# On the Epidemiology, Diagnosis and Treatment of Upper Tract Urothelial Carcinoma

Bjarte Almås

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
2021

UNIVERSITY OF BERGEN

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Date of defense: 17.09.2021

Year: 2021

Title: On the Epidemiology, Diagnosis and Treatment of Upper Tract Urothelial Carcinoma

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Print: Skipnes Kommunikasjon / University of Bergen

*“If you can’t explain something simply you don’t understand it well enough”*

- Albert Einstein

*“Even if we agree on something there is always a fair chance that we both are wrong”*

- Someother Stein

# Scientific environment

The work in this thesis has been carried out through the PhD programme at the Department of Clinical Medicine (K1), University of Bergen, Norway.

The clinical work has been carried out at the Department of Urology, Haukeland University Hospital, at the Department of Urology at the Vestfold Hospital Trust, Tønsberg, Norway, and at the Norwegian Cancer Registry, Oslo, Norway.

## Acknowledgements

Firstly, I want to thank my boss and main supervisor Professor Christian Beisland. His support and capacity for helping me and my colleagues in our academic work is seemingly limitless. This PhD project would not have been possible without his never ending help, guidance, corrections and encouragements. My Co-supervisor Professor Ole Johan Halvorsen is also an invaluable part of my PhD project. The thoroughness he demonstrates in all aspects of his work is inspiring and impressive.

I want to thank Stein Øverby and other coworkers at Tønsberg sykehus for all help with the patient material used for paper 2 and 3 in this thesis. I equally want to thank Tom Børge Johannsesen at the NCR for his help and support with paper 1.

I further want to thank the department I am a part of. I have had countless discussions about my work with my treasured colleagues that have helped move the project in the right direction. I want to especially mention Karin Hjelle, Øyvind Ulvik and Peder Gjengstø for everything they have taught me about research and kidney surgery. I want to mention Lars Reisæter, co-author of two of my papers with a remarkable capacity when it comes to radiological issues, graphic design and puns. Per Odland deserves gratitude for introducing me to Urology at a time where my future career was not yet determined. Especially thanks to my friend, office companion and sparring partner for discussions on larger or smaller matters, Alfred Honoré.

At last I want to thank my family. They provide the meaningful pause and recreation that is absolutely necessary when doing work like this. I thank my beloved children Torjus, Jenny and Mari, you make every day brighter. Finally a large thanks to my wife for always being supportive when work has to be done in the evenings or weekends. Through her writing skills, she has also helped form the manuscript into its current form. So a wholehearted thank you to Lill, love of my life.

# Abstract

**Aims:** The overall aim of this thesis was to increase our knowledge about the epidemiology, diagnostics and treatment of upper tract urothelial carcinoma (UTUC). For paper 1, the aim was to obtain contemporary knowledge about UTUC incidence, UTUC tumour and patient characteristics, and possible changes over time using national, population based data. For paper 2 and 3, the aim was to evaluate current standard diagnostics before radical nephroureterectomy (RNU), and see if our findings could be used for selecting patients for intensified treatment. Further, we aimed to evaluate a previously published diagnostic model through an external validation. For paper 4, we aimed to evaluate the outcomes of endoscopic treatment for UTUC given at our hospital with particular emphasis on tumour grade.

**Materials and methods:** For paper 1, the study population included all patients registered with an International Classification of Diseases tenth version (ICD-10) diagnosis code C65 (cancer of the renal pelvis) and C66 (cancer of the ureter) at the Norwegian Cancer Registry (NCR) during 1999-2018. After an inclusion/exclusion process, 3096 cases of verified UTUC in 2818 patients were included in the study. For purpose of comparisons with other urothelial cancers and renal cell carcinoma (RCC), 24467 cases of bladder cancer (BC), 287 cases of urethral cancer, and 13619 cases of RCC were drawn from the same main database during the same time period. Statistical analyses were performed to calculate UTUC age standardized rates (ASR), UTUC incidence rates compared to other urothelial cancers and RCC, and to look for possible changes over time regarding incidence rates, epidemiological variables and survival.

For paper 2 and 3, all patients treated with a RNU for UTUC at Haukeland University Hospital and Vestfold Hospital Trust during 2005-2017 were evaluated. After an inclusion/exclusion process, 179 patients were included in the study. For paper 2, all available preoperative features regarding the patients, the CT scan and the ureteroscopy (URS) were analysed regarding their abilities to predict tumour stage and survival. Further analyses were performed to evaluate if our findings could be

used to select patients for intensified treatment. For paper 3, 162 of the 179 patients had complete dataset needed for external validation of the published Margulis nomogram and were included in the study. An external validation assessing both model calibration and discrimination was performed.

For paper 4, 43 patients treated endoscopically with curative intent at Haukeland University Hospital 2001-2012 were included. Statistical analyses were performed regarding survival, kidney protections rates and recurrence both for the whole cohort and stratified by indication for treatment and tumour grade.

**Results:** Paper 1. The ASR according to the European standard population was 3.88 for the whole period, increasing significantly from 3.21 to 4.70 from the first to last five-year period, corresponding to an estimated annual increase of 2.5%. The proportion of UTUC compared to all urothelial cancers and RCC significantly increased. UTUC constituted 12.6% of all urothelial cancers in Norway during 2014-2018. Mean age at diagnosis increased from 71.8 to 73.9 years during the study period. The 5-year overall survival (OS) increased moderately over time from 44.3% to 51.7% comparing last decade with the first. In paper 2, we found that local invasion and the presence of pathological lymph nodes at CT predicted both tumour stage at final pathology and survival in uni-and multivariate regression analyses. These variables can be used when selecting patients for intensified treatment. Diagnostic URS has a limited role in preoperative tumour staging. In paper 3, we found an overall high concordance between *predicted* risk of non-organ confined disease using the Margulis nomogram, and the *observed* risk in our cohort. The accuracies of both the predicted and observed risks were 0.83 to indicate adequate model discrimination. The calibration was assessed in a scatter plot where the overall concordance was high, quantified with a Cronbach Alpha of 0.96. There seems to be a mis-calibration at the low-risk levels. In paper 4 we found that the five –year disease specific survival (DSS) of patients treated endoscopically with an elective indication or for a low grade tumour (according to the World Health organization (WHO) classification from 2004) was high (DSS 94% and 96% respectively). The

survival of patients treated with an imperative indication or for a high-grade tumour were significantly lower (DSS 41% and 39% respectively). 25 of 43 patients were assessed as tumour free at one point during follow-up, and the five-year recurrence free survival among these patients were 76%. The five-year kidney protection rate (KPR) for patients with low-grade tumours was 60%. The KPR for patients tumour free at first follow-up (14 of 43), was 90%.

**Conclusions:** The incidence of UTUC in Norway was higher than expected, and increasing. Patient age at diagnosis is increasing. Local invasion and pathological lymph nodes at CT can predict tumour stage and survival after RNU, and can be used when selecting patients for intensified treatment. The Margulis nomogram is considered validated for clinical use. Tumour grade according to the WHO classification from 2004 is a strong predictor of outcomes after endoscopic treatment for UTUC, and should be considered when selecting patients for this treatment modality.

# List of Publications

I. Almås B, Halvorsen OJ, Johannesen TB, Beisland C. Higher than expected and significantly increasing incidence of upper tract urothelial carcinoma. A population based study. World journal of urology 2021.

II. Almås B, Øverby S, Halvorsen OJ, Reisæter LAR, Carlsen B, Beisland C. Preoperative predictors of pathological tumour stage and prognosis may be used when selecting candidates for intensified treatment in upper tract urothelial carcinoma. Scandinavian journal of urology 2021:1-8.

III. Almås B, Øverby S, Halvorsen OJ et al. Tumour architecture, grade and location remain predictors of non-organ-confined upper tract urothelial carcinoma at time of radical nephroureterectomy: results from a multicenter Norwegian external validation study. World journal of urology 2020; 38:717-23.

IV. Almås B, Halvorsen OJ, Gjengstø P, Ulvik Ø, Beisland C. Grading of urothelial carcinoma of the upper urinary tract according to the World Health Organization/International Society of Urological Pathology classification from 2004 is a valuable tool when considering whether a patient is suitable for endoscopic treatment. Scandinavian journal of urology 2016; 50:298-304.

# Contents

## Abbreviations

| | |
|---|---|
| **ADC** | Apparent diffusion coefficient |
| **ASA** | American Society of Anaesthesiologists |
| **ASR** | Age standardized rate |
| **AUC** | Area under the curve |
| **BC** | Bladder cancer |
| **CIS** | Carcinoma in situ |
| **CNU** | Candidates for nephroureterectomy |
| **CSS** | Cancer specific survival |
| **CTU** | Computed tomography urography |
| **DSS** | Disease specific survival |
| **FU** | Follow up |
| **ICD-10** | International Classification of diseases tenth version |
| **IVR** | Intra vesical recurrence |
| **KPR** | Kidney protection rate |
| **LND** | Lymph node dissection |
| **MID** | Muscle invasive disease |
| **MRI** | Magnetic resonance imaging |
| **NCNU** | Non-candidates for nephroureterectomy |
| **NCR** | Norwegian Cancer Registry |
| **NOCD** | Non-organ confined disease |
| **NSS** | Nephron sparing surgery |
| **OR** | Odds ratio |
| **OS** | Overall survival |
| **RCC** | Renal cell carcinoma |
| **RCT** | Randomized controlled trial |
| **REK** | Regional ethics committee |
| **RNU** | Radical nephroureterectomy |
| **ROC** | Receiver operating characteristic |
| **SU** | Segmental ureter resection |
| **URS** | Ureteroscopy |
| **UTUC** | Upper tract urothelial carcinoma |
| **UUT** | Upper urinary tract |
| **WHO** | World health Organization |

# 1. Introduction

### 1.1.1 Normal anatomy and function of the upper urinary tract

The upper urinary tract (UUT) consists of the kidneys, the renal pelvis and the ureters. While the urine is produced in the kidney, the collecting system (the calyces, the renal pelvis and the ureters) transports the urine from the calyces to the urinary bladder. Anatomically, the urothelial lining of the upper urinary tract is similar to the urothelial lining of the bladder, but the thickness of the muscle layers are markedly thicker in the bladder. The specialized epithelium of the urinary organs previously designated transitional epithelium, is currently referred to as the urothelium. The urothelium consists of three layers, see Figure 1. The innermost basal cells consist of small, long-living cells which are precursors for the outer layers. The intermediate layer consists of pyriform cells with a differing number of cell layers. The outer cells are large, rounded or cuboidal. These specialized cells are referred to as umbrella cells [1]. This configuration is well adapted for increasing or decreasing the surface area to accommodate different volumes of urine. The urothelium is a barrier for water, ions, solutes and pathogens. It also serves a sensory organ transmitting signals of its milieu to the underlying nervous systems [2]. The urothelial lining is continuous from the calyces to the ureteral ostium. The innermost layer is the urothelium, deeper lies the sub epithelial connective tissue (the lamina propria), the muscularis propria and the peripelvic/periureteric fatty tissue. In the calyces, the renal pelvis and upper ureter, the muscularis propria consists of two layers of smooth muscle. In the lower part of the ureter, an additional third layer of smooth muscle is present. All three layers merge with the corresponding muscle layers of the bladder as the ureters enter the bladder wall [3].

### 1.1.2 Anatomical considerations

The thin muscularis propria of the UUT has implications for the proper staging of tumours in the UUT, as it can be hard to distinguish superficial tumours from tumours invading the muscularis or the perimuscular layers by radiology or endoscopy.

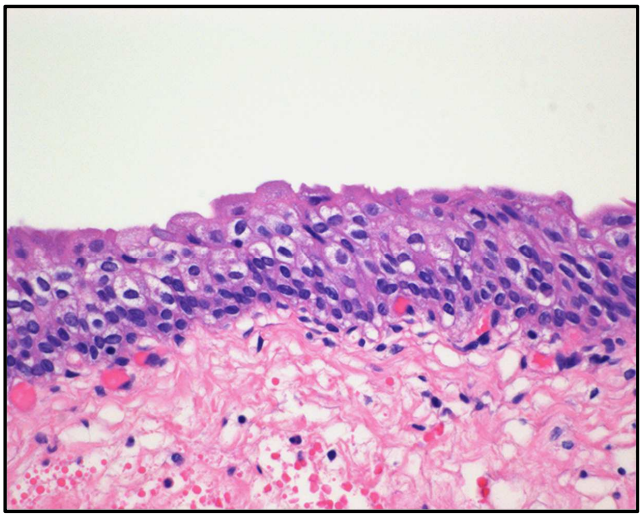

*Figure 1. Illustration of a normal urothelium with umbrella cells in the outermost layer.*

### 1.1.3 Pathology of urothelial carcinoma of the upper urinary tract

UTUC can be defined as a urothelial carcinoma arising from the urothelium in the calyces, the kidney pelvis, or the ureters down to and including the ureteral ostium of the bladder. Pure UTUC and UTUC with variant histology constitute more than 90% of all carcinomas arising from the lining of the UUT, but pure squamous cell carcinoma, adenocarcinoma, sarcomas, lymphomas and other tumours can also arise from the UUT [4]. Further description of non-urothelial carcinomas in the UUT is beyond the scope of this thesis.

## 1.2 Epidemiology

### 1.2.1 Incidence

Compared to bladder cancer, UTUC is relatively uncommon. The incidence is typically referred to be 1-2:100.000, or 5-10% of all urothelial carcinomas. The yearly publication from the American Cancer Society is often quoted as a reference for these incidence figures [5].

### 1.2.2 Calculation of age standardized rates

The incidence of a disease in a population is typically referred to as an incidence rate per 100.000 people of that population. The *crude* rate of a disease is the number of new cases per year / (total population/100.000). While some cancers are common among children or adolescents, most cancers have an increasing incidence with increasing age [6]. The incidence of a disease will then depend on the age distribution in the population the incidence rates are gathered from. Since the age distribution in different parts of the world is highly variable, it is standard to present incidence rates as ASRs to make results from incidence studies from different regions or time periods more comparable. The most common way to perform standardization is by direct age-standardization [7]. The crude rates are by that method adjusted to a chosen standard population. Many such standard populations are available with quite different age composition, as can be seen in Table 1.

| Age | World std. 1966 | European std. 1976 | American std. 2000 | Nordic std. 2000 | European std. 2013 |
|---|---|---|---|---|---|
| 00-04 | 0,120 | 0,08 | 0,069135 | 0,059 | 0,05 |
| 05-09 | 0,100 | 0,07 | 0,072533 | 0,066 | 0,055 |
| 10-14 | 0,090 | 0,07 | 0,073032 | 0,062 | 0,055 |
| 15-19 | 0,090 | 0,07 | 0,072169 | 0,058 | 0,055 |
| 20-24 | 0,080 | 0,07 | 0,066478 | 0,061 | 0,06 |
| 25-29 | 0,080 | 0,07 | 0,064529 | 0,068 | 0,06 |
| 30-34 | 0,060 | 0,07 | 0,071044 | 0,073 | 0,065 |
| 35-39 | 0,060 | 0,07 | 0,080762 | 0,073 | 0,07 |
| 40-44 | 0,060 | 0,07 | 0,081851 | 0,07 | 0,07 |
| 45-49 | 0,060 | 0,07 | 0,072118 | 0,069 | 0,07 |
| 50-54 | 0,050 | 0,07 | 0,062716 | 0,074 | 0,07 |
| 55-59 | 0,040 | 0,06 | 0,048454 | 0,061 | 0,065 |
| 60-64 | 0,040 | 0,05 | 0,038793 | 0,048 | 0,06 |
| 65-69 | 0,030 | 0,04 | 0,034264 | 0,041 | 0,055 |
| 70-74 | 0,020 | 0,03 | 0,031773 | 0,039 | 0,05 |
| 75-79 | 0,010 | 0,02 | 0,026999 | 0,035 | 0,04 |
| 80-84 | 0,005 | 0,01 | 0,017842 | 0,024 | 0,025 |
| 85+ | 0,005 | 0,01 | 0,015508 | 0,019 | 0,025 |
| Sum | 1 | 1 | 1 | 1 | 1 |
| % >70 years | 4% | 7% | 9.3% | 11.7% | 14% |

*Table 1. The table shows some different standard populations that can be used for calculation of age standardized incidence rates. Note the different weights, especially at high ages.*

In the World standard population from 1966, people aged over 70 years constitute only 4% of the total population. In comparison people over 70 years constitute 14% of the latest updated European standard population. This is important to bear in mind when discussing UTUC incidence, since it is a disease which predominantly drab the elderly. For example, adjusting UTUC crude rates to the 2013 version of the European standard population will result in markedly different (higher) ASRs than if the crude rate was adjusted to the World standard of 1966.

### 1.2.3 Published incidence rates

The published series on UTUC incidence have shown conflicting results. Three historic cohorts from the USA, the Netherlands and England have demonstrated an increasing incidence. In England, the age standardized incidence rate for men increased from 1.2 to 1.6 during 1985-2009, while the incidence for women increased from 0.5 to 0.8 [8]. An American study found a more moderate increase from 1.88 to 2.06 from 1973 to 2005 [9]. A Dutch study described an increase from 2.10 to 2.40 from 1995-2005 [10]. An Australian study found a stable and relatively low incidence of 1.4 from 2001-2011[11], while a Danish study using a more historic cohort described an increase in incidence until 1985, followed by a decline to 2.45 for men and 1.25 for women 1985-2003 [12].

Two recent publications have also shown conflicting results. In a population based Dutch study, an increasing ASR (adjusted to the European standard 1976) from 2.0 - 3.2 was reported during 1993-2017 [13]. Contrary to this, a study based on the American SEER database found a decreasing incidence in the USA from 1.3-1.1 adjusted to the American standard population [14].

Especially high incidences of UTUC have been registered in South Eastern Taiwan, with a probable relation to Blackfoot disease caused by arsenic in the drinking water, a known risk factor for UTUC [15]. At the Balkan a high UTUC incidence has also been reported, related to environmental exposure to aristolochic acid. UTUC constitute up to 50% of all urothelial carcinomas in these areas [16].

### 1.2.4 Age, sex and anatomical location

Mean age at diagnosis is increasing, and is in the more recent cohorts reported to be in the range 70-74 years [9, 13]. A majority (61%-77%) of the patients are reported to be men, and a majority (51%-66%) of the tumours are located in the renal pelvis [9, 11, 13].

### 1.2.5 Previous or synchronous bladder cancer

Previous and synchronous BC is described in 14-28% and 10-12% of UTUC patients respectively [17, 18].

## 1.3 Risk factors

### 1.3.1 Smoking

Smoking is associated with a 3-7 fold increase in risk of UTUC. The increased risk is dose-dependent. Smoking cessation > 10 years reduces UTUC risk [19, 20]. It also adversely affects prognosis after RNU [21].

### 1.3.2 Aristolochic Acid

Aristolochic acid is a carcinogenic compound found in the aristolochiaceae plant, commonly used in herbal medicine. It is a known risk factor for kidney disease, liver disease and UTUC. Exposure to aristolochic acid is shown to be the cause of Balkan nephropathy, where unusually high incidences of UTUC have been reported [16]. In China, exposure to aristolochic acid is a suggested factor to explain the unusually high UTUC incidence among women [22].

### 1.3.3 Alcohol consumption

Alcohol consumption >15 gram/day compared to non-drinking is shown to be a risk factor for UTUC [23].

### 1.3.4 Lynch syndrome

Hereditary nonpolyposis colorectal cancer (Lynch syndrome) is an autosomal dominant syndrome associated with colorectal cancer, UTUC and other cancers. The cumulative risk of UTUC for patients with Lynch syndrome is estimated to 3-14% [24]. Screening for Lynch syndrome in UTUC patients <65 years is recommended [25].

## 1.4 Diagnosis

### 1.4.1 Symptoms

At diagnosis UTUC patients can present with local symptoms (haematuria, flank pain), systemic symptoms (anorexia, weight loss, fevers etc.) or no symptoms (incidental finding at imaging or during endoscopy). In one publication, local symptoms were most common (61%), followed by no symptoms (33%) and systemic symptoms (6%) [26]. Haematuria was the most common presenting symptom described in 73% of UTUC patients in another patient series [27]. Both these studies found that the presence of systemic symptoms at diagnosis was associated with a worse prognosis.

### 1.4.2 Imaging

**Computed Tomography Urography**

Historically, retrograde or conventional intravenous ureteropyelography was the imaging method of choice in the diagnosis of UTUC. As computed tomography urography (CTU) technology improved and results showed that CTU was superior to other modalities, CTU took over as standard imaging modality for tumours in the UUT [28, 29]. In a recent meta-analysis, the pooled sensitivity and specificity in

setting the correct diagnosis for UTUC in the reviewed publications using multi detector CTU was 92% and 95% respectively [30].

Regarding the staging of UTUC, the predictive abilities of CTU is more debatable. The presence of hydronephrosis has been found to predict advanced stage UTUC in several publications [31, 32]. Other authors have however concluded that hydronephrosis is not a risk factor for tumour stage [33, 34]. Despite some conflicting results, hydronephrosis at diagnosis is generally accepted as a predictor of advanced tumour stage and poor prognosis [25]. Radiological stage is in two smaller studies found to predict pathological tumour stage with a sensitivity of 67-75% and a specificity of 84-97% [35, 36]. Local invasion at CTU defined as invasion into the renal parenchyma, the peripelvic or periureteric tissue, is shown to be a predictor of non-organ confined disease (NOCD, pT3+ and/or N+) in two published diagnostic models [37, 38]. Tumour size is in one multicentre study found to be a predictor of NOCD [39].

**Magnetic resonance urography**

Available data on magnetic resonance imaging (MRI) in the preoperative evaluation of UTUC is limited. The apparent diffusion coefficient (ADC) value measured in a diffusion weighted MRI was in one study found to be significantly lower for high-grade compared to low-grade UTUC [40]. Another study found that a low ADC value was associated with increased metastatic potential [41]. The use of diffusion weighted images in addition to conventional MRI was described to improve tumour staging in another study [42]. It is possible that ADC could be a potential biomarker for aggressive disease and prognosis. Due to limited data available, the use of MRI in the evaluation and staging of UTUC is only recommended when a CTU is contraindicated [25].

**Positron Emission Tomography**

One study has described a sensitivity and specificity of 82% and 84% respectively when using $^{18}$F-fluorodeoxyglucose positron emission tomography in the detection of

lymph node metastasis in patients treated with RNU and lymph node dissection (LND) for UTUC [43]. The usefulness of positron emission tomography in the diagnosis of UTUC has to be confirmed in other studies before it can be recommended for daily practice.

### 1.4.3 Ureteroscopy with biopsy and cytology

URS with biopsy and selective cytology *in situ* is recommended as a part of diagnostic work-up for suspected UTUC if the results of the URS would influence treatment strategy [25]. URS is particularly useful if a nephron sparing surgery (NSS) is considered. If the UUT is accessible for a URS, it allows visual inspection of tumour location, potential multifocality and evaluation of tumour size. Visual assessment of tumour grade and tumour traits (papillary, broad based etc.) is possible, but not always accurate [44].

**Ureteroscopic biopsy**

Tumour biopsy during URS is possible using multiple available tools, both endoscopic forceps and baskets. Back loaded forceps allowing larger biopsy specimens have emerged as a biopsy alternative [45]. In a prospective study, biopsies taken with standard forceps, back loaded forceps and basket were compared [46]. Biopsy with basket was found to be superior to both forceps devices, and the back loaded forceps was found superior to conventional forceps. Discordance between tumour grade at URS biopsy and final histopathological evaluation after RNU has been described in several papers. Upgrading from low-grade tumour at biopsy to high grade histology after RNU was in a large meta-analysis concerning >2000 biopsies with subsequent RNU reported to be 32% [47]. The use of confocal laser endomicroscopy during URS is a novel method for peroperative visual grading of UTUC. Initial results are promising, but needs further verification before it can be taken into clinical practise [48].

**Cytology**

A urinary cytology sample may be obtained from the bladder (voided or catheterized) or as a selective sample taken via ureteral catheterization or *in situ* during URS. The cytology specimen is evaluated microscopically for cytomorphological features and classified according to the Paris classification [49]. The sensitivity of cytology to detect low-grade tumours is low, and the aim of the cytology sample is generally to detect high-grade tumours. Because of the described upgrading from biopsy to final pathology, cytology is potentially important especially among patients with low-grade biopsy considered for endoscopic treatment. Cytology can in some cases reveal a true high-grade tumour when the biopsy is described as low-grade.

However, the sensitivity of conventional cytology in detecting high-grade UTUC is described to be relatively low; in the range of 39-56% [50, 51]. In the study from Messer et al. the sensitivity increased when analysing the samples taken using selective ureteral catheterization only. In a prospective study using a very strict protocol for the collection of in situ barbotage cytology during URS, the sensitivity of the cytology increased to 91% [52].

### 1.4.4 Diagnostic predictive models

Several predictive diagnostic models have been presented using patient variables or variables from imaging, URS, biopsy, cytology, blood samples, or a combination of these [37, 38, 53, 54]. The aims of these models have been to use preoperative variables to predict muscle invasive disease (MID) or NOCD at final pathology after RNU. The idea is that a prediction MID or NOCD preoperatively can be used in decision making regarding the potential use of neoadjuvant chemotherapy or extended LND during RNU. The use of diagnostic models will be discussed further in the discussion part of this thesis.

## 1.5 Staging and Classification systems

### 1.5.1 UTUC classification and staging

UTUC is histopathologically classified in the same manner as BC. Distinctions between non-invasive, invasive UTUC and carcinoma in situ (CIS) can be made.

Approximately 75% of the tumours are pure urothelial carcinomas, but variant histology can also occur with several variants described [55]. The presence of variant histology is associated with a worse prognosis.

*Table 2. The table describes the TNM classification for UTUC [56]. The classification of UTUC is similar to the TNM for bladder cancer, but simpler in some aspects.*

| **T – PRIMARY TUMOUR** | |
|---|---|
| **TX** | Primary tumour cannot be assessed |
| **T0** | No evidence of primary tumour |
| | Ta Non-invasive papillary carcinoma |
| | Tis Carcinoma *in situ* |
| **T1** | Tumour invades subepithelial connective tissue |
| **T2** | Tumour invades muscularis |
| **T3** | (Renal pelvis) Tumour invades beyond muscularis into peripelvic fat or renal parenchyma<br>(Ureter) Tumour invades beyond muscularis into periureteric fat |
| **T4** | Tumour invades adjacent organs or through the kidney into perinephric fat |
| **N - REGIONAL LYMPH NODES** | |
| **NX** | Regional lymph nodes cannot be assessed |
| **N0** | No regional lymph node metastasis |
| **N1** | Metastasis in a single lymph node 2 cm or less in the greatest dimension |
| **N2** | Metastasis in a single lymph node more than 2 cm, or multiple lymph nodes |
| **M - DISTANT METASTASIS** | |
| **M0** | No distant metastasis |
| **M1** | Distant metastasis |

### 1.5.2 Tumour grading

In 1973 the WHO presented a three-tiered grading system for urothelial carcinomas that was the reference until the revised ISUP/WHO grading was adopted and published by WHO in 2004 [57, 58]. An updated version was presented in 2016 without major changes [59]. In the WHO classification from 1973, the grading of urothelial carcinomas was poorly defined. Grade 1 was described as tumours having minimal anaplasia, and grade 3 having severe degrees of anaplasia, rendering grade 2 as a large group in between and not otherwise defined. In contrast, the two-tiered WHO/ISUP grading system from 2004 utilizes specific histologic and cytological criteria for the distinction of low- and high-grade tumours. Briefly, the WHO 1973 was based on three grades with increasing cytological atypia. In the WHO/ISUP 2004 grading system, however, low-grade carcinomas give a predominant impression of both architectural and cytological order by scanning magnification, with minimal nuclear atypia (Figure 2a), while high-grade carcinomas are characterized by architectural disorder, marked nuclear atypia and mitosis frequently found at all levels of the urothelium (Figure 2b). Tumours are in general graded according to the highest grade found.

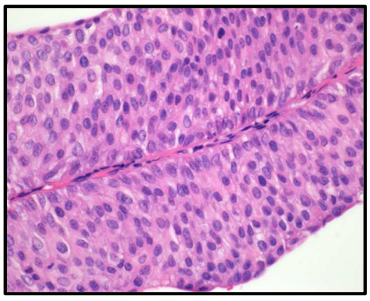

*Fig 2a. Low-grade urothelial carcinoma*

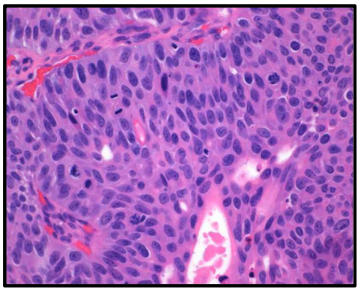

*Fig 2b. High-grade urothelial carcinoma*

There was a delay in the implementation of the new grading system, so many publications regarding UTUC have used the 1973 grading system when presenting their patients. It is necessary to be familiar with both the new and the old grading system when reading papers regarding UTUC.

## 1.6 Prognosis and survival outcomes

### 1.6.1 Natural history

The literature on the natural course of UTUC treated with no-curative intent is sparse. Two population based studies using different cohorts of patients treated non-surgically for UTUC is available [60, 61]. The study populations consisted of 8% and 11% of their respective cohorts of UTUC patients. Median OS was 1.9 and 2.2 years, and 3 year cancer specific survival (CSS) was 74%. Median age was 79 and 81 years, significantly higher than the age of patients treated surgically in the cohorts the samples were drawn from. One of the studies evaluated potential effects of treatment with chemo- or radiotherapy, but found no indication that such treatment improved survival outcomes in patients treated non-surgically.

### 1.6.2 Outcomes after RNU

Open RNU is considered the gold standard treatment for UTUC, and outcomes after RNU is therefore considered the main reference when discussing UTUC prognosis. The unadjusted five-year CCS in large cohorts after RNU are in the range 74-87% [62-65]. The primary predictors for outcome are tumour stage and grade at final pathology after RNU [25]. Several other variables are also found to predict outcomes. The variables that determine prognosis after RNU can be split into preoperative patient or tumour related factors and postoperative tumour related factors.

### 1.6.3 Preoperative patient related factors

**Age**

Higher age has been shown to be a predictor of lower OS and CSS in several studies [66, 67]. However, other studies have shown that age is not an independent predictor of CSS when adjusting for all other factors in a multivariate analysis [68].

**Smoking**

Smoking is a known risk factor for development of UTUC. It is also recognized as a predictor of poorer survival outcomes. In a multicentre study of 864 patients treated with RNU for UTUC, the patients were stratified according to tobacco consumption, and survival outcomes were analysed. The smokers had a lower CSS compared to never smokers. Previous smokers who quit >10 years showed an improved CSS compared to smokers who quit < 10 years ago [69]. Later studies have shown an increased risk of disease progression after RNU among smokers [21].

**Genetic and molecular markers**

Genetic studies have concluded that UTUC has a different mutation profile than BC. Mutations in the *FGFR3, TP53* and *RB1* gene have been identified. While mutations in the FGFR3 gene are more frequent in low-grade than high-grade UTUC, mutations in *TP53* and *RB1* were more common in high-grade UTUC and were associated with reduced OS [70, 71].

A reduced level of E-Cadherin (a protein involved in the stability of intercellular adhesion in the urothelium) has been shown to be a predictor of aggressive UTUC and reduced survival after RNU in univariate analyses [72]. The presence of programmed cell death protein 1 has been shown to be a predictor of poor survival while the presence of programmed cell death ligand has been reported as a predictor of favourable survival outcomes [73, 74]. Several other molecular markers have been tested in smaller studies showing different potential as predictors of outcome but further research is needed before any of these can be integrated in the daily clinical practice.

**Other patient related factors**

Systemic symptoms at diagnosis are shown to be predictors of worse survival outcomes [26, 27]. A higher preoperative ASA score is demonstrated to have a negative effect on CSS [75]. Similarly, pre-operative anaemia [76], malnutrition [77] as well as obesity [78], hypoalbuminemia [79] and a reduced De Ritis ratio [80] (aspartate aminotransferase/alanine aminotransferase ratio) have shown to have

negative impact on survival outcomes after RNU. Neither gender nor ethnicity is regarded to be independent risk factors for survival after RNU.

### 1.6.4 Preoperative tumour related factors

The presence of multifocality has been described as a negative predictor of survival outcomes [81, 82]. Despite some contradictory results in the literature, ureteral location is in general considered to be a predictor for poorer survival [25, 82, 83]. The presence of hydronephrosis has been described to be a predictor for poorer survival outcomes [84].

**Presence of previous or synchronous bladder cancer**

A large multi institutional study from Japan, patients with previous or synchronous BC demonstrated a poorer OS compared to patients without BC [18]. Another smaller study from South Korea found that previous or synchronous BC predicted bladder and local recurrence, but not survival [85].

**Surgical delay**

One population based study suggested that surgical waiting time >120 days could have a negative impact on prognosis [86]. Other studies have shown that shorter delays in time from diagnosis to final treatment does not impact prognosis allowing for supplementary investigations of the patient if indicated [87, 88].

**Hospital volume**

A recent American study reported improved survival both in the short- and long term for high-volume centres compared to low-volume centres. The authors conclude that these differences can be both due to surgeon volume, but also due to better ancillary services available at high-volume centres [89].

### 1.6.5 Postoperative tumour related factors

**Tumour stage (pT)**

Multi institutional studies have shown that outcomes after RNU are strongly dependent upon pT-stage. The 5-year CSS according to stage has been reported to be 94% for Ta tumours, 91-94% for T1 tumours, 75-86% for T2 tumours, 54-65% for T3 tumours, and 13-55% for T4 tumours [63, 90].

**Nodal status (pN)**

Survival outcomes are also strongly dependent upon pN-status. The 5-year CSS for patients with node positive disease is referred to be 34-35% vs 77% for pNx/N0 patients [63, 90]. OS for node positive patients have been reported in the same range [91], indicating that death due to UTUC is predominant over other causes of overall mortality among node positive patients.

Outcome for patients with node positive disease is however also dependent on tumour stage. Lugghezzani et al. found that node positive patients with pT1-2 had a significantly higher 5-year CSS compared to node positive patients with pT3-4, (69% vs 29%, p=0.006) respectively [63].

**Tumour grade**

Histological tumour grade according to the two-tiered WHO/ISUP grading system is shown to be an independent strong predictor of survival outcomes after RNU. Unadjusted 5-year CSS for high-grade UTUC is referred to be 57% vs 88% for low-grade tumours [90]. Many published papers on UTUC have presented tumour grade data using the older three-tiered grading system. A survival benefit for lower vs higher tumour grades is also described using the older three-tiered grading system [92].

**Tumour architecture**

A description of tumour architecture is a part of the gross macroscopic evaluation performed by the pathologist on the RNU specimen postoperatively. Sessile architecture is described as flat growing with an invasive pattern as opposed to papillary, which is often polypoid and frequently with a thin tumour stem [93].

Sessile architecture is reported to be present in 20-25% of the patients [90], and is reported to be a predictor of poor survival outcomes (five-year CSS 65% for sessile tumour architecture vs 90% for papillary tumour architecture, $p<0.001$ [93].

**Other postoperative tumour related factors**

In addition to the described factors, the presence of lymphovascular invasion [94], positive surgical margins [95], large tumour size [39], extensive tumour necrosis [96], concomitant CIS [97] and variant histology [55, 98] are reported to be predictors of poor survival outcomes after RNU.

### 1.6.6 Bladder recurrence

Intra vesical recurrence (IVR) after RNU has been described to occur in about 30% of the cases with a median time to recurrence of 22 months. A meta-analysis reviewing 18 published papers on the topic concluded that several patient, surgical and pathological factors were identified as independent risk factors for IVR [99]. A nomogram for the prediction of IVR has been published [100]. An association between diagnostic and/or therapeutic URS and IVR after RNU has been described. Two larger meta-analyses analysing data including several thousand patients, concluded that preoperative URS increases the risk of IVR, but does not impact survival outcomes [101, 102]. Two randomized controlled trials (RCT) have shown that a postoperative instillation of mitomycin or pirarubicin to the bladder after RNU reduces the risk of IVR by about 30%, and is considered standard treatment according to guidelines [25, 103, 104].

### 1.6.7 Prognostic models

Several models for prediction of survival after RNU using postoperative factors are available [62, 105, 106]. Most published models include age, pT-stage and nodal disease in their models, while tumour architecture, lymphovascular invasion and tumour grade are other factors frequently used in the presented models. Most models

are presented as nomograms with accuracies in the range of 0.78-0.82. Scoring systems have also been presented [107].

## 1.7 Disease management

### 1.7.1 Localized non-metastatic disease

Localized UTUC is defined as urothelial carcinoma confined within the kidney pelvis or ureter, or with local tumour growth into the renal parenchyma, peripelvic or periureteric tissue. Regional spread into lymph nodes in the hilum, retroperitoneum or pelvic lymph nodes on the ipsilateral side can also be considered as localized disease. Patients with localized disease can be treated with a curative intent.

The standard treatment of localized UTUC is a RNU with complete excision of the ipsilateral bladder cuff. However, surgical removal of a kidney with some or all kidney function intact, will inevitably lead to a reduction of the total kidney function for the patient. Studies from the treatment of RCC where NSS have become increasingly common indicate that NSS can reduce the risk of cardiovascular events, reduce the risk of end-stage kidney failure, and even improve OS compared to standard radical nephrectomy during follow-up (FU) [108-110].

Early on, NSS for UTUC was reserved for patients where RNU was considered contraindicated due to solitary or functional solitary kidney, grave comorbidities, and/or high age. As increasing evidence showed that NSS for UTUC could be performed with comparable oncologic results as RNU, NSS in the treatment of UTUC gained popularity. Taking into consideration the demonstrated benefit in preserving kidney function, NSS is now part of the standard treatment for selected cases of localized UTUC, also among patients with normal contralateral kidney and without significant comorbidities [25].

### 1.7.2 Nephron sparing surgery

NSS for UTUC can be performed as a segmental ureter resection (SU), URS with tumour ablation or using a percutaneous access for tumour ablation.

**Segmental ureter resection**

SU is most commonly performed as a distal ureter resection with primary ureteroneocystostomy in the case of distal ureteral tumours. The procedure is traditionally performed as an open procedure [64], but robot assisted laparoscopic SU is also described with acceptable results [111]. A pelvic LND is feasible in the same procedure if indicated [112]. Before SU can be performed for UTUC, it is of great importance to rule out concomitant UTUC in the remaining ureter and kidney pelvis. Both CT and particularly URS have demonstrated a high sensitivity in ruling out UTUC in the remaining part of the upper urinary tract [30, 52].

Segmental ureter resection has in several publications demonstrated equivalent survival results compared to RNU with better preservation of kidney function [64, 112, 113]. As a result of this, SU is now considered an optional standard treatment for low-risk UTUC in the distal ureter when feasible [25]. Regarding high-risk UTUC, the topic is more controversial. Data available for analysis is more limited, but most published studies suggest oncological results for SU are comparable to RNU also for high-risk tumours [63, 114-116]. SU is considered an optional treatment strategy among selected patients with high-risk UTUC. Ipsilateral recurrence rates after SU is reported to be 7% [115].

**URS with tumour ablation**

This treatment modality has the advantage over SU that it can potentially be used in the entire UUT, and not only in the distal ureter. Endoscopic tumour ablation can be achieved by electrocautery or by the use of different lasers [117-119]. Survival outcomes equivalent to RNU can be expected when using endoscopic tumour ablation for low-grade tumours. The KPR in larger published series have been 67-83%, and recurrence rates 55-77% [118, 120, 121]. A more exhaustive discussion about this topic is done in the discussion part of this thesis.

**Percutaneous access with tumour ablation**

Percutaneous access to the kidney pelvis for UTUC treatment is achieved by the same procedure as pyelolithotripsy for the treatment of urinary calculus. Tumour ablation can be achieved by electrocautery or laser ablation. Percutaneous tumour ablation is used less frequently than URS ablation and available literature on the subject is limited. Published series indicate oncological results comparable to RNU when treating low-risk tumours [122].

### 1.7.3 Radical nephroureterectomy

Since the first descriptions of RNU in the treatment of UTUC was published in 1940 [123], RNU has been the standard treatment for UTUC. Even though substantial developments have been made in the diagnostics and treatment of UTUC, open RNU still remains the gold standard treatment for high-risk UTUC [25].

**Open radical nephroureterectomy**

A radical RNU should be performed removing the entire kidney including the Gerota's fascia and the entire ureter with surrounding ureteral fatty tissue including the intramural part of the ureter, with a complete excision of the ureteral ostium [124]. Care should be taken to minimize manipulation of the tumour, avoid tumour spillage, and limit the urine leakage as much as possible. After open RNU, the overall complication rate has been reported to be 8-17%, while major complications (Clavien-Dindo 3 or more) in a meta-analysis is reported to occur in 4% of the patients. The perioperative mortality is reported to be 0.7-1.1% [125, 126]. Per-operative blood loss has been estimated to 250-500ml with 15-25% of the patients subsequently requiring blood transfusions. Hospital stay is typically 4-7 days [125, 127].

**Minimal invasive radical nephroureterectomy**

A minimal invasive RNU can be performed as a purely laparoscopic nephroureterectomy, or as a robot assisted laparoscopic RNU. The first successful laparoscopic RNU was described by Clayman in 1991 [128]. Later, a robot assisted procedure has been described [129]. A template based LND is shown to be feasible in

the same procedure [130]. Retroperitoneal laparoscopic RNU has also been described, but is less used [131]. Studies on minimally invasive RNU have repeatedly reported lower blood loss, fewer patients in need for blood transfusions, and shorter hospital stays compared to open RNU [127, 132]. Regarding other complications, several studies and one meta-analysis have found a similar complication rate comparing minimal invasive RNU to open RNU [126, 132].

Outcomes regarding recurrence and survival of minimal invasive RNU have been described as comparable to open RNU for localized tumours (pTa-T2) [129, 133-135]. However, one RCT described poorer survival outcomes for patients with NOCD treated with laparoscopic RNU compared to open RNU [136]. This finding has also been described by later studies verifying that patients with pT3+ tumours have a poorer CSS if treated with laparoscopic RNU compared to open RNU [137, 138]. An open RNU is recommended as standard treatment for clinically advanced stage UTUC [25]. Port-site metastasis has been reported to occur in 0-2.8% of the patients [139].

### 1.7.4 Lymph node dissection

A LND is a part of the standard treatment of bladder cancer, where a LND has shown both therapeutic and diagnostic efficacy, and is routinely performed in adjunct to radical cystectomy for muscle invasive BC [140]. Regarding UTUC, the topic is more controversial. The landing sites for regional metastases have been described [141, 142]. Regarding tumours in the renal pelvis and upper ureter, 80-90% of metastatic regional lymph nodes can be removed using a template of the hilum and paracaval or paraaortic template. Regarding tumours in the lower ureter, 70-80% of pathological lymph nodes can be removed using an ipsilateral template similar to extended lymph node dissection used for BC.

The risk of lymph node metastasis is strongly dependent upon tumour stage. While lymph node metastasis is uncommon in pTa-pT1 tumours (<5%), it is increasingly common in pT2+ tumours (15-40%), [91, 143]. A recent review of available literature

has concluded that performing LND in muscle-invasive UTUC will increase CSS [144], and a template based LND for muscle-invasive UTUC is now recommended in current guidelines [25].

### 1.7.5 Management of the ureteral ostium and bladder cuff

Complete resection of the intramural part of the ureter including the ureteral orifice has been shown to reduce the risk of later intravesical recurrence compared to incomplete resection, and is a mandatory part of RNU according to current guidelines [25, 99, 145]. Several methods for bladder cuff management have been suggested including intravesical and extravesical approaches, stripping, intussusception and transurethral techniques. None have convincingly shown to be superior to other methods as long as a complete resection is performed [146, 147].

### 1.7.6 Local instillation treatment in the upper urinary tract

Instillation of Bacillus Calmette-Guerin is part of the standard treatment regimen for BC [148]. Postoperative instillation of intra vesical chemotherapy after transurethral resection of bladder tumours has been shown to prevent later bladder recurrence [148, 149].

The use of similar topical agents instilled in the UUT has been described in several papers. Due to great heterogeneity of the published patient series, it has been difficult to come to any conclusion regarding a potential effect on recurrence or survival. The papers differ regarding patient selection, agent used, methods for administration and outcome measures. A meta-analysis published in 2019 included 27 different studies on the subject. The conclusion was that no significant differences in recurrence rates, progression, CSS or OS could be demonstrated between different agents or different methods for instillation. The authors conclude that to date, the efficacy of endocavitary instillations in treating UTUC or preventing UTUC recurrence is yet to be proved [150].

A novel method using a mitomycin containing slowly dissolvable gel applied via ureteral catheter directly to the kidney pelvis for low-grade UTUC has recently been presented in a phase 3 clinical trial [151]. Results are promising with a complete

response rate of 60%, but these need further verification before the method can be taken into clinical practice.

### 1.7.7 Perioperative chemotherapy

Neoadjuvant cisplatin based chemotherapy before radical cystectomy has in RCTs proved to improve long-term survival for BC patients and is part of the standard management of muscle-invasive BC [140]. Regarding UTUC, no RCTs assessing the potential benefits of chemotherapy in a neoadjuvant setting is available. The effect of neoadjuvant chemotherapy in down-staging UTUC and obtaining complete remission at final pathology after RNU has been demonstrated, and a survival benefit has also been described in a retrospective non-randomized study [152-154].

Population based studies have suggested a moderate benefit in OS for patients treated with adjuvant chemotherapy after RNU compared to observation alone [155]. One recent RCT comparing the use of RNU + adjuvant chemotherapy with RNU only supported this finding. The patients treated with adjuvant chemotherapy in addition to RNU, had a significant lower recurrence rate than the patients treated with RNU only [156].

### 1.7.8 Adjuvant Radiotherapy

Studies have shown that radiotherapy used as adjuvant to surgery and/or chemotherapy have no significant impact on survival, and can be recommended only in very selected cases [157, 158].

## 1.8 Metastatic disease

Metastatic UTUC is defined as metastasis of UTUC to distant organs or distant lymph nodes. Patients in this category can only rarely be cured, and the main goal in treatment is to prolong survival, optimize quality of life and provide the best available palliative care. Untreated, median OS for metastatic BC is 3-6 months [159]. The outcomes of metastatic UTUC are poor. Colla Ruvolu et al. described a 1-year OS of

39.7% with a median survival of 9 months among patients with metastatic UTUC in the USA. Patients treated with chemotherapy and/or RNU demonstrated improved survival compared to non-treated patients [14].

### 1.8.1 Radical nephroureterectomy

Several observational studies have indicated a moderate but significant (10-14%) improved 3-year OS for patients treated with RNU with or without chemotherapy for metastatic UTUC [160, 161]. This benefit might be limited to patients with only one metastatic site [162]. The evidence for the potential benefit of RNU for this patient group is limited, and the timing of the procedure (before or after chemotherapy) has not been studied. RNU can be an option for selected metastatic UTUC patients.

### 1.8.2 Metastasectomy

Metastatic urothelial cancer is generally regarded as a systemic disease where surgery has a very limited role in patient treatment. However, some patient series on metastasectomy for urothelial cancer both from BC and UTUC have been published. It seems that a minority (15%) of the patients can experience long-term survival after metastasectomy, primarily after resection of metastases in the lungs and lymph nodes [163, 164]. Metastasectomy can be regarded as an optional treatment for a highly selected group of patients.

### 1.8.3 Chemotherapy

As a result of early studies on metastatic BC, and later subsequent RCTs on metastatic BC with sub-analyses regarding UTUC, cisplatin based chemotherapy is regarded as first line treatment for metastatic UTUC [165-167]. A survival benefit of 12-14 months in OS can be expected compared to observation. Studies on metastatic BC shows that carboplatin based regimens are inferior to cisplatin based regimens regarding survival [168]. Still, an objective response rate of 30-42% can be expected when treating metastatic UTUC patients unfit for cisplatin with carboplatin based regimens [169]. An objective response rate of 22-24% can be expected for vinflunine regimens which is an alternative in the second line treatment of metastatic UTUC [170].

### 1.8.4 Immunotherapy

Immune checkpoint inhibitors have emerged as an attractive treatment option in many fields of cancer treatment in recent years, including urothelial cancer [25].

Both the programmed cell death protein inhibitor pembrolizumab and the programmed death ligand inhibitor atezolizumab have been tested as first line treatment for cisplatin ineligible patients in phase II studies for metastatic urothelial cancer. *Post-hoc* analyses of metastatic UTUC patients in these studies have shown similar response rates for metastatic UTUC patients compared to patients with metastatic BC. The objective response rate was 23-29% with a complete response rate of 7-9%. The toxicity profiles were favourable for both regimens [171, 172]. On the basis of these findings, both these drugs are approved as first line treatment for programmed death ligand inhibitor positive patients with metastatic BC patients ineligible for cisplatin based therapy. Both pembrolizumab and atezolizumab and have shown objective response rates from 21-26% as second line treatment for metastatic urothelial cancer relapse after treatment with cisplatin based regimens, and are considered viable options for metastatic UTUC patients in these categories [173, 174].

## 1.9 Follow-up

To the best of our knowledge, no publications dedicated solely to the evaluation of FU regimens after treatment for UTUC are presented. As a result, all recommendations in guidelines are recommendations based on standard practice and expert opinions.

The aims of FU after RNU are the detection of IVR and metastatic disease after RNU. IVR after RNU is frequent, and cystoscopy should be performed regularly. In current guidelines, cystoscopy is recommended after three months, and then at set intervals for five years depending on the risk of recurrence. The risk of recurrence should be taken into account when deciding intervals for cystoscopy. The risk of

metastatic disease after RNU is considerable, but also strongly dependent upon several factors as described previously. However, the potential benefit for the patient in detecting metastasis in a pre-symptomatic phase is debatable. If a patient is fit for available treatment (chemotherapy and/or immune checkpoint inhibitors) for metastatic disease, a CTU should be performed regularly. According to guidelines, a CTU every 6 months for two years and then yearly is recommended for high-risk patients.

In FU after NSS, a risk of ipsilateral recurrence exists in addition to the risk of IVR and metastatic disease. Regarding FU after endoscopic treatment, the authors of published series on this topic recommend a rigorous FU since the recurrence rates after this treatment modality are high. Scotland et al. recommend URS surveillance every 3 months until the patient is considered tumour free, and then URS every six months [118]. It was not stated how long this surveillance program should continue, or whether a CTU could replace the URS in the later FU.

# 2. Aims of the thesis

There is a paucity of high-quality studies regarding UTUC, and a considerable knowledge gap concerning several aspects of the disease. Basic epidemiologic knowledge about the current incidence and possible changes over time in Norway and Europe is lacking. Despite its relative rarity, the diagnostic work up and treatment possibilities of UTUC have changed substantially in the last decades. Proper preoperative staging to tailor the right treatment for any given patient is one of the main challenges in UTUC treatment today. The use of NSS in the treatment of UTUC has become more common, but the indications for these treatment options are not fully understood.

The main aim of the present thesis was to improve our understanding of the epidemiology, diagnostic work-up and treatment of UTUC. Fig 3 illustrates how the different parts of the thesis stand together to create an entity.

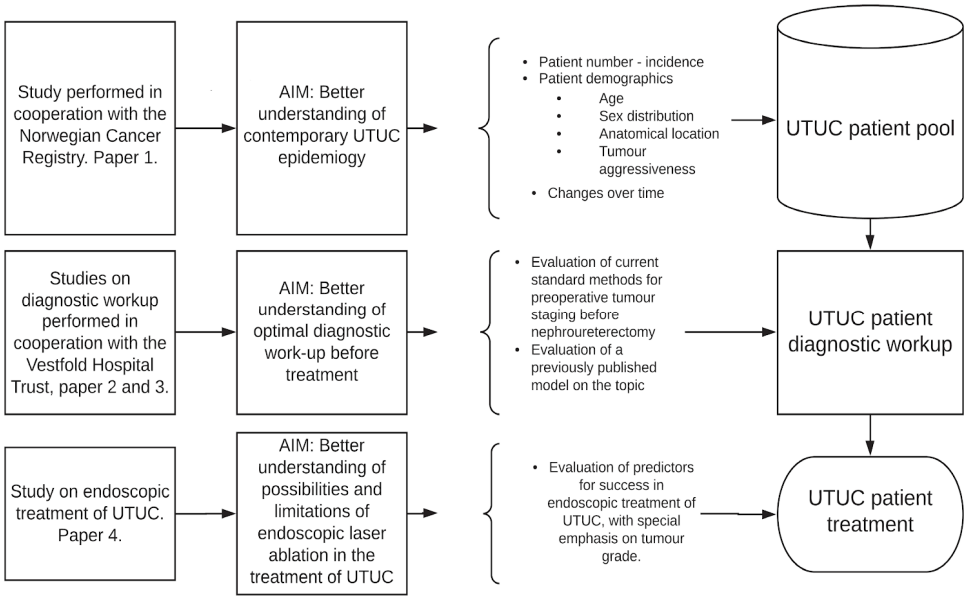

*Figure 3. Illustrates how the different elements of the thesis are integrated as a whole. As demonstrated, the ultimate goal is to improve UTUC patient treatment.*

**Paper 1**

The aim of paper 1 was to obtain contemporary knowledge about UTUC incidence including incidence relative to other urothelial cancers and RCC in Norway. Further to look for and analyse possible changes over time regarding UTUC incidence, patient demographic variables, and tumour characteristics.

**Paper 2**

The aim of paper 2 was to evaluate standard preoperative staging with CT and URS when done before RNU to see if our staging is adequate to select patients for the right treatment modality. Specifically we evaluated all registered preoperative variables regarding the patient, the CT scan, URS and cytology and analysed their respective abilities to predict NOCD at final pathology, and survival after RNU.

**Paper 3**

The aim of paper 3 was to perform an external validation of a previously published diagnostic model [54] generated to predict non-organ confined UTUC at final histopathological examination after RNU.

**Paper 4**

The aim of paper 4 was to evaluate endoscopic treatment given at our hospital during 2001-2012, with focus on outcome measures stratified by treatment groups and tumour grade.

# 3. Materials and methods

## 3.1 Permissions and ethical considerations

Regarding paper number 1, scientific studies performed at the NCR are exempt from the general rule that ethical approval from the regional ethics committee (REK) is necessary for scientific research in Norway. One of the purposes of the NCR is to facilitate scientific research. Regarding paper number 2 and 3, ethical approval of the studies was obtained from REK (reference no. 2017/854 and 2017/930). Regarding paper number 4, ethical approval from the REK was not necessary, as the study was a purely retrospective single centre study assessing a treatment already given. Prior to collection and storage of data, approval of this study was obtained from the internal review board at Haukeland University Hospital.

## 3.2 Study populations and methods

**Paper 1**

Regarding paper 1, the study population was gathered at the NCR. The NCR is nationwide, and has since 1953 kept a complete registry of all new cases of malignant neoplasms. All patients classified with ICD-10 diagnosis code C65 (cancer in the kidney pelvis) and C66 (cancer in the ureter) registered during 1999-2018 were inquired from the main database at NCR. From a total of over >1.900.000 cancer cases registered at the NCR, 3502 cases were extracted from the main database for evaluation. After an exclusion process, 406 cases were excluded due to uncertainty regarding the diagnosis (n= 334) or non-urothelial cancer (n=72), leaving 3096 cases with verified UTUC in 2818 patients for analysis in the study. All analyses were made according to the number of cases. The database included information about e.g. patient sex, age at diagnosis, date of birth, histopathological data, clinical data ( cancer report, death report etc.), treatment and current status (deceased or alive).

One of the aims of the study was to compare UTUC incidence with the incidence of other urothelial cancers and RCC. Additional extractions were made regarding cases with diagnosis code C67 (BC), C68 (Urethral cancer) and C64 (RCC) during 1999-2018. After an exclusion process resembling the one used for UTUC patients, 24467 cases of BC, 287 cases of urethral cancer, and 13619 cases of RCC were included in the study.

**Paper 2 and 3**

The medical records of 209 patients treated with a RNU between 2005 and 2017 for suspected UTUC at Haukeland University Hospital (n=130) and the Vestfold Hospital Trust (n=79), were retrospectively examined. 30 patients were excluded, 15 of these due to non-urothelial cancer (most of them RCC), nine due to concomitant bladder cancer with cystectomy in the same procedure as RNU, and six because no viable cancer was present at the final histopathological specimen after RNU, leaving 179 patients for evaluation.

Patient age, sex, comorbidities, kidney function, presenting symptoms and smoking status were registered together with the presence of prior bladder cancer or prior endoscopic treatment for UTUC. 176 patients were examined with a CT scan, 159 of these with i.v. contrast. All CT scans were re-examined and evaluated regarding tumour location, size, contrast enhancement, the presence of reactive oedema surrounding the tumour, hydronephrosis and local invasion into the renal parenchyma, the peripelvic or periureteric tissue. 95 patients were examined with a diagnostic URS with biopsy and 60 patients had a cytology taken. Data regarding tumour location, stage and grade were gathered from the pathology reports at the respective institutions. Tumours were graded according to the two-tiered WHO 2004 classification and staged according to TNM 2017 classification. All specimens originally not concurring with these two classifications were re-examined and reclassified by uropathologists (OJH and BC).

For paper 3, histological tumour grade and gross architecture from the final pathology report were registered and used together with the variables already registered and used for paper 2.

**Paper 4**

The medical journals of 140 patients treated surgically for UTUC at Haukeland University Hospital during 2001-2012 were retrospectively examined. 90 of these were treated with a RNU, seven with a SU, and 43 endoscopically with a curative intent. These 43 were all considered to be potential candidates for endoscopic treatment after initial radiological imaging. A URS was then performed and biopsies were taken when possible. Endoscopic treatment was given in the same procedure if it seemed feasible. The patients were treated with either URS (n=34) or with percutaneous nephroscopy (n=9). The URS were performed using either a semi-rigid or a flexible ureteroscope, while the percutaneous nephroscopy was performed using a rigid nephroscope. Tumour destruction was performed using a YAG-Holmium laser or electrofulguration.

All relevant demographic information about the patients was registered. After finishing the inclusion of patients, all the initial biopsy specimens were re-examined by a uropathologist (OJH) and graded in accordance with the three-tiered WHO 1973 system (grades 1, 2 and 3), and the two-tiered WHO/ISUP 2004 system (low- and high-grade). A complete histopathological evaluation from the biopsies was possible in 40 of 43 patients (93%).

The patients were divided into groups for the purpose of analysis. Firstly, the patients were divided into two groups according to indication for endoscopic treatment. Patients with an elective indication were placed in the candidates for nephroureterectomy (CNU) group, while patients considered not fit for RNU due to comorbidities and/or high age were placed in non-candidates for nephroureterectomy

(NCNU) group. Secondly, the patients were divided into groups according to tumour grade, one low-grade, and one high-grade group.

## 3.3 Statistical analysis

**All papers**

Databases for the study populations of the respective studies were generated using IBM® SPSS® statistical software versions 21-26 according to publication date and version available at the time the work was done.

- Differences between groups regarding continuous variables were analysed using a Student's t-test
- Differences between groups regarding categorical variables were analysed using a chi-square test
- Survival, recurrence and kidney preservation estimates were calculated using the Kaplan-Meier method, and a log rank test was used when comparing groups
- P–values less than 0.05 were considered statistically significant for all tests

**Paper 1**

Crude incidences of UTUC were calculated for each year (1999-2018) using population data for Norway from *Statistics Norway* the corresponding year [175]. Crude incidences for each 5-year age interval for each year were calculated to facilitate population adjustment. The population adjustment was then performed using the updated European standard population (2013) as the main reference [176]. Both crude incidences and ASR according to the European standard population were presented in the paper. For purposes of changes over time analysis and presentation, the material was split into 5-year periods (1999-2003, 2004-2008, 2009-2013 and 2014-2018). The relative proportion of UTUC cases compared to all urothelial cancer cases and pelvic urothelial tumours compared to RCC cases were calculated for each

5-year period. Analyses regarding changes in patient age, sex distribution and location of the tumour were performed in the same manner. The five-year periods were compared using the chi-square method, and for further analyses of changes over time, linear regression analyses were made calculating yearly changes and assessing statistical significance. Survival estimates for the 5, 10 and 15 year OS and CSS were calculated using the Kaplan–Meier method, and a log-rank test was used to compare groups.

**Paper 2**

For prediction of tumour stage at final histopathological examination after RNU, all candidate variables regarding patient features, CT and ureteroscopic findings were analysed using univariate and multivariate logistic regression analysis to assess their abilities to NOCD. Survival estimates for the 5- and 10 year OS and CSS were calculated using the Kaplan–Meier method, and a log-rank test was used to compare groups. Furthermore, multivariate cox regression analyses including both patient features and final histopathology were performed to evaluate independent predictors of all-cause and cancer-specific mortality. For the comparison of groups, continuous and categorical variables were analysed using a Student's t-test and a chi-square test, respectively.

**Paper 3**

The external validation was performed according to principles described by Altman et al. to include both model calibration and discrimination [177]. Each patient in our cohort was allocated points from the nomogram corresponding to tumour grade, location and architecture. The total score was evaluated using the Margulis nomogram to determine the *predicted* risk of NOCD for each patient. This was compared to the true *observed* risk of NOCD seen in the cohort. Comparisons between predicted and observed risk were made to assess model calibration and the results were graphically explored in a scatterplot. Reliability analysis to assess

interclass correlation between observed and predicted risks was performed using Cronbach alpha measurement. The predictive accuracy of the Margulis model and the present model was assessed by calculating the area under curve (AUC) in a Receiver Operating Characteristic (ROC) model. Model discrimination was assessed comparing the AUC from the Margulis model and the present model.

**Paper 4**

Differences between the patient groups and tumour grade groups were assessed using Student's t-test, and chi-square tests. Survival and recurrence estimates were made using the Kaplan-Meier method, and a log-rank test was used to compare groups. Predictors for survival, recurrence and KPR were further analysed using uni- and multivariate regression analyses.

# 4. Summary of results

**Paper 1**

The crude incidence of UTUC in the whole time period was 3.17:100.000, increasing significantly from 2.54 to 3.98 from the first to the last five-year period. The ASR according to the European standard population was 3.88 for the whole period, increasing significantly from 3.21 to 4.70 from the first to last five-year period. The population adjusted estimated annual increase in incidence was 0.10 (CI 0.06-0.13, $p<0.001$), corresponding to an average annual increase of 2.5%.

UTUC incidence increased significantly for all age groups (decades) over 60 years of age. The mean age at diagnosis increased significantly from 71.8 to 73.9 years from the first to the last five-year period. The proportion of UTUC of all urothelial cancers also increased over time, and constituted 12.6% in Norway during 2014-2018. Of 3096 cases, 1811 (58.5%) were located in the renal pelvis. The proportion of urothelial cancers in the renal pelvis increased over time, and constituted 12.9% of all renal tumours in Norway during 2014-2018.

We found a 5, 10 and 15-year OS of 47.7%, 32.7% and 22% respectively. The 5, 10 and 15-year CSS was 75.3%, 72.9% and 70.8% respectively. OS improved over time, comparing the last decade with the first (five-year OS 44.3% vs 51.7%, p=0.003). No differences were found in survival regarding gender or tumour location.

**Paper 2**

Local invasion and pathological lymph nodes at CT predicted NOCD in uni- and multivariate regression analyses (OR 3.36, p=0.004 and OR 6.21, p=0.03, respectively). Fatty tissue reaction surrounding the tumour (OR 2.55, p=0.02), tumour size (4.8 *vs.* 3.9 cm, p=0.006) and histological high-grade tumour at URS biopsy (OR 3.59, p=0.04) predicted NOCD at univariate regression analyses. No patient variable was found to predict NOCD in the present cohort. The five-year CSS and OS for the

entire cohort was 79% and 60%. Only the pathological tumour stage (at final pathology after RNU) predicted CSS at multivariate analysis. Histological evaluation of the URS biopsy could verify the diagnosis in 66/95 (69%) of the cases. 12 of 34 (35%) low-grade tumours at biopsy were upgraded to high-grade at final pathology after RNU. Local invasion at CT was found to be the best suited variable to consider when selecting patients for intensified treatment.

**Paper 3**

A comparison between the Margulis cohort and our cohort regarding patients and tumour characteristics was made. The patients in our cohort more often presented with local symptoms (74% vs 61%, p=0.01), a larger proportion had Eastern Cooperative oncology Group score of ≥1 (48% vs 37%, p=0.01), a higher proportion of the tumours were high-grade by histology (75% vs 60%, p<0.001) and a higher proportion of the tumours had a sessile architecture upon gross pathological examination of the surgical specimen (34% vs 25%, p=0.02).

Tumour grade and tumour architecture were significant predictors of NOCD on final pathology at multivariate regression analysis (OR 28, p=0.001, and OR 4.7, p<0.001 respectively). Tumours in the renal pelvis had a higher occurrence of NOCD compared to tumours in the ureter in the present cohort, but in contrast to the cohort of Margulis et al., the difference was not statistically significant in our cohort (OR 1.5, p=0.4).

The results of the model calibration evaluation are shown in figure 4.

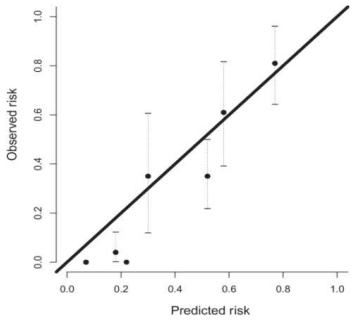


*Figure 4. Illustrates the concordance between observed in the cohort and predicted risk according to the Margulis nomogram. The overall concordance was high, quantified as a Cronbach Alfa of 0.96.*

Overall concordance between predicted and observed risk was high, quantified as a Cronbach Alpha of 0.96. The scatterplot indicates some mis-calibration of the model at low risk levels. The AUCs of both the predicted and observed risks in predicting NOCD in a ROC model were 0.83 (95% CI 0.77 -0.89), indicating that predicted and observed risk discriminated equally well between patients with low- and high risk for NOCD. The overall predictive performance was high, and we considered the Margulis nomogram validated for clinical use.

**Paper 4**

The 43 primary endoscopic treatment procedures were followed by 69 later treatments, and 77 follow-up procedures without treatment. Mean (median) number of procedures per patient was 4.72 (3), with a range of 1-12.

Comparing the CNU and the NCNU groups, the patients in the NCNU group were significantly older (77 vs 70 years, p=0.003), had a higher comorbidity when comparing Charlson comorbidity index (p=0.005), and a poorer kidney function (eGFR 92 vs 66 ml/min, p= 0.003). OS (71% vs 25%, p<0.001) and Disease specific survival (DSS), (94% vs 41%, p<0.001) were significantly higher in the CNU group

compared to the NCNU group. Survival data stratified by grade is demonstrated in figure 5.

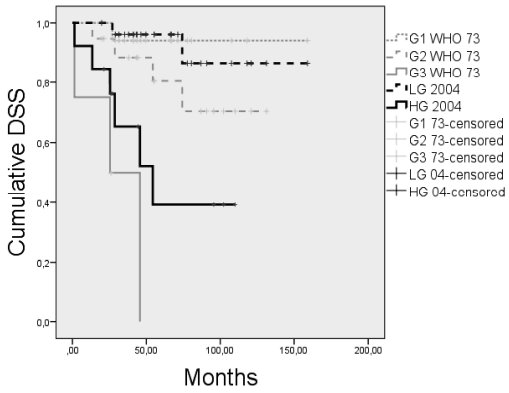


*Figure 5. Disease specific survival (DSS) stratified by histological grade according to WHO/ISUP 2004 and WHO 1973. The grey lines show DSS among patients with G1, G2 and G3 tumours according to WHO 1973. The black lines show DSS among patients with low-grade and high-grade tumours according to WHO/ISUP 2004. The difference in DSS between the WHO/ISUP 2004 low-grade tumours and high-grade tumours was statistically significant (p=0.001).*

Patients with low-grade tumours had a higher DSS (96% vs 39%, p<0.001) and OS (75% vs 23%, p<0.001) compared to patients with high-grade tumours. In multivariate analyses, age was the only significant predictor for OS, and tumour grade was the only significant predictor for DSS.

25 of 43 (58%) of the patients became tumour free at one point during FU after endoscopic treatment. Patients were regarded as tumour free only after a negative URS was performed. Among these patients the five-year recurrence free survival was 76%.

In the CNU group, 14 of 28 patients experienced perceived progressions and a RNU was performed. The five-year KPR was 51%. The KPR among patients with low-

grade tumours was 60%. Four of the RNU specimens were pT0 with no viable tumour tissue at final histopathological evaluation after RNU, and those four all had low-grade tumour from a prior endoscopic biopsy.

Among 14 patients regarded as tumour free at first endoscopic follow-up, only two had a later RNU. The patients deemed tumour free at first follow-up had a five-year KPR of 90%. In a multivariate regression analysis, an absence of tumour at the first follow-up URS was a significant predictor of KPR.

# 5. Discussion

## 5.1 On the epidemiology of UTUC

### 5.1.1 Background

In paper 1, we described an increasing incidence of UTUC. The ASR in Norway is presently at 4.7:100.000 during 2014-2018. UTUC currently constitutes close to 13% of all UC in Norway. Together with the recent Dutch study [13], this is the highest UTUC incidence reported outside endemic areas.

The results of previous studies on the topic are somewhat contradictory, as is described in the introduction part of this thesis. It is not easy to get a clear insight into the current incidence of UTUC and changes over time from these publications. The analysed populations come from different parts of the world and are drawn from different time periods. The inclusion criteria are different, and the population adjustments are performed according to different standard populations. The general impression from these studies however, was a lower UTUC incidence than we described in the present study, and more in line with the commonly quoted incidence of 1-2:100.000.

### 5.1.2 Changing incidence and possible explanations

An incidence rate of 1-2:100.000 should result in ~55-110 new cases of UTUC every year in Norway. Contrary to this estimate, an average of 208 yearly cases the last five years were found. This corresponds to a crude rate of 3.98, and an ASR of 4.70 adjusted to the 2013 version of the European standard population. The increase in the ASR over the last 20 years has been at an average of ~2.5%, resulting in an 80% increase in UTUC cases in the time period.

A comparable increase in incidence was described in the recent study by Van Doeveren et al. [13]. They described a 50% increase in ASR (adjusted to the 1976 version of the European standard population) from 2.0 to 3.2 from 1993-2017 using a cohort of more than 13.000 cases. These incidence rates are actually higher than the rates we reported. Adjusted to this older version of the European standard population,

we found an increase in UTUC incidence from 2.0-2.7 during 1999-2018 in our cohort (the details are available in supplementary table 2 in the paper published). A considerable increase in incidence to a higher level than previously described is thus the finding in two recent European publications based on national population based cohorts. Contrary to this, a recent study based on the American SEER database found a decreasing incidence in the USA from 1.3-1.1 adjusted to the American standard population from 2000 [14]. This latter study is hampered by the fact that Ta/CIS tumours were not included in the version of the SEER database used, and will thus underestimate total UTUC incidence. In a previously quoted more historical study also using the SEER database, an increasing incidence *of in situ (*Ta/CIS) tumours to 31% of total was reported in the USA 1997-2005 [9]. It is thus probable that the underestimation of UTUC incidence in the study from Colla Ruvolo et al. is substantial.

It seems clear that the incidence of UTUC in Europe is rising, but the reasons for the demonstrated increase is not clear. One possible reason could be that older patients are more thoroughly examined for symptoms presently compared to earlier. The last two decades the access to high quality CT and flexible ureterrenoscopes have improved significantly. Older patients are also more often in better physical shape and could be candidates for a RNU at a high age in case a high-risk UTUC was found at diagnostic work up of e.g. haematuria. An increased effort in examining symptoms would increase the detection rate of UTUC and result in higher reported incidences.

One potential effect of increased diagnostic work up among the elderly could be an increased mean age at diagnosis. This fits well with our findings. There has been an absolute increase in cases over 80 years at diagnosis from 115 to 303 cases, (263%) from the first to last five-year period. The proportion of patients >80 years of age at diagnosis increased from 21% to 29%. This increase is the main reason why the mean age at diagnosis has increased from 71.8 to 73.9 during the study period. One might speculate that such increased diagnostics should result in a stage migration toward

lower tumour stage at diagnosis in the latest periods. We do not have firm evidence of this in our cohort as data on staging is not complete. There are however some indications that this might be so. The proportion of invasive vs non-invasive tumours decreased non-significantly (50% to 41%, p=0.07) during the study period, while survival improved. At the same time, diagnoses verified by biopsy without following surgery increased from 11% to 24% and the use of conventional radical surgeries declined. The decrease in radical surgeries might be because more patients got a diagnosis without following treatment, but it could also be due to increased use of endoscopic treatment, as this is not registered as radical surgeries at the NCR. Increased examination of symptoms and an increased detection rate among the elderly seems like a probable cause of increased UTUC incidence, but the magnitude of such an effect would be difficult to measure exactly. Further examination into this possible effect could be the scope of future research on the topic.

It is also possible that there is a true increase in the UTUC incidence in the Norwegian population, and not just an increased detection rate. The main established risk factors for UTUC are smoking, alcohol consumption and exposure to aristolochic acid [25]. There has been a decline in smoking in Norway, but the reduction in smoking among the elderly is smaller than for other age groups [175]. Even though the number of current smokers has declined over the years, the total number of current or *previous* smokers has probably risen over the time period. It is possible that a larger proportion of people over 70 years of age have been exposed to cigarette smoking presently compared to earlier, and could be an explanation to increased UTUC incidence. Specific data on the individual alcohol consumption and exposure of aristolochic acid in the Norwegian population is limited. Further discussion about this topic is beyond the scope of this thesis.

**Survival**

Publications describing changing UTUC survival over time are limited. The largest cohorts available present the survival outcomes after radical treatments as a snapshot, and do not analyse possible changes in survival over time. Eylert et al. found a five

year survival rate 48%, decreasing over time. Woodford et al. described a stable but low five year CSS of 32%. In our cohort we found a five-year OS and CSS of 61% and 48% respectively. A non-invasive tumour, lower age, and radical treatment were indicators of better survival, as can be expected. The described survival from the NCR cohort is poorer than the survival described in the cohort user for paper 2 and 3, where a CSS of 79% and OS 60% was found. This is probably because the NCR cohort includes all UTUC patients, and not just patients treated with RNU. Survival improved moderately over time. This could be due to a stage migration, although there is no firm evidence for this in our cohort. Gender and tumour location did not predict survival in our cohort. Since an accurate description of tumour stage and treatments given is not available in our data, further in-depth analyses regarding survival is not meaningful.

### 5.1.3 Epidemiological variables

There are no evident changes in the distribution of new cases according to gender or anatomical location. A majority (61%-77%) of the patients are reported to be men, well in line with our findings, with no signs of changes over time. Likewise, a majority of the tumours (51%-66%) are located in the kidney pelvis, also in line with our findings, with no significant changes over time. Mean age however, has been reported to be increasing. Both Raman et al. and Eylert et al. described an increased age at diagnosis from 68 to 73 years [8, 9]. This corresponds well with our findings of an increased age from 71.8 to 73.9 years during the study period. In the recent Dutch study, an increased age at diagnosis from 70 to 72 years was reported [13].

### 5.1.4 Implications

These findings could have several possible implications. An increasing number of UTUC patients would mean that more resources for diagnostics, treatment, follow-up and research should be allocated to this patient group. Another implication could be recruitment into studies. Enrolment into studies could be quicker than expected, making studies on UTUC with adequate patient numbers easier to conduct.

## 5.2 On the diagnostic work-up of UTUC

Paper 1 described the incidence and demographics of the patient pool of UTUC we meet as clinicians. We will now move on to discuss the diagnostic work up of these patients. The diagnostic work up of patients presenting with symptoms potentially caused by UTUC serves two purposes. Firstly, the purpose is to establish the correct diagnosis – in this case to verify if the patient has UTUC or not. The second purpose is to provide information about tumour characteristics and stage, so that the clinician can choose the appropriate treatment for the diagnosis.

### 5.2.1 Setting the correct diagnosis

According to current guidelines, a CTU together with a cystoscopy is standard diagnostic work-up for a patient presenting with symptoms potentially due to UTUC. The sensitivity and specificity of multi-detector CTU to detect UTUC has in a meta-analysis been found to be >90% [30]. In a study by Commander et al. including 1123 patients, no further cases of UTUC were detected during a FU of three to ten years after a negative CTU, indicating a very low false negative rate [178]. The high specificity might lead to the conclusion that CTU is sufficient diagnostic work-up in most cases, since the false positive rate is below 10%. Other studies have however described a lower specificity. A prospective Swedish study including 174 patients found a sensitivity and specificity of high-quality multi detector CTU of 89% and 51% respectively in detecting UTUC [52]. In this study all patients were examined with a diagnostic URS regardless of the result of the CTU. The low specificity of 51% was due to overestimation of a possible tumour at CTU, as a following examination with URS including cytology and biopsy in many cases ruled out a tumour. The false negatives in that study were due to cases of CIS not detected at CTU. An Israeli study found that the rate of misdiagnosis at RNU dropped from 15% to 2.2% after the introduction of routine URS in the preoperative diagnostics at their department [178]. Current guidelines recommend the use of a diagnostic URS if the findings at the CTU and cytology is not sufficient to set the diagnosis or to risk

stratify the tumour [25]. To conclude, current evidence shows that the sensitivity of the CTU is high, so the risk of missing tumours when the CTU is negative is low. The exception to this general rule is cases where cytology shows CIS, as this tumour can be hard to detect on CTU. These patients should be followed-up with a URS and/or repeat imaging. If the CTU is inconclusive, there is a need to examine further with URS to verify or rule out a malignant tumour in the UUT.

### 5.2.2 UTUC staging

**Background**

The accurate preoperative staging of UTUC is more challenging than setting the correct diagnosis. The issue has been studied by several groups, and factors from radiology and the URS have been described as predictors of tumour stage, as described in the introduction part of this thesis. Since staging using a single feature can be challenging, diagnostic models have been developed. None of these models have until now been subject to external validation.

The ability to preoperatively stage the tumour as accurately as possible is important for several reasons. A low-stage and low-grade tumour can be a good candidate for NSS, while a more advanced tumour could be a candidate for intensified treatment such as perioperative chemotherapy and/or extended LND. There is also evidence that non-organ confined tumours (pT3+) should be treated with an open RNU, while localized (pTa-T2) could be treated safely with a laparoscopic or robot assisted RNU [133, 135]. The benefit of intensified treatment for advanced cases of UTUC has been demonstrated in several papers. However, there are also potential negative side effects of these treatments, such as toxicity regarding chemotherapy and potential morbidity for the extended LND. The indication for intensified treatment should be considered closely, and current evidence suggests that it should be reserved for advanced cases of UTUC, underscoring the importance of accurate preoperative staging.

### 5.2.3 Evidence gap and background for our studies

Despite advances in radiology, endoscopy and the developments of diagnostic models, the clinician still often faces difficulties in deciding the optimal treatment for a given UTUC patient. It is clear that a knowledge gap exists on this issue. As a result of this, we decided to evaluate the preoperative staging and diagnostic work-up regarding our UTUC patients, and evaluate if our findings could help elucidate a difficult topic. In paper 2 we evaluated the standard diagnostic work-up before RNU to identify predictors of tumour stage and prognosis. In the following section we will discuss our specific findings described in paper 2 in context of existing literature with special emphasis on selection of patients for intensified treatment in addition to conventional RNU. Intensified treatment in this setting means the use of perioperative chemotherapy or the use of extended LND at RNU. Further we will discuss our findings in paper 3 in relation to the use of diagnostic models.

### 5.2.4 Prediction of tumour stage

**Patient factors**

No patient factors were found to predict NOCD in our cohort. Several patient factors have been described as predictors of outcome, but these have to our knowledge not been analysed regarding the prediction of tumour stage. Poor performance status, high age, or reduced kidney function could of course make the patient unfit for perioperative chemotherapy, but to date, no patient factors have been identified that could aid the clinician in the selection of patients for intensified treatment.

**The diagnostic URS**

The indication for the diagnostic URS in case the CTU is inconclusive, or if the patient is a candidate for NSS, seems well established. When it comes to the *staging* of UTUC among patients with an established indication for RNU, the usefulness of the diagnostic URS is more debatable.

In our cohort, a diagnostic URS with biopsy was performed in 95 patients. In 66 (69%) of the patients, the biopsy could be used to confirm UTUC diagnosis, and in 57 (60%) the biopsy material was sufficient to determine histological tumour grade. 12 of 34 (35%) of low-grade tumours at biopsy were upgraded to high-grade at final pathology after RNU. The diagnostic accuracy in our study might seem unacceptably low, but both the diagnostic yield and the rate of upgrading are in line with the findings of other authors [46]. We found in our study that the presence of a high-grade tumour at biopsy predicted NOCD (OR 3.59, p=0.04). The sensitivity and specificity of high-grade biopsy to predict NOCD was 63% and 68% respectively. The predictive ability of high-grade biopsy has also been evaluated by Brien et al. and Favaretto et al. Brien et al. found a sensitivity and specificity of 59% and 70% of high grade biopsy to predict MID. Both groups further described that high-grade biopsy predicted NOCD with an OR of 3.7-3.9 [38, 53].

When considering the indication for a URS, it is important to remember potential negative side effects of the procedure. Two meta-analyses have shown an increased risk of post RNU bladder recurrence among patients examined with diagnostic URS prior to RNU [101, 102]. In addition to this, the URS would take time and resources, and cause delay in definite treatment.

The predictive ability of histological tumour grade and cytology to predict NOCD is demonstrated both in our cohort and by other authors. The question is how this information can be used in clinical practice. The described sensitivity and specificity in the range of 60-70% in predicting NOCD is in our opinion too low to be clinically useful when selecting patients for intensified treatment. We conclude that the diagnostic URS as a *staging* procedure for selecting patients for intensified treatment is of limited worth, as the results only rarely will impact treatment choice. The method has considerable limitations, and there are possible negative side effects of the procedure. We argue that the diagnostic URS in most cases could be omitted when a decision to perform a RNU has already been made.

**Cytology**

In our cohort, a cytology sample was taken in 60 patients, 43 of these taken during URS. Malignant cells were detected among 37 (62%) of these. Positive cytology by the finding of malignant cells did not predict NOCD in the present material. In the cohort of Brien et al. a positive cytology was found in 80% of the patients, and the presence of a positive cytology was found to be a significant predictor of NOCD. Despite the findings of Brien et al., we argue that the predictive abilities of a positive cytology is not well enough documented for it to be used as a factor when considering a patient for intensified treatment.

**CT Urography**

Multi detector CTU has been described as superior to conventional CTU and other CT modalities in tumour staging, and should be the method of choice, especially in cases where there is doubt about the diagnosis or staging [52].

**Hydronephrosis:** Hydronephrosis was present among 65% of the patients in our cohort, and was not found to be a predictor of NOCD. There are conflicting results in the literature about whether the presence of hydronephrosis predicts advanced stage UTUC. Several authors have reported that hydronephrosis is an independent risk factor for NOCD [31, 32]. Hydronephrosis as an adverse factor for tumour stage was included in the diagnostic models of both Favaretto et al. and Brien et al. Contrary to this, other authors have studied the same issue and have concluded that hydronephrosis is *not* a predictor for tumour stage, in line with our findings [33, 34]. As the results are contradictory, it does not seem that the presence of hydronephrosis is a suitable feature to use when deciding to use intensified treatment or not.

**Tumour size:** In our cohort, we found that patients with NOCD had larger tumours (as measured at CT) than patients with organ confined disease (4.8cm vs 3.9cm, p=0.006). A similar conclusion was drawn by Shibing et al [39]. We found however, that it was difficult to set a specific cut-off point regarding tumour size, and we concluded that tumour size was not well suited as a parameter when selecting patients for intensified treatment.

**Fatty tissue reaction:** During the re-examinations of the CT scans as part of the development of the database, we noticed a reaction in the fatty tissue surrounding many of the tumours. This is radiologically similar to the fatty tissue reaction you can see surrounding e.g. appendicitis or diverticulitis. This fatty tissue reaction was found to be a predictor of NOCD. This was particularly true regarding a sub analysis for ureteral tumours where this fatty tissue reaction predicted NOCD with an OR of 8.0, p=0.003. The sensitivity and specificity of this feature was 55% and 87% respectively (data not shown). This is potentially clinically meaningful, since NOCD was uncommon in the absence of fatty tissue reaction, with a NPV of 80%. One could hence argue that intensified could be omitted in absence of fatty tissue reaction. This is an interesting finding that to our knowledge has not been described before. However, its predictive abilities should be confirmed in further studies before it is taken into clinical use.

**Pathological lymph nodes:** The presence of pathological lymph nodes at the preoperative CT scan was in the present cohort found to be a significant predictor of NOCD in multivariate analysis (OR 3.36, p=0.004). Its predictive abilities have been reported by other authors [179]. The sensitivity and specificity in predicting NOCD was 22% and 98% respectively. This high specificity is clinically useful since the risk of "over-treating" a patient with non-muscle invasive disease in case of pathological lymph nodes disease is very low. The presence of pathological lymph nodes could be used for selecting patients for intensified treatment. The low sensitivity however means that many patients with advanced disease would be missed out if this was the only criteria for intensified treatment.

**Local invasion:** The presence of local invasion on CT was found to be a significant predictor of both NOCD and survival in the present cohort in multivariate analysis. In the diagnostic model presented by Favaretto et al., local invasion at CT was found to predict NOCD and was included in their diagnostic model. A recently published study reported a sensitivity and specificity of 75% and 83% correspondingly using CT to detect advanced stage (T3/T4) UTUC [36].

Local invasion on CT in the present study showed a relatively low sensitivity of 48% but a corresponding high specificity of 85% in predicting NOCD. By using the accuracy from the present study, local invasion at CT as a guide for who could benefit from intensified treatment would result in only half of the patients with NOCD receiving Neoadjuvant chemotherapy. However, few patients with non-muscle invasive disease would be "over-treated" with chemotherapy. Patients *not* treated with neoadjuvant chemotherapy, but with MID at final pathology, could be treated with adjuvant chemotherapy using the protocol described in the POUT study [156]. Pending evidence from high quality randomized studies comparing Neoadjuvant with adjuvant chemotherapy in the treatment of UTUC, we suggest that this very simple and readily available feature can be used as a guide for selecting patients for intensified treatment.

### 5.2.5 Diagnostic models

The demonstrated limitations of single factors available make the use of diagnostic models appealing. Several such models have been published, using different variables. During our studies of the literature on the topic, it became clear to us that none of these diagnostic models had been subject to external validation. After some consideration, we found that our cohort could be used to perform an external validation of the Margulis nomogram [54]. Margulis et al. published a nomogram using histological tumour grade, gross architecture and location from the final pathology report to generate a model with an accuracy of 0.77. This work resulted in paper 3 in this thesis.

A diagnostic model should not be taken into clinical practice before its predictive ability is tested on a dataset independent of the one used for development. External validation in this setting denotes the testing of a model's performance in a different but similar cohort and preferably by different authors, as opposed to internal validation where the model performance is tested on a sample drawn from the development cohort. To summarize our findings, we identified the same predictors for NOCD as Margulis et al., the model discriminated adequately between patients at

low- and high risk of NOCD, and the calibration was adequate, in spite of some miscalibration at the low risk levels. We concluded that the nomogram was validated for clinical use.

The big drawback with the Margulis nomogram however, is that the variables used were gathered from final pathology after RNU. The assumption is that all these variables are available in the preoperative setting and that the nomogram therefore can be used preoperatively. It is not yet clear if these assumptions are correct. The upgrading from URS biopsy to final pathology has been clearly demonstrated [47]. It is probable that the accuracy of the model would be affected if URS biopsies were used for the predictions. The ability of URS or radiology to predict tumour architecture on the final surgical specimen has been postulated in several papers, but has to our knowledge not yet been examined in studies. In our opinion, it is therefore necessary to use information regarding assessment of tumour grade and architecture determined solely with URS or radiology with caution, when considering the ability to predict NOCD. Ideally, a new external validation of the nomogram using true preoperative data in a prospective setting should be performed.

As described, several diagnostic models have been published. However, for the proper use of these models, all variables included would have to be available, meaning that e.g. a diagnostic URS has to be performed for the purpose of the model. Even if all variables are present, the use of the models in clinical practice is unclear. In general, the models are precise if all or none of the risk factors are present, while in clinical practice, often one or maybe two of these risk factors are present, and the precision in prediction is much lower. Though models increase our general knowledge about UTUC and can be beneficial in select cases, its use in everyday practice is challenging.

### 5.2.6 Implications of our findings and conclusions

In paper 2, we have performed an evaluation of current standard diagnostic work-up with special emphasis on detecting potential candidate variables for selecting patients for intensified treatment. A novel feature in the preoperative staging, fatty tissue reaction surrounding the tumours at CTU has been described, and should be examined further. Using the findings from our own research and in the literature we conclude that the accuracy of current preoperative staging of UTUC remains suboptimal. In the lack of more accurate predictors, it seems local invasion on CTU are the most promising feature to use when selecting patients for intensified treatment. A proposed flowchart for the diagnostic work-up and treatment of UTUC using this suggested feature is illustrated in figure 7.

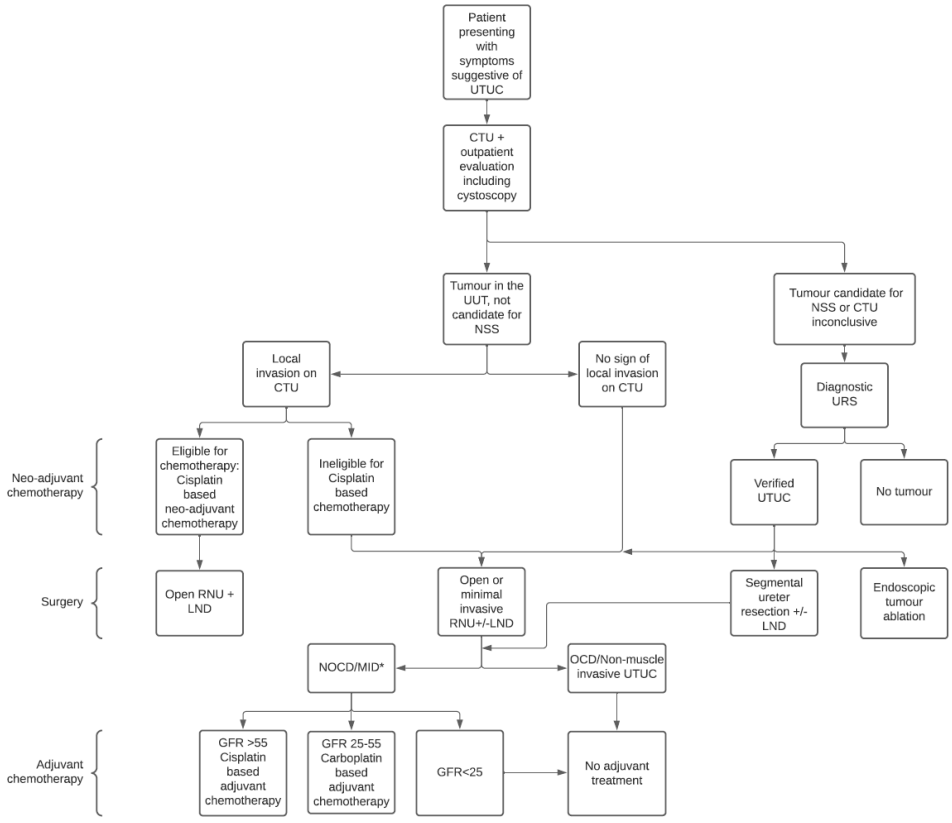

*Figure 7. Illustrates a proposed flowchart that can be used in the diagnostic work-up and treatment of UTUC. CTU: CT urography, UUT: Upper urinary tract, NSS: Nephron sparing surgery, URS: Ureteroscopy, RNU: Radical nephroureterectomy, LND: Lymph node dissection, NOCD: Non-organ confined disease (pT3+ and/or N+), OCD: Organ confined disease (pTa-T2N0M0), MID: Muscle invasive disease (pT2+), GFR: Glomerular filtration rate*

There is a clear role of the diagnostic URS in case of diagnostic uncertainty or if nephron sparing treatment is considered. As a staging procedure however, the URS has clear limitations and possible negative side effects, and should be performed only in selected cases. The use of diagnostic models can aid in decision making, depending on the preoperative data available for the clinician, and can be beneficiary in cases of doubt. In paper 3, one of the diagnostic models previously published has been validated by our research group, though we acknowledge the need for further validation in a truly preoperative setting.

## 5.3 On the nephron sparing treatment of UTUC

There is increasing evidence that preserving kidney function can reduce the risk of cardiovascular disease and even improve overall survival [108, 110]. Nephron sparing treatment of UTUC can be achieved by a segmental ureter resection or by endoscopic tumour ablation through URS or percutaneous access.

### 5.3.1 Segmental ureter resection and percutaneous access

Equivalent oncologic results between SU and RNU have been demonstrated for low-risk tumours [113]. Regarding high-risk tumours there is less documentation. Existing literature indicates that SU can also be an option in selected cases of high-risk UTUC. Since the evaluation of SU or tumour ablations using percutaneous access were not a topic in any of the published papers included in this thesis, no further discussion on these topics will be done here.

### 5.3.2 Endoscopic treatment

This treatment modality has the advantage over SU that it can potentially be used in the entire UUT. Endoscopic treatment of UTUC can be done using electrocautery fulguration or as laser ablation. Tumour biopsy using a basket has been found to be superior to biopsy with forceps. In situ cytology has a sensitivity of up to 90%, and could further allow for correct grading of the tumour.

### 5.3.3 Review of literature in field

The first publications in this topic were published in the late 1990s, and included patients treated since the mid-1980s [117, 180]. As with other NSS approaches, this treatment modality was historically reserved for imperative cases where RNU was considered contraindicated due to kidney failure, comorbidities and/or high age. However, as results started to show equivalent oncological results compared to RNU among patients with favourable tumour characteristics [181], the treatment modality gained popularity also in elective cases. Data from the NCR do not include the use of endoscopic treatment. Still, a decline in proportion of patients treated by conventional surgery was discovered indicating that endoscopic might be increasingly used in Norway the last 20 years.

The largest published series have presented a 5-year CSS of 87-93% [44, 118, 120, 121], comparable to the outcomes registered in large cohorts of patients treated with RNU [63, 90]. Studies comparing directly the outcomes of endoscopic treatment vs RNU for low-grade tumours have come to the same conclusion [182, 183]. The kidney preservation rates in larger published series have been 67-83%, and recurrence rates 55-77% [118, 121].

### 5.3.4 Tumour grade

The presented results after endoscopic treatment have been shown to be highly dependent on histological tumour grade. Grasso et al. have presented a prospective study with results regarding 160 UTUC patients treated with either endoscopic treatment or RNU followed over a 15-year period with a mean FU of 38.2 months [120]. Survival outcomes were favourable for low-grade tumours. High-grade

tumours were in that study treated with endoscopic treatment for palliative purposes, and demonstrated poor survival with a 2-year OS of only 54%. Tumour grade was at multivariate regression analysis the only significant predictor for survival. Larger patient series from Cuttress et al. and Scotland et al. have also described considerably poorer results for high-grade tumours compared to low-grade tumours [118, 121]. Different outcomes according to tumour grade seems well documented. Tumour grade is however reported differently in different studies. In the study from Cuttress et al. and Scotland et al., the grading is reported according to the old three-tiered WHO classification, while Grasso et al. have reported according to the two-tiered grading system from 2004. Results of outcomes stratified by grade according to the WHO/ISUP classification from 2004 are limited.

Given the demonstrated difference in outcomes according to tumour grade, it is important to be aware of the previously mentioned sampling error at biopsy, as there is a considerable risk that a low-grade biopsy would be upgraded to a high-grade tumour at final histopathology if a RNU is done. The reason for this upgrading is not completely understood, but is probably due to heterogeneity of the tumour and small samples at biopsy making accurate assessment of tumour grade more difficult. Discordance between tumour grade at URS biopsy and final histopathological evaluation after RNU is described in several papers. In the cohort used for paper 2 and 3 in this thesis, the upgrading from biopsy to RNU specimen was 35%. In a recent meta-analysis evaluating 2232 patients in 23 studies, the rate of upgrading in different studies varied from 0-97%, the average pooled rate was 34% (CI 23-45%) [47]. Downgrading from high grade biopsy to low-grade final specimen after RNU was very rare, described in 3% of the biopsies.

### 5.3.5 Tumour size

A population based study analysing OS in patients treated with endoscopic treatment or RNU concluded with equivalent results regarding tumours of less <10mm. If the tumour was >20mm, the OS was higher in patients treated with RNU. The smallest tumour size with equivalent outcomes was for tumours 15mm or smaller [184].

Scotland et al. treated tumours with an average size 16.8 mm. Tumour size (>10mm) was found to be a predictor of recurrence, but not survival.

### 5.3.6 Our results in context

In paper 4, we describe the results of primary endoscopic treatment of UTUC at our hospital during 2001-2012. 43 patients were included in the study. In 15 of these, RNU was considered contraindicated, while 28 had an elective indication. The results were analysed separately for these two groups. Further analyses were performed according to tumour grade. The results were acceptable and comparable to what has been reported previously for patients with an elective indication and/or with a low-grade tumour. The results for patients with high-grade tumours were poor.

Though the number of patients in the study is low, the study still has some strengths. It was prioritized to have a biopsy of the patients, and a histopathological verification was present among 40 of the 43 patients (93%). All biopsies were re-examined and graded according to the two-tiered WHO/ISUP grading system from 2004. A significant proportion (13/40, 35%) of the tumours were high-grade.

There are a limited number of patients in this study, and all results must be interpreted with caution. We still think that some conclusions can be made. Patients with low-grade tumour had markedly better DSS and OS compared to patients with high-grade tumours (96% vs 39% and 75% vs 23% respectively, both $p<0.01$). Tumour grade was the only significant predictor of DSS in multivariate analysis ($p=0.003$). The outcomes for patients with low-grade tumours are in line with previous publications and confirm that histologically verified low-grade tumours are suitable for endoscopic treatment. It further confirms that the WHO/ISUP classification from 2004 distinguishes between low- and high-grade tumours in the UUT in an adequate way that makes it suitable for selecting patients for endoscopic treatment. The literature regarding the endoscopic treatment of high-grade tumours is limited, and our results help underline that these tumours are not suited for endoscopic treatment.

A lower KPR (51%) was found in our study compared to what has been presented by others. For low-grade tumours the KPR was 60%. It is important to notice that 4 of 14 patients treated with RNU had pT0 at final histopathology. In all of these cases, URS as a part of FU revealed changes to the urothelium that was misinterpreted as urothelial cancer. It seems probable that endoscopic treatment causes changes to the urothelium that resembles UTUC, and a biopsy is recommended in cases of doubt. If these unnecessary RNUs had been avoided, the KPR among patients with low-grade disease would have been comparable to the findings of other authors. Status at first FU visit proved to be an excellent predictor of long-term results regarding KPR and recurrence. Patients deemed tumour free at first FU had a KPR of 90%. As far as we know, this feature has not been described before. The finding is promising, but the absolute number of patients is small, and the finding should be confirmed by others before firm conclusions are drawn. The recurrence free survival at 76% presented in this study was higher than what has been presented by others. We think this is due to the way recurrence was defined in our study. A recurrence was only recorded among patients tumour free at some point during FU. We would like to argue that this way to analyse recurrence is better, since the presence of tumour at first FU often is the result of a residual tumour, rather than of a true recurrence.

### 5.3.7 Impact and conclusions

The study confirms that low-grade tumours are suited for endoscopic treatment, and should be considered standard treatment if the tumour has a location and size that makes it suitable for this treatment modality. Survival results comparable to RNU and a kidney preservation rate of 70-80% can be expected. The study further confirms that high-grade tumours are not suited for endoscopic treatment, a patient group less described in previous literature. Due to the different outcomes according to tumour grade, it is important to obtain histological verification of tumour grade through biopsy and cytology. The histological tumour grade should be given according to the WHO/ISUP grading system from 2004. It is important to be aware of the risk of biopsy sampling error, as approximately 1/3 of tumours classified as low-grade at

biopsy will be upgraded to high-grade if a RNU is performed. A low-grade biopsy should be verified as far as possible with cytology and visual assessment of the tumour in the same session as the biopsy was taken. In case of recurrence, repeat biopsies should be performed to detect a previous misclassification or tumour grade progression. Status at first FU is a promising new predictor of recurrence and KPR that should be examined further. Current evidence suggests that tumours larger than 15mm might have poorer outcomes than smaller tumours, and indication in these cases should be considered closely. Ipsilateral recurrence after endoscopic treatment is frequent, and a stringent FU using both URS and radiology is necessary. The optimal FU is not yet clarified.

# 6. Strengths and limitations

**Paper 1**

Paper 1 is based on national data from Norway covering a 20-year period, analysing 3096 UTUC cases, a sufficient number of cases to make reliable conclusions about a relatively rare disease. The NCR has documented a high degree of data quality including key aspects such as completeness, comparability and validity [185]. The data material was quality assured including a thorough inclusion/exclusion process to ensure that the final database was as accurate as possible.

The study is not without limitations. One weakness of the study is that the analyses were based on registry data partly based on clinical reports made from a wide range of clinicians, with an inherent risk of coding errors. More specifically the dataset is limited by a lack of accurate data regarding tumour stage and specific data on treatment e.g. the use of endoscopic treatment. The dataset also has limitations regarding the registration of CIS, prior bladder cancer, race and the use of adjuvant treatments. These limitations reduce the ability to draw firm conclusions about the causality of our findings.

**Paper 2 and 3**

The cohorts used for paper 2 and 3 were gathered from two larger centres in Norway to allow sufficient patients to make robust analyses of staging and survival. All CT scans were re-evaluated by a uro-radiologist and all re-evaluations of histopathological specimens were performed by uro-pathologists (OJH and BC) to increase data quality as much as possible. For paper 3, a statistician (JA) aided in statistical analyses to ensure that the external validation was performed correctly.

These studies are done by retrospective analysis of the dataset, with the inherent weaknesses associated with this study design. Increasing the number of patients by

collaborating with additional centres would have increased the generalizability of our findings further.

**Paper 4**

This study is strengthened by the review of all histopathological specimens by a dedicated uropathologist (OJH). The specimens included 93% of the patients available for evaluation using both three- and two-tiered grading systems, which enabled robust analyses on outcome stratified by grade.

This study is a retrospective study, with its associated weaknesses. The study focused mostly on histological tumour grade as a predictor of outcome. It is probable that other factors contribute as well, such as tumour size, location and multiplicity, though the potential impact of these factors were not considered. The validity of the findings would have been strengthened if these factors had been considered simultaneously. The study concerns a less frequently used treatment for a quite rare disease, which explains the patient number in the study. The number of patients and follow-up time in this paper are fair compared to other publications. There is however no doubt that the study would have been strengthened by a larger number of participants.

# 7. Conclusions

- The incidence of UTUC in Norway is increasing, and is currently at higher level than has been described before outside endemic areas
- This increase affects all ages above 60 years irrespective of gender and tumour location. Survival is improving
- The reason for this increase is not completely understood, but one possible reason could be that older people are more thoroughly examined for symptoms compared to earlier
- Several factors at the CTU were shown to be predictors of pathological tumour stage (pT) and prognosis. Of these, local invasion at CTU is the most promising feature to use when selecting patients for intensified treatment
- The value of the diagnostic URS as a staging procedure for patients set for RNU is limited and can probably be omitted in most cases
- The Margulis nomogram in the preoperative prediction of NOCD is validated for clinical use
- The nomogram should still be used with caution since the variables used when generating the nomogram were gathered from final pathology after RNU, and is not automatically transferable to a truly preoperative setting
- Tumour grade assessed using the two-tiered WHO/ISUP (2004) classification is confirmed as a suitable predictor for treatment results after endoscopic treatment for UTUC
- Endoscopic treatment for high-grade tumours have poor results, and should be used only in very selected cases

# 8. Future aspects

In paper 1, we described an incidence of UTUC in Norway which was higher than expected and rapidly increasing. It is so far unclear if this increase is equally present in the rest of Europe or even globally, and further studies on the subject from other countries are needed. Using our population based cohort, we also had limited possibility to assess the causality of the described increase, and further studies are needed to explore these questions further.

Regarding the treatment of UTUC, we have seen an increased focus on individualized treatment in the last decade, where both nephron sparing treatments and intensified treatment have become increasingly common. Essential in this process is adequate clinical staging as examined and discussed in paper 2 and 3. Despite developments in staging, further studies are needed. One promising possibility is the use of the MRI where the ADC can serve as a potential biomarker for aggressive disease. Another interesting topic is the use of confocal laser tumour grade assessment during URS, as described in the introduction part of this thesis. The efficacy of perioperative chemotherapy has been demonstrated, but it is still unclear if chemotherapy is best administered as neoadjuvant or adjuvant treatment. Results from the ongoing URANUS trial (Clinical trials no NCT02969083) can hopefully elucidate this question. Further high quality studies regarding the use of LND at RNU are also highly warranted. Questions remain regarding the potential benefits of the treatment, the optimal template for dissection and optimal patient selection. Regarding nephron sparing treatment, the use of intra-cavitary gel mitomycin for the treatment of tumours of limited size in the renal pelvis is exciting. Studies evaluating follow-up regimes after radical surgery for UTUC are lacking and should be a focus for future studies.

# 9. Errata

In paper 3, supplementary table 1 should be titled as supplementary table 1 in the table heading, not as table 3.

In chapter 4. Summary of results p.46 section 3:

*We found a 5, 10 and 15-year OS of 47.7%, 32.7% and 22% respectively. The 5, 10 and 15-year CSS was 75.3%, 72.9% and 70.8% respectively. OS improved over time, comparing the last decade with the first (five-year OS 44.3% vs 51.7%, p=0.003). No differences were found in survival regarding gender or tumour location.*

It should be the same numbers as in the original paper:

We found a 5, 10 and 15-year OS of 48.3%, 33.2% and 22.5% respectively. The 5, 10 and 15-year CSS was 61.4%, 56.1% and 51.1% respectively. OS improved over time, comparing the last decade with the first (five-year OS 44.0% vs 53.2%, p=<0.001). No differences were found in survival regarding gender or tumour location.

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World Journal of Urology
https://doi.org/10.1007/s00345-020-03576-3

ORIGINAL ARTICLE

# Higher than expected and significantly increasing incidence of upper tract urothelial carcinoma. A population based study

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Received: 6 September 2020 / Accepted: 17 December 2020


## Abstract

**Purpose** To register all cases of urothelial cancer and renal cell carcinoma (RCC) in Norway during 1999–2018 to obtain the contemporary incidence of UTUC and UTUC incidence relative to other urothelial cancers and RCC. Further to analyse possible changes over time regarding UTUC incidence, UTUC patient characteristics, tumour characteristics and survival.

**Methods** 3502 cases registered with ICD code C65 and C66 during 1999–2018 at the Norwegian cancer registry were entered into a database. After a selection process 3096 cases were included in the study. The crude incidences of UTUC were calculated for each year adjusting for the corresponding population data. Age-standardized rates adjusting to the European standard population (2013) were calculated. Comparisons were made with other cases of urothelial cancer and RCC. For changes over time, the material was split into 5-year periods. Regression analysis was used to calculate yearly changes and for assessing statistical significance. Survival outcomes were calculated using the Kaplan–Meier method.

**Results** The overall age-standardized incidence rate was 3.88, increasing from 3.21 to 4.70 from first to last 5-year periods. The increase affected all ages except those < 60 years of age, and were observed regardless of gender or anatomical location. UTUC constituted 11.8% of all urothelial cancers, increasing from 9.9 to 12.8%. Mean patient age at diagnosis increased from 71.5 to 73.4 years. The 5-years Cancer-specific survival improved from 57.4 to 65.4%.

**Conclusion** The incidence of UTUC was higher than expected and increasing. Patient age at diagnosis was increasing.

**Keywords** Upper tract urothelial carcinoma · Epidemiology · Incidence · Registry data · Population based study

## Introduction

Compared to urothelial cancer of the bladder (BC), upper tract urothelial carcinoma (UTUC) is relatively uncommon. The incidence is typically referred to be 1–2:100.000 per year or 5–10% of all urothelial carcinomas. Urothelial cancer in the kidney pelvis has been referred to constitute 7% of all renal tumours. As a source of these numbers, the yearly publication from the American Cancer Society is often quoted [1]. In the yearly publication from the Norwegian national database at the Cancer Registry of Norway (NCR) all new cancer cases of UTUC are merged with cases of the much more common BC and cancer of the urethra [2]. Specific contemporary data regarding the incidence of

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00345-020-03576-3.

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Published online: 09 January 2021

UTUC and changes over time is limited. Some authors have reported an increasing incidence of UTUC [3, 4], while others have reported a stable incidence, or even a decline [5, 6]. To our knowledge, currently published papers on this topic do not include patient cohorts after 2011. Basic epidemiological knowledge is essential in the planning of diagnostic evaluations, treatment and research of a particular disease. We, therefore, decided to gather and analyse available data regarding UTUC from the NCR in Norway during 1999–2018. We formulated the following aims for the study.

### Primary objective

To register all cases of UTUC together with all other cases of urothelial cancer and renal cell carcinoma (RCC) in Norway during 1999–2018 to obtain the contemporary incidence of UTUC in Norway together with UTUC incidence relative to other urothelial cancers and RCC.

### Secondary objective

To look for and analyse possible changes over time regarding UTUC incidence, patient and tumour characteristics and survival outcomes.

## Material and method

All patients classified with the International Classification of Diseases tenth revision [7] (ICD-10) diagnosis code C65 (cancer in the kidney pelvis) and C66 (cancer in the ureter) registered during 1999–2018 were extracted from the main database at NCR. A dataset of 3502 cases was obtained. For comparison, a similar extraction was made for renal cell carcinoma (RCC, C64, $n = 14{,}500$), BC (C67, $n = 27{,}427$ and Urethral cancer (C68, $n = 440$). The database included information about patient sex, age at diagnosis, date of birth, histopathological data, clinical data (cancer report, death report including the cause of death etc.), treatment and current status (deceased or alive). The data from the NCR include nodal status and metastasis at diagnosis if present, but complete data on pathological or clinical tumour stage is not available. As a substitute, the tumours are coded as invasive (pT2 +) or non-invasive (pTa/T1). This classification is available for pure urothelial carcinomas only (see Table 1). The inclusion/exclusion process is illustrated in supplementary Fig. 1. In the case of diagnostic uncertainty, the cases were examined manually together with NCR personnel to clarify the basis of the diagnosis code and consider if the cases could be included or not. Of 1026 uncertain UTUC cases, 305 were excluded, typically where the diagnosis code was based on atypical cells by cytology or biopsy, when the tumour was coded wrong and was benign (i.e. benign papilloma) or when there was doubt whether the cells were benign or malignant. In 29 cases, the diagnosis code was based on very sparse information, i.e. only a death report or a clinical report based on autopsy or clinical examination, and these were excluded. In addition, 72 cases of pure non-urothelial cancers (i.e. squamous cell carcinoma or adenocarcinoma) were excluded. All cases of pure urothelial carcinoma and cases of urothelial carcinoma with divergent differentiation were included. A comprehensive list of included and excluded cases is shown in Table 1. In all, 3096 cases in 2818 patients were included in the final analysis. More than one case of UTUC on the same patient was uncommon and only registered if data suggested a truly new tumour, i.e. considerable time between cases or a new tumour on the opposite side. All analyses were performed according to number of cases, not number of patients. Of all 3096 cases, 2969 (95.9%) were verified with histopathological examination of a surgical specimen ($n = 2327$, 75.2%), biopsy ($n = 576$, 18.6%) or cytology ($n = 66$, 2.1%). In the remaining 127 (4.1%), the basis was a clinical report using radiological examination, endoscopic procedure or radiation therapy data as sources for the diagnosis codes. Similar inclusion and exclusion

**Table 1** Description of included and excluded cases in the study

| Tumour characteristics | *n* | %[a] |
|---|---|---|
| All cases | 3502 | 100 |
| Included | 3096 | 88.4 |
| Pure urothelial carcinoma | 2856 | 81.6 |
| Urothelial carcinoma with divergent differentiation | 45 | 1.3 |
| Carcinoma in situ | 68 | 1.9 |
| No histopathological verification | 127 | 3.6 |
| Excluded | 406 | 11.6 |
| Other malignant tumour | 72 | 2.1 |
| Squamous cell carcinoma | 27 | 0.8 |
| Adenocarcinoma | 26 | 0.7 |
| Sarcoma | 9 | 0.3 |
| Lymphoma | 5 | 0.1 |
| Neuroendocrine tumour | 4 | 0.1 |
| Other | 1 | < 0.1 |
| Benign tumour/uncertain | 305 | 8.8 |
| Urothelial Atypia/dysplasia etc | 288 | 8.2 |
| Benign tumour | 17 | 0.5 |
| Limited data available | 29 | 0.8 |
| Death certificate only | 11 | 0.3 |
| Autopsy only | 8 | 0.2 |
| Clinical examination only | 10 | 0.3 |

[a]Percentages given as % of both included and excluded cases and might differ from % in manuscript

processes were performed regarding BC, urethral cancer and RCC resulting in 24,467 included cases of BC, 13,619 with RCC and 287 with urethral cancer.

For incidence rates, crude rates were calculated using population data in Norway corresponding to each year from 1999 to 2018. To adjust for demographic differences between the Norwegian and other populations, age-standardized rates (ASR) according to the European standard population published in 2013 were calculated [8]. ASRs adjusted to other available standard populations were also calculated for comparison (see supplementary Table 1 and 2).

### Statistical analysis

For the purpose of analysing changes over time, the material was split into 5-year periods (1999–2003, 2004–2008, 2009–2013 and 2014–2018). The relative proportion of UTUC cases compared to all urothelial cancer cases and pelvic urothelial tumour cases compared to RCC cases were calculated for each 5-year periods. Analyses regarding potential changes in patient age, gender distribution, location of the tumour and tumour features were performed in the same manner. For further analyses of changes over time, the estimated average percentage changes (EAPC) for incidence rates were calculated and linear regression analyses were used to calculate yearly changes and for assessing statistical significance. Survival analyses included both overall survival (OS) and cancer-specific survival (CSS) and were performed using the Kaplan–Meier method. Categorical data were analysed using the Chi-square method. Data were analysed using IBM® SPSS® Statistics v. 26. *P* values less than 0.05 were considered statistically significant.

## Results

The developments in crude rates and ASRs of UTUC during the study period are illustrated in Fig. 1. Specific ASR regarding UTUC in the kidney pelvis and the ureter are also included in the figure. The crude incidence of UTUC in the whole time period was 3.17:100.000, increasing from 2.54 to 3.98 from the first to last 5 year periods. The estimated annual increase was 0.09 (CI 0.07–0.12), $p < 0.001$) resulting in an EAPC of 3%. The ASR adjusted to the European standard population was 3.88 for the whole period, increasing from 3.21 to 4.70. The increase per year was 0.10 (CI 0.06–0.13, $p < 0.001$) with an EAPC of 2.5%. The ASR of UTUC in the kidney pelvis increased from 1.77 to 2.88 from first period to last, $p < 0.001$. For ureteral tumours the increase was from 1.44 to 1.82 during the same period, $p < 0.001$. The proportion of tumours in the renal pelvis compared to all UTUC increased non-significantly from

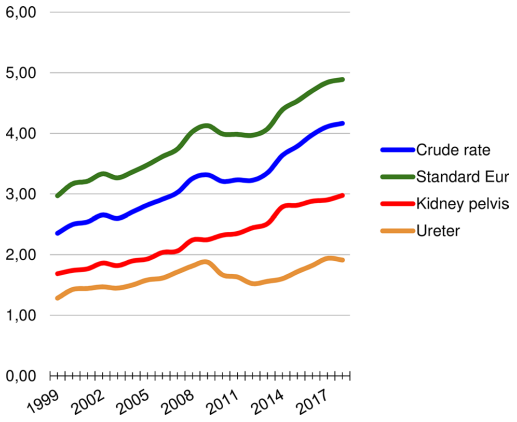


**Fig. 1** Demonstrates the 5-years average UTUC incidence per 100.000 and changes over time. Illustrates the crude rates (blue) and the age-standardized incidence rates adjusted to the European standard population, 2013 version, green). Includes the incidence rates of UTUC in the kidney pelvis (red) and the ureter (orange)

55.6 to 61.2%, $p = 0.06$. The ASRs adjusted to other standard populations are presented in Supplementary Table 1 and 2.

Analyses showed that UTUC incidence increased in all age-spans above 60 years age, see supplementary Fig. 2. There was no increase over time in new yearly UTUC cases among patients under the age of 60, but comparing first 5-year periods with the last the increase was apparent and significant for each decade from 60 to 69 years (131–254 cases, 94% increase) 70–79 years (243–399 cases, 64% increase) and 80 + years (121–303 cases, 150% increase), all $p < 0.001$.

Patient demographics, tumour features and developments over time are shown in Table 2. The table also includes comparisons between UTUC and other urothelial cancers and RCC.

Mean (median, IQR) age of all UTUC patients during the whole period was 72.8 (73.8, 65.8–79.8) years. Patient mean age at diagnosis increased from 71.8 to 73.9 from the first to last 5 year periods, $p < 0.001$. No gender-specific changes over time were observed.

No statistically significant stage migration over time was observed. The proportion of invasive tumours decreased non-significantly from 50.0 to 41.7% compared to non-invasive tumours ($p = 0.07$). Invasive tumours were equally frequent irrespective of gender or age. Similarly, analyses were performed regarding regional node or distant metastases, but no differences over time were observed for the entire cohort or stratified by age or gender. The proportion of cases where invasiveness was not assessable increased over time, corresponding to an increase in cases verified by biopsy only, and a decrease in radical surgery.

**Table 2** Changes over time regarding patient demographics, tumour features and new cases of upper tract urothelial carcinoma compared to other urothelial cancers and renal cell carcinoma

| Variable | All | 1999–2003 | 2004–2008 | 2009–2013 | 2014–2018 | %[a] | $p^b$ |
|---|---|---|---|---|---|---|---|
| Mean age (years) | 72.8 | 71.8 | 72.0 | 72.6 | 73.9 | | < 0.001 |
| Gender % | | | | | | | |
| Female | 37 | 41.1 | 32.3 | 39.3 | 36.1 | | 0.3 |
| Male | 63 | 58.9 | 67.7 | 60.7 | 63.9 | | |
| Location | | | | | | | |
| Kidney pelvis | 58.5 | 55.6 | 56.1 | 59.1 | 61.2 | | 0.06 |
| Ureter | 41.5 | 44.4 | 43.9 | 40.9 | 38.8 | | |
| Tumour stage % | | | | | | | |
| Invasive (T2–T4) | 46.9 | 50.0 | 47.7 | 50.7 | 41.7 | | 0.07[c] |
| Non-invasive (Ta–T1) | 41.4 | 42.5 | 42.7 | 39.1 | 41.8 | | |
| Invasiveness not assessable (Tx) | 11.7 | 7.5 | 9.5 | 10.1 | 16.5 | | < 0.001 |
| Regional node metastases | 5.2 | 4.7 | 5.4 | 6.6 | 4.2 | | 0.9 |
| Distant metastases | 9.6 | 9.9 | 10.4 | 9.8 | 8.8 | | 0.5 |
| Upper tract urothelial carcinoma (*n*) | 3096 | 574 | 681 | 800 | 1041 | 81 | < 0.001 |
| Bladder cancer | 24,467 | 5251 | 5910 | 6181 | 7125 | 36 | < 0.001 |
| Urethral cancer | 287 | 61 | 74 | 54 | 98 | 61 | 0.2 |
| Total Urothelial cancer | 27,850 | 5886 | 6665 | 7035 | 8264 | 40 | < 0.001 |
| % Upper tract urothelial carcinoma | 11.1 | 9.8 | 10.2 | 11.4 | 12.6 | 29 | < 0.001 |
| Renal tumours (*n*) | | | | | | | |
| Urothelial carcinoma kidney pelvis | 1811 | 319 | 382 | 473 | 637 | 100 | < 0.001 |
| Renal cell carcinoma | 13,619 | 2501 | 3103 | 3711 | 4304 | 72 | < 0.001 |
| Total | 15,430 | 2820 | 3485 | 4184 | 4941 | 75 | < 0.001 |
| %Upper tract urothelial carcinoma | 11.7 | 11.3 | 11.0 | 11.3 | 12.9 | 14 | 0.04 |

[a]Increase in percent from first to last 5-year periods

[b]*p* values based on regression analyses assessing yearly changes

[c]Chi-square comparing invasive with non-invasive

During the whole study period, 75.2% of the patients were treated with radical surgery. The absolute number of patients treated with radical surgery increased by 55.5% during the study period, but since number of cases increased by 81.4%, there was a net decline in the *proportion* of patients treated with radical surgery over time from 82.6 to 70.8% ($p < 0.001$). The proportion of patients with a biopsy verified diagnosis without following radical surgery increased correspondingly from 10.8 to 23.7% in the same period.

Regarding the oldest patients (> 80 years of age) fewer patients (59.3%) were treated with radical surgery, decreasing from 64.5 to 55.6% in the study period. More of these patients were diagnosed with biopsy without following radical treatment, increasing from 18.2 to 31.2% in the study period. Among these oldest patients, it was also more common that the diagnosis was not verified with a histopathological specimen, (16.0% vs 2.8% for patients < 80 years age), stable during the study period.

The 5, 10 and 15-years OS were 48.3%, 33.2% and 22.5%, respectively. The 5, 10 and 15-years CSS were 61.4%, 56.1% and 51.1%, respectively (Fig. 2). All the following survival data are given as 5-years CSS. Patients treated with radical surgery had significantly higher survival compared to patients not treated with radical surgery (67.2% vs 41.6%, $p < 0.001$), respectively. The patients with non-invasive

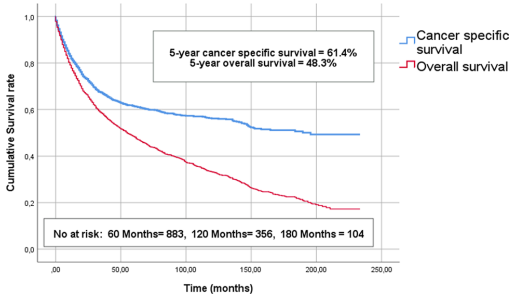


**Fig. 2** Shows the estimated overall- and cancer-specific survival curves of the entire cohort using the Kaplan–Meier method. The 5, 10 and 15-years OS were 48.3%, 33.2% and 22.5%, respectively. The 5, 10 and 15-years CSS were 61.4%, 56.1% and 51.1%, respectively

tumours had higher survival compared to patients with invasive UTUC (79.4% vs 49.8%, $p < 0.001$). Survival deteriorated with increasing age, patients < 70 years 68.1%, 70–80 age 63.5% and > 80 years of age 46.7%, respectively, $p < 0.001$. No differences in survival stratified by gender or tumour location were detected.

Both OS and CSS improved over time, comparing the last decade with the first (5-year OS 44.0% vs 53.2%, $p \leq 0.001$ and 5-year CSS 57.4% vs 65.4%, $p \leq 0.001$), respectively. This improvement over time was present for all sub-groups irrespective of age, gender, type of treatment and tumour location.

## Discussion

If the commonly quoted incidence rate of 1–2:100.000 from the American Cancer society serves as a reference, the ASR of 4.7:100.000 in the present study was higher than expected, and to our knowledge the highest incidence rate published based on a population outside endemic areas. There was an estimated annual percentage change in the incidence rate of 2.5%, corresponding to an 81% increase in new cases comparing first with last 5-year periods.

The reason for the demonstrated increase is not clear. One possible explanation could be that symptoms i.e. haematuria are more vigorously examined in older patients now than before. An improved access to high-quality computed tomography and better equipment for flexible ureteroscopy could add to this effect. This could lead to a higher detection rate of UTUC and increased age at diagnosis. Indeed, we have seen a considerable increase in biopsy verified cases without following radical surgeries. This increase is even more evident among patients > 80 years of age, the same age group that showed the greatest increase in new yearly cases. These data indicate that at least some of the demonstrated increase in incidence could be due to increased diagnostics, especially among the oldest patients.

The decrease in radical treatments could be caused by an increased use of endoscopic treatment. Unfortunately, the data from the NCR does not include data on endoscopic treatment. However, an increasing number of publications with relatively larger cohorts on the use of endoscopic treatment could indicate an increased use of this treatment modality [9, 10]. Another reason could be that observation was chosen over radical surgery due to high age, poor performance status or favourable tumour characteristics. Data on performance status are not available in the present dataset, but a considerable and increasing proportion of patients were at a high age where larger surgeries might not be recommended.

In spite of these possible reasons for the described increase, it seems likely that there is a true increase in UTUC in Norway for the last 20 years, and not just an increased detection rate. The known risk factors for UTUC include smoking [11, 12], excessive alcohol consumption and exposure to aristolochic acid [13]. The dataset obtained from the NCR does not contain information about smoking, alcohol use or exposure to possible carcinogens. An evaluation about the potential effect of changing exposure to known risk factors is for this reason not possible without obtaining further data and was beyond the scope of this paper. Further studies to clarify the reasons for the described increase are needed.

In the present cohort, we found an all-cohort 5-years CSS and OS of 61.4% and 48.3%, respectively. Other population-based publications on UTUC which include survival data have demonstrated similar survival outcomes. Raman et al. presented a 5-years OS of ~ 50% in their cohort [3], while Eylert et al. reported a falling 5-years relative survival rate from 60 to 48% during their study period [14]. Woodford et al. reported a 5-years overall survival rate of 32% [5]. Compared to these more historic cohorts, the present study demonstrated comparable or favourable survival outcomes. A moderate improvement in survival over time was observed. The reason for this improvement is unclear. Increased use of adjuvant therapies for UTUC including both perioperative chemotherapy [15, 16] and the introduction of immunotherapies [17] could possibly explain some of the demonstrated improved survival in the present cohort. Unfortunately, the data at NCR is very limited regarding the use of adjuvant treatment, and no firm conclusions can be drawn.

As UTUC is a potentially lethal disease if left untreated, one would expect that earlier detection and treatment could result in improved survival. In the present cohort, we found an increased use of biopsies without following radical treatment. As stated earlier, the present data set is not complete regarding tumour stage, but a non-significant decline in the proportion of invasive tumours was observed. It is possible that more cases are detected at an earlier stage presently compared to previously, resulting in improved survival.

Our findings could have several possible implications. One implication could be an increased focus on UTUC, simply because more patients than expected would be affected by the disease. Another implication could be enrolment into studies. There are many unanswered questions regarding the diagnostic work-up and treatment of UTUC, such as the optimal use of perioperative chemotherapy or the use of lymph node dissection at the time of RNU. A higher incidence would result in quicker enrolment into much needed studies on the topic, and make studies with adequate patient numbers more feasible to conduct.

## Strengths and weaknesses

The present publication is based on national data from Norway, analysing 3096 UTUC cases during 20 years, a sufficient number of cases to make reliable conclusions about a relatively rare disease. The NCR is nationwide and has since 1953 kept a complete registry of all new cases of malignant neoplasms. It has documented a high degree of data quality including key aspects such as completeness, comparability and validity [18]. The data material was quality assured, based on clinical and pathology reports, and statistical advice was sought to make sure the methods used for incidence measurements, population adjustment and changes over time were performed in the correct way.

This study is not without limitations. One weakness of the study is that the analyses were based on registry data partly based on clinical reports made from a wide range of clinicians, with an inherent risk of coding errors. More specifically the dataset is limited by a lack of accurate data regarding tumour stage and specific data on treatment i.e. the use of endoscopic treatment. The data also has limitations regarding the registration of CIS, prior bladder cancer, race and the use of adjuvant treatments. As the present study is a population-based registry study with the described limitations, the ability to draw firm conclusions about the causality concerning our findings is limited. Further studies to explore further possible reasons for the increased incidence, changing demographics and improved survival are warranted.

## Conclusion

The incidence of UTUC was higher than previously reported, and increasing. UTUC incidence in Norway during 2014–2018 was 4.7:100.000. UTUC currently constitutes close to 13% of all urothelial cancers, and urothelial cancers of the renal pelvis currently constitute close to 13% of all malignant renal tumours. The increase was not accompanied by stage migration, but survival moderately improved. The patients are older at the time of diagnosis currently compared to earlier, but no other changes in patient demographics were detected.

**Author contributions** BA: protocol/project development, data collection or management, data analysis, manuscript writing/editing. OJH: protocol/project development, manuscript writing/editing. TBJ: protocol/project development, data collection or management, data analysis, manuscript writing/editing. CB: protocol/project development, data analysis, manuscript writing/editing.

**Funding** Open Access funding provided by University of Bergen (incl Haukeland University Hospital).

**Data availability** The data material used for the study can be inquired from the corresponding author if necessary.

**Code availability** Only simple coding and common statistics software was used.

## Compliance with ethical standards

**Conflict of interest** No conflict of interest or disclosures from any of the authors.

**Ethics approval** Scientific work done at the Norwegian Cancer Registry using data from their database is exempt from the general rule of informed consent of participants, and ethical approval from the regional ethics committee for scientific research in Norway.

**Consent to participate** Not applicable.

**Consent for publication** Not applicable.



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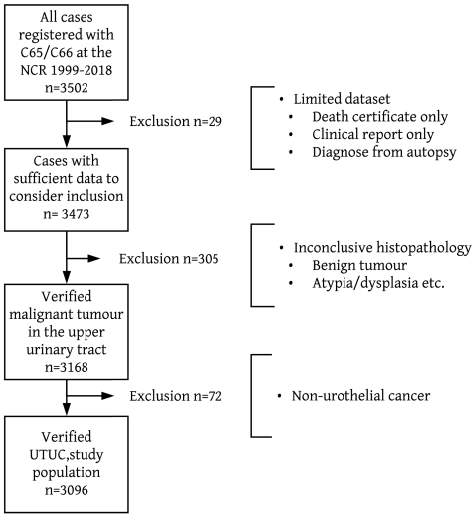
Supplementary table 1. Table showing different standard populations that can be used for calculation of age standardized incidence rates. Note the different weights especially at high ages. This causes the relatively large differences in age standardized incidence rates demonstrated in supplementary table 2.

| Age | European standard 2013 | European standard 1976 | Ameri can standard 2000 | World standard 1966 | Nordic standard 2000 |
|---|---|---|---|---|---|
| 00-04 | 0,05 | 0,08 | 0,069135 | 0,120 | 0,059 |
| 05-09 | 0,055 | 0,07 | 0,072533 | 0,100 | 0,066 |
| 10-14 | 0,055 | 0,07 | 0,073032 | 0,090 | 0,062 |
| 15-19 | 0,055 | 0,07 | 0,072169 | 0,090 | 0,058 |
| 20-24 | 0,06 | 0,07 | 0,066478 | 0,080 | 0,061 |
| 25-29 | 0,06 | 0,07 | 0,064529 | 0,080 | 0,068 |
| 30-34 | 0,065 | 0,07 | 0,071044 | 0,060 | 0,073 |
| 35-39 | 0,07 | 0,07 | 0,080762 | 0,060 | 0,073 |
| 40-44 | 0,07 | 0,07 | 0,081851 | 0,060 | 0,07 |
| 45-49 | 0,07 | 0,07 | 0,072118 | 0,060 | 0,069 |
| 50-54 | 0,07 | 0,07 | 0,062716 | 0,050 | 0,074 |
| 55-59 | 0,065 | 0,06 | 0,048454 | 0,040 | 0,061 |
| 60-64 | 0,06 | 0,05 | 0,038793 | 0,040 | 0,048 |
| 65-69 | 0,055 | 0,04 | 0,034264 | 0,030 | 0,041 |
| 70-74 | 0,05 | 0,03 | 0,031773 | 0,020 | 0,039 |
| 75-79 | 0,04 | 0,02 | 0,026999 | 0,010 | 0,035 |
| 80-84 | 0,025 | 0,01 | 0,017842 | 0,005 | 0,024 |
| 85+ | 0,025 | 0,01 | 0,015508 | 0,005 | 0,019 |
| | 1 | 1 | 1 | 1 | 1 |

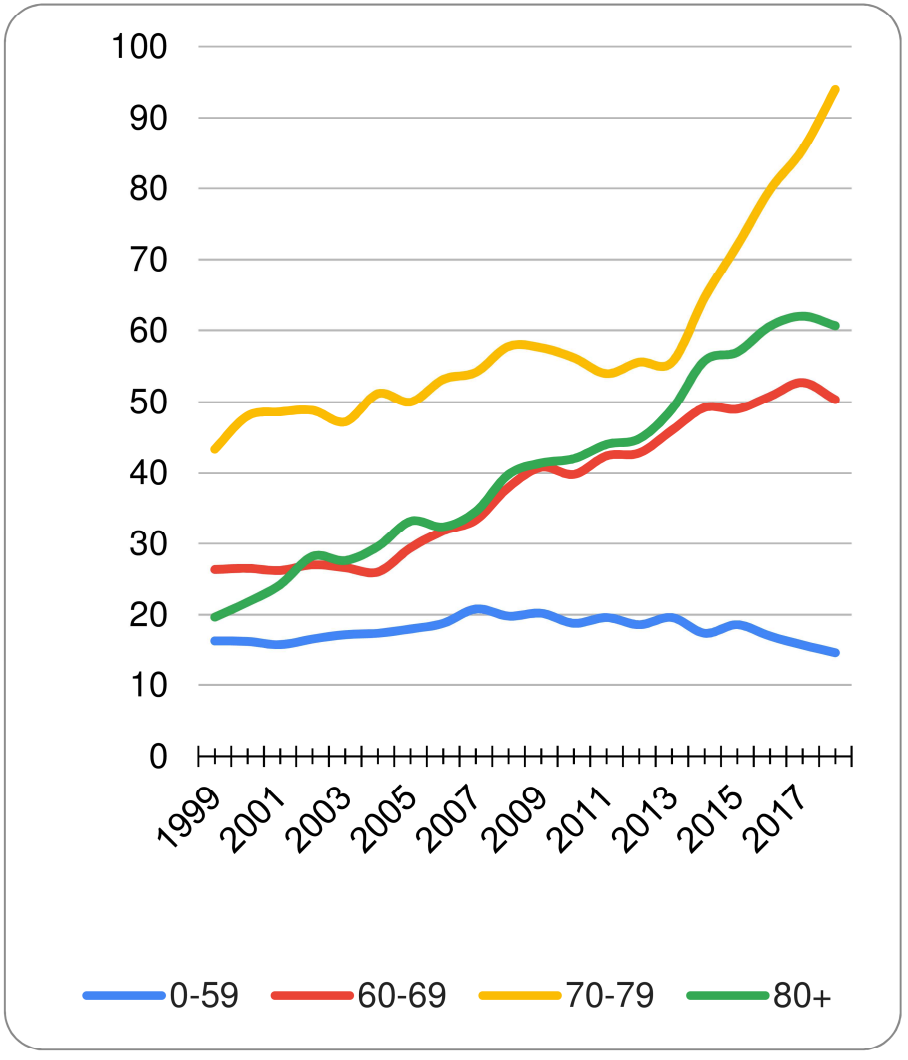
Supplementary table 2. Yearly, 5-yearly and study period crude UTUC incidence rates and age standardized incidence rates adjusted for different standard populations. Due to the different distributions of different age-spans shown in supplementary table 1, the adjusted incidence rates vary greatly.

| Year | Crude rate | European standard 2013 | European standard 1976 | American standard 2000 | World standard 1966 | Nordic standard 2000 |
|---|---|---|---|---|---|---|
| **1999** | 2,35 | 3,00 | 1,93 | 2,01 | 1,30 | 2,50 |
| **2000** | 2,47 | 3,08 | 1,94 | 2,10 | 1,30 | 2,60 |
| **2001** | 2,24 | 2,83 | 1,88 | 1,94 | 1,28 | 2,38 |
| **2002** | 2,93 | 3,76 | 2,31 | 2,51 | 1,51 | 3,12 |
| **2003** | 2,72 | 3,39 | 2,05 | 2,28 | 1,32 | 2,87 |
| **2004** | 2,92 | 3,61 | 2,22 | 2,43 | 1,47 | 3,03 |
| **2005** | 2,18 | 2,74 | 1,74 | 1,87 | 1,15 | 2,31 |
| **2006** | 2,77 | 3,32 | 2,04 | 2,40 | 1,40 | 2,89 |
| **2007** | 3,50 | 4,34 | 2,64 | 2,92 | 1,72 | 3,64 |
| **2008** | 3,19 | 4,07 | 2,51 | 2,76 | 1,65 | 3,44 |
| **2009** | 3,48 | 4,23 | 2,61 | 2,87 | 1,70 | 3,59 |
| **2010** | 3,33 | 4,17 | 2,47 | 2,79 | 1,59 | 3,49 |
| **2011** | 3,07 | 3,82 | 2,37 | 2,61 | 1,55 | 3,25 |
| **2012** | 2,97 | 3,66 | 2,13 | 2,42 | 1,36 | 3,05 |
| **2013** | 3,31 | 4,04 | 2,47 | 2,75 | 1,62 | 3,43 |
| **2014** | 3,45 | 4,16 | 2,47 | 2,83 | 1,60 | 3,53 |
| **2015** | 3,95 | 4,70 | 2,75 | 3,17 | 1,77 | 3,99 |
| **2016** | 4,51 | 5,39 | 3,06 | 3,59 | 1,93 | 4,52 |
| **2017** | 3,73 | 4,38 | 2,53 | 2,93 | 1,59 | 3,68 |
| **2018** | 4,25 | 4,89 | 2,85 | 3,25 | 1,82 | 4,08 |
| | | | | | | |
| **1999-2003** | 2,54 | 3,21 | 2,02 | 2,17 | 1,34 | 2,69 |
| **2004-2008** | 2,91 | 3,62 | 2,23 | 2,48 | 1,48 | 3,06 |
| **2009-2013** | 3,23 | 3,98 | 2,41 | 2,69 | 1,56 | 3,36 |
| **2014-2018** | 3,98 | 4,70 | 2,73 | 3,15 | 1,74 | 3,96 |
| **1999-2018** | **3,17** | **3,88** | **2,35** | **2,62** | **1,53** | **3,27** |




Paper I - Suppl. figure 1

Paper I - Suppl. figure 2



SCANDINAVIAN JOURNAL OF UROLOGY
2021, VOL. 55, NO. 2, 100–107
https://doi.org/10.1080/21681805.2021.1877343

ARTICLE

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# Preoperative predictors of pathological tumour stage and prognosis may be used when selecting candidates for intensified treatment in upper tract urothelial carcinoma

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**ABSTRACT**

**Purpose:** Intensified treatment such as extended lymph node dissection (LND) and/or perioperative chemotherapy in addition to radical nephroureterectomy (RNU) has been suggested for high-risk cases of upper tract urothelial carcinoma (UTUC). We aimed to identify preoperative predictors of tumour stage and prognosis in the diagnostic work-up before RNU. Further to evaluate if our findings could be used in selecting patients for intensified treatment.

**Patients and methods:** A total of 179 patients treated with RNU for UTUC at Haukeland University Hospital (HUS) and Vestfold Hospital Trust (VHT) during 2005–2017 were included in this retrospective study. All relevant preoperative variables regarding the patient, the CT and the ureteroscopy (URS) were registered and analysed regarding their ability to predict non-organ confined disease (NOCD, pT3+ and/or N+) at final pathology after RNU. The prognosis was assessed calculating survival for the cohort and stratified by preoperative variables.

**Results:** Local invasion and pathological lymph nodes at CT predicted NOCD in uni and multivariate regression analyses (OR 3.36, $p$=.004 and OR 6.21, $p$=.03, respectively). Reactive oedema surrounding the tumour (OR 2.55, $p$=.02), tumour size (4.8 *vs.* 3.9 cm, $p$=.006) and high-grade tumour at URS biopsy (OR 3.59, $p$=.04) predicted NOCD at univariate regression analyses. The 5-year CSS and OS for the entire cohort was 79% and 60%. ECOG, local invasion, pathological lymph nodes and reactive oedema surrounding the tumour at CT predicted CSS.

**Conclusions:** Several variables at the CT predicted both stage and survival. Local invasion at CT seems the most promising feature for selecting patients for intensified treatment.

**ARTICLE HISTORY**
Received 7 September 2020
Revised 4 January 2021
Accepted 12 January 2021

**KEYWORDS**
Upper tract urothelial carcinoma; diagnostic work-up; urothelial carcinoma; intensified treatment; ureteroscopy; computed tomography

## Introduction

Urothelial carcinoma in the upper urinary tract (UTUC) is referred to constitute 5–10% of all urothelial carcinomas [1]. UTUC is an aggressive disease and at diagnosis about 40% of the tumours are non-organ confined. The 5-year cancer-specific survival (CSS) in these cases is below 50% [2,3]. The standard treatment of invasive UTUC is a radical nephroureterectomy (RNU) with complete excision of the ipsilateral bladder cuff. Due to the high mortality of the disease, intensified treatment including chemotherapy as neo-adjuvant or adjuvant treatment or extended lymph node dissection (LND) have been suggested for high-risk patients [4–7]. Due to the lack of accurate staging tools of the disease preoperatively, it can be challenging to identify the right indication for intensified treatment. Current EAU-guidelines recommend computed tomography (CT) urography as standard in diagnosis and preoperative staging of UTUC. A ureteroscopy (URS) is recommended if imaging and cytology are not sufficient for the diagnosis and/or risk-stratification of the tumour [8].

The aim of this study was to analyse available preoperative factors regarding their ability to predict histopathological tumour stage and subsequent prognosis after RNU for UTUC in a contemporary cohort in Norway. We further sought to evaluate if our findings could be used in the selection of patients for intensified treatment.

## Material and method

### *Patient selection*

After obtaining approval from the Regional ethics committee (reference no. 2017/854), the medical records of 209 patients treated with a RNU between 2005 and 2017 for suspected

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UTUC at Haukeland University Hospital (HUS, $n = 130$) and the Vestfold Hospital Trust (VHT, $n = 79$), were retrospectively examined. A total of 30 patients were excluded due to concomitant bladder cancer with cystectomy in the same procedure as RNU ($n = 9$), non-urothelial cancer ($n = 15$, most of them renal cell carcinoma) or no malignancy detected at the final histopathological specimen after RNU ($n = 6$), leaving 179 patients for inclusion in the study.

### *Diagnostic work-up, treatment and follow-up*

Standard preoperative assessment was a CT scan with contrast unless contraindicated. If there was doubt about the diagnosis or the patient was a potential candidate for kidney sparing treatment, a URS was performed. Endoscopic treatment or segmental ureter resection was considered among patients with low-stage UTUC of limited size clinically. The indication for RNU was a high-grade or invasive UTUC unless contraindicated due to comorbidity and/or high age. The RNU was performed as an open or laparoscopic procedure with complete excision of the bladder cuff. Chemotherapy was not standard treatment and neo-adjuvant chemotherapy was given to only one patient prior to RNU. LND was performed at the discretion of the surgeon. Follow-up included cystoscopy every three months for the first two years. A CT scan was commonly performed after 12 months or whenever the patient presented with symptoms suggestive of metastatic disease. Later follow-up was individualized.

### *Patient factors*

Patient age, sex, comorbidities, kidney function, presenting symptoms and smoking status were registered together with the presence of prior bladder cancer or prior endoscopic treatment for UTUC.

### *Radiological analysis*

A total of 176 (98%) of the patients were examined with a CT scan, 159 (90%) of these with a contrast-enhanced CT, 17 patients were examined with a CT without contrast due to kidney failure. One patient was examined with magnetic resonance imaging only, one with a conventional intravenous urography only and one lacked preoperative radiological examination of the upper urinary tract. All CT scans were re-evaluated by a uro-radiologist (LAR) together with a urologist (BA) and assessed regarding tumour size, location, contrast enhancement, the presence of hydronephrosis, pathological lymph nodes, reactive oedema surrounding the tumour and local invasion into renal parenchyma, the renal pelvis or perirureteric tissue. Each variable was considered by the radiologist in each patient to assess if a reliable measurement could be made in that particular case. If for example reliable measurements regarding tumour size and/or contrast enhancement could not be made in one particular case, the variable was recorded as missing in the dataset. This results in a different number of patients available for analysis for each variable, as demonstrated in Table 3.

### *Ureteroscopy with biopsy and cytology evaluation*

A total of 95 (53%) patients were examined with a preoperative URS with biopsy before RNU. A total of 60 patients were examined with a preoperative urinary cytology and 43 of these had cytology taken during URS. The ability of the biopsy to confirm UTUC diagnosis was registered together with information about biopsy tumour grade and stage.

### *Histopathological examination*

Data regarding tumour location, stage and grade were gathered from the pathology reports at the respective institutions. Tumours were graded according to the two-tiered WHO 2004 classification [9] and staged according to TNM 2017 classification [10]. All specimens originally not concurring with these two classifications were re-examined and reclassified by uropathologists (OJH and BC).

### *Statistical analysis; prediction of prognosis and tumour stage*

Continuous and categorical variables were analysed using a Student's t-test and a chi-square test, respectively. Survival estimates were calculated using the Kaplan–Meier method, and a log-rank test was used to compare groups. The estimated 5- and 10 year overall survival (OS) and cancer (UTUC) specific survival (CSS) were calculated for the entire cohort. Furthermore, multivariate cox regression analyses including both patient features and final histopathology were performed to evaluate independent predictors of all-cause and cancer-specific mortality. The purpose of these analyses was to evaluate if survival and prognostic factors in the present cohort were similar to other larger published patient series on operated UTUC patients.

Univariate prediction of prognosis according to pure preoperative variables was then assessed by Kaplan–Meier estimates. Recurrence and metastasis after RNU for UTUC will in most cases result in death from UTUC, thus 5-year CSS was chosen as the primary outcome parameter. For prediction of tumour stage at final histopathological examination after RNU, all candidate variables regarding patient features, CT and ureteroscopic findings were analysed using univariate and multivariate logistic regression analysis to assess their abilities to predict non-organ confined disease (NOCD). NOCD was defined as pT3 or more (invasion into the renal parenchyma, renal pelvis or periureteral tissue) and/or N+ (lymph node positive) at final pathology.

Both the cox and logistic multivariate regression analyses were performed in a backward manner. To pre-select included candidate variables a cut off of $p < .2$ in univariate analyses were chosen. For all analyses, a $p$ value less than .05 were considered statistically significant. All analyses were performed by use of SPSS version 26.0 (IBM, Armonk, NY).

## Results

The patient demographics and tumour characteristics are presented in Table 1.

Table 1. Patient and tumour characteristics.

| | | Percentage of total |
|---|---|---|
| Age years mean (median) | 72 (73) | |
| Gender | No. | |
| Male | 120 | 67 |
| Female | 59 | 33 |
| Symptoms | | |
| None | 47 | 26 |
| Local | 132 | 74 |
| ECOG[a] | | |
| 0 | 93 | 52 |
| 1 | 72 | 40 |
| 2+ | 14 | 8 |
| Smoking status | | |
| Current smoker | 63 | 35 |
| Previous smoker | 48 | 27 |
| Never smoked | 68 | 38 |
| Previous bladder cancer | | |
| Yes | 41 | 23 |
| No | 138 | 77 |
| Previous endoscopic treatment | | |
| Yes | 20 | 11 |
| No | 159 | 89 |
| Tumour primary location | | |
| Renal pelvis | 115 | 64 |
| Ureter | 64 | 36 |
| Tumour grade[b] | | |
| Low | 48 | 27 |
| High | 129 | 72 |
| Missing | 2 | 1 |
| Non-organ confined disease[c] | | |
| Yes | 68 | 38 |
| No | 111 | 62 |

[a]Eastern Cooperative oncology group.
[b]tumour grade according to WHO/ISUP classification 2004.
[c]pT3 or more and/or N + disease at final pathology after nephroureterectomy.

Table 2. Univariate odds ratios for non-organ confined disease according to patient risk variable.

| Variable | OR[b] | 95 % CI[a] | *p* Value |
|---|---|---|---|
| Age | 0.99 | 0.96–1.02 | .5 |
| Female *vs.* male | 1.07 | 0.56–2.02 | .8 |
| Symptoms | | | |
| Local *vs.* none | 1.26 | 0.63–2.53 | .5 |
| ECOG[c] | | | |
| 1 or more *vs.* 0 | 1.03 | 0.56–1.89 | .9 |
| Smoking status | | | |
| Never smoking *vs.* history of smoking | 1.68 | 0.90–3.11 | .1 |
| Previous bladder cancer | 0.93 | 0.45–1.90 | .8 |
| Previous endoscopic treatment | 0.51 | 0.18–1.47 | .2 |
| Tumour location | | | |
| Ureter *vs.* kidney pelvis | 0.71 | 0.37–1.34 | .3 |

No patient variable was shown to predict non-organ confined disease at final pathology after RNU.
[a]Confidence interval.
[b]Odds ratios.
[c]Eastern cooperative oncology group.

## Prediction of survival

The 5- and 10 year CSS of the whole cohort was 79% and 75%, respectively. The 5- and 10-year OS was 60% and 35%, respectively. Patients with OCD had a higher CSS (93% *vs.* 55%, $p<.001$) and OS (71% *vs.* 42%, $p<.001$) compared to patients with NOCD (Supplementary Figures 1 and 2). Mean (median) follow-up time in patients alive without recurrence was 58 (47) months. In a multivariate cox regression analysis, pathological tumour stage and ECOG were significant predictors of all-cause mortality. Pathological tumour stage predicted UTUC specific mortality (Supplementary Tables 1 and 2).

The presence of local invasion (64% *vs.* 86%, $p=0.002$), pathological lymph nodes (41% *vs.* 83%, $p<.001$) and fatty tissue reaction surrounding the tumour (58% *vs.* 84%, $p=.001$) at CT predicted CSS in the present material. Regarding patient factors, ECOG 0 predicted improved CSS compared to ECOG $\geq$ 1 (85% *vs.* 70%, $p=.03$). No other features regarding the patient, radiological examinations or ureterrenoscopic variables predicted CSS in this study.

## Prediction of tumour stage

### Patient features

The results of the univariate regression analyses regarding patient factors ability to predict NOCD are shown in Table 2. No patient factors were shown to be predictors of NOCD at final pathology in this study.

### Radiological variables

The results of the univariate regression analyses regarding CT variables are shown in Table 3. Non-organ confined tumours were larger than organ-confined tumours (4.8 cm *vs.* 3.9 cm, $p=.006$). The presence of reactive oedema in the fatty tissue surrounding the tumour predicted NOCD (OR 2.55, $p=.016$). This was particularly true for tumours in the ureter with an OR of 8.0 for those tumours ($p=.002$). The presence of pathological lymph nodes and local invasion on CT predicted NOCD (OR 14.5, $p=.001$ and 5.31, $p<.001$, respectively). The sensitivity and specificity of local invasion at CT to predict NOCD was 49% and 85%, respectively. The sensitivity and specificity of pathological lymph nodes CT to predict NOCD was 22% and 98%, respectively. Hydronephrosis was present in 114 of 173 patients (66%). Contrast enhancement and the presence of hydronephrosis did not predict NOCD in this patient material.

### Ureterrenoscopic variables

The results of the univariate regression analyses regarding the ureterrenoscopic variables are described in Table 4. A diagnostic URS with biopsy was performed in 95 patients. In 66 (69%) of the patients, the biopsy could be used to confirm UTUC diagnosis, and in 57 (60%) the biopsy material was sufficient to determine tumour grade. Presence of high-grade tumour at biopsy predicted NOCD (OR 3.59, $p=.04$). The sensitivity and specificity of high-grade biopsy to predict NOCD was 63% and 68%, respectively. Out of 34 low-grade tumours at biopsy, 12 (35%) were upgraded to high-grade at final pathology after RNU. No high-grade tumours were downgraded. The tumour stage at biopsy did not predict NOCD in the present material. A cytology sample was taken in 60 patients, 43 of these taken during URS. Malignant cells were detected among 37 (62%) of these. Malignant cells at cytology did not predict NOCD in the present material.

Table 3. Univariate analyses for prediction of non-organ confined disease according to variables at CT scan.

| Variable | *n* (%)[a] | | | | | | |
|---|---|---|---|---|---|---|---|
| Continuous variables | | All | NOCD | 95% CI[b] | OCD | 95% CI[c] | *p* Value |
| Tumour size (cm) | 163 (91) | 4.2 | 4.8 | 4.2–5.3 | 3.9 | 3.6–4.3 | .006[d] |
| Contrast enhancement (HU) | 111(62) | 38 | 36 | 32–40 | 39 | 35–43 | .4[a] |
| Categorical variables | | | | | OR[e] | 95% CI[b] | *p* |
| Fatty tissue oedema (all) | 164 (92) | | | | 2.55 | 1.19–5.46 | .016[b] |
| Fatty tissue oedema (ureter only) | 55 (31) | | | | 8.0 | 2.13–30.1 | .002[b] |
| Hydronephrosis | 173 (97) | | | | 0.62 | 0.32–1.17 | .14[b] |
| Pathological lymph nodes | 173 (97) | | | | 14.5 | 3.19–66.4 | .001[b] |
| Local invasion | 162 (91) | | | | 5.31 | 2.53–11.1 | <.001[b] |

Tumour size, oedema in the fatty tissue surrounding the tumour, the presence of pathological lymph nodes and local invasion into renal, peripelvic or periureteric tissue were shown to be significant predictors of non-organ confined disease at final pathology after nephroureterectomy.
[a]Refers to total number and % of total study population with adequate CT scan quality to assess the given variable.
[b]Logistic regression.
[c]Confidence interval.
[d]Students *t*-test.
[e]Odds ratios.

Table 4. Results of the analyses made from the ureterenoscopic variables regarding determination of biopsy tumour grade and prediction of non-organ confined disease at final pathology after nephroureterectomy.

| Variable | *n* | % | OR[a] | CI[b] | *p* Value |
|---|---|---|---|---|---|
| Diagnostic URS performed | 95 | 100 | | | |
| Biopsy method | | | | | |
| Forceps only | 66 | 70 | | | |
| Basket only | 14 | 15 | | | |
| Both forceps and basket | 13 | 14 | | | |
| N/A | 2 | 2 | | | |
| Biopsy verified UTUC | 66 | 69 | | | |
| Biopsy WHO grade 2004 | 57 | 60 | | | |
| High grade | 23 | | 3.59 | 1.07–12.0 | .04 |
| Low grade | 34 | | | | |
| Low-grade tumours at URS | 34 | | | | |
| Remain low-grade at final pathology | 22 | 65[c] | | | |
| Upgraded to high-grade at final pathology | 12 | 35[c] | | | |
| Biopsy tumour stage | 60 | 63 | | | |
| Ta/Tx | 50 | | | | |
| T1 or T2 | 10 | | 3.55 | 0.87–14.5 | .08 |
| Cytology taken | 60 | 63 | | | |
| Malignant cells | 37 | | 1.84 | 0.55–6.14 | .3 |

[a]Odds ratios.
[b]Confidence interval.
[c]Percentage of low-grade tumours at biopsy either verified as low-grade tumours or upgraded to high-grade tumours at final pathology after radical nephroureterectomy.

### *Multivariate analyses*

All variables with a predictive value for NOCD with a p-value <0.2 (smoking status, presence of hydronephrosis, fatty tissue reactive oedema or pathological lymph nodes together with tumour size and local invasion at CT) were entered into a multivariate logistic regression analysis. The results from these analyses are shown in Table 5. Pathological lymph nodes and local invasion on CT remained significant predictors of NOCD (6.21, $p$=.03 and 3.36, $p$=.004, respectively).

## Discussion

In this study, several variables from the CT images and biopsy tumour grade were identified as preoperative predictors for NOCD. With the exception of biopsy tumour grade and tumour size, these factors also predicted survival.

One of the unanswered questions regarding the preoperative diagnostic procedures before RNU for UTUC is the role of the diagnostic URS. In the current EAU-guidelines, a URS is recommended if imaging and cytology are not sufficient for the diagnosis and/or risk-stratification of the tumour [8]. There is a role for the diagnostic URS in case the result of the CT is unclear and further examinations to *set the correct diagnosis* are necessary. Moreover, another indication is if the patient is a potential candidate for nephron-sparing treatment, such as a segmental ureter resection or endoscopic laser tumour ablation. The evaluation of the diagnostic URS in these settings was not among the aims of this paper, and will not be discussed further here.

When it comes to the *staging* of UTUC, the role of the diagnostic URS is much more unclear. Tumour grade is regarded as a predictor of tumour stage at final pathology [2]. However, the problem with tumour grade from biopsy is that it is often not possible to get a biopsy at all at the procedure, and in case a low-grade biopsy is found, it is frequently upgraded to high-grade at final pathology. In the present paper, the biopsy could confirm UTUC diagnosis only in 69% of the cases. This might seem like a low rate of histological verification, but is in line with the findings in a prospective study evaluating URS biopsies. Breda et al. found that a histological evaluation was possible in 78% of the biopsies, with complete histopathological assessment only among 46%. [11]. One could of course turn this around and say that histological confirmation from URS biopsy is possible in a majority of the cases, and such verification is a requirement for the oncologists before considering neo-adjuvant chemotherapy. However, histological verification can also be achieved through cytology at cystoscopy which is mandatory before RNU. In the present cohort, the sensitivity of cytology to verify UTUC was 62%, not very different from the sensitivity of 69% from the URS biopsy. Another aspect of the URS biopsy was that 35% of the low-grade biopsies were upgraded to high-grade at final pathology. Such upgrading is a known phenomenon. A meta-analysis on the topic analysing more than 2000 URS biopsies from 23 studies concluded that the pooled upgrading rate from low- to high-grade tumours was at 34% [12], and thus in line with our results.

Table 5. Multivariate regression analyses for prediction of NOCD at final specimen according to risk variables.

| Variable | OR[a] | CI[b] | *p* Value |
|---|---|---|---|
| Tumour size at CT | 0.94 | 0.77–1.16 | .6 |
| History of smoking *vs.* never smokers | 1.53 | 0.72–3.24 | .3 |
| Hydronephrosis at CT | 0.59 | 0.28–1.23 | .2 |
| Reactive oedema in fatty tissue surrounding tumour at CT | 0.62 | 0.26–1.50 | .3 |
| Pathological lymph nodes at CT | 6.21 | 1.21–31.3 | .03 |
| Local invasion into renal parenchyma or periureteric tissue | 3.36 | 1.47–7.69 | .004 |

Variables with a *p* value of <.2 were taken into the analysis. Pathological lymph nodes and local invasion into renal parenchyma, peripelvic or periureteric tissue assessed at CT were significant predictors of non-organ confined disease at final pathology.
[a]Odds ratios.
[b]Confidence intervals.

In spite of the demonstrated limitations regarding the diagnostic URS, biopsy tumour grade was still a significant predictor of NOCD at univariate analyses in the present material, and further analyses were made to assess potential clinical benefit. The sensitivity and specificity of high-grade tumour at biopsy to predict NOCD were 63% and 68%, respectively. We think that the accuracies of these predictions are too low to be clinically useful. Furthermore, there is also the aspect that URS requires time and resources, and thus delays definite treatment. Finally, in two meta-analyses, an increased risk of post-RNU bladder recurrence has been demonstrated among patients examined with URS [13,14].

To conclude, URS as a diagnostic measure among patients where a decision for RNU has already been made has considerable limitations, and will only rarely influence the decision about intensified treatment. It causes curative treatment delay and an increased risk of bladder recurrence after RNU. We argue that a preoperative URS should be spared for cases where the diagnosis is uncertain or when nephron-sparing treatment might be an option.

How can our findings be used in a clinical practice? If a URS is omitted in the preoperative diagnostic work-up, the clinician is left with the findings (a) in the CT scan and (b) at cystoscopy visit when deciding on potential intensified treatment. There is emerging evidence of the efficacy of perioperative chemotherapy, but selecting the appropriate patients for this is challenging. Indeed, in Norway, different approaches to perioperative chemotherapy at different hospitals exist. The POUT study has recently demonstrated the efficacy of adjuvant chemotherapy in case of muscle-invasive disease [4], and one could argue that the best strategy is simply to wait for final pathology and then decide whether to give adjuvant chemotherapy or not. However, neo-adjuvant chemotherapy in the treatment of UTUC has some appealing advantages. Neo-adjuvant chemotherapy before cystectomy for bladder cancer has demonstrated survival benefit, and is standard treatment according to guidelines [15]. Second and perhaps more importantly, a RNU will inevitably reduce the kidney function of the patient. We know that this will make a significant proportion of the patients ineligible for adjuvant chemotherapy due to reduced kidney function postoperatively. On the other hand, giving neo-adjuvant to *all* chemo-eligible patients undergoing RNU will inevitably result in giving a toxic and potentially lethal treatment to a large group of patients with non-muscle invasive disease. In the present material, the proportion of patients with Ta and T1 disease was 47%. The proportion of patients with organ-confined disease was 62%. We think that giving neo-adjuvant treatment to patients with non-muscle invasive disease would result in unacceptable side effects to a patient group where the potential benefit of the treatment is highly debatable.

So how can we select the appropriate patients for neo-adjuvant chemotherapy? Both pathological lymph nodes and fatty tissue oedema predicted NOCD in the present cohort. However pathological lymph nodes had a very low sensitivity of 22% in predicting NOCD and would result in missing out many potential candidates for neo-adjuvant chemotherapy. Fatty tissue reaction surrounding the tumour also demonstrated predictive ability, but this is a feature that to our knowledge has not been demonstrated as a predictor for tumour stage after RNU before. Its predictive abilities should be confirmed in further studies before it is taken into standard clinical practice.

The presence of local invasion on CT seems a more promising feature to use in patient selection for neo-adjuvant chemotherapy. It was found to be a significant predictor of NOCD and survival in the present cohort. The predictive ability of local invasion at CT has been described by other authors. In a diagnostic model presented by Favaretto et al., local invasion at CT was found to predict NOCD and was used as a part of their presented diagnostic model [16]. A recently published study reported a sensitivity and specificity of 75% and 83% correspondingly using CT to detect advanced stage (T3/T4) UTUC [17].

Local invasion on CT in this study showed a relatively low sensitivity of 48% but a corresponding high specificity of 85% in predicting NOCD. A sensitivity of 48% might seem unacceptably low, but this sensitivity as a cut off is the same as suggested in a recently published model by Petros et al. The authors of that study generated a predictive model that included findings at CT, URS and blood samples to reach a sensitivity of 49% and specificity of 95% in predicting NOCD [18]. The higher specificity demonstrated in their model is beneficiary, but comes at the cost of a highly complicated model using parameters from URS and blood samples in addition to findings at the CT in a nomogram. In our opinion, the complexity of the model makes it less useful in day to day clinical practice.

By using the accuracy from this study, invasion at CT as a guide for who could benefit from neo-adjuvant, would result in only half of the patients with NOCD receiving chemo as a

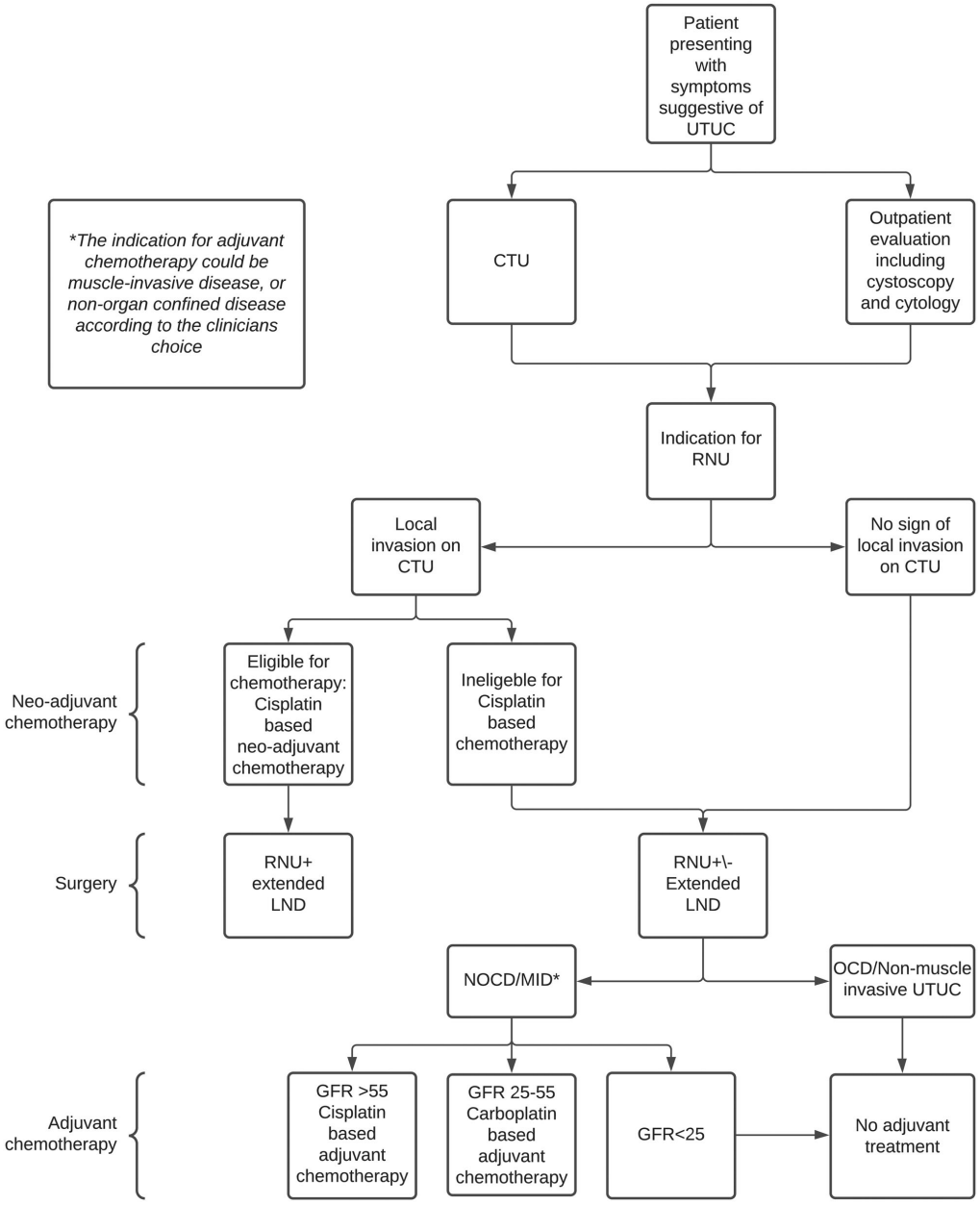


Figure 1. Demonstrating a proposed flowchart that can be used in the selection of patients for perioperative chemotherapy and/or extended LND in adjunct to radical nephroureterectomy for upper tract urothelial carcinoma. UTUC: upper tract urothelial carcinoma. RNU: Radical nephroureterectomy. LND: Lymph node dissection; NOCD: non-organ confined disease; OCD: organ-confined disease; MID: muscle-invasive disease; GFR: glomerular filtration rate.

neoadjuvant. However, few patients with non-muscle invasive disease would be 'overtreated' with chemotherapy. The patients with muscle-invasive disease that did not receive neo-adjuvant chemotherapy could be good candidates for adjuvant chemotherapy. If the kidney function was still acceptable (GFR $>$ 55), Cisplatin-based regimens would be preferred. If not, Carboplatin based regimens could be an option. Both these regimens of adjuvant chemotherapy were included and shown to be beneficial in the POUT study. High-quality randomized studies comparing neo-adjuvant

with adjuvant chemotherapy in the treatment of UTUC are urgently needed. Pending evidence from such high-quality studies, we suggest that this very simple and readily available feature can be used as a guide for selecting patients for either neo-adjuvant or adjuvant chemotherapy. Its use is demonstrated in a proposed flowchart (Figure 1).

The same approach can be used when selecting patients for extended LND. Current EAU guidelines recommend that a template-based LND should be performed during RNU [8]. In case pathological but resectable lymph nodes are present on the preoperative CT, an LND should be performed. However, the presence of lymph nodes metastasis is strongly dependent on tumour stage, and an LND appears to be unnecessary in Ta/T1 tumours [19]. In case the CT is negative for pathological lymph nodes but local invasion is present, an LND could be performed with an indication similar to that of neo-adjuvant chemotherapy (Figure 1).

The inclusion of survival analyses presented in this study serve two purposes. First, the 5-year DSS of 79% in this study is comparable to the DSS presented in larger cohorts [20,21]. This suggests that our cohort is a representative sample of UTUC cohorts in general, and could increase the generalizability of our findings. Second, the same predictors of tumour stage at CT also predicted survival in our study. This was as expected, but these findings further underscore the importance of the predictors we discovered both regarding stage and survival.

### *Strengths and weaknesses*

The strengths of this article include using patients from two larger centres in Norway to allow enough patients to make robust analyses of staging and survival. However, increasing the number of patients by collaborating with additional centres would have increased the generalizability of our findings further. All CT scans were re-evaluated by a uro-radiologist and all re-evaluations of histopathological specimens were performed by uro-pathologists to increase data quality as much as possible. The weakness of the study is its retrospective study design, with the inherent weaknesses associated with this study design.

## Conclusion

Several features in the preoperative diagnostics before RNU for UTUC were shown to predict tumour stage and survival in this study. Of these, local invasion on CT seems to be the most promising feature when selecting the appropriate patients for intensified treatment for UTUC. The role of the diagnostic URS in the staging of UTUC seems limited. The preoperative staging of UTUC before RNU remains challenging, and further studies on the topic are warranted.

## Disclosure statement

The authors report no conflicts of interest.

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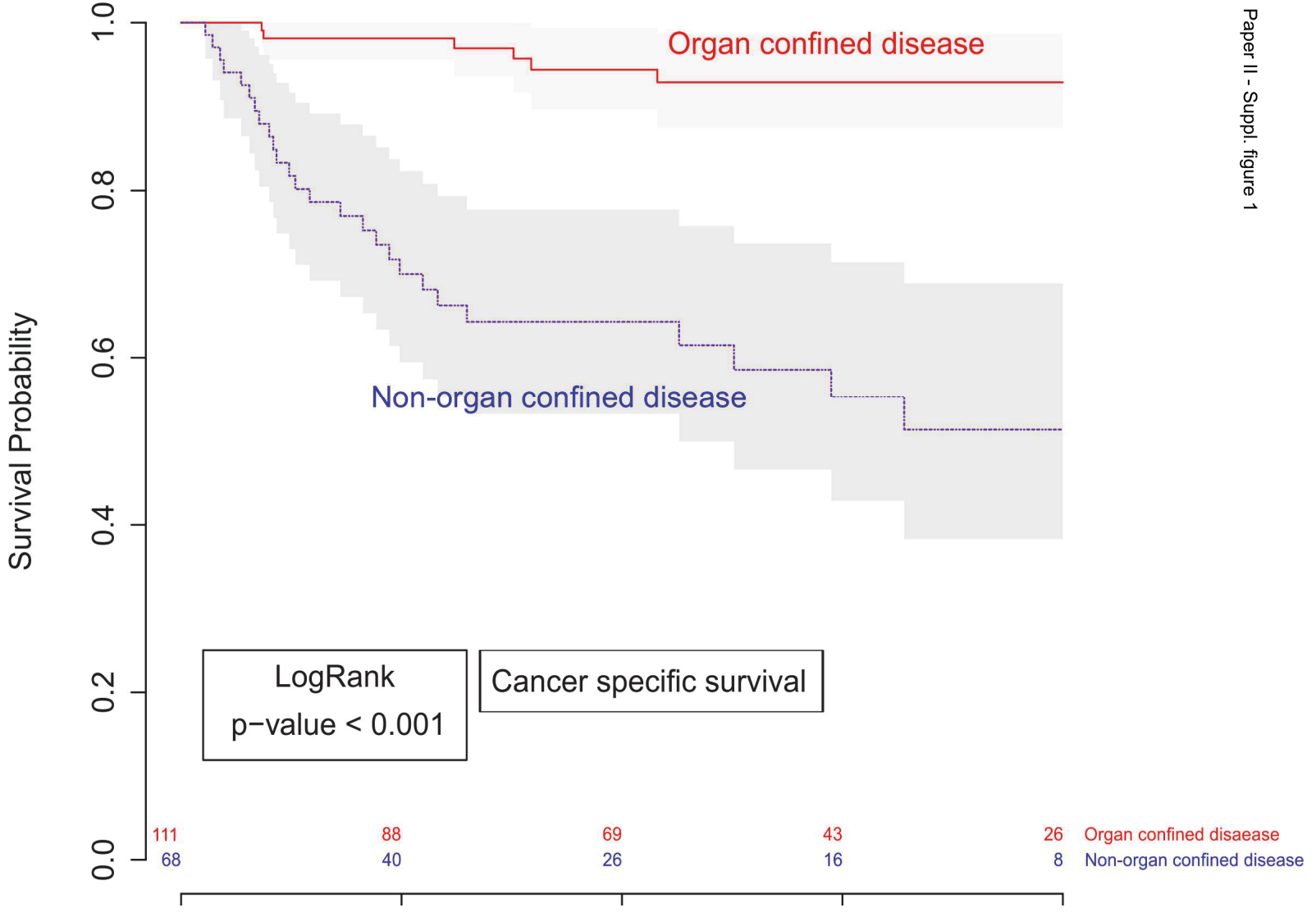
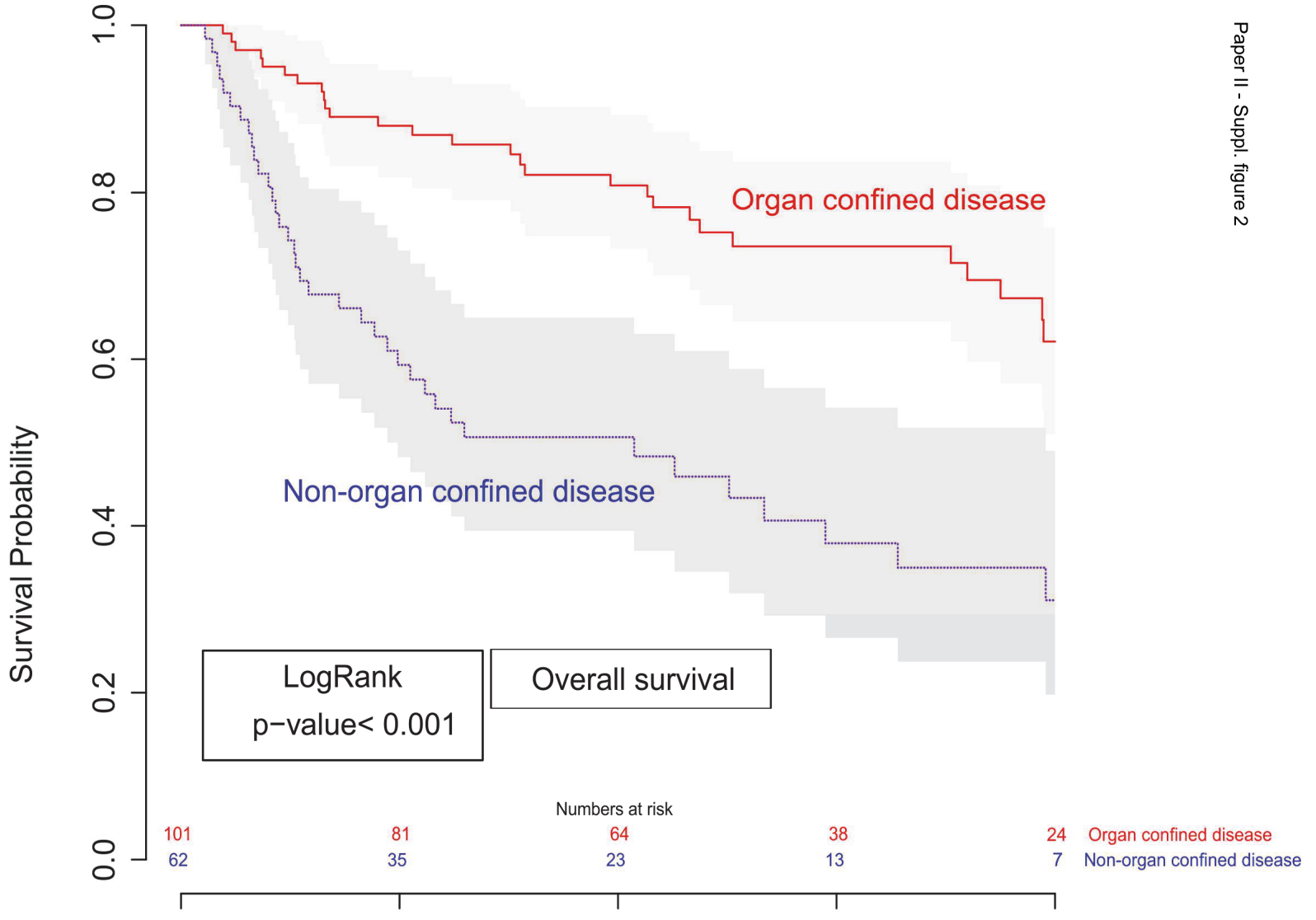
Supplementary table 1. Multivariate regression analyses for prediction of all-cause mortality after radical nephroureterectomy for upper tract urothelial carcinoma. ECOG[5] and tumour stage predicted all-cause mortality. [1]Hazard ratios. [2]Confidence intervals. [3]Organ confined disease. [4]Non-organ confined disease. [5]Eastern Cooperative Oncology group.

| **Variable** | | | |
|---|---|---|---|
| | **HR[1]** | **CI[2]** | **p** |
| Age | 1.00 | 0.96-1.05 | 0.9 |
| Tumour grade high vs low | 1.55 | 0.66-3.61 | 0.3 |
| Tumour stage NOCD[4] vs OCD[3] | 3.28 | 1.66-6.48 | 0.001 |
| ECOG[5] 1 or more vs 0 | 4.68 | 2.30-9.13 | <0.001 |

Supplementary table 2. Multivariate regression analyses evaluating potential predictors of cancer specific mortality after radical nephroureterectomy for upper tract urothelial carcinoma. Only tumour stage predicted cancer specific mortality in the present cohort. [1]Hazard ratios. [2]Confidence intervals.

| **Variable** | | | |
|---|---|---|---|
| | **HR[1]** | **CI[2]** | **p** |
| Tumour grade high vs low | 5.64 | 0.67-47.4 | 0.11 |
| Tumour stage OCD vs NOCD | 0.15 | 0.06-0.40 | <0.001 |
| ECOG 1 or more vs 0 | 2.27 | 0.97-5.31 | 0.06 |


Paper II - Suppl. figure 1
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
Organ confined disease
Non-organ confined disease
LogRank
p−value < 0.001
Cancer specific survival
111
88
69
43
26
Organ confined disaease
68
40
26
16
8
Non-organ confined disease


Paper II - Suppl. figure 2
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
Organ confined disease
Non-organ confined disease
LogRank
p−value< 0.001
Overall survival
Numbers at risk
101
81
64
38
24
Organ confined disease
62
35
23
13
7
Non-organ confined disease

Graphic design: Communication Division, UiB / Print: Skipnes Kommunikasjon AS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