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CLINICAL INVESTIGATION

LONG-TERM OUTCOMES AFTER MAXIMAL SURGICAL RESECTION AND INTRAOPERATIVE ELECTRON RADIOTHERAPY FOR LOCOREGIONALLY RECURRENT OR LOCOREGIONALLY ADVANCED PRIMARY RENAL CELL CARCINOMA

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Purpose: To report outcomes of a multimodality therapy combining maximal surgical resection and intraoperative electron radiotherapy (IOERT) for patients with locoregionally (LR) recurrent renal cell carcinoma (RCC) after radical nephrectomy or LR advanced primary RCC.
Methods and Materials: From 1989 through 2005, a total of 22 patients with LR recurrent (*n* = 19) or LR advanced primary (*n* = 3) RCC were treated with this multimodality approach. The median patient age was 63 years (range 46-78). Twenty-one patients (95%) received perioperative external beam radiotherapy (EBRT) with a median dose of 4,500 cGy (range, 4,140–5,500). Surgical resection was R0 (negative margins) in 5 patients (23%) and R1 (residual microscopic disease) in 17 patients (77%). The median IOERT dose delivered was 1,250 cGy (range, 1,000–2,000). Overall survival (OS) and disease-free survival (DFS) and relapse patterns were estimated using the Kaplan–Meier method.
Results: The median follow-up for surviving patients was 9.9 years (range, 3.6–20 years). The OS and DFS at 1, 5, and 10 years were 91%, 40%, and 35% and 64%, 31%, and 31%, respectively. Central recurrence (within the IOERT field), LR relapse (tumor bed or regional lymph nodes), and distant metastases at 5 years were 9%, 27%, and 64%, respectively. Mortality within 30 days of surgery and IOERT was 0%. Five patients (23%) experienced acute or late National Cancer Institute Common Toxicity Criteria (NCI-CTCAE) Version 4 Grade 3 to 5 toxicities.
Conclusions: In patients with LR recurrent or LR advanced primary RCC, a multimodality approach of perioperative EBRT, maximal surgical resection, and IOERT yielded encouraging results. This regimen warrants further investigation. © 2011 Elsevier Inc.

Intraoperative radiotherapy, Renal cell carcinoma, Nephrectomy, Combined modality therapy.

INTRODUCTION

In the United States, approximately 58,240 patients were diagnosed with cancer of the kidney or renal pelvis in 2010 (1). The majority of patients with this disease present with clinically localized renal cell carcinoma (RCC) and are candidates for potentially curative nephrectomy. However, some patients present with locoregionally advanced disease of borderline resectability. In addition, 1% to 3% of patients experience isolated locoregional (LR) recurrence in the retroperitoneal soft tissue and/or nodal basins after nephrectomy (2–5). The optimal management of isolated LR recurrent disease remains unknown, given its relative infrequency. In carefully selected patients with resectable LR recurrent disease, salvage surgery is associated with long-term survival in only a small portion of patients (2–9). In the setting of salvage or primary surgery, margin status was reported to be an important prognostic factor for survival (4, 10). However, a wide resection of tumor is often unachievable due to its close proximity or frank invasion into adjacent unresectable structures such as major vessels and/or vertebral bodies. Therefore, in patients with LR recurrence or LR advanced primary RCC of borderline resectability, it is appropriate to consider additional LR therapies adjunct to surgery to optimize LR control and survival.

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Since 1989, we have treated selected patients with isolated LR recurrence after nephrectomy or LR advanced primary RCC with a multimodality approach consisting of perioperative external beam radiotherapy (EBRT), maximal resection, and intraoperative electron radiotherapy (IOERT). In 1994, we reported favorable early outcomes in an initial cohort of patients (11). In addition, we have reported high rates of local control and acceptable toxicity with this multimodality approach for patients with other LR advanced primary or LR recurrent abdominal and pelvic tumors (12–17). Here we report long-term outcomes on an expanded series of patients with LR recurrence or LR advanced primary RCC treated with a multimodality approach incorporating IOERT.

METHODS AND MATERIALS

The prospective departmental IORT database was searched for patients with RCC treated with IOERT at Mayo Clinic, Rochester, MN. Inclusion criteria included primary or recurrent RCC treated with surgery and IOERT to LR disease as a component of potentially curative therapy. Exclusion criteria included surgery and IOERT to a distant metastatic site for palliation of symptoms only. Twenty-two consecutive patients treated between 1989 and 2005 met the above criteria and were included in this analysis. The Mayo Foundation Institutional Review Board approved this retrospective study.

Patients were selected for the multimodality approach by the surgeon and radiation oncologist because of concern that surgery alone would be unlikely to remove all gross and/or microscopic LR disease. All patients underwent pretreatment staging, typically consisting of the following: physical examination; laboratory evaluation; computed tomography (CT) of the chest, abdomen, and pelvis; bone scan; abdominal ultrasound; and/or brain imaging at the discretion of the attending physicians. In patients with recurrent disease, histologic confirmation of recurrence was obtained before treatment. Patients with resectable distant oligometastatic disease were considered candidates for the multimodality therapy.

Patients with no prior radiotherapy were treated with perioperative EBRT (either preoperatively, postoperatively, or a combination of both) to the tumor bed and regional lymphatics using megavoltage photons. Institutional preference was to deliver EBRT preoperatively (45 Gy in 25 fractions over 5 weeks to extended fields,. followed by a smaller boost field receiving 5 to 9 Gy in three to five fractions). One patient with LR recurrence had a history of prior EBRT was not given perioperative EBRT. No patients received concurrent systemic therapy.

Details regarding IOERT delivery at Mayo Clinic have been previously described and are briefly summarized here (12). After maximal surgical resection of disease, the primary surgeon and radiation oncologist determined the area of suspected microscopic residual disease. A circular (diameter, 6–9.5 cm) or elliptical (width, 6–9 cm; length, 11–15 cm) Lucite applicator encompassing the area of disease was immobilized using a Buchwalter retractor system. Retractors and lead shielding were used as needed to displace and protect critical structures adjacent to the treatment field. The applicator was then docked to the linear accelerator. 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 a dedicated operating room containing a refurbished Clinic 18 linear accelerator (Varian, Palo Alto, CA). IOERT was delivered in a single fraction, with the dose selected on the basis of amount of residual disease, proximity of critical structures, and the dose of preoperative and/or anticipated postoperative EBRT.

Table 1. Patient characteristics at pretreatment evaluation

Characteristic	*n* (%)
Age, y	
Median	63
Range	43–78
Sex	
Male	17 (77)
Female	5 (23)
Disease status	
Primary	3 (14)
Recurrent	19 (86)
Grade	
2	9 (41)
3	10 (45)
4	3 (14)
Maximum locoregional tumor dimension, cm	
Median	7
Range	0–20*
Additional known site of oligometastatic disease	
No	19 (86)
Lung	2 (9)
Liver	1 (5)
Prior external beam radiotherapy	
No	21 (95)
Yes	1 (5)

* One patient with microscopic residual disease after resection at an outside institution (0 cm).

Follow-up data including survival, patterns of failure, and toxicity were recorded prospectively in an institutional IOERT database. These data were verified by retrospective chart review. Endpoints were defined from the date of surgery and 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, local lymphatics, or regional lymphatics, all of which were typically included in the perioperative EBRT field. Distant failure (DF) was defined as any relapse beyond LRF. Toxicities were initially recorded using criteria developed by the National Cancer Institute (NCI) IORT working group (18). Subsequently, toxicities were reclassified using the NCI Common Toxicity Criteria Version 4 (19). The time point of 90 days after surgery and IOERT was used to distinguish between acute and late toxicity.

The Kaplan–Meier (KM) method was used to analyze survival and relapse outcomes (20). Potential factors associated with LRF and overall survival (OS) were examined in a univariate analysis using the log-rank test. Variables examined included gender (male vs. female), age (< median vs. ≥ median), histologic grade (2 vs. 3 or 4), time to recurrence after nephrectomy (< median vs. ≥ median), advanced primary vs. recurrence, size (< 5 cm vs. ≥ 5 cm), resected oligometastatic disease (yes vs. no), margin status (negative [R0] vs. microscopic positive [R1]), and IOERT dose (< median vs. ≥ median). A p value < 0.05 was considered significant. Follow-up data were collected through March 2010. Statistical analysis was performed with JMP 8.0 (SAS Institute Inc., Cary, NC)

RESULTS

Patient characteristics are detailed in Table 1. Three patients had LR advanced primary disease with extensive

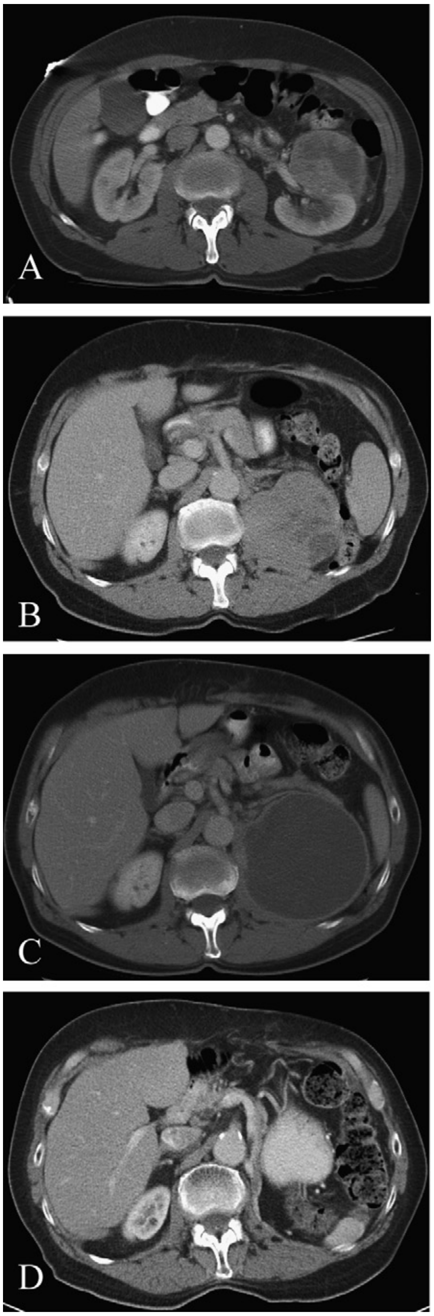

Fig. 1. Serial computed tomography (CT) scans in a 70-year-old man with renal cell carcinoma (RCC). (A) In August 2000, he underwent nephrectomy for a 10-cm Grade 4 RCC of the left kidney. (B) In April 2002, he developed an 8-cm recurrence in the left prevertebral region. After biopsy confirmation, he received preoperative external beam radiotherapy (45 Gy in 25 fractions). (C) In July 2002, repeat CT scan 4 weeks after completion of radiotherapy revealed extensive treatment effect. At the time of resection, the medial margin was initially positive on intraoperative frozen section examination; however, after re-excision, all final margins were negative. Intraoperative radiotherapy (10 Gy) was delivered to the medial margin against the vertebral body, aorta, and inferior venal cava. (D) As of February 2010, he has remained free of disease.

retroperitoneal nodal involvement, pancreas involvement, or nephrectomy with positive margins at an outside institution. Nineteen patients had an LR recurrence in the retroperitoneal soft tissue and/or lymph nodes at a median interval of 2.0 years (range, 0.7–13.7 years) after nephrectomy (Fig. 1). Eighteen patients were treated for first recurrence and 1 patient was treated for a second recurrence (after previous resection for first recurrence). Two patients had received immunotherapy at an outside institution before referral for potential resection with IOERT.

Treatment characteristics are detailed in Table 2. There were 3 patients with known sites of oligometastatic disease at the initiation of multimodality therapy; 2 patients had lung metastases removed with wedge resection before surgery and IOERT, and 1 patient had liver metastases resected at the time of surgery and IOERT. One additional patient was found to have omental metastases at the time of surgery and IOERT, which were resected. Of these 4 patients with resected oligometastatic disease, 1 patient who had a lung metastasis removed before surgery and IOERT is alive without recurrent disease at 14.4 years of follow-up, whereas the other 3 patients experienced DF and died of disease.

Six patients were alive at a median of 9.9 years (range, 3.6–20 years) at last follow-up. KM estimates of OS at 1, 5, and 10 years were 91%, 40%, and 35%, respectively. KM estimates of disease-free survival at 1, 5, and 10 years were 64%, 31%, and 31%, respectively (Fig. 2).

Thirteen patients (59%) experienced disease relapse after multimodality therapy. KM estimates of CF, LRF, and DF at 5 years were 9%, 27%, and 64%, respectively (Fig. 3). The median time to relapse was 0.8 years (range, 0.2–4.0). The first site of relapse was LRF only in 1 patient, LRF and DF in 2, and DF only in 10. The most common sites of DF were lung and liver. The total number of patients experiencing CF and LRF at any point, including at the time of or subsequent to DF, was 2 and 5, respectively. Six patients received systemic therapy (immunotherapy) after relapse. No patient received tyrosine kinase inhibitor (TKI) therapy as part of multimodality therapy or after relapse.

In univariate analysis, R0 resection (vs. R1 resection) was associated with a trend toward improved survival. KM estimates of OS at 5 years were 80% vs. 29%, respectively ($p = 0.057$). None of the examined variables were significantly associated with LRF.

Mortality within 30 days of surgery and IOERT was 0%. Five patients (23%) experienced acute or late Grade 3 or greater toxicity potentially related to the multimodality therapy. Acute toxicities included postoperative adult respiratory distress syndrome requiring mechanical ventilation (Grade 4), pancreatic pseudocyst (Grade 3), and perforated duodenal ulcer (Grade 3). There were two fatal late toxicities (pyloric ulcer hemorrhage and duodenal ulcer perforation) possibly related to the therapy.

DISCUSSION

The optimal management of LR recurrent or LR advanced primary RCC is unknown. In selected patients with LR recurrence, salvage surgery has been performed (2–7). However, in many patients, a wide margin resection is difficult to achieve because tumor is intimately associated with critical,

Table 2. Treatment characteristics of study patients

Perioperative EBRT (n = 21)	
Total dose, cGy	
Median	4,500
Range	4,140–5,500
Timing	
Preoperative only	17 (81)
Postoperative only	2 (10)
Preoperative and postoperative	2 (10)
Surgery	
No residual disease (R0), n (%)	5 (23)
Microscopic residual disease (R1), n (%)	17 (77)
IOERT	
Dose, cGy	
Median	1,250
Range	1,000–2,000
Energy, MeV	
Median	9
Range	6–12
No. of fields, n (%)	
One	19 (86)
Two	3 (14)

Abbreviations: cGy = centigray; EBRT = external beam radiotherapy; IOERT = intraoperative electron radiotherapy; MeV = megaelectron volts.

unresectable structures. Therefore, despite resection of all gross disease, patients are at high risk for further relapse and death (2–7). In an effort to optimize LR control for patients with LR recurrent or LR advanced primary RCC, a few institutions have adopted a strategy of combining maximal surgical resection with IOERT, which specifically targets areas at highest risk for residual microscopic disease (7, 21, 22). Combining EBRT and IOERT allows dose escalation above that capable with EBRT alone, which is limited by the tolerance of surrounding structures.

For patients with recurrent or advanced primary RCC, other groups have demonstrated high rates of local control with combined modality therapy consisting of surgical resection and IOERT with or without perioperative EBRT (Table 3) (7, 21, 22). However, these series included small numbers of patients with relatively short follow-up. Investigators from the University of Pamplona published early outcomes on a cohort of 11 patients with advanced primary or recurrent RCC treated with surgical resection with IOERT (22). Seven patients received perioperative EBRT (dose range, 30–45 Gy). With short follow-up, there was no toxicity attributable to IOERT, and only 1 patient experienced local tumor recurrence. At the University of Heidelberg, 12 patients with advanced primary or recurrent RCC were treated with resection, IOERT (mean, 16.2 Gy), and postoperative EBRT (mean, 40 Gy in 20 fractions)(21). Ten patients had microscopic or gross residual disease at the time of IOERT. No patient experienced local recurrence. At the University of California–San Francisco, 10 patients with locally recurrent RCC underwent resection and IOERT (mean 15 Gy) without perioperative EBRT (7). Two patients experienced local recurrence. In the present study, with mature follow-up, the multimodality approach (combining perioperative EBRT, maximal surgical resection, and IOERT) was associated with durable LR control, with only 2 patients experiencing failure within the IOERT field. Therefore, our data further support the role of this combined modality therapy for patients with LR recurrent or advanced primary RCC.

In patients with an isolated LR of RCC after nephrectomy, there are limited data reporting local control rates after salvage surgery alone. In a series of 54 patients undergoing resection of isolated LR recurrence of RCC after nephrectomy (median follow-up, 3.4 years), isolated second recurrence in the postoperative bed occurred in 14.8%, with half of these patients requiring further radical resections (4). Another 50% of patients developed DF alone or with a component of local failure; however, the incidence of local failure in this group was not specified. In a series of 16 patients with LR recurrence of RCC after nephrectomy who underwent resection (median follow-up, 1.3 years), local recurrence occurred in 6 (38%) (2). In our study, patients were referred for IOERT along with surgical resection because of borderline resectability; therefore, patients in our series likely had more adverse disease characteristics than those in the above-mentioned series. In spite of this, long-term LR control in our series appears to be at least as good as that reported in other large series examining salvage surgery alone that had relatively short follow-up.

Despite aggressive LR therapy, DF occurred in many patients in our series. In other retrospective series of patients with LR recurrence of RCC after nephrectomy, rates of

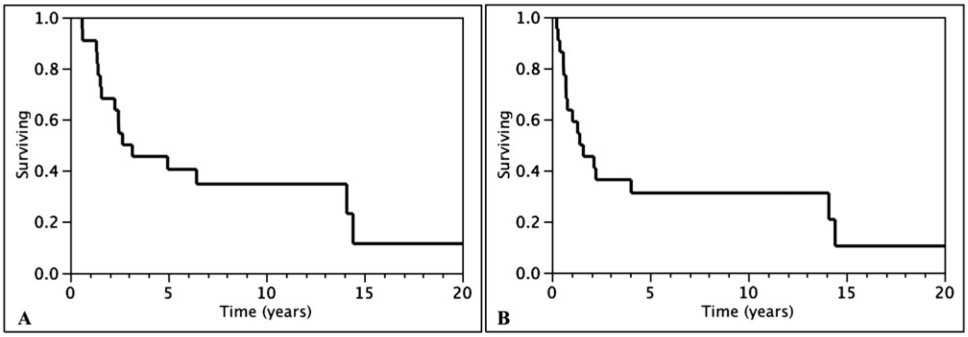

Fig. 2. Kaplan–Meier estimates of overall survival (A) and disease-free survival (B) measured from the time of surgery and intraoperative electron radiotherapy for all patients (n = 22).

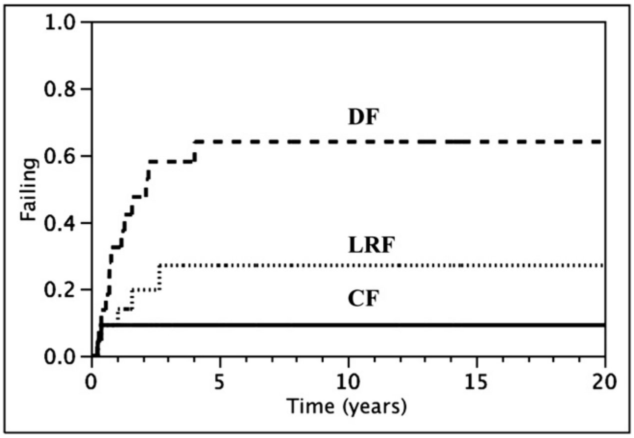

Fig. 3. Kaplan–Meier estimates of central failure (CF), locoregional failure (LRF), and distant failure (DF) measured from the time of surgery and intraoperative electron radiotherapy for all patients (n = 22).

DF were similarly high, ranging from 50% to 62% (4, 5). In these series, there was no apparent benefit from perioperative systemic therapy; however, these series largely predated the discovery of novel TKIs (4, 5). In the setting of metastatic RCC, TKIs have demonstrated high response rates with relatively low toxicity (23–26). Thus, studies are needed to investigate the safety, efficacy, and optimal timing of adding systemic therapies to radiotherapy and surgery for patients with LR recurrence of RCC.

In our series, the rate of Grade 3 to 5 toxicity was significant (23%), although consistent with other studies evaluating salvage surgery alone for LR recurrence of RCC. In the Esrig *et al.* series of 13 patients undergoing radical resection for recurrent RCC, 4 patients (31%) experienced fatal toxicity within 6 months of surgery, and 2 patients developed significant late complications (8). Tanguay *et al.* observed significant complications in 5 of 15 patients with recurrent RCC undergoing resection (9). In a series of 54 patients with recurrent RCC treated with resection, Margulis *et al.* reported a 30-day mortality of 3.7% and Grade III/IV morbidity in 14.8% (4). Our study had comparable toxicity, suggesting that the addition of perioperative EBRT and IOERT to salvage surgery did not appear to significantly add morbidity in patients with LR recurrent or LR advanced primary RCC. Nonetheless, the rate of toxicity observed with this aggressive approach is not trivial, highlighting the need for appropriate patient selection and treatment by an experienced multidisciplinary team.

There are limitations to our series. First, the inclusion/exclusion criteria and endpoints for this analysis were retrospectively defined, although outcomes data were defined and collected prospectively in the IORT database with regard to relapse, survival, and toxicity. Accordingly, our results should be interpreted with caution because of the risk of unrecognized biases and/or confounding factors. Second, the number of patients examined is relatively small, preventing a thorough analysis of prognostic factors. Third, all patients received both surgical resection and IOERT, thus preventing a direct analysis of the potential incremental benefit of IOERT and perioperative EBRT over surgery alone. Fourth, all patients received an IOERT boost; thus it is unclear as to whether adjunctive EBRT without IOERT would be associated with a similar high rate of local control but potentially less toxicity. Fifth, a limited number of radiotherapy departments are able to perform IOERT, thus restricting the applicability of our findings in general practice and limiting the ability to further investigate this modality.

Newer therapeutic modalities may offer additional treatment options for patients with LR recurrent or LR advanced primary RCC. Radiofrequency ablation and stereotactic body radiotherapy have been used to treat a small, unresectable LR recurrence of RCC (27–29). Several new systemic agents have been associated with improved OS or DFS for metastatic RCC (23–26). As survival is suboptimal for patients with LR recurrent and LR advanced primary RCC, further studies are needed to identify optimal combinations of LR and systemic treatments to improve outcomes.

CONCLUSION

To our knowledge, our study represents the largest series examining a potential utility of the multimodality therapy consisting of perioperative EBRT, maximal surgical resection, and IOERT for patients with LR recurrent or LR advanced primary RCC. With mature follow-up, this treatment approach was associated with a low rate of LR recurrence, acceptable toxicity, and long-term survival in a significant number of patients. This regimen warrants further investigation to better define appropriate patients, the optimal sequence of therapies, and the potential role of systemic therapy.

Table 3. Outcomes after surgery and intraoperative radiotherapy for primary or recurrent renal cell carcinoma

Study authors[Ref]	Primary/ Recurrent	Median follow-up (y)	Mean IORT dose (Gy)	Mean EBRT dose (Gy)	3–Year OS (%)	Local control
Santos *et al.* (22) (n = 11)	8/3	0.7	15	NS*	NS	10/11
Master *et al.* (7) (n = 10)	0/10	5.9	15	None	~33	8/10
Eble *et al.* (21) (n = 12)	3/9	3.3	16.2	40	47	12/12
Current series (n = 22)	3/19	9.9	13.5	48	50	17/22†

Abbreviations: EBRT = external beam radiotherapy; Ref = reference; IORT = intraoperative radiotherapy; NS = not stated; OS = overall survival.

* Seven patients received EBRT with a dose range of 30 to 45 Gy.

† Local and regional control.

REFERENCES

1. Jemal A, Siegel R, Xu J, *et al*. Cancer statistics, 2010. *CA Cancer J Clin* 2010;60:277–300.
2. Bruno JJ 2nd, Snyder ME, Motzer RJ, *et al*. Renal cell carcinoma local recurrences: Impact of surgical treatment and concomitant metastasis on survival. *BJU Int* 2006;97:933–938.
3. Itano NB, Blute ML, Spotts B, *et al*. Outcome of isolated renal cell carcinoma fossa recurrence after nephrectomy. *J Urol* 2000;164:322–325.
4. Margulis V, McDonald M, Tamboli P, *et al*. Predictors of oncological outcome after resection of locally recurrent renal cell carcinoma. *J Urol* 2009;181:2044–2051.
5. Schrodter S, Hakenberg OW, Manseck A, *et al*. Outcome of surgical treatment of isolated local recurrence after radical nephrectomy for renal cell carcinoma. *J Urol* 2002;167:1630–1633.
6. Gogus C, Baltaci S, Beduk Y, *et al*. Isolated local recurrence of renal cell carcinoma after radical nephrectomy: Experience with 10 cases. *Urology* 2003;61:926–929.
7. Master VA, Gottschalk AR, Kane C, *et al*. Management of isolated renal fossa recurrence following radical nephrectomy. *J Urol* 2005;174:473–477. discussion 477.
8. Esrig D, Ahlering TE, Lieskovsky G, *et al*. Experience with fossa recurrence of renal cell carcinoma. *J Urol* 1992;147:1491–1494.
9. Tanguay S, Pisters LL, Lawrence DD, *et al*. Therapy of locally recurrent renal cell carcinoma after nephrectomy. *J Urol* 1996;155:26–29.
10. Rabinovitch RA, Zelefsky MJ, Gaynor JJ, *et al*. Patterns of failure following surgical resection of renal cell carcinoma: Implications for adjuvant local and systemic therapy. *J Clin Oncol* 1994;12:206–212.
11. 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.
12. 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.
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. 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.
15. 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.
16. Haddock MG, Gunderson LL, Nelson H, *et al*. Intraoperative irradiation for locally recurrent colorectal cancer in previously irradiated patients. *Int J Radiat Oncol Biol Phys* 2001;49:1267–1274.
17. 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* 2011;79:143–150.
18. Tepper JE, Gunderson LL, Orlow E, *et al*. Complications of intraoperative radiation therapy. *Int J Radiat Oncol Biol Phys* 1984;10:1831–1839.
19. National Cancer Institute. Common Toxicity Criteria. Version 4.02. Rockville, MD: National Cancer Institute. 2011.
20. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–481.
21. Eble MJ, Stahler G, Wannenmacher M. IORT for locally advanced or recurrent renal cell carcinoma. *Front Radiat Ther Oncol* 1997;31:253–255.
22. Santos M, Ucar A, Ramos H, *et al*. [Intraoperative radiotherapy in locally advanced carcinoma of the kidney: Initial experience]. *Actas Urol Esp* 1989;13:36–40.
23. Motzer RJ, Hutson TE, Tomczak P, *et al*. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007;356:115–124.
24. Escudier B, Eisen T, Stadler WM, *et al*. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007;356:125–134.
25. Hudes G, Carducci M, Tomczak P, *et al*. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 2007;356:2271–2281.
26. Yang JC, Haworth L, Sherry RM, *et al*. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med* 2003;349:427–434.
27. Wersall PJ, Blomgren H, Lax I, *et al*. Extracranial stereotactic radiotherapy for primary and metastatic renal cell carcinoma. *Radiother Oncol* 2005;77:88–95.
28. McLaughlin CA, Chen MY, Torti FM, *et al*. Radiofrequency ablation of isolated local recurrence of renal cell carcinoma after radical nephrectomy. *AJR Am J Roentgenol* 2003;181:93–94.
29. Svedman C, Sandstrom P, Pisa P, *et al*. A prospective phase II trial of using extracranial stereotactic radiotherapy in primary and metastatic renal cell carcinoma. *Acta Oncol* 2006;45:870–875.