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REVIEW ARTICLE

# Ureteroscopic and percutaneous management of upper tract urothelial carcinoma (UTUC): systematic review

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**What's known on the subject? and What does the study add?**
Endoscopic management of upper tract urothelial carcinoma (UTUC) using either ureteroscopy and laser ablation, or percutaneous resection, is a management option for treating selected low-grade tumours with favourable characteristics. However, the evidence base for such practice is relatively weak, as the reported experience is mainly limited to small case series (level of evidence 4), or non-randomised comparative studies that are unmatched for tumour stage (level of evidence 3b), with variability of follow-up duration and reported outcome measures.

The present systematic review comprehensively reviews the outcomes of all studies of endoscopic management of UTUC, including the role of topical adjuvant therapy. It establishes for the first time a structured reference for endoscopic management of UTUC, and is a foundation for further clinical studies.

**OBJECTIVE**

- To systematically review the oncological outcomes of upper tract urothelial carcinoma (UTUC) treated with ureteroscopic and percutaneous management.
- The standard treatment of UTUC is radical nephroureterectomy (RNU). However, over the last two decades several institutions have treated UTUC endoscopically, either via ureteroscopic ablation or percutaneous nephroscopic resection of tumour (PNRT), for both imperative and elective indications.

**METHODS**

- For evidence acquisition the Pubmed database was searched for English language publications in December 2011 using the following terms: upper tract (UT) transitional cell carcinoma (TCC), upper tract TCC, UTTCC, upper tract urothelial cell carcinoma, upper tract urothelial carcinoma, UTUC, endoscopic management, ureteroscopic management, laser ablation, percutaneous management, PNRT, conservative management, ureteroscopic biopsy, biopsy, BCG, mitomycin C, topical therapy.

**RESULTS**

- There are no randomised trials comparing endoscopic management with RNU. Most published studies were retrospective case series (and database reviews), or unmatched comparative studies.
- There was strong selection bias for favourable tumour characteristics in many endoscopically treated groups.
- There was variation in medical comorbidity and indication for treatment across different study groups.
- The biopsy verification of underlying UTUC pathology was inconsistent.
- The follow-up in most studies was limited, typically to a mean 3 years.

**CONCLUSIONS**

- There is a high rate of UT recurrence with endoscopically managed UTUC, and a grade-related risk of tumour progression and disease-specific mortality.
- Overall, renal preservation may be high with ≈20% of patients proceeding eventually to RNU. For highly selected Grade 1 (or low-grade) disease managed in experienced centres, 5-year disease-specific survival (DSS) may be equivalent to RNU, although the small study groups and short follow-ups preclude comments on less favourable Grade 1 (or low-grade) tumour characteristics, or DSS, in the longer-term.





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• For Grade 3 (or high-grade) disease, DSS outcomes are poor and endoscopic management should only be considered for compelling imperative indications in the context of the patient's overall life expectancy and competing comorbidity.

**KEYWORDS** upper tract urothelial carcinoma, upper tract transitional cell carcinoma, ureteroscopy, percutaneous resection, biopsy, adjuvant treatment

## INTRODUCTION

Upper tract urothelial carcinoma (UTUC) is a rare, accounting for just 5–10% of all urothelial tumours, with an incidence of just 1–2 : 100 000 in Western populations [1,2]. Furthermore, the incidence of non-invasive urothelial cancer is rarer still, accounting for only 40% of UTUCs compared with 80% of bladder cancers [2–5]. Radical nephroureterectomy (RNU) is therefore the 'gold standard' of care for UTUC, mainly due to the proven durable outcomes reported [2,6] and the invasive prevalence of UTUC.

Historically, experience with endoscopic management of UTUC was limited to few institutions treating small sub-groups of patients with mainly imperative indications (patients with solitary kidney, bilateral UTUC, end-stage chronic kidney disease [CKD]), either via ureteroscopy with ablation using electro-diathermy or laser (URSa), or percutaneous nephroscopic resection of tumour (PNRT) [7–10]. As experience developed, endoscopic management has been extended to selected patients with elective indications (low-grade tumours with normal contralateral kidneys) in certain experienced centres [11,12].

The recently published 2011 European Association of Urology Guidelines indicate that conservative management of UTUC can be considered in imperative or elective cases, for low-grade, low-stage tumours [2]. It now appears that nephron-sparing surgery for RCC may offer better overall survival to RNU, perhaps due to preservation of renal function and reduced progression to postoperative CKD [13–16]. There are clear changes in renal function following RNU [17,18] and there is therefore renewed interest in the outcomes of patients with UTUC who may be spared RNU by undergoing endoscopic management. The reported utility of endoscopic management of UTUC is currently very low, as only six institutions for URSa, and one for PNRT, have published series of >40 patients [11,12,19–23].

This review reports the outcomes of patients treated with URSa or PNRT over the last 20 years, with a focus on overall survival (OS), disease-specific survival (DSS) and renal-unit survival (RUS).

## METHODS

### Evidence acquisition

The Pubmed database was searched for English language publications in December 2011 using the following terms (limited to humans): upper tract transitional cell carcinoma, upper tract TCC, UTTCC, upper tract urothelial cell carcinoma, upper tract urothelial carcinoma, UTUC. This was used in conjunction with corresponding terms for evaluation of endoscopic management (endoscopic management, ureteroscopic management, laser ablation, percutaneous management, PNRT, conservative management), biopsy (ureteroscopic biopsy, biopsy), and topical treatment (BCG, mitomycin C, topical therapy).

In all, 885 papers were evaluated initially. After excluding reviews, and studies reporting on <10 patients, 56 papers were eligible for final scrutiny.

## RESULTS

### Published reports of endoscopically managed UTUC using URSa and PNRT

There are no randomised trials comparing endoscopic management with RNU. All published reports were case series (level of evidence 4), or non-randomised comparative studies (level of evidence 3b), and these are listed in Tables 1 (URSa) [7,10,11,19–37] and 2 (PNRT) [9,12,19,24,38–45].

'There are no randomised trials comparing endoscopic management with RNU'

*TABLE 1 Outcomes of patients with UTUC managed with URSa. Studies were included containing a minimum of 10 patients. In all, 31% of patients had imperative indications for ureteroscopic management through studies which reported this criterion. Follow-up was variable. Although overall mortality was 28%, disease-specific mortality was<10%. In all, 19% of patients underwent RNU. Kaplan–Meier estimated survivals were only illustrated if raw figures were not reported. Several previous studies have been excluded [43,46–49,51,65,91–93] as updated reports from the same institutes are given below*

| Study | *N* (%) | Bx confirmed UTUC, *n* (%) [G1/G2/G3] | Prior UC bladder | Follow-up, months | UT-recur., *n* (%) | Bl-recur., *n* (%) | OM, *n* (%) | DSM, *n* (%) | NU rate, *n* (%) | Progression, *n* (%) | Failed endo management, *n* (%) | Stricture rate/ complication rate, *n* (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Schmeller *et al.*, 1989 [10] | 16 (50) | 16 (100) [6/10/–] | ND | median 14 | 3 (19) | ND | 0 | 0 | 0 | 0 | 2 (13) | 4 (25) strictures |
| Andersen *et al.*, 1994 [24] | 10 | ND | ND | mean 25 | ND | ND | ND | ND | 2 (20) | ND | ND | ND |
| Gaboardi *et al.*, 1994 [25] | 18 | 18 (100) [12/6/–] | ND | mean 15 | 8 (50) | ND | 0 | 0 | 1 (6) | 1 (6) | 1 (6) | 2 (11) sepsis |
| Engelmyer *et al.*, 1996 [7] | 10 (70) | 10 (100) [9/1/–] | ND | mean 43 | 7 (70) | ND | 1 (10) | 0 | 0 | 0 | 0 | 2 (20) stricture |
| Martinez-Pineiro *et al.*, 1996 [19] | 54†, 59 RU (24) | 55/59 (93) [24/18/10] | 24/54 (44) | mean 31 | 9/39 (23) | ND | 11/44 (25)‡ | 4/44 (9)‡ | 4/39 (10) | ND | 11/39 (28) | 9/39 (23) strictures/ ureteric perforations |
| Grasso *et al.*, 1999 [26] | 14 | 14 (100) [1/11/1] | 5 (36) | mean 17 | 7 (50) | 4 (29) | ND | 0 | 4 (29) | ND | >4 (29) | 1 (7) stricture |
| Deligne *et al.*, 2002 [20] | 61‡ | 53/53 (100) [21/24/8] | 15/61 (25) | mean 40 | 15/61 (25) | 14/61 (23) | 13/55 (24) | 8/55 (15) | 11/61 (18)** | ND | 11/61 (18) | 2 (3) strictures. |
| Daneshmand *et al.*, 2003 [27] | 30 | 27 (90) [7/6/14] | 7 (23) | median 31 | 27 (90) | 7 (23) | 7 (23) | 1 (3) | 4 (13)** | 6 (20) | 14 (47) | 5 (17) strictures |
| Matsuoka *et al.*, 2003 [28] | 27 (26) | ND [10/2/–] | ND | median 33 | 7 (26) | 4 (15) | ND | 3 (11) | ND | ND | ND | ND |
| Iborra *et al.*, 2003 [29] | 23 | ND | ND | ND | 8 (35) | ND | ND | 1 (4) | 2 (9) | 3 (13) | ND | ND |
| Johnson *et al.*, 2005 [30] | 35 | 35 (100) [35/–/–] | 21 (60) | mean 32 | 24 (68) | ND | ND | 0 | 1 (3) | 0 | 1 (3) | 3 (9) |
| Roupret *et al.*, 2006 [31] | 27 | 27 (100) [LG19/ HG8] | ND | mean 52 | 4 (15) | 6 (22) | 9 (33) | LG 19%† | 7 (26) | 2 (7) mets | ND | 2 (7) ureteric perforation, 1 (4) haemorrhage |
| Reisiger *et al.*, 2007 [32] | 10 | 10 (100) [10/–/–] | ND | mean 73 | 5 (50) | 7 (70) | 0 | 0 | 1 (10) | 0 | 1 (10) | 1 (10) stricture |
| Krambeck *et al.*, 2007 [33] | 37 (100) | 22 (59) [2/13/7] | 29 (78) | median 32 | 23 (62) | 13 (37) | 24 (65) | 11 (30) | 11 (30) | ≥11 (30) mets | ≥11 (30) | 19 (51) overall 5 (14) strictures |
| Thompson *et al.*, 2008 [11] | 83† (0) | 40 (48) [14/18/8] | 61 (74) | median 55 | 46 (55) | 37 (45) | 35 (42) | 9 (11) | 27 (33) | 12 (14) upgraded/ upstaged | ≥27 (33) | |
| Lucas *et al.*, 2008 [34] | 39 (67) | 39 (100) [LG27/ HG12] | 11 (28) | median 33 | 17 (46) | ND | 38%† | 18%† | 11 (28) | 8 (21) upgraded/ upstaged | ≥11 (28) | ND |
| Painter *et al.*, 2008 [21] | 45 | ND | ND | ND | ND | ND | ND | 5 (11) | 4 (9) | ND | ND | 2 (4) strictures |

*TABLE 1 Continued*

| Study | *N* (I%) | Bx confirmed UTUC, *n* (%) [G1/G2/G3] | Prior UC bladder | Follow-up, months | UT-recur., *n* (%) | Bl-recur., *n* (%) | OM, *n* (%) | DSM, *n* (%) | NU rate, *n* (%) | Progression, *n* (%) | Failed endo management, *n* (%) | Stricture rate/ complication rate, *n* (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pak *et al.*, 2009 [22] | 57 | ND | ND | mean 53 | 51 (90) | ND | 4 (7) | 3 (5) | 11 (19) | 4 (7) mets | >11 (19) | ND |
| Cornu *et al.*, 2010 [35] | 35 (43) | 22 (63) [LG16/ HG6] | 12 (34) | mean 24 | 21 (60) | 14 (40) | 0 | 0 | 4 (11) | 0 | 4 (11) | 3 (9) sepsis, AKI |
| Gadzinski *et al.*, 2010 [36] | 34 (47) | 34 (100) | 20 (59) | mean 58 | 27 (84) | ND | LG 25%†, HG 75%† | LG 0%†, HG 14%† | 32 (11) | ND | ND | 21/226 (9) overall |
| Raymundo *et al.*, 2011 [37] | 21–67‡ | 20 (95)‡ | 8 (38)‡ | mean 18 | 4 (31) | 2 (15) | ND | 1 (8) | ND | 2 (15) mets | ND | ND |
| Cutress *et al.*, 2012‡ [23] | 73 (11) | 59 (81) [34/19/6] | 34 (49) | median 54 | 50 (69) | 31 (43) | 29 (40) | 7 (10) | 14 (19) | 14 (19) upgraded/ upstaged | 22 (30) | 12 (16) strictures; 1x bowel perforation with NdYAG laser |
| **Overall** | **736 (32)** | **520 (71)** [184/133/60] | **240/486 (49)** | **14–73** | **363/679 (53)** | **139/410 (34)** | **133/470 (28)** | **55/631 (9)** | **130/683 (19)** | **56/364 (15); 33/374 (9) mets** | **131/550 (24)** | **89/631 (14) overall; 48/450 (11) strictures** |

*n (I%) number of patients with parentheses denoting percentage of imperative indications for ureteroscopic management; RU, renal units; UT-recur, UT recurrence; Bl-recur, bladder recurrence; OM, overall mortality; ND,* n *ot disclosed; AKI, acute kidney injury.*
*‡Includes ureteroscopically and percutaneously treated patients; †Kaplan–Meier estimated 5-year outcomes; **RNU including partial pyelectomy/partial nephrectomy. Failed endo management, failed endoscopic treatment includes DSM, pathological progression, or patients who underwent RNU/partial nephrectomy/ureterectomy.*

Several important points are made about these series. The mean study size was 33 for URSa and 24 for PNRT and only three institutions for URSa [11,22,23] and one for PNRT [12], have published mature outcomes on cohorts of ≥40 patients with >50 months follow-up. There was considerable selection bias for favourable tumour characteristics in many of the studies, e.g. unifocality and size <2 cm [29,31,36,46]. The study populations also had significant medical comorbidities, with the proportion designated as American Society of Anesthesiology score 3 being 56–66% in some series [33,47]. These studies do not therefore reflect the long-term outcomes of the full-spectrum of non-invasive UTUC in 'fit' patients over the long-term, but rather the intermediate-term outcomes of specially selected tumours, often with favourable characteristics, in patients with competing medical comorbidity.

## UT RFS

Overall UT recurrence is high with endoscopic management, with pooled figures of 52% and 37% for URSa and PNRT studies respectively, with a grade-dependent trend (Table 3). As these figures were uncensored to vital status (patients remaining at risk), they under-estimate true RFS, and the 5-year RFS has been estimated at only 13–54% [11,23,36,48]. Multivariate analysis has shown the following to be significant factors for UT recurrence: tumour size >2 cm, prior history of bladder tumours, and more than three previous bladder tumours [20,29,31]. Grade and multifocality have also been reported as predictors for UT recurrence [43,49]. Renal tumour location has been reported as a significant factor for recurrence in some [29,43], but not all studies [31]. It is possible that this variance between groups is attributable to differences in underlying tumour pathology or adequacy of surgical access to the UTs, as recent large multicentre studies have shown that tumour location has no effect on oncological outcomes when controlling for grade and stage [50].

## Bladder RFS

Intravesical recurrence is dependent on several confounding factors, including prior

*TABLE 2 Outcomes of patients with UTUC managed with PNRT. Studies containing a minimum of 10 patients were included. In all, 26% of patients had imperative indications for percutaneous management through studies which reported this criterion. Follow-up was variable. Although overall mortality was 21%, DSM was 11%. In all, 19% of patients underwent RNU. Kaplan–Meier estimated survivals were only illustrated if raw figures were not reported. Previous reports from the Long Island Jewish Medical Centre were excluded from analysis [8,12,52,54,82,94], as the most recent study by Rastinehad* et al. *[12], is illustrated in the table below. In the overall summation of PNRT studies, complication rate and DSM outcomes include data from the penultimate report from the Long Island Jewish Medical Centre [52], as the latest study did not include these [12]*

| Study | *N* (I%) | Grade distribution [G1/G2/G3] | Prior UC bladder, *n* (%) | Follow-up, months | UT-recur., *n* (%) | Bl-recur., *n* (%) | OM, *n* (%) | DSM, *n* (%) | RNU rate, *n* (%) | Progression, *n* (%) | Failed endo management, *n* (%) | Complications, *n* (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Tasca *et al.*, 1992 [38] | 10 | [1/5/–] | ND | mean 19 | 5/10 | ND | 1/10 | 0 | 3/10 | ND | 3/10 | ND |
| Fuglsig *et al.*, 1995 [39] | 26, 27 RU (27) | ND | 14 (54) | mean 21 | 8 (31) | ND | 1 (4) | 0 | 9 (35) | 2 (8) | 9 (35) | 2 (8) haemorrhage, 1 (4) tumour seeding along percutaneous nephrostomy tract |
| Plancke *et al.*, 1995 [40] | 10 (10) | [6/3/1] | 1 (10) | mean 28 | 1/10 | 1/10 | 1/10 | 0 | 1/10 | 0 | 1/10 | None (0/10) |
| Patel *et al.*, 1996 [41] | 26 (42) | [11/11/1] | 7 (27) | mean 45 | 9 (35) | 11 (42) | 8 (31) | 2 (8) | 5 (19) | 2 (8) | 6 (23) | 7 (27) overall complications; 3 (12) haemorrhage and 1(4) death from adjuvant thiotepa |
| Martinez-Pineiro *et al.*, 1996‡ [19] | 18 | ND | 24/54 (44)‡ | mean 31 | 2 (11) | ND | 11/44 (25)‡ | 4/44 (9)‡ | 1 (6) | ND | 3 (17) | 7 (33) overall; 4 renal/colonic perforations; 1(6) hydrothorax; 1(6) TUR syndrome |
| Clark *et al.*, 1999 [9] | 17, 18 RU (82) | [6/8/4] | 11 (65) | mean 24 | 6 (33) | ND | 6 (35) | 3 (18) | 2 (12) | ≥3 (33) mets | – | 2 (12) blood transfusion; 1 (6) UTI |
| Goel *et al.*, 2003 [42] | 20 (15) | [LG15/HG5] | 1 (5) | mean 64 | 13 (65) | 3 (15) | ND | 5 (25) | 10 (50) | 7 (35) | 10 (50) | 1 (5) emergency RNU for haemorrhage, 1 (5) RNU for stricture, 2 (10) ESRF with dialysis |
| Suh *et al.*, 2003 [43] | 14 (86) | [LG8/HG6] | 40/58 (69)‡ | mean 21 | 14/14 | ND | 3/14 | 2/14 | 5/14** | 1/14 mets | 8/14 | 6/31 (19) overall; 1 (7) transfusion, 1 (7) pneumothorax, 1 (7) fluid overload, 1 (7) fungal UTI |
| Palou *et al.*, 2004 [44] | 34 (47) | [7/21/5] | 27 (79) | mean 51 | 15 (44) | ND | 9 (26) | 2 (6) | 9 (26) | ND | – | 1 (3) emergency RNU for haemorrhage, 1 (3) stricture; 14 BCG, 5 MMC |
| Roupret *et al.*, 2007 [45] | 24 (38) | [LG17/HG7] | 4 (17) | median 62 | 3 (13) | 4 (17) | 5 (21) | 4 (17) | 5 (21) | 4 (17) | – | 3 (13) blood transfusion; 3 (13) ESRF with dialysis; 1 (4) colonic perforation |
| Rastinehad *et al.*, 2009 [12] | 89 (29) | [LG50/HG39] | 17 (19) | mean 61 | 30 (33) | ND | 42%† | ND | 12 (13) | 18 (20) | – | ND |
| | *n* (I%) | Grade distribution [G1/G2/G3] | Prior UC bladder | Follow-up, months | UT-rec, *n* (%) | Bl-rec, *n* (%) | OM, *n* (%) | DSM, *n* (%) | NU rate, *n* (%) | Progression, *n* (%) | Failed Endo Management, *n* (%) | Complications, *n* (%) |
| Overall | 288 (26) | [36/47/11] [LG90/HG57] | 68/220 (31) | 19–64 | 106/288 (37) | 19/80 (24) | 34/161 (21) | 28/248 (11) | 62/288 (22) | 33/195 (17) | 40/124 (32) | 64/236 (27) overall; 37/218 (17) transfusion; 5/256 (2) ESRF with dialysis; 2/189 (1) emergency RNU/embolisation for bleeding; 1/236 (<1) tract seeding |

*N (I%), number of patients with parentheses denoting percentage of imperative indications for ureteroscopic management; ESRF, end-stage renal failure; RU, renal units; UT-recur., UT recurrence; Bl-recur., bladder recurrence; OM, overall mortality; ND, not disclosed. ‡Includes ureteroscopically and percutaneously treated patients; †Kaplan–Meier estimated 5-year outcomes; **RNU including partial pyelectomy/partial nephrectomy. Failed endo management, failed endoscopic treatment includes DSM, pathological progression, or patients who underwent RNU/partial nephrectomy/ureterectomy.*

*TABLE 3 Grade-stratified pooled UT recurrence and DSS outcomes from URSa and PNRT studies. A clear trend for increasing UT recurrence and reduced DSS is apparent with higher grade UTUC. The outcomes were derived from the following studies: URSa G1–G3 [7,10,19,23,26,27,30,47–49]:; LG/HG [34,36]:; PNRT: G1–G3 [9,38,40–42,44,52,53]:; LG/HG [12,43,45]*

| | *n*/*N* (%) | | | | |
|---|---|---|---|---|---|
| | G1 | G2 | G3 | LG | HG |
| URSa | | | | | |
| UT recurrence | 77/149 (52) | 45/84 (54) | 28/37 (76) | 13/27 (48) | 12/20 (60) |
| DSS | 126/129 (98) | 71/81 (88) | 27/34 (79) | 23/24 (96) | 7/8 |
| PNRT | | | | | |
| UT recurrence | 11/47 (23) | 17/56 (30) | 20/50 (40) | 26/75 (35) | 22/52 (42) |
| DSS | 46/47 (98) | 41/42 (98) | 21/35 (60) | 25/25 (100) | 7/13 |

history of bladder cancer. The pooled studies indicate bladder recurrence of 34% and 24% for URSa and PNRT respectively, but as only 15/33 of the pooled studies report intravesical recurrence status, these figures are unlikely to be an accurate figure for the wider population. The 5-year intravesical RFS has been estimated as 46–54% in the largest studies [11,33,47,48].

### OS

The OS in the pooled studies was poor, being only 72% for URSa and 79% for PNRT, at a typical follow-up of 37 months. The estimated 5-year OS have been reported as 57–75% [12,20,23,34,36,46,51] and 10-year OS as 40–47% [12,23], which may reflect the advanced age and competing comorbidity of the study populations.

### DSS

The DSS in the pooled studies was 91% for URSa (Table 1) and 89% for PNRT (Table 2) at a typical follow-up of 37 months, with a grade-dependent trend (Table 3) [7,9,10,12,19,23,26,27,30,34,36,38,40–45, 47–49,52,53].

These DSS figures are likely to be over-estimates, due to limitations in pathological verification, patient censoring and follow-up duration. Verification of underlying UTUC pathology in these studies was variable and benign underlying pathology may exist in up to 13–16% of cases of visually presumed UTUC [20,39,54]. The limited pathological verification of ≈50% in the largest reports of URSa [11,47] inherently precludes definitive interpretations of DSS. Moreover, the raw DSS figures were uncensored to overall vital status (patients remaining at risk during follow-up), which is a major factor as OS is only 72–74% overall. Those studies which did censor patients showed notably lower Kaplan–Meier 5-year DSS estimates of 49–89% for patients unstratified by grade [11,23,31,33,47,48], or perhaps 100% 5-year DSS for Grade 1 [23] vs 32–38% for Grade 3 [11,47,48], or 81–100% 5-yeary DSS for low-grade vs 69–86% for high-grade disease [31,34,36].

Multivariate analysis has shown grade and stage of UTUC to be significant factors for adverse DSS [23,31]. Univariate analysis has also shown prior or subsequent radical cystectomy, and imperative indication for endoscopic management, to be adverse DSS factors [47].

### Metastatic progression

Metastatic progression has only been sporadically reported in these studies, with pooled figures of 9% and 6% for URSa and PNRT, respectively. As few studies report these statistics, these figures are unlikely to be representative of the true metastatic progression rates. The 5-year metastatic-free survival rates have been estimated as 94% and 86%, for low- and high-grade disease respectively in one study [36].

### Renal preservation

The pooled studies indicate that a proportion of patients proceed ultimately to RNU, although most renal units are preserved, with RUS of 81% and 78% for URSa and PNRT, respectively. However, RUS may only be 68% in the largest URSa studies with longer follow-ups [11,47], and these figures are still likely to over-estimate the 5-year RUS, as the raw data was uncensored to vital status. The 5-year RUS has been estimated as 85% in one study, showing a grade-dependent outcome with a 5-year RUS of 96% and 20% for Grade 1 and Grade 3 UTUC, respectively [23].

### Complications

Overall pooled complications were 14% for URSa, with a stricture rate of 11% (Tables 1,2). Overall pooled complication for PNRT were 27%, with a 17% blood transfusion risk, 2% risk of renal failure requiring dialysis, and a 1% risk of emergency RNU or renal artery embolization for haemorrhage. The incidence of seeding of UC within the percutaneous tract was extremely rare, just 0.3% overall, or 0.75% (1/133) in the most experienced centre [12].

### Failed endoscopic management

Endoscopic management may be considered to have failed in cases of tumour progression (pathological up-grading or up-staging on final RNU specimen, clinical or radiological evidence of locally advanced or metastatic disease), RNU, or disease-specific mortality (DSM). Although these parameters were not universally reported, the pooled data indicate endoscopic failure in at least 24% of URSa and 32% PNRT studies.

## DANGERS OF UTUC PROGRESSION WHILST ON ENDOSCOPIC MANAGEMENT AND IMPACT ON DSS

A key concern with endoscopic management, especially with non-imperative cases, is the risk of tumour up-grading, or up-staging [55], which could adversely affect DSS and could otherwise have been avoided by potentially curative RNU at the outset. The overall risk of such progression is unclear due to inconsistent reporting from different institutions and the inherent

‘A key concern with endoscopic management is the risk of tumour up-grading, or up-staging’

limitations in diagnostic accuracy of ureteroscopic biopsy. In large single-centre series, the risk of grade migration may be 4–19% and the risk of stage migration 8–14% [11,33,34,47,48]. At short-term follow-up (mean 32 months), the risk of progression may be 0% for low-grade, but 88% for high-grade cases [30]. Multivariate analysis has shown more than three previous bladder tumours to be significant factors for progression [29]; and high grade or stage to be significant factors for DSM [23,31]. Although progression may clearly occur, delayed RNU is ultimately carried out in a significant proportion of cases, and was used in ≈20% of study populations. It is therefore pertinent to address whether delayed RNU in such patients adversely affects DSS compared with RNU at outset.

It appears that a short delay to RNU, either due to diagnostic URS [56] or a brief period of URSa [57], does not appear to impact negatively on outcome. Hendin *et al.* [56] showed no difference in 5-year metastasis-free survival, DSS or OS in 48 patients who underwent RNU after diagnostic URS, compared with 45 patients who underwent immediate RNU without prior diagnostic URS. Boorjian *et al.* [57] compared the disease-free status of 12 patients treated with delayed RNU after 6 months of URSa with 34 patients (with comparable pathological distributions) who underwent immediate RNU, and found no significant difference (83% vs 85%) at a mean follow-up of 39 months. The limited study populations and durations of follow-up clearly preclude any definitive conclusions to be made about more significant delays and longer-term outcomes.

## COMPARATIVE STUDIES OF ENDOSCOPIC MANAGEMENT AND RNU

It is not possible to establish firmly the performance of endoscopic management in treating UTUC compared with RNU, as high-quality evidence for the former does not exist. There are no prospective randomised controlled studies comparing the two. Five institutions have compared the oncological outcomes of endoscopic management and RNU in non-randomised studies, with mean follow-ups of 18–58 months [31,34,36,37,54]. It is imperative to emphasise that these studies represent non-randomised retrospective series, with fairly small study groups (21–49 patients) and limited follow-up, with delayed RNU used as a 'rescue' procedure in certain cases. There is inherent strong selection bias for favourable tumour characteristics in the endoscopically managed arms of these studies, e.g. small tumour size (<2 cm), unifocality, low grade and low stage. The distribution of invasive UTUC stage (≥ pT2) in the RNU study arms was significantly higher in the studies that reported this data (26–67% for RNU vs 10–24% for endoscopic management) [31,34,37,54], which potentially influences oncological outcomes when stratifying purely by grade.

'For high-grade patients, evidence is lacking to support endoscopic management'

The level of evidence for endoscopic management compared with RNU is therefore relatively poor (level of evidence 3b). Delayed RNU was carried out in 28–43% of the endoscopic groups at an early median time of 10–22 months [31,34,36,37]. For low-grade disease, the 5-year DSS figures for endoscopic management were comparable to immediate RNU (80–100% vs 84–89%), for endoscopic study groups of 24–30 patients. For high-grade disease, the limited study populations (8–13 patients for endoscopic management) and follow-up durations preclude statistical comparison, although DSS did appear to favour RNU in at least two studies [34,54].

Despite the non-randomised retrospective nature of these studies, and acknowledging the inherent selection bias for favourable tumour characteristics in the endoscopically managed arms, these studies indicate that there may well be DSS equivalence for highly selected low-grade endoscopically managed patients in experienced centres at 5 years. The limited published follow-up durations currently preclude the evaluation of low-grade DSS in the longer-term. For high-grade patients, evidence is lacking to support endoscopic management and current evidence from the UTUC Collaboration indicates superiority of RNU [6]. Although the UTUC Collaboration did not report grade-stratified outcomes of RNU for specifically non-invasive disease, the 5-year DSS of 93.5% for pT0/pTa/pTis stage or 91.0% for pT1 stage, from a cohort with 64% high-grade disease overall, would

indicate RNU as the benchmark standard of care for treatment of UTUC [6].

Clearly the benefits of renal preservation with endoscopic management come at a cost of greater disease recurrence, with 5-year RFS of only 13–54% for endoscopically managed patients [11,23,33,36,47,48] compared with 88–92% 5-year RFS for RNU [6], and the inherent need for more intensive follow-up on endoscopic surveillance. It is difficult to estimate the financial cost of renal preservation with endoscopic management compared with the cost of RNU, mainly due to the heterogeneity of study populations and the effect of tumour grade on follow-up intensity, CKD on progression to haemodialysis or other renal replacement therapy, and competing medical comorbidity on overall life-expectancy and follow-up duration. The final long-term cost for either endoscopic management or RNU is clearly dependent on the duration of follow-up, number of recurrences, and progression to end-stage renal failure with subsequent costs for arteriovenous fistula placement and haemodialysis. For elective cases with favourable low-grade disease in patients without comorbidity, it is possible that RNU may be the more cost-effective management, based on the above factors. However, for an extreme imperative case of a solitary kidney with CKD treated with endoscopic management and with annual recurrences at each follow-up over 5 years, estimated cost analyses would indicate a financial saving of >$250 000 (USA dollars), enough to cover the cost of five cadaveric renal transplantations, compared with RNU and subsequent haemodialysis over the same period [22].

## THE ROLE AND IMPORTANCE OF URETEROSCOPIC BIOPSY IN THE ENDOSCOPIC MANAGEMENT OF UTUC

A comprehensive appraisal of ureteroscopic biopsy studies is not the main focus of the present review, so the following discussion is limited to biopsy accuracy. It is clear that UTUC grade is a significant determining factor for DSS, with poorer outcomes clearly associated with higher tumour grades [11,23,31,33,34,36,47,48]. Pathological assessment with ureteroscopic biopsy therefore plays an axiomatic role in selecting patients for endoscopic management.

It is clear that ureteroscopic inspection of UT tumours alone, without biopsy, has a very limited role to play in management, for several reasons. Firstly, 13–16% of UT tumours may be histologically benign [20,39]; secondly, ureteroscopic appearance of UT tumours is inaccurate for predicting definitive pathological grade in ≈30% of cases undergoing RNU [58]; and thirdly, the subsequent progression to Grade 2/3 disease (35%) [11] and the overall DSM (15–20%) [47,48] of patients with 'visual low-grade' diagnoses are higher than might be predicted during follow-up, implying major under-grading of initial tumour grade based on visual (ureteroscopic) appearance. These findings collectively question the validity of assigning visually diagnosed tumours to 'low-grade' status and underscore the importance of ureteroscopic biopsy as an essential requirement for UTUC diagnosis and endoscopic treatment planning.

> 'ureteroscopic inspection of UT tumours alone, without biopsy, has a very limited role to play in management'

There are several factors that are critical for achieving accurate histopathological interpretation, including a good biopsy yield from multiple biopsies (using cold cup, resecting loop, flat-wire basket or Piranha forceps), the use of additional cytology from ureteric or renal pelvic washings or brushings, and the analysis in a pathology unit with high-volume UTUC biopsy experience [58–62]. Despite such a strategy, biopsy accuracy is still inherently limited due to inadequate tissue volume, crush artifact [63] and unrepresentative tumour sampling [64], which may mislead the histopathologist and perhaps 20% or more of ureteroscopic biopsies may be non-diagnostic in some reports [63].

It is clear from several studies that biopsy grade may successfully predict definitive histopathological (RNU) grade in 69–91% cases [23,27,43,60,61,64–67]. However, whilst there is a clear role in biopsies for grade prediction, it is apparent that biopsy stage cannot reliably predict definitive histopathological (RNU) stage, and it appears that biopsy grade may be the stronger surrogate predictor of pathological stage due to the concordance of high-grade with high-stage disease [60,61,67]. Biopsy appears to under-stage definitive histopathological stage and it appears that ureteroscopic biopsy cannot reliably predict the integrity of the lamina propria with tumour present. In all, 45% (10/22) of biopsy-classified Ta tumours may be subsequently up-staged on final histopathological specimen, whilst biopsy-classified T1 tumours appear not to be over-staged [66]. Biopsy grade appears to be a strong predictor for histopathological stage with 68–100% of Grade 1 biopsies correctly predicting non-invasive stage (≤pT1) and 62–100% of Grade 3 biopsies correctly predicting invasive stage (≥pT2) [60,61,67–69]. High-grade ureteroscopic biopsy used in conjunction with abnormal urine cytology and hydronephrosis may improve the prediction (positive predictive value) of muscle-invasive stage (≥pT2) to 89% [69]. Grade 2 biopsies do not appear to reliably predict invasive histopathological stage, with invasive stage (≥pT2) reportedly ranging from 17% to 80% across different institutions [60,61,67,68]. Cytological analysis of ureteric washings may be used to augment the accuracy of Grade 2 ureteroscopic biopsies, especially for predicting high-grade (Grade 3) or muscle-invasive disease. By combining urine cytology with Grade 2-biopsies, the sensitivity and specificity of high-grade (Grade 3) tumour detection may improve from 43–55% and 23–85% respectively [70], and muscle-invasive stage prediction (positive predictive value) improve by 37% [61]. In the latter case, the presence of histopathological muscle-invasive disease (≥pT2) may be present in only one of six cases with negative urine cytology, but eight of 14 with positive urine cytology [61].

Further improvements in UTUC endoscopic treatment may develop from the use of URS with blue-light photodynamic diagnosis (PDD) and 5-aminolevulinic acid, or with narrow-band imaging digital flexible URS, as early pilot studies have shown promise [71–73]. It is possible that these new methods may improve the diagnostic sensitivity of URS for UTUC by 14–27%, define the extent of UTUC burden (which

may not be completely apparent with white-light URS), and may also be applied therapeutically to ensure comprehensive endoscopic tumour ablation [72,73]. In cases where UT biopsy samples are non-diagnostic, fluorescent *in situ* hybridisation analysis of UT washings with labeled fluorescent probes to detect abnormalities on chromosomes 3, 7, 17, and 9p21 that are typical for UC, may improve the detection of UTUC with a sensitivity and specificity of 100% and 90%, respectively [74].

## ADJUVANT TOPICAL TREATMENT FOR UTUC

There is no proven efficacy for the use of adjuvant topical therapy (BCG or mitomycin C [MMC]) in the treatment of papillary UTUC. Reports have been typically limited to retrospective, small cohort studies with limited follow-up (typically <36 months), mainly assessing the use of BCG, with very few assessing MMC [9,12,19,23,24, 35,44,75–78]. These studies are summarised in Table 4. For papillary UTUC, only three institutes report the outcomes of >20 renal units treated with BCG [12,78], or MMC [75]. It is inherently difficult to establish any therapeutic benefit from such studies, as most did not include control (non-treatment) arms for comparison [9,75–80].

Furthermore, the few case-controlled series that have been reported have been non-randomised and retrospective in design, often with limited study groups, and with significant potential differences in underlying UTUC grade distributions between the treatment and control arms [8,19,52,81,82]. Four of these studies were published by the same institution and are likely to contain updated outcomes on previously reported patients [8,52,81,82]. These factors conspire against any statistical analysis and preclude any firm statements on therapeutic benefit. The main body of evidence arises from a single institution that recently reported its 20-year experience with adjuvant BCG after PNRT for UTUC. BCG was administered as a 6-week course to 50 renal units with outcomes compared with 39 controls, with similar underlying grade distributions. Overall, there was no statistical difference for recurrence, time to recurrence, or progression between the treatment and control arms when stratified by grade and stage [12].

Although these studies do not show collectively any strong benefit of topical adjuvant therapy for papillary UTUC, it also has to be acknowledged that they are insufficiently powered to definitively exclude a potential benefit. Although speculative, it is possible that papillary UTUC *may* respond to adjuvant treatment, albeit not with the suboptimal drug concentrations (Table 4) or modes of delivery (percutaneous nephrostomy tube, ureteric catheter, and ureteric stent) that have been used to date. In the absence of such positive evidence, any consideration to administer adjuvant treatment would have to be assessed carefully against the potential significant side-effects (Table 4).

Whilst adjuvant topical BCG therapy has not proven beneficial for papillary UTUC, positive outcomes have been reported for UT-carcinoma *in situ* (CIS) in several studies (Table 5) [78,83–88]. These report collectively a 73% positive initial response rate, 26% UT recurrence rate, 14% progression rate and 10% DSM on >100 renal units, with a mean follow-up of 20–51 months (Table 5). It must be emphasised that the diagnosis of UT-CIS in many of these studies was presumptive, based on the presence of positive selective urine cytology and negative radiological findings, and without confirmatory URS. The response rates were determined by restitution of normal urine cytology. The diagnosis of CIS was therefore inherently flawed, and limited by the sensitivity of radiological imaging of that time (10–20 years ago), and the specificity of urine cytology. Although the initial positive response rates with adjuvant BCG for UT-CIS would appear encouraging overall, the DSM outcomes vary significantly, typically between 9–40% beyond 3 years, which cautions long-term optimism.

## CONCLUSIONS

UTUC is rare, with relatively few patients undergoing endoscopic management. The reported literature indicates that endoscopic

'UTUC is rare, with relatively few patients undergoing endoscopic management'

*TABLE 4 Outcomes of studies using topical adjuvant therapy for UTUC. Only studies treating 10 or more renal units are shown. Where a single institution published multiple studies, only the largest or most recent publication was included to prevent duplicate reporting. Several early studies are therefore not included [8,52,79–82,94]*

| Study | *n* (RU) | Pathology [G1/G2/G3] | Adjuvant therapy | Study design | Follow-up, months | UT-recur., *n* (%) | RNU rate, *n* (%) | DSM, *n* (%) | Complications, *n* (%) | Benefit |
|---|---|---|---|---|---|---|---|---|---|---|
| MMC | | | | | | | | | | |
| Martinez-Pineiro *et al.*, 1996 [19] | (41) | [21/10/3] | MMC 40 mg (0.4 mg/mL) in 14 RU | Case series; URS + laser ablation or PNRT | mean 31 | 10/41 (24) | 4/39 (10) | 4/44 (9) | 1/33 (3) death secondary to systemic absorption of MMC | UT-recur. 14% with MMC vs 25% in unmatched controls. Unequal pathological grade distributions amongst groups precludes direct comparison. |
| Keeley *et al.*, 1997 [75] | 19 (21) | [5/8/4] | MMC in 21 RU; 40 mg (1.3 mg/mL) | Case series; URS + laser ablation | mean 30 | 6/11 (54) | 4/19 (21) | 0 | 1/21 (5) local reaction, 1/21 (5) stricture | No progression. Safety demonstrated. Benefit not shown. |
| Cornu *et al.*, 2010 [35] | 35 | [LG16/HG6] | MMC (11 RU); or BCG (6 RU) | Case series; URS + laser ablation | mean 24 | 21/35 (60) | 4/35 (11) | 0 | 2/35 (6) sepsis, 1/35 (3) acute kidney injury | No sub-analysis performed for adjuvant groups. Benefit not evaluated. |
| Cutress *et al.*, 2012 [23] | 73 | [34/19/6] | MMC in 18 RU; 40 mg | Retrospective non-randomised case-control series; URS + laser ablation or PNRT | mean 63 | 50 (68) | 14 (19) | 7 (10) | 12/73 (16) strictures, 1/73 (1) RNU for bleeding after PNRT, 1/73 (1) bowel injury | No benefit shown with MMC for UT-RFS (UT-RFS 54% in both groups). |
| BCG | | | | | | | | | | |
| Patel *et al.*, 1998 [76] | 12 (16) | [8/5/–] | BCG in 16 RU, 6-week course | Case series; URS + laser ablation | mean 15 | 2 (13) | 2/16 (13) | 0 | 3/16 (19) UTI, 1/16 (6) persistent PUO | No non-treatment group. Benefit not evaluated. |
| Clark *et al.*, 1999 [9] | 17 (18) | [6/8/4] | BCG in 16 RU, 6-week course; 50 mg (1 mg/mL) | Case series; PNRT | mean 21 | 6/18 (33) | 2/17 (12) | 3/17 (18) | ND | No non-treatment group. Safety demonstrated. Benefit not evaluated |
| Palou *et al.*, 2004 [44] | 34 | [7/21/5] | BCG 81 mg in 14 RU; MMC 40 mg in 5 RU | Case series; PNRT | mean 51 | 15 (44) | 9 (26) | 2 (6) | 1 (3) emergency RNU for haemorrhage, 1 (3) stricture; | No benefit with adjuvant treatment. UT-recur. 58% in adjuvant treatment vs 27% in unmatched controls. |
| Katz *et al.*, 2007 [77] | 10 (11) | [G2/3 7] | BCG-IFNα2B in 11 RU, 6 weeks course | Case series; URS + ablation | median 24 | ND | ND | ND | ND | 8/11 (73) initial response (no recurrence). Safety demonstrated. Benefit not evaluated. |
| Rastinehad *et al.*, 2009 [12] | 89 | [LG50/HG39] | BCG in 50 RU, 6-week course; 81 mg (1.6 mg/mL) | Retrospective non-randomised case-control series; PNRT | mean 61 | 18/50 (36) | 9/50 (18) | ND | 1/50 (2) death from sepsis, 1/50 (2) testicular granuloma, 1/50 (2) disseminated BCG | 10/50 (20) progression. No statistical difference for recurrence, time to recurrence, or progression between treated and non-treated groups when stratified by grade/stage. No benefit shown for BCG. |
| Giannarini *et al.*, 2011 [78] | 22 | ND | BCG in 22 RU, 6-week course 360 mg (2.4 mg/mL) | Case series; endoscopic resection/ablation | median 42 | 13/22 (59) | 5/22 (23) | 5/22 (23) | 11/55 (20) adverse events*, including 1 fatal septicaemia | No non-treatment group. Benefit not demonstrated. |

*RU, renal units; PUO, pyrexia of unknown origin; RFS, recurrence-free survival; ND, not disclosed. *includes series of both CIS and papillary UTUC.*

*TABLE 5 Outcomes of studies using topical adjuvant BCG therapy for UT CIS. Only studies treating ≥10 renal units are shown*

| Study | *n* (RU) | BCG course | Follow-up, months | Initial positive response, *n* (%) | UT-recur., *n* (%) | Progression, *n* (%) | DSM, *n* (%) | Complications, *n* (%) |
|---|---|---|---|---|---|---|---|---|
| Sharpe *et al.*, 1993 [83] | 11 (17) | 120 mg (1.2 mg/mL), 6 weeks | mean 37; median 36 | 12/17 (71) | 0/12 (0) | 3/17 (18) | 1/11 | 6/11 troublesome LUTS; 3/11 haematuria; 1/11 fever requiring full anti-tuberculosis therapy |
| Nonomura *et al.*, 2000 [84] | 11 (11) | 80 mg (2 mg/mL), 6 weeks | mean 20 | 9/11 | 2/9 | 2/11 | 1/11 | 8/11 troublesome LUTS, 4/11 pyrexia >38 °C |
| Okubo *et al.*, 2001 [85] | 11 (14) | 40 mg (0.8 mg/mL), 6 weeks | median 49 | 9/14 | 2/9 | 4/14 | 1/11 | ND |
| Irie *et al.*, 2002 [86] | 9 (13) | 80–240 mg (0.5–2 mg/mL), 6 weeks | mean 36 | 13/13 | 3/13 | 0/13 | 0/9 | 5/13 troublesome LUTS, 2/13 pyrexia >38 °C |
| Miyake *et al.*, 2002 [87] | 16 (17) | 80 mg (1 mg/mL), 6 weeks | mean 31 | 17/17 (100) | 3/17 (18) | 2/17 (12) | 0/16 | 12/16 (75) troublesome LUTS, 9/16 (56) pyrexia >38 °C |
| Hayashida *et al.*, 2004 [88] | 10 (11) | (0.8–1.6 mg/mL), 6 weeks | mean 51 | 11/11 | 2/11 | 4/11 | 4/10 | 10/10 troublesome LUTS, 9/10 pyrexia >38 °C, 2/10 hydronephrosis, 1/10 ureteric stricture |
| Giannarini *et al.*, 2011 [78] | (42) | 360 mg (2.4 mg/mL), 6 weeks | median 42 | – | 17/42 (40) | 2/42 (5) | – | 11/55 (20) adverse events*, including 1 fatal septicaemia |
| **Total** | **68 (125)** | | | **61/83 (73)** | **29/113 (26)** | **17/125 (14)** | **7/68 (10)** | **13/20 (65) troublesome LUTS, 25/57 (44) pyrexia >38 °C** |

*RU, renal unit; PUO, pyrexia of unknown origin; ND, not disclosed. *Includes series of both CIS and papillary UTUC.*



 

experience has mainly been confined to few centres, with only four institutions publishing outcomes of >40 patients, beyond 50 months [11,12,22,23,47]. There are inherent difficulties in comparing the outcomes of different studies, due to differences in selection criteria (the distribution of imperative and elective cases), favourable tumour characteristics, changes in the WHO grading system (1973 Grade 1/2/3 and 2004 LG/HG) [89], and follow-up duration. However, collectively, several conclusions can be drawn from these studies. UTUC recurrence is common and occurs in most patients, which mandates regular endoscopic surveillance (motivation and compliance is essential). There appears to be a grade-related risk of tumour progression and a significant proportion of patients will ultimately fail endoscopic management with RNU ultimately carried out. For elective cases with selected favourable LG disease characteristics, endoscopic management appears to provide effective oncological control (5-year DSS) and renal preservation, but this has to be balanced against the risk of tumour progression and lower RFS compared with RNU outcomes [6]. The long-term (10-year DSS) outcomes are currently undefined and the patient's overall life-expectancy is a pivotal factor when considering endoscopic management. There is no place for endoscopic management for HG disease in elective (non-imperative) patients. For imperative HG cases with CKD, a balanced decision must be made regarding the patient's overall life expectancy in the context of their pre-existing comorbidity. The risk of poor oncological control and tumour progression with endoscopic management must be weighed up against the perioperative risks of undergoing major surgery (RNU), with the poor life expectancy associated with end-stage renal failure and haemodialysis as the consequence. This issue merits some attention as the annual mortality associated with end-stage renal disease is considerable, with an age-related trend of 21.4% for those aged 65–74 years, 38% for those aged >75 years, and 49.6% for those aged >85 years [90]. The mortality is about seven-times greater than that of the general population and 5-year OS for combined ages is only 39%. Even for patients with CKD stage 3–5 aged >65 years, the overall annual mortality may be as high as 16.9% with comorbidity, e.g. diabetes and cardiac failure [90].

It is likely in future that prospective collaborative studies using the new WHO grading system will provide more accurate information on longer-term (10-year) oncological outcomes on larger, more well-defined patient cohorts, where the durability of endoscopic management is currently undefined. Such studies may ultimately establish the long-term efficacy of endoscopic management and fully define its role in the management of non-invasive UTUC.

## CONFLICT OF INTEREST

None declared.

## REFERENCES


1 **Jemal A, Siegel R, Xu J, Ward E.** Cancer statistics, 2010. *CA Cancer J Clin* 2010; **60**: 277–300

2 **Roupret M, Zigeuner R, Palou J *et al*.** European guidelines for the diagnosis and management of upper urinary tract urothelial cell carcinomas: 2011 update. *Eur Urol* 2011; **59**: 584–94

3 **Hall MC, Womack S, Sagalowsky AI, Carmody T, Erickstad MD, Roehrborn CG.** Prognostic factors, recurrence, and survival in transitional cell carcinoma of the upper urinary tract: a 30-year experience in 252 patients. *Urology* 1998; **52**: 594–601

4 **Stewart GD, Bariol SV, Grigor KM, Tolley DA, McNeill SA.** A comparison of the pathology of transitional cell carcinoma of the bladder and upper urinary tract. *BJU Int* 2005; **95**: 791–3

5 **Babjuk M, Oosterlinck W, Sylvester R *et al*.** EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder, the 2011 update. *Eur Urol* 2011; **59**: 997–1008

6 **Margulis V, Shariat SF, Matin SF *et al*.** Outcomes of radical nephroureterectomy: a series from the Upper Tract Urothelial Carcinoma Collaboration. *Cancer* 2009; **115**: 1224–33

7 **Engelmyer EI, Belis JA.** Long-term ureteroscopic management of low-grade transitional cell carcinoma of the upper urinary tract. *Tech Urol* 1996; **2**: 113–6

8 **Jarrett TW, Sweetser PM, Weiss GH, Smith AD.** Percutaneous management of transitional cell carcinoma of the renal collecting system: 9-year experience. *J Urol* 1995; **154**: 1629–35

9 **Clark PE, Streem SB, Geisinger MA.** 13-year experience with percutaneous management of upper tract transitional cell carcinoma. *J Urol* 1999; **161**: 772–6

10 **Schmeller NT, Hofstetter AG.** Laser treatment of ureteral tumors. *J Urol* 1989; **141**: 840–3

11 **Thompson RH, Krambeck AE, Lohse CM, Elliott DS, Patterson DE, Blute ML.** Endoscopic management of upper tract transitional cell carcinoma in patients with normal contralateral kidneys. *Urology* 2008; **71**: 713–7

12 **Rastinehad AR, Ost MC, Vanderbrink BA *et al*.** A 20-year experience with percutaneous resection of upper tract transitional carcinoma: is there an oncologic benefit with adjuvant bacillus Calmette Guerin therapy? *Urology* 2009; **73**: 27–31

13 **Huang WC, Levey AS, Serio AM *et al*.** Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. *Lancet Oncol* 2006; **7**: 735–40

14 **Weight CJ, Larson BT, Fergany AF *et al*.** Nephrectomy induced chronic renal insufficiency is associated with increased risk of cardiovascular death and death from any cause in patients with localized cT1b renal masses. *J Urol* 2010; **183**: 1317–23

15 **Weight CJ, Larson BT, Gao T *et al*.** Elective partial nephrectomy in patients with clinical T1b renal tumors is associated with improved overall survival. *Urology* 2010; **76**: 631–7

16 **Thompson RH, Boorjian SA, Lohse CM *et al*.** Radical nephrectomy for pT1a renal masses may be associated with decreased overall survival compared with partial nephrectomy. *J Urol* 2008; **179**: 468–73

17 **Kaag MG, O'Malley RL, O'Malley P *et al*.** Changes in renal function following nephroureterectomy may affect the use of perioperative chemotherapy. *Eur Urol* 2010; **58**: 581–7

18 **Lane BR, Smith AK, Larson BT *et al*.** Chronic kidney disease after nephroureterectomy for upper tract urothelial carcinoma and implications for the administration of perioperative chemotherapy. *Cancer* 2010; **116**: 2967–73

19 **Martinez-Pineiro JA, Garcia Matres MJ, Martinez-Pineiro L.** Endourological

treatment of upper tract urothelial carcinomas: analysis of a series of 59 tumors. *J Urol* 1996; **156**: 377–85

20 **Deligne E, Colombel M, Badet L *et al*.** Conservative management of upper urinary tract tumors. *Eur Urol* 2002; **42**: 43–8

21 **Painter DJ, Denton K, Timoney AG, Keeley FX.** Ureteroscopic management of upper-tract urothelial cancer: an exciting nephron-sparing option or an unacceptable risk? *J Endourol* 2008; **22**: 1237–9

22 **Pak RW, Moskowitz EJ, Bagley DH.** What is the cost of maintaining a kidney in upper-tract transitional-cell carcinoma? An objective analysis of cost and survival. *J Endourol* 2009; **23**: 341–6

23 **Cutress ML, Stewart GD, Wells-Cole S, Phipps S, Thomas BG, Tolley DA.** Long-term endoscopic management of upper tract urothelial carcinoma (UTUC): 20-year single centre experience. *BJU Int* 2012; doi:10.1111/j.1464-410X.2012.11169.x

24 **Andersen JR, Kristensen JK.** Ureteroscopic management of transitional cell tumors. *Scand J Urol Nephrol* 1994; **28**: 153–7

25 **Gaboardi F, Bozzola A, Dotti E, Galli L.** Conservative treatment of upper urinary tract tumors with Nd:YAG laser. *J Endourol* 1994; **8**: 37–41

26 **Grasso M, Fraiman M, Levine M.** Ureteropyeloscopic diagnosis and treatment of upper urinary tract urothelial malignancies. *Urology* 1999; **54**: 240–6

27 **Daneshmand S, Quek ML, Huffman JL.** Endoscopic management of upper urinary tract transitional cell carcinoma: long-term experience. *Cancer* 2003; **98**: 55–60

28 **Matsuoka K, Lida S, Tomiyasu K, Inoue M, Noda S.** Transurethral endoscopic treatment of upper urinary tract tumors using a holmium:YAG laser. *Lasers Surg Med* 2003; **32**: 336–40

29 **Iborra I, Solsona E, Casanova J, Ricos JV, Rubio J, Climent MA.** Conservative elective treatment of upper urinary tract tumors: a multivariate analysis of prognostic factors for recurrence and progression. *J Urol* 2003; **169**: 82–5

30 **Johnson GB, Fraiman M, Grasso M.** Broadening experience with the retrograde endoscopic management of upper urinary tract urothelial malignancies. *BJU Int* 2005; **95** (Suppl. 2): 110–3

31 **Roupret M, Hupertan V, Traxer O *et al*.** Comparison of open nephroureterectomy and ureteroscopic and percutaneous management of upper urinary tract transitional cell carcinoma. *Urology* 2006; **67**: 1181–7

32 **Reisiger K, Hruby G, Clayman RV, Landman J.** Office-based surveillance ureteroscopy after endoscopic treatment of transitional cell carcinoma: technique and clinical outcome. *Urology* 2007; **70**: 263–6

33 **Krambeck AE, Thompson RH, Lohse CM, Patterson DE, Elliott DS, Blute ML.** Imperative indications for conservative management of upper tract transitional cell carcinoma. *J Urol* 2007; **178**: 792–7

34 **Lucas SM, Svatek RS, Olgin G *et al*.** Conservative management in selected patients with upper tract urothelial carcinoma compares favourably with early radical surgery. *BJU Int* 2008; **102**: 172–6

35 **Cornu JN, Roupret M, Carpentier X *et al*.** Oncologic control obtained after exclusive flexible ureteroscopic management of upper urinary tract urothelial cell carcinoma. *World J Urol* 2010; **28**: 151–6

36 **Gadzinski AJ, Roberts WW, Faerber GJ, Wolf JS Jr.** Long-term outcomes of nephroureterectomy versus endoscopic management for upper tract urothelial carcinoma. *J Urol* 2010; **183**: 2148–53

37 **Raymundo EM, Lipkin ME, Banez LB *et al*.** Third prize: the role of endoscopic nephron-sparing surgery in the management of upper tract urothelial carcinoma. *J Endourol* 2011; **25**: 377–84

38 **Tasca A, Zattoni F, Garbeglio A, Villi G, Bassi P, Meneghini A.** Endourologic treatment of transitional cell carcinoma of the upper urinary tract. *J Endourol* 1992; **6**: 253–6

39 **Fuglsig S, Krarup T.** Percutaneous nephroscopic resection of renal pelvic tumors. *Scand J Urol Nephrol* 1995; **172**: 15–7

40 **Plancke HR, Strijbos WE, Delaere KP.** Percutaneous endoscopic treatment of urothelial tumours of the renal pelvis. *Br J Urol* 1995; **75**: 736–9

41 **Patel A, Soonawalla P, Shepherd SF, Dearnaley DP, Kellett MJ, Woodhouse CR.** Long-term outcome after percutaneous treatment of transitional cell carcinoma of the renal pelvis. *J Urol* 1996; **155**: 868–74

42 **Goel MC, Mahendra V, Roberts JG.** Percutaneous management of renal pelvic urothelial tumors: long-term followup. *J Urol* 2003; **169**: 925–30

43 **Suh RS, Faerber GJ, Wolf JS Jr.** Predictive factors for applicability and success with endoscopic treatment of upper tract urothelial carcinoma. *J Urol* 2003; **170**: 2209–16

44 **Palou J, Piovesan LF, Huguet J, Salvador J, Vicente J, Villavicencio H.** Percutaneous nephroscopic management of upper urinary tract transitional cell carcinoma: recurrence and long-term followup. *J Urol* 2004; **172**: 66–9

45 **Roupret M, Traxer O, Tligui M *et al*.** Upper urinary tract transitional cell carcinoma: recurrence rate after percutaneous endoscopic resection. *Eur Urol* 2007; **51**: 709–14

46 **Elliott DS, Segura JW, Lightner D, Patterson DE, Blute ML.** Is nephroureterectomy necessary in all cases of upper tract transitional cell carcinoma? Long-term results of conservative endourologic management of upper tract transitional cell carcinoma in individuals with a normal contralateral kidney. *Urology* 2001; **58**: 174–8

47 **Krambeck AE, Thompson RH, Lohse CM *et al*.** Endoscopic management of upper tract urothelial carcinoma in patients with a history of bladder urothelial carcinoma. *J Urol* 2007; **177**: 1721–6

48 **Thompson RH, Krambeck AE, Lohse CM, Elliott DS, Patterson DE, Blute ML.** Elective endoscopic management of transitional cell carcinoma first diagnosed in the upper urinary tract. *BJU Int* 2008; **102**: 1107–10

49 **Keeley FX Jr, Bibbo M, Bagley DH.** Ureteroscopic treatment and surveillance of upper urinary tract transitional cell carcinoma. *J Urol* 1997; **157**: 1560–5

50 **Chromecki TF, Bensalah K, Remzi M *et al*.** Prognostic factors for upper urinary tract urothelial carcinoma. *Nat Rev Urol* 2011; **8**: 440–7

51 **Elliott DS, Blute ML, Patterson DE, Bergstralh EJ, Segura JW.** Long-term follow-up of endoscopically treated upper urinary tract transitional cell carcinoma. *Urology* 1996; **47**: 819–25

52 **Liatsikos EN, Dinlenc CZ, Kapoor R,**

**Smith AD.** Transitional-cell carcinoma of the renal pelvis: ureteroscopic and percutaneous approach. *J Endourol* 2001; **15**: 377–83

53 **Rastinehad AR, Ost MC, Greenberg KL *et al*.** Does adjuvant BCG therapy reduce the incidence or time to recurrence in upper tract transitional cell carcinoma? A 20 years experience. *J Urol* 2007; **177** (Suppl.): 138

54 **Lee BR, Jabbour ME, Marshall FF, Smith AD, Jarrett TW.** 13-year survival comparison of percutaneous and open nephroureterectomy approaches for management of transitional cell carcinoma of renal collecting system: equivalent outcomes. *J Endourol* 1999; **13**: 289–94

55 **Waldert M, Karakiewicz PI, Raman JD *et al*.** A delay in radical nephroureterectomy can lead to upstaging. *BJU Int* 2010; **105**: 812–7

56 **Hendin BN, Streem SB, Levin HS, Klein EA, Novick AC.** Impact of diagnostic ureteroscopy on long-term survival in patients with upper tract transitional cell carcinoma. *J Urol* 1999; **161**: 783–5

57 **Boorjian S, Ng C, Munver R *et al*.** Impact of delay to nephroureterectomy for patients undergoing ureteroscopic biopsy and laser tumor ablation of upper tract transitional cell carcinoma. *Urology* 2005; **66**: 283–7

58 **El-Hakim A, Weiss GH, Lee BR, Smith AD.** Correlation of ureteroscopic appearance with histologic grade of upper tract transitional cell carcinoma. *Urology* 2004; **63**: 647–50

59 **Tawfiek E, Bibbo M, Bagley DH.** Ureteroscopic biopsy: technique and specimen preparation. *Urology* 1997; **50**: 117–9

60 **Keeley FX, Kulp DA, Bibbo M, McCue PA, Bagley DH.** Diagnostic accuracy of ureteroscopic biopsy in upper tract transitional cell carcinoma. *J Urol* 1997; **157**: 33–7

61 **Williams SK, Denton KJ, Minervini A *et al*.** Correlation of upper-tract cytology, retrograde pyelography, ureteroscopic appearance, and ureteroscopic biopsy with histologic examination of upper-tract transitional cell carcinoma. *J Endourol* 2008; **22**: 71–6

62 **Painter DJ, Timoney AG, Denton K, Alken P, Keeley FX Jr.** The modern management of upper urinary tract urothelial cancer: tumour diagnosis, grading and staging. *BJU Int* 2007; **99**: 973–7

63 **Tavora F, Fajardo DA, Lee TK *et al*.** Small endoscopic biopsies of the ureter and renal pelvis: pathologic pitfalls. *Am J Surg Pathol* 2009; **33**: 1540–6

64 **Smith AK, Stephenson AJ, Lane BR *et al*.** Inadequacy of biopsy for diagnosis of upper tract urothelial carcinoma: implications for conservative management. *Urology* 2011; **78**: 82–6

65 **Chen GL, El-Gabry EA, Bagley DH.** Surveillance of upper urinary tract transitional cell carcinoma: the role of ureteroscopy, retrograde pyelography, cytology and urinalysis. *J Urol* 2000; **164**: 1901–4

66 **Guarnizo E, Pavlovich CP, Seiba M, Carlson DL, Vaughan ED Jr, Sosa RE.** Ureteroscopic biopsy of upper tract urothelial carcinoma: improved diagnostic accuracy and histopathological considerations using a multi-biopsy approach. *J Urol* 2000; **163**: 52–5

67 **Shiraishi K, Eguchi S, Mohri J, Kamiryo Y.** Role of ureteroscopic biopsy in the management of upper urinary tract malignancy. *Int J Urol* 2003; **10**: 627–30

68 **Brown GA, Matin SF, Busby JE *et al*.** Ability of clinical grade to predict final pathologic stage in upper urinary tract transitional cell carcinoma: implications for therapy. *Urology* 2007; **70**: 252–6

69 **Brien JC, Shariat SF, Herman MP *et al*.** Preoperative hydronephrosis, ureteroscopic biopsy grade and urinary cytology can improve prediction of advanced upper tract urothelial carcinoma. *J Urol* 2010; **184**: 69–73

70 **Skolarikos A, Griffiths TR, Powell PH, Thomas DJ, Neal DE, Kelly JD.** Cytologic analysis of ureteral washings is informative in patients with grade 2 upper tract TCC considering endoscopic treatment. *Urology* 2003; **61**: 1146–50

71 **Somani BK, Moseley H, Eljamel MS, Nabi G, Kata SG.** Photodynamic diagnosis (PDD) for upper urinary tract transitional cell carcinoma (UT-TCC): evolution of a new technique. *Photodiagnosis Photodyn Ther* 2010; **7**: 39–43

72 **Somani B, Ahmed S, Nabi G, Kata SG.** Diagnosis of upper and lower urinary tract transitional cell carcinoma (TCC) using oral 5-Aminolevulanic acid (5-ALA) and phtodynamic diagnosis (PDD): prospective cohort study. *BJU Int* 2011; **108** (Suppl. 1): (P74) 47

73 **Traxer O, Geavlete B, de Medina SG, Sibony M, Al-Qahtani SM.** Narrow-band imaging digital flexible ureteroscopy in detection of upper urinary tract transitional-cell carcinoma: initial experience. *J Endourol* 2011; **25**: 19–23

74 **Mian C, Mazzoleni G, Vikoler S *et al*.** Fluorescence in situ hybridisation in the diagnosis of upper urinary tract tumours. *Eur Urol* 2010; **58**: 288–92

75 **Keeley FX Jr, Bagley DH.** Adjuvant mitomycin C following endoscopic treatment of upper tract transitional cell carcinoma. *J Urol* 1997; **158**: 2074–7

76 **Patel A, Fuchs GJ.** New techniques for the administration of topical adjuvant therapy after endoscopic ablation of upper urinary tract transitional cell carcinoma. *J Urol* 1998; **159**: 71–5

77 **Katz MH, Lee MW, Gupta M.** Setting a new standard for topical therapy of upper-tract transitional-cell carcinoma: BCG and interferon-alpha2B. *J Endourol* 2007; **21**: 374–7

78 **Giannarini G, Kessler TM, Birkhauser FD, Thalmann GN, Studer UE.** Antegrade perfusion with bacillus Calmette-Guerin in patients with non-muscle-invasive urothelial carcinoma of the upper urinary tract: who may benefit? *Eur Urol* 2011; **60**: 955–60

79 **Vasavada SP, Streem SB, Novick AC.** Definitive tumor resection and percutaneous bacille Calmette-Guerin for management of renal pelvic transitional cell carcinoma in solitary kidneys. *Urology* 1995; **45**: 381–6

80 **Thalmann GN, Markwalder R, Walter B, Studer UE.** Long-term experience with bacillus Calmette-Guerin therapy of upper urinary tract transitional cell carcinoma in patients not eligible for surgery. *J Urol* 2002; **168**: 1381–5

81 **Orihuela E, Smith AD.** Percutaneous treatment of transitional cell carcinoma of the upper urinary tract. *Urol Clin North Am* 1988; **15**: 425–31

82 **Jabbour ME, Smith AD.** Primary percutaneous approach to upper urinary tract transitional cell carcinoma. *Urol Clin North Am* 2000; **27**: 739–50

83 **Sharpe JR, Duffy G, Chin JL.** Intrarenal bacillus Calmette-Guerin therapy for upper urinary tract carcinoma in situ. *J Urol* 1993; **149**: 457–60

84 **Nonomura N, Ono Y, Nozawa M *et al*.** Bacillus Calmette-Guerin perfusion therapy for the treatment of transitional cell carcinoma in situ of the upper urinary tract. *Eur Urol* 2000; **38**: 701–5
85 **Okubo K, Ichioka K, Terada N, Matsuta Y, Yoshimura K, Arai Y.** Intrarenal bacillus Calmette-Guerin therapy for carcinoma in situ of the upper urinary tract: long-term follow-up and natural course in cases of failure. *BJU Int* 2001; **88**: 343–7
86 **Irie A, Iwamura M, Kadowaki K, Ohkawa A, Uchida T, Baba S.** Intravesical instillation of bacille Calmette-Guerin for carcinoma in situ of the urothelium involving the upper urinary tract using vesicoureteral reflux created by a double-pigtail catheter. *Urology* 2002; **59**: 53–7
87 **Miyake H, Eto H, Hara S, Okada H, Kamidono S, Hara I.** Clinical outcome of bacillus Calmette-Guerin perfusion therapy for carcinoma in situ of the upper urinary tract. *Int J Urol* 2002; **9**: 677–80
88 **Hayashida Y, Nomata K, Noguchi M *et al*.** Long-term effects of bacille Calmette-Guerin perfusion therapy for treatment of transitional cell carcinoma in situ of upper urinary tract. *Urology* 2004; **63**: 1084–8
89 **Montironi R, Lopez-Beltran A, Scarpelli M, Mazzucchelli R, Cheng L.** 2004 World Health Organization Classification of the Noninvasive Urothelial Neoplasms: Inherent Problems and Clinical Reflections. *Eur Urol Suppl* 2009; **8**: 453–7
90 **USRDS.** *United States Renal Data System 2010 Annual Data Report. Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2010
91 **Blute ML, Segura JW, Patterson DE, Benson RC Jr, Zincke H.** Impact of endourology on diagnosis and management of upper urinary tract urothelial cancer. *J Urol* 1989; **141**: 1298–301
92 **Lee D, Trabulsi E, McGinnis D, Strup S, Gomella LG, Bagley D.** Totally endoscopic management of upper tract transitional-cell carcinoma. *J Endourol* 2002; **16**: 37–41
93 **Sowter SJ, Ilie CP, Efthimiou I, Tolley DA.** Endourologic management of patients with upper-tract transitional-cell carcinoma: long-term follow-up in a single center. *J Endourol* 2007; **21**: 1005–9
94 **Jabbour ME, Desgrandchamps F, Cazin S, Teillac P, Le Duc A, Smith AD.** Percutaneous management of grade II upper urinary tract transitional cell carcinoma: the long-term outcome. *J Urol* 2000; **163**: 1105–7

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Abbreviations: **(UT)UC**, (upper tract) urothelial carcinoma; **RNU**, radical nephroureterectomy; **CKD**, chronic kidney disease; **URS(a)**, ureteroscopy (with ablation using electro-diathermy or laser); **PNRT**, percutaneous nephroscopic resection of tumour; **OS**, overall survival; **DSS**, disease-specific survival; **RUS**, renal-unit survival; **DSM**, disease-specific mortality; **MMC**, mitomycin C; **CIS**, carcinoma *in situ*.