Upper Urinary Tract Urothelial Cancer

Demographics

Uncommon
5% of all urothelial tmours
5% of all renal tumours
5% bilateral (synchronous or metachronous)
Peak incidence 10/100,000 population
Peak age 75-79 yrs
Male:female – 2:1
White:black – 2:1
More common in industrialised countries – pocket of high incidence in Balkans

Aetiology

Smoking – increased RR x7
Analgaesic abuse
- Phenacetin most commonly described – increased RR 3.6x. Also associated with codeine, paracetamol and salyicylates
- Associated papillary necrosis on imaging associated with risk increase x7, which is synergistic with phenacetin abuse (20x)
- Characteristic finding of thickened basement membrane on histology – should alert physician to need for careful surveillance of contralateral kidney.

Occupation
- Chemical/petroleum/plastics/coal/tars/asphalt/aniline dyes – increased RR x4-5

Heredity
- Lynch syndrome – young women; familial non-polyposis colon tumours/extracolonic lesions including UUT tumours

Balkan nephropathy
- Familial but not obviously inherited
- In some families increased RR x 100+
- Degenerative interstitial nephropathy and UUT TCC
- Tumours typically low-grade, bilateral and multifocal

NB. Coffee consumption – not associated when smoking controlled for.

Pathology

<u>Molecular</u>
Many molecular events shared with bladder cancer. Typically loss/inactivation of tumour suppressor genes predominate:

Chromosome 9	p19 and p16	a/w early low grade/stage lesions
Chromosome 17	p53	a/w progression from low – high grade disease
Chromosome 13q	RB1 gene	a/w invasion/mets

Many other markers investigated (MSI, p27, surviving). Only E-cadherin appears to be independently prognostic.

Microscopic

UUT tumours shown to progress through hyperplasia – dysplasia – CIS
Inverted papilloma associated with ~ 18% incidence of malignancy (grainger 1990) – therefore surveillance recommended
Urothelial tumours of the UUT (and LUT) display **'clonal expansion'.** Two major theories:

- Monoclonality – single genetically transformed cell which 'seeds' urothelium
- Field change – exposure to specific carcinogen leads to identical genetic changes in susceptible cells throughout urothelium.

Most evidence derived from bladder cancer, supporting monoclonality. However it is now known that a significant proportion of multifocal cancers are are derived from different clones (Hafner 2002)
Vast majority of tumours TCC: small proportion of squamous (stones) and adenocarcinomas.

TCC	90% +	
SCC	1-7%	[chronic inflammation/analgaesics – usually renal pelvis]
Adeno	<1%	[obstruction, inflammation, calculi

Macroscopic/spread

Layers: urothelium, lamina propria, 2/3 layers of smooth muscle, serosa
Upper two-thirds of ureter – 2 layers of smooth muscle: inner loose-coiled spiral (longitudinal); outer tight-coiled spiral (circular). In distal third, an additional outer layer of loose-coiled spiral muscle merges with outer coat of bladder.

Distribution*:	5%	proximal
	25%	mid-ureter
	70%	distal

* thought to be due to seeding. Risk of subsequent bladder cancer ~50% at 5 yrs.

Overall 55-75% of UUT cancers low grade and low stage
85% papillary, 15% sessile
T1/T2 in 50% papillary and 80% sessile tumours – overall 50-60% superficially or muscle invasive
Lymph node spread to para-aortic/paracaval/ipsilateral common iliac and pelvic nodes
Haematogenous spread to liver lung and bone

Staging

Box 1 The American Joint Committee on Cancer (AJCC) TNM Clinical Classification for Renal Pelvis and Ureteral Tumors.[107]

Primary tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Ta Papillary noninvasive carcinoma
Tis Carcinoma *in situ*
T1 Tumor invades subepithelial connective tissue
T2 Tumor invades the muscularis
T3 Tumor invades into periureteric fat, peripelvic fat, or the renal parenchyma
T4 Tumor invades adjacent organs, or through the kidney into the perinephric fat

Regional Lymph Nodes (N)

Nx Regional nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single lymph node, 2 cm or less in greatest dimension
N2 Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, none more than 5 cm in greatest dimension
N3 Metastasis in a lymph node, more than 5 cm in greatest dimension

Distant Metastasis (M)

Mx Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

<u>Prognostic factors</u>

Location; Renal pelvis tumours believed to do better cf. ureteric tumours.
renal parenchyma may act as barrier. Large multicentre series (n=611) eeport 5YS of 54% and 24% for T3 tumours of the renal pelvis and ureter respectively (Guinan 1992)

Stage Ta 100% 5YS
Tis 100% 5YS
T1 97% 5YS
T2 73% 5YS
T3 41% 5YS (Hall 1998)

Grade
Ash's modification of Broder's classification for TCC originally used
Supplanted by WHO (grades 1-3; Mostofi)
Some centres using PUNLMP or Epstein (low/high grade)

Other factors associated with the development of metastases:

Renal parenchymal invasion	95% mets	
Vascular invasion	83% mets	
Lymphatic invasion	77% mets	(Davis 1987)

Presentation

Haematuria	56-98%
Flank pain	30%
Asymptomatic	15%

Advanced cases (mass, haematuria, wt loss, anaorexia) relative minority
NB. Almost all cases present in life. Incidental autopsy finding very rare

Investigation/imaging

CT urogram

Sensitivity 100%; specificity 60% NPV 100% (Caoili 2002). Problems with small filling defects < 5mm (volume averaging) and increased radiation. Also superior to IVU/USS for staging: Correct 60%, understaged 16%, overstaged 24% (Scolieri 2000).

Contrast study diagnosis:

- Filling defect 50-75%*
- Obstruction
- Non-visualisation
- Enhancing lesion

*DD – blood clot, stone, bowel gas, sloughed papilla, fungus ball.
TCC ~ average 46 HU cf. >100HU for renal stone; therefore pre-contrast CT scan helpful. Stones also don't enhance!

Retrograde pyelography

Useful for non-filled/obstructed calyx and for further investigation of radiolucent, non-calcified filling defects.
75% accurate (Murphy 1981) – increased to 90% when combined with ureteroscopy (Blute 1989)

Ureteroscopy and biopsy

Useful in patients in whom diagnosis is unclear or those who may be considered for endoscopic treatment (eg. Older patient with pre-existing renal dysfunction & negative cytology) – not required for patients in whom the diagnosis is straightforward and where the procedure will not change the management (i.e young fit patient with normal renal function and positive cytology)
Grade correlation of biopsy with final specimen ~90% (Keeley 1997) cf. visual assessment of grade by urologist of 70% (Hakim 2004).
Fresh specimens required for accurate prediction
Specimens too small to accurately predict stage – grade however appears to be very useful in predicting stage: 85% G1/G2 lesions are Ta/T1; ~70% G3 lesions T2/T3 (Heney 1981; Keeley 1997).

Cytology

Sensitivity of **voided urine cytology** for UUT TCC

Grade 1	20%	
Grade 2	45%	
Grade 3	75%	(Murphy 1982; Konety 2001)

Equivalent results for ureteric washings (saline best). Sp/Sn of ~ 90% with ureteric brushings but occasional haemorrhage (Blute 1981)

Cystoscopy
Mandatory. Usually performed as part of UUT Ix. If diagnosis on CT book flexi.

Endoscopic Management
Indications:

- Anatomic or functional solitary kidney
- Bilateral UUT TCC
- Baseline renal insufficiency
- Significant co-morbidity
- Selected patients with normal contralateral kidney with low-volume low-grade disease

Retrograde ureteropyeloscopy and resection
Low volume ureteric and pelvic tumours – limited by instrument size
Initial debulking using cold-cup forceps or basket, followed by laser to base
[Holmium:YAG – tissue penetration 0.5mm – good for ureter; Neodymium: YAG (yttrium-aluminium-garnet) 5-6mm – better for large lesions in relanl pelvis]

Complications:	Perforation	10%
	Stricture rate	5-13.5% (diathermy > laser)

Antegrade ureteropyeloscopy and resection
Large volume tumours of the renal pelvis/upper ureter
Better access to lower pole tumours, distorted anatomy and those with urinary diversions
Percutaneous access and Amplatz placement as per PCNL. Cold cup debulking or TUR. Laser/diathermy to base.
Complications:

- Bleeding
- Infection
- Pleural injury
- Electrolyte imbalance
- Tract seeding*

* Initially thought to be a significant risk, based on tumour biology and a few case reports, but not borne out by long-term, larger series (Clark PE 1999: 18 patients – no reported recurrences; Jarrett TW 1995; 30 kidneys – no recurrence) However in both series a majority of patients received BCG down nephrostomy tract post-op, which may have reduced recurrence.

Results of endoscopic management
Overall recurrence ~ 33% for renal pelvic and ureteral tumours (Tawfiek 1997 – combined analysis of 205 pts)
Most frequent site of recurrence bladder
Recurrence rate related to grade: 25% grade1; 50% for grade 2+
Studies comparing grade at biopsy vs. pathological stage at NU have shown that 15% have T1 disease – some have advocated endoscopic management of G2 disease in selcted patients only (unfit, solitary kidney etc.) However:
Initial endoscopic management does not appear to predict a worse outcome
Endoscopic management performed before nephroureterectomy does not affect subsequent post-op prognosis (Boojian 2005)

When percutaneous Rx alone considered:

Recurrence rate 30%; 5YS 80% (Roupret 2007)

No significant difference stage for stage cf. nephroureterectomy (Lee 1999)

What about adjuvant treatment after endoscopic resection?

Cumulative experience appears to favour adjuvant treatment (either via PCN or with JJ stent) but due to small numbers a prospective trial has not been performed. No trial to date has shown improvement in either recurrence rates ot survival. Orihuela reported significantly lower recurrence in those with BCG via PCN (16.6% vs. 80%) but untreated group had inexplicably high recurrence rates and susbsequent follow-up (Jarrett) showed no survival advantage.

Segmental Resection

Segmental Resection of renal pelvic tumours

Largely historical – supplanted by modern ureteroscopic/percutaneous techniques. Laparoscopy another alternative in those borderline for significant open surgery.

Local recurence rates 7-70% (Campbells)

Distal ureterectomy and re-implantation

Indicated for patients with high-grade, invasive or large distal ureteric tumours

Especially advantageous vs. nephroureterectomy in patients with borderline renal function who may require chemotherapy.

Crucial to exclude concurrent prx ureteric lesion – thus pre-procedure RPG or intra-operative flexible URS may be required (useful if complete obstruction caused by distal tumour)

Segmental ureterectomy and uretero-uretereostomy or ileal interposition generally not recommended.

Outcomes similar to NU for distal ureteric tumours: Combined figures from multiple trials indicate an overall local recurrence 10-25% (<5% for low grade low stage lesions) 5YS only 65% for T1 and 50% for T2.

Radical nephroureterectomy

With ipsilateral bladder cuff = gold standard

Removal of entire ureter crucial - risk of tumour recurrence in ureteric stump 33-75% (McCarron 1983)

Ipsilateral adrenalectomy originally described but unnecessary unless tumour superior or direct invasion suspected

Multiple approaches:

- Totally open
  - Flank + Gibson/Pfannenstiel/lower midline
  - Long midline – poor exposure to kidney, esp. on left
- Totally laparoscopic*
- Upper laparoscopic and lower open*

* depends upon attitude towards distal ureter

Management of distal ureter:

- Open BC excision: gold standard but adds time and morbidity.
- Transvesical vs. extravesical. Transvesical, typically thro' anterior

cystotomy recommended as allows easy circumcision of ureteric orifice with bladder cuff. Extravesical avoids second cystotomy but associated with retention of intramural ureter.
Endoscopic detachment: Originally described by McDonald (1952). Modified by Abercrombie in 1974. Previously thought to be associated with increased risk of tumour implantation. Large series however show no difference between open excision and endoscopic detachment for tumour recurrence rates, DSS or OS (Walton 2008). Not recommended for distal ureteric tumours.
Intussusception technique: Post-NU resection of distal ureter. Requires transection of ureter to complete manoeuvre. Failure rates almost 20% however (Giovansili 2004)
Transvesical laparoscopic: Gill and colleagues associated with a number of techniques designed to simulate open BC excision.

Lymphadenectomy
No evidence to support routine LND
May improve staging and precipitate earlier referral for chemotherapy
Proximal tumours: perihilar/paraaortic LND
Distal tumours: ipsilateral pelvic LND

Neoadjuvant and adjuvant chemotherapy
UUT urothelial tumours are chemosensitive
No large scale prospective clinical trials – most dataextrapolated from bladder cancer trials
Neoadjuvant chemo theoretically attractive:
- Good evidence from ABC in bladder cancer
- Early eradication of subclinical disease
- Better tolerability pre-op
- Ability to deliver higher doses pre-op (2 kidneys)

Role of adjuvant chemotherapy undefined
Adjuvant instillation:
ODMITC: Tim O'Brien. Closed, abstract only to date. Recurrence rate reduced with MMC at 10 days post-op from 26% to 17% at one year [9% absolute risk reduction, 35% relative risk reduction: NNT 10]. Awaiting formal report.

Outcomes following radical nephroureterectomy
Radical NU associated with improved recurrence-free and OS cf. simple nephrectomy (Zungri 1990)
Outcome related to stage and grade. Overall:

Stage	Ta	100% 5YS
	Tis	100% 5YS
	T1	97% 5YS
	T2	73% 5YS
	T3	41% 5YS
	T4	<5% 5YS (Hall 1998)

No apparent difference in outcomes for laparoscopic, laparoscopic hand-assisted and open. Laparoscopic better however in terms of patient cosmesis, hospital stay, post-op pain, cosmesis and convalescence:

Table 1 Comparative series of laparoscopic or hand-assisted laparoscopic versus open nephroureterectomy for upper-tract transitional cell carcinoma.

Series	Number of patients (laparoscopic/open)	EBL (ml)	OR time (min)	Hospital stay (days)	Follow-up (months)	Recurrence rate (%)[a]	Cancer-specific survival (%)
McNeill[78]	25/42	NR	165/165	9.1/10.7	32.9/42.3	NR	84/79
Seifman[79]	16/11	557/345	320/199	3.9/5.2	19.3/15.8	19/64	NR
Raman[80]	38/52	191/478	244/243	4.6/7.1	31.7/52.0	40/50	97/83
Roupret[81]	26/20	310/280	NR	4.0/9.0	78.0/69.0	54/20	90/62
Manabe[82]	58/166	NR	NR	NR	13.6/28.0	25/18	85/87
Gill[85]	42/35	242/696	222/282	2.3/6.6	11.1/34.4	23/37	97/87
Shalhav[86]	25/17	199/441	462/234	6.112	24.0/43.0	23/54	77/77

[a]All sites of recurrence (bladder, contralateral upper-tract, metastatic). Abbreviations: EBL, estimated blood loss; OR, operating room; NR, not reported.

Surveillance

Bladder cancers in 15-50% of patients post-op. Greatest incidence within 24 months of UUT surgery. Although usually lower grade and stage (60%) a significant proportion develop high-grade bladder cancer.
Metachronous contralateral UUT tumour 6% (Kang 2003)
Development of metastasis amenable to palliative chemotherapy evidence from other tumours that volume of metastasis predictor of both response to chemotherapy and overall survival)
Therefore:

- Lifelong cystoscopic surveillance with cytology*
- CXR and CT abdo/pelvis regularly*
- Ipsilateral endoscopy (NSS)*

* No specified surveillance protocol. Raman et al recommend cysto/cyto every 3 mo., with imaging and endoscopy every 6mo.for 2 years, then yearly.

Algorithm

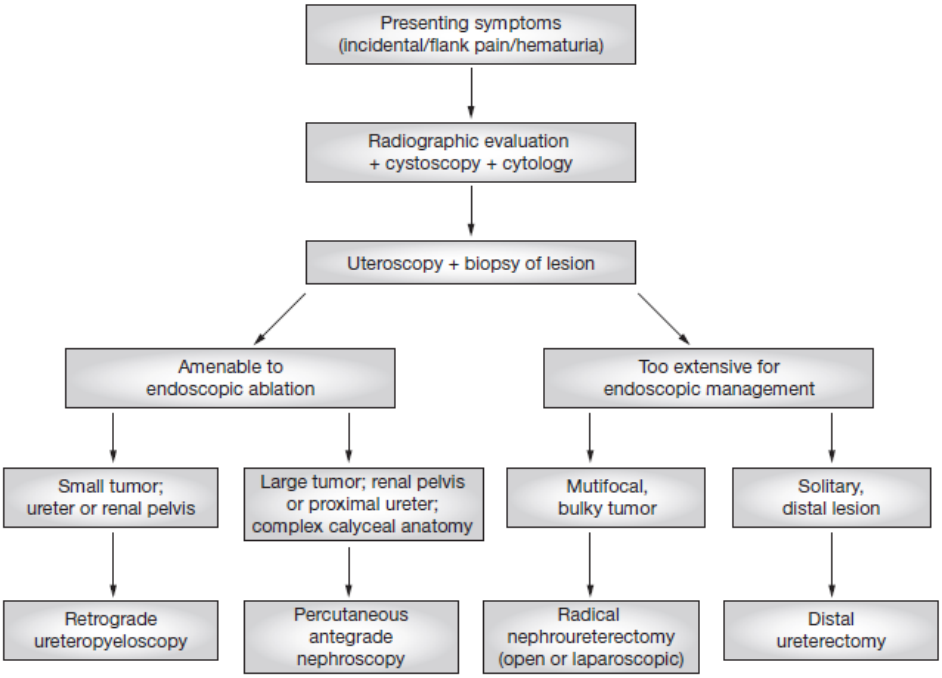

Figure 1 Algorithm for the management of upper-tract TCC. After a tissue diagnosis is obtained by ureteroscopy and biopsy, lesions that are amenable to endoscopic ablation will be managed either by a retrograde ureteroscopic or an antegrade percutaneous technique. Larger, bulkier lesions will require a more substantive procedure such as a segmental ureterectomy or a radical nephroureterectomy.