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# Long-term endoscopic management of upper tract urothelial carcinoma: 20-year single-centre experience

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Study Type – Therapy (case series)
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**What's known on the subject? and What does the study add?**
Endoscopic management of small, low-grade, non-invasive upper tract urothelial cell carcinoma (UTUC) is a management option for selected groups of patients. However, the long-term survival outcomes of endoscopically-managed UTUC are uncertain because only four institutions have reported outcomes of more than 40 patients beyond 50 months of follow-up. Moreover, there is significant variance in the degree of underlying UTUC pathology verification in some of these reports, which precludes an analysis of disease-specific survival outcomes.

The present study represents one of the largest endoscopically managed series of patients with UTUC, with a long-term follow-up. The degree of verification of underlying UTUC pathology is one of the highest, which allows a grade-stratified analysis of different outcomes, including upper-tract recurrence-free survival, intravesical recurrence-free survival, renal unit survival and disease-specific survival. These outcomes provide further evidence suggesting that endoscopic management of highly selected, low-grade UTUC can provide effective oncological control, as well as renal preservation, in experienced centres.

## OBJECTIVE

- To report the long-term outcomes of patients with upper tract urothelial cell carcinoma (UTUC) who were treated endoscopically (either via ureteroscopic ablation or percutaneous resection) at a single institution over a 20-year period.

## PATIENTS AND METHODS

- Departmental operation records were reviewed to identify patients who underwent endoscopic management of UTUC as their primary treatment.
- Outcomes were obtained via retrospective analysis of notes, electronic records and registry data.
- Survival outcomes, including overall survival (OS), UTUC-specific survival (disease-specific survival; DSS), upper-tract recurrence-free survival, intravesical recurrence-free survival, renal unit survival and progression-free survival, were estimated using Kaplan–Meier methods and grade-stratified differences were analyzed using the log-rank test.

## RESULTS

- Between January 1991 and April 2011, 73 patients underwent endoscopic management of UTUC with a median age at diagnosis of 67.7 years.
- All patients underwent ureteroscopy and biopsy-confirmation of pathology was obtained in 81% ($n = 59$) of the patients. In total, 14% ($n = 10$) of the patients underwent percutaneous resection.
- Median (range; mean) follow-up was 54 (1–223; 62.8) months.
- Upper tract recurrence occurred in 68% ($n = 50$). Eventually, 19% ($n = 14$) of the patients proceeded to nephroureterectomy.
- The estimated OS and DSS were 69.7% and 88.9%, respectively, at 5 years, and 40.3% and 77.4%, respectively, at 10 years. The estimated mean and median OS times were 119 months and 107 months, respectively. The estimated mean DSS time was 190 months.

## CONCLUSIONS

- The present study represents one of the largest reported series of endoscopically-managed UTUC, with high pathological verification and long-term follow-up.
- Upper-tract recurrence is common, which mandates regular ureteroscopic surveillance.
- However, in selected patients, this approach has a favourable DSS, with a relatively low nephroureterectomy rate, and therefore provides oncological control and renal preservation in patients more likely to die eventually from other causes.

## KEYWORDS

endoscopic management, percutaneous resection, upper tract urothelial carcinoma, ureteroscopy

*TABLE 1 Comparison of studies reporting outcomes of patients undergoing ureteroscopic management of upper tract urothelial cell carcinoma (UTUC), where N > 40*

| Study (year) | *N* | Bx (G1/G2/G3), *n* | Previous urothelial carcinoma of the bladder, *n* (%) | Follow-up (months) | UT-Rec, *n* (%) | Bl-Rec, *n* (%) | OM, *n* (%) | DSM, *n* (%) | NU, *n* (%) | Complications, *n* (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Martinez-Pineiro *et al.* [22] (1996) | 54 | 52 (24/18/10)* | 24 (44) | Mean 31 | 9/39 (23) | ND | 11/44 (25) | 4/44 (9) | 5/44 (11) | 9 (23) ureteric stricture/ perforation |
| Keeley *et al.* [23] (1997)† | 41 | 40 (21/14/5) | 20 (49) | Median 26 | 8/41 (20) | 15/41 (37) | ND | 0 | 8/41 (20) | 2 (5) strictures, 2 (5) renal failure |
| Deligne *et al.* [25] (2002) | 61 | 53 (21/24/8) | 15 (25) | Mean 40 | 15/61 (25) | 14/61 (23) | 13/55 (24) | 8/55 (15) | 11/61 (18) | 2 (3) strictures – both required nephroureterectomy |
| Krambeck *et al.* [15] (2007)‡ | 90 | 48 (14/21/13) | 90 (100) | Median 51 | 55/90 (61) | 38/90 (42) | 48/90 (53) | 17/90 (19) | 29/90 (32) | 27 (30) overall: 11 (12) stricture, 8 (9) sepsis, 4 (4) perforation |
| Thompson *et al.* [16] (2008)‡ | 83 | 40 (14/18/8) | 61 (73) | Median 55 | 46/83 (55) | 37/83 (45) | 35/83 (42) | 9/83 (11) | 27/83 (33) | ND |
| Pak *et al.* [26] (2009)† | 57 | ND | ND | Mean 53 | 51/57 (90) | ND | 4/57 (7) | 3/57 (5) | 11/57 (19) | ND |
| Present study | 73 | 59 (34/19/6) | 34 (47) | Median 54 | 50/73 (68) | 31/73 (53) | 29/73 (40) | 7/73 (10) | 14/73 (19) | 14 (19) overall: 12 (16) strictures, 1 (1) nephroureterectomy for bleeding, 1 (1) small bowel injury |

*A number of the reported studies are from the same institute and contain updated clinical information on the same patients. Verification of underlying UTUC pathology is variable. Upper tract recurrence is significant, and ≈20% of patients eventually undergo nephroureterectomy. Disease-specific mortality (DSM) is generally low in these series. Bx, histopathologically proven UTUC. *Including some patients treated with percutaneous nephroscopic resection of tumour. ND, not disclosed; †‡From the same institution. Bl-Rec, bladder recurrence; DSM: disease-specific mortality; NU, patients proceeding to nephroureterectomy; OM, overall mortality; UT-Rec, upper tract recurrence.*

## INTRODUCTION

Upper tract urothelial cell carcinomas (UTUCs) are relatively uncommon tumours, comprising 10% of all renal tumours and 5% of all urothelial malignancies [1–3]. The annual incidence is Western countries is ≈2 : 100 000 of the population, with a peak age incidence of 70–80 years [1,3]. Unlike bladder cancer, UTUC is a more aggressive disease and typically presents with a higher grade and stage [4] and, consequently, has a poorer prognosis [1]. Accordingly, radical nephroureterectomy (RNU) with excision of the ipsilateral bladder cuff is considered to be the gold standard treatment [3,5].

However, it has become increasingly recognized that, despite radical surgery, a significant proportion of patients still die from their disease, perhaps as a result of micro-metastatic disease at the time of surgery, with a 5-year disease specific mortality of 15–30% [5–8].

Although the oncological outcomes of RNU are clear, there are several factors that have renewed the interest in the local management of UTUC with ureteroscopy and laser ablation therapy, including the multifocal recurrent nature of UTUC and the potential benefits of nephron-sparing surgery. Overall, ≈5% of patients develop a contralateral upper tract recurrence [3], which precludes the use of RNU in all patients. There is also evidence that nephron-sparing surgery minimizes the risk of progression to new onset chronic kideney disease stage 3b (GFR <45 mL/min) disease, compared to radical nephrectomy, for the treatment of RCC (5% vs 36%) [9] and this may improve both cardiovascular and overall survival [10–13].

Although ureteroscopic management of UTUC is a recognized option for select patients [3], there is a natural inertia for active adoption for the endoscopic management of UTUC, principally as a result of three main factors: a paucity of large-scale studies, poor pathological verification in many published studies and a limited follow-up [14]. These factors preclude any meaningful interpretation of disease-specific survival (DSS) outcomes and only four different institutions have reported outcomes for cohorts of more than 40 patients, with variable levels of pathological verification and duration of follow-up (Table 1). To date, only one institution has reported outcomes of more than 40 patients beyond a median follow-up >50 months, and the proportion of patients with pathological verification of UTUC was in the range 48–54% [15,16].

Our institution has over 20 years of experience in the minimally-invasive management of UTUC. The present study aimed to report the long-term outcomes of the endoscopic management of UTUC patients who were treated either ureteroscopically or percutaneously (percutaneous nephroscopic resection of tumour, PNRT). A strong feature of the present study is the high proportion of patients with pathological verification of UTUC and long-term follow-up compared to other published studies, which permits stratification of long-term outcomes by grade.

## PATIENTS AND METHODS

### PATIENTS AND PROCEDURES

A departmental retrospective review of all endourology operative records spanning a 20-year period (January 1991 to April 2011) was undertaken aiming to identify patients who had undergone endoscopic management of UTUC as their primary treatment. This included both ureteroscopic ablation and percutaneous resection (i.e. PNRT) using techniques described previously [16]. A number of patients received adjuvant topical treatment with mitomycin C, administered via nephrostomy tube after PNRT, or via a ureteric catheter after ureteroscopic ablation.

Hospital medical records (including case notes and electronic records) were retrospectively studied to assess the mode of presentation, pathological verification, indication for treatment and outcome data (including recurrence, progression, further intervention, complications and vital status). The cause of death for all deceased patients was obtained from death certificates held at the General Registry Office of Scotland.

### PATHOLOGICAL VERIFICATION

Pathological verification was obtained via ureteroscopic cold-cup biopsy (Cook 3 F [Cook Medical, Inc., Bloomington, IN, USA] or Piranha 3 F [Boston Scientific, Natick, MA, USA]) or percutaneous resection specimens as described previously by our group [17] and in other studies [18–20]. Pathological grading was conducted in accordance with the 1973 WHO criteria [21].

### FOLLOW-UP

Patients initially underwent cystoscopy and ureteroscopy surveillance at 3 months as described previously [16]. The length of further follow-up intervals was determined by the presence of any recurrence, with further cystoscopy and ureteroscopy carried out at 6–12-month intervals. The frequency of cystoscopic assessment was also determined by previous bladder cancer. Further upper tract imaging was via retrograde ureteropyelography, IVU or CT urography.

### STATISTICAL ANALYSIS

The last follow-up date was taken at the point of most recent upper tract assessment, or the date of death. Disease recurrence was defined as ipsilateral or contralateral upper-tract recurrence determined ureteroscopically or radiologically, or the presence of distant metastases. Intravesical recurrence was determined cystoscopically with pathological confirmation. DSS was determined by the number of deaths directly attributable to urothelial carcinoma according to registry data and a review of clinical case notes. Disease progression was defined as clinical or radiological upstaging, or subsequent pathological upgrading or upstaging in patients who underwent nephroureterectomy. Overall survival (OS), UTUC-specific survival (DSS), local recurrence-free survival (UT-RFS), bladder recurrence-free survival (BI-RFS), renal unit survival (RUS) and progression-free survival (PFS) were estimated using the Kaplan–Meier method. Statistical analysis was performed using SPSS, version 20 (IBM, New York, NY, USA) using the log-rank test. $P < 0.05$ was considered statistically significant. Cox regression analysis was used for multivariate analysis.

## RESULTS

### PATIENT DEMOGRAPHICS AND TUMOUR CHARACTERISTICS

Table 2 illustrates the descriptive characteristics of the patients who were treated endoscopically for UTUC. The median (range) age was 69.3 (36–87) years and patient anaesthetic fitness was generally classified as American Society of Anesthesiologists (ASA) grade 2 or ASA grade 3, in similar proportions (45.2% and 41.1%, respectively). There were 34 (46.6%) patients with a previous history of bladder cancer (i.e. urothelial carcinoma). The most common modes of presentation were with haematuria (49.3%) or as a result of routine upper tract imaging investigations conducted during bladder cancer follow-up. Most upper tract tumours were in the lower third ureter (54.8%) or renal pelvis (35.6%). A significant proportion was also multifocal (21.9%).

Pathological verification of urothelial carcinoma via biopsy was obtained in 59 (80.8%) patients. Overall, 46.6% of all upper tract tumours were grade 1, with ≈26% being grade 2. Patients with grade 3 urothelial carcinoma comprised just 8.2% of the study population. In 14 patients, biopsies were not obtained (or were insufficient for pathological diagnosis) and were assigned as 'visual low grade'. These were excluded from the grade-stratified survival outcomes.

The indication for endoscopic management was considered to be imperative in eight patients as a result of the presence of a single kidney in six (8.2%) patients and bilateral UTUC in two (2.7%) patients. These patients with bilateral UTUC underwent unilateral nephroureterectomy soon after diagnosis aiming to treat the side with the larger tumour bulk. Other indications were relative, including medical comorbidity in 18 (24.7%) patients, or elective, including small low grade (including visual low grade) urothelial carcinoma in 37 (50.7%) patients. Mean follow-up for all patients was 62.8 months (5.2 years) with a median follow-up of 54.0 months (4.5 years).

### PROCEDURES

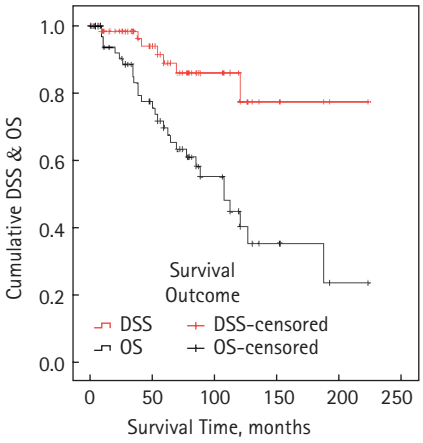
A total of 417 recorded ureteroscopic procedures (a median of four per patient) were performed, representing 96.5% of all procedures. Fifteen percutaneous resections (i.e. PNRT) were carried out in 10 patients, representing 3.5% of all procedures. There were no recorded instances of urothelial carcinoma seeding through percutaneous access tracts. Adjuvant treatment with mitomycin C was administered to 18 (24.7%) patients, with a total of 29 instillations. These were administered via nephrostomy tube (10 instillations, including one 6-week course) or via placement of ureteric catheter or in the presence of ureteric stent (19 instillations).

| Variable | Value |
|---|---|
| Patient characteristic | |
| Age (years), median (range) | 69.3 (35.8–87.1) |
| Sex (male/female), *n* (%) | 45 (61.6)/28 (38.4) |
| Laterality (left/right/bilateral), *n* (%) | 38 (52.1)/33 (45.2)/2 (2.7) |
| ASA grade, *n* (%) | |
| 1 | 3 (4.1) |
| 2 | 33 (45.2) |
| 3 | 30 (41.1) |
| 4 | 1 (1.4) |
| Unclassified | 7 (9.6) |
| Indications for management, *n* (%) | |
| Imperative | |
| Solitary kidney | 6 (8.2) |
| Bilateral UTUC | 2 (2.7) |
| Relative | |
| Advanced medical comorbidity | 18 (24.7) |
| Elective | |
| Small low-grade tumour | 37 (50.7) |
| Previous urothelial carcinoma of the bladder, *n* (%) | 34 (46.6) |
| Mode of presentation, *n* (%) | |
| Haematuria | 36 (49.3) |
| Routine upper tract imaging for urothelial carcinoma of the bladder | 24 (32.9) |
| Loin pain | 6 (8.2) |
| Incidental | 7 (9.6) |
| Follow-up duration (months) | |
| Median (years; range) | 54.0 (4.5; 1–223) |
| Mean (years) | 62.8 (5.2) |
| Tumour characteristics | |
| Tumour size (mm), median (range) | 10 (3–30) |
| Tumour location, *n* (%) | |
| RP | 26 (35.6) |
| UU | 4 (5.5) |
| MU | 5 (6.8) |
| LU | 41 (56.2) |
| Multifocal | 16 (21.9) |
| Bx – tumour grade, *n* (%) | |
| G1 | 34 (46.6) |
| G2 | 19 (26.0) |
| G3 | 6 (8.2) |
| Unverified – vlg | 14 (19.2) |
| Bx – tumour stage, *n* (%) | |
| pTa | 56 (7.7) |
| pT1 | 3 (4.1) |
| Unverified | 14 (19.2) |
| Operative characteristics | |
| Procedures performed | |
| URSa | |
| Total (proportion of procedures; %) | 417 (96.5) |
| Number of patients undergoing procedure (%) | 73 (100) |
| Median (mean) per patient | 4 (5.2) |
| PNRT | |
| Total (proportion of procedures; %) | 15 (3.5) |
| Number of patients undergoing procedure (%) | 10 (13.7) |
| Median (mean) per patient | 1 (1.5) |
| Adjuvant topical mitomycin C, *n* (%) | 18 (24.7) |
| Complications, *n* (%) | |
| Stricture | 12 (16.4) |
| Nephroureterectomy for haemorrhage | 1 (1.4) |
| Small bowel injury | 1 (1.4) |

*TABLE 2*
*Descriptive characteristics of 73 patients undergoing endoscopic management of upper tract urothelial cell carcinoma (UTUC)*

*Bx, biopsy; LU, lower ureter; MU, mid-ureter; PNRT, percutaneous resection of tumour; RP, renal pelvis; URSa, ureteroscopic ablation; UU, upper ureter; vlg, visual low-grade.*

*FIG. 1. Overall survival (OS) and disease-specific survival (DSS) for endoscopically-managed upper tract urothelial cell carcinoma (UTUC) patients. Endoscopic management provides effective oncological control for patients who are more likely to die from other causes.*




The overall complication rate was 19%. This included the formation of strictures in 12 (16.4%) patients, one of whom underwent a nephroureterectomy for failed ureteroscopic access. Other complications included one ureteric perforation with Nd:YAG laser injury to the small bowel (treated with laparotomy and small bowel resection) and secondary haemorrhage after PNRT (treated with nephroureterectomy the next day).

Kaplan–Meier estimations of different survival outcomes are shown in Figs 1 and 2 and Table 3. Multivariate analysis showed the upper tract tumour grade to be an independent prognostic factor for all survival outcomes analyzed (Table 4). The different survival outcomes have therefore been stratified by grade (Fig. 3 and Table 3).

## PATIENT SURVIVAL: OS AND DSS

Overall, 29 (39.7%) patients died during follow-up, after a median period of 54 months. There were seven (9.6%) patients with disease-specific mortality (DSM). The estimated OS and DSS was 69.7% and 88.9%, respectively, at 5 years, and 40.3% and 77.4%, respectively, at 10 years (Fig. 1 and Table 3). Median OS was 107 months and the mean DSS time was 189.7 months.

When stratifying patients by tumour grade, G1 patients had superior DSS to G2 ($P =$

0.002) and G3 ($P = 0.023$) (Fig. 3a). There was only one DSM for those with grade 1 tumours (2.9%) compared to six DSMs for those with grade 2 and 3 tumours (24%).

### UPPER TRACT RECURRENCE (UT-REC)

A total of 50 (68.5%) patients experienced 164 upper tract recurrence over follow-up, with a mean of 3.3 amongst these patients or 2.2 per patient for the entire cohort. The remaining 23 (31.5%) patients were recurrence-free after initial treatment, and the mean follow-up and pathological verification were 69.7 months and 17/23 (73.9%), respectively, for this recurrence-free subgroup. Estimated UT-RFS was 53.4% at 5 years and 20.5% at 10 years (Fig. 2). There was a clear trend for early UT-Rec with increasing grade ($P = 0.002$), as shown in Fig. 3b and Table 3. Overall, the median UT-RFS was 72 months.

A total of 18 (24.7%) patients underwent adjuvant topical treatment with mitomycin C. The estimated 5-year UT-RFS was 53.8% for patients treated with adjuvant mitomycin C and 54.2% for those without adjuvant treatment ($P = 0.185$). Even when sub-stratifying by UTUC grade, adjuvant treatment did not show any difference in UT-RFS for G1 ($P = 0.686$), G2 ($P = 0.153$) or G3 ($P = 0.898$) UTUC.

### INTRAVESICAL RECURRENCE (BL-REC)

A total of 31 (42.5%) patients experienced bladder recurrence over follow-up. The estimated BI-RFS was 68.9% at 5 years and 36.4% at 10 years (Fig. 2). There was a clear trend for early BI-Rec with increasing grade ($P < 0.001$), as shown in Fig. 3c and Table 3. Overall, the median BI-RFS was 119 months. BI-RFS was superior in patients with no previous history of urothelial carcinoma of the bladder (group A) compared to those with a previous history of urothelial carcinoma of the bladder (group B) ($P = 0.029$) (Table 3) and multivariate analysis showed that both UTUC grade and previous urothelial carcinoma of the bladder were independent prognostic factors for BI-Rec (Table 4).

### NEPHROURETERECTOMY AND RUS

A total of 14 (19.2%) patients proceeded to nephroureterectomy over follow-up. The estimated RUS was 84.6% at 5 years and 65.4% at 10 years (Fig. 2). There was a clear trend for early nephroureterectomy with increasing tumour grade ($P = 0.001$), with G1 and G2 showing superior RUS to G3 disease ($P < 0.001$ and $P = 0.011$, respectively) (Fig. 3d and Table 3). Overall, the median RUS was 187 months.

There was a strong pathological concordance of initial pathological biopsy grade and final nephroureterectomy specimen for 10 of 13 (76.9%) patients. A single nephroureterectomy pathology report was unrecorded in a patient who died after surgery.

### DISEASE PROGRESSION AND ENDOSCOPIC MANAGEMENT FAILURE

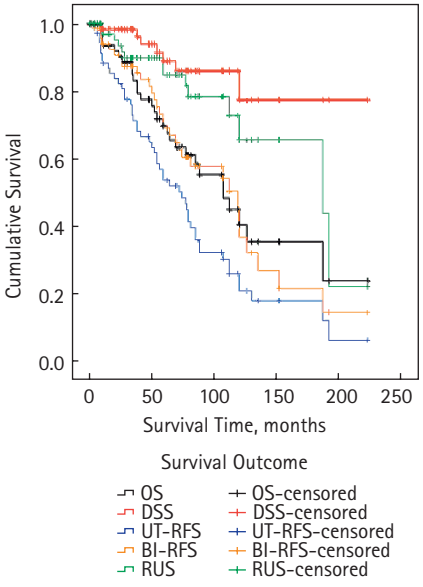
A total of 14 (19.2%) patients had evidence of disease progression. These included seven DSMs and three tumour upgradings on final nephroureterectomy specimen, as well as one metastatic and one locally-advanced disease progression. Two patients who were assigned visual low-grade tumours on ureteroscopic appearance were subsequently found to have G2pTa and G3pTa with carcinoma *in situ*. The estimated PFS was 84.1% at 5 years and 60.3% at 10 years. There was a trend for early progression with higher increasing tumour grade ($P = 0.001$), with G1 showing superior PFS compared to G2 or G3 ($P = 0.008$ and 0.004, respectively) (Fig. 3e and Table 3). The median PFS was 187 months.

Overall, a total of 22 (30.1%) patients could be considered to have failed endoscopic management, defined by DSM, disease progression or subsequent nephroureterectomy for any cause. The estimated endoscopic failure-free survival was 74.7% at 5 years and 51.5% at 10 years, with a clear trend for early failure with increasing tumour grade ($P = 0.001$) (Fig. 3f and Table 3). The median endoscopic failure-free survival was 17 months.

## DISCUSSION

The present series represents one of the largest patient cohorts of endoscopically-treated UTUC. A strength of the present study is the high pathological verification (80.8%) and the long-term follow-up (mean of 62.8 months) compared to previous studies [15,16,22,23] (Table 1), which permits a grade-stratified analysis of long-term survival outcomes (Fig. 3).

*FIG. 2. All outcomes of endoscopically-managed upper tract urothelial cell carcinoma (UTUC) patients, including overall survival (OS), disease-specific survival (DSS), local recurrence-free survival (UT-RFS), intravesical recurrence-free survival (BI-RFS) and renal unit survival (RUS).*




It is recognized that endoscopic management of UTUC is an option for solitary low-grade UTUC [3], although the lack of any substantive studies of pathologically-confirmed patients inherently precludes any definitive oncological conclusions on the long-term efficacy of endoscopic treatment, particularly DSS. The strength of pathological confirmation in the present study does, however, provide sound evidence that endoscopic treatment of UTUC offers effective oncological control with an acceptable DSS for selected patients. The UTUC Collaborative recently reported the outcomes of 1363 patients treated with nephroureterectomy, with a DSS >91% (91–93.5%) at 5 years and >85% (85.4–89.6%) at 10 years for pTa/Tis/T1 disease [5]. The estimated DSS of the present series compares favourably, with a 5- and 10-year DSS of 88.9% and 77.4%, respectively, overall, and 100% and 80% for G1 UTUC. DSS does, however, reduce significantly with increasing grade, highlighting the importance of pathological confirmation and appropriate patient selection for endoscopic

*TABLE 3 Different survival outcomes of upper tract urothelial cell carcinoma patients managed endoscopically, stratified by grade*

| Factor | Analysis | Survival (months), mean (95% CI) (years) | Survival (months), median (95% CI) (years) | Estimated 5-year survival (%) | Estimated 10-year survival (%) | *P* |
|---|---|---|---|---|---|---|
| OS | Overall | 118.5 (94.7–142.2) (9.9) | 107.0 (71.3–142.7) (8.9) | 69.7 | 40.3 | <0.001* |
| | G1 | 103.6 (84.1–123.0) (8.6) | 120.0 (74.2–165.8) (10) | 74.5 | 43.3 | G1 vs G2: 0.111 |
| | G2 | 74.6 (49.7–99.6) (6.2) | 64.0 (50.3–77.7) (5.3) | 55.6 | 16.7 | G1 vs G3: 0.001* |
| | G3 | 44.8 (5.2–84.5) (3.7) | 10.0 (0.0–23.6) (0.8) | 33.3 | – | G2 vs G3: 0.098 |
| DSS | Overall | 189.7 (166.0–213.6) (15.8) | – | 88.9 | 77.4 | 0.001* |
| | G1 | 145.6 (134.4–156.8) (12.1) | – | 100 | 80 | G1 vs G2: 0.002* |
| | G2 | 100.4 (67.6–133.1) (8.4) | 69.0 (–) (5.8) | 62.5 | 46.9 | G1 vs G3: 0.023* |
| | G3 | 90.7 (113.8–144.1) (7.6) | – | 83.3 | – | G2 vs G3: 0.903 |
| UT-RFS | Overall | 83.6 (66.9–100.3) (7.0) | 72.0 (49.4–94.6) (6) | 53.4 | 20.5 | 0.002* |
| | G1 | 79.8 (63.3–96.2) (6.7) | 79.0 (71.8–86.2) (6.6) | 63.4 | 21.3 | G1 vs G2: 0.067 |
| | G2 | 58.4 (39.6–77.1) (4.9) | 54.0 (43.7–64.3) (4.5) | 33.9 | 9.0 | G1 vs G3: 0.006* |
| | G3 | 31.7 (1.4–62.0) (2.6) | 10.0 (0–23.6) (0.8) | 16.7 | – | G2 vs G3: 0.161 |
| BI-RFS | Overall | 109.8 (88.8–130.8) (9.2) | 119.0 (88.6–149.4) (9.9) | 68.9 | 36.4 | <0.001* |
| | G1 | 114.9 (97.8–132.1) (9.6) | 126.0 (117.3–134.7) (10.5) | 88.5 | 51.8 | G1 vs G2: 0.006* |
| | G2 | 67.9 (46.7–89.1) (5.7) | 59.0 (50.5–67.5) (4.9) | 39.4 | 15.7 | G1 vs G3: 0.001* |
| | G3 | 56.5 (11.2–101.8) (4.7) | 26.0 (0.0–57.4) (2.2) | 44.4 | – | G2 vs G3: 0.413 |
| | Group A | 139.9 (104.5–175.2) (11.7) | 126 (60.7–191.3) (10.5) | 76.7 | 54.3 | Group A vs Group B, 0.029* |
| | Group B | 88.3 (66.7–109.9) (7.4) | 81.0 (23.5–138.5) (6.8) | 59.7 | 21.1 | |
| RUS | Overall | 156.2 (131.2–181.2) (13.0) | 187.0 (72.5–301.5) (15.6) | 84.6 | 65.4 | 0.001* |
| | G1 | 132.9 (117.1–148.6) (11.1) | – | 96.4 | 62.0 | G1 vs G2: 0.10 |
| | G2 | 98.6 (57.1–140.2) (8.2) | 77.0 (50.7–103.3) (6.4) | 71.4 | 35.7 | G1 vs G3: <0.001* |
| | G3 | 36.2 (4.5–67.9) (3.0) | 26.0 (0.0–60.4) (2.2) | 20.0 | – | G2 vs G3: 0.011* |
| PFS | Overall | 158.0 (131.0–185.0 (13.2) | 187.0 (70.6–303.4) (15.6) | 84.1 | 60.3 | 0.001* |
| | G1 | 132.8 (117.1–148.6) (11.1) | – | 96.0 | 61.7 | G1 vs G2: 0.008* |
| | G2 | 94.5 (61.8–127.2) (7.9) | 69.0 (46.5–91.5) (5.8) | 58.6 | 43.9 | G1 vs G3: 0.004* |
| | G3 | 68.2 (26.4–109.9) (5.7) | – | 55.6 | – | G2 vs G3: 0.527 |
| Endo-FFS | Overall | 135.1 (110.7–159.4) (11.3) | 187.0 (88.3–285.7) (15.6) | 74.7 | 51.5 | 0.001* |
| | G1 | 128.9 (111.9–145.9) (10.7) | – | 92.6 | 59.5 | G1 vs G2: 0.001* |
| | G2 | 73.7 (46.2–101.1) (6.1) | 59.0 (45.0–73.0) (4.9) | 48.8 | 18.3 | G1 vs G3: <0.001* |
| | G3 | 31.7 (4.0–59.3) (2.6) | 10.0 (0–23.6) (0.8) | 16.7 | – | G2 vs G3: 0.061 |

*Overall values include visual low-grade diagnoses (i.e. those made on ureteroscopic appearance and without biopsy confirmation). These visual low-grade diagnoses are excluded from the G1–G3 analyses. Log-rank test performed for significance. Group A: no previous urothelial carcinoma of the bladder; group B: previous urothelial carcinoma of the bladder. BI-RFS, bladder recurrence-free survival; DSS, disease-specific survival; Endo-FFS, endoscopic failure-free survival; OS, overall survival; PFS, progression-free survival; RUS, renal unit survival; UT-RFS, local recurrence-free survival.*

management. It would appear that the G3 DSS in the present study cohort may have been higher than anticipated, and this is probably because most of this G3 cohort (66.7%) underwent early nephroureterectomy at a median time of 4 months for poor local control (Fig. 3d). The DSS outcome therefore reflects that of a definitive nephroureterectomy.

The mean age, sex and anaesthetic fitness (ASA grade) of the present study are similar to those reported previously [16], with most patients being fairly evenly distributed amongst ASA grades 2 and 3. The overall mortality was 39.7%, with an estimated 5- and 10-year OS of 69.7% and 40.3%, respectively, reflecting the comorbidity of some of the patients. It could be argued that the low OS inherently limits the follow-up of some patients, thereby effecting a potential underestimation for DSS via introduction of a lead-time bias of overall mortality before UTUC progression. A natural counterweight to this factor is the potential selection bias of patients for endoscopic treatment who were not ideal candidates (i.e. extensive multifocal urothelial carcinoma; large urothelial carcinoma; single kidney; patient choice) as a result of their perceived excessive risk with respect to undergoing nephroureterectomy. The similarity of the 5-year DSS of the present study (88.9%) compared to those reported in previous studies (71–85%) (Table 1) [16,24] indicates a limited collective impact of such theoretical factors compared to other studies.

Despite the favourable DSS, endoscopic treatment does have a relatively high overall UT-recurrence rate of 68.5%. The UTUC Collaboration shows the unquestionable superiority of nephroureterectomy for preventing recurrence, with an RFS >88%

(88–91.8%) at 5 years and >81% (81–90%) at 10 years, respectively, for pTa/Tis/T1 disease, compared to the 5- and 10-year UT-RFS of 53.4% and 20.5% in the present endoscopically-treated cohort. It is evident that UT-recurrence increases with time (Fig. 3b) and it is possible that the lower UT-recurrence rates reported in previous endoscopic studies (20–5%) [22,23,25] may be a product of the more limited duration of follow-up (Table 1). The UT-RFS rates in the present study appear to be similar to those in institutions reporting median follow-ups >50 months (55–90%) [15,16,26], although they are low compared to nephroureterectomy [5]. These low RFS results highlight the importance of long-term follow-up and patient compliance as prerequisites for successful endoscopic management. However, despite the high overall recurrence rate, 31.5% of patients remained recurrence-free after initial treatment, and therefore may have avoided an unnecessary nephroureterectomy. This RFS result is probably a true reflection of the potential efficacy of ablative treatment over the long-term because sub-analysis of this recurrence-free cohort showed high pathological verification (74%; 17/23) and long-term follow-up (mean of 69.7 months). G1 UTUC patients had a mean UT-Rec of 2.2 per patient (median 2, range 0–7) but, remarkably, the G1 RUS was 96.4% and 62% at 5 and 10 years, respectively. This observation supports the principle that endoscopic management can successfully deal with many local UT-recurrences for G1 UTUC, and can durably maintain renal unit survival in the long-term, thereby avoiding potentially unnecessary nephroureterectomy in a significant proportion of appropriately selected patients.

*TABLE 4 Multivariate analysis of outcomes using Cox regression analysis*

| | Upper tract grade | | Previous urothelial carcinoma of the bladder | | Multifocality | | RP locus | |
|---|---|---|---|---|---|---|---|---|
| Outcome | *P* | OR | *P* | OR | *P* | OR | *P* | OR |
| OM | 0.001* | 2.2 | 0.709 | 1.2 | 0.432 | 1.4 | 0.286 | 0.6 |
| DSM | 0.003* | 10.5 | 0.095 | 4.8 | 0.936 | 0.9 | 0.075 | 0.1 |
| UT-Rec | 0.002* | 1.8 | 0.864 | 1.1 | 0.408 | 1.3 | 0.812 | 0.9 |
| BI-Rec | <0.001* | 2.4 | 0.034* | 2.2 | 0.129 | 0.9 | 0.174 | 0.6 |
| NU | 0.001* | 3.6 | 0.413 | 0.6 | 0.769 | 1.2 | 0.628 | 0.8 |
| Progression | 0.003* | 3.3 | 0.377 | 1.6 | 0.184 | 2.2 | 0.117 | 0.3 |
| Endo-failure | <0.001* | 3.5 | 0.638 | 1.2 | 0.985 | 1.0 | 0.346 | 0.6 |

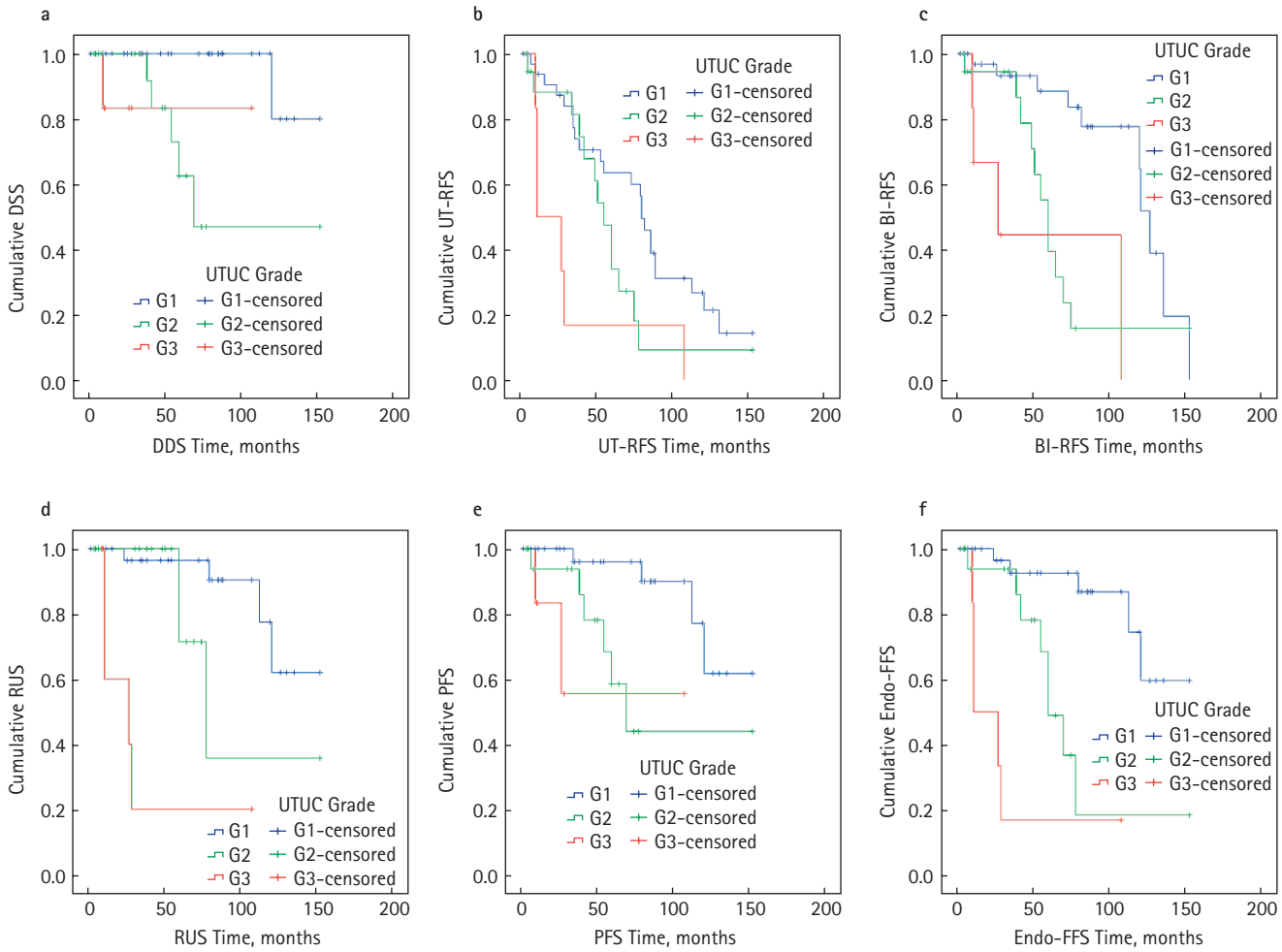
*Upper tract urothelial cell carcinoma (UTUC) grade was an independent prognostic factor for all outcomes analyzed. Previous urothelial carcinoma of the bladder was an independent prognostic factor for bladder recurrence. UTUC renal pelvis (RP) locus and UTUC multifocality were not shown to be independent prognostic factors for any outcome analyzed. P-values and odds ratios (OR) are provided. *Statistically significant (P < 0.05). BI-Rec, intravesical recurrence; DSM, disease-specific mortality; Endo-failure, endoscopic failure; NU, patients proceeding to nephroureterectomy; OM, overall mortality; UT-Rec, upper tract recurrence.*

It is inherently difficult to establish, retrospectively, the optimal way of assessing upper tract progression in the present cohort. Well documented clinical or radiological progression, nephroureterectomy and DSM are all factors that constitute a failure of endoscopic management. Overall, 14 (19.2%) patients underwent nephroureterectomy, with a grade-dependent trend. The nephroureterectomy rate in the present study (19.2%) is well within the parameters of previous studies (11–33%) (Table 1). The indication for nephroureterectomy was not documented in all patients, and it is possible that patient or surgeon choice was a factor in some patients, in addition to sub-optimal endoscopic control in others. Overall failure of endoscopic treatment was apparent in 30.1% of patients, with a grade-dependent trend. It is very clear from Fig. 3f and Table 3 that endoscopic management is an option for appropriately selected G1 patients but performs very poorly for G2 or G3 disease. Very few studies report such information, which precludes making any comparative definitive conclusions about endoscopic performance, although the failure rate reported in the present study (30.1%) is consistent with the rate of 17–43% reported in other experienced centres [16,22,24].

A significant proportion of patients (42.5%) went on to develop intravesical recurrences, and both UTUC grade and a previous of urothelial carcinoma of the bladder were shown to be independent prognostic factors for BI-Rec (Table 4). The 5-year BI-RFS was significantly lower in patients with a previous history of urothelial carcinoma of the bladder (59.7% vs 76.7%), which is consistent with the 5-year BI-RFS of 54% reported by Krambeck *et al.* [15]. Although the intravesical recurrences tended to be papillary, there were notable recurrences invading bladder muscle in patients with no previous history of urothelial carcinoma of the bladder. There were two patients with original G2pTa upper tract pathology who developed intravesical recurrences invading bladder muscle (G3pT2) and died from advanced urothelial carcinoma 59–69 months after initial upper tract diagnosis. A further patient with initial G3pTa upper tract histology developed an intravesical recurrence invading bladder muscle, and died from general medical causes as a result of their competing comorbidities. These observations highlight the importance of routine surveillance cystoscopies in addition to upper tract assessment, along with pathological assessment and the prompt treatment of intravesical recurrences.

There is a strong policy for pathological verification of upper tract pathology in patients who are undergoing endoscopic management of UTUC in our institution. Overall, 80.8% patients had UTUC verified by ureteroscopic biopsy in the present study. Ureteroscopic biopsy grade correctly predicted final nephroureterectomy grade in 10 of 13 (76.9%) patients and is consistent with that reported in previous studies (78–91%) [18–20,27]. The role of ureteroscopic biopsy in diagnosis of UTUC has been reviewed elsewhere and is not used for conventionally assessing pathological stage [19]. A clear observation from the present study is that the

*FIG. 3. Grade-stratified survival outcomes for endoscopically managed upper tract urothelial carcinoma (UTUC): **a**, disease-specific survival (DSS); **b**, upper-tract recurrence-free survival (UT-RFS); **c**, intravesical recurrence-free survival (BI-RFS); **d**, renal unit survival (RUS); **e**, upper-tract progression-free survival (PFS); **f**, endoscopic failure-free survival (Endo-FFS).*




ureteroscopic appearance of the upper tract tumour cannot reliably predict tumour grade because four of 13 (30.8%) unverified 'visual low-grade' lesions escaped endoscopic control, with three (23.1%) requiring nephroureterectomy. The definitive final pathology in two patients was G2pTa or G3pTa with carcinoma *in situ*. These findings echo those of other studies showing that ureteroscopic inspection alone is inaccurate for predicting tumour grade in ≈30% of patients undergoing nephroureterectomy [28], as well as those of the Mayo Clinic indicating that ≈35% of 'visual low grade' diagnoses are upgraded to G2 (14%) or G3 (21%) urothelial carcinoma during follow-up [16]. These findings collectively question the validity of assigning visually diagnosed tumours to 'low-grade' status and highlight the importance of the ureteroscopic biopsy grade as a requirement for diagnosis and therapeutic planning, as well as for delineating survival prognoses (Fig. 3 and Table 4).

Adjuvant topical therapy with mitomycin C was used in 18 patients in the present study, although no benefit of UT-RFS was found. To the best of our knowledge, the present study represents one of the only case–control reports to assess the use of mitomycin C for papillary UTUC. Although early case series cited the safe use of mitomycin C [29,30], the lack of control arms precluded any assessment of efficacy. To date, no study has reported a benefit of UT-RFS with adjuvant mitomycin C for papillary UTUC.

The present cohort included patients with a distribution of imperative (10.9%), relative (24.7%) and elective (50.7%) indications for endoscopic management. Overall, the present study shows that endoscopic management can provide effective oncological control (5-year DSS, 88.9%; 10-year DSS, 77.4%) and renal unit preservation (5-year RUS, 84.6%; 10-year RUS, 65.4%) in elderly comorbid patients (5-year OS, 69.7%; 10-year OS, 40.3%). However, the real significance of the present study is the reporting of long-term grade-stratified outcomes for endoscopically-managed UTUC. This shows that, in the context of an experienced centre, endoscopic treatment of appropriately selected G1 UTUC patients shows excellent oncological control (5-year

DSS, 100%; 10-year DSS, 80%) and renal preservation (5-year RUS, 96.4%; 10-year RUS, 62%) in patients who will probably eventually die from other causes (5-year OS, 74.5%; 10-year OS, 43.3%). It must be emphasized that the present cohort of patients does not represent the entire spectrum of new UTUC presentations but, instead, comprises a highly selected subgroup with tumour characteristics generally amenable to endoscopic management.

Despite the positive findings reported in the present study, the number of centres currently reporting their experience with the endoscopic management of UTUC is extremely low (Table 1) and long-term (10 years) outcomes are presently undefined. There have been no randomized prospective studies aiming to compare endoscopic management with nephroureterectomy. Five institutions have reported outcomes of endoscopic management compared to nephroureterectomy in the form of non-randomized retrospective studies [31–35]. These studies did not show any definitive significant inferiority of endoscopic management compared to nephroureterectomy for high-grade disease, although this may be a result of the relatively small cohorts (21–49 patients), variable follow-up (18–54 months) and an unmatched invasive stage distribution in the comparative arms (12–24% for the endoscopic arms compared to 54–61% in the nephroureterectomy arms).

The incidence of non-invasive UTUC is extremely rare, perhaps as low as 1 : 250 000 [3], which poses a significant challenge to the design and recruitment of prospective studies aiming to assess long-term outcomes compared to nephroureterectomy. It is likely multi-institution or multinational studies will be required to determine the long-term efficacy of endoscopic management compared to nephroureterectomy [36] and recruitment will probably be slow. Patient selection is pivotal to successful endoscopic management. The assessment of a patient's overall life expectancy is a major consideration for elective cases. Patients must be counselled appropriately with regard to compliance and motivation for regular inpatient treatment, as well as the different outcomes of endoscopic management, including UT-recurrence, disease progression and endoscopic failure.

## CONFLICT OF INTEREST

None declared.

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Abbreviations: **ASA**, American Society of Anesthesiologists; **BI-Rec**, intravesical recurrence; **BI-RFS**, bladder recurrence-free survival; **DSM**, disease-specific mortality; **DSS**, disease-specific survival; **OS**, overall survival; **PFS**, progression-free survival; **PNRT**, percutaneous nucleus replacement; **RNU**, radical nephroureterectomy; **RUS**, renal unit survival; **UT-Rec**, upper tract recurrence; **UT-RFS**, local recurrence-free survival; **UTUC**, upper tract urothelial cell carcinoma.