ENDOSCOPIC TREATMENT OF UROTHELIAL TUMOURS OF THE RENAL PELVIS AND URETER

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Summary.- Endoscopic treatment of urothelial tumors of renal pelvis and ureter is gaining acceptance as a conservative treatment modality. Technological advances have increased its applicability. Ureteroscopic and percutaneous tumor ablation have become reasonable treatment options for patients with imperative indications, such as bilateral disease, renal insufficiency or solitary kidney. However, endoscopic tumor ablation is being utilized more frequently for patients with UTCC even in the setting low grade disease and a normal contralateral kidney, provided long-term close surveillance to detect and treat recurrences is ensured. This paper reviews the current role of endoscopic management of UTCC.

Keywords: Upper-tract transitional cell carcinoma. Ureteroscopic treatment. Percutaneous treatment.

Resumen.- OBJETIVO: El tratamiento endoscópico de los tumores uroteliales de la pelvis renal y el uréter está ganando aceptación como modalidad de tratamiento conservador. Los avances tecnológicos han aumentado su aplicabilidad. La ablación ureteroscópica y percutánea de los tumores se ha convertido en una opción de tratamiento razonable para pacientes con indicaciones imperativas, tales como enfermedad bilateral, insuficiencia renal o riñón único. Sin embargo, la ablación endoscópica de tumores se está utilizando con mayor frecuencia en pacientes con carcinoma de células uroteliales del tracto urinario incluso en el escenario de enfermedad de bajo grado y riñón contralateral normal, con la condición de que se asegure un estrecho seguimiento a largo plazo para detectar y tratar las recurrencias. Este artículo revisa el papel actual del manejo endoscópico del tumor urotelial del tracto urinario superior.

Palabras clave: Carcinoma de células transicionales del tracto urinario superior. Tratamiento ureteroscópico. Tratamiento percutáneo.

INTRODUCTION

Upper urinary tract urothelial tumors are relatively uncommon, representing approximately 5% of all urothelial tumors, 1 to 2% of all genitourinary tumors and 7% of all renal tumors [1,2]. The vast majority are transitional cell carcinomas (TCC - 90%), whereas only 10% are squamous cell carcinomas and 1% adenocarcinomas. Urothelial tumors of the renal pelvis are three to four times more frequent than those located in the ureter [3]. Of ureteric urothelial tumors, 70% occur in the distal third with a further...
24% occurring in the mid-ureter. The incidence of upper tract TCC (UTTCC) increases with age in both genders and appears most frequently during the sixth and seventh decades of life (mean age of occurrence 65-67 years). Men present with this disease three times more frequently than women.

Like that of the bladder, UTTCC most likely represents a field change disease with multifocality and multiple recurrences in both time and space. The nature of these changes is not fully understood but might relate to factors such as cellular implantation or widespread dysplastic change in the urothelium (4). Whatever the etiology is, this observed polychronotopism is generally confined to the ipsilateral upper tract. Although recurrence at an additional site in the genitourinary system will occur in 30-50% of patients, recurrence in the contralateral renal unit will develop only in 1% to 5.8% (5). The incidence, however, may be higher in the setting of associated carcinoma in situ. The association of UTTCC and bladder cancer has been well established, but the disparity between their incidences underlines the poor understanding of the condition. Traditionally patients with a history of primary bladder cancer are thought to have a less than 4% occurrence of UTTCC. The incidence is significantly increased in patients with high grade (G3) non-muscle invasive bladder tumor, concurrent carcinoma in situ, prostatic urethra involvement, or recurrence after BCG therapy (4,6). Conversely of patients who have UTTCC, 30-75% subsequently develop bladder cancer, which may be a result of tumor multifocality, unstable urothelium field effect or descending tumor seeding (5,7,8).

This natural history has made nephroureterectomy with bladder cuff excision the gold standard treatment for UTTCC for more than 60 years (9). However the fact that TCC tumors are often of low grade and stage has created the need for a more conservative management leading to less extensive resections of the urinary tract (10). Experience with open nephron-sparing approaches and a better understanding of UTTCC pathology has suggested that radical treatment may not always be necessary. Endoscopic management is the natural evolution of this trend towards minimally invasive therapy and has been utilized to treat UTTCC in an attempt to remove the malignant lesion while preserving renal function.

Although nephron-sparing surgery for UTTCC was first proposed by Vest in 1945, this practice did not find acceptance until many years later. Case reports of endoscopic resection of the upper tract urothelial lesions were sporadic in the 1950’s and 1960’s (11,12). Minimally invasive procedures were first utilized in the management of UTTCC in the mid-80’s (13). With the advances in endoscopic technology, namely the development of better optics, progressively smaller and more durable rigid and flexible endoscopes, actively deflecting telescopes and adjunctive instrumentation, endoscopic procedures have become more practical and efficacious, employed for both diagnostic and therapeutic purposes.

In fact direct visualization of the tumor allows obtaining a tumor biopsy and selective urine cytology. Tumor grading in this setting is very accurate and is 90% in agreement with the grade of the final pathological specimen. Ureteroscopy has not been demonstrated to be a dependable method of staging and therefore has been characterized by some authors as unreliable in determining stage (14). However preoperative stage determination may be possible due to the reliable correlation between grade and stage (15,16) and the high accuracy of the CT or MRI scans in detecting evidence of tumor extending beyond the wall of the ureter or renal pelvis (17). Therefore the combination of low grade on ureteroscopic biopsy and absence of frank extension outside of the urinary tract by CT scan strongly suggest that the disease is superficial. Thus diagnostic ureteroscopy has emerged as the standard in evaluating upper tract urothelial lesions and is essential in developing the therapeutic plan for each patient (18).

Traditionally endoscopic management of UTTCC was reserved for patients with imperative indications, such as bilateral disease, renal insufficiency or solitary kidney. The currently accepted indications for endoscopic treatment of UTTCC are (19):

- Inadequate renal reserve (chronic renal impairment or solitary kidney)
- Actual or high risk of bilateral disease (e.g. Balkan nephropathy)
- Significant comorbidity
- Palliation (where cure is not possible)
- Papillary, superficial, low grade (G1-2) disease, with low invasive potential.

However, more recent reports suggest that endoscopic tumor ablation is being utilized more frequently for patients with UTTCC even in the setting of a normal contralateral kidney.

The endoscopic treatment of UTTCC can be achieved via two approaches: either the
ureteroscopic, or the percutaneous access. Rarely a combined approach may be used.

**Ureteroscopic treatment**

Ureteroscopic ablation of UTTCC is best reserved for patients with small, low-grade tumors, that have no evidence of invasion or local metastasis and in whom the risk of subsequent renal failure after definitive surgical resection outweighs that of tumor progression (4). After gaining retrograde access, the distal ureter is visualized with a rigid ureteroscope and the remainder of the ureter and entire renal collecting system are examined with a flexible ureteroscope. After the biopsy is performed the available treatment options are mechanical debulking (cold cup or basket), electroresection, laser photocoagulation or ablation (Nd:YAG, Ho:YAG) and electrofulguration. The holmium YAG laser is effective, it can both coagulate and ablate tissue and has minimal tissue penetration (< 0.5mm) (20). Mechanical removal of small tumors can also be a very effective technique in treatment and significant volumes of tumor can be removed in the biopsy process.

The complications of ureteroscopic tumor ablation have decreased with the advancements in instrumentation and technique. Perforation of the ureter or renal pelvis is less common occurring in 0 to 10% of patients. The stricture rate ranges from 5% to 14% (21). The higher incidence of ureteral stricture with the use of Nd:YAG is well documented (22). The other potential complication is the dissemination of the tumor either through extraluminal spillage or throughout the urothelium, although some authors consider it as theoretical risk only (23). In general ureteroscopic treatment has a significant lower blood transfusion and overall complication rate than antegrade percutaneous treatment (24).

**Percutaneous treatment**

The percutaneous approach is preferred for larger tumors (>1,5 cm) located proximally in the renal pelvis and/or upper ureter. It is also best for ureteric recurrences after cystectomy for bladder cancer. The main advantage of the percutaneous approach is the ability to remove a larger tumor volume from any site of the collecting system owing to the use of instruments with larger working channels, which allows better visualization and faster resection. Deeper biopsies can be obtained when compared to those taken with ureteroscopy, whereas the percutaneous approach may avoid the limitations encountered even by flexible ureteroscopy, especially in complicated caliceal systems or areas difficult to access (25). Thus access to any renal unit is possible irrespective of any prior surgical intervention, such as urinary diversion.

A variety of modalities have been described for tumor ablation, including monopolar and bipolar cautery, laser, rollerball electrode and electrovaporization (26). The entire tumor should be ablated and the base fulgurated or resected. Flexible nephroscopy should be carried out to ensure that all areas of the kidney are clear of tumor (27).

<table>
<thead>
<tr>
<th>Series</th>
<th>Nº of patients</th>
<th>Recurrence n (%)</th>
<th>DSS (%)</th>
<th>Follow up (months)</th>
</tr>
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<tbody>
<tr>
<td>Martinez-Pineiro et al. (35)</td>
<td>28</td>
<td>8(29)</td>
<td>93</td>
<td>2-119</td>
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<tr>
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<td>15(65)</td>
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<td>17(38)</td>
<td>86.5</td>
<td>3-132</td>
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<td>23(88)</td>
<td>100</td>
<td>4-106</td>
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<td>Suh et al. (44)</td>
<td>18</td>
<td>3(37.5)</td>
<td>100</td>
<td>3-48</td>
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<tr>
<td>Johnson et al. (18)</td>
<td>35</td>
<td>24(68)</td>
<td>100</td>
<td>3-84</td>
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<tr>
<td>Sowter et al. (49)</td>
<td>35</td>
<td>26(74)</td>
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established nephrostomy tract can be maintained for immediate postoperative nephroscopy and/or administration of topical adjuvant therapy. Some authors advocate a second look nephroscopy in one or two days to ensure the entire tumor was resected (28,29). Endoscopic vision is usually better at a later date when bleeding has stopped and tissue debris settled down.

The complication rates are relatively low and are related to the extent of disease and number of sessions (44). The main disadvantage with the antegrade access is the increased morbidity compared to ureteroscopic treatment. Bleeding is a potential complication of percutaneous resection because of the vascularity of the kidney. Renal vein injury caused by resection of a fold inside the renal pelvis overlying the vein has been reported (30). Transfusion rates are >20% in many series, while less common are obstruction of the pyelo-ureteric junction from stricture and tract seeding (55). For the latter some authors have proposed placing a large sheath in the collecting system to decrease pressures (54). Nephrostomy tube placement has inherent risks and therefore requires inpatient admission. In addition, loss of urothelial integrity and exposure of nonurothelial surfaces to tumor cells carries the risk of tumor seeding along the nephrostomy tract, which remains a significant clinical concern (31). Another relevant issue for percutaneous treatment is whether urologic surgeons are adequately trained in establishing renal access. Although recent survey data show that 92% of urologists trained in percutaneous renal surgery, only 27% obtain access independent of an interventional radiologists (32).

**Treatment outcomes**

The results of ureteroscopic treatment of UTTCC are summarized in Table I. Upper tract and bladder recurrence rates for patients treated endoscopically are reported to be 30-40% and 35-40% respectively, regardless of primary upper tract locations of the tumors (7,33). Other studies with limited follow up demonstrated an 86-93% survival rate (34,35). Chen et al. (36) in a series of 23 patients with UTTCC and normal contralateral kidney treated ureteroscopically reported an organ-preservation rate of 83% with 100% disease specific survival. Elliot et al. (37) reported on 21 patients who had no contraindications to open surgery, a recurrence rate of 38%, with renal preservation rate of 81%, whereas no death as a result of the conservative management were reported.

In a recent study, 20 patients with elective and 7 with imperative indications were treated with ureteroscopy for UTTCC. In the imperative-treatment group, the recurrence rate was 86% and 57% were tumor free at 37 months of follow-up. The elective group had 20% recurrence rate and a 93% disease-free rate at 33 months (38). The point of relevance is that survival is not compromised by minimal invasive ureteroscopic treatment of UTTCC in spite of an increased recurrence rate and in properly selected patients a renal salvage rate of up to 78-81% can be expected (39).

Table II outlines selected series of percutaneously treated UTTCC from the literature. The recurrence rates depend on the grade of the tumor, with low grade tumors having a lower recurrence rate (18-28%) than high-grade tumors (approx. 50%) (39).

<table>
<thead>
<tr>
<th>Series</th>
<th>Nº of patients</th>
<th>Recurrence n (%)</th>
<th>DSS (%)</th>
<th>Follow up (months)</th>
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<td>54</td>
<td>38</td>
<td>84</td>
<td>11-168</td>
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<tr>
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<td>19</td>
<td>88</td>
<td>89.5</td>
<td>3-58</td>
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<tr>
<td>Goel et al. (52)</td>
<td>22</td>
<td>55</td>
<td>69.2</td>
<td>24-132</td>
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<tr>
<td>Palou et al. (53)</td>
<td>34</td>
<td>44.2</td>
<td>94.1</td>
<td>3-131</td>
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<tr>
<td>Roupret et al. (54)</td>
<td>24</td>
<td>33</td>
<td>79.5</td>
<td>18-188</td>
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Cancer specific death rates range from 13-35%, with deaths seen mainly in patients with high-grade and high-stage tumors (35,40). Lee et al. (41) demonstrated in a series of 110 patients treated percutaneously that high-grade disease recurs at a higher rate whatever therapeutic modality is used (25% and 31% in open and percutaneously treated grade 3 tumors vs 14% and 6% in open and percutaneously treated grade 1-2 tumors respectively). Overall, according to several findings, disease specific survival (DSS) was no different between stages in patients treated percutaneously or with an open procedure, suggesting that percutaneous therapy offers results equivalent to those of open nephroureterectomy (27,28,40). Therefore it can be stated that because both treatment methods offer similar long-term survival, the percutaneous approach may provide an improvement in quality of life if need for dialysis is avoided or even delayed (27,28).

These findings have expanded the role of endoscopic treatment for UTTCC from patients with imperative indications to patients electively willing to adhere to strict surveillance protocols (42). As experience with minimally invasive treatment of UTTCC increases, certain cohorts are being identified as at increased risk for treatment failure, including patients with a history of bladder cancer, large tumor size and multifocal disease (43). Many studies have sought independent predictors of recurrence after endoscopic treatment for UTTCC. Suh et al. (44) reported that higher grade, larger size, location in the renal pelvis and tumor multifocality correlated with shorter recurrence-free survival. Boorjian et al. (45) suggest that post-treatment positive cytology itself is an independent predictor of UTTCC-recurrence after endoscopic ablation. This likely reflects either unrecognized or persistent tumor and thus predisposes patients to tumor recurrence in the future. In addition, while previous reports suggest a low rate of grade and stage progression (34,37), more recent reports suggest that tumor progression remains a distinct possibility (14,46).

Thus endoscopic treatment of UTTCC alone for high grade tumors is not advised due to high rates of both local recurrence and disease progression (47), while many authors do not recommend primary endoscopic management of UTTCC in elective situations if pathological analysis and tumor grade is unable to be obtained.

**Adjuvant therapy**

Topical immunotherapy or chemotherapy can has been the mainstay of adjuvant therapy in bladder cancer. It has also been employed after endoscopic treatment for UTTCC in an effort to decrease recurrences in these patients. Topical immunotherapy or chemotherapy can be administered via catheters and stents placed after resection, either in antegrade or in retrograde fashion. Various agents have been used, including mitomycin C, thiopeta, Adriamycin and interferon, but the most commonly used is BCG4. Adjuvant therapy with BCG and mitomycin C has been the most extensively studied, as these agents are thought to provide the best results in decreasing the recurrence rates of UTTCC (35). However there is no level 1 evidence from randomized controlled trials to assess efficacy and the available data are conflicting, particularly in the case of high grade disease. Studies have reported similar efficacy of intracavitary instillation of BCG and mitomycin C, when used for low grade UTTCC compared with bladder cancer (56,57) Generally the available data suggest that intracavitary adjuvant therapy can be administered safely, provided it is followed by close follow-up, however its efficacy has yet to be proven.

**Follow-up**

Long term endoscopic surveillance of the upper tract and bladder is mandatory. Follow-up, as for any other organ-sparing procedure should be strict. Every patient considered as a candidate for such management should be counseled and be motivated enough to adhere to a regular evaluation (55). Most authors agree that cystoscopy, ureteroscopy and cytology examination should be performed in diminishing intensity as is done with bladder TCC surveillance protocol. This upper-tract surveillance should be tailored to the patient’s tumor grade and stage. According to Ho et al. (33), a reasonable schedule would be cystoscopy and cytology every 3 months, alternating with cystoscopy, retrograde pyelogram, cytology and flexible ureteroscopy every 6 months for the first 2 years, then cystoscopy every 6 months and ureteroscopy annually. Imaging of the contralateral upper tract is usually performed annually, because of the low risk of contralateral disease (21). Generally a 3 month interval surveillance protocol for the first year is the most acceptable pattern (49,50). However, the patient must be willing to comply with and capable of undergoing frequent endoscopic surveillance.

**CONCLUSION**

Nephroureterectomy with removal of a bladder cuff remains the gold standard in the treatment of UTTCC. The ultimate goal of endoscopic management is cancer control while simultaneously preserving renal function and minimizing morbidity. Traditionally endoscopic management of UTTCC was
reserved for patients with imperative indications, such as bilateral disease, renal insufficiency or solitary kidney. However, more recent reports suggest that endoscopic tumor ablation is being utilized more frequently for patients with UTTCC even in the setting of a normal contralateral kidney. Endourologic management of UTTCC has therefore become an accepted treatment option in highly selected patients, provided long-term close surveillance to detect and treat recurrences is ensured. However absolute conclusions about the outcome cannot be made because of the relatively low frequency of these tumors and the lack of randomized trials.

ABBREVIATIONS AND ACRONYMS

UTTCC: Upper-Tract Transitional Cell Carcinoma
CT: Computed Tomography
DSS: Disease Specific Survival

REFERENCES AND RECOMMENDED READINGS

(*of special interest, **of outstanding interest)

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