PIONEER
ACADEMIC PUBLISHING LIMITED

Current Research in Medical Sciences
ISSN 2958-0390
www.pioneerpublisher.com/crms
Volume 4 Number 2 March 2025

Application of Stereotactic Body Radiation Therapy in the Local Treatment of Primary Renal Cell Carcinoma: A Review

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doi:10.56397/CRMS.2025.03.03

Abstract

Renal cell carcinoma (RCC) is one of the most common malignant tumors of the urinary system in adults, with its incidence steadily increasing, posing a significant threat to the health of elderly patients. Surgery remains the standard treatment for primary RCC; however, surgical intervention is often limited in elderly patients due to the frequent presence of multiple comorbidities. In recent years, stereotactic body radiation therapy (SBRT), with its high dose per fraction, high precision, and non-invasive nature, has been widely used for local management of primary RCC. This article reviews the application and related research of SBRT in the local treatment of primary RCC.

Keywords: stereotactic body radiation therapy, primary renal cell carcinoma, non-surgical treatment

1. Introduction

Renal cell carcinoma (RCC) is one of the most common tumors of the urinary system, with its incidence steadily increasing (TORRE L A, BRAY F, SIEGEL R L, et al., 2015). According to data from the Chinese Cancer Registry, the incidence rate of RCC in China in 2022 was about 3.13/100,000, with a total of approximately 73,700 new cases and a mortality rate of about 0.91/100,000, leading to 24,000 deaths (FUSCO V, PARISI S, D'ANDREA B, et al., 2017). It primarily affects the elderly population, with a median diagnosis age of 65 years (DENGINA N, TSIMAFEYEU I & MITIN T., 2017). The cancer-specific mortality (CSM) of RCC patients increases with age, and the CSM of patients over 80 years old may be 1.9 times higher than that of patients under 50 years old. Moreover, advanced age has a particularly adverse impact on patients with stage I RCC, as the risk of CSM may be 3.8 times higher compared to patients with other stages at the same age (SUN M, ABDOLLAH F, BIANCHI M, et al., 2011). This suggests that even early-stage RCC exhibits aggressive behavior in the elderly population. The selection and implementation of treatment strategies for elderly patients with RCC are complex and challenging. Surgery remains the standard treatment for primary RCC (DENGINA N, TSIMAFEYEU I & MITIN T.,

2017), however, advanced age and the frequent presence of comorbidities such as diabetes, hypertension, chronic kidney disease, and cardiovascular diseases, which exacerbate renal functional burden, may hinder the feasibility of anesthesia and surgery (CORREA R J M, LOUIE A V, ZAORSKY N G, et al., 2019). For patients deemed unsuitable for surgery, it is imperative to develop and validate non-surgical treatment options in prospective clinical trials.

Stereotactic Body Radiation Therapy (SBRT) is a radiation therapy technique capable of delivering high fractional doses. By utilizing high doses of radiation, it precisely targets tumor tissues while minimizing damage to surrounding normal tissues. It combines the precision of stereotactic radiosurgery (SRS) with the techniques of external beam radiation therapy (EBRT), enabling the delivery of high-dose radiation to tumors in a small number of sessions. With the continuous advancements in modern linear accelerators and precise image-guided capabilities, SBRT is rapidly being integrated into many radiation therapy departments (KOTHARI G, LOUIE A V, PRYOR D, et al., 2017), and SBRT's advantages in precise dose control and normal tissue protection have become more evident (Le Z, Liu Y, et al., 2018). Several phase II clinical trials have evaluated the effectiveness and safety of SBRT for the treatment of Primary RCC. This article provides a review of the relevant research and advancements in the application of SBRT for the local treatment of primary RCC.

2. Biological Mechanisms of SBRT in Killing RCC Cells

For a long time, RCC has been considered resistant to radiotherapy, as RCC cell lines are among the most resistant to conventional fractionated radiotherapy in vitro (LEEMAN J E., 2023). Deacon et al. classified malignant histologies into five groups based on their in vitro radiosensitivity, with RCC grouped alongside sarcomas, melanomas, and glioblastomas in the most "radioresistant" category (JD, JPM & GSG., 1984). However, a study on two human RCC cell lines (Caki-1 and A498) showed that RCC has a low α/β ratio, making it potentially more sensitive to high-dose fractionated radiotherapy, especially when the single dose is increased to 6 Gy, significantly reducing cell survival rates (NING S, TRISLER K, WESSELS B W, et al., 1997). Unlike traditional radiotherapy, which kills tumor cells by damaging DNA double strands through ionizing radiation (Feng Y, Tu W, Yu D, et al., 2023), ablative dose fractionated radiotherapy activates acidic sphingomyelinase, hydrolyzing sphingomyelin on the cell surface to generate pro-apoptotic ceramide (Liang C, Shen Y, et al., 2019). The production of ceramide sensitizes tumor endothelial cells to radiation, leading to endothelial cell apoptosis (ALI M, MOOI J, LAWRENTSCHUK N, et al., 2022). High-dose radiation can also induce vascular collapse within the endothelium, causing microvascular damage to tissues and leading to tumor cell apoptosis, which is crucial for targeting vascular malignancies such as RCC (SATHISHKUMAR S, BOYANOVSKY B, KARAKASHIAN A, et al., 2005). Recent studies have shown that SBRT can enhance the body's immune response to tumors by triggering the release of pro-inflammatory mediators, upregulating tumor-associated antigen (TAA) expression, and increasing T-cell infiltration, thereby inducing tumor inflammation (SINGH AK, WINSLOW TB, KERMANY MH, et al, 2017). Overall, high-dose fractionated radiotherapy can not only directly eliminate tumor cells to stop tumor growth but also potentially induce vascular damage and enhance anti-tumor immune responses, indirectly promoting tumor cell death. This finding provides a new approach for RCC treatment, indicating the potential application value of SBRT in RCC therapy.

3. SBRT Applied to Local Treatment of Primary RCC

3.1 SBRT Is Suitable for Patients Who Are Unable to Tolerate Surgery

Historically, primary RCC have achieved favorable treatment outcomes through surgical intervention. However, surgery is an invasive treatment option and is unsuitable for patients with bilateral renal tumors, a solitary kidney, pre-existing chronic kidney disease (CKD), or those in poor physical condition who cannot tolerate surgery (KOTHARI G, LOUIE A V, PRYOR D, et al., 2017). Currently, the National Comprehensive Cancer Network (NCCN) guidelines for kidney cancer state that "SBRT may be considered for medically inoperable patients with stage I renal cancer (Category 2B) and stage II/III renal cancer (Category 3)." Similar recommendations are also found in the guidelines of the European Association of Urology (EAU) and the European Society for

Medical Oncology (ESMO) (BE, CP, MS, et al., 2019; BöRJE L, LAURENCE A, YASMIN A, et al., 2022; JMR, ERIC J, NEERAJ A, et al., 2022). In one study, Grelier et al. (2021) reported outcomes for 23 frail primary RCC patients treated with SBRT, with a median age of 81 years. All patients were medically ineligible for surgery due to comorbidities and advanced age, and unsuitable for thermal ablation due to tumor size (>4 cm) or proximity to renal pelvic structures. After a median follow-up of 22 months, local recurrence-free survival, cancer-specific survival (CSS), and overall survival (OS) were 96%, 96%, and 83%, respectively, with no grade 3-4 toxicities. SBRT appears to be a promising alternative for treating primary RCC in frail patients.

In a 2019 meta-analysis by Correa et al. (2019), changes in renal function before and after SBRT were reported in 372 RCC patients. The mean difference in estimated glomerular filtration rate (eGFR) before and after treatment was -7.7 ml/min. Most patients had some degree of renal impairment (mild to moderate CKD) prior to SBRT, resulting in a weighted mean eGFR of 59.0 ml/min. These data suggest that SBRT may be a safe strategy even in patients with pre-existing renal impairment, offering a viable option for those unsuitable for surgical resection. In this meta-analysis, none of the 35 patients with a solitary kidney required dialysis. Another study of 7 patients with a solitary kidney reported that only 2 experienced a moderate increase in creatinine levels to 160 μmol/L, and no patients required dialysis (SVEDMAN C, KARLSSON K, RUTKOWSKA E, et al., 2008). These findings suggest that SBRT can be safely administered to patients with a solitary kidney, as renal function can be adequately preserved even without a contralateral kidney. A retrospective study involving 74 primary RCC patients found that over time after treatment, ipsilateral renal function progressively declined while contralateral renal function progressively increased. Additionally, a larger volume of unirradiated renal cortex was significantly associated with better long-term renal function (GLICKSMAN R M, CHEUNG P, KOROL R, et al., 2023). This suggests that, although many studies have provided encouraging results, further data are needed to establish safe dose limits for patients with pre-existing renal impairment. Minimizing high-dose exposure to the ipsilateral renal parenchyma is crucial to better preserve post-treatment renal function.

3.2 SBRT Is Suitable for Patients with Larger Primary Tumor Volumes (>T1b)

Partial nephrectomy, which preserves kidney function, is a viable option for T1b primary renal cell carcinoma in patients who can tolerate surgery. However, evidence for its use in T2 stage patients is limited (BE, CP, MS, et al., 2019; BöRJE L, LAURENCE A, YASMIN A, et al., 2022). For larger tumors, thermal ablation techniques such as Radiofrequency Ablation (RFA) and Cryoablation (CA) are associated with higher local recurrence rates (up to 14.3% for RFA and 23% for CA) (CAPUTO P A, ZARGAR H, RAMIREZ D, et al., 2017; PSUTKA S P, FELDMAN A S, MCDOUGAL W S, et al., 2013) and increased rates of major complications, such as bleeding (KURUP A., 2014) or patients with larger tumors, SBRT may be a favorable alternative, offering advantages such as non-invasive ablation, the ability to treat larger tumors, and excellent local control rates (LCR) with low toxicity. In a retrospective report from the International Radiosurgery Oncology Consortium for Kidney (IROCK), Siva et al. presented outcomes of SBRT in 95 patients with T1b renal cancer (median tumor diameter: 4.9 cm). With a median follow-up of 2.7 years, the local treatment failure rate was 2.9%, and the 4-year overall survival (OS), and progression-free survival (PFS) rates were 69.2% and 64.9%, with no grade 3-5 treatment-related adverse events (AEs) were reported (SIVA S, CORREA R J M, WARNER A, et al., 2020). Another retrospective study of ≥T1b primary renal cancer patients treated with MRI-guided SBRT included 36 patients with a median tumor size of 5.6 cm, who received 40 Gy in five fractions over two weeks. At a median follow-up of 16.4 months, the 1-year LCR, OS, and PFS rates were 95.2%, 91.2%, and 91%, respectively (TETAR S U, BOHOUDI O, SENAN S, et al., 2020). Additionally, a prospective, multi-institutional Phase II study (NCT02613819) by the Trans-Tasman Radiation Oncology Group (TROG) and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) is ongoing, involving 70 patients with primary RCC. The study has completed full accrual, and the results are highly anticipated (SIVA S, CHESSON B, BRESSEL M, et al., 2018).

3.3 SBRT for Primary RCC with Inferior Vena Cava Tumor Thrombus

Primary renal cell carcinoma can form tumor thrombi within the renal vein, extending into the inferior vena cava (IVC) in approximately 4-10% of patients, resulting in IVC tumor thrombus (IVC-TT), which may even reach the right atrium. IVC-TT can lead to severe complications such as pulmonary embolism or Budd-Chiari syndrome. The only potentially curative treatment option for IVC-TT is nephrectomy. However, this procedure carries a risk of severe surgical complications, including mortality, and a high risk of tumor recurrence (HADDAD A Q, WOOD C G, ABEL E J, et al., 2014). Neoadjuvant SBRT has been explored with the aim of improving disease control in RCC patients with IVC-TT. Margulis et al. (2021) reported preliminary results from the safety run-in phase of an ongoing Phase II trial (NCT02473536) investigating neoadjuvant SBRT for newly diagnosed RCC tumor thrombi, involving 6 patients. All patients received SBRT (40 Gy in 5 fractions) targeting the IVC tumor thrombus, followed by surgery. A total of 81 adverse events were reported within 90 days post-surgery: 4% were grade 3, with no grade 4 or 5 events. At a median follow-up of 24 months, all patients were alive. Neoadjuvant SBRT resulted in a reduction in Ki-67 and an increase in PD-L1 expression within the IVC-TT. In patients without progressive disease, inflammatory cytokines and autoantibody titers reflecting an improved host immune state were observed. The results of the Phase I trial demonstrate that neoadjuvant SBRT for primary RCC with IVC-TT is feasible and safe, and the ongoing Phase II trial's efficacy evaluation is highly anticipated.

4. Exploration of Optimal Fractionation Doses for SBRT

In SBRT for early-stage non-small cell lung cancer (NSCLC), regimens with a BED_{10} ≥100 Gy have been shown to improve local control and overall survival (ONISHI H, ARAKI T, SHIRATO H, et al., 2004). However, no consensus has been reached on the optimal dose fractionation for renal SBRT. In a systematic review and meta-analysis reported by Correa et al. (2019), various dose fractionation schemes were used for primary renal cell carcinoma across the included studies. The most common regimens were single-fraction 26 Gy and five-fraction 40 Gy. Reported local failures often occurred in the low-dose groups or in cases where tumor dose was limited by adjacent tissue constraints. A retrospective study of 74 primary RCC patients treated with SBRT primarily used 35 Gy in 5 fractions (BED_{10} 59.5 Gy) or 40 Gy in 5 fractions (BED_{10} 72 Gy). The study found that when the mean PTV (planning target volume) dose was ≥40 Gy, over 95% of patients achieved local tumor control (GLICKSMAN R M, CHEUNG P, KOROL R, et al., 2023). Grubb et al. (2021), PONSKY L, LOSS, ZHANG Y, et al. (2015) conducted a prospective dose-escalation study of SABR in 11 primary RCC patients. Initial SBRT doses of 48 Gy in 4 fractions (BED_{10} 105.6 Gy) were well-tolerated, prompting escalation to 60 Gy in 3 fractions (BED_{10} 124.8–180 Gy). At a median follow-up of 34.3 months, the 3-year local control rate was 90%, with no dose-limiting toxicities (DLTs). Acute toxicities were limited to grade 1 fatigue and nausea, while late toxicities occurred at rates of 18.1% and 9.1%, respectively.

Currently, extensive prospective data are still needed to determine the maximum safe dose levels for optimizing local control rates while minimizing toxicity. Until longer follow-up and more prospective studies are available, clinical practice should adhere to the IROCK consensus statement, which recommends single-fraction doses of 25-26 Gy, three-fraction doses of 35-45 Gy, and five-fraction doses of 40-50 Gy (SHANKAR S, J E R, LEE P, et al., 2016).

5. Future Directions

Current studies have demonstrated high long-term local control rates with SBRT for primary renal cell carcinoma. However, longer follow-up data are still needed to evaluate its impact on overall survival. Future efforts should focus on long-term follow-up and establishing comprehensive systems to promptly identify and manage potential late toxicities. And the optimal dose fractionation scheme for renal SBRT has not yet reached a consensus. Future research should continue to explore more effective dose fractionation strategies to improve efficacy and reduce toxicity. Thermal ablation techniques and surgical intervention, are also recommended by the NCCN guidelines for the local treatment of renal cell carcinoma. Future randomized controlled trials are needed to compare the safety and efficacy of SBRT with these treatment modalities, further clarifying which RCC patients may benefit most from SBRT to develop more personalized treatment strategies.

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