Optimizing staging and treatment of muscle-invasive bladder cancer

H.M. Bruins

Design: *Ruben Huis in 't Veld*
Cover Photo: *Emmanuel Keller/Flickr (CC BY-ND 2.0)*
Printed by: *Ipskamp Drukkers B.V.*
ISBN: *978-90-9029331-8*

This research was performed at the departments of urology of the Radboud University Medical Center and University of Southern California.

This research was supported by a grant from the Netherlands Organization for Health Research and Development (ZonMw AGIKO stipendium, grant 92003570).

The production of this thesis was supported by:
Abbvie, Astellas, American Medical Systems, AMGEN, Bayer Healthcare, Boehringer Ingelheim, Chipsoft, Coloplast, ERBE, Ferring, Hoogland Medical, Ipsen Farmaceutica, Janssen-Cilag, MOVIR, Olympus, Pohl Boskamp, Sanofi Aventis, Stöpler, Toshiba Medical Systems, Zambon-Nederland.

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Proefschrift
ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus,
volgens besluit van het college van decanen
in het openbaar te verdedigen op vrijdag 11 december 2015
om 12.30 uur precies

door
Harman Maxim Bruins
geboren op 23 juli 1986
te Leiden

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Dankwoord

Klaar!

Beginnen met het dankwoord is niet gebruikelijk, maar eigenlijk wel logisch. Promoveren zonder hulp van velen is onmogelijk en het is bovendien het meest (enige?) gelezen deel van het proefschrift. Genoeg reden dus om met het dankwoord te beginnen waarin ik in het bijzonder de volgende mensen wil bedanken:

Prof. dr. J.A. Witjes, beste Fred. Natuurlijk gaat de grootste dank uit naar jou. Vanaf het begin, zelfs toen ik nog student was, heb je alle voorwaarden geschept om deze promotie tot stand te brengen. Je liet me vrij om mijn eigen weg te vinden, maar hielp mij meteen wanneer ik daar om vroeg. Dat bewonder ik enorm gezien je drukke werkzaamheden als clinicus, wetenschapper en opleider; taken die je allen op het hoogste niveau beheerst. Ik kijk er naar uit om ook veel van je te leren in de kliniek.

Prof. dr. E.C. Skinner, dear Eila. I greatly appreciate your supervision at USC in 2012 especially since you didn't really know me that well before. You allowed me to initiate my own projects and execute them with full support of you and the bladder cancer team. It is a honour to have you as my promotor.

Dr. A.G. van der Heijden, beste Toine. Jouw rol als co-promotor is van grote waarde geweest. Regelmatig was jij mijn eerste aanspreekpunt. Natuurlijk wist jij altijd precies weer die vraag te stellen waar ik even niet aan gedacht had en daar heb ik veel aan gehad en van geleerd!

Prof. dr. J.P. Stein, dear John. It saddens me that you won't be able to see the end result of what basically started at USC in 2008, but I think you would be proud of this work. Your expertise, hard work, and true interest in people continues to inspire me.

De leden van de manuscriptcomissie, Prof. dr. H. de Wilt, Prof. dr. S. Horenblas, Prof. dr. L. Massuger, wil ik bedanken voor het beoordelen van het manuscript op zijn wetenschappelijke inhoud.

Dr. S. Daneshmand and dr. H. Djaladat, dear Sia and Hooman. You both acted as a true motivator for me: always open for suggestions and quick corrections of my work. And Hooman, sorry for misspelling your name on some papers, but at least I got it right this time!

Dear Gus and Jie. Many, many credits for both of you. This thesis would not have been possible without your assistance. Thank you very much.

Prof. dr. D.F. Penson, dear David. Many thanks for your supervision and for the laughs at the office. I never thought you would actually start watching football! (as you understand I refuse to call it soccer)

Prof. dr. L.A.L.M. Kiemeney, beste Bart. Hartelijk dank voor je begeleiding en geduld bij de studie over urachustumoren.

Dr. C.A. Hulsbergen-vandeKaa, beste Christina. Dank voor jouw expertise bij de verschillende studies in en buiten deze thesis.

Dr. O. Visser, beste Otto. Het project over urachustumoren leek te gaan stranden totdat jij het project nieuw leven inblies. Veel dank hiervoor!

Dr. M. Ploeg, beste Martine. Als toch een beetje jouw opvolger wil ik ook jou bedanken voor je hulp, met name bij het urachustumoren project.

Dr. K.K.H. Aben, beste Katja. Jij hebt een belangrijke bijdrage geleverd bij de totstandkoming van het laatste artikel over wachttijd tot cystectomie. Ik waardeer je kritische blik, een domme opmerking kreeg ik nooit rechtgeluld!

Prof. Dr. J.A. Schalken, beste Jack. Bedankt voor de werkplek op het lab. Een echt labdier ben ik niet (geworden), maar heb wel genoten van je mooie verhalen tijdens mijn ontbijt aan de koffietafel.

Alle medewerkers van het experimentele lab. Inhoudelijk hebben we weliswaar niet samengewerkt, maar bedankt voor de gezelligheid tijdens de pauzes!

Mijn collega AIOS en arts-onderzoekers wil ik bedanken voor de gezelligheid op de werkvloer, maar ook daarbuiten! Speciale dank voor mijn roomies (Gisèle, Hans, Jos, Rianne(s), Siebren en 'de muggendokters') waarmee ik veel gelachen heb en nog meer dumpert heb gekeken. Tom, dank voor je hulp bij het laatste artikel!

USC fellows and Angel. Thanks for the great time in LA. Highlights were definitely the shooting range and our weekly soccer matches with our own urology team. It is great to have you as my friends and to meet up at conferences!

De opleiders, chirurgen en oud-collega's van de chirurgie uit het Rijnstate wil ik bedanken voor de zeer goede en gezellige vooropleiding. Vooral de OK dagen in Zevenaar waren prachtig evenals de borrels bij Nescio. Gelukkig zie ik veel van jullie nog regelmatig!

Aerts, Appie, Bultje, Exsel, Lamberts, Lau, Wardo: Bedankt voor support de afgelopen jaren maar vooral ook voor de mooie feestjes en (ski)reizen. Ondanks onze drukke agenda's is er altijd wel iemand in voor een koffie, biertje, BBQ of wielrennen. Na vandaag moet ik op zoek naar een nieuw excuus om niet mee te hoeven wielrennen.

De Freunds uit Groenlo. Inmiddels wonen we verspreid over het land, maar gelukkig zien we elkaar nog regelmatig. Ons vaste Freunds weekend in september nadert het 2e lustrum! Natuurlijk speciale dank voor Rubèn voor het ontwerp van de voorkant en het verzorgen van de lay-out van dit proefschrift.

Mannen van QZ H3, nog niet zo lang een team, maar nu al een succes. Uitrazen op (soms erna) het veld met daarna wat biertjes is een mooie invulling van de zondag.

Beste golfvrienden, dank voor de mooie golfuitjes in binnen-en buitenland. Weliswaar geen golfpro geworden, maar toch nog iets met ballen!

Dear Gonzalez family. There are just too many things to thank you for, so I would like to summarize it by saying that you are like family to me.

Mijn paranimfen, Maarten en Laurens, top dat jullie mij vandaag terzijde staan. Maarten ('en Bruins, al dingen ontdekt'), bedankt voor al meer dan 10 jaar goede vriendschap.

Laurens, helaas zien we elkaar wat minder vaak door de reisafstand, maar elk excuus in Utrecht wordt aangegrepen en dan is het weer lachen zoals op het Albertinum. We staan snel op jouw feest!

Jos en Marja, pa en ma, bedankt voor de support bij alles wat ik heb gedaan en doe. Jullie staan altijd voor mij (en anderen) klaar en dat zeg ik misschien wat minder vaak dan jullie zou toekomen. Groenlo voelt nog steeds echt als thuiskomen, maar voor ritjes naar Nijmegen of zelfs LA voor 3 dagen, draaien jullie je hand niet voor om. Dat is heel bijzonder en waardeer ik enorm.

Dolf, als grote broer heb jij je altijd over mij ontfermd wanneer dit nodig was en is. Ik kom te weinig in Den Haag, maar ook telefonisch voorzie jij mij van tips of trucs! Dank voor je hulp bij alles.

Lieve Sally, klein van stuk maar voor mij een grote rots in de branding. Jij voelt mensen als geen ander aan en weet ook mij aan/bij te sturen wanneer nodig. Het leven met jou is fijn sinds de eerste dag samen met als hoogtepunt natuurlijk onze trouwdag in juni.
Ik hou van je.

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PART I

Introduction

CHAPTER 1

General introduction and outline of the thesis

(Adaption of)
Risk factors and clinical outcomes of patients with node-positive disease after radical cystectomy for muscle-invasive bladder cancer.

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Expert Review of Anticancer Therapy 2008;8(7):1091-101

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Bladder cancer epidemiology and diagnosis

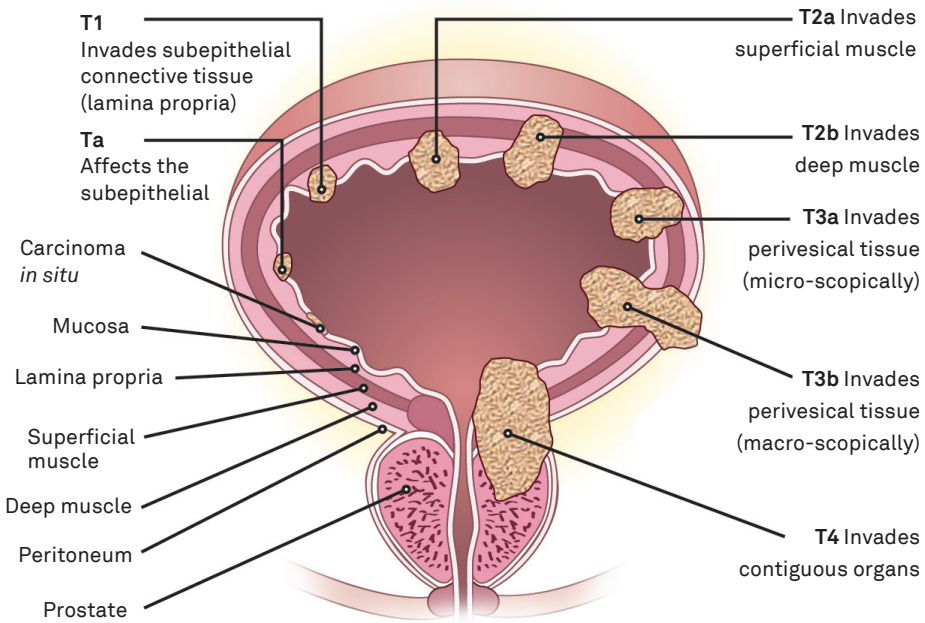
Bladder cancer (BC) is an important health problem. In 2013, a total of 6,426 patients were diagnosed with BC accounting for approximately 5.5% of all new cancer cases in the Netherlands.[1] Beyond the major impact on an individual level, the financial burden of BC for our society is significant. In fact, the per-patient costs are higher for BC than for any other cancer due to the high recurrence rate requiring multiple treatments and in a substantial number of cases life-long follow-up.[2] A number of risk factors for BC have been established of which tobacco smoking and occupational exposure to aromatic amines and certain organic chemicals are the most important risk factors.[3,4]

Symptoms of BC may include painless macroscopic hematuria, recurrent urinary tract infections and urinary urgency. These symptoms require further analysis including an urethrocystoscopy. When finding a lesion suspicious for BC during urethrocystoscopy, a complete transurethral resection of the bladder tumor (TURBT) is required to confirm the diagnosis of BC and to determine the extent of invasion in the bladder wall. A complete TURBT indicates that both the tumor and a part of the underlying detrusor muscle have been resected. Both aspects are important from a staging perspective and likely have a therapeutic value as well.[5]

Staging

Various histological types of BC have been reported, but the vast majority (>90%) are urothelial carcinomas (UC). Regardless of the histological type, the American Joint Committee on Cancer-tumor, node, metastasis (AJCC-TNM) classification is used for BC staging.[6] This staging classification separately assesses the extent of tumor growth in the bladder wall, lymph node status and whether distant metastasis are absent or present (Table 1). At presentation most patients have non-muscle invasive bladder cancer (NMIBC), that is a form of bladder cancer confined to the bladder mucosa (Ta, Tis) or submucosa (T1). Overall, 20-40 % of bladder cancer patients present with, or develop muscle-invasive bladder cancer (MIBC; ≥T2) that may eventually extend outside the bladder to involve the perivesical fat (T3) and adjacent organs (T4, Figure 1).

Figure 1: TNM staging of bladder cancer [6]



Recently, the 7th edition (published in 2009, implemented in 2010) of the AJCC-TNM staging classification has taken effect.[6] This current edition differs from the previous 6th edition (published in 2002) [7] in a number of aspects including:

1. Primary tumor staging: sub-epithelial invasion of prostatic urethra does not constitute T4 staging status.

This modification is based on studies reporting that BC invading the prostatic urethra/ducts confers a better prognosis compared to BC invading the prostatic stroma.[8-11] However, despite the difference in prognosis, limited data is available on the occurrence rate and risk factors for prostatic ducts and prostatic stoma invasion in patients undergoing radical cystectomy (RC) for BC. Obtaining this data was one of the goals of a study where the histology- and clinical records of nearly 1,500 male patients who underwent RC was reviewed (chapter 2).

2. Lymph node (LN) staging: LN staging is based on the location of the LN(s) involved. Location-based LN staging has replaced size-based LN staging. Also, LN metastasis at the common iliac vessels are now considered regional LN metastasis rather than distant metastatic disease. Nevertheless, the rationale for these modifications are not clear as no data was available supporting this modification at the time of its effectuation. In fact, it has been suggested that the site of LN metastasis is not associated with survival.[12-14] Hence, a study was performed evaluating whether prognostication for LN-positive patients has improved in the 7th TNM edition (chapter 8).

Table 1: The AJCC-TNM bladder cancer staging classification (7th edition) [6]

T - Primary Tumor	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ: "flat tumor"
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscle:
	T2a Tumor invades superficial muscle (inner half)
	T2b Tumor invades deep muscle (outer half)
T3	Tumor invades perivesical tissue:
	T3a Microscopically
	T3b Macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
	T4a Tumor invades prostate stroma, seminal vesicles, uterus, or vagina
	T4b Tumor invades pelvic wall or abdominal wall

N - Regional Lymph Nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph-node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in common iliac lymph node(s)
M - Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis

Surgical treatment

Non-muscle invasive bladder cancer

The standard therapy for Ta-T1 BC is a complete TURBT. In case of an incomplete TURBT, absence of detrusor muscle in the specimen, T1 tumor or high-grade tumor (except for primary CIS) a second TURBT is recommended.[15] All patients with NMIBC are offered adjuvant intravesical treatment to reduce the recurrence rate. Yet, as NMIBC is a heterogeneous disease, the risk of progression and/or recurrence differs. Adjuvant intravesical treatment strategies are therefore based on well-defined risk factors.[15,16] RC for NMIBC should be considered in patients with high-risk NMIBC who fail to respond on intravesical therapy.

Muscle-invasive bladder cancer

If left untreated, less than 15% of the patients with MIBC will survive more than 2 years. [17] To improve survival in patients with MIBC, an aggressive treatment paradigm has been advocated. In patients with localized MIBC the gold standard treatment is RC. This treatment consists of complete resection of the urinary bladder with its adjacent organs and the construction of a urinary diversion. The classical technique in male patients is to entirely resect the prostate, while in female patients the uterus, fallopian tubes, ovaries, upper third of the anterior vaginal wall are removed. The most frequently used urinary diversion techniques are the ileal conduit according to Bricker [18] and the orthotopic neobladder (various types used).

In experienced hands, RC can provide good local control in most patients, however, impairment of quality of life is reported by many. For this reason, a sexual organ sparing cystectomy has been advocated in both males and females.[19-24] In this approach, the prostate is preserved in men while in females (parts of) the reproductive organs (vagina, uterus and adnexa) are preserved. Although often technically feasible, the oncological outcomes of these procedures are inferior to RC if routinely performed.[19,25] Thus, careful patient selection is crucial. To understand in whom a sexual organ sparing cystectomy may be safely performed, it is important to have knowledge of the incidence and risk factors of BC invading its adjacent organs. In addition, the risk of leaving behind incidental, yet clinical significant, prostate cancer is an important consideration in male patients. Aiming to assess the incidence and risk factors for UC invading the adjacent organs, a detailed clinical and histopathological analysis of RC specimens was performed in both males and females using a large RC database (chapters 2 and 3).

Lymph node dissection in bladder cancer

Despite the early and aggressive approach in patients with MIBC, approximately 25% of patients have regional LN metastasis at the time of RC providing a sound rationale to perform a LND.[26] Nonetheless, several studies have suggested that LND is often not performed.[27,28] In 2010, an estimated 20% of patients in the Netherlands underwent RC without LND.[29] The reason for this may vary, but one hypothesis is that LND may not ought to be of benefit in patients undergoing RC for clinical NMIBC. Indeed, data on the incidence as well as the distribution of LN metastasis in this patient group is lacking. This raises the question whether or not to perform LND, and how extended the LND template should be. For these reasons, a LN mapping study was undertaken to assess the incidence and location of LN metastasis in patients undergoing RC for clinical NMIBC (chapter 5).

The discussion on the optimal extent of LND is not restricted to patients with NMIBC but applies to patients with MIBC as well, if not more. In the absence of prospective randomized trials, current data on the role of LND originate from observational studies. The results of these studies are conflicting and difficult to interpret as no uniform definition for the different LND templates have been used. In addition, most studies suffered from several biases. Although two randomized controlled trials (RCTs) looking at the staging and therapeutic value of the extent of LND are ongoing, it may years before the final results are published.[30,31] Also, there is no guarantee that these studies provide the definitive answer to the question. Lacking level 1 evidence, it is important to base

current treatment decisions on the second best possible evidence base. Such evidence can arise from a systematic review of the literature including a critical appraisal of bias. A systematic review was performed evaluating the impact of the extent of LND on survival and peri-operative outcomes in patients undergoing RC (chapter 6).

Chemotherapy

Neo-adjuvant therapy has been advocated in patients with MIBC. The most commonly used chemotherapy regimens include a combination of methotrexate, vinblastine, doxorubicin and cisplatinum (MVAC) or gemcitabine with cisplatinum (GC). Data from RCTs have reported neo-adjuvant chemotherapy to increase the absolute 5-year overall survival by 5-8%.[32,33] Despite this level 1 evidence, neo-adjuvant chemotherapy has been infrequently used for many years, although increasing over time.[34] The role of adjuvant chemotherapy is under debate.[35] Although there is some evidence that adjuvant chemotherapy may prolong survival, this evidence originates from older RCTs with methodological concerns.[36-39] A recent RCT did not find a survival difference between adjuvant chemotherapy and deferred chemotherapy in patients with (locally) advanced MIBC, but was closed early due to poor recruitment.[40] Thus, we still do not know which patients, if any, may actually benefit from adjuvant chemotherapy. Further research is needed and an updated individual patient data meta-analysis may provide more definitive answers on this topic.

Prognosis

The prognosis of patients with MIBC varies greatly depending on a number of patient related and histopathological variables. Arguably the most consistent and important prognostic variables are the pathological tumor stage and LN status.[41] As shown in table 2, the 5-year recurrent free survival ranges between 22% in patients with LN positive and extravesical (>pT2) disease to 85% in patients with LN negative and organ-confined (pTo-T2) disease.[26] Over the last years a number of other clinical and pathological prognostic factors have been identified (e.g. lymphovascular invasion) that may allow further refinement of prognostication. In addition, multiple potential biomarkers have been suggested to improve prognostication. Yet no single biomarker, nor panel of biomarkers, is routinely used at this time. Ultimately, improved prognostication allows for better selection of those patients that may benefit from neo-adjuvant or adjuvant chemotherapy. For this reason, a number of studies looking at potential risk factors for

disease recurrence or progression in patients requiring RC (chapter 9) and patients that have undergone RC (chapters 4,7,8) were performed.

Table 2: Relation between LN status and pathologic stage for 5-year recurrence free survival [26]

Author	Median follow-up *(months)*	No Pts	Probability of 5 year recurrence-free survival in %					
			Entire cohort	LN+ Pts	LN+/EV Pts	LN+/OC Pts	LN-/EV Pts	LN-/OC Pts
Stein	122	1054	68	35	30	46	58	85
Vieweg	92	686	57	31	22	58	43	82
Madersbacher	31	507	62	33	N/A	N/A	56	73

OC=organ-confined (pTo-pT2), EV=extravesical (pT2-pT4), LN+=lymph node positive, LN-=lymph node negative

Outline of this thesis

As outlined in the previous paragraphs, several questions regarding the staging, treatment and prognosis of patients with MIBC were the basis for further research that resulted in this thesis.

Part I, the introduction, contains the current **chapter 1** providing a general introduction and outline of the thesis.

Part II focuses on cancer of the urinary bladder and/or its adjacent organs.
In chapters 2 and 3, the BC database of the University of Southern California (USC) was used, containing comprehensive data of over 2,000 patients who underwent RC. In **chapter 2**, the incidence and risk factors of UC involving the prostate and incidental prostate adenocarcinoma were analyzed reviewing the records of nearly 1,500 male patients. Similarly, in **chapter 3**, the records of approximately 250 female patients who underwent anterior pelvic exenteration were reviewed to evaluate the incidence and risk factors of BC invading the adjacent reproductive organs. **Chapter 4** focuses on cancer of the urachus; an embryonic remnant anatomically closely related to the urinary bladder. Due to its low incidence, long-term survival data on a population-based level is scarce. Data from the Netherlands Cancer Registry (NCR) was analyzed to describe the long-term clinical outcomes and identify potential prognostic variables.

Part III addresses the role of LND at the time of RC.
In **Chapter 5**, the results of a LN mapping study that was performed at USC are presented looking at the incidence and location of LN metastasis in patients undergoing RC for clinical NMIBC. **Chapter 6** describes the results of a systematic review of the literature that was performed aiming to determine the current evidence base in regard to oncological benefits and peri-operative outcomes of different LND templates in patients with MIBC.

Part IV discusses potential prognostic variables in (locally advanced) bladder cancer.
In **chapter 7**, the results of a study evaluating survival outcomes and potential prognostic variables in patients with low-volume LN (1 or 2 positive LNs) positive disease are presented. **Chapter 8** contains a critical evaluation of both the 6th and 7th edition of the TNM nodal classification system and aimed to evaluate whether the current 7th edition has improved prognostication in patients with node-positive disease. Both chapters 7 and

8 were performed using the USC bladder cancer database. In **chapter 9**, the impact of the time from diagnosis of MIBC to RC on staging and survival was assessed analyzing the nationwide database of the NCR including nearly 1,800 patients.

Part V, the epilogue, includes the general discussion and future perspectives in **chapter 10** and summary (samenvatting) in **chapter 11**.

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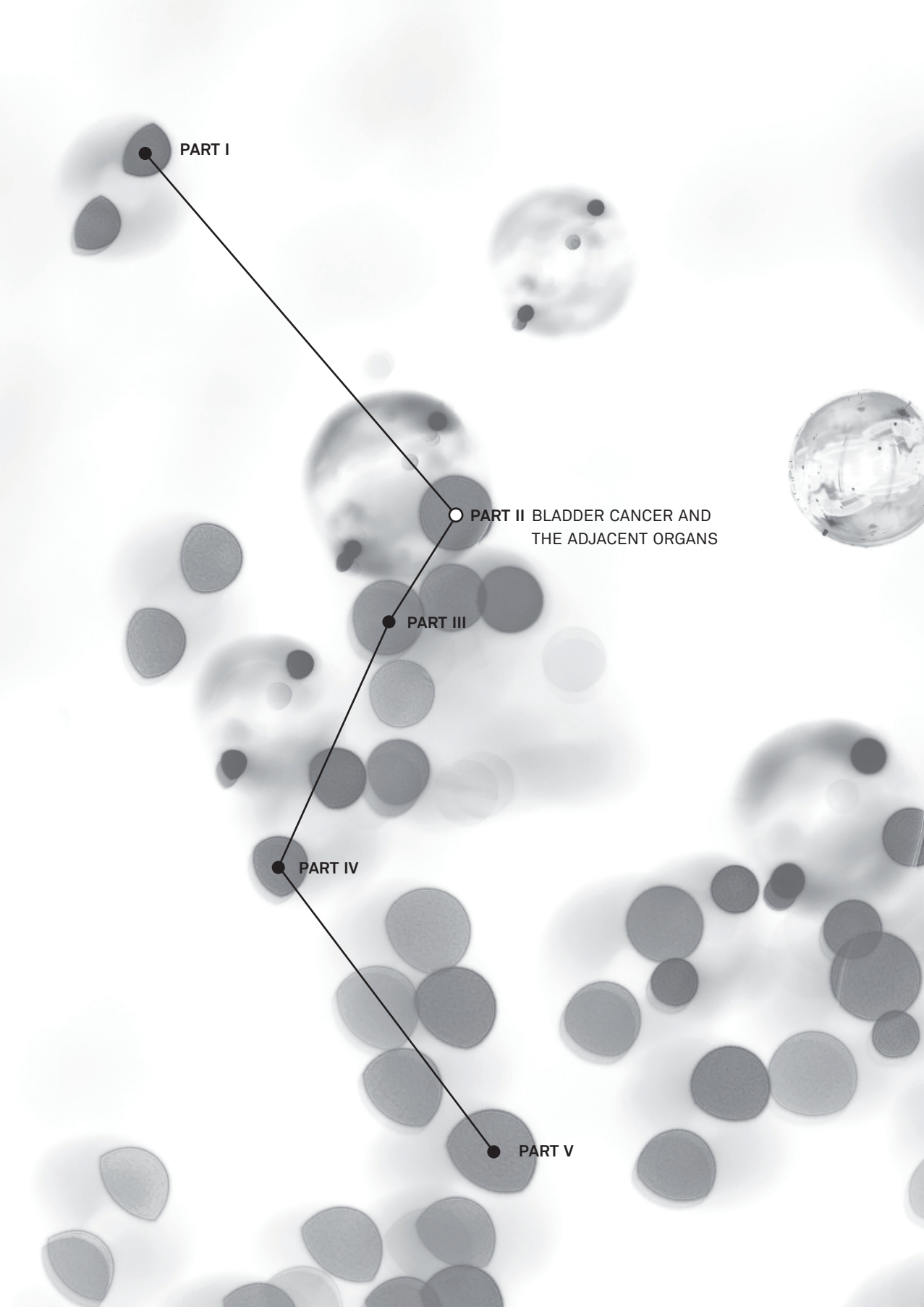
PART I
PART II BLADDER CANCER AND
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PART II

Bladder cancer and the adjacent organs

2 Incidental prostate cancer in patients with bladder urothelial carcinoma: comprehensive analysis of 1,476 radical cystoprostatectomy specimens
J Urol 2013;190(5):1704-1709

3 Reproductive organ involvement in female patients undergoing radical cystectomy for urothelial bladder cancer
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CHAPTER 2

Incidental prostate cancer in patients with bladder urothelial carcinoma: comprehensive analysis of 1,476 radical cystoprostatectomy specimens

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Journal of Urology 2013;190(5):1704-1709

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Abstract

Purpose

To identify risk factors and determine the incidence and prognosis of incidental, clinically significant prostate adenocarcinoma, prostatic urothelial carcinoma and HGPIN in patients treated with radical cystoprostatectomy for urothelial carcinoma of the bladder.

Materials and Methods

We analyzed the records of 1,476 patients without a history of prostatic adenocarcinoma. We determined the incidence of clinically significant prostatic adenocarcinoma, prostatic urothelial carcinoma and HGPIN in the total cohort and in select patient subgroups. Prostatic urothelial carcinoma was stratified in prostatic stromal and prostatic urethra/duct involvement. Univariable and multivariable analyses were performed with multiple variables. Recurrence-free and overall survival rates were calculated. Median follow-up time was 13.2 years.

Results

Of the 1,476 patients 753 (51.0%) had cancer involving the prostate. Prostatic adenocarcinoma, clinically significant prostatic adenocarcinoma, prostatic urothelial carcinoma and HGPIN were present in 37.9%, 8.3%, 21.1% and 51.2% of patients, respectively. Of the 312 patients (21.1%) with prostatic urothelial carcinoma 163 (11.0%) had prostatic urethral/duct involvement only and 149 (10.1%) had prostatic stromal involvement. We identified risk factors for clinically significant prostatic adenocarcinoma, prostatic urothelial carcinoma and HGPIN but the absence of these risk factors did not rule out their presence. Ten-year overall survival in patients with no prostatic urothelial carcinoma, and prostatic urethral/duct and prostatic stromal involvement was 47.1%, 43.3% and 21.7%, respectively ($p < 0.001$). No patient with clinically significant prostatic adenocarcinoma died of prostatic cancer.

Conclusions

More than half of the patients undergoing radical cystoprostatectomy had cancer involving the prostate. Prostatic urothelial carcinoma, particularly with prostatic stromal involvement, was associated with a worse prognosis, while clinically significant prostatic adenocarcinoma did not alter survival. Preoperative clinical and histopathological

risk factors are not reliable enough to accurately predict clinically significant prostatic adenocarcinoma and/or prostatic urothelial carcinoma.

Abbreviations and Acronyms

cNMIBC	= clinically nonmuscle invasive bladder cancer
csPCA	= clinically significant PCA
HGPIN	= high grade intra-epithelial neoplasia
OS	= overall survival
PCA	= prostatic adenocarcinoma
PSA	= prostate specific antigen
PUC	= prostatic urothelial carcinoma
PUC-d	= PUC with prostatic urethral and/or prostatic duct involvement
PUC-s	= PUC with prostatic stromal involvement
RCP	= radical cystoprostatectomy
RFS	= recurrence-free survival

Introduction

The standard surgical approach in male patients with muscle-invasive bladder cancer is radical cystoprostatectomy (RCP) with lymphadenectomy and urinary diversion. To improve sexual and functional outcomes, prostate sparing cystectomy was advocated. [1-3] While it is technically feasible, the oncological safety of a prostate sparing approach is under debate. [4] Oncological concerns include the risk of incidental csPCA, PUC and to a lesser extent HGPIN. Several studies demonstrated that prostatic involvement is common at RCP. [5-12] However, few studies mention the incidence of prostatic involvement (PUC, (cs)PCA and/or HGPIN) in subgroups of patients considered to be at low risk based on pre-operatively available data. [5-7] In addition, limited pre-operative risk factors for prostatic involvement have been identified. [5,11]

In this study we report the incidence of prostatic involvement in RCP specimens in the total cohort and select subgroups of patients. We identified pre-operative risk factors for prostatic involvement and assessed the impact of prostatic involvement on survival outcomes after RCP.

Materials and methods

Cohort selection

A total of 1,553 men underwent RCP for primary urothelial bladder carcinoma at the University of Southern California between 1971 and 2008. After excluding 77 patients with previously histologically proven (31) or treated (46) PCA, we reviewed data of 1,476 patients. Clinical and histopathologic data were prospectively collected by an experienced data-entry team, double-checked by a single database manager (G.M.) and stored in our institutional review board approved database. The incidences of (cs)PCA and PUC were determined in all 1,476 patients. The incidence was also determined in patient subgroups often eligible for inclusion in prostate sparing cystectomy series, including age 60 years or younger, pre-operative PSA ≤ 2.5, cNMIBC (cT1 or less) and/or a bladder tumor located outside the bladder neck/trigone. For the purpose of this analysis we considered only the 1,003 patients treated between 1990 and 2008 ('PSA-era cohort') since PSA information was not routinely available before 1990. This PSA-era cohort was also used to determine the incidence of HGPIN, because presence of HGPIN was not routinely reported before 1990.

Specimen processing

After RCP, the prostatic surface was inked and fixed in 10% neutral buffered formalin solution for 24 hours. The prostate was subsequently cross-sectioned at 3 to 5 mm intervals perpendicular to the urethra from apex to base to the junction of the seminal vesicles and prostate. In addition to the prostatic apex, representing the distal margin if not submitted separately for frozen section, a complete slice or cross-section of the distal, mid and proximal prostate was submitted along with any other abnormal or suspicious areas and sections including the right and left seminal vesicles at the junction with the prostate. Each section was embedded in paraffin, sectioned by microtome and mounted on glass slides according to standard procedure. Hematoxylin and eosin staining was done. As needed, immunohistochemical staining with monoclonal antibodies was performed to aid in diagnosing PCA. Tissue samples were microscopically examined by a team of dedicated uropathologists.

Histopathologic variables

Bladder cancer and PCA were staged according to the 2002 American Joint Committee on Cancer (AJCC) TNM staging classification.[13] csPCA was defined as extraprostatic extension, seminal vesicle invasion, positive surgical margin, lymph node metastasis or Gleason score 7 or greater. We used the 2005 modified Gleason score.[14] HGPIN was defined as grade II or higher prostatic epithelial neoplasia.[15] PUC was stratified as PUC-d and PUC-s.

Follow-up and statistical analysis

We performed univariable analysis with the Pearson chi-square or Fisher exact test for categorical variables and the Wilcoxon rank sum test for not normally distributed continuous variables as well as multivariable analysis with multiple logistic regressions to test the association of demographic and clinical characteristics with prostatic involvement. Multivariable analysis included preoperative variables only except for bladder cancer location and disease focality. Since the latter 2 variables were not available preoperatively, they were based on the RCP specimen. Median bladder cancer follow-up was 13.2 years (range 0.1 to 36.6). Bladder cancer OS and RFS were calculated using Kaplan-Meier plots. The log rank test and Cox proportional hazard modeling were used to compare OS and RFS between subgroups with 2-sided $p < 0.05$ considered significant.

Results

Of the 1,476 patients included in analysis 753 (51.0%) had PCA and/or PUC, of whom 96 (6.5%) received neo-adjuvant chemotherapy. A total of 462 patients (31.3%) had recurrent disease, including 357 (77.3%) with distant and 105 (22.7%) with local pelvic recurrence.

Prostatic Adenocarcinoma

PCA was present in 559 patients (37.9%) with a median age of 69 years and a median preoperative PSA of 1.66 ng/ml (range 0.01 to 83). Six patients (0.4%) had preoperative PSA greater than 20 ng/ml, including 2 with csPCA and 1 with PCA. csPCA was present in 123 cases (8.3%), due to a Gleason score of 7 or greater in 90 (73.2%; Table 1). Preoperative variables independently associated with csPCA were increasing age and PSA (Table 4). Table 2 lists the incidence of PCA and csPCA in the patient subgroups. Of the 162 patients 60 years or younger with PSA 2.5 ng/ml or less PCA was present in 61 (37.7%), including 9 (14.8%) with csPCA. The 10-year bladder cancer RFS rate was not impacted by csPCA (64.8% vs 64.2%, p = 0.92). The 10-year OS rate was higher in patients without than with csPCA (45.2% vs 27.8%, p = 0.02). This was most likely due to the higher median age in the csPCA group (70 vs 66 years) since no patient with csPCA died of prostatic cancer. Also, csPCA was not associated with OS after adjusting for age, bladder cancer stage, lymph node status and lymphovascular invasion (HR = 1.20, p = 0.13).

Table 1: Characteristics of 559 patients with incidental prostatic adenocarcinoma

	Number of patients (%)
Age	
65 or less	199 (35.6)
Greater than 65	360 (64.4)
Pre-operative PSA	
2.5 or less	272 (48.7)
2.6 – 3.9	50 (8.9)
4.0 – 9.9	63 (11.3)
10.0 – 19.9	10 (1.8)
20.0 or greater	3 (0.5)
Missing	62 (11.1)
Not applicable*	99 (17.7)

Gleason score	
5 or less	184 (32.8)
6	274 (49.0)
7	78 (14.0)
8-10	12 (2.2)
Missing	11 (2.0)
PCA pathologic stage	
pT2a	320 (57.2)
pT2b/c	207 (37.0)
pT3a	25 (4.5)
pT3b	6 (1.1)
pT4a	1 (0.2)
PCA lymph node involvement	
Negative	552 (98.7)
Positive	7 (1.3)
PCA surgical margin status	
Negative	535 (95.5)
Positive	24 (4.3)
Clinically significant PCA	123 (22.0)
- Gleason score ≥ 7	90
- Extraprostatic extension	32
- Seminal vesicle involvement	6
- Positive surgical margin	24
- Lymph node involvement	7

PCA = prostate adenocarcinoma

** PSA data were not available before 1990*

Table 2: Prostatic involvement in the PSA-era cohort

	No of pts (%)	No. Age 60 or less (%)	No. PSA 2.5ng/ml or less (%)	No. cTa-cT1 bladder cancer (%)	No. cancer outside bladder neck/ trigone
Overall	1,003	249	592	392	677
Prostate adenocarcinoma	460 (45.9)	90 (36.1)	270 (45.6)	174 (44.4)	304 (44.9)

Clinical significant prostate adeno-carcinoma	103 (10.3)	15 (6.0)	46 (7.8)	42 (10.7)	70 (10.3)
Prostatic urothelial carcinoma	203 (20.2)	41 (16.5)	117 (19.8)	84 (21.4)	80 (11.8)
High-grade prostatic intra-epithelial neoplasia	514 (51.2)	110 (44.2)	333 (56.3)	196 (50.0)	347 (51.3)

Prostatic Urothelial Carcinoma

PUC was present in 312 patients (21.1%), including 163 (52.2%) with PUC-d only and 149 (47.8%) with PUC-s (table 3). Of the 149 patients with PUC-s 120 (80.5%) had stromal invasion secondary to PUC-d (noncontiguous) and 29 (19.5%) had stromal invasion from an extravesical tumor (contiguous). We analyzed the total cohort to identify PUC risk factors (Table 4). PUC was present in 6 of the 76 patients (7.9%) 60 years or younger with cNMIBC outside the bladder neck/trigone. Ten-year RFS in patients with no PUC, PUC-d and PUC-s was 68.2%, 59.6% and 39.5%, respectively (p <0.001, part A of figure 1). PUC-d (HR 1.34, 95% CI 1.01-1.78, p = 0.043) and PUC-s (HR 1.36, 95% CI 1.04-1.78, p = 0.023) were associated with decreased RFS after adjusting for age, bladder cancer stage and grade, lymph node status, surgical margin status, lymphovascular invasion and adjuvant chemotherapy. Ten-year OS in patients with no PUC, PUC-d and PUC-s was 47.1%, 43.3% and 21.7%, respectively (p <0.001; part B of figure 1). After adjusting for the mentioned variables, PUC-s (HR 1.26, 95% CI 1.03-1.57, p = 0.038) was independently associated with decreased OS, while PUC-d (HR 1.00, 95% CI 0.82-1.24, p = 0.96) did not alter OS. Contiguous invasion was associated with lower 10-year RFS than noncontiguous invasion (27.3% vs 40.3%, p <0.001). However, this effect did not attain statistical significance after adjusting for the mentioned variables (HR 1.65, p = 0.07).

Table 3: Characteristics of patients with prostatic urothelial carcinoma

	No. PUC-d only (%)	No. PUC-s (%)
Overall	163	149
Age		
Younger than 65	75 (46.0)	56 (37.6)
Older than 65	88 (54.0)	93 (62.4)
Urinary diversion		
Orthotopic	90 (55.2)	67 (45.0)
Non-orthotopic	73 (44.8)	82 (55.0)

Clinical stage		
cT2 or less	147 (90.2)	94 (63.1)
Greater than cT2	16 (9.8)	55 (36.9)
Pathological subgroup		
≤ pT2, pN0	110 (67.5)	-
> pT2, pN0	14 (8.6)	84 (56.4)
pTany, pN1-3	39 (23.9)	65 (43.6)
Tumor grade		
Low	20 (12.3)	6 (4.0)
High	143 (87.7)	143 (96.0)
Multifocal disease		
Yes	66 (40.5)	77 (51.7)
No	97 (59.5)	72 (48.3)
Lymphovascular invasion		
Yes	117 (71.8)	73 (49.0)
No	46 (28.2)	76 (51.0)
Carcinoma-in-situ		
Yes	35 (21.5)	41 (27.5)
No	128 (78.5)	108 (72.5)
Tumor location		
At or below trigone	82 (50.3)	85 (57.0)
Other	81 (49.7)	64 (43.0)
Adjuvant chemotherapy		
Yes	35 (21.5)	61 (40.9)
No	128 (78.5)	88 (59.1)

PUC-d = Prostatic urothelial carcinoma involving the prostatic ducts

PUC-s = Prostatic urothelial carcinoma involving the prostatic stroma

High Grade Prostatic Intra-epithelial Neoplasia

Analysis of the PSA era cohort of 1,003 patients revealed that 514 (51.2%) had HGPIN, including 289 of 460 (62.8%) with PCA, 55 of 103 (53.4%) with csPCA and 225 of 543 (41.4%) without PCA. Factors associated with HGPIN on univariable analysis included increasing age, increasing PSA and csPCA (each $p < 0.001$). On multivariable analysis including age and PSA, only increasing age was associated with HGPIN (OR 1.02, 95% CI 1.01-1.04, $p = 0.005$). Ten-year OS rates were similar in patients with and without HGPIN (41.6% and 44.7%, respectively, $p = 0.73$).

Table 4: Association of clinical and histopathologic variables with presence of clinical significant prostatic adenocarcinoma and prostatic urothelial carcinoma

	csPCA (N = 123)	
	Univariable analysis	**Multivariable analysis OR (95%CI)**
Clinical variables		
Increasing age	p < 0.001	OR 1.03 (1.01-1.06) p = 0.004
Increasing PSA	p < 0.001	OR 1.09 (1.04-1.14) p < 0.001
Pre-operative radiotherapy (yes vs no)	p = 0.07	-
Pre-operative chemotherapy (yes vs no)	p = 1.00	-
TURBT specimen related variables		
Bladder cancer stage (>cT2 vs ≤cT2)	p = 0.62	-
Bladder cancer grade (high vs low)	p = 1.00	-
Concomitant LVI (present vs absent)	p = 1.00	-
Concomitant CIS (present vs absent)	p = 0.30	-
RCP specimen related variables		
Bladder cancer stage (> pT2 vs ≤ pT2)	p = 0.62	-
Bladder cancer focality (multifocal vs unifocal)	p = 0.85	-
Bladder cancer at or below trigone (yes vs no)	p = 0.92	-
Concomitant LVI (present vs absent)	p = 0.83	-
Concomitant CIS (present vs absent)	p = 0.44	-

OR = Odds Ratio; 95% CI = 95% confidence Interval

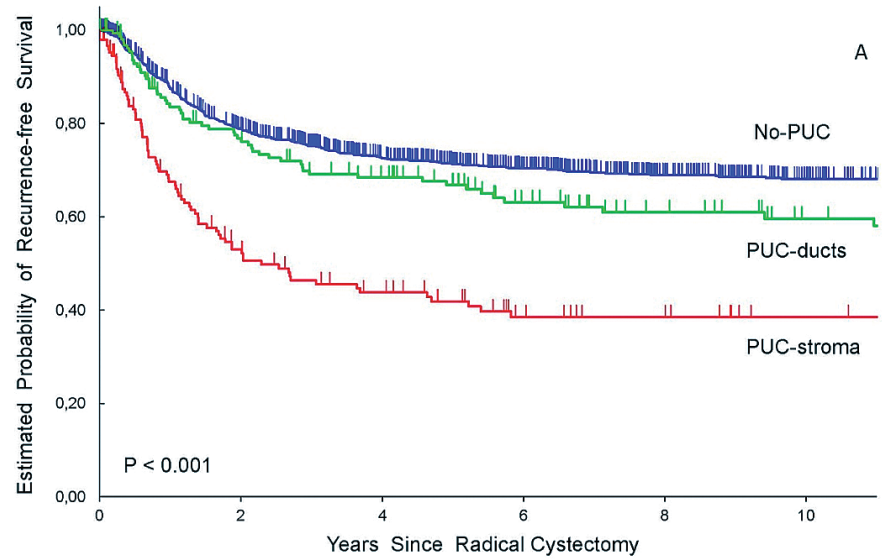
csPCA = clinical significant prostatic adenocarcinoma; PUC = prostatic urothelial carcinoma

TURBT = transurethral resection of bladder tumor; RCP = radical cystoprostatectomy;

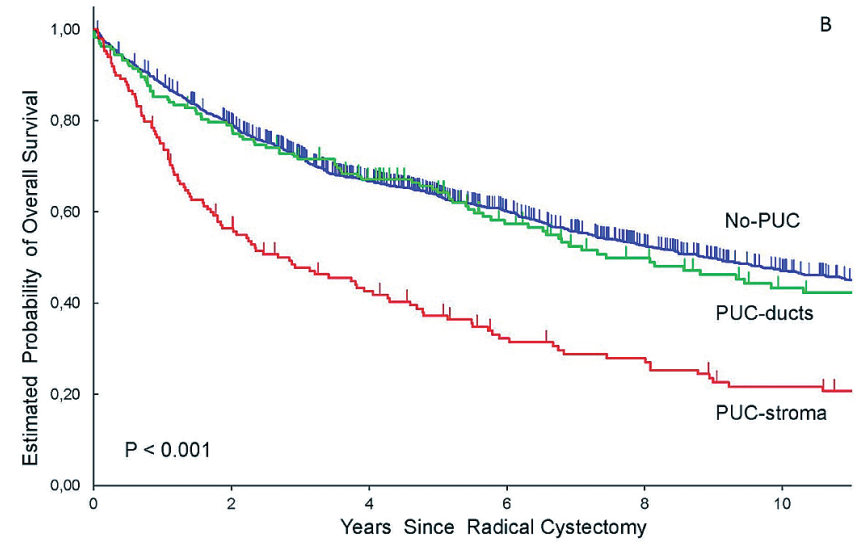
PUC-ducts only (N = 163)		PUC-stroma (N = 149)	
Univariable analysis	**Multivariable analysis OR (95%CI)**	**Univariable analysis**	**Multivariable analysis OR (95%CI)**
p = 0.94	-	p = 0.021	OR 1.02 (0.99-1.03) p = 0.10
p = 0.69	-	p = 0.27	-
p = 0.76	-	p = 0.41	-
p = 0.61	-	p = 0.73	-
p = 0.029	OR 2.64 (1.43-4.87) p = 0.002	p < 0.001	OR 10.2 (6.60-15.70) p < 0.001
p = 0.19		p = 0.021	OR 1.67 (1.05-2.67) p = 0.029
p = 0.31	-	p = 0.73	-
p < 0.001	OR 1.97 (1.38-2.81) p < 0.001	p = 0.70	-
p = 0.032	-	p < 0.001	-
p < 0.001	OR 2.24 (1.56-3.21) p < 0.001	p = 0.001	OR 1.51 (1.03-2.21) p = 0.034
p < 0.001	OR 2.54 (1.79-3.60) p < 0.001	p < 0.001	OR 3.23 (2.21-4.72) p < 0.001
p = 0.27	-	p < 0.001	
p < 0.001	-	p < 0.001	-

CIS = carcinoma-in-situ; *LVI = Lymphovascular invasion*

Figure 1: Recurrence-free survival (A) and overall survival (B) stratified by presence of prostatic urothelial carcinoma



	No. at risk					
No PUC	1164	821	631	510	398	307
PUC-d	163	112	91	65	50	39
PUC-s	149	67	49	31	26	19



	No. at risk					
No PUC	1164	901	675	539	420	127
PUC-d	163	127	102	73	56	43
PUC-s	149	81	57	38	32	23

Discussion

More than half of the study patients had cancer involving the resected prostate. PCA and PUC were present in 37.9% and 21.1% of cases, respectively. Comparing the incidence among studies is challenging due to differences in study eras, patient populations and pathological processing.[5-12] To illustrate this point, a recent review described an average 28.5% PCA rate but PCA rates up to 50% to 60% were reported in the individual studies.[8,9,12] The high rate of PCA is not surprising, given the advanced age of patients with bladder cancer. Many of these PCAs may have remained clinically silent and yet 22.0% of incidental PCAs were clinically significant based on histopathological criteria. Although csPCA did not alter survival after RCP, it might impact survival when the prostate is preserved.

A few, mostly small studies mention the incidence of precancerous lesions in RCP specimens. HGPIN incidence rates of 14% to 75% in patients without PCA and 50% to 95% in patients with PCA were reported.[8,16,17] In our series, which to our knowledge is the largest to date, HGPIN was present in 51.2% of patients and it was also associated with PCA and csPCA. However, the clinical significance of this finding requires future investigation. Nonetheless, our study underscores the frequent involvement of the prostate with cancer or precancerous lesions at RCP.

The AJCC TNM classification for bladder cancer was recently revised based on previous studies suggesting that the depth of PUC invasion affects prognosis.[18-22] In the current 7th edition prostatic urethral/duct invasion by bladder cancer is excluded as pT4a disease.[22] Our study supports this revision since the PUC-s prognosis was worse than the PUC-d prognosis. In addition, on univariable analysis contiguous prostatic stromal invasion was associated with decreased RFS compared to noncontiguous prostatic stromal invasion. This finding is consistent with our smaller previous study.[19] Notably, this effect was not seen on multivariable analysis (HR 1.65,p = 0.07), most likely due to the limited number of patients (29) with contiguous PUC-s. In contrast to PUC, csPCA was not associated with the prognosis after RCP, indicating that the prognosis after RCP relies on bladder cancer. Nonetheless, the treatment burden of csPCA may have been present since data on PSA recurrence were not available.

Concomitant carcinoma in situ and trigonal tumors were reported to be risk factors for PUC.[5,11,23] However, most groups did not analyze risk factors for PUC-d and PUC-s separately despite the difference in prognosis. In our study clinically nonorgan confined disease, multifocal disease and trigonal tumor location were independent risk factors for PUC-d and PUC-s. Carcinoma in situ in the transurethral resection specimen

was independently associated with PUC-d but not with PUC-s. With respect to PCA, a limited number of risk factors were identified. Pettus et al reported increasing age as a risk factor for PCA.[5] Voigt et al analyzed transurethral prostatic resection specimens and found that increasing body mass index and decreasing prostatic volume were associated with PCA.[24] We found that increasing age and PSA were independent risk factors for PCA and csPCA, while body mass index was not (data not shown). Prostatic volume was not available.

An important finding of our study is that prostatic involvement cannot be ruled out using standard available preoperative data. For example, more than a third of patients 60 years or younger with PSA 2.5 ng/ml or less had PCA. PUC was also present in 8% of patients younger than 60 years with disease less than cT2 located outside the bladder trigone. Others reported similar observations. [5,10] Ward et al noted a 23% PCA rate in patients with preoperative PSA less than 2.0 ng/ml and normal digital rectal examination. [10] Pettus et al found that 41% of patients with cNMIBC had PUC. [5] Together these data suggest that performing prostate sparing cystectomy based on the standard available variables carries a considerable oncological risk.

While preoperative magnetic resonance imaging, prostatic biopsies or transurethral resection may possibly increase the preoperative detection rate of prostatic involvement, to our knowledge the diagnostic panel that offers the optimal detection rate remains unknown. Also, oncological outcomes in prostate sparing cystectomy series are inconsistent. Some groups reported outcomes comparable to those of RCP, while others reported a remarkably high rate of metastatic disease.[1-3,25] These concerns, coupled with the consistent outcomes of radical cystoprostatectomy, suggest that a prostate sparing approach requires optimal patient selection and surgical technique to achieve adequate oncological control.

This study has limitations. It was retrospective with the inevitable risks of selection bias and missing data. Whole mount step sectioning was not done that may have resulted in cancer under detection. Also, tumor volume was not part of the csPCA definition, possibly underestimating the incidence of csPCA. In addition, slides were not re-reviewed, allowing for interobserver variability. Routine prostatic biopsies were not done, although they may have preoperatively identified patients with prostatic tumor involvement. Lastly, data on recurrence and/or treatment for PCA after RCP were lacking, although cause of death was available. While we acknowledge these limitations, to our knowledge this is currently the largest study of this topic with comprehensive data

analysis and a standardized surgical technique.

Conclusions

More than half of the patients undergoing RCP for urothelial cancer of the bladder had cancer involving the prostate. PUC, particularly PUC-s, was associated with a worse prognosis, while the presence of csPCA did not alter survival. Preoperative clinical and histopathological risk factors are not reliable enough to accurately predict csPCA and/or PUC.

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CHAPTER 3

Reproductive organ involvement in female patients undergoing radical cystectomy for urothelial bladder cancer

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Journal of Urology 2012;188(6):2134-2138

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Abstract

Purpose

To evaluate pathological involvement of the reproductive organs in a cohort of female patients treated with anterior pelvic exenteration for invasive urothelial carcinoma of the bladder.

Materials and Methods

A total of 2,098 patients with bladder cancer underwent cystectomy at our institution between 1971 and 2008, including 458 females, of whom 411 had urothelial carcinoma of the bladder. Median follow-up was 12.2 years (range 0.1 to 35.5). We reviewed the clinicopathological features of female patients treated with cystectomy who had pathological reproductive organ involvement. Recurrence-free and overall survival is reported using Kaplan-Meier survival curves.

Results

Of 411 patients with urothelial carcinoma of the bladder 267 underwent reproductive organ removal with cystectomy. A total of 20 patients (7.5%) had reproductive organ involvement, including 10 (3.8%) with vaginal, 2 (0.7%) with cervical and 1 (0.3%) with uterine involvement only, while the remaining 7 (2.6%) had multiple reproductive organs involved. Median age was 71 years. Clinical stage T4a was diagnosed in 25% of cases. A palpable mass, hydronephrosis and positive lymph nodes at anterior pelvic exenteration (each $p < 0.001$) were associated with reproductive organ involvement. Recurrence developed in 14 patients (70%) at a median of 7 months (range 1 to 22). Five-year recurrence free and overall survival rates were 14.9% and 8.8%, respectively.

Conclusions

The risk of reproductive organ involvement in female patients who undergo anterior pelvic exenteration for urothelial carcinoma of the bladder was about 7.5% with the vagina the most commonly involved organ. A palpable mass and hydronephrosis were among the preoperative clinical factors associated with reproductive organ involvement. The prognosis is poor in patients with reproductive organ involvement.

Abbreviations and Acronyms

APE	= anterior pelvic exenteration
BSO	= bilateral salpingooophorectomy
OS	= overall survival
RFS	= recurrence-free survival
RO	= reproductive organ
TAH-BSO	= total abdominal hysterectomy-BSO
UC	= urothelial carcinoma

Introduction

In female patients with muscle invasive bladder cancer, APE is traditionally the treatment of choice. This operation includes cystectomy, bilateral pelvic lymph node dissection, hysterectomy, BSO and resection of the upper third of the anterior vaginal wall. [1] With the close proximity of the uterus, cervix and vagina, APE is believed to provide optimal local control since local tumor extension may affect these ROs. Although this approach aims to optimize local cancer control, removing ROs at radical cystectomy has a great impact on sexual outcomes. [2] While it is technically feasible to preserve ROs at radical cystectomy, the question remains whether the routine removal of ROs is required in all female patients. [3,4]

To answer this question, it is important to investigate the incidence of RO involvement. Moreover, to identify possible candidates for RO preservation, clinicopathological factors predicting RO involvement at APE must be identified. A few groups have investigated RO involvement at APE but most cohorts were rather small or included all types of histology.[5–10] As a result, data on risk factors for RO involvement are limited.[10] In this study we focused on the incidence of RO involvement in what is to our knowledge the largest reported cohort of female patients who underwent APE for UC of the bladder.

Materials and Methods

A total of 2,098 patients underwent radical cystectomy for bladder cancer with intent to cure at our institution between 1971 and 2008, of whom 458 (21.8%) were female. To focus on female patients with bladder UC, 47 (10.3%) with nonUC histology were excluded from analysis. The total cohort consisted of 411 female patients. Clinical and pathological characteristics of all patients were prospectively collected and stored in our institutional review board approved bladder cancer database.

A total of 267 patients underwent APE, including removal of the bladder, bilateral pelvic lymph nodes, uterus, fallopian tubes and anterior vaginal wall.[11] TAH-BSO was done before cystectomy in 94 patients and 45 underwent partial resection sparing at least 1 ovary, while data were missing on 5. The ovaries were spared in young patients and based on urologist discretion.

All cystectomy specimens were examined using the same pathological protocol. Multiple sectioning and histological evaluation was performed on the primary bladder tumor, bladder wall (adjacent and distant bladder mucosa of the primary

tumor), uterus, cervix, vagina, fallopian tubes, ovaries and lymph nodes. Pathological evaluation of all parts of the specimen followed a standardized protocol for prosection and microdissection. Pathological tumor staging and grading were standardized to the American Joint Committee on Cancer 2002 TNM classification and 1973 WHO recommendations, respectively.[12,13] Pathological subgroups were divided based on tumors that were organ confined (pTa, pTis, pT1, pT2a and pT2b, N0), extravesical (pT3a, pT3b and pT4, N0) and lymph node positive. Lymphovascular invasion was defined as tumor cells in an endothelium lined space with no underlying muscular walls.

All patients were routinely followed postoperatively at 4-month intervals in year 1, 6-month intervals in year 2 and annually thereafter. Median follow-up was 12.2 years (range 0.1 to 35.5). From the whole cohort 11 patients who were lost to follow-up were censored from analysis at the last follow-up date.

Time to OS was calculated from the date of radical cystectomy to the date of death from all causes. RFS was calculated from the date of radical cystectomy to the date of first documented clinical recurrence or the date of death, whichever occurred first. If lost to follow-up before recurrence, patients were censored at the date of last follow-up. A Kaplan-Meier curve was used to calculate survival functions. Chi-square analysis was performed to test associations between clinicopathological factors and RO involvement. Statistical analyses were performed using SAS®, version 9.2.

Results

Of the 411 female patients with bladder UC, 267 underwent APE at cystectomy and 20 (7.5%) had RO involvement (Table 1). Ten patients (3.8%) had vaginal involvement only, 2 (0.7%) had cervical involvement only and 1 (0.3%) had uterine involvement only. Seven patients (2.6%) had multiple reproductive organs involved. In 1 patient with tumor involvement of the fallopian tubes and deep cervix the ovary was also involved. This was the only case of ovarian involvement. In addition, in a patient with vaginal and cervical involvement, the urethra was positive for UC. In all cases of RO involvement direct tumor extension was the mechanism of involvement.

Table 1: Reproductive organ involvement in the present study and the literature

	No. of pts	Histo-logy	RO involvement (%)				
			Overall	Uterus only	Vagina only	Cervix only	Multiple ROs
Salem et al. [5]	250	All	12 (4.8)	1 (0.4)	11 (4.4)	0	0
Chang et al. [6]	68	All	2 (5.0)*	2 (5.0)	0	0	0
Groutz et al. [7]	37	All	1 (2.7)	1 (2.7)	0	0	0
Chen et al. [8]	115	TCC	6 (5.2)	0	2 (1.7)	1 (0.9)	3 (2.6)**
Varkarakis et al. [9]	52	TCC	3 (5.8)	1 (1.9)	1 (1.9)	0	1 (1.9)
Ali-El-Dein et al. [10]	98	TCC	7 (7.1)	-	-	-	-
Present series	267	TCC	20 (7.5)	1 (0.3)	10 (3.8)	2 (0.7)	7 (2.6)***

RO = reproductive organ; TCC = transitional cell carcinoma

* *Excluding third patient with primary uterine sarcoma with incidence based on 40 patients with intact ROs removed.*

** *Also urethral involvement in 2 patients*

*** *Also ovarian involvement in 1 patient*

Table 2 lists the clinical and histopathologic features of patients with RO involvement. A review of this cohort revealed a median age of 71 years (range 38 to 89). Of the patients 95% had a high grade tumor. Clinical staging was done using bimanual examination and radiological imaging, mostly computerized tomography, in all patients preoperatively. Clinical stage T4a was diagnosed in 5 patients (25%), while 10 (50%) were thought to have organ confined disease preoperatively. Greater than 90% of the cases were treated in the computerized tomography era. Lymph node positive disease was found in 12 patients (60%).

Three (15%) and 7 patients (35%) underwent neo-adjuvant and adjuvant chemotherapy, respectively. Only 1 patient (5%) underwent orthotopic diversion. As expected, patients without RO involvement had less frequent lymph node involvement (24%) and a higher percent of orthotopic diversion (43%).

Table 2: Baseline characteristics of total study cohort

Variable	No of pts with RO involvement (%)	No of pts without RO involvement (%)
Total	20	391
Age		
Less than 60	6 (30)	94 (24.0)
60-69	3 (15)	143 (36.6)
70-79	6 (30)	114 (29.2)
Greater than 80	5 (25)	40 (10.2)
Urinary diversion		
Orthotopic	1 (5)	168 (43.0)
Non-orthotopic	19 (95)	223 (57.0)
Clinical tumor stage		
pT2 or less	10 (50)	370 (94.7)
Greater than pT2	10 (50)	21 (5.4)
Pathological tumor stage		
pT0-pTis	0	86 (22.0)
pT1	0	62 (15.9)
pT2a	0	35 (9.0)
pT2b	0	62 (15.9)
pT3a	0	43 (11.0)
pT3b	0	100 (25.6)
pT4a	19 (95)	0
pT4b	1 (5)	3 (0.8)
Pathologic subgroups		
pT0-2,pN0	0	220 (56.3)
pT3-4, pN1-3	8 (40)	76 (19.4)
pTany, pN1-3	12 (60)	95 (24.3)
Tumor grade		
Low	1 (5.0)	61 (15.6)
High	19 (95)	330 (84.4)
Concomitant Cis		
Present	9 (45)	217 (55.5)
Absent	11 (55)	174 (44.5)
Multifocal disease		
Present	16 (80)	274 (70.1)
Absent	4 (20)	117 (29.9)
Lymphovascular invasion		
Present	10 (50)	119 (30.4)
Absent	10 (50)	272 (69.6)

Margin status		
Positive	1 (5)	2 (0.5)
Negative	19 (95)	389 (99.5)
Urethral involvement		
Present	1 (5.0)	4 (1.1)
Absent	16 (80.0)	356 (91.0)
Missing	3 (15.0)	31 (7.9)
Neo-adjuvant radiotherapy		
Yes	3 (15)	25 (6.4)
No	17 (85)	366 (93.6)
Neo-adjuvant chemotherapy		
Yes	3 (15)	18 (4.6)
No	17 (85)	373 (95.4)

RO = reproductive organ

The clinical variables associated with RO involvement were hydronephrosis and a palpable mass (each $p < 0.001$). Hydronephrosis was present in 13 patients and a palpable mass was reported in 10 of 20. Of pathological factors in the radical cystectomy specimen associated carcinoma in situ, multifocality and lymphovascular invasion had no significant association with RO involvement. However, lymph node positive disease was associated with RO involvement ($p < 0.001$). Due to few patients with RO involvement, we could not analyze whether any associated variables had an independent association.

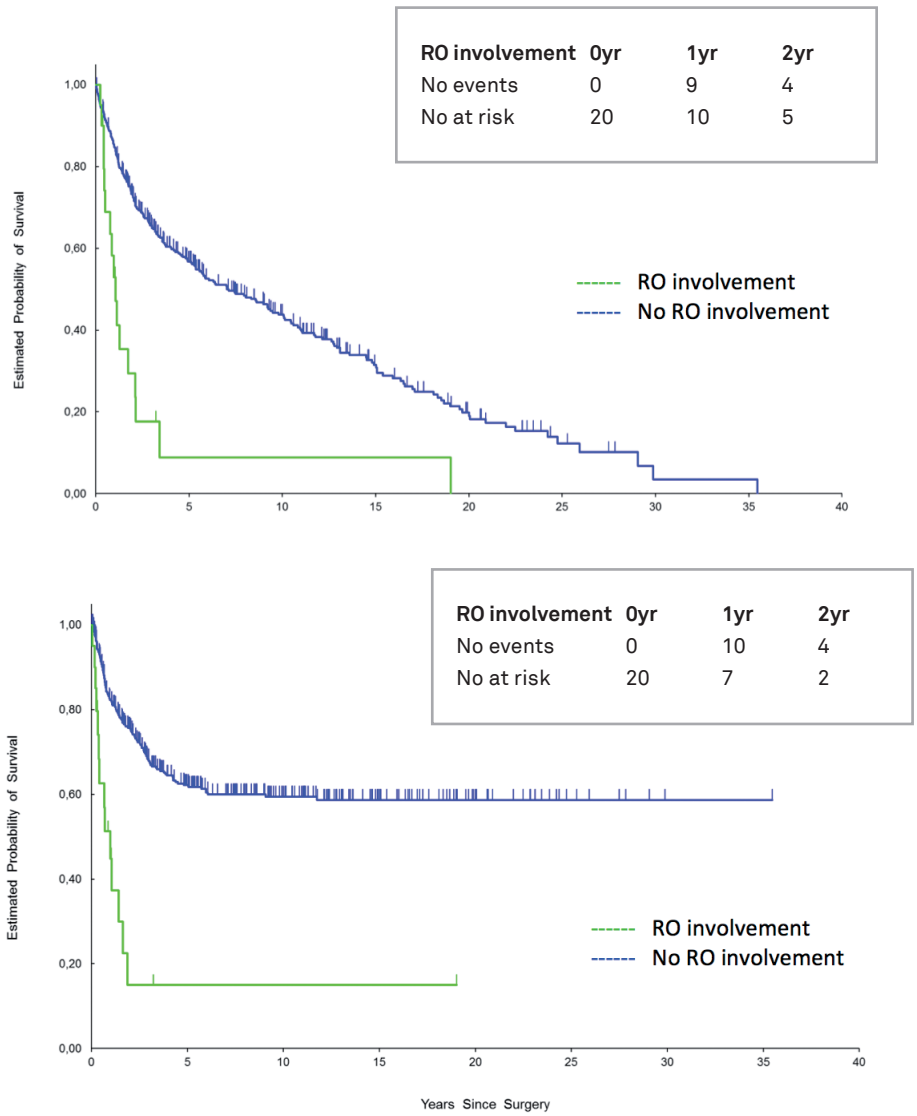
Disease recurred in 14 patients (70%) with RO involvement at a median of 7 months (range 1 to 22). Five of these patients (25%) had local recurrence, which was biopsy proven when suspicious or equivocal, and 9 (45%) had distant metastases. Table 3 shows a lower recurrence rate in female patients without RO involvement, as expected. Overall survival at 5 years was 56.8% for patients without RO involvement, which was significantly higher than the 8.8% in those with RO involvement ($p < 0.0001$, figure 1A). Single RO involvement was present in 13 patients, of whom 8 died of bladder cancer. Six patients had 2 ROs involved, of whom 4 died of disease. The patient with involvement of 3 ROs also died of disease. Two and 5-year RFS in patients without RO involvement was 75.7% and 62.2%, respectively. In patients with RO involvement all 14 recurrences developed within 2years, resulting in a 2-year RFS of 14.9% ($p < 0.001$,figure 1B).

Table 3: Overall survival and recurrence free survival stratified by reproductive organ involvement

	RO- involvement	No RO involvement	Total cohort
No of pts	20	391	411
Mean % overall survival (±SE)			
2 year	29.4 ± 10.8	73.0 ± 2.3	71.0 ± 2.3
5 year	8.8 ± 7.7	56.8 ± 2.6	54.7 ± 2.6
Mean % recurrence free survival (±SE)			
2 year	14.9 ± 9.5	75.7 ± 2.3	73.2 ± 2.3
5 year	14.9 ± 9.5	62.2 ± 2.7	60.1 ± 2.7

RO = reproductive organ; SE = standard error

Figure 1: Overall survival (a) and recurrence free survival (b) of patients with (green curves) and without (blue curves) reproductive organ involvement (RO)



Discussion

Anterior pelvic exenteration in females includes removal of the internal genitalia and causes a significant impact on quality of life. The functional and sexual impairments described include loss of libido, difficult intromission and lack of orgasm.[2,14] Improvement in surgical techniques with an increasing number of females undergoing orthotopic diversion has resulted in excellent functional and oncological outcomes in well selected patients.[14,15]

Despite advances in functional outcomes, little improvement has been made in preserving sexual function with routine removal of the ROs as the standard of care. RO preservation while performing orthotopic diversion is feasible and decreases the risk of neobladder-vagina fistula.[4,16] However, oncological safety has not been extensively studied. In the current series using a large, homogeneous cohort of 411 female patients 267 underwent TAH-BSO at cystectomy, of whom 7.5% had RO involvement. Although a few groups have reported this topic with an incidence rate of between 2.7% and 5.8%, the cohorts have been rather small and/or included all histological types. [5–10] In the large series of 609 female patients undergoing cystectomy reported by Ali-El-Dein et al only 16.1% had UC (Table 1).[10] However, the incidence of RO involvement depended on histological tumor type. A significantly higher incidence was found in patients with UC than in those with squamous cell carcinoma (7.1% vs 1.8%). In smaller studies of UC only Chen [8] and Varkarakis [9] et al reported similar incidence rates of 5.2% and 5.8%, respectively.

We found the vagina to be the most frequently involved sexual organ. It was involved in 14 patients, of whom 10 had vaginal involvement only, while 4 had vaginal combined with other RO involvement. This corresponded to an overall incidence of 5% of all cystectomy cases. In 15 patients (75%) UC was located at the posterior or the base of the bladder, suggesting that direct invasion may account for most RO involvement. Our finding is fairly consistent with those in the other UC only series by Chen [8] and Varkarakis [9] et al, in which the vagina was involved as a single organ or in combination with other organs in 4.3% and 3.8% of cases, respectively.

Survival of patients with RO involvement is generally poor. Five-year RFS was 14.9% in patients with RO involvement compared to 62.2% in those without RO involvement. A total of 14 patients (70%) in the RO group had recurrence, which was local in 5 and distant in 9, all within 2 years after APE with a poor survival outcome (fig. 1). We found no late recurrences at a median follow-up of more than 12 years. These poor outcomes in patients with RO involvement were expected and underscore the need for

aggressive treatment. Based on low overall incidence rates of RO involvement, it was suggested that routine removal of ROs would be unnecessary.[10] However, with RO involvement in approximately 1 of 13 women with 30% 2-year OS, we believe that preserving ROs in unselected female patients is not oncologically safe. However, we think that a subset of female patients may benefit from RO preservation. Unfortunately, identifying these patients remains a challenge with clinical under staging as a major drawback.

In this study 10 patients (50%) had RO involvement when the tumor was believed to be organ confined preoperatively (cT2) (50% up staging). To identify patients suitable for RO preservation, some groups investigated the association between histopathological variables and RO involvement. [9,10] Only 1 series included a sufficient number of patients to show an association between clinicopathological factors and RO involvement. [10] Ali-El-Dein et al found that higher tumor grade and lymph node metastatic disease were associated with RO involvement. They recommended not preserving ROs in these patients.

Although we agree that patients with lymph node metastases are not suitable candidates, this cannot adequately be determined preoperatively. Also, some patients with high grade disease may be suitable candidates for RO preservation but more preoperative factors must be analyzed. We found that hydronephrosis and a palpable mass were associated with RO involvement. Unfortunately, we did not identify a sufficient number of patients for multivariable analysis to investigate whether these variables are, in fact, associated with RO involvement. This clearly outlines the need for a large cohort and a multi-institutional study to investigate which female patients are suitable for RO preservation.

The majority of RO involvement was a result of direct tumor invasion. Thus, when extensive disease is suspected at preoperative evaluation, RO preserving surgery should not be performed. We also emphasize that in the modern neo-adjuvant era neo-adjuvant chemotherapy is recommended for patients with preoperative suspicion of RO involvement. This might decrease the risk of pathological RO involvement.

The incidence of ovarian involvement is extremely rare. Of almost 1,000 female patients only 2 with ovarian involvement have been described (table 1). Groutz et al reported metastatic disease in 1 patient with a preserved ovary 2 years after cystectomy. [7] They stated that suboptimal initial treatment and a significant subsequent delay in cystectomy might have contributed to this outcome. The second patient with ovarian involvement was found in the current study. In this case all represented sections of the bladder, cervix and fallopian tubes were also involved with tumor. This is consistent

with findings that direct invasion is the mechanism of RO involvement. Therefore, ovarian preservation appears to be oncologically safe, especially in young females, if the tumor is not found to extensively invade outside the bladder intra-operatively.

Study limitations include its retrospective nature. Because some patients underwent TAH-BSO before cystectomy, the incidence rate of uterine involvement may have been underestimated. Also, oophorectomy was not routinely performed but rather based on urologist decision. However, because ovarian involvement is rare, it is unlikely that a significant number of cases would have been identified. Also, quality of life data are not discussed and the true effect of RO sparing on sexual activity may need more future investigation.

Conclusions

The incidence of RO involvement in a large, homogenous cohort of female patients undergoing APE for bladder UC was approximately 7.5% with the vagina the most commonly involved organ. A palpable mass and hydronephrosis were among the preoperative clinical factors univariabely associated with RO involvement. Larger multi-institutional studies may be needed to determine additional risk factors for RO involvement and probably define the eligibility criteria for RO preservation.

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CHAPTER 4

The clinical epidemiology of urachal carcinoma: results of a large, population based study

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Abstract

Purpose

Survival data on urachal carcinoma are sparse due to the low prevalence of this cancer. We report urachal carcinoma clinical outcomes and prognostic factors in a large, population based cohort of patients with long term follow-up.

Materials and Methods

Data were collected from the nationwide Netherlands Cancer Registry. Urachal carcinoma cases were also cross-referenced using the PALGA (Nationwide Network and Registry of Histology and Cytopathology) database. Pathology report summaries were reviewed. A total of 152 patients diagnosed with urachal carcinoma between 1989 and 2009 were included in analysis. The Sheldon staging system was used to classify urachal carcinoma. Median follow-up was 9.2 years. Primary outcomes were overall and relative survival. Prognostic factors were calculated using univariable and multivariable hazard regression models.

Results

The incidence of urachal carcinoma was 0.2% of all bladder cancers. A total of 45 patients (30%) presented with lymph node or distant metastasis. Five-year overall and relative survival was 45% and 48%, respectively. On multivariable analysis prognostic factors for impaired survival were lymph node metastasis (HR 1.7, 95% CI 1.2–2.6), tumor growth in the abdominal wall, peritoneum and/or adjacent organs (HR 5.2, 95% CI 2.6 –10.3), distant metastasis (HR 5.3, 95% CI 2.8 –9.9) and macroscopic residual tumor (HR 5.2, 95% CI 1.2–21.8).

Conclusions

Urachal carcinoma is rare, accounting for 0.2% of all bladder cancers. Many patients present with advanced disease. The prognosis of urachal carcinoma depends mostly on tumor stage, particularly the presence or absence of metastatic disease.

Abbreviations and Acronyms

GBA	= Population Municipality Registry
NCR	= Netherlands Cancer Registry
OS	= Overall survival
PSM	= Positive surgical margin
RS	= Relative survival
UraC	= Urachal carcinoma

Introduction

The urachus is a canal that connects the allantois to the fetal bladder. During fetal development the urachal lumen is obliterated into a fibromuscular cord stretching between the umbilicus and the bladder dome. Urachal anomalies such as UraC can develop if the urachal canal partly persists into adulthood. However, urachal malignancies are rare and account for less than 0.5% of all bladder cancers. [1] Patients with UraC often present with advanced disease that cannot be treated with surgery. While the reported results of a 5-fluorouracil/cisplatin based chemotherapy regimen are promising, [2] there is currently no standardized effective treatment for metastasis. Since UraC is also rather insensitive to radiotherapy, patients with metastasized UraC are likely to have a poor prognosis. Thus, adequate surgery is crucial in patients with localized disease.

Nonetheless, the optimal surgical procedure must be further defined. Partial cystectomy provides oncological outcomes similar to those of radical cystectomy.[1,3,4] However, it was suggested that umbilectomy and lymphadenectomy should be an integral part of surgery.[2–5] Although some groups have reported on UraC outcomes, most data are from referral centers with potential referral bias and fairly few patients. Moreover, even at referral centers primary treatment is heterogeneous. [4] For an uncommon disease such as UraC population based data are valuable since they provide unbiased epidemiological insight into the disease. Furthermore, with a larger study population and consequently higher power prognostic factors are more likely to be identified.

To our knowledge no population based study of UraC has been performed in Europe. We present data from a large, population based study with long term follow-up to provide insight into the clinical outcomes and prognostic factors of this rare disease.

Materials and Methods

Data were collected from the nationwide, population based NCR. All primary cases documented with the ICD-3 topography code for urachus (C67.7) between 1989 and 2009 were selected for analysis. Also, to cross-reference UraC cases reported in the NCR an additional search for UraC was performed in the PALGA database. [5] This database contains all reports generated by the pathology departments in The Netherlands. PALGA data were then matched with NCR data and summaries of all histopathology reports were reviewed.

Cases were included in study when the pathologist reported that the tumor was of urachal origin. Four patients with a history of gastrointestinal or urological malignancy were excluded to minimize the risk of including those

with nonprimary UraC. The final cohort consisted of 152 patients with UraC, including 98 from NCR and PALGA, 28 from NCR only and 26 from PALGA only.

UraC was staged according to the Sheldon staging system, which defines 4 stages, including I—no invasion beyond urachal mucosa, II—invasion confined to the urachus, III—local extension into bladder (IIIA), abdominal wall (IIIB), peritoneum (IIIC) or viscera other than the bladder (IIID) and IV—metastasis to regional lymph nodes (IVA) or distant sites (IVB).[1] We defined 4 main treatment groups, that is 1) surgery, including patients who also received radiotherapy and/or chemotherapy, 2) radiotherapy without surgery, including those who also received chemotherapy, 3) chemotherapy and 4) other/no treatment.

Follow-up was completed until February 1, 2011 by record linkage to the nationwide GBA, which holds the vital status of all Dutch residents. OS was calculated using the Kaplan-Meier survivor estimator. Since cause of death is not available in NCR or GBA, cancer specific survival could not be calculated. Instead, RS (which is the ratio of observed to expected survival in the general population of The Netherlands of the same age and gender) was calculated according to Dickman et al [6] as a good approximation of cancer specific survival. Univariable and multivariable hazard regression models were used to identify prognostic variables. All analysis was done using STATA®. The study required no formal ethics committee approval; instead the principles of the Helsinki Declaration were followed.

Results

Cohort Characteristics

A total of 152 UraC cases were diagnosed with a median of 7.5 cases annually. UraC accounted for 0.2% of all bladder cancers and 20% of all bladder adenocarcinomas in The Netherlands. There was a slight increase in UraC diagnoses with time with 64 UraC cases diagnosed between 1989 and 1999, and 88 diagnosed between 2000 and 2009. Table 1 lists baseline characteristics. Of UraC cases 94% were adenocarcinoma. The male-to-female ratio was 1.4:1. Median patient age was 58 years (range 20 to 90). A total of 45 patients (29.6%) had metastatic disease at presentation, including 15 (33.3%) with regional lymph node metastasis only, which was clinically apparent in 10 and discovered after lymphadenectomy in 5. The other 30 patients (66.6%) presented with distant metastasis. The peritoneum was the most common site of distant metastasis.

Primary Treatment

A total of 104 patients (68.4%) were treated only at community hospitals. Overall 118 patients (77.6%) underwent surgery, which was partial cystectomy in 81. Adjuvant or neo-adjuvant radiotherapy was administered in 30 operated patients (25.4%). Of the 100 patients with clinical stage I–IIIA disease 94 (94%) were treated with surgery and 6 (6%) received primary radiotherapy. Treatment for stage IVB disease in 30 patients was rather heterogeneous and only 10 (33.3%) received systemic chemotherapy. For 5 patients this was the primary treatment while another 5 underwent chemotherapy combined with surgery and/or radiotherapy (Table 2). Information on lymphadenectomy status was available for 111 of 118 operated patients. Lymphadenectomy was done in 43 cases (36.4%) (Table 1).

Table 1: Baseline characteristics of 152 patients with urachal carcinoma

	No pts (%)
Gender	
Male	88 (57.9)
Female	64 (42.1)
Age at diagnosis	
Less than 45	30 (19.7)
45-59	53 (34.9)
60-75	56 (36.8)
Greater than 75	13 (8.6)
Tumor differentiation	
Well	13 (8.6)
Moderate	38 (25.0)
Poor	34 (22.4)
Not available	67 (44.0)

Sheldon tumor stage*	
I	0
II	22 (14.5)
III	85 (55.9)
IIIA	74 (48.7)
IIIB	9 (5.9)
IIIC	1 (0.7)
IIID	1 (0.7)
IV	45 (29.6)
IVA	15 (9.9)
IVB	30 (19.7)
Histology	
Adenocarcinoma not otherwise specified	50 (32.9)
Mucin-producing adenocarcinoma	73 (48.0)
Singet ring cell adenocarcinoma	20 (13.2)
Transitional cell carcinoma	7 (4.6)
Undifferentiated carcinoma	2 (1.3)
Primary treatment	
Surgery with/without radiotherapy or chemotherapy	118 (77.6)
- Urachal excision or TURBT	17 (11.1)
- Partial cystectomy	81 (53.3)
- Radical cystectomy	20 (13.2)
Radiotherapy with/without chemotherapy	10 (6.6)
Chemotherapy	8 (5.3)
None/ no data available	16 (10.5)
Lymph node dissection**	
Yes	43 (36.4)
No	68 (57.6)
No data available	7 (5.9)
Surgical margin status**	
Negative	76 (64.4)
Microscopic positive	9 (7.6)
Macroscopic positive	6 (5.1)
Not available	27 (22.9)
Treated a tertiary referral center	
Yes	48 (31.6)
No	104 (68.4)

** Postoperative stage but clinical stage in non-operated patient*

*** Operated patients only (n=118)*

Table 2: Treatment by clinical Sheldon stage

	No. Stage II (%)	No. Stage IIIa (%)	No. Stage IIIb-IIId (%)	No. Stage IVa (%)	No. Stage IVb (%)	Total No. (%)
Urachal excision or transurethral bladder tumor resection	8 (15)	6 (13)	2 (17)	-	1 (3)	17 (11)
Partial cystectomy	39 (74)	29 (62)	1 (8)	6 (60)	6 (20)	81 (53)
Radical cystectomy	5 (9)	7 (15)	4 (33)	1 (10)	3 (10)	20 (13)
Radiotherapy	1 (2)	5 (11)	1 (8)	1 (10)	2 (7)	10 (7)
Chemotherapy	-	-	1 (8)	2 (20)	5 (17)	8 (5)
No treatment / unknown	-	-	3 (25)	-	13 (43)	16 (11)
Totals	53 (100)	47 (100)	12 (100)	10 (100)	30 (100)	152 (100)

Survival and Predictors of Survival

Median follow-up was 9.2 years. Median overall survival was 48 months. Three, 5 and 10-year OS was 55%, 45% and 39%, and 3, 5 and 10-year RS was 57%, 48% and 46%, respectively. Five-year RS was 37% (95% CI 20–54) at ages less than 45 years, 65% (95% CI 49–77) at 45 to 59 years, 43% (95% CI 27–59) at 60 to 74 years and 17% (95% CI 1–55%) at 75 years or greater. Stage III–IV disease was most common (47%) in patients younger than 45 years.

Statistical significant survival differences were found among stages II or less, IIIA and IIIB or greater, respectively ($p < 0.0001$, fig. A). For stage IIIA disease no significant survival difference was found for patients with bladder invasion only vs perivesical/urachal fat invasion ($p = 0.96$). In patients with metastatic disease (stage IV) 5-year RS was 15% compared to 61% in those with nonmetastatic disease (stage III or less). Radical cystectomy did not provide an outcome superior to that of partial cystectomy (HR 1.00, 95% CI 0.45–2.21, $p = 0.996$, fig. 1E).

On univariable analysis factors prognostic for OS were tumor growth in the abdominal wall, peritoneum and/or adjacent organs, lymph node metastasis, distant metastasis, microscopic PSM, macroscopic residual tumor, poor differentiation tumor grade and

signet ring cell adenocarcinoma subtype (Table 3). On multivariable analysis tumor growth in the abdominal wall, peritoneum and/or adjacent organs (HR 5.13, 95% CI 2.57–10.30, p < 0.001), lymph node metastasis (HR 1.73, 95% CI 1.17–2.56, p < 0.006), distant metastasis (HR 5.28, 95% CI 2.81–9.94, p < 0.001) and macroscopic residual tumor (HR 5.20, 95% CI 1.23–21.84, p = 0.024) were independently associated with decreased OS (Table 3).

Table 3: Prognostic factors for overall survival

	No. of pts	Univariable analysis		Multivariable analysis	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Age					
Less than 45	30	1		1	
50-59 years	53	0.54 (0.29 – 0.99)	0.046	0.90 (0.45 – 1.81)	0.78
60-74 years	56	1.14 (0.65 – 2.00)	0.64	1.73 (0.88 – 3.42)	0.11
Greater than 75	13	2.54 (1.20 – 5.40)	0.015	4.36 (1.70 – 11.1)	0.002
Tumor stage **					
T1-T2	51	1		1	
T3	55	1.21 (0.71 – 2.08)	0.48	1.10 (0.62 – 1.95)	0.73
T4	21	5.71 (3.12 – 10.47)	< 0.001	5.13 (2.57 – 10.3)	< 0.001
Tx	25				
Histology					
Adenocarcinonoma (not specified)	50	1		1	
Mucin-producing adenocarcinoma	73	0.63 (0.39 – 1.02)	0.06	0.78 (0.45 – 1.36)	0.38
Signet ring cell adenocarcinoma	20	1.86 (1.03 – 3.36)	0.040	0.89 (0.41 – 1.93)	0.78
Transitional cell carcinoma	7	0.54 (0.13 – 2.27)	0.40	0.65 (0.15 – 2.86)	0.57
Undifferentiated carcinoma	2	0.66 (0.09 – 4.89)	0.69	1.48 (0.18 – 12.07)	0.71
Tumor grade					
Well	13	1		1	
Moderate	38	1.35 (0.50 – 3.63)	0.55	0.90 (0.32 – 2.54)	0.85
Poor	34	2.71 (1.04 – 7.13)	0.042	1.72 (0.56 – 5.21)	0.34
Not available	67				

Surgical margins *					
Negative	76	1		1	
Microscopic positive	9	3.64 (1.58 – 8.41)	0.002	2.11 (0.70 – 6.32)	0.18
Macroscopic positive	6	8.26 (3.28 – 20.80)	< 0.001	5.20 (1.23 – 21.84)	0.024
Not available	27				
Lymphadenectomy performed *					
No	68	1		1	
Yes	43	1.09 (0.56 – 2.11)	0.80	0.80 (0.34 – 1.86)	0.59
Not available	7				
Lymph node metastasis					
No	137	1		1	
Yes	15	2.40 (1.74 – 3.32)	< 0.001	1.73 (1.17 – 2.56)	0.006
Distant metastasis					
No	122	1		1	
Yes	30	3.49 (2.16 – 5.62)	< 0.001	5.28 (2.81 – 9.94)	< 0.001
Treatment hospital					
Community hospital	104	1		1	
Referral center	48	0.71 (0.45 – 1.14)	0.16	0.79 (0.45 – 1.40)	0.42

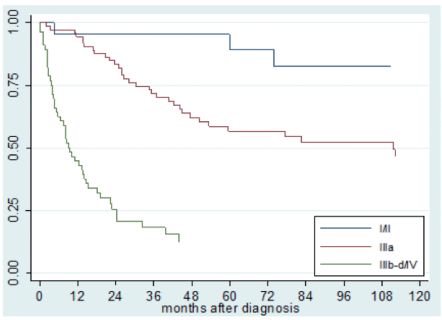
HR = Hazard ratio; 95%CI = 95% confidence interval

** Operated patients only*

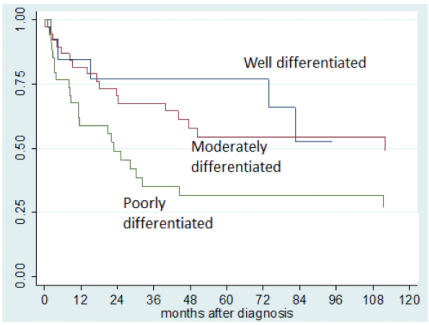
*** Postoperative stage but clinical stage in non-operated patients*

Figure 1: Overall survival in patients with urachal carcinoma by

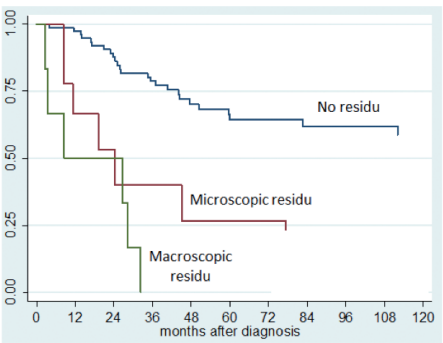
A) Sheldon stage



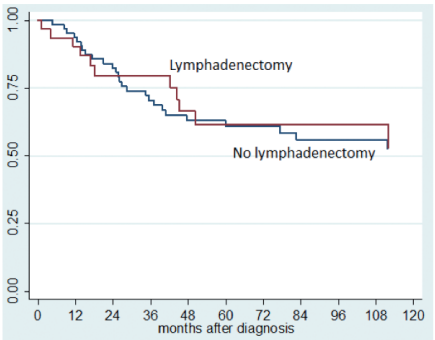
B) differentiation



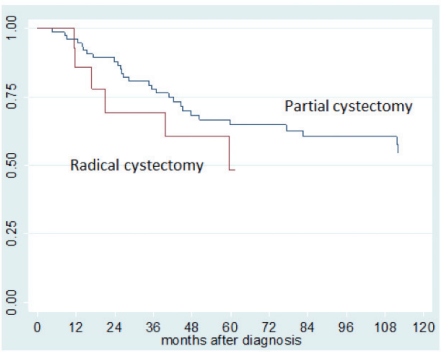
C) surgical margin status



D) lymphadenectomy



E) type of cystectomy



Discussion

Using a large, nationwide cohort with long-term follow-up this study provides valuable clinical information. Up to 30% of patients presented with regional or distant metastasis with subsequent poor survival outcomes. Distant metastasis was the most important prognostic factor and it was most common (47%) in patients younger than 45 years. These findings suggest that increased awareness of UraC is important, particularly in younger patients with urinary symptoms, since detection of UraC at an early stage benefits survival. Furthermore, no significant survival difference was found between patients with lymph node metastasis and those with distant metastasis. Survival in each group was poor with fewer than 20% surviving after 5 years. This clearly underlines the need for effective systemic chemotherapy regimens.[4,7] In patients with localized disease a long-term OS rate of up to 70% was reported in referral center series.[3,4]In our study using population based data we found a lower OS rate of 45% after 5 years. This finding is fairly similar that in a Canadian population based study with a 51% 5-year OS rate. [8] The difference between population and hospital based outcomes may have been caused by selective referral of patients to specialized centers.

Since most UraCs are adenocarcinoma invading the bladder dome, partial cystectomy may provide oncological safety and efficacy similar to those of radical cystectomy. While to our knowledge a randomized trial comparing these 2 treatments is lacking, current literature suggests that partial cystectomy provides good oncological results. Herr et al reported excellent outcomes for partial cystectomy in a series of 50 patients. [4] Ashley et al compared the 2 treatments and found no significant difference in survival [2], similar to our findings (fig. 1E).

A number of studies demonstrate the importance of en bloc urachal resection at partial cystectomy, including the umbilicus, to provide optimal local control. [1–4] In our study we could not identify whether umbilical resection was done. Nonetheless, based on the current literature, en bloc resection of the urachal ligament including the umbilicus is important to achieve optimal local control. Data on the role of lymphadenectomy in UraC is limited. In 1 series some patients with node positive disease were cured by partial cystectomy and lymphadenectomy, although the number of resected lymph nodes did not correlate with survival. [4] In our population based study lymphadenectomy was done in 36.4% of cases. In patients treated with lymphadenectomy no significant survival advantage was found. However, patients were not randomized to treatment, and detailed information on lymphadenectomy and adjuvant therapy was not available. Thus, we suggest that the role

of lymphadenectomy for UraC should be further investigated in a multi-institutional study.

The Sheldon staging system, which defines 8 stages, potentially offers greater prognostication than other, more simplistic classifications. [2,8] In our study and that by Herr et al [4] a significant survival difference was found between stages IIIA or less and IIIB or greater disease. However, in our series perivesical/urachal fat invasion was considered stage IIIA since survival was comparable to that of bladder confined tumors but significantly higher than that of abdominal wall invasion (stage IIIB). Nonetheless, our study confirms the finding that peritoneal or abdominal wall invasion confers a poor prognosis that can rarely be cured by surgery.

PSM was proposed as an independent prognostic factor.[1,2,4] In the study by Herr et al only 17% of patients with PSM survived compared to 77% with negative surgical margins.[4] In our series, as expected, macroscopic residual tumor was independently associated with decreased survival. Microscopic PSM was prognostic on univariable analysis but it did not remain an independent prognostic factor on multivariable analysis. This effect is most likely attributable to a stronger prognostic value of lymph node and distant metastatic disease. Thus, we believe that achieving negative surgical margins is important for local control, as suggested by others.[1-3]

An interesting finding was that most patients with UraC were treated at community hospitals. This differs from the only study addressing this topic, in which the referral hospital-to-community hospital treatment ratio was fairly equal. [8] As in that series, we found no significant survival advantage for patients treated at referral hospitals. However, as demonstrated, survival in patients with stage IV disease is poor and to our knowledge there is no effective standard chemotherapy regimen. Treatment at referral hospitals offers the potential advantage of including patients with metastasized disease in clinical trials to improve the outcome.

Although population based studies are valuable, we acknowledge inherent limitations. 1) Detailed information was not always available. This was specifically true for umbilical resection at cystectomy, which was reported to be important for local control. 2) Since the GBA registry does not hold information on recurrence or cause of death, we could not report treatment after recurrence or disease specific survival. As a proxy for disease specific survival, we used relative survival. 3) UraC was diagnosed by different pathologists. Review pathology was not possible since we had no access to pathology specimens. However, to make the best effort to detect true UraC cases NCR data were cross-referenced

with PALGA data and pathology report summaries were reviewed. 4) Since this study was not randomized, confounding by indication may have influenced the effect of prognostic factors.

Conclusions

Surviving this rare disease mainly depends on tumor stage, particularly the presence or absence of metastatic disease. Patients with localized disease can be treated well with surgery when umbilical resection is performed and negative surgical margins are pursued. If that is the case, partial cystectomy likely provides outcomes similar to radical cystectomy. The role and template of lymphadenectomy must be further investigated, preferably in a multi-institutional manner. Patients who present with distant metastasis have a poor prognosis. Early detection of UraC and the development of effective chemotherapeutic regimens are key factors to improve survival.

Acknowledgments

The authors acknowledge dr. Lucy Overbeek for providing data from the PALGA database.

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PART I
PART II
PART III BLADDER CANCER AND
LYMPH NODE DISSECTION
PART IV
PART V

PART III

Bladder cancer and lymph node dissection

CHAPTER 5

Incidence and location of lymph node metastases in patients undergoing radical cystectomy for clinical non–muscle invasive bladder cancer: Results from a prospective lymph node mapping study

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Urologic Oncology - Seminars and Original Investigations
2012;32(1):2413-2419

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Abstract

Objectives

To investigate the role and extent of lymph node dissection (LND) in patients undergoing radical cystectomy for clinical non-muscle invasive bladder cancer (NMIBC).

Materials and Methods

Prospectively collected data of 637 patients who underwent radical cystectomy with intent-to-cure for urothelial carcinoma of the bladder between 2002 and 2008 were examined. Inclusion criteria were (a) clinical stage Ta, Tis-only or T1, (b) muscle-presence at diagnostic transurethral resection in clinical T1 patients, (c) no prior diagnosis of ≥T2 disease, (d) no neo-adjuvant therapy and (e) lymphatic tissue sample submitted from all 13 pre-designated locations. Median follow-up time was 4.7 years. Recurrence-free survival (RFS) and overall survival (OS) were reported.

Results

A total of 114 patients were included of whom 9 patients (7.9%) had LN metastases (LNM). LNM were present in 6/67 (9.0%) patients with cT1, 3/25 (12.0%) patients with cTis-only and none of the 22 patients with cTa. Three out of 9 node-positive patients (33.3%) had LNM proximal to the aortic bifurcation. No skip metastases were found. After RC, 27 patients (23.7%) were upstaged to muscle-invasive disease; of whom 16.7% had cT1, 2.6% had cTa and 4.4% had cTis-only. Of the remaining 87 patients with pathological NMIBC, 1 patient (1.1%) had LNM, limited to the true pelvis. Five-year RFS was 82.3%, 81.5% and 62.0% in patients with pathological NMIBC, clinical NMIBC and pathological muscle-invasive bladder cancer, respectively.

Conclusions

Routine LND is important in patients with cT1 and cTis-only bladder cancer, but may have limited value in patients with cTa. LNM beyond the boundaries of a standard LND occurred in up to one-third of node-positive patients. In the absence of skip metastases, however, performing a standard LND would correctly identify all node-positive patients. Whether removal of LNM proximal to the common iliac vessels provides a survival benefit remains to be evaluated in future prospective studies

Introduction

Most patients who present with urothelial cancer (UC) of the urinary bladder have non-muscle invasive bladder cancer (NMIBC; Ta, Tis-only, T1). Despite intravesical treatment, patients with NMIBC are at risk of progression to muscle-invasive bladder cancer (MIBC). The risk of progression varies from less than 5% in low-risk patients up to 40-50% in high-risk patients with MIBC. [1] There is accumulating evidence that patients with progression from NMIBC to MIBC have a worse prognosis when compared with patients who had MIBC at initial presentation. [2] Hence, there is an increasing trend towards performing early radical cystectomy (RC) in NMIBC patients with a high risk of progression and/or patients who have failed intravesical therapy.

It is estimated that between 6-15% of patients who undergo RC for clinical NMIBC (cNMIBC) harbor lymph node metastases (LNM).[3-5] Although performing lymph node dissection (LND) in patients with cNMIBC may be beneficial, LND is often not performed, even in patients with MIBC.[6] In addition, it is unknown whether the template of LND in patients with cNMIBC should be similar to clinical MIBC, as lymph node (LN) mapping data is lacking. A recent study, however, suggested that with increasing clinical stage, more LNs should be removed, with a minimum of six LNs for cTa-cTis disease and a minimum of 25 LNs in patients with ≥cT2 disease. [7] One caveat to this study's conclusion is that the number of retrieved LNs cannot be translated into a reproducible surgical template as the total number of LNs is influenced by several factors. [8,9] In fact, a recent study suggested the thoroughness of LND to be of more importance than the number of removed LNs. [10] Thus, defining the optimal template of LND would serve the urologist as a better guideline.

In this study, we aimed to investigate the incidence and distribution of LNM in patients undergoing RC and LND for cNMIBC. In addition, we report survival outcomes for this cohort using a standardized 'super'extended LND to the level of the inferior mesenteric artery takeoff.

Materials and Methods

Cohort selection

A total of 637 patients underwent RC with intent-to-cure for urothelial carcinoma (UC) of the bladder between May 2002 and December 2008. Included patients met all of the following criteria: (a) clinical stage Ta, Tis-only or T1 prior to RC, (b) muscle-presence at diagnostic transurethral resection of the bladder tumor (TURBT) in clinical T1 patients,

(c) no prior diagnosis of MIBC, (d) no neo-adjuvant chemotherapy or radiotherapy and (e) lymphatic tissue sample submitted from all 13 pre-designated locations. A total of 114 patients were included in this study. Patients either had high-risk of progression (i.e. high grade tumor and/or concomitant Tis and/or lymphovascular invasion (LVI) at TURBT) and underwent early cystectomy or had recurrent/persistent disease despite intravesical therapy. All patients underwent 'super'extended LND including the following boundaries: the inferior mesenteric artery takeoff proximally, the genitofemoral nerves laterally, the circumflex iliac vein and LN of Cloquet distally, the internal iliac vessels posteriorly, including the obturator fossa and presciatic (fossa Marcille) LNs, and the presacral LNs overlying the sacral promontory. LNs were submitted in 13 pre-designated anatomically defined packets as described previously and shown in Figure 1. [10]

Clinical and pathological staging

Pre-operative clinical staging was based on tumor stage at TURBT specimen and results of cross sectional imaging and physical examination. Pathology specimens were routinely reviewed centrally at our institution. Multiple sections and histological evaluation were performed on the primary bladder tumor, bladder wall, and all LNs. LNs were identified visually and by palpation without clearing techniques, solvents or special stains. Pathological tumor staging and grading were standardized to the 2010 TNM classification of the American Joint Committee on Cancer and 1973 World Health Organization recommendations, respectively. [11,12] For analytical purposes, the location of LNM was divided in 3 levels as described previously. [10,13]

Data management and statistical analysis

Data were prospectively collected by a dedicated data entry team, double-checked by an experienced database manager, and stored in our secured and review-board approved database. Median follow-up time was 4.7 years. Kaplan-Meier plots were used to estimate overall survival (OS) and recurrence-free survival (RFS). Recurrence of disease included local recurrence (pelvic, urethral and upper tract) as well as the development of distant metastasis. The log-rank test was used to compare subgroups of patients. The Cox proportional hazard model was used to test the association of multiple variables with recurrence. The Mann-Whitney-U test was used to test the association of non-parametric variables. The level of statistical significance was set at $p < 0.05$. All p-values are two-sided.

Results

Of the 114 patients included in this study, 67 patients (58.8%) had clinical T1, 25 patients (21.9%) clinical Tis-only and 22 patients (19.3%) clinical Ta. Concomitant carcinoma-in-situ was present in 29 patients (43.3%) with cT1 disease. A total of 59 (51.8%) patients underwent intravesical treatment prior to RC. The median number of TURBTs prior to RC was 2 (range: 1-18). Median time from first TURBT and last TURBT to RC was 5.0 months and 1.7 months, respectively. Clinical and pathological features of all patients at the time of RC are listed in Table 1.

Table 1: Study cohort characteristics

	Number of patients (%)
Total cohort	114 (100)
Age	
65 years or less	54 (47.4)
Greater than 65	60 (52.6)
Gender	
Male	95 (83.3)
Female	19 (16.7)
Clinical tumor stage and grade[a]	
Ta, low grade	7 (6.1)
Ta, high grade	15 (13.2)
Tis, high grade	25 (21.9)
T1, low grade	2 (1.8)
T1, high grade	65 (57.0)
Pathologic tumor stage[b]	
pT0	13 (11.4)
pTa	8 (7.0)
pTis	29 (25.4)
pT1	37 (32.5)
pT2a	6 (5.3)
pT2b	12 (10.5)
pT3a	4 (3.5)
pT3b	3 (2.6)
pT4a	2 (1.8)
Pathologic tumor grade[b,c]	
Low grade	14 (13.8)
High grade	87 (86.1)

Carcinoma-in-situ[b,d]	
Yes	76 (66.7)
No	38 (33.3)
Multifocal disease[b]	
Yes	53 (46.5)
No	61 (53.5)
Lymphovascular invasion[b]	
Present	19 (16.7)
Absent	95 (83.3)
Lymph node metastases[b]	
Yes	9 (7.9)
No	105 (92.1)

a) Based on transurethral resection specimen

b) Based on radical cystectomy specimen

c) 13 patients had no evidence of disease

d) Includes patients with pTis-only

A total of 9 patients (7.9%) had LNM and stratified by clinical stage, LNM were present in 6 patients with cT1(9.0%), 3 patients with cTis-only (12.0%) and none of the patients with cTa. Of the 6 cT1 patients with LNM, 3 patients underwent 1 TURBT (with muscle presence) and 3 patients underwent 2,4 and 5 TURBTs, respectively. Of the latter group, detrusor muscle was present in at least the last TURBT prior to RC. Of note, 1 patient with cT1 and LNM had concomitant carcinoma-in-situ on TURBT specimen. The histopathological characteristics of all 9 node-positive patients are summarized in Table 2.

Table 2: Characteristics of the 9 node-positive patients

	Number of patients (%)
Clinical stage and grade[a]	
Ta, any grade	0
Tis, high grade	3 (33.3)
T1, low grade	0
T1, high grade	6 (66.7)

Histologic de-differentiation[a]	
None	8 (88.9)
Micropapillary	1 (11.1)
Concomitant carcinoma-in-situ[a]	
Yes	4 (44.4)
No	5 (55.6)
Lymphovascular invasion[a]	
Present	2 (22.3)
Absent	3 (33.3)
Not mentioned in pathology report	4 (44.4)
Pathologic tumor stage[b]	
pT0/Ta/Tis	0
pT1	1 (11.1)
pT2a	1 (11.1)
pT2b	2 (22.2)
pT3a	1 (11.1)
pT3b	3 (33.3)
pT4a	1 (11.1)
Pathologic tumor grade[b]	
Low	0
High	9 (100)
Concomitant carcinoma-in-situ[b]	
Yes	7 (77.8)
No	2 (22.2)
Lymphovascular invasion[b]	
Present	7 (77.8)
Absent	2 (22.2)
Highest level of node-positive disease	
Level 1	6 (66.6)
Level 2	0
Level 3	3 (33.3)
Number of positive lymph nodes	
1	1 (11.2)
2	2 (22.2)
>2	6 (66.6)

a) Based on transurethral resection specimen.

b) Based on radical cystectomy specimen.

Age (p = 0.41), gender (p = 0.35), multifocal disease (p =1.00), number of TURBTs prior to RC (p = 0.90),time from last TURBT to RC (p = 0.40), and tumor stage (cTa/cTis vs cT1; p = 0.73), tumor grade (p = 0.34), LVI (p = 0.34), concomitant carcinoma in situ (p = 1.00) on TURBT specimen were all not associated with the presence of LNM (n=9).

The median number of removed LNs was 70 in node-positive and 68 in node-negative patients. Figure 2 shows the highest level of positive LNs in node-positive patients, both as part of the total cohort (N=114) and all patients with LNM (N=9). Three node-positive patients had level 3 as the highest level involved with LNM, of whom all patients had level 2 and level 1 involvement as well. Of these patients, 2 patients had cT1 and 1 patient had cTis-only. Pathological stage was T2a in 1 patient and T3b in 2 patients. The 5-year RFS and OS estimates for all cNMIBC patients were 81.5% and 77.4%, respectively (Figure 3AB).

In total, 27 patients (23.7%) were upstaged to MIBC at RC. Upstaging occurred in 3/22 patients (13.6%) with cTa, 5/25 patients (20.0%) with cTis-only and 19/67 patients (28.4%) with cT1. Of the remaining 87 patients with pNMIBC, only 1 patient (1.1%) had LNM, all confined to level 1. Both concomitant carcinoma-in-situ and LVI were present on the TURBT specimen. Final pathology showed a pT1 tumor with concomitant carcinoma-in-situ.

Five-year RFS and OS in all patients with pNMIBC was 58.8% and 62.0%, respectively (Figure 3AB). Presence of LNM was associated with decreased survival on both univariable analysis (p < 0.001) and multivariable analysis (HR 3.38 (95% confidence interval 1.34 - 8.51); p < 0.001) correcting for stage, grade, age and LVI at RC.

Figure 1: Anatomical boundaries of lymph node packets and corresponding level of lymph node dissection

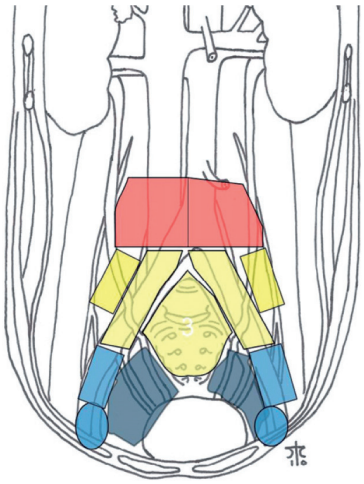
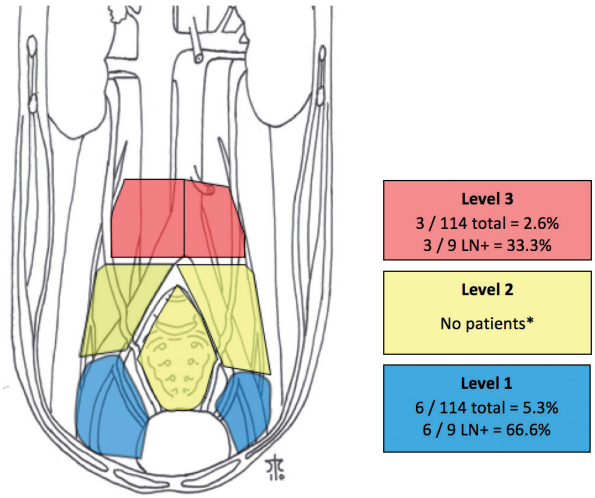


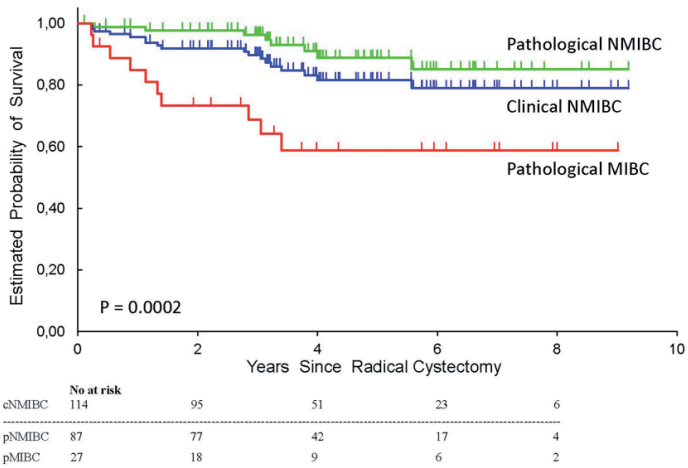
Figure 2: Highest level of positive lymph nodes in patients with node-positive disease at the time of radical cystectomy



** No patients had level 2 as the highest level of nodal involvement, as all patients with level 2 involvement also had level 3 involvement*

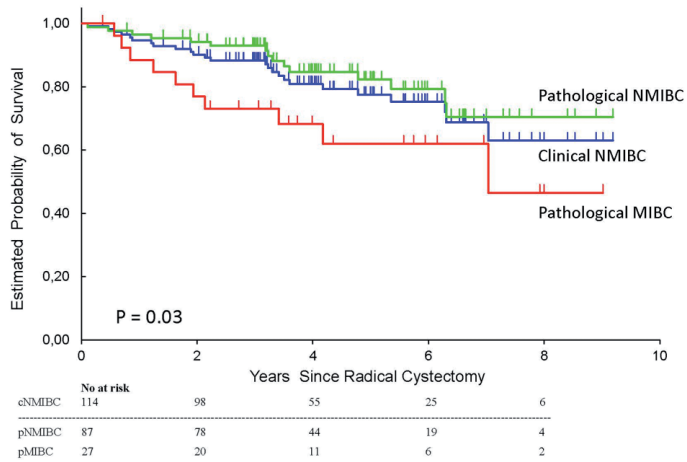
Figure 3. (a) Recurrence-free survival and (b) overall survival in patients with clinical non-muscle invasive bladder cancer (NMIBC), pathological NMIBC and pathological muscle invasive bladder cancer (MIBC)

(a) Recurrence-free survival



No at risk					
cNMIBC	114	95	51	23	6
pNMIBC	87	77	42	17	4
pMIBC	27	18	9	6	2

(b) Overall survival



No at risk					
cNMIBC	114	98	55	25	6
pNMIBC	87	78	44	19	4
pMIBC	27	20	11	6	2

Discussion

The optimal surgical template for LND in patients who undergo RC for bladder cancer is a topic of continued debate. In patients with MIBC, a number of LN mapping studies have been performed to determine the lymphatic drainage aiming to define the optimal template of LND. [10,13] LN mapping studies in patients with cNMIBC, however, are lacking partly owing to the infrequent employment of RC and 'superextended' LND in these patients. The reason to perform RC differs among patients with cNMIBC. In the current study, the majority of patients underwent RC due to high risk of progression. The remaining patients had a low risk of progression, in particular patients with cTa, but had disease not amenable to endoscopic management, multiply recurrent disease and/or functional bladder issues.

We performed, to our knowledge, the first LN mapping study focusing on patients undergoing RC for cNMIBC. The rationale for focusing on clinical stage is based on the significant role it plays in the initial management of bladder UC. Though important for decision making, clinical stage correlates imperfectly to pathologic findings. Current literature reports understaging rates varying between 32% and 44%. [14-16] In this study, despite the inclusion of only cT1 patients who had detrusor muscle present at TURBT, up to 23% of patients were upstaged at RC. Thus, clinical understaging is a frequent finding which has implications for the role of lymphadenectomy as demonstrated in this study. Although only 1% of patients with pNMIBC had LNM, nearly 8% of patients with cNMIBC had LNM. Stratified by clinical stage, LNM occurred in 9.0% of cT1 patients, 12.0% of cTis-only patients and none of the patients with cTa. These findings imply that LND may have limited value in cTa patients, but underscore the need for LND in patients with cT1 and cTis-only to adequately asses the nodal status. To investigate whether further risk stratification for LNM would be possible, univariable analysis was performed. None of the variables were statistically significantly associated with LNM, but it should be noted that these tests were likely underpowered as only 9 patients had LNM.

Performing extended LND is associated with increased surgical time although the 30-day morbidity appears to be equal compared to a standard or limited LND. [17,18] Nonetheless, it may benefit patients to reduce the template of LND, while maintaining oncologic efficacy. To date, however, it is unknown whether the extent of LND can be tailored based on risk stratification. Shariat et al.[7], analyzing over 4000 patients undergoing RC, aimed to define the minimum number of LNs that should be removed based on clinical stage. It was reported that in patients with cTa-cTis at least 6 LNs should be removed, while in T1 patients at least 10 LNs should be retrieved. Unfortunately,

as the number of LNs cannot be translated into a surgical template, the question whether 'one template fits all' remained to be answered. In this LN mapping study, all patients underwent 'superextended' LND with a median of 70 LNs removed, which is a higher number compared with most other series. [13,18] A total of 9 node-positive patients of whom 3 patients (33.3%) had LNM proximal the aortic bifurcation (Level 3; Figure 2). This is a slightly higher percentage compared to a recent large LN mapping study including all clinical stages, reporting 28% of patients with level 3 involvement. [10] The higher incidence in this study is likely caused by the relatively low number of node-positive patients. Nonetheless, both studies demonstrate that a substantial number of node-positive patients have LNM at level 3, regardless of clinical stage. Fortunately, none of the patients with level 3 involvement had skip metastases, which is similar to other studies reporting a very low incidence of skip metastases. [13,19,20] This finding suggests that if a standard LND had been performed, all patients with node-positive disease would have correctly been identified, although performance of a 'superextended' LND might be of benefit in these patients. [18,19,21]Randomized studies are, however, needed to investigate the effect of (super)extended LND survival outcomes.

This study has important limitations. Despite prospective collection of data, this was a retrospective study with its inherent limitations. We present data from a single, tertiary referral center with high rate of referred patients and consequently variance in pre-cystectomy management. Not all cT1 patients underwent bimanual examination and or repeat TUR prior to surgery. Conversely, only patients who had presence of detrusor muscle at TURBT were included and the TURBT specimen was routinely reviewed at our institution. Although our RC cohort is one of the largest of its kind, the number of patients may not be sufficient to accurately reflect the distribution of LNM in all patient populations. In addition, only patients with cNMIBC who underwent RC were included, and the reported incidence of LNM may not reflect the incidence for all patients with cNMIBC. Furthermore, confounding by indication may have been present as the majority of patients who underwent RC were at high risk of progression. Acknowledging these limitations, this study provides insight into the incidence and distribution of LNM in patients undergoing RC for NMIBC.

Conclusions

Routine LND is important in patients with cT1 and cTis only bladder cancer, but may have limited value in patients with cTa. Although LNM were rarely found in patients with pathologic NMIBC, pathologic upstaging to MIBC and subsequent presence of LNM was a common finding. LNM beyond the boundaries of a standard LND occurred in up to one-third of node-positive patients. In the absence of skip lesions, however, performing a standard LND would correctly identify all node-positive patients. Whether removal of LNM proximal to the common iliac vessels provides a survival benefit remains to be evaluated in future prospective studies.

Conflict of interest

None.

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CHAPTER 6

The impact of the extent of lymphadenectomy on oncologic outcomes in patients undergoing radical cystectomy for bladder cancer: a systematic review

Bruins HM [a], Veskimae E [b], Hernandez V [c], Imamura M [d], Neuberger MM [e], Dahm P [e,f], Stewart F [d], Lam TB [d], N'Dow J [d], van der Heijden AG [a], Compérat E [g], Cowan NC [h], De Santis M [i], Gakis G [j], Lebret T [k], Ribal MJ [l], Sherif A [m], Witjes JA [a]

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Abstract

Context

Controversy exists regarding the therapeutic value of lymphadenectomy (LND) in patients undergoing radical cystectomy (RC) for muscle-invasive bladder cancer (MIBC).

Objective

To systematically review relevant literature assessing the impact of LND on oncological and peri-operative outcomes in patients undergoing RC for MIBC.

Evidence acquisition

MEDLINE, MEDLINE-in-Process, Embase, the Cochrane Central Register of Controlled Trials and the Latin American and Caribbean Center on Health Sciences Information (LICACS) were searched up to December 2013. Comparative studies reporting on no, limited, standard, extended, and super-extended LND, and oncological and peri-operative outcomes were included. Risk of bias and confounding assessments were performed.

Evidence synthesis

Twenty-three studies reporting on 19,793 patients were included. All but one study were retrospective. Planned meta-analyses were not possible due to study heterogeneity therefore data were synthesized narratively. There were high risks of bias and confounding across most studies, and extreme heterogeneity in the definition of the anatomic boundaries of LND templates. All seven studies comparing LND with no LND favored LND in terms of better oncological outcomes. Seven of 14 studies comparing (super-)extended with limited or standard LND reported a beneficial outcome for (super-)extended LND in at least a subset of patients. No difference in outcome was reported in two studies comparing extended and super-extended LND. The comparative harms of different extents of LND remain unclear.

Conclusions

Although the quality of the data was poor, the available evidence indicates that any kind of LND is advantageous over no LND. Similarly, extended LND appears to be superior to lesser degrees of dissection, while super-extended LND offered no additional benefits. Data from ongoing randomized clinical trials will hopefully clarify remaining uncertainties.

Patient summary

The current literature suggests that removal of lymph nodes in bladder cancer surgery is beneficial and might result in better outcomes in terms of prolonging survival. However, the quality of the available studies is poor and high quality studies are needed.

1. Introduction

Lymphadenectomy (LND) combined with radical cystectomy (RC) is considered the standard of care for patients with muscle-invasive bladder cancer (MIBC). Up to 25% of patients harbor lymph node (LN) metastases at the time of RC, and the staging role of LND is unequivocal. In 1982, Skinner [1] was the first to report long-term survival in LN-positive patients undergoing RC and LND without systemic treatment. The therapeutic value of LND, however, remains a topic of continuous debate. While the results of two ongoing randomized clinical trials (RCTs) evaluating the impact of different LND templates on survival are awaited, the current evidence base remains uncertain with regard to the true benefits and harms of LND. In this study, we systematically reviewed the available literature to evaluate the impact of the extent of LND on survival and peri-operative outcomes in patients undergoing RC for MIBC.

2. Evidence acquisition

2.1 Search strategy

The review was performed in accordance with the PRISMA statement and principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions. [2,3] Highly sensitive electronic searches were conducted to identify all reports of RCTs or non-randomized comparative studies (NRCS) assessing LND in patients undergoing RC for MIBC. The searches were not limited by language or publication date. The databases searched were MEDLINE (1946 to December 2013), MEDLINE In-Process (December 20th 2013), Embase (1974 to December 2013), Cochrane Central Register of Controlled Trials (The Cochrane Library, Issue 8, 2013) and Latin American and Caribbean Center on Health Sciences Information (LILACS; December 2013). The database search was complemented by additional sources, including the reference lists of included studies which were hand searched, and additional reports identified by an expert panel (European Association of Urology (EAU) Working Group on MIBC). Ongoing trials were identified on clinicaltrials.gov. The full search strategy is presented in Supplement 1.

Two reviewers independently screened titles and abstracts of all citations identified by the search strategies. Full text copies of all potentially relevant reports were obtained and independently assessed by the reviewers to determine whether they met the pre-defined inclusion criteria. Any disagreements were resolved by consensus or

arbitration by a third person. A data extraction form was developed specifically for the purpose of this assessment to collect information on study design, characteristics of participants, characteristics of interventions, and outcome measures.

2.2 Inclusion and exclusion criteria

The inclusion criterion was comparative studies only, and these included RCTs, prospective NRCS, prospective observational studies with a comparator arm, and retrospective comparative studies. Registry or database studies were also eligible, if the analysis was clearly structured as a comparison between control and intervention groups. Studies with no comparator group (e.g. single-arm case series), non-effectiveness studies (e.g. nomogram studies), reviews, or studies with fewer than 10 patients in each arm, were excluded.

The study population was limited to patients with localized muscle-invasive urothelial or squamous cell carcinoma of the bladder (cT2-4 N0M0). Studies including predominantly patients with variant histology other than squamous cell carcinoma were excluded because of its low incidence and the potentially different biological behavior of these cancers. Clinical staging was preferred, but if this was not reported, staging based on RC specimen was accepted. Studies with mixed populations (e.g. cTa, cTis, cT1) were retained for consideration for inclusion if there were no studies which included patients with MIBC exclusively. Studies including patients who underwent neo-adjuvant or adjuvant treatment were also retained.

The types of interventions included LND undertaken during RC for bladder cancer. Due to the expected heterogeneity in defining the extent of LND across studies, the extent of LND was determined a priori based on discussion in an expert panel (EAU Working Group on MIBC) and were categorized as follows: (1) limited LND (or L-LND): LND confined to the obturator and/or peri-vesical fossa only; (2) standard LND (or S-LND): LND performed up to the proximal boundary of the common iliac arteries; (3) extended LND (or E-LND): LND performed up to the proximal boundary of the crossing of the common iliac vessels with the ureters or the aortic bifurcation, with or without the pre-sacral lymph nodes; and (4) super-extended LND (or SE-LND): LND performed up to the proximal boundary of the inferior mesenteric artery. The primary outcome was overall survival (OS); secondary outcomes included recurrence-free survival (RFS), disease-free survival (DFS), progression-free survival (PFS), cancer-specific survival (CSS) and peri-operative outcomes (e.g. operative time, blood loss, lymphocele).

2.3 Assessment of risks of bias

Two reviewers independently assessed the risk of bias (RoB) of individual studies. Any disagreement was resolved by discussion or reference to a third reviewer. The standard Cochrane Collaboration RoB tool [4] was used to assess the RoB in RCTs, whilst for NRCS, the RoB tool recommended by the Cochrane Non-Randomised Studies Methods Group was used. [5,6] In addition, for NRCS, the main confounders were identified a priori based on a study by Palmer et al. [7] In this study, a survey among bladder cancer experts was performed to identify and rank potential confounding variables and defining thresholds for imbalance for these variables. The main confounders identified are summarized in Table 1. Each confounder was assessed according to whether it had been considered by the authors, whether the confounder was balanced across the groups, and the degree to which adjustment had been made for the confounder. [7] The risk of confounding bias was considered to be high if the confounder was not described/considered, imbalanced between the groups or was not adjusted for in the statistical analysis. Review Manager 5.2 was used to present these results (Table 1). [8]

2.4 Data analysis

A narrative synthesis was performed. [9] Descriptive statistics were used to summarize baseline characteristics data. For continuous outcomes, data were summarized using mean (+/- standard deviation if available) and median (+/- interquartile range if available); for categorical outcomes, data were summarized using proportions. For summarizing outcome data, categorical outcomes were presented as proportions at 5 and 10 year time points following surgery based on crude point estimates as reported by authors, with level of significance set at 5%. Outcomes at other time points were narratively described. For time-to-event data reported by authors using univariable or multivariable Cox regression analysis, data were summarized as hazard ratios (HRs) and 95% confidence intervals (CIs).

Table 1: Risk of bias assessment using the Cochrane risk of bias tool

= High Risk of Bias

= Low Risk of Bias; the variable was either balanced between the groups (assessed as 'no' or 'small imbalance') or was adjusted for in the analysis

= Unclear risk of Bias

Simone 2012a compared standard LND vs extended LND;
Simone 2012b compared extended LND vs superextended LND

3. Evidence synthesis

3.1 Quantity of evidence identified and characteristics of included studies

A total of 1897 abstracts were identified by the search (Figure 1). Of these, 38 were selected for full-text screening. One additional study was identified through reference searching. After full-text screening, a total of 23 studies met the inclusion criteria. [10-32] Seven studies were reported only in the form of conference meeting abstracts, while 16 studies were reported in full-text papers. With one exception, all studies were retrospective comparative studies. Sixteen studies were single-centre studies, of which eight studies used a historical cohort as control group, and seven studies were multicenter studies.

3.2 Risk of bias and confounding assessment of included studies

Risk of bias (RoB) and confounding assessment for each of the individual studies were performed and the results are presented in Table 1. Due to the retrospective design in 22 of 23 studies, there was high or unclear RoB across all domains. The issue of confounding was also poorly addressed by the majority of studies, as it was unclear in most studies if any of the confounding factors had been considered, either prospectively, or retrospectively through statistical adjustment.

3.3 Results of comparisons of interventions

3.3.1 No LND vs LND

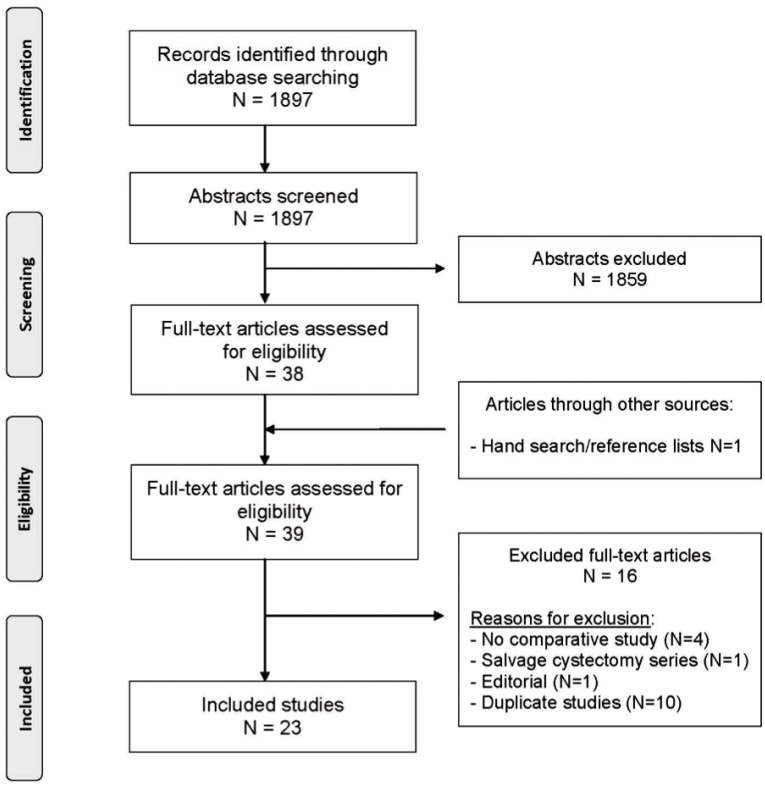
3.3.1.1 Baseline characteristics

A total of seven studies comparing LND with no LND were identified, including a total of 13,833 patients (Table 2a). [10-16] The intervention differed among the studies and included any LND [10,14,15], L-LND [13], S-LND [11,12,16], E-LND [16] or SE-LND [16].

3.3.1.2 Oncological outcomes

Table 2b summarizes the oncological outcomes comparing no LND vs any LND. All studies reported a benefit for LND in at least one oncological outcome. Liu et al. [10] did not report any numerical data but stated that LND was associated with improved OS and DFS in pT1 patients only compared with no LND.

Figure 1: PRISMA flow diagram



3.3.1.3 Peri-operative outcomes

No studies reported on peri-operative outcomes.

3.3.2 Limited LND vs standard LND

No studies were identified for comparison of limited LND and standard LND.

3.3.3 Limited LND vs (super-)extended LND

3.3.3.1 Baseline characteristics

Five studies addressed this question involving a total of 1,394 patients (Table 3a). [17-21] Brossner et al. [21] focused on peri-operative outcomes. Bostrom et al. [19] compared L-LND with E-LND, however, an unknown number of patients in the E-LND group underwent SE-LND and over 50% of patients in the L-LND group did not undergo LND at all.

Table 2a: Descriptive outcomes of studies comparing no lymphadenectomy (LND) versus any LND

	LE	Type of LND		Number of patients		Time period of recruitment	
		C	I	C	I	C	I
Liu 2011 [10]	3	No LND	Any	334	1606	1995-2008	
Isaka 1985 [11]	4	No LND	Standard	15	80	1975-1978	1979-1988
Miyakawa 1985 [12]	4	No LND	Standard	45	65*	1975-1980	1980-1984
Yuasa 1988 [13]	4	No LND	Limited	8	22	1975-1978	1979-1985
Abdollah 2012 [14]	3	No LND	Any	2789	8394	1988-2006	
Zhang 2013 [15]	4	No LND	Any	24	63	1997-2001	
Brunocilla 2013 [16]	3	No or limited LND	Standard	116 19 No-LND 97 L-LND	94	10/1995-12/2011	
		No or limited LND	Extended/ super-extended	116 19 No-LND 97 L-LND	62 39 E-LND 23 SE-LND	10/1995-12/2011	

C = control group; *I = intervention group* *L-LND = limited LND*

S-LND = standard LND; *E-LND = extended LND* *SE-LND = superextended LND*

Neo-adj rad = neo-adjuvant radiotherapy N/A = not applicable; *NR = not reported*

** 70 patients were included of whom 65 patients underwent no LND*

Follow-up duration (range)		pN+ (number, %)		pT stage (number, %)		(Neo-)adjuvant therapy (number, %)	
C	I	C	I	C	I	C	I
NR		N/A	NR	NR		NR	
40 mo (5-143)	40 mo (2-110)	N/A	9 (11)	≤pT2: 10 (67) >pT2: 5 (33)	≤pT2: 55(69) >pT2: 25 (31)	NR	Neo-adj rad 58 (72)
NR		N/A	NR	≤cT2: 6 (13) cT2: 24 (53) cTx: 15 (33)	≤cT2: 26 (37) >cT2: 38 (54) cTx: 6 (9)	NR	
Minimum 1 year		N/A	NR	NR		NR	
NR		N/A	2182 (26)	≤pT2: 1787 (64) >pT2: 1002 (36)	≤pT2: 4157 (49) >pT2: 4237 (51)	NR	
2002-2011		NR	N/A	NR	NR	NR	
Mean 59.2 mo (1-171)		26 (22)	28 (30)	NR		Excluded	
Mean 59.2 mo (1-171)		26 (22)	19 (31)	NR		Excluded	

Table 2b: Oncological outcomes of studies comparing no lymphadenectomy (LND) versus any LND

	LND comparator	OS (%)		RFS/DFS (%)	
		5 year	10 year	5 year	10 year
Liu 2011 [10]	No LND	NR	NR	NR	NR
	Any LND	NR	NR	NR	NR
Isaka 1985 [11]	No LND	25.0	NR	NR	NR
	Standard	64.0 p<0.05	NR	NR	NR
Miyakawa 1985 [12]	No LND	35.0	NR	NR	NR
	Standard	66.0 p<0.05	NR	NR	NR
Yuasa 1988 [13]	No LND	50.0	NR	NR	NR
	Limited	67.8 p<0.01	NR	NR	NR
Abdollah 2012 [14]	No LND	±41*	27.2*	NR	NR
	Any LND	±47 p<0.01*	34.1 p<0.01*	NR	NR
Zhang 2013 [15]	No LND	NR	NR	NR	NR
	Any LND	NR	NR	NR	NR
Brunocilla 2013 [16]	No/L-LND	NR	NR	NR	NR
	1. S-LND	NR	NR	NR	NR
	2. E/SE-LND	NR	NR	NR	NR

L-LND = *limited LND*;
S-LND = *standard LND*;
E-LND = *extended LND*;
SE-LND = *superextended*
NR = *not reported*;
NS = *not significant*
OS = *overall survival*;
RFS = *recurrence-free survival*;

CSS/DSS (%)		Multivariable Cox Regression analysis			Authors conclusion
5 year	10 year	Hazard Ratio (HR)	95% confidence interval	p-value	
NR	NR	NR	NR	NR	Favors LND (pT1 only)
NR	NR	NR	NR	NR	
NR	NR	NR	NR	NR	Favors LND
NR	NR	NR	NR	NR	
NR	NR	NR	NR	NR	Favors LND
NR	NR	NR	NR	NR	
NR	NR	NR	NR	NR	Favors LND
NR	NR	NR	NR	NR	
±58	52.5	Cancer specific mortality** All patients HR 1.33 pTa-pTis: HR 2.09 pT1: HR 1.60 pT2: HR 1.68 pT3: HR 1.15 pT4: HR 1.11	 1.24 - 1.44 1.16 - 3.79 1.18 - 2.17 1.47 - 1.91 1.01 - 1.33 0.96 - 1.28	 < 0.01 < 0.05 < 0.05 < 0.01 NS NS	Favors LND (CSS < pT3 only)
±61 p < 0.01	57.5 p < 0.01	HR 1.00 (reference)	-	-	
NR	NR	NR	NR	NR	Favors LND
NR	NR	NR	NR	NR	
± 50	± 35	HR 1.00 (reference)	-	-	Favors LND
± 60 p = 0.010	± 75 p = 0.010	Cancer specific survival Total cohort: HR 0.99	 0.55 – 1.35	 0.49	
± 78 p = 0.010	± 75 p = 0.010	Cancer specific survival Total cohort: HR 0.46	 0.37 – 0.89	 0.036	

DFS = disease-free survival; CSS = cancer-specific survival DSS = disease-specific survival

The ± symbol indicates the Kaplan-Meier curve was used to estimate the percentage

** Overall mortality ** Adjusting for age, gender, race tumor grade and year of cystectomy*

Table 3a: Descriptive outcomes of studies comparing limited lymphadenectomy (LND) versus (super)extended LND

	LE	Type of LND		Number of patients		Follow-up duration (range)	
		C	I	C	I	C	I
Hori 2013 [17]	4	Limited	Extended	53	47	NR	
Holmer 2009 [18]	4	Limited	Extended	69	101	Median 94 mo (61-122)	Median 38 mo (13-70)
Bostrom 2011 [19]	4	Limited	Extended or super-extended	563		NR	
Jensen 2012 [20]	4	Limited	Standard, extended or super-extended	204 202 L-LND 2 no-LND	265 170 SE-LND 46 E-LND 49 S-LND	Median 113 mo (86-143)	Median 45 mo (24-84)
Brossner 2004 [21]	3	Limited	Super-extended	46	46	30 days	

C = control group; I = intervention group

L-LND = limited LND;

E-LND = extended LND;

NR = not reported

S-LND = standard LND;

SE-LND = superextended LND

Adj = adjuvant; neo-adj = neo-adjuvant; chemo = chemotherapy

pN+ (number, %)		pT stage (number, %)		Neo-adjuvant or adjuvant therapy (number, %)	
C	I	C	I	C	I
10 (19)	14 (30)	NR		NR	
12 (17)	38 (38)	≤pT2: 46 (67) >pT2: 23 (33)	≤pT2: 53 (52) >pT2: 48 (48)	Neo-adj: excluded Adj chemo 13% vs 16%	
NR (7)	NR (26)	NR		Neo-adj: Excluded Adj chemo: 1 vs 21%	
43 (21)	61 (23)	≤pT2: 112 (55) >pT2: 92 (45)	≤pT2: 160 (60) >pT2: 105 (40)	Excluded	
10 (22)	18 (39)	≤pT3a: 24 (52) >pT3a: 22 (48)	≤pT3a: 28 (61) >pT3a: 18 (39)	NR	

Table 3b: Oncological outcomes of studies comparing limited lymphadenectomy (LND) versus (super)extended LND

	LND comparator	OS (%)		RFS/DFS (%)	
		5 year	10 year	5 year	10 year
Hori 2013 [17]	Limited	61	NR	NR	NR
	Extended	47 p=0.65	NR	NR	NR
Holmer 2009 [18]	Limited	NR	NR	±66	±65
	Extended	NR	NR	±75 p=0.27	No cases p=0.27
Bostrom 2011 [19]	Limited	NR	NR	NR	NR
	Extended or super-extended	NR	NR	NR	NR
Jensen 2012 [20]	Limited	All patients 55 ≤pT2 77 >pT2 43 LN negative 66 LN positive 12	NR	All patients 62 ≤pT2 83 >pT2 54 LN negative 75 LN positive 8	NR
	Standard, extended or super-extended	All patients 67 p<0.05 ≤ pT2 77 NS >pT2 71 p<0.05 LN negative 75 NS LN positive 38 p<0.05	NR	All patients 64 NS ≤pT2 80 NS >pT2 61 NS LN negative 74 NS LN positive 29 p<0.05	NR
Brossner 2004 [21]	Limited	NR	NR	NR	NR
	Super-extended	NR	NR	NR	NR

NR = *not reported*; NS = *not significant*; OS = *overall survival*;
RFS = *recurrence-free survival*; DFS = *disease-free survival*; CSS = *cancer-specific survival*;

CSS/DSS (%)		Multivariable Cox Regression analysis			Authors conclusion
5 year	10 year	Hazard Ratio (HR)	95% confidence interval	p-value	
73	NR	NR	NR	NR	No difference
50 p=0.27	NR	NR	NR	NR	
±66	No cases	HR 1.00 (reference)	-	-	Favors extended LND in subgroup >pT2 and RFS only
±73 p=0.45	No cases	<u>Disease specific mortality*</u> All patients HR 0.81 ≤ pT2 HR 0.80 >pT2 HR 0.54 <u>Recurrence-free survival*</u> All patients HR 0.73 ≤ pT2 HR 0.88 > pT2 HR 0.42	 0.44- 1.47 0.28-2.32 0.26-1.14 0.41 – 1.30 0.34 - 2.30 0.20 - 0.88	 0.48 0.68 0.10 0.28 0.79 0.022	
NR	NR	HR 1.00 (reference)	-	-	Favors extended LND
NR	NR	<u>Disease specific survival</u> All patients HR 0.53	 0.31 – 0.93	 0.026	
All patients 67 ≤ pT2 88 >pT2 62 LN negative 80 LN positive 14	NR	HR 1.00 (reference)	-	-	Favors extended LND (locally advanced disease only)
All patients 72 p<0.05 ≤ pT2 88 NS >pT2 62 p<0.05 LN negative 80 NS LN positive 14 p<0.05	NR	<u>Recurrence-free survival</u> All patients HR 0.90 <u>Disease specific survival</u> All patients HR 0.71 <u>Overall survival</u> All patients HR 0.60	 0.65 – 1.24 0.50 – 1.01 0.45 – 0.81	 0.51 0.06 < 0.01	
NR	NR	NR	NR	NR	Comparable peri-operative outcomes
NR	NR	NR	NR	NR	

DSS = disease-specific survival. ** Adjusting for sex, age and adjuvant chemotherapy*

The ± symbol indicates the Kaplan-Meier curve was used to estimate the percentage

3.3.3.2 Oncological outcomes

Table 3b summarizes the oncological outcomes comparing L-LND with E/SE-LND. Of the five studies included, three studies reported improvement of at least one oncological outcome for E/SE-LND. [18-20] Brossner et al. [21] did not report oncological outcomes, while Hori et al. [17] found no statistically significant difference in oncological outcomes for L-LND and E-LND performing univariable analysis.

3.3.3.3 Peri-operative outcomes

Jensen et al. [20] reported no prolonged operative time for E-LND compared with L-LND (mean 306 vs 302 minutes, $p = 0.92$). Brossner et al. [21], however, reported prolonged operative time for SE-LND compared with L-LND (median 330 vs 277 minutes, $p < 0.01$). This study reported no differences in number of blood units transfused (1.15 vs 0.38 respectively, $p = 0.37$), lymphoceles (none in both groups), 30-day complication rate (11% vs 9% respectively, $p=0.28$), and 30-day mortality (3 vs 1 event respectively, $p = 0.57$). [21]

3.3.4 Standard LND vs (super-)extended LND

3.3.4.1 Baseline characteristics

Nine studies were identified involving 3,104 patients (Table 4a). [22-30] Four studies used data from the Cleveland Clinic. [22, 23, 25,28] Abd El Latif [23] differed from their previous study [22] by extending the study period by 2 years (2004-2010 vs 2006-2010). One study specifically looked at the outcomes of laparoscopic LND. [25]

3.3.4.2 Oncological outcomes

Table 4b summarizes the oncological outcomes comparing S-LND with E/SE-LND and contradicting results were reported. Four studies noted no difference in oncological outcomes between S-LND and E-LND [22-24,30], although only one study on data from multivariable analysis. [22] Three studies reported a benefit for E-LND and one study reported a benefit for SE-LND for at least one oncological outcome. Subgroup analysis in these studies revealed no consistent subgroup that benefited most from E-LND. For example, Poulsen et al. [26] reported a RFS benefit for E-LND in patients with organ-confined disease, while Dhar et al. [28] only found a RFS benefit for patients with >pT2 disease.

3.3.4.3 Peri-operative outcomes

Poulsen et al. [26] reported a lymphocele rate of 1.6% for E-LND and 1.5% for S-LND. One patient (0.8%) in the E-LND group died peri-operatively from complications unrelated to LND. Finelli et al. [25], performing laparoscopic LND, reported an estimated increase in operative time from 30-45 minutes for S-LND to 90 minutes for E-LND (no p-value reported).

3.3.5 Extended LND vs super-extended LND

3.3.5.1 Baseline characteristics

Two multi-institutional studies, involving 1,462 patients were included. (Table 5a) [31,32]

3.3.5.2 Oncological outcomes

Table 5b summarizes the oncological outcomes comparing E-LND with SE-LND. Both studies reported no statistically significant difference in survival outcomes between E-LND and SE-LND, irrespective of tumor stage or nodal status.

3.3.5.3 Peri-operative outcomes

No studies reporting on peri-operative outcomes were identified.

Table 4a: Descriptive outcomes of studies comparing standard lymphadenectomy (LND) versus (super)extended LND

	LE	Type of LND		Number of patients		Follow-up duration (range)	
		C	I	C	I	C	I
Abd-El-Latif 2011 [22]	3	Standard	Extended or super-extended	122	199	Median 24 mo (IQR 12 - 36)	
Abd-El-Latif 2012 [23]	3	Standard	Extended or super-extended	183	240	Median 24 mo	
Dharaskar 2011 [24]	4	Standard a. en bloc b. LN packets	Extended	51	27	a. median 24 mo (0-49) b. Median 14 mo (0-43)	Median 6 mo (0-37)
Finelli 2004 [25]	3	Standard	Extended	11	11	Mean 11 mo (2-4)	
Poulsen 1998 [26]	4	Standard	Extended	68	126	Median: 5.14 yrs (0.2-7.9)	Median: 1.96 yrs (0.3-4.7)
Simone 2012a [27]	3	Standard	Extended	584	349	NR	
Dhar 2008 [28]	3	Standard	Extended	336	322	For RFS 25 mo (1.1-166) For OS 36 mo (1.1-166)	For RFS 40 mo (range 1-229) For OS 51 mo (range 1-229)
Abol-Enein 2011 [29]	3	Standard	Super-extended	200	200	50.2 months (IQR 69.0) for patients alive at last follow-up	
Wang 2013 [30]	3	Standard	Extended	42	33	NR	

C = control group; I = intervention group; NR = not reported; *Adj = adjuvant; neo-adj = neo-adjuvant;*

pN+ (number, %)		pT stage (number, %)		Neo-adjuvant or adjuvant therapy (number, %)	
C	I	C	I	C	I
Excluded		NR		Neo-adj: 17 (5) Adj: NR	
NR		NR		NR	
13 (26)	7 (26)	≤pT2: 32 (63) >pT2: 19 (37)	≤pT2: 20 (74) >pT2:7 (26)	NR	
3 (27)	3 (27)	≤pT2: 5 (45) >pT2: 6 (55)	≤pT2: 9 (82) >pT2: 2 (18)	Neo-adj: NR Adj: chemo 2 (9)	
15 (22)	35 (28)	≤pT2: 34 (50) >pT2: 33 (49) pTx: 1 (1)	≤pT2: 55 (43) >pT2: 69 (55) pTx: 2 (2)	Excluded	
187 (32)	107 (31)	≤pT2: 271 (46) >pT2: 313 (54)	≤pT2: 192 (55) >pT2: 157 (45)	Neo-adj: Excluded- Adj chemo 101 (11) Adj rad 8 (0.8)	
44 (13)	83 (26)	≤pT2: 200 (60) >pT2: 136 (40)	≤pT2: 150 (47) >pT2: 172 (53)	Neo-adj: Excluded Adj: NR	
48 (24)	48 (24)	≤pT2: 61 (31) >pT2: 139 (70)	≤pT2: 70 (35) >pT2: 129 (65)	0	
NR		NR		Excluded	

chemo = chemotherapy; rad = radiotherapy. IQR = interquartile range; RFS = recurrence-free survival; OS = overall survival

Table 4b: Oncological outcomes of studies comparing standard lymphadenectomy (LND) versus (super)extended LND

	LND compara-tor	OS (%)		RFS/DFS (%)	
		5 year	10 year	5year	10 year
Abd-El-Latif 2011 [22]	Standard	NR	NR	NR	NR
	E/SE-LND	NR	NR	NR	NR
Abd-El-Latif 2012 [23]	Standard	±58	NR	NR	NR
	E/SE -LND	±40 p=0.14	NR	NR	NR
Dharaskar 2011 [24]	Standard	No cases	No cases	NR	NR
	E-LND	No cases	No cases	NR	NR
Finelli 2004 [25]	Standard	NR	NR	NR	NR
	E-LND	NR	NR	NR	NR
Poulsen 1998 [26]	Standard	NR	NR	All patients 56 ≤ pT3** 85 >pT3 27 pN0 71 pN+ 7	NR
	E-LND	NR	NR	All patients 62 p=0.33 ≤ pT3** 64 p < 0.02 >pT3 39 p = 0.87 pN0 90 p < 0.02 pN+ 24 p = 0.15	NR

L-LND = limited LND; S-LND = standard LND; E-LND = extended LND;
E-LND = superextended LND, NR = not reported; LN = lymph node;
OS = overall survival; RFS = recurrence-free survival; DFS = disease-free survival;
CSS = cancer-specific survival; DSS = disease-specific survival

The symbol '±' indicates the Kaplan-Meier curve was used to estimate the percentage

CSS/DSS (%)		Multivariable Cox Regression analysis			Authors conclusion
5 year	10 year	Hazard Ratio (HR)	95% confidence interval	p-value	
NR	NR	HR 1.00 (reference)	-	-	No difference
NR	NR	Overall survival: All patients HR 2.50 Cancer specific survival: All patients HR 2.00 Recurrence-free survival: All patients HR 2.60	 0.9 – 6.5 0.4 – 11.1 0.7 – 9.9	 NR NR NR	
NR	NR	NR	NR	NR	No difference
NR	NR	NR	NR	NR	
NR	NR	NR	NR	NR	No difference
NR	NR	NR	NR	NR	
NR	NR	NR	NR	NR	Not assessed
NR	NR	NR	NR	NR	
NR	NR	NR	NR	NR	Favors E-LND (≤ pT2 and pN0 only)
NR	NR	NR	NR	NR	

** HR was re-calculated using the same reference group (standard LND) as in the subgroup analysis*

*** ≤pT3a indicated organ-confined disease in this study*

**** adjusting for pT stage, pN stage, age, gender, tumor grade and histology*

Table 4b (Cont.)

	LND comparator	OS (%)		RFS/DFS (%)
		5 year	10 year	5 year
Simone 2012a [27]	Standard	NR	NR	42.6
	E-LND	NR	NR	63.1 p<0.01
Dhar 2008 [28]	Standard	pT2,N0 68 pT2,N+ 64 pT3,N0 26 pT3,N+ 22	NR	pT2,N0 67 pT2,N+ 63 pT3,N0 23 pT3,N+ 19
	E-LND	pT2,N0 66 p = 0.12 pT2,N+ 61 p = 0.10 pT3,N0 46 p = 0.002 pT3,N+ 42 p = 0.002	NR	pT2,N0 77 p = 0.12 pT2,N+ 71 p = 0.22 pT3,N0 57 p < 0.01 pT3,N+ 49 p < 0.01
Abol-Enein 2011 [29]	Standard	NR	NR	All patients 55 LN- 66 LN + 28
	SE-LND	NR	NR	All patients 67 p = 0.04 LN - 72 p = 0.24 LN + 48 p = 0.02
Wang 2013 [30]	Standard	NR	NR	NR
	E-LND	NR	NR	NR

RFS/ DFS (%)	CSS/DSS (%)		Multivariable Cox Regression analysis			Authors conclusion
10 year	5 year	10 year	Hazard Ratio (HR)	95% confidence interval	p-value	
NR	50.9	NR	HR 1.00 (reference)	-	-	Favours E-LND
NR	68.8 p<0.01	NR	<u>Disease free survival</u> All patients HR 0.51* pT2 HR 0.41 pT3 HR 0.55 pT4 HR 0.33 pN0 HR 0.63 pN1 HR 0.19 pN2 HR 0.40 <u>Cancer specific survival</u> All patients HR 0.56* pT2 HR 0.40 pT3 HR 0.65 pT4 HR 0.33 pN0 HR 0.54 pN1 HR 0.15 pN2 HR 0.45	 0.40 – 0.65 0.22 - 0.78 0.40 - 0.77 0.20 – 0.55 0.44 – 0.91 0.08 – 0.49 0.24 – 0.67 0.42 - 0.73 0.19 – 0.83 0.44 – 0.94 0.19 – 0.58 0.30 – 0.95 0.05 – 0.41 0.25 – 0.80	 < 0.01 0.004 0.001 < 0.001 0.011 < 0.001 < 0.001 < 0.01 0.011 0.019 < 0.001 0.034 < 0.001 < 0.001	
NR	NR	NR	NR	NR	NR	Favors E- LND (≤ pT3 only)
NR	NR	NR	NR	NR	NR	
NR	NR	NR	<u>Disease free survival</u> HR 1.45***	1.06 – 1.99	0.02	Favors SE-LND
NR	NR	NR	HR 1.00 (ref)	-	-	
NR	59.0	NR	NR	NR	NR	No difference
NR	77.0 p=0.08	NR	NR	NR	NR	

Table 5a: Descriptive outcomes of studies comparing extended lymphadenectomy (LND) versus (super)extended LND

	LE	Type of LND		Number of patients		Follow-up duration (range)	
		C	I	C	I	C	I
Simone2012b [31]	3	Extended	Super extended	503		Median 9.9 years (0-22.3)	
Zehnder 2011 [32]	3	Extended	Super extended	405	554	Median 10.9 years (0-24.1)	

C = control group; I = intervention group; NR = not reported
Adj = adjuvant; neo-adj = neo-adjuvant; chemo = chemotherapy

Table 5b: Oncological outcomes of studies comparing extended lymphadenectomy (LND) versus (super)extended LND

	LND comparator	OS (%)		RFS/DFS (%)	
		5 year	10 year	5 year	10 year
Simone 2012b [31]	Extended	NR	NR	±59	NR
	Super-extended	NR	NR	±64 p=0.41	NR
Zehnder 2011 [32]	Extended	±54	±42	±61	±59
	Super-extended	±50 p=0.45	±40 p=0.45	±61 p=0.75	±59 p=0.75

NR = *not reported*; OS = *overall survival*; RFS = *recurrence-free survival*;
DFS = *disease-free survival*; CSS = *cancer-specific survival*; DSS = *disease-specific survival*

The symbol ± indicates the Kaplan-Meier curve was used to estimate the percentage

pN+ (number, %)		pT stage (number, %)		(Neo-)adjuvant therapy (number, %)	
C	I	C	I	C	I
Excluded		NR		Excluded	
NR		114 (28)	195 (35)	Neo-adj: excluded Adj chemo: 46 (11)	Neo-adj: excluded Adj chemo: 195 (35)

CSS/DSS (%)		Multivariable Cox Regression analysis			Authors conclusion
5 year	10 year	Hazard ratio	95% Confidence interval	p-value	
NR	NR	NR	NR	NR	No difference
NR	NR	NR	NR	NR	
NR	NR	NR	NR	NR	No difference
NR	NR	NR	NR	NR	

3.4 Discussion

3.4.1 Principal findings

To the best of our knowledge, this study represents the most robust literature review focusing on the impact of the anatomical extent of LND on post-RC oncological and peri-operative outcomes. The findings of this study suggest that any extent of LND is better than no LND for patients undergoing RC for MIBC, in terms of oncological outcomes. Additionally, E-LND might improve oncological outcomes compared with lesser degrees of dissection, although extending the dissection beyond E-LND is unlikely to yield any further benefits. With respect to peri-operative outcomes, a secondary outcome of this study, SE-LND resulted in increased operative time compared with less extended LND templates, but does not appear to substantially increase post-operative morbidity.

3.4.2 Clinical implications of our study findings

The data in this study support the routine performance of LND in patients undergoing RC. Whether the reported beneficial oncological outcomes are a result of stage migration (the so-called Will-Rogers Phenomenon), a true therapeutic benefit of LND, or a combination of both, remains uncertain. There is, however, a clear staging role of LND as supported by LN mapping studies. [33, 34] Thus, in spite of the lack of RCTs, the current evidence base is sufficiently convincing to recommend LND for patients undergoing RC for MIBC.

While limited LND may contribute to disease staging, performing LND outside the true pelvis (i.e. ≥S-LND) should be considered a potential therapeutic intervention as skip nodal lesions are rare, therefore unlikely contributing to disease staging. [33,34] To date, however, questions remain about the potential therapeutic value of LND and what extent of LND is the most efficacious. Based on the current data, consisting of retrospective studies with a significant risk of bias and confounding, the evidence base is not strong enough to provide firm recommendations regarding the most optimal extent of LND. Conversely, these studies are currently the best available evidence and fairly consistently report an oncological benefit for E-LND compared with less extended LND templates. In addition, E-LND appears not to increase peri-operative morbidity. Collectively, there is accumulating evidence that E-LND may be beneficial for patients undergoing RC for MIBC and is therefore recommended in patients undergoing RC for MIBC.

3.4.3 How does this systematic review compare with other recent reviews?

To our knowledge, two systematic reviews on the importance of LND in bladder cancer have been published. [35,36] Fan et al. [36] performed a systematic review and meta-analysis of studies comparing E-LND and non-extended LND and its impact on RFS. The authors concluded that E-LND was associated with improved RFS compared with non-extended LND. Subgroup analysis revealed that patients with ≥pT3 bladder cancer, independently of LN status, benefit from E-LND. Tilki et al. [35] performed a systematic review only and concluded that the extent of LND may influence DFS after RC, independently of LN status and pT stage.

The outcomes of our present study are in line with these reviews. However, there are important methodological differences which deserve discussion. Tilki et al. [35] included studies using the LN count as a surrogate for the extent of LND. Although an association between LN count, the extent of LND or even post-RC outcomes have been suggested [37-39], using the LN count as a surrogate for the extent of LND has limitations as acknowledged by the authors. Differences in surgical technique, sample processing and pathologic assessment greatly influence the LN count and consequently affect reproducibility. [37,40,41] Furthermore, the LN count cannot adequately be determined intra-operatively whereas surgeons can adhere to anatomic templates, making studies comparing LND templates more clinically relevant. For these reasons, only studies describing anatomic templates for the extent of LND were included in our review. In addition, although Tilki et al. [35] described some studies comparing LND templates (references 26,28,29,32), an additional 19 studies were included in this study providing a more comprehensive overview of studies comparing different LND templates.

The attempt by Fan et al. [36] to perform a meta-analysis is noteworthy. Yet, the results of this study should be interpreted with caution. Aside from the low quality studies included in the analysis with its associated bias, differences in the definition of the extent of LND were not adjusted for in this study. Reflecting the lack of consensus on what constitutes a limited, standard, and extended or super-extended LND, there was significant heterogeneity in the definition regarding the extent of LND across studies. To illustrate, Abol-Enein et al. [29] and Dhar et al. [28] were both classified as E-LND studies while the proximal boundaries were the inferior mesenteric artery and crossing of the ureter with the common iliac vessels, respectively. For this reason, we chose to define the LND templates a priori and, if necessary, re-classify accordingly if sufficiently large numbers of studies did not match our chosen definitions. Although the definitions

chosen for each of the LND templates may not be universally accepted by all clinicians, it at least allows for a certain degree of standardization, which enables a comparison of outcomes among different LND templates.

3.4.4 Strengths and limitations of the review

The strength of the current study is the comprehensive literature review evaluating the impact of the extent of LND on post-RC outcomes using a robust and transparent methodological approach based on Cochrane review principles, incorporating the assessment of RoB and confounding which are essential in any review involving non-randomized studies. The search strategy was complemented by additional sources for potentially important articles, which included an expert panel (EAU Working Group on MIBC). The review was limited to comparative studies, in order to maintain at least moderate levels of evidence. Throughout the entire review process, peer review was obtained from the expert panel, which represents a reference group of international experts. This approach ensured a comprehensive review of the literature, whilst maintaining methodological rigour, and enabled the authors to put into clinical context the relevance and implication of the review findings.

The major limitation of the review is the quality of included studies; except for one prospective study, all studies were retrospective, non-standardized comparative studies with high risks of bias and confounding. This review highlights the lack of high quality and reliable evidence concerning the benefits and harms of LND during RC in terms of oncological and peri-operative outcomes. The results, on the other hand, are supported by the fact that these studies are fairly consistent in reporting an oncological benefit. Currently, two phase III RCTs, one in Germany and one initiated by the Southwest Oncology Group (SWOG S1011), evaluating the impact of different LND templates on survival are ongoing. The final results of these studies, which will take several years (personal communication), may provide a more definitive answer to some aspects of this important clinical question. Standardization of the LND templates and surgeon expertise, however, are of critical importance for the success of these trials.

4. Conclusions

This systematic review set out to determine the evidence base in regard with the comparative effectiveness of LND in patients undergoing RC for MIBC, in terms of oncological benefits

and peri-operative outcomes. The findings reveal a lack of randomized studies, and an evidence base derived mainly from retrospective studies with significant risks of bias and confounding. Nevertheless, the data indicate that any form of LND produces more favorable oncological outcomes compared with no LND. There was no evidence that LND results in increased peri-operative adverse events than no LND. In terms of how different extents of LND influence outcomes, the findings indicate that E-LND might be superior to lesser degrees of dissection from an oncological perspective; however, extending the dissection beyond this (e.g. SE-LND) is not beneficial. The results of ongoing RCTs will hopefully clarify the remaining uncertainties regarding the role of LND during RC for MIBC.

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Supplement 1

Embase 1974 to December 2013,
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MEDLINE 1946 to December 2013

Ovid Multifile search URL: http://gateway.ovid.com

1	urinary bladder neoplasms/
2	bladder cancer/
3	((cancer$ or tumo$r$ or carcinoma or neoplas$) adj3 bladder).tw.
4	(squamous adj5 bladder).tw.
5	transitional cell carcinoma.tw.
6	transitional cell carcinoma/
7	Carcinoma, Transitional Cell/
8	or/1-7
9	Lymph Node Excision/
10	exp lymphadenectomy/
11	(lymphadenectomy or lnd).tw.
12	(lymph node$ adj3 (dissect$ or excis$ or remov$)).tw.
13	or/9-12
14	comparative study/ use prmz
15	follow-up studies/ use prmz
16	time factors/ use prmz
17	Treatment outcome/ use oemezd
18	major clinical study/ use oemezd
19	controlled study/ use oemezd
20	clinical trial/ use oemezd
21	(preoperat$ or pre operat$).tw.
22	(chang$ or evaluat$ or reviewed or baseline).tw.
23	(prospective$ or retrospective$).tw.
24	(cohort$ or case series).tw.
25	(compare$ or compara$).tw.
26	case report/ use oemezd
27	case reports.pt.
28	exp clinical trial/
29	Randomized Controlled Trials as Topic/
30	randomized controlled trial.pt.
31	controlled clinical trial.pt.
32	randomization/ use oemezd

33 randomi?ed.ab.
34 placebo.ab.
35 drug therapy.fs.
36 randomly.ab.
37 trial.ab.
38 groups.ab.
39 (database$ or data?base$ or regist$).ab.
40 or/14-39
41 8 and 13 and 40
42 (letter or editorial or comment*).pt.
43 exp animals/ not humans/
44 41 not (42 or 43)
45 remove duplicates from 44

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1 MeSH descriptor: [Urinary Bladder Neoplasms] this term only
2 MeSH descriptor: [Carcinoma, Transitional Cell] this term only
3 MeSH descriptor: [Carcinoma, Transitional Cell] this term only
4 bladder near/3 (cancer* or tumo*r* or carcinoma* or neoplas*)
5 squamous near/5 bladder
6 transitional cell carcinoma
7 #1 or #2 or #3 or #4 or #5 or #6
8 MeSH descriptor: [Lymph Node Excision] this term only
9 lymphadenectomy or lnd
10 (lymph node*) near/3 (dissect* or excis* or remov*)
11 #8 or #9 or #10
12 #7 and #11

LILACS (Latin American and Caribbean Center on Health Sciences Information)

http://lilacs.bvsalud.org/en/

Bladder cancer [Subject descriptor] or bladder and (cancer$ or tumo$ or carcinoma$ or neoplas$) [Words] and "LYMPHADENECTOMY" or lymph node dissection or lymph node

excision [Words]

Database of Abstracts of Reviews of Effects
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1. MeSH DESCRIPTOR Urinary Bladder Neoplasms
2. bladder adj3 (cancer* or tumor* or tumour* or carcinoma* or neoplas*)
3. MeSH DESCRIPTOR Carcinoma, Transitional Cell
4. transitional cell carcinoma
5. #1 OR #2 OR #3 OR #4
6. MeSH DESCRIPTOR Lymph Node Excision
7. lymphadenectomy or lnd
8. lymph node* adj3 (dissect* or excis$* or remov*)
9. #6 OR #7 OR #8
10. #5 AND #9

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PART I
PART II
PART III
PART IV BLADDER CANCER
AND PROGNOSIS
PART V

PART IV

Bladder cancer and prognosis

7 Clinical outcomes and recurrence predictors of lymph node positive urothelial cancer after cystectomy
J Urol 2009;182(5):2182-2187

8 Critical evaluation of the American Joint Committee on Cancer TNM nodal staging system in patients with lymph node–positive disease after radical cystectomy
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9 The impact of the time interval between diagnosis of muscle-invasive bladder cancer on staging and survival: a Netherlands Cancer Registry analysis
Accepted for publication in Urologic Oncology

CHAPTER 7

Clinical outcomes and recurrence predictors of lymph node positive urothelial cancer after cystectomy

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Journal of Urology 2009;182:2182-2187

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Abstract

Purpose

Lymph node metastasis in patients who undergo radical cystectomy for bladder transitional cell carcinoma is considered a poor prognostic factor. However, patients with minimal lymph node involvement likely have a better outcome than those with extensive disease. We examined outcomes in patients with low volume lymph node metastasis and identified variables associated with disease recurrence.

Materials and Methods

Our institution maintains a database of 1,600 patients with bladder transitional carcinoma who underwent radical cystectomy from 1971 to 2005 with intent to cure. All patients with low volume lymph node metastasis, defined as 1 or 2 positive lymph nodes, without concomitant distant metastasis were included in study.

Results

A total of 181 patients were identified. Median follow-up was 12.8 years, during which 96 patients experienced recurrence. Estimated 5 and 10-year recurrence-free survival was 43.8% and 40.9%, respectively. Multivariable analysis indicated that pathological stage/subgroup (RR 1.733, p = 0.015), lymph node density (RR 1.935, p = 0.014) and adjuvant chemotherapy (RR 0.538, p = 0.004) were independently associated with recurrence-free survival.

Conclusions

A considerable proportion of patients with low volume lymph node metastasis in our cohort remained free of recurrence during follow-up. Extravesical tumor extension and lymph node density greater than 4% were associated with a higher recurrence risk and adjuvant chemotherapy was associated with a lower risk. Although some patients with low volume lymph node metastasis may be cured by surgery alone, these data support adjuvant chemotherapy in these patients.

Abbreviations and Acronyms

LND = lymph node density
LNM = lymph node metastasis

Introduction

Radical cystectomy combined with appropriate lymph node dissection is standard treatment in patients with high grade invasive bladder cancer. [1] Metastasis are found in regional lymph nodes in approximately 25% of patients at surgery, which is associated with a higher incidence of disease progression.[1-3] Several variables were reported to provide risk stratification in patients with lymph node involvement after radical cystectomy, including the number of lymph nodes involved with tumor (nodal tumor burden), the primary bladder tumor pathological stage/subgroup and the extent of lymphadenectomy. [1-8]More recently lymph node density was identified as an independent prognostic factor. Lymph node density is defined as the number of lymph nodes involved with tumor divided by the total number of lymph nodes removed. [4,5]

In a large cohort from our institution approximately 50% of patients with node positive disease at radical cystectomy had only 1 or 2 nodes involved.[4] While it is likely that they have a better outcome than patients with higher volume LNM, to our knowledge there are no reports to date specifically of outcomes in these patients. Thus, we assessed clinical outcomes and identified independent prognostic variables in patients with low volume LNM.

Materials and Methods

Cohort Assembly

All 1,600 patients who underwent radical cystectomy for urothelial cancer at our institution with intent to cure between November 1971 and September 2005 were eligible for study inclusion. Data on all patients were collected using a standardized retrospective medical record review and stored in our institutional bladder cancer database. This established database includes information on all patients who undergo cystectomy at the department of urology at our institution and it is approved by the University of Southern California human subject committee. Of the 1,600 patients (23%) 369 had lymph node positive disease, including 181 (49%) with only 1 or 2 lymph nodes involved. These 181 patients comprise the study population.

Pathological Variables

All cystectomy specimens were examined using the same pathological protocol. Multiple sections and histological evaluation was performed on the primary bladder tumor,

bladder wall (adjacent and distant bladder mucosa of the primary tumor) and all lymph nodes. All bladder tumors were primary urothelial carcinoma. Patients with another primary tumor type, i.e. adenocarcinoma, squamous cell carcinoma etc, were excluded from study. Histological grading was done according to the method of Bergkvist and Moberger. [9] The 1997 American Joint Committee on Cancer TNM classification was used to pathologically stage bladder tumors. [10] Pathological subgroups were divided into organ confined (pTa, pTcis, pT1, pT2a and pT2b) and extravesical (pT3a, pT3b and pT4) tumors. No clearing techniques or solvents were used to identify lymph nodes. All lymph nodes were identified visually or by palpation.

Follow-up and Clinical Outcomes

All patients were routinely followed postoperatively at 4-month intervals in year 1, at 6-month intervals in year 2 and annually thereafter according to our database protocol. Follow-up consisted of physical examination and routine serum chemistry studies, including a biochemical liver profile and alkaline phosphatase determination. Radiographic evaluation of the urinary diversion, upper urinary tract with excretory urography or ultrasonography and chest radiography were done 4 months postoperatively and annually thereafter unless otherwise clinically indicated. Median follow-up in the 181 patients with low volume LNM was 12.8 years (range: 23 days to 34.6 years).

The primary outcomes of interest in this analysis were overall survival and recurrence-free survival. Time to overall survival was calculated from the date of radical cystectomy to the data of death from all causes. If lost to follow-up, patients were censored from analysis at the date of last follow-up. Recurrence-free survival was calculated from the date of radical cystectomy to the date of first documented clinical recurrence or death, whichever occurred first. If lost to follow-up before recurrence, patients were censored at the date of last follow-up. Operative mortality was defined as any death within 30 days after surgery.

Statistical Analysis

Pearson's chi-square or Fisher's exact test was used to examine the association between categorical demographic and clinical variables. The Wilcoxon rank sum test was used to test differences in not normally distributed continuous variables between groups or subgroups. Kaplan-Meier plots were used to estimate the probability of overall and recurrence-free survival with time since radical cystectomy. The log rank test was used

to compare differences in survival or recurrence in subgroups. Proportional hazards models were used to estimate the independent relationship between various clinical and sociodemographic factors, and the 2 primary outcomes. All p values are 2-sided.

Results

Patients

Of patients with low volume LNM, 118 (65.2%) had only 1 positive lymph node and 63 (35%) had 2 lymph nodes involved. Operative mortality was low and occurred in 1 of the 181 patients (0.55%) with low volume LNM. Median age in patients with low volume LNM was 66 years (range 36 to 88). Of the patients 55% had pT3a or higher disease (table 1). A total of 173 patients (96%) had localized lymphatic involvement, defined as involvement of the pelvic/external iliac, hypogastric, presacral or perivesical lymph nodes only. Eight patients (4%) had distant lymphatic involvement, including involvement of the common iliac lymph nodes in 4, interaortocaval lymph node involvement in 3 and para-aortic involvement in 1.

Table 1: Characteristics of 181 patients with 1 or 2 positive lymph nodes, 188 patients with more than 2 positive lymph nodes and all 369 node-positive patients after radical cystectomy

	Patients with 1 or 2 LN+ (n=181)	Patients with > 2 LN+ (n=188)	All patients with LN+ (n=369)
No. Age (%)			
Greater than 65	91 (50.3)	109 (58)	200 (54.2)
65 or less	90 (49.7)	79 (42)	169 (45.8)
No. Gender (%)			
Male	142 (78.5)	143 (76.1)	285 (77.2)
Female	39 (21.5)	45 (23.9)	84 (22.8)

Table 1: continued

No. Pathological stage (%)			
pT1 or less	21 (11.7)	14 (7.4)	35 (9.5)
pT2a	18 (9.9)	8 (4.3)	26 (7)
pT2b	38 (21)	22 (11.7)	60 (16.3)
pT3a	28 (15.5)	32 (17)	60 (16.3)
pT3b	54 (29.8)	62 (33)	116 (31.4)
pT4	22 (12.2)	50 (22.6)	72 (19.5)
No. Pathological subgroup (%)			
Organ confined (pT2b or less)	77 (42.5)	44 (23.4)	121 (32.8)
Extravesical (greater than pT2b)	104 (57.5)	144 (76.6)	248 (67.2)
No. Lymphovascular invasion (%)			
Present	101 (56)	123 (65)	224 (61)
Absent	58 (32)	40 (21)	98 (27)
Unknown	22 (12)	25 (14)	47 (12)
No. Neoadjuvant therapy (%)			
Systemic chemotherapy	9 (36)	9 (50)	18 (42)
Radiotherapy	16 (64)	9 (50)	25 (58)
No. Adjuvant therapy(%)			
Systemic chemotherapy	89 (97.8)	116 (96.7)	205 (97.2)
Radiotherapy	2 (2.2)	2 (1.7)	4 (1.9)
Both	0	2 (1.7)	2 (0.9)
No. Positive surgical margins (%)			
Present	3 (1.7)	6 (3)	9 (2)
Absent	178 (98.3)	182 (97)	360 (98)
No. peri-operative mortality (%)			
Yes	1 (0.6)	4 (2.1)	5 (1.4)
No	180 (99.4)	184 (97.9)	364 (98.6)
Median yrs follow-up time (days - yrs range)	12.8 (23-34.6)	16.5 (5-30.6)	13.1 (5-34.6)
Median months overall survival (days-yrs range)	36.4 (23-34.6)	19.5 (5-30.6)	25.2 (5-34.6)
Median months to recurrence (days-yrs range)	37.1 (23-25.0)	16.2 (5-21.5)	22.4 (5-25.0)

LN = lymph node

Neo-adjuvant and Adjuvant Therapy

Neo-adjuvant therapy was given in 25 patients (13.8%), including 9 (5%) with neo-adjuvant systemic chemotherapy and 16 (8.8%) with neo-adjuvant radiotherapy. A total of 91 patients (50.3%) received adjuvant therapy, including 2 (1.1%) with radiotherapy and 89 (49.2%) with chemotherapy. The most common adjuvant chemotherapy was cisplatin based chemotherapy in 70 patients, followed by carboplatin in 5, cisplatin and carboplatin in 3, cytoxan in 4 and another type in 4. In 3 patients the chemotherapy type was unknown. Five and 10-year overall survival rates in the neo-adjuvant therapy group were 30.2% and 17.2% versus 40.8% and 34.6% in the remaining 156 patients. While this difference did not attain statistical significance (log rank test $p = 0.08$), a larger sample size might have shown a statistical significant difference.

Recurrence Site

A total of 96 cases recurred during follow-up. Initial recurrence sites were the upper tract in 1 patient (0.6%), urethra in 3 (1.7%), local/pelvis in 10 (5.5%) and distant metastasis in 82 (45.3%). As expected, prognosis after recurrence was poor. Five and 10-year overall survival rates after recurrence were only 5.3% and 2.7%, respectively.

Margin Status

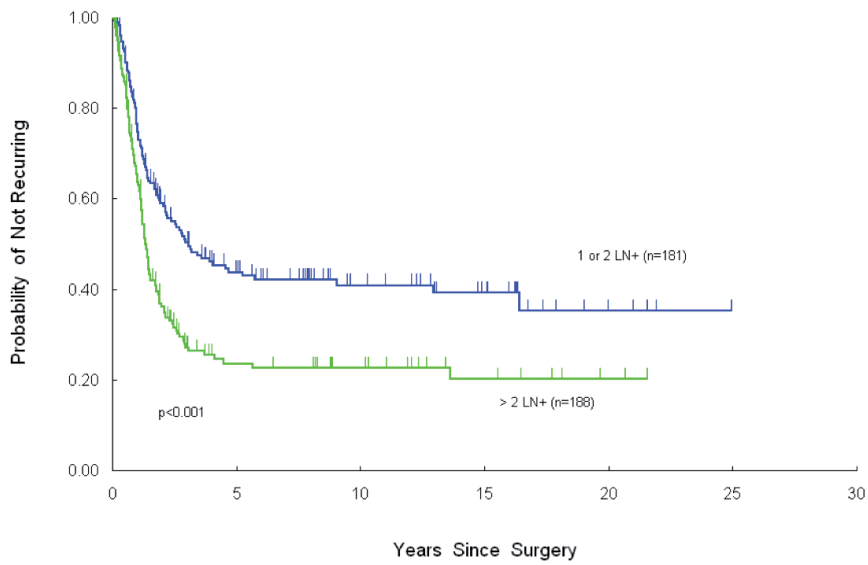
Six patients had positive urethral margins and 3 had soft tissue margins. No patients had final positive ureteral margins. Five of 9 patients (56%) with positive margins and 91 of 172 (55%) with negative margins had recurrence. The recurrence site did not necessarily correlate with urethral margin status since 4 patients with urethral margins had no recurrence, 1 had local recurrence and 1 had distant recurrence. No patient with positive urethral margins had urethral recurrence, partly because most of them also underwent urethrectomy at cystectomy or at a second operation. However, soft tissue positive margins correlated with the recurrence site. All 3 patients with positive soft tissue margins had recurrence and all recurrences were distal.

Recurrence-Free and Overall Survival

Estimated 5 and 10-year recurrence-free survival rates in the 181 patients with low volume LNM was 43.8% and 40.9%, respectively. These recurrence outcomes were significantly better than in the 188 patients with more than 2 positive lymph nodes ($p < 0.001$, figure 1). On univariable analysis, the primary bladder tumor pathological subgroup bladder tumor

pathological subgroup was associated with recurrence. Patients with low volume LNM and an organ confined tumor had 52% and 48% 5 and 10-year recurrence free survival, respectively. In patients with extravesical tumor extension 5 and 10-year recurrence-free survival was significantly lower at 37% and 35%, respectively ($p = 0.009$, table 2). The 89 patients (49%) with low volume LNM who received adjuvant chemotherapy had a more favorable recurrence rate on univariable analysis. Five and 10-year recurrence-free survival rates in this group were 54% and 52%, respectively. In contrast, 5 and 10-year recurrence-free survival in the remaining 92 patients (51%) was lower at 33% and 30%, respectively ($p = 0.0022$, table 2). In 84 patients with no neo-adjuvant or adjuvant therapy 5 and 10-year survival was 27.2% and 17.5%, respectively ($p < 0.0001$).

Figure 1: Recurrence-free survival in 181 and 188 patients with low-volume lymph node metastasis (1 or 2 LN+) and more than 2 positive lymph nodes (>2 LN+), respectively, after radical cystectomy



Lymph node density was also associated with recurrence rates on univariable analysis. A lymph node density of 4% was chosen a priori based on the data spread to maximize statistical power. Recurrence-free survival was significantly lower in patients with a lymph node density of 4% or higher. Five and 10-year recurrence-free survival in

113 patients (62%) with lymph node density 4% or less was 52% and 50% vs 29% and 26%, respectively, in 68 (38%) with lymph node density greater than 4% (table 2).

Table 2: Recurrence-free and overall survival in 181 patients with low-volume lymph node metastasis after radical cystectomy

	Mean ± SE No recurrence probabiblity			Mean ± SE Overall survival probabiblity		
	5 yrs	10 yrs	p-value	5 yrs	10 yrs	p-value
Node positive disease (all)	0.34 ± 0.03	0.32 ± 0.03		0.29 ± 0.02	0.22 ± 0.02	
Greater than 2 positive nodes	0.24 ± 0.04	0.23 ± 0.04		0.19 ± 0.03	0.12 ± 0.03	
2 positive nodes or less	0.44 ± 0.04	0.41 ± 0.04		0.39 ± 0.04	0.32 ± 0.04	
Age			0.29			0.25
65 or less	0.41 ± 0.05	0.36 ± 0.05		0.42 ± 0.05	0.32 ± 0.05	
Greater than 65	0.47 ± 0.06	0.47 ± 0.06		0.37 ± 0.05	0.32 ± 0.05	
Gender			0.48			0.51
Male	0.45 ± 0.05	0.43 ± 0.05		0.41 ± 0.04	0.33 ± 0.04	
Female	0.41 ± 0.09	0.33 ± 0.09		0.34 ± 0.08	0.28 ± 0.08	
No. pos lymph nodes			0.26			0.35
One node involved	0.46 ± 0.05	0.45 ± 0.05		0.41 ± 0.05	0.34 ± 0.05	
Two nodes involved	0.39 ± 0.07	0.33 ± 0.07		0.36 ± 0.06	0.28 ± 0.06	
Lymph node density			0.002			0.003
4 % or less	0.52 ± 0.05	0.50 ± 0.05		0.46 ± 0.05	0.37 ± 0.05	
Greater than 4 %	0.29 ± 0.06	0.26 ± 0.07		0.28 ± 0.05	0.23 ± 0.05	
Pathological subgroup			0.009			<0.001
Organ-confined (≤pT2)	0.52 ± 0.06	0.48 ± 0.06		0.53 ± 0.06	0.46 ± 0.06	
Extravesical (>pT2)	0.37 ± 0.05	0.35 ± 0.05		0.30 ± 0.05	0.22 ± 0.04	
Lymphovascular invasion			0.87			0.36
Absent	0.46 ± 0.06	0.44 ± 0.06		0.43 ± 0.06	0.40 ± 0.06	
Present	0.42 ± 0.05	0.39 ± 0.05		0.36 ± 0.05	0.26 ± 0.05	
Adjuvant chemotherapy			0.002			<0.001
Yes	0.54 ± 0.06	0.52 ± 0.06		0.52 ± 0.06	0.48 ± 0.06	
No	0.33 ± 0.06	0.30 ± 0.05		0.27 ± 0.05	0.17 ± 0.04	

SE = *standard error*

On multivariable proportional hazards analysis the pathological tumor subgroup, adjuvant chemotherapy and lymph node density at a 4% cutoff were independently associated with time to recurrence and overall survival. Gender, age, lymphovascular invasion status and the number of positive lymph nodes (1 or 2) were not statistically significantly associated with time to recurrence or overall survival on univariable or multivariable analysis (table 3).

To identify prognostic factors in patients with low volume LNM who did not receive adjuvant or neo-adjuvant chemotherapy we performed subgroup analysis. When including 84 patients, lymph node density at a 4% cutoff and pathological tumor stage/subgroup were independent prognostic factors of time to recurrence and overall survival. Patients with extravesical tumor extension or lymph node density greater than 4% had significantly lower recurrence-free and overall survival (table 3).

Table 3: Multivariable analysis in 181 patients with low-volume lymph node metastasis, including 84 patients without (neo)-adjuvant chemotherapy

	Recurrence-free survival			Overall survival		
	Hazard radio	95% confidence interval	p-value	Hazard radio	95% confidence interval	p-value
Low volume LNM:						
Patient age (greater than 65 vs 65 or less)	0.73	0.48 – 1.12	0.15	1.103	0.76 – 1.59	0.60
Gender (female vs male)	1.06	0.66 – 1.71	0.82	1.041	0.68 – 1.59	0.85
Number of positive lymph nodes (2 vs 1)	0.82	0.48 – 1.42	0.48	0.764	0.47 – 1.25	0.28
Lymphovascular invasion (present vs absent)	0.96	0.63 – 1.48	0.86	1.143	0.78 – 1.68	0.49
Lymph node density (greater than 4% vs 4% or less)	1.94	1.14 – 3.28	0.014	1.923	1.19 – 3.10	0.007
Pathological tumor stage (extravesical vs organ-confined)	1.73	1.11 – 2.70	0.015	1.896	1.28 – 2.82	0.002
Adjuvant chemotherapy (yes vs no)	0.54	0.35 – 0.82	0.004	0.483	0.33 – 0.70	< 0.001
Low volume LNM: no chemotherapy						
Patient age (greater than 65 vs 65 or less)	0.69	0.38 – 1.23	0.21	1.13	0.68 – 1.87	0.64
Gender (female vs male)	1.05	0.53 – 2.05	0.89	0.97	0.55 – 1.73	0.92
Number of positive lymph nodes (2 vs 1)	0.66	0.32 – 1.36	0.26	0.65	0.34 – 1.25	0.20
Lymphovascular invasion (present vs absent)	0.73	0.39 – 1.36	0.33	1.11	0.65 – 1.90	0.71
Lymph node density (greater than 4% vs 4% or less)	2.48	1.24 – 4.97	0.010	2.24	1.20 – 4.19	0.012
Pathological tumor stage (extravesical vs organ-confined)	2.52	1.24 – 5.15	0.011	2.05	1.09 – 3.86	0.026

Discussion

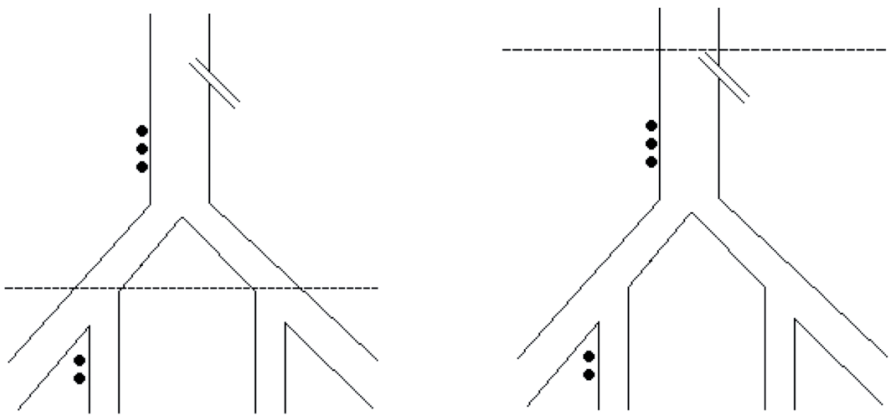
There is little doubt that positive lymph nodes after radical cystectomy are an adverse prognostic factor. However, it is important to identify variables that can further stratify the recurrence risk in patients with node positive disease since clinical outcomes in this group may vary greatly. Some studies indicate that patients with low volume lymph node disease may even be cured by surgery alone.[6,11,12] Our results indicate that patients with 1 or 2 positive lymph nodes may expect reasonable clinical outcomes since almost 40% did not have recurrence after 10 years. Furthermore, in this population pathological tumor stage, lymph node density and adjuvant chemotherapy were independently associated with disease-free survival.

The prognostic value of pathological tumor stage and adjuvant chemotherapy in this population is not surprising. It is generally thought that adjuvant chemotherapy in patients with high risk disease who do not receive neo-adjuvant chemotherapy provides a survival advantage, [3,4,13,14] although prospective studies supporting this view have been criticized for methodological problems.[15] Similarly pathological tumor stage has consistently been an independent predictor of survival in numerous studies.[1–4]

The observation that lymph node density is predictive in a population with low volume lymph node positive disease is somewhat unexpected. As previously described by Stein et al [4] and Herr, [5] lymph node density has been associated with bladder cancer recurrence. According to the literature a lymph node density of 20% to 25% is a cutoff above which recurrence-free survival is significantly higher.[4,5,8,13] While lymph node density was associated with recurrence in our study, the cutoff was lower at 4%. The fact that the numerator in lymph node density was fixed in this study at 1 or 2 positive nodes implies that removing more lymph nodes likely influences recurrence-free survival in low volume LNM cases. In fact, a 4% cutoff suggests that in patients with 1 or 2 positive lymph nodes removing at least 25 and 50 nodes, respectively, is associated with better recurrence-free survival. Leissner et al noted significantly higher survival in patients with 5 or fewer positive lymph nodes when more than 15 lymph nodes were removed. [11] Although the exact number of lymph nodes that should be removed at surgery remains unclear due to surgical and pathological variation among institutions, our study suggests a survival benefit in patients with low volume lymph node positive disease when more extensive lymphadenectomy is done. The exact reason why lymph node density is associated with recurrence-free survival in low volume lymph node positive cases is unclear but it is likely to be related to more accurate pathological staging

of the retroperitoneum. The likelihood that patients with 1 or 2 positive nodes truly have true low volume LNM increases when more nodes are removed, reflecting more adequate sampling (fig. 2). In turn more accurate staging leads to more appropriate application of adjuvant chemotherapy, possibly increasing survival. [16]

Figure 2: Lymph node sampling in 2 identical patients with 5 positive lymph nodes, including 2 nodes at the obturator/hypogastric region and 3 nodes above the aortic bifurcation.



Left: The lymph node dissection limited proximally by the common iliac bifurcation did not detect the 3 positive nodes above the aortic bifurcation. This patient would be incorrectly staged with low-volume LNM.

Right: With lymph node dissection carried up to the inferior mesenteric artery, sampling was more adequate since all 5 positive lymph nodes were detected at surgery.

Adjuvant chemotherapy in the setting of low volume lymph node involvement may provide a survival advantage and should be considered in all patients with this disease. However, almost a third of the patients who did not receive adjuvant chemotherapy survived for 10 years, underscoring the need for novel biomarkers or more refined prognostic models to better identify which patients with low volume LNM really need adjuvant therapy. Until such tests are available we must consider adjuvant chemotherapy in all patients with low volume LNM except those who cannot tolerate the well-known toxicity of platinum based chemotherapy. Specifically in patients with numerous co morbid conditions, advanced

age, poor functional status or renal insufficiency there is some use in identifying those who could potentially be observed and only receive chemotherapy if disease recurs. Our data indicate that lymph node density and primary tumor stage are independently associated with recurrence in patients who do and do not receive neo-adjuvant or adjuvant chemotherapy. Thus, in frail older patients with low volume lymph node involvement who are poor candidates for chemotherapy, it may be reasonable to observe them when lymph node density is less than 4% or disease is organ confined. However, these patients are in the minority. If a patient has the physical reserve to tolerate radical cystectomy, it is likely that the patient can also tolerate adjuvant chemotherapy, if needed.

As in all studies, our analysis has limitations. Despite promising outcomes in patients with low volume LNM all data were reviewed retrospectively. Moreover, no study patients were randomized to adjuvant chemotherapy, allowing selection bias to influence the results. Also, patients received various chemotherapy regimens, limiting our ability to make definitive statements on the effectiveness of adjuvant chemotherapy.

Conclusions

Patients with low volume lymph node positive urothelial carcinoma who undergo radical cystectomy and lymph node dissection can expect reasonable clinical outcome. Extended lymph node dissection is crucial for accurate staging and may also have a therapeutic effect. Despite the potential curative effect of this aggressive surgical treatment, additional adjuvant chemotherapy might be of benefit. Furthermore, we identified important prognostic variables that may be useful when deciding whether to use adjuvant chemotherapy, including pathological stage and lymph node density.

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CHAPTER 8

Critical evaluation of the American Joint Committee on Cancer TNM nodal staging system in patients with lymph node–positive disease after radical cystectomy

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European Urology 2012;62(4):671-676

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Abstract

Background

The current 7th edition of the American Joint Committee on Cancer TNM staging system for bladder cancer stages lymph node (LN)–positive disease based on LN location rather than LN size. In addition, common iliac LNs are now considered regional LNs. Whether these changes improve prognostication for node-positive patients, however, remains unclear.

Objective

To investigate whether the 7th edition of the TNM nodal staging system provides superior prognostication compared with the 6th edition.

Design, setting, and participants

Patients between 2002 and 2008 with LN metastases after radical cystectomy combined with extended or superextended LN dissection were included. Patients were staged using both TNM staging systems. Median follow-up was 54 months.

Outcome measurements and statistical analysis

Kaplan-Meier curves were used to estimate overall survival (OS) and recurrence-free survival (RFS). Log-rank tests and Cox proportional hazard regression models were used to test associations of pathologic variables with OS and RFS.

Results and limitations

Included were 146 patients with LN metastases of whom 131 patients underwent superextended LN dissection and 15 patients underwent extended LN dissection. Although in the 7th TNM edition many patients moved from the N2 category to the N3 category, RFS did not significantly differ within the nodal subgroups in either edition. LN metastases at or above the aortic bifurcation were not associated with decreased RFS ($p = 0.67$). On multivariable analysis, the presence of extravesical disease (hazard ratio [HR]: 2.84; $p = 0.002$), absence of adjuvant chemotherapy (HR: 0.32; $p < 0.0001$), and more than six positive LNs (HR: 2.72; $p = 0.007$) were associated with decreased RFS. This was a retrospective study with inherent limitations.

Conclusions

LNs at or above the aortic bifurcation should be considered regional LNs. Neither the 6th nor the 7th TNM staging system performed well as a prognostic tool. A better staging system for LN-positive bladder cancer needs to be developed.

Introduction

The gold standard treatment for patients with muscle-invasive bladder cancer (MIBC) is radical cystectomy (RC) combined with lymph node dissection (LND). Approximately 25% of patients with MIBC have lymph node metastases (LNMs) at the time of RC, which is associated with decreased survival.[1,2] Nonetheless, prognosis within the group of patients with LNMs varies. Although long-term survivors after surgery alone have been reported, other patients die of progressive disease despite adjuvant chemotherapy.[3] The American Joint Committee on Cancer (AJCC) TNM staging system accounts for the burden of nodal disease with three distinct categories.[4,5] In the 6th edition of the TNM staging system (2002), substaging of node-positive disease was based on the number and maximum diameter of LNMs. [4] In 2010 an update of the 2002 AJCC TNM staging system for bladder cancer was published. [5] In this 7th edition, substaging of nodal disease is based on lymph node (LN) location rather than LN size. In addition, LNMs at the common iliac vessels are considered regional LNs, whereas in the former edition involvement of these LNs was considered M1 disease.

It remains unclear whether the new nodal staging system improves prognostication in patients with LNMs. Although recent studies reported that LNMs at the common iliac vessels should indeed be considered regional LNMs [6,7], the location of LNMs does not appear to provide sufficient prognostication. To our knowledge, however, no study has directly compared the prognostic value of both the 2002 (6th edition) and 2010 (7th edition) TNM nodal staging systems. In addition, whether LNs proximal to the common iliac vessels should be considered regional LNs is unknown. In this study, we investigated whether the changes in the 7th TNM nodal staging system improve prognostication for node-positive patients, analyzing a cohort of patients with LNMs who underwent extended LND or superextended LND to the level of the inferior mesenteric artery (IMA) takeoff and prospective LN mapping. In addition, we evaluated several LN variables to determine which LN factors may have independent prognostic value.

Materials and methods

Patient selection and data collection

Data of patients treated with intent to cure RC for urothelial carcinoma of the bladder between 1971 and 2008 were prospectively collected in our database approved by the institutional review board. Starting in May 2002, LNs were submitted to the pathologist

in predesignated anatomically defined packets, allowing for location-based LN staging. Thus patients who underwent RC from May 2002 to December 2008 were eligible for inclusion (n = 637). Further inclusion criteria included the presence of regional or distant LNMs (n = 154; 24.2%) and an extended or superextended template of LND (n = 146). None of the patients had distant (organ) metastases at the time of RC. Superextended LND (n = 131) included the following boundaries: IMA (proximal), LN of Cloquet (distal), internal iliac vessels including obturator fossa and presciatic fossa (posterior), genitofemoral nerve (lateral), and presacral. Extended LND (n = 15) included the same lateral and distal boundaries, but the proximal boundary was defined as the level of the aortic bifurcation.

Pathologic analysis and staging

LNs were detected by palpation and microscopically, without the use of solvent techniques. The presence of an LN was defined as any aggregates of lymphocytes or lymphoid tissue that was at least partially encapsulated. Data on the number, size, location, and presence of extranodal extension in LNMs were collected. The RC specimen and LNs were analyzed by dedicated genitourinary pathologists.[8] Patients were staged according to the 6th TNM staging system (2002) and the 7th TNM staging system (2010) separately.[4,5] Table 1 summarizes the modifications of the 7th edition TNM staging system compared with the 6th edition. To investigate the prognostic significance of defining regional and distant LNMs, survival analysis was performed both separating regional and distant LNMs and including patients with any LNMs. LN density was defined as the number of positive LNs divided by the total number of LNs removed.

Follow-up and clinical outcomes

Follow-up time was defined as the time from RC to the date of death (death from all causes) or to the date of last follow-up if the patient was still alive at the last follow-up (censored). Median follow-up time was 54 mo (range:24 d to 7.7 yr). Kaplan-Meier plots were used to estimate the probabilities of overall survival (OS) and recurrence-free survival (RFS) over time since RC. The log-rank test was used to compare the differences of survival or recurrence in subgroups. The Cox proportional hazard model was used to test the association of multiple variables with recurrence and survival. The maximal chi-square method was used to determine the optimal cut-off point for positive LNs.[9] All p values reported in the analyses are two sided with the level of significance set at $p < 0.05$.

Table 1: Nodal subcategories according to the 6th and 7th edition of the American Joint Committee on Cancer TNM nodal staging system

	6th edition TNM staging system (2002)	7th edition TNM staging system (2010)
N1	Single LNM ≤ 2 cm	Single LNM in the true pelvis
N2	Single LNM between 2-5 cm or multiple LNM not greater than 5 cm	Multiple LNM in the true pelvis
N3	Any LNM >5 cm	LNM to the common iliac vessels
M1	LNM at the common iliac vessels and/or metastatic disease in distant organs	LNM at the aortic bifurcation and/or metastatic disease in distant organs

LNM = lymph node metastasis

Results

Clinical and pathologic characteristics

The cohort included 146 patients with LNMs. Median age was 68 yr (range: 41–88). The male-to-female ratio was 3.2:1. Superextended LND and extended LND was performed in 131 patients (89.7%) and 15 patients (10.3%), respectively. The median number of removed LNs was 71 (range: 15–170). The median number of positive LNs was 3 (range: 1–97). Median LN density was 5%. Table 2 shows the distribution of various clinical and pathologic variables in patients with LNMs (including both regional and distant LNMs).

Survival outcomes

Of all 146 patients with LNMs (regional and distant), 88 patients (60.3%) died (any cause), and 77 patients (52.7%) developed recurrent disease. The 5-yr RFS and OS was 40.3% and 32.7%, respectively.

Table 2: Clinical and pathological characteristics divided per nodal substage

		2002 TNM staging system (6th edition)*			2010 TNM staging system (7th edition)*		
	All LN+ (n=146)	N1 (n=30)	N2 (N=110)	N3 (N=6)	N1 (N=33)	N2 (N=56)	N3 (N=57)
Tumor stage (%)							
T0	3 (2.0)	-	3 (2.7)	-	-	1 (1.8)	2 (3.5)
Ta/Tis	2 (1.4)	1 (3.3)	1 (0.9)	-	1 (3.0)	-	1 (1.8)
T1	6 (4.1)	2 (6.7)	4 (3.6)	-	2 (6.1)	2 (3.5)	2 (3.5)
T2	26 (17.8)	10 (33.3)	16 (14.6)	-	10 (30.3)	11 (19.7)	5 (8.7)
T3	82 (56.2)	13 (43.3)	66 (60.0)	3 (50.0)	15 (45.5)	33 (58.9)	34 (59.7)
T4	27 (18.5)	4 (13.3	20 (18.2)	3 (50.0)	5 (15.1)	9 (16.1)	13 (22.8)
Extranodal extension (%)	32 (21.9)	4 (13.3)	26 (23.6)	2 (33.3)	7 (21.2)	10 (17.9)	15 (26.3)
Adjuvant chemotherapy (%)	84 (57.5)	18 (60)	65 (59.1)	3 (50)	19 (57.6)	35 (62.5)	32 (56.1)
Neo-adjuvant chemotherapy (%)	10 (6.8)	0	9 (8.2)	1 (16.7)	2 (6.0)	4 (7.1)	4 (7.0)

LN = lymph node

** Including patients with regional and distant lymph node metastasis*

Survival analysis in the 6th TNM staging system

According to the 6th TNM edition, 28 patients (19.2%) were N1, 59 patients (40.4%) were N2, 2 patients (1.4%) were N3, and 57 patients (39.0%) had M1 disease. Five-year RFS was 53.6%, 39.5%, 0%, and 35.2% in N1, N2, N3, and M1 patients, respectively (p = 0.31; Fig. 1b). Patients with M1 disease did not have significantly lower RFS compared with patients with regional LNMs (N3–N1) disease (p = 0.79). Including patients with distant LNMs (former M1 patients) in the nodal staging system, 30 patients (20.5%) had N1,110 patients (75.3%) had N2, and 6 patients (4.1%) had N3 disease. The 5-yr OS in N1, N2, and N3 patients was 37.6%, 31.3%, and 0%, respectively (p = 0.28). The 5-yr RFS in N1, N2, and N3 patients was 53.5%, 37.2%, and 0%, respectively (p = 0.30). The proportion of patients receiving adjuvant chemotherapy was statistically similar among N-stage subgroups (Table 2).

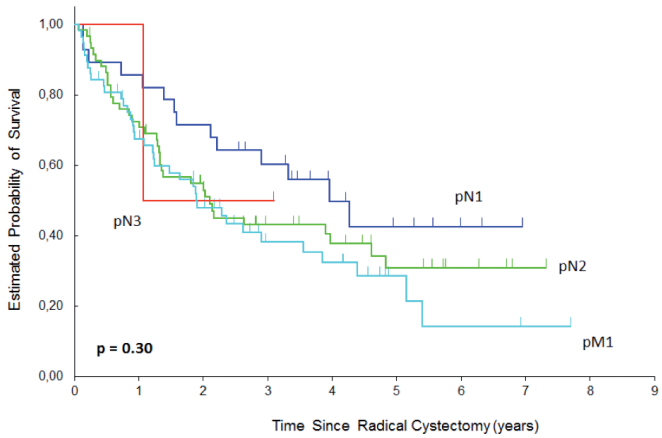
Table 3: Multivariable analysis including the 6th edition of the TNM staging system (2002)

	All LN+ (n=146) (%)	Recurrence-free survival		Overall survival	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Nodal stage (2002)*					
N1	30 (20.5)	1.00 (Reference)		1.00 (Reference)	
N2	110 (75.3)	0.80 (0.41 – 1.57)	0.51	0.93 (0.51 – 1.71)	0.81
N3	6 (4.1)	0.96 (0.28 – 3.30)	0.95	1.18 (0.36 – 3.80)	0.78
Tumor stage					
Organ-confined (≤ pT2b)	37 (25.3)	1.00 (Reference)		1.00 (Reference)	
Extravesical (> pT2b)	109 (74.7)	2.73 (1.42 – 5.25)	0.0027	2.20 (1.25 – 3.90)	0.0067
Lymphovascular invasion					
No	41 (28.1)	1.00 (Reference)		1.00 (Reference)	
Yes	105 (71.9)	1.54 (0.86- 2.73)	0.14	1.09 (0.65 – 1.82)	0.73
Number of LNM					
< 6 LNs	93 (63.7)	1.00 (Reference)		1.00 (Reference)	
≥ 6 LNs	53 (36.3)	1.64 (0.99 – 2.71)	0.05	1.72 (1.07 – 2.75)	0.0244
Adjuvant chemotherapy					
No	60 (41.1)	1.00 (Reference)		1.00 (Reference)	
Yes	86 (58.9)	0.32 (0.21 – 0.49)	< 0.0001	0.32 (0.21 – 0.49)	< 0.0001

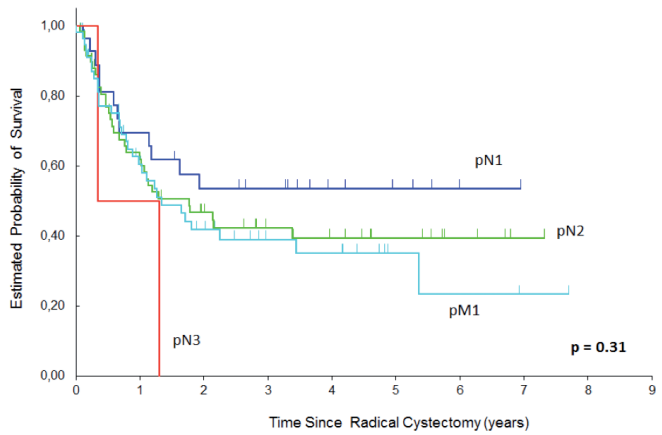
HR = hazard ratio; CI = confidence interval; LN = lymph node; LNM = lymph node metastasis * *Including patients with regional and distant LNM*

Figure 1: (a) Overall survival and (b) recurrence-free survival in all patients with lymph node metastases according to the 6th edition of the TNM staging system (2002)

(a) Overall survival



(b) Recurrence-free survival



Survival analysis in the 7th TNM staging system

According to the 7th TNM edition, 27 patients (20.6%) were N1, 50 patients (38.2%) were N2, 13 patients (9.9%) were N3, and 41 patients (31.3%) had M1 disease (LNMs at or above the aortic bifurcation). Patients who did not undergo superextended LND (n = 15) were excluded from this analysis. The 5-yr RFS was 54.0%, 35.6%, 53.9%, and 27.0% for N1, N2, N3, and M1, respectively (p = 0.67; Fig. 2b). Patients with LNMs at or above the aortic bifurcation (M1) did not have a statistically significant lower RFS compared with patients with regional LNMs (N1–N3; p = 0.44). Including patients with distant LNMs (former M1 patients) in the nodal staging system, 33 patients (22.6%) had N1 disease, 56 (38.4%) patients had N2 disease, and 57 (39.0%) patients had N3 disease. The 5-yr OS was 37.9%, 33.0%, and 28.8% in N1, N2, and N3 patients, respectively (p = 0.29). The 5-yr RFS was 48.0%, 40.3%, and 35.2% in N1, N2, and N3 patients, respectively (p = 0.65). The percentage of patients who received adjuvant chemotherapy was again statistically similar among N-stage subgroups (Table 2).

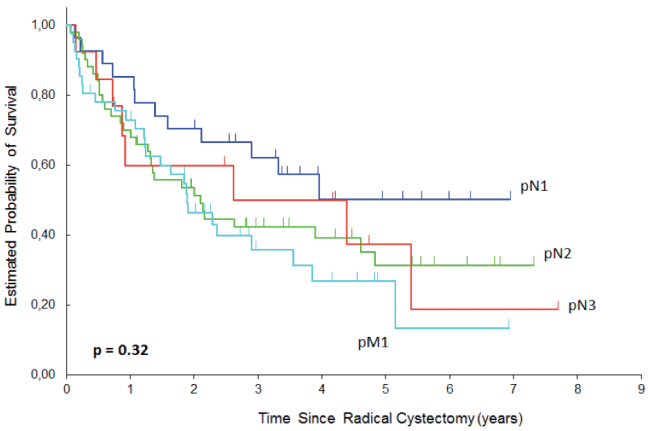
Table 4: Multivariable analysis including the 7th edition of the TNM staging system (2010)

	All LN+ (n=146) (%)	Recurrence-free survival		Overall survival	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Nodal stage (2010)*					
N1	33 (22.6)	1.00 (Reference)		1.00 (Reference)	
N2	56 (38.4)	0.94 (0.50 – 1.74)	0.83	1.03 (0.57 – 1.85)	0.92
N3	57 (39.0)	0.44 (0.18 – 1.07)	0.07	0.70 (0.31 – 1.61)	0.40
Tumor stage					
Organ-confined (≤ pT2b)	37 (25.3)	1.00 (Reference)		1.00 (Reference)	
Extravesical (> pT2b)	109 (74.7)	2.88 (1.50 – 5.52)	0.0014	2.26 (1.23 – 3.99)	0.0050
Lymphovascular invasion					
No	41 (28.1)	1.00 (Reference)		1.00 (Reference)	
Yes	105 (71.9)	1.67 (0.95 – 2.96)	0.07	1.14 (0.69 – 1.90)	0.61
Number of LNM					
< 6 LNs	93 (63.7)	1.00 (Reference)		1.00 (Reference)	
≥ 6 LNs	53 (36.3)	2.85 (1.36 – 6.00)	0.0056	2.25 (1.13 – 4.49)	0.0217
Adjuvant chemotherapy					
No	60 (41.1)	1.00 (Reference)		1.00 (Reference)	
Yes	86 (58.9)	0.34 (0.22 – 0.54)	< 0.0001	0.32 (0.21 – 0.49)	< 0.0001

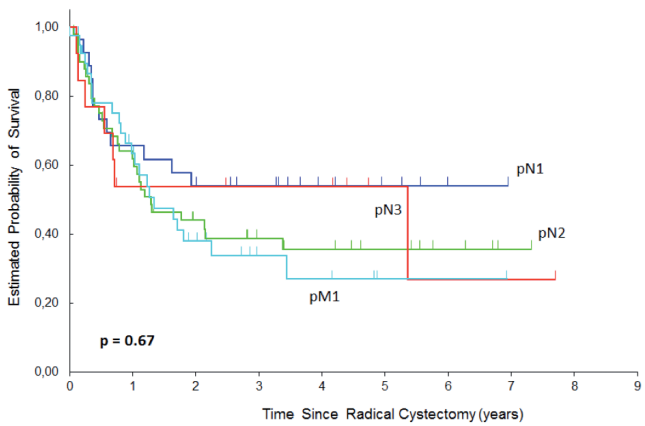
HR = hazard ratio; *CI = confidence interval;* *LN = lymph node;*
LNM = lymph node metastasis ** Including patients with regional and distant LNM*

Figure 2: (a) Overall survival and (b) recurrence-free survival in all patients with lymph node metastases according to the 7th edition of the TNM staging system (2010)

(a) Overall survival



(b) Recurrence-free survival



Prognostic factors

On univariable analysis, extravesical (≥pT3) disease ($p = 0.0031$), more than six positive LNs ($p = 0.0015$), positive soft tissue margins ($p < 0.0001$), and the absence of adjuvant chemotherapy ($p < 0.0001$) were associated with decreased RFS. Tables 3 and 4 show the results of the multivariable analysis including tumor stage, lymphovascular invasion, number of LNMs, adjuvant chemotherapy, and both editions of the TNM staging system separately. In both multivariable analyses, the presence of extravesical disease and use of adjuvant chemotherapy were independently associated with OS and RFS. In addition, in the multivariable analysis including the 7th edition staging system, more than six positive LNs was independently associated with decreased RFS and OS (Table 4).

Discussion

The presence of LNMs at the time of RC has consistently been associated with decreased survival [1–3]. However, because the prognosis within the group of patients with LNMs varies, the AJCC TNM staging system traditionally divides nodal disease into three categories. Although in the recent update of the staging system the three categories remain, size-based nodal staging has changed into location based nodal staging, and LNMs at the common iliacs are now considered regional LNMs [4,5]. In this study, we confirmed the finding of two recent studies demonstrating that inclusion of the common iliac nodes as regional LNMs is justified.[6,7] In addition, analyzing 41 patients with LNMs at or above the aortic bifurcation, we found that these patients did not have significantly lower RFS compared with patients with regional LNMs and should therefore be classified as nodal disease rather than distant metastatic disease. This outcome differs from a recent Danish study of 43 node-positive patients, reporting that LNMs above the aortic bifurcation were independently associated with decreased RFS. [6] Potential explanations for this difference may be shorter follow-up (not mentioned), lower sample size (seven patients with LNMs above the aortic bifurcation), differences in LND technique, or the exclusion of patients who received adjuvant chemotherapy in their study.

To our knowledge, this is the first study to critically analyze both the 6th and 7th edition TNM nodal staging systems. In the 6th edition, the vast majority of patients had N2 disease, whereas the 7th edition staging system shifted many patients from the N2 category into the N3 category. However, it has been recently suggested that the location of LNMs is not an independent prognostic factor in patients with regional LNMs [6,7]. In this study, we found not only location-based nodal staging to have insufficient

prognostic value but also size-based nodal staging. This result was consistent regardless of the inclusion or exclusion of patients with distant LNMs. These findings suggest that the TNM staging system needs to be modified to further define the prognosis in node-positive patients.

The only LN-related variable to be significantly associated with survival and recurrence was the number of LNMs, which is consistent with previous studies.[6,10,11] Although we found more than six positive LNs to be associated with decreased survival, the exact cut-off point for the number of LNMs remains uncertain because it has varied widely across previous large series.[3,6,10,11] Defining a strict cut-off point in this quantitative variable is not free of bias. For example, we previously reported more than eight LNMs to be independently associated with decreased survival using an older cohort of patients between 1971 and 1997.[11] However, it has been demonstrated that several factors influence total LN count, such as the technique and extent of LND, method of LN submission, and pathologic processing and evaluation.[12–14] Because practice has evolved during the last decade, for example routinely performing LN packaging, these differences likely explain the different cut-off findings. LN density is affected in similar, if not greater, fashion because this factor includes both the number of LNMs and the number of LNs removed. In the current study, we found a lower median LN density of 5% compared with the 18% reported previously.[11] Thus the cut-off point of LNMs varies not only between institutions but also by era within an institution. In the absence of a worldwide standardization of factors influencing LN count, the number of LNMs cannot be adequately incorporated in the TNM staging system. Addition of a qualitative nodal variable, such as extranodal extension, would be easier to standardize and incorporate, but its prognostic value is under debate.[15–17] In this study, the presence of extranodal extension was not independently associated with RFS or OS, although accurate evaluation of this variable would require pathologic re-review of the specimens, which was not done for this study.

This study has limitations that need to be acknowledged. First, despite the prospective collection of data, this is a retrospective study with its inherent limitations. Second, only patients who underwent extended (up to the aortic bifurcation, including common iliac and presacral LNs) or superextended LND were included in this study, and the extent of LND was not randomized. Nonetheless, 90% of patients underwent a superextended LND using very similar techniques. Finally, the use of neo-adjuvant chemotherapy was limited, and treatment with (neo-)adjuvant chemotherapy was

not randomized, predisposing to a potential selection bias. Also, intersurgeon and interpathologist variability may have affected LN location and LN count. However, this cohort comprises a homogeneous set of patients with a limited number of surgeons who were all institutionally trained. In addition, specimens were reviewed by dedicated genitourinary pathologists. Acknowledging these limitations, this study provides further insight into the prognosis of patients with LNMs and effectively compares the two most contemporary TNM staging systems using the largest reported cohort of patients undergoing (super)extended LND and LN mapping.

Conclusions

This study demonstrates that both the 6th and 7th editions of the TNM staging system have limited prognostic value in the stratification of patients with LNMs. Although the number of LNMs was an independent prognostic factor, this variable is not uniformly analyzed worldwide. Improving the TNM system with regard to nodal staging will therefore require future studies to elucidate highly reproducible variables with significant prognostic value.

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CHAPTER 9

The impact of the time interval between diagnosis of muscle-invasive bladder cancer on staging and survival: a Netherlands Cancer Registry analysis

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Abstract

Introduction

Data from single-center series suggest that a delay in time to radical cystectomy (RC) more than 3 months after diagnosis of muscle-invasive bladder cancer (MIBC) is associated with pathological upstaging and decreased survival. Limited data is, however, available from population-based studies. In this study, the impact of delayed RC was assessed in a nationwide cohort.

Materials and Methods

Patients who underwent RC between 2006 and 2010 with primary clinical T2-T4N0M0 urothelial bladder cancer were selected using the Netherlands Cancer Registry (NCR) database. Data from the NCR was supplemented with data from the Nationwide Network and Registry of Histo- and Cytopathology (PALGA) database in case of incomplete information. The cohort was divided in patients who underwent RC ≤3 months (group I) versus patients who underwent RC >3 months (group II). Median time to RC, variables associated with delayed RC >3 and the impact of delayed RC on staging and overall survival (OS) were evaluated in patients who underwent neo-adjuvant therapy and patients who did not.

Results

1,782 patients were included. Median follow-up time was 5.1 years for living patients and 1.3 years for deceased patients. Median time to RC was 50 days (interquartile range (IQR): 27 days) and 93% of patients underwent RC ≤3 months. Patients older than 75 years (OR 0.50; 95CI 0.32-0.77), referred for RC (OR 0.41; 95CI 0.26-0.69) and treated in a university hospital (OR 0.34; 95CI 0.21-0.56) were less likely to undergo RC ≤3 months. Pathologic upstaging rate (43.9% vs 42.1%) and node-positive disease rate (20.2% vs 21.7%) did not differ for group I and II. Delayed RC >3months was not associated with decreased OS adjusting for confounding variables (HR 1.16; 95CI 0.91-1.48, p = 0.25). Median time to RC in patients that received neo-adjuvant therapy (n=105) was 133 days (IQR: 62 days). Adjusting for confounding variables, delayed RC>3 months was not associated with OS (HR 0.90, 95CI 0.45-1.82).

Conclusions

The vast majority of patient underwent RC within 3 months after diagnosis of MIBC, as recommended in the EAU MIBC guideline. Delayed RC for more than 3 months had no adverse impact on staging and survival.

Introduction

Radical cystectomy (RC) is considered the standard treatment for patients with muscle-invasive bladder cancer (MIBC). The aggressive nature of the disease requires timely treatment, but this can be challenging for various reasons. Thorough patient medical evaluation, pre-operative counseling and often, due to the increasing centralization of bladder cancer care, referral to another hospital is required. Also, patients may be reluctant to undergo major surgery and postpone the decision to undergo RC or request a second opinion. Furthermore, neo-adjuvant chemotherapy is increasingly used in MIBC patients. Collectively, these factors may contribute to a potential delay in RC.

The European Association of Urology (EAU) recommends to perform RC within 3 months after MIBC diagnosis, as a delay of more than 3 months has been reported to increase the risk of progression and cancer-specific mortality.[1] This recommendation, however, relies heavily on data from referral centers with a selected cohort of patients that may not reflect the general population.[2-5] An unselected nationwide population-based dataset could provide valuable information on the impact of delayed RC on the pathologic upstaging rate and survival, but such studies are scarce.[6,7]

In this nationwide study, the aim was to evaluate I) the median delay from MIBC diagnosis to RC and adherence to the EAU MIBC guideline recommendation concerning the timing of RC, II) what parameters are associated with prolonged time to RC, III) the impact of a delay of more than 3 months on staging and survival.

Materials and Methods

Patient cohort

Using the database of the Netherlands Cancer Registry (NCR), a nationwide cancerregistry, all patients who underwent RC between 2006 and 2010 with clinical T2-T4N0M0 urothelial carcinoma of the bladder were included. As the NCR records primary non-invasive and invasive cancer diagnoses, patients diagnosed with T1 invasive bladder cancer who progress to MIBC, could not be identified. Therefore, only patients with primary clinical T2-T4N0M0 urothelial bladder cancer were included. Patients with a partial cystectomy were excluded. The cohort was divided into 2 RC groups; patients who underwent RC ≤3 months after transurethral resection of the bladder tumor (TURBT; group I) versus patients who underwent RC >3 months after TURBT (group II). Patients that received neo-adjuvant therapy were included were retained in this study, but analyzed separately.

Data retrieval and management

The secured NCR database holds patient and tumor characteristics as well as information on treatment and vital status. Vital status of all patients recorded in the NCR is updated annually through record linkage with the Dutch Municipality Registry (GBA) which includes information on birth, death and emigration of all Dutch inhabitants. Data is collected by an independent well-trained team of registration personnel. The date of TURBT in which MIBC was present, was not available in the NCR for all patients. Therefore, the dataset from the NCR was linked to the database held by the Nationwide Network and Registry of Histo- and Cytopathology (PALGA), containing all histopathologic reports generated in the Netherlands. Data concerning the date of TURBT with MIBC and the date of RC were anonymously linked to the NCR database through irreversible pseudonymisation by a Third Trusted Party (ZorgTTP, Houten, The Netherlands). The study received approval by the NCR internal ethics committee and data from the PALGA and NCR databases were anonymously provided to the principal investigator.

Histopathologic and clinical variables

Pre-operative clinical staging was based on the TURBT specimen and results of cross-sectional imaging and physical examination. Pathologic tumor staging was based on the RC specimen and standardized to the 2002 TNM staging system of the American Joint Committee on Cancer. [8] Pathologic upstaging was defined as a higher pathologic stage compared to the clinical stage, whereas pathologic downstaging indicates a lower pathologic stage compared to the clinical stage.

Follow-up and statistical analysis

Follow-up was completed until the 31th of December 2013 and defined as time between TURBT and date of death or date of censuring whichever came first. Descriptive analyses were used to characterize both the total cohort and groups I and II. Univariable and multivariable logistic regression analyses were performed to identify factors associated with delayed RC. Overall survival (OS) was calculated from the time from TURBT to the date of death. Univariable and multivariable Cox proportional hazard regression analyses were performed to assess which clinical and pathologic variables were associated with OS. Different cut-off points concerning the time to RC were evaluated for survival differences by use of long-rank tests. The cut-off points used ranged from 12 to 20 weeks.

All of the above mentioned analysis were repeated for the neo-adjuvant group. Analyses were performed using SAS.

Results

Table 1 summarizes the characteristics of the 1,782 included patients. Median time from MIBC to RC was 50 days (range: 1-295 days, interquartile range (IQR) 27 days). The median time to RC was longer for patients ≥75 years of age, for patients referred for RC and for patients treated in an university hospital (Table 1). Median follow-up time of patients alive at the 31th of December 2013 was 5.1 years (range: 0.7-8.0 years) and 1.3 years (range: 0.1-7.3 years) for deceased patients. Increasing time to RC did not result in a higher pathologic upstaging rate (Table 2).

Table 1: Characteristics of the study population

Variable	Number of patients (%)	Median time to cystectomy (days)
Total cohort	1,782 (100)	
Gender		
Male	1325 (74.4)	50
Female	457 (25.6)	49
Age		
< 60 years	392 (22.0)	48
60-74 years	1004 (56.3)	49
≥75 years	386 (21.7)	54
Year of diagnosis		
2006	331 (18.6)	49
2007	333 (18.8)	52
2008	356 (20.0)	48
2009	365 (20.5)	49
2010	397 (22.3)	50
Clinical stage		
cT2	1534 (86.1)	50
cT3	177 (9.9)	48

cT4	71 (4.0)	48
Pathologic stage		
≤pT1	55 (3.1)	49
pT2	760 (42.6)	51
pT3	735 (41.3)	48
pT4	194 (10.9)	50
pTx	38 (2.1)	56
Lymph node status		
No lymph node dissection	220 (12.3)	51
Lymph node dissection	1562 (87.7)	50
Negative	1245 (79.7)	50
Positive	317 (20.3)	48
Adjuvant chemotherapy		
Yes	48 (2.7)	38
No	1734 (97.3)	50
Referred for cystectomy		
Yes	310 (17.4)	64
No	1472 (82.6)	48
Cystectomy hospital		
Non-university	1504 (84.4)	49
University	264 (14.8)	63
Time to cystectomy		
≤ 4 weeks	186 (10.4)	
5-8 weeks	915 (51.3)	
9-12 weeks	507 (28.5)	
13-16 weeks	123 (6.9)	
>16 weeks	51 (2.9)	

Table 2: The impact of the time interval from muscle-invasive bladder cancer diagnosis to radical cystectomy on cancer staging

	Total cohort (n=1,782)		Group I	Group II
	Number of pts (%)	Median time to RC in days (range)	(RC < 3 months) N=1659	(RC > 3 months) N=123
Downstaging*	105 (5.9)	48 (15-176)	97 (5.9)	8 (6.5)
No staging difference*	924 (51.9)	50 (1-295)	863 (52.0)	61 (49.6)
Upstaging*	753 (42.3)	49 (7-245)	699 (42.1)	54 (43.9)

** Comparing clinical stage with pathological stage*

RC = radical cystectomy

As shown in Table 3, a total 1,659 patients (93.1%) underwent RC ≤3 months (group I) and 123 patients (6.9%) did not (group II). Patients were less likely to undergo RC ≤3 months when older than 75 years (odds ratio (OR) 0.50; 95% confidence interval (95CI) 0.32-0.77), referred for RC (OR 0.41; 95CI 0.26-0.69) and treated in a university hospital (OR 0.34; 95CI 0.21-0.56; Table 3). Both the pathologic upstaging rate (43.9% vs 42.1%) and rate of node-positive disease (20.2% vs 21.7%) did not differ for group I and II.

Table 3: Association of clinical and histopathologic variables with the time interval from muscle-invasive bladder cancer diagnosis to radical cystectomy

	Total cohort (n=1,782)	Group I (RC ≤ 3 months, n=1,659) No of pts (%)	Group II (RC >3 months, n=123) No of pts (%)	Univariable logistic regression analysis for RC <3months OR (95% CI)	Multivariable logistic regression analysis for RC <3months OR (95% CI)
Gender					
Male	1325	1228 (74.0)	97 (78.9)	0.76 (0.49-1.20	0.79 (0.49-1.27)
Female	457	431 (26.0)	26 (21.1)	ref	ref

Year of diagnosis					
2006	331	314 (18.9)	17 (13.8)	ref	ref
2007	333	299 (18.0)	34 (27.6)	0.48 (0.26-0.87)	0.42 (0.22-0.80)
2008	356	329 (19.8)	27 (22.0)	0.66 (0.35-1.23)	0.61 (0.32-1.86)
2009	365	343 (20.7)	22 (17.9)	0.84 (0.44-1.62)	0.82 (0.41-1.62)
2010	397	374 (22.6)	23 (18.7)	0.88 (0.46-1.68)	0.73 (0.37-1.45)
Age					
Less than 60 years	392	371 (22.4)	21 (17.1)	1.16 (0.70-1.94)	1.42 (0.84-2.43)
60-74 years	1004	942 (56.8)	62 (50.4)	ref	ref
75 years or greater	386	346 (20.8)	40 (32.5)	0.57 (0.38-0.86)	0.50 (0.32-0.77)
Clinical stage					
cT2	1534	1427 (86.0)	107 (87.0)	ref	ref
cT3	177	165 (10.0)	12 (9.8)	1.03 (0.56-1.91)	1.40 (0.72-2.75)
cT4	71	67 (4.0)	4 (3.2)	1.26 (0.45-3.51)	1.71 (0.56-5.27)
Pathological stage *					
pT1 or less	55	50 (3.0)	5 (4.1)	ref	ref
pT2	760	709 (42.7)	51 (41.5)	1.39 (0.53-3.64)	1.30 (0.47-3.64)
pT3	735	690 (41.6)	45 (36.6)	1.53 (0.58-4.04)	1.30 (0.46-3.64)
pT4	194	176 (10.6)	18 (14.6)	0.98 (0.35-2.77	0.82 (0.27-2.56)
Referred for cystectomy					
Yes	310	260 (15.7)	50 (40.7)	0.27 (0.19-0.40)	0.41 (0.26-0.69)
No	1472	1399 (84.3)	73 (59.3)	ref	ref
Cystectomy hospital **					
Community	1504	1430 (86.2)	74 (60.2)	ref	ref
University	264	216 (13.0)	48 (39.0)	0.23 (0.16-0.34)	0.34 (0.21-0.56)

** pathological stage was missing in 38 patients*

*** patients who underwent radical cystectomy in a hospital outside the Netherlands were excluded*

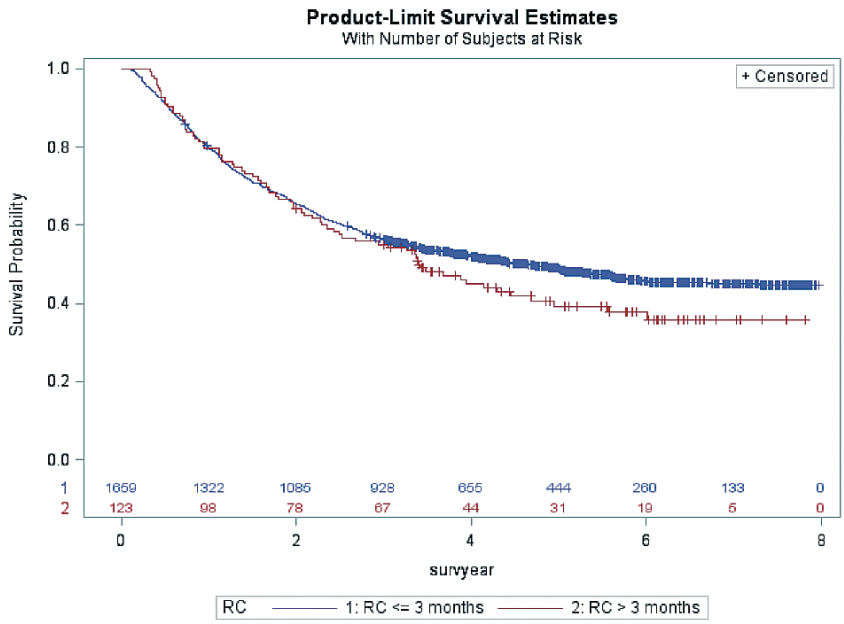
RC = radical cystectomy; OR = odds ratio; 95%CI = 95% confidence interval

In Figure 1 overall survival of both RC groups is presented. Log-rank analysis demonstrated no statistical significant difference between the groups (p=0.67), although, although after 3 years of follow-up patients in group I seem to have a better survival. Proportional hazards regression analysis showed that delayed RC >3 months was not associated with decreased OS (Hazard ratio (HR) 1.17; 95% confidence interval (95CI) 0.92-1.49). This finding did not change after adjustment for age, gender, pT stage,

pN stage, referral status and type of treatment hospital (HR 1.16; 95CI 0.91-1.48, p = 0.25). As expected, age, pT stage and pN stage were independently associated with OS.

The impact of delayed RC on OS was assessed using several cut-off points ranging between 12 and 20 weeks. No statistical significant difference in OS was found in any of the used cut-off points.

Figure 1:
Overall survival in patients undergoing radical cystectomy within 3 months (blue line) or after 3 months (red line) after diagnosis of muscle-invasive bladder cancer



Neo-adjuvant therapy cohort

A total of 105 patients underwent neo-adjuvant therapy of whom 91 patients neo-adjuvant chemotherapy and 14 patients neo-adjuvant radiotherapy. Downstaging to pT0 occurred in 23 patients (21.9%). Of the 95 patients who underwent LND, 22 patients (23.2%) had node-positive disease. Three (2.9%) patients were treated with adjuvant therapy. Median time to RC was 133 days (IQR: 62 days) and 17 patients (16.2%) underwent RC ≤3 months. The pathologic upstaging rate was higher in patients who underwent RC ≤3 months compared to patients who did not (41.2% vs 15.9%; Chi2 p-value = 0.05). Median

follow-up time was 4.7 years (range: 0.5-7.6 years) for patients alive at 31th of December 2013 and 1.2 years (range: 0.2-5.0 years) for deceased patients. OS was not statistically significantly different for group II compared with group I both on univariable analysis (HR 0.82, 95CI 0.43-1.61) and adjusted for age, pT stage and lymph node status (HR 0.90, 95CI 0.45-1.82).

Discussion

To our knowledge, this study represents the first nationwide analysis in Europe to evaluate the impact of timing of RC on staging and survival outcomes in MIBC patients. The median time interval from MIBC diagnosis to RC was 50 days and adherence to the EAU MIBC guideline recommendation was good with 93% of patients undergoing RC ≤3 months. Delayed RC for >3 months was not associated with a higher upstaging rate or decreased OS.

Several factors may contribute to delayed RC and are both healthcare system-related and patient-related. In this study, advanced age was associated with delayed RC that presumably reflects a higher comorbidity rate requiring extensive and time consuming pre-operative medical evaluation. Comorbidity has previously been associated with prolonged time to RC, in fact, Lee et al. reported it to be the second most important reason for delay after surgical schedule issues. [2] Hospital transition for RC was another factor independently associated with delayed RC, which has been reported in a recent study as well. [9] In the current study, 16% of patients who were referred to another hospital to undergo RC did not undergo RC ≤3months and the median time to RC was on average 2 weeks longer compared to patients not referred for treatment to another hospital. After adjusting for referral status, treatment in a university hospital remained associated with delayed RC. The reason for this finding is unknown but may include both patient-related factors (comorbidity/performance score) as well as logistics within university hospitals.

A number of studies from tertiary referral centers have investigated the impact of time from MIBC diagnosis to RC on staging and survival. Sanchez-Ortiz et al. [5] reported one of the first studies in which a higher pathologic upstaging rate and decreased OS was found in patients in whom RC was delayed for >12 weeks. Later, several other studies have been performed using a similar cut-off point (i.e. 12 weeks / 3 months / 90 days), reporting conflicting results. In three studies, the pathologic upstaging and nodal disease rate were reported to be equivalent for patients who underwent RC ≤3 months and those who did not. [2-4] Chang et al. [10] reported higher extravesical disease rates in patients in whom RC was delayed for >3 months, although no association between

the time to RC and pathologic stage was found with time to RC as a continuous variable.

The impact of delayed RC on survival has been more extensively studied. In two studies, no association between prolonged time to RC and survival outcomes was found. [3,11] On the other hand, several studies did report poorer survival outcomes in patients with delayed RC >3 months [2,4,5,10] It should be noted, however, that most of these studies were single-center series with often small cohorts and excessive delays. In one study, only 19 patients did not undergo RC ≤3 months of whom 6 patients waited for over 2 years.[5] The impact of delayed RC on staging and survival is probably better evaluated in an unselected population-based cohort with a larger study size. In our nationwide study, delayed RC >3 months was not associated with a higher upstaging rate, higher occurrence of nodal metastasis and OS. To our knowledge, two previous population-based study studies have been performed, both focusing on survival outcomes lacking data to assess the upstaging rate.[6,7] Mahmud et al. [7], in a cohort covering the Quebec province in Canada, reported no association between the time to RC as a continuous variable and survival. Stratified by </>12 weeks delay, a delay of >12 weeks was independently associated with decreased survival calculated from date of diagnosis (HR1.7 95CI 1.2-2.4). Gore et al. [6] analyzed data of 441 patients included in the American SEER-medicare database and concluded that both disease-specific survival and OS was higher in patients with a time to RC of <12 weeks calculated from the date of diagnosis. It should be noted, however, that the date of biopsy that confirmed MIBC diagnosis was not available for all patients and that patients who underwent RC within 4 weeks or >52 weeks were excluded. As a result, only 65% of patients underwent RC within 12 weeks compared to 90% in our cohort making comparison between studies challenging.

Limited data is available on the impact of prolonged time to RC in patients undergoing neo-adjuvant therapy (NAC). In one study, reporting on 153 patients, the median time from initiation of NAC to RC was 112 days and performance of RC within 10 days following completion of NAC did not compromise survival.[12] In the current study, the median time from MIBC diagnosis to RC was 133 days. The upstaging rate was higher in patients who underwent RC ≤3 months. This finding is likely the result of lack of response or suffering from side-effects, although data on the number of chemotherapy cycles received by each patient was not available. Delaying RC for >3 months, however, had no adverse impact on OS. Collectively, the current available data suggests that even though NAC does often cause a delay in RC >3 months, oncological outcomes are not jeopardized.

The strong aspect of this study is the large unselected cohort of MIBC patients.

Nonetheless, this study is subject to limitations. This was an observational study based on available registry data. Factors associated with the timing and choice of treatment like comorbidity and performance were not recorded in the NCR and could therefore not be included in the analysis. The finding that OS appears to be better in patients who underwent RC ≤3 months after 3 years of follow-up is unlikely the result of timing of RC and is likely to be caused by initial differences between the two patients groups (like comorbid conditions or performance status). Also, findings from this study may not apply for patients who progressed from non-MIBC to MIBC as only primary MIBC patients were included.

Conclusions

The median delay from MIBC diagnosis to RC in this nationwide study was 50 days with over 93% of patients undergoing RC within 3 months, as recommended in the EAU MIBC guideline. Delaying RC for >3 months did not result in a higher upstaging rate, higher occurrence of nodal metastasis or decreased OS. In patients treated with NAC, a higher upstaging rate was found in patients who underwent RC ≤3 months, but OS was similar to patients with delayed RC > 3 months. These findings suggest that the current 3-month recommendation should not apply for patients undergoing NAC and that in patients not treated with NAC, it might serve as a reasonable guide rather than a fixed point in time within RC should performed.

Acknowledgements

The authors acknowledge dr. Annette Gijsbers for providing data from the PALGA database and the registration staff from the Netherlands Comprehensive Cancer Organisation for data collection.

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PART V

Epilogue

CHAPTER 10

General discussion and future perspectives

General discussion and future perspectives

In spite of aggressive surgical management for muscle-invasive bladder cancer (MIBC), on average 50% of patients die of the disease, of which the majority dies within 2 years following treatment.[1] Even more alarming: survival of MIBC has hardly improved over the last 30 years.[2] These facts underscore the need for further research in this field, but also raises the question what should be the focus of our research and clinical activities to improve MIBC survival, while reducing treatment related morbidity. Although this thesis has addressed some questions regarding the staging, surgical treatment and prognosis of bladder cancer (BC), several issues remain unsolved and new questions have arisen. In the following section, the findings in this thesis will be discussed in a broader perspective and those areas in BC research that should receive (more) attention will be highlighted.

Bladder cancer staging

A major problem in the treatment of BC is the inaccuracy of clinical BC staging, with an estimated understaging rate of 32%-44%. [3-5] In chapter 5, it was demonstrated that clinical understaging affects the decision whether to perform lymph node dissection (LND) in patients with non-muscle invasive bladder cancer (NMIBC). Although lymph node (LN) metastasis were rarely found in patients with pathologic NMIBC, pathologic upstaging to MIBC and subsequent presence of LN metastasis was less uncommon. Based on this finding, it was concluded that LND should be performed in all patients with cT1 and cTis disease to adequately assess the nodal status. As LND in itself may not be free of harm, the aim should be to only perform LND in those patients that benefit from it. Therefore, it is important to improve on the clinical understaging rate. Arguably the most important step in clinical staging is to perform a radical transurethral biopsy of the bladder tumor (TURBT) with presence of detrusor muscle in the specimen. In our study, only patients with detrusor muscle in the TURBT specimen were selected. Nonetheless, still 25% of patients with NMIBC were upstaged to MIBC. This may in part be due to the lack of routine repeat TURBT in T1/high grade patients and bimanual palpation, two important components of clinical staging, which is a limitation of our study. [6-8] Therefore, to further investigate the role of LND in NMIBC, this study should be repeated in a prospective manner including all essential components of clinical staging (i.e. radical TURBT, repeat TURBT in high risk patients, bimanual palpation).

Next to clinical staging, there is a need for improved pathologic LN staging. Both the current 7th and previous 6th edition of the TNM nodal staging provide limited

risk stratification for BC recurrence and/or death (chapter 8). A nodal staging system providing prognostic information is important to improve on the selection of candidates that may benefit from adjuvant therapy. In chapters 7 and 8, we found the number of LN metastasis and LN density (ratio of positive LNs and LNs removed) to be independently associated with (recurrence-free) survival. It would seem obvious to develop a nodal staging system based on these parameters, however, it has extensively been reported that both parameters are influenced by several factors and that reproducibility worldwide is poor. [9] Hence, these quantative LN variables are less suitable to use in a nodal staging system. Qualitative LN variables on the other hand, may be more suitable as they are better reproducible. Recently, extranodal extension [10-11] and perinodal lymphovascular invasion [12] have been reported to be independently associated with prognosis. Future studies are required to externally validate the findings in these studies and, when the findings are repeated, to develop a new nodal staging system based on qualitative parameters.

The role of lypmhadenectomy in bladder cancer

The staging benefit of LND in BC has been demonstrated in chapters 5 and 6, yet, the role of LND as a therapeutic intervention remains unclear. The impact of the extent of LND on survival outcomes after radical cystectomy (RC) was investigated in a systematic review of the literature (chapter 6). Based on 23 included studies, it was concluded that a LND up to the aortic bifurcation might be beneficial over less extended LND templates in terms of oncological outcomes, without a significant increase in treatment-related morbidity. Extending the LND cephalad of the aortic bifurcation was, however, not beneficial. Is this evidence sufficiently convincing to firmly recommend an extended LND in all MIBC patients? Not really. First, there was a clear lack of consensus on what is considered a limited, standard and (super)extended LND with definitions varying in virtually all of the 23 included studies. Although the extent of LND was often redefined for comparison purposes, this is not without bias. Second, all studies were subject to risks of selection bias and confounding. Although the systematic review was performed according to the highest methodological standards, it cannot compensate for the low quality of the individual studies. As such, a meta-analysis was not performed. Clearly, a randomized controlled trial (RCT) is needed to provide a definitive answer on whether a more extended LND provides a survival benefit over less extended LND templates. At the moment, two well designed RCTs are ongoing evaluating whether extended LND benefits disease free

survival compared with standard (*American SWOG trial, NCT01224665*) or limited (*German LEA trial, NCT01215071*) LND.[13-14] The first results are expected in 2015-2016 and are eagerly awaited.

Surgery related morbidity and quality of life

To reduce RC related morbidity and improve the quality of life, modifications in the surgical technique have been suggested. A sexual organ preserving cystectomy (SOPC), preserving the prostate in males and reproductive organs (RO; vagina, uterus and/or ovaries) in females, is feasible but its oncological safety is under debate. In chapter 2, analyzing nearly 1,500 radical cystoprostatectomy specimens, it was demonstrated that the risk of prostatic urothelial carcinoma (PUC) and/or incidental prostate adenocarcinoma (PAC) can be as high as 50% in unselected male patients. In fact, this rate may even be higher would whole mount sectioning of the prostate have been performed instead of partial embedding. One of the study goals was to identify what patient and tumor characteristics are associated with PAC and PUC. We hypothesized that the routine available clinical and histopathologic variables may be useful in selecting candidates for a prostate sparing cystectomy. Although a number of risk factors were established, its absence did not rule out clinical significant PAC and/or PUC. These data suggest that careful patient selection is important and that routine available clinical and histopathologic variables should be extended with pre-operative evaluation of the bladder neck and prostate. This may include taking biopsies, although with increasing experience, MRI of the prostate might be an alternative in the future. To date, the diagnostic panel that offers the optimal detection rate of PUC and PAC in the least invasive manner is unknown. Next to optimal selection, SOPC requires an optimal surgical technique as metastatic spread is a concern raised in SOPC series that has been linked to the surgical technique.[15-16] It has been demonstrated that when these criteria are met (optimal selection and surgical technique), comparable long-term oncological outcomes to RC can be achieved.[17] In female patients, RO involvement is present in approximately 7.5% of patients and is associated with a poor 5-year recurrence-free survival of 15% (chapter 3). Similar to chapter 2, we aimed to establish risk factors for involvement of the RO. Patients with pre-operative signs of presence of extensive disease, such as hydronephrosis and palpable mass on bimanual palpation, were more likely to have RO involvement. Our study was, however, limited by the small cohort size prohibiting analysis to establish independent risk factors for RO involvement. To develop appropriate selection criteria in

female patients, a large and multi-institutional study of RC specimens including detailed clinical and histopathologic data is required. Nonetheless, this study underscores that, similar to male patients, strict patient selection is important when SOPC is considered.

Next to SOPC, a robotic assisted radical cystectomy (RARC) has been advocated to reduce the peri-operative morbidity rate. To date, the role of RARC is unclear. Although the use of RARC is rapidly increasing, it is still considered an experimental procedure lacking level 1 evidence supporting the claimed morbidity advantage over open RC.[18,19] Currently, a randomized study (*RAZOR trial, NCT01157676*) [20] is under way evaluating the oncological outcomes, complications and health-related quality of life. Until these data become available (expected 2017), RARC should be restricted to high-volume centers preferably in a clinical trial setting.

Bladder cancer prognosis and systemic (chemo)therapy

Bladder cancer is a heterogeneous disease that requires personalized treatment. In essence, this means selecting the right therapy for the right patient at the right time. In patients with locally advanced MIBC, the challenge is to identify those patients that might benefit from systemic therapy. In this thesis, a number of studies aimed to define pre-and postcystectomy clinical and pathologic variables that may improve risk stratification of disease-recurrence and/or BC death (chapters 7,8 and 9). For these studies, the RC database of the University of Southern California, considered to be the largest and highest quality RC database worldwide, was retrospectively reviewed. These studies are important as these parameters may be used in the selection of patients that may benefit from systemic treatment based on their high risk profile. Unfortunately, these parameters cannot be used to identify those patients that *respond* to (neo-)adjuvant therapy. Ideally, targeted treatment is based on both tumor characteristics and the (epi) genomic background of the patient. Hence, the role of biomarkers in BC is under extensive investigation. Reports about potential new biomarkers have been published abundantly, particular in the field of p53 tumor expression, serum vascular endothelial growth factor and circulating tumor cells.[21-23] At the moment of this writing, however, no biomarker has reached the clinic as most have not been externally validated, have not appeared to be cost-effective or shown to alter treatment decisions. In particular internal and external validation is of great importance that is too often not performed prior to publication/ implementation. Future studies should aim to tackle these issues, as biomarkers likely have the future to further improve risk stratification and direct targeted treatment.

The efficacy and timing of systemic therapy in adjunct to meticulous surgical treatment in patients with (locally advanced) MIBC is a topic of debate. Neo-adjuvant chemotherapy has been reported to improve the overall survival rate by 5-8%.[24] For adjuvant chemotherapy, evidence is less convincing with older RCTs facing methodological issues.[25,26] Recently, the results of the early closed EORTC 30994 trial (poor accrual) have been published reporting that adjuvant chemotherapy did not improve overall survival, but did improve progression-free survival.[27] In spite of the evidence favoring (mainly neo-adjuvant) systemic treatment in patients with locally advanced BC, its worldwide use is still low.[28,29] One of the reasons is the risk of overtreatment in patients without micro metastasis and delayed cystectomy in those patients that do not respond to chemotherapy (estimated 30-50%). With improved prediction of treatment response, the use of (neo-)adjuvant chemotherapy is likely to increase.

The role of immunotherapy as an alternative adjuvant treatment in MIBC is under investigation. [30,31]. Recently, very promising results have been published with the inhibition of the programmed death-ligand 1 by MPDL3280A in patients with advanced bladder cancer previously treated with chemotherapy. [31] In 2014, a phase II trial (*NCT02108652*) has been initiated and is currently recruiting patients. [32]

Concluding remark

It is obvious that staging, prognostication and treatment of MIBC can be further improved to reduce the still high mortality and morbidity rates. In this thesis it was demonstrated that a tailored approach in MIBC care is the next step forward that requires ongoing efforts to further unravel the individual nature of both the cancer and the patient. To achieve this goal, time, budget and strong collaborations are needed.

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CHAPTER 11

Summary of the thesis / Samenvatting van het proefschrift

Summary

A short overview of the current challenges in the staging, treatment and prognostication of muscle-invasive bladder cancer (MIBC) is provided in part one (**chapter 1**).

The second part of this thesis discusses cancer of the urinary bladder and its adjacent organs. To understand in which bladder cancer patient it might be oncologically safe to perform a sexual organ preserving cystectomy, knowledge about the incidence and risk factors of bladder cancer invading the adjacent sexual organs is important. Also, in male patients, the risk of incidental prostate cancer should be taken into consideration.

In **chapter 2**, the incidence and risk factors for prostatic urothelial carcinoma (PUC) and/or incidental prostate cancer (PCA) was assessed in 1,476 patients who underwent radical cystoprostatectomy. It was found that over 50% of patients had PUC and/or PCA. Clinical significant PCA and PUC invading the prostatic stroma (PUC-s) were present in 10.1% and 8.3% of patients, respectively. PUC-s was independently associated overall survival (HR 1.26, 95% CI 1.03-1.57) while PUC confined to the prostatic ducts was not (HR 1.00, 95% CI 0.82-1.24). Presence of PCA did not alter overall survival. Pre-operative risk factors for PUC-s included higher clinical stage, multifocal disease and trigonal tumor location. Increasing age and PSA were risk factors for clinical significant PCA. Absence of these risk factors, however, did not rule out PUC and/or PCA. Therefore, using standard pre-operative available risk factors alone to select candidates for prostate preserving surgery are likely inaccurate.

Chapter 3 describes the incidence and risk factors of urothelial carcinoma involving the adjacent reproductive organs (uterus, vagina and/or ovaries; RO) in female patients who underwent anterior pelvic exenteration. RO involvement was present in 7.5% of the 267 patients included. The vagina was the most frequently involved organ (5%), while the ovaries were least frequently involved (0.4%). Pre-operative variables associated with RO involvement were presence of hydronephrosis and a palpable mass on pre-operative bimanual palpation. These findings underscore that, equivalent to male patients, careful patient selection is important when a sexual organ-preserving approach is considered.

Cancer of the urachus (UraC), stretching between the umbilicus and the bladder dome, is rare and long-term survival data are scarce. In **chapter 4**, the 152 UraC cases diagnosed over a 20-year period in the Netherlands were analyzed. There was a wide variation in the primary treatment modality, but partial cystectomy was most common (53%). Up to 30% of patients had lymph node (LN) or distant metastatic disease at initial

presentation and these patients were often younger of age. Survival in this group was poor, with a 5-year overall survival rate of less than 20%. Increased awareness of UraC, particularly in younger patients with urinary symptoms, is important since detection of UraC at an early stage benefits survival.

In the third part of this thesis, the role and extent of lymph node dissection (LND) in bladder cancer was discussed.

To evaluate whether LND benefits nodal staging in non-muscle invasive bladder cancer (NMIBC), a lymph node mapping study was performed in **chapter 5**. A total of 114 patients with NMIBC who underwent radical cystectomy (RC) with 'superextended' LND were included, of whom 8% of patients had LN metastasis. Stratified by clinical stage, LN metastasis were present in 9% of patients with cT1, 12% of patients with cTis-only and absent in patients with cTa disease. Metastatic LNs were found at or above the aortic bifurcation in 33% of node-positive patients, but all of these patients had positive LNs in the true pelvis as well. While LN metastasis were rarely found in patients with pathologic NMIBC (1%), pathologic upstaging to MIBC (found in 25% of patients) and subsequent presence of LN metastasis was more prevalent, although still not very common (8%). Thus, unless clinical staging is improved, LND benefits staging in all bladder cancer patients undergoing RC except for those patients with cTa disease.

In patients with MIBC, there is little doubt that LND is important from a staging perspective, but its therapeutic value remains unknown. In **chapter 6** it was demonstrated that there is a lack of randomized studies on this topic and that the current evidence base is based on 23 mainly retrospective comparative studies with substantial risks of bias and confounding. Acknowledging these important limitations, these studies indicate that any form of LND produces more favorable oncologic outcomes compared with no LND. Extending the LND up to the aortic bifurcation might be superior to lesser degrees of dissection from an oncologic perspective; however, further extending the dissection is not beneficial. There is no evidence that LND substantially increases the number of peri-operative adverse events compared to no LND.

Part four of this thesis addresses prognostication in MIBC patients. LN status is a well-established prognostic factor in BC. Yet, survival within the node-positive group may vary greatly and it has been suggested that tumor burden may play a role.

In **chapter 7**, the long term survival outcomes and prognostic factors in patients with low-volume disease (i.e. 1 or 2 positive LNs) after RC were described. Nearly half of the patients with node-positive disease had low-volume node-positive disease. In this patient subgroup, up to 40% of patients did not have recurrence after 10 years suggesting that reasonable clinical outcomes can be expected. Variables associated with recurrence-free survival included pathological tumor stage and lymph node density, the latter suggesting that removal of more LNs might be beneficial.

Chapter 8 reflects on the recent changes in the American Joint Committee on Cancer-TNM nodal staging system, which is used as a prognostication tool for node-positive patients. Analyzing a large cohort of node-positive patients, it was found that the 7th edition shifts many patients from the N2 category into the N3 category. The prognosis of patients with LN metastasis at the common iliac vessels did not differ from patients with N1-N2 disease, suggesting that common iliac LNs involvement may indeed reflect regional rather than distant metastatic disease. The 7th edition did, however, not outperform the previous 6th edition in terms of prognostication. In fact, both editions had limited prognostic value indicating the need for a better nodal classification system.

In **chapter 9**, the impact of prolonged time to RC on staging and survival outcomes was assessed in a nationwide cohort of primary MIBC patients. The median time to RC was 50 days and over 93% of patients underwent RC within 3 months after MIBC diagnosis as recommended in the MIBC guideline of the European Association of Urology. Time to RC was prolonged in patients older than 75 years of age, in referred patients and in patients treated in a university hospital. Delayed RC for >3 months was not associated with higher a mortality rate irrespective of whether neo-adjuvant chemotherapy was given. These data do imply that, if needed, time allows for extensive pre-operative medical evaluation and/or neo-adjuvant chemotherapy to improve on the medical condition of the patient or to reduce the tumor burden.

The final part includes the general discussion and future perspectives (**chapter 10**) and the summary of this thesis (**chapter 11**).

Samenvatting

Het eerste deel (**hoofdstuk 1**) van dit proefschrift schetst een kort overzicht van de huidige problemen bij de stadiëring, behandeling en prognose bepaling van spierinvasief blaaskanker (SIBK).

In het tweede deel van dit proefschrift wordt ingegaan op blaaskanker en de omliggende (voortplantings)organen. Om te bepalen bij welke patiënten met blaaskanker het oncologisch verantwoord is om een seksueel orgaan sparende cystectomie (SOSC) te verrichten, is het belangrijk kennis te hebben van het vóórkomen van en risicofactoren op ingroei van blaaskanker in de omliggende voortplantingsorganen. Daarnaast dient bij mannen rekening gehouden te worden met het risico op de aanwezigheid van prostaatkanker.

In **hoofdstuk 2** wordt ingegaan op de risicofactoren van doorgroei van het urotheelcarcinoom van de blaas in de prostaat in het algemeen (PUC), prostaatbuizen (PUC-d) en prostaat stroma (PUC-s) evenals het incidenteel aanwezig zijn van prostaatadenocarcinoom (PAC). Bij meer dan 50% van de 1476 patiënten die een radicale cystoprostatectomie hadden ondergaan, werd PUC en/of PAC gevonden. Klinisch significant PAC en PUC-s was aanwezig in respectievelijk 10,1% en 8,3% van de patiënten. Risicofactoren voor PUC-s waren een hoger klinisch stadium, multifocale ziekte en blaaskanker gelokaliseerd in het trigonum. Zowel een hogere leeftijd als hogere PSA waarde waren risicofactoren voor klinisch significant PAC. Belangrijk is de bevinding dat afwezigheid van deze risicofactoren PUC en/of PAC niet volledig uitsluit. Derhalve is het gebruik van deze risicofactoren alleen, niet voldoende voor het selecteren van geschikte patiënten voor een SOSC. De aanwezigheid van PUC-d was niet onafhankelijk geassocieerd met de overleving (HR 1,00, 95% betrouwbaarheidsinterval(BI) 1,03-1,57), maar de aanwezigheid van PUC-s was dit wel (HR 1,26, 95%BI 1,03-1,57). De aanwezigheid van PAC had geen invloed op de overleving.

Hoofdstuk 3 beschrijft het vóórkomen van en risicofactoren op doorgroei van urotheelcarcinoom van de blaas in de interne genitalia (IG; uterus, vagina, eileiders, eierstokken) van vrouwen die een voorste excenteratie van het kleine bekken hadden ondergaan. Ingroei in de IG was aanwezig in 7,5% van de 267 patiënten. De vagina was het vaakst betrokken (5%), terwijl ingroei in de eierstokken zeldzaam was (0,4%). Pre-operatieve parameters geassocieerd met een hogere kans op ingroei in de IG waren de aanwezigheid van hydronefrose en een palpabele massa bij bimanueel toucher. Deze bevindingen suggereren dat, evenals bij mannelijk patiënten, SOSC

niet in elke patiënt uitgevoerd kan worden maar strikte selectie noodzakelijk is.

Een carcinoom van de urachus (UraC), welke zich bevindt tussen de navel en het blaasdak, is zeldzaam en er is wereldwijd weinig data bekend over de lange-termijn overleving van deze ziekte. In **hoofdstuk 4** werden 152 UraC gevallen, gediagnosticeerd in Nederland de afgelopen 20 jaar, geanalyseerd. Er bleek een grote variatie te bestaan hoe deze ziekte primair behandeld werd, waarbij een partiële cystectomie het meest voorkomend was (53%). In meer dan 30% van de patiënten was er bij de eerste presentatie reeds sprake van lymfekliermetastasen (LK) en/of metastasen op afstand en vaak betrof dit jongere patiënten. De overleving in deze groep patiënten is uitermate slecht, met een 5-jaars overlevingspercentage van minder dan 20%. Kennis van deze ziekte bij de uroloog is van groot belang, met name bij jonge patiënten van mictieklachten, aangezien vroege detectie van UraC de kans overleving sterk kan vergroten.

In deel drie van dit proefschrift wordt de rol van lymfeklierdissectie (LKD) bij blaaskanker besproken.

Om te bepalen of het verrichten van een LKD zinvol is bij patiënten die een radicale cystectomie (RC) ondergaan voor niet-spierinvasief blaaskanker (NSIBK), werd in **hoofdstuk 5** een zogenaamde lymfeklier (LK) 'mapping' studie verricht. Er werden 114 NSIBK patiënten geïncludeerd die allen RC met zeer uitgebreide LKD tot aan de arteria mesenterica inferior hadden ondergaan. In totaal was er bij 7,9% van de patiënten sprake van LK gemetastaseerde ziekte. Van deze LK positieve patiënten had 33% LK metastasen ter hoogte van of proximaal van de aortabifurcatie, maar altijd in combinatie met aanwezigheid van LK metastasen in het kleine bekken. Er werden dus geen zogenaamde 'skip-metastasen' gevonden. Gestratificeerd per klinisch stadium, had 9% van de cT1 patiënten, 12% van de cTis patiënten en 0% van de cTa patiënten LK metastasen. LK metastasen waren uiterst zeldzaam indien NSIBK werd bevestigd in het RC preparaat (1%). In meer dan 25% van de gevallen werd echter toch SIBK gevonden met als gevolg dus een hogere kans op LK metastasen. Voor adequate stadiering is LKD derhalve aan te bevelen in alle patiënten die RC ondergaan voor blaaskanker (behalve cTa). Bij patiënten met spierinvasief-blaaskanker (SIBK) is er geen twijfel dat LKD bijdraagt aan de stadiëring, echter of de LKD zelf ook positief bijdraagt aan de overleving is onbekend.

In **hoofdstuk 6** werd een literatuuronderzoek gericht op deze vraag. Er werden 23 vergelijkende studies gevonden waarbij een uitgebreide LKD tot aan de aortabifurcatie lijkt te resulteren in betere oncologische uitkomsten ten opzichte van een minder

uitgebreide LKD. Het verrichten van een nog uitgebreidere LKD ('superextended') LKD lijkt echter geen overlevingswinst te bieden. Er is geen bewijs in de huidige literatuur dat het verrichten van een LKD de kans op peri-operatieve complicaties sterk vergroot ten opzichte van het niet verrichten van een LKD. Helaas zijn de huidige studies van lage kwaliteit waardoor er op dit moment geen harde conclusies getrokken kunnen worden.

Deel vier van dit proefschrift behandelt de prognose van patiënten met SIBK. Hoewel de LK status één van de belangrijke prognostische parameters is, bestaan er desondanks grote verschillen in overleving binnen de groep patiënten met LK metastasen. Mogelijk speelt hierbij de uitgebreidheid van LK metastasen een rol. In **hoofdstuk 7** worden de lange termijnuitkomsten beschreven van patiënten met laag-volume LK metastasen (gedefinieerd als 1 of 2 LK metastasen) na RC en LKD. In totaal hadden 181 van de 369 patiënten (49%) laag-volume metastasen. In deze groep bleek 41% van de patiënten geen recidief van de ziekte te hebben binnen 10 jaar, hetgeen beduidend hoger was dan bij patiënten met >2 LK metastasen (23%). Er mag dus een redelijke overleving verwacht worden in de groep met laag-volume LK metastasen. Variabelen onafhankelijk geassocieerd met recidief-vrije overleving waren het pathologisch tumor stadium en LK densiteit, waarbij het laatste suggereert dat het verwijderen van meer LK een voordeel kan bieden.

Hoofdstuk 8 reflecteert op de recente veranderingen in de American Joint Committee on Cancer (AJCC)-TNM lymfeklier classificatie welke gebruikt wordt voor het stadiëren van patiënten met LK metastasen. Er werd een groot cohort van LK positieve patiënten geanalyseerd waarbij bleek dat veel patiënten die in de voorgaande 6e editie (2002) als N2 werden geclassificeerd in de huidige 7e editie (2010) als N3 worden geclassificeerd. De prognose van patiënten met LK metastasen ter hoogte van de iliacale vaten was niet statistisch significant verschillend ten opzichte van patiënten met N1-N2 ziekte, hetgeen suggereert dat LK metastasen op deze locatie mogelijk nog beschouwd kunnen worden als regionale ziekte in plaats van metastasen op afstand. De prognostische waarde van de huidige 7e editie lijkt echter niet beter ten opzichte van de voorgaande editie. Beide edities hebben beperkte prognostische waarde en daarom is er behoefte aan een nieuwe prognostische classificatie voor patiënten met LK metastasen.

In **hoofdstuk 9** werd de invloed van de tijdsduur tussen de diagnose SIBK en RC op de stadiëring en overleving onderzocht in een Nederlands cohort van 1782 SIBC patiënten. De mediane duur tot RC was 50 dagen en meer dan 93% van de patiënten onderging RC binnen de door de Europese Associatie van Urologie (EAU) gestelde termijn

van 3 maanden. De tijdsduur tot RC was gemiddeld langer in patiënten ouder dan 75 jaar, patiënten verwezen RC en patiënten die RC ondergingen in een academisch centrum. Een vertraging van meer dan 3 maanden resulteerde echter niet in progressie van het stadium of lagere overleving, ook niet indien er neo-adjuvante chemotherapie was gegeven. Deze uitkomsten suggereren dat een langere wachttijd tot RC niet perse een negatieve invloed hoeft te hebben op de prognose.

Het laatste deel van dit proefschrift bevat de algemene discussie en toekomstperspectief (**hoofdstuk 10**) en de samenvatting (**hoofdstuk 11**).

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Curriculum Vitae

Harman Maxim (Max) Bruins was born on the 23th of July 1986 in Leiden, the Netherlands. In 2004 he passed his Atheneum exam at the R.K.S.G Marianum in Groenlo and started to study medicine at the Radboud University Nijmegen. During his study he competed in national golf competitions and served as a board member of the Nijmegen Studenten Golf Genootschap (NSGG). In 2008, he conducted his research internship at the University of Southern California in Los Angeles (Prof. Dr. J.P. Stein and Prof. Dr. D.F. Penson) that would later turn out to be the start of his PhD project. In 2010 he obtained his medical degree at the Radboud University Nijmegen.

In 2011, he was rewarded an AGIKO stipendium by the Netherlands Organisation for Health Research and Development (ZonMw) allowing him to combine his clinical training to become an urologist with his PhD training. For 2 years, he conducted research at the urology departments of the University of Southern California (Prof. Dr. E.C. Skinner, current: Stanford University) and Radboudumc (Prof. Dr. J.A. Witjes). He presented most of his work at (inter)national conferences.

Currently, Max works as an urology resident at the Radboudumc in Nijmegen (mentor: Prof. Dr. J.A. Witjes) after finishing his general surgery rotation at the Rijnstate Hospital (mentor: Dr. M.M.P.J. Reijnen) in 2014. He also serves as an associate member of the muscle-invasive and metastatic bladder cancer guideline of the European Association of Urology (EAU).