Role of Primary and Metastasis-Directed Stereotactic Radiation Therapy for Advanced Renal Cell Carcinoma

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Introduction

Kidney cancer is a heterogeneous disease associated with variable clinical course and histologic types. Renal cell carcinoma (RCC) originates from the renal cortex and represents 80–85% of primary renal neoplasms. Subtypes of RCC include clear cell (75–85%), papillary (10–15%), chromophobe (5–10%), and other rare subtypes (3–5%) [1]. Approximately 25% of patients with RCC present with regional and distant metastasis at the time of diagnosis [2]. For patients with localized disease, up to 25% of these patients may eventually develop metastasis [2, 3]. RCC has the potential to spread by local invasion through the surrounding tissue, venous drainage, lymphatic spread, or hematogenous dissemination. Surgery has been the primary treatment modality for the management of localized kidney cancer, and historically, systemic therapy for metastatic RCC was limited to cytokine therapies, including high-dose interleukin-2 (IL-2) and interferon. However, due to the considerable toxicity, IL-2 was limited to patients with excellent performance status and few medical comorbidities. In recent years, systemic therapy with immune checkpoint inhibitors (ICI), tyrosine kinase inhibitors (TKI), or a combination of the two, have become the new standard of care for metastatic RCC (mRCC) [4–8].

In addition to surgery and systemic therapy, radiation therapy is an important treatment modality for RCC. Due to a 1996 study of multiple human cancer cell lines that examined radiosensitivity in vitro, RCC was traditionally thought to be radioresistant to conventionally fractionated radiation therapy [9]. Additionally, a clinical trial published in 1987 showed that adjuvant radiation therapy for RCC provided no improvement in local recurrence with severe toxicities, including death [10]. However, RCC has subsequently been shown to be radiosensitive in numerous

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in vivo and in vitro studies, especially when delivered with a higher dose-per-fraction [11, 12]. For instance, one study of an implanted human RCC in a nude mouse model showed effective tumor control when treated with 48 Gy in 3 fractions [11].

Stereotactic ablative body radiation (SAbR) is an emerging treatment paradigm defined by the American Society of Therapeutic Radiology and Oncology guidelines as a "treatment method to deliver a high dose of radiation to the target, utilizing either a single dose or a small number of fractions with a high degree of precision within the body [13]." Potential indications for SAbR include a broad spectrum of tumor types and locations [14]. The safety and efficacy of SAbR to multiple sites is excellent, and it has been assessed prospectively in multiple studies [15–18]. Clinical experience using SAbR or hypofractionated radiotherapy (HFRT) for both intracranial and extracranial RCC metastases showed excellent local control rates between 90% and 98% [19–21]. A Swedish retrospective series of 50 patients with 162 lesions treated with SAbR showed a 90% local control rate with minimum toxicity at a median follow-up time of 37 months [19]. Wang et al. reported a 91% 1-year local control rate post-SAbR in a retrospective series reviewing 175 treated metastatic RCC lesions, with a favorable safety profile including improved outcomes and a biologically effective dose (BED) greater than 115 [22]. Their analysis further revealed that spinal location, re-irradiation and > 1 of prior systemic therapy had higher levels of local failures that can be overcome with higher radiation dose.

Given the excellent local control efficacy and safety profile of SAbR for the treatment of both primary and metastatic RCC, effective integration of this relatively new modality with the emerging systemic therapy landscape for RCC will lead to optimal outcomes for kidney cancer patients. This chapter will discuss the available evidence on the sequencing and integration of SAbR with available local and systemic therapies, highlighting the lack of data and opportunities for future clinical trial development and challenges.

SAbR for Primary RCC

While surgery remains the standard curative treatment for primary RCC, patient characteristics such as inoperability or tumor size may favor observation or other focal treatments. Among these focal treatments is SAbR, which will be the emphasis of this chapter. Several retrospective studies of SAbR for primary RCC are among the earliest to show promising outcomes [20, 23, 24]. The first prospective dose escalation trial of SAbR showed that doses >27 Gy in three fractions did not have any failures and reported an overall local control (LC) of 93.7%. Interestingly, while they noticed a decrease in the SAbR treated lesions indicating tumor cell killing, they did not notice any change in tumor enhancement suggesting that the vasculature in the lesion was not affected by SAbR [25]. A phase 2 trial of 37 primary RCC patients treated with SAbR reported a LC of 100% at a median follow-up of 24 months [26]. They also reported 3% grade 3 toxicity with no grade 4–5 toxicities.

A pooled analysis performed by the International Radiosurgery Oncology Consortium for Kidney (IROCK) published outcomes for 223 patients from nine institutions who had RCC treated with SAbR [27]. In this cohort, the 4-year LC, overall survival (OS), and progression-free survival (PFS) were 97.8%, 70.7%, and 65.4%, respectively. There were only three (1.3%) patients who experienced grade 3/4 bowel toxicity and the mean reduction in estimated glomerular filtration rate (eGFR) was 5.5 mL/min. This study showed that larger tumor size predicted worse PFS, as well as cancer-specific survival (CSS) [27, 28]. An additional pooled analysis reaffirmed these positive results of SAbR for primary RCC [29]. Published in 2020, the authors describe 95 patients deemed not suitable for surgery who had primary tumors greater than 4 cm. Definitive SAbR was effective with 4-year LC of 98.1%, no grade 3–5 toxicities, and had an impact on renal function with an average eGFR decrease of 7.9 mL/min.

Locally Advanced RCC

Standard of care treatment for patients with locally advanced RCC is and has traditionally been radical or partial nephrectomy, as clinically indicated. Adjuvant treatment options have ranged from observation to systemic therapy, both on and off clinical trials. More recently, investigators are exploring an increasingly nuanced approach given a variety of patient factors.

Up to 10% of newly diagnosed patients with RCC have disease that invades the inferior vena cava (IVC). This invasion can surge from the renal vein and travel to the right atrium. The extent of IVC disease can portend a poor prognosis, and if left untreated can lead to venous congestion, Budd-Chiari syndrome, pulmonary embolism, or metastasis. The only curative treatment for locally advanced RCC involving IVC tumor thrombus is surgery, however, there is approximately a 35% rate of high-grade perioperative morbidity, and up to a 13% rate of peri or postoperative mortality [30]. Unfortunately, an increased risk of relapse and metastasis still exists even after curative resection [31]. A 1-year recurrence rate of greater than 40% exists for patients with RCC IVC tumor thrombus. Multiple possible explanations exist for the mechanism of this high rate of recurrence, with one possibility being that the IVC tumor thrombus may invade the IVC wall, resulting in positive surgical margins, ultimately leading to local recurrence. Alternatively, the IVC tumor thrombus may produce tumor emboli, thus causing metastasis.

One alternative adjuvant treatment approach supported by emerging evidence to reduce the risk of RCC recurrence is preoperative SAbR to the RCC IVC tumor thrombus. An initial case report of two patients treated with preoperative SAbR showed no acute or late treatment-related toxicity, as well as a median survival of 20 months at the time of publication [30]. This lead to the design of a safety lead-in phase II clinical trial of neoadjuvant SAbR for RCC IVC tumor thrombus (NCT02473536). The safety lead-in phase of the trial demonstrated that neoadjuvant SAbR of IVC tumor thrombus followed by radical nephrectomy and thrombectomy is feasible and safe, however, the oncologic outcome data is not yet fully

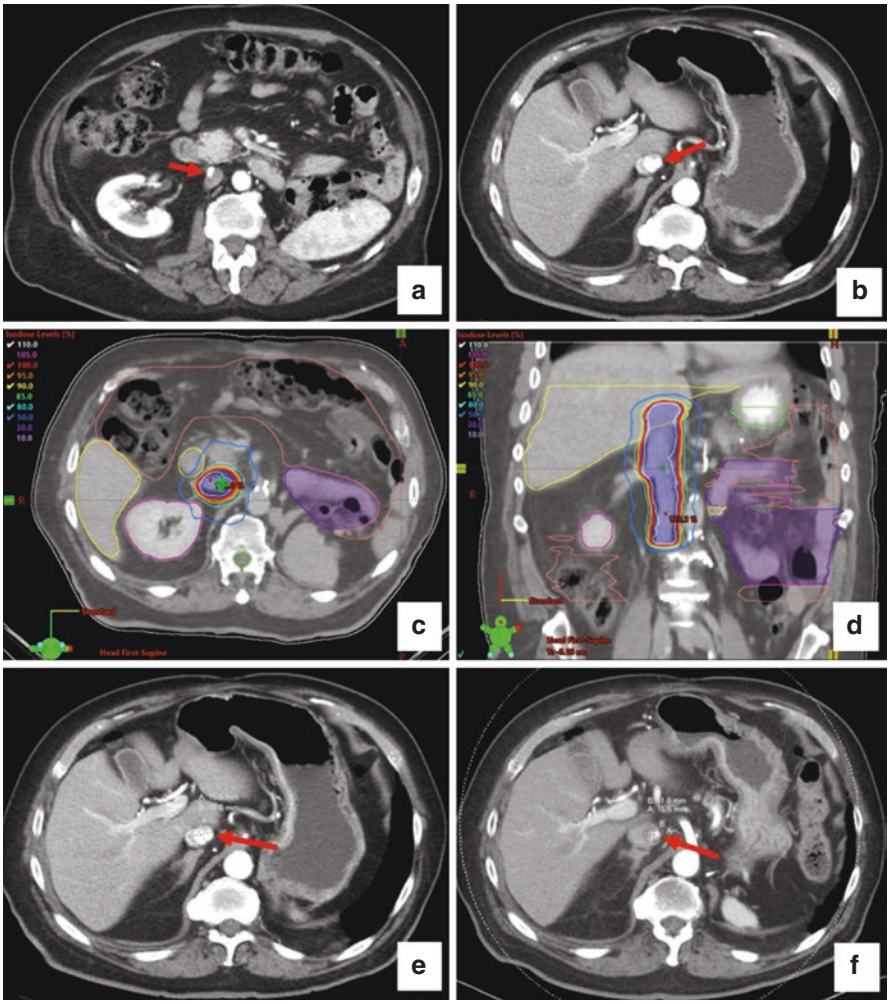

Fig. 15.1 Sample images of a case of a patient with RCC IVC tumor thrombus with adherence of the tumor thrombus to the IVC wall, making resection not possible. The patient was treated with SAbR 36 Gy/3 fractions. (**a**, **b**) Axial abdominal CT with contrast, arrows highlighting arterially enhancing mass in the infra-hepatic IVC consistent with RCC recurrence. (**c**, **d**) Axial and coronal abdominal CT with radiation dose distribution as a percentage of prescription dose. Nearby organs at risk are also contoured—duodenum (yellow), right kidney (pink), liver (yellow), and bowel space (salmon). (**e**) Pre-SAbR tumor thrombus 1.6 × 2.0 cm. (**f**) 6-month post-SAbR tumor thrombus 1.2 × 1.6 cm. *IVC* inferior vena cava, *RCC* renal cell carcinoma, *SAbR* stereotactic ablative radiation therapy

matured [32]. Potential additional indications for SAbR of IVC tumor thrombus include: palliation of Budd-Chiari syndrome, unresectable or recurrent disease after surgery (Fig. 15.1), disease refractory to surgery and systemic therapy, cytoreduction (with systemic therapy) to increase respectability by alleviation of Budd-Chiari/

hepatic venous congestion (which significantly increase surgical mortality), MRI evidence of IVC wall invasion, or a patient eligible for radical nephrectomy but not for tumor thrombectomy. Again, this paradigm is evolving and prospective evidence is currently lacking.

Patients with locally advanced RCC without tumor thrombus may also be unresectable due to the extent of disease, medical inoperability, surgical risks, or simply due to a lack of evidence of clinical benefit as demonstrated by multiple clinical trials [33]. Debulking or consolidative SAbR may have applications in these clinical scenarios. Phase 1 feasibility data is provided by Singh et al. in a small study that treated large kidney tumors neoadjuvantly with SAbR [34]. With the improvement of systemic therapy it is possible for a patient initially diagnosed with metastatic disease to have a near complete response with systemic therapy, with the primary tumor being the only remaining, yet inoperable site of disease where SAbR can be utilized. Ongoing multi-center clinical trials (CYTOSHRINK NCT04090710 and SAMURAI/GU012 NCT05327686) are evaluating this strategy, leveraging potential synergy of SAbR with immunotherapy.

Oligometastatic RCC

Oligometastatic RCC is a broad category of disease where SAbR is effective. Metastatic RCC represents a wide spectrum of disease aggressiveness. For example, patients with International Metastatic Database Consortium (IMDC) poor-risk disease have historically poor outcomes with survival of less than 1 year, while those with favorable-risk disease may have a smoldering progression over many years [35, 36]. Patients may also present with widely disseminated disease or they may exhibit oligometastatic disease. Oligometastatic RCC can be divided into subcategories based on the risk of distant micrometastasis. This can dictate the probability of future progression at distant sites, as well as the speed of progression of the detectable metastases.

The first subcategory are those patients that present with metachronous metastases that develops more than 1 year after resection of the primary kidney tumor. This suggests that the patient's disease is indolent and portends the best prognosis. A subgroup of these patients may represent the "true" oligometastatic state and can be cured with local therapy. For these patients, treatment options include either active surveillance, metastasectomy, SAbR, or systemic therapy [36–41], with a preference for local therapy. The second subcategory are patients with favorable or intermediate IMDC risk. This represents a heterogeneous patient population who will eventually need systemic therapy, however, carefully selected patients can be treated with upfront sequential SAbR that can preserve health-related quality of life as well as available systemic therapy options. Retrospective and prospective studies have both shown disease control in excess of 15 months for these patients with sequential SAbR [38–41]. The third subcategory are patients with a high chance of distant micrometastatic disease, including those with IMDC poor-risk, grade 4 histology, or sarcomatoid component histology. Despite having oligometastatic disease, this

group of patients generally requires up-front systemic therapy, however there may still be a role for consolidation with SAbR to the bulky therapy-resistant metastatic sites. Nevertheless, these patient scenarios provide a framework in which SAbR may be considered as part of the treatment plan.

Active surveillance is a treatment approach for select patients with oligometastatic RCC. A prospective trial of patients with oligometastatic RCC with proven indolent growth of metastases after primary nephrectomy showed that this subset of patients could safely undergo active surveillance for a median of 14.9 months before starting systemic therapy [36].

Metastasectomy is also a treatment option for patients with oligometastatic RCC, but local control, safety, and prospective outcome data are limited [37]. A Japanese retrospective study of 1463 patients in which 20.8% underwent metastasectomy reported prognostic factors for metastatic RCC, including performance status, hemoglobin, lactate dehydrogenase, serum calcium, C-reactive protein, and time from initial visit to metastasis being less than 1 year. Patients with no risk factors had a median survival of 55.3 months compared to 29.6 months for those with 1 to 2 risk factors (1 year OS of 92.8% vs. 76.6%, respectively) [42]. More recently, Tosco et al. investigated the survival impact of prognostic factors in patients with metastatic RCC who underwent metastasectomy [43]. Their results indicated that advanced primary tumor stage, high tumor grade, non-pulmonary metastases, disease-free interval of less than 12 months, and multi-organ metastases were independent factors for survival. Patients with 0 to 1, 2, 3, greater than 4 factors had 2-year cancer-specific survival rates of 95.8%, 89.9%, 65.6%, and 24.7%, respectively [43]. These tools may help clinical decision making for appropriate local therapy patient selection.

SAbR is a promising treatment option for patients with oligometastatic RCC. SAbR has not only shown favorable local control rates of greater than 90%, but can also provide an option for local therapy at an otherwise inoperable location. A phase II prospective trial from Sweden using SAbR in primary and metastatic RCC showed an OS of 32 months with 79% sustained local control rate at a median follow-up of 52 months [20]. A prospective study from the University of Chicago showed that the majority of initial metastatic progression (81%) was limited to less than five sites in oligometastatic RCC patients after treatment with SAbR, and approximately half had either no or limited metastatic progression after a median follow-up of 20.9 months [44]. These experiences suggest aggressive upfront sequential SAbR as an effective local therapy that can potentially control disease progression in patients with limited metastases. Retrospective analyses have supported the use of SAbR for oligometastatic disease due to the ability to defer the start of systemic therapy and possibly extend survival [38]. This has recently become the subject of prospective studies, including one that supported the efficacy and safety of this approach with SAbR [45]. Moreover, this strategy can be employed sequentially in the setting of additional oligometastatic lesions, thus providing durable disease control with subsequent focal SAbR. This approach was described in a retrospective study where 30% of patients received two or more courses of SAbR to additional sites of metastatic disease [38]. A

prospective version of this study confirmed that sequential SAbR in systemic therapy-naïve oligometastatic RCC patients can confer 1-year freedom from systemic therapy in 91.3% of patients [40, 41]. This phase 2 trial also demonstrated a preservation of patient's quality of life using pre- and post- treatment patient-reported quality of life questionnaires. In another prospective feasibility study by Tang et al., SAbR and showed a median PFS of 22.7 months with acceptable toxicity [39]. While the study met its feasibility endpoint, it did not meet its pre-specified efficacy estimate of 71% 1-year PFS and reported a 1-year PFS of 64%. It is important to note that this study allowed pre-treatment with systemic therapy. A phase 3 non-inferiority trial (EA 8211, SOAR) randomizing systemic therapy-naïve oligometastatic RCC patients to be treated with up front sequential SAbR followed by systemic therapy at progression versus systemic therapy up front is currently being designed.

Although the safety of SAbR has been excellent, caution must be exercised in certain scenarios. One such scenario is ultra-central lung metastasis, where given the vascular nature of RCC, rare instances of serious life-threatening hemoptysis or hemothorax have been noticed as a late effect that occurs years after treatment. It is often difficult in these situations to assess the contribution of radiation, tumor recurrence, and systemic therapy as the etiology of the hemoptysis. A second potential cautionary scenario is the use of future systemic therapy which may have side effects that can synergize with the toxicity of current SAbR, leading to a radiation-recall-type side effect.

Oligoprogressive RCC

Individuals with metastatic RCC can develop progression at only a few select sites of disease, deemed oligoprogressive. To date, there has been limited research on patterns of progression. For example, conventionally used criteria for response assessment in clinical trials, such as Response Evaluation Criteria in Solid Tumors (RECIST) criteria, do not distinguish patterns of progression. In clinical practice, the current approach to progression, even if it is only to a few sites, is to switch systemic therapy. This also applies to patients who are otherwise tolerating the ongoing systemic therapy well. However, different modes of progression likely reflect differential disease responsiveness to therapy and biology. Limited progression may indicate overall responsiveness to therapy and may be explained by mutational heterogeneity and clonally propagated branched evolution that fosters tumor adaptation and therapeutic failure through Darwinian selection [46–48]. Different modes of progression may be optimally managed with different approaches, and a change of systemic therapy may be favored for patients with overt progression. The introduction of focal therapies for controlling oligoprogressive sites could be advantageous by increasing the duration of the current therapy and preserving the limited available subsequent therapies. By extending the duration of the current systemic therapy and altering the course of the disease through elimination of resistant metastasis, this approach could also improve survival outcomes. It is

important to keep in mind that subsequent lines of systemic therapy are typically associated with shorter progression-free survival (PFS) intervals, and they are often associated with increased toxicity [49]. Furthermore, local therapy seems unlikely to undermine future systemic therapy, and such an approach may extend patient survival.

Multiple retrospective studies have evaluated SAbR for mRCC, but only a few on oligoprogression [19, 50–56]. A retrospective analysis from Santini et al. found a median PFS of 14 months after evaluating 55 mRCC patients on first line systemic therapy and oligoprogression managed with focal approaches (including SAbR) [51]. In this study, SAbR was used in approximately 46% of patients, and appeared to be effective. Another single-institution retrospective review of 72 patients with mRCC on systemic therapy treated with SAbR to oligoprogressive sites showed similar PFS, regardless of systemic therapy [56]. In a multi-institutional study, Meyer et al. reported 180 patients with mRCC who had been treated with SAbR; of these, 101 patients were treated for oligoprogressive disease [52]. The median local recurrence-free survival, PFS, time to systemic therapy, and OS were 19.3, 8.6, 10.5, and 23.2 months, respectively. UT Southwestern Medical Center performed a retrospective review of SAbR for oligoprogression in mRCC, which showed a median mPFS of 9.2 months [50]. Data on this topic is emerging, with one prospective phase 2 trial showing that SAbR to oligoprogressive sites is able to extend the duration of ongoing systemic therapy by more than 6 months in 70% of patients, with a median duration of SAbR-aided systemic therapy of 24.4 months [57]. All together, prospective studies on SAbR for oligoprogressive RCC are lacking and may be difficult to conduct given concerns and lack of data on side effects of concurrent administration of some of the systemic therapies with SAbR. Few phase 2 trials are ongoing and may provide further insight (GETUG-StORM-01 NCT04299646 and NCT04974671).

SAbR for oligoprogressive mRCC has been shown to be generally well-tolerated, however, toxicity may also be exacerbated by both ICIs and TKIs, and the safety of SAbR in conjunction with systemic therapy continues to be evaluated. SAbR with concurrent ICI/TKI was started with caution due to concerns for potential increased toxicity, but no enhanced toxicity was observed yet, warranting more prospective studies [58–60]. Mohamad et al. evaluated the safety of concurrent ICI and hypofractionated radiotherapy in 59 patients with mRCC, concluding that any grade or greater than grade 3 adverse events did not significantly differ from historical rates of ICI therapy alone [61]. In a phase I trial, Tang et al. treated 55 patients with ipilimumab and either concurrent or sequential SAbR. They reported that 34% rate of grade 3 toxicity which is comparable to treatment with ipilimumab alone [62]. Furthermore, a meta-analysis of 13 prospective randomized trials with concurrent TKI and radiation therapy showed increased grade 3 or greater toxicity [63], with another pooled analysis of 68 prospective trials of ICIs showed that those who received an ICI within 90 days following radiation therapy did not appear to be associated with an increased risk of serious adverse events [64].

CNS and Spine Metastasis

Brain metastases has been reported in up to 17% of patients with RCC [65]. Recently, approved systemic therapies have allowed patients with mRCC to live longer, resulting in an expected increase in incidence for patients with mRCC who develop brain metastases [4, 6–8]. Despite improvements in systemic therapies, the blood–brain barrier poses a persistent challenge to treat RCC brain metastases and is a key contributor to why a local therapy such as surgery or radiation remains necessary [66]. Surgical resection has been a traditional treatment approach for these metastatic tumors, however, surgery may not always be possible due to patient or tumor factors such as medical comorbidities, proximity of eloquent cortex, or the number of intracranial metastases. Classic radiation treatment for intracranial metastases has generally involved whole-brain radiation therapy (WBRT). This paradigm, however, has shifted to prefer stereotactic radio surgery (SRS). SRS is an attractive treatment option because it is a minimally invasive outpatient procedure, can be performed on patients unfit for surgery, and can be used if a lesion is in a location deemed unresectable. Moreover, SRS has been shown to have less neurocognitive toxicity without a survival detriment compared to WBRT with SRS [67]. SRS for RCC-specific brain metastases also allows greater dose-per fraction treatments to combat this traditionally considered radioresistant histology. Local control rates have been excellent and even close to 98% to 100% in certain series [65, 68–71].

Second to pulmonary metastasis, osseous involvement is a common site of metastasis and can occur in up to 27% of patients with mRCC [72]. Of those with osseous metastases secondary to RCC, the spinal column is the most common site [73]. A multi-disciplinary approach is highly recommended for RCC spinal metastasis, as certain clinical factors such as the severity of a patient's pain, neurologic symptoms, presence of spinal cord compression, or associated edema may give priority to one treatment over another [74]. Treatment options include conservative pain management, steroids, surgery, radiotherapy, or a combination of these. RCC patients with isolated spine metastasis or otherwise oligometastatic disease may be considered for curative intent local therapy. SAbR, including single-fraction treatments, for RCC spine metastases has been shown to provide an 83% local control at 1 year, few to no grade 3 or greater toxicity, as well as fast, durable pain relief [75, 76]. If the metastasis has extensively infiltrated the spinal canal, and the proximity of the spinal cord keeps from delivering an ablative radiation dose or safe surgical resection, a multi-modal approach can be taken with neoadjuvant systemic therapy followed by local therapy. In the setting of spinal cord compression or cord abutment of the tumor, if ablative radiation alone is not feasible, a surgical decompression and debulking is performed followed by high-ablative radiation to achieve durable local control. One retrospective review showed that postoperative SAbR following epidural spinal cord decompression provided a 1-year local control greater than 95% [77]. Moreover, osseous metastasis from RCC is lytic and can cause significant cortical destruction, placing patients at increased risk for compression fracture. SAbR can increase the risk of vertebral compression fracture further, and it is therefore recommended to pursue prophylactic kyphoplasty [78]. Surgical

resection for RCC metastasis, which is often vascular, also poses an intraoperative bleeding risk that can be addressed with arterial embolization prior to resection. Consequentially, a multi-disciplinary approach is ideal for the proper management of spinal metastasis from RCC.

Palliation

In addition to various scenarios where SAbR may be indicated for the treatment of RCC with curative, consolidative, and adjuvant intent, multiple palliative indications for RCC irradiation also exits. The most common sites of metastatic disease in patients with RCC have been documented as: lung (45%), bone (30%), lymph node (22%), liver (20%), brain (9%), and adrenal (9%) [79]. Indications for palliative radiation include radiologic evidence of metastatic disease and a corresponding sign or symptom such as pain, spinal cord compression, superior vena cava syndrome, brain metastasis, fracture, prevention of fracture in the weight bearing bones, bleeding, as well as others. Hematuria is a frequent presenting symptom for metastatic RCC that can be palliated with radiation therapy [80]. Given RCC's radioresistance to conventional fractionation, hypofractionation schemes favoring a higher dose per fraction are preferred and a regimen of 20 Gy in 5 fractions is preferred over the 30 Gy in 10 fractions. Whenever possible, applicable dose escalation should be considered with intensity-modulated radiation therapy or SAbR.

Conclusion

SAbR is both an established and emerging treatment option with curative or palliative intent, ranging from early inoperable RCC to oligometastatic RCC to widely metastatic RCC. Given SAbR's safety and efficacy for both primary and metastatic RCC, the onus is on the physician to successfully integrate this modality with the available and emerging local and systemic therapies in order to maximize outcomes for RCC patients. While a number of clinical trials are ongoing, many more are required to provide high-level prospective evidence regarding integration of SAbR for the management of primary and metastatic RCC.

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