Treatment and survival of patients with muscle-invasive bladder cancer:
A nationwide register-based approach

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Abbreviations

BC	Bladder cancer
CR	Complete pathological response
CRN	Cancer Registry of Norway
CSS	Cancer-specific survival
CT	Computed tomography
DS	Pathological downstaging of the primary tumour
EAU	European Association of Urology
ICD	International Classification of Diseases
LN	Lymph node
MIBC	Muscle-invasive bladder cancer
MRI	Magnetic resonance imaging
MVAC	Methotrexate, vinblastine, doxorubicin, and cisplatin
NAC	Neoadjuvant chemotherapy
NPR	Norwegian Patient Registry
NMIBC	Non-muscle-invasive bladder cancer
Non-UC	Non-urothelial variant histology
OS	Overall survival
RC	Radical cystectomy
RT	Radiotherapy
TNM	Tumour Node Metastasis
TURB	Transurethral resection of bladder tumour
UC	Urothelial carcinoma
UTC	Urinary tract cancer

Thesis summary

Bladder cancer presents as localised muscle-invasive bladder cancer (MIBC) or metastatic bladder cancer in approximately 25% of cases, and the remaining 75% present as unaggressive and good prognosis non-invasive bladder cancer. The prognosis of MIBC and metastatic bladder cancer is poor, with a five-year survival of approximately 50% after curative treatment for MIBC and a median survival of approximately three months for untreated patients with metastatic bladder cancer. Treatment management and survival in a population-based cohort of patients with MIBC and metastatic bladder cancer have not previously been investigated in Norway. Such knowledge is necessary to identify gaps in care, areas for improvement, and future understanding of the impact on management and prognosis of new developments in clinical practice.

The standard curative intent treatment for MIBC is the surgical removal of the bladder (radical cystectomy) with or without preceding cisplatin-based chemotherapy (neoadjuvant chemotherapy). Radiotherapy of the bladder with or without concurrent chemotherapy may be offered to patients unable or unwilling to undergo cystectomy. It is unclear if there is a difference in survival outcomes after cystectomy alone for patients initially presenting with MIBC (primary) compared to patients progressing from non-muscle invasive bladder cancer to MIBC (secondary). This has not been investigated for patients treated with radiotherapy. Paper one of this thesis presents the first Norwegian results of long-time survival outcomes for all curatively treated patients with MIBC and compares survival between patients with primary and secondary MIBC. Independent of type of treatment, the type of MIBC did not impact the mortality risk for all patients.

Clinical trials have shown that neoadjuvant chemotherapy before cystectomy provides patients with superior survival compared to patients treated with cystectomy alone. The survival benefit is associated with downstaging of the primary tumour (downstaging). Population-based studies have investigated if the survival benefit of neoadjuvant chemotherapy also can be demonstrated in the general population of patients with MIBC, but results have been inconclusive. The second paper of this thesis is the first Norwegian study of patients with MIBC, investigating the impact of neoadjuvant chemotherapy on downstaging and overall survival compared to cystectomy alone. The study supplements previous international studies by using additional modern statistical methods. Results could not be commensurate with the expected survival benefit of neoadjuvant chemotherapy over cystectomy alone found in clinical trials, except when the effect of neoadjuvant chemotherapy

was mediated by downstaging. Patients with downstaging had superior survival compared to patients without downstaging. Neoadjuvant chemotherapy increased the proportion and probability of downstaging and indirectly affected overall survival.

The standard first-line treatment for metastatic bladder cancer is platinum-combination chemotherapy and has been largely unchanged since the beginning of the millennium. Recent advances with new therapeutic options are changing the treatment landscape. The final paper in this thesis describes the patient- and disease characteristics of patients with primary metastatic bladder cancer. In addition, it describes the survival and hospitalisations for these patients according to the initial treatment received before the approval of immunotherapy: chemotherapy, local tumour treatment, a combination of chemotherapy and local tumour treatment, or no anti-cancer treatment. The study demonstrates that a large proportion of patients do not receive any anti-cancer treatment and is potentially an underserved population. Median survival was ten months for patients treated with chemotherapy, and these patients spent four times more days hospitalised compared to untreated patients.

This thesis provides evidence-based knowledge of treatment management and survival of patients with MIBC with and without metastatic disease on a population-based level in Norway. The findings may assist clinicians in pre-treatment and post-treatment counselling of patients and serve as a basis for future comparative studies of similar outcomes in more recent patient cohorts and after treatment with new therapeutic options.

Norsk sammendrag

Blærekreft presenterer seg i ca. 25% av tilfellene som en svulst som vokser inn i blæreveggens muskelvev (muskel-invasiv) eller som blærekreft med spredning (metastatisk). De resterende 75% består av svulster i blærens slimhinne (ikke-muskel-invasiv) som generelt har en god prognose. Prognosen for muskel-invasiv blærekreft og metastatisk blærekreft er alvorlig. Fem år etter kurativ behandling er ca. 50% av pasientene i live. Ubehandlede pasienter med metastatisk blærekreft har en median overlevelse på bare tre måneder. Behandling og overlevelse av pasienter med muskel-invasiv blærekreft og metastatisk blærekreft på populasjonsnivå har ikke tidligere blitt undersøkt i Norge. Denne kunnskapen er nødvendig for å kunne identifisere områder innen kreftomsorgen med forbedringspotensial og for å kunne forstå hvilken innvirkning nye behandlingsmetoder har på behandlingsmønstre og prognose.

Standard kurativ behandling for muskel-invasiv blærekreft består av kirurgisk fjernelse av blæren (cystektomi) med eller uten forutgående cellegiftbehandling (neoadjuvant behandling). Strålebehandling mot blæren med eller uten samtidig cellegift er et alternativ for pasienter som ikke kan eller vil opereres. Det er uavklart om det er forskjell i overlevelse etter cystektomi for pasienter som debuterer med muskel-invasiv blærekreft (primær) sammenlignet med pasienter med en ikke-muskel-invasiv blærekreft som har utviklet seg til muskel-invasiv sykdom (sekundær). For pasienter behandlet med strålebehandling er dette ikke tidligere undersøkt. Det første delarbeid av denne avhandlingen presenterer de første norske tall for langtidsoverlevelse etter cystektomi eller strålebehandling for pasienter med muskel-invasiv blærekreft, og sammenligner overlevelsen mellom pasienter med primær og sekundær sykdom. Resultatene viste ingen forskjell i overlevelse mellom primær og sekundær muskel-invasiv blærekreft, uavhengig av type av behandling.

Kliniske studier har vist at pasienter med muskel-invasiv blærekreft som mottar cellegift før cystektomi (neoadjuvant behandling) har en bedre overlevelse enn pasienter som behandles med cystektomi alene. Overlevelsesgevinsten er assosiert med tumorskrumpning etter operasjon. Resultater fra populasjonsstudier som har undersøkt sammenhengen mellom neoadjuvant behandling og overlevelse i den generelle befolkningen har vært inkonklusive. Det andre delarbeid av denne avhandlingen er det første norske studie som sammenligner overlevelsen hos pasienter som har og ikke har mottatt neoadjuvant behandling med bruk av

mere moderne statistiske metoder sammenlignet med lignende studier. I tillegg undersøkes sammenhengen mellom neoadjuvant behandling og tumorskrumpning, samt mellom tumorskrumpning og overlevelse. Tumorskrumpning er en god prognostisk faktor. Sammenlignet med pasienter uten tumorskrumpning hadde pasienter med tumorskrumpning bedre overlevelse. For pasienter som mottok og ikke mottok neoadjuvant behandling, fikk henholdsvis over 40% og 20% av pasientene tumorskrumpning. Sannsynligheten for tumorskrumpning var høyere med neoadjuvant behandling enn uten. For alle pasienter, var det ingen forskjell i overlevelse for pasienter behandlet med og uten neoadjuvant behandling.

Standard behandling av metastatisk blærekreft har de siste 20 årene uendret bestått av platinaholdige kombinasjoner av cellegift. Nye medisinske behandlinger er i ferd med å endre dette paradigmet. Det siste delarbeid i denne avhandlingen beskriver pasient og sykdomsrelaterte faktorer for pasienter med blærekreft som debuterer med metastatisk sykdom. I tillegg beskrives overlevelse og hospitalisering for disse pasienter i henhold til den første behandling de har mottatt etter diagnosen fra før immunterapi ble godkjent for bruk: cellegift, lokal svulst behandling, en kombinasjon av cellegift og lokal svulst behandling, eller ingen kreftrettet behandling. Studien viser at over halvdelen av disse pasientene ikke mottar noen initial kreftrettet behandling, og hadde en median overlevelse på to måneder. Median overlevelse var ti måneder for pasienter som ble behandlet med cellegift. Disse pasientene var innlagt på sykehus i fire ganger flere dager enn de ubehandlede pasientene.

Denne avhandlingen bidrar til økt kunnskap om behandlingsmønster og overlevelse hos pasienter med muskel-invasiv blærekreft med og uten spredning i Norge. Resultatene kan brukes av klinikere i rådgivningen av pasienter før og etter behandling, og som grunnlag for fremtidige studier av behandlingsmønstre og overlevelse etter innføring av nye medisinske behandlinger.

Articles in the thesis

Paper I

Christina Tanem Møller, Sophie D Fosså, Gunnar Tafjord, Ronnie Babigumira, Viktor Berge, and Bettina Kulle Andreassen. "**Primary versus secondary muscle-invasive bladder cancer: survival after curative treatment"**. Scandinavian Journal of Urology. 2022;56(3):214-220.

Paper II

Christina Tanem Møller, Nathalie C Støer, Augun Blindheim, Viktor Berge, Gunnar Tafjord, Sophie D Fosså and Bettina Kulle Andreassen. "**Downstaging and survival after Neoadjuvant Chemotherapy for bladder cancer in Norway; a population-based study**". BMC Cancer. 2022;22(1):1301

Paper III

Christina Tanem Møller, Gunnar Tafjord, Augun Blindheim, Viktor Berge, Sophie D Fosså and Bettina Kulle Andreassen. **"Initial Management and Survival of Patients with Primary Metastatic Bladder Cancer before the Immunotherapy Era: A Population-based study from Norway".** In manuscript, submitted to Scandinavian Journal of Urology 2022.

Introduction

The treatment and survival of patients with muscle-invasive bladder cancer (MIBC) and metastatic bladder cancer (BC) have not previously been described and evaluated in Norway. The treatment of MIBC and metastatic BC has largely been unchanged for the past decades, but recent advances within medical oncology are changing the treatment landscape. With this background, data and analyses of contemporary treatment strategies and survival, as presented in this thesis, are necessary to provide a benchmark for future research of novel treatment strategies and survival in routine clinical practice.

This first section of this thesis provides an overview of the epidemiology of BC and the diagnosis and treatment of MIBC and metastatic BC. In the second section, the aims, methods, and results of this thesis are presented and discussed.

1. Bladder cancer

Localised bladder cancer (BC) is categorised as MIBC, or non-muscle invasive bladder cancer (NMIBC) based on the depth of tumour invasion into the bladder wall. MIBC is defined by tumour invasion into the muscularis propria of the bladder wall and beyond (Tumour, Node, Metastasis (TNM) classification tumour category T2-T4) [1]. Tumours confined to the urothelium (Ta, Tis) and the lamina propria (T1) are considered NMIBC (Figure 1)[2]. *Primary MIBC* and *metastatic BC* comprise approximately 25% of all newly diagnosed cases, whilst 75% of cases present with NMIBC [3]. Approximately 15% of patients initially diagnosed with NMIBC progress to muscle-invasive disease, *secondary MIBC.* The majority of tumours (>90%) are urothelial carcinomas (UC), and the remaining tumours have non-urothelial variant histologies (non-UCs)[4].

NMIBC often recur, has a low risk of developing metastases and an overall good prognosis[5, 6]. In contrast, MIBC is an aggressive disease with a high risk of progression to metastatic BC and cancer-specific mortality[7]. The clinical implication is that MIBC and NMIBC has different disease courses and treatment management. The most common sites for BC metastases are regional lymph nodes, bone, lung and liver[8]. *Metastatic BC* is a highly aggressive disease with a poor prognosis if left untreated[9, 10]

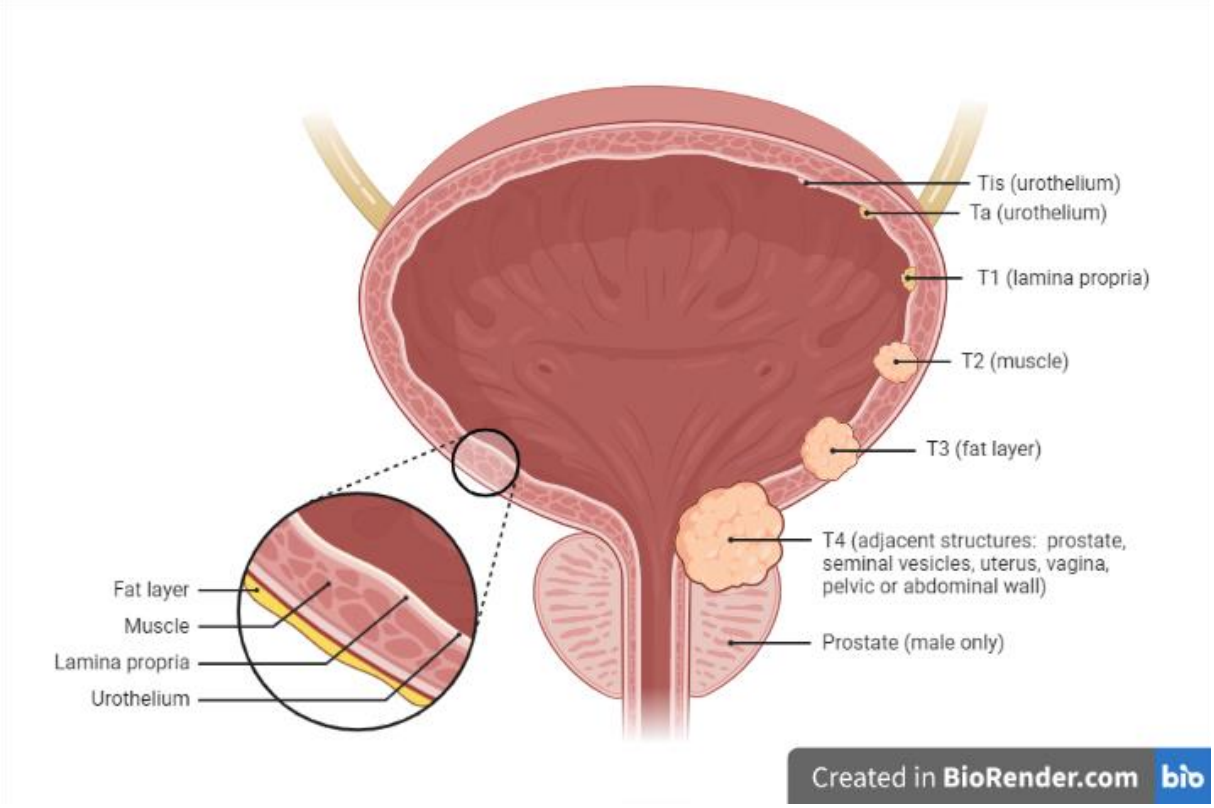

Figure 1. Bladder wall and T-category. *Copyright has been obtained.*

2. Epidemiology

2.1 Incidence

In 2020, an estimated 573,000 new cases of BC (International Classification of Diseases (ICD)-10 C67) were diagnosed worldwide, which accounts for 3% of all new cancers and makes BC the 10th most diagnosed cancer worldwide[11]. With four times higher global age-standardised incidence rate of BC in men compared to women (9.5 versus 2.4), BC is the 6th most diagnosed cancer among men. The median age at diagnosis is >70 years[12-14]. Geographically, the highest age-standardized incidence rates (per 100,000/year) are found in Southern Europe, Western Europe and Northern America, and the lowest rates are in Middle and Western Africa. There is a wide variation of BC incidence for the male population, ranging from 2.2 in Middle Africa to 26.5 in Southern Europe. The variation for women is not as wide, ranging from 0.7 in South-Central Asia to 5.8 in Southern Europe[11] (Figure 2).

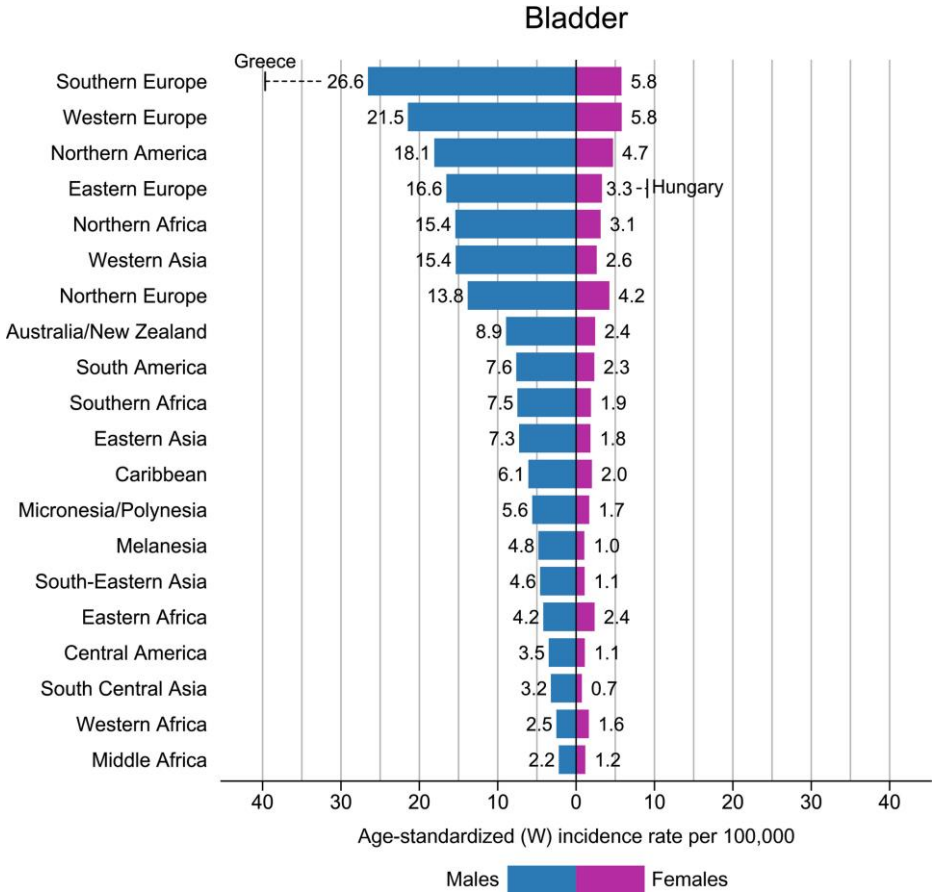

Figure 2. Region-Specific Incidence Age-Standardized Rates by Sex for Bladder Cancer in 2020. *Source: GLOBOCAN 2020. https://gco.iarc.fr/. Copyright has been obtained.*

The worldwide geographical distribution of BC incidence may reflect the prevalence of the main risk factor for BC, tobacco smoking[15]. Bladder infection with the protozoan Schistosoma haematobium relates to the incidence rate in endemic regions such as Northern Africa and the Middle East [16]. Occupational chemical exposures (aromatic amines, rubber, aluminium, arsenic) are a risk factor dependent on the geographical location of such industries.

In the annual report of cancer incidence, mortality, survival and prevalence in Norway published by the Cancer Registry of Norway (CRN), the cancer statistics for BC (ICD-10 C67) are reported together with other urinary tract cancers (UTC) (ICD-10 C65-C68). In 2021, the total incidence of UTC was 1,871 cases, of which 1,659 (89%) cases were BC (C67)[13]. UTC represented 5% of all cancer cases in Norway in 2021. The incidence is approximately three times higher among men compared to women, with an age-standardised incidence rate for men of 48.8 and 15.5 for women. Of the 1,871 cases of UTC, 1,376 (74%) were among men, accounted for 10% of all new cases of cancer in men and was the 5th most

common cancer diagnosed among men in Norway. In women, there were 495(25%) cases which comprised 3% of all new cancers for women. The median age at diagnosis was 73 years in 2017-2021, and unchanged compared to earlier time periods (1987-1991, 1997-2001, 2007-2011).

Since 1962 the incidence rate of UTC was increasing until it stabilized in the 1990s (

Figure 3). In Norway, the percentage of male smokers between 16-74 years decreased from 52% in 1973 to 13% in 2014, whereas the percentage for females remained approximately 30% in the same period[17, 18]. UTCs are smoking-related cancers and the stabilized level of incidence may reflect changes in smoking habits[18].

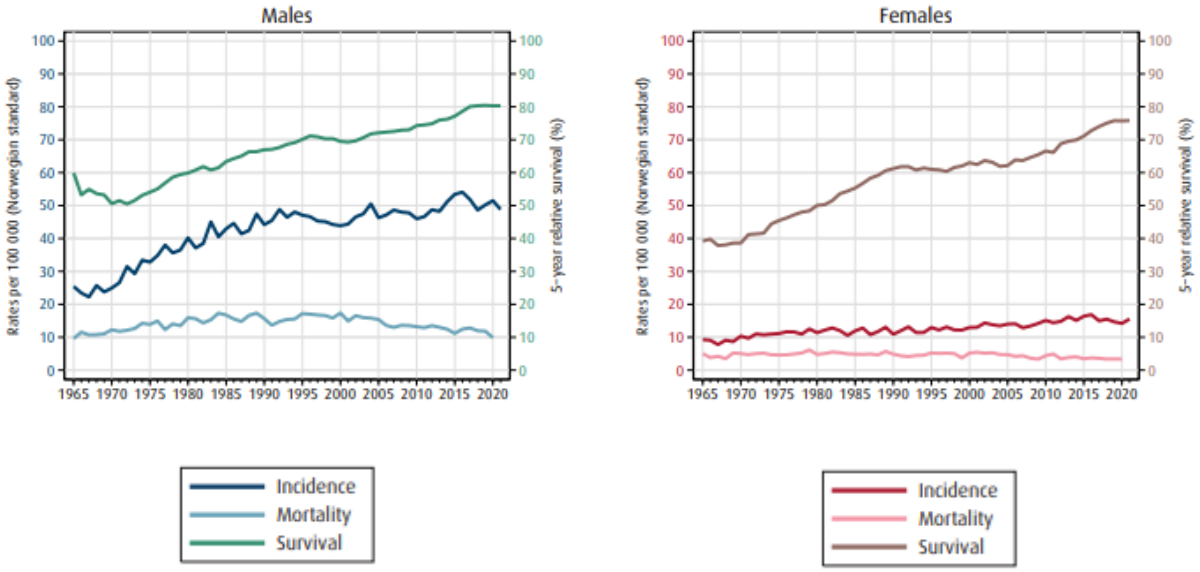

Figure 3 Trends in incidence and mortality rates, and five-year relative survival proportions. Source: Cancer Registry of Norway. *Copyright has been obtained*

Global incidence rates for MIBC are unavailable since there are large variations in cancer registry practices of distinguishing between NMIBC and MIBC[11, 15]. In Norway, age-standardised incidence rates for MIBC have been unavailable. Up until 2018, the CRN registration practice only separated between non-invasive BC (<pT1) and invasive BC (≥T1). The reported incidence rates of invasive cancer (≥T1) was 8.4 for men and 2.3 for women in 2011-2014[18]. By use of statistical methods, the estimated proportion of patients with MIBC was 34% in patients diagnosed with BC (UC) between 2001 and 2010[19]

2.2 Mortality

Worldwide, an estimated 213,000 cancer deaths were caused by BC in 2020. This constitutes 2.1% of all cancer deaths[11]. The higher incidence of BC among men is reflected in the mortality rate, with mortality rates (per 100,000/year) of 3.3 for men and 0.9 for women. Age-standardised mortality rates are the highest in Northern Africa, the Middle East, Eastern Europe, Western and Southern Europe. Egypt has the highest mortality rate of 7.8 for both sexes [20].

In Norway, UTC constitutes 3.1% of all cancer deaths, with 349 deaths from UTC in 2020, of which 241 were men and 108 were women[13]. The age-standardised mortality rates were 9.9 for men and 3.3 for women. Over the last 20 years, a slight decline in the mortality of BC has been observed for both sexes (

Figure 3). The mortality rates are more useful for comparing temporal trends and disease control of MIBC, as they mainly reflect this more aggressive entity compared to good prognosis NMIBC. The decreased mortality is possibly associated with increased disease awareness, the earlier detection of aggressive disease, and treatment changes.

2.3 Survival

Global population-based survival data are not available since not all nations have national or regional cancer registries. There are some data from Europe for non-invasive BC (<pT1) and invasive BC (≥T1) combined, with estimated five-year relative survival of 68% in 2000-2007 [21]. Scotland and the Netherlands based survival estimates on invasive tumours (≥T1) only and reported five-year relative survival of 49% and 52%, respectively.

The five-year relative survival of Norwegian patients with UTC has increased over the last 50 years. The relative five-year survival for men was 64.3% in 1982-1986 and increased to 80.3% in 2017-2021 [13]. The same trend can be seen for women with a five-year relative survival of 56.7% in the early period and 75.8% in the latest period. The five-year relative survival for patients with distant metastases has increased from 2.9% (1982-1986) to 9.5% (2017-2021). For BC only, the five-year relative survival in 2011-2014 of non-invasive BC (<pT1) was 88-93% for men and 88-89% for women, and 58% for men and 50% for women for invasive BC (≥T1)[18]. For MIBC, the estimated range of crude possibility for death was 0.42- 0.74 at five years for patients diagnosed between 2001-2010[19]

2.4 Risk factors

The most significant single risk factor for developing BC is increasing age. The cumulative exposure to carcinogens causing DNA damage increases with age, whereas the ability for DNA repair decreases[22].

Tobacco contains carcinogens (polycyclic aromatic hydrocarbons, aromatic amines, N-nitroso compounds) which accumulate in the urothelium and cause DNA damage, making tobacco smoking a major risk factor for BC development[23]. Compared to non-smokers, the risk of BC is three-fold increased for smokers, and associated with age of first exposure, smoking intensity and duration [23-25]. Smoking cessation reduces the risk, but even after 25 years, the risk is still 1.5 higher than non-smokers[24]. The estimated proportion of BC cases in Europe which are attributable to smoking is 43% in men and 26% in women[24]. Other carcinogenic chemical compounds (e.g., arsenic, benzidine, chlornaphazine)[26] are also associated with increased risk of BC. Exposure to such compounds is associated with professions such as firefighters and painters, as well as occupations in industries involved in the production of aluminium, dye, and rubber.

There are other exposures besides chemical compounds that are associated with risk of BC, such as the parasite Schistosoma haematobium and X- and Gamma-radiation used in radiation therapy (RT). Infection with Schistosoma is associated with the histological type, squamous cell carcinoma of the bladder. External beam pelvic RT increases the risk of secondary BC. For instance, the risk of developing secondary BC after RT for prostate cancer is increased by 1.2-2.5 times compared to patients treated with radical prostatectomy [27-29]

The effect of diet on BC risk has been studied extensively in a European multicentre and prospective study (EPIC); results have shown no strong association between dietary components such as fruits, vegetables, red meat with associated dietary nitrosamines and hem iron, or vitamin C and risk of BC [30-32]. Nor is there any supportive evidence of a clear association between alcohol [33], coffee [34], tea, cola or energy drinks[35] and risk of BC.

The incidence of BC is greater in men than in women, but women present with more advanced disease and have an adverse prognosis compared to men [36, 37]. The reason for the disadvantageous prognosis of women is unclear. Differences in metabolism and exposure to carcinogens, delay of diagnosis, as well as differences in gender hormones have been suggested to influence the disparity in survival outcomes between women and men.[38]

Other patient related factors such as elevated blood pressure, triglycerides, and body mass index have also been found to be associated with risk of BC, although with significant inter-gender differences[39].

3. Diagnosis and staging of muscle-invasive bladder cancer

3.1 Symptoms

Painless, visible haematuria (macroscopic) is the most common presenting symptom of BC. Patients can also present with non-visible haematuria (microscopic) and irritative voiding symptoms (dysuria, urgency, increased frequency). Patients with locally advanced bladder tumours may present with pelvic pain and clinical findings related to urinary tract obstruction

3.2 Diagnosis

The diagnosis is made by visualisation of the tumour by cystoscopy or imaging and a histopathologic verification of BC cells in a histological specimen from the bladder retrieved by a TURB.

Patients suspected of BC are initially clinically examined by bimanual palpation of the bladder (rectal or vaginal) and cystoscopy. Bimanual palpation is performed to uncover a potential palpable mass, which can be found in patients with locally advanced disease. With cystoscopy, the inner lining of the bladder wall can be inspected, and suspicious lesions can be assessed. In the clinical work-up of patients suspected of BC, cystoscopy may be omitted if preceded by computed tomography (CT) or magnetic resonance imaging (MRI) providing a complete image of the bladder tumour.

A supplement to the initial assessment of suspected cases of MIBC is an examination of a urine sample, which can be used to detect exfoliated cancer cells (urinary cytology). A positive cytology indicates there is a tumour in the urinary tract but not its location. However, a negative cytology does not exclude the presence of a tumour [40].

The purpose of a subsequent diagnostic TURB, after visual confirmation of a bladder tumour by cystoscopy or imaging, is to obtain a histopathological diagnosis and assess the depth of tumour invasion into the bladder wall. TURB can also be potentially therapeutic in MIBC, with reports of 12-15% of patients treated with radical cystectomy (RC) with a complete response in the cystectomy specimen[41-44].

3.3 Staging

Staging at diagnosis

For the classification of disease burden, the TNM classification published by the Union for International Cancer Control is recommended by the European Association of Urology (EAU) and used in Norway (Table 1)[1]

Table 1. Tumour Node Metastasis (TNM) Classification of urinary bladder cancer.

T - Primary Tumour	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ: “flat tumour”
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T2a	Tumour invades superficial muscle (inner half)
T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue:
T3a	Microscopically
T3b	macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate stroma, seminal vesicles, uterus, or vagina
T4b	Tumour 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
M1a	Non-regional lymph nodes
M1b	Other distant metastasis

Accurate *clinical staging of the primary tumour* is dependent on the histopathological evaluation of the depth of tumour invasion in a histological specimens from TURB, findings from a bimanual clinical examination under anaesthesia, and cross-sectional imaging of the primary tumour [45].

The histopathological evaluation of the TURB specimen includes an assessment of the depth of tumour invasion and histological tumour type. To determine depth of invasion into the bladder wall (Ta, Tis: urothelium, T1: lamina propria, ≥T2 muscularis propria), presence of bladder muscle in the specimen is required. Tumour invasion beyond the muscularis propria cannot be determined in a TURB specimen. The World Health Organisation histological classification system is used for histological classification of UTCs[46]. UC is the most common histology of BC and can be present in its pure form or mixed with non-UC tumours (e.g., micropapillary, sarcomatoid, neuroendocrine). Pure non-UC tumours can also arise in the genitourinary tract (e.g., squamous cell, adenocarcinoma, neuroendocrine). Furthermore, UCs are histologically graded as low-grade or high-grade tumours according to malignant potential [46]. By definition, all MIBC are considered high-grade[47].

A bimanual palpation of the bladder before and after TURB is performed to clinically assess if the tumour is extravesical (clinical cT3b) or has infiltrated adjacent structures (cT4) [48].

Cross-sectional imaging of the abdomen and pelvis by CT or MRI is used to assess the primary tumour. Perivesical inflammation following TURB can render the evaluation of tumour extent difficult, and therefore imaging should be performed before TURB [49]. CT is useful for detecting a bladder tumour, involvement of the perivesical fat layer (≥cT3) and hydronephrosis. With CT, it is difficult to distinguish between the different layers in the bladder wall and therefore CT has an estimated accuracy of 40-60% in differentiating NMIBC from MIBC[50]. Multiparametric MRI combines anatomical and functional imaging sequences and provides good resolution images of the layers of the bladder wall. The Vesical Imaging Reporting and Data System is a proposed standardised reporting system based on tumour appearance in the different multiparametric MRI sequences for predicting the

probability of clinically significant BC[51], and has shown good sensitivity and specificity for detecting MIBC[52].

Clinical staging of lymph node (LN) involvement and distant metastases is done by cross-sectional imaging of the thorax, abdomen, and pelvis. Evaluation of LN involvement is based on LN size and appearance, and the accuracy of CT and MRI is similar. Positron emission tomography CT is not recommended in the clinical staging of MIBC[45].

Staging after treatment

Histopathological staging of cystectomy specimens allows an evaluation of the full extent of tumour invasion according to the TNM classification (pathological T-category pT0-pT4). An evaluation of LN specimens includes the recording of the total number of LNs, the number of malignant LNs and extranodal spread[50]. During a MIBC disease course, imaging with CT or MRI of the thorax, abdomen and pelvis is repeated to assess response to therapy and in case of suspected, recurring disease.

4. Treatment of muscle-invasive bladder cancer and metastatic bladder cancer

This thesis is about the primary treatment and survival of curatively treated patients with MIBC and of patients initially diagnosed with BC and distant metastasis (primary metastatic BC). The EAU treatment guidelines for treatment of BC are updated annually and are based on the best evidence available[53]. Since their first release in 2000, these guidelines have guided clinical practice in Norway. National guidelines on BC became available in Norway in 2013[54].

4.1 Curative treatment

Standard curative treatment for localised MIBC (cT2-T4a, cN0-Nx, M0) with RC has remained unchanged for decades. Based on compelling evidence of a survival benefit of cisplatin-based neoadjuvant chemotherapy (NAC) compared to RC alone[55], NAC has been recommended by the EAU as part of the standard treatment of cisplatin-eligible MIBC patients since 2008[56]. The role of adjuvant chemotherapy in the treatment of MIBC is unclear. Immunotherapy with check-point inhibitors in the curative setting of MIBC is currently not in use outside of clinical trials[49].

RT of the bladder has been considered as an alternative approach for patients unfit or unwilling to undergo RC. With growing evidence of a significantly improved survival for trimodal treatment with TURB, chemotherapy and RT compared to RT[57], Trimodal treatment has since 2012 gradually replaced RT[54]. It is currently the recommended alternative curative approach to RC [49, 58].

This thesis evaluates survival after curative treatment with RC with or without NAC and RT, since trimodal treatment was not in use during the study period.

Radical cystectomy

RC involves the complete removal of the bladder, prostate, seminal vesicles, distal ureters and regional LNs in men. In women, RC includes removal of the bladder, the entire urethra and adjacent vagina, uterus, distal ureters, and regional LNs. Recurrence-free survival, proportion of major complications, proportion of positive margins and quality of life do not appear to differ according to the type of operating technique (robot-assisted RC versus open RC)[59, 60]. However, robot-assisted RC probably reduces per-operative blood loss and length of hospital stay[60]. Urinary and sexual dysfunctions are prevalent in both men and women after RC[61]. Surgical techniques for the preservation of sexual function have been developed for both men and women but should only be offered to well-selected patients. [62, 63].

LN dissection is an integrated part of RC, but the optimal extent has yet to be established. A systematic review found that survival is superior with LN dissection compared to no dissection, but no conclusion regarding the extent could be drawn[64]. Currently, no significant survival advantage has yet been shown for extended LN dissection (LN regions up to the inferior mesenteric artery) over limited LN dissection (bilateral obturator, internal and external iliac nodes)[65].

Following cystectomy, the urinary tract must be reconstructed to create a new form for urinary diversion. The two most common types of urinary diversions are incontinent cutaneous diversion and continent urethral diversion [66, 67]. Incontinent cutaneous diversion includes ureteral anastomosis to the abdominal wall (uretero-cutaneostomy) and ureteral anastomosis to a segment of the small bowel (ileal conduit) with passage of urine out to a stoma and into an ostomy bag. Continent urethral diversion is created by constructing a neobladder from different segments of the intestinal tract and attaching it to the urethra.

Survival

The five-year overall survival (OS) after RC for MIBC patients is approximately 50%[7],

Prognostic markers

The histopathologic stage of the primary bladder tumour and the presence of regional lymph node metastases are the most important prognostic factors for survival in cystectomised MIBC patients[7]. Other histopathological features of the primary tumour such as lymphovascular invasion and concomitant carcinoma in situ have also been associated with increased risk of BC death[68, 69]. Tumour involvement of the prostatic urethra has also been found to be an adverse prognostic factor[70]. Furthermore, macroscopic features such as the tumour's location and LN-related parameters appear to be of prognostic value. Compared to tumours located in the dome, tumours of the lateral walls and base (trigone, bladder neck) often cause hydronephrosis and are associated with increased mortality risk[71]. LN-related parameters include the number of positive LNs, the number of LNs removed and the ratio of these two measures (LN density), as well as extranodal extension[72, 73].

The timing of RC is of importance for the prognosis of patients after RC. In a 2020 meta-analysis, a delay of RC for over three months after diagnosis significantly increased the risk of mortality compared to patients who underwent RC within three months [74].

MIBC is a molecularly heterogeneous disease. Based on the Cancer Genome Atlas two molecular groups of MIBC have been identified, luminal and basal-squamous, which are classified into six subtypes[75, 76]. The different subtypes are associated with differences in prognosis[76]. The routine clinical use of molecular subtyping is not yet established but has the potential to become part of the future management of MIBC[77].

Neoadjuvant systemic therapy

Because of the relatively low survival of 50% after RC for MIBC, clinical trials have extensively tested cisplatin-based NAC to improve survival. The Nordic Cystectomy Trials I and II were conducted between 1986 and 1997, which explored cisplatin in combination with doxorubicin or methotrexate [41, 42]. A combined updated analysis of these two trials published in 2004 showed an absolute survival benefit of 8% and a significant difference in OS favouring NAC over RC only[78]. Two pivotal trials published in 2003 and 2011

established cisplatin-based NAC as standard treatment in cisplatin-eligible MIBC patients. An American trial showed a significant improvement in survival in patients who received neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) compared to RC alone [44], whereas a large European multinational phase III trial showed that neoadjuvant cisplatin, methotrexate and vinblastine followed by definitive local therapy (RC or RT) decreased the mortality risk by 16% compared to definitive local treatment alone [43]. Meta-analyses published between 2003-2005 combined the results from these clinical trials and others and showed that cisplatin-based NAC before RC improved OS by 6-8% compared to RC only[79, 80].

Results from population-based studies on the effect of NAC on survival are conflicting. In two population-based studies of patients with MIBC undergoing RC with or without NAC from the USA and Sweden, receipt of NAC was not associated with an OS benefit[81, 82]. In another study from the USA, treatment with NAC was associated with a survival benefit over RC alone, but when stratified for pathological tumour stage (<pT2 or ≥pT2), this was only true for patients with <pT2 whereas patients with ≥pT2 had increased mortality risk[83].

Downstaging

The survival benefit of NAC demonstrated in clinical trials is associated with downstaging of the primary tumour as demonstrated in the RC specimen [84, 85]. A meta-analysis of 13 trials estimated that post-NAC complete pathological response of the primary tumour (CR, pT0) is associated with a 55% reduction in mortality risk compared to patients with residual disease[85]. The proportion of patients achieving post-NAC CR depends on the type of chemotherapy regimen.

The proportion of CR after NAC ranges from 20-38% in clinical trials[44, 78, 86]. The chemotherapy regimens used in these trials have been replaced in routine practice by gemcitabine-cisplatin and intensified dose-dense MVAC (two weekly regimen plus granulocyte stimulation factor). Despite no level one evidence for use of gemcitabine-cisplatin and dose-dense MVAC in the neoadjuvant setting, these regimes were adopted into routine practise based on results from clinical trials in the metastatic BC setting published in 2001[87-90]. Only recently the efficacy of these two chemotherapy regimens in the neoadjuvant setting were compared in a phase III trial published in 2021[91]. CR was observed more frequently in patients treated with dose-dense MVAC (42% vs 36%) compared

to gemcitabine-cisplatin. The progression-free survival of dose-dense MVAC (66% vs 56%) was significantly superior to that of gemcitabine-cisplatin, suggesting dose-dense MVAC should be the preferred first-choice of NAC[92].

In the neoadjuvant setting, several checkpoint inhibitors have been shown to have clinical efficacy and to be generally safe both as monotherapy and in combination with chemotherapy[93-95]; however, results from ongoing trials of long-term oncological outcomes are pending[96]. Furthermore, an ongoing trial is testing the combination of a checkpoint inhibitor with another novel agent, an anti-body drug conjugate[97]

There are currently no predictive clinical markers or biomarkers for response to NAC[98]. Secondary MIBC was associated with lower proportions of post-NAC downstaging compared to primary MIBC in a retrospective observational study, possibly related to increased expression of mutations in the DNA damage repair gene ERCC2 in primary MIBC[99]. Non-UC histologies may also respond poorly to NAC[98]. Biomarkers such as serum vascular endothelial growth factor, circulating tumour cells and defects in DNA damage repair genes (ERCC2, ATM, RB1, FANCC) have been investigated as potential predictive markers [100-102], but not validated in prospective studies for use in routine practice. For patients treated with NAC, delayed RC (> 3 months) did not reduce OS[74, 103].

Adjuvant systemic therapy

The role of adjuvant cisplatin-based chemotherapy after RC for patients with high-risk factors (pT3/pT4 or LN positive (pN+)) is not clear because there is no prospective data supporting its use [104]. Despite the lack of high-level evidence, current EAU guidelines support the use of adjuvant cisplatin-based chemotherapy in selected patients (pT3/pT4, pN+) not treated with NAC[49]. Results from studies of check-point inhibitors are inconclusive, with findings of both improved survival [105] and similar survival compared to observation[106] and are not recommended for routine use.

Radiotherapy

RT of the bladder with a target dose of 60-66 Gy has long been considered as an alternative approach for patients unfit to undergo RC, although there are no successfully completed randomised trials comparing survival after RC to survival after RT[107]. Observational

studies have evaluated the use and survival outcomes of RC and RT, with discrepant results of inferior survival for RT[108] or no survival difference[109, 110].

The principles of trimodal therapy are to achieve maximum local tumour control by TURB and RT with radio-sensitising chemotherapy and to target micrometastases with chemotherapy. Two fractionation regimes are commonly used, either conventional 2 Gray fractions to a total dose of 60-66 Gy to the bladder[111] or the recently suggested hypofractionated dosing schedule of 2.75 Gray to a total dose of 55 Gy[112]. Cisplatin, gemcitabine or mitomycin plus 5-fluorouracil are used as radiosensitising chemotherapy[57, 111, 113]. Bladder biopsies are routinely performed after complete treatment to detect non-responders eligible for salvage cystectomy[111].There are no comparative clinical trials of trimodal therapy versus RC, but it is shown that trimodal therapy significantly improves OS compared to RT alone[57, 114].[114].

Preoperative RT using a dose of 45-50 Gy has shown an effect on downstaging but not on OS and is no longer in use [115]. Similarly, there are no conclusive data regarding survival benefits following post-operative adjuvant RT for patients with adverse post-operative risk factors (pT3/pT4, pN0–2)[116]. However, in these select patients, it is still considered a reasonable approach in current European guidelines[49].

4.2 Non-curative treatment

In addition to patients with metastatic disease, patients not undergoing curative treatment are patients with unresectable locally advanced tumours, and patients otherwise considered unfit to undergo radical treatment. A large Swedish observational study showed that up to 57% of patients diagnosed with MIBC did not receive therapy with curative intent. These patients experienced frequent hospitalisations during the first year after diagnosis and had a poor prognosis with median OS of approximately nine months[3]. Various non-curative treatment approaches consist of local tumour and metastasis treatments, and systemic cancer therapy.

Local tumour treatment

Patients with unresectable locally advanced tumours may experience symptoms such as bleeding, pain, dysuria, and urinary obstruction, which greatly affects their quality of life. Various options exist to control tumour bleeding; these include intravesical irrigation (e.g., formalin, prostaglandin), TURB, and RT [117]. RT is also effective in managing pain caused

by the bladder tumour, tumour invasions into neighbouring structures and metastatic lesions (e.g., bone). Tumour-related urinary tract obstruction by itself may be asymptomatic, but patients develop symptoms from the resulting kidney failure. Urinary tract obstruction is most often managed with unilateral or bilateral nephrostomies or ureteral stenting, both approaches require regular replacement of tubes. In selected patients where symptoms cannot be managed by minimally invasive methods, palliative cystectomy is an option.

Systemic treatments

Median survival of patients with metastatic BC not treated with systemic treatment is approximately three months[9, 10]. Since the beginning of the millennium, the standard first-line treatment option has been cisplatin-combination chemotherapy in patients fit for cisplatin with a median OS of 12-14 months[87, 118]. Carboplatin-combination therapy is offered to patients unfit for cisplatin and has a median OS of approximately nine months[119, 120]. Second-line treatment options have been limited. Since 2009, vinflunine has been the only evidence-based option with an overall response rate of less than 10% and a median OS of approximately seven months [121]. This changed in 2016 with the emergence of immunotherapy with check-point inhibitors as the new standard of second-line therapy in patients previously treated with platinum-based chemotherapy. New and promising drugs include anti-body drug conjugates and fibroblast growth factor receptor inhibitors.

First-line systemic treatment

Cisplatin induces neurotoxicity (peripheral neuropathy, ototoxicity) and renal toxicity. The toxicity profile renders up to 50% of patients ineligible for receipt of cisplatin and is the basis for dividing patients with metastatic BC in the first-line setting into three categories: fit for cisplatin-based combination therapy, unfit for cisplatin-based chemotherapy, and unfit for any platinum-based chemotherapy[119, 120]. The consensus definitions of platinum-eligible and ineligible patients are presented in Table 2 [122].

Table 2. Definitions of platinum-eligible and ineligible patients for first-line treatment of muscle-invasive bladder cancer

Platinum-eligible		**Platinum-ineligible**
Cisplatin-eligible	***Carboplatin-eligible***	***Any of the following:***
ECOG PS[1] 0-1 *and*	ECOG PS[1] 2 *or*	ECOG PS[1] > 2
GFR[2] > 50–60 mL/min *and*	GFR[2] 30–60 mL/min *or*	GFR[2] < 30mL/min
Audiometric hearing loss grade[3] < 2 *and*	not fulfilling other cisplatin-eligibility criteria	ECOG PS[1] 2 and GFR[2] < 60 mL/min
Peripheral neuropathy grade[3] < 2 *and*		Comorbidities > Grade[3] 2
Cardiac insufficiency NYHA[4] class < III		

[1] Eastern Cooperative Oncology Group Performance status

[2] glomerular filtration rate

[3] Common Terminology Criteria for Adverse Events(CTCAE)[123]

[4] New York Heart Association[124]

Cisplatin-eligible patients are offered first-line MVAC or gemcitabine-cisplatin. Due to a favourable toxicity profile gemcitabine-cisplatin is the preferred choice [87, 89]. Sometimes cisplatin is administered in a split-dose schedule to patients with borderline GFR values (30-60 ml/min) but otherwise fulfilling cisplatin-eligibility criteria. However, no clinical trial has compared split-dose to the conventional schedule.

For platinum-eligible patients, there is currently no prospective data in support of replacement of platinum-based combination therapy with immunotherapy combinations in the first-line setting [125-127]. However, there is evidence supporting the use of maintenance avelumab after initial platinum-based chemotherapy in patients with stable disease[128]. The addition of avelumab significantly prolonged the median OS from 14 months in the control group to 21 months in the treatment group. In conclusion, for platinum-fit patients, the current standard first-line treatment is platinum-based chemotherapy followed by maintenance avelumab.

For *platinum-unfit* patients, there is evidence of no survival benefit from carboplatin-combination therapy, and therefore, best supportive care is recommended for this patient

group[120]. Check-point inhibitors as monotherapy and in combination with an anti-body drug conjugate have been investigated in this patient group[129-131], but neither are currently approved for use in Europe[49].

Adverse prognostic factors for outcome after treatment for metastatic BC include poor performance status, presence of visceral metastases, high alkaline phosphatase levels and a number of disease sites (≥ three)[87, 132]. Non-UC histologies may impact prognosis, but no evidence exists for differential treatment[133].

Second-line systemic treatment

Recent advances have replaced vinflunine in the second-line with immunotherapy after the approval of several check-point inhibitors (pembrolizumab, atezolizumab and nivolumab) by American and European drug regulatory agencies in 2017/2018. Pembrolizumab has demonstrated a response rate of 21% and a significant median OS improvement (10.3 vs 7.4 months) compared to monotherapy chemotherapy (taxan or vinflunine), whereas atezolizumab and nivolumab displayed similar outcomes but more favourable toxicity profiles compared to chemotherapy[134, 135]. Ranked according to the highest level of evidence, pembrolizumab is the standard first choice in the second-line setting of metastatic BC followed by atezolizumab and nivolumab.

Third-line systemic treatment

Third-line systemic treatment after treatment with platinum-based chemotherapy and check-point inhibitors first became available and approved for use both in the US and in Europe in 2022[136, 137]. Enfortumab vedotin, an anti-drug conjugate, has shown a response rate of over 40% and a significant OS benefit over monotherapy with a taxan or vinflunine (13 vs nine months)[138, 139]. Approval of enfortumab vedotin for use in Norway is pending.

Another anti-drug conjugate (sacituzumab govitecan) and a fibroblast growth factor receptor inhibitor (erdafitinib) have shown promising results of response in the third-line setting[140, 141]. These drugs are approved for use in this setting in the US but not yet in Europe.

5. Motivation for thesis

Treatment management and long-term survival outcomes of curatively treated MIBC patients and patients with metastatic BC have not previously been investigated in a population-based study in Norway. The first two papers in this thesis focused on the treatment and survival of curatively treated patients, whereas the third paper focused on the treatment and survival for patients with metastatic BC.

Patients may present with MIBC at initial diagnosis (primary MIBC) or progress to MIBC from an initial diagnosis of NMIBC (secondary MIBC). These patients are offered the same curative treatment with RC or RT. It is unclear whether there is a survival difference between patients with primary and secondary MIBC after curative treatment with RC or RT. There are reports from observational studies of worse[142-146], better[147-150] or similar[147, 151-159] survival for patients with secondary MIBC compared to patients with primary MIBC after RC, none investigating survival after RT. The first paper supplements the existing literature on this subject by investigating a cohort of patients from a national cancer registry and provide survival data after curative treatment for both RC and RT.

The survival benefit associated with NAC before RC has been shown in clinical trials, but results from population-based studies are inconclusive[81-83]. The survival benefit of NAC is associated with downstaging of the primary tumour [84, 85]. The second paper of this thesis further investigates in a nationwide cohort of patients, the relationship between NAC and survival by also evaluating the impact of NAC on downstaging and of downstaging on survival.

The first-line treatment with platinum-based chemotherapy for metastatic BC has been unchanged since 2001, whereas immunotherapy became the first choice for second-line therapy in 2017/2018. Patients with metastatic BC experience high disease-specific morbidity and frequent hospitalisations[3]. Limited numbers of population-based studies have evaluated pre-immunotherapy treatment patterns, outcomes, and hospitalisations after chemotherapy in patients with metastatic BC, and none in Norway. It is of importance for future evaluation of immunotherapy to benchmark pre-immunotherapy treatment and survival, and to have prior knowledge of healthcare use in this patient population to detect any changes associated with new therapeutic strategies. The third paper of this thesis describes the treatment patterns, survival, and hospitalisations of patients with primary metastatic BC.

Thesis

1. Aims

The overall objective of this research project was to improve the treatment management of patients with non-metastatic MIBC and metastatic BC in Norway. By investigating on a population-based level the treatment and associated survival outcomes of curatively treated patients with MIBC and patients with primary metastatic BC, this thesis will provide evidence-based knowledge which may assist clinicians in treatment counselling and future management of patients with MIBC and metastatic BC.

The specific aims of the thesis were:

- *Paper I:* To describe the patient characteristics, the type of curatively intended treatment and survival of Norwegian patients with non-metastatic MIBC, and to compare patient characteristics and cancer-specific survival (CSS) by type of MIBC (primary versus secondary) and according to type of treatment (RC or RT)
- *Paper II:* To describe the patient and tumour characteristics of patients with non-metastatic MIBC undergoing RC with or without NAC and evaluate on a population-based level the impact of NAC on downstaging of the primary tumour (DS) and OS.
- *Paper III:* To describe the patient characteristics, OS and hospitalisations of patients diagnosed with primary metastatic BC according to initial treatment management

2. Material and methods

2.1. Data sources

Data used in this thesis were extracted from the Cancer Registry of Norway (CRN) and the Norwegian Patient Registry (NPR). The underlying cohort comprised all BC patients diagnosed between 2008-2016, with follow-up until December 31st, 2019. The information is identified and linked by the personal identification number assigned to all new-borns and residents in Norway since 1964.

The CRN is a national cancer registry established in 1953. The registration of all malignant neoplasms to the CRN is compulsory by law, with an estimated 99% completeness [13, 160]. The main sources of the CRN data are clinical notifications from clinicians in hospitals and private specialist practices and pathology reports from hospitals and independent pathology laboratories. National registries (The Norwegian Population Registry, the Cause of Death Registry, and the NPR) provide supplementary data. The Norwegian Population Registry and the Cause of Death Registry send monthly updates on vital status and information on cause of death to the CRN. The information is matched to the registered cancer cases in the CRN by an automated process. The Cause of Death Registry and the NPR are important sources for detecting unreported cancer cases.

The CRN data used in this thesis comprises three sub-registries: *the CRN incidence registry, a CRN research database* for a subset of BC patients, and *the CRN RT database*,

The *CRN incidence registry* contains patient demographic and clinical information including age at diagnosis, sex, place of residency, date of cancer diagnosis, histology, disease spread at diagnosis, surgery, RT, and cause of death[13]. For BC, histology from TURBs, biopsies and cystectomies are registered. Up until 2018, the CRN morphology coding system only differentiated between flat-lesions (carcinoma in situ), non-invasive (<pT1) and invasive cancer (≥pT1) for UCs. Information on disease spread at diagnosis is retrieved either from the diagnostic clinical notification or pathology reports. Data from imaging is unavailable. Metastases discovered within the month of BC diagnosis plus four months (≤150 days) are registered as synchronous or primary metastases. Only histologically verified subsequent metastases are registered. LN metastases are registered as either located in the true pelvis (within the linea terminalis) or located elsewhere. Visceral metastases are categorised as either present in the true pelvis or outside the true pelvis.

The CRN research database contains information on all BC patients, UC only, diagnosed between 2008-2012 and followed until the 31st of December 2016, based on a quality review of all available pathology reports by urologist and PhD Augun Blindheim [161, 162]. The CRN research database contains information on the type of surgery (TURB, biopsy, cystectomy). For TURB specimens, the histological tumour characteristics were recorded as non-muscle invasive (<T2) or muscle-invasive (T2-T4), along with other histological parameters (concomitant carcinoma in situ, tumour grade[46], presence of muscle tissue). Information on other clinical tumour characteristics was unavailable (size, multiplicity, widespread carcinoma in situ). For cystectomy specimens, the pT-category is recorded without sub-classification (a,b) for pT2-pT4 and the pN-category was described as pN0 or pN+ without further details on number of malignant LNs. The CRN research database also contains information on LN and visceral metastases derived from clinical notifications at diagnosis or histologically verified at any time after BC diagnosis but lacks information from imaging enabling clinical staging of N-category and M-category.

The CRN RT database registers RT data from all RT centres in Norway. The RT database contains information from individual treatment courses and information on the target volumes. Each RT record includes diagnosis, target region, treatment intention, total number of fractions, total radiation dose, as well as start dates and end dates for RT treatment [163].

The Cause of Death Registry contains digitalised information on causes of death from 1951. It is administered by The Norwegian Institute of Public Health, and it contains information on the underlying and contributing causes of death obtained from death certificates of all residents' deaths in Norway and abroad. The Norwegian death certificate adheres to the structure established by the World Health Organisation and uses the ICD coding system.

The NPR holds data from 2008 and onward on individual administrative, demographic, and coded medical information (diagnoses, surgical and medical procedures, and type of anti-cancer drugs) from all patients' contacts with public specialist healthcare services in Norway[164]. NPR data are available upon request for specific research projects. The type of patient contact is categorised as daypatient, outpatient or inpatient and registered with corresponding dates for admission and discharge. In this thesis, the NPR was the only source of chemotherapy administration. Data on administration of intravenous anti-cancer therapy in the NPR was recorded in four different ways; 1) ICD-10 code (Z51.1), 2) a medical procedure code for administration of an intravenous anti-cancer drug, 3) a specific anti-cancer drug code

(National register for medical cancer treatment), 3) an Anatomical Therapeutic Chemical (ATC, World Health Organisation classification) drug code.

2.2. Ethical considerations

This project was approved by the Regional Committee for Medical and Health Research Ethics, Southeast Norway, approval number 2016/2286. The committee waived the requirement for informed consent. In addition, the use data collected CRN and the NPR is, by law, exempt from individual consent (the Health Registry Act, chapter 2, § 11)[165]. To inform on the individual patient's right to withdraw from the project, a general description of the project and instructions on how to withdraw from the project were published on the CRN project website[166]. The data from CRN and NPR is de-identified without any possibility for individual identification.

2.2. Study design

The studies in this thesis are population-based observational studies of a historical cohort of patients with BC.

2.3. Patients and Measures

The underlying cohort comprised 12,477 patients registered in the *CRN incidence registry* with a diagnosis of BC in 2008-2016. In papers I and II, the study populations were based on the 5,521 BC patients (UC only) in the *CRN research database*, whereas the study population in paper III were patients identified in the *CRN incidence registry* (Figure 4).

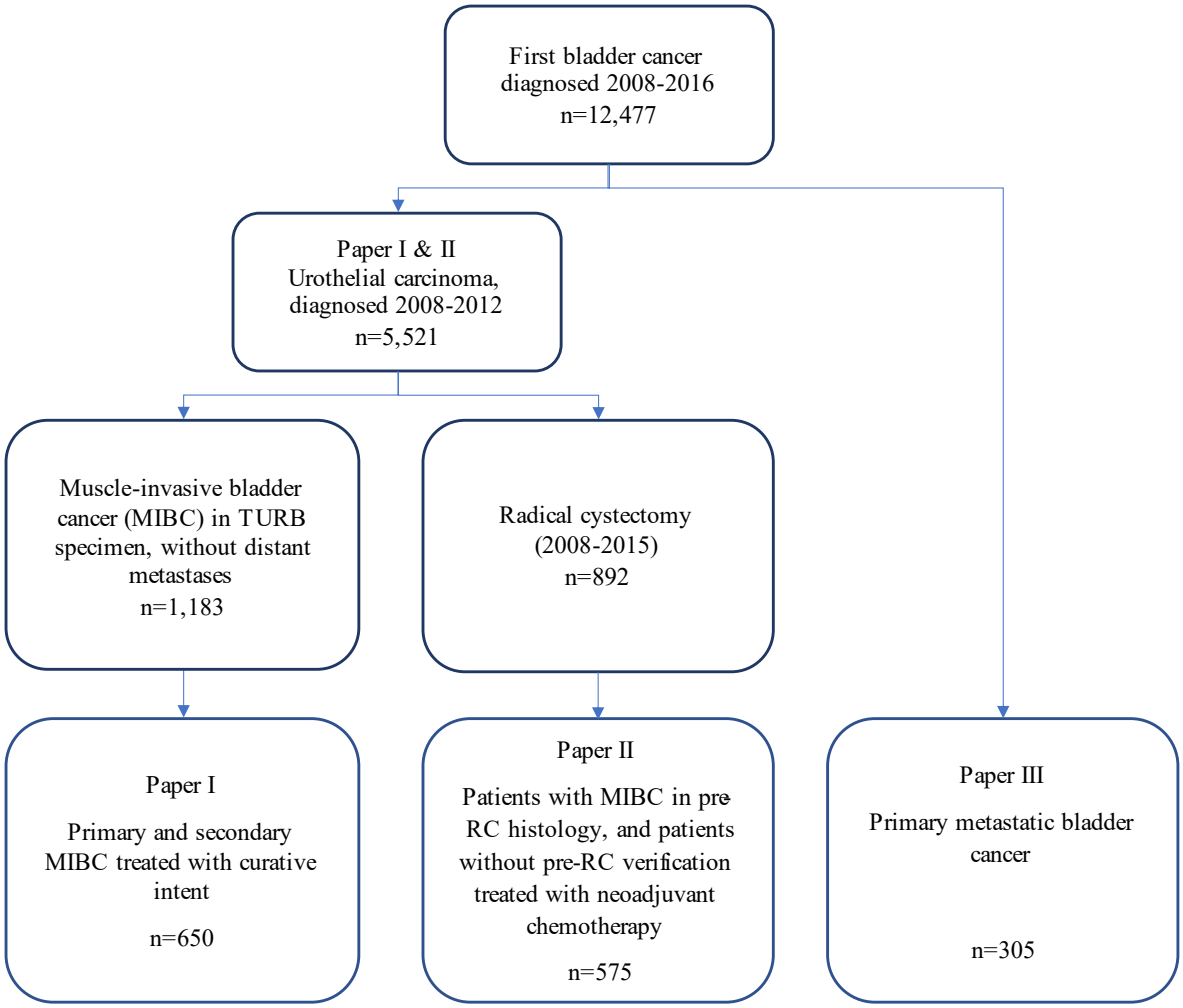

Figure 4. Flowchart study populations

Paper I

Patient selection

This study included patients with non-metastatic primary and secondary MIBC with a BC diagnosis between 2008 and 2012. Primary MIBC was defined as histologically verified tumour invasion into the muscularis propria (T2-T4) in the initial diagnostic TURB specimen or in a TURB specimen acquired less than four months after the first BC diagnosis. Secondary MIBC progressed from initial NMIBC and had histologically confirmed MIBC in a TURB specimen acquired over four months after BC diagnosis. Patients registered in the CRN research database with visceral metastases before or at diagnosis of muscle-invasion were excluded from the study. All evaluable patients underwent curatively intended treatment with

either RC or RT. RT was defined as RT for C67 towards pelvic soft tissue tumour manifestations with a total target dose of ≥60 Gy.

Measures

Patients were stratified according to the type of MIBC (primary or secondary MIBC) and the type of curative treatment (RC or RT). The primary outcome was CSS

Paper II

Patient selection

This study included all patients undergoing RC for non-metastatic MIBC with histologically verified muscle-invasion (T2-T4) in a TURB specimen, or patients who based on the application of NAC were clinically considered to have MIBC since NAC is not a part of the management of NMIBC. Patients registered with visceral metastases before or at the date of RC were excluded from the study, as well as patients treated with pre-operative RT. NAC was defined as any intravenous administration of chemotherapy as registered in the NPR between BC diagnosis and RC.

Measures

Independent of the use of NAC, DS was defined as pT0/pTa/pTis/pT1 demonstrated in the cystectomy specimen with complete response (CR; pT0) as a subgroup and without considering nodal downstaging. Patients were stratified according to receipt of NAC. The primary outcome was OS, and the secondary outcome was DS.

Paper III

In this study, all patients presenting with metastatic BC at first diagnosis were included. All morphologies were included. Primary metastatic BC was defined as BC with distant metastases diagnosed within 150 days of BC diagnosis. Distant metastases included non-regional LN metastases and non-pelvic visceral metastases.

Measures

Patients were grouped according to the type of initial treatment (chemotherapy, major local treatment (RC or RT), multimodal treatment, no anti-cancer treatment) initiated within 150 days after BC diagnosis. Major local treatments included RC or pelvic RT, defined as any

total RT dose of pelvic soft tissue tumour manifestations for BC *(local)*. Multimodal treatment was defined as the receipt of a combination of chemotherapy and major local tumour treatments within the first 150 days after BC diagnosis*(multimodal)*. Patients with *no treatment* may have had TURB within the first 150 days after BC diagnosis but no chemotherapy or major local treatments. Only inpatient contacts after BC diagnosis were considered hospitalisations. The primary outcome was OS, and the secondary outcome was days of hospitalisations.

2.4. Statistical methods

In all three papers, standard descriptive methods for continuous (mean, median, interquartile range (IQR)), categorical/binary (proportions) and survival outcomes (Kaplan Meier approach) were applied. In addition, a logistic regression model was used in paper II to investigate the association between NAC treatment and DS. In paper III, distributions of variables between treatment groups were compared with Chi-square test for categorical variables and the Kruskal-Wallis test (rank test) for continuous variables.

The event of interest and endpoint for all survival models in this thesis was death of any cause (OS) or death of BC (CSS). The date of entry was the date of diagnosis of MIBC in paper I, the date of RC in paper II, and the date of BC diagnosis in paper III. In all three papers, patients were followed until death, emigration, or end of study (December 31st, 2019). For all three studies, time in years from start of study until end of study was used as the timescale in all survival analyses.

The Kaplan Meier (KM) approach was used in all three studies to estimate and display both unstratified and stratified KM curves of observed survival (OS and CSS) for the study population. The Log-rank test evaluated the (unadjusted) differences between the survival curves in paper I and II.

In paper I, univariate and multivariate flexible parametric survival models (FPSM) were used to assess the association between the type of MIBC (primary vs secondary MIBC) and CSS overall, as well as stratified by type of curative treatment (RC or RT). All FPSM models used 4 degrees of freedom for the splines to model the baseline hazard for estimation of BC-specific mortality risk and prediction of the difference in adjusted CSS between primary and secondary MIBC.

In paper II, a multivariate Cox regression model documented the association between DS and OS and the association between NAC and OS. The proportional hazard assumption of the Cox models was assessed visually by hazard curves. For further assessment of the *causal* effect of NAC on OS, we applied the instrumental variables approach, a statistical method used to infer causality in the presence of unmeasured confounders, typically for observational studies. The approach utilises an instrumental variable which is associated with the exposure (NAC) and only affects the outcome (OS) through the exposure (NAC)[167]. For this purpose, type of hospital was chosen as the instrumental variable in this study. To further investigate the role of DS in the association between NAC and OS, we applied a mediation approach which partitions the total effect of NAC on OS into 1) the direct effect of NAC on OS independent of DS and the indirect effect of NAC on OS mediated by DS (Figure 5).

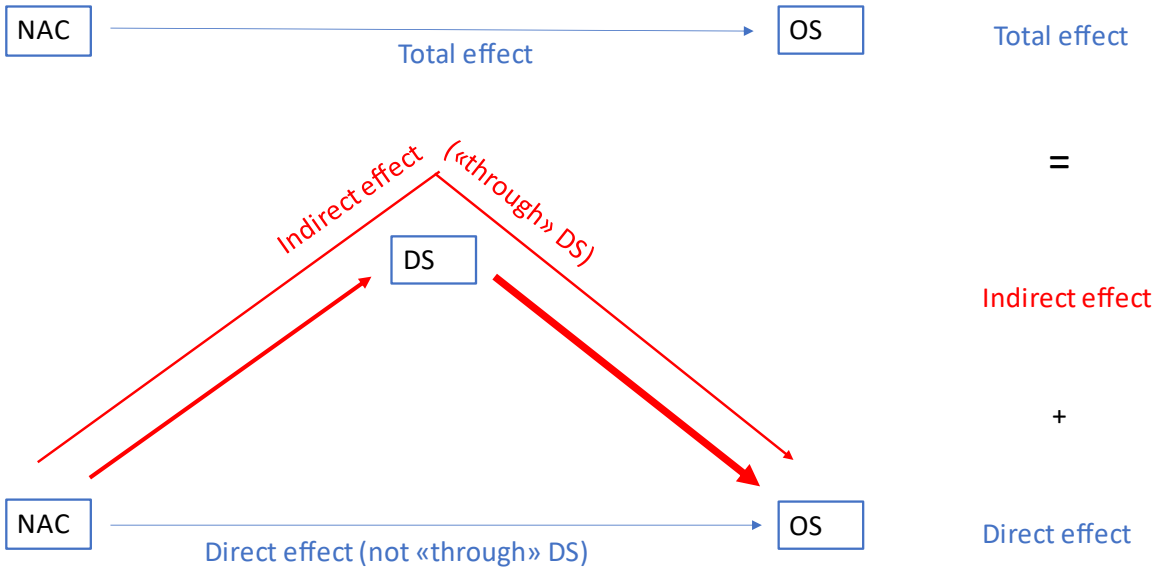

Figure 5. Mediation approach for investigating the role of downstaging (DS) in the association between neoadjuvant chemotherapy (NAC) and overall survival (OS): Total effect=Indirect effect + direct effect

For all three papers, the effect estimates' quantities reported from the model-based analyses are odds ratios (ORs) or hazard ratios (HRs), including 95% confidence intervals (CI) and *p*-values. The statistical significance level was set at $p<0.05$. Data was analysed using Stata 17 (StataCorp, College Station, TX) and R (version 4.1.4). In Stata, the "stpm2" command was

used for FPSM estimations used in paper I[168]. For the mediation approach used in paper II the R package “mediation” was used[169], and for the IV approach the R package “ivtools” was applied[167].

3. Main findings

Paper I

Out of 5521 BC patients in the CRN research database, 1,183 (21.4 %) patients had histologically verified muscle-invasion demonstrated in a TURB specimen and no distant metastases at diagnosis. Of these patients, 650 (55%) patients underwent curatively intended treatment (RC or RT) and were eligible for the study, 589 (91%) patients with primary MIBC and 61 (9%) patients with secondary MIBC. The majority (n=556, 86%) of patients underwent RC.

For all 650 patients, median follow-up time was 3.5 years with a crude five-year OS of 44% and CSS of 57%. The five-year crude CSS did not differ significantly between primary MIBC (56%) and secondary MIBC (59%), nor did type of MIBC (primary or secondary) have any significant impact on BC-specific risk of mortality.

For the 556 cystectomized patients, the crude CSS was 58%. There was no significant difference in crude CSS between primary MIBC and secondary MIBC (five-year CSS 58% vs 59%) and no association between type of MIBC and mortality risk. Similarly, for all irradiated patients we found no statistically different difference in crude CSS (five-year CSS 48% vs 57%) or risk of mortality between primary MIBC and secondary MIBC.

Paper II

For this study, 575 patients were eligible for inclusion: 493(86%) patients treated with RC only (NoNAC group) and 82 patients (14%) treated with NAC plus RC (NAC group).

Median follow-up time was 3.9 years. The crude five-year OS was 47%, with no significant difference between the treatment groups (NAC 50% vs NoNAC 47%). However, DS was achieved in a larger proportion of patients in the NAC group compared to the NoNAC group and showed a 2.5-fold significant increase in the odds of achieving DS over NoNAC. The proportion of patients with pN0 was higher (89% vs 60%) among patients with DS compared to patients without DS, and the overall mortality risk was significantly reduced by 78% in patients with DS compared to patients without DS. NAC did show a significant indirect effect on survival through DS, with improved survival for NAC over NoNAC.

Paper III

From the CRN incidence database, 305 patients with primary metastatic BC were included in this study. Within the first 150 days after BC diagnosis, approximately one third of the included patients received chemotherapy as part of the initial treatment, and more than half of the patients did not receive any anti-cancer treatment.

Median follow-up time was 154 days, and median OS for all included patients was 5.1 months. Median OS ranged from 2.3 months in the untreated group to 9.8 months in the chemotherapy group. Independent of survival time, patients treated with chemotherapy spent four times more days hospitalised than patients in the untreated group.

4. Discussion

4.1 Methodological aspects

4.1.1 Data quality

The Cancer Registry of Norway

The value of a population-based cancer registry relies upon the quality of the data it contains. Four key indicators are used when considering the data quality of such registries; comparability, completeness, validity and timeliness[170]. *Comparability* refers to the extent to which the data generated for one population can be compared to another. For cancer registries, the quality of comparability can be assessed based on the adherence to international standards of disease classification and definitions. *Completeness* refers to the extent to which new cancer cases are registered in the registry database. *Validity* refers to the accuracy of the information registered in the database. *Timelines* refers to the degree of completeness in registered cases at the time of publication of, for example, annual reports.

The data quality in the CRN was comprehensively evaluated in 2007[160]. The authors concluded that the data in the CRN is *comparable* to other cancer registry data by largely following international guidelines for disease coding and classification, as well as the definition of incidence, date of incidence and multiple primary cancers. The overall *completeness* for all cancers in 2001-2005 was estimated to be 98.8%. The assessment of *validity* included the percentage of morphologically verified cases and the percentage of death certificate only registration in 2001-2005. For all cancer cases, 93.8% were morphologically verified cases, and 0.9% were registered only by death certificate. *Timeliness* was reported as a percentage of underreporting of cases in the annual report 2005. In total, for all cases, 2.2 % were underreported in the published report of cancer incidence in 2005. This comprehensive evaluation has not been updated since then but there has been an important change impacting completeness: individual patient data from the NPR became available in 2008. CRN data can be validated by the data in NPR and is also a key source for detecting unregistered cancer cases. However, the CRN publishes the annual report Cancer in Norway, and since the 2020 edition both completeness, indicators of validity (morphologically verified, death certificate only) and timeliness are included[13].

BC is reported together with other UTCs (C66-C68) in the annual publication of the CRN: *Cancer in Norway*. Relevant for the time period used in this thesis, the 2012 edition of *Cancer in Norway* reported 96.6% of UTCs were morphologically verified cases and 1.2% were death certificate only (validity). There was an underreporting of 2.5% in incidence compared to the numbers reported in the 2011 edition (timeliness). Completeness was first reported in the 2020 edition of *Cancer in Norway*, and the estimated completeness in the time period 2016-2020 was 99.6% for UTCs.

In summary, the CRN contains internationally comparable data which are near-complete and accurate, and close to real-time when evaluated by certain principles and methods for quality evaluation of cancer registry data described in the literature[170, 171].

Cause of Death Registry

Measures for assessing the data quality of causes of death registries include the degree of population coverage and completeness, data accuracy for the cause of death and proportion of deaths registered with unspecified diagnostic codes for underlying cause (garbage codes)[172]. In Norway, the coverage and completeness in the Cause of Death Registry is close to complete (>98%). Data accuracy is ensured by using an updated ICD coding system and aided by a computer program designed to allocate ICD codes. However, the use of garbage codes is high, with 29% of all deaths over a 24-period (1996-2019) registered as garbage codes. The assignment of garbage codes was associated with advanced age and place of death outside of the hospital[173]. The misclassification of the underlying cause of death is another limitation of the Cause of Death Registry. For BC, a comparison of five-year estimates for relative survival and five-year estimates for CSS suggested that BC was underreported as the cause of death.

The CRN research database

This database was created by a qualified professional (urologist) through a comprehensive review of all available pathology reports in the CRN, as described in section 2.1 of this thesis.

The CRN Radiotherapy database

Individual RT data (total number of fractions, total radiation dose, start dates and end dates for RT treatment) are extracted directly from the software controlling the linear accelerators

delivering the treatment. Other variables, such as target region and treatment intention, are manually registered by the treating physician before treatment. The National Service for Validation and Completeness conducts annual analyses comparing data from selected national medical quality registries with data from the NPR. There is no national quality registry for bladder cancer, but in an analysis of the national quality registry for prostate cancer, a 99.8% completeness was reported for radiotherapy registrations in the CRN.

The National Patient Registry

The data quality of the NPR is assessed by measures such as the level of completeness of the personal identification number, which was 99.4% in 2017[164]. In addition, the data in the NPR are annually compared to data in the national medical quality registries, which in general show a high level of completeness for the NPR data[174].

4.1.2. Study design

The population-based observational design of this thesis provides insight into the treatment and survival of all MIBC patients in the Norwegian population, as opposed to the selected patient populations in clinical trials and institutional observational studies. The study population also includes the elderly and more comorbid patients, which are generally underrepresented in clinical trials[175, 176]. The cohort is historical, but the data provides long-term follow-up and survival, which is useful for clinicians guiding patients on treatment options and can serve as a basis for future comparative studies of novel agents in the treatment of metastatic BC. Treatment effects in observational studies, such as NAC in paper II of this thesis, must be interpreted with caution. Patients in clinical trials are randomised to different treatment arms and relevant confounders are either measured or can be assumed to be equally distributed across treatment arms. In contrast, population-based studies are based on non-randomised patients from routine clinical practice without detailed information on patient-related factors important for treatment decisions (e.g., comorbidities, performance status). In observational studies the indication for treatment is largely unknown and they suffer from confounding by indication leading to biased effect estimates.

4.1.3. Patients and measures

Paper I

The study population comprised patients with histologically confirmed muscle-invasion in a TURB specimen without distant metastases who underwent curatively intended treatment with RC or RT and was based on the CRN research database (Figure 4).

The restriction to include only patients with histologically verified muscle-invasion in a TURB specimen was similar to the inclusion criteria of several retrospective studies[144, 155, 156] and prospective series[152, 157]. Patients undergoing RC without histologically verified muscle-invasion have a significantly better prognosis than patients undergoing RC for MIBC [143, 151, 153], and were therefore excluded from the study.

Cystectomies with corresponding dates were identified in the CRN research database. Subsequently, identified cystectomies were cross-checked against the information in NPR to identify unreported cystectomies, which also were included, although without any information on pathology. The date of cystectomy from the CRN was derived from pathology reports, whereas cystectomy codes in the NPR are not registered to a specific date but with the associated hospitalisation. If the date of a cystectomy in the CRN did not correspond to the date of hospitalisation or the cystectomy was registered only in the NPR, the date of cystectomy was defined as the date of admittance + 1 day. This was based on the assumption that the routine clinical practice is admittance the day before the planned operative procedure.

Patients treated with curative doses of RT for BC had to be identified since the existing treatment intention variable only reflects planned and not received treatment. Curative dose RT was defined as a total dose of ≥60 Gray in standard 2 Gray equivalents towards the target region, defined as either bladder or pelvic soft tissue tumour manifestations. The following method was used to link records with the defined target region associated with the same treatment course: If the start date of the second record was within the range between the start and end date of the first record or within 14 days of the end date of the first record, these records were counted as the same treatment course. For subsequent records, the same method was used. Data on type of RT technique used was unavailable.

Primary MIBC and secondary MIBC were defined based on whether the TURB specimen confirming muscle-invasion was performed within or over four months after BC diagnosis.

This was to allow the performance of a re-TURB in patients with insufficient diagnostic TURB[162, 177]. Other similar studies have also taken this into account by including patients with proven muscle-invasion in a TURB specimen performed two to twelve weeks after the first diagnosis of NMIBC[144, 152, 156]. The CRN defines the diagnostic period as the month of diagnosis plus four months, a definition used in previous studies using data from the CRN, therefore, the chosen timeframe was extended to four months in this study.

Paper II

Based on the CRN research database, the study population comprised patients with non-metastatic MIBC who underwent RC with or without NAC (Figure 4). The identification of cystectomy and RT described under *Paper I* of this section also applied for *Paper II.*

NAC was defined as any intravenous administration of chemotherapy registered in the NPR between diagnosis of BC and RC for the included patients. The binary variable "Administration of chemotherapy yes/no" comprised information from all available variables on anti-cancer drug administration in the NPR as described under section 2.1. Anti-cancer drug administration in the study period of this thesis is largely registered with unspecified drug codes, limiting the possibilities of describing treatment with specific chemotherapy regimens. Details of dosage, number of cycles and drug changes were unavailable.

The absence of muscle-invasion in the cystectomy specimen identified downstaging. Our definition of downstaging was in line with definitions used in similar studies[81, 83, 178]. Since information on clinical nodal status was not available, any nodal downstaging could not be assessed.

Paper III

This study was based on the CRN incidence database and included all patients diagnosed at first presentation with BC and distant metastasis (Figure 4). The basis for defining primary metastatic disease as distant metastases diagnosed within 150 days of BC diagnosis was the routine practices at the CRN of registering metastases as previously described under section 2.1. Patients with development of metastases which were clinically diagnosed over 150 days after the BC diagnosis could not be identified in the CRN, only patients with histologically verified metastases. Therefore, patients with development of metastases over 150 days after the BC diagnosis are not in the study.

Distant metastases were defined as LN and visceral metastases located outside the true pelvis, since the CRN registration practice does not allow for separation of LN metastases in a common iliac LN (TNM cN3) from a non-regional LN metastasis (TNM cM1a) and visceral metastasis located in the true pelvis were interpreted as direct tumour infiltration into a neighbouring organ. Factors of prognostic significance for patients with metastatic BC such as the specific anatomical location (e.g., brain, bone, liver or lung) of visceral metastases and the number of disease sites are unavailable [16].

Patients were categorized according to the type of primary treatment received within 150 days after diagnosis: chemotherapy, major local therapy (cystectomy or bladder RT), a combination of chemotherapy and major local treatment, no systemic or local therapy except TURB. The 150 days cut-off was chosen to follow the registration practice of metastases at the CRN.

Chemotherapy was identified from the NPR by the previously described variable "Administration of chemotherapy yes/no" used in *Paper II*. All chemotherapy administered after BC diagnosis and co-registered with ICD-10 codes C65-C68 (UTC), C80 (unspecified location of malignant tumour) and C77-C79 (metastases) were considered chemotherapy for bladder cancer, and patients had to receive at least one chemotherapy administration to be considered as recipients of chemotherapy.

Data on cystectomy, RT and TURB were retrieved from the CRN incidence database. The indication of cystectomy is unavailable. Patients may have undergone palliative cystectomy or metastases may have been registered after curatively intended cystectomy or RT. The date of RT and target region for each treatment course with the indication C67 was extracted, the dose was disregarded. Target regions were then categorized into five groups: soft tissue, bladder (including pelvic soft tissue tumour manifestations), CNS, bone and other/unspecified.

"Hospitalisation" includes only inpatient contacts recorded in the NPR. For each patient, the days from admittance to discharge for all hospitalisations were summarized. Then the median days of hospitalisation for each group was calculated. For intergroup comparison this information was of limited value due to differences in survival between the groups. However, the measure of hospitalisation is important as a reference for future evaluations of

hospitalisations for the chemotherapy group after the implementation of less toxic novel agents.

4.1.4. Statistical methods

For the purpose of the modelling of age to be in accordance with how age was displayed in the paper, age was treated as a categorical variable and not as a continuous variable in all models applied in both papers I and II.

As noted under section 2.3.1, there seems to be an underreporting of bladder cancer deaths in the Cause of Death Registry. This must be taken into consideration when interpreting the results from paper I where CSS was reported. CSS was chosen over OS to allow comparisons with international cohorts from the existing literature on the subject. However, when dealing with an aggressive disease such as MIBC, CSS and OS are almost the same and the impact of underreporting is negligible. For papers II and III, OS was reported and underreporting of BC as the cause of death would have no impact on the results.

In paper I, FPSMs were applied to assess differences in mortality risk between primary and secondary MIBC. A FPSM provides similar HR estimates as the Cox model but allow for prediction of outcomes for a given combination of covariates. In paper I, we used FPSMs to predict and display the difference in CSS between primary MIBC and secondary MIBC for all patients, as well as stratified by type of CIT.

In paper II, the relationship between NAC and OS was assessed by several statistical models. The non-randomized design of observational studies limits the interpretation of the causal effect of a treatment on survival. In an attempt to overcome this limitation (confounding by indication in section 4.1.2), the instrumental variables approach was used. The instrumental variables approach mimics randomization by using an instrumental variable not associated with the outcome. Compared to the Cox model where the HR was over 1 indicating an increased mortality risk for NAC, the HR shifted towards NAC reducing the mortality risk with this approach, although the results of these analyses were not statistically significant. From the available variables, type of hospital as an instrumental variable may have been the most reasonable choice for this study but might still be a weak instrument as the verification of the assumptions of IV analysis seemed difficult. First, the association between type of hospital and NAC treatment was difficult to verify (relevance assumption) and second, it was

difficult to verify that type of hospital solely influences the survival outcome through NAC treatment (exclusion restriction assumption). In the results from the mediation approach, the effect estimates of the direct effect of NAC on OS suggested NAC increased the risk of mortality whereas the indirect effect of NAC on OS through DS significantly decreased the risk of mortality. These opposite effects might partly be explained by confounding by indication dominating the direct effect estimates.

4.2. Main findings

Paper I

This is the first population-based study from Norway of curative treatment and survival in patients with non-metastatic MIBC. The study complements previous population-based studies assessing differences in outcome between primary and secondary MIBC by presenting a homogenous population of patients with pre-treatment histological confirmation of muscle-invasion and assessing outcomes following RC as well as RT.

Non-metastatic MIBC was diagnosed in 21.4% of all patients diagnosed with BC in Norway between 2008-2012. In comparison, a population-based study of a Swedish cohort of BC patients (1997-2014) showed that 25% of the included patients were diagnosed with MIBC by TURB[3], a mere 3.6% more than in our study. As opposed to our study, this cohort of patients comprised all BC patients, including all patients with both UC and non-UC morphologies and patients with distant metastasis. In addition, the study did not separate between primary MIBC and secondary MIBC.

Compared to other population-based studies[147, 150], a lower proportion had secondary MIBC in our study (9% vs 20-43%). Our study population consisted of patients with histologically confirmed muscle-invasion before RC or RT, whereas all patients undergoing RC for BC regardless of pre-RC confirmation of muscle-invasion were included in the previous studies due to unavailable pre-RC staging[147, 150]. However, in one of the studies a post-inclusion pathological review showed that approximately half of the included secondary MIBC patients had histologically confirmed MIBC before RC [147]. Different definitions of primary and secondary MIBC may contribute to the different distributions for type of MIBC across studies. One study defined patients as secondary MIBC if there was >1

TURB prior to RC and there were over two months between two subsequent TURBs[147], as opposed to over four months after the diagnostic TURB and confirmed muscle-invasion in our study. This difference means that some patients categorized as primary MIBC in our study would have been categorized as secondary MIBC in the former study, increasing the proportion of secondary MIBC relative to our study. The selection of patients based on pre-RC histopathological verification of muscle-invasion in our study is similar to the inclusion criteria of two prospective non-randomized institutional studies[152, 157]. Accordingly, the proportion of patients with secondary MIBC in our study is closer to the proportions (16-23%) reported in these studies[152, 157].

Noteworthy is that nearly half (47%) of patients with non-metastatic MIBC did not undergo curative treatment. However, similar population-based studies reveal the same tendency. In a nationwide Swedish study, 57% of patients did not receive curative treatment. Of those, 84% of patients had organ-confined disease (T2-T3, M0) [3]. Moreover, in an American study of patients with non-metastatic MIBC only 27% of patients underwent RC[179].

Another interesting finding is that there were no differences in pT-stage or pN-stage between primary and secondary MIBC. The proportion of patients receiving NAC, which may have influenced the pT and pN distributions, was similar between the two groups. Compared to patients with primary MIBC, patients with secondary MIBC would be expected to have less advanced disease due to rigorous follow-up for early detection of progression to MIBC. However, the proportion of pT3/pT4 was 55 % in the secondary MIBC group and 56% in the primary MIBC group. Several institutional retrospective observational studies have found the same pattern of no difference in post-RC stage distribution between primary MIBC and secondary MIBC [144, 152, 156]

Superior post-RC survival for secondary MIBC over primary MIBC was reported in a large multi-institutional series[148]. The included primary MIBC patients had significantly more advanced disease (hydronephrosis, pT3, pT4, lymphovascular invasion, pN+) compared to patients with secondary MIBC which may explain the superior survival for secondary MIBC found in this study. Despite similar pathological outcomes (pT and pN), secondary MIBC had worse survival than primary MIBC following RC in two large single-institutional studies [143, 144], suggesting that some patients initially may have been understaged and

consequently received delayed curative treatment which may have compromised survival [74].

Superior survival for secondary MIBC over primary MIBC was suggested in another population-based study [150]. In this study information on histopathology was unavailable and patients were presumed to present with secondary MIBC if they had ≥2 TURBs with >4 months apart[150]. Without pre-RC confirmation of muscle-invasion, most likely prognostically advantageous patients undergoing RC before MIBC[143, 151, 153, 180] were included as secondary MIBC. This may have skewed the results in favour of secondary MIBC.

In line with our study, a similar population-based study found no significant difference in CSS or OS between secondary and primary MIBC for all patients nor when restricted to patients with pre-RC MIBC verification[147].

In this first population-based series from Norway which compared survival between primary and secondary MIBC after curative RT, type of MIBC had no impact on survival. Trimodal treatment with concurrent radio chemotherapy was not used and could not be assessed.

Paper II

This nationwide population-based study on the effect of NAC on OS in patients with MIBC, complements results from previous studies with the addition of mediation analysis to evaluate downstaging as a potential mediator of this association.

Despite the proven beneficial effect of NAC on survival [44, 78, 86], observational studies evaluating utilization trends on a population-based level have reported low use of NAC (7-20%) although increasing over time[181, 182]. In this study, 14% of patients undergoing RC for MIBC received NAC but the proportion increased over time from 8.5% in 2008-2009 to 34% in 2012-2015. This increase over time is possibly related to the gradual implementation of NAC into clinical practice after NAC was recommended as a part of standard treatment for MIBC in the 2008 EAU guidelines. Other comparable population-based studies with similar inclusion periods have reported higher proportions (19%-30%) of patients who have received NAC [81, 82]. The reasons for this low proportion observed in our study are unknown, but

may be associated with interstudy differences in for us unknown patient-related factors potentially influencing the receipt of NAC (e.g., increased comorbidities, clinical stage) [181, 182].

Like in this study, several population-based studies have documented that real-world patients receiving NAC were younger than patients treated with RC only and more likely to have received treatment at an academic hospital[81, 82]. Given the toxicity profile of cisplatin-containing NAC regimes it is no surprise that older patients with an increasing risk of comorbidities are less likely to be offered NAC. Although there was no measure for evaluating comorbidities in this study, the proportion of non-cancer deaths was higher among patients who did not receive NAC, which may indirectly imply that the presence of competing risks was high in this group. Furthermore, with the multidisciplinary approach required for planning of NAC and RC it is not unexpected that the majority of patients are treated within academic hospitals. Compared to the patients in the two pivotal trials, the SWOG trial[44] and the MRC/EORTC[43] trial, the patients treated with NAC in this study were older (median 69 years vs 63-64 years) and more often of female gender (22% vs 12-18%), factors associated with adverse prognosis [22, 183].

This study provided good quality data on post-operative pT- and pN-category. More patients in the group of patients treated with RC only had pathologically more advanced disease (pT3: 47% vs 27%, pN+: 35% vs 25%) and fewer patients achieved DS (22% vs 43%) compared to the patients treated with NAC.

Downstaging is defined differently between studies of different designs. In population-based studies such as ours, the definition of downstaging has been limited to downstaging of the primary tumour (DS: <pT2)[81, 83, 178], whereas nodal status has been included in the definition of downstaging in various clinical trials (<pT2pN0)[84, 91]. The rate of downstaging is an effect measure in studies examining the efficacy of NAC and is dependent on the type of chemotherapy. For instance, the combination of cisplatin+ doxyrubicin/methotrexate used in two Nordic trials yielded post-NAC downstaging(<pT2pN0) for 38% of the patients[84]. Whereas in the most recent clinical trial comparing the efficacy of two modern NAC regimes, 49% of the patients achieved downstaging (<pT2pN0) with gemcitabine-cisplatin and 63% with dose-dense MVAC [91]. In other population-based studies where the type of chemotherapy is unspecified, the

proportion of patients achieving DS ranges from 24-61% for patients treated with NAC and 7-33 % for patients treated with RC only[81, 83, 178]. This shows that DS can be achieved by complete TURB as well as by NAC. Such surgically achieved DS probably accounts for some of the cases of DS in patients treated with NAC. However, as shown in our study DS is achieved to a lesser extent following complete TURB compared to following NAC and the odds of achieving DS were 2.5 times higher for patients treated with NAC over NoNAC.

The relationship between downstaging and the demonstration of pN0 was examined in our study. The proportion of pN0 was higher in patients with DS compared to patients without DS (89% vs 60%). Between patients with DS treated with or without NAC, there was no difference in pN0 proportions (92% vs 88%). These results are in line with a retrospective analysis of downstaging in the two Nordic cystectomy trials [84], which also showed that a larger proportion of DS patients had pN0 (97% vs 81%) compared to patients without DS and no difference in pN0 between patients treated with and without NAC (both 97%). This indicates that DS reflects the absence of regional LN metastases. The achievement of DS by any means had a significant impact on OS with a 78% reduction in mortality risk for patients with DS compared to patients with residual muscle-invasive tumour (pT≥pT2) and since the odds of DS is greater with NAC, these results may also reflect the favourable effect of NAC on undetected metastases. The interpretation of the findings of no difference in proportions of pN0 between DS patients treated with or without NAC is difficult due to the lack of detailed information on clinical N-category in both our study and the two Nordic trials[84]. One explanation may be that there are inherent differences in pre-RC disease aggressivity between the groups, with possibly less aggressive tumours in the group of patients not receiving NAC. This relationship between downstaging and pN0 has not been reported in other clinical trials and various population-based studies [43, 44, 81, 83, 91, 178].

Clinical trials have established that complete response (pT0pN0) with NAC is associated with a significant OS benefit over post-NAC residual muscle-invasive disease[44, 84], and this was confirmed in a meta-analysis of 13 retrospective and prospective trials[85]. A population-based study showed that the survival benefit also applies to pathological downstaging to non-muscle invasive tumours (<pT2)[83], results now confirmed by this present study.

In addition to our study, the generalisability of the beneficial effect of NAC on survival established by clinical trials[43, 44, 78, 80] has been evaluated in several previous population-

based series[81, 82]. None of the studies have clearly demonstrated the efficacy of NAC related to OS, despite using various statistical modelling techniques (propensity score weighting, instrumental variables analyses) in an attempt to mitigate potential bias inherent in the observation study design due to lack of randomisation (unknown confounders and confounding by indication). Our analyses were complemented by a mediation analysis, which showed that NAC was indirectly associated with a favourable OS (mediated by DS).

Most likely differences in for us unknown factors (e.g., clinical stage) between patients treated with and without NAC obscures the beneficial effect of NAC mediated by DS when evaluating the total effect of NAC on OS. It is possible that in the initial implementation of NAC into routine practice clinicians may have selected younger patients with more advanced initial disease and a poorer prognosis for NAC, whereas patients with less advanced tumours were treated with standard RC. Although we cannot show this in our study, this notion is supported by the results from a comparative study of a propensity score matched population-based cohort and the SWOG trial population, which found that patients in the population-based cohort had more advanced disease stage at time of diagnosis[81]. The negative impact on total OS by these patients with advanced disease in the NAC group may have equalized the positive effect of NAC on total OS by patients with DS. However, in other comparable population-based studies with available clinical stage the majority of patients (82-86%) had cT2N0M0[81, 82]. In comparison, the proportion of cT2N0M0 ranges from 34-40% in clinical trials [43, 44, 78]. Clinical trials have either not shown a clear survival advantage of NAC in patients with cT2 [78] or have not evaluated mortality risk stratified by clinical stage[43, 44]. A population-based study examined OS after treatment with NAC for cT2N0M0 MIBC patients only, and could not demonstrate a significant survival benefit for NAC over RC only [184]. Therefore, any overweight of this subgroup of patients with debatable benefits from NAC may contribute to the lack of a total effect of NAC on OS as shown in population-based studies.

Paper III

This first Norwegian population-based study of management and survival in primary metastatic BC, provide an overview of treatment patterns before the introduction of novel agents into routine clinical practice. This study highlights that there is an area of unmet need among patients with primary metastatic BC, a mere 30% of patients received systemic anti-

cancer treatment and more than 50% of patients did not receive anti-cancer therapy and had a poor prognosis.

Primary metastatic BC was diagnosed in 2.7% of all patients diagnosed with BC in 2008-2016, in comparison the annual report from the CRN reported distant stage in 4% of all patients diagnosed with UTC (ICD-10 C65-67) in 2017-2021. The slight difference in incidence is explained by the inclusion of C67 only in our study and as opposed to the CRN annual report, the definition of distant metastases did not include visceral metastasis located in the true pelvis.

In accordance with other comparable real-world studies, approximately one third of the study population was treated with systemic anti-cancer therapy including patients treated with a multimodal approach [9, 10, 185]. These studies demonstrated median OS of 11-13 months, whereas median OS for patients in our chemotherapy group only was slightly lower (9.8 months). Compared to these previous studies, our study comprised of patients with more adverse prognostic factors such as visceral metastases (80% vs 61-69%) and non-UC histologies (29% vs 0-15%) which in part may explain the observed difference in survival[87, 132, 133]. In addition, the choice of treatment and prognosis may be influenced by for us unknown adverse risk factors such as poor performance status, comorbidities and renal functions[132, 186].

Median OS was 9.8 months for patients treated with chemotherapy in our study. Relevant clinical trials have demonstrated median OS of 12-14 months for metastatic UTC (UC only) treated with first-line gemcitabine-cisplatin [89, 118]. This survival difference may be explained by several factors. Apart from the inherent differences in study design of observational studies (selected population, randomisation), there are differences between our real-world population and the trial populations. Our population was restricted to BC only but allowed inclusion of poor prognosis non-UC histologies. The trial populations included potentially more prognostically advantageous patients (locally advanced disease, secondary metastases) [89, 118]. In addition, all trial patients received cisplatin whereas type of chemotherapy was unspecified in our study.

The number of hospitalisations was higher among patients treated with systemic chemotherapy or multimodal therapy compared to patient in the local treatment group and the

untreated patients. The low number of hospitalisations in the untreated group is to be expected since the median OS was 2.3 months in this group. Meaningful intergroup comparisons are difficult due to many unknown confounders such as comorbidities which impact the need for hospitalisation. Compared to a study from the American SEER database[9], the average number of all cause hospitalisations for metastatic BC patients treated with chemotherapy was lower (5.2 versus 9). Our population had relatively more advanced disease with visceral metastases in 91% of patients compared to 69% in the former study. More advanced disease may increase the need for hospitalisation. The higher average of all-cause hospitalisations in Norway can possibly be explained by differences in the setting of chemotherapy delivery. In Norway, patients with BC receiving cisplatin-containing chemotherapy are routinely hospitalised. If we only considered non-chemotherapy related hospitalisation, the average was the same in our study indicating that possibly more patients in Norway received chemotherapy as inpatients.

Notably, more than 50% of the study population did not receive any initial anti-cancer treatment. Other observational studies have reported similar findings, with 60-66% of patients not receiving systemic anti-cancer treatment[9, 10, 185]. Compared to patients treated with systemic anti-cancer treatment, observational studies including ours describe the untreated patients as older, being more often women and more frequently harbour more disseminated disease with non-regional LN metastases or visceral metastases[9, 185]. In addition, these patients are described as less fit with poorer renal function and performance status compared to treated patients[9, 185]. These unfit patients have a very poor prognosis (median 2-3 months) but are not well characterised. They, represent a potentially under-served population.

5. Summary

Paper I

- Non-metastatic MIBC was diagnosed in 21.4% of all patients diagnosed with BC in Norway between 2008-2012.
- Less than 50% of non-metastatic MIBC patients underwent curatively intended treatment with RC or RT.
- The five-year cancer-specific survival was 57% for all MIBC patients undergoing RC or RT
- Both overall and stratified by type of treatment (RC or RT), the type of MIBC (primary or secondary) did not impact the BC-specific mortality risk.

Paper II

- For Norwegian patients diagnosed with non-metastatic MIBC between 2008-2012, the five-year OS after RC with and without NAC was 47%.
- NAC significantly increased the proportion of DS in the RC specimens compared to RC only and DS significantly increased survival.
- NAC did not have a beneficial survival effect versus RC only, except for when the effect of NAC on OS went through DS.
- DS was related to absence of regional lymph node metastases and is a good prognostic factor associated with an OS benefit compared to residual muscle-invasive disease.

Paper III

- Primary metastatic BC was diagnosed in 2.7% of all patients diagnosed with BC in 2008-2016.
- Approximately one third of patients diagnosed with primary metastatic BC were treated with chemotherapy.
- More than 50% of patients did not receive initial anti-cancer treatment
- With a median OS of 9.8 months, survival in chemotherapy-treated patients was inferior to median OS of 12-14 months found in contemporary trials investigating cisplatin-containing first-line chemotherapy.
- Days of hospitalisation per patient was high in patients treated with chemotherapy

6. Conclusion: Clinical implications and future studies

- The population-based five-year cancer-specific survival and overall survival in non-metastatic MIBC patients following curative intent treatment (RC with or without NAC, RT) documented in this thesis should be compared with outcomes following current and more modern treatments (e.g., trimodal therapy) in more recent Norwegian cohorts.
- A large proportion of MIBC patients remain untreated. This thesis shows that almost 50% of non-metastatic MIBC patients did not undergo curative intent treatment, and more than 50% of primary metastatic MIBC patients did not receive systemic cancer treatment. Further characterization of these patients to understand predictors of no treatment is necessary, as well as further research into whether use of less toxic new therapeutic options enables treatment of these patient groups and improves prognosis.

- The current literature, including our study of survival differences between patients with primary MIBC and secondary MIBC following curative intent treatment, does not warrant differential curative management and emphasizes the importance of continued close surveillance of patients with NMIBC for early detection and treatment of secondary MIBC.
- There is a need for improved pre-treatment patient selection in patients eligible for curative treatment of muscle-invasive bladder cancer, e.g., reduce staging errors by use of more advanced imaging-guided approaches than CT.
- Identification of reliable clinical markers and biomarkers for predicting response to chemotherapy in the neoadjuvant setting is needed.
- Downstaging is a good prognostic marker and efforts should be made to identify patients most likely to achieve DS with or without NAC.
- The lack of clinical information on tumours, nodes and metastases in the CRN incidence registry is a subject of limitation for answering clinical research questions in BC.

- Future studies should explore whether the use of novel agents in metastatic BC increases the proportion of patients receiving systemic anti-cancer treatment and survival.

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8. Appendix

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Primary versus secondary muscle-invasive bladder cancer: survival after curative treatment

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Primary versus secondary muscle-invasive bladder cancer: survival after curative treatment

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ABSTRACT

Purpose: To assess if cancer-specific survival (CSS) following curative intent treatment (CIT) for muscle-invasive bladder cancer (MIBC) differs between patients presenting with MIBC (primary) and patients presenting with non-muscle-invasive bladder cancer who progress to MIBC (secondary).

Methods: This study uses data from the Cancer Registry of Norway on patients initially diagnosed with bladder cancer in 2008–2012 and treated with radical cystectomy (RC) or radiotherapy (RT). To ensure a clinically relevant population, we selected patients with a pre-treatment histology confirming muscle-invasion. Survival models were applied to evaluate differences in observed and adjusted CSS by type of MIBC and stratified by type of CIT. Adjustment was made for age group, sex, previous cancer, diagnostic hospital's academic status and geographical region, and type of CIT.

Results: We identified 650 eligible patients: 589 (91%) primary MIBC and 61 (9%) secondary MIBC. A total of 556 (86%) patients underwent RC and 94 (14%) RT. The 5-year CSS for primary MIBC was 56% and 59% for secondary MIBC ($p = 0.68$). The type of MIBC did not impact the risk of bladder cancer death (HR = 0.85, CI = 0.55–1.33, $p = 0.48$), nor when stratified for CIT (RC: HR = 0.93, CI = 0.57–1.53, $p = 0.78$); RT: HR = 0.71, CI = 0.24–2.16, $p = 0.55$).

Conclusion: This first nation-wide population-based study comparing CSS between primary and secondary MIBC showed no significant difference in survival regardless of type of CIT. Continued surveillance of patients with non-muscle-invasive bladder cancer is necessary to detect early progression to MIBC. Future studies should include molecular and genetic characteristics in addition to detailed clinicopathologic information.

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Introduction

In Norway, 1,626 cases of bladder cancer (BC) were diagnosed in 2020, of which 1,273 (78%) cases were men, making it the 4th most frequent cancer form among Norwegian men [1]. In Europe, more than 90% of BC cases are urothelial carcinomas (UC) [2] and approximately 25% of all BC cases are muscle-invasive bladder cancer (MIBC) [3]. MIBC can be present at first BC diagnosis (primary MIBC = priMIBC) or have a prior history of non-muscle invasive bladder cancer (NMIBC) before presenting with MIBC (secondary MIBC = secMIBC).

Regardless of type of MIBC (priMIBC or secMIBC), radical cystectomy (RC) has been the standard curative intent treatment (CIT) for the past decades. In selected patients RC is combined with neoadjuvant cisplatin-based chemotherapy (NAC) [2], which in Norway became recommended as part of routine practice in 2013 [4]. Pelvic radiotherapy (RT; $\geq$ 60 Gy) is offered as CIT to patients unfit or unwilling to undergo RC. Trimodal therapy combining transurethral resection of the bladder (TURB), chemotherapy, and RT [2] was gradually introduced into clinical practice after the publication of national guidelines for treatment of bladder cancer in Norway in 2013 [4].

Several studies have compared post-RC survival in patients with priMIBC and secMIBC [5–18]. Results are conflicting with reports of worse [6,14,16], better [11,17] or comparable survival [5,7–10,12,13,15,18] for secMIBC vs. priMIBC. To our knowledge, no study has compared survival in patients with priMIBC vs. secMIBC based on data from a national cancer registry on patients with histologically confirmed MIBC by TURB and included both RC and RT as CIT.

To fill this gap, the present study uses nationwide data from the Cancer Registry of Norway (CRN) and the National Patient Registry (NPR) on patients initially diagnosed with BC in 2008–2012. Our objective was to describe the patient and

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Supplemental data for this article is available online at here

treatment characteristics of curatively treated, non-metastatic priMIBC and secMIBC, and to compare bladder cancer specific survival (CSS) between patients with priMIBC and secMIBC, as well as stratified by type of CIT (RC and RT).

Materials and methods

Data sources

We used data from the CRN to identify patients with a first-time morphologically verified UC of the bladder diagnosed in 2008–2012. A personal identification number has been assigned to all residents in Norway since 1960, which was used to link data from the CRN and the NPR.

Study population

Patients finally evaluable for the current study had to fulfil the following criteria:

1. Pre-CIT muscle-invasion demonstrated in the histological specimen from a TURB.
2. No distant metastases (M0) at the time of MIBC diagnosis.
3. Curative intent treatment (CIT) with RC or RT.

PriMIBC required proof of histological muscle-invasion present in the initial diagnostic TURB specimen. To capture patients initially under-staged who underwent a second TURB, patients presenting with histological muscle-invasion in a TURB specimen obtained $\leq$4 months after the first BC diagnosis were categorized as priMIBC. In patients with secMIBC, muscle-invasion had to be present in a TURB specimen acquired $>$4 months after the first BC diagnosis and before December 2015.

Based on previous publications using BC data from the CRN [19] and other relevant studies [10,15,16], we chose a cut-off at 4 months to separate priMIBC from secMIBC.

Assessments

From the CRN, in addition to age at BC diagnosis, sex and previous cancer diagnoses, we retrieved information and corresponding dates on BC diagnosis, TURB, RC, RT, status at last observation and cause of death. Age was divided into four groups ($\leq$59, 60–69, 70–79 and $\geq$80).

For the whole BC patient cohort, all histological reports available at the CRN were quality ensured by the research team concerning muscle-invasion in the TURB specimens, though without detailed information on the depth of invasion. For RC patients, the histopathological T and N category (pT; pN) was identified without sub-classification into a and b in pT2-pT4 [20]. No information on molecular or genetic markers was available.

The NPR provided information on treatment codes (medical, surgical and chemotherapy), the diagnostic hospital's academic status (academic vs. community) and geographical region in Norway (Southeast, West, Central, North) from all patients' contacts within public hospitals and from publicly funded private specialists.

To capture patients treated with RC but not registered in the CRN, we cross-checked the information on RC obtained from the CRN with surgical codes for RC in the NPR and identified 56 additional patients.

Statistical analysis

Descriptive statistics (mean, median, interquartile range (IQR), proportions) were applied. Patients were followed from MIBC diagnosis until death, emigration, or end of study (31 December 2019), whichever came first. The total follow-up time was 3,100 person-years (median 3.5 years). Kaplan-Meier (KM) curves were applied to illustrate crude overall survival (OS) and CSS, and a log-rank test evaluated the (unadjusted) differences between them. The association of type of MIBC (secMIBC vs. priMIBC) with CSS was evaluated by flexible parametric survival models (FPSM) [21] adjusting for age group, sex, previous cancer, diagnostic hospital's academic status and geographical region, and type of CIT (RT vs. RC). The analysis for RC treated patients was additionally adjusted for post-cystectomy pT-category ($<$pT2, $\geq$pT2, missing pT), pN-category (pN0, pN+, missing pN), and concomitant CIS (no, yes, missing). In all FPSMs, the baseline hazard was modelled using 4 degrees of freedom (4df) for the splines. Quantities reported from the model-based analyses are hazard ratios (HRs) including 95% confidence intervals (CI) and *p*-values.

The statistical significance level was set to $\leq$ 0.05. Statistical analyses were performed using Stata 17 (StataCorp, College Station, TX), stpm2 command for estimating FPSMs.

Results

Patients and treatment

From the CRN, 5,521 patients were identified with a first-time morphologically verified UC BC diagnosis from 2008 through 2012. Muscle-invasive disease was histologically verified in in 1,337 patients (24.2%). We excluded 101 patients in whom muscle-invasion was found solely in a cystectomy specimen, and 53 patients with a record of distant metastases in the CRN at the time of MIBC diagnosis. In total, 1,183 (21.4%) patients fulfilled the criteria of pre-CIT muscle-invasion demonstrated in the histological specimen from a TURB and no distant metastasis. Of those patients, 650 (55%) patients underwent CIT (Supplementary Figure S1). Out of 650 MIBC patients treated with CIT, we identified 589 (91%) patients with priMIBC and 61 (9%) patients with secMIBC. Compared to patients with secMIBC, more patients with priMIBC were treated with CIT (56% vs. 44%: Supplementary Figure S1).

Median age of the patients at BC diagnosis was 71 (IQR = 63–77) years and the patients were predominantly male (79%) (Table 1a). A total of 556 (86%) patients underwent RC, of whom 56 (10%) patients received NAC. RT represented CIT in 94 (14%) patients, of whom 6 (6%) patients underwent

Table 1. Primary and secondary MIBC patients treated with curative intent: (a) All patients: Patient- and treatment characteristics, (b) Patients treated with radical cystectomy (RC): pT-category, (c) Patients treated with RC: pN-category (d) Patients treated with RC: Concomitant CIS.

(a) All patients	Primary MIBC (*N* = 589)	Secondary MIBC (*N* = 61)	Total (*N* = 650)
Age (median) (IQR)	71 (63–77)	72 (64–77)	71 (63–77)
Sex (% men)	462 (78)	51 (83)	513 (79)
Previous cancer (% yes)	87 (15)	11 (18)	98 (15)
Hospital (% Community)	354 (60)	31 (51)	385 (59)
Region:			
Southeast	295 (50)	30 (49)	325 (50)
West	137 (23)	14 (23)	151 (23)
Central	88 (15)	7 (11)	95 (14)
North	69 (12)	10 (16)	79 (12)
Radical cystectomy (RC) (%)	506 (86)	50 (82)	556 (86)
Neoadjuvant chemotherapy (% RC patients)	50 (10)	6 (12)	56 (10)
Radiotherapy (RT) (%)	83 (14)	11 (18)	94 (14)
Post-RT cystectomy (% RT patients)	6 (7)	0	6 (6)
Cause of death (%)			
Bladder cancer	251 (43)	23 (38)	274 (42)
Other cancer	68 (12)	7 (11)	75 (12)
Other causes	61 (10)	7 (11)	68 (10)
(b) pT available	Primary MIBC (*N* = 449)	SecondaryMIBC (*N* = 47)	Total (*N* = 496)
pT category			
pTa	10 (2)	5 (11)	15 (3)
pTis	24 (5)	1 (2)	25 (5)
pT0	45 (10)	5 (11)	50 (10)
pT1	25 (6)	1 (2)	26 (5)
pT2	93 (21)	9 (19)	102 (21)
pT3	204 (45)	19 (40)	223 (45)
pT4	48 (11)	7 (15)	55 (11)
≥pT2 (%)	345 (77)	35 (74)	380 (77)
(c) pN available	Primary MIBC (*N* = 365)	SecondaryMIBC (*N* = 46)	Total (*N* = 411)
pN category			
pN+	124 (34)	13 (28)	137 (33)
pN0	241 (66)	33 (72)	274 (67)
(d) Concomitant CIS available	Primary MIBC (*N* = 451)	SecondaryMIBC (*N* = 48)	Total (*N* = 499)
Yes	100 (22)	11 (23)	111 (22)
No	351 (78)	37 (77)	388 (78)

post-RT RC. During the follow-up period 274 (42%) patients died of BC. Patient and treatment characteristics were similar in the priMIBC and secMIBC groups. In patients with secMIBC, a median time of 1.1 year (IQR = 0.5–3.1) elapsed from diagnosis of NMIBC to diagnosis of MIBC.

Out of 556 patients undergoing RC, histopathological information from the RC was registered in the CRN for 500 (90%) patients: pT and pN were available in 496 (99%) and 411 (82%) patients, respectively. The distributions of pT- and pN-categories were similar in the priMIBC and the secMIBC group (Table 1b and c). Concomitant CIS was present in 111 (22%) of the patients with a similar distribution in the priMIBC and secMIBC group (Table 1d).

Out of 500 patients treated with RC and no NAC, 449 (90%) patients underwent RC ≤90 days of MIBC diagnosis, with no difference in elapsed median time (49 days) or the number of patients undergoing RC within 90 days (90 vs. 91%) between patients with priMIBC and secMIBC (Supplementary Table S1a).

In all cystectomized and irradiated patients, there was no difference in age and sex distributions between priMIBC and secMIBC (Supplementary Table S1b and c).

Survival

All patients: Crude 5-year OS and CSS were 44% and 57% (Figure 1a). The 5-year CSS was 56% for priMIBC and 59% for secMIBC ($p = 0.68$) (Figure 1b). The adjusted survival analysis revealed that the type of MIBC had no impact on the risk of BC death (HR = 0.85, CI = 0.55–1.33, $p = 0.48$). Sex, previous cancer, academic status and type of CIT were not associated with the risk of death, but higher age (≥80 vs. ≤59) and region (North vs. Southeast) significantly increased this risk (Table 2).

Radical cystectomy: Crude 5-year CSS was 58% for all 556 patients: 58% for priMIBC and 59% for secMIBC ($p = 0.85$) (Figure 1c). The type of MIBC was not associated with the adjusted CSS (HR = 0.93, CI = 0.57–1.53, $p = 0.78$). Sex, previous cancer, academic status and region did not impact CSS, but higher age (≥80 vs ≤59), higher pT-category (≥pT2 vs < pT2) and pN+ (vs. pN0) were significantly associated with increased risk of BC death (Supplementary Table S2).

Radiotherapy: Crude 5-year CSS for priMIBC was 48% and 57% for secMIBC ($p = 0.49$) (Figure 1d). There was no

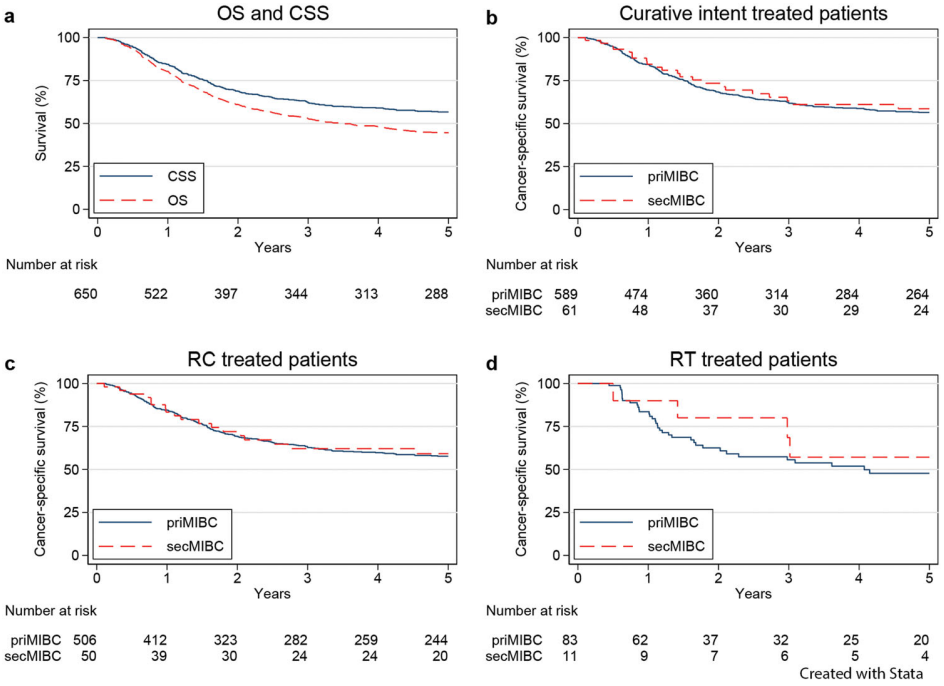

Figure 1. Survival after diagnosis of MIBC in 650 patients undergoing curative treatment: (a) All patients; Crude overall survival (OS = dashed) and cancer-specific survival (CSS = solid), (b) CSS in all patients; primary (priMIBC = solid) vs. secondary MIBC (secMIBC = dashed), (c) CSS in patients treated with radical cystectomy (RC); primary vs. secondary MIBC, (d) CSS in patients treated with radiotherapy (RT); primary vs. secondary MIBC.

Table 2. Flexible parametric survival model evaluating associations with cancer-specific survival for all included MIBC patients ($N = 650$).

		Cancer-specific survival		
		HR	CI	*p*-value
Secondary MIBC	No	1		
	Yes	0.85	0.55–1.33	0.484
Age	≤59	1		
	60–69	1.10	0.73–1.67	0.628
	70–79	1.41	0.95–2.09	0.085
	≥80	1.84	1.16–2.92	0.009
Sex	Male	1		
	Female	1.13	0.85–1.52	0.378
Previous cancer	No	1		
	Yes	0.89	0.61–1.29	0.527
Academic	No	1		
Hospital	Yes	1.05	0.81–1.35	0.718
Region	Southeast	1		
	West	0.94	0.68–1.30	0.710
	Central	0.99	0.68–1.45	0.968
	North	1.51	1.05–2.17	0.025
Treatment	Radical cystectomy	1		
	Radiotherapy	1.04	0.71–1.52	0.850

significant impact of the type of MIBC on the adjusted CSS (HR = 0.71, CI = 0.24–2.16, $p = 0.55$). Age, sex, previous cancer, academic status and region were not associated with CSS (Supplementary Table S3).

The lack of significant differences in CSS (priMIBC–secMIBC) in the adjusted analyses for all patients and those treated with RC or RT are illustrated in Figure 2.

Discussion

To our knowledge, this paper presents the first nationwide, population-based study that compares survival between patients with priMIBC and secMIBC for all curatively treated patients and where all patients had confirmed muscle-invasion prior to treatment. We did not find a significant difference in crude or adjusted CSS between all patients with priMIBC and secMIBC, nor when stratified by type of CIT.

In agreement with our findings, two prospective studies [12,15] and several retrospective studies [5,7–10] evaluating survival in patients undergoing RC for a diagnosis of MIBC by TURB, found similar crude CSS for MIBC patients and no significant difference between priMIBC and secMIBC or association with CSS to the type of MIBC. These data are confirmed by two meta-analyses [22,23]. In line with our results, a recently published Canadian population-based study [18] did not find a significant difference in survival between priMIBC and secMIBC. In that study, all patients undergoing RC for BC were included, and the pre-treatment pathology confirmed muscle-invasion in only 49% of patients with secMIBC (79% of priMIBC). The present population-based study therefore represents a more homogenous patient population since all patients included had pre-CIT confirmed MIBC, and thus serves as a better basis for survival comparison between curatively treated priMIBC and secMIBC.

Other studies have reported conflicting effects of secMIBC vs. priMIBC with respect to survival. Favourable post-RC survival (CSS, OS) for secMIBC vs. priMIBC was reported in two Canadian series [11,17]. In a multicentre study [11], patients with priMIBC were more frequently diagnosed with poor prognosis factors (hydronephrosis, pT3, pT4, lymphovascular invasion, pN+) than patients with secMIBC. In our study, we found similar pT and pN distributions in priMIBC and secMIBC, which is in line with several other clinical studies reporting no difference in survival between patients with priMIBC and secMIBC [10,15], suggesting that the favourable outcome for patients with secMIBC in the former series [11]

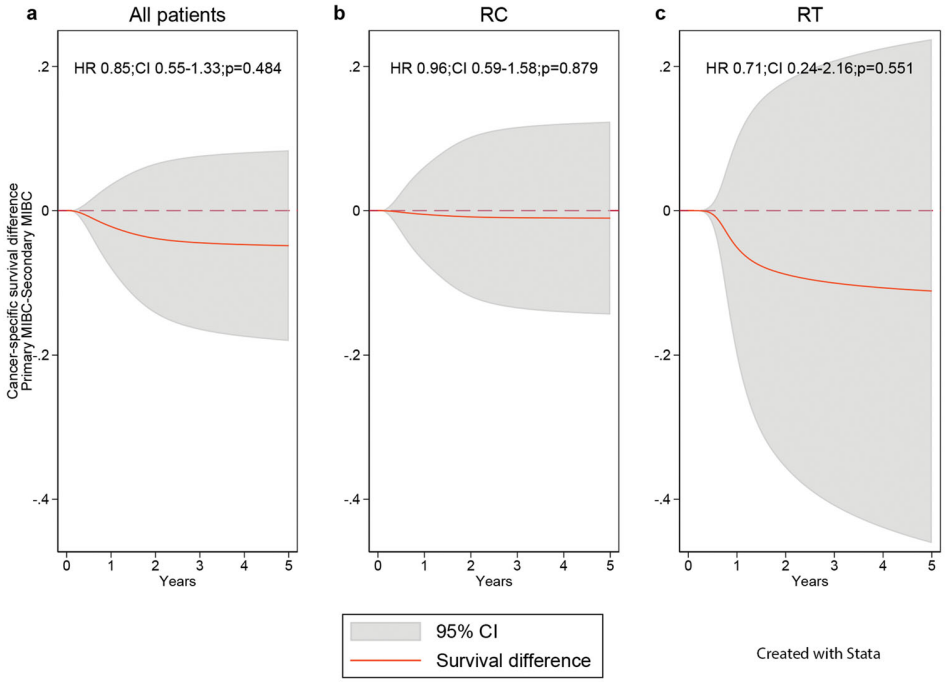

Figure 2. Adjusted difference in cancer-specific survival between patient with primary and secondary MIBC by treatment; no difference (dashed), observed survival difference (solid), confidence interval (CI = grey area); (a) All patients, both types of curative intent treatment, (b) Post-cystectomy (RC), (c) Post-radiotherapy (RT).

may be related to significantly more advanced disease in patients with priMIBC. In another Canadian population-based series [17] which included all BC patients undergoing RC, no histopathologic or clinical information for pre-RC staging was available. Patients were presumed to have secMIBC if they had undergone two TURBs or more over 4 months apart before RC, while all other patients were presumed to have priMIBC. No subsequent pathological review was conducted. The previously mentioned Canadian population-based study had a similar selection of the study population (RC for BC) and revealed that only 49% of the secMIBC patients had MIBC prior to RC in a subsequent pathological review [18]. Thus, it is very likely that a proportion of secMIBC patients in the former study were treated with RC for NMIBC. Patients undergoing RC before muscle-invasion have a significantly better prognosis compared to priMIBC and secMIBC [5,7,9,14] and including these patients probably contributed to the superior OS for secMIBC in this study [17].

On the other hand, worse survival for secMIBC compared to priMIBC has been reported in retrospective series [6,14,16] and is supported by two meta-analyses [24,25]. Patients in the retrospective studies [6,14,16] were selected based on pre-RC histopathological verification of muscle-invasion and reported similar clinicopathologic characteristics in priMIBC and secMIBC patients. However, information on the surveillance regime and time to progression was not available in two of the studies [6,16]. As noted by the authors in one of the studies [16], the worsened prognosis of secMIBC patients compared to priMIBC patients could be caused by a proportion of secMIBC patients receiving inadequate treatment or surveillance. Delayed RC (>3 months) has been shown to have a detrimental effect on overall survival [26]. In one of the studies [14] surveillance cystoscopy was performed regularly but a second TURB was not routinely performed in the first half of the study period. Some of the patients in the secMIBC group may have been under-staged at initial TURB, resulting in a delayed RC which may have impacted on the worsened survival for secMIBC.

Post-RC survival (recurrence free survival, CSS, OS) and pathologic response after treatment with NAC was worse for patients with secMIBC compared to patients with priMIBC in a recent retrospective study [27]. This finding was supported by a meta-analysis [23]. The effect was hypothesized to be linked to the predominant occurrence of a cisplatin sensitizing DNA damage repair gene (ERCC2) [28] in priMIBC tumours, predicting response to cisplatin. We did not exclude patients treated with NAC, but due to limited numbers we were not able to compare survival between NAC treated patients with priMIBC and secMIBC.

We found that the proportion of patients undergoing RC with secMIBC was 9%. In comparison, the proportion of patients with secMIBC ranges from 20% to 42% in population-based studies [17,18], from 22% to 38% in retrospective single- and multi-institutional studies [5,7–10,14,16] and from 16% to 23% in prospective series [12,15]. The lower proportion of secMIBC in our study may partly be explained by differences in patient selection and definitions of priMIBC and secMIBC. Compared to other population-based studies, we did not include patients undergoing RC before MIBC [17,18] as secMIBC, which potentially increased the proportion of secMIBC in these studies. Our definition of priMIBC is also slightly different compared to the most recent population-based study [18], since we allowed for patients with MIBC in a TURB less than 4 months after first BC diagnosis to be included as priMIBC as opposed to less than 2 months apart. Thus, some priMIBC patients in our study would have been

categorized as secMIBC in that study [18]. Compared to retrospective and prospective studies, our selection of patients for study inclusion is similar but our definitions of priMIBC and secMIBC differs slightly. In some studies patients were considered priMIBC if a subsequent TURB performed within 3 months of the first BC diagnosis showed MIBC [7,10,16], in comparison we extended this timeframe to 4 months. Some of these patients would be considered secMIBC in the previous studies [10,15,16].

In summary, the impact of priMIBC and secMIBC on patient prognosis remains unclear as the available evidence continues to show conflicting results. Neither can we rule out the possibility of secMIBC having a worse prognosis than priMIBC. SecMIBC may be of a more aggressive nature due to the extended duration of the malignancy compared to priMIBC increasing the risk of micro-metastatic dissemination, possible tumour clone selection after prior intravesical therapy [6] and possible local tumour spread after multiple TURBs [29]. On the other hand, the effect may be compensated by the close follow-up of primary NMIBC by urologists and early detection and treatment of MIBC.

Our results in the RT group comprise patients treated before 2015 and do not reflect more modern radiotherapy techniques allowing dose-escalated tumour boosting with possibly improved survival [30]. Today, it is important to continuously assess the real-life use of and effect of radiotherapy multimodal treatment.

A limitation of our study is the unavailability of risk factors such as smoking habits, socioeconomic status and comorbidities. On the other hand, we present a population-based cohort where we assume these factors are evenly distributed. Unfortunately, we do not have a quality register for BC in Norway with pre-treatment results of imaging or clinical findings enabling clinical TNM categorization. However, the verification of histological muscle-invasion upon study entry ensured clinically relevant and comparable patient groups. Type of operational technique (Open RC vs. robot assisted), extent of lymph node dissection, lymphovascular invasion, number of positive lymph nodes vs. numbers removed could not be assessed.

Conclusion

We found no difference in post-CIT survival in patients with priMIBC compared to those with secMIBC, regardless of type of CIT (RC, RT). With today's knowledge, differential curative management of patients with priMIBC and secMIBC is not warranted. Continued close surveillance of patients with NMIBC is necessary to ensure early detection and management of MIBC. To improve our understanding of priMIBC vs. secMIBC, future studies should not only investigate in depth clinicopathological parameters in MIBC, but also molecular and genetic differences to aid physicians in tailoring treatment for MIBC patients.

Ethics approval

Approved by the Regional Committee for Medical and Health Research Ethics (REC), Southeast Norway. Approval number: 2016/2286/REK sørøst A. The requirement for consent was waived by the ethics committee.

Disclosure statement

No potential conflict of interest was reported by the authors. Dam Foundation (https://dam.no) has made this project possible.

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II

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Downstaging and survival after Neoadjuvant chemotherapy for bladder cancer in Norway; a population-based study

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Abstract

Background: Neoadjuvant chemotherapy (NAC) before radical cystectomy is associated with pathological downstaging (DS) and improved overall survival (OS) in patients with muscle-invasive bladder cancer (MIBC). Population-based studies have not unequivocally shown improved survival. The aim of this population-based study was to evaluate the effect of NAC on DS and OS in Norwegian patients with MIBC.

Methods: Patients in the Cancer Registry of Norway undergoing radical cystectomy (2008–2015) with or without NAC diagnosed with MIBC between 2008 and 2012 were included. Follow-up data were available until 31 December 2019. Logistic regression estimated the odds of DS with NAC, and a Cox model investigated the effect of DS on OS. Cox models, a mediator analysis and an instrumental variable approach were used to investigate the effect of NAC on OS.

Results: A total of 575 patients were included. NAC was administered to 82 (14%) patients. Compared to cystectomy only, NAC increased the proportion (43% vs. 22%) and the odds of DS (OR 2.51, CI 1.37–4.60, $p=0.003$). Independent of NAC, the proportion of pN0 was higher in patients with DS (89% vs. 60%) and DS yielded a 78% mortality risk reduction (HR 0.22, CI 0.15–0.34, $p=1.9{\cdot}10{-}12$), compared to patients without DS. We did not find an association between NAC and OS, neither by Cox regression (HR 1.16, CI 0.80–1.68, $p=0.417$) nor by an instrumental variable approach (HR = 0.56, CI = 0.07–4.57, $p=0.586$). The mediation analysis ($p=0.026$) confirmed an indirect effect of NAC on OS through DS. Limitations include limited information of the primary tumour, details of NAC treatment and treatment indications.

Conclusions: NAC increases the probability of DS and is indirectly associated to OS. DS is related to the absence of regional lymph node metastases and is associated with an OS benefit. Improved staging and biomarkers are needed to identify patients most likely to achieve DS and to benefit from NAC.

Keywords: Bladder cancer, Neoadjuvant chemotherapy, Pathological downstaging, Population-based, Overall survival

Background

In Europe [1] and in the USA [2], *cisplatin-containing neoadjuvant chemotherapy (NAC)* before radical cystectomy (RC) is recommended for patients with localized *(T2-T4a, cN0, M0)* muscle-invasive bladder cancer (MIBC) fit for cisplatin treatment. The European

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Association of Urology recommended NAC for MIBC in the 2008 guidelines [1] after several randomized controlled trials (RCT) [3–6] and meta-analyses [7, 8] had demonstrated a beneficial effect of NAC in MIBC. The survival benefit of NAC found in RCTs has been shown to be associated with *pathologic downstaging (DS*) of the primary tumour in the RC-specimen [6, 9, 10].

Meta-analyses based on results from RCTs have shown an absolute five-year *overall survival (OS)* benefit of 6–8% favouring NAC over RC alone [7, 8, 11]. Results from population-based studies have been inconclusive. Some authors did not find an association between NAC and improved survival [12, 13], while others did show a survival benefit for NAC relative to RC alone [14]. With this background, more data and analyses are warranted to establish the beneficial effect of NAC on a population-based level. Therefore, we aimed to describe the clinical characteristics of an unselected population of Norwegian patients with MIBC treated with NAC and RC (*NAC group*) vs. RC only (*NoNAC group*) and to evaluate the association between NAC and DS, the effect of DS on OS and the overall association between NAC and OS.

Methods

Material

The Cancer Registry of Norway (CRN) captures nearly 99% of new cancer diagnoses in Norway [15]. The collected data includes patient demographics, tumour characteristics, treatment codes (surgical, radiotherapy) and causes of death. For bladder cancer, histopathology of specimens from transurethral resection of bladder tumour (TURB), cystectomy and biopsies of metastases are registered, along with the corresponding dates for the procedures.

The Norwegian Patient Registry contains individual administrative, demographic, and coded medical information (diagnoses, procedures, chemotherapy) from all patients' contacts with public hospitals. This data was linked to the CRN by the personal identification number assigned to all residents of Norway [16].

Study population

We included patients undergoing RC (2008–2015) with or without NAC who were diagnosed with MIBC (*urothelial carcinoma)* without known distant metastases between 2008 and 2012. The pre-RC status of regional lymph node metastases was unknown (cNx). Patients with a pre-RC histology verifying muscle-invasion and patients without such verification but treated with NAC were considered as having MIBC. We chose this period since we had quality ensured histopathological information from this period and to ensure sufficient follow-up time for survival analysis. Patients with pre-RC radiotherapy were excluded.

Measures

Muscle invasion

For the evaluable patients, the research team reviewed all available clinical notifications and histology reports at the CRN. The presence of MIBC was confirmed in the histology reports from TURB specimens. Muscle-invasion was defined as tumour invasion into the muscularis propria (≥T2). From the histology reports from cystectomy specimens, the histopathological T and N category (pT; pN) [17] without sub-classification into a and b for pT2-pT4 were confirmed. All MIBC are high-grade [18].

Neoadjuvant chemotherapy

We identified relevant specified intravenous chemotherapy codes (e.g., gemcitabine and cisplatin, methotrexate, vinblastine, doxorubicin and cisplatin (MVAC), carboplatin) and codes for intravenous administration of non-specified chemotherapy from the Norwegian Patient Registry. We excluded chemotherapy events concurrently registered with ICD-10 codes for a different cancer than C67. NAC was defined as any chemotherapy administered intravenously between diagnosis of bladder cancer and RC.

Downstaging

Based on the available data and definitions used in similar studies [12, 14, 19], we defined *downstaging of the primary tumour (DS)* as pT0/pTa/pTis/pT1 with the subunit of pT0 as *complete response (CR)*, identified independent of the use of NAC. Patients without DS *(non-DS)* were characterized by having residual muscle-invasive disease (pT2-pT4) in the specimen. Downstaging can occur after TURB and NAC. Nodal downstaging could not be assessed because information about cN was not available.

Statistical analyses

The observation time started at the date of RC until death, emigration, or end of study (December 31st, 2019), whichever came first. Time in years from date of RC was used as timescale in all analyses.

We applied descriptive statistics (mean, median, interquartile range (IQR), proportions) to present pre- and post-operative characteristics in all patients as well as in the NAC and NoNAC group. The association between NAC and DS was estimated using logistic regression adjusted for all available *pre-operative variables*: age at diagnosis (≤59, 60–69, 70–79, ≥80), sex, type of hospital *(academic* vs. *community)*, geographical health region *(Southeast, West, Central, North)* and the year of RC *(2008–2009, 2010–2011, 2012–2015)*. OS was presented

by Kaplan-Meier curves and the difference between them was evaluated with the log-rank test. The associations between DS with OS, as well as NAC with OS (*total effect*) were assessed with a Cox regression model adjusted for all available pre-operative variables.

The association between NAC and OS was additionally investigated by applying a mediation approach adjusted for available pre-operative variables. We applied a causal inference approach [20, 21] implemented in the R mediation package [22]. The *total* effect of NAC on OS (unadjusted for DS) evaluated with a Cox regression model was decomposed into two parts [23]: the *indirect* effect between NAC and OS mediated by DS, and the *direct* effect between NAC and OS (not through DS) This approach allowed us to assess the indirect effect of NAC on OS through DS.

In order to overcome the confounding by indication bias induced by missing information of factors leading to the decision of treatment, we applied an instrumental variable approach to estimate the causal effect of NAC on OS [24]. We used type of hospital as the instrumental variable and G-estimation [24–26] with adjustment for the remaining pre-operative variables.

Quantities reported from the model-based analyses are odds ratios (ORs) and hazard ratios (HRs) including 95% confidence intervals (CI) and *p*-values. The statistical significance level was set at 0.05. Statistical analyses were performed using Stata 17 (StataCorp, College Station, TX) and R (version 4.1.4).

Results

Patient characteristics

Between 2008 and 12, 5521 patients were diagnosed with first-time diagnosis of bladder cancer (urothelial carcinoma) and 917 of these patients underwent RC by the end of 2015. After exclusions, 575 patients were finally evaluable in our study (Supplementary Fig. S1): 82 (14%) patients in the NAC group and 493 (86%) patients in the NoNAC group. In the NAC group, 23 (28%) patients received gemcitabine and cisplatin, 10 (12%) patients MVAC and 1 (1%) patient Carboplatin. For 48 (59%) patients, the type of chemotherapy was unknown. The median follow-up time was 3.9 years.

The median age at diagnosis for the evaluable patients was 69 (IQR: 62,75) years and 124 (22%) of the patients were female (Table 1). Patients in the NAC group were younger (median 65 vs. 70 years), more frequently female (29% vs 20%) and more likely operated in an academic hospital (76% vs 61%) compared to the NoNAC group. Median time from the most recent TURB to cystectomy was 48 days for the patients undergoing cystectomy only, and 109 days for patients treated with NAC. The proportion of patients treated with NAC was increasing over time, with the largest proportions of patients (70%) treated between 2012 and 2015. Among the 82 patients in the NAC group, 47 (57%) patients died, compared to 301 (61%) patients out of 493 patients in the NoNAC group. The proportion of deaths due to other causes was larger in the NoNAC group (20% vs 12%) compared to the NAC group.

Table 1 Patient characteristics of the study population with respect to treatment

	NAC[a]	NoNAC[b]	All
Patients, n (%)	**82 (14%)**	**493 (86%)**	**575 (100%)**
Age, median (IQR)	65 (56,68)	70 (63,76)	69 (62,75)
Females, n (%)	24 (29%)	100 (20%)	124 (22%)
Academic hospital, n (%)	62 (76%)	299 (61%)	361 (63%)
Health region, n (%)			
Southeast	40 (49%)	274 (56%)	314 (55%)
West	22 (27%)	99 (20%)	121 (21%)
Central	11 (13%)	57 (12%)	68 (12%)
North	9 (11%)	63 (13%)	72 (13%)
Cystectomy year, n (%)			
2008–2009	16 (20%)	172 (35%)	188 (33%)
2010–2011	9 (11%)	211 (43%)	220 (38%)
2012–2015	57 (70%)	110 (22%)	167 (29%)
Number of deaths, n (%)	47 (57%)	301 (61%)	348 (60%)
Cause of death, n (%)			
Bladder cancer	37 (45%)	204 (41%)	241 (42%)
Other causes	10 (12%)	97 (20%)	107 (19%)

[a] *NAC* Pre-cystectomy neoadjuvant chemotherapy

[b] *NoNAC* Cystectomy only

Out of 575 patients, pT was recorded in 514 (89%) patients and thus evaluable for DS, and pN was recorded for 433 (75%) of patients (Table 2). The proportions of pT3 (47% vs 27%) and pN+ (35% vs 25%) in the NoNAC group were larger compared to the NAC group, while the proportion of CR (9% vs 24%) was smaller. Out of 29 patients with DS in the NAC group, 16 (55%) patients had CR, whilst 38 (40%) out of 96 patients with DS in the NoNAC group had CR.

Out of 514 patients evaluable for DS, pN was recorded for 427(83%) patients (Supplementary table S1). The proportion of patients with pN0 among patients with DS (89% vs 60%) was larger compared to patients with non-DS without difference between patients treated with and without NAC (92% vs 88%).

Neoadjuvant chemotherapy and downstaging

Compared to patients in the NoNAC group, a larger proportion of patients achieved DS (43% vs. 22%) in the NAC group (Fig. 1). NAC significantly increased

Table 2 Postoperative tumour characteristics for patients with available histopathological information according to treatment

	NAC[a]	NoNAC[b]	All
Patients, n (%)	**67 (13%)**	**447 (87%)**	**514 (100%)**
Pathological T category, n (%)			
Downstaging of primary tumour			
pT0	16 (24%)	38 (9%)	54 (11%)
pTa	2 (3%)	13(3%)	15 (3%)
pTis	6 (9%)	21(5%)	27 (5%)
pT1	5 (7%)	24(5%)	29 (6%)
Residual muscle-invasive disease			
pT2	12 (18%)	92 (21%)	104 (20%)
pT3	18 (27%)	212 (47%)	230 (45%)
pT4	8 (12%)	47 (11%)	55 (11%)
Pathological N category, n (%)	**65 (15%)**	**368 (85%)**	**433 (100%)**
pN+	16 (25%)	129 (35%)	145 (33%)
pN0	49 (75%)	239 (65%)	288 (67%)

[a] *NAC*: Pre-cystectomy neoadjuvant chemotherapy

[b] *NoNAC* Cystectomy only

the odds for DS (OR 2.51, CI 1.37–4.60, $p=0.003$) compared to NoNAC (Supplementary table S2).

Downstaging and overall survival

For patients with DS, the crude five-year OS was larger compared to patients with non-DS (80% vs. 38%, $p<0.001$) (Fig. 2 a). The adjusted survival analysis revealed a 78% risk reduction of all-cause death (HR 0.22, CI 0.15–0.34, $p=1.9{\cdot}10^{-12}$) in patients with DS compared to patients with non-DS (Supplementary table S2).

Neoadjuvant chemotherapy and overall survival

The crude five-year OS for all patients ($n=575$) was 47%: NAC 50% vs. NoNAC 47% (Fig. 2 b). NAC was not significantly associated with OS in the crude analysis ($p=0.552$), in the Cox analysis (HR 1.16, CI 0.80–1.68, $p=0.417$) nor when we applied the instrumental variable approach (HR 0.56, CI 0.07–4.57, $p=0.586$) (Supplementary table S3).

The mediation analysis confirmed the above results by revealing an indirect effect of NAC on OS through DS ($p=0.026$), but no total or direct effect of NAC on OS (Fig. 3, Supplementary table S4).

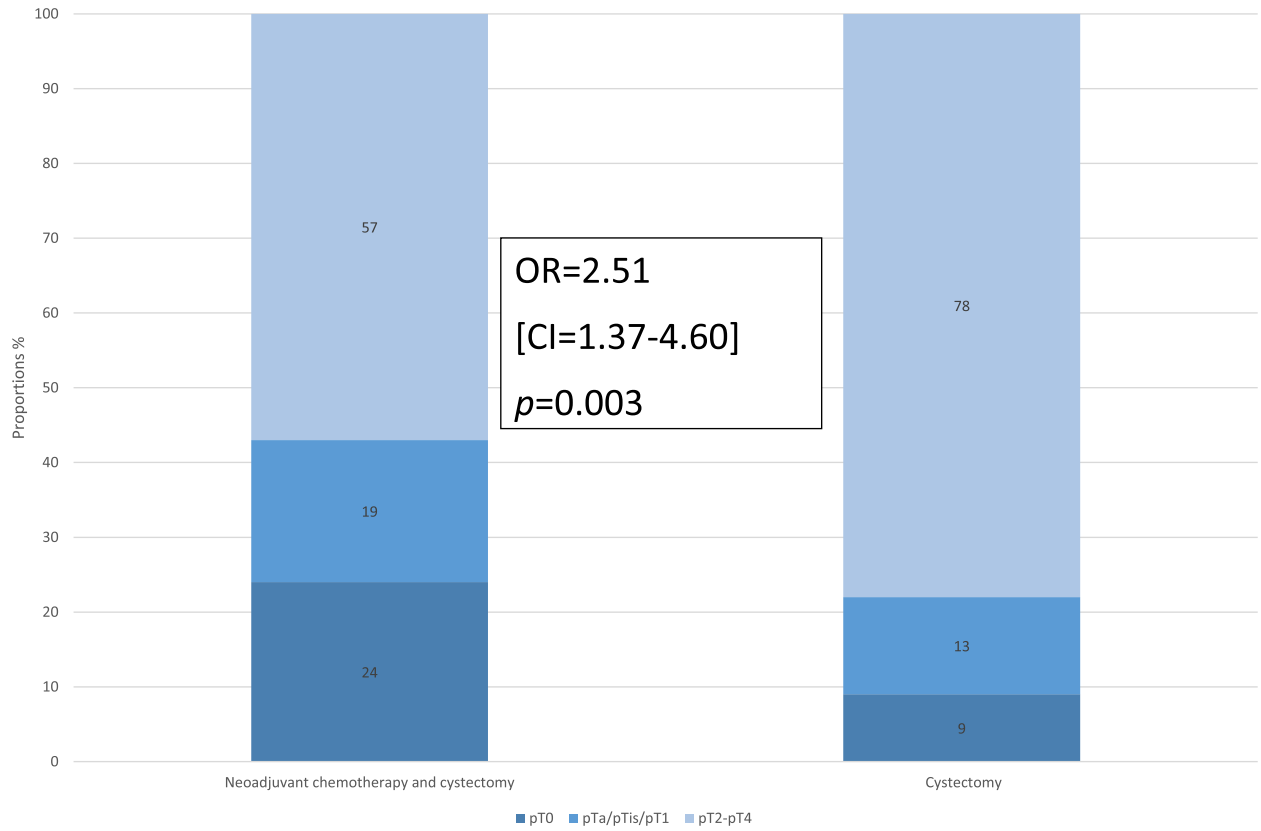

Fig. 1 Comparison of the proportions of patients with (pT0/pTa/pTis/pT1) and without downstaging (pT2-pT4) by treatment. Logistic regression results (odds ratio OR, 95% confidence interval CI and *p*-value)

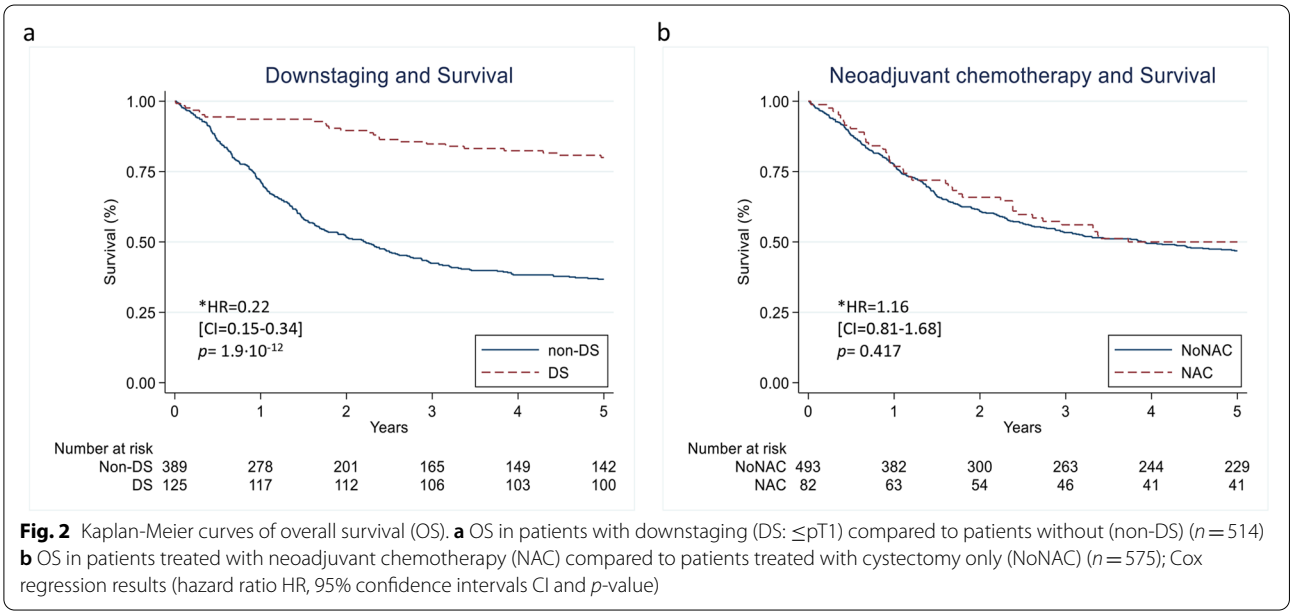

Fig. 2 Kaplan-Meier curves of overall survival (OS). **a** OS in patients with downstaging (DS: ≤pT1) compared to patients without (non-DS) ($n = 514$) **b** OS in patients treated with neoadjuvant chemotherapy (NAC) compared to patients treated with cystectomy only (NoNAC) ($n = 575$); Cox regression results (hazard ratio HR, 95% confidence intervals CI and *p*-value)

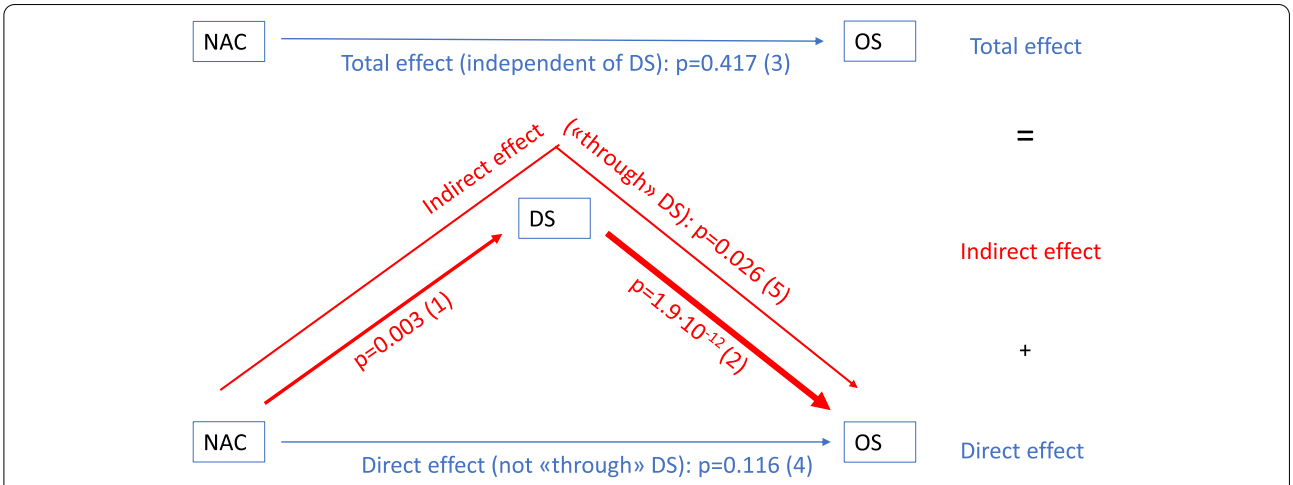

Fig. 3 Summary of results. Summary of the results; logistic regression (1), Cox regression (2-3) and mediation analysis (4–5). (1) Neoadjuvant chemotherapy (NAC) is significantly associated with pathological downstaging (DS: ≤pT1), (2) DS is significantly associated with overall survival (OS), (3) NAC is not significantly associated with OS (unadjusted for DS) *(Total effect)*, (4) NAC is not significantly associated with OS (not through DS) *(Direct effect)*, (5) NAC is significantly associated with OS through DS *(Indirect effect)* (red arrow: significant; the thicker, the more significant; blue arrow: not significant). *All analyses were adjusted for age, sex, type of hospital, health region and cystectomy year

Discussion

In this population-based study, NAC increased the probability of achieving DS in patients with MIBC by a factor of 2.5. Independent of the means for obtaining DS (NAC or TURB), achievement of DS in MIBC patients was associated with a 78% risk reduction of all-cause mortality compared to non-DS and related to a decreased proportion of patients with regional node lymph node metastases verified in the RC specimen. NAC did not provide a beneficial survival over NoNAC, except for when the effect of NAC on OS went through DS.

Post-NAC DS was found in 43% of the patients in our study. In comparison, post-NAC DS was reported in 36% of patients in a US population-based study [14], in 51% of the patients in a large single-institution registry study [27] and in 61% in a Danish population-based study [19]. In two Nordic RCTs post-NAC

DS was reported in 38% of the patients receiving cisplatin+doxyrubicin/methotrexate [9]. For the more modern chemotherapeutic regimens, the proportion of post-NAC DS was higher (Gemcitabine and cisplatin: 49%, dose dense MVAC: 63%) [28]. Different study designs have used different definition of DS. In our and other relevant population-based studies [12, 14, 19], DS was defined as downstaging of the primary tumour(<pT2) and independent of pN-status [12, 14, 19], whereas in selected clinical trials pN0 was included in the definition (<pT2pN0) [9, 28]. Notably DS can be the effect of NAC but can also be achieved after an extensive TURB.

We show that the proportions of pN0 was higher in patients with DS compared to patients with non-DS, although without any difference in downstaged patients treated with or without NAC. These results are in line with the corresponding combined results from two previous clinical trials [9]. Further, the demonstration of DS independent of the receipt of NAC revealed a beneficial survival, as patients with DS had a 78% risk reduction of all-cause death compared to patients without DS. These results indicate that independent of NAC, DS is related to the absence of regional lymph node metastases and indicates a more favourable prognosis compared to patients without DS. However, NAC significantly increased the odds of DS and possibly reflect the favourable effect of NAC on regional lymph node metastases and micrometastases.

Our findings of no survival benefit in the NAC group vs. NoNAC group is in agreement with the results from two other population-based studies from the US [12] and Sweden [13]. Despite efforts to account for selection bias and unrecognized confounders with statistical methods like propensity score weighting or the instrumental variable approach in our study, no OS benefit for NAC over NoNAC was found. However, we are the first to identify an indirect effect of NAC on survival through the demonstration of DS as we show that NAC has an effect on OS mediated by DS. We suggest the following explanations: The patients in the NAC group initially may have had a more advanced and aggressive disease compared to the patients in the NoNAC group, reducing the potential survival advantage gained by post-NAC DS when evaluating the total effect of NAC on OS. On the other hand, the population may consist of subgroups of patients who do not benefit from NAC, as the selection of patients treated with NAC in the real-world is most probably different from clinical trials [29]. Notably, in other population-based studies the proportions of cT2N0M0 (82–86%) [12, 13] were larger than in RCTs (34–40%) [5, 6, 30]. For this subgroup, RCTs have either not evaluated the mortality risk after NAC [5, 6] or found no survival benefit from NAC [30], and in two population-based studies no survival benefit over NoNAC was found [31, 32].

Our findings underline the necessity to determine which MIBC patients benefit from NAC in clinical practice. Identification of subgroups of patients most likely to achieve DS with or without NAC is necessary. The latter are of particular interest as they are possible candidates for bladder preserving strategies. Clinical staging by computed tomography is challenging with an estimated accuracy of 40–92% to predict pT and of 54–86% to predict pN [33]. Advances in image-guided approaches with multiparametric magnetic resonance imaging may reduce staging errors in the management of MIBC and aid in predicting treatment response to NAC [34]. Reliable biomarkers for chemotherapy sensitivity are needed.

Limitations of our study include the lack of pre-RC information about cT- and cN category and limited information about the primary tumour (lack of size, multiplicity, and widespread carcinoma in situ). To our knowledge, only cisplatin-based NAC was used in Norway in the study period. Although application details of NAC were not available to us, the results reflect the real-world situation where dosage reduction and uncompleted cycles often are necessary. We do not know *why* some patients received NAC and others did not (confounding by indication). For this reason, we applied the instrumental variable approach, although limited by a suboptimal instrumental variable and limited power. However, we had solid information on pT, and we were the first population-based study to apply a mediator analysis and identify an indirect effect of NAC on survival through DS.

Conclusion

In this nationwide population-based study of patients with MIBC, we found that on a population-based level DS demonstrated in the RC specimen is a good prognostic factor and provides a survival benefit over non-DS. NAC increases the odds of DS and is indirectly associated with an OS benefit. DS is related to absence of regional lymph nodes. Future perspectives include improvement of clinical staging, identification of patient subgroups most likely to achieve DS or non-DS, and identification of patients in whom NAC is necessary to achieve DS.

Abbreviations

CI: Confidence interval; CRN: Cancer Registry of Norway; DS: Pathological downstaging of the primary tumour; HR: Hazard ratio; IQR: Interquartile range;

NAC: Neoadjuvant chemotherapy; Non-DS: Residual muscle-invasive bladder cancer; MIBC: Muscle-invasive bladder cancer; MVAC: Methotrexate, vinblastine, doxorubicin and cisplatin; OR: Odds ratio; OS: Overall survival; RC: Radical cystectomy; RCT: Randomized controlled trial; TURB: Transurethral resection of bladder tumour.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-022-10394-w.

Additional file 1: Figure S1. Study population.

Additional file 2: Table S1. Pathological N-category after cystectomy with regards to downstaging of primary tumour and treatment.

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Authors' contributions
CTM, VB, GT, SDF and BKA contributed to the conception and design of the study; AB and BKA contributed to the acquisition of data; CTM, NCS, SDF and BKA contributed with the analysis, interpretation, and manuscript preparation. All authors contributed to drafting and revising the article. The author(s) read and approved the final manuscript.

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Availability of data and materials
The data that support the findings of this study are available from the Cancer Registry of Norway, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Cancer Registry of Norway.

Declarations

Ethics approval and consent to participate
Approved by the Regional Committee for Medical and Health Research Ethics, Southeast Norway. Approval number: 2016/2286/REK sør-øst A. The study is also approved by the Cancer Registry of Norway and the Norwegian Patient Registry. All data management and analyses were conducted according to current legislation and regulation of privacy, without any possibilities for individual identification. The requirement for informed consent was waived by the Regional Committee for Medical and Health Research Ethics, Southeast Norway.

Consent for publication
The requirement for informed consent was waived by the Regional Committee for Medical and Health Research Ethics, Southeast Norway, approval number: 2016/2286/REK sør-øst A.

Competing interests
The authors declare that they have no conflict of interest.

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Publisher's Note

III

Initial management and survival of patients with primary metastatic bladder cancer before the immunotherapy era: A population-based study from Norway

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Initial management and survival of patients with primary metastatic bladder cancer before the immunotherapy era: A population-based study from Norway

Abstract

Introduction: Before the introduction of immunotherapy into the management of metastatic bladder cancer (mBC) in 2018, platinum-based chemotherapy was the only approved systemic cancer therapy for patients with mBC. The objective of this study was to describe patient characteristics, treatment, overall survival, and hospitalisations of patients diagnosed in 2008-16 with primary mBC, before the use of novel agents in routine clinical practice in Norway.

Material and Methods: Nationwide population-based study of primary mBC patients registered in the Cancer Registry of Norway. Four treatment options were considered based on the type of primary cancer treatment applied ≤150 days after diagnosis: chemotherapy, major local treatment, multimodal treatment, and no treatment. Descriptive statistics were applied. Overall survival was estimated with Kaplan-Meier.

Results: Out of 305 mBC patients, chemotherapy was the primary cancer treatment in 76 (25%) patients, major local treatment in 46(15%) patients, multimodal treatment in 21(7%) patients and no treatment in 162 (53%) patients. Median OS ranged from 2.3 months (no treatment) to 9.8 months (chemotherapy). Compared to the no treatment group, the median total days of hospitalisation per patient was three to four times higher in the other three groups.

Conclusion: More than 50% of patients with mBC did not receive local or systemic cancer therapy and had a poor prognosis. Compared to clinical trials, patients treated with comparable systemic strategies had an inferior survival. Our results provide a basis for comparative analyses of novel agents for mBC.

Keywords: survival; metastatic bladder cancer; pre-immunotherapy; population-based; chemotherapy

Introduction

In metastatic bladder cancer (mBC), platinum-based combination chemotherapy is the standard first-line treatment in the current guidelines from European Association of Urology (EAU) [1]. This recommendation has remained unchanged since pivotal trials were published more than 20 years ago[2-4]. Approximately 50% of eligible patients are however unfit for cisplatin due to impaired renal function, heart failure or poor performance status[5,6], and carboplatin can be offered as an alternative[7]. Recently, novel agents were approved for use in the management of mBC. In 2017/2018, the American and European drug regulatory agencies approved three immune check-point inhibitors (ICIs)[8-10], and an additional ICI and a novel antibody drug conjugate were approved in 2021[11-13]. Current European guidelines recommend maintenance ICI after first-line platinum-based chemotherapy in patients with stable disease, ICIs as standard second-line therapy and an antibody drug conjugate as third-line therapy[14].

Real-world studies describing the pre-immunotherapy management and outcomes of patients with mBC are scarce but needed as references for upcoming studies of novel agents for patients in routine clinical practice. Moreover, according to population-based studies, a large proportion of patients (60-65%) are left untreated by chemotherapy[15-17]. Characteristics and survival of these patients has not been well described in the literature.

In Norway, 1659 patients were diagnosed with bladder cancer (BC) in 2021, of which 5% of patients had primary metastatic disease[18]. Norwegian guidelines for treatment of mBC are in line with the EAU treatment recommendations[19,20] and eligible patients are treated with first-line platinum-based chemotherapy. ICIs as standard second-line treatment were approved for use in Norway in 2018. However, antibody drug conjugates are not yet approved. To our knowledge, there are no Norwegian studies describing patient characteristics, treatment, survival, and hospitalisation of patients with mBC.

Thus, in this Norwegian population-based study of BC patients with distant metastases at diagnosis (2008-16), we aimed to describe patient characteristics, overall survival (OS) and hospitalisations of patients initially treated with chemotherapy, major local tumour treatment, multimodal treatment and of patients who did not receive any initial local or systemic anti-cancer treatments.

Material and methods

Data sources

The Cancer Registry of Norway (CRN) is a national cancer registry established in 1953. Information about age, sex, health region, date of diagnosis, histology and metastases is available in the CRN. Metastases are registered present at the time of primary cancer diagnosis if discovered within the *diagnostic period*, defined by the CRN as the month of diagnosis plus four months (≤150 days). In addition, information about type of treatment (surgery, radiotherapy (RT)) and causes of death with corresponding dates have been retrieved from the CRN.

Since 2008, the Norwegian Patient Registry (NPR) has registered individual administrative, demographic, and coded medical information (diagnoses, surgical and medical procedures, chemotherapy) from all patients' contacts with public hospitals. Information from this registry was linked to data from CRN by the personal identification number assigned to all new-borns and residents in Norway since 1960.

Study population

From the CRN, we selected all patients diagnosed with primary mBC (International Classification of Diseases (ICD)-10 C67) between 2008-2016. Patients with secondary metastases were not included due to incomplete registration in the CRN. Patients were excluded if another malignancy was diagnosed within one year prior to the mBC diagnosis or within the diagnostic period (≤150 days). We excluded patients with no information on BC diagnosis before the date of death.

Measures

We defined primary mBC as BC (ICD-10 C67) with distant metastases detected within the diagnostic period *(*≤150 days). Non-regional LN metastases and visceral metastases localized outside the true pelvis were considered distant metastases. Patients with regional LN only were excluded. Place of residence was categorised according to the four official health regions in Norway (Southeast, West, Central and North). Year of diagnosis was categorised in three periods (2008-2010, 2011-2013, 2014-2016). From the CRN RT database, we identified the application of RT registered with C67. Pelvic RT (PRT) was defined as RT of pelvic soft tissue tumour manifestations. We defined the underlying cause of death to be BC if registered with ICD-10 code C67, C68 (unspecified urinary tract) or C80 (unspecified location of malignant tumour).

From the NPR, we identified relevant surgical codes (transurethral resection of bladder tumour (TURB), cystectomy) as well as procedure codes for administration of unspecified chemotherapy and specified drug codes for platinum-based combination chemotherapy for BC (cisplatin or carboplatin-based). After the mBC diagnosis we considered all chemotherapy provided to patients with ICD-10 codes C65-C68 (urinary tract cancer), C80 and C77-C79 (metastases) as chemotherapy treatments for bladder cancer.

Patients were allocated into four treatment categories based on type of primary treatment received within the diagnostic period (≤150 days) and after the diagnostic TURB (**Table 1**). Patients had to receive at least one chemotherapy administration to be considered as recipients of chemotherapy.

In the NPR the patients are categorised according to the type of hospital contact: daypatient, outpatient or inpatient, with corresponding dates for admission and discharge. Our term *"hospitalisation"* considers only inpatient contacts of any cause after BC diagnosis. For each individual hospitalization, we calculated the interval number of days from hospital admittance to discharge (days of hospitalization). We then summarized the days of hospitalisation for each patient within the follow-up time (total days of hospitalisation per patient).

Statistical methods

Patient and treatment characteristics are presented applying descriptive statistics (median, interquartile range (IQR), proportions). Distributions of variables between treatment groups were compared with Chi-square test for categorical variables and Kruskal-Wallis equality of populations rank test for continuous variables. The statistical significance level was set to ≤0.05.

Patients were followed from the date of BC diagnosis until date of death, migration, or end of follow-up (Dec 31, 2019). whichever came first. Time in years from date of diagnosis was used as timescale in all analyses. Unadjusted survival curves (Kaplan Meier) displayed OS from the diagnosis to end of follow-up.

Statistical analyses were performed using Stata 17 (StataCorp, College Station, TX).

Results

Patient characteristics

Out of 12,477 patients with a BC diagnosis between 2008-2016, 345 (2.7%) patients were diagnosed with primary mBC, resulting in 305 evaluable patients. (**Figure 1**). Median follow-up time was 154 days.

Median age at diagnosis was 73 years (**Table 2**), and most patients were male (69%). Women were older than men (median 76 vs. 72 years). Two patients were diagnosed with another cancer (ICD-10 C65 and C34) after the diagnostic period (>150 days), and 48 (16%) patients had a history of previous cancer. The predominant histology was urothelial carcinoma (UC) (70%). Distant metastases located exclusively in lymph nodes were present in 38 (12%) patients. At end of follow-up, 11 (4%) patients were still alive with BC being the cause of death in 255 (87%) out of 294 deaths. The characteristics of patients still alive at end of follow up are listed in **supplementary table S1**.

The primary treatment was chemotherapy for 76 (25%) of the 305 patients (*chemo*), cystectomy (21 patients) or PRT (25 patients) for 46 (15%) patients (*local*), multimodal treatment for 21 (7%) patients (*multimodal*) and for 162 (53%) patients no anti-cancer treatment was recorded (*untreated*) (**Table 2**). For the multimodal group, the treatment sequences by initial local or systemic treatment are shown in **supplementary table 2**. Time between BC diagnosis and start of primary treatment was shorter (median 1 month) for the *multimodal* group compared to the *chemo* and *local* groups where more than half of the major treatments were initiated within 1.5 months after BC diagnosis. In the *untreated* group, 16 patients had a second TURB within the diagnostic period.

Univariable analyses showed that patients treated in the *chemo* and *multimodal* groups were younger than patients in the *local* and *untreated* groups (**Table 2**). Patients in the *untreated* group were more often women, residents of the Western health region and died more often of a non-cancer related cause, compared to patients treated with local, multimodal or chemotherapy treatment. Lymph node metastases were more frequent in the *chemo* group compared to the other three groups.

At any time after the BC diagnosis, nearly half of the patients in the *multimodal* group and one third of the patients in the *chemo* and *local* groups received palliative non-pelvic radiotherapy. In contrast, such treatment was recorded in less than 10% of patients in the *untreated* group (**Table 3**).

After the diagnostic period (>150 days), 24 (32%) patients of the 76 patients in the *chemo* group underwent local tumour treatments (TURB, cystectomy, PRT) (Table 3). Only 2-10% of patients in the other three groups received additional local tumour treatments. Regarding systemic therapy, 48 (63%) patients in the *chemo* group and 9 (45%) patients in the *multimodal* group continued or started chemotherapy.

Survival

Median OS for all patients with primary mBC was 5.1 months and the one, three and five-years survival proportions were 23%, 10% and 8% (**Figure 2a**).

Median OS was 9.8 months for patients in the *chemo* group, 5.9 months for patients in the *local* group, 9.7 months for patients in the *multimodal* group and 2.3 months for the patients in the *untreated* group (**Figure 2b**). Corresponding one, three- and five-year OS for all four groups are listed in table 3.

Hospitalization

Between 2008-2016, there were a total of 5,635 registered contacts with the hospital of which 1,498 (27%) were inpatient contacts. The average number of hospitalisations of any cause for all patients was 5.0 and ranged from 2.5 (*untreated*) to 9.1 hospitalizations (*multimodal*) (**Table 3**). For patients in the *chemo* group, the average number of hospitalisations was 5 when chemotherapy related hospitalizations were excluded. Median total days of hospitalisation per patient was 22 days (Table 3). Compared to the *untreated* group (median 12 days, IQR 1-27), the median total days of hospitalisation per patient was three to four times higher among patients in the *local* (38 days, IQR 19-54), *multimodal* (49 days, IQR 39-77), and *chemo* (43 days, IQR 21-65) groups.

Discussion

In this nationwide population-based study of patients with primary mBC, approximately one-third of the patients started chemotherapy within 150 days after diagnosis. During the first 150 days after diagnosis, few patients were treated with initial major local tumour procedures and more than 50% of the patients were not treated with any local or systemic cancer treatment. Median overall survival was 7 months longer for patients treated with chemotherapy compared to patients in the untreated group. Patients in the chemotherapy group had almost four times more days in hospital compared to the patients in the untreated group.

Table 4 compares our results with those from relevant published data. Median OS for our patients in the *chemo* group was inferior to the results from two clinical trials (9.8 months vs 12-14 months) which investigated the effect of gemcitabine and cisplatin on OS [2,21]. Median age of patients in our study was similar to the age of patients included in these two trials. However, 30% of patients included in our study were diagnosed with non-UC histologies, whereas all patients in the displayed trials had UC[22]. Moreover, the prevalence of visceral metastases, a poor prognosis feature[4,23], was largest in our cohort. Other possible prognostic differences between our and the displayed trial populations are the inclusion of patients with locally advanced disease (T4bN0M0) and secondary metastatic disease. Furthermore, unlike our study, all patients in these trials were treated with cisplatin, whereas we also included patients treated with carboplatin-based chemotherapy. In accordance with this, median OS in our study was closer to median OS (9.3 months) in a clinical trial with gemcitabine and carboplatin (not listed in Table 4)[7].

Compared to other real-world studies, a lower proportion of our patients received chemotherapy (**Table 4**) [15,16,24]. However, if we include patients treated with a multimodal approach, which included chemotherapy, approximately 31% of patients received initial chemotherapy, similar to the registry-based studies by Flannery et al[15] and Richters et al[16]. Compared to our study, the patients of these registry-[15,16] and multicentre-based[24,25] studies were older. However, fewer patients had visceral metastases and non-UC histologies. This might explain the slightly better median OS (11-13 months) in these studies compared to our results (9.8 months)[15,16,24,25]. Finally, a survival difference may also be explained by other for us unknown adverse risk factors in our population (performance status, comorbidities, renal function) which may have impacted choice of treatment and prognosis[6,23].

Patients treated with chemotherapy were frequently hospitalised with an average of 9 all-cause hospitalizations during follow-up. In comparison, Flannery et al[15] reported an average of 5.2 all-cause hospitalisations in the same patient group. The difference between our population and the population in Flannery et al[15] may be related to differences in the setting of care for chemotherapy administration, with possibly more patients in Norway receiving chemotherapy as inpatients.

In accordance with comparable studies, a large proportion of patients did not receive chemotherapy (Table 4)[15,16,24]. Similar to these studies, the untreated patients were older, more frequently female and more had visceral metastases compared to patients treated with

chemotherapy. Median OS in our study was comparable to the survival reported in these studies. We observed that very few patients received RT directed towards metastases.

A limitation of this study is missing information about important factors that may influence the intention to treat such as performance status, comorbidities, and renal function[6,23]. Because we lacked the relevant information, we could not report on the number and location of distant metastases. Due to the CRN's routines, metastatic disease was registered as primary up to 150 days after diagnosis sometimes following cystectomy or PRT, treatment modalities usually restricted to patients without distant metastases. We lacked detailed information on application routines, specific drugs of combination chemotherapy as well as start and type of second-line systemic therapy. However, we provide an overview over initial treatment modalities and prognosis in an unselected population of BC patients with distant metastases at the time of diagnosis before the introduction of novel agents into routine clinical practice.

Conclusion

In this population-based cohort, the majority of BC patients with distant metastases at diagnosis did not receive any kind of local or systemic cancer therapy and had a dismal prognosis. Such patients treated with chemotherapy had inferior OS compared to relevant clinical trials. Further studies should evaluate whether the introduction of novel therapies, such as less toxic immunotherapy, enables treatment of primary metastatic bladder cancer patients with favourable impact on survival and days of hospitalisation.

Authors' contributions

CTM: Project development, Data management and analysis, Manuscript writing
GT: Project development, Manuscript editing
AB: Data collection, Manuscript editing
VB: Project development, Manuscript editing
SDF: Project development, Manuscript writing
BKA: Protocol and project development, Data collection, management and analysis, Manuscript writing.
All authors read and approved the final manuscript.

Declarations

Declarations of interest: The authors report no conflicts of interest

Ethics approval and consent to participate

Approved by the Regional Committee for Medical and Health Research Ethics, Southeast Norway. Approval number: 2016/2286/REK sør-øst A. The study is also approved by the Cancer Registry of Norway and the Norwegian Patient Registry. All data management and analyses were conducted according to current legislation and regulation of privacy, without any possibilities for individual identification. The requirement for informed consent was waived by the Regional Committee for Medical and Health Research Ethics, Southeast Norway.

Availability of data and materials

The data that support the findings of this study are available from the Cancer Registry of Norway. Restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Cancer Registry of Norway.

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TABLE CAPTIONS

Table 1. Groups based on the type of initial treatment received within 150 days after diagnosis of primary metastatic disease for patients with bladder cancer diagnosed between 2008-2016 in Norway

Table 2. Patient characteristics for patients diagnosed with primary metastatic bladder cancer between 2008-2016 in Norway, grouped by primary treatment received within 150 days after diagnosis

Table 3. Additional treatment, survival, and hospitalization by primary treatment group for patients diagnosed with primary metastatic bladder cancer between 2008-2016 in Norway.

Table 4 Comparison of patient characteristics and survival of patients with metastatic bladder cancer diagnosed in 2008-2016 with those from relevant clinical trials and observational studies of patients with metastatic bladder cancer

Table 1

Group	Primary treatment
1	Chemotherapy ("*chemo"*)
2	Major local treatment: cystectomy or pelvic radiotherapy ("*local"*)
3	Combination of major local and systemic treatment ("*multimodal"*)
4	No major local or systemic treatment, or TURB only (*untreated*)

Table 2	**All**	**Chemo**	**Local**	**Multimodal**	**Untreated**	**Unadjusted *p*-value**
Patients, n (%)	305	76(25)	46(15)	21(7)	162(53)	
Days to primary treatment, median (IQR)	39 (29-70)	40 (28-71)	48 (33-75)	30 (24-41)	N/A	*p*=0.0096
Age in years, median (IQR)	73 (65-82)	63 (57-69)	75 (67-82)	61 (50-69)	79 (73-86)	*p*=0.0001
Female (%)	94(31)	22(29)	11(24)	6(29)	55(34)	*p*=0.583
Health region (%)						*p*=0.310
Southeast	183(100)	42(23)	26(14)	13(7)	102(56)	
West	49(100)	10(20)	7(14)	2(4)	30(61)	
Central	39(100)	12(31)	5(13)	3(8)	19(48)	
North	31(100)	11(35)	8(26)	3(10)	9(29)	
Missing	3(100)	1(33)	0	0	2(67)	
Previous non-BC cancer	48(16)	13(17)	8(18)	1(5)	26(16)	*p*=0.548
Year of BC diagnosis						*p*=0.422
2008-2010	112(100)	24(21)	13(12)	9(8)	66(59)	
2011-2013	101(100)	26(26)	21(21)	6(6)	48(48)	
2014-2016	92(100)	26(28)	12(13)	6(7)	48(52)	
Histology						
Urothelial carcinoma	214(70)	54(71)	33(72)	17(81)	110(68)	*p*=0.649
Metastases						*p*=0.145
Lymph nodes exclusively	38(12)	15(20)	6(13)	2(10)	15(9)	
Visceral	267(88)	61(80)	40(87)	19(90)	147(91)	
Number of deaths	294 (96)	71(93)	44(96)	20(95)	159(98)	
Causes of death						
Bladder cancer	255(87)	69(97)	37(84)	19(95)	130(82)	
Other cancer	16 (5)	1(1)	5(11)	1(5)	9(6)	
Non-cancer cause	23(8)	1(1)	2(5)	0	20(12)	

Table 3

	All	Chemo	Local	Multi-modal	Untreated
Patients, n (%)	305(100)	76(25)	46(15)	21(7)	162(53)
Non-pelvic radiotherapy (%), at any time after BC diagnosis	58(19)	24(32)	12(26)	9(43)	13(8)
Bone	28(48)	11(46)	6(50)	5(55)	6(46)
Later treatments (>150 days) (%)					
TURB	7(2)	5(7)	1(5)*	0	1(1)
Cystectomy	6(2)	6(8)	0	0	0
Pelvic radiotherapy	20(7)	13(17)	1(5)**	2(10)	4(2)
Overall survival					
One-year	23%	45%	22%	38%	12%
Three-year	10%	12%	10%	10%	5%
Five-year	8%	10%	7%	5%	3%
Hospitalization					
Average number, any cause	5.0	9.0	5.3	9.1	2.5
Total days per patient, median (IQR)	22 (7-46)	43 (21-65)	38 (19-54)	49 (39-77)	12 (1-27)

*after pelvic radiotherapy, **after cystectomy

Table 4	**Our study**	**von der Maase[1] (2000)**	**Bellmunt[2] (2012)**	**Flannery[3] (2018)**	**Richters[4] (2020)**	**Reesink[5] (2020)**	**Omland[6] (2021)**
Type of study	Observational	Clinical trial	Clinical trial	Observational	Observational	Observational	Observational
Data	National cancer registry			SEER	National Cancer registry	Multi-centre	Nationwide multicentre
Country	Norway	Multinational	Multinational	USA	The Netherlands	The Netherlands	Denmark
Period	2008-2016	1996-1998	2001-2004	2007-2011	2016-2017	2008-2016	2010-2016
Primary metastatic	Yes	No	No	Yes	Yes	Yes	No
Patients, n	305	405	626	1215	636	64	952
Cancer	BC	UTC	UTC	BC	BC	BC	UTC
Systemic chemotherapy	**Unspecified**	**Gemcitabine and cisplatin**	**Gemcitabine and cisplatin**	**Unspecified**	**Platinum-based**	**Platinum-based**	**Platinum-based or gemcitabine**
Patients, n (%)	76(25)	203(100)	314	411(34)	198(31)	24(38)	952(100)
Age (median)	63	63	61	75	70(carboplatin) 66(cisplatin)	65	69
Sex (% male)	69	79	81	70		88	72
Urothelial carcinoma (%)	71	100	100	-	85	100	92
Visceral metastases (%)	80	69	49	61	69		69
Median overall survival (months)	9.8	14	12.7	13.2	11.1(carbo-platin), 12.9 (cisplatin)	12.6	11.7
Untreated							
Patients, n (%)	162(53%)			804(66%)	415(65%)	40(62%)	
Age(median)	79			80	76	78	
Sex (% male)	66			58	67	72	

Urothelial carcinoma (%)	68		77	100
Visceral metastases (%)	91	69	81	100
Median overall survival (months)	2.3	3.2	2.5	2.0

Figure 1. Study population

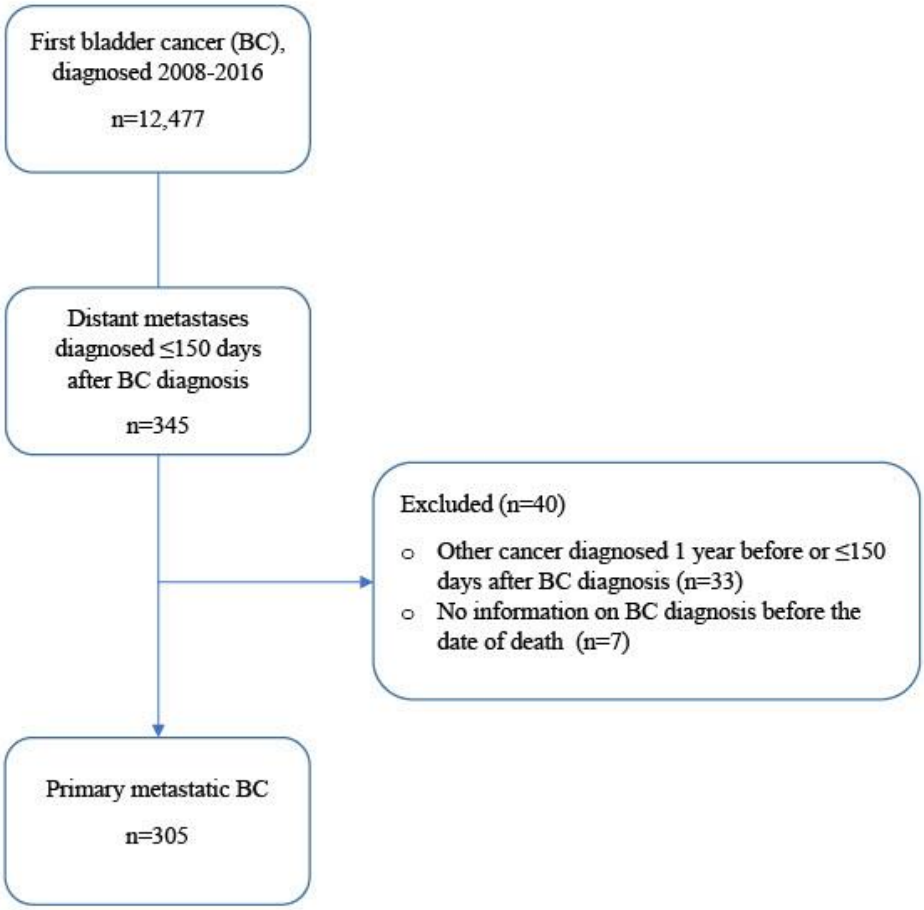
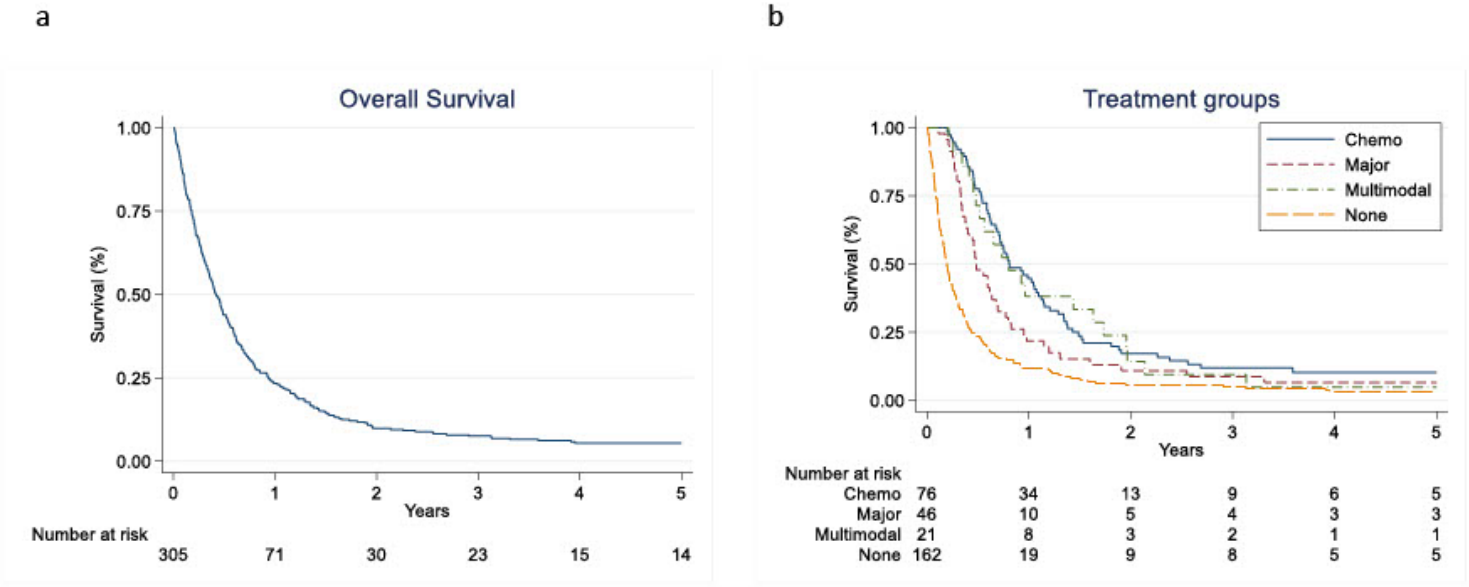


Figure 2. Patients with primary metastatic bladder cancer diagnosed between 2008-2016 in Norway a) Overall survival b) Overall survival stratified for treatment (*Chemo:* chemotherapy, *Major:* Major local treatment: cystectomy or pelvic radiotherapy; *Multimodal:* Combination of major local and systemic treatment; *None:* No major local or systemic treatment, or TURB only)



Supplementary

Table S1. Patients with primary metastatic bladder cancer diagnosed between 2008-2016 in Norway: Patient characteristics for patients still alive at end of follow-up **(**31st of December 2019)

	Survivors
Patients, n (%)	11(4%)
Age (years, IQR)	70(55,73)
Sex (%female)	6(55)
Year of diagnosis	
2008-2010	5(46)
2011-2013	3(27)
2014-2016	3(27)
Metastases	
Lymph nodes, non-regional (LN)	6(55)
Visceral	5(45)
Primary treatment, n (%)	
Systemic chemotherapy	5(45)
Major local	2(18)
Multimodal	1(9)
Untreated	3(27)

Table S2**.** Patients with primary metastatic bladder cancer diagnosed between 2008-2016 in Norway : Treatment sequences within 150 days after diagnosis of bladder cancer for patients treated with a combination of initial local tumour treatment and systemic anti-cancer treatment by initial treatment (cystectomy or chemotherapy).

Initial treatment	**Cystectomy**	**Chemotherapy**
Patients, n=21 (%)	10 (42)	11(46)
Subsequent treatment combinations		
TURB*	0	1(9)
Cystectomy	0	2(18)
Pelvic radiotherapy of bladder	1(10)	8(73)
Chemotherapy	9(90)	0

* Transurethral resection of bladder tumour