

Treatment of Upper Tract Urothelial Carcinoma: A Review of Surgical and Adjuvant Therapy

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Upper tract urothelial carcinoma is a disease entity that has not been as extensively studied and reviewed as carcinoma of the bladder. Recent advances in technology and adjuvant therapy have changed the treatment armamentarium of oncologists and urologists. A literature review was conducted that focused on newer surgical techniques, including laparoscopy and endoscopic management of upper tract disease. Adjuvant therapy including immunotherapy, chemotherapy, and radiation is also reviewed. Nephroureterectomy with removal of a bladder cuff still remains the gold standard of treatment. However, laparoscopic nephroureterectomy is quickly becoming popular, with equivalent recurrence rates. Because of the relatively recent introduction of laparoscopy into the urologic field, long-term data with respect to recurrence rates and survival rates are not yet available. Immunotherapy has also shown promise, but with higher recurrence rates than surgery. Chemotherapy and radiation also show some improvement in recurrence rates, but there have been no randomized, prospective trials. Endoscopic management is acceptable in patients with severe medical comorbidities or solitary kidneys but requires rigorous and close follow-up. Adjuvant therapy with either chemotherapy or radiation is still debated but does offer some improvement in disease-specific survival. Randomized, prospective, placebo-controlled studies are required but are difficult to perform because of the relatively low incidence and prevalence of this disease.

[Rev Urol. 2006;8(2):61-70]

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Key words: Urothelial carcinoma • Immunotherapy • Chemotherapy • Radiation

Urothelial neoplasms occur with varying frequency at different sites along the urothelial tract. Approximately 5% of all urothelial neoplasms occur in the kidneys and ureters (upper tract). The vast majority of upper tract tumors arise in the kidney, comprising 4% to 15% of all primary kidney neoplasms in the United States, whereas ureteral tumors represent only 1%.¹

Consequently, urothelial disease of the bladder has been evaluated to a greater extent than urothelial tumors elsewhere.

The gold standard of treatment for patients with upper tract urothelial neoplasms and a normal contralateral kidney is complete nephroureterectomy with removal of a cuff of urinary bladder. It is important to complete the nephroureterectomy with a cuff of urinary bladder due to the high rate of ureteral stump recurrence, which has been reported to be between 30% and 75%.²⁻¹⁰ Hall and colleagues¹¹ reported in one of the largest series in the literature on 252 patients who were treated for upper tract urothelial tumors with a median follow-up of 64 months. One hundred ninety-four (76.7%) patients underwent open radical nephroureterectomy with removal of bladder cuff, 42 (16.7%) patients underwent parenchymal-sparing surgery, 14 (5.6%) patients underwent nephrectomy alone, and 2 (0.8%) had exploration only for unresectable

resection of a bladder cuff is being challenged by minimally invasive approaches to managing upper tract transitional cell carcinoma (TCC). Laparoscopic nephroureterectomy has recently been used as an alternative to an open procedure for upper tract urothelial carcinoma.¹²⁻²² Since the first laparoscopic nephroureterectomy performed by Clayman in May 1991 at Washington University (St. Louis, MO), numerous reports have been published regarding the safety and efficacy of this procedure.¹²⁻²² This article will cover the therapeutic approaches to upper tract TCC, including laparoscopic nephroureterectomy and endoscopic approaches. Topical immunotherapy, adjuvant chemotherapy, and adjuvant radiation therapy will also be discussed.

Surgical Treatment

Laparoscopic Nephroureterectomy

Gill and colleagues recently reported their experience with 42 patients who underwent laparoscopic retroperitoneal nephroureterectomy with a

(26 mg morphine sulfate equivalent vs 228 mg), and a quicker convalescence (8 vs 14.1 weeks).

Complications occurred in 5 (12%) and 10 (29%) patients in the laparoscopic and open group, respectively. These included 1 renal vein injury, 1 patient with fluid extravasation from mobilization of the bladder cuff, and 3 patients with atelectasis in the laparoscopic group. The open group had 4 patients with atelectasis, 5 patients with postoperative ileus, and 1 patient with a pneumothorax. Two cases required open conversion because of a renal injury and an elective conversion secondary to local tumor infiltration with obliteration of tissue planes near the hilum.

Mean pathologic grade was 2.3 for both groups, with the laparoscopy group having 9, 10, and 23 patients with grades 1, 2, and 3 tumors and the open group having 6, 10, and 16 patients with grades 1, 2, and 3 tumors, respectively. Surgical margins were positive in 3 (7%) patients in the laparoscopic group and 5 (15%) patients in the open group. All 3 patients in the laparoscopic group received systemic chemotherapy postoperatively, and pulmonary metastases developed in 1 patient during follow-up. For comparable stage and grade of primary tumor, the negative surgical margin rate was similar between the 2 groups. Between the laparoscopic and open groups, there was no difference in bladder recurrence (23% vs 37%), retroperitoneal or port site/incisional recurrence (0 vs 0), or distant metastases (8.6% vs 13%). There was no difference in either cancer-specific survival (97% vs 87%) or crude survival (97% vs 94%) after adjusting for the shorter follow-up period (11 vs 34 months) between the laparoscopic and open groups, respectively, during follow-up. Mortality occurred in 2 patients (6%) in the laparoscopic group and in 6 in the open group (30%).¹³

The gold standard of open radical nephroureterectomy with resection of a bladder cuff is being challenged by minimally invasive approaches to managing upper tract transitional cell carcinoma.

disease. Overall, patients undergoing parenchymal-sparing surgery had a lower actuarial 5-year disease-free survival rate than those treated with initial aggressive surgical resection (23% vs 45%, $P = .0009$). There was no difference between these 2 groups in terms of proportion of patients with grade 1 versus grade 2 tumors. This study supported the use of aggressive open surgical resection for initial treatment of upper tract urothelial tumors, with a 5-year disease-free survival rate of 45%.

However, the gold standard of open radical nephroureterectomy with

mean follow-up of 11.1 months at the Cleveland Clinic.¹³ A combined laparoscopic and endoscopic transvesical approach was used to manage the distal ureter.²² These patients were compared with 35 patients who underwent open nephroureterectomy at their institution. Blood loss was significantly less in the laparoscopic group (242 vs 696 mL). Postoperatively, patients in the laparoscopic group had a significantly more rapid resumption of ambulation (1.4 vs 2.5 days), oral intake (1.6 vs 3.2 days), shorter hospital stay (2.3 vs 6.6 days), decreased analgesic requirements

Transperitoneal laparoscopic nephroureterectomy has had similar successes, as seen in the literature.^{23,24} Advantages to a transperitoneal approach compared with a retroperitoneal approach include a familiarity with anatomic landmarks and a larger working space. The retroperitoneal approach, however, has distinct advantages, including early control of the renal artery and vein, no manipulation of the bowel leading to less incidence of ileus and possibly a shorter hospital stay, and confinement of possible urinomas or seromas to the retroperitoneal space.^{13,25}

Advantages to a transperitoneal approach compared with a retroperitoneal approach include a familiarity with anatomic landmarks and a larger working space.

Hand-Assisted Laparoscopic Nephroureterectomy

While standard laparoscopic nephroureterectomy has been gaining popularity among urologists, hand-assisted laparoscopic nephroureterectomy has also gained acceptance.^{17,19} Kawauchi and colleagues¹⁷ described their experience with 34 consecutive patients who underwent hand-assisted laparoscopic nephroureterectomy using a Lap Disc (Hakko Shoji, Tokyo, Japan). These 34 patients were compared with their previous 34 patients who underwent open nephroureterectomy. Mean follow-up was 13.1 months in the hand-assisted group and 48.8 months in the open group.¹⁷

Patients in the hand-assisted group had a similar operative time (233 vs 236 minutes), decreased blood loss (236 vs 427 mL), decreased analgesia frequency (2.1 vs 4.1 days), faster return to ambulation (1.5 vs 2.5 days), and shorter hospital stay (13 vs 21.1 days). The lengthy hospital stay in Japan compared with American series is a social issue and not reflective of

actual patient recovery. There were 4 (12%) complications in both groups, with 1 open conversion in the hand-assisted group. The 4 complications in the hand-assisted group include 1 conversion due to bleeding from the left adrenal gland, 2 wound infections, and 1 pulmonary infarction in a patient who recovered with conservative treatment.¹⁷

Pathologic studies revealed that the hand-assisted group had 5, 20, and 9 patients with grade 1, 2, and 3 tumors, and the open group had 4, 17, and 13 patients with grade 1, 2, and 3 tumors, respectively. Recurrence rate

was 12% (4 patients) in the hand-assisted group, with a mean time to recurrence of 9.5 months. Patients in the open group had a longer mean time to recurrence at 14.4 months, with a 47% (16 patients) recurrence rate.¹⁷

Seifman and colleagues²⁶ completed a prospective study comparing 16 patients (mean follow-up, 19 months) who underwent hand-assisted laparoscopic nephroureterectomy to 11 patients (mean follow-up 16 months) who underwent the open technique. Although operative time was longer in the hand-assisted group (320 vs 199 minutes), there was a decrease in the length of hospital stay (3.9 vs 5.2 days), time to oral intake (33 vs 38 hours), analgesic requirements (20 vs 31 tablets), and return to normal activity (18 vs 38 days). Tumor recurrence appeared in 3 of 16 laparoscopic cases and in 7 of 11 open cases. However, the open series had a higher number of patients with grade 3 (6 of 11) and T3 disease (5 of 11) compared with the laparoscopic group (5 of 16 with grade 3, 3 of 16 with T3 disease).

Landman and colleagues¹⁹ compared 16 patients who underwent hand-assisted versus 11 patients who underwent a standard laparoscopic nephroureterectomy. Mean follow-up was 27.4 months in the standard group and 9.6 months in the hand-assisted group. Compared with the standard technique, patients who underwent the hand-assisted technique had a decreased operative time (4.4 vs 5.3 hours), similar blood loss (201 vs 190 mL), longer time to oral intake (20 vs 13 hours), similar analgesic use (33 vs 29.3 mg of morphine), longer hospital stay (4.5 vs 3.3 days), and longer time to complete recovery (8 vs 5.2 weeks).

Complications occurred in 5 patients in both groups, with 1 open conversion in the hand-assisted group due to failure to progress. One postoperative death occurred in the hand-assisted group secondary to a myocardial infarction and respiratory failure. Pathologic stage and grade were similar in the 2 groups, with the majority of patients having low-grade and low-stage tumors. Metastatic disease developed in 3 of the 15 hand-assisted cases and in 2 patients in the standard group.¹⁹

The previous studies support the use of both hand-assisted and pure laparoscopic techniques for nephroureterectomy. The hand-assisted technique does offer the advantage of tactile sensation and blunt manual dissection. Cancer control seems to parallel that of open techniques. However, most of the studies were recent, and long-term follow-up (>5 years) is required.

Management of Distal Ureter and Bladder Cuff

Although there is minimal controversy regarding the role of laparoscopic nephroureterectomy, the management of the distal ureter and bladder cuff with laparoscopy varies

among many surgeons. Techniques include 1) open excision, 2) transvesical laparoscopic detachment and ligation technique, 3) laparoscopic stapling of the distal ureter and bladder cuff, and 4) the “pluck” technique. These techniques were recently reviewed by Steinberg and Matin.²⁰

Open Technique

An open technique involves initial dissection of the renal unit laparoscopically. Once this is completed, the ureter is clipped but not ligated to prevent potential downstream seeding of tumor cells. The laparoscopic ports are removed and either a midline, Gibson, or Pfannenstiel incision is performed. The distal ureter is identified and dissected toward the bladder. The specimen is then removed en bloc with a rim of bladder cuff. The bladder may either be opened and the ureter dissected intravesically and extravesically, or the bladder may be spared and the full dissection performed extravesically.

Matsui and colleagues²¹ reported their results on 17 patients who underwent laparoscopic nephroureterectomy using an open technique to excise the distal ureter and bladder cuff. These patients were compared with 17 patients who underwent standard nephroureterectomy. Mean follow-up was 8.8 months in the laparoscopic group and 23.0 months in the standard group. High-risk patients with good performance status received adjuvant chemotherapy in this study. In the laparoscopic group, 1, 6, and 10 patients had grade 1, 2, and 3 disease on final pathologic examination. The standard group had 0, 6, and 11 patients with grade 1, 2, and 3 disease on final pathologic examination. Five patients were found to have T3 disease in both groups, with the rest of the patients having T2 or lower disease. Three and 4 patients received adjuvant chemotherapy in the laparoscopic

group and standard group, respectively. Recurrence occurred in fewer patients in the laparoscopic group (1 vs 6 patients), but this could be due to the shorter follow-up of the laparoscopic group. After adjusting for this difference in follow-up, there was no significant difference in the disease-free survival rate between the 2 groups.²¹

Klingler and colleagues¹⁵ also reported on 19 patients who underwent laparoscopic nephroureterectomy (mean follow-up, 22.1 months) with an open approach to excise the distal ureter and bladder cuff. These patients were compared with 15 standard cases (mean follow-up, 23.1 months). Pathologic features were 12

passed through the laparoscopic bladder ports. A grasper is used to tent the ureter anteriorly and a Collins knife is used to dissect the bladder cuff and ureter. The intramural ureter and bladder cuff are completely detached en bloc from the bladder. The dissection is continued with the Collins knife into the pelvic extraperitoneal fatty tissues.

Gill and colleagues¹³ compared 42 patients who underwent this technique with 35 patients who underwent the standard open nephroureterectomy. This study was discussed earlier in this review, and concluded that patients had comparable cancer-specific survival and tumor recurrence. The follow-up,

Potential criticisms of the transvesical laparoscopic technique are the risk of fluid extravasation and subsequent potential tumor seeding.

T1 versus 10 T1, 2 T2 versus 2 T2, and 5 T3 versus 3 T3 in the laparoscopic and standard groups, respectively. One tumor recurrence occurred in both groups associated with grade 3, T3 disease at final histologic examination. This study also concluded that the risk for tumor recurrence and cancer control rates was similar between the standard technique and the laparoscopic group with an open technique of handling the distal ureter and bladder cuff.

Transvesical Laparoscopic Technique

Gill and colleagues²² described a transvesical laparoscopic technique to excise the distal ureter and bladder cuff. This is performed by using 2 needleoscopic ports placed suprapubically into the bladder under cystoscopic guidance. The patient is repositioned into the dorsal lithotomy position before placing the bladder ports. A ureteral catheter is then placed in the ipsilateral orifice through an endoloop that is

however, was shorter for patients who underwent the transvesical laparoscopic technique.

Stifelman and colleagues²⁷ also reported using a combined transvesical laparoscopic and endourologic technique on 22 patients with an average follow-up of 13 months. Final pathologic examination revealed that 3, 10, and 9 patients had grade 1, 2, and 3 tumors. Five lesions were Ta, 8 were T1, 2 were T2, and 7 were T3 disease. All specimens had negative margins. Six patients had disease recurrence: 4 with low-grade, low-stage bladder tumors, not involving the resection site, and 2 with grade III T3 tumors who manifested later with metastatic lesions. All patients were alive at 18 months.

This technique simulates established open principles for upper tract urothelial tumors. Potential criticisms of this technique are the risk of fluid extravasation and subsequent potential tumor seeding. This is minimized,

however, by continuous suction from the transvesical ports. Furthermore, a meta-analysis of the literature reveals no reports of tumor seeding in over 50 patients to date.^{13,20,22,27,28} Contraindications for this technique include the presence of tumors in the distal and intramural ureter, presence of active bladder disease, and patients who have received prior pelvic radiation therapy.

Laparoscopic Stapling Technique

Laparoscopic stapling of the distal ureter and bladder cuff has been combined with cystoscopic unroofing.^{20,23} With this procedure, ureteral unroofing is performed initially via cystoscopy and placement of a balloon catheter in the intramural ureter. The distal ureter and bladder cuff are then stapled laparoscopically during the distal dissection using an Endo-GIA (US Surgical, Norwalk, CT) stapler.

Shalhav and colleagues²³ reported their experience using the laparoscopic stapling technique in 25 patients who underwent laparoscopic nephroureterectomy and compared them with 17 patients who underwent open radical nephroureterectomy. One patient in the laparoscopic group underwent the “pluck” technique, which will be discussed later in this review. Mean follow-up was shorter in the laparoscopic group (24 vs 43 months). Thirteen patients in both groups had grade 2 disease or greater. Distal metastases developed in 4 (31%) patients in the laparoscopic group and 3 (23%) patients in the open group. Local recurrence rate was lower in the laparoscopic group (3 vs 7 patients), but this could be attributable to shorter follow-up. All 3 patients in the laparoscopic group had tumors that recurred in the bladder, which were treated with transurethral resection. The authors argue in this series that the stapling technique minimizes the risk of tumor spillage because the

bladder cuff just caudal to the ureter is secured and occluded with 6 rows of titanium staples before it is incised.

Yoshino and colleagues²⁹ also reported their experience with 23 patients using the flexible endoscopic gastrointestinal automatic stapler (Ethicon Endosurgery, Cincinnati, OH) in their laparoscopic series. At a mean follow-up period of 15 months, 4 patients had bladder recurrence that was successfully treated by transurethral resection. Three of these patients had no evidence of disease at greater than 20 months follow-up, whereas 1 died of other medical comorbidities.

Whereas the preceding studies support the use of the stapling technique for distal ureteral and bladder cuff management, Matin and Gill²⁸ evaluated outcome and patterns of recurrence based on the form of bladder

The “Pluck” Technique

The “pluck” technique involves an aggressive transurethral resection of the ipsilateral ureteral orifice with a simultaneous “plucking” of the distal ureter during the laparoscopic procedure. This resection is performed initially via a resectoscope before dissection of the renal unit and ureter. McNeill and colleagues³² described their experience using this technique on 25 patients and compared them with 42 patients who underwent open nephroureterectomy. Follow-up was shorter in the laparoscopic group (mean 32.9 vs 42.3 months). Pathologic analysis of the specimen revealed grade 1, 2, and 3 in 4, 6, and 9 patients in the laparoscopic group and 2, 8, and 6 patients in the open group. Pathologic examination also revealed T1, T2, and T3 disease in 0,

One of the largest criticisms of the pluck technique is tumor seeding and the potential to leave behind a segment of incompletely resected ureter.

cuff control. They concluded that positive margins were higher with a laparoscopic stapling approach when compared with either the open or transvesical technique. Furthermore, the stapling technique was associated with poorer recurrence-free survival.

Another criticism of this technique could be the theoretical risk of stone formation secondary to the migration of staples into the bladder mucosa. Chandhoke and colleagues³⁰ reported neither stone formation nor visible staples in the bladder after using the stapling technique. A recent case report revealed the presence of a nearly complete intravesical titanium staple line on surveillance cystoscopy at 6 months follow-up.³¹ However, there was no identifiable encrustation in this patient, and a successful transurethral resection of the staple line was performed without sequelae.

1, and 9 patients in the laparoscopic group and 0, 3, and 6 patients in the open group. There were 13 deaths in this series: 4 in the laparoscopic group, and 9 in the open group. The authors conclude that there was no increase in local recurrence within the laparoscopic group during the follow-up, but the exact incidence of recurrence was not reported.

One of the largest criticisms of this technique is tumor seeding and the potential to leave behind a segment of incompletely resected ureter.^{20,33-35} Arango and colleagues³³ described a case of a fatal recurrence at the resection site after endoscopic resection of the intramural ureter. Histologic studies revealed a stage I grade 2 TCC with a normal lower ureter and bladder. However, 7 months later, the patient presented with pelvic pain and urgency. Computed tomography showed

a large vesical mass at the site of the resected lower ureter. The tumor was now stage IV grade 3, and the patient underwent salvage cystectomy with adjuvant chemotherapy. The patient died 3 months after cystectomy. The exact incidence of tumor seeding is unknown and difficult to assess. However, the theoretical potential combined with the above reports has led some authors to abandon this technique.³³⁻³⁵

In summary, laparoscopic nephroureterectomy with open distal ureterectomy is a safe and acceptable alternative to open nephroureterectomy. Cancer control rates seem to be similar with superior convalescence. In terms of managing the distal ureter and bladder cuff, the open technique is the most efficacious in terms of achieving negative margins and de-

comorbidities. Whereas various techniques have been described, including the use of a resectoscope, cold cup biopsy forceps, Nd:YAG laser, VaporTrode®, and roller ball electrode, the standard resection with a cutting loop and hemostasis is the most widely accepted technique.³⁶

Goel and colleagues³⁶ recently reported on 24 patients who underwent primary percutaneous resection of an upper tract urothelial lesion with a mean follow-up of 64 months. Of the 24 patients with tumor on resection (2 patients were found to have no tumor after resection), 15 had low-grade disease, 5 had high-grade disease, and 2 were found to have squamous cell carcinoma. Both patients with squamous cell carcinoma died at a mean of 27 months. Of the 5 patients with high-grade disease, 4 un-

surgery salvaged 9 of 15 (60%) renal units with low-grade lesions after a follow-up of 64 months.

Chen and Bagley³⁷ recently reviewed their experience using ureteroscopic management in 23 patients with upper tract TCC with a mean follow-up of 17 months. The patients underwent ureteroscopic evaluation for filling defects on excretory urogram or gross unilateral hematuria on office cystoscopy. Biopsy specimens of the lesion were obtained, and the lesions were then treated with laser coagulation, ablation or resection, or electrofulguration. Nine patients were treated initially for solitary upper tract tumors, whereas 12 patients were treated initially for solitary lesions in the ureter. Two patients had multifocal tumors treated at initial resection. Pathologic examination revealed that 5, 8, 9, and 1 patients had grades 1, 1-2, 2, and 2-3 tumors. There were multiple recurrences in 15 of 23 (65%) patients and no recurrences in 8 (35%). Average time to recurrence was 9.5 months. There were no metastases or mortality in this cohort, and all patients were alive at follow-up. Nephroureterectomy was performed in 4 patients (2 for recurrent grade 2 to 3 disease and 2 for multiple recurrences). Two patients received intravesical bacillus Calmette-Guérin (BCG) with a stent in place, and 3 patients who were at increased risk for recurrence received mitomycin C. Of the 23 patients, 15 (65%) are free of ipsilateral disease at a mean of 17 months. The authors concluded that ureteroscopic resection of small, low-grade upper tract TCC can be a safe alternative treatment to nephroureterectomy in patients with normal contralateral kidneys. However, patients must be compliant with lifetime follow-up.

Keeley and colleagues³⁸ also reported their experience with

A nephron-sparing approach may be used in patients with a solitary kidney, patients with bilateral disease, and patients who would not be able to tolerate a major surgical procedure secondary to other medical comorbidities.

creased risk of cancer seeding. However, because of the relatively small series in the literature (due to the low incidence and prevalence of the disease) and because most literature is fairly recent (due to recent advances), long-term follow-up and larger series are necessary to assess cancer-specific survival and recurrence rates.

Endoscopic Treatment

With newer technology and better optics, percutaneous and ureteroscopic management of upper urothelial neoplasms have also been described as a nephron-sparing approach for select patients. A nephron-sparing approach may be used in patients with a solitary kidney, patients with bilateral disease, and patients who would not be able to tolerate a major surgical procedure secondary to other medical

derwent nephroureterectomy, whereas no further surgical management was required in 1 patient who was 96 years old. Of the 15 patients with low-grade disease, 6 underwent nephroureterectomy: for a large recurrence in 1, multifocal disease in 2, lower ureteral disease in 1, severe hemorrhage in 1, and ureteropelvic junction stricture in 1. All 6 patients underwent complete excision of the nephrostomy tract, and histopathologic examination revealed no evidence of tumor seeding in the tracts. Nine of 15 patients (60%) maintained their renal units under surveillance. During surveillance, flexible ureterorenoscopy was performed 24 times in these 9 patients and found 4 small renal pelvic recurrences and 3 late TaG1 bladder tumors. In summary, percutaneous nephron-sparing

ureteroscopic management of upper tract urothelial tumors. Thirty-eight patients (41 kidneys) underwent ureteroscopic management with a combination of neodymium:YAG and holmium:YAG lasers for coagulation and ablation of tumors. Indications for ureteroscopic management included a solitary kidney (7), bilateral disease (8), palliation (2), renal insufficiency (2), high medical risk for open surgery (8), preference (4), and small, low-grade tumors (7). The authors stated that select patients with multifocal, large, or incompletely treated tumors received either mitomycin C or BCG with a ureteral stent.

Grades 1, 2, and 3 tumors were found in 21, 14, and 5 renal units. From the data available, 16 of 21 (76%) renal units with grade 1 disease were tumor free, and 4 had recurrences at a mean follow-up of 40.3 months. Of the patients with grade 2 diseases, 9 of 14 (64%) renal units were tumor free with 4 having recurrent disease at a mean follow-up of 27.6 months. Finally, 2 of 5 (40%) with grade 3 disease were tumor free at a mean follow-up of 21 months. The recurrence rate was not reported for this group. The authors concluded that ureteroscopic treatment of upper urinary tract TCC can be performed with minimal morbidity and excellent success for patients with solitary, low-grade tumors in patients requiring a nephron-sparing procedure. Close follow-up is necessary for all patients.³⁸

Endoscopic management of upper tract TCC is a technique that has been described by several other authors with similar results.³⁹⁻⁴⁶ Indications for this form of treatment include solitary kidneys, medical comorbidities preventing the patient from undergoing major open surgery, bilateral disease, and low-grade disease. Almost all authors agree that high tumor grade and stage were associ-

ated with tumor recurrence and persistence and therefore, these, as well as patients with low-grade disease, require a strict follow-up protocol including frequent cytology, cystoscopy/ureteroscopy, and upper tract imaging.

Whereas the potential risk of tract seeding has been mentioned in the literature with respect to percutaneous management of urothelial tumors, Goel and colleagues³⁶ suggested using water irrigation to decrease this risk. Furthermore, because of the limited number of patients who have undergone this form of treatment, the actual tract recurrence is difficult to quantify, but it is thought to be minimal. To our knowledge, only 1 case of tract seeding that involved a high-grade lesion with the bulk of the tumor left in situ has been reported in the literature.⁴⁷

Adjuvant Therapy

Immunotherapy

There are few reports in the literature addressing the specific role of upper tract immunotherapy and topical chemotherapy. Thalmann and colleagues⁴⁸ reported on 41 renal units

patients with CIS, 9 (41%) died of disease, 6 (27%) died of other causes, and 7 (32%) are alive at a median follow-up of 50 months. Median overall survival and time to recurrence were 44 and 25 months, respectively. Fifteen patients with papillary disease of the urinary tract in 16 renal units were treated (TaG1 in 2, TaG2 in 6, TaG3 in 2, T1G3 in 2, and Tx in 4). Overall survival was 40 months (range, 1 to 59). Thirteen (87%) patients had recurrence after a median interval of 10 months (range, 1 to 69) and progression after a median interval of 11 months (range, 5 to 27). Of the 15 patients, 4 are alive, 6 died of disease, and 5 died of other causes with tumor present in the upper urinary tract. The authors concluded that papillary and solid tumor recurrences of the upper urinary tract could not be prevented with BCG therapy. However, BCG therapy did provide cure in approximately 50% of renal units with CIS. Several other studies also support the use of BCG for upper tract CIS.⁴⁹⁻⁵⁴

Vasavada and colleagues⁵⁵ also reported on the use of BCG in the adjuvant setting for upper tract urothelial

Bacillus Calmette-Guérin (BCG) therapy provided cure in approximately 50% of renal units with CIS, and several other studies also support the use of BCG for upper tract CIS.

treated in 37 patients with BCG via percutaneous nephrostomy tube with a mean follow-up of 44 months. Twenty-five renal units were treated for carcinoma in situ (CIS), and 16 renal units received adjuvant BCG therapy for superficial tumors in 15 patients. No tumor seeding occurred along the nephrostomy tract in this study. Indications for treatment in this study included solitary renal units, renal insufficiency, bilateral disease, and inoperable disease. Of the

tumor. Eight patients received adjuvant BCG therapy after surgical resection for upper tract TCC. Grades 1, 2, and 3 disease were present in 2, 5, and 1 patients, and Ta, T1, and T2 disease occurred in 5, 2, and 1 patients in this cohort. At a mean follow-up of 23.8 months, 5 of 8 (62.5%) patients were disease free, 2 of 8 (25%) patients died of disease, and 1 of 8 (12.5%) was alive with metastatic disease and receiving systemic chemotherapy. Although the study

number was small, the authors concluded that the application of BCG after definitive resection of the primary tumor may result in a decreased incidence of local tumor recurrence.

To our knowledge, there has not been any randomized, prospective, placebo-controlled trial specifically addressing the effectiveness of topical immunotherapy or chemotherapy for adjuvant treatment of upper tract urothelial tumors.⁴⁸⁻⁵⁶ Until such studies become available, adjuvant therapy may be used in patients undergoing nephron-sparing management of upper tract TCC with their consent and the addition of a strict surveillance protocol.

Radiation and Systemic Chemotherapy

Transitional cell carcinoma of the renal pelvis and ureter is relatively

the role of adjuvant radiation treatment for upper tract urothelial malignancies. The role of adjuvant chemotherapy alone for transitional cell carcinoma also remains controversial.⁶⁷

Maulard-Durdoux and colleagues⁶⁵ reported their experience with adjuvant radiation therapy in 26 patients who underwent complete surgical resection of upper tract tumors. The disease was pathologic stage B (muscular invasion) in 11 (42%) patients and stage C (perireteral fat invasion) in 15 (58%) patients. Histopathologic examination revealed the tumor to be grade 2 in 10 (40%) patients and grade 3 in 15 (60%) patients and unknown in 1. All patients received adjuvant radiation therapy to a total dose of 45 Gy. After a mean follow-up of 45 months, 13 (50%) patients were alive, with 11 patients being

vival rate was 21% to 49%. The series of patients who had surgery only (the number of patients in these series ranged from 11 to 81) without adjuvant treatment had a crude locoregional failure rate of 45% to 65% and a 5-year survival rate of 17% to 33%. With these studies, one may conclude that with radiation, there seems to be some improvement in the failure rate and survival rate, but large studies need to be performed.

Whether adjuvant systemic chemotherapy is beneficial to patients after complete resection of locally advanced upper urothelial tumors is another area without much information in the literature because of the low prevalence and incidence of the disease. However, a recent study by Czito and colleagues⁶⁷ reported on their experience with both adjuvant radiation and concurrent chemotherapy for locally advanced disease. Thirty-one patients underwent adjuvant radiation therapy after surgery. All patients had grade 2 or higher disease and 84% were found to have a pathologic stage of T3 or higher. Nine patients received methotrexate, cisplatin, and vinblastine chemotherapy for 2 to 4 cycles. Univariate analysis revealed that patients had improved 5-year actuarial overall and disease-specific survival with the administration of concurrent chemotherapy when compared with patients receiving adjuvant radiation alone (27% vs 67%, $P = .01$; and 41% vs 76%, $P = .06$, respectively).

Conclusions

Treatment of upper tract urothelial carcinoma has developed and changed with advances in technology. Treatment has evolved from open radical nephroureterectomy to percutaneous resection to ureteroscopic treatment. Adjuvant treatments are also evolving with topical immunotherapy, radiation, and

Without adjuvant therapy, several studies have reported between 45% and 60% incidence of locoregional recurrence of transitional cell carcinoma at 5 years after definitive surgery.

rare, which leads to a paucity of studies analyzing adjuvant radiation and chemotherapy for locally advanced but completely resected upper tract urothelial tumors. Patients who harbor disease beyond the muscularis have a 5-year survival rate between 0 and 34%.⁵⁷⁻⁶⁰ Without adjuvant therapy, several studies have reported between 45% and 60% incidence of locoregional recurrence at 5 years after treatment with definitive surgery.⁶¹⁻⁶³ This high recurrence rate has been a strong argument for adjuvant therapy for all patients with locally advanced disease even after complete resection. However, the studies that currently exist are of limited numbers of patients because of the rarity of this disease. Studies have both supported^{61,62,64} and rejected^{65,66}

disease free. Disease metastasized in 14 patients to the bone, liver, and lungs. The overall 5-year survival rates and 5-year survival with no evidence of disease were 49% and 30%, respectively. The authors concluded that adjuvant radiation therapy did not improve long-term survival and is not recommended except for prospective randomized studies.

A recent review of select series of surgery with or without adjuvant radiation therapy for carcinoma of the upper urinary tract revealed some improvement in percent crude locoregional failure.^{61-63,65-67} Six series of patients who received adjuvant radiation revealed a failure rate between 9% and 38%. The number of patients ranged from 9 to 45, with 1 series having 86 patients. The 5-year sur-

chemotherapy. The optimal treatment must take into account the specifics of each individual patient with regard to renal function, medical comorbidities, location of disease, tumor stage, and tumor grade. Most series in the literature are of limited number because of the relatively low prevalence and incidence of this tumor. The standard, however, still remains surgical removal with radical nephroureterectomy and with select patients, segmental ureterectomy may be performed. Endoscopic management is also certainly reasonable in patients with low-grade and low-stage disease as long as they adhere to a strict follow-up protocol that includes frequent cytology and endoscopy. The benefits of adjuvant radiation and chemotherapy are still debated, but the literature does reveal some improvement in disease-specific survival with both forms of treatment. ■

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Main Points

- The gold standard of open radical nephroureterectomy with resection of a bladder cuff is being challenged by minimally invasive approaches to managing upper tract transitional cell carcinoma.
- While standard laparoscopic nephroureterectomy has been gaining popularity among urologists for the treatment of upper tract urothelial neoplasms, hand-assisted laparoscopic nephroureterectomy has also gained acceptance.
- Laparoscopic nephroureterectomy with open distal ureterectomy is a safe and acceptable alternative to open nephroureterectomy.
- Various nephron-sparing techniques have been described, including the use of a resectoscope, cold cup biopsy forceps, Nd:YAG laser, VaporTrode®, and roller ball electrode; however, standard resection with a cutting loop and hemostasis is the most widely accepted technique.
- The benefits of adjuvant radiation and chemotherapy are still debated, but the literature does reveal some improvement in disease-specific survival with both forms of treatment.

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