Discordance Between Clinical and Pathological Staging and Grading in Upper Tract Urothelial Carcinoma

Keiichiro Mori, Satoshi Katayama, Ekaterina Laukhtina, Victor M Schuettfort, Benjamin Pradere, Fahad Quhal, Reza Sari Motlagh, Hadi Mostafaei, Nico C Grossmann, Pawel Rajwa, et al.

Original Study

Discordance Between Clinical and Pathological Staging and Grading in Upper Tract Urothelial Carcinoma

Keiichiro Mori,[1,2] Satoshi Katayama,[1,3] Ekaterina Laukhtina,[1,4] Victor M. Schuettfort,[1,5] Benjamin Pradere,[1,6] Fahad Quhal,[1,7] Reza Sari Motlagh,[1,8] Hadi Mostafaei,[1,9] Nico C. Grossmann,[1,10] Pawel Rajwa,[1,11] Kristin Zimmermann,[12] Pierre I. Karakiewicz,[13] Mohammad Abufaraj,[1,14] Harun Fajkovic,[1,15] Morgan Rouprêt,[16] Vitaly Margulis,[17] Dmitry V. Enikeev,[4] Shin Egawa,[2] Shahrokh F. Shariat, M.D[1,4,14,15,17,18,19]

Abstract

This study evaluated ureteroscopic biopsy and computed tomography urography for their diagnostic ability to accurately predict final pathological tumor stage and grade in patients with upper tract urothelial carcinoma (UTUC). Clinical understaging/undergrading and upstaging to muscle-invasive disease occurred in a high proportion of UTUC patients. These findings should be considered when utilizing preoperative, risk-adapted strategies.

Introduction: This study aimed to evaluate the concordance in tumor stage and grade between ureteroscopic (URS) biopsy and radical nephroureterectomy (RNU) in patients with upper tract urothelial carcinoma (UTUC). **Patients and Methods:** Records of 1,214 UTUC patients who had undergone URS biopsy followed by RNU were included. Univariable and multivariable logistic regression analyses were performed to identify factors contributing to the pathological upstaging. **Results:** The concordance between URS biopsy-based clinical and RNU pathological staging was 34.5%. Clinical understaging occurred in 59.5% patients. Upstaging to muscle-invasive disease occurred in 240 (41.7%) of 575 patients diagnosed with ≤cT1 disease. Of those diagnosed with muscle-invasive disease on final pathology, 89.6% had been clinically diagnosed with ≤cT1 disease. In the univariable analyses, computed tomography urography (CTU)–based invasion, ureter location, hydronephrosis, high-grade cytology, high-grade biopsy, sessile architecture, age, and women sex were significantly associated with pathological upstaging ($P < .05$). In the multivariable analyses, CTU-based invasion and hydronephrosis remained associated with pathological upstaging ($P < .05$). URS biopsy-based clinical and pathological gradings were concordant in 634 (54.2%) patients. Clinical undergrading occurred in 496 (42.4%) patients. **Conclusions:** Clinical understaging/undergrading and upstaging to muscle-invasive disease occurred in a high

[1]Department of Urology, Medical University of Vienna, Vienna, Austria
[2]Department of Urology, The Jikei University School of Medicine, Tokyo, Japan
[3]Department of Urology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan
[4]Institute for Urology and Reproductive Health, Sechenov University, Moscow, Russia
[5]Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[6]Department of Urology, CHRU Tours, France; Université François Rabelais de Tours, PRES Centre Val de Loire, Tours, France
[7]Department of Urology, King Fahad Specialist Hospital, Dammam, Saudi Arabia
[8]Men's Health and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[9]Research Center for Evidence Based Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[10]Department of Urology, University Hospital Zurich, Zurich, Switzerland
[11]Department of Urology, Medical University of Silesia, Zabrze, Poland
[12]Clinic for Urology, Central Military Hospital Koblenz, Koblenz, Germany
[13]Cancer Prognostics and Health Outcomes Unit, University of Montreal Health Centre, Montreal, Canada
[14]Division of Urology, Department of Special Surgery, The University of Jordan, Amman, Jordan
[15]Karl Landsteiner Institute of Urology and Andrology, Vienna, Austria
[16]Sorbonne University, GRC 5 Predictive Onco-Uro, AP-HP, Urology, Pitie-Salpetriere Hospital, F-75013 PARIS, France
[17]Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX
[18]Department of Urology, Second Faculty of Medicine, Charles University, Prague, Czech Republic
[19]Department of Urology, Weill Cornell Medical College, New York, NY

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Address for correspondence: Shahrokh F. Shariat, Währinger Gürtel 18-20, 1090, Vienna, Austria.
E-mail contact: shahrokh.shariat@meduniwien.ac.at

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proportion of UTUC patients undergoing RNU. Despite the inherent selection bias, these data underline the challenges of accurate UTUC staging and grading. In daily clinical practice, URS biopsy and CTU offer the most accurate preoperative information albeit with limited predictive value when used alone. These findings should be considered when utilizing preoperative, risk-adapted strategies.

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Introduction

Upper tract urothelial carcinoma (UTUC) is a relatively rare malignancy, accounting for 5% to 10% of all urothelial carcinomas.[1] To improve oncological outcomes in patients with UTUC, preoperative predictive models have been developed to guide clinical decision-making and patient counseling.[2,3] These models stratify tumors into low- and high-risk categories based on their multifocality, size, biopsy- and cytology-derived grade, hydronephrosis, and imaging findings; thereby facilitating the decision-making regarding kidney-sparing therapy versus radical nephroureterectomy (RNU), with or without lymphadenectomy and perioperative chemotherapy.[1,4,5]

Computed tomography urography (CTU) has become the new gold standard for tumor detection.[6,7] However, despite the availability of advanced imaging technologies, it remains difficult to achieve sufficient staging accuracy to ensure a tailored treatment strategy for patients with UTUC.[1,6] Additionally, CTU appears to have limited value for providing accurate information regarding tumor stage and grade.[8] As tumor stage and grade represent the strongest prognostic factors, correct grading and staging are critical for establishing the best treatment approach for each patient.[9,10]

With the development of conservative endoscopic treatment and the implementation of neoadjuvant chemotherapy for patients with UTUC, ureteroscopic (URS) biopsy has gained importance in the diagnosis, follow-up, and treatment decision-making. URS biopsy has been described as the most accurate predictor of the pathological stage and grade of surgical specimens.[11,12] The European Association of Urology (EAU) UTUC guidelines recommend the consideration of URS biopsy when additional information is likely to affect treatment decisions.[1] Despite this recommendation, however, accurate preoperative predictions of pathological features remain difficult because of the limited tissue available from biopsy specimens.[13] Moreover, concerns have been raised about the potential of tumor seeding associated with URS manipulations and the resultant higher risk of intravesical recurrence.[14,15] Pathological upstaging has also been proposed to represent a poor prognostic feature, independent of final pathological stage, and that the presence of pathological up-staging may be an indication for adjuvant chemotherapy in patients with urothelial carcinoma.[16]

Thus, the present study was conducted to assess URS biopsy and CTU for their diagnostic ability to accurately predict final pathological tumor stage and grade in surgical specimens following RNU.

Patients and Methods

Study Design

This multi-center, retrospective analysis involved 21 academic centers, within the UTUC Collaboration, in North America, Europe, and East Asia. Each institution's institutional review board approved the data-sharing agreement necessary for the conduct of this study. Computerized databases provided by the participating sites were merged and checked for consistency and integrity. Prior to analysis, all irregularities were resolved through communication, and the resulting final database was frozen.

Eligibility Criteria and Data Collection

Overall, we collected the records from 1,441 patients who had undergone diagnostic URS and tumor biopsy, followed by RNU for UTUC, between 2000 and 2017. Patients with evidence of metastasis (n = 9), clinically positive lymph nodes (n = 72), bilateral synchronous tumors (n = 1), or had undergone preoperative chemotherapy (n = 145) were excluded. We did not exclude variant histology. Accordingly, 1214 patients were available for the final analysis.

Detailed data were collected for the EAU UTUC risk stratification parameters, including biopsy grade, urine cytology, CTU evidence of invasion, tumor size, preoperative hydronephrosis, history of radical cystectomy, tumor multifocality, and the presence of variant histology in biopsy material. All patients underwent urine cytology using voided, instrumented, or selectively instrumented samples. Urine cytology findings were classified as "negative" (for urothelial cell abnormality), "abnormal" (urothelial cell abnormalities, including atypia, low-grade and suspicious high-grade urothelial carcinoma), and "high-grade" (positive for high-grade urothelial carcinoma) to allow comparisons across the classification systems. Preoperative clinical T staging was performed according to URS-based biopsy and CTU. CTU evidence of invasion was defined as ≥cT3 disease, consistent with previous studies.[3] Magnetic resonance imaging (MRI) findings were included for the analysis of patients whose CTU findings were unavailable or in whom CTU had been contraindicated. Preoperative hydronephrosis and tumor size were also determined using CTU and MRI, with the tumor size (maximum diameter) measured radiographically or endoscopically if the tumor was too small to be measured radiographically. Tumor architecture was determined by visual inspection during URS. Two or more tumors present within the same upper urinary tract unit, in cross-sectional images or visually during URS, were considered multifocal.[17]

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Additionally, patient age, sex, and final pathological stage and grade (at RNU) data were collected. RNUs were performed using open, laparoscopic, or robotic approaches, according to each center's choice. Although the surgical modalities were not standardized among the participating centers, removal of the kidney, entire length of the ureter, and bladder cuff was the standard of care at all participating centers. Bladder cuff removal was performed using an extravesical or transvesical approach.[18] Lymphadenectomy was performed in patients with intraoperatively suspected lymph node involvement, at the surgeon's discretion.[4]

Histopathological Assessment

Histopathological examinations were performed by genitourinary pathologists at each participating center. The 2002 American Joint Committee on Cancer/International Union Against Cancer Staging System was used for pathological staging; tumor grades were determined using the 2004 World Health Organization/International Society of Urologic Pathologists consensus classification.

Statistical Analysis

The primary endpoint for the study is the correlation between clinical and pathological staging and the secondary endpoint is the correlation between clinical and pathological grading. Upstaging (understaging) and downstaging in URS are defined as follows: upstaging (understaging), cTa on biopsy but ≥ pTis following RNU, cTis on biopsy but ≥ pT1 following RNU, cT1 on biopsy but ≥ pT2 following RNU, cT2 on biopsy but ≥ pT3 following RNU, and cT3 on biopsy but ≥ pT4 following RNU; downstaging, cTa on biopsy but pT0/x following RNU, cTis on biopsy but ≥ pTa following RNU, cT1 on biopsy but pTis following RNU, cT2 on biopsy but ≤ pT1 following RNU, cT3 on biopsy but ≤ pT2 following RNU, and cT4 on biopsy but ≤ pT3 following RNU. Upgrading (undergrading) and downgrading in URS are defined as follows: upgrading (undergrading), low-grade on biopsy but high-grade following RNU or Gx/unclear on biopsy but low-/high-grade following RNU; downgrading, high-grade on biopsy but low-grade following RNU. The association between pathological upstaging and categorical variables was assessed for using chi-square or Fisher's tests, and differences in continuous variables were analyzed using Mann-Whitney *U* tests. Univariable and multivariable logistic regression analyses were performed to investigate the factors contributing to pathological upstaging. In receiver operating characteristics curves, the area under the curve was calculated to determine the predictive accuracy of the logistic regression model. DeLong's test was used to test for statistical significance between different areas under the curve. Sub-analyses were performed on patients in whom upstaging occurred from cTa/Tis/T1 to pT2 or above as well as on the preoperative staging accuracy. All *P*-values were two-sided, and statistical significance was defined as $P < .05$. Statistical analyses were performed using Stata/MP 14.2 statistical software (Stata Corp., College Station, TX).

Results

A total of 1,214 patients met the study's inclusion criteria and were included in the analyses. Supplementary Table 1 summarizes the clinicopathological features of the study population. Of the 1,214 URS biopsies taken before RNU, 267 (22.0%) were of undetermined tumor grade; variant histology was identified in 24 (2%) of these biopsy samples. The pathology of the RNU specimen revealed that 663 (54.6%) and 551 (45.4%) patients had ≤pT1 and ≥pT2 disease, respectively. High-grade disease was detected in 883 (72.7%) RNU specimens. Pathological upstaging occurred in 359 patients (59.5%) and was associated with age, women sex, CTU invasion, ureter location, hydronephrosis, high-grade cytology and biopsy, and sessile architecture ($P < .05$; Supplementary Table 1). In biopsy-based clinical T staging, high grade on cytology, high grade on biopsy, and sessile architecture were shown to be associated with higher clinical T stages (Supplementary Table 2). In imaging-based clinical T staging, hydronephrosis, high grade on biopsy, sessile architecture, multifocality of tumor, and larger tumor size were shown to be associated with higher clinical T stages (Supplementary Table 3).

Correlation Between Clinical and Pathological Stage

The distribution and correlation between URS biopsy-based clinical and pathological staging for all patients are shown in Table 1. URS biopsy-based clinical and pathological staging were concordant in 208 (34.5%) patients. Downstaging occurred in 36 (6.0%) patients, and clinical understaging occurred in 359 (59.5%) patients. Clinical under-staging by ≥2 stages occurred in 297 (49.3%) patients. Upstaging to muscle-invasive disease occurred in 240 (41.7%) of 575 patients with ≤T1 clinical disease. Of those diagnosed with muscle-invasive disease on final pathology, 89.6% of patients had been diagnosed with ≤ cT1 disease.

In the univariable logistic regression analyses, CTU invasion, ureter location, hydronephrosis, high-grade cytology and biopsy, sessile architecture, age, and women sex were significantly associated with pathological upstaging ($P < .05$). In the multivariate logistic regression analyses adjusted for the above factors, CTU invasion (odds ratio [OR], 2.87; 95% confidence interval [CI], 1.40-5.88) and hydronephrosis (OR, 1.77; 95% CI, 1.12-2.81) remained associated with pathological upstaging (Supplementary Table 4).

Among those in whom upstaging occurred from cTa/Tis/T1 to pT2 or above, pathological upstaging was significantly associated with age, CTU-based invasion, CTU-based hydronephrosis, high grade on cytology, high grade on biopsy, VH and sessile architecture ($P < .05$, Supplementary Table 5). In the multivariate logistic regression analyses, CTU-based invasion (OR, 4.06; 95% CI, 1.90-8.69), CTU-based hydronephrosis (OR, 2.23; 95% CI, 1.38-3.59), high grade on cytology (OR, 1.53; 95% CI, 1.11-2.10), and sessile architecture (OR, 2.19; 95% CI, 1.21-3.96) remained associated with pathological upstaging of cTa/Tis/T1 to pT2 or above (Supplementary Table 6). Regarding pre-operative staging, inaccurate pre-operative staging was significantly associated with CTU invasion, hydronephrosis, high grade on cytology, high grade on biopsy, ureter tumor, multifocal tumor, and sessile architecture ($P < .05$, Supplementary Table 7). In the multivariate logistic regression analyses, CTU-based invasion (OR, 0.47; 95% CI, 0.23-0.97), CTU-based hydronephrosis (OR, 0.56; 95% CI, 0.40-0.94), high grade on cytology (OR, 0.65; 95% CI, 0.50-0.83), multifocal tumor (OR, 1.82; 95% CI, 1.16-2.88), and sessile architecture

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Table 1 The Distribution and Correlation Between (Ureteroscopy Biopsy-Based) Clinical and Pathological Staging

	pT0/x	pTa	pTis	pT1	pT2	pT3	pT4	Down stage	Same stage	Up stage	Total
cTa	8	165	15	85	60	88	4	8 (1.9%)	165 (38.8%)	252 (59.3%)	425
cTis	0	15	8	3	4	11	0	15 (36.6%)	8 (19.5%)	18 (43.9%)	41
cT1	1	9	3	23	29	38	6	13 (11.9%)	23 (21.1%)	73 (67.0%)	109
cT2	0	0	0	0	6	15	1	0	6 (27.3%)	16 (72.7%)	22
cT3	0	0	0	0	0	4	0	0	4 (100%)	0	4
cT4	0	0	0	0	0	0	2	0	2 (100%)	-	2
Total	9	189	26	111	99	156	13	36 (6.0%)	208 (34.5%)	359 (59.5%)	603

Table 2 The Distribution and Correlation Between (Ureteroscopy Biopsy-Based) Clinical and Pathological Grading

	Low grade	High grade	Down grade	Same grade	Up grade	Total
Biopsy Gx/unclear	117	138	-	-	255 (100%)	255
Biopsy Low grade	142	241	-	142 (37.1%)	241 (62.9%)	383
Biopsy High grade	40	492	40 (7.5%)	492 (92.5%)	-	532
Total	299	871	40 (3.4%)	634 (54.2%)	496 (42.4%)	1170

(OR, 0.79; 95% CI, 0.31-0.99) remained associated with inaccurate pre-operative staging (Supplementary Table 8). Addition of factors shown to be significantly associated with pathological upstaging, pathological upstaging from cTa/Tis/T1 to pT2 or above and preoperative staging in the univariate analyses to the multivariate models improved their discriminatory ability (Table 2 and Supplementary Tables 6, 8) to predict pathological upstaging (accuracy, 70%; $P >$ .001), pathological upstaging from cTa/Tis/T1 to pT2 (accuracy, 74%; $P >$ .001), and preoperative staging (accuracy, 67%; $P >$ .001).

The distribution and correlation between CTU-based clinical and pathological staging for all patients are shown in Supplementary Table 9. Clinical and pathological staging concurred in 829 (75.3%) patients. Down-staging occurred in 61 (5.5%) patients, and clinical understaging occurred in 211 (19.2%) patients.

Correlation Between Clinical and Pathological Grading

The distribution of tumor grades and the correlations between URS biopsy-based clinical and pathological grading for all patients are shown in Table 2. Clinical and pathological grading were concordant in 634 (54.2%) patients. Downgrading occurred in 40 (3.4%) patients, and clinical undergrading occurred in 496 (42.4%) patients.

The distribution of tumor grades and the correlation between cytology-based clinical and pathological grading for all patients are shown in Supplementary Table 10. The clinical and pathological grading were concordant in 413 (41.1%) patients. Down-grading occurred in 91 (9.0%) patients, and clinical undergrading occurred in 502 (49.9%) patients.

Discussion

Accurate clinical staging and grading of UTUC remain an enormous challenge facing urologists, given the high upgrading and upstaging rates occurring between biopsy- and radical surgery specimen-based diagnoses [13]. In our multi-center cohort, clinical understaging and undergrading occurred in 59.5% and 42.4% of patients diagnosed based on URS biopsies, respectively, clearly limiting the utility of URS biopsy when considered on their own. Further adding to this limitation, clinical understaging and undergrading also occurred in 19.2% of CTU-diagnosed patients and in 49.9% of cytologically diagnosed patients, respectively. Our analysis showed that CTU-based clinical understaging occurred in only approximately 20% of patients, which is, however, far from accurate as compared to patients with $\leq$ cT3 disease and $\geq$ cT2 disease. In particular, CTU falls short in reliably predicting the true tumor stage and/or grade, specifically for small lesions such as carcinoma in situ. Thus, both modalities are thought likely to be associated with underestimation of tumor stage and grade. To add to this, upstaging to muscle-invasive disease occurred in 240 (41.7%) of 575 patients with $\leq$ T1 clinical disease in this study. Of the patients diagnosed with muscle-invasive disease as per their final tumor pathology, almost 90% had been diagnosed with $\leq$ cT1 disease. It is thus suggested that URS biopsy alone is insufficient for correct tumor grading and staging and that a multimodal approach is required for accurate risk stratification. Specifically, accurate clinical decision-making should take into account multiple factors including URS biopsy and CTU, with the final clinical status determined based not only on clinical judgement but on consideration of a wide array of contributing factors.

In line with our results, previous studies have shown high levels of discordance between tumor staging and grading on URS biopsy and surgical pathology.[13,19] Acquisition of adequate samples of sufficient quality for accurate pathologic interpretation is a technical challenge.[19] The most important issue is the sample size. Modern, miniaturized endourological equipment allows adequate navigation within the upper urinary tract, but the volume and size of the tissue sampled may be limited.[19] Although physicians should attempt to obtain large biopsy samples from UTUC patients whenever feasible, they should also weigh the benefits of obtaining such samples against the potential risks associated with deep biopsies, such as

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urinary tract perforation and tumor seeding, albeit these complications are rare.[20,21] Tumor size represents another factor limiting the diagnostic accuracy of URS biopsies.[19] In fact, URS biopsies provide pathological data on a limited area of the tumor tissue. Thus, the accuracy of URS biopsies for predicting the tumor grade in the final pathology specimen appears to be limited for tumors measuring >2 cm, suggesting that the tumor grade determined using URS biopsy specimen may not represent the entire tumor.[22] Moreover, given that high-grade URS biopsy and cytology were significantly associated with higher disease upstaging rates than low-grade biopsy and cytology, in the univariable analysis, the URS biopsy is suggestive of problems in reliability for staging high-grade UTUC. Ways to overcome the sampling issue are the use of an access sheath that allows for repeated sampling, imaging, and make for biomarkers.[23-27]

Moreover, how accurate preoperative staging may prove and whether upstaging may occur from cTa/Tis/T1 to pT2 or above remain an issue of utmost importance. To address this, multivariable logistic regression analyses were performed, which showed that high grade on cytology, CTU-based invasion, CTU-based hydronephrosis, and sessile architecture were significantly associated with both inaccurate preoperative staging and upstaging from Ta/Tis/T1 to T2 or above. Thus, patients shown to have high grade tumor, CTU-based invasion or hydronephrosis, or URS-based sessile architecture may be inaccurately staged using URS and upgraded to ≥ pT2 and thus may require more careful preoperative therapeutic strategy. Further, inclusion in analysis of multiple factors led to significant improvement in the area under the receiver operating characteristic curve (AUC) ($P < .001$), suggesting that preoperative staging should be performed using multiple modalities.

Concerns have been raised over the use of URS biopsies due to the reported association between the use of diagnostic URS and a higher intravesical recurrence risk in some meta-analyses[14,15]; the use of high intrapelvic pressures during URS results in pyelolymphatic and pyelovenous backflows that are potential routes of tumor seeding.[28] However, preliminary data have shown that the use of intravesical chemotherapy after URS decreases this risk.[29,30] In addition, URS does not affect the final oncological outcomes in UTUC patients, such as recurrence-free, metastasis-free, and cancer-specific survival.[31] Another concern is the URS-associated delay in performing RNU. However, a meta-analysis showed that RNU delay does not have a negative oncological impact on survival, recurrence, or metastatic disease in patients undergoing RNU after URS biopsy.[31]

The observational design of this multi-institutional study resulted in several study limitations. First, this retrospectively collaborative analysis of a well-selected cohort of UTUC patients has inherent selection bias, among other limitations. Second, while pathological upstaging has been proposed to represent a poor prognostic feature independent of the final pathological stage, the present study focused on only tumor upstaging and upgrading as they occurred with different diagnostic approaches; their impact on survival remains unclear. Third, surgical approaches to RNU and lymph node dissection were not standardized. The lack of centralized radiological and pathological reviews is an additional limitation, despite all participating institutions having unique strengths and being staffed by dedicated uropathologists with expertise in UTUC. Despite the need for extensive URS biopsy in staging cT3-4 disease, 6 patients had been diagnosed as cT3-4 disease on URS biopsies. This may be accounted for by the multicenter retrospective nature of the study in which the URS biopsy procedure (eg, biopsy sampling protocols and devices used among the surgeons at each center) may not have been standardized, which is a further limitation of the study. Finally, while the study enrolled a total of 1214 patients, not all these patients were available for full analysis. These limitations remain to be addressed in future, prospective, well-designed studies that will assess the diagnostic performance of URS biopsy in predicting the tumor stage and grade observed in the final pathology specimens. Moreover, the use of NAC may affect the discordance between clinical and pathological staging and grading. Thus, we excluded all patients undergoing NAC. Given the increasing number of patients undergoing NAC, however, there may arise a need to include those undergoing NAC for analysis in the future.

In conclusion, in this study, clinical understaging occurred in almost 60% of patients undergoing RNU for UTUC. Moreover, of those diagnosed with muscle-invasive disease, based on the final tumor specimen pathology, nearly 90% had been diagnosed with ≤cT1 disease. In daily clinical practice, the pathological characteristics determined following URS biopsy offer the most accurate preoperative information; however, when used alone, the predictive value of the biopsy appears to be limited. The decision to treat a tumor conservatively needs to be made in light of the specific tumor characteristics, and not based solely on URS stage and grade. Future decision-making can be improved by the inclusion of reliable, accurate biomarkers.

Clinical Practice Points

- Accurate clinical staging and grading of UTUC remain an enormous challenge facing urologists, given the high upgrading and upstaging rates occurring between biopsy- and radical surgery specimen-based diagnoses. Pathological upstaging has also been proposed to represent a poor prognostic feature, independent of final pathological stage, and that the presence of pathological upstaging may be an indication for adjuvant chemotherapy in patients with urothelial carcinoma.
- In our multi-center cohort, clinical understaging/undergrading and upstaging to muscle-invasive disease occurred in a high proportion of UTUC patients diagnosed based on URS biopsies. Furthermore, clinical understaging and undergrading also occurred in 19.2% of CTU-diagnosed patients and in 49.9% of cytologically diagnosed patients, respectively.
- In daily clinical practice, URS biopsy and CTU offer the most accurate preoperative information albeit with limited predictive value when used alone suggesting that a multimodal approach is required for accurate risk stratification. Moreover, these findings should be considered when utilizing preoperative, risk-adapted strategies.

Author Contributions

Conceptualization, Data curation, Methodology, Formal analysis, Project administration, Software, Visualization, Writing – original draft: Keiichiro Mori; Data curation, Formal analysis, Writing – review & editing: Satoshi Katayama; Data curation, Writing –

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review & editing: Ekaterina Laukhtina; Formal analysis, Writing – review & editing: Victor M. Schuettfort; Data curation, Writing – review & editing: Benjamin Pradere; Data curation, Writing – review & editing: Fahad Quhal; Data curation, Writing – review & editing: Reza Sari Motlagh; Data curation, Writing – review & editing: Hadi Mostafaei; Data curation, Writing – review & editing: Nico C. Grossmann; Data curation, Writing – review & editing: Pawel Rajwa; Data curation, Writing – review & editing: Kristin Zimmermann; Data curation, Supervision, Writing – review & editing: Pierre I. Karakiewicz; Data curation, Writing – review & editing: Mohammad Abufaraj; Data curation, Supervision, Writing – review & editing: Harun Fajkovic; Data curation, Supervision, Writing – review & editing: Morgan Rouprêt; Data curation, Supervision, Writing – review & editing: Vitaly Margulis; Data curation, Supervision, Writing – review & editing: Dmitry V. Enikeev; Supervision, Writing – review & editing: Shin Egawa; Conceptualization, Data curation, Formal analysis, Project administration, Supervision, Writing – review & editing: Shahrokh F. Shariat.

Disclosure

The authors declare that they have no conflict of interest.

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Ethics Approval

Each institution's institutional review board approved the data-sharing agreement necessary for the conduct of this study. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clgc.2021.10.002.

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