Role of Radiation Therapy for Renal Tumors

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Abstract

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Renal cell carcinoma (RCC) is an aggressive malignancy that carries a poor prognosis, especially in patients presenting with advanced stage. Primary treatment for localized RCC is surgical resection however, a significant number of patients still develop locoregional and distant metastasis after curative resection. In metastatic disease, radiation therapy (RT) has been used for palliation routinely for brain and other extracranial lesions with respectable response rates. However, RT for primary RCC has questionable benefit. In this article, the authors discuss the evidence with regards to the role of RT in primary RCC either as a primary treatment, adjuvant treatment, or preoperatively to improve resection outcomes. In addition, novel RT techniques such as stereotactic body radiation therapy and its use in RCC management are also addressed. Finally, the authors discuss the techniques and doses of RT for primary RCC.

Objectives: Upon completion of this article, the reader will be able to explain the role of radiotherapy in the treatment algorithm of renal cell carcinoma.

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Renal cell carcinoma (RCC) represents 3% of adult malignancies and over 90 to 95% of malignant kidney cancers.¹ RCC is an aggressive cancer, and 20 to 30% patients present with metastatic disease due to the absence of a screening test and insidious nature of the disease. Patients with metastatic cancer have a 5-year survival of 10 versus 85% for patients with localized disease.

RCC typically arises in the seventh decade of life with a median age of 65 years. It is the sixth most common cancer in men. Recently, there has been an increase in the incidence of RCC probably due to better imaging.² A Surveillance, Epidemiology, and End Results (SEER) study evaluating incidence rates in North America showed the age-adjusted incidence rates increased from 7.6 per 100,000 person-years in 1988 to 11.7 per 100,000 person-years in 2006 (2.39%; $p < 0.001$). In addition, there was a stage-specific age-adjusted increased incidence rate for localized stage that increased from 3.8 in 1988 to 8.2 in 2006 ($p < 0.001$), and decreased incidence of distant stage disease during the same time frame (2.1–1.6; $p = 0.01$).²

A study to analyze patterns of disease presentation and outcome of RCC by American Joint Committee on Cancer (AJCC) stage using data from the National Cancer Database over a 12-year period revealed an increase in stage I disease and decrease in stages II, III, and IV disease ($p \leq 0.001$). The size of stage I tumors also decreased from a mean of 4.1 cm in 1993 to 3.6 cm in 2003. In addition, there was a 3.3% increase in survival for patients diagnosed in 1998 compared with patients diagnosed in 1993.³

Although, the natural history of renal pelvis tumors is similar to other urothelial cancers, this article will focus on the management of RCC exclusively.

General Management

Surgery remains the standard of care for localized RCC. Radical nephrectomy involves removal of the kidney with perinephric tissues including Gerota fascia and the ipsilateral adrenal gland. Despite a curative resection for localized disease, approximately 30% of patients will experience recurrence of cancer.⁴ In a series from Mayo clinic that reported outcomes retrospectively in 1,547 patients with RCC treated with surgical resection from 1970 to 1998, authors investigated the prognostic significance of tumor classification and compared outcomes based on 1987 versus 1997 AJCC staging. Prognostic discrimination for cause-specific survival at 10 years was noted for the 1987 and 1997 TNM (tumor-node-metastasis) classifications (T1, 97 vs. 91%; T2, 84 vs. 70%; T3a, 53 vs. 53%; T3b, 48 vs. 42%; and T3c, 29 vs. 43%).⁵

The risk of relapse is dependent on tumor stage, nodal stage, grade, metastasis, and performance status. These factors are used to classify patients as low, intermediate, and high risk in the stage, size, grade, and necrosis (SSIGN) score developed at Mayo clinic and the University of California Los Angeles Integrated Staging System (UISS) score developed at the University of California.

The SSIGN score was created as an outcome prediction tool for clear cell RCC using pathological review. In a validation study for SSIGN scoring criteria, 10-year cancer-specific survival (CSS) rates for respective SSIGN scores ranged from 96.5 (scores 0–1) to 19.2% (scores ≥ 10). Tumor categories, lymph node status, distant metastases, high tumor grade (size ≥ 5 cm), and necrosis were each independent predictors of CSS.⁶ The UISS scoring criteria is based on a postoperative model on TNM stage, Fuhrman grade, and Eastern Cooperative Oncology Group (ECOG) performance status.

Role of Radiation Therapy

Radiation sensitivity of renal cancers is an area of much debate, with some studies showing reasonably good sensitivity with others showing radiation resistance.^{7,8} There are reports of sensitizers enhancing the effects of radiation therapy in renal cancer cells. In a recent study,⁹ evaluating the role of the biphosphonate zoledronic acid (ZA), there was radiation sensitization observed independent of its osteoclast activity by potentiating the caspase-3-mediated apoptosis pathway. The radiosensitization by ZA was observed in several renal cancer cell lines including 786-O, A-498, and ACHN cells, but not in Caki-1 cells. The signal transducer and activator of transcription 1 (STAT1) seemed to play a key role in this sensitization. However, the clinical application of radiation sensitizers in RCC is still an area of active research.

Preoperative Radiation

The role of preoperative radiation therapy for RCC has been evaluated for advanced or unresectable RCCs. In a small study

from Mayo Clinic,¹⁰ 11 patients with locally recurrent or persistent cancer following nephrectomy (RCC in eight, transitional cell or squamous cell cancer in three) usually received 45 to 50.40 Gy preoperative RT followed by maximal surgical debulking and intraoperative electron irradiation (10–25 Gy). Of eight RCC patients, six were alive and four were without disease progression at 15 to 50 months (75% of patients without disease progression at 29 months or longer). One patient died free of disease at 10.5 months and three developed metastases (regional in one and distant in two). Of the three transitional or squamous cell carcinoma patients, one died free of disease 28.5 months after initiation of treatment for recurrence, and two died of disease progression (liver in one and local in one).

Several other retrospective reports have shown a benefit to using preoperative RT in advanced RCCs.¹¹ However, two prospective randomized studies failed to show benefit of preoperative RT. In one study from Rotterdam, there was no advantage with respect to overall survival to preoperative RT versus upfront surgery. RT dose in this study was 30 Gy in 15 sessions. The follow-up study used a higher RT dose with no additional benefit.^{11–13} In the second European study evaluating the role of preoperative RT, similar results showed no benefit of adding preoperative RT to nephrectomy.¹⁴

Postoperative Radiation

Postoperative radiation after nephrectomy has also been studied in both prospective and retrospective manners. Overall, some studies demonstrated benefit of adding RT, but there was no convincing benefit seen in other prospective studies.^{15–19}

In a retrospective study of 147 patients¹⁵ with histologically proven RCC treated between 1977 and 1988, postoperative irradiation was given to a dose of 46 Gy to 56 patients. The 5- and 10-year actuarial survivals in irradiated patients were 50 and 44%, respectively, and in nonirradiated patients were 40 and 32%, respectively. Local recurrence by stage was as follows: T2 NOMO: RT+ 0/17, RT– 2/28; T3 NOMO: RT+ 4/37 (10%), RT– 11/30 (37%) ($p < 0.05$); T4 NOMO: RT+ 1/2, RT– 1/5. Two of the local recurrences in irradiated patients developed in a surgical scar, which was not included in the RT treatment volume. Significant toxicity developed in three patients (5%). It was concluded from this study that postoperative irradiation could reduce local recurrence rate in T3 NOMO RCC, and it was also recommended that the surgical scar should always be included in the treatment volume and irradiated to a full dose.

In another retrospective comparison in 24 patients of RT versus no RT in stage III–IV RCC patients after nephrectomy,¹⁶ no patients who received RT developed locoregional recurrence, despite disease at the surgical margins in six patients. The actuarial disease-free survival at 5 years was 75 versus 62% in the no RT group. The 5-year actuarial local failure rate in the surgery-only group was 30% ($p < 0.01$).

A study from Poland¹⁷ reviewed records of 186 patients with locally advanced RCC. The postoperative RT median dose was 50.0 Gy. The 5-year overall and disease-free survival rates

were 36.2 and 30.5%, respectively. A total of 29 patients (15.6%) developed local recurrences. Local failure by stage was as follows: T3N0 without postoperative RT was 15.8%, with RT was 8.8%; T3 N+ without RT was 33.3% and with RT was 33.3%. The median time to relapse for local recurrence/distant metastases were approximately two times longer in patients with adjuvant RT compared with those without (27.0/21.0 vs. 16.0/12.5 months, respectively). The authors concluded that postoperative RT reduces the probability of local recurrence (LR) in selected patients, mainly with pathological stage T3N0, but its impact on survival is minimal.

Randomized prospective trials evaluated the role of adjuvant RT after nephrectomy. In a study published by Kjaer et al^{18,19} evaluating adjuvant RT in stage II/III RCC patients, 33 patients received no RT after surgery while 32 patients received 55 Gy in 2.5 Gy/fraction. Overall 5-year survival was 63% in the no RT versus 38% in those undergoing RT. There were significantly increased complications in the RT group that resulted in higher mortality rates. These randomized studies showed no benefit of adjuvant RT in resected RCC patients and showed a higher complication rate and mortality, thereby ensuring diminished RT use in the adjuvant setting in this aggressive disease. However, it is important to realize that these studies used a fraction size that was higher than 1.8 to 2.0 Gy, which may contribute to increased short- and long-term toxicity.

Stereotactic Radiation

Stereotactic body radiation therapy (SBRT) enables the delivery of high-dose radiation to the tumor while sparing normal tissues. This novel technology takes advantage of image guidance and radiation dose delivery to deliver high ablative doses of radiation to the tumor. Initially developed as an advancement in treating brain tumors (stereotactic radiosurgery), it is being increasingly used for extracranial sites including the thorax and abdomen. SBRT allows delivery of high-dose radiation per fraction (e.g., 20 Gy) to the tumor (vs. 1.8 or 2 Gy per fraction in conventional radiation treatments). It is usually delivered to tumors smaller than 5 cm with no lymph node involvement; treatment of larger tumors has a high probability of toxicity due to the high fractional dose and large volume of normal tissue treated.

For RCCs, SBRT can be applied to patients where surgery is not the best option, for example, single functional kidney, bilateral renal cancers, medically inoperable or locally recurrent tumors after conservative surgical resection. The relative radioresistance of RCC and previous experience with improvement in local control of renal brain metastasis has led to a growing interest in the treatment of primary RCC with SBRT.

Beitler et al²⁰ treated nine patients with primary RCC with SBRT. The total dose was 40 Gy in five fractions over 15 days. With a median follow-up of 26.7 months, four of nine patients were alive with no evidence of locoregional disease.

In a series of studies by a Swedish group, SBRT was utilized for both primary and metastatic RCC. In the initial study published in 2005,²¹ 50 patients from metastatic RCC and 8 patients with inoperable primary RCC received SBRT. The most common dose/fractionation schedules used were 8 Gy $\times$ 4, 10 Gy $\times$ 4, and 15 Gy $\times$ 3. SBRT-treated tumor lesions regressed totally in 30% of the patients at 3 to 36 months, whereas 60% of the patients had a partial volume reduction or no change after a median follow-up of 37 months. Side effects were generally mild. Of 162 treated tumors, only 3 recurred, showing a local control rate of 90 to 98% (**► Table 1**).

In a follow-up prospective study by the same group,²² 30 patients with metastatic RCC or inoperable primary RCC received SBRT. Fractionation was similar to the retrospective study mentioned above.²¹ In total, 82 lesions were treated. Local control, defined as radiologically stable disease or partial/complete response, was obtained in 98% of treated lesions; one of five lesions, however, was in patients with a follow-up time of less than 6 months. Complete response was observed in 21% of the patients, and 58% of the patients had a partial volume reduction or stable local disease after a median follow-up of 52 months (range 11–66) for living patients, and 18 months (range 4–57) for deceased patients. Local progression was seen in two lesions. Side effects were grade I–II in 90% of cases and the overall survival was 32 months.²²

In a retrospective study,²³ evaluating outcomes in RCC patients with a single functional kidney, seven patients were treated for metastases from a malignant kidney to its contralateral counterpart. Dose/fractionation schedules varied between 10 Gy $\times$ 3 and 10 Gy $\times$ 4. Local control was obtained

Table 1 Stereotactic radiation in renal cell carcinomas

Study	Patients (n)	Total dose (Gy)	Fractions/fractional dose (Gy)	Outcomes
Beitler et al ²⁰	9 patients, 2 with bilateral RCC	40	8	4/9 patients alive at median f/u 26.7 mo
Svedman et al ²²	30 patients, 82 lesions	32, 40, 30, 45	8, 10, 15, 15	Stable disease, partial/complete response in 98% of lesions
Teh et al ²⁵	14 patients, 23 extracranial sites, 2 primary RCC	24–40	3–6	Median f/u 9 mo; 93% symptomatic relief, 87% LC

Abbreviations: f/u, follow-up; Gy, gray; LC, local control; mo, months; RCC, renal cell carcinoma.

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