Faculty of Health Sciences

Treatment of bladder cancer with neoadjuvant chemotherapy at the University Hospital of North Norway in the years 2011-2019

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Preface

In this thesis, the aim was to investigate circumstances surrounding chemotherapy treatment for bladder cancer at the University Hospital of North Norway. Knowing that neoadjuvant chemotherapy increases survival of these patients, I wanted to find out how many of patients with bladder cancer are treated with neoadjuvant chemotherapy at this hospital. My work on this thesis started in the fall of 2019 during my fourth year at medical school and continued to June of 2021, as I finished my fifth year as medical student.

I previously had minimal experience with both bladder cancer and writing a thesis prior to this. Throughout this process I have learned a great deal about both. It has been a fun and interesting subject to work with, which I have enjoyed. This new interest for oncology led me to applying for work as medical student with temporary license at the Oncology Department at the University Hospital of North Norway, where I started working in March of 2021.

My resources for this project were the medical record program for patients at the hospital and literature available from the University Library. I registered clinical data for alle patients included in the study and performed simple descriptive statistics on my own, while my supervisor helped me with the more advanced statistical work. I received no external funding for this project.

I would like to thank my main supervisor professor in oncology Hege Sagstuen Haugnes, for whom this project could not have been done without. She has contributed with her great knowledge in oncology and excellent guidance in scientific research and writing. I would also like to thank my co-supervisor urologist, PhD Eivind Bjerkaas for his contribution to this thesis with his knowledge of surgical aspects.

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Innholdsfortegnelse

Summary

Introduction: Previously, radical cystectomy alone has been the standard treatment for localized, muscle invasive bladder cancer (MIBC), with the introduction of neoadjuvant chemotherapy (NAC) in 2011 in Norway. Outcome advantages for patients receiving NAC are thoroughly documented. Our primary aim with this study was to investigate whether patients treated for MIBC at UNN during 2011-2019 were offered NAC. Secondary, we wanted to evaluate feasibility, side effects and efficacy of NAC, along with surgical complications and survival.

Material and method: This study included 154 patients with urothelial carcinoma in bladder cystectomized at the University Hospital of North Norway (UNN) in the years 2011-2019 who were identified by looking up procedure codes in the medical record program DIPS. Of these, 99 (MIBC) and were considered for NAC. NAC consisted of three cycles of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) given every second week.

Results: Out of the MIBC patients, 47.5% received NAC. This number increased significantly during the study period, from 29.3% in the years 2011-2014, to 60.3% in the years 2015-2019. Old age was the most frequent reason for not receiving NAC, accounting for 50%, followed by reduced kidney function and heart disease, both making up 9.6%. Overall, 57.4% and 75.1% completed all three cycles and two cycles of chemotherapy, respectively. Most common reasons for discontinuation were reduced kidney function or infection. Neutropenic sepsis was seen in 17% of patients. Amongst the 27 patients who completed all three rounds, 56% did not experience any complications throughout chemotherapy. The actuarial 2-year overall survival was numerically higher for patients treated with NAC (78%; 95% CI 66%-90%) than those without NAC (58%; 95% CI 43%-72%).

Conclusion: Chemotherapy coverage at UNN was high compared to other studies. Feasibility was low and complication rates high, most likely due to extensive chemotherapy use.

Abbreviations

AC – Adjuvant chemotherapy

BCG – Bacillus Calmete-Guérin

BMI – Body mass index

COPD – Chronic obstructive pulmonary disease

CT – Computed tomography

G-CSF – Granulocyte colony-stimulating factor

GFR – Glomerular filtration rate

HR – Hazard ratio

MSH2 – MutS homolog 2

MIBC – Muscle-invasive bladder cancer

MVAC – Methothrexate, Vinblastine, Adriamycin, Cisplatin

NAC – Neoadjuvant chemotherapy

NMIBC – Non-muscle-invasive bladder cancer

TURB – Transurethral resection of bladder

UNN – University Hospital of North Norway

Introduction

Epidemiology

Bladder cancer is currently the fourth most common cancer type in Norway amongst men, and seventh in total when including both genders, with approximately 1500 new cases each year (1). Men make up about three out of four of these cases. The incidence for men in 2019 was around 50 per 100 000, with a stable incidence since the early 1990s (Figure 1). Prior to 1990, the incidence for men had been steadily increasing. For women the incidence for 2019 was about 15 per 100 000 (Figure 2). This number increased gradually until 10 years ago, after which it has flattened out. As for survival rates, these have been increasing in Norway for the past 50 years for both genders (2). The five-year relative survival for patients diagnosed in the period 2010-2014 was 76.3% for men and 70.1% for women (1). Median age at diagnosis in Norway in 2018 was 72 years for men and 74 for women (3).

There are several known risk factors in bladder cancer. Among modifiable risk factors, smoking is strongest related, with some studies showing 40-50% of bladder cancer cases in both men and women being smoking-related (4, 5). There are also a multitude of other chemicals that increase the risk of bladder cancer, but to a lesser degree (6). Genetic predisposition has been shown in several studies. Most notably, patients with Lynch syndrome carrying an MutS homolog 2 (MSH2) mutation have an increased lifetime risk of developing urothelial cancer. The increased risk is greater for men than women (7, 8). In Norway, the national guidelines recommend that members of families with Lynch Syndrome and history of urothelial cancer should be screened yearly with urinary stix and cytology from the age of 35. Urothelial cancer secondary to prior cancer treatment has been studied in recent years. A large meta-analysis has shown that radiation treatment of prostate cancer increases the relative future risk of developing bladder cancer by 67%, but with a modest increase in the absolute risk (9).

Diagnostics and histology

In the early stages of bladder cancer there are usually relatively few symptoms, with the most common one being hematuria (10). Gross hematuria (visible blood in urine) without

known cause is always referred to an urologist, while microscopic hematuria (blood in urine that is not visible) is only referred for patients above 50 years old with risk factors and/or symptoms and no known cause. In Norway, there is a standard set diagnostic pathway called "pakkeforløp" for patients that meet the aforementioned criteria. This pathway secures a standardized and predictable diagnostic work-up within given time limits for patients with suspected cancer. For bladder cancer, the guidelines for the pathway recommend that once patients are referred, they should be seen by a specialist and have initial investigations done within seven days. After these investigations, the further treatment course should be decided within 25 days, and after this decision is made, the chosen treatment option should commence within 14 days. Put in simpler terms, treatment must start within 46 days from when the referral is received (3).

Initial investigations for bladder cancer include cystoscopy and Computed tomography (CT) scan. Any tumor found during cystoscopy are biopsied with a method called transurethral resection of bladder (TURB), which is a procedure where cancer suspicious tissue in the bladder is removed. The material from this procedure is analyzed by a pathologist, and combined with CT scans, determines the tumor stage. In some cases of early-stage bladder cancer, TURB is curative treatment in itself.

Histologically, urothelial carcinomas are the dominant type, making up about 90% of bladder cancers (11). Squamous cell carcinomas are second most abundant, followed by adenocarcinomas. Sarcomas and lymphomas are also seen. We will only describe the urothelial carcinomas later on in this report. Bladder tumors are staged according to the TNM-system, which grades the tumor from T1 to T4(3). In addition, superficial in situ urothelial carcinoma are classified as Tis. Tumors that only invade the subepithelial connective tissue of the bladder are classified as T1. If the tumor penetrates the muscular layer surrounding the bladder (muscularis propria), it is classified as T2. These are also further divided into T2a and T2b, for respectively superficial and deep penetration of the muscle layer. T3 tumors invade soft tissue surrounding the bladder and are subcategorized as T3a if invasion is only microscopically detectable and T3b if macroscopically detectable. If the tumor invades surrounding organs it is classified as T4. Bladder cancer with T2 or more advanced tumor stage is collectively termed muscle-invasive bladder cancer (MIBC), while

the ones with less advanced tumor stage are termed non-muscle-invasive bladder cancer (NMIBC).

Treatment

Treatment will vary according to tumor stage. For patients with NMIBC, the TURB can be sufficient treatment if all tumor tissue is removed, but some of them will need additional treatment consisting of instillation of Mitomycin-C or Bacillus Calmette-Guérin (BCG) into the bladder via a transurethral catheter. Mitomycin-C is a chemotherapeutic agent and BCG an immunotherapeutic agent. Studies have shown that instillation of Mitomycin-C within a few hours after TURB reduces the risk of recurrence by up to 35% in low-grade NMIBC (12-15). For those with intermediate risk tumors, immediate instillation of Mitomycin-C, followed by regular treatment with instillation of Mitomycin-C or BCG has proven to be effective (16-21). The instillations are given weekly for six weeks and then monthly for a full year. Further treatment effect after one year is not thoroughly documented, but some receive BCG-instillations for up to three years. BCG is currently the first choice for patients with intermediate and high-risk tumors. In some few cases of NMIBC, radical cystectomy will be required. For patients with localized MIBC, radical cystectomy plus pelvic lymph node dissection is the standard treatment. Patients who are not able or willing to undergo surgery can be offered radiotherapy, or preferably trimodal treatment (maximal TURB, chemotherapy and radiotherapy) (3). Treatment of metastatic disease is beyond the scope of this study and will not be described.

MIBC has been proven to be highly chemotherapy sensitive and studies show that patients with localized/locally advanced MIBC who receive chemotherapy in addition to cystectomy have a greater survival-rate (22-26). In general, when giving chemotherapy as an addition to surgery you must decide whether to give it before (neoadjuvant chemotherapy (NAC)) or after (adjuvant chemotherapy (AC)) the surgery. Both NAC and AC have shown better results vs cystectomy alone. NAC is currently preferred due to better documented effect and that patients who receive chemotherapy after surgery cannot tolerate the chemotherapy as well and on average finish less cycles of chemotherapy (27).

Cisplatin has proven to be the most effective cytostatic agent in bladder cancer (26). Three cycles of cisplatin-based NAC increases the overall 5-year survival-rate from 45 to 50% (all stages included) in patients with localzlied/locally advanced MIBC, according to studies (22-26). The relative increased survival rate is higher the more advanced the cancer is (22, 28). These results have led to both international and national guidelines recommending that all patients with MIBC are considered for NAC in addition to cystectomy. In Norway, these guidelines were implemented in 2011.

Treatment with dose-dense methotrexate, vinblastine, doxorubicin and cisplatin (MVAC), where a total of three cycles of chemotherapy are given every second week, has shown to be very feasible, with patients ready for surgery as early as seven to eight weeks after the first cycle of chemotherapy (29, 30). This has been, and currently still is, the standard regimen used at the University Hospital of North Norway (UNN) for neoadjuvant treatment of bladder cancer. The treatment effect is evaluated with a CT scan after two cycles of dose-dense MVAC.

As with most chemotherapy treatments, this treatment can be very tough on the patients, with considerable risk of side effects such as neutropenic infection, neuropathy, nausea and malnutrition. The patients who are being considered for this treatment are therefore discussed at a multidisciplinary meeting, consisting of specialists from several departments, to determine if NAC is likely to be beneficial for the patients. In general, the treatment is not recommended for patients above 75 years old or those with comorbidities such as reduced kidney function and cardiovascular disease. The reason it is not recommended for patients with reduced kidney function is because of cisplatin, which is very nephrotoxic. In addition, cisplatin is poorly tolerated among older patients and it should be used with caution in patients with cardiovascular disease since it demands considerable hydration to prevent nephrotoxicity

Surgical complications

Radical cystectomy is often associated with complications. In a large study including 1142 patients who underwent radical cystectomy in the period 1995-2005, 64% of the patients

had some degree of complication within the first 90 days after surgery (31). The complications were graded using the Clavien-Dindo classification system (32) and showed that 51% of patients experienced grade 1-2 complications and 13% grade 3-5 complications. The most common complications were gastrointestinal and infectious, making up 29% and 25% respectively. More recent studies have showed that the complication frequency is not higher in patients who receive NAC prior to cystectomy versus those who do not (33).

Aims of the study

NAC before cystectomy as a treatment option for localized/locally advanced MIBC was gradually introduced in Norway and UNN from 2011. We did not know to what extent this treatment was offered to patients treated at UNN prior to this research, nor did we know anything about the outcome for patients who received the treatment. Studies show that too few patients with MIBC are offered NAC, despite its proven effect (34, 35).

The main aim of this study was to investigate whether patients who were treated for localized/locally advanced MIBC at UNN during 2011-2019 were offered NAC, and reasons for not being offered such treatment. Secondary aims include evaluating the feasibility, side effects and efficacy of the NAC, including effects of NAC on weight and kidney function. Finally, we wanted to study surgical complications and survival with NAC plus cystectomy versus cystectomy alone.

Material and method

Patient selection and treatment

All patients who were cystectomized at UNN in the period 01.01.2011-31.12.2019 were identified by looking up procedure codes in the medical record program DIPS (N=199, flow chart). Inclusion criteria included patients who had a curative cystectomy for urothelial carcinoma in the bladder. Consequently, patients who were cystectomized for other reasons than bladder cancer, had other histology than urothelial carcinoma or were cystectomized for palliative purposes were excluded from this study (flow chart). After these exclusions, the total number of patients included in the study was 154.

Since only patients with MIBC are treated with NAC, we wanted to look at this patient group when comparing data in relation to chemotherapy. Out of the 154 patients, 99 (64.3%) had muscle-infiltrating bladder cancer (T2 or more advanced, determined by looking at both histology and CT images). We wanted to see how the NAC coverage developed over the years we studied. For this, we chose to compare the first four years (2011-2014) to the last five years (2015-2019) combined. The reason for this is that some of the individual years did not have enough patients to give a representative picture.

Neoadjuvant chemotherapy consisted of in total three cycles of MVAC given every second week if the treatment was well tolerated. Each cycle consisted of methotrexate 30 mg/m^2 day one, and vinblastine 3 mg/m^2, doxorubicin 30 mg/m^2 and cisplatin 70 mg/m^2 on day two. In case of creatinine clearance < 60 ml/min/1.73m^2, the cisplatin dose was given over two days (35 mg/m^2 on days one and two). Growth-colony stimulating factor (G-CSF) was given at day four. The patients underwent a radiological evaluation with CT or MRI scan prior to the third cycle. In case of radiological progression, the third cycle was cancelled and the patient went directly to surgery.

A radical cystectomy includes removal of the bladder plus prostate and seminal vesicles in men, and removal of the bladder plus uterus and adnexa in women, and in addition a pelvic lymph node dissection. A urinary diversion is always performed, most commonly as an ileac conduit (3). Surgery was exclusively performed as open surgery until the fall of 2019, with the gradual implementation of robotic-assisted laparoscopic surgery from this point on.

Variables

The following data was collected from the medical records: patient characteristics including age, gender, height, weight and smoking status, tumor stage (histological and radiological) at date of diagnosis and after cystectomy, creatinine levels during chemotherapy and before cystectomy, complications and feasibility of chemotherapy, date of surgery, complications after surgery, time spent in hospital after surgery, cancer recurrence status and outcome for all patients up to the date of this study.

Relative weight change was calculated for all patients who initiated NAC as (($weight_{cystectomy}$-$weight_{chemotherapy}$)/$weight_{chemotherapy}$) x 100%. Relative weight change was categorized as moderate gain (>5%), small gain (3% to <5%), maintenance (+/- <3%), small loss (3% to 5%) and moderate loss (> 5%), as described previously (36). Body mass index (BMI) was calculated as weight (in kg) divided by height (in meters) squared.

Creatinine clearance was calculated based on age and serum creatinine (37), and 90 ml/min/1.73m^2 was used as cut-off for slightly decreased renal function (38). In addition, Creatinine clearance < 60 ml/min/1.73^2 was used to identify those with moderately decreased kidney function.

Surgical complications were quantified using the Clavien-Dindo classification system (32), which is a scoring system where complications are categorized from 1-5 on a severity scale. We chose to simplify this by putting grade 1-2 complications together in one group and grade 3-5 together in another. Complications were identified at two different intervals after cystectomy, the first within 30 days and the other within six months. We also chose to investigate how many of the patients had an infection within 30 days after the operation.

Statistics

Continuous variables are presented as median (range), and categorial variables are presented as counts (proportion). Comparisons between the NAC and the no NAC group were performed using Chi square test for categorical variables, and Mann Whitney U test for continuous variables. Comparisons between median values (e.g. weight) at start chemotherapy and at cystectomy within the NAC group were performed with the Wilcoxon matched pairs signed rank sum test. The overall observation time in years was calculated from date of cystectomy until death or end of follow up (as of June 2020). Time was calculated in days from initiation of the first chemotherapy cycle until cystectomy, and in months from cystectomy until relapse for relapsing patents.

Cumulative survival was calculated with the Kaplan-Meier method. Cox regression was used

to assess the association between NAC vs. no NAC and risk of relapse and overall mortality, presented as hazard ratio (HR) and 95% confidence interval (95%CI), adjusted for age and tumor stage pre-cystectomy. A test of parallel lines confirmed that the proportional hazard assumption was met. Statistical analyses were performed using the SPSS 26.0 package (SPSS Inc., Chicago IL, USA). Two-sided p-values <0.05 were considered significant.

Ethics

The study was approved by the data protection officer at UNN (project number 02386).

Results

Study patient characteristics

Overview of patient characteristics at cystectomy for all included patients are presented in table 1. Of the 154 patients included, 120 (77.9%) were male and 34 (22.1%) female. Overall, 42 (27.3%) were current smokers, 71 (46.1%) ex-smokers and 39 (25.3%) never smokers. Median age was 71.8 years (range 42.5-92.6). Median creatinine was 93.5 µmol/L (range 47-212). Median weight 77.5 kg (range 49.7-122).

In total, 99 of the 154 patients included in this study had MIBC and thus were considered for NAC. The remaining 55 patients had less advanced cancer, in which case guidelines do not recommend chemotherapy. These 55 patients were included in analyses of surgical complications, but not in analyses regarding chemotherapy coverage, effects, complications, relapse and survival.

Chemotherapy implementation/coverage

Overall, 47 (47.5%) of the 99 patients with MIBC received NAC. Patient characteristics according to NAC vs. no NAC is presented in table 2. Patients who received NAC were younger at cystectomy than those without NAC (median age 68 years vs. 75 years, p-value <0.001), otherwise there were no statistically significant differences in patient characteristics presented in table 2 between these two groups. For the remaining 52 (52.5%) of those with MIBC, the most frequent reason for not receiving chemotherapy was old age, accounting for

50% of the cases (table 3). Other frequent reasons were reduced kidney function (9.6%) and heart disease (9.6%). Overall, 13.5% were contributed to other comorbidities than heart or kidney disease, such as chronic obstructive pulmonary disease (COPD), obesity and other concurrent malignancy. The remaining 17.3% were grouped as “Other reasons” and consisted mainly of cases where there was no obvious reason found in the patient journal, but also one case with an emergency cystectomy and one where the patient did not want chemotherapy. All cases where there was no clear reason for not receiving NAC described in the medical records happened prior to 2014.

Since the introduction in 2011 there has been a steady increase in the number of patients who received NAC. In the first years from 2011 through 2014, only 12 of 41 (29.3%) patients received NAC. From 2015 through 2019, the amount was 35 out of 58 (60.3%) (table 4). After excluding patients aged above 75 years, the percentage of patients who received NAC were overall 63.4% (45 out of 71 patients). The number increased from 36.7% (11 out of 30 patients) during 2011-2014 to 82.9% (34 out of 41 patients) in the years 2015-2019.

Chemotherapy feasibility and side-effects

For those who received NAC, 27 (57.4%) received all three chemotherapy cycles, while seven (14.9%) patients discontinued after cycle one and another thirteen (27.7%) after cycle two (table 5). Of the seven who discontinued after cycle one, four (57.1%) were because of reduced kidney function. Among those ones who dropped out after cycle two, the reasons were more diversified, with infection responsible for four out of 13 (30.8%), nausea/anorexia three out of 13 (23.1%) and increased creatinine/reduced kidney function two out of 13 (15.4%). One of the patients only received two cures because the evaluation after two cures showed significant remission and the patient was deemed ready for surgery. The remaining four patients were categorized as others, further described under table 5.

During the first cycle of chemotherapy, 24 patients 51.1% did not experience any complications. For cycle two and three the percentage without severe complications was 65% and 81.5% respectively. The most common complications were nausea/anorexia and neutropenic sepsis for all three cycles (table 6). Neutropenic sepsis occurred in 6 patients

(12.8%) after cycle one, 3 (7.5%) after cycle two and 2 (11.1%) after cycle three, despite the prophylactic use of G-CSF. Worth noting is that four patients experienced neutropenic sepsis after more than one cycle. Overall, of the 47 patients who received NAC, 8 (17%) had neutropenic sepsis at some time during chemotherapy. There were no deaths related to complications during chemotherapy. Among the 27 patients who completed all the cycles, 15 (56%) did not have complications after any of the cycles. Median time from first chemotherapy cycle until cystectomy was 52 days (range 28-76).

Median weight at start of chemotherapy for all 47 patients was 81 kg (range 55-114), and it decreased to 76 kg (range 53-114) at cystectomy ($p<0.001$). In total 25 patients (53%) had a small weight gain or stable weight from chemotherapy initiation to cystectomy, while 22 (47%) experienced a weight loss, of whom 14 (30%) had a moderate weight loss. Median BMI was 25.5 kg/m^2 (range 19-35) at start chemotherapy and decreased to 24.6 kg/m^2 (range 19-35) at cystectomy ($p<0.001$).

Median creatinine for all 47 patients was 86 µmol/L (range 54-129) at start of chemotherapy and increased to median 90 µmol /L (range 61-200) at cystectomy ($p<0.001$). Creatinine clearance was median 79 (range 45-123) at start of chemotherapy and decreased to median 72 (range 29-110) at cystectomy ($p=0.041$). The number of patients with slightly decreased renal function increased from 35 (75%) at start chemotherapy, to 41 (87%) at cystectomy. The number of patients with moderately decreased renal function increased from 11 (23%) at start of chemotherapy to 14 (30%) at cystectomy.

Efficacy of chemotherapy

Prior to chemotherapy, 42 of the patients (89%) had histologically T2 or more advanced cancer in the biopsies (figure 3). The remaining five patients with histologically pTis or pT1 were considered to have radiological T2 stage and were thus offered NAC. After chemotherapy, the percentage of patients with pT2 or more advanced cancer was reduced to 51% (24 out of 47). Overall, 13 patients (28%) were downgraded to pT0 (pathologic complete response). A total of 23 patients (49%) had a histological downgrading of the tumor, 12 (25.5%) had no change and 12 (25.5%) had histological upgrade of tumor.

Surgical complications

The surgical complications for patients in this study are presented in table 7. Infection was the most frequent complication for all categories. Other frequent complication categories were gastrointestinal, bleeding/anemia, heart/circulatory, wound rupture and kidney failure. Among all 154 patients included, 53.2% experienced any grade 1-2 complications and 24% any grade 3-5 complications within 30 days. Overall, 60.4% had any grade 1-2 complications, and 29.2% any grade 3-5 complications within six months.

No NAC patients had a slightly higher prevalence of grade 1-2 complications within 30 days (55% vs. 48.9%, p=0.38), but it was not statistically significant. For grade 3-5 complications in the same time period, numbers were almost equal (24.3% vs 23.4%). Grade 1-2 complications within six months were also quite similar for NAC vs no NAC (57.4% vs 61.7%). The NAC group had a higher frequency, although not significant, of any grade 3-5 complications within six months (34% vs. 27.4%, p=0.36).

Relapse and survival

Overall, 55 (55%) of included patients were alive at the end of follow-up (table 8). A total of 30 patients (including two patients who never were tumor-free after surgery) had experienced recurrence at end of follow-up (June 2020). Of these 30, five had recurrence only in regional lymph nodes, two only in liver, one only in lungs and the remaining 22 in multiple regions/organs. Median time to relapse was 10.5 (range 1.8-66.5) months after cystectomy. Age-adjusted Cox-regression showed that NAC compared with no NAC did not influence the risk of relapse (HR for relapse 0.80, 95% 0.36-1.77), while increasing pre-cystectomy tumor stage was associated with risk for relapse (p for trend 0.003).

The actuarial 2-year overall survival was 68% for all patients (95% CI 58%-77%), and it was numerically higher for patients treated with NAC (78%; 95% CI 66%-90%) than those without NAC (58%; 95% CI 43%-72%), but not statistically significant (overlapping Cis). Bladder cancer was the most common cause of death for both patient groups. In the NAC group, 13 patients (27%) died because of bladder cancer, while in the no NAC group 14 patients (27%) died due

to bladder cancer. A considerable larger proportion of patients with no NAC compared with NAC died of treatment-related complications (14% vs. 2%, not possible to perform significant testing due to only one observation in the NAC group). Age-adjusted Cox regression showed that NAC compared with no NAC did not influence overall survival (HR for death 0.68, 95% 0.35-1.32) (figure 4), and increasing pre-cystectomy tumor stage was not associated with overall mortality risk (p for trend 0.13).

Discussion

Chemotherapy coverage

This study showed that the total NAC coverage in the time period 2011-2019 at UNN was 47.5%. Since this number increased drastically during the study time period, it probably does not represent to what extent NAC is currently offered to patients with MIBC. For the first four years after implementation the total coverage was as low as 29.3%, rising to 60.3% for the last five years. There may be several reasons as to why the coverage was so low in the first years. Firstly, this was a newly implemented treatment option, and as with most new treatments, there will always be some skepticism and reluctancy, especially when there already are well established treatment options. It is also normal for new treatments to be gradually introduced. Second, because dose dense MVAC was a relatively new treatment option for bladder cancer, there was less available research of outcome for patients at the time. Third, the structure of the multidisciplinary meeting has improved during the study period, along with the diagnostic pathway that was introduced in 2015.

It is reasonable to think that the current NAC coverage number is closer to the one of the later years (around 60%), when the treatment was more established and patient outcome better documented. A similar study looking at NAC coverage numbers for MIBC across all urological departments in Denmark in the years 2014-2017 showed a coverage of 61% (39). In this study however, patients aged above 75 years old were excluded. If we had used the same exclusion criteria, the coverage number in our study would rise to 63.4% (45 out of 71 patients) overall and 82.9% (34 out of 41 patients) in the years 2015-2019. A large study across major European centers from 2012 showed that only around 12% of the 5000

patients with MIBC included were considered for NAC (34). Another large study, from the US, with 7101 patients included, showed that NAC coverage increased from 22.9% to 32.3% from 2011 to 2015 (40). It also showed that AC was used quite often, with total chemotherapy coverage going from 46.4% to 57.2% in the same years. When looking at these studies we see that the NAC coverage in general seems to increase, and that coverage at UNN has been relatively extensive in the recent years we studied.

In our study we saw that old age was by far the most important factor for patients not being offered NAC, accounting for 50% of cases with MIBC did not offered NAC. The age restriction of 75 is not definitive. National guidelines advice that patients above 75 years should be thoroughly evaluated before given NAC. In our study there were two patients aged above 75 who received NAC.

Reduced kidney function and heart disease were also listed frequently, both making up 9.6% of cases each. Because MVAC is a cisplatin-based chemotherapy regimen, which is very nephrotoxic, there is good reason to be careful when giving this treatment to patients with reduced kidney function. The national guidelines recommend that patients with glomerular filtration rate (GFR) between 50 and 60 should receive cisplatin over two days, and those with GFR below 50 should not be given cisplatin-based chemotherapy. At UNN the limit has been set to 45, slightly lower than the national recommendations. Several studies have looked at where to draw the line for acceptable kidney function. A study on cisplatin-based NAC conducted at the Cleveland Clinic in the US showed that patients with GFR < 60 mL/min were less likely to complete all three rounds of chemotherapy and more likely having to modify it. It also showed that they had lower pathologic complete response than patients with normal kidney function (41).

The advantages of NAC ahead of cystectomy are already well documented as mentioned earlier. However, for some patients the cons outweigh the benefits, and they are better off without NAC. The difficult part is to select which patients will benefit from the treatment. Several studies have looked at ways to identify these patients, and this is still an ongoing process, where different biomarkers are being evaluated.

Feasibility, side-effects and efficacy

Of the 47 patients who received NAC, 57.4% underwent all three rounds and 85.1% at least two rounds. In the earlier mentioned study from the Cleveland Clinic, 87% of patients with GFR > 60 mL/min finished all cycles, while only 70% of patients with GFR between 35 and 59 finished all cycles, highlighting the fact that renal function is essential for cisplatin-based chemotherapy tolerance (41). In our patient group, 75% of patients who received NAC had slightly decreased kidney function (creatinine clearance < 90 mL/min/1.73m^2) and 23% moderately decreased kidney function (creatinine clearance < 60 mL/min/1.73m^2), which could partly explain why the NAC feasibility was so low in our study. In total, six (30%) of the 20 patients who discontinued chemotherapy were because of reduced kidney function. Consequently, it is advisable to carefully select patients for NAC based on kidney function in addition to age and other comorbidities.

Neutropenic sepsis is one of the most feared complications in chemotherapy treatment. In our study, neutropenic sepsis was, in total over all three cycles, seen in 8 (17%) out of 47 patients. A study by Bamias et al. evaluating the toxicity of MVAC, showed that neutropenic sepsis occurred in 11.6% of the 109 patients included (42). In this study the MVAC was given each four weeks, with a total of six cycles, and all patients received G-CSF. In another study, conducted by Von der Maase et al., 12% of patients who received MVAC experienced neutropenic sepsis (43). This study also had a slightly different treatment regimen, with cycles given each four weeks, and G-CSF was not given routinely, only on indication. Thus, neutropenic sepsis was slightly more common in our study. These studies are not truly compatible though, since they did not use the dose dense, but rather the standard dose MVAC regimen, and number of cycles with chemotherapy and G-CSF administration differs from the regimen in our study. Furthermore, the chemotherapy coverage at UNN is quite comprehensive compared to other studies. This, probably, means that patients who are in worse health and more susceptible to adverse effects are given chemotherapy, which could explain some of the increased amount of neutropenic sepsis. Still, a total of 15 (56%) of the 27 patients who completed all cycles did not experience any serious complications.

This study showed a complete pathologic response (tumor downgrade to pT0) in 13 (28%) of the 47 patients who received NAC. This is comparable to a study conducted in 2014 by Choueiri et al., which showed a complete pathologic response of 26%. Another study, by Plimack et al. showed a higher response rate of 38%. A large meta-analysis by Yin et al. including a total of 667 patients who received MVAC treatment, showed a complete pathological response of 24.3% (26).

In our study, 49% of patients had a histological downgrading of the tumor, while 25.5% had no change and 25.5% had an upgrade in tumor stage. In the study performed by Plimack et al, these numbers were 65%, 17.5% and 17.5% respectively. However, 93% of patients in that study finished all three cycles of chemotherapy, compared to 57.4% in our study. This is a plausible explanation for the difference. Also, worth noting is that 57% of included patients in that study had more advanced tumor stage than T2, compared to only 4.3% in our study, which might affect downgrading percentages.

Surgical complications

Surgical complications for all 154 patients were 53.2% grade 1-2 complications within 30 days. Shabsigh et al. conducted a large study including 1142 patients which showed similar numbers, with 59.2% of patients experiencing grade 1-2 complications within 30 days (31). Grade 3-5 complication on the other hand were significantly higher in our study (24% vs 11.2%). The reason for this is unknown, however only 12% of patients in the other study had priorly received NAC and it was not specified what kind of chemotherapy or how long before surgery this was given.

Outcome, relapse and survival

The actuarial 2-year overall survival was higher for patients treated with NAC (78%) than those with no NAC (58%), but not statistically significant since both groups were too small to identify any significant differences. Our problem with reduced power due to few included cases also in part explain the lack of an association between NAC and improved relapse-free and overall survival.

A total of seven (14%) of the 52 patients with MIBC who did not receive NAC died of treatment complications, compared to only one (2%) of the 49 who received NAC. This is quite a substantial difference, but most likely due to patient selection. Patients in the no NAC group are patients who, in most cases, were deemed not eligible for NAC due to old age and/or extensive comorbidities. Consequentially, patients in this group would probably be more susceptible to complications.

Strengths of this study include an unselected study sample, reflecting all patients treated for bladder cancer in Troms and Finnmark. Consequently, it also reflects clinical practice. Another strength is the registration of complete and comprehensive details for patients included. To the best of our knowledge, this is the first study that evaluates chemotherapy coverage in this patient group in Norway.
The main weakness in this study is the small patient group, which causes problems with statistical significance and thus type 2 errors. Since patients were not randomized to receive chemotherapy or not, this introduces skewness in the way that patients in the no NAC group likely were in worse health condition than the NAC group prior to cystectomy.

Conclusion

Our study showed that total chemotherapy coverage at UNN in the period 2011-2019 was 47.5%. This number increased greatly during the years we studied and was higher than other comparable studies. Old age was by far the most important reason for not receiving chemotherapy, followed by heart disease and reduced kidney function. Only 57.4% of patients completed all three cycles of chemotherapy. Most frequent reasons for discontinuation were reduced kidney function, infection and nausea/anorexia. Nausea/anorexia and neutropenic sepsis were the most common complications during chemotherapy. Neutropenic sepsis was seen in 17% of patients who received NAC. Given that chemotherapy coverage was higher in our study, patients with more extensive comorbidity were more likely to be given NAC than in other studies, which could explain why feasibility was relatively low and complication rate high. There were no significant differences in surgical complications between NAC and no NAC patients. Of the 99 MIBC patients, 30% had relapsed at the end of follow-up (June 2020). Chemotherapy did not affect

risk of relapse. 2-year overall survival was higher in the NAC group, but not statistically significant. This must be investigated further, with larger datasets and longer follow-up time.

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Tables and figures

Flow chart

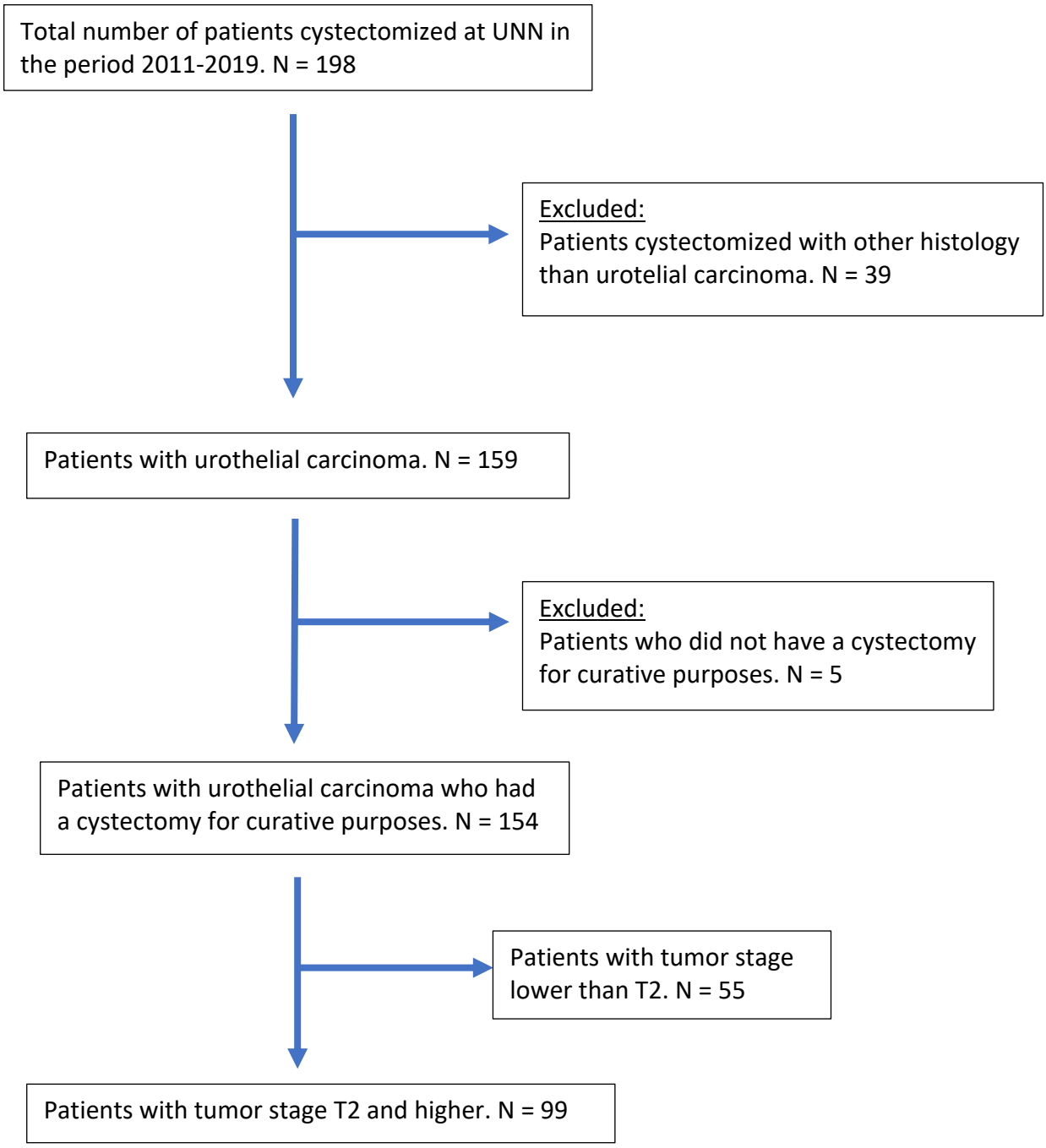

Figure 1. Incidence (rate per 100 000), mortality and 5-year relative survival (%) for males in Norway (1).

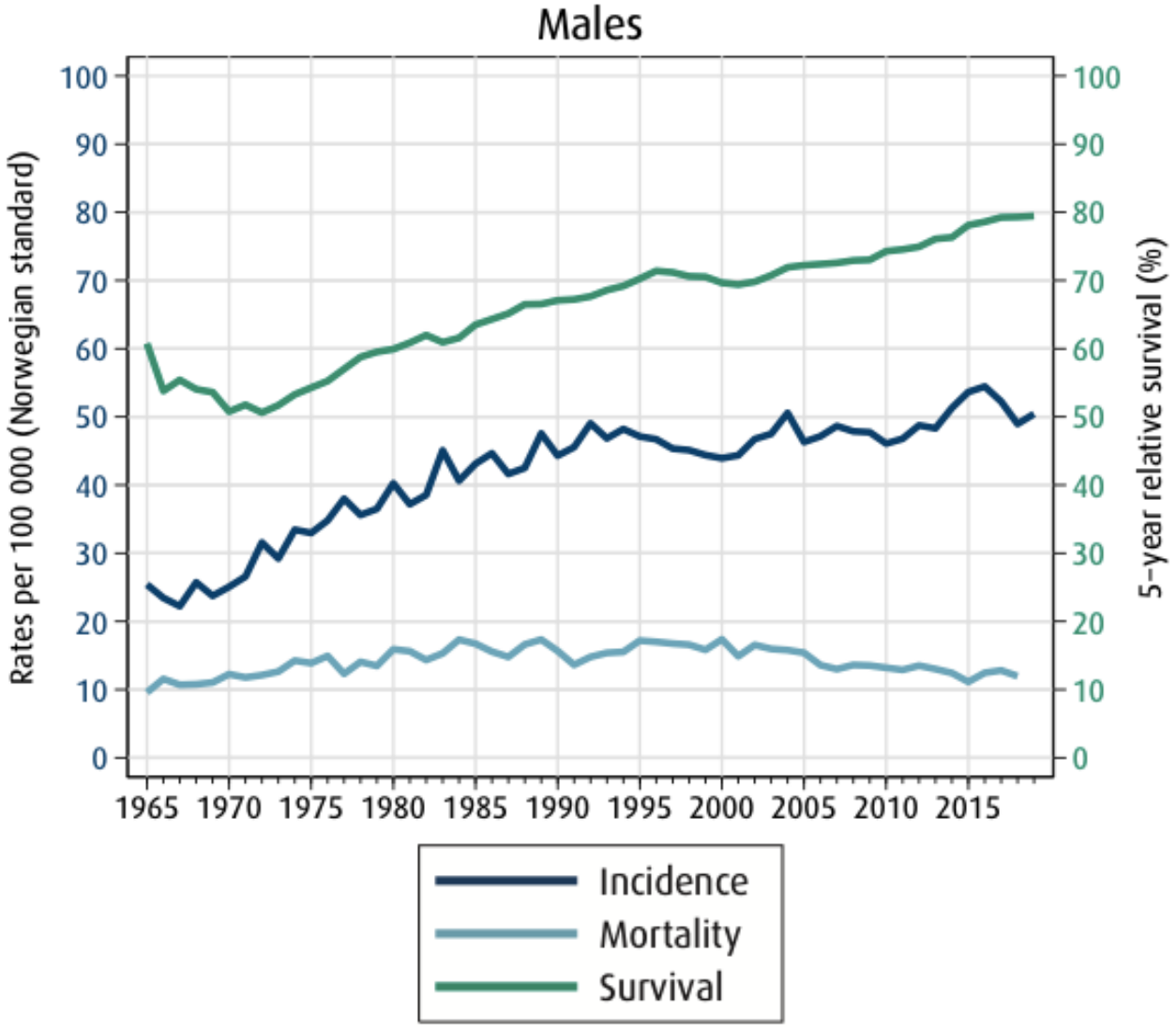

Figure 2. Incidence (rate per 100 000), mortality and 5-year relative survival (%) for females in Norway (1).

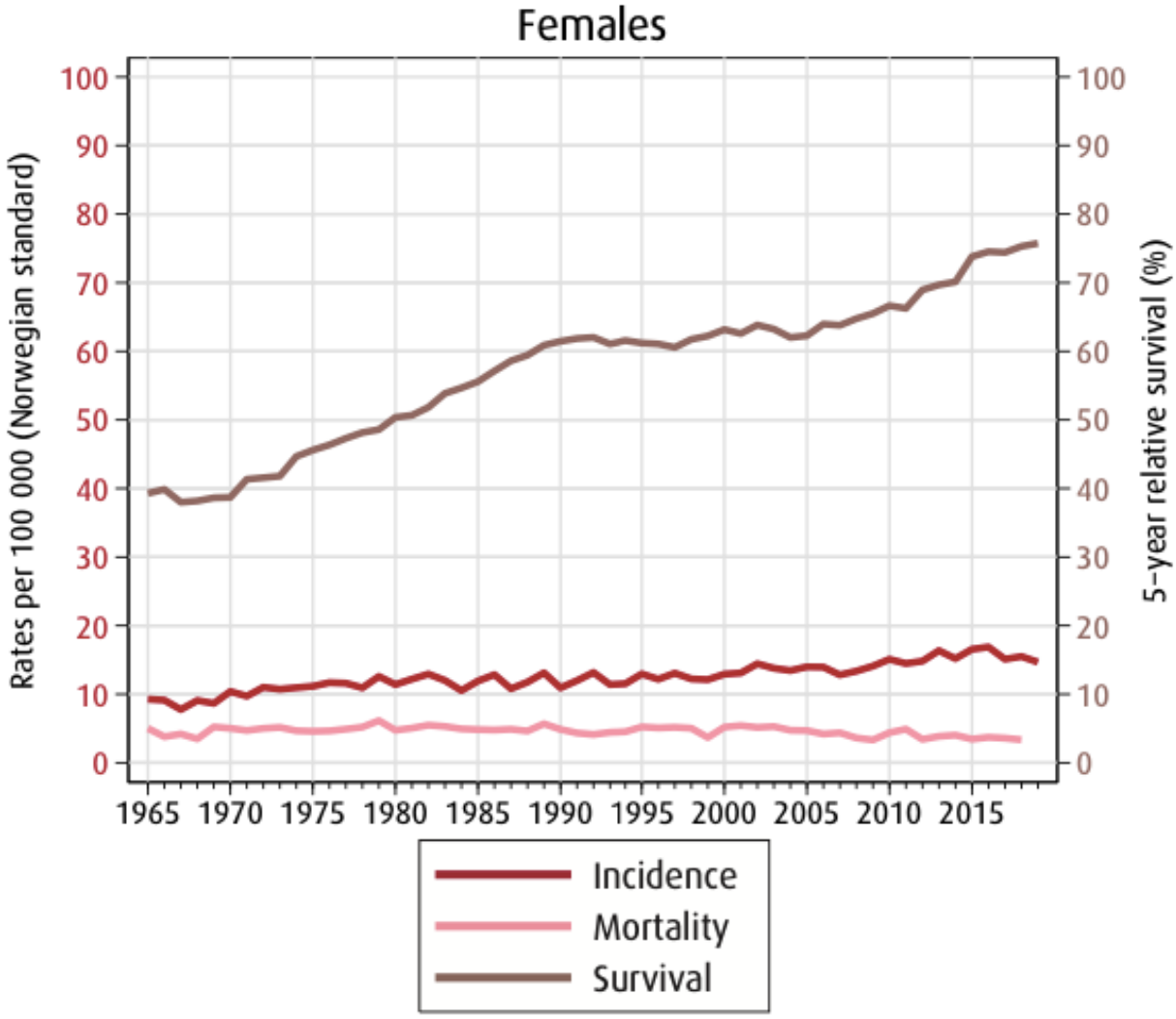

Figure 3. Histological tumor stage before and after chemotherapy (CX). Numbers are given in total amount.

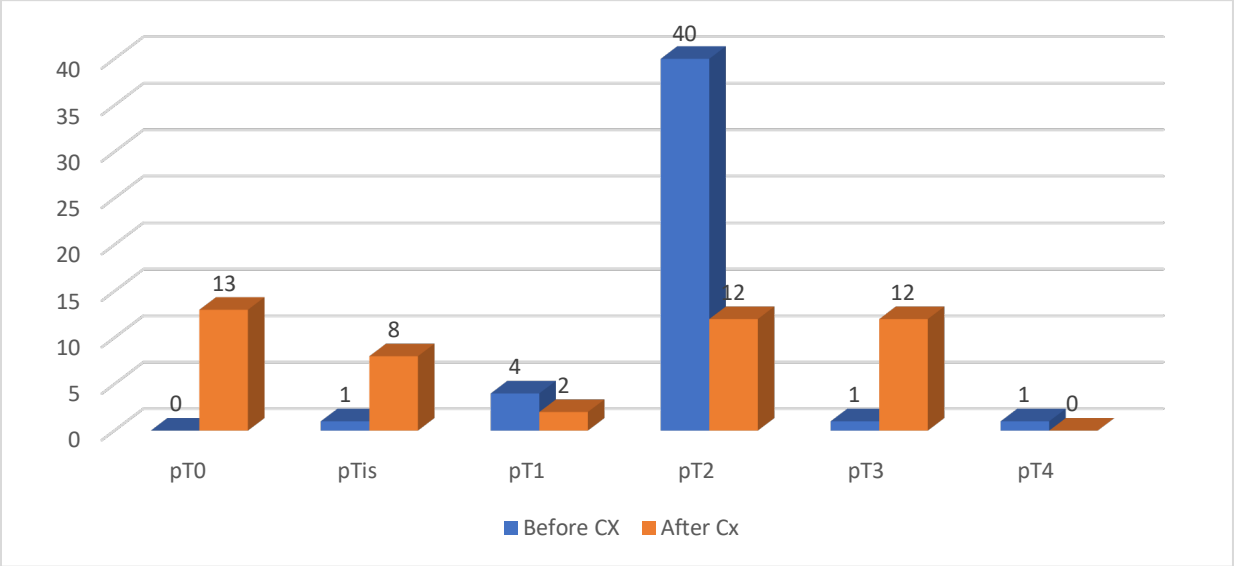

Figure 4. Age-adjusted overall survival according to neoadjuvant chemotherapy (NAC) vs. no NAC.

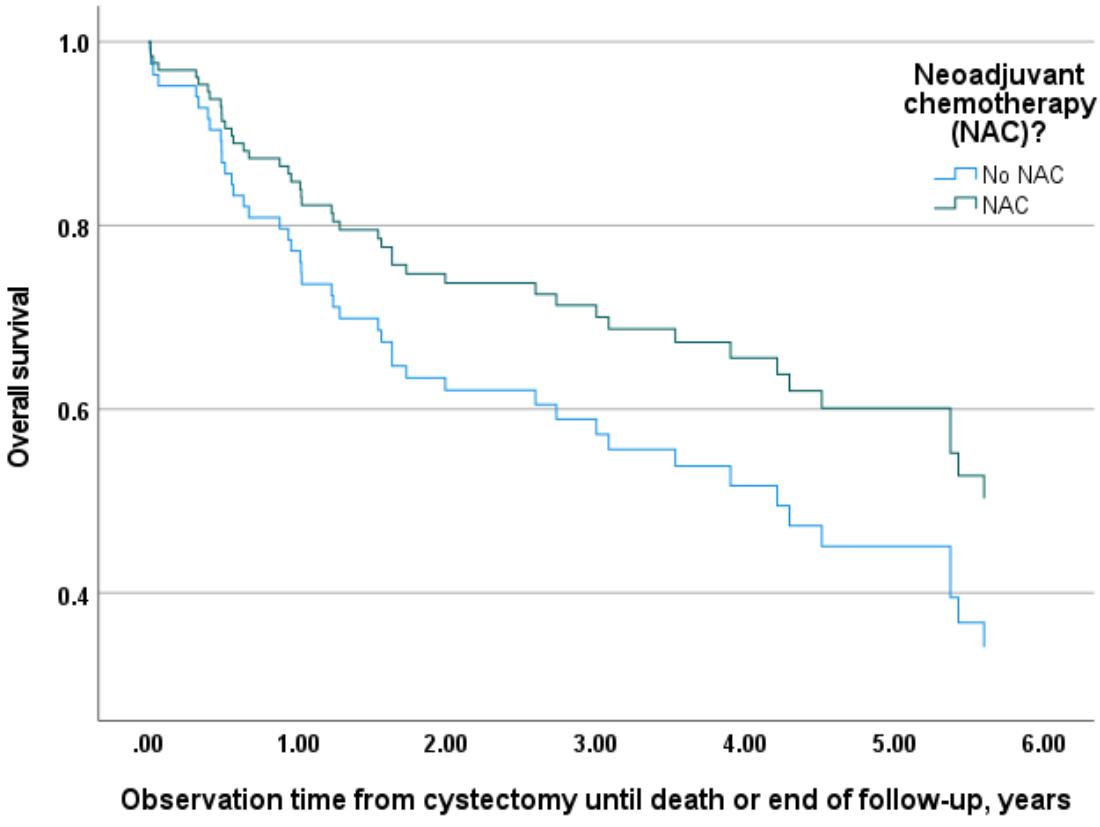

Table 1. Study characteristics at cystectomy for all patients who underwent radical cystectomy at UNN during 2011-2019.

Characteristic	Period 2010-2014 N=65	Period 2015-2019 N=89	Total N=154
Sex			
Male	50 (76.9)	70 (78.7)	120 (77.9)
Female	15 (23.1)	19 (21.3)	34 (22.1)
Age, median (range), years	70.7 (44.8-88.7)	72.3 (42.6-92.6)	71.8 (42.5-92.6)
Smoking status			
Never	15 (23.1)	24 (27)	39 (25.3)
Previous	31 (47.7)	40 (44.9)	71 (46.1)
Current	17 (26.2)	25 (28.1)	42 (27.3)
Weight, median (range), kg	75 (52-115)	79 (49.7-122)	77.5 (49.7-122)
BMI, median (range), kg/m^2	24.7 (16.7-33.7)	25.6 (18-35.7)	24.9 (16.7-35.7)
Creatinine, median (range), µmol/L	92 (47-212)	97 (48-200)	93.5 (47-212)
Creatinine clearance, median (range), µmol/L	69.9 (26.3-107)	63.7 (29-109.6)	66 (26.3-109.6)
pT stage before cystectomy			
Tis	5 (7.7)	5 (5.2)	10 (6.5)
T1	19 (29.2)	28 (31.5)	47 (30.5)
T2	40 (61.5)	53 (59.6)	93 (60.4)
T3	0 (0)	1 (1.1)	1 (0.6)
T4	0 (0)	1 (1.1)	1 (0.6)
Uncertain	1 (1.5)	1 (1.1)	2 (1.3)
Type of surgery			
Open cystectomy	65 (100)	81 (91)	146 (94.8)
Robot-assisted	0 (0)	8 (9)	8 (5.2)

Data are presented as numbers (%) unless otherwise specified.
There were missing data for some of the variables: smoking n=2, weight n=2, BMI n=2.
Abbreviations: BMI (body mass index), kg (kilograms), pT (histological tumor stage)

Table 2. Study characteristics at cystectomy for muscle-invasive bladder cancer patients who underwent radical cystectomy at UNN during 2011-2019.

Characteristic	NAC N=47	NO NAC N=52	Total N=99
Sex			
Male	40 (85.1)	38 (73.1)	78 (78.8)
Female	7 (14.9)	14 (26.9)	21 (21.2)
Age, median (range), years	68.4 (42.5-79.2)	75.2 (53-88.7)	70 (42.5-88.7)
Smoking status			
Never	7 (14.9)	13 (25)	20 (20.2)
Previous	21 (44.7)	27 (51.9)	48 (48.5)
Current	19 (40.4)	12 (23.1)	31 (31.3)
Weight, median (range), kg	76 (52.5-114)	73 (49.7-115)	77.1 (49.7-115)
BMI, median (range), kg/m^2	24.6 (19.2-34.9)	24.9 (16.7-33.9)	24.7 (16.7-34.9)
Creatinine, median (range), µmol/L	90 (61-200)	98.5 (47-212)	98.1 (47-212)
Creatinine clearance, median (range), $mL/min/1.73m^2$	72.3 (29.0-109.6)	60.5 (26.3-107)	64.5 (26.3-109.6)
pT stage before cystectomy			
Tis	1 (2.1)	0 (0)	1 (1)
T1	4 (8.5)	0 (0)	4 (4)
T2	40 (85.1)	52 (100)	92 (92.3)
T3	1 (2.1)	0 (0)	1 (1)
T4	1 (2.1)	0 (0)	1 (1)
Uncertain	0 (0)	0 (0)	0 (0)
Type of surgery			
Open cystectomy	47 (100)	51 (98.1)	98 (99)
Robot-assisted	0	1 (1.9)	1 (1)

Data are presented as numbers (%) unless otherwise specified.
Abbreviations: BMI (body mass index), kg (kilograms), pT (histological tumor stage)

Table 3. Reasons for not receiving neoadjuvant chemotherapy.

Reason	Number	%
Old age (>75 years old)	26	50
Other reasons[1]	9	17.3
Other comorbidities[2]	7	13.5
Heart disease	5	9.6
Reduced kidney function	5	9.6

[1] Includes one case of emergency cystectomy due to bleeding and one where the patient did not want chemotherapy. No obvious reasons were found in the journal for the remaining patients.
[2] Includes diabetes, drug addiction, obesity, other concurrent malignancy, epilepsy and duodenal ulcus

Table 4. Amount of patients with muscle-invasive bladder cancer who received chemotherapy by year.

	Amount	%
2011		
Number of patients	10	
Received chemotherapy	1	10
2012		
Number of patients	10	
Received chemotherapy	4	40
2013		
Number of patients	13	
Received chemotherapy	3	23.1
2014		
Number of patients	8	
Received chemotherapy	4	50
2015		
Number of patients	13	
Received chemotherapy	9	69.2
2016		
Number of patients	13	
Received chemotherapy	9	69.2
2017		
Number of patients	15	
Received chemotherapy	8	53.3
2018		
Number of patients	12	
Received chemotherapy	7	58.3
2019		
Number of patients	5	
Received chemotherapy	2	40
2010-2014		
Number of patients	41	
Received chemotherapy	12	29.3
2015-2019		
Number of patients	58	
Received chemotherapy	35	60.3
Total		
Number of patients	99	
Received chemotherapy	47	47.5

Table 5. Reasons for chemotherapy discontinuation for patients who were treated with cisplatin-based chemotherapy before cystectomy.

	After cycle 1 N=7	After cycle 2 N=13
Reduced kidney function	4 (57.1)	2 (15.4)
Nausea/anorexia	1 (14.3)	3 (23.1)
Infection	1 (14.3)	4 (30.8)
Other[1]	1 (14.3)	4 (30.8)

Data are presented as numbers (%) unless otherwise specified.
[1]Others include: urethral bleeding, tumor progress, tumor downgraded enough for surgery and two patients who did not wish further chemotherapy

Table 6. Complications during chemotherapy for patients who were treated with cisplatin-based chemotherapy before cystectomy.

	Cycle 1 N=47	Cycle 2 N=40	Cycle 3 N=27
None	24 (51.1)	26 (65)	22 (81.5)
Nausea/anorexia	7 (14.9)	8 (20)	2 (7.4)
Neutropenic sepsis	6 (12.8)	3 (7.5)	2 (11.1)
Other[1]	7 (14.9)	3 (7.5)	1 (3.7)
Reduced kidney function	3 (6.4)	1 (2.5)	0 (0)

Data are presented as numbers (%) unless otherwise specified.
Others include: diarrhoea, acid reflux, urinary tract infection, urethral bleeding, problem with nephrostomy catheter, fatigue and infections

Table 7. Surgical complications follow cystectomy for patients with urothelial bladder cancer. Scored using the Clavien-Dindo classification system. Several patients experienced multiple complications within one grading category. For these patients we only counted the complication we deemed most severe.

	No NAC N=107	NAC patients N=47	All patients N=154
Infection	44 (41.1)	19 (40.4)	63 (40.9%)
Grade 1-2 within 30 days	59 (55)	23 (48.9)	82 (53.2)
Infection	33 (30.8)	13 (27.7)	46 (29.9)
GI	12 (11.2)	6 (12.8)	18 (11.7)
Bleeding/anemia	4 (3.7)	2 (4.3)	6 (3.9)
Heart/circulation	2 (1.9)	1 (2.1)	3 (1.9)
Wound rupture	6 (5.6)	0 (0)	6 (3.9)
Others	2 (1.9)	1 (2.1)	3 (1.9)
Grade 3-5 within 30 days	26 (24.3)	11 (23.4)	37 (24)
Infection	15 (14)	6 (12.8)	21 (13.6)
GI	1 (0.9)	1 (2.1)	2 (1.3)
Bleeding/anemia	1 (0.9)	1 (2.1)	2 (1.3)
Heart/circulation	5 (4.7)	1 (2.1)	6 (3.9)
Kidney failure	2 (1.9)	0 (0)	2 (1.3)
Wound rupture	2 (1.9)	1 (2.1)	3 (1.9)
Others	0 (0)	1 (2.1)	1 (0.6)
Grade 1-2 within 6 months	66 (61.7)	27 (57.4)	93 (60.4)
Infection	38 (35.5)	12 (25.5)	50 (32.5)
GI	11 (10.3)	7 (14.9)	18 (11.7)
Bleeding/anemia	3 (2.8)	3 (6.4)	6 (3.9)
Heart/circulation	2 (1.3)	1 (2.1)	3 (1.9)
Wound rupture	6 (3.9)	0 (0)	6 (3.9)
Others	6 (3.9	4 (8.5)	10 (6.5)
Grade 3-5 within 6 months	29 (27.4)	16 (34)	45 (29.2)
Infection	12 (11.2)	9 (19.1)	21 (13.6)
GI	3 (2.8)	0 (0)	3 (1.9)
Bleeding/anemia	1 (0.9)	0 (0)	1 (0.6)
Heart/circulation	5 (4.7)	2 (4.3)	7 (4.5)
Wound rupture	2 (1.9)	1 (2.1)	3 (1.9)
Kidney failure	4 (3.7)	0 (0)	4 (2.6)
Others	2 (1.9)	4 (8.5)	6 (3.9)

Data are presented as numbers (%) unless otherwise specified.
Abbreviations: GI (gastrointestinal)

Table 8. Vital status, relapse and causes of death according to NAC vs. no NAC for 99 patients with muscle invasive bladder cancer.

	No NAC N=52	NAC N=47	All patients N=99
Observation time, years (median, range)	2.1 (0-9.2)	3.0 (0-8.1)	2.6 (0-9.2)
Vital status			
Alive without relapse	22 (42)	29 (62)	51 (51)
Alive with relapse	2 (4)	2 (4)	4 (4)
Overall death	28 (54)	16 (34)	44 (44)
Relapse, overall	14 (27)	14 (30)	28 (28)
Relapse and later dead	12 (23)	12 (26)	24 (24)
Relapse and still alive	2 (4)	2 (4)	4 (4)
Relapse, site specific			
Regional lymph nodes	2 (12.5)	3 (21.4)	5 (5.1)
Lungs	1 (6.3)	0 (0)	1 (1)
Liver	1 (6.3)	1 (7.1)	2 (2)
Combinations[1]	12 (75)	10 (71.4)	22 (22.2)
Causes of death			
Bladder cancer (metastatic disease)	14 (27)	13 (27)	27 (27)
Treatment-related complications	7 (14)	1 (2)	8 (8)
Other causes	7 (14)	2 (4)	9 (9)

Data are presented as numbers (%) unless otherwise specified.
For “relapse, site specific”, percentage is derived from the “relapse, overall” number.
[1]This group includes the above-mentioned specific sites when there were more than one of them present

Referanse: Choueiri TK, Jacobus S, Bellmunt J, Qu A, Appleman LJ, Tretter C, et al. Neoadjuvant dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin with pegfilgrastim support in muscle-invasive urothelial cancer: pathologic, radiologic, and biomarker correlates. J Clin Oncol. 2014;32(18):1889-94.			**Studiedesign: Pasientserie** **Grade - kvalitet** Lav
Formål	**Materiale og metode**	**Resultater**	**Diskusjon/kommentarer/sjekkliste**
Undersøke toleranse og effekt av neoadjuvant doseintensivert kjemoterapi bestående av metotreksat, vinblastin, doksorubicin og cisplatin (ddMVAC) hos pasienter med muskelinfiltrerende urotelialt carsinom i blære **Konklusjon** ddMVAC var godt tolerert og førte til signifikant tumornedgradering hos pasientgruppen som ble studert **Land** USA **År data innsamling** 2008-2012	**Populasjon** 39 pasienter med urotelialt carsinom grad T2-T4 i blære, som som fikk ddMVAC i forkant av cystektomi. **Utfall – hoved utfall** Tolerabilitet av kjemoterapi Tumornedgradering etter kjemoterapi **Viktige konfunderende faktorer** Seleksjonsbias **Statistiske metoder** Simons optimal two-stage design Fishers exact test Kaplan-Meier method Atkinson and brown method Log-rank test	**Hovedfunn** **Effektstørrelse** **CI** 49% (to-sidet 80% CI, 38-61) oppnådde tumornedgradering. 26% (80% CI, 17-37) oppnådd komplett tumor respons (ingen kreft funnet) 95% av pasientene fullførte alle rundene med kjemoterapi. Høygradig toksisitet (grad 3-4) ble sett hos 10% (90% CI 4-22) av pasientene.	• Er formålet klart formulert? **Ja** • Var studien basert på et tilfeldig utvalg fra en egnet pasientgruppe? **Ja** • Var inklusjonskriteriene klart definert?* **Ja** • Var alle pasientene i samme stadium av sykdommen? **Nei. Fra T2-T4** • Ble det brukt objektive kriterier for å vurdere/validere endepunktene? **Ja** • Er prognostiske/konfunderende faktorer beskrevet7tatt hensyn til i design/anal? **Nei** • Var registreringen prospektiv? **Ja** • Var oppfølgningen lang nok! **Lang nok for valgte endepunkter ja.** • Var oppfølgningen tilstrekkelig for å nå endepunktene? **Ja** • Stoler du på resultatene? **Usikker. Liten pasientgruppe og mye ikke statistisk signifikante resultater** • Kan resultatene overføres til praksis? **Ja.** • Annen litteratur som støtter resultatene? **Ja** Hva diskuterer forfatterne som: • Styrke: **tilfeldig utvalgt pasientgruppe** • Svakhet **Liten pasientgruppe** Har resultatene plausible biologiske forklaringer? **Ja. Blærekreft er dokumentert kjemoterapisensitiv.**

Referanse: Freedman ND, Silverman DT, Hollenbeck AR, Schartzkin A, Abnet CC. Association between smoking and risk of bladder cancer among men and women. JAMA. 2011;306(/):737-45.			Studiedesign: Kohortestudie Grade - kvalitet: Moderat
Formål	Materiale og metode	**Resultater**	**Diskusjon/kommentarer/sjekkliste**
Undersøke sammenhengen mellom røyking og blærekreft **Konklusjon** Sigarettrøyking økte sannsynlighet for blærekreft signifikant blant både kvinner og menn. Det var også signifikant høyere insidens blant nåværende røykere enn tidligere røykere. **Land** USA **År data innsamling** 1995-2006	**Populasjon:** 281 394 menn og 186 134 kvinner fra USA. Kohorter: Nåværende røykere, tidligere røykere og ikke-røyker blant kvinner og menn. **Hoved utfall:** Insidens (per 100 000), Hazard ratio (HR) og population-attributable risk (PAR). **Viktige konfunderende faktorer** Undersøkelsen ble gjennomført ved spørreskjemaer som ble sendt ut til alle pasienter hvor man inkludert de som svarte. Dette åpner opp for betydelig seleksjonsbias. Grunnet selvrapportering fra pasienter er det også stor sannsynlighet for noe informasjonbias. **Statistiske metoder** «We calculated age-standardized incidence rates and 95% CIs using 5-year age bands standardized to the entire NIH-AARP Diet and Health Study population». Sitert fra artikkel. Finner ingen god oversettelse av dette til norsk. Relativ risiko, hazard ratio og 95% KI ble kalkulert ved bruk av Cox proportional hazard regression modeller.	**Hovedfunn** Insidens per 100 000 var 177.3 (HR, 4.06; 95% KI 3.66-4.50) blant nåværende røykere, 119.8 (HR 2.22; 95% KI 2.03-2.44) blant tidligere røykere og 39.8 blant ikke røykere. PAR ved røyking (nåværende eller tidligere) var 0.50 (95% KI 0.45-0.54) hos menn og 0.52 (95% KI 0.45-0.59) hos kvinner. **Bifunn** Selv om røykeprevalnes blant menn og kvinner var mer lik enn ved tidligere studier var insidensen for blærekreft ikke betydelig mye likere enn tidligere.	• Formålet klart formulert? **Ja** • Er gruppene rekruttert fra samme populasjon/befolkningsgruppe? **Ja.** • Var gruppene sammenliknbare i forhold til viktige bakgrunnsfaktorer? **Menn drakk mer alkohol og spiste mer usunt, samt røykte større mengder blant røykerne, ellers sammenlignbare forhold.** • Var de eksponerte individene representative for en definert befolkningsgruppe/populasjon? **Ja** • Ble eksposisjon og utfall målt likt og pålitelig (validert) i de to gruppene? **Ikke fullstendig. Menn som røykte var i større grad storrøykere, samt at enkelte pasienter plassert i »nåværende røyker»-gruppen sluttet å røyke under oppfølgingstiden.** • Er den som vurderte resultatene (endepunkt- ene) blindet for gruppetilhørighet? **Ikke aktuelt da insidens av kreft ikke vil påvirkes av eventuell blinding.** • Var studien prospektiv? **Ja.** • Ble mange nok personer i kohorten fulgt opp? (Attrition bias/follow-up-bias). **Ja. 566 401 av 617 199.** • Er det utført frafallsanalyser? **Ja.** • Var oppfølgingstiden lang nok til å påvise positive og/eller negative utfall? **Ja, men trolig ville insidens økt enda mer ved lengre oppfølgingstid.** • Er det tatt hensyn til viktige konfunderende faktorer i design/ gjennomføring/analyser? **For de faktorene det var mulig å ta hensyn til, blant annet aldersforskjeller. Enkelte faktorer, som nøyaktig antall pack-years var ikke mulig å ta høyde for.** • Tror du på resultatene? **Ja. Jamfør Hills kriterier er dette troverdige resultater.** • Kan resultatene overføres til den generelle befolkningen? **Ja.** • Annen litteratur som styrker/svekker resultatene? **Ja. Blant annet Hemelt M. et al, The effect of smoking on the male excess of bladder cancer, som styrker funnene.** • Hva betyr resultatene for endring av praksis? **Vil trolig føre til økt nedkjempelse av røykeprevalens i befolkningen.** **Hva diskuterer forfatterne som:** • **Styrke:** stor pasientgruppe både totalt og antall som fikk kreft. • **Svakhet:** manglet alder ved opptart røyking for mange, der av vanskelig å regne ut pack-years. Flere av pasientene plasser i «nåværende røykere» sluttet å røyke i løpet av studien.

Referanse: Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med. 2003;349(9):859-66.

Studiedesign: RCT

Grade – kvalitet: Høy

Formål	Materiale og metode	Resultater	Diskusjon/kommentarer\sjekkliste
To see if neoadjuvant chemotherapy improved outcome in patients with bladder cancer **Konklusjon** Neoadjuvant chemotherapy prior to radical cystectomy improves survival outcome compared to radical cystectomy alone in bladder cancer patients. **Land** USA **År data innsamling** 1987-1998	**Rekruttering deltakere** Pasienter med nyoppdaget blærekreft fra multiple internasjonale institusjoner over en 11 års periode **Inklusjons-/eksklusjonskrit.** Pasienter med urotelialt karsinom grad T2N0M0 til T4N0M0 i blære som var kvalifisert til å gjennomgå cystektomi. **Datagrunnlaget** 317 pasienter med nyoppdaget blærekreft grad T2-T4. **Utfall (outcome) validering (for eks. diagnose)** Median overlevelsestid etter cystektomi (måneder) og femårs overlevelse etter cystektomi. Sekundære: kvantifisere effekt av neoadjuvant kjemoterapi i form av tumornedgradering **Eksponeringsvariabler (validert/ikke validert)** Pasienter ble tilfeldig utvalgt til å gjennomgå tre runder med kjemoterapi bestående av metotreksat, vinblast, doksorubicin og cisplatin før cystektomi eller gå direkte til cystektomi uten kjemoterapi. **Viktige konfunderende faktorer** Ingen åpenbare **Statistiske metoder** Stratifisert log-rank test	**Hovedfunn** **Hvor stor er «intervensjons-effekten»?** Median overlevelse i kjemoterapigruppen var 77 måneder (95% KI 55-104) sammenlignet med 46 måneder (95% KI 25-60) i gruppen som ikke fikk kjemoterapi. Fem-års overlevelse var 57% i kjemoterapigruppen mot 43% i gruppen som ikke fikk kjemoterapi (P=0.06 ved stratifisert log-rank test) Tumornedgradering til komplett patologisk respons (T0) var 38% i kjemoterapigruppen og 15% i gruppe som ikke fikk kjemoterapi (P<0.001). **Bifunn – andre viktige endepunkter** Sannsynlighet for gjennomføring av cystectomi var ikke lavere for de som fikk kjemoterapi i forkant enn de som ikke fikk.	• **Er formålet klart formulert?** • Ja • **Hvem er inkludert/ekskludert?** • Pasienter med urotelialt karsinom grad T2N0M0 til T4N0M0 i blære som var kvalifisert til å gjennomgå cystektomi. • **Var gruppene like ved starten?** • Gruppene var lik både i antall (153 vs 154) og for kategorier vurdert som av betydning (kjønn, alder og tumorstadium). • **Randomiseringsprosedyre?** • Pasienter ble tilfeldig utvalgt til en av gruppe. • **Ble deltakere/studiepersonell blindet mht gruppetilhørighet?** • Nei, trolig ikke gjennomførbart med blinding ved kjemoterapi. • **Ble gruppene behandlet likt utover «intervensjonen»?** • Pasienter i kjemoterapigruppen ble cystektomert 115 dager (gj. snitt) etter randomisering, mens pasienter i gruppen som ikke fikk kjemoterapi ble cystektomert etter 17 dager (gj. snitt) • **Primære endepunktet – validert?** • Ja. • **Ble deltakernne gjort rede for på slutten av studien?** • Ja • **Hva er resultatene? Presisjon?** • Resultatene viser statistisk signifikant økt median overlevelse og tumornedgradering, samt økt tumornedgradering på ikke statistisk signifikant nivå for pasienter som fikk kjemoterapi. • **Kan resultatene overføres til praksis?** • Ja. Resultatene kan føre til økt bruk av kjemoterapi for pasienter med blærekreft. • **Ble alle utfallsmål vurdert?** • Ja • **Er fordelene verdt ulemper/kostnader?** • Trolig. Det var betydelige bivirkninger/komplikasjoner forbundet med kjemoterapi, men ingen dødsfall. Dette må undersøkes videre. • **Annen litteratur som styrker resultatene?** • Ja. Flere studier har vist samme resultater, blant annet Yin et al. Neoadjuvant chemotherapy for muscle-invasive bladder cancer: a systemic review and two-step meta-analysis of randomized trials. **Hva diskuterer forfatterne som:** **-styrke:** lang oppfølgingstid. Lite seleksjonsbias. **-svakhet:** Ingen nevnte **Har resultatene plausible forklaringer?** Ja. Kjemoterapieffekt på blærekreft er godt dokumentert fra tidligere.

Referanse: Peyton CC, Tang D, Reich RR, et al. Downstaging and Survival Outcomes Associated With Neoadjuvant Chemotherapy Regimens Among Patients Treated With Cystectomy for Muscle-Invasive Bladder Cancer. *JAMA Oncol.* 2018;4(11):1535–1542.

Studiedesign: Tverrsnittstudie

Grade - kvalitet: Lav

Formål	Materiale og metode	Resultater	Diskusjon/kommentarer/sjekkliste
Undersøke hvilket kiemoregime av metotreksat, vinblastin, doksorubicin og cisplatin (MVAC) vs. Gemcitabin og cisplatin (GCis) eller carboplatin (GCar) som ga best utfall. **Konklusjon** Pasienter i MVAC-gruppen hadde betydelig større andel nedgradering av tumorstadium og komplett patologisk respons. Overlevelse var høyere ved MVAC, men ikke statistisk signifikant. **Land** USA **År data innsamling** 2007-2017	**Populasjon:** Pasienter med blærekreft grad T2 eller høyere som ble cystektomert ved Moffitt Cancer Center i Tampa, Florida mellom 2007 og 2017. Kohorter: MVAC, GCis og GCar **Hoved utfall:** Tumornedgradering, komplett patologisk respons (T0) og overlevelse. **Viktige konfunderende faktorer** Seleksjonsbias **Statistiske metoder** Wilcoxon rank sum test Kaplan-Meier kurver Cox proportional hazard regression	**Hovedfunn** Nedgraderingsrate var 52.2% for MVAC, 41.3% for GCis og 27% for GCar. Komplett patologisk respons var 41.3% for MVAC, 24.5% for GCis og 9.4% for GCar (P<0.001) Sannsynlighet for nedgradering med MVAC vs GCis var OR 1.84; CI 95% 1.10-3.09 og komplett responsrate OR 2.67; 95% CI 1.50-4.77 Pasienter som fikk MVAC hadde bedre overall overlevelse, men ikke statistisk signifikant (HR 0.44; 95% CI 0.14-1.38) (P=0.16)	**Sjekkliste:** • Formålet klart formulert? **Ja** • Er gruppene rekruttert fra samme populasjon/befolkningsgruppe? **Ja** • Var gruppene sammenliknbare i forhold til viktige bakgrunnsfaktorer? **Ikke fullstendig. Pasienter som fikk neoadjuvant kjemoterapi va generelt litt yngre og hadde i snitt mer avansert tumorstadium.** • Var de eksponerte individene representative for en definert befolkningsgruppe/populasjon? **Ja** • Ble eksposisjon og utfall målt likt og pålitelig (validert) i de to gruppene? **Ja** • Er den som vurderte resultatene (endepunkt- ene) blindet for gruppetilhørighet? **Ikke nevnt i artikkel, men vil ikke ha betydning da endepunkter er definitive og ikke tolkbar.** • Var studien prospektiv? **Nei** • Ble mange nok personer i kohorten fulgt opp? (Attrition bias/follow-up-bias) **Ja, alle pasienter ble fulgt opp.** • Er det utført frafallsanalyser? (Eval. attrition bias) **Nei. Ikke nevnt.** • Var oppfølgingstiden lang nok til å påvise positive og/eller negative utfall? **Ikke aktuelt.** • Er det tatt hensyn til viktige konfunderende faktorer i design/ gjennomføring/analyser? **Ja.** • Tror du på resultatene? **Ja** • Kan resultatene overføres til den generelle befolkningen? **Trolig.** • Annen litteratur som styrker/svekker resultatene? **Ja. Effekten av MVAC på blærekreftpasienter er godt dokumentert.** • Hva betyr resultatene for endring av praksis? **Resultatene forsterker allerede kjent kunnskap om at MVAC er et godt regime for blærekreftpasienter.** **Hva diskuterer forfatterne som:** • **Styrke:** Stort pasientgruppe. • **Svakhet:** noe seleksonsbias innenfor grupper

Referanse: Plimack ER, Hoffman-Censits JH, Viterbo R, Trabulsi EJ, Ross EA, Greenberg RE, et al. Accelerated methotrexate, vinblastine, doxorubicin, and cisplatin is safe, effective, and efficient neoadjuvant treatment for muscle-invasive bladder cancer: results of a multicenter phase II study with molecular correlates of response and toxicity. J Clin Oncol. 2014;32(18):1895-901.			**Studiedesign: Pasientserie** **Grade - kvalitet** Moderat
Formål	**Materiale og metode**	**Resultater**	**Diskusjon/kommentarer/sjekkliste**
Undersøke om neoadjuvant kjemoterapi bestående av metotreksat, vinblastin, doksorubicin og cisplatin (samlet kalt MVAC) kunne bli gitt ila 6 uker (doseintensivert) istedenfor 12 og samtidig være trygt og gi like god tumornedgradering **Konklusjon** Doseintensivert MVAC ble tolerert godt av pasienter og ga samme resultater som 12-ukers regimer når det gjaldt tumornedgradering. **Land** USA **År data innsamling** 2009-2012	**Populasjon** 44 pasienter med urotelial blærekreft grad T2-T4 diagnostisert i tidsrommet desember 2009 til februar 2012. **Utfall – hoved utfall** Gjennomførbarhet av kjemoregime. Tumornedgradering **Viktige konfunderende faktorer** Seleksjonsbias da tumorstadium for pasienter kan være varierende **Statistiske metoder** Two-stage Simon design Kaplan-Meier metoder Log-rank tester Wilcoxon rank sum test	**Hovedfunn** **Effektstørrelse** **CI** 38%; 95% CI, 23-53% hadde ikke lenger påviselig kreft. 53% (95% CI, 37-68%) hadde tumornedgradering til under muskel-invasivt nivå. Kjemoterapi var godt tolerert. 82% rapporterte bare grad 1-2 bivirkninger, som var sammenlignbart med andre studier.	• Er formålet klart formulert? **Ja** • Var studien basert på et tilfeldig utvalg fra en egnet pasientgruppe? **Ja** • Var inklusjonskriteriene klart definert? **Ja. Inklusjon: Urotelialt carcinom i blære med grad T2-T4aM0. Eksklusjon: Creatinine clearance < 50 ml/min. Venstre ventrikkel ejeksjonsfrekvens < 50%** • Var alle pasientene i samme stadium av sykdommen? **Nei. Pasienter var mellom stadium T2-T4a.** • Ble det brukt objektive kriterier for å vurdere/validere endepunktene? **Ja** • Var registreringen prospektiv? **Ja** • Var oppfølgningen lang nok! **Ja, for hovedutfall var det det.** • Var oppfølgningen tilstrekkelig for å nå endepunktene? **Ja, aktuelle endepunkter ble målt.** • Stoler du på resultatene? **Ja** • Kan resultatene overføres til praksis? **Ja. Pasienter kan få doseintensivert MVAC uten betydelig større risiko.** • Annen litteratur som støtter resultatene? • **Ja** Hva diskuterer forfatterne som: • Styrke: **Diskuteres ikke** • Svakhet: **Liten studiepopuplasjon** Har resultatene plausible biologiske forklaringer? **Ja. Blærekreft er dokumentert kjemoterapisensistiv**