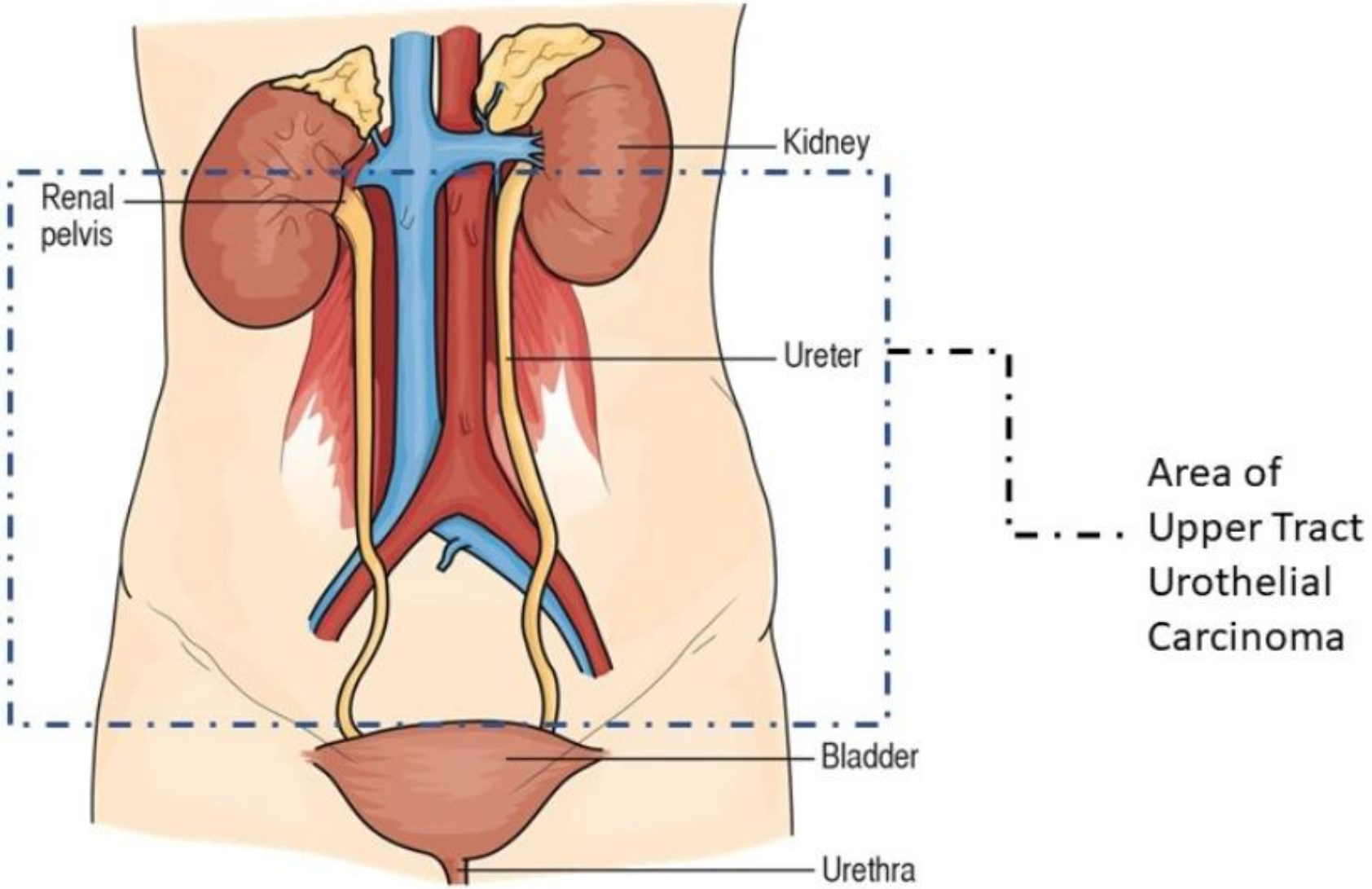
Upper urinary tract urothelial carcinoma (UTUC)

(住院醫師教案)

李祥生

The urinary system



UTUC-Epidemiology

- Urothelial carcinomas are the fourth most common tumours.
- Lower (bladder and urethra)
  Upper (pyelocaliceal cavities and ureter).
- Bladder tumours :90–95% UCs
  UTUCs :5–10% of UCs
- Pyelocaliceal tumours : ureteral tumours = 2:1.
  17% UTUC- concurrent BCa.
- 22–47% UTUC: Recurrence in the bladder
- 2–6% UTUC: contralateral upper tract.

UTUC-Epidemiology

- 60% of UTUCs are invasive at diagnosis compared with 15–25% of bladder tumours.

- UTUCs have a peak incidence in individuals aged 70–90 yr and are three times more common in men.

UTUC-Epidemiology

- Familial/hereditary UTUCs are linked to hereditary nonpolyposis colorectal carcinoma. (HNPCC syndrome) (lynch syndrome)
- Patients identified at high risk for HNPCC syndrome should undergo DNA sequencing for patient and family counselling.

UTUC-Risk factors

- Tobacco exposure
- Occupational exposure: carcinogenic aromatic amines, benzidine and B-naphthalene.
- Aristolochic acid: Chinese herbs
- Blackfoot disease, arsenic exposure in drinking water-Southwest coast of Taiwan.

UTUC-Histology and classification

- Squamous cell carcinoma of the upper urinary tract represents <10% of pyelocaliceal tumours and is even rarer within the ureter.
- Squamous cell carcinoma -chronic inflammatory diseases and infections (stone).
- Micropapillary and sarcomatoid carcinomas, and lymphoepithelioma.

UTUC-Staging and classification systems

- Non-invasive papillary tumors:
  papillary urothelial tumors of low malignant potential
  low- grade papillary UC
  high-grade papillary UC
- Flat lesions: carcinoma in situ
- invasive carcinoma
- Histologic variants confers an adverse risk factor.

Table 1 – TNM classification 2017 for upper tract urothelial carcinoma [18]

T—primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
	Ta Noninvasive papillary carcinoma
	Tis Carcinoma *in situ*
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscularis
T3	Tumour invades beyond muscularis into peripelvic fat or renal parenchyma (renal pelvis) Tumour invades beyond muscularis into periureteric fat (ureter)
T4	Tumour invades adjacent organs or through the kidney into perinephric fat
N—regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node $\leq$2 cm in the greatest dimension
N2	Metastasis in a single lymph node $>$2 cm, or multiple lymph nodes
M—distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

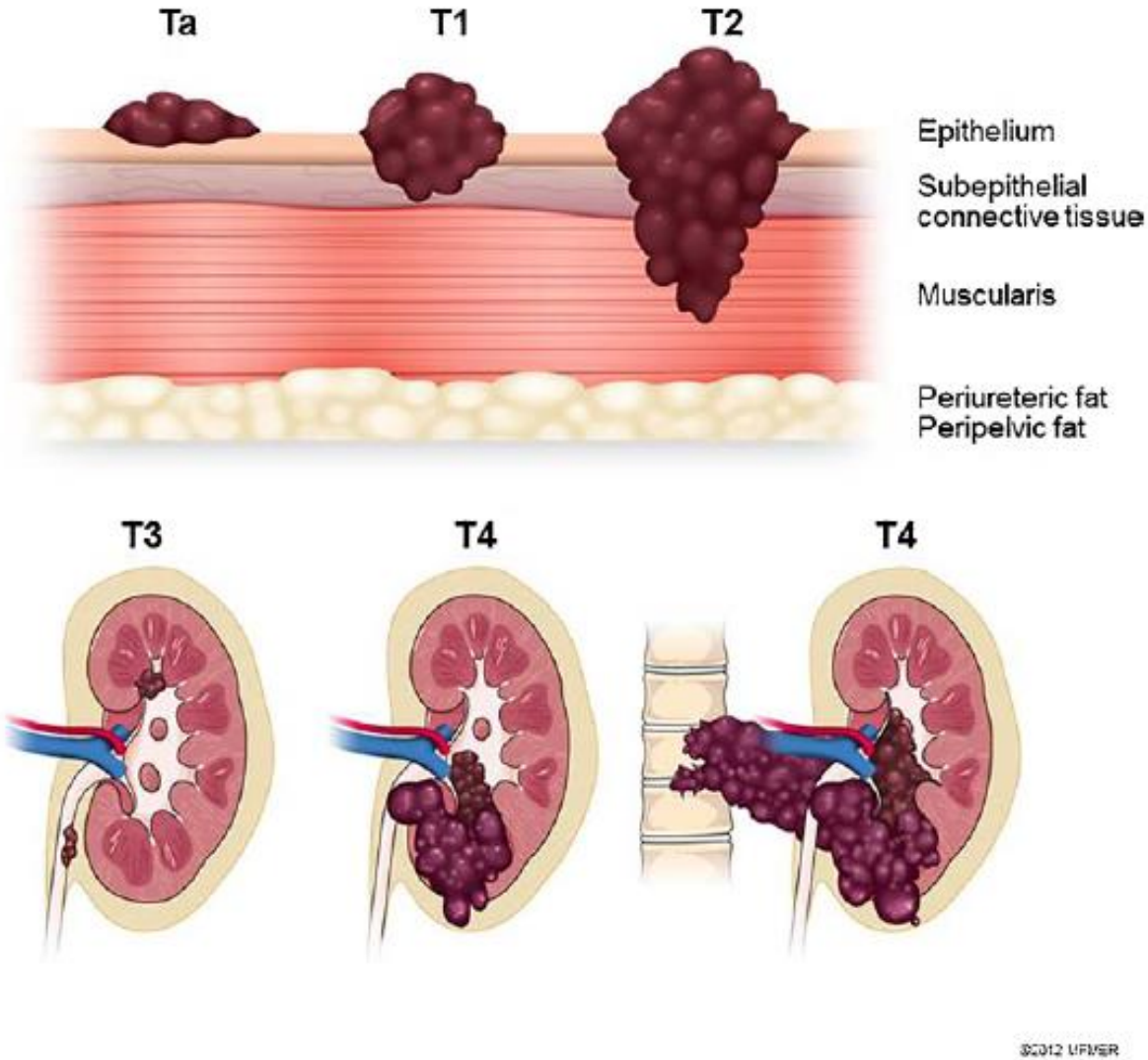


Fig. 1. Upper tract T staging. Ta (in situ) cancer is typically not apparent on imaging, and is detected endoscopically. T1 is superficial tumor, T2 muscle invasive. Locally advanced extension through the ureteral wall to the periureteral/pericalyceal fat is stage T3. Invasion of the renal parenchyma or any retroperitoneal structures beyond fat is stage T4. Modified from Reference 2.

UTUC-Staging

Renal pelvic pT3

pT3a: microscopic infiltration of the renal parenchyma.

pT3b: macroscopic infiltration or invasion of peripelvic adipose tissue.

pT3b UTUC has a higher risk of disease recurrence after RNU.

UTUC-Symptoms

- Gross or micro-hamaturia (70–80%).
- Flank pain (20%), a lumbar mass (10%).
- Systemic symptoms (including anorexia, weight loss, malaise, fatigue, fever, night sweats, or cough) –metastatic status.

UTUC-Diagnosis

- Computed tomography (CT) urography has the highest diagnostic accuracy of the available imaging techniques. The sensitivity of CT urography for UTUC is 0.67–1.0 and specificity is 0.93–0.99.
- Epithelial “flat lesions” without mass effect or urothelial thickening are generally not visible with CT.
- The secondary sign of hydronephrosis is associated with advanced disease and poor oncological outcome.
- The presence of enlarged lymph nodes is highly predictive of metastases in UTUC .

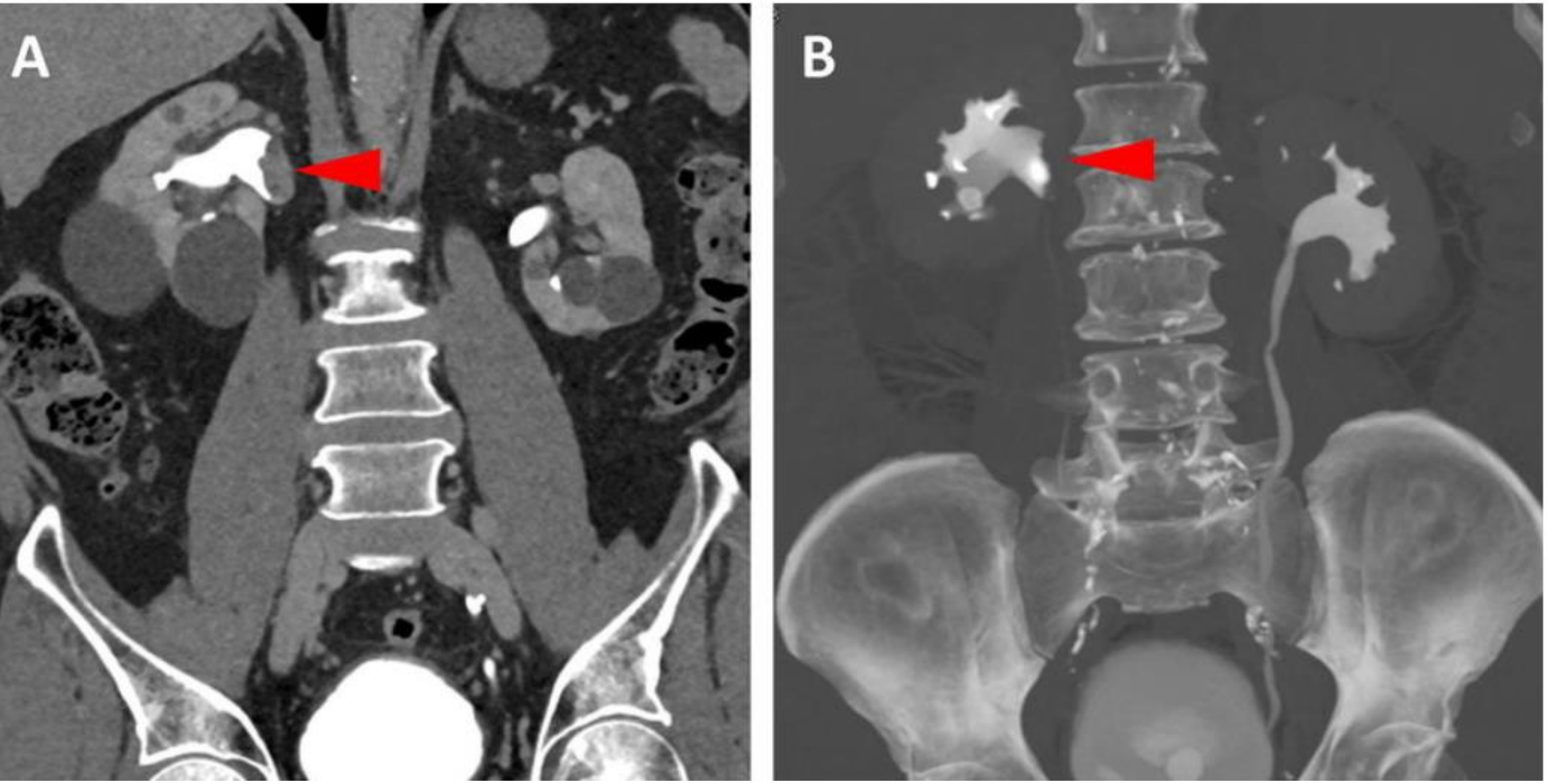
UTUC-Diagnosis

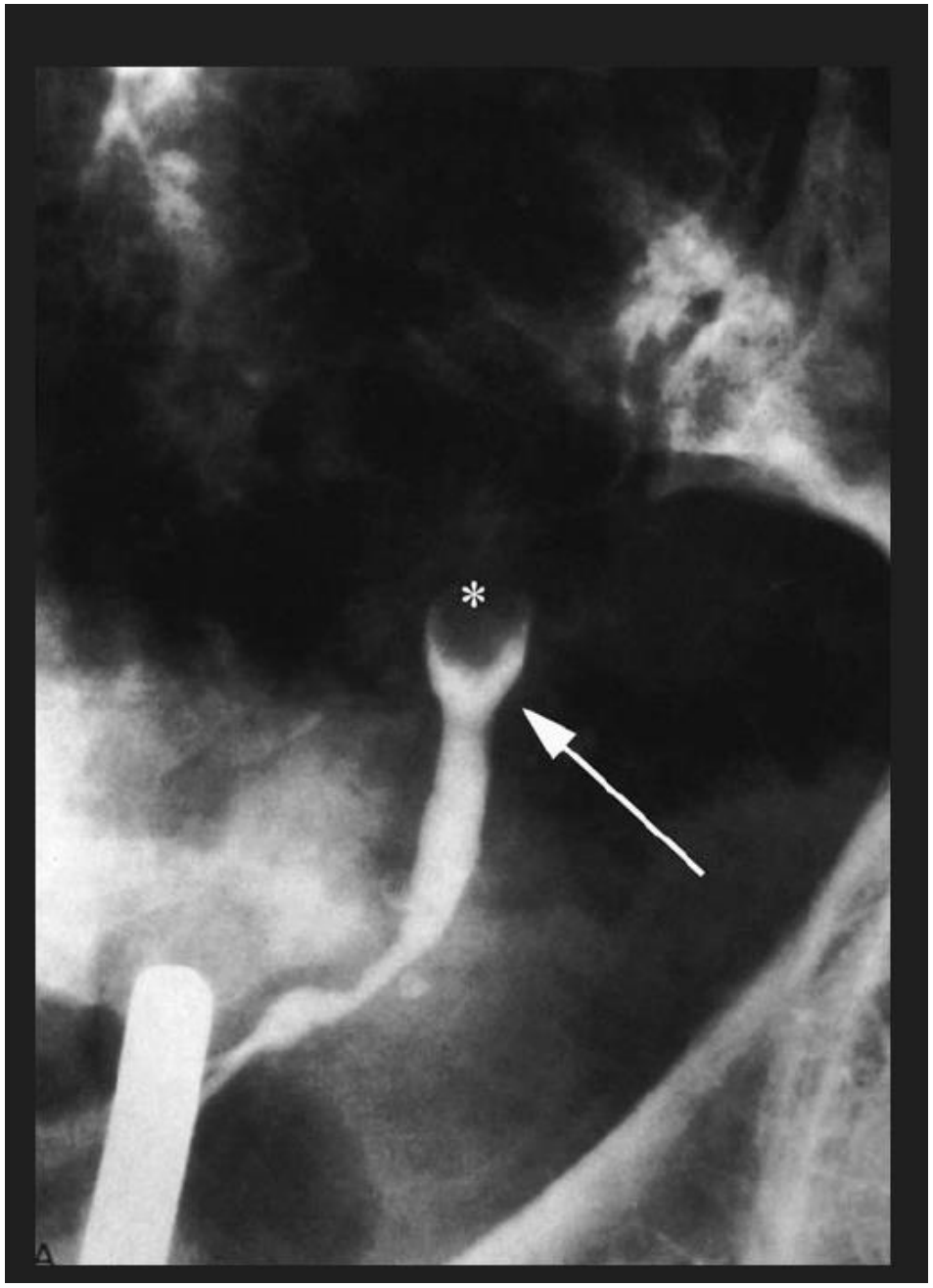
- Magnetic resonance (MR) urography is indicated in patients who cannot undergo CT urography, usually when radiation or iodinated contrast media are contraindicated.
- The sensitivity of MR urography is 0.75 after contrast injection for tumors <2 cm.
- CT urography is generally preferred to MR urography for diagnosing and staging UTUC.

UTUC-Diagnosis

- Positive urine cytology is suggestive of UTUC when bladder cystoscopy is normal.
- Cytology is less sensitive for UTUC than bladder tumors and should be performed in situ in the renal cavities.
- Retrograde ureteropyelography remains an option to detect UTUCs.

FIGURE 38-1 A 72-year-old man presenting with visible haematuria. (A) Axial section of an excretory-phase CT urogram showing a filling defect in the left renal pelvis, white arrow, which was a urothelial carcinoma, G2 pT1. (B) A coronal reconstruction of the left renal pelvis urothelial carcinoma. (C) The extensive nature of the tumour at retrograde ureteropyelography.


A
B



Goblet sign (ureter)

UTUC-Diagnosis

- Diagnostic ureteroscopy. Flexible ureteroscopy is used to visualize the ureter, renal pelvis, and collecting system and biopsy suspicious lesions.
- Ureteroscopic biopsies can determine tumor grade in 90% of cases with a low false-negative rate, regardless of sample size.
- Undergrading may occur following diagnostic biopsy.

UTUC-Diagnosis

- Combining ureteroscopic biopsy grade, imaging findings such as hydronephrosis, and urinary cytology may help in the decision-making process between radical nephroureterectomy (RNU) and kidney-sparing therapy.

Table 2 – Summary of evidence and guidelines for the diagnosis of upper tract urothelial carcinoma

Summary of evidence	LE
The diagnosis of upper tract urothelial carcinoma depends on computed tomography urography and ureteroscopy.	2
Selective urinary cytology has high sensitivity in high-grade tumours including carcinoma *in situ*.	3
Recommendations	**GR**
Perform urinary cytology as part of a standard diagnostic workup.	A
Perform a cystoscopy to rule out concomitant bladder tumour.	A
Perform a computed tomography urography for upper tract evaluation and for staging.	A
Use diagnostic ureteroscopy and biopsy in cases where additional information will impact treatment decisions.	C

GR = grade of recommendation; LE = level of evidence.

UTUC-Prognostic factors

- UTUCs that invade the muscle wall usually have a very poor prognosis.
- The 5 yr specific survival:

<50% for pT2/pT3

<10% for pT4.

UTUC-Prognostic

- Age and sex: no longer considered an independent prognostic factor influencing UTUC mortality
- Ethnicity: African-American: worse outcomes
- Tobacco consumption: increased recurrence and mortality.
- Tumor location: patients with ureteral and/or multifocal tumors seem to have a worse prognosis than renal pelvic tumors.

Postoperative factors

- Stage and grade
- Lymph node involvement
- Lymphovascular invasion
- Surgical margins
- Pathological factors: necrosis, sessile. Concomitant CIS in organ-confined UTUC and a history of bladder CIS are associated with a higher risk of recurrence and cancer-specific mortality.

UTUC-Bladder recurrence after RUN

- Patient-specific factors: male gender, previous BCa, smoking and preoperative chronic kidney disease
- Tumor-specific factors: positive preoperative urinary cytology, ureteral location, multifocality, invasive pT stage, and necrosis
- Treatment-specific factors: laparoscopic approach, extravesical bladder cuff removal, and positive surgical margins.

Table 3 – Summary of evidence and guidelines for prognosis

Summary of evidence	LE
Age, sex, and ethnicity are no longer considered as independent prognostic factors.	3
Primary recognised postoperative prognostic factors are tumour stage and grade, extranodal extension, and lymphovascular invasion.	3

Recommendations	LE	GR
Use microsatellite instability as an independent molecular prognostic marker to help detect germline mutations and hereditary cancers.	3	C
Use the American Society of Anesthesiologists score to assess cancer-specific survival following surgery.	3	C

GR = grade of recommendations; LE = level of evidence.

Risk stratification

to identify those who are more suitable for kidney sparing treatment rather than radical extirpative surgery

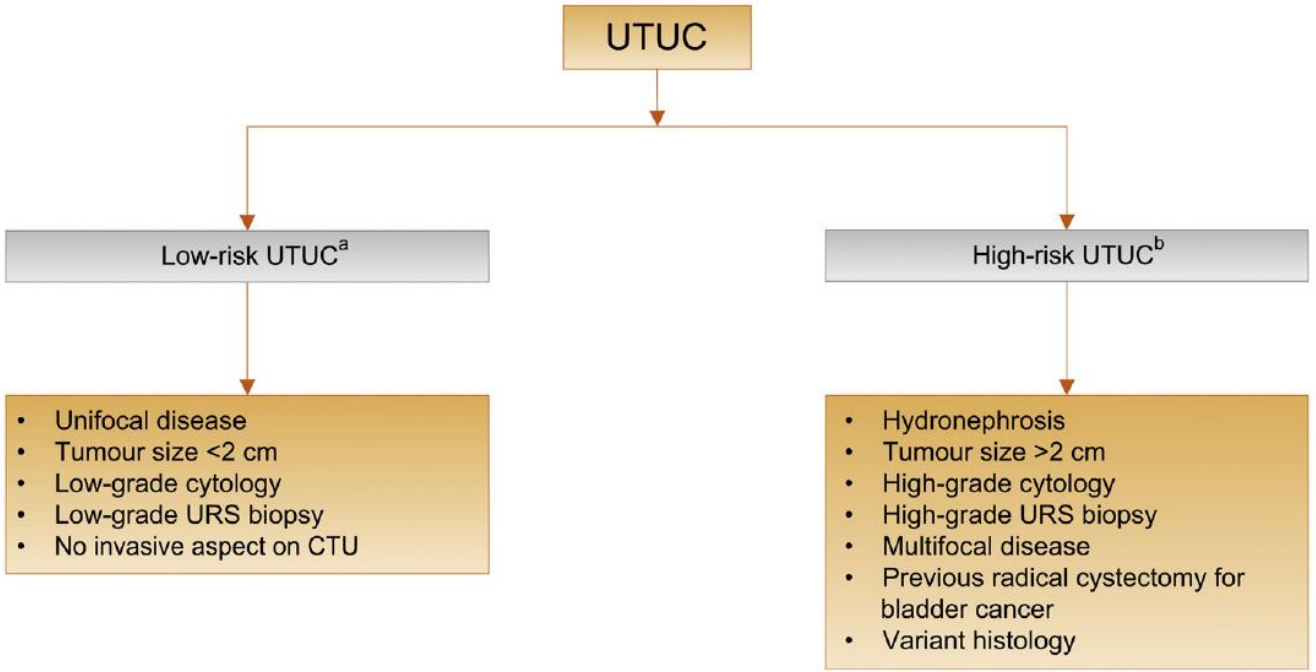


Fig. 3 – Risk stratification of upper urinary tract urothelial carcinoma. CTU = computed tomography urography; URS = ureteroscopy; UTUC = upper urinary tract urothelial carcinoma. [a] All these factors need to be present. [b] Any of these factors need to be present.

Management-Localized disease

- Kidney-sparing surgery (KSS) for low-risk UTUC allows sparing the morbidity associated with radical surgery, without compromising oncological outcomes and kidney function.
- In select patients with serious renal insufficiency or solitary kidney.

Table 4 – Guidelines for kidney-sparing management of upper tract urothelial carcinoma

Recommendations	GR
Offer kidney-sparing management as primary treatment option to patients with low-risk tumours and two functional kidneys.	C
Offer kidney-sparing management in patients with solitary kidney and/or impaired renal function, provided that it will not compromise the oncological outcome. This decision will have to be made on a case-by-case basis, engaging the patient in a shared decision-making process.	C
Offer a kidney-sparing approach in high-risk cancers for distal ureteral tumours and in imperative cases (solitary kidney and/or impaired renal function).	C
Use a laser for endoscopic treatment of upper tract urothelial carcinoma.	C

GR = grade of recommendation.

Management-Localized disease

- Endoscopic ablation can be considered in patients with clinically low-risk cancer in the following situations
- 1. Laser generator and pliers available for biopsies.
- 2. In case a flexible (rather than a rigid) ureteroscope is available
- 3. The patient is informed of the need for early (second
- look), closer, more stringent, surveillance
- 4. Complete tumor resection or destruction can be achieved

A risk of understaging and undergrading remains with endoscopic management.

Management-Localized disease

- Percutaneous management : low-risk UTUC in the renal pelvis.
- This may be offered for low-risk tumors in the lower caliceal system that are inaccessible or difficult to manage by flexible ureteroscopy.
- A risk of tumor seeding remains with a percutaneous access.

- Segmental ureteral resection with wide margins provides adequate pathological specimens for staging and grading while preserving the ipsilateral kidney.

Management-Localized disease

- Antegrade instillation of bacillus Calmette-Guérin (BCG) vaccine or mitomycin C in the upper urinary tract by percutaneous nephrostomy (after complete tumor eradication) is feasible after kidney-sparing management or for treatment of CIS.

Management-Localized disease

- Open radical nephroureterectomy with bladder cuff excision is the standard for high-risk UTUC, regardless of tumor location .
- Resection of the distal ureter and its orifice is performed because there is a considerable risk of tumor recurrence in this area.

Management-Localized disease

Laparoscopic RNU.

- 1. Avoid entering the urinary tract.
- 2. Avoid direct contact between instruments and the tumor.
- 3. Laparoscopic RNU must take place in a closed system. Avoid morcellation of the tumor and use an endobag for tumor extraction.
- 4. The kidney and ureter must be removed en bloc with the bladder cuff.
- 5. Invasive or large (T3/T4 and/or N+/M+) tumors are contraindications for laparoscopic RNU until proved otherwise.

Management-Localized disease

Lymph node dissection (LND)

- LND appears to be unnecessary in cases of TaT1 UTUC because lymph node retrieval is reported in only 2.2% of T1 versus 16% of pT2–4 tumors.

Management-Localized disease

- Adjuvant bladder instillation. The rate of bladder recurrence after RNU for UTUC is 22–47%.
- Two prospective randomized trials have demonstrated that a single postoperative dose of intravesical chemotherapy (mitomycin C, pirarubicin) soon after surgery (<72 h) reduces the risk of bladder tumor recurrence within the 1st year post-RNU.

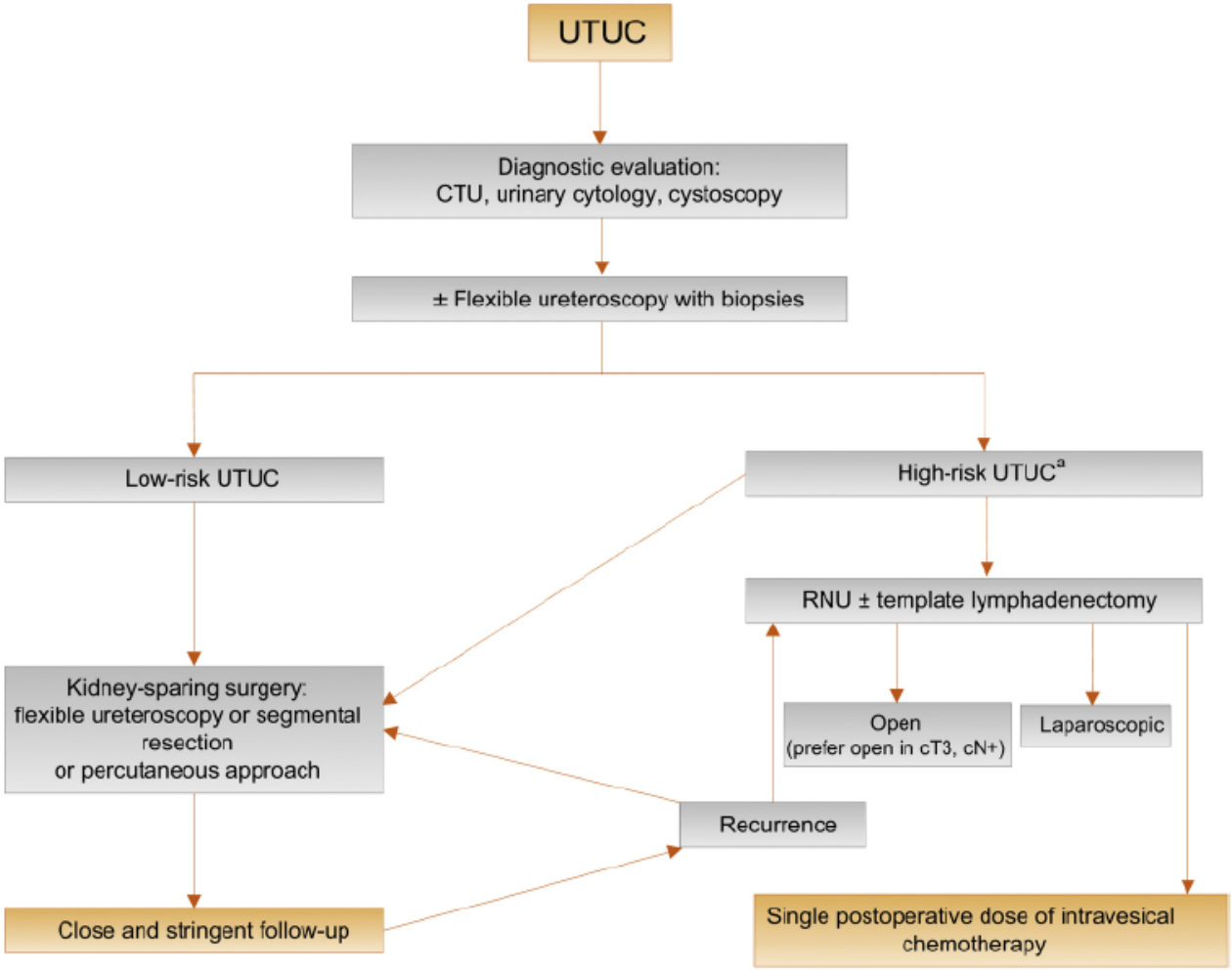


Fig. 4 – Proposed flowchart for the management of upper urinary tract urothelial cell carcinoma. CTU = computed tomography urography; RNU = radical nephroureterectomy; UTUC = upper urinary tract urothelial carcinoma. [a] In patients with solitary kidney, consider a more conservative approach.

Table 5 – Summary of evidence and recommendations for radical nephroureterectomy

Summary of evidence	LE
Radical nephroureterectomy is the standard in high-risk upper tract urothelial carcinoma, regardless of tumour location.	2
Open and laparoscopic approaches have equivalent efficacy and safety in T1–2/N0 upper tract urothelial carcinoma.	2
Recommendations	**GR**
Perform radical nephroureterectomy in the following situations: 1. Suspicion of infiltrating upper tract urothelial carcinoma on imaging 2. High-grade tumour (urinary cytology) 3. Multifocality (with two functional kidneys) 4. Noninvasive but large (>2 cm) upper tract urothelial carcinoma	B
Technical steps of radical nephroureterectomy	
Remove the bladder cuff.	A
Perform a lymphadenectomy in invasive upper tract urothelial carcinoma.	C
Offer postoperative bladder instillation to lower the bladder recurrence rate.	B

GR = grade of recommendation; LE = level of evidence.

Management-Advanced disease

- Radical nephroureterectomy. There is no oncological benefit for RNU alone in patients with metastatic UTUC except for palliative considerations.

Management-Advanced disease

- Systemic chemotherapy. platinum-based combination chemotherapy is expected to be efficacious in UTUC.
- Comorbidities and impaired renal function after radical surgery may reduce survival due to chemotherapy-related toxicity, particularly nephrotoxicity.
- In a select cohort of patients fit to receive systemic chemotherapy for metastatic UTUC, there was an OS benefit to combine chemotherapy and RNU versus chemotherapy alone.
- A recent study has assessed a clear OS benefit in patients who received adjuvant chemotherapy versus observation after RNU for pT3/T4 and/or pN+ UTUC.

Management-Advanced disease

- Radiotherapy is no longer relevant, either alone or as an adjunct to chemotherapy.

Management- Follow-up

- Surveillance regimens are based on cystoscopy and urinary cytology for >5 yr .
- When KSS is performed, the ipsilateral upper urinary tract requires careful follow-up due to the high risk of disease recurrence.
- Despite endourological improvements, follow-up after kidney-sparing management is difficult, and frequent, repeated endoscopic procedures are necessary.

Management- Follow-up

Table 6 – Summary of evidence and follow-up of UTUC

Summary of evidence	LE
Follow-up is more frequent and stricter in patients who have undergone kidney-sparing treatment compared to radical nephroureterectomy.	3
Recommendations	**GR**
After radical nephroureterectomy, >5 yr	
Noninvasive tumour	
Perform cystoscopy/urinary cytology at 3 mo, and then annually.	C
Perform computed tomography urography every year.	C
Invasive tumour	
Perform cystoscopy/urinary cytology at 3 mo, and then annually.	C
Perform computed tomography urography every 6 mo for 2 yr, and then annually.	C
After kidney-sparing management, >5 yr	
Perform urinary cytology and computed tomography urography at 3 and 6 mo, and then annually.	C
Perform cystoscopy, ureteroscopy, and cytology *in situ* at 3 and 6 mo, and then every 6 mo for 2 yr, and then annually.	C

GR = grade of recommendation; LE = level of evidence; UTUC = upper urinary tract urothelial carcinoma.