Kidney Cancer 8 (2024) 45–50
DOI 10.3233/KCA-230020
IOS Press

Review

The Role of Targeted Radiation Therapy in the Treatment of Renal Cell Carcinoma

Albert Lee[a], Karie D. Runcie[b] and James B. Yu[c,d,*]
[a]*Department of Radiation Oncology, Columbia University Irving Medical Center, New York, NY, USA*
[b]*Department of Medical Oncology, Columbia University Irving Medical Center, New York, NY, USA*
[c]*Department of Radiation Oncology, St. Francis Hospital, Hartford, CT, USA*
[d]*Department of Internal Medicine, Section of Medical Oncology, Yale School of Medicine, New Haven, CT, USA*

Received 4 November 2023
Accepted 16 January 2024
Published 16 February 2024

Abstract. Over the past decade, innovations in radiation technology and technique have led to the increasing use of stereotactic body radiotherapy (SBRT) for the treatment of renal cell carcinoma. We provide an overview of SBRT and review the role of SBRT for treatment of localized and oligometastatic RCC. We also provide a brief overview of the current state of knowledge with regards to the combination of SBRT and novel systemic agents commonly used in the treatment of RCC. As outcomes from trials investigating SBRT mature, showing excellent efficacy and tolerability, it is likely that SBRT use will continue to increase in future years.

Keywords: SBRT, renal cell carcinoma, radiotherapy

INTRODUCTION

Over the past decade, innovations in radiation technology and technique have led to the increasing use of stereotactic body radiotherapy (SBRT), otherwise known as stereotactic ablative body radiotherapy (SABR) and stereotactic radiosurgery (SRS) for the treatment of localized cancer noninvasively. SBRT has radiobiological advantages in the treatment of tumors which are otherwise thought to be resistant to radiotherapy delivered with smaller daily doses of radiation. By utilizing larger radiation doses in fewer but more precisely targeted treatments, SBRT can overcome intrinsic resistance to standard doses per treatment.

Renal cell carcinoma presents a unique challenge as well as opportunity for SBRT. Given that the risk factors for RCC include smoking, obesity, hypertension, and chronic kidney disease [1], many patients are not candidates for surgical resection of their tumors due to underlying comorbid illness. SBRT overcomes this challenge by being non-invasive and requiring no anesthesia for treatment. Originally thought to be relatively resistant to standard radiotherapy, recent clinical evidence indicates excellent treatment responses and local control, even for larger tumors that are typically more difficult to ablate with non-radiotherapy technique. Another challenge

*Correspondence to: James B. Yu MD MHS FASTRO, 94 Woodland St., Saint Francis Radiation Oncology, Hartford, CT 06105, USA. Tel.: +1 860 714 4568. E-mail: james.yu@trinityhealthofne.org.

to SBRT treatment of the kidney is the fear of kidney damage with radiation. However, with modern stereotactic technique, the impact on kidney function has been minimized, rarely requiring dialysis after treatment. Finally, for metastatic disease, treatment of tumors should maximize convenience as well as local control, while minimizing toxicity for patients who may be frail or with limited survival. SBRT has been shown much promise in all aspects of metastatic treatment. This manuscript will provide a general review of SBRT for localized and oligometastatic RCC.

STEREOTACTIC BODY RADIATION THERAPY OVERVIEW

Stereotactic body radiation therapy is a radiotherapy technique that aims to deliver doses of 5Gy or greater per fraction [2]. Conventional courses of radiotherapy are typically given in 1.8–2.0Gy per fraction over as many as 7 weeks. The large doses seen per treatment with SBRT can be safely delivered because of the improvement in accuracy of all steps of radiotherapy including simulation, treatment planning, and treatment delivery. These shorter courses achieve greater biologically effective doses (BED) compared to conventional fractionations. Synonymous with SBRT is "Stereotactic Ablative Radiation Therapy (SABR)", so named because of the emphasis on delivering "ablative" doses of radiation. In this review, SBRT and SABR will be used interchangeably.

EVIDENCE FOR SBRT FOR LOCALIZED RCC

The most robust data for the efficacy of SBRT/SABR in localized RCC comes from the International Radiosurgery Oncology Consortium for Kidney (IROCK) [3]. This multi–institutional international consortium examined individual patient data from 12 institutions to assess safety, efficacy, and survival of SABR for primary RCC. In their most recent long term efficacy report, they analyzed data from 190 patient with localized renal cell carcinoma. A majority (75%) of these patients were deemed medically inoperable and median tumor size was 4.0 cm. Single fraction SABR with a median dose of 25Gy accounted for 43% of the treatments, while multifraction SABR with median dose of 42Gy delivered in 2–10 fractions accounted for the other 53%. The primary outcome of cumulative incidence of local failure was 5.5%, 5.5%, and 8.5% at 3 years, 5 years, and 7 years respectively. Cancer specific survival was 95.5%, 92.0%, and 92.0% at 3 years, 5 years, and 7 years respectively. These results are comparable to outcomes following partial nephrectomy and percutaneous ablative therapies despite a cohort determined to be medically inoperable and with tumors typically treated with ablative therapies [4]. The relative efficacy of SABR vs RFA is currently being evaluated in the RADSTER trial (NCT03811665) [5].

The long term IROCK data also demonstrates that SABR is a safe treatment option. 37% of patient experienced grade 1–2 toxicities [3]. There was only one patient with grade 4 toxicity and no grade 5 toxicities. Additionally, eGFR decreased by 5.5 mL/min per 1.73 m^2, 10.3 mL/min per 1.73 m^2, and 14.2 mL/min per 1.73 m^2 at 1 year, 3 years, and 5 years respectively from a baseline of 60.0 mL/min per 1.73 m^2. The IROCK study also noted a significant improvement in progression free survival and local failure in patients treated with single fraction SABR compared to multi-fraction SABR. No difference in renal function was noted between single fraction and multifraction SABR courses.

The FASTRACK II trial was performed to validate this data in a single arm multi-institutional prospective study [6]. FASTRACK II was reported at the American Society for Radiation Oncology (ASTRO) Annual meeting in 2023 [7]. The study enrolled 70 patients of median age 77 (range 47–91) with a single renal cell carcinoma mass. The average size of the renal mass was 4.7 cm. Patients with tumors less than 4 cm were treated with a single SBRT treatment whereas those with greater than 4 cm were treated with three SBRT treatments. After a median follow up of 43 months, local control was 100%. One patient had a distant disease recurrence. Overall survival was 99% at 1 year and 82% at three years. Treatment was very well tolerated, with 10% of patients experiencing grade 3 toxicity (mostly abdominal pain), and no patients with grade 4 or 5 toxicity. Renal function was well preserved, with an average decline in EGFR of only 10.8 mLs/min at 1 year and 14.6 mLs/min at 2 years post treatment. Of these mostly elderly patients, only 1 out of 77 patients required dialysis following treatment [7].

Efficacy and safety of SABR may be further improved with stereotactic magnetic resonance (MR)-guided adaptive radiotherapy (SMART) [8]. In a prospective phase 1 trial, SMART was deployed with real time MR tracking and daily adaptive planning to deliver 40Gy in 5 fractions to 20 patients

with localized RCC. Daily plan adaptation was utilized to improve target coverage or reduce dose to nearby GI structures in two-thirds of the patients. Only one patient experienced treatment related toxicities (grade 2 nausea) and no grade 3 or higher toxicities were noted. Local control at median follow-up of 17 months was 100% and there was only a mean decrease of 1.8 mL/min per 1.73 m^2. While early, this data suggests a promising role for real time tumor tracking as well as daily adaptive planning.

EVIDENCE FOR SBRT FOR LOCALLY ADVANCED RCC

Up to 10% of patients with newly diagnosed RCC present with tumor thrombus (TT), which can cause lower extremity swelling, pulmonary embolism, or Budd-Chiari syndrome. Radical nephrectomy with thrombectomy is standard of care with reports demonstrating 5-year cancer specific survival of 49% [9]. However, 20% of patients are managed non-operatively as these procedures are associated with a high rate of perioperative complications. Patients with untreated tumor thrombi have poor outcomes with a median survival of 5 months and a 1-year disease specific survival of 30% [10].

In the safety lead-in portion of a phase I/II trial from UT Southwestern Medical Center, 6 patients with level II or less IVC TT were treated with neoadjuvant SABR (40Gy in 5 fractions) followed by radical nephrectomy and IVC thrombectomy [11]. Neoadjuvant SABR was associated with low rates of AEs. All patients proceeded with surgery and no intraoperative complications were reported. Median follow up was 24 months and all patients were alive. Efficacy is being further evaluated by the ongoing phase II portion of the study.

There are also retrospective studies suggesting that SABR is effective in treating patients with significant (level III or greater) TT burden. Freifeld et al demonstrated TT regression in 58% (7/12) patients within a median of 478 days from SABR [12]. Therefore, SABR can be useful option for patient with medically inoperable RCC-TT.

OLIGOMETASTATIC RCC

Oligometastatic cancer has been much discussed in recent years. Though the definition of oligometastatic is both practical and varied, the consensus definition of ESTRO and ASTRO is any number that can be treated in a safe manner (though typically is less than 5) [13]. For patients who present with oligometastatic disease, SABR can be beneficial. In a phase II trial, Hannan et al. treated international metastatic database consortium (IMDC) criteria favorable and intermediate risk metastatic RCC patients who were systemic therapy naïve [14]. Patients with 3 or less extracranial metastatic site were treated with SABR. With a median follow up of 21.7 months, they noted that one year freedom from systemic therapy was 91.3% and LC rate of SABR treated lesions was 100%. Treatments were well tolerated. In a separate phase II trial, Hannan et al also noted favorable results in patients with oligoprogressive metastatic RCC [15]. 20 patients with mRCC on systemic therapies with 3 or few sites of progression were treated to all metastatic sites. With a median follow up of 11.1 months, local control rate was 100% and 32% of patients receiving SABR remained on the same systemic therapy. There are currently multiple clinical trials investigating the interaction between immunotherapy and SBRT [16], including NRG-GU012 (SAMURAI trial) [17].

INTEGRATION OF SYSTEMIC THERAPY AND SBRT

As the number of systemic therapies approved for the treatment of RCC proliferate, whether these therapies are compatible with SBRT remains an open question. Generally, the combination of immunotherapy and SBRT has been thought to be potentially synergistic given preclinical evidence that SBRT may increase antigen presentation and overall tumor response to immunotherapy [18]. As noted previously, this synergy is being tested in clinical trials. However, there is also a concern that SBRT in combination with therapy that increases radiation sensitivity may cause more than additive toxicity.

Traditional cytotoxic chemotherapy has traditionally been considered to sensitize both tumor and normal tissue to radiation. Therefore, the combination of cytotoxic chemotherapy and SBRT is generally avoided based upon a prospective clinical trial [19], though this strategy has been investigated for pancreatic cancer [20]. Newer agents can be unpredictable in terms of potential interaction with SBRT, and so caution is warranted any time there is a new systemic agent that has not been formally tested in combination with radiation [21]. Therapies that target the VEGF receptor such as axitinib are

Table 1
Combination systemic therapy and SBRT

Systemic agent	Mechanism of action	Evidence regarding combination treatment
Cytotoxic chemotherapy	Variable	Cytotoxic chemotherapy is thought to cause sensitization of normal tissue to radiotherapy. Avoid combination with SBRT off trial
Axitinib	Tyrosine Kinase/VEGF inhibitor	This class of therapy generally considered safe in combination with SBRT [22] though caution is needed radiating near bowel [23]
Pembrolizumab	Anti PD-1	No additional toxicity with SBRT [32]
Cabozantinib	Tyrosine Kinase inhibitor	Combination with radiotherapy appears safe without increase in major toxicity. [25]
Lenvatinib	Tyrosine Kinase inhibitor	Cautiously considered safe [28]
Tensirolimus	mTOR kinase inhibitor	Has been investigated in other cancers and appears safe [36], though tensirolimus may cause radiation recall
IL-2	Interkeukin-2	Combination appears safe [29]
Sunitinib	Tyrosine Kinase inhibitor (multikinase including VEGF)	Combination appears safe [5, 37]. Caution near bowel [23]
Pazopanib	Tyrosine Kinase inhibitor (multikinase including VEGF)	Combination appears safe [26]. Caution near bowel [23]
Sorafenib	Tyroskine Kinase inhibitor (multikinase including VEGF)	Combination generally safe [27]. Caution near bowel [23]. Consider holding within 5–10 days of radiation if treatment near bowel [38]
Ipilimumab	CTLA-4 blockade	Combination appears safe [30]

generally thought to be safe in combination with SBRT [22], though caution should be taken when treating near bowel as one study suggested increased toxicity for the multikinase inhibitors that target VEGF [23]. Generally, away from the bowel, tyrosine kinase inhibitors are cautiously considered safe with SBRT [24], including cabozantinib [25], sunitinib [5], pazopanib [26], sorafenib [27] and Lenvatinib [28]. Immune targeted agents such as IL-2 [29], pembrolizumab and ipilimumab [30] are also generally thought to be safe in combination with SBRT for renal cell carcinoma [31, 32], though there is some suggestion that the combination of immunotherapy with intracranial radiosurgery for brain metastases may increase treatment related inflammatory changes [33]. There are also case reports that immune targeted agents may cause radiation recall if given after radiation in idiosyncratic instances [34]. Despite these potential toxicities, early phase studies have shown that SBRT in combination with systemic therapy may prolong the duration of ongoing systemic therapy including multikinase inhibitors, immune checkpoint inhibition and combination therapies [15]. These insights are summarized in Table 1. There are ongoing trials testing SBRT in combination with immune checkpoint inhibition such as NCT04974671 as well as in combination with standard of care treatments in mRCC such as the such as the GETUG-StORM-01 trial [35].

CONCLUSION

In conclusion, SBRT represents a promising non-invasive, effective, and well tolerated treatment. As patients get older and present with more comorbid illness, non-invasive treatment will likely be utilized more frequently in the future. SBRT technology continues to improve in ways relevant to the treatment of RCC. Novel systemic therapies generally appear safe in combination with SBRT, though future studies are ongoing to further investigate the integration of SBRT and novel systemic therapies.

ACKNOWLEDGMENTS

The authors have no acknowledgments.

FUNDING

The authors report no funding.

AUTHOR CONTRIBUTIONS

All authors were responsible for the conception, drafting, and approval of this review article.

CONFLICTS OF INTEREST

Albert Lee: None.

James B. Yu: Research funding from Pfizer/Myovant, speaking fees from Pfizer/Myovant, Boston Scientific, and RefleXion Medical, all outside the scope of this work.

Karie Runcie: Research funding from BMS and Exelixis, steering committee for Janssen, all outside the scope of this work.

REFERENCES

[1] Capitanio U, Bensalah K, Bex A, et al. Epidemiology of Renal Cell Carcinoma. Eur Urol. 2019;75:74-84.

[2] Benedict SH, Yenice KM, Followill D, et al. Stereotactic body radiation therapy: The report of AAPM Task Group 101. Med Phys. 2010;37:4078-101.

[3] Siva S, Ali M, Correa RJM, et al. 5-year outcomes after stereotactic ablative body radiotherapy for primary renal cell carcinoma: An individual patient data meta-analysis from IROCK (the International Radiosurgery Consortium of the Kidney). Lancet Oncol. 2022;23:1508-16.

[4] Andrews JR, Atwell T, Schmit G, et al. Oncologic Outcomes Following Partial Nephrectomy and Percutaneous Ablation for cT1 Renal Masses. Eur Urol. 2019;76:244-51.

[5] Hoogenes J, Swaminath A, Mironov O, et al. A prospective randomized parallel-controlled pilot trial of stereotactic body radiation therapy versus radiofrequency ablation for the management of small renal masses. Journal of Clinical Oncology. 2022;40:363-3.

[6] Siva S, Chesson B, Bressel M, et al. TROG 15.03 phase II clinical trial of Focal Ablative STereotactic Radiosurgery for Cancers of the Kidney – FASTRACK II. BMC Cancer. 2018;18:1030.

[7] Siva S, Bressel M, Sidhom M, et al. TROG 15.03/ANZUP International Multicenter Phase II Trial of Focal Ablative STereotactic RAdiotherapy for Cancers of the Kidney (FASTRACK II). International Journal of Radiation Oncology, Biology, Physics. 2023;117:S3.

[8] Yim K, Hsu SH, Nolazco J, et al. Stereotactic Magnetic Resonance-guided Adaptive Radiation Therapy for Localized Kidney Cancer: Early Outcomes from a Prospective Phase 1 Trial and Supplemental Cohort. Eur Urol Oncol. 2023.

[9] Haddad AQ, Wood CG, Abel EJ, et al. Oncologic outcomes following surgical resection of renal cell carcinoma with inferior vena caval thrombus extending above the hepatic veins: A contemporary multicenter cohort. J Urol. 2014;192:1050-6.

[10] Reese AC, Whitson JM, Meng MV: Natural history of untreated renal cell carcinoma with venous tumor thrombus. Urol Oncol. 2013;31:1305-9.

[11] Margulis V, Freifeld Y, Pop LM, et al. Neoadjuvant SABR for Renal Cell Carcinoma Inferior Vena Cava Tumor Thrombus-Safety Lead-in Results of a Phase 2 Trial. Int J Radiat Oncol Biol Phys. 2021;110:1135-42.

[12] Freifeld Y, Pedrosa I, McLaughlin M, et al. Stereotactic ablative radiation therapy for renal cell carcinoma with inferior vena cava tumor thrombus. Urol Oncol. 2022;40:166.e9-166.e13.

[13] Lievens Y, Guckenberger M, Gomez D, et al. Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document. Radiother Oncol. 2020;148:157-66.

[14] Hannan R, Christensen M, Christie A, et al. Stereotactic Ablative Radiation for Systemic Therapy-naive Oligometastatic Kidney Cancer. Eur Urol Oncol. 2022;5:695-703.

[15] Hannan R, Christensen M, Hammers H, et al. Phase II Trial of Stereotactic Ablative Radiation for Oligoprogressive Metastatic Kidney Cancer. Eur Urol Oncol. 2022;5:216-24.

[16] Tang C, Msaouel P, Hara K, et al. Definitive radiotherapy in lieu of systemic therapy for oligometastatic renal cell carcinoma: A single-arm, single-centre, feasibility, phase 2 trial. Lancet Oncol. 2021;22:1732-9.

[17] Hall WA, Karrison T, McGregor BA, et al. NRG-GU012: Randomized phase II stereotactic ablative radiation therapy (SABR) for patients with metastatic unresected renal cell carcinoma (RCC) receiving immunotherapy (SAMURAI). Journal of Clinical Oncology. 2023;41:TPS4604.

[18] Lin AJ, Roach M, Bradley J, et al. Combining stereotactic body radiation therapy with immunotherapy: Current data and future directions. Transl Lung Cancer Res. 2019;8:107-15.

[19] Higgins KA, Pillai RN, Chen Z, et al. Concomitant Chemotherapy and Radiotherapy with SBRT Boost for Unresectable Stage III Non-Small Cell Lung Cancer: A Phase I Study. J Thorac Oncol. 2017;12:1687-95.

[20] Gurka MK, Kim C, He AR, et al. Stereotactic Body Radiation Therapy (SBRT) Combined With Chemotherapy for Unresected Pancreatic Adenocarcinoma. Am J Clin Oncol. 2017;40:152-7.

[21] Niyazi M, Maihoefer C, Krause M, et al. Radiotherapy and "new" drugs-new side effects? Radiat Oncol. 2011;6:177.

[22] 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;25:766-74.

[23] Barney BM, Markovic SN, Laack NN, et al. Increased bowel toxicity in patients treated with a vascular endothelial growth factor inhibitor (VEGFI) after stereotactic body radiation therapy (SBRT). Int J Radiat Oncol Biol Phys. 2013;87:73-80.

[24] He L, Liu Y, Han H, et al. Survival Outcomes After Adding Stereotactic Body Radiotherapy to Metastatic Renal Cell Carcinoma Patients Treated With Tyrosine Kinase Inhibitors. Am J Clin Oncol. 2020;43:58-63.

[25] Loo Gan C, Huang J, Pan E, et al. Real-world Practice Patterns and Safety of Concurrent Radiotherapy and Cabozantinib in Metastatic Renal Cell Carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium. Eur Urol Oncol. 2023;6:204-11.

[26] De Wolf K, Rottey S, Vermaelen K, et al. Combined high dose radiation and pazopanib in metastatic renal cell carcinoma: A phase I dose escalation trial. Radiation Oncology. 2017;12:157.

[27] Dawson LA, Winter K, Knox J, et al. NRG/RTOG 1112: Randomized Phase III Study of Sorafenib vs. Stereotactic Body Radiation Therapy (SBRT) Followed by Sorafenib in Hepatocellular Carcinoma (HCC) (NCT01730937). International Journal of Radiation Oncology, Biology, Physics. 2022;114:1057.

[28] Ji X, Xu Z, Sun J, et al. Lenvatinib with or without stereotactic body radiotherapy for hepatocellular carcinoma with

portal vein tumor thrombosis: A retrospective study. Radiat Oncol. 2023;18:101.

[29] Seung SK, Curti BD, Crittenden M, et al. Phase 1 study of stereotactic body radiotherapy and interleukin-2–tumor and immunological responses. Sci Transl Med. 2012;4:137ra74.

[30] Hammers HJ, Vonmerveldt D, Ahn C, et al. Combination of dual immune checkpoint inhibition (ICI) with stereotactic radiation (SBRT) in metastatic renal cell carcinoma (mRCC) (RADVAX RCC). Journal of Clinical Oncology. 2020;38:614.

[31] Peng J, Lalani AK, Swaminath A: Cytoreductive stereotactic body radiotherapy (SBRT) and combination SBRT with immune checkpoint inhibitors in metastatic renal cell carcinoma. Can Urol Assoc J. 2021;15:281-6.

[32] Siva S, Bressel M, Wood ST, et al. Stereotactic Radiotherapy and Short-course Pembrolizumab for Oligometastatic Renal Cell Carcinoma-The RAPPORT Trial. Eur Urol. 2022;81:364-72.

[33] Qian JM, Yu JB, Kluger HM, et al. Timing and type of immune checkpoint therapy affect the early radiographic response of melanoma brain metastases to stereotactic radiosurgery. Cancer. 2016;122:3051-8.

[34] Riviere P, Sumner W, Cornell M, et al. Radiation Recall Pneumonitis After Treatment With Checkpoint Blockade Immunotherapy: A Case Series and Review of Literature. Front Oncol. 2021;11:662954.

[35] Le Guevelou J, Sargos P, Siva S, et al. The Emerging Role of Extracranial Stereotactic Ablative Radiotherapy for Metastatic Renal Cell Carcinoma: A Systematic Review. Eur Urol Focus. 2023;9:114-24.

[36] Waqar SN, Robinson C, Bradley J, et al. A phase I study of temsirolimus and thoracic radiation in non-small-cell lung cancer. Clin Lung Cancer. 2014;15:119-23.

[37] Kao J, Chen CT, Tong CC, et al. Concurrent sunitinib and stereotactic body radiotherapy for patients with oligometastases: Final report of a prospective clinical trial. Target Oncol. 2014;9:145-53.

[38] Guimond E, Tsai CJ, Hosni A, et al. Safety and Tolerability of Metastasis-Directed Radiation Therapy in the Era of Evolving Systemic, Immune, and Targeted Therapies. Adv Radiat Oncol. 2022;7:101022.