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Scientific Article

Nephron-Sparing Robotic Radiosurgical Therapy for Primary Renal Cell Carcinoma: Single-Institution Experience and Review of the Literature

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Abstract

Purpose: We report our single-institution stereotactic body radiation therapy (SBRT) experience on stage I renal cancer with prospectively collected toxicity and efficacy data.

Methods and Materials: A total of 21 patients with solitary renal tumors, including 14 surgical candidates who refused surgery (66%), were treated with SBRT. Histologic confirmation was obtained on all patients before treatment; 2 had transitional cell carcinoma and 19 had renal cell carcinoma. The median age was 71 years (range, 58-88). Nearly all patients received 48 Gy in 3 fractions.

Results: The median follow-up was 78 months (range, 5-107). At 5 years post treatment, the local tumor control rate was 100%. Tumor size decreased by a median value of 5.3% at 1 year post treatment, 15.6% at 2 years post treatment, and 15.4% at 5 years post treatment. Glomerular filtration rate had decreased by a median value of 1.5% at 1 year post treatment, 7.0% at 2 years post treatment, and 14.2% at 5 years post treatment. Three patients experienced grade 1 toxicity; no other treatment-related adverse effects were reported.

Conclusions: SBRT is a promising noninvasive treatment in the management of primary renal cell carcinoma, with evolving clinical evidence demonstrating encouraging results with respect to local control and toxicity.

Introduction

The American Cancer Society estimates approximately 73,820 new cases of kidney cancer in the United States in 2019, with 14,770 associated deaths.[1] The incidence of new kidney cancers has been rising since the 1990s, paralleling an aging population and more frequent utilization of imaging studies. Specifically, the expanded use of cross-sectional imaging techniques has led to a surge in the detection of small renal masses in asymptomatic patients. This has catalyzed enthusiasm for a less invasive approach to manage these primary tumors.[2] Radical nephrectomy is employed for up to 49% of T1a (<4 cm) renal cell cancers (RCCs).[3] In addition, survivors remain

at long-term risk for contralateral tumors, with a risk ratio of 13.7 at 10 years.[4] Renal-relevant comorbidities exist in most patients, contributing to an increased risk of subsequent renal malignancies.[5] This population at baseline typically demonstrates high rates of chronic kidney disease (CKD)[6] and is at high risk of developing end-stage renal disease.[7] For patients with renal tumors smaller than 4 cm, partial nephrectomy is the preferred primary treatment option, and when this is not feasible, radical nephrectomy, active surveillance, thermal ablation, or cryoablation are often advised, sometimes with mixed results.[8-12]

Stereotactic body radiation therapy (SBRT), also referred to as stereotactic ablative radiation therapy, delivers precise beams of radiation at various intensities guided by a sophisticated imaging system that tracks the exact 3-dimensional location of a tumor. Such precision allows high doses of radiation to be safely delivered to the tumor while minimizing damage to healthy tissue. Favorable early results with early-stage lung cancer, gastrointestinal tumors, and prostate and liver tumors demonstrate that SBRT is more effective than standard radiation therapy. SBRT as a treatment modality is attractive as it is noninvasive, it avoids general anesthesia, and it can treat large tumors, including those in the perihilar location. SBRT has shown encouraging efficacy in metastatic renal cell cancers (mRCCs).[13,14] A recent study by Wang et al on the safety and efficacy of SBRT for extracranial mRCC demonstrated excellent local control of mRCC with a favorable safety profile.[15] Several reports using SBRT for primary renal tumors have demonstrated excellent rates of tumor control with minimal effects on renal function.[16-18] These encouraging results led us to offer SBRT to patients who refused surgery or who were medically inoperable. We report our single-institutional experience with prospectively collected toxicity and efficacy data of SBRT on patients with stage I renal cancers.

Methods and Materials

Twenty-one consecutive patients with solitary renal tumors, including 14 surgical candidates who refused surgery (66%), were treated with SBRT. All patients were treated between November 2009 and August 2018. Histologic confirmation was obtained on all patients before treatment; 2 had transitional cell carcinoma and 19 had RCC. The age range of the patients was 58 to 88 with a median age of 71 years. The patient population consisted of 12 men and 9 women and was composed of 17 non-Hispanic whites, 2 Hispanics, 1 African American, and 1 Asian.

Contrast-enhanced computed tomography and magnetic resonance imaging scans were obtained after fiducial placement and after fiducial-to-fiducial fusion was performed. Tumor delineation (gross tumor volume) was performed on both data sets, and a 3- to 5-mm expansion was used to generate the planning target volume (Fig 1). A 4-dimensional computed tomography scan was performed selectively in patients with significant or irregular fiducial movement noted at the time of verification simulation on the CyberKnife. Additional margin considerations were made based on fiducial location with respect to the tumor and individual movement characteristics. Nearly all patients (n = 20) received 48 Gy in 3 fractions; 1 patient with a central renal pelvis tumor received 42 Gy in 3 fractions. Treatments were typically performed on consecutive working days. Before treatment, patients were placed on antiemetics and were selectively placed on steroids.

The median time from diagnosis to SBRT was 3 months (range, 0-37 months). The median axial dimension of the tumor was 2.85 cm (range, 1.2-7.7 cm); 19 renal lesions were less than 4 cm in diameter, 1 was 7.7 cm, 1 was 4.7 cm, and 1 was 4.1 cm. The RENAL (radius, exophytic and endophytic, nearness of tumor to collecting system or sinus, anterior and posterior, and hilar tumor touching main renal artery or vein and location relative to polar lines) complexity score among RCC lesions was low (4-6) in 10 patients, moderate (7-9) in 6, and high (10-12) in 2.[19] Eight patients had a pretreatment Eastern Cooperative Oncology Group (ECOG) performance score of 0 (Karnofsky Performance Status [KPS] of 100%), 8 had a pretreatment ECOG score of 1 (KPS 90% or 80%), and 5 had a pretreatment ECOG score of 2 (KPS of 70%). Pretreatment patient characteristics are noted in Table 1. All patients gave informed written consent, and institutional review board approval was obtained.

SBRT administration system

SBRT was delivered using the CyberKnife robotic radiosurgery system, which uses a 6-MV linear accelerator attached to a robotic manipulator with 6° of freedom,

Table 1 Pretreatment patient characteristics

	Median (n = 21) [min, max]
Age, y	71 [58, 88]
Greatest tumor dimension, cm	2.85cm [1.2, 7.7]
RENAL complexity score	6 [4, 10]
ECOG (Karnofsky) performance score	1 (80%) [0, 2 (70%, 100%)]
Total dose, Gy	48 [42,48]
No. of fractions	3 [3,3]
EGFR, mL/min	70 [33, 99]
Tumor volume, cm³	13.54 [2.06, 185.13]

Abbreviations: ECOG = Eastern Cooperative Oncology Group; EGFR = estimated glomerular filtration rate.
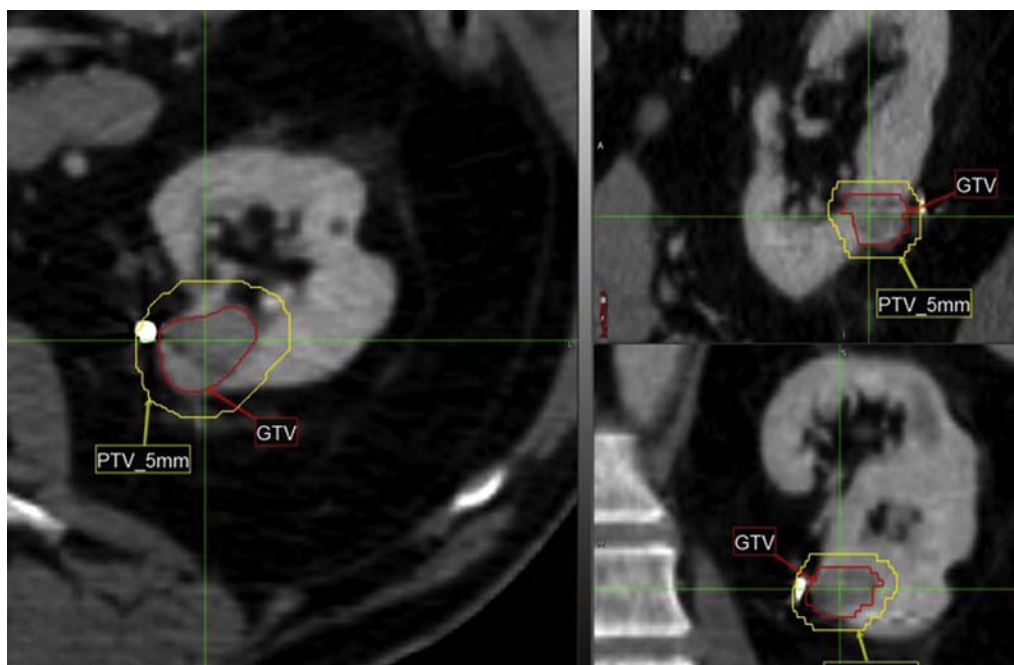
Figure 1   Delineation of planning gross tumor volume and planning target volume.

permitting radiation to be delivered from thousands of angles. CyberKnife uses orthogonally positioned x-ray tubes to image the patient during treatment. These images are used to track, map, and build a model of the predictive position of internal markers. This map and model can be used to adjust the robotic manipulator in real time to account for changes in body position and breathing. In this study, gold fiducials were used to track the planning target volumes.

Accounting for respiratory motion

To account for movement, CyberKnife collects respiratory amplitude signals and correlates the fiducial position at time of the orthogonal x-ray to the respiratory signal. This mapping process creates a continuously updated prediction model of the fiducials' position (and by proximity, the tumor's position). Respiratory motion was mapped with the CyberKnife's synchrony tracking method, which uses external cameras to record the positioning of infrared markers placed on the patient's chest. These measurements create a correlation model that predicts tumor location throughout the respiratory cycle. CyberKnife continuously updates the correlative model during treatment. Model validity is verified by our physicians and physics team daily.

Measuring treatment response

Tumor volume, disease progression, serum creatinine, and adverse events (AEs) were assessed during follow-up visits. Tumor volume was measured using computerized tomography and magnetic resonance imaging scans and then analyzed using RECIST guidelines.[20] According to RECIST guidelines, a decrease in tumor size greater than 30% is defined as partial response, complete tumor disappearance is defined as complete response, a 20% size increase or the appearance of a new lesion characterizes progression, and neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progression is defined as stable disease.[21] Serum creatinine was measured with blood tests and used to calculate glomerular filtration rate (GFR) using the CKD Epidemiology Collaboration equation.[22] GFR was calculated to identify CKD, kidney failure, and GFR decreases of more than 20% from baseline. Patients were assessed for AEs after treatment and during follow-up visits.

Dose metrics, adverse events, and statistical analyses

The volume of kidney tissue exposed to more than 16 Gy of radiation was recorded (200 cm^3 has been reported as being critical to maintain basal kidney function).[23] Additionally, the dose delivered to nearby critical structures such as the liver, small bowel, and spinal cord was assessed to limit potential toxicity.[24] AEs were scored using CTCAE (Common Terminology Criteria for Adverse Events), version 4.03. Kaplan–Meier estimations with log-rank tests were performed, and confidence intervals ($\alpha = 5\%$) were generated. Wilcoxon signed-rank tests were performed to assess change in tumor volume and GFR.
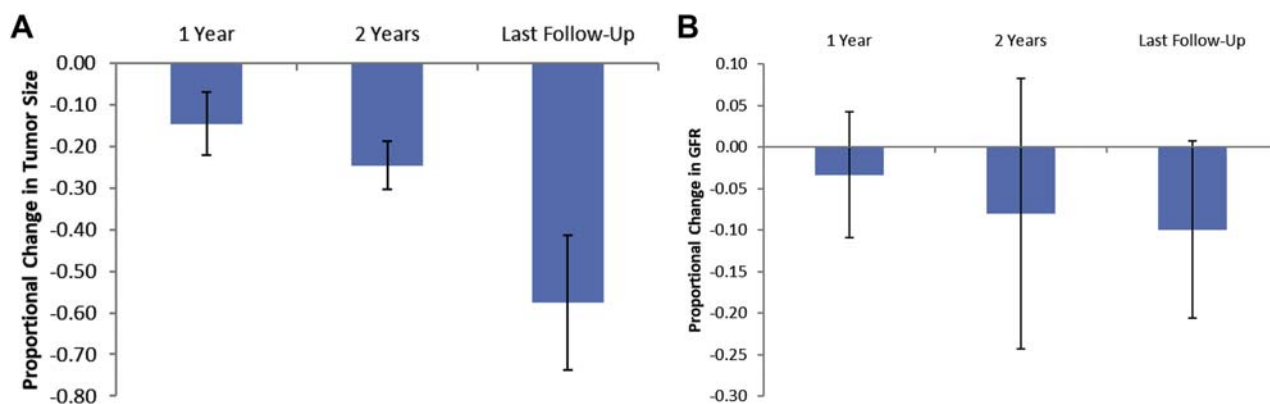
Figure 2   (A) Proportional change in tumor volume. (B) Proportional change in glomerular filtration rate. (Mean ± standard error; 1 year: n = 18; 2 years: n = 15; last follow-up: n = 21).

Results

Nineteen RCC and 2 transitional cell carcinoma lesions received SBRT. The median follow-up was 78 months (range, 2-110 months). At 5 years posttreatment, the local tumor control rate was 100%. According to RECIST criteria, complete response, partial response, and stable disease were obtained in 5, 13, and 3 patients, respectively, at last follow-up. Tumor volume decreased by a median value of 5.3% (range, −17.6%-100%) at 1 year post treatment, 15.6% (range, −17.6%-100%) at 2 years post treatment, and 48.8% (range, 0%-100%) at last follow-up ($P < .001$) (Fig 2). The median values of the mean doses to the ipsilateral and contralateral kidneys were 10.6 Gy and 0.9 Gy, respectively. The median volume receiving >16 Gy of radiation (V16 Gy) was 18.8 cm^3 for the ipsilateral kidney and 0.0 cm^3 for the contralateral kidney. GFR decreased by a median value of 1.5% (range, −21.3% to 21.4%) at 1 year, 7.0% (range, −13.6% to 28.9%) at 2 years, and 7.1% (range, −31.7% to 51.4%) at last follow-up (Fig 3). The change in GFR posttreatment was not significant ($P = .12$). After treatment, 3 patients who did not previously have CKD developed moderate CKD, and 3 who had moderate CKD developed severe CKD.

Three patients died of intercurrent disease at 3, 22, and 93 months posttreatment. There were no local or distant disease progressions. Median progression-free and overall survival were not obtained by the end of the study (Fig 4). Changes in GFR and tumor volume were reported for all patients (Table 2).

Two patients experienced grade 1 back pain; 1 experienced grade 1 constipation, likely from Vicodin; and 1 experienced grade 1 nausea during treatments that immediately subsided afterward. No other treatment-
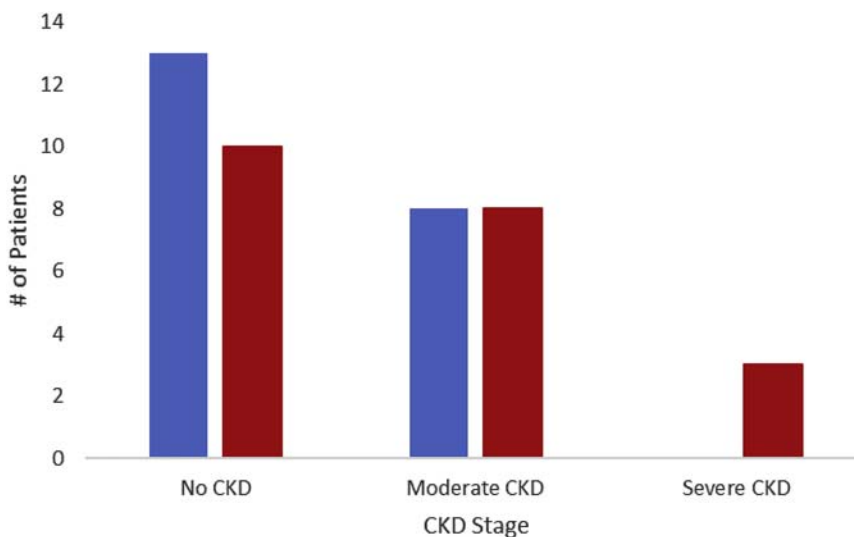

Figure 3   CKD stage of patients. Three patients who had no CKD developed moderate CKD, and 3 patients who had moderate CKD developed severe CKD by last follow-up. Moderate CKD indicates stage 3A or 3B. Severe CKD indicates stage 4. Blue: pretreatment. Red: last follow-up. *Abbreviation:* CKD = chronic kidney disease.
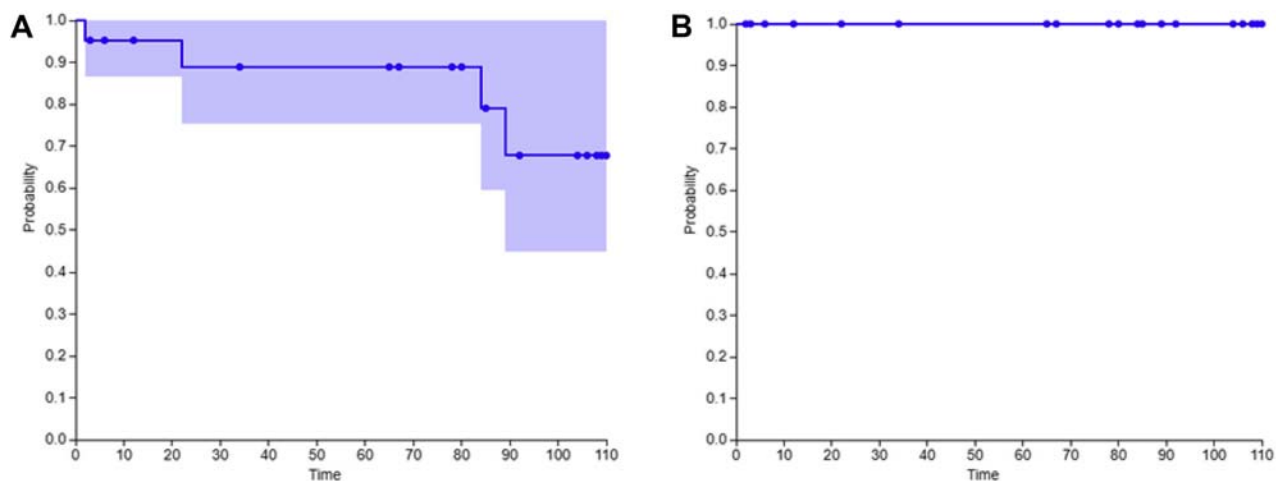
Figure 4   (A) Kaplan–Meier analysis of overall survival after stereotactic body radiation therapy. (B) Kaplan–Meier analysis of progression-free survival after stereotactic body radiation therapy. Time: months. Median not yet attained. Confidence interval shown in gray and found using log-ranked regression.

related AEs were reported. Posttreatment, no patients required dialysis. One patient with a 7.7-cm tumor underwent a nephrectomy out of concern for poor response at 2 years post-SBRT. The final pathology of the nephrectomy specimen only demonstrated necrotic tissue. There were no SBRT-associated deaths or serious complications.

Discussion

Surgery remains the standard of care for localized RCC, yet many patients are inoperable owing to medical comorbidities or advanced age. Radical and even partial nephrectomy may cause some patients to need chronic hemodialysis, which worsens quality of life and leads to lower overall survival.[24,25] To these patients, ablative therapies, including SBRT, can be offered. SBRT is being increasingly used and demonstrates high local control rates throughout the body, including in the lung, liver, and prostate. RCC has long been considered a "radioresistant" histology when treated with a conventional fractionated course radiation therapy. Radiosurgical ablation of RCC metastases has demonstrated excellent efficacy with high local control rates.

The treatment of primary renal tumors with SBRT is not well defined, but early data have been encouraging. Walsh et al have reported results demonstrating that high-dose radiation therapy delivered using a hypofractionated schedule results in RCC cell kill. A total of 19 nude mice were injected with A498 RCC cell lines into the R flank, and then 12 of the mice were treated with 48 Gy in 3 fractions and the 7 remaining mice served as controls. At 7 weeks post-RT, investigators noted a 30% tumor volume reduction in the irradiated mice and a demonstrative

increase in the control mice. At 4 weeks posttreatment, histologic assessment of 4 tumor specimens in the treated mice showed no active mitoses, compared with 9 to 14 mitoses and high-powered fields in 6 sacrificed control mice.[26] Ponsky et al reported their preclinical data using the CyberKnife radiosurgical system delivering a single SBRT fraction up to 48 Gy on the kidneys of pigs. Evaluation at 8 weeks post treatment demonstrated complete tissue ablation of the treated region with sparing of adjacent renal parenchyma but no histologic evidence of damage.[27]

SBRT applicability for lung, liver, and prostate cancer is well established; however, its role in treating primary RCC is limited to nonrandomized data. In a recent multi-institutional pooled analysis conducted by the International Radiosurgery Oncology Consortium for Kidney, 223 patients were treated with SBRT targeting primary RCC. They reported a local control rate of 98% at 2 years with a CTCAE ≥grade 3 toxicity rate of 1.3%.[28] Kaplan et al reported results of a phase 1 dose-escalation SBRT hypofractionated study in which 12 medically inoperable patients were treated for renal tumors using CyberKnife with doses ranging from 21 to 39 Gy in 3 fractions. The toxicity profile was favorable, with no RTOG grade 1 or higher toxicity and stability of baseline renal function. Only 1 local recurrence was observed in the study, in the patient who received the lowest dose, 21 Gy.[29]

Siva et al performed a systematic review of the literature and identified a total of 10 publications (7 retrospective and 3 prospective) using a wide range of techniques, doses, and dose fractionation schedules to treat inoperable RCC. A total of 126 patients were treated across these studies, with the largest series containing 33 patients. Total dose and fractionation in these trials was variable, with the most commonly employed fractionation

Table 2 Individual patient characteristics

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Age at SBRT, y	73	83	60	58	81	81	80	60	69	65	59	60	79	63	73	71	88	77	66	69	76
Initial tumor volume, cm³	14	32	185	3.1	34	31	29	13	18	12	21	4.7	19	8.6	2.1	4.2	7.0	29	10	31	12
Initial GFR, mL/min	89	69	99	71	33	51	53	81	43	84	76	81	74	60	70	95	52	53	81	51	46
Tumor response, cm³	−8.0	−8.0	−185	−3.1	X	−19	−13	−6.7	−8.0	−4.6	−13	0.0	−15	−8.6	−2.0	−1.3	−2.2	−12	−10	−14	−4.2
ΔGFR, mL/min	−9.7	−1	−33	+3	−4	−26	−13	+18	−19	−6	+16	−2	−27	+19	+13	−40	−13	+2	−27	0	+7
Follow-up, mo	89	22	110	78	2	67	85	65	84	106	104	92	80	108	109	44	12	12	6	3	3

Abbreviations: GFR = glomerular filtration rate; SBRT = stereotactic body radiation therapy.

schedule being 40 Gy delivered over 5 fractions. Median and mean follow-up ranged from 9 to 57.5 months. Local control was reported at 93.91% (range, 84%-100%). The rate of severe grade 3 or higher adverse events was 3.8% (range, 0%-19%). The rate of grade 1 to 2 minor adverse events was 21.4% (range, 0%-93%).[30]

After publication of this systematic review, Pham, Staehler, and Grubb reported on prospective studies. Pham et al published a phase 1 trial of SBRT for primary inoperable renal cell carcinoma with 20 patients. Eleven underwent fractionated treatment and 9 received a single fraction. A dose of 42 Gy in 3 fractions was used on tumors >5 cm, and for tumors <5 cm, 26 Gy in 1 fraction was delivered. Minimal short-term toxicity was seen, with 12 of 20 patients (60%) experiencing <grade 2 toxicity and nausea, chest wall pain, and fatigue, which are the most common toxicities reported. Eight of 20 patients (40%) were asymptomatic.[31] A second prospective case-control study of 40 patients undergoing single-fraction stereotactic radiosurgery was reported by Staehler et al. A total of 45 renal tumors were treated with a median follow-up of 28 months. The reported crude local control rate was 87%, and 5-year overall survival was 80%. There was a measurable size reduction in 38 lesions, including complete remission in 19.[32] Grubb et al reported on a phase 2 dose-escalation study for poor surgical candidates with localized RCC, demonstrating no dose-limiting toxicity from SBRT when it was administered to a total dose of 60 Gy in 3 fractions.[33]

Most recently, a prospective phase 1 dose-escalation trial of SBRT as an alternative to cytoreductive nephrectomy for inoperable patients with metastatic RCC on 12 patients with intermediate (67%) or poor (25%) International Metastatic Renal Cell Carcinoma Database Consortium prognostic class was reported. These patients had a median KPS of 70% and a median tumor size of 8.7 cm (range, 4.8-13.8 cm). They were enrolled in successive dose cohorts of 25 (n = 3), 30 (n = 6), and 35 Gy (n = 3) in 5 fractions. They concluded that renal-ablative SBRT to 35 Gy in 5 fractions for inoperable mRCC patients yielded acceptable toxicity, renal function preservation, and stable quality of life.[34] Also, a recent systematic review of the literature on SBRT for primary RCC along with a meta-analysis evaluating local control, toxicity, and renal function was published. The analysis included 383 tumors in 372 patients, most of whom were deemed inoperable. RCC histology was confirmed in 78.9% of patients. Dose fractionations of 26 Gray in 1 fraction and 40 Gy in 5 fractions were most commonly used. Local control of 97.2% (95% confidence interval [CI], 93.9%-99.5%), grade 3 to 4 toxicity of 1.5% (95% CI, 0%-4.3%), and a post-SBRT estimated glomerular filtration rate change of −7.7 mL/min (95% CI, −12.5 to −2.8) were reported. Only 6 patients had preexisting renal dysfunction, and 2.9% required dialysis.[35]

The strength of this analysis is that our SBRT experience provides data with some of the longest follow-up available for the definitive radiotherapeutic management of primary RCC. We demonstrate excellent local control rates, safety, and efficacy consistent with the available literature. Another strength of our series is the use of a consistent technique and dose. Limitations of this study include its retrospective nature and the small study group size. The retrospective nature is subject to potential temporal relationships, which are difficult to assess. The small study population limits the ability to perform any detailed statistical analysis.

Conclusions

SBRT is a promising noninvasive treatment in the management of primary RCC, with evolving clinical evidence demonstrating encouraging results. SBRT offers several distinct advantages in the management of primary kidney cancers over other modalities, including lack of anatomic restrictions, short duration of treatment, favorable toxicity profile, no required convalescence, and noninvasiveness. Given the paucity of outcomes data, prospective trials of SBRT specifically evaluating quality of life and cost-effectiveness compared with other modalities are needed.

References

1. American Cancer Society. *Cancer Facts & Figures 2019*. Atlanta, GA: American Cancer Society; 2019.
2. Znaor A, Lortet-Tieulent J, Laversanne M, et al. International variations and trends in renal cell carcinoma incidence and mortality. *Eur Urol*. 2015;67:519.
3. Talenfeld AD, Gennarelli RL, Elkin EB, et al. Percutaneous ablation versus partial and radical nephrectomy for T1a renal cancer: A population-based analysis. *Ann Intern Med*. 2018;169:69-77.
4. Rabbani F, Herr HW, Almahmeed T, Russo P. Temporal change in risk of metachronous contralateral renal cell carcinoma: Influence of tumor characteristics and demographic factors. *J Clin Oncol*. 2002;20:2370-2375.
5. Miller DC, Ruterbusch J, Colt JS, et al. Contemporary clinical epidemiology of renal cell carcinoma: Insight from a population based case-control study. *J Urol*. 2010;184:2254-2258.
6. Mashni JW, Assel M, Maschino A, et al. New chronic kidney disease and overall survival after nephrectomy for small renal cortical tumors. *J Urol*. 2015;86:1137-1145.
7. Huang WC, Levey AS, Serio AM, et al. Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. *Lancet Oncol*. 2006;7:735-740.
8. Rendon RA, Kapoor A, Breau R, et al. Surgical management of renal cell carcinoma: Canadian Kidney Cancer Forum Consensus. *Can Urol Assoc J*. 2014;8:E398-412.
9. Berger A, Brandina R, Atalla MA, et al. Laparoscopic radical nephrectomy for renal cell carcinoma: Oncological outcomes at 10 years or more. *J Urol*. 2009;182:2172-2176.
10. Tracy CR, Raman JD, Donnally C, et al. Durable oncologic outcomes after radiofrequency ablation: Experience from treating 243 small renal masses over 7.5 years. *Cancer*. 2010;116:3135.
11. Hegarty NJ, Gill IS, Desai MM, et al. Probe-ablative nephron-sparing surgery: Cryoablation versus radiofrequency ablation. *Urology*. 2006;68:7.
12. Volpe A, Cadeddu JA, Cestari A, et al. Contemporary management of small renal masses. *Eur Urol*. 2011;60:501.
13. Zelefsky MJ, Greco C, Motzer R, et al. Tumor control outcomes after hypofractionated and single-dose stereotactic image-guided intensity modulated radiotherapy for extracranial metastases from renal cell carcinoma. *Int J Radiat Oncol Biol Phys*. 2012;82:1744-1748.
14. Ning S, Trisler K, Wessels BW, et al. Radiobiologic studies of radioimmunotherapy and external beam radiotherapy in vitro and in vivo in human renal cell carcinoma xenografts. *Cancer*. 1997;80:2519-2528.
15. Wang J, Christie A, Lin M, et al. Safety and efficacy of stereotactic ablative radiation therapy for renal cell carcinoma extracranial metastases. *Int J Radiation Oncol Biol Phys*. 2017;98:91-100.
16. Svedman C, Karlsson K, Rutkowska E, et al. Stereotactic body radiotherapy of primary and metastatic renal lesions for patients with only one functioning kidney. *Acta Oncol*. 2008;47:1578-1583.
17. Wersäll PJ, Blomgren H, Lax I, et al. Extracranial stereotactic radiotherapy for primary and metastatic renal cell carcinoma. *Radiother Oncol*. 2005;77:88-95.
18. Beitler JJ, Makara D, Silverman P, et al. Definitive, high-dose-per-fraction, conformal, stereotactic external radiation for renal cell carcinoma. *Am J Clin Oncol*. 2004;27:646-648.
19. Kutikov A, Uzzo RG, The RENAL. nephrometry score: A comprehensive standardized system for quantitating renal tumor size, location and depth. *J Urol*. 2009;182:844.
20. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228.
21. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604.
22. Buwenge M, Cilla S, Guido A, et al. Individually optimized stereotactic radiotherapy for pancreatic head tumors: A planning feasibility study. *Rep Pract Oncol Radiother*. 2016;21:548-554.
23. Thompson RH, Boorjian SA, Lohse CM, et al. Radical nephrectomy for pT1a renal masses may be associated with decreased overall survival compared with partial nephrectomy. *J Urol*. 2008;179:468-473.
24. Kim DWN, Medin PM, Timmerman RD. Emphasis on repair, not just avoidance of injury, facilitates prudent stereotactic ablative radiotherapy. *Semin Radiat Oncol*. 2017;27:378-392.
25. Lane BR, Babineau DC, Poggio ED, et al. Factors predicting renal functional outcome after partial nephrectomy. *J Urol*. 2008;180:2363-2369.
26. Walsh L, Stanfield JL, Cho LC, et al. Efficacy of ablative high-dose-per-fraction radiation for implanted human renal cancer in a nude mouse model. *Eur Urol*. 2006;50:795-800.
27. Ponsky LE, Crownover RL, Rosen MJ, et al. Initial evaluation of CyberKnife technology for extracorporeal renal tissue ablation. *Urology*. 2003;61:498.
28. Siva S, Muacevic A, Staehler M, et al. Individual patient data meta-analysis of SBRT kidney: A report from the International Radiosurgery Oncology Consortium for Kidney (IROCK). *Int J Radiat Oncol Biol Phys*. 2017;99:S153-S154.
29. Kaplan ID, Redrosa I, Martin C, et al. Results of a phase I dose escalation study of stereotactic radiosurgery for primary renal tumors. *Int J Radiat Oncol Biol Phys*. 2010;78:S191.
30. Siva S, Pham D, Gill S, et al. A systematic review of stereotactic radiotherapy ablation for primary renal cell carcinoma. *BJU Int*. 2012;110:E737-E743.
31. Pham D, Thompson A, Kron T, et al. Stereotactic ablative body radiation therapy for primary kidney cancer: A 3-dimensional conformal technique associated with low rates of early toxicity. *Int J Radiat Oncol Biol Phys*. 2014;90:1061-1068.
32. Staehler M, Bader M, Schlenker B, et al. Single fraction radiosurgery for the treatment of renal tumors. *J Urol*. 2015;193:771-775.

33. Grubb W, Ponsky L, Lo SS, et al. Dose escalation to 60 Gy in 3 fractions with stereotactic body radiation therapy (SBRT) for poor surgical candidates with localized renal cell carcinoma: Expansion of a phase I study. *Int J Radiat Oncol Biol Phys*. 2018;102:e91.

34. Correa R, Ahmad B, Warner A, et al. A prospective phase I dose-escalation trial of stereotactic ablative radiotherapy (SABR) as an alternative to cytoreductive nephrectomy for inoperable patients with metastatic renal cell carcinoma. *Radiat Oncol*. 2018; 13:47.

35. Correa R, Louie A, Zaorsky N, et al. The emerging role of stereotactic ablative radiotherapy for primary renal cell carcinoma: A systematic review and meta-analysis [e-pub ahead of print]. *Eur Urol Focus*. https://doi.org/10.1016/j.euf.2019.06.002. Accessed September 8, 2019