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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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CONDENSED ABSTRACT:

SABR is well tolerated and effective for primary RCC with acceptable impact on renal function. Patients receiving single-fraction SABR appear less likely to progress distantly and die of cancer.

Keywords: stereotactic ablative radiotherapy, radiosurgery, RCC, SBRT, kidney cancer

ABSTRACT

Background: SABR is an emerging therapy for primary renal cell carcinoma (RCC). This study assessed safety, efficacy and survival in a multi-institutional setting. Outcomes between single and multi-fraction SABR were compared.

Methods: Individual patient datasets from nine IROCK institutions across Germany, Australia, USA, Canada and Japan were pooled. Toxicities were recorded using CTCAE v4.0. Patient, tumor and treatment characteristics were stratified by number of 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 and 105 received multi-fraction SABR. Mean patient age was 72 years, with 69.5% being male. There were 83 patients with grade 1-2 toxicity (35·6%), and 3 patients with grade 3-4 toxicities (1·3%). Local control (LC), cancer specific survival (CSS), and progression free survival (PFS) at 2 years were 97·8%, 95·7% and 77·4% and at 4 years were 97·8%, 91·9%, 65·4%, respectively. On multivariable analysis, larger tumour diameter and multi-fraction SABR were associated with poorer PFS (HR 1·16 [p<0·01] and HR 1·13 [p=0·02], respectively) and CSS (HR 1·28 [p<0·01] and HR 1·33 [p=0·01] respectively. There was no differences in local failure for single (n=1) versus multi-fraction (n=2) cohorts (p=0·60). The mean (±SD) eGFR at baseline was 59·9 (±21·9) mL/min, and decreased by 5·5 mL/min (± 13·3), p<0·01.

Conclusions: SABR is well tolerated and locally effective for primary RCC with acceptable impact on renal function. An interesting observation is that patients receiving single-fraction SABR appear less likely to progress distantly and die of cancer.

INTRODUCTION

Renal cell carcinoma (RCC) is the 8th most common cancer worldwide [1]. In the United States alone there were 62,700 estimated new cases and 9,200 deaths [2] in 2016. There has been rapidly increasing incidence of the disease, predominantly in earlier localized cancer due to increased access to and utilization of cross-axial abdominal imaging. According to the SEER 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], with a slight male preponderance. While surgery is the standard of care for primary RCC, patients undergoing partial or total nephrectomy for renal cancer experience post-operative nephron loss, which may result in new onset chronic kidney disease or advancement of pre-existing renal dysfunction [4,5]. Additionally, some patients have coexisting medical issues that preclude them from surgery and others may refuse surgery. A recent analysis of the SEER database found that of patients over 65 years who underwent non-surgical management for T1a disease, the 5-year survival was 46·4% versus 83·1% in those having partial nephrectomy ($p < 0{\cdot}01$) [6]. Death attributed to RCC was four times higher in those not undergoing surgery.

Non-surgical treatment options for this population of patients include radiofrequency ablation (RFA) and cryotherapy [7]. These thermal techniques have significant limitations. They can typically only treat smaller RCCs as well as those away from the ureter and vascular structures due to the risk of heat sink effects, 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, with access to the

kidney through percutaneous incisions. This can be problematic in the increasing numbers of patients who may require continuous anticoagulative medications.

Stereotactic ablative radiotherapy (SABR), also known as stereotactic body radiotherapy (SBRT), is an emerging treatment option in the context of medically unfit patients with primary kidney cancer. Whilst established in 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. Following publication of a consensus statement [10] on SABR for primary RCC, this second work from 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 two commonest approaches, single fraction and multi-fraction SABR, were compared.

METHODOLOGY

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 datasets (prospective or retrospective) with individual patient data. Central institutional ethical review board (IRB) approval was granted at the Peter MacCallum Cancer Centre, and local data transfer agreement and/or IRB approval was obtained based on individual ethics and governance procedures. All patients received SABR between 2007 and 2016 at one of the nine participating institutions. Patient data were

de-identified and transferred using data encryption techniques to the London Health Sciences Centre (London, Ontario, Canada) through secure file transfer protocol (FTP), 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. Biological equivalent dose using an $\alpha/\beta=10$ (BED_{10}) was calculated using the linear quadratic formula [11]. Clinical endpoints analysed were overall survival, progression-free survival, local control, distant control and cancer-specific survival. Local control was defined using RECIST criteria version 1·0. Treatment related toxicities were defined using CTCAE version 4·0. All time-to-event end points were calculated from date of SABR start to the specified event. Biochemistry results for serum creatinine, urea and estimated glomerular filtration rate (eGFR) were collected at baseline and all available results post-treatment. For patients with unknown eGFR and known creatinine values, eGFR was estimated from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [12].

Statistical Analysis

Descriptive statistics were generated for patient demographics, tumor and treatment characteristics and were stratified by number of fractions. These were compared using the Chi-square test, Fisher's exact test, two-sample T-test or Wilcoxon rank sum test as appropriate. Change in renal function pre-SABR vs. post-SABR for serum creatinine and eGFR was evaluated using the paired T-test. Univariable and multivariable Cox proportional hazards regression was performed for all time-to-event end points to identify significant prognostic factors. Variables with univariable

p-values < 0·05 and available in > 70% of patients were incorporated into multivariable regression and sequentially removed using backward elimination techniques until all remaining covariates had p-values < 0·05. Kaplan-Meier estimates were generated for all time-to-event end points and stratified by number of fractions and compared using the log-rank test. All statistical analyses were performed using SAS version 9·4 software (SAS Institute, Cary, USA), with 2-sided statistical testing at the 0·05 significant level.

RESULTS

In total, 223 patients from nine institutions across Germany, Australia, USA, Canada and Japan were included in this meta-analysis. The median follow-up period was 2·6 years with 118 patients receiving single fraction and 105 receiving multi-fraction SABR. The mean age was 72 years, with 69·5% of patients being male and 87·4% having an ECOG performance of 0-1. The mean (± SD) maximal tumour diameter was 43·6mm (± 27·7). The mean time between initial diagnosis and treatment with SABR was 28·1 months. Pre-treatment diagnostic CT was used in 212 (95·1%), MRI in 174 (78·0%), bone scans in 30 (13·5%) and PET scan in 8 (3·6%). Pathological confirmation prior to treatment was achieved in 189 patients (84·8%). Clear cell was the most common histological subtype (86.2%). Baseline patient characteristics can be found in **Table 1,** stratified by fractionation schedule. Patients treated with fractionated SABR were younger with better performance status and harbored smaller tumors ($p < 0.01$). The median (range) dose for single fraction SABR was 25 Gy (14-26) and for multi-fraction was 40 Gy (24-70) delivered in 2-10 fractions. This equated

to a median (range) BED_{10} of 87.5 Gy (33.6 - 93.6 Gy) in the single fraction cohort, which was similar to a BED_{10} of 80.0 Gy (37.5 - 124.8 Gy) in the multi-fraction cohort (p=0.577). Details of the radiotherapy delivery techniques used are summarized in **Supplementary Table 1**.

Local Control (LC) at 2- and 4-years was 97·8%. Cancer-specific survival (CSS), overall survival (OS), and progression free survival (PFS) at 2 years were 95·7%, 82·1% and 77·4% and at 4 years were 91·9%, 70·7%, 65·4%, respectively. Kaplan-Meier plots are shown in **Figure 1**. Eighteen patients had disease recurrence (8·1%), three 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 site of failure. All 3 local failures occurred within 2 years, with no difference for single (n=1) versus multi-fraction (n=2) cohorts (p=0·603). Eighty-six patients had at least grade 1 toxicity (38·6%), 83 (35·6%) had grade 1-2 toxicity only. One patient had grade 3 nausea and grade 2 bowel toxicity simultaneously (0·5 months after start of SABR), 1 patient had grade 4 bowel toxicity alone (4·3 years after start of SABR) and 1 patient had both grade 4 gastritis and grade 4 bowel toxicity (at 1·4 months and 15·8 months after start of SABR, respectively). A higher rate of overall nausea in the single fraction cohort was observed (17·0% versus 6·8%, p = 0·005), but otherwise there was no difference in the toxicity profile of either treatment approach.

The pre-treatment mean (± SD) eGFR was 59·9 mL/min (± 21·9), and mean (± SD) serum creatinine was 130·8 μmol/L (± 78·2). The mean (± SD) change of eGFR at last follow-up was -5·5 mL/min (± 13·3), $p < 0·001$. The corresponding rise in serum creatinine was 28·1 μmol/L (± 74·4). There was no difference in mean renal function

change in those patients who had T1a disease (-4·8 mL/min) versus >T1a disease (-6·5 mL/min), $p = 0·354$. There was no difference in mean renal function change between those patients receiving single fraction (-6·1 mL/min) and multi-fraction (-4·9 mL/min) SABR, $p = 0·660$. Within the entire cohort, there was a subgroup of 52 patients (26·5%) who had an increase of eGFR post-treatment, representing a 17% increase in global function (a mean [±SD] increase of 8·0 mL/min [± 10·8]). Individual patient change in serum creatinine and eGFR is depicted in **Figure 2.** A total of 6 patients (2·7%) underwent dialysis during the study period. Pre-treatment split function testing was available in 54 patients, with a median of 47·0% relative function in the affected kidney.

Results from univariable and multivariable Cox proportional hazards regression are shown in **Table 2**. Multivariable analysis identified both maximum tumour diameter (HR per 10 mm increase: 1·16, $p < 0·001$) and multi-fraction SABR (HR per 1 fraction increase: 1·13, $p = 0·017$) as having independent prognostic significance for progression free survival. Similarly for cancer-specific survival, maximum tumour diameter (HR per 10 mm increase: 1·28, $p < 0·001$) and multi-fraction SABR (HR per 1 fraction increase: 1·33, $p = 0·011$) also significantly predicted for worse outcome. This was likely attributable to differences in distant control rates between single and fractionated SABR (**Figure 1D**); fractionated SABR was associated with a higher likelihood of distant failure (HR 3·80, $p = 0.021$). Interaction testing between tumour size and fractionation was performed and found to be non-significant for both progression-free survival ($p = 0·714$) and cancer-specific survival ($p = 0·255$). With respect to overall survival, maximum tumour diameter was a significant predictor of death (HR per 10 mm increase: 1·18, $p < 0·001$).

DISCUSSION

SABR is a contemporary, non-invasive technique characterized by high-precision delivery of ablative therapeutic radiation. Conveniently from the patient's perspective, SABR is delivered in a single or few outpatient treatment sessions. In this pooled individual patient data meta-analysis, we demonstrate that SABR was associated with excellent local cancer control, with 2- and 4-year local control rate of 97·8%. The treatment was well tolerated, with a 1·3% rate of grade 3-4 toxicity and largely preserved renal function. This is consistent with a previous systematic review in 2012 of 126 patients which demonstrated a weighted local control rate of 94% and grade 3+ toxicity rate of 3·8%.[13] Since that systematic review, three modern single-institutional prospective studies of 19 patients [14], 40 patients [15], and 33 patients [16] have reported similar findings with local control ranging from 98%-100% and grade 3+ toxicity rates of 0-15·8%. Additionally, the phase I study reported above [14] (NCT00458484) has completed its phase II enrolment and data should be forthcoming shortly.

As an emerging treatment modality for kidney cancer, oncological outcomes from SABR compares favorably to established ablative techniques. As is the case for 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 RFA. The mean size of tumors in this cohort was 26·4 mm. By comparison, we observed a 1.4% local failure rate in our cohort despite larger

tumours (mean size of 43·6mm). In terms of survival, a more recent systematic review in 2016 of 60 studies reporting on oncological outcomes after nephrectomy and thermal ablation [18] showed that cancer-specific survival estimates for all strategies varied between 95%-100% with a median follow-up ranging from 22 to 120 months. These rates, however, dropped to 90-91% for T1b tumors (≥ 40mm) and 82·5%-86·7% for T2 tumors (≥ 70mm). In this cohort receiving SABR, the 2- and 4-year cancer-specific survival rates were comparable at 95·7% and 91·9%, respectively. However, overall survival rates in our SABR cohort (82·1% and 70·7% at 2- and 4-years, respectively) were poorer, which may be due in part to competing risks related to advanced age and increased medical comorbidities in this non-surgical cohort.

An interesting finding on multivariable analysis of this cohort was that single-fraction SABR was associated with better PFS and CSS than multi-fraction regimens ($p <$ 0·05). By contrast, whilst age and ECOG 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 since LC was similarly excellent for both regimens (**Figure 1c**, $p = 0·439$). Distant disease control, however, was poorer (**Figure 1d,** $p = 0·013$) with a multi-fraction approach. When determining choice of single versus multi-fraction approaches, large tumor size was a factor favoring fractionation in two of the nine institutions. However, on interaction testing, primary tumor diameter, which was also associated with poorer PFS and CSS, was not found to be a confounding factor. This indicates that even when accounting for variation in tumor diameter, there appears to be less likelihood of systemic failure and cancer

related death associated with single fraction SABR in comparison to fractionated SABR to the primary disease. One potential explanation may be an enhanced "abscopal effect" of distant tumor cell eradication due to single fraction irradiation[19], an effect demonstrated in preclinical models of RCC [20]. An alternative hypothesis may be that some circulating tumor cells, which are released in the circulation during radiotherapy [21], may still be viable after smaller doses of fractionated radiotherapy and result in distant cancer seeding. Nevertheless, this interesting observation should be considered hypothesis-generating. Due to possible confounding by other possible variables not included in the modeling, this observation should be confirmed with a directly randomized trial comparing single and multi-fraction approaches. One notable drawback of the single treatment approach, however, was a higher rate of overall nausea at 17·0% as compared to 6·8% in the multi-fraction 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/min, 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, as the operative approach (partial versus radical nephrectomy), along with other factors such as warm ischemia time, impacts considerably on outcome. In a randomized study comparing elective nephron-sparing surgery and radical nephrectomy, the mean loss of eGFR was 16·6 mL/min for partial nephrectomy, and 23·5 mL/min after radical nephrectomy [22]. Renal dysfunction after thermal ablation is proportional to tumor diameter and volume of ablation zones, with most ablated tumors in the literature ranging from 2-3 cm in diameter. In a recent systematic review and meta-analysis of 18 studies comparing change in eGFR after

partial nephrectomy versus thermal ablation for small renal masses, a mean loss of GFR of -6·2 mLs/min and -4·5 mLs/min was observed for each modality, respectively [23]. The results in this cohort for patients receiving SABR for T1a disease are comparable (-4·5 mLs/min) to these other modalities, despite many patients having 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 of eGFR after treatment, representing a 17% increase in global function (average increase of 8·0 mL/min). It is unclear what the underlying pathophysiological mechanism of this finding could be, whether this is secondary to tumor response and subsequent renal function recovery, a hyperfiltration state post-treatment, or 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 mechanise, as data from a previous clinical trial that used serial ^{51}Cr-EDTA and ^{99m}Tc-DMSA SPECT/CT demonstrated a mean increase in calculated GFR in the contralateral kidney of 12·3 mLs/min 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 of RCC patients treated with SABR to date. While merging data from multiple institutions

increased the generalizability and statistical power, a limitation of this approach is the introduction of bias due to variation in data collection procedures across institutions. Furthermore, retrospective reporting of toxicity may lead to underreporting of events. Due to variability 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 local response assessment after SABR; it is unclear whether RECIST 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 present multi-institutional pooled analysis marks an important step in demonstrating that SABR can achieve this trifecta in localized RCC. At present several multicenter clinical trials are underway which may affirm these findings (clinicaltrials.gov ID NCT02613819, NCT03108703, and UMIN-CTR ID UMIN000004172). Moving forward, prospective randomized controlled trials comparing extirpative or thermal ablative approaches to SABR would be ideal but will be difficult to complete, owing to 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 medically-comorbid patients are now standardly treated with SABR for early-stage lung cancer, a similar paradigm could unfold in RCC. This

large-scale individual patient pooled analysis marks an important step in advancing this new paradigm, demonstrating a favorable toxicity profile and excellent oncological outcomes. Nonetheless, prospective, randomized trials and comparative effectiveness studies are needed to further evaluate this ablative modality in the treatment of RCC.

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Table 1: Baseline characteristics of all patients and stratified by single versus multi-fraction delivery (n=223).

Characteristic	N	All Patients (n=223)	1 Fraction (n=118)	> 1 Fraction (n=105)	p-value
Age at SABR – mean ± SD	223	72·0 ± 11·8	69·0 ± 11·9	75·3 ± 10·9	**< 0·001**
Male – n(%)	223	155 (69·5)	82 (69·5)	73 (69·5)	0·996
Good Performance Status (ECOG 0-1 or KPS ≥ 70) – n(%)	223	195 (87·4)	114 (96·6)	81 (77·1)	**< 0·001**
Pathological Confirmation – n(%)	223	189 (84·8)	116 (98.3)	73 (69.5)	**< 0·001**
Histology Type – n(%) Clear Cell Papillary Chromophobe Other Renal Cell Carcinoma Urothelial	189	 163 (86.2) 9 (4.8) 2 (1.1) 11 (5.8) 4 (2.1)	 114 (97.4) 2 (1.7) -- -- 1 (0.9)	 49 (68.1) 7 (9.7) 2 (2.8) 11 (15.3) 3 (4.2)	**< 0.001**
Maximum Diameter (mm) – mean ± SD	223	43·6 ± 27·7	37·1 ± 10·6	50·9 ± 37·6	**0·009**
Maximum Diameter ≥ 40 mm – n(%)	223	110 (49·3)	52 (44·1)	58 (55·2)	0·096
Total Dose (Gy) – median, (min, max)	223	25·0 (14·0, 70·0)	25·0 (14·0, 26·0)	40·0 (24·0, 70·0)	**< 0·001**
Number of Fractions – median, (min, max)	223	1 (1, 10)	1·0	4 (2, 10)	--
BED_{10} (Gy) – median, (min, max)	223	87.5 (33.6, 124.8)	87.5 (33.6, 93.6)	80.0 (37.5, 124.8)	0.577
Serum Urea Pre-SABR (mmol/L) – mean ± SD	109	9·9 ± 5·5	11·9 ± 7·2	9·5 ± 5·0	0·121
Serum Creatinine Pre-SABR (µmol/L) – mean ± SD	220	130·8 ± 78·2	132·5 ± 84·8	128·9 ± 70·6	0·738
eGFR Pre-SABR (mL/min)[1] – mean ± SD	220	59·9 ± 21·9	66·4 ± 20·6	52·6 ± 21·2	**< 0·001**

SABR – Stereotactic ablative radiotherapy; **eGFR** – Estimated glomerular filtration rate; **ECOG** – Eastern Cooperative Oncology Group; **KPS** – Karnofsky Performance Status; **BED_{10}** – Biological equivalent dose ($\alpha/\beta=10$); P-values < 0·05 shown in **BOLD**; [1]Values derived using CKD-EPI equation for patients with missing eGFR.

Table 2: Univariable and multivariable Cox proportional hazards regression models for survival outcomes (n=223).

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:						
Age at SABR (per 5 year increase)	1·18 (1·03, 1·35)	**0·018**	1·13 (1·00, 1·28)	0·050	1·40 (1·02, 1·91)	**0·038**
Male	1·04 (0·55, 1·97)	0·903	1·03 (0·58, 1·83)	0·934	1·21 (0·33, 4·48)	0·773
ECOG Performance Status > 1	3·25 (1·68, 6·28)	**< 0·001**	3·17 (1·73, 5·82)	**< 0·001**	3·05 (0·82, 11·38)	0·097
Pathological Confirmation	0·76 (0·36, 1·64)	0·488	0·65 (0·34, 1·26)	0·205	0·16 (0·05, 0·50)	**0·002**
Histology Type (vs. Clear cell)		0·264		0·530		--
Papillary	0·45 (0·06, 3·29)	0·427	0·74 (0·18, 3·10)	0·681	--	--
Other Renal Cell Carcinoma	2·08 (0·73, 5·92)	0·171	1·71 (0·61, 4·81)	0·311	5·22 (0·54, 50·21)	0·153
Maximum Diameter (per 10 mm increase)	1·18 (1·12, 1·25)	**< 0·001**	1·18 (1·11, 1·25)	**< 0·001**	1·31 (1·21, 1·42)	**< 0·001**
Maximum Diameter ≥ 40 mm	1·63 (0·91, 2·91)	0·103	1·55 (0·92, 2·62)	0·103	5·40 (1·18, 24·64)	**0·030**
Diagnosis to SABR (per 3 month increase)	0·99 (0·97, 1·01)	0·354	0·98 (0·96, 1·01)	0·120	0·96 (0·89, 1·03)	0·266
Total Dose (per 5 Gy increase)	1·06 (0·95, 1·18)	0·279	1·10 (1·01, 1·21)	**0·038**	1·08 (0·88, 1·33)	0·459
Number of Fractions (per 1 unit increase)	1·08 (0·98, 1·20)	0·135	1·12 (1·03, 1·22)	**0·011**	1·27 (1·08, 1·49)	**0·005**
> 1 Fraction	1·68 (0·94, 3·00)	0·079	2·03 (1·19, 3·47)	**0·009**	6·14 (1·35, 28·06)	**0·019**
Fraction Dose (per 1 Gy increase)	0·97 (0·93, 1·00)	0·059	0·96 (0·93, 0·99)	**0·006**	0·86 (0·78, 0·95)	**0·003**
BED_{10} (per 5 Gy increase)	0.98 (0.92, 1.06)	0.622	0.99 (0.93, 1.06)	0.756	0.82 (0.72, 0.94)	**0.005**
Serum Creatinine Pre-SABR (per 10 µmol/L increase)	1·01 (0·98, 1·04)	0·620	1·01 (0·99, 1·04)	0·296	0·91 (0·78, 1·06)	0·234
eGFR Pre-SABR (per 10 mL/min increase)	0·90 (0·79, 1·02)	0·105	0·89 (0·79, 1·00)	0·056	0·97 (0·75, 1·25)	0·795
Multivariable:						
Maximum Diameter (per 10 mm increase)	1·18 (1·12, 1·25)	**< 0·001**	1·16 (1·10, 1·23)	**< 0·001**	1·28 (1·19, 1·39)	**< 0·001**
Number of Fractions (per 1 unit increase)	--	--	1·13 (1·02, 1·24)	**0·017**	1·33 (1·07, 1·66)	**0·011**

HR – Hazard Ratio, **CI** – Confidence interval; **ECOG** – Eastern Co-operative Group; **SABR** – Stereotactic ablative radiotherapy; **eGFR** – Estimated glomerular filtration rate; **BED_{10}** – Biological equivalent dose ($\alpha/\beta=10$); P-values < 0·05 shown in **BOLD**;

FIGURE LEGENDS

Figure 1: Kaplan-Meier plots stratified by number of fractions for (a) overall survival (b) progression-free survival, (c) local control, (d) distant control, and (e) cancer-specific survival.

Figure 2(a-d). Scatterplots and waterfall plots showing change in (a-b) serum creatinine and (c-d) estimated glomerular filtration rate pre-SABR vs. post-SABR by number of fractions (1 vs. >1) for waterfall plots only. *P-values reported from paired T-test.*

SABR – stereotactic ablative radiotherapy; eGFR – estimated glomerular filtration rate

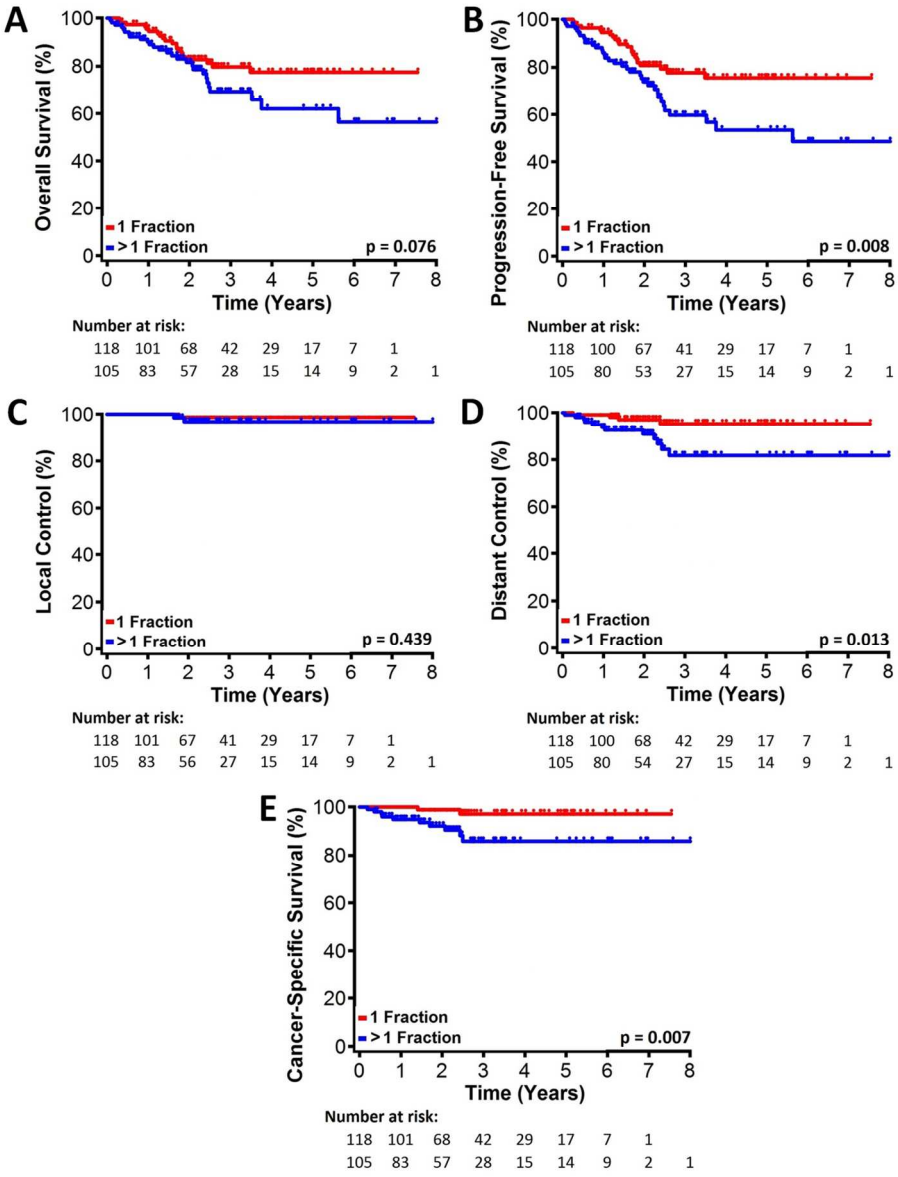
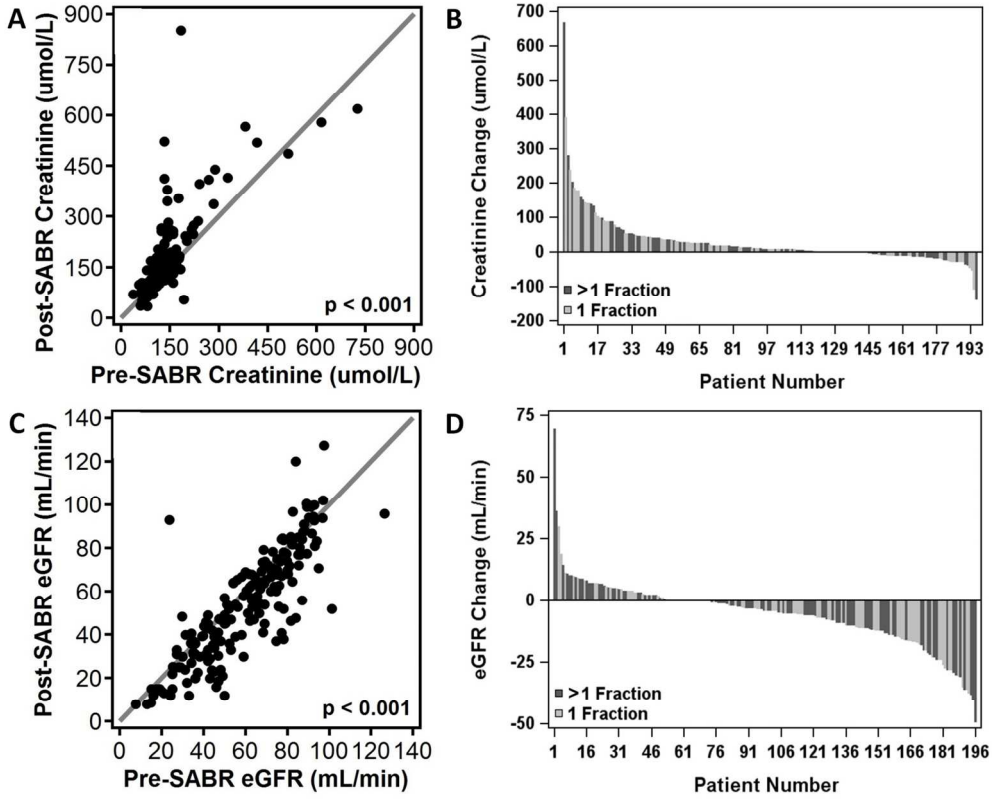


Figure 1: Kaplan-Meier plots stratified by number of fractions for (a) overall survival (b) progression-free survival, (c) local control, (d) distant control, and (e) cancer-specific survival.

183x239mm (300 x 300 DPI)



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SABR – stereotactic ablative radiotherapy; eGFR – estimated glomerular filtration rate.

230x186mm (300 x 300 DPI)

Supplementary Table 1: Radiotherapy treatment techniques employed at participating IROCK institutions and reported at the institutional level (n = 9).

Treatment Parameter	Value – N (%) or otherwise indicated
Radiotherapy Delivery	
Radiotherapy delivery unit†:	
C-arm based linear accelerator	6 (67)
CyberKnife	4 (44)
Helical tomotherapy	2 (22)
Radiotherapy delivery technique†:	
VMAT	5 (56)
CyberKnife	4 (44)
Fixed-field IMRT	3 (33)
3D-CRT	2 (22)
Tomotherapy	2 (22)
Image-guidance prior to treatment delivery†:	
Cone-beam CT	4 (44)
Stereoscopic x-ray with fiducials	2 (22)
Synchrony vest	2 (22)
Megavoltage CT	2 (22)
CT-on-rails	1 (11)
Simulation	
CT slice thickness (mm) – *Median (Range)*	1 (1 – 3)
CT simulation fused with diagnostic scan†:	
Diagnostic-quality CT scan (± contrast)	7 (78)
MRI	6 (67)
PET/CT	2 (22)
Split-function renal scan	2 (22)
Immobilization and organ motion control techniques†:	
4D-CT	5 (56)
Robotic tracking with fiducials	4 (44)
Vacuum cushion	4 (44)
BodyFIX	2 (22)
Abdominal compression	1 (11)
Respiratory gating with fiducials	1 (11)
None	1 (11)
Planning	
Treatment volumes delineated†:	
PTV expansion (for set-up and positioning)	8 (89)
ITV (integrating all respiratory motion)	6 (67)
GTV	4 (44)
CTV expansion (for microscopic disease)	2 (22)
PTV trimmed to avoid organ-at-risk overlap	6 (67)
Dosimetric objectives utilized†:	
PTV – D ≥ 95	7 (78)
GTV – D ≥ 90	3 (33)
ITV – D ≥ 98	3 (33)
Photon energies (MV) - *Range*	6-23
Dose-limiting organs-at-risk†:	
Small bowel	7 (78)
Spinal Cord	3 (33)
Contralateral kidney	3 (33)
Stomach	3 (33)
Ipsilateral kidney	2 (22)

Liver	2 (22)
Chest wall	2 (22)
Large bowel	1 (11)
Large vessels	1 (11)
Heart	1 (11)

[†]Categories not mutually-exclusive.

IMRT – intensity-modulated radiaton therapy; VMAT – volumetric arc therapy; CT – computed tomography; PET – positron emission tomography; MRI – magnetic resonance imaging; GTV – gross tumour volume; CTV – clinical target volume; ITV – internal target volume; PTV - planning target volume; D ≥ 90/95/98 – the respective volume must receive ≥ 90, 95, or 98% of the prescription dose.