

Upper tract urothelial cancer, explained from the guidelines

Upper tract urothelial cancer starts in the lining of the inside of the kidney (the renal pelvis) or the ureter, the tube that carries urine to the bladder. It is the same type of cancer as most bladder cancers, but it is much less common and is managed in its own way. This page explains what the European (EAU) and US (NCCN) guidelines say about finding it, treating it and following up afterwards.

How common

About 5 to 10% of urothelial cancers; most of the rest start in the bladder

How it is found

Usually blood in the urine; confirmed with CT urography, cystoscopy, urine cytology and often ureteroscopy

Risk groups

Low risk or high risk, based on size, grade, number of tumors and CT findings

Main treatments

Kidney-sparing endoscopic treatment for low risk; nephroureterectomy with a bladder cuff for high risk

Why the bladder is watched

22 to 47% of people later develop a tumor in the bladder

Typical follow-up

Regular cystoscopy for at least 5 years, plus CT urography and sometimes ureteroscopy

Upper tract urothelial cancer at a glance

Urothelial cancer is cancer of the urothelium, the lining that covers the inside of the urinary tract from the kidney down to the urethra. Most urothelial cancers start in the bladder. When the same cancer starts higher up, in the renal pelvis or the ureter, it is called upper tract urothelial carcinoma, often shortened to UTUC. The EAU guideline estimates that upper tract tumors make up only 5 to 10% of urothelial cancers, with almost two new cases per 100,000 people each year in Western countries. The NCCN guideline gives a similar picture: more than 90% of urothelial tumors start in the bladder, 8% in the renal pelvis and the remaining 2% in the ureter and urethra.

Although the cells look the same as in bladder cancer, the disease behaves differently. According to the EAU guideline, about two-thirds of people with UTUC already have invasive cancer (cancer that has grown below the surface lining) when it is found, compared with 15 to 25% of people with bladder tumors. About 9% have spread to distant sites at diagnosis. It is most common between the ages of 70 and 90 and is twice as common in men.

Upper tract cancer and bladder cancer are closely linked. About 17% of people with UTUC also have a bladder tumor at the time of diagnosis, and after treatment a new tumor appears in the bladder in 22 to 47% of people. By contrast, a new tumor in the upper tract on the other side happens in only 2 to 5%. This is why a camera check of the bladder (cystoscopy) is part of the first workup and of every follow-up plan.

There is no dedicated AUA guideline for this cancer. This page draws on the EAU guideline on upper urinary tract urothelial carcinoma (2023) and on the NCCN bladder cancer guideline (version 5.2024), which contains a full pathway for tumors of the renal pelvis and ureter. Because the cancer is uncommon, much of the evidence comes from studies that look back at past patients rather than from randomized trials. The EAU panel says this openly, and this page points out where the evidence is weak.

How this cancer starts

Each kidney filters the blood and makes urine. The urine collects in small cup-shaped spaces called calyces, which drain into a funnel called the renal pelvis. From there the urine flows down the ureter, a narrow tube, into the bladder. The calyces, the renal pelvis, the ureter and the bladder are all lined by the same kind of tissue, the urothelium. Doctors call the kidney's drainage system and the ureter the upper urinary tract.

Upper tract urothelial cancer begins in this lining. Some tumors grow as finger-like (papillary) shapes into the hollow space; others are flat patches of abnormal cells called carcinoma in situ (CIS). Over time a tumor can grow through the lining into the connective tissue beneath it, then into the thin muscle wall, and then into the fat around the renal pelvis or ureter or into the kidney tissue itself. The EAU guideline reports that tumors of the renal pelvis and calyces are about twice as common as tumors of the ureter, that 10 to 20% of people have more than one tumor, and that CIS is found alongside the main tumor in 11 to 36%.

This cancer is different from the more common kind of kidney cancer, renal cell carcinoma, which starts in the filtering tissue of the kidney. The NCCN guideline notes that a tumor in the renal pelvis must be told apart from those kidney tissue cancers, because the treatment is different. Almost all upper tract tumors are urothelial, but about 25% contain other cell patterns (histological subtypes, such as squamous or micropapillary), which tend to be more aggressive.

Risk factors

Smoking is the best established risk factor. The EAU guideline reports that tobacco raises the risk of UTUC between 2.5 and 7 times. Smoking at the time of diagnosis is also linked to a higher chance of the cancer coming back, both in the upper tract and in the bladder, and the guideline notes that stopping smoking improves cancer control.

Aristolochic acid is a chemical made by aristolochia plants. It damages the kidneys and causes changes in DNA that lead mainly to upper tract cancer. People are exposed in two ways: by taking herbal remedies that contain aristolochia, which are used around the world and especially in China and

Taiwan, and through contamination of crops, as described in a kidney disease called Balkan endemic nephropathy. Fewer than 10% of exposed people develop UTUC. Arsenic in drinking water has been tentatively linked to UTUC in Taiwan and Chile, and a large study found a higher risk with regular alcohol use above about 15 grams a day (roughly one drink).

Lynch syndrome is an inherited condition caused by changes in genes that repair DNA mistakes (mismatch repair genes). It raises the risk of colorectal, endometrial and several other cancers, and also of UTUC. The EAU guideline reports that 9% of people with UTUC carry a Lynch syndrome gene change, compared with 1% of people with bladder cancer, which it calls one of the highest rates of undiagnosed genetic disease among urological cancers. For this reason both guidelines ask about personal and family history in everyone with UTUC.

A past history of bladder cancer also raises the risk. People who needed a ureteral stent during bladder tumor surgery, and people with multiple or high-risk bladder tumors, have a higher chance of a later upper tract tumor.

- Signs that suggest a hereditary (Lynch) cause, per the EAU guideline: age under 60; a personal history of a Lynch-spectrum cancer; a first-degree relative diagnosed with a Lynch-spectrum cancer before age 50; or two first-degree relatives with a Lynch-spectrum cancer.
- When Lynch syndrome is suspected, germline (inherited) DNA testing and genetic counseling are advised, along with checks for other Lynch-related cancers such as colorectal, other digestive, endometrial, ovarian and skin cancers.
- A positive mismatch repair test on the tumor itself, even without a family history, should lead to germline testing.

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Ask about personal and family history using the Amsterdam criteria to identify people whose UTUC may be hereditary (weak recommendation), and ask about exposure to smoking and aristolochic acid (weak recommendation).

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Consider germline testing and referral to a genetic counselor for people diagnosed at a younger age and for those with a personal or family history of Lynch syndrome-related cancer.

Symptoms and how it is usually found

The most common sign is blood in the urine, which may be visible (pink, red or cola-colored urine) or found only on a urine test. The EAU guideline reports blood in the urine in 70 to 80% of people with UTUC. It is worth knowing, though, that blood in the urine is much more often due to something else: in a large review, only 0.75% of people with visible blood and 0.17% with blood seen only under the microscope turned out to have UTUC.

About 20 to 32% of people have pain in the side or back (flank pain). This usually happens when a blood clot or the tumor blocks the flow of urine and the kidney swells, a condition called

hydronephrosis. Symptoms such as weight loss, loss of appetite, tiredness, fever, night sweats or cough are less common and should prompt tests to look for spread.

Some tumors are found by chance on a scan done for another reason. Others are found when a urine test shows abnormal cells but the bladder looks normal on cystoscopy, which leads doctors to look higher up. Upper tract tumors are also found during follow-up of people treated for bladder cancer. The NCCN guideline recommends upper tract imaging at the start for everyone with non-muscle-invasive bladder cancer and, for high-risk bladder cancer, again at 12 months and every 1 to 2 years for up to 10 years. The EAU bladder guideline notes that the chance of an upper tract tumor at the time of a bladder cancer diagnosis is low overall (1.8%) but higher (7.5%) when the bladder tumor sits near the ureter openings, in an area called the trigone.

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In people with high-risk non-muscle-invasive bladder cancer, image the upper tracts at baseline, at 12 months and then every 1 to 2 years for up to 10 years.

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The risk of an upper tract tumor during bladder cancer follow-up is higher with multiple and high-risk bladder tumors (level of evidence 2b to 3).

How the diagnosis is made

The main imaging test is CT urography, a CT scan done with contrast dye and timed so that the dye fills the kidneys, ureters and bladder. The EAU guideline calls it the most accurate imaging test available, with a pooled sensitivity of 92% and specificity of 95%. It also shows enlarged lymph nodes, which strongly suggest spread. Its limit is that flat lesions such as CIS usually cannot be seen. When CT contrast cannot be used, for example because of an allergy or poor kidney function, MR urography is an alternative, and a PET/CT scan may be used to look at lymph nodes.

Cystoscopy, a look inside the bladder and urethra with a thin camera, is done in everyone to check for a bladder tumor at the same time. Urine cytology looks for cancer cells under the microscope. Voided urine cytology is less sensitive for upper tract tumors than for bladder tumors, so a sample may be taken directly from the affected kidney or ureter during a procedure. Abnormal cells in the urine when the bladder looks normal point toward a high-grade upper tract tumor.

Ureteroscopy uses a very thin, flexible camera passed through the urethra and bladder up into the ureter and kidney, under anesthesia. It shows where the tumors are, how many there are and how big they are, and it allows a small biopsy. A biopsy taken this way identifies the grade in more than 90% of cases, but it can underestimate the grade and it cannot reliably tell how deep the tumor goes. Studies reviewed by the EAU also found that ureteroscopy, and especially ureteroscopy with a biopsy, is linked to a higher chance of later bladder tumors. In 2023 the EAU therefore changed its advice to favor diagnostic ureteroscopy preferably without a biopsy, and only when imaging and urine tests are not enough to decide. The NCCN workup lists ureteroscopy with biopsy, a biopsy through the skin, or selective washings of the upper tract as options.

Before any treatment meant to cure, the team checks whether the cancer has spread, usually with CT of the chest, abdomen and pelvis. The NCCN workup also includes blood counts and chemistry, kidney function tests, an optional nuclear medicine scan to measure how much each kidney contributes, and a bone scan only if there are symptoms. Once a decision for kidney removal has been made, the EAU guideline suggests the operation take place within 12 weeks when possible, because longer delays may let invasive tumors progress (low-level evidence).

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Perform cystoscopy to rule out a bladder tumor (strong) and CT urography for diagnosis and staging (strong). Use diagnostic ureteroscopy, preferably without biopsy, if imaging and urine cytology are not enough to diagnose or risk-stratify the tumor (strong). MR urography or FDG PET/CT may be used when CT cannot be done (weak).

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Workup includes upper tract imaging, cytology, cystoscopy, ureteroscopy and biopsy or percutaneous biopsy and/or selective washings, kidney function tests, chest x-ray or CT, and blood tests, with a bone scan only if symptoms suggest bone spread.

Stages and grades in plain words

Upper tract cancer is staged with the TNM system (AJCC/UICC 8th edition, 2017), the same framework used for bladder cancer. T describes how deep the main tumor has grown, N describes whether nearby lymph nodes are involved, and M describes whether there is spread to distant organs.

Grade describes how abnormal the cells look. Urothelial tumors are called low grade or high grade. High-grade tumors are more likely to grow deeply and spread. Because biopsies from the upper tract are very small, it is often hard to know the true stage before surgery, so the EAU guideline notes that grade is often used to guide decisions because it is closely tied to stage.

Stage and grade are the most important predictors of outcome. In a large Dutch series cited by the EAU, 5-year cancer-specific survival was 86% for tumors that had not reached the muscle, 70% for tumors in the muscle but still confined, and 44% for locally advanced tumors. These are group averages from past patients; your team can explain what applies to you.

TNM categories for cancer of the renal pelvis and ureter (8th edition), as used by EAU and NCCN

Category	What it means
Ta	Papillary tumor on the surface lining only, not invasive
Tis	Carcinoma in situ: flat, high-grade abnormal cells in the lining
T1	Grows into the connective tissue just under the lining
T2	Grows into the muscle wall
T3	Renal pelvis: grows beyond the muscle into the surrounding fat or into the kidney tissue. Ureter: grows beyond the muscle into the surrounding fat
T4	Grows into nearby organs, or through the kidney into the fat around it
N1	Spread to a single lymph node 2 cm or smaller
N2	Spread to a single lymph node larger than 2 cm, or to several lymph nodes
M1	Spread to distant organs

Low-risk and high-risk disease

Because the true stage is hard to know before surgery, the EAU guideline sorts cancer that has not spread into two groups, low risk and high risk, using information available beforehand. The goal is to find the people who can safely keep their kidney and those who are better served by removing it. To be low risk, every low-risk feature in the table must be present. A single high-risk feature is enough to place someone in the high-risk group.

The NCCN guideline uses a similar list of favorable features for keeping the kidney: low grade on cytology and biopsy, a papillary shape, size under 1.5 cm, a single tumor, and no sign of invasion on cross-sectional imaging. Less favorable features include several tumors, a flat or broad-based shape, size over 1.5 cm, high grade, signs of T2 or deeper invasion, and tumors in the middle or upper ureter or crossing narrow junctions inside the kidney, which are technically harder to treat through a scope. Note that the two guidelines use slightly different size cut-offs (2 cm for EAU, 1.5 cm for NCCN).

EAU risk stratification of upper tract urothelial cancer that has not spread

Feature	Low risk (all must be present)	High risk (any one is enough)
Number of tumors	One tumor (unifocal)	More than one tumor (multifocal)
Size	Smaller than 2 cm	2 cm or larger
Urine cytology	No high-grade cells	High-grade cells
Ureteroscopic biopsy	Low grade	High grade
CT scan	No sign of invasion	Signs of local invasion
Kidney swelling (hydronephrosis)	Not present	Present
Past bladder surgery	Not applicable	Previous radical cystectomy for high-grade bladder cancer
Cell pattern	Pure urothelial	Histological subtype present

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Use prognostic factors to sort patients into risk groups to guide treatment (weak recommendation).

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Favorable features for keeping the kidney are low grade on cytology and biopsy, papillary shape, size under 1.5 cm, a single tumor, and no concern for invasion on imaging.

How treatment decisions are made

Treatment depends on the risk group, where the tumor sits (kidney, upper, middle or lower ureter), how well both kidneys work, whether the other kidney is healthy, your general health, and your own priorities. The EAU guideline repeatedly asks that decisions be made with the patient, case by case, and the NCCN guideline encourages discussion of the risks of under-treatment and over-treatment because staging before surgery is imprecise.

In broad terms, low-risk tumors are treated with kidney-sparing approaches, and high-risk tumors are treated by removing the kidney and the whole ureter with a small cuff of bladder (radical nephroureterectomy). Some people have what the guidelines call imperative indications: a single kidney, cancer in both upper tracts, or chronic kidney disease. For them, losing a kidney could mean dialysis, so kidney-sparing treatment may be chosen even for high-risk disease, accepting a higher risk of the cancer progressing.

Care usually involves a team. A urologist performs the procedures. A medical oncologist is involved when chemotherapy or immunotherapy is considered before or after surgery, or for cancer that has

spread. A pathologist and radiologist help define the stage and grade, and a genetic counselor may be involved if Lynch syndrome is suspected.

Surgical options by tumor location and risk, simplified from EAU Figure 7.2 (1 = first option, 2 = second option)

Location	Low risk	High risk
Renal pelvis	1. Ureteroscopy. 2. Percutaneous (through the skin) treatment	Nephroureterectomy, with or without lymph node dissection and chemotherapy
Calyx	1. Ureteroscopy. 2. Nephroureterectomy if not reachable by scope	Nephroureterectomy, with or without lymph node dissection and chemotherapy
Middle or upper ureter	1. Ureteroscopy. 2. Removing the segment and rejoining the ureter if not manageable by scope	Nephroureterectomy, with or without lymph node dissection and chemotherapy
Lower (distal) ureter	1. Ureteroscopy or 2. Distal ureterectomy	1. Nephroureterectomy or 2. Distal ureterectomy, with or without lymph node dissection and chemotherapy

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Offer kidney-sparing management to high-risk patients with an imperative indication (such as a solitary kidney, cancer on both sides or chronic kidney disease) on a case-by-case basis, in consultation with the patient (strong recommendation).

Kidney-sparing treatment for low-risk cancer

For low-risk tumors, the EAU guideline says kidney-sparing surgery is the preferred approach, because survival is similar to removing the kidney while avoiding the loss of kidney function. It recommends discussing this option in every low-risk case, whether or not the other kidney is healthy. The NCCN guideline agrees that for favorable tumors, treatment through a scope gives survival similar to nephroureterectomy, based on reviews of past patients rather than randomized trials.

The most common method is ureteroscopic ablation: the tumor is reached with a flexible ureteroscope and destroyed, usually with a laser, or removed with small baskets or cups. The tumor must be completely removed or destroyed. People choosing this path need to be willing to return for an early second-look ureteroscopy and for close, long-term surveillance, because some tumors turn out to be more aggressive than the first tests suggested. A percutaneous approach, working through a small tunnel made through the skin of the back into the kidney, can be used for low-risk tumors in the renal pelvis or in lower calyces that are hard to reach with a scope, though it is used less now and carries a small risk of tumor cells seeding along the tract.

For tumors in the ureter that cannot be fully removed through a scope, part of the ureter can be removed surgically. For the lower ureter this is a distal ureterectomy, with the healthy end of the ureter reattached to the bladder (reimplantation). This gives a full tissue sample for staging and allows nearby

lymph nodes to be removed. Removing segments of the upper two-thirds of the ureter has higher failure rates. Replacing the whole ureter with a piece of bowel is possible only in highly selected cases.

Mitomycin gel (also called UGN-101 or mitomycin for pyelocalyceal solution) is a chemotherapy gel placed into the renal pelvis through a thin tube. It is liquid when cold and becomes a gel at body temperature, so it stays in contact with the tumor. It is FDA-approved for low-grade UTUC. In the OLYMPUS trial, described by both guidelines, 59% of patients had a complete response after six weekly treatments, and about 56% of those were still free of tumor 12 months later. Side effects were common, especially narrowing of the ureter (44%). The NCCN guideline suggests it is most suitable for a single, low-grade, small (5 to 15 mm) residual tumor after the visible tumor has been removed or destroyed as completely as possible, in someone who is not a candidate for, or does not want, nephroureterectomy.

Other drugs such as BCG or mitomycin C can be instilled into the upper tract after the tumor is removed. The evidence for this is weak. The EAU guideline notes that recurrence rates after these treatments look similar to those without them, and the NCCN guideline states that their benefit in the upper tract has not been established, although it allows them to be considered for low-grade tumors of the renal pelvis, starting 3 to 4 weeks after the procedure.

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Offer kidney-sparing management as the primary treatment option to patients with low-risk tumors (strong recommendation).

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Complete or near-complete endoscopic removal is recommended before mitomycin gel, which is best suited to a residual, low-grade, low-volume (5 to 15 mm), single tumor in someone not seeking nephroureterectomy. Intrapelvic BCG, mitomycin C or gemcitabine may be considered after endoscopic removal of low-grade renal pelvis tumors, though their benefit is not established.

Radical nephroureterectomy for high-risk cancer

Radical nephroureterectomy is the standard treatment for high-risk UTUC that has not spread, wherever the tumor sits. The surgeon removes the kidney, the whole ureter and a small cuff of bladder wall around the opening where the ureter enters the bladder, all in one piece. The cuff matters: the lowest part of the ureter and its opening are common places for the cancer to come back, and the EAU guideline reports that failing to remove the complete cuff increases the risk of bladder recurrence. Simpler techniques for handling the lower ureter have not been shown to be as good as complete cuff removal.

The operation can be done as open surgery, by laparoscopy or with robotic assistance. The EAU guideline finds similar cancer outcomes for these approaches when the tumor is confined to the organ. For tumors that look locally advanced (T3 or T4) or have involved lymph nodes, it favors open surgery, based on a small randomized trial. It also notes that a robotic approach can be considered, with recent data suggesting similar cancer outcomes and a shorter hospital stay than standard laparoscopy.

Whatever the approach, the surgeon follows rules to avoid spilling tumor cells, such as keeping the urinary tract closed, removing the specimen in a bag, and not cutting the tumor into pieces.

Lymph node dissection means removing the lymph nodes that drain the kidney and ureter. It gives the most accurate staging, and studies suggest that removing nodes according to a defined template improves survival in muscle-invasive disease and lowers the risk of the cancer returning locally. Because the stage cannot be known for sure before surgery, the EAU guideline suggests a template-based lymph node dissection for everyone having nephroureterectomy for high-risk disease. The NCCN guideline recommends regional lymph node dissection for high-grade tumors.

For selected high-risk tumors limited to the lower ureter, removing only the lower ureter and reimplanting it into the bladder (distal ureterectomy), with a lymph node dissection, may give results similar to nephroureterectomy while keeping the kidney. The evidence is limited. The NCCN pathway for lower ureter tumors lists distal ureterectomy with reimplantation of the ureter (preferred when clinically feasible) and lymph node removal for high grade, alongside endoscopic treatment for low-grade tumors and nephroureterectomy.

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Perform radical nephroureterectomy for high-risk non-metastatic UTUC (strong). Perform open nephroureterectomy for tumors that are not organ-confined (weak). Perform a template-based lymph node dissection in high-risk non-metastatic UTUC (weak). Offer distal ureterectomy to selected patients with high-risk tumors limited to the distal ureter (weak).

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For high-grade, large or kidney-invading tumors of the renal pelvis: nephroureterectomy with a cuff of bladder plus regional lymph node dissection, with or without perioperative intravesical chemotherapy, and cisplatin-based neoadjuvant chemotherapy in selected patients.

Chemotherapy and bladder instillation around surgery

A single dose of chemotherapy placed into the bladder after nephroureterectomy lowers the chance of a new bladder tumor. Two randomized trials and two meta-analyses reviewed by the EAU showed this with mitomycin C or pirarubicin given 2 to 10 days after surgery, and side effects were very uncommon. The NCCN guideline notes that trials mostly gave the dose within 24 to 48 hours, that some centers wait up to a week to first confirm with an x-ray (cystogram) that the bladder has healed, and that mitomycin is most common while gemcitabine is an option. More than one instillation probably adds little. There is no direct evidence for a bladder instillation after kidney-sparing treatment.

Neoadjuvant chemotherapy means chemotherapy before surgery. Its main advantage in UTUC is timing: after one kidney is removed, overall kidney function drops, and many people no longer qualify for cisplatin, the most effective drug. The NCCN guideline states that neoadjuvant chemotherapy is preferred for UTUC, especially for higher stage or grade tumors or worrying scan findings, and supports split-dose gemcitabine and cisplatin for high-grade disease. The EAU guideline describes encouraging results, including a 14% complete response rate in a phase II trial, but stresses that there

are no randomized trials and that the evidence is not conclusive. It also notes there is currently no evidence to support immunotherapy before surgery.

Adjuvant chemotherapy means chemotherapy after surgery. The NCCN guideline describes the phase III POUT trial, in which 261 people with tumors that were pT2 to pT4 or had positive lymph nodes were randomly assigned to gemcitabine with cisplatin or carboplatin, started within 90 days of surgery, or to surveillance. Chemotherapy improved disease-free survival: at three years, 71% were free of events compared with 46% with surveillance. Serious (grade 3 or higher) side effects occurred in 44% of those who started chemotherapy compared with 4% under surveillance. The EAU recommends offering this for pT2 to T4 and/or node-positive disease. The NCCN guideline recommends discussing it for pT3, pT4 or node-positive disease when no platinum chemotherapy was given before surgery.

Nivolumab is an immunotherapy drug. The CheckMate 274 trial gave it after surgery to people with high-risk muscle-invasive urothelial cancer; most had bladder cancer, and about 21% had UTUC. Disease-free survival improved overall, but the EAU guideline notes that the UTUC subgroup did not seem to benefit, and both guidelines call for caution. The EAU suggests discussing nivolumab with people who cannot have or decline platinum chemotherapy. The NCCN lists it as an option (category 2B), most suited to people who value delaying recurrence even if the chance of cure is not improved. Radiation after surgery is not recommended by the NCCN, and the EAU finds the data insufficient.

If CT shows enlarged lymph nodes before any surgery, the EAU guideline advises starting with chemotherapy, and surgery with lymph node removal can be discussed if the cancer responds.

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Deliver a post-operative bladder instillation of chemotherapy to lower the bladder recurrence rate (strong). Offer adjuvant platinum-based chemotherapy after nephroureterectomy for pT2 to T4 and/or node-positive disease (strong). Discuss adjuvant nivolumab with patients unfit for or declining platinum chemotherapy for pT3 or higher and/or node-positive disease (weak).

WHAT THE GUIDELINES SAY · NATIONAL COMPREHENSIVE CANCER NETWORK VERSION 5.2024

Neoadjuvant chemotherapy is preferred for UTUC, particularly for higher stage or grade tumors, because kidney function falls after nephroureterectomy. Adjuvant therapy should be considered if none was given before surgery. Perioperative bladder chemotherapy should be strongly considered after nephroureterectomy.

Cancer that has spread

When UTUC has spread to distant organs, treatment is with medicines that work throughout the body. Upper tract and bladder urothelial cancers respond in a similar way, so the same regimens are used.

The EAU guideline (2023) recommends platinum-based combination chemotherapy as first treatment, with gemcitabine and cisplatin or a high-dose regimen called HD-MVAC for people who can receive cisplatin, and gemcitabine with carboplatin for those who cannot. For people whose cancer shrinks or stays stable after 4 to 6 cycles, it recommends maintenance immunotherapy with avelumab, which

lengthened survival in a phase III trial in which almost 30% of patients had UTUC. Pembrolizumab or atezolizumab may be offered to people who cannot have platinum chemotherapy and whose tumors are PD-L1 positive.

The more recent NCCN guideline (version 5.2024), which covers urothelial cancer from any site, now lists the combination of enfortumab vedotin with pembrolizumab as the preferred first treatment (category 1) for people who can and cannot receive cisplatin. Gemcitabine with cisplatin or carboplatin followed by avelumab maintenance remains a recommended option. The EAU text used here does not yet include this combination. Your medical oncologist will explain which options fit your health and kidney function.

After first treatment, options include pembrolizumab after platinum chemotherapy, enfortumab vedotin after both platinum chemotherapy and immunotherapy, and erdafitinib for tumors with specific FGFR gene changes, which requires testing of the tumor. Removing the kidney when cancer has already spread is mainly reserved for relieving symptoms such as bleeding or pain; the EAU guideline notes that a survival benefit has been seen only in highly selected patients, with a high risk of bias in those studies. Removing individual metastases is decided case by case through shared decision-making.

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Offer platinum combination chemotherapy to platinum-eligible patients (strong), gemcitabine/carboplatin to cisplatin-ineligible patients (strong), and maintenance avelumab after 4 to 6 cycles without progression (strong). Offer pembrolizumab after platinum chemotherapy (strong) and enfortumab vedotin after platinum chemotherapy and a PD-1 or PD-L1 inhibitor (strong). Offer nephroureterectomy as palliative treatment to symptomatic patients with resectable tumors (weak).

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Preferred first-line treatment for locally advanced or metastatic urothelial cancer is pembrolizumab with enfortumab vedotin (category 1), whether or not the patient can receive cisplatin.

Side effects and how they are managed

Kidney-sparing treatment keeps the kidney but has its own costs. The NCCN guideline notes that it usually means repeated procedures under anesthesia, that it can cause anxiety, that tumor cells can be spread along the tract during percutaneous work, and that some people eventually need nephroureterectomy anyway. Because biopsies can underestimate how aggressive a tumor is, there is a real risk that a cancer will progress while being managed this way, which is why close surveillance is required.

Mitomycin gel caused frequent side effects in the OLYMPUS trial: narrowing of the ureter in 44% of patients, urinary infection in 32%, blood in the urine in 31%, flank pain in 30% and nausea in 24%. About 27% had a serious side effect related to the drug or procedure, and no deaths were linked to treatment. A narrowed ureter may need a stent or further procedures. Instilling drugs into the upper

tract through a tube or a nephrostomy also carries a risk if the urine flow is blocked, because the drug can be absorbed into the blood.

Nephroureterectomy is major surgery with the general risks of any abdominal operation, which your surgical team will discuss with you. Its most lasting effect is the loss of one kidney. Both guidelines point out that kidney function falls after the operation, and this can make some people ineligible for cisplatin chemotherapy afterwards. This is one reason the timing of chemotherapy is discussed before surgery. A single dose of chemotherapy in the bladder after surgery has a very low rate of side effects.

Chemotherapy can cause tiredness, nausea, lowered blood counts with a risk of infection, and other effects that depend on the drugs. In the POUT trial, 44% of people who started chemotherapy had a grade 3 or higher side effect. With adjuvant nivolumab, serious treatment-related side effects occurred in 17.9% of patients compared with 7.2% on placebo. Your oncology team will monitor you, adjust doses, and treat side effects as they arise.

Follow-up after treatment

Follow-up has three goals: to find new tumors in the bladder, to find a return of cancer in the treated upper tract or on the other side, and to find spread elsewhere. Because the bladder is the most common place for a new tumor, cystoscopy is the backbone of every schedule. The EAU guideline is clear that recommendations on follow-up are based on low-level evidence at best, so schedules vary between centers.

Follow-up is more frequent and more demanding after kidney-sparing treatment than after nephroureterectomy, because the treated kidney and ureter remain at risk. After kidney-sparing treatment for low-risk disease, an early second-look ureteroscopy is usually done 6 to 8 weeks later. People treated with kidney-sparing surgery for high-risk disease need careful, long-term checks, even beyond 5 years. The NCCN guideline also calls for surveillance lasting more than 5 years after kidney-sparing treatment.

The EAU guideline notes that after nephroureterectomy for high-risk disease, the risk of bladder and other recurrences falls after about 4 years, so less intense checks may be reasonable after that. It also notes that it is not yet known how best to follow people with Lynch syndrome.

Typical follow-up schedules from the guidelines (your team may adjust these)

Situation	Bladder checks	Imaging and upper tract checks	Source
After nephroureterectomy, low risk	Cystoscopy at 3 months; if clear, again 9 months later, then yearly for 5 years	CT urography and scans for spread are not mandatory if the bladder stays clear	EAU (weak)
After nephroureterectomy, high risk	Cystoscopy and urine cytology at 3 months, then every 3 months for 2 years, every 6 months until 5 years, then yearly	CT urography and chest CT every 6 months for 2 years, then yearly	EAU (weak)
After kidney-sparing treatment, low risk	Cystoscopy at 3 and 6 months, then yearly for 5 years	CT urography at 3 and 6 months, then yearly for 5 years; ureteroscopy at 3 months if no second-look ureteroscopy was done	EAU (weak)
After kidney-sparing treatment, high risk	Regular cystoscopy	Ureteroscopy with cytology taken from the upper tract at 3 and 6 months, then long-term follow-up	EAU (weak)
pT0 or pT1 (NCCN)	Cystoscopy every 3 months for 1 year, then at longer intervals; consider cytology for high grade	If the kidney was kept: upper tract imaging or ureteroscopy every 3 to 12 months, with or without abdomen and pelvis CT or MRI	NCCN
pT2 to pT4 or node-positive (NCCN)	Cystoscopy and cytology every 3 months for 1 year, then at longer intervals	As above, plus abdomen and pelvis CT or MRI and chest imaging	NCCN

WHAT THE GUIDELINES SAY · EUROPEAN ASSOCIATION OF UROLOGY LIMITED UPDATE, MARCH 2023

After nephroureterectomy for high-risk tumors, perform cystoscopy and urine cytology at 3 months, then every 3 months for 2 years, every 6 months until 5 years and then yearly, with CT urography and chest CT every 6 months for 2 years and then yearly (weak recommendations).

WHAT THE GUIDELINES SAY · NATIONAL COMPREHENSIVE CANCER NETWORK VERSION 5.2024

For pT0 to pT1 tumors, cystoscopy every 3 months for the first year and then at longer intervals; after kidney-sparing surgery, add upper tract imaging or ureteroscopy every 3 to 12 months.

Living with and after this cancer

Most people live well with one healthy kidney, but after nephroureterectomy overall kidney function is lower than before. Your care team will keep an eye on kidney function in follow-up, and it is worth

telling any doctor who prescribes you new medicines that you have one kidney. If you kept your kidney after kidney-sparing treatment, the repeated scopes and scans can feel like a heavy schedule.

Stopping smoking is one of the most useful things you can do. The EAU guideline links smoking at diagnosis with a higher chance of the cancer coming back and states that quitting improves cancer control. If you use herbal remedies, ask your care team about them, since remedies containing aristolochia are a recognized cause of this cancer.

If you have Lynch syndrome, or tests suggest it, the diagnosis matters for your whole family. The EAU guideline recommends genetic counseling for the family and checks for other Lynch-related cancers, such as colorectal and endometrial cancer, alongside your urology follow-up. Relatives can then decide about their own testing.

Living with the possibility of recurrence is stressful. Feeling anxious around each cystoscopy or scan is common and understandable. Tell your team if worry, low mood or sleep problems are affecting your life; support from counselors, support groups and family can help.

Clinical trials and second opinions

Because UTUC is uncommon, many questions remain open. The EAU guideline lists several, including whether newer urine tests can replace cytology, whether ureteroscopy or CT is better for checking the treated side after kidney-sparing treatment, whether drugs instilled into the upper tract allow lighter follow-up, whether a bladder instillation helps after ureteroscopy, and how to follow people with Lynch syndrome. The NCCN guideline states that the best management of any patient with cancer is in a clinical trial and that participation is especially encouraged.

Ask your team whether a trial is open that fits your situation. You can also search the public registry at [ClinicalTrials.gov](https://clinicaltrials.gov). A second opinion is a normal part of care for an uncommon cancer, especially when you are weighing kidney-sparing treatment against removing the kidney, and a good team will welcome it.

When to contact your care team

Between visits, some symptoms deserve a prompt call. Your team will give you specific instructions after each procedure or treatment; the list below is a general guide and does not replace their advice. In an emergency, call 911 or go to the nearest emergency department.

- New or returning blood in the urine, especially if you are passing clots or cannot pass urine.
- Fever, chills or burning with urination after ureteroscopy, a stent, a nephrostomy or a drug instillation, which can signal an infection.
- New or worsening pain in the side or back, which can mean the ureter is blocked.
- Much less urine than usual, swelling of the legs, or unusual tiredness, which can reflect kidney problems.
- Unexplained weight loss, a persistent cough, new bone pain or night sweats.

- During chemotherapy or immunotherapy: fever, diarrhea, shortness of breath, rash, or any new symptom your team asked you to report.

Questions patients often ask

Is this the same as kidney cancer?

Not quite. The usual kind of kidney cancer, renal cell carcinoma, starts in the kidney's filtering tissue. Upper tract urothelial cancer starts in the lining of the kidney's drainage system and the ureter, and it behaves much more like bladder cancer. The two are treated differently.

Why do I need cystoscopies if the cancer was in my kidney or ureter?

Because the bladder is the most common place for a new tumor afterwards. According to the EAU guideline, 22 to 47% of people develop a bladder tumor after treatment for UTUC. Regular cystoscopy finds these early, when they are easier to treat.

Can I keep my kidney?

For low-risk tumors, both guidelines support kidney-sparing treatment as the preferred approach, with survival similar to removing the kidney. For high-risk tumors, removing the kidney and ureter is standard, but kidney-sparing treatment may be considered if you have only one kidney, cancer on both sides or poor kidney function. Your team will talk through the trade-offs with you.

Why is part of my bladder removed with the kidney?

The lowest part of the ureter passes through the bladder wall, and cancer often comes back there. Removing a small cuff of bladder around the ureter opening takes out all of the ureter. The EAU guideline reports that incomplete removal of this cuff raises the risk of bladder recurrence.

Will I need chemotherapy?

Not everyone does. Chemotherapy may be offered before surgery for higher stage or grade tumors, or after surgery if the final pathology shows the cancer reached the muscle or beyond, or the lymph nodes. Your team will weigh the benefit against side effects and your kidney function.

Why does kidney function affect chemotherapy?

Cisplatin, the most effective chemotherapy drug for this cancer, needs good kidney function. After one kidney is removed, overall kidney function drops, and some people can no longer receive it. This is why the NCCN guideline prefers giving chemotherapy before surgery in suitable patients.

What is the dose of chemotherapy in my bladder after surgery?

It is a single dose of a drug such as mitomycin C placed in the bladder through a catheter, usually within days after nephroureterectomy. Randomized trials show it lowers the chance of a new bladder tumor, and side effects are very uncommon.

Should my family be tested for Lynch syndrome?

If you are under 60, have had another Lynch-related cancer, or have close relatives with such cancers, your team may recommend genetic testing. If you test positive, the EAU guideline recommends genetic counseling for your family so relatives can decide about their own testing.

Is robotic surgery an option for nephroureterectomy?

Yes, the EAU guideline says a robotic approach can be considered, with recent data suggesting similar cancer outcomes to open and laparoscopic surgery and a shorter hospital stay than laparoscopy. For tumors that look locally advanced or have spread to lymph nodes, it favors open surgery. Your surgeon will explain which approach suits your tumor.

How long will follow-up last?

At least 5 years for most people, and longer after kidney-sparing treatment or for high-risk disease. Checks are most frequent in the first two years and then spread out. Your team will give you a written schedule.

Glossary

Urothelium

The lining of the urinary tract, from the inside of the kidney to the urethra.

Renal pelvis

The funnel-shaped space inside the kidney where urine collects before draining into the ureter.

Calyx (plural calyces)

Small cup-shaped spaces inside the kidney that collect urine and drain into the renal pelvis.

Ureter

The narrow tube that carries urine from each kidney to the bladder.

UTUC

Upper tract urothelial carcinoma: urothelial cancer of the renal pelvis, calyces or ureter.

Carcinoma in situ (CIS)

Flat, high-grade cancer cells confined to the surface lining.

Grade

How abnormal the cancer cells look under a microscope; urothelial tumors are called low grade or high grade.

Hydronephrosis

Swelling of the kidney's drainage system because urine flow is blocked.

CT urography

A CT scan with contrast dye timed to show the kidneys, ureters and bladder.

Urine cytology

A microscope test that looks for cancer cells in urine, either voided or collected directly from the upper tract.

Cystoscopy

A look inside the bladder with a thin camera passed through the urethra.

Ureteroscopy

A procedure using a thin camera passed up into the ureter and kidney to see, sample or treat tumors.

Kidney-sparing surgery

Treatment that removes or destroys the tumor while keeping the kidney, such as ureteroscopic ablation or segmental ureterectomy.

Radical nephroureterectomy

Surgery that removes the kidney, the whole ureter and a small cuff of bladder around the ureter opening.

Bladder cuff

The small piece of bladder wall around the ureter opening, removed with the ureter to lower the risk of recurrence.

Distal ureterectomy

Removal of the lower part of the ureter, with the remaining ureter reattached to the bladder.

Lymph node dissection

Removal of lymph nodes that drain the area, to check for and remove cancer spread.

Mitomycin gel

A chemotherapy gel placed into the renal pelvis to treat low-grade tumors; also called UGN-101.

Intravesical instillation

Placing a drug directly into the bladder through a catheter.

Neoadjuvant therapy

Treatment given before surgery.

Adjuvant therapy

Treatment given after surgery to lower the chance of the cancer returning.

Lynch syndrome

An inherited condition affecting DNA repair genes that raises the risk of colorectal, endometrial, upper tract urothelial and other cancers.

Aristolochic acid

A plant chemical found in some herbal remedies that damages the kidneys and can cause upper tract cancer.

Imperative indication

A situation, such as a single kidney or cancer on both sides, where removing a kidney would seriously threaten kidney function.

Sources

These are the professional guidelines this page is written from. They are copyrighted by their societies and are linked here rather than copied. Where a society publishes a free patient version, that link is included too.

- **European Association of Urology Limited update, March 2023:** EAU Guidelines on Upper Urinary Tract Urothelial Carcinoma
<https://uroweb.org/guidelines/upper-urinary-tract-urothelial-cell-carcinoma>
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- **National Comprehensive Cancer Network Version 5.2024:** NCCN Clinical Practice Guidelines in Oncology: Bladder Cancer (including Upper GU Tract Tumors)
<https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1417>
<https://www.nccn.org/patientresources/patient-resources/guidelines-for-patients>
- **European Association of Urology 2023:** EAU Guidelines on Non-muscle-invasive Bladder Cancer
<https://uroweb.org/guidelines/non-muscle-invasive-bladder-cancer>
<https://patients.uroweb.org/>

This guide is general education written from published clinical guidelines. It is not medical advice, does not describe any individual's care, and does not replace the judgment of your own care team. Guidelines change; the versions used are listed above.