Original Article

Pooled Analysis of Stereotactic Ablative Radiotherapy for Primary Renal Cell Carcinoma: A Report From the International Radiosurgery Oncology Consortium for Kidney (IROCK)

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BACKGROUND: Stereotactic ablative radiotherapy (SABR) is an emerging therapy for primary renal cell carcinoma. The authors assessed safety, efficacy, and survival in a multi-institutional setting. Outcomes between single-fraction and multifraction SABR were compared. **METHODS:** Individual patient data sets from 9 International Radiosurgery Oncology Consortium for Kidney institutions across Germany, Australia, the United States, Canada, and Japan were pooled. Toxicities were recorded using Common Terminology Criteria for Adverse Events, version 4.0. Patient, tumor, and treatment characteristics were stratified according to the number of radiotherapy fractions (single vs multiple). Survival outcomes were examined using Kaplan-Meier estimates and Cox proportional-hazards regression. **RESULTS:** Of 223 patients, 118 received single-fraction SABR, and 105 received multifraction SABR. The mean patient age was 72 years, and 69.5% of patients were men. There were 83 patients with grade 1 and 2 toxicity (35.6%) and 3 with grade 3 and 4 toxicities (1.3%). The rates of local control, cancer-specific survival, and progression-free survival were 97.8%, 95.7%, and 77.4%, respectively, at 2 years; and they were 97.8%, 91.9%, and 65.4%, respectively, at 4 years. On multivariable analysis, tumors with a larger maximum dimension and the receipt of multifraction SABR were associated with poorer progression-free survival (hazard ratio, 1.16 [$P < .01$] and 1.13 [$P = .02$], respectively) and poorer cancer-specific survival (hazard ratio, 1.28 [$P < .01$] and 1.33 [$P = .01$], respectively). There were no differences in local failure between the single-fraction cohort (n = 1) and the multifraction cohort (n = 2; $P = .60$). The mean (± standard deviation) estimated glomerular filtration rate at baseline was 59.9 ± 21.9 mL per minute, and it decreased by 5.5 ± 13.3 mL per minute ($P < .01$). **CONCLUSIONS:** SABR is well tolerated and locally effective for treating patients who have primary renal cell carcinoma and has an acceptable impact on renal function. An interesting observation is that patients who receive single-fraction SABR appear to be less likely to progress distantly or to die of cancer. ***Cancer* 2017;000:000–000.** © *2017 American Cancer Society.*

KEYWORDS: kidney cancer, radiosurgery, renal cell carcinoma (RCC), stereotactic ablative radiotherapy, stereotactic body radiotherapy.

INTRODUCTION

Renal cell carcinoma (RCC) is the eighth most common cancer worldwide.[1] In the United States alone, there were 62,700 estimated new cases and 9200 deaths[2] from RCC in in 2016. There has been a rapidly increasing incidence of the disease, predominantly for earlier localized cancer, because of increased access to and use of cross-axial abdominal imaging. According to the National Cancer Institute's Surveillance, Epidemiology, and End Results database, the incidence of RCC increased annually by 3.2% between 1997 and 2008.[3] RCC affects predominantly an older population, with a median age at diagnosis of 65 years,[2] and there is a slight male preponderance. Although surgery is the standard of care for primary RCC, patients who undergo partial or total nephrectomy for renal cancer experience postoperative nephron loss, which may result in new-onset chronic kidney disease or the advancement of pre-existing renal dysfunction.[4,5] In addition, some

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Additional supporting information may be found in the online version of this article

DOI: 10.1002/cncr.31156, **Received:** October 6, 2017; **Revised:** October 26, 2017; **Accepted:** October 30, 2017, **Published online** Month 00, 2017 in Wiley Online Library (wileyonlinelibrary.com)

patients have coexisting medical issues that preclude them from surgery, and others may refuse surgery. A recent analysis of the Surveillance, Epidemiology, and End Results database indicated that, among patients aged >65 years who underwent nonsurgical management for T1a disease, the 5-year survival was 46.4% versus 83.1% in those who underwent partial nephrectomy ($P < .01$).[6] The number of deaths attributed to RCC was 4 times higher in those who did not undergo surgery.

Nonsurgical treatment options for this population of patients include radiofrequency ablation and cryotherapy.[7] These thermal techniques have significant limitations. They typically can treat only smaller RCCs and those located away from the ureter and vascular structures because of the risk of heat-sink effects and stricture and/or fistula development.[8] Larger tumors pose significant risks of hemorrhage, which may require a nephrectomy to control.[8] Both approaches are invasive, requiring access to the kidney through percutaneous incisions. This can be problematic for the increasing numbers of patients who may require continuous anticoagulative medications.

Stereotactic ablative radiotherapy (SABR), also known as stereotactic body radiotherapy, is an emerging treatment option in the context of medically unfit patients with primary kidney cancer. Although it has been established for the treatment of malignancies in the lung, liver, and spine, radiotherapy is an often overlooked approach in RCC.[9] The International Radiosurgery Oncology Consortium for Kidney (IROCK) was formed to harmonize treatment approaches and collaborate in further research in this field. After publication of a consensus statement[10] on SABR for primary RCC, this second work from the IROCK is a pooled, multi-institutional analysis of patient outcomes. The objectives of this study were to assess safety, efficacy, and survival in a multi-institutional setting. In particular, outcomes between the 2 most common approaches—single-fraction and multifraction SABR—were compared.

MATERIALS AND METHODS

Methodology

Nine institutions with previously published data on SABR for the treatment of primary RCC were invited to contribute to the IROCK consortium. Authors were contacted and invited to submit data sets (prospective or retrospective) with individual patient data. Central institutional ethical review board approval was granted at the Peter MacCallum Cancer Center, and local data transfer agreement and/or institutional review board approval was obtained based on individual ethics and governance procedures. All patients received SABR between 2007 and 2016 at 1 of the 9 participating institutions. Patient data were deidentified and transferred using data-encryption techniques to the London Health Sciences Center (London, Ontario, Canada) through a secure file transfer protocol, followed by data quality-assurance procedures. Baseline patient characteristics, radiotherapy treatment characteristics, and post-treatment laboratory and clinical outcome data were assessed using descriptive statistics. The biologic equivalent dose using an α/β value of 10 (BED_{10}) was calculated using the linear quadratic formula.[11] The clinical endpoints analyzed were overall survival, progression-free survival (PFS), local control (LC), distant control, and cancer-specific survival (CSS). LC was defined using Response Evaluation Criteria in Solid Tumors, version 1.0. Treatment-related toxicities were defined using Common Terminology Criteria for Adverse Events, version 4.0. All time-to-event endpoints were calculated from the date SABR was started to the specified event. Biochemistry results for serum creatinine and urea values and the estimated glomerular filtration rate (eGFR) were collected at baseline; and all available results were collected after treatment. For patients with unknown eGFR and known creatinine values, the eGFR was estimated from the Chronic Kidney Disease Epidemiology Collaboration equation.[12]

Statistical Analysis

Descriptive statistics were generated for patient demographics and for tumor and treatment characteristics and were stratified according to the number of SABR fractions. These were compared using the chi-square test, the Fisher exact test, the 2-sample t test, or the Wilcoxon rank-sum test, as appropriate. Changes in renal function before versus after SABR for serum creatinine and the eGFR were evaluated using the t test for paired data. Univariable and multivariable Cox proportional-hazards regression was performed for all time-to-event endpoints to identify significant prognostic factors. Variables with univariable P values $< .05$ that were available in >70% of patients were incorporated into the multivariable regression and sequentially removed using backward-elimination techniques until all remaining covariates had P values $< .05$. Kaplan-Meier estimates were generated for all time-to-event endpoints stratified by the number of SABR fractions and were compared using the log-rank test. All statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC), with 2-sided statistical testing at the .05 significance level.

TABLE 1. Baseline Characteristics of All Patients and Stratified by Single-Fraction Versus Multifraction Delivery, n = 223

		No. (%), Mean ± SD, or Median [Min, Max]			
Characteristic	No. of Patients	All Patients, n = 223	1 Fraction, n = 118	>1 Fraction, n = 105	*P*
Age at SABR, y	223	72.0 ± 11.8	69.0 ± 11.9	75.3 ± 10.9	< .001[a]
Men	223	155 (69.5)	82 (69.5)	73 (69.5)	.996
Good performance status: ECOG 0-1 or KPS ≥ 70	223	195 (87.4)	114 (96.6)	81 (77.1)	< .001[a]
Pathologic confirmation	223	189 (84.8)	116 (98.3)	73 (69.5)	< .001[a]
Histologic type	189				
Clear cell		163 (86.2)	114 (97.4)	49 (68.1)	< .001[a]
Papillary		9 (4.8)	2 (1.7)	7 (9.7)	
Chromophobe		2 (1.1)	—	2 (2.8)	
Other RCC		11 (5.8)	—	11 (15.3)	
Urothelial		4 (2.1)	1 (0.9)	3 (4.2)	
Greatest tumor dimension, mm	223	43.6 ± 27.7	37.1 ± 10.6	50.9 ± 37.6	.009[a]
Greatest tumor dimension ≥ 40 mm	223	110 (49.3)	52 (44.1)	58 (55.2)	0.096
Total dose, Gy	223	25.0 [14.0, 70.0]	25.0 [14.0, 26.0]	40.0 [24.0, 70.0]	< .001[a]
No. of fractions	223	1 [1, 10]	1.0	4 [2, 10]	—
BED_{10}, Gy	223	87.5 [33.6, 124.8]	87.5 [33.6, 93.6]	80.0 [37.5, 124.8]	.577
Serum urea pre-SABR, mmol/L	109	9.9 ± 5.5	11.9 ± 7.2	9.5 ± 5.0	.121
Serum creatinine pre-SABR, μmol/L	220	130.8 ± 78.2	132.5 ± 84.8	128.9 ± 70.6	.738
eGFR pre-SABR, mL/min[b]	220	59.9 ± 21.9	66.4 ± 20.6	52.6 ± 21.2	< .001[a]

Abbreviations: BED_{10}, biologic equivalent dose ($\alpha/\beta = 10$); CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; Gy, grays; HR, hazard ratio; KPS, Karnofsky performance status; RCC, renal cell carcinoma; SABR, stereotactic ablative radiotherapy; SD, standard deviation; y, years.

[a] $P < .05$.

[b] Values were derived using the Chronic Kidney Disease Epidemiology Collaboration equation for patients with missing eGFR.

RESULTS

In total, 223 patients from 9 institutions across Germany, Australia, the United States, Canada, and Japan were included in this meta-analysis. The median follow-up was 2.6 years; 118 patients received single-fraction SABR, and 105 received multifraction SABR. The mean patient age was 72 years, 69.5% of patients were men, and 87.4% had an Eastern Cooperative Oncology Group performance of 0 or 1. The mean ± standard deviation (SD) maximal tumor dimension was 43.6 ± 27.7 mm. The mean time between initial diagnosis and treatment with SABR was 28.1 months. We obtained pretreatment diagnostic computed tomography scans for 212 patients (95.1%), magnetic resonance images for 174 patients (78.0%), bone scans for 30 patients (13.5%), and positron emission tomography scans for 8 patients (3.6%). Pathologic confirmation before treatment was achieved in 189 patients (84.8%). Clear cell RCC was the most common histologic subtype (86.2%). Baseline patient characteristics stratified by fractionation schedule are provided in Table 1. The patients who received single-fraction SABR were younger, had better performance status, and harbored smaller tumors ($P < .01$). The median dose for single-fraction SABR was 25 gray (Gy) (range, 14-26 Gy); and, for multi-fraction SABR, it was 40 Gy (range, 24-70 Gy) delivered in 2 to 10 fractions. This equated to a median BED_{10} of 87.5 Gy (range, 33.6-93.6 Gy) in the single-fraction cohort, which was similar to a BED_{10} of 80.0 Gy (range, 37.5-124.8 Gy) in the multi-fraction cohort ($P = .577$). Details of the radiotherapy delivery techniques used are summarized in Supporting Table 1 (see online supporting information).

LC at 2 years and 4 years was 97.8%. CSS, overall survival, and PFS were 95.7%, 82.1%, and 77.4%, respectively, at 2 years; and 91.9%, 70.7%, and 65.4%, respectively, at 4 years. Kaplan-Meier plots are provided in Figure 1. Eighteen patients had disease recurrence (8.1%), 3 had a local recurrence (1.4%), and 16 had a distant recurrence (7.2%). One patient had both local and distant recurrence as the first sites of failure. All 3 local failures occurred within 2 years, and no difference was observed between the single-fraction (n = 1) and multi-fraction (n = 2) cohorts ($P = .603$). Eighty-six patients had at least grade 1 toxicity (38.6%), and 83 (35.6%) had grade 1 or 2 toxicity only. One patient had simultaneous grade 3 nausea and grade 2 bowel toxicity (0.5 months after starting SABR), 1 had grade 4 bowel toxicity alone (4.3 years after starting SABR), and 1 had both grade 4 gastritis and grade 4 bowel toxicity (at 1.4 months and 15.8 months after starting SABR, respectively). A higher rate of overall nausea in the single-fraction cohort was observed (17.0% vs 6.8%; $P = .005$); however, otherwise there was no difference in the toxicity profile of either treatment approach.

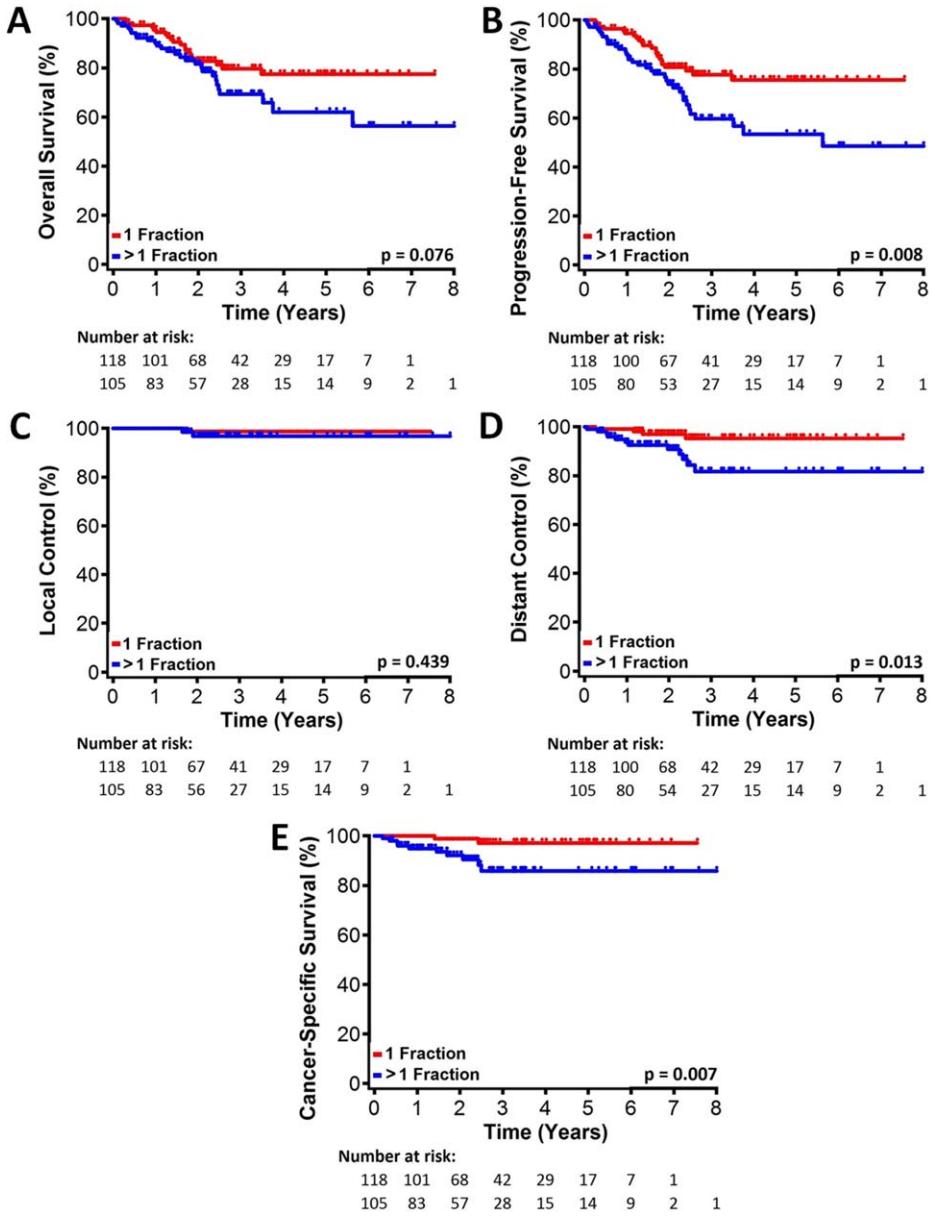

Figure 1. Kaplan-Meier plots are stratified by the number of fractions for (A) overall survival, (B) progression-free survival, (C) local control, (D) distant control, and (E) cancer-specific survival.

The pretreatment mean ± SD eGFR was 59.9 ± 21.9 mL per minute, and the mean ± SD serum creatinine level was 130.8 ± 78.2 μmol/L. The mean ± SD change in eGFR at the last follow-up was −5.5 ± 13.3 mL per minute ($P < .001$). The corresponding rise in serum creatinine was 28.1 ± 74.4 μmol/L. There was no difference in mean renal function change in patients who had T1a disease (−4.0 mL per minute) versus those who had >T1a disease (−6.8 mL per minute; $P = .129$). There was no difference in mean renal function change between patients who received single-fraction SABR (−6.1 mL per minute) and those who received multifraction SABR (−4.9 mL per minute; $P = .660$). Within the entire cohort, there was a subgroup of 52 patients (26.5%) who had an increase in the eGFR posttreatment, representing a 17% increase in global function (a mean ± SD increase of 8.0 ± 10.8 mL per minute). Individual patient changes in serum creatinine levels and eGFR are depicted in Figure 2. In total, 6 patients (2.7%) underwent dialysis during the study period. Pretreatment

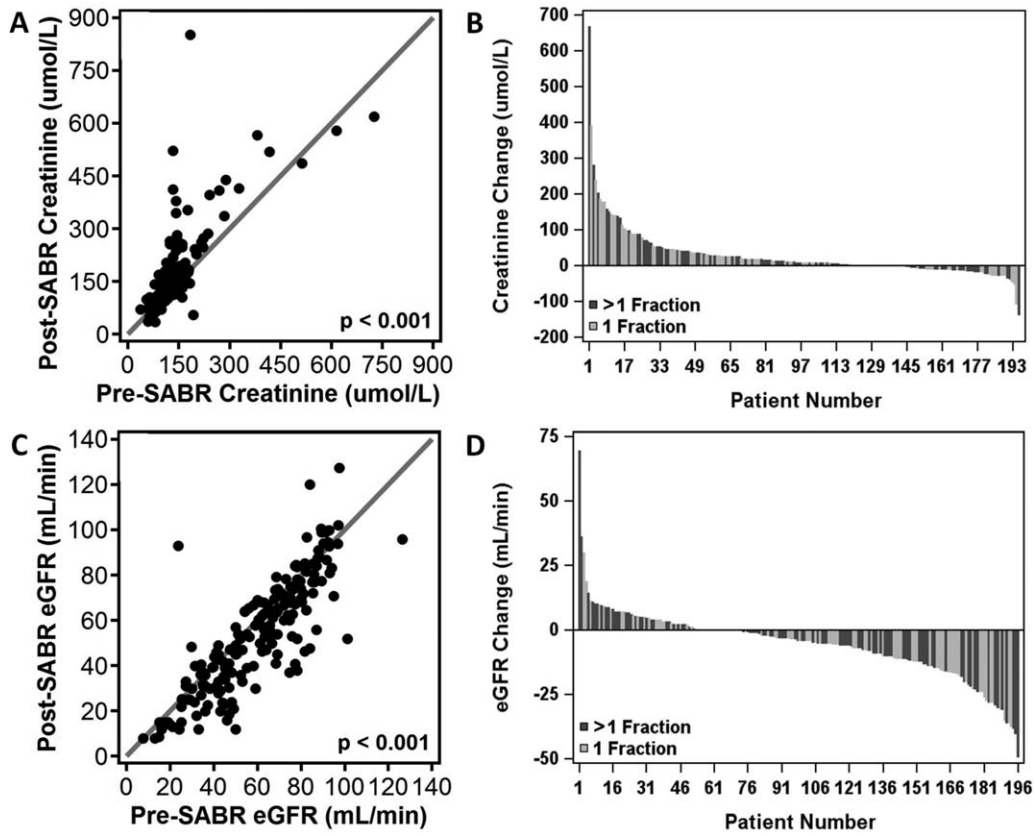

Figure 2. Scatterplots and waterfall plots showing changes in (A,B) serum creatinine levels and (C,D) the estimated glomerular filtration rate (eGFR) before versus after stereotactic ablative radiotherapy (SABR) according to the number of fractions (1 vs >1) for waterfall plots only. *P* values are reported from *t* tests for paired data.

split-function testing was available for 54 patients, and the median relative function was 47.0% in the affected kidney.

Results from univariable and multivariable Cox proportional hazards regressions are provided in Table 2. Multivariable analysis identified that both the maximum tumor dimension (hazard ratio [HR] per 10-mm increase, 1.16; $P < .001$) and multifraction SABR (HR per 1-fraction increase, 1.13; $P = .017$) had independent prognostic significance for PFS. Similarly, for CSS, the maximum tumor dimension (HR per 10-mm increase, 1.28; $P < .001$) and multifraction SABR (HR per 1-fraction increase, 1.33; $P = .011$) also significantly predicted a worse outcome. This was likely attributable to differences in distant control rates between single-fraction and fractionated SABR (Fig. 1D); fractionated SABR was associated with a greater likelihood of distant failure (HR, 3.80; $P = .021$). Interaction testing between tumor size and fractionation was performed and indicated that they were nonsignificant for both PFS survival ($P = .714$) and CSS ($P = .255$). With respect to overall survival, the maximum tumor dimension was a significant predictor of death (HR per 10-mm increase, 1.18; $P < .001$).

DISCUSSION

SABR is a contemporary, noninvasive technique characterized by high-precision delivery of ablative therapeutic radiation. Conveniently, from the patient's perspective, SABR is delivered in a single or a few outpatient treatment sessions. In the current pooled individual patient data meta-analysis, we demonstrate that SABR was associated with excellent local cancer control, with a 2-year and 4-year LC rate of 97.8%. The treatment was well tolerated, with a 1.3% rate of grade 3 and 4 toxicity and largely preserved renal function. This is consistent with a previous systematic review in 2012 of 126 patients, in which a weighted LC rate of 94% and a grade ≥ 3 toxicity rate of 3.8% were reported.[13] Since that systematic review, 3 modern, single-institution, prospective studies of 19 patients,[14] 40 patients,[15] and 33 patients[16] have reported

TABLE 2. Univariable and Multivariable Cox Proportional Hazards Regression Models for Survival Outcomes, n = 223

Variable	Overall Survival		Progression-Free Survival		Cancer-Specific Survival	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Univariable model						
Age at SABR per 5-y increase	1.18 (1.03-1.35)	.018[a]	1.13 (1.00-1.28)	.050	1.40 (1.02-1.91)	.038[a]
Men	1.04 (0.55-1.97)	.903	1.03 (0.58-1.83)	.934	1.21 (0.33-4.48)	.773
ECOG performance status > 1	3.25 (1.68-6.28)	< .001[a]	3.17 (1.73-5.82)	< .001[a]	3.05 (0.82-11.38)	.097
Pathologic confirmation	0.76 (0.36-1.64)	.488	0.65 (0.34-1.26)	.205	0.16 (0.05-0.50)	.002[a]
Histologic type vs clear cell		.264		.530		—
Papillary	0.45 (0.06-3.29)	.427	0.74 (0.18-3.10)	.681	—	—
Other RCC	2.08 (0.73-5.92)	.171	1.71 (0.61-4.81)	.311	5.22 (0.54-50.21)	.153
Maximum dimension per 10-mm increase	1.18 (1.12-1.25)	< .001[a]	1.18 (1.11-1.25)	< .001[a]	1.31 (1.21-1.42)	< .001[a]
Maximum dimension ≥ 40 mm	1.63 (0.91-2.91)	.103	1.55 (0.92-2.62)	.103	5.40 (1.18-24.64)	.030[a]
Time from diagnosis to SABR per 3-mo increase	0.99 (0.97-1.01)	.354	0.98 (0.96-1.01)	.120	0.96 (0.89-1.03)	.266
Total dose per 5-Gy increase	1.06 (0.95-1.18)	.279	1.10 (1.01-1.21)	.038[a]	1.08 (0.88-1.33)	.459
No. of fractions per 1-unit increase	1.08 (0.98-1.20)	.135	1.12 (1.03-1.22)	.011[a]	1.27 (1.08-1.49)	.005[a]
>1 Fraction	1.68 (0.94-3.00)	.079	2.03 (1.19-3.47)	.009[a]	6.14 (1.35-28.06)	.019[a]
Fraction dose per 1-Gy increase	0.97 (0.93-1.00)	.059	0.96 (0.93-0.99)	.006[a]	0.86 (0.78-0.95)	.003[a]
BED_{10} per 5-Gy increase	0.98 (0.92-1.06)	.622	0.99 (0.93-1.06)	.756	0.82 (0.72-0.94)	.005[a]
Serum creatinine pre-SABR per 10-μmol/L increase	1.01 (0.98-1.04)	.620	1.01 (0.99-1.04)	.296	0.91 (0.78-1.06)	.234
eGFR pre-SABR per 10 mL/min increase	0.90 (0.79-1.02)	.105	0.89 (0.79-1.00)	.056	0.97 (0.75-1.25)	.795
Multivariable model						
Maximum dimension per 10-mm increase	1.18 (1.12-1.25)	< .001[a]	1.16 (1.10, 1.23)	< .001[a]	1.28 (1.19-1.39)	< .001[a]
No. of fractions per 1-unit increase	—	—	1.13 (1.02, 1.24)	.017[a]	1.33 (1.07-1.66)	.011[a]

Abbreviations: BED_{10}, biologic equivalent dose ($\alpha/\beta = 10$); CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; Gy, grays; HR, hazard ratio; mo, month; RCC, renal cell carcinoma; SABR, stereotactic ablative radiotherapy; y, years.
[a] $P < .05$.

similar findings, with LC ranging from 98% to 100% and grade ≥ 3 toxicity rates from 0% to 15.8%. In addition, the phase 1 study reported above[14] (clinicaltrials.gov identifier NCT00458484) has completed its phase 2 enrolment, and those data will be shortly forthcoming.

Oncologic outcomes from SABR, as an emerging treatment modality for kidney cancer, compare favorably with established ablative techniques. Like SABR, thermal ablative approaches have relatively limited prospective data to support their use. An analysis by Kunkle and Uzzo[17] of mostly retrospective data demonstrated local tumor progression rates of 5.2% after renal cryoablation and 12.9% after radiofrequency ablation. The mean size of tumors in that cohort was 26.4 mm. By comparison, we observed a 1.4% local failure rate in our cohort despite larger tumors (mean size, 43.6 mm). In terms of survival, a more recent systematic review in 2016 of 60 studies reporting on oncologic outcomes after nephrectomy and thermal ablation[18] indicated that CSS estimates for all strategies varied between 95% and 100%, with a median follow-up ranging from 22 to 120 months. However, those rates dropped to between 90% and 91% for T1b tumors (≥40 mm) and between 82.5% and 86.7% for T2 tumors (≥70 mm). In our current cohort of patients who received SABR, the 2-year and 4-year CSS rates were comparable at 95.7% and 91.9%, respectively. However, the overall survival rates in our SABR cohort (82.1% and 70.7% at 2 years and 4 years, respectively) were poorer, which may have been caused part by competing risks related to advanced age and increased medical comorbidities in these nonsurgical patients.

An interesting finding on multivariable analysis of this cohort was that single-fraction SABR was associated with better PFS and CSS than multifraction regimens ($P < .05$). By contrast, although patient age and Eastern Cooperative Oncology Group performance status were not balanced between groups, these factors were not independently prognostic of survival outcomes on multivariable analysis. The association of fractionation with PFS and CSS was not explained by decreased local efficacy, because LC was similarly excellent for both regimens ($P = .439$) (Fig. 1C). However, distant disease control was poorer ($P = .013$) (Fig. 1D) with a multifraction approach. When determining the choice between single-fraction and multifraction approaches, large tumor size was a factor in favor of fractionation at 2 of the 9 institutions. However, on interaction testing, primary greatest tumor dimension, which also was associated with poorer PFS and CSS, was not identified as a confounding factor. This indicates that, even when accounting for variation in

greatest tumor dimension, there appears to be less likelihood of systemic failure and cancer-related death associated with single-fraction SABR compared with fractionated SABR to the primary disease. One potential explanation may be an enhanced *abscopal effect* of distant tumor cell eradication because of single-fraction irradiation,[19] an effect that has been demonstrated in preclinical models of RCC.[20] An alternative hypothesis may be that some circulating tumor cells released in the circulation during radiotherapy[21] may still be viable after smaller doses of fractionated radiotherapy and could result in distant cancer seeding. Nevertheless, this interesting observation should be considered hypothesis-generating. Because of possible confounding by other potential variables that were not included in the modeling, this observation should be confirmed with a directly randomized trial comparing single-fraction and multifraction approaches. However, 1 notable drawback of the single-fraction approach was a higher rate of overall nausea at 17.0% compared with 6.8% in the multifraction cohort.

We observed an impressive preservation of renal function after SABR in this cohort. The mean decrease in eGFR at last follow-up was 5.5 mL per minute, corresponding to a rise in serum creatinine of 28.1 μmol/L. Rates of nephrotoxicity and renal dysfunction are difficult to compare between treatment modalities. Meaningful comparisons with surgery are particularly challenging, because the operative approach (partial vs radical nephrectomy), along with other factors like warm ischemia time, has a considerable impact on outcome. In a randomized study comparing elective nephron-sparing surgery with radical nephrectomy, the mean loss of eGFR was 16.6 mL per minute for partial nephrectomy and 23.5 mL per minute after radical nephrectomy.[22] Renal dysfunction after thermal ablation is proportional to the greatest tumor dimension and the volume of ablation zones, with most ablated tumors in the literature ranging in size from 2 to 3 cm in greatest dimension. In a recent systematic review and meta-analysis of 18 studies comparing changes in eGFR after partial nephrectomy versus thermal ablation for small renal masses, mean GFR losses of −6.2 mL per minute and −4.5 mL per minute, respectively, were observed for each modality.[23] The results from the current cohort of patients who received SABR for T1a disease are comparable (−4.0 mL per minute) to these other modalities, although many patients had pre-existing renal dysfunction.

Another notable and novel finding was that a substantial proportion of patients exhibited increased eGFR post-SABR. There were 52 patients (26.5%) who demonstrated an improvement in eGFR after treatment, representing a 17% increase in global function (average increase, 8.0 mL per minute). It is unclear what the underlying pathophysiologic mechanism of this finding could be, whether it is secondary to tumor response and subsequent renal function recovery, a hyperfiltration state post-treatment, or a compensatory functional improvement in the contralateral kidney. After partial nephrectomy, for patients with bilateral kidneys, most series support the preservation of approximately 88% to 91% of global function, with compensatory hypertrophy representing preservation of between 2.2% and 6% of global function. Improvement of renal function beyond baseline after extirpative approaches is not reported as an expected outcome. Compensatory function may be the most plausible putative mechanism, because data from a previous clinical trial that used serial radioactive chromium complexed with ethylene diamine tetraacetic acid (^{51}Cr-EDTA) and technetium-99m pentavalent dimercaptosuccinic acid single-photon emission computed tomography/computed tomography (^{99m}Tc-DMSA SPECT/CT) demonstrated a mean increase in calculated GFR in the contralateral kidney of 12.3 mL per minute from baseline.[24] The underlying mechanisms that underpin these observations warrant further exploration.

A key strength of the current study is that it reports on the largest cohort to date of patients with RCC who received treatment with SABR. Although merging data from multiple institutions increased the generalizability and statistical power, a limitation of this approach is the introduction of bias because of variations in data-collection procedures across institutions. Furthermore, retrospective reporting of toxicity may lead to underreporting of events. Because of variations in treatment practice, not all data requested from individual institutions could be collected from all patients. Inherent population-level biases may have been introduced through data sampling of widely disparate populations from Japanese, European, North American, and Australian patients. Another limitation to the interpretation of data is the local response assessment after SABR; it is unclear whether Response Evaluation Criteria in Solid Tumors should remain the optimal assessment criteria in this setting.[25]

Local control, minimal complications, and preserved renal function are considered to constitute "the trifecta" after minimally invasive partial nephrectomy.[26] The current multi-institutional, pooled analysis marks an important step in demonstrating that SABR can achieve this trifecta in localized RCC. Currently, several multicenter clinical trials are underway that may affirm these

findings (clinicaltrials.gov identifiers NCT02613819 and NCT03108703; University Hospital Medical Information Network Clinical Trials Registry identifier UMIN-CTR ID UMIN000004172). Moving forward, prospective, randomized controlled trials comparing extirpative or thermal ablative approaches with SABR would be ideal but will be difficult to complete because of challenges in both patient and physician equipoise.[27,28] Thus, other forms of comparative-effectiveness research with novel endpoints in the realms of patient-reported outcomes, quality of life, and economic considerations are urgently needed to inform the relative merits of each treatment modality for primary RCC.

In conclusion, just as patients who have comorbid medical conditions now receive standard treatment with SABR for early stage lung cancer, a similar paradigm could unfold in patients who have RCC. The current large-scale, individual patient pooled analysis marks an important step in advancing this new paradigm, demonstrating a favorable toxicity profile and excellent oncologic outcomes. Nonetheless, prospective, randomized trials and comparative-effectiveness studies are needed to further evaluate this ablative modality in the treatment of RCC.

FUNDING SUPPORT

No specific funding was disclosed.

CONFLICT OF INTEREST DISCLOSURES

Shankar Siva reports grants from Varian Industries outside the submitted work. Alexander V. Louie reports personal fees from Varian Medical Systems Inc outside the submitted work. Simon S. Lo reports research support from Elekta AB and travel expenses from Accuray Inc outside the submitted work. The remaining authors made no disclosures.

AUTHOR CONTRIBUTIONS

Shankar Siva: Conceptualization, methodology, formal analysis, investigation, resources, data curation, writing–original draft, writing–review and editing, visualization, supervision, and project administration. **Alexander V. Louie**: Conceptualization, methodology, formal analysis, investigation, resources, data curation, writing–original draft, writing–review and editing, visualization, supervision, and project administration. **Andrew Warner**: Conceptualization, methodology, formal analysis, investigation, resources, data curation, writing–original draft, writing–review and editing, visualization, and project administration. **Alexander Muacevic**: Conceptualization, methodology, resources, and writing–review and editing. **Senthilkumar Gandhidasan**: Conceptualization, methodology, resources, writing–original draft, and writing–review and editing. **Lee Ponsky**: Conceptualization, methodology, and resources. **Rodney Ellis**: Conceptualization, methodology, and resources. **Irving Kaplan**: Conceptualization, methodology, and resources. **Anand Mahadevan**: Conceptualization, methodology, and resources. **William Chu**: Conceptualization, methodology, and resources. **Anand Swaminath**: Conceptualization, methodology, and resources. **Hiroshi Onishi**: Conceptualization, methodology, and resources. **Bin Teh**: Conceptualization, methodology, resources, and writing–review and editing. **Rohann J. Correa**: Conceptualization, methodology, resources, writing–original draft, writing–review and editing, visualization, and project administration. **Simon S. Lo**: Conceptualization, methodology, resources, and writing–review and editing. **Michael Staehler**: Conceptualization, methodology, resources, and writing–review and editing.

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