VILNIUS UNIVERSITY
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Final Thesis

Treatment of Upper Urinary Tract Urothelial Carcinoma. Minimal invasive treatment options

Literature review

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Dedicated to my mother and Ferdy, grandma & grandpa

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1. SUMMARY

Upper Urinary Tract Urothelial Cancer (UTUC) involves either the renal pelvis or the ureter. Radical nephroureterectomy is still seen as the gold standard treatment method for UTUC. Nevertheless, minimal invasive treatment options like endoscopic management seem to be more of a prevalent alternative for certain patient groups, due to the fact that the morbidity and the risk of dialysis is decreasing and the likelihood of the patient's survival is not impacted.

At present, under the European Association of Urology (EAU) guidelines, if all conditions such as; (a) unifocal disease, (b) tumour size < 2 cm, (c) negative for high-grade cytology (d) low-grade URS biopsy, (e) no invasive aspect on CT, (1) are being fulfilled, then kidney sparing surgery should be performed. The purpose of this literature review is to compare different minimal invasive treatment procedures and their oncologic outcomes. The criteria from the EAU guidelines (2022) were taken to define low-risk UTUC. Another point of discussion is the instillation of topical agents, such as bacillus-calmette-guéurin (BCG) in the upper urinary tract (UUT). Conclusions are done based on the analyzed studies.

2. KEYWORDS

Upper tract urothelial cell cancer, laparoscopic, endoscopic, radical nephroureterectomy, kidney sparing surgery, segmental ureterectomy, percutaneous approach, topical agents, bacillus Calmette-Guérin (BCG), microhematuria, macrohematuria, risk stratification, topical agents.

3. METHODS

A systemic literature review was conducted using PubMed scientific database and Google Scholar search engines looking at the different aspects involving the minimal invasive treatment options of UTUC with the keywords mentioned above. The search was limited to articles available in the English language. The Majority of articles were from the period between 1986-2022. 111 publications were reviewed and discussed to compare minimal invasive treatment options versus radical procedures.

4. INTRODUCTION

In our society cancer is still a huge public health problem all over the world and shows the second leading cause of death in the United States of America (2). The sixth most common tumours in developed countries are urothelial carcinomas (2). Location of UCs can be either in the lower (bladder and urethra) and/ or in the upper tract (pyelocaliceal cavities and ureter), but

the most common (90-95%) of UCs occur in the bladder, which makes the largest incidence of urinary tract tumours (3). The incidence of 5-10% makes upper urinary tract UCs (2). Even though it is fundamentally a urothelial cell carcinoma, it must be treated differently from bladder cancer. Multifocal tumours are present in 10-20% of cases, while pyelocaliceal tumours are twice as prevalent as ureteral tumours (4). More studies have been done in recent decades in an attempt to enhance treatment results and to see UTUC as a distinct entity. UTUC is an uncommon type of cancer. Hematuria can signify serious malignancies, occasionally upper urinary tract urothelial carcinoma. An "UTUC is considered low-risk if it has all of the following criteria (5):

- Unifocal disease
- Tumour size <2 cm
- Negative for high-grade cytology
- Low-grade URS biopsy
- No invasive aspect on CT

5. RISK FACTORS

Gender

Upper urinary tract UCs are more frequent in males than in women, with a 2:1 incidence ratio between males and females. with a peak prevalence in those aged 70–90 years (6).

Smoking

Smoking is one of the most significant risk factors. In comparison to non-smokers, tobacco exposure is linked to a 2.5–7-fold increased risk of developing a UTUC (7) (8).

Lynch Syndrome

In Lynch syndrome-related malignancies, UC is the third most prevalent malignancy type (9). LS is a hereditary nonpolyposis colorectal cancer (HNPCC) and is an autosomal-dominant cancer syndrome, which causes about 3% of new colon cancer diagnoses and is associated with a higher incidence of urothelial carcinoma (9).

Aromatic amines

Several environmental factors cause the development of tumours in the upper urinary tract (UUT). Exposure to aromatic amines, which were used in many western industrialized

countries for instance in dyes, rubber, and textiles, are responsible for the carcinogenicity of specific chemicals like benzidine or beta-naphtylanine which are linked to UTUC (7).

Black foot disease (BFD)

A significant high incidence of UUTC-UCC was noticed in a certain area of the south-west coast of an island in Taiwan, but the link between BFD and UUT-UCC is still unclear, because in other areas on the island, there is also a high number of UUC, but a reduced rate of BFD cases (7).

Balkan endemic nephropathy

Balkan endemic nephropathy (BEN), first characterized in the 1950s in south-eastern Europe, is a chronic tubulointerstitial nephropathy with a slow onset and progression to end-stage renal disease (ESRD), which is very closely linked to upper urothelial carcinoma of the renal pelvis and ureter (10). This condition affected specific people from specific regions like from the tributaries of the Danube River in Bosnia-Herzegovina, Croatia, Macedonia, Serbia, Bulgaria, and Rumania, connected with farming activities (10). There are currently no clear-cut criteria for defining the condition, however, it is worth noting that individuals from endemic areas got UTUC at a rate 100-200 times higher than those from larger cities (11).

Chronic kidney disease (CKD)

According to their nephrotoxic and carcinogenic properties, some nephrotoxins, such as analgesics and aristolochic acid, may explain the bidirectional link between CKD and UTUCs. (12). UTUC and analgesic nephropathy are linked to an abuse of compound analgesics, especially for phenacetin, in kidney transplant recipients (KTRs) (12).

Analgesic abuse

1961 in Sweden a few cases of UUT-UCCs are linked to the usage of phenacetin in the anesthetic department, which has a direct mutagenic effect and was first recognized (7).

Aristolochic acid

Aristolochic acids are linked with carcinogenic, mutagenic, and nephrotoxic phytochemicals in the urinary tract system (13). UTUCs are mainly caused by the mutagenic effect of this chemical carcinogen (13). Furthermore, Aristolochic acid is associated with renal cell carcinoma,

hepatocellular carcinoma, intrahepatic cholangiocarcinoma, and most important bladder cancer (14).

Chinese herbal medicine

Chinese herbal medicine, containing Aristolochia was used for approximately more than 2500 years (14). Taiwan, where substantial usage of Aristolochia herbal treatments have been verified by a systematic review of prescriptions in a national database and has the highest recorded incidence of UUC. According to these findings, almost one-third of Taiwan's population has been exposed to herbs containing or likely to contain AA (14) Furthermore, a linear dose-response association has been demonstrated between the use of AA-containing herbal treatments and the likelihood of acquiring UUC (14).

Alcohol abuse

Smoking is a well-known UTUC risk factor, whereas alcohol consumption might be an independent risk factor for UTUC. This was shown by a large case-control study (1,569 cases and 506,797 controls) in Japan, where the risk of developing UTUC is extremely higher in ever-drinkers in comparison to never drinkers (OR = 1.23, 95% CI, 1.08–1.40; P = 0.001), with a low-risk threshold of 15 g of alcohol per day (15).

Table 1: *Urothelial Cancer Risk Factors*

Risk Factors Included in AUA Microhematuria Risk Stratification System	**Additional Urothelial Cancer Risk factors***
• Age • Male sex • Smoking history • Degree of microhematuria • Persistence of microheamturia • History of gross hematuria	• Irritative lower urinary tract symptoms • Prior pelvic radiation therapy • Prior cyclophosphamide/ifosfamdide chemotherapy • Family history of urothelial cancer or Lynch Syndrome • Occupational exposures to benzene chemicals or aromatic amines (rubber, petrochemicals, dyes) • Chronic indwelling foreign body in the urinary tract

*The panel recognizes that this list is not exhaustive

Table 1 adapted from Barocas DA, Boorjian SA, Alvarez RD, Downs TM, Gross CP, Hamilton BD, et al. Microhematuria: AUA/SUFU Guideline. J Urol. 2020 Oct;204(4):778–86.

6. Histology

Pure non-urothelial histology is less common and therefore biggest part of upper urinary tract tumours are UCs (16,17). Chronic inflammatory infections and infections caused by urolithiasis are connected with pure squamous cell carcinoma (18,19) and variants are seen in 25% of UTUCs (20,21). UC shows deviating squamous divergence occurring in about 15% of urothelial cases (22,23). Squamous cell carcinoma of the urinary tract (UT) is mostly linked to infections from urolithiasis and chronic inflammatory diseases (22,23). A special surveillance is needed in case of squamous cell cancers, because keratinizing squamous metaplasia of urothelium is a risk factor (1). UTUCs showing variant histology are marked as high-grade and have therefore a worse prognosis in contrast with pure UCs (19,24,25). Sarcomatoid and UCs with inverted growth are two more types that are seldomly seen (24). Collecting duct carcinomas are classified as renal tumours, because they might have similar features with urothelial carcinomas and demonstrate an exclusive transcriptomic signature comparable to RC (renal carcinoma), with an alleged source in the kidney, specified in the distal convoluted tubules (26).

7. Classification

Bladder carcinoma and upper urinary tract carcinomas have almost equal classification and morphology (27), but unfortunately, it is still very hard to classify the taken samples into non-invasive papillary carcinoma, carcinoma in situ (CIS), and invasive carcinoma (28). The histological grade of the diagnosed tumour is important for further clinical steps because the defined grade is almost identical to the pathological stage (29).

8. Risk stratification

The treatment options for UTUCs have improved due to the innovation of small calibre fiber-optic flexible digital ureteroscopes, in combination with the current laser technology (30), and therefore radical nephroureterectomy (RNU) is no longer the gold standard for all UTUCs (31). More important and challenging is to analyze and identify which patient will be treated with

the most appropriate technique (31). In most cases only postoperatively, it is easier to stage and grade a tumour, from the RNU specimen in UTUC, and in general, for almost all malignancies, the important classic prognostic factors like stage and grade stay the same after surgery (31). With the help of CT, MRI, and tumour resection a precise staging and grading of bladder cancer is possible (31). Concerning UTUC, unfortunately, the preoperative predictive staging and grading are still suboptimal, even with advanced cross-sectional imaging and taking a specimen of the muscular layer (31). Postoperatively after RNU, Brown et al. analyzed 119 patients of whom 71 patients suffered from high-grade tumours recognized preoperatively for RNU management on ureteroscopic specimens. 47 of those 71 patients had ≥ T2 UTUC while having done RNU (positive predictive value [PPV]: 66%). 35 out of 48 patients with the non-high-grade disease, were affected with <T2 malignancy in the RNU biopsy (negative predictive value [NPV]: 72%) (32). Concluding, the degree of tumour has been shown to be an accurate substitute for the stage of the disease. Therefore, risk stratification of non-metastatic UTUC is divided into low- and high-risk UTUC. All following features of low-risk UTUC need to be present a) unifocoal disease b) tumour size < 2 cm c) negative for high-grade cytology d) low-grade URS biopsy e) no invasive aspect on CT. In contrast to low-risk UTUC, any high-risk UTUC features need to be present a) multifocal disease b) tumour size > 2 cm c) high-grade cytology d) high-grade URS biopsy e) local invasion on CT f) hydronephrosis g) previous radical cystectomy for high-grade bladder cancer h) variant histology (33,34).

In daily practice it is not easy to evaluate the patient's UTUC`s tumour stage on a clinical basis before surgery, therefore it is helpful to "risk-stratify" UTUC between low- and high-risk for choosing the right treatment, like minimal invasive treatment options or radical ones (31,35). The European Association of Urology has updated these factors to consider for risk stratification, which can be seen in figure 1.

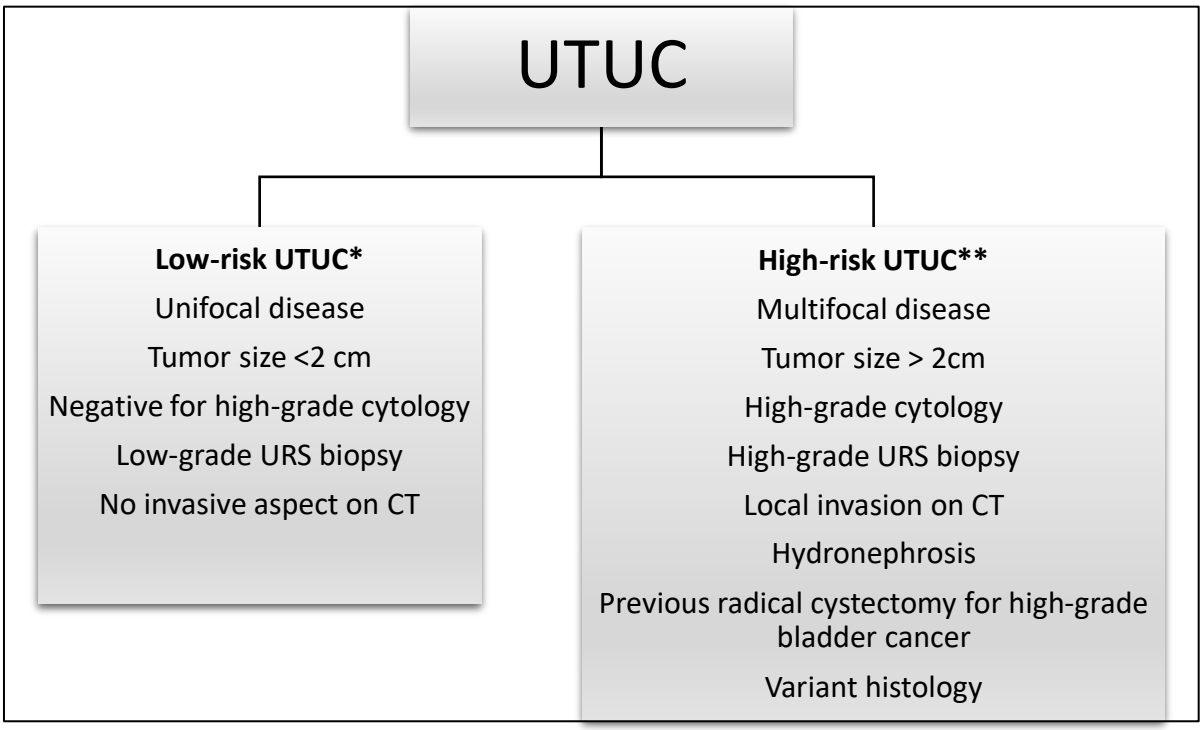

Figure 1. adapted from *EAU Guidelines on Upper Urinary Tract Urothelial Carcinoma, European Association of Urology 2022 (5).*

CT = computed tomography; URS = ureteroscopy; UTUC = upper urinary tract urothelial carcinoma.

* All these factors need to be present.

**Any of these factors need to be present.

9. DIAGNOSTICS

9.1 Hematuria

UTUC can be either a symptom-related or an incidental finding, whereas the most typical symptom is micro- or macrohematuria (70-80%) (36). Hematuria is defined as the presence of erythrocytes (red blood cells) in the urine. Either red blood cells are visible, which indicates a symptom, or they are nonvisible, which indicates a sign (36)(37). In the UK dipstick test for diagnosing nonvisible hematuria is the golden standard, showing a high sensitivity of 91-100%, but a lesser specificity of 61-99%, because hematuria alone, may signify many different diseases like bladder cancer, UTUC, renal cell carcinoma or even urinary tract stones (36). The division into high and low-risk patients with hematuria, based on the risk factors such as (a) history of smoking, (b) exposure to chemicals, (c) benzenes or aromatic, (d) macrohematuria, (e) older age (>40 years), (f) usage of phenacetin, into patients with a positive dipstick test,

need to be consulted by an urologist to rule out any life-threatening malignancies in the lower and upper urinary tract, because all these factors increase the risk of diagnosing urothelial cancer. (36). They can be used for clinical workup. Compared to the American Urological Association guidelines, a positive dipstick test needs to be followed by a microscopic investigation, showing three or more erythrocytes per high-power field on a microscopic evaluation, taken from the midstream urine (36). At the moment, recommended standard diagnostic includes a minimum of two urinalyses at different times, when having a patient with asymptomatic microhematuria, however in the case of macrohematuria only one positive urinalysis, and exclusion of urinary tract infection (UTI) and transient causes, is needed. Moreover, one has to differentiate the cause of hematuria, whether it originates from the epithelium or in the nephron, to refer to a urologist or nephrologist. Patients showing proteinuria, elevated serum creatinine, erythrocytes on the microscopic investigation, or hypertension, should be referred to the nephrology department (36).

The next step would include imaging studies for further diagnosing possible benign or malignant diseases like kidney stones, renal cell cancer, or UUT-UCC. The gold standard used to be intravenous urography (IVU) and ultrasonography (US) as the first steps. Many observational series have been done for deciding what single or even combinational investigation for determining the cause of hematuria can be done. Since 2006, CT urography has been the initial imaging step to investigate the cause of hematuria (36). Since 1973, when the first CT machine was introduced, which was invented by Godfrey Hounsfield, a huge improvement can be seen. Not only the image quality, which is capable to acquire 320 body sections per gantry rotation, which can be used for clinical practice but also the increased speed of imaging and spatial resolution make up a big step forward in diagnostics (36). Therefore isotropic resolution with multiplana imaging leads to a very high diagnostic accuracy of CT urography for UUT-UCC and makes it difficult to overlook even small tumours of the upper urinary tract or bladder (36). CT angiography, CT colonography, and CT urography include the use of isotropic resolution which develops fast in daily clinical practice (38). In 2008, guidelines from the Upper Urinary tract Imaging Group of the European Society of urogenital Radiology were introduced (36,39).

9.2 Urinary Tract Evaluation

The American Urological Association has developed a microhematuria risk stratification system, which is divided into low, intermediate, and high-risk grading. Table 1 shows a summary of all criteria, which can be met for each risk stratification (40). When finding MH in

low-risk patients, the AUA recommends either a follow-up urinalysis within the next 6 months or directly continuing with cystoscopy and renal ultrasound (40). The risk of diagnosing a urologic malignancy in low-risk patients showing MH is quite low; because of that, the risks and benefits of the specific imaging need to be evaluated and as well the consequences of a false positive detection (40,41). Cystoscopy is the golden standard for detecting bladder tumours (40,42–45). If patients again are presented with MH within 6 months, then they should be reclassified as intermediate- or high-risk patients, therefore cystoscopy and an imaging evaluation of the upper urinary tract should be done immediately (40). This kind of re-classification is the patient's guarantee to go through a risk-stratified evaluation again (40). Patients with continuous MH on UA have an increased rate of urologic tumours compared with a negative MH result within the 6 months follow-up (40,46). Studies of MH patients have permanently shown that most of the time bladder cancer is found if a urologic malignant disease is diagnosed (47–56). Cystoscopy compared to imaging diagnostic, has a much higher sensitivity (98%) (57) for detecting bladder cancer, and therefore cystoscopy is recommended in intermediate-risk MH patients (40). Ultrasound as a diagnostic for UTUC has a low sensitivity of only 14%, but still, the Guideline Panel of the American Urological Association Education and Research recommends ultrasound of over axial imaging due to the limited benefit and its little incidence of this malignancy (40,58). Axial imaging and cystoscopy of the upper tract are reserved for patients which are categorized as high-risk, presenting persistent MH and it shows different ways (40). Option one is the multiphasic CT urography which also means the imaging of the urothelium. (40). Option two, includes MR urography, instead of option one, if there is a contraindication given, for instance, chronic kidney disease or the patient is allergic to iodine-based contrast media (40). If option one and two is contraindicated, clinicians might use retrograde pyelography in conjunction with non-contrast CT or renal sonography (40). Clinicians who have already performed renal ultrasound before on patients with recurrent or persistent MH have a higher possibility of UTUC malignancy, therefore CT urography, MR urography, or retrograde pyelography should be considered (40).

Table 2: *AUA Microhematuria Risk Stratification System*

Low (patient meets all criteria)	**Intermediate (patient meets any one of these criteria)**	**High (patient meets any one of these criteria)**
• Women age <50 years; Men age <40 years • Never smoker or <10 pack years • 3-10 RBC/HPF on a single urinalysis • No risk factors for urothelial cancer	• Women age 50-59 years; Men age 40-49 years • 10-30 pack years • 11-25RBC/HPF on a single urinalysis • Low-risk patients with no prior evaluation and 3-10 RBC/HPF on repeat urinalysis • Additional risk factors for urothelial carcinoma	• Women or Men age >60 years • >30 pack years • >25 RBC/HPF on a single urinalysis • History of gross hematuria

Table 2 adapted from Barocas DA, Boorjian SA, Alvarez RD, Downs TM, Gross CP, Hamilton BD, et al. Microhematuria: AUA/SUFU Guideline. J Urol. 2020 Oct;204(4):778–86.

10. MINIMAL INVASIVE PROCEDURES

Radical nephroureterectomy with bladder-cuff removal is still the gold-standard for UTUC treatment in high-risk tumour patients (1). In the past years, minimally invasive treatment techniques have been applied to urologic diseases. 1964, Marshall reported the first use of a flexible ureteroscopy (fURS) (59). Marshall could see the ureteral stone passing through the 26 Fr cystoscope (59). In the 90s, fURS gained acceleration because of having an irrigation channel and flexible tip now (59). Active and passive deflection was possible (59). Decreasing the diameter of the devices and increasing the deflection angles were the main goal back at this period (59). Almost 15 years later, in 2001 a fURS with a 2-way deflection (270 degrees) has been developed and produced (59). Urologists were able to access into the entire pelvicalyceal system (59). 5 years later, in 2006 digital fURS were developed and produced. The devices became smaller, with a much better resolution and color quality and a second working channel, to increase the irrigation power was manufactured (59). In 2010, Yinghao et al. described the first combination with a rigid and fURS, which was called “the Sun`s utereoscope”(59,60). Present development of technology, like endoscope or laser ablation devices, urologists can

approach tumours in the upper urinary tract and resect them easily. These methods are reserved for tumours which are defined as low-risk diseases (Fig.1). They have been introduced especially for diseases that affect the upper and lower urinary tracts. Lastly, researchers reported robotic RIRS system, to bring technological advances and give a chance to improve the minimally invasive treatment options for urothelial carcinoma in the upper urinary tract (61,62). Effects and outcomes of robotic RIRS is not yet clear. The urological department has many tools to aid at the moment in the management of UUT-UCC.

10.1 Kidney sparing surgery (KSS) vs. radical nephroureterectomy (RNU)

Traditionally radical nephroureterectomy (RNU) with bladder-cuff removal was confirmed as the golden standard procedure for localized diseases in the upper tract urothelial carcinomas (UTUCs) because the preoperative staging has been difficult (63).

The improvement of diagnostic imaging and endoscopic armamentarium (64,65) have increased the importance of kidney sparing surgeries (KSS) for specific cases of UTUC with low-risk tumors (63,64). KSS was actually reserved for patients which were not physically able to undergo radical nephroureterectomy, or for those who have bilateral or patients with functionally and anatomically solitary kidneys and patients with chronic kidney disease (63,64). However, the oncologic safety still stays debatable (66–68).

Seisen et al. compared seven studies (69–75) including 1923 patients and analyzed the outcomes of KSS (*n*=547) versus RNU (*n*=1376), but without comparing each different treatment option that was used to maintain the kidney (64). In several different studies (69,70,72,74) a difference could be seen in terms of preoperative characteristics (64). Cutress et al. mentioned younger patients' age, greater proportions in terms of patients with an adverse general condition, and smaller tumour size in patients treated with KSS (70). RNU operated patients had more pathologically confirmed high-grade (69,70,72,74) and more advanced-stage (74) diseases compared to patients operated with KSS (64).

10.1.2 Oncologic outcomes

Comparing the 5-yr, 10-yr, or last follow-up CSS in all seven studies, no marked differences could be seen between KSS and RNU treated patients (64). Cutress et al reported that KSS treated patients for grade 2 disease died because of cancer reasons (70). KSS treated patients with a grade 3 disease had a less long 5-yr and 10-yr OS (70), whereas the 5-yr and last follow-up metastasis recurrence-free survival (MFRS) were quite the same in KSS and RNU treated patients, even when the numbers of developing metastases was not zero after KSS, and also not

in low-grade UTUC (64,73). A higher chance of bladder recurrence, also a shorter 5-yr and 10-yr BRFS for grade 2 and 3 diseases were seen (64,70). In general talking about recurrence, a shorter 5-yr and 10-yr local recurrence-free survival (LRFS) after KSS was seen (64,70). Only Cutress et al reported a higher chance of upstaging and/ or upgrading after patients who were treated with KSS versus RNU ($p = 0.037$) and that was specifically marked for UTUCs affected by grades 2 and 3 ($p = 0.027$ and $p = 0.033$) (64). Moreover, Simhan et al reported a higher chance of overall mortality when treated with KSS (64,69) and at the same time different studies reported a decline in LRFS and BFRS when treated with KSS (64,70,72).

10.2 Percutaneous approach vs. radical nephroureterectomy

In urology, a percutaneous approach represents a method where the operator access the kidney directly from the skin into the kidney (from the back) through a tract to be able to use larger instruments for larger tumours or solitary kidney.

Seisen et al compared two studies (76,77) that included 180 patients in terms of oncologic results after being treated percutaneously (*n = 66)* versus being treated with RNU ($n = 114$). Preoperative and postoperative characteristics did not show any relevant differences, only less big tumour size by patients treated with PC surgery was mentioned in the study analyzed by Roupret et al (76). Post-operation, low-grade and non-invasive malignancies were more seen in patients operated with PC than in patients operated with RNU (64).

10.2.1 Oncologic outcomes

If comparing the 5-yr CSS which was reported by Roupret et al, no relevant differences were seen in the PC and RNU groups (64,76). Significantly for high-grade disease patients, Lee et al reported a decline in time to cancer-specific death in patients treated percutaneously (77). In terms of OS, the same observation could be made, but no marked differences in these two patient groups concerning time-point MRFS, LRFS, and also BFRS were reported (64). However, in the study by Lee et al a quicker time of local recurrence was seen when patients were treated with PC (64,77).

10.3 Segmental ureterectomy vs. radical nephroureterectomy

Segmental ureterectomy (SU) is a surgical excision of the diseased portion of the ureter with reestablishment of continuity of the urinary tract. SU includes a segmental resection with re-anastomosis of the ureter. It could be an alternative treatment option in patients who are

stratified with low-risk ureteral tumours or also even with high-risk pathology, but where a conservative treatment method might be more favored (64).

Veccia et al did a systematic review and a meta-analysis with 18 studies assessing the outcomes of SU vs. RNU in patients suffering from UTUC (66,78–95). All used studies were retrospective, except for one prospective (91) and all have been of intermediate quality (66). In total 4797 patients were included in the meta-analysis, 1313 patients treated with SU, and 3848 patients treated with RNU (66).

10.3.1 Oncologic outcomes

In the large study by Veccia et al, it was reported that patients treated with SU had less severe pathology, a lower rate of pT ≥ 2 (OR, 0.66; 95% CI, 0.53-0.82; *P* = .0002) and a lower rate of high-grade pathologies (OR, 0.62; 95% CI, 0.50-0.78; *P* < .0001) (66,78–94). In regard to positive surgical margin, there were no marked different statistics evaluated (66).

10.3.2 Survival outcomes

Regarding the recurrence in both groups (SU and RNU), there were no marked different statistics evaluated "(overall [*P* = .13] and bladder [*P* = .50], metastasis (*P* = .18), and cancer-related death (*P* = .95)" (66). Furthermore, "the SU group showed lower 5-year RFS (OR, 0.64; 95% CI, 0.43-0.95; *P* = .03)" (66,82,83,85,86,88,90,91,94,95). At the same time, this was also accredited in the cumulative report of hazard ratios, because patients treated with RNU showed an increased RFS (HR, 1.26; 95% CI, 1.07-1.49; *P* = .006), which has been found by Veccia et al. (66,83,88,91,95). On the contrary, in the 5-year MFS and CSS, no marked statistical change was analyzed by Veccia et al and no change in the survival statistics of distal pathologies regarding 5-year RFS and CSS in patient groups, either treated with SU or RNU was noticed (66).

10.4 Endoscopic surgery versus radical nephroureterectomy

In urology, endoscopic surgery represents a method where a needle and guidewire access to the kidney and the upper urinary tract. When guidewire access is given, you can place various catheters into the kidney for ureteral endoscopic procedures. It is an efficient and safe alternative to open surgical approaches.

Endoscopic surgery means nothing else than a ureteroscopic approach (URS) or retrograde intrarenal (RIRS) surgery. In the total of the researched five studies, 529 patients were taken (96–100). 162 patients were operated with ureteroscopic (URS) approach (*n* = 162) and the rest

were operated with RNU (*n* = 367). What could be already seen is that the URS-treated patients are way younger (99) than the patients which were treated with RNU. The URS group had an adverse general condition (100) and also a smaller UTUC in size (97). Characteristics like preoperative low-grade and non-invasive tumours were more detected in patients treated with URS, but nevertheless in comparison with the RNU treated patients, no marked difference could be noticed (101). So low-grade (97) and non-invasive (96,97,100) tumours have been more seen and confirmed in groups operated endoscopically.

10.4.1 Oncologic outcomes

Comparing CSS and all other survival outcomes (5-yr, 10-yr, or last follow-up) in both groups (96–101), a marked difference could not be seen concerning 5-yr and 10-yr CSS (101). Patients with diagnosed high-grade UTUC and who were operated endoscopically, had a higher risk of a cancer-specific death (98,102). In the case of MRFS (97,98) and BRFS (97), analyses showed the same outcomes and only the OS was much better with RNU, also for patients with a low-grade tumours (100,101). It was found by Grasso et al that a high amount of 77% of low-grade patients was afflicted by a recurrence (98,101). The recurrence was again then removed endoscopically and 15% of them suffered from a progression (98,101). Grasso et al (98) and Roupret et al (97) found rates of salvage RNU between 16.7% in patients who were diagnosed with a low-grade and up to 28.6% for patients diagnosed with a high-grade (101).

10.5 Laparoscopic Nephroureterectomy (LNU)

Many surgeons are trying to switch a lot of procedures to minimal invasive surgeries like laparoscopic ones. These procedures are more beneficial for the patients, because they need to stay less long in the hospital. Moreover, patients need not so many drugs and also less blood transfusions. These advantages are only valid in the near term if the oncological outcome is similar to that of a radical open procedure. In the timeline, we can see that nephrectomy belongs to the last treatment option. LNU can be done in two ways, firstly transperitoneally or secondly retroperitoneally. The risk of visceral injuries can be decreased by performing an LNU through the retroperitoneum, which also needs less bowl mobilization (103). Compared to the radical treatment tactics, the LNU oncological outcomes have been worse but after the introduction of the robotic approach. Furthermore, it is important to pay attention to possible Port Site Metastasis (PSM), which could occur with LNU. These tumours might develop in the abdominal wall, especially in the scar region, where the laparoscopic device was put into the abdomen (104). In the review of Kang q et al. the incidence rate of PSM at their institution was

1.7% in UTUC (105). The staging and the grade of the tumour were important factors, that had an influence on the occurrence. Their conclusion was that there is a higher probability of this occurring in high-risk tumours (105).

10.6 Installation of topical agents in the upper urinary tract

RNU as the gold standard for CIS. Unfortunately, it is not available for every patient and therefore topical immunomodulator agents are an alternative, but still experimental (106). Topical agents as a treatment option for UTCIS is already practiced for more than 20 years, even if the pathology of this disease is still under research (107). The treatment of UTCIS with topical agents was mostly done with the immunomodulatory substance BCG (Bacillus Calmette-Guérin) (107–109). Chemotherapeutic agents like mitomycin C are also being used (110,111). In order to spare its kidney function and the kidney itself, BCG instillation have been experimentally used.

Giannatini et al conducted a retrospective analysis of 55 consecutive patients who received an antegrade BCG perfusion of the UUT (110). It was done with two different intentions, first as a curative treatment option for CIS and second with an adjuvant intent after ablation of Ta/T1 tumours and in total 64 renal units (RUs) with non-muscle-invasive urothelial carcinoma (NMIUC) in the UUT were assessed between 1986 and September 2010 (110).

The patient needed to lay in a prone position, while a 10-F nephrostomy tube was inserted with local anesthesia under the guidance of an ultrasound device (110). Most important bacteria in the urine were excluded and the outflow of UUT was checked by fluoroscopic control in advance. An infusion with 360 mg Immun BCG Pasteur F or 243 mg ImmuCyst, both dissolved in a 150 mL mixture of sodium chloride 0,9%, was set 20 cm above the patient's kidney (110). The infusion rate was 1 ml/min, for having a perfusion rate at a continuous level of the UUT over 2 hours, which can be seen in Fig.1 (110). The patient was discharged from the hospital and needed to take antibiotics for 5 days and the treatment plan includes six weekly perfusions (110). The follow-up in case of a prospective protocol was a 3 months cystoscopy with a bladder barbotage cytology in the first 2 years and every 6 months in the following 3 years (110). For imaging check-ups, MRI, CT, or excretory urography was done 1 year and 3 years after, and if either a positive culture or imaging study was found, further individual treatment options were discussed (110).

Fig 2. The technique used for percutaneous bacillus Calmaette-Guérin (BCG) instillation

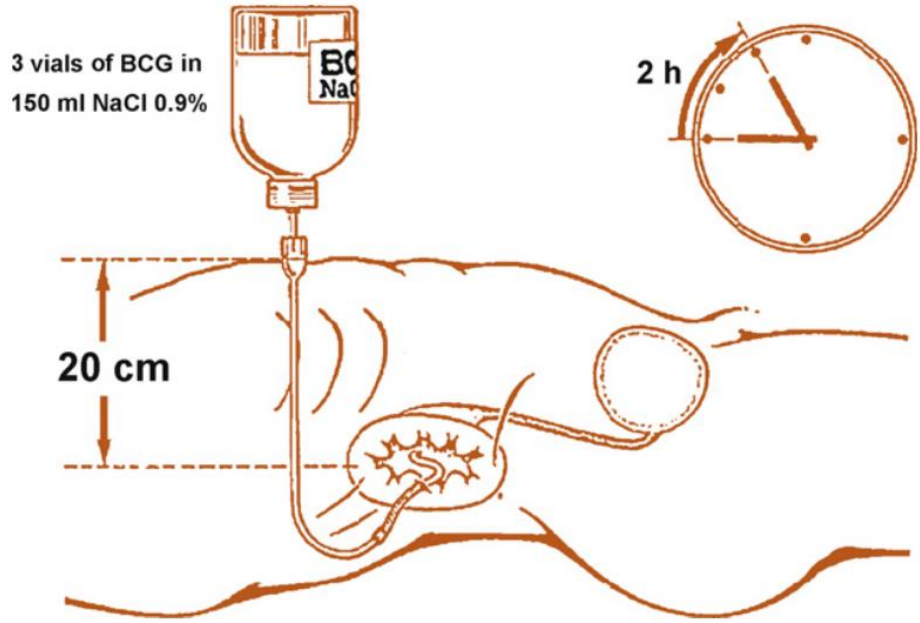

Fig. 2 – adapted from Giannarini G, Kessler TM, Birkhäuser FD, Thalmann GN, Studer UE. Antegrade Perfusion With Bacillus Calmette-Guérin in Patients With Non–Muscle-Invasive Urothelial Carcinoma of the Upper Urinary Tract: Who May Benefit? Eur Urol. 2011 Nov;60(5):955–60. Thalmann GN, Markwalder R, Walter B, Studer UE. Long-term experience with bacillus Calmette-Guerin therapy of upper urinary tract transitional cell carcinoma in patients not eligible for surgery. J Urol 2002;168:1381–5

In the past, all included patients were treated for UC before (contralateral UUT n = 4, in the bladder n = 48, or in both n = 3) and within an age range of 26 – 87 years (median age = 69 years (110). In table 4 you can find the rate of recurrence of Giannarini et al retrospective analysis. BCG perfusion for both renal units was performed for nine patients (110). In 7 out of 64 renal units, approximately 11%, had eventually undergone nephroureterectomy. One of them received BCG perfusion in case of elective conditions (1%), 2 of 42 patients (5%) from Tis curative intent, and 5 of 22 patients (23%) from Ta/T1 adjuvant intent group (110).

In the study by Giannarini et al (110), they found out that the curative-intent group had a greater degree of recurrence-free survival (p = 0.42), remarkably better progression-free survival (p < 0.01), and also remarkably better nephroureterectomy-free survival (p = 0.05) in contrast to patients receiving kidney perfusion with an adjuvant intent (110). 57% of the Tis patients had a 5-years recurrence-free survival rate and 49% had even a 10-years recurrence-free survival rate (110). Patients with no prior or subsequent cystectomy who received BCG with curative

intent (6 of 26 and 1 of 26 respectively) had considerably lower recurrence and nephroureterectomy rates than those who received BCG with adjuvant intent (7 of 13 and 4 of 13) (p = <0.05 for both) (110). Side effects included fever in five patients, haematuria in one patient, infection in two patients, storage of lower urinary tract symptoms in five patients, pericarditis in one patient and *E. coli septicaemia* in two patients (110).

Table 4 – Rate of recurrence/ progression of a retrospective analysis

	Giannarini et al (2011) (110)	
Number of patients (n)	Tis curative intent n = 42 RUs	
	Ta/T1 adjuvant intent after ablation of Ta/T1 tumours n = 22 RUs 4 RUs in pelvis/ calices, 17 RUs in the ureter, 1 RU in both	
	n = 9 BCG perfusion for both RUs	
Recurrence total (%)	47%	
Recurrence in each (%)	Tis 40%	
	Ta/T1 59%	
Progression total (%)	17%	
Progression each (%)	Tis 5%	
	Ta/T1 41%	
Indications/ Regimen (%)/ (*n*)	Imperative = 35%	*n* = 23
	Relative = 47%	*n* = 30
	Elective = 18%	*n* = 11
Recurrence-free survival in BCG curative intent for Tis	*p* = 0.42	
Progression-free survival in BCG curative intent for Tis	*p* <0,01	
Nephroureterectomy-free survival	*p* = 0.05	
5y recurrence-free survival (%)	57%	
10y recurrence-free survival	49%	

The majority of the 64 patients with UUT NMIUC were not able to undergo a radical type of surgery (110). Therefore the antegrade BCG perfusion treatment technique was an alternative (110). Overall, in about 90%, it appears that the patient's kidneys could be preserved (110). Comparing the curative and adjuvant intent groups, the Tis curative intent group had a better outcome, by having a better local disease control than the adjuvant intent Ta/T1 tumours group after ablation (110). 50% of the curative-intent group survived 10 years and there were very few treatment side effects (110). It was reported of one fatal case, caused by *E. coli* septicaemia (110).

Giannarini et al mainly concluded the patients kidneys could be preserved in approximately 89% and also a negative progression of chronic renal failure and the need of dialysis could be avoided (110). This treatment option can "buy time" and quality of life could be therefore maintained (110), especially for patients who are unfortunately in a high risk of dying from metastatic UC (110). A good renal function has therefore a big advantage in case of UC progression, when a patient needs platinum-based chemotherapy (110). The benefits in the curative intent group who received BCG therapy was much better compared to the adjuvant intent group (110). Overall, it appears that the Tis group have markedly lower recurrence, progression and nephroureterectomy rates, excluding the patients getting cystectomy for invasive bladder UC) (110). Furthermore Giannarini et al did not see a big difference in terms of survival between the two groups, maybe because of the poor prognosis for those patients in general (110).

11. CONCLUSION

First it is necessary to evaluate the patient and family history based on the Amsterdam criteria to identify patients with upper tract urothelial carcinoma. Exposure to smoking and aristolochic acid should be evaluated. The strength rating is weak though.

Urethrocystoscopy is recommended to rule out bladder tumour as a second step. CT urography for diagnosis and staging should be done next. Ureteroscopy and biopsy should be performed, if the previous investigations (imaging and cytology) are not sufficient for diagnosis and risk-stratification of the tumour. All three recommendations have a strong strength rating.

Low-risk UTUCs, which fulfil all needed factors are recommended for kidney-sparing management. Prognostic factors should be included into the risk-stratification for further therapeutic steps, but strength rating is weak. Patients who are elderly, in need of nephron-sparing surgery, or who have concomitant conditions benefit from this form of risk assessment. Each therapeutic strategy has to be clear and acceptable to the patients in advance.

When comparing the present literature, KSS (RIRS or URS) versus RNU show similar survival rates, but only for patients with low-grade and non-invasive UTUCs. According to EAU guidelines, certain distal ureter high-grade and invasive UTUC patients should be treated with SU methods (when feasible) because they could also benefit from it, in terms of a better preservation of the renal function. The oncologic outcomes need to be maintained and observed after radical nephroureterectomy. Therefore, the recommendation is PC surgery only for low-risk patients in distal ureter, as it also recommended in the current EAU guidelines. Meticulous and stringent postoperative follow-up is mandatory for detecting and treating a recurrence fast. On the other hand, SU could also include selected high-risk patients, but evidence-based research is still poor and only potentially biased. Patients with high-risk conditions should be sent to early RNU without further discussion with the tumour board by default.

RNU in advanced high-risk patients still remains the gold standard as a treatment strategy.

Regarding immunomodulatory substances such as BCG can be seen as a first-line treatment in UUT Tis instead of performing nephroureterectomy, because patients have a high chance for cure in selected cases. After ablation of Ta/T1 tumours, BCG perfusion is less evident and should be considered on an individual basis. However, cancer-specific outcomes should remain a top priority, and the development of new systemic medicines must keep pace with breakthroughs in surgical procedures.

Follow up for low-risk tumours include cystoscopy and CT urography at 3 and 6 months, and then yearly for 5 years. URS at 3 months after surgery is recommended as well.

12. ABBREVIATIONS

UTUC – Upper tract urothelial carcinoma

UUT-UCC – upper urinary tract urothelial cell carcinoma

CKD – Chronic kidney disease

AA – Aristolochia acid

UTI – Urinary tract infection

URS – Ureterorenoscopy

MH – Microhematuria

UA – Urinalysis

UT – urinary tract

CSS – cancer-specific survival

OS – overall survival

MFRS – metastasis recurrence-free survival

BRFS – bladder recurrence-free survival

LRFS – local recurrence-free survival

PC – Percutaneous

OP – Operation

RNU – Radical nephroureterectomy

LNU – Laparoscopic Nephroureterectomy

KSS – Kidney sparing surgery

SU – Segmental ureterectomy

OR – odds ratio

CI – Confidence interval

RFS – relapse-free survival

MFS – metastasis-free survival

CSS – cancer-specific survival

HR – Hazard ratio

CIS – Carcinoma in situ

UTCIS – Upper tract carcinoma in situ

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