Urothelial Cell Carcinoma

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chapter 1

Introduction, objective, aim and outline of the thesis

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1 General introduction, objective and outline of the thesis

Urothelial cell carcinoma

Urothelial cell carcinoma (UCC) is a pan-urothelial disease potentially affecting any part of the urinary tract from the collecting system of the kidney to the distal urethra. Differences in location of UCC comprise distinctive features of the disease and therefore two separate entities are distinguished: bladder cancer and upper urinary tract tumors (UUTT). This introduction provides the background on the epidemiology, biology, diagnosis and treatment of both forms of UCC. Subsequently the objectives are pointed and the outline of the thesis is summarized.

1 Epidemiology

1.1 Bladder Cancer

Bladder carcinoma is the most common malignancy of the urinary tract. Worldwide more than 380.000 patients are diagnosed every year [1], in the Netherlands more than 5000. [www.cijfersoverkanker.nl] In men the incidence is four times higher than in women. Women are more often older when diagnosed and have greater risk on delayed diagnosis. Over all, the median age at diagnosis varies from 65 to 70. There is a peak incidence at 85 years.[2] Cigarette smoking and aromatic amines from occupational exposure are well-known risk factors. Initially, seventy percent of the new patients are diagnosed as Non Muscle Invasive Bladder Cancer (NMIBC) and approximately thirty percent as Muscle Invasive Bladder Cancer (MIBC). Although increased in certain hereditary syndromes, familial bladder cancer is fairly rare. In recent years, genome-wide association studies showed evidence for a genetic component to its etiology. A high number of genetic variants have been identified. Though, the individual influence on developing bladder cancer or not is very low. The variants identified so far explain only approximately 5-10% of the overall inherited risk.[3] In the Netherlands, the mortality rate (European Standardized Rate; ESR) in men declined from 11.99 in 1989 to 8.26 in 2011. The mortality rate in women remains relatively stable during the last two decades and

consequently the overall mortality rate of bladder cancer declined marginally. (Figure 1) [www.cijfersoverkanker.nl]
In Europe, bladder cancer mortality declined both for men and women in the years after 1992.[4] These favorable trends largely reflect the changing tobacco smoking pattern throughout Europe but an increased standard of care may play a favorable role as well.[5]

1.2 Upper Urinary Tract Tumor

UCC of the UUT accounts for 5% to 10% of all UCC. The estimated annual incidence of UUTT in Western countries is about two new cases per 100,000 inhabitants.[6] In contrast to bladder cancer there is a slight
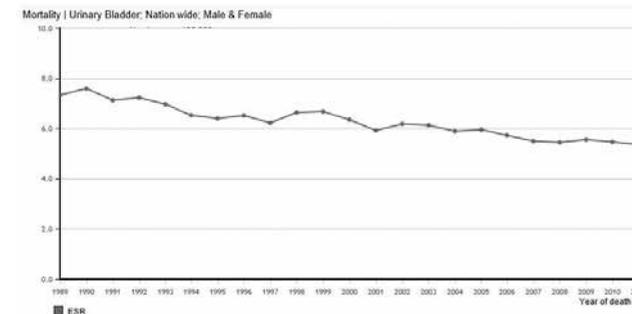
Figure 1 Mortality rate of urothelial cell carcinoma of the bladder in the Netherlands
(European Standardized Rate; ESR)
(www.cijfersoverkanker.nl)
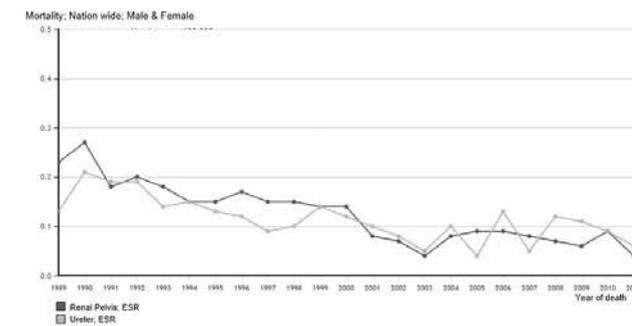
Figure 2 Mortality rate of urothelial cell carcinoma of the upper tract in the Netherlands
(European Standardized Rate, ESR)
(www.cijfersoverkanker.nl) Rate)
(www.cijfersoverkanker.nl)

increase in incidence of UCC of the upper tract in the Netherlands since 1995 whereas at the same time there is a more prominent decrease in mortality rate in both men and women, although the absolute numbers are low. (Figure 2) In 2011 of the 2647 deceased of UCC 25 patients died from a UUTT. At the time of diagnosis of a low risk NMIBC there is an up to two percent risk on synchronous UUT. This risk increases up to 7.5 % in trigonum located tumors. Patients with multiple and high risk tumors in the bladder have a three-fold higher risk of future UUTT than patients with a single bladder tumor.[7,8] Likewise development of metachronous UUTT bladder cancer can arise after treated UUTT, particularly in the first

two years following treatment. The overall incidence varies from 15-50% and remains lifelong.[9]

2 Biological behavior histology of urothelial cell carcinoma

There are two theories explaining the underlying mechanism of the multifocal behavior of UCC throughout the whole urinary tract. One theory suggests that multiple tumors arise from a single transformed cell that proliferates and spreads through the urothelium either by intraluminal implantation or by intraepithelial migration.[10,11] The other theory implies that multiple genetically unrelated tumors develop as a result of urinary carcinogen exposure that causes independent genetic alterations at different sites in the urinary tract.[12] Besides the similarities strong evidence suggests that there are distinct genetic and epigenetic differences between some UUTT and bladder UCC. For instance patients with Lynch syndrome or Hereditary Non Polyposis Colorectal Cancer have, besides a predisposition to early onset colonic cancer, a higher relative risk for developing malignancies of other sites such as the endometrium, ureter or renal pelvis, or small bowel than age matched controls. These patients are at increased lifetime risk for development of UUTT with an incidence up to 10 %.[13,14] The cause is an autosomal dominant inherited mutation in one of four mismatch repair genes.

2.1 Bladder Cancer

Histopathologically more than ninety percent of all bladder cancers, both NMIBC and MIBC, are of urothelial origin. Squamous cell carcinoma and adenocarcinoma are less common and accounting for 3 - 5 % and 0.5 - 2% of bladder tumors in Western countries.

2.2 Upper Urinary Tract Tumor

Histopathologically nonurothelial tumors of the upper urinary tract are very rare.[15] Epidermoid carcinomas represent <10% of pyelocaliceal tumors and are even more rare within the ureter. Other histologic subtypes are adenocarcinomas (<1%), endocrine carcinomas, and sarcomas. With respect to the location of upper urinary tract tumors the renal pelvis and ureter are equally affected. Once the ureter is involved the frequency of distal tumors is two times of those in the proximal or middle part.[16]

3 Diagnosis and Staging

3.1 Bladder Cancer

The most common presentation of a patient with a bladder tumor is hematuria (microscopic or macroscopic). Besides, irritative lower urinary tract symptoms as urgency pollakisuria and dysuria may be signs of bladder cancer. Flexible or rigid cystoscopy is performed to reveal any pathologically feature of the bladder mucosa. Trans urethral resection of the tumor (TURT) including detrusor muscle will confirm the histological diagnosis. In addition to cystoscopy urinary cytology plays a role in detecting high risk NMIBC and carcinoma in situ (CIS). Especially, the former entity is poorly visualized with cystoscopy and warrants random biopsies of the bladder mucosa, preferably supported by photo dynamic diagnostics. In case of negative cystoscopy with positive cytology there is an indication for evaluation of the upper urinary tract.

In NMIBC the disease is confined to the mucosa (stage Ta, CIS) or submucosa (stage T1) (Figure 3). In MIBC the tumor invades the detrusor muscle layer (stage T2), the perivesical fat (stage T3) or organs adjacent to the bladder (stage T4).
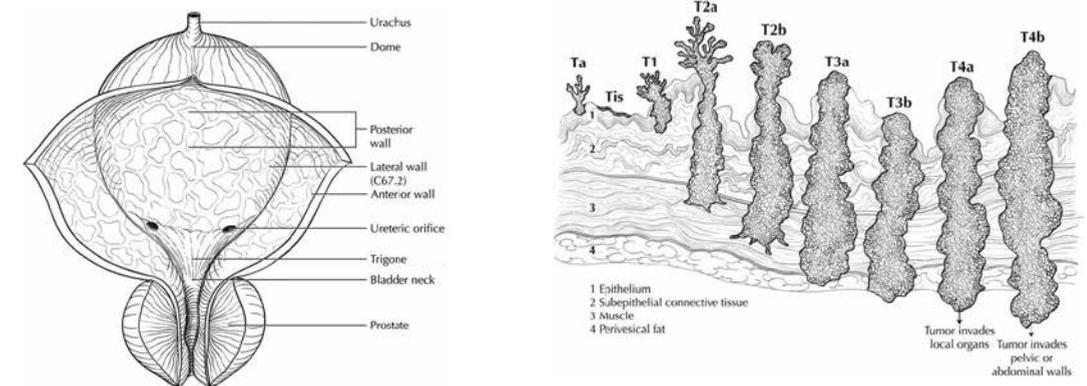

Figure 3
A. Anatomy of the bladder.
B. T stages of urothelial cell carcinoma of the bladder.

(Adapted from AJCC Cancer Staging Atlas, A Companion to the Seventh Editions of the AJCC Cancer Staging Manual and Handbook Second Edition, Springer)

In 1973 the World Health Organization (WHO) developed a grading system for urothelial cell carcinoma, which was revised in 2004. To improve the accuracy the controversial intermediate grade (grade 2) was eliminated. However, according to the most recent EAU guidelines, tumors should be graded using both the 1973 and the 2004 WHO classifications until the most recent classification has been sufficiently validated by more clinical trials.[17] (Figure 4)

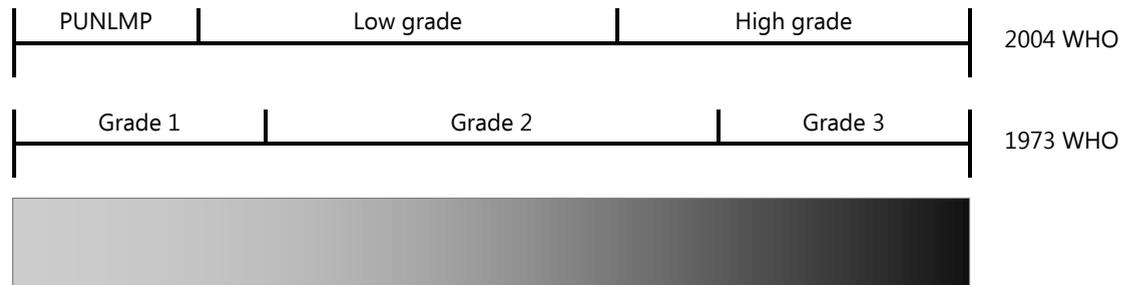| PUNLMP	Low grade	High grade	2004 WHO
Grade 1	Grade 2	Grade 3	1973 WHO

Figure 4
Histologic stratification of tumors according to grade in WHO 1973 and 2004 classifications. (Adapted from Mac Lennan GT, Kirkali Z, Cheng L. Histological grading of noninvasive urothelial neoplasms, Eur Urol 2007 Apr 51(4): 889 - 98.

3.2 Stage and grade related to outcome
Stage and grade are strongly related and both important prognostic factors in predicting treatment outcome. The classic way to categorize patients with NMIBC is to divide them into risk groups based on prognostic factors derived from multivariate analyses. Tumors in the low risk group comprise single TaG1 tumors <= 3 cm in diameter, which show low recurrence rates and fairly no progression. The high risk group includes T1G3, multifocal or highly recurrent (>= 3 recurrences in 24 months) Ta-T1 tumors and CIS. Seventy-five percent of these patients will have recurrences and thirty to fifty percent will progress to muscle invasive disease. The intermediate risk group comprises all other tumors between the low and high risk groups; Ta-T1, G1-G2, multifocal, > 3 cm in diameter. Patients belonging to this group often develop NMIBC recurrences, although progression is less common than in high risk groups it is still significantly higher than in low risk groups.[18]
With data of 2,596 patients diagnosed with Ta-T1 tumors, randomized in seven trials, the European Organization for Research and Treatment of Cancer (EORTC) developed a scoring system based on the six most significant clinical and pathologic factors: Number of tumors; Tumor size;

Prior recurrence rate; T category; Presence of concurrent CIS; Tumour grade (WHO 1973).[19] The aim of this scoring system is to categorize patients in the aforementioned risk groups. Currently, this scoring system is used in the European and Dutch guidelines regarding decision making after a TURT.
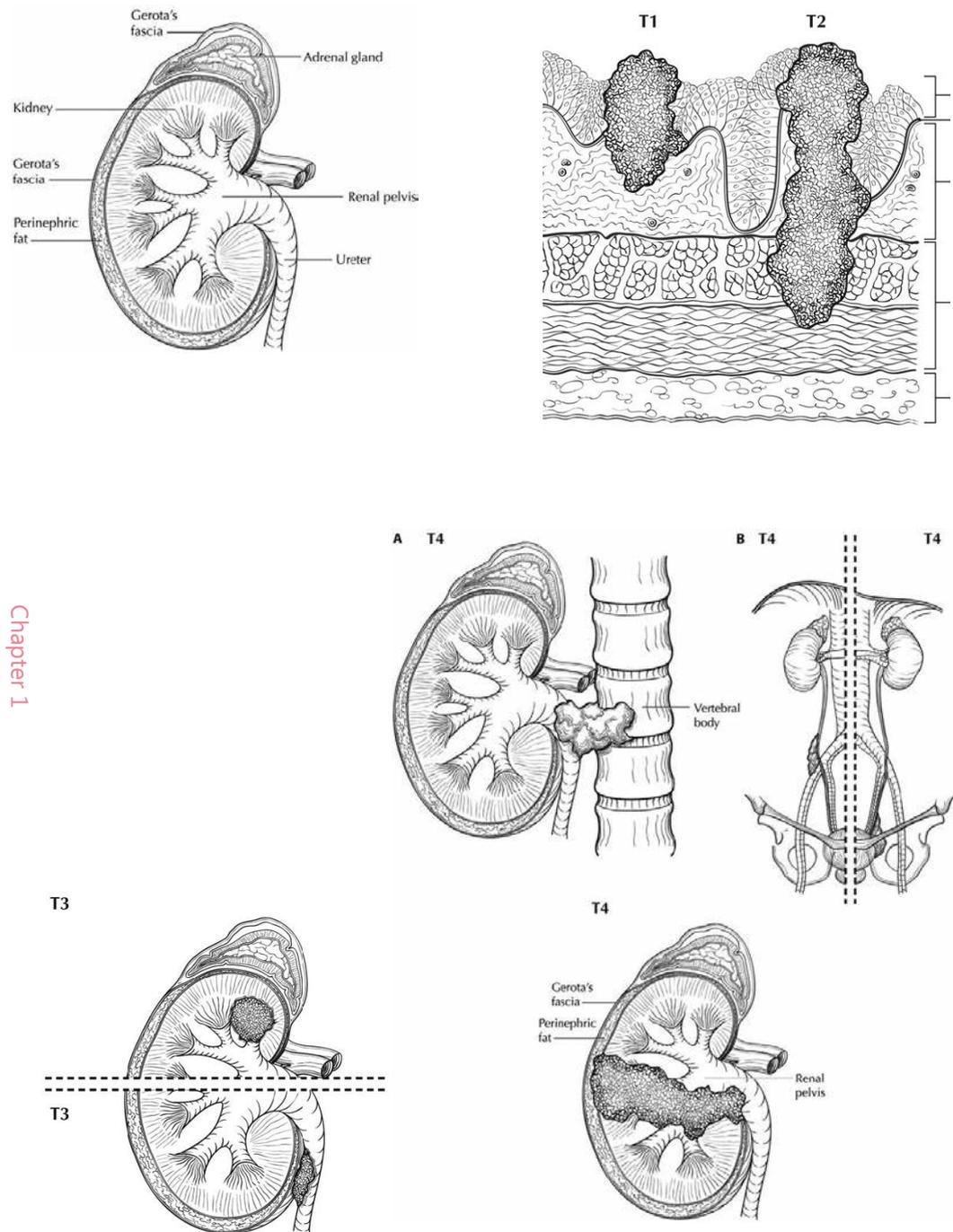
3.3 Upper Urinary Tract Tumor
The presentation of UUTT is often similar to that of patients with bladder cancer. Thereby larger tumors can cause flank pain as result of a unilateral obstruction of the UUT with tumor or lumbar mass. In patients initially diagnosed with a high risk bladder need to be evaluated for presence of a concurrent UUTT. [20] For diagnosing a UUTT visualization of the UUT is essential. With the predominantly practiced Multidetector Computer Tomography with urinary phase (MDCTU) most of the tumors can be detected. Depending on renal function and eventually other patient factors alternative imaging techniques like magnetic resonance imaging (MRI) and retrograde ureteropyelography (RUP) are feasible.
Besides depicting the UUTT histology is needed to confirm the diagnosis. With a flexible or semi-rigid ureteroscope the ureter can be macroscopically explored. The classification of upper tract tumors is similar to that of bladder carcinoma. The same papillary non-invasive (stage Ta, T1) and invasive (T2-T4) stages are distinguished. In addition the same grading system is applied to these tumors. (Figure 5 - page 14)

3.4 Stage, grade and location related to outcome
Similar to UCC of the lower tract stage and grade are strongly related to treatment outcome. Thereby the aspect of the macroscopic tumor architecture has been documented as a strong independent prognostic value of more aggressive disease.[21,22] The presence of concomitant CIS in patients with organ confined UUTT is associated with a higher risk of recurrent disease and cancer-specific mortality.[23]
Formerly, the initial anatomical location of the tumor in the proximal part of the UUT was considered as a poor prognostic factor however in a recent large cohort of UUTTs distal ureter location, particularly when associated with multifocal disease in the renal pelvis, is significantly associated with an increased risk of disease recurrence and cancer specific death.[16,24,25]

Figure 5
Anatomy renal pelvis and ureter, and T stages of urothelial cell carcinoma of the upper urinary tract.
(Adapted from AJCC Cancer Staging Atlas, A Companion to the Seventh Editions of the AJCC Cancer Staging Manual and Handbook Second Edition, Springer)

4 Treatment

4.1 Non muscle invasive bladder cancer

A state-of-the-art TURT by itself can eradicate a Ta-T1 tumor completely but a high percentage of cases will recur (15 - 61% within one year). The high 3-month recurrence rate indicates that it is not only the behavior of the tumor to recur so early but also that the TURT was incomplete in a considerable percentage.[26] The development of combining photo dynamic diagnosis with TURT and follow up cystoscopy diminished the amount of residual disease. Prospective randomized studies with hexaminolevulinate fluorescence cystoscopy showed long term recurrence free survival.[27]
For reasons of prevention of possible implantation of tumor at the time of the TURT it is recommended to give all patients a single immediate instillation of chemotherapy after the TURT, especially in patients with the first presentation of estimated low and intermediate risk NMIBC.[6,28] For intermediate and high risk groups one single instillation of mitomycine after TURT alone is not the optimal treatment. Adjuvant intravesical chemotherapy or immunotherapy (Bacille Calmette Guérin, BCG) can reduce recurrence. A meta-analysis of EORTC and Medical Research Council data, comparing TURT plus intravesical chemotherapy versus TURT alone, demonstrated that chemotherapy prevents the rate of frequent recurrence but not the rate of progression to a higher T stage in case of recurrence.[29] However, the ideal duration and intensity of the instillation schedules remain still undefined.[30]
Patients with high risk of tumor progression are recommended to undergo either BCG bladder instillations or immediate radical cystectomy. BCG in maintenance schedule was, besides delaying recurrences, also considered to prevent or delay progression. However recent meta-analyses have shown it particularly prevents recurrence. Thereby no significant overall- or disease-specific survival advantages have been proven of BCG compared to no intravesical therapy so far.[17]

4.2 Muscle invasive bladder cancer

In patients with high risk NMIBC resistant for conservative therapy and patients with primary diagnosed muscle invasive disease need radical therapy to get cured.[31] Radical cystectomy, combined with an extended lymph node dissection and urinary diversion, is the gold standard treatment in the absence of distant metastases. Radical cystectomy consists of removal of the bladder including prostate, seminal vesicles and vasa deferentia in

man, and uterus, adnexa and anterior vaginal wall in woman. The lymph node dissection not only provides diagnostic evaluation but there is growing evidence it also has therapeutic benefit in node-negative as well in node-positive patients.[32,33] The 5-year disease-free survival rate after radical cystectomy decreases with increasing pT stage, with disease-free rate up to 72 % for pT2 stage disease to less than 29 % for pT4 stage disease.[34]

A bladder sparing alternative treatment is external beam radiation therapy. Radiation therapy alone leads to local recurrences in one third of the patients.[35] Patients who undergo radiation therapy are often not fit for surgery due to high age and/or major comorbidity and/or decreased performance status. The overall 5-year survival rate after radiation therapy alone varies between 32 and 61 %.[36–38] Organ conservation by combined-modality therapy offering long-term survival rates comparable with contemporary cystectomy series. Hence that results of bladder preserving therapy are confounded by the possible underestimation of the clinical staging (TURT) versus the pathological staging (cystectomy).[39] Maximal TURT is followed by an induction course of concurrent radiation therapy and sensitizing chemotherapy. Patients achieving a clinical complete response continue with consolidation chemo-radiotherapy. This therapy will preserve the bladder in 70% of the patients.[40]

Alternatively, patients with small (< 5 cm) unifocal, non-metastasized muscle invasive tumors can be treated with a combined treatment of external beam radiation and brachytherapy. This treatment involves limited surgery of the pelvis.

The presence of micrometastases in localized (T2 - T4 on imaging) MIBC is the rationale for considering adjuvant chemotherapy. Most recent meta-analyses showed a small but statistically significant survival benefit in favor of cisplatin based combined neo-adjuvant chemotherapy.[41] In fit patients with MIBC, without compromised renal function, this treatment can be considered.[42]

4.3 Upper Urinary Tract Tumor

The golden standard for treatment of localized disease is a nephro-ureterectomy with bladder cuff around the distal ureter performed either by open or laparoscopic surgery. However in selected cases more conservative surgery is warranted. As in patients with renal insufficiency or patients with limited disease in the distal ureter. Then endoscopic resection or segmental removal of the distal ureter can be a superior alternative. To keep having control of the disease the UUT of these patients need to be visualized

regularly as they have lifelong increased risk on developing recurrences. As patients diagnosed with a high risk NMIBC have an increased risk on having simultaneously or developing metachronous UUTT their UUT should be evaluated one to two yearly.[8]

Objective and outline of this thesis

Objective

UCC has a heterogeneous character with respect to the location in the urinary tract and its aggressiveness. The different clinical manifestations of this disease require different approaches of diagnosis and treatment. The outcome in terms of mortality rate of bladder cancer patients has not improved remarkably the last decades. With the nation and worldwide availability of evidence based guidelines at the beginning of this century one would expect more patients are treated by the state-of-the-art treatment with improvement of survival figures accordingly. However, it has been observed that the minority of patients will be treated according the guidelines.[43] Obviously patient as well as doctor factors are contributing to that discrepancy. As UCC is a typical disease in elderly people comorbidity increases with age. Combined with increasing age this can act as an interfering factor as it comes to selection of therapy options. Besides, doctors treat their patients based on evidence but doctors also make choices based on unknown certain considerations known as clinical decision-making. Nonetheless the influence of the stage of the disease itself will affect the outcome very importantly. The Dutch results of bladder cancer care are collected by the Netherlands Cancer Registry. With the information of this registry added with the information of medical records the impact of the current management and possible influencing clinicopathological factors can be evaluated. With these retrospective data we become more aware of consequences of common practice which can help changing treatment patterns in order to improve survival and diminish disease burden in patients with UCC.

Imaging is of crucial importance in diagnosing UCC of the upper tract. Urography plays an important role in the visualization of the upper urinary tract. Many different techniques use opacification in order to depict a lesion, presenting as a cut-away in the contrast. Intravenous ureterography, RUP, CTU and MRU have been used for this indication. Currently CTU has been used most frequently worldwide. In our hospital, during the last three decades, RUP was and still is performed very frequently in diagnosing upper

tract tumors. Although guide lines dictate the use of CTU there is relatively limited evidence for its superior role in tumor detection of the UUT. In this thesis we attempt to accrue more evidence concerning whether the prominent role of RUP in our daily practice is superseded and needs to be abandoned or there is still an indication left.

The aim of this thesis is twofold regarding issues on actual pattern of care in patients diagnosed with UCC. One covers treatment of patients with bladder cancer, the other diagnosis of UCC of the UUT, particularly the visualization of the UUT.

Part I What is the impact of potential patient, tumor and doctor related factors on treatment and outcome of high risk NMIBC and MIBC in daily practice?

Part II What is the feasibility and efficacy of RUP in the diagnosis of UCC of the UUT?

Outline of the thesis

Part I Urothelial cell carcinoma of the bladder - Pattern of care
This part includes three epidemiological studies focusing on current treatments and their outcome in Dutch bladder cancer patients within the Comprehensive Cancer Center North-Netherlands (CCCN) and the Eindhoven Cancer Registry (ECR). The CCCN network consists out of sixteen hospitals and three independent radiation oncology departments in the three training hospitals. The ECR covered about 10 medium to large community hospitals in which the number of practising urologists increased from 30 to 40 overtime. The nationwide Dutch network and registry of histo- and cytopathology (PALGA) regularly submits reports of all diagnosed malignancies to the comprehensive cancer centers. Data on recurrence and additional treatments were collected using the medical files by well-trained staff.[44]

In **Chapter 2** the actual pattern of care in patients with high risk NMIBC within the CCCN region is evaluated. The evaluated cohort dates from a period before the Dutch guideline on bladder cancer became available. Although a European guideline exists before. Besides an evaluation on outcome several factors, like age at diagnosis, sex, comorbidity, hospital type and year of treatment, possibly associated with the choice of treatment, 5 year recurrence and progression free survival rates were assessed. In **Chapter 3** treatment and survival of patients with newly diagnosed MIBC

in the CCCN region are studied. Again this cohort of 548 patients has been treated in an era without national guideline. In general, the preferred treatment for patients with MIBC is radical cystectomy with urinary diversion. However there are clinicopathological factors which could influence the choice for cystectomy or for an alternative treatment. These factors were identified and studied in this study. Then associations of those factors with the choice of treatment and disease specific and overall survival were assessed.

In the growing group of elderly people more MIBC will be diagnosed. Older people have more comorbidity and this might influence the selection of therapy. In **Chapter 4** the third study assessed whether rising age, social economic status (SES) and presence of serious comorbidity affected treatment choice and survival in a series of patients with MIBC in ECR region, preceding centralisation of cystectomy in the Netherlands. A cohort of 2445 patients, coming from a longer and more recent period of time than in the former two studies were stratified by age and different treatment groups. In addition to the results of the study of the CCCN (Chapter 3) also in this study the minority of patients with MIBC were treated with radical surgery. The consequences for survival are evaluated and with assessment of factors as age, SES and comorbidity an explanation for this practice is made.

Part II Urothelial cell carcinoma of the upper urinary tract – Urography
This part of this thesis include a review of literature and two studies on the vizualisation of UUT in patients with high risk UCC. First, in **Chapter 5** the history and background of the urography is summarized. Techniques for the detection of lesions in the UUT are abundant but standardization is not stated. In our referral hospital the RUP has been the technique of choice to determine lesions of the UUT primarily or in surveillance of patients with high risk NMIBC or UUTT. Although there is no standard imaging technique for UUT, the CTU is nowadays worldwide the most practiced modality for depicting lesions of the UUT. The concept of filling the system with contrast (opacification) is still the base for a good performance of as well as RUP as CTU. The grade of opacification is subject of the study in **Chapter 6**. In this study the grade of opacification of RUP and CTU is compared in 100 paired UUTs using a semi-quantitative scoring system in four segments of the UUT. In both imaging techniques not every segment of the UUT will reach an optimal opacification at any time point. In addition technical improvements on the optimalisation of opacification and the question of the imperative need for opacification are discussed. In **Chapter 7** the clinical efficacy of RUP in

the diagnosis of UUTT is studied in patients with histology proven UCC. In a retrospective cohort study the initial RUP is evaluated by assessing feasibility, sensitivity, specificity, and accuracy. These results are compared with sparse data from literature including few studies comparing (retrograde) urography and CTU. Besides, advantages and disadvantages of RUP versus CTU are highlighted. In **Chapter 8** the studies are summarized and in **Chapter 9** the studies are discussed in the light of perspectives for the future.

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part 1
Urothelial cell carcinoma of the bladder - Pattern of care in relation to outcome