Cytoreductive stereotactic body radiotherapy (SBRT) and combination SBRT with immune checkpoint inhibitors (ICIs) in metastatic renal cell carcinoma

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Abstract

Introduction: Preclinical evidence demonstrates the immunogenic potential of stereotactic body radiotherapy (SBRT). There is growing interest in investigating this interplay with the immune system in metastatic renal cell carcinoma (mRCC). Cytoreduction with SBRT and combination therapy with SBRT and checkpoint inhibitor immuno-oncology agents (IO) are two potential therapeutic strategies in mRCC. In this review, we summarize the current clinical evidence for the use of cytoreductive SBRT to primary kidney and combination SBRT with IO.
Methods: A literature review for articles and abstracts published between January 2000 and March 2020 was conducted through the PubMed, the American Society of Clinical Oncology (ASCO), and the American Society of Radiation Oncology (ASTRO) database. Evaluation of studies followed the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) criteria.
Results: A total of three articles for cytoreductive SBRT and one article and three abstracts for combination SBRT and IO in mRCC met inclusion criteria for this review. Evidence for SBRT to primary kidney is limited by small series and pilot studies. Outcomes vary widely due to small patient numbers and study heterogeneity. Local control ranges from 85–100% and one- and two-year overall survival ranges from 38–71% and 19é53%, respectively. Combination SBRT and IO are tolerable for patients with early data, suggesting grade 3–4 adverse event rates of 0–24%. Long-term survival data is not yet available.
Conclusions: Cytoreductive SBRT and combination SBRT with IO therapy represent promising treatment strategies in mRCC. The evidence for clinical benefit is currently limited and requires further study with well-designed, randomized, controlled trials.

Introduction

Systemic therapy for metastatic renal cell carcinoma (mRCC) has advanced significantly in recent years. Initially, cytokine agents were the only options available for mRCC as it's generally resistant to traditional chemotherapy. Response rates to cytokine therapy was approximately 12% and had only a small improvement in median overall survival of 3.8 months (1) at the expense of significant toxicities (2,3). Eventually targeted monotherapy with tyrosine kinase inhibitors (TKIs) showed both improved survival outcomes and tolerability compared to cytokine therapy (4,5) and subsequently became first line for mRCC.

More recently, targeted agents were replaced as first line treatment by dual checkpoint inhibitor immuno-oncology agents (IO) (6-9). The role of cytoreductive nephrectomy (CN) in mRCC, previously established in the cytokine era, has been revisited in the targeted therapy era where there may be upfront utility in appropriately selected patients (10-13). Historically, radiation therapy has played a limited role in the management of RCC as it is traditionally thought to be a radioresistant tumor.

The use of ablative doses with stereotactic body radiotherapy (SBRT) however has demonstrated favourable results in localized RCC (14) and to sites of metastases in mRCC (15). In addition, there is ample preclinical evidence that demonstrates the ability for SBRT to promote anti-tumor immune response in the tumor microenvironment (16,17) and to work synergistically with IO to amplify the immune response (18-20). Thus, the use of cytoreductive SBRT to primary kidney (as an alternative to CN) and combination SBRT with IO in mRCC are potential therapeutic strategies that could take advantage of this interplay with the immune system. We performed this review to summarize the current clinical evidence evaluating the role of SBRT to primary kidney in mRCC as well as the use of IO and SBRT for mRCC.

Methods

A literature review was conducted for full length research articles and abstracts published between Jan 2000- March 2020 using the Pubmed, American Society of Clinical Oncology (ASCO) and American Society for Radiation Oncology (ASTRO) databases. A broad search strategy with "text word" method was used. Details regarding search terms are available in eTable 1 in the online Supplement. Evaluation of studies followed the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) criteria. SBRT, according to ASTRO, was defined as high dose external beam radiation delivered precisely to an extracranial target in one or few fractions. It is characterized by patient immobilization, sparing of normal tissues from high dose radiation with steep dose gradients, sub-centimeter accuracy and accounting for organ motion.

For the first part of this review, studies were eligible for inclusion if SBRT was delivered to the primary kidney tumor in mRCC. Studies that combined the results of SBRT to primary and SBRT to metastatic sites in mRCC were excluded. For the second half of this review, we

included articles where SBRT and IO were used together in mRCC. Studies that included ablative radiation to brain metastases alone, non-IO immunotherapy or multiple histologies where renal cell was <10% of the patients were excluded. We limited our search to studies published in the English language. Case reports, reviews, editorials, and commentaries were excluded.

Results

After a comprehensive search of the Pubmed, ASTRO and ASCO databases, 3 full length articles were included in our review of SBRT to primary kidney in mRCC and 1 article and 3 abstracts were included in our review of combination SBRT and IO therapy for mRCC. A glossary index of terms in eTable2 is included in the online supplement for radiation specific details. The CONSORT diagram for the literature search is demonstrated in Figure 1 (SBRT to primary) and Figure 2 (combination SBRT and IO). A summary of the study details is depicted in Table 1 (SBRT to primary) and Table 2 (combination SBRT and IO).

SBRT to primary in mRCC

Treatment technique, parameters, and toxicity

Singh et al (21) examined the use of SBRT with a single dose of 15 Gy followed by CN 4 weeks later in a prospective series. SBRT was delivered using volumetric arc therapy (VMAT). The median planning target volume (PTV) was 441 cm^3. CN was feasible with no intra-op or immediate post-surgical complications. The rate of grade 2 and 3 toxicities was 25% and 6% respectively, however this toxicity rate is reported post-surgery and not specific to SBRT.

Correa et al published both a prospective (22) (N=12) and retrospective (23) (N=11) series examining the role of SBRT for patients not candidates for CN. The prospective series utilized a dose escalation scheme and the maximum tolerated dose was 35 Gy. Treatment was delivered using either VMAT or TomoTherapy. The tumor and entire ipsilateral kidney were included in the treatment volume to mimic CN. The median PTV was 763 cm^3 with ≥95% of the volume receiving 95% of the dose. The majority of patients (75%) experienced GI related toxicity. Grade 3 toxicities were experienced by 25% of patients. The retrospective series identified patients treated with doses ranging from 25-40 Gy, with 7 patients being treated to the tumor alone and 4 being treated to the whole kidney. The techniques used were VMAT, TomoTherapy or intensity modulated radiation therapy (IMRT). The median PTV was 819 cm^3 with ≥95% volume receiving 95% of the dose. SBRT was well tolerated as grade 2 and 3 toxicity was reported in 1 patient (9.1%) and grade 1 toxicity was reported in 5 patients (45.5%). Creatinine clearance (CrCl) did not differ pre and post SBRT.

Local control and survival
Local control and survival outcomes vary widely between studies. The 1-year overall survival (OS) ranged from 38-71% and 2-year OS ranged from 19-53%. Median survival and local control rate is only reported in the Correa et al prospective and retrospective series. Median survival was 6.7 and 20.4 months and local control was 100% and 85% respectively. All three studies are representative of mostly biopsy proven clear cell histology.

Systemic therapy use
All three studies report use of systemic therapy either pre or post SBRT with no concurrent use. In the prospective Correa et al series, 2 patients received mTOR inhibitors (Temsirolimus or Everolimus) and 5 received a TKI (Pazopanib or Sunitinib) while in the retrospective series 4 patients received TKIs (type not specified). No immunotherapy with IO is reported in either Correa et al series. In Singh et al, 9 patients received a TKI (Pazopanib, Sunitinib or Sorafenib) and 1 received bevacizumab. In addition, 6 of these patients also received Nivolumab (Nivo). Details regarding dose and timing of systemic therapy in relation to SBRT and subsequent response is not reported.

Combination SBRT and IO in mRCC
The studies detailed in Table 2 use various combinations of SBRT with IO. RADVAX (24) and NIVES (25) are ongoing clinical trials with published preliminary results in abstract form. RADVAX RCC is a multi-institution single arm phase II trial assessing the outcomes of combination SBRT to 1-2 metastatic sites with dual IO therapy using Nivo and Ipilimumab (Ipi). The primary outcome is safety and secondary outcome is objective response rate (ORR). NIVES is also a single arm phase II multicenter study with single agent Nivo and SBRT to a single metastasis. The primary outcome is ORR and secondary outcomes are progression free survival (PFS), overall survival (OS) and toxicity. Both RADVAX and NIVES have timed SBRT to be delivered after the first cycle of IO. Dengina et al (26) conducted a single arm prospective study in patients with stable mRCC currently on systemic therapy with either TKIs or IO. Of the 17 patients enrolled, only 5 were treated with IO therapy using Nivo. There was no standardized dose for SBRT delivery to a targeted lesion, with the mean equivalent dose in 2 Gy per fraction (EQD2) being 114 Gy (ranging from 40-276 Gy). A non-irradiated control lesion in the same organ was identified. Primary outcome was safety and secondary outcome was treatment response and time to progression in treated lesion vs. control lesion. Ansari et al (27) retrospectively reviewed 15 patients with either mRCC (N=7) or metastatic non-small cell lung cancer (mNSCLC, N=8). In total, 32 sites of metastases were treated in the 15 patients with 5 of these sites receiving SBRT and 27 receiving traditional palliative radiation. Patients were on immunotherapy with Nivo and received either palliative doses or SBRT doses of radiation, with

the most common indication for radiation being oligoprogressive disease (59% of patients). Outcomes of interest were radiologic response rate in target lesion, toxicity and symptom relief.

Toxicity

Toxicity of combination SBRT and IO is reported in Table 2. In RADVAX, 40% of patients experienced immune related adverse events (AE) requiring oral prednisone however the specific AE and breakdown in severity is not detailed. No patients were reported to have discontinued therapy due to AE. In NIVES, 10.1% of patients discontinued IO therapy due to AE with 24.6% of patients experiencing grade 3-4 immune related AE (most commonly diarrhea, amylase/lipase increase or hypothyroidism). SBRT toxicity rates are mentioned in NIVES, where it is reported that no grade 3-4 AE with SBRT occurred. Ansari et al report 2 patients who experienced grade 2 pneumonitis and no grade 3-4 AE. Toxicity rates for the mRCC patients in this series was not specified. Dengina et al reported no grade 2 or higher AE seen from SBRT. Grade 1 AE were experienced in 2 patients, with 1 experiencing esophagitis and the other experiencing radiation dermatitis. The authors of all studies conclude that the safety profile of combination SBRT with IO is acceptable.

Response outcomes

RADVAX reports an ORR of 56% in non-irradiated lesions, all partial responses (PR). Additional outcomes are yet to be reported with ongoing follow up. NIVES reports a 19% ORR in non-irradiated lesions with 1 patient experiencing a complete response (CR). Preliminary PFS and OS are reported as 4 months and 22.4 months respectively. Further results from NIVES with ongoing follow up will be reported. Dengina et al report 76% response in the treated lesion with 1 patient experiencing an abscopal response with SBRT and TKI therapy. Specific outcomes for patients who received Nivo is not detailed however the authors found no differences in response rate between those treated with Nivo vs those treated with TKIs. Ansari et al report a 70% response rate in the radiated lesion with 3 lesions demonstrating a complete response. In addition, 9 metastatic lesions were treated with radiation due to pain and of these sites responded to radiotherapy.

Discussion

Cytoreduction in mRCC was originally developed in the interferon (IFN) era (10,11) and supported by retrospective series (12) suggesting a role in the targeted era. It was hypothesized that removal of the primary prevented further seeding of metastatic disease, prevented complications of pain and hemorrhage from the primary tumor, and improved performance status for systemic therapy (11). The role of CN with contemporary combination IO approaches has come into question. The CARMENA trial demonstrated non-inferior survival with sunitinib alone compared to CN followed by sunitinib (13) in intermediate/poor risk patients. As yet, prospective evidence supporting the use of CN with combination IO remains an unmet need.

Preclinical models suggest that radiation can induce the tumor microenvironment and draining lymph nodes to promote both the primer and effector phases of the anti-tumor immune response (28). Examples include promoting anti-tumor immunity through major histocompatibility complex (MHC) 1 expression (29) and IFN-gamma secretion (30), expression and generation of molecular signals to promote the uptake and presentation of tumor derived antigens by dendritic cells (16) and increasing tumor infiltrating lymphocytes and effector T cells (17). CN may remove these primer and effector processes, thus potentially dampening the immune response. SBRT offers an alternative and less invasive cytoreductive approach in mRCC, particularly for those patients deemed unsuitable for CN, while still maintaining the pro-immunogenic advantages. This is supported by the demonstration by Singh et al (21) where increased expression of tumor associated antigens (TAA) and proliferating $CD8^+$ T cells after SBRT were found in radiated tumor specimens compared to historical controls. The use of SBRT for cytoreduction is a novel concept in mRCC and this review demonstrates the limited literature dealing with SBRT to primary kidney in mRCC. All 3 studies demonstrated that SBRT can be safely delivered with acceptable toxicity, even in the scenario of planned surgery. However, the low patient numbers and heterogeneity between studies makes it difficult to draw any significant conclusions despite promising results, particularly as Singh et al did not use SBRT for cytoreductive purposes.

With IO now becoming standard first line care in mRCC there is growing interest in utilizing these agents with SBRT. The exact mechanism of SBRT immunomodulation in the setting of IO in an active area of research. Thus, a number of prospective clinical trials are currently underway to investigate the combination of IO and SBRT in mRCC. As previously mentioned, there is optimism that SBRT and IO therapy may be the basis to understanding the abscopal response, whereby both targeted and non-targeted sites of disease respond post radiation (18-20). RADVAX and NIVES are still ongoing and have yet to publish long term data of all outcomes. Current results are mostly limited to safety profile and radiologic response rates with short follow up. There is limited survival data reported with only NIVES reporting an OS and PFS rate. Based on preliminary data from these prospective trials, the toxicity profile of combination therapy with IO and SBRT doesn't appear to be worse than toxicity rates reported in major clinical trials establishing dual IO as first line systemic therapy (29,30). Whether the ORR ends up translating to meaningful benefit for patients will have to await longer follow up data. Conclusions from the Dengina et al and Ansari et al series are difficult given the heterogeneous patient populations. Various systemic therapies were used in Dengina et al with a minority receiving Nivo. Various radiation doses were used in both series, and in Ansari et al, majority of lesions received what would be considered more traditional palliative doses rather than true ablative doses. Given this, combination therapy appears to be tolerable and safe for patients however for now, the standard of care remains systemic therapy alone with IO.

An aspect of combination SBRT and IO therapy that remains unclear is the sequencing and dose fractionation of SBRT. There appears to be differences in optimal timing depending on IO agent (31). Blockade of PD-1 and PD-L1 appears to work best when administered concurrently with radiation due to the effect on newly activated and exhausted T cells (32) while CTLA-4 inhibition works best when administered prior to radiation due to action on naïve and regulatory T cells (33). In addition, pre-clinical models suggest that the largest possible dose per fraction may not be the most immunogenic and that doses ranging from 8-10 Gy per fraction in 1-3 fractions may be sub therapeutic but provide the strongest anti-tumor immune response (34,35). As demonstrated in our search for prospective and retrospective evidence, the timing and dose/fraction is still unclear with variation in how SBRT and IO are being delivered in clinical practice.

To that end, this review points to the dire need of well-conducted, pragmatic trials to address these questions. One trial of particular interest is CYTOSHRINK (NCT04090710), a phase II multi-center randomized controlled trial evaluating upfront cytoreductive SBRT to primary kidney in mRCC with combination Ipi/Nivo in patients who are deemed CN-ineligible (36). The primary outcome is progression free survival. We eagerly await the results of this trial and others to inform our management of mRCC.

Conclusions

Cytoreductive SBRT and combination SBRT with IO therapy represent promising treatment strategies in mRCC. The evidence for clinical benefit is currently limited and require further study with well-designed randomized controlled trials to inform our practice. Systemic therapy with dual IO remains standard of care. Ultimately, patients with mRCC would benefit from multi-disciplinary discussion to ensure rational timing and use of systemic therapy, surgery, and/or radiation where appropriate. Our care for these patients would be further enhanced by the availability of nimble, pragmatic clinical trials that reflect the remarkably evolving landscape of this disease.

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Figures and Tables

Fig. 1. CONSORT diagram, literature review for SBRT to primary kidney in metastatic renal cell carcinoma. ASCO: American Society of Clinical Oncology; ASTRO: American Society for Radiation Oncology; SBRT: stereotactic body radiotherapy.

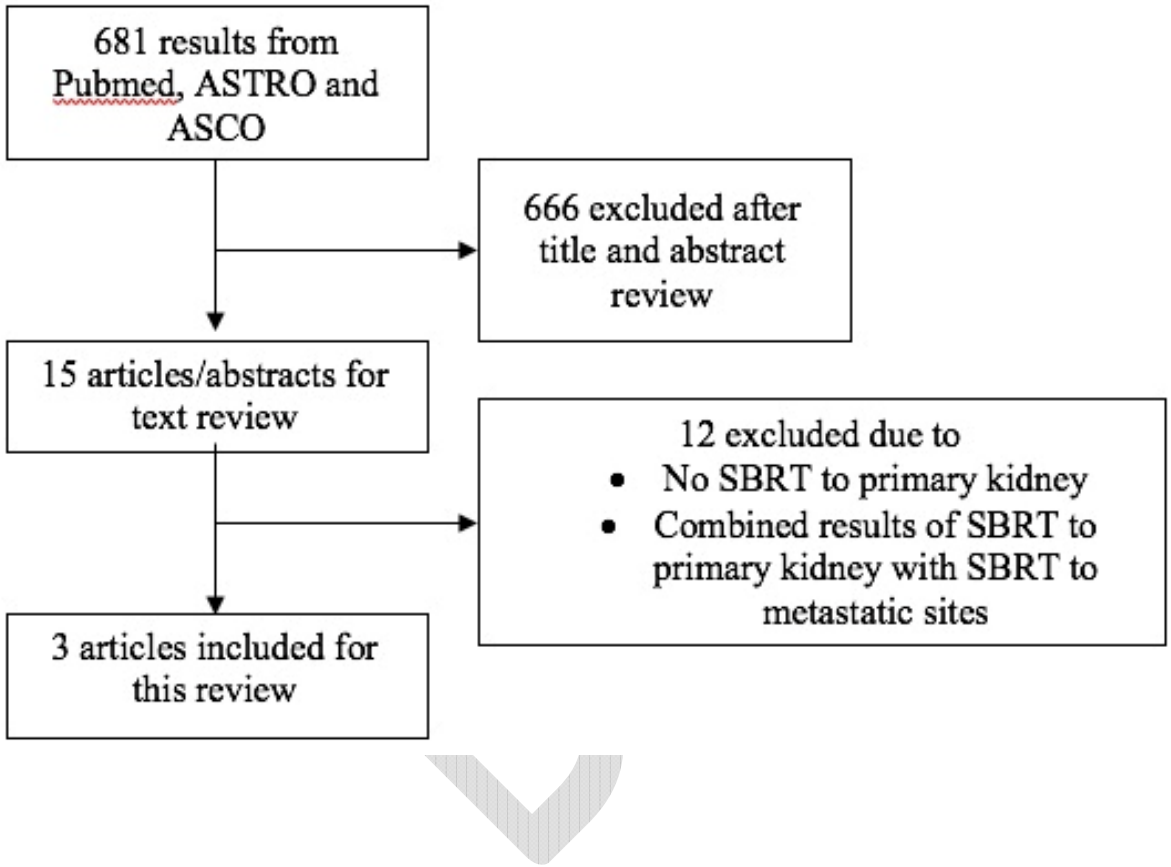

Fig. 2. CONSORT diagram, literature review for SBRT and ICIs in metastatic renal cell carcinoma. ASCO: American Society of Clinical Oncology; ASTRO: American Society for Radiation Oncology; ICI: immune checkpoint inhibitor; SBRT: stereotactic body radiotherapy.

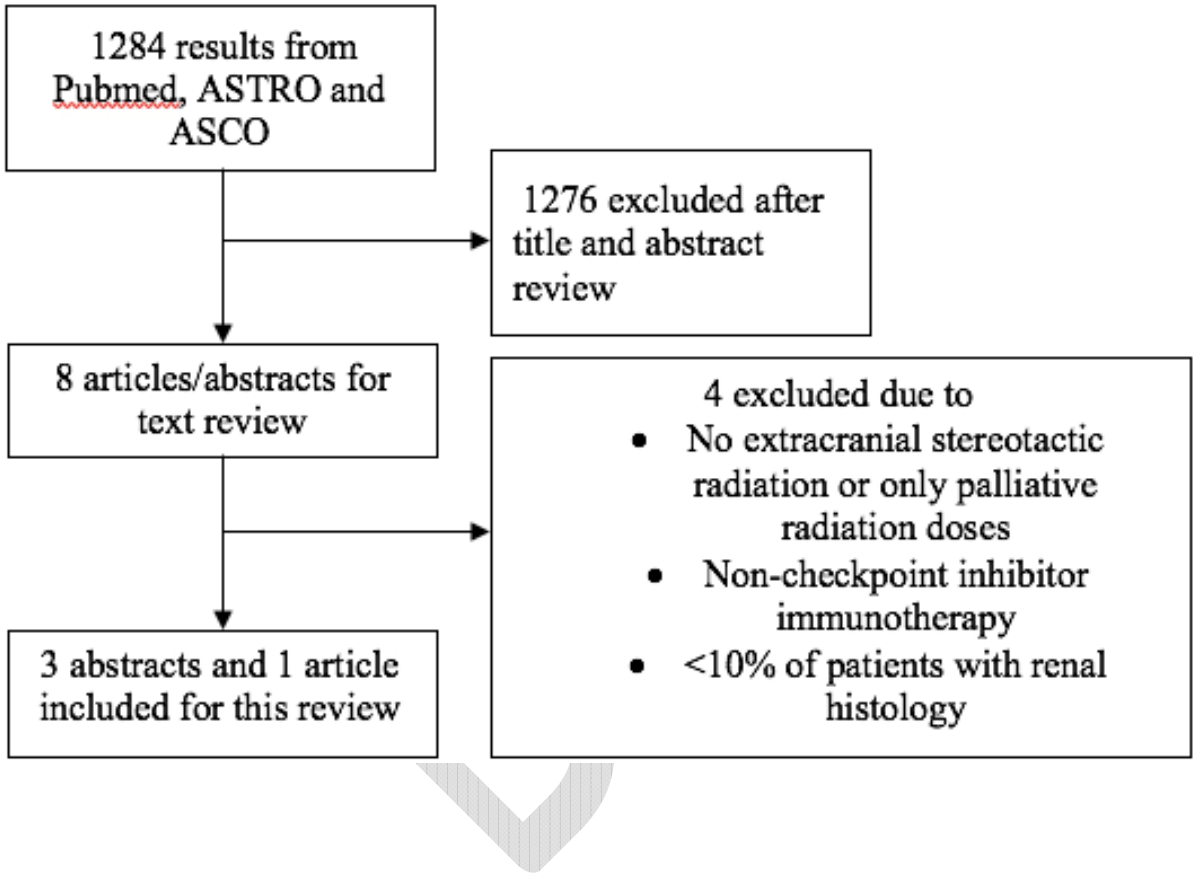

Table 1. Summary of articles using SBRT to primary kidney in mRCC									
Authors	**Number of patients**	**Median age**	**IMDC group (%)**	**Histology**	**Median size, cm**	**Radiation dose (Gy)/fraction**	**Local control**	**Overall survival**	**Median followup (months)**
Singh et al, 2017	14[a]	64	Intermediate: 13 Poor: 1	Clear-cell: 12 Chromophobe: 1 Papillary urothelial: 1	Not reported	15/1	Not reported	1-year: 71% 2-year: 48% Median: Not reported	Not reported
Correa et al, 2018 – prospective	12	67	Favorable: 1 Intermediate: 8 Poor: 3	Clear-cell: 9 Papillary: 2 Poorly differentiated carcinoma: 1	8.7	25/5: 3 30/5: 6 35/5: 3	100%	1-year: 38% 2-year: 19% Median: 6.7 months	5.8
Correa et al, 2018 – retrospective	11[c]	79	Intermediate: 6 Poor: 5	Clear-cell: 5 Spindle-cell: 1 Undifferentiated: 1 Unknown: 4	9.5	25/5: 6 30/5: 3 35/5: 1 40/5: 1	85%[d]	1-year: 53% 2-year: 53% Median: 20.4 months	46.8

[a]Initially 16 but 2 patients did not go on to receive surgery. [b]Only clear-cell histology patients included in statistical analysis. [c]Three patients were locally advanced unresectable. [d]Only 7 patients had followup imaging to assess for local control. IMDC: International Metastatic RCC Database Consortium; mRCC: metastatic renal cell carcinoma; SBRT: stereotactic body radiotherapy.

Table 2. Summary of articles using combination SBRT and ICI therapy in mRCC								
Authors	**Number of patients**	**Median age**	**IMDC group**	**Histology**	**Immunotherapy**	**Radiation dose (Gy)/fraction**	**Toxicity**	**Outcomes**
Hammers et al, 2020 RADVAX RCC – abstract	25	Not reported	Favorable: 2 Intermediate: 20 Poor: 3	Clear-cell: 25	Nivolumab (Nivo) (3 mg/kg) and ipilimumab (Ipi) (1 mg/kg) IV q3weeks followed by Nivo monotherapy	50/5 delivered to 1–2 metastatic lesions between the 1st and 2nd cycle of Nivo/Ipi	40% patients required oral prednisone for classic immune-related AEs 8% grade 2 pneumonitis	56% ORR of non-irradiated lesions, all PR
Masini et al, 2020 NIVES – abstract	69	67	Favorable: 14 Intermediate/Poor: 55	Clear-cell: 55 Other not specified: 14	Nivo 240 mg IV Day 1 q2weeks x 6 months then 480 mg IV q4weeks in responding patients until progression or unacceptable toxicity	30/3 delivered to 1 metastatic lesion 7 days after 1st Nivo	10% discontinued treatment due to AE 25% experienced grade 3–4 immune-related toxicity	19% ORR of non-irradiated lesions, 1 patient had CR Median PFS 4 months, median OS 22.4 months

							No grade 3–4 toxicities from SBRT	
Dengina et al, 2019	17	54.5	Not reported	Clear-cell: 17	Nivo (n=5), dose and scheduling not specified[a]	Various doses not specified,[b] delivered same day as systemic therapy (n=15) or in between cycles (n=2)	Grade 1 toxicity 12% No grade 2 or higher toxicity seen	76% response rate in target lesion, 5 patients had CR and 8 had PR
Ansari et al, 2018 – *abstract*	15[c]	59	Not reported	Not reported	Nivo, dose and schedule not specified	Various doses not specified,[d] delivered to a total of 32 lesions within 2 weeks of Nivo	No grade 3–4 AE, 2 patients had grade 2 pneumonitis	70% response rate in target lesion with 3 lesions demonstrating CR

[a]Others treated with sunitinib (n=6), everolimus (n=3), lenvatinib + everolimus (n=1), temsirolimus (n=1), and sorafenib (n=1). [b]Mean equivalent dose in 2 Gy (EQD2) 114 Gy (range 40–276). [c]N=7 with mRCC, other 8 patients had metastatic non-small-cell lung cancer. [d]both SBRT and traditional palliative doses given. AE: adverse event; CR: complete response; IMDC: International Metastatic RCC Database Consortium; mRCC: metastatic renal cell carcinoma; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; SBRT: stereotactic body radiotherapy.