

## Scientific Article

# Utilization of Stereotactic Ablative Body Radiation Therapy for Intact Renal Cell Carcinoma: Trends in Treatment and Predictors of Outcome



Rodney E. Wegner, MD,<sup>a,\*</sup> Stephen Abel, DO,<sup>a</sup> Gautham Vemana, MD,<sup>b</sup> Shifeng Mao, MD,<sup>c</sup> and Russell Fuhrer, MD<sup>a</sup>

<sup>a</sup>Division of Radiation Oncology, <sup>b</sup>Division of Urology, and <sup>c</sup>Division of Medical Oncology, Allegheny Health Network Cancer Institute, Pittsburgh, Pennsylvania

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## Abstract

**Purpose:** Surgery is the standard-of-care treatment in patients with localized renal cell carcinoma (RCC), offering excellent chance of cure. However, there is a subset of patients who are ineligible for surgery and instead manage with ablative therapies, such as stereotactic ablative body radiation therapy (SABR). We used the National Cancer Database to examine trends in the use of SABR for inoperable RCC and identify any predictors of outcome.

**Methods and Materials:** We queried the National Cancer Database for patients with unresected RCC between 2004 and 2016 who were treated with SABR. Kaplan–Meier analyses were used to determine overall survival. Multivariable Cox regression was used to identify predictors of survival.

**Results:** We identified 347 patients meeting eligibility criteria. Median age was 74, and the majority of patients were clinical stage T1-2 (80%) and N0 (97%). The median tumor size was 3.8 cm (interquartile range [IQR], 2.8-5.2 cm). Six percent of patients received systemic therapy. The median dose of SABR was 45 Gy (IQR, 35-54 Gy) in 3 fractions (IQR, 1-5 fractions). The median follow-up was 36 months (IQR, 1-156 months). Predictors of decreased survival were age >74, larger tumors, and N1 or M1 disease. Median survival across the entire cohort was 58 months. Median survival was 92 months, 88 months, 44 months, and 26 months for primary tumors ≤2.5 cm, 2.6-3.5 cm, 3.5-5.0 cm, and >5.0 cm, respectively ( $P < .0001$ ).

**Conclusions:** SABR is being increasingly used for renal cell carcinoma across the United States with excellent outcomes in smaller tumors.

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## Introduction

Diagnosed in approximately 75,000 individuals each year in the United States, renal cell carcinoma (RCC) represents the vast majority of primary renal neoplasms.<sup>1</sup>

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\* Corresponding author: Rodney E. Wegner, MD; E-mail: [rodney.wegner@ahn.org](mailto:rodney.wegner@ahn.org)

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The standard of care for early-stage lesions is surgical resection alone, which often leads to cure.<sup>2</sup> As more lesions are detected incidentally (ie, on imaging for other reasons), there will conceivably be a subset of patients ineligible for surgery due to medical comorbidities or patient refusal.<sup>3</sup> For such situations, other less-invasive ablative therapies, such as radiofrequency and cryoablation, have played a role in management.<sup>4-6</sup> Radiation therapy is often overlooked in these situations because historic preclinical data report RCC as being relatively radioresistant to external beam radiation at conventional doses. As such, using traditional radiation techniques to deliver a tumoricidal dose is exceedingly difficult.<sup>7</sup>

In recent history, stereotactic ablative body radiation therapy (SABR) has emerged as a noninvasive, highly effective, and safe method for ablation of lung, brain, liver, adrenal, prostate, and bone tumors.<sup>8,9</sup> With SABR's ability to deliver highly conformal dose-escalated radiation, it has occasionally been used in kidney tumors to overcome the relative radioresistance.<sup>10,11</sup> A multi-institutional international consortium recently presented results on a cohort of patients treated with SABR for RCC showing excellent clinical results.<sup>12,13</sup> In that vein, we sought to use the National Cancer Database to look at rates of utilization of SABR in the United States for patients with unresected RCC.

## Methods and Materials

The methods of analyzing the National Cancer Database have previously been detailed.<sup>14,15</sup> We searched the database for patients with RCC treated nonsurgically between 2004 and 2016 with SABR directed at the kidney (both of which are coded for in the NCDB) in 1 to 5 fractions and with at least 1 month of follow-up. Full inclusion criteria are outlined in Figure 1. The NCDB contains deidentified data; therefore, these analyses are exempt from institutional review board approval. The data set is managed and maintained by the American Cancer Society and Commission on Cancer and is estimated to capture up-front treatment and staging data on ~70% of patients with cancer each year.

Within the database, race was reclassified into Caucasian, African American, and other. Comorbid conditions were quantified using the widely approved Charlson and Deyo comorbidity index.<sup>16</sup> The most current NCDB files use the seventh edition of the American Joint Committee on Cancer's clinical guidelines. The degree of high school education was quantified by percentage without a high school diploma by zip code, as was median household income. Facility type was categorized as community cancer center, comprehensive community cancer center, and academic or research program according to Commission on Cancer status. Locations were assigned based on US Department of

Agriculture Economic Research Service data. Insurance status was reflected as it appears on the admission page and was categorized as none, private, or governmental (Medicare and Medicaid). It should be noted that the American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytical or statistical methodology employed or the conclusions drawn from these data by the investigators.

Data were analyzed using Medcalc version 18 (Ostend, Belgium). Overall survival was calculated in months from time of diagnosis to date of last contact or death. Multivariable Cox regression was used to identify predictors of overall survival.<sup>17</sup> Kaplan–Meier curves were used to calculate cumulative probability of survival.<sup>18</sup> Log-rank statistics were used to test whether there was a statistically significant difference in the cumulative proportions across groups when comparisons were made.

## Results

Using the aforementioned eligibility, we identified 347 patients with RCC who received SABR targeting the kidney. The majority of patients were male (62%), and the median age was 74 (interquartile range [IQR], 32-90). Of note, 98 patients (28%) in this cohort did not have pathologic confirmation of diagnosis and were coded as RCC based on imaging. Almost all treatments (>95%) were carried out at either an academic program or comprehensive cancer program. Eighty percent of patients were stage cT1-2, and 97% were cN0. Seven percent of patients did have documented metastatic disease. Very few patients (22 in total) received systemic therapy. See Table 1 for full patient baseline characteristics. Of patients with radiation directed at the kidney, the use of SABR increased over time, from 11% in 2004 to 35% to 40% in more recent years (Fig 2).

Median SABR dose was 45 Gy (IQR, 35-54 Gy) in 3 (IQR, 1-5) fractions corresponding to a median BED<sub>10</sub> of 112.5 Gy (IQR, 60-151 Gy). The median follow-up was 36 months (IQR, 1-156) for all patients. Kaplan–Meier analysis revealed a median overall survival of 58 months (95% confidence interval, 49-69 months; Fig 3). Multivariable Cox regression identified increased age and M1 and N1 disease as predictive of decreased survival. In addition, patients with tumors >3.5 cm had worse outcomes on Cox regression (Table 2). On Kaplan–Meier analysis, median overall survival was 92 months, 88 months, 44 months, and 26 months for primary tumors ≤2.5 cm, 2.6-3.5 cm, 3.5-5.0 cm, and >5.0 cm, respectively ( $P < .0001$ ; Fig 4). We also examined outcomes by BED<sub>10</sub> using a cutoff of 112.5 Gy (the median) and 100 Gy (extrapolating from lung SABR<sup>19</sup>), which showed no difference in survival ( $P > .05$ ).

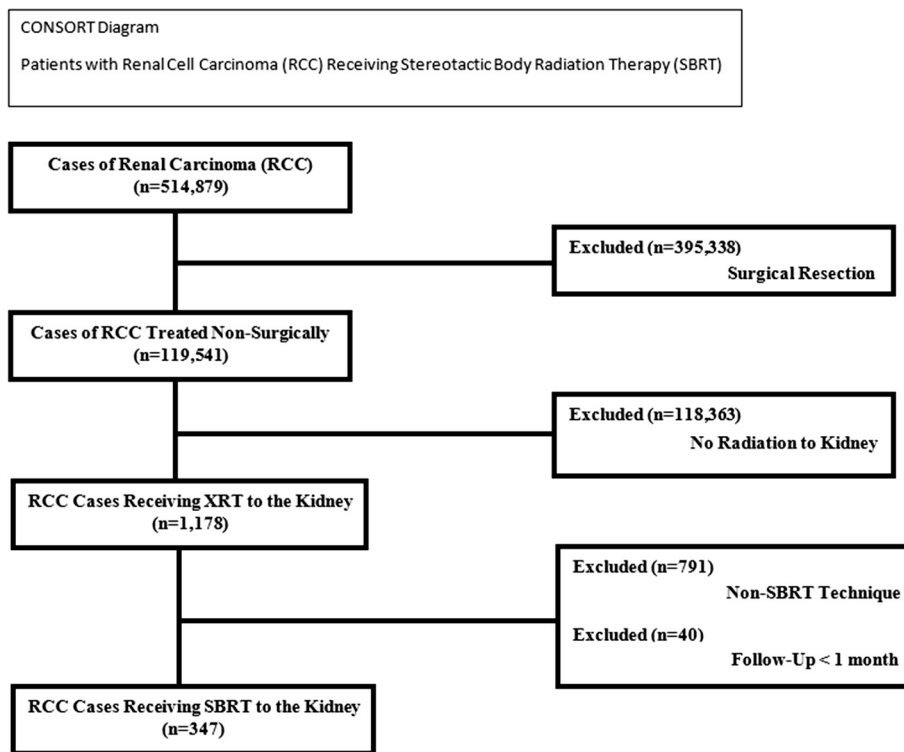


Figure 1 CONSORT diagram.

## Discussion

This study represents the largest US series on the use of SABR for patients with RCC to date. The results presented demonstrate excellent post-SABR outcomes, with median overall survival in the range of 7 to 8 years for smaller lesions. This is particularly impressive considering that many of these patients were likely medically inoperable. As expected, there were worse outcomes with larger tumors, potentially owing to lower delivered doses, although a change in outcomes using BED cutoffs was not shown. Also of note, and not surprisingly, the vast majority of kidney SABR is done at academic centers with a slight increase over time, highlighting the importance of appropriate technology and training when delivering this technique. In addition, despite showing an increase in use, one must be aware of the overall context, and we do acknowledge that the overall rate of utilization across this diagnosis is quite small.

That being said, surgery remains the standard of care for this patient population when feasible and can range from partial nephrectomy to a radical nephrectomy depending on tumor size, stage, renal function, or unusual anatomy (solitary kidney). Cytoreductive nephrectomies are even done in the metastatic setting, although on a more limited basis now due to data presented at the American Society of Clinical Oncology Annual Meeting

2018 potentially showing limited benefit.<sup>20,21</sup> Regardless, for early-stage disease, outcomes after surgery are excellent. A large series from the Cleveland Clinic showed 7-year survival rates of between 75% and 85% after open and laparoscopic nephrectomies for patients with a median age of 60 and tumors in the range of 5 to 6 cm.<sup>2</sup> A study from Europe also compared nephron-sparing surgery to radical nephrectomy in over 500 patients, again showing excellent outcomes with both techniques and 10-year survival rates in the range of 70% to 80%.<sup>22</sup> When interpreting these results in the context of our current study, one must be cognizant that patients treated with surgery are generally younger than our cohort (median age 74) and likely with less comorbidities.

For those patients who cannot undergo surgery, other less invasive treatment options do exist such as radiofrequency ablation (RFA) and cryoablation. The underlying principle is that the technique can deliver sharply delineated areas of high or low temperature to produce tumor cell death.<sup>23</sup> The group from Washington University in St Louis compared outcomes in patients treated with cryoablation (267 patients) and partial nephrectomy (233 patients).<sup>6</sup> With 5 years of follow-up, the overall survival rate was 77% in the cryoablation group compared with 91% in the partial nephrectomy group, in line with our NCDB results for SABR. There was no difference in complication risk between techniques, taking into consideration a more frail population getting cryoablation. A meta-analysis from 2008 further examined outcomes in

**Table 1** Patient characteristics (n = 347)

Characteristics	No. (%)
Sex	
Male	216 (62)
Female	131 (38)
Race	
White	296 (85)
African American	39 (11)
Other	12 (4)
Comorbidity score	
0	266 (77)
1	53 (15)
≥2	28 (8)
Insurance	
Not insured	4 (1)
Private payer	67 (19)
Government	271 (78)
Unrecorded	5 (2)
Education %	
≥29	66 (19)
20-28.9	80 (23)
14-19.9	111 (32)
<14	85 (24)
Unrecorded	5 (2)
Treatment facility type	
Community cancer program	7 (2)
Comprehensive community cancer program	146 (42)
Academic or research program	192 (55)
Unrecorded	2 (1)
Treatment facility location	
Metro	292 (84)
Urban	32 (9)
Rural	8 (3)
Unrecorded	15 (4)
Income, US dollars	
<30,000	61 (18)
30,000-35,000	66 (19)
35,000-45,999	81 (23)
>46,000	134 (39)
Unrecorded	5 (1)
Distance to treatment facility, miles	
≤11	174 (50)
>11	173 (50)
Age distribution, y	
≤74	177 (51)
>74	170 (49)
Year of diagnosis	
2004-2006	34 (10)
2007-2009	94 (27)
2010-2012	108 (31)
2013-2016	111 (32)
T stage	
X	54 (16)
1	262 (76)
2	13 (4)
3	17 (4)
4	1 (<1)

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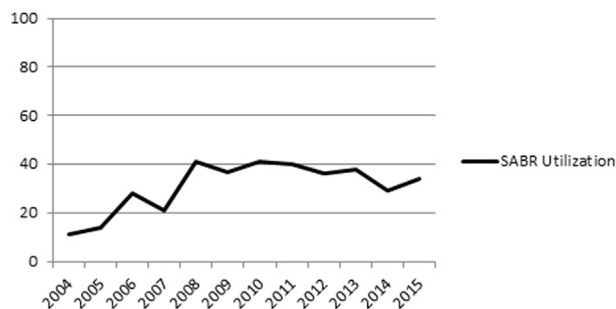
**Table 1** (continued)

Characteristics	No. (%)
N Stage	
N0	336 (97)
N1	11 (3)
M Stage	
0	324 (93)
1	23 (7)
Tumor size, cm	
≤2.5	75 (22)
2.6-3.5	83 (24)
3.6-5.0	98 (28)
>5.0	91 (26)
Grade	
Well-differentiated	35 (10)
Moderately differentiated	59 (17)
Poorly differentiated	17 (5)
Not recorded	236 (68)
Systemic therapy	
No	325 (94)
Yes	22 (6)

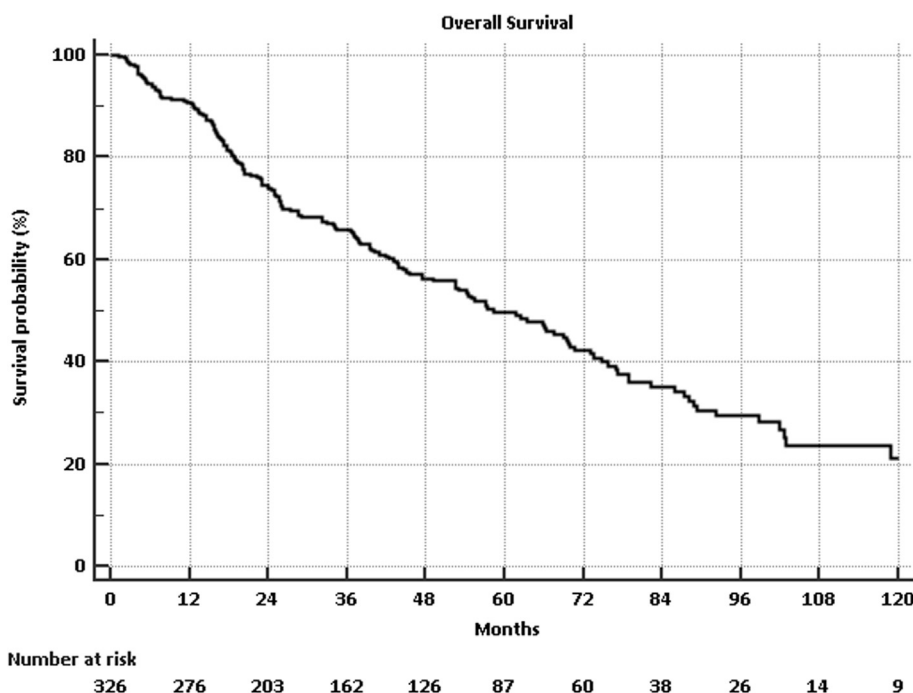
patients with small renal lesions treated with both RFA and cryoablation.<sup>4</sup> In that analysis, local control across 1375 treated lesions was 95% and 88% for cryoablation and RFA, respectively, with a median follow-up of 18 months. Survival and safety data were not reported.

SABR offers another noninvasive manner of delivering ablative therapy in the form of high doses of radiation across 1 to 5 fractions. The concept was initially applied intracranially, and in the late 1990s and early 2000s advances in imaging and radiotherapeutic technologies have helped to facilitate the treatment of extracranial sites such as the liver, bone, prostate gland, adrenal gland, etc.<sup>8,9</sup> Traditionally, RCC has been considered radioresistant, with some in vitro studies revealing it to be among the most resistant cancer types.<sup>7</sup> More contemporary data suggest RCC is more accurately

### Kidney SABR



**Figure 2** Trends in kidney-directed stereotactic ablative body radiation therapy over time. The rate rose from 11% in 2004 to 35% to 40% across 2011 to 2015 (percent of patients with kidney-directed radiation).



**Figure 3** Overall survival from time of diagnosis for the entire cohort (n = 347). Median survival was 58 months (95% confidence interval, 49-69).

described as “relatively radioresistant,” that is, requiring more overall dose or dose per fraction to see an effect.<sup>10,24</sup> With that in mind, interest has been increasing in the use of SABR for cases of nonoperable RCC. A European multi-institutional study prospectively treated 40 patients with single-fraction radiosurgery.<sup>25</sup> Median follow-up was 28 months, and local control at 9 months was an impressive 98%. Renal function remained stable with no grade 3 or higher toxicity. A phase 2 study from Sweden treated 82 renal lesions (primary and metastatic) in 30 patients with dosing ranging from 15 Gy x 2 to 10 Gy x 4

depending on target size and proximity of critical structures.<sup>26</sup> With 52 months of follow-up, local control was excellent at 98% with no significant toxicity.

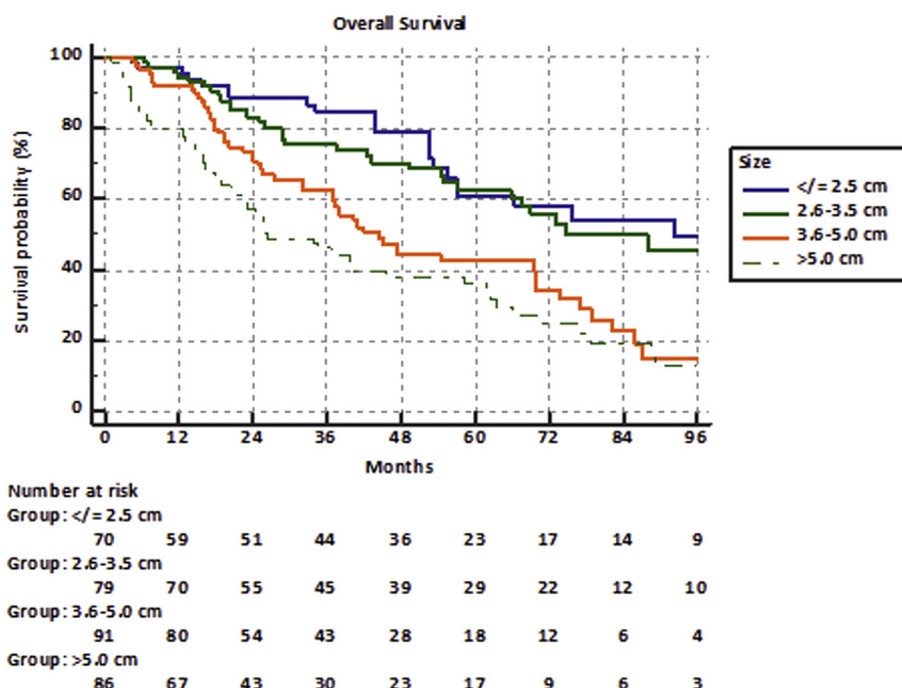
The largest clinical experience in this arena comes from the International Radiosurgery Oncology Consortium for Kidney, which spans institutions in the US, Japan, Canada, Europe, and Australia. Last year, the consortium reported results of a pooled analysis involving 223 patients treated with SABR (ranging from 1-10 fractions).<sup>13</sup> Overall, the mean age of the cohort (72 years old) was comparable to the median age of patients included in our study. Median follow-up was 2.6 years with an actuarial local control of 98% at 4 years. Treatment was generally well tolerated; however, there were 2 cases of serious toxicity in the form of bowel toxicity and gastritis. Similar to our series, worse outcomes were seen with increasing target size, most notably using a cutoff of 4 cm. More recently, the authors updated their experience using SABR in patients with a solitary kidney, again showing local control approaching 100% with no significant toxicity or change in renal function.<sup>12</sup>

There are also emerging data to support the notion that ablative doses of radiation via SABR may help stimulate antigen presentation. Relating specifically to RCC, a pilot study from Roswell Park Cancer Institute treated 14 patients with metastatic disease preoperatively with 15 Gy to the primary lesion followed by nephrectomy 4 weeks later.<sup>27</sup> Tumors treated with SABR showed increased expression of tumor-associated antigen and the immunomodulatory molecule calreticulin. Importantly, the ability to perform surgery was not affected, and the changes seen

**Table 2** Multivariable Cox regression for predictors of overall survival

Characteristic	HR (95% CI)	P
Age, y		
≤74	Reference	
>74	1.79 (1.25-2.55)	.001
M stage		
M0	Reference	
M1	2.93 (1.29-6.66)	.01
N Stage		
N0	Reference	
N1	3.42 (1.37-8.50)	.0083
Size, cm		
≤2.5	Reference	
2.6-3.5	1.29 (0.72-2.30)	.39
3.6-5.0	2.78 (1.65-4.69)	.0001
>5.0	2.84 (1.65-4.90)	.0002

Abbreviations: CI = confidence interval; HR = hazard ratio.



**Figure 4** Overall survival by size of primary tumor. Median overall survival was 92 months, 88 months, 44 months, and 26 months for primary tumors  $\leq 2.5$  cm, 2.6-3.5 cm, 3.5-5.0 cm, and  $>5.0$  cm, respectively ( $P < .0001$ ).

in the immune landscape highlight the possibility that the efficacy of immunotherapy may even be enhanced. This phenomenon has also been seen across other disease sites with varying ablative therapies (RFA, cryoablation, laser ablation), the scope of which is beyond this paper.<sup>28</sup>

The present study is not without limitations. The largest limitation is the retrospective nature and inherent, often strong, selection biases that exist. In addition, exact reasons for nonsurgical intervention are not often documented within the NCDB. Importantly, local control and toxicity are also not recorded, which are of utmost importance when delivering focused, high-dose radiation with SABR. Additionally, salvage therapy is not recorded in the NCDB, which would also contribute to differential outcomes in this patient population.

## Conclusions

In the largest reported series on the subject to date, the use of SABR for intact RCC tumors continues to increase in the United States with excellent outcomes. Further prospective research is needed to verify its safety and efficacy.

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