

# Upper Tract Urothelial Carcinoma: Special Considerations

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**Abstract:** Upper tract urothelial carcinoma (UTUC) is an uncommon disease with a prognosis worse than that of primary urothelial carcinoma (UC) of the bladder. Although surgery remains the mainstay of UTUC therapy, there is increasing enthusiasm for combined-modality approaches in both adjuvant and neoadjuvant settings. Nephron-sparing surgical strategies, including partial ureterectomy and purely endoscopic tumor resection, are also increasingly used. Through the development of multi-institutional consortiums, novel treatment algorithms can now be used to evaluate patients more efficiently and thoroughly than in the past. In addition, the genome of UC isolates has recently been sequenced and published, making it possible to identify molecular targets for future therapies. By reviewing the epidemiology, current management strategies, and areas of ongoing research in UTUC, we hope to provide a background of knowledge useful to clinicians managing patients with this challenging disease.

## Epidemiology and Etiology

Urothelial carcinoma (UC) is the ninth most common cancer globally and the eighth most lethal neoplasm in men in the United States.<sup>1</sup> It is the most costly cancer in the US health care system on a per-patient basis.<sup>1</sup> Between 5% and 10% of primary urothelial cancers originate in the ureter or renal pelvis and are collectively called upper tract urothelial cancers (UTUCs). Of note, when epidemiologic data are collected in the United States, an anatomical distinction is made between tumors of the kidney and renal pelvis and those of the ureter; as a result, estimating the annual total number of cases of UTUC is challenging. In 2014, the extraction of data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database and the Centers for Disease Control and Prevention National Program of Cancer Registries (NPCR) led to an estimate of 63,920 new cases of cancer of the kidney and renal pelvis and of 3000 new cases of cancer of the ureter.<sup>2</sup> Between

### Keywords

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3700 and 7400 new cases of UTUC were diagnosed in the United States in 2014, assuming historical ratios of UTUCs to primary bladder cancers. Likely because of an increased use of cross-sectional imaging and detection during urinalysis at the primary care level, a slow migration to earlier-stage disease is taking place.<sup>3</sup>

In developed countries, tobacco smoking is the greatest risk factor for the development of all urothelial cancers, including UTUC. Tobacco exposure increases the risk for UTUC between 3- and 7-fold and does so in a dose-dependent fashion.<sup>4</sup> Patients with long-standing tobacco exposure generally have a high number of medical comorbidities, including chronic kidney disease, which is worsened by treatment for UTUC.<sup>5</sup> Electronic cigarettes are a new and poorly understood alternative to traditional cigarettes. Although there has been early enthusiasm that they may be less carcinogenic, the topic is still controversial and informed only by low-level evidence.<sup>6,7</sup> At least one more-rigorous prospective nonrandomized 5-year cohort study (NCT01785537) of electronic cigarette users has been initiated to better address these questions.<sup>8</sup>

Internationally, important associations have been identified between exposure to certain environmental factors and UC, including UTUC. Aristolochic acid, a compound found in Balkan and Chinese herbs used for medicinal purposes, has been identified as the primary risk factor for Balkan endemic nephropathy.<sup>9</sup> This agent has been linked to a more than 5-fold increase in the incidence of UC.<sup>4</sup> Phenacetin, a pain reliever and fever reducer, has been associated with an increased incidence of UC and UTUC. Widespread bans on the use of phenacetin have nearly eliminated this drug as an etiologic agent in modern practice.<sup>4</sup> Certain aromatic amines used in the dye industry have been identified as occupational risk factors.<sup>10</sup> Subsequent bans on the industrial use of these chemicals have eliminated them as major contributors to UC, including UTUC.

## Diagnosis and Staging

The most common way in which UTUC is diagnosed is through a workup for hematuria. Less frequently, UTUC presents as flank pain, a flank mass, or an incidental finding on imaging obtained for other indications.<sup>11,12</sup> The standard investigation for hematuria includes urinary cytology, upper tract imaging, and cystoscopy.<sup>11,12</sup> First-line upper tract imaging consists of computed tomographic (CT) urography owing to its wide availability and its sensitivity and specificity for kidney stones and UTUC of more than 90%.<sup>13</sup> In practice, upper tract imaging can be done with any number of alternatives based on resource availability, patient age, pretest risk, and local

practice patterns. Although there has been enthusiasm for fluorodeoxyglucose <sup>18</sup>F positron emission tomography/computed tomography (<sup>18</sup>FDG-PET/CT) in monitoring for recurrence of UTUC, its role as an initial imaging modality is limited.<sup>14</sup> Similarly, magnetic resonance urography can accurately image soft-tissue lesions in the upper urinary tract and provides an option when iodinated contrast medium is contraindicated.<sup>15</sup> As an initial screening test, urinary cytology has performed poorly, even in patients with high-grade UTUC and even when done in a selective fashion with barbotage.<sup>16</sup> Hydronephrosis is a poor prognostic sign in UTUC, and the degree of hydronephrosis has been shown to be independently correlated with a negative prognosis.<sup>17</sup> Regardless of the modality selected, no imaging method is completely accurate for the staging of localized UTUC or tumors that have spread to regional lymph nodes. Preoperative risk factors, histologic grade, and surgeon discretion all must play a role in the ultimate management of these tumors.

## Tissue Diagnosis

Ureteroscopic biopsy is the initial step in tissue diagnosis. In patients who have findings on imaging that are concerning for distant metastases or who would be considered ineligible for general anesthesia, CT- or ultrasound-guided percutaneous biopsy of the primary lesion or a presumed metastasis can be used if the lesion can be targeted accurately. Ureteroscopy is advantageous in that it allows preoperative tumor grading and has been shown to spare some patients from unnecessary nephroureterectomy.<sup>18</sup> Having a tissue diagnosis before nephroureterectomy is valuable because tumor grade has been shown to be correlated with muscle invasion and may guide the consideration of lymphadenectomy or the administration of neoadjuvant chemotherapy.<sup>19</sup> Ureteroscopy also offers the surgeon a practical, accurate evaluation of tumor location, which is useful if nephron-sparing approaches are to be considered.

At diagnosis, UTUC carries a worse prognosis than primary UC of the bladder.<sup>20</sup> A number of factors play a role in this finding, including difficulties with screening, later stage at diagnosis, and the anatomically thinner ureter wall compared with the bladder wall.<sup>11</sup> Patient attributes, including advanced age, African-American race, poor Eastern Cooperative Oncology Group (ECOG) performance status, obesity, current smoking, high tumor grade, presence of hydronephrosis, presence of symptoms at presentation, and history of UC of the bladder, negatively affect the prognosis in UTUC.<sup>21</sup> The most important factors in patient survival in UTUC are tumor grade, tumor stage, and patient age.<sup>21-23</sup> Long-term prognosis appears to follow first-order extinction with fewer incident disease-related deaths as time from treatment increases. As with

malignancies of the respiratory and gastrointestinal tracts, conditional survival increases as the recurrence-free time from the initial intervention increases.<sup>24</sup> Rare histologic subtypes of UC that portend a worse prognosis in lower tract disease are also thought to be negative prognostic factors in UTUC, and this has recently been shown to be true for the micropapillary variant.<sup>25</sup>

### ***Localized Disease and Carcinoma In Situ***

Low-grade UTUC carries a more favorable prognosis than high-grade UTUC. In the population of patients with low-grade disease, radical nephroureterectomy has a high cure rate,<sup>26</sup> and lymphadenectomy at the time of surgery is often omitted. Non-extirpative management in this subgroup has been met with enthusiasm. In patients with low-volume, completely endoscopically resectable low-grade UTUC of the ureter, endoscopic management is a viable treatment option if the patient is willing to undergo adequate postoperative surveillance. Most series have shown a correlation of 85% to 90% between tumor grade of the ureteroscopic biopsy specimen and that of the final specimen after nephroureterectomy.<sup>27</sup> Although ureteroscopic biopsy results correlate well with final nephroureterectomy pathologic findings in most series, concerns about undergrading, failure to identify concomitant carcinoma in situ, and grade progression warrant thorough informed consent.<sup>28-32</sup>

The standard treatment for high-grade UC and carcinoma in situ of the upper tract is surgical extirpation, but some patients cannot or will not undergo this therapy. Case reports of the topical instillation of bacillus Calmette-Guérin (BCG) in patients with upper tract carcinoma in situ have shown success, but long-term follow-up data are lacking, and monitoring for topical recurrence is burdensome to both the patient and the health care system.<sup>33,34</sup>

### ***Locally Advanced Disease***

Neoadjuvant chemotherapy has been used in patients with UC of the bladder, in whom it appears to achieve a modest survival benefit.<sup>35</sup> This experience has been extrapolated to UTUC—both high-grade UTUC that appears confined to the organ and clinically node-positive disease—in the hope of rendering patients eligible for surgery. For patients with UTUC, presurgical consolidation chemotherapy has shown promise in a few retrospective nonrandomized series. In 80% of patients with clinically node-positive status and questionable resectability, the response was adequate for them to undergo subsequent surgery, and 20% achieved T0N0 status<sup>36</sup> in one series. In another nonrandomized retrospective study, patients with clinically node-positive disease were compared based on whether or not they had received preoperative platinum-based chemotherapy. The

median overall survival was 38 months in patients who had received preoperative chemotherapy and 9 months in those who had not. Although there is concern about selection bias, these data are encouraging in a population of patients who otherwise have a grave prognosis.

Pragmatically, chemotherapy before surgery offers unique advantages. Therapy administered up front may be more viable in regard to renal function, given the nephrotoxicity of chemotherapy regimens for UC. It may also spare those patients whose disease carries an extremely poor prognosis from undergoing noncurative surgery.<sup>37,38</sup> A recent cohort study offers compelling evidence for the benefit of neoadjuvant chemotherapy, showing a 5-year disease-specific survival of 90% with neoadjuvant chemotherapy vs 58% without it.<sup>39</sup> Despite the nonrandomized nature of this study, its findings will be the highest level of evidence available supporting a survival benefit for neoadjuvant chemotherapy until the data from prospective studies currently in progress (NCT02412670 and NCT01261728) are complete.

Among patients who are candidates for chemotherapy after nephroureterectomy for high-risk disease, promising results have been shown for those with disease that is not confined to the organ but is not metastatic (pT3-4N0M0).<sup>40,41</sup> Interestingly, another retrospective review showed that in patients with node-positive disease who had undergone nephroureterectomy and lymph node dissection, those with T3 or T4 disease benefited from adjuvant chemotherapy, whereas those with a lower T stage did not.<sup>42</sup> This finding provides further support for the use of adjuvant therapy in patients believed to have lower-risk disease that is later significantly upstaged at the time of pathologic analysis after surgery.

Adjuvant radiation has been studied in high-risk patients who were not candidates for chemotherapy. Radiation given after surgery for pathologic tumor stage 3 or 4 or node-positive disease has been shown to reduce 3-year locoregional recurrence from 39% to 11% in at least one series. No high-level evidence exists to generalize this finding, however.<sup>43</sup> Given the difficulty of administering nephrotoxic chemotherapy in the adjuvant setting after nephroureterectomy, adjuvant radiation is a reasonable option for patients without adequate renal function after surgery. In the salvage setting, radiotherapy in conjunction with salvage chemotherapy for eligible patients has poor results. One study showed a 3-year survival rate of 16%, making it a treatment option to be considered only when all others are nonviable.<sup>44</sup>

### ***Metastatic Disease***

The standard management of metastatic UTUC involves systemic chemotherapy. Although initial overall response rates for current cisplatin-based regimens are higher than

50%, 5-year survival is only 33% in the patients who have the best prognosis (ie, good performance status and no visceral metastases).<sup>45,46</sup> Reflecting the medical disease burden in this population, up to 50% of patients with metastatic UTUC are ineligible for cisplatin-based chemotherapy because of poor renal function or performance status. A number of alternatives exist, including carboplatin substitution and single-agent therapy, although they appear to have decreased efficacy when compared with cisplatin and gemcitabine.<sup>47</sup> Although survival rates are low in keeping with the biology of the disease, current chemotherapy regimens for UC are well tolerated and can be given on an outpatient basis.<sup>48,49</sup>

### ***Ureteroscopy***

Before the widespread use of ureteroscopy, nephroureterectomy was performed without a preoperative tissue diagnosis of UC based on a combination of imaging results, selective urinary cytology, and clinical intuition. Obtaining a tissue diagnosis of UC via ureteroscopy before nephroureterectomy has been shown to decrease the rate of nephroureterectomy, allow nephron-sparing approaches, and avoid unnecessary nephroureterectomy.<sup>18</sup> Tissue is not, however, universally obtainable, and the results for tumor grade and depth of invasion on ureteroscopic biopsy and on final pathology at nephroureterectomy can be discordant.<sup>27</sup> Early concerns about a delay in surgical therapy when ureteroscopy is performed before definitive therapy appear unfounded.<sup>50</sup> Although not standard practice at this time, endoluminal ultrasound as an adjunct to the endoscopic evaluation of UTUC showed a 100% negative predictive value for detecting invasive disease before nephroureterectomy in one study.<sup>51</sup> As in decisions regarding the surgical management of all urologic malignancies, the sound clinical judgment of the surgeon must weigh heavily in the surgical management of UTUC.

## **Management Principles**

Practice guidelines for the management of UTUC are scarce owing to the rarity of the disease and a lack of high-level evidence. As a result, the management principles for UTUC often are derived from those for primary bladder cancer. The formation of multi-institutional consortiums has made it possible for adequate numbers of patients to be assessed to guide therapy in this subset of patients with UC. The disease burden of UTUC is greater in Japan than in North America, and the Japanese Urological Association was the first to publish formal clinical practice guidelines for the management of UTUC.<sup>52</sup> In keeping with the literature on UTUC, which consists largely of case series and nonrandomized studies, many of the Japanese guidelines are clinical recommendations based on

low-level evidence rather than practice rules derived from high-level evidence.

### ***Endoscopic Management***

Purely endoscopic management is the most minimally invasive approach for organ-preserving tumor removal in patients with UTUC. Endoscopic management involves identifying the tumor, removing it with ureteroscopic biopsy forceps or ureteroscopic baskets, and possibly fulgurating the resection site with a laser or monopolar electrode. In clinical practice, purely endoscopic management has been limited to 2 groups of patients: those who have contraindications to nephroureterectomy (eg, a solitary kidney) and those who have low-grade, small-volume tumors that can be removed completely via endoscopy. This approach must be reserved for patients who are readily available for follow-up because the 5-year local recurrence rate was as high as 50% in one large series.<sup>53</sup> Size appears to be a driving factor in recurrence, with lesions smaller than 1.5 cm being the least likely to recur.<sup>54</sup>

In a recent review and meta-analysis, oncologic outcomes in these series were equivalent to those for nephroureterectomy.<sup>55</sup> However, the same caveats that apply to the data for partial ureterectomy apply even more so to data for endoscopically managed UTUC. No prospective randomized comparative studies have been performed, and there is likely some degree of selection bias in the assignment of patients to radical vs endoscopic surgery.

### ***Partial Ureterectomy***

Removal of only the cancerous portion of the ureter and reconstruction of the upper urinary tract is an appealing option in a patient population with a high baseline incidence of chronic kidney disease.<sup>5</sup> The ideal candidates are patients with small, unifocal tumors of the distal ureter. The procedure is performed as a distal ureterectomy, with reimplantation of the mid ureter into the bladder. Because of technical considerations, tumor multifocality, and the inability to rule out renal parenchymal invasion, partial ureterectomy is less commonly performed in patients with tumors in the middle or proximal part of the ureter.

One concern with using an organ-preserving approach to nephroureterectomy is the possibility of compromising oncologic control. Although the results of studies in this area have been conflicting, recent large multi-institutional studies have shown no difference in cancer-specific survival or recurrence rates between patients undergoing partial ureterectomy and those undergoing nephroureterectomy.<sup>56-58</sup> Moreover, this approach has been shown to better preserve renal function.<sup>59,60</sup> Despite this evidence, these studies were nonrandomized in nature and generally included more low-grade, distal tumors in the partial ureterectomy groups.<sup>61</sup>

### ***Neoadjuvant Chemotherapy***

Owing to the success seen in patients with primary bladder cancers, there is enthusiasm for the use of neoadjuvant chemotherapy in patients with localized high-grade UTUC.<sup>62</sup> Three clinical trials have been vested, one by the ECOG (NCT02412670), one by the University of Michigan (NCT01663285), and a third by a consortium of 3 institutions: Memorial Sloan Kettering Cancer Center, the Mayo Clinic, and Hartford Hospital (NCT01261728). The ECOG study was opened in April 2015 and is seeking patients with UTUC to undergo presurgical therapy with accelerated methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) or with gemcitabine and carboplatin, depending on renal function. Unfortunately, the University of Michigan study was closed because of difficulties with recruitment. The study from Memorial Sloan Kettering is estimated to take until the end of 2016 (5 years) to accrue 54 patients.

### ***Nephroureterectomy***

Nephroureterectomy with removal of a bladder cuff remains the gold standard treatment for localized UTUC.<sup>12</sup> A number of operative approaches—both open and minimally invasive techniques, such as pure laparoscopy, hand-assisted laparoscopy, and robotically assisted laparoscopy—are currently used to achieve this goal.<sup>63-66</sup> The surgical approach is dictated by patient characteristics, the need for lymphadenectomy, and provider preference. A minimally invasive approach appears to offer a more rapid convalescence with less operative blood loss.<sup>65</sup> A recent analysis of American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) data on nephroureterectomy showed that 69% of cases between 2006 and 2012 were completed with a minimally invasive approach and that perioperative complications were similar for open and minimally invasive techniques. Length of hospital stay, however, was shorter for minimally invasive nephroureterectomy.<sup>65</sup> From an oncological perspective, these approaches appear safe and equivalent when the indications for lymphadenectomy are the same. A large modern series has shown encouraging outcomes for patients with UTUC able to undergo nephroureterectomy. In this review of 1363 patients, the 5-year recurrence-free survival rate was 69% and the 5-year cancer-specific survival rate was 73%.<sup>20</sup>

### ***Lymphadenectomy***

Lymphadenectomy is often performed at the time of nephroureterectomy in patients with high-grade invasive disease found via ureteroscopy or in those whose preoperative staging studies indicate concern for locally advanced disease. UTUC metastasizes most commonly to regional lymph nodes before spreading to the viscera. The

nodal pattern for right- and left-sided proximal tumors is intuitive, with hilar and paracaval nodes most commonly involved on the right side and hilar and para-aortic nodes most commonly involved on the left side.<sup>67</sup> This predictable anatomic pattern of nodal spread is useful clinically to inform the boundaries of node dissection. Although not standardized, these observations have been extrapolated to proposed lymphadenectomy templates that correlate with renal pelvic or ureteral locations of the primary tumor.<sup>68</sup> For tumors of the right renal pelvis and proximal ureter, a dissection encompassing the hilar, paracaval, retrocaval, and interaortocaval nodes to the level of the inferior mesenteric artery (for renal pelvic tumors) or to the level of the aortic bifurcation (for proximal ureteral tumors) has been advocated. For tumors on the left side, a dissection covering the renal hilar and para-aortic nodes to the level of the inferior mesenteric artery (for renal pelvic tumors) or the level of the aortic bifurcation (for proximal ureter tumors) has been published.<sup>68</sup> For distal ureter tumors requiring lymphadenectomy, removal of the ipsilateral common iliac, external iliac, obturator, and internal iliac nodes is recommended. The final decision regarding the utility and extent of lymphadenectomy is at the discretion of the surgeon and can be modified by the intraoperative findings.<sup>69</sup>

Lymphadenectomy may have both diagnostic and therapeutic uses. In keeping with data suggesting that the presence of positive nodes is a significant negative prognostic factor, retrospective studies have suggested some clinical benefit to lymphadenectomy in patients at risk for nodal metastases.<sup>70</sup> In at least one nomogram, the absence of lymphadenectomy was a negative predictor of survival after radical nephroureterectomy,<sup>71</sup> and removal of more than 5 regional nodes was shown to have a possible therapeutic benefit in one series of high-risk patients.<sup>72</sup>

### ***Topical Adjuvant Therapies***

Multiple agents, including BCG,<sup>73,74</sup> mitomycin,<sup>75</sup> thiotepa, and epirubicin, have been trialed as adjuvant therapies for patients with UTUC who are not candidates for nephroureterectomy. Achieving adequate dwell time of topical therapy is more challenging in the ureter than in lower tract UC. Topical therapy has been administered in both antegrade fashion, through a nephrostomy tube, and in retrograde fashion, through a temporary ureteral catheter. Initial outcomes were encouraging, with many patients with UTUC able to convert from positive to negative urine cytology. Overall recurrence and progression rates were higher than 50%,<sup>74</sup> however, and rates were even higher in patients with upper tract carcinoma in situ. Nonetheless, these treatment options are reserved for patients in whom organ preservation is an absolute requirement or for patients with medical comorbidity sufficient that definitive surgery is contraindicated.



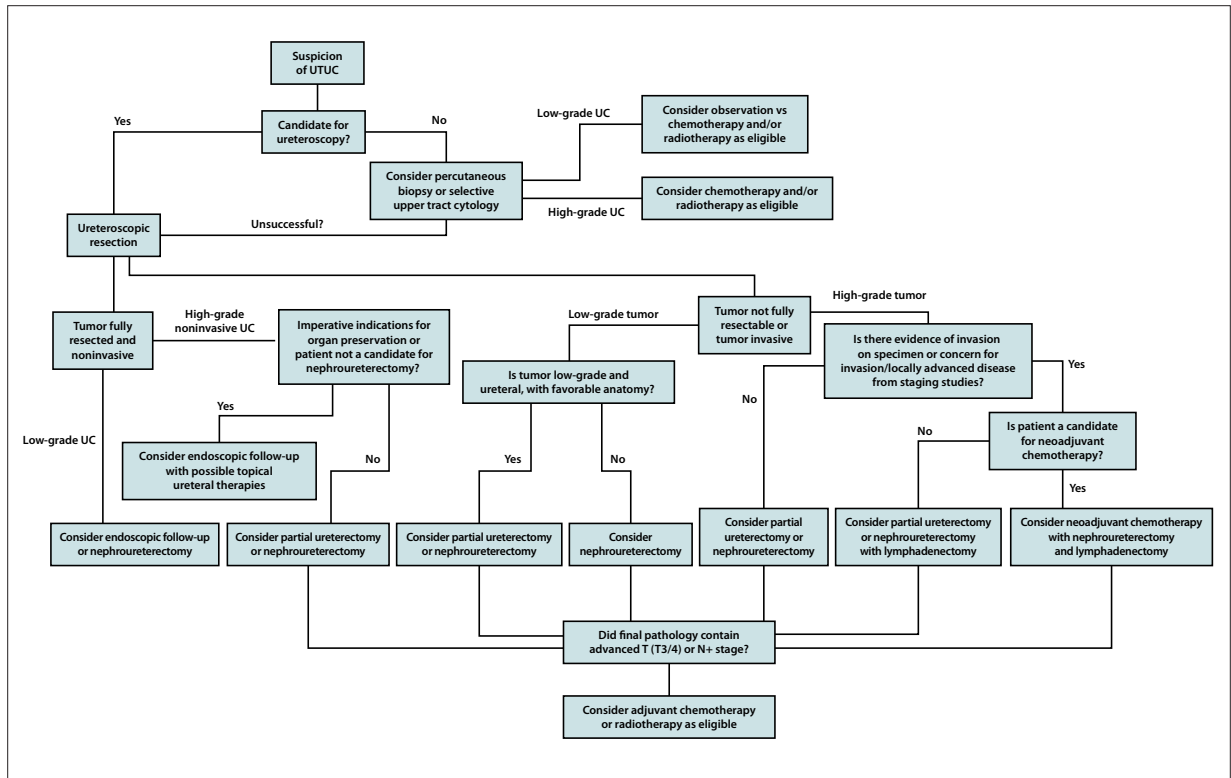


Figure. Suspicion of upper tract urothelial carcinoma.

### Areas of Current Development

Recent multi-institutional collaborations on the treatment of UTUC and better genetic characterization of the disease have yielded exciting new pathways to investigate. As previously mentioned, one multi-institutional phase 2 study (NCT01261728) of neoadjuvant chemotherapy for biopsy-confirmed high-grade UTUC is seeking to enroll 54 patients. This study, which was opened in 2010, is likely to have initial data available for analysis in 2016. The time line reflects the difficulties of performing high-level studies in a disease with an incidence as low as that of UTUC, which reinforces the necessity of multi-institutional collaborative studies.

In 2014, the Cancer Genome Atlas Research Network published an analysis of the pooled results of sequencing in 131 unique UC samples, identifying molecular targets for intervention in 69% of sampled tumors.<sup>76</sup> Targeted agents developed from this knowledge may help to individualize tumor therapy, offering more favorable risk-to-benefit profiles than those of current options. Even small-volume ureteroscopic biopsy specimens have been shown to provide adequate material for obtaining tumor biomarker profiles.<sup>77</sup> Although UTUC occurs twice as frequently in the renal pelvis as in the ureter itself, these

tumors have been shown to have similar tumor biomarker profiles and so can be considered as a group when new therapies are developed.<sup>78</sup> All of the following pathways are currently under investigation as therapeutic targets in lower tract UC: vascular endothelial growth factor receptor (VEGFR), c-Met, epidermal growth factor receptor (EGFR)/ERBB1, human epidermal growth factor receptor 2 (HER2)/ERBB2, phosphoinositide 3-kinase (PI3K), protein kinase B (PKB)/Akt, mammalian target of rapamycin (mTOR)/TOR1/TOR2, tuberous sclerosis 1 and 2, neurofibromatosis 1, fibroblast growth factor receptor (FGFR), CREB binding protein (CREBBP)/EP300, and heat shock protein 27 (HSP27). Agents targeting VEGFR, FGFR, mTOR, PI3K, HER2, c-Met, and HSP27 already have reached phase 2 or later studies.<sup>1</sup>

The instillation of topical agents for UTUC is another area of ongoing research. One new therapy for the treatment of these tumors is a thermally state-dependent polymer gel impregnated with mitomycin C (Mitogel). This agent makes it possible to instill mitomycin C with improved dwell time. In 2014, based on promising pre-clinical data, it received an orphan drug designation for use in UTUC.<sup>79</sup>

Work has been done on new immunotherapies for UC that may also have relevance in UTUC. This is based

partially on prior studies showing that tumor-infiltrating lymphocytes are a positive prognostic factor in patients with UC,<sup>80,81</sup> and partially on the effects seen after the administration of BCG for non-muscle-invasive lower tract UC. Ipilimumab (Yervoy, Bristol-Myers Squibb), an inhibitory T-lymphocyte ligand agent that blocks cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), is under investigation as an adjunct for gemcitabine and cisplatin in the treatment of UC.<sup>1</sup> Similarly, the programmed death 1/ligand 1 (PD-1/PD-L1) antibodies PMPDL3280A, pembrolizumab (Keytruda, Merck), nivolumab (Opdivo, Bristol-Myers Squibb), and MEDI4736 are being trialed in early-stage studies in multiple tumors, including UC.<sup>1</sup>

To our knowledge, no prospective randomized trials have addressed partial ureterectomy vs radical nephroureterectomy or purely endoscopic management of UTUC vs radical nephroureterectomy. Given the numbers noted in published series over several decades, recruitment for such studies would be daunting. New diagnostic avenues are being explored in a French study of laser confocal microscopy for the initial evaluation and follow-up of patients managed endoscopically for UTUC that is recruiting patients (NCT02276924). If an accurate UTUC evaluation can be performed endoscopically, physicians can more safely guide and assign patients to nephroureterectomy or more conservative approaches. A treatment algorithm incorporating currently available data can help to assist surgeons caring for patients with UTUC (Figure).

## Summary

UTUC remains a rare disease with a poor but improving prognosis. Although the original guidance for the management of these tumors was based on principles established in lower tract disease, modern multi-institutional consortiums are helping to shed light on the specific nuances of treating patients with UTUC. In the coming years, more mature series of studies on endoscopic management and partial ureterectomy will help delineate which patients are best served by these treatment modalities. We will also have a more definitive data set for counseling patients with high-grade disease about neoadjuvant chemotherapy before nephroureterectomy. With targeted therapies derived from the UC literature, we may be able to treat even advanced UTUC more effectively. Regardless, a multimodality approach and multicenter collaboration will be needed to provide optimal outcomes for all patients with UTUC.

## Disclosures

*Drs Hutchinson, Haddad, Sagalowsky, and Margulis have no relevant conflicts of interest.*

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