

UPPER URINARY TRACT TRANSITIONAL CELL CARCINOMA: CURRENT TREATMENT OPTIONS AND MINIMALLY INVASIVE APPROACHES

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Summary.- *OBJECTIVES:* Upper urinary tract transitional cell carcinoma (UUT-TCC) is a rare disease. Open nephroureterectomy remains the gold standard for surgical treatment. We aim to evaluate the standing of novel surgical treatment in UUT-TCC.

METHODS: Extensive review of available literature on UUT-TCC, with emphasis in surgical treatment. English medical literature available in PubMed, Ovid, EMBASE y Science Direct was employed for the study.

RESULTADOS: Laparoscopic nephroureterectomy, ureteroscopy and percutaneous treatment are the available surgical options that based on adequate patient selection offer acceptable cancer control.

CONCLUSIONES: Indications for the treatment of UT-TCC are expanding and this allows clinicians to tailor treatment while preserving oncological results.

Keywords: Transitional cell carcinoma. Nephroureterectomy. Percutaneous treatment. Ureteroscopy.

Resumen.- *OBJETIVO:* El carcinoma de células transicionales del tracto urinario superior (CCT-TUS) es una enfermedad poco común. La opción de tratamiento tradicional ha sido siempre la nefroureterectomía abierta (NUA); nosotros examinamos el rol de los nuevos métodos de tratamiento.

MÉTODOS: Revisión de la literatura disponible en carcinoma de células transicionales con énfasis en tratamiento quirúrgico incluyendo las bases de dato de PubMed, Ovid, EMBASE y Science Direct, para artículos en ingles.

RESULTADOS: Nefroureterectomía laparoscópica, ureteroscopia y tratamiento percutáneo constituyen las opciones de tratamiento disponibles con adecuados resultados de control oncológico según las características específicas de cada paciente.

CONCLUSIONES: Las indicaciones de tratamiento mínimamente invasivo para CCT-TUS se están expandiendo e incluyen diferentes opciones que permiten racionalizar el tratamiento.



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INTRODUCTION

Upper urinary tract TCC (UUT-TCC) is an uncommon disease, but its incidence appears to be increasing as a result of progress in imaging, endoscopy and improved survival from bladder cancer (1,2). The development of more sophisticated endoscopic equipment has led to changes in everyday practice and a trend towards more conservative management. However, a significant proportion of this population requires radical treatment, because of the aggressive nature of UUT-TCC and the likelihood of bladder recurrences, metachronous ipsilateral (up to 30–75%) or even contralateral metastases (3–5). The traditional treatment approach has been open nephroureterectomy (ONU) with excision of a bladder cuff; the issue is whether ONU remains the first therapeutic option, as progress in laparoscopy now provides an attractive alternative. In this review we examine the place of newer methods of treatment. One of the key points in selecting the optimum treatment is correct staging by endoscopic/ureteroscopic evaluation and biopsy, combined with cross-sectional imaging. Low-stage and -grade tumours have been treated by conservative methods since the 1980s. Nephron-sparing surgery (NSS) was initially advocated for those patients in whom extirpative surgery was contraindicated. However, currently patients with normal contralateral kidneys might be considered candidates for NSS, as Elliott et al. (6) and Chen et al. (7) suggested. There are significant differences in the 5-year survival rates, of 60–90% in stages Ta/T1/carcinoma in situ, to only 5% in T3/T4, N + or M + disease. The most important factors for survival are tumour stage, grade and presence of multifocal lesions (8). Furthermore, tumour grade correlates well with the final pathological stage in both low- and highgrade lesions (9).

SEARCH STRATEGY

Our search included the PubMed, EMBASE, Ovid and ScienceDirect databases for English language articles with the following headings: 'upper urinary tract carcinoma', 'nephroureterectomy', 'laparoscopic', 'ureteroscopy', 'percutaneous', and their combinations. The most recent papers were selected in an effort to clarify each method's position in the current therapeutic options, assess advances in every minimally invasive treatment and their adherence to the well-established surgical and oncological principles. This was followed by a review of classical

papers published on the subject. In recent articles, all abstracts and citations were checked, and important information retrieved.

LAPAROSCOPIC NU (LNU)

Clayman et al. (10) reported the first LNU > 15 years ago. The renewed interest in the field soon overcame concerns about oncological safety and led to this approach being used by several centres. The kidney and ureter are removed by either a retroperitoneal or a transperitoneal approach; the removal of the ureter being an essential step of the whole procedure (11,12). Recurrences usually develop distally to the original tumour, and tumour stage and grade correlate well with survival (13).

Initial reports offered only short-term results, with 2- or 3-year data, and comparison to ONU was limited. The first multicentre study of LNU was presented by El Fettouh et al. in 2002 (14); collective data from five major centres in Europe and the USA, of 116 patients, were gathered, and the 2-year disease-specific survival (DSS) was 87%. Bariol et al. (15), in a study from Edinburgh in 2004, reported data on oncological control, comparing LNU and ONU in 64 patients, with the longest published mean follow-up of 101 and 96 months, respectively. Both the DSS and overall survival were comparable in the two groups. A meta-analysis was also reported by Rassweiler et al. (16) in the same year, where all the available data on LNU were compared; 1365 patients treated by both procedures were included (377 LNU and 969 ONU), and the mean 5-year DSS was 81.2% for LNU and 61% for ONU. In the last few years many publications have supplied valuable data on LNU. We present a review of all these series in Table 1 (15–38), which approaches a total of ≈ 700 patients, and highlight issues that are still under debate (15–39).

ONCOLOGICAL EFFICACY

Based on initial studies of the 2-year follow-up, the DSS rate was 71.5–91% (18–20,22,29), while the 5-year DSS was 81–91% (16,22,29,36). Extended follow-up for 7 years was reported from one series comparing LNU and ONU, with a DSS of 72% for LNU vs 82% for ONU (P = 0.26, not statistically significant) (15). This verifies the oncological efficacy of LNU. Furthermore, with data for both wholly laparoscopic (LNU) and hand-assisted LNU (HALNU), no significant difference between the two approaches has been identified, the DSS being 71.5–91% for LNU and 80–100% for HALNU (up to 3-years of follow-up data for HALNU).

RECURRENCE RATES – DISTANT METASTASES

A vital issue for the efficacy of LNU is the rate of bladder, local/regional recurrence and distant metastases. Recurrence in UUT-TCC is thought to be mainly the result of a mucosal defect, and such characteristics (e.g. cellular atypia and in situ carcinoma) are usually related with high-grade lesions (40). The bladder recurrence rate is 6–55%, while local recurrence (including the local lymph nodes) occurs in 3–29% (15,16,18–20,22,28,29,32,34,36). Distant metastases to other organs were detected in none (1-year data) to 28%. In series of LNU and HALNU with > 2 years of follow-up, the range is almost identical (6–28% vs 0–25% for HALNU) (19,28,32,34).

PORT-SITE METASTASES

Just seven cases with port-site metastases in LNU were identified, but most were related to either no use of or tearing of an organ bag (16,41). Only three should be considered as metastases from TCC. Encatchment bags should therefore be regarded as mandatory, especially when there is suspicion or proof of a high-grade tumour, and the specimen should be removed without morcellation.

ADVANTAGES OF LNU OVER ONU

Several centres have shown the benefits of LNU over ONU (15,16,20,21,23,26–29,31,37). Despite the usually longer operating time of LNU, 17 of 24 series reported a mean operative duration of up to 300 min, and at least four up to 200 min (15,18,27,29). The main differences relate to different techniques for dealing with the distal ureter, lymphadenectomy and hand-assisted approach. The mean blood loss was significantly lower for LNU, with four series reporting a blood loss of < 200 mL (20,21,23,26). Similar results are shown for hospital stay, now down to just 3–5 days in many series, and return to normal everyday activities.

MORBIDITY

The rate of minor and major complications for LNU is lower than for ONU, at 0–40% and 0–19%, respectively. For studies published in the last 3 years these rates seem to be further decreasing (31–38), with no significant differences between LNU and HALNU. PROGNOSTIC FACTORS UUT-TCC is an aggressive disease, especially when high-grade tumours are discovered. Most UUT-TCCs are grade II (18.5–48.2%) or III (42.5–47.0%) (42). A close co-

relation of the stage and grade of the disease has been established, together with a tendency of high-grade tumours to progression, muscle invasion and hence a poor prognosis.

ISSUES STILL UNDER DEBATE REGARDING LNU

Access for LNU and the use of a hand-assisted technique have not yet been standardized.

The transperitoneal (308 patients) and retroperitoneal (357 patients) access both have their supporters. Many groups have advocated the hand-assisted approach (309 patients) in an attempt to reduce operating time, facilitate ureterectomy and decrease the 'learning curve' (21,23–25,29,30,32–36,38). The most controversial issue is the management of the distal ureter, and various techniques have been used. The open dissection represents a compromise to the laparoscopic technique. Laparoscopic stapling of the distal ureter and bladder cuff avoids tumour spillage, but viable urothelial tissue might remain in the staple line and the margin cannot be evaluated. The transvesical laparoscopic detachment and ligation of the distal ureter adheres to oncological principles, but has the disadvantages of the 'learning curve' and need for repositioning. Finally, transurethral resection of the ureteric orifice ('pluck' technique) and stripping of the ureter, even after modifications, still remains questionable, because of the possibility of tumour seeding, although results from the Edinburgh study might decrease the concern about the oncological safety of this method (15,43). Recent data support a transvesical detachment technique or the hand-assisted laparoscopic en bloc excision of the distal ureter, but long-term comparative data in larger cohorts of patients are needed (30,31). The role of lymph node dissection is still far from being resolved; benefit has only been reported in low-volume disease (up to pN1). Studies in the last 2 years reported pN + disease in 0–14% of cases, with a DSS at 2 years of up to 94.5% in one study (32). Assessment of invasion of lymphatic vessels in the pathology specimen by tumour cells might be of value here (44).

ENDOSCOPIC TREATMENT OF UUT-TCC

Ureteroscopic and percutaneous management of tumours has seen significant changes. These procedures were initially advocated for patients requiring NSS (solitary kidney, renal insufficiency) or when significant comorbidities precluded radical surgery. The 5-year survival rate of dialysis patients, approaching 40% at best, is lower than the antici-

TABLE I. SERIES ON LUN FOR UUT/TC (24 SERIES).

Series	N	LUN technique	Ureterectomy technique	Operative duration, min.	Blood loss, ml	Complications minor/major, %	Bladder rec., %	Local rec, %	Distant met, %	DSS, % (years)
17	7	rp	Open	275	SI	4/0	SI	SI	SI	SI
18	22	tp	Open	200	SI	14/5	22.7	4.5	13.6	91 (2)
18	7	tp	ND	SI	SI	SI	SI	14.3	28.5	71.5 (2.2)
20	25	tp	ES	462	199	40/8	23	15.3	15.3	77 (2)
21	11	tp/ha	TD	291	147	0/0	18	SI	9	SI
22	25	tp	ES/open	329	440	24/12	48	8	16	86 (2)
23	7	tp/ha	Open	224	140	SI	14.3	0	0	SI
24	10	rp/ha	Open	456	462	30/10	SI	SI	SI	SI
25	16	tp/ha	ES+TR	294	201	25/6	27	13.3	20	100 (1.3)
26	17	rp	Open	239	151	12	29	6	0	SI
27	9	rp	Open	189	275	22.2	22.2	SI	22.2	77.8 (1.2)
28	34	rp	Open+TR	233	236	6/6	6	0	6	87 (2)
29	19	tp/ha	Open	198	282	0/0	10.5	5.3	10.5	91 (5)
15	25	tp	TR	165*	SI	12/4*	28	8	28	72 (7)
16	23	rp	Open	200	450	9/9	34.8	0	17.4	81 (5)
30	58	rp/ha	Open	230/259	409	SI	8.6	0	10.3	100 (1.3)
31	60	rp	>3 methods	269*	242*	7/5*	27	7	12	97 (1)*
32	55	tp/ha	>3 methos	298-382	185-810	SI	34.5	3	0/7/19	95 (2)
33	33	tp/rp/ha	E/TR	335	223	24.2	6	SI	0	100 (0.8)
34	54	tp/ha	TR/modified TR	279	SI	33/15	55	11	25	80 (3)
35	34	tp/ha	Open	317	252	SI	0	0	0	100 (1.2)
36	89	rp	ES/open	258-306	354-580	SI	35-55	24-29	9.4-16.7	81 (5)
37	25	rp	Open	306	322	15	14.3	SI	0	SI
38	31	SI/ha	Open+TR+ES	236	365	26	42	3.2	6.4	96.8 (2.3)
total	686			165-462	140-450		0-55	0-29	0-28.5	81-91 (5)

**data from earlier publication, where they were not available in most recent paper. ND, no data; Tp, transperitoneal; Rp, retroperitoneal; TD, transvesical detachment; ES, extravesical stapling; TR, transurethral resection; rec., recurrence; met., metastasis.

ted 5-year survival of patients treated conservatively (40). An endoscopic approach should replace ONU, without jeopardizing the oncological result. Management for UUT-TCC by ureteroscopy has resulted in a successful outcome in a significant proportion of patients. Comparable results were reported for percutaneous approaches, especially in selected low-grade tumours.

URETEROSCOPY FOR UUT-TCC

Flexible) ureteroscopy represents great progress in the treatment of UUT tumours. Initial use of these instruments for diagnostic purposes now encompasses therapy, with tumour destruction by laser or electrocautery. Advantages include limited morbidity, outpatient treatment and maintenance of urothelial continuity. Disadvantages include the inability to treat large lesions in one session, access difficulties and staging errors. Ureteroscopy should be reserved for cases of low-grade UUT-TCCs of ≤ 1.5 cm in diameter, as treatment of high-grade tumours has been associated with higher rates of local recurrence and disease progression (45,46). Guarnizo et al. (47) recently stressed the importance of multiple and, when possi-

ble, deep biopsies for correct staging, even though practice is not widespread (48). Published data suggest a significant association of tumour stage and grade in NU specimens; pathological stage pT2 + was discovered in only 5% of low-grade tumours, but in 65% of high-grade tumours (45). The TNM stage was the only predictive factor associated with overall survival ($P = 0.03$) in a multivariate analysis reported by the same group. Furthermore, there is a good correlation between ureteroscopic and NU specimens from the same patients (9). The uretero-resectoscope and electrocautery probes (Bugbee electrode) have been supplanted by other methods. The major therapeutic advance has been due to the use of the holmium laser (Ho:YAG) with optical fibres of 200 and 365 μ m, as well as the Nd:YAG laser; both have been used to cauterize and ablate UUT-TCC, with results comparable to open resection DSS rates. The use of a ureteric access sheath was proposed to decrease intrarenal pressures during ureteroscopy and minimize risk of micrometastases (49). It must be emphasized that not all patients are amenable to endoscopic resection, mainly due to large tumour size, as reported by Suh et al. (50). The outcomes in many studies of ureteroscopy for treating UUT-TCC, shown in Table 2 (1,6,7,9,46,50–53), have been encouraging. The

TABLE II. SERIES ON URETEROSCOPY TREATMENT FOR UUT - TCC.

Serie	N	Recurrence, n (%)	DSS, %	Follow up, months
52	28	8 (29)	93	2-119
1	205	65 (31.7)	SI	2-132
51	38 (41 kidneys)	8 (28)	100	3-116
7	23	15 (65)	100	8-103
6	44	17 (38)	86.5	3-132
9	26	23 (88)	100	4-106
50	18	3 (37.5)	100	3-48
46	35	24 (68)	100	3-84
5	35	26 (74)	100	5-115

ND, No Data

complication rates of 8–13% are mostly minor, with a rate of perforation of 1–4%, and ureteric strictures up to 9% (up to 40% might be a result of recurrent tumour) (9). A major analysis was published in the late 1990s (1). The authors reviewed treatment in 205 kidneys and ureters from various studies between 1985 and 1997, and determined local recurrence rates of 33% and 31.2% for renal pelvis and ureteric tumours, respectively. The bladder recurrence rate was 43%. Later studies, of > 250 patients, showed a wide range of recurrence rates of 28–88% and DSS up to 86.5%, suggesting better results than the initial studies. This might be explained by more vigilant follow-up and case selection. Disease recurrences were related to the location, size, grade and multifocality of tumours. Data are too weak to support any recommendation about adjuvant therapy with chemotherapeutic agents. Careful lifelong follow-up is a critical requirement after ureteroscopy, as the disease-free interval is often low, and recurrences can occur even after 5 years (46).

PERCUTANEOUS TREATMENT FOR UUT-TCC

Percutaneous treatment for UUT-TCC should now be offered only to patients with large tumours of the renal pelvis (> 1.5 cm), bulky tumours of the proximal ureter, or those inaccessible using ureteroscopy. The results of recent studies are summarized in Table III.

(50,54–60). The stage, grade and location (ureter or renal pelvis) of the tumour are considered to be the most important prognostic factors, more than extensive surgical resection (40). Visualization is much better through the percutaneous approach, and large tumours can be resected in one session; adjuvant treatment can be administered through the nephrostomy tube, although it should be delayed for at least 2 weeks. The complication rates are low and are related to the number of sessions (50). Transfusion rates are > 20% in many series, while less common are obstruction of the PUJ from stricture and tract seeding. The latter has only been reported twice, and others have proposed placing a large sheath in the collecting system to decrease pressures (61). Studies before 2000 reported a recurrence rate of 23–56% and disease-specific mortality of 0–36%, with the worst results in grade III patients (56,57). Other groups have shown even higher rates of recurrence of up to 88%, with a renal preservation rate of 79.1% (50,54,55,58–60). A recent study comparing endoscopic treatment to ONU found no significant differences in survival for lowgrade tumours (62). Higher recurrence rates might reflect a strict follow-up protocol, as the disease-specific mortality rate is low for large, low-grade tumours (53). Adjuvant therapy, as for the ureteroscopic approach, has not been standardized (57). We have used mitomycin C in most cases, with good results, but no results are yet available from a prospective randomized study. Follow-up, as for any other organ-

TABLE III. SERIES ON PERCUTANEOUS TREATMENT FOR UUT - TCC.

Serie	N (renal units)	Recurrence, n (%)	DSS, %	Follow up, months
57	34 (36)	33	87	9-111
56	26 (26)	23	92.3	1-100
54	17 (18)	33	83	1.7-75
55	54 (54)	38	84	11-168
58	22 (22)	55	69.2	24-132
50	19 (19)	88	89.5	3-58
59	34 (34)	44.2	94.1	3-131
60	24 (24)	33	79.5	18-188

sparing procedure, should be strict. Every patient considered as a candidate for such management should be counselled and be motivated enough to adhere to a regular evaluation by ureteroscopy and biopsy.

CONCLUSIONS

The indications for minimally invasive treatment for UUT-TCC are expanding. LNU is comparable to ONU in effectiveness and oncological efficacy, especially for low-grade tumours. Long-term data on survival of up to 7 years have verified that the DSS and recurrence rates are comparable to ONU. For those patients in whom renal preservation is the goal, ureteroscopy is best reserved for treating low-grade ureteric tumours up to 1.5 cm, but careful pretreatment staging is always required. Percutaneous treatment can be used for renal, lower calyceal, bulky proximal ureteric or otherwise inaccessible tumours of > 1.5 cm, with similar outcomes to those obtained with ureteroscopy.

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