



Tumor Review

A contemporary review of management and prognostic factors of upper tract urothelial carcinoma

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ABSTRACT

Background: Upper tract urothelial carcinoma (UTUC) accounts for <5% of all urothelial cancers. Although the main treatment is radical nephroureterectomy (NU), oncologic outcomes are not comparable to lower tract urothelial cancers. Identifying prognostic factors can help guide management and potentially improve outcomes. This article systematically reviews current literature on prognostic factors and management options for UTUC.

Methods: A comprehensive literature search was performed to identify all studies examining prognostic factors and management options for UTUC. The search included the Medline, Embase, Cochrane Central Register of Controlled Trials databases, and abstracts from the American Society of Clinical Oncology meetings up to November 2014. An updated systematic review was performed.

Results: Preoperative prognostic factors for UTUC patients include age, race, performance status, obesity, smoking status, elevated fibrinogen levels, hydronephrosis, tumor size, multi-focality, location, clinical grade and previous/synchronous bladder cancer. Postoperative variables include tumor stage/grade, multifocality, nodal involvement, lympho-vascular invasion, initial ureteral location, necrosis, sessile architecture, variant histologies and presence of tissue ALDH1 and SOX2. Curative treatment of choice is NU, with lymphadenectomy conferring survival benefits. Minimally invasive surgery has equivalent oncologic and better peri-operative outcomes compared to open surgery. Conservative therapy includes adjuvant BCG and intravesical mitomycin C. Two randomized trials investigating postoperative instillation of mitomycin C suggest bladder recurrence benefits. Adjuvant chemo-radiotherapy may be useful for patients with advanced T3/4 and/or N+ disease.

Conclusion: Gold-standard treatment for UTUC remains NU, increasingly performed using minimally invasive surgery. Nomograms including pre- and post-operative variables can aid prognostication and guide further therapy.

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Introduction

Upper tract urothelial carcinoma (UTUC) accounts for less than 5% of all urothelial cancers and 5–10% of all renal cancers [1]. Overall, oncologic outcomes after radical nephroureterectomy (NU) remain relatively poor. The UTUC Collaboration reported results from 1363 patients treated with NU at 12 academic centers and found that 5-year recurrence-free and cancer-specific survival probabilities were 69% and 73%, respectively. Another review of 184 patients treated at MD-Anderson Cancer Center showed that

across the study period from 1986 to 2004, disease-specific survival rates were no different [2], highlighting that current treatment paradigms may need to be augmented with multi-modal therapy, including peri-operative chemotherapy.

Currently, the gold standard treatment for UTUC remains a NU with excision of a bladder cuff. Recently, there have been advances in minimally invasive technology and development of advanced instruments, coupled with increasing experience from other major urologic surgery such as radical prostatectomy and cystectomy. Consequently, laparoscopic and to a lesser extent robot-assisted NU has gained popularity, especially after equivalent short and mid-term oncologic outcomes have been reported. However, there have been no randomized trials examining these competing approaches, with current available evidence limited to single-center series.

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Several preoperative and postoperative factors are useful in prognostication. Tumor stage and grade are the most well established prognostic factors together with others such as nodal involvement, lymphovascular invasion, and tumor multifocality. However most of these data are only reliably obtained post-operatively. Increasingly, preoperative variables such as age, and radiologic features are used to guide management. These variables may be combined to produce predictive nomograms to guide personalized clinical decision-making regarding management options. For example, does a patient need adjuvant chemotherapy or chemo-radiotherapy? Would the patient benefit from postoperative instillation of topical agents like mitomycin C to reduce bladder recurrence?

To better inform clinicians and patients, this paper aims to perform a contemporary systematic review of the literature on UTUC, focusing on the state-of-the-art for surgical and other management options and an overview of recognized prognostic factors for patients diagnosed with UTUC.

Methods

A comprehensive literature search of English-language studies using the PubMed/MEDLINE and EMBASE databases was performed to identify studies examining the role of chemotherapy for UTUC. Search terms used include “ureteral neoplasms”, “urothelium”, “ureter”, “upper tract urothelial”, “chemotherapy”, “adjuvant”, “neoadjuvant” and relevant variants of these search terms. Search results were independently reviewed by two authors (JJL, JB). Full articles were retrieved for further qualitative review. In addition to review of the literature search results, an additional search of abstracts presented at meetings of the American Society of Clinical Oncology (ASCO) from January 2007 onwards was conducted. Finally, the Cochrane Controlled Trials Register (CCTR) was queried for pertinent ongoing or unpublished studies. All studies and abstracts were identified up to November 2014.

Results and discussion

Surgical management

Radical nephroureterectomy

NU remains the mainstay of treatment in UTUC [1]. This is typically performed in conjunction with bladder cuff removal. There are various surgical techniques for NU. Conventionally there are two approaches of bladder cuff removal via open surgery through the trans-vesical or extra-vesical approach, both of which appear similar in terms of oncologic outcomes [3]. Endoscopic innovations gave rise to the “pluck” technique, introduced by McDonald et al. in 1952 but it was not popularized until 1995 when the endoscopic approach to the distal ureter was found to have equivalent oncologic outcomes [4] and reduced operative time [5]. These three methods of bladder cuff excision (transvesical, extravesical and endoscopic) were evaluated in a recent large study of 2681 patients from the UTUC Collaboration [3], where the authors found no differences in terms of recurrence-free survival, cancer-specific survival and overall survival among the 3 methods. However, patients who underwent the endoscopic approach were at significantly higher risk of intravesical recurrence compared with those who underwent the transvesical ($p = 0.02$) or extravesical approaches ($p = 0.02$), with no differences between the latter two groups.

As for retroperitoneal lymph node dissection (LND), while it is not standard practice yet, there is growing evidence for its utility. In a retrospective study examining 82 patients with T2–4 upper

tract TCC, the 40 patients who received RPLD had significantly longer median time to recurrence and overall survival at 51.2 and 52.5 months compared to those who only had NU ($n = 42$), at 18.5 and 21.2 months, respectively. This study showed that LND was an independent factor affecting overall survival after adjustment in a Cox proportional hazard model [6]. Another study of 552 patients showed that the extent of lymphadenectomy in pT0 UTUC patients is associated with cancer-specific mortality, with longer survival seen in those who had at least 8 nodes removed [7]. LND has been recommended to be performed according to lymphatic drainage: for ureteropelvic tumors, LN medial to the ureter; for higher ureteral tumors and renal pelvis tumors; retroperitoneal LN should be removed [8].

As for surgical approach, NU has traditionally been performed in an open fashion but there has been a move toward minimally invasive surgery, as experience with laparoscopic nephrectomy has increased. Initial concerns about laparoscopic surgery revolved around whether laparoscopy is associated with a higher risk of peritoneal dissemination and port-site metastases, however such occurrences are declining due to improvements in surgical technique [9].

The only prospective randomized study of 80 patients who underwent either open or laparoscopic NU found equivalent oncologic outcomes, but shorter hospital LOS and reduced blood loss among those receiving laparoscopic surgery [10]. A recent systematic review and meta-analysis of 21 studies with 1235 cases and 3093 controls examining the oncologic and perioperative outcomes of open vs. laparoscopic NU did not find any statistically significant differences in 2-years CSS, 5-years recurrence-free survival (RFS), 5-years overall survival (OS), 2-years OS, and metastasis rates between the 2 approaches [11]. Short- to mid-term oncologic outcomes appear similar between open and laparoscopic NU [11–13], but long-term results are sparse, especially for high-risk disease (e.g., pT2, N+) [14]. The study with the longest median follow-up of 13.7 years found oncologic equivalence in terms of OS, PFS and CSS between open and laparoscopic NU [15].

As for perioperative outcomes, the aforementioned meta-analysis [11] also did not find any significant differences between the 2 approaches in terms of intraoperative complications, postoperative complications, and perioperative mortality. However, a 2012 US population-based analysis showed that laparoscopic NU is associated with fewer adverse intra- and post-operative outcomes compared to open NU [16]. Robot-assisted laparoscopic NU remains in its infancy, with 10 studies reporting their initial experience [17]. A large contemporary analysis of open vs. minimally invasive (laparoscopic and robot-assisted) NU did not find any differences in 90-day mortality and major complications as defined by Clavien classification system. However, minimally invasive surgery was associated with 34% decreased odds of prolonged hospital length of stay (>median) (OR: 0.66, 95% CI: 0.55–0.79, $p < 0.001$) [18]. The robotic platform has been touted to have some potential advantages in terms of surgical dexterity and maneuverability. Surgeons are gaining familiarity from their robot-assisted radical prostatectomy and partial nephrectomy experience. A recent population-based study in the US has compared perioperative outcomes of robot-assisted NU versus laparoscopic NU and found no significant differences in terms of postoperative transfusion and length of stay [19]. However, patients who underwent robot-assisted NU were less likely to suffer any complications compared to those who underwent laparoscopic NU. While it must be cautioned that the investigators were not able to account for important confounders such as tumor stage and grade, it nevertheless highlights the feasibility and safety of robot-assisted NU, which will undoubtedly be increasingly popular among urologists in the near future.

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