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REVIEW ARTICLE

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Role of Radiotherapy in Metastatic Renal Cell Carcinomas: An Evolutionary Journey in a Misunderstood Histological Type

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Renal cell carcinoma (RCC) has traditionally been considered one of the most radioresistant tumors based on *in vitro* and clinical studies that utilized a low biologically effective dose. However, recent studies have suggested that administering a higher radiation dose to RCC can lead to satisfactory local control and potentially long-lasting disease control. Thanks to significant advances in radiotherapy technology, it is now feasible to deliver higher radiation doses to tumors while preserving the organs at risk. Furthermore, over the past decade, a crucial role of radiotherapy has emerged in metastatic cancers, both for symptom palliation and for the elimination of tumor niches. This review discusses the current evidence and future perspectives concerning the role of radiotherapy in metastatic RCC.

Key Words: Renal cell carcinoma, Radiotherapy, Radiation therapy, SABR, Oligometastasis

INTRODUCTION

Kidney cancer affects approximately 400,000 patients worldwide annually year, resulting in nearly 200,000 fatalities [1]. Renal cell carcinoma (RCC), the most common histological subtype of kidney cancer, accounts for over 90% of all cases. This type of cancer is most prevalent in developed regions, including North America and Western Europe. In Korea, the incidence of RCC has reached levels comparable to those seen in Western countries. In 2020, kidney cancer accounted for over 2% of new cancer diagnoses and approximately 1% of cancer-related deaths in Korea [2]. Data from the Surveillance, Epidemiology, and End Results database indicate that the survival rate for patients with RCC has gradually improved over the past few decades, mirroring trends seen in other types of malignancies [3]. As patients' survival duration increases, the need to address metastatic disease becomes increasingly urgent. The survival rate for patients with metastatic RCC (mRCC) is also expected to rise due to the approval of immune checkpoint inhibitors such as pembrolizumab, nivolumab, avelumab, and ipilimumab. These can be used either as standalone treatments or in combination with tyrosine kinase inhibitors (TKIs) [4-7].

Radiotherapy (RT) plays a fundamental role in cancer treatment, with the primary objectives being to cure the disease, prevent its recurrence, and provide palliative relief from symptoms. Historically, due to the prevailing belief that RCC is radioresistant [8], the use of RT in managing mRCC has been largely limited to symptom management, particularly in addressing pain or neurological symptoms caused by bone or brain metastases. In fact, the use of RT has seen a decline from 1998 to 2010 for localized, locally advanced, and mRCC, as per the National Cancer Database [9]. However, with the advent of technological advancements

in RT that allow for the precise delivery of radiation beams to the target while minimally impacting surrounding healthy tissues, a shift in the role of RT in managing (oligo)metastatic RCC is taking place. The American Society of Clinical Oncology, European Association of Urology, and National Comprehensive Cancer Network guidelines now recommend RT as a treatment option for mRCC, either as a metastasis-directed ablative or palliative treatment [10-12]. In this review, our aim is to discuss the current evidence and future perspectives on the emerging, or perhaps already established, role of RT in treating extracranial (oligo)metastatic RCC.

RADIOSENSITIVITY OF RCC

RCC has long been considered a histological type of cancer that is resistant to conventionally fractionated RT, with doses of ≤1.8–2 Gy per fraction. In a study by Deschavanne and Fertil [8], RCC was found to be the most radioresistant among 76 types of isolated cancer and normal cells. It required the highest radiation dose for cell inactivation and demonstrated the highest survival rate at 2-Gy irradiation *in vitro*. DiBiase and colleagues observed clinically that in patients with mRCC who underwent palliative RT for symptomatic lesions, a lower RT dose below the biologically effective dose (BED = total dose × [1 + daily dose/(α/β ratio)]) of 50 Gy (using an α/β ratio of 10 Gy) resulted in a significantly lower complete symptomatic response rate (59% vs. 39%). This implies that RCC cells may not respond effectively to lower RT doses [13]. Additionally, RCC has been observed to upregulate the α-subunits of the hypoxia-inducible factors (HIF-1α), which could potentially be associated with radioresistance in hypoxic conditions. The regulation of HIF-1α is influenced by mutations or methylation of the von Hippel-Lindau tumor suppressor gene, a common occurrence in most clear-cell RCCs [14]. These findings have led to the widespread misconception that RCC is radioresistant.

However, a paradigm shift has occurred in the field of RT, spurred by technological advancements that allow for precise tumor targeting and the delivery of a higher biological RT dose to the tumor, while sparing normal tissues. This represents a significant improvement over past methods [15]. Ning et al. [16] studied 2 human RCC cell lines (Caki-1 and A498) and reported that the α/β ratio of RCC cells ranged from 2.6 to 6.9 Gy, which is lower than the dose delivered to most radiosensitive tumor types (α/β ratio of approximately 10 Gy). From a radiobiological perspective, this suggests that a higher dose per fraction of RT could be more effective in killing RCC cells. It has also been reported that endothelial cell apoptosis, which may contribute to cancer cell death, can be inhibited by activated HIF-1α when irradiated at a dose range of 1.8–3 Gy per fraction *in vitro* [17]. When a dose of ≥8 Gy per fraction was used, endothelial cell apoptosis led to cancer cell death.

Promising results have been reported for primary RCC using a higher fractional dose, radiosurgery, or ultrahigh-dose stereotactic "ablative" RT (SABR or stereotactic body radiation therapy) [18-20]. SABR is an ultra-hypofractionated form of RT, which is a highly focused form of RT that delivers an intense dose per fraction (>5 Gy) concentrated on a tumor while limiting the dose to the surrounding organs. This therapy is typically administered in 1 to 5 fractions. Staehler et al. [18] reported an impressive local control rate of 98% at 9 months and a complete remission rate of 42.2% in 45 primary renal tumors, including RCC and transitional cell carcinoma of the renal pelvis, using CyberKnife robotic radiosurgery. The International Radiosurgery Oncology Consortium for Kidney reported an excellent 4-year local control rate of 97.8% in 223 patients receiving single-fraction SABR with a median dose of 25 Gy or multifraction SABR of 40 Gy in 4 fractions for primary RCC [19]. Although the estimated glomerular filtration rate declined by 5.5±13.3 mL/min/1.73 m^2 from baseline after SABR, this treatment strategy could be a valuable option for patients who are inoperable or may require hemodialysis after surgery. According to a previous meta-analysis, the most commonly used SABR schedule for primary RCC is 26 Gy in one fraction and 40 Gy in 5 fractions [20]. These treatments resulted in a random-effect estimated local control rate of 97.2%, and local failure tended to occur in low-dose arms.

DOSE-RESPONSE RELATIONSHIP IN RT FOR mRCC

Clinical studies have gathered evidence supporting a dose-response relationship in RT for mRCC, with the response

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including symptom relief and tumor control. In the study conducted by DiBiase et al. [13], a BED (using an α/β ratio of 10 Gy) of more than 50 Gy led to significantly improved symptom relief. This contrasts with earlier studies that used conventional fractionation with moderate doses in the treatment of RCC. Wersäll et al. [21] reported a high local control rate following RT with a high dose-per-fraction (8–15 Gy per fraction) regimen in patients with either primary or mRCC lesions. After administering dose-fractionation schedules of 8 Gy × 4 fractions, 10 Gy × 4 fractions, and 15 Gy × 3 fractions, recurrence was noted in only 3 out of 162 treated patients, the majority of whom had metastatic lesions. A retrospective study from the Memorial Sloan-Kettering Cancer Center assessed the effectiveness of a single fraction of 18–24 Gy and hypofractionation with 20–30 Gy in 3 to 5 fractions in 105 patients with mRCC lesions [22]. Compared to a single fraction of 24 Gy, corresponding to the highest BED, a single fraction of less than 24 Gy or hypofractionation resulted in a significantly lower 3-year local progression-free survival (PFS) rate (88% vs. 17%–21%, respectively). However, this finding should be interpreted with caution, as this study is among those that reported the lowest local control following fractionated SABR.

Despite the notably higher tumor control rates associated with high total doses of RT and increased doses per fraction using SABR, it is important to exercise caution when using RT for metastatic lesions from RCC due to potential treatment-related toxicity. Thibault et al. [23] conducted a multi-institutional analysis of osteolytic vertebral metastases from RCC, finding a 43% incidence of vertebral compression fractures in patients treated with a single 24 Gy fraction of SABR. In contrast, the rates were 24% and 14% in patients treated with 20–23 Gy and less than 20 Gy, respectively. However, the crude 1- to 2-year local control of metastatic lesions from RCC treated with a higher total dose and higher dose per fraction, particularly with SABR, is reported to be approximately 85%–100% in the literature. While a balance between tumor control and toxicity must be considered, there is a clear RT dose-response relationship in RCC. The impressive local control rates associated with high-dose RT suggest that RCC is no longer resistant to high-dose regimens. From our perspective, a BED of at least 100 Gy or higher (using an α/β ratio of 3 Gy) is necessary to locally control lesions with an RCC histology. Moreover, we recommend a higher BED through the use of SABR when feasible, as most reported and ongoing studies have utilized SABR and a BED of over 100 Gy in the treatment of mRCC. This will be further discussed later in this review.

EMERGING ROLE OF RT IN OLIGOMETASTATIC CANCER

The survival rate of patients with metastatic cancer has gradually improved over the past several decades. This is primarily due to advancements in cancer treatment strategies, which are based on a more profound understanding of cancer biology and the prognosis of oligometastatic cancer [24]. In this context, RT serves to eliminate primary or metastatic cancer sites or to alleviate progressively worsening symptoms [25]. The term "oligometastasis" was first introduced by Hellman and Weichselbaum in 1995 to describe tumors with a limited number of distant metastases [26]. There is ongoing debate regarding the establishment of a threshold for metastatic sites, whether it be 3, 4, or more. However, it is clear that patients with a limited number of metastases have significantly longer survival rates than those with extensive metastases [27]. The "seed and soil" concept, which emphasizes the importance of eradicating the metastatic tumor niche, is widely accepted today. This concept has demonstrated clinical relevance over the past 5 years across various types of cancers (Table 1) [28-38].

The most revolutionary study published in recent years is the SABR-COMET phase II trial conducted by Palma et al. [28,29]. This trial involved 99 patients with various types of cancer, all of whom had ≤5 metastatic lesions and a life expectancy of >6 months. These patients were randomly assigned to receive either the standard of care (SOC) or SOC in conjunction with SABR for all metastatic sites. After a median follow-up period of 51 months, it was found that SABR not only improved PFS, but also significantly increased overall survival (OS). The 5-year survival rate was 42.3% for the SABR group, compared to 17.3% for the SOC group, with a median survival benefit of 22 months [29]. The success of this phase II trial led to the initiation of 2 phase III trials, SABR-COMET-3 [30] and SABR-COMET-10 [31]. These trials are exploring the benefits of adding SABR to

Table 1. Summary of randomized trials demonstrating the benefit of radiotherapy in oligometastatic cancers

Histology	Study	Year of publication	Treatment	Endpoint	Beneficial outcome
Any	SABR-COMET [28,29]	2019	RT	OS and PFS	OS: 28 → 50 months (p=0.006) PFS: 5.4 months → not reached (p=0.001)
Prostate	ORIOLE [32]	2020	RT	PFS	5.8 → Not reached (p=0.002)
	EXTEND [33]	2023	RT	PFS	15.8 → Not reached (p<0.001)
	STOMP [34]	2018	RT or surgery	ADT-free survival	13 → 21 Months (p=0.11)
	ARTO [35]	2023	RT	6-month biochemical response PFS	6-Month biochemical response: 68.3% → 92% (p=0.001) Biochemical PFS: 36 months → not reached (p=0.002)
NSCLC	Gomez et al. [36]	2016	RT or surgery	PFS	3.9 → 11.9 Months (p=0.005)
	Iyengar et al. [37]	2018	RT	PFS	3.5 → 9.7 Months (p=0.01)
	SINDAS	2023	RT	PFS and OS	PFS: 12.5 → 20.2 months (p<0.001) OS: 17.4 → 25.5 months (p<0.001)

RT, radiotherapy; OS, overall survival; PFS, progression-free survival; ADT, androgen deprivation therapy; NSCLC, non-small cell lung cancer.

SOC in the standard treatment of patients with ≤3 and 4–10 metastases, respectively.

Individual trials for specific types of cancer have demonstrated the benefits of incorporating metastasis-directed SABR without causing excessive toxicity in patients with oligometastasis. The ORIOLE/EXTEND [32,33] and STOMP [34] phase II trials have indicated that adding metastasis-directed SABR to the standard treatment for patients with hormone-sensitive oligometastatic prostate cancer enhances both the PFS and androgen deprivation therapy-free survival. Moreover, the Italian ARTO phase II study reported a significant improvement in PFS when metastasis-directed SABR of BED (α/β ratio of 3 Gy) exceeding 100 Gy was included with abiraterone acetate in the treatment of patients with castrate-resistant prostate cancer with ≤3 bone or lymph node metastases [35]. The beneficial impact of metastasis-directed SABR (or surgery) on PFS and OS has also been confirmed in patients with oligometastatic non-small cell lung cancer through several prospective clinical trials [36-38]. When combined with first-line TKI, metastasis-directed RT significantly extended the OS from 17.4 to 25.5 months, as reported in the SINDAS trial conducted on patients with oligometastatic non-small cell lung cancer [38]. In general, SABR for oligometastatic cancer achieves a 1-year local control rate of approximately 95% and a 1-year OS rate of 85%, with acute and late grade 3 or higher toxicity rates of approximately 1%–2% [39].

The role of RT is increasingly recognized as significant in the treatment of patients with metastatic cancer, with the aim of mitigating the severe consequences associated with metastasis. A recent study by Gillespie et al. [40] showed that prophylactic RT for high-risk asymptomatic bone metastases can significantly reduce the risk of subsequent skeletal-related events. These events include pathologic fractures, spinal cord compression, orthopedic surgery to the bone, and/or palliative RT for pain [40]. High-risk asymptomatic bone metastasis was defined in the study as: a bulky site of disease in the bone (≥2 cm); disease involving the hip, shoulder, or sacroiliac joints; disease in the long bones occupying one-third to two-thirds of the cortical thickness; disease in the vertebrae of the junctional spine (C7–T1, T12–L1, and L5–S1); and/or disease with posterior element involvement.

RT FOR OLIGOMETASTATIC RCC

One of the earliest reports of successful oligometastasis eradication in RCC was documented in 1939 by Barney and Churchill [41]. They performed a nephrectomy and subtotal lobectomy on a patient with kidney adenocarcinoma and a single lung metastasis. The patient lived for over 5 years without any signs of the disease. Since that time, cytoreductive nephrectomy of the primary disease has significantly improved OS, providing an absolute benefit of several months for patients with mRCC [42-44]. Surgical metastasectomy also appears to extend OS (with a median survival of 36–142 months) compared to cases where surgical metastasectomy was not performed (with a median survival of 8–27 months) in patients with oligometastatic RCC. A subset of patients with mRCC can be safely monitored for a certain period before starting systemic treatment, particularly those with fewer International Metastatic Database Consortium adverse risk factors or metastatic disease sites [45,46].

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These findings imply that RT could have a significant role in mRCC, potentially aiding in the cytoreduction of metastatic tumor sites or postponing the start of systemic treatment.

1. Retrospective Studies on SABR in Oligometastatic/ Oligoprogressive RCC

To date, several published retrospective studies have reported excellent local control and safety of SABR for metastatic sites in patients with oligometastatic RCC [47]. Here, we discuss some of the most notable studies found in the literature [47-52]. Each of these studies was a retrospective review and included fewer than 100 patients.

Stenman et al. [48] reported the outcomes of SABR and/or surgical metastasectomy for oligometastatic RCC in the era of targeted agents. They found a median survival time of 51 months, which was significantly longer than anticipated. Of the 60 patients treated with curative intent, 15% remained relapse-free, with a median follow-up period of 87 months. Zhang et al. [49] examined the role of SABR in postponing the systemic treatment of patients with oligometastatic RCC. They found a local control rate of 91.5% at 2 years, with no reported grade 3 or higher toxicities following SABR. The median duration of freedom from systemic therapy was 15 months post-SABR. Schoenhals et al. [50] reported a median PFS of 9 months and a 1-year local control rate of 93% following SABR with a median dose of 36 Gy in 3 fractions. Notably, patients who received immunotherapy showed a significantly longer PFS than those who did not (>28 months vs. 9 months, p=0.0001). Researchers from the MD Anderson Cancer Center reported a 1-year PFS rate of 52% following SABR with a BED (α/β ratio of 2.63 Gy) of >100 Gy for patients with oligometastatic RCC [51]. In this study, the PFS was similar among patients who escalated, maintained, or discontinued systemic treatment at oligoprogression. This result underscores the potential value of SABR in delaying the escalation of systemic treatments, leading to decreased toxicity and improved quality of life. A previous meta-analysis of 28 studies assessing the outcomes of SABR for oligometastatic RCC, which included over 1,000 extracranial metastatic lesions, reported 1-year survival and local control rates of 86.8% and 89.1%, respectively [47]. Only 0.7% of the patients developed grade 3–4 toxicity.

2. Prospective Studies on SABR in Oligometastatic or Oligoprogressive RCC

Unfortunately, no prospective phase III randomized trials have assessed the role of metastasis-directed SABR in oligometastatic RCC. However, a number of single-arm prospective studies have demonstrated encouraging results with SABR, either in terms of postponing the start of systemic treatments or in its combination with systemic therapies such as TKI or immune checkpoint blockade (ICB) (Table 2) [53-57].

In the multicenter prospective Volga trial conducted by Dengina et al. [54], 17 patients with mRCC who had maintained stable disease for at least 4 months following TKI or ICB therapy were enrolled. In this study, SABR was administered to selected target lesions, while nontarget lesions in the same organ were identified and deliberately excluded from the RT field. As a result, only a subset of the metastatic lesions received irradiation, and a third of the patients had only a single metastatic site. A higher response rate was observed when the fraction size exceeded 10 Gy per fraction and the equivalent dose was 100 Gy or higher (2-Gy per fraction; α/β ratio of 2.6 Gy). Despite reporting a promising response rate of 76% for the irradiated lesions, this study did not provide data on PFS and OS. This omission hinders further interpretation and the clinical application of partial irradiation of metastatic lesions in mRCC.

SABR could potentially delay the initiation of systemic treatment in patients with oligometastatic mRCC, which could positively affect their quality of life. A prospective phase II feasibility study was conducted by our colleagues at MD Anderson Cancer Center to explore the use of SABR as an alternative to systemic therapy in patients with oligometastatic mRCC, defined as having 1–5 metastases [55]. All metastatic sites underwent metastasis-directed SABR; the most commonly used RT dose-fractionation regimen was 50 Gy in 4 fractions. All patients had either stopped or had never started systemic treatment before SABR. In the first round of RT, a total of 43 lesions in 30 patients were irradiated. The median PFS and local control rates were 22.7 months and 97%, respectively. While the OS outcomes of this "upfront" approach combined with SABR are still unknown, given the significant toxicity burden associated with systemic

Table 2. Summary of prospective trials evaluating SABR for oligometastatic renal cell carcinoma

Study	Year of publication	Trial phase	No. of lesions	RT dose	Systemic treatment	Outcome	Comment
Svedman et al. [53]	2006	II	82	8 Gy × 4 fractions 10 Gy × 4 fractions 15 Gy × 2 fractions 15 Gy × 3 fractions	Any	Local control: 98%	Approximately 19% of patients were followed up for less than 6 months.
VOLGA [54]	2019	Ib	17	Mean equivalent dose in 2-Gy fraction (EQD2), 114 Gy (range, 40–276 Gy)	TKI or immune checkpoint inhibitors	Complete or partial remission: 76%	Not all lesions were irradiated; fraction size of 10 Gy or higher (EQD2 dose of 100 Gy or higher) most often led to complete response (p<0.01).
Tang et al. [55]	2021	II	43	1–5 fractions with 7 Gy or higher per fraction (the most common regimen, 50 Gy in 4 fractions)	None	PFS: 22.7 months	All patients had nephrectomy prior to treatment.
Cheung et al. [56]	2021	II	57	Lung: 48–60 Gy in 3–8 fractions Liver: 30–60 Gy in 3–6 fractions Adrenal/kidney/lymphadenopathy/ nonspine bone: 30–40 Gy in 5 fractions Spine: 18–40 Gy in 1–5 fractions Brain: 15–30 Gy in 1–5 fractions	Last >3 months of TKI	1-yr local control: 93% Median PFS after SABR: 9.3 months Median time to change in systemic therapy: 12.6 months-year overall survival: 92%	Oligoprogressive patients during TKI treatment
RAPPORT [57]	2022	I/II	83	20 Gy × 1 fraction	Pembrolizumab following RT	2-yr local control: 92% Progression-free survival: 45% Overall survival: 74%	Four patients (13%) with grade 3 toxicity

SABR, stereotactic ablative radiotherapy; RT, radiotherapy; TKI, tyrosine kinase inhibitor, PFS, progression-free survival.

treatments, this strategy, as explored by Tang et al. [55], merits further investigation.

In addition to the "upfront" strategy, where all metastatic lesions are irradiated before systemic treatment begins, the "oligoprogression" strategy can also be considered for patients already receiving systemic treatment. A prospective phase II trial in Canada assessed the role of SABR during TKI treatment in patients with oligoprogressive mRCC, defined as having 1–5 progressive sites [56]. SABR was administered to all oligoprogressive sites, with a predetermined RT dose fractionation for each anatomical site. The PFS following SRT was 9.3 months, and the 1-year local control rate was 93%, suggesting that most treatment failures occurred after the first year of treatment. The "oligoprogression" strategy showed a somewhat shorter PFS compared to the "upfront" strategy, as reported by Tang et al. [55]. This difference is likely due to the emergence of a subclinical disease that may have developed resistance to the patient's ongoing TKI treatment. However, this strategy did prevent changes to the systemic treatment regimen for over a year in nearly half of the patients.

Recently, ICBs have been used to treat patients with mRCC, either with or without TKIs [4-7]. In summary, SABR has the potential to enhance the effectiveness of ICBs by functioning as an *in situ* vaccine and initiating proinflammatory processes within the tumor microenvironment. Following the initiation of immunogenic cell death via RT, tumor-associated antigens are released from the cancer cells, leading to the recruitment of cytotoxic T cells [58-60]. Clinical trials that have combined ICBs with RT have demonstrated promising results, particularly in the case of non-small cell lung cancer [61,62]. As previously mentioned, Schoenhals et al. [50] reported that the combination of SABR, delivered at a median dose of 36 Gy in 3 fractions, with ICBs resulted in superior PFS compared to the combination of SABR and other systemic treatments. In the RAPPORT trial, as reported by Siva et al. [57], a single-fraction SABR of 20 Gy was administered to all metastatic sites, followed by 8 cycles of pembrolizumab in 30 patients with oligometastatic (1–5 metastases) mRCC. A total of 83 oligometastases were irradiated, resulting in 2-year local control and PFS rates of 92% and 45%, respectively. Future research should focus on addressing several key issues: the optimal RT dose-fractionation regimen when combined with ICBs, the sequence of combination, the duration of maintenance, and the dosage of ICBs.

When considering the combination of SABR and ICBs, *in*

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vitro studies have suggested that a fractional dose of 8–12 Gy may be the most effective for antitumor immunity [63,64]. A pivotal report by Vanpouille-Box et al. [63] showed that RT fractions exceeding 12–18 Gy can elevate the expression of the endonuclease Trex1, which in turn can lead to diminished immunogenicity. However, in practical applications, a higher fractional dose and total BED might enhance clinical outcomes in patients with oligometastasis, irrespective of antitumor immunity. While the optimal dose-fractionation regimen for oligometastasis-directed SABR in RCC still needs to be established, a recent phase III randomized trial reported that a single fraction of 24 Gy (BED 432 Gy with α/β ratio of 3 Gy) led to a significantly improved local control rate compared to 27 Gy in 3 fractions (BED 108 Gy with α/β ratio of 3 Gy) [65]. Importantly, distant metastasis was also significantly reduced with a higher BED at 3 years (5.3% vs. 22.5%, p=0.010). Eight patients (6.8%) participating in this study had renal cancers [65]. Therefore, further research is necessary.

3. Palliative RT for Bone Metastasis From RCC

Historically, RT has been extensively utilized for several decades to alleviate symptoms associated with metastatic lesions from RCC, and its effectiveness is well-documented [66-69]. However, the correlation between the dose-response relationship and the effectiveness of treatment in symptom relief remains a topic of debate. Lee et al. [69] carried out a prospective phase II trial to evaluate the effectiveness of palliative RT, using a regimen of 30 Gy in 10 fractions, which is the most commonly employed RT regimen for symptom relief. While pain relief was noted in 83% of patients following RT, the median duration of site-specific pain response was a mere 3 months, which is suboptimal.

Moreover, although not confined to the RCC histology (renal cancer, 7%), Sprave et al. [70] reported that a single-fraction SABR dose of 24 Gy resulted in a superior 6-month pain response compared to a 30 Gy SABR dose delivered in 10 fractions for patients with painful spinal metastases. In the NRG Oncology/RTOG 0631 phase III trial, which compared a single-fraction 16–18 Gy dose with a single-fraction 8 Gy dose for vertebral metastases, no significant difference was observed in patient-reported pain response at 3 months post-RT [71]. However, only 15% of patients had a "radioresistant" histology such as RCC, melanoma, and soft tissue sarcoma. Sahgal et al. [72] conducted a comparison of the efficacy of a 24 Gy dose in 2 fractions versus a 20 Gy dose in 5 fractions for painful spinal metastases (RCC accounted for 8.7% of cases) in a phase II/III randomized trial. The complete response rate for pain was significantly higher in patients treated with 24 Gy in 2 fractions, and this difference was maintained at 6 months post-RT. The patients included in this study had relatively stable vertebrae, as indicated by a Spinal Instability in Neoplasia Score of ≤12. A recent retrospective study, in which 30% of patients had radioresistant histology (including gastrointestinal, RCC, thyroid, sarcoma, and melanoma), suggested that a slight difference between 24 Gy in 2 fractions and 28 Gy in 2 fractions might lead to better local control without increasing the risk of vertebral compression fracture [73]. For patients with painful metastases, this marginal dose difference could be associated with a durable response. Following treatment with intermediate hypofractionated RT delivered in 24 fractions (2.5 Gy per fraction; total dose: 60 Gy; BED: 110 Gy with an α/β ratio of 3 Gy), all infiltrative and expansile bone lesions disappeared. A durable response was observed for more than 2 years, and reossification occurred in the treated bones [74].

Given the "radioresistance" of RCC to low-dose conventional fractionation, a hypofractionated regimen with a higher BED could potentially yield more favorable outcomes. These outcomes could include symptom relief and the achievement of a durable response [8,13-17,74]. However, the optimal dose fractionation for patients with mRCC still needs to be determined in future studies. When choosing an RT dose regimen, factors such as the symptomatic response rate, the probability of a durable response, and the risk of RT-related toxicity should be taken into account.

ONGOING RANDOMIZED TRIALS ON RT FOR mRCC

1. Cytoreduction of Primary Disease in Patients With mRCC

The CYTOSHRINK (NCT04090710) trial is a phase II randomized study that evaluated the effectiveness of

ipilimumab plus nivolumab, in comparison to the combination of ipilimumab, nivolumab, and SABR (30–40 Gy in 5 fractions) for primary renal mass in patients with mRCC. The goal of this trial was to improve survival outcomes by employing cytoreductive nephrectomy, which offers a more convenient approach for cytoreduction in patients who are either unwilling or unsuitable for nephrectomy [42-44]. Similarly, the NRG-GU012 trial (also known as the SAMURAI study, NCT05327686) assessed the efficacy of ICB, with or without cytoreductive SABR, for primary renal tumors in patients with inoperable mRCC.

2. Metastasis-Directed SABR in mRCC

In the GETUG-StORM-01 (NCT04299646) trial, patients with oligoprogressive clear-cell RCC (1–3 lesions) will be randomized to either receive systemic treatment with SABR at all progressive sites, or without it. This trial is anticipated to offer further insights into the role of RT in managing oligoprogressive mRCCs. The EORTC 1945 OligoRARE trial is also open to patients with oligometastatic RCC (1–5 metastases), but it excludes those with lung, breast, colon, and prostate cancers. In this trial, patients with oligometastatic cancer will be assigned to 1 of 2 groups: one will receive standard palliative treatment with SABR at all metastatic sites, and the other will receive the same treatment but without SABR.

SUMMARY AND FUTURE PERSPECTIVES

In summary, due to advancements in technology that allow for the precise delivery of high-dose RT targeted at the tumor, metastasis-directed RT in mRCC has emerged as a strategy to either mitigate or delay systemic treatment, or to enhance survival when used in conjunction with TKIs and ICBs. While this review primarily discussed SABR as the form of RT for patients with mRCC, it is important to note that not only SABR, but also various RT dose-fractionation regimens delivering higher (ablative) doses, can be utilized for this purpose. In this context, the treating radiation oncologist must strike a careful balance between the tumor control probability and the normal tissue complication probability. Future studies should aim to establish the optimal RT dose fractionation and the best sequence for combining it with systemic treatments. Factors such as the probability of local and overall disease control, antitumor immunity, and the risk of toxicity should all be considered in a comprehensive manner. Thus, a new chapter in the understanding of RCC, which has been mischaracterized as a "radioresistant" histology for decades, has begun.

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