

# Muscle-Invasive Upper Tract Urothelial Carcinoma

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Upper tract urothelial carcinoma (UTUC) is an uncommon disease, only accounting for 5–10% of all urothelial carcinomas. Current clinical practice guidelines encourage a risk-adapted approach to UTUC management, including lymph node dissection (LND) in patients with muscle-invasive or high-risk tumors.

carcinoma

transitional cell

kidney

pelvis

renal

ureteral neoplasm

lymph node excision

## 1. Introduction

Upper tract urothelial carcinoma (UTUC) is an uncommon disease, only accounting for 5–10% of all urothelial carcinomas <sup>[1][2][3]</sup>. The current standard of care for non-metastatic UTUC is radical nephroureterectomy (RNU) with the excision of a bladder cuff. Unfortunately, UTUC is a biologically aggressive tumor with a high potential for disease recurrence, metastasis, and cancer-specific mortality (CSM) <sup>[4][5]</sup>. Trying to overcome this issue, current clinical practice guidelines encourage a risk-adapted approach to UTUC management. Including a detailed preoperative tumor invasiveness assessment, and recommending either neoadjuvant chemotherapy (NAC) or lymph node dissection (LND) in patients with muscle-invasive or high-risk tumors, which includes patients with clinical high grade (cHG) when the diagnosis is made by means of cytology or ureteroscopic biopsy and pathological high grade (pHG) when the diagnosis has been made by radical or nephron-sparing surgery <sup>[6]</sup>. Due to the low incidence of UTUC, the majority of studies mainly consist of single-institution studies, resulting in low-level evidence for most recommendations <sup>[1][2][6][7][8][9]</sup>.

If pathological characteristics could be more accurately predicted from preoperative data, we could optimize perioperative management strategies and outcomes. Beyond the established prognostic factors such as clinical stage (cT), high grade ureteroscopic (URS) biopsy, and positive urine cytology, another subset of factors may play an important role in predicting the need for LND, such as lymphovascular invasion (LVI), hydronephrosis, length of the ureteral tumor, tumor location, glomerular filtration rate (GFR), and neutrophil counts <sup>[1][2][6][7][8][9]</sup>. Recent efforts to combine imaging and ureteroscopic variables to accurately identify  $\geq$  pT2 disease have been made. The integration of these factors in predictive tools or models is gaining acceptance to guide decision-making for personalized care delivery <sup>[2]</sup>.

## 2. Predictors of Muscle-Invasive UTUC

Preoperative risk factors for either muscle-invasive UTUC ( $\geq pT2$ ), extra urothelial recurrence (EUR), locally advanced disease, or high-risk UTUC have been described [1][2][3][5][8][9]. These factors can either be derived from URS findings, cytology, URS biopsy, or from preoperative radiographic findings. Most of these tests are included in routine preoperative evaluation for suspected UTUC.

Discordance between URS biopsy and final surgical pathology is high, and the major challenge is that the use of small caliber biopsy forceps or baskets normally yields small fragments of tissue, which increase the difficulty of accurately establishing tumor clinical grade and stage. Clinical staging by radiographic characteristics has its limitations; it can be difficult to predict tumor stage in UTUC, mainly because of different tumor locations and characteristics. Prior research showed that cross-sectional imaging has an accuracy of only 52%, tending to overstage most patients, especially when hydronephrosis was present, which was found in 80% of overstaged cases [10].

## 2.1. Ureteroscopic Predictive Factors

Margolin et al. [11] evaluated 314 patients with UTUC who had undergone URS biopsy and subsequently RNU to determine pathology discordance. They reported that on URS biopsy, 61% had cHG tumors and 21% had subepithelial connective tissue invasion (cT1+). As expected in RNU pathology, 79% had pHG tumors and 45% had stage  $\geq pT2$ . Urine cytology was collected and analyzed in 230 cases, and it was positive only in 37% of the cases. The probability of missing invasion (cT1+) when URS was performed was significantly increased when biopsy fragments were  $\leq 1$  mm, and using forceps was associated with a higher likelihood of identifying smaller fragments. Only three preoperative factors for  $\geq pT2$  UTUC were statistically significant in multivariate analysis: cHG (OR 2.4, 95% CI 1.1–5.2,  $p = 0.04$ ), cT1+ (OR 9.0, 95% CI 3.2–25.6,  $p < 0.001$ ), and advanced age (OR 1.0, 95% CI 1.0–1.1,  $p = 0.02$ ). cHG combined with cT1+ reached a positive predictive value (PPV) of 86% [11].

Few studies have assessed predictors of recurrence in ureteral carcinoma [5]. Ito et al. conducted a retrospective study including 70 patients, and they found that 30% developed EUR, and 66% in regional lymph nodes [5]. EUR-free survival was significantly worse in patients with  $\geq pT3$  disease (HR 7.69), length of ureteral cancer along the ureter  $\geq 3$  cm (HR 3.90), positive cytology (HR 4.90), eGFR  $< 60$  mL/min/1.73 m<sup>2</sup> (HR 6.57), maximal diameter of ureteral cancer  $\geq 1.6$  cm, and neutrophil-to-lymphocyte ratio (NLR)  $> 3.0$ . They stratified patients into three risk groups, according to the number of risk factors present (0, 1–2, and  $\geq 3$ ), a 3-year EUR-free survival of 100%, 81.4%, and 25.1% was found according to the aforementioned risk groups, respectively. One of the main limitations of this study was that not all patients underwent LND, they did not use a template-based LND, and adjuvant chemotherapy was administered to patients with  $\geq pT2$  disease, which could have altered the rate of EUR [5].

## 2.2. Radiographic Predictive Characteristics

Optimal preoperative radiographic staging is required to appropriately tailor surgical treatment for individual patients. Hydronephrosis on preoperative axial computed tomography (CT) has been associated with features of

high-risk UTUC and is a good predictor of advanced stage ( $\geq$ pT2) for both, renal pelvis and ureteral tumors [8].

Messer J. et al., in a study of 469 patients, evaluated whether ipsilateral hydronephrosis was a reliable predictor of advanced pathological stage—55% had preoperative ipsilateral hydronephrosis. At final pathology revision, 47% had  $\geq$ pT2 disease, 36% non-organ-confined disease ( $\geq$ pT3 and/or pathological positive nodes (pN+)) and 73% had high grade UTUC. Hydronephrosis was a statistically significant predictor of  $\geq$ pT2 disease (HR 7.4,  $p < 0.001$ ),  $\geq$ pT3, pN+ (HR 5.5,  $p < 0.001$ ), and pHG (HR 1.6,  $p < 0.03$ ) [8]. The conclusion was that the simplest radiographic predictive factor to determine muscle-invasive, non-organ confined disease or pHG was hydronephrosis [8]. These findings are in contrast to a previous study, in which hydronephrosis tended to overstage 80% of the tumors [10]. This study was conducted between 1984 and 1995 and included 31 patients. The technological improvements in the cross-sectional imaging techniques in the upcoming years, as well as the limited number of patients, might explain the contradictory findings regarding Messer's et al. study.

### 2.3. Combined Radiographic and Ureteroscopic Variables

Attempts at combining radiographic characteristics with URS biopsy and urine cytology have been made in order to improve prediction of  $\geq$ pT2 stage UTUC. Brien et al. reported a study of 172 patients, 54% with ipsilateral hydronephrosis, 43% with cHG on URS biopsy, and 80% with a positive cytology. On multivariate analysis, ipsilateral hydronephrosis was a significant predictor of pT2 (HR 12.0,  $p < 0.001$ ), non-organ confined (HR 5.2,  $p < 0.001$ ), and high grade (HR 2.3,  $p = 0.04$ ). Positive cytology was a predictor of non-organ confined UTUC (HR 3.1,  $p = 0.035$ ) instead of pT2 or pHG. URS biopsy grade was associated with pT2 (HR 4.5,  $p < 0.001$ ), non-organ confined (HR 3.9,  $p < 0.001$ ), and pHG (HR 25.9,  $p < 0.001$ ) [9]. When combining all three variables into a single model (hydronephrosis, cHG, and positive cytology), they found 89% PPV for pT2 stage and 73% for non-organ confined UTUC. A negative predictive value (NPV) of 100% was reported when all three variables were normal [9].

Chen XP et al. analyzed data of 729 patients. They found in multivariate analysis that male gender (hazard ratio (HR) 1.898,  $p = 0.001$ ), sessile architecture (HR 3.249,  $p < 0.001$ ), cHG (HR 5.007,  $p < 0.001$ ), ipsilateral hydronephrosis (HR 4.768,  $p < 0.001$ ), renal pelvis UTUC (HR 2.620,  $p < 0.001$ ), and no multifocality (HR 1.639,  $p = 0.028$ ) were significant predictors for muscle-invasive UTUC [1]. The reported accuracy was 79% for both pT2 stage and non-organ confined UTUC.

Favaretto et al. aimed to create a preoperative model to identify patients at risk of  $\geq$ pT2 stage and non-organ confined UTUC. They retrospectively analyzed data from 274 patients treated with RNU. Overall, 49% had  $\geq$ pT2 stage and 30% had non-organ confined UTUC at final pathology. In the univariate analysis, local invasion in imaging (defined as renal sinus fat or periureteric fat) ( $p < 0.001$ ), hydronephrosis ( $p = 0.011$ ), and URS biopsy cHG tumors were all significantly associated with increased risk of  $\geq$ pT2 stage, and all variables, with the exception of hydronephrosis, were also significantly associated with non-organ confined UTUC. Tumor location and hydronephrosis were not significant predictors of  $\geq$ pT2 stage or non-organ confined UTUC at the multivariable models ( $p = 0.6$  and  $p = 0.7$ ), ( $p = 0.065$  and  $p = 0.4$ ), respectively. However, cHG ( $p = 0.04$  and  $p = 0.005$ ) and local invasion on imaging ( $p = 0.017$  and  $p = 0.001$ ) were both significantly associated with  $\geq$ pT2 stage and non-

organ confined UTUC. The accuracy to predict  $\geq$ T2 and non-organ confined UTUC was 71% and 70%, respectively [2].

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