The promising role of radiotherapy in the treatment of advanced or metastatic renal cell carcinoma: a narrative review

Qinghong Wei[1#], Hongmei He[2#], Long Lv[3], Xiaoying Xu[1], Weibing Sun[3]

[1]Department of Radiation Oncology, The Second Affiliated Hospital of Dalian Medical University, Dalian, China; [2]Department of medical Oncology, The Second Affiliated Hospital of Dalian Medical University, Dalian, China; [3]Department of Urology, The Second Affiliated Hospital of Dalian Medical University, Dalian, China

Contributions: (I) Conception and design: X Xu, W Sun; (II) Administrative support: H He; (III) Provision of study materials or patients: X Xu, W Sun; (IV) Collection and assembly of data: Q Wei; (V) Data analysis and interpretation: Q Wei, L Lv; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work as co-first authors.

Correspondence to: Xiaoying Xu; Weibing Sun. The Second Affiliated Hospital of Dalian Medical University, Dalian, China.
Email: xiaoyingxu73@aliyun.com; weibingsun_dyfemw@163.com.

Abstract: Traditionally, renal cell carcinoma (RCC) has been regarded to be "radioresistant". Conventional fractionated radiation (CFRT) has played a limited role in RCC as a palliative treatment to relieve pain and bleeding. Succeed to the rapid development of precise radiotherapy techniques, realizing safe delivery of high-dose radiotherapy, an increasing amount of convincing data suggests that the delivery of high-dose-per-fraction radiation through stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT), also known as stereotactic ablative radiotherapy (SABR) can help to overcome resistance to radiotherapy. Herein, we summarized and analyzed the data from randomized controlled trials, retrospective and prospective studies, and meta-analyses relating to the treatment of advanced and metastatic RCC (mRCC) with CFRT, SBRT, or SBRT combined with systemic therapy. CFRT has a limited effect on local control (LC) of advanced RCC and mRCC, but it is a major palliative treatment which could obviously relieve pain caused by cancer. SBRT and SRS have the significant advantage of being able to precisely deliver a high dose of radiation to the target tissues. SBRT could cause a higher LC for advanced and metastatic RCC and could be used as an alternative to surgery for patients with oligometastatic RCC. The combination of SBRT with systemic therapy, such as targeted therapy or immunotherapy, is safe and tolerable. Concurrent immunotherapy and SBRT is a promising treatment strategy for patients with advanced or metastatic RCC. However, research on radiotherapy combined with systemic therapy is still limited and further studies to explore this treatment for RCC are urgently needed.

Keywords: Renal cell carcinoma (RCC); conventional fractionated radiation (CFRT); stereotactic radiosurgery (SRS); stereotactic body radiation therapy (SBRT); targeted therapy; immunotherapy

Introduction

Renal cell carcinoma (RCC), which is the eighth most common malignancy among adults in the United States, is rising in incidence (1). In most cases of RCC, surgery is still an indispensable treatment option, and radical surgery or surgery combined with multiple therapies is still a standard strategy for treating patients with this malignancy (2). However, about 5% of RCC patients suffer from local recurrence and as many as 20–30% of patients progress to metastatic disease after undergoing surgery for localized lesions (3,4). The response rate among patients

with advanced disease is extremely low, and their survival rate is considerably reduced compared to that of patients with early-stage disease (5). National Comprehensive Cancer Network (NCCN) guidelines recommend the use of radiation as a palliative therapy, especially to relieve the pain caused by bone metastases. For patients with multifocal brain metastases (BM), whole-brain irradiation is recommended as an effective measure, whereas stereotactic body radiation therapy (SBRT) is a potential option for patients who undergo nephrectomy and experience oligometastatic recurrence years later (6).

Stereotactic radiosurgery (SRS) or fractionated stereotactic radiotherapy (FSRT) is a treatment modality through which a high dose of radiation can be delivered to target areas in single or multiple fractions, while minimizing the damage to normal tissue caused by radiation exposure (7). Ning *et al.* reported that high dose radiation could efficiently eradicate RCC cells *in vitro* (8). Several clinical studies on the use of SRS or SBRT to treat patients with primary or metastatic RCC (mRCC) have reported promising results. Furthermore, emerging preclinical and clinical data have suggested that local RT could supplement the effects of immunotherapy to enhance anti-tumor immunity (9). This review aimed to summarize the current evidence of the role of RT in the treatment of advanced or metastatic RCC from studies focusing on the use of CFRT, SRS, SBRT, or SBRT in combination with systemic therapy.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/tau-20-1466).

Methods

Database search: electronic databases used to conduct literature searches included PubMed, Web of Science (February 15, 1983–September 29, 2019). Key words used to search titles and abstracts included renal cell carcinoma OR RCC OR advanced RCC OR metastatic RCC, AND radiotherapy OR palliative radiotherapy OR SBRT OR stereotactic radiosurgery. Retrieved studies included randomized controlled trials, retrospective and prospective studies, and meta-analyses.

Palliative RT

RCC has traditionally been considered to be radioresistant. Therefore, RT has played only a limited role in the treatment of RCC to date. A recent review concluded that

neoadjuvant RT should not be recommended as a routine treatment for patients with locally advanced or unresectable RCC, because it did not improve the actuarial survival (10). According to the NCCN guidelines, adjuvant RT after nephrectomy also failed to show benefit for patients, even those with nodal involvement or partial resection (6).

However, conventional RT is a useful palliative therapeutic option for relieving the symptoms of patients with metastatic lesions. Results from several studies indicated that RT could relieve pain by bone metastasis in RCC patients. In 1983, Halperin *et al.* reported a clinical trial of RT for pain relief in RCC patients with 36 metastatic bone sites. The treatment response rate was 77% (28/36 sites); of the 28 sites that showed a response, 24 (86%) were partially or completely free of pain for the remainder of the patients' lives (11). Similar results were reported in another retrospective study involving 34 patients with painful spinal metastases from RCC who were treated with conventional external beam RT (8–30 Gy in 1–10 fractions); the overall pain response rate was 68% (12). Wilson *et al.* conducted a retrospective study about biological effective dose (BED) for palliative RT treatment in mRCC. One hundred and forty-three independent metastatic sites were included, and the overall response rate was 73%. The BED was based on the calculation of the α/β ratios of 3 and 7 Gy (BED 3 and BED 7, respectively). Comparison showed that relief of bone pain was more likely to be durable than the alleviation of symptoms at other metastatic sites. This article also concluded that it was not appropriate to use a higher BED dose as an indicator to predict response or sustained response in the palliative treatment of RCC (13).

A phase II study was conducted to evaluate the effect of RT on the symptoms of 31 patients with mRCC. Bone pain (n=24) was the most common symptom reported, with the most commonly employed schedule being 30 Gy/10 fractions. After a mean follow-up time of 4.3 months, the authors reported that 19 (83%) of 23 evaluable patients showed site-specific pain relief after treatment with RT (14). A later systematic review supported this result; with 30 Gy in 10 fractions as the most common radiation dose, 73.6% of patients with metastatic bone disease from RCC gained significant pain control (15).

SBRT or SRS for advanced RCC

Emerging evidence indicates that high-dose single-fraction RT can overcome the radioresistance of RCC and SBRT, which delivers high-dose single-fraction irradiation, has

high rate of local control (LC) for both primary and metastatic RCC.

Biological mechanism

In a review article (16), De Meerleer *et al.* showed that CFRT induced tumor cell death mostly by oxygen-dependent DNA damage (double-strand breaks, or unrepaired or misrepaired breaks). But in about 60% of RCC cases, a tumor suppressor gene, the von Hippel Lindau (VHL), was found to lose function (16). Mutations in VHL had been found to result in the up-regulation of hypoxia-inducible genes (17). Under hypoxic conditions, HIF1α couldn't go through ubiquitylation and proteasomal degradation and accumulated. This accumulation resulted in the upregulation of some related proangiogenic factors, such as vascular endothelial growth factor (VEGF) and fibroblast-derived growth factor, and downregulation of angiogenic inhibitors. These factors played an important role in protecting the endothelium of tumor cells, which was responsible for radioresistance (16). Under this circumstance, the effect of CFRT was limited.

This article also reviewed radiobiological difference between low and high dose per fraction of radiation and explained the biological principle underlying the phenomenon of RCC's sensitivity to SBRT. The authors suggested that SBRT overcame radioresistance mostly via the ASMase pathway (15). They reported that single-fraction SBRT (e.g., 15 Gy) results in the translocation of ASMase from intracellular compartments, such as lysosomes, to the outer leaflet of the plasma membrane, where it is captured in sphingolipid-enriched and cholesterol-enriched membrane micro-domains called rafts. During the hydrolysis of sphingomyelin by ASMase, ceramide, a pro-apoptotic messenger, is produced, which leads to endothelial apoptosis. Thus, ceramide plays a prime role in radiation-induced cell death in RCC. However, the specific mechanism of ASMase translocation to the outer leaflet of the plasma membrane requires further research.

In another experiment, Zhou *et al.* also hypothesized that hypoxia-inducible factor 2α (HIF2α) markedly activated the SHH-GLI1 signaling pathway, which was critical for embryonic development, leading to the radioresistance of RCC (18). The specific mechanism still needed to be further studied. Now, there are only three FAD-approved drugs for cancers that affect the Shh pathway. Two of compounds, vismodegib and sonidegib, target Smoothened (SMO). The other approved compound is arsenic trioxide

(ATO), which can suppress this pathway at the level of the GLI proteins, although current evidence suggests it also has other targets. But none of them apply to RCC (19).

SBRT exerts prominent local therapeutic effect and has low toxicity for primary RCC patients

Several prospective trials have attempted to evaluate the efficacy of SRS or SBRT for primary RCC. Pham *et al.* (20) carried out a phase I trial of SBRT for primary inoperable RCC. Eleven patients (gross tumor diameter ≥5 cm) underwent treatment with 42 Gy/3 fractions and 9 patients (gross tumor diameter <5 cm) received a single fraction of 26 Gy. The author concluded for the first time that a three-dimensional conformal radiological technique of 8–10 beam could safely deliver highly stereotactic ablation to primary lesion targets. No grade 3 or 4 toxicities were reported during the 6-month follow-up period. Other prospective clinical trials have applied a similar regimen (42 Gy/3f for tumor size in diameter ≥5 cm, 26 Gy/1f for tumor size <5 cm). The results demonstrated relationship between renal dysfunction and high-dose regions. Although SBRT results in a clinically acceptable decrease in renal function after 1 year (21). Furthermore, Siva *et al.* (22) showed that stereotactic ablative radiotherapy (SABR) was well tolerated by patients with small and large primary RCC. Within 2 years follow-up period, none of the patients had experienced local progression. The distant progression free and the overall survival (OS) rates were 89% and 92%. No grade 4–5 toxicities were recorded and 18% of patients reported no related toxicity. Next, two other dose-escalation studies of SBRT for inoperable patients showed that dose level of 48 Gy/4f and 35 Gy/5f successfully achieved a satisfactory response, yielded acceptable toxicity, and preserved renal function (23,24). A dose of 60 Gy in 3 fractions would be further evaluated in the next experimental research study. To observe the change in tumor size over time, Funayama *et al.*'s prospective study (25) enrolled 13 patients with primary RCC lesions, who were treated with SBRT. All of the renal tumors shrank slowly but continuously for years after SBRT. The 3-year local progression-free survival (PFS) rate was 92.3%. The 2- and 3-year OS rates were 91.7% and 71.3%, respectively. However, the above clinical trials had several limitations. Firstly, the amount of enrolled patients was insufficient, and secondly, the median follow-up was generally limited.

In addition to the prospective trials, a meta-analysis study from IROCK (26) analyzed and compared the

therapeutic effects of single-fraction (median dose, 25 Gy) and multifraction (range 24–27 Gy, 2–10f) SABR. The two cohorts had similar ideal local cancer control. The 2-year and 4-year LC rate was both 97.8%. However, single-fraction SABR could obtain better PFS and cancer-specific survival (CSS) than a multifraction schedule (P<0.05). The authors also inferred that patients who received multifraction SABR were more inclined to progress in distant organs or to die due to cancer-related causes.

In 2019, another meta-analysis (27) reported that SABR was feasible for primary RCC, with a high LC rate. It analyzed 26 studies (including 11 prospective trials) involving 372 patients with 383 lesions, most of whom were diagnosed as inoperable. Radiation schedules of 26 Gy/1f and 40 Gy/5f were the most common. The LC rate was 97.2%, and the rate of grade 3–4 toxicities was 1.5%. The authors suggested that SABR was an effective treatment for primary RCC and it was the preferred option for larger or centrally located tumors near the renal pelvic. Even for elder patients or patients with more comorbidities or patients with a higher risk of chronic kidney disease (CDK) progression, SABR was a reasonable treatment after an initial period of active surveillance (AS).

SBRT can improve the LC rate for extracranial metastases, especially for oligometastasis

Some reports suggested that complete metastasectomy could improve the CSS and quality of life of patients with locally metastatic lesions. However, local treatment is controversial (28,29). In recent years, SBRT has emerged as a non-invasive alternative treatment for cases that are technically difficult to treat with surgery or for selected RCC patients with limited metastases (28,30). Common sites of extracranial metastatic disease include the lungs and bones. Several clinical reports have shown SBRT to have a high LC rate and acceptable toxicity for treating metastases. Svedman et al. (30) reported a prospective phase II trial in which 82 lesions (including 63 in the lung/mediastinum) were treated with stereotactic RT. The overall median follow-up time was 52 months. The results showed a high rate of LC (98%) and low toxicity. For spinal metastases, RT had traditionally been used as a palliative therapy; However, more and more studies found that the effect of SBRT was far better than that of CFRT. Amini et al. (31) compared SBRT with conventional fractionated external beam RT (CF-EBRT) in patients with RCC spinal metastases. The control rates of SBRT and CF-EBRT at 10,

12, and 24 months after treatment were 74.9% versus (vs.) 44.1%, 74.9% vs. 39.9%, and 74.9% vs. 35.7%, respectively. A significant difference was observed in the symptom control rates between the two treatments (P=0.020). A phase I/II study included 74 spinal metastatic lesions treated with SBRT, and the results indicated SBRT to be a safe and effective treatment for spinal metastases. Seventy-four spinal metastatic lesions were measured, of which the median tumor volume was 37.4 cm^3 (range, 1.6–358 cm^3). The 1-year PFS rate was 84% for all involved lesions (32). Another prospective study (33) proposed that different BEDs may account for improved LC. Single-fraction spinal SRS (24 Gy in 1f) was associated with improved LC compared with multifraction (27 Gy/3f or 30 Gy/5f) and should be considered in the upfront management of patients with RCC spinal metastases.

SBRT is also applied more in oligometastatic RCC. Oligometastasis is described as an intermediate condition in which the number of metastatic lesions is limited, involving either single or multiple organs (34). Some retrospective trials have demonstrated that patients with 1–3 metastases treated with SBRT had fewer distant recurrences and a longer survival time than patients with >3 metastatic sites (35,36). Another study (37) reported that because SABR had a 1-year LC rate of 91.2%, as well as minimal acute and late complications, it should be considered as a treatment option for RCC patients with a limited number of metastatic sites.

SRS has a high LC rate for brain metastasis, especially for smaller lesions

The brain is one of the most common metastatic sites in RCC, and the survival of patients with BM is always poor (38). Advancements in imaging technology such as magnetic resonance imaging (MRI) and the longer surviving period of RCC patients have seen an increase in the incidence of BM (39). Nevertheless, there is no standard therapeutic regimen for BM. Treatment options include corticosteroids, surgery, whole-brain radiotherapy (WBRT), and SRS. Surgery is not frequently advocated for patients with multiple sites of intracranial disease or widespread metastatic disease. Marek et al. reported that patients who received WBRT alone had a high rate of local brain tumor progression and further emphasized the importance of radiosurgery. WBRT combined with radiosurgery was suitable for newly diagnosed and recurrent BM. It was also suggested that survival was not

an accurate endpoint for evaluating treatment of BM. Symptom control can greatly improve the quality of life of patients with BM (40). Surgical removal of a solitary brain metastasis followed by WBRT has been found to be superior to WBRT alone, and WBRT alone should be reserved for patients with multiple metastases (41,42). Furthermore, a systematic review concluded that there was no significant difference in OS comparing surgery plus WBRT *vs.* SRS plus WBRT in patients with single or solitary BM (43).

SRS is emerging as an attractive and effective treatment modality for newly diagnosed BM in patients with radioresistant malignant tumors, such as melanoma and RCC (42,44,45). The 1-year LC rate for RCC BM treated with SRS is 91% (45). Studies have found that smaller tumor volume is a positive predictor of response in RCC (38,44). Consistent with this, a systematic review revealed that LC was significantly correlated with the volume of metastases. The LC rates for BM at 1 and 2 years after treatment were 91.8% and 86.1%, respectively; however, the LC rate declined for larger tumors (>2 cm). Survival was not found to be statistically different between patients with a different number of metastases (<5 versus ≥5 BM) (46). Whether or not WBRT should be combined with SRS in the treatment of radioresistant BM remains controversial (43). A phase II trial conducted by Rafael *et al.* showed the 3- and 6-month intracranial failure rates without WBRT to be 25.8% and 48.3%, respectively. However, the generalizability of these results is limited due to the small number of patients involved (n=31) (42). A retrospective clinical trial showed that the median OS times between SRS and SRW + WBRT (12 *vs.* 16 months, respectively) had no statistical difference, but the addition of WBRT to SRS increased the intracerebral control rate in patients with one to three cerebral lesions (47). A similar result was reported in another retrospective study, in which patients with 1–3 BM were involved. The authors suggested that additional WBRT was justified, particularly in recursive partitioning analysis (RPA) class I patients (48).

The recent studies for BM mostly involved non-RCC patients. Further prospective research involving RCC patients with BM is urgently needed.

SBRT combined with systemic therapies

NCCN Guidelines recommend that systemic therapies are the current standard treatment strategies in clear cell histology with poor-risk features for advanced RCC or

mRCC (6). However, we found some clinical evidence that SBRT combined with systemic therapy has a synergistic antitumor effect on RCC.

Concurrent SBRT and targeted therapy is tolerable and has a synergistic antitumor effect on RCC

Tyrosine kinase inhibitors (TKIs) and anti-VEGF antibodies, which are the most commonly used targeted therapy, are now widely used as first- and second-line treatments for advanced RCC. Anticancer drugs targeting the mammalian target of rapamycin (mTOR) are also widely used. The United States Food and Drug Administration (FDA) has approved a number of targeted agents as first or subsequent lines of treatment for advanced RCC including sunitinib, sorafenib, pazopanib, axitinib, temsirolimus, and everolimus (6).

Endothelial angiogenesis and a paucity of endothelial apoptotic response are considered to be the likely main causes of radiation resistance. Endothelial apoptosis is the key to radiation-induced cell death in RCC (16). Therefore, antiangiogenic drugs, such as TKIs, are theoretically considered to be radiosensitizers. Currently, the clinical evidence of the effect of concurrent targeted drug therapy and RT on RCC is limited and inconsistent. Most studies to date have used sunitinib, which is a small molecule receptor TKI that targets multiple pathways including receptor tyrosine kinase (KIT), vascular endothelial growth factor receptor (VEGFR1, VEGFR2, VEGFR3), platelet derived growth factor receptor a (PDGFRa), Fms-like tyrosine kinase-3 receptor (FLT3), and the receptor encoded by the ret proto-oncogene (RET) (49).

A phase 1 dose-escalation study of concurrent sunitinib and image-guided radiotherapy (IGRT) focused on the safety and maximum tolerated dose. The authors proposed that the addition of sunitinib (25–37.5 mg) to IGRT was tolerable in selected subjects with 1–5 metastatic sites and did not potentiate RT toxicity (49). A phase II trial focusing on concurrent sunitinib and IGRT for oligometastases was next carried out. The treatment schedule was 37.5 mg sunitinib daily (days 1–28) and IGRT 50 Gy (days 8–12 and 15–19). The 18-month LC, distant control, PFS, and OS rates were 75%, 52%, 56%, and 71%, respectively (50). Similarly, more specific data in another study of the same treatment showed that the 4-year LC, distant control, PFS, and OS rates were 75%, 40%, 34%, and 29%, respectively (51). Another study involved 41 patients with cerebral or spinal metastatic

lesions from RCC who were treated synchronously with sunitinib and hypo-fractionated high-dose RT. Concurrent SRS and anti-angiogenic therapy was confirmed to be a non-invasive, safe, and efficient treatment for patients with spinal or cerebral metastasis from RCC (52). Kusuda *et al.* reviewed the effect of the combination sunitinib with RT in five RCC patients with BM. Sunitinib was administered after RT, and all patients displayed shrinkage of the BM. Treatment-related adverse events did not differ significantly between patients treated with the combination of sunitinib with RT and those who received sunitinib alone. Moreover, four out of the five patients with BM had a long survival period, with OS of 10.5, 12.5, 20.8, and 21.5 months, respectively. The result of the study demonstrated that concurrent sunitinib and SRS could be safely employed to treat RCC patients with BM and yielded favorable prognostic outcomes. However, four of the five patients showed disease progression of BM. Therefore, to acquire more convincing results, more cases are needed (53). Another retrospective study reported sequential therapy combined with targeted therapies followed by RT for mRCC. Only seven cases were enrolled and the response of metastatic lesions to the treatment was obvious (54). A larger-scale retrospective study involving 362 RCC BMs, of which 65% were treated with SRS combined with TKIs, reported 12- and 36-month OS rates to be 52% and 29%, respectively. The median OS was 13.5 months (95% CI, 11–20 months). This result suggested that concurrent TKI and SBS treatment could be a promising approach to optimize LC of mRCC, without increasing neurologic toxicity (55).

Pazopanib is also a first-line TKI, targeting VEGFR. De Wolf *et al.* reported a phase I dose-escalation experiment combining with high-dose RT and pazopanib in mRCC. The radiation dose was escalated in three dose levels (24 Gy/3, 30 Gy/3, and 36 Gy/3). The results showed that the maximum tolerated dose was not reached, which provided evidence that the combination treatment had a synergistic antitumor effect. The patients, who had inoperable localized disease or limited metastatic disease, initially achieved an ideal curative effect. The 1-year LC and PFS rates were 83% and 28%, respectively (56).

Everolimus is another type of targeting drug for mRCC, which is an orally available analogue of rapamycin that inhibits the activation of the mTOR pathway. A case report described that a patient with mRCC gained radiological complete response (CR) after treatment with radiation (total dose: 30 Gy in 10 fractions) and everolimus (10 mg/daily).

The treatment was well tolerated and the patient presented only limited mucositis, and moderate hypertriglyceridemia and hypercholesterolemia (57).

A recent retrospective study by He *et al.* reported outcomes of 350 consecutive patients with mRCC who were treated with SBRT combined with TKIs. The study focused on survival benefits and the timing of SBRT combined with targeted treatment. The median OS was 61.2 months, and the median PFS was 11.5 months. The 2-year LC rate reached 94%. CR was obtained in 16 (34%) lesions in patients irradiated before TKI failure, but in only 4 (7%) lesions in patients who were irradiated after TKI failure (P=0.001). Four (7%) patients experienced grade 3 toxicities. Therefore, in the treatment with TKIs, SBRT could achieved better PFS, OS, and CR rates. It should be delivered before the failure of TKI therapy, but not after (58).

Immunotherapy and SBRT have a synergistic antitumor effect

The standard of treatment for mRCC is systemic therapy. In recent years, immune checkpoint inhibitors (ICIs), including anti-cytotoxic T lymphocyte antigen-4 (anti-CTLA-4) and anti-programmed cell death-1 (anti-PD-1)/PD-L1 blockers, have emerged as a popular treatment for several advanced or metastatic solid tumors.

Programmed cell death-1 (PD-1) checkpoint inhibitors selectively block the PD-1/PD-1 ligands 1 and 2 pathway. In November 2015, nivolumab was the first ICI approved by the FDA as a therapy for patients with advanced RCC (59).

In the randomized, open-label, phase III CheckMate 025 study (NCT01668784), nivolumab was demonstrated to shrink tumors and to effectively improve symptoms for advanced RCC patients (60). However, the number of patients who achieved remarkable outcomes was limited. Still, a considerable proportion of patients did not obtain a clinically effective response. Also, some patients who initially obtained a durable response to ICI therapy showed significant progression in the follow-up , and more than 55% of RCC patients who did not receive combined treatments developed resistance to different immunotherapies (59,61). These findings were supported by the results of Chowdhry *et al.*'s study. Nivolumab alone had limited efficacy in the treatment of BM. But Nivolumab with either RT or surgery had been strongly suggested to achieve more satisfactory efficacy and LC (62).

Some scholars have put forward the hypothesis that RT and immunotherapy have a synergistic antitumor effect, with preclinical evidence showing that immunotherapy combined with RT increased loco-regional and systemic disease control (63-65).

The combination of RT and immunotherapy is based on the abscopal effect, which results from immune activation by RT and accounts for the regression of metastatic cancer at distant sites with no exposure to radiation (66). The CR and abscopal effects of RCC treated with ICI and RT have mostly been described in case reports (67). Multiple clinical trials of immunotherapy combined with RT in the treatment of RCC are ongoing.

Conclusions

Conventional fractionated RT has traditionally been used as a palliative treatment to relieve pain and has a limited effect on LC. SBRT has a high LC rate for advanced or mRCC and could be used as an alternative to surgery for oligometastatic RCC patients. It is safe and tolerable to combine SBRT with systemic therapies. Concurrent immunotherapy and SBRT is a promising therapeutic strategy for patients with advanced or mRCC. However, evidence from clinical trials is still limited, and the efficacy, proper timing, and safety of the combination of immunotherapy and RT need to be further explored.

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Footnote

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