REVIEW

Endoscopic management of upper tract urothelial carcinoma

Anthony J. Polcari, MD, Cory M. Hugen, MD, Thomas M. Turk, MD
Department of Urology, Loyola University Stritch School of Medicine, Maywood, Illinois, USA

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While radical nephroureterectomy remains the gold standard of treatment for patients with upper tract urothelial tumors, technological advances have made endoscopic management possible. The careful selection of patients for such an approach is dependent upon an accurate diagnosis and an understanding of the natural history of the disease. High grade tumors behave aggressively and warrant radical extirpation unless an absolute contraindication exists. Motivated patients with low grade tumors and relative contraindications to nephroureterectomy can be managed with percutaneous or retrograde ureteroscopic techniques. High recurrence rates in the ipsilateral upper tract and bladder mandate close surveillance of patients treated conservatively. We review the important diagnostic, staging, technical, and surveillance issues in the endoscopic treatment of upper tract urothelial carcinoma.

Key Words: endoscopic, upper tract, urothelial carcinoma, ureteroscopic, percutaneous

Introduction

Urothelial carcinoma (UC) of the upper urinary tract is relatively uncommon, accounting for 5% of all urothelial carcinomas.[1] Primary tumors of the renal pelvis occur more frequently than those of the ureter by a ratio of 1.5:1.[2] Cancers of the ureter tend to occur distally, with 70% of tumors occurring in the distal ureter, 25% in the midureter, and 5% in the proximal ureter.[3] Nephroureterectomy with excision of the ipsilateral ureteral orifice and a cuff of bladder has traditionally been considered the standard of treatment for upper tract urothelial cancer.[4] Advances in percutaneous and ureteroscopic techniques have made an endoscopic approach to the treatment of this disease possible. An accurate grade and stage assignment to the tumor, when possible, combined with an understanding of the natural history of the disease, help to determine which patients are appropriate candidates for a nephron sparing approach.

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Address correspondence to Dr. Anthony J. Polcari, Department of Urology, Loyola University Medical Center, Fahey Center, Room 200, Maywood, IL 60153 USA

Natural history

By examining retrospective reviews of multiple treatment modalities, it has become apparent that the overall prognosis of upper tract UC is principally related to the grade and stage of the tumor.[5] In an examination of 252 patients treated for upper tract UC with nephroureterectomy and nephron sparing approaches, Hall et al found that the actuarial 5 year survival was 100% for stage Ta and T1 tumors but dropped to 72% for T2 and 40% for T3 lesions.[6]

Tumor grade is also an important prognostic factor. Roupret et al found that tumor grade was an independent adverse prognostic factor among 97 patients undergoing treatment of upper tract UC with a variety of treatment methods. While the 5 year survival of patients with low grade tumors was 82%, those with high grade tumors demonstrated a considerably lower 42% survival. Among patients with low grade tumors, disease specific survival rates were independent of treatment modality.[7] Multiple other series have found survival rates of > 90% for patients with low grade tumors.[8-10]

Tumor grade correlates well with stage,[7,11] which is an important concept given that treatment decisions are often based solely upon tumor grade without a reliable

stage determination. Brown et al reviewed the records of 184 patients undergoing nephroureterectomy at the MD Anderson Cancer Center and found that patients with clinical grade 1 or 2 tumors had only a 28% chance of having pathologic ≥ T2 disease while 66% of those with clinical grade 3 tumors had ≥ T2 disease.[12] Other factors associated with a poor prognosis include multifocality[13,14] and lymphovascular invasion.[15,16]

Multiple series have noted a high incidence of recurrence in the bladder, regardless of treatment type.[5] Intravesical lesions develop in 23%-75% of patients with upper tract TCC,[17] and recurrences are more common in patients with a previous history of bladder tumors. This necessitates long term endoscopic surveillance of the bladder among patients treated for upper tract UC.

Diagnosis and staging

Computed tomography (CT) urography has become the study of choice for the evaluation and initial diagnosis of upper tract UC. Its sensitivity for detecting upper tract tumors is over 95%,[18] compared with a sensitivity of 75% for traditional intravenous urography.[13] Although CT is highly sensitive for initial diagnosis, it is of limited value in staging upper tract UC. While CT may be helpful when direct extension through the renal pelvic or ureteral wall is visible, this modality is unable to reliably differentiate Ta/T1 from T2 lesions.[19,20]

Ureteroscopy with direct tissue sampling is the technique of choice for evaluating upper tract filling defects. In addition to allowing direct visualization of the lesion, it can be combined with saline wash, brush biopsy, and direct vision biopsy with either a cold cup forceps or a wire basket.[21] While the sensitivity of voided cytology alone is only about 35%,[22] the diagnostic yield of cytologic examination can be improved to 80%-90% when samples are obtained from ureteral catheterization and brush biopsy.[23-26] Using the technique of aspiration and wash directly at the lesion before and after biopsy, Keeley et al found that a cytologic diagnosis of UC was possible in 94% of cases and that a grade could be assigned in 82%. Furthermore, the grade on cytology correlated well with the grade of the open surgical specimen in over 90% of cases.[27]

Histopathology also has a role in the diagnosis of upper tract UC. While the small forcep size used for ureteroscopic biopsy limits the ability to make a histopathological diagnosis in up to half of cases,[28,29] a multiple biopsy approach provides more tissue and may heighten the yield of this technique.[30] Unfortunately, ureteroscopic tissue biopsies are not always reliable in providing an accurate tumor stage.[31] Several series have shown that histopathology may understage the lesion in up to 54% of cases, even when lamina propria is obtained.[30,32] Thus, the importance of an accurate cytologic grade assignment cannot be overstated.[33]

Indications for endoscopic management

Radical nephroureterectomy is the gold standard of treatment for patients with a normal contralateral kidney, especially for those with high grade tumors. The frequency of multifocality, a significant recurrence rate in the ipsilateral tract following more conservative excision, and the low rates of bilaterality are the primary rationale for this treatment. Several reports with intermediate term follow up suggest that when nephroureterectomy is warranted, a laparoscopic approach yields similar cancer related outcomes to an open technique with arguably lower morbidity.[34-36]

Standard indications for endoscopic therapy include a solitary kidney, chronic renal insufficiency, bilateral upper tract tumors, and medical comorbidity precluding nephroureterectomy. Recently, several authors have advocated endoscopic therapy for patients with small, low grade tumors and normal contralateral kidneys. This is based on reports which have demonstrated comparable disease specific survival among patients undergoing open and endoscopic treatment.[9,37,38] However, a significant recurrence rate among patients treated endoscopically mandates careful preoperative counseling regarding the need for lifelong surveillance and the potential requirement of a more aggressive approach in the event of upper tract recurrence or tumor progression.

Endoscopic techniques

Ureteroscopy

Initially, ureteroscopy was introduced into the management of upper tract UC as a diagnostic modality. However, with technological advances in ureteroscopes and working elements it is now possible to definitively treat upper tract tumors with ureteroscopic techniques. One of the main advantages of ureteroscopic treatment is that the collecting system is not violated, theoretically minimizing the risk of tumor seeding outside of the urinary tract. Thus, for ureteral lesions and small (< 1.5 cm) renal pelvic or calyceal tumors that are easily accessible, the ureteroscopic approach is preferable. Other advantages include minimal morbidity and the ability to perform the procedure on an outpatient

basis.[17] Irrigant pressure should be minimized to reduce the theoretical risk of pyelovenous or pyelolymphatic backflow of malignant cells.

Several methods are available for tumor ablation. Distal tumors that are accessible with a rigid ureteroscope may be resected with a ureteral resectoscope loop. Caution must be exercised with this approach, since the submucosal and muscularis layers of the ureter are delicate and easily perforated. Another technique is mechanical debulking of the tumor with a cold cup biopsy forceps or stone basket and fulguration of the base with either a 2-3 Fr Bugbee electrocautery or laser. When possible, separate biopsies of the tumor base should be obtained to rule out invasion.

The neodymium doped yttrium aluminium garnet (Nd:YAG) and holmium yttrium aluminium garnet (Ho:YAG) are the lasers most commonly used to treat ureteral tumors. The Nd:YAG laser has a depth of penetration of 5 mm-6 mm and at a power of 20 Watts to 30 Watts is used predominantly for deep tissue ablation and coagulation.[39] The laser fiber should not be placed in direct contact with the tumor itself to avoid charring. The Ho:YAG laser has a much more shallow depth of penetration at 0.4 mm, and thus provides more superficial ablation with less risk of perforation. It can also coagulate tissue, aiding in hemostasis. Keeley et al described a technique using a combination of these lasers, whereby the Nd:YAG is used first to coagulate the tumor and then the Ho:YAG is used for ablation.[13]

Percutaneous

The percutaneous approach for upper tract tumors is best suited for patients with large (> 1.5 cm) tumors of the kidney or proximal ureter. Advantages include larger working instruments, better visibility, and the ability to leave a nephrostomy tube which facilitates both a "second look" procedure and the delivery of adjuvant therapy.[17] In addition, working maneuverability with rigid elements is often superior to retrograde ureteroscopy, especially in the lower pole calyces.[34] Disadvantages include the potential morbidity of percutaneous renal surgery as well as the theoretical risk of seeding the nephrostomy tract.

Once access to the desired calyx has been obtained, the tract is dilated and a 30 Fr sheath is placed. This allows excellent visibility with low intrarenal pressures. A number of modalities may be used to ablate the tumor. The loop resectoscope is best suited for bulky tumors, although the vascularity of the kidney and thin submucosal layers make bleeding a potential complication. The rollerball electrode may be used to fulgurate the base of resection or to vaporize flat lesions while aiding in hemostasis. The neodymium and holmium laser can also be used via a percutaneous approach. Rigid nephroscopy should be combined with flexible nephroscopy to ensure that all areas of the kidney are free of tumor. A ureteral stent or nephrostomy tube may be left in place to facilitate adjuvant therapy.

Results

Ureteroscopic

There are numerous reports on the ureteroscopic management of upper tract tumors. The results of several highlighted studies are summarized in Table 1. Tawfiek and Bagley pooled the results from several series which included 205 upper tract tumors and found local recurrence rates of 33% for renal pelvic tumors and 31% for ureteral tumors. Forty-three percent of patients ultimately developed a recurrence in the bladder.[5] It should be noted that the local recurrence rates reported in the literature vary widely, ranging from 25% to 90%.[9,13,40-42] The higher rates reported in more recent series are likely attributable to longer follow up and stricter surveillance protocols.

TABLE 1. **Ureteroscopic management – results from selected series**

Reference	No. of pts.	Mean follow up (mos)	Grade I-II (%)	Disease specific mortality (%)	Recurrence (%)	No. undergoing NU
Thompson 2008[43]	76	55	90	11	55	27
Sowter 2007[41]	37	41	90	0	74	12
Chen and Bagley 2000[38]	23	35	95	0	65	4
Keeley 1997[13]	38	35	87	0	29	8
Martinez-Pineiro 1996[42]	28	31	84	7	29	3

NU = nephroureterectomy

Martinez-Pineiro et al reviewed their experience among 54 patients with upper tract UC, 28 of which were amenable to primary ureteroscopic treatment. During a mean follow up of 30 months, 8 of these (28.5%) developed recurrences. The cause specific mortality of their group of patients treated endoscopically was 13.6%.[42] Keeley et al reviewed 41 renal units undergoing ureteroscopic treatment from 1985 to 1995. Although 28% developed recurrences, 86% were tumor free at most recent follow up and no patient had progression of disease. Recurrence in this series was associated with high tumor grade, size > 1.5 cm, and multifocality.[13]

Several series have specifically addressed the issue of ureteroscopic treatment in patients with normal contralateral kidneys. Thompson et al reviewed the Mayo Clinic experience among 83 such patients in the largest of these series. Ninety percent of patients were pathologic grade 1 or 2 or diagnosed as "visual low-grade", highlighting the careful selection of this cohort. The disease specific mortality among this mostly elderly group of patients was 15%, although one third of patients ultimately required nephroureterectomy for stage or grade progression. They noted a significant rate of progression among patients with "visual low-grade tumors", where the diagnosis was made based on appearance rather than cytology due inadequate tissue sampling.[13] Thus, the authors caution against endoscopic management in patients without a pathologic diagnosis of low grade tumor.[43]

Percutaneous

The results of percutaneous therapy for selected patients with upper tract tumors have also been promising, despite the fact that this technique is often reserved for large tumors in the renal pelvis, Table 2. Liatsikos et al reported their experience among 69 patients with a mean follow up of 49 months. The overall recurrence rate was 36%, with a recurrence rate of 56% for grade 3 tumors compared with 26% for grade 1 lesions. Disease specific survival was 100% for grade 1, 96% for grade 2, and 64% for grade 3 tumors. Four of 42 patients with grades 1-2 disease eventually underwent nephroureterectomy for disease recurrence, and 4 of 25 patients with grade 3 tumors underwent immediate nephroureterectomy due to incomplete resection or parenchyma invading disease.[37]

Palou et al reported on a series of 34 patients treated with percutaneous resection, 20% of which had grade 1, 62% had grade 2 and 15% had grade 3 tumors. After a mean follow up of 51 months ipsilateral upper tract recurrence developed in 41% of patients, over half of which were treated with nephroureterectomy. At the end of the study period only two patients (6%) died of their disease and the rate of kidney preservation was 73%.[44]

Finally, in a large series with extensive follow up of 13 years, Lee et al compared the disease specific survival rates between 60 patients undergoing nephroureterectomy and 50 undergoing percutaneous resection. Similar to the results found in other series, patients with grade 1 lesions did well regardless of the treatment type with few cancer-related deaths in either group. Among patients with grade 2 lesions, disease specific survival was not different between those treated with radical versus percutaneous procedures (53.2 months versus 53.8 months). Those with grade 3 lesions that were treated with percutaneous resection fared poorly, with a mean cancer specific survival of 28 months compared to 57 months for those treated with radical surgery.[45]

Adjuvant therapy

The significant recurrence rate observed among patients managed endoscopically has prompted the use of adjuvant therapy in this setting. The most reliable way of delivering these agents is through a nephrostomy tube, which is often left

TABLE 2. **Percutaneous management – results from selected series**

Reference	No. of pts.	Mean follow up (mos)	Grade I-II (%)	Disease specific mortality (%)	Recurrence (%)	No. undergoing NU
Roupret 2007[72]	24	62	71	20	33	5
Palou 2004[44]	34	51	82	15	41	9
Deligne 2002[73]	61	40	89	16	36	6
Liatsikos 2001[37]	69	49	63	15	36	7
Clark 1999[74]	17	20	78	35	30	0

NU = nephroureterectomy

in situ following percutaneous treatment. After ureteroscopic management, intravesical instillations can be administered with a double J stent in place, allowing reflux into the upper tract. Patel and Fuchs described cystoscopic placement of a single J stent with a proximal curl in the upper pole and a free end exiting suprapubically.[46] Other authors place a 5 Fr ureteral catheter via office cystoscopy prior to each instillation.[47]

Bacillus Calmette-Guérin (BCG) and mitomycin C are the most commonly used agents to prevent recurrence and progression of upper tract tumors. In a retrospective, nonrandomized study of 14 patients, Orihuela and Smith found that the recurrence rate among six patients treated with BCG through a nephrostomy tube following percutaneous resection was 16%, compared with 80% among the eight patients who were not treated with BCG.[48] Martinez-Pineiro also noted a decreased rate of recurrence (50% versus 27%) in patients with grade 2 or 3 disease treated with mitomycin or BCG versus those without adjuvant therapy.[42] However, other studies have failed to demonstrate a clear benefit from topical immunotherapy following endoscopic treatment in terms of recurrence and overall survival.[9,13,49]

BCG has also been used to treat carcinoma in situ (CIS) of the upper urinary tract with mixed short term results.[50-52] Okubo et al found that following BCG therapy, 7 of 14 patients with upper tract CIS were disease free at 46 months.[53] However, Hayashida et al recently demonstrated that while short term results appeared promising, after a mean of 54 months, 4 of 8 (50%) patients treated with BCG for upper tract CIS eventually recurred with a mortality rate of 100%.[54] Therefore, BCG alone should be used with caution in patients with upper tract CIS.

The available data do not allow conclusions to be drawn regarding the benefit of adjuvant therapy. The best studies to date are small, retrospective series without randomization. Despite these shortcomings, many investigators who manage upper tract tumors endoscopically elect to administer adjuvant therapy, primarily due to its tolerability and proven efficacy with urothelial tumors of the bladder.

Complications

There are several unique complications associated with endoscopic treatment of upper tract tumors. With ureteroscopic management, the most common complications noted are perforation and stricture formation. Perforation, which may occur in up to 10% of cases, can be managed conservatively with temporary placement of a ureteral stent.[55] The rate of stricture formation following ureteroscopic resection has ranged from 5%-14%, and appears to be decreasing due in part to the use of smaller scopes and newer lasers with minimal tissue penetration.[29] Daneshmand et al noted that 2 of 5 (40%) patients who developed stricture were found to have malignant disease following open surgical resection.[40] Thus, any stricture that develops following endoscopic treatment should be directly inspected and biopsied. Nephroureterectomy should be strongly considered for malignant strictures, whereas benign strictures can be managed with balloon dilation or laser incision.[56]

The most feared complication of treating tumors ureteroscopically is extravasation of malignant cells under high intrarenal pressures. This issue was initially raised in a report by Tomera et al in which local recurrence in the renal fossa was noted in 2 of 18 patients with low grade disease who had undergone intraoperative pyeloscopy during open resection.[57] Lim et al found tumor cells in the submucosal vascular and lymphatic spaces on open resection following ureteroscopic biopsy of a small grade 2 lesion, and theorized that this was a result of pyelolymphatic backflow.[58] Daneshmand et al raised a similar concern, noting that one patient with a grade 2 tumor treated endoscopically developed a distant nodal metastasis despite being free of tumor elsewhere in the urinary tract.[40] However, other series have not found evidence of tumor spread or differences in metastasis free survival among patients undergoing nephroureterectomy following ureteroscopy.[59,60]

With percutaneous resection of tumors, bleeding is a significant concern with transfusion rates approaching 20%-50%.[15] There is one report of a renal vein injury caused by resection of a fold overlying the vein.[61] Percutaneous tract seeding is a rare but feared complication. There are several isolated reports in the literature,[57,60,62-66] most of which are associated with large, invasive tumors or long term nephrostomy tubes. However, the rate of seeding in almost all large series is zero. Placing and maintaining a 30 Fr Amplatz sheath directly inside the collecting system during resection to ensure low intrarenal pressure with free flow of irrigant extracorporally minimizes this risk.[21]

Surveillance

Patient motivation and willingness to participate in a strict surveillance regimen is prerequisite to the endoscopic management of upper tract tumors. As discussed previously, most patients will develop a recurrence either in the upper tract or in the bladder,

necessitating close follow up. It has become apparent that interval ureteroscopy, rather than cytology or imaging alone, is an important component of the surveillance protocol. Keeley et al found that 75% of recurrent tumors were not identified radiographically.[13] Chen et al examined their surveillance techniques, and found that the sensitivity of bladder cytology and intraoperative retrograde pyelography to detect recurrence was 50% and 72%, respectively.[67] While no standardized surveillance protocols exist, many authors now recommend cystoscopy, cytology, and ureteroscopy every 3 months for first year and then every 6 moths thereafter.[17,37,43,68] Surveillance of the contralateral upper tract and metastatic survey with chest x-ray, laboratory studies, and abdominal imaging should be performed every 1 to 2 years depending on the grade and stage of the lesion.[11]

Several authors have described office based techniques for endoscopic upper tract evaluation.[69,70] Reisiger et al recently reported their 13 year experience with office ureteroscopy facilitated by previous unroofing of the ureteral orifice. As these authors point out, the lack of real time fluoroscopy and placement of a safety wire in an awake patient make this practice difficult for the novice ureteroscopist.[71]

Conclusion

While the gold standard for the treatment of upper tract TCC remains radical nephroureterectomy, advances in equipment and techniques have made endoscopic management a reasonable option in well selected patients. An accurate diagnosis with a specific grade assignment is critical to the stratification and counseling of patients. Since high grade tumors behave aggressively, they are best managed with radical surgery unless an absolute contraindication exists. Recent data suggests that low grade lesions amenable to complete resection can be treated endoscopically with good outcomes, even in those with a normal contralateral kidney. Significant recurrence rates in the ipsilateral upper tract and bladder mandate lifelong surveillance of patients treated endoscopically.

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