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Effect of Stereotactic Body Radiotherapy on the Growth Kinetics and Enhancement Pattern of Primary Renal Tumors

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Abstract

OBJECTIVE.—The objective of our study was to assess the growth rate and enhancement of renal masses before and after treatment with stereotactic body radiotherapy (SBRT).

MATERIALS AND METHODS.—This retrospective study included all patients with renal masses who underwent SBRT during a 5-year period. Orthogonal measurements of renal masses were obtained on pre- and posttreatment CT or MRI. Pre- and posttreatment growth rates were compared for renal mass diameter and volume using the *t* test. Pre- and posttreatment tumor enhancement values were compared for tumors that underwent multiphasic contrast-enhanced MRI.

RESULTS.—Forty patients underwent SBRT for the treatment of 41 renal tumors: clear cell renal cell carcinomas (RCCs) ($n = 16$), papillary RCCs ($n = 6$), oncocytic neoplasms ($n = 8$), unclassified RCCs ($n = 2$), urothelial carcinoma ($n = 1$), and no pathologic diagnosis ($n = 8$). The mean maximum tumor diameter before treatment was 3.9 cm (range, 1.6–8.3 cm). Three hundred thirty-eight pre- and posttreatment imaging studies were analyzed: 214 MRI studies and 124 CT studies. The mean pre- and posttreatment lengths of observation were 416 days (range, 2–1800 days) and 561 days (83–1366 days), respectively. The mean pretreatment tumor growth rate of 0.68 cm/y decreased to -0.37 cm/y post treatment ($p < 0.0001$), and the mean tumor volume growth rate of 21.2 cm³/y before treatment decreased to -5.35 cm³/y after treatment ($p = 0.002$). Local control—defined as less than 5 mm of growth—was achieved in 38 of 41 (92.7%) tumors. The Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 showed progression in one

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tumor (2.4%), stability in 31 tumors (75.6%), partial response in eight tumors (19.5%), and complete response in one tumor (2.4%). No statistically significant change in tumor enhancement was shown (mean follow-up, 142 days; range, 7–581 days).

CONCLUSION.—Renal tumors treated with SBRT show statistically significant reductions in growth rate and tumor size after treatment but do not show statistically significant differences in enhancement in the initial (mean, 142 days) posttreatment period.

Keywords

renal masses; stereotactic body radiotherapy (SBRT); tumor response

The standard of care for the treatment of localized primary renal tumors is surgical excision, through either radical or partial nephrectomy [1]. Less invasive ablative treatments (radiofrequency ablation [RFA] or cryoablation) have also become acceptable treatment choices for some primary renal tumors in patients with comorbidities resulting in increased surgical risk [2–6], but these treatments are invasive procedures and have attendant risks [7]. Stereotactic body radiotherapy (SBRT), also termed “stereotactic radiosurgery” or “SRS” and “stereotactic ablative radiotherapy” or “SABR,” has emerged as an additional therapeutic option to treat tumors throughout the body. Several methods may be used to perform SBRT, including the method used in this study. In this study, a linear accelerator was mounted on a highly movable robotic arm that tracks the location of fiducial markers placed within or near a tumor in real time. SBRT allows high-dose radiotherapy to be delivered to the tumor while minimizing dose to adjacent normal tissues [8]. The results of initial studies using SBRT in the treatment of primary renal tumors are promising [9–13]. These preliminary results support a role for SBRT as an alternative treatment option for patients with primary renal cell carcinoma (RCC) and comorbidities that exclude total or partial nephrectomy.

Although the utilization of SBRT for the treatment of renal tumors is increasing, data regarding the effect of this treatment on tumor growth kinetics and tumor vascularity are limited. Changes in tumor size on cross-sectional imaging studies remain the reference standard for assessing the response of renal tumors to therapy [14, 15]. However, tumor enhancement is an additional imaging feature with a recognized role in the diagnosis and evaluation of renal tumors. The sensitivity of contrast-enhanced CT and MRI for diagnosing renal neoplasms is excellent and based on the detection of tissue enhancement [16–18]. Furthermore, different histopathologic subtypes show characteristic enhancement patterns on contrast-enhanced CT and MRI [19–22]. CT and MRI are routinely used to assess for tumor recurrence after surgical or ablation therapy in patients with renal tumors. Masslike enhancement in the surgical bed or in an ablated renal lesion on contrast-enhanced CT or MRI raises concern for recurrent or persistent neoplastic disease. However, these criteria may not be applicable to assess response to SBRT. For example, persistent enhancement is observed in vestibular schwannomas successfully treated with SBRT [23], and early enhancement may be observed in hepatocellular carcinomas after treatment with SBRT [24].

As experience with this technique develops, benchmark data regarding expected changes in size, rate of growth, and enhancement for primary renal tumors treated with SBRT are

needed to allow the technique to become more widely adopted clinically and to assess its therapeutic benefit in clinical trials. The goal of this study was to assess the growth rate and enhancement of renal masses before and after treatment with SBRT.

Materials and Methods

A retrospective study was performed of all patients who received SBRT (CyberKnife, Accuray) for renal masses at our institution from May 2006 through May 2011. Patients were identified using clinical records from the department of radiation oncology. This research was performed collaboratively by investigators from the departments of radiology, radiation oncology, and urology. Informed consent was waived for this retrospective study, which was approved by the institutional review board and was compliant with HIPAA.

All patients had at least two imaging studies to allow assessment of tumor growth before treatment and at least one imaging study after treatment. Repeat cycles of SBRT were excluded from analysis to avoid the confounding effect of the pretreatment period for the second cycle overlapping the posttreatment period of the first treatment. There were no other exclusion criteria.

Stereotactic Body Radiotherapy Protocol

Patients with primary renal tumors who were followed for known renal masses (active surveillance) and who were deemed, after multidisciplinary review by oncologists, radiologists, and urologists, to be poor surgical candidates for partial or total nephrectomy or other forms of minimally invasive tumor ablation (RFA or cryoablation) were referred for SBRT. Before treatment, one to four gold fiducial markers were placed percutaneously in the target lesion, adjacent renal parenchyma, or both under CT or ultrasound guidance. If possible, a concurrent biopsy of the tumor was performed if one had not been previously performed. MDCT was performed for radiation simulation using a 16-MDCT scanner (Aquilion, Toshiba Medical Systems) with acquisitions at end inspiration and end expiration. IV contrast material (iohexol [Omnipaque, GE Healthcare]) was administered to patients without contraindications to iodinated contrast material (i.e., renal insufficiency or contrast allergy). In patients with a relative contraindication to iodinated contrast material (i.e., moderate renal failure), the treatment planning scan was acquired without contrast material to reduce repeated exposure to contrast material; image fusion software (MultiPlan, version 3.5.2 Accuray) was used to fuse these images with contrast-enhanced CT or MR images acquired at an earlier time for diagnostic purposes. The gross target volume and clinical target volume were contoured using the margins of the tumor on each image showing visible tumor, and 3-mm uniform expansion was applied for the planning tumor volume [25]. Treatment planning was performed using MultiPlan software.

SBRT was delivered using the CyberKnife system. This radiosurgical device uses a 6-MV linear accelerator mounted on a robotic arm. The Synchrony system (Accuray) was used to track tumor movement during treatment. The treatment was delivered in daily fractions. Initially patients received 21 Gy ($7.0 \text{ Gy} \times 3 = 21 \text{ Gy}$), and the dose was gradually increased during the study period to 48 Gy ($16.0 \text{ Gy} \times 3 = 48 \text{ Gy}$). The prescription dose was typically to the 70–80% isodose line. Dose was recorded for each patient.

Data Collection

Data regarding patient demographics, imaging findings, and pathologic results were collected by three authors. Clinical data collected included dates of treatment, pathologic diagnoses, and method of biopsy specimen collection (e.g., core biopsy, FNA, urothelial brushings), when available. Pathologic diagnoses were classified as clear cell RCC, papillary RCC, oncocytic neoplasm, unclassified RCC, or urothelial carcinoma. Chromophobe RCCs and oncocytomas were grouped into the category “oncocytic neoplasm” because none of the specimens in this case series allowed a more specific diagnosis.

Imaging Analysis

A retrospective analysis of all available pre- and posttreatment CT or MRI examinations of the abdomen was performed for each patient by two authors in consensus; at the time of the study, one author had 7 years of experience in abdominal imaging and the other had 5 years of experience in abdominal imaging. Reviewed studies included MRI and CT examinations performed at the study institution and at outside hospitals and CT examinations obtained at the time of percutaneous CT-guided biopsy or fiducial marker placement. Limited unenhanced imaging studies performed as part of radiotherapy treatment planning were excluded from analysis. CT protocols, outside institution imaging protocols and equipment, and the use of contrast medium varied by necessity because of the number of sites at which imaging was performed. CT examinations performed at the time of biopsy or at fiducial marker placement consisted of helically acquired axial MDCT images (Aquilion, Toshiba Medical Systems; GE Discovery CT590, GE Healthcare) displayed using a 5-mm slice thickness.

MRI examinations performed at our institution were performed at either 1.5 T (Vision, Symphony, or Espree, Siemens Healthcare; Excite Twinspeed, GE Healthcare) or 3 T (Signa Excite, GE Healthcare) using a previously described protocol that included multiphase dynamic contrast-enhanced images in the corticomedullary and early and late nephrographic phases: A timing run was used to time the corticomedullary phase to the arterial arrival time, and early and late nephrographic phases were obtained with 20- and 40-second, respectively [20]. Patients who could not receive IV gadolinium-based contrast agents (GBCAs) due to renal insufficiency received a shortened version of this protocol omitting the contrast-enhanced images.

Measurements of maximum tumor diameter were made in three orthogonal dimensions (transverse, anteroposterior [AP], craniocaudal [CC]) for each imaging study reviewed. Imaging studies were excluded from analysis if image quality was not sufficient to permit accurate measurement of the lesion because of unenhanced technique, lesion inconspicuity, or motion or if images were not available for review because of PACS error. For each imaging study, the imaging sequence (if MRI) or phase of contrast administration (if CT) subjectively assessed to best show the lesion was used for analysis. AP and transverse diameter measurements were obtained using axial images. Reference was made to prior examinations when executing subsequent measurements to ensure that the planes of measurement remained constant across comparisons for each dimension within the same patient. CC diameter measurements were taken as the largest diameter measurement in

either the coronal or sagittal planes. For 20 CT examinations in which neither coronal nor sagittal plane reformatted images were available, the CC dimension was calculated as the number of axial images including the lesion multiplied by the slice thickness. Tumor volume was calculated assuming an ellipsoid shape for the tumor as follows:

$$\left(TR \times AP \times CC \times 0.52 \text{ cm}^3 \right),$$

where *TR* is the measurement in the transverse dimension, *AP* is the measurement in the anteroposterior dimension, and *CC* is the measurement in the craniocaudal dimension.

Tumor Enhancement Analysis

Analysis of enhancement was performed by a single author with 5 years of experience in abdominal imaging at the time of the study. Tumors were included in the enhancement analysis if at least one GBCA-enhanced MRI examination had been performed at the study institution both before and after SBRT. CT examinations and non-study institution MRI examinations were excluded from the enhancement analysis because nonstandardized techniques with variable timing of contrast-enhanced acquisitions were used.

The maximum tumor enhancement was assessed by placement of an ROI of approximately 1 cm² on the portion of the tumor subjectively judged to show the greatest enhancement in the corticomedullary phase. Whole-tumor enhancement was assessed through the creation of a freeform ROI matched to the contours of the entire lesion in the center of the lesion. ROIs were generated using corticomedullary phase images and were digitally propagated to other sequences, with manual corrections when necessary to account for respiratory or other motion between acquisitions using previously described methods [20, 21]. The area of each ROI was recorded.

Image analysis was performed using a workstation (Advantage Workstation, GE Healthcare). Tumor percentage enhancement was calculated as (contrast-enhanced signal intensity – unenhanced signal intensity) / (unenhanced signal intensity) × 100% [21]. For all tumors with enhancement data, the percentage enhancement before treatment was compared with the percentage enhancement after treatment without and with subgroup analysis by radiation dose administered. Analysis of enhancement by pathologic subtype was also performed for patients with pathologic diagnoses of RCC or oncocytic neoplasm: The percentage enhancement before treatment was compared with the percentage enhancement after treatment of each pathologic group (i.e., clear cell RCC, papillary RCC, oncocytic neoplasm). Analyses were performed in the corticomedullary, early nephrographic, and late nephrographic phases using both whole-lesion ROI and maximum-enhancement (i.e., focal) ROI values.

Total growth rate, defined as the overall rate of growth of the lesion before treatment and after treatment, was calculated for pre- and posttreatment intervals for both tumor diameter (in cm/y) and tumor volume (in cm³/y) in patients with at least two pre- and posttreatment examinations available for review. The total pretreatment growth rate was calculated as follows: (last pretreatment measurement – first pretreatment measurement) / time interval

between first and last pretreatment examinations. The total posttreatment growth rate was calculated as follows: (last posttreatment measurement – first posttreatment measurement) / time interval between first and last posttreatment examinations. Imaging studies performed at intervals of less than 7 days were excluded from analysis. The pretreatment relative growth rate was calculated for the pretreatment interval as follows:

$$\frac{(last\ M_{pre}) - (first\ M_{pre})}{(first\ M_{pre}) \times (TI_{pre})} \times 100,$$

where M_{pre} is the pretreatment measurement and TI_{pre} is the time interval between the first and last pretreatment examinations.

The posttreatment relative growth rate was calculated for the posttreatment interval as follows:

$$\frac{(last\ M_{post}) - (first\ M_{post})}{(first\ M_{post}) \times (TI_{post})} \times 100,$$

where M_{post} is the posttreatment measurement and TI_{post} is the time interval between the first and last posttreatment examinations.

The relative growth rates were calculated for each linear dimension and for total tumor volume. Negative growth rates were assigned for tumors decreasing in size.

To assess for local control, we calculated the overall change in tumor size by subtracting the largest diameter on the last pretreatment study from the largest diameter on the last posttreatment study. Local control was defined as tumors exhibiting an increase in size of less than 5 mm during the study period. Tumor growth of 5 mm or greater was considered progressive disease.

In addition, oncologic outcomes were assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [26] and were defined as follows: progressive disease, 20% or greater increase in maximum tumor diameter and absolute increase of at least 5 mm; partial response, reduction in tumor size of 30% or greater; complete response, disappearance of the tumor; and stable disease, changes in tumor size that did not qualify for progressive disease or partial response [26]. To assess the durability of response, we assessed for changes in size at all posttreatment time points to identify any tumors that met RECIST 1.1 criteria for partial response (reduction in tumor size of 30%) at any point in treatment but did not meet the RECIST 1.1 criteria for partial response at the end of the observation period because of subsequent growth.

Statistical Analysis

Paired *t* tests were used to compare total and relative growth rates. Pretreatment total growth rate, posttreatment total growth rates, and decrease in volume growth rate were calculated

for each of four pathologic diagnosis categories including clear cell RCC, papillary RCC, oncocytic neoplasm, and other. The other category included lesions without a pathologic diagnosis and cases with a non-RCC diagnosis (urothelial carcinoma) or an unclassified RCC diagnosis. The Kruskal-Wallis test was used to compare growth rates between these categories. In addition, this analysis was also performed to compare total and relative growth rates for lesions with known malignant diagnoses (clear cell RCC, papillary RCC, unclassified RCC, and the single urothelial carcinoma) with lesions with a pathologic diagnosis that is either not known or of uncertain malignant potential (e.g., oncocytic neoplasm). Pre- and posttreatment maximum and whole-tumor percentage enhancement values were compared as follows: The Wilcoxon rank sum test was used to compare enhancement in the corticomedullary, early nephrographic, and late nephrographic phases before and after treatment and to compare enhancement before and after treatment according to the radiation dose administered for all tumors. The Wilcoxon rank sum test was also used to compare enhancement in each phase before and after treatment according to the pathologic diagnosis for patients with pathologic diagnoses of RCC or oncocytic neoplasm. Correlation coefficients were used to investigate the relationship of dose with posttreatment growth and the relationship of dose with change in enhancement. The level of statistical significance was set at $p < 0.05$. Statistical analysis was performed using statistics software (Matlab, MathWorks).

Results

Patient and tumor characteristics and SBRT doses are summarized in Table 1. During the study period, 40 patients underwent SBRT for 41 renal tumors. One patient underwent concurrent SBRT of two separate renal masses located in a solitary kidney, and each of these lesions was included in the analysis. Two patients underwent second cycles of SBRT for the same renal mass, and these second cycles were excluded from analysis. The total radiation dose administered ranged from 21 to 48 Gy.

Pathologic diagnoses were available for 33 of the 41 (80.5%) lesions and are provided in Table 1. Diagnoses were obtained through core biopsy ($n = 22$), fine-needle aspiration ($n = 2$), both core biopsy and fine-needle aspiration ($n = 5$), and ureteroscopic brushings ($n = 1$); in two cases, pathologic diagnoses were performed at an outside institution and the biopsy technique was not recorded in the report. Biopsy was not performed in eight of the 41 (19.5%) renal masses.

Tumor Size Analysis

A total of 360 pre- and posttreatment imaging studies were obtained to evaluate the size of the lesions of interest. Twenty-two imaging studies were excluded from the analysis because it was not possible to adequately visualize the lesion. A total of 338 pre- and posttreatment MRI and CT studies were therefore included in the analysis (170 pretreatment and 168 posttreatment). There were 214 MRI examinations (contrast-enhanced, $n = 205$; unenhanced, $n = 9$) and 124 CT examinations (contrast-enhanced, $n = 100$; unenhanced, $n = 24$). The mean number of imaging examinations performed per patient before and after therapy was 4.2 (range, 2–17) and 4.1 (range, 1–13), respectively. The median number of

imaging examinations performed per patient before and after therapy was 3 (interquartile range [IQR], 2) and 3 (IQR, 4), respectively. The mean lengths of observation before and after therapy were 416 days (range, 2–1800 days) and 561 days (range, 83–1366 days), respectively. The median lengths of observation before and after therapy were 237 days (IQR, 491 days) and 489 days (IQR, 631 days), respectively.

The mean and median pretreatment diameters of the renal masses (maximum diameter in any dimension at the time of the last pretreatment imaging study) were 3.9 cm (range, 1.6–8.3 cm) and 3.7 cm (IQR, 2 cm), respectively. The mean and median pretreatment tumor volumes at the time of last pretreatment imaging study were 31.02 cm³ (range, 1.1–185.6 cm³) and 18.2 cm³ (IQR, 32.9 cm³). The total growth rates measured in centimeters per year before and after SBRT treatment are shown in Table 2. Statistically significant reductions in total growth rate were observed for each of the three measured dimensions and for tumor volume. The mean tumor total growth rate, averaging all three linear dimensions, was 0.68 cm/y before treatment and –0.37 cm/y after treatment ($p < 0.0001$ for each dimension). The mean tumor volume growth rate before treatment was 21.21 cm³/y, whereas the mean volume growth rate after treatment was –5.35 cm³/y ($p = 0.002$).

There was a statistically significant reduction in tumor size and volume relative growth rates during the posttreatment interval ($p < 0.0001$) (Table 3). There was no statistically significant correlation, however, between average change in growth rate and radiation dose (Appendix 1).

In separate subgroup analyses, both tumors with known malignant diagnoses ($n = 15$) (i.e., clear cell RCC, papillary RCC, unclassified RCC, and the single urothelial carcinoma) and tumors with unknown or indeterminate diagnoses ($n = 15$) (i.e., tumors without pathologic diagnosis and oncocytic neoplasms) showed statistically significant reductions in tumor growth after treatment (Table 3).

Local control (i.e., < 5 mm growth) was achieved in 38 of the 41 (92.7%) tumors treated with SBRT (Fig. 1). According to the RECIST 1.1 criteria, tumor responses to SBRT were as follows: progressive disease, one tumor (2.4%); stable disease, 31 tumors (75.6%); partial response, eight tumors (19.5%); and complete response, one tumor (2.4%) (Fig. 2). Tumors that met the RECIST 1.1 criteria for response to treatment were assessed for subsequent growth; none grew such that they did not meet criteria for response at the conclusion of the follow-up interval.

Tumor Enhancement Analysis

There were 22 tumors in 22 patients that met the criteria for analysis of tumor enhancement. The mean number of pre- and posttreatment GBCA-enhanced MRI studies was 2.8 (range, 1–6 studies; median, 2.5 studies; IQR, 2 studies) and 3.5 (range, 1–8 studies; median, 3.0 studies; IQR, 3 studies), respectively. The mean length of the pre- and posttreatment observation periods were 573 days (range, 20–1797 days; median, 493 days; IQR, 2 days) and 142 days (range, 7–581 days; median, 97 days; IQR, 3 days), respectively. The pathologic diagnoses for these tumors included clear cell RCC ($n = 6$, 27.3%); papillary RCC ($n = 5$, 22.7%); oncocytic neoplasm ($n = 5$, 22.7%); and other ($n = 6$, 27.3%), the latter

including lesions without a pathologic diagnosis ($n = 5$) and urothelial carcinoma ($n = 1$). The results of the mean percentage enhancement in the corticomedullary, early nephrographic, and late nephrographic phases before and after SBRT are provided for each pathologic group in Appendix 2 and plotted in Figure 3. There was no statistically significant change in tumor percentage enhancement between pre- and posttreatment measurements for any of the pathologic groups using either maximum-enhancement ROI or whole-lesion ROI measurements in the corticomedullary, early nephrographic, or late nephrographic phases. However, trends were noted for increased tumor enhancement after treatment in the clear cell RCCs (Fig. 4) and decreased tumor enhancement after treatment in papillary RCCs and oncocytic neoplasms.

There was no statistically significant correlation between the change in percentage enhancement in corticomedullary, early nephrographic, or late nephrographic phases and radiation dose (Appendix 1).

Discussion

The initial reports of experience using SBRT in the treatment of primary renal tumors are promising [9–13]. In a meta-analysis of 10 published clinical studies encompassing 126 treated patients, crude local control rates ranged from 84% to 100% [27]. Histopathologic evidence for tumor response has been reported in case reports and small series [12, 28]. Reported toxicities after SBRT of primary renal tumors appear to be tolerable with a weighted rate of severe toxicity of 3.8% and a weighted rate of minor toxicity of 21.4% in a meta-analysis [27]. More-over, SBRT has been reported to provide local control with preservation of adequate renal function in solitary kidneys [29] and in patients with preexisting chronic kidney disease [30]. These preliminary results support a role of SBRT as an alternative treatment option for patients with primary RCC and comorbidities that exclude total or partial nephrectomy.

As the use of SBRT for the treatment of primary renal tumors continues to develop, knowledge of the expected imaging appearance of treated tumors is necessary for posttreatment assessments. Several tumor imaging characteristics may be used to assess tumor response to treatment, including assessment of tumor vascularity with dynamic contrast-enhanced techniques such as ultrasound [31], CT [32], and MRI [33]; arterial spin labeling [34]; and measuring the apparent diffusion coefficient (ADC) on DWI [35]. Validation of these methods is ongoing. How-ever, changes in tumor size on cross-sectional imaging studies remain the reference standard for assessing response to therapy [14, 15]. Our results showed a statistically significant decrease of both the rate of growth and the size of renal tumors after SBRT. Our results are in concordance with the results of a smaller series of patients in which 14 tumors treated with SBRT exhibited a mean decrease in tumor volume of 44% at 12 months [9].

The observed tumor growth rates before treatment in our study can be compared with other data in the literature on active surveillance of renal masses [36–40]. In our patient cohort, tumors showed an average growth rate of 0.68 cm/y in diameter and a volume growth rate of 21.21 cm³/y before therapy, which are concordant with previously reported results [40]

given an average tumor diameter of 3.9 cm. The fact that the observed rates of growth in our study are higher than those reported in other prior active surveillance series may relate in part to the proportion of cases with a pathologic diagnosis of malignancy in our series (at least 60.9%, with an additional 19.5% diagnosed as oncocytic neoplasm). Furthermore, a selection bias toward tumors exhibiting obvious growth contributed to the decision to offer SBRT in our patient series of poor surgical candidates on active surveillance.

An interesting observation in our study is the persistent enhancement of renal masses after SBRT. This finding is not entirely surprising on the basis of prior experiences with neoplasms undergoing SBRT in other sites in the body [24, 41]. However, this finding indicates that an adjustment in the interpretation of posttreatment imaging studies is required because persistent enhancement after surgical resection or ablative therapy (e.g., radiotherapy, cryotherapy) would be normally considered as a sign of treatment failure. Instead, persistent enhancement in a renal mass with documented growth before SBRT may be irrelevant if the treatment provides durable local control and prevents the development of distant metastases. The average length of follow-up for the subset of patients meeting the criteria for analysis of enhancement (142 days) was shorter than that for the cohort in general (561 days). Therefore, future research with longer lengths of follow-up time will be needed to further elucidate whether the lack of change in tumor enhancement persists over time and to assess the correlation between tumor enhancement and progression of disease.

SBRT-induced changes in the pattern of tumor enhancement are also interesting. Although there were no statistically significant differences in the changes observed in tumor percentage enhancement after SBRT, clear cell RCCs exhibited increased posttreatment enhancement and papillary RCCs and oncocytomas showed decreased enhancement. Although data about contrast enhancement kinetics in tumors undergoing SBRT are lacking, decreased enhancement on CT or MRI has been reported for other abdominopelvic tumors including prostate cancer [42] and liver metastases [41]. Inflammation and tissue damage after SBRT has been proposed as a potential explanation for the observed changes in the contrast enhancement pattern of clear cell RCCs [43]; however, an underlying mechanism to explain the differences observed for papillary RCCs and oncocytomas is not known. The significance of the observed trend toward increased enhancement in clear cell RCCs requires further evaluation.

This study is limited by its retrospective nature, with resultant heterogeneity of SBRT treatment parameters and the imaging protocols that were used to assess the study tumors. At the study institution, patients typically undergo follow-up imaging 3, 6, 12, 18, and 24 months after treatment and then yearly thereafter. Imaging follow-up can be with CT or MRI, a choice that is directed by clinical parameters, with consistency of modality maintained whenever possible. Future prospective studies performed with standardized treatment and imaging protocols may be helpful to confirm these results. The nature of an SBRT cohort suggests the possibility of selection bias for patients with larger, unfavorably located, or more rapidly growing tumors impacting their surgical risk assessment and influencing the recommendation for SBRT. At the study institution, SBRT is offered as a therapeutic option for patients who are deemed, after multidisciplinary review by oncologists, radiologists, and urologists, to be poor surgical candidates for partial or total

nephrectomy or for other forms of minimally invasive tumor ablation (i.e., RFA or cryoablation). Additional studies will also be required to correlate pathologic response of renal tumors and oncologic outcome with these observations of treatment effect on tumor size, growth, and enhancement.

In conclusion, renal tumors treated with SBRT show statistically significant reductions in tumor growth and tumor volume after treatment, but no significant difference in tumor enhancement pattern was observed in the early post-SBRT period. These findings will provide initial data to radiologists and radiation oncologists who are expected to be helpful in evaluating the imaging examinations of this growing population of patients.

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APPENDIX 1:: Relationship of Total Radiation Dose to Average Change in Percentage Enhancement and Average Change in Growth Rates for Renal Tumors After Treatment With Stereotactic Body Radiotherapy

Dose (Gy)	Average Change in Percentage Enhancement				Average Change in Growth Rate				
	No. of Tumors	CM Phase	EN Phase	LN Phase	No. of Tumors	AP Dimension (cm/y)	Transverse Dimension (cm/y)	CC Dimension (cm/y)	Volume (cm ³ /y)
21	1	-18.8	-38.9	-48.5	2	-0.5	0.3	-1.1	-3.7
27	2	-16.3	29.3	26.8	4	-0.6	-1.0	-0.8	-17.5
30	4	15.4	8.9	14.5	4	-1.6	-1.2	-1.7	-22.0
33	0	NA	NA	NA	2	-0.7	0.0	-0.2	1.9
36	2	10.2	-30.9	-35.3	2	-0.7	-0.9	-0.6	-4.0
39	4	-1.3	-77.6	-88.3	8	-0.3	-0.7	-0.8	-11.9
45	1	11.8	51.6	48.3	1	-1.7	-0.6	-0.6	-10.2
48	8	4.9	13.2	1.0	11	-0.7	-0.7	-0.9	-14.5
Correlation coefficient		0.05	0.06	0.01		0.04	-0.04	0.09	-0.02
<i>p</i>		0.83	0.79	0.96		0.8	0.84	0.60	0.89

Note—There was no statistically significant correlation between radiation dose and either average change in percentage enhancement or average change in growth rate. CM = corticomedullary, EN = early nephrographic, LN = late nephrographic, AP = anteroposterior, CC = craniocaudal, NA = not applicable.

APPENDIX 2:: Pre- and Posttreatment Percentage Enhancement of Renal Masses by Pathologic Diagnosis

Pathologic Diagnosis and ROI Type	Percentage Enhancement of Renal Masses (Mean ± SD)					
	Corticomedullary Phase		Early Nephrographic Phase		Late Nephrographic Phase	
	Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment
Clear cell RCC, <i>n</i> = 6						
Maximum-enhancement ROI ^a	129 ± 65	148 ± 72	218 ± 121	252 ± 87	197 ± 106	231 ± 106
Whole-lesion ROI ^b	121 ± 54	131 ± 59	196 ± 97	213 ± 83	177 ± 87	212 ± 81
Papillary RCC, <i>n</i> = 5						
Maximum-enhancement ROI ^a	94 ± 106	56 ± 74	128 ± 110	75 ± 86	124 ± 99	79 ± 81
Whole-lesion ROI ^b	78 ± 80	50 ± 58	114 ± 90	81 ± 72	116 ± 87	86 ± 67
Oncocytic neoplasm, <i>n</i> = 5						
Maximum-enhancement ROI ^a	134 ± 82	108 ± 71	228 ± 147	197 ± 89	275 ± 146	202 ± 91
Whole-lesion ROI ^b	122 ± 70	101 ± 52	208 ± 132	184 ± 72	210 ± 128	187 ± 73

Note—There were no statistically significant differences in enhancement between pre- and posttreatment intervals for any pathologic diagnosis or phase of enhancement; all *p* values were 0.05. RCC = renal cell carcinoma.

^aMaximum-enhancement ROI refers to an ROI of approximately 1 cm² placed on location of maximum enhancement in corticomedullary phase and propagated to other imaging phases.

^bWhole-lesion ROI refers to an ROI that follows the margins of the lesion.

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Fig. 1—.

Overall change in size of renal masses treated with stereotactic body radiotherapy. Columns show magnitude and direction of change from last pretreatment size (maximum diameter in any plane) to last posttreatment size. Columns above baseline indicate lesion growth, and columns below baseline indicate reduction in lesion size. In 38 of the 41 (92.7%) tumors, local control was achieved; local control was defined as overall tumor decrease in size, lack of change in size, or tumor size increase of less than 5 mm. Threshold is indicated by dashed line.

Fig. 2—

73-year-old man with clear cell renal cell carcinoma (RCC) and decrease in tumor size (partial response) 30 months after stereotactic body radiotherapy (SBRT). Renal tumor measurements were obtained before and after treatment with SBRT. AP = anteroposterior, TR = transverse, CC = craniocaudal.

A and B, Axial (**A**) and sagittal reformatted (**B**) images from nephrographic phase contrast-enhanced CT performed before SBRT show mass (*arrow*) in interpolar region of right kidney. Biopsy at time of fiducial marker placement revealed clear cell RCC, Fuhrman grade II.

C and D, Axial (**C**) and sagittal reformatted (**D**) images from early nephrographic phase contrast-enhanced CT after SBRT show reduction in size of mass (*arrow*). Fiducial marker is visible as hyperdense focus centrally located within mass.

Fig. 3—

Percentage enhancement of renal masses in corticomedullary (CM), early nephrographic (EN), and late nephrographic (LN) phases before and after stereotactic body radiotherapy by pathologic diagnosis.

A–C, Percentage enhancement as measured using whole-lesion ROI for clear cell renal cell carcinomas (RCCs) (**A**), papillary RCCs (**B**), and oncocytic neoplasms (**C**).

D–F, Percentage enhancement as measured using focal ROI in area of maximum tumoral enhancement for clear cell RCCs (**D**), papillary RCCs (**E**), and oncocytic neoplasms (**F**).

Fig. 4—

66-year-old woman with clear cell renal cell carcinoma (RCC) occurring in transplanted kidney and increased renal tumor enhancement 7 months after treatment with stereotactic body radiotherapy (SBRT). Mean and SD signal intensity values are shown at top of images for ROI 1 (*circle*).

A–D, Coronal unenhanced (**A**), contrast-enhanced corticomedullary (**B**), early nephrographic (**C**), and late nephrographic (**D**) phase T1-weighted spoiled gradient-recalled (SPGR) images from contrast-enhanced MRI before SBRT show mass in interpolar region of transplanted kidney located in right lower quadrant.

E–H, Coronal unenhanced (**E**) and contrast-enhanced corticomedullary (**F**), early nephrographic (**G**), and late nephrographic (**H**) phase T1-weighted SPGR MR images obtained 7 months after treatment show increased tumor enhancement. Percentage enhancement as measured by whole-tumor ROI analysis before treatment in corticomedullary, early nephrographic, and late nephrographic phases was 54.9%, 106.0%, and 87.2%, respectively, whereas percentage enhancement after treatment was 253.4%, 351.2%, and 357.8% in same three phases, respectively. According to Response Evaluation Criteria in Solid Tumors 1.1 criteria, tumor size measurements were consistent with stable disease.

Table 1:

Patient and Tumor Characteristics and Stereotactic Body Radiotherapy (SBRT) Dose

Characteristic	Value
No. of tumors	
Mean	1
Range	1–2
Age	
Mean	74.5
Range	45–93
Sex, no. of patients	
M	20
F	20
Renal mass size before SBRT (cm)	
Mean	3.9
Range	1.6–8.3
T category, no. (%) of tumors	
T1a	22 (53.7)
T1b	18 (43.9)
T2a	1 (2.4)
Renal mass volume before SBRT (cm ³)	
Mean	31.02
Range	1.1–185.6
Histology, no. (%) of tumors	
Clear cell RCC	16 (39.0)
Papillary RCC	6 (14.6)
Oncocytic neoplasm	8 (19.5)
Unclassified RCC	2 (4.9)
Urothelial carcinoma	1 (2.4)
No pathologic diagnosis	8 (19.5)
SBRT dose (Gy)	
Mean	38
Range	21–48
SBRT dose, no. of tumors	
21 Gy	3
24 Gy	1
27 Gy	4
30 Gy	5
33 Gy	2
36 Gy	2
39 Gy	8
45 Gy	1
48 Gy	15

Note—RCC = renal cell carcinoma.

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Table 2:
Total Growth Rates of Renal Tumors for Linear Dimensions and Volume Before and After Stereotactic Body Radiotherapy Treatment

Linear Dimensions and Volume of Renal Tumors	Total Growth Rate		Mean Reduction in Total Growth Rate	p
	Mean $\pm$ SD	Median		
Dimension 1 (transverse), cm/y				
Pretreatment	0.67 $\pm$ 1.24	0.38	0.72	< 0.0001
Posttreatment	-0.35 $\pm$ 0.52	-0.30		
Dimension 2 (AP), cm/y			0.69	< 0.0001
Pretreatment	0.69 $\pm$ 1.54	0.40		
Posttreatment	-0.37 $\pm$ 0.68	-0.35		
Dimension 3 (CC), cm/y			0.90	< 0.0001
Pretreatment	0.67 $\pm$ 1.02	0.44		
Posttreatment	-0.39 $\pm$ 0.68	-0.30		
Volume, cm ³ /y			12.79	0.002
Pretreatment	21.21 $\pm$ 75.6	4.63		
Posttreatment	-5.35 $\pm$ 15.2	-2.96		

Note—Statistically significant reductions in total growth rate were observed for each of the three measured dimensions and for tumor volume. AP = anteroposterior; CC = craniocaudal.

Table 3:

Reduction of Relative Growth Rates After Treatment

Tumors	Relative Growth Rate (%)		Mean Reduction in Relative Growth Rate (%/y)	p
	Mean ± SD	Median ± IQR		
All tumors				
Dimension 1 (TR)			28.1	< 0.0001
Pretreatment	22.4 ± 27.4	17.3 ± 26.0		
Posttreatment	-11.1 ± 14.7	-12.0 ± 18.3		
Dimension 2 (AP)			25.9	< 0.0001
Pretreatment	24.3 ± 37.3	17.2 ± 25.0		
Posttreatment	-10.3 ± 20.9	-14.2 ± 18.7		
Dimension 3 (CC)			32.0	< 0.0001
Pretreatment	22.9 ± 24.8	17.7 ± 29.7		
Posttreatment	-11.3 ± 15.2	-11.3 ± 15.4		
Volume			112.3	< 0.0001
Pretreatment	104.4 ± 125.4	56.5 ± 113.8		
Posttreatment	-22.9 ± 36.3	-33.0 ± 27.5		
Tumors with malignant pathologic diagnosis				
Dimension 1 (TR)			31.62	< 0.0001
Pretreatment	25.8 ± 30.83	24.93 ± 29.17		
Posttreatment	-12.62 ± 16.76	-12.05 ± 18.48		
Dimension 2 (AP)			24.8	< 0.0001
Pretreatment	26.78 ± 43.92	24.45 ± 25.5		
Posttreatment	-9.49 ± 19.05	-11.01 ± 22.36		
Dimension 3 (CC)			37.47	< 0.0001
Pretreatment	26.28 ± 26.7	21.39 ± 37.58		
Posttreatment	-14.58 ± 14.58	-14.01 ± 14.37		
Volume			119.5	< 0.0001
Pretreatment	115.6 ± 130.5	81.65 ± 126.1		
Posttreatment	-25.94 ± 34.62	-31.18 ± 29.3		
Tumors with unknown or indeterminate pathologic diagnosis				

Tumors	Relative Growth Rate (%)		Mean Reduction in Relative Growth Rate (%/y)	p
	Mean $\pm$ SD	Median $\pm$ IQR		
Dimension 1 (TR)				
Pretreatment	16.2 $\pm$ 19.16	13.25 $\pm$ 24.46	21.52	< 0.0001
Posttreatment	-8.65 $\pm$ 10.48	-9.47 $\pm$ 14.4		
Dimension 2 (AP)				
Pretreatment	19.76 $\pm$ 20.9	13.47 $\pm$ 7.45	27.82	< 0.0001
Posttreatment	-11.53 $\pm$ 24.36	-18.29 $\pm$ 11.43		
Dimension 3 (CC)				
Pretreatment	16.68 $\pm$ 20.07	14.04 $\pm$ 19.85	21.87	< 0.0001
Posttreatment	-5.83 $\pm$ 15.08	-9.20 $\pm$ 19.16		
Volume				
Pretreatment	83.71 $\pm$ 117.1	54.57 $\pm$ 28.29	99.06	< 0.0001
Posttreatment	-17.77 $\pm$ 39.94	-36.46 $\pm$ 28.05		

Note—Relative tumor growth showed statistically significant reductions between the pre- and posttreatment intervals for all three linear dimensions and for tumor volume. IQR = interquartile range. TR = transverse, AP = anteroposterior, CC = craniocaudal.