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Upper Tract Urothelial Cancer: Guideline of Guidelines

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Simple Summary: The creation of a guideline of guidelines could help physicians apprehend different approaches to malignancies and better-tailoring patients' management. In this context, international guidelines on upper tract urothelial carcinoma (UTUC) have previously never been compared in their similarities and differences. The present effort could guide further researchers to provide more high-quality evidence to homogeneously assess, treat, and follow up patients affected by UTUC worldwide. Moreover, by highlighting similarities and differences, we aim to encourage more conscious and critical use of guidelines and push research to fill knowledge gaps.

Abstract: Background: Upper tract urothelial carcinoma (UTUC) is a rare disease with a potentially dismal prognosis. We systematically compared international guidelines on UTUC to analyze similarities and differences among them. Methods: We conducted a search on MEDLINE/PubMed for guidelines related to UTUC from 2010 to the present. In addition, we manually explored the websites of urological and oncological societies and journals to identify pertinent guidelines. We also assessed recommendations from the International Bladder Cancer Network, the Canadian Urological Association, the European Society for Medical Oncology, and the International Consultation on Bladder Cancer, considering their expertise and experience in the field. Results: Among all the sources, only the American Urologist Association (AUA), European Association of Urology (EAU), and the National Comprehensive Cancer Network (NCCN) guidelines specifically report data on diagnosis,

treatment, and follow-up of UTUC. Current analysis reveals several differences between all three sources on diagnostic work-up, patient management, and follow-up. Among all, AUA and EAU guidelines show more detailed indications. Conclusions: Despite the growing incidence of UTUC, only AUA, EAU, and NCCN guidelines deal with this cancer. Our research depicted high variability in reporting recommendations and opinions. In this regard, we encourage further higher-quality research to gain evidence creating higher grade consensus between guidelines.

Keywords: upper tract urothelial carcinoma (UTUC); guidelines; diagnosis; management; follow-up

1. Introduction

Upper tract urothelial carcinoma (UTUC) accounts for 5–10% of urothelial cancers, of which bladder cancer (BC) represents by far the most frequent one [1]. Environmental factors such as smoking exposure and aristolochic acid are the most established risk factors [2]. The most common presentation symptoms are hematuria in almost 80% of cases and flank pain in 20%. In more advanced stages, constitutional symptoms—indicative of metastatic disease—often emerge. These include weight loss, fever, night sweats, anorexia, and hemoptysis [3–5]. However, UTUC is occasionally diagnosed incidentally during routine cross-sectional imaging with evidence of a collecting system mass [6].

The pauci-symptomatic nature of the disease is the main factor contributing to late detection and high rates of invasive cancer at diagnosis [7]. Indeed, only 15–20% of patients with urothelial BC present an invasive disease at diagnosis, whilst literature data show rates of approximately 70% in patients with UTUC [8]. Moreover, despite several similarities, UTUC has a more aggressive course than BC, with more than doubled rates of 5-year mortality (more than 50% vs. less than 25%, respectively) [9].

Due to specific challenges in disease identification and management, there is some disagreement regarding the management of this complex disease. This is also reflected by differences in the multiple guidelines from different scientific organizations that are available to the treating physician. In this study, we sought to systematically compare current international guidelines and recommendations and to identify both discrepancies and similarities regarding the management of UTUC.

2. Materials and Methods

2.1. Data Source

We conducted a search on MEDLINE/PubMed, Scopus, and Web of Science databases for guidelines on UTUC from 2010 to the present. In addition, we manually explored the websites of the main international urological and oncological societies to identify pertinent guidelines.

We explored the existence of guidelines on the topic by the American Urological Association (AUA), the American Society of Clinical Oncology (ASCO), the Society of Urologic Oncology (SUO), the European Association of Urology (EAU), the European Society for Medical Oncology (ESMO), the National Comprehensive Cancer Network (NCCN), and the National Institute for Health and Care Excellence (NICE). We also evaluated any recommendations on the topic from the International Bladder Cancer Network (IBCN), the International Bladder Cancer Group (IBCG), the Canadian Urological Association (CUA), and the International Consultation on Urologic Diseases (ICUD).

When multiple guidelines from the same scientific society were found, only the most recent ones were considered.

2.2. Guideline Evaluation

The assessment of guidelines was carried out using the Appraisal of Guidelines, Research, and Evaluation II (AGREE II) instrument, which offers a structured framework for comparing the quality of various guidelines [10,11]. This tool was employed by four

authors independently (SDP (Assistant Professor); SC (Senior Urology Resident); AA (Urologist); CM (Researcher, PhD)). It is crucial to emphasize that all assessors involved in the evaluation process have been engaged in UTUC as professionals for at least 5 years, enhancing the reliability of their contributions to this research. The AGREE II instrument consists of 23 items categorized into six domains: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence (Supplementary Table S1). Assessors assigned ratings to each item on a scale of 1 to 7, where 1 represents 'strongly disagree' and 7 signifies 'strongly agree'.

Following the AGREE II methodology, mean domain scores were determined by summing the scores for individual items within a domain and then scaling the total as a percentage of the maximum attainable score for that domain, considering the assessments of all four reviewers. These six domain scores remain separate and are not combined into a single overall quality score. Instead, appraisers assign a distinct overall score ranging from 1 to 7 and indicate whether they would recommend the guideline for use. An average overall score for each guideline was calculated based on the overall scores provided by the four reviewers.

2.3. Data Synthesis

The data were reported as in the original guidelines. Sums, means, percentages, and ranges were used to give a better overview of the results. No statistical tests were applied.

3. Results

3.1. International Guidelines on UTUC

Recent international guidelines on the topic were only available from the EAU, AUA, and NCCN.

3.1.1. EAU Guidelines

UTUC clinical guidelines have been compiled by the non-muscle-invasive BC (NMIBC) guidelines panel to provide clinicians with evidence-based information and recommendations. The panel consists of 20 international multidisciplinary clinicians, including urologists, uro-oncologists, one radiologist, one pathologist, and, in the course of 2021, two patients joint representing the lay public.

The 2023 guidelines edition represents a limited update of the 2022 version [8]. The inaugural EAU guidelines for UTUC were released in 2011. The latest guidelines, along with a summary of any updates, are available on the following webpage: <https://uroweb.org/guidelines/upper-urinary-tract-urothelial-cell-carcinoma/chapter/introduction> (accessed on 1 January 2024).

Instead of using the modified Oxford Centre for Evidence-Based Medicine Levels of Evidence (LE), the system for evaluating the strength of the evidence (SE) now categorizes recommendations as either 'weak' or 'strong'.

3.1.2. AUA/SUO Guidelines

In 2021, the UTUC panel was established by the American Urological Association Education and Research, Inc. (AUAER) to work with the Society of Urologic Oncology (SUO) in creating clinical guidelines for treating localized or locally advanced UTUC. The latest update was released in April 2023 [9].

The AUA categorizes evidence strength into Grades A, B, and C. Grade A represents highly reliable evidence from well-conducted trials or strong observational studies. Grade B indicates moderately strong evidence with some weaknesses, while Grade C suggests evidence with serious deficiencies, small sample sizes, or inconsistency. In the absence of evidence, clinical principles and expert opinions (EOs) could be found as additional information.

3.1.3. NCCN Guidelines

UTUC practical guidelines have been published on an annual basis as a chapter of BC Guidelines to complete the educational path of all healthcare providers, from nurses and pharmacists to urologists and oncologists.

Thanks to the clinical practice nature, the NCCN guidelines on BC briefly summarize treatment options on UTUC to guide healthcare providers in each step of diagnosis, treatment, and follow-up; on the other hand, they miss specific sections regarding epidemiology and risk factors.

The latest version of the guidelines was published in 2023 (third version) as an update of the 2022 version [12]. Recommendations were graded with the NCCN categories of evidence and consensus. These categories of evidence and consensus are ranged as follows: 1 (uniform consensus based on high-level evidence), 2A (uniform consensus based on lower-level evidence), 2B (consensus based on lower-level evidence), and 3 (major disagreement). Recommendations without high-level evidence were mainly based on expert opinion.

3.2. Assessment of Guidelines (AGREE II)

The authors separately evaluated guidelines with a measured overall reliability of 0.96 among them, indicating perfect agreement.

The mean scores of the various domains of the AGREE II were 87.3 (scope and purpose), 79.5 (stakeholder involvement), 95.2 (rigor of development), 96.4 (clarity of presentation), 98.5 (applicability), and 68.7 (editorial independence).

3.3. Epidemiology and Risk Factor

Both the EAU and AUA guidelines report UTUC as less common compared to BC, constituting about 5–10% of all urothelial carcinomas [13]. UTUC most commonly occurs in individuals aged between 70 and 90, with men being twice as susceptible as women [14].

The observed increase in incidence over recent years can be attributed to advancements in detection methods and enhanced survival rates for BC [15,16]. With regards to UTUC occurring after BC, a significant incidence rate has been reported by EAU, with a 7.5% incidence of UTUC in a 402-patient multicenter study of NMIBC cases treated with BCG over 50 months of follow-up. Intravesical recurrence and non-papillary tumors at TURB were identified as key predictors [17]. Even following radical cystectomy for muscle-invasive BC, there is an observed association rate, with 3–5% of patients developing metachronous UTUC [18]. Thus, there are shared risk factors and molecular pathways between UTUC and BC.

Guidelines acknowledge that environmental factors may contribute to the development of UTUC [19,20]. Overall, the EAU guidelines do not offer strong supporting evidence for this assertion, except in the case of aristolochic acid and smoking (LE: 2A, SE: weak), where tobacco exposure elevates the relative risk of UTUC from 2.5 to 7.0 [21].

Conversely, AUA/SUO offers a set of somewhat generic risk indications that could benefit from revision to provide a more detailed and in-depth description. This would offer more precise and comprehensive guidance, particularly in predicting possible post-operative kidney function impairment (expert opinion, EO). Moreover, among personal habits, EAU guidelines state that patients with a history of alcohol consumption > 15 g/day have a significantly higher risk of UTUC when compared with never-drinkers [22].

However, hereditary factors like Lynch and Lynch-like syndromes are equally mentioned as risk factors in all the analyzed guidelines [23,24]. EAU guidelines propose the Amsterdam criteria to identify families with a high probability of having Lynch syndrome (LE: 2A, SE: weak); the AUA panel proposes Amsterdam II criteria and refers to revised Bethesda guidelines, whilst the NCCN guidelines recommend obtaining a thorough family history in each patient with high-risk UTUC [25].

3.4. Diagnosis

Among all the three guidelines dealing with UTUC, only the ones by EAU clearly describe suspicious symptoms of this tumor by reporting micro/macro-hematuria, flank pain, and systemic symptoms associated with metastatic disease (anorexia, weight loss, malaise, fatigue, fever, night sweats, or cough) [26–28].

However, in the diagnostic work-up of suspicious UTUC, contrast-enhanced abdomen and pelvis Computer Tomography (CT) scans are recommended for investigation, offering a pooled sensitivity of 92% (CI: 0.85–0.96) and specificity of 95% (CI: 0.88–0.98) [29,30]. In case of contraindications to contrast-medium, guidelines recommend performing a Magnetic Resonance (MR) with urography, even if less sensitive and specific for the diagnosis and staging of UTUC, followed by renal ultrasound [31,32]. An integral part of the diagnostic workup of UTUC includes a careful inspection of the bladder through cystoscopy. Only the NCCN clearly recommends a direct urine sample collection for cytologic assessment (category 2A), while the other guidelines recommend urine sampling by standard collection or directly from the renal pelvis or the ureteral lumen during endourological assessment [33].

In case of uncertainty, ureteroscopy could be detrimental to the diagnosis. In this setting, the AUA panel highlights that endoscopic procedures are intended as low-impact and typically brief interventions, whereas therapeutic endoscopic procedures with curative intent are often longer with a greater risk for surgical complications. Lastly, AUA guidelines recommend the collection of bioptic specimens of suspected lesions during endoscopic procedures, whilst the EAU panel states that biopsies should preferably be avoided due to undegrading risks (SE: strong) [34,35].

The diagnostic work-up of UTUC is completed by ruling out possible organs or node metastasis with imaging. EAU recommends CT scans of the whole body for diagnosis and staging (SE: strong) or, in case of contraindications, MR urography, whilst 18F-Fluorodeoxyglucose positron emission tomography/CT is preferred to assess nodal metastasis (SE: weak) [32,36]. Only NCCN includes the chest radiograph as an alternative (category 2A). In this regard, AUA guidelines are published in the non-metastatic setting, thus avoiding any assessment of secondary localization of the malignancy (Figure 1).

3.5. Risk Stratification and Prognosis

Clinical findings are crucial to stratify and inform patients about disease, treatment, and peri-operative management.

Apart from NCCN, guidelines recommend pre-operatively stratifying patients into low- and high-risks. According to this classification, on the one hand, the EAU recommends risk stratification to identify patients more likely to benefit from kidney-sparing treatment and those who should undergo radical treatment (LE: 3, SE: weak) [37,38]. On the other hand, the AUA/SUO panel recognizes the need for further stratification to guide the correct treatment option between ablative treatments and systemic therapy.

The main discriminating factors for the high-risk classification are positive cytology for high-grade urothelial cancer cells, local invasion at the imaging, and nodal involvement. The EAU panel further considers the high-risk group patients with a tumor size over 2 cm and/or hydronephrosis and/or multifocality [39,40]. Differently, AUA/SUO further differentiates the two risk classes according to prognosis (favorable vs. unfavorable) in the presence of urinary obstruction, multifocality or contralateral UTUC diagnosis, and involvement of the lower urinary tract [41]. Moreover, high-grade urinary cytology, suspicious nodal involvement, and the non-papillary tumor pattern are exclusive characteristics of the high-grade unfavorable UTUC [42].

Lastly, EAU guidelines also report, among risk factors for more aggressive cancer, patients' related characteristics, such as ethnicity, with African-American patients having worse outcomes, advancing age, tobacco consumption, delayed surgery, high comorbidity and performance indices scores, and several blood-based biomarkers even if no prognostic biomarkers are validated for clinical use (LE: 3) [43–47]. These latter characteristics are mentioned in the AUA/SUO, but the panel considers them to be not widely available, easily

identified, or measured, thereby limiting broad applicability. However, AUA recommends identifying the risk of post-operative chronic renal failure or dialysis in patients who are candidates for radical nephroureterectomy (RNU) [48].

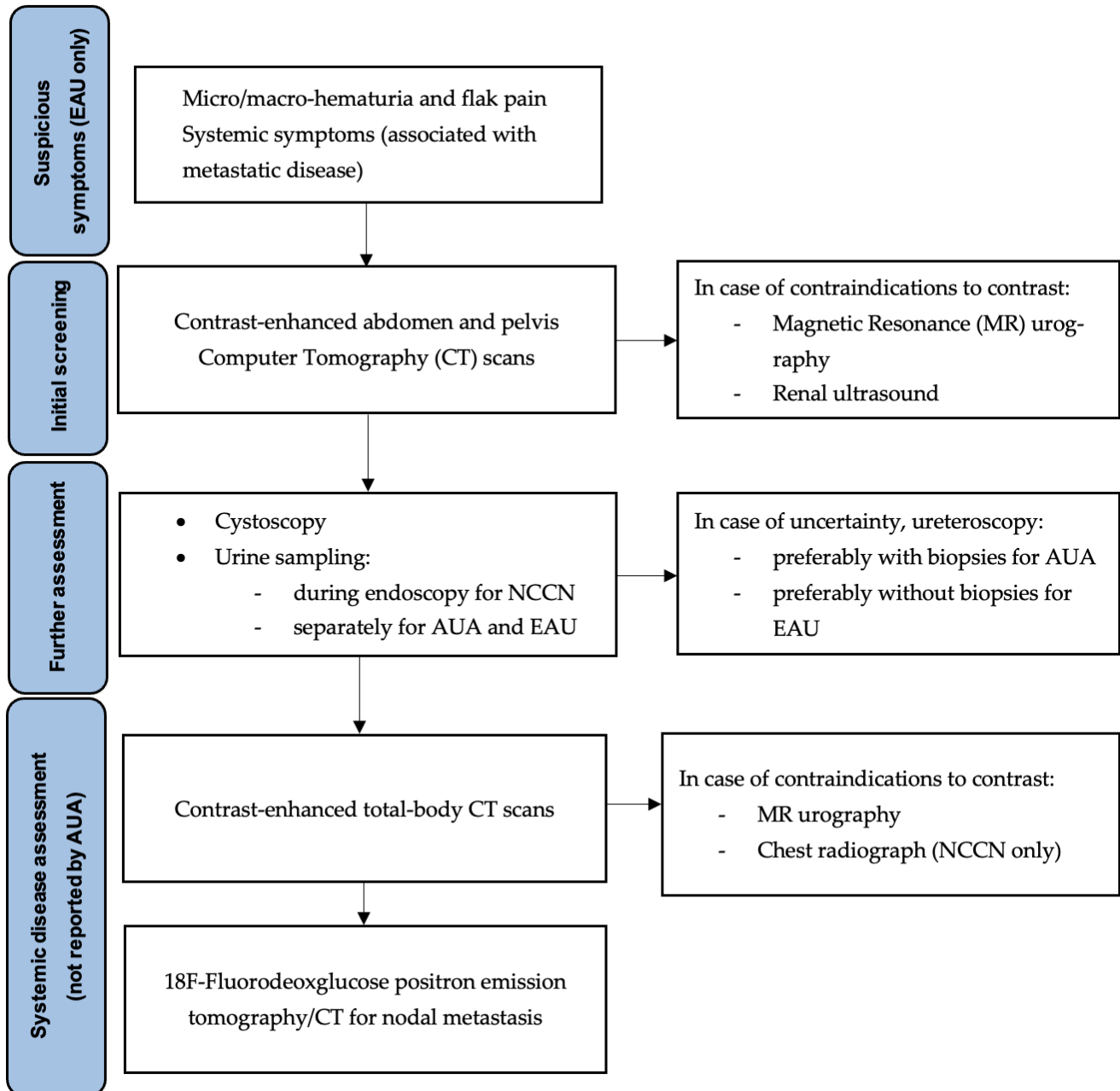


Figure 1. Diagnostic work-up of UTUC according to the AUA, EAU, and NCCN guidelines. Abbreviations: UTUC: upper tract urothelial carcinoma; AUA: American Urology Association; EAU: European Association of Urology; NCCN: National Comprehensive Cancer Network.

3.6. Disease Management

The three guidelines deal with disease management differently (Table 1). Indeed, NCCN considers localization firstly (e.g., renal vs. other sites) and tumor grade subsequently; the AUA/SUO panel reports recommendations according to kidney sparing management vs. surgical approach; the EAU guidelines present management as per localized low-grade, localized high-grade, and metastatic disease.

Table 1. Differences in UTUC management according to AUA, EAU, and NCCN guidelines.

| Management Type | AUA | EAU | NCCN |
|---|--|---|---|
| Neoadjuvant platinum-based chemotherapy | Patients with local or distant invasive tumors or involved lymph nodes When GFR is expected to lower after surgical treatment | When GFR is expected to lower after surgical treatment | Patients with retroperitoneal lymphadenopathy, bulky (>3 cm) high-grade tumor, sessile histology, or suspected parenchymal invasion |
| Endoscopic management | Low-risk and high-risk favorable UTUC | Low-risk masses | Only for selected patients or those who are not suitable for RNU |
| Post-endoscopic instillation | Mitomycin C gel or BCG | Mitomycin C gel | Mitomycin C gel |
| RNU with bladder cuff and LND | Open/laparoscopic according to surgeon preference Remove <i>en block</i> , watertight fashion LND in high-risk UTUC | Open approach is superior for fewer risks of cells dissemination LND in high-risk UTUC | No specific indication |
| Post-RNU bladder instillation (Mitomycin C or Gemcitabine) | According to availability | Gemcitabine preferred in case of risk of extravasation | No specific indication |
| Adjuvant chemotherapy | Up to a GFR of 60 mL/min | Up to a GFR of 45 mL/min | Up to a GFR of 60 mL/min |
| Immunotherapy in high-risk muscle-invasive UTUC, undergone RNU and cell PD-L1 expression > 1% | No specific indication | No specific indication | No specific indication |

Abbreviations: UTUC: upper tract urothelial cancer; AUA: American Urology Association; EAU: European Association of Urology; NCCN: National Comprehensive Cancer Network; RNU: radical nephroureterectomy; LND: lymph node dissection; GFR: Glomerular Filtration Rate.

3.6.1. Endoscopic and Surgical Approaches

Consensus exists among EAU and AUA to adopt nephron-sparing approaches (either endoscopic or percutaneous) as first-line therapy for low-risk tumors or high-risk masses with favorable prognosis. The ureteral resection with simultaneous lymphadenectomy is indicated only in case of masses that were not completely removable endoscopically (LE: 2A; SE: strong) [49]. The NCCN recommends endoscopic management only for selected patients or those who are not suitable for RNU due to clinical or biochemical criteria; otherwise, a surgical approach is always recommended [50]. After the endoscopic management, AUA and NCCN recommend at least one instillation of Mitomycin C (or local application in the gel format) in the upper tract, able to decrease rates of local recurrence [51,52]. Accordingly, EAU reports data on Mitomycin C gel used as a single therapeutic option to chemo-ablate low-risk UTUC, whilst AUA reports considerations regarding technical procedures for upper tract instillation and to instill adjuvant pelvicalyceal chemotherapy (conditional recommendation; Grade C) or the use of a six-week induction course of BCG as the primary treatment of in situ UTUC and as an adjuvant treatment for localized non-invasive disease (EO) [53,54]. No data support the instillation of the bladder after kidney-sparing management.

In the management of high-risk non-metastatic UTUC, the guidelines reach a consensus on recommending RNU with bladder cuff excision and lymphadenectomy as the standard therapeutical approach. The kidney, together with the ureter and the bladder cuff should be removed *en block*, with the AUA panel encouraging the securing of the urinary tract in a watertight fashion to avoid the spreading of cancer cells [55]. In this context, the AUA leaves the choice of the surgical approach to the surgeon (laparoscopic or robotic minimally invasive or open), whilst according to the EAU guidelines, the open approach is more radical and safer than the laparoscopic one due to the risk of dissemination along the trocar pathway [56,57]. Moreover, AUA and EAU guidelines agree on better long-term outcomes in patients with high-risk non-metastatic UTUC who underwent regional lym-

phadenectomy. Otherwise, even if this procedure is recommended by the NCCN panel, data on outcome improvements are not reported.

Lastly, evidence agrees that patients who undergo RNU have a high risk of bladder recurrence (22–47%). Thus, all the guidelines recommend a post-operative single instillation of chemotherapeutic agents [58,59]. The most adopted agent is Mitomycin C and, in selected patients or in the presence of risk of intrabdominal extravasation, Gemcitabine can be used. However, the AUA panel reports that due to the absence of a direct comparison of these two agents, the choice should be based on agent availability and workflow suitable to the clinician [60,61].

3.6.2. Medical Therapy

Neoadjuvant Chemotherapy

All the guidelines agree on the use of neoadjuvant chemotherapy with platinum-based protocols. NCCN recommends neoadjuvant chemotherapy in selected patients with both the renal pelvis and ureteral masses and with retroperitoneal lymphadenopathy, bulky (>3 cm) high-grade tumor, sessile histology, or suspected parenchymal invasion (category 2B) [62–64]. EAU reports that the primary advantage of neoadjuvant platinum-based therapy is to profit from better renal function before RNU and lower the disease recurrence and mortality [65–67]. However, the evidence presented above is not conclusive, given the significant bias and heterogeneity of the available data. Accordingly, the AUA guidelines support the use of neoadjuvant chemotherapy in patients with local or distant invasive tumors (T2–T4) or with lymph nodal involvement (N+). In particular, patients expecting an important decrease in glomerular function that would preclude post-operative platinum-based chemotherapy could benefit the most (strong recommendation; Grade B) [62,68–70].

Adjuvant Chemotherapy

In patients with UTUC who have not received neoadjuvant therapy, adjuvant cisplatin-based chemotherapy can be discussed considering that after RNU the renal function may deteriorate limiting the adoption of this strategy. To this regard, a GFR of 45 mL/min is considered a suitable threshold for the EAU guidelines panel, whilst AUA and NCCN adopt the historically used threshold of 60 mL/min (strong recommendation; Grade A) [71,72].

Immunotherapy

Consensus exists between the AUA, EAU, and NCCN in supporting the use of adjuvant Nivolumab in patients with high-risk muscle-invasive UTUC who had undergone radical surgery and had a tumor cell PD-L1 expression > 1% [73]. This was particularly the case in patients receiving neoadjuvant platinum-based chemotherapy or those patients who, due to comorbidities, were non-eligible for platinum-based therapies. Nonetheless, in these patients, a network meta-analysis suggests a superior oncological benefit from adjuvant platinum-based chemotherapy over immune checkpoint inhibitors [74].

3.7. Staging and Classification

Due to similarities between the classification and morphology of UTUC and BC, most of the guidelines do not consider a separate staging classification for the two malignancies. Indeed, only the EAU guidelines provide a complete classification of UTUC referring to the 2022 update of the 2004/2016 WHO grading classification [75] and the 8th edition of the TNM classification of malignant tumors [76].

3.8. Follow-Up

Follow-up in UTUC is required to detect recurrent or new primary tumors within the urothelium and regional and distant metastases. In this setting, the EAU panel states that bladder recurrence is not considered a distant recurrence.

Among sources on follow-up strategies, heterogeneity exists providing an overall low level of concordance. Similar to the approach used to describe the diagnostic management

of UTUC, the three guidelines differ in reporting the follow-up criteria. In fact, NCCN reports indications according to tumor staging, EAU based on risk class, and AUA depending on the treatment chosen (Tables 2 and 3).

Table 2. Summary of surveillance plan according to AUA, EAU, and NCCN guidelines in case of UTUC managed with kidney-sparing procedures.

| LOW-RISK UTUC | | | | | | | |
|-------------------------|-----------|-------------------|--|---------------------|---------------------|--------------------|---|
| Diagnostic Procedure | Guideline | Early Second-Look | First Year | Second Year | Third Year | Fourth–Fifth Years | Further Assessment |
| Cystoscopy and cytology | AUA | Within 4–8 weeks | At 6 to 9 months | At 6 to 9 months | Yearly | Yearly | Decision made between the patient and clinician |
| | EAU | Within 6–8 weeks | 3 and 9 months | Yearly | Yearly | Yearly | Stop after 5 years |
| | NCCN | NA | Every 3-months | Not specified | Not specified | Not specified | Not specified |
| Ureteroscopy | AUA | Within 4–8 weeks | At 6 to 9 months | At 6 to 9 months | Yearly | Yearly | Decision made between the patient and clinician |
| | EAU | Within 6–8 weeks | 3 and 6 months | Yearly | Yearly | Yearly | Stop after 5 years |
| | NCCN | NA | 3 to 12 months | Not specified | Not specified | Not specified | Not specified |
| Imaging | AUA | NA | At 6 to 9 months | At 6 to 9 months | Yearly | Yearly | Stop after 5 years |
| | EAU | NA | CT-urography at 3 and 6 months | Yearly | Yearly | Yearly | Stop after 5 years |
| | NCCN | NA | Abdominal/pelvic CT or MRI at 3 to 12 months | Not specified | Not specified | Not specified | Not specified |
| HIGH-RISK UTUC | | | | | | | |
| Diagnostic Procedure | Guideline | Early Second-Look | First Year | Second Year | Third Year | Fourth–Fifth Years | Further Assessment |
| Cystoscopy and cytology | AUA | Within 4–8 weeks | Every 3 to 6 months | Every 3 to 6 months | Every 3 to 6 months | Yearly | Encourage to continue follow-up |
| | EAU | Within 6–8 weeks | A 3 and 9 months | Yearly | Yearly | Yearly | Continue in accordance with the patient |
| | NCCN | NA | Every 3-months | Not specified | Not specified | Not specified | Not specified |
| Ureteroscopy | AUA | Within 4–8 weeks | At 6 and 12 months | At 6 to 9 months | Yearly | Yearly | Encourage to continue follow-up |
| | EAU | Within 6–8 weeks | 3 and 6 months | Yearly | Yearly | Yearly | Continue in accordance with the patient |
| | NCCN | NA | Not specified | Not specified | Not specified | Not specified | Not specified |
| Imaging | AUA | NA | Every 3 to 6 months | Every 3 to 6 months | Every 3 to 6 months | Yearly | Encourage to continue follow-up |
| | EAU | NA | CT-urography at 3 and 6 months | Yearly | Yearly | Yearly | Continue in accordance with the patient |
| | NCCN | NA | Not specified | Not specified | Not specified | Not specified | Not specified |

Abbreviations: AUA: American Urology Association; EAU: European Association of Urology; NCCN: National Comprehensive Cancer Network; UTUC: upper tract urothelial carcinoma; CT: Computer Tomography; MRI: Magnetic Resonance Imaging; NA: not available.

Table 3. Summary of surveillance plan according to AUA, EAU, and NCCN guidelines in case of UTUC managed with radical nephroureterectomy.

| LOW-RISK UTUC | | | | | | |
|-------------------------|---------------|--|----------------------------------|-----------------------------|--------------------|---|
| Diagnostic Procedure | Guideline | First Year | Second Year | Third Year | Fourth–Fifth Years | Further Assessment |
| Cystoscopy and cytology | AUA | At 3 months and then at 6 to 9 months | At 6 to 9 months | Yearly | Yearly | Decision made between the patient and clinician |
| | EAU | 3 and 9 months | Yearly | Yearly | Yearly | Stop after 5 years |
| | NCCN | Every 3-months | Not specified | Not specified | Not specified | Not specified |
| Imaging | AUA | At 6 to 9 months | At 6 to 9 months | Yearly | Yearly | Decision made between the patient and clinician |
| | EAU | CT-urography at 3 and 6 months | Yearly | Yearly | Yearly | Stop after 5 years |
| | NCCN | Abdominal/pelvic CT or MRI at 3 to 12 months | Not specified | Not specified | Not specified | Not specified |
| HIGH-RISK UTUC | | | | | | |
| Diagnostic Procedure | Guideline | First Year | Second Year | Third Year | Fourth–Fifth Years | Further assessment |
| Cystoscopy and cytology | AUA | At 3 to 6 months | At 3 to 6 months | At 3 to 6 months | Yearly | Encourage to continue follow-up |
| | EAU | 3 and 9 months | Yearly | Yearly | Yearly | Stop after 5 years |
| | NCCN | Every 3-months | Not specified | Not specified | Not specified | Not specified |
| Imaging | AUA (<T2N0M0) | Abdominal/pelvic CT or MRI within 6 months | Yearly | Yearly | Yearly | Encourage to continue follow-up |
| | AUA (>T2N0M0) | CT-urography every 3 to 6 months | CT-urography every 3 to 6 months | CT-urography every 6 months | | |
| | EAU | CT-urography at 3 and 6 months | Yearly | Yearly | Yearly | Stop after 5 years |
| | NCCN | Abdominal/pelvic CT or MRI at 3 to 12 months | Not specified | Not specified | Not specified | Not specified |

Abbreviations: AUA: American Urology Association; EAU: European Association of Urology; NCCN: National Comprehensive Cancer Network; UTUC: upper tract urothelial carcinoma; CT: Computer Tomography; MRI: Magnetic Resonance Imaging; NA: not available.

After primary treatment for localized low-risk tumors, NCCN recommends, independently from surgical or endoscopic management, serial cystoscopies at 3-month intervals for the first year and, if negative, at longer intervals without specifying timing or end of the follow-up period (category 2A). Moreover, imaging of the upper tract collecting system or ureteroscopy at 3- to 12-month intervals \pm abdominal/pelvic CT or MRI with and without contrast are recommended without clear timing. Similar indications for the low-risk malignancies treated with RNU come from the EAU panel, which does not indicate the need for a cystoscopy at 6 months and recommends stopping yearly cystoscopy after 5 years [77,78]. In the case of the kidney-sparing therapeutic approach, the EAU indicates a very stringent follow-up (LE: 3) with an early second-look ureteroscopy after 6 to 8 weeks

and cystoscopy and CT-urography at 3 and 6 months and then yearly for 5 years (SE: weak) [79,80]. According to AUA guidelines, in the case of kidney sparing management, the early second-look should be performed within one to three months, with cystoscopy at least every six to nine months for the first two years and then annually, and upper tract imaging should be performed at least every six to nine months for two years, then annually for 5 years (EO). Meanwhile, after RNU, patients should undergo cystoscopy and cytology within three months after surgery, then every six to nine months for the first two years, and then annually for up to 5 years. Moreover, imaging should be performed at least every six to nine months for two years and then annually for up to 5 years. In the absence of recurrence, further planning of the follow-up should be based on a shared decision between the patient and the physician (EO). The consensus among the guidelines is that further investigations for distant metastasis whose risk of occurrence is very low be avoided.

For higher-grade tumors, NCCN states that follow-up should follow the same indications with the addition of chest imaging and stronger recommendation for cytology, without clearly indicating timing (category 2A). A similar strategy is recommended by EAU guidelines for high-grade UTUC treated endoscopically, with the warning to continue the follow-up beyond 5 years (SE: weak) [81]. When RNU is preferred, the EAU recommends stringent follow-up, also to detect metachronous BC, whose probability increases over time up to 4 years; after that, the risk of recurrences decreases [82,83].

In the high-risk setting, the AUA guidelines recommend a different follow-up. When the patient has undergone kidney-sparing treatment, an early cystoscopy and upper tract endoscopy with cytology should be performed within one to three months (EO) [84]. If negative for BC, patients should undergo cystoscopy and cytology every three to six months for the first three years and then annually. Upper tract endoscopy should be repeated at least at six months and one year; while imaging should be performed every three to six months for three years and then annually for up to five years. In the case of RNU, cystoscopy and cytology should be repeated at least every three to six months for the first three years and then at least annually thereafter [85,86]. Regarding post-operative imaging follow-up, AUA sub-classify according to tumor staging as follows:

- <T2N0M0, scans of abdomen and pelvis within 6 months and then annually (EO).
- >T2N0M0, multiphasic contrast-enhanced CT urography every three to six months for two years, every six months in the third year, and annually thereafter. A chest CT is indicated every 6–12 months for the first 5 years (EO).

In the absence of recurrence, further surveillance plans should be encouraged and based on a shared decision between the patient and physician.

4. Discussion

UTUC is a rare malignancy belonging to the family of urothelial carcinoma and shares similarities with BC. Nevertheless, only three eminent international scientific societies (NCCN, EAU, and AUA) provide clear guidelines dealing with its epidemiology, symptoms, diagnosis, treatment, and follow-up.

Our research outlined an uneven picture of reported evidence in its structure and contents. In this regard, NCCN guidelines on UTUC are presented as a chapter of Version 3.2023 guidelines on BC. Consequently, this source lacks its own important sections such as epidemiology and risk factors (apart from a brief outline on Lynch syndrome). NCCN guidelines are focused on the management of UTUC, with brief presentations of the diagnosis and follow-up of such malignancy. For this reason, the main strength point of this resource is to guide urologists easily and straightly in the correct management of the malignancy with the limitation of not providing enough evidence on its detection and prosecution of the follow-up after the first year from the main intervention.

Differently, EAU and AUA guidelines appear to be more complete resources dealing with all the aspects of UTUC, from suggestive symptoms to management and follow-up. Both these guidelines are mostly supported by strong recommendations and high-quality LE in their common points. However, our analysis highlights some differences between

these eminent sources, especially on risk stratification and consequent strategies to treat UTUC. Moreover, EAU guidelines are the only ones to elaborate and report a proper TNM staging system, separated from the one of BC.

The most important difference among all the guidelines is related to follow-up timing and methods. All report different follow-up approaches according to the adopted surgical approach, with further differentiation in accordance with cancer grade. Indeed, the timing of early assessment and of performance of procedures such as cystoscopy, ureteroscopy, and imaging differs from one source to another without reaching a complete consensus. In this setting, the AUA panel released the most detailed plans of follow-up by also stratifying this based on pathological histology. Nonetheless, this detailed follow-up is composed of EOs, which were achieved by consensus of the panel, which is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence and not based on evidence and recommendations.

5. Conclusions

In conclusion, due to its relative rarity and similarities among urothelial carcinomas, most sources treat UTUC as a variant of BC. Indeed, among all the eminent sources created to guide physicians, only AUA, EAU, and NCCN guidelines discuss UTUC. Between these three, our research depicted high variability in the addressed sections and approaches in reporting recommendations and opinions. In this regard, we encourage urologists to always consider UTUC as an entity per se with its own diagnosis, management, and follow-up strategies. In accordance, further high-quality research is needed to gain evidence creating higher grade consensus between guidelines.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/cancers16061115/s1>, Table S1: Details of the Appraisal of Guidelines, Research, and Evaluation II (AGREE II) instrument along with the domains and corresponding items.

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References

1. Siegel, R.L.; Miller, K.D.; Fuchs, H.E.; Jemal, A. Cancer Statistics, 2021. *CA Cancer J. Clin.* **2021**, *71*, 7–33. [CrossRef]
2. Colin, P.; Koenig, P.; Ouzzane, A.; Berthon, N.; Villers, A.; Biserte, J.; Rouprêt, M. Environmental factors involved in carcinogenesis of urothelial cell carcinomas of the upper urinary tract. *BJU Int.* **2009**, *104*, 1436–1440. [CrossRef]
3. Zganjar, A.J.; Thiel, D.D.; Lyon, T.D. Diagnosis, workup, and risk stratification of upper tract urothelial carcinoma. *Transl. Androl. Urol.* **2023**, *12*, 1456–1468. [CrossRef]
4. GGrob, G.; Rogers, D.; Pandolfo, S.D.; Vourganti, S.; Buscarini, M.; Mehrazin, R.; Grob, B.M.; Mir, M.C.; Perdonà, S.; Derweesh, I.H.; et al. Oncologic outcomes following radical nephroureterectomy for upper tract urothelial carcinoma: A literature review. *Transl. Androl. Urol.* **2023**, *12*, 1351–1362. [CrossRef]
5. Wu, Z.; Li, M.; Wang, L.; Paul, A.; Raman, J.D.; Necchi, A.; Psutka, S.P.; Buonerba, C.; Zargar, H.; Black, P.C.; et al. Neoadjuvant systemic therapy in patients undergoing nephroureterectomy for urothelial cancer: A multidisciplinary systematic review and critical analysis. *Minerva Urol. Nephrol.* **2022**, *74*, 518–527. Available online: <https://www.minervamedica.it/index2.php?show=R19Y2022N05A0518> (accessed on 2 May 2023). [CrossRef]
6. Kumar, R.; Kumar Airon, R.; Mittal, A.; Singal, R.; Sharma, K.; Singal, S. Evaluation of Multidetector Computed Tomography in Haematuria. *Maedica* **2017**, *12*, 87–94.
7. Calace, F.P.; Napolitano, L.; Arcaniolo, D.; Stizzo, M.; Barone, B.; Crocetto, F.; Olivetta, M.; Amicuzi, U.; Cirillo, L.; Rubinacci, A.; et al. Micro-Ultrasound in the Diagnosis and Staging of Prostate and Bladder Cancer: A Comprehensive Review. *Medicina* **2022**, *58*, 1624. [CrossRef] [PubMed]

8. Rouprêt, M.; Seisen, T.; Birtle, A.J.; Capoun, O.; Compérat, E.M.; Dominguez-Escrig, J.L.; Gürses Andersson, I.; Liedberg, F.; Mariappan, P.; Hugh Mostafid, A.; et al. European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma: 2023 Update. *Eur. Urol.* **2023**, *84*, 49–64. [[CrossRef](#)] [[PubMed](#)]
9. Coleman, J.A.; Clark, P.E.; Bixler, B.R.; Buckley, D.I.; Chang, S.S.; Chou, R.; Hoffman-Censits, J.; Kulkarni, G.S.; Matin, S.F.; Pierorazio, P.M.; et al. Diagnosis and Management of Non-Metastatic Upper Tract Urothelial Carcinoma: AUA/SUO Guideline. *J. Urol.* **2023**, *209*, 1071–1081. [[CrossRef](#)] [[PubMed](#)]
10. Brouwers, M.C.; Kho, M.E.; Browman, G.P.; Burgers, J.S.; Cluzeau, F.; Feder, G.; Fervers, B.; Graham, I.D.; Grimshaw, J.; Hanna, S.E.; et al. AGREE II: Advancing guideline development, reporting and evaluation in health care. *Can. Med Assoc. J.* **2010**, *182*, E839–E842. [[CrossRef](#)]
11. Brouwers, M.C.; Kerkvliet, K.; Spithoff, K.; AGREE Next Steps Consortium. The AGREE Reporting Checklist: A tool to improve reporting of clinical practice guidelines. *BMJ* **2016**, *352*, i1152. [[CrossRef](#)] [[PubMed](#)]
12. Flaig, T.W.; Spiess, P.E.; Abern, M.; Agarwal, N.; Bangs, R.; Boorjian, S.A.; Buyyounouski, M.K.; Chan, K.; Chang, S.; Friedlander, T.; et al. NCCN Guidelines® Insights: Bladder Cancer, Version 2.2022. *J. Natl. Compr. Can. Netw.* **2022**, *20*, 866–878. [[CrossRef](#)] [[PubMed](#)]
13. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer statistics, 2020. *CA Cancer J. Clin.* **2020**, *70*, 7–30. [[CrossRef](#)] [[PubMed](#)]
14. Shariat, S.F.; Favaretto, R.L.; Gupta, A.; Fritsche, H.M.; Matsumoto, K.; Kassouf, W.; Walton, T.J.; Tritschler, S.; Baba, S.; Matsushita, K.; et al. Gender differences in radical nephroureterectomy for upper tract urothelial carcinoma. *World J. Urol.* **2011**, *29*, 481–486. [[CrossRef](#)] [[PubMed](#)]
15. Soria, F.; Shariat, S.F.; Lerner, S.P.; Fritsche, H.-M.; Rink, M.; Kassouf, W.; Spiess, P.E.; Lotan, Y.; Ye, D.; Fernández, M.I.; et al. Epidemiology, diagnosis, preoperative evaluation and prognostic assessment of upper-tract urothelial carcinoma (UTUC). *World J. Urol.* **2017**, *35*, 379–387. [[CrossRef](#)] [[PubMed](#)]
16. Almås, B.; Halvorsen, O.J.; Johannesen, T.B.; Beisland, C. Higher than expected and significantly increasing incidence of upper tract urothelial carcinoma. A population based study. *World J. Urol.* **2021**, *39*, 3385–3391. [[CrossRef](#)] [[PubMed](#)]
17. Nishiyama, N.; Hotta, H.; Takahashi, A.; Yanase, M.; Itoh, N.; Tachiki, H.; Miyao, N.; Matsukawa, M.; Kunishima, Y.; Taguchi, K.; et al. Upper tract urothelial carcinoma following intravesical bacillus Calmette-Guérin therapy for nonmuscle-invasive bladder cancer: Results from a multi-institutional retrospective study. *Urol. Oncol.* **2018**, *36*, 306.e9–306.e15. [[CrossRef](#)] [[PubMed](#)]
18. Sanderson, K.M.; Rouprêt, M. Upper urinary tract tumour after radical cystectomy for transitional cell carcinoma of the bladder: An update on the risk factors, surveillance regimens and treatments. *BJU Int.* **2007**, *100*, 11–16. [[CrossRef](#)]
19. Uroweb–European Association of Urology. EAU Guidelines on Upper Urinary Tract Urothelial Cell Carcinoma–INTRODUCTION–Uroweb. Available online: <https://uroweb.org/guidelines/upper-urinary-tract-urothelial-cell-carcinoma/chapter/introduction> (accessed on 4 December 2023).
20. Diagnosis and Management of Non-Metastatic Upper Tract Urothelial Carcinoma: AUA/SUO Guideline–American Urological Association. Available online: <https://www.auanet.org/guidelines-and-quality/guidelines/non-metastatic-upper-tract-urothelial-carcinoma> (accessed on 4 December 2023).
21. Dickman, K.G.; Fritsche, H.M.; Grollman, A.P.; Thalmann, G.N.; Catto, J. Epidemiology and Risk Factors for Upper Urinary Urothelial Cancers. In *Upper Tract Urothelial Carcinoma*; Shariat, S.F., Xylinas, E., Eds.; Springer: New York, NY, USA, 2015; pp. 1–30. [[CrossRef](#)]
22. Zaitso, M.; Kawachi, I.; Takeuchi, T.; Kobayashi, Y. Alcohol consumption and risk of upper-tract urothelial cancer. *Cancer Epidemiol.* **2017**, *48*, 36–40. [[CrossRef](#)]
23. Cerrato, C.; Pandolfo, S.D.; Autorino, R.; Panunzio, A.; Tafuri, A.; Porcaro, A.B.; Veccia, A.; De Marco, V.; Cerruto, M.A.; Antonelli, A.; et al. Gender-specific counselling of patients with upper tract urothelial carcinoma and Lynch syndrome. *World J. Urol.* **2023**, *41*, 1741–1749. [[CrossRef](#)]
24. Metcalfe, M.J.; Petros, F.G.; Rao, P.; Mork, M.E.; Xiao, L.; Broaddus, R.R.; Matin, S.F. Universal Point of Care Testing for Lynch Syndrome in Patients with Upper Tract Urothelial Carcinoma. *J. Urol.* **2018**, *199*, 60–65. [[CrossRef](#)] [[PubMed](#)]
25. Umar, A.; Boland, C.R.; Terdiman, J.P.; Syngal, S.; Chappelle, A.D.L.; Rüschoff, J.; Fishel, R.; Lindor, N.M.; Burgart, L.J.; Hamelin, R.; et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J. Natl. Cancer Inst.* **2004**, *96*, 261–268. [[CrossRef](#)] [[PubMed](#)]
26. Rai, B.P.; Escrig, J.L.D.; Vale, L.; Kuusk, T.; Capoun, O.; Soukup, V.; Bruins, H.M.; Yuan, Y.; Violette, P.D.; Santesso, N.; et al. Systematic Review of the Incidence of and Risk Factors for Urothelial Cancers and Renal Cell Carcinoma Among Patients with Haematuria. *Eur. Urol.* **2022**, *82*, 182–192. [[CrossRef](#)] [[PubMed](#)]
27. Baard, J.; Cormio, L.; Cavadas, V.; Alcaraz, A.; Shariat, S.F.; de la Rosette, J.; Laguna, M.P. Contemporary patterns of presentation, diagnostics and management of upper tract urothelial cancer in 101 centres: The Clinical Research Office of the Endourological Society Global upper tract urothelial carcinoma registry. *Curr. Opin. Urol.* **2021**, *31*, 354–362. [[CrossRef](#)]
28. Jakus, D.; Šolić, I.; Borovac, J.A.; Šitum, M. The influence of the initial clinical presentation of upper tract urothelial carcinoma on histopathological tumor features. *Int. Urol. Nephrol.* **2023**. [[CrossRef](#)] [[PubMed](#)]
29. Rud, E.; Galtung, K.F.; Lauritzen, P.M.; Baco, E.; Flatabø, T.; Sandbæk, G. Examining the upper urinary tract in patients with hematuria-time to revise the CT urography protocol? *Eur. Radiol.* **2020**, *30*, 1664–1670. [[CrossRef](#)] [[PubMed](#)]

30. Janisch, F.; Shariat, S.F.; Baltzer, P.; Fajkovic, H.; Kimura, S.; Iwata, T.; Korn, P.; Yang, L.; Glybochko, P.V.; Rink, M.; et al. Diagnostic performance of multidetector computed tomographic (MDCTU) in upper tract urothelial carcinoma (UTUC): A systematic review and meta-analysis. *World J. Urol.* **2020**, *38*, 1165–1175. [[CrossRef](#)]
31. Tsikitas, L.A.; Hopstone, M.D.; Raman, A.; Duddalwar, V. Imaging in Upper Tract Urothelial Carcinoma: A Review. *Cancers* **2023**, *15*, 5040. [[CrossRef](#)]
32. Razavi, S.A.; Sadigh, G.; Kelly, A.M.; Cronin, P. Comparative effectiveness of imaging modalities for the diagnosis of upper and lower urinary tract malignancy: A critically appraised topic. *Acad. Radiol.* **2012**, *19*, 1134–1140. [[CrossRef](#)]
33. Potretzke, A.M.; Knight, B.A.; Vetter, J.M.; Anderson, B.G.; Hardi, A.C.; Bhayani, S.B.; Figenshau, R.S. Diagnostic Utility of Selective Upper Tract Urinary Cytology: A Systematic Review and Meta-analysis of the Literature. *Urology* **2016**, *96*, 35–43. [[CrossRef](#)]
34. Vashistha, V.; Shabsigh, A.; Zynger, D.L. Utility and diagnostic accuracy of ureteroscopic biopsy in upper tract urothelial carcinoma. *Arch. Pathol. Lab. Med.* **2013**, *137*, 400–407. [[CrossRef](#)] [[PubMed](#)]
35. Mori, K.; Katayama, S.; Laukhtina, E.; Schuettfort, V.M.; Pradere, B.; Quhal, F.; Motlagh, R.S.; Mostafaei, H.; Grossmann, N.C.; Rajwa, P.; et al. Discordance Between Clinical and Pathological Staging and Grading in Upper Tract Urothelial Carcinoma. *Clin. Genitourin. Cancer.* **2022**, *20*, 95.e1–95.e6. [[CrossRef](#)]
36. Voskuilen, C.S.; Schweitzer, D.; Jensen, J.B.; Nielsen, A.M.; Joniau, S.; Muilwijk, T.; Necchi, A.; Azizi, M.; Spiess, P.E.; Briganti, A.; et al. Diagnostic Value of 18F-fluorodeoxyglucose Positron Emission Tomography with Computed Tomography for Lymph Node Staging in Patients with Upper Tract Urothelial Carcinoma. *Eur. Urol. Oncol.* **2020**, *3*, 73–79. [[CrossRef](#)]
37. Rouprêt, M.; Colin, P.; Yates, D.R. A new proposal to risk stratify urothelial carcinomas of the upper urinary tract (UTUCs) in a predefinitive treatment setting: Low-risk versus high-risk UTUCs. *Eur. Urol.* **2014**, *66*, 181–183. [[CrossRef](#)] [[PubMed](#)]
38. Seisen, T.; Colin, P.; Rouprêt, M. Risk-adapted strategy for the kidney-sparing management of upper tract tumours. *Nat. Rev. Urol.* **2015**, *12*, 155–166. [[CrossRef](#)]
39. Messer, J.C.; Terrell, J.D.; Herman, M.P.; Ng, C.K.; Scherr, D.S.; Scoll, B.; Boorjian, S.A.; Uzzo, R.G.; Wille, M.; Eggner, S.E.; et al. Multi-institutional validation of the ability of preoperative hydronephrosis to predict advanced pathologic tumor stage in upper-tract urothelial carcinoma. *Urol. Oncol.* **2013**, *31*, 904–908. [[CrossRef](#)]
40. Foerster, B.; Abufaraj, M.; Mari, A.; Seisen, T.; Bandini, M.; Schweitzer, D.; Czech, A.K.; Moschini, M.; D'andrea, D.; Bianchi, M.; et al. The Performance of Tumor Size as Risk Stratification Parameter in Upper Tract Urothelial Carcinoma (UTUC). *Clin. Genitourin. Cancer.* **2021**, *19*, 272.e1–272.e7. [[CrossRef](#)]
41. Zeng, S.; Ying, Y.; Yu, X.; Wang, L.; Zhang, Z.; Xu, C. Impact of previous, simultaneous or intravesical recurrence bladder cancer on prognosis of upper tract urothelial carcinoma after nephroureterectomy: A large population-based study. *Transl. Androl. Urol.* **2021**, *10*, 4365–4375. [[CrossRef](#)]
42. Ma, R.; Xia, H.; Qiu, M.; Tao, L.; Lu, M.; Huang, R.; Lu, J.; Ma, L. A Diagnostic Nomogram of Pathologic Grade for Preoperative Risk Stratification in Upper Tract Urothelial Carcinoma. *Clin. Med. Insights Oncol.* **2020**, *14*, 1179554920927662. [[CrossRef](#)] [[PubMed](#)]
43. Cerrato, C.; Patel, D.; Autorino, R.; Simone, G.; Yang, B.; Uzzo, R.; Porpiglia, F.; Capitanio, U.; Porter, J.; Beksac, A.T.; et al. Partial or radical nephrectomy for complex renal mass: A comparative analysis of oncological outcomes and complications from the ROSULA (Robotic Surgery for Large Renal Mass) Collaborative Group. *World J. Urol.* **2023**, *41*, 747–755. [[CrossRef](#)] [[PubMed](#)]
44. Shigeta, K.; Kikuchi, E.; Abe, T.; Hagiwara, M.; Ogihara, K.; Anno, T.; Umeda, K.; Baba, Y.; Sanjo, T.; Shoji, K.; et al. A Novel Risk-based Approach Simulating Oncological Surveillance after Radical Nephroureterectomy in Patients with Upper Tract Urothelial Carcinoma. *Eur. Urol. Oncol.* **2020**, *3*, 756–763. [[CrossRef](#)]
45. Cerrato, C.; Meagher, M.F.; Autorino, R.; Simone, G.; Yang, B.; Uzzo, R.G.; Kutikov, A.; Porpiglia, F.; Capitanio, U.; Montorsi, F.; et al. Partial versus radical nephrectomy for complex renal mass: Multicenter comparative analysis of functional outcomes (Rosula collaborative group). *Minerva Urol. Nephrol.* **2023**, *75*, 425–433. [[CrossRef](#)] [[PubMed](#)]
46. Aziz, A.; Fritsche, H.-M.; Gakis, G.; Kluth, L.A.; Hassan, F.A.-S.; Engel, O.; Dahlem, R.; Otto, W.; Gierth, M.; Denzinger, S.; et al. Comparative analysis of comorbidity and performance indices for prediction of oncological outcomes in patients with upper tract urothelial carcinoma who were treated with radical nephroureterectomy. *Urol. Oncol.* **2014**, *32*, 1141–1150. [[CrossRef](#)]
47. Nardelli, C.; Aveta, A.; Pandolfo, S.D.; Tripodi, L.; Russo, F.; Imbimbo, C.; Castaldo, G.; Pastore, L. Microbiome Profiling in Bladder Cancer Patients Using the First-morning Urine Sample. *Eur. Urol. Open Sci.* **2024**, *59*, 18–26. [[CrossRef](#)] [[PubMed](#)]
48. Kaag, M.; Trost, L.; Thompson, R.H.; Favaretto, R.; Elliott, V.; Shariat, S.F.; Maschino, A.; Vertosick, E.; Raman, J.D.; Dalbagni, G. Preoperative predictors of renal function decline after radical nephroureterectomy for upper tract urothelial carcinoma. *BJU Int.* **2014**, *114*, 674–679. [[CrossRef](#)]
49. Lughezzani, G.; Jeldres, C.; Isbarn, H.; Sun, M.; Shariat, S.F.; Alasker, A.; Pharand, D.; Widmer, H.; Arjane, P.; Graefen, M.; et al. Nephroureterectomy and segmental ureterectomy in the treatment of invasive upper tract urothelial carcinoma: A population-based study of 2299 patients. *Eur. J. Cancer.* **2009**, *45*, 3291–3297. [[CrossRef](#)]
50. Yakoubi, R.; Colin, P.; Seisen, T.; Léon, P.; Nison, L.; Bozzini, G.; Shariat, S.; Rouprêt, M. Radical nephroureterectomy versus endoscopic procedures for the treatment of localised upper tract urothelial carcinoma: A meta-analysis and a systematic review of current evidence from comparative studies. *Eur. J. Surg. Oncol.* **2014**, *40*, 1629–1634. [[CrossRef](#)] [[PubMed](#)]

51. Matin, S.F.; Pierorazio, P.M.; Kleinmann, N.; Gore, J.L.; Shabsigh, A.; Hu, B.; Chamie, K.; Godoy, G.; Hubosky, S.G.; Rivera, M.; et al. Durability of Response to Primary Chemoablation of Low-Grade Upper Tract Urothelial Carcinoma Using UGN-101, a Mitomycin-Containing Reverse Thermal Gel: OLYMPUS Trial Final Report. *J. Urol.* **2022**, *207*, 779–788. [[CrossRef](#)]
52. Gallioli, A.; Boissier, R.; Territo, A.; Reyes, H.V.; Sanguedolce, F.; Gaya, J.M.; Regis, F.; Subiela, J.D.; Palou, J.; Breda, A. Adjuvant Single-Dose Upper Urinary Tract Instillation of Mitomycin C After Therapeutic Ureterscopy for Upper Tract Urothelial Carcinoma: A Single-Centre Prospective Non-Randomized Trial. *J. Endourol.* **2020**, *34*, 573–580. [[CrossRef](#)]
53. Kleinmann, N.; Matin, S.F.; Pierorazio, P.M.; Gore, J.L.; Shabsigh, A.; Hu, B.; Chamie, K.; Godoy, G.; Hubosky, S.; Rivera, M.; et al. Primary chemoablation of low-grade upper tract urothelial carcinoma using UGN-101, a mitomycin-containing reverse thermal gel (OLYMPUS): An open-label, single-arm, phase 3 trial. *Lancet Oncol.* **2020**, *21*, 776–785. [[CrossRef](#)]
54. Fontanet, S.; Gallioli, A.; Baboudjian, M.; Huguet, J.; Territo, A.; Gaya, J.M.; Gavrillov, P.; Izquierdo, P.; Verri, P.; Algaba, F.; et al. Topical instillation of BCG immunotherapy for biopsy-proven primary upper urinary tract carcinoma in situ: A single institution series and systematic review. *Urol. Oncol.* **2023**, *41*, 274–283. [[CrossRef](#)]
55. Ha, Y.-S.; Chung, J.-W.; Choi, S.H.; Lee, J.N.; Kim, B.S.; Kim, T.-H.; Yoo, E.S.; Kwon, T.G.; Byun, S.-S.; Choi, Y.D.; et al. Impact of a bladder cuff excision during radical nephroureterectomy on cancer specific survival in patients with upper tract urothelial cancer in Korea: A retrospective, multi-institutional study. *Minerva Urol. Nefrol.* **2017**, *69*, 466–474. [[CrossRef](#)]
56. Rouprêt, M.; Smyth, G.; Irani, J.; Guy, L.; Davin, J.-L.; Saint, F.; Pfister, C.; Wallerand, H.; Rozet, F. Oncological risk of laparoscopic surgery in urothelial carcinomas. *World J. Urol.* **2009**, *27*, 81–88. [[CrossRef](#)]
57. Piszczek, R.; Nowak, Ł.; Krajewski, W.; Chorbińska, J.; Poletajew, S.; Moschini, M.; Kaliszewski, K.; Zdrojowy, R. Oncological Outcomes of Laparoscopic Nephroureterectomy Versus Open Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma: An European Association of Urology Guidelines Systematic Review. *Eur. Urol. Focus.* **2019**, *5*, 205–223.
58. Xylinas, E.; Rink, M.; Cha, E.K.; Clozel, T.; Lee, R.K.; Fajkovic, H.; Comploj, E.; Novara, G.; Margulis, V.; Raman, J.D.; et al. Impact of distal ureter management on oncologic outcomes following radical nephroureterectomy for upper tract urothelial carcinoma. *Eur. Urol.* **2014**, *65*, 210–217. [[CrossRef](#)] [[PubMed](#)]
59. Hwang, E.C.; Sathianathen, N.J.; Jung, J.H.; Kim, M.H.; Dahm, P.; Risk, M.C. Single-dose intravesical chemotherapy after nephroureterectomy for upper tract urothelial carcinoma. *Cochrane Database Syst. Rev.* **2019**, *5*, CD013160. [[CrossRef](#)] [[PubMed](#)]
60. Freifeld, Y.; Ghandour, R.; Singla, N.; Woldu, S.; Bagrodia, A.; Lotan, Y.; Rapoport, L.M.; Gazimiev, M.; Delafuente, K.; Kulangara, R.; et al. Intraoperative prophylactic intravesical chemotherapy to reduce bladder recurrence following radical nephroureterectomy. *Urol. Oncol.* **2020**, *38*, 737.e11–737.e16. [[CrossRef](#)]
61. Yoo, S.H.; Jeong, C.W.; Kwak, C.; Kim, H.H.; Choo, M.S.; Ku, J.H. Intravesical Chemotherapy after Radical Nephroureterectomy for Primary Upper Tract Urothelial Carcinoma: A Systematic Review and Network Meta-Analysis. *J. Clin. Med.* **2019**, *8*, 1059. [[CrossRef](#)]
62. Margulis, V.; Puligandla, M.; Trabulsi, E.J.; Plimack, E.R.; Kessler, E.R.; Matin, S.F.; Godoy, G.; Alva, A.; Hahn, N.M.; Carducci, M.A.; et al. Phase II Trial of Neoadjuvant Systemic Chemotherapy Followed by Extirpative Surgery in Patients with High Grade Upper Tract Urothelial Carcinoma. *J. Urol.* **2020**, *203*, 690–698. [[CrossRef](#)]
63. Kim, D.K.; Lee, J.Y.; Kim, J.W.; Hah, Y.S.; Cho, K.S. Effect of neoadjuvant chemotherapy on locally advanced upper tract urothelial carcinoma: A systematic review and meta-analysis. *Crit. Rev. Oncol. Hematol.* **2019**, *135*, 59–65. [[CrossRef](#)] [[PubMed](#)]
64. Audenet, F.; Yates, D.R.; Cussenot, O.; Rouprêt, M. The role of chemotherapy in the treatment of urothelial cell carcinoma of the upper urinary tract (UUT-UCC). *Urol. Oncol.* **2013**, *31*, 407–413. [[CrossRef](#)]
65. Meng, X.; Chao, B.; Vijay, V.; Silver, H.; Margolin, E.J.; Balar, A.; Taneja, S.S.; Shah, O.; Bjurlin, M.A.; Anderson, C.B.; et al. High Response Rates to Neoadjuvant Chemotherapy in High-Grade Upper Tract Urothelial Carcinoma. *Urology* **2019**, *129*, 146–152. [[CrossRef](#)]
66. Kubota, Y.; Hatakeyama, S.; Tanaka, T.; Fujita, N.; Iwamura, H.; Mikami, J.; Yamamoto, H.; Tobisawa, Y.; Yoneyama, T.; Yoneyama, T.; et al. Oncological outcomes of neoadjuvant chemotherapy in patients with locally advanced upper tract urothelial carcinoma: A multicenter study. *Oncotarget* **2017**, *8*, 101500–101508. [[CrossRef](#)] [[PubMed](#)]
67. Hosogoe, S.; Hatakeyama, S.; Kusaka, A.; Hamano, I.; Iwamura, H.; Fujita, N.; Yamamoto, H.; Tobisawa, Y.; Yoneyama, T.; Yoneyama, T.; et al. Platinum-based Neoadjuvant Chemotherapy Improves Oncological Outcomes in Patients with Locally Advanced Upper Tract Urothelial Carcinoma. *Eur. Urol. Focus.* **2018**, *4*, 946–953. [[CrossRef](#)] [[PubMed](#)]
68. Leow, J.J.; Chong, Y.L.; Chang, S.L.; Valderrama, B.P.; Powles, T.; Bellmunt, J. Neoadjuvant and Adjuvant Chemotherapy for Upper Tract Urothelial Carcinoma: A 2020 Systematic Review and Meta-analysis, and Future Perspectives on Systemic Therapy. *Eur. Urol.* **2021**, *79*, 635–654. [[CrossRef](#)] [[PubMed](#)]
69. Coleman, J.A.; Yip, W.; Wong, N.C.; Sjoberg, D.D.; Bochner, B.H.; Dalbagni, G.; Donat, S.M.; Herr, H.W.; Cha, E.K.; Donahue, T.F.; et al. Multicenter Phase II Clinical Trial of Gemcitabine and Cisplatin as Neoadjuvant Chemotherapy for Patients With High-Grade Upper Tract Urothelial Carcinoma. *J. Clin. Oncol.* **2023**, *41*, 1618–1625. [[CrossRef](#)]
70. Crocerossa, F.; Fiori, C.; Capitanio, U.; Minervini, A.; Carbonara, U.; Pandolfo, S.D.; Loizzo, D.; Eun, D.D.; Larcher, A.; Mari, A.; et al. Estimated Glomerular Filtration Rate Decline at 1 Year after Minimally Invasive Partial Nephrectomy: A Multi-model Comparison of Predictors. *Eur. Urol. Open Sci.* **2022**, *38*, 52–59. [[CrossRef](#)]
71. Lane, B.R.; Smith, A.K.; Larson, B.T.; Gong, M.C.; Campbell, S.C.; Raghavan, D.; Dreicer, R.; Hansel, D.E.; Stephenson, A.J. Chronic kidney disease after nephroureterectomy for upper tract urothelial carcinoma and implications for the administration of perioperative chemotherapy. *Cancer* **2010**, *116*, 2967–2973. [[CrossRef](#)]

72. De Santis, M.; Bellmunt, J.; Mead, G.; Kerst, J.M.; Leahy, M.; Maroto, P.; Skoneczna, I.; Marreaud, S.; de Wit, R.; Sylvester, R. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer «unfit» for cisplatin-based chemotherapy: Phase II—Results of EORTC study 30986. *J. Clin. Oncol.* **2009**, *27*, 5634–5639. [[CrossRef](#)] [[PubMed](#)]
73. Bajorin, D.F.; Witjes, J.A.; Gschwend, J.E.; Schenker, M.; Valderrama, B.P.; Tomita, Y.; Bamias, A.; Lebret, T.; Shariat, S.F.; Park, S.H.; et al. Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma. *N. Engl. J. Med.* **2021**, *384*, 2102–2114. [[CrossRef](#)] [[PubMed](#)]
74. Laukhtina, E.; Sari Motlagh, R.; Mori, K.; Katayama, S.; Rajwa, P.; Yanagisawa, T.; Quhal, F.; Mostafaei, H.; Grossmann, N.C.; König, F.; et al. Chemotherapy is superior to checkpoint inhibitors after radical surgery for urothelial carcinoma: A systematic review and network meta-analysis of oncologic and toxicity outcomes. *Crit. Rev. Oncol. Hematol.* **2022**, *169*, 103570. [[CrossRef](#)] [[PubMed](#)]
75. Board WC of TE. Urinary and Male Genital Tumours. Available online: <https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/Urinary-And-Male-Genital-Tumours-2022> (accessed on 11 January 2024).
76. Wiley.com. *TNM Classification of Malignant Tumours*, 8th ed.; Wiley: Hoboken, NJ, USA; Available online: <https://www.wiley.com/en-us/TNM+Classification+of+Malignant+Tumours,+8th+Edition-p-9781119263579> (accessed on 11 January 2024).
77. Oge, O.; Erdem, E.; Atsü, N.; Ahin, A.; Ozen, H. Proposal for changes in cystoscopic follow-up of patients with low-grade pTa bladder tumor. *Eur. Urol.* **2000**, *37*, 271–274. [[PubMed](#)]
78. Klemm, J.; Bekku, K.; Abufaraj, M.; Laukhtina, E.; Matsukawa, A.; Parizi, M.K.; Karakiewicz, P.I.; Shariat, S.F. Upper Tract Urothelial Carcinoma: A Narrative Review of Current Surveillance Strategies for Non-Metastatic Disease. *Cancers* **2023**, *16*, 44. [[CrossRef](#)] [[PubMed](#)]
79. Klemm, J.; Bekku, K.; Abufaraj, M.; Laukhtina, E.; Matsukawa, A.; Parizi, M.K.; Karakiewicz, P.I.; Shariat, S.F. Early repeated ureteroscopy within 6–8 weeks after a primary endoscopic treatment in patients with upper tract urothelial cell carcinoma: Preliminary findings. *World J. Urol.* **2016**, *34*, 1201–1206.
80. Holmäng, S.; Johansson, S.L. Long-term follow-up of patients with tumours of the renal pelvis and ureter: How often is a bladder tumour diagnosed after five tumour-free years? *Scand. J. Urol.* **2014**, *48*, 65–72. [[CrossRef](#)]
81. Mohapatra, A.; Strobe, S.A.; Liu, N.; Winer, A.; Benfante, N.E.; Coleman, J.A.; Vetter, J.; Murray, K.S. Importance of long-term follow-up after endoscopic management for upper tract urothelial carcinoma and factors leading to surgical management. *Int. Urol. Nephrol.* **2020**, *52*, 1465–1469. [[CrossRef](#)]
82. Shigeta, K.; Kikuchi, E.; Hagiwara, M.; Ando, T.; Mizuno, R.; Abe, T.; Mikami, S.; Miyajima, A.; Nakagawa, K.; Oya, M. The Conditional Survival with Time of Intravesical Recurrence of Upper Tract Urothelial Carcinoma. *J. Urol.* **2017**, *198*, 1278–1285. [[CrossRef](#)]
83. Martini, A.; Lonati, C.; Nocera, L.; Fallara, G.; Raggi, D.; Herout, R.; Zamboni, S.; Ploussard, G.; Predere, B.; Mattei, A.; et al. Oncologic Surveillance after Radical Nephroureterectomy for High-risk Upper Tract Urothelial Carcinoma. *Eur. Urol. Oncol.* **2022**, *5*, 451–459. [[CrossRef](#)]
84. Katims, A.B.; Say, R.; Derweesh, I.; Uzzo, R.; Minervini, A.; Wu, Z.; Abdollah, F.; Sundaram, C.; Ferro, M.; Rha, K.; et al. Risk Factors for Intravesical Recurrence after Minimally Invasive Nephroureterectomy for Upper Tract Urothelial Cancer (ROBUUST Collaboration). *J. Urol.* **2021**, *206*, 568–576. [[CrossRef](#)]
85. Locke, J.A.; Hamidizadeh, R.; Kassouf, W.; Rendon, R.A.; Bell, D.; Izawa, J.; Chin, J.; Kapoor, A.; Shayegan, B.; Lattouf, J.-B.; et al. Surveillance guidelines based on recurrence patterns for upper tract urothelial carcinoma. *Can. Urol. Assoc. J.* **2018**, *12*, 243–251. [[CrossRef](#)]
86. Li, X.; Cui, M.; Gu, X.; Fang, D.; Li, H.; Qin, S.; Yang, K.; Zhu, T.; Li, X.; Zhou, L.; et al. Pattern and risk factors of local recurrence after nephroureterectomy for upper tract urothelial carcinoma. *World J. Surg. Oncol.* **2020**, *18*, 114. [[CrossRef](#)] [[PubMed](#)]

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