Multimodality Therapy Including Surgical Resection and Intraoperative Electron Radiotherapy for Recurrent or Advanced Primary Carcinoma of the Urinary Bladder or Ureter

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Objectives: To report outcomes of multimodality therapy incorporating surgical resection and intraoperative electron radiotherapy (IOERT) for patients with locoregionally (LR) recurrent or advanced primary urothelial carcinoma.

Methods: From 1983 to 2009, 17 patients, consisting of 11 with LR recurrence after cystectomy for bladder carcinoma, 4 with LR recurrence after nephroureterectomy for ureteral carcinoma, and 2 with advanced primary bladder carcinoma were treated with multimodality therapy. In 8 patients with LR recurrence, the multimodality treatment was a second salvage attempt. Sixteen patients received perioperative external beam radiotherapy (median dose, 50.4 Gy; range, 21.6 to 60 Gy). Extent of resection was R0 (n = 7), R1 (n = 1), and R2 (n = 9). The median IOERT dose was 12.5 Gy (range, 10 to 20 Gy). Overall survival (OS) and relapse patterns were determined from the date of resection and IOERT using the Kaplan-Meier method.

Results: The median follow-up for surviving patients was 3.6 years (range, 1.1 to 10 y). OS at 1, 2, and 5 years was 53%, 31%, and 16%, respectively. Central (within the IOERT field), LR (tumor bed or regional lymph nodes), and distant relapses at 2 years were 15%, 49%, and 67%, respectively. On univariate analysis, resection of all gross disease (R0-1) was associated with improved OS ($P = 0.03$). Mortality within 30 days was 0%. Two patients (12%) experienced NCI-CTCAE grades 4 and 5 late adverse events.

Conclusions: In patients with recurrent or advanced urothelial carcinoma, this multimodality approach yielded a low rate of recurrence within the IOERT field with acceptable toxicity. However, LR and distant relapse were common, indicating a need for better patient selection, LR therapy, and systemic therapy.

Key Words: bladder carcinoma, combined modality therapy, radiotherapy

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In the United States, approximately 38,000 patients were diagnosed with invasive cancer of the urinary bladder or ureter in 2010.[1] In patients with organ-confined, node-negative invasive bladder cancer, radical cystectomy results in a 10-year progression-free survival of over 75% with a low risk of locoregional (LR) recurrence.[2] However, in patients presenting with LR advanced disease (extravesicular tumor spread and/or pelvic lymph node involvement), there is substantial risk of LR recurrence or distant metastasis after radical cystectomy.[2–6]

Patients with LR tumor recurrence have median survival duration of 4 to 7 months,[3,4,6,7] and may experience significant morbidity for much of their remaining lifespan. Thus, there is a need for treatment strategies that prevent or effectively treat LR recurrence. Single modality approaches such as salvage surgery, chemotherapy, or external beam radiotherapy (EBRT) are largely unsuccessful in achieving long-term disease control.[3,4,6,7] Salvage surgery is often difficult because of tumor extension to the pelvic sidewall or adjacent organs. Similarly, salvage EBRT alone is often only palliative, because the tolerance of adjacent normal organs precludes delivery of sufficiently high radiation dose. In an effort to overcome these limitations, we treated selected patients with LR recurrent or advanced primary tumors of the bladder and ureter with a multimodality approach consisting of EBRT, maximal surgical resection, and intraoperative electron radiotherapy (IOERT) boost. With a similar strategy, we observed high rates of local control with acceptable toxicity for various malignancies including recurrent colorectal, gastric, endometrial, and renal cell carcinoma.[8–13] In the current study, we examined the efficacy and safety of this multimodality therapy for patients with LR recurrent or advanced primary tumors of the bladder or ureter.

MATERIALS AND METHODS

The prospective IOERT database was queried for patients with tumors of the urinary bladder or ureter treated with IOERT at Mayo Clinic, Rochester, MN. Seventeen consecutive patients treated between 1983 and 2009 were identified and included in this analysis. The Mayo Foundation Institutional Review Board approved this medical record study.

Patient selection for the multimodality approach was determined by the surgeon and radiation oncologist when it was estimated that surgery alone would be unlikely to remove all disease and when IOERT was anticipated to be technically feasible. All patients underwent pretreatment staging, typically consisting of physical exam; laboratory evaluation; computed tomography (CT) of the chest, abdomen, and pelvis; and abdominal/pelvic ultrasound. No patient had evidence of distant metastases at the initiation of multimodality treatment. Histologic confirmation of the primary tumor and of the recurrence was obtained before treatment in all patients.

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When EBRT had not been given previously, it was generally delivered preoperatively with megavoltage photons. A dose of 45 Gy in 25 fractions over 5 weeks was given to the tumor and regional lymphatics followed by a boost dose of 5 to 9 Gy in 3 to 5 fractions to the gross tumor. In patients who had previously received EBRT, low dose (20 to 30 Gy) perioperative EBRT was administered when assessment of the prior EBRT led to the conclusion that the risk to normal organs was acceptable. Concurrent chemotherapy was administered at the discretion of the treating physician.

Details regarding IOERT were previously described,[11] and are only summarized here. Before 1989, patients were transferred from the operating room under anesthesia to the radiation oncology department for IOERT. Since 1989, IOERT has been delivered in an operating room containing a dedicated Clinac 18 (1989 to 2002) or 2100C (2002 to present) linear accelerator (Varian, Palo Alto, CA). After maximal surgical resection, the surgeon and radiation oncologist determined the area of gross or suspected microscopic residual disease. A circular (diameter, 4 to 9 cm) or elliptical (width, 6 to 7 cm; length, 11 to 12 cm) Lucite applicator was positioned to encompass the target volume and was stabilized using a modified Buchwalter retractor system. Retractors and lead shielding were used to displace and protect critical structures adjacent to the treatment field. IOERT was delivered in a single fraction with the dose selected on the basis of the amount of residual disease (gross vs. microscopic), proximity of critical structures, and the dose of preoperative and/or anticipated postoperative EBRT. The IOERT dose (range, 10 to 20 Gy) was typically prescribed to the 90% isodose level.

Follow-up data including survival, patterns of failure, and adverse events were recorded prospectively in an institutional IOERT database. These data were verified by an additional review of the medical record conducted during this review. Endpoints were defined from the date of IOERT. Disease progression was discerned by radiographic imaging and/or clinical examination. Central failure (CF) was defined as recurrence within the IOERT field. LR failure (LRF) was defined as failure in the tumor bed or local or regional lymphatics, all of which were typically included in the perioperative EBRT field. Distant failure (DF) was defined as any recurrence beyond LRF. Adverse events were initially recorded using criteria developed by a National Cancer Institute (NCI) working group.[14] Subsequently, adverse events were reclassified using the NCI Common Toxicity Criteria version 4.[15] The time-point of 90 days after IOERT was used to distinguish between early and late events.

The Kaplan-Meier (KM) method was used to estimate survival and relapse outcomes. Candidate variables associated with overall survival (OS) were examined in a univariate analysis using the log-rank test. Variables included sex (male vs. female), age ($<$median vs. $\geq$median), primary site (ureter vs. bladder), prior EBRT (yes vs. no), prior chemotherapy (yes vs. no), prior salvage treatment (yes vs. no), tumor size (<5 cm vs. ≥ 5 cm), chemotherapy concurrent with EBRT (yes vs. no), and gross residual disease immediately before IOERT (yes vs. no). A $P<0.05$ was considered significant. Multivariate analysis was not performed because of a small number of patients. Follow-up data were collected through September 2010. Statistical analysis was performed with JMP 8.0 (SAS Institute Inc., Cary, NC).

RESULTS

Patient characteristics at the time of referral for multimodality therapy are detailed in Table 1. Before multimodality therapy, 14 of 17 patients (82%) had symptoms related to local tumor involvement, including pain (7 patients), vaginal bleeding (2 patients), hematuria (2 patients), deep venous thrombosis (2 patients), and rectal obstruction (1 patient).

Two patients had advanced primary urothelial cell carcinoma of the urinary bladder: one with unresectable T4 N1 disease on initial surgical exploration and the other with T4 (vaginal invasion) N1 disease.

Fifteen patients had recurrent tumor in the abdomen or pelvis after radical cystectomy for bladder carcinoma (11 patients) or nephroureterectomy for ureteral carcinoma (4 patients). Nine patients had received adjuvant chemotherapy with the initial surgery. The median time from initial surgery to recurrence was 2.3 years (range, 0.3 to 8.5 y). The multimodality therapeutic approach was the first salvage attempt for 7 patients and the second salvage attempt for 8 patients. In these 8 patients, the first salvage treatment was chemotherapy alone (4 patients); EBRT alone (2 patients); chemotherapy and EBRT (1 patient); and surgery, chemotherapy, and EBRT (1 patient). In total, 13 of 15 patients with recurrent disease had received chemotherapy at some point before referral for multimodality therapy. The median interval from recurrence to salvage surgery with IOERT was 0.2 years (range, 0 to 1.0 y).

Multimodality therapy characteristics are detailed in Table 2. Sixteen patients received EBRT either preoperatively or postoperatively, including 3 patients who received EBRT (range, 42.5 to 45 Gy) before referral for multimodality therapy. In these 3 patients, the dose range of EBRT given at the time of multimodality therapy was 21.6 to 25.2 Gy. The IOERT treatment site was the pelvic sidewall (11 patients), urinary bladder fossa (3 patients), para-aortic region (2 patients), or both the pelvic sidewall and para-aortic region (1 patient).

Four patients were alive at last follow-up at a median of 3.6 years (range, 1.1 to 10.0 y). For the entire cohort, the median OS was 12.5 months. In those with recurrent disease, the median OS was 12.5 months from IOERT and 14.4 months from the date of first LR. For the entire cohort, KM estimates of OS at 1, 2, and 5 years were 53%, 31%, and 16%, respectively (Fig. 1). KM estimates of disease-free survival at 1, 2, and 5 years were 24%, 18%, and 18%, respectively. In

TABLE 1. Patient Characteristics at Pretreatment Evaluation

Characteristics	N (%)
Age, years	
Median	63
Range	51-76
Sex	
Male	9 (53)
Female	8 (47)
Primary site	
Urinary bladder	13 (76)
Ureter	4 (24)
Histology	
Urothelial carcinoma	16 (94)
Squamous cell carcinoma	1 (6)
Disease status	
Primary	2 (12)
Recurrent	15 (88)
Prior external beam radiotherapy	
No	13 (76)
Yes	4 (24)
Prior chemotherapy	
No	4 (24)
Yes	13 (76)

TABLE 2. Treatment Characteristics

	N (%)
Surgery	
No residual disease (R0)	7 (41)
Microscopic residual disease (R1)	1 (6)
Gross residual disease (R2)	9 (53)
IOERT	
Dose (Gy)	
Median	12.5
Range	10-20
Energy (MeV)	
Median	9
Range	6-18
No. fields	
One	15 (88)
Two	1 (6)
Three	1 (6)
Perioperative EBRT	
Timing	
No EBRT	1 (6)
Preoperative EBRT	14 (82)
Postoperative EBRT	2 (12)
Total dose (Gy)	
Median	50.4
Range	0-60
Concurrent chemotherapy	
Yes	5 (29)
No	12 (71)

EBRT indicates external beam radiotherapy; IOERT, intraoperative electron radiotherapy.

univariate analysis, gross total resection (R0 or R1, n = 8), versus gross residual (R2, n = 9) was associated with higher OS (2-year OS 56% vs. 11%, $P = 0.03$). No other variable was identified as having association with OS.

Twelve patients (71%) experienced tumor recurrence after multimodality therapy. The median time to recurrence was 0.5 years (range, 0.3 to 1.0 y). KM estimates of CF, LRF, and DF at 2 years were 15%, 49%, and 67%, respectively. Two patients experienced CF, both of whom had gross residual disease (R2) after maximal possible surgical resection. The first site of relapse was LRF only in 4 patients, LRF and DF in 3 patients, and DF only in 5 patients. The most common site of DF was the liver. Seven patients received further systemic therapy after relapse. Five patients were free of relapse at the time of death or last follow-up. Of the 7 patients who underwent R0 resection and IORT, 3 were alive and free of disease at last follow-up. Of the 9 patients who underwent R2 resection and IORT, none were alive and free of disease at last follow-up.

No patient died within 30 days of surgery and IOERT. There were a total of 9 grade 3 adverse events potentially related to therapy (4 gastrointestinal, 3 genitourinary, 1 pulmonary, and 1 neurological). Two patients (11%) had grades 4 and 5 late adverse events. One patient experienced ureteral stricture causing a nonfunctioning kidney that required nephrectomy at 4 years after the multimodality therapy (grade 4). One patient experienced a sigmoid colon fistula, pelvic abscess, and fatal sepsis at 6 months after the multimodality therapy (grade 5). Of the 4 patients with late ureteral stricture, none were recorded as having the ureter in the IOERT field.

DISCUSSION

This series evaluated the efficacy and safety of a multimodality treatment approach incorporating perioperative EBRT, maximal surgical resection, and IOERT for recurrent or advanced primary carcinoma of the bladder and ureter. Key findings include: (1) a low rate of failure in the high-risk tumor bed targeted with IOERT, (2) encouraging survival results with a small subgroup of long-term survivors, (3) no perioperative mortality, and (4) a low risk of serious adverse events in a group of patients who received intensive surgical and radiotherapeutic interventions.

The rationale for adding IOERT is that it allows delivery of higher dose directly to the tumor while displacing normal critical structures, thus increasing the therapeutic ratio. The dose-response relationship was supported, as tumor control within the IOERT field was achieved in 85% of all patients and in all patients with resection of all gross disease (R0-1 resection). This result compares favorably with an objective clinical response rate of 46% reported with chemotherapy +/− EBRT +/− surgery.[6] Therefore, our results suggest that the combination of maximal surgical resection and a high radiation dose to the tumor bed provides a method to improve local tumor control.

Most patients in our series had isolated LR recurrence of bladder or ureter carcinoma after primary surgical resection. Most had previously received chemotherapy in the adjuvant setting or for recurrence. The median OS duration of 14.4 months from diagnosis of recurrence and 12.5 months from IOERT compares favorably with other salvage approaches reported in the literature (Table 3).[3,4,6,7] Our results are particularly noteworthy considering that this multimodality treatment was the second salvage attempt for 8 out of 15 patients in our series. To our knowledge, there has been no other published series of salvage therapy incorporating IOERT in this setting. Despite an intensive multimodality salvage approach, LR recurrence outside of the IOERT field was common, and distant metastases developed subsequently in

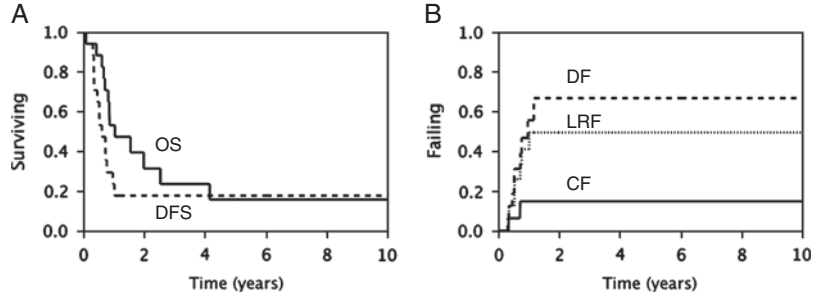

FIGURE 1. A, Overall survival (OS) and disease-free survival (DFS) estimates by the Kaplan-Meier method. B, Central (CF), locoregional (LRF), and distant failure (DF) estimates by the Kaplan-Meier method.

TABLE 3. Outcomes for Locoregionally Recurrent Bladder or Ureter Carcinoma

Series	DM at Recurrence (%)	Treatment	Median OS*(mo)
Dhar et al[4]			
n = 48	0	Chemotherapy	5.5
n = 7	0	EBRT	3.6
n = 75	0	None	4.6
Hautman and Simon[3]			
n = 22	40	Chemotherapy +/− EBRT	12
n = 22		None	3
Westney et al[6]			
n = 18	17	Chemotherapy +/− EBRT +/− surgery	8
Greven et al[7]			
n = 13	NS	NS	4
Current series			
n = 15	0	EBRT, surgery, IOERT +/− chemotherapy	14.4

*Measured from the time of diagnosis of recurrence.
DM indicates distant metastases; EBRT, external beam radiotherapy; IOERT, intraoperative electron radiotherapy; NS, not stated.

most patients (67%). The temporal nature of this pattern of relapse (Fig. 1) suggests that many patients had subclinical regional and/or distant disease at the time of IOERT. This translated into a low OS rate and demonstrated a need for more effective treatment strategies and/or improved patient selection for this approach.

Taken together, our study suggests that the following strategies need to be considered in the context of LR recurrent disease: (1) careful selection of patients to maximize the likelihood for gross total resection (R0-1), (2) enhanced preoperative imaging to exclude patients with metastatic disease, (3) prophylactic management of the regional lymphatics, (4) treatment of microscopic residual with IOERT at the time of salvage surgery, (5) the addition of concurrent chemotherapy during perioperative EBRT, and (6) consideration of adjuvant systemic therapy.

A few prior studies suggested that IOERT might have a role in the management of locally advanced bladder cancer.[16,17,] Shipley et al[16] reported local tumor control in 4 patients with locally advanced (T3 to T4) urinary bladder or ureter cancer treated with an organ preserving approach consisting of preoperative EBRT (40 to 50 Gy) to the primary tumor and regional lymph nodes followed by IOERT boost (18 to 22 Gy). Calvo et al[17] described a multimodality approach of IOERT (15 Gy) and EBRT (46 Gy) followed by cystectomy in 18 patients with locally advanced (T3 to T4) bladder cancer, and noted a high rate (61%) of pathologic complete response with acceptable toxicity. In our series, 1 of 2 patients with LR advanced primary disease is free of disease with over 10 years of follow-up. Further studies are needed to evaluate the potential role of adding IOERT for patients with LR advanced bladder or ureter cancer in a primary clinical setting.

In our study, the multimodality regimen was associated with a modest amount of grade 3 adverse events, particularly gastrointestinal or genitourinary. However, life-threatening or fatal events were uncommon. The most common adverse event was ureteral stricture, occurring in 24% of patients, despite the effort to exclude both ureters completely from the IOERT field. A similar observation was made in a larger group of patients receiving IOERT for abdominal or pelvic malignancies.[18] Animal models suggest that the probability of ureteral injury is low after conventionally fractionated EBRT to 50 Gy followed by single-fraction IOERT up to 17.5 Gy.[19] The etiology of ureteral stricture in our series may be multifactorial, including desmoplastic reaction to tumor and/or previous surgical manipulation. The incidence of late grade ≥ 3 events (9 of 17 patients) in our series argues for early referral of patients for IOERT, so a coordinated effort utilizes the minimal number and types of treatment. That is, that multiple surgeries, the use of palliative EBRT, and the effect of tumor progression during palliative chemotherapy is reduced. Nonetheless, this multimodality approach represents in our estimation a balance between the poor prognosis of LR advanced or recurrent disease and the therapeutic ratio described in this report.

There are several limitations to our series. First, the inclusion criteria and endpoints for this analysis were retrospectively defined, although relapse, survival, and adverse events were defined and collected prospectively. Therefore, results should be interpreted with caution due to the risk of unrecognized biases and/or confounding factors. Second, the number of patients is small. As a result, drawing any concrete conclusion or analyzing other relevant endpoints such as prognostic factors is not feasible. Third, the cohort of our patients was compiled over a long span of time between 1983 and 2009. Over this period, there has been a significant advance in diagnostic and therapeutic modalities. Thus, our study findings may have a significant limitation in its relevance to current practices. Nonetheless, patients with pelvic recurrence of bladder or ureter carcinoma after primary surgery presently have an extremely poor prognosis and very limited salvage treatment options. Thus, our study should yet provide an insight for a possible novel salvage therapeutic approach incorporating IOERT.

Diagnostic tools and therapeutic modalities have significantly improved in recent years. Modern imaging modalities, including high-resolution CT, magnetic resonance imaging, and positron emission tomography,[20] may allow better selection of patients for this multimodality approach by excluding those with distant metastatic or grossly unresectable LR disease. EBRT techniques have also significantly improved with the advent of image guidance, intensity modulation, and stereotactic approaches, which allow more precise dose delivery to the target while minimizing the risk of radiation injury to the normal tissue. Nonetheless, surgical resection with IOERT provides the advantages of tumor debulking, direct visualization of the tumor bed, and physical displacement of critical structures out of the treatment field. Currently, the management approach for patients with isolated LR recurrence of bladder or ureter cancer at our institution includes multidisciplinary evaluation, evaluation with CT, magnetic resonance imaging, and positron emission

tomography/CT staging, and a salvage treatment consisting of preoperative EBRT with concurrent chemotherapy, maximal surgical resection, and IOERT. Further studies are needed to refine this approach with respect to optimal patient selection, timing of therapies, and incorporation of novel systemic agents.

REFERENCES

1. Jemal A, Siegel R, Xu J, et al. Cancer statistics, 2010. *CA Cancer J Clin*. 2010;60:277–300.
2. Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol*. 2001;19:666–675.
3. Hautmann RE, Simon J. Ileal neobladder and local recurrence of bladder cancer: patterns of failure and impact on function in men. *J Urol*. 1999;162:1963–1966.
4. Dhar NB, Jones JS, Reuther AM, et al. Presentation, location and overall survival of pelvic recurrence after radical cystectomy for transitional cell carcinoma of the bladder. *BJU Int*. 2008;101:969–972.
5. Honma I, Masumori N, Sato E, et al. Local recurrence after radical cystectomy for invasive bladder cancer: an analysis of predictive factors. *Urology*. 2004;64:744–748.
6. Westney OL, Pisters LL, Pettaway CA, et al. Presentation, methods of diagnosis and therapy for pelvic recurrence following radical cystectomy for transitional cell carcinoma of the bladder. *J Urol*. 1998;159:792–795.
7. Greven KM, Spera JA, Solin LJ, et al. Local recurrence after cystectomy alone for bladder carcinoma. *Cancer*. 1992;69:2767–2770.
8. Miller RC, Haddock MG, Gunderson LL, et al. Intraoperative radiotherapy for treatment of locally advanced and recurrent esophageal and gastric adenocarcinomas. *Dis Esophagus*. 2006;19:487–495.
9. Dowdy SC, Mariani A, Cliby WA, et al. Radical pelvic resection and intraoperative radiation therapy for recurrent endometrial cancer: technique and analysis of outcomes. *Gynecol Oncol*. 2006; 101:280–286.
10. Frydenberg M, Gunderson L, Hahn G, et al. Preoperative external beam radiotherapy followed by cytoreductive surgery and intraoperative radiotherapy for locally advanced primary or recurrent renal malignancies. *J Urol*. 1994;152:15–21.
11. Gunderson LL, Nelson H, Martenson JA, et al. Intraoperative electron and external beam irradiation with or without 5-fluorouracil and maximum surgical resection for previously unirradiated, locally recurrent colorectal cancer. *Dis Colon Rectum*. 1996;39:1379–1395.
12. Haddock MG, Miller RC, Nelson H, et al. Combined modality therapy including intraoperative electron irradiation for locally recurrent colorectal cancer. *Int J Radiat Oncol Biol Phys*. 2010;79:143–150.
13. Petersen IA, Haddock MG, Donohue JH, et al. Use of intraoperative electron beam radiotherapy in the management of retroperitoneal soft tissue sarcomas. *Int J Radiat Oncol Biol Phys*. 2002;52:469–475.
14. Tepper JE, Gunderson LL, Orlow E, et al. Complications of intraoperative radiation therapy. *Int J Radiat Oncol Biol Phys*. 1984;10:1831–1839.
15. National Cancer Institute. Common Toxicity Criteria. Version 4.02. Rockville, MD: National Cancer Institute; 2011.
16. Shipley WU, Kaufman SD, Prout GR Jr. Intraoperative radiation therapy in patients with bladder cancer. A review of techniques allowing improved tumor doses and providing high cure rates without loss of bladder function. *Cancer*. 1987;60:1485–1488.
17. Calvo FA, Henriquez I, Santos M, et al. Intraoperative and external beam radiotherapy in invasive bladder cancer: pathological findings following cystectomy. *Am J Clin Oncol*. 1990; 13:101–106.
18. Miller RC, Haddock MG, Petersen IA, et al. Intraoperative electron-beam radiotherapy and ureteral obstruction. *Int J Radiat Oncol Biol Phys*. 2006;64:792–798.
19. Gillette SL, Gillette EL, Powers BE, et al. Ureteral injury following experimental intraoperative radiation. *Int J Radiat Oncol Biol Phys*. 1989;17:791–798.
20. Apolo AB, Riches J, Schoder H, et al. Clinical value of fluorine-18 2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography in bladder cancer. *J Clin Oncol*. 2010;28: 3973–3978.