Challenges, Treatment Options, and Costs Linked With Upper Tract Urothelial Carcinoma

By Julie Gould

Bladder cancer was the sixth most[1] common cancer type in the United States in 2020, behind breast, lung, prostate, colon, and skin cancers.

The American Cancer Society[2] estimates 81,180 new diagnoses of bladder cancer in 2022—61,700 in men and 19,480 in women—and 17,100 deaths.

Bladder cancers are more common in men and the incidence and death rates for women with bladder cancers appear to be trending downwards.[2] The risk of contracting bladder cancer is about 1 in 27 for men and 1 in 89 for women.

WHAT IS UPPER TRACT UROTHELIAL CARCINOMA?

While more than 50% of bladder-related cancers occur in the bladder itself, upper tract urothelial carcinoma (UTUC) is a specific subset of urothelial cancer that primarily affects the lining of the kidney or renal pelvis and the ureter.[2-4] Approximately 5% to 10% of urothelial cancer cases[3] are attributed to UTUC, qualifying it as rare.

Risk factors are very similar to bladder cancer and include race/ethnicity (White people are at higher risk compared with Black, Hispanic, Asian American, and Native American), increased age, gender, family history, smoking, and exposure to certain chemicals.[2]

Johns Hopkins Medicine's Greenberg Bladder Cancer Institute explains: "As the lining of the bladder, kidney and ureter are the same, there are many similarities and some differences between UTUCs and bladder cancers. For instance, both bladder cancers and UTUCs can present with hematuria (blood in the urine). However, UTUCs can block the ureter or kidney, causing swelling (known as hydronephrosis) and infections, and they can even affect kidney function in some patients."

Symptoms related to UTUC may also include flank pain if the tumor is causing an obstruction. Low-grade UTUC may also present without any signs or symptoms and may only be detected in patients when looking for other health-related problems with radiology tests or scans.[5]

Two main types of UTUC include noninvasive and invasive. Tumor development can be classified as low or high grade with different treatment strategies for each. High-grade UTUCs can spread and typically result in a radical nephrouretectomy (surgical removal of the kidney and ureter). While low-grade UTUCs tend to be less invasive and remain in the kidney or ureter, they tend to reoccur prompting additional management and need to preserve the urinary tract.[3]

Surena F Matin, MD, urologist, MD Anderson Cancer Center, in a recent webinar[6] explained that while bladder cancer occurs in approximately a 4 to 1 ratio for men vs women, UTUC occurs in a 2 to 1 ratio, respectively. Other unique risks, limitations, and key points associated with UTUC according to Dr Matin include:

- Lynch syndrome: An inheritable genetic syndrome that increases the risk of certain cancers that occurs in an estimated 4% of patients with UTUC
- Limited imaging technology: UTUC growth occurs by the millimeter, so imaging for smaller organs can be challenging
- Intracavitary therapy: Compared to the bladder, which is built for storage, the upper tract works more similarly to a funnel so treatments do not "stick around" very long to be efficient enough
- Genetic considerations: Many patients with UTUCs have FGFR3 genetic mutations

UNDERSTANDING TREATMENT OPTIONS

Treatment strategy is determined primarily by the risk and grade levels for individual patients. In the case of low-grade UTUC, the primary goals are to reduce tumor growth, avoid radical surgery, and maintain quality of life.

Upon clinical presentation or suspected bladder cancer/UTUC diagnosis, the National Comprehensive Cancer Network Guidelines for Bladder Cancer[7] recommend a trans urethra resection of the bladder tumor (TURBT).

Kate Murray, DO, University of Missouri Medical Center, explained in a webinar[6] how TURBT is used to determine the grade of the tumor and determine next steps. Depending on the grade and risk characterization for the patient, treatment options may include:

- Nephroureterectomy with lymph node dissection
- Primary ureterectomy with lymph node dissection
- Endoscopic tumor ablations (antegrade or retrograde)
- Primary chemoablation
- Chemotherapy or immunotherapy

Dr Murray emphasized how treatment and goals are evolving to save the kidneys because of the potential implications on patients such as metachronous disease, blood pressure-related problems, and other comorbidities.

Dr Murray went on to explain how chemoablation is one of her top choices for low-risk patients. "It's familiar to us as urologists. It's quite tolerable for the patients, and it can avoid repetitive surgeries, repetitive anesthetics for our patients, if possible."

EXAMINING UTUC COSTS

The extensive treatment procedures associated with this condition can result in a significant burden of care.[8] A study published in *Urology Practice* aimed to investigate the economic impact of treating low-grade UTUC.

Researchers searched various databases and conference proceedings for relevant studies published between January 2009 and March 2019. They identified 15 studies that reported on the economic burden of treatment interventions for upper tract urothelial cancer.[8]

The findings revealed that radical nephroureterectomy accounted for the highest treatment costs. These costs included initial procedural expenses, which ranged from $11,793 to $23,235 per patient, as well as readmission/retreatment costs amounting to $31,697 per patient. Additionally, long-term costs associated with end stage renal disease and chronic kidney disease reached as high as $385,464 per patient over a 5-year period.[8]

However, the study also highlighted kidney-sparing management as a cost-saving alternative to radical nephroureterectomy.[8] By adopting kidney-sparing treatments, a potential saving of $252,272 per patient over 5 years could be achieved.

In conclusion, low grade UTUC imposes a substantial economic burden due to the costs associated with patient comorbidities, multiple treatment episodes, and complications arising from radical nephroureterectomy.[8] Therefore, there is a pressing need for a shift towards cost-effective, minimally invasive, kidney-sparing treatments. Such an approach would not only alleviate the financial burden but also improve patient outcomes in the management of this condition.

A different study published in *JNCI Cancer Spectrum*[9] aimed to assess treatment patterns, costs, and survival outcomes among patients with nonmetastatic UTUC. The researchers analyzed data from 4114 patients diagnosed with nonmetastatic UTUC between 2004 and 2013 from the Surveillance, Epidemiology, and End Results (SEER)–Medicare database.

The patients were stratified into low- or high-risk disease groups based on certain factors such as tumor grade, stage, and location. Most patients (95.1%) underwent at least one surgical intervention, and 68.4% underwent at least one endoscopic intervention.[9] Patients with high-risk UTUC were more likely to undergo nephroureterectomy compared to low-risk patients. Few patients with low-risk disease were managed exclusively with endoscopic interventions.

The study found that the costs of care for high-risk UTUC were significantly higher than for low-risk UTUC. At 365 days after diagnosis, the median costs for high-risk UTUC were $108,520 compared to $91,233 for low-risk UTUC. This indicates that managing high-risk UTUC is associated with higher costs up to one year from diagnosis.

Furthermore, patients with high-risk UTUC had worse overall and cancer-specific survival compared to patients with low-risk UTUC. The hazard ratio for cancer-specific survival was 4.14 for high-risk UTUC compared to low-risk UTUC, and the hazard ratio for overall survival was 1.78.[9]

This study highlights that UTUC is primarily managed with nephroureterectomy, regardless of risk stratification,[9] suggesting that the use of renal preservation strategies may be infrequent. Patients with high-risk UTUC have poorer survival outcomes, reinforcing the importance of appropriate risk stratification and tailored treatment approaches.

NEW TREATMENT GUIDELINES RELEASED

On April 25, 2023, the American Urological Association (AUA) and the Society of Urologic Oncology (SUO) jointly released the 2023 clinical practice guideline for the diagnosis and management of nonmetastatic UTUC.[10]

The new guideline aims to provide updated strategies for the specialized approach required for UTUC and improve cancer control and survival rates.[13] The guideline panel, led by Dr Jonathan Coleman from Memorial Sloan Kettering Cancer Center, has developed 38 recommendations to assist clinicians in diagnosing and managing non-metastatic UTUC based on the best available evidence.

The key highlights of the guideline include recommendations on various aspects of UTUC management, including diagnosis and evaluation, risk stratification, kidney-sparing management, surgical management, lymph node dissection, neoadjuvant/adjuvant chemotherapy and immunotherapy, post-treatment surveillance, and survivorship.[10] The aim is to provide clinicians with the most up-to-date information to evaluate patients and make informed decisions on treatment and follow-up care.

Dr Jeffrey Holzbeierlein, president of SUO, emphasizes the importance of disseminating the latest information on challenging diagnoses like nonmetastatic UTUC. The collaboration between AUA and SUO in developing guidelines in urology aims to provide clinicians with comprehensive and evidence-based recommendations to enhance patient care.[10]

The release of the 2023 clinical practice guideline for nonmetastatic UTUC is a significant step towards improving the diagnosis and management of this rare cancer. By incorporating the latest research and evidence, the guideline serves as a valuable resource for urologists and other health care professionals involved in the care of patients with UTUC.[10] ■

REFERENCES

1. Cancer statistics. National Cancer Institute. Updated September 25, 2020. Accessed September 15, 2022. https://www.cancer.gov/about-cancer/understanding/statistics
2. American Cancer Society. Key statistics for bladder cancer. Updated January 12, 2022. Accessed September 15, 2022. https://www.cancer.org/cancer/bladder-cancer/about/key-statistics.html
3. Johns Hopkins Medicine. Greenberg Bladder Cancer Institute. Upper tract urothelial cancer. 2022. Accessed September 15, 2022. https://www.hopkinsmedicine.org/greenberg-bladder-cancer-institute/utuc/
4. Urothelial cancer. National Cancer Institute. Accessed September 15, 2022. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/urothelial-cancer
5. Bladder Cancer Advocacy Network. What is upper tract urothelial carcinoma (UTUC)? December 16. 2021. Accessed September 15, 2022. https://bcan.org/what-is-upper-tract-urothelial-carcinoma-utuc/
6. Bladder Cancer Advocacy Network. Understanding upper tract urothelial carcinoma. April 25, 2022. Webinar available at: https://bcan.org/understanding-upper-tract-urothelial-carcinoma/
7. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Bladder Cancer. Version 2.2022-May 20, 2022. Accessed September 15, 2022. https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdfUS Food & Drug Administration.
8. Thacker K, Raman JD, McLean T, Said J, Oliver L, Gore JL. Understanding the Economic Burden of Treating Low-Grade Upper Tract Urothelial Cancer in the United States. *Urol Pract*. 2021;8(1):1-7. doi:10.1097/UPJ.0000000000000161
9. Fero KE, Shan Y, Lec PM, et al. Treatment Patterns, Outcomes, and Costs Associated With Localized Upper Tract Urothelial Carcinoma. *JNCI Cancer Spectr*. 2021;5(6):pkab085. Published 2021 Oct 1. doi:10.1093/jncics/pkab085
10. American Urological Association. American Urological Association releases non-metastatic upper tract urothelial carcinoma guideline. News Release. Cision. April 25, 2023. Accessed June 1, 2023. https://www.prnewswire.com/news-releases/american-urological-association-releases-non-metastatic-upper-tract-urothelial-carcinoma-guideline-301807070.html