Is Radical Nephroureterectomy and Lymph Node Dissection Necessary for Upper-tract TCC?

S. Joniau a,*, B. Van Cleynenbreugel a, W. Blyweert a, I. Romics b, H. Van Poppel a

a Department of Urology, University Hospital Leuven, K.U.Leuven, Belgium
b Urology, Semmelweis University, H-1082 Budapest, Hungary

1. Introduction

The incidence of upper urinary tract transitional cell carcinoma (UUTT) is 0.6–1.1 out of 100 000 per year. UUTT constitutes 5–7% of all urothelial tumours, with 4% located in the renal pelvis and calices and about 3% in the ureter. It seldom presents as bilateral disease (2–4%) [1]. Eighty percent of UUTT is preceded by bladder cancer (BCa). Patients who present with superficial bladder transitional cell carcinoma (TCC) have a 2–4% incidence of metachronous upper-tract tumours. Incidence of metachronous UUTT increases with time: 2.7% within 8–10 yr and 8.1% within 10–15 yr. Carcinoma in situ (CIS) of the bladder is the highest risk factor for upper-tract recurrence (up to 21%) [2,3]. Of patients who present with initial UUTT, 20–75% will develop metachronous BCa. Most of these will be diagnosed within 2 yr of the diagnosis of initial UUTT. These observations point to the need for close surveillance of the bladder in patients with UUTT [4].

The natural history of UUTT has been reported to be more aggressive than bladder TCC. Muscle-invasive disease at presentation is common and reported to be 40% more common than in BCa. Up to 50% of renal pelvis and ureteral tumours are invasive, and 19% present with metastatic disease [5]. The disease-specific survival (DSS) in UUTT depends on the TNM stage of the disease. In situ and superficial UUTT have a 89–95% 5-yr DSS, while regional disease and muscle-invasive localised disease have a 63% 5-yr DSS. Patients who present with metastatic disease have a poor prognosis, with 16% DSS at 5 yr [6]. It has been questioned whether tumour localisation constitutes a prognostic factor in patients with UUTT. In a multicentre analysis of 1249 patients with UUTT, Raman and co-workers showed that location of TCC within the renal pelvis had no...
different recurrence-free survival (RFS) or DSS compared to location within the ureter ($p = 0.7$ and $p = 0.8$, respectively). In the subgroup of patients who presented with organ-confined UUTT, they noted significant differences in RFS and DSS compared to patients with renal pelvis TCC versus ureteric TCC ($p = 0.02$ and $p = 0.02$, respectively). However, when tumour localisation was entered in a Cox multivariable analysis, tumour location had no predictive significance when corrected for pT classification, tumour grade, and pN classification (hazard ratio: 1.22; 95% confidence interval, 0.942–1.58; $p = 0.133$) [7].

2. Rationale for radical treatment of upper urinary tract transitional cell carcinoma

Open nephroureterectomy (NU) with en bloc excision of the ureter using a periureteral bladder cuff has long been considered the gold standard treatment of UUTT. However, TCC of the bladder is managed conservatively in most patients. The question now arises whether conservative management comparable to TCC of the bladder can be used in UUTT.

There are several arguments against this. First, staging accuracy of computed tomography (CT) urography for UUTT is only 60%. CT may miss lesions <5 mm and is not ideal for lymph node staging. Nevertheless, detection rates by CT urography are much better than intravenous urography, and sensitivity for detection is at 96%, while specificity for detection approaches 100% [8]. Second, although ureteroscopy with biopsy may show a good correlation of biopsy grade with surgical grade, the correlation of biopsy grade with surgical stage is only moderate. Keeley et al showed a 90% grade correlation for low-grade tumours and a 92% correlation in high-grade tumours. Of grade I–II lesions on biopsy, 87% had low-stage disease on final histopathology, while in high-grade lesions, only 67% will have high-stage disease on final histopathology [9].

Thus, muscular invasion may be missed by both CT urography and biopsy, and CT may miss lymph node invasion. An important group of patients presenting with UUTT will be at risk for understaging, and conservative management or kidney-sparing treatments in those patients may be largely insufficient.

Another argument in favour of radical surgery is that recurrence of UUTT is common after local therapy. Ipsilateral recurrence rates after endoscopic resection have been reported to be 31–65%. Recurrence of TCC in a retained stump after NU has been reported to be 10–70%. Furthermore, recurrence is invariably distal to the primary tumour. Contralateral upper-tract tumours are rare [4]. These points may further argue for radical treatment of UUTT.

3. Is there a role for nephron-sparing surgery in upper urinary tract transitional cell carcinoma?

There is a general consensus that for low-stage, low-grade lesions, for solitary lesions; and in absolute indications, nephron-sparing surgery (NSS) may be offered to the patient. However, this surgery may be technically demanding, and regular upper-tract follow up is mandatory. A detailed description hereof is provided elsewhere in this issue.

4. Open or laparoscopic nephroureterectomy?

In the last decade, we have witnessed a dramatic shift in surgical approach for kidney and prostate cancer in favour of conventional laparoscopy and robot-assisted laparoscopic surgery. The same has happened in the field of UUTT, where in many expert institutions laparoscopic NU is now preferred over the open approach. However, several questions remain unanswered. Some surgeons prefer the transperitoneal approach over the retroperitoneal approach. Some prefer a full laparoscopic approach, others a hand-assisted approach. The technique of excision of the distal ureter and bladder cuff remains another controversial issue. Several techniques have been described, such as the Stapling technique, the Pluck technique, ureteral stripping, and open excision, and the issue was recently reviewed by Srirangam et al [10].

Whatever the approach and whichever route is chosen, sound oncologic surgical principles should remain identical: a complete en bloc resection with intact bladder cuff should be performed, avoiding tumour seeding. Table 1 lists advantages, disadvantages, and contraindications of the different approaches to the distal ureter and bladder cuff during laparoscopic NU [11–15].

There are some limitations in the urologic literature regarding comparison between laparoscopic NU and open NU. In most of the studies on laparoscopic NU, follow-up is short, patient numbers are limited, and the setting is almost exclusively retrospective. However, all laparoscopic techniques show good results—comparable to open NU. There seems to be a general consensus on the management of the distal ureter in favour of open cuff resection, implying that after laparoscopically freeing the kidney and controlling the hilar vessels, the kidney is placed in the iliac fossa and the laparoscopic access wounds closed. The patient is then usually repositioned, and a Pfannenstiel or oblique lower abdominal incision is made through which the kidney and ureter are delivered and the distal ureterectomy and bladder cuff resection completed. Table 2 provides an overview of comparative series of laparoscopic or hand-assisted laparoscopic versus open NU for UUTT.

5. What is the role of lymphadenectomy in nephroureterectomy?

In a recent multicenter analysis of 1130 patients undergoing open NU, Roscigno et al noted 25.4% positive lymph nodes in the 552 patients who underwent lymphadenectomy. In contrast, 578 (51.1%) patients did not undergo lymph node dissection (LND), the reason being unclear. In a further subanalysis, the DSS of patients who did not receive LND was consistently worse than patients who had undergone LND and were N0 at histopathology. This effect was even stronger in those patients with muscle-invasive UUTT [23]. This study clearly showed the value of a LND in staging and
outcome assessment. However, the study did not provide insight into a possible benefit of an extended LND in patients with UUTT. In fact, the therapeutic benefit of a lymphadenectomy in UUTT remains controversial. Brausi et al found a positive correlation between LND and survival; Roscigno et al did not.[23–25]

However, as mentioned above, LND adds to correct staging and delivers prognostic information. It is recommended in high-grade upper-tract lesions and in clinical T2 to clinical T4 lesions. In a further analysis of the patients, Roscigno et al clearly stated that at least eight nodes should be removed to achieve 75% accuracy of probability of finding one or more positive nodes[23]. Thus far, predictive tools are absent.

6. Complete urinary tract extirpation

Complete urinary tract extirpation (CUTE) is a reasonable option in a highly selected patient population with T1–3 bladder TCC/CIS and massive bilateral UUTT with no metastases or unilateral UUTT with an afnuncular contralateral kidney. Recently, Blyweert et al presented their results of CUTE in 17 patients. This is so far the largest series of CUTE; from the analysis, the feasibility of this elaborate surgery was shown. There was, however, an elevated perioperative risk, with three perioperative mortalities. Major non-lethal early complications were identified in four other patients. The mean follow-up was 39 mo. During follow-up, kidney transplantation was performed on an ileal conduit in four patients. Patients who were on preoperative immunotherapy (cardiac transplantation \[n = 2\] or kidney transplantation \[n = 3\]) had the worst outcomes [26].

7. Conclusions

UTCC is a rare condition, and literature on this disease is rather scarce. There are no internationally validated guidelines on how to treat these lesions. Invasive and metastatic disease is more common than in bladder TCC. Ureteroscopy with biopsy and CT urography add diagnostic accuracy, but in high-grade lesions, muscle invasion and lymph nodes may be missed in 10–40% of the cases. The treatment of UUTT should be tailored both to patient factors and tumour factors.

Open NU remains the gold standard against which other approaches should be compared. Laparoscopic NU is becoming widely accepted as a minimally invasive alternative, delivering similar oncologic outcomes at short and intermediate follow-up. For low-stage, low-grade lesions; solitary lesions; and in absolute indications, NSS may be offered to the patient.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Contraindications</th>
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<tbody>
<tr>
<td>Stapler technique</td>
<td>Urinary tract remains closed</td>
<td>Tumoural implations in staple line</td>
<td>Distal ureteral tumours</td>
</tr>
<tr>
<td>Pluck technique (TURUO)</td>
<td>No intraoperative confirmation of complete resection</td>
<td>Damage to contralateral ureteral orifice</td>
<td>Bladder tumours near ureteral orifice</td>
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<tr>
<td>Striping of the ureter</td>
<td>Exposition of bladder and urethra to the mucosa of the stripped ureter</td>
<td>Retention of the intramural ureter</td>
<td>TCC of the distal ureter and bladder</td>
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<tr>
<td>Open bladder cuff resection</td>
<td>Intact, en bloc removal</td>
<td>Risk of damage to the contralateral ureter orifice (extravesical technique)</td>
<td>TCC in the proximity of UVJ</td>
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<tr>
<td>Open bladder cuff resection</td>
<td>Wide excision of bladder cuff possible</td>
<td>Possibility of incomplete resection (extravesical technique)</td>
<td>Active bladder TCC</td>
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<td></td>
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<td>Difficulty in obese patients; following RT</td>
<td>Active bladder TCC (risk of extravasation)</td>
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TURUO = transurethral resection of the ureteral orifice; TCC = transitional cell carcinoma; UVJ = ureterovesical junction; RT = radiation therapy

<table>
<thead>
<tr>
<th>Series</th>
<th>No. patients, laparoscopic/open</th>
<th>Follow-up, mo, laparoscopic/open</th>
<th>Recurrence rate, % *, laparoscopic/open</th>
<th>DSS, laparoscopic/open</th>
</tr>
</thead>
<tbody>
<tr>
<td>McNeill [16]</td>
<td>25/42</td>
<td>33/42</td>
<td>NR</td>
<td>84/79</td>
</tr>
<tr>
<td>Seifman [17]</td>
<td>16/11</td>
<td>19/16</td>
<td>40/50</td>
<td>NR</td>
</tr>
<tr>
<td>Raman [18]</td>
<td>38/52</td>
<td>32/52</td>
<td>54/20</td>
<td>90/62</td>
</tr>
<tr>
<td>Roupéret [19]</td>
<td>26/20</td>
<td>78/69</td>
<td>25/18</td>
<td>85/87</td>
</tr>
<tr>
<td>Gill [21]</td>
<td>42/35</td>
<td>11/34</td>
<td>23/54</td>
<td>77/77</td>
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<tr>
<td>Shalhav [22]</td>
<td>25/17</td>
<td>24/43</td>
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DSS = disease-specific survival; NR = not reported

* All sites of recurrence (bladder, contralateral upper tract, metastatic)
The role of lymphadenectomy lies in correct staging. Its likely therapeutic benefit remains controversial. Ideally, large international, prospective trials should assess the best management of UUTT. Of note in the last 2 yr, multicenter collaborative, retrospective studies have been initiated and have provided new insights into this infrequent condition and its management [7,23,24]. These may be used as a basis to initiate further prospective studies.

Conflicts of interest

The authors have nothing to disclose.

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References