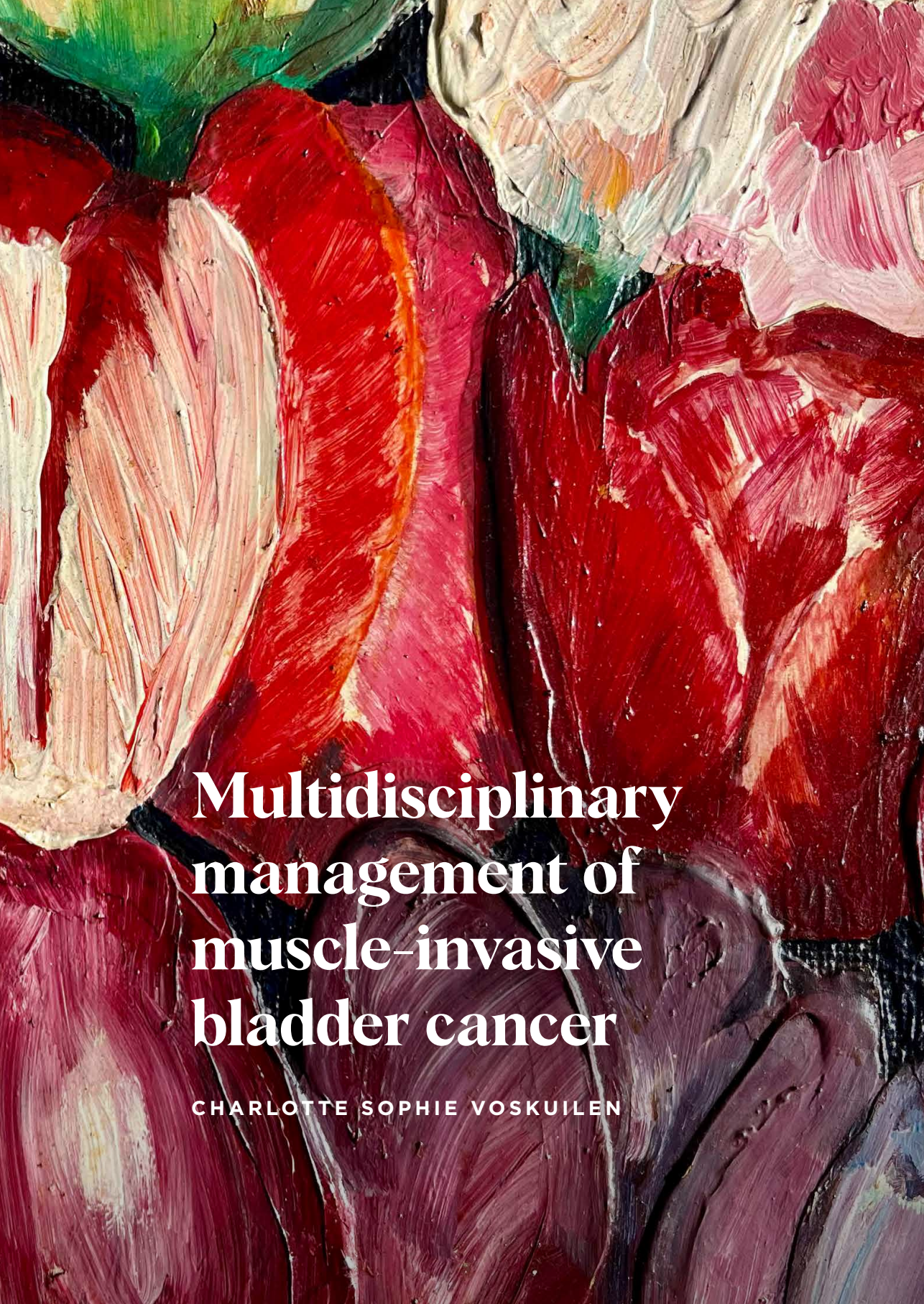

Multidisciplinary management of muscle-invasive bladder cancer

CHARLOTTE SOPHIE VOSKUILEN

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Colofon

ISBN	978-90-393-7660-7
Cover art	Ben Voskuilen, *Tulpen 1977*
Layout and cover design	Jelle Heijman
Printing	Ridderprint
DOI	10.33540/2172

The printing of this thesis was financially supported by the Netherlands Cancer Institute

Multidisciplinary management of muscle-invasive bladder cancer

Multidisciplinaire diagnostiek, stadiëring en behandeling van het spierinvasief blaascarcinoom
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof. dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

donderdag 16 mei 2024 des middags te 2.15 uur

door

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geboren op 17 januari 1991
te Amersfoort

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General introduction and thesis outline

General introduction

The urinary tract

The urinary tract is the organ system which produces and stores urine and discharges it from the body. It consists of an upper tract (kidney, renal pelvis, and ureter) and a lower tract (bladder and urethra) (Figure 1). Urine is produced by the kidneys and collected in the renal pelvis. Next, urine flows from the renal pelvis of each kidney through the ureters into the urinary bladder. The urinary bladder is a temporary storage reservoir for urine, with an average capacity of 300-500mL in adult humans. Average urine production is around 1.5L of urine per day, depending on intake, activity level, environmental factors, weight, and the individual's health.

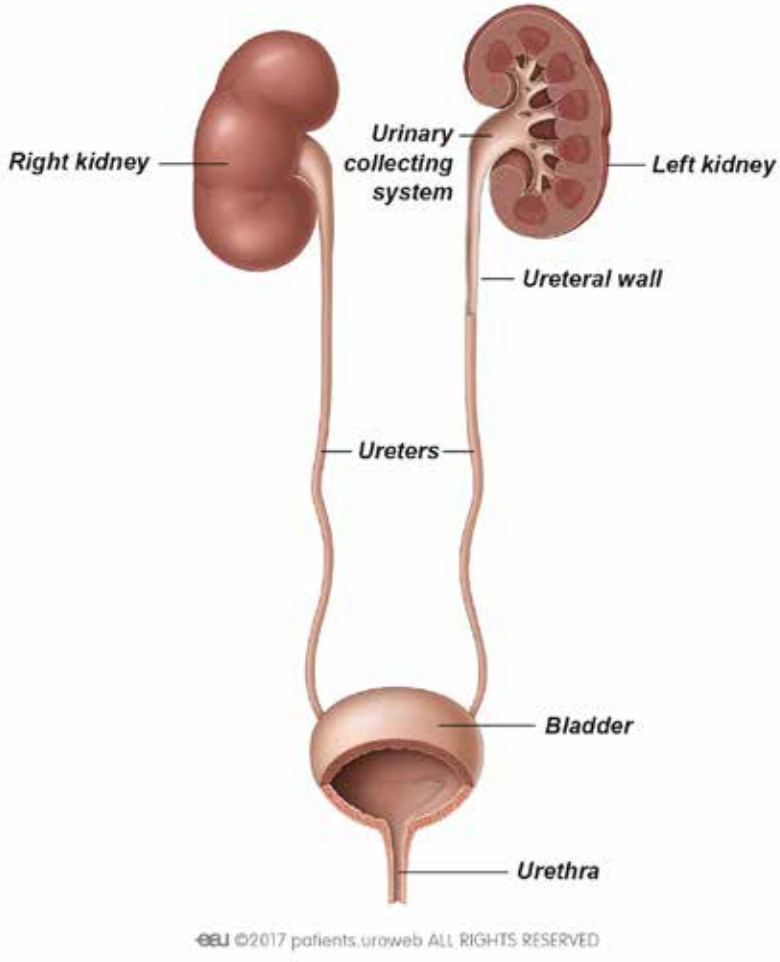
The inner lining of the urinary tract consists of a specialized epithelium: the urothelium. The urothelium is surrounded by the lamina propria (also called the submucosa), which is a thin layer of connective tissue containing blood vessels, lymphatic tissue, and occasional small smooth muscle fibers. These smooth muscle fibers in the lamina propria are called muscularis mucosae. At the level of the bladder, the lamina propria is surrounded by the muscularis propria. This thick outer muscle layer of the bladder is also referred to as the musculus detrusor. Finally, the outermost layer of the bladder is formed by a layer of fat: the perivesical fat.

Urothelial carcinoma (UC) is cancer that arises from the urothelium. Urothelial carcinoma can be located in the lower and/or the upper urinary tract. Approximately 90% of UCs are located in the bladder, making bladder cancer (BC) the most common urinary tract malignancy. Upper urinary tract urothelial carcinomas (UTUC) are uncommon and account for only 5-10% of UCs[1].

Epidemiology and risk factors

Bladder cancer is the 7th most common cancer in the Netherlands, with approximately 7000 new cases each year[2]. The risk of developing bladder cancer increases with age. Ninety percent of patients with bladder cancer are older than 55 years and the average age at diagnosis is 73 years[3]. Men are three to four times more likely to develop bladder cancer than women. This difference is most likely caused by gender differences in smoking tobacco. Up to 50% of bladder cancer cases can be directly attributed to cigarette smoking, making tobacco use the leading preventable risk factor for bladder cancer[4,5]. Tobacco smoke contains multiple carcinogens, such as polycyclic aromatic hydrocarbons and aromatic amines. These substances are absorbed in the lungs and excreted in the urine, causing damage to the urothelium. Another risk factor for bladder cancer is workplace exposure to carcinogenic chemicals, for example in processing dye, paint, metal and petroleum products. Workplace exposure accounts for approximately 10% of all bladder cancers[6]. Finally, schistosomiasis is a well-known risk factor for bladder cancer. Schistosomiasis is an infection with a parasitic worm, which is endemic in parts of Africa and the Middle East. In Western countries, this infection is a very rare cause of bladder cancer.

Figure 1. Schematic representation of the upper urinary tract (the kidneys and ureters) and the lower urinary tract (the bladder and urethra). Reprinted with permission from the European Association of Urology.



Diagnosis

The most important symptom of bladder cancer is hematuria: the presence of blood in a person's urine. Hematuria can be macroscopic (visible to the eye) or microscopic (not visible to the eye). Hematuria is usually painless and intermittent. This frequently causes a delay in the diagnosis. Microscopic hematuria is often an incidental finding on routine urine analysis. Only 3.3% of patients referred to a urologist with microscopic hematuria are diagnosed with bladder cancer[7]. For macroscopic hematuria this percentage is much higher: 17% of patients referred to a urologist with macroscopic hematuria are diagnosed with bladder cancer[7]. Other causes of hematuria are trauma, vigorous exercise, stones in the urinary tract, urinary tract infections and vascular malformations. Hematuria can also be caused by prostate cancer or by

cancer of the upper urinary tract. Besides hematuria, other presenting symptoms of bladder cancer include lower urinary tract symptoms such as dysuria, urgency or increased frequency. In more advanced tumors, pelvic pain and symptoms related to urinary tract obstruction can be present due to ingrowth of the bladder tumor in surrounding structures.

When bladder cancer is suspected, a cystoscopy is performed. During a cystoscopy, the urologist uses a flexible scope to visually inspect the inside of the bladder and urethra. This can be performed in the out-patient clinic. Urine cytology is used as an adjunct to cystoscopy to detect high-grade bladder cancer. In a urine cytology test, the pathologist inspects cells collected from a urine specimen. Ultimately, the diagnosis of bladder cancer is based on histopathological evaluation of tumor tissue. Therefore, a transurethral resection of the bladder tumor (TURB) is performed in the operating room. During TURB, the urologist will scrape the bladder tumor of the bladder wall. TURB is both a diagnostic and a therapeutic procedure. The goal is complete macroscopic and microscopic removal of the tumor. To enable adequate staging, inclusion of bladder muscle in the resection specimen is required.

Staging I: Pathology

The pathologist will analyze the removed tissue to determine the histological subtype, grade and the depth of invasion of the bladder tumor. Approximately 75% of bladder cancers are pure urothelial carcinoma[8]. The remaining 25% are histological variants. This comprises urothelial carcinomas with variant differentiation and nonurothelial subtypes. The urothelial carcinomas with variant differentiation originate from urothelium. They are characterized by the presence of conventional urothelial carcinoma along with some percentage of variant histology, such as squamous cell differentiation or micropapillary differentiation. Nonurothelial subtypes originate from other cell types, leading to, for example, squamous cell carcinoma (about 5% of all bladder cancers) or adenocarcinoma (about 1% of all bladder cancers)[8,9].

Complementary to histopathological subtype, tumor grade is used to classify bladder cancer. Tumor grade is determined by the pathologist and reflects how much the cancer cells differ from normal cells. The World Health Organization adopted the first bladder cancer grading classification in 1973, dividing urothelial cell carcinomas into three categories: grade 1, grade 2 and grade 3. Grade 1 tumors are associated with a better prognosis compared to grade 2 or grade 3 tumors. However, the WHO 1973 classification has a high interobserver variability since there are no clear definitions for each grade category[10]. In 2004, a new classification system was adopted, comprising papillary urothelial neoplasms of low malignant potential (PUNLMP), low grade (LG) urothelial carcinoma and high grade (HG) urothelial carcinoma. This classification has recently been updated without major changes and is now known as the WHO 2016. Whether the WHO 2016 is superior to the WHO 1973 in terms of prognostic value and reproducibility is a topic of debate[11]. Guidelines recommend using both classifications simultaneously[12].

Finally, bladder cancer is classified based on depth of invasion of the tumor. Invasion depth is described according to the Tumor, Node, Metastasis (TNM) classification system, in which

Table 1. TNM classification of bladder cancer[13]

T	**Primary tumor**
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ: "flat tumor"
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscle
T2a	Tumor invades superficial muscle (inner half)
T2b	Tumor invades deep muscle (outer half)
T3	Tumor invades perivesical tissue:
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumor invades prostate stroma, seminal vesicles, uterus, or vagina
T4b	Tumor invades pelvic wall or abdominal wall
N	**Regional Lymph Nodes**
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in a common iliac lymph node(s)
M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph nodes
M1b	Other distant metastasis

T-stage reflects invasion depth (Table 1, Figure 2)[13]. Bladder cancer can be subdivided into non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC). Non-muscle-invasive bladder cancer is confined to the urothelium (stage Ta or Tis) or the lamina propria (stage T1). Stage Tis refers to carcinoma in situ (CIS), a high-grade flat type of bladder cancer, with a high chance of progression to MIBC if left untreated[12]. Muscle-invasive bladder cancer grows into the musculus detrusor (stage T2), the perivesical fat (stage T3) or surrounding tissues such as the uterus, prostate or abdominal wall (stage T4). Within stage T2, T3 and T4, a further distinction of invasion depth is made and this is reflected by the affix 'a' or 'b' (Table 1).

The distinction between MIBC and NMIBC is very important, since treatment and prognosis differ greatly. At first diagnosis, the majority (>70%) of bladder cancers are non-muscle-invasive[3]. Patients with NMIBC are treated by TURB, eventually in combination with intravesical instillations of chemotherapy (e.g., mitomycin-C) or immunotherapy (Bacillus Calmette-Guérin, BCG). Although NMIBC will recur in up to 78% of patients and long-term follow-up is necessary, prognosis in terms of survival is good[14]. The chance of lymph node metastases or distant metastases is low. However, a small subset of patients with NMIBC (stage T1G3 and/or CIS) are classified as high risk for progression to MIBC. In these patients, more aggressive treatment similar to MIBC treatment is considered. This thesis will focus on MIBC. In some studies, high-risk NMIBC was also considered. The next paragraphs of this introduction are focused on staging and treatment of MIBC.

Staging II: Imaging

Next to pathological staging, clinical staging is essential to determine the most optimal treatment for bladder cancer patients. The pathologist can determine whether muscle invasion is present in the TURB tissue (stage T2), but further T-stage determination (e.g., stage T3 or T4) is based on physical examination and imaging. Moreover, the presence of nodal (N-stage) and distant metastases (M-stage) can only be evaluated by imaging. The goal of imaging in patients with bladder cancer is fourfold:

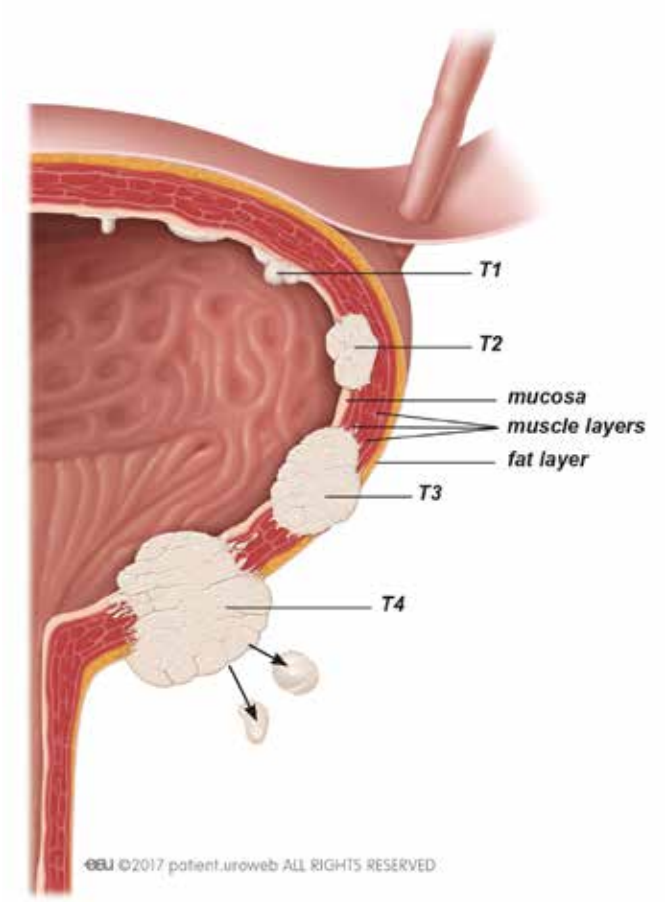
1. Determine local tumor invasion (T-stage)
2. Detect upper urinary tract malignancies
3. Evaluate lymph nodes for presence of lymph node metastases (N-stage)
4. Detect distant metastases (M-stage)

Several imaging modalities are used for staging bladder cancer. Contrast-enhanced computed tomography (CECT) of the chest, pelvis and abdomen is the most commonly used imaging method. It is combined with CT urography for optimal urothelial evaluation. This is important since up to 8% of bladder cancer patients may have an upper tract urothelial carcinoma[15]. Computed tomography has important limitations when it comes to T-stage, since it poorly differentiates between T2 and T3a tumors[16]. Magnetic resonance imaging (MRI) provides better contrast between different soft tissues (e.g., bladder wall and fat), but similar to CECT it is unable to accurately diagnose microscopic invasion of the perivesical fat (stage T2 vs T3a)[17].

Considering N-stage, both CECT and MRI are unable to detect lymph node metastases in normal-sized lymph nodes. This possibly results in understaging since normal-sized lymph nodes may contain micrometastasis. On the other hand, enlargement of lymph nodes may be due to benign disease or reaction to TURB, resulting in overstaging. In current guidelines, pelvic lymph nodes >8 mm and abdominal lymph nodes >10 mm in maximum short-axis diameter are regarded as pathologically enlarged[18].

Besides lymph node metastases, it is essential to evaluate the presence of other distant metastases (M-stage). Common sites of distant bladder cancer metastases are the lungs, liver, bones, peritoneum and adrenal glands. Computed tomography is the diagnostic technique of choice to detect lung metastases, whereas MRI has a higher sensitivity and specificity for detecting liver metastases[19].

Figure 2. Schematic representation of the invasion depth of different T-stages of bladder cancer. Reprinted with permission from the European Association of Urology.



Over the last decade, 18F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) with computed tomography (CT) has become an established imaging modality for preoperative staging of several cancer types, such as lung cancer and breast cancer. FDG consists of sugar (glucose), combined with a radioactive label (18F). FDG is trapped in cells with high metabolic activity, such as cancer cells. A PET scan can visualize the radioactive label, and therefore the tissues with high metabolic activity. PET images are combined with CT images for anatomic correlation. Emerging evidence suggests that FDG-PET/CT has potential use for staging bladder cancer because of improved accuracy for lymph node assessment and detection of distant metastases[20].

Treatment

After accurate staging, all muscle-invasive bladder cancer patients should be discussed in multidisciplinary rounds, including urologists, pathologists, radiologists, nuclear medicine physicians, medical oncologists and radiation oncologists. Together, the most appropriate treatment can be determined.

Radical cystectomy (RC) with pelvic lymph node dissection (PLND) is considered standard treatment for non-metastatic MIBC. Survival rates after radical cystectomy are poor, with only 50% of patients surviving for 5 years[21]. This suggests the presence of occult micrometastases in a subset of patients undergoing radical cystectomy. To improve survival, chemotherapy prior to surgery (neoadjuvant chemotherapy (NAC)) has been used since the 1980s. Neoadjuvant chemotherapy results in only a 5-8% improvement in 5-year overall survival because the response to treatment differs greatly between patients[22–24]. Recent research has focused on the application of neoadjuvant immunotherapy (PD-1/PDL-1 and CTLA-4 checkpoint inhibitors) in muscle-invasive bladder cancer patients. Although initial study results are promising, the use of immunotherapy prior to radical cystectomy is currently only recommended in clinical trials[25–27].

Radical cystectomy can be an open or a robot-assisted laparoscopic procedure. Robot-assisted radical cystectomy is associated with longer operative time and higher costs, but shorter length of hospital stay and less blood loss compared to open surgery. Oncological outcomes are similar for both approaches[28]. Whether an open or robot-assisted approach is used mainly depends on the experience of the urologist. In men, standard radical cystectomy includes removal of the prostate, bladder, seminal vesicles, distal ureters and regional lymph nodes. In women, radical cystectomy includes removal of the bladder, uterus, anterior vaginal wall and entire urethra, distal ureters and regional lymph nodes. After removal of the urinary bladder a continent (neobladder) or incontinent (ileal conduit/Bricker) urinary diversion is created from the small bowel.

Radical cystectomy has a major impact on long-term urinary continence and sexual function in both men and women[29]. Over the years, several sexual-preserving cystectomy techniques have been developed, aimed at minimizing postoperative incontinence and sexual dysfunction. Besides these long-term effects on continence and sexual function, radical cystectomy is associated with a high postoperative complication rate. Thirty-day overall complication rates

vary from 26 to 78%[30-32]. The most common complications are infectious or gastrointestinal related, with postoperative ileus as one of the most frequent[33].

All in all, radical cystectomy is an extensive surgical procedure with considerable risks and long-term adverse effects. As a result, and in line with organ-preserving treatment in other malignancies, bladder-preserving treatment strategies have gained interest. The most widely used alternative to radical cystectomy is trimodality therapy, comprising TURB followed by concurrent chemotherapy and external beam radiotherapy. This bladder-sparing procedure has been recognized as an alternative to radical cystectomy for selected patients in international guidelines[18,34]. Another bladder-preservation strategy includes a combination of TURB, low-dose external beam radiotherapy and brachytherapy. Brachytherapy can be offered to strictly selected patients with small, solitary, cT1-T2 tumors. This technique is only used in the Netherlands, Belgium and France and seems to be a reasonable treatment option[35,36].

Thesis outline

Management of muscle-invasive bladder cancer in terms of diagnosis, staging and treatment relies on a close collaboration between urologists, pathologists, radiologists, nuclear medicine physicians, medical oncologists and radiation oncologists. In this thesis, several aspects of the multidisciplinary management of muscle-invasive bladder cancer were studied, with a focus on neoadjuvant chemotherapy, staging by FDG-PET/CT, and organ-preserving therapies.

Part I Neoadjuvant treatment for muscle-invasive bladder cancer

Despite careful selection of patients before surgery, radical cystectomy only provides five-year survival in about 50% of patients with muscle-invasive bladder cancer. Many efforts have been made to improve survival by adding neoadjuvant treatment modalities to radical cystectomy. In **Chapter 2** an overview of neoadjuvant treatment for bladder cancer through the years is provided. Neoadjuvant chemotherapy (NAC) is currently the most frequently applied neoadjuvant treatment. While guidelines recommend NAC for all patients with cT2-4aN0M0 bladder cancer, administration of NAC in cT2 disease is a topic of debate. In **Chapter 3** we compared the outcome of treatment with NAC and radical cystectomy in patients with cT2N0M0 bladder cancer versus cT3-4aN0M0 bladder cancer. Although NAC followed by radical cystectomy has become the standard of care in MIBC, the optimal chemotherapy regimen remains undefined. This issue is addressed in **Chapter 3A**. After NAC, up to 60% of patients have residual muscle-invasive bladder cancer at radical cystectomy. These patients have a worse overall survival compared to patients in which the tumor is completely gone after NAC, a so-called pathological complete response. Histopathologic tumor regression grades (TRG), which quantify the extent of tumor response to NAC, have been shown to be a prognostic factor for patient outcome in several malignancies, including gastric, esophageal and rectal carcinoma. Whether TRG is also a prognostic parameter in muscle-invasive bladder cancer is discussed in **Chapter 4**.

Part II FDG-PET/CT for staging urothelial carcinoma

Considering the high risk of systemic relapse following initial therapy for muscle-invasive bladder cancer, improved pretreatment staging is needed: to improve patient selection for (neoadjuvant) systemic therapies and to avoid futile surgical attempts. Moreover, in the neoadjuvant setting, adequate on-treatment response assessment may aid in decisions to continue or cease neoadjuvant chemotherapy. In several cancers, FDG-PET/CT is an established imaging modality for preoperative staging. Part II of this thesis focuses on the role of FDG-PET/CT in staging urothelial carcinoma. In **Chapter 5** we analyzed the impact of FDG-PET/CT on pretreatment bladder cancer staging and patient management, compared with standardized conventional staging. In **Chapter 6** we evaluated the accuracy of FDG-PET/CT for on-treatment response assessment in muscle-invasive bladder cancer patients receiving neoadjuvant chemotherapy. In muscle-invasive bladder cancer, sensitivity of FDG-PET/CT for detection of lymph node metastases is superior to CECT, with comparable specificity. Whether FDG-PET/CT is also useful for lymph node staging in patients with upper tract urothelial carcinoma was studied in **Chapter 7**.

Part III Locoregional treatment and outcome of muscle-invasive bladder cancer

Radical cystectomy has a major impact on voiding and sexual function. In order to improve sexual function, several sexual-sparing techniques have been developed. In **Chapter 8** the oncologic and functional outcomes of two prostate-sparing techniques are investigated. Besides sexual-sparing surgical techniques, the entire bladder can be preserved by radiation with concurrent radiosensitizing chemotherapy. This treatment is recognized as a viable alternative to surgery in selected bladder cancer patients. Although it is clear that concurrent chemoradiation is superior to radiation alone, the ideal chemotherapy regimen has not yet been determined. In **Chapter 9**, we evaluated the outcomes of patients treated with concurrent radiation and a chemotherapy regimen using mitomycin-C and capecitabine tablets. Another bladder-preserving strategy includes the combination of TURB, low-dose radiotherapy and brachytherapy of the bladder. This technique is used in the Netherlands, Belgium and France, but is controversial due to fear of jeopardizing oncologic outcome. In **Chapter 10** we examined the outcome in terms of survival, complications and bladder preservation after brachytherapy. Radical cystectomy for bladder cancer is associated with a high risk of postoperative complications. Standardized perioperative protocols, such as enhanced recovery after surgery (ERAS) protocols, aim to improve postoperative outcome. Postoperative feeding strategies are an important part of these protocols. In **Chapter 11**, we compared complications and length of hospital stay between an ERAS-protocol with early oral nutrition and a protocol with early enteral feeding with a nasojejunal tube.

Finally, **Chapter 12** provides a summary and discussion of all the chapters as well as future perspectives.

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Part I

Neoadjuvant treatment for muscle-invasive bladder cancer


2

Neoadjuvant treatment for muscle-invasive bladder cancer: the past, the present and the future

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Urol Oncol. 2018 Sep;36(9):413-422.

Abstract

Background

Approximately half of patients who undergo radical cystectomy (RC) for muscle-invasive bladder cancer (MIBC) will succumb to metastatic disease. We summarize the evidence for neoadjuvant radiation (NAR), chemo (NAC), and immunotherapy (checkpoint inhibition) prior to RC for MIBC.

Methods

Data were obtained by a search of PubMed, ClinicalTrials.gov, and Cochrane databases for English language articles published from 1925 up to 2017.

Results

NAC usage has increased over the last decade, while NAR is rarely administered. Although NAR results in downstaging, its impact on survival is inconclusive. Based on level I evidence, cisplatin-based NAC (CB-NAC) is considered standard of care in cT2-4aN0M0 MIBC. NAC results in a 6% absolute 10-year overall survival (OS) benefit. In-depth analyses of key randomized controlled trials showed that failure to correct for uniform staging, surgical variation, and patient selection compromises the ability to identify factors predictive of response to NAC. The benefit appears to be restricted to patients downstaged to ypT1N0 or less. In these patients, 5-year OS is 80% to 90%. Regarding a number needed to treat of 17, most patients with cT2-4aN0M0 MIBC will be exposed to toxicity without benefit. Possible approaches to reduce overtreatment are suggested in this article and include patient selection, the chosen NAC regimen, and emerging molecular data to predict responsiveness to NAC. Neoadjuvant immunotherapy with checkpoint inhibitors is a promising future perspective currently under investigation.

Conclusions

Past studies on NAR show inconclusive results and NAR is rarely administered. Instead, CB-NAC is advised in eligible patients with cT2-4aN0M0 MIBC prior to RC. In the near future, predictive biomarkers will be the key to tailor the use of CB-NAC and reduce harm to nonresponders.

Introduction

After radical cystectomy (RC) for muscle invasive bladder cancer (MIBC), approximately half of patients will eventually succumb due to pre-existing metastatic disease or local recurrence[1]. In this context, many efforts have been undertaken to improve oncological outcome by adding various neoadjuvant treatment modalities to RC.

Population-based data have shown that use of neoadjuvant chemotherapy (NAC) has significantly increased over the last decade, while neoadjuvant radiotherapy (NAR) is rarely administered anymore[2,3]. Due to inherent study limitations, the robustness of evidence for these treatment modalities can be questioned. One of the main reasons for the slow adoption of neoadjuvant treatment modalities, especially NAC, is the inability to select accurately patients who will benefit versus those who may potentially be harmed[4].

In this review on past, present and future neoadjuvant treatments for MIBC, we summarize the evidence and limitations of studies describing NAR (the past), NAC (the present) and immunotherapy (the future). Two timelines are presented highlighting the landmarks in bladder cancer (BC) care and those specifically for neoadjuvant treatment in MIBC (Figure 1). We also aim to provide guidance for clinicians to further improve individualized treatment for MIBC.

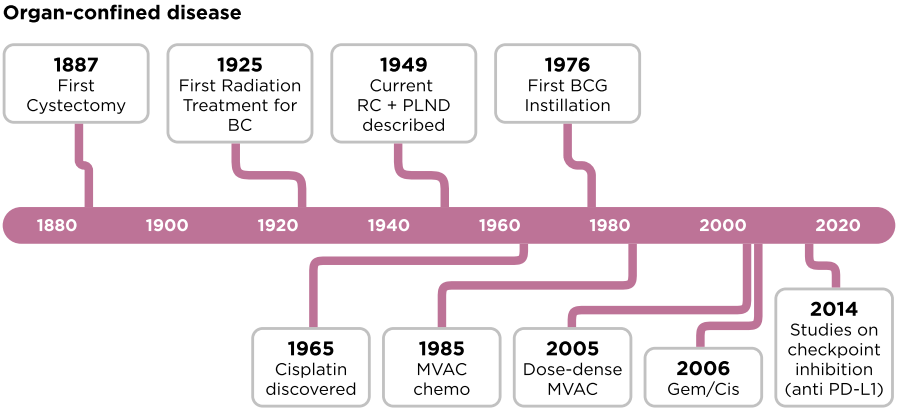
The Past: Neoadjuvant radiation treatment

As early as 1925, Frank Kidd described the first experiences of radiation treatment (RT) for BC. In eight patients, he observed a decrease in tumor load, a relief of local symptoms and/or an impressive improvement in life expectancy[5]. However, many patients suffered from severe skin burns or mucosal reactions until Henri Coutard developed the principle of fractionation, the basis of current RT, in 1934[6]. In an attempt to decrease local failure and improve survival, urologists and radiation oncologists soon began to use RT as a preoperative adjunct to RC[7].

In the 1960s-80s, multiple efforts were made to evaluate the role of NAR plus RC in MIBC[8-10]. A meta-analysis by Huncharek et al.[11] combined the results of 751 patients from four RCTs assessing 5-year overall survival (OS) for NAR plus RC versus RC alone[8,12-14]. Five-year OS favored patients who received NAR prior to RC, but this finding was not statistically significant (hazard ratio (HR): 0.71, 95%-CI 0.48-1.06)[11]. The largest RCT in this meta-analysis randomized 475 patients to NAR (45 Gy) plus RC versus RC alone[8]. After definitive surgery, a second randomization to 5-fluorouracil or placebo was conducted. Unfortunately, only 49% of randomized patients completed the prescribed therapy and final survival analysis was conducted only in these patients. Complete pathological downstaging (pCD) to ypT0 was observed in 34% of patients undergoing NAR plus RC and 9% of those undergoing RC alone. Five-year OS in patients receiving NAR was 55% if pCD was achieved, versus 33% for those

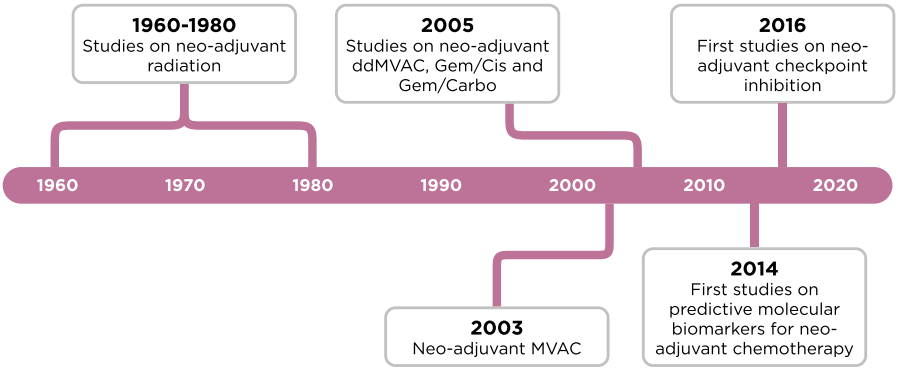
with residual disease in the RC specimen[8]. These results are severely limited by the absence of an intention to treat analysis. Moreover, the isolated effect of NAR could not be assessed due to the use of concomitant adjuvant chemotherapy (AC). Overall, results from this trial with respect to OS were inconclusive.

Figure 1A. Landmarks in the treatment of organ-confined and metastatic bladder cancer.



Abbreviations: BC, Bladder cancer; BCG, Baccillus Calmette-Guérin; Gem/Cis, Gemcitabine/Cisplatin; MVAC, Methotrexate Vinblastine Doxorubicin Cisplatin; PLND, Pelvic Lymph Node Dissection; RC, Radical Cystectomy.

Figure 1B. Landmarks in the neoadjuvant treatment of muscle-invasive bladder cancer.



Abbreviations: Gem/Carbo, Gemcitabine/Carboplatin; Gem/Cis, Gemcitabine/Cisplatin; MVAC, Methotrexate Vinblastine Doxorubicin Cisplatin.

A second meta-analysis was conducted with data of the three remaining RCTs. Although these studies were smaller and all independently insignificant, they were of higher quality[11-14]. In contrast, this second analysis did not report an OS benefit for NAR (HR: 0.94 95%-CI: 0.57-1.55). Of note, all studies, except for the studies of Smith et al.[12] and Ghoneim et al.[14], used different radiation doses. The study of Ghoneim et al.[14] mostly consisted of patients with squamous cell carcinoma. Furthermore, the radiation techniques would be considered suboptimal by today's standards. These RCTs did not stratify patients according to clinical stage and they suffered from a lack of power to address the potential benefit of NAR[8,12-14]. In a more recent retrospective study, Granfors et al.[15] evaluated the role of NAR in 187 patients treated for cT1-3 BC. They confirmed superior rates of pCD (ypT0) after NAR (39-52 Gy). There was no evidence of residual tumor in 7% of patients after RC alone versus in 57% after NAR plus RC. This effect was most evident in cT3 tumors (pCD in 0% RC alone vs. 56% NAR plus RC). Moreover, patients in this subgroup had superior OS and cancer specific survival (CSS) after NAR, which was not observed for clinically organ-confined tumors[15]. These results suggest enhanced efficacy of NAR specifically in patients with locally advanced disease. In another larger retrospective, single institution, case-control study, Cole et al.[16] compared NAR plus RC (N=301) versus RC alone (N=220) in patients with cT2-4 BC. NAR had a significant impact on local control in patients with cT3b disease (91% vs. 72% local progression-free survival (PFS) after 5 year) and, although not statistically significant, these patients fared slightly better at 5 years in terms of CSS (59% vs. 47%) and OS (52% vs. 40%)[16]. Disparate use of perioperative chemotherapy may have resulted in an underestimation of the effects of NAR in this study.

In conclusion, NAR results in better downstaging, but its effects on survival are inconclusive and its use is generally not advised[17]. The low quality of the studies cited, in combination with recent advances in the care of patients with MIBC, limit assessment of the true impact of NAR. Staging modalities have improved, the extent of surgery has changed (e.g. extended PLND), radiation techniques have advanced and the administration of perioperative chemotherapy has evolved. However, NAR remains a local treatment modality that will not affect distant micrometastases, so that perioperative systemic therapy is likely to have a more significant impact.

The Present: Neoadjuvant chemotherapy

Both neoadjuvant and adjuvant cisplatin-based chemotherapy may be used to eliminate or slow progression of micrometastatic BC[17,18]. While NAC is based on inaccurate clinical staging, AC is more effectively administered in a risk-adapted fashion based on the definitive pathology of the RC specimen. The largest RCT (N=284) observed a 49% 5-year PFS in patients with pT3-4 and/or N1-3M0 BC receiving immediate cisplatin-based AC vs. 30% in those receiving deferred chemotherapy[19]. This translated into a substantial and significant median PFS benefit of 2.0 years, but the study had inadequate power to demonstrate an OS benefit[19]. Meta-analyses have estimated an absolute 5-year OS benefit of 6% with AC, which is comparable to

the benefit of CB-NAC[19-22]. Recently similar findings were reported in a real world data set[23]. The poor accrual in AC trials (<50% of the intended enrollment) reveals the Achilles heel of the prospective evaluation of this treatment strategy: 25-33% of patients who undergo RC are unable to receive AC due to postoperative problems, such as a decreased performance status or deterioration of renal function[24,25]. In the Nordic Cystectomy Trials and the SWOG-8710 trial 86% and 82% of patients, respectively, underwent RC after randomization to NAC, compared to 87% and 81% after RC alone (Table 1)[26,27]. Furthermore, the BA06-30894 trial, which randomized patients to CB-NAC versus no NAC prior to RC or RT (N=976, of whom 428 had RC), showed that RT can still be offered as a curative treatment option if NAC makes a patient unsuitable for RC[28]. In the BA06-30894 trial, the CB-NAC related mortality rate was 1%[28]. In addition, 4.7%, 3.6% and 2.9% received less than the intended three cycles because of renal toxicity, other chemotherapy related toxicity, or disease progression and early death, respectively[28]. Concerning OS, Grossman et al.[27] reported no difference for patients who had residual disease after either NAC prior to RC or RC alone. In contrast, a retrospective analysis showed that patients with residual BC after NAC have a worse prognosis compared to stage-matched controls undergoing RC alone[29]. Altogether, the likelihood of a patient both undergoing chemotherapy and undergoing RC is greater in the NAC than AC setting. Nevertheless, some important questions remain and are addressed below.

1) What evidence do we have for the application of this potentially toxic treatment?

In Table 1, we have summarized the most relevant findings and limitations of the key RCTs on CB-NAC. A meta-analysis of seven RCTs reported that CB-NAC in cT2-4aN0-XM0 BC resulted in an absolute 5-year OS benefit of 5%[22]. In contemporary MIBC guidelines, CB-NAC is considered the standard of care for patients with cT2-4aN0M0 BC[17]. In the three largest RCTs on CB-NAC, the benefit of NAC appeared to be restricted to the larger number of patients downstaged to (y)pT0 compared to TUR alone (25-38% vs. 12-15%)[26-28,30,31]. A complete response (ypT0N0) after CB-NAC is associated with a 5-year OS of 80-90%, which drops to approximately 45% for patients with residual carcinoma[26,32]. Subsequent evidence suggests that downstaging to non-MIBC (<ypT2N0) is associated with a comparably favorable outcome, reducing the overall risk of death by 75% (HR: 0.25 (95% CI 0.16-0.40)) compared to patients who still have residual MIBC or nodal disease[33,34].

Due to variations in chemotherapy sensitivity and the potential of cure by RC alone, it is estimated that if all patients with cT2-4aN0M0 BC eligible for NAC did indeed receive NAC, up to 70% of them would be exposed to potential toxicity without clear benefit[4,35]. Notably, a more in-depth analysis of the key published RCTs[26-28], as discussed below, reveals that failure to correct for uniform clinical (nodal) staging, surgical variation (e.g. PLND) and patient selection compromises the robustness of the evidence that has established the OS benefit of CB-NAC for all patients with cT24aN0M0 BC[4,36].

Table 1. Results and limitations of key randomized controlled trials on neoadjuvant cisplatin-based chemotherapy prior to radical cystectomy

	Nordic I[30]	Nordic II[31]	SWOG 8710[27]	BA06 30894[28]
Patient selection	cT2-4aNxM0	cT2-4aNxM0	cT2-4aN0M0	cT2-4aN0/xM0
Years enrolled	1986-1989	1991-1997	1987-1998	1989-1995
Centers (n)	36	30	126	106
Central pathology	No	No	Yes	Yes
NAC regimen	Cisplatin, Doxorubicin	Cisplatin, Methotrexate	Methotrexate, Vinblastine, Doxorubicin, Cisplatin	Cisplatin, Methotrexate, Vinblastine
Cycles (n)	2	3	3	3
NAR	All 20 Gy	-	-	-
NAC + RC vs. upfront RC (n)	151 vs. 160	155 vs. 154	153 vs. 154	491 vs. 485*
RC (n, %) **NAC+RC** **Upfront RC**	 130/151 (86) 134/160 (84)	 132/155 (85) 139/154 (90)	 126/153 (82) 124/154 (81)	 246/284 (87) 239/277 (86)
RC plus full NAC dose (n, %)	108 (72)	103 (66)	131 (87)**	392 (80)
pT0 (n, %) **NAC+RC** **Upfront RC**	 33/130 (25) 17/134 (13)	 37/132 (28) 16/139 (12)	 48/126 (38) 18/124 (15)	 67/206 (33) 26/211 (12)
Overall survival (HR, 95%-CI)	0.69 (0.49-0.98)***	0.80 (0.60-1.10)***	1.33 (1.00-1.76)****	0.84 (0.72-0.99)
Major limitations	1) Preoperative radiotherapy 2) Insufficient clinical nodal staging 3) Insufficient PLND	1) No effect on overall survival 2) Insufficient clinical nodal staging 3) Insufficient PLND	1) Accrual in 126 centers 2) No PLND in 9%, insufficient PLND in 46% 3) NAC did not independently predict OS on multivariable analysis when controlled for extent of PLND[36]	1) Accrual in 106 centers 2) Insufficient clinical nodal staging (cNx in 25%) 3) No analysis of surgical variability 4) Pathology results only available for 417 RC specimens.

** Of the patients 415 were randomized to external beam therapy, including 207 NAC and 208 non-NAC patients.*
*** At least 1 full dose of NAC.*
****Combined data did show a significant effect on overall survival.*
***** Reversed HR.*
CI, Confidence interval; HR, Hazard ratio; NAC, Neoadjuvant chemotherapy; NAR, Neoadjuvant radiotherapy; PLND, Pelvic lymph node dissection; RC, Radical cystectomy.

The SWOG-8710 trial (N=317) was the first RCT to describe an OS benefit for CB-NAC prior to RC[27]. At a median follow up of 8.7 years, median OS for patients who underwent CB-NAC plus RC vs. RC alone was 77 vs. 46 months, respectively (p=0.05). In cT3-4aN0M0 BC, NAC was associated with a median OS benefit of 41 months (65 vs. 24 months), which was longer compared to the benefit (30 months; 105 vs. 75 months) reported in patients with cT2N0M0 disease (p=0.05)[27]. The BA06-30894 trial showed an absolute 10-year OS benefit of 6% for those who received CB-NAC prior to definitive local treatment (RC in 428)[28]. Overall, the combined results of the Nordic Cystectomy trials (N=620) did not show any OS benefit for CB-NAC. However, the absolute reduction of risk of death at 5-years in patients with cT3 tumors was 13% in favor of CB-NAC (p=0.019), but there was no difference for cT2 tumors[26].

The results of the SWOG-8710 trial are subject to selection bias due to an accrual period of 11 years and treatment in 126 institutions[36]. The BA06-30894 trial accrued more efficiently (976 patients in 6 years), but is also potentially confounded by accrual across 106 institutions[28]. The main concern with the number of participating institutions is the substantial variability in surgical parameters between trial sites. A secondary ad-hoc retrospective analysis of SWOG-8710 showed that 9% of patients did not undergo PLND and up to 46% received less than a standard bilateral PLND (i.e. node sampling only)[36]. In multivariable analysis, lymph node count was significantly associated with OS and local recurrence, whereas the previously reported beneficial effect of NAC was lost (HR: 1.0, P=0.97)[36]. The question therefore persists whether NAC would retain its favorable impact on OS if the extent of surgery and especially the PLND were standardized[34]. Similar concerns about the extent of surgery and clinical staging are applicable to the BA06-30894 trial and Nordic Cystectomy trials. Indeed, 25% of the patients undergoing RC in the BA06-30894 trial were staged cNx and the extent of PLND was not described[28]. Clinical nodal staging was not specified in the Nordic trials and patients underwent only a PLND limited to the obturator fossa. All three of the trials discussed here appear to represent high-risk cohorts with poor 5-year survival even with CB-NAC. The 5-year OS for patients with CB-NAC was less than 50% in both the SWOG-8710 and the BA06-30894 trials, and only up to 56% in the Nordic trials[27,28]. However, outcomes were also likely affected by clinical under-staging and suboptimal surgical therapy. In the current era, staging is usually done with at least a CT-scan of the abdomen/pelvis and chest X-ray. In conclusion, the results of these landmark studies may be questioned because clinical and surgical nodal staging was not up to current standards.

2) Which patients are likely to benefit most and from which patients could we consider withholding therapy?

The results of the SWOG-8710 and Nordic cystectomy trials demonstrated that the largest benefit of CB-NAC is in patients with locally advanced disease (cT3-4a)[26,27,37,38]. The above-cited meta-analyses indicate that the number needed to treat to save one life at 5 years with CB-NAC if all patients with MIBC are treated is 17. A risk-adapted approach could potentially reduce the number needed to treat. However, clinical staging of MIBC is notoriously inaccurate, and any tailoring of CB-NAC to patient risk must be balanced with the potential of under-treatment[39].

The group at MD Anderson Cancer Center (MDACC) has developed a risk-adapted approach to CB-NAC, which they validated in an external patient cohort[35]. In their case-control study 297 patients who underwent RC and PLND without NAC were categorized as having low-, or high-risk MIBC. High-risk disease was present in 98 patients and was defined as the clinical presence of hydroureteronephrosis, cT3-4a BC on CT/MRI or examination under anesthesia, histological evidence of lymphovascular invasion and/or micropapillary/neuroendocrine features in the TUR specimen. Even though 49% of clinically low-risk patients were upstaged to pT3/4 and/or pN1-3 disease at RC, the 5-year CSS of this risk group was 84%[35]. This study suggests that immediate RC without NAC is an option to reduce the potential toxicity of CB-NAC in patients with low-risk cT2 MIBC. AC may still be offered to eligible patients who are upstaged at RC, even though only a minority of such patients received AC in the MDACC series. In Figure 2, we outline the implications of administering CB-NAC only to patients with high-risk disease, instead of all patients with cT2-4aN0M0 MIBC. Assuming that between 1 (scenario B) and 2 (scenario A) out of 5 patients have high-risk disease[2,40,41], chemotherapy toxicity can be prevented in 40-53% of cases while potential benefit is only lost in 10-13%.

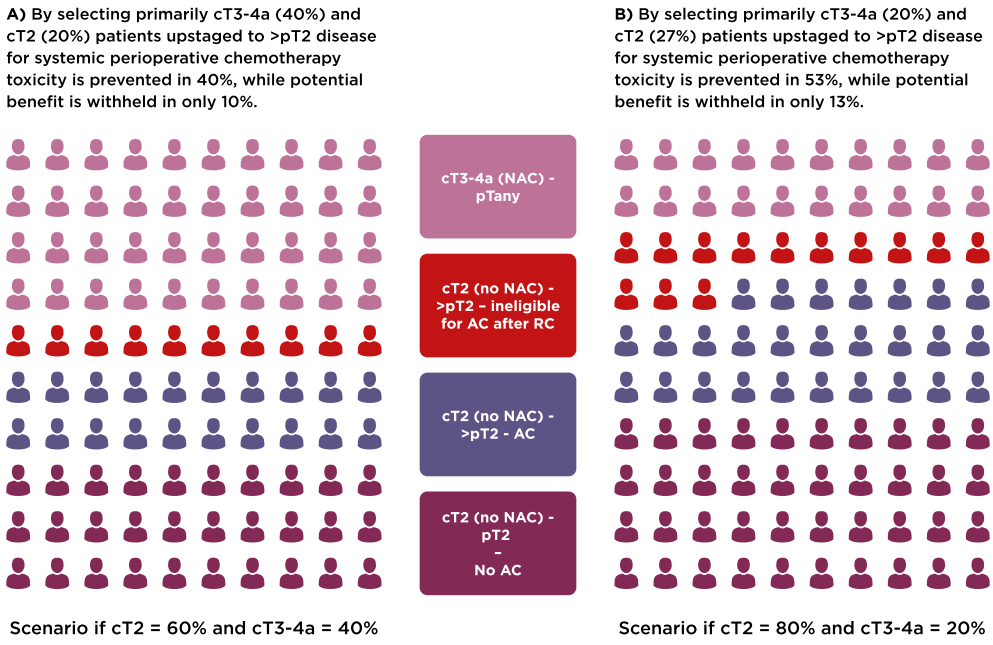
3) Which available neoadjuvant chemotherapy regimens should we administer?

Another strategy to reduce toxicity may be the choice of chemotherapy regimen. The landmark trial of Grossman et al.[27] established three cycles of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) as the NAC regimen supported by the best evidence. The BA06-30894 trial would suggest that CMV would be a reasonable alternative. However, in recent years, the combination of gemcitabine and cisplatin (GC) is used more often than MVAC[33,42] based on results from a RCT in patients with metastatic BC[43]. This trial reported significantly lower toxicity profiles for GC but detected no difference in oncological outcomes[43]. RCTs comparing GC versus MVAC or non-cisplatin based regimens in the neoadjuvant setting have not been undertaken. A large retrospective multicenter analysis on contemporary real world data in 935 cT24aN0M0 BC patients did not report a difference in pCD (ypT0N0) for neoadjuvant GC (23.9%) versus MVAC (24.5%)[33]. RCTs comparing neoadjuvant GC versus MVAC or non-cisplatin based regimens have not been undertaken.

The classic MVAC regimen has been mostly replaced by dose-dense (dd)MVAC in centers that prefer MVAC. ddMVAC is a 2-week-per cycle regimen (instead of 4-week-per-cycle classic MVAC scheme) supported by granulocyte colony-stimulating factor, enabling doubling of cisplatin and doxorubicin dose intensities with reduction of methotrexate dose intensity. This approach decreases the time to RC by 6 weeks compared to the classic MVAC regimen. In a phase III RCT in patients with metastatic BC, ddMVAC had a more favorable toxicity profile compared to classic MVAC, fewer dose delays and higher response rates[44]. In a retrospective, single-center study comparing GC (N=51), MVAC (N=35) and ddMVAC (N=80) in patients with clinically non-organ confined or node positive MIBC, pCD (ypT0N0) was reported in 32% (p=0.845), 20% (p=0.366) and 29% (reference) of patients, respectively[45]. Grade 3-4 toxicity rates for ddMVAC (32%) and GC (44%) were significantly lower than for the classic MVAC regimen (55%)[45]. Since 3 cycles of ddMVAC are 3 weeks shorter than 3 cycles of GC, the authors concluded that ddMVAC should be the preferred option for pre-operative

chemotherapy[45]. Moreover, in a recent retrospective multi-center analysis, ddMVAC was associated with a complete response in one third of patients and a partial response (pT1N0) was observed in nearly half of the cases[46]. In the ongoing SWOG-1314 trial, patients with MIBC are randomly assigned to neoadjuvant GC or ddMVAC in order to determine the utility of a gene-expression-based biomarker approach for the prediction of pCD. OS, pCD and toxicity rates will also be compared for both regimens[47].

Figure 2. The magnitude of toxicity prevention by selecting only patients with cT3-4aN0M0 bladder cancer for neoadjuvant cisplatin-based chemotherapy, depending on the population: A) 60%, or B) 80% of patients staged cT2N0M0. Scenarios for patients eligible to cisplatin-based chemotherapy prior to radical cystectomy. AC, adjuvant chemotherapy; NAC, neoadjuvant chemotherapy; RC, Radical cystectomy



4) Do we have neoadjuvant chemotherapy options in patients ineligible for cisplatin?

Nearly half of patients with MIBC are not eligible for treatment with CB-NAC due to poor renal function (GFR<50-60ml/min), poor performance status (ECOG-PS≥2), severe (grade ≥2) neuropathy or hearing loss, or heart failure (NYHA-class-III/IV)[25,48]. These patients could be treated with gemcitabine and carboplatin, but there is no clinical trial data to support this practice. In fact, we know that carboplatin is inferior to cisplatin in multiple trials in the metastatic setting, and the modest benefit observed with CB-NAC would suggest that

carboplatin-based NAC would have marginal if any benefit. However, retrospective single-center studies show comparable pCD rates for carboplatin regimens versus CB-NAC[49,50]. Non-cisplatin based regimens are currently only advised for downstaging of a surgically unresectable tumor[17]. Neoadjuvant therapy for cisplatin-ineligible patients remains a critical unmet need in the care of patients with MIBC.

5) What are tools to predict response to neoadjuvant chemotherapy?

Considering the toxicity of chemotherapy and the potential delay of RC in non-responders, accurate prediction and evaluation of response is essential. The value of computed tomography to evaluate response to NAC is limited due to the inability to differentiate residual cancer from treatment-induced changes[51]. This results in contradictory clinical and pathological staging in up to 40% of patients[52]. Preliminary studies have shown that novel imaging techniques, such as FDG-PET/CT and diffusion-weighted MRI, might be able to distinguish between responders and non-responders, but further validation is required[53,54].

Gene mutation and expression analyses have recently been described for identification of biomarkers to predict response to NAC. Three groups identified specific gene mutations in MIBC that correlated with response and survival after CB-NAC[55-57]. Van Allen et al.[55] conducted whole-exome sequencing of TUR specimens from 50 MIBC patients who underwent RC after CB-NAC. Nine out of 25 complete responders (ypT0/is) had a mutation in the nucleotide excision repair gene ERCC2, but none of 25 non-responders harbored this mutation ($p<0.01$)[55]. Within the unselected Cancer Genome Atlas (TCGA) MIBC patient cohort (N=130), ERCC2 mutations were present in 12% of patients[58]. Groenendijk et al.[57] sequenced 178 cancer-associated genes in 94 MIBC TUR specimens. An ERBB2 mutation was found in 9/38 complete responders (ypT0N0) and in 0/33 non-responders (>ypT2/N+) (p=0.003)57. ERBB2 mutations occurred in approximately 8% of tumors in TCGA-cohort[58]. Groenendijk et al.[57] found six ERCC2 mutations among responders, but also two in non-responders, both of whom received carboplatin-based NAC. We calculated that if only patients with an ERCC2 or ERBB2 mutation would receive NAC, a complete response will be withheld in 32%[55] and 31%[57] of cases, illustrating the relative importance of these two mutations in the absence of other markers. Plimack et al.[56] conducted another interesting study in this domain. In a discovery cohort (N=34), they identified that ≥1 mutations in three genes (ATM, RB1, and FANCC) predicted complete pathological downstaging (ypT0N0) to CBNAC in 100%[56]. The correlation was less robust in a validation cohort of 24 patients, of whom 11 (46%) had a complete response[56].

Four independent groups have used gene-expression to identify intrinsic subtypes of MIBC[58-61]. Subtypes across these studies showed considerable overlap and distinct responses to CB-NAC[62]. Choi et al.[59] identified a basal, a luminal and a so-called p53-like subtype. Approximately one-third of patients belonged to each subtype[59]. They initially reported that p53-like tumors were more resistant to NAC than luminal or basal tumors[59]. The same group subsequently highlighted the remarkable shift in survival observed for patients with basal tumors. In the absence of NAC, basal tumors were associated with the worst prognosis, but they had the best prognosis after NAC[63].

Recently, Seiler et al. developed a single-sample genomic subtyping classifier based on samples classified according to the molecular subtyping methods of the aforementioned projects[62]. OS and pCD according to subtype (claudin-low, basal, luminal-infiltrated and luminal) were retrospectively compared for 343 MIBC NAC and 476 MIBC non-NAC cases. Luminal tumors had the longest OS with and without NAC. Nevertheless, OS differed according to the response to NAC. Claudin-low tumors were associated with poor OS irrespective of treatment regimen. Basal tumors showed the highest improvement in OS with NAC compared with surgery alone[62].

Altogether, we can conclude that results on gene mutation and expression analyses are promising but still preliminary. Validation in larger prospective cohorts is needed. As previously mentioned, the SWOG-1314 trial started to evaluate the ability of a gene-expression profiling algorithm (COXEN) to predict pathological responses to ddMVAC or GC[47,64]. There are grounds for optimism that predictive biomarkers will soon be used in clinical practice to guide use of NAC in patients with MIBC.

The Future: Neoadjuvant immunotherapy with checkpoint inhibitors

Immune modulation by checkpoint inhibition is an exciting recent development in BC. This treatment modality has mainly been investigated as second line treatment after progression on platinum-based chemotherapy in patients with metastatic urothelial cancer and as first line treatment in ciplatin-ineligible patients[65-69]. Within this setting, reported objective response rates range from 15% to 31%[65-69]. Results on duration of response have to be awaited. In these studies, grade 3-4 adverse autoimmune reactions were present in 5% to 18% of patients[65-69]. Reactions mainly consisted of fatigue, pruritus and rash. However, severe reactions like hepatitis, pneumonitis and colitis also occurred and these prohibited continuation of therapy[65-69]. In the neoadjuvant setting, this could imply definitive surgical intervention has to be discarded. Nevertheless, the success in terms of response rates in the advanced disease state has supported ongoing clinical trials in the adjuvant and neoadjuvant settings in patients with non-metastatic MIBC. Toxicity profiles should be taken into account.

Tumor cells are able to escape from the inherent immunological status – or 'cancer-immune set-point' - of an individual[70]. Current cancer immunotherapy strategies generally aim at restoring T-cell mediated antitumor activity. Expression of cell ligands on antigen presenting cells or tumor cells and engagement with inhibitory receptors on T-cells can withhold either an allogeneic or an antitumor cell response[70,71]. These mechanisms contribute to the protection against autoimmune diseases, whereas tumor cells may exploit their defense mechanisms using these pathways. These T-cell mediated inhibitory pathways are called immune checkpoints and antibodies counteracting the ligand-receptor interaction are called checkpoint inhibitors[71]. Monoclonal antibodies currently used in BC studies are mainly active

in counteracting the checkpoints PD-L1/PD-1 and CTLA-471.

Hypothetically, immunotherapy may be more effective in the neoadjuvant compared to the adjuvant setting since a higher load of tumor antigens is likely to be present if the primary tumor is still in situ[72]. However, it is challenging to conduct trials of neoadjuvant immunotherapy for two principle reasons. Since level I evidence supports the use of CB-NAC, it is difficult to justify withholding CB-NAC in eligible patients. Furthermore, in the metastatic setting only approximately 20% of patients achieve an objective response to single agent checkpoint blockade, so it is difficult to delay RC for the sake of a systemic therapy that is likely not to help the vast majority of patients. On the other hand, approximately half of patients are ineligible for CB-NAC, and CB-NAC is generally underutilized around the world[2,3,25]. The toxicity of immunotherapy is likely less, although a severe immune-related adverse event prior to RC could preclude subsequent surgery. This might be of special concern in patients who are borderline candidates for RC.

Given the modest improvement of 6% OS after ten years, the associated toxicity and the previously mentioned flaws in the landmark NAC RCTs, we consider it justified to investigate checkpoint inhibition in the neoadjuvant setting. Given the results of the IMVigor210 trial, it is also highly interesting to further clarify the potential role of checkpoint inhibitors in patients with intrinsic subtypes known to be resistant to CB-NAC, for example those with p53-like or luminal-infiltrated tumors[59,62,69]. Currently initiated neoadjuvant phase II trials are investigating safety and downstaging of MIBC prior to RC by checkpoint inhibitors in combination with GC or by using multiple, instead of solo, checkpoint inhibitors[73-76]. Neoadjuvant immunotherapy is likely to have the greatest impact if its use can be guided by predictive biomarkers, such as molecular subtypes[59].

Conclusions

RC alone for MIBC is often insufficient treatment and is associated with a high rate of cancer-specific mortality. Many efforts have been undertaken to improve oncological outcomes by adding neoadjuvant treatment. NAR results in better downstaging but its overall impact in patients with MIBC is inconclusive and its use is generally not advised. The use of NAC has increased in recent years. The absolute OS benefit was between 58% in the three landmark RCTs on CB-NAC. In-depth analyses of key randomized controlled trials showed that failure to correct for uniform staging, surgical variation and patient selection compromises the ability to identify factors predictive of response to NAC. However, only a subset of MIBC patients will benefit from CB-NAC, and non-responders are even likely to suffer harm, so that predictive biomarkers will be key to tailoring use of CB-NAC in the near future. For now, selecting patients based on high-risk clinical features (NAC only cT3-4a) might be an approach to reduce overtreatment in the neoadjuvant setting. Looking further to the future, the role of neoadjuvant immunotherapy with checkpoint inhibition is promising and currently under investigation.

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3

Superior efficacy of neoadjuvant chemotherapy and radical cystectomy in cT3-4aN0M0 compared to cT2N0M0 bladder cancer

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Int J Cancer. 2019 Mar 15;144(6):1453-1459.

Abstract

In this study we compared complete pathological downstaging (pCD, ≤(y)pT1N0) and overall survival (OS) in patients with cT2 versus cT3-4aN0M0 UC of the bladder undergoing radical cystectomy (RC) with or without neoadjuvant chemo- (NAC) or radiotherapy (NAR).

A population-based sample of 5,517 patients, who underwent upfront RC versus NAC+RC or NAR+RC for cT2-4aN0M0 UC between 1995-2013, was identified from the Netherlands Cancer Registry. Data were retrieved from individual patient files and pathology reports. pCD-rates were compared using Chi-square tests and OS was estimated by Kaplan-Meier analyses. Multivariable analyses were conducted to determine odds (OR) and hazard ratios (HR) for pCD-status and OS, respectively.

We included 4,504 (82%) patients with cT2 and 1,013 (18%) with cT3-4a UC. Median follow-up was 9.2 years. In cT2 UC, pCD-rate was 25% after upfront RC vs. 43% (p<0.001) and 33% (p=0.130) after NAC+RC and NAR+RC, respectively. In cT3-4a UC, pCD-rate was 8% after upfront RC vs. 37% (p<0.001) and 16% (p=0.281) after NAC+RC and NAR+RC, respectively. In cT2 UC, 5-year OS was 57% and 51% for NAC+RC and upfront RC, respectively (p=0.135), whereas in cT3-4a UC, 5-year OS was 55% for NAC+RC vs. 36% for upfront RC (p<0.001). In multivariable analysis for OS, NAC was beneficial in cT3-4a UC (HR: 0.67, 95%CI 0.51-0.89) but not in cT2 UC (HR: 0.91, 95%CI 0.72-1.15). NAR did not influence OS.

In conclusion, NAC+RC was associated with superior pCD compared to RC alone and NAR+RC. Superior OS for NAC+RC compared to RC alone was especially evident in cT3-4a disease.

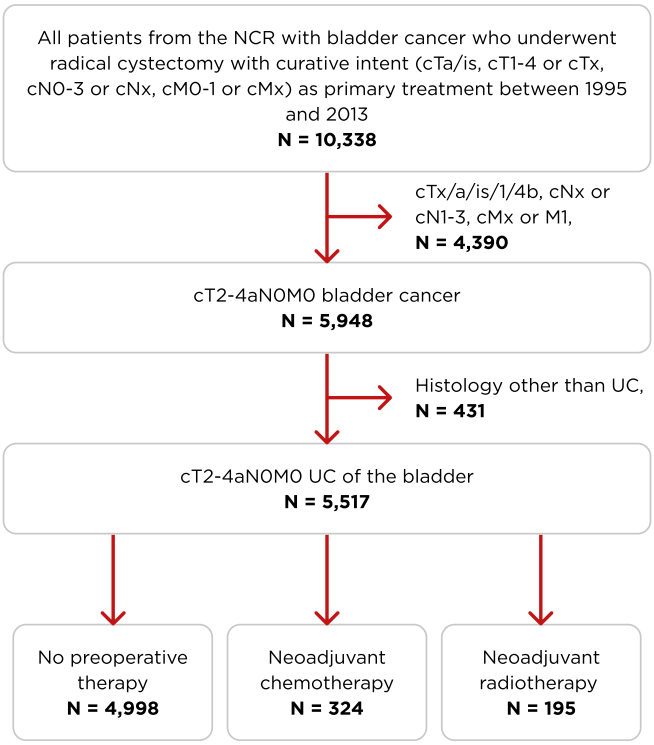
Introduction

Muscle-invasive bladder cancer (MIBC) is an aggressive type of cancer with a 5-year overall survival (OS) of approximately 50%[1]. At upfront radical cystectomy (RC) for cN0M0 MIBC, approximately 25% of patients have lymph node metastases and eventually 30-40% will develop local or distant recurrent disease[2,3]. In cT2-4a, N0-x, M0 bladder cancer (BC), a meta-analysis of seven randomized controlled trials (RCT) showed that neoadjuvant cisplatin-based combination chemotherapy (CB-NAC) was associated with an absolute OS benefit of 5% after 5 years[4]. This meta-analysis led to Grade A recommendations in contemporary MIBC Guidelines[5]. However, certain issues regarding the key RCTs addressing the value of CB-NAC remained. Failure to correct for uniform clinical (nodal) staging, surgical variation (e.g. pelvic lymph node dissection (PLND)) and patient selection, compromise the ability to conclusively determine a significant beneficial link between the addition of NAC to RC and a more favorable outcome[6-8]. In the three largest RCTs, the benefit of NAC appears to be restricted to the larger number of patients downstaged to (y)pT0 in the RC specimen compared to transurethral resection (TUR) alone (25-38% vs. 12-15%)[9-11]. Moreover, the potential of cure by RC only, the toxicity of NAC and considerable variation in chemotherapy sensitivity result in a relative high number needed to treat (NNT) (estimated 17-20) if all patients with cT2-4N0M0 BC would be treated with NAC[4,9-12]. As long as response to chemotherapy cannot reliably be predicted by imaging or molecular alterations in the TUR-specimen, current decision-making is based on the predictive value of clinical parameters. While NAC is currently recommended in all patients with cT2-4aN0M0 BC and administration is gaining popularity among all stages in Europe and North America[13,14], administration of NAC in cT2 disease without high-risk features is still subject of debate[12]. The role of neoadjuvant radiation (NAR) in MIBC is less clear because no high quality data exists to support additive value in terms of OS[15]. The aims of this nationwide Netherlands Cancer Registry (NCR) study were to compare complete pathological downstaging (pCD, ≤(y)pT1N0) and OS for patients who underwent upfront RC versus patients who underwent NAC or NAR prior to RC for cT2N0M0 versus cT3-4aN0M0 urothelial carcinoma (UC) of the bladder.

Materials and methods

In total, 5,517 of 10,338 patients[14], who underwent either upfront RC, or NAC or NAR prior to RC as primary treatment for cT2-4aN0M0 UC between 1995 and 2013 were selected from the NCR (Figure 1). To circumvent limitations concerning clinical and surgical staging, we only selected patients with cN0M0 UC and took PLND as a variable into account. Clinical staging was based on physical examination, findings at cystoscopy and TUR, CT-scan of the abdomen/pelvis and chest imaging (at least a chest X-ray). Patients who underwent neoadjuvant treatment or patients who were scheduled for upfront RC but did not proceed to RC could not be retrieved from the NCR database. Nationwide data on all newly diagnosed malignancies is recorded in the NCR.

Figure 1. Identification of patients with cT2-4aN0M0 urothelial carcinoma of the bladder who underwent radical cystectomy with or without neoadjuvant chemo- or radiotherapy as primary treatment in the Netherlands between 1995 and 2013. Abbreviations: NCR, Netherlands Cancer Registry; UC, Urothelial Carcinoma.



Notification is obtained from the registry of histopathology and cytopathology (PALGA) and the National Registry of Hospital Discharge Diagnosis[16]. After this identification, independent and trained registration clerks collected clinical data on predefined patient, tumor and treatment characteristics from the individual patient files at each hospital. In addition, five authors of this manuscript (TH, CV, MD, LM, BvR) crosschecked all 5,517 pathology reports to evaluate pathological downstaging at RC. Topography and morphology were classified according to the International Classification of Diseases for Oncology (ICD-O) and tumor stage according to the TNM classification system[17]. For this particular study period (1995–2013), previous TNM classifications were converted to the most recent one, the 7th TNM-classification system[18]. As recently published, pCD was defined as downstaging to non-muscle invasive disease without lymph node metastases (≤(y) pT1N0)[19]. Patient and tumor characteristics were compared by chi-square tests for categorical variables and by independent sample T-tests for continuous variables. The Kaplan-Meier method was applied to estimate 3-year and 5-year OS rates in patients who underwent either upfront RC or NAC or NAR prior to RC and for pCD. Log-rank tests were used to compare survival distributions. To circumvent an immortal time bias, date of RC was taken as start of follow-up. Follow-up was censored at February 1st, 2017.

Multivariable logistic regression analyses were performed to evaluate factors associated with pCD for patients with cT2N0M0 and cT3-4aN0M0 UC. Cox proportional hazard analyses were carried out to determine the hazard ratio (HR) of age, sex, NAC, NAR and PLND on OS. Statistical analyses were performed with SPSS statistical software (version 19.0; SPSS Inc., Chicago, III., USA). P-values <0.05 were considered statistically significant.

Results

In total, 4,504 (82%) patients with cT2N0M0 and 1,013 (18%) patients with cT3-4aN0M0 UC were identified. Patient characteristics are shown in Table 1. NAC was administered in 4.2% (N=191) of cT2 and in 13% (N =133) of cT3-4a disease. For NAR, these rates were 3.3% (N=149) and 4.5% (N =46), respectively. Median follow-up for cT2 patients who underwent either upfront RC or NAC or NAR prior to RC was 9.2 (IQR: 5.8-14.0), 4.3 (3.4-7.6) and 17.8 (15.5-19.2) years, respectively. In cT3-4a disease, this was 10.5 (IQR: 6.2-14.3), 4.4 (3.6-7.3) and 16.0 (14.1-17.7) years, respectively. In patients without neoadjuvant treatment, PLND was omitted in 14%. These rates were 8.0% in the NAC group (p<0.002) and 47% in the NAR group (p<0.001), respectively.

In cT2 UC, the proportion of pCD was 43% and 33% in patients who underwent NAC (p<0.001) or NAR (p=0.130) versus 25% for upfront RC (Table 2). In cT3-4a UC, the proportion of pCD was 37% and 16% of patients who underwent NAC (p<0.001) or NAR (p=0.281) versus 8.2% for upfront RC (Table 3). In univariable analysis, the estimated 5-year OS in patients having pCD were 75% (upfront RC), 79% (NAC+RC, p=0.430) and 76% (NAR+RC, p-value not applicable), respectively. In multivariable logistic regression analysis, the administration of NAC, but not NAR, was significantly associated with pCD, both in cT2 and cT3-4a disease (Table 4).

Univariable analysis showed that NAC+RC in cT2 disease was not significantly associated with superior OS compared to RC alone (5-year OS: 51 vs. 57%, p=0.135)(Figure 2A). In contrast, in cT3-4a disease, NAC was associated with an absolute 5-year OS benefit of 19% (54 vs. 36%, p<0.001)(Figure 2B). NAR was not associated with superior OS (p=0.599), nor if stratified according to stage of disease (Figure 2). If patients without PLND at RC were excluded, significance for NAC+RC in cT2 disease was even less evident (p=0.387).

In the Cox proportional hazard analyses with (pre-)operative clinical variables NAC was not beneficial in cT2 UC (HR: 0.91, 95%-CI 0.72-1.15). In cT2 UC, performance of any PLND was associated with superior OS (HR: 0.88 95%-CI 0.78-0.99) (Table 2). In cT3-4a disease, NAC usage was associated with a 33% decrease in the risk of death (HR: 0.67, 95%-CI 0.51-0.89) (Table 2) and an absolute risk reduction of 19% resulting in a NNT of 5.3. NAR was not associated with beneficial hazard ratios. Hazard ratios in both cT2 and cT3-4a disease did not significantly alter if patients without PLND at RC were excluded (data not shown). Moreover, multivariable results did not change if NAR was excluded (data not shown).

Table 1. Patient characteristics

	No NT (N=4998)	NAC (N=324)	p-value no NT vs. NAC	NAR (N=195)	p-value No NT vs. NAR
Age in years, median (IQR)	67.0 (61-73)	63.0 (56-70)	<0.001	65.0 (58-70)	<0.001
Male, n (%)	3820 (76.4)	238 (73.5)	0.22	150 (76.9)	0.87
cT-stage, n (%)					
T2	4164 (83.3)	191 (59.0)	<0.001	149 (76.4)	0.012
T3-4a	834 (16.7)	133 (41.0)		46 (23.6)	
Grade WHO73, n (%)					
G1	23 (0.5)	1 (0.3)	0.002	0 (0.0)	0.67
G2	364 (7.3)	12 (3.7)		17 (8.7)	
G3	4499 (90.0)	295 (91.0)		173 (88.7)	
Missing	112 (2.2)	16 (4.9)		5 (2.6)	
Year of treatment, n (%)					
1995-1999	743 (14.9)	12 (3.7)	<0.001	123 (63.1)	<0.001
2000-2004	1107 (22.1)	30 (9.3)		48 (24.6)	
2005-2010	1558 (31.2)	59 (18.2)		22 (11.3)	
2010-2013	1590 (31.8)	223 (68.8)		2 (1.0)	
No PLND, n (%)	712 (14.2)	26 (8.0)	<0.002	91 (46.7)	<0.001
Adjuvant radiotherapy, n (%)	70 (1.4)	7 (2.2)	0.420	12 (6.2)	<0.001
Adjuvant chemotherapy, n (%)	65 (1.3)	1 (0.3)	0.125	1 (0.5)	0.350

Abbreviations: NAC, Neoadjuvant chemotherapy; NAR, Neoadjuvant radiotherapy; NT, Neoadjuvant treatment; PLND, Pelvic lymph node dissection; Note 4 patients underwent NAC and NAR, these are within in the NAC group.

Because NAR was mainly administered in the first two time periods of our study (1995-2004; Table 1), we repeated prediction of pCD (uni- and multivariable analyses) and OS (uni- and multivariable analyses) for NAR vs upfront RC for all patients (N=2,021), cT2N0M0 (N=133/1,630) and cT3-4aN0M0 (N=38/391) in this time period. We found no shifts in significance for NAR in the prediction of pCD and for OS in uni- and multivariable analyses (supplementary Table 1A).

Because NAC was mainly administered in the last two time periods of our study (2005-2013; Table 1), we repeated prediction of pCD (uni- and multivariable analyses) and OS (uni- and multivariable analyses) for NAC vs upfront RC for all patients (N=3,430), cT2N0M0 (N=161/2,828) and cT3-4aN0M0 (N=118/602). We found no shifts in significance for NAC in the prediction of pCD and for OS in uni- and multivariable analyses (supplementary Table 1B).

Table 2. Correlation between clinical stage and pathological downstaging after neoadjuvant treatment for cT2N0M0 and cT3-4aN0M0 urothelial carcinoma

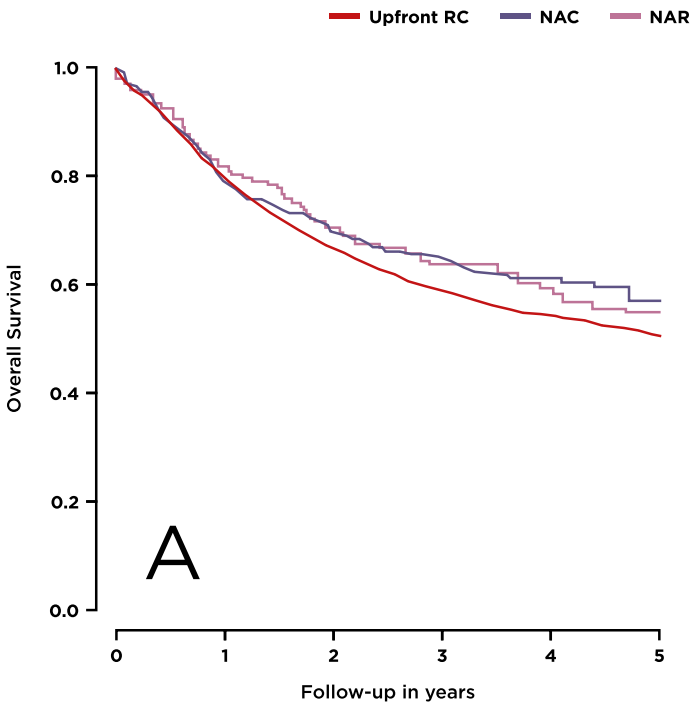
All patients (cT2-4aN0M0), pTanyNx excluded (N=852), pTx excluded (N=16)					
	No NT	**NAC**	**p-value no NT vs NAC**	**NAR**	**p-value No NT vs NAR**
	N=4261	N=298		N=101	
≤pT1N0* (pCD)	936 (22.2)	120 (40.3)	<0.001	30 (29.7)	<0.151
pT2N0	940 (22.3)	45 (15.1)		25 (24.8)	
pT3-4 N0 or pTany N1-3	2385 (56.5)	134 (44.6)		49 (45.5)	

Clinical T2N0M0 Urothelial carcinoma, pTanyNx (N=691), pTx excluded (N=15)					
	N=3565	N=169		N=79	
≤pT1N0* (pCD)	879 (24.7)	72 (42.6)	<0.001	26 (32.9)	
pT2N0	858 (24.1)	33 (18.9)		21 (26.6)	
pT3-4 N0 or pTany N1-3	1828 (51.3)	65 (38.5)		32 (40.5)	

Clinical T3-4aN0M0 Urothelial carcinoma, pTanyNx excluded (N=161), pTx excluded (N=1)					
	N=696	N=129		N=25	
≤pT1N0 (pCD)	57 (8.2)	48 (37.2)	<0.001	4 (16.0)	0.281
pT2N0	82 (11.8)	12 (9.3)		4 (16.0)	
pT3-4 N0 or pTany N1-3	557 (80.0)	69 (53.5)		17 (68.0)	

*Abbreviations NAC, Neoadjuvant chemotherapy; NAR, Neoadjuvant radiotherapy; NT, Neoadjuant treatment; pCD, Complete pathological downstaging; *pT0/a/is/p*

Figure 2A. Overall survival for cT2N0M0-disease with and without neoadjuvant chemotherapy and neoadjuvant radiation

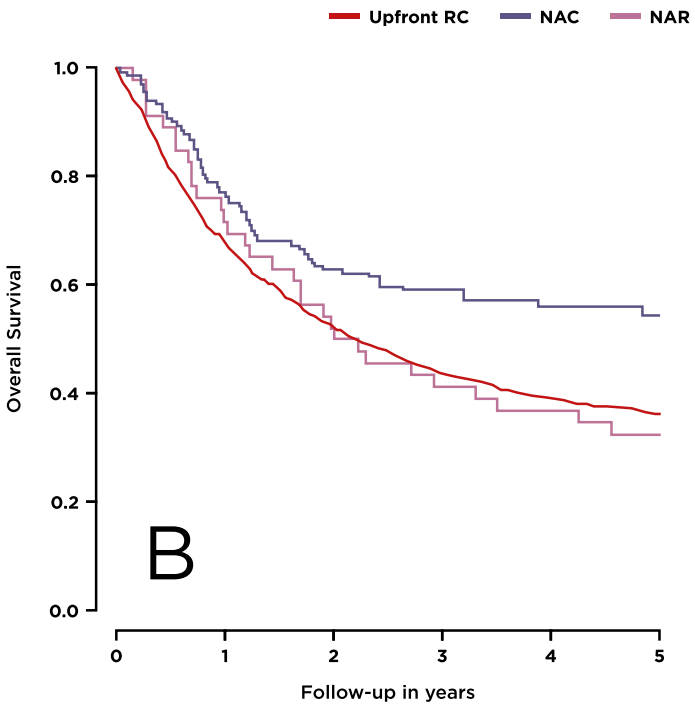


Number at risk						
Follow-up	0	1	2	3	4	5
Upfront RC	4164	3445	2885	2523	2115	1795
NAC	191	149	131	107	67	42
NAR	149	121	104	95	88	81

	3 yr. OS (%)	95%-CI	5 yr. OS (%)	95%-CI	p-value vs. No NT
No NT	59.1	57.5-60.7	50.7	49.1-52.3	
NAC	64.8	57.9-71.7	57.1	49.3-64.9	0.135
NAR	62.9	55.3-70.5	53.6	45.6-61.6	0.501

Abbreviations: CI, confidence interval; NAC, Neoadjuvant chemotherapy; NAR, Neoadjuvant radiation, NT, Neoadjuvant treatment; OS, overall survival.

Figure 2B. Overall survival for cT3-4aN0M0-disease with and without neoadjuvant chemotherapy and neoadjuvant radiation



Number at risk						
Follow-up	0	1	2	3	4	5
Upfront RC	834	561	429	359	299	259
NAC	132	102	84	71	48	34
NAR	45	33	23	19	17	15

	3 yr. OS (%)	95%-CI	5 yr. OS (%)	95%-CI	p-value vs. No NT
No NT	43.8	40.5-47.1	36.1	33.0-39.2	
NAC	59.1	50.7-67.5	54.6	45.8-63.4	<0.001
NAR	59.1	50.7-67.5	32.6	19.1-46.1	0.625

Abbreviations: CI, confidence interval; NAC, Neoadjuvant chemotherapy; NAR, Neoadjuvant radiation, NT, Neoadjuvant treatment; OS, overall survival.

Table 3. Multivariable cox regression analysis on overall survival in cT2 and cT3-4a disease. Variables in bold were statistically significant (P-values <0.05).

cT2 disease, N=4504		
Variable	**Hazard ratio**	**95%-CI**
Female	1.01	0.91-1.12
Age (continuous)	**1.02**	**1.02-1.03**
NAC	0.91	0.72-1.15
NAR	0.93	0.73-1.19
PLND	**0.88**	**0.78-0.99**
cT3-4a disease, N=1013		
Variable	**Hazard ratio**	**95%-CI**
Female	0.93	0.78-1.10
Age (continuous)	**1.01**	**1.01-1.02**
NAC	**0.67**	**0.51-0.89**
NAR	1.02	0.71-1.48
PLND	0.92	0.74-1.13

Outcomes did not significantly alter if patients without PLND at RC were excluded.
Abbreviations: CI, confidence interval; NAC, Neoadjuvant chemotherapy; NAR, Neoadjuvant radiotherapy; PLND, Pelvic lymph node dissection.

Table 4. Multivariable logistic regression analysis on the prediction of pCD in cT2 and cT3-4a disease. Variables in bold were statistically significant (P-values <0.05).

cT2 disease (Nx excluded), N=3828		
Variable	**Odds ratio**	**95%-CI**
Female	**0.75**	**0.62-0.90**
Age (continuous)	**1.01**	**1.01-1.02**
NAC	**2.23**	**1.63-3.06**
NAR	1.38	0.85-2.22
cT3-4a disease (Nx excluded), N=851		
Variable	**Odds ratio**	**95%-CI**
Female	**0.39**	**0.22-0.69**
Age (continuous)	1.01	0.98-1.02
NAC	**6.73**	**4.21-10.7**
NAR	2.23	0.73-6.78

Discussion

In this large population-based study using individual patient data, NAC was associated with higher pCD rates in cT2-4aN0M0 BC, but a significant OS benefit was only evident in patients with locally advanced disease (cT3-4aN0M0). NAR did not result in better pCD, nor improved OS.

The SWOG-8710 trial (N=317) was the first RCT to describe an OS benefit for NAC prior to RC[9]. At a median follow-up of 8.7 years, median OS for patients who underwent NAC plus RC vs. RC alone was 77 vs. 46 months, respectively (p=0.05). In this study, the HR in favor of NAC was 0.67 (95%CI: 0.2-1.0), comparable to the effect found in our study in cT3-4a disease[9]. In SWOG-8710, NAC was associated with a median OS benefit of 41 months (65 vs. 24 months) in cT3-4aN0M0 BC, which was longer than the benefit (30 months; 105 vs. 75 months) reported in cT2N0M0 disease (p=0.05)[9]. The BA06-30894 trial showed an absolute 10-year OS benefit of 6% for those who received NAC prior to definitive local treatment[10]. This resulted in a HR in favor of NAC of 0.84 (0.72-0.99)[10]. This trial did not stratify results according to clinical stage of disease. Overall, the combined results of the Nordic Cystectomy trials (N=620) did not show any OS benefit for NAC[11]. However, the absolute reduction in risk of death in cT3 BC was 13% in favor of NAC (p=0.019)[11], no difference was found for cT2 tumors. These numbers are in line with the results of our study; an absolute and significant 5-year OS benefit of 19% (NNT=5) in cT3-4a disease and a minor and non-significant benefit of 6% (NNT=17) in cT2 disease, without effect confirmation in multivariable analysis.

However, clinical staging of MIBC is notoriously inaccurate, and any tailoring of CB-NAC to patient risk must be balanced with the potential of undertreatment. To challenge the value of the latter assumption in relation to our conclusions, we hereby discuss the results from Culp et al. who developed a risk-adapted approach to NAC[12]. In their case-control study, 297 patients underwent RC and PLND without NAC for low-, or high-risk MIBC. High-risk disease was present in 98 patients and was defined as the clinical presence of hydroureteronephrosis, cT3-4a BC on CT or MRI and/or clinical examination, histological evidence of lymphovascular invasion and/or micropapillary/neuroendocrine features in the TUR specimen. Even though 49% of cT2 low-risk patients were upstaged to pT3-4 and/or pN1-3 disease at RC, the 5-year CSS of this group was 84%[12]. This high 5-year CSS suggests that, despite frequent upstaging at RC, usage of neoadjuvant systemic treatment can be debated in the majority of patients with cT2N0M0 disease. If we contemplate the evidence from the largest RCTs in the field[9-11], the results of Culp et al.[12], and our own results in 5,517 patients, we presume that the best strategy to improve the harm-to-benefit ratio is usage of NAC in patients with clinical high-risk disease only (cT3-4aN0M0 and cT2N0M0 with high-risk features, for example lymphovascular invasion). Adjuvant chemotherapy (AC) may still be offered to eligible patients (estimated 66%[20]) who are upstaged at RC. Moreover, meta-analyses on AC have estimated an absolute 5-year OS benefit of 6%, comparable to the benefit of NAC[21]. In our opinion, motivated patients with cT2 disease should at least be informed on the NNT (at least 17-20[9-11]) for NAC, stressing the role of shared decision making.

The role of NAR is less clear than the role of NAC, since no high quality data exists to support an additive value in terms of survival[15]. A meta-analysis conducted by Huncharek et al. on currently outdated RCTs reported a non-significant 29% relative reduction in the overall death risk after 5 years (95%-CI: 0.48-1.06)[15]. Results are considered inconclusive, since almost 50% of patients from the largest trial included, did not receive the planned treatment[15,22]. A more recent single center retrospective study, applying modern radiation techniques reported significant longer OS in patients with cT3 tumors treated with NAR prior to RC[23]. A population-based study by Diaz et al. reported a significant reduction in mortality after NAR in patients with cT2b-3 MIBC (HR 0.74)[24]. Our study does not point towards downstaging or survival benefits, but is restricted by a limited number of patients who had NAR and other factors inherent to the study design. Results on NAR can currently be considered inconclusive. It might be interesting to evaluate modern radiation techniques in patients with an incomplete response to NAC or as an adjunct to chemotherapy to improve pCD rates, but more importantly OS.

Certain important limitations of our study need to be acknowledged. First, the number of patients scheduled for upfront RC, NAR+RC or NAC+RC who did not proceed to RC could not be captured in the NCR. Therefore, a potential disproportional drop out between groups prior to RC may bias our results. However, in the SWOG-8710 and the BA06-30894 RCTs, the percentage of patients proceeding to RC after randomization was equal for the NAC+RC and the upfront RC groups (82 vs. 81% (SWOG-8710) and 87 vs. 86% (BA06-30894))[9,10]. The data from these two RCTs suggest that the effect of this potential bias may be minimal. Furthermore, due to our study design and to prevent a potential immortal time bias, date of RC was selected as starting point for follow-up. The fact that in general the time to RC is longer after NAC only strengthens our study results.

Second, if we compare OS for all treatment groups, a time related cohort bias should be taken into account. NAC is increasingly endorsed by guidelines[5] and applied in more recent years[14]. Also, surgical standards have been altered and may influence survival (e.g. PLND)[3]. However, we stratified results according to different time cohorts in which NAR (early-time-cohorts) and NAC (recent-time-cohorts) were applied more frequently. The similar results obtained by narrowing time cohorts only suggest a limited bias.

Third, it was not possible to adjust for potential confounders and important prognostic factors such as performance status, comorbidity, cause of mortality, hydronephrosis, the presence of lymphovascular invasion on histology, and variability in the extent of PLND[25]. As a result, meaningful propensity score matched analyses were not possible. However, substantial bias regarding performance status and the extent of PLND at RC are also evident in the 3 largest RCTs on NAC[8-11]. Moreover, one might argue that OS is better in the NAC groups due to selection of patients with less comorbidity. A counter-argument against this assumption is that, in contrast to cT3-4a disease, the OS benefit for NAC usage in cT2 disease is absent.

Fourth, due the lack of specifications on particular chemotherapeutic agents, number of treatment cycles, radiation dose and fractionation, we could not determine correlations for these factors and pCD and OS. It seems plausible to assume that less effective chemotherapeutic

agents were more frequently used in cT3-4a compared to cT2 disease because cT3-4a is often associated with bulky disease, hydronephrosis and impaired renal function. However, in a large multicentre retrospective study in 19 Northern American and European centres the administration rates of non-cisplatin based regimens for cT2 vs. cT3-4a disease were comparable. In 935 patients with cT2-4aN0M0 urothelial carcinoma of the bladder, non-cisplatin-based regimens were administered in 15.6% (94/603) and 15.1% (50/332) in cT2 and cT3-4a disease, respectively[26].

Notwithstanding the limitations, our study involves and reflects real world data of a very large nationwide population sample. Additional strengths of our study are the use of individual patient data collected by independent data managers who visited the hospitals, the review of the 5,517 pathology reports to assess pathological stage and clinical staging by abdominal, pelvic and chest imaging.

Conclusions

In this large population-based cohort of clinically non-metastatic urothelial BC patients treated with RC, NAC+RC was associated with superior pCD compared to RC alone and NAR+RC. We reported an absolute and highly significant 5-year OS benefit of 19% (NNT=5) in cT3-4a disease versus a non-significant benefit of 6% (NNT=17) in cT2 disease, without effect confirmation in multivariable analysis. Our study results contribute to the debate to consider a more tailored use of perioperative chemotherapy, whereby usage of NAC is strongly recommended in locally advanced cT3-4aN0M0 urothelial BC.

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Supplementary Table 1A. Multivariable cox regression analysis on overall survival in cT2 and cT3-4a disease – selection time cohort 1995-2004

cT2 disease, N=1630		
Variable	**Hazard ratio**	**95%-CI**
Female	1.06	0.89-1.26
Age (continuous)	1.02	1.02-1.03
NAC	0.61	0.37-1.00
NAR	0.97	0.78-1.30
PLND	0.98	0.83-1.15
cT3-4a disease, N=391		
Variable	**Hazard ratio**	**95%-CI**
Female	1.00	0.76-1.31
Age (continuous)	1.01	0.97-1.02
NAC	1.34	0.63-2.91
NAR	0.94	0.62-1.42
PLND	0.90	0.68-1.21

Outcomes did not significantly alter if patients without PLND at RC were excluded.
Abbreviations: CI, confidence interval; NAC, Neoadjuvant chemotherapy; NAR, Neoadjuvant radiotherapy; PLND, Pelvic lymph node dissection.

Supplementary Table 1B. Multivariable cox regression analysis on overall survival in cT2 and cT3-4a disease – selection time cohort 2005-2013

cT2 disease, N=2828		
Variable	**Hazard ratio**	**95%-CI**
Female	0.98	0.86-1.12
Age (continuous)	1.02	1.02-1.03
NAC	0.83	0.64-1.09
NAR	0.47	0.20-1.14
PLND	**0.83**	**0.70-0.98**
cT3-4a disease, N=602		
Variable	**Hazard ratio**	**95%-CI**
Female	0.88	0.70-1.10
Age (continuous)	1.02	1.01-1.03
NAC	0.66	0.49-0.89
NAR	0.92	0.38-2.22
PLND	0.90	0.64-1.26

Outcomes did not significantly alter if patients without PLND at RC were excluded.
Abbreviations: CI, confidence interval; NAC, Neoadjuvant chemotherapy; NAR, Neoadjuvant radiotherapy; PLND, Pelvic lymph node dissection.


3A

Words of Wisdom
Re: Multicenter prospective phase II trial of neoadjuvant dose-dense gemcitabine plus cisplatin in patients with muscle-invasive bladder cancer

C.S. Voskuilen, M.S. van der Heijden, B.W.G. van Rhijn

Eur Urol. 2019 Dec;76(6):870-871.

Response to: Iyer G, Balar AV, Milowsky MI, et al. J Clin Oncol 2018;36:1949-56.

Experts' Summary:

This multicenter phase 2 study assessed the efficacy and tolerability of neoadjuvant dose-dense gemcitabine and cisplatin (ddGC) in 49 patients with non-metastatic muscle-invasive bladder cancer (MIBC). Patients received six 14-day cycles of ddGC: gemcitabine 2500 mg/m^2 on day 1, cisplatin 35 mg/m^2 on days 1 and 2 (achieving a planned dose intensity of 1.875 times and 1.5 times standard gemcitabine and cisplatin, respectively), and pegfilgrastim on day 3. Downstaging to <ypT2N0 was found in 57% of patients, but only 15% of patients had a pathologic complete response (pCR, ypT0N0). Responders (<ypT2N0) had significantly better recurrence-free survival and overall survival compared to non-responders at a median follow-up of 26 months for surviving patients. Grade 3-4 toxicity occurred in 37% of patients, but no patient experienced toxicity-related delays to radical cystectomy (RC). Median time to RC was 6.5 weeks. The authors concluded that ddGC is an active, well-tolerated neoadjuvant regimen.

Experts' comments:

Cisplatin-based neoadjuvant chemotherapy (NAC) followed by RC has become the standard of care in MIBC[1]. However, the optimal regimen in terms of both dose-schedule and agents remains undefined. After the landmark SWOG-8710 trial established methotrexate, vinblastine, doxorubicine, and cisplatin (MVAC) as the standard NAC regimen[2], routine clinical practice has shifted towards more modern regimens like gemcitabine and cisplatin (GC) and dose-dense MVAC (ddMVAC)[1,3].

None of these regimens has been compared in randomised controlled trials in the neoadjuvant setting. Nevertheless, in retrospective series ddMVAC has yielded response rates similar to response rates after standard-dose MVAC and GC, while toxicity rates were lower[3]. Importantly, ddMVAC was associated with higher pCR and improved survival rates compared to GC in a retrospective cohort of patients with locally advanced (i.e. cT3-4aN0M0) MIBC[4]. Although the superiority of ddMVAC has not been prospectively proven, these high pCR rates, higher long-term survival in the metastatic setting and a shorter time to RC suggest that ddMVAC should be the NAC treatment of choice. Iyer and colleagues studied the efficacy of GC in a dose-dense schedule. Although limited by lack of a comparator arm, their study supports the effectiveness and tolerability of ddGC. Notably, their pCR rate was rather low (15%) even though the majority of patients (67%) completed six cycles of NAC. Survival outcomes for patients with pCR and patients with downstaging were not reported separately, probably because of the small sample size.

Despite the lower toxicity rates of dose-dense cisplatin regimens, up to 50% of MIBC patients are considered unfit for cisplatin-based chemotherapy[1,5]. As an alternative, carboplatin-based NAC regimens have been evaluated, with response rates approaching cisplatin-based NAC

in small retrospective series[5]. However, gemcitabine with carboplatin appeared inferior to cisplatin-based regimens in the metastatic setting and it is therefore not recommended for NAC[1].

The application of neoadjuvant immunotherapy will likely change the established standard of care in MIBC. In the first prospective study (PURE-01) on immunotherapy in the neoadjuvant setting, 50 patients received three cycles of pembroluzimab 200mg every three weeks before RC[6]. Pathologic complete response was achieved in 21/50 (42%) patients and down-staging to <ypT2N0 was found in 54%[6]. Although these results are promising, long-term follow-up is required to allow for assessment of survival outcomes. Several studies on different combinations of immunotherapy and combinations of immunotherapy with NAC will report findings in the next years. While we await these results, comparative studies on the efficacy of different NAC regimens and the number of cycles needed, remain of major clinical importance.

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4

Multicenter validation of histopathologic tumor regression grade after neoadjuvant chemotherapy in muscle-invasive bladder carcinoma

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Am J Surg Pathol. 2019 Dec;43(12):1600-1610.

Abstract

Response classification after neoadjuvant chemotherapy in muscle-invasive bladder carcinoma is based on TNM stage at radical cystectomy. We recently showed that histopathologic tumor regression grades (TRG) add prognostic information to TNM.

Our aim was to validate the prognostic significance of TRG in muscle-invasive bladder cancer in a multicenter setting. We enrolled 389 patients who underwent cisplatin-based chemotherapy prior to radical cystectomy in 8 centers between 2010 and 2016. Median follow-up was 2.2 years. TRG was determined in radical cystectomy specimens by local pathologists. Central pathology review (CPR) was conducted in 20% of cases, which were randomly selected. Major response was defined as ≤pT1N0. Remaining patients were grouped in partial-responders (≥ypT2N0-3 and TRG2) and non-responders (≥ypT2N0-3 and TRG3).

TRG was successfully determined in all cases and interobserver agreement in CPR was high (κ=0.83). After combining TRG and TNM, 47%, 15% and 38% of patients were major, partial and non-responders, respectively. Combination of TRG and TNM showed significant prognostic discrimination of overall survival (Major-responder: ref.; Partial-responder: hazard ratio 3.5 [95%CI 1.8-6.8]; Non-responder: hazard ratio 6.1 [95%CI 3.6-10.3]). This discrimination was superior compared to TNM staging alone, supported by two goodness-of-fit criteria (p=0.041).

TRG is a simple, reproducible histopathologic measurement of response to neoadjuvant chemotherapy in muscle-invasive bladder cancer. Integrating TRG with TNM staging resulted in significantly better prognostic stratification than TNM staging alone.

Introduction

Neoadjuvant chemotherapy followed by radical cystectomy is the gold standard treatment for patients with muscle-invasive bladder carcinoma[1]. However, up to 60% of patients treated with neoadjuvant chemotherapy have residual muscle-invasive bladder cancer at radical cystectomy[2]. These patients have a significantly worse overall survival (OS) compared to patients achieving pathological complete response after neoadjuvant chemotherapy[3,4].

Since patients who do not respond to neoadjuvant chemotherapy have no obvious benefit from therapy but suffer potential toxicity of therapy as well as delay in definitive surgery, it stands to reason that the ability to select patients for neoadjuvant chemotherapy based on likelihood of response would improve patient outcomes. Therefore, research has focused on discovery and validation of predictive biomarkers. However, previous studies investigating predictive biomarkers have used different TNM categories to define response to neoadjuvant chemotherapy[5–7]. This variability may indicate the need for a more granular definition of response, determined in bladder carcinoma treated with neoadjuvant chemotherapy. Furthermore, while it is presumed that patients with residual muscle-invasive bladder cancer after neoadjuvant chemotherapy have derived no benefit from neoadjuvant chemotherapy, this has not been definitively demonstrated.

Histopathologic tumor regression grades (TRG), which quantify the extent of tumor response to systemic treatment, have shown to be a prognostic factor for patient outcome in several malignancies, including gastric, esophageal and rectal carcinoma[8–10]. In muscle-invasive bladder cancer, Fleischmann et al. found that TRG predicted survival after neoadjuvant chemotherapy independently and better than conventional pathologic TNM response classification[11]. The aim of the present study was to investigate whether the prognostic significance of TRG could be validated in a multicenter cohort of muscle-invasive bladder cancer patients who underwent neoadjuvant chemotherapy followed by radical cystectomy.

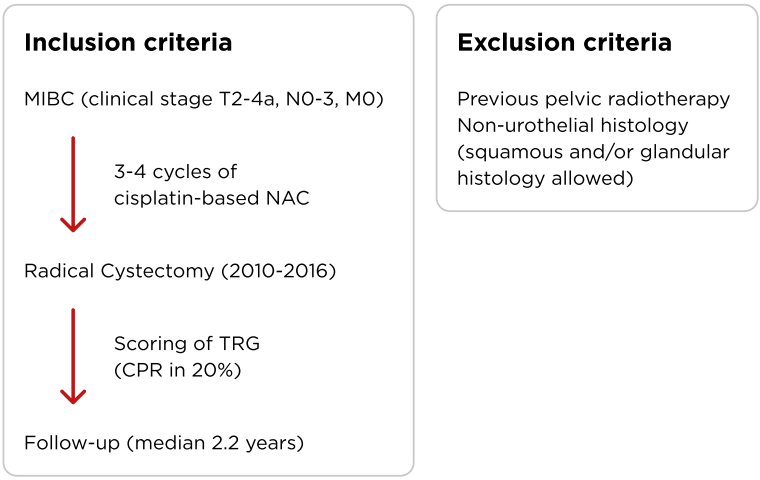
Materials and Methods

Patient population

We enrolled a consecutive cohort of patients who underwent neoadjuvant chemotherapy followed by radical cystectomy for cT2-4aN0-3M0 bladder carcinoma between 2010 and 2016 in 8 institutions. Although systemic chemotherapy for cN1-3 bladder carcinoma is conventionally referred to as induction chemotherapy, we included it here under the term neoadjuvant chemotherapy. Data were collected in accordance with institutional and national ethical guidelines. Only patients who underwent three or four cycles of cisplatin-based neoadjuvant chemotherapy were included. Exclusion criteria were a history of pelvic radiotherapy and non-urothelial primary histology. Urothelial carcinoma with squamous and/or glandular differentiation was allowed (Figure 1). Follow-up was performed according to

institutional protocols. Generally, patients were evaluated every 3-4 months for the first year after radical cystectomy, semiannually for the second year, and annually thereafter.

Figure 1. Flow-chart of patient selection. Abbreviations: CPR: central pathology review, MIBC: muscle-invasive bladder cancer, NAC: neoadjuvant chemotherapy, TRG: tumor regression grade



Pathology

Each center processed the radical cystectomy specimens according to its own institutional protocols. In general, protocols for fixation and pathological examination were similar between pathology departments. Radical cystectomy specimens were fixed in 10% neutral buffered formalin (4% formaldehyde) for 24-48 hours at room temperature. Characteristics of bladder lesions (residual tumors, ulcers, scars) were described (location, relation to the bladder wall and surrounding tissues), and corresponding tissue samples were taken for histologic examination. Generally, samples from the bladder neck with trigone, dome, anterior and posterior wall, and the resection margins of ureters and urethra were embedded. Microscopically, tumor grade and tumor stage were noted. Lymph node specimens were examined by inspection and palpation, and all macroscopically detected lymph nodes were embedded completely. For this study, all Hematoxylin & Eosin-stained sections from all patients were re-evaluated by uropathologists (HZO, VG, LS, JF, JFC, MM, MC, LB) in each center. Scoring of regression is described in detail in the next paragraph.

A random selection of 20% of cases from each center was reviewed independently by two pathologists: the institution's local uropathologist and a central pathology reviewer (VG). One center (INT Milan) could not participate in central pathology review (CPR) due to logistical constraints. All pathologists were blinded from clinical information, treatment regimens, and study end points. In addition, the central pathology reviewer was blinded from other pathologists' interpretations.

Major pathologic response to neoadjuvant chemotherapy according to conventional TNM staging was defined as ≤ypT1N0. Non-major pathologic response was defined as ypT2-4Nany or ypTanyN1-3.

Classification of Tumor Regression Grade

TRG was based on an estimation of the percentage of viable cancer cells in relation to the macroscopically identifiable tumor bed, indicated by zones of fibrosis in the bladder wall and in the perivesical soft tissue, as previously described[11]. The following three TRGs were distinguished (Figure 2A and Supplemental Figure 1):

TRG 1: Complete response: Absence of histologically identifiable residual cancer cells and extensive fibrosis of the tumor bed

TRG 2: Strong response: Predominant fibrosis of the tumor bed with residual cancer cells occupying less than 50% of this area

TRG 3: Weak and no response: Residual cancer cells occupying ≥50% of the tumor bed or absence of regressive changes

This grading system was used separately for primary tumors and LN metastases (Figure 3-4). For every patient the dominant TRG, defined as the higher TRG between primary tumor and LNs, was used as the final grade. Response to neoadjuvant chemotherapy was classified into three categories based on a combination of TNM stage and TRG: Major response, Partial response and No response (Figure 2B). Major response was defined by absence of muscle-invasive disease and LN involvement (≤ypT1N0). Partial response was defined as ≥ypT2N0-3 with TRG 2. Finally, patients with ≥ypT2N0-3 and TRG 3 were considered to have no response to neoadjuvant chemotherapy.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 22.0 (Armonk, NY, IBM Corp.) and R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided with the level of significance set at $p<0.05$. The three TRGs were compared to clinicopathological characteristics using analysis of variance for continuous data and Pearson's chi-square test for categorical data. Kaplan-Meier plots were used to estimate overall survival from time of radical cystectomy to the date of death. Comparisons between response groups were made using the log-rank test. Patients still alive were censored at the date of last follow-up. Median follow-up was calculated using the reverse Kaplan-Meier method.

The level of agreement between TRG score by the local pathologist and the central pathology reviewer was expressed by means of a Cohen's kappa coefficient (κ). In case of discrepancy between the local pathologist and the central pathology reviewer, the TRG determination of the former was used for further analysis.

Figure 2. (A) Representative H&E images of TRG 1 (uppermost) with inflammatory infiltrate (arrows), TRG 2 (middle) and TRG 3 (lowermost) with muscle-invasive bladder cancer cells, within the original tumor bed. The dashed line delimits cancer cells. The respective zoomed images from the insets (left panel) are shown on the right. Scale bar represents 100 µm. (B) Schematic description of the combination of TRG and TNM stage, showing how TRG stratifies partial- and non-responders based on histopathological response. Abbreviations: H&E: hematoxylin and eosin; TRG: tumor regression grade

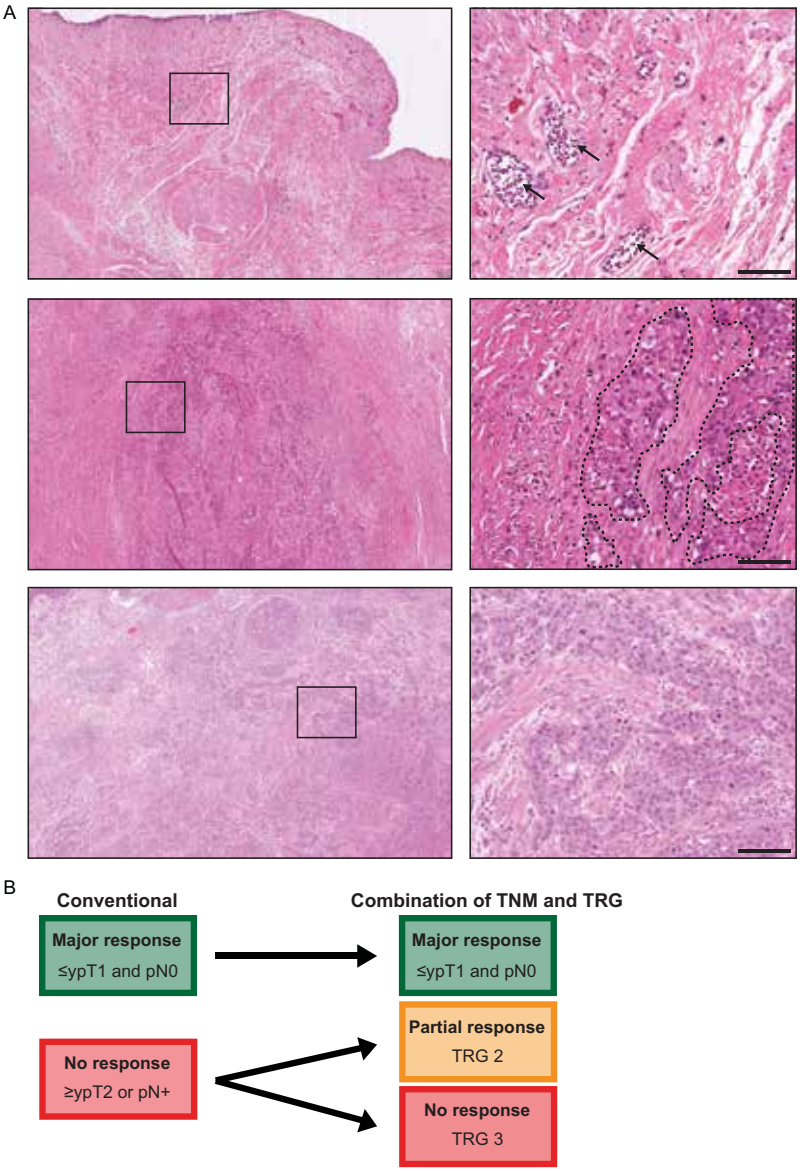
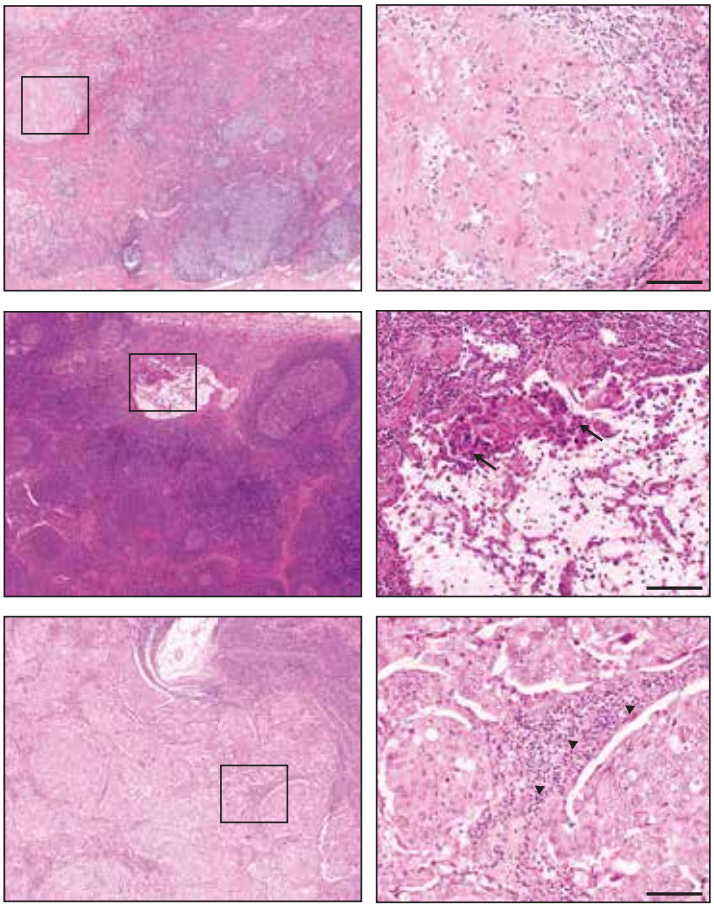
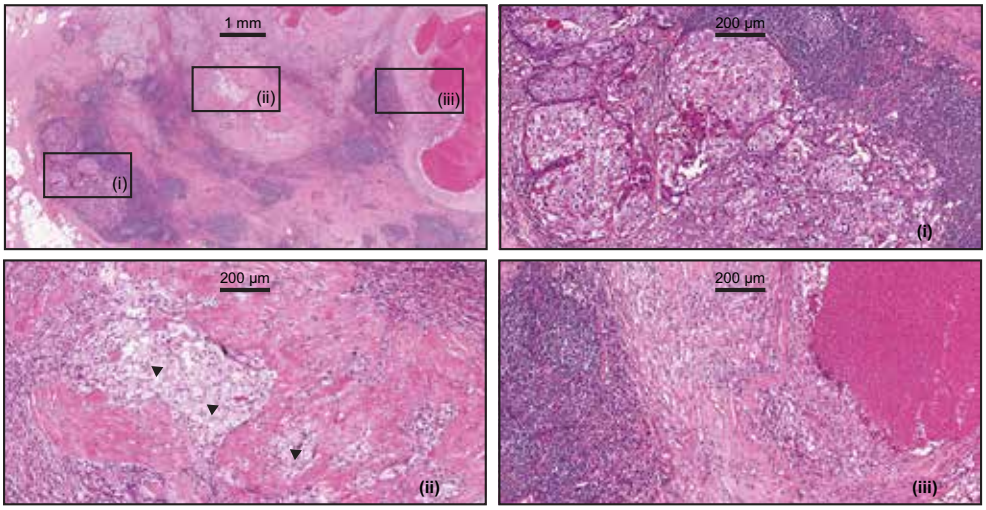


Figure 3. Representative H&E images of lymph node TRG 1 (uppermost) with fibrotic tumor bed and remaining lymph node. Lymph node TRG 2 (middle) with necrosis and a small island of residual cancer cells (arrows). Lymph node TRG 3 (lowermost) with cancer cells displacing the almost entire lymph node and arrowheads show the remaining lymph node. The respective zoomed images from the insets (left panel) are shown on the right. Scale bar represents 100 µm. Abbreviations: H&E: hematoxylin and eosin; TRG: tumor regression grade



The association between pathologic response and overall survival was assessed using Cox proportional hazard models. To compare response according to conventional pathologic stage and according to staging including TRG, two models were created. Model 1 included age, sex, surgical margin status and conventional pathologic response as covariates, whereas Model 2 included a combination of TNM stage and TRG. Model fit was compared using the likelihood ratio test and the Akaike information criterion (AIC). The AIC adjusts the -2 log likelihood statistic for the number of parameters in the model and number of observations used. A smaller AIC indicates a more desirable model for predicting outcome.

Figure 4. Representative H&E images in a partially regressed lymph node metastasis with a scanty piece of viable cancer cells, TRG 2. The respective zoomed images (i, ii, iii) of the insets from the original tumor bed (top left, low power view) are shown. (i) Remaining bladder cancer cells in the displaced lymph node structure. Higher magnification shows a dense fibrosis and a nodular accumulation of foamy macrophages (arrowheads) (ii) and nodular zone of necrosis, surrounded by granulation tissue and remaining lymph node (iii). Abbreviations: H&E: hematoxylin and eosin



Sample size calculation

The minimum size of the study cohort was determined by a power analysis based on observed outcomes in the previous study on TRG in muscle-invasive bladder cancer[11]. The anticipated event rate was 35%. Assuming a cox-regression coefficient of 1.8 and a standard deviation of 0.4, approximately 44 non-responders were needed to achieve 80% power at a 0.05 significance level. In addition, approximately 26 partial responders were needed (20% partial responders in previous datasets). With use of these variables, a total of at least 130 patients was required.

Results

Patient and tumor characteristics

Radical cystectomy specimens of 389 patients were evaluated. Clinicopathological characteristics stratified by TRG are shown in Table 1. Lower TRG was associated with lower ypT categories ($p<0.001$) and with absence of LN metastases ($p<0.001$). There was also a significant association between variant histology (i.e. urothelial carcinoma with either squamous differentiation (n=34) or glandular differentiation (n=4)) and higher TRG, with more patients having variant histology in the TRG 3 group ($p=0.002$).

Table 1. Patient and tumor characteristics by TRG

		Total	TRG 1	TRG 2	TRG 3	
		n (%)	n (%)	n (%)	n (%)	*p*
Total number of patients		389 (100)	132 (34)	107 (28)	150 (39)	-
Median age, years (IQR)		63 (55-69)	63 (55-70)	63 (55-68)	63 (55-68)	0.8
Sex	**Male**	282 (72.5)	109 (71.2)	69 (80.2)	104 (69.3)	0.2
	Female	107 (27.5)	44 (28.8)	17 (19.8)	46 (30.7)	
cT stage	**cT2**	196 (50.4)	93 (60.8)	38 (44.2)	65 (43.3)	0.2
	cT3	145 (37.3)	44 (28.8)	36 (41.9)	65 (43.3)	
	cT4a	48 (12.3)	16 (10.5)	12 (14.0)	20 (13.3)	
cN stage	**cN0**	309 (79.4)	127 (83.0)	59 (68.6)	123 (82.0)	0.2
	cN1-3	80 (20.6)	26 (17.0)	27 (31.4)	27 (18.0)	
NAC regimen	**GC**	298 (76.6)	115 (75.2)	62 (72.1)	121 (80.7)	0.4
	MVAC	91 (23.4)	38 (24.8)	24 (27.9)	29 (19.3)	
NAC cycles	**3**	116 (29.8)	44 (28.8)	28 (32.6)	44 (29.3)	0.8
	4	273 (70.2)	109 (71.2)	58 (67.4)	106 (70.7)	
ypT stage	**ypT0**	139 (35.7)	132 (100)	7 (6.5)	0 (-)	<0.001
	ypTa/is/1	55 (14.1)	0 (-)	53 (49.5)	2 (1.3)	
	ypT2	98 (25.2)	0 (-)	31 (30.0)	67 (44.7)	
	ypT3	72 (18.5)	0 (-)	12 (11.2)	60 (40.0)	
	ypT4	25 (6.4)	0 (-)	4 (3.7)	21 (14.0)	
ypN stage	**ypN0**	305 (78.4)	153 (100)	61 (70.9)	91 (60.7)	<0.001
	ypN1-3	84 (21.6)	0	25 (29.1)	59 (39.3)	
Histology	**Urothelial**	351 (90.2)	147 (96.1)	80 (93.0)	124 (82.7)	0.002
	Squamous diff.	34 (8.7)	6 (3.9)	5 (5.8)	23 (15.2)	
	Glandular diff.	4 (1.0)	0 (-)	1 (1.2)	3 (2.0)	
LVI	**Yes**	66 (23.4)	122 (99.2)	50 (79.4)	44 (45.8)	<0.001
	No	216 (76.6)	1 (0.8)	13 (20.6)	52 (54.2)	
	Missing	107				
Surgical margin	**Positive**	19 (4.9)	0 (-)	2 (2.3)	17 (22.3)	<0.001
	Negative	370 (95.1)	153 (100)	84 (97.7)	133 (88.7)	

Abbreviations: diff.: differentiation, GC: Gemcitabine and Cisplatin, IQR: Interquartile range, LVI: lymphovascular invasion, MVAC: Methotrexate, Vinblastine, Doxorubicin and Cisplatin, NAC: neoadjuvant chemotherapy, No.: number; TRG: tumor regression grade

Pathologic response

At time of radical cystectomy, 139/389 (36%) patients had no residual primary tumor (ypT0) and 305/389 (78%) patients had no LN metastases (ypN0). Seven patients had no residual primary tumor, but were lymph node positive (ypT0N+). According to the conventional TNM response definition, 181/389 patients (47%) had a major response, whereas 208/389 (53%) were non-major responders. TRG was successfully determined in all cases. For every patient, the corresponding TRG in the primary tumors and in the LNs is given in Table 2. When combining TRG with the TNM stages 181 (47%), 59 (15%) and 149 (38%) patients were major, partial and non-responders, respectively.

Central pathology review

Local pathologists and the central pathology reviewer agreed on TRG in 88% (46/52) of cases. The overall kappa between the central pathology reviewer and local pathologists was 0.82.

Survival

During a median follow-up of 2.2 years (95% confidence interval (CI) 2.0-2.4), 112/389 patients had cancer recurrence and 98/389 patients died. In the TRG 1 group, median overall survival was not reached whereas in the TRG 2 and TRG 3 groups, median overall survival was 3.3 (95% CI 2.4-4.1) and 2.6 years (95% CI 1.6-3.6), respectively (p=0.026). As expected, higher ypT and higher ypN stage were significantly associated with worse overall survival in Kaplan-Meier analysis (p<0.001, Figure 5A-B). Positive surgical margin status was also significantly associated with worse overall survival (p<0.001, Figure 5C), whereas variant histology was not (p=0.06, Figure 5D).

Kaplan-Meier analysis showed a significant difference in overall survival between major responders and non-major responders based on TNM staging alone (p<0.001, Figure 6A). Integrating TRG in the conventional TNM staging showed further stratification of survival curves, discriminating three groups of patients with significantly different overall survival (p<0.001, Figure 6B). Subgroup analysis of TRG 2 vs TRG 3 within ypT2 or ypT3/4 stages showed no significant difference in overall survival (ypT2: TRG 2 (n=31) vs TRG 3 (n=67) p=0.3; ypT3/4: TRG 2 (n=16) vs TRG 3 (n=81) p=0.2, Figure 7A-B). Subgroup analysis of TRG 2 vs TRG 3 within patients with LN metastases (n=84) showed a significant difference in overall survival (p=0.03, Figure 7C)

Table 2. TRGs of primary tumours and lymph node metastases

		Primary tumour	
LN metastases	**TRG 1**	**TRG 2**	**TRG 3**
TRG 1	132	75	91
TRG 2	7	25	0
TRG 3	0	0	59

Table 3. Univariable Cox regression analyses of the association between clinicopathologic factors and overall survival

		HR	95% CI	p-value
Age	**continuous**	0.99	0.97-1.01	0.5
Sex	**Male**	1		
	Female	1.36	0.90-2.06	0.14
NAC regimen	**GC**	1		
	MVAC	1.17	0.76-181	0.5
No. NAC cycles	**3**	1		
	4	1.09	0.71-1.70	0.7
ypN stage	**ypN0**	1		
	ypN1-3	3.34	2.21-5.03	<0.001
ypT stage	**pT0**	1		
	pT1/a/is	2.75	1.16-6.53	0.022
	pT2	5.30	2.72-10.34	<0.001
	pT3/T4	8.68	4.58-16.43	<0.001
Histology	**Urothelial carcinoma**	1		
	Variant	1.66	0.97-2.84	0.063
Surgical margin	**Negative**	1		
	Positive	3.36	1.74-6.50	<0.001
TRG	**1**	1		
	2	5.81	2.77-12.18	<0.001
	3	9.82	5.03-19.18	<0.001
Conventional response	**Major response**	1		
	Non-major response	5.320	3.18-8.90	<0.001
Response TNM with TRG	**Major response**	1		
	Partial response	3.419	1.74-6.73	<0.001
	Non response	6.169	3.65-10.44	<0.001

Abbreviations: CI: confidence interval, GC: gemcitabine and cisplatin, HR: hazard ratio, MVAC: methotrexate, vinblastine, doxorubicin and cisplatin, NAC: neoadjuvant chemotherapy, No.: number, TRG: tumor regression grade, TNM; Tumor Node Metastasis

Table 4. Multivariable Cox regression analyses of overall survival. Model 1 represents conventional response classification and Model 2 represents TRG integrated with TNM staging

	Model 1			Model 2		
Characteristics	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age (continuous)	1.01	0.98-1.02	0.98	0.99	0.98-1.02	0.92
Female sex	1.33	0.88-2.02	0.18	1.27	0.83-1.93	0.27
Positive surgical margin	1.66	0.89-3.10	0.11	1.53	0.82-2.87	0.19
Conventional response:						
Major responder	1					
Non-major responder	5.03	2.98-8.49	<0.001			
Response TNM with TRG:						
Major responder				1		
Partial responder				3.44	1.74-6.81	<0.001
Non responder				5.75	3.36-9.84	<0.001

Abbreviations: CI: confidence interval, HR: hazard ratio, TRG: tumor regression grade, TNM: Tumor Node Metastasis

In univariable analysis, a higher TRG significantly correlated with worse survival (p<0.001, Table 3). Other factors associated with worse overall survival were higher ypT and ypN stages and positive surgical margins (all p<0.001). In multivariable analysis, combination of TRG and TNM showed a significant association with survival (p<0.001), discriminating three groups of patients with significantly different overall survival (Table 4).

Comparison of prognostic models

To assess the prognostic value of the combination of TRG and TNM in addition to the value of conventional TNM staging, the two Cox proportional hazard models (Table 4) were compared using a likelihood ratio test. Model 2 (including the combination of TRG and TNM) had a lower test statistic than Model 1 (including conventional response classification) (489.54 vs 491.64, p=0.041). Therefore, the model including TRG and TNM proved to be a more desirable model for prognostication. Also, AIC value was smaller for the combination of TRG and TNM (AIC: 967.58) compared to TNM staging alone (AIC: 973.14), indicating the former has a better prognostic stratification. Sensitivity analysis excluding patients from the center that did not participate in CPR did not impact the study findings (data not shown).

Figure 5. Kaplan-Meier plots for overall survival stratified according to (A) ypT stage, (B) ypN stage, (C) Surgical margin status and (D) Histology type.

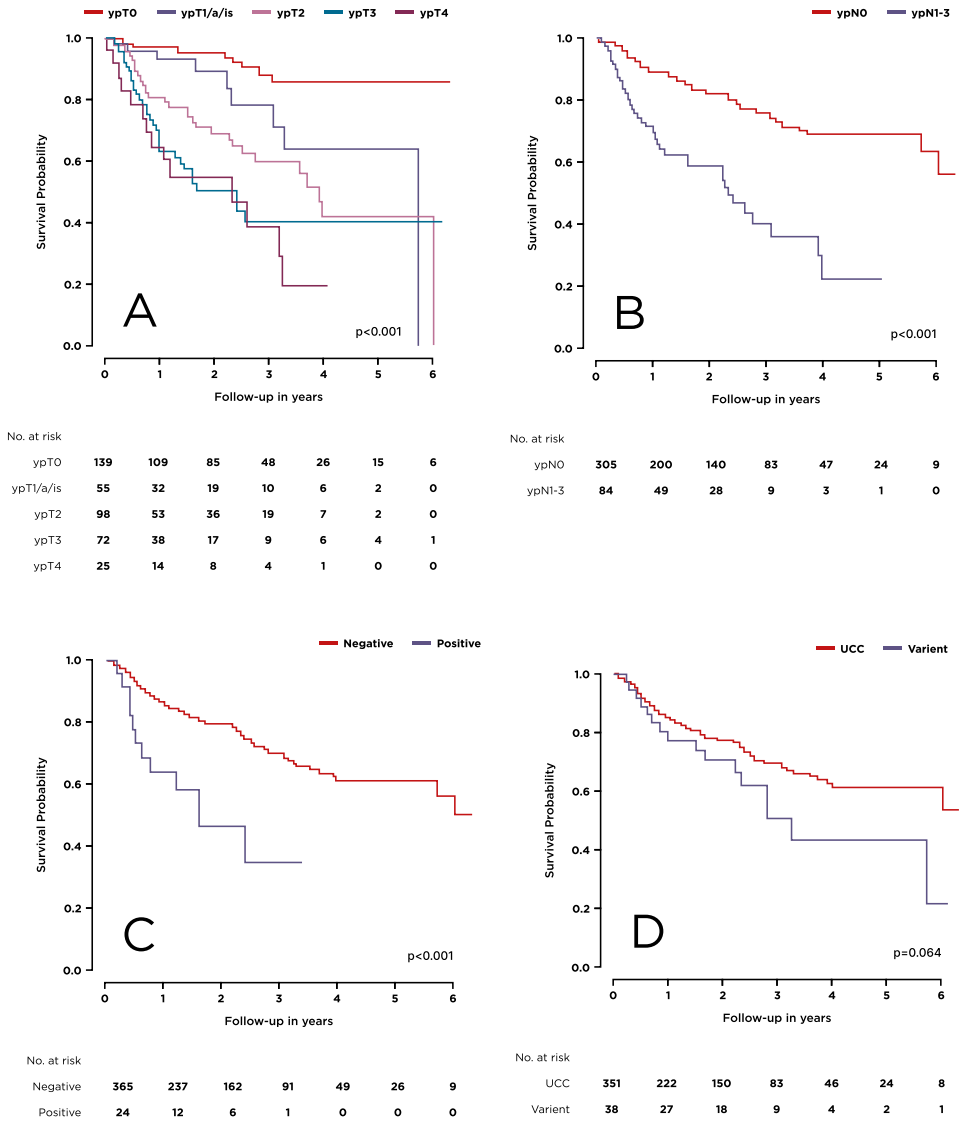
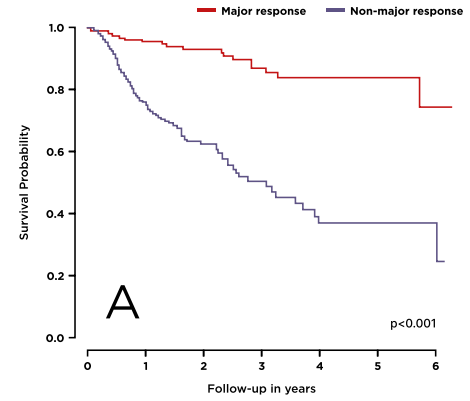
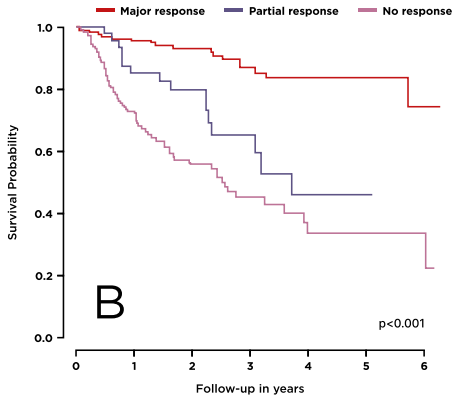


Figure 6. Kaplan-Meier plots for overall survival stratified according to (A) conventional TNM response classification (major responder and non-major responder) and (B) TRG integrated with TNM staging. Abbreviations: TRG: tumor regression grade

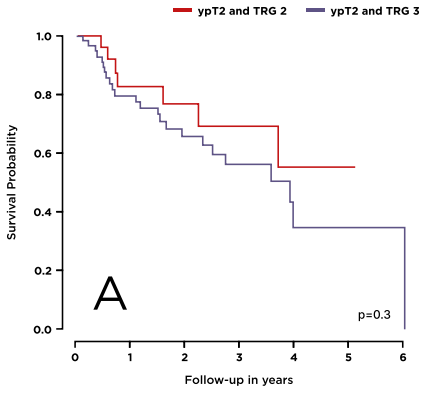


No. at risk							
Major	181	131	98	58	34	19	6
Non-major	208	118	70	34	7	3	3

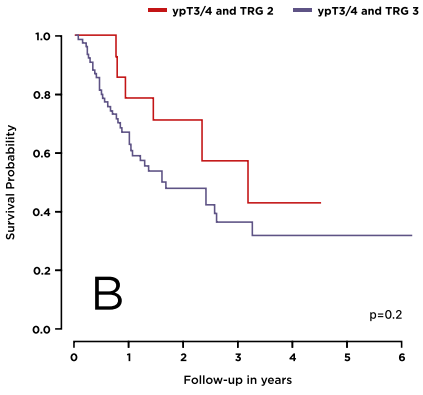


No. at risk							
Major	181	131	98	58	34	19	6
Partial	59	37	26	12	6	2	0
No	149	81	44	22	10	5	3

Figure 7. Kaplan-Meier plots for overall survival stratified according to TRG within (A) ypT2 (B) ypT3/4 and (C) ypN1-3. Abbreviations: TRG: tumor regression grade

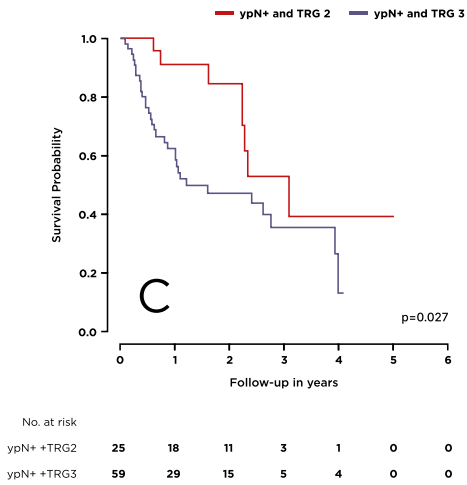


No. at risk							
ypT2+TRG2	31	16	13	6	4	2	0
ypT2+TRG3	67	38	24	14	4	1	1



No. at risk							
ypT3/4+TRG2	16	11	6	4	2	0	0
ypT3/4+TRG3	81	42	19	7	6	4	2

Figure 7. ***(continued)***



Discussion

In this retrospective multicenter analysis, we determined histopathologic TRGs in radical cystectomy specimens of muscle-invasive bladder cancer patients after neoadjuvant chemotherapy. TRGs were confirmed by independent pathological review with low interobserver variability. We could not only validate the prognostic significance of TRG but also provided an easily applicable score, including TNM and TRG, that serves as a prognostic post-treatment classification system. Determination of this score in radical cystectomy specimens after neoadjuvant chemotherapy is simple, reproducible and provides additional prognostic information. If this can be confirmed in a prospective study, TRG may be routinely added to pathology reports of radical cystectomy specimens after neoadjuvant chemotherapy.

In contrast to other cancers[8–10], classification of response to neoadjuvant chemotherapy in muscle-invasive bladder cancer is only based on TNM staging at radical cystectomy[12]. However, since TNM staging is developed in untreated muscle-invasive bladder cancer it does not consider specific alterations caused by neoadjuvant chemotherapy and may therefore conceal prognostic information in post-treatment specimens. In addition, variability in pathologic TNM staging is a recognized problem in non-muscle-invasive bladder carcinoma[13] and some studies suggest that interobserver variability may also affect TNM staging in muscle-invasive bladder cancer[14,15]. These issues substantiate a need to improve post-treatment stratification.

Fleischmann et al. were the first to show that histomorphological classification of post-chemotherapy cystectomy specimens into TRGs harbors prognostic information[11]. However, this was a single center cohort that mainly consisted of patients with advanced muscle-invasive bladder cancer (cT3/4 and/or cN+). In the current study, we performed independent

validation of the findings of Fleischmann et al. in an evenly balanced cohort, including cT2N0 patients. Thus, the present cohort represents a practice of treating "all-comers" with neoadjuvant chemotherapy and confirms that TRG also harbors prognostic information in a clinically lower-staged muscle-invasive bladder cancer cohort.

Our findings may be in contrast to another study investigating the prognostic value of TRG in muscle-invasive bladder cancer[16]. This multicenter study by Brimo et al. also identified TRGs as a prognostic parameter in univariable analyses but this was not confirmed in multivariable analysis. However, there are some important differences between the study of Brimo et al. and our study. First, our sample size met the requirement of the power calculation, while the study of Brimo et al. may have been underpowered (n=165). Moreover, we excluded aggressive histomorphological variants, in line with the large randomized controlled trials on neoadjuvant chemotherapy in muscle-invasive bladder cancer[17,18], whereas Brimo et al. did not[16]. Taken together, our study provided a multicenter validation of the prognostic significance of TRG in muscle-invasive bladder cancer after neoadjuvant chemotherapy.

Several reasons may explain why TRGs are commonly used in gastrointestinal malignancies and not in muscle-invasive bladder carcinoma. Histomorphologically, the layers of the gastrointestinal wall are clearly defined, in contrast to the layers of the bladder wall. This may contribute to less accurate clinical staging in bladder carcinoma and a more challenging estimation of tumor shrinkage due to chemotherapy. Moreover, while diagnostic biopsy of e.g. esophageal carcinoma has limited effect on tumor size and architecture, transurethral resection of the bladder tumor (TUR) affects not only tumor size but also histopathological findings. Two studies addressed the potential confounding effect of TUR in relation to neoadjuvant chemotherapy. Wang et al. found that both neoadjuvant chemotherapy and TUR cause fibroblastic reaction and necrosis, while hyalinization of the bladder wall is specifically seen after neoadjuvant chemotherapy[19]. Brant et al. evaluated histologic changes after neoadjuvant chemotherapy in 139 patients with cT2 bladder carcinoma and estimated that 38% of pathological response could be attributed to TUR alone[20]. They did not include higher staged patients and both did not assess clinical outcomes. Also, the residual tumor size in relation to the estimated former tumor bed was not considered although this is an important feature of TRG determination. Even if TUR causes regressive changes, these will be limited to the bladder wall and will neither affect the perivesical fat, nor impact the size of the former tumor bed. Finally, the prognostic significance of TRG in the present more evenly balanced cohort including high stage muscle-invasive bladder cancer patients, cannot be negated and suggests clinical applicability.

TRG may serve as a useful tool in clinical practice and research for several reasons. First, integrating TRG with TNM staging resulted in more accurate survival prediction and may be helpful in decisions regarding timing of follow-up[21]. Second, TRG could be used to tailor therapeutic adjuvant strategies in patients with residual tumor after neoadjuvant chemotherapy. TRG provides the opportunity to gauge antitumor efficacy of agents and persistence of viable tumor after therapy might indicate the need to alter or explore novel treatments in the adjuvant setting. Third, TRG could be used as comparative parameter for

biomarker studies. A standard approach for grading pathologic response to neoadjuvant chemotherapy is important for the assessment of predictive biomarkers and will facilitate comparison of results across studies.

Our study is limited by its retrospective design, possibly resulting in differences in grossing protocols across institutions. Nevertheless, we performed CPR and found high interobserver agreement. One center could not participate in CPR but sensitivity analysis restricted to centers who did participate in CPR did not alter the main study findings. Importantly, we enrolled a homogenous cohort of neoadjuvant chemotherapy patients, including only common variant histologies in line with current clinical trials and all patients received at least three cycles of cisplatin-based neoadjuvant chemotherapy.

In conclusion, this study validates TRG as an independent predictor of overall survival in a multicenter series of patients with muscle-invasive bladder cancer who received cisplatin-based chemotherapy prior to radical cystectomy. TRG is a simple and highly reproducible measurement of response to neoadjuvant chemotherapy. Importantly, integrating TRG with TNM staging resulted in significantly better prognostic stratification than conventional TNM staging alone. Therefore, we suggest that TRG may routinely be included in post-chemotherapy pathological reports of radical cystectomy specimens. In addition to predicting patient outcome, combining TRG and TNM may be used to tailor postoperative treatment and may serve as a comparative parameter for predictive biomarkers.

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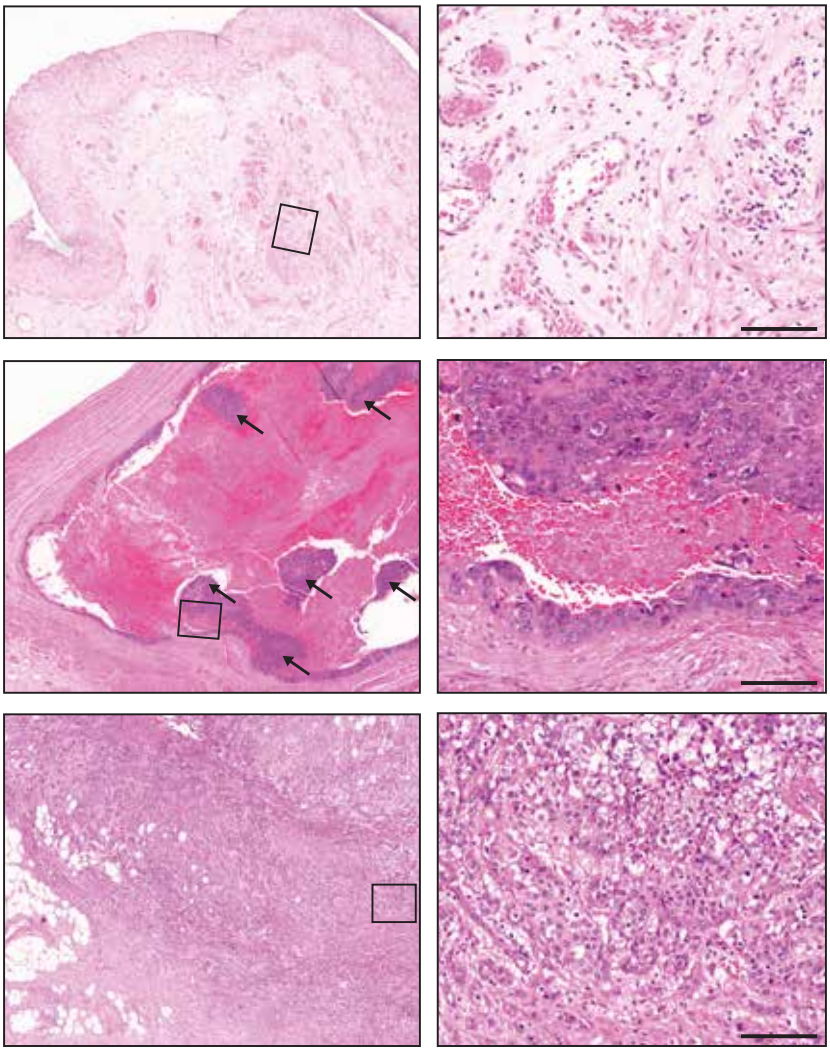
Supplementary material

Supplemental Figure 1. Representative H&E images of TRG 1 (uppermost) with highly vascularized tumor bed showing elastosis and immune infiltration. TRG 2 (middle) with abundant necrosis and small islands of residual cancer cells (arrows). TRG 3 (lowermost) with no apparent tumor regressive changes. The respective zoomed images from the insets (left panel) are shown on the right. Scale bar represents 100 µm. Abbreviations: H&E: hematoxylin and eosin; TRG: tumor regression grade



Part II

FDG-PET/CT for staging urothelial carcinoma


5

Staging 18F-fluorodeoxy-glucose-positron emission tomography/computed tomography changes treatment recommendation in invasive bladder cancer

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Eur Urol Oncol. 2021 Feb 11:S2588-9311(21)00029-8.

Abstract

Given the high risk of systemic relapse following initial therapy for muscle-invasive bladder cancer (MIBC), improved pre-treatment staging is needed. We evaluated the incremental value of FDG-PET/CT after standard conventional staging, in the largest cohort of MIBC patients to date. This is a retrospective analysis of 711 consecutive patients with invasive urothelial BC who underwent staging contrast-enhanced CT (CECT) (chest and abdomen) and FDG-PET/CT in a tertiary referral centre between 2011 and 2020. We recorded the clinical stage before and after FDG-PET/CT and treatment recommendation based on the stage before and after FDG-PET/CT.

Clinical stage changed after FDG-PET/CT in 184/711 (26%) patients. Consequently, the recommended treatment strategy based on imaging changed in 127/711 (18%). In 65/711 (9.1%) patients, potential curative treatment changed to palliative treatment because of the detection of distant metastases by FDG-PET/CT. Fifty (7.0%) patients were selected for neoadjuvant/induction chemotherapy based on FDG-PET/CT. Moreover, FDG-PET/CT detected lesions suspicious for second primary tumors in 15%; a second primary malignancy was confirmed in 28/711 (3.9%), leading to treatment change in 10 (1.4%) patients. Contrarily 57/711 (8.1%) had false positive secondary findings.

In conclusion, FDG-PET/CT provides important incremental staging information, which potentially influences clinical management in 18% of MIBC patients, but leads to false positive results as well.

Patient summary: In this report, we investigated the impact of FDG-PET/CT scanning on treatment of bladder cancer patients. We found that FDG-PET/CT potentially influences treatment of almost one fifth of patients. We therefore suggest to perform FDG-PET/CT as part of bladder cancer staging.

Brief Correspondence

Contrast-enhanced computed tomography (CECT) of the abdomen/pelvis and chest is recommended to clinically stage patients with muscle-invasive bladder cancer (MIBC)[1]. Emerging evidence suggests that 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT also has potential use for staging MIBC, because of improved accuracy for lymph node assessment and detection of distant metastases[2]. Moreover, it has been suggested that FDG-PET/CT impacts MIBC patient management[2–5]. In this study, we evaluated the impact of FDG-PET/CT on clinical stage and treatment recommendations in the largest cohort of invasive bladder cancer (BC) patients to date.

We retrospectively identified all consecutive patients (n=957) who were referred to our outpatient BC clinic between January 2011 and January 2020. Patients were included if they (1) had histologically proven MIBC or high-grade T1 urothelial cancer with high-risk of progression or BCG-failure for which radical cystectomy was considered; (2) underwent FDG-PET/CT as well as CECT of the abdomen/pelvis and chest prior to FDG-PET/CT. Patients with non-urothelial histology (n=52), incomplete CECT staging (n=136; no chest CT in 88, non-contrast-enhanced CT in 48) were excluded, as well as patients who received any form of treatment prior to referral (n=58), leaving 711 patients (median age 66 years; 27% female; Supplementary Table 1) eligible for analysis. CECT imaging results were reported by radiologists as part of standard clinical practice. Staging information was extracted from the radiology reports. After CECT, patients underwent FDG-PET/CT scanning. FDG-PET/CT images were interpreted by experienced nuclear medicine physicians, who were aware of previous staging information. Detailed methods are described in the Supplementary material.

The median interval between CECT and FDG-PET/CT was 16 days (IQR 0-32 days; maximum 40 days). Clinical stage changed after FDG-PET/CT in 184/771 (26%) patients (Table 1). Upstaging was more frequent than downstaging (25.5% vs 0.4%) and occurred most frequently in patients with cM1a disease (44% upstaging to cM1b).

For all patients, CECT and FDG-PET/CT findings were discussed in multidisciplinary rounds. We retrospectively checked the clinical records of the patients with the corresponding reports of these multidisciplinary discussions. Treatment recommendations, based on clinical staging, before FDG-PET/CT and after FDG-PET/CT, were determined for each patient. For the purpose of this study, we divided the patients into three categories of treatment recommendations: (1) local treatment with curative intent (cystectomy, chemoradiation, brachytherapy) in case of organ-confined disease; (2) neoadjuvant/induction chemotherapy (NAIC) followed by local curative treatment in case of locally advanced disease and/or pelvic nodal metastases or nodal metastases in the retroperitoneum; or (3) palliative treatment in case of distant metastases.

Table 1. Comparison of tumor stage by CECT and tumor stage by FDG-PET/CT of the 711 eligible patients

		FDG-PET/CT						Total	Down-staged	Up-staged
		cT1 N0M0	cT2 N0M0	cT3-4 N0M0	cTx N1-3M0	cTxNx M1a	cTxNx M1b		n (%)	n (%)
CECT	**cT1N0M0**	81	0	0	9	0	2	92	0 (-)	11 (12)
	cT2N0M0	0	189	0	43	2	18	252	0 (-)	63 (25)
	cT3-4N0M0	0	0	178	50	11	16	255	0 (-)	77 (30)
	cTxN1-3M0	0	0	0	49	12	7	68	0 (-)	19 (28)
	cTxNxM1a	0	0	0	1	13	11	25	1 (4.0)	11 (44)
	cTxNxM1b	0	0	0	2	0	17	19	2 (11)	0 (-)
								711	3 (0.4)	181 (26)

Legend: Upstaging was more frequent than downstaging (26% vs 0.4%) and occurred most frequently in patients with cM1a disease (44% upstaging to cM1b). Three patients were down-staged after FDG-PET/CT imaging: one patient had enlarged LNs above the aortic bifurcation (cM1a) on CECT that were not suspicious on FDG-PET/CT and 2 patients had a lung nodule on CECT that was not suspicious for pulmonary malignancy or metastasis on FDG-PET/CT. Upstaging was present in 126/516 (24%) patients with an interval between CECT and FDG-PET/CT of <30 days versus 55/195 (28%) patients with an interval of >30 days (p=0.3).
Abbreviations: CECT contrast-enhanced computed tomography, FDG-PET/CT 18F-fluorodeoxyglucose-positron emission tomography with computed tomography

Treatment recommendations based on CECT versus treatment recommendations based on FDG-PET/CT are shown in Table 2. Upstaging based on FDG-PET/CT led to a change in treatment recommendation in 117/711 patients (16%) (Supplementary Figure 1). In 50/711 (7.0%) patients, additional findings on FDG-PET/CT led to a change of treatment recommendation from upfront local therapy to NAIC before local treatment. In 65/711 (9.1%) patients, the treatment recommendation changed from potentially curative to palliative, because of distant metastases on FDG-PET/CT.

Details on changes in treatment recommendations can be found in the Supplementary material. FDG-PET/CT detected lesions suspicious for second primary tumors in 110/711 (15%) patients (Supplementary Table 2). A second primary malignancy was confirmed in 28/711 (3.9%) patients. This influenced treatment of BC in 10/711 (1.4%) patients. In 57/110 (52%) patients histopathology results were false positive. In 25/110 patients, histopathology of the suspicious lesion was not obtained because this would not lead to a treatment change (e.g. because of a palliative strategy for BC). Details on second primary malignancies can be found in the Supplementary material and in Supplementary Table 2. Altogether, FDG-PET/CT scans led to a change in treatment recommendation in 127 of 711 patients (18%).

Table 2. Comparison of treatment recommendation based on CECT and FDG-PET/CT imaging.

		FDG-PET/CT			Total	Treatment change
		Local treatment	NAIC + Local treatment	Palliative treatment		n (%)
CECT	Local treatment	274	50	20	344	70 (20)
	NAIC+Local treatment	0	297	45	342	45 (13)
	Palliative treatment	0	2	23	25	2 (8.0)
					711	117 (16)

Legend: In 50/711 (7.0%) patients, additional findings on FDG-PET/CT led to a change in treatment recommendation from local therapy to NAIC. In another 65/711 (9.1%) patients, the preferred treatment strategy changed from potentially curative to palliative because FDG-PET/CT showed distant metastases. In two patients, curative treatment instead of palliative treatment was considered after FDG-PET/CT because the lesions suspect for distant metastases on CT were not suspect on FDG-PET/CT. Abbreviations: NAIC neoadjuvant or induction chemotherapy; FDG-PET/CT 18F-fluorodeoxyglucose-positron emission tomography with computed tomography.

A unique feature of our study is the highly standardized setting; we included all patients presenting at our BC outpatient clinic in the past decade. We used a standardized staging scheme, including CECT of the chest and the abdomen/pelvis, which is recommended by the EAU guideline in all patients[1].

Remarkably, FDG-PET/CT showed incidental findings, suspicious for second malignant lesions in 15% of patients. In 26% of these cases, second primary tumors were confirmed, while results were false positive in 54%. The majority of false positive lesions were tubulovillous adenomas in the colon. However, tubulovillous adenomas >2 cm have a 46% chance of containing cancer[6]. The question remains whether this percentage justifies colonoscopy in all patients with unexpected colonic uptake[7]. Second most commonly, false positive FDG uptake in the prostate was found. It is known that incidental prostatic uptake on FDG-PET/CT has a positive predictive value of only 30% for prostate cancer[8]. In summary, if FDG-PET/CT shows suspicion for second primary tumors, the choice for further evaluation should be weighed against the BC prognosis and the risk of treatment delay.

A limitation of this study is the retrospective assessment of preferred treatment before and after FDG-PET/CT. To minimize the effect of this limitation, and to be able to compare current findings to those previously described[3], we categorized possible treatment policies into three groups based on cTNM stage. This possibly led to an underestimation of changes in treatment recommendations since we did not take comorbidity and/or performance status into account. Also, the retrospective assessment over a large time period, makes the study prone to bias caused by interobserver variability in the judgement of CECT and FDG-PET/CT and the eventual variability among the multidisciplinary board members.

Also, our institutional treatment protocols differ from guideline recommendations[1]. In particular, we consider NAIC for ≥cT3 tumors or cT2 with high risk features. This approach is based on the anticipated superior efficacy of neoadjuvant chemotherapy in cT3-4a tumors compared to cT2N0M0 BC[9]. This (unconventional) strategy has influenced our data: If NAIC had been considered for all ≥cT2 tumors, some of the patients would not have been reclassified to a different treatment strategy. However, if patients with non-regional lymph node metastases (cM1a) would be considered beyond cure, a larger proportion of patients would have shifted to palliative care.

In conclusion, FDG-PET/CT has a significant impact on treatment in almost one fifth of patients with invasive BC, particularly in patients with the highest risk of metastases. On the other hand, FGD-PET/CT scanning leads to false positive results as well. Whether the information provided by FDG-PET/CT, and any subsequent treatment change, will be translated into prolonged survival, remains to be investigated. This potential benefit should outweigh the potential drawbacks of additional imaging, such as delay of treatment, unneeded (invasive) procedures and additional costs due to false positive results.

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Supplementary Material

Supplementary Materials and Methods

This study was approved by the institutional review board of the Netherlands Cancer Institute (IRBd18137).

Staging

Patients were systematically staged by physical examination, cystoscopy, laboratory studies and CECT of chest and abdomen/pelvis. Imaging results were reported by radiologists as part of standard clinical practice. Staging information was extracted from the radiology reports, and was determined according to the TNM-classification (8th edition, 2017)[10].

PET Protocol

The FDG-PET/CT procedure was as follows: Patients fasted for ≥6 hours and received oral prehydration before intravenous injection of 190-240 MBq FDG. One hour after injection, images were acquired with the patient in a supine position. PET/CT was acquired on integrated PET/CT scanners (Gemini TF or Gemini TF Big Bore, Philips, Amsterdam, the Netherlands). No contrast agents were used. First, a low-dose CT scan (dose modulated, 40mAs, 2mm slice thickness) from the groins to the skull base was performed. Afterwards, a PET scan was made (2 minutes per bed position). Images were corrected for attenuation using the CT images and reconstructed with 4mm isotropic voxels.

PET Interpretation

Preferred treatment strategies were based on the EAU guidelines and institutional consensus[1]. In short, at our hospital, NAIC is considered in patients with locally advanced disease (cT3-T4a) and/or LN metastases (cN+) or in case of cT2 BC with high-risk histological features. Patients with non-regional nodal metastases in the retroperitoneum (cM1a) are also considered for NAIC if complete resection could be obtained in case of (complete) clinical response. Patients with distant metastases (cTxNxM1b), are considered for palliative treatment (radiotherapy or chemotherapy) or supportive care.

Actual Treatment

For all patients, a multidisciplinary discussion, with urologists, medical oncologists, radiation oncologists, radiologists and nuclear medicine physicians, was performed. Actual treatment was determined at this multidisciplinary tumor board meeting, based on all available investigations, including additional information from FDG-PET/CT, but also on patient age, performance status, renal function, comorbidities and the availability of clinical studies. Here, we also determined whether fine-needle aspiration (FNA) or biopsy had to be performed to confirm an additional FDG-PET/CT finding or whether the finding was considered clinically evident. All patients received counselling regarding their treatment options. We retrospectively checked the clinical records of the patients with the corresponding reports of these multidisciplinary discussions, during which the CECT and FDG-PET/CT findings were

discussed. Of note, actual treatment may have been different from the treatment suggested by the tumor board, depending on patient preference.

Statistical Analysis

Descriptive statistics were used to describe tumor stage and preferred treatment category before and after FDG-PET/CT (paired proportions for binary data). To assess the potential influence of the interval between CECT and FDG-PET/CT, we compared changes in stage of patients with an interval of ≤30 days to patients with an interval of >30 days (chi-square test). Statistical analyses were performed using IBM SPSS Statistics version 25.0 (Armonk, NY, IBM).

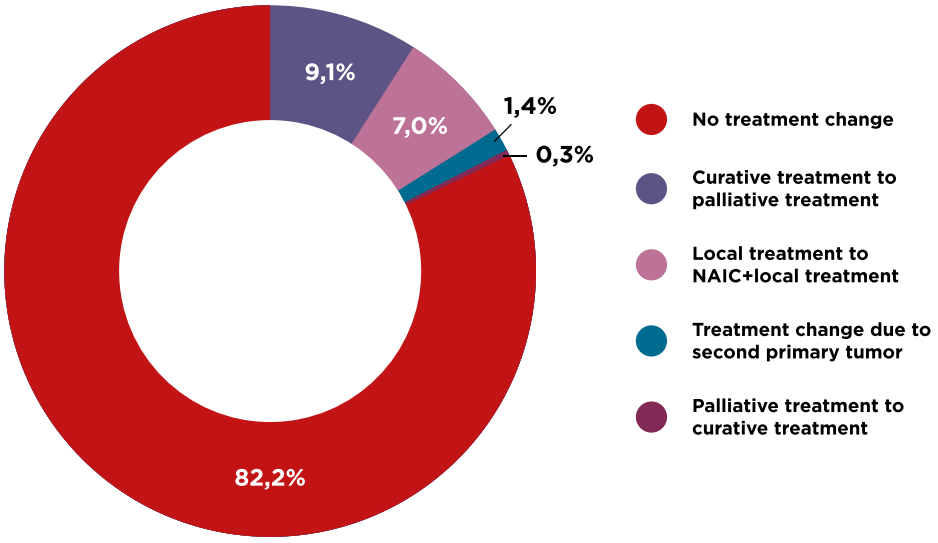
Supplementary results

Change in treatment recommendation

Preferred treatment based on CECT versus preferred treatment based on FDG-PET/CT is shown in Table 2. Upstaging based on FDG-PET/CT led to a change in treatment recommendation in 117/711 patients (16%) (Supplementary Figure 1).

In 54 patients initially planned for local treatment, NAIC was considered, because of suspicion of LN metastases on FDG-PET/CT. In 20/54 (37%) of these, FNA was considered necessary to confirm suspicious LNs. FNA was negative in 4 cases. These patients did not receive NAIC. So, in 50/711 (7.0%) patients, additional findings on FDG-PET/CT led to a change of preferred management from upfront local therapy to NAIC before local treatment.

Supplementary Figure 1. Treatment changes based on FDG-PET/CT results in the 711 eligible patients.



Abbreviations: NAIC neoadjuvant or induction chemotherapy; FDG-PET/CT 18F-fluorodeoxyglucose-positron emission tomography with computed tomography

In 66 patients, palliative treatment instead of curative treatment (i.e. local treatment or NAIC followed by local treatment) was recommended because of suspicion of distant metastatic lesions on FDG-PET/CT. In 33/66 (50%) patients, metastatic lesions were confirmed by biopsy or fine-needle aspiration (n=29) or by additional imaging (n=4). In the remaining 33/66 (50%) patients, metastatic lesions were not confirmed due to rapid progressive disease or because these lesions were considered clinically evident metastatic disease by the complete tumor board. In 1 patient with suspect lung lesions, inaccessible for fine-needle aspiration or biopsy, repeat imaging after 2 months showed unchanged lesions. This case was considered false positive and the patient received curative treatment. So, in 65/711 (9.1%) patients, the preferred treatment strategy changed from potentially curative to palliative, because of distant metastases on FDG-PET/CT.

Second primary malignancies

In addition to the metastatic BC lesions, FDG-PET/CT detected lesions suspicious for second primary tumors in 110/711 (15%) patients (Supplementary Table 2). A second primary malignancy was confirmed in 28/711 (3.9%) patients. Most common locations were the prostate, lung, colon and oesophagus. In 57/110 (52%) patients with suspicion of second primary malignancies, histopathology did not reveal malignancy. Most common false positive foci were located in the colon (n=27, representing tubulovillous adenomas of the colon requiring follow-up in 18 cases) and in the prostate (n=11). In 25/110 patients, histopathology of the suspicious lesion was not obtained because this would not lead to a treatment change (e.g. because of a palliative strategy for BC).

Actual treatment

Five patients were lost to follow-up, leaving 706 patients for analysis of actual treatment. In 635/706 (90%), the post-FDG-PET/CT treatment recommendation was followed. In 71/706 (10%), this recommendation was not followed because of poor performance status, comorbidities and/or patient preference. Actual treatment consisted of local curative treatment (RC (n=166), chemoradiation (n=54), brachytherapy (n=40), transurethral resection (n=30)), NAIC followed by RC (n=234), NAIC followed by chemoradiation (n=56) or palliation (n=126).

Supplementary Table 1. Patient characteristics

Total number of patients		711
Age in years, median (IQR)		66 (58-73)
		n (%)
Sex	**Male**	518 (73)
	Female	193 (27)
cTNM stage	**cT1N0M0**	92 (13)
	cT2N0M0	252 (36)
	cT3-4N0M0	255 (35)
	cTxN1-3M0	68 (10)
	cTxNxM1a	25 (4)
	cTxNxM1b	19 (3)

Abbreviations: CECT contrast-enhanced computed tomography

Supplementary Table 2. Locations of lesions suspicious for second primary tumors and the results of histopathologic assessment (if applicable).

Location	Results of histopathologic assessment		No histo-pathologic assessment*	Total	Influencing BC treatment
	Second primary malignancy	No malignancy			
Prostate	9**	11	4	24	1
Lung	7	5	0	12	3
Colon	5	27***	9	41	3
Oesophagus	2	1	1	4	2
Thyroid	1	4	4	9	-
Salivary gland	1	3	2	6	1
Oropharynx	1	-	-	1	-
Duodenum	1	-	-	1	-
Mesenteric LN	1	-	-	1	-
Adnex	-	1	1	2	-
Liver	-	1	1	2	-
Breast	-	1	-	1	-
Skin	-	1	-	1	-
Paraganglioma	-	1	-	1	-
Kidney	-	1	-	1	-
Pancreas	-	-	1	1	-
Adrenal gland	-	-	1	1	-
Schwannoma	-	-	1	1	-
Total	28	57	25	110	10

Legend: In 110/711 patients, FDG-PET/CT detected lesions suspicious for second primary malignancies. In 28 (25%, 3.9%), a second primary malignancy was confirmed. This influenced treatment of BC in 10/711 (1.4%) patients: Two patients with colorectal carcinoma required hemicolectomy in addition to RC; another patient with colorectal carcinoma had liver metastases and received palliative care. Two patients with lung carcinoma underwent palliative chemotherapy and another patient with lung carcinoma underwent lobectomy prior to RC. Two patients were diagnosed with oesophageal carcinoma requiring surgery prior to BC treatment. One patient with advanced prostate cancer underwent concurrent palliative radiotherapy. Finally, one patient had oropharynx carcinoma requiring radiotherapy and he received palliative radiotherapy of the bladder due to poor performance status.

** In these patients no histopathologic diagnosis was obtained because this would not lead to a management change*

*** In 7 patients, prostate cancer was confirmed in the radical cystectomy specimen, in 2 patients prostate cancer was confirmed by biopsies prior to cystectomy (these patients were opting for prostate-sparing cystectomy)*

**** 18 patients were diagnosed with tubulovillous adenomas of the colon requiring follow-up*

Abbreviations: BC bladder cancer, LN lymph nodes


6

Prospective evaluation of FDG-PET/CT for on-treatment assessment of response to neoadjuvant or induction chemotherapy in invasive bladder cancer

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Bladder Cancer 9;(2023);49–57.

Abstract

Purpose

Neoadjuvant/induction chemotherapy (NAIC) improves survival in patients with muscle-invasive bladder carcinoma (MIBC). On-treatment response assessment may aid in decisions to continue or cease NAIC. We investigated whether 18F-fluoro-2-deoxy-D-glucose-Positron Emission Tomography/Computed Tomography (FDG-PET/CT) could predict response to NAIC and compared to contrast-enhanced Computed Tomography (CECT).

Materials and Methods

Between 2014 and 2018, 83 patients with MIBC (i.e. high-risk cT2-4N0M0 or cT1-4N+M0-1a) were prospectively included. Response to NAIC was assessed after 2-3 cycles with FDG-PET/CT (Peter-Mac and EORTC criteria) and CECT (RECIST1.1 criteria). We assessed prediction of complete pathological response (pCR; ypT0N0), complete pathological down-staging (pCD; ≤ypT1N0), any down-staging from baseline (ypTN<cTN) and progression (inoperable tumor/ypN+/M+). The reference standard was histopathological assessment or clinical follow-up. Sensitivity, specificity, and accuracy were calculated.

Results

Pathological response rates were 21% for pCR, 29% for pCD, and 10% progressed. All patients underwent FDG-PET/CT and 61 patients also underwent CECT (73%). Accuracy of FDG-PET/CT for prediction of pCR, pCD, and progression were 73%, 48%, and 73%, respectively. Accuracy of CECT for prediction of pCR, pCD, and progression were 78%, 65%, and 67%, respectively. Specificity of CECT was significantly higher than FDG-PET/CT for prediction of pCD and any down-staging (p=0.007 and p=0.022). In all other analyses, no significant differences between FDG-PET/CT and CECT were found.

Conclusions

Routine FDG-PET/CT has insufficient predictive power to aid in response assessment compared to CECT.

Introduction

Radical cystectomy (RC) with pelvic lymph node dissection (PLND) is the standard treatment for muscle-invasive bladder carcinoma (MIBC)[1]. Complementary treatment with neoadjuvant cisplatin-based combination chemotherapy (CBCC) is recommended for non-metastatic MIBC[1], while patients with regional lymph node (LN) metastases may be treated with induction chemotherapy[2,3]. Neoadjuvant chemotherapy improves 5-year survival by 5-8%[4-6]. Likewise, response to induction chemotherapy in is associated with significant survival benefit[3,7].

Survival is highest in patients with complete pathological response (pCR; i.e. ypT0N0)[8] to CBCC, and seems comparable to survival of patients with complete pathological down-staging (pCD; i.e. ≤ypT1N0)[9] to CBCC. Clinical trials reported pCR rates of 25-42%[4-6,10], suggesting overtreatment in many patients[11]. Patients with chemotherapy-insensitive tumors are exposed to risk of chemotoxicity and RC is delayed. This overtreatment may be reduced by on-treatment assessment of response to NAIC and selection of responders for continued treatment with NAIC. On the other hand, non-responders could stop NAIC and proceed to RC[12].

While imaging with 18F-fluoro-2-deoxy-D-glucose Positron Emission Tomography/Computed Tomography (FDG-PET/CT) has been extensively studied for the initial staging of MIBC[13-16], data on FDG-PET/CT for assessment of response to NAIC is very limited[17-21]. The aim of this prospective study was to determine the accuracy of standard FDG-PET/CT for on-treatment response assessment to NAIC and to compare accuracy of FDG-PET/CT to contrast-enhanced CT (CECT). We hypothesized that FDG-PET/CT would predict pathological response to chemotherapy more accurately than CT.

Materials and Methods

This study has been approved by the Institutional Review Board of the Netherlands Cancer Institute (X14BSB).

Patients

We prospectively included 83 consecutive patients from our outpatient bladder cancer clinic between June 2014 and August 2018. Patients were included if they presented with high-risk muscle-invasive urothelial carcinoma (UC), underwent pre- and on-treatment imaging in our institution with both CECT and FDG-PET/CT, were treated with NAIC and were scheduled to undergo RC. High-risk MIBC included ≥cT3 tumors on imaging, nodal involvement (below the renal vein), palpable mass at physical exam, lympho-vascular invasion in the TUR-specimen and/or hydro-ureteronephrosis (considered a cT3 tumor). Patients with visceral metastases and/or LN metastases above the renal vein were treated with palliative intent and excluded from this study. All patients were discussed at multidisciplinary tumorboard meetings. The

sample size for this study was based on the sample size calculation included in the study protocol (Supplementary Materials).

Pretreatment staging

Routine pretreatment staging included physical examination, cystoscopy, laboratory studies, and same-day imaging with CECT and FDG-PET/CT. Cytological or histological confirmation of nodal status was acquired if this was the only indication for chemotherapy. Clinical TNM stage was determined according to the Union for International Cancer Control (8th edition)[22].

Neoadjuvant and induction chemotherapy

Patients with (high-risk) cT2-4aN0M0 tumors were eligible for 4 cycles of neoadjuvant chemotherapy. As of 2017, patients with node-positive bladder cancer (cT1-4aN+M0-1a) were eligible for 6 cycles of induction chemotherapy. Cisplatin-eligible patients were treated with cisplatin-based combination chemotherapy, which consisted of either accelerated cycles of methotrexate, vinblastine, doxorubicin and cisplatin (accMVAC) or gemcitabine-cisplatin. Cisplatin-ineligible patients were treated with gemcitabine-carboplatin. Patients were considered cisplatin-ineligible if they met at least one of the criteria formulated by Galsky et al., which includes poor performance status (ECOG-PS ≥2), poor renal function (GFR <50-60 mL/min), severe neuropathy or hearing loss (grade ≥2), or heart failure (NYHA-class-III/IV)[23].

CECT protocol

CECT images of the chest and abdomen/pelvis were acquired with the patient in supine position with the arms above the head. The acquisition parameters for CECT were slice thickness 5x5mm, table speed 1.2x2.4mm per rotation, pitch 1.2 to 0.844, and reconstruction intervals 1 and 5mm. The intravenous contrast agent was OmnipaqueTM-300 with a concentration of 300mg iodide per ml. The dose was calculated to be weight plus 40ml (minimum 90ml and maximum 130ml). The injection time was 3ml per second.

FDG-PET/CT protocol

Whole-body FDG-PET/CT images were acquired with the patient in supine position with arms above the head. Imaging was performed with integrated PET/CT scanners (Gemini TF or Gemini TF Big Bore, Philips, Amsterdam, the Netherlands). A low-dose CT scan (dose modulated, 40mAs, 2mm slice thickness) from the groins to the skull base was performed followed by a PET scan (2 minutes per bed position). PET images were attenuation-corrected and anatomically correlated using the low-dose CT images and reconstructed in 4mm isotropic voxels.

The protocol for imaging of urothelial carcinoma includes both a direct scan as well as a delayed scan to minimize interference of excreted urinary FDG. Patients were instructed to fast for ≥6 hours and received oral prehydration. FDG (190-260 MBq, depending on body mass index) was administered and imaging was performed 1 hour after injection of FDG. For delayed imaging, furosemide (20mg) was administered 1,5 hours after injection of FDG, followed by delayed imaging of the pelvis at 3 hours later.

Response assessment

Response to chemotherapy was assessed mid-treatment, i.e. response was assessed after 2 and 3 cycles of neoadjuvant and induction chemotherapy, respectively. On-treatment response evaluation consisted of cystoscopy and FDG-PET/CT and CECT imaging, all performed on the same day. For the purposes of this study, the radiologist and nuclear medicine physicians were blinded to the results of cystoscopy and only based their assessment on imaging results.

All pre- and on-treatment CECT images were assessed according to the RECIST1.1 criteria by the same experienced radiologist (AB) blinded to patient data and FDG-PET/CT results[24]. All pre- and on-treatment FDG-PET/CT images were separately reviewed by two experienced nuclear medicine physicians (MD and EV) blinded to patient data and CECT results. Incongruous results were resolved in a consensus reading to minimize introduction of non-random variation. In the context of MIBC, there are no validated response assessment criteria for FDG-PET/CT yet. Therefore, we used two response assessment methods. We evaluated FDG uptake (semi-quantitatively) with the widely used European Organization for Research and Treatment of Cancer (EORTC) criteria[25] using SUVmax. SUVmax was measured in volumes of interest (VOIs) - i.e. the primary tumor and suspicious LNs - and compared in the pre- and on-treatment scan. We used the Peter Mac criteria[26] to assess visual, qualitative response to NAIC. The Peter Mac criteria rely on subjective interpretation of changes in FDG uptake on the pre- and on-treatment scan rather than measurements. Patients with clinical response or stable disease upon response assessment finished the remaining cycles of NAIC and underwent RC. Those with progressive disease at response assessment or clinical follow-up were again discussed in multidisciplinary rounds again to assess (palliative) treatment options.

Pelvic Lymph Node Dissection

In our high volume center (>100 RCs/year), a standardized template for PLND is maintained. This template includes removal of LNs in the region between the genitofemoral nerve, the obturator fossa, along the internal iliac artery, including the triangle of Marcille, and along the common iliac artery, up to the crossing of the ureter. A retroperitoneal LN-dissection was performed in case of retroperitoneal LNs (i.e. cM1a). All RC-surgeons meet a surgeon volume requirement of 20 RCs/year.

Data analysis

The sample size for this study was calculated with the (two-sided) McNemar's test for equality of paired proportions with significance level $\alpha=0.05$, difference in proportions ($\delta=|\pi_1 - \pi_2|$) = 0.148, proportion of discordant parts ($\eta=\pi_{10}+\pi_{01}$) = 0.168, yielding n=48 for the number of pairs (FDG-PET/CT and CECT). We included more than the 48 patients required according to the sample size calculation to establish the largest cohort in this research area.

The standard of reference for response on FDG-PET/CT and CECT was pathologic response based on histopathological examination of the RC and PLND specimens or clinical follow-up in case of progression. A true positive for pCR was defined as complete response on imaging and no residual tumor in the histological specimen. A true positive for pCD was

defined as either complete or partial response on imaging and down-staging to ≤ypT1/a/isN0 in the histological specimen. A true positive for any down-staging (ypTN<cTN) was defined as complete or partial response on imaging and any down-staging compared to clinical stage in the histological specimen. Finally, a true positive for progression was defined as the occurrence of new extravesical lesions on imaging as well as in the histological specimen and/or ycN+-ycM+ as determined by multidisciplinary rounds and clinical follow-up.

Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables with a non-normal distribution were presented as median and interquartile range. Performance of FDG-PET/CT and CECT were established by calculation of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy with corresponding 95% confidence intervals. Outcomes for FDG-PET/CT and CECT were compared with the two-sided McNemar test; $p<0.05$ was considered statistically significant.

Results

We included 83 MIBC patients who underwent FDG-PET/CT. An additional CECT was made in 61 of these patients. One patient (1%) refused RC after chemotherapy and was lost to follow-up. Hence, it was possible to assess accuracy of response of FDG-PET/CT and CECT in 82 (99%) and 60 (72%) patients, respectively. Of the evaluable FDG-PET/CT scans, 77% were performed with delayed imaging of the pelvis. Cytological confirmation of cN-status was obtained in 7 patients as cN+-status was the only indication for starting chemotherapy.

Patient and tumor characteristics are displayed in Table 1. Median age was 64 years (interquartile range 56-72 years). Of the 83 patients, 43 (52%) were treated in the neoadjuvant setting and 40 (48%) in the induction setting. Eight patients (10%) did not undergo RC due to progressive disease. In total, 74 patients (89%) underwent RC. Two patients had suspect retroperitoneal LNs, for which retroperitoneal rather than pelvic LND was performed. After surgery, 17 patients (21%) achieved pCR, 24 patients (29%) achieved pCD, and 17 patients (21%) had progressive disease.

Diagnostic parameters of FDG-PET/CT and CECT for prediction of response to NAIC are shown in Table 2. In general, FDG-PET/CT had higher sensitivity and CECT had higher specificity for response prediction. Accuracy was more or less comparable. FDG-PET/CT correctly identified pCD in 23 out of 24 patients with complete downstaging, whilst CECT correctly identified pCD in 15 out of 16 patients with complete downstaging. Accuracy of FDG-PET/CT and CECT for prediction of pCD were 51% and 65%, respectively. The difference in specificity of CECT compared to FDG-PET/CT for prediction of pCD was statistically significant (55% vs 34%; $p=0.007$), while the other differences were not (Table 2).

Table 1. Patient and tumor characteristics. The 83 patients undergoing neoadjuvant or induction chemotherapy are shown. The patients were treated with a cisplatin-based regimen or gemcitabine-carboplatin in case of cisplatin-ineligibility. Please note that the 11 patients with cT2 disease were either cN+ and/or had lympho-vasular invasion in their TUR specimen

		Whole cohort (n=83)
Age, years (median, IQR)		64 (56-72)
Sex (n, %)	**Female**	30 (36)
	Male	53 (64)
cT-stage (n, %)	**cT2**	11 (13)
	cT3	49 (59)
	cT4	23 (28)
cN-stage (n, %)	**cN0**	43 (52)
	cN1	19 (23)
	cN2	16 (19)
	cN3	5 (6)
cM-stage (n, %)	**cM0**	76 (92)
	cM1a[a]	7 (8)
Setting (n, %)	**Neoadjuvant**	43 (52)
	Induction	40 (48)
Histology (cystectomy) (n, %)	**UC**	62 (75)
	UC with variant[b]	21 (25)
NAIC regimen[c] **(n, %)**	**MVAC**	17 (21)
	Gem-Cis	53 (64)
	Gem-Carbo	13 (16)
Number of NAIC cycles (n, %)	**2**	4 (5)
	3	7 (8)
	4	64 (77)
	5	2 (2)
	6	6 (7)
Pathological response (n, %)	**Complete pathological response (ypT0N0)**	17 (21)
	Complete pathological down-staging (≤ypT1N0)	24 (29)
	Any down-staging	41 (49)
	No pathology (progressive disease during NAIC)	8 (10)

Abbreviations: cN = clinical nodal stage; cM = clinical metastatic stage; cT = clinical tumour stage; IQR = interquartile range; MVAC= methotrexate, vinblastine, doxorubicine, cisplatin; NAIC = neoadjuvant or induction chemotherapy; pCR = complete pathological response; pCD = complete pathologic down-staging; UC = urothelial carcinoma
a. Involvement of retroperitoneal lymph nodes up to the renal vein
b. Urothelial carcinoma (UC) with squamous cell differentiation (n=9), UC with adeno differentiation (n=2), UC with neuro-endocrine (small cell) differentiation (n=2), UC with sarcomatoid differentiation (n=2), UC with micropapillary differentiation (n=1), UC with other differentiations (n=5)
c. Some patients changed regimen during therapy; from Gemcitabine-Cisplatin to Gemcitabine-Carboplatin (n=9) and vice versa (n=1)

Table 2. Diagnostic parameters of FDG-PET/CT and CECT for prediction of response to neoadjuvant or induction chemotherapy for muscle-invasive urothelial carcinoma. FDG-PET/CT was not more accurate than CECT for prediction of complete response or downstaging and progression.

Overall	% FDG-PET/CT EORTC	95% CI	% CECT RECIST1.1	95% CI	p-value
Complete pathological response (ypT0N0)					
Sensitivity	53	0.29-0.76	8	0.004-0.40	n.e.
Specificity	75	0.63-0.85	96	0.85-0.99	n.e.
Positive predictive value	36	0.19-0.57	33	0.02-0.87	n.e.
Negative predictive value	86	0.74-0.93	81	0.68-0.90	n.e.
Accuracy	72		78		n.e.
Complete pathological downstaging (≤ypT1N0)					
Sensitivity	92	0.72-0.99	94	0.68-0.997	1
Specificity	34	0.23-0.48	55	0.39-0.69	0.007
Positive predictive value	37	0.25-0.50	43	0.27-0.60	1
Negative predictive value	91	0.69-0.98	96	0.78-0.998	n.e.
Accuracy	51		65		1
Clinically significant progression (ypN+/ypM+)					
Sensitivity	21	0.08-0.43	5	0.003-0.27	0.625
Specificity	96	0.87-0.99	98	0.85-0.999	1
Positive predictive value	71	0.30-0.95	50	0.03-0.97	n.e.
Negative predictive value	74	0.63-0.83	67	0.53-0.79	1
Accuracy	73		67		n.e.

95% CI = 95% confidence interval; CECT = contrast-enhanced Computed Tomography; EORTC = European Organization for Research and Treatment of Cancer; FDG-PET/CT = (18) F-fluorodeoxyglucose Positron Emission Tomography / Computed Tomography; n.e. = not evaluable; RECIST = Response Evaluation Criteria in Solid Tumours; ypM = distant metastases after neoadjuvant treatment; ypN = pathological nodal stage after neoadjuvant treatment; ypT = pathological tumor stage after neoadjuvant treatment

Furthermore, FDG-PET/CT correctly identified progression in 5 out of 17 patients, whilst CECT correctly identified progression in 1 out of 14 patients. Accuracy of FDG-PET/CT and CECT for detection of progression were 73% and 67%, respectively. Results for FDG-PET/CT and CECT were not statistically significantly different (p>0.625). Specifically, progression in lymph node status (cN0 to ypN+) remained undetected by both imaging techniques.

In Supplementary Table 1, we included comparison of the EORTC and Peter Mac criteria for FDG-PET/CT. We found that the Peter Mac criteria and EORTC yielded similar results for prediction of response to NAIC. Furthermore, we did separate analyses for accuracy of response to NAIC in the in the LNs (Supplementary Table 2). Results for prediction of complete nodal response (ypN0) were not statistically significantly different between FDG-PET/CT and CECT ($p>0.5$). Finally, Supplementary Table 3 shows results for the induction setting separately. Again, FDG-PET/CT was not more accurate than CECT for prediction of response or progression.

Discussion

On-treatment assessment of response to NAIC aims to accurately differentiate between (complete) responders and non-responders to adjust treatment accordingly. In this prospective study we evaluated whether on-treatment FDG-PET/CT could assess response to NAIC and compared the results to CECT. In general, our results showed that prediction of pathological response during NAIC was not statistically significantly different between FDG-PET/CT and CECT. Furthermore, we found that the EORTC criteria and Peter Mac criteria yielded similar results for response assessment by FDG-PET/CT. Low specificity of CECT and especially FDG-PET/CT for prediction of complete down-staging indicated that response was often overestimated. In contrast, progression in lymph nodes often remained undetected even by FDG-PET/CT. These findings suggest that routine FDG-PET/CT has insufficient predictive power to aid in response assessment.

The rationale for the use of FDG-PET/CT rather than CECT is that metabolic response of the tumor (reflected by uptake of FDG) may precede anatomical response (i.e. shrinkage), allowing for earlier detection. Both imaging modalities correctly identified patients with pCD and high negative predictive value indicated that both also correctly identified non-response (≥ypT2N0). However, low specificity suggests that many patients with residual invasive disease were wrongfully characterized as having pCD. These results indicate response was often overestimated by both FDG-PET/CT and CECT.

The results for detection of pCR were surprising. Low sensitivity of FDG-PET/CT and especially CECT indicated that pCR was often missed. Possible explanations may be that CECT cannot accurately distinguish between benign changes (e.g. fibrosis due to NAIC) and viable tumor, and that FDG-PET/CT may overlook pCR by misinterpreting urinary FDG as residual viable tumor. Hence, response evaluation with FDG-PET/CT proved not more accurate than CECT due to its inherent limitations.

In clinical practice, especially assessment of response in lymph nodes will guide patient management. In the induction setting, accurate assessment of (non-)response in LNs may not only reduce overtreatment from NAIC but from futile RC as well. We hypothesized that FDG-PET/CT would predict LN-response more accurately than CECT. However, in separate analyses for accuracy of LN-response and the induction setting, we found that FDG-PET/CT

did not perform better than CECT. Low specificity and positive predictive value for complete response indicate that nodal response was often overestimated. Importantly, low sensitivity for progression indicates lymph node progression was often missed by both imaging modalities, suggesting neither are sufficiently accurate to guide patient management in the induction setting. A possible explanation may be that new micro-metastases (≤10mm) remained undetected by both CECT and FDG-PET/CT.

Limited evidence is available on response assessment methods for MIBC[17–21]. Our prospective study confirmed previous findings that sensitivity of FDG-PET/CT for response evaluation is relatively high, although comparison is not straightforward because study-designs are heterogeneous in factors affecting accuracy, such as timing of evaluation (on- or post treatment) and evaluated lesions (tumor-only, LNs-only, both). This may explain the wide range for both sensitivity and specificity. Moreover, comparison to CECT is lacking in all but one (Mertens et al.[21]) of the five previous studies.

Finally, the timing of response assessment remains subject of debate. Currently, no reliable pretreatment radiological- or biomarkers are recommended to predict response to NAIC in clinical practice. On-treatment response assessment with FDG-PET/CT often yields more false-positive results, which may be caused by a transient decrease of metabolic activity in the tumor ('stunning') shortly after chemotherapy[27]. Fransen van de Putte et al. evaluated FDG-PET/CT for post-treatment assessment of response to NAIC and found higher specificity for detection of any down-staging from baseline (75% vs 32%)[18]. While post-treatment assessment could increase specificity of FDG-PET/CT, it should be considered that non-responders would still be exposed to the full chemotherapy regimen and subsequent risk of toxicity.

Our results should be interpreted bearing some limitations in mind. To an extent, the distorting effect of urinary FDG can be mitigated by use of a delayed protocol, which was not used in all patients in this study (Table 2). Staging inaccuracy, especially of nodal status, could also influence the results of response evaluation. In addition, results for FDG-PET/CT and CECT should be compared with caution, as not all patients also underwent response-CECT. A further limitation to our study is that we were not able to capture all patients who received NAIC due to the pre-specified criteria of our protocol (Supplementary Materials), e.g. in case patients had undergone primary staging in another center. Important strengths of this study are its prospective nature and the relatively large cohort. Furthermore, results for FDG-PET/CT were compared to CECT.

Conclusions

In the present prospective study, routine FDG-PET/CT was not more accurate than CECT for prediction of response to NAIC and response was often overestimated by both imaging modalities. Our findings indicate that standard use of FDG-PET/CT has insufficient predictive power to aid in response assessment.

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Supplementary Materials

Supplementary Table 1. Assessment of response to neoadjuvant/induction chemotherapy for urothelial carcinoma on FDG-PET/CT according to the EORTC criteria versus the Peter Mac criteria. Both the EORTC and Peter Mac criteria were used to predict response to neoadjuvant/induction chemotherapy for urothelial carcinoma on FDG-PET/CT. The response criteria rarely yielded different results and accuracy was similar.

Overall	% FDG-PET/CT EORTC	95% CI	% FDG-PET/CT PeterMac	95% CI
Complete pathological response (ypT0N0)				
Sensitivity	53	0.29-0.76	59	0.33-0.81
Specificity	75	0.63-0.85	77	0.65-0.86
Positive predictive value	36	0.19-0.57	40	0.22-0.61
Negative predictive value	86	0.74-0.93	88	0.76-0.95
Accuracy	71		73	
Complete pathological downstaging (≤ypT1N0)				
Sensitivity	92	0.72-0.99	96	0.77-0.998
Specificity	34	0.23-0.48	28	0.17-0.41
Positive predictive value	37	0.25-0.50	35	0.24-0.48
Negative predictive value	91	0.69-0.98	94	0.69-0.997
Accuracy	51		48	
Clinically significant progression (ypN+/ypM+)				
Sensitivity	21	0.08-0.43	21	0.08-0.43
Specificity	96	0.87-0.99	96	0.87-0.99
Positive predictive value	71	0.30-0.95	71	0.30-0.95
Negative predictive value	74	0.63-0.83	74	0.63-0.83
Accuracy	73		73	

95% CI = 95% confidence interval; CECT = contrast-enhanced Computed Tomography; EORTC =European Organization for Research and Treatment of Cancer; FDG-PET/CT = 18F-fluorodeoxyglucose Positron Emission Tomography / Computed Tomography; ypM = distant metastases after neoadjuvant treatment; ypN = pathological nodal stage after neoadjuvant treatment; ypT = pathological tumor stage after neoadjuvant treatment

Supplementary Table 2. Separate assessment of response to neoadjuvant/induction chemotherapy in the lymph nodes. FDG-PET/CT was not more accurate than CECT for prediction of complete response in the lymph nodes.

	% FDG-PET/CT PeterMac	95% CI	% CECT RECIST1.1	95% CI	p-value
Complete response (ypN0)					
Sensitivity	69	0.39-0.90	78	0.40-0.96	1
Specificity	61	0.38-0.80	33	0.09-0.69	0.5
PPV	50	0.27-0.73	54	0.26-0.80	1
NPV	78	0.52-0.93	60	0.17-0.93	n.e.
Accuracy	64		56		1

95% CI = 95% confidence interval; CECT = contrast-enhanced Computed Tomography; EORTC = European Organization for Research and Treatment of Cancer; FDG-PET/CT = (18) F-fluorodeoxyglucose Positron Emission Tomography / Computed Tomography; n.e. = not evaluable; RECIST = Response Evaluation Criteria in Solid Tumours; ypM = distant metastases after neoadjuvant treatment; ypN = pathological nodal stage after neoadjuvant treatment; ypT = pathological tumor stage after neoadjuvant treatment

Supplementary Table 3. FDG-PET/CT and CECT diagnostic accuracy for identifying response as well as progression in patients treated with induction chemotherapy (TanyN+M0-1a). FDG-PET/CT was not more accurate than CECT for prediction of response in the induction setting. Importantly, low sensitivity for progression indicates progression in lymph nodes was often missed by both imaging modalities.

Overall	FDG-PET/CT (%) PeterMac	95% CI	CECT (%) RECIST1.1	95% CI
Complete pathological response (ypT0N0)				
Sensitivity	80	0.30-0.99	25	0.01-0.78
Specificity	82	0.65-0.93	100	0.83-1
PPV	40	0.14-0.73	100	0.05-1
NPV	97	0.80-0.998	89	0.70-0.97
Accuracy	85		76	
Complete pathological downstaging (≤ypT1N0)				
Sensitivity	100	0.63-1	89	0.51-0.99
Specificity	27	0.13-0.46	33	0.18-0.53
PPV	29	0.15-0.48	29	0.14-0.49
NPV	100	0.60-1	91	0.57-0.995
Accuracy	46		66	
Response (ypTN < cTN)				
Sensitivity	100	0.79-1	91	0.57-0.995
Specificity	40	0.20-0.64	67	0.41-0.86
PPV	61	0.42-0.78	63	0.36-0.84
NPV	100	0.60-1	92	0.62-0.996
Accuracy	69		76	
Clinically significant progression (ypN+/ypM+)				
Sensitivity	43	0.12-0.80	20	0.01-0.70
Specificity	97	0.82-0.998	100	0.83-1
PPV	75	0.22-0.97	100	0.05-1
NPV	86	0.72-0.96	86	0.66-0.95
Accuracy	87		86	

Appendix A - Study protocol (X14BSB)

Prospective evaluation of on-treatment chemotherapy response with FDG-PET/CT and CECT in invasive bladder cancer patients

Introduction

The standard treatment for muscle invasive bladder cancer (MIBC) is radical surgical removal of the bladder including regional lymph nodes[1]. As administration of neoadjuvant or induction chemotherapy (NAIC) has established a significant survival benefit, it is nowadays recommended in locally advanced bladder cancer[1]. However, induced morbidity and non-response rate are considerable[2,3]. Thus, early and adequate identification of non-responders is important in order to reduce both unnecessary chemotoxicity and delay in primary treatment. At the moment, first response evaluation is performed using contrast-enhanced CT of the abdomen and chest (CECT) following 2 cycles of neoadjuvant chemotherapy. Previous literature suggests that response after 2 cycles of NAC is related to outcome, but studies are limited and populations small[1]. In addition, it is suggested that FDG-PET/CT can identify response before CT or MRI, due to visualization of early alterations in tumour metabolism that occur before morphological change (tumour shrinkage) becomes visible[4]. A recent pilot study by our group has suggested that FDG-PET/CT may be useful for evaluating the nodal response after 4 cycles of NAIC[5]. The accuracy of FDG-PET/CT for evaluating nodal response after 2 cycles of NAIC has not yet been investigated. We hypothesize that after 2 cycles of NAIC, FDG-PET/CT is better than CECT at predicting nodal response after the end of NAIC, as evaluated by pelvic lymphadenectomy and pathology.

Patient selection

Patients with muscle invasive transitional cell carcinoma, eligible for neoadjuvant chemotherapy or induction chemotherapy, based on CECT and TUR findings. NAIC should consist of MVAC, GEM/cisplatin or GEM/carboplatin based chemotherapy. Exclusion criteria are: patients not eligible for NAIC due to renal impairment (GFR below 30 ml/min), patients ineligible for cystectomy due to high ASA score, low performance status and/or unwillingness to undergo NAIC, patients with distant (organ and LN above renal vein) metastasis.

Objective

To assess accuracy in distinguishing responders from non-responders with FDG-PET/CT imaging after 2 cycles of NAC/IC for MIBC and compare results with conventional CECT.

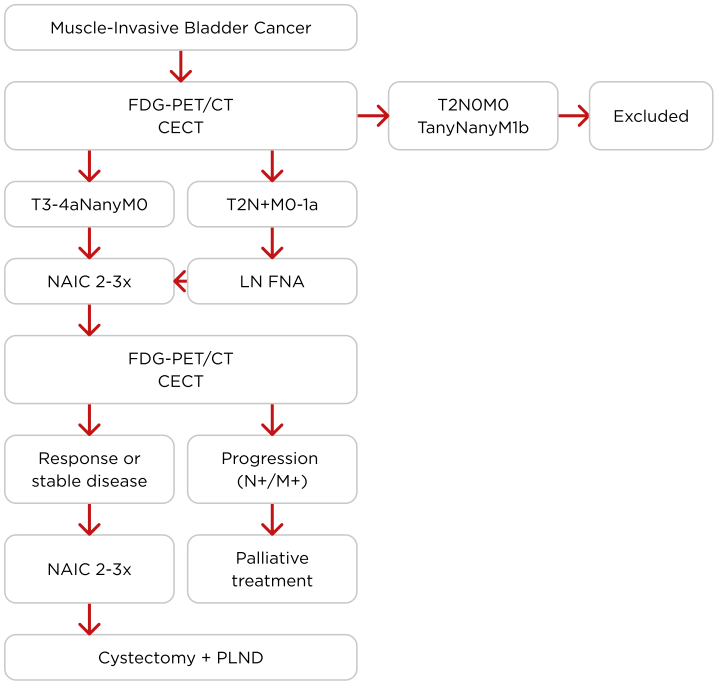
Study design

At our institution, initial staging for BC consists of TUR-B, CECT and FDG-PET/CT, including delayed imaging after forced diuresis (method previously described[6]). Patients with cT2N0M0 BC are treated with radical cystectomy and lymph node dissection within 6 weeks. Patients with locally or regionally advanced disease (T3+ or nodal metastases below the renal vein) are treated with neoadjuvant or induction chemotherapy, respectively, followed by radical

cystectomy and PLND, if progression does not occur. When lymph node metastases are suspected on staging CT or FDG-PET/CT, fine needle aspiration (FNA) of suspicious lymph nodes is performed before administration of NAIC. In case of inconclusive FNA results, FNA is repeated with a maximum of 2 aspirations in total. All patients are discussed in multidisciplinary rounds with representatives from urology, radiation oncology, medical oncology, radiology, nuclear medicine and pathology. At the moment, response to NAIC is assessed by CECT imaging 2 weeks after 2 cycles of chemotherapy and by FDG-PET/CT imaging 2 weeks after 4 cycles of chemotherapy. Surgery is planned, based on CECT findings after 2 cycles of chemotherapy. Based on previous study results, as described above, our institutional standard evaluation of chemotherapy response will be altered: after 2 cycles of NAIC, response evaluation will consist of both CECT and FDG-PET/CT imaging (including delayed PET imaging after forced diuresis). Surgery will be planned based on both imaging results (Figure 1). After completion of NAIC, no further evaluation will be performed before surgery unless clinical suspicion of progression.

In this prospective cohort study, clinical NAIC responses based on FDG-PET/CT and on CECT findings will be registered and compared. Cystectomy and lymph node dissection histology after completion of chemotherapy will serve as the golden standard for NAIC response identification, unless obvious progression is detected at clinical response evaluation. In patients without histological confirmation, further progression at clinical follow-up will be used as a confirmation.

Figure 1. Outline of the future treatment and evaluation procedures for patients with MIBC.



Primary study end point

Sensitivity and specificity, PPV and NPV in distinguishing responders from non-responders with FDG-PET/CT imaging after 2 cycles of NAIC.

Secondary study end point

Sensitivity and specificity, PPV and NPV in distinguishing responders from non-responders with CECT imaging after 2 cycles of NAIC and a comparison with FDG-PET/CT results.

Conventional pre-treatment staging

In our institutional bladder cancer clinic, patients will be staged by physical examination, cystoscopy and laboratory studies. CECT scans of the abdomen and chest will be evaluated by an experienced radiologist. Lymph nodes >10mm in maximum short axis diameter are regarded as enlarged on CECT imaging. Tumour stage is determined according to the criteria of the Union for International Cancer Control (UICC)[7]. FDG-PET/CT imaging consist of a primary scan including oral prehydration and fasting for at least 6h, followed by administration of 190-240 MBq FDG with imaging from head till upper thigh after one hour and delayed pelvic imaging (20mg furosemide injection after 90 minutes, 500ml oral hydration and frequent voiding, imaging after 3h). Evaluation will be done qualitatively by an experienced nuclear medicine physician, as part of standard clinical practice. FDG-avid foci in a non-physiological distribution are determined visually. An additional lesion is classified as a suspect nodal or distant lesion outside the bladder or as a new primary proliferative lesion. Suspect nodal lesions will be evaluated using FNA. Tumour FDG uptake will be quantified using the maximum standardized uptake value (SUVmax).

Response evaluation using CECT

For this study CECT images after 2 cycles of NAIC will be revised by a dedicated radiologist, blinded for PET/CT results. The treatment effect is assessed according to Response Evaluation Criteria In Solid Tumours (RECIST 1.1).

Metabolic response evaluation using FDG PET/CT

PET/CT imaging after 2 cycles of NAIC will be performed as described above for pre-treatment staging. Response evaluation for this study will be done qualitatively and quantitatively by an experienced nuclear medicine physician, blinded for CECT results. Tumour FDG uptake will be quantified using SUVmax. Retrospectively, treatment effect will be determined by the relative reduction of various metabolic parameters (SUVmax, metabolic tumour volume and total lesion glycolysis).

Statistical analysis

Specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV) will be calculated for PET parameters and compared to response CECT response evaluation with the (two-sided) McNemar's test.

Sample size determination

Sample size was calculated with the (two-sided) McNemar's test for equality of paired proportions with significance level α=0.05, difference in proportions ($\delta=|\pi_1 - \pi_2|$)=0.148, proportion of discordant parts ($\eta=\pi_{10}+\pi_{01}$) = 0.168, yielding n=48 for the number of pairs (FDG-PET/CT and CECT).

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7

Diagnostic value of 18F-fluorodeoxyglucose positron emission tomography with computed tomography for lymph node staging in patients with upper tract urothelial carcinoma

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Eur Urol Oncol. 2021 Feb 11:S2588-9311(21)00029-8.

Abstract

Background

Presence of lymph node metastases (LNM) is an important prognostic factor for cancer-specific survival (CSS) in patients with upper tract urothelial carcinoma (UTUC). In various neoplasms, 18F-fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT) is an established modality for preoperative lymph node (LN) staging. In UTUC, the diagnostic value of FDG-PET/CT for LN staging is unknown.

Objective

To determine the diagnostic value of FDG-PET/CT for LN staging in patients with UTUC.

Design, Setting, and Participants

Data of 152 patients with UTUC who underwent FDG-PET/CT followed by surgical treatment in eight centers between 2007 and 2017 were retrospectively collected. Patients receiving neoadjuvant chemotherapy were excluded.

Outcome Measurements and Statistical Analysis

FDG-PET/CT results were compared with histopathology after lymph node dissection (LND). Recurrence-free survival (RFS), CSS, and overall survival (OS) were analysed using Kaplan-Meier estimates and compared for patients with and without suspicious LNs on FDG-PET/CT.

Results and Limitations

We included 117 patients, of whom 62 underwent LND. Seventeen patients had LNM at histopathologic evaluation. Sensitivity and specificity of FDG-PET/CT for diagnosis of LNM were 82% (95% confidence interval (CI): 57-96) and 84% (95% CI: 71-94), respectively. RFS was significantly worse in patients with LN positive FDG-PET/CT than in those with LN negative FDG-PET/CT (p=0.03). CSS (p=0.11) and OS (p=0.5) were similar between groups. This study is limited by its retrospective design and by its sample size. Our results warrant further validations.

Conclusion

FDG-PET/CT has 82% sensitivity and 84% specificity for the detection of LN metastases in patients with UTUC. Presence of suspicious LNs on FDG-PET/CT is associated with worse RFS.

Introduction

Upper tract urothelial carcinoma (UTUC) is a relatively rare malignancy, accounting for 5-10% of all urothelial carcinomas (UC)[1]. Approximately 60% of UTUCs are invasive (cT2-T4) at diagnosis. In these cases, radical nephroureterectomy (RNU) with bladder cuff excision is considered standard treatment[2]. Despite treatment, prognosis of invasive UTUC is poor with 5-year overall survival (OS) rates of ~50% for pT2-T3 tumors and ~10% for pT4 tumors[1].

Lymph node (LN) metastases are reported in 14 to 40% of UTUC patients with higher T-stages (≥pT2)[3]. Presence of LN metastases is associated with worse OS[3]. Although regional lymph node dissection (LND) at the time of RNU improves staging, its therapeutic benefit in UTUC remains debated[3]. According to the European Association of Urology (EAU) guidelines, LND should be considered in selected patients with high-risk UTUC. However, indication and extent of LND are not standardized[2].

Accurate LN staging before treatment has the potential to improve treatment selection and could help to prolong survival. Over the last decade, 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) with computed tomography (FDG-PET/CT) has become an established imaging modality for preoperative staging of various neoplasms. In UC of the bladder, FDG-PET/CT has shown high diagnostic accuracy for detecting LN metastases[4,5].

In UTUC, data on the value of FDG-PET/CT in detecting LN metastases are very sparse. A small pilot study in a heterogeneous cohort of UTUC patients (n=53) concluded that FDG-PET/CT provides additional information to CT imaging in detection of metastases[6]. However, this has not been confirmed in larger series nor in multicenter settings. The aim of this study was to evaluate the diagnostic value of preoperative FDG-PET/CT for the detection of LN metastases in patients with UTUC in a multicenter cohort.

Patients and Methods

Patients

We retrospectively identified patients with cM0 UTUC who underwent FDG-PET/CT in the diagnostic work-up, followed by surgical treatment (i.e. RNU, nephrectomy or ureterectomy with or without LND) between 2007 and 2017 in eight centers. Patients who had received neo-adjuvant chemotherapy (NAC) were excluded. Data were collected from institutional databases in accordance with national and institutional ethical guidelines. Follow-up was performed following individual institutions' practice and at least involved CT urography every six months for two years and yearly thereafter. Patients without LND were excluded from the calculations of test performances.

FDG-PET/CT acquisition and interpretation

FDG-PET/CT scanning was performed according to European Association of Nuclear Medicine (EANM) procedure guidelines for tumor imaging[7,8]. EANM Research Ltd (EARL) accredited scanners were used in all centers. FDG-PET/CT images were post hoc reconstructed according to local guidelines and evaluated by local nuclear medicine physicians and radiologists as part of standard clinical practice. Presence or absence of LN metastases was extracted from the PET/CT reports. Presence of elevated FDG uptake in a LN was considered suspicious for malignancy regardless of the size of the LN on CT. In six centers, metabolic activity of the primary tumor was quantified using the maximum standardized uptake value (SUVmax). SUVmax was measured using a volume of interest placed over sites of abnormal FDG uptake in the upper urinary tract.

Surgery and pathology

Patients underwent RNU, nephrectomy or ureterectomy with or without LND, at the discretion of the treating urologist. LND was not performed according to a standardized template. Surgical specimens were evaluated by local pathologists as part of standard clinical practice, according to the 7th TNM classification system and the 2004/2016 WHO classification[9,10]. FDG-PET/CT findings were compared with histopathological examination of the LND specimen.

Statistical analysis

The results of FDG-PET/CT and LND were compared using 2x2 contingency tables. Test performance measures (sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy) were calculated where LND was considered as the gold standard test. 95% confidence intervals (CI) were calculated by the Clopper-Pearson method. The association between SUVmax of the primary tumor and clinicopathological factors (tumor grade, pT stage and pN stage) was analyzed using the Kruskal-Wallis rank sum test.

This study also explored the association between FDG-PET/CT findings and clinical outcomes, including recurrence-free survival (RFS), cancer-specific survival (CSS) and OS. RFS was defined as the time from date of surgery to the date of recurrence, censoring patients without recurrence at death or last contact. OS was defined as the time from date of surgery to the date of death of any cause. CSS was defined as the time from date of surgery to the date of death from disease. Survivors were censored at the date of last contact. A positive FDG-PET/CT was defined as presence of elevated FDG uptake in one or more LNs. RFS, CSS and OS in FDG-PET/CT-negative and -positive subgroups were estimated using Kaplan-Meier curves and compared using the log-rank test.

Median follow-up was calculated using the reverse Kaplan-Meier method. Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA) and R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two sided, with the level of significance set at $p<0.05$.

Results

Patient characteristics

We identified 152 patients with UTUC who underwent staging by FDG-PET/CT. Thirty-five patients were excluded because they received NAC. Characteristics of 117 included patients are shown in Table 1. Sixty-two of the 117 patients (53%) underwent LND. Patient and tumor characteristics of patients with and without LND were similar, except for clinical nodal stage and tumor location. More patients in the LND group had a positive clinical nodal stage based on FDG-PET/CT (p=0.005). The majority of patients in the LND group had a tumor in the renal pelvis whereas multifocal tumors were more frequent in patients without LND, although this difference was not statistically significant (p=0.06). The median time between FDG-PET/CT and surgery was 29 days (interquartile range (IQR) 21-58 days).

Primary tumor assessment and SUVmax measurements

Visualization of the primary tumor was not possible in 20/117 (17%) patients. Three patients were pT0 at pathologic examination (Table 1). SUVmax was measured in 60/117 patients. Median SUVmax was 9.4 (IQR 7.3-14.9). There was no correlation between SUVmax and pT stage (p=0.8) or tumor grade (p=0.9). Thirty-one of 60 patients with available SUVmax measurements underwent LND. In these patients, SUVmax was not associated with pN stage (p=0.2).

Lymph node staging

The median LN yield per patient was 6 (IQR 4-9, range 2-29). In total, 17/62 (27%) patients had tumor-positive LNs at pathologic examination. Table 2 shows the association between PET/CT results and histopathology of LND. FDG-PET/CT demonstrated LN metastases in 21 patients, fourteen of whom proved to have positive LNs at pathologic examination. In seven patients, FDG-PET/CT showed suspicious LNs that were not confirmed at pathologic examination (false positive).

FDG-PET/CT demonstrated no evidence of LN metastases in 41 patients, three of whom proved to have positive LNs at pathologic examination (false negative). The corresponding sensitivity, specificity and accuracy of FDG-PET/CT were thus 82% (95% confidence interval (CI): 57-96), 84% (95% CI: 71-94) and 84% (95% CI: 72-92), respectively. The NPV and PPV of FDG-PET/CT for detection of LN metastases were 92% (95% CI: 80-98) and 67% (95% CI: 43-85), respectively.

Table 1. Patient and tumor characteristics shown for the entire cohort and for patients with and without lymph node dissection

		Total		LND		No LND		*p* value
Total number of patients		**117**		**62**		**55**		
Median follow-up, months (95% CI)		**32 (25-38)**		**29 (9-49)**		**34 (30-38)**		
Median age, years (IQR)		**71 (66-77)**		**70 (65-76)**		**72 (66-77)**		
		n	**%**	**n**	**%**	**n**	**%**	
Sex	**Male**	77	65.8	44	71.0	33	60.0	0.2
	Female	40	34.2	18	29.0	22	40.0	
Tumor location	**Renal pelvis**	37	31.6	25	40.3	12	21.8	0.06
	Ureter	49	41.9	25	40.3	24	43.6	
	Multifocal	31	26.5	12	19.4	19	34.5	
Invasive aspect on CTU	**Yes**	59	49.6	30	48.4	28	52.7	0.6
	No	58	50.4	32	51.6	26	47.3	
cN stage on FDG-PET/CT	**cN0**	93	79.5	41	66.1	52	94.5	5
	cN+	24	20.5	21	33.9	3	5.5	
Type of surgery	**RNU**	107	91.4	54	87.1	53	96.4	0.2
	Nephrectomy	3	2.6	2	3.2	1	1.8	
	Ureterectomy	7	6.0	6	9.7	1	1.8	
pT stage	**pT0**	3	2.6	2	3.2	1	1.8	0.9
	pTis	1	0.9	0	-	1	1.8	
	pTa	27	23.1	13	21.0	14	25.5	
	pT1	18	15.4	8	12.9	10	18.2	
	pT2	16	13.7	9	14.5	7	12.7	
	pT3	41	35.0	24	38.7	17	30.9	
	pT4	11	9.4	6	9.7	5	9.1	
Tumor grade	**Low grade**	13	11.1	5	8.1	8	14.5	0.4
	High grade	101	86.3	56	90.3	45	81.8	
	Unknown	3	2.6	1	1.6	2	3.6	
pN stage	**pNx**	55	47.0	NA	-	55	100	NA
	pN0	45	38.5	45	72.6	NA	-	
	pN1	8	6.8	8	12.9	NA	-	
	pN2	9	7.7	9	14.5	NA	-	
Adjuvant chemo-therapy	**Yes**	37	31.6	18	29.0	19	34.5	0.5
	No	80	68.4	44	71.0	36	65.5	

Abbreviations: CI: confidence interval, CTU: computed tomography urography, FDG-PET/CT: 18F-fluorodeoxyglucose positron emission tomography with computed tomography, IQR: interquartile range, LND: lymph node dissection, NA: not applicable, pN: pathological lymph node stage, pT: pathological tumor stage, RNU: radical nephroureterectomy

Table 2. Test performances of FDG-PET/CT in comparison with pathology of lymph node dissection

		Pathology		
		+	-	Total
FDG-PET/CT	**+**	14	7	21
	-	3	38	41
	Total	17	45	62

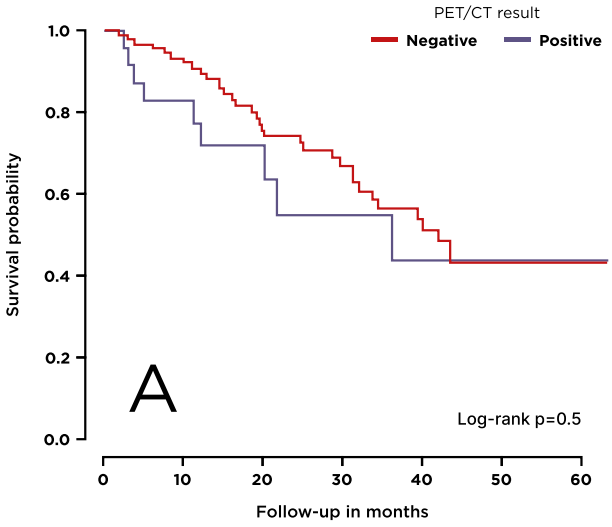
Sensitivity	82.4%	95%CI: 56.6-96.2
Specificity	84.4%	95%CI: 70.5-93.5
PPV	66.7%	95%CI: 43.0-85.4
NPV	92.7%	95%CI: 80.1-98.5
Accuracy	83.9%	95%CI: 72.3-92.0

Abbreviations: CI: confidence interval, FDG-PET/CT: 18F-fluorodeoxyglucose positron emission tomography with computed tomography, PPV: positive predictive value, NPV: negative predictive value

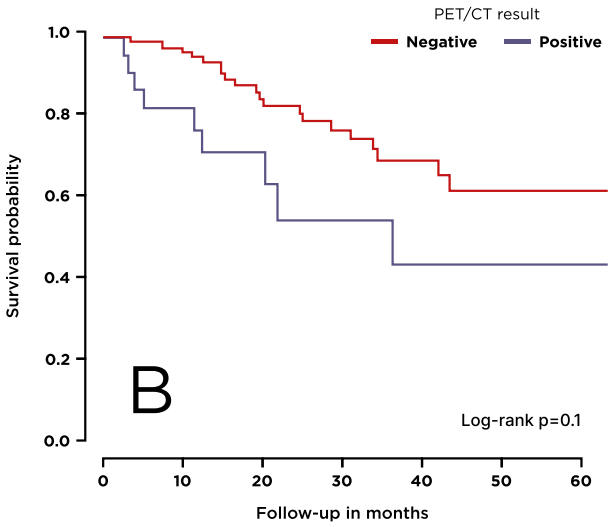
Survival analyses

During a median follow-up of 32 months (95% CI: 25-38 months) 44 patients died, of whom 29 died due to UC. Figure 1A shows Kaplan-Meier curves for OS of patients with a positive versus patients with a negative LN stage on FDG-PET/CT. Median OS was 42 months (95% CI: 32-51) in patients with a positive FDG-PET/CT result and 36 months (95% CI: 26-48) in patients with a negative FDG-PET/CT result (log-rank p=0.5). Figure 1B shows the Kaplan-Meier curves for CSS of patients with a positive versus patients with a negative LN stage on FDG-PET/CT (log-rank p=0.11; median CSS not reached). In total, 55 patients developed a recurrence during follow-up. Figure 1C shows the Kaplan-Meier curves for RFS of patients with a positive versus patients with a negative LN stage on FDG-PET/CT. Median RFS was lower for patients with a positive FDG-PET/CT (16 months (95% CI: 2-32)) compared to patients with a negative FDG-PET/CT (36 months (95%CI 21-50), p=0.03).

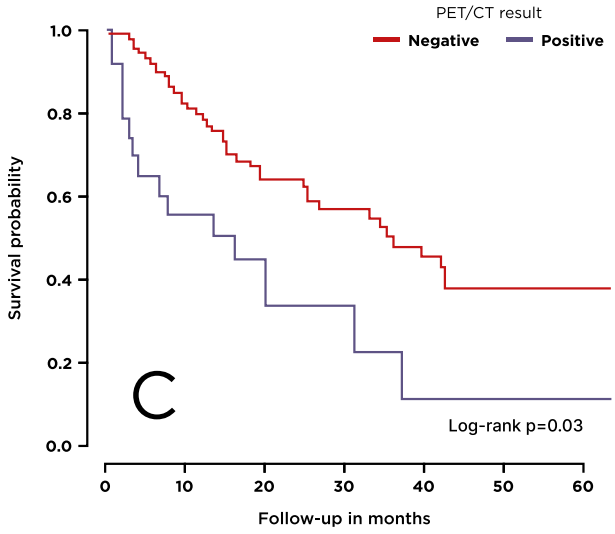
Figure 1. Kaplan-Meier plots of (A) overall survival (B) cancer-specific survival and (C) recurrence-free survival for FDG-PET/CT-negative patients (n=93) and FDG-PET/CT-positive patients (n=24)



No. at risk							
Negative	93	74	49	32	19	14	10
Positive	24	15	8	5	3	2	2



No. at risk							
Negative	93	74	49	33	20	15	12
Positive	24	15	8	5	3	2	2



No. at risk							
Negative	93	63	40	28	18	12	10
Positive	24	12	4	3	2	2	2

Discussion

Patients with UTUC have a 2.2% to 40% risk of LN involvement, depending on primary tumor stage[3,11,12]. Currently, staging of patients with UTUC depends on ureteroscopy (with biopsy of suspicious lesions) and CT urography (CTU). Although CTU has a high diagnostic accuracy for diagnosis of the primary tumor[13], its value in detecting LN metastases is limited[14]. We hypothesized that FDG-PET/CT would aid preoperative LN staging in patients with primary UTUC. We found a sensitivity, specificity and accuracy of FDG-PET/CT for detecting LN metastases of 82%, 84%, and 84%, respectively. Moreover, presence of FDG-PET/CT positive lesions was associated with worse RFS.

The value of FDG-PET/CT in assessment of UTUC has previously been examined in three retrospective studies. First, the most relevant study by Tanaka et al.[6] compared the diagnostic accuracy of FDG-PET/CT and conventional CT for detecting metastases in 53 patients with primary or recurrent UTUC. This study is limited by diversity in treatment options: patients underwent upfront surgery (n=30), NAC followed by surgery (n=9) or palliative treatment (n=14). In total, 32 patients underwent LND. For the remainder, a “new” lesion detected by imaging within three months after surgery was considered a positive reference standard. Overall, sensitivity and specificity of FDG-PET/CT were comparable to those of CT (95% and

91% for FDG-PET/CT versus 82% and 85% for CT; p=0.3 and p=0.5, respectively). In a lesion-based analysis of a subgroup of patients who underwent RNU and LND without NAC (n=24), sensitivity and specificity of FDG-PET/CT for detecting LN metastases was 40% and 99%, respectively. This low sensitivity contrasts with our sensitivity of 84%. This difference may be explained by a low number of patients with LN metastases at histopathology in the study by Tanaka et al. (2.2% versus 27% in our study). Secondly, Asai et al.[15] analysed the value of FDG-PET/CT in primary tumor detection in 48 patients with UTUC. Detection of LN metastases by FDG-PET/CT was assessed in a subgroup of patients who underwent LND (n=28). The authors report a sensitivity of FDG-PET/CT for LN staging of 60%. However, this result was based on only three patients with confirmed LN metastases. No other measures of test performance (e.g. specificity) nor confidence intervals were reported. Finally, Zattoni et al.[16] evaluated the role of FDG-PET/CT in staging of recurrent UC (either UTUC or UC of the bladder) after primary treatment for UC. However, diagnostic accuracy of FDG-PET/CT was not separately reported for UTUC patients (n=74) and the reference standard was not clearly defined. Overall, Zattoni et al. reported a sensitivity and specificity of FDG-PET/CT for detection of LN metastases of 60% and 95%, respectively. In contrast to the previous studies, we investigated the diagnostic value of FDG-PET/CT in a cohort of patients with only primary UTUC, who underwent FDG-PET/CT in the preoperative setting. Furthermore, we excluded patients who underwent NAC, resulting in a homogenous cohort. Patient selection and diversity in treatment hamper the validity of any comparisons between our test performances and those reported in previous studies.

This retrospective study has inherent biases that cannot be accounted for and therefore our results should be interpreted with caution. Although we only included patients with primary UTUC and excluded patients who underwent NAC, heterogeneity may have been introduced by identifying patients within a ten-year time span in various hospitals. Patient selection and timing of FDG-PET/CT were not standardized, introducing selection bias. Other limitations include the lack of standardization of the indication for LND and the lack of standardization of the anatomical extent of LND. No reference standard was available in 47% of patients since they did not undergo LND. Excluding patients from analysis who did not receive the reference standard can lead to partial verification bias. The exclusion of patients with LN metastases who were falsely negative may bias sensitivity up, while the exclusion of patients without LN metastases who were truly negative may bias specificity down.

Notwithstanding the aforementioned limitations, we were able to determine the diagnostic accuracy of FDG-PET/CT for LN staging of patients with UTUC in the largest cohort to date. Given the potential for lymphatic spread in UTUC[3], accurate non-invasive staging is important for optimal treatment planning. This includes decisions regarding performance of LND and administration of NAC. Although recent studies have shown a beneficial effect of LND on oncological outcomes in patients with ≥pT2 UTUC, the selection criteria and extent of LND remain to be established[3,17.] In our study, clinical characteristics (e.g. tumor location and tumor aspect on CTU) of patients with and without LND were similar, reflecting this lack of standardization. Accurate preoperative staging of LN metastases could identify patients who are most likely to benefit from neoadjuvant chemotherapy (NAC). Administration of NAC

in UTUC has yielded favorable pathologic outcomes, but a beneficial effect on survival has not yet been proven[18]. In the future, the addition of FDG-PET/CT to the staging algorithm of UTUC may enable more personalized treatment by aiding in the decision to perform LND or administer NAC. First, our reported measures of diagnostic accuracy should be confirmed in a prospective study.

Besides determination of diagnostic accuracy, we explored the correlation between SUVmax of the primary upper urinary tract tumor and presence of LN metastases. Studies on FDG-PET/CT in lung cancer and in head and neck cancer have concluded that primary tumors with higher SUVmax showed higher prevalence of LN metastases[19,20]. However, we did not find a correlation between SUVmax of the primary tumor and presence of LN metastases. A possible explanation for this might be the relatively low number of patients with available SUVmax measurements and LN metastases.

We also explored the association between FDG-PET/CT findings and survival. Patients with FDG-PET-positive LNs had statistically significant shorter RFS than patients without FDG-PET-positive LNs in univariable analysis. Presence of FDG-PET-positive LNs was also associated with worse OS and CSS, although this association was not statistically significant. This is consistent with reports on UC of the bladder, which have shown that presence of FDG-PET-positive lesions is prognostic for OS, CSS and RFS[21,22]. Whether presence of FDG-PET-positive LNs is an independent prognostic factor of survival in UTUC patients should be topic of future study.

Conclusions

We demonstrated that FDG-PET/CT has a sensitivity, specificity and accuracy of 82%, 84%, and 84%, respectively, for detection of LN metastases in patients with UTUC. Presence of suspicious LNs on FDG-PET/CT was associated with worse recurrence-free survival. Before any recommendations on clinical use of FDG-PET/CT can be made, prospective research on preoperative staging modalities for the detection of LN metastases in UTUC is needed.

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Part III

Locoregional treatment and outcome of muscle-invasive bladder cancer


8

Prostate sparing cystectomy for bladder cancer: a two-center study

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Eur J Surg Oncol. 2018 Sep;44(9):1446-1452.

Abstract

Purpose

To assess long-term functional and oncologic outcomes of prostate sparing cystectomy (PSC) as a sexuality-preserving alternative to radical cystectomy in a selected group of bladder cancer (BC) patients.

Materials and Methods

Between 1995 and 2014, 185 BC patients underwent PSC according to one of two standardized procedures at two centers. All patients had received extensive evaluation to rule out prostate cancer and BC at the bladder neck and prostatic urethra (PU), including prostate specific antigen blood analysis, transrectal ultrasound and/or prostate biopsies, PU biopsies and/or PU frozen section analysis. All patients received an orthotopic ileal neobladder. Overall survival (OS) was assessed by Kaplan–Meier estimates. Cumulative incidence of cancer specific mortality, any recurrence and loco-regional recurrence were calculated using competing-risk methods. Finally, functional outcomes (voiding, continence and erectile function) were evaluated.

Results

185 patients (cTa-3N0M0) with a mean age of 57 years (SD: 9) were included. Median follow-up was 7.5 years (IQR: 5.6-10.8). Five-year OS was 71% and 5-year cumulative incidence of recurrence was 31%. Twenty patients (10.8%) had a loco-regional recurrence, two recurrences were in the PU. During follow-up, prostate cancer was detected in six patients (3.2%). Erectile function was preserved in 86.1% of patients, complete daytime and nighttime continence in 95.6% and 70.2%, respectively.

Conclusion

This two-center study shows that in men with BC in whom the prostate and PU were proven free of malignancy, PSC would represent a valid treatment option with excellent functional outcome. Oncologic outcomes were comparable to what is known from radical cystoprostatectomy series.

Introduction

Standard treatment for muscle-invasive bladder cancer (BC) and persistent non-muscle invasive BC is radical cystectomy (RC)[1]. In men, standard RC includes resection of the bladder, regional lymph nodes, prostate and seminal vesicles. This surgery has major impact on urinary continence and sexual function[2,3].

Over the years, several cystectomy techniques have been developed, aimed at minimizing postoperative incontinence and erectile dysfunction. Single center series report on preserving the neurovascular bundles and urinary sphincter function by sparing the vasa deferentia, the seminal vesicles and prostate capsule, or the entire prostate[4–7]. Reported functional results of the prostate-sparing cystectomy (PSC) techniques are excellent[8]. In a recent systematic review, none of the included comparative studies found any differences in oncological results between PSC and RC[9]. However, PSC is still heavily debated for fear of jeopardizing oncologic outcome. In this two-center study, we investigated long-term functional and oncologic results following two standardized PSC techniques.

Materials and Methods

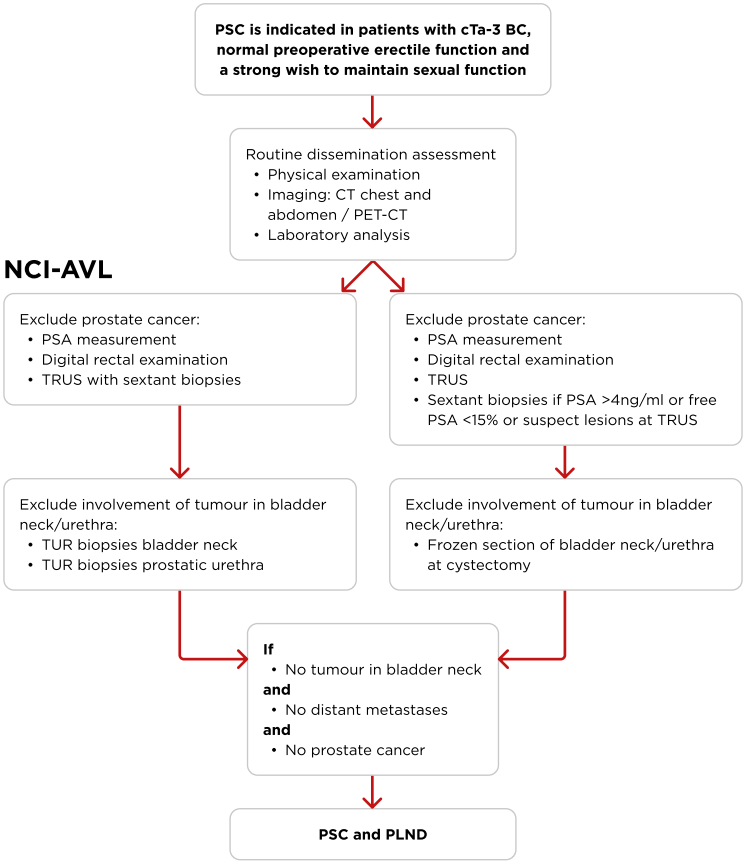
Patient Selection

Consecutive patients, who received PSC according to the standardized techniques at either one of two hospitals until 2014 were included. All patients had either muscle-invasive BC or persistent/recurrent non-muscle invasive BC despite intravesical bacillus Calmette-Guérin (BCG) treatment. In one center (Netherlands Cancer Institute-Antoni van Leeuwenhoek hospital; NCI-AVL), the entire prostate was left in situ and prostatic involvement with urothelial carcinoma was excluded with transurethral biopsies prior to surgery. In the other center (Institut Mutualiste Montsouris; IMM), peroperative frozen section analysis of the prostatic urethra (PU) was used for this purpose, and PSC was combined with a simple adenectomy.

At the NCI-AVL, patients were included from 1995; at the IMM, the standardized PSC technique was introduced in 2001. Our cohort concerns the combined, extended, and refined series previous described by Mertens et al.[6] and Rozet et al.[10.] PSC was offered to patients with cTa-3 BC, normal preoperative erectile function and a strong wish to maintain sexual function. An overview of inclusion criteria and diagnostic evaluation in both centers is shown in Figure 1. Preoperative evaluation included physical examination, cystoscopy, urinalysis, laboratory blood studies and imaging (at least abdominal/pelvic computed tomography and chest X-ray).

All patients received digital rectal examination and transrectal ultrasonography. At the NCI-AVL, transurethral bladder neck and PU biopsies and at least sextant prostate biopsies were taken prior to treatment, irrespective of prostate specific antigen (PSA) measurements, as previously described[6]. At the IMM, prostate biopsies were only taken if patients had palpable

Figure 1. Study inclusion/exclusion and diagnostic evaluation.



Abbreviations: BC bladder cancer; IMM Institute Mutualiste Montsouris; NCI-AVL Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital; PET, positron emission tomography; PLND pelvic lymph node dissection; PSA prostate specific antigen; PSC prostate sparing cystectomy; TRUS transrectal ultrasound; TUR transurethral resection.

nodules, PSA >4ng/ml, free PSA <15% or hypoechoic lesions on transrectal ultrasound[4,10]. Work-up at the IMM did not include standard transurethral biopsies. Exclusion criteria were BC PU/bladder neck involvement or presence of prostate cancer.

Surgery

Surgical techniques were as previously described[4,6,10]. In brief, a pelvic lymph node dissection (PLND) was performed according to standardized templates. At the NCI-AVL the boundaries of PLND were distally the circumflex vein and node of Cloquet, laterally the iliac artery, medially the bladder and prostate, and dorsally the hypogastric artery and obturator nerve.

Since 2000, the boundaries have been enlarged proximally to the crossing of the ureter over the common iliac artery, laterally to the genitofemoral nerve and dorsally/caudally the bottom of the obturator fossa. At the IMM, the latter template was used in all included patients. PLND was followed by resection of the bladder, leaving the prostate and seminal vesicles in situ. At the IMM, the procedure included a simple adenectomy. At the NCI-AVL, the prostate was left in place. At both institutes an orthotopic ileal neobladder was constructed and anastomosed to the prostate capsule. At the IMM, standard intraoperative frozen section analysis of the urethral prostate capsule was performed to confirm negative surgical margins. At the NCI-AVL, this was only performed if there was a suspicion of bladder neck involvement despite negative preoperative transurethral biopsies.

Outcomes

Patients were followed according to the European Association of Urology guidelines and follow-up included urethro-cystoscopy, digital rectal examination, PSA and free PSA measurements[1]. Oncologic end-points for cancer-specific mortality (CSM), overall recurrence and local recurrence were date of death due to BC or treatment, date of disease recurrence, and date of local recurrence, respectively, or the last event-free follow-up date. Local recurrence was defined as recurrent lesion(s) in the surgical bed, specifically in the PU or bladder neck, or pelvic lymph nodes.

Functional outcomes were assessed by interviews on continence, pad use, voiding and sexual function. Normal erectile function was defined as sufficient erectile function for intercourse with or without PDE-5 inhibitors. Complete continence was defined as completely dry both day and night with no need to wear pads. Continence was defined as satisfactory if a patient required 1 pad per day/night and poor for >1 pad per day/night. Clean intermittent catheterization (CIC) was indicated for post-void residual volume ≥150cc as measured by ultrasound or transurethral catheterization.

Statistical Analysis

Baseline characteristics and outcome data were analyzed using descriptive statistics. Probabilities of death from any cause were estimated using the Kaplan-Meier method. For CSM, overall recurrence and local recurrence cumulative incidence functions are provided in order to account for competing events. For CSM, death unrelated to bladder cancer was treated as competing event. For overall recurrence, death without recurrence was treated as competing event. Finally, for local recurrence, recurrence other than in the surgical bed or pelvic lymph nodes and death without recurrence were treated as competing events. Median follow-up was calculated using the reverse Kaplan-Meier method[11]. Statistical analyses were performed using IBM SPSS Statistics version 22.0 (Armonk, NY, IBM Corp.) and R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient and tumor characteristics

A total of 185 patients (122 NCI-AVL, 63 IMM) with a mean age of 57 years (SD: 9) underwent PSC. Patient and tumor characteristics are shown in Table 1. Before PSC, 42 (23%) patients received neoadjuvant chemotherapy. Histological examination of PSC specimens revealed ypT0 in 35 (19%) patients. Patients treated at the NCI-AVL had relatively higher cT and cN classifications than patients treated at the IMM, and relatively more often received perioperative chemotherapy and/or radiotherapy (Table 1). Likewise, the NCI-AVL cohort contained more pN+ BCs than the IMM cohort (Table 1).

Positive surgical margins were found in ten (5.4%) patients, of whom seven (3.8%) had positive urethral margins (all were NCI-AVL patients, Table 1). These urethral margins were all positive for carcinoma in situ (CIS) and none of these patients had undergone urethral frozen sections intraoperatively.

Survival

Median follow-up was 7.5 years (IQR 5.6-10.8 years). In total, 69 of 185 patients (37.3%) died, of whom 53 (28.6%) died of BC. Five-year overall survival (OS) was 70.6% (95% confidence interval (CI), 64.1-77.8) for the entire cohort and 74.2% (95% CI 67.2-81.9) for those with ≤cT2N0 BC (n=149). Furthermore, 5-year OS according to pathologic stage was 78.8% (95% CI 71.6-86.8) for those with ≤pT2N0 BC (n=123) and 53.7% (95% CI 42.2-68.3) for those with >pT2N0 BC (n=62). Cumulative 5-year incidence of bladder cancer death, overall recurrence and local recurrence by clinical and pathologic stage are shown in Table 2A and Table 2B, respectively. Three cancer related deaths were within three months follow-up. Two were caused by postoperative complications (one pulmonary embolism, one pneumonia), and one patient died of unknown cause. The Kaplan-Meier curve of OS for the entire cohort is shown in Figure 2. The cumulative incidences of bladder cancer death, overall recurrence and local recurrence are shown in Figure 3.

Recurrence

In total, 64 patients (34.6%) had recurrent BC. Median time to recurrence was 12.3 months (IQR 7.1-35.9). Of the 64 patients with recurrent disease, 41 (64.0%) had a recurrence within two years. The site of recurrence was distant in 44 patients (M+, 23.8%), loco-regional in 12 (local or N+, 6.5%) and 8 patients (4.3%) had concurrent distant and loco-regional recurrence. There was no difference in loco-regional recurrences between the NCI-AVL and IMM (6.6% vs 6.3%, p=0.935, Table 3).

Two patients (1.1%), both treated at the NCI-AVL, presented with a recurrence in the PU. One patient with pTis-Ta at PSC presented with CIS in the PU at 41 months follow-up. He was treated with transurethral resection followed by BCG instillations and has had no further recurrence eight years after surgery.

Table 1. Baseline patient and tumor characteristics

		Total N=185	NCI-AVL N=122	IMM N=63	p-value
Mean age in years (SD)		57 (9)	56 (8)	60 (10)	0.001
		n (%)	n (%)	n (%)	
cT stage	**≤cT1**	44 (23.8)	32 (26.2)	12 (19.0)	0.003
	cT2	122 (65.9)	72 (59.0)	50 (79.4)	
	cT3	19 (10.3)	18 (14.8)	1 (1.6)	
cN stage	**cN0**	161 (87.0)	98 (80.3)	63 (100)	<0.001
	cN1	10 (5.4)	10 (8.2)	0 (-)	
	cN2-3	14 (7.6)	14 (11.5)	0 (-)	
Chemotherapy	**Neoadjuvant**	42 (22.7)	25 (20.5)	17 (27.0)	0.117
	Adjuvant	7 (3.8)	7 (5.7)	0 (-)	
	None	136 (73.5)	90 (73.8)	46 (73.0)	
Perioperative Radiotherapy	**Yes**	26 (89.9)	26 (21.3)	0 (-)	<0.001
	No	158 (14.1)	96 (78.7)	63 (100)	
pT stage	**pT0**	35 (18.9)	22 (18.0)	13 (20.6)	0.576
	pT1/a/is	44 (23.8)	27 (22.1)	17 (27.0)	
	pT2	64 (34.6)	45 (36.9)	19 (30.2)	
	pT3	41 (22.2)	28 (23.0)	13 (20.6)	
	pT4	1 (0.5)	0 (-)	1 (1.6)	
pN stage	**pN0**	150 (81.1)	90 (73.8)	60 (95.2)	<0.001
	pN1	14 (7.6)	12 (9.8)	2 (3.2)	
	pN2-3	21 (11.4)	20 (16.4)	1 (1.6)	
Surgical margins	**Positive**				0.045
	Ureter(s)	1 (0.5)	1 (0.8)	0 (-)	
	Urethra	7 (3.8)	7 (3.8)	0 (-)	
	Soft tissue	2 (1.1)	0 (-)	2 (3.2)	
	Negative	175 (94.6)	114 (61.6)	61 (96.8)	

Abbreviations: IMM Institute Mutualiste Montsouris; NCI-AVL Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital; SD standard deviation

The other patient, initially treated for locally advanced disease (pT3aN2), had a recurrence in the PU together with a pelvic lymph node metastasis. He received palliative chemotherapy and subsequently progressed. He received palliative external beam radiotherapy (1x8 Gy) for multiple metastatic bone lesions and died of metastatic BC two years after surgery.

Table 2A. Cumulative 5-year incidence of bladder cancer death, overall recurrence and local recurrence for the entire cohort (cTa-3N0-3) and for ≤cT2N0 bladder cancer

	cTa-3N0-3 (N=185)	≤cT2N0 (N=149)
	% (95%CI)	% (95%CI)
Bladder cancer death	27.1 (20.1-33.5)	23.7 (16.2-30.5)
Overall recurrence	30.9 (23.7-37.4)	25.9 (18.3-32.8)
Local recurrence	0.097 (0.052-0.139)	0.085 (0.038-0.130)

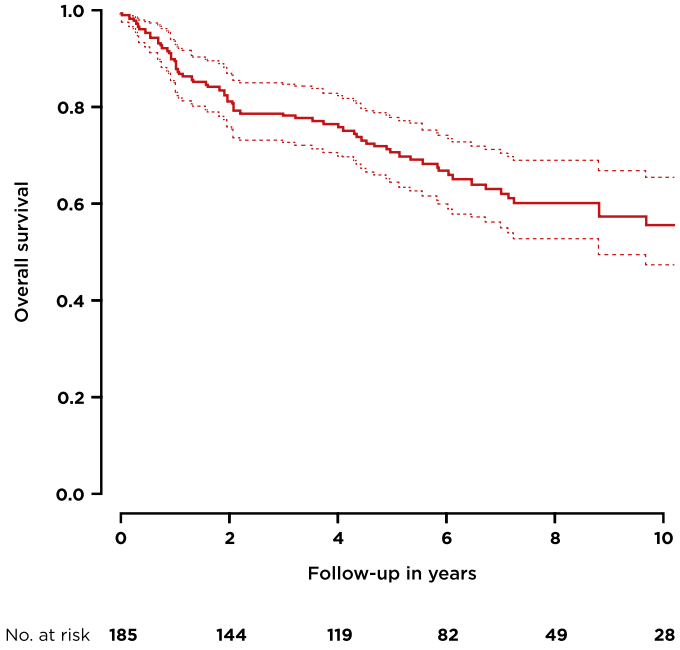
Table 2B. Cumulative 5-year incidence of bladder cancer death, overall recurrence and local recurrence for ≤pT2N0 and for >pT2N0 bladder cancer

	≤pT2N0 (N=123)	>pT2N0 (N=62)
	% (95%CI)	% (95%CI)
Bladder cancer death	18.6 (11.0-25.6)	44.6 (30.1-56.1)
Overall recurrence	20.7 (12.9-27.8)	51.5 (37.0-62.6)
Local recurrence	0.070 (0.022-0.115)	0.152 (0.055-0.239)

Prostate cancer

Six patients (3.2%) were diagnosed with prostate cancer either at PSC (n=3) or during follow-up (n=3). The incidence of prostate cancer did not differ between the NCI-AVL cohort and the IMM cohort (both n=3, Table 3). One patient, treated at the NCI-AVL, had a Gleason 7 prostate carcinoma in the surgical margins despite negative preoperative biopsies. He was followed with active surveillance and is progression-free at 9.6 years follow-up. In two patients, both treated at the IMM, prostate cancer was diagnosed during the final pathological examination of the prostate tissue, despite negative frozen section analysis. Both patients were followed with active surveillance. One of these patients died from metastatic BC at 1.9 years FU without signs of prostate cancer. The other patient was progression-free at a follow-up of 7.5 years. Three patients were diagnosed with prostate cancer at 5 months, 4, and 5 years follow-up after cystectomy, respectively. One patient died of prostate cancer 6.5 years following diagnosis, despite radiotherapy and hormonal therapy. One patient was successfully treated with brachytherapy (cancer-free follow-up 8.6 years), and one patient received active surveillance only (progression-free at 7.3 years follow-up).

Figure 2. Kaplan-Meier curve with 95%-confidence intervals of overall survival for the entire cohort (cTa-3N0M0)



Functional results

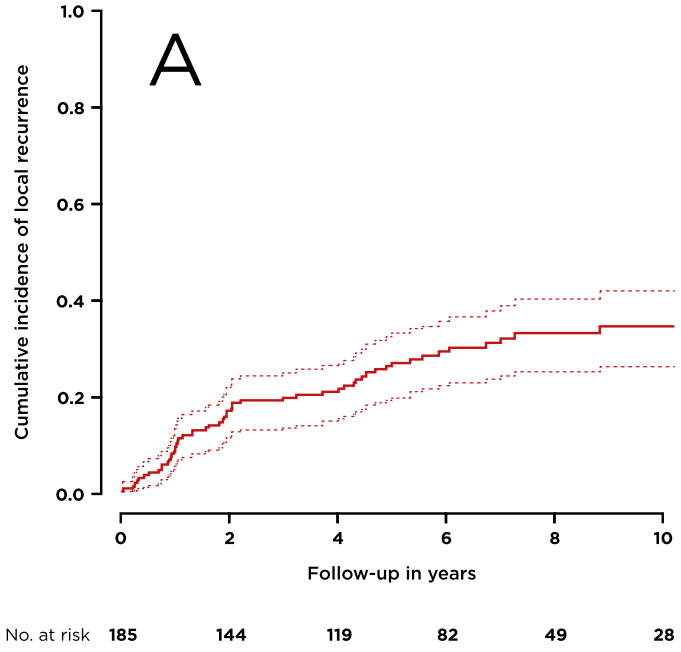
Continence and voiding function could be determined in 181 of 185 patients (97.8%). The results are displayed in Table 4. Complete to satisfactory daytime continence was achieved in 98.4% of patients (NCI-AVL 99.1% vs. IMM 96.8% p=0.273). Complete to satisfactory continence at night was achieved in 92.9% of patients (NCI-AVL 95.8% vs. IMM 87.6%, p=0.126). In total, 39 patients (21.5%) required CIC: 26 patients needed CIC because of post-void residual volume and 13 patients because they had no spontaneous voiding at all. Five NCI-AVL patients ultimately underwent transurethral resection of prostatic tissue (TURP), of whom four still needed CIC once per day. Results are shown in Table 4. In total, 136 patients (86.1%) maintained erectile function, of whom 27 (19.9%) successfully used sildenafil, and 6 patients (4.4%) used intra-cavernous injections.

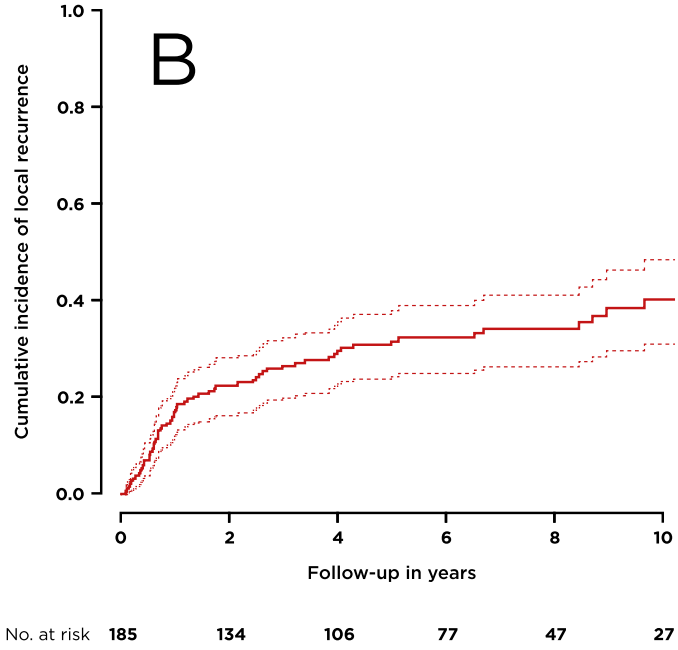
Table 3. Number of recurrences per hospital and per anatomical region, and the number of prostate cancers diagnosed following or at PSC.

	Total N=185	NCI-AVL N=122	IMM N=63	p-value
	n (%)	n (%)	n (%)	
Overall recurrence	64 (34.6)	47 (38.5)	17 (27.0)	0.118
Local recurrence	12 (6.5)	8 (6.6)	4 (6.3)	0.935
Distant recurrence	44(23.8)	32 (26.2)	12 (19.0)	0.313
Concurrent local and distant recurrence	8 (4.3)	7 (5.7)	1 (1.6)	0.184
Prostate cancer	6 (3.2)	3 (2.6)	3 (4.8)	0.409

Abbreviations: IMM Institute Mutualiste Montsouris; NCI-AVL Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital; SD standard deviation

Figure 3. Cumulative incidence curves with 95%-confidence intervals. (A) Bladder cancer death. (B) Overall recurrence. (C) Local recurrence.

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Cumulative incidence of local recurrence
1.0
0.8
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0.4
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2
4
6
8
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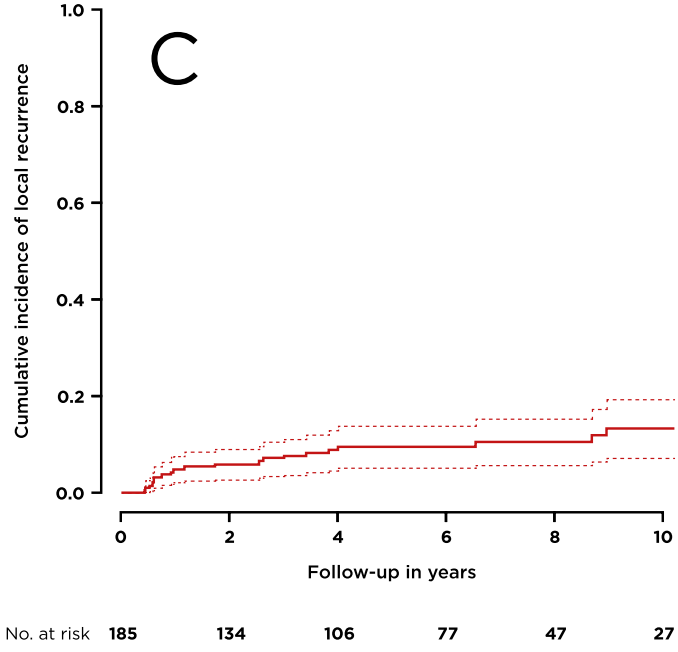
Follow-up in years
No. at risk 185 134 106 77 47 27


C
Cumulative incidence of local recurrence
1.0
0.8
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0.4
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Follow-up in years
No. at risk 185 134 106 77 47 27

Table 4. Results on urinary continence and voiding function (174 evaluable patients), and erectile function (153 evaluable patients)

	Total N=185	NCI-AVL N=122	IMM N=63	p-value
	n (%)	n (%)	n (%)	
Daytime continence				
Unknown* (early death)	4	3	1	
Complete	173 (95.6)	117 (98.3)	56 (90.3)	0.088
Satisfactory	5 (2.8)	1 (0.8)	4 (6.5)	
Poor	3 (1.7)	1 (0.8)	2 (3.3)	
Nighttime continence				
Unknown* (early death)	4	3	1	
Complete	127 (70.2)	95 (79.8)	32 (51.6)	0.003
Satisfactory	41 (22.7)	19 (16.0)	22 (36.0)	
Poor	13 (7.2)	5 (4.2)	8 (12.9)	
Need to catheterize				
Unknown* (early death)	4	3	1	
No	142 (78.5)	92 (77.3)	50 (80.6)	0.283
For post-void residual urine†	26 (14.4)	16 (13.4)	10 (16.1)	
No spontaneous voiding††	13 (7.1)	11 (9.2)	2 (3.2)	
Sexual function				
Erectile function				
Unknown*	27	24	3	
Satisfactory	136 (86.1)	83 (84.7)	53 (88.3)	0.483
Without medication	103	64	39	
With sildenafil	27	16	11	
With intra-cavernous injections	6	4	2	
Erectile dysfunction	22 (13.9)	15 (15.3)	7 (11.7)	

** Patients with unknown functional results were not included in calculation of percentages.*
† Three patients at the NCI-AVL underwent TURP, after which one could stop CIC.
†† Two patients at the NCI-AVL underwent TURP, both still need CIC because of persistent post-void residual volume.
Abbreviations: CIC clean intermittent catheterization; IMM Institute Mutualiste Montsouris; NCI-AVL Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital; TURP transurethral resection of the prostate

Discussion

Despite the positive effect on voiding and sexual function established in previous series[9], PSC remains a controversial surgical approach. The main reason for this controversy is concern regarding oncological safety. Our results show that PSC is an oncologically safe procedure and confirm the excellent functional outcomes.

In the current study, we found a 5-year OS of 70% and a 5-year cumulative recurrence incidence of 31%. These results compare favorably to those described in large series of cystoprostatectomies. In a single-center study of 1054 patients undergoing RC for BC (20% women), 5-year OS was 66% and 5-year recurrence free survival (RFS) was 68%[12]. In another single institution series of 507 patients (21% women) who underwent RC, Madersbacher et al. reported 5-year OS and RFS rates of 59% and 62%, respectively[13]. It is essential to note, however, that patients undergoing PSC are highly selected and relatively young and this hampers direct comparison to the published long-term results of cystoprostatectomy series. Evaluating survival in the subgroup of patients with stage cT2N0M0 or less, we found a 5-year CSM of 24% and a 5-year cumulative recurrence incidence of 26% respectively. In a similar cohort of patients undergoing RC for organ-confined disease, Hautmann et al. found a 5-year cancer specific survival (CSS) of 72%[14]. In the aforementioned study by Madersbacher et al., 5-year RFS for patients with ≤cT2N0 disease was 73%. Thus, with respect to clinical tumor stage, our values are comparable to those reported in the literature on RC. Additionally, in a systematic review by Hernandez et al. nine studies comparing sexuality-preserving cystectomy and RC were analyzed[9]. Local and distant recurrence rates as well as CSS and OS did not differ in any of the studies at a median follow-up of three to five years. The authors concluded that sexuality-preserving cystectomy does not compromise oncological outcome. The present study underlines these findings.

In general, the plea against PSC is based on the fear for local recurrence. The local BC recurrence rate in our study was 11%. This is similar to series of cystoprostatectomies, which report local recurrence rates ranging from 5% to 15%[1]. In other studies on PSC, local recurrence rates were 5% to 8%[15]. However, these studies often did not include patients with locally advanced and/or lymph node positive disease. In series of patients with BC who underwent standard cystoprostatectomy, the incidence of prostatic urothelial carcinoma has shown to be considerable, with reported rates between 33% and 48%[16,17]. In our study, only two patients had a recurrence in the PU. Therefore, we believe that by careful selection including either preoperative biopsies of the PU or PU frozen section analysis, prostatic involvement of urothelial carcinoma can be adequately ruled out. Our low number of PU recurrences is encouraging and proved our extensive preoperative screening to be sufficient.

Another concern if leaving the prostate in situ is the risk of occult prostate adenocarcinoma. The reported incidence of prostate cancer in patients undergoing radical cystoprostatectomy ranges from 25% to 50%[18]. Approximately half of the prostate cancers reported in these series can be considered potentially significant. Evidently, these studies are based on pathologic RC specimens of an unselected patient group with the consequent inclusion of indolent prostate

carcinoma. The prostate cancer incidence in our study was 3%, half of which was oncologically significant. Previous series on PSC reported values between 0% and 15%[9]. Again, this low incidence is the result of meticulous screening before PSC.

The aim of prostate-sparing techniques is to maintain sexual function after RC. In our study erectile function was preserved in 86% of patients. This is in accordance with the results of other PSC series, with reported preservation of erectile function in 80% to 95% of patients[9]. Importantly, these results are better than reported after nerve sparing cystectomy, where erectile function is preserved in 29% to 78%[19,20]. It should be noted that 27 patients in our cohort used sildenafil to improve erectile function. However, the fact that sildenafil was used successfully, indicates that the nervi erigentes were adequately preserved during surgery.

Preoperative screening and PSC techniques differed slightly between the NCI-AVL and the IMM: NCI-AVL patient work-up included standard prostate biopsies, whereas the IMM did not, and NCI-AVL PSC was complete prostate-sparing, whereas IMM PSC included simple adenectomy. Although resection margins were significantly more often tumor-positive at the NCI-AVL, there was no difference in the number of loco-regional recurrences (both 6%). We decided not to compare CSM because of differences in baseline characteristics. Prostate cancer incidence was slightly lower at the NCI-AVL (3% vs. 5% at the IMM), where prostate biopsies were taken irrespective of PSA measurements or findings on physical examination. This could imply that prostate biopsies should always be part of the preoperative screening before PSC as it may lower the risk of occult prostate adenocarcinoma even more.

With regard to functional results, performing a simple adenectomy (IMM) could influence postoperative continence and bladder outlet obstruction. Table 4 demonstrates significantly favourable continence results for PSC without adenectomy. However, these results should be interpreted with caution, as they could be the result of differences in follow-up interviews. Overall, complete to satisfactory day- and nighttime continence was achieved in 98% and 93%, respectively. These results confirm excellent reported outcomes in previous PSC literature[9]. Following PSC, 21% of patients required CIC because of post-void residual urine or no spontaneous micturition (7.1%). The need for CIC varies widely across PSC studies, with reported values of 1% to 75%[21,22]. It is believed that total prostate preservation, as was the case at the NCI-AVL, exposes the patient to a higher risk of obstructive complications. However, only five patients underwent TURP for bladder outlet obstruction. This is in line with the findings of Meinhardt et al., who found that, according to urodynamics, the prostate did not interfere with micturition in the majority of patients who underwent PSC[23].

This study has some limitations. Although data were collected prospectively, with robust selection criteria for PSC, analyses were done retrospectively. Another limitation is the fact that no validated questionnaires were used to assess sexual or urinary function. Because data on functional outcome were retrieved during follow-up interviews, patients might have understated their complaints. Notwithstanding the aforementioned limitations, we believe this study merits consideration since it represents the largest cohort of patients treated by PSC so far. Also, to our knowledge, our median follow-up of 7.5 years is the longest described to

date. Foremost, our study demonstrates that proper patient selection is the key in minimizing treatment aggressiveness without jeopardizing oncological outcome. In the future, this may be enhanced by novel diagnostic tools.

In conclusion, PSC represents a feasible surgical alternative to RC with superior functional results. If patients are carefully selected, oncological results are equivalent to what is reported in previous literature.

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9

Radiation with concurrent radiosensitizing capecitabine tablets and single-dose mitomycin-C for muscle-invasive bladder cancer: a convenient alternative to 5-fluorouracil

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Radiother Oncol. 2020 Aug 6;150:275-280.

Abstract

Background and purpose

Chemoradiation (CRT) with mitomycin-C (MMC) and 5-fluorouracil (5-FU) has been shown to be superior to radiation alone in patients with muscle-invasive bladder cancer (MIBC). MMC/capecitabine is an effective replacement for 5-FU as a radiosensitizer in other malignancies but has not been studied in bladder cancer. We evaluated the outcomes of MIBC patients treated with concurrent radiation and MMC/capecitabine.

Materials and Methods

MIBC patients treated with CRT (60Gy in 5 weeks with single-dose MMC and capecitabine orally twice daily) between 2014 and 2019 were identified. Acute (<90 days) and late toxicity were registered. Endpoints were clinical complete response (cCR) in the bladder assessed by cystoscopy 3 months after CRT, locoregional disease-free survival (LDFS) and the number of salvage cystectomies.

Results

We analysed 71 cT2-4aN0-2M0 MIBC patients (median age 70 years). Twenty-one (30%) patients received neoadjuvant or induction chemotherapy and 14 (20%) patients underwent a pelvic lymph node dissection prior to CRT. All patients received the full dose of planned radiation. Seven (10%) patients experienced acute grade 3-4 toxicities and 2 (3%) patients experienced late grade 3-4 toxicities. Sixty-eight (96%) patients achieved cCR. Eight (11%) patients had a bladder recurrence, of whom 3 (4%) required salvage cystectomy. Two-year LDFS was 79% (95% CI: 68-88) at a median follow-up of 23 (95% CI: 17-28) months.

Conclusion

Radiation with concurrent MMC/capecitabine is a well-tolerated bladder-sparing treatment. Severe toxicity is infrequent and locoregional tumor control and short-term disease free survival appear similar to previous studies with MMC/5-FU.

Introduction

Concurrent chemoradiation (CRT) is recognized as an alternative to radical cystectomy (RC) in selected patients with muscle-invasive bladder cancer (MIBC) by the European Association of Urology, American Urological Association, and National Comprehensive Cancer Network guidelines[1–3]. Although it is clear that CRT is superior to radiation alone[4], the ideal concurrent chemotherapy regimen has not yet been determined. No comparative radiosensitizer data for the treatment of MIBC exist and CRT is currently administered with cisplatin, mitomycin-C (MMC) plus 5-fluorouracil (5-FU), gemcitabine or tumor hypoxia-reducing drugs such as carbogen and nicotinamide[5].

The regimen using MMC and 5-FU has been shown to be superior to radiation alone in a randomized phase III trial[4]. Capecitabine is an oral prodrug that is converted to 5-FU after enzymatic metabolism in the liver. The choice of capecitabine over 5-FU is primarily based on ease of administration, avoiding hospital admission, the need for intravenous catheters and infusion pumps, and administration related complications. Numerous studies, including a large randomized controlled trial in colorectal cancer, have shown that capecitabine is comparable in terms of efficacy to 5-FU, when used as part of concurrent CRT in gastro-intestinal malignancies[6–8]. Given this ease of administration and similar efficacy to 5-FU in other cancer types, capecitabine has been used instead of 5-FU for MIBC CRT in our hospital. However, data on the toxicity and efficacy of capecitabine as part of concurrent CRT in MIBC are currently lacking. The aim of our study was to evaluate the outcomes of MIBC patients treated with radiation and concurrent MMC/capecitabine radiosensitizing chemotherapy.

Materials and Methods

Patients

This study was approved by the institutional review board of the Netherlands Cancer Institute - Antoni van Leeuwenhoek hospital (IRBd18089). Consecutive patients with MIBC (cT2-4aN0-2) who received CRT with MMC/capecitabine between January 2014 and January 2019 were retrospectively identified. Patients who were treated with palliative intent (i.e. CRT for local tumor control in patients with surgically unresectable disease), were excluded from analysis. General eligibility criteria for CRT included adequate bladder capacity and function (functional capacity ≥100cc, voiding frequency ≤1/hr); small tumor size (≤5 cm) in the absence of a palpable mass; the ability to safely perform a resection of all visible tumor with transurethral resection (TURBT); the absence of tumor-associated hydronephrosis; the absence of extensive CIS; and the absence of diffuse multifocal disease; and no previous radiation to the pelvis or lower abdomen.

Pretreatment staging

Pretreatment staging included physical examination, TURBT, laboratory studies and computed tomography (CT) of the abdomen/pelvis and chest. All patients underwent maximal TURBT prior to CRT, and no patient underwent TURBT after the initiation of CRT.

Neoadjuvant chemotherapy and pelvic lymph node dissection

Neoadjuvant or induction chemotherapy (NAIC) was considered in patients with cT3-4a BC, cTanyN+ BC, or in case of cT2 BC with high-risk histological features in the TURBT specimen (eg. lymphovascular invasion or presence of histomorphologic variants of urothelial carcinoma). NAIC consisted of 4 cycles of dose-dense methotrexate, vinblastine, doxorubicin and cisplatin in a 2-weekly schedule (day 1 methotrexate 30mg/ m2; day 2 vinblastine 3 mg/ m2, doxorubicin 30 mg/m2, cisplatin 70 mg/m2; day 3 pegfilgrastim 6 mg) or gemcitabine/ cisplatin in a 3-weekly schedule (cisplatin 70 mg/m2 day 1 and gemcitabine 1,000 mg/m2 day 1 and 8). A small subset of patients deemed unfit for cisplatin-based NAIC were treated with 4 cycles of gemcitabine/carboplatin in a 3-weekly (carboplatin 5AUC day 1 and gemcitabine 1,000 mg/m2 day 1 and 8) schedule.

Generally, NAIC was followed by pelvic lymph node dissection (PLND). If a patient with cN+ disease at initial staging did not undergo PLND, a radiologic complete response was required to proceed with CRT. PLND was performed according to a standardized anatomical template, including all lymph nodes (LN) between the genitofemoral nerve, obturator fossa, along the internal iliac artery, including the triangle of Marcille, and along the common iliac artery, up to the crossing of the ureter.

Chemoradiation

In a five-week schedule, 60 Gy radiotherapy was administered in 25 fractions of 2,4 Gy, using Volumetric modulated arc therapy (VMAT) or intensity modulated radiotherapy (IMRT). Mitomycin-C was administered intravenously on day one at a dose of 12 mg/m^2 with a maximum dose of 20 mg. Capecitabine was given twice daily at a dose of 825 mg/m^2 throughout radiotherapy, excluding weekends. Radiotherapy and capecitabine were started on the same day and capecitabine was stopped on the last day of radiotherapy. Capecitabine dose was given roughly 12h apart and within 30min after a meal, usually breakfast and dinner. The first daily dose was given approximately 1h before radiotherapy. Prior to capecitabine treatment, patients underwent DPYD genotyping to screen for dihydropyrimidine dehydrogenase (DPD) deficiency[9]. In case of DPD-deficiency, a dose reduction was applied per institutional guidelines.

Radiotherapy treatment volumes comprised the total bladder and visible tumor for multifocal bladder cancer. For solitary tumors, partial bladder radiation was applied after tumor boundary demarcation with cystoscopic lipiodol injections[10]. A library of plans (LOP) was reconstructed based on an full-bladder CT scan and empty-bladder CT scan. The clinical target volume (CTV) was expanded with 1cm to the planning target volume (PTV). For whole bladder irradiation without LOP possibility, target volume was expanded with 2.0 cm in cranial direction, 1.5 cm

in dorsal and ventral direction and 1.0 cm in other directions. For partial bladder irradiation, CTV was uniformly expanded by 1cm to PTV. Pelvic LN were not included in the radiation field.

Follow-up

Clinical response was assessed by cystoscopy (and biopsy or resection if indicated) at 3 months, followed by cystoscopic evaluation every 3 months and abdominal/pelvic CT at 6 months follow-up, followed by every 6 months. Transurethral resection was performed for tumor recurrence or in case of suspicion of tumor recurrence. Non-muscle-invasive bladder cancer (NMIBC) recurrences were treated by TURBT with or without additional intravesical chemo- or immunotherapy. MIBC recurrences were treated by salvage cystectomy (SC), provided that no systemic disease was found and patients' general condition was sufficient. Whilst SC was not systematically offered to all patients with NMIBC recurrence, patients with a high-risk tumor or failed intravesical treatment were also considered for SC.

Toxicity and Complications

Data on any chemotherapy dose reductions, treatment breaks, and treatment discontinuation were obtained by chart review. Similarly, detailed radiation therapy data was obtained, including total dose received and total number of therapy days. Radiation treatment interruptions and radiation dose reductions were recorded, and reasons for treatment interruptions were obtained from physician notes.

Acute (≤90 days from start of CRT) and late (>90 days from start of CRT) toxicities were retrospectively assigned according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0[11]. Haematologic toxicities were evaluated for the duration of treatment only. Complications following PLND and SC were registered according to the Clavien Dindo Classification of surgical complications[12].

Statistical analysis

Baseline patient characteristics, treatment details and toxicities were summarized using descriptive statistics. Median follow-up was calculated using the reverse Kaplan-Meier method. Locoregional disease-free survival (LDFS), bladder intact event-free survival (BI-EFS) and overall survival (OS) were estimated using the Kaplan-Meier method. Starting point for time-to-event analyses was the start date of CRT. LDFS was defined as the rate of survival free of recurrence in pelvic LN or bladder, with data censored at the first sign of metastasis, a second primary tumor, or death. BI-EFS was defined as the time to the first documented occurrence of any of the following events: 1) Residual/recurrent MIBC (confirmed by TURBT), 2) Nodal or distant metastases as assessed by CT and/or biopsy results, 3) Salvage cystectomy, 4) Death from any cause. A second primary malignancy was not considered an event. Additionally, the presence of NMIBC was not considered an event. BI-EFS represents a clinically relevant composite endpoint for MIBC patients receiving CRT for bladder preservation, incorporating clinical efficacy outcomes and bladder preservation. OS was defined as time-to-death (any cause). Statistical analyses were performed using IBM SPSS Statistics version 25.0 (Armonk, NY, IBM Corp.).

Results

A total of 75 patients were treated with MMC/capectabine CRT. Four patients were excluded from analysis due to cT4b (n=3) or M1 (n=1) bladder cancer. Clinicopathological and treatment characteristics of 71 included patients are shown in Table 1.

Median duration of CRT was 33 days (interquartile range (IQR) 32-35 days). All patients received the full dose of planned RT, although three (4%) patients required some RT interruptions. Reasons for RT interruptions were ileus (n=1, RT interruption 7 days) or logistics reasons not related to toxicity (n=2, RT interruption 1 day and 2 days, respectively).

Sixty-one (86%) patients completed their planned courses of capecitabine. One patient completed capecitabine after a 30% dose reduction after day 20. Seven patients (10%) experienced treatment-related grade 3-4 toxicities. These patients required discontinuation of capecitabine treatment due to trombocytopenia (n=5 after 19, 17, 16, 15 and 13 treatment days, respectively, n=3 of these patients underwent NAIC), diarrhea (n=1 after 17 treatment days) and ileus (n=1 after 17 treatment days). Two (3%) patients discontinued capecitabine after 4 and 23 days respectively, unrelated to toxicity but due to patient preferences. Late toxicity was observed in 10 (14%) patients, of whom 2 had grade 3-4 toxicities: 1 patient developed an urethral stricture requiring internal urethrotomy and 1 patient developed hydronephrosis requiring percutaneous nephrostomy. Toxicities are summarized in Table 2.

In total, 14 patients underwent a PLND prior to CRT, of whom 12 also received NAIC. Clinical stage was cTanyN1-2 (n=4), cT3-4aN0 (n=8) and cT2N0 (n=2, these patients had high-risk histological features in the TURBT specimen), respectively. One patient, clinically staged cT2N0, was staged ypN2. The remaining 13 patients were staged (y)pN0. Four out of 14 (29%) patients had complications after PLND. Three (21%) patients had infected lymphoceles, of whom 2 required drainage (Clavien 3a) and 1 required relaparotomy (Clavien 3b). One patient developed lymphedema and was treated with physiotherapy (Clavien 2).

Complete response at cystoscopy three months after CRT was achieved in 68/71 (96%) patients. One patient, initially staged cT2N0M0, had extensive residual disease and concurrent pelvic LN metastases. This patient received best supportive care and died 5 months after start of CRT. Two patients refused cystoscopy during follow-up. They are alive with no evidence of disease at 15 and 9 months follow-up, respectively.

Median follow-up was 23 (95% CI 17-28) months. LDFS, BI-EFS and OS curves are shown in Figure 1. Nineteen patients had recurrent disease after CRT. Treatment and outcome of these patients are summarized in Figure 2. NMIBC recurrences included 4 patients with Ta BC, who were treated with TURBT and BCG or mitomycin instillations (disease-free at 20, 21, 29 and 46 months follow-up respectively), 1 patient with multifocal CIS who was treated by hyperthermic intravesical chemotherapy (disease-free at 49 months follow-up), 1 patient with T1 BC who was treated with BCG instillations (disease-free at 36 months follow-up) and 2 patients with T1 BC who underwent SC. One patient had a recurrence in a pelvic LN and was treated with 6

Table 1. Clinicopathological and treatment characteristics of N=71 included patients

Age in years, median (IQR)		70 (62-76)
		n (%)
Sex	**Male**	54 (76)
	Female	17 (24)
WHO performance status	**0**	54 (76)
	1	15 (21)
	2	2 (2.8)
CCI	**0**	49 (69)
	1	13 (18)
	≥ 2	9 (13)
cTNM stage	**cT2N0M0**	43 (61)
	cT3N0M0	20 (27)
	cT4aN0M0	4 (5.6)
	cTanyN1-2M0	4 (5.6)
TURBT histology	**Urothelial carcinoma only**	58 (82)
	UC + squamous differentiation*	7 (10)
	UC + micropapillary differentiation*	3 (4.2)
	UC + glandular differentiation*	2 (2.8)
	UC + sarcomatoid differentiation*	1 (1.4)
Multifocal tumor		21 (30)
Focal concomitant CIS (adjacent to primary tumor)		12 (17)
NAIC	**Total**	21 (30)
	NAIC + PLND	12 (17)
PLND	**Total**	14 (20)
Radiotherapy	**Whole bladder**	56 (79)
	Partial bladder	15 (21)

**All patients had urothelial carcinoma as the predominant histology*
Abbreviations: CCI: Charlson comorbidity index, NAIC: Neoadjuvant or induction chemotherapy, PLND: Pelvic lymph node dissection, TURBT: Transurethral resection, UC: Urothelial carcinoma

courses induction chemotherapy followed by PLND (ypN0 but clear regressive changes in two LN, disease-free at 22 months follow-up). Nine patients developed distant metastases without a local recurrence. Finally, eight patients died of bladder cancer. None of the 4 patients with cN1-2 BC developed a recurrence with a disease-free survival at 17 to 30 months follow-up.

Table 2. Acute and late toxicities by category

	Number (%) of patients per grade		
Acute toxicity	**Grade 1-2**	**Grade 3***	**Grade 4**
Overall hightest grade	52 (73)	6 (8.5)	1 (1.4)
Genitourinary	32 (45)	2 (2.8)	-
Gastrointestinal	17 (24)	-	1 (1.4)
Haematologic	34 (48)	5 (7.0)	-
Cutaneous	5 (7.0)	-	-

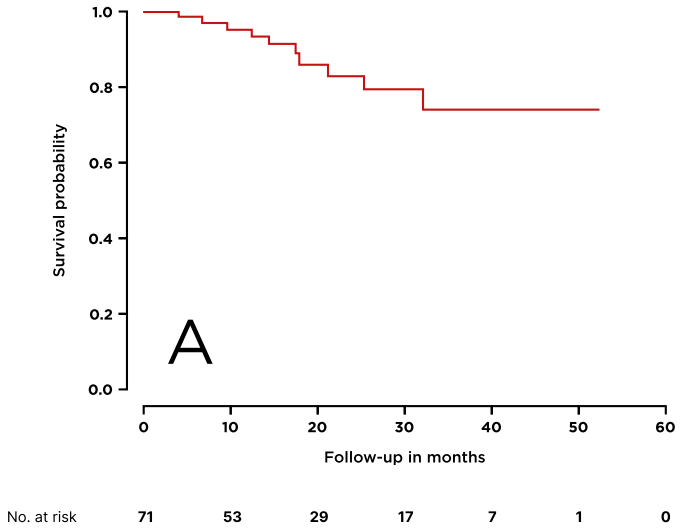
Late toxicity	**Grade 1-2**	**Grade 3**	**Grade 4**
Overall hightest grade	8 (11)	2 (2.8)	-
Genitourinary	6 (8.5)	2 (2.8)	-
Gastrointestinal	2 (2.8)	-	-
Haematologic	-	-	-
Cutaneous	-	-	-

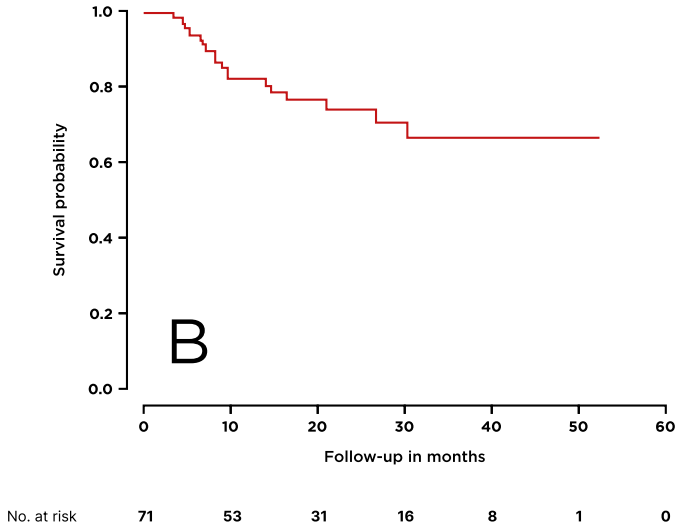
** One patient experienced two acute grade 3 genitourinary toxicities*

In total, 3 patients underwent SC and time to SC was 14, 15 and 21 months respectively. One patient was diagnosed with cT2N0 recurrence by TURBT and showed pT0N0 in the SC specimen (disease-free at 18 months follow-up). One patient had CIS in biopsies of the prostatic urethra and pT4aN0 (due to CIS in seminal vesicles) in the SC specimen (disease-free at 24 months follow-up).

Finally, one patient with a multifocal cT1N0 recurrence had pT3aN0 urothelial carcinoma with small cell component (15%) and squamous differentiation in the SC specimen. This patient developed pelvic LN metastasis 6 months after SC and died 40 months after start of CRT. Two patients experienced complications after SC: 1 patient developed a neobladder vaginal fistula requiring surgical correction (Clavien 3b) and 1 patient developed a severe ileus temporarily requiring total parenteral nutrition (Clavien 2). No patients experienced ureteral strictures or urinary leakage after SC.

Figure 1. (A) Locoregional disease-free survival, (B) Bladder-intact event-free survival and (C) Overall survival following chemoradiation (n=71). At 2 years follow-up, the locoregional disease-free proportion was 79% (95% CI: 68-88), the bladder-intact event-free proportion was 74% (95% CI 62-83) and the overall survival was 85% (95% CI: 73-91).





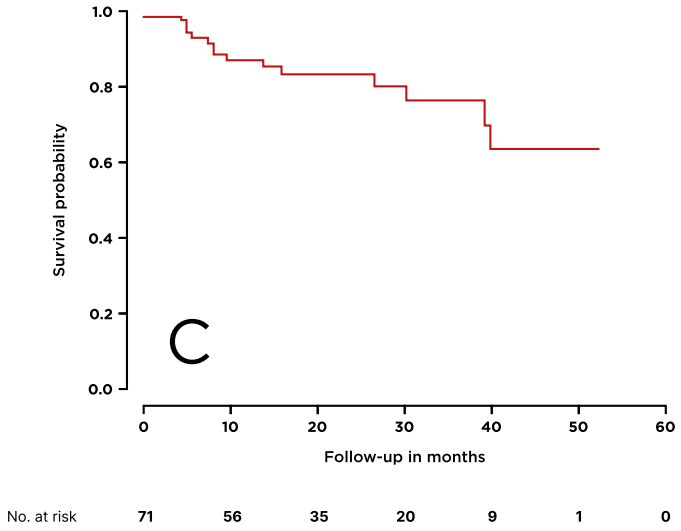
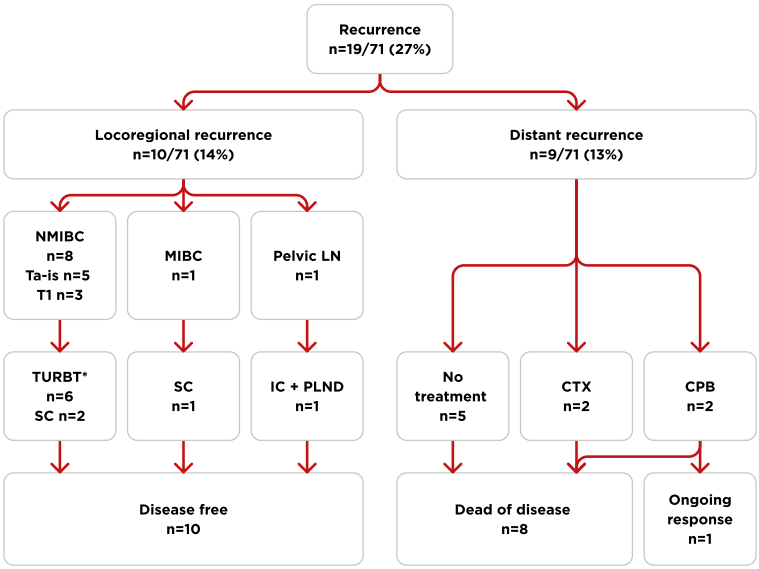


Figure 2. Treatment and outcome of recurrences after chemoradiation.



*Abbreviations: CPB: checkpoint blockade, CTx: chemotherapy, IC: induction chemotherapy, LN: lymph nodes MIBC: Muscle-invasive bladder cancer, NMIBC: Non-muscle-invasive bladder cancer, PLND: pelvic lymph node dissection, SC: salvage cystectomy, TURBT: transurethral resection. *followed by mitomycin, hyperthermic intravesical mitomycin or Bacillus Calmette-Guérin instillations.*

Discussion

In this retrospective study we evaluated a bladder-sparing approach that used concurrent MMC/capecitabine and radiation in patients with MIBC. We report a complete response rate of 96% at cystoscopy after three months follow-up, a 2-year local disease-free survival of 79%, and a 2-year bladder-intact event-free survival of 74%. Acute grade 3-4 toxicities occurred in 10% of patients. This suggests that capecitabine is a reasonable alternative to 5-FU, with the advantage of oral administration and possibly less toxicity.

Comparisons between a randomized trial (such as James et al.) and a retrospective study are problematic for several reasons. Still, the randomized trial by James et al. using MMC and 5-FU, can be seen as a benchmark for MIBC CRT treatment[4]. Median age, distribution of clinical stages and the proportion of patients undergoing NAIC in our study were comparable to those in the study by James et al. However, there were also some important differences. For example, in our study a PLND was performed in selected patients (n=14). Compared to James et al., we observed less acute grade 3-4 toxicities (10% vs. 36%). The difference in acute toxicity may be explained by the fact that reporting is more accurate in clinical trials. Nevertheless, these results are in line with studies comparing capecitabine versus 5-FU use in other malignancies such as colorectal cancer and anal cancer[6-8,13]. James et al. report a 2-year LDFS of 67% after a median follow-up of 69 months[4]. Two-year LDFS was 79% in our study, but our relatively short median follow-up of 23 months and differences in patient and treatment characteristics limit any direct comparison.

Although the results of the benchmark trial by James et al. established 5-FU and MMC as a viable alternative to cisplatin-based regimens, the latter are still frequently applied. The CR rate in our study (96%) compares favourably to previous studies on cisplatin-based regimens. In a retrospective analysis of 475 MIBC patients treated at the Massachusetts General Hospital and enrolled on prospective institutional or Radiation Therapy Oncology Group cisplatin-based protocols, CR rates varied from 66% to 88%[18]. Data on the efficacy and toxicity of capecitabine if used as a radiosensitizing component in combination with MMC in CRT for bladder cancer are sparse. Two small single-center studies describe the use of capecitabine monotherapy without MMC in an elderly patient population[14,15]. Patel et al. report an overall response rate of 85% in a cohort of 14 patients (median age 80 years) ineligible for platinum-based chemotherapy[14]. Twenty-nine percent of the patients required dose modification due to grade 3 toxicities. Similarly, Leng et al. report high local control rates (80% at 2 years) but also high numbers of grade 3 toxicities (64%) in 11 patients (median age 80 years)[15]. Although capecitabine was combined with MMC in our study, grade 3-4 toxicity rates in our study were much lower (10%). This may be explained by the lower age (median age 70 years) and better performance status (76% WHO 0) of the patients in our study. Importantly, our study is the first study evaluating the combination of MMC/capecitabine in MIBC patients.

In this analysis, 30% of patients underwent NAIC. The role for NAIC in the context of CRT remains unclear. Whereas neoadjuvant chemotherapy has a proven survival benefit in patients with MIBC treated with RC or radiotherapy[16,17], CRT studies have failed to demonstrate

improvements in either disease-specific survival or OS[18]. Similarly, the value of a PLND has not been established in CRT. In MIBC patients undergoing RC, PLND is a standard diagnostic staging procedure, but controversy exists regarding its therapeutic value[19]. Our retrospective analysis describes institutional practice regarding PLND and conclusions regarding therapeutic contribution cannot be drawn. Out of fourteen patients undergoing a diagnostic PLND, only one had LN metastases in the PLND specimen. This low number of LN metastasis is likely due to the use of NAIC in twelve of these fourteen patients. In our series PLND showed a high complication rate (29% Clavien grade 3 toxicity), comparable to a previous study[20]. PLND was complicated by symptomatic lymphoceles in 21% of patients. The high rate of lymphoceles might be the result of encapsulation by an intact retroperitoneal border following PLND only, opposed to intraperitoneal drainage and reabsorption following RC with PLND.

Recent advances in the molecular understanding of MIBC have led to the discovery of molecular biomarkers associated with patient outcomes after bladder preservation therapy[21,22]. In the future, these biomarkers may aid the selection of patients who will benefit most from CRT. Also, instead of refining the CRT component, bladder preservation trials are now focusing on incorporating immunotherapy into the treatment regimen. Phase III randomized trials of concurrent CRT with or without the addition of atezolizumab [ClinicalTrials.gov identifier: NCT03775265] or pembrolizumab [ClinicalTrials.gov identifier: NCT04241185] are currently recruiting.

This is the first study evaluating the combination of MMC/capecitabine in MIBC patients. We acknowledge that a longer follow-up is required to draw definitive conclusions regarding survival and recurrence outcomes. Also, the retrospective assessment of toxicities by chart review may have caused an underreporting of toxicity. Ultimately, comparative studies are needed to compare capecitabine to other radiosensitizers. Quality of life outcome measurements should be involved in the analysis of the different regimens as well.

In conclusion, radiation with concurrent MMC and orally administered capecitabine is a well-tolerated bladder-sparing treatment. Severe toxicity is infrequent and locoregional tumorcontrol and disease free survival appear similar to previous studies with MMC/5-FU.

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10

Long-term survival and complications following bladder-preserving brachytherapy in patients with cT1-T2 bladder cancer

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Radiother Oncol. 2019 Dec;141:130-136.

Abstract

Background and purpose

Radical cystectomy (RC) is considered standard treatment for muscle-invasive bladder cancer (BC) and high-risk non-muscle invasive BC. In selected cases, bladder-sparing treatment using brachytherapy can be offered. We examined the outcome after brachytherapy in comparison to RC in terms of survival, complications and bladder preservation in patients with cT1G3-T2N0M0 BC.

Materials and Methods

Between 1988-2016, 301 patients underwent brachytherapy in two centres. Overall survival (OS) and disease specific survival (DSS) after brachytherapy and RC were assessed using Kaplan-Meier curves. Cox proportional hazards modelling was used to determine variables associated with OS and DSS. Local recurrences, bladder preservation and salvage cystectomy (SC) after brachytherapy were reported. Complications after brachytherapy, RC and SC were compared using CTCAE criteria.

Results

Median follow-up was 9.6 years (95% confidence interval (CI): 8.8-10.4) after brachytherapy and 10.6 years (95% CI: 10.0-11.2) after RC. Five/10-year OS was 66%/49% after brachytherapy and 68%/53% after RC (p=0.4). Five/10-year DSS was 73%/67% after brachytherapy and 75%/65% after RC (p=0.8). Intravesical recurrence occurred in 58/259 brachytherapy patients after which salvage cystectomy was performed in 32 patients. In total, 84% of brachytherapy-treated patients preserved their bladder. The brachytherapy cohort experienced less high grade complications than the RC cohort (p=0.02).

Conclusion

In selected patients with solitary, ≤5cm cT1G3-T2N0M0 bladder tumours brachytherapy is a bladder-sparing therapy with good survival outcome and with a favourable complication rate compared to RC.

Introduction

Radical cystectomy (RC) is still considered standard of treatment for patients with non-metastatic muscle-invasive bladder cancer (MIBC) and high-risk non-muscle-invasive bladder cancer (NMIBC) refractory to intravesical therapy in most countries[1]. However, RC has significant morbidity and mortality[2].

In an effort to preserve the bladder, alternative treatment strategies have been developed. Trimodal therapy (TMT), comprising transurethral resection of the tumour (TURBT), followed by concurrent chemoradiation has been recognized as an alternative to RC for select patients in several international guidelines[1,3]. Another bladder preservation strategy includes a combination of TURBT, low-dose external beam radiation (EBRT) and brachytherapy. According to Dutch guidelines, this combination can be offered to patients with solitary cT1G3/T2G1-3, ≤5 cm, cN0M0 bladder cancer (BC) as a bladder-sparing alternative to RC[4–6]. However, despite promising results achieved with brachytherapy, its use remains controversial[7]. The main concern is long-term oncological safety and late toxicity.

Given the lack of prospective studies comparing brachytherapy to RC, we performed an observational study to examine outcome in terms of survival, complications and bladder preservation of brachytherapy for cT1G3-T2N0M0 BC. In addition, we compared survival and complications of patients treated with brachytherapy with a matched population of patients treated with RC for cT1G3-T2N0M0 BC.

Materials and Methods

We retrospectively analysed patients who underwent brachytherapy or RC for cT1G3-T2 BC between 1988 and 2016 in two hospitals in Amsterdam: the Netherlands Cancer Institute (NCI-AVL) and the Amsterdam UMC Vrije Universiteit Amsterdam (VUMC). In the NCI-AVL, patients were identified from a prospectively maintained institutional BC database. In the VUMC, patients treated with brachytherapy were retrospectively identified. Patients with non-urothelial histology were excluded from analysis. Previously, the outcomes of two smaller series with a shorter follow-up were described by Nieuwenhuijzen et al. (n=108)[8] and Bosschieter et al. (n=26)[9]. We now present the results of a larger cohort with a median follow-up of 10 years.

Brachytherapy

Selection criteria for brachytherapy are shown in Table 1. Diagnosis and staging consisted of TURBT and computed tomography (CT) of the chest/abdomen/pelvis. Tumour size was estimated at cystoscopy. All patients underwent EBRT (15-20 x 2 Gy) prior to brachytherapy catheter insertion to prevent tumour cell seeding[10]. The clinical target volume included only the bladder. Up to two weeks after EBRT, the flexible plastic tubes for afterloading interstitial radiation therapy were inserted. Either an open retropubic approach or a robot-assisted

laparoscopic (RAL) approach was used as previously described[9]. In brief, 3 to 4 brachytherapy catheters were inserted through the bladder wall at the tumour area with a minimal bilateral 5mm margin from the tumour/scar. Entry and exit sites into the bladder were marked with metal clips. In case of a RAL-approach, the tumour area was identified by simultaneous cystoscopy. In some cases, the insertion of brachytherapy catheters was combined with partial cystectomy (PC) of the tumour/scar.

In the VUMC, a pelvic lymph node dissection (LND) was routinely performed. In the NCI-AVL, a limited LND was performed in case of suspicion of lymph node metastasis (LNM) during surgery. In case of proven LNM at pathology, adjuvant chemotherapy was considered. Afterloading therapy for VUMC patients consisted of pulsed-dose rate (PDR) brachytherapy in the Academic Medical Center (29 x 1.04 Gy, Paris-system dosimetry)[11]. In the NCI-AVL, patients were treated with 40 Gy low-dose rate brachytherapy until 2003. From 2003 onwards, either high-dose rate (10 x 2.5 Gy) or PDR (29 x 1.02 Gy) brachytherapy was used. These radiation schedules are considered radiobiologically equivalent.

Table 1. Selection criteria for brachytherapy

Solitary tumour with a maximum diameter of 5 cm
Clinical stage T1-T2
No concomitant carcinoma in situ elsewhere in the bladder
Tumour not located in the bladder neck or the prostatic urethra in male patients
No distant metastasis (N0M0)

Radical cystectomy

Diagnosis and staging before RC was similar to diagnosis and staging before brachytherapy. All RC patients underwent PLND. None of the patients were treated with neoadjuvant chemotherapy. Adjuvant chemotherapy was considered in case of pN+ disease. In order to create more comparable groups in terms of estimated risk of recurrence and survival, we excluded patients who underwent RC instead of brachytherapy for oncological reasons (i.e. multiple tumours, tumour size >5cm or concomitant CIS). Patients who underwent RC instead of brachytherapy due to impaired bladder capacity, patient's preference or due to a tumour location unsuitable for brachytherapy (i.e. tumour located in the bladder neck or the prostatic urethra) were included in the RC cohort.

Follow-up and salvage treatment

Follow-up included a yearly CT-abdomen/pelvis and chest X-ray for both patient groups. Follow-up after brachytherapy also included cystoscopy with urine cytology at 3-monthly intervals for the first 2 years and 6-monthly intervals thereafter. Bladder function after brachytherapy was assessed by interviews. Transurethral resection was performed when in doubt of tumour recurrence. NMIBC recurrences were treated by TUR with or without additional intravesical chemo- or immunotherapy. MIBC recurrences were treated by salvage

cystectomy (SC), provided that no systemic disease was found and general condition was sufficient. Whilst SC was not systematically offered to all patients with NMIBC recurrence, patients with a high-risk tumour or failed intravesical treatment were also considered for SC.

Complications

Acute (≤90 days) and late (>90 days) complications after brachytherapy, RC and SC were retrospectively assigned according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0[12].

Statistical analysis

Median follow-up was calculated using the reverse Kaplan-Meier method. Bladder recurrence after brachytherapy was defined as a lesion in the bladder confirmed by histological evaluation. Pelvic LN recurrences and pelvic soft tissue recurrences after brachytherapy were separately reported. Local recurrence after RC was defined as recurrence in soft tissue in the true pelvis. Kaplan-Meier curves for overall survival (OS), disease-specific survival (DSS) after brachytherapy and RC were constructed and compared using the log-rank test. Starting point for time-to-event analyses was the implantation date of brachytherapy catheters or date of RC. OS was defined as time-to-death (any cause). DSS was defined as time-to-death due to BC or treatment related death. A multivariable Cox proportional-hazard model was used to evaluate potential prognostic factors for OS and DSS. Statistical analyses were performed using IBM SPSS Statistics version 25.0 (Armonk, NY, IBM Corp.). Tests were two-sided and the significance level was set at 0.05.

Results

In total, 301 patients underwent brachytherapy (NCI-AVL n=294, VUMC n=7) between 1988 and 2016. Patients with variant histology (n=9) and patients with urachal adenocarcinoma (n=26) and patients with cN+ (n=7) were excluded, leaving a total of 259 evaluable brachytherapy patients. Baseline characteristics are shown in Table 2. An open and a robot-assisted laparoscopic approach was used in 91% (235/259) and 9.3% (24/259) of patients, respectively. PC was performed in 32/259 (12%) of patients. Reasons for PC were: tumour in a diverticulum (n=10, 31%), tumour in the bladder dome (n=11, 34%), residual macroscopic tumour after TURBT (n=6, 19%) and concurrent ureteral reimplantation (n=2, 6.2%). In three patients (9.4%), the reason for PC was not recorded. In total, 16/259 patients (6.2%) underwent ureteral reimplantation, because the tumor was close to the ureteral orifice and resection was performed. LND was performed in 32/259 (12%) brachytherapy patients. Seven patients underwent elective LND (VUMC) and 23 patients underwent LND due to suspicious LN during surgery. Additionally, one patient underwent LND as a staging procedure in the referring hospital and one patient insisted on undergoing LND. Six out of 32 (19%) patients had LNM proven at pathology. These patients all had suspicious LN during surgery. Two of these 6 patients with LNM received adjuvant chemotherapy.

Table 2. Baseline patient and tumour characteristics

		Brachytherapy	RC	P-value
Total number of patients		259	60	
Median age in years (IQR)		64 (55-72)	60 (54-67)	0.11
		n (%)	**n (%)**	
Sex	**Male**	199 (76.8)	42 (70.0)	0.32
	Female	60 (23.2)	18 (30.0)	
cT stage	**cT1**	26 (10.0)	6 (10.0)	1
	cT2	233 (90.0)	54 (90.0)	
Grade	**G2**	17 (6.6)	4 (6.7)	1
	G3	242 (93.4)	56 (93.3)	
Histology	**Urothelial carcinoma**	249 (96.1)	56 (93.3)	0.62
	+ squamous cell diff.	7 (2.6)	3 (5.0)	
	+ glandular diff.	3 (1.1)	1 (1.7)	
Tumour diameter	**<3 cm**	133 (51.4)	13 (21.7)	0.006*
	3-5 cm	97 (37.5)	26 (43.3)	
	Unknown	29 (11.2)	21 (35.0)	
Prior recurrence rate	**Primary**	232 (89.6)	44 (73.3)	2
	Recurrence	27 (10.4)	16 (26.7)	
pN stage	**pN0**	26 (81.3)	55 (91.7)	0.2**
	pN1-3	6 (18.8)	5 (8.3)	
	pNx	227	0	

Abbreviations: Diff.: differentiation, IQR: interquartile range, RC: radical cystectomy
**Excluding patients with unknown tumour size*
***Excluding patients with pNx*

Between 1988 and 2016 914 patients underwent RC for BC in the NCI-AVL, of whom 227 underwent RC for cT1G3-T2N0M0 BC. These patients were no candidates for brachytherapy for the following reasons: multiple tumours (n= 135, 59%) tumour size >5cm (n=16, 7.0%), concomitant CIS (n=16, 7.0%), tumour location unsuitable for brachytherapy (n=27, 12%), impaired bladder capacity (n=6, 2.6%) and patients' preference (n=5, 2.2%). In 22 (9.7%) patients the reason for RC instead of brachytherapy was not recorded. Patients who underwent RC instead of brachytherapy for oncological reasons (multiplicity, tumour size >5cm and/or CIS,) were excluded (n=167), leaving a total of 60 RC patients for comparison to the brachytherapy cohort. Baseline characteristics of RC patients are also shown in Table 2. Five out of 60 (8.3%)

patients had LNM at pathology, of whom one received adjuvant chemotherapy. In the RC group, the majority of tumours (43%) were 3-5 cm, while in the brachytherapy group the majority of tumours (51%) were <3cm (p=0.006). In the RC group, more patients had a history of NMIBC (27% vs 10% in the brachytherapy group, p=0.002).

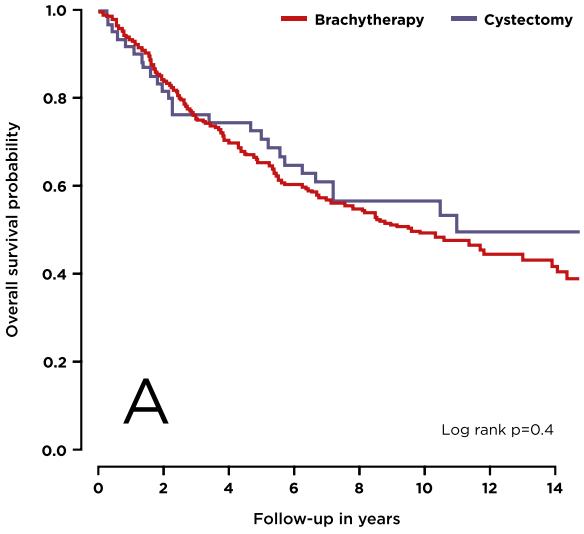
Median follow-up was 9.6 years (95% confidence interval (CI): 8.8-10.4) after brachytherapy and 10.6 years (95%CI: 10.0-11.2) after RC. A total of 129/259 and 27/60 patients died in the brachytherapy and RC group, respectively. Kaplan-Meier curves of OS and DSS are shown in Figure 1. Five/10-year OS after brachytherapy was 66% (95%CI: 59-71) and 49% (95%CI: 43-57), 5/10-year OS after RC was 68% (95%CI: 61-73) and 53% (95%CI: 48-59; p=0.4). Five/10-year DSS after brachytherapy was 73% (95%CI: 67-77) and 67% (95%CI: 60-73), 5/10-year DSS after RC was 75% (95%CI: 66-78) and 65% (95%CI: 58-72; p=0.8). Uni- and multivariable analyses for OS and DSS are shown in Table 3. No prognostic factors for OS and DSS were found.

In total, 105/259 patients had recurrent BC after brachytherapy versus 19/60 patients after RC (Supplementary Table 1). Median time to recurrence was 1.6 years (IQR 0.8-3.1, range 0.1-17.2 years) after brachytherapy and 1.1 years (IQR 0.5-2.9, range 0.2-5.2 years) after RC. Of the patients who developed a recurrence after brachytherapy, the recurrence site was soft tissue in the true pelvis in 2/105 (1.9%), pelvic LN in 4/105 (3.8%), distant in 41/105 (39%) and the bladder in 58/105 (55%) patients (Supplementary Table 1). All patients with pelvic LN recurrence (n=4) underwent palliative chemotherapy and died due to metastatic disease after a median of 8 months (range 1.1-23 months).

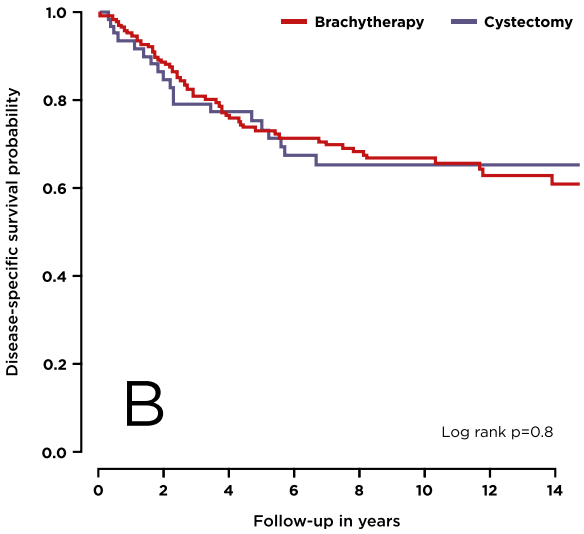
Treatment and outcome of bladder recurrence after brachytherapy are summarized in Figure 2. Bladder recurrences (n=58) occurred after a median follow-up of 1.9 years (IQR 0.22-3.7 years, range 0.22-17.1 years). Seventeen out of 58 (29%) bladder recurrences were true infield recurrences and 22/58 (38%) were located elsewhere in the bladder. In 19/58 (33%) patients, it was unknown whether the tumour was a true infield recurrence. In 25/58 (43%) patients the recurrence was NMIBC and in 33/58 (57%) MIBC. Thirty-two patients underwent SC (24 for MIBC and 8 for NMIBC). Five out of 32 patients underwent SC with palliative intent. In these cases secondary local control could not be achieved. Three more patients did not achieve secondary local control due to a recurrence in the surgical bed after SC. Four patients developed a local (i.e. soft tissue in the true pelvis) recurrence after RC and 15 patients developed distant metastasis (Supplementary Table 1). These patients were all treated with palliative intent.

The bladder was preserved in 217/259 (84%) of brachytherapy patients. Thirty-two patients underwent SC and 10 patients underwent cystectomy because of a small non-compliant bladder.

Figure 1. Kaplan-Meier curves showing (A) overall survival and (B) disease-specific survival for patients treated with brachytherapy (n=259) versus radical cystectomy (n=60).

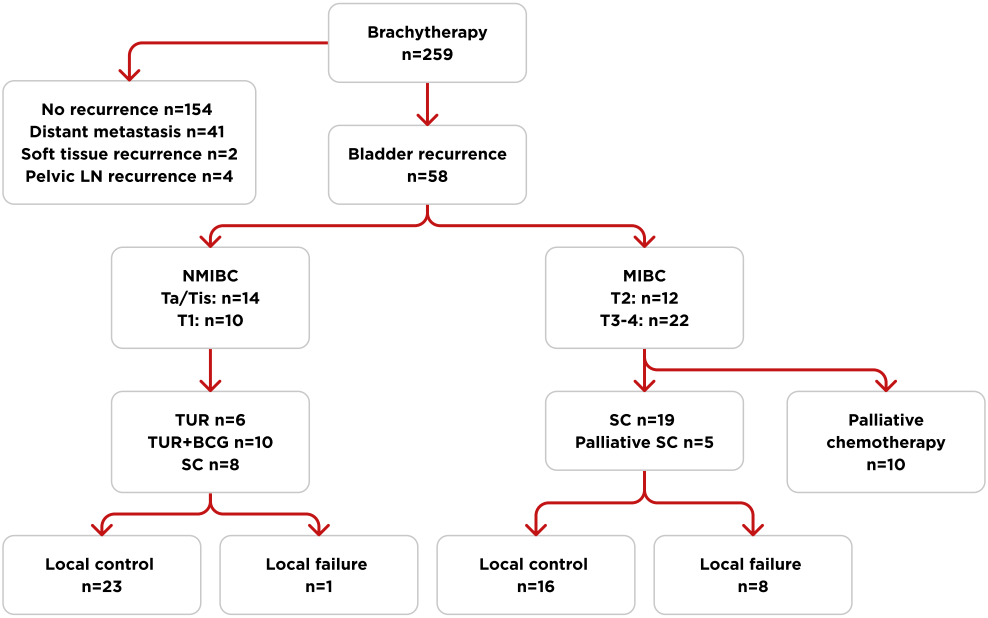


Number at risk								
Brachytherapy	259	201	154	114	91	58	42	29
Cystectomy	60	46	38	32	26	20	8	5



Number at risk								
Brachytherapy	259	201	154	114	91	58	42	29
Cystectomy	60	46	38	32	26	20	8	5

Figure 2. Bladder recurrence and local control after salvage treatment in brachytherapy patients.



Complications are listed in Table 4. Early (≤90 days) complications occurred in 12% (32/259) of the brachytherapy patients, whereas after RC early complications occurred in 40% (24/60) of patients ($p<0.001$). Late (>90 days) complication rates were similar after brachytherapy and RC (18% vs 17%, $p=0.8$). After RC, all late complications were grade 3-4 (10/10, 100%); whilst after brachytherapy, 63% (29/46) of late complications were grade 3-4 ($p=0.02$). Mortality ≤90 days was 1.7% after RC (n=1, sepsis) and 0.4% (n=1, myocardial infarction) after brachytherapy. After SC, early and late complications occurred in 31% (10/32) and 22% (7/32) of patients, respectively. One patient died within 90 days after SC due to kidney insufficiency.

Table 3. Cox proportional hazard analysis for overall survival and disease-specific survival

Overall survival		Univariable			Multivariable		
		HR	95% CI	p-value	HR	95% CI	p-value
Age (continuous)			1.02-1.05	<0.001	1.03	1.02-1.05	<0.001
Sex	**Male**	1			1		
	Female	0.90	0.61-1.31	0.6	1.05	0.71-1.56	0.8
cT stage	**T1**	1			1		
	T2	1.24	0.74-2.08	0.4	1.26	0.75-2.14	0.4
Grade	**G2**	1			1		
	G3	1.29	0.71-2.34	0.4	1.35	0.73-2.47	0.3
Tumour diameter	**<3cm**	1			1		
	3-5cm	1.38	0.98-1.93	0.07	1.39	0.98-1.97	0.06
	Unknown	1.01	0.61-1.65	0.7	1.07	0.63-1.83	0.6
Prior recurrence rate	**Primary**	1			1		
	Recurrence	1.03	0.66-1.61	0.9	1.07	0.63-1.74	0.7
Treatment	**RC**	1			1		
	Brachytherapy	1.17	0.77-1.77	0.5	1.17	0.75-1.81	0.5

Disease-specific survival		Univariable			Multivariable		
		HR	95% CI	p-value	HR	95% CI	p-value
Age (continuous)		1.01	0.99-1.02	0.6	1.01	0.99-1.03	0.5
Sex	**Male**	1			1		
	Female	1.17	0.75-1.84	0.5	1.20	0.75-1.92	0.4
cT stage	**T1**	1			1		
	T2	1.49	0.72-3.07	0.3	1.47	0.70-3.08	0.3
Grade	**G2**	1			1		
	G3	2.20	0.80-6.00	0.12	2.23	0.81-6.14	0.12
Tumour diameter	**<3cm**	1					
	3-5cm	1.37	0.88-2.11	0.15	1.35	0.87-2.11	0.2
	Unknown	1.13	0.65-1.74	0.7	1.20	0.63-2.30	0.6
Prior recurrence rate	**Primary**	1			1		
	Recurrence	0.96	0.54-1.74	0.9	1.08	0.59-1.99	0.8
Treatment	**RC**	1			1		
	Brachytherapy	0.92	0.56-1.50	0.7	0.98	0.58-1.67	0.9

Abbreviations: CI: Confidence interval, HR: Hazard ratio, RC: radical cystectomy

Table 4. Complications after brachytherapy, radical cystectomy and salvage cystectomy determined according to the Common Terminology Criteria for Adverse Events (CTCAE)

	Brachytherapy N=259	RC N=60	SC N=32
	n (%)	**n (%)**	**n (%)**
Complication rate ≤90 days	32 (12)	24 (40)	10 (31)
Complication rate >90 days	46 (18)	10 (17)	7 (22)
Grade 1-2 complications ≤90 days			
Ileus	1 (0.4)	4 (6.7)	-
Urinary tract infection	3 (1.2)	1 (1.7)	1 (3.1)
Wound infection	2 (0.7)	-	-
Abdominal abscess	2 (0.7)	-	-
Pneumonia	-	1 (1.7)	-
Bladder spasms	1 (0.4)	-	-
Delirium	1 (0.4)	-	-
Hematuria	1 (0.4)	-	-
Grade 3-4 complications ≤90 days			
Fascial dehiscence	-	4 (6.7)	1 (3.1)
Ureteric anastomotic leak	1 (0.4)	3 (5.0)	1 (3.1)
Infected lymphocele	3 (1.2)	1 (1.7)	-
Dislocated brachytherapy catheter	3 (1.2)	-	-
Hematuria	2 (0.8)	1 (1.7)	-
Hydronephrosis	1 (0.4)	1 (1.7)	-
Urinary tract infection	2 (0.8)	1 (1.7)	2 (6.3)
Wound infection	2 (0.8)	-	-
Infected urinoma	2 (0.8)	-	-
Sepsis	2 (0.8)	-	2 (6.3)
Pneumonia	-	2 (3.3)	-
Ileus	-	1 (1.7)	-
Intestinal anastomotic leak	-	2 (3.3)	1 (3.1)
Vesico-cutaneous fistula	1 (0.4)	-	-
Dislocated abdominal drain	1 (0.4)	-	-
Dehydration	-	1 (1.7)	-
Arterial thrombosis	-	-	1 (3.1)
Grade 5 complications ≤90 days			
Myocardial infarction	1 (0.4)	-	-
Sepsis	-	1 (1.7)	-

Table 4. ***(continued)***

	Brachytherapy N=259	RC N=60	SC N=32
Grade 1-2 complications >90 days			
LUTS without hematuria	7 (2.7)	-	-
Hematuria	5 (1.9)	-	-
LUTS with hematuria	2 (0.8)	-	-
Urethral stenosis	1 (0.4)	-	-
Bladder perforation	1 (0.4)	-	-
Urinary tract infection	1 (0.4)	-	-
Grade 3-4 complications >90 days			
Ureteral stenosis	8 (3.1)	3 (5.0)	3 (9.3)
Contracted bladder	10 (3.9)	-	-
Stone formation radiation ulcer	5 (1.7)	-	-
Urethral stenosis	3 (1.2)	-	-
Vesico-vaginal/vesico-enteral fistula	2 (0.8)	1 (1.7)	2 (6.3)
Incisional/parastomal herniation	1 (0.4)	2 (3.3)	1 (3.1)
Urostomy stenosis	-	2 (3.3)	1 (3.1)
Intestinal obstruction	-	1 (1.7)	-
Sepsis	-	1 (1.7)	-

Abbreviations: LUTS: Lower urinary tract symptoms, RC: radical cystectomy, SC: salvage cystectomy

Discussion

RC with urinary diversion is considered standard treatment for MIBC and NMIBC refractory to intravesical therapies. In an effort to preserve the bladder, several alternative treatment modalities have emerged. In order to be considered as a true alternative to RC, bladder-sparing treatments should preserve sufficient bladder function without jeopardizing oncological outcome. In this study, we showed that highly selected bladder cancer patients who were treated with the combination of TURBT, pre-operative limited EBRT and brachytherapy had similar long-term survival to selected patients who underwent RC. Furthermore, the bladder was preserved in the vast majority of brachytherapy patients. In addition, comparison to RC showed that brachytherapy was associated with fewer complications.

Although brachytherapy for BC is being used since 1980, it is not universally recognized as a therapeutic option for selected BC as, for example, is the case in localized prostate cancer. The main reason could be concern regarding oncological outcome. Several observational studies on survival after brachytherapy are available. In a multicentre cohort comprising 1040

brachytherapy patients, 5 and 10-year OS was 62% and 44% respectively[7]. Some smaller single centre studies reported 5-year OS rates between 63% and 67% after brachytherapy[13–15]. These findings are in line with our results (5 and 10-year OS after brachytherapy of 66% and 49%, respectively).

Unfortunately, prospective studies comparing outcomes after brachytherapy and RC are lacking. Besides our previous reported results in a smaller cohort[8], there is one other group that has evaluated the outcome after RC and brachytherapy retrospectively. Van der Steen-Banasik et al. compared outcome of 76 brachytherapy patients to 65 matched RC patients with solitary tumours ≤5cm[16]. They found 5/10-year OS rates of 57%/33% in the brachytherapy group versus 52%/42% in the RC group (p=0.7). In our study, OS and DSS after brachytherapy were also similar to OS and DSS after RC. However, these results should be interpreted with caution because of the limitations of a retrospective study design. This resulted in several differences between RC and brachytherapy groups. The RC group included more patients with a history of NMIBC, who are known to have a worse prognosis as compared to patients with primary MIBC[17]. Additionally, tumours were larger in the RC group (43% 3-5cm in the RC group versus 38% in the brachytherapy group). Finally, a selection bias could not be avoided. Therefore, our analysis does not demonstrate a comparison of two totally equal patient groups but rather shows the results of two treatment strategies in a selective subgroup of bladder cancer patients. The results demonstrate that outcomes of brachytherapy are promising in terms of tumour control and OS. Furthermore, with this strategy, the bladder can be preserved in a selected group of patients. Moreover, brachytherapy resulted in less early complications as compared to RC (12% versus 40%, p<0.001). Although late complication rates did not differ between the two groups (18% versus 17%), the late complications were of a higher grade in the RC group (10/10, 100% after RC and 29/46, 63% after brachytherapy, p=0.02). However, due to the retrospective character of our study low grade late complications are likely to be underscored in our cohort. This also explains the relatively high percentage of high grade complications as compared to low grade complications in both groups.

An important concern regarding brachytherapy is that it represents incomplete cancer surgery with the potential inability to salvage patients who recur. In our study, 58 patients developed a bladder recurrence after brachytherapy of whom 32 underwent SC. Our SC rate (32/259, 12%) is comparable to those of other brachytherapy series[16,18]. Importantly, secondary local control could be achieved in the majority of patients. Studies have shown that primary tumour stage at time of SC drives outcomes and that there is no difference in survival compared to stage-matched patients undergoing primary RC[19]. This underlines the importance of timely diagnosis in case of recurrence. Therefore, close follow-up as outlined in the Materials and Methods section is recommended after bladder-preserving treatment.

The value of a LND has not been established in bladder-sparing treatment modalities. In our study LND was not routinely performed in the majority of brachytherapy patients, whereas pelvic LND is a pivotal step in RC. The benefit of LND in brachytherapy patients is thought to be limited, since the selection criteria for brachytherapy include favourable prognostics (maximal cT2, solitary tumour and <5cm). Pelvic LNM are less common in these patients.

In our study, six patients had LNM at pathology. All these patients underwent LND due to clinically suspicious LN during surgery. On the other hand, four patients without suspicious LN during surgery developed a recurrence in the pelvic LN. In theory, patients who were not treated with LND could have been denied the option of adjuvant chemotherapy in case of LNM. Determining the value of a LND in brachytherapy patients would require a very large study. Until then, partly based on the described results here, we continue to perform LND in case of suspicious nodes. Similarly, the value of neoadjuvant chemotherapy in the context of TMT remains unclear. While neoadjuvant chemotherapy has a proven OS benefit in MIBC patients treated with RC[20], studies have failed to demonstrate improvements in either OS or DSS after TMT[21,22]. Moreover, the survival benefit of neoadjuvant chemotherapy seems especially evident in patients with cT3-4a BC[23]. Since brachytherapy is offered to patients with maximal cT2 BC, we believe the benefit of neoadjuvant chemotherapy in this group will be limited.

Besides brachytherapy, other bladder-sparing treatments are emerging. The most-studied modality is TMT. A systematic review showed comparable survival outcomes after TMT and RC[22]. Comparison of bladder-sparing modalities is challenging because of varying selection criteria. For example, TMT is offered to patients with tumour stage cT2-T4, which makes it a possible treatment for a broader range of patients. A possible benefit of brachytherapy is that radio-sensitizing chemotherapy is not necessary because there is no expected benefit additional to the radio-biologically high-dose radiation to the tumour area in solitary cT1-T2 tumours. Consequently, possible side-effects of chemotherapy may be avoided. Furthermore, since EBRT prior to brachytherapy is low dose the risk of bowel toxicity may be lower than in EBRT as part of TMT.

Notwithstanding the aforementioned limitations, we believe our study is of merit since it represents the largest study on brachytherapy to date. Moreover, our median follow-up of 10 years is, to the best of our knowledge, the longest described for patients undergoing brachytherapy. Foremost, our study demonstrated that adequate patient selection is key in minimizing treatment aggressiveness and possible complications without negatively affecting oncological outcome.

In conclusion, bladder-preserving therapy with brachytherapy may be considered a reasonable treatment option in highly selected patients with a solitary bladder tumour ≤5 cm staged cT1G3/cT2N0M0. We reported a 10-year DSS of 67% after brachytherapy with bladder preservation in 84% of patients. Compared to RC, we found fewer high grade complications in the brachytherapy cohort. Strict patient selection is critical and patients should be counseled that long-term bladder monitoring is essential since the bladder remains a potential source of recurrence.

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Supplementary Material

Supplementary Table 1. Number of recurrences per anatomical region

	Brachytherapy			RC
	Total N= 259	**Without LND N=227**	**With LND N=32**	**Total N=60**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Bladder	58 (22)	50 (22)	8 (25)	-
Soft tissue in the true pelvis	2 (0.7)	2 (0.9)	-	4 (6.7)
Pelvic lymph nodes	4 (1.5)	4 (1.8)	-	-
Distant metastasis*	41 (16)	38 (17)	3 (9)	15 (25)
Total	105 (41)	94 (41)	11 (34)	19 (32)

**cases with simultaneous local and distant recurrence were classified as distant metastasis*
Abbreviations: LND: lymph node dissection, RC: radical cystectomy


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Short-term outcome after cystectomy: comparison of early oral feeding in an enhanced recovery protocol and feeding using Bengmark nasojejunal tube

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World J Urol. 2018 Feb;36(2):221-229.

Abstract

Purpose

Cystectomy for bladder cancer is associated with a high risk of postoperative complications. Standardized perioperative protocols, such as enhanced recovery after surgery (ERAS) protocols, aim to improve postoperative outcome. Postoperative feeding strategies are an important part of these protocols. In this two-centre study, we compared complications and length of hospital stay (LOS) between an ERAS-protocol with early oral nutrition and a protocol with early enteral feeding with a Bengmark nasojejunal tube.

Methods

We retrospectively reviewed 154 consecutive patients who underwent cystectomy for bladder cancer in two hospitals (Hospital A and B) between 2014 and 2016. Hospital A uses an ERAS-protocol (n=45), which encourages early introduction of an oral diet. Hospital B uses a fast-track protocol comprising feeding with a Bengmark nasojejunal tube (Bengmark-protocol, n=109). LOS and complications according to Clavien classification were compared between protocols.

Results

Overall 30-day complication rates in the ERAS and Bengmark-protocol were similar (64.4% and 67.0%, respectively; p=0.463). The rate of postoperative ileus (POI) was significantly lower in the Bengmark-protocol (11.9% vs. 34.4% in the ERAS-protocol, p=0.009). This association remained significant after adjustment for other variables (odds ratio 0.32, 95% confidence interval 0.11–0.96; p=0.042). Median LOS did not differ significantly between protocols (10 vs. 11 days in the ERAS and Bengmark-protocols, respectively; p=0.861).

Conclusions

Early oral nutrition in Hospital A was well tolerated. However, the Bengmark-protocol was superior with respect to occurrence of POI. A prospective study may clarify whether the lower rate of POI was due to the use of early nasojejunal tube feeding or other reasons.

Introduction

Radical cystectomy (RC) for bladder cancer (BC) is associated with a high complication rate. Thirty day overall complication rates vary from 26% to 78% with mortality rates of 1.0% to 4.0%[1–3]. The most common complications are infectious or gastrointestinal related, with postoperative ileus (POI) as one of the most frequent[4]. POI is an important reason for prolonged length of hospital stay (LOS) after RC[4–6].

In recent years, attempts have been made to improve recovery and reduce LOS by introducing enhanced recovery after surgery (ERAS) programmes. Their objective is to minimize physiologic stress effects in major surgery and thereby decrease time to return of normal function. Postoperative feeding strategies are an important part of these protocols and usually comprise oral intake within 24 hours after surgery. In clinical practice, however, perioperative intake differs greatly between ERAS-protocols[7, 8].

In the current study perioperative protocols for RC in two hospitals were compared. Hospital A is an academic hospital with an annual number of 25 cystectomies for BC. Hospital B is a tertiary national referral cancer-hospital. In this hospital over 60 cystectomies for BC are performed annually. There is a close collaboration between the oncologic urology departments of both hospitals in a multidisciplinary tumorboard and in research but their perioperative protocols for RC differ. In Hospital A the traditional perioperative protocol was replaced by an ERAS-protocol in 2014. In this ERAS-protocol, oral diet is started the day after surgery, when tolerated by the patient. Hospital B uses a protocol comprising early enteral feeding via a Bengmark nasojejunal tube (Bengmark-protocol).

The aim of this study was to compare postoperative outcomes and LOS of RC patients in an ERAS-protocol comprising early oral nutrition and in a protocol comprising early enteral feeding via a Bengmark-tube.

Methods

All consecutive patients who underwent cystectomy for BC between January 2014 and October 2016 in Hospital A or B were included. Both open and robot-assisted procedures were analysed. Patients who needed an adjunctive procedure (e.g. nephroureterectomy) were excluded. Also, patients who received an ureterocutaneostomy were excluded, as this procedure does not include bowel surgery. Comorbidity was assessed by the Charlson Comorbidity Index (CCI)[9]. Hospital stay was measured from the day of admission until discharge after RC. Differences in perioperative care between the protocols are highlighted below. An overview of all elements of both protocols is provided in the Appendix.

Preoperative care

In the ERAS-protocol (Hospital A), patients were admitted the morning of surgery. They did not receive bowel preparation. All patients, excluding insulin dependent diabetics, were administered 400cc of a carbohydrate rich drink 2-3h prior to surgery.

In Hospital B patients were admitted one day before surgery to place a nasojejunal feeding tube (Bengmark). This is a self-propelling, auto-positioning post-pyloric feeding tube. In addition, patients in this hospital were treated with selective digestive decontamination (SDD; see Appendix).

Surgery

Surgical teams of both hospitals were equally trained and experienced. In both hospitals surgeons adhered to the same surgical techniques for both open radical cystectomy (ORC) and robot-assisted radical cystectomy (RARC) including similar pelvic lymph node dissection templates. In hospital A, patients were operated by one of two staff urologists. In hospital B, patients were operated by one of four staff urologists. In this cohort, RARC was performed by one urologist in hospital A and two urologists in hospital B.

Both protocols used a combination of general and regional anaesthesia, with insertion of a thoracic epidural for postoperative pain management. The ERAS-protocol underwent revision regarding epidural analgesia in November 2015, omitting a thoracic epidural in patients undergoing a robot-assisted procedure. Blood loss and operation time were measured.

Postoperative care

In the ERAS-protocol, the nasogastric tube (NGT) was removed directly after surgery. Patients were allowed to try a normal diet on POD 2. Until normal intake was achieved, they were advised to take 1 to 2 high calorie nutritional drinks (Nutridrink®). In order to prevent POI, patients were given chewing gum three times a day and magnesium oxide two times a day. Epidural analgesia, if administered, was replaced by non-opioid pain control 48h after surgery. Early mobilisation was promoted, aiming for two hours out of bed on POD 1 and at least 6 hours out of bed from POD 2 onwards.

In the Bengmark-protocol the NGT was removed within 24h after surgery. Patients started with enteral nutrition at 20 ml/h via the Bengmark-tube on POD 1. On POD 2, enteral nutrition was raised to 40 ml/h and patients were encouraged to eat soft foods. From day 3 to day 5, enteral nutrition was gradually raised to 60 ml/h and patients were allowed to eat normally if possible. Enteral nutrition was stopped if normal intake was achieved. Epidural analgesia was stopped on POD 4. Duration of enteral nutrition via the Bengmark-tube was recorded. In both protocols time to removal of NGT and time to last drain removal were recorded. Finally, in both hospitals patients were discharged if they had met predefined criteria (Appendix).

Complications

Hospital and outpatient clinical records were reviewed in detail and complications and

unplanned readmissions occurring within 30 and 90 days of surgery were recorded. All complications were graded according to the Clavien-Dindo grading system[10]. POI was defined as requirement for cessation of an oral intake regime for >24h, the need for a NGT and/or absence of bowel function beyond POD 4.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 21.0. (Armonk, NY, IBM Corp.). Normally and non-normally distributed data were analysed using independent t-tests and Mann-Whitney U tests, respectively. Categorical data were analysed using chi-squared tests. Associations of protocol and surgical factors with the occurrence of complications were determined using univariable logistic regression. Multivariate logistic regression was used to identify independent effect of protocol on POI. Co-variates included age, ASA scores, surgical approach and use of epidural analgesia. Statistical significance was defined as a p-value <0.05.

Results

Patient characteristics

In Hospital A, 50 patients were treated in the ERAS-protocol versus 121 patients in Hospital B in the Bengmark-protocol. Forty-five patients in the ERAS-protocol and 109 patients in the Bengmark-protocol met our predefined inclusion criteria. Patient characteristics are shown in Table 1. Patients in the ERAS-protocol were significantly older than patients in the Bengmark-protocol (mean 69.9 and 64.9 years respectively; p=0.005) and had higher ASA scores (ASA 3: 28.9 and 11.0%, respectively; p=0.001). There were significantly more patients in the Bengmark-protocol who received neoadjuvant chemotherapy (49.5% vs. 24.4% in the ERAS-protocol, p=0.007). Furthermore, in the Bengmark-group more patients were previously exposed to pelvic radiation (23.9% vs. 8.6% ERAS-protocol, p=0.043).

Surgical and postoperative details

In Table 2 surgical and postoperative details are shown. A robotic approach was used approximately twice as often in the ERAS-protocol (64.4% vs. 27.5% in the Bengmark-protocol; p<0.001). Epidural analgesia was used less frequently in the ERAS-protocol (64.4% vs. 99.1%; p<0.001). Median LOS did not differ significantly (10 vs. 11 days for ERAS vs. Bengmark, respectively; p=0.861). Comparing RARC and ORC within the protocols, LOS was shorter in RARC in both the ERAS and Bengmark-protocols. This difference between open and robotic surgery was most apparent in the ERAS-protocol (9 vs. 15.5 days for RARC and ORC in the ERAS-group, respectively; 10 vs. 11 days for RARC and ORC in the Bengmark-group, respectively).

Table 1. Patient characteristics

		ERAS (N = 45)	Bengmark (N = 109)	p-value
Age, years	**Mean (±SD)**	69.9 (10.0)	64.9 (9.9)	0.005
BMI, kg/m2	**Mean (±SD)**	25.4 (4.8)	26.0 (3.7)	0.421
		n (%)	**n (%)**	
Sex	**Male**	34 (75.6)	79 (72.5)	0.847
	Female	11 (24.4)	30 (27.5)	
Diabetes	**Yes**	7 (15.6)	9 (8.3)	0.289
	No	38 (84.4)	100 (91.7)	
Charlson comorbidity index	**0**	21 (46.7)	70 (64.2)	0.117
	1	14 (31.1)	25 (22.9)	
	≥2	10 (22.2)	14 (12.8)	
Diversion type	**Bricker**	44 (97.8)	86 (78.9)	0.009
	Neobladder	1 (2.2)	17 (15.6)	
	Indiana pouch	0	6 (5.5)	
T-stage before surgery	**≤T2**	28 (62.2)	61 (56.0)	0.592
	≥T3	17 (37.8)	48 (44.0)	
N-stage before surgery	**Negative**	38 (84.4)	94 (86.2)	0.988
	Positive	7 (15.6)	15 (13.8)	
Neoadjuvant chemotherapy	**Yes**	11 (24.4)	54 (49.5)	0.007
	No	34 (75.6)	55 (50.5)	
Previous pelvic radiation*	**Yes**	4 (8.6)	26 (23.9)	0.043
	No	41 (91.4)	83 (76.1)	
ASA score	**ASA 1**	3 (6.7)	33 (30.3)	0.001
	ASA 2	29 (64.4)	64 (58.7)	
	ASA 3	13 (28.9)	12 (11.0)	

*Abbreviations: ASA = American Society of Anesthesiologists, BMI = Body Mass Index, SD = Standard deviation * Salvage cystectomies after radiotherapy included*

Table 2. Surgical and postoperative details

		ERAS	Bengmark	p-value
Previous pelvic radiation*	**No**	16 (35.6)	79 (72.5)	<0.001
	Yes	29 (64.4)	30 (27.5)	
Epidural analgesia, n (%)	**Overall**	29 (64.4)	108 (99.1)	<0.001
	ORC	14 (87.5)	79 (100)	0.027
	RARC	15 (51.7)	29 (96.7)	<0.001
Median duration of surgery, minutes (range)	**Overall**	340 (180-510)	243 (145-480)	<0.001
	ORC	240 (180-380)	240 (145-480)	494
	RARC	360 (285-510)	285 (180-450)	0.001
Median blood loss, cm^3, (range)	**Overall**	400 (50-2000)	800 (10-4900)	0.010
	ORC	850 (400-2000)	1100 (50-4900)	0.221
	RARC	200 (50-900)	125 (10-1100)	0.016
Median LOS, days (range)	**Overall**	10 (8-79)	11 (8-52)	0.861
	ORC	15.5 (8-52)	11 (8-52)	0.183
	RARC	9 (8-79)	10 (8-22)	0.752
NGT removal, POD, median (range)		0 (0-8)	1 (0-15)	<0.001
Patients requiring NGT replacement, n (%)		14 (31.1)	20 (18.3)	0.128
Epidural removal, POD, median (range)		2 (1-5)	5 (2-11)	<0.001
Patients with enteral tube feeding, n (%)		5 (11.4)	103 (94.5)	<0.001
Duration of enteral tube feeding, days, median (range)		5 (4-6)	5 (0-26)	0.651
Patients with TPN, n (%)		12 (26.7)	14 (13.0)	0.069
Duration of TPN, days, median (range)		10 (6-28)	7 (2-25)	0.039

Abbreviations: LOS = Length of hospital stay, NGT = Nasogastric tube, ORC = Open radical cystectomy, POD = Postoperative day, RARC = Robot-assisted radical cystectomy, TPN = Total parenteral nutrition

Table 3. Complications, return to theatre and readmissions

		ERAS n (%)	Bengmark n (%)	p-value
Overall complication rate ≤30 days		29 (64.4)	73 (67.0)	0.763
Return to theatre ≤30 days		8 (17.8)	11 (10.1)	0.187
Minor complications ≤30 days[a]	**Ileus**	14 (31.4)	13 (11.9)	0.009
	Urinary tract infection	5 (11.1)	19 (17.4)	0.325
	Wound infection	3 (6.7)	4 (3.7)	0.417
	Blood transfusion	4 (8.9)	20 (18.3)	0.141
	Pneumonia	6 (13.3)	6 (5.5)	0.110
	Atrial fibrillation	2 (4.4)	3 (2.8)	0.630
	Delirium	2 (4.4)	6 (5.5)	1
Major complications ≤30 days[a]	**Intestinal suture leakage**	3 (6.7)	2 (1.8)	0.124
	Fascial dehiscence	4 (8.9)	3 (2.8)	0.216
	Ureteroileal leakage requiring drainage	5 (11.1)	15 (13.8)	0.906
	Lymphocele requiring drainage	3 (6.7)	5 (4.6)	0.253
	Pelvic/abdominal abscess	0	1 (0.9)	1
	Bleeding	0	4 (3.7)	0.322
	Sepsis	0	6 (5.5)	0.181
	Pulmonary embolus	1 (2.2)	0	0.292
	Renal failure	0	2 (1.8)	1
	Cerebrovascular accident	0	1 (0.9)	1
Clavien grade ≤30 days[b]	**No complications**	16 (35.6)	36 (33.0)	0.767
	I-II	18 (40.0)	40 (36.7)	
	≥III	11 (24.4)	33 (30.3)	
Clavien grade 31-90 days[b]	**No complications**	40 (88.9)	91 (84.3)	0.868
	I-II	3 (6.7)	9 (8.3)	
	≥III	2 (4.4)	8 (7.4)	
Readmissions	**Within 30 days**	3 (6.7)	17 (15.6)	0.134
	Within 90 days	8 (17.8)	32 (29.4)	0.136

[a] Some patients experienced multiple complications
[b] If more than one complication occurred in one patient, the highest grade was scored

In the ERAS-protocol the NGT was removed right after surgery in most cases, but 30.4% of patients required replacement of the NGT. More patients in the ERAS-protocol needed total-parenteral-nutrition (TPN), although the difference was not statistically significant (26.7% vs. 13.0% in the Bengmark-protocol; p=0.069). Median duration of epidural analgesia was two days in the ERAS-protocol (n=29) compared to five days in the Bengmark-protocol (n=103) (p<0.001.)

Complications and readmissions

In Table 3 complications occurring within 30 days after RC are shown according to protocol, with multiple complications in some patients. Furthermore, 30-day and 90-day readmission rates are shown. Overall complication rates were similar (64.4% vs. 67.0% for the ERAS and Bengmark-protocols, respectively; p=0.763). The perentage of POI was significantly lower in the Bengmark-protocol (11.9% vs. 31.4% in the ERAS-protocol; p=0.009). In univariable logistic analysis, only the Bengmark-protocol was significantly associated with a lower risk of POI (odds ratio (OR) 0.30, 95% confidence interval (CI) 0.13-0.71; p=0.006). This association remained significant after adjusting for age, surgical approach, higher ASA scores and the use of epidural analgesia (OR 0.32, 95% CI 0.11-0.96; p=0.042, Table 4). Readmission rates were higher in the Bengmark-group, although the differences were not statistically significant (p=0.136). Urinary tract infection was the most common reason for readmission in both hospitals (data not shown).

Table 4. Multivariable logistic regression analysis identifying factors associated with postoperative ileus

	OR	95% CI	p-value
Bengmark protocol	0.32	0.11-0.96	0.042
Robot-assisted approach	0.70	0.24-2.00	0.500
ASA II	0.80	0.25-2.58	0.710
ASA III	0.86	0.20-3.76	0.840
Epidural analgesia	0.85	0.21-3.45	0.820
Age (increase of 1 year)	1.05	1.00-1.10	0.050

Discussion

Enhanced recovery protocols after RC are widely used and have led to improved overall complication rates and shorter LOS[11]. However, for some individual ERAS components, such as postoperative feeding strategies, evidence from the literature is sparse. In this retrospective study, we compared complications and LOS between an ERAS protocol with early oral nutrition and a protocol with early enteral feeding with a Bengmark nasojejunal tube. The latter was superior with respect to occurrence of POI, while overall complication rates and LOS were similar.

Overall complication rates in our study were in the higher range of earlier reported rates, which vary between 26% and 78%[1–3]. However, definition and types of reported complications differ between studies and are subject to the thoroughness of registration. Evaluating a specific complication like POI, our rates are also in the higher range of previous series, specifically considering the POI rate of 31.4% in the ERAS-protocol. In a systematic review, POI incidence after RC ranged from 1.6% to 23.5% [4]. However, the definition of POI is highly variable across urologic literature and therefore true incidence is hard to determine[12]. In our study, clinical records were reviewed in detail and POI was scored if our strict predefined criteria (see Methods) were met. Nevertheless, when studying POI retrospectively, observation bias cannot be excluded. The higher POI rate in the ERAS protocol may partly be explained by the fact that introduction of a new perioperative protocol (i.e. ERAS) makes caregivers more conscious of complications and LOS. Several previous reports on ERAS-protocols have demonstrated this effect[13, 14].

Notwithsanding this limitation, it is interesting that we found a lower rate of POI in the Bengmark-group. Most ERAS-protocols in urologic surgery are adapted from protocols in colorectal surgery. In this field many high-quality clinical studies have shown that early oral intake as a route for enteral nutrition is safe and effective[15]. However, these data may not be directly applicable to RC, because the construction of a urinary diversion, the uretro-enteric anastomosis, potential urinary leakage and large pelvic dissection differ between RC and colorectal surgery. Early introduction of enteral feeding is inherent to any enhanced recovery protocol, because of positive effects on insulin resistance, muscle function and wound healing; the latter being specifically relevant to the integrity of the bowel anastomosis after creation of a urinary diversion[15–17]. Now the question is which route of enteral nutrition should be preferred. Only one study prospectively reviewed the impact of early oral feeding on complications and LOS after RC[18]. In this randomized trial, patients either received access to liquids and then a regular diet on POD 1 and further (n=50), which is comparable to the ERAS-protocol in the current study, or care as usual with introduction of a liquid diet after return of bowel activity (n=52). Although the trial did not meet the enrolment target, no differences in complications (including POI) were found and early oral feeding was well tolerated[18].

Apart from our study, no other studies have evaluated the outcome of early enteral tube feeding in RC patients. Nasojejunal early nutrition was introduced in Hospital B after a meta-analysis of studies in abdominal surgery showed decreased mortality in patients who were fed

enterally compared to patients without enteral feeding[19,20]. In the literature, no causal relation of nasojejunal enteral feeding and lower ileus rates has been described. We hypothesize that after creation of a urinary diversion a period of gastroparesis may develop, which may be circumvented by the nasojejunal enteral feeding. Whereas a lower POI rate may be interpreted as an advantage of the Bengmark-protocol, there are downsides to consider. First, despite the fact that the Bengmark-tube is an auto-positioning device in presence of normal gastric motility, it remains an invasive procedure with possible complications. Second, the tube has to be inserted at least 12h prior to surgery, because of the time the self-propelling mechanism takes to migrate into the jejunum. Consequently, patients need to be admitted the day before surgery. Finally, feeding tubes cause nasopharyngeal discomfort in the postoperative course.

In our study, the association between the Bengmark-protocol and the lower rate of POI was independent of other factors, such as epidural use. Previous studies in colorectal surgery have suggested that postoperative epidural analgesia, in contrast to opiate use, can lead to a decrease in ileus[21]. Further research should be undertaken to investigate the effects of different pain medications on RC patients.

Main limitations of this study are its retrospective character, the limited sample size in one of the arms and the differences in patient and surgical characteristics between the two centers. Since Hospital B is a comprehensive cancer center, more patients in this hospital underwent neoadjuvant chemotherapy or had a history of pelvic radiation. Another difference is due to the surgical approach, with more patients undergoing RARC in the ERAS-group. In our study, however, multivariable analysis showed that the association between the Bengmark-protocol and POI was independent of surgical approach. This is in line with the results of Bochner et al. Their randomized trial comparing outcome after ORC and RARC, did not show any differences regarding LOS or complication rates[22]. We acknowledge the limitation of comparing perioperative care between two hospitals. However, many aspects of perioperative care (e.g. postoperative nursing care or perioperative anaesthetic care) are difficult to account for and may confound outcomes even within the same hospital or protocol.

Conclusions

In conclusion, this study showed that early oral nutrition in the ERAS-protocol was well tolerated. There were no differences in overall complication rates comparing the two protocols. Importantly, the protocol using nasojejunal feeding was superior considering the frequency of POI. However, because of the retrospective study design conclusions have to be interpreted with caution. A prospective study is needed to determine if the lower rate of POI in the Bengmark-group was due to the use of nasojejunal feeding or other reasons.

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Appendix: Overview of pre- intra- and postoperative elements of ERAS and Bengmark protocols

Preoperative care

Counselling	
ERAS	Patient education about procedure by surgeon at preclinical visit together with specific education about ERAS-protocol by nurse practitioner. Written information about ERAS-protocol provided.
Bengmark	Patient education about procedure and Bengmark-tube at preclinical visit, together with written information.
Admission	
ERAS	All patients admitted morning of surgery. Consultation by an enterostomal therapist.
Bengmark	All patients admitted 1 day before surgery for consultation by an enterostomal therapist and to place a jejunal feeding tube (Bengmark).
Preoperative bowel preparation	
ERAS	None.
Bengmark	None.
Preoperative carbohydrate loading	
ERAS	Carbohydrate rich drink 2-3h before surgery for all patients (insulin dependent diabetics excluded).
Bengmark	None.
Preoperative fasting	
ERAS	Solid foods up to 6h before surgery, clear fluids up to 2h before surgery, then nil oral intake.
Bengmark	Solid foods up to 6h before surgery, clear fluids up to 4h before surgery, then nil oral intake.
Premedications	
ERAS	Acetaminophen 1000mg on the day of surgery.
Bengmark	Temazepam 10mg the evening before surgery. Oxazepam 10 mg and acetaminophen 1000mg day of surgery. SDD: this consisted of the administration of three antibiotics: polymyxine E, tobramycin and amphotericin B. SDD was started the evening before surgery and was given until the first solid oral diet or when enteral feeding exceeded one liter after surgery.

Thromboembolic prophylaxis	
ERAS	Start LMWH prophylactic evening before surgery. Compressive stockings and sleeves for 24h, starting the morning of surgery.
Bengmark	Start LMWH prophylactic evening before surgery. Compressive stockings, starting the morning of surgery.

Intraoperative care

Epidural analgesia	
ERAS	Thoracic epidural (Th11/12) in all patients undergoing ORC, since November 2015 omitted in patients undergoing RARC.
Bengmark	Thoracic epidural (Th11/12) in all patients.
Antimicrobial prophylaxis	
ERAS	Kefzol 2g/Flagyl 500mg started intravenously just before the operation and continued for 24 hours.
Bengmark	Kefzol 2g/Flagyl 500mg started intravenously just before the operation and continued for 24 hours.
Perioperative fluid management	
ERAS	Restrictive fluid management.
Bengmark	Restrictive fluid management.
Preventing intraoperative hypothermia	
ERAS	Upper-body air-warming (Bairhugger)
Bengmark	Warming mattress and warming blanket (WarmTouch)
Preventing PONV	
ERAS	Depending on PONV-score calculated at preoperative screening: ondansetron 4mg at the end of surgery.
Bengmark	Depending on PONV-score calculated at preoperative screening: dexamethasone 5mg and/or droperidol 1.25mg

Postoperative care

Nasogastric intubation	
ERAS	Removal after surgery (in recovery, end of day).
Bengmark	Removal 24h after surgery, unless adhesiolysis, nausea or >1000 ml production.

Drain removal	
ERAS	Removed on POD 2 (if suspect for urinary leakage, creatinine measurement first)
Bengmark	Removed on POD 3 (if suspect for urinary leakage, creatinine measurement first)
Nutrition	
ERAS	POD 0: Start with 1-2 bottles of high calorie nutritional drinks, continue until discharge. Aim for at least 800 ml of oral liquids. POD 1: Light oral diet (bread and liquids). POD 2: Normal oral diet in the absence of nausea, vomiting or abdominal distension.
Bengmark	Start with enteral nutrition via Bengmark on POD 0. First 6h 42ml/h, second 6h 65ml/h, after that depending on dietary need as determined by dietician. Start oral intake depending on peristalsis.
Prevention of postoperative ileus	
ERAS	Magnesium oxide twice daily and chewing gum for 5-45 minutes thrice daily.
Bengmark	Magnesium oxide in some patients, depending on bowel movement. Chewing gum as often as possible.
Postoperative analgesia	
ERAS	Stop epidural 48h after surgery. Acetaminophen 1000mg four times a day starting on POD 0. Diclofenac (50mg thrice daily) starting before removal of epidural (not in case of impaired renal function).
Bengmark	Stop epidural on POD 4. Acetaminophen 1000mg four times a day starting on POD 0.
Mobilisation	
ERAS	POD 1: 2h on chair. POD 2: 6h on chair.
Bengmark	Start mobilisation on POD 0, not further specified.
Discharge criteria	
ERAS	Normal diet, return of normal bowel function, mobilisation on pre-operative level, able to take care of urinary diversion, adequate oral pain management
Bengmark	Normal diet, return of normal bowel function, mobilisation on pre-operative level, able to take care of urinary diversion, adequate oral pain management

Abbreviations: LMHW=low molecular weight heparine, ORC=open radical cystectomy, POD=postoperative day, RARC=robot-assisted radical cystectomy, SDD=selective digestive decontamination

Part IV

Concluding remarks


12

Summarizing discussion, future perspectives, and conclusions

Summarizing discussion, future perspectives, and conclusions

Muscle-invasive bladder cancer (MIBC) is an aggressive disease with high risk of progression or death if left untreated. Unlike many other cancers, there has been no significant improvement in survival rates for bladder cancer for three decades[1]. To improve survival and quality of life, a multidisciplinary approach is essential. In this thesis, several aspects of the multidisciplinary management of muscle-invasive bladder cancer were studied, with a focus on neoadjuvant chemotherapy, staging by FDG-PET/CT, and organ-preserving therapies. This chapter provides a general discussion and summary of all presented chapters, and subsequent conclusions and future perspectives.

Neoadjuvant treatment for muscle-invasive bladder cancer

In **Chapter 2** we provided an overview of neoadjuvant treatment for bladder cancer over the years. Neoadjuvant chemotherapy (NAC) is currently the most frequently applied neoadjuvant treatment in MIBC. However, despite being one of few treatment recommendations contributing to an increase in survival, NAC is still underutilized. Approximately 30% of patients with cT2-T4aN0M0 bladder cancer in the Netherlands receive NAC, while it is estimated that up to 50% of patients undergoing radical cystectomy are eligible for NAC[2,3]. Urologists may be hesitant to refer bladder cancer patients for NAC because of treatment-related toxicity and the modest 5% to 10% increase in 10-year survival[3,4]. Furthermore, the lack of reliable tools to select patients who will benefit most from NAC may also result in withholding NAC. Response rates to NAC differ greatly between patients. Approximately 25% of patients have a pathological complete response, in which the primary tumor and possible lymph node metastases are completely eradicated on pathological assessment after NAC. These patients have a 5-year overall survival rate of up to 80% which is significantly better than non- or partial responders[4]. On the other hand, 30% of patients do not respond to NAC[4]. These patients receive no benefit in terms of better survival but do suffer potential toxicity from the therapy.

Currently, selection for NAC is based on clinical staging and guidelines recommend offering NAC to patients with cT2-T4aN0M0 bladder cancer[5]. However, because metastases are more frequent in cT3-T4aN0M0 bladder cancer, it is anticipated that the benefit of NAC will be greater in this particular subgroup. In **Chapter 3**, we compared overall survival in 5517 patients with cT2N0M0 (n=4504) versus cT3-4aN0M0 (n=1013) bladder cancer undergoing radical cystectomy with or without NAC. Patients were identified from the nationwide Netherlands Cancer Registry. We found that in cT3-4a bladder cancer, NAC was associated with an absolute and statistically significant 5-year overall survival benefit of 19%. In cT2 bladder cancer, the overall survival benefit after NAC was only 6% and this was not statistically significant compared to cT2 bladder cancer patients who did not receive NAC.

Should we consider a more tailored use of neoadjuvant chemotherapy? This could improve patient outcomes, as it prevents toxicity in patients who do not respond to NAC. However, undertreatment is a possible negative consequence. Moreover, inaccurate clinical staging

could result in withholding NAC from patients who are eligible in retrospect. Hence, the results of **Chapter 3** underline the importance of identification of biomarkers that may predict response to chemotherapy.

Several research groups have shown that tumor classification by gene expression profiling and molecular subtyping can identify patients who are more likely to benefit from NAC[6–10]. However, none of these biomarkers has reached widespread clinical use due to widely varying study designs with different survival endpoints, treatments, and selection principles. Ongoing research focuses on more robust and clinically useful biomarkers for predicting NAC response. The need to stratify MIBC into subtypes that require different systemic treatment approaches will become even more important following the introduction of immunotherapy in the neoadjuvant setting. This thesis only studied neoadjuvant chemotherapy, but in the future the application of neoadjuvant immunotherapy will likely change the established standard of care in MIBC. Prospective studies on immunotherapy in the neoadjuvant setting have shown promising results[11–13]. Long-term follow-up is awaited to allow for assessment of survival outcomes and further application in clinical practice. While we await these results, cisplatin-based chemotherapy remains the most important neoadjuvant treatment in MIBC.

In **Chapter 3A** we reflected on a phase II study by Iyer et al. on dose-dense gemcitabine and cisplatin prior to radical cystectomy[14]. Cisplatin-based NAC is considered standard of care in MIBC, but the optimal regimen in terms of both dose-schedule and agents remains undefined. Iyer et al. conclude that dose-dense gemcitabine and cisplatin is an active and well-tolerated neoadjuvant regimen with 57% of patients downstaged to <pT2N0. Dose-dense regimens are considered to have lower toxicity rates compared to standard-dose regimens, but still up to 50% of MIBC patients are considered unfit for cisplatin-based chemotherapy[15]. This further underlines the importance of new neoadjuvant therapies such as immunotherapy.

In contrast to other cancers, classification of response to NAC in MIBC is only based on TNM staging at radical cystectomy[16]. However, since TNM staging is developed in untreated MIBC, it does not consider specific alterations caused by neoadjuvant chemotherapy and may therefore conceal prognostic information in post-treatment specimens. In several cancers, histopathologic tumor regression grades (TRG) have been shown to be a prognostic factor for patient outcome after NAC[17–19]. Tumor regression grades quantify the extent of tumor response to NAC, by estimating the percentage of viable cancer cells in relation to the macroscopically identifiable tumor bed. In **Chapter 4** we studied the prognostic value of TRG in MIBC in a multicenter setting. We determined histopathologic TRGs in radical cystectomy specimens of 389 MIBC patients after NAC. TRGs were confirmed by independent pathological review with low interobserver variability. The combination of TRG and TNM showed prognostic discrimination of overall survival and this discrimination was superior compared with TNM staging alone. We conclude that determination of TRGs in radical cystectomy specimens after NAC is simple, reproducible and provides additional prognostic information. If this can be confirmed in a prospective study, TRG could be routinely added to pathology reports of radical cystectomy specimens after NAC.

In conclusion, neoadjuvant chemotherapy remains the most prevailing neoadjuvant treatment for MIBC for now. It is expected that in the future immunotherapy will overtake this role and patient selection for neoadjuvant treatment, either chemotherapy, immunotherapy or a combination, will be guided by biomarkers. Meanwhile, in the absence of reliable biomarkers to serve as staging adjuncts, we continue to rely heavily on basic clinical staging: physical examination and imaging modalities.

FDG-PET/CT in preoperative staging of muscle-invasive bladder carcinoma

According to international guidelines, the recommended imaging modality to stage patients with MIBC is contrast-enhanced computed tomography (CECT) of the chest, abdomen, and pelvis[5,20]. However, CECT has some important limitations. For example, it may not differentiate between normal and pathological tissues of similar densities and it may not detect lymph node metastases in normal-sized lymph nodes. 18F-Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) offers several advantages over CECT alone since it combines anatomic and metabolic information. The challenge for FDG-PET/CT is to detect lymph node metastases and distant metastases which are not detected by CT alone. A recent review suggested that FDG-PET/CT has potential clinical use for staging MIBC[21]. For lymph node assessment, the sensitivity of FDG-PET/CT is superior to CECT with comparable specificity in an analysis of 19 studies[21]. Moreover, for detection of distant metastases, data from eight studies suggest that FDG-PET/CT is accurate[21].

In **Chapter 5** we evaluated whether the reported advantages of FDG-PET/CT staging (e.g., higher sensitivity for the detection of lymph node metastases, accurate detection of distant metastases) are in fact reflected in changes in the clinical management of patients with MIBC. We found that FDG-PET/CT scans led to a management change in 127 of the 711 patients (18%). The reason for this change is threefold: First, and most importantly, FDG-PET/CT detects distant metastases leading to a shift from curative potential to palliative care in 9.1% of patients. Secondly, in 7.0% of patients, additional findings on FDG-PET/CT lead to selection for NAIC instead of local therapy only. And finally, FDG-PET/CT detects second primary malignancies in 3.9% of patients. One could argue that detection of a second tumor in patients with such an aggressive disease as MIBC does not modify the poor prognosis and is lacking clinical significance. On the other hand, if a second primary malignancy would influence the BC treatment (e.g., the decision to perform RC), this does deserve accurate examination. It should be noted that 8.1% of patients had false positive secondary findings, for example benign tubulovillous adenomas in the colon or incidental prostatic uptake[22]. This could result in unnecessary invasive diagnostic testing. Altogether, FDG-PET/CT provides important incremental staging information, which potentially influences clinical management in almost one fifth of MIBC patients, but also leads to false positive results. This is consistent with our previous findings and the results of other research groups[23–25.] Of course, this percentage is highly dependent on an institution's treatment guideline and may vary between centers.

The ultimate goal of improved staging is to better select patients for treatment, in order to improve survival and prevent overtreatment. Whether the information provided by FDG-PET/

CT, and any subsequent management change, will be translated into prolonged survival, remains to be investigated (e.g., among patients who are selected for NAC based on PET/CT). The same applies for the effect on quality of life and healthcare costs: will refraining from extensive surgery in patients with distant metastases increase quality of life by avoiding postoperative morbidity, as well as save costs? These potential benefits should outweigh the potential drawbacks of additional imaging, such as delay of treatment, unneeded invasive procedures and additional costs. The cost of diagnostic imaging is increasingly recognized as a major component of healthcare expenditure. The cost of FDG-PET/CT varies and increased adoption will result in increased spending[26]. On the other hand, if futile surgery can be avoided, the cost of treatment may decrease because of FDG-PET/CT. The clinical versus economic benefits of advanced staging among MIBC patients need to be evaluated in further value-based research.

FDG-PET/CT for assessment of response to neoadjuvant chemotherapy

Besides pretreatment staging, FDG-PET/CT can also be utilized for response evaluation during or after NAC. Since NAC is increasingly used in MIBC, accurate response evaluation has gained importance. Up to 30% of patients do not respond to NAC[4]. Early recognition of these non-responders may reduce overtreatment and can spare patients from unnecessary toxicity. Currently, no reliable radiological- or biomarkers are recommended to predict response to NAC in clinical practice. In various malignancies, FDG-PET/CT has proven to be useful for on-treatment assessment of response to NAC[27,28]. The rationale for the use of FDG-PET/CT rather than CECT is that metabolic response of the tumor (reflected by uptake of FDG) may precede anatomical response (i.e., shrinkage), allowing for earlier detection. In MIBC, data on FDG-PET/CT for on-treatment response assessment is very limited.

In **Chapter 6** we prospectively investigated whether FDG-PET/CT could predict response to neoadjuvant or induction chemotherapy (NAIC) and we compared the accuracy of FDG-PET/CT to the accuracy of CECT. Response to NAIC was assessed in 83 patients with high-risk MIBC after two (neoadjuvant setting) or three (induction setting, i.e., in case of N+ disease) cycles of chemotherapy. CECT images were assessed according to the RECIST1.1 criteria. FDG-PET/CT images were assessed quantitatively (EORTC criteria using the maximal standardized uptake values) and qualitatively (Peter Mac criteria). Specificity of CECT was higher than FDG-PET/CT for prediction of complete pathological response and any down-staging. In all other analyses, no statistically significant differences between FDG-PET/CT and CECT were found. Notably, progression in lymph node status remained undetected by both FDG-PET/CT and CECT. This is important since assessment of response in lymph nodes will often guide patient management. In the induction setting, accurate assessment of non-response in lymph nodes may reduce NAIC overtreatment as well as futile radical cystectomy. In conclusion, while FDG-PET/CT seems useful in the initial staging of MIBC, it has insufficient predictive power to aid in routine response assessment after neoadjuvant or induction chemotherapy.

How can staging of MIBC by PET/CT be improved? Advancements in PET/CT hardware can lead to higher image resolution. Increasing the spatial resolution of PET images may lead to

more detailed visualization of small lesions and low-level metabolic activity. Micro-metastases (≤10mm) may be detected more frequently. This can improve the accuracy of staging and especially the accuracy of response assessment, where lymph node progression is often missed (**Chapter 6**). Furthermore, the development of more specific radiotracers can enhance the accuracy of staging and response assessment. Both 11C-acetate and 11C-choline have been studied as an alternative to 18F-FDG in small cohorts of MIBC patients[29–32]. None of these studies demonstrated a clear advantage of 11C-acetate or 11C-choline over 18F-FDG. Recently, fibroblast activation protein-ligands, a novel class of tracers for PET/CT imaging, demonstrated promising results in various malignancies compared to standard FDG PET/CT[33]. The fibroblast activation protein (FAP) can be overexpressed in tumor-associated fibroblasts in the tumor microenvironment. In bladder cancer, a small study showed that an increased FAP expression correlates with tumor aggressiveness[34]. In another small pilot study in bladder cancer, 68Ga-labeled-FAP-inhibitor revealed superiority over 18F-FDG in detection of lymph node and distant metastases[35]. These results suggest that 68Ga-FAP-inhibitor may be a useful radiotracer in MIBC, but this needs to be confirmed in larger studies. Finally, the application of artificial intelligence (AI) algorithms can help in quantifying and analyzing features within PET/CT images. Artificial intelligence can potentially identify subtle changes in tumor metabolism that might be missed by human observers, leading to earlier and more accurate staging and response evaluation. Moreover, AI could enable a standardized interpretation of PET/CT imaging in new studies. In a recent study, a machine learning algorithm based on manually measured PET and CT features performed as well as physicians in detecting lymph node metastases on FDG-PET/CT at initial staging for MIBC[36]. To date, there is no published study on the use of fully automated deep learning methods on FDG-PET images for bladder cancer, but promising results of its application using CT and MRI images have been reported in terms of predicting the depth of invasion of the primary tumor, detection of lymph node metastases, and the assessment of treatment response[37–39].

FDG-PET/CT in preoperative staging of upper tract urothelial carcinoma

Primary tumor staging of patients with upper tract urothelial carcinoma depends on ureteroscopy (with biopsy of suspicious lesions) and CT urography. For assessment of lymph node and distant metastases, CECT of the abdomen, chest and pelvis is recommended, similar to staging MIBC[40]. However, CECT has a low sensitivity of only 25% for detection of lymph node metastases in UTUC[41]. Lymph node metastases are reported in 14-40% of UTUC patients with higher T stages (≥pT2) who underwent lymph node dissection[42]. Given this potential for lymphatic spread in UTUC, better non-invasive staging is important for optimal treatment planning. While FDG-PET/CT has a superior sensitivity for detection of lymph node metastases compared to CECT in MIBC, its diagnostic accuracy in UTUC is unclear.

In **Chapter 7** we studied the diagnostic accuracy of FDG-PET/CT for lymph node staging in 117 patients with UTUC. Patients receiving neoadjuvant chemotherapy were excluded. In total, 62 patients underwent lymph node dissection and seventeen patients had lymph node metastases at histopathological evaluation. Sensitivity and specificity of FDG-PET/CT for diagnosis of lymph node metastases were 82% and 84%, respectively. In the future, the

addition of FDG-PET/CT to the staging algorithm of UTUC may enable more personalized treatment by aiding in the decision to perform a lymph node dissection and/or administer neoadjuvant chemotherapy. First, our reported findings regarding diagnostic accuracy should be confirmed in a prospective study.

Locoregional treatment and outcome of muscle-invasive bladder cancer

Radical cystectomy with or without NAC is considered standard of treatment for patients with MIBC[5]. Although mortality rates have declined in recent decades, radical cystectomy remains an extensive surgical procedure with considerable morbidity and long-term functional impairment[43,44]. Importantly, studies have shown that quality of life after MIBC treatment is worse than after treatment for other pelvic cancers, such as colorectal cancer[44]. Due to increasing awareness of the functional implications of standard radical cystectomy, alternative surgical techniques, such as prostate sparing cystectomy, have been developed. Moreover, robot-assisted radical cystectomy has become increasingly popular. Robot-assisted radical cystectomy results in less blood loss and a shorter length of stay when compared to open radical cystectomy, but to date no longer-term advantages have been demonstrated[45]. Finally, attempts have been made to improve recovery and reduce length of stay after surgery by implementing standardized perioperative protocols. Besides these improvements in surgical techniques and perioperative care, bladder-sparing therapies involving radiotherapy have gained interest. In this thesis several studies on improving the outcome after surgery as well as bladder-sparing therapies were described.

Organ-preserving surgery

In men, standard radical cystectomy includes removal of the prostate, bladder, seminal vesicles, distal ureters and regional lymph nodes. After this standard surgery, loss of erectile function and incontinence (in case of a neobladder as urinary diversion) are very common[44,46]. Erectile function in males is dependent on parasympathetic innervation via the cavernous nerves. These nerves travel to the penis via the pelvic and prostatic plexus and have a close anatomical relationship to the bladder, seminal vesicles, prostate and urethral sphincter. Likewise, the nerves which control urinary function also lie in close proximity to these structures. Prostate sparing cystectomy (PSC) is designed to remove the bladder while minimizing damage to the relevant nerves, thereby preserving sexual and urinary function. Of course, the primary goal is to achieve effective cancer control. Over the years, several studies have shown comparable oncologic outcomes for PSC and standard radical cystectomy[47]. Nevertheless, PSC remains a controversial surgical approach and is debated for fear of incomplete resection and incidental prostate carcinoma.

In **Chapter 8** we investigated long-term functional and oncologic results following two standardized PSC techniques in 185 patients with organ-confined MIBC. All patients received extensive evaluation to rule out prostate cancer and bladder cancer at the bladder neck and prostatic urethra. With a 5-year overall survival of 71% and two recurrences in the prostatic urethra, oncologic outcomes were comparable to those of radical cystectomy. During follow-up, 3.2% of patients developed prostate cancer, half of which was oncologically significant.

Obviously, this low incidence is the result of meticulous screening before PSC. Functional results were excellent, although only subjective measures of continence and erectile function were registered. Future research should validate the patient's perception of functional advantages by means of quality of life questionnaires. Our study confirms that oncologic outcomes after PSC are acceptable, provided that extensive work-up including preoperative prostatic urethral biopsies or per-operative frozen section analysis is performed. Foremost, our study demonstrates that proper patient selection is the key to minimizing treatment aggressiveness without jeopardizing oncological outcome. Prostate-sparing cystectomy should be offered to eligible men who are motivated to preserve their sexual function.

In **Chapter 8** we only studied prostate sparing cystectomy. However, with a rising incidence of bladder cancer among women, organ-preserving surgery in women is just as important. In women, standard radical cystectomy includes removal of the bladder, entire urethra, the anterior vaginal wall, uterus, distal ureters and regional lymph nodes. As with the male population, this surgery has a major negative impact on sexual function. Several organ-preserving techniques, such as sparing the neurovascular bundle and/or vagina, have been described, but there is a paucity of studies on the outcome of these techniques[48]. In the future, more studies should focus on females, to bridge the knowledge gap concerning organ-preserving surgery in females with bladder cancer.

Perioperative care

Besides long-term effects on continence and sexual function, radical cystectomy is associated with a high postoperative complication rate. Thirty-day overall complication rates vary from 26 to 78%[49,50]. Most complications are infectious or gastrointestinal related, with postoperative ileus as one of the most frequent[50,51]. Enhanced recovery after surgery (ERAS) protocols are multimodal care pathways that aim to standardize and improve perioperative management. The core principle behind successful ERAS protocols is multidisciplinary collaboration: for example, with anesthesiologists regarding perioperative fluid management and analgesia or with physiotherapists regarding postoperative mobilization. ERAS protocols have led to improved overall complication rates and shorter length of stay after radical cystectomy[52].

However, for some individual ERAS components, such as postoperative feeding strategies, evidence from the literature is sparse. In **Chapter 11**, we compared complications and length of stay after radical cystectomy between two protocols using different postoperative feeding strategies. We analyzed 154 patients who underwent radical cystectomy in two hospitals: one using an ERAS protocol encouraging early introduction of an oral diet, the other using a protocol comprising feeding with a Bengmark nasojejunal tube. The latter was superior with respect to occurrence of postoperative ileus, while overall complication rates and length of stay were similar. Whether the lower rate of postoperative ileus was due to the use of early nasojejunal tube feeding or other reasons should be clarified in a prospective study.

Besides the need for further refinement of individual ERAS components, there is a need for earlier optimization of a patient's functional status. It is known that a poor preoperative functional status is associated with a higher complication rate in MIBC patients[50]. ERAS

protocols usually start as soon as the patient is admitted for surgery, but the preoperative period is a window of opportunity to address the patient's lifestyle. Prehabilitation, also known as preoperative rehabilitation, is a proactive strategy that involves preparing patients physically and mentally for surgery in the period leading up to surgery. The goal of prehabilitation is to improve a patient's overall health, functional capacity, and resilience before surgery, thereby enhancing their ability to withstand the stress of surgery and recover more quickly afterward. Prehabilitation typically includes exercise programs, nutritional counseling, smoking cessation support and stress-reduction techniques. To date, no adequately powered study has been performed to establish the effectiveness of a prehabilitation program prior to radical cystectomy. A randomized trial is currently recruiting in the Netherlands to address the role of such a prehabilitation program[53] [ClinicalTrials.gov identifier NCT05480735].

Bladder-sparing treatment

Despite outcome-enhancing measures such as prostate-sparing techniques and advancements in perioperative care and prehabilitation, cystectomy remains a complex surgical procedure associated with considerable morbidity. Therefore, bladder-sparing treatment should be considered as an alternative in selected patients. Trimodal therapy, comprising transurethral resection of the tumor followed by concurrent chemoradiation, is the most frequently applied bladder-sparing treatment and is acknowledged as an alternative to radical cystectomy by several guidelines[5,20,54]. While it is evident that chemoradiation is superior to radiation alone, the optimal chemotherapy protocol remains undetermined. Although there are no comparative studies on radiosensitizing chemotherapy, the following are the most frequently used radiosensitizers: cisplatin; mitomycin-C (MMC) combined with 5-fluorouracil (5-FU); and gemcitabine. The regimen using MMC and 5-FU has been shown to be superior to radiation alone in a randomized phase III trial[55,56]. Capecitabine is an effective replacement for 5-FU as a radiosensitizer in gastro-intestinal malignancies but has not been studied in bladder cancer.

In **Chapter 9**, we evaluated the outcome of MIBC patients treated with concurrent radiation and MMC/capecitabine. Capecitabine is administered orally in the form of tablets, which makes it more convenient for patients compared to intravenous chemotherapy. Moreover, hospital admission and complications related to intravenous administration of chemotherapy can largely be avoided. We analyzed 71 patients with cT2-4aN0M0 bladder cancer who were treated with concurrent radiation and MMC/capecitabine. We found a complete response rate of 96% at cystoscopy after three months follow-up, a 2-year local disease-free survival of 79%, and a 2-year bladder-intact event-free survival of 74%. Acute grade 3-4 toxicities (according to the Common Terminology Criteria for Adverse Events v4.0) occurred in 10% of patients. We concluded that capecitabine is a reasonable alternative to 5-FU, with the advantage of oral administration. Severe toxicity is infrequent and locoregional tumor-control and disease-free survival appear similar to previous studies with MMC/5FU. Of course, a longer follow-up is required to draw definitive conclusions regarding survival and recurrence outcomes. Furthermore, long-term quality of life outcomes should be considered in future studies. It is one thing to preserve the bladder, but the actual goal is to also preserve bladder function.

Our study adds to the growing evidence supporting the safety and feasibility of trimodal therapy for MIBC. Nevertheless, its adoption in clinical practice remains limited and trimodal therapy is often restricted to patients with significant comorbidities for whom surgery is not an option. What is the reason behind this reluctance? First and foremost, randomized controlled trials directly comparing bladder preservation with radical cystectomy are lacking. Several trials ended due to insufficient accrual because patients and clinicians are hesitant to leave the decision about the loss of one's bladder up to a randomization process. Future trials are unlikely[57]. In the absence of randomized trials, several propensity-score matched studies have been conducted. They suggest that long-term oncological outcome after trimodal therapy is comparable to outcome after radical cystectomy[58,59]. However, unknown residual confounders are inherent to the study design and therefore comparing oncological outcomes of trimodal therapy and radical cystectomy remains difficult. Another possible reason for reluctance is that trimodal therapy requires highly specialized multidisciplinary cooperation: to select the right patients, perform a maximal transurethral resection of the tumor, complete chemoradiation and take care of diligent follow-up. In case of treatment failure, a salvage radical cystectomy should be performed. A dedicated multidisciplinary team is crucial but may not be available in every hospital.

In a recent study using data from the Dutch National Cancer registry, it was shown that in the Netherlands one in five patients with non-metastatic MIBC remain untreated[60]. This is in line with studies in other countries[61,62]. Obviously, these untreated patients have worse survival outcomes compared to patients who received treatment. For a subset of these untreated patients, bladder-sparing treatment may be a viable option. A broader discussion on various treatment options, including radical cystectomy and trimodal therapy, should be offered to all suitable patients with MIBC. Again, it all starts with selecting the right patients. How can patient selection for bladder-preserving therapy be improved? Advances in the molecular understanding of MIBC have led to the discovery of molecular biomarkers associated with patient outcomes after bladder preservation therapy[63,64]. In the future, these biomarkers may aid the selection of patients who are more likely to benefit from bladder-preserving strategies. Moreover, instead of refining the chemotherapy component as we studied in **Chapter 9**, bladder preservation trials are focusing on incorporating immunotherapy as a fourth treatment modality. Phase III randomized trials of concurrent chemoradiation with or without the addition of atezolizumab [ClinicalTrials.gov identifier: NCT03775265], pembrolizumab [ClinicalTrials.gov identifier: NCT04241185] or durvalumab [ISRCTN.com identifier: ISRCTN43698103] are currently recruiting.

In **Chapter 10** we studied another bladder-preserving strategy: a combination of transurethral resection of the tumor, low-dose external beam radiation and brachytherapy. According to Dutch guidelines, this combination can be offered to patients with small (5 centimeters or less), solitary cT1-T2 tumors. We analyzed the outcome in terms of long-term survival and complications in 259 patients treated with brachytherapy in comparison to radical cystectomy. We excluded patients who underwent radical cystectomy instead of brachytherapy for oncological reasons (i.e., multiple tumors, tumor size >5cm or concomitant CIS). Overall survival at 5/10 years was 66%/49% after brachytherapy and 68%/53% after RC (p = 0.4). Intravesical

recurrence occurred in 58/259 brachytherapy patients after which salvage cystectomy was performed in 32 patients. Our salvage cystectomy rate of 12% was comparable to those of other brachytherapy series[65]. In total, 84% of the brachytherapy-treated patients preserved their bladder. Moreover, brachytherapy resulted in fewer early complications as compared to RC (12% versus 40%, $p<0.001$). We did not assess quality of life. However, a recent study amongst Dutch patients who underwent brachytherapy showed excellent quality of life after treatment[66]. Strikingly, there was no difference in quality of life of brachytherapy patients compared to an age-matched general Dutch population[66]. This strengthens the idea that for a selected patient population, brachytherapy is a well-tolerated bladder-sparing therapy with good outcome, both in terms of survival and quality of life.

All in all, improving bladder-preserving strategies could provide patients with a choice of treatment and may have a positive impact on quality of life. Any bladder-preserving strategy requires close multidisciplinary cooperation to select the right patient for the right treatment. Increasing knowledge regarding biomarkers of response to chemotherapy, radiation, or radical cystectomy may pave the way for selecting patients for different modalities.

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13

Nederlandse samenvatting

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Blaaskanker staat op de zevende plek van meest voorkomende vormen van kanker in Nederland. Elk jaar krijgen bijna 7000 mensen voor het eerst de diagnose blaaskanker. Ongeveer 30% daarvan heeft een tumor die doorgroeit in de spier van de blaas: een spierinvasief blaascarcinoom. Spierinvasieve blaaskanker is een agressieve vorm van kanker doordat spierinvasieve tumoren snel doorgroeien of zich verspreiden (metastaseren) in de lymfeklieren of in organen op afstand (lever, longen, botten).

De behandeling van blaaskanker vergt samenwerking tussen verschillende medische disciplines. Naast de uroloog zijn vaak de patholoog, radioloog, nucleair geneeskundige, oncoloog en radiotherapeut betrokken. In dit proefschrift zijn studies beschreven waarin verschillende aspecten van de multidisciplinaire behandeling van het spierinvasief blaascarcinoom werden onderzocht. De focus lag hierbij op neoadjuvante (preoperatieve) chemotherapie, stadiëring door middel van een PET/CT-scan en orgaansparende behandelingen. **Hoofdstuk 1** is een algemene inleiding over de diagnostiek, stadiëring en behandeling van het spierinvasief blaascarcinoom.

Deel I: Neoadjuvante behandeling van spierinvasief blaascarcinoom

De standaard chirurgische behandeling van het spierinvasief blaascarcinoom is een radicale cystectomie (blaasverwijdering). Voorafgaand aan chirurgie kan neoadjuvante behandeling plaatsvinden. Het doel van neoadjuvante behandeling is het verkleinen van de tumor en het voorkomen danwel behandelen van micrometastasen en daarmee zorgen voor overlevingswinst. In Deel I van dit proefschrift onderzochten we verschillende aspecten van de neoadjuvante behandeling van het spierinvasief blaascarcinoom.

Hoofdstuk 2 is een literatuurstudie naar het verleden, heden en de toekomst van de neoadjuvante behandeling van het spierinvasief blaascarcinoom. In het verleden werd neoadjuvante radiotherapie toegepast, maar dit is inmiddels verlaten. Momenteel adviseren internationale richtlijnen neoadjuvante chemotherapie voor patiënten met spierinvasief blaascarcinoom. Veel patiënten komen echter niet in aanmerking voor chemotherapie, bijvoorbeeld door een slechte nierfunctie. Daarbij is het effect van neoadjuvante chemotherapie op de overleving gering. Daarom is veel onderzoek gedaan naar een veelbelovend alternatief: immunotherapie. Op dit moment wordt neoadjuvante immunotherapie alleen nog in onderzoeksverband toegepast, maar het is de verwachting dat dit in de toekomst uitgebreid zal worden.

In **Hoofdstuk 3** vergeleken wij de pathologische respons en overleving na neoadjuvante chemotherapie en radicale cystectomie tussen verschillende stadia van het spierinvasief blaascarcinoom. Patiënten met stadium cT3-4aN0M0 blaaskanker die neoadjuvante chemotherapie en een radicale cystectomie kregen, hadden een betere algehele overleving dan patiënten die uitsluitend zijn behandeld met radicale cystectomie. Bij patiënten met cT2N0M0 blaaskanker werd geen overlevingsvoordeel gevonden na neoadjuvante chemotherapie. De

uitkomsten van deze studie suggereren dat bij het toepassen van neoadjuvante chemotherapie meer maatwerk wenselijk is. Het standaard neoadjuvante chemotherapieschema bij spierinvasief blaascarcinoom bevat altijd cisplatinum. Daarnaast worden één of meer andere middelen gebruikt. Het optimale schema wat betreft dosering en middelen staat echter niet vast. **Hoofdstuk 3A** is een korte evaluatie van een studie waarin een verhoogde dosisintensiteit van gemcitabine en cisplatinum werd onderzocht.

Na een radicale cystectomie bekijkt een patholoog de verwijderde blaas en lymfeklieren onder de microscoop en bepaalt het tumorstadium. Hiervoor wordt de TNM classificatie gebruikt. Het TNM-stadium heeft een relatie met overleving: hoe hoger het tumorstadium, hoe slechter over het algemeen de overleving. Wanneer patiënten behandeld zijn met neoadjuvante chemotherapie wordt de mate van tumorrespons beoordeeld. Ook dit is gebaseerd op de TNM classificatie. Bij andere vormen van kanker is het echter gebruikelijk om de mate van respons uit te drukken in zogenaamde 'tumor regression grades' (TRG). In **Hoofdstuk 4** onderzochten we of een combinatie van TNM en TRG een betere voorspeller is van overleving dan TNM alleen. We concludeerden dat TRG een simpele, reproduceerbare manier is om de pathologische respons na neoadjuvante chemotherapie te kwantificeren. Door TRG met TNM te combineren kan er mogelijk een betere uitspraak over de prognose van de patiënt met spierinvasieve blaaskanker worden gedaan.

Deel II: Stadiëring van urotheelcarcinoom met FDG-PET/CT

Voorafgaand aan behandeling van spierinvasieve blaaskanker wordt de aanwezigheid van lymfeklier- en/of afstandsmetastasen bepaald met behulp van beeldvorming. Volgens de huidige richtlijnen moet er een CT-scan van de thorax en het abdomen gemaakt worden. Positron emissie tomografie (PET) is een andere beeldvormingstechniek, waarbij een radioactieve tumortracer (FDG) wordt toegediend die op dezelfde manier als glucose in de cellen wordt opgenomen. Doordat kankercellen een verhoogde verbranding hebben, nemen de cellen de radioactieve stof op en wordt de kanker zichtbaar. Tegenwoordig wordt een PET-scan vaak gecombineerd met een CT-scan: PET/CT.

Eerder onderzoek heeft aangetoond dat PET/CT beter is in het diagnosticeren van lymfeklier- en afstandmetastasen dan CT alleen. Of deze toegenomen diagnostische waarde ook van klinisch belang is, moet blijken uit de mate waarin de behandeling van blaaskankerpatiënten verandert. In **Hoofdstuk 5** onderzochten we de meerwaarde van PET/CT ten opzichte van conventionele CT bij de stadiëring van spierinvasieve blaaskanker. We vergeleken het tumorstadium volgens de TNM-classificatie en de voorkeursbehandeling na conventionele CT met die na PET/CT. Bij ruim een kwart van de patiënten was het tumorstadium voor en na PET/CT verschillend. Hierdoor veranderde de voorkeursbehandeling bij bijna 20% van de patiënten: sommige patiënten werden geselecteerd voor neoadjuvante chemotherapie, bij anderen bleek sprake van uitgebreide metastasering waardoor er van curatieve behandeling werd afgezien. Bij 4% van de patiënten werd een tweede primaire tumor gevonden, bijvoorbeeld in de darm of in de slokdarm, wat bij een deel van de patiënten ook weer invloed had op de behandeling van de blaaskanker. We concludeerden dat beeldvorming

met FDG-PET/CT aanvullende stadiëringsinformatie oplevert ten opzichte van conventionele CT. Hierdoor verandert potentieel de behandeling van 1/5 van de patiënten met spierinvasief blaascarcinoom. PET/CT kan patiëntenselectie voor neoadjuvante chemotherapie verbeteren en tevens niet geïndiceerde cystectomieën voorkomen.

Naast de stadiëring voorafgaand aan de behandeling van blaaskanker, vindt er in sommige gevallen ook stadiëring plaats tijdens de behandeling: bijvoorbeeld tijdens neoadjuvante chemotherapie. Door tijdens de behandeling te bepalen of de tumor reageert, kan de behandeling bijgestuurd worden. Wanneer de tumor niet lijkt te reageren op de chemotherapie, kunnen zinloze chemotherapiekuren voorkomen worden. In **Hoofdstuk 6** onderzochten we of PET/CT de respons op neoadjuvante chemotherapie betrouwbaar kan vaststellen. We vergeleken de responsevaluatie door PET/CT met die van conventionele CT. De diagnostische waarde van PET/CT bleek niet beter dan CT bij het vaststellen van respons op chemotherapie. Voor deze indicatie lijkt het gebruik van PET/CT dus niet zinvol.

Tenslotte onderzochten we in **Hoofdstuk 7** de rol van PET/CT bij een andere vorm van kanker van de urinewegen: de hoge urineweg tumoren. De urinewegen (plasbuis, blaas, urineleiders en nierbekken) zijn bedekt met een slijmvlieslaag. Deze slijmvlieslaag noemen we urotheel. Kanker van het urotheel heet urotheelcarcinoom. Urotheelcarcinoom komt in 95% van de gevallen voor in de blaas; dit noemen we blaaskanker. Urotheelcarcinoom kan echter ook in de hoge urinewegen voorkomen, dan spreken we van een hoge urineweg tumor. Omdat PET/CT bij blaaskanker beter is dan CT in het diagnosticeren van lymfekliermetastasen, onderzochten we of PET/CT ook nuttig is bij de stadiëring van hoge urinewegtumoren. In onze retrospectieve studie bleek FDG-PET/CT een hoge sensitiviteit en specificiteit te hebben voor het diagnosticeren van lymfekliermetastasen bij patiënten met hoge urinewegtumoren.

Deel III: Locoregionale behandeling van spierinvasief blaascarcinoom

In het laatste deel van dit proefschrift werden studies beschreven die zich richtten op het minimaliseren van ongewenste effecten van de behandeling van spierinvasief blaascarcinoom.

Bij mannen wordt bij een standaard radicale cystectomie ook de prostaat verwijderd. Dit leidt vaak tot erectiestoornissen. Prostaatsparende cystectomie is een alternatief voor radicale cystectomie en is gericht op het behoud van seksuele functie en continentie. In **Hoofdstuk 8** werden de oncologische en functionele resultaten na prostaatsparende cystectomieën in twee ziekenhuizen beschreven. De oncologische resultaten waren vergelijkbaar met die van radicale cystectomie, met onder andere een 5-jaars overleving van 71%. De functionele uitkomsten (continentie en erectiele functie) waren goed. Wat dit betekent voor de kwaliteit van leven werd in deze studie niet onderzocht, maar dit is een belangrijk onderwerp van toekomstige studie. Prostaatsparende cystectomie lijkt een oncologisch veilig alternatief voor radicale cystectomie, mits vooraf wordt vastgesteld dat deze mannen geen prostaatkanker en geen doorgroei van blaaskanker in de prostaat hebben.

Voor geselecteerde patiënten met spierinvasief blaascarcinoom is chemoradiatie een alternatief voor cystectomie, waarbij de blaas behouden blijft. Bij chemoradiatie krijgen patiënten naast

de bestraling chemotherapie toegediend. Deze zogenaamde 'radiosensitizing' chemotherapie zorgt ervoor dat de kankercellen gevoeliger zijn voor de bestraling. Zo wordt het effect van de bestraling versterkt. In een eerdere studie heeft mitomycine met 5-fluorouracil intraveneus als 'radiosensitizing' chemotherapie winst laten zien ten opzichte van radiotherapie alleen. In ons ziekenhuis wordt 5-fluorouracil sinds 2014 vervangen door capecitabine tabletten, waardoor patiënten niet meer op de dagbehandeling worden opgenomen voor een infuus. Capecitabine is bewezen effectief bij chemoradiatie voor andere maligniteiten, maar is niet eerder onderzocht bij het spierinvasief blaascarcinoom. In **Hoofdstuk 9** analyseerden wij de resultaten van chemoradiatie met eenmalig mitomycine en capecitabine bij patiënten met spierinvasief blaascarcinoom. We vonden dat chemoradiatie met capecitabine tabletten een goed te verdragen blaassparende behandeling is. Ernstige toxiciteit was zeldzaam en locoregionale tumorcontrole en ziektevrije overleving zijn veelbelovend. Als deze resultaten bij langere follow-up vergelijkbaar blijven, zou een vergelijkende studie met verschillende chemoradiatie schema's kunnen volgen.

Een andere vorm van blaassparende therapie is brachytherapie van de blaas. Dit is een combinatie van uitwendige bestraling, gevolgd door inwendige bestraling (brachytherapie). Hiervoor worden holle katheters rond de tumor in de blaaswand geplaatst, waarna deze katheters gedurende een aantal dagen enkele malen per dag met een radioactieve bron worden geladen. De tumor wordt zo heel gericht bestraald en de blaas blijft behouden. De uitkomst van deze behandeling werd onderzocht in **Hoofdstuk 10**. In totaal werden 310 patiënten die met brachytherapie werden behandeld retrospectief geanalyseerd. De 5- en 10-jaarsoverleving na brachytherapie was vergelijkbaar met die na radicale cystectomie. Een recidief in de blaas werd gezien in 58/259 patiënten die behandeld werden met brachytherapie, waarna alsnog een cystectomie werd uitgevoerd bij 32 patiënten. In totaal behield 82% van de brachytherapiepatiënten hun blaas. Hierdoor werd bevestigd dat in patiënten met een solitair, ≤5 cm cT1G3-T2N0M0 blaascarcinoom brachytherapie kan worden aangeboden als alternatief voor radicale cystectomie.

Wanneer een patiënt geen blaassparende behandeling ondergaat, maar een radicale cystectomie, is het belangrijk aandacht te besteden aan de zorg rondom de operatie. De laatste jaren is veel onderzoek gedaan naar zogenaamde ERAS (Enhanced Recovery After Surgery) protocollen. Een ERAS protocol omvat allerlei factoren die kunnen zorgen voor een beter en sneller herstel na de operatie, zoals optimale pijnbestrijding en aandacht voor mobiliseren na de operatie. Ook voeding maakt een belangrijk deel uit van perioperatieve protocollen. In **Hoofdstuk 11** vergeleken we twee verschillende voedingsstrategieën na radicale cystectomie in twee ziekenhuizen. In het ene ziekenhuis werden patiënten gestimuleerd om vanaf de tweede dag na de operatie een licht verteerbare maaltijd te eten, in het andere ziekenhuis kregen patiënten vanaf de dag na de operatie voeding via een speciale sonde. Er was geen verschil in opnameduur tussen de twee protocollen. Bij patiënten die via een sonde werden gevoed trad minder vaak een ileus op. Het is op basis van deze retrospectieve studie echter lastig vast te stellen of dit het gevolg is van de voedingsstrategie, of dat andere factoren een rol spelen.

Na deze drie delen vormde **Hoofdstuk 12** een samenvattende discussie van dit proefschrift.

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Dankwoord

Het is al even geleden dat ik de deur van het O-gebouw voor de laatste keer achter me dicht liet vallen, maar ik denk nog regelmatig terug aan mijn tijd in het Antoni van Leeuwenhoek. Ik ben trots en dankbaar dat ik in dit bijzondere ziekenhuis en onderzoeksinstituut mijn promotieonderzoek heb mogen uitvoeren. Vele collega's, vrienden en familieleden zijn in meer of mindere mate betrokken geweest bij de totstandkoming van dit proefschrift. Een aantal wil ik in het bijzonder bedanken.

Prof. dr. Horenblas, Simon, vanaf het moment dat jij me kwam halen voor mijn sollicitatiegesprek heb ik grote bewondering voor je. Je humor, directheid, en het feit dat je naast oog voor het inhoudelijke ook altijd oog hebt voor het persoonlijke, maken je de perfecte promotor. Bedankt voor je vertrouwen.

Dr. van Rhijn, Bas, bedankt voor alle kansen die jij gecreëerd hebt. Jouw vermogen en enthousiasme om samenwerkingen tot stand te brengen is niet te evenaren. Je bent een geboren opleider en begeleider en weet elk manuscript tot een succes te maken. Zonder jou was dit proefschrift een heel stuk dunner geweest, dankjewel voor alles!

Dr. Hendricksen, Kees, wat ben ik blij dat ook jij mijn copromotor bent. Je onuitputtelijke stroom ideeën voor nieuwe projecten maakten dat het me soms duizelde als ik van je kamer kwam, maar je aanstekelijke enthousiasme voor het onderzoek maakte dat altijd meer dan goed. Samen met een dikke jetlag rondstruinen in San Francisco behoort zonder twijfel tot de hoogtepunten van mijn onderzoekstijd.

Dr. Meijer, Richard, met het laatste hoofdstuk van dit boekje is het allemaal begonnen. Ik ben je heel dankbaar voor de introductie in het blaaskankeronderzoek en vind het nog altijd fijn samenwerken!

Geachte **leden van de promotiecommissie**, dank voor het beoordelen van mijn proefschrift en deelname aan de commissie.

Beste co-auteurs, bedankt voor de samenwerking en jullie waardevolle aanvullingen. Dear co-authors, thank you for all your input, revisions and feedback. **Eva Schaake**, bedankt voor je betrokken begeleiding bij het chemoradiatie stuk. Dear **Roland Seiler** and **Cedric Poyet**, thank you for the opportunity to collaborate on the TRG project. **Laura Smit**, bedankt voor het samen coupes kijken! **Michiel van der Heijden**, bedankt voor je altijd kritische blik. **Erik van Werkhoven**, veel dank voor je statistische optimisme als ik het even niet meer zag zitten. **Erik Vegt**, **Maarten Donswijk** en **Annemarie Bruining**, bedankt voor jullie hulp bij het herbeoordelen van scans voor het responsevaluatie stuk. **Judith Bosschieter**, nooit eerder was data inkloppen zo gezellig!

Urologen en verpleegkundig specialisten van het AVL, bedankt voor alle data, de gezelligheid op congressen en jullie geduld bij het oefenen van praatjes.

Marja en Joke, veel dank voor alle praktische ondersteuning. Ook veel dank aan de **Core Facility** en natuurlijk aan **Tony van de Velde**. Zonder de database was dit proefschrift er nooit geweest, bedankt voor al je hulp.

Stafleden, arts-assistenten en medewerkers van de Urologie in het UMC Utrecht en het Centraal Militair Hospitaal, bedankt voor de fijne tijd, van semi-arts tot AIOS. **Vincent de Kemp**, bedankt voor je vertrouwen bij mijn eerste stappen in de kliniek. Je bent een voorbeeld!

Lieve **Saar**, wat heb ik genoten van het dagelijkse cabaret op kamer O3.23. Ik bewonder je eindeloze precisie en geduld en zou willen dat ik voor de rest van m'n carrière tegenover jou kon zitten! Lieve **Joost**, samen altijd perfect op de hoogte van het wie/wat/waar en aan één blik genoeg. Wat heerlijk dat we weer collega's zijn in het UMCU! Lieve **Nick**, strikt genomen geen kamergenoot maar wat hebben we gelachen! Van TLS tot de Charlotte Voskuilen starter pack, bedankt dat je me mee op sleeptouw nam. Jij bent en blijft natuurlijk de enige echte bladder babe! Lieve **Merijn** en **Hielke-Martijn**, bedankt voor jullie altijd nuchtere kijk op de zaak als ik me weer eens druk kon maken om vrij weinig.

Elies, bedankt voor al het voorwerk, dankzij jou voelde ik me vanaf het eerste moment helemaal op mijn plek. **Tom**, ook jij hebt me een vliegende start gegund en daarvoor ben ik je heel dankbaar! Ook veel dank aan alle andere Team Blaas voorgangers, in het bijzonder **Laura**. Niemand die een idee zo snel tot een praktisch en haalbaar onderzoeksproject kan omtoveren als jij. Dankjewel voor je hulp en motiverende woorden bij de laatste loodjes. Opvolger **Sarah**, bedankt voor je hulp bij hoofdstuk 5, ik ben natuurlijk blij dat ik toch nog nét voor jou promoveer!

Lieve **PhDiva's**, wat was het gezellig! Nu zijn we dan toch echt allemaal klaar, tijd voor diner!

Lieve **onderzoekers uit het O-gebouw**: het was een groot feest! Alle koffietjes in de zon, lunches op het dakterras, het bootje varen en de eindeloze vrijdagmiddagborrels die bij voorkeur op donderdag begonnen: ik heb genoten van mijn onderzoekstijd en dat is dankzij jullie.

Lieve **Marieke**, samen de vooropleiding in Hoorn, wat een toevallig geluk! Het lachen en huilen tijdens de ritjes over de A7 in m'n geliefde Upje was genieten!

Lieve **Tessa en Simone**, Febo girls, bedankt voor de onvergetelijke tijd op de Ferdinand Bol. Ik mis jullie dagelijkse wijze raad en scherpzinnigheid!

Lieve **Anouk en Leonie**, mijn forever studiematen maar inmiddels zo veel meer! Niemand met wie ik zo heerlijk over werk kan klagen en lachen als met jullie. Anouk, jou (en John) ben ik natuurlijk eeuwig dankbaar voor de liefde van mijn leven!

Lieve **clubgenoten**, bedankt voor jullie interesse in mijn werk en dit proefschrift, maar vooral heel veel dank voor alle knusse eetclub avondjes!

Lieve **oudhuisgenoten van de B52**, in het bijzonder **Aad**, **Bets**, **Botje**, **Kees**, **Miep** en natuurlijk **Tom en Jack**: wat is het fijn om zulke inspirerende vrouwen om me heen te hebben! Bedankt voor alle wijze woorden en de eindeloze etentjes, culturele uitjes en weekendjes weg. Met jullie zijn voelt altijd weer als thuiskomen en dat is heerlijk!

Lieve **Heijmannen**, schoonfamilie heb je niet voor het kiezen, maar wat bof ik met de mijne! Lieve **Carda**, bedankt dat je altijd voor ons klaarstaat.

Lieve **Henny en Marco**, bedankt voor jullie interesse in alles wat ik meemaak. Heel bijzonder en fijn dat jullie al zo lang met mij meeleven.

Lieve **Rox, Eef en Lo**, bedankt dat jullie er altijd voor me zijn. Lieve **Roxie**, al meer dan 25 jaar de meest loyale vriendin die ik me kan wensen, wat zou ik zonder je moeten! Lieve **Eef**, niemand die me op zo'n relativerende manier tot andere inzichten kan brengen als jij. Lieve **Lo**, zonder twijfel de meest zorgzame en veerkrachtige (en stijlvolle!) vrouw die ik ken. Wat een geluk dat jullie naast me staan, vandaag, maar eigenlijk altijd!

Dear **Aynsleys**, dear **Vince, Bella, Ben, Sophie, Anna and Sara**, who would have thought a tiny town called Waimumu would become my favorite place in the world? Bushypark has always felt like home and that is because of all of you. Lieve **Bella**, toen ik zelf achttien werd, realiseerde ik me pas hoe bijzonder onze band is, ondanks (of misschien dankzij?) het verschil in leeftijd. Jij bent mijn grote zus en dat zeg ik altijd met ongelofelijk veel trots. Ik mis je!

Lieve **papa en mama**, bedankt voor jullie liefdevolle steun. Jullie staan echt altijd voor mij klaar; vroeger bij verhuizingen of met de zoveelste nieuwe fiets, tegenwoordig met zelfgekookte maaltijden en een achterbak vol bloemen. Lieve pap, jouw brede interesse en nieuwsgierigheid (kom, we zoeken het even op!) hebben mij in grote mate gevormd en daarvoor ben ik je voor altijd dankbaar. Lieve mama, dat onze dochter zonder twijfel jouw naam kreeg, zegt eigenlijk alles. Je zorgzaamheid en lieve adviezen maken dat ik altijd bij jou terecht kan. Ik ben trots op je.

Liefste **Jelle**, jij maakt me zo gelukkig! Dankjewel voor je onvoorwaardelijke liefde. Ik voel me door jou gesteund in alles wat ik doe en dat is het meest heerlijke gevoel van de wereld. Ik heb zo ongelofelijk veel zin in de rest van ons leven samen, met natuurlijk onze allerliefste **Lucy**! ♥

Curriculum vitae

Charlotte Sophie Voskuilen was born in Amersfoort, the Netherlands, on the 17th of January 1991. After graduating from the Corderius College Amersfoort in 2009, she took courses in chemistry, biology and physics at the James Boswell Institute, Utrecht, to meet the requirements for medical school. In 2010 she started medical school at Utrecht University. During her studies, she went to Cape Town, South Africa for a clinical internship in Dermatology.

Her interest in Urology was born during a surgical rotation, and in her final year of medical school she did a combined clinical and research internship at the Urology department of the University Medical Center Utrecht under the supervision of Drs. M.T.W.T. Lock and Dr. R.P. Meijer. The results of this research internship formed the basis for Chapter 11 of this dissertation. After receiving her medical degree in 2017, Charlotte continued her research on bladder cancer as a PhD candidate at the Department of Urology of the Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital under the supervision of Prof. dr. S. Horenblas, Dr. B.W.G. van Rhijn and Dr. K. Hendricksen. In 2020 she began as a resident not-in-training in the Central Military Hospital in Utrecht under the supervision of Drs. V.F. de Kemp.

Charlotte is currently appointed as a resident in training at the Urology department of the University Medical Centre Utrecht under the supervision of Prof. dr. L.M.O. de Kort and Dr. R.P. Meijer. She lives in Utrecht with Jelle Heijman and their daughter Lucy.