80.6)	
Hospital characteristics							
Type of hospital							0.0019
Community hospital	910	(43.0)	190	(46.3)	720	(42.2)	
Non-university referral hospital	1115	(52.7)	215	(52.4)	900	(52.8)	
University hospital	91	(4.3)	5	(1.2)	86	(5.0)	
Discussed in MDTM							<.0001
Yes, discussed in MDTM	1963	(92.8)	314	(76.6)	1649	(96.7)	
No MDTM documented	153	(7.2)	96	(23.4)	57	(3.3)	

IQR: Interquartile range; ECOG: Eastern Cooperative Oncology Group; eGFR: estimated glomerular filtration rate; MDTM: Multidisciplinary team meeting

** P-value was calculated using Chi-square for categorical variables and ANOVA for continuous variables.*

*** Type of comorbidity was only considered for patients with a Charlson Comorbidity Index score of 1 or higher*

Table 3.Uni- and multivariable logistic regression analysis on the association between patient, tumour and hospital characteristics and receiving no treatment, in patients diagnosed with non-metastatic muscle-invasive bladder cancer between 1 November 2017 and 31 October 2019, included in the BlaZIB study.

	Univariable model						Multivariable model					
	Overall		<75 years		75 years and older		Overall		<75 years		75 years and older	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Patient characteristics												
Gender												
Male	ref.	ref.	ref.	ref.	ref.	ref.						
Female	1.17	0.93 - 1.48	1.25	0.75 - 2.08	1.15	0.87 - 1.53						
Age at diagnosis												
(per year increase)	1.14	1.12 - 1.16	1.04	1.00 - 1.08	1.19	1.16 - 1.23	1.09	1.07 - 1.12	1.01	0.97 - 1.06	1.15	1.11 - 1.19
Body Mass Index												
(per kg/m² increase)	0.95	0.92 - 0.98	0.97	0.91 - 1.02	0.96	0.92 - 0.99	0.97	0.93 - 1.00	0.98	0.92 - 1.03	0.97	0.93 - 1.02
Weighted Charlson Comorbidity Index												
0	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
1	1.94	1.44 - 2.62	2.05	1.10 - 3.82	1.48	1.03 - 2.13	1.25	0.86 - 1.82	1.48	0.71 - 3.09	1.22	0.77 - 1.93
2	2.56	1.84 - 3.56	2.63	1.27 - 5.45	1.66	1.12 - 2.47	1.29	0.84 - 1.97	1.54	0.65 - 3.66	1.24	0.74 - 2.07
3 or more	3.58	2.57 - 4.97	3.49	1.62 - 7.51	2.11	1.43 - 3.10	1.19	0.76 - 1.86	1.05	0.39 - 2.83	1.26	0.75 - 2.13
Performance status												
ECOG 0	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
ECOG 1	2.35	1.48 - 3.73	1.56	0.69 - 3.51	1.83	1.05 - 3.20	1.47	0.90 - 2.40	1.29	0.55 - 3.01	1.44	0.79 - 2.62
ECOG 2 or higher	14.84	9.37 - 23.49	15.67	7.41 - 33.13	8.07	4.70 - 13.86	6.32	3.63 - 11.01	12.16	5.10 - 28.95	4.90	2.53 - 9.47
Renal function (eGFR)												
(mL/min/1.73 m²)	0.97	0.96 - 0.97	0.97	0.96 - 0.99	0.97	0.97 - 0.98	0.99	0.98 - 0.99	0.99	0.97 - 1.00	0.99	0.98 - 1.00
Socio-economic status (SES)												
Low	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
Middle	0.71	0.54 - 0.92	0.49	0.27 - 0.89	0.86	0.63 - 1.18	1.13	0.79 - 1.61	0.62	0.31 - 1.26	1.44	0.96 - 2.16
High	0.67	0.50 - 0.89	0.45	0.24 - 0.86	0.96	0.67 - 1.37	1.11	0.75 - 1.64	0.76	0.36 - 1.60	1.30	0.82 - 2.06

Table 3. Continued.

	Univariable model						Multivariable model					
	Overall		<75 years		75 years and older		Overall		<75 years		75 years and older	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Previous surgery												
No	ref.	ref.	ref.	ref.	ref.	ref.						
Yes	1.06	0.83 - 1.36	0.88	0.49 - 1.58	0.95	0.71 - 1.27						
Previous radiation												
No	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
Yes	1.92	1.19 - 3.08	1.05	0.25 - 4.54	1.57	0.91 - 2.71	2.17	1.20 - 3.90	0.92	0.18 - 4.65	2.77	1.42 - 5.41
Tumour characteristics												
cT stage (TNM)												
cT2	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
cT3	0.80	0.61 - 1.04	0.97	0.54 - 1.72	0.89	0.64 - 1.24	0.90	0.64 - 1.28	0.92	0.48 - 1.77	0.85	0.56 - 1.30
cT4a	1.45	0.97 - 2.18	3.05	1.53 - 6.08	1.26	0.73 - 2.17	2.49	1.46 - 4.23	3.23	1.36 - 7.66	2.23	1.12 - 4.42
Focality of the tumour												
Unifocal	ref.	ref.	ref.	ref.	ref.	ref.						
Multifocal	1.14	0.88 - 1.46	1.48	0.87 - 2.50	1.03	0.76 - 1.39						
Hospital characteristics												
Type of hospital (diagnosis)												
Community hospital	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
Non-university referral hospital	0.91	0.73 - 1.13	0.80	0.49 - 1.30	0.93	0.72 - 1.21	0.98	0.73 - 1.30	0.73	0.41 - 1.30	1.04	0.74 - 1.46
University hospital	0.22	0.09 - 0.55	0.71	0.21 - 2.38	0.11	0.03 - 0.47	0.28	0.10 - 0.76	0.53	0.13 - 2.09	0.15	0.03 - 0.71
Discussed in MDTM												
Yes, discussed in MDTM	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
No MDTM documented	8.85	6.24 - 12.54	4.83	2.35 - 9.95	10.74	6.52 - 17.69	5.40	3.20 - 9.10	3.56	1.28 - 9.86	6.80	3.63 - 12.75

OR: Odds Ratio for remaining untreated; 95% CI: 95% Confidence Interval; ECOG: Eastern Cooperative Oncology Group; eGFR: estimated glomerular filtration rate; MDTM: Multidisciplinary team meeting

** The multivariable model includes age, body mass index, Weighted Charlson Comorbidity Index, performance status, renal function, socio-economic status, tumour stage and previous radiation in abdomen/pelvic area, type of hospital of diagnosis and whether the patient was discussed in a MDTM.*

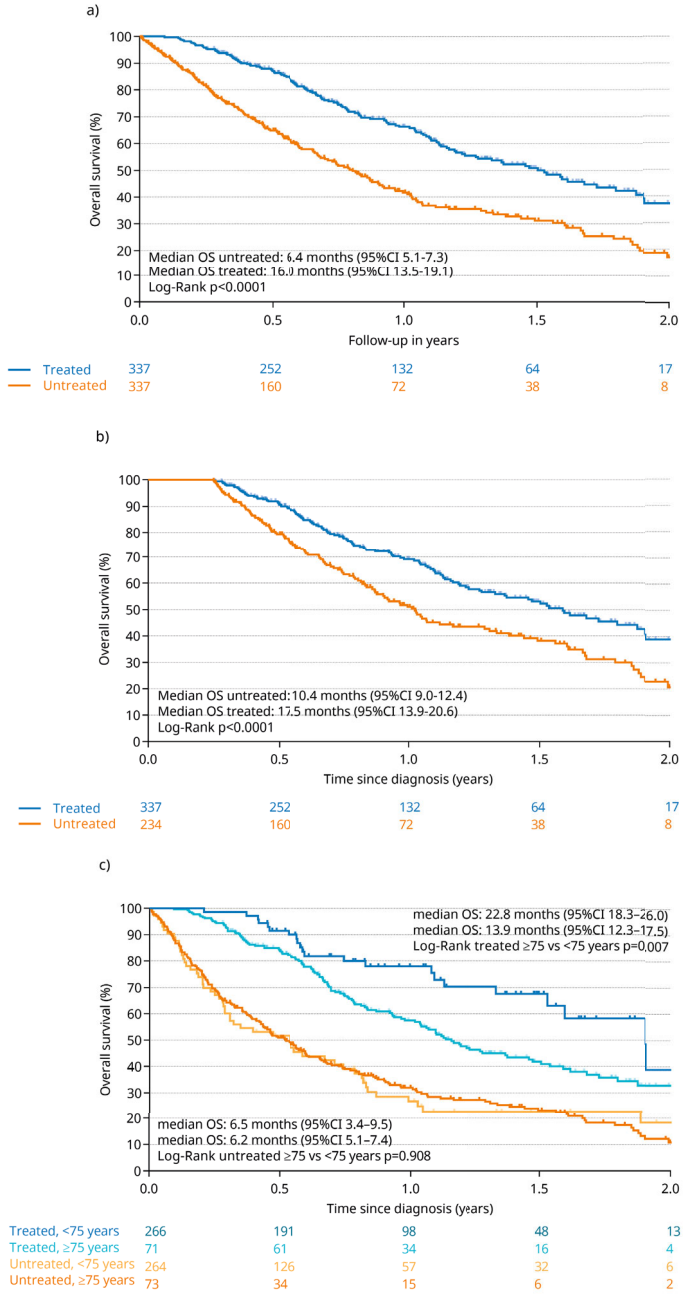


Figure 2. Overall survival (OS) of untreated patients vs treated patients with non-metastatic muscle-invasive bladder cancer (MIBC), matched on age, body mass index, renal function, performance status, tumour stage, and previous radiation in abdomen/pelvic area (A), with patients who deceased within 90 days after diagnosis excluded (B), and stratified by age (C).

DISCUSSION

In this population-based cohort study, we aimed to provide insight into the characteristics of the untreated patient population with non-metastatic MIBC, the factors associated with remaining untreated, and the survival of untreated vs treated patients matched on prognostic characteristics. A substantial proportion of patients, especially elderly patients, remained untreated. Next to age, several other factors affected the probability of remaining untreated. There was large variation in the proportion of untreated, elderly patients among hospitals, even after adjusting for case-mix factors. In addition, untreated patients fared significantly worse compared to treated patients with a similar prognostic profile. This study therefore provides a rationale to re-evaluate whether we should treat a larger proportion of these patients in the near future. One-fifth of patients with non-metastatic MIBC was not treated. This is largely consistent with the limited number of earlier studies evaluating untreated patients with non-metastatic MIBC[9–13]. In our study, the proportion of untreated patients decreased slightly over time. A US study by Fletcher et al. showed a larger trend over time; between 2004 and 2013, the proportion of untreated patients decreased from 47% to 34%[14]. Furthermore, the median age at diagnosis and comorbidity of untreated patients increased over time, indicating that, over time, more older and fragile patients have been treated. Use of chemoradiotherapy, often applied in the context of trimodality therapy as an alternative to RC, increased over time. It should be noted that the application of trimodality therapy can differ among countries, which may affect the generalizability of our results: in countries applying trimodality therapy more often, the proportion of untreated patients might be smaller since the characteristics of patients undergoing trimodality therapy resemble, in part, the characteristics of the untreated patient group in our cohort.

Even though international guidelines state that chronological age is of less importance than biological age with regard to treatment decisions[2], chronological age still appeared to be an important factor associated with remaining untreated. On average, 10% of patients aged <75 years remained untreated (other than best supportive care, i.e. no anticancer treatment, but radiotherapy, for example, to control hematuria or pain). However, this percentage steeply increased to 34% for patients aged ≥75 years. Even after stratification by age, age remained significantly associated with remaining untreated in patients aged ≥75 years. This indicates that age and/or its associated characteristics such as comorbidity and performance status play an important role in being untreated. It could be questioned whether the weight given to age as a determinant of treatment candidacy is appropriate. Because

international guidelines do not exclude patients for curative treatment based on age and explicitly state that chronological age is of limited relevance, we feel that disease stage, comorbidity, disease-related complaints and life expectancy, next to patient preference, should be the determinants of treatment decisions. It seems that in current clinical practice, chronological age is an important determinant in treatment decision-making, but chronological age may differ significantly from biological age. This should be emphasized in the guidelines. The focus should shift from chronological age to the biological age of the patient, which could for instance be assessed using the frailty index or by consulting a geriatrician.

Previous studies, although mostly not focusing specifically on the untreated patient population, showed that elderly patients less often receive curative treatment, probably due to the presence of multiple or severe comorbidities[16,17,25]. Leliveld et al. examined the association between patient and tumour characteristics and receiving RC, and showed that comorbidity was associated with receiving RC in univariable analysis. However, when adjusting for age, this association was no longer present[10]. Likewise in our study, comorbidity was univariably associated with remaining untreated, but was no longer associated with this in multivariable analysis. This could possibly be explained by the strong association between age and treatment, and several other patient and tumour characteristics also associated with comorbidity but even more so with remaining untreated.

In contrast to comorbidity, performance status remained significantly associated with being untreated throughout all of our analyses, even after stratification by age. We also observed that in patients aged ≥75 years, a more advanced disease stage and previously having received radiotherapy in the abdomen or pelvic area (not bladder cancer-related) were associated with not receiving treatment. Better renal function showed a borderline significant inverse association in both age groups. Even though inferior renal function and previous radiotherapy are a contraindication for treatment with (neoadjuvant) chemotherapy or radiotherapy, respectively, this should not be a contraindication for receiving any type of treatment[2,27].

Next to patient and tumour characteristics, hospital-related factors might also affect treatment decision-making. We observed large interhospital variation in the proportion of untreated patients, especially in patients aged ≥75 years, even after adjustment for case-mix factors such as age. This indicates differences in hospital policy and an interplay of doctors' advice and patient preferences, since patient preferences partly reflect the doctor's advice. In our study, we found that 25% of patients remained untreated as a result of patient preference. This is probably an

underestimate as only one reason to abstain from treatment could be documented and patient preferences often go hand in hand with the patient's condition and (quality of) life expectancy[28]. However, it is unlikely that the large hospital variation can be completely explained by differences in patient preferences. Therefore, our results suggest that here is room for improvement regarding treatment of patients with non-metastatic MIBC. Re-evaluation of the guidelines, that is, improved selection of patients with appropriate treatment candidacy, is warranted. This will hopefully decrease interhospital variation and potential under-treatment, which in turn will increase the consistency in quality of care for each patient independent of the hospital providing treatment.

In order to compare OS, untreated patients were matched to treated patients with similar characteristics. It is important to note that the matched patients receiving treatment represent a subgroup of older patients with worse condition as compared to the overall MIBC patient population. Therefore, the mOS of matched, treated patients does not reflect the survival of the total population of treated MIBC patients and was only 16 months. The mOS of untreated patients was 6 months. In addition, we observed that the mOS of untreated patients was similar in the younger and older age groups, implying that treatment, and not age, is crucial for better survival.

This large, population-based, nationwide cohort study provides detailed and relevant insight into the group of untreated patients with non-metastatic bladder cancer, which, to our knowledge, has not previously been described. Nevertheless, the retrospective data collection and observational character of this study have to be recognized as limitations. Missing values, which are inherent to this study design using administrative data, were addressed by employing imputation[24]. For this study we also collected information on the reason why a patient was not treated, for example, patient preference. Unfortunately, this was documented poorly in the electronic medical files: information was missing in two-thirds of patients; therefore, we could not take this into account in our analyses. However, we do not expect patient populations to differ much among hospitals with regard to patient preference. Therefore, the large interhospital variation we observed in this study is unlikely to be fully explained by patient preference. The results of this study are based on observational data collected from the electronic health records and therefore the results depend on the completeness of reporting, which might be considered to be a limitation. Nevertheless, the data collected in the NCR are collected in a standardized manner by well-trained data managers and are subject to regular quality controls, thereby guaranteeing high quality. For our study we used CCI score as a summary score of the patients' comorbidity status[23]. Using

CCI score as a measure of treatment candidacy has some limitations, as shown by Austin et al.[26]. One limitation is that if patients, based on their characteristics, have an almost 100% chance of (not) being assigned to a treatment arm, the CCI score might not control for confounding by comorbidity as well as it should[26]. However, we have shown that, even within our study population, untreated patients are a heterogenous population and could potentially have been considered treatment-eligible. To avoid selection bias occurring from the systematic baseline differences between treatment groups, propensity-score matching was performed before evaluating OS. We assume that after employing propensity-score matching, any confounding by treatment indication, if present, would be minimal. Despite the detailed information that was collected, it is possible that residual bias remained because of unmeasured confounding factors. Patients treated with (re)TURBT only were categorized in the untreated patient group. However, maximal TURBT could be regarded a curative treatment in a small minority of patients[29] and these patients were thus wrongfully classified as being untreated. We estimate that the effect of the potential misclassification would be minimal.

The insight gained from the results of our study could aid doctors and patients in the decision-making process regarding whether or not to treat patients with non-metastatic MIBC, potentially improving patient outcomes. Whereas the untreated patients were mostly elderly, survival of patients treated with any type of treatment was better compared to that of untreated patients, regardless of age. Therefore, treatment decision-making should not be solely based on chronological age. This is also supported by multiple studies, reviews[16,28,30–32] and international guidelines[2]. From our analysis it is clear that elderly patients are still undertreated even though treatment possibilities, for example, with trimodality therapy or immune checkpoint inhibition, are expanding and are quite well endured by elderly patients[5,33]. Therefore, clinicians should consider treating elderly patients with curative intent if no other contraindications are present. For untreated patients, often no documentation was found in the medical file regarding an MDTM. Discussing these patients in an MDTM could be a useful aid in deciding on (abstaining from) treatment. If it is unclear whether an elderly patient could opt for RC, or any kind of treatment, a geriatrician could be consulted. Further centralization of bladder cancer care could also positively influence the treatment decision-making process as this might alleviate any doubt on whether an (elderly) patient should, for instance, undergo surgery. Furthermore, the results of our study highlight the need for improved selection of patients with appropriate treatment candidacy, as well as for better predictors of response to treatment. For this, alternative treatment modalities should also be

taken into account because they may also result in cure, or delay progression or time of death in elderly patients. This could be addressed in the guidelines.

In conclusion, one-fifth of patients with non-metastatic MIBC remained untreated. Untreated patients were generally older and had a more unfavourable prognostic profile. Untreated patients showed significantly worse OS compared to treated patients with similar characteristics, regardless of age. Chronological age alone should, therefore, not affect treatment decision-making. Considering the difference in survival of untreated vs treated patients with similar characteristics and, given the large, case-mix-adjusted interhospital variation, a proportion of untreated patients might be wrongfully denied life-prolonging treatment.

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DISCLOSURE OF INTERESTS

The authors declare that they have no conflicts of interest.

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).

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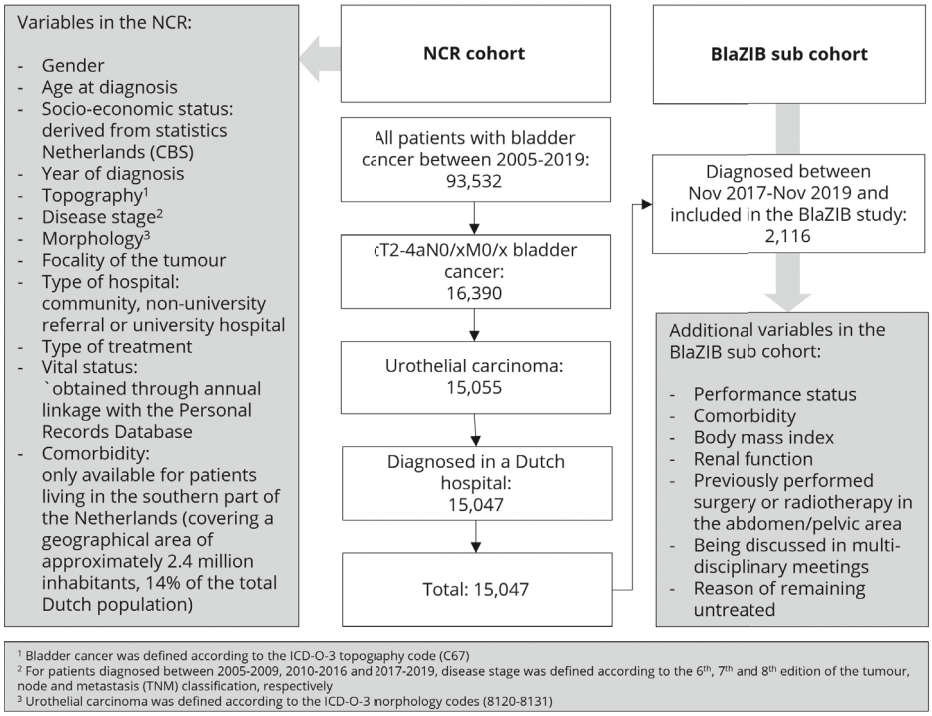
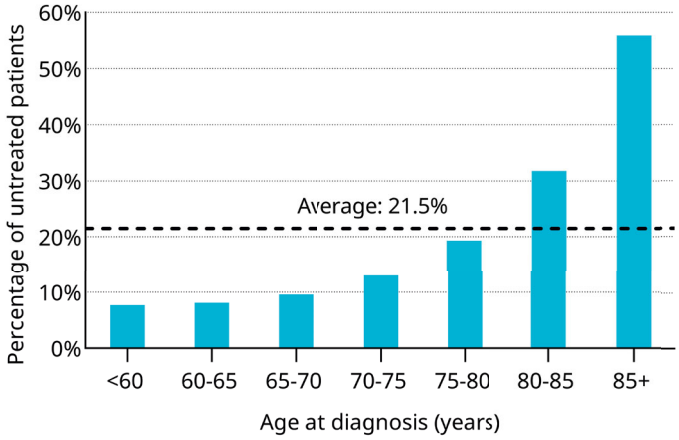
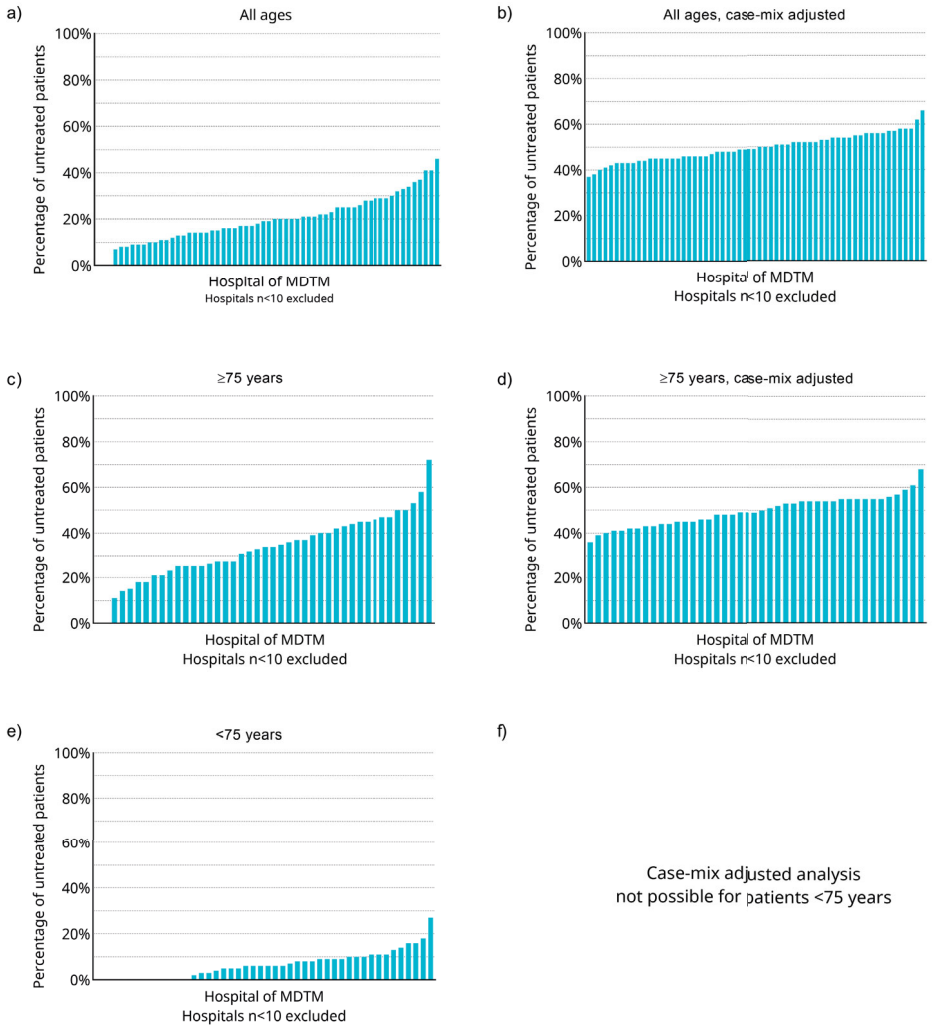
SUPPLEMENTARY MATERIAL



Supplementary Figure 1. Inclusion of patients with cT2-T4aN0/xM0/x urothelial MIBC in the Netherlands and available variables per cohort.



Supplementary Figure 2. Percentage of untreated patients with non-metastatic MIBC between 2005–2019 per age group.



Supplementary Figure 3. Observed and case-mix adjusted variation between hospitals of multidisciplinary meeting in the proportion of untreated patients of all ages (a,b) 75 years and older (c, d) and younger than 75 years (e, f) diagnosed with cT2-4aN0/xM0/x urothelial bladder carcinoma between 1 November 2017 and 31 October 2019.

MDTM: Multidisciplinary team meeting

Supplementary Table 1. Patient, tumour and hospital characteristics of patients diagnosed with non-metastatic MIBC between 2005 and 2019, by treatment.

			Treatment				
	Total		Untreated		Treated		
	n	(%)	n	(%)	n	(%)	p-value*
Total	15047	(100.0)	3236	(21.5)	11811	(78.5)	
Patient characteristics							
Gender							0.0002
Male	10990	(73.0)	2282	(70.5)	8708	(73.7)	
Female	4057	(27.0)	954	(29.5)	3103	(26.3)	
Age at diagnosis (median, IQR)	74.0	66.0-81.0	82.0	75.0-86.0	72.0	66.0-81.0	<.0001
Age at diagnosis							<.0001
<75 years	7819	(52.0)	777	(24.0)	7042	(59.6)	
≥75 years	7228	(48.0)	2459	(76.0)	4769	(40.4)	
Weighted Charlson Comorbidity Index							<.0001
0	1455	(36.5)	184	(23.7)	1271	(39.7)	
1	1101	(27.6)	213	(27.4)	888	(27.7)	
2	607	(15.2)	153	(19.7)	454	(14.2)	
3 or more	499	(12.5)	166	(21.3)	333	(10.4)	
Unknown	320	(8.0)	62	(8.0)	258	(8.1)	
Type of comorbidity							
Diabetes	641	(29.0)	160	(30.1)	481	(28.7)	0.5476
Chronic pulmonary disease	613	(27.8)	160	(30.1)	453	(27.0)	0.1740
Myocardial infarct	447	(20.3)	91	(17.1)	356	(21.3)	0.0381
Peripheral vascular disease	473	(21.4)	122	(22.9)	351	(21.0)	0.3330
Any tumour	357	(16.2)	97	(18.2)	260	(15.5)	0.1391
Cerebrovascular disease	414	(18.8)	125	(23.5)	289	(17.3)	0.0013
Moderate or severe renal disease	274	(12.4)	79	(14.8)	195	(11.6)	0.0506
Congestive heart failure	152	(6.9)	64	(12.0)	88	(5.3)	<.0001
Ulcer disease	99	(4.5)	30	(5.6)	69	(4.1)	0.1401
Connective tissue disease	92	(4.2)	17	(3.2)	75	(4.5)	0.1974
Dementia	77	(3.5)	48	(9.0)	29	(1.7)	<.0001
Metastatic solid tumour (other than bladder cancer)	38	(1.7)	21	(3.9)	17	(1.0)	<.0001
Mild liver disease	34	(1.5)	6	(1.1)	28	(1.7)	0.3749
Diabetes with end organ damage	43	(1.9)	12	(2.3)	31	(1.9)	0.5561
Hemiplegia or paraplegia	19	(0.9)	8	(1.5)	11	(0.7)	0.0654
HIV	5	(0.2)	-	-	5	(0.3)	0.2071
Socio-economic status (SES)							<.0001
Low	4956	(32.9)	1291	(39.9)	3665	(31.0)	
Middle	4707	(31.3)	888	(27.4)	3819	(32.3)	
High	3603	(23.9)	588	(18.2)	3015	(25.5)	
Unknown	1781	(11.8)	469	(14.5)	1312	(11.1)	
Tumour characteristics							
cT stage (TNM)							<.0001
cT2	11664	(77.5)	2525	(78.0)	9139	(77.4)	
cT3	2362	(15.7)	402	(12.4)	1960	(16.6)	

Supplementary Table 1. Continued.

			Treatment				
	Total		Untreated		Treated		
	n	(%)	n	(%)	n	(%)	p-value*
Total	15047	(100.0)	3236	(21.5)	11811	(78.5)	
cT4a	1021	(6.8)	309	(9.5)	712	(6.0)	
Focality of the tumour							<.0001
Multifocal	3009	(20.0)	667	(20.6)	2342	(19.8)	
Unifocal	11059	(73.5)	2240	(69.2)	8819	(74.7)	
Unknown	979	(6.5)	329	(10.2)	650	(5.5)	
Localisation of the tumour							<.0001
Trigone	1091	(7.3)	256	(7.9)	835	(7.1)	
Dome	622	(4.1)	113	(3.5)	509	(4.3)	
Right or left wall	3490	(23.2)	693	(21.4)	2797	(23.7)	
Anterior wall	399	(2.7)	85	(2.6)	314	(2.7)	
Posterior wall	979	(6.5)	191	(5.9)	788	(6.7)	
Bladder neck	572	(3.8)	134	(4.1)	438	(3.7)	
Left or right ureteral orifice	844	(5.6)	167	(5.2)	677	(5.7)	
Overlapping localisations	5449	(36.2)	1161	(35.9)	4288	(36.3)	
Unknown	1601	(10.6)	436	(13.5)	1165	(9.9)	
Hospital characteristics							
Type of hospital (diagnosis)							0.0027
Community hospital	6385	(42.4)	1408	(43.5)	4977	(42.1)	
Non-university referral hospital	7831	(52.0)	1688	(52.2)	6143	(52.0)	
University hospital	831	(5.5)	140	(4.3)	691	(5.9)	

IQR: Interquartile range

** P-value was calculated using Chi-square for categorical variables and ANOVA for continuous variables.*

Supplementary Table 2. Patient and tumour characteristics of untreated and treated patients in the BlaZIB cohort after propensity-score matching*.

			Treatment				
	Total		Untreated		Treated		
	n	(%)	n	(%)	n	(%)	p-value**
Total	674	(100.0)	337	(50.0)	337	(50.0)	
Patient characteristics							
Gender							0.4559
Male	461	(68.4)	235	(69.7)	226	(67.1)	
Female	213	(31.6)	102	(30.3)	111	(32.9)	
Age at diagnosis (median, IQR)	81.0	76.0-85.0	82.0	76.0-86.0	80.0	76.0-85.0	0.3135
Body Mass Index (median, IQR)	24.8	22.4-28.1	24.8	22.3-27.7	25.0	22.7-28.4	0.8989
Weighted Charlson Comorbidity Index							0.8333
0	165	(24.5)	79	(23.4)	86	(25.5)	
1	195	(28.9)	101	(30.0)	94	(27.9)	
2	149	(22.1)	77	(22.8)	72	(21.4)	
3 or more	165	(24.5)	80	(23.7)	85	(25.2)	
Performance status							0.8969
ECOG 0	120	(17.8)	62	(18.4)	58	(17.2)	
ECOG 1	190	(28.2)	93	(27.6)	97	(28.8)	
ECOG 2 or higher	364	(54.0)	182	(54.0)	182	(54.0)	
Renal function (eGFR)							
(mL/min/1.73 m^2)	54.0	37.0-69.0	54.0	35.0-72.0	54.0	39.2-68.0	0.5793
Socio-economic status (SES)							0.0314
Low	284	(42.1)	127	(37.7)	157	(46.6)	
Middle	241	(35.8)	124	(36.8)	117	(34.7)	
High	149	(22.1)	86	(25.5)	63	(18.7)	
Previous surgery							0.7277
Yes	180	(26.7)	88	(26.1)	92	(27.3)	
No	494	(73.3)	249	(73.9)	245	(72.7)	
Previous radiation							
Yes	47	(7.0)	23	(6.8)	24	(7.1)	0.8798
No	627	(93.0)	314	(93.2)	313	(92.9)	
Tumour characteristics							
cT stage (TNM)							0.6904
cT2	475	(70.5)	241	(71.5)	234	(69.4)	
cT3	143	(21.2)	67	(19.9)	76	(22.6)	
cT4a	56	(8.3)	29	(8.6)	27	(8.0)	
Focality of the tumour							0.4388
Multifocal	187	(27.7)	98	(29.1)	89	(26.4)	
Unifocal	487	(72.3)	239	(70.9)	248	(73.6)	

IQR: Interquartile range; ECOG: Eastern Cooperative Oncology Group; eGFR: estimated glomerular filtration rate; MDTM: Multidisciplinary team meeting

** Patients were matched on age, body mass index, renal function, performance status, tumour stage, and previous radiation in abdomen/pelvic area.*

*** P-value was calculated using Chi-square for categorical variables and ANOVA for continuous variables.*

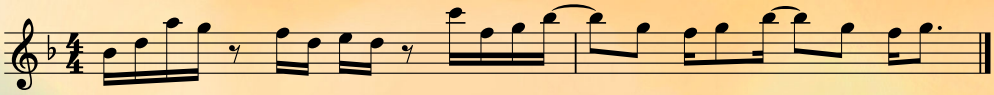
Supplementary Table 3. Uni- and multivariable Cox proportional hazards regression analyses on the association between patient, tumour and hospital characteristics and survival, in patients diagnosed with non-metastatic MIBC between 1 November 2017 and 31 October 2019, included in the BlaZIB study.

	Univariable model								
	overall			<75 years			≥75 years		
	HR	95% CI		HR	95% CI		HR	95% CI	
Treatment									
Treated	ref.	ref.		ref.	ref.		ref.	ref.	
Untreated	4.71	4.08	5.43	6.61	4.89	8.93	3.24	2.73	3.84
Propensity score (continuous)	14.62	10.73	19.93	639.34	140.93	2900.36	7.95	5.26	12.01
	Multivariable model 1*								
	overall			<75 years			≥75 years		
	HR	95% CI		HR	95% CI		HR	95% CI	
Treatment									
Treated	ref.	ref.		ref.	ref.		ref.	ref.	
Untreated	2.78	2.31	3.36	4.06	2.80	5.87	2.40	1.96	2.95
Propensity score (continuous)	5.36	3.67	7.83	178.69	36.00	887.02	3.43	2.12	5.55
	Multivariable model 2**								
	overall			<75 years			≥75 years		
	HR	95% CI		HR	95% CI		HR	95% CI	
Treatment									
Treated	ref.	ref.		ref.	ref.		ref.	ref.	
Untreated	2.88	2.38	3.47	4.79	3.33	6.90	2.46	1.98	3.05
Propensity score (continuous)	0.22	0.07	0.65	8.92	0.16	508.91	0.70	0.02	30.31

HR: Hazard Ratio; 95% CI: 95% Confidence Interval; ECOG: Eastern Cooperative Oncology Group; eGFR: estimated glomerular filtration rate; MDTM: Multidisciplinary team meeting

** Multivariable model 1 includes treatment (yes/no) and propensity score.*

*** Multivariable model 2 includes treatment (yes/no), propensity score, gender, age, body mass index, Weighted Charlson Comorbidity Index, performance status, renal function, socio-economic status, tumour stage, whether the patient was discussed in a MDTM, previous surgery in abdomen/pelvic area, previous radiation in abdomen/pelvic area.*



[Instrumental]

Pick up the pieces - Candy Dulfer (1993)

7

The impact of the COVID-19 pandemic on bladder cancer care in the Netherlands

Lisa M.C. van Hoogstraten, Lambertus A. Kiemeney, Richard P. Meijer, Geert J.L.H. van Leenders, Ben G.L. Vanneste, Luca Incrocci, Tineke J. Smilde, Sabine Siesling, J. Alfred Witjes, Katja K.H. Aben, on behalf of the BlaZIB study group and the COVID and Cancer-NL consortium

Bladder Cancer (2022)

ABSTRACT

Background

The COVID-19 pandemic has disrupted regular health care with potential consequences for non-COVID diseases like cancer. To ensure continuity of oncological care, guidelines were temporarily adapted.

Objective

To evaluate the impact of the COVID-19 outbreak on bladder cancer care in the Netherlands.

Methods

The number of bladder cancer (BC) diagnoses per month during 2020-2021 was compared to 2018-2019 based on preliminary data from the Netherlands Cancer Registry (NCR). Additionally, detailed data were retrieved from the NCR for the cohort diagnosed between March 1st-May 31st 2020 (first COVID wave) and 2018-2019 (reference cohort). BC diagnoses, changes in age and stage at diagnosis, and time to first-line treatment were compared between both periods. Changes in treatment were evaluated using logistic regression.

Results

During the first COVID wave (week 9-22), the number of BC diagnoses decreased by 14%, corresponding with approximately 300 diagnoses, but increased again in the second half of 2020. The decline was most pronounced from week 13 onwards in patients ≥70 years and patients with non-muscle invasive BC. Patients with muscle-invasive disease were less likely to undergo a radical cystectomy (RC) in week 17-22 (OR=0.62, 95% CI=0.40-0.97). Shortly after the start of the outbreak, use of neoadjuvant chemotherapy decreased from 34% to 25% but this (non-significant) effect disappeared at the end of April. During the first wave, 5% more RCs were performed compared to previous years. Time from diagnosis to RC became 6 days shorter. Overall, a 7% reduction in RCs was observed in 2020.

Conclusions

The number of BC diagnoses decreased steeply by 14% during the first COVID wave but increased again to pre-COVID levels by the end of 2020 (i.e. 600 diagnoses/month). Treatment-related changes remained limited and followed the adapted guidelines. Surgical volume was not compromised during the first wave. Altogether, the impact of the first COVID-19 outbreak on bladder cancer care in the Netherlands appears to be less pronounced than was reported for other solid tumors, both in

the Netherlands and abroad. However, its impact on bladder cancer stage shift and long-term outcomes, as well as later pandemic waves remain so far unexamined.

INTRODUCTION

The COVID-19 pandemic is an ongoing outbreak of a novel coronavirus (Severe Acute Respiratory Syndrome-coronavirus-2, or SARS-CoV-2). The virus has spread rapidly from Wuhan, China, where it was first detected in December 2019, to all over the world in a matter of months[1]. In the Netherlands, the first patient infected with the coronavirus was diagnosed on February 27th 2020[2]. After that, the number of hospitalized COVID-19 patients has increased rapidly. To prevent further spreading of the coronavirus, a national lockdown was announced on the 23rd of March 2020 (week 13). To accommodate the increase in hospitalized COVID-19 patients, all regular medical care was downscaled, e.g. national screening programs were halted[3].

Preliminary data presented by the Netherlands Comprehensive Cancer Organisation (Integraal Kankercentrum Nederland, IKNL) showed a significant decrease in the number of new cancer diagnoses during the first wave of the COVID-19 pandemic: up to 25% less cancer diagnoses as compared to previous years[4,5]. For bladder cancer diagnoses, a decrease of almost 30% was observed[6]. Explanatory factors for this decrease involve patients postponing their visit to the general practitioner (GP) in case of complaints or symptoms. Also, many GPs switched to consultation by phone or video in case of non-urgent symptoms, thereby postponing physical examination of the patient, possibly leading to a delayed referral to a hospital in case of any cancer suspicion following from the examination[5]. In the hospitals, reduced capacity and prioritization of care could also have led to a delayed diagnosis.

The COVID-19 pandemic also impacted cancer-related healthcare in other ways. A study by Van de Poll-Franse et al. showed that during the first weeks of the COVID-19 pandemic in the Netherlands, one in three cancer patients received a different form of healthcare, e.g. consultation by video or phone, or adapted, delayed or cancelled treatment[7]. Adapted guidelines and recommendations were formulated by the European Association of Urology (EAU) and Dutch scientific associations[8,9]. In the Netherlands, it was recommended to defer transurethral resection for low-risk bladder tumors by more than six months, to omit neo-adjuvant chemotherapy prior to radical cystectomy and to postpone systemic chemotherapy, as patients receiving chemotherapy might possibly experience a more severe COVID-19 infection.

A radical cystectomy with curative intent was recommended to be performed within three months, as usual.

The exact impact of the COVID-19 pandemic on bladder cancer care is largely unknown, as data so far were incomplete. Therefore, the objective of this study was to evaluate the impact of the COVID-19 pandemic in the Netherlands on the number of bladder cancer diagnoses, age and disease stage at diagnosis, initial treatment and time from diagnosis to initial treatment. Also the effect of the COVID outbreak on surgical capacity in hospitals was evaluated.

MATERIALS AND METHODS

Patient selection

For this historic cohort study, data from the Netherlands Cancer Registry (NCR), hosted by the Netherlands Comprehensive Cancer Organisation (Integraal Kankercentrum Nederland, IKNL) were used. All patients newly diagnosed with or treated for bladder cancer (International Classification of Diseases for Oncology (ICD-O-3) topography code C67) between January 2018-May 2020 were identified in the NCR. Detailed data on patient characteristics (age at diagnosis, gender, postal code, socioeconomic status (SES), comorbidity), tumor characteristics (disease stage, morphology), and primary treatment characteristics (type and date of treatment) were retrieved from the NCR. Comorbidity was defined according to the 1987 weighted Charlson Comorbidity Index (CCI) score[10]. SES was derived from Statistics Netherlands (CBS) and was based on the patients' full six-digit postal code at diagnosis. Disease stage was defined according to the 8th edition of the tumor, node and metastasis (TNM) classification[11]. Tumor morphology was based on the ICD-O-3 morphology codes[12].

To evaluate recent effects of the COVID outbreak on the number of bladder cancer diagnoses and surgical volume of radical cystectomies (RC), we derived, in addition to the previously described dataset, preliminary data from bladder cancer cases diagnosed in the period June 2020-July 2021 from the NCR. These data are largely based on data from the Nationwide Histopathology and Cytopathology Data Network and Archive (PALGA) and included only date of diagnosis, gender, topography, morphology, and date of radical cystectomy (if applicable).

Definitions

Patients diagnosed or treated between March 1st-May 31st 2020 are considered the COVID cohort, and March-May 2018/2019 is considered the reference-cohort.

Both cohorts were divided into time periods based on COVID-19-related events occurring in 2020: week 9-12, week 13-16 and week 17-22. The reasoning behind these periods is as follows: in week 9, the first Dutch COVID-19 patient was diagnosed. In week 13, the Netherlands went into national lockdown. In week 15, a national call was made to the general public urging people with symptoms to visit a GP, as a strong decline in GP visits was observed[4]. Effects of this call were to be expected from week 17 onwards. Week 2-8 (January-February) are considered the pre-COVID period. Due to the large difference in working days in week 1 of every year, week 1 was excluded.

Age at diagnosis is included in the analyses both as a continuous and categorical variable; <60, 60-70, 70-80 and >80 years. SES was categorized into low (first and second septile), medium (third, fourth and fifth septile) and high (sixth and seventh septile). CCI score was categorized into a score of 0, 1, 2 or ≥3. Disease stage was categorized into non-muscle invasive bladder cancer (NMIBC, Ta/Tis/T1N0M0), muscle-invasive bladder cancer (MIBC, T2-4aN0M0), and metastasized disease (mBC, T4b/N+/M+). For descriptive purposes, NMIBC was further categorized into low risk (LR-NMIBC, Ta) and high risk (HR-NMIBC, Tis/T1). Tumor morphology was categorized into urothelial carcinoma (UC, ICD-O-3 morphology codes 8120-8131) and non-UC (all other ICD-O-3 morphology codes for bladder cancer). Primary treatment for NMIBC consisted of either transurethral resection of the bladder tumor (TURBT) only, TURBT followed by bladder instillations (BCG or chemotherapy), radical cystectomy, or other. Treatment for MIBC and mBC was categorized into upfront radical cystectomy, neo-adjuvant chemotherapy followed by radical cystectomy, radiotherapy, chemoradiotherapy, systemic therapy (chemotherapy or immunotherapy), no treatment, or other.

Statistical analyses concerning bladder cancer diagnosis

The number of new bladder cancer diagnoses over time was calculated per month and compared between 2020/2021 and 2018/2019 (averaged). For a more detailed description of the first COVID-19 wave (week 9-22) and preceding pre-COVID period (week 2-8), we compared the number of bladder cancer diagnoses per week for January-May of 2020 and January-May of 2018/2019 (averaged). The relative change in number of diagnoses in 2020 was assessed, considering the average number of diagnoses per week in 2018/2019 as 100%. To smooth variation, three-week moving averages were used. A correction for working days was applied in case a week consisted of less than five working days due to national holidays. Descriptive analyses were performed to characterize the patient cohort diagnosed before (week 2-8) and during the first COVID wave in 2020 (week 9-22), and the reference cohort

2018/2019 (week 9-22), per time period. Incidence rates per 100.000 person years were calculated for each time period in 2020 and 2018/2019 and week 9-22 in total, and were evaluated stratified by age group and disease stage, using the iri command in STATA. P<0.05 was considered statistically significant.

Statistical analyses concerning treatment of bladder cancer

For patients diagnosed between week 2-22 of 2020 and 2018/2019, the total number of patients and the average number of patients per week were calculated per treatment modality per time period and for week 9-22 combined in 2020 versus 2018/2019. A correction for the number of working days per week was applied. Logistic regression analyses were performed to evaluate the association between time period and probability of receiving a certain treatment, presented as odds ratios (OR) and 95% confidence intervals (CI). Analyses were performed per type of treatment and per disease stage, adjusted for age at diagnosis.

To evaluate the effect of the COVID-19 outbreak on surgical volume, we analyzed the number of RCs per week in patients treated in 2020, irrespective of their date of diagnosis, versus the average of 2018/2019 which was considered to be 100%, using three-week moving averages. A correction for number of working days was applied.

We also calculated time from diagnosis to start treatment per time period and for week 9-22 combined, per treatment type, in patients treated between week 2-22 of 2020 and 2018/2019.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA) and STATA version 16.1 software (StataCorp, College Station, Texas, USA). 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 of the retrospective design of the study. This study was approved by the Netherlands Cancer Registry's Supervisory Committee (reference number K21.057).

RESULTS

After the start of the COVID-19 outbreak in March 2020, a substantial decrease in bladder cancer diagnoses was observed (Figure 1). After reaching its lowest point in May 2020, the number of diagnoses increased again and was even slightly higher at the end of the year compared to 2018/2019. The number of diagnoses in 2021 appears to be largely as expected. Focusing on the first COVID-19 wave, i.e. week

9-22, the number of bladder cancer diagnoses decreased with 14% compared to 2018/2019 (Figure 2a). In absolute numbers, this corresponds with approximately 300 bladder cancer diagnoses. The largest decline in bladder cancer diagnoses was observed in week 19: 22% (Figure 2b).

Patient characteristics of patients diagnosed in 2020 were largely similar to those from the reference cohort 2018/2019 (Table 1). Tumor characteristics were also comparable, except in week 17-22: disease stage was significantly different from the reference period in 2018/2019. Less patients were diagnosed with NMIBC, causing a relative yet no absolute increase in patients with MIBC.

No large differences were found regarding the trend in bladder cancer incidence over time per age group. A statistically significant decline was first observed in the oldest patients, aged ≥70 years after week 13 (Figure 3). After week 17, a significant decline was observed in all age groups. When stratified by disease stage, again, no large differences were found in bladder cancer incidence over time. From week 13 onwards, however, incidence of LR-NMIBC showed a statistically significant decline and after week 17, incidence was also lower for HR-NMIBC (Figure 4).

In patients diagnosed with NMIBC, no significant changes in initial treatment were observed during the first COVID-19 wave (Table 2a, Table 3a). Although not statistically significant, patients diagnosed with MIBC seemed to undergo a RC slightly more often in the first weeks after the outbreak (50%) compared to the pre-COVID period (44%) and 2018/2019 (48%). After week 13, the proportion of patients with RC decreased to 38-39%, becoming statistically significant in week 17-22 (OR 0.62, 95% CI=0.40-0.97). Shortly after the outbreak, i.e. week 9-12, less patients within the surgery group appeared to receive NAC compared to 2018/2019, although this was not significant (25% vs 33%; OR=0.70, 95% CI=0.33-1.45). This effect disappeared after week 17; use of NAC increased again to 43%. For patients with metastasized disease, no clear differences in treatment over time were observed, but the number of patients was small (Table 2c, Table 3c).

Time to treatment was evaluated per time period in patients treated between week 9-22 of 2020 and 2018/2019, irrespective of date of diagnosis. Time to upfront RC decreased during the first COVID wave, from 72 days before start of the COVID wave (week 2-8) to 66 days at the end of the COVID wave (week 17-22) (Figure 5a). For patients treated with NAC, time to start NAC was on average 5 days shorter at the end of the COVID wave; i.e. 45 days pre-COVID versus 40 days in week 17-22 (Figure 5b). For patients treated with systemic chemotherapy, time to systemic

chemotherapy showed an increasing trend, i.e. from 50 days pre-COVID to 61 days in week 17-22, although the standard deviations were large (Figure 5c). Time to radiotherapy appeared not to be affected by the COVID outbreak (Supplementary Figure 1a). Time to chemoradiotherapy became on average 51 days shorter; i.e. 113 days pre-COVID versus 62 days in week 17-22, although the large standard deviations should be taken into account (Supplementary Figure 1b).

We also evaluated the effect of the COVID-19 outbreak on surgical volume. In Figure 6, the three-week moving average of the number of radical cystectomies in 2020 relative to 2018/2019 is shown. During the first COVID wave in week 9-22, 5% more RCs were performed as compared to 2018/2019. Between week 22-38, 23% less RCs were performed. And at the end of 2020 (week 38-52) the number of RCs is again slightly higher; +2.5%. Overall, almost 7% less RCs were performed in 2020.

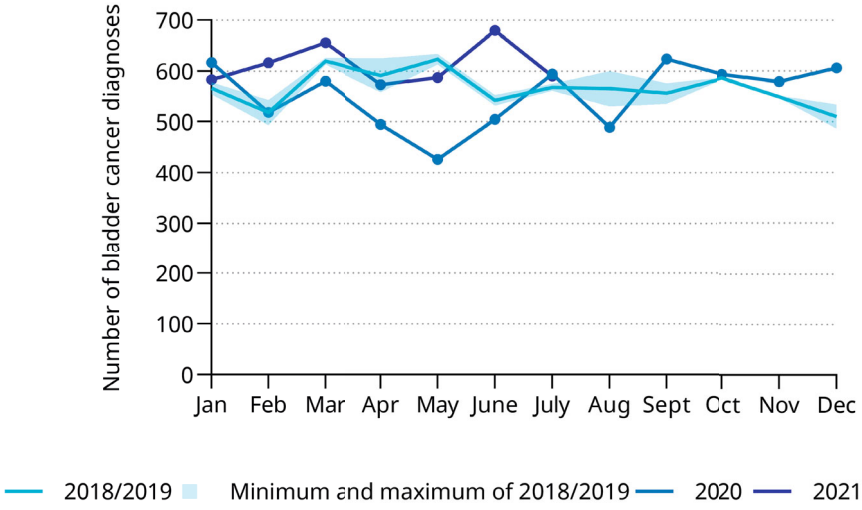


Figure 1. Bladder cancer diagnoses per month in the Netherlands in 2020 and 2021 versus the reference period 2018/2019.

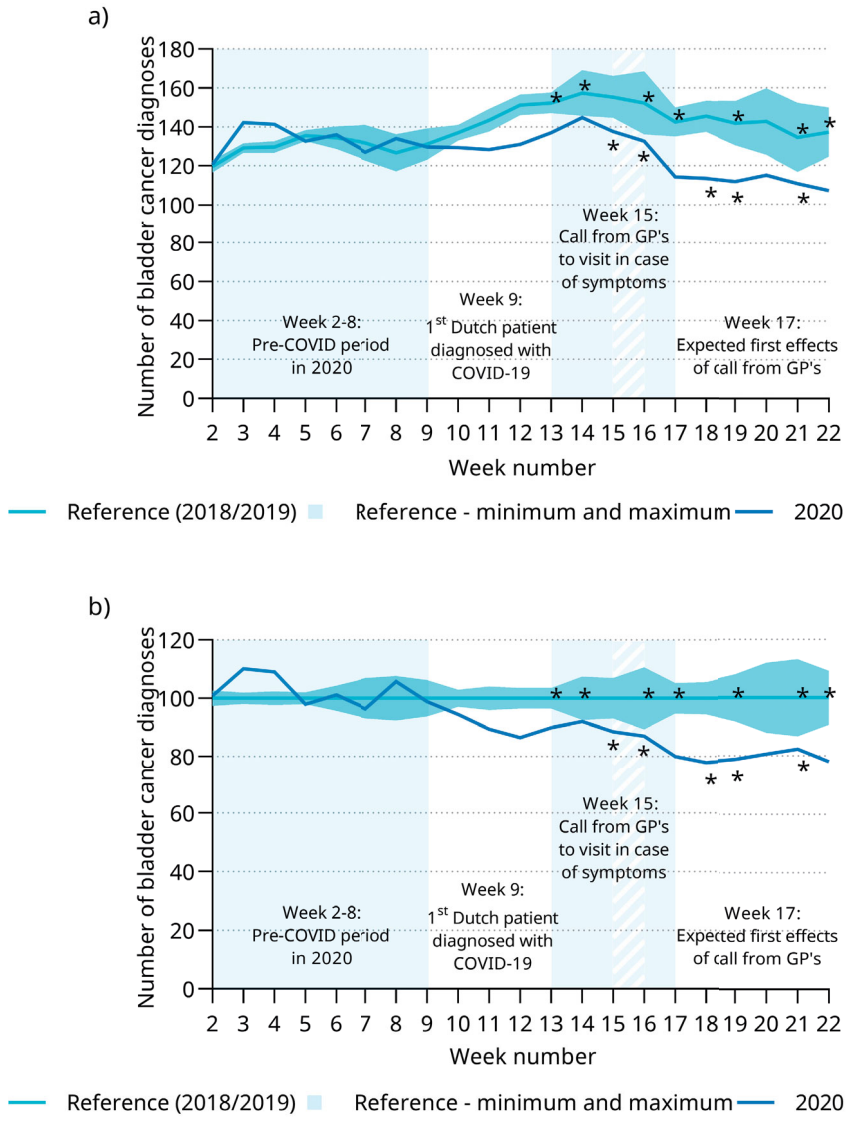


Figure 2. Three-week moving average of new bladder cancer diagnoses per week in the Netherlands in 2020 versus the reference period 2018/2019 (a) and relative to the reference period 2018/2019 (b), adjusted for the number of working days per week.

GP: general practitioner

** A correction for working days was applied since this week does not contain 5 working days due to national holidays.*

Table 1. Baseline characteristics of patients newly diagnosed* with bladder cancer in January-May 2020 and January-May 2018/2019.

	week 9-22 2018/2019 (averaged) (n=1924)		**week 9-22 2020 (n=1634)**			**week 2-8 2020 (n=952)** pre-COVID-19 period			**week 9-12 2020 (n=521)** 1st Dutch patient diagnosed with COVID-19			**week 13-16 2020 (n=502)** start national lockdown			**week 17-22 2020 (n=611)** call to visit GP in case of symptoms		
	n	**(%)**	**n**	**(%)**	**p-value**	**n**	**(%)**	**p-value**	**n**	**(%)**	**p-value**	**n**	**(%)**	**p-value**	**n**	**(%)**	**p-value**
Patient characteristics																	
Gender					0.29			0.90			0.85			0.14			0.44
Male	1488	(77.3)	1285	(78.6)		738	(77.5)		401	(77.0)		403	(80.3)		481	(78.7)	
Female	436	(22.7)	349	(21.4)		214	(22.5)		120	(23.0)		99	(19.7)		130	(21.3)	
Age at diagnosis																	
(median, IQR)	72	65.0-79.0	73	65.0-79.0	0.09	73	65.0-79.0	0.15	73	66.0-79.0	0.06	72	65.0-78.0	0.91	72	66.0-79.0	0.24
Age at diagnosis					0.22			0.82			0.25			0.30			0.52
<60 years	263	(13.6)	194	(11.9)		129	(13.6)		59	(11.3)		61	(12.2)		74	(12.1)	
60-70 years	501	(26.0)	429	(26.3)		242	(25.4)		127	(24.4)		149	(29.7)		153	(25.0)	
70-80 years	714	(37.1)	642	(39.3)		346	(36.3)		213	(40.9)		185	(36.9)		244	(39.9)	
≥80 years	447	(23.2)	369	(22.6)		235	(24.7)		122	(23.4)		107	(21.3)		140	(22.9)	
Weighted Charlson Comorbidity Index					**0.05**			0.42			**0.05**			0.24			0.63
0	415	(21.5)	333	(20.4)		186	(19.5)		99	(19.0)		113	(22.5)		121	(19.8)	
1	275	(14.3)	199	(12.2)		131	(13.8)		58	(11.1)		56	(11.2)		85	(13.9)	
2 or more	270	(14.0)	222	(13.6)		131	(13.8)		73	(14.0)		67	(13.3)		82	(13.4)	
Unknown	965	(50.1)	880	(53.9)		504	(52.9)		291	(55.9)		266	(53.0)		323	(52.9)	
Socioeconomic status					0.62**			**0.05**			0.54			0.16**			0.76
Low	588	(30.6)	479	(29.3)		263	(27.6)		149	(28.6)		151	(30.1)		179	(29.3)	
Middle	709	(36.9)	620	(37.9)		390	(41.0)		191	(36.7)		204	(40.6)		225	(36.8)	
High	627	(32.6)	533	(32.6)		299	(31.4)		181	(34.7)		145	(28.9)		207	(33.9)	
Unknown	0	0	2	(0.1)		0	(0.0)		0	(0.0)		2	(0.4)		0	(0.0)	

Table 1. Continued.

	week 9-22 2018/2019 (averaged) (n=1924)		week 9-22 2020 (n=1634)			week 2-8 2020 (n=952) pre-COVID-19 period			week 9-12 2020 (n=521) 1st Dutch patient diagnosed with COVID-19			week 13-16 2020 (n=502) start national lockdown			week 17-22 2020 (n=611) call to visit GP in case of symptoms		
	n	(%)	n	(%)	p-value	n	(%)	p-value	n	(%)	p-value	n	(%)	p-value	n	(%)	p-value
Geographical region					0.83			**0.02**			0.49			0.42			0.96
North	162	(8.4)	138	(8.4)		61	(6.4)		37	(7.1)		52	(10.4)		49	(8.0)	
East	195	(10.1)	181	(11.1)		97	(10.2)		63	(12.1)		51	(10.2)		67	(11.0)	
Middle	409	(21.2)	353	(21.6)		222	(23.3)		105	(20.2)		115	(22.9)		133	(21.8)	
South	452	(23.5)	374	(22.9)		256	(26.9)		117	(22.5)		116	(23.1)		141	(23.1)	
West	707	(36.8)	588	(36.0)		316	(33.2)		199	(38.2)		168	(33.5)		221	(36.2)	
Tumor characteristics																	
Disease stage (cTNM)					0.23			0.06			0.98			0.34			**<0.01**
Ta (LR-NMIBC)	1042	(54.2)	838	(51.3)		502	(52.7)		278	(53.4)		252	(50.2)		308	(50.4)	
Tis, T1 (HR-NMIBC)	398	(20.7)	344	(21.1)		209	(22.0)		108	(20.7)		119	(23.7)		117	(19.1)	
T2-T4aN0M0 (MIBC)	325	(16.9)	300	(18.4)		153	(16.1)		91	(17.5)		83	(16.5)		126	(20.6)	
T4b/cN+/cM1 (mBC)	150	(7.8)	139	(8.5)		75	(7.9)		42	(8.1)		46	(9.2)		51	(8.3)	
Unknown	10	(0.5)	13	(0.8)		13	(1.4)		2	(0.4)		2	(0.4)		9	(1.5)	
Urothelial carcinoma (UC)					0.08			0.08			0.83			**0.01**			0.47
UC	1882	(97.8)	1586	(97.1)		930	(97.7)		509	(97.7)		482	(96.0)		595	(97.4)	
Non-UC	42	(2.2)	48	(2.9)		22	(2.3)		12	(2.3)		20	(4.0)		16	(2.6)	

GP: general practitioner; IQR: interquartile range; LR: low-risk; HR: high-risk; NMIBC: non-muscle invasive bladder cancer; MIBC: muscle-invasive bladder cancer; mBC: metastasized bladder cancer

**n=14 patients were diagnosed with a second bladder tumor. In those patients, the first invasive tumor (grade 3) was taken into account for this analysis.*

***unknown values of SES were not included in calculating the p-value*

P-value was calculated using Chi-square for categorical variables and ANOVA for continuous variables, comparing week 9-22 2020 overall and per period with 2018/2019 (week 9-22). P-values in bold are statistically significant (p<0.05).

Table 2. Initial treatment of patients with bladder cancer per disease stage and per period of diagnosis in 2020 compared to the reference period 2018/2019, corrected for the number of working days.

2a: NMIBC	Week 9-22				Week 2-8				Week 9-12				Week 13-16				Week 17-22			
(Ta/Tis/T1N0M0)	Ref		2020		Ref		2020		Ref		2020		Ref		2020		Ref		2020	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients (unadjusted)	1436		1178		693		706		403		385		450		371		583		422	
Average per week (adjusted)	108.3		90.0		99.0		100.9		100.8		96.3		120.9		102.0		105.3		77.4	
TURBT only	28.3	26.1	23.1	25.7	24.9	25.1	28.3	28.0	26.5	26.3	27.3	28.3	29.3	24.2	25.6	25.1	28.9	27.4	18.5	23.9
TURBT + instillations	76.9	71.0	65.3	72.6	71.3	72.0	69.9	69.3	70.8	70.2	66.8	69.4	87.3	72.2	75.6	74.1	74.2	70.5	57.4	74.2
Radical cystectomy	2.2	2.0	0.8	0.8	1.7	1.7	1.6	1.6	2.3	2.2	1.0	1.0	3.0	2.4	0.6	0.5	1.6	1.5	0.7	0.9
Other	0.9	0.8	0.8	0.8	1.0	1.0	1.1	1.1	1.0	1.0	1.3	1.3	1.1	0.9	0.3	0.3	0.5	0.5	0.7	0.9

NMIBC: Non-Muscle Invasive Bladder Cancer; TURBT: Transurethral Resection of the Bladder Tumor

2b: MIBC	Week 9-22				Week 2-8				Week 9-12				Week 13-16				Week 17-22			
(T2-T4aN0M0)	Ref		2020		Ref		2020		Ref		2020		Ref		2020		Ref		2020	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients (unadjusted)	318		292		132		151		97		90		90		79.		131		123	
Average per week (adjusted)	24.0		22.3		18.9		21.6		24.3		22.5		24.2		21.7		23.7		22.6	
Radical cystectomy +/- NAC	11.4	47.5	9.4	42.1	8.9	46.9	9.6	44.3	12.0	49.5	11.3	50.0	11.8	48.9	8.6	39.2	10.6	45.0	8.7	38.3
Upfront radical cystectomy	7.7	67.5	6.3	67.0	6.3	70.8	6.3	65.6	8.0	66.7	8.5	75.2	7.8	66.1	6.1	70.9	7.4	69.8	5.0	57.5
NAC + radical cystectomy	3.7	32.5	3.1	33.0	2.6	29.2	3.3	34.4	4.0	33.3	2.8	24.8	4.0	33.9	2.5	29.1	3.2	30.2	3.7	42.5
Radiotherapy	4.4	18.6	4.5	20.2	3.3	17.4	2.6	11.9	3.8	15.5	3.5	15.6	4.6	18.9	5.5	25.3	4.7	19.8	4.6	20.3
Chemoradiotherapy	2.3	9.4	2.7	12.0	1.7	9.1	3.7	17.2	1.5	6.2	2.0	8.9	1.9	7.8	3.0	13.9	2.9	12.2	2.9	13.0
Other	1.4	6.0	1.3	5.8	0.9	4.5	1.0	4.6	1.8	7.2	1.5	6.7	1.1	4.4	0.6	2.5	1.4	6.1	1.7	7.3
No treatment	4.4	18.2	4.4	19.9	4.0	21.2	4.7	21.9	5.0	20.6	4.3	18.9	4.6	18.9	4.1	19.0	3.8	16.0	4.8	21.1

MIBC: Muscle Invasive Bladder Cancer; NAC: Neo-Adjuvant chemotherapy

Table 2. Continued.

2c: mBC	Week 9-22				Week 2-8				Week 9-12				Week 13-16				Week 17-22			
(T4b/N+/M+)	Ref		2020		Ref		2020		Ref		2020		Ref		2020		Ref		2020	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients (unadjusted)	148		134		86		72		45		41		43		42		59		51	
Average per week (adjusted)	11.2		10.2		12		10.3		11		10.3		12		11.6		11		9.4	
Radical cystectomy	1.8	16.2	2.3	22.4	1.7	14.0	0.9	8.3	2.3	20.0	2.3	22.0	1.9	16.3	3.0	26.2	1.4	13.6	1.8	19.6
Systemic therapy (chemotherapy or immunotherapy)	2.5	22.3	2.8	26.9	3.7	30	2.1	21	2	18	3	29	3.5	30	3	26	2.2	20	2.4	26
Other	1.6	14.2	1.3	12.7	1.6	13	1.7	17	1.3	11	1	9.8	1.9	16	1.7	14	1.4	14	1.3	14
No treatment	5.2	46.6	3.9	38.1	5.1	42	5.6	54	5.8	51	4	39	4	35	3.9	33	5.6	53	3.9	41

mBC: Metastasized Bladder Cancer

Table 3. Logistic regression analyses on the odds of receiving treatment, per type of initial treatment, per disease stage and per period of diagnosis in 2020 compared to the reference period (week 9-22 of 2018/2019, OR=1.00), adjusted for age at diagnosis.

3a: NMIBC	2020 week 9-22		2020 week 2-8		2020 week 9-12		2020 week 13-16		2020 week 17-22	
(Ta/Tis/T1N0M0)	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
TURBT only	0.97	0.83 - 1.13	1.10	0.91 - 1.32	1.09	0.86 - 1.38	0.96	0.74 - 1.23	0.88	0.69 - 1.12
TURBT + instillations	1.09	0.94 - 1.27	0.93	0.77 - 1.11	0.95	0.75 - 1.19	1.16	0.91 - 1.49	1.19	0.94 - 1.50
Radical cystectomy	**0.42**	**0.21 - 0.82**	0.76	0.40 - 1.45	0.52	0.19 - 1.43	0.26	0.06 - 1.06	0.47	0.17 - 1.30
Other	1.01	0.48 - 2.11	1.35	0.60 - 3.02	1.51	0.57 - 3.99	0.33	0.04 - 2.43	1.12	0.39 - 3.25

NMIBC: Non-Muscle Invasive Bladder Cancer; OR: Odds Ratio; 95% CI: 95% Confidence Interval; TURBT: Transurethral Resection of the Bladder Tumor

Table 3. Continued.

3b: MIBC	2020 week 9-22		2020 week 2-8		2020 week 9-12		2020 week 13-16		2020 week 17-22	
(T2-T4aN0M0)	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Radical cystectomy +/- NAC	0.79	0.58 - 1.08	0.87	0.59 - 1.29	1.09	0.67 - 1.77	0.80	0.47 - 1.34	**0.62**	**0.40 - 0.97**
Upfront radical cystectomy*	0.96	0.60 - 1.52	0.86	0.48 - 1.54	1.43	0.69 - 2.99	1.06	0.46 - 2.43	0.65	0.34 - 1.24
NAC + radical cystectomy*	1.04	0.66 - 1.66	1.16	0.65 - 2.07	0.70	0.33 - 1.45	0.94	0.41 - 2.16	1.54	0.81 - 2.93
Radiotherapy	1.09	0.75 - 1.58	**0.57**	**0.33 - 0.98**	0.81	0.43 - 1.52	1.37	0.77 - 2.43	1.13	0.68 - 1.88
Chemoradiotherapy	1.32	0.85 - 2.05	**2.00**	**1.22 - 3.30**	0.94	0.43 - 2.04	1.59	0.80 - 3.18	1.44	0.80 - 2.59
Other	1.05	0.58 - 1.92	0.81	0.35 - 1.86	1.18	0.48 - 2.91	0.48	0.11 - 2.04	1.30	0.60 - 2.79
No treatment	1.12	0.76 - 1.64	1.37	0.83 - 2.25	1.14	0.60 - 2.19	0.91	0.46 - 1.77	1.27	0.74 - 2.15

MIBC: Muscle Invasive Bladder Cancer; OR: Odds Ratio; 95% CI: 95% Confidence Interval; NAC: Neo-Adjuvant chemotherapy
** The odds of receiving upfront radical cystectomy or neo-adjuvant chemotherapy (followed by radical cystectomy) was calculated within the group of patients undergoing surgery.*

3c: mBC	2020 week 9-22		2020 week 2-8		2020 week 9-12		2020 week 13-16		2020 week 17-22	
(T4b/N+/M+)	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Radical cystectomy	1.57	0.92 - 2.69	0.60	0.24 - 1.51	1.65	0.71 - 3.81	1.87	0.84 - 4.15	1.28	0.57 - 2.85
Systemic therapy (chemotherapy or immunotherapy)	1.27	0.79 - 2.04	1.05	0.55 - 2.00	1.49	0.71 - 3.11	1.19	0.56 - 2.53	1.17	0.58 - 2.34
Other	0.88	0.48 - 1.61	1.16	0.57 - 2.36	0.65	0.22 - 1.91	1.02	0.40 - 2.57	0.97	0.41 - 2.29
No treatment	0.66	0.43 - 1.03	1.09	0.63 - 1.89	0.65	0.32 - 1.31	0.55	0.27 - 1.12	0.78	0.41 - 1.47

mBC: Metastasized Bladder Cancer; OR: Odds Ratio; 95% CI: 95% Confidence Interval

*P-values in **bold** are statistically significant (p<0.05).*

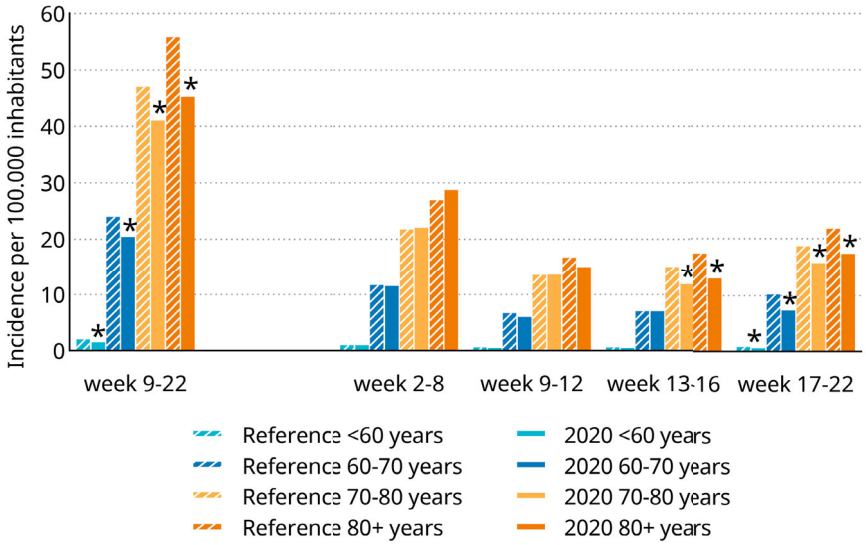


Figure 3. Incidence of bladder cancer per 100,000 inhabitants per period of diagnosis, stratified by age at diagnosis.

** In 2020, the incidence is significantly lower compared to the average incidence in 2018/2019 (p<0.05).*

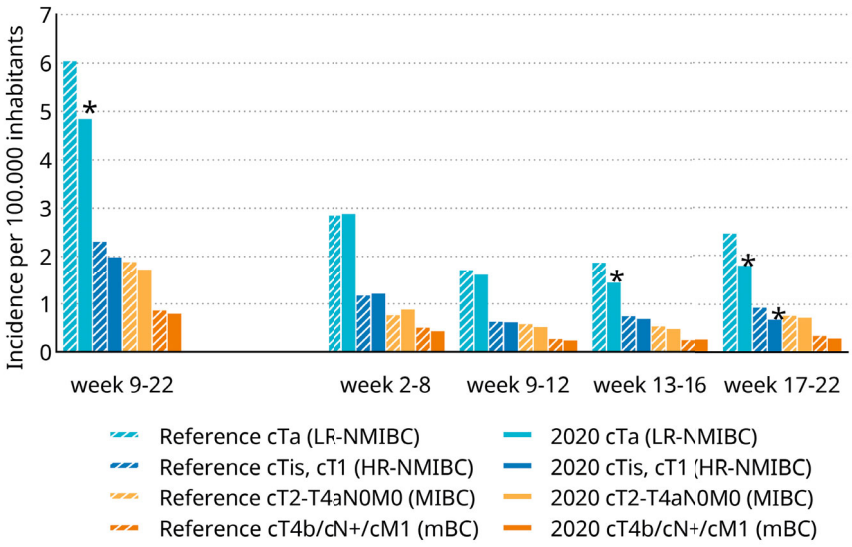


Figure 4. Incidence of bladder cancer per 100,000 inhabitants per period of diagnosis, stratified by disease stage.

LR: low-risk; HR: high-risk; NMIBC: non-muscle invasive bladder cancer; MIBC: muscle-invasive bladder cancer; mBC: metastasized bladder cancer

** In 2020, the incidence is significantly lower compared to the average incidence in 2018/2019 (p<0.05).*

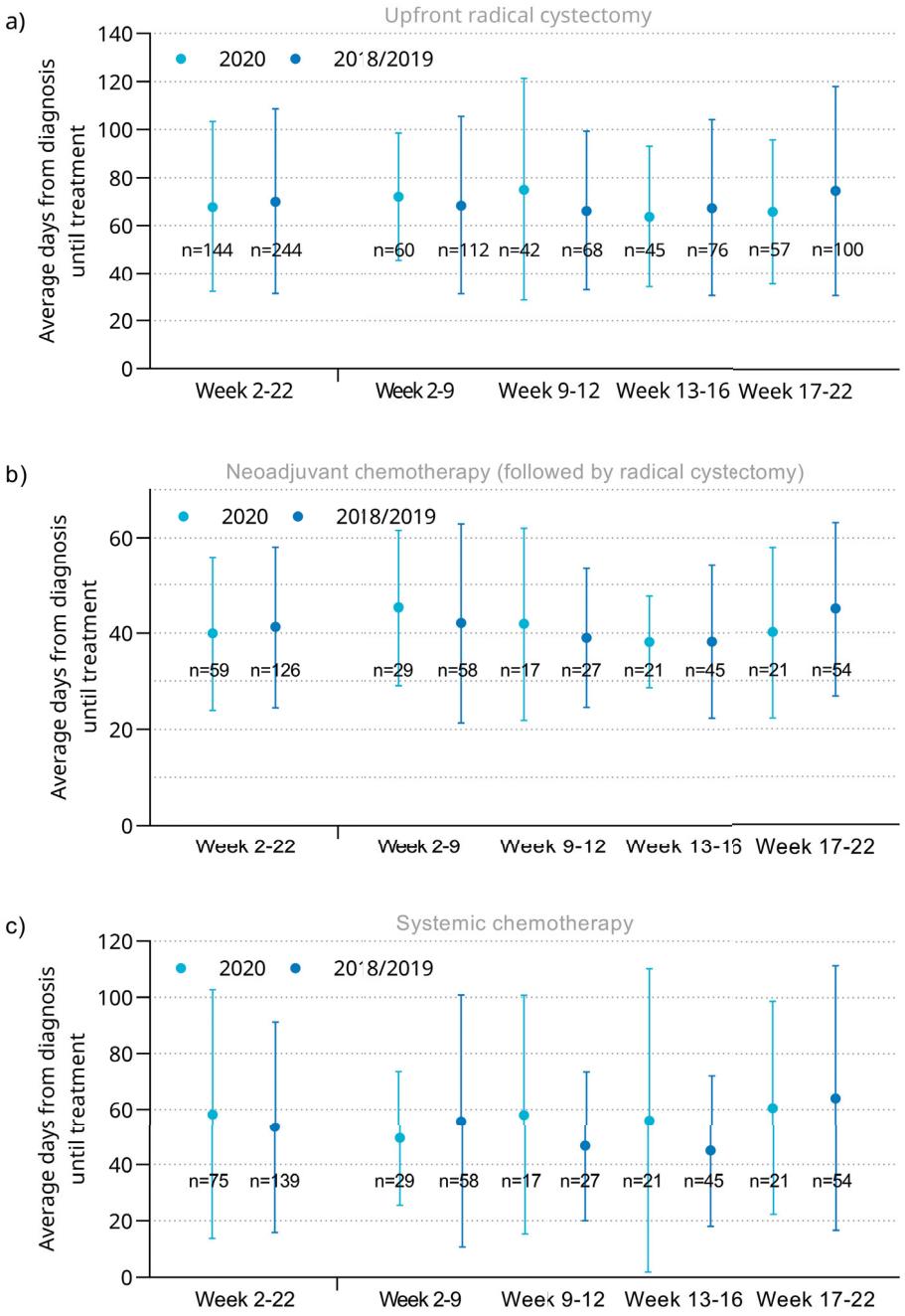
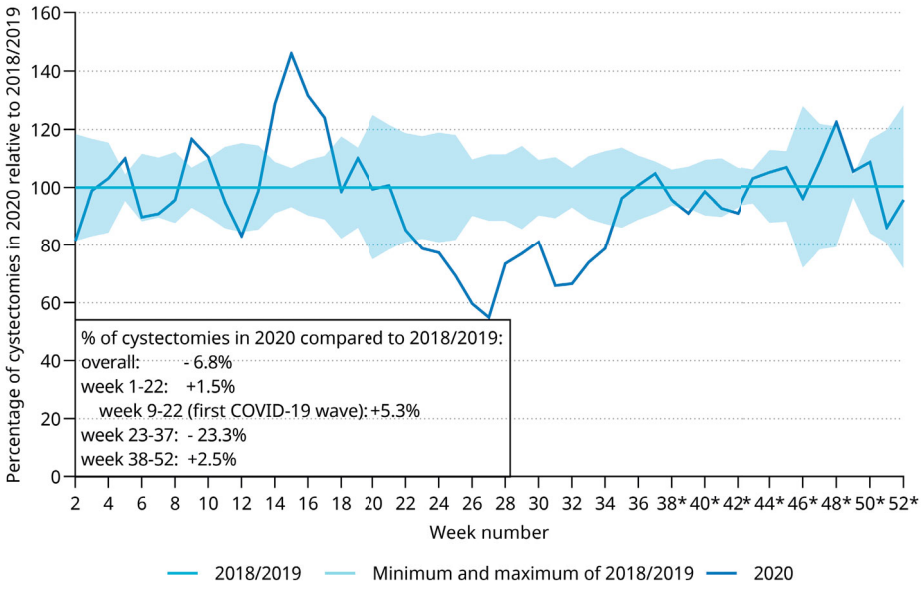


Figure 5. Average time and standard deviation to upfront radical cystectomy (a), neoadjuvant chemotherapy followed by radical cystectomy (b) and systemic chemotherapy (c) in days of patients with bladder cancer per period of treatment in 2020, compared to the reference period 2018/2019.



Week number	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
2020	12.9	16.7	16.3	18.0	15.0	15.3	13.7	17.7	18.0	18.0	17.3	20.0	23.7	25.6	23.3	21.3	14.9
Reference	15.3	16.8	15.8	16.2	16.8	17.0	15.0	15.0	16.3	19.0	20.7	21.2	20.0	18.3	18.1	17.1	15.5
(continued)	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
2020	14.9	13.3	16.5	16.0	16.2	14.2	12.0	10.0	10.0	13.0	13.7	12.7	10.0	9.7	12.0	13.0	15.3
Reference	13.6	14.1	17.7	19.9	20.8	18.4	17.0	16.5	18.2	18.3	18.3	15.2	15.3	14.8	16.3	16.8	16.7
(continued)	36	37	38*	39*	40*	41*	42*	43*	44*	45*	46*	47*	48*	49*	50*	51*	52*
2020	16.3	18.7	18.3	17.0	16.7	16.0	14.7	16.3	16.0	17.7	16.3	18.7	20.7	18.3	17.3	12.8	10.1
Reference	17.0	18.2	19.2	18.8	17.2	17.8	16.3	16.2	15.8	17.5	17.8	17.3	17.0	17.8	16.7	15.3	13.2

Figure 6. Three-week moving average of radical cystectomies (for bladder cancer only) performed in the Netherlands** in 2020 relative to the reference period 2018/2019, corrected for the number of working days per week.

**The number of cystectomies (for bladder cancer only) from week 38 on is partly based on provisional data.*

***One hospital was excluded from analysis due to a delay in registration leading to incomplete data.*

DISCUSSION

In this population-based cohort study we found that the COVID-19 outbreak largely impacted the number of bladder cancer diagnoses, with the lowest number of new bladder cancer diagnoses in May 2020. After that, the number of diagnoses restored and was slightly higher at the end of the year compared to the reference years 2018/2019. In 2021, no clear effect of COVID-19 on bladder cancer diagnoses is seen. Zooming in on the effect of the first COVID-19 wave, we observed that less

patients were diagnosed with NMIBC. The effects on treatment appear to be limited although the proportion of patients undergoing upfront radical cystectomy declined significantly approximately 2 months after the outbreak, after an initial increase. Also, neo-adjuvant chemotherapy prior to radical cystectomy was applied less frequently, but this was only temporary. The surgical capacity of radical cystectomies in the Netherlands was not affected shortly after the COVID-19 outbreak but did drop halfway 2020. In the second part of 2020 the capacity largely recovered resulting in an overall decrease in performed RCs of approximately 7%.

The decrease in bladder cancer diagnoses was most prominent among elderly patients and patients with non-muscle invasive disease. Especially elderly patients might have postponed their visit to the general practitioner or to the hospital due to fear of a COVID-19 infection, which is more severe or even fatal in elderly[13]. Regarding the decrease in NMIBC, transurethral resection may have been postponed in order to preserve surgical capacity in case the urologist suspected low grade disease during cystoscopy. This hypothesis was strengthened by the finding that the number of TURBTs (source: PALGA) in 2020 was lower compared to what could be expected based on the trend observed in previous years (Supplementary Table 1)[14]. Also, an international survey by Rosenzweig et al., evaluating adherence to adapted guidelines during the COVID-19 pandemic, showed that over 65% of TURBTs for Ta-bladder tumors were postponed of which over 40% was postponed more than a month[15].

Excess mortality due to COVID-19, accounting for approximately 9,000 extra deaths in the COVID-19 period week 9-22 2020 (source: Statistics Netherlands[16]), could potentially deprive patients of being diagnosed with bladder cancer. However, we estimated the number of bladder cancer diagnoses that have been missed due to COVID-related mortality between week 9-22 of 2020, using the age and gender-specific incidence of bladder cancer patients in our cohort. This resulted in <15 cases of bladder cancer missed and is, therefore, unlikely to have impacted our results.

We observed minor changes in treatment of patients diagnosed during the first COVID wave in 2020 following the national and international recommendations that were published in order to ensure continuity of uro-oncological care[8]: since the first COVID-19 case was confirmed in the Netherlands in week 9, less patients appeared to have received NAC prior to RC. This is in agreement with the adapted guidelines anticipating the risk of immunosuppression related to chemotherapy (i.e. neutropenia), increasing the risk of a more severe COVID infection. Time to start NAC and first-line systemic chemotherapy was prolonged, probably for the

same reason. The only change in treatment that could not directly be related to the adapted guidelines was the decreasing number of patients undergoing radical cystectomy near the end of the first wave. It is hypothesized that because of the downscaling of regular care, surgical capacity remained available for oncological care during the first COVID-19 wave. Anticipating potential worsening of the COVID-19 situation, waiting lists for radical cystectomies might have been caught up as much as possible. And, since use of NAC declined, part of the RCs was brought forward in time. After the first COVID wave, i.e. week 23, a large decrease in the number of RCs was observed, which might be an interplay of, among others, the decrease in number of bladder cancer diagnoses, caught up waiting lists for RC and summer holidays. Another potential factor in play here is the increasing use of bladder sparing treatments such as maximal TURBT followed by chemoradiotherapy as an alternative for RC[17]. Near the end of 2020, the number of RCs seemed to restore again although this is based on preliminary data, resulting in an overall small decrease of 7%.

Compared to other malignancies, the effect of the COVID-19 outbreak on bladder cancer care (i.e. number of diagnoses and treatment), appears to be limited[18-20]. One explanation might be the alarming symptoms related to bladder cancer, such as hematuria, urging patients to visit the GP even in times of COVID-19. By comparison, the number of breast cancer diagnoses decreased with 30-36% both in the Netherlands[18] and abroad[19], which can be related to halting national screening programs. Regarding treatment of breast cancer, in the Netherlands, less patients underwent surgery and received hormonal therapy instead[18]. The number of prostate cancer diagnoses also strongly decreased between March-May 2020 compared to previous years, with 25-42%, in the Netherlands as well as abroad[6,19,20]. However, treatment was not affected much; a population-based study evaluating the impact of COVID-19 on the number of prostate cancer diagnoses and treatment in Sweden reported that the number of radical prostatectomies remained unchanged during the first COVID-19 wave, despite less prostate cancer diagnoses in that same period[19]. In accordance, Rosenzweig et al. showed in their international survey that 93% of all RCs were performed according to schedule or with a delay of at most <1 month[15]. Our findings indicate continuity of uro-oncological care and surgical capacity, hopefully limiting any adverse effects due to COVID-19 on Dutch bladder cancer care.

To our knowledge, this is the first study to investigate the nationwide impact of COVID-19 on bladder cancer care. We used up-to-date and high-quality data from the nationwide Netherlands Cancer Registry supplemented with data from the

nationwide pathology archives (PALGA), providing relevant insights into the effect of the first wave of the COVID-19 pandemic on bladder cancer care. For specific subgroups, the number of bladder cancer cases in the Netherlands is limited. Therefore, the results of our analysis stratified by disease stage and treatment type should be interpreted with caution since the analyses may be underpowered. No elaborate adjustment for potentially relevant factors could be performed since this would cause overfitting and therefore yield unreliable results. Also, subtle fluctuations in, for instance, treatment are probably not detected in our data. Nevertheless, we were able to identify several relevant trends that were to be expected, and the results of this study do not show unexpected large changes in bladder cancer care during the first COVID-19 wave. Our findings are in agreement with clinicians' experiences in current practice and with the adapted guidelines that were published in order to ensure continuity of (uro)oncological care[8,9]. Changes in numbers of newly diagnosed bladder cancer patients might cause an underestimation of the observed decrease in bladder cancer diagnoses. However, in recent years the bladder cancer incidence in the Netherlands flattens or even slightly decreases[21] and thus the potential underestimation of our results is estimated to be minimal.

Preliminary data does not indicate a new decrease in diagnoses during the second and third COVID-19 wave. Therefore there is no direct cause for concern or further research. However, since the long-term effects of the first COVID-19 wave are currently unknown, this would be interesting to evaluate. Knowing that less patients were diagnosed with bladder cancer than expected, it is possible that the patients with a delayed diagnosis will present themselves later with a more advanced disease stage. Until July of 2021, we have not yet observed a catch up in number of diagnoses and, therefore, we cannot yet draw any conclusions about a possible stage shift. This should be monitored in the upcoming months. A UK modelling study evaluating the effect of a delay in cancer diagnosis for different cancer types calculated that a 3-month delay in bladder cancer diagnosis resulted in a 14-17% reduction of 10-year survival[22]. A 6-month delay resulted in an even higher survival reduction of 29-35%. The consequences of a delayed diagnosis, potentially resulting in a stage shift, and its subsequent impact on recurrence, progression and mortality rates are currently unknown and future research is recommended to evaluate this. Another consequence from the COVID-19 pandemic is that scientific research involving patients, such as randomized trials, was largely affected. For example, trials suffered from lower accrual rates or were put on hold[23-25]. The implications for both the patients potentially benefitting from this research, as well as for scientific progress, are unknown.

CONCLUSIONS

During the first wave of the COVID-19 pandemic in the Netherlands, the number of bladder cancer diagnoses decreased, mostly for older patients and patients with non-muscle invasive disease. At the end of 2020, the number of bladder cancer diagnoses increased again to pre-COVID levels. Changes in treatment remained limited and followed adapted guidelines. Surgical volume was not compromised during the first wave whereas for the entire year of 2020, 7% less cystectomies were observed. In conclusion, the impact of the first COVID-19 outbreak on bladder cancer care appears to be less pronounced than has been reported in other countries for solid tumors, both in the Netherlands and abroad. It is, however, possible that delayed diagnosis has led to a stage shift, impacting long-term outcomes such as recurrence, progression and survival rates. Also, later pandemic waves remain so far unexamined. Both matters may be addressed in future research.

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The members of the COVID and Cancer-NL consortium are: Prof. dr. S. Siesling: Dept of Research and Development, Netherlands Comprehensive Cancer Organisation (IKNL) Utrecht, the Netherlands; Technical Medical Centre, Dept Health Technology and Services Research, University of Twente, Enschede, the Netherlands; Dr. J.C. van Hoeve: Dept of Research and Development, Netherlands Comprehensive Cancer Organisation (IKNL) Utrecht, the Netherlands; Prof. dr. M.A.W. Merkx: Dept of Research and Development, Netherlands Comprehensive Cancer Organisation (IKNL) Utrecht, the Netherlands; dept of Oral and Maxillofacial Surgery, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; Prof. dr. N.J. de Wit: Dept of General Practice, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht (UMCU), Utrecht University, Utrecht, The Netherlands; Dr. C.W. Helsper: Dept of General Practice, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht (UMCU), Utrecht University, Utrecht, The Netherlands; M.Sc. I. Dingemans: Dutch Federation of Cancer Patient Organisations (NFK), Utrecht, The Netherlands; Prof. dr. I.D. Nagtegaal: Dept of Pathology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, on behalf of the Automated Pathology Archive (PALGA); Drs. R. Saathof: Dutch Hospital Data (DHD),

Utrecht, The Netherlands; Prof. dr. C.H. van Gils: Dept of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, The Netherlands; Prof. dr. H.C.P.M. van Weert: Dept of General Practice, Amsterdam Public Health, Amsterdam UMC location AMC, Amsterdam, The Netherlands; Prof. dr. M. Verheij: Dept of Radiation Oncology, Radboud University Medical Center, Nijmegen, The Netherlands, on behalf of SONCOS (Dutch Multidisciplinary Oncology Foundation).

The members of the BlaZIB study group are: Katja K.H. Aben, PhD (PI, Netherlands Comprehensive Cancer Organisation), Lambertus A. Kiemeney, PhD, Prof (PI, Radboud University Medical Centre), J. Alfred Witjes, MD, PhD, Prof (PI, Radboud University Medical Centre), Lisa M.C. van Hoogstraten, MSc (project coordinator, Netherlands Comprehensive Cancer Organisation), Theodora M.R. Ripping, PhD (researcher, Netherlands Comprehensive Cancer Organisation), Joost Boormans, MD, PhD (Erasmus Medical Centre), Catharina A. Goossens-Laan, MD, PhD (Alrijne hospital), Antoine G. van der Heijden, MD, PhD (Radboud University Medical Centre), Michiel S. van der Heijden, MD, PhD (Netherlands Cancer Institute), Sipke Helder (Patient association 'Leven met blaas- of nierkanker'), Maarten C.C.M. Hulshof, MD, PhD (Amsterdam University Medical Centres, location AMC), Anna M. Leliveld, MD, PhD (University Medical Centre Groningen), Geert J.L.H. van Leenders, MD, PhD (Erasmus Medical Centre), Richard P. Meijer, MD, PhD (University Medical Centre Utrecht), Reindert J.A. van Moorselaar, MD, PhD, Prof (Amsterdam University Medical Centres, location VUmc), Sasja F. Mulder, MD, PhD (Radboud University Medical Centre), Ronald I. Nooter, MD (Franciscus Gasthuis & Vlietland hospital), Juus L. Noteboom, MD, PhD (University Medical Centre Utrecht), Jorg R. Oddens, MD, PhD (Amsterdam University Medical Centres, location AMC), Theo M. de Reijke, MD, PhD (Amsterdam University Medical Centres, location AMC, University of Amsterdam), Bas W.G. van Rhijn, MD, PhD, FEBU (Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital), Joep G.H. van Roermund, MD, PhD (Maastricht University Medical Centre), Tineke J. Smilde, MD, PhD (Jeroen Bosch Hospital), Guus W.J. Venderbosch (Patient association 'Leven met blaas- of nierkanker'), Bart P. Wijsman, MD, PhD (Elisabeth-TweeSteden Ziekenhuis).

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AUTHOR CONTRIBUTIONS

LMCH: conception, data collection, data analysis, data interpretation, writing the article. LAK: conception, data interpretation, writing the article. RPM: conception, data interpretation, writing the article. GJLHL: data interpretation, writing the article. BGLV: data interpretation, writing the article. LI: data interpretation, writing the article. TJS: data interpretation, writing the article. SS: conception, data interpretation, writing the article. JAW: conception, data interpretation, writing the article. KKHA: conception, data collection, data interpretation, writing the article. BlaZIB study group: writing the article. COVID and Cancer-NL consortium: writing the article. LMCH and KKHA had access to the data.

CONFLICTS OF INTEREST

Lambertus A. Kiemeney and J. Alfred Witjes are Editorial Board members of this journal, but were not involved in the peer-review process nor had access to any information regarding its peer-review.

Lisa M.C. van Hoogstraten, Richard P. Meijer, Geert J.L.H. van Leenders, Ben G.L. Vanneste, Luca Incrocci, Tineke J. Smilde, Sabine Siesling, Katja K.H. Aben, the BlaZIB study group and the COVID and Cancer-NL consortium declare that they have no conflict of interest.

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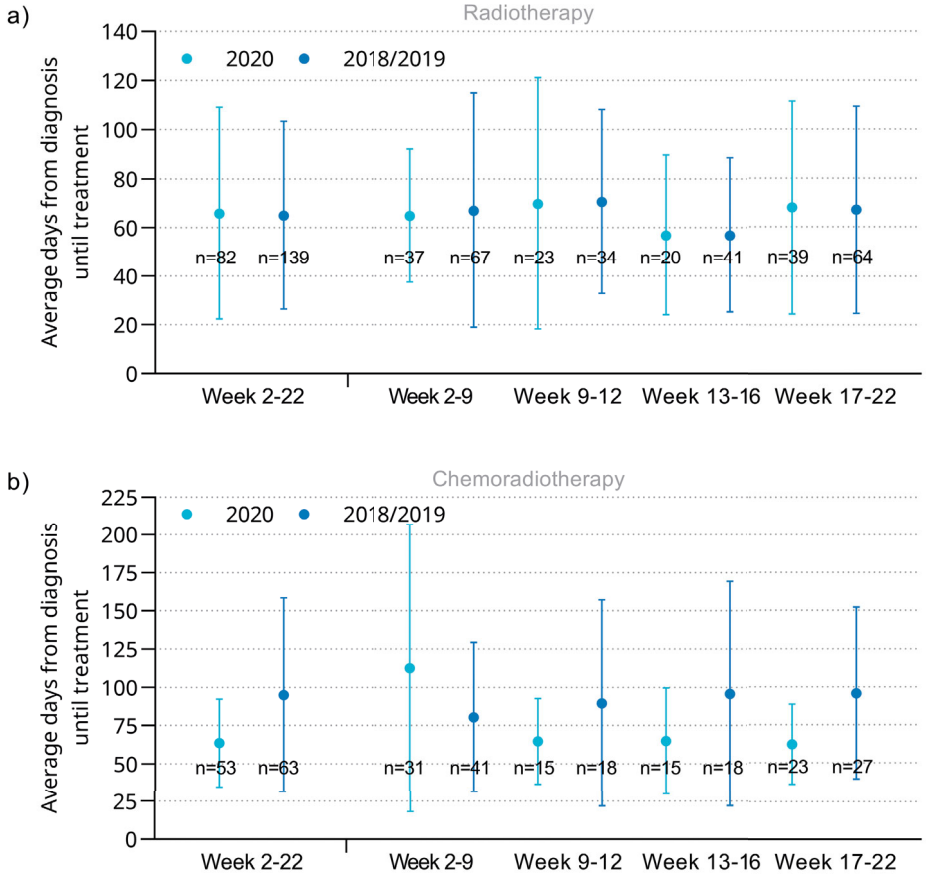
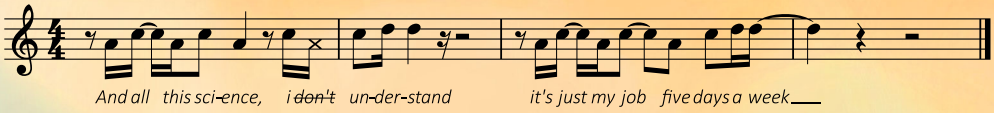
SUPPLEMENTARY MATERIAL

Supplementary Table 1. Number of transurethral resections of the bladder tumor (TURBTs) overall and by pathology result and number of radical cystectomies (RCs) performed over time in the Netherlands (source: PALGA, NCR).

	2015		2016		2017		2018		2019		2020	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Total n TURBTs	8094	-	8546	(+5.6%)	9049	(+5.9%)	9592	(+6.0%)	10.576	(+10.6%)	10.527	(-0.5%)
Benign tissue	1786	(22.1)	1775	(20.8)	1854	(20.5)	1998	(20.8)	2273	(21.5)	2141	(20.3)
Malign tissue	6270	(77.5)	6736	(78.8)	7173	(79.3)	7573	(79.0)	8274	(78.2)	8360	(79.4)
No pathology result	38	(0.5)	35	(0.4)	22	(0.2)	21	(0.2)	29	(0.3)	26	(0.2)
Total n RCs	925	-	890	(-3.8%)	934	(+4.9%)	932	(-0.2%)	808	(-13.3%)	820	(+1.5%)



Supplementary Figure 1. Average time and standard deviation to radiotherapy (a) and chemoradiotherapy (b) in days of patients with bladder cancer per period of treatment in 2020, compared to the reference period 2018/2019.



Rocket man - Elthon John (1972)

8

General discussion

Every patient with cancer should be treated optimally. Treatment should be based on patient and tumor characteristics and patient preferences, independent of the hospital in which the patient is being diagnosed or treated. The patient should be treated in a hospital equipped and experienced to provide this treatment, according to the standards applicable at that time.

The research in this thesis shows that there is considerable variation between hospitals in the treatment of patients with bladder cancer in the Netherlands. This variation is unlikely to be fully explained by case-mix factors and patient preferences. Furthermore, this interhospital variation appears to affect patient outcomes such as survival. Therefore, part of this variation may be considered unwanted variation.

In this chapter, recommendations to improve bladder cancer care in the Netherlands are discussed, based on the results from the studies described in this thesis. Then, the strengths and limitations of the BlaZIB study are discussed. Finally, I will conclude by discussing future challenges and opportunities.

RECOMMENDATIONS TO IMPROVE BLADDER CANCER CARE IN THE NETHERLANDS

Increase the use of a single bladder instillation of chemotherapy (Chapter 2)

The beneficial effects of a single bladder instillation of chemotherapy after transurethral resection of the bladder tumor (TURBT) are well described[1], but implementation in clinical practice shows room for improvement. As described by Dunsmore et al.[2], many barriers, facilitators and beliefs are in play, varying on a professional and organizational level. But perhaps the most important factor associated with the suboptimal use of a single instillation (SI) is the fear of severe complications. As we have shown in our study, this risk turns out to be low. Increasing awareness regarding the low complication risk and the oncological benefit of SI is a first step in improving SI administration rates. In order to properly evaluate improvement in future administration rates, the patient's eligibility assessed by the urologist should be taken into account, which makes evaluation of these rates challenging. The eligibility of a patient to receive a SI is mainly based on the outcomes of the TURBT[3]. Perforation of the bladder wall is a clear contraindication, but not always recognized during surgery[4,5], making the assessment of a patient's eligibility not completely straightforward.

Changing the timing of the instillation to the neoadjuvant setting might be a solution, as the risk of extravasation of the chemotherapy instillation would be omitted and post-operative assessment of eligibility for SI would become redundant. This way, health care professionals might be more inclined to administer a SI. The efficacy of a SI in the neoadjuvant setting is currently being investigated in the PRECAVE trial[6], concerning patients with Ta/T1 G1-G3 non-muscle invasive bladder cancer who are randomized between a neoadjuvant bladder instillation with Mitomycin C followed by TURBT, or upfront TURBT, with or without adjuvant treatment. Results from the interim analysis did not reveal a difference in recurrence-free survival between the two treatment arms. A subgroup analyses was performed as well, and a significant difference was found in favor of a single neoadjuvant instillation in patients who did not receive adjuvant treatment[7]. The trial is not powered to compare the efficacy of a neoadjuvant SI with post-operative SI. Still, the final results of this trial might pave the way for increasing use of SI.

Re-evaluate the recommended use of neoadjuvant chemotherapy (Chapter 3)

Only one in three eligible patients with muscle-invasive bladder cancer (MIBC) received the recommended treatment with neoadjuvant chemotherapy (NAC) prior to radical cystectomy. NAC use was much higher in patients with T3-4a bladder cancer compared to patients with T2-disease, reflecting the available evidence which is in favor of NAC for T3-4a but not convincing for T2-disease[8]. Although the existing evidence insinuates a tailored approach by disease stage, NAC is recommended for all stages of localized MIBC. This recommendation is based on controlled trials which included selected patients, i.e., who are younger, more often have T2-disease, better performance status and a lower comorbidity score compared to real-world patients[9-13]. The available real-world evidence could potentially lead to a refinement of this recommendation for patients with T2-disease, as the discrepancy between clinical trials and real-world practice often translates into a weaker effect of the therapy in question[13].

Better patient selection based on additional features is needed so that patients with T2-disease will either benefit from treatment with NAC, or can be directly referred for radical cystectomy without a delay due to ineffective NAC treatment. Personalized biomarker-based and molecular subtyping strategies could be useful in guiding patient selection for NAC[14,15]. For example, patients with a basal/squamous tumor subtype or alterations in DNA damage repair-genes appear to benefit substantially from NAC treatment[16]. In the future, traditional neoadjuvant treatment with chemotherapy

might be replaced by new therapies and therapy combinations such as neoadjuvant immuno(chemo)therapy[17-19].

Enable off-label use of capecitabine for chemoradiotherapy (Chapter 4)

The most commonly used chemoradiotherapy (CRT) regimens in the Netherlands are oral capecitabine-based CRT and intravenous 5-FU based CRT. The type of CRT regimen differs per hospital and geographic region. Capecitabine-based CRT is more patient friendly and more convenient for health care professionals as this regimen requires less medical procedures, i.e., less hospital visits due to the possibility of at-home administration of capecitabine and a lower number of fractions as part of the radiotherapy schedule. Also, no statistically significant differences were found between both regimens in terms of survival and toxicity. It is, therefore, surprising that capecitabine-based CRT is not recommended in the guidelines as the preferred CRT-regimen. This could be explained by the fact that capecitabine is not reimbursed (yet). As the oncological outcomes of both regimens are similar, we advocate the use of capecitabine-based CRT. This should be facilitated through obtaining approval for off-label use.

Off-label use may also facilitate future adoption of capecitabine-based CRT-regimens combined with immune checkpoint inhibitors, if proven effective. Several ongoing studies evaluate a combination of chemoradiotherapy and immunotherapy[20]. One of these studies specifically considers capecitabine-based CRT. This CRIMI study evaluates capecitabine-based CRT combined with nivolumab monotherapy versus a combination of nivolumab and ipilimumab. Preliminary results of the phase 1b-2 trial revealed that adding nivolumab or a combination of nivolumab and ipilimumab to chemoradiotherapy is feasible with acceptable toxicity profiles[21]. However, adding immunotherapy to the capecitabine-based CRT-regimen will probably increase the burden for the patient (e.g., in terms of adverse effects, hospital visits) and/or health care professional (e.g., more medical procedures). It will be interesting to see whether the beneficial effect on patient outcomes will outweigh the extra burden.

Discuss treatment of the pelvic lymph nodes with patients opting for bladder sparing treatment (Chapter 5)

Downstaging is present in 25% of patients with muscle-invasive bladder cancer who underwent upfront radical cystectomy, meaning that the tumor found in the cystectomy specimen has a lower disease stage compared to the initial diagnosis, or 'no evidence of disease' is found[8]. This rate is even higher (43%) in patients treated with neoadjuvant chemotherapy prior to radical cystectomy[8]. Patients with tumor

downstaging have a better prognosis compared to patients without downstaging. However, we showed that 4% of patients with tumor downstaging had occult lymph node metastases (LNM), resulting in considerable worse survival. For this reason, additional treatment of the lymph nodes might be considered in patients undergoing bladder sparing treatment, i.e., chemoradiation. This might be especially important for patients undergoing chemoradiation in current practice, as radiation fields have become smaller and are being optimized even further[22,23].

Whole bladder radiation might prove beneficial as was suggested in the BC2001 trial, evaluating survival outcomes in patients treated with whole-pelvis versus bladder-only radiation: the trial resulted in less LNM than expected[24]. A possible explanation for this result might be the large radiation field used in the chemoradiation regimen, including the lymph nodes in the pelvis. In a recent retrospective study, Kool et al. compared bladder-only with whole-pelvis radiation-based therapy with curative intent (i.e., also including chemoradiation) in patients with cT2-4aN0-2M0 bladder cancer using inverse probability of treatment weighting. The study, presented at ASCO-GU 2023, showed that whole-pelvis radiation might indeed be beneficial concerning overall and cancer-specific survival compared to bladder-only radiation[25]. The downside of whole-pelvis radiation is that healthy tissues surrounding the bladder are affected as well. Although pelvic lymph node dissection (PLND) is generally not recommended or performed as standard of care in patients undergoing bladder sparing treatment[24,26], combining chemoradiotherapy (bladder-only radiation) with a PLND could potentially serve as a suitable alternative. Further research is required to evaluate the added value of a PLND in this scenario. Additional treatment of the lymph nodes should be kept in mind when discussing bladder sparing treatment and the risk of occult LNM with patients.

Forget about a patient's calendar age, consider biological age instead (Chapter 6)

Patients with non-metastatic muscle-invasive bladder cancer should be treated with curative intent, regardless of their age[26]. We found that one in five patients did not receive any treatment other than best supportive care and this proportion increased with age. In a matched cohort of patients with similar prognostic characteristics, regardless of age, median overall survival was significantly worse for patients who remained untreated compared to patients treated with any type of treatment. A more holistic view of the patient should be pursued: the biological age of the patient, for example including a patient's frailty or fitness, will paint a more complete picture than calendar age alone[27-29].

Our data did not comprise sufficient information on whether the patient's preferences, life expectancy and quality of life were discussed between the patient and doctor. Nevertheless, the substantial interhospital variation that was observed is unlikely to be fully explained by this patient-doctor interplay and indicates that a proportion of untreated patients might be wrongfully denied life-prolonging treatment. Interhospital variation and the proportion of untreated patients might be reduced by maintaining a more structured approach of managing the elderly patient. This could be accomplished by consulting a geriatrician[30] or using standardized tools such as the clinical frailty scale[31]. The percentage of untreated patients will not decrease to zero; there should always be room to deviate from the guidelines and/or incorporate a patient's wish not to undergo treatment. The intended effect should be to increase a patient's chance of survival and optimal care, whichever hospital is in play.

Change current practice with the same urgency experienced during the COVID-pandemic (Chapter 7)

Changing clinical practice is hard and often takes a lot of time[32]. A great sense of urgency was widely shared due to the COVID-19 pandemic, since corona disrupted health care worldwide[33]. In a matter of weeks, guidelines were debated, adapted and acted upon, including those for bladder cancer management[34,35]. Our research showed that the (short term) impact of the first COVID-19 outbreak on Dutch bladder cancer care was limited and temporarily adapted guidelines were adhered to. We might even say that bladder cancer-related surgical capacity benefitted from the first COVID-wave, as the waiting lists for radical cystectomy were caught up. The COVID-19 pandemic therefore provided a bittersweet proof of concept that a quick change of current practice is in fact possible, if urgent enough. We recognize that this occurred at the expense of patients with other conditions[36], and that many people in- and outside health care were affected by COVID. Even though the impact of COVID-19 on bladder cancer care appeared to be limited, we need to keep monitoring the potential long term effects such as an anticipated stage shift due to delayed diagnosis. Furthermore, we should learn from this proof of concept that emerged during COVID and incorporate best practices in the process of future, planned changes.

STRENGTHS AND LIMITATIONS OF THE BLAZIB STUDY

The Netherlands Cancer Registry facilitates evaluation of bladder cancer care using high-quality data

All of the research described in this thesis was based on data from the Netherlands Cancer Registry (NCR), one of the best cancer registries in the world. Containing high-quality, unselected, population-based data with nationwide coverage and collected

in a uniform manner by well-trained data managers, the NCR provides a unique and ideal framework to evaluate bladder cancer care. The NCR consists of a standard set of items, providing a comprehensive overview of the patient's initial diagnosis and treatment[37]. By embedding the data collection of the BlaZIB study into the NCR, even more detailed data were efficiently collected, now capturing the total patient journey with a follow-up period of at least 2 years[38]. In addition, NCR data can be linked to different databases and systems for further enrichment of data, for example regarding health-related quality of life[39]. For the BlaZIB study, the NCR served as a sampling frame to quickly identify which patients should be invited on behalf of their treating physician for the health-related quality of life data collection using questionnaires[40]. Using the NCR is, thus, a quick and efficient way to provide insights into daily clinical practice and identify in which aspects of cancer care there is room for improvement.

Missing data in observational studies using real-world patient data are a challenge

Observational studies using real-world patient data rely on the information documented in the electronic patient files. Missing data, i.e., data that were not documented and could thus not be collected, are inherent to this study design. BlaZIB was designed as a prospective cohort study to limit the amount of missing data, but missing data could not entirely be avoided. One example of an important data item which is of interest for several research questions addressed in this thesis, is the performance status of the patient[26]. Although the patient's performance status is judged by the treating physician and acknowledged in current practice, it is often not documented. There were also insufficient data on patient preferences. More information on treatment decision-making, from both patient and doctor perspective, would allow for a more in-depth understanding of the treatment choices that were made. Although different methods exist to cope with these missing data, providing some assumptions are met[41], physicians are urged to clearly document the patient's performance status and preferences. Of course, the large administrative burden for health care professionals is recognized and debated later in this discussion.

Real-world data are essential in medical research

BlaZIB is an observational, nationwide, prospective cohort study. The population-based, real-world character of BlaZIB is a major benefit, especially when evaluating current practice. Pursuing a 'true' reflection of clinical practice, unselected population-based cohorts allow for good generalizability to the total patient population. Another advantage of studies based on real-world data is that these studies allow evaluation of current clinical practice regarding the entire patient journey; from the uptake of

diagnostics, to the adoption of treatment regimens, the follow-up of patients and the outcomes of variation in current practice. Health-related quality of life data are also part of a comprehensive evaluation of bladder cancer care and were collected (and can be evaluated) alongside the clinical data. In addition, BlaZIB allows for a critical reevaluation beyond the guidelines. By obtaining insight into current clinical practice we can also evaluate whether we are still considering the appropriate quality indicators, and if we are collecting the right data to do so.

Prioritization in research is key, especially when dealing with limited resources

Next to the limitation of missing data (addressed above), some other methodological considerations of the BlaZIB study need to be recognized. Due to limited resources, no additional data were collected on patients with Ta-stage bladder cancer. Patients with metastatic disease were also not included in BlaZIB although this is an interesting patient group; previous research revealed that only a small proportion of patients with metastatic disease receives systemic treatment[42]. New and often expensive (immuno) therapies for patients with metastatic disease are rapidly being developed and tested in clinical trials[43]. Evaluation of the effectiveness and uptake of these drugs in the real-world setting is solicited, as the results from clinical trials have limited generalizability and the costs and side-effects might not outweigh the (limited) benefit.

Next to the clinical data, health-related quality of life data were collected, but only in a subset of patients who were diagnosed in a hospital participating in the quality of life-measures and provided informed consent. Although health-related quality of life was an underexposed topic in this thesis, this topic and other aspects of bladder cancer care such as diagnosis, imaging and multidisciplinary management of bladder cancer are currently being addressed in other studies. The data from the BlaZIB study will remain available for research[44].

FUTURE CHALLENGES AND OPPORTUNITIES

Bladder cancer deserves more attention

A survey by the European Association of Urology (EAU) revealed that symptoms of bladder cancer, the most important one being hematuria, are often not recognized by European adults[45]. Thus, more attention for bladder cancer is warranted. Discussing our research with experts from the field and publishing our findings in scientific journals is a first step, but this is primarily aimed at the scientific community. Distributing our findings through other media like newsletters, LinkedIn posts, presentations at international conferences, brochures (like our brochure

summarizing the main findings of BlaZIB[46]) or public campaigns will reach a larger and more diverse audience, including patients, policy makers and the general public. Their awareness and support will facilitate, for instance, timely diagnosis of bladder cancer, benchmarking, guideline revision or even centralization of certain parts of bladder cancer care. This will contribute to the improvement of bladder cancer care and patient outcomes.

Anticipating the increase in bladder cancer diagnoses, special attention should be paid to prevention of bladder cancer[47]. The most important risk factor for bladder cancer is smoking[48], but patients with bladder cancer, even those who smoke, are often not aware of this[49]. Reducing the smoking prevalence will lead to a reduction in the number of patients diagnosed with and living with bladder cancer and reduce the pressure on bladder cancer care. There is currently no evidence in favor of secondary prevention, i.e., screening[50]. Regarding tertiary prevention, limited evidence suggests that smoking cessation after bladder cancer diagnosis might improve patient outcomes such as treatment response rates[51], complication rates and mortality rates after surgery for muscle-invasive disease[51-53], and recurrence rates in patients with non-muscle invasive disease[54,55]. A recent Dutch prospective cohort study evaluated the association between adherence to the 2018 World Cancer Research Fund/American Institute for Cancer Research lifestyle recommendations and the risk of recurrence and progression in patients with non-muscle invasive bladder cancer[56]. Based on 856 patients with Ta, T1 and Tis bladder cancer from the UroLife cohort, better post-diagnosis adherence to healthy lifestyle recommendations was associated with a 26% lower risk of first recurrence. More research is needed to confirm and quantify the beneficial effects of smoking cessation and adherence to lifestyle recommendations after a bladder cancer diagnosis on patient outcomes and bladder cancer care.

The large administrative burden should be reduced, both for clinicians and patients

In order to evaluate and eventually improve health care, insight into current practice is needed and subsequently, extensive data are required. The data collected in BlaZIB are derived from different data sources, for example electronic patient files and questionnaires, as documented by clinicians and patients, respectively. There is a delicate balance; for a more comprehensive evaluation of health care, more detailed data are needed. But obtaining more detailed data often comes at the cost of a higher administrative burden.

A survey distributed among Dutch clinicians revealed that clinicians spend 40% of their working hours on administrative duties[57]. In the Netherlands, a consultation takes about 10-20 minutes, during which administrative tasks have to be performed as well. Complete administration is necessary for justifying the management of patients and ensuring multidisciplinary coordination, but the time spent on administration cannot be spent on a patient, i.e., not only discussing disease management but also the patient's personal goals, which has shown to increase patient satisfaction, improve treatment compliance and decrease regret after treatment[58-60]. Artificial intelligence techniques such as automatic speech recognition (ASR) and natural language processing (NLP) could potentially take over administrative tasks[61]. For example, Leiden University Medical Center and Cloud Technology Solutions (CTS) developed an application that records and transcribes patient-doctor conversations, structures the collected data and, after verification by the doctor, transfers the data into the electronic patient file[62]. A pilot is currently running in three hospitals and will be upscaled to other hospitals and other health care providers such as general practitioners[63].

Patients face a large administrative burden as well. They receive many letters and patient information folders for studies. Often, patients receive identical or similar questionnaires, by different organizations or even within the same organization[64]. In the best case scenario, patients fill in this same questionnaire twice. In the worst case scenario, patients do not fill in any questionnaire or even withdraw from a study. Collecting the same data more than once is highly inefficient and poses a needless burden on the patient. Identifying all initiatives collecting questionnaire-data will provide insight into whether data can be obtained by combining or exchanging already collected data, without posing an extra burden on the patient[65]. Questionnaires could also be partly replaced by wearables, for instance to measure physical activity, pulse rate, core temperature or daily food intake[66,67]. Using wearables can thus reduce the administrative burden of patients. In addition, the data will also be more objective and biases associated with (self-reported) surveys (e.g., recall bias, social desirability bias) will be avoided.

Standardization and harmonization of data facilitates exchange of information

Enabling exchange of data will aid in efficient data collection, but this is often complicated by the use of different systems and a lack of unity of language. There are several ongoing initiatives addressing these issues, aimed at standardized and harmonized registration. 'Registratie aan de Bron' is a Dutch initiative by the NFU (the Dutch federation of university medical centers) and Nictiz (the national ICT-institute in

health care). This initiative aims for one-time, unambiguous registration of data that, once collected, is made available to the patient as well as to all relevant health care professionals involved in the patient's trajectory[68]. Through this initiative, a standard set of items was developed consisting of information building blocks describing what and how to document regarding the patient's trajectory. The concept of unity of language strongly relates to this; maintaining one single terminology system assures that all parties involved use (and understand) the same definitions and improves exchangeability of data and data acquisition for research[69].

The Netherlands Comprehensive Cancer Organisation (Integraal Kankercentrum Nederland, IKNL) is currently working on registering data at the source and standardized reporting of patient information in all Dutch hospitals, to facilitate automatic data import (and exchange) for all cancer types in the future[70]. This will improve the quality and exchangeability of the data collected. Collecting data will become less labor intensive and time consuming, moving towards real-time data that is made available as soon as it is generated.

Avoid reinventing the wheel: make use of existing data registries and infrastructures

IKNL, hosting the NCR, embraces the FAIR principles[70]. The NCR is a nationally and internationally well-known registry with extensive information available online (https://iknl.nl/en/ncr) (Findable), available for scientific research or statistics purposes (Accessible). By adhering to international coding agreements based on guidelines from the World Health Organisation (WHO) and the International Association of Cancer Registries (IACR), the NCR facilitates international comparison of data (Interoperable)[71]. In line with the R (Reusable) of FAIR, streamlining the collection of data through existing registries and infrastructures is encouraged as this will prevent researchers from collecting the same data, and thus potentially burdening the patient or professional, multifold. The NCR serves as a best practice: for every patient with cancer in the Netherlands, information is collected on demographics, patient and tumor characteristics and treatment. It is possible to expand this dataset with more detailed data. In addition, the NCR allows for linkage with health-related quality of life data from the PROFILES system, population data from Statistics Netherlands (CBS), Dutch Hospital Data (DHD), insurance data and pharmaceutical data, among others[39]. This way, double registration of the same information is avoided and bladder cancer care can be evaluated from different perspectives, which will appeal to a broader audience as well.

Linkage based on an individuals' social security number would provide many more opportunities, but national and European legislation (e.g., the General Data Protection Regulation (AVG)), complicate this objective. Nordic countries have shown that this is not impossible: Denmark, Sweden, Norway, Finland and Iceland allow for linkage of different registries, facilitating large cohort studies on many different topics (i.e., not only cancer or health-related)[72]. Hopefully, this proof of concept will convince policy makers to facilitate such initiatives in the Netherlands as well.

Bladder cancer care evaluation will remain relevant

The Dutch health care system, including Dutch cancer care, is under enormous pressure[47]. In September 2022, the integrated care pact (Integraal Zorgakkoord, IZA) was signed by relevant parties in Dutch health care, aiming to ensure accessibility, quality and affordability of our health care in the future[73]. IZA revolves around the principle of appropriate care (in Dutch: passende zorg). Care evaluation, regional cooperation and distribution or centralization of care, among others, are part of the strategy described in IZA. For example, IZA aspires to increase the minimum volume standards of complex (surgical) interventions to 50-100 interventions per institution per year. The effects of changes in health care on the quality and continuity of care need to be monitored[73].

Real-world data provide direction on how to improve bladder cancer care. The data can be used to describe different scenario's, monitor the transition of the bladder cancer field and evaluate its' effects on patient outcomes, as was shown before: in 2010, a minimum volume standard of 10 radical cystectomies (RCs) per hospital per year was introduced and in 2015, this standard was increased to 20 RCs[74]. An NCR-based study revealed that the introduction and increase of minimum volume standards resulted in fewer hospitals performing radical cystectomies, and it did not lead to an unwanted incentive to perform more cystectomies outside the recommended indication (i.e., patients with cT1 or cT4b/N+/M+ disease)[75]. Another study found that the minimum volume standard should be increased to at least 30 RCs in order to reduce postoperative mortality[76]. With IZA in play, these type of studies are likely to be required more often, but the limited (financial) resources are a bottleneck. As the importance of real-world data is clear, there is a clear role for policy makers to facilitate research and initiatives to improve (bladder) cancer care through more funding. This might mean that research funds have to be prioritized if we want to ensure accessible and affordable care, now and in the future. Instead of subsidizing fundamental research like the development of new (expensive) drugs, we should allocate more funds to improvement of current clinical practice through insights from population-based, real-world research.

Bladder cancer care evaluation continues with the Prospective Bladder Cancer Infrastructure

After BlaZIB, its successor, the Prospective Bladder Cancer Infrastructure (ProBCI), was initiated. ProBCI is an open cohort of patients with bladder cancer (including patients with metastatic disease as well), covering the entire course of the disease from diagnosis to death[77]. In ProBCI, the clinical data as collected in the NCR are supplemented with health-related quality of life data and biomaterials from patients with bladder cancer. ProBCI can be linked to other systems and databases, allowing for a tailored study design, for example through additional data collection or randomization between treatment arms. Thus, ProBCI is an infrastructure that facilitates comprehensive data collection for all types of studies, ranging from retrospective observational studies to investigator-initiated prospective clinical studies (a so-called trial within a cohort or TWIC[78]) and from descriptive studies to biomarker validation studies. Furthermore, patients included in ProBCI are asked for informed consent to participate in TWICs studies, including consent to serve as a control without being notified (as they will receive standard of care) and to be contacted for participation in future clinical trials. With this infrastructure, comprehensive evaluation of bladder cancer care can be continued and even be expanded to other topics and types of research within the field of bladder cancer.

Concluding remark

The research in this thesis revealed substantial variation in current bladder cancer care. In specific aspects of bladder cancer care, this variation appeared to affect patient outcomes such as survival. Recommendations were formulated to improve bladder cancer care. All recommendations following from the BlaZIB study, both addressed in this thesis and beyond the scope of this thesis, are communicated to the scientific associations involved in Dutch bladder cancer care. Research based on data from the BlaZIB-study evaluating bladder cancer care will continue untiringly in order to further improve bladder cancer care, with the ultimate goal of providing the best care possible for patients with bladder cancer.

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Appendices

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SUMMARY

Bladder cancer is a common malignancy, ranking among the top ten most common cancer types worldwide. Bladder cancer requires intensive treatment and monitoring and is one of the most expensive cancer types, posing a significant burden on patients, health care and society. Despite the discouragement of smoking, which is the most important risk factor for bladder cancer, the absolute global incidence is expected to increase in the upcoming decades due to population growth and population aging. This will increase the already existing burden on health care systems. Over the last decades, survival rates for bladder cancer have barely improved. However, recent developments in treatment options for metastatic urothelial carcinoma, i.e., immune checkpoint inhibitors, might result in better oncological outcomes in the near future.

Improving bladder cancer care can improve patient outcomes such as survival. In order to do so, we need more insight into bladder cancer care. By evaluating the (variation in) adherence to (inter)national guidelines in current bladder cancer care, we can ultimately formulate specific recommendations for bladder cancer care improvement. For this, more comprehensive, detailed clinical data are needed. Therefore, the nationwide, prospective BlaZIB cohort study was initiated. The data collection of the BlaZIB study was embedded into the Netherlands Cancer Registry, providing an efficient way to collect detailed, high-quality data. By assessing variation regarding specific aspects of bladder cancer care between hospitals in the Netherlands, identifying underlying factors, and/or assessing the effect of this variation on patient outcomes, we created a solid foundation for evidence-based recommendations to improve bladder cancer care.

In the study described in **Chapter 2**, we evaluated the guideline adherence and risks of the recommended single, post-operative instillation of intravesical chemotherapy in patients with TaG1G2 bladder cancer. A single instillation after transurethral resection of the bladder tumor is known to reduce the risk of recurrence. However, variation exists in its use, which is mainly due to the fear of severe complications after the single instillation. On average, 55% of patients had a single instillation after transurethral resection of the bladder tumor, varying from 0 to over 80% between hospitals. The 30-day mortality risk was 0.02% and the 14-day risk of severe complications was 1.6%. Although a single instillation can therefore be considered a safe treatment, these results also imply that a part of eligible patients is denied effective treatment. When indicated, a single instillation should be administered in order to reduce risk of recurrence.

International guidelines recommend neoadjuvant chemotherapy (NAC) preceding radical cystectomy in eligible patients with non-metastatic muscle-invasive bladder cancer. In the study described in **Chapter 3**, we evaluated the uptake of and factors associated with the recommended use of NAC, and we evaluated the effect of interhospital variation in the probability of NAC on the patients' survival. Guideline adherence was low; only 34% of eligible patients (based on performance status and renal function) received neoadjuvant chemotherapy (NAC). The proportion of patients who received NAC was larger in patients with cT3–4a disease compared to patients with cT2-disease (55% versus 26%). In patients with T2-disease, age was negatively associated and body mass index was positively associated with NAC use. For T3-4a disease, age and presence of comorbidity were both negatively associated with NAC use. Interhospital variation was large, i.e., 7–57% for patients with T2-disease and 31–62% for patients with T3-4a disease. Although not significant, patients diagnosed in hospitals more likely to give NAC appeared to have better survival compared to patients in hospitals with low probability, regardless of whether patients actually received NAC. Hospitals with higher NAC probability might have higher patient volumes and more surgical experience, resulting in e.g., better surgical outcomes affecting survival, but further research is warranted to elucidate the underlying mechanism. Guidelines currently recommend neoadjuvant chemotherapy for all patients with localized muscle-invasive bladder cancer. As literature clearly shows the potential survival benefit of neoadjuvant chemotherapy in patients with cT3-4a disease, better guideline adherence might be pursued for this patient group. For patients with cT2-disease the benefit of neoadjuvant chemotherapy remains debatable and guideline recommendations for these patients should be reconsidered.

In the study described in **Chapter 4**, we compared two commonly used chemoradiotherapy regimens in the Netherlands. 5-Fluorouracil (5-FU) based and capecitabine-based chemoradiotherapy were compared regarding treatment completion, toxicity and survival. A curative chemoradiotherapy protocol 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 overall survival (73% vs 61%, $p = 0.07$) and 2-year disease-free survival (56% vs 50%, $p = 0.50$) did not differ significantly between groups. Capecitabine-based chemoradiotherapy is more patient-friendly and more convenient for health care professionals as this regimen avoids intravenous administration of the radiosensitizer and requires fewer fractions of radiotherapy compared to 5-FU based chemoradiotherapy, resulting in fewer hospital visits and less medical procedures. In the Netherlands, capecitabine is not reimbursed (yet). Enabling

off-label use of capecitabine could increase the adoption of this more convenient chemoradiotherapy regimen, for both patients and healthcare professionals.

Little is known about the prevalence of occult lymph node metastases after tumor downstaging, although survival is known to be adversely affected. In the study described in **Chapter 5**, we estimated the prevalence of occult lymph node metastases (LNM) in patients with tumor downstaging at radical cystectomy and assessed the survival of patients with and without occult LNM. We found that occult LNM were present in 4.3% of patients without residual muscle-invasive disease at radical cystectomy. This was irrespective of neoadjuvant chemotherapy prior to surgery, or clinical T-stage. Patients with occult LNM showed considerable worse survival compared to patients without occult LNM: median overall survival was 3.5 years (95% CI 2.5–8.9) versus 12.9 years (95% CI 11.7–14.0), respectively. Based on these results, additional treatment of the lymph nodes is recommended, especially since the use of bladder sparing treatment, which does not include a pelvic lymph node dissection by standard, is increasing and the radiation fields have become smaller (i.e., excluding the pelvic lymph nodes) due to improved radiation techniques. The risk of occult lymph node metastases and additional treatment should be discussed with patients opting for bladder-sparing treatments.

Non-metastatic muscle-invasive bladder cancer is potentially curable but a part of patients remains untreated. In the study described in **Chapter 6**, we investigated the characteristics and survival of this understudied group of untreated patients. We found that one in five patients remained untreated and this proportion increased with age. Even after stratification by age, increasing age remained positively associated with remaining untreated in the group of patients aged ≥75 years. Worse performance status, worse renal function, cT4a-disease and previous radiotherapy in the abdomen/pelvic area also increased the probability of remaining untreated. In patients aged <75 years, significant associations were found for performance status, renal function and cT4a-disease. Considering the large interhospital variation for remaining untreated, a proportion of untreated patients might be wrongfully denied life-prolonging treatment. In a matched cohort of patients with similar prognostic characteristics, median overall survival was significantly worse for patients who remained untreated compared to treated patients. Our data show that chronological age is an important determinant in treatment decision-making in current clinical practice. Chronological age may differ significantly from biological age, which incorporates the fitness or frailty of the patient as well. The focus should thus shift from chronological age to the biological age of the patient.

In the study described in **Chapter 7,** we addressed the impact of the first COVID-19 wave on bladder cancer care in the Netherlands on the number of diagnoses, treatment and surgical capacity. During the first COVID-wave, the number of bladder cancer diagnoses decreased by 14% and increased again in the second half of 2020. The decline was most pronounced in patients aged 70 years or older and in patients with non-muscle invasive bladder cancer. Changes in treatment remained limited. Guidelines were temporarily adapted to ensure continuity of oncological care, and were adhered to; use of neoadjuvant chemotherapy decreased temporarily (and non-significantly) from 34% to 25%, and time to neoadjuvant chemotherapy was temporarily longer in patients diagnosed shortly after the start of the outbreak. Patients with muscle-invasive disease diagnosed at the end of the first COVID wave were less likely to undergo a radical cystectomy (OR 0.62, 95% CI 0.40–0.97). If patients underwent surgery, time until surgery became 6 days shorter. Compared to previous years, 5% more RCs were performed during the first wave. Overall, a 7% reduction in RCs was observed in 2020. Altogether, the impact of the first COVID-19 outbreak on bladder cancer care in the Netherlands appears to be limited and the pandemic has shown that, if urgent enough, a quick change in current practice is actually possible. Future research may address the impact of the bladder cancer diagnoses that were missed, i.e., bladder cancer stage shift and long-term outcomes.

In **Chapter 8**, we conclude with a general discussion of all of the studies described above. In addition, we discuss the strengths and limitations of the BlaZIB study, and future challenges and opportunities. The research in this thesis revealed substantial variation in current bladder cancer care. In specific aspects of bladder cancer care, this variation appeared to affect patient outcomes such as survival. Recommendations were formulated to improve bladder cancer care. All recommendations following from the BlaZIB study, both addressed in this thesis and beyond the scope of this thesis, are communicated to the scientific associations involved in Dutch bladder cancer care. Research based on data from the BlaZIB-study evaluating bladder cancer care will continue untiringly in order to further improve bladder cancer care, with the ultimate goal of providing the best care possible for patients with bladder cancer.

NEDERLANDSE SAMENVATTING

Blaaskanker staat in de top-10 van meest voorkomende kankersoorten wereldwijd. Het is bovendien een van de duurste vormen van kanker. Dat komt vooral door het hoge risico op terugkeer van de ziekte, waardoor patiënten vaak controles en behandelingen moeten ondergaan. Daarmee is blaaskanker belastend voor de patiënt, de gezondheidszorg én de maatschappij. Roken is de belangrijkste risicofactor voor het krijgen van blaaskanker. Ondanks het ontmoedigingsbeleid ten aanzien van roken in diverse landen, zal naar verwachting de absolute wereldwijde incidentie van blaaskanker de komende decennia blijven stijgen. Oorzaken hiervan zijn de groei en de vergrijzing van de populatie. Deze stijging in incidentie zal de reeds bestaande druk op de gezondheidszorg vergroten. De afgelopen decennia zijn de overlevingskansen van blaaskanker nauwelijks gestegen. Recente ontwikkelingen op het gebied van blaaskanker, bijvoorbeeld behandeling met immuuntherapie met checkpointremmers in de gemetastaseerde setting, zouden in de toekomst mogelijk kunnen leiden tot een verbetering van de overleving.

Meer inzicht in hoe de blaaskankerzorg in Nederland eruit ziet, geeft ook meer inzicht in waar verbetering mogelijk is. Uiteindelijk kan dit leiden tot betere oncologische uitkomsten, zoals een betere overleving en/of kwaliteit van leven. Door onderzoek te doen naar de (variatie in) naleving van (inter)nationale richtlijnen voor blaaskanker, kunnen aanbevelingen geformuleerd worden ter verbetering van de blaaskankerzorg. Hiervoor zijn meer uitgebreide en gedetailleerde data nodig. Daarom zijn we gestart met de BlaZIB-studie, een landelijke prospectieve cohortstudie. Door de dataverzameling van de BlaZIB-studie in te bedden in de Nederlandse Kankerregistratie (NKR), is op efficiënte wijze gedetailleerde data van hoge kwaliteit verzameld. Op basis van die data zijn verschillende aspecten van de blaaskankerzorg in kaart gebracht, is gekeken naar variatie tussen ziekenhuizen en naar factoren die deze variatie kunnen verklaren. Waar mogelijk is ook gekeken naar het effect van deze variatie op de oncologische uitkomsten. Met dit onderzoek is een sterk fundament gelegd voor wetenschappelijk onderbouwde aanbevelingen ter verbetering van de blaaskankerzorg in Nederland, en mogelijk zelfs voor in het buitenland.

In **Hoofdstuk 2** wordt een studie beschreven waarin de naleving van de richtlijnen en de risico's van de aanbevolen eenmalige, postoperatieve spoeling met intravesicale chemotherapie voor patiënten met laag-risico blaaskanker (stadium TaG1G2) is onderzocht. Eerdere studies hebben al laten zien dat een eenmalige blaasspoeling met chemotherapie na transurethrale resectie van de blaastumor (TURT) de kans op

een recidief verlaagt. Desondanks varieert het gebruik van de eenmalige spoeling in Nederland. Een factor die waarschijnlijk een grote rol speelt is de angst voor ernstige complicaties na het geven van de spoeling. Uit het onderzoek bleek dat ongeveer 55% van de patiënten na TURT een eenmalige spoeling onderging. Dit percentage varieerde tussen ziekenhuizen van 0% tot meer dan 80%. Het risico op overlijden binnen 30 dagen na de behandeling bleek laag te zijn; 0,02% en het risico op ernstige complicaties binnen 14 dagen na de behandeling was 1,6%. Op basis van deze resultaten kan een eenmalige spoeling na TURT als een veilige behandeling worden beschouwd, mits er geen sprake is van contra-indicaties. Op basis van deze resultaten kan geconcludeerd worden dat een deel van de patiënten op dit moment mogelijk onterecht een effectieve behandeling wordt onthouden. Om de kans op een recidief te verkleinen, zouden meer patiënten, mits ze hiervoor in aanmerking komen, een eenmalige blaasspoeling moeten krijgen.

De aanbevolen behandeling voor patiënten met gelokaliseerde spierinvasieve blaaskanker is een radicale cystectomie, voorafgegaan door neoadjuvante chemotherapie (NAC) in patiënten die daarvoor in aanmerking komen. In de studie beschreven in **Hoofdstuk 3** onderzochten we de toepassing van- en de factoren geassocieerd met het gebruik van NAC. Ook onderzochten we het effect van ziekenhuisvariatie in het gebruik van NAC op de overleving. Het bleek dat slechts 34% van alle patiënten die voor NAC in aanmerking kwamen (gebaseerd op de performance status en nierfunctie), daadwerkelijk behandeld werd met NAC. Dit percentage was groter in de patiënten met stadium cT3-4a blaaskanker, vergeleken met de patiënten met stadium T2-blaaskanker (55% versus 26%). Bij patiënten met T2-stadium bleek dat leeftijd en BMI een rol speelden bij het al dan niet geven van NAC (hoe ouder, hoe minder vaak NAC en hoger het BMI, hoe vaker NAC). Ook bij patiënten met stadium T3-4a bleek leeftijd een rol te spelen, maar daarnaast ook het hebben van comorbiditeiten (meer comorbiditeit, minder vaker NAC). De variatie in het gebruik van NAC tussen ziekenhuizen was aanzienlijk, met 7-57% voor patiënten met T2-stadium en 31-62% voor patiënten met stadium T3-4a. Patiënten die waren gediagnosticeerd in een ziekenhuis dat meer genegen was NAC te geven, leken een betere overleving te hebben (niet statistisch significant) in vergelijking met patiënten gediagnosticeerd in ziekenhuizen die dit minder vaak deden. Een verklaring voor dit mogelijke verschil zou kunnen zijn dat ziekenhuizen die meer genegen zijn NAC te geven, meer expertise hebben op het gebied van blaaskanker, maar er is meer onderzoek nodig. In de huidige richtlijnen wordt NAC aanbevolen voor alle patiënten met gelokaliseerde spierinvasieve blaaskanker, mits ze hiervoor in aanmerking komen. Omdat uit eerdere studies blijkt dat patiënten met T3-4a blaaskanker en behandeling met NAC een betere overleving

hebben, zou de naleving van de richtlijnen verbeterd moeten worden. Het bewijs voor het overlevingsvoordeel van NAC bij patiënten met T2-stadium blaaskanker daarentegen is echter veel minder overtuigend. De aanbeveling in de richtlijn voor deze patiëntengroep zou heroverwogen moeten worden.

In de studie beschreven in **Hoofdstuk 4** vergeleken we twee veelgebruikte chemoradiatie-behandelingen in Nederland, namelijk chemoradiatie met 5-Fluorouracil (5-FU) en chemoradiatie met capecitabine. Daarbij keken we naar welk deel van de patiënten de behandeling voltooide, de bijwerkingen (toxiciteit) en overleving. In 77% van de patiënten in de capecitabine-groep werd het curatieve behandelschema voltooid versus 62% van de patiënten in de 5-FU groep (p = 0.06). Er was geen statistisch significant verschil in bijwerkingen (14% versus 21%, p = 0.29), 2-jaars algemene overleving (73% versus 61%, p = 0.07) en 2-jaars ziektevrije overleving (56% versus 50%, p = 0.50) tussen beide behandelgroepen. Chemoradiatie met capecitabine is vriendelijker voor zowel de patiënt als de zorgverlener, omdat capecitabine in tabletvorm wordt gegeven en niet intraveneus zoals 5-FU, en omdat de behandeling met capecitabine gepaard gaat met minder bestralingen vergeleken met chemoradiatie met 5-FU. Hierdoor vereist de chemoradiatie-behandeling met capecitabine minder ziekenhuisbezoeken en minder medische handelingen. Chemoradiatie met capecitabine zou daarom de voorkeur moeten krijgen. Echter, capecitabine wordt in Nederland (nog) niet vergoed. Het verkrijgen van off label-indicatiestelling voor capecitabine zou het gebruik van deze behandeling, welke vriendelijker is voor zowel de patiënt als de zorgverlener, kunnen vergroten.

Er is weinig bekend over de prevalentie van occulte lymfekliermetastasen na tumor downstaging (lager ziektestadium), terwijl dit wel een negatieve invloed heeft op de overleving van de patiënt. In de studie beschreven in **Hoofdstuk 5** is de prevalentie en prognose van occulte lymfekliermetastasen onderzocht in patiënten gediagnosticeerd met niet-gemetastaseerde, spierinvasieve blaaskanker met tumor downstaging na de radicale cystectomie. Het bleek dat bij 4.3% van deze patiënten occulte lymfekliermetastasen aanwezig waren. Dit risico bleek niet beïnvloed te worden door het wel of niet geven van neoadjuvante chemotherapie, of het klinisch ziektestadium. De mediane overleving van patiënten met occulte lymfekliermetastasen was aanzienlijk slechter vergeleken met die van patiënten zonder occulte lymfekliermetastasen, namelijk 3.5 jaar (95% CI 2.5-8.9) versus 12.9 jaar (95% CI 11.7-14.0). Op basis van deze resultaten wordt aanvullende behandeling van de lymfeklieren aanbevolen, zeker nu blaassparend behandelen aan populariteit wint. De blaassparende behandeling bestaat meestal uit chemoradiotherapie. Hierbij wordt niet standaard een pelviene lymfeklierdissectie gedaan. Ook

worden bij chemoradiotherapie de lymfeklieren vaak niet bestraald. Dit komt doordat met moderne bestralingstechnieken het stralingsveld kleiner is geworden en de lymfeklieren niet in het bestraalde gebied liggen. Het risico op occulte lymfekliermetastasen en eventueel aanvullende behandeling van de lymfeklieren zou daarom besproken moeten worden met patiënten die voor een blaassparende behandeling kiezen.

Een aanzienlijk deel van de patiënten met niet-gemetastaseerde spierinvasieve blaaskanker krijgt geen tumorgerichte behandeling. In de studie beschreven in **Hoofdstuk 6** onderzochten we de karakteristieken en overleving van deze onderbelichte groep patiënten. Het blijkt dat een op de vijf patiënten geen behandeling met curatieve intentie krijgt, en dit deel neemt toe naarmate patiënten ouder zijn. Wanneer apart wordt gekeken naar jongere (<75 jaar) en oudere patiënten (75 jaar en ouder) dan blijkt dat binnen de groep oudere patiënten, leeftijd nog steeds significant geassocieerd is met het niet behandeld worden. Andere factoren die een rol speelden waren een slechtere performance status, slechtere nierfunctie, hoger ziektestadium (cT4a) en eerdere bestralingen in het abdomen/bekkengebied. In de groep patiënten jonger dan 75 jaar bleken deze factoren (performance status, nierfunctie en hoger ziektestadium) ook geassocieerd met niet behandeld worden. De variatie tussen ziekenhuizen voor wat betreft het percentage patiënten dat geen tumorgerichte behandeling kreeg, bleek groot te zijn. Een vergelijking van behandelde versus onbehandelde patiënten met een soortgelijk prognostisch profiel laat zien dat de mediane overleving van de groep van onbehandelde patiënten aanzienlijk slechter was. Gezien de grote ziekenhuisvariatie en het overlevingsvoordeel in behandelde patiënten, wordt een deel van de patiënten met niet gemetastaseerde spierinvasieve ziekte mogelijk onterecht een levensverlengende behandeling onthouden. Kalenderleeftijd bleek een belangrijke factor in de behandelbesluitvorming te zijn. Echter, kalenderleeftijd is niet hetzelfde als de biologische leeftijd. Daarbij speelt bijvoorbeeld de conditie en de kwetsbaarheid van de patiënt mee. Bij de keuze om wel of niet te behandelen zou de focus daarom meer moeten liggen op de biologische leeftijd van de patiënt.

In de studie beschreven in **Hoofdstuk 7** onderzochten we de impact van de eerste COVID-19 golf op de blaaskankerzorg in Nederland. Daarbij keken we naar het aantal diagnoses, de behandeling en operatiecapaciteit. Tijdens de eerste coronagolf, van februari tot en met mei van 2020, nam het aantal blaaskankerdiagnoses af met 14%. Deze afname werd vooral gezien bij patiënten van 70 jaar en ouder en bij patiënten met niet-spierinvasieve blaaskanker. In de tweede helft van 2020 herstelde het aantal diagnoses weer naar de aantallen die je zou verwachten op

basis van eerdere jaren. Veranderingen in de behandeling van blaaskanker bleven beperkt. De richtlijnen die tijdelijk aangepast waren om de continuïteit van de zorg te kunnen blijven waarborgen, bleken in de praktijk goed opgevolgd te worden. Het gebruik van neoadjuvante chemotherapie daalde tijdelijk van 34% naar 25% (niet statistisch significant) en de tijd tot start neoadjuvante chemotherapie werd tijdelijk langer voor patiënten die kort na de uitbraak van de coronapandemie met blaaskanker werden gediagnosticeerd. Aan het einde van de eerste coronagolf werden patiënten met spierinvasieve blaaskanker minder vaak geopereerd (OR 0.62, 95% CI 0.40–0.97). Echter, bij de patiënten die een cystectomie ondergingen, was de tijd tot de operatie gemiddeld 6 dagen korter. Het aantal operaties tijdens de eerste coronagolf was 5% hoger in vergelijking met eerdere jaren maar over heel 2020 was dit aantal 7% lager. Concluderend lijkt de impact van de eerste coronagolf op de Nederlandse blaaskankerzorg beperkt zijn. De COVID-pandemie heeft laten zien dat er een snelle verandering van de klinische praktijk mogelijk is, als de urgentie hoog genoeg is. De lange termijn effecten konden in dit onderzoek nog niet onderzocht worden. Eventueel vervolgonderzoek zou moeten uitwijzen of het later stellen van de diagnose blaaskanker heeft geleid tot een hoger ziektestadium en/of slechtere oncologische uitkomsten zoals de (ziektevrije)overleving.

In **Hoofdstuk 8** worden bovenstaande studies samengevat in een algemene beschouwing, en wordt gereflecteerd op de sterke punten en beperkingen van de BlaZIB-studie en de toekomstige uitdagingen en kansen. Het onderzoek in dit proefschrift laat zien dat er aanzienlijke variatie is in de blaaskankerzorg in Nederland. In sommige gevallen blijkt ook dat die variatie gevolgen heeft voor de oncologische uitkomsten, zoals de overleving. Op basis van de studies beschreven in dit proefschrift, en op basis van andere studies binnen BlaZIB, zijn aanbevelingen geformuleerd om de blaaskankerzorg te verbeteren. Een rapport met aanbevelingen is aangeboden aan de wetenschappelijke verenigingen in Nederland die betrokken zijn bij de blaaskankerzorg. Het onderzoek stopt hier niet. De BlaZIB-data worden nog steeds gebruikt om onderzoek te doen waarmee de blaaskankerzorg steeds verder kan worden verbeterd, met als uiteindelijke doel om de best mogelijke zorg te bieden aan patiënten met blaaskanker.

RESEARCH DATA MANAGEMENT

All studies in this thesis are based on clinical data of patients with bladder cancer that were collected by well-trained data managers of the Netherlands Cancer Registry (NCR) by consulting the electronic patient files. For most studies, additional data were collected. For the study described in Chapter 2, linkage with the Dutch Hospital Data (DHD) register was performed to retrieve information on severe complications and readmissions, which is not readily available in the NCR. To retrieve cause of death, the electronic health records of patients deceased within 30 days post-treatment were re-examined by data managers of the NCR. For the study described in Chapter 3, a survey was conducted among urologists regarding institutional practice patterns. In Chapter 4, data on health-related quality of life was collected by questionnaires using the PROFILES application. The type and source of the data per chapter used are specified in the table below.

Chapter	Title	Type and source of data used
Chapter 1	General introduction and thesis outline	-
Chapter 2	Low risk of severe complications after a single, post-operative instillation of intravesical chemotherapy in patients with TaG1G2 urothelial bladder carcinoma	Clinical data collected from the electronic patient files and stored in the NCR Linkage with the Dutch Hospital Data register, stored in a separate folder on the G-disk of IKNL Additional clinical data from electronic patient files, stored in a separate folder on the G-disk of IKNL
Chapter 3	Low guideline adherence to recommended use of neoadjuvant chemotherapy in patients with non-metastatic muscle-invasive bladder cancer	Clinical data collected from the electronic patient files and stored in the NCR Survey among specialists, stored in a separate folder on the G-disk of IKNL
Chapter 4	Concurrent chemoradiation for muscle-invasive bladder cancer using 5-fluorouracil versus capecitabine: a nationwide cohort study	Clinical data collected from the electronic patient files and stored in the NCR Health-related quality of life data collected by questionnaires, stored in the PROFILES application
Chapter 5	Occult lymph node metastases in patients without residual muscle-invasive bladder cancer at radical cystectomy with or without neoadjuvant chemotherapy: a nationwide study of 5,417 patients	Clinical data collected from the electronic patient files and stored in the NCR
Chapter 6	Muscle-invasive bladder cancer: the role of age in receiving treatment with curative intent	Clinical data collected from the electronic patient files and stored in the NCR
Chapter 7	The impact of the COVID-19 pandemic on bladder cancer care in the Netherlands	Clinical data collected from the electronic patient files and stored in the NCR
Chapter 8	General discussion	-

Ethics and privacy

According to the Central Committee on Research involving Human Subjects (CCMO), the studies in this thesis are not subject to the Medical Research Involving Human Subjects Act (WMO) and do not require approval from an ethics committee in the Netherlands. Every study conducted in this thesis was approved by the Netherlands Cancer Registry's Supervisory Committee. Informed consent was obtained from all study participants from hospitals participating in the health-related quality of life measurements. Technical and organizational measures were followed to safeguard the availability, integrity and confidentiality of the data. These measures include the use of pseudonymization, access authorization and secure data storage. All data used in this thesis were handled according to the privacy statement of IKNL[1].

Data collection and storage

All clinical data in the NCR are registered by well-trained data managers and stored in the Registratie Applicatie van de Nederlandse Kankerregistratie (RANK). The NCR is hosted by Integraal Kankercentrum Nederland (IKNL). IKNL is certified according to NEN7510, the Dutch standard for information security in healthcare. IKNL is ISO 27001-certified as well. To ensure consistency among data managers and high-quality data, a detailed coding manual was developed and manual data checks were performed regularly. Where possible, data was registered according to international coding agreements. Only authorized IKNL employees can inspect personal data in the NCR, and only after logging into a secured digital environment using two-factor authentication. Researchers have access to pseudonymized data. Every patient is provided with a unique patient number. The data in the NCR will be stored for as long as the NCR exists. The data extracted from the NCR, used for the studies in this thesis are stored in a separate folder on the IKNL server.

All HRQoL data were collected through paper or online questionnaires. Patients could fill in the questionnaire online after logging in with a personal password and two-factor authentication. Patients filling in a paper questionnaire received their questionnaire in an enclosed envelope without any logo's, so others could not derive that this envelope originated from IKNL and is thus related to cancer research. Patients returned their completed questionnaire in an enclosed envelope. All collected HRQoL data were processed and are stored digitally in the Patient-Reported Outcomes Following Initial Treatment and Long-Term Evaluation of Survivorship (PROFILES) application[2]. Data stored in PROFILES is handled according to the Dutch law (Dutch Data Protection Act) and can only be accessed by authorized personnel after logging in using two-factor authentication. Paper (hardcopy) data are stored in cabinets at IKNL for 15 years.

For Chapter 2 and Chapter 3, sources other than the NCR and PROFILES were used, i.e. linkage was performed with the Dutch Hospital Data register, additional clinical data was collected from the medical files that was not stored in the RANK, and a survey was distributed among specialists participating in the BlaZIB study. These data were stored in separate folders on the G-disk of IKNL. For analysis, exports of the data were made to SAS (SAS Institute, Cary, North Carolina, USA) and saved on the IKNL network with limited access for project members. When the data are analyzed by others, confidentiality and anonymity of patients is guaranteed with the assignation of a unique study number to each patient.

Availability of data

The papers in Chapter 2 up to Chapter 7 are published open access. Anonymous data can be requested from the NCR[3]. 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. Statistical code used for the studies in this thesis can be made available post publication by the authors upon request.

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1. https://iknl.nl/en/privacystatement
2. https://www.profielstudie.nl/
3. https://iknl.nl/nkr/cijfers-op-maat/gegevensaanvraag

PHD PORTFOLIO

PhD portfolio of L.M.C. van Hoogstraten

Department: **Health Evidence**
PhD period: **01/11/2019 – 31/12/2022**
PhD Supervisor(s): **Prof. dr. L.A.L.M. Kiemeney, Prof. dr. J.A. Witjes**
PhD Co-supervisor(s): **Dr. K.K.H. Aben, Dr. R.P. Meijer**

Training activities	Year(s)	Hours
Courses		
• RIHS - Introduction course for PhD candidates	2020	15.00
• Radboud University - Projectmanagement voor promovendi	2020	56.00
• Radboud University - Scientific writing for PhD candidates	2021	84.00
• Radboud University - BMS84: Multilevel and longitudinal data analysis	2021	84.00
• Radboudumc - Scientific integrity	2021	20.00
• EAU ESU course (2x)	2021	4.00
• Alumni Career Night incl. 2 workshops	2021	3.00
• VvE workshop - Longitudinal growth modelling	2021	2.00
• IKNL workshop (3x)	2021-2022	5.50
• RIHS/Graduate School workshop (5x)	2021-2023	6.50
• IKNL - Trusted advisorship trajectory	2022	16.00
• IKNL - Business English	2022	28.00
• Radboudumc - eBROK course	2023	42.00
Seminars		
• Radboud BMS lecture - Unmet needs of bladder cancer	2020	1.00
• MEDtalk NVMO - Welke gevolgen heeft het coronavirus voor mijn kankerbehandeling	2020	1.00
• Webinar - International perspectives on COVID-19 in cancer care	2020	1.50
• EAU Theme week session (3x)	2020	3.00
• RIHS webinar (3x)	2020-2021	3.00
• Radboud Research Integrity Round (3x)	2020-2022	5.00
• URO webinar (10x)	2020-2022	10.00
• Refereerbijeenkomst IKNL (6x)	2020-2022	19.50
• VvE webinar COVID-series (4x)	2021	4.00
• IKNL webinar - What editors want	2021	1.00
• BEMC talk - The circle of life: epidemiologic methods for dealing with treatment-confounder feedback	2021	1.50
• KNAW-webinar - Toeval in de geneeskunde	2021	1.50
• Personal Grant Info Meeting 2021 - External funding opportunities for early/mid-career researchers	2021	2.00
• VvE spring event - Bridging the gap between epidemiological science and policy	2022	2.00
• Webinar Real - World Evidence in Advanced Bladder Cancer	2023	1.50

Conferences		
• EAU VIRTUAL congress (video presentation)	2020	35.00
• NKR symposium - uitgezaaide kanker in beeld	2020	7.00
• BLADDR - Global conference on bladder cancer (video presentation)	2020	21.00
• IBCN conference	2020	7.00
• CaRe days	2021	7.00
• WEON (video presentation)	2021	28.00
• EAU VIRTUAL congress (2 poster presentations)	2021	35.00
• IACR (poster presentation)	2021	28.00
• ENCR (video presentation)	2021	28.00
• NKR symposium - Samen naar morgen (2 poster presentations)	2021	14.00
• RIHS PhD retreat (oral presentation)	2022	21.00
• WEON (oral presentation)	2022	28.00
• IBCN conference (2 poster presentations)	2022	28.00
• NKR symposium - Kanker in 2032 (2 poster presentations)	2022	14.00
• BLADDR - Global conference on bladder cancer (poster presentation & oral presentation)	2022	28.00
• Masterclass spierinvasief blaascarcinoom	2023	7.00
• Radboudumc Cancer Research Retreat (laptop presentation)	2023	21.00
Other		
• Journal club Dept. for Health Evidence (5x)	2020-2022	196.00
• IKNL PhD Journal club & methodology	2021-2022	56.00
• IKNL PhD Council chair/committee member	2021-2022	56.00
• IKNL PhD Intervisie	2021-2023	16.00
• IKNL PhD Council co-organising a 2-day PhD retreat	2022	28.00
Teaching activities		
Lecturing		
• Teaching CKO-9 course (3x)	2020-2021	84.00
• SAS training for students (4x)	2020-2022	24.00
• Lecture epidemiology internships	2020	4.00
• Lecture applied medical research (2x)	2021-2022	6.00
• Meet the PhD	2022	14.00
• Lecture Meet the PhD	2023	1.00
Supervision of internships / other		
• Supervision student internship (6x)	2020-2023	168.00
Total		**1433.5**

LIST OF PUBLICATIONS

Publications included in this thesis

Ripping TM, Kiemeney LA, **van Hoogstraten LMC**, Witjes JA, Aben KKH. Insight into bladder cancer care: study protocol of a large nationwide prospective cohort study (BlaZIB) (2020). BMC Cancer; 20(1):455. DOI: 10.1186/s12885-020-06954-7.

van Hoogstraten LMC, Witjes JA, Ripping TM, Nooter RI, Kiemeney LA, Aben KKH, et al. Low Risk of Severe Complications After a Single, Post-Operative Instillation of Intravesical Chemotherapy in Patients with TaG1G2 Urothelial Bladder Carcinoma (2021). Bladder Cancer; 7:193-203. DOI: 10.3233/BLC-201515.

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patients with non-metastatic muscle-invasive bladder cancer (2023). World J Urol; 41(7):1837-1845. DOI: 10.1007/s00345-023-04443-7.

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Brück K, Meijer RP, Boormans JL, Kiemeney LA, Witjes JA, **van Hoogstraten LMC**, et al. Disease-free survival of patients with muscle invasive bladder cancer treated with radical cystectomy versus bladder preserving therapy: a nationwide study (2023). Int J Radiat Oncol Biol Phys; 28:S0360-3016(23)07686-1. DOI: 10.1016/j.ijrobp.2023.07.027.

* Shared first authorship

ABOUT THE AUTHOR

Lisa Maria Catharina van Hoogstraten was born on the first of May, 1995 in Oss, the Netherlands. After her pre-university education at Titus Brandsma Lyceum in Oss, she started her Bachelor Biomedical Sciences at the Radboud University Nijmegen in 2013, focusing on epidemiology and health technology assessment. After successfully completing her scientific internship at the department of IQ Healthcare at Radboudumc regarding the quality of life in patients with head and neck cancer, she obtained her Bachelor degree in 2016. She continued with the Master Biomedical Sciences at the Radboud University, again focusing on health technology assessment and epidemiology. After combining the first year of the Master's program with a consultancy profile to broaden her scope, she returned to epidemiology in the last year of her Master. Motivated to gain experience in international research, she performed her final scientific internship at the Spanish National Cancer Research Center (Centro Nacional de Investigaciones Oncológicas, CNIO) in Madrid, Spain, evaluating the association between lifetime smoking patterns and the risk of pancreatic cancer.

She graduated cum laude in October 2018 and obtained her basic Epidemiological Researcher-degree (Epidemiologist A). In November 2018, she started working as a junior researcher at the Netherlands Comprehensive Cancer Organisation (Integraal Kankercentrum Nederland, IKNL) in the team of genitourinary cancers. She focused on the project 'Insight into bladder cancer care' (BlaaskankerZorg In Beeld, BlaZIB), evaluating the quality of bladder cancer care in the Netherlands. In November 2019, she started her PhD research on the same project. In addition to performing scientific research, she presented her research at different national and international scientific conferences, was involved in the coordination of the registration of bladder cancers in the Netherlands Cancer Registry, supervised students, and performed other educational activities as well. Together with three other PhD students, she set up a PhD council at IKNL and organized a PhD-retreat.

After completing her PhD, she will obtain her Epidemiological Researcher-degree at PhD level (Epidemiologist B). Currently, she is continuing her work parttime at IKNL as a postdoctoral researcher and she will be focusing on bladder cancer research, grant applications and educational activities. For the remainder of the week, she is working at the Department of Urology at Radboudumc as a postdoctoral researcher. There, she coordinates the BladParadigm trial, aiming to evaluate multiparametric MRI as a new staging method for patients suspected of having muscle-invasive bladder cancer.

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Richard, halverwege mijn PhD heb ik je in het promotieteam mogen verwelkomen als tweede copromotor. Als oncologisch uroloog van het UMC Utrecht haalde je ons regelmatig uit de Radboud-bubbel, dat leverde waardevolle inzichten op.

Dank aan de leden van de manuscriptcommissie, **Prof. dr. Rovers**, **Prof. dr. van Poppel** en **Dr. Westgeest**, voor jullie bereidheid tot het lezen en beoordelen van dit proefschrift en zitting te nemen in de promotiecommissie. Tevens dank aan **Prof. dr. Verheij, Prof. dr. Siesling** en **Dr. Mertens**, voor jullie bereidheid om zitting te nemen in de promotiecommissie.

BlaZIB zou niet tot stand zijn gekomen zonder de medewerking van alle deelnemende **ziekenhuizen**, **zorgverleners**, en uiteraard, alle **patiënten**. Heel veel dank voor

jullie bijdrage. Ik hoop dat we met (onder andere) dit proefschrift mooie stappen kunnen zetten om de blaaskankerzorg te verbeteren.

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KNL Netherlands comprehensive cancer organisation

Radboudumc university medical center

IN DEI NOMINE FELICITER

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