Case Report

Consolidation With Radiation or Concurrent Chemo-Radiation After Chemotherapy Results in Durable Complete Remissions of Isolated Nodal Recurrences of Urothelial Cancer: A Case Series and Review

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Clinical Practice Points

- Locoregional nodal recurrence of urothelial cell carcinoma of the bladder or upper tract can occur after definitive surgical management as the solitary site of metastasis. This may be related to the extent of the lymphadenectomy done at the time of the initial surgical extirpation of the cancer. Historically, lymph node dissection has been the mainstay of treatment for nodal recurrence of urothelial cancer when it occurs in the retroperitoneal area even in the setting of previously dissected retroperitoneal lymph nodes and typically after chemotherapy. Chemotherapy alone may be utilized, resulting in major responses, including complete responses, but these typically are not durable over time without surgical consolidation.
- The role of radiation therapy alone or concurrent with chemotherapy in the setting of nodal recurrence in urothelial cancer has not been described. We describe the new finding from our experience with this modality in 4 patients, 2 of them with upper tract disease, in whom all had durable remissions after chemotherapy followed by consolidation with radiation alone (1 patient) or concurrent chemoradiation with acceptable toxicity.
- Our conclusion was that radiation or chemoradiation as consolidative therapy should be considered in the treatment of retroperitoneal nodal recurrences of urothelial carcinoma. This finding might impact the clinical practice in isolated nodal recurrences of urothelial cancer.

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Introduction

Locoregional nodal recurrence of urothelial cell carcinoma (UCC) of the bladder or upper tract can occur after definitive surgical management of curative intent. Nodal recurrence in the retroperitoneal area is considered metastatic disease. Historically, lymph node (LN) dissection has been the mainstay of treatment for LN recurrence in UCC when it occurs in the retroperitoneal area even in the setting of previously dissected retroperitoneal LNs, typically performed after systemic chemotherapy.[1,2] Alternatively, chemotherapy alone may be utilized, resulting in major responses, including complete (CR) ones, but these typically are not durable over time without surgical consolidation.[3,4] This temporary response is presumably because chemotherapy does not eliminate all cancer stem cells despite of an apparent radiographic CR to chemotherapy. Chemotherapy may be followed by consolidative surgery, resulting in better long-term outcomes.[2,5-8]

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The role of radiation therapy alone or concurrent with chemotherapy in the setting of nodal recurrences in UCC has not been described. It is well known, however, that definitive concurrent chemoradiation can result in durable CRs of bladder cancer when given as part of a bladder sparing treatment, with acceptable toxicity. In this report, we describe our experience with definitive consolidative radiation alone, or as concurrent chemoradiation, given for nodal recurrences of urothelial carcinoma which occurred after definitive surgical treatment, in 4 patients (see Table 1). We used this modality instead of surgical consolidation.

Case Series

Case 1

A 77-year-old woman was referred for evaluation for systemic therapy for high-risk muscle invasive ureteral cancer in 2006. She was initially diagnosed in August 2005 with a large left ureteropelvic junction transitional cell carcinoma (TCC) with hydronephrosis, which was treated with a laparoscopic left nephroureterectomy in January 2006. The pathology report described high-grade muscle invasive papillary TCC. No lymphovascular invasion was noted. Final staging was therefore pT2N0M0G4R0. She had some renal insufficiency, and was treated with 4 cycles of adjuvant paclitaxel-carboplatin every 3 weeks (used area under the curve [AUC] 5 of carboplatin and 175 mg/m^2 for paclitaxel), and tolerated this well. Her computed tomography (CT) scans in July 2006 did not reveal any evidence of disease. Surveillance CT imaging in December 2006 revealed a possible recurrence at the stump of the ureter where it entered the bladder. This was excised with negative margins. Her surveillance CT scans afterwards were without evidence of disease recurrence until November 2007, when they revealed new retroperitoneal LNs, verified by positron emission tomography scan as fludeoxyglucose avid within the left iliac, left internal mammary, and left post mediastinal para-aortic LNs.

The patient had a prior history of receptor-positive breast cancer for which she had declined adjuvant therapy. Due to the left internal mammary LN, she underwent magnetic resonance imaging of her breasts, which did not show any clear masses. She underwent biopsies for both the left iliac LN and left internal mammary LN. The iliac LN was positive for metastatic TCC; the internal mammary LN, however was positive for ductal (breast) carcinoma. She received 6 cycles of palliative gemcitabine-carboplatin chemotherapy for the metastatic TCC (used 1000 mg/m^2 for gemcitabine on days 1 and 8, and AUC 5 for carboplatin on day 1 of 3 weeks cycles), and her follow-up scans revealed an excellent response in all LNs consistent with clinical complete remission from TCC, but a persistent left internal mammary focus without change. The internal mammary LN was then resected, which confirmed metastatic estrogen receptor + breast cancer. She was considered grossly without disease and began anastrazole to prevent breast cancer recurrence. She then received consolidative concurrent chemotherapy with radiation to the pelvic LNs to maximize disease-free survival (DFS) from TCC. She completed chemo-radiation (CRT), given 50 Gray

Table 1 Characteristics, Treatments, and Outcomes of the 4 Discussed Cases

	Case 1	Case 2	Case 3	Case 4
Diagnosis	Left ureter TCC	Bladder TCC	Left renal pelvic TCC	Bladder TCC
Age at diagnosis/gender	77 F	73 M	66 M	60 F
Stage at diagnosis	pT2 N0 M0 R0 G4	pT2 N0 M0 R0 G4	pT3 N0 M0 R0 G4	pT2 N0 M0 R0 G4
Prior treatment	Left nephron-ureterectomy, LND, adjuvant carboplatin and paclitaxel.	Cystoprostatectomy, LND, orthotopic neobladder.	Left nephron-ureterectomy, LND.	Cystectomy, TAH/BSO, LND, orthotopic neobladder
Time to recurrence	22 months	88 months	21 months	22 months
Site of recurrence	Left iliac LNs	Retroperitoneal LNs	Retroperitoneal LNs	Retroperitoneal LNs
Treatment of recurrence	Gem-carbo ×6 then CRT (weekly carbo)	Carbo-taxol ×4 then CRT (weekly carbo-taxol)	Gem-cis-taxol ×4 then CRT (weekly cis)	Gem-cis ×2, carbo-taxol ×2, then RT alone
Chemotherapy details	Gem-carbo ×6 (used 1000 mg/m^2 for gem day 1 and 8 and AUC 5 for carbo) then CRT (weekly carbo AUC 2)	Carbo-paclitaxel ×4 cycles (used AUC 5 of carbo and 175 mg/m^2 for paclitaxel) then CRT (weekly carboplatin AUC of 2 and paclitaxel 45 mg/m^2)	Gem-cis-taxol ×4 cycles (used 1000mg/m2 of Gem day 1 and 8, 70 mg/m^2 of Cis day 1, and 80 mg/m^2 of taxol day 1 and 8 of 3 weeks) then CRT (with weekly Cis 40 mg/m^2)	Gem-cis every 3 weeks ×2 cycles (used 1000 mg/m^2 day 1 and 8 for gem and 70 mg/m^2 day 1 for cis), carbo-taxol every 3 weeks ×2 cycles (used AUC 5 of carbo and 175 mg/m^2 for taxol), then RT alone
Radiation details	50 Gy, 25 Fx	50.4 Gy, 28 Fx	50.4 Gy, 28 Fx	60 Gy, 30 Fx
Response to chemotherapy	CR	Near CR	CR	CR
Response to CRT or RT alone	CR	CR	CR	CR
Complications	None	None	Thrombocytopenia with Cisplatin	Delayed nausea/vomiting, chemo-phobia, Zofran allergy with angioedema
Recurrence after RT or CRT	None	None	None	None
DFS from end of radiation	65 months	17 months	18 months	105 months
Condition at time of our report	Alive, NED	Alive, NED	Alive, NED	Alive, NED

Abbreviations: AUC = area under the curve; Carbo = carboplatin; Cis = cisplatin; CR = complete response; CRT = concurrent chemotherapy and radiation; DFS = disease-free survival; F = female; Fx = fractions; Gem = gemcitabine; Gy = gray; LND = lymph node dissection; LNs = lymph nodes; M = male; NED = no evidence of disease; RT = radiation therapy; TAH/BSO = total abdominal hysterectomy and bilateral salpingo-oophorectomy; taxol = paclitaxel; TCC = transitional cell carcinoma.