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Management of the Distal Ureter during Nephroureterectomy for Upper Urinary Tract Transitional Cell Carcinoma: A Review

Key Words

Endourology • Surgery • Ureter • Transitional cell carcinoma

Abstract

Introduction: The standard treatment for upper urinary tract transitional cell carcinoma (UUT-TCC) is open radical nephroureterectomy with excision of a bladder cuff. We assess the successful endoscopic completion and oncological efficacy of the various minimally invasive transurethral techniques devised for the management of the intramural ureter during nephroureterectomy. **Materials and Methods:** A comprehensive review of the English literature until February 2009 using the PubMed database returned 42 relevant papers. Five methods of endoscopic management of the distal ureter were identified and compared to the open technique. **Results:** There are no randomised studies. Successful completion of the endoscopic procedure was less (91%) for the ureteric stripping technique than for the other endoscopic modalities (99.8–100%). Recurrences were highest for laparoscopic extravesical ureteric stapling in conjunction with cystoscopic detachment of the ureter, although the numbers analysed were small. For the other endoscopic modalities, bladder recurrence, positive margins and retroperitoneal recurrence (20–37, 0–4 and 1–3%, respectively) in case series were similar compared with the open method

(36, 5 and 3%, respectively). **Conclusions:** Current non-randomised evidence is open to selection bias and is insufficient to support or refute endoscopic management of the distal ureter as an alternative to open bladder cuff excision. We highlight the reported inefficiency of the ureteric stripping technique.

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Introduction

Upper urinary tract transitional cell carcinoma (UUT-TCC) is an uncommon cancer. It represents 5% of all urothelial cancers, and of these, 75% are located in the pelvicalyceal system. Two contemporary studies have analysed the diagnostic yield of haematuria clinics, and found that UUT-TCC is only detected in 0.6–0.7% of patients referred with haematuria [1, 2]. Although UUT-TCC usually presents at a more advanced tumour stage and histological grade than bladder TCC, when controlled for stage and grade it is unclear if UUT-TCC has a worse prognosis than bladder TCC [3]. Stage, grade and lymphovascular invasion are currently the only established prognostic indicators. Five-year disease-free survival rates following open nephroureterectomy are 80–100% for pTa UUT-TCC, but only 16–29% for pT4 UUT-TCC [4].

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While laparoscopic nephroureterectomy has become established in recent years for low-stage tumours, open excision of bladder cuff is still considered the gold standard. Minimally invasive approaches to the distal ureter were introduced to reduce the operative duration and morbidity associated with open pelvic dissection and excision of bladder cuff. Endoscopic management of the distal ureter to complement open nephroureterectomy was tried as early as 1952 [5] and laparoscopic nephroureterectomy was introduced in the early 1990s [6]. Today, 57 years since the first report of endoscopic resection of the ureteric orifice during radical nephroureterectomy for UUT-TCC, concerns persist regarding its oncological safety because of the theoretical risk of tumour seeding. The hallmarks of tumour implantation following nephroureterectomy are the development of an invasive resection site recurrence or retroperitoneal metastasis. Therefore, we conducted this comprehensive review to assess the successful endoscopic completion and oncological efficacy of the various minimally invasive transurethral techniques devised for the management of the distal ureter during nephroureterectomy.

Materials and Methods

A broad electronic search of the literature published in English until February 2009 was performed using the PubMed database using the key words 'nephroureterectomy', 'orifice' and 'distal ureter'. We included all studies that described alternate endoscopic methods of managing the distal ureter during nephroureterectomy or presented series of patients comparing the efficacy and safety of these methods amongst them and to the open approach. We also reviewed all relevant isolated series and case reports. All nephroureterectomy series were reviewed, and those that utilised any form of transurethral surgery for the management of the distal ureter and stratified outcomes according to the technique used were considered for this review. Comparative data from series of patients who underwent open excision of bladder cuff presented from the studies reviewed were evaluated.

Forty-two relevant papers were identified [7–48]. Two of the studies were prospective [19, 27] and none were randomised. Four were excluded because of overlapping series with other more updated ones [43–46], or due to inadequacy of data [47]. In total, 72 series of patients treated with radical nephroureterectomy were identified (table 1). In 47 of them, the distal ureter was managed endoscopically. Five series included patients treated with more than one modality, with no stratification of the results, and distal ureterectomy was performed by the classical open transvesical method in 15 series. Extravesical resection of the intramural ureter was recorded in 3 series, of which one also involved stapling, while in another series it was not removed.

Although minor modifications were introduced by many authors, 5 major techniques of cystoscopic management of the distal ureter have been described:

Table 1. Operative parameters for each distal ureteric treatment modality

Type	Success (%) ¹	Complications (%) ²
P	576/577 (99.8)	8/508 (1.6)
S	160/169 (91)	0/169 (0)
LS	61/61 (100)	0/18 (0)
ELS	114/114 (100)	0/38 (0)
O	271/271 (100)	2/183 (1)

P = Cystoscopic detachment of ureter without ligation/stapling; S = ureteric stripping technique; LS = extravesical laparoscopic stapling of ureter; ELS = cystoscopic detachment of the ureter with endoscopic ligation/stapling; O = open excision of bladder cuff.

¹ Proportion of cases where endoscopic management of the distal ureter could be completed.

² Proportion of completed cases where complications were related to endoscopic management of the distal ureter.

(1) Cystoscopic detachment of the intramural ureter by transurethral resection prior to nephroureterectomy ('pluck' technique) [49].

(2) Cystoscopic detachment of the ureter by transurethral complete circumferential incision of the intramural ureter with a bladder cuff without resection, ligation or stapling [49].

(3) Division and intussusception of the ureter, followed by cystoscopic detachment and transurethral removal (ureteric stripping technique) [49].

(4) Laparoscopic extravesical ureteric stapling before or after cystoscopic detachment of the intramural ureter by complete circumferential incision of the intramural ureter with a bladder cuff [15, 21].

(5) Transurethral partial circumferential incision of the intramural ureter with a bladder cuff followed by transvesical or cystoscopic ligation/stapling of the stump and cystoscopic detachment of the ureter [46].

Patients from group 1 treated with the 'pluck' technique and those from group 2 were reviewed as one group due to the similarities in these two methods. For each parameter studied, only the series that provided full data were considered. Thus, the final percentages do not correspond to the entire cohort of patients but are calculated from subsets with complete data.

Results

Tables 1–4 show the overall results for each of the treatment modalities studied. Except for the stripping technique, the tumour characteristics were similar in each of our groups, which is suggestive of similar patients selected for these techniques (table 2). Grade 3 lesions comprised 39–58% of cancers, except for the ureteric

Table 2. Patient characteristics for each distal ureteric treatment modality

Type	Patients	TCC	Concurrent bladder tumour (%)	Previous bladder tumour (%)	G3 (%)	T2–T4 (%)
P	663	646	5/524 (1)	60/297 (20)	134/344 (39)	128/316 (40)
S	169	159	0/123 (0)	7/72 (10)	17/73 (23)	31/105 (29)
LS	61	61	0/9 (0)		7/12 (58)	7/12 (58)
ELS	114	114	0/16 (0)	–	40/73 (55)	28/71 (39)
O	305	303	2/246 (1)	15/196 (8)	78/180 (43)	98/180 (54)

P = Cystoscopic detachment of ureter without ligation/stapling; S = ureteric stripping technique; LS = extravesical laparoscopic stapling of ureter; ELS = cystoscopic detachment of the ureter with endoscopic ligation/stapling; O = open excision of bladder cuff; G3 = grade 3 UUT-TCC; T2–T4 = stage T2–T4 UUT-TCC.

Table 3. Margin status and recurrence rate for each distal ureteric treatment modality

Type	Positive margins (%)	Bladder recurrence (%) ¹	Scar recurrence (%) ²
P	0/27 (0)	150/402 (37)	13/342 (4)
S	1/26 (4)	28/135 (21)	0/110 (0)
LS	5/28 (18)	5/12 (42)	2/14 (14)
ELS	0/74 (0)	14/70 (20)	0/71 (0)
O	1/21 (5)	83/228 (36)	6/148 (4)

P = Cystoscopic detachment of ureter without ligation/stapling; S = ureteric stripping technique; LS = extravesical laparoscopic stapling of ureter; ELS = cystoscopic detachment of the ureter with endoscopic ligation/stapling; O = open excision of bladder cuff.

¹ Recurrence anywhere within the bladder.

² Recurrence at the resection site.

stripping group where the rate was only 23%, probably because patients with a smaller tumour burden were selected. Similarly, fewer muscle-invasive lesions were reported in this group (30%), whereas in the remaining groups the range was between 39 and 58%.

Cystoscopic Detachment of the Ureter by Transurethral Resection or Complete Circumferential Incision of the Intramural Ureter with a Bladder Cuff but with No Ligation or Stapling of the Stump

Overall, 27 studies presented 663 patients treated by transurethral resection/circumferential incision of the distal ureter without ligation or stapling of the stump [8–14, 16–18, 22–27, 29, 30, 32, 33, 35, 38–40, 42, 49]. Of the operations, 646 were performed for UUT-TCC. Of 524

Table 4. Recurrence pattern and disease-specific mortality for each distal ureteric treatment modality

Type	Extravesical recurrence (%)	Retroperitoneal recurrence (%)	Distant disease (%)	DSM (%)
P	0/425 (0)	4/295 (1)	15/218 (7)	41/456 (9)
S	0/128 (0)	3/100 (3)	7/106 (7)	7/77 (9)
LS	0/42 (0)	2/30 (7)	3/17 (18)	0/9 (0)
ELS	0/78 (0)	0/38 (0)	6/71 (8)	1/38 (3)
O	1/205 (0.5)	4/118 (3)	13/99 (13)	23/177 (13)

P = Cystoscopic detachment of ureter without ligation/stapling; S = ureteric stripping technique; LS = extravesical laparoscopic stapling of ureter; ELS = cystoscopic detachment of the ureter with endoscopic ligation/stapling; O = open excision of bladder cuff; DSM = disease-specific mortality.

patients, 5 had a concurrent bladder tumour that was resected prior to the operation while 60 of 297 (20%) had a history of previous bladder tumours. The mean endoscopic times were 15–46 min. The bladder defect was closed in only 40 of 597 patients (7%). The technique failed to complete in only 1 of 577 cases (0.2%) where periureteral fibrosis necessitated conversion to an open procedure [18]. Only 8 of 508 patients (2%) developed complications related to cystoscopic detachment: haematuria (1), retroperitoneal extravasation requiring prolonged drainage (3), urinary retention (3) and urinary tract infection (1) [9, 13, 49]. The final pathology showed high-grade TCC in 39% and muscle-invasive TCC in 40%. Very few patients had node-positive disease (8/279, 3%) and none had metastases at the time of treatment. The incidence of concomitant carcinoma in situ was very variable and in many studies the authors did not comment on the

presence or absence of carcinoma in situ. Thus, it was not possible to stratify patients accordingly.

A mean or median follow-up of >24 months was available for 448 patients in 16 studies. Most of the studies did not comment on the margin status of the resection. Recurrence of TCC in the bladder was documented in 150 of 402 patients (37%), whereas recurrence at the resection scar was uncommon (13/342, 4%). Four patients were reported to have developed retroperitoneal recurrences (renal fossa, 4/295), but none of the 425 patients had an extravesical recurrence. Of 218 patients, distant disease occurred in 15 (7%) during follow-up and the disease-specific mortality during the same period was 9% (41/456).

Ureteric Stripping Technique

Ten articles included 169 patients treated by the ureteric stripping technique [9, 17, 19, 20, 31, 34, 36, 37, 41, 43]. Of 169 procedures performed for UUT-TCC, two thirds were selected patients where the tumour was not located in the distal ureter. No patient was reported to have a concurrent bladder tumour, although 10% (7/72) had a history of bladder TCC. The mean time for completion of stripping was reported by 3 studies to be 30–45 min and the bladder defect was left open in all 169 cases. Although none of the authors reported any complication following this procedure (0/169), 15 procedures (9%) had to be converted due to: dislodgement or the catheter breaking (6), periureteral fibrosis (2), retained ureter (5) and inability to extract the ureter through the urethra (2).

The tumours were high-grade in 23% (17/73) and muscle-invasive in 29% (31/105) of cases. Only one patient treated by ureteric stripping was staged as node-positive and M1 (1/133, 0.8%). Most authors did not comment on margin status and information was available for only 26 patients with positive margins in 1 (4%). Follow-up was again very variable, although 5 studies comprising 125 patients had a mean or median follow-up of more than 24 months. Bladder recurrence occurred in 28 of 135 patients (21%), but away from the resection site in all 110 patients where the location of the recurrences was recorded. Retroperitoneal and distant disease developed in 3 of 100 patients (3%) and 7 of 106 (7%), respectively, but there was no occurrence of extravesical recurrence (0/128). During follow-up, 7 patients died of the disease (7/77, 9%).

Laparoscopic Extravesical Stapling of the Ureter before or after Transurethral Complete Circumferential Incision with a Bladder Cuff

Five studies included 61 patients treated by this method [15, 17, 21, 25, 26]. Information on previous history of

bladder TCC was provided in only one study where all nine patients were free of bladder tumours at the time of surgery [21]. The mean operative time for this technique was noted to be 29 min [26]. The procedure was concluded successfully in all 61 cases and there were no postoperative complications related to this part of the operation (0/18). Pathology reports were provided for 12 of the 61 patients; tumours were high-grade and muscle-invasive in 58% (7/12) with no nodal or metastatic disease identified preoperatively. Margin status was available for 28 patients and was positive in 5 (18%). All five of the positive margins were in patients who underwent laparoscopic extravesical stapling after cystoscopic detachment of the ureter [15, 17].

In 2 of 30 patients (7%), the disease recurred in the retroperitoneum and at distant sites in 3 of 17 (18%). However, no patient developed juxtavesical recurrence. None of the studies reported follow-up specifically following this technique and information on frequency and pattern of bladder recurrences was limited. Matin and Gill [15], however, reported subsequent bladder tumours in 5 of 12 patients treated with this modality. Interestingly, two of these tumours developed at the site of the incision. In their series, cystoscopic deroofting and fulguration preceded laparoscopic extravesical stapling.

Transurethral Partial Circumferential Incision of the Intramural Ureter with a Bladder Cuff Followed by Transvesical or Endoscopic Ligation/Stapling of the Stump and Cystoscopic Detachment of the Ureter

A total of 114 cases were treated by this technique [7, 15, 21, 25, 27]. Information on previous bladder tumours was limited. Only one study reported the mean operative time, which was 28 min [7]. All cases were successfully concluded with the bladder defect left open. No postoperative complications related to the resection of the distal ureter were reported (0/38) and the final pathology showed high-grade tumours in 55% (40/73) and muscle-invasive tumours in 39% (28/71). In one study, 4 patients (4/36, 11%) were found to have nodal involvement [15]. Margin status was reported negative in 74 cases. Only one study specified mean follow-up (15 months) following this technique [7]. Across all studies, recurrent bladder tumours were reported in 14 of 70 patients evaluated (20%). None of the recurrent tumours were located on the resection scar and there were no extravesical or retroperitoneal recurrences. Of 38 patients evaluated for recurrence at distal sites, 6 patients developed metastasis, with 1 patient dying from TCC (3%).

Open Excision of Bladder Cuff

Open series were included in 13 studies [10, 15, 17, 19, 21–27, 41, 49] and were used by the authors as controls to compare their minimally invasive techniques. These series comprised 303 patients, who were all treated for TCC located throughout the upper tract. Of 246 patients, 2 (1%) had concomitant bladder tumours at the time of surgery, which were treated by transurethral resection, and 15 of 196 (8%) had a history of bladder TCC. Data on the duration of excision of bladder cuff were available in two studies, and showed a mean operative time of 29 and 46 min, respectively. The bladder defect was closed in 95 of 149 cases (68%) where this was documented. None of the authors reported failures of the method. The only reported postoperative complications related to excision of bladder cuff were two urinary tract infections [49]. Histology revealed high-grade TCC in 42% (97/228) and muscle-invasive tumours in 52% (119/228). No patient was found to have nodal or metastatic disease and the positive distal margin rate was 5% (1/21) [15].

In all but three series [19, 22, 49], length of follow-up was not reported specifically for the open procedure. During follow-up, evaluation of bladder tumour recurrence was reported for 228 patients. Of these, 83 (36%) developed a recurrence. Of the 148 patients where the site of bladder tumour recurrence (if present) was described, only 6 (4%) had a recurrence at the resection site. Evaluation of retroperitoneal recurrence was reported for 118 patients, of whom 4 (3%) developed recurrences. Of 99 evaluated patients, 13 (13%) developed distant metastases, and of 177 patients evaluated for cancer-specific death, 23 died of TCC (13%). In the three series reporting follow-up time, the median follow-up times were 39 and 42 months [19, 49]; the other had a mean follow-up of 49 months [22]. The site of primary TCC was renal pelvic in one [19], and renal pelvic and ureteric in the other two [22, 49]. In these three series, 22–48% developed a recurrent bladder tumour and 8–19% developed distant metastases.

Conclusions

The urological community has embraced laparoscopic nephroureterectomy for low-stage UUT-TCC despite the initial fears of port site seeding, but at the same time has been skeptical about endoscopic management of the distal ureter because of fears of extravesical tumour seeding. A recent review reported 11 cases of port site seeding [4], while published reports of dissemination of the dis-

ease following endoscopic manipulation of the distal ureter are just as sparse. In the series considered for this review, three extravesical recurrences were confirmed. Brown et al. [17] reported on a patient treated by extravesical resection of the distal ureter during hand-assisted laparoscopic nephroureterectomy who later developed an extravesical mass at the site of resection, as did a patient treated by the open technique in the series of El Fettouh et al. [25]. Seifman et al. [27] published a series of 11 cases treated either by the open (7) or the 'pluck' (4) technique. One patient developed an extravesical recurrence, but it is unclear which method was used for this case. In the literature, there are four frequently cited case reports which have given rise to much of the concerns about the oncological safety of the transurethral techniques [50–53]. In 1985, Hetherington et al. [50] published a case report on two patients who developed extravesical disease following nephroureterectomy by the 'pluck' technique. While one could advocate that in the first case the recurrence was probably the result of seeding, in the second case the authors speculate that it was caused by lymphatic spread. Jones and Moisey [51], Arango et al. [52] and Fernández Gómez et al. [53] also published case reports of extravesical recurrences following endoscopic resection of the intramural ureter. Surgeons across all studies tried to minimise the risk of seeding by excluding patients with concurrent bladder tumours and ligating the ureter as early as possible. In some series, only patients with a tumour in the renal pelvis and/or the proximal ureter were included. Very variable operative times were reported, but removal of the ureter was feasible and uneventful in all cases and by all methods, with the exception of the ureteric stripping technique, which had a high failure rate (9%; table 1).

Follow-up was limited in most studies, but it is well established that for the majority of solid tumours, most recurrences occur in the first two years post-operatively. The rate of bladder recurrence for the open procedure was 36% and almost identical for cystoscopic detachment of the intramural ureter by transurethral resection or complete circumferential incision (37%), and lower for the ureteric stripping (21%) and cystoscopic or transvesical ligation methods (20%). The high percentage of bladder recurrence after extravesical laparoscopic stapling of the ureter (42%) is of concern, although only 12 patients were evaluated. The development of tumour recurrences in the resection scar was an uncommon event in all series except after extravesical stapling (14%; table 3). Several studies have shown that overall bladder recurrence rates following nephroureterectomy for UUT-TCC are not de-

pendent on the technique used for the distal ureter [49, 54, 55]. Instead, multivariate analyses suggest that a history of previous bladder tumours is the most important factor [56], or if there is no history of previous bladder TCC, then multifocality and stage $\leq$ pT1 are independent risk factors [57]. A recent study by Joung et al. [58] suggests that Ki-67 overexpression may also be an independent predictor of bladder recurrence. It is possible that some of those with high-stage UUT-TCC will die before developing recurrent bladder cancer.

The application of an extravesical stapler to the ureter appears to be associated with a high positive margin rate (18%). However, comparison is difficult because most series do not quote their overall positive margin rates. Martin and Gill [15] treated 60 patients with various modalities, of whom 5 had positive margins: 4 located at the distal end of the ureter. These 4 patients had been treated with endoscopic excision and stapling (3) or by open excision of bladder cuff (1). Overall, 3 died of TCC during follow-up. Brown et al. [17] reported 4 positive margins out of 55 specimens. None of these patients was treated with endoscopic methods. In 2 cases, extravesical excision of bladder cuff was performed during hand-assisted laparoscopic nephroureterectomy. In the other 2 cases, extravesical stapling of the bladder cuff was carried out. Unfortunately, no information is given on oncological outcome in these cases. El Fettouh et al. [25] reported on 2 positive margins in 116 nephroureterectomies; one of these patients was treated by open excision of bladder cuff, developed a recurrence at the bladder scar and was treated with intravesical bacille Calmette-Guérin, but later developed local recurrence and disseminated disease. Jacobsen et al. [37] reported a single case of incomplete resection within a series of 18 ureteric stripping operations. This patient developed a bladder recurrence but was alive with no retroperitoneal disease at the last follow-up. In another study, 3 patients were reported to have invasive resection site recurrence following nephroureterectomy and 'pluck technique' for muscle-invasive tumours in the lower third of the ureter [49]. In 2 of the cases the distal ureteric margin was positive, in the other case it was positive for carcinoma in situ. In the same study, one of the two patients who developed an invasive resection site recurrence following open excision of bladder cuff had a history of a positive distal ureteric margin [49]. Again, in both cases the nephroureterectomy was for a muscle-invasive TCC in the lower third of the ureter.

Retroperitoneal and distant disease was diagnosed in 3 and 13%, respectively, of patients treated with open excision of bladder cuff compared with 1 and 7% for groups

1 and 2, 3 and 7% for the ureteric stripping technique, and 0 and 8% for the ligation methods. Disease-specific mortality was not inferior for the endoscopic approaches (3–9%) compared with open excision of bladder cuff (13%; table 4). Several studies have also shown no correlation between disease-specific mortality and the method of distal ureteric management [49, 55]. Walton et al. [49] showed that patients undergoing cystoscopic detachment of the ureter without ligation or stapling had similar disease-specific survivals to those undergoing open bladder cuff excision. Dragicevic et al. [59] showed that the method of surgery for UUT-TCC can affect oncological outcome. They compared the results of open conservative surgery with radical extirpative surgery in a small series of patients with UUT-TCC [59], and showed that radical nephroureterectomy was a significant predictor of poorer outcome. However, such a series is open to selection bias because patients in the conservative surgery group had smaller tumours.

There is a shortage of published guidelines regarding the treatment of UUT-TCC. The American Urological Association, Scottish Intercollegiate Network, and National Institution for Health and Clinical Excellence publications do not include relevant chapters as do the current European Association of Urology guidelines, although in 2004 some recommendations were published [3]. The 2008 National Comprehensive Cancer Network guidelines cover this domain and suggest nephroureterectomy with a bladder cuff for the management of the distal ureter. Preliminary data has recently been presented on a multi-centre prospective randomised study (ODMIT-C), whose aim was to establish the value of a single post-operative intravesical installation of 40 mg of mitomycin C on removal of the catheter following nephroureterectomy in reducing the recurrence of tumour in the bladder [60]. Of 122 patients in the mitomycin arm, 21 (17%) recurred compared with 33 of 123 (26%) of the observation arm at 12 months ($p = 0.05$). The number needed to treat to prevent one bladder tumour in the first year post-surgery was 10. Of note, the endoscopic resection of the distal ureter was the second most common technique used ($n = 87$). The differences in recurrence in the bladder amongst the open, 'pluck' and laparoscopic modalities at 12 months were not significant.

In conclusion, the technique of distal ureteric excision remains debatable. None of the endoscopic techniques have been evaluated extensively, data reporting is inconsistent, and in the absence of randomised trials, comparative data on outcomes is open to selection bias. Many authors consider distal ureteric tumours a contraindica-

tion to the endoscopic resection technique, thereby biasing the oncological outcomes. However, the data against cystoscopic detachment of the ureter are few for patients with pelvicalyceal UUT-TCC. The most important point arising from this review is the need for more high-quality

studies with uniformity of reporting. Additionally, it highlights the inefficiency of the ureteric stripping technique. The rarity of UUT-TCC represents a significant problem for the comparison of different techniques in randomised studies.

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