Urothelial Cell Carcinoma

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chapter 9

General discussion and future perspectives

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This thesis covers two aspects of different manifestations of urothelial cell carcinoma (UCC): UCC of the bladder, also known as bladder cancer, and UCC of the upper urinary tract (UUT).
The first part of the thesis focuses on the actual pattern of the care in high risk non muscle invasive bladder cancer (NMIBC) and of muscle invasive bladder cancer (MIBC), in different regions in the Netherlands, and it includes three studies. These studies were conducted in an era when American and European guidelines were available but when there was still no national Dutch guideline. The first American guideline on the management of bladder cancer became available in 1998 through the National Comprehensive Cancer Network (NCCN). The American Urological Association (AUA) published its first Clinical Practice Guideline (CPG) for NMIBC in 1999, updated in 2007, and recently reviewed in 2010. The European Association of Urology (EAU) presented the first European guideline in 2002, with the latest update in 2013 for both NMIBC and MIBC. The first national Dutch guideline, based on the EAU guideline, became available in 2009. The aim of the studies in the first part of the thesis was to explore the impact of patient-, tumor-, and doctor-related factors concerning treatment and outcome of high risk NMIBC and MIBC in daily practice.

The second part of the thesis focuses on the diagnosis of UCC of the UUT, particularly in terms of the visualization of the UUT using urography in order to depict a urothelial neoplasm. The aim was to study the feasibility and efficacy of retrograde ureteropyelography (RUP) in the diagnosis of UCC of the UUT.

Part I: Urothelial cell carcinoma of the bladder – Patterns of care

The pattern of care study in patients with high risk NMIBC (Chapter 2) shows fewer instances of application of the adjuvant intravesical instillations of chemotherapy or BCG after TUR, as compared to the recommended treatment, based on actual guidelines. Factors associated with this underuse of adjuvant instillation in our cohort study are age of the patient and treatment in non-teaching hospitals. The observed differences in treatment, however, do not significantly affect the five-year recurrence-free and progression-free survival rates in our cohort.

The two pattern of care studies on MIBC (chapters 3 and 4) reported independently that only one-third of patients were treated with a radical cystectomy, at that time the treatment gold standard. Both studies assessed higher age as a predictive factor for abstaining from cystectomy. In one study, a more advanced stage of the tumor and, in the other, a higher number of comorbidities were independent variables for abstaining from cystectomy. Considered independently from age, socioeconomic status (SES), and serious comorbidity, patients who underwent radical cystectomy lived longer.

We observed in three pattern of care studies that patients with UCC of the bladder were undertreated with respect to adjuvant intravesical instillations and radical cystectomy. This implies that compliance with the guidelines for the management of bladder cancer was suboptimal. This observation of the poor adherence to recommendations from guidelines regarding bladder cancer has been described earlier in both patient- and physician-based survey studies. Cookson and collegues showed a wide variation in the use of intravesical postoperative chemotherapy in a survey with retrospective review of the last four patients treated for NMIBC among 259 urologists.[1] Another more recent survey, with exclusively intermediate or high risk NMIBC patients, based on a retrospective chart review including 971 patients treated by 102 urologists from Europe and North America, found that 47% of the intermediate-risk patients received a form of intravesical treatment and that 50% of the high risk patients received maintenance BCG instillations, as recommended by the EAU and AUA guidelines, thus indicating an underuse of adjuvant instillations especially in the high risk NMIBC group of patients.[2] Witjes and collegues did observe largely matching policies for treating NMIBC using the EAU guideline among Dutch and Belgian-Flanders practices in the absence of a national guideline. Not

only was underuse observed in the recommended early single instillation of chemotherapy in NMIBC but also overuse of intravesical therapy in a small group of patients with low risk NMIBC.[3] In addition to the survey studies, the pattern of care studies analyzing sizeable data from the Surveillance, Epidemiology, and End Results Program (SEER), as well as records from the National Cancer Data Base in the United States, also showed underutilization of recommended treatments. Chamie and collegues observed that within a cohort of 4545 patients with high-risk NMIBC, treated between 1992 and 2002, only one patient received all the recommended diagnostics, treatment, and surveillance. No overuse of treatment was reported.[4]
In the management of MIBC, the treatment according to the recommended guidelines is significantly less likely to be received by the elderly, racial minorities, those with inadequate insurance coverage, and patients seen at low volume centers, as reported by Gray and collegues[5] In a retrospective analyzed cohort of 28,691 patients with T2-T4 MIBC, where only 52% were treated with curative treatments such as radical cystectomy, partial cystectomy, or radiation therapy. Porter and collegues and David and collegues both reported on the underuse of neoadjuvant chemotherapy: Only 11% respectively 1.2 % of all patients with surgically resectable MIBC, received neoadjuvant chemotherapy.[6,7] At that time randomized controlled clinical trials had already proved that there was a survival benefit for neoadjuvant chemotherapy in T2-4 MIBC.[8]

Reflecting on our data with respect to the literature, the non-adherence to recommendations from guidelines on NMIBC and MIBC is very similar. The only difference is the lack of a national guideline at that time. On what grounds do urologists decide not to use the available guidelines? And are they aware of what the guidelines entail in making this decision? Before exploring the rationale for underuse, the clinical consequences of this underuse should be clarified first.
In our studies with NMIBC, we did not find a significant difference in the five-year recurrence-free and progression-free survival rates, despite underutilization of adjuvant intravesical instillations. Apparently in NMIBC, the clinical outcomes of the observed treatment schemes are not so different in the cohorts of patients studied. This immediately raises the question of whether this lack of difference in recurrence-free and progression-free survival is due to the specific cohort studied and/or to a low or lower clinical impact on the part of the recommendations from the guidelines. In general, the recommendations in the guidelines are

created by means of evaluation of a systematic literature search by panels of expert clinicians, frequently in combination with clinical epidemiologists. The highest levels of evidence regarding the management having the best benefits in terms of recurrence-free, progression-free, or overall survival are derived from large randomized controlled trials (RCTs) or a meta-analysis.[9,10] The quality of evidence generated in the RCTs on bladder cancer itself is up for discussion. A recent systematic literature review of 13 RCTs on immediate instillation of chemotherapy in NMIBC patients explored the quality of evidence in the light of contemporary methodology. This meta-analysis still supports the fact that immediate instillation prolongs a recurrence-free interval but suggests the quality of evidence is low.[11] The cause cited was the high risk of bias in all but one trial due to lack of blinding and unclear randomization. Other reasons were the presence of significant statistical heterogeneity and the concern that studies with large negative effects were not published. Although RCTs provide the highest grade of evidence, only a small number of valid RCTs are published: 238 out of 29,106 studies in the period between 1995 and 2010.[12] Regarding the quality, only 8% of these studies was double-blinded, and less than one-third of trials reported a statistical power calculation (31.5%), and an even fewer number reported completing planned accrual (23.5%).[12] This underscores the need for more well-designed trials with larger sample sizes in order to optimize and validate diagnostic and treatment strategies. On the other hand, results from trials regarding a selected group of patients with specific age, comorbidity, and tumor characteristics that do not reflect the bladder cancer population, who have been treated in daily practice. The majority of patients developing bladder cancer are elderly, often with a history of smoking and with a variety of comorbidities comprising pulmonary and cardiac problems that might have disqualified them from participation in such RCTs.

So we do not know if the guideline recommendations for NMIBC, based on a scarcity of good quality RCTs, are truly representative and thus applicable to the contemporary group of NMIBC patients, who have never been eligible or willing to participate in one of those trials. In an attempt to deal with this issue, the results of observational studies, as we have presented them, could provide the additional information needed to refine the current general recommendations found in the guidelines for bladder cancer.
For MIBC, we did find longer survival in MIBC patients after radical cystectomy versus other treatment schemes. This was to be expected, as radical cystectomy is recommended as the first choice of treatment. There is

no evidence from comparative studies to support such a recommendation, however. All the evidence is based on large retrospective unicenter and multicenter series with some prospective data.[13] Since the results of cystectomy are superior, then it is remarkable that our series as well as other published series report utilization of cystectomy in no more than half of the patients with MIBC. One explanation could be that the large retrospective series concentrate on cystectomy but not on the treatment of MIBC disease in its entirety.

Motives for minor adherence to one of the guidelines (NCCN, AUA, or EAU) are numerous and varied. Physician surveys referring to practices at the time before the dissemination of the modern clinical practice guidelines of the AUA have reported clear associations between variation in management of NMIBC and number of years in practice, practice type (academic versus community hospital), and other physician-related factors.[14] Although Nielsen and collegues reported that the contemporary self-reported practices were generally aligned with the AUA 2007 guidelines on the early instillation of chemotherapy, and that the observed variations are still associated with practice type and number of years in practice.[15] In a population-based study on NMIBC using claims data, Chamie and collegues found no statistically significant increase in provider compliance after publication of clinical practice guidelines, with the exception of the use of BCG in high risk patients. Increasing surgeon volume was associated with higher rates of compliance with perioperative intravesical chemotherapy.[4] Other explanations cited for the heterogeneous compliance with the guidelines, particularly for NMIBC, are the organization of reimbursement, or hospital and coordination difficulties between operating room, pharmacy, and recovery room.

The individual treating urologist plays a pivotal role in decision-making in terms of the choice of treatment. Several conditions have an effect on his/her decision process. First, the availability of guidelines has greatly improved over the last two decades, with easy access to a national or an international guideline nowadays. The personal opinion and beliefs of the treating urologist about the recommendations in the guidelines also play a role. The EAU Research Foundation survey found uncertainty about efficacy outweighing toxicity, concerns about delaying cystectomy, and patient refusal as the major reasons for the very low use of neoadjuvant chemotherapy observed in selected major European tertiary centers (with

only 12% of the 5000 patients with MIBC undergoing cystectomy).[16] Furthermore, there are subtle differences in recommendations in the different guidelines, and also variations in the guideline updates and adjustments. As a result, recommendations have been provided by assigning a level of evidence and grade (highest level A to lowest level D) in the EAU guidelines or different grades of statements (standard, recommendation, option) in the AUA guidelines. These differences imply a certain degree of scientific uncertainty resulting in potential variability in approaching disease management on the part of clinicians.

Besides physician and practice factors, the patient preferences for surveillance and non-invasive treatment strategies in NMIBC may also play a role. For instance, the invasive nature of evaluation every three months and its subsequent impact on quality of life, as well as the adverse effects of intravesical therapy, may also contribute to noncompliance with the guidelines in a subset of patients. For MIBC, patients' physical status-derived factors, such as advanced age or pre-existing comorbid conditions, will hamper compliance to the preferred management. This is illustrated by Thompson and collegues who reported that half of the 767 patients who underwent radical cystectomy (single treatment) for MIBC T2-4 N0 M0 disease would not have been eligible for cisplatin-based neoadjuvant chemotherapy, having a GFR < 60mL/min pre-operatively.[17] With an increasing population of elderly patients with MIBC, the limitations due to chronic kidney failure will increase within the upcoming decades. In addition to kidney failure, probably other comorbidities also prevent patients from being treated with neoadjuvant chemotherapy. As we already saw in the last decade, two-thirds of all patients with MIBC suffered from at least one comorbid condition, and one-third had at least two concomitant comorbid conditions. And the percentage of patients without comorbidity decreased with increasing age to less than one-third of the patients aged ≥75 years.

The most important concern in contemporary bladder cancer treatment is how to reduce the under-treatment observed, which limits patients' quality and duration of life. One of the strategies should be to find a way to overcome the gap between best clinical practice recommendations and routine execution. As a result, profiting from these recommendations could be improved by more individualized, guided adaptation of them.
It has been shown that improving provider-level adoption of guidelines for BCG use and immediate single instillation after TUR not only improve

the care of patients with intermediate- and high-risk NMIBC but can subsequently lead to cost reduction by reducing recurrences.[2,18,19] Theoretically, guideline adoption could be stimulated by linking the financial incentive of the physician to a greater adherence to clinically effective measures, so as to facilitate positive patient outcomes and avoid complications. However, this might lead to an undesirable situation, where patients are refused invasive bladder-cancer treatment by their urologist, based on the believed unfit status of these patients, with the accompanying higher risk for complications.

To apply the guidelines on bladder cancer care to the contemporary bladder cancer patient population with frail elderly and various comorbidities, the guidelines could benefit from an update with additional data in addition to the results of RCTs. Collected relevant information from pattern of care studies and prospective registry data will better reflect daily practice. With these supplementary data on factors associated with disease-specific outcome, the guidelines could be enriched. This would allow for an individualization of guiding treatment, particularly in the growing group of elderly patients. As screening tools to distinguish between fit and frail patients are validated, doctors are better equipped to increase their patients' chance of survival and to maintain optimal quality of life. With the growing diversity in the psychological, physical, and social status of elderly cancer patients, close collaboration with geriatric doctors would appear obvious. Several standardized comprehensive geriatric assessment scales and indicators have been developed for the elderly referred for chemotherapy, but these are rarely applied to patients treated with other treatment modalities.[20] In cases where cystectomy is considered, the Charlson comorbidity score and the performance status (e.g., Karnofsky, ECOG, or ASA) will contribute to the assessment of the peri- and postoperative risks. In the end, the outcome of bladder cancer management is greatly dependent on how suggestions for improvement can and will be implemented in the healthcare organization.

In recent years, there have been several developments leading towards higher quality in bladder cancer care, which have occurred in the Netherlands. Since 2005, urologists have been requested by the Healthcare Inspectorate to provide information from their clinical practice on measurable parameters regarding bladder cancer treatment that does not directly reflect the outcome. After feedback from the Dutch Association

of Urologists, a more comprehensive list of requirements for better quality of care was developed. Recently, Dutch urologists have been obliged to present every newly diagnosed genito-urinary cancer patient at multidisciplinary case conferences. In these conferences, guidelines are principally the rule, but well-motivated treatment decisions not matching the recommendations can also be discussed and subsequently documented. These meetings can contribute to greater adherence to the guidelines, and the likelihood of under-treatment can be diminished.

In addition to the multidisciplinary perioperative approach, the centralization of treatment in MIBC optimizes its quality as well. In 2011 in the Netherlands, a volume-based centralization norm was implemented with a minimum standard of ≥ 10 cystectomies per year. {www.nvu.nl/kwaliteit/kwaliteitsnormen}. The surgical teams performing these operations should become more experienced, particularly in handling complications, and quality of care should increase. It is to be expected that the volume level will be 20 cystectomies per year in the near future. Then the 30- and 90-day mortality directly related to the surgery will probably diminish. However, more cystectomies in the elderly create a higher risk of non-disease-specific mortality. As a result, it is doubtful whether the disease-specific survival of these patients will increase. Perhaps additional centralization of the MIBC disease treatment itself can attain this. This might improve the selection of patients for cystectomy with or without neoadjuvant chemotherapy or alternative treatments such as radiotherapy, partial cystectomy, or brachytherapy of the bladder. To evaluate the results of such alterations in clinical practices, a reliable registration of patient characteristics, and treatment and outcome is crucial.

Part II Urothelial cell carcinoma of the upper urinary tract (UUT): The role of urography

The study that semi-quantitatively assessed the opacification-grade within the upper urinary tract of both retrograde uretero pyelography (RUP) and computer tomography urography (CTU) in the same patients showed that CTU underperformed compared to RUP in all segments of the ureter, although not in the renal pelvis and calyceal system. The study on initial RUP for the detection of lesions in the UUT showed that RUP is a feasible, sensitive, and highly specific diagnostic technique.

Over the past two decades, intravenous urography (IVU) has obviously been replaced by CTU for indications of upper urinary tract tumor (UUTT). Although there is no agreement on the optimal protocol, according to the European and American guidelines of urology and radiology, CTU is the preferred imaging modality for detecting upper tract lesions.[21,22] In the EAU guidelines, sensitivity and specificity from 0.67 to 1.0 and from 0.93 to 0.99, respectively, are reported, depending on the technique used.[21] Magnetic resonance urography (MRU) remains the preferred option in patients who cannot undergo CTU, usually in those cases where radiation or iodinated contrast media are contraindicated. The use of RUP might only be reserved for those patients who are not candidates for CTU or MRU, such as patients with renal impairment or proximal obstruction of the upper tract.

The accuracy of RUP for detecting UUTT has not been systematically evaluated. Only two studies have reported on similar diagnostic sensitivity and specificity for diagnosing UUTT in RUP, compared to CTU and MRU.[23,24] One of the reasons why explicit investigation of RUP has not been conducted might be its invasive nature. However, this argument may be less relevant now, since RUP is performed at the same time as a trans urethral resection (TURT) of the bladder tumor (under anesthesia) or when routine follow-up with cystoscopy (outpatient clinic) is performed. Another reason may be the revolutionary development of computer tomography (CT) technology since 1990, which has resulted in an enormous quantity of studies on a broad range of urological indications. At first the advent of the spiral (helical) CT made a volumetric acquisition of the abdominal cavity possible, such that small stones could be imaged with CT. Later the introduction of the multidetector CT, comprising a large number of thin section images in a short period of time, resulted in superior spatial, temporal, and contrast resolution that is as good as conventional radiography. With a scanning phase before and after intravenous contrast material, a comprehensive examination (referred to as CTU) of the urothelium of the UUT has become available. As a result, CTU for the urologist is no longer a time-consuming task and, for the patient, it is a negligibly invasive examination.

Though, with respect to the growing use of CTU and the ever-decreasing use of RUP in the detection of UUTT, there are negative consequences that need to be mentioned. First, the radiation dose for CTU is substantial as compared to RUP (9.73 to 14.8 mSv versus 0.5 - 0.9 mSv per single

acquisition, respectively).[25,26] Several studies have addressed the cumulative radiation burden from medical imaging.[27–29] Not knowing the exact cancer risk from radiation exposure, the risk does slightly increase in many patients, when undergoing radiation-based imaging. Another concern about the exponential growth of contrast-enhanced CTU utilization is the risk of contrast-induced nephropathy (CIN), particularly in patients with pre-existing renal impairment. Due to increased awareness of the clinical setting, improvement of prophylactic strategies, and the introduction of contrast media with lower nephrotoxicity, the incidence of CIN after CTU has decreased in the last decade.[30] However, particular attention remains to be drawn to the population diagnosed with UCC, because these patients frequently have major risk factors for developing CIN (e.g., in diabetes mellitus the risk of CIN ranges from 5.7 to 29.4%).

In addition to the considerations concerning the harm of radiation exposure and intravenous contrast in CTU itself, we should question whether all this radiographic imaging is beneficial in the diagnosis and follow-up of all patients with high risk NMIBC of the bladder or UUTT. The EAU recommends considering annual UUT imaging in high risk NMIBC.[31] Recently Sternberg and collegues assessed the need for routine upper-tract imaging in asymptomatic patients followed for NMIBC. In this study, 51 of 935 patients developed a UUTT, while only 29% of the tumors were detected on routine imaging with CTU. Overall 3,074 routine imaging scans were conducted for an overall efficacy of 0.49%.[32] In similar older series, the incidence of detected UUTT was even less (40 out of 1529 and 16 out of 680 patients, respectively).[33,34] In the latter study, only two of the 16 patients with metachronous UUTT were diagnosed by routine imaging (IVU); all other patients had symptoms indicating tumors in the urinary tract or had tumor from the ureteral orifice during routine cystoscopy. The same pattern is seen in the follow-up of the upper tract of patients treated for MIBC. In a meta-analysis, 5885 patients underwent routine UUT imaging (loopgraphy, urography, or CT) to identify only 40 recurrences with imaging, of 161 patients with recurrent disease.[35] In the end, all these imaging examinations lead to low detection efficacy, due to the low incidence of the disease and inaccuracy, and will also lead to low cost-effectiveness.

The fundamental basis for a more effective way of diagnosing UUTT calls for a twofold approach. In one respect, it must be apparent which radiographic modality has the best accuracy in terms of the explicit indication versus the least harm, and favorability versus the lowest cost. On the other hand,

the question is which patient is at what risk for having (or developing) a UUTT. By combining these two issues, an individual approach is considered necessary in every single patient. Although a review of the literature on the diagnostic accuracy of CTU, IVU, and RUP reveals a lack of comparative studies with RUP, we show that an initial RUP is a feasible, sensitive, and highly specific diagnostic technique. This must be a sufficient motive for the exploration of a comparative study of RUP as opposed to CTU or MRU in terms of diagnosing UUTT. Contrary to what the guidelines suggest, RUP might not only be reserved for those patients who are not candidates for CTU or MRU. RUP could perhaps also be used, without detriment to the patient, in combination with the TUR in newly diagnosed NMIBC or MIBC patients who need an initial evaluation of the UUT. In addition, RUP makes selective urine sampling of the UUT possible at the same time. In patients with suspected or proven MIBC, CTU may be a superior choice, because a CTU gives additional information on the T-stage and potential metastases in the same scan.

In choosing and timing the UUT imaging in the follow-up for NMIBC or MIBC, the odds of development of UUTT play a crucial role. One of the aims of regular follow-up is to increase the likelihood of the early detection of any subsequent UUTT, enabling treatment at a curable stage. As discussed previously, the available imaging techniques and the timing are apparently not adequate for detecting all lesions before these cause complaints. Sternberg and collegues also assessed alternatives to routine CTU, such as patient history, physical examination, urine cytology, and ultrasound upper-tract surveillance. These would have identified all but three patients (6%) in the cohort. When directing the use of CTU based on the results of such investigations, exposure to radiation and contrast media for the majority of the patients can be decreased.[32] On the other hand, risk factors for developing UUTT have been introduced in order to make decisions regarding the timing of imaging. In the follow-up of patients treated for NMIBC, annual imaging of the UUT is recommended for the high risk group and biannually for the intermediate group, although patients with a history of recurrent bladder cancer and cystectomy for NMIBC are at higher risk as well.[33,35–37] In the follow-up of patients with MIBC, no recommended follow-up strategy regarding timing is mentioned in the guidelines. Since most UUT recurrences occur later than three years after RC, at a time when the risk of local and systemic recurrence is decreasing, a panel of experts performing a critical analysis of the literature on follow-up after cystectomy for MIBC has

recommended lifelong annual UUT imaging for all patients.[38] Perhaps this interval could be adapted, depending on risk of recurrence. Risk factors for UUTT consist of superficial UCC involvement in the urethra, positive surgical margins of the urethra, and ureter of the cystectomy specimen.[35,39]

Conclusions

Patient-, tumor-, and doctor-related factors influence the choice of treatment and outcome of high risk NMIBC and MIBC in daily practice. When referring to current national and international guidelines, the vast majority of patients appear to be undertreated. Bladder cancer care could be improved by optimizing the adaptation of clinical guidelines in daily practice. However, the guidelines themselves should be adapted using data from observational studies in order to generate guidelines which are more appropriate for the contemporary bladder cancer patient. Therefore, an individual approach towards each and every patient is of significant importance.

As long as there are no comparative studies on different imaging techniques and follow-up schedules regarding imaging strategy in UUTT, decisions are best made by the treating physician, who has detailed knowledge regarding the patient's history, status, and risk factors, and these decisions further depend on the availability of imaging options in the clinical setting. In the end, that same physician needs to bear in mind that he is the primary physician who can contribute to improving the imaging strategy of UUTT patients by familiarizing himself with the advantages of various techniques, however often used.

Future perspectives

Regarding the improvement of clinical care in bladder cancer, various aspects require consideration. The results of pattern of care studies have already shown that recommended treatments will not always be or can be performed on all patients, and consequently an inferior outcome is to be expected. The prospective registration (studies) of current practice, doctor- and patient-related factors in terms of decision-making and treatment outcome can now be elucidated. In 2011, the Dutch registration database for MIBC and cystectomy began operation. Participation by the treating urologists is obligatory. An important aspect of prospective registration is the opportunity to benchmark against other treating physicians and hospitals. Theoretically, this should contribute to revising current daily practice in an indirect way. Combined with the implementation of a minimum volume for cystectomies per institute per year, this has already led to centralization, which can lead to an improved level of bladder cancer care.

As a result, prospectively gathered information on bladder cancer treatment can serve as important input for the design of future studies, for example, by increasing the study participation of the growing population of elderly with MIBC. Increased comorbidity and frailty will require broader inclusion criteria and a more observational character for the study design.

Furthermore, estimating quality of daily-care developments in new agents and techniques is urgently needed as well. In the treatment of NMIBC several intravesical treatment modalities, other than those the guidelines recommend, have been investigated, but more phase III trials and longer follow-up are warranted before these can be implemented in daily practice. Future studies on intravesical treatment should focus more on personalized decision-making based on specific tumor characteristics.[40]

Despite the increasing international availability of guidelines on bladder cancer treatment, for over a decade, the survival rates for NMIBC and MIBC have not significantly improved. The methodology of guidelines is based on levels of evidence, where the highest level (evidence obtained from meta-analysis of randomized trials) generally leads to the highest grade of recommendation. As previously discussed, it is very likely that there is an underrepresentation of older and more comorbid patients in those trials. Promoting more interest in observational studies that contribute to the recommendation grades could favor the implementation and execution of guidelines, and hopefully result in improved outcome.

Regarding future perspectives for the imaging of UUTT, there are two aspects that deserve further attention. First, the choice for CTU as the preferred technique for detection of UUTT, while comparative studies (on other techniques) are lacking and its widespread increased use is leading to rising costs and potential harm from radiation exposure and intravenous use of contrast. The rarity of the disease hampers conducting a prospective study, although a multicenter trial including patients with hematuria and patients who are in follow-up for UUTT could probably enroll enough UUTT patients. When conducting a prospective study, comparing CTU to RUP, not only the performance of the techniques but also the impact of radiation and

intravenous contrast exposure and the financial consequences should be analyzed.

Second, the different guidelines on the follow-up scheme (imaging modality and timing) of the UUT in high risk NMIBC, MIBC, and UUTT patients are not totally similar and complete. Rationally, the negative effects for patient and society of following any chosen technique along with the timing of imaging in the specific patient should be balanced with the risk of developing recurrent disease. The translation of theory to daily practice will require a lot of pragmatism, given the lack of studies with a clinical endpoint that can contribute to any sustainable evidence.

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part 4
Appendices

List of abbreviations

ASA	physical status classification system adopted by the American Society of Anesthesiologists
AUA	American Association of Urology
BCG	Bacille Calmette Guérin
CCI	Charlson Comorbidity Index
CIS	Carcinoma in Situ
CPG	Clinical Practice Guideline
CT	Computer Tomography
CTU	Computer Tomography Urography
CCCN	Comprehensive Cancer Center North-Netherlands
DFS	Disease Free Survival
DSS	Disease Specific Survival
EAU	European Association Urology
EBRT	External Beam Radiation Therapy
ECOG	Performance status adopted by the Eastern Cooperative Oncology Group
ECR	Eindhoven Cancer Registry
EORTC	European Organization for Research and Treatment of Cancer
ESR	European Standardized Rate
GFR	Glomerular Filtration Rate
HR	Hazard Ratio
IV	Intra Venous
IVP	Intra Venous Pyelography
IRT	Interstitial Radiation Therapy
MDCTU	Multidetector Computer Tomography with urinary phase
MIBC	Muscle Invasive Bladder Cancer
MMC	Mitomycin C
MRU	Magnetic Resonance Urography
NCCN	National Comprehensive Cancer Network
NMIBC	Non Muscle Invasive Bladder Cancer
NVU	Dutch Association of Urology
OR	Odds Ratio
OS	Overall Survival
PALGA	Dutch network and registry of histopathology and cytopathology
PFS	Progression Free Survival
PLND	Pelvic Lymph Node Disection
PUNLMP	Papillary Urothelial Neoplasm of Low Malignant Potential
RCT	Randomized Controlled Trial
RFS	Recurrence Free Survival
RS	Relative Survival
RUP	Retrograde Ureteropyelography
SEER	Surveillance, Epidemiology, and End Results
SES	Socio Economic Status
TNM	Tumor Node Metastasis
TUR(T)	Trans Urethral Resection (of Tumor)
UCC	Urothelial Cell Carcinoma
UUT	Upper Urinary Tract
UUTT	Upper Urinary Tract Tumor
WHO	World Health Organization

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Curriculum Vitae

Annemarie Leliveld-Kors werd geboren op 20 augustus 1970 te Groningen. Zij volgde de lagere en middelbare school in Hengelo (O) en haalde haar VWO diploma in 1988 aan het Twickel College. In dat zelfde jaar startte zij met de studie geneeskunde in Groningen alwaar zij in 1994 haar doctoraal afrondde. Om niet afhankelijk te zijn van het toevallige lot om ergens in noordoost Nederland voor de coschappen geplaatst te worden deed zij een verzoek aan de Vrije Universiteit in Amsterdam om deze daar te volgen. Maar voor aanvang van de coschappen ging zij, vooral vanwege haar interesse in de Italiaanse taal, naar Bologna om daar een stage van vier maanden te lopen op de afdeling dermatologie in het universiteitsziekenhuis San Orsola-Malpighi. Na het keuzecoschap urologie, onder begeleiding van prof. dr. D.W.W. Newling, deed zij in 1996 haar artsexamen. De liefde voor de urologie hield aan gedurende de twee jaren nadien toen zij in het Kennemer Gasthuis te Haarlem als arts-assistent werkte onder de enthousiaste supervisie van drs. R.M. Groenteman en drs. J.J.W. van Haga en later drs. M.G. Weissglas. In de buitengewoon frequente voorwachtdiensten stonden ook de urologen uit het Spaarne Ziekenhuis, haar bij. In 1999 werd zij aangenomen voor de opleiding urologie in Groningen. De twee jaar durende vooropleiding chirurgie werd gevolgd in het Martini Ziekenhuis te Groningen onder leiding van wijlen dr. H.B. Oeseburg en zijn opvolger dr. P.C. Baas. Vervolgens werd de urologische opleiding gedurende drie jaar gevolgd in het toenmalige Academisch Ziekenhuis Groningen (prof. dr. H.J.A. Mensink) en afgerond in het Martini Ziekenhuis (dr. N.P. Tjon Pian Gi). Sinds 2005 maakt zij deel uit van de staf urologie in het Universitair Medisch Centrum Groningen. Hier heeft zij zich toegelegd op de oncologische urologie en de reconstructieve chirurgie van de urinewegen. Tevens heeft zij zich gespecialiseerd in laparoscopische ingrepen, in het bijzonder in de verwijdering van diep infiltrerende endometriose haarden in en nabij de urinewegen. Dat laatste gebeurt uiteraard in multidisciplinair verband. Sinds 2009 is zij IKNL consulent voor noordoost Nederland. Zij maakt deel uit van verscheidene commissies binnen het UMCG en is actief lid van het Oncoforum voor Nederland en Europa. Tevens is zij lid van de landelijke werkgroep Oncologische Urologie. Deze werkgroep speelt de hoofdrol inzake het opstellen van kwaliteitscriteria en de eisen ten aanzien van de registratie van de behandelingen van urologische tumoren. Het afgelopen jaar is zij ook actief geworden binnen de landelijke Commissie Kwaliteitsvisitatie en de Werkgroep Endo-urologie van de Nederlandse Vereniging voor Urologie.

Het uitvoeren van dit promotieonderzoek vond plaats naast de klinische werkzaamheden en nam derhalve geruime tijd in beslag. Na de zeer gewaardeerde begeleiding door collega en eerste promotor prof. dr. I.J. de Jong kon door nieuwe impulsen van de tweede promotor prof. dr. G.T. de Bock van de afdeling epidemiologie, de afronding van het proefschrift plaats vinden.

Annemarie Leliveld-Kors dankt haar gedrevenheid in het vak en fysiek actieve karakter aan zowel haar vader, gepensioneerd maar werkend kinderarts, als aan haar moeder die een drukke kleinvee boerderij gaande houdt. Zij is getrouwd met Lucas Leliveld en samen hebben ze drie kinderen: Vera (10), Peer (8) en Tibbe (6).

Curriculum Vitae

Annemarie Leliveld-Kors was born in Groningen on August 20, 1970. She attended elementary school and high school in Hengelo (Overijssel) and graduated in 1988. In the same year she started studying medicine at the University of Groningen and graduated in 1994. By leaving nothing to chance she requested the Free University Hospital in Amsterdam to complete her internships right there. Primarily for reasons of interest in the Italian language she followed a clinical internship at the Department of Dermatology of the Ospedale San Orsola-Malpighi in Bologna just before that. After a voluntary internship under supervision of prof. dr. D.W.W. Newling at the Department of Urology of the Free University she passed her final exams in medicine in 1996. Her interest in urology increased during working as a house officer in urology for two years in the Kennemer Gasthuis in Haarlem under the enthusiatic supervision of drs. R.M. Groenteman and drs. J.J.W. van Haga and later drs. M.G. Weissglas. The urologists from the Spaarne Hospital also rendered their assistance in very frequent calls. In 1999 she started her training with two years general surgery at the Martini Hospital in Groningen under the supervision of deceased dr. H.B. Oeseburg and his successor dr. P.C. Baas. She completed her residency in urology with three years of urological training at the University Hospital in Groningen (prof. dr. H.J.A. Mensink) and the final year in the Martini Hospital (dr. N.P. Tjon Pian Gi). Since 2005 she is working as a senior-staff member within the Department of Urology of the University Medical Center Groningen. She got well experienced in oncological and reconstructive urology. In addition, she has specialized in laparoscopic surgery, particularly in the removal of deep infiltrating endometriosis, the latter in a multidisciplinary setting. Since 2009 she has been a consultant for IKNL in the northeastern part of The Netherlands. Besides participating in various committees within the hospital, she is an active member of the Oncoforum Netherlands and Europe. She is also a member of the national committee on oncological urology. This committee plays a key role in developing criteria for quality and registration data bases for the treatment of urological malignancies. In 2013 she became a member of the committee for monitoring the quality of national urological care and the committee of endo-urology of the Dutch Association of Urology.

While this dissertation was executed besides the clinical activities it took considerable time. Following the very appreciated supervision of the first promoter, prof. dr. I.J. de Jong, fresh impulses from prof. dr. G.T. de Bock led to the completion of the thesis.

Annemarie Leliveld-Kors inherited her passion for the field of medicine and the physical active character from her father, a `retired` but still working pediatrician, as well as her mother who is running a cattle farm during many many years. She is married to Lucas Leliveld and together they have three children: Vera (10), Peer (8) and Tibbe (6).

Dankwoord

“Je studie is geen renbaan maar een loopbaan”, zei mijn vader altijd. Zo is het ook voor de afronding van mijn proefschrift gebleken. Met wisselende intensiteit in de afgelopen jaren, heb ik het proces van promoveren volbracht. Niet dat ik me nu rijk reken met zeeën van tijd maar ondertussen kijk ik uit naar mogelijkheden om mij verder te ontwikkelen. Het opzetten van onderzoek met collega stafleden behoort daartoe. Maar niet voordat ik een aantal mensen heb bedankt voor de hulp die zij mij hebben verleend waardoor het nu geworden is wat het is.

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