Review

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Adjuvant Intraluminal Therapies in Upper Urinary Tract Urothelial Tumors

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Abstract

The gold standard treatment option for upper urinary tract urethelial tumors is radical nephroureterectomy and bladder cuff resection. On the other hand, with the development of surgical techniques, improvement in endoscopic instruments and better risk stratification in recent years, minimally invasive endoscopic procedures and renal-sparing surgical approaches such as segmental/total ureterectomy have begun to be applied. Metachronous tumor recurrences can be seen despite the use of renal-sparing approaches in selected patients. Adjuvant intraluminal treatments are applied in upper urinary tract tumors to reduce tumor recurrences. In this review, we discussed the role of adjuvant intraluminal therapies.

Keywords: Upper urinary tract urethelial tumor, renal-sparing approach, adjuvant intraluminal therapy

Introduction

Urothelial tumors take the 4th place among cancers seen in developed countries (1). Upper urinary tract urothelial tumors (UUTUTs) are relatively rare and constitute 5-10% of all urothelial tumors (2). Although it is mostly diagnosed unilaterally, synchronous bilateral UUTUTs can be seen rarely (1.6%) (3). The incidence of contralateral UUTUTs has been reported as 1-6% in the literature (4). It is thought that environmental factors may be effective in the formation of UUTUTs. Smoking and aristolochic acid are scientifically proven environmental factors in etiology (5,6). In addition, there are strong findings that there is a relationship between hereditary UUTUTs and hereditary non-polyposis colorectal carcinoma (7).

The gold standard treatment option in UUTUTs is radical nephroureterectomy and resection around the bladder orifice (8). However, in recent years, the view that radical nephroureterectomy may be overtreatment in low-stage and high-risk UUTUTs has been accepted (9). On the other hand, the development in surgical techniques and endoscopic instruments used in recent years allows better risk stratification and the introduction of minimally invasive endoscopic procedures such as segmental/total ureterectomy and renal-sparing surgical approaches (10,11). On the other hand, metachronous tumor recurrences can be seen despite the use of renal-sparing approaches in selected patients. Adjuvant intraluminal treatments are applied in UUTUTs to reduce tumor recurrences. In this review, we discussed the role of adjuvant intraluminal therapies.

Renal-sparing Surgery Indications and Risk Stratification

European Urology Guidelines defined indications for renal-sparing surgery (12). Anatomical or functional solitary kidney, presence of bilateral tumors, detection of kidney failure, and poor performance of the patient for radical surgery are definite indications. However, low-risk tumor or selected patients with high-risk tumors (multifocal tumors, large, low-risk and superficial tumors) are relative indications (Table 1). In addition, the risk stratification of UUTUTs was defined in the 2019 European Urology Guideline to determine which patients were more suitable for a renal-sparing approach (12). According to the European Urology Guideline risk stratification; single focus, tumor size <2 cm, low-grade cytology or ureteroscopic biopsy results, and no invasive spread on computer tomography-urography are features of low-risk UUTUT. Presence of hydronephrosis, tumor size >2 cm, high-grade cytology or ureteroscopic biopsy result, multifocal tumor, variant histology, and a history of radical cystectomy are features of a high-risk UUTUT (Table 2).

Renal-sparing Endoscopic Approach

In recent years, with the development of endoscopic instruments, retrograde or antegrade endoscopic approach has been started

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Table 1. Indications for renal-sparing surgery in upper urinary tract urothelial tumors
Strong Recommendations
Anatomical or functional solitary kidney Bilateral tumor Chronic renal failure Not suitable for radical nephroureterectomy
Weak Recommendations
Low risk upper urinary tract urothelial tumor Appropriate high-risk upper urinary tract urothelial tumor: Multifocal tumor, large tumor, tumor with low-risk features, superficial tumor

Table 2. Risk stratification in upper urinary tract urothelial tumors
High risk upper urinary tract urothelial tumor
• Hydronephrosis • High grade (Ureteroscopic biopsy or cytology) • Tumor size >2 cm • Multifocal disease • Variant histology • History of radical cystectomy
Low risk upper urinary tract urothelial tumor
• Single focus • Tumor size <2 cm • Low grade (Ureteroscopic biopsy or cytology) • No invasive spread in computer tomography-urography

to be used frequently in UUTUTs, especially in low-risk patient group. In a meta-analysis, Seisen T. showed that low-risk patients who underwent ureteroscopy or percutaneous renal-sparing surgical approach had similar survival compared to patients who underwent radical nephroureterectomy (13). Similar oncological outcomes, better renal function after renal-sparing surgery, and lower morbidity made the renal-sparing approach to be preferred more often than the radical approach in low-risk patients. The current European Urology Guideline states that endoscopic ablation can be applied in low-risk patients if there are suitable instruments for ablation and biopsy, if there is a flexible ureteroscope, if the patient is informed about the need for close follow-up, and if complete tumor resection can be performed (14). Although the percutaneous approach is applied in patients with low-risk renal pelvis or calyx tumors, it has been used less frequently in recent years due to the development of retrograde endoscopic instruments and the risk of tumor seeding in the percutaneous approach (15).

Intraluminal Treatments

Although the indications for the use of intraluminal therapies in bladder cancer are stated in European and American Urology Guidelines, there is still insufficient evidence regarding the use of intraluminal therapies in UUTUTs. Although there are no randomized clinical studies conducted to date, most of the available data in the literature are based on retrospective studies.

Intraluminal treatments are applied antegrade or retrograde way in UUTUTs. In both methods, there is no standard approach in terms of duration, frequency, and the agent applied. For antegrade administration, a 10F percutaneous nephrostomy tube is inserted into the patient and it is waited for 2 weeks for the tract to form before starting the infusion. For antegrade intraluminal immunotherapy [Bacillus Calmette-Guerin (BCG)], 360 mg Immune BCG Pasteur or 243 mg ImmuCyst is dissolved in 150 mL 0.9% saline and given as an infusion over 2 hours at 1 mL per minute over 20 cm above the patient's kidney level (16,17). Antegrade intraluminal chemotherapy (mitomycin C) is administered using a similar procedure by dissolving 40 mg of mitomycin in 20 mL of 0.9% saline. During the treatment, the nephrostomy tube is changed every 3 months (17). Although antegrade method with percutaneous nephrostomy tube is a more direct method, the nephrostomy tube should remain on the patient during the treatment process. This may adversely affect the patient's quality of life. On the other hand, in retrograde method, a 5F ureteral catheter is placed in the patient with cystoscopy. In patients who are infused through a ureteral catheter, the pressure of the manometer is kept below 20-30 mmHg, and the patient is told to change positions every 15-20 minutes for the infusion to affect the entire urinary tract (right side, left side, supine and prone positions) (18). The agent used, dose and duration of administration are similar to antegrade method. Retrograde method is seen as a more comfortable method by patients, especially since it can be performed under local anesthesia and there is no permanent catheter on the patient during the treatment process. Before both applications, urine cultures are taken from the patients and prophylactic antibiotics are given. The induction dose for intraluminal chemotherapy (mitomycin C) and immunotherapy (BCG) is given once a week for 6 weeks. Although the maintenance dose for intraluminal chemotherapy is not clear, it is given once a month for at least 3 months (18). The maintenance dose for intraluminal BCG is once a week for 3 weeks at the 3rd, 6th, 12th, 18th, 24th, 30th and 36th months (19). One of the main problems in retrograde method is the time it takes for the applied agent to pass and act in the upper urinary tract tract. It should be ensured that the proximal end of the inserted catheter is in the renal pelvis and that there is no mucosal injury. Methods such as ureteral meatotomy and permanent ureteral stenting which causes retrograde reflux have been described. However, before induction therapy, it should be ensured that there is sufficient volume to activate the reflux (20).

It has been thought that intraluminal treatments would prevent recurrence after a renal-sparing approach, especially in low-risk patients, as in bladder cancer. Chemotherapeutic and immunotherapeutic agents have been applied for a short time in UUTUTs (21,22). The results of adjuvant intraluminal BCG administration after UUTUT resection or ablation are not promising. In a study by Giannarini et al. (16), recurrence-free survival and progression-free survival (PFS) were found 41% and 59%, respectively, in patients with Ta or T1 UUTUT treated with BCG antegrade perfusion as an induction regimen (16). In another study by Rastinehad et al. (23), no statistically significant difference was found in terms of recurrence in patients who received adjuvant intraluminal BCG in both high-grade and low-grade UUTUTs compared to those who did not (low grade 26%-33% vs high grade 38%-39%). On the other hand, it has been shown that adjuvant intraluminal BCG induction therapy gives better results in upper urinary tract carcinoma *in situ* (CIS) (24). Carmignani et al. (25) evaluated 12 studies involving a total of 185 patients and stated that the mean recurrence rate was 32%

in a mean follow-up period of 19-57 months after 6 weeks of BCG induction therapy in 165 patients with upper urinary tract CIS. On the other hand, Shapiro et al. (26) evaluated the role of BCG-interferon therapy in biopsy-confirmed upper urinary tract CIS in a study they conducted. In a study involving 11 patients, complete response was observed in 8 (73%) patients and only 1 patient had biopsy-proven recurrence. Based on the available data in the literature, it can be concluded that adjuvant intraluminal BCG therapy is effective and can be used as a primary treatment option in upper urinary tract CIS without papillary tumor. However, prospective randomized clinical studies with larger patient populations are needed.

Just as adjuvant chemotherapeutic agents are used to prevent progression and recurrence after transurethral resection in bladder tumors; adjuvant chemotherapeutic agents are used to reduce recurrence after resection in low-risk patients with UUTUTs. The recurrence rate in patients who have received adjuvant intraluminal mitomycin c after resection is between 29-54%, and the rate of nephroureterectomy is between 5-21% (27,28). In a study by Metcalfe et al. (18), 28 patients with low-grade Ta-T1 UUTUTs were given adjuvant induction and maintenance intraluminal mitomycin c after resection, and the 3-year recurrence-free, progression-free, and nephroureterectomy-free survival rates were 60%, [confidence interval (CI) (95% CI): 42, 86%], 80% (95% CI: 64,100%), and 76% (95% CI: 60, 97%), respectively (18). On the other hand, postoperative single dose intravesical chemotherapy can be applied to prevent bladder recurrence after radical nephroureterectomy. The bladder recurrence rate after radical nephroureterectomy in UUTUTs is 22-47%. In a study by Alma et al. (29), bladder tumor recurrence was observed in 22.7% (5 patients) of 22 patients who underwent radical nephroureterectomy due to UUTUT during a mean follow-up period of 32 months. In a meta-analysis, it was shown that administration of a single dose of intravesical chemotherapy (mitomycin c, epuribicin) within 2-10 days after radical nephroureterectomy statistically significantly reduced the rate of bladder recurrence within 1 year (30). In the current European Urology Guideline, post-operative single-dose intravesical chemotherapy is recommended after radical nephroureterectomy.

Conclusion

Although minimally invasive renal-sparing surgical methods have been used frequently with the development of endoscopic instruments in low-risk patients with UUTUTs, the role of adjuvant intraluminal therapies used to reduce recurrence and progression after renal-sparing surgery is still not clear according to current literature data. There are still no recommendations regarding adjuvant intraluminal therapies in the current European Urology Guidelines. Randomized clinical trials with larger populations and meta-analyses investigating the effectiveness of adjuvant intraluminal therapies in UUTUTs are needed.

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