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# Upper tract urothelial carcinoma: a different disease entity in terms of management

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## ABSTRACT

Upper tract urothelial carcinomas (UTUCs) consist of 5%–10% of all urothelial carcinomas, the rest being urothelial carcinomas of the bladder (UCB). There is increasing evidence to show that UTUC is a distinct disease entity from UCB based on phenotypical and genotypical (genetic and epigenetic) differences. This may account for why the natural history of UTUC is different from that of UCB, with >60% of UTUCs and only 15%–25% of UCB presenting with invasion at diagnosis. Management of UTUC is thus different from UCB in a variety of ways, ranging from surgical management, postoperative instillation therapy, postoperative surveillance and medical management (neoadjuvant and adjuvant chemotherapy). This review paper aims to highlight these differences with an emphasis on the distinct management of UTUC, along with the latest updates.

## INTRODUCTION

Urothelial carcinomas can arise along any part of the urinary tract lined with urothelium, with majority of cases (90%–95%) in the lower tract (bladder, urethra) and the rest (5%–10%) in the upper tract (renal pelvis, ureter).<sup>1</sup> In the USA, the 2016 American Cancer Society estimates the incidence of bladder, kidney/renal pelvis and ureter/other urinary organs cases to be 76 960, 62 700 and 3530 respectively<sup>2</sup> (note: there is no separate breakdown for renal pelvis and ureter only). Unlike urothelial carcinoma of the bladder (UCB), biopsy specimens from ureteroscopic staging do not allow for accurate assessment of the depth of infiltration into the upper urinary tract wall. The decision to remove or preserve the kidney is predominantly based on results of preoperative imaging attained from either CT or magnetic resonance urography, combined with tumor grade of possibly insufficient biopsy specimens.<sup>3</sup>

While upper tract urothelial carcinoma (UTUC) is morphologically similar to UCB, there are phenotypical and genotypical (genetic and epigenetic) differences between transitional cell carcinoma of the upper and lower urinary tracts. These interesting differences at the embryological and molecular levels<sup>4</sup> may portend important implications

in terms of their management. First, urothelial cells from the bladder and ureter arise from different embryological tissues.<sup>5</sup> Second, bladder and ureter urothelial tissues differ in terms of uroplakin content, keratin expression pattern, propensity to keratinise and how extracellular matrix-associated proteins with counter adhesive properties react within.<sup>6–7</sup> Third, UTUCs have been found to demonstrate more microsatellite instability<sup>8–9</sup> and hypermethylation<sup>10–11</sup> compared with UCB. Some speculate that the natural history of UTUC is consequently different from that of UCB, with >60% of UTUCs and only 15%–25% of UCBs presenting with invasion at diagnosis.<sup>12</sup> Prognosis is poor, with 5-year extravesical recurrence and overall survival rates at 28% and 23%, respectively.<sup>12</sup>

It is with little surprise UTUCs and UCBs are increasingly being recognised as different disease entities. This paper aims to highlight the differences between UTUC and UCB in terms of management.

## METHODS

A systematic literature search of Pubmed/Medline was performed up to September 2016 to identify all relevant articles describing the management of UTUC.

## RESULTS/DISCUSSION

Differences in management of UTUC and UCB were found in both surgical and medical managements as well as follow-up regimes.

### Surgical management

The key aim of surgical resection is to reduce tumour load and obtain an accurate histological diagnosis. For non-invasive low-risk disease, kidney-sparing surgery is indicated for selected cases,<sup>13</sup> similar to transurethral resection of bladder tumour for UCB. A recent systematic review by the EAU (European Association of Urology) non-muscle invasive (NMI) bladder cancer guidelines panel found seven studies

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comparing kidney-sparing surgery with radical nephroureterectomy (RNU); there were no significant differences in survival outcomes between segmental ureterectomy and RNU.<sup>14</sup> This can be considered in NMI UTUC given that kidney function can be preserved without compromising on oncological outcomes.<sup>15</sup>

As for invasive high-risk disease, RNU, bladder cuff removal and lymph node dissection remains the standard of care for UTUC.<sup>1</sup> This is in contrast to radical cystectomy, urinary diversion and lymph node dissection for UCB. Three different methods exist to excise the intramural ureter—extravesical, transvesical or endoscopic ‘pluck’ techniques. They have been shown to have no differences in terms of cancer-specific or overall survivals, however the endoscopic technique has higher local bladder recurrence rates.<sup>16</sup> Lymph node dissection is recommended by the 2013 European Association of Urology guidelines for invasive disease<sup>17</sup> since it contributes to accurate disease staging<sup>18</sup> as well as improves disease-specific survival.<sup>19,20</sup>

In selected patients with a poor comorbidity profile or who declined RNU, endoscopic resection or ablation of renal pelvis or ureteric tumours is possible. However this requires regular imaging and endoscopic surveillance for repeat ablative procedures.

### Postoperative instillation therapy

In the setting of low grade (Ta, T1) UCB tumours removed by transurethral resection, postoperative instillation therapy is given to prevent bladder recurrence.<sup>21</sup> This is achieved by a single immediate postoperative instillation of chemotherapy (eg, mitomycin) which aims to destroy circulating tumour cells resulting from the surgery (given the continuous irrigation during transurethral resection of bladder tumour), and to kill any residual tumour cells at the resection site. There is level 1 evidence supporting its use from three large meta-analyses comprising 1473 to 3103 patients showing a reduction of recurrence rate by up to 13% compared with transurethral resection of bladder tumour alone.<sup>22–24</sup> For intermediate risk tumours, EAU guidelines recommend one immediate postoperative instillation of chemotherapy followed by 1-year full-dose BCG treatment. This aims to reduce bladder recurrence and also prevents tumour progression.<sup>21</sup>

Similarly, for UTUC, the concept of postoperative instillation therapy translates to post-RNU bladder instillation. In a multicentre review of 1363 patients after RNU, urothelial cancer recurred in 28% and caused cancer-specific death in 61% of all deaths.<sup>12</sup> To reduce bladder recurrence, several strategies were studied. In a phase II randomised trial, patients were given intravesical pirarubicin 30mg compared with standard care within 48 hours after RNU. Local bladder recurrences were reduced in the treatment group at 1 year (16.9% vs 31.8%) and at 2 years (16.9% vs 42.2%) after RNU, respectively ( $p=0.025$ ).<sup>25</sup> A single intravesical dose of 40mg mitomycin C given at the time of catheter removal has also been investigated and using a modified intention-to-treat analysis, researchers found decreased localised bladder recurrence at 1 year when

compared with standard care (17% and 27%, respectively) ( $p=0.55$ ).<sup>26</sup>

If localised urothelial carcinoma of the renal pelvis is managed with endoscopic resection or laser ablation, intrapelvic installation of BCG or chemotherapy into renal pelvis should be done to prevent local recurrence. Due to lack of efficacy studies in UTUC, the recommended regimes are identical to the intravesical therapy regimes for NMI UCB.

The intrapelvic installation methods include (A) intravesical therapy to attempt retrograde reflux up the self-retaining ureteric double-J stents, or (B) direct intrapelvic installation through an open-ended ureteric catheter placed through the ureter into the renal pelvis, or (C) direct intrapelvic installation through a percutaneous nephrostomy (PCN) tube.<sup>27–31</sup> These were small studies and direct comparison among the three methods was not meaningful. Local recurrence rates were between 17% and 50% and cancer-specific mortality was 38% to 50%, respectively. One key specific concern for direct intrapelvic installation through a percutaneous nephrostomy (PCN) tube is the possible risks of PCN track seeding. Attempts to use ureteric-stent refluxing method may be less reliable than either of the direct intrapelvic installation techniques because vesicoureteric reflux (VUR) was detected only in 56% of a cohort study on 100 consecutive patients with ureteric double-J stents.<sup>32</sup>

### Postoperative surveillance

Bladder recurrence occurs in 22%–47% of patients with UTUC<sup>33–35</sup> and 2%–6% in the contralateral upper tract.<sup>36</sup> As such, there is a need for continued postoperative surveillance with flexible cystoscopy and upper tract imaging. Post-RNU patients should undergo flexible cystoscopy at 3 months after RNU and then yearly. CT urogram should be performed yearly for non-invasive tumours, and 6 monthly for the first 2 years for invasive cases.<sup>1</sup>

### Medical management: neoadjuvant chemotherapy

The lack of reliable preoperative pathological specimens for UTUC cases precludes physicians from selecting those with muscle-invasive disease for neoadjuvant chemotherapy prior to RNU. Reliable preoperative specimens are difficult to attain in UTUC due to the technical challenges of obtaining sufficient tissue to diagnose stage T2 (muscle-invasive) or T3 (peripelvic or ureteral) disease. It is important to prevent upper tract perforation when a diagnostic ureteroscopy with biopsy is attempted, therefore grade but not stage can be assessed.<sup>17</sup>

This might explain why neoadjuvant chemotherapy for UTUC has only thus far been limited to select tertiary centres with no more than 50 patients in any published study. The MD-Anderson Cancer Center has started phase 2 trials assessing the role of different neoadjuvant chemotherapeutic regimens evaluating high-grade UTUC; so far early results show 60%–75% pathological downstaging rates.<sup>37,38</sup> A recent retrospective Japanese study with 55 patients found that the 24 patients who underwent neoadjuvant chemotherapy had significantly longer 5-year overall survival (44%

vs 29%) compared with the 31 who had surgery alone, with an adjusted HR of 0.47 (95% CI 0.22 to 0.99,  $p=0.047$ ).<sup>39</sup>

The advantages of neoadjuvant chemotherapy are clear. First, patients are more likely able to tolerate chemotherapy with two functioning kidneys prior to RNU. Second, the attainment of pathological downstaging gives clinicians important prognostication information. Third, the evidence coming from urothelial carcinoma of the bladder is strong, with level 1 evidence recommending neoadjuvant chemotherapy prior to radical cystectomy.<sup>40,41</sup>

Disadvantages of neoadjuvant chemotherapy include a delay to definitive surgical management, particularly in the case of chemoresistant disease, and a concern about possible increase in perioperative morbidity. A retrospective study from MD Anderson Cancer Center in the USA identified 26 patients with UTUC who underwent neoadjuvant chemotherapy prior to laparoscopic RNU, and compared perioperative outcomes with 56 other patients who underwent laparoscopic RNU alone. There were no differences in terms of estimated blood loss, intraoperative blood transfusion rates, length of hospital stay or perioperative complication rates.<sup>42</sup> Chemotherapy in itself also carries side effects, which can prolong the wait for surgery as well. Finally, neoadjuvant chemotherapy involves the risk of giving toxic drugs to patients who do not have pathologically proven muscle invasive disease given the limitations of preoperative staging and diagnosis as previously discussed. This may represent overtreatment in patients who may simply have low-risk disease.

Overall, given the level 1 evidence available for UCB,<sup>43</sup> we advocate that physicians actively enrol patients into existing trials (NCT01993979, NCT01261728, NCT02412670, NCT02876861). Two other trials have either been completed or terminated due to poor recruitment (NCT00028860, NCT01663285).

### Medical management: adjuvant chemotherapy

The evidence for adjuvant chemotherapy in UCB is more robust, with a meta-analysis of nine randomised trials demonstrating its overall survival and disease-free survival benefit.<sup>44</sup> Additionally, the recently published EORTC 30994 trial demonstrated better progression-free survival.<sup>45</sup> Despite this, guidelines still do not recommend routine adjuvant chemotherapy postradical cystectomy in patients with UCB; instead its use is only recommended for high-risk patients such as those with nodal disease.<sup>46</sup>

Comparatively, for UTUC the best evidence for supporting adjuvant chemotherapy comes from a meta-analysis of nine retrospective cohort studies.<sup>47</sup> A total of 482 patients received adjuvant chemotherapy compared with 1300 patients receiving surgery alone for UTUC; this showed an overall survival benefit favouring the former, with an HR of 0.43 (95% CI 0.21 to 0.89,  $p=0.023$ ) and a disease-free survival benefit with a pooled HR of 0.49 (95% CI 0.24 to 0.99,  $p=0.048$ ).<sup>47</sup> However, one has to keep in mind that in the same study, sensitivity analyses revealed inconsistency in observed outcomes when pooling treatment estimates from studies including small proportions of individuals even less

than 25% receiving non-cisplatin-based regimens. This suggests that the regimen of choice should be cisplatin-based if any adjuvant chemotherapy is being considered for patients with UTUC. In terms of what specific cisplatin-based regimen is recommended, a recent multi-institutional study from Japan found that those who received adjuvant methotrexate, vinblastine, doxorubicin, cisplatin had favourable recurrence-free survival rates compared with those who received gemcitabine and cisplatin (71.4% vs 48.2%,  $p=0.022$ ).<sup>48</sup> It must be remembered that unfortunately for some patients, renal dysfunction after RNU precludes them from receiving cisplatin-based adjuvant regimens.

The advantages of adjuvant chemotherapy include the availability of accurate postoperative pathological staging in order not to overtreat non-invasive disease, and eradication of any subclinical micrometastases in order to maximise a patient's survival. Disadvantages include subjecting patients to potentially nephrotoxic chemotherapy after removal of one kidney.

A study of 388 patients who underwent RNU found that mean estimated glomerular filtration rate decreased by 24% postoperatively; this reduced the original 80% of patients who were eligible for chemotherapy before surgery down to 55% after surgery (based on the cut-off of 45 mL/min).<sup>49</sup>

### Conclusions

In summary, UTUC should be considered a different disease entity from UCB even though both are urothelial in origin. There are clear molecular biological differences, potentially leading to differences in stage at diagnosis. Consequently, its surgical and medical management is distinct in order to achieve the best outcomes. Further studies are needed to optimise treatment of UTUC.

**Competing interests** None declared.

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