



## Open to Debate Con

# Conservative Treatment of Upper Urinary Tract Urothelial Carcinoma: Con

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### Article info

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Conservative treatment of upper tract urothelial carcinoma (UTUC) is defined as any type of kidney-sparing surgery (KSS), including segmental ureterectomy (SU) and endoscopic ablation (EA) techniques.

Radical nephroureterectomy (RNU), including resection of a bladder cuff with or without retroperitoneal template lymphadenectomy (LND), has been the gold standard for surgical treatment of UTUC over the past decades [1].

According to the current European Association of Urology (EAU) guidelines [1], RNU is recommended for any high-risk disease, defined as meeting one of the following criteria:

- Tumor size  $\geq 2$  cm;
- Multifocal disease;
- Histological/cytological evidence of high-grade disease;
- Invasion on computed tomography urography (CTU);
- Hydronephrosis;
- History of radical cystectomy; and
- Variant histology.

The only exception to this rule applies to the (distal) ureter, for which SU with or without template LND is an option, even in high-risk disease. Cancer-specific survival

(CSS) does not differ in comparison to RNU, although there are only series with very small numbers of salvage RNU cases [2]. Distal SU with ureterocystoneostomy has lower recurrence rates compared to SU of the proximal ureter with ureteroureterostomy [1,3]. Complete resection of the ureter and substitution (eg, with ileum) is technically feasible but should be reserved for low-risk tumors in highly selected cases as it is only supported by low-level evidence [4].

For low-grade cases, RNU is also an option in cases with no imperative indication for KSS such as a solitary kidney or unfavorable renal function [1].

In contrast to UC of the bladder, many of the above-mentioned features in UTUC can be difficult to determine before surgery.

CTU shows high sensitivity and specificity of  $\geq 92\%$  in UTUC [5]. Unfortunately, CTU can only differentiate between T2 and T3 tumors with sensitivity and specificity of approximately 85%, with no certain differentiation between non-muscle-invasive (Tis/Cis, Ta, T1) and muscle-invasive (T2) tumors, which is essential for planning of conservative therapy [6]. In particular, flat lesions can escape detection, even by experienced investigators [6]. Magnetic resonance imaging with the current protocols (sensitivity 75%) and positron emission tomography-CT (sensitivity and specificity between 80% and 85% [7]) suffer from lower detection rates and are not recommended routinely [1].

Preoperative cytology for barbotage urine from the suspicious side of the upper tract is an option for grading and has a positive predictive value of up to 90% for high-grade tumors, but not for staging [8]. Otherwise, cytology of randomly obtained urine does not yield satisfactory results [9], so additional diagnostic ureterorenoscopy (URS) is often

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performed in combination with urine cytology for the affected side [8]. However, ureteroscopic biopsy is associated with a high risk of sampling error. A recent systematic review and meta-analysis reported undergrading in 32% and understaging in 46% of cases [10]. Consequently, this proportion of patients will be undertreated with EA. New technologies such as confocal laser microscopy [11] have been introduced over the past two decades to address this issue, but none of them have validated diagnostic criteria yet. Unfortunately, neither approach has been anchored in the current EAU guidelines to safely push the limits of KSS [1].

This uncertainty regarding grading and especially staging applies not only to newly diagnosed but also to recurrent tumors when salvage RNU should be discussed with the patient.

Aberrant histology, advanced cases such as cT3 and cT4 (if surgery is an option), and any case that involves preoperative measures such as neoadjuvant chemotherapy are not indications for KSS. Retrospective data suggest better quality of life and better overall survival (OS) for selected patients requiring palliative treatment, even with single-site metastasectomy [12–14]. These cases should be offered RNU without [13] or with adjuvant chemotherapy [12]. In these cases, KSS should be regarded as experimental [1].

Purely open RNU results in significant surgical trauma. This trauma can be minimized using either pure or robot-assisted laparoscopy (lapRNU) with special attention to correct handling of the distal ureter/bladder cuff and LND (via a template). Advanced cases (cT3–T4, N+, M+) are traditionally offered open RNU [1], but a newer meta-analysis suggests that lapRNU can achieve comparable results [15].

Port-side metastasis after RNU occurs in up to 3% of cases, depending on the handling of the specimen [16], and a thoughtful and evidence-based approach to this issue is advisable.

Correct LND for SU is still a matter of debate, whereas no LND is possible in excision/ablation via URS or percutaneous access, although it might be curative in certain cases. Furthermore, LND is the best method for lymph node staging, as cross-sectional imaging lacks specificity and sensitivity [1].

Furthermore, there are several other issues associated with EA that patients need to consider. CSS and OS might be comparable in cases for which the indication for KSS is evidence-based after a benefit-risk evaluation [3]. However, the risk of recurrence after EA is up to 40% [17], comparable to the rate for non-muscle-invasive bladder cancer. Thus, stringent follow-up including regular URS, with a probable need for anesthesia, is mandatory and increases the overall risk in this primarily elderly patient population. In addition, this regimen requires excellent patient compliance. Unfortunately, insufficient data regarding patient adherence to URS follow-up are available.

Furthermore, follow-up includes serial cross-sectional imaging. A single CTU scan (depending on the protocol) exposes the patient to 15–35 mSV [18], which could

increase the risk of developing other types of cancer. Ultimately, any follow-up protocol for KSS is based on low-level evidence [1].

Adjuvant therapy after RNU includes intravesical instillation of a chemotherapeutic agent such as mitomycin C, which decreases bladder recurrence [1]. In the case of KSS, adjunctive adjuvant treatment of the upper urinary tract administered either in a retrograde (via a JJ stent) or antegrade (via a nephrostomy tube) manner did not yield lower recurrence rates when compared to untreated patients [19]. Further adjuvant options include systemic therapy with chemotherapy and/or immunotherapy, although this is currently reserved for advanced cases after RNU only.

In conclusion, KSS for UTUC yields oncological outcomes comparable to those with RNU only in select cases of localized ureteral tumors amenable to SU. However, this approach is not as “conservative” as EA techniques. These are associated with a high risk of undergrading and understaging, which makes the definition of a low-risk tumor unreliable and consequently could result in a high recurrence rate.

**Conflicts of interest:** The authors have nothing to disclose.

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