Upper Urinary Tract Urothelial Carcinoma

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Editors
Michael Grasso III
Lenox Hill Hospital
Department of Urology
New York Medical College
Valhala, NY
USA

Demetrius H. Bagley
Department of Urology
Thomas Jefferson University
Philadelphia, PA
USA

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Preface

Recently, there have been changes in the diagnosis, treatment, and overall management of upper tract urothelial carcinoma. Although there have been suggestions that there is an increased frequency of these lesions, it is difficult to be certain because renal carcinoma and renal pelvic tumors are grouped together by coding. General success of various treatments in the lower urinary tract with preservation of the bladder leave the upper urinary tract naïve to intravesical therapies. Thus, it may remain as a reservoir of untreated urothelial tissue. The many studies of nephrectomy for renal cell carcinoma have demonstrated the value of preserving nephrons. This has been extended to increase the urgency of preservation with urothelial carcinoma as well.

The presentation of upper urinary tract urothelial carcinoma (UTUC) may be very nonspecific with hematuria as the most common finding. Radiographic studies may be indicative but are rarely definitive. Cytology and urinary markers similarly are often not diagnostic or specific. Endoscopic diagnosis is thus essential, most commonly requiring meticulous inspection of the upper tract urothelium with a steerable, flexible ureteropyeloscope and biopsy of any lesion detected.

As in the bladder, UTUC can present in various forms, some of which have a local indolent course (i.e., of lower grade) while others are aggressively malignant from the onset. Differentiating lesions based on endoscopic findings, urine cytology, and biopsies obtained with progressively small-diameter, mechanically refined ureteroscopes is essential in developing a treatment strategy. Genetic differentiation remains in its infancy. These same small-caliber ureteroscopes can then be employed to deliver a variety of energy sources to treat both ureteral and intrarenal lesions. Recurrence after endoscopic therapy parallels the lower urinary experience, underscoring the need for surveillance and the importance of developing adjuvant topical and systemic treatments.

While low-grade lesions can be treated endoscopically with organ preservation, high-grade and invasive lesions are most commonly treated with extirpative laparoscopic and surgical procedures. In these patients, there are significant risks of regional and widely metastatic disease, many of which might benefit from systemic chemotherapy before or after nephrectomy. Thus, it is the risk of transformation, or progression in grade, with a recurrence after endoscopic therapy of a low-grade lesion that is of paramount importance, framing an argument for lifelong surveillance protocols.

With diagnostic and treatment strategies evolving, based in part on new technologies and expanding experience, a comprehensive collaborative text focusing on upper tract urothelial carcinoma is timely. In this volume, authoritative specialists from various disciplines present a balanced scientific and practical approach to each subject.

New York, NY, USA — Michael Grasso III
Philadelphia, PA, USA — Demetrius H. Bagley

Contents

Contributors

Editors

Demetrius H. Bagley, MD Department of Urology, Thomas Jefferson University, Philadelphia, PA, USA

Michael Grasso III, MD Department of Urology, New York Medical College, Valhalla, New York, USA

Authors

Bobby S. Alexander, MD Department of Urology, Lenox Hill Hospital, New York, NY, USA

Christophe B. Anderson, MD Urology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Marluce Bibbo, MD, ScD Department of Pathology, Thomas Jefferson University, Philadelphia, PA, USA

Bruce M. Boman, MD, PhD Department of Medical Oncology, Thomas Jefferson University, Philadelphia, PA, USA

Mieke T.J. Bus, MD Department of Urology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Jonathan Cloutier, MD, FRCSC Department of Urology, Tenon University Hospital, Hôpitaux de Paris, Pierre et Marie Curie University, Paris, France

Michael J. Conlin, MD, MCR, FACS OHSU Center for Health and Healing, Oregon Health and Science University, Portland, OR, USA

Daniel Martin de Bruin, PhD Department of Urology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Department of Biomedical Engineering and Physics, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Theo M. de Reijke, MD, PhD Department of Urology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Jean J.M.C.H. de la Rosette, MD, PhD Department of Urology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Brian Duty, MD OHSU Center for Health and Healing, Oregon Health and Science University, Portland, OR, USA

Andrew I. Fishman, MD Department of Urology, New York Medical College, Valhalla, NY, USA

Kelly Healy, MD Department of Urology, Thomas Jefferson University, Philadelphia, PA, USA

John Michael Henderson, BMBS, BMedSci(Hons), FRCS, FEBU Bristol Urological Institute, Southmead Hospital, Bristol, UK

Harry W. Herr, MD Urology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Jean Hoffman-Censits, MD Department of Medical Oncology, Kimmel Cancer Center, Thomas Jefferson University Hospital, Philadelphia, PA, USA

Scott G. Hubosky, MD Department of Urology, Thomas Jefferson University, Philadelphia, PA, USA

Gary Israel, MD Diagnostic Radiology, Yale New Haven Hospital, New Haven, CT, USA

Guido M. Kamphuis, MD Department of Urology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Francis X. Keeley Jr. , MD, FRCS (Urol) Bristol Urological Institute, Southmead Hospital, Bristol, UK

Costas D. Lallas, MD Department of Urology, Thomas Jefferson University, Philadelphia, PA, USA

Marc J. Mann, MD Department of Urology, Thomas Jefferson University, Philadelphia, PA, USA

John E. Musser, MD Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Lynn J. Paik, DO Department of Urology, Lenox Hill Hospital, New York, NY, USA

Shuyue Ren, MD, PhD Department of Pathology, Anatomy and Cell Biology, Thomas Jefferson University, Philadelphia, PA, USA

John P. Sfakianos, MD Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Sarah L. Steenbergen, MD Diagnostic Radiology, Yale New Haven Hospital, New Haven, CT, USA

Ryuta Tanimoto, MD Department of Urology, Thomas Jefferson University, Philadelphia, PA, USA

Edouard J. Trabulsi, MD, FACS Department of Urology, Kimmel Cancer Center,
Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA

Oliver Traxer, MD, PhD Department of Urology, Tenon University Hospital, Hôpitaux de Paris, Pierre et Marie Curie University, Paris, France

Luca Villa, MD Department of Urology, Universita Vita-Salute San Raffaele, San Raffaele Hospital, Milan, Italy

Upper Tract Urothelial Carcinoma: Ureteroscopic Biopsy and Specimen Preparation

1

Demetrius H. Bagley, Ryuta Tanimoto, and Kelly A. Healy

Abbreviations

BTA	Bladder tumor antigen
CKD	Chronic kidney disease
CROES	Clinical research office of the endourological society
CSS	Cancer specific survival
F	French
FDP	Fibrin/fibrinogen degradation product
FISH	Fluorescence in situ hybridization
FU	Flexible ureteroscope
H & E	Hematoxylin and eosin
Ho	Holmium
MDCTU	Multidetector computed tomographic urography
NBI	Narrow band imaging
Nd	Neodymium
OS	Overall survival
PHH3	Phospho-histone H3
RNU	Radical nephroureterectomy
RPG	Retrograde ureteropyelogram
SPIES	Storz Professional Imaging Enhancement System
TUR	Transurethral resection
UTUC	Upper tract urothelial carcinoma
WL	White light
YAG	Yttrium aluminum garnet

1.1 Epidemiology

Upper tract urothelial carcinoma is relatively rare. Although urothelial carcinomas are the fourth most common tumor, most of these are located in the urinary lower urinary tract and upper tract urothelial carcinoma (UTUC) accounts for only 5 % of urothelial tumors and 8 % of renal tumors [1, 2]. In Western countries, the estimated annual incidence of UTUC is approximately 1–2 new cases per 100,000 inhabitants. The peak incidence occurs in people in their 70s and 80s and it is three times more prevalent in men than women. Concurrent bladder cancer is present in 8–13 % of cases. After treatment recurrent disease develops in the bladder in 15–50 % of UTUC tumor patients [3] (see Chap. 10). Tumors developed in the contralateral upper tract in 2–6 % of patients [4, 5].

There are several modifiable risk factors related to UTUC. Cigarette smoking is by far the most important of these, producing an incidence three times that seen in non-smokers [6]. Coffee consumption and analgesic abuse have been reported as risk factors [7, 8]. Environmental

D.H. Bagley, MD (✉) • R. Tanimoto, MD
K.A. Healy, MD
Department of Urology, Thomas Jefferson University, 1025 Walnut Street, Suite 1112 College Building, Philadelphia, PA 19107, USA
e-mail: Demetrius.bagley@jefferson.edu

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factors exhibited in employment exposures can be extremely important and risky. Exposure for those employed in the chemical, petroleum, or plastic industries has been seen to increase the relative risk to four. Exposure to coal or coke increases the risk by fourfold. Those exposed to asphalt or tar have a relative risk of 5.5. Aniline dyes, beta-naphthyamine and benzidine have also been associated as causative.

Ingestion of aristolochic acid as a Chinese medicinal herb or as a component of other medical compounds has been related to higher risk of UTUC and has even been responsible for a shift in the sex preponderance in populations where the medicines are popular. With all environmentally related neoplasms there may be a multi-year lag after exposure, up to 15 years or more.

There are also familial or hereditary cases of UTUC. The most common of these is nonpolyposis colorectal carcinoma (HNPCC). This is described later in Chap. 10.

1.2 Symptoms

There are really very few symptoms related to the presence of upper tract urothelial carcinoma. By far, the most common presentation is observation of gross or microscopic hematuria (73–78 %). Flank pain may occur in up to 18–32 % of cases. It is generally dull or achy and is thought to be secondary to a gradual onset of obstruction and hydronephrosis. Less commonly pain may be acute and similar to renal colic. This is typically associated with the passage of clots that obstruct the collecting system [5, 9]. About 15 % of patients are totally asymptomatic at presentation and are diagnosed when an incidental lesion is found on radiologic evaluation. Patients also may have only late symptoms with advanced disease, such as flank or abdominal mass, weight loss, anorexia, and bone pain. There is no difference in prognosis between patients who have preoperative symptoms and those who remain symptom free. Systemic symptoms including anorexia, weight loss, malaise, fatigue, fever, night sweats, or cough associated with UTUC are more commonly associated with advanced disease and should raise concern for a thorough metastatic evaluation and consideration of perioperative chemotherapy regimens [10].

1.3 Options in Treatment

The majority of UTUC are invasive at the time of diagnosis compared to only 15 % of bladder tumors [9, 11, 12]. Overall 5-year cancer specific survival (CSS) is approximately 75 % but is highly stage dependent. The 5-year CSS exceeds 90 % for pTa and T1 disease, it declines to 74.7 %, 54 %, and 12.2 % for pT2, pT3, and pT4 disease, respectively [13]. These differences in survival are seen with radical surgical nephroureterectomy, laparoscopic resection or endoscopic treatment. While radical nephroureterectomy with bladder cuff incision has been the gold standard for UTUC, the options are changing. Radical nephroureterectomy can be performed using an open, laparoscopic or robotic assisted approach.

However, about half of patients with UTUC have pre-existing renal insufficiency with GFR less than 60 mL/min/1.73 m [14]. With advances in ureteroscopes as well as ablative devices, ureteroscopic resection has emerged as an attractive alternative nephron-sparing option in carefully selected patients with acceptable long-term outcomes [15–17]. Though initially reserved for patients with absolute indications for nephron preservation [18–21], ureteroscopic management is now electively done in those with a normal contralateral kidney [22, 23] with renal maintenance in approximately 70–80 % of cases [20, 24]. Recently, the risks of chronic kidney disease (CKD) have become increasingly recognized and CKD is associated with a wide range of causes of increased mortality, particularly cardiovascular [25–27]. As such, emphasis has been placed on nephron preservation, specifically partial nephrectomy for renal cell carcinoma [28–30]. These same arguments can be extrapolated to UTUC. The concept of renal preservation is also appealing due to the risk of panurothelial recurrences. The appropriate selection of patients for conservative management is imperative. Currently, accurate staging remains a challenge

and grade serves as a surrogate for stage. Thus, obtaining an accurate tissue diagnosis is a critical step in the decision making process for UTUC patients.

1.4 Imaging Studies

Multidetector computed tomographic urography (MDTCU) is presently the imaging standard for evaluation of the upper urinary tract [31–35]. It has been seen to be extremely accurate to identify lesions. For polypoid tumors between five and 10 mm, it has a sensitivity of 96 % and specificity of 99 %. Sensitivity decreases to 89 % for lesions less than 5 mm and 40 % for polyploid lesions less than 3 mm but flat lesions are considerably more difficult to diagnose until they become massive. However, CT has the advantage of providing staging information.

Magnetic resonance urography (MRU) can be used in patients who cannot have a CT scan because of contrast allergy or azotemia [37]. It does appear to be less sensitive with the detection rate of only 75 % for tumors <2 cm [38]. It also is generally considered to be contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min) because of the risk of the very rare nephrogenic systemic fibrosis [39]. Other options in imaging include excretory urography or retrograde ureteropyelography, possibly combined with noncontrast CT scan or renal ultrasound to search for both intraluminal filling defects and renal masses.

Several reports have noted that hydronephrosis is an ominous sign predicting higher grade and stage tumors [36, 40, 41].

Imaging studies alone are not adequate to diagnose UTUC definitively. Numerous benign lesions may cause filling defects including polyp, blood clot, fungus ball, inflammatory lesion, or noncalcified radiolucent lesion such as a matrix calculus. Ureteral endoscopy is necessary in these patients to define the subject lesion. Endoscopic visualization alone cannot provide the exact diagnosis. Endoscopic appearance was accurate in only 70 % of patients to determine the malignancy or grade of an upper tract tumor in one series [42]. In another, patients with only a visual endoscopic diagnosis developed grade 3 UTUC during follow up in 21 % [43] indicating the inadequacy of inspection alone.

The decision for treatment can be based to some extent on the tumor grade which reflects the tumor stage. Low-grade, low volume tumors have responded well to endoscopic treatment. With overall survival and cancer specific survival equivalent to that achieved with radical nephroureterectomy in low grade and stage disease. Those with high-grade disease do poorly with either approach [15, 18]. Ureteroscopy with biopsy and possibly simultaneous resection has been the most accurate technique so far for grading and also possibly staging, as well as treating upper tract lesions [44–46].

Herein, we describe our techniques for the ureteroscopic biopsy and specimen handling of upper urinary tract tumors. In doing so, patients may be appropriately selected for a nephron-sparing ureteroscopic laser ablation versus extirpative surgery with RNU and bladder cuff excision for the management of UTUC.

1.5 Urine Based Markers in Diagnosis of UTUC

The ideal diagnostic study for UTUC would be from voided urine collected noninvasively which could demonstrate both high sensitivity and specificity. Unfortunately, no currently available marker fulfills these criteria. Numerous immunologic studies and assays for urinary proteins have failed to achieve better accuracy than cytology alone. Several improved sensitivity and/or specificity when added to cytology but not to the point that would allow treatment without endoscopic biopsy.

Cytology of voided urine has been shown to have a sensitivity of only 30 % for the detection of bladder cancer. The sensitivity varies by grade: Grade one was 12 %, grade two 26 % and grade three 64 % [47]. Cytology is even less sensitive to detect UTUC [48]. Other techniques have been employed in an attempt to enhance the yield for cytology for upper tract tumors. Bibbo et al. used