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Clinical Investigation

Outcomes in a Multi-institutional Cohort of Patients Treated With Intraoperative Radiation Therapy for Advanced or Recurrent Renal Cell Carcinoma

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Summary

In this multi-institutional investigation, we report on the largest known cohort of patients with advanced or recurrent renal cell carcinoma managed by intraoperative radiation therapy (IORT) and have identified several factors associated with survival. Outcomes following IORT in the setting of local recurrence compare favorably to similar cohorts treated by local resection

Purpose/Objective(s): This study aimed to analyze outcomes in a multi-institutional cohort of patients with advanced or recurrent renal cell carcinoma (RCC) who were treated with intraoperative radiation therapy (IORT).

Methods and Materials: Between 1985 and 2010, 98 patients received IORT for advanced or locally recurrent RCC at 9 institutions. The median follow-up time for surviving patients was 3.5 years. Overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS) were estimated with the Kaplan-Meier method. Chained imputation accounted for missing data, and multivariate Cox hazards regression tested significance.

Results: IORT was delivered during nephrectomy for advanced disease (28%) or during resection of locally recurrent RCC in the renal fossa (72%). Sixty-nine percent of the patients were male, and the median age was 58 years. At the time of primary resection, the T stages were as follows: 17% T1, 12% T2, 55% T3, and 16% T4. Eighty-seven percent of the patients had a visibly complete resection of tumor. Preoperative or postoperative external beam radiation therapy was administered to 27% and 35% of patients, respectively. The 5-year OS was 37% for advanced disease and 55% for locally recurrent disease. The respective 5-year DSS was 41% and 60%. The respective 5-year DFS was 39% and 52%. Initial nodal

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alone, suggesting the potential for improved disease-free survival with IORT.

involvement (hazard ratio [HR] 2.9-3.6, $P<.01$), presence of sarcomatoid features (HR 3.7-6.9, $P<.05$), and higher IORT dose (HR 1.3, $P<.001$) were statistically significantly associated with decreased survival. Adjuvant systemic therapy was associated with decreased DSS (HR 2.4, $P=.03$). For locally recurrent tumors, positive margin status (HR 2.6, $P=.01$) was associated with decreased OS.

Conclusions: We report the largest known cohort of patients with RCC managed by IORT and have identified several factors associated with survival. The outcomes for patients receiving IORT in the setting of local recurrence compare favorably to similar cohorts treated by local resection alone suggesting the potential for improved DFS with IORT.

Introduction

Renal cell carcinoma (RCC) is the predominant histology among renal neoplasms, and roughly one-third of patients presenting with RCC will have locally advanced disease (eg, clinical T3/T4), although the majority of these patients do not have distant metastases evident at that time (1). The standard treatment for T2-4 disease includes nephrectomy with or without adjuvant immunotherapy, targeted therapy, or both (2). Up to 9% of all RCC patients will experience a local tumor recurrence apparently limited to the renal fossa after nephrectomy (3-5). The treatment options for this cohort include targeted therapies, immunotherapy, and surgical resection with or without intraoperative radiation therapy (IORT). IORT is a treatment modality commonly used in colorectal and breast cancers, although its use has been explored in other disease sites (6). The treatment of RCC with IORT for locally advanced disease at the time of nephrectomy or for locally recurrent disease at time of resection relapse has been performed since the 1980s and may be combined with preoperative or postoperative external beam radiation therapy (EBRT). IORT is intended to address microscopically or macroscopically persistent disease at the margins when tumor is incompletely resected. When there is extensive local burden at presentation or recurrence and eradication by surgery appears to be unlikely, several institutions now take a planned approach that combines perioperative EBRT with an IORT boost. Similar to treating RCC metastases with radiosurgery, the large single-fraction dose provided by IORT may be particularly useful against a tumor that is commonly thought to be relatively radiation resistant (7). The addition of IORT in primary and recurrent settings has been previously reported in small single-institution cohorts, with encouraging initial results (8-12). In this study, we sought to examine prognostic factors and disease outcomes in a large pooled multi-institutional cohort of patients who received IORT for RCC.

Methods and Materials

Patient and clinical variables

After receiving institutional review board approval, we retrospectively identified 98 patients at 9 institutions who were treated with IORT during surgery for locally advanced or locally recurrent RCC between 1985 and 2010. A wide range of variables was collected from each institution, assessing demographic details, initial clinical and pathologic stages, information on treatment methods for primary and recurrent tumors, duration of in-patient hospital stay, prevalence of perioperative complications, time to disease progression, and cause and date of death. The American Joint Committee on Cancer 2010 TNM classification staging system and Fuhrman tumor grading system were used (13).

Treatment techniques and planning

Treatment techniques and equipment for IORT varied across institutions, although in general, conical or elliptical collimators/applicators approximately 10 cm wide in the long axis (range, 4-15 cm) were used on fixed (n = 8 institutions) or mobile linear (n = 1) accelerators. Treatment volumes and doses were determined with input from the radiation oncologist, medical physicist, and surgeon

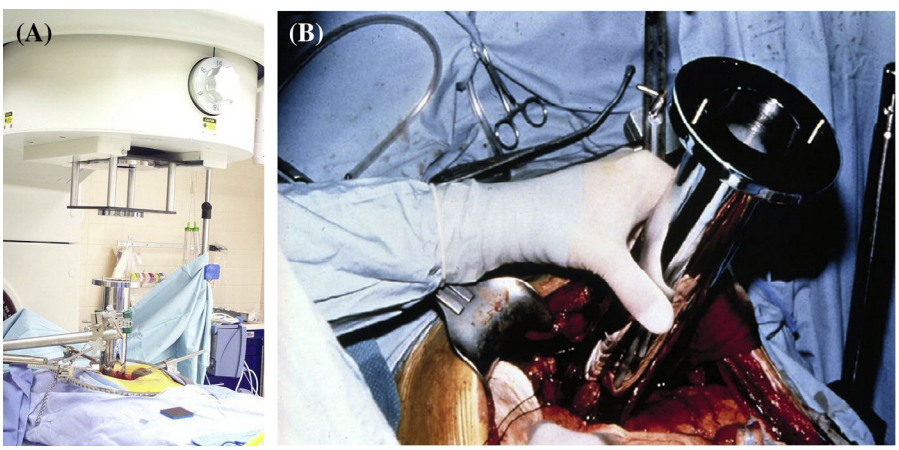

Fig. 1. (A) Intraoperative radiation therapy setup using fixed linear accelerator. (B) Conical collimator placement.

based on the risk of remaining microscopic or gross disease. Treatment planning differed slightly across institutions. At our home institution, the depth of treatment, corresponding appropriate electron energy, applicator size, and daily cGy/MU calibration factor were used to compute final treatment parameters. Other institutions chose to select a preconfigured treatment plan based on the desired treatment depth, electron energy, cone size, and angle of beveled edge. Dose–volume histograms were not specifically calculated during planning because these would simply mimic the premeasured electron beam data for the selected energy and cone. The treatment isodose was 90% for all but 2 patients, and all patients were treated exclusively with electron radiation during IORT. The median treatment energy was 9 MeV. Care was taken to angle beams away from the great vessels (when uninvolved) and spinal column. When possible, uninvolved organs were displaced or shielded for the procedure. Bolus and shielding were applied to ensure a more uniform dose distribution and sparing of adjacent structures, respectively. The treatment setup is shown in Figure 1.

Statistical methods

Overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS) were estimated from date of IORT by the Kaplan-Meier method and were stratified by IORT setting (primary or recurrent). DSS was defined as freedom from death resulting from RCC. DFS was defined as freedom from any recurrence after IORT. Chained multiple imputation was performed to account for missing data. A multivariate Cox hazards model based on variables obtained from a stepwise regression was used to assess the predictive power of pretreatment and treatment variables. Tests of statistical significance were 2-sided, and a P value $<.05$ was considered statistically significant. Stata, version 11, statistical software (StataCorp, College Station, TX) was used.

Results

Patient and tumor characteristics

Patient demographics and disease characteristics are presented in Table 1. Sixty-nine percent of patients were male, and the median age at RCC diagnosis was 58 years. At the time of primary resection, the T stage was 17% T1, 12% T2, 55% T3, and 16% T4.

Treatment characteristics

IORT was delivered during nephrectomy for advanced disease as determined by the treating institution (28% of patients) or during

Table 1 Patient characteristics and disease features

Variable	All* Median (range)	Advanced* Median (range)	Recurrent Median (range)
n	98	27	71
Age	58 (16-79)	61 (40-79)	57 (16-76)
Tumor size	8 cm (1.5-17)	8.5 cm (3.5-17)	6 cm (1.5-17)†
Year of nephrectomy	1993 (1984-2009)	1989 (1985-2008)	1996 (1984-2009)
	n (%)	n (%)	n (%)
Male	67 (68)	19 (70)	48 (68)
Surgical T stage			
T1	15 (17)	2 (8)	13 (21)*
T2	10 (12)	0 (0)	10 (16)*
T3	47 (55)	11 (46)	36 (58)*
T4	14 (16)	11 (46)	3 (5)*
Unknown	12	3	9*
Cell type			
Clear cell	57 (64)	11 (44)	46 (72)
Papillary	10 (11)	2 (8)	8 (13)
Sarcomatoid features	11 (12)	6 (24)	5 (8)
Other	11 (12)	6 (24)	5 (8)
Unknown	9	2	7
Tumor grade			
1	7 (8)	3 (12)	3 (5)†
2	38 (42)	12 (46)	20 (36)†
3	34 (38)	7 (27)	23 (23)†
4	11 (12)	4 (15)	9 (16)†
Unknown	8	1	16
+Node status	16 (18)	9 (35)	7 (11)†
Metastases at IORT	13 (13)	2 (7)	11 (16)†
Time to local recurrence after nephrectomy	N/A	N/A	22 mo (range 1.6-180)

Abbreviation: IORT = intraoperative radiation therapy.

* Values indicate clinical information collected at time of diagnosis/nephrectomy.

† Values collected at time of recurrence.

resection of locally recurrent RCC in the renal fossa (72%). Three patients received IORT twice during subsequent resections of recurrent disease. Before receiving IORT, 87% of patients had a visibly complete surgical resection of tumor. The median IORT dose delivered was 15 Gy (range, 9.5-20 Gy). Preoperative or postoperative EBRT was administered to 27% (median, 45 Gy; range 5-72 Gy) and 35% (median, 40 Gy; range 10-56 Gy) of patients, respectively (2% received both preoperative and postoperative EBRT). Nine percent and 10% of patients received neoadjuvant and adjuvant systemic therapy for the treatment of recurrent RCC, respectively, and 15% of patients received adjuvant systemic therapy for the treatment of advanced primary RCC. Other treatment characteristics are shown in Table 2.

Treatment morbidity

There was an overall reported 29% perioperative complication rate. Among these there were 5 grade 3 and 2 grade 4 complications, which included 3 grade 3 pancreatic leaks, 1 grade 4 gastritis, and 1 grade 4 adult respiratory distress syndrome. Two patients succumbed to postoperative complications, including 1 from an inferior vena cava hemorrhage 8 days after the procedure and another who died more than 3 months after treatment due to sepsis and infarct.

Survival and disease outcomes

The median follow-up time after IORT for surviving patients was 3.5 years. OS at 1 and 5 years after IORT was 69% and 37% for patients with advanced disease and 94% and 55% for patients with locally recurrent disease, respectively (Fig. 2A). DSS at 1 and 5 years was 72% and 41% for patients with advanced disease and 96% and 60% for patients with locally recurrent disease, respectively (Fig. 2B). DFS at 1 and 5 years was 72% and 39% for patients with advanced disease and 96% and 52% for patients with locally recurrent disease, respectively (Fig. 2C).

The median time between initial nephrectomy and IORT for a recurrence was 22 months (range, 1.6-180 months). The median recurrent tumor size was 6.0 cm (range, 1.5-17 cm). Of the 27 and 71 patients who received IORT for primary and recurrent RCC, 70% and 69% eventually relapsed, respectively. Seventy-six percent of all first relapses after IORT were distant, 11% were in-field, and 13% were regional.

Prognostic factors

For the entire cohort, initial nodal involvement (hazard ratio [HR] 2.9-3.6, $P<.01$), presence of sarcomatoid features (HR 3.7-6.9, $P<.05$), and higher IORT dose (continuous, HR 1.3, $P<.001$), had a statistically significant association with decreased OS, DSS, and DFS. Patients who received adjuvant systemic therapy after IORT showed decreased DSS (HR 2.4, $P=.03$). When locally recurrent tumors alone were analyzed, positive margin status (HR 2.6, $P=.01$) was associated with decreased OS. Additional details of the multivariate Cox regression are presented in Tables 3, 4, and 5.

Discussion

In the setting of advanced primary or locally recurrent RCC, IORT has been performed internationally for 3 decades, although rigorous evidence supporting this practice has been lacking. In this multi-institutional pooled analysis, we report on the largest known cohort of RCC patients managed with IORT and have identified several factors associated with survival.

The results from our cohort compare favorably with those of other cohorts treated by local resection alone. The largest contemporary surgical series by Margulis et al (5) reported on 54 patients with recurrent RCC in the renal fossa after nephrectomy managed by surgical resection without radiation. Age, clinical stage, and cell type were similar to those in our cohort. Despite a higher prevalence of metastases at time of local resection in our cohort (16% vs 0%) and greater use of adjuvant systemic therapies in the Margulis cohort, the relapse rates were similar. Although a similar proportion of IORT (69%) and surgery-only (65%) patients eventually had further recurrent

Table 2 Treatment characteristics

Variable	All	Advanced	Recurrent
	Median (range)	Median (range)	Median (range)
IORT dose (Gy)	15 (9.5-20)	15 (12.5-20)	15 (9.5-20)
Energy (MeV)	9 (4-15)	9 (6-15)	9 (4-15)
Inpatient days after IORT	10 (3-30)	10 (3-26)	8 (3-30)
Overall follow-up after IORT (years)	1.6	1.6 (0.2-25.7)	1.6 (0.02-20.4)
Follow-up after IORT for surviving patients (years)	3.5	22.2 (0.2-25.7)	3.3 (0.02-20.4)
EBRT	n (%)	n (%)	n (%)
Preoperative	26 (27)	3 (11)	23 (32)
	Median 45 Gy	Median 44.1 Gy	Median 45 Gy
Postoperative	34 (35)	12 (44)	22 (31)
	Median 40 Gy	Median 40 Gy	Median 43 Gy
Visibly complete resection	84 (87)	22 (85)	62 (87)
Positive surgical margin	57 (59)	16 (59)*	41 (59)†

Abbreviations: EBRT = external beam radiation therapy; IORT = intraoperative radiation therapy.

* Values indicate clinical information collected at time of diagnosis/nephrectomy. Margin status for 1 patient was unavailable.

† Values collected at time of recurrence. Margin status for 1 patient was unavailable.

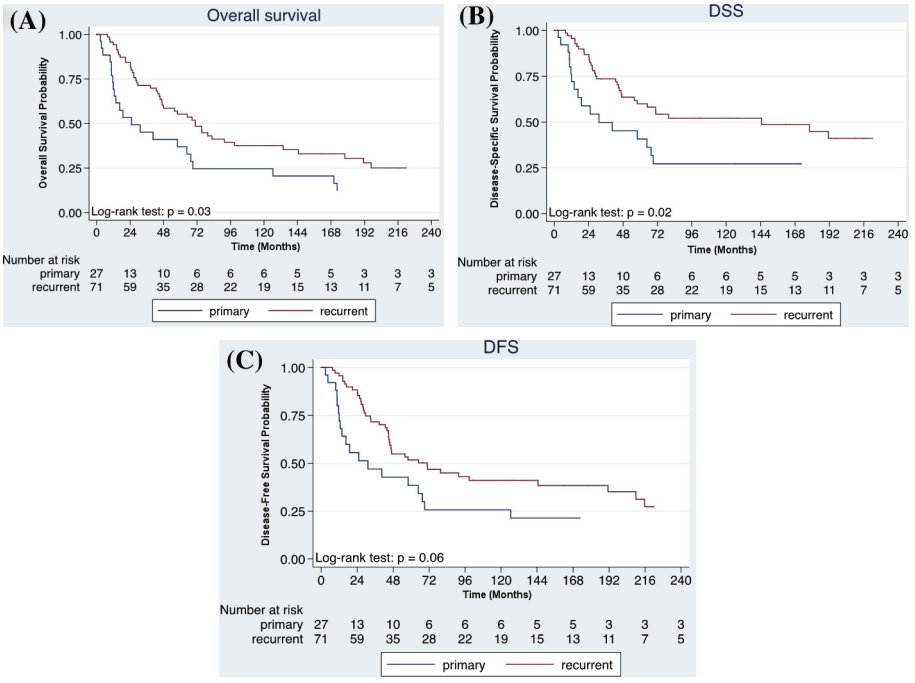

Fig. 2. (A) Overall survival after intraoperative radiation therapy (IORT). (B) Disease-specific survival after IORT. (C) Disease-free survival after IORT.

disease, our 5-year DFS appears favorable (52% vs 30%), with a median DFS of 66 months compared with 11 months in the surgical series. Our 5-year DSS also suggests a modest benefit (60% vs 50%).

Although our cohort included patients with metastases at initial relapse and 59% had positive margins, our results are comparable with those of a small surgical series by Bruno et al (4) that included 11 patients with local relapse, negative margins, and no metastases. The 5-year DSS for this surgery-alone group was 62%, compared with 60% in our cohort for patients with local recurrence receiving surgery and IORT.

It is also notable that although 59% of the patients treated in our cohort who experienced local recurrence had microscopically incomplete resections (ie, positive surgical margins), only 24% of all relapses were local (76% of first relapses were distant), suggesting a potential benefit in local control when IORT is added. Although RCC has traditionally been considered relatively radiation resistant, modern data using hypofractionation and stereotactic radiosurgery for primary or metastatic lesions suggest that this resistance can be overcome (7, 14, 15). The large single doses delivered by IORT may mimic these radiosurgery scenarios.

Our results are consistent with those of other studies in identifying several factors associated with survival. Smaller, single-institution series have suggested that complete resection of tumor, small tumor size, and absence of sarcomatoid features may predict for longer DSS in patients with locally advanced or locally recurrent RCC (5, 16). We identified a higher IORT dose to be associated with decreased survival for all groups and endpoints. This is presumably the result of higher doses being prescribed in the setting of more advanced and more bulky disease. Given the low number of treatment-related deaths and relatively narrow range of prescribed dose, it is unlikely that higher IORT doses contributed significantly to mortality. A decrement in DSS for those receiving systemic therapy may have been seen for a similar reason. Margulis et al (5) describe a similar lack of benefit from systemic therapy. Sarcomatoid features and positive nodal status are also significant risk factors in our cohort, consistent with other studies (5, 17, 18). Of

Table 3 Multivariate analysis of factors significant for overall survival

Cohort	Variable	Hazard ratio (95% CI)	*P* value
Recurrent and primary	Higher IORT dose	1.3 (1.2-1.5)	*P*<.001
Recurrent and primary	Positive nodal status	2.9 (1.2-6.9)	*P*=.016
Recurrent and primary	Presence of sarcomatoid features	6.9 (2.5-18.9)	*P*<.001
Recurrent	Higher IORT dose	1.3 (1.1-1.4)	*P*<.001
Recurrent	Positive nodal status	4.0 (1.1-13.8)	*P*=.03
Recurrent	Presence of sarcomatoid features	4.6 (1.1-18.7)	*P*=.03
Recurrent	Recurrent positive surgical margin status*	2.6 (1.3-5.3)	*P*=.009

Abbreviations: CI = confidence interval; IORT = intraoperative radiation therapy.
* Following resection of recurrent disease.

Table 4 Multivariate analysis of factors significant for disease-specific survival

Cohort	Variable	Hazard ratio (95% CI)	*P* value
Recurrent and primary	Higher IORT dose	1.3 (1.2-1.5)	$P<.001$
Recurrent and primary	Delivery of adjuvant systemic therapy	2.4 (1.1-5.4)	$P=.03$
Recurrent and primary	Presence of sarcomatoid features	5.9 (1.7-19.9)	$P=.006$
Recurrent and primary	Positive nodal status	3.6 (1.5-8.6)	$P=.004$

Abbreviations: CI = confidence interval; IORT = intraoperative radiation therapy.

the 11 patients in our cohort with sarcomatoid features, 3 had no evidence of disease at the last follow-up visit, including 1 who remained disease free 9 years after treatment.

Certain limitations to our study must be considered, including the retrospective nonrandomized nature of the cohort, which spans many years among different centers. Contributing institutions may have used varying treatment methods for which complete details were not always available. In addition, our results also need to be put into the context of the more recent emergence and use of targeted therapies. Although the rates of perioperative complications appear comparable with those in the surgery-alone series, it is difficult to assess IORT specific morbidity after aggressive therapy that includes surgery.

Conclusions

In summary, we believe that a good candidate for consideration of IORT would include a patient without evidence of distant disease who has a local recurrence of RCC in the renal fossa after nephrectomy for which surgery alone is unlikely to achieve durable local control and for whom external beam dose would be limited by surrounding normal tissues. In light of the encouraging results of our study, namely the potential for improved DFS, we feel that a prospective evaluation of multimodality therapy that includes maximally safe surgical resection and IORT along with targeted systemic therapies may be warranted (19).

Table 5 Multivariate analysis of factors significant for disease-free survival

Cohort	Variable	Hazard ratio (95% CI)	*P* value
Recurrent and primary	Higher IORT dose	1.3 (1.1-1.4)	$P<.001$
Recurrent and primary	Presence of sarcomatoid features	3.7 (1.1-12.9)	$P=.04$
Recurrent and primary	Positive nodal status	3.1 (1.3-7.1)	$P=.009$

Abbreviations: CI = confidence interval; IORT = intraoperative radiation therapy.

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