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Clinical Investigation

Stereotactic Ablative Radiotherapy for ≥T1b Primary Renal Cell Carcinoma: A Report From the International Radiosurgery Oncology Consortium for Kidney (IROCK)

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Purpose: Patients with larger (T1b, >4 cm) renal cell carcinoma (RCC) not suitable for surgery have few treatment options because thermal ablation is less effective in this setting. We hypothesize that SABR represents an effective, safe, and nephron-sparing alternative for large RCC.

Methods and Materials: Individual patient data from 9 institutions in Germany, Australia, USA, Canada, and Japan were pooled. Patients with T1a tumors, M1 disease, and/or upper tract urothelial carcinoma were excluded. Demographics, treatment, oncologic, and renal function outcomes were assessed using descriptive statistics. Kaplan−Meier estimates and univariable and multivariable Cox proportional hazards regression were generated for oncologic outcomes.

Results: Ninety-five patients were included. Median follow-up was 2.7 years. Median age was 76 years, median tumor diameter was 4.9 cm, and 81.1% had Eastern Cooperative Oncology Group performance status of 0 to 1 (or Karnofsky performance status ≥70%). In patients for whom operability details were reported, 77.6% were defined as inoperable as determined by the referring urologist. Mean baseline estimated glomerular filtration rate (eGFR) was 57.2 mL/min (mild-to-moderate dysfunction), with 30% of the cohort having moderate-to-severe dysfunction (eGFR <45mL/min). After SABR, eGFR decreased by 7.9 mL/min. Three patients (3.2%) required dialysis. Thirty-eight patients (40%) had a grade 1 to 2 toxicity. No grade 3 to 5 toxicities were reported. Cancer-specific survival, overall survival, and progression-free survival were 96.1%, 83.7%, and 81.0% at 2 years and 91.4%, 69.2%, 64.9% at 4 years, respectively. Local, distant, and any failure at 4 years were 2.9%, 11.1%, and 12.1% (cumulative incidence function with death as competing event). On multivariable analysis, increasing tumor size was associated with inferior cancer-specific survival (hazard ratio per 1 cm increase: 1.30; $P <$ .001).

Conclusions: SABR for larger RCC in this older, largely medically inoperable cohort, demonstrated efficacy and tolerability and had modest impact on renal function. SABR appears to be a viable treatment option in this patient population. © 2020 Elsevier Inc. All rights reserved.

Introduction

Surgical extirpation is the standard of care for primary renal cell carcinoma (RCC). Both radical nephrectomy (RN) and partial nephrectomy (PN), also known as nephron-sparing surgery (NSS), are accepted standards of care. An analysis of the National Cancer Database published in 2019 indicated a 4:1 ratio of RN to NSS treatment utilization in the United States.[1] This ratio did not change appreciably over the decade period that was assessed. This pattern of practice is supported by the EORTC 30904 trial, which randomized patients with RCC ≤5 cm to RN versus NSS. In this trial RN was associated with a higher overall survival (OS; primary endpoint) of 81%, compared with 76% for NSS at a median follow-up of 9.3 years ($P = .03$). After exclusion of patients with positive surgical margins, NSS was associated with equivalent OS compared with RN, suggesting that the effort to spare nephrons may have translated to suboptimal oncological outcomes.[2]

For older patients, particularly those with pre-existing comorbidities and chronic kidney disease (CKD), efforts to spare renal function during the curative treatment of primary RCC are of particular importance. Although an older patient population may sometimes be eligible for active surveillance, up to 42% require delayed intervention—often triggered by tumor growth,[3] as the increased risk of progression and metastases associated with larger tumors (>3-4 cm) is considered to outweigh competing risks for death.[4] The "trifecta" for NSS is represented by negative cancer margins, minimal renal functional decrease, and no urologic complications.[5] As SABR is emerging as a treatment modality in this more vulnerable cohort of patients, it is of interest to investigate whether the trifecta of oncologic control, renal function preservation, and low complication rate can be achieved.

The International Radiosurgery Oncology Consortium for Kidney (IROCK)[6] is a collaborative group that has published pooled individual patient analyses on SABR for primary RCC.[7,8] In this study, we investigate outcomes in those patients with larger primary RCC (≥T1b or ≥4 cm) receiving SABR. The main objective is to assess oncologic outcomes in this cohort with higher-risk primary disease, and the secondary objective is to assess renal function outcomes and treatment-related complications.

Methods and Materials

Nine institutions with previously published data for SABR in 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 Centre, and local data transfer agreement and/or central institutional ethical 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 Centre (London, Ontario, Canada) through secure file-transfer protocol, followed by data quality-assurance procedures.

Patients with tumors <4 cm in maximum diameter (T1a), M1 disease, and/or upper tract urothelial carcinoma

were excluded from the analysis. Baseline patient characteristics, radiation therapy treatment characteristics, and post-treatment laboratory and clinical outcome data were assessed using descriptive statistics. Medical inoperability was defined by the referring urologist. Medical comorbidities were neither consistently collected in retrospective series nor reported in prospective trial data sets comprising this cohort; thus, they were not included due to the propensity for error in retrospectively abstracting this data. Biological equivalent dose using an $\alpha/\beta = 10$ (BED_{10}) was calculated using the linear quadratic formula.[9] Clinical endpoints analyzed were OS, progression-free survival (PFS), cancer-specific survival (CSS), local failure, distant failure, and any failure. Local progression was determined on imaging using the Response Evaluation Criteria in Solid Tumors classification. Treatment-related toxicities were recorded in the domains of nausea, fatigue, chest wall pain, gastritis, bowel and skin toxicity and were defined using Common Terminology Criteria for Adverse Events version 4.0. All time-to-event endpoints were calculated from the starting date of SABR to the date of (1) local and/or distant recurrence (if applicable), (2) death of any cause or cancer-related death (if applicable), or (3) last follow-up, whichever occurred first. Biochemistry results for serum creatinine, urea, and estimated glomerular filtration rate (eGFR) were collected at baseline and at all available follow-up data post-treatment. For patients with unknown eGFR and known creatinine values, eGFR was estimated from the Chronic Kidney Disease Epidemiology Collaboration equation.[10] Renal function was assessed using eGFR CKD classification: normal (≥90 mL/min), mild (≥60 to <90 mL/min), mild-moderate (≥45 to <60 mL/min), moderate-severe (≥30 to <45 mL/min), and severe (<30 mL/min).[11] CKD status was defined based on eGFR data: no CKD (post-SABR eGFR ≥60 mL/min), pre-SABR CKD (pre-SABR <60 mL/min and post-SABR <60 mL/min), and post-SABR CKD (pre-SABR ≥60 mL/min and post-SABR <60 mL/min).

Statistical analysis

Descriptive statistics were generated for baseline patient characteristics for all patients (n = 95). Changes in renal function pre-SABR versus post-SABR for eGFR and CKD classification were evaluated using the paired *t*-test and McNemar's test, respectively. Kaplan−Meier estimates were generated for OS, PFS, CSS, local failure, distant failure, and any failure. Local, distant, and any failure were analyzed using cumulative incidence functions and competing risk models with death as competing event. Univariable and multivariable Cox proportional hazards regression was performed for OS, PFS, CSS, any failure, and distant failure. Any and distant failure were modelled as competing risk with death as competing event. Local failure was not analyzed using Cox proportional hazards regression analysis because only 2 local failure events were observed. All eligible variables with univariable *P* values <.05 and available in >70% of patients were incorporated into a multivariable regression model and sequentially removed using backward elimination techniques until all remaining covariates had *P* values <.05. All statistical analysis was performed using SAS version 9.4 software (SAS Institute, Cary, NC) using 2-sided statistical testing at the .05 significance level.

Results

Baseline characteristics

In total, 95 patients from 9 institutions across Germany, Australia, USA, Canada and Japan were included in this meta-analysis. Baseline patient characteristics are summarized in Table 1. The median follow-up (95% confidence interval [CI]) was 2.7 years (2.3-3.4). The median age (range) was 76 years (45.7-91.9), with 67 (70.5%) of patients being male and 77 (81.1%) having an Eastern Cooperative Oncology Group (ECOG) performance status

Table 1 Baseline characteristics of all patients (n = 95)

Patient characteristic	All patients (n = 95)
Age (y), median (range)	76.4 (45.7-91.9)
Male, n (%)	67 (70.5)
Good performance status (ECOG 0-1 or KPS ≥70), n (%)	77 (81.1)
Medically inoperable, n (% of evaluable)	45 (77.6)
Solitary versus dual kidneys, n (%)	
Solitary kidney	28 (29.5)
Dual kidneys	67 (70.5)
Split-function assessment, n (% of dual kidney)	35 (52.2)
Ipsilateral/target kidney % function, median (min, max)	47 (20, 100)
Pathologic confirmation, n (%)	81 (85.3)
Histology type, n (%)	
Clear cell	73 (90.1)
Papillary	3 (3.7)
Chromophobe	2 (2.5)
Other renal cell carcinoma	3 (3.7)
Maximum dimension (cm), median (interquartile range)	4.9 (4.4-5.7)
Diagnosis to SABR (mo), median (interquartile range)	4.4 (2.0-17.1)
Total dose (Gy), median (min, max)	26.0 (14.0, 48.0)
No. of fractions, median (min, max)	1 (1, 5)
>1 fraction, n (%)	47 (49.5)
Fraction dose (Gy), median (min, max)	16.0 (5.0, 26.0)
BED_{10} (Gy), median (min, max)	87.5 (33.6, 124.8)

Abbreviations: BED_{10} = biologic equivalent dose ($\alpha/\beta = 10$); ECOG = Eastern Cooperative Group; KPS = Karnofsky performance status; SABR = stereotactic ablative radiation therapy.

of 0 to 1 (or Karnofsky performance status [KPS] ≥70%). The median maximal tumor diameter was 4.9 cm (interquartile range [IQR], 4.4-5.7). The median time between initial diagnosis and treatment with SABR was 4.4 months (IQR, 2.0-17.1). Forty-five (77.6%) out of 58 patients for whom operability details were reported were defined as inoperable by the referring urologist. Pathologic confirmation before treatment was achieved in 81 patients (85.3%). Twenty-eight patients (29.5%) had a solitary kidney (prior nephrectomy) and 67 patients (70.5%) had dual kidneys. All patients with a solitary kidney, and 53 of 67 patients (79.1%) with dual kidneys, received pathologic confirmation ($P = .009$). Clear cell was the most common histologic subtype (90.1%). The median number of fractions was 1 (range, 1-5) and the median total dose was 26 Gy (range, 14-48 Gy), equivalent to a median BED_{10} of 87.5 Gy (range, 33.6-124.8 Gy).

Oncologic outcomes

CSS, OS, and PFS were 96.1%, 83.7%, and 81.0% at 2 years and 91.4%, 69.2%, and 64.9% at 4 years, respectively. Similarly, local, distant, and any failure were 2.9%, 3.4%, and 6.3% at 2 years and 2.9%, 11.1%, and 12.1% at 4 years, respectively, based on the cumulative incidence function (with death as competing event). Kaplan–Meier plots are shown in Figure 1. Eight patients had disease recurrence (8.4%); 2 had local progression (2.1%), and 7 had a distant recurrence (7.4%). One patient had both local and distant recurrence as the first sites of failure. Both local failures occurred within 2 years. Seven patients (7.4%) reported at least 1 grade 2 toxicity. The rate of grade 2 fatigue was 6.3%, and the rates of grade 2 nausea and grade 2 chest wall toxicity were both 1.1%, respectively. No grade 3, 4, or 5 toxicities were recorded in this cohort.

Renal function

Renal function at baseline and post-SABR are described in Table 2. The pre-treatment mean (± standard deviation [SD]) eGFR was 57.2 mL/min (± 21.8), and mean (± SD) serum creatinine was 133.4 μmol/L (± 67.4). The mean (± SD) change in eGFR at last follow-up was −7.9 mL/min (± 11.3) ($P < .001$). The corresponding rise in serum creatinine was 35.1 μmol/L (± 61.8). A subgroup of 18 patients (20.0%) had an increase in eGFR post-treatment, representing a mean (± SD) increase of 10.0% (± 7.9) equivalent to a mean (± SD) increase of 5.0 mL/min (± 3.2). Individual patient change in eGFR is depicted in Figure 2A and 2B as a scatterplot of pre-versus post-SABR eGFR and a waterfall plot of change in eGFR, respectively.

Of the 67 patients (70.5%) with bilateral kidneys, pre-treatment split-function testing was available in 35 (36.8%), demonstrating a median of 47.0% relative function in the affected kidney. Classification of CKD status distributed before and after SABR is summarized in Table 3. CKD classification remained the same for 55 of 90 patients (61.1%), worsened for 30 patients (33.3%), and improved

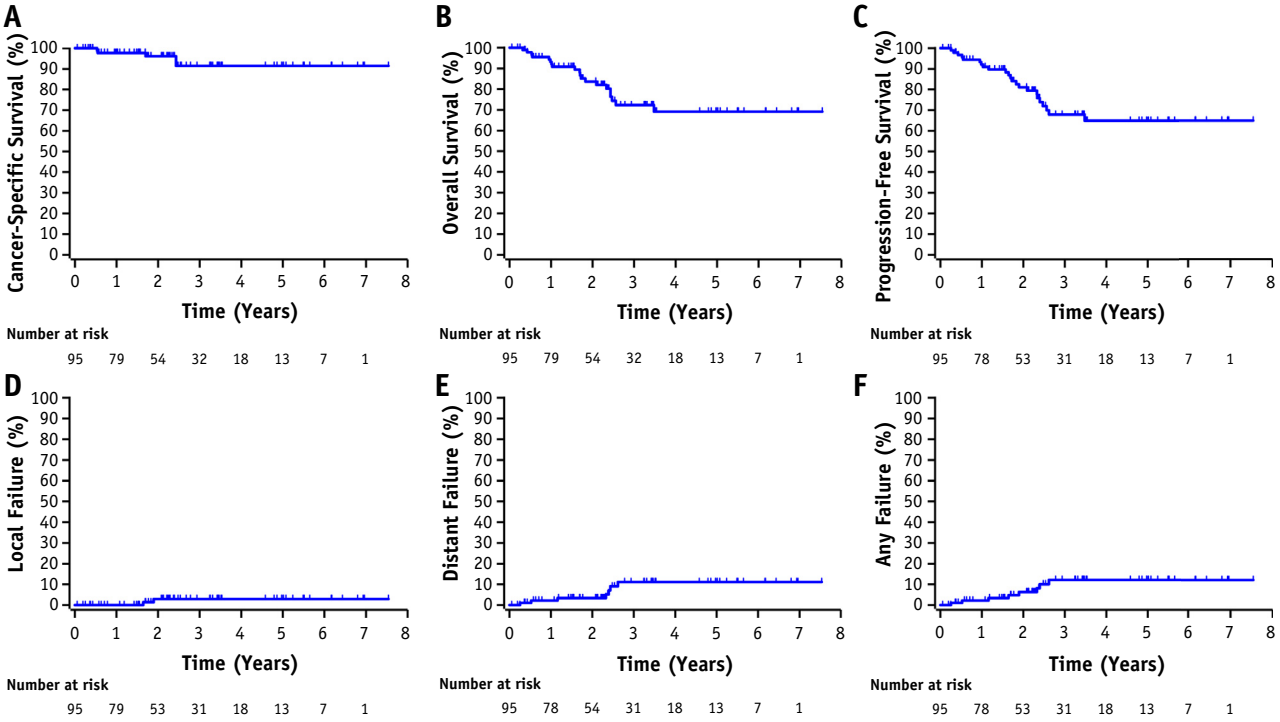

Fig. 1. Kaplan–Meier plots for (A) cancer-specific survival, (B) overall survival, (C) progression-free survival, (D) local failure, (E) distant failure, and (F) any failure. Local failure, distant failure, and any failure based on cumulative incidence functions and competing risk models with death as competing event.

Table 2 Renal function outcomes for all patients (n = 95)

Characteristic	All patients (n = 95)
Serum creatinine (μmol/L), mean ± SD	
Pre-SABR	133.4 ± 67.4
Post-SABR	169.1 ± 100.2
Change	+35.1 ± 61.8
Serum creatinine increase, n (%)	66 (73.3)
eGFR (mL/min),* mean ± SD	
Pre-SABR	57.2 ± 21.8
Post-SABR	49.1 ± 22.1
Change	−7.9 ± 11.3
eGFR increase, n (%)	18 (20.0)
Pre-SABR CKD classification,* n (%)	
Normal (eGFR ≥90)	5 (5.4)
Mild (eGFR ≥60 to <90)	41 (44.1)
Mild-moderate (eGFR ≥45 to <60)	19 (20.4)
Moderate-severe (eGFR ≥30 to <45)	17 (18.3)
Severe (eGFR <30)	11 (11.8)
Post-SABR CKD classification,* n (%)	
Normal (eGFR ≥90)	4 (4.4)
Mild (eGFR ≥60 to <90)	27 (29.7)
Mild-moderate (eGFR ≥45 to <60)	21 (23.1)
Moderate-severe (eGFR ≥30 to <45)	23 (25.3)
Severe (eGFR <30)	16 (17.6)
Dialysis, n (%)	3 (3.2)

Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; SABR = stereotactic ablative radiation therapy.

* Values derived using Chronic Kidney Disease Epidemiology Collaboration equation for patients with missing eGFR.

for 5 patients (5.6%) (P = .037). Thirty-one patients (34.4%) had no CKD before and after treatment (eGFR ≥60 mL/min), with 43 patients (47.8%) having CKD (eGFR <60 mL/min) both before and after treatment. Sixteen patients (17.8%) had no pre-existing CKD before treatment and developed CKD a median of 20.1 months (IQR, 14.8-30.2) after SABR, 4 of whom had a solitary kidney. A total of 3 patients (3.2%) underwent dialysis during the study period, none of whom had a solitary kidney. One of these patients was already on dialysis before SABR but was nonetheless counted to ensure the most conservative outcomes reporting. This patient had a pre-SABR eGFR of 14.8 mL/min (end-stage renal dysfunction), which fell to 8.6 mL/min after SABR.

Cox proportional hazards regression

Results from univariable and multivariable Cox proportional hazards regression are shown in Table 4. Multivariable analysis identified that increasing tumor size had independent prognostic significance for CSS (HR per 1 cm increase: 1.30; 95% CI, 1.14-1.49; P < .001). Poor performance status (ECOG >1) was associated with worse PFS (HR: 6.53; 95% CI, 2.68-15.94; P < .001) and OS (HR: 3.85; 95% CI, 1.52-9.72; P = .004). Similarly, higher pre-SABR creatinine was associated with worse PFS (HR per 10 μmol/L increase: 1.11; 95% CI, 1.04-1.18; P = .001) and OS (HR: 1.08; 95% CI, 1.03-1.14; P = .002). Although a higher eGFR pre-SABR was associated with improved OS on univariable analysis (HR per 10 mL/min: 0.79; 95% CI, 0.64-0.98; P = .030), this finding was not significant on multivariable analysis.

Discussion

This study reports on outcomes of SABR exclusively for primary RCC larger than 4 cm (≥T1b). The median time between initial diagnosis and treatment with SABR of 4.4 months (IQR, 2.0-17.1) implies that in a proportion of patients, treatment was initiated after a period of initial active surveillance. The analysis demonstrated that this treatment approach was well tolerated; no grade 3 or greater toxicities were observed. In addition, the treatment demonstrated efficacy, with local failure at 2 and 4 years of 2.9%. CSS was 96.1% at 2 years and 91.4% at 4 years. Renal function was well preserved, with a mean reduction in eGFR at last follow-up of −7.9 mL/min. These outcomes are comparable to those of nephron-sparing approaches such as PN or thermal ablation, particularly in the context of a cohort with 28 patients (29.5%) having a solitary kidney and 77.6% of patients being medically inoperable.

It should be acknowledged that the natural history of CKD itself is characterized by progressive renal dysfunction, independent of antineoplastic treatment. Our cohort was composed of patients with at least grade 3 CKD, 30% of whom had CKD grade 4 (eGFR 15-29 mL/min). In large population-based studies of patients with at least CKD grade 3, mean eGFR decline occurs at a rate of −1 to −4.5 mL/min annually,[12] with higher rates generally reported for patients with comorbidities.[13] The rate of renal replacement therapy varies from 1% to 20% in patients with grade 3 to 4 CKD (eGFR 15-59 mL/min, n = 12,055), depending on factors such as age, initial eGFR, and comorbidities.[12,14] These rates are confounded, however, by the high competing risk of cardiovascular mortality[15] before progression to end-stage renal dysfunction (24% and 46% at 5 years in CKD grade 3 and 4, respectively).[14]

Renal functional preservation is a critical consideration in nephron-sparing approaches to primary RCC. In this multicenter cohort, the mean change of eGFR was −7.9 mL/min post-treatment, with a corresponding mean rise in serum creatinine of 35.1 μmol/L. We previously demonstrated that single-fraction SABR was not associated with worse renal function, although it was not specifically assessed in this cohort[7]; this was true even in patients with a solitary kidney.[8] Despite this cohort having pre-existing CKD (mean eGFR of 57.2 mL/min, consistent with mild-to-moderate or grade 3 dysfunction), and 29.5% of the patients presenting with a solitary kidney, few patients underwent dialysis (n = 3, 3.2%). A similar analysis of PN outcomes in patients with T1b tumors (n = 67 consecutive

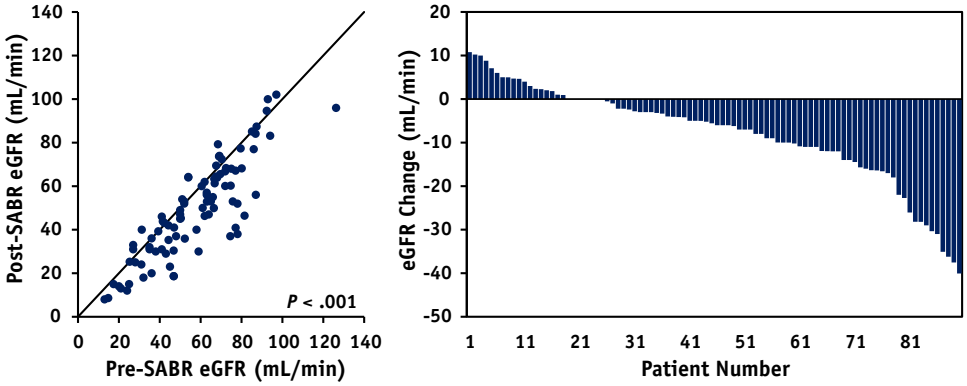

Fig. 2. Distribution of change in eGFR before and after SABR as (A) scatterplot and (B) waterfall plot. *Abbreviations:* eGFR = estimated glomerular filtration rate; SABR = stereotactic ablative radiation therapy.

patients, mean tumor size of 4.5 cm) showed that a comparable proportion (3%) of patients required dialysis after NSS.[16] Furthermore, an analysis of outcomes in 1169 patients undergoing PN in all tumor sizes found that baseline CKD grade 3 was associated with a chronic end-stage renal failure rate of 3.7%.[17] By comparison, total nephrectomy, which is an established standard of care for larger renal masses, was found to be 3.82 times more likely to induce new-onset CKD grade 3 and 11.8 times more likely to induce new onset CKD grade 4 than PN in a large cohort study of 662 T1a tumors.[18] A smaller direct comparison of 95 patients with T1a-T2 and pre-existing CKD revealed that in those patients with pre-existing CKD grade 3a, the probability of having a worse CKD class postoperatively was 43% in the PN group versus 79% in the RN group.[19]

An intriguing observation in our cohort is the increase in eGFR seen in a subset (20%) of patients after SABR, a phenomenon that to our knowledge has not been widely reported after nephrectomy or thermal ablation. The etiology of this phenomenon remains unclear; however, we have previously hypothesized that a plausible putative mechanism is compensatory hyperfiltration of remaining functional nephrons.[7] This is supported by prior trials using radionuclide-based functional renal scans, which have demonstrated a mean calculated GFR increase of 12.3 mL/min in the contralateral kidney after SABR.[20] Although increased filtration per nephron can be an adaptive response to nephron loss, it can eventually lead to progressive renal dysfunction.[21] The underlying mechanism of hyperfiltration remains unclear, both in the context of renal SABR and other disease states.[21] Moreover, its implications for late renal function remain to be elucidated; long-term follow-up studies are thus anticipated to provide some clarity in this regard.

The low rates of local failure (2.9%) reported for SABR in this multicenter cohort are comparable to other nephron-sparing techniques. In the EORTC 30904 randomized trial, the local failure rate in the PN arm was 2.3% (6/256) for a median tumor size of 3 cm.[2] For large renal tumors (≥T1b) specifically, a systematic review and meta-analysis of comparative studies of PN versus RN revealed a local recurrence rate of 8.5% for NSS (82 events in 970 patients across 14 studies).[22] With respect to thermal ablation, a matched-group comparative analysis comparing 31 patients undergoing cryoablation (mean tumor size of 4.6 cm) with 161 patients undergoing PN for T1b disease (mean tumor size of 4.3 cm) found a significantly higher rate of local recurrence in the cryoablation cohort within 1 year (23% vs 0%, $P = .019$).[23]

Complication rates with SABR also compare favorably with nephron-sparing approaches. Surgical complications of PN include perioperative bleed, ureteric fistula, pleural

Table 3 Changes in CKD classification pre-SABR versus post-SABR for patients with complete data (n = 90)

	Post-SABR CKD classification*†				
Pre-SABR CKD classification*†	Normal (≥90)	Mild (≥60 to <90)	Mild-moderate (≥45 to <60)	Moderate-severe (≥30 to <45)	Severe (<30)
Normal (≥90)	4 (4.4)	1 (1.1)	0 (0)	0 (0)	0 (0)
Mild (≥60 to <90)	0 (0)	24 (26.7)	13 (14.4)	3 (3.3)	0 (0)
Mild-moderate (≥45 to <60)	0 (0)	2 (2.2)	7 (7.8)	6 (6.7)	3 (3.3)
Moderate-severe (≥30 to <45)	0 (0)	0 (0)	1 (1.1)	11 (12.2)	4 (4.4)
Severe (<30)	0 (0)	0 (0)	0 (0)	2 (2.2)	9 (10.0)

Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; SABR = stereotactic ablative radiation therapy.
* Values derived using Chronic Kidney Disease Epidemiology Collaboration equation for patients with missing eGFR.
† eGFR ranges shown in parentheses.

Table 4 Univariable and multivariable Cox proportional hazards regression models for survival outcomes for all patients (n = 95)

Dependent variable:	Overall survival		Progression-free survival		Cancer-specific survival	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Univariable analysis						
Poor performance status (vs Good)	3.70 (1.50-9.13)	.005*	4.96 (2.14-11.46)	<.001*	3.60 (0.60-21.80)	.163
Maximum dimension (per 1 cm)	1.15 (1.04-1.27)	.006*	1.16 (1.05-1.27)	.003*	1.30 (1.14-1.49)	<.001*
Maximum dimension ≥6 cm (vs <6)	1.19 (0.40-3.58)	.756	1.78 (0.70-4.57)	.228	6.93 (1.16-41.50)	.034*
Creatinine pre-SABR (per 10 μmol/L)	1.09 (1.03-1.15)	.003*	1.08 (1.02-1.14)	.013*	0.85 (0.66-1.09)	.198
eGFR pre-SABR (per 10 mL/min)	0.79 (0.64-0.98)	.030*	0.84 (0.69-1.02)	.081	0.93 (0.61-1.41)	.737
Multivariable analysis						
Poor performance status (vs Good)	3.85 (1.52-9.72)	.004*	6.53 (2.68-15.94)	<.001*	—	—
Maximum dimension (per 1 cm)	—	—	—	—	1.30 (1.14-1.49)	<.001*
Creatinine pre-SABR (per 10 μmol/L)	1.08 (1.03-1.14)	.002*	1.11 (1.04-1.18)	.001*	—	—

Abbreviations: CI = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio; SABR = stereotactic ablative radiation therapy.

* *P* values < .05.

damage, and splenic injury; these were reported in 37.2%, 3.7%, 11.2%, and 0.4% of patients, respectively, in the EORTC 30904 randomized trial.[2] A large systematic review and meta-analysis of PN versus RN for large renal tumors (≥T1b) demonstrated a higher likelihood of postoperative complications with PN (relative risk 1.74, *P* < .001) occurring at a rate of approximately 25% (143 events in 564 patients across 10 studies).[22] Complications associated with radiofrequency ablation (RFA) include hemorrhage, nerve injury, urothelial stricture, and urine leak, but these occur infrequently; a review of 573 RFA procedures at the Mayo Clinic noted a major complication (Clavien−Dindo grade 2-4) rate of 6.6% of all procedures.[24] The most common complications were urothelial stricture (2.1%) and nerve injury (3.9%). Complication rates after microwave ablation of larger renal masses appear to be similar to that of RFA. Complications (Clavien−Dindo grade 1-4) occur in 3% to 17% of patients and have been reported to include perirenal hematoma, urinoma formation, and skin dysesthesia.[25-28] Importantly, the high heat generated by microwave ablation can lead to significant urothelial injury. Secondary ureteropelvic strictures, including those remote from the ablation site, have been reported in multiple series.[25,26] With cryoablation of larger tumors, significant bleeding (CTCAE version 4.0 grade >2) can result from the use of multiple applicators and/or central placement of the applicators.[24,29] Disruption of the ice ball due to differential expansion and contraction of tissue during dynamic temperature fluctuations may also occur and result in significant hemorrhage.[30,31] Taken together, these findings indicate that caution is warranted when pursuing effective thermal ablation of larger tumors. Adjunctive maneuvers to reduce complication risks can be undertaken, such as prophylactic selective renal-artery embolization to minimize this risk of bleeding, or hydrodisplacement of the kidney from the adjacent psoas muscle or body wall to reduce complications such as nerve injury. In contrast, in this IROCK analysis of tumors T1b or greater, no severe grade 3 or above complications were noted, even though no invasive adjunctive maneuvers were used to limit complication rates.

There is ongoing international interest in investigating the utility of cytoreductive nephrectomy in the context of immune checkpoint blockade inhibitors. Contemporary studies in the tyrosine-kinase inhibitor era indicate a lack of benefit for broad application of cytoreductive nephrectomy, such as the SURTIME[32] and CARMENA[33] studies, in patients with metastatic clear cell RCC. However, some patients present with large primary RCC in the context of relatively small volume metastases, and nephrectomy in this context can prevent symptoms and may potentially prolong survival.[34,35] In contrast, few data are available for the use of SABR to the primary in the metastatic setting. Correa et al.[36] reported outcomes for cytoreductive SABR in large renal primaries with a median tumor diameter of 9.5 cm and a median OS of 20.4 months. Only 1 grade 3 event (nausea) was observed. Singh et al reported on 14 patients undergoing SABR before cytoreductive nephrectomy. A single patient had a grade 3 toxicity (blood transfusion), and there were no postoperative complications.[37] In the modern immunotherapy era, survival gains with cytoreductive nephrectomy have yet to be definitely demonstrated. Stereotactic radiation therapy is showing particular promise as a therapeutic strategy with the capacity to activate the immune system synergistic to immunotherapy.[38-40] As such in the context of metastatic RCC, SABR to the primary in combination with immunotherapy could hypothetically be of particular interest.

Our results from this IROCK cohort suggest that the efficacy and safety profile of SABR for larger primary RCC suggests feasibility of a cytoreductive approach to the primary in patients receiving immunotherapy. Studies currently investigating the combination of this approach with immunotherapy include the Canadian CYTOSHRINK trial (NCT04090710), which is currently accruing; additionally, an NRG-sponsored trial proposal is currently under development in this population (SAMURAI, personal communication, Rana McKay, February 2020).

There are several key limitations of this work. Some of the toxicity data collection at individual institutions was retrospective and therefore is likely to be underreported. Medical comorbidities, including renal function—relevant diagnoses such as diabetes and hypertension, were not captured in this data set. Longer-term follow-up is not yet available in this cohort to confirm oncologic outcomes. Although the rate of histopathologic confirmation is comparable to thermal ablation series in small renal masses, not all patients included in this series had pathologic confirmation of RCC. Comparisons of outcomes among different treatment modalities for primary RCC are challenging owing to the variability in response criteria used. Various treatment platforms and immobilization techniques (including robotic and c-arm gantry accelerators) were used, so no conclusions could be drawn regarding optimal treatment strategy.

Conclusions

In this multi-institutional pooled analysis of patients with large RCC, SABR appears to be a safe and tolerable treatment that achieves low rates of recurrence. We observed a modest impact on renal function in the context of an older and mainly medically inoperable population. Larger tumor size, higher baseline creatinine, and worse performance status portended poorer prognosis in this group. Although limited by length of follow-up and partly retrospective nature, these data nonetheless demonstrate favorable outcomes and provide strong justification for further prospective study of SABR for large primary RCC.

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