Early results of chemotherapy with retroperitoneal lymph node dissection for isolated retroperitoneal recurrence of upper urinary tract urothelial carcinoma after nephroureterectomy

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Purpose: *Retroperitoneal lymph nodes are a recognized site of relapse in patients undergoing nephroureterectomy (NU) for high grade upper tract urothelial carcinoma (UC). Retrospective studies suggest that retroperitoneal lymph node dissection (RPLND) may be curative at the time of NU for high grade upper tract UC. We hypothesized that chemotherapy followed by RPLND may successfully salvage select patients with isolated retroperitoneal relapse of upper tract UC following prior NU.*

Materials and methods: *We identified four patients with metastatic UC isolated to the subdiaphragmatic retroperitoneal lymph nodes after NU for upper tract UC. These patients had either a stable response or a complete response to chemotherapy and subsequently underwent a complete full bilateral template RPLND. Our primary study endpoints were disease-specific survival and recurrence-free survival.*

Results: *There was no perioperative mortality or long lasting surgery related sequelae in any patient. Two patients had no pathologic evidence of viable cancer at RPLND and are disease-free at 56 and 74 months from surgery. Two patients had evidence of active residual disease and subsequently developed distant disease at 2 months and 32 months after surgery. Both of these patients died of progressive disease at 3 months and 42 months following RPLND. The 5 year DSS and RFS rates were 50% and 50%.*

Conclusions: *Chemotherapy followed by RPLND for isolated retroperitoneal recurrence after NU for upper tract UC urothelial carcinoma is a feasible and safe treatment that may be potentially therapeutic in select patients.*

Key Words: urothelial carcinoma, upper tract, metastasis, survival

Introduction

Urothelial carcinoma (UC) of the upper tract accounts for approximately 5% of urothelial tumors.[1] Traditionally, the standard treatment for high grade invasive upper tract UC has been nephroureterectomy (NU) with excision of the ipsilateral ureteral orifice and bladder cuff.[2]

Long term outcomes and patterns of relapse following radical NU are strongly related to tumor grade and stage.[3] The most common sites of metastatic spread include the retroperitoneal lymph nodes, lungs, liver and bone.[4] Isolated retroperitoneal recurrence of upper tract UC following initial NU is an uncommon event representing 9% of recurrences and is traditionally managed with systemic chemotherapy.[5]

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Systemic chemotherapy alone for retroperitoneal recurrence of upper tract UC is unlikely to be curative, with median disease-specific survival (DSS) durations of only 8 to 20 months reported for metastatic UC after NU.[5,6] Retrospective studies have suggested a potential therapeutic role of retroperitoneal lymph node dissection (RPLND) at the time of NU for upper tract UC.[7-10] We have previously reported a therapeutic role for chemotherapy and RPLND for isolated retroperitoneal lymph node metastasis of UC of the bladder.[11] Furthermore, multiple retrospective reports suggest a therapeutic role for metastasectomy for isolated UC recurrence in specific subgroups of patients.[12-18] In this study, we hypothesized that aggressive chemotherapy followed by consolidative surgical resection consisting of RPLND is a feasible and potentially curative treatment option for isolated retroperitoneal recurrence after NU for upper tract UC. To our knowledge, there have been no prior studies evaluating the role of combined chemotherapy followed by RPLND for isolated retroperitoneal recurrence of upper urinary tract UC after NU. We therefore sought to review our experience using this multi-modality approach in a select group of patients with isolated retroperitoneal recurrence of upper tract UC.

Materials and methods

Study design

Prior to conducting the present study, a retrospective study protocol was approved by our Institutional Review Board. A search of the genitourinary database at The University of Texas M. D. Anderson Cancer Center from December 1996 to June 2009 was conducted to identify patients who had previously undergone a NU for UC of the upper tract and who subsequently developed isolated subdiaphragmatic retroperitoneal lymph node recurrence and who were treated with chemotherapy followed by consolidative RPLND. Clinical staging prior to RPLND consisted of cystoscopy and examination under anesthesia, a computerized tomography (CT) scan of the abdomen and pelvis, CT guided needle biopsy, chest radiography and a bone scan.[19]

Chemotherapy prior to RPLND

The regimen and number of cycles of chemotherapy given prior to RPLND was determined by the attending oncologist and was tailored for each patient according to co-morbid conditions, tolerance, response, and previous treatments. Patients received chemotherapy for two cycles beyond the best clinical response. Patients restaged after chemotherapy who demonstrated any response to or stable disease after chemotherapy and who demonstrated isolated disease in the retroperitoneum were considered for consolidative surgery with RPLND.

RPLND

Surgical consolidation of isolated retroperitoneal metastases was performed by full bilateral template RPLND. The boundaries of the surgical resection were the renal vessels superiorly, the psoas muscle (on the side of the prior nephroureterectomy), the contralateral ureter (on the side opposite to the side of the prior NU), and the bifurcation of the common iliac vessels at the inferior border. Pathologic specimens were examined to identify the presence of metastatic UC and the total number of lymph nodes.

Follow up and surveillance

Following surgery, laboratory and radiologic studies as well as cystoscopy were performed at 3 to 6 month intervals.[14] Patients were eligible for additional chemotherapy in the form of adjuvant (n = 1) or salvage chemotherapy as determined by the treating genitourinary medical oncologist. Patients were monitored for disease-recurrence and survival, with the primary study endpoints being disease-specific survival (DSS) calculated from the time of RPLND to death from metastatic UC and recurrence-free survival (RFS) calculated from the time of RPLND to date of disease recurrence.

Statistical analysis

Clinical variables including age, patient comorbidities, chemotherapy administered (regimen and number of cycles), surgical outcomes of RPLND (intraoperative blood loss, operative time, perioperative complications, length of stay), pathologic findings at RPLND, and disease status at last follow up were all noted. Kaplan-Meier DSS and RFS analyses were performed for our study population. Statistical analyses were performed using the software program S-PLUS 8 (Insightful Corporation, Seattle, WA).

Results

Patient population

A review of our genitourinary institutional database identified four patients with isolated subdiaphragmatic retroperitoneal recurrences that were subsequently treated with chemotherapy followed by full bilateral template RPLND. Three patients had biopsy proven recurrence while one refused CT guided biopsy and

was treated based on high clinical suspicion. Table 1 summarizes the clinical, pathologic and treatment outcomes. All patients were men. The median age at RPLND was 57 years (range 39 to 72 years). Only one patient had significant comorbidities which included hypertension, diabetes, chronic renal failure, and stable coronary artery disease. Prior to RPLND, the four patients were administered a median of 10 cycles (range 6 to 16 cycles) of platinum-based chemotherapy. One patient had a complete response to eight cycles of cisplatin, gemcitabine, and ifosfamide (CGI). Another patient had stable disease after three cycles of CGI, two cycles of Taxol and gemcitabine, and four cycles of doxorubicin, Taxol, and cisplatin. A third patient also had stable disease after receiving six cycles of gemcitabine and cisplatin (GC), 4 weeks of 5 fluorouracil followed by 45 Gy of external-beam radiotherapy (in 25 fractions), and six cycles of methotrexate, vinblastine, doxorubicin, and cisplatin. The last patient had a complete response to six cycles of GC. As detailed in Table 1, all patients had isolated retroperitoneal recurrence after NU at a median of 12.5 months (range 5-22 months).

Surgery related outcomes

All four patients underwent a full bilateral RPLND. The median blood loss was 2500 mL (range 1500 mL to 4250 mL). The median transfusion requirement per patient was 4 units of packed red blood cells (range 2 to 6 units). The median operative time was 481 minutes (range 289 to 612 minutes). There were no perioperative deaths. The median duration of the hospital stay was 12 days (range 8 to 16 days). All four patients experienced postoperative complications. One patient required readmission 2 days following discharge due to development of ileus and chylous

TABLE 1. **Clinical summary and outcomes of RPLND after chemotherapy for isolated retroperitoneal recurrence of UC after NU.**

Age (yrs)	Nodal relapse (Diameter in cm)	Time from NU (months)	Upper tract UC stage/ grade at NU	Fine needle aspiration	Clinical response	Lymph nodes removed/positive nodes	Recurrence location	Survival		
								RFS months	DSS months	Disease status
63	Interaortocaval (6)	15	T3/GIII	Positive	CR	17/0	None	74	74	No disease evidence
69	Interaortocava l (4.5) Retrocrural (1)	22	T2/GIII	Positive	Stable	23/0	None	56	56	No disease evidence
50	Para-aortic (5)	5	T3/GIII	Positive	Stable	6/0†	Local and lung	2	3	Died of disease
38	Retrocaval (2)	10	T1/GIII	None*	CR	28/3	Lung and distant nodes	32	42	Died of disease

*Refused by patient.
†Para-aortic area mass of metastatic urothelial carcinoma confined within fibroconnective tissue.
Lymphoid tissue free of tumor cell.
NU = Nephroureterectomy; UC = Urothelial carcinoma;
CR = Complete response; RFS = Recurrence free survival;
DSS = Disease specific survival

ascites. Two other patients experienced chylous ascites during their postoperative course. All cases of chylous ascites resolved with conservative management after a median of 26 days of total parental nutrition (range 14 to 35 days) followed by 3 weeks of elementary diet. The patient who did not experience chylous ascites experienced prolonged postoperative pelvic and lower extremity pain consistent with a neuropathic pain syndrome which completely resolved with a tapering course of gabapentin over a 3 month period. The median number of retroperitoneal lymph nodes resected at RPLND was 19 (range 6 to 28) with viable carcinoma in 3 of 28 nodes in one patient and viable carcinoma involving a fibroconnective tissue mass resected from another patient. Two patients had no viable cancer in the surgical specimens.

Treatment related outcomes

The two patients with residual active disease at RPLND ultimately had disease recurrence as shown in Table 1. The patient with three positive nodes had distant recurrence in the axillary and cervical lymph nodes at 32 months following RPLND and subsequently died of disease 42 months after surgery. This patient received both adjuvant chemotherapy after RPLND and salvage chemotherapy after metastatic recurrence. The patient with viable carcinoma in the resected retroperitoneal mass developed metastatic spread to the lungs and retroperitoneal recurrence 2 months after RPLND and died of disease progression in 1 month. He did not receive any additional chemotherapy. The remaining two patients did not receive any additional chemotherapy and are alive and disease-free with no long-lasting sequelae related to the RPLND. Overall, the 5 year DSS and RFS rates were 50% and 50%, respectively, Figure 1 and 2.

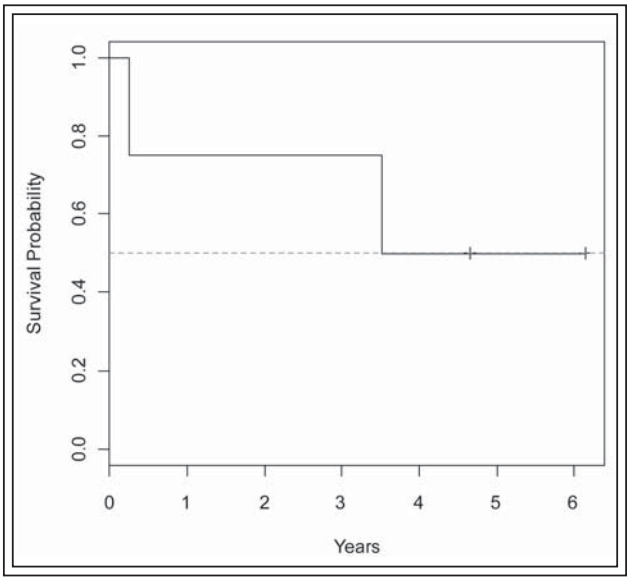

Figure 1. Survival probability (in years).

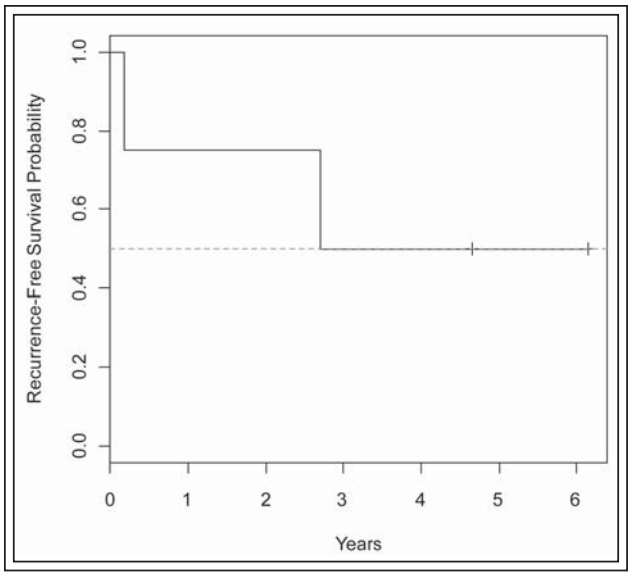

Figure 2. Recurrence-free survival probability (in years).

Discussion

Metastatic UC to the retroperitoneal lymph nodes is associated with a poor prognosis and is generally considered incurable.[5,6,9] Traditional therapy for recurrence of upper tract UC following NU has consisted of systemic chemotherapy alone which is unlikely to be curative with median DSS durations of 8 to 20 months.[5,6] It has been previously proposed that multimodality systemic chemotherapy and surgical consolidation may be therapeutic in a subset of patients with metastatic UC of the bladder isolated to retroperitoneal lymph nodes.[11]

Additional reports further suggest the therapeutic role of multimodality systemic chemotherapy and surgical consolidation in subsets of patients with metastatic UC.[12-14,16-18,20] The role of surgery in metastatic UC is further demonstrated by the therapeutic advantage of lymph node dissection at cystectomy for UC of the bladder which may be due to extirpation of micrometastatic disease of the lymph nodes.[20-24] Similarly, although more controversial, upper tract UC, retrospective studies have also suggested a therapeutic role of RPLND at the time of NU.[7-9,25-27] On the basis of these observations, we sought to evaluate the potential therapeutic benefit to treating patients with isolated retroperitoneal metastasis using chemotherapy followed by RPLND.

The rationale for post-chemotherapy RPLND in patients with retroperitoneal recurrence of UC of the upper tract is supported by our experience with a select subset of patients with metastatic bladder UC isolated to the retroperitoneal lymph nodes who benefited from post-chemotherapy RPLND[11] as well as the experience of others who demonstrated a therapeutic role for surgery combined with chemotherapy for metastatic UC. In our experience with metastatic UC to the retroperitoneal lymph nodes, we demonstrated that 10 patients were alive at 4 years after chemotherapy and RPLND.[11] Because the retroperitoneal lymph nodes are the primary nodal basin for upper tract UC, we hypothesized that RPLND would have the same therapeutic benefit in patients with isolated retroperitoneal nodal relapse in the context of upper tract UC. To our knowledge, systemic chemotherapy combined with RPLND for retroperitoneal recurrence of upper tract UC after NU has never previously been evaluated.

We recognize that our study is limited by its retrospective nature, our single center experience, and the small subset of patients who develop isolated retroperitoneal relapse after an initial NU. Our study is further limited by the fact that all patients underwent NU at different medical facilities prior to presentation to our institution. We thus cannot account for variations in the surgical techniques used, particularly the extent of lymph node dissection at NU. Furthermore, none of the patients treated at our center received the same chemotherapeutic regimen, which may have affected disease-related outcomes. Compared to contemporary RPLND series, the number of lymph nodes resected at the time of RPLND may be fewer than expected as a result of previous lymph node dissection at NU as well as the difficulty of interpreting the number of lymph nodes in desmoplastic nodal tissue following multiple regimens of chemotherapy.

Nevertheless, our report demonstrates a 5 year DSS rate of 50% and RFS rate of 50% in our cohort of patients treated with chemotherapy followed by RPLND. In a previous study, by Hall et al, no patient with retroperitoneal recurrence of upper tract UC was cured by chemotherapy alone, with all patients ultimately dying from disease at a median of 37 months (range 4 to 52 months).[5] In comparison, our experience shows two patients disease free at 56 month and 74 months thus suggesting multimodality chemotherapy and RPLND for isolated retroperitoneal recurrence after NU is therapeutic and potentially curative. Although longer follow up of our patient population is needed, we believe systemic chemotherapy followed by full bilateral template RPLND offers the maximum chance for cure for isolated retroperitoneal recurrence of upper tract UC.

Conclusions

Although RPLND after chemotherapy and prior NU is technically challenging and has significant risks to the patient, our study shows that it is feasible and potentially therapeutic to patients with isolated retroperitoneal recurrence of upper tract UC. In addition to the benefits of this multi-modality approach, patients considering this treatment approach should be counseled regarding the significant risks of perioperative complications, particularly chylous ascites. □

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