Radiation Therapy for Patients with Advanced Renal Cell Carcinoma

Joseph A. Miccio, MD[a], Oluwadamilola T. Oladeru, MD[b], Sung Jun Ma, MD[c], Kimberly L. Johung, MD, PhD[a,*]

KEYWORDS

• Stereotactic radiosurgery • Stereotactic body radiation therapy • Renal cell carcinoma
• Radiotherapy

KEY POINTS

- The role of radiotherapy in advanced renal cell carcinoma has been increasing since the advent of high-dose-per-fraction treatment techniques.
- Excellent local control rates with minimal toxicity are possible with the use of stereotactic radiosurgery for intracranial metastases and stereotactic body radiation therapy (SBRT) for oligometastases to bone and visceral sites.
- Data are emerging supporting the efficacy and safety of SBRT as management of the primary tumor in select nonsurgical patients.
- Current research is focused on combining SBRT with immune checkpoint inhibitors in patients with metastatic renal cell carcinoma in an effort to potentiate the immune response and improve survival outcomes.

INTRODUCTION

Historically the role of radiotherapy (RT) in the management of renal cell carcinoma (RCC) was limited given several negative trials evaluating the effect of RT on survival in the neoadjuvant[1,2] and adjuvant[3,4] settings for patients with localized disease, and early in vitro studies reporting that RCC is a relatively radioresistant histology.[5] However, as higher-dose-per-fraction treatments became possible through the advent of stereotactic radiosurgery (SRS) for intracranial sites[6–9] and stereotactic body radiation therapy (SBRT; synonymous with stereotactic ablative RT) for extracranial sites,[8–15] there has been a resurgence of interest in RT for RCC. There are now published experiences showing the utility of RT in the treatment of RCC in a variety of clinical scenarios, including SBRT for RCC limited to the kidney,[13,16–24] SBRT for locally advanced (LA) RCC,[13,25–29] SRS for brain metastasis from RCC,[6–9] and SBRT for extracranial metastasis from RCC.[8–15] This article reviews the role of RT in patients with advanced RCC, including LA disease (≥T3 or >N0, M0) as well as metastatic RCC (mRCC), and ongoing efforts to optimize the incorporation of RT into the multimodality treatment paradigm for patients with mRCC to improve survival outcomes.

[a] Department of Therapeutic Radiology, Yale School of Medicine, 35 Park Street, New Haven, CT 06519, USA; [b] Harvard Radiation Oncology Program, Massachusetts General Hospital, Boston, MA, USA; [c] Department of Radiation Medicine, Roswell Park Comprehensive Cancer Center, Elm and Carlton Streets, Buffalo, NY 14263, USA
* Corresponding author.
E-mail address: Kimberly.johung@yale.edu

Urol Clin N Am 47 (2020) 399–411
https://doi.org/10.1016/j.ucl.2020.04.011

RADIOTHERAPY IN LOCALLY ADVANCED RENAL CELL CARCINOMA

Approximately 16% of patients with RCC present with LA, stage III disease.[30] Upfront radical nephrectomy remains the standard of care, followed by adjuvant sunitinib in select cases with clear cell histology.[31] However, recurrences after nephrectomy can be seen in up to 40% of LA RCC,[32] with a predominantly distant pattern of recurrence.[32] Treatment options for recurrent RCC include further surgery or radiation if local recurrence or systemic therapy.

RT has a limited role in LA RCC given the negative historical trials in this patient population. The role of neoadjuvant radiation therapy for surgical downstaging was investigated in the 1960s and 1970s, including 2 prospective clinical trials that compared neoadjuvant radiation therapy and upfront surgery. Both studies did not show an overall survival benefit at 5 years.[1,2] Similarly, the role of adjuvant radiation therapy was explored in 2 prospective clinical trials and failed to show a survival benefit, at least in part because of significant complication rates.[3,4] In a more recent meta-analysis including these trials and other retrospective studies, adjuvant radiation therapy was associated with a significant reduction in locoregional failure, but no survival benefit.[28] However, this analysis is limited by many of the included studies using outdated RT techniques and only a few studies being prospective. However, based on these data, current guidelines do not support routine fractionated radiation therapy in the neoadjuvant and adjuvant settings.

More recently, advanced radiation techniques have been evaluated in the treatment of RCC. Intraoperative radiation therapy (IORT) allows precise localization of the tumor bed while minimizing radiation dose to the surrounding normal organs. This approach was studied in multiple retrospective series,[33–35] the largest of which was a multicenter cohort of 98 patients, 71% of whom had T3 to T4 disease.[35] More than half of these patients received either neoadjuvant or adjuvant external beam RT, and 5-year disease-free survival was favorable compared with surgery alone, although in general isolated local recurrence is a rare event even in patients with LA RCC.[31] Given the lack of prospective evidence and no indication of an overall survival benefit, IORT is not routinely indicated in current guidelines.

Prospective data are emerging to support consideration of SBRT to the primary tumor as an option for patients with LA RCC who are not operable candidates. Treatment of the primary RCC tumor with SBRT is associated with excellent rates of local control for T1 to T2 lesions (local control rates of 70%–100% in a systematic review)[24] and thus has been gaining interest in recent years for early-stage disease.[36] However, extrapolation of this technique to LA RCC should be done with caution because it is not as well characterized in this patient population. One phase I dose escalation study included patients with up to T3 tumors, and none of the 15 patients with evaluable response had progressive disease, although outcomes for the subset with T3 tumors were not reported.[20] Most other prospective studies of SBRT for localized RCC did not report T stage,[17–19,21,22] although some of these studies did include tumors larger than 5 cm[18,22,23] and thus possibly some LA cases.

Data for SBRT specifically in T3 or greater tumors is largely restricted to reported outcomes in the small subset of LA patients included in some cohorts. In a dose escalation study of SBRT for RCC, 1 patient with T4 disease had local progression 11 months after treatment with SBRT (8 Gy in 5 fractions), which was successfully salvaged with repeat irradiation to the same dose and fractionation.[13] Three patients with T3 disease in 2 other studies showed no disease progression after follow-up of greater than 1 year.[25,26] The largest series of patients with LA tumors was published by Wang and colleagues,[27] who evaluated the efficacy of SBRT for patients with asynchronous bilateral RCC who previously had nephrectomy and developed a second primary in the contralateral kidney. Of the 4 patients with T3a tumors included, 3 had no local relapse at 3, 6, and 29 months of follow-up and 1 had local relapse at 12 months. One patient with T4 disease was included, who experienced local failure 6 months after treatment. However, the study is limited by its small fractionation size (3–5 Gy/fraction) with an extended fractionation scheme (10–17 fractions) and use of a gamma body irradiator.[27]

Although small retrospective and prospective studies are accumulating to support a role for SBRT to the primary tumor in early-stage RCC, data for patients with LA RCC are therefore limited, and the potential toxicities associated with treating these larger tumors have not been well described. Responses in the reported cases suggest that SBRT may provide a benefit in terms of local control and palliation of symptoms in LA RCC, although further studies are warranted.

RADIOTHERAPY IN METASTATIC RENAL CELL CARCINOMA

Management of Central Nervous System Metastasis

Although the rate of brain metastasis development in all patients with mRCC is approximately 2%, up

to 16% of patients with thoracic and bone metastasis develop intracranial metastasis.[37] The development of brain metastases is associated with clear cell histology, sarcomatoid differentiation, larger tumor size, and node-positive disease at diagnosis.[38] In an epidemiologic evaluation of intracranial RT use in mRCC, the frequency of SRS use for brain metastasis from RCC increased from 27% in 2005 to 44% in 2014, and this trend was associated with improved overall survival.[39]

Local control rates with SRS for RCC brain metastasis are excellent, and generally approach or exceed 90% at 1 year (**Table 1**).[6–9,40–52] The largest study to date evaluating SRS for RCC brain metastasis is reported by Kano and colleagues,[45] who examined 531 lesions treated in 158 patients. With a median marginal dose of 18 Gy (range 10–22 Gy), the local control at 1 year was 87%, although survival at 1 year was only 38%. No studies are available evaluating survival of patients treated with SRS for RCC brain metastasis who are receiving modern systemic therapy (either ipilimumab/nivolumab or pembrolizumab/axitinib), but improved survival would be expected in this setting because most deaths in patients receiving radiosurgery for brain metastasis are attributable to non-neurologic causes, particularly for patients with limited (<4) brain metastasis.[53,54]

The use of focal therapy alone in the management of brain metastasis incurs the increased risk of distant intracranial failure compared with patients receiving whole-brain RT (WBRT).[53] In patients treated with single-fraction SRS or fractionated SRS, single metastasis and supratentorial location were associated with reduced risk of subsequent intracranial lesions.[55] For patients with a high intracranial disease burden, the benefit of additional whole-brain radiation in the setting of SRS has been suggested in select studies for patients with adequate performance status.[41,51] Despite this, given the cognitive sequelae of adding WBRT to SRS[56] and the success of salvage SRS,[57] WBRT is typically reserved for patients who cannot tolerate SRS or those with a high burden of intracranial disease or extensive intracranial relapse after initial SRS. Alternatively, for patients with a limited number of large, symptomatic, surgically accessible lesions, surgical metastasectomy with postoperative SRS can be considered for patients with good performance status.[58] For this patient population, preoperative SRS is an area of active study to reduce the rates of relapse with leptomeningeal disease after surgery and postoperative SRS.[59]

SRS for brain metastasis from mRCC is well tolerated, although there is evidence that SRS in combination with common systemic agents for SRS may increase toxicity. A series of 912 lesions treated with SRS showed that use of a tyrosine kinase inhibitor (TKI) within 30 days of SRS caused a significantly greater rate of radionecrosis (RN) (10.9% vs 6.4%),[60] although generally these rates are lower than the risk of RN in other series, which is reported to be approximately 17.2% at 1 year.[61] However, in combination with immune checkpoint inhibitors (ICIs), SRS carries a greater risk of symptomatic RN with a doubling of the incidence from 20% to 40% at approximately 3 years from treatment of patients on ICI.[62] Despite these risks, SRS for RCC is routine even in the setting of ICI given the excellent control rates and ability to control RN symptoms with supportive medications,[63] laser coagulation,[64] or surgery[65] for more severe cases.

SRS is an important tool in the management of brain metastasis from RCC. Most patients needing SRS have excellent local control with minimal toxicity. Surveillance MRI is warranted to assess for disease progression because distant intracranial failure requiring salvage therapy is common. Monitoring for neurologic symptoms after SRS is important for the early detection and treatment of RN, the rate of which is increased when combining SRS with TKI and especially ICI.

Spine Stereotactic Body Radiation Therapy

Bone is the second most common site of metastasis in patients with mRCC, with approximately 27% of patients diagnosed with bone metastasis at initial evaluation and 18% of patients with recurrent RCC recurring in the bone.[66,67] Among bone metastasis, the spine is the most frequently involved site,[66] with pain being the most frequently reported symptom.[68] Although surgery is indicated for select patients for spine stabilization, operative morbidity and complications with intraoperative blood loss may be significant.[69] Thus, SBRT is an alternate, noninvasive therapeutic tool that has shown promising local control rates with minimal toxicity in the prospective setting.[70–72]

One of the earliest prospective studies of SBRT for spine metastases from RCC evaluated single-fraction SBRT for 60 spine lesions, 70% of which were previously treated with conventional radiation therapy. With tumor doses ranging from 17.5 to 25 Gy in a single fraction and a median follow-up of 37 months, no radiation-induced toxicity was observed, 89% of lesions treated for pain (34 out of 38) had improvements in pain, and local control rate for tumors treated for radiographic progression was 88% (7 out of 8).[71] Similar outcomes were reported in a study by Nguyen and

Table 1
Studies evaluating stereotactic radiosurgery and stereotactic body radiation therapy in metastatic renal cell carcinoma

Author (Year)	Patients (Number of Lesions)	Sites Treated	Marginal Dose in Gy (Range)	Median Follow-up (mo)	1-y LC (%)	Toxicity
Schöggl et al,[88] 1998	23 (44)	Brain	Median 18 (8–30)	NR	NR (crude rate 100)	9% peritumoral edema 4% radionecrosis
Goyal et al,[41] 2000	29 (66)	Brain	Median 18 (7–24)	7	85	14% radiation necrosis
Payne et al,[47] 2000	21 (37)	Brain	Mean 20 (11–40)	NR	NR (crude rate 100)	0% radiation toxicity
Amendola et al,[40] 2000	22 (131)	Brain	Mean 18 (15–22); unknown whether marginal	NR	NR (crude rate 91)	5% radiation necrosis
Ikushima et al,[44] 2000	10 (24)	Brain	All 42 Gy in 7 fractions to isocenter	5	90	0% acute or late toxicity
Hernandez et al,[42] 2002	29 (92)	Brain	Median 17 (13–30)	7	100	NR
Hoshi et al,[43] 2002	42 (113)	Brain	Median 25 (20–30)	10	91	1 mortality secondary to tumor hemorrhage
Noel et al,[46] 2004	28 (65)	Brain	Median 17 (11–22) to isocenter	14	93	4% radionecrosis 4% seizure 4% tumor hemorrhage
Muacevic et al,[50] 2004	85 (376)	Brain	Median 21 (15–35)	11	94	4% grade V toxicity caused by tumor hemorrhage 13% symptomatic radiation toxicity
Samlowski et al,[48] 2008	32 (71)	Brain	NR (15–24)	NR	86	6% symptomatic radiation necrosis
Shuto et al,[49] 2010	105 (444)	Brain	Mean 22 (8–30)	7	71	2% tumor hemorrhage requiring surgery 5% peritumoral edema

Fokas et al,[51] 2010	68 (81)	Brain	Median 19 (15–22)	NR	83	2% grade III acute toxicity with SRS only, 3% with SRS + WBRT, overall 3% acute toxicity 4% grade III late toxicity with SRS only, 5% with SRS + WBRT, overall 6% late toxicity
Kano et al,[45] 2011	158 (531)	Brain	Median 18 (10–22)	8	87	7% symptomatic adverse effects 6% tumor hemorrhage
Staehler et al,[8] 2011	51 (135)	Brain	Median 20 (20–20)	16	100	4% grade II tumor hemorrhage 6% grade II convulsions
Cochran et al,[6] 2012	61 (124)	Brain	Median 20 (13–24)	9	93	10% radiation-induced edema or necrosis 3% hemorrhage
Kim et al,[89] 2012	46 (99)	Brain	Mean 21 (12–25)	NR	NR (crude rate 85)	2% symptomatic tumor hemorrhage 2% hydrocephalus
Meyer et al,[52] 2018[a]	82 (120)	Brain	Median BED_3 75.1 Gy (SD 21.2)	13	82	Including extracranial metastasis 50% grade I–II toxicity (asthenia, nausea, dyspnea, headache) 5% grade III toxicity (esophageal fistula, seizure, intratumoral hemorrhage, and increased ICP)
Stenman et al,[90] 2018[a]	31 (167)	Brain	Median 22 Gy (16.5–35.5)	63 (for all patients)	NR (crude rate 96)	NR for entire cohort For all patients receiving targeted agents, 30% grade II–III toxicity (seizure, fatigue, pneumonitis most common)

(*continued on next page*)

Table 1
(*continued*)

Author (Year)	Patients (Number of Lesions)	Sites Treated	Marginal Dose in Gy (Range)	Median Follow-up (mo)	1-y LC (%)	Toxicity
Gerszten et al,[71] 2005	48 (60)	Spine	Mean 16 Gy in 1 fraction	37	96	0% radiation toxicity
Wersall et al,[80] 2005	50 (154)	117 lung, 6 adrenal gland, 12 kidney metastases, 5 thoracic wall, 4 bone, 3 mediastinum, 3 abdominal lymph gland, 2 liver, 1 spleen, 1 pancreas	Modal: 32 Gy in 4 fractions, 40 Gy in 4 fractions, and 45 Gy in 3 fractions	37	99	40% any toxicity 2% grade V toxicity
Svedman et al,[13] 2006	26 (77)	63 lung/mediastinum, 5 kidney metastases, 5 adrenal, 4 thoracic wall, 3 abdominal glands, 3 liver, 1 pelvis, 1 spleen	40 Gy in 4 fractions	52	100	58% grade I–II toxicity 4% Grade V toxicity
Teh et al,[14] 2007	14 (23)	Orbits, head and neck, lung, mediastinum, sternum, clavicle, scapula, humerus, rib, spine, abdominal wall	Modal 24 Gy in 3 fractions	9	81	No grade 2 or higher toxicity
Nguyen et al,[72] 2010	48 (55)	Spine	Modal 27 Gy in 3 fractions	13	80	No grade 3 or 4 neurologic toxicity 23% grade I fatigue 13% grade II fatigue 11% grade II nausea 7% grade II vomiting 2% grade III pain 2% grade III anemia
Staehler et al,[8] 2011	55 (105)	Spine	Median 20 Gy in 1 fraction	33	94	2% grade I abdominal pain
Balagamwala et al,[10] 2012	57 (88)	Spine	Median 15 Gy in 1 fraction (unknown whether marginal)	5	50	33% any toxicity 10.5% grade 1 fatigue 2% grade 3 nausea/vomiting 8% pain flare

Jhaveri et al,[11] 2012	18 (24)	14 spine, 4 ribs/clavicle, 6 pelvis	Modal 40 Gy in 5 fractions	10	NR	6% grade I toxicity
Zelefsky et al,[12] 2012	55 (105)	59 spine, 22 pelvic bones, 14 other, 9 femur, 1 lymph node	Modal 24 Gy in 1 fraction	12	72	4% grade 2 dermatitis 7% fractures 2% grade 4 erythema
Ranck et al,[81] 2013	18 (39)	11 bone, 10 abdominal lymph node, 7 mediastinum/hilum, 4 lung, 2 kidney metastases, 2 adrenal, 2 liver, 1 soft tissue	Modal 50 Gy in 10 fractions, (unknown whether marginal)	16	96	61% grade I fatigue 11% grade 1 rib fracture 6% grade 2 radiculitis 6% grade 2 bone pain
Wang et al,[73] 2017	84 (184)	49 abdomen, 42 spine, 35 thorax, 25 nonspine, 16 soft tissue, 5 kidney, 3 spinal cord	Median 11 Gy in median 3 fractions	16	91	4% acute grade 3 toxicity (progressive pain and UTI) 2% late grade 3 toxicity (gastrointestinal bleed, compression fracture, and radiculopathy)
Meyer et al,[52] 2018[a]	109 (132)	75 spine, 11 nonspine bone and soft tissue, 46 visceral metastases	Median BED_3 90.6 Gy (SD 55.1) including brain metastasis	13	84	Including brain metastasis 50% grade I–II toxicity (asthenia, nausea, dyspnea, headache) 5% grade III toxicity (esophageal fistula, seizure, intratumoral hemorrhage, and increased ICP)
Stenman et al,[90] 2018[a]	65 (117)	68 lung, 18 lymph node, 7 adrenal, 5 kidney, 5 liver, 5 soft tissue, 4 bone, 4 local recurrence, 1 other	Modal 45 Gy in 3 fractions, unknown whether marginal)	63 (for all patients)	NR (crude rate 76)	NR for entire cohort For all patients receiving targeted agents, 30% grade II–III toxicity (seizure, fatigue, pneumonitis most common)
Franzese et al,[91] 2019	58 (73)	39 lungs, 19 lymph nodes, 7 bone, 5 adrenal, 3 liver	Median 45 Gy in 5 fractions	16	90	12% acute grade 1 toxicity (fatigue, pain, and nausea) 7% late grade 1–2 pneumonitis

Abbreviations: ICP, intracranial pressure; NR, not reported; SD, standard deviation; UTI, urinary tract infection; WBRT, whole-brain radiotherapy.

[a] Brain and extra–central nervous system metastasis are reported in separate rows.

Adapted from Kothari G, Foroudi F, Gill S, Corcoran NM, Siva S. Outcomes of stereotactic radiotherapy for cranial and extracranial metastatic renal cell carcinoma: a systematic review. Acta Oncol. 2015;54(2):148-157 and Zaorsky NG, Lehrer EJ, Kothari G, Louie AV, Siva S. Stereotactic ablative radiation therapy for oligometastatic renal cell carcinoma (SABR ORCA): a meta-analysis of 28 studies. European Urology Oncology. 2019;2(5):515-523.

colleagues,[72] who evaluated outcomes after treatment of 55 spinal lesions with several SBRT regimens: 24 Gy in 1 fraction, 27 Gy in 3 fractions, or 30 Gy in 5 fractions. At 1 year, progression-free survival (PFS) was 82% with no high-grade neurologic toxicity observed, and there was pain resolution in 52% of patients. With the varying dose fractionation regimens of spine SBRT used in prior studies, 2 studies compared single versus multifraction regimens. A single fraction of 24 Gy had improved local control compared with single-fraction doses less than 24 Gy or multifraction regimens of 20 to 30 Gy in 3 to 5 fractions, attributed to a higher biologically effective dose (BED).[12,70] Additional retrospective studies provide evidence supporting spine SBRT for RCC with local control ranging from 72% to 96% at 1 year with differences primarily driven by dose and fractionation.[8,10,12,73] In addition, systemic therapy activity likely affects the efficacy of spine SBRT for RCC metastasis because 1 retrospective study reported an independent association of concurrent TKI with improved local control.[74]

In summary, SBRT is shown to be well tolerated with minimal toxicities and favorable outcomes in terms of pain relief and local control. Patient selection for spine SBRT is key, and ideal candidates have at least a 3-month life expectancy, adequate performance status, low epidural disease grade, with involvement of a maximum of 2 to 3 contiguous or noncontiguous spinal segments, no frank spinal cord compression, and the ability to lie flat and tolerate the treatment.[75] For patients who are not candidates for SBRT but may benefit from palliative treatment of spinal metastasis, conventionally fractionated RT (ie, 30 Gy in 10 fractions) can be delivered, although this treatment strategy is less effective than SBRT.[76]

Management of Other Sites of Metastatic Disease

Outside of the central nervous system and spine, RT has a role in the palliation and local control of RCC metastasis to bone and visceral sites, and as well as treatment of the primary tumor in patients with mRCC. Patients with pain from RCC skeletal metastasis have been shown to have significant pain response to both fractionated RT[77] and SBRT.[78] A phase II trial of palliative RT for mRCC treated 24 patients for bone pain to 30 Gy in 10 fractions and showed that 83% of patients experienced site-specific pain relief after RT, although with a varied duration of response (median 3 months, range 1–15 months). However, this study may be limited because, since the time of publication in 2005, more effective systemic regimens have emerged which may affect local control and thus pain response. A more recent study from 2018 retrospectively reviewed outcomes of patients with skeletal metastasis from RCC treated with fractionated RT, mostly 30 Gy in 10 fractions. Fifty-three sites were palliated in 40 total patients, with pain control achieved in 73.6% of lesions with a median duration of pain response of 22.9 months.[77]

More recently, SBRT has been evaluated in the palliation and local control of painful bone metastases. The biological rationale for this makes particular sense for RCC, because historical in vitro studies showed relative radioresistance of RCC[5] and a retrospective review showed increased pain response rates with higher BED.[79] A retrospective review comparing patients receiving either SBRT (most common dose 27 Gy in 3 fractions) or fractionated RT (most common dose 20 Gy in 5 fractions) to painful bony metastasis from RCC showed greater efficacy with SBRT. Symptom control rates were approximately twice as high and more durable for patients receiving SBRT versus fractionated RT, with 1-year rates of 74.9% versus 39.9% and 2-year rates of 74.9% versus 35.7%. Furthermore, on multivariable analysis, BED greater than or equal to 80 was significantly associated with improved clinical response, radiographic response, and local control.[78] These results are corroborated by another report showing high BED (in this case >85 Gy) leading to faster and more durable pain relief compared with lower BED.[11]

SBRT has also proved effective for the management of visceral metastases from RCC, with a prospective study evaluating 77 target lesions showing 100% local control at 1 year with minimal toxicity.[13] Additional retrospective reviews of SBRT in this setting have shown relief of pain correlating to the treated metastatic sites and local control of 72% to 99% at 1 year.[12,14,80–82]

There have been several studies evaluating SBRT to the primary tumor in patients with mRCC as well. One study retrospectively reviewed the outcomes of SBRT to the primary tumor in patients with RCC and included 6 patients with mRCC.[26] The local control was reported to be 100%, but the rationale for treating these patients was not reported; presumably the patients were symptomatic with pain and/or hematuria. The investigators do report that all 4 patients in this series that had flank pain and/or hematuria before RT had resolution of their symptoms after RT, suggesting a palliative benefit to SBRT for LA disease in select patients. A pilot study from Roswell Park Cancer Institute examined cytoreductive nephrectomy specimens after neoadjuvant SBRT in

patients with mRCC. Compared with archived RCC tumors without neoadjuvant RT, the SBRT-treated tumors had evidence of immunomodulation with higher expression of calreticulin and tumor-associated antigens, and a higher percentage of proliferating T cells.[83] These data suggest that SBRT to the primary RCC tumor in patients with mRCC has the potential to affect the efficacy of immunotherapeutic agents given this altered tumor microenvironment.

COMBINATION OF RADIOTHERAPY WITH SYSTEMIC THERAPY AND FUTURE DIRECTIONS

It is clear that RT has a role in palliation of LA RCC and mRCC, and that SBRT and SRS have the ability to provide excellent local control to the primary tumor as well as metastatic sites with limited toxicity. However, strategies to optimally combine RT with systemic therapy in an effort to improve survival outcomes is a topic of active study. The current efforts can be conceptually broken down into 2 scenarios: treatment of oligometastatic patients (typically with 1–5 total sites of disease) and treatment of oligoprogressive patients (typically with 1–5 progressing sites of disease with any number of metastases). In patients with oligoprogressive disease, SBRT is being evaluated as a noninvasive measure of eliminating clones that have become resistant to systemic therapy. In patients with oligometastatic disease, SBRT has been evaluated as a way to defer systemic therapy and/or improve PFS.

Table 2
Current trials involving immunotherapy in combination with stereotactic body radiation therapy in metastatic renal cell carcinoma

NCT Number	Study Phase	SBRT Dose and Fractionation	Intervention in Combination with SBRT	Estimated Enrollment	Expected Primary Completion Date
NCT01896271	Single-arm phase II	8–20 Gy in 1–3 fractions	High-dose IL-2	26	12/2019
NCT02306954	Randomized phase II	40 Gy in 2 fractions	High-dose IL-2	84	01/2020
NCT01884961	Single-arm phase II	18–36 Gy in 3 fractions	High-dose IL-2	35	06/2019
NCT03474497	Single-arm phase II	24 Gy in 3 fractions	Intralesional IL-2 and pembrolizumab	45	07/2021
NCT03065179	Single-arm phase II	Not specified	Ipilimumab and nivolumab	25	01/2020
NCT02781506	Single-arm phase II	Dose not specified, 1–3 fractions	Nivolumab	87	12/2020
NCT02855203	phase I/II	18–20 Gy in 1 fraction	Pembrolizumab	30	07/2020
NCT02318771	phase I	20 Gy in 5 fractions or 8 Gy in 1 fraction	Pembrolizumab	40	12/2019
NCT02599779	phase II	Not specified	Pembrolizumab	25	03/2020
NCT03115801	Randomized phase II	30 Gy in 3 fractions	Nivolumab	112	12/2020
NCT03511391	Randomized phase II	24 Gy in 3 fractions	Pembrolizumab or nivolumab	97	02/2022
NCT03050060	Single-arm phase II	Not specified	Nelfinavir and pembrolizumab, nivolumab, or atezolizumab	120	12/2021

Abbreviations: IL, interleukin; NCT, National Clinical Trial.

One major study from the Groupe d'étude des tumeurs urogénitales (GETUG) retrospectively evaluated the outcomes of 188 oligometastatic and oligoprogressive patients with mRCC treated with SBRT to 1 to 5 sites. A total of 101 patients received SBRT for oligoprogressive mRCC, mostly while on first-line therapy with TKIs, and these patients showed a median PFS of 8.6 months from the time of SBRT to all sites of progression. The 63 patients who presented with oligometastatic disease were treated exclusively with SBRT and no systemic therapy; approximately one-third of these patients did not relapse at the end of follow-up (median follow-up of 15 months), with a median time to systemic therapy initiation of 14.2 months.[52] In line with this are findings from Zhang and colleagues,[84] where SBRT was used to defer systemic therapy in patients with oligometastatic RCC. In their retrospective review of a prospective database, 47 patients were identified, ~75% of whom had a single site of metastatic disease, most commonly to bone. The median time from SBRT to the start of systemic therapy was 15.2 months, and almost 40% of patients received no systemic therapy and were alive after SBRT at a median follow-up of 25 months.[84]

These promising studies show that, for select patients with mRCC, it is possible that aggressive local therapy can delay systemic therapy for treatment-naive patients and prevent changing systemic therapy in patients with oligoprogressive disease who may still be experiencing systemic benefit from their current therapy. Compared with other forms of local therapy, such as surgery and thermal ablation techniques, SBRT is noninvasive and causes minimal, if any, delay in the systemic therapy schedule, which remains the backbone of therapy for patients with widely metastatic disease.

Because 2 first-line systemic regimens for mRCC now include ICI (combination ipilimumab/nivolumab and pembrolizumab/axitinib), many groups are interested in combining SBRT with ICI to evaluate whether SBRT can potentiate the systemic response to immunotherapy given the known immunomodulatory effects of SBRT[83] and reports on abscopal response in patients with mRCC treated with RT.[85,86] There have been more than a dozen trials initiated combining SBRT with ICI and other immuno-oncology agents in patients with mRCC,[87] which are described in **Table 2**. The results of these trials are awaited to help define the utility of SBRT in combination with ICI for patients with mRCC.

SUMMARY

With the advent of high-dose-per-fraction RT techniques, namely SRS and SBRT, the role of RT in RCC is increasing. RT can be considered for palliation and local control of patients with LA RCC tumors who are not operative candidates, as well as palliation and local control of intracranial and extracranial metastases. Current research is focused on the use of SBRT in patients receiving immunotherapeutic agents in an effort to improve survival outcomes.

REFERENCES

1. van der Werf-Messing B. Carcinoma of the kidney. Cancer 1973;32(5):1056–61.
2. Juusela H, Malmio K, Alfthan O, et al. Preoperative irradiation in the treatment of renal adenocarcinoma. Scand J Urol Nephrol 1977;11(3):277–81.
3. Finney R. The value of radiotherapy in the treatment of hypernephroma–a clinical trial. Br J Urol 1973; 45(3):258–69.
4. Kjaer M, Iversen P, Hvidt V, et al. A randomized trial of postoperative radiotherapy versus observation in stage II and III renal adenocarcinoma. A study by the Copenhagen Renal Cancer Study Group. Scand J Urol Nephrol 1987; 21(4):285–9.
5. Deschavanne PJ, Fertil B. A review of human cell radiosensitivity in vitro. Int J Radiat Oncol Biol Phys 1996;34(1):251–66.
6. Cochran DC, Chan MD, Aklilu M, et al. The effect of targeted agents on outcomes in patients with brain metastases from renal cell carcinoma treated with Gamma Knife surgery. J Neurosurg 2012;116(5): 978–83.
7. Kim YH, Kim JW, Chung HT, et al. Brain metastasis from renal cell carcinoma. Prog Neurol Surg 2012; 25:163–75.
8. Staehler M, Haseke N, Nuhn P, et al. Simultaneous anti-angiogenic therapy and single-fraction radiosurgery in clinically relevant metastases from renal cell carcinoma. BJU Int 2011;108(5):673–8.
9. Kothari G, Foroudi F, Gill S, et al. Outcomes of stereotactic radiotherapy for cranial and extracranial metastatic renal cell carcinoma: a systematic review. Acta Oncol 2015;54(2):148–57.
10. Balagamwala EH, Angelov L, Koyfman SA, et al. Single-fraction stereotactic body radiotherapy for spinal metastases from renal cell carcinoma. J Neurosurg Spine 2012;17(6):556–64.
11. Jhaveri PM, Teh BS, Paulino AC, et al. A dose-response relationship for time to bone pain resolution after stereotactic body radiotherapy (SBRT) for renal cell carcinoma (RCC) bony metastases. Acta Oncol 2012;51(5):584–8.

12. Zelefsky MJ, Greco C, Motzer R, et al. Tumor control outcomes after hypofractionated and single-dose stereotactic image-guided intensity-modulated radiotherapy for extracranial metastases from renal cell carcinoma. Int J Radiat Oncol Biol Phys 2012; 82(5):1744–8.
13. 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(7):870–5.
14. Teh B, Bloch C, Galli-Guevara M, et al. The treatment of primary and metastatic renal cell carcinoma (RCC) with image-guided stereotactic body radiation therapy (SBRT). Biomed Imaging Interv J 2007;3(1):e6.
15. Corbin KS, Ranck MC, Hasselle MD, et al. Feasibility and toxicity of hypofractionated image guided radiation therapy for large volume limited metastatic disease. Pract Radiat Oncol 2013;3(4):316–22.
16. Miccio J, Johung K. When surgery is not an option in renal cell carcinoma: the evolving role of stereotactic body radiation therapy. Oncology (Williston Park) 2019;33(5):167–73, 177.
17. Staehler M, Bader M, Schlenker B, et al. Single fraction radiosurgery for the treatment of renal tumors. J Urol 2015;193(3):771–5.
18. Siva S, Pham DJ, Tan TH, et al. Principal analysis of a phase ib trial of stereotactic body radiation therapy (SBRT) for primary kidney cancer. Int J Radiat Oncol Biol Phys 2016;96(2):S96.
19. McBride SM, Wagner AA, Kaplan ID. A phase 1 dose-escalation study of robotic radiosurgery in inoperable primary renal cell carcinoma. Int J Radiat Oncol Biol Phys 2013;87(2):S84.
20. Ponsky L, Lo SS, Zhang Y, et al. Phase I dose-escalation study of stereotactic body radiotherapy (SBRT) for poor surgical candidates with localized renal cell carcinoma. Radiother Oncol 2015;117(1): 183–7.
21. Kaplan ID, Redrosa I, Martin C, et al. Results of a Phase I Dose Escalation Study of Stereotactic Radiosurgery for Primary Renal Tumors. Int J Radiat Oncol Biol Phys 2010;78(3):S191.
22. Pham D, Thompson A, Kron T, et al. Stereotactic ablative body radiation therapy for primary kidney cancer: a 3-dimensional conformal technique associated with low rates of early toxicity. Int J Radiat Oncol Biol Phys 2014;90(5):1061–8.
23. Siva S, Pham D, Kron T, et al. Stereotactic ablative body radiotherapy for inoperable primary kidney cancer: a prospective clinical trial. BJU Int 2017; 120(5):623–30.
24. Correa RJM, Louie AV, Zaorsky NG, et al. The emerging role of stereotactic ablative radiotherapy for primary renal cell carcinoma: a systematic review and meta-analysis. Eur Urol Focus 2019;5(6): 958–69.
25. Kaidar-Person O, Price A, Schreiber E, et al. Stereotactic body radiotherapy for large primary renal cell carcinoma. Clin Genitourin Cancer 2017;15(5): e851–4.
26. Chang JH, Cheung P, Erler D, et al. Stereotactic ablative body radiotherapy for primary renal cell carcinoma in non-surgical candidates: initial clinical experience. Clin Oncol 2016;28(9):e109–14.
27. Wang YJ, Han TT, Xue JX, et al. Stereotactic gamma-ray body radiation therapy for asynchronous bilateral renal cell carcinoma. Radiol Med 2014;119(11):878–83.
28. Tunio MA, Hashmi A, Rafi M. Need for a new trial to evaluate postoperative radiotherapy in renal cell carcinoma: a meta-analysis of randomized controlled trials. Ann Oncol 2010;21(9):1839–45.
29. Nikolaev A, Benda R. Palliative radiation therapy for symptomatic control of inoperable renal cell carcinoma. Urol Case Rep 2015;4:51–2.
30. Surveillance E, and End Results Program. Cancer Stat FActs: Kidney and Renal Pelvis Cancer. 2019. Available at: https://seer.cancer.gov/statfacts/html/kidrp.html. Accessed November 25, 2019.
31. Otaibi MA, Tanguay S. Locally advanced renal cell carcinoma. Can Urol Assoc J 2007;1(2 Suppl): S55–61.
32. Janzen NK, Kim HL, Figlin RA, et al. Surveillance after radical or partial nephrectomy for localized renal cell carcinoma and management of recurrent disease. Urol Clin North Am 2003;30(4):843–52.
33. Pilar A, Gupta M, Ghosh Laskar S, et al. Intraoperative radiotherapy: review of techniques and results. Ecancermedicalscience 2017;11:750.
34. Calvo FA, Sole CV, Martinez-Monge R, et al. Intraoperative EBRT and resection for renal cell carcinoma: twenty-year outcomes. Strahlenther Onkol 2013;189(2):129–36.
35. Paly JJ, Hallemeier CL, Biggs PJ, et al. Outcomes in a multi-institutional cohort of patients treated with intraoperative radiation therapy for advanced or recurrent renal cell carcinoma. Int J Radiat Oncol Biol Phys 2014;88(3):618–23.
36. Wegner RE, Abel S, Vemana G, et al. Utilization of stereotactic ablative body radiation therapy for intact renal cell carcinoma: trends in treatment and predictors of outcome. Adv Radiat Oncol 2019; 5(1):85–91.
37. Bianchi M, Sun M, Jeldres C, et al. Distribution of metastatic sites in renal cell carcinoma: a population-based analysis. Ann Oncol 2011;23(4):973–80.
38. Sun M, De Velasco G, Brastianos PK, et al. The development of brain metastases in patients with renal cell carcinoma: epidemiologic trends, survival, and clinical risk factors using a population-based cohort. Eur Urol Focus 2019;5(3):474–81.
39. Haque W, Verma V, Butler EB, et al. Utilization of stereotactic radiosurgery for renal cell carcinoma brain

metastases. Clin Genitourin Cancer 2018;16(4): e935–43.
40. Amendola BE, Wolf AL, Coy SR, et al. Brain metastases in renal cell carcinoma: management with gamma knife radiosurgery. Cancer J 2000;6(6): 372–6.
41. Goyal LK, Suh JH, Reddy CA, et al. The role of whole brain radiotherapy and stereotactic radiosurgery on brain metastases from renal cell carcinoma. Int J Radiat Oncol Biol Phys 2000;47(4):1007–12.
42. Hernandez L, Zamorano L, Sloan A, et al. Gamma knife radiosurgery for renal cell carcinoma brain metastases. J Neurosurg 2002;97(5 Suppl): 489–93.
43. Hoshi S, Jokura H, Nakamura H, et al. Gamma-knife radiosurgery for brain metastasis of renal cell carcinoma: Results in 42 patients. Int J Urol 2002;9(11): 618–25.
44. Ikushima H, Tokuuye K, Sumi M, et al. Fractionated stereotactic radiotherapy of brain metastases from renal cell carcinoma. Int J Radiat Oncol Biol Phys 2000;48(5):1389–93.
45. Kano H, Iyer A, Kondziolka D, et al. Outcome predictors of gamma knife radiosurgery for renal cell carcinoma metastases. Neurosurgery 2011;69(6): 1232–9.
46. Noel G, Valery CA, Boisserie G, et al. LINAC radiosurgery for brain metastasis of renal cell carcinoma. Urol Oncol 2004;22(1):25–31.
47. Payne BR, Prasad D, Szeifert G, et al. Gamma surgery for intracranial metastases from renal cell carcinoma. J Neurosurg 2000;92(5):760–5.
48. Samlowski WE, Majer M, Boucher KM, et al. Multidisciplinary treatment of brain metastases derived from clear cell renal cancer incorporating stereotactic radiosurgery. Cancer 2008;113(9):2539–48.
49. Shuto T, Matsunaga S, Suenaga J, et al. Treatment strategy for metastatic brain tumors from renal cell carcinoma: selection of gamma knife surgery or craniotomy for control of growth and peritumoral edema. J Neurooncol 2010;98(2):169–75.
50. Muacevic A, Kreth FW, Mack A, et al. Stereotactic radiosurgery without radiation therapy providing high local tumor control of multiple brain metastases from renal cell carcinoma. Minim Invasive Neurosurg 2004;47(4):203–8.
51. Fokas E, Henzel M, Hamm K, et al. Radiotherapy for brain metastases from renal cell cancer: should whole-brain radiotherapy be added to stereotactic radiosurgery?: analysis of 88 patients. Strahlenther Onkol 2010;186(4):210–7.
52. Meyer E, Pasquier D, Bernadou G, et al. Stereotactic radiation therapy in the strategy of treatment of metastatic renal cell carcinoma: A study of the Getug group. Eur J Cancer 2018;98:38–47.
53. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. J Clin Oncol 2011;29(2):134–41.
54. McTyre ER, Johnson AG, Ruiz J, et al. Predictors of neurologic and nonneurologic death in patients with brain metastasis initially treated with upfront stereotactic radiosurgery without whole-brain radiation therapy. Neuro Oncol 2017;19(4):558–66.
55. Rades D, Dziggel L, Blanck O, et al. Predicting the risk of developing new cerebral lesions after stereotactic radiosurgery or fractionated stereotactic radiotherapy for brain metastases from renal cell carcinoma. Anticancer Res 2018;38(5):2973–6.
56. Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical TrialSRS with or without WBRT and cognitive function in patients with brain MetastasesSRS with or without WBRT and cognitive function in patients with brain metastases. JAMA 2016;316(4):401–9.
57. Fritz C, Borsky K, Stark LS, et al. Repeated courses of radiosurgery for new brain metastases to defer whole brain radiotherapy: feasibility and outcome with validation of the new prognostic metric brain metastasis velocity. Front Oncol 2018;8:551.
58. Choi CY, Chang SD, Gibbs IC, et al. Stereotactic radiosurgery of the postoperative resection cavity for brain metastases: prospective evaluation of target margin on tumor control. Int J Radiat Oncol Biol Phys 2012;84(2):336–42.
59. Prabhu RS, Patel KR, Press RH, et al. Preoperative vs postoperative radiosurgery for resected brain metastases: a review. Neurosurgery 2018;84(1): 19–29.
60. Juloori A, Miller JA, Parsai S, et al. Overall survival and response to radiation and targeted therapies among patients with renal cell carcinoma brain metastases. J Neurosurg 2019;1–9. https://doi.org/10.3171/2018.8.JNS182100.
61. Kohutek ZA, Yamada Y, Chan TA, et al. Long-term risk of radionecrosis and imaging changes after stereotactic radiosurgery for brain metastases. J Neurooncol 2015;125(1):149–56.
62. Martin AM, Cagney DN, Catalano PJ, et al. Immunotherapy and symptomatic radiation necrosis in patients with brain metastases treated with stereotactic radiation. JAMA Oncol 2018;4(8): 1123–4.
63. Vellayappan B, Tan CL, Yong C, et al. Diagnosis and management of radiation necrosis in patients with brain metastases. Front Oncol 2018;8:395.
64. Sharma M, Balasubramanian S, Silva D, et al. Laser interstitial thermal therapy in the management of brain metastasis and radiation necrosis after radiosurgery: An overview. Expert Rev Neurother 2016; 16(2):223–32.

65. Patel U, Patel A, Cobb C, et al. The management of brain necrosis as a result of SRS treatment for intracranial tumors. Transl Cancer Res 2014;3(4):373–82.
66. Swanson DA, Orovan WL, Johnson DE, et al. Osseous metastases secondary to renal cell carcinoma. Urology 1981;18(6):556–61.
67. Levy DA, Slaton JW, Swanson DA, et al. Stage specific guidelines for surveillance after radical nephrectomy for local renal cell carcinoma. J Urol 1998;159(4):1163–7.
68. Kassamali RH, Ganeshan A, Hoey ETD, et al. Pain management in spinal metastases: the role of percutaneous vertebral augmentation. Ann Oncol 2010; 22(4):782–6.
69. Sundaresan N, Choi IS, Hughes JE, et al. Treatment of spinal metastases from kidney cancer by presurgical embolization and resection. J Neurosurg 1990; 73(4):548–54.
70. Ghia AJ, Chang EL, Bishop AJ, et al. Single-fraction versus multifraction spinal stereotactic radiosurgery for spinal metastases from renal cell carcinoma: secondary analysis of Phase I/II trials. J Neurosurg Spine 2016;24(5):829–36.
71. Gerszten PC, Burton SA, Ozhasoglu C, et al. Stereotactic radiosurgery for spinal metastases from renal cell carcinoma. J Neurosurg Spine 2005;3(4): 288–95.
72. Nguyen QN, Shiu AS, Rhines LD, et al. Management of spinal metastases from renal cell carcinoma using stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys 2010;76(4):1185–92.
73. Wang CJ, Christie A, Lin MH, et al. Safety and efficacy of stereotactic ablative radiation therapy for renal cell carcinoma extracranial metastases. Int J Radiat Oncol Biol Phys 2017;98(1):91–100.
74. Miller JA, Balagamwala EH, Angelov L, et al. Spine stereotactic radiosurgery with concurrent tyrosine kinase inhibitors for metastatic renal cell carcinoma. J Neurosurg Spine 2016;25(6):766–74.
75. Kumar R, Nater A, Hashmi A, et al. The era of stereotactic body radiotherapy for spinal metastases and the multidisciplinary management of complex cases. Neurooncol Pract 2015;3(1):48–58.
76. Sohn S, Chung CK, Sohn MJ, et al. Stereotactic radiosurgery compared with external radiation therapy as a primary treatment in spine metastasis from renal cell carcinoma: a multicenter, matched-pair study. J Neurooncol 2014;119(1):121–8.
77. Ganju RG, TenNapel M, Mahan N, et al. The efficacy of conventionally fractionated radiation in the management of osseous metastases from metastatic renal cell carcinoma. J Oncol 2018;2018:6384253.
78. Amini A, Altoos B, Bourlon MT, et al. Local control rates of metastatic renal cell carcinoma (RCC) to the bone using stereotactic body radiation therapy: Is RCC truly radioresistant? Pract Radiat Oncol 2015;5(6):e589–96.
79. DiBiase SJ, Valicenti RK, Schultz D, et al. Palliative irradiation for focally symptomatic metastatic renal cell carcinoma: support for dose escalation based on a biological model. J Urol 1997;158(3 Pt 1): 746–9.
80. Wersall PJ, Blomgren H, Lax I, et al. Extracranial stereotactic radiotherapy for primary and metastatic renal cell carcinoma. Radiother Oncol 2005;77(1): 88–95.
81. Ranck MC, Golden DW, Corbin KS, et al. Stereotactic body radiotherapy for the treatment of oligometastatic renal cell carcinoma. Am J Clin Oncol 2013; 36(6):589–95.
82. Zaorsky NG, Lehrer EJ, Kothari G, et al. Stereotactic ablative radiation therapy for oligometastatic renal cell carcinoma (SABR ORCA): a meta-analysis of 28 studies. Eur Urol Oncol 2019;2(5):515–23.
83. Singh AK, Winslow TB, Kermany MH, et al. A pilot study of stereotactic body radiation therapy combined with cytoreductive nephrectomy for metastatic renal cell carcinoma. Clin Cancer Res 2017;23(17): 5055–65.
84. Zhang Y, Schoenhals J, Christie A, et al. Stereotactic ablative radiation therapy (SAbR) used to defer systemic therapy in oligometastatic renal cell cancer. Int J Radiat Oncol Biol Phys 2019;105(2):367–75.
85. LaPlant Q, Deselm C, Lockney NA, et al. Potential abscopal response to dual checkpoint blockade in RCC after reirradiation using dose-painting SBRT. Pract Radiat Oncol 2017;7(6):396–9.
86. Van de Walle M, Demol J, Staelens L, et al. Abscopal effect in metastatic renal cell carcinoma. Acta Clin Belg 2017;72(4):245–9.
87. Solanki AA, Bossi A, Efstathiou JA, et al. Combining immunotherapy with radiotherapy for the treatment of genitourinary malignancies. Eur Urol Oncol 2019;2(1):79–87.
88. Schöggl A, Kitz K, Ertl A, et al. Gamma-knife radiosurgery for brain metastases of renal cell carcinoma: results in 23 patients. Acta Neurochir (Wien) 1998; 140(6):549–55.
89. Kim WH, Kim DG, Han JH, et al. Early significant tumor volume reduction after radiosurgery in brain metastases from renal cell carcinoma results in long-term survival. Int J Radiat Oncol Biol Phys 2012;82(5):1749–55.
90. Stenman M, Sinclair G, Paavola P, et al. Overall survival after stereotactic radiotherapy or surgical metastasectomy in oligometastatic renal cell carcinoma patients treated at two Swedish centres 2005-2014. Radiother Oncol 2018;127(3):501–6.
91. Franzese C, Franceschini D, Di Brina L, et al. Role of stereotactic body radiation therapy for the management of oligometastatic renal cell carcinoma. J Urol 2019;201(1):70–6.