UNIVERSITY OF TURKU

NEOADJUVANT CHEMOTHERAPY IN MUSCLE-INVASIVE BLADDER CANCER

Antti Salminen

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
SARJA - SER. D OSA - TOM. 1485 | MEDICA - ODONTOLOGICA | TURKU 2020

UNIVERSITY OF TURKU

NEOADJUVANT CHEMOTHERAPY IN MUSCLE-INVASIVE BLADDER CANCER

Antti Salminen

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
SARJA - SER. D OSA – TOM. 1485 | MEDICA – ODONTOLOGICA | TURKU 2020

University of Turku

Faculty of Medicine
Surgery
Doctoral Programme in Clinical Research
Department of Urology, Turku University Hospital

Supervised by

Adjunct Professor Peter J. Boström
Head of Urology department
Turku University Hospital
Turku, Finland

Reviewed by

Adjunct Professor Jussi Koivunen
Department of Oncology and Haematology
Oulu University Hospital
Oulu, Finland

Adjunct Professor Harri Visapää
Department of Radiotherapy
Helsinki University Hospital
Comprehensive Cancer Centre
Helsinki, Finland

Opponent

Professor, Vesa Kataja
Chief Medical Officer
Kaiku Health Ltd
Helsinki, Finland

The originality of this publication has been checked in accordance with the University of Turku quality assurance system using the Turnitin OriginalityCheck service.

ISBN 978-951-29-8045-1 (PRINT)
ISBN 978-951-29-8046-8 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)
Painosalama Turku, Finland 2020

UNIVERSITY OF TURKU
Faculty of Medicine
Surgery
Department of Urology, Turku University Hospital
ANTTI SALMINEN: Neoadjuvant chemotherapy in muscle-invasive bladder cancer
Doctoral Dissertation, 91 pp.
Doctoral Programme in Clinical Research
April 2020

ABSTRACT

Bladder cancer can be divided into non-muscle-invasive and muscle-invasive types. In the muscle-invasive type of bladder cancer, removal of the bladder and internal genitalia is the cornerstone of treatment. Treatment results can be improved with pre-operative use of chemotherapy (neoadjuvant chemotherapy).

In order to evaluate neoadjuvant chemotherapy associated adverse events and the effect on radical cystectomy related complications, we collected essential clinical and pathological data for all patients treated with or without neoadjuvant chemotherapy during 2005-2014 in Finland. The key findings were that patient selection for neoadjuvant chemotherapy is successful, most severe adverse events can be seen already after the first cycle and the use of neoadjuvant chemotherapy does not increase post-operative surgical complications.

The other objective was to evaluate the potential of Positron emission tomography in combination with Magnetic resonance imaging in the evaluation of the primary staging of bladder cancer and treatment response to neoadjuvant chemotherapy. The key finding was that radical cystectomy cannot be avoided even when a complete radiological response is detected.

KEYWORDS: Bladder cancer, Neoadjuvant chemotherapy, Adverse events, Positron emission tomography/Magnetic resonance imaging, Complications

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Kirurgia
Urologia, Turun yliopistollinen keskussairaala
ANTTI SALMINEN: Neoadjuvantti-kemoterapia lihasinvasiivisen virtsarakkosyövän hoidossa
Väitöskirja, 91 s.
Turun kliininen tohtoriohjelma
Huhtikuu 2020

TIIVISTELMÄ

Virtsarakkosyöpä voidaan jakaa lihakseen invasoivattomaan ja lihakseen invasoivaan tyyppiin. Lihakseen invasoivan syövän hoidon kulmakivi on virtsarakon ja sisägenitaalien poistoleikkaus. Hoitotuloksia kyetään parantamaan leikkausta edeltävällä solusalpaajahoidolla (neoadjuvantti-kemoterapia).

Arvioimme neoadjuvantti-kemoterapiaan liittyviä hoidon aikaisia haittoja sekä kyseisen terapian vaikutusta radikaalileikkauksen jälkeisiin komplikaatioihin. Tutkimusta varten kerättiin keskeinen kliinis-patologinen data kaikista virtsarakon poistoleikkauksessa olleista potilaista Suomessa vuosina 2005–2014. Keskeisimmät löydökset ovat, että potilasvalinta onnistuu hyvin, vakavimmat solusalpaajahoitoihin liittyvät haitat tulevat ilmi heti ja neoadjuvantti-kemoterapia ei vaikuta leikkauksen jälkeisiin komplikaatioihin.

Tutkimme myös positroniemissiotomografian ja magneettiresonanssikuvantamisen tarkkuutta virtsarakkosyövän levinneisyyden ja neoadjuvantti-kemoterapian tehon arvioinnissa. Tärkein havainto on, että radikaalileikkaukselta ei voida välttyä, vaikka kuvantamisella arvioituna solusalpaajahoidon jälkeen ei ole syöpää havaittavissa.

AVAINSANAT: Virtsarakkosyöpä, Neoadjuvantti-kemoterapia, Lääkehaitat, Positroniemissiotomografia/Magneettiresonanssikuvantaminen, Komplikaatiot

Table of Contents

Abbreviations

^{11}C	Carbon eleven
AC	Adjuvant chemotherapy
ACCI	Age-adjusted Charlson Comorbidity Index
AE	Adverse Event
ASA	American Association of Anaesthesiologists scale to evaluate fitness for surgical operations
AUC	Area under receiver operating characteristic curve
BC	Bladder cancer
BT	Bladder tumour
CCI	Charlson Comorbidity Index
CG	Cisplatin – gemcitabine
CI	Confidence interval
CSS	Cancer specific survival
CT	Computed tomography
CTCAE	Common Terminology Criteria of Adverse Events
DCE	Dynamic Contrast Enhancement
dd	Dose dense
DWI	Diffusion Weighted Imaging
EPLND	Extended pelvic lymph node dissection
FDG	2-deoxy-2-[^{18}F]fluoro-D-glucose
FDR	False discovery rate
FWHM	Full width at half maximum
HR	Hazard ratio
LN	Lymph node
LND	Lymph node dissection
LNM	Lymph node metastasis
LRC	Laparoscopic radical cystectomy
MIBC	Muscle-invasive bladder cancer
MMT	Multimodality treatment
MRI	Magnetic Resonance Imaging
MVAC	Methotrexate-vinblastine-doxorubicin-cisplatin

NAC	Neoadjuvant chemotherapy
NCIC	Non continent ileal conduit
NMIBC	Non-muscle-invasive bladder carcinoma
OCNB	Orthotopic continent ileal neobladder
OR	Odds ratio
OS	Overall survival
PAH	Polycyclic aromatic hydrocarbon
PET	Positron Emission Tomography
QoL	Quality of life
RARC	Robot assisted radical cystectomy
RC	Radical cystectomy
RCT	Randomised clinical trial
RT	Radiation therapy
SD	Standard deviation
SM	Secondary malignancy
SUV_{max}	Standardised uptake value
TNM	Tumour Node Metastasis classification
TUR-BT	Transurethral resection of bladder tumour
USPIO	Ultra small paramagnetic particles of iron oxide

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Antti Salminen, Ivan Jambor, Harri Merisaari, Otto Ettala, Johanna Virtanen, Ilmari Koskinen, Erik Veskimae, Jukka Sairanen, Pekka Taimen, Jukka Kemppainen, Heikki Minn[+] and Peter J. Boström[+]. ^{11}C-acetate PET/MRI in bladder cancer staging and treatment response evaluation to neoadjuvant chemotherapy: a prospective multicenter study (ACEBIB trial). *Cancer Imaging* 2018 18–25.

II Antti P. Salminen, Ileana Montoya Perez, Riku Klén, Otto O. Ettala, Kari T. Syvänen, Laura L. Elo, and Peter J. Boström. Adverse events during Neoadjuvant chemotherapy for Muscle Invasive Bladder cancer. *Bladder Cancer* 5 (2019) 273–279.

III Antti P. Salminen, Ilmari Koskinen, Ileana Montoya Perez, Saija Hurme, Teemu J. Murtola, Markku H. Vaarala, Timo K. Nykopp, Marjo Seppänen, Taina Isotalo, Timo Marttila, Lasse Levomäki, Sebastian Becker, Mikael Anttinen, Tapani Liukkonen, Matti Säily, Dimitri Pogodin-Hannolainen, Jouko Viitanen, Christian Palmberg, Juhani Ottelin, Jukka Sairanen, Otto O. Ettala and Peter J. Boström. Neoadjuvant chemotherapy does not increase morbidity of radical cystectomy – a 10-year retrospective nationwide study. *European Urology Oncology* 1 (2018) 525–530

IV Riku Klén[*], Antti P. Salminen[*], Mehrad Mahmoudian, Kari T. Syvänen, Laura L. Elo[+], Peter J. Boström[+]. Prediction of complication related death after radical cystectomy for bladder cancer with machine learning methodology. *Scand J Urol.* 2019 Oct;53(5):325–331

[+]Shared last authorship; [*]Equal contribution

The original publications have been reproduced with the permission of the copyright holders.

1 Introduction

Radical cystectomy (RC) is not a new method for treating bladder cancer (BC). However, it did not become an established treatment method before problems with urinary diversion were resolved. The history of the early years covering diversion aspects is presented nicely by Pannek et al. (1998). During the 1950s, Bricker described a method for ileal conduit diversion still in use today (Bricker 1950). When combining two different organ systems, complications cannot be avoided. Early experiences of the nature of the complications of the Bricker method were described by Butcher et al. (1962) and the nature of the complications has not changed.

Besides the RC operation itself containing many risks, one issue in BC is that without aggressive treatment, muscle-invasive bladder cancer (MIBC) leads to the death of the patient. Even when treated, nearly half of the patients die within five years (Abdollah et al. 2013). One way to improve cancer specific survival (CSS) is to add chemotherapy to the treatment. It can be given either before (neoadjuvant chemotherapy [NAC]) or after RC (adjuvant chemotherapy [AC]). Studies with NAC have been available for three decades, suggesting that for a proportion of NAC responders, bladder preserving strategies could be a viable option (Meyer et al. 2014). However, a key element in selecting patients for bladder preserving strategies is staging accuracy. Metastases can be detected with fairly good accuracy by using conventional cross-dimensional imaging, but regional evaluation of especially the pelvic lymph nodes (LNs) remains challenging.

This thesis is focused on the experience of NAC treatment in Finland. Treatment response to NAC was evaluated using ^{11}C-acetate PET-MRI. A database was constructed to evaluate adverse events (AEs) during NAC treatment and the impact of NAC on post-operative surgical complications. Finally, risk factors to predict early post-operative mortality were identified using a machine learning methodology.

2 Review of the Literature

2.1 Epidemiology and risk factors

Globally BC is recognised as the 6th most common cancer in males and 12th most common in total, with nearly 550,000 new diagnosed cases and causing nearly 200,000 deaths per year (Bray et al. 2018). In Finland, BC statistics are combined with ureteral and pelvic carcinomas, with 1,343 new cases diagnosed in 2017 (Syöpärekisteri 2017). In men, BC is the 4th most common, representing roughly 6% of newly diagnosed cancers (Syöpärekisteri 2017). Men are more commonly affected with distribution between the sexes at 4:1 (men:women) (Bray et al. 2018, Syöpärekisteri 2017). BC is also more common in Western societies (Bray et al. 2018). Possibly this is due to longer life expectancy, but it also correlates with cigarette smoking, which is a known risk factor for BC (Brennan et al. 2000, Brennan et al. 2001). Both duration and quantity matter, with the threshold being 15-20 cigarettes daily, making the pack years definition meaningful (Brennan et al. 2000, Brennan et al. 2001). Cessation of smoking reduces risk, but even after 25 years of abstinence, the risk level does not reach that of a never-smoker (Brennan et al. 2000, Brennan et al. 2001). Other identified risk factors include exposure to certain chemical agents (mineral oils, diesel engine fumes, painting, barber and hairdresser products, aromatic amines and polycyclic aromatic hydrocarbon compounds (PAHs) (Rushton et al. 2010). Similar to cigarette smoking, occupational exposure is a risk factor that can be influenced, leading to risk reduction.

Radiation therapy (RT) has been shown to increase the risk of secondary malignancies (SM) on a population level (Wang et al. 2019). With modern technologies, RT seems to be better tolerated and less harmful; even if SM is detected, it is seldom lethal (Zelefsky et al. 2012).

Chronic infection is a solid risk factor, but the trend in the most commonly known infectious agent, the bilharzia parasite, seems to be in decline (Salem & Mahfouz 2012).

2.2 Diagnosis and staging

With visible haematuria the risk of bladder tumour is 19% (Khadra et al. 2000). The standard diagnostic pathway comprises of urine sample, urine cytological evaluation, cystoscopy and imaging (Babjuk et al. 2019). Staging follows the Tumor Node Metastasis (TNM) classification (Brierley et al. 2017) as demonstrated in Table 1.

Table 1. TNM classification of bladder tumour (8th edition).

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

2.2.1 Histopathology and cytology

Most bladder tumours (BT) (75%) are non-invasive (Burger et al. 2013). All MIBC tumours are however high-grade tumours and strict pathological classifications that are useful in non-muscle-invasive bladder carcinoma (NMIBC) have no or little impact on prognosis in MIBC (Jimenez et al. 2000). Urine cytology alone has no use in MIBC diagnostics as described in the DETECT 1 study (Tan et al. 2019).

Histopathological evaluation was updated in 2016 (Humphrey et al. 2016). It is clear that while the vast majority of BTs are urothelial in origin, there is an abundance of subtypes or histopathological variances especially in invasive tumours

(Humphrey et al. 2016). Currently ten different subtypes have been identified: Nested, Microcystic, Micropapillary, Lymphoepithelioma-like, Plasmacytoid, Sarcomatoid, Giant cell, Poorly differentiated, Lipid rich and Clear cell (Humphrey et al. 2016). Evaluation of these subtypes is vital, since they often behave aggressively and may mimic the metastasis of another primary tumour, as in the plasmocytoid variant (Wang & McKenney 2019).

2.2.2 Cystoscopy and transurethral resection

Ultimately, BT visualization is done with cystoscopy. It is best performed in an outpatient clinic with flexible videoscope under local anaesthesia (Krajewski et al. 2017). However, visualisation of tumour invasiveness is not reliable in cystoscopy. If BT has been visualised by accident on imaging studies done for other purposes, cystoscopy can be left undone and the patient can go straight to the operating room for resection (Witjes et al. 2017).

As a diagnostic procedure transurethral resection of a bladder tumour (TUR-BT) specimen should contain muscle to reveal possible invasion. This is best done by separate sample of the tumour bed, or in the absence of muscle in the specimen, a re-TUR-BT is advisable (Witjes et al. 2017).

2.2.3 Cross-sectional imaging

Computed tomography (CT) is an anatomical imaging method, reliable, fast, and easily accessible. CT-urography is accurate in visualisation of BT with accuracy of 92.8% (Capalbo et al. 2015). An adequate imaging protocol has a key role in BT identification – BTs should have enhancement and are more likely focal than expressing diffuse bladder wall enhancement (Raman & Fishman 2017). However, with a macroscopic imaging method like CT, microscopic invasion through the bladder wall is impossible to detect and CT's main utility is to visualise local spread and distant metastases (Witjes et al. 2017).

In LN evaluation, CT also relies on the size of the LN, which is problematic, since LN metastases (LNM) may also be present in normal size LNs. The accuracy of CT in LNM detection is approximately 83%, with poor sensitivity, 53% (Horn et al. 2016).

Magnetic resonance imaging (MRI) is a radiation free, non-invasive, safe imaging modality (Sammet 2016). The use of intravenous contrast medium is optional and tissue contrast can be modified with different sequences. The diagnostic performance (sensitivity and specificity) of MRI in MIBC evaluation has been reported to be 0.92 (95% confidence interval [CI] 0.88–0.95) and 0.87 (95% CI 0.78–0.93) in a systematic review and meta-analysis (Woo et al. 2017). Overall accuracy

has been reported in a prospective MRI study utilising dynamic gadolinium contrast enhancement (DCE). The study enrolled 122 patients and overall accuracy in MIBC evaluation was 74% (Daneshmand et al. 2012).

In LN evaluation, functional applications, such as diffusion weighted imaging (DWI) improve detection of LNM compared to standard cross-sectional imaging (Thoeny et al. 2014). Overall sensitivity is 56% and specificity 87% in a systematic review and meta-analysis (Woo et al. 2018). Daneshmand et al. had 27/122 (22%) LNM-positive patients. The overall accuracy of DCE-MRI in LN positivity evaluation with correlation to histopathology was 80.3%. However, the false negative rate was as high as 59% (Daneshmand et al. 2012).

2.2.4 Positron emission tomography

Positron emission tomography (PET) is accompanied by an anatomical imaging method, such as CT. In urology PET has gained popularity, but current evidence does not support routine use in BC diagnostics (Rauscher et al. 2018). Although pooled sensitivity 0.82 (95% CI, 0.75 to 0.88) and pooled specificity 0.92 (95% CI, 0.87 to 0.95) values have been reported by Zhang et al. 2015, PET is considered most useful in search of metastases; that is to select patients for NAC and to avoid RC on patients with metastases (Kibel et al. 2009). In LN imaging, the performance of PET-CT relies too much on LN size and is not recommended (Pichler et al. 2017). One critical issue in PET imaging is that the most commonly used 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}F-FDG) is secreted in urine, making its use especially in BC diagnostics problematic (Agarwal et al. 2016).

Other tracer options in BC diagnostics include carbon-eleven (^{11}C)-choline and ^{11}C-acetate which are not secreted in urine. Preliminary results with ^{11}C-choline were promising in BT evaluation, but LN evaluation left room for improvement in a 27-patient prospective series by Picchio et al. 2006. Another small study nearly a decade later showed similar results with a sensitivity of 42% and specificity of 84% in LN imaging (Brunocilla et al. 2014).

^{11}C-acetate has been evaluated in two prospective studies (Schöder et al. 2012, Vargas et al. 2012) with a total of 33 patients. Schöder et al. reported promising results, but underlined interpretation difficulties if prior instillation therapies to the bladder had been used. Vargas et al. verified this finding and reported similar results with ^{11}C-acetate PET-CT vs. MRI vs. CT alone.

^{11}C-choline PET-CT and ^{11}C-acetate PET-CT have been compared in one 14-patient series, with similar performance (Orevi et al. 2012). The slight difference was that the standardised uptake value (SUV_{max}) was higher in BT with ^{11}C-choline and higher in LN with ^{11}C-acetate (Orevi et al. 2012). Since BT evaluation eventually relies on histopathological diagnosis, the special emphasis of ^{11}C-acetate and ^{11}C-

choline has been in LN imaging. A systematic review and meta-analysis by Kim et al. (2018) sums up PET-CT's capability in LN imaging with these two tracers nicely: sensitivity is low and specificity moderate.

PET has been combined with MRI in only one study using ^{18}F-FDG as a tracer (Rosenkranz et al. 2017).

2.3 Surgical treatment

Most bladder tumours are local and organ-preserving strategies may be utilised (Burger et al. 2013, Babjuk et al. 2019). In small non-invasive tumours even an outpatient procedure may be a viable option (Rivero Guerra et al. 2018). In MIBC this is not the case.

2.3.1 Transurethral resection of bladder tumour (TUR-BT)

Surgery starts with endoscopic procedures. In the case of MIBC the strategy of performing TUR-BT differs from that of NMIBC. There are three strategies:

1. Total removal of bladder tumour and possible satellites with intent to cure
2. Adequate biopsy material for identification of tumour histology and depth of invasion
3. Palliative coagulation of bleeding tumours in patients unfit for radical surgery.

In MIBC patients TUR-BT alone is mainly a diagnostic tool; as a monotherapy modality for highly selected patients, it has been suggested in only a few studies (Herr 1987, Solsona et al. 1992, Solsona et al. 2010). However the guideline recommendation is strong to avoid TUR-BT as a sole treatment (Witjes et al. 2017).

Surgical complications of TUR-BT are common with roughly 30% prevalence and include haematuria, infection and bladder perforation (Avallone et al. 2017). Death is however rare (0.1–0.5%) (Liem et al. 2018, Avallone et al. 2017). Bipolar resection may be safer than monopolar resection (Avallone et al. 2017, Bolat et al. 2016, Bolat et al. 2018, Mahmoud et al. 2019). Although the total number of complications may be greater in bipolar TUR-BT, severe complications are more often seen with monopolar TUR-BT (Liem et al. 2018). Adding intraoperative instillation of a chemotherapeutic agent is not beneficial with MIBC patients and thus chemotherapy-related complications can be avoided (Nieuwenhuijzen et al. 2003, Elmamoun et al. 2014).

2.3.2 Radical cystectomy and pelvic lymph node dissection

In NMIBC patients RC may be a viable option for cancer treatment, but not the primary option (Babjuk et al. 2019). In MIBC RC should follow NAC in eligible patients (Witjes et al. 2017). Standard RC consists of removal of the bladder and distal ureters accompanied by adequate LN dissection. The operation includes removal of the prostate and seminal vesicles in men and removal of the urethrae, uterus and anterior wall of the vagina in women (Stenzl et al. 2005). Recently, however, a prostate-sparing method has been described as an alternative for maintaining continence and sexual function (Mertens et al. 2014). In females, continent neobladder with pelvic organ preservation has been studied in systematic review with a positive functional outcome (Veskimae et al. 2017). Currently, organ preservation techniques are not as strongly recommended in women as in men and patient selection is of critical value (Witjes et. al 2017).

RC is accompanied by pelvic lymph node dissection (PLND). The standard PLND boundaries are the distal common iliac artery proximally, the genitofemoral nerve laterally, the inguinal ligament distally and the bladder wall medially (Herr et al. 2004). The extended (EPLND) template includes the sacral nodes and the proximal boundary is aortic bifurcation or in some instances even slightly above (Herr et al. 2004). EPLND is normally suggested for better staging (Simone et al. 2013). The template follows the lymphatic spread pathways described by Roth et al. (2010). Even in the presence of micro metastases or known positive LNs, cure is possible (Karl et al. 2009). But, although staging may be more accurate by expanding the LN template to extended, only the rate of complications increases (Gschwend et al. 2019) without improvement in CSS (Zehnder et al. 2011).

In Finland, RCs have mainly been done as open surgery. Laparoscopic RC (LRC) and robotic-assisted laparoscopic RC (RARC) have gained popularity as less invasive methods and have been shown to be equal in terms of oncological outcome (Kim et al. 2016). The CORAL study is a prospective RCT with 60 patients randomised to RC, LRC or RARC. There was no difference in 5-year surveillance (Khan et al. 2019). A recent systematic review and meta-analysis shows a similar tendency (Albisinni et al. 2019). More data is awaited from the Dutch RACE-study which should be completed in the near future (Wijburg et al. 2018).

Removal of the bladder requires urinary diversion. Various techniques for urinary diversion have been described (Hautmann et al. 2007). Each has its pros and cons and complication profiles of different diversion methods have been evaluated recently by Faba et al. (2018) and Anderson & McKiernan (2018). In Finland mainly non-continent ileal conduit (NCIC) and orthotopic continent ileal neobladder (OCNB) have been used.

2.4 Chemotherapy

One particular problem with MIBC is that staging is inaccurate (Shariat et al. 2009, Türker et al. 2012). Differentiation of T2b or T3a tumours is virtually impossible with imaging. In order to improve CSS, NAC is suggested for all MIBC patients eligible for platinum (Witjes et al. 2017).

2.4.1 Neoadjuvant chemotherapy

NAC should be platinum-based (Witjes et al. 2017, Chang et al. 2017). Although NAC treatment for BC started as early as in the 1980s, it was not until 2006 that the cisplatin-gemcitabine (CG) regimen was introduced (Hermans et al. 2017). In Finland methotrexate-vinblastine-doxorubicin-cisplatin (MVAC) has not been widely utilised, but CG started in Turku 2008 and has gained popularity. All key randomised clinical trials (RCTs) have however been done with other regimens than CG (Hermans et al. 2017, Yin et al. 2018). Only three prospective studies with CG exist (Osman et al. 2014, Khaled et al. 2014, Iyer at al 2018) accompanied by one systematic review covering seven retrospective studies and one phase II study (Yuh et al. 2013). Despite the modality, NAC has been shown to improve survival in study populations (Yin et al. 2018). These results do not necessarily correlate with daily clinic populations, where overall survival (OS) benefit could not be shown (Hanna et al. 2018). But NAC is strongly recommended by the guidelines as a standard of care in MIBC (Witjes et al. 2017). The overall efficacy of NAC is presented in Table 2.

Table 2. NAC + RC compared to RC alone. Adopted from Advanced Bladder Cancer (ABC) Meta-analysis collaboration (Collaboration A.B.C.A.M-a 2005).

Modality	OS improvement	CSS improvement
SAP	-5% (-14–4%)	-5% (-16–7%)
PBC	5% (2–9%)	9% (5–12%)

SAP = Single agent platinum; PBC = Platinum based combinations

Common adverse events (AEs) caused by platinum compounds include haematological, renal, vascular, ototoxic and neural damage (Oun et al. 2018). Nearly all (90%) patients have at least grade 1 AEs (Iyer et al. 2018). In the comparison of different NAC regimens, Grade 3 to 4 toxicity rates for ddMVAC (32%) and CG (44%) have been reported as significantly lower than for the classic MVAC regimen (55%) (Hermans et al. 2018). A CG NAC dd regimen however seems to increase AEs (Anari et al. 2018). The NAC regimen typically used in Finland contains three or four cycles of CG with three weeks interval compared to

the dd protocol executed in two weeks (Anari et al. 2018). The standard dosing of one cycle is
Day 1: cisplatin 75mg / m² + gemcitabine 1000mg / m²
Day 8: gemcitabine 1000mg / m²

2.4.2 Adjuvant chemotherapy

Five-year survival in MIBC for organ confined disease is roughly 70%, but with local spread to LNs only 36% (SEER). LN-positive BC is seen in 18-28% of MIBC-patients (Stein & Skinner 2006). While LN positivity has a clear impact on survival, the majority of MIBC patients are LN-negative and in organ confined disease RC only gives comparable results to NAC + RC (Malmström et al. 1995).

AC has the benefit of avoiding unnecessary chemotherapy, since NAC is always started based on more-or-less inaccurate staging (Hermans et al. 2017). However, 30% of RC patients may suffer from surgery related complications that prohibit the use of AC (Donat et al. 2009).

Node-positive patients have been shown to benefit most from AC in terms of progression-free survival (Leow et al. 2014). However, this does not affect OS (Sternberg et al. 2015). This may be due to the fact that some LN+ patients may be cured with surgery alone (Zehnder et al. 2014). At the moment, guideline recommendations suggest AC for pT3/4 and/or pN+ patients, who have not received NAC (Witjes et al. 2017).

2.4.3 Other treatment options

Radiotherapy (RT) of the bladder is mainly reserved for older frail people unfit for surgery (MacHaffie et al. 2016). A combination of chemotherapy and RT has worse results compared to NAC + RC, but for patients who tolerate this treatment, organ preservation is possible (Lin et al. 2018). The rationale is to improve quality of life (QoL) with organ preservation and thus it is not suggested for patients with poor bladder function (MacHaffie et al. 2016). One method to effectively reduce bowel irradiation is adaptive radiotherapy (Tuomikoski et al. 2011).

In multimodality treatment (MMT), TUR-BT is accompanied by chemotherapy and radiation therapy (RT) with special emphasis on bladder preservation and QoL (Ploussard et al. 2014). MMT seems to be comparable to RC (García-Perdomo et al. 2018, Kulkarni et al. 2017). Although MMT seems to be comparable to RC, the possibility to salvage RC should be discussed already when deciding treatment strategy (Leow et al. 2019). Palliative purposes are not in the context of this thesis.

The current medical therapy comprises platinum-based chemotherapy. Immunological programmed cell death protein 1 / ligand 1 (PD-1) / (PD-L1)

checkpoint inhibitors have shown potential in a metastatic setting (Lattanzi & Balar 2019). With this promising experience, these immunological drugs have also been started to be studied in NAC setting.

One study (PURE-1) evaluated pembrolizumab in a neoadjuvant setting for MIBC patients with variant histology (Necchi et al. 2019). Lymphoepithelioma-like and squamous cell bladder carcinoma patients were most likely to benefit; a similar response was not seen in other types of MIBC (Necchi et al. 2019).

Two studies are recruiting platinum-ineligible patients [NCT03234153 (durvalumab and tremelimumab) and NCT03520491 (nivolumab and ipilimumab)]. The NCT03732677 "NIAGARA" study is designed to add durvalumab to perioperative medical treatment [Durvalumab + CG (NAC) and Durvalumab (AC)]. Results are awaited in 2021-2025.

3 Aims

The specific aims of the thesis were:

1) To evaluate NAC treatment response with novel ^{11}C-acetate PET-MRI with surgical pathology as a reference.
2) To evaluate AEs during NAC treatment and identify possible risk factors for poor tolerance.
3) To analyse the effect of NAC on early post-operative complications of RC.
4) To identify potential risk factors predicting early post-operative mortality after RC using a deep learning methodology.

4 Materials and Methods

4.1 PET-MRI (Study I)

The study (Acetate PET-MRI and Biomarkers in Bladder cancer, ACEBIB) was carried out as a prospective multicentre study. The participating centres were Turku University Hospital, Helsinki University Hospital and Tampere University Hospital. The ethical committee of the Hospital District of Southwest Finland approved the study. The study was registered at ClinicalTrials.gov (NCT01918592). The study was conducted in compliance with the current revision of the Declaration of Helsinki guiding physicians and medical research involving human subjects. Patient recruiting was organised in urological outpatient units in all participating hospitals. Inclusion and exclusion criteria are presented in Table 3.

Table 3. Inclusion and exclusion criteria in the ACEBIB study.

Inclusion criteria	Exclusion criteria
Age: 18 to 85 years old	History of serious cardiovascular, liver or kidney disease
Language spoken: Finnish or Swedish	Uncontrolled serious infection
Invasive or locally advanced bladder cancer based on cystoscopical evaluation.	Contraindications for MRI (cardiac pacemaker, intracranial clips, etc.)
Mental status: Patients must be able to understand the meaning of the study	Patient refusing radical cystectomy or chemotherapy
Informed consent: The patient must sign the appropriate Ethical Committee approved informed consent documents in the presence of the designated staff	Intravesical Bacillus Calmette-Guerin instillations within 6 months

The PET-MRI imaging was performed using the Philips Ingenuity PET-MRI system. Initially, data for attenuation correction was obtained followed by T2-weighted turbo spin echo and T1-weighted anatomic imaging in the axial, sagittal and coronal directions. Diffusion weighted imaging (DWI) was obtained with single-shot spin-echo echo-planar imaging followed by gadolinium-enhanced T1-weighted imaging. After acquiring the MRI data, the patient's table was rotated to continue with PET

imaging. Two table positions covering the whole pelvis were acquired. The sinogram data was corrected for dead time, decay and photon attenuation and reconstructed in a 256 x 256 matrix. Image reconstruction followed a fully 3-D maximum-likelihood ordered subset. The expectation maximum algorithm incorporated random and scatter correction with 2 iterations and 28 subsets. The final in-plane full width at half maximum (FWHM) was about 6 mm.

The remote-controlled and automated synthesis of ^{11}C-acetate used in PET scan was prepared from ^{11}C carbon dioxide and methyl magnesium bromide with the radiochemical purity of the final product ≥98%. The synthesis method followed the method originally described by Pike et al. (1982). A detailed description of the synthesis is available as Quality Document MET4500 on the PET Centre Intranet.

Bladder filling was standardised by catheterisation. Before imaging, the bladder was emptied and filled with 100cc sterile saline. After PET, the bladder was emptied, radioactive urine was disposed of and the bladder was filled with 100cc sterile saline. After imaging, the bladder was emptied and the catheter removed. The isotope was injected via a G20 i.v. cannula, which was inserted into the v. cephalica of the non-dominant hand. The activity of the isotope was documented to ensure adequate image quality.

All images were evaluated by experienced radiologists and isotope physicians using the template described in Study I for LN areas.

After imaging, a complete TUR-BT was executed by an experienced urologist in the treating hospital in primary staging and the RC & EPLND pathology was analysed to estimate the NAC treatment response. The pathology specimen was investigated by an experienced uropathologist. Imaging results were compared to the pathology, which served as a ground truth.

4.2 Finnish Radical cystectomy database (Study II & III)

The database is a secure Internet application created for the collection of essential clinic-pathological data of RC patients operated on all Finnish hospitals. Basic requirements and technical requirements – provided by Turku University – are presented in Table 4.

Table 4. Basic and technical requirements of the Finnish Radical Cystectomy Database.

Basic requirements	Technical requirements
Patient privacy and confidentiality are protected	Web Server
Data integrity is maintained	URL Domain
Data input is user-friendly	Python 3.3
Application is flexible and maintainable	Django 1.6
Application is secured for authorised users only	PostgreSQL 9.3.4
Access is controlled with user privileges[1]	PyCharm 3.1

[1]Standard user can see only own centre's data. Main researcher can compare different centres.

System security was vital. All inputted data was coded and no personal data was collected. Authentication and authorisation of users were implemented to preserve patient confidentiality, which was not jeopardised in any way. To prevent attacks and unauthorised disclosure of data that could risk the integrity and availability of the data, the following security considerations were applied. All users who had access to the system needed a valid username and password. The use of the system was controlled, with authorised users having explicit privileges and able to perform only specific tasks. Moreover, during the development of the web application, concepts such as CSRF (Cross Site Request Forgery), SQL injection, input validation and output escaping, among others were taken into account to avoid security holes and different types of tests were performed during development and before deployment allowing security assessment of the web application.

Patients were identified by their diagnosis number (ICD-10) [C67*] or NCSP (Nordic Classification of Surgical Procedures) code [KCC*]. Data collection involved all 16 hospitals that performed RCs in Finland during the observation period covering 2005–2014 and was inputted retrospectively. Study II was designed to evaluate AEs during NAC treatment and identify potential risk factors forecasting AEs during NAC treatment. NAC-associated AEs were reported using Common Terminology Criteria for Adverse Events (CTCAE) v. 5.0 2018 (available on the Internet https://ctep.cancer.gov/protocoldevelopment/.../ctcae_v5_quick_reference_5x7.pdf). Study III was designed to evaluate the effect of NAC on early post-operative complications of RC. Complications were reported by Clavien classification (Dindo et al. 2004). The collected data parameters are presented in Table 5.

Table 5. Complete list of variables collected in the Finnish radical cystectomy database.

Type of Data	Variable	Measure
Basic characteristics	Date of birth	
	Gender	Male / Female
	Height	cm
	Weight	kg
	Smoking, status	current, former, never
	Smoking, quantity	pack years
	ASA class	
	CCI	
	Body mass index	kg/m^2
	Centre	
Tumour characteristics	TUR-BT histology	
	TUR-BT grade	WHO 1973, WHO/ISUP 2004
	TUR-BT T-category	
	cTNM	
	RC Histology	
	RC TN category	
Neoadjuvant chemotherapy	Start date	
	Regimen	
	Number of cycles	
	Clinical response	
	Adverse events	CTCAE v.5
Radical cystectomy	Date of surgery	
	Haemoglobin	mg/l
	Creatinine	µmol/l
	Surgeon	
	Type of diversion	
	Duration	minutes
	Blood loss	ml
	Transfusions	number of units
Post-operative care	In-hospital stay	days
	Transfusions	number of units
	Anticoagulation prophylaxis	Type, duration (days)
Adjuvant therapy	Chemotherapy (if given)	Regimen, cycles
	Radiation (if given)	Dose, (Gy)
Complication / Adverse events	Treatment phase	NAC, RC, post-operative
	Date	
	Severity	Grade (Clavien class)
	Affected organ system	

4.3 Machine-learning methodology to predict mortality (Study IV)

A machine-learning project was created for identification of potential pre-operative risk factors to predict early post-operative mortality. The pre-operatively available RC data was utilised. After random division of the data into testing data (33.3%) and training data (66.7%), the model-building was done in two stages. In the first stage, the training data was used to build 100 lasso logistic regression models using 10-fold cross-validation to minimise the cross-validation error. In the second stage, variables for the final model were added one by one based on the frequency of their occurrence in these 100 models until the area under the receiver operating characteristic curve (AUC) in the training data no longer increased. In the second stage, 10-fold cross-validation was used. The ASA class and age-adjusted Charlson co-morbidity index (ACCI) were divided into low and high groups: ASA classes into 1–2 and 3–4, ACCI into 0–4 and 5–12.

4.4 Statistical analysis

Study I Performance of ^{11}C-acetate PET-MRI for BT staging was evaluated in 15 treatment-naïve patients. The classification was performed in a binary class for clinical relevance: benign + NMIBC (Ta, Tis, T1) vs MIBC (T2-T4). NAC response was evaluated for five patients who underwent RC and EPLND. LNs were evaluated by patient level and with regional classification (10 regions of interest, in total 50 regions) between benign vs. malignant LNs. Sensitivity, specificity and accuracy were calculated. Ninety-five percent CI for AUC values were calculated from 100 000 bootstrap samples using the trapezoid rule. Standardised uptake value (SUV) measurements were compared using the Bonferroni multiple comparison test (DeGroot & Schervish 2011). The statistical analysis was performed using MATLAB (version r2013a, The MathWorks Inc, Natick, MA).

Study II Spearman correlation between AEs and 22 clinical variables was calculated. P-values were corrected for multiple testing by controlling false discovery rate (FDR) using the Benjamini-Hochberg method (Benjamini & Hochberg 1995). Statistical analysis was done using R (R Core Team 2017).

Study III The material was divided into three cohorts and different analyses were applied to the cohorts to comprehensively analyse the effect of NAC on post-operative complications.

Simple binary logistic regression and multivariable logistic regression analyses were utilised in *Entire cohort* analyses, where all RC patients were compared to NAC + RC patients.

The *Neoadjuvant era cohort* was first analysed using a simple logistic regression model. Next, a multivariable stratified logistic model with propensity score was

calculated using the variables patient age, gender, BMI, ASA class, CCI score, tumour histology, stage and grade (WHO 1973 or 2004) from the TUR-BT specimen, hospital volume, and glomerular filtration rate. The propensity score was categorised into five groups based on the quintiles and that variable was used in the multivariable stratified logistic model as a stratum. The results of the models were also adjusted for volume of hospital (three categories: high, medium and low), CCI score and age.

The third cohort was *cognitively matched* – patients fit for NAC based on characteristics but operated on before NAC was initiated in Finland – compared to NAC patients. A simple logistic regression model and multivariable stratified logistic regression analysis were performed.

All analyses were made for all complications (Clavien grades 1–5), severe/major complications (Clavien grades 3–5) and deaths (Clavien grade 5). Continuous variables were characterised using means and standard deviations (SD) or range of values, and in the case of categorical variables, frequencies and percentages were used. The results of the analyses were quantified using odds ratios (ORs) with 95% CI. P-values less than 0.05 were considered statistically significant. Statistical analyses were carried out using the SAS system for Windows, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

Study IV Twenty-two pre-operatively available variables were individually tested to reveal correlation with variable and early (90d) post-operative mortality. Numerical variables were tested with the Wilcoxon rank sum test and categorical variables with the chi-squared test. The false discovery rate (FDR) to eliminate false correlations was adjusted using the Benjamini–Hochberg procedure (Benjamini & Hochberg 1995).

Hazard ratios (HR) for each variable in the training data were estimated using the Cox proportional hazards regression. The Cox proportional hazards regression in the testing data was done using R package survival (R Core Team 2017) and the model-building and statistical analysis were performed using the R statistical computing environment (version 3.4) (R Core Team 2017). The R package *glmnet* was used for logistic regression model with lasso regularisation (Friedman et al. 2010, Therneau et al. 2000, Therneau 2015).

5 Results

5.1 PET-MRI in treatment response evaluation (Study I)

Eighteen patients were enrolled, 15 in primary tumour evaluation and 5 in NAC treatment response evaluation. Two patients attended both phases of the study. Despite careful and hygienic catheterisation, three patients developed urinary tract infections. Cannulation was successful on all patients. NAC-associated AEs were not documented and it was not necessary to make dose adjustments to anticancer drugs or postpone cycles. Basic characteristics of the study population are presented in Table 6.

Table 6. Study population in the ACEBIB study.

	Primary tumour	**NAC response**
Number of patients	15	5
Gender (male / female)	13 / 2	5 / 0
Age (Years) Mean (range)	67 (55–79)	65 (57–69)
ASA Mean (range)	2 (1-3)	2
BMI (kg/m^2) Mean (range)	27 (23–31)	26 (23–30)

Primary staging (n=15):

All primary tumours were urothelial cancers and demonstrated positive uptake of ^{11}C-acetate. The median maximum standardised uptake value (SUVmax) was 2.9 (range, 1.3–4.7). There was no difference between the SUVmax of MIBC versus NMIBC. The sensitivity, specificity, accuracy and the AUC (95% CI) values of ^{11}C-acetate PET-MRI for the detection of MIBC (primary BT staging) were 1.00, 0.69 and 0.73, and 0.85 (0.55–1.00). None of the MIBC patients were understaged.

Evaluation of therapy response to NAC (n=5):

Compared to histopathology, ^{11}C-acetate PET-MRI correctly staged three patients, overstaged one and understaged one patient. True negative findings in BT were reported in two patients and true positive in one patient. The performance of PET-MRI in NAC treatment response evaluation is presented in Table 7.

Table 7. PET-MRI in NAC treatment response evaluation compared to RC histopathology (n=5).

Patient	PET-MRI		RC	
	Primary tumour (T)	LNM[1]	Primary tumour	LN ntot / n+[2]
1	T0	Yes	T0	27 / 0
2	T4	Yes	T2	42 / 3
3*	T0	No	T3	27 / 9
4	T0	No	T0	43 / 0
5	T3	No	T2	36 / 0
				175 / 12

[1]LNM = Lymph node metastasis present yes / no; [2]LN ntot / n+ = total amount of Lymph nodes removed / cancer-positive lymph nodes *The patient had bilateral hip prostheses, which distorted the image quality

Lymph node metastasis detection:

The sensitivity, specificity and accuracy of ^{11}C-acetate PET/MRI for the detection of LN metastases on the predetermined 10 nodal areas were 0.2, 0.96, 0.88, respectively, and the AUC (95% CI) value was 0.58. The corresponding values on a patient level were 0.5, 0.67, 0.6, and 0.58.

5.2 Adverse events during NAC treatment (Study II)

Thirty-one percent of MIBC patients were assigned to NAC during the observation period. The total number of patients in the final analysis was 229. Basic characteristics of the study population are presented in Table 8.

Table 8. Basic characteristics of the study population in NAC-related AEs.

Variable	Description		
Gender	Male Female	N (%)	189 (83) 40 (17)
Age	Years	Mean (range)	65 (44–81)
BMI	kg / m^2	Mean (range)	26 (16–39)
ASA	1–2 3–4 Unknown	N (%)	96 (42) 105 (46) 28 (12)
ACCI		Mean (range)	4 (1–10)
NAC modality	Cis – gem Car – gem Other	N (%)	205 (90) 16 (7) 8 (3)
Cycles	number	Mean (range)	3 (1–6)
Clinical response to NAC	Yes No (stable disease) Progression Lack of tolerance Unknown	N (%)	111 (48) 42 (18) 9 (4) 31 (13) 36 (16)

105 patients (46%) had no AEs and 124 (54%) had AEs. Severe (grade 3–5) AEs were seen in 33% of patients, one death occurred and the operation was cancelled for four patients. Ninety-seven point five per cent of patients were eligible for RC after NAC treatment. The distribution of different AEs based on severity by CTCAE are presented in Table 9. Although one patient may suffer from many AEs, only the most severe AE / patient is reported in the table 9.

Table 9. Distribution of AEs during NAC treatment by CTCAE grade.

Severity	N=229	%
0	105	46
1	17	7
2	31	14
3	49	21
4	26	11
5	1	0.5

The only statistically significant correlation with the pre-operatively available 22 investigated variables was found between number of NAC cycles delivered and AEs. The correlation -0.37 refers to the low number of cycles $P<0.001$. This negative correlation was confirmed using FDR. All investigated variables and FDR-corrected correlations are presented in Table 10.

Table 10. Correlation between 22 pre-operatively available variables and AEs during NAC.

Variable	Correlation coefficient	P-value
Number of cycles	– 0.37	<0.001
Renal disease	0.17	0.052
Cerebrovascular disease	– 0.13	0.205
Rheumatoid disease	– 0.13	0.229
Peripheral arterial disease	0.12	0.239
Myocardial infarction	– 0.11	0.257
Heart insufficiency	0.10	0.359
Body mass index	– 0.10	0.371
Age	0.06	0.442
Height	0.08	0.442
ASA class	0.07	0.442
Smoking, pack years	0.08	0.442
Dementia	0.06	0.442
Chronic pulmonary disease	– 0.08	0.442
Peptic ulcer	0.06	0.442
Liver disease	– 0.07	0.442
Leukaemia	– 0.07	0.442
CCI score	– 0.06	0.470
Other solid tumour	– 0.03	0.747
ACCI	0.03	0.747
Diabetes	– 0.01	0.860
Weight	0.00	0.960

5.3 Effect of NAC on post-operative complications (Study III)

We were able to collect data for 1402 RC patients in the database. Due to missing values, 17 patients were excluded and the total study population constituted 1385 patients: 1171 in the RC-only population and 214 in the NAC+ RC population. The population was divided into cohorts: RC only, NAC + RC, RC only during NAC era and a cognitively matched cohort of RC patients from the pre-NAC era. Basic characteristics of the study population and cohorts is presented in Table 11.

Table 11. Basic characteristics of the RC database population and study cohorts.

Variable			Entire cohort			NAC era	Matched cohort
			Total	RC	NAC+RC	RC	RC
Patients		n	1385	1171	214	522	231
Age	Years	Mean (SD)	67.9 (9.2)	68.5 (9.3)	64.5 (7.6)	69.5 (9.4)	65.0 (7.8)
Gender	Male	%	80	79	82	80	78
	Female		20	21	18	20	22
BMI	kg / m^2	mean (SD)	26.5 (4.6)	26.5 (4.7)	26.3 (4.0)	26.5 (4.7)	26.3 (4.0)
ASA	1-2	%	38	37	44	29	52
	3		45	46	41	53	39
	4		4	5	1	5	2
	Unknown		12	12	14	13	7
Histology	Urothelial	%	87	85	94	88	84
	Other / unknown		13	15	6	12	16
cTcategory	MIBC	%	61	57	83	57	60
	NMIBC / unknown		39	43	17	43	40
eGFR		median	69	68	72	65	75

The total rate of complications was 61%: 65% of complications occurred in hospital and 35% after hospital discharge. Of the complications, Clavien 3–5 (severe) were seen in 56% and Clavien 1–2 (minor) in 44%. Mortality of RC was 4.0% in RC-only patients and 1.9 % in NAC + RC patients. NAC did not increase early post-operative complications in any of the investigated three cohorts. A detailed description of the risk of complications and the use of NAC in three different cohorts is presented in Table 12.

Table 12. Risk of post-operative complications. NAC + RC was compared to RC only in three different patient cohorts and statistical analyses. Complications were presented with five-tiered Clavien grade (Dindo et al. 2004).

Cohort	**Total study population**		**NAC era**		**Matched cohort**	
No of patients	N=1385 RC=1171, NAC+RC=214		N=736 RC=552, NAC+RC=214		N=445 RC=231, NAC+RC=214	
Statistical method	Multivariable logistic regression analysis		Multivariable stratified logistic model with propensity score		Multivariable stratified logistic regression analysis	
Complication group	OR	P-value	OR	P-value	OR	P-value
All (1-5)	1.05 (0.73 to 1.50)	0.804	0.73 (0.48 to 1.12)	0.151	1.32 (0.89 to 1.98)	0.168
Major (3-5)	0.69 (0.47 to 1.03)	0.068	0.56 (0.35 to 0.87)	0.010	0.78 (0.47 to 1.30)	0.339
Death (5)	0.79 (0.29 to 2.13)	0.639	0.62 (0.18 to 2.1)	0.439	0.57 (0.11 to 2.87)	0.493

5.4 Identification of novel risk factors to predict post-operative mortality (Study IV)

Twenty-two pre-operatively available variables presented in Table 10 were tested and only four had a statistically significant impact on risk of early post-operative death. These were:

1) ASA (HR 2.63, 95% CI: 1.14–6.09, P = 0.02)
2) ACCI (HR 4.02, 95% CI: 1.41–11.46, P = 0.009)
3) Chronic heart insufficiency (HR 4.86, 95% CI: 2.18–10.81, P = 0.0001)
4) Chronic pulmonary disease (HR 3.02, 95% CI: 1.46–6.26, P = 0.003)

Chronic heart insufficiency and chronic pulmonary disease were identified as independent novel risk factors.

6 Discussion

6.1 Evaluation of treatment response to NAC

We evaluated primary tumours as shown in **Study I** and cannot recommend the use of PET-MRI in that context. Although PET-MRI was sensitive and did not understage any patient, adding PET to the current standard of staging is unnecessary, since pathological evaluation of BT and possible muscle invasion is more accurate and the decision on whether cystectomy is required or not cannot be based on imaging alone. The main interest was in the evaluation of treatment response to NAC.

Complete pathological response (pT0 finding in RC specimen) is considered to reflect good prognosis (Petrelli et al. 2014). A NMIBC residual has not been reported to worsen the prognosis (Zargar et al. 2016). On the other hand, if there is no carcinoma left, why remove the bladder at all? This rationale has been behind MMT protocols. We evaluated treatment response to NAC with novel imaging (**Study I**). In MMT, imaging should have been replenished with TUR-BT and RT would have been given. Since TUR-BT does not include LND, re-staging of the bladder remains local; in LN evaluation, even in MMT, all depends on imaging.

We selected ^{11}C-acetate as a tracer. In a small comparison study it showed greater SUV_{max} in LNs, making it a logical selection for LN evaluation (Orevi et al. 2012). We chose MRI for anatomical imaging, because it is shown to be superior compared to CT in soft tissue (Barentsz et al. 1996). Each study subject received conventional CT after two cycles of NAC to exclude progression during NAC based on normal clinical praxis; by using MRI we were also able to avoid unnecessary radiation from repeated CT scans.

Concerning MRI, the use of ultra-small paramagnetic particles of iron oxide (USPIO), Ferumoxtran® has been interesting in terms of LN imaging, since it can also detect LNM in normal-sized LNs (Birkhauser et al. 2013). Approximately 30% of LNMs are however missed with this application, too (Birkhauser et al. 2013). Moreover, this MRI application is not clinically available, is very laborious and AEs can be seen in 11% of patients, which is not necessarily acceptable for a diagnostic investigation (Triantafyllou et al. 2013). USPIO-associated AEs can be considered

as minor – urticaria, hot flash, hypertension and headache, swelling of neck and nose and diarrhoea (Triantafyllou et al. 2013).

We had only five RC patients with correlation to pathology. The sample size is not large enough to state whether PET-MRI is useful or not. It is however clear that with the use of ^{11}C-acetate, forced urinary protocols, which have been shown to be beneficial in PET imaging utilising ^{18}F-FDG, can be avoided. In a study by Harkirat et al. (2010) patients were orally hydrated with 1000-1500ml water and were asked to urinate at least three times before imaging took place (Harkirat et al. 2010). It is debatable whether to use a catheter. On the other hand, it is invasive and may cause urinary tract infection, as happened in three of our patients. Some of them could have possibly been avoided, if the urine was screened in advance. Then again, BC patients may have urinary incontinence and a 90-minute scan may cause discomfort, which can be avoided with catheter in place during imaging. Another benefit is that bladder volume is controlled in some way; we had 100cc in our study. Through repeated emptying and filling of the bladder we were able to standardise bladder volume, which is essential in image fusion, and without catheterisation this could have not been achieved. But discussion whether or not to use a catheter is speculative, since the main interest in functional imaging is LNM detection and in that no imaging modality can be considered reliable enough (Horn et al. 2016, Thoeny et al. 2014, Woo et al. 2018, Pichler et al. 2017, Birkhauser et al. 2013).

6.2 Neoadjuvant chemotherapy-related complications

Our studies showed that even severe AEs seldom prohibit execution of RC and that the use of NAC does not increase early (90d) post-operative mortality or severe complications (**Study II & III**). Patients with high ASA, high ACCI, existing severe cardiac dysfunction or severe respiratory disease are at the highest risk for early post-operative mortality (**Study IV**).

AEs are best described in RCTs. This can be clearly seen if we compare the Grade 1 AEs reported in our study vs. the rate reported in the prospective study by Iyer et al. We found only 7% of AEs compared to 90% of anaemia in Iyer at al. (2018). However, minor AEs seldom have a critical impact on the timing of RC, and concerning NAC treatment in MIBC, key RCTs are done with different regimens [(MVAC) Grossman et al. 2003, (MVC) Griffiths et al. 2011]. CG has been studied far less in the NAC setting. Khaled et. al. had 59 patients in their NAC arm, but eradicated 10 patients from final analysis. Grade III-IV haematological toxicities were reported in 14% of NAC patients and nausea and vomiting in 40% of patients. However, all received the scheduled regimen without dose adjustments (Khaled et al. 2014). Dose adjustments were studied in the phase II study by Anari et al. They

had to close early due to a higher than expected rate of vascular events with a dose-dense regimen (Anari et al. 2018). CG has been compared to MVAC in one retrospective propensity matched study, where there was no difference between these two regimens (Galsky et al. 2015). In our study we did find that lack of tolerance is seen already after the first cycle (**Study II**). Although this was the only statistically significant finding, there was a statistically insignificant tendency with vascular diseases (chronic heart insufficiency and peripheral arterial disease) being more relevant than, for instance, diabetes (**Study II**). Renal impairment had a similar tendency, but this was already known. In a study by Dash et al., nearly 40% of patients, who could possibly benefit from NAC were platinum-ineligible (Dash et al. 2006).

AEs during NAC may prohibit execution of RC, as happened to 2.5% of patients in our study (**Study II**). This does not seem much, since in the landmark paper by Grossman et al, RC was not executed in 17% of patients treated with NAC for various reasons. On the other hand, in patients scheduled for RC only, an operation was performed for a similar proportion of patients (Grossman et al. 2003). However, this finding may explain why NAC does not seem to improve OS in the "real-life population" (Hanna et al. 2014). If the absolute benefit of NAC is 5%, but 2.5% NAC-treated patients do not receive surgery for whatever reasons, this simply undermines the total benefit of NAC and underlines the importance of proper patient selection for NAC. We do know that negative studies are not that easily published and that study populations differ from those of daily clinics material. And we also know that adequately planned retrospective or observational studies may be surprisingly similar to RCTs (Concato et al. 2000). So, our study, although retrospective, adds to data concerning NAC and especially CG NAC.

The reported rate of post-operative mortality ranges from 2.1% (Afshar et al. 2017) to 8.2% (Gandaglia et al. 2014). Our post-operative 90d mortality of RC was 4%. In NAC + RC patients it was even lower (1.9%) mainly reflecting differences between the RC-only and NAC + RC populations. The total level of reported complications was 61%. This reflects the fact that even in a retrospective setting, data collection can be done with proper precision. While retrospective methods have their flaws, with current guideline recommendations (Witjes et al. 2017), it would be unethical to try to evaluate CG NAC in a prospective randomised setting. From this perspective, the observational method seems adequate and valid (Silverman 2009). In order to randomise retrospective material, we used a propensity score, which can be described as the probability of treatment assignment (Austin 2011). In comparison to RCT, where random allocation of treatments is often involved, but random selection of subjects is rarely involved (Little & Rubin 2000), matching patients with pre-treatment covariates may be considered acceptable. That is, if we consider covariates being variables whose values are not affected by the treatment assignment

and subsequent outcomes, and whose adjustment is essential to reduce or avoid bias (such as variables that are recorded before randomisation into treatment groups) (Little & Rubin 2000). Since other observational registry studies have shown a similar effect of NAC on post-operative complications (Gandaglia et al. 2014, Johnson et al. 2014, Tyson et al. 2014), we can safely say that CG NAC does not increase risk for early post-operative surgical complications.

ASA is a known risk factor to predict post-operative complications or mortality after RC (Schultz et al. 2018, Korbee et al. 2019, Boström et al. 2009). But ASA comprises several factors that may not be equally important. We were able to detect that chronic heart insufficiency and chronic obstructive pulmonary disease were the most relevant risk factors, when risk factors were evaluated separately. Risk factors have been investigated before (Novotny et al. 2016). The most comorbid patients never receive RC. Our rationale was to identify those high ASA-class patients, who could be suitable for aggressive treatment, MMT, at least in the future. Even in the presence of high ASA, without evidence of vascular, kidney or liver disease, RC may be considered.

6.3 Limitations of the studies

Major limitations of the studies include the small sample size (**Study I**). However, no similar study has yet been done and justifying further research always starts with a small preliminary series to evaluate whether it is wise to continue research with the chosen modality. We feel that PET-MRI may have potential, especially when MMT protocols start to be adjusted in daily clinics in Finland.

The retrospective nature of data collection and heterogeneity between RC centres (**Studies II-IV**) presents another limitation. But in order to create something new, we need information on the performance of current treatment algorithms. We acknowledge that NAC-associated AEs were collected by urologists and not by medical oncologists, who could probably have identified more AEs. The reported rate of minor AEs is not at all comparable to what it should be. However, the rate of more severe AEs, which have more impact on treatment, is in line with international series. Now, after a decade with national experience of the use of NAC, it was time to thoroughly evaluate where the level of treatment of MIBC in Finland is compared to international trends. We are happy to say, based on the numbers, that our results are not inferior to international trends, patient selection to NAC is successful and the mortality rates are acceptable.

6.4 Future directions

The RC database will be utilised in many ways. There is evidence that OCNB is associated with more complications than NCIC diversion (van Hemelrijk et al. 2013). We did not compare diversion methods, and this remains a matter for further research from the Finnish national radical cystectomy database. Centralisation of RCs has lowered perioperative mortality in Europe (Williams et al. 2019). The centre's effect on mortality will be analysed. The effect on CSS with NAC will be investigated. The Finnish Cystectomy database data is combined with other registry data to further analyse mortality.

A machine-learning methodology has already been utilised. Digitalisation and computer aided work is a growing industry. We will continue utilising artificial intelligence to create more personalised treatment protocols for our patients.

A PET-MRI protocol is established and can be utilised when MMT is started in Finland. The imaging data will be combined with repeated TUR-BT and liquid biopsy information. We have also investigated MRI only to create a faster MRI protocol, which will be useful in the future. This MRI-only study should be reported during 2020 and we are ready to go with MMT.

7 Summary/Conclusions

^{11}C-acetate PET-MRI alone is insufficient in NAC treatment response evaluation. A combination of hybrid imaging, accurate histopathology and liquid biopsies is worth investigating in the future if bladder-preserving strategies are considered.

Patient selection for NAC treatment in Finland is justified. Severe AEs occurring during NAC treatment seldom prohibit the execution of RC and the level of minor AEs is acceptable.

Fear of the influence of NAC on post-operative complications should not preclude its use. If NAC is tolerated, it does not increase post-operative surgical complications. These results should encourage to increase the use of NAC in MIBC patients.

A high ASA class should not automatically avert patients from receiving RC in the absence of cardiac or chronic respiratory disease. A more personalised approach to evaluating fitness for surgical operation is needed. On the other hand, bladder-preserving MMT strategies should be developed to aid those unfit for RC.

Acknowledgements

This thesis work was carried out in the Department of Urology, Turku University Hospital in 2013-2019. Other institutes that were involved in the studies and to whom I am deeply grateful were the Department of Information Technology, University of Turku; the Turku Bioscience Centre, University of Turku and Åbo Akademi University and The National PET Centre, Turku Finland. This work would have not been possible without the excellence of Ileana Montoya Perez, who programmed the database. I wish to thank Riku Klén for all the efforts put into the machine learning methodology and vital assistance in statistical evaluations. The director of the PET Centre, Juhani Knuuti, made imaging studies possible and earned my gratitude.

The most influential person behind this project was my supervisor, dos Peter Boström. Without your ideas and constant support this would have not been possible. I`m honoured by the opportunity you gave me and cannot thank you enough.

The reviewers of this thesis, docent Jussi Koivunen and docent Harri Visapää, are acknowledged for their thorough evaluation and constructive criticism. I wish to thank them for giving me an opportunity to improve the quality of my book by their kind guidance. I also wish to thank the language editor Liz Dexter for the professional linguistic revision of my thesis.

Prof Matti Laato and prof Heikki Minn have kept a close eye on my progress with repeated meetings. I am in debt for the time you invested in me.

Ivan Jambor is a true gem in radiology. Your knowledge, especially in MRI, is overwhelming and I enjoyed the imaging sessions with you a great deal. I owe you my deepest gratitude for all the efforts you`ve put in these studies.

No science can be created without proper statistical expertise. It was not at the easiest phase that Saija Hurme took over statistical analysing, but it could not have gone any better. Thank you, Saija, for your contribution to getting the statistics right.

I wish to thank Dr. Otto Ettala and dos Kari Syvänen for assistance. You were always the first to turn to, even on the most ridiculous issues. I would also like to thank Dr. Heikki Seikkula, who challenged me and supported me in getting my hands dirty with science.

Dos Jukka Kemppainen and dos Johanna Virtanen were key persons in evaluating imaging studies. Prof Heikki Minn was almost a second writer with thorough editing. Dos Pekka Taimen gave valuable comments and with Dr Harri Merisaari I spent many hours calculating results. I want to thank you all. Prof Laura Elo was very open-minded regarding joint projects. Thank you, Laura, for lending Riku Klén from other projects. Mehrad Mahmoudian checked computing analyses with precision and is thanked for that. Marko Seppänen gave some decent camera time in the PET Centre. Thank you.

This thesis involved a wide spectrum of specialists working in different hospitals in Finland. Ilmari Koskinen did quite a lot of data insertion and also attended imaging studies. Teemu J. Murtola, Markku H. Vaarala, Timo K. Nykopp, Marjo Seppänen, Taina Isotalo, Timo Marttila, Lasse Levomäki, Sebastian Becker, Mikael Anttinen, Tapani Liukkonen, Matti Säily, Dimitri Pogodin-Hannolainen, Jouko Viitanen, Christian Palmberg, Juhani Ottelin, Jukka Sairanen and Erik Veskimäe were the urologists who helped me in data-gathering. The students Venla Syri, Petri Virtanen and Samuli Virtanen helped tremendously under supervision in the data collection. Without you this would not have been possible.

I would like to thank people in the PET Centre and the isotope lab and the PET nurses. Dos Mika Teräs gave me permission to use radio-pharmaceuticals, which was nice and worth a thank you. To the urologists in the Turku urology clinic, Kimmo Kuusisto, Antero Horte, Esa Kähkönen, Sari Liesjärvi, Mikael Anttinen, nowadays retired Martti Nurmi and Lauri Reunanen, Pertti Nurminen, Ville Sell, Ilkka Nikulainen, Juha Knaapila and Abdiwahid Alibeto who worked as residents during my excursion into the academic world, thank you for your assistance in recruiting and taking care of clinical duties, when I was working with computers. I also wish to thank Harri Hakovirta, Michal Sopyllo, Pekka Salminen, Arsi Broberg, Jevgeni Aniskov and Teemu Joutsi for guidance in my early clinical years. Veikko Anttila and Karita Astila I have enjoyed working with a great deal – I could not think of better working partners with understanding of my mind's absence occasionally. Many thanks to dos Salvatore Giordano for constant help, interest and material support and my dear friend dos Jussi Posti for valuable advice concerning writing.

Many friends have followed my struggle in the scientific world: Matti Artosalo, Juho Niskanen, Jussi Posti, Mikko Pystynen, Miika Stenholm, Teppo Stenholm I hope our professional relations will stay the same and we will continue having a good time together outside working hours as well. Timo Javanainen, Jukka Liukkonen, Mikko Tapaninen and Ville Tähtinen are my most long-standing friends. Thank you for many good events and many more to come. Tuomas Rimpiläinen, Anders Riska and Markus Lähteenoja, it is always nice to get together with such fine gentlemen.

My parents Arja and Jorma Salminen: you provided me with a great childhood, and have always supported me and fuelled my determination. You are also responsible for giving me two great sisters, Anna Reetta and Aliisa who are very dear to me. You earn my deepest gratitude for raising me to be the man I am.

Ulla and Tapio: Thank you for all the help with our children during the last decade. It has been vital.

Finally, my dear wife Sirkka. To you I owe the most. You are the one I love the most. I cannot really tell how good a mother you are to our children, Maija, Liisa and Lauri. Without your constant flexibility this project would have been impossible. I am very grateful for all you`ve tolerated during the past years. Thank you, Sirkka.

Funding is always necessary and I wish to thank the Finnish Urology association, TYKS-säätiö and Astellas for funding my research. I also wish to thank dos Peter Boström, who took care of all the financial aspects so I could concentrate on my own business. Thank you.

April 2020
Antti Salminen

References

Abdollah, F., G. Gandaglia, R. Thuret, J. Schmitges, Z. Tian, C. Jeldres, N. M. Passoni, A. Briganti, S. F. Shariat, P. Perrotte, F. Montorsi, P. I. Karakiewicz and M. Sun. (2013), 'Incidence, Survival and Mortality Rates of Stage-Specific Bladder Cancer in United States: A Trend Analysis', *Cancer Epidemiol* Vol. 37, No. 3, pp. 219–25.

Afshar, M., H. Goodfellow, F. Jackson-Spence, F. Evison, J. Parkin, R. T. Bryan, H. Parsons, N. D. James and P. Patel. (2017), 'Centralisation of Radical Cystectomies for Bladder Cancer in England, a Decade on from the 'Improving Outcomes Guidance': The Case for Super Centralisation', *BJU Int*.

Agarwal, K. K., S. G. Roy and R. Kumar. (2016), 'Diuretic 18f-Fluorodeoxyglucose Pet/Computed Tomography in Evaluation of Genitourinary Malignancies', *PET Clin* Vol. 11, No. 1, pp. 39–46.

Albisinni, S., A. Veccia, F. Aoun, R. Diamand, F. Esperto, F. Porpiglia, T. Roumeguère and C. De Nunzio. (2019), 'A Systematic Review and Meta-Analysis Comparing the Outcomes of Open and Robotic Assisted Radical Cystectomy', *Minerva Urol Nefrol*.

Alfred Witjes, J., T. Lebret, E. M. Compérat, N. C. Cowan, M. De Santis, H. M. Bruins, V. Hernández, E. L. Espinós, J. Dunn, M. Rouanne, Y. Neuzillet, E. Veskimäe, A. G. van der Heijden, G. Gakis and M. J. Ribal. (2017), 'Updated 2016 Eau Guidelines on Muscle-Invasive and Metastatic Bladder Cancer', *Eur Urol* Vol. 71, No. 3, pp. 462–475.

Anari, F., J. O'Neill, W. Choi, D. Y. T. Chen, M. Haseebuddin, A. Kutikov, E. Dulaimi, R. K. Alpaugh, K. Devarajan, R. E. Greenberg, M. Bilusic, Y. N. Wong, R. Viterbo, J. H. Hoffman-Censits, C. D. Lallas, E. J. Trabulsi, M. Smaldone, D. M. Geynisman, M. Zibelman, J. Lin, W. K. Kelly, R. Uzzo, D. McConkey and E. R. Plimack. (2018), 'Neoadjuvant Dose-Dense Gemcitabine and Cisplatin in Muscle-Invasive Bladder Cancer: Results of a Phase 2 Trial', *Eur Urol Oncol* Vol. 1, No. 1, pp. 54–60.

Anderson, C. B. and J. M. McKiernan. (2018), 'Surgical Complications of Urinary Diversion', *Urol Clin North Am* Vol. 45, No. 1, pp. 79–90.

Austin, P. C. (2011), 'An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies', *Multivariate Behav Res* Vol. 46, No. 3, pp. 399–424.

Avallone, M. A., B. S. Sack, A. El-Arabi, D. K. Charles, W. R. Herre, A. C. Radtke, C. M. Davis and W. A. See. (2017), 'Ten-Year Review of Perioperative Complications after Transurethral Resection of Bladder Tumors: Analysis of Monopolar and Plasmakinetic Bipolar Cases', *J Endourol* Vol. 31, No. 8, pp. 767–773.

Babjuk, M., M. Burger, E. M. Compérat, P. Gontero, A. H. Mostafid, J. Palou, B. W. G. van Rhijn, M. Rouprêt, S. F. Shariat, R. Sylvester, R. Zigeuner, O. Capoun, D. Cohen, J. L. D. Escrig, V. Hernández, B. Peyronnet, T. Seisen and V. Soukup. (2019), 'European Association of Urology Guidelines on Non-Muscle-Invasive Bladder Cancer (Tat1 and Carcinoma in Situ) – 2019 Update', *Eur Urol* Vol. 76, No. 5, pp. 639–657.

Barentsz, J. O., G. J. Jager, J. A. Witjes and J. H. Ruijs. (1996), 'Primary Staging of Urinary Bladder Carcinoma: The Role of Mri and a Comparison with Ct', *Eur Radiol* Vol. 6, No. 2, pp. 129–33.

Benjamini, Y., and Hochberg, Y. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. Journal of the Royal Statistical Society Series B 57, 289–300

Birkhäuser, F. D., U. E. Studer, J. M. Froehlich, M. Triantafyllou, L. J. Bains, G. Petralia, P. Vermathen, A. Fleischmann and H. C. Thoeny. (2013), 'Combined Ultrasmall Superparamagnetic Particles of Iron Oxide-Enhanced and Diffusion-Weighted Magnetic Resonance Imaging Facilitates Detection of Metastases in Normal-Sized Pelvic Lymph Nodes of Patients with Bladder and Prostate Cancer', *Eur Urol* Vol. 64, No. 6, pp. 953–60.

Bolat, D., B. Gunlusoy, O. Aydogdu, M. E. Aydin and C. Dincel. (2018), 'Comparing the Short-Term Outcomes and Complications of Monopolar and Bipolar Transurethral Resection of Bladder Tumors in Patients with Coronary Artery Disese: A Prospective, Randomized, Controlled Study', *Int Braz J Urol* Vol. 44, No. 4, pp. 717–725.

Bolat, D., B. Gunlusoy, T. Degirmenci, Y. Ceylan, S. Polat, E. Aydin, O. Aydogdu and Z. Kozacioglu. (2016), 'Comparing the Short-Term Outcomes and Complications of Monopolar and Bipolar Transurethral Resection of Non-Muscle Invasive Bladder Cancers: A Prospective, Randomized, Controlled Study', *Arch Esp Urol* Vol. 69, No. 5, pp. 225–33.

Boström, P. J., J. Kössi, M. Laato and M. Nurmi. (2009), 'Risk Factors for Mortality and Morbidity Related to Radical Cystectomy', *BJU Int* Vol. 103, No. 2, pp. 191–6

Bray, F., J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A. Torre and A. Jemal. (2018), 'Global Cancer Statistics 2018: Globocan Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries', *CA Cancer J Clin* Vol. 68, No. 6, pp. 394–424.

Brennan, P., O. Bogillot, E. Greiser, J. Chang-Claude, J. Wahrendorf, S. Cordier, K. H. Jöckel, G. Lopez-Abente, A. Tzonou, P. Vineis, F. Donato, M. Hours, C. Serra, U. Bolm-Audorff, W. Schill, M. Kogevinas and P. Boffetta. (2001), 'The Contribution of Cigarette Smoking to Bladder Cancer in Women (Pooled European Data)', *Cancer Causes Control* Vol. 12, No. 5, pp. 411–7.

Brennan, P., O. Bogillot, S. Cordier, E. Greiser, W. Schill, P. Vineis, G. Lopez-Abente, A. Tzonou, J. Chang-Claude, U. Bolm-Audorff, K. H. Jöckel, F. Donato, C. Serra, J. Wahrendorf, M. Hours, A. T'Mannetje, M. Kogevinas and P. Boffetta. (2000), 'Cigarette Smoking and Bladder Cancer in Men: A Pooled Analysis of 11 Case-Control Studies', *Int J Cancer* Vol. 86, No. 2, pp. 289–94.

Bricker EM. Bladder substitution after pelvic evisceration. Surg Clin North Am. 1950 Oct;30(5):1511–1521.

Brierley et al. TNM classification of malignant tumors. UICC International Union Against Cancer. 8th edn. 2017, Oxford

Brunocilla, E., F. Ceci, R. Schiavina, P. Castellucci, A. M. Maffione, M. Cevenini, L. Bianchi, M. Borghesi, F. Giunchi, M. Fiorentino, S. Chondrogiannis, P. M. Colletti, D. Rubello, S. Fanti and G. Martorana. (2014), 'Diagnostic Accuracy of (11)C-Choline Pet/Ct in Preoperative Lymph Node Staging of Bladder Cancer: A Systematic Comparison with Contrast-Enhanced Ct and Histologic Findings', *Clin Nucl Med* Vol. 39, No. 5, pp. e308–12.

Burger, M., J. W. Catto, G. Dalbagni, H. B. Grossman, H. Herr, P. Karakiewicz, W. Kassouf, L. A. Kiemeney, C. La Vecchia, S. Shariat and Y. Lotan. (2013), 'Epidemiology and Risk Factors of Urothelial Bladder Cancer', *Eur Urol* Vol. 63, No. 2, pp. 234–41.

Butcher R, H. R., W. L. Sugg, C. A. McAfee and E. M. Bricker. (1962), 'Ileal Conduit Method of Ureteral Urinary Diversion', *Ann Surg* Vol. 156, pp. 682–91.

Capalbo, E., A. Kluzer, M. Peli, M. Cosentino, E. Berti and M. Cariati. (2015), 'Bladder Cancer Diagnosis: The Role of Ct Urography', *Tumori* Vol. 101, No. 4, pp. 412–7.

Chang, S. S., B. H. Bochner, R. Chou, R. Dreicer, A. M. Kamat, S. P. Lerner, Y. Lotan, J. J. Meeks, J. M. Michalski, T. M. Morgan, D. Z. Quale, J. E. Rosenberg, A. L. Zietman and J. M. Holzbeierlein. (2017), 'Treatment of Non-Metastatic Muscle-Invasive Bladder Cancer: Aua/Asco/Astro/Suo Guideline', *J Urol* Vol. 198, No. 3, pp. 552–559.

Clinicaltrials:
https://clinicaltrials.gov/ct2/results?cond=muscle+invasive+bladder+cancer&term=chemotherapy%2C+immunotherapy&cntry=&state=&city=&dist=

Collaboration, A. B. C. A. M.-a. (2005), 'Neoadjuvant Chemotherapy in Invasive Bladder Cancer: Update of a Systematic Review and Meta-Analysis of Individual Patient Data Advanced Bladder

Cancer (Abc) Meta-Analysis Collaboration', *Eur Urol* Vol. 48, No. 2, pp. 202–5; discussion 205–6.

Common Terminology Criteria of Adverse Events (CTCAE) v. 5.0: https://ctep.cancer.gov/protocoldevelopment/.../ctcae_v5_quick_reference_5x7.pdf

Concato, J., N. Shah and R. I. Horwitz. (2000), 'Randomized, Controlled Trials, Observational Studies, and the Hierarchy of Research Designs', *N Engl J Med* Vol. 342, No. 25, pp. 1887–92.

Daneshmand, S., H. Ahmadi, L. N. Huynh and N. Dobos. (2012), 'Preoperative Staging of Invasive Bladder Cancer with Dynamic Gadolinium-Enhanced Magnetic Resonance Imaging: Results from a Prospective Study', *Urology* Vol. 80, No. 6, pp. 1313–8.

Dash, A., M. D. Galsky, A. J. Vickers, A. M. Serio, T. M. Koppie, G. Dalbagni and B. H. Bochner. (2006), 'Impact of Renal Impairment on Eligibility for Adjuvant Cisplatin-Based Chemotherapy in Patients with Urothelial Carcinoma of the Bladder', *Cancer* Vol. 107, No. 3, pp. 506–13.

DeGroot MH, Schervish MJ. Kolmogorov–Smirnov tests. In: Probability and statistics. Pearson; 2011. London (4th ed.) p. 657–58)

Dindo, D., N. Demartines and P. A. Clavien. (2004), 'Classification of Surgical Complications: A New Proposal with Evaluation in a Cohort of 6336 Patients and Results of a Survey', *Ann Surg* Vol. 240, No. 2, pp. 205–13.

Donat, S. M., A. Shabsigh, C. Savage, A. M. Cronin, B. H. Bochner, G. Dalbagni, H. W. Herr and M. I. Milowsky. (2009), 'Potential Impact of Postoperative Early Complications on the Timing of Adjuvant Chemotherapy in Patients Undergoing Radical Cystectomy: A High-Volume Tertiary Cancer Center Experience', *Eur Urol* Vol. 55, No. 1, pp. 177–85.

Elmamoun, M. H., T. J. Christmas and C. R. Woodhouse. (2014), 'Destruction of the Bladder by Single Dose Mitomycin C for Low-Stage Transitional Cell Carcinoma (Tcc)--Avoidance, Recognition, Management and Consent', *BJU Int* Vol. 113, No. 5b, pp. E34–8.

Faba, O. R., M. D. Tyson, W. Artibani, B. H. Bochner, F. Burkhard, S. M. Gilbert, T. Kälble, S. Madersbacher, R. Seiler, E. C. Skinner, G. Thalmann, J. Thüroff, P. Wiklund, R. Hautmann and J. Palou. (2019), 'Update of the Icud-Siu International Consultation on Bladder Cancer 2018: Urinary Diversion', *World J Urol* Vol. 37, No. 1, pp. 85–93.

Friedman, J., Hastie, T., Tibshirani, R. (2010). Regularization Paths for Generalized Linear Models via Coordinate Descent. Journal of Statistical Software, 33(1), 1–22.

Gandaglia, G., I. Popa, F. Abdollah, J. Schiffmann, S. F. Shariat, A. Briganti, F. Montorsi, Q. D. Trinh, P. I. Karakiewicz and M. Sun. (2014), 'The Effect of Neoadjuvant Chemotherapy on Perioperative Outcomes in Patients Who Have Bladder Cancer Treated with Radical Cystectomy: A Population-Based Study', *Eur Urol* Vol. 66, No. 3, pp. 561–8.

García-Perdomo, H. A., C. E. Montes-Cardona, M. Guacheta, D. F. Castillo and L. O. Reis. (2018), 'Muscle-Invasive Bladder Cancer Organ-Preserving Therapy: Systematic Review and Meta-Analysis', *World J Urol* Vol. 36, No. 12, pp. 1997–2008.

Griffiths, G., R. Hall, R. Sylvester, D. Raghavan, M. K. Parmar, I. C. o. Trialists, M. R. C. A. B. C. W. P. n. t. N. C. R. I. B. C. C. S. Group), E. O. f. R. a. T. o. C. G.-U. T. C. Group, A. B. C. S. Group, N. C. I. o. C. C. T. Group, Finnbladder, N. B. C. S. Group and C. U. E. d. T. O. Group. (2011), 'International Phase Iii Trial Assessing Neoadjuvant Cisplatin, Methotrexate, and Vinblastine Chemotherapy for Muscle-Invasive Bladder Cancer: Long-Term Results of the Ba06 30894 Trial', *J Clin Oncol* Vol. 29, No. 16, pp. 2171–7.

Grossman, H. B., R. B. Natale, C. M. Tangen, V. O. Speights, N. J. Vogelzang, D. L. Trump, R. W. deVere White, M. F. Sarosdy, D. P. Wood, D. Raghavan and E. D. Crawford. (2003), 'Neoadjuvant Chemotherapy Plus Cystectomy Compared with Cystectomy Alone for Locally Advanced Bladder Cancer', *N Engl J Med* Vol. 349, No. 9, pp. 859–66.

Gschwend, J. E., M. M. Heck, J. Lehmann, H. Rübben, P. Albers, J. M. Wolff, D. Frohneberg, P. de Geeter, A. Heidenreich, T. Kälble, M. Stöckle, T. Schnöller, A. Stenzl, M. Müller, M. Truss, S. Roth, U. B. Liehr, J. Leißner, T. Bregenzer and M. Retz. (2019), 'Extended Versus Limited Lymph

Node Dissection in Bladder Cancer Patients Undergoing Radical Cystectomy: Survival Results from a Prospective, Randomized Trial', *Eur Urol* Vol. 75, No. 4, pp. 604–611.

Hanna, N., Q. D. Trinh, T. Seisen, M. W. Vetterlein, J. Sammon, M. A. Preston, S. R. Lipsitz, J. Bellmunt, M. Menon, T. K. Choueiri and F. Abdollah. (2018), 'Effectiveness of Neoadjuvant Chemotherapy for Muscle-Invasive Bladder Cancer in the Current Real World Setting in the Usa', *Eur Urol Oncol* Vol. 1, No. 1, pp. 83–90.

Harkirat, S., S. Anand and M. Jacob. (2010), 'Forced Diuresis and Dual-Phase F-Fluorodeoxyglucose-Pet/Ct Scan for Restaging of Urinary Bladder Cancers', *Indian J Radiol Imaging* Vol. 20, No. 1, pp. 13–9.

Hautmann, R. E., H. Abol-Enein, K. Hafez, I. Haro, W. Mansson, R. D. Mills, J. D. Montie, A. I. Sagalowsky, J. P. Stein, A. Stenzl, U. E. Studer, B. G. Volkmer and W. H. O. W. C. C. o. B. Cancer. (2007), 'Urinary Diversion', *Urology* Vol. 69, No. 1 Suppl, pp. 17–49.

Herr, H. W. (1987), 'Conservative Management of Muscle-Infiltrating Bladder Cancer: Prospective Experience', *J Urol* Vol. 138, No. 5, pp. 1162–3.

Herr, H., C. Lee, S. Chang, S. Lerner and B. C. C. Group. (2004), 'Standardization of Radical Cystectomy and Pelvic Lymph Node Dissection for Bladder Cancer: A Collaborative Group Report', *J Urol* Vol. 171, No. 5, pp. 1823–8; discussion 1827–8.

Horn, T., T. Zahel, N. Adt, S. C. Schmid, M. M. Heck, M. K. Thalgott, G. Hatzichristodoulou, B. Haller, M. Autenrieth, H. R. Kübler, J. E. Gschwend, K. Holzapfel and T. Maurer. (2016), 'Evaluation of Computed Tomography for Lymph Node Staging in Bladder Cancer Prior to Radical Cystectomy', *Urol Int* Vol. 96, No. 1, pp. 51–6.

Humphrey, P. A., H. Moch, A. L. Cubilla, T. M. Ulbright and V. E. Reuter. (2016), 'The 2016 Who Classification of Tumours of the Urinary System and Male Genital Organs-Part B: Prostate and Bladder Tumours', *Eur Urol* Vol. 70, No. 1, pp. 106–119.

Iyer, G., A. V. Balar, M. I. Milowsky, B. H. Bochner, G. Dalbagni, S. M. Donat, H. W. Herr, W. C. Huang, S. S. Taneja, M. Woods, I. Ostrovnaya, H. Al-Ahmadie, M. E. Arcila, J. C. Riches, A. Meier, C. Bourque, M. Shady, H. Won, T. L. Rose, W. Y. Kim, B. E. Kania, M. E. Boyd, C. K. Cipolla, A. M. Regazzi, D. Delbeau, A. S. McCoy, H. A. Vargas, M. F. Berger, D. B. Solit, J. E. Rosenberg and D. F. Bajorin. (2018), 'Multicenter Prospective Phase Ii Trial of Neoadjuvant Dose-Dense Gemcitabine Plus Cisplatin in Patients with Muscle-Invasive Bladder Cancer', *J Clin Oncol* Vol. 36, No. 19, pp. 1949–1956.

Jimenez, R. E., E. Gheiler, P. Oskanian, R. Tiguert, W. Sakr, D. P. Wood, J. E. Pontes and D. J. Grignon. (2000), 'Grading the Invasive Component of Urothelial Carcinoma of the Bladder and Its Relationship with Progression-Free Survival', *Am J Surg Pathol* Vol. 24, No. 7, pp. 980–7.

Johnson, D. C., M. E. Nielsen, J. Matthews, M. E. Woods, E. M. Wallen, R. S. Pruthi, M. I. Milowsky and A. B. Smith. (2014), 'Neoadjuvant Chemotherapy for Bladder Cancer Does Not Increase Risk of Perioperative Morbidity', *BJU Int* Vol. 114, No. 2, pp. 221–8.

Karl, A., P. R. Carroll, J. E. Gschwend, R. Knüchel, F. Montorsi, C. G. Stief and U. E. Studer. (2009), 'The Impact of Lymphadenectomy and Lymph Node Metastasis on the Outcomes of Radical Cystectomy for Bladder Cancer', *Eur Urol* Vol. 55, No. 4, pp. 826–35.

Khadra, M. H., R. S. Pickard, M. Charlton, P. H. Powell and D. E. Neal. (2000), 'A Prospective Analysis of 1,930 Patients with Hematuria to Evaluate Current Diagnostic Practice', *J Urol* Vol. 163, No. 2, pp. 524–7.

Khaled, H. M., H. E. Shafik, M. S. Zabhloul, M. Ghoneim, R. A. Saber, M. Manie, H. A. Enein, H. A. Megeed, O. Mansur, M. E. Sherbini, T. Z. Mahran, M. E. Kalawee, A. Badran and S. M. Ramadan. (2014), 'Gemcitabine and Cisplatin as Neoadjuvant Chemotherapy for Invasive Transitional and Squamous Cell Carcinoma of the Bladder: Effect on Survival and Bladder Preservation', *Clin Genitourin Cancer* Vol. 12, No. 5, pp. e233–40.

Khan, M. S., K. Omar, K. Ahmed, C. Gan, M. Van Hemelrijck, R. Nair, R. Thurairaja, P. Rimington and P. Dasgupta. (2019), 'Long-Term Oncological Outcomes from an Early Phase Randomised

Controlled Three-Arm Trial of Open, Robotic, and Laparoscopic Radical Cystectomy (Coral)', *Eur Urol*.

Kibel, A. S., F. Dehdashti, M. D. Katz, A. P. Klim, R. L. Grubb, P. A. Humphrey, C. Siegel, D. Cao, F. Gao and B. A. Siegel. (2009), 'Prospective Study of [18f]Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography for Staging of Muscle-Invasive Bladder Carcinoma', *J Clin Oncol* Vol. 27, No. 26, pp. 4314–20.

Kim, S. J., P. J. Koo, K. Pak, I. J. Kim and K. Kim. (2018), 'Diagnostic Accuracy of C-11 Choline and C-11 Acetate for Lymph Node Staging in Patients with Bladder Cancer: A Systematic Review and Meta-Analysis', *World J Urol* Vol. 36, No. 3, pp. 331–340.

Kim, T. H., H. H. Sung, H. G. Jeon, S. I. Seo, S. S. Jeon, H. M. Lee, H. Y. Choi and B. C. Jeong. (2016), 'Oncological Outcomes in Patients Treated with Radical Cystectomy for Bladder Cancer: Comparison between Open, Laparoscopic, and Robot-Assisted Approaches', *J Endourol* Vol. 30, No. 7, pp. 783–91.

Korbee, M. L., C. S. Voskuilen, K. Hendricksen, R. Mayr, E. M. Wit, P. J. van Leeuwen, S. Horenblas, W. Meinhardt, M. Burger, A. Bex, H. G. van der Poel and B. W. G. van Rhijn. (2019), 'Prediction of Early (30-Day) and Late (30-90-Day) Mortality after Radical Cystectomy in a Comprehensive Cancer Centre over Two Decades', *World J Urol*.

Krajewski, W., K. Kościelska-Kasprzak, J. Rymaszewska and R. Zdrojowy. (2017), 'How Different Cystoscopy Methods Influence Patient Sexual Satisfaction, Anxiety, and Depression Levels: A Randomized Prospective Trial', *Qual Life Res* Vol. 26, No. 3, pp. 625–634.

Kulkarni, G. S., T. Hermanns, Y. Wei, B. Bhindi, R. Satkunasivam, P. Athanasopoulos, P. J. Bostrom, C. Kuk, K. Li, A. J. Templeton, S. S. Sridhar, T. H. van der Kwast, P. Chung, R. G. Bristow, M. Milosevic, P. Warde, N. E. Fleshner, M. A. S. Jewett, S. Bashir and A. R. Zlotta. (2017), 'Propensity Score Analysis of Radical Cystectomy Versus Bladder-Sparing Trimodal Therapy in the Setting of a Multidisciplinary Bladder Cancer Clinic', *J Clin Oncol* Vol. 35, No. 20, pp. 2299–2305.

Lattanzi, M. and A. V. Balar. (2019), 'Current Status and Future Direction of Immunotherapy in Urothelial Carcinoma', *Curr Oncol Rep* Vol. 21, No. 3, pp. 24.

Leow, J. J., J. Bedke, K. Chamie, J. W. Collins, S. Daneshmand, P. Grivas, A. Heidenreich, E. M. Messing, T. J. Royce, A. I. Sankin, M. P. Schoenberg, W. U. Shipley, A. Villers, J. A. Efstathiou, J. Bellmunt and A. Stenzl. (2019), 'Siu-Icud Consultation on Bladder Cancer: Treatment of Muscle-Invasive Bladder Cancer', *World J Urol* Vol. 37, No. 1, pp. 61–83.

Leow, J. J., W. Martin-Doyle, P. S. Rajagopal, C. G. Patel, E. M. Anderson, A. T. Rothman, R. J. Cote, Y. Urun, S. L. Chang, T. K. Choueiri and J. Bellmunt. (2014), 'Adjuvant Chemotherapy for Invasive Bladder Cancer: A 2013 Updated Systematic Review and Meta-Analysis of Randomized Trials', *Eur Urol* Vol. 66, No. 1, pp. 42–54.

Liem, E. I. M. L., M. McCormack, E. S. Y. Chan, Y. Matsui, P. Geavlete, Y. D. Choi, T. M. de Reijke, Y. Farahat, B. A. Inman, J. J. M. C. de la Rosette and S. Naito. (2018), 'Monopolar Vs. Bipolar Transurethral Resection for Non-Muscle Invasive Bladder Carcinoma: A Post-Hoc Analysis from a Randomized Controlled Trial', *Urol Oncol* Vol. 36, No. 7, pp. 338.e1–338.e11.

Lin, H. Y., H. Ye, K. M. Kernen, J. M. Hafron and D. J. Krauss. (2018), 'National Cancer Database Comparison of Radical Cystectomy Vs Chemoradiotherapy for Muscle-Invasive Bladder Cancer: Implications of Using Clinical Vs Pathologic Staging', *Cancer Med* Vol. 7, No. 11, pp. 5370–5381.

Little, R. J. and D. B. Rubin. (2000), 'Causal Effects in Clinical and Epidemiological Studies Via Potential Outcomes: Concepts and Analytical Approaches', *Annu Rev Public Health* Vol. 21, pp. 121–45.

Mahmoud, M. A., A. Tawfick, D. E. Mostafa, H. Elawady, M. Abuelnaga, K. Omar, H. Elshawaf and M. Hasan. (2019), 'Can Bipolar Energy Serve as an Alternative to Monopolar Energy in the Management of Large Bladder Tumours >3 Cm? A Prospective Randomised Study', *Arab J Urol* Vol. 17, No. 2, pp. 125–131.

Malmström, P. U., E. Rintala, R. Wahlqvist, P. Hellström, S. Hellsten and E. Hannisdal. (1996), 'Five-Year Followup of a Prospective Trial of Radical Cystectomy and Neoadjuvant Chemotherapy: Nordic Cystectomy Trial I. The Nordic Cooperative Bladder Cancer Study Group', *J Urol* Vol. 155, No. 6, pp. 1903–6.

McHaffie, D. R., T. J. Kruser, K. Gaston, J. Mahoney, D. Graham and M. Haake. (2016), 'Chemoradiation for Organ Preservation in the Treatment of Muscle-Invasive Bladder Cancer', *Urol Oncol* Vol. 34, No. 6, pp. 271–8.

Mertens, L. S., R. P. Meijer, R. R. de Vries, J. A. Nieuwenhuijzen, H. G. van der Poel, A. Bex, B. W. van Rhijn, W. Meinhardt and S. Horenblas. (2014), 'Prostate Sparing Cystectomy for Bladder Cancer: 20-Year Single Center Experience', *J Urol* Vol. 191, No. 5, pp. 1250–5.

Meyer, A., R. Ghandour, A. Bergman, C. Castaneda, M. Wosnitzer, G. Hruby, M. Benson and J. McKiernan. (2014), 'The Natural History of Clinically Complete Responders to Neoadjuvant Chemotherapy for Urothelial Carcinoma of the Bladder', *J Urol* Vol. 192, No. 3, pp. 696–701.

Necchi, A., D. Raggi, A. Gallina, R. Madison, M. Colecchia, R. Lucianò, R. Montironi, P. Giannatempo, E. Farè, F. Pederzoli, M. Bandini, M. Bianchi, R. Colombo, G. Gandaglia, N. Fossati, L. Marandino, U. Capitanio, F. Dehò, S. M. Ali, J. H. Chung, J. S. Ross, A. Salonia, A. Briganti and F. Montorsi. (2019), 'Updated Results of Pure-01 with Preliminary Activity of Neoadjuvant Pembrolizumab in Patients with Muscle-Invasive Bladder Carcinoma with Variant Histologies', *Eur Urol*.

Nieuwenhuijzen, J. A., A. Bex and S. Horenblas. (2003), 'Unusual Complication after Immediate Postoperative Intravesical Mitomycin C Instillation', *Eur Urol* Vol. 43, No. 6, pp. 711–2.

Novotny, V., M. Froehner, R. Koch, S. Zastrow, U. Heberling, S. Leike, M. Hübler and M. P. Wirth. (2016), 'Age, American Society of Anesthesiologists Physical Status Classification and Charlson Score Are Independent Predictors of 90-Day Mortality after Radical Cystectomy', *World J Urol* Vol. 34, No. 8, pp. 1123–9.

Orevi, M., M. Klein, E. Mishani, R. Chisin, N. Freedman and O. N. Gofrit. (2012), '11c-Acetate Pet/Ct in Bladder Urothelial Carcinoma: Intraindividual Comparison with 11c-Choline', *Clin Nucl Med* Vol. 37, No. 4, pp. e67–72.

Osman, M. A., A. M. Gabr and M. S. Elkady. (2014), 'Neoadjuvant Chemotherapy Versus Cystectomy in Management of Stages Ii, and Iii Urinary Bladder Cancer', *Arch Ital Urol Androl* Vol. 86, No. 4, pp. 278–83.

Oun, R., Y. E. Moussa and N. J. Wheate. (2018), 'The Side Effects of Platinum-Based Chemotherapy Drugs: A Review for Chemists', *Dalton Trans* Vol. 47, No. 19, pp. 6645–6653.

Pannek, J. and T. Senge. (1998), 'History of Urinary Diversion', *Urol Int* Vol. 60, No. 1, pp. 1–10.

Petrelli, F., A. Coinu, M. Cabiddu, M. Ghilardi, I. Vavassori and S. Barni. (2014), 'Correlation of Pathologic Complete Response with Survival after Neoadjuvant Chemotherapy in Bladder Cancer Treated with Cystectomy: A Meta-Analysis', *Eur Urol* Vol. 65, No. 2, pp. 350–7.

Picchio, M., U. Treiber, A. J. Beer, S. Metz, P. Bössner, H. van Randenborgh, R. Paul, G. Weirich, M. Souvatzoglou, R. Hartung, M. Schwaiger and M. Piert. (2006), 'Value of 11c-Choline Pet and Contrast-Enhanced Ct for Staging of Bladder Cancer: Correlation with Histopathologic Findings', *J Nucl Med* Vol. 47, No. 6, pp. 938–44.

Pichler, R., T. De Zordo, J. Fritz, A. Kroiss, F. Aigner, I. Heidegger, I. Virgolini, W. Horninger and C. Uprimny. (2017), 'Pelvic Lymph Node Staging by Combined', *Clin Genitourin Cancer* Vol. 15, No. 3, pp. e387–e395.

Pike, V. W., M. N. Eakins, R. M. Allan and A. P. Selwyn. (1982), 'Preparation of [1-11c]Acetate--an Agent for the Study of Myocardial Metabolism by Positron Emission Tomography', *Int J Appl Radiat Isot* Vol. 33, No. 7, pp. 505–12.

Ploussard, G., S. Daneshmand, J. A. Efstathiou, H. W. Herr, N. D. James, C. M. Rödel, S. F. Shariat, W. U. Shipley, C. N. Sternberg, G. N. Thalmann and W. Kassouf. (2014), 'Critical Analysis of Bladder Sparing with Trimodal Therapy in Muscle-Invasive Bladder Cancer: A Systematic Review', *Eur Urol* Vol. 66, No. 1, pp. 120–37.

R Core Team 2017 R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria URL https://www.R-project.org/)

Raman, S. P. and E. K. Fishman. (2017), 'Upper and Lower Tract Urothelial Imaging Using Computed Tomography Urography', *Radiol Clin North Am* Vol. 55, No. 2, pp. 225–241.

Rauscher, I., M. Eiber, W. A. Weber, J. E. Gschwend, T. Horn and T. Maurer. (2018), 'Positron-Emission Tomography Imaging in Urological Oncology: Current Aspects and Developments', *Int J Urol* Vol. 25, No. 11, pp. 912–921.

Rivero Guerra, Á., T. Fernández Aparicio, I. Barceló Bayonas, A. Pardo Martínez, V. Muñoz Guillermo, D. Jiménez Peralta, C. Carrillo George, B. N Pietricica, E. Izquierdo Morejón, A. Rosino Sánchez, A. Romero Hoyuela and G. Hita Villaplana. (2018), 'Outpatient Holmium Laser Fulguration: A Safe Procedure for Treatment of Recurrence of Nonmuscle Invasive Bladder Cancer', *Actas Urol Esp* Vol. 42, No. 5, pp. 309–315.

Rosenkrantz, A. B., K. P. Friedman, F. Ponzo, R. A. Raad, K. Jackson, W. C. Huang and A. V. Balar. (2017), 'Prospective Pilot Study to Evaluate the Incremental Value of Pet Information in Patients with Bladder Cancer Undergoing 18f-Fdg Simultaneous Pet/Mri', *Clin Nucl Med* Vol. 42, No. 1, pp. e8–e15.

Roth, B., M. P. Wissmeyer, P. Zehnder, F. D. Birkhäuser, G. N. Thalmann, T. M. Krause and U. E. Studer. (2010), 'A New Multimodality Technique Accurately Maps the Primary Lymphatic Landing Sites of the Bladder', *Eur Urol* Vol. 57, No. 2, pp. 205–11.

Rushton, L., S. Bagga, R. Bevan, T. P. Brown, J. W. Cherrie, P. Holmes, L. Fortunato, R. Slack, M. Van Tongeren, C. Young and S. J. Hutchings. (2010), 'Occupation and Cancer in Britain', *Br J Cancer* Vol. 102, No. 9, pp. 1428–37.

Salem, H. K. and S. Mahfouz. (2012), 'Changing Patterns (Age, Incidence, and Pathologic Types) of Schistosoma-Associated Bladder Cancer in Egypt in the Past Decade', *Urology* Vol. 79, No. 2, pp. 379–83.

Sammet, S. (2016), 'Magnetic Resonance Safety', *Abdom Radiol (NY)* Vol. 41, No. 3, pp. 444–51.

Schöder, H., S. C. Ong, V. E. Reuter, S. Cai, E. Burnazi, G. Dalbagni, S. M. Larson and B. H. Bochner. (2012), 'Initial Results with (11)C-Acetate Positron Emission Tomography/Computed Tomography (Pet/Ct) in the Staging of Urinary Bladder Cancer', *Mol Imaging Biol* Vol. 14, No. 2, pp. 245–51.

Schulz, G. B., T. Grimm, A. Buchner, F. Jokisch, A. Kretschmer, J. Casuscelli, B. Ziegelmüller, C. G. Stief and A. Karl. (2018), 'Surgical High-Risk Patients with Asa ≥ 3 Undergoing Radical Cystectomy: Morbidity, Mortality, and Predictors for Major Complications in a High-Volume Tertiary Center', *Clin Genitourin Cancer* Vol. 16, No. 6, pp. e1141–e1149.

Shariat, S. F., G. S. Palapattu, P. I. Karakiewicz, C. G. Rogers, A. Vazina, P. J. Bastian, M. P. Schoenberg, S. P. Lerner, A. I. Sagalowsky and Y. Lotan. (2007), 'Discrepancy between Clinical and Pathologic Stage: Impact on Prognosis after Radical Cystectomy', *Eur Urol* Vol. 51, No. 1, pp. 137–49; discussion 149–51.

Silverman, S. L. (2009), 'From Randomized Controlled Trials to Observational Studies', *Am J Med* Vol. 122, No. 2, pp. 114–20.

Simone, G., R. Papalia, M. Ferriero, S. Guaglianone, E. Castelli, D. Collura, G. Muto and M. Gallucci. (2013), 'Stage-Specific Impact of Extended Versus Standard Pelvic Lymph Node Dissection in Radical Cystectomy', *Int J Urol* Vol. 20, No. 4, pp. 390–7.

Solsona, E., I. Iborra, A. Collado, J. Rubio-Briones, J. Casanova and A. Calatrava. (2010), 'Feasibility of Radical Transurethral Resection as Monotherapy for Selected Patients with Muscle Invasive Bladder Cancer', *J Urol* Vol. 184, No. 2, pp. 475–80.

Solsona, E., I. Iborra, J. V. Ricós, J. L. Monrós and R. Dumont. (1992), 'Feasibility of Transurethral Resection for Muscle-Infiltrating Carcinoma of the Bladder: Prospective Study', *J Urol* Vol. 147, No. 6, pp. 1513–5.

Stein, J. P. and D. G. Skinner. (2006), 'Radical Cystectomy for Invasive Bladder Cancer: Long-Term Results of a Standard Procedure', *World J Urol* Vol. 24, No. 3, pp. 296–304.

Stenzl, A., Nagele, U., Kuczyk, M., Sievert, K-D., Anastasiadis, A., Seibold, J., Corvin, S.: Cystectomy – Technical Considerations in Male and Female Patients. EAU Update Series, Volume 3, Issue 3,2005, Pages 138–146

Sternberg, C. N., I. Skoneczna, J. M. Kerst, P. Albers, S. D. Fossa, M. Agerbaek, H. Dumez, M. de Santis, C. Theodore, M. G. Leahy, J. D. Chester, A. Verbaeys, G. Daugaard, L. Wood, J. A. Witjes, R. de Wit, L. Geoffrois, L. Sengelov, G. Thalmann, D. Charpentier, F. Rolland, L. Mignot, S. Sundar, P. Symonds, J. Graham, F. Joly, S. Marreaud, L. Collette and R. Sylvester. (2015), 'Immediate Versus Deferred Chemotherapy after Radical Cystectomy in Patients with Pt3-Pt4 or N+ M0 Urothelial Carcinoma of the Bladder (Eortc 30994): An Intergroup, Open-Label, Randomised Phase 3 Trial', *Lancet Oncol* Vol. 16, No. 1, pp. 76–86.

Surveillance, epidemiology and end result program (SEER database): https://seer.cancer.gov/statfacts/html/urinb.html

Syöpärekisteri: www.syoparekisteri.fi

Tan, W. S., R. Sarpong, P. Khetrapal, S. Rodney, H. Mostafid, J. Cresswell, D. Watson, A. Rane, J. Hicks, G. Hellawell, M. Davies, S. J. Srirangam, L. Dawson, D. Payne, N. Williams, C. Brew-Graves, A. Feber, J. D. Kelly and D. I. t. collaborators. (2019), 'Does Urinary Cytology Have a Role in Haematuria Investigations?', *BJU Int* Vol. 123, No. 1, pp. 74–81.

Therneau TM. A Package for Survival Analysis in S. [Internet]. Survival (Lond). 2015;Available from: http://cran.r-project.org/package=survival.

Therneau TM. and Grambsch PM. Modeling Survival Data: Extending the Cox Model. New York, NY: Springer New York; 2000;

Thoeny, H. C., J. M. Froehlich, M. Triantafyllou, J. Huesler, L. J. Bains, P. Vermathen, A. Fleischmann and U. E. Studer. (2014), 'Metastases in Normal-Sized Pelvic Lymph Nodes: Detection with Diffusion-Weighted Mr Imaging', *Radiology* Vol. 273, No. 1, pp. 125–35.

Triantafyllou, M., U. E. Studer, F. D. Birkhäuser, A. Fleischmann, L. J. Bains, G. Petralia, A. Christe, J. M. Froehlich and H. C. Thoeny. (2013), 'Ultrasmall Superparamagnetic Particles of Iron Oxide Allow for the Detection of Metastases in Normal Sized Pelvic Lymph Nodes of Patients with Bladder and/or Prostate Cancer', *Eur J Cancer* Vol. 49, No. 3, pp. 616–24.

Tuomikoski, L., J. Collan, J. Keyriläinen, H. Visapää, K. Saarilahti and M. Tenhunen. (2011), 'Adaptive Radiotherapy in Muscle Invasive Urinary Bladder Cancer--an Effective Method to Reduce the Irradiated Bowel Volume', *Radiother Oncol* Vol. 99, No. 1, pp. 61–6.

Turker, P., P. J. Bostrom, M. L. Wroclawski, B. van Rhijn, H. Kortekangas, C. Kuk, T. Mirtti, N. E. Fleshner, M. A. Jewett, A. Finelli, T. V. Kwast, A. Evans, J. Sweet, M. Laato and A. R. Zlotta. (2012), 'Upstaging of Urothelial Cancer at the Time of Radical Cystectomy: Factors Associated with Upstaging and Its Effect on Outcome', *BJU Int* Vol. 110, No. 6, pp. 804–11.

Tyson, M. D., A. H. Bryce, T. H. Ho, E. M. Carballido and E. P. Castle. (2014), 'Perioperative Complications after Neoadjuvant Chemotherapy and Radical Cystectomy for Bladder Cancer', *Can J Urol* Vol. 21, No. 3, pp. 7259–65.

van Hemelrijck, M., A. Thorstenson, P. Smith, J. Adolfsson and O. Akre. (2013), 'Risk of in-Hospital Complications after Radical Cystectomy for Urinary Bladder Carcinoma: Population-Based Follow-up Study of 7608 Patients', *BJU Int* Vol. 112, No. 8, pp. 1113–20.

Vargas, H. A., O. Akin, H. Schöder, S. Olgac, G. Dalbagni, H. Hricak and B. H. Bochner. (2012), 'Prospective Evaluation of Mri, ^{11}C-Acetate Pet/Ct and Contrast-Enhanced Ct for Staging of Bladder Cancer', *Eur J Radiol* Vol. 81, No. 12, pp. 4131–7.

Veskimäe, E., Y. Neuzillet, M. Rouanne, S. MacLennan, T. B. L. Lam, Y. Yuan, E. Compérat, N. C. Cowan, G. Gakis, A. G. van der Heijden, M. J. Ribal, J. A. Witjes and T. Lebrét. (2017), 'Systematic Review of the Oncological and Functional Outcomes of Pelvic Organ-Preserving Radical Cystectomy (Rc) Compared with Standard Rc in Women Who Undergo Curative Surgery and Orthotopic Neobladder Substitution for Bladder Cancer', *BJU Int* Vol. 120, No. 1, pp. 12–24.

Wang, C., A. U. Kishan, J. B. Yu, A. Raldow, C. R. King, K. S. Iwamoto, F. I. Chu, M. L. Steinberg and P. A. Kupelian. (2019), 'Association between Long-Term Second Malignancy Risk and

Radiation: A Comprehensive Analysis of the Entire Surveillance, Epidemiology, and End Results Database (1973–2014)', *Adv Radiat Oncol* Vol. 4, No. 4, pp. 738–747.

Wang, G. and J. K. McKenney. (2019), 'Urinary Bladder Pathology: World Health Organization Classification and American Joint Committee on Cancer Staging Update', *Arch Pathol Lab Med* Vol. 143, No. 5, pp. 571–577.

Wijburg, C. J., C. T. J. Michels, J. R. Oddens, J. P. C. Grutters, J. A. Witjes and M. M. Rovers. (2018), 'Robot Assisted Radical Cystectomy Versus Open Radical Cystectomy in Bladder Cancer (Race): Study Protocol of a Non-Randomized Comparative Effectiveness Study', *BMC Cancer* Vol. 18, No. 1, pp. 861.

Williams, S. B., M. D. Ray-Zack, H. K. Hudgins, J. Oldenburg, Q. D. Trinh, P. L. Nguyen, N. D. Shore, M. P. Wirth, T. O'Brien and J. W. F. Catto. (2019), 'Impact of Centralizing Care for Genitourinary Malignancies to High-Volume Providers: A Systematic Review', *Eur Urol Oncol* Vol. 2, No. 3, pp. 265–273.

Woo, S., C. H. Suh, S. Y. Kim, J. Y. Cho and S. H. Kim. (2017), 'Diagnostic Performance of Mri for Prediction of Muscle-Invasiveness of Bladder Cancer: A Systematic Review and Meta-Analysis', *Eur J Radiol* Vol. 95, pp. 46–55.

Woo, S., C. H. Suh, S. Y. Kim, J. Y. Cho and S. H. Kim. (2018), 'The Diagnostic Performance of Mri for Detection of Lymph Node Metastasis in Bladder and Prostate Cancer: An Updated Systematic Review and Diagnostic Meta-Analysis', *AJR Am J Roentgenol* Vol. 210, No. 3, pp. W95–W109.

Yin, M., M. Joshi, R. P. Meijer, M. Glantz, S. Holder, H. A. Harvey, M. Kaag, E. E. Fransen van de Putte, S. Horenblas and J. J. Drabick. (2016), 'Neoadjuvant Chemotherapy for Muscle-Invasive Bladder Cancer: A Systematic Review and Two-Step Meta-Analysis', *Oncologist* Vol. 21, No. 6, pp. 708–15.

Yuh, B. E., N. Ruel, T. G. Wilson, N. Vogelzang and S. K. Pal. (2013), 'Pooled Analysis of Clinical Outcomes with Neoadjuvant Cisplatin and Gemcitabine Chemotherapy for Muscle Invasive Bladder Cancer', *J Urol* Vol. 189, No. 5, pp. 1682–6.

Zargar, H., K. Zargar-Shoshtari, Y. Lotan, J. B. Shah, B. W. van Rhijn, S. Daneshmand, P. E. Spiess, P. Black and Collaborators. (2016), 'Final Pathological Stage after Neoadjuvant Chemotherapy and Radical Cystectomy for Bladder Cancer-Does Pt0 Predict Better Survival Than Pta/Tis/T1?', *J Urol* Vol. 195, No. 4 Pt 1, pp. 886–93.

Zehnder, P., U. E. Studer, E. C. Skinner, R. P. Dorin, J. Cai, B. Roth, G. Miranda, F. Birkhäuser, J. Stein, F. C. Burkhard, S. Daneshmand, G. N. Thalmann, I. S. Gill and D. G. Skinner. (2011), 'Super Extended Versus Extended Pelvic Lymph Node Dissection in Patients Undergoing Radical Cystectomy for Bladder Cancer: A Comparative Study', *J Urol* Vol. 186, No. 4, pp. 1261–8.

Zehnder, P., U. E. Studer, S. Daneshmand, F. D. Birkhäuser, E. C. Skinner, B. Roth, G. Miranda, F. C. Burkhard, J. Cai, D. G. Skinner, G. N. Thalmann and I. S. Gill. (2014), 'Outcomes of Radical Cystectomy with Extended Lymphadenectomy Alone in Patients with Lymph Node-Positive Bladder Cancer Who Are Unfit for or Who Decline Adjuvant Chemotherapy', *BJU Int* Vol. 113, No. 4, pp. 554–60.

Zelefsky, M. J., X. Pei, T. Teslova, D. Kuk, J. M. Magsanoc, M. Kollmeier, B. Cox and Z. Zhang. (2012), 'Secondary Cancers after Intensity-Modulated Radiotherapy, Brachytherapy and Radical Prostatectomy for the Treatment of Prostate Cancer: Incidence and Cause-Specific Survival Outcomes According to the Initial Treatment Intervention', *BJU Int* Vol. 110, No. 11, pp. 1696–701.

Zhang, H., W. Xing, Q. Kang, C. Chen, L. Wang and J. Lu. (2015), 'Diagnostic Value of [18f] Fdg-Pet and Pet/Ct in Urinary Bladder Cancer: A Meta-Analysis', *Tumour Biol* Vol. 36, No. 5, pp. 3209–14.

UNIVERSITY OF TURKU

Painosalama Oy, Turku, Finland 2020

ISBN 978-951-29-8045-1 (PRINT)
ISBN 978-951-29-8046-8 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)