Review

Current Role of Radiotherapy for Renal-Cell Carcinoma: Review

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Abstract

Surgery is the standard of care for patients with renal-cell carcinoma (RCC). Radiotherapy (RT) can decrease the risk of local recurrence after surgery and can lead to excellent outcomes in patients unfit for surgery. We reviewed clinical experience with various forms of RT, including conventional fractionated RT and intraoperative radiotherapy (IORT) as adjunct to surgery, hypofractionated high-dose stereotactic body radiotherapy (SBRT), and particle therapy in unresectable RCC. We discuss future directions for using RT in the treatment of RCC. We encourage clinicians to incorporate RT modalities in prospective clinical trials.

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Introduction

Renal-cell carcinoma (RCC) is one of the 10 most common malignancies in the developed world, with incidence rates steadily increasing.[1] It affects predominantly the older population, with a median age at diagnosis of 65 years. Surgery is the reference standard treatment for primary RCC. Unfortunately, local recurrences after surgery occur in 20% of patients,[2] necessitating development of adjuvant and neoadjuvant therapies to reduce this rate. For patients unfit for surgery, nonsurgical treatment options must be developed and validated in prospective clinical trials. Radiotherapy (RT) has long been considered an ineffective modality as a result of documented RCC radioresistance and radiation-induced adverse effects, but newer RT techniques may overcome these limitations and may offer modalities that complement the existing armamentarium of RCC treatments.

Palliative Low-Dose RT Is Effective in Managing Symptoms From Metastatic RCC

The topic of differential radiosensitivities among different malignant histologies appeared in the literature in the early 1950s and was further confirmed by in vitro studies, in which the survival of 25 human tumor cell lines after irradiation varied by a factor of 5, ranging from 14% to 77%.[3] Deacon et al[4] classified malignant histologies into 5 groups according to their in vitro radiosensitivities, from the most "radiosensitive" group (containing lymphoma, myeloma, and neuroblastoma) to the most "radioresistant" group (containing sarcoma, melanoma, glioblastoma, and RCC). In the next decade, radioresistance of RCC to conventional RT was further supported by preclinical studies.[5]

Nevertheless, the efficacy of palliative, conventionally fractionated RT for metastatic RCC is well documented in a prospective phase 2 trial.[6] Thirty-one patients were treated with a standard palliative regimen of 30 Gy in 10 fractions. Pain level, use of analgesics, cancer-related symptoms, and quality of life using validated questionnaire instruments were assessed before and after palliative RT. Among patients treated for pain, 83% experienced site-specific pain relief after RT, and 48% did not require increased analgesic medication. Improvement in global quality of life was reported by 33% of patients as measured by the European Organization for Research and Treatment of Cancer questionnaire, with a median duration of improvement of 2 months.

Conventional Fractionated RT May Improve Outcomes in Select Patients With RCC Treated With Surgery

Several randomized phase 3 trials in the early 1970s and 1980s used an obsolete hemiabdominal RT technique with no liver and small bowel shielding (Figure 1), which dampened enthusiasm for conventional RT in combination with nephrectomy, either preoperatively[7] or in the adjuvant setting.[8-10] A large meta-analysis of 7 randomized clinical trials of radical nephrectomy with or without

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postoperative RT (PORT) in 735 patients with localized RCC[11] found no difference in overall survival ($P = .29$) and disease-free survival ($P = .14$). However, this analysis revealed a significant association between reduced risk of locoregional recurrence and the use of PORT. Moreover, a retrospective analysis of 325 patients with histologically confirmed RCC treated with and without adjuvant RT after nephrectomy revealed an association between improved 5-year overall survival (OS) and addition of PORT for patients with capsular invasion (OS5 of 72% and 20% with and without PORT, respectively) and with renal pelvis involvement (OS5 of 85% and 33%, respectively).[12] These data suggest that for select patients after nephrectomy, adjuvant RT with modern techniques that minimize treatment-related toxicity may improve outcomes. Adjuvant RT may also play an important role in management of patients after partial nephrectomy, especially in the setting of positive margins. Adjuvant conventional fractionated RT should be studied in prospective clinical trials.

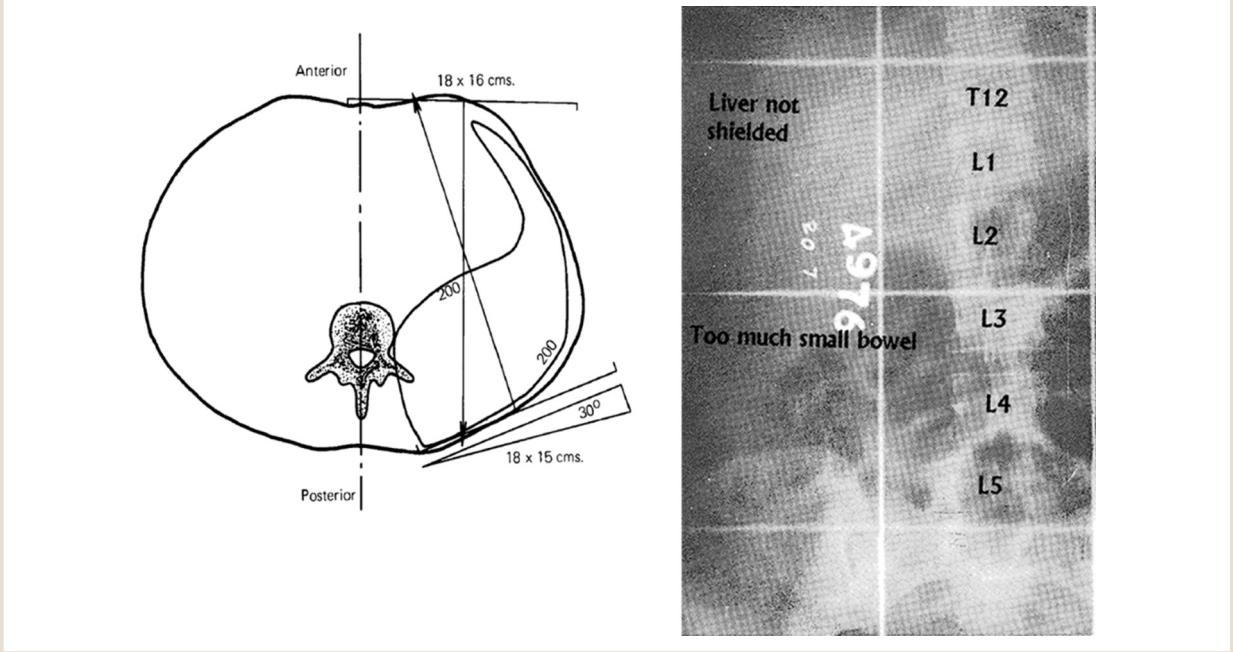
Ablative Hypofractionated High Dose per Fraction RT Shows Promising Results in Patients With RCC Unfit for Surgery

While RCC remains more radioresistant than other histologies when using conventional fractionation, early in vitro cell culture studies revealed that ablative doses of radiation—in which high-dose RT is delivered over very few fractions—can effectively eradicate RCC cells.[13] Survival curves in Caki-1 and A498 cell lines exhibited a small decrease in survival with radiation doses between 0 and 6 Gy, yet an exponential decrease in survival ensued at doses over 6 Gy. This finding was supported by further work in mouse models with an implanted human RCC cell line.[14] Biological mechanisms other than mitotic catastrophe after double-strand DNA breaks are likely responsible for the increased sensitivity of RCC to large fractional doses. One proposed mechanism is through the production of proapoptotic second messenger ceramide molecules that stimulate endothelial cell apoptosis when a large fraction of 15 to 20 Gy is administered.[15]

Stereotactic body radiotherapy (SBRT) has become an attractive treatment modality because of its ability to deliver highly conformal, large radiation doses to a well-localized treatment volume in the course of a small number of fractions. SBRT as a treatment modality was a logical extension of cranial stereotactic radiosurgery (SRS) outside of the brain. SRS was developed by Leksell in the 1960s and involves a single fraction of high-dose RT to a well-visualized and -localized area in the brain. It was used successfully for years in the management of brain metastases, including those from RCC, with local control rates reaching 90%. A single SRS fraction of an average dose of 21 Gy (range, 12-25 Gy) led to a local control of 85% and a significant early regression of brain metastases from RCC.[16] Of note, patients whose disease responded to therapy had a longer median survival than those with no response to SRS: 18 months versus 9 months ($P = .025$), respectively.

Stereotactic RT demonstrated its effectiveness in cases of extracranial RCC metastases. An Memorial Sloan Kettering Cancer Center series of 105 RCC metastatic lesions treated with SBRT (1 fraction of 18 or 24 Gy or 3 to 5 fractions with total doses of 20 to 30 Gy)[17] revealed a 3-year local progression-free survival of 88% for a single dose of 24 Gy, 21% for a single dose of < 24 Gy, and 17% for a hypofractionated SBRT. The study suggested that a high dose per fraction treatment led to better survival, either through better local control or by other biological mechanisms that elicited systemic effects.

Figure 1 Older Techniques of Irradiation of Primary Renal-Cell Carcinoma Before and After Surgery



One should not assume that good local control achieved with SBRT and SRS in the setting of metastatic RCC would automatically translate into desirable treatment outcomes in primary RCC, as tumor biology can vary dramatically in primary and metastatic settings, leading to different treatment response. However, over the past decade, clinical reports have emerged showing promising results of SBRT in patients with inoperable primary RCC. In 2012, a systematic review of prospective and retrospective series of SBRT in management of primary RCC[18] analyzed outcomes in 126 patients and showed local control rates ranging from 84% to 100% with a weighted grade 3+ toxicity of 4%. Similarly, 4 new prospective studies since the publication of the meta-analysis showed excellent local control rates and minimal significant toxicities (Table 1).[19-22]

The significant limitations of these series include a highly limited number of patients, an inherent selection bias, and a lack of pathologic confirmation of the effectiveness of SBRT. The reference standard measure of treatment effectiveness is pathologic confirmation of tumor necrosis, whereas imaging follow-up can be deceptive and difficult to interpret. Nevertheless, promising early results of SBRT in treatment of primary inoperable RCC led to the establishment of an International Radiosurgery Oncology Consortium for Kidney (IROCK), consisting of 8 institutions in Australia, Germany, Japan, Sweden, and the United States. IROCK has published its consensus statement in 2016, delineating appropriate patient selection, a SBRT dose and fractionation scheme, technical details regarding SBRT delivery, and clinical follow-up of patients after treatment.[23]

Particle Therapy Shows Early Promise in Management of Inoperable RCC but Requires Validation

Local control, and possibly overall survival, improves with increased dose of radiation. However, there is a limit to RT dose escalation, imposed by normal tissues and organs constraints. Particle therapy (ie, protons), compared to conventional photon therapy, can theoretically minimize the dose to the surrounding tissues. Photons deposit their peak dose very close to their entrance into the tissue, near skin, and thereafter there is an exponential decrease of deposited dose with increasing depth. By contrast, charged particles enter and travel through the tissue with minimal dose deposition along the path until the end of their paths, where a peak of energy—known as the Bragg peak—deposition occurs. The dose deposited before the Bragg peak is about 30% of the Bragg peak maximum dose, whereas beyond the Bragg peak, the dose falls practically to zero. The difference in physical properties leads to an approximately 60% reduction in integral dose when particles are compared to photons. In addition to the Bragg peak advantage, at shallow and moderate depths, protons also have a sharper beam penumbra, which is a measurement of the rapidity of dose falloff at the lateral edges of a beam. The sharper penumbra facilitates delivery of high radiation doses to targets that are close to critical structures, which are usually the dose-limiting factors, and this in turn can lead to target treatment dose escalation. Nomiya et al[24] irradiated 10 patients with primarily inoperable, histologically proven RCC with carbon ions using a median total dose of 72 Gy in 16 fractions. With a median follow-up of surviving patients of 57.5 months, the 5-year local control, progression-free survival, cause-specific survival, and overall survival rates were 100%, 100%, 100%, and 74%, respectively. Of interest, treated tumors showed a very slow shrinkage pattern; in one case, the tumor continued to exhibit shrinkage over a period of 9 years. These intriguing data regarding particle therapy require confirmation through validation studies.

Intraoperative Radiotherapy (IORT) May Be an Excellent Adjunct to Surgery in Select Patients With RCC

The best way to avoid irradiating normal tissues is to move them out of the radiation field, and this can be done best only at the time of surgery with IORT. This technique combines the effect of a biologically favorable high dose per fraction treatment, exploiting RCC's low α/β ratio, with the physical ability to separate the target tissue from surrounding tissues. IORT does not replace surgery—the standard treatment for RCC—but aims to reduce the risk of local recurrence.

A number of institutions have adopted a strategy of combining maximal surgical resection with IORT, targeting only small areas with the highest risk of residual microscopic disease, as determined by the team composed of a surgeon, pathologist, and radiation oncologist. Twenty-two patients were treated with maximal surgical resection, IORT, and adjuvant RT at the Mayo Clinic.[25] The median dose of IORT was 12.5 Gy (range, 10-20 Gy), whereas the median external beam RT dose was 45 Gy. Local recurrence rate within the IORT field at 5 years was 9%, despite a high rate (77%) of incomplete resection in this series. The overall survival at 1, 5, and 10 years was 91%, 40%, and 35%. Five patients (23%)

Table 1 Summary of Recent Large Prospective Studies of Stereotactic Body Radiotherapy in Primary Renal-Cell Carcinoma Since Publication of 2012 Meta-Analysis

Study	Year	No. of Patients	Study Design	Median or Mean Follow-Up (mo)	Dose and Fractionation	Outcome—Crude Local Control	Toxicities
McBride[19] (abstract)	2013	15	Prospective phase 1	36.7	7 Gy × 3, 9 Gy × 3, 11 Gy × 3, 13 Gy × 3, 16 Gy × 3	87% 1 failure at 30.7 months; 1 failure at 31.2 months	1 G3 renal toxicity, 5 G1 fatigue, 2 G1 nausea
Pham[20]	2014	20	Prospective phase 1	6	23 Gy × 1 or 14 Gy × 3	Not reported	60% G1-2 (no G3, G4)
Ponsky[21]	2015	19	Prospective phase 1	13.7	Max 12 Gy × 4 CyberKnife	95%	5.2% G2, 15.8% G3-4
Staehler[22]	2015	30	Prospective	28.1	25 Gy × 1 CyberKnife	98% (at 9 months)	13% G1-2 (no G3, G4)

Abbreviation: G = grade.

experienced acute or late grade 3 to 5 toxicities. These results were updated with a larger cohort of RCC patients and published in 2014[26]; the outcomes for patients receiving IORT in the setting of local recurrence compared favorably to similar cohorts treated by local resection alone, suggesting the potential for improved disease-free survival with IORT.

Future Perspectives: Combining RT With Targeted and Immunomodulatory Agents

An even more exciting mechanism to increase the effectiveness of RT without further dose escalation is through combination of RT with targeted agents. Tyrosine kinase inhibitors (TKIs) are now the cornerstone of systemic therapy in metastatic RCC. Experimental data indicate that both vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) inhibit radiation-induced endothelial apoptosis in vitro and in vivo.[27,28] VEGF and FGF families play an important role in RCC progression.[29,30] Thus, combinations of TKIs or monoclonal antibodies with RT could inhibit the main growth pathways and enhance sensitivity of RCC cells to SBRT.[31] There is, however, a heightened concern over toxicity risks with the combination of abdominal RT with TKI, particularly in light of published reports of bowel perforation in this clinical scenario.[32] Careful evaluation of appropriate timing and dosing of TKI and RT will need to be conducted in prospective clinical trials to establish a safe and effective combination approach.

Early immunomodulatory agents, such as interleukin (IL)-2 and tumor necrosis factor alpha, have been largely replaced from clinical practice by targeted agents because of the significant systemic toxicities of cytokines. Nevertheless, a minority of patients with metastatic disease experienced complete or prolonged remission with IL-2 treatment,[33] highlighting an important role for immunomodulation in the management of patients with RCC. More recently, a new generation of targeted immunotherapies has emerged as a powerful tool in oncology, in particular checkpoint inhibitors—antibody therapies that counteract the molecular mechanisms by which tumor cells evade immune recognition.[34] The randomized phase 3 trial CheckMate 025 was stopped after a prespecified interim analysis showed impressive survival results in patients randomized to nivolumab as well as a durable response in over 20% of patients.[35] On the basis of these results, the US Food and Drug Administration approved nivolumab for patients with advanced RCC in 2015. The Abscopal effect—regression of tumors distant from the site of the irradiation—has been frequently observed with SBRT, especially in melanoma and RCC, and is believed to be mediated by immune mechanisms. Therefore, it is only a matter of time before clinical trials will start exploring immunomodulatory agents (cytokines or checkpoint inhibitors) in combination with SBRT in patients with RCC and other malignancies.

Conclusion

Despite a commonly held notion that RT plays a limited role in the management of RCC as a result of the radioresistance of this malignancy, there is growing evidence of this treatment modality's effectiveness, especially with hypofractionated regimens, which take advantage of RCC's inherent low α/β ratio. Clinical trials show excellent control rates and minimal toxicity with SBRT treatments of primary RCC, and there are intriguing results with particle therapy and IORT. Even more exciting are novel clinical trials combining targeted and immunomodulatory agents with RT, with the ultimate goal of improving surgical outcomes and providing medically unfit patients with treatments that are equally effective to surgery. Radiation oncologists should participate in multidisciplinary management of patients with RCC to offer RT modalities in adjunct to surgery in select patients and SBRT to medically inoperable patients. Optimally, these treatments should be offered in clinical trials so that in the future we know how to select patients for the most appropriate RT modalities and how to deliver the safest and most effective treatments.

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Disclosure

The authors have stated that they have no conflict of interest.

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