Stereotactic Ablative Radiotherapy in Renal Cell Carcinoma Management

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Contributor: Rohit K. Raj , Rituraj Upadhyay , Shang-Jui Wang , Eric A. Singer , Shawn Dason

Stereotactic ablative radiotherapy (SABR) has challenged the conventional wisdom surrounding the radioresistance of renal cell carcinoma (RCC). There has been a significant accumulation of clinical data to support the safety and efficacy of SABR in RCC.

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1. Introduction

Kidney cancers are amongst the top 10 cancers in the United States, with an estimated incidence of 81,000 cases and 14,890 attributable deaths in 2023 [1]. Malignant neoplasms of the kidney are complex, with several histologic types and distinct disease processes with variable clinical outcomes, the most prevalent of which is renal cell carcinoma (RCC), accounting for 80–85% of primary renal neoplasms [2]. Major subtypes of RCC include clear-cell (75–85%), papillary (10–15%), and chromophobe (5–10%) tumors. Other histological types of renal neoplasms are oncocytoma and angiomyolipoma (3–5%). At diagnosis, over one-fourth of patients present with regional and/or distant metastatic disease, and over half of patients eventually develop metastatic disease [3][4]. Overall survival across several prior studies ranges from 6 to 12 months in these patients with metastatic RCC (mRCC). While surgery remains the standard-of-care treatment modality for patients with localized RCCs, systemic therapy is the mainstay of treatment for mRCC. Historically, systemic therapies were limited to cytokine therapies, but more recently, several newer options have emerged, including immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs) [5][6][7].

In the context of management of localized, locally advanced, and metastatic RCC, stereotactic ablative radiotherapy (SABR) has emerged as another promising technique. Historically, RCC was considered to be a relatively radioresistant tumor, especially when treated with conventional fractionation utilizing a dose of <5 Gy per fraction. Radio-resistance to conventionally fractionated RT was demonstrated by Deschavanne and Fertil using cell survival curves from in vitro studies [8]. However, more advanced radiation techniques have allowed the delivery of a higher dose per fraction to renal tumors safely, which results in more effective cell killing, as demonstrated by several recent studies in vitro as well as in vivo [9][10]. Although the underlying radiobiological phenomenon responsible for this effect is poorly understood, several hypotheses include alternate mechanisms of cell killing induced by SABR (vs. conventional RT) rather than mitotic catastrophe from DNA damage, including

ceramide pathway cell killing, apoptosis, and vascular endothelial damage [11][12][13]. Another plausible explanation of the radiation response seen with SABR involves the immunostimulatory effects, especially in combination with immunotherapy [14]. Chow et al. evaluated the pathology specimens of patients with primary RCC treated with single-fraction SABR to a dose of 15 Gy followed by nephrectomy four weeks later, and observed broad transcriptional immune activation and clonality of immune cells within the tumor microenvironment [15].

SABR is generally defined as a radiotherapy technique in which high doses of radiation (>5–8 Gy per fraction) are administered to the target in 1–5 fractions with a high degree of anatomic accuracy [16]. Recent clinical studies have evaluated SABR for both primary and mRCC and have shown the safety as well as efficacy of this approach, with local control (LC) rates of 90–98% [17][18][19] and grade-3 toxicities attributable to SABR of less than 5% [20].

Current North American and European society guidelines recommend SABR as a subsequent line of local therapy for unresectable or medically inoperable primary RCC, or for the local treatment of metastatic sites in select patients with oligometastatic (OM) RCC or oligoprogression [21].

2. Primary Localized RCC

Most patients with localized RCC present with a renal mass noted incidentally on imaging for another indication [22]. Local symptoms of RCC include flank discomfort and hematuria. Patients with RCC are typically staged with imaging of the chest, abdomen, and pelvis [23]. Bone and brain metastases are uncommon in the absence of symptoms or lab abnormalities.

Management of the small renal mass (≤4 cm) is highly individualized [23]. Historically, most patients with a small renal mass were managed with surgical resection. A number of trends have emerged in the past decade to limit the morbidity of small renal mass management:

- Renal mass biopsy. There is a high rate (31%) of benign pathology in resected renal masses [24]. An effort to reduce the morbidity of resecting benign renal masses has prompted increasing use of renal mass biopsy in patients with a small renal mass. A renal mass biopsy is diagnostic in 90% of small renal masses [25]. Utilization of biopsy prior to surgical resection is highly variable—it is likely most essential when a diagnosis other than renal cell carcinoma is suspected or biopsy results would impact the decision to proceed with treatment. A young patient unwilling to accept the uncertainties of a biopsy or a comorbid patient who would undergo active surveillance regardless of biopsy are good indications to avoid a biopsy [23]. Additional imaging with 99 mTc-sestamibi SPECT/CT [26] and 89Zr-DFO-girentuximab [27] are likely to become reasonable adjuncts to biopsy in the near future.

- Active surveillance is also increasingly utilized for small renal masses. Intermediate-term outcomes with this approach are excellent. The metastatic rate is generally low (<1–2%) in well-selected patients [28]. The DISSRM registry is a prospective active surveillance registry that has recently reported on 585 patients with a 3.39 year median follow-up [29]. The rate of delayed intervention on active surveillance is 15%, with no difference in

cancer-specific survival between those that elected primary vs. delayed intervention. The most common reasons for intervention are growth rate >0.5 cm/year or patient preference [30].

- If treatment is elected, most patients are amenable to a robot-assisted partial nephrectomy. This has reduced morbidity over open partial nephrectomy and radical nephrectomy.

- Other local therapies. percutaneous ablation offers a reasonable alternative to surgery and can be performed with cryoablation or radiofrequency ablation [31]. A biopsy should confirm malignancy before ablation. This approach has reduced morbidity relative to surgery, which may be particularly relevant to the patient with elevated surgical risk. LC rates may be slightly lower than that of a partial nephrectomy, which is relevant to a patient with a long life expectancy.

- SABR. As discussed in the following sections, SABR is being increasingly considered.

Surgical candidates with a larger (>4 cm) renal mass generally undergo surgical resection with a partial or radical nephrectomy. A biopsy is less commonly performed given the higher rates of malignancy in this setting [32]. Ablative techniques [33], active surveillance [34], and SABR are alternatives to surgery that can be considered in a patient at elevated surgical risk.

3. Locally Advanced RCC

Renal cell carcinoma extending outside of the kidney without distant metastases is described as locally advanced. This may include involvement of the perinephric or renal sinus fat, renal vein or inferior vena cava (IVC), regional lymph nodes, or adjacent organs. In surgical candidates, locally advanced RCC is managed with surgical resection [35]. Adjuvant ICIs with pembrolizumab (anti-PD-1) for up to 1 year have been shown to reduce disease recurrence after nephrectomy by 37% for patients with locally advanced clear cell RCC [36][37]. Whether adjuvant pembrolizumab improves CSS has not yet been established.

4. Metastatic RCC

Metastatic RCC encompasses a wide range of disease aggressiveness that varies both in terms of rates of disease progression and disease burden. The International Metastatic Database Consortium (IMDC), externally validated by Heng et al. and now one of the most widely used risk stratification and prognostic models for mRCC, stratifies patients into three risk groupings—favorable (0 risk factors), intermediate (1–2 risk factors) and poor (3 or more risk factors)—based on the following risk factors:

- Karnofsky performance < 80%;

- Neutrophils > upper limit of normal;

- Corrected calcium > upper limit of normal;

- Platelets > upper limit of normal;
- Hemoglobin < lower limit of normal;
- <1 year from diagnosis to systemic therapy [38].

Management of mRCC involves multimodality management. Patients with a high burden of metastatic disease and multiple IMDC risk criteria are managed with upfront systemic therapy. Treatment of the kidney or metastatic lesions is not performed upfront unless symptomatic. Consolidative treatment of the renal primary or metastatic sites can be considered in the event of significant overall response or oligoprogression.

Newer systemic therapies in the form of targeted therapy or ICIs, either alone or in combination, have improved oncologic outcomes in mRCC. Unfortunately, eventual resistance to systemic therapy remains unavoidable [39]. In the context of this inevitable failure of systemic therapy, there remains a role for SABR as a local metastasis-directed therapy in selected mRCC patients. Patients with oligometastatic (OM) RCC are more frequently considered for upfront cytoreductive nephrectomy, active surveillance, and metastasis-directed therapy, especially to delay systemic therapy. In synchronous OM RCC, the decision to perform cytoreductive nephrectomy depends on the plan for metastatic disease—it is indicated when remaining metastatic disease will be managed with active surveillance or metastasis-directed therapy. For those patients in whom systemic therapy is intended, cytoreductive nephrectomy is reasonable when no other IMDC risk factors are present and the majority of disease burden is in the kidney [40][41]. Patients who can have complete control of metastatic lesions with metastasis-directed therapy are also considered for this approach. About half of patients who undergo cytoreductive nephrectomy with synchronous metastasis-directed therapy or active surveillance will remain off systemic therapy for at least one year [42][43]. Those with OM metachronous recurrences may remain off systemic therapy for much longer periods with metastasis-directed therapy [44].

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