ANTICANCER RESEARCH *42*: 667-674 (2022)
doi:10.21873/anticanres.15525

Review

SBRT in Localized Renal Carcinoma: A Review of the Literature

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Abstract. *Stereotactic body radiotherapy (SBRT) allows high doses of radiation to be administered in a limited number of fractions. The high doses per session might allow the theoretical radioresistance of renal carcinoma to be overcome. SBRT may be a therapeutic alternative in inoperable patients with localized renal carcinoma. This review studied the available literature on the use of SBRT in inoperable localized renal carcinoma. The review including data from English-language studies was conducted in PubMed and MEDLINE between January 2010 and December 2020. Articles were included with data from patients with renal carcinoma treated with SBRT, their indications, simulation, dose and fractionation, local control, survival and side effects, comparison with other treatments, response assessment and radioimmunotherapy. The articles included were evaluated for content and validation. The immobilization systems were variable between studies. Doses and fractions were variable from 25-26 Gy in single fractions to 21-48 Gy in 3-5 fractions, with local control being around 90% with a low rate of side-effects. We review the state of the art in SBRT for renal cell carcinoma. More research is needed to determine optimal doses and fractionation, and to develop a reliable response assessment tool. The role of radioimmunotherapy in renal carcinoma is being studied.*

Renal carcinoma is the sixth most common tumor in men and the 10th in women. Its incidence is increasing (1). The median age at diagnosis is 64 years. The World Health Organization subdivides renal carcinomas into more than 40 subtypes (2). Approximately 90% of renal tumors are carcinomas and out of these, 80% are clear-cell carcinomas; other less common types include papillary renal carcinoma, chromophobic carcinoma, transitional cell carcinoma of the renal pelvis and Bellini's duct carcinoma. Renal carcinomas most often originate in the renal cortex. Their diagnosis has been increased by the advancement of diagnostic imaging. Risk factors involved in their development include smoking, hypertension, obesity, dialysis, chronic pain medication use, chemotherapy, and infection with hepatitis C virus (2-4). The most important prognostic factors that determine 5-year survival are the tumor stage, grade and local extent, the presence of involved nodes and the presence of metastases (5).

The 5-year survival rate for patients with localized lesions is greater than 90%. Traditionally, renal carcinoma is considered resistant to radiotherapy and chemotherapy. The development of targeted treatments such as sunitinib, temsirolimus, bevacizumab, interferon alpha or sorafenib has improved the outcomes. There are alternatives in patients considered non-surgical due to their comorbidities or unresectable tumors, such as active surveillance, cryotherapy, radiofrequency or microwave ablation, and, more recently, stereotactic body radiotherapy (SBRT). Active surveillance would include patients with small, inoperable tumors with limited life expectancy. Radiofrequency ablation is used for tumors of less than 3-3.5 cm, separated from the renal hilum, after partial nephrectomy, in monorenal or kidney transplant patients. Invasive ablative techniques can cause stenosis, fistulas and bleeding (6). SBRT can be used for large, central tumors, with proximity to vessels and ureter, and can be advantageous in patients taking anticoagulants and the elderly population, being a non-invasive technique with a low toxicity profile. The use of SBRT increased from 2004 to 2013 from 25% to 95.4% as shown by Haque *et al*. (7).

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Key Words: Kidney, renal cell carcinoma, SBRT, SABR, review.

This review focuses on the use of SBRT for primary renal carcinoma. This study discusses the challenges and opportunities presented by SBRT, in terms of its indications, technical considerations, clinical outcomes, and safety data. It is compared with other local techniques and in assessment of the response. It is hoped that this review can provide guidance to both established and developing SBRT practitioners and centers.

Methodology

We conducted a review including data from prospective and retrospective studies, meta-analyses, reviews, and systematic reviews of English language studies in PubMed and MEDLINE between January 2010 and December 2020. The MeSH term utilized were SBRT OR SABR AND renal cell carcinoma OR RCC. We examined 150 articles. We included studies by analyzing the abstract text. After examining them, the articles that met the selection criteria were included: Series with renal cell carcinoma, local control, and toxicity data, published in the past 10 years. Finally, 42 articles were included. Most were retrospective studies. Articles were included with data from patients with renal carcinoma treated with SBRT, their indications, simulation, dose and fractionation, local control, survival and side-effects, comparison with other treatments, response assessment and radioimmunotherapy.

Results of the Review

Indications for SBRT in localized renal cell carcinoma. Recently, Muller *et al*. published guidelines for radiation therapy in renal carcinoma, dividing the possible indications of renal SBRT (8). SBRT provides local control at 2 years in more than 90% of such cases in small renal masses. In patients with oligometastatic disease, treatment with SBRT is possible after discussion in a multidisciplinary committee. Radiation therapy in palliative and symptomatic sittings is indicated as for other tumors. In the future, SBRT will have its role in medically inoperable patients with renal carcinoma and in patients with oligometastatic disease. Neither the European Society of Medical Oncology (9) nor National Comprehensive Cancer Network (6) recommend this treatment as an alternative to surgery or ablative techniques.

Indications for renal SBRT would include inoperable patients as an ablative alternative in those with preserved renal function [glomerular filtration rate (GFR) ≥70 ml/min] and lesions ≥1.5 cm and ≤7 cm.

Immobilization and simulation. For conventional linear accelerator treatment, the placement of fiducial markers is optional; if fiducial markers are used, ideally three are needed, one for each dimension and they are usually placed in the Diagnostic Radiology Department by the interventional radiology team. After the placement of the fiducials, it is recommended to delay the planning computed tomography (CT) from 1 week to 10 days. The planning CT is performed with intravenous contrast if the patient's renal function allows it. The patient is placed in a supine position, arms on each side of the head, with an alpha cradle or vacuum mattress and an abdominal compression system.

In units such as CyberKnife®, three to six fiducial markers must be placed on a mandatory basis; after placing them, the planning CT scan is delayed from 7 to 10 days. The planning CT scan is performed with the patient in a supine position, with the arms along the body, and it is not necessary to use an abdominal compression system thanks to the tracking performed by the unit (4-5, 10-27).

Dose and fractionation. The optimal dose and fractionation have not been established. Studies employed doses from 25-26 Gy in single fractions to 21-48 Gy in 3-5 fractions. Ponsky *et al*. in their phase I dose escalation study in 19 patients compared 24, 32, 40 and 48 Gy in 4 fractions, demonstrating that 48 Gy in 4 fractions can be applied without dose-limiting toxicity, with a partial response rate of 20% and a stable disease rate of 80% (11). With these data, a dose-escalation study was designed at 60 Gy in 3 fractions. The study by Siva *et al*. showed that use of the single dose was not related to a worse kidney function (4).

Local control and survival. Local control (LC) ranged from 84-100% according to series, with up to 5 years of follow-up in some of them. In a systematic review of Siva *et al*., 126 patients with inoperable renal carcinoma treated with SBRT in 1-6 fractions were analyzed, 40 Gy in 5 fractions being the scheme most used. The median and mean follow-up ranged from 9 to 57.5 months. After reviewing, 161 articles, three prospective and seven retrospective articles were included. An LC of 84-100% was demonstrated (12). In a prospective study by Staehler *et al*., 40 patients with 45 unresectable lesions smaller than 4 cm were treated with CyberKnife® in a single dose of 25 Gy at 70% isodose. The median follow-up was 28.1 months. An 86.7% remission was achieved, with 42.2% complete responses (13). In a study by Chang *et al*., 16 patients were treated with SBRT of 30-40 Gy in 5 fractions. Eleven patients presented stable disease after treatment, four patients showed partial response, and no patients showed progression. The median follow-up was 19 months (range=7-30 months) and showed LC was 100% (14). Siva *et al*. published a prospective trial with 37 patients with histologically confirmed renal carcinoma (92%) with T1a in 35%, T1b in 62%, and T2a in 3%. One patient presented with bilateral tumor. They used doses of 26 Gy in a single fraction or 42 Gy in 3 fractions, and 89% of the patients were able to complete the treatment. The median follow-up was 24 months. The 2-year LC, progression-free survival (PFS), and overall

survival (OS) rates were 100%, 89%, and 92% (15). In a subsequent study by the same authors, 223 patients from nine centers were included; 118 patients were treated with a single dose of 25 Gy [biologically effective dose (BED)=87.5 Gy] and 105 patients with 40 Gy/2-10 fractions (median BED=80 Gy). At 4 years, the LC, cancer-specific survival (CSS), and OS rates were 97.8%, 91.9%, and 70.7%, respectively (4).

Correa *et al*. included 11 patients treated with 25-40 Gy in 3-5 fractions. The median planning target volume was 9.5 cc (range=7.5-24.4 cc). The median follow-up was 3.9 years. Seven patients were evaluable at follow-up, five with stable disease, one with partial response, and one with progression. The median survival was 20.4 months (16). Peddada *et al*. reported their experience with a total of 21 patients treated with 48 Gy SBRT in 3 fractions. Fourteen of the patients refused surgery. Two patients had transitional cell carcinoma and 19 patients had renal cell carcinoma. The median follow-up was 78 months (range=5-107 months). At 5 years, the LC rate was 100%. Tumor size had decreased a median of 5.3% at 1 year, 15.6% at 2 years, and 15.4% at 5 years (17). In another study, Correa *et al*. included 81 monorenal patients and found LC, PFS, CSS and OS rates of 98%, 77.5%, 98.2%, and 81.5% at 2 years (18). Siva *et al*. investigated the role of SBRT in renal carcinoma larger than 4 cm (>T1b). They included patients from nine centers, a total of 95 patients with a median follow-up of 2.7 years. The median tumor diameter was 4.9 cm and 81.1% of the patients had an Eastern Cooperative Oncology Group performance score of 0-1; 77.6% of the tumors were defined as inoperable. Local, remote and any failure at 4 years were 2.9%, 11.1% and 12.1%. The CSS, OS, and PFS were 96.1%, 83.7%, and 81% at 2 years and 91.4%, 69.2%, 64.9% at 4 years, respectively. Multivariate analysis showed that increased tumor size was associated with reduced CSS (19). Wegner *et al*. published data from the National Cancer Database from 2004 to 2016. They included 347 patients with tumors of a median size of 3.8 cm, treated with 34-54 Gy in 1-5 fractions. The median follow-up was 36 months (range=1-156 months). Predictors of reduced survival included age >74 years, large tumor, and N1 or M1 stage. The median survival was 58 months. The median survival for those with tumors ≤2.5 cm, 2.6-3.5 cm, and more than 5 cm was 92, 88, 44, and 26 months ($p<0.0001$) (20).

Most of the available studies used SBRT with photons. There were some studies with charged particles, however, our review did not focus on these. The dosimetric advantages of protons and carbon ions compared to photon irradiation have been demonstrated in many studies. However, whether these advantages lead to improved clinical results in localized renal cell carcinoma needs to be studied in clinical trials (21). Table I summarizes the most important studies.

We are awaiting the results of the prospective, multi-institutional, phase II FASTRACKII clinical trial, aiming to recruit 70 patients with renal carcinoma confirmed by biopsy and medical inoperability or rejection of surgery (22).

Adverse Events

Non-renal adverse events. In the systematic review by Siva *et al*., the grade 1-2 non-renal toxicities were 21.4%, with a grade 3 toxicity of 3.8% or higher (12). Pham *et al*. in their phase I study evaluated the safety of SBRT treatment in 20 patients. The doses used were from 26 Gy in a single fraction to 42 Gy in 3 fractions. Eight patients did not present toxicity, the rest presented grade 1 and 2 toxicities in the first 6 months after treatment. There were no grade 3-4 toxicities (23). The study by Chang *et al*. included 16 patients. The authors reported one patient with acute nausea. Four patients had symptoms before SBRT and resolved after it (14). Siva *et al*. in 2017 included 37 patients; nonrenal toxicities included minor toxicities in 78% of patients, with acute grade 1 fatigue and late grade 1 chest wall pain being the most common. Severe toxicities were rare, with only one patient experiencing late G3 fatigue. No G4-5 toxicities were observed (15). Correa *et al*. included 11 patients with tumors of 9.5 cm median planning target volume, five patients presented grade 1 toxicity, the patient with the largest tumor grade 2 diarrhea and grade 3 nausea (16). Siva *et al*. reported non-renal grade 3 and 4 toxicity of 1.3% (4). Peddada *et al*. reported grade 1 toxicity of 14.2%, with no other adverse events (17). Siva *et al*. included 38 patients, 40% had grade 1-2 toxicities. There were no grade 3-5 toxicities (19).

Patients with preserved renal function before SBRT. The impact of SBRT on renal function is very important. Dialysis rates after SBRT in renal carcinoma are low (24, 25). There are some data suggesting that there is a dose–response relationship, with minimal deterioration of kidney function, seen in patients receiving 10 Gy or less in a single fraction, and with doses above 100 Gy (BED3). Siva *et al*. related the R50%, which is a derived unitless quantity obtained from the volume of the 50% prescription isodose cloud, compliance index to the decrease in GFR, which may be a parameter to consider (24). In their 25 Gy single-dose study on 45 tumors, Staehler *et al*. reported no patients with impaired renal function, although the study had a median follow-up of 28.1 months and did not include tumors larger than 4 cm (13). Siva *et al*. included 37 patients with mildly impaired renal function, which dropped to 44 ml/min at 1 and 2 years ($p<0.001$) (15). Peddada *et al*. observed a decrease in GFR with a median of 1.5% at 1 year, 7% at 2 years, and 14.2% at 5 years (17). After the treatment of 13 lesions in 10 patients, Senger *et al*. demonstrated stability of renal function of 51.3±19.7 ml/min baseline and 51.6±25.8 ml/min follow-up (26). On the other hand, Siva *et al*. observed a slight decrease in GFR (4). However, GFR was improved in 26.5% (4). In the study by Siva *et al*., an increase in GFR was described in 18 patients (20%); it was not observed with nephrectomy or radiofrequency due to a possible

Table I. *Studies of stereotactic body radiotherapy in renal carcinoma.*

Study	Type	n	Mean size	Dose × fractions	Local control	Overall survival	Toxicity
Kaplan *et al*., 2010 (28)	Prospective (Phase I)	12	NR	21-39 Gy ×3	91.7%	NR	None >G1
Nair *et al*., 2013 (29)	Retrospective	3	21.3 cm^3	39 Gy ×3	100% At 1 year	NR	No
McBride *et al*., 2013 (30)	Prospective (Phase I)	15	3.4 cm	21-48 Gy ×3	87%	NR	Late G1, n=1 Renal dysfunction, n=3.
Pham *et al*., 2014 (23)	Prospective	20	3-9 cm (range=22.7-322.5 cm^3)	42 Gy ×3 26 Gy ×1	NR	NR	60% G1-2
Wang *et al*., 2014 (31)	Retrospective	9	4 cm	36-51 Gy ×10-17	64.8%, 43.2% And 43.2% at 1, 3, 5 years	66.7, 53.3, 35.6% At 1, 3 and 5 years	Acute toxicity: G1 leukocytopenia, n=2, G1 gastrointestinal, n=2. G2 late toxicities, n=2
Lo *et al*., 2014 (32)	Retrospective	3	4.77 cm	40 Gy ×5	100%	100% At 1 year	Acute G1, n=1 No grade 3
Ponsky *et al*., 2015 (11)	Prospective (Phase I)	19	NR	48 Gy ×4	NR	NR	5.2% G2, 15.8% G3-4
Staehler *et al*., 2015 (13)	Prospective	40	7.5-120 cm	25 Gy ×1	98% At 9 months	Not attained after 28.1 months	13% G1-2
Chang *et al*., 2016 (14)	Retrospective	16		30-40 Gy ×5	100%	NR	Acute G2, n=1 Late G4, n=2
Siva *et al*., 2017 (15)	Prospective	33	NR	26 Gy ×1 42 Gy ×3	100% At 2 years	92% At 2 years	78% G1-2 3% G3 No G4
Correa *et al*., 2018 (16)	Retrospective	11	9.5 cm (range=7.5-24.4 cm)	25-40 Gy ×5		Median= 20.4 months	G1, n=5 G2 diarrhea and G3 nausea, n=1
Peddada *et al*., 2019 (17)	Prospective	21	NR	48 Gy ×3	100%		G1, n=3
Senger *et al*., 2019 (26)	Retrospective	10 (13 lesions)	NR	24-25 Gy ×1 36 Gy ×3	92.3% Of all lesions at 27 months	NR	Renal function stable
Funayama *et al*., 2019 (33)	Prospective	13	9-43 mm	60-70 Gy ×10	92.3% At 3 years	91.7% At 2 years 71.3% At 3 years	Mild/moderate decrease in renal function. G4-5, n=2

NR: Not reported. G: grade.

compensatory hyperfiltration mechanism of the functioning nephrons. The mean GFR was 57.2 ml/min, after SBRT it decreased by 7.9 ml/min and three patients required dialysis, none was monorenal) (19).

Renal atrophy, defined by the change in kidney volume, is another measure of kidney dysfunction that has been studied in relation to the effects of radiation therapy. Renal atrophy after SBRT was studied in the study by Yamamoto *et al*. The authors demonstrated strong correlation after SBRT between V20 and V30 and renal atrophy. Attention should be paid to the dose distribution of 20-30 Gy in 10 fractions in SBRT in renal carcinoma. Fiducial marking may be beneficial in reducing renal atrophy. There was no major grade 2 renal toxicity (27).

Patients with impaired renal function prior to SBRT. Small data series are emerging indicating that even in patients with pre-existing kidney damage, SBRT may be a safe strategy. One study included nine patients treated with SBRT with GFR of 52 ml/min who were considered at high risk of requiring postoperative dialysis (24). A significant reduction in GFR was observed after SBRT to 43 ml/min; no patients required dialysis. Another small study of three patients with even poorer kidney function, with GFRs between 17.51 and 34.79 ml/min, used CyberKnife®-based SBRT to administer 40 Gy in 5 fractions (32). In this study, one patient with a GFR of 17.51 ml/min experienced a reduction in GFR at 26 months to 12.28 ml/min. The ipsilateral kidney received 28% V15 Gy. The

other two patients experienced a small reduction in GFR to 30 ml/min, not requiring dialysis. No patient experienced local failure. Recently, the International Radiosurgery Oncology Consortium for Kidney performed a multicenter analysis investigating SBRT for renal cell carcinoma in 81 patients with a solitary kidney with an excellent oncologic outcome. The mean GFR rate decreased from 64.6±21.7 to 59.2±23.9 ml/min/1.73 m^2 after a median of 20.4 months, and no patients required dialysis after treatment. Interestingly, 26.2% of patients experienced an increase in their GFR rate (18). However, Chang *et al*. reported two patients with grade 4 renal toxicity in patients with previous chronic renal disease (14).

These small series provide encouraging results, although more data on patients with pre-existing renal dysfunction and the establishment of safe limitations are needed to better predict renal outcomes after treatment.

Comparison With Other Treatments

Radiofrequency ablation and cryoablation are local therapeutic alternatives for inoperable, small renal carcinomas or patients who refuse surgery. Other techniques such as microwave ablation or high-intensity focused ultrasound are experimental and only reported in small case series. Radiofrequency ablation and microwave ablation are limited to small renal carcinomas up to 4 cm in diameter, whereas cryoablation may be an alternative for larger tumors. However, the rate of complications and the probability of tumor recurrence after cryoablation increased when the tumor size exceeded 3.5 cm or 3 cm, respectively.

There is an absence of randomized controlled trials comparing thermal ablation techniques and SBRT for renal carcinoma; only indirect comparisons of retrospective and prospective series are possible. Local control rates were repeatedly similar among the different local treatments. The rate of complications associated with radiofrequency ablation was around 6.6%, including bleeding, nerve damage (3.9%), ureteral stenosis (2.1%), and urine leakage (34, 35). Complications after microwave ablation are similar to those of radiofrequency ablation, occurring in 3-17%, including perirenal hematoma, urinoma, or skin dysesthesia (35). Bleeding is possible with cryoablation (34).

Comparison between treatments is a major challenge, as the criteria for tumor recurrence are different. For example, after radiofrequency ablation, any contrast enhancement is considered recurrence, whereas after SBRT, enhancement may persist even when the tumor is stable or controlled.

Evaluation After Treatment

The evaluation of the tumor response after SBRT in renal carcinoma is complicated. Ionizing radiation can cause a delay in cell death through mechanisms such as mitotic catastrophe, and viable tumor cells can be found soon after SBRT (36). In diagnostic tests, contrast enhancement in CT can persist for a long period after treatment, and it is not a diagnostic parameter for treatment failure (37). Tumor size is not an adequate criterion either for follow-up after SBRT, and pseudoprogression may develop, with an increase in size in the initial 3 to 6 months, due to initial inflammation after treatment.

Given these uncertainties, assessments at 6 months after treatment are recommended, and the use of absence of progression instead of response to assess the success of the treatment. Other strategies include follow-up with magnetic resonance imaging or positron-emission tomography (38). Response evaluation times and follow-up serum biomarkers are being studied.

Radioimmunotherapy

The treatment of metastatic renal carcinoma has changed significantly in recent years with the development of immunotherapy. SBRT induces microvascular damage, which increases the cytotoxic effect of radiotherapy. Renal carcinoma is a highly vascularized tumor and angiogenesis is central to its development and progression. Vascular damage and functional disruption of the vascular endothelium allows for greater penetration of systemic treatment (39). In addition, the abscopal effect, which consists of regression of metastases in areas away from the radiotherapy site, has been described in renal carcinoma treated with SBRT and hypofractionation (40).

The phase III Checkmate 025 study demonstrated the efficacy of immunotherapy in metastatic renal carcinoma compared to everolimus in patients previously treated with antiangiogenic drugs, improving OS from 19.6 months to 25 months and establishing it as the standard second-line treatment (41). Checkmate 214 demonstrated superior OS with the combination of nivolumab and ipilimumab compared to sunitinib in previously untreated patients (42). The KEYNOTE-426 study demonstrated longer survival with the combination of pembrolizumab and axitinib compared to sunitinib (43, 44). Following these studies, ipilimumab, pembrolizumb, and avelumab have been approved and others are under study for metastatic renal carcinoma (45).

Some trials in metastatic renal carcinoma have demonstrated the safety of combination radioimmunotherapy. A phase I study combining pembrolizumab and SBRT in patients with advanced tumours who progressed on standard treatment showed an abscopal effect in 13.3% of patients (46). The phase II NIVES study is evaluating the combination of immunotherapy and SBRT in metastatic renal carcinoma (47) and the RADVAX study is evaluating the combination

of nivolumab and ipilimumab with SBRT (48). Two studies currently underway are the CYTOSHRINK study, a phase II study involving patients with advanced renal carcinoma who decline cytoreductive nephrectomy, with patients receiving nivolumab or ipilimumab (ClinicalTrials.gov Identifier: NCT04090710) and SBRT to the primary renal lesion or immunotherapy alone, and the RAPPORT study, a phase I/II study of radiotherapy and pembrolizumab in patients with oligometastatic renal carcinoma (ClinicalTrials.gov Identifier: NCT02855203). The combination of radiotherapy and immunotherapy has important advantages and theoretical benefits; however, more studies are needed to support this hypothesis and allow for adequate patient selection.

Limitations

The limitations of this review include the nature of the studies, most were retrospective series or small prospective series, very heterogeneous with different criteria for inclusion and response assessment. Some prognostic factors for renal carcinoma include size or previous renal function, and numerous studies included heterogeneous patients, complicating the establishment of conclusions. In addition, limited and ambiguous information makes it difficult to interpret the data.

Conclusion

Radiation therapy in renal cancer has been relegated to palliative treatments. SBRT in inoperable renal carcinoma with doses between 25-26 Gy in a single fraction, with up to 21-48 Gy in 3-5 fractions achieves important LC, with low non-renal toxicity and mild toxicity in renal function, even in patients with poor basal renal function. There are no comparative studies with other ablative techniques, but indirect comparisons show similar results in LC and side-effects. Post-treatment response assessment is complex and should be delayed for up to 6 months. More studies are needed to establish SBRT in renal carcinoma as an alternative in these patients and its combination with immunotherapy.

Conflicts of Interest

The Authors declare they have no conflicts of interest.

Authors' Contributions

Conceptualization, data curation and formal analysis: Raquel Fuentes. Data curation, formal analysis, methodology: Raquel García Latorre. Conceptualization, data curation, formal analysis, methodology, supervision, writing – original draft, writing – review and editing: Carolina de la Pinta.

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Received December 2, 2021
Revised December 18, 2021
Accepted January 11, 2022