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ORIGINAL ARTICLE

Adherence to guideline recommendations in the management of upper tract urothelial carcinoma: an analysis of the CROES–UTUC registry

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Abstract

Background The European Association of Urology provides Clinical Practice Guideline on upper tract urothelial carcinoma (UTUC). Due to the rarity of UTUC, guidelines are necessary to help guide decision-making based on the highest quality of care evidence available.

Objectives To evaluate guideline adherence in the management of UTUC by assessing recommendations on diagnostics needed for risk classification and subsequent treatment selection; to assess predictors for the latter.

Participants Data from the Clinical Research Office of the Endo Urology Society UTUC-registry were included for analysis.

Statistical analysis Overall compliance were evaluated by cross-tables, differences in risk groups characteristics and treatment selection were assessed by Chi-square tests, predictors for treatment selection by logistic regression analysis.

Results Data from 2380 patients were included. Imaging by CT-scan had highest adherence (85%) but was low for other diagnostics (17.7–49.7%). Multivariable regression analysis showed higher odds of receiving radical nephroureterectomy in patients with large tumours (OR 5.45, 95% CI 3.77–7.87, $p < 0.001$), signs of invasion (OR 3.07,CI 2.11–4.46, $p < 0.001$), high tumour grade (OR 2.05, CI 1.38–3.05, $p < 0.001$) and multifocality (OR 1.76,CI 1.05–2.97, $p = 0.032$).

Conclusions CT-imaging is the most used and most impactful decision tool for risk-stratification and treatment selection in UTUC. Due to the low compliance in most of the diagnostic recommendations, proper risk stratification is not possible in a significant group of patients raising the question whether current stratification is deemed applicable in daily practice. Established prognostic factors on survival guides decision-making regarding radical versus kidney-sparing surgery. Tumour size was the most influencing factor on treatment decision.

Clinical trial registration The study was registered at ClinicalTrials.gov (ClinicalTrials.gov NCT02281188; https://clinicaltrials.gov/ct2/show/NCT02281188).

Keywords Clinical practice guidelines · Guidelines · Urothelial carcinoma · Upper tract urothelial carcinoma · UTUC

Introduction

In the last decades there has been an increasing interest in the development and use of clinical practice guidelines (CPGs). CPGs aim to improve the quality of care, provide evidence-based recommendations for clinical care delivery and thereby improve health care outcomes [1, 2]. Guidelines should be based on rigorous and unbiased review of relevant evidence to provide comprehensive evidence-based recommendations and address relevant patient questions [1, 3–6]. Upper Tract Urothelial Cancer (UTUC) is a rare urological malignancy and CPGs are a challenge to develop in rare diseases due to a lack of high-level evidence [7, 8]. Randomized clinical trials are for example extremely rare in UTUC. Despite of these existing hurdles the EAU guidelines office developed a dedicated guideline on UTUC. Since the first edition in 2011, multiple updates of this resource have been published including the most recent insights and evidence. The main shift in UTUC management, as reflected in the guidelines, has resulted from the incorporation of ureteroscopic evaluation in the diagnostic process as well

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as the recommendation to offer endoscopic kidney sparing surgery (KSS) for selected patients with low-risk disease. To avoid over- and under-treatment, the guidelines developed a precise risk-stratification strategy with the goal of delivering KSS for low-risk disease and RNU for high-risk disease [7]. However, adherence to guidelines by clinicians is often poor with several categories of barriers recognized including lack of familiarity and awareness of CPGs, lack of agreement or outcome expectancy and lack of motivation [9, 10]. Guidelines should be generalizable and applicable in daily practice. Data from a global real world registry were analyzed with the aim to assess the compliance to guideline recommendations in patients with UTUC regarding diagnostics, adherence to recommendations on risk classification and subsequent treatment allocation [7, 11–16]. We hypothesized that there should be a relationship between the strength of the recommendation and the adherence. Further we hypothesized that the applicability of the proposed risk stratification could be compromised by its compulsory character and would not be directive in treatment allocation. Insights on guideline compliance might drive changes in care, overcome existing hurdles with the aim improve implementation in daily practice.

Patients and methods

Data were extracted from all adult patients (18 years) with UTUC included in the prospective CROES UTUC-registry [17]. Patients were evaluated and treated according to local standard of care practice. Patient information was collected from diagnosis, treatment and follow-up. A detailed description of the registry is published elsewhere [17].

Study objectives

To evaluate guideline adherence in the management of UTUC by assessing recommendations on diagnostics needed for risk classification and treatment selection and to assess predictors of treatment selection (KSS vs. RNU).

Guideline recommendations on diagnosis and treatment

Guidelines recommendations on diagnosis and risk stratification were scrutinized across the different annual versions from the initiation until closure of the registry and changes in guideline recommendations were accounted for [11–16]. Diagnostic variables mentioned in the guidelines and taken into analysis included practice of urine cytology, cystoscopy, imaging by Computed Tomography (CT), retrograde pyelography (X-RPG) and diagnostic ureteroscopy (dURS) (Supplement Table 1).

The time interval of data collection was divided into 5 segments: 2014–2015, 2015–2016, 2016–2017, 2017–2018 and 2018–2019. Due to the lack of definitions of high- vs. low-volume centers in UTUC, we dichotomized into low-, and high-number of inclusions based on the interquartile range (IQR) of number of inclusions per center.

Treatment modality

Subsets of patients were created based on the risk stratification proposed by the guidelines. (Supplement Table 2). Clinical variables taken into account included signs of invasive disease on imaging, tumour grade (biopsy *or* cytology result), tumour size (based on imaging) and tumor focality (based on imaging). Tumor size was defined as 'large' according to the definition of the guidelines, > 1 cm until 2017 and > 2 cm from 2018, changes over the years were accounted for.

Statistical analysis

The data were analyzed using SPSS version 27 (IBM Corporation Armonk, New York) and are summarized by descriptive statistics. Overall compliance with the guideline recommendations based on treatment selection was evaluated by cross-tables. Differences in characteristics between risk groups and treatment selection were assessed by Chi-square tests. To identify predictors for treatment selection, a multivariable logistic regression analysis was performed to estimate the odds of receiving KSS vs. RNU. We created 2 models for multivariable logistic regression analysis. In the first model we included the variables recommended by the guidelines for risk stratification (size, invasiveness, focality and grade). In the second model, we also included several patient and center characteristics (gender, age, ASA and CKD classification, number of inclusions per center, geographics and inclusion period). The models were tested by goodness-of-fit statistics.

Results

During the study period (November 2014–November 2019), 2380 patient from 101 centers (37 countries) were included. Patient characteristics are described in Table 1. Of this cohort 60 patients (2.5%) had metastatic disease. Patients were predominantly males (70.5%) from European centers (70.5%). Centers were dichotomized as low- (60%) and high-number of inclusions with a cutoff of 48 cases based on the IQR of the number of inclusions.

Table 1 Baseline characteristics of enrolled patients

Characteristics	No. (%)
No. patients	2380
Gender	
Female	697 (29.3)
Male	1677 (70.5)
Missing	6 (0.3)
ASA score	
Low (ASA I,II)	1369 (57.5)
High (ASA III, IV, V)	769 (32.3)
Missing	242 (10.2)
CKD classification	
CKD grade 1 and 2	1159 (48.7)
CKD grade 3–5	801 (33.7)
Missing	420 (17.6)
Number of inclusions per center	
Low < 48 inclusions	1427 (60.0)
High > 48 inclusion	953 (40.0)
Demographics	
European	1679 (70.5)
Non-European	701 (29.5)
Year of inclusion	
2014–2015	356 (15.0)
2016	669 (28.1)
2017	567 (23.8)
2018	636 (26.7)
2019	152 (6.4)

ASA American Society of Anesthesiologists, *CKD* chronic kidney disease

Adherence to guideline recommendations

Diagnosis

Analysis of adherence to guideline recommendations on diagnostics in the whole cohort ($n = 2380$) revealed that 47.85% ($n = 1139$) received urine cytology, 50.5% ($n = 1202$) a cystoscopy, 85.04% ($n = 2024$) imaging by CT, 17.7% ($n = 422$) X-RPG and 49.75% ($n = 1184$) a dURS. An endoscopic biopsy was performed in 752 from the 1184 patients (63.5%) who underwent dURS. Figure 1 and Supplement Table 3 depict adherence to recommendations over the different time periods. There were no clinically relevant changes in compliance with guidelines recommendations over time.

Risk classification and definitive treatment

The complete set of necessary diagnostic variables for recommended risk stratification was available in 1709 (71.81%) patients (Fig. 2). From them, 5.7% ($n = 97$) could be classified as having low-risk disease of whom 76% ($n = 74$) were treated by KSS using percutaneous tumour resection (PCR) in 5, and URS in 69 patients. In the remaining 24%, a RNU was performed. Overall, 1612 patients (94.32%) were classified as having high-risk disease of whom the majority was treated by RNU (1238/1612, 76.80%). Treatment by KSS was performed in 19.0% ($n = 306$) with 53 having received segmental ureter resection (SUR), 13 PCR and 240 (78.4%) by URS.

When comparing composed risk stratification with the final treatment selection we found that patients classified as having low-risk disease more often received treatment by KSS opposed to patients classified as high-risk disease who were more often treated by RNU ($p < 0.001$).

Differences in characteristics between patients with classified high- and low-risk disease and definite treatment selection were evaluated. Patients with high-risk disease, treated by KSS were more often treated with imperative indication ($p < 0.001$), of older age ($p = 0.003$)and had higher Charlson comorbidity index score ($p = 0.001$) (Table 2).

Predictors of treatment selection

Multivariable logistic regression analysis, including the variables recommended by the guideline for risk stratification, showed that all variables influenced treatment selection (Tables 3, 4). Patients with large tumors had the highest odds of receiving treatment by RNU (OR 5.45, 95% CI 3.77–7.87, $p < 0.001$), followed by invasiveness on imaging (OR 3.07, CI 2.11–4.46, $p < 0.001$), high grade diseases (OR 2.05, CI 1.38–3.05, $p < 0.001$) and multifocality (OR 1.76, CI 1.05–2.97, p = 0.032).Our model was statistically significant ($p < 0.001$), explained 30% of the variance in treatment selection and correctly classified 75.5% of cases.

The second model, including several patient and center characteristics, showed that patients with large tumors were 6.08 times more likely to be treated by RNU (95% CI 4.11–9.00, $p < 0.001$). Furthermore, signs of invasive disease (OR2.57, CI 1.71–3.85, $p < 0.001$), high-grade tumors (OR2.04, CI 1.33–3.12, $p = 0.001$), multifocality (OR1.965, CI 1.13–3.41, $p = 0.016$) were all associated with increased odds of treatment by RNU. Patients of older age were less likely to be treated by RNU (OR0.65, CI 0.43–0.99, $p = 0.043$). No effects were seen for patient characteristics such as gender or CKD classification. Patients treated in non-European centers were more likely to be treated by RNU (OR2.16, CI1.36–3.41, $p = 0.001$). No difference was seen between centers with low- or high number of inclusions. This model was statistically significant ($p < 0.001$), explained 34% of the variance and correctly classified 76.4% of cases.

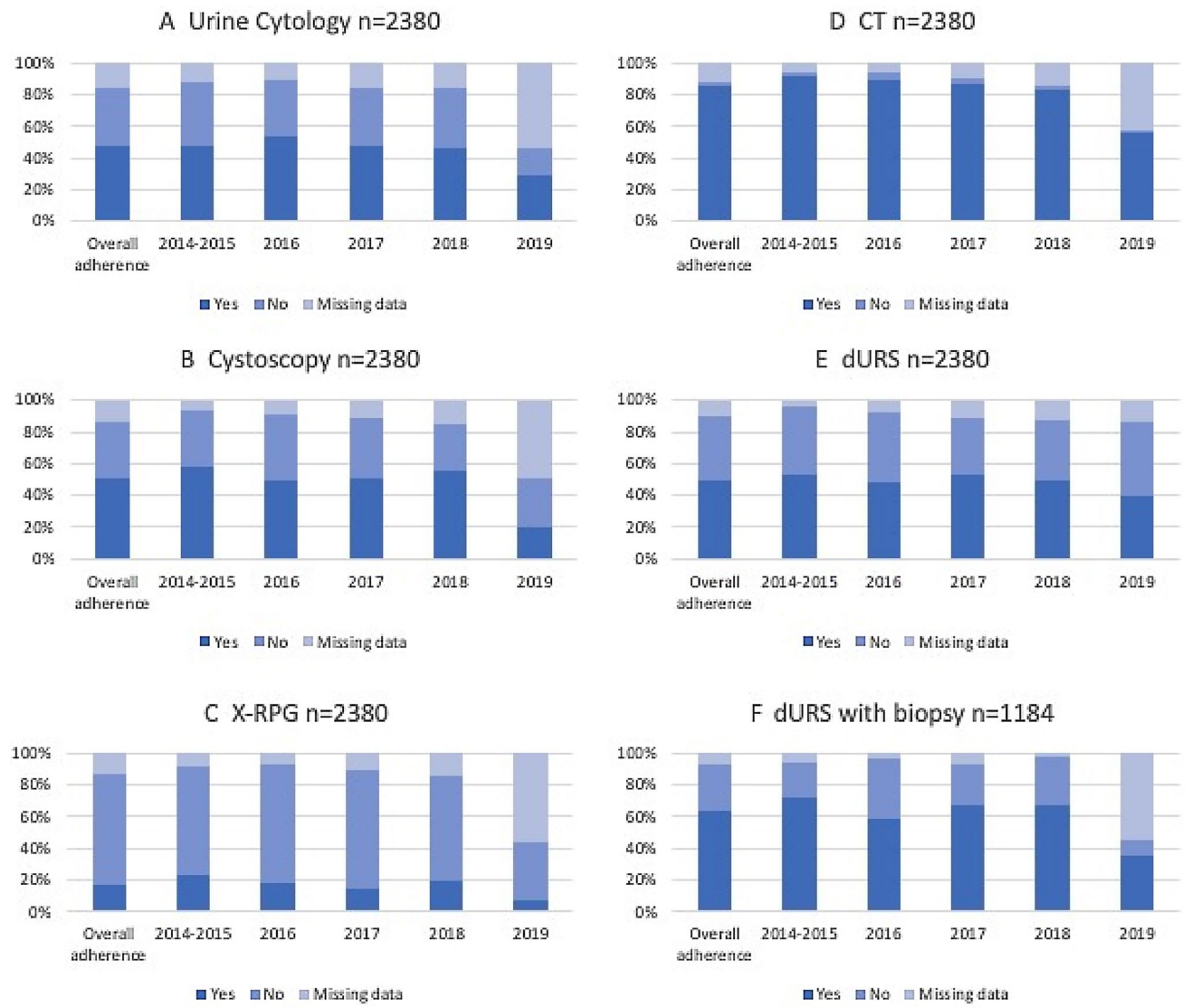

Fig. 1 Adherence to the EAU Guideline recommendations on diagnostics across time

Discussion

We assessed the adherence to the diagnostic recommendations of the EAU Guidelines in a real-world large cohort with UTUC. Compliance with the different recommend test at diagnostic was overall low (maximum 50%) with exception of CT-urography. Adherence remained stable across the different time periods. Our prediction models indicate that treatment selection is guided by the variables recommended for risk stratification. Large tumor size provides the highest odds for radical surgery.

Adherence to guideline recommendations on diagnostics

The overall practice of urine cytology was relatively low in our cohort, although a level A recommendations until 2017, and was only performed in half of the patients (47.9%). In UTUC, cytology is less sensitive than in bladder cancer, even in case of high-grade tumors and limits its value as a diagnostic test in UTUC [18–20]. The low reported practice of urine cytology in our cohort likely reflects the low evidence and lack of physician's confidence. However, the

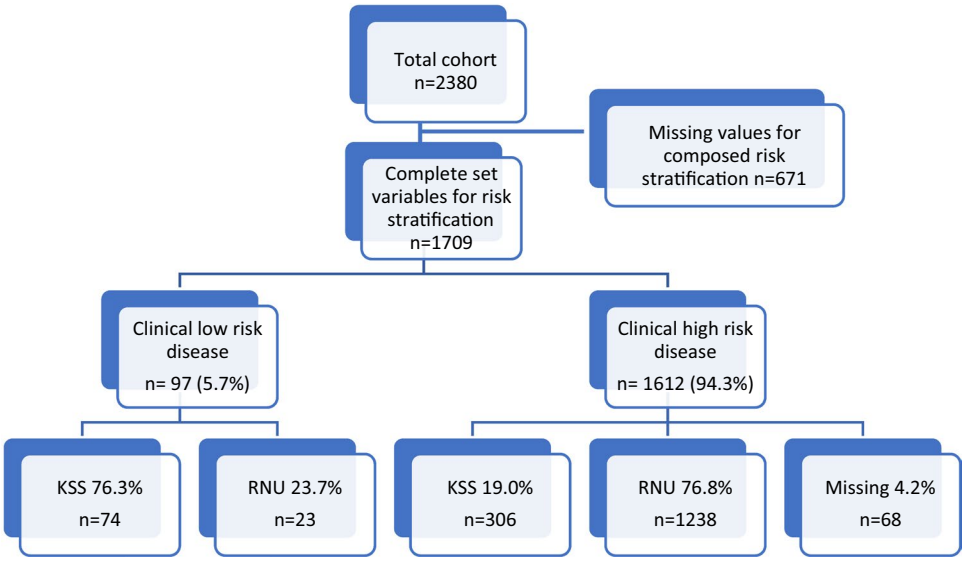

Fig. 2 Risk stratification according to the EAU guidelines and treatment received

Table 2 Characteristics based on composite risk stratification and treatment received

	Low risk			High risk		
	RNU	KSS	*p*	RNU	KSS	*p*
Gender						
Female	8	32	0.472	337	91	0.348
Male	15	42		900	213	
Age groups						
< 70 years	10	36	0.664	574	113	0.003*
> 70 years	13	38		661	193	
ASA						
Low (ASA I and II)	15	45	0.873	765	183	0.741
High (ASA > 2)	8					
Charlson comorbidity index						
0	7	11	0.158	301	55	0.001*
1–2	6	30		367	94	
> /3	7	14		234	86	
CKD level						
CKD 1 and 2	13	43	0.786	664	165	0.523
CKD > 2	10	29		462	125	
Indication						
Elective	18	7	0.593	1082	56	< 0.001*
Imperative	3	2		114	16	
Geographics						
European	15	51	0.740	850	227	0.060
Non-European	8	23		388	79	
Number of inclusions per center						
< 48 inclusions	15	54	0.473	764	182	0.472
> 48 inclusions	8	20		474	124	

ASA American Society of Anesthesiologists, *CKD* chronic kidney disease

*The Chi-square statistic is significant at the 0.05 level

Table 3 Multivariable logistic regression analysis including variables recommended by the guidelines for treatment selection

			95% CI for Exp(*B*)	
	Sig.	Exp(*B*)	Lower	Upper
Tumour focality (uni-/multifocal)	0.032	1.764	1.049	2.966
Tumour invasiveness (absent/present)	< 0.001	3.067	2.108	4.463
Tumour size (small/large according guidelines definition over time)	< 0.001	5.449	3.772	7.871
Tumour grade (low/high)	< 0.001	2.053	1.384	3.047

use and outcome of cytology is mentioned in the guidelines as decisive step when deciding to perform a dURS and is a variable in the composed risk stratification [18]. Considering the low sensitivity of urinary cytology, it is debatable whether it should be included for the choice of performing a dURS. The low use of urinary cytology in daily practice in our cohort underlines this matter of debate.

The low rate of reported cystoscopies is (50.5%) is striking. It is strongly recommended (level A until 2017, from 2018 as "strong") to rule out concurrent bladder tumours as 17% of patients present with synchronic urothelial carcinoma in both the upper tract and bladder [18]. A possible explanation may be that cystoscopy was performed during the definitive surgical procedure and prior to radical surgery or KSS and not registered as such.

In our series the imaging of choice, performed in the majority of patients, is by CT (level A until 2017, from 2018 as "strong"). Several studies have demonstrated the high accuracy of the CT-urography in the detection of upper tract intraluminal masses; however, its accuracy decreases for small lesions and different (benign) pathological conditions may mimic CT-urography appearance of UTUC supporting the additional benefits of endoscopic evaluation [21]. However, only half of patients received evaluation by dURS and biopsy was taken in approximately 2/3 of them that may allow for histologic confirmation of the disease. The dURS was incorporated to the guidelines recommendations in 2015 [11], initially as a grade C recommendation in cases, where additional information could impact treatment decisions. From the 2018 edition of the UTUC guidelines this grade C recommendations turned out to a *"strong"* recommendation (Supplement Table 1) and remained "strong" from then onwards [7, 15, 16, 18].

Considering the poor performance of urinary cytology and the lack of reliable urinary markers, dURS with biopsy seems the best available option to confirm the histological diagnosis and to dichotomize patients in low- or high-risk disease. Furthermore, it provides information on size, focality and tumor grade in up to 90% of cases irrespective of sample size. Nonetheless, data show upgrading from ureteroscopic biopsy to RNU sample and is described in up to one-third of cases mandating a strict follow-up in patients treated by KSS [22–24]. Based on our data, we have to conclude that most patients were offered treatment modality without endoscopic inspection or histological tumour or grade confirmation.

Risk stratification

The low compliance in most of the diagnostic recommendations prevented the proper assessment of the clinical risk according to the EAU Guidelines in almost a third of the patients. One of the reasons for this could have been the composite and mandatory nature of the four diagnostic outcomes

Table 4 Multivariable logistic regression analysis including patient and center-related factors

			95% CI for Exp(*B*)	
	Sig.	Exp(*B*)	Lower	Upper
Tumour focality (uni-/multifocal)	0.016	1.965	1.134	3.405
Tumour invasiveness (absent/present)	< 0.001	2.567	1.712	3.850
Tumour size (mm) (small/large according guidelines definition over time)	< 0.001	6.081	4.108	9.001
Tumour grade (low/high)	0.001	2.037	1.328	3.124
Gender (female/male)	0.158	1.359	0.888	2.082
Age (< 70/ > 70)	0.043	0.650	0.428	0.987
ASA (low (ASA I and II)/High (ASA > 2))	0.892	1.030	0.676	1.568
CKD (CKD 1 and 2/CKD > 2)	0.927	1.019	0.677	1.534
Number of inclusions per center (low (< 48 inclusions)/high(> 48 inclusions))	0.886	1.031	0.680	1.564
Geographics (European/non-European)	0.001	2.156	1.364	3.407
Inclusion period	0.059	1.570	0.983	2.508

ASA American Society of Anesthesiologists, *CKD* chronic kidney disease

(non-invasion by CT and solitary tumor, and < 2 cm and low grade) necessary to identify the low-risk category. Second, imaging by CT may determine in a high percentage of patients the variables invasion, size and multifocality and might have identified high-risk tumour characteristic leading to subsequent treatment selection without additional histopathologic confirmation. Data from our registry show that patients in the high-risk category were mostly treated by RNU. The small percentage of them that received KSS (19%), were more often having imperative reasons as older age and higher Charlson comorbidity index scores.

Only a minority (5.7%) could be classified as having low-risk disease based on the risk stratification. This scarce percentage raises the question on the realistic character of the low-risk definition and eligibility for KSS. Recently, different proposals for new classification models emerged including multivariable risk models combining imaging and ureteroscopic features, a three-level classification scheme including an intermediate risk group, all with the aim to improve current risk stratification and better identification of those patients eligible for KSS [25–28].

Of the low-risk group almost a quarter of patients were overtreated by radical surgery. Endoscopic KSS can only be offered with adequate armamentarium and experience available. Furthermore, a strict follow-up protocol is mandatory that may become cumbersome for patient and surgeon. Notably, even when all necessary clinical diagnostic variables for a risk categorization are present, other factors linked to patient's characteristics or preferences and structural factors may supersede the clinical relevance of the preoperative risk categorization (e.g., solitary kidney, renal insufficiency, comorbidity).

To improve the care in UTUC and to minimize over- and undertreatment, there is a growing tendency to concentrate and coordinate the treatment of rare pathologies at regional and national centres.

Treatment selection

All the well-established factors influencing survival had effect on the choice of treatment and gave significant higher odds for receiving RNU [18, 29]. Tumour size was found to have the largest effect on treatment selection. URS treatment of large tumours is challenging, though flexible scopes and different laser types facilitate location, approach and technical issues broadening the spectrum of KSS. This is reflected by the guidelines by changing the low-risk category tumor size cutoff from 1 to 2 cm in 2018. Whether this change resulted in relevant impact in clinical practice remains unknown. Unfortunately we lack the information on armamentarium of the different centers; one can only offer the treatment modalities they have available.

Strengths and weakness

Major strength of the study relies on the contemporary, multicenter, multinational, and consecutive character of the data. A large set of patients was gathered in a relative short period of time, centrally collected, and audited which is unique in a rare disease. Registry-based studies as the present are not devoid of limitations and are prone to several forms of bias. In our case the lack of standardized diagnostic and treatment protocols represent a limitation and introduces heterogeneity in the population and in the diagnostic compliance; however, it depicts very well the real-world practice. In absence of RCTs, difficult to successful implementation in low prevalent conditions, registry generated hypothesis are a valuable source of information and provide essential and generalizable evidence. The lack of high-quality evidence and the low certainty of the evidence of the literature on the subject affects the UTUC guideline and may at least partially drive the low adherence to several recommendations. We believe that insights on guideline compliance from this registry may drive changes in care, overcome existing hurdles and barriers and ultimately improve compliance and adherence to EAU guidelines. With regard to missing data, percentages for the respective variables were acceptable for this type of study and exists even in prospective well-designed studies, several study parameters were imaging or histology-based and lacked central review.

Conclusions

The results of our study provide a real-world insight of guideline adherence for the diagnostics and treatment of UTUC. A good adherence during the diagnostic process is only seen for CT imaging. This seems to be, not only the most important diagnostic tool but also the most important decisive tool for urologists when it comes to treatment selection. Changes in practice, based on guidelines recommendations over the years, could not be identified. Due to the low compliance in most of the diagnostic recommendation, risk stratification according to the EAU Guidelines is not possible in almost a third of patients and raises the question whether current stratification is deemed valuable and applicable in daily practice. Known factors of influence on survival in patients with UTUC gave higher likelihood of treatment by radical surgery.

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Authors contribution JB: data management, data analysis, manuscript writing. SFS: manuscript editing. MR: manuscript editing. TY: manuscript editing. AS: manuscript editing. IS: manuscript editing.

JBR: manuscript editing. OC: manuscript editing. JR: protocol/project development, data collection or management, manuscript editing. PL: protocol/project development, data collection or management, manuscript editing.

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Declarations

Conflict of interest Joyce Baard: None. Shahrokh F. Shariat: advisor for Urogen. Morgan Roupret: advisor for Urogen, Roche, Ipsen, Astellas, Astra Zeneca, Janssen. Takashi Yoshida: none. Alberto Saita: none. Iliya Saltirov: none. Javier Burgos Revilla: none. Orcun Celik: none. Jean de la Rosette: none. Pilar Laguna**:** none.

Informed consent This is an observational study. Institutional review board approval was requested and was waived according to the Medical Research Involving Human Subjects Act (date of resolution: October 15, 2014; ref W14-273#14.17.329). Informed consent was not required, all information was anonymized and the submission does not include any images that may identify the participants.

Human and animal rights All the procedures being performed were part of the routine care and in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

References

1. Djulbegovic B, Guyatt GH (2017) Progress in evidence-based medicine: a quarter century on. Lancet 390(10092):415–423. https://doi.org/10.1016/S0140-6736(16)31592-6
2. Grimshaw JM, Russel IT (1993) Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. Lancet 342:1317–1322
3. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-coello P et al (2008) GRADE : an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336(7650):924–926
4. Cai T, Cocci A, Gacci M, Verze P, Bonkat G, Koves B et al (2020) Guidelines in urology: lights and shadows. Urol J. https://doi.org/10.1177/0391560320917805
5. MacLennan SJ, MacLennan S, Bex A, Catto JWF, De Santis M, Glaser AW et al (2017) Changing current practice in urology: improving guideline development and implementation through stakeholder engagement. Eur Urol 72(2):161–163. https://doi.org/10.1016/j.eururo.2017.02.008
6. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G et al (2010) AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ 182(18):839–842
7. Rouprêt M, Babjuk M, Burger M, Capoun O, Cohen D, Compérat EM et al (2020) European association of urology guidelines on upper urinary tract urothelial carcinoma: 2020 update. Eur Urol 79(1):62–79
8. Pavan S, Rommel K, Marquina MEM, Höhn S, Lanneau V, Rath A (2017) Clinical practice guidelines for rare diseases: the orphanet database. PLoS ONE 12(1):1–14
9. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud P-AC et al (1999) Why don t physicians follow a framework for improvement. JAMA 282:1458–1465
10. Barth JH, Misra S, Aakre KM, Langlois MR, Watine J, Twomey PJ et al (2016) Why are clinical practice guidelines not followed? The European Federation of Clinical Chemistry and Laboratory Medicine and European Union of Medical Specialists joint working group on Guidelines. Clin Chem Lab Med 54(7):1133–1139
11. Rouprêt M, Babjuk M, Compérat E, Zigeuner R, Sylvester R, Burger M et al (2014) European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma: Limited update April 2014. http://uroweb.org
12. Rouprêt M, Babjuk M, Compérat E, Zigeuner R, Sylvester RJ, Burger M et al (2015) European association of urology guidelines on upper urinary tract urothelial cell carcinoma: 2015 update. Eur Urol 68(5):868–879
13. Roupret M, Babjuk M, Böhle M, Burger E, Compérat N, Cowan E et al (2016) European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma. http://uroweb.org
14. Rouprêt M, Babjuk M, Burger M, Compérat E, Cowan N, Gontero P et al (2018) European association of urology guidelines on upper urinary tract urothelial carcinoma: 2017 update. Eur Urol 73(1):111–122
15. Roupret M, Babjuk M, Burger M, Compérat E, Cowan NC, Gontero P et al (2018) European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma. http://uroweb.org
16. Rouprêt M, Babjuk M, Burger M, Compérat E, Cowan NC, Gontero P et al (2019) European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma. http://uroweb.org
17. Baard J, Celebi M, de la Rosette J, Alcaraz A, Shariat S, Cormio L et al (2020) Evaluation of patterns of presentation, practice, and outcomes of upper tract urothelial cancer: Protocol for an observational, international, multicenter, cohort study by the clinical research office of the endourology society. JMIR Res Protoc 9(1):1–10
18. Rouprêt M, Babjuk M, Burger M, Capoun O, Cohen D, Compérat EM et al (2021) European association of urology guidelines on upper urinary tract urothelial carcinoma: 2020 update. Eur Urol 79(1):62–79
19. Messer J, Shariat SF, Brien JC, Herman MP, Ng CK, Scherr DS et al (2011) Urinary cytology has a poor performance for predicting invasive or high-grade upper-tract urothelial carcinoma. BJU 108:701–705
20. Potretzke AM, Knight BA, Vetter JM, Anderson BG, Hardi AC, Bhayani SB et al (2016) Diagnostic utility of selective upper tract urinary cytology: a systematic review and meta-analysis of the literature. Urology 96:35–43. https://doi.org/10.1016/j.urology.2016.04.030
21. Martingano P, Cavallaro MFM, Bozzato AM, Baratella E, Cova MA (2020) Ct urography findings of upper urinary tract carcinoma and its mimickers: a pictorial review. Medicina (B Aires) 56(12):1–15
22. Rojas CP, Castle SM, Llanos CA, Cortes JAS, Bird V, Rodriguez S et al (2013) Low biopsy volume in ureteroscopy does not affect tumor biopsy grading in upper tract urothelial carcinoma. Urol Oncol Semin Orig Investig 31(8):1696–1700. https://doi.org/10.1016/j.urolonc.2012.05.010
23. Freund JE, Duivenvoorden MJC, Sikma BT, Vernooij RWM, Savci-Heijink CD, Legemate JD et al (2020) The diagnostic yield and concordance of ureterorenoscopic biopsies for grading of upper tract urothelial carcinoma: a Dutch nationwide analysis. J Endourol 34(9):907–913
24. Subiela JD, Territo A, Mercadé A, Balañà J, Aumatell J, Calderon J et al (2020) Diagnostic accuracy of ureteroscopic biopsy in predicting stage and grade at final pathology in upper tract urothelial carcinoma: systematic review and meta-analysis. Eur J Surg Oncol 46(11):1989–1997

25. Marcq G, Foerster B, Abufaraj M, Matin SF, Azizi M, Gupta M et al (2021) Novel classification for upper tract urothelial carcinoma to better risk-stratify patients eligible for kidney-sparing strategies: an international collaborative study. Eur Urol Focus 8:491–497
26. Favaretto RL, Shariat SF, Savage C, Godoy G, Chade DC, Kaag M et al (2012) Combining imaging and ureteroscopy variables in a preoperative multivariable model for prediction of muscle-invasive and non-organ confined disease in patients with upper tract urothelial carcinoma. BJU Int 109(1):77–82
27. Katayama S, Mori K, Schuettfort VM, Pradere B, Mostafaei H, Quhal F et al (2021) Accuracy and clinical utility of a tumor grade- and stage-based predictive model in localized upper tract urothelial carcinoma. Eur Urol Focus 8:4–11
28. Foerster B, Abufaraj M, Matin SF, Azizi M, Gupta M, Li WM et al (2021) Pretreatment risk stratification for endoscopic kidney-sparing surgery in upper tract urothelial carcinoma: an international collaborative study. Eur Urol 80(4):507–515
29. Seisen T, Granger B, Colin P, Leon P, Utard G, Mozer P et al (2015) A systematic review and meta-analysis of clinicopathologic factors linked to intravesical recurrence after radical nephroureterectomy to treat upper tract urothelial carcinoma. Eur Urol 67:1122–1133

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