5-year outcomes after stereotactic ablative body radiotherapy for primary renal cell carcinoma: an individual patient data meta-analysis from IROCK (the International Radiosurgery Consortium of the Kidney)

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Summary

Background Stereotactic ablative body radiotherapy (SABR) is a non-invasive treatment option for primary renal cell carcinoma, for which long-term data are awaited. The primary aim of this study was to report on long-term efficacy and safety of SABR for localised renal cell carcinoma.

Methods This study was an individual patient data meta-analysis, for which patients undergoing SABR for primary renal cell carcinoma across 12 institutions in five countries (Australia, Canada, Germany, Japan, and the USA) were eligible. Eligible patients had at least 2 years of follow-up, were aged 18 years or older, had any performance status, and had no previous local therapy. Patients with metastatic renal cell carcinoma or upper-tract urothelial carcinoma were excluded. SABR was delivered as a single or multiple fractions of greater than 5 Gy. The primary endpoint was investigator-assessed local failure per the Response Evaluation Criteria in Solid Tumours version 1.1, and was evaluated using cumulative incidence functions.

Findings 190 patients received SABR between March 23, 2007, and Sept 20, 2018. Single-fraction SABR was delivered in 81 (43%) patients and multifraction SABR was delivered in 109 (57%) patients. Median follow-up was 5·0 years (IQR 3·4–6·8). 139 (73%) patients were men, and 51 (27%) were women. Median age was 73·6 years (IQR 66·2–82·0). Median tumour diameter was 4·0 cm (IQR 2·8–4·9). 96 (75%) of 128 patients with available operability details were deemed inoperable by the referring urologist. 56 (29%) of 190 patients had a solitary kidney. Median baseline estimated glomerular filtration rate (eGFR) was 60·0 mL/min per 1·73 m² (IQR 42·0–76·0) and decreased by 14·2 mL/min per 1·73 m² (IQR 5·4–22·5) by 5 years post-SABR. Seven (4%) patients required dialysis post-SABR. The cumulative incidence of local failure at 5 years was 5·5% (95% CI 2·8–9·5) overall, with single-fraction SABR yielding fewer local failures than multifraction (Gray's p=0·020). There were no grade 3 toxic effects or treatment-related deaths. One (1%) patient developed an acute grade 4 duodenal ulcer and late grade 4 gastritis.

Interpretation SABR is effective and safe in the long term for patients with primary renal cell carcinoma. Single-fraction SABR might yield less local failure than multifraction, but further evidence from randomised trials is needed to elucidate optimal treatment schedules. These mature data lend further support for renal SABR as a treatment option for patients unwilling or unfit to undergo surgery.

Funding None.

Introduction

The incidence of renal cell carcinoma is rising, especially in patients older than 70 years.[1] Increased age is associated with a greater burden of medical comorbidities, which increase risks from anaesthesia and major surgery, or independently lead to chronic kidney disease (CKD). Guideline-recommended alternatives to radical or partial nephrectomy in patients unsuitable for surgery include nephron-sparing approaches, such as thermal ablation[2] and stereotactic ablative body radiotherapy (SABR).[3,4] SABR is a non-invasive treatment alternative in the multidisciplinary management of renal cell carcinoma.[5] A National Cancer Database analysis showed that the use of SABR for renal cell carcinoma has increased in the past two decades.[6] Previous reports showed promising safety and efficacy of SABR for patients with comorbidities,[7] tumours of stage T1b or higher (ie, ≥4 cm),[8] and in solitary kidneys.[9] A meta-analysis including 26 studies with 372 patients and a median weighted follow-up of 28 months was published in 2019.[10] However, long-term outcome data are awaited. The purpose of the current analysis was to assess long-term multicentre outcomes after SABR in primary renal cell carcinoma from the International Radiosurgery Oncology

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed for articles published in English between Jan 1, 2001, and Dec 31, 2021, with the search terms ("renal cell carcinoma" or "renal cell carcinoma" or "kidney cancer") AND ("SBRT" or "SABR"). We found multiple small retrospective and prospective studies highlighting the feasibility, safety, and efficacy of stereotactic ablative body radiotherapy (SABR) in patients with localised renal cell carcinoma. However, most of these studies had short follow-up periods. The weighted average of median follow-up in a systematic review and meta-analysis published in 2019, involving 372 patients with localised renal cell carcinoma in 26 studies, was 28·0 months. Furthermore, the reports were uniformly from single-centre studies. We aimed to report the long-term follow-up of patients with renal cell carcinoma treated with SABR across the multi-institutional International Radiosurgery Oncology Consortium of the Kidney (IROCK).

Added value of this study

To our knowledge, this report is the first to describe long-term, multicentre outcomes after SABR for primary renal cell carcinoma. In the long term, SABR is observed to be locally effective and safe with minimal impact on renal function, particularly in the context of a population with pre-existing chronic kidney disease. Single-fraction SABR was associated with a lower likelihood of local failure compared with multifraction SABR.

Implications of all the available evidence

SABR for primary renal cell carcinoma is a viable treatment option for patients who are inoperable or at high risk for surgery. This approach is effective in the long term for patients with both T1a and larger renal masses. The superiority of single-fraction SABR has been previously observed in metastatic renal cell carcinoma and this observation needs to be tested in the context of primary renal cell carcinoma through a dedicated randomised clinical trial.

Consortium of the Kidney (IROCK), with extended follow-up of patients in the existing IROCK database, and additional patient data from new contributing institutions.

Methods

Study design and participants

Patients with primary renal cell carcinoma receiving SABR across 12 international institutions in five countries (Australia, Canada, Germany, Japan, and the USA) between 2007 and 2018 were included. Inclusion criteria were a minimum potential follow-up of 2 years, non-metastatic renal cell carcinoma, adult patients (aged ≥18 years, no upper age limit) of any performance status, and no contraindication to primary renal cell carcinoma SABR (no comorbidities specifically contraindicated). Patients with previous abdominal radiotherapy or upper tract urothelial carcinoma were excluded. Medical inoperability was defined by the referring urologist. Performance status was classified as good (Eastern Cooperative Oncology Group score 0–1 or Karnofsky performance status ≥70%) or poor (not meeting at least one of these criteria). Individual patient data were either prospective or retrospective.

Central ethical review board approval was granted at the Peter MacCallum Cancer Centre, with a waiver for written consent of participants, and data transfer agreements and ethical approvals were obtained based on individual institutional ethics and governance procedures. Patient data were deidentified and transferred with encryption through secure file transfer protocol.

Procedures

Details of treatment delivery including dose, fractionation, margin settings, and respiratory motion management by participating institution are summarised in the appendix (pp 11–12).

Biological effective doses using an α/β value of 10 (BED_{10}) were calculated using the linear quadratic formula.[11] As the optimal α/β value for dose normalisation is unknown, alternative BEDs were calculated using estimates for two common human renal cell carcinoma cell lines, Caki-1 (α/β 6·9, $BED_{6\cdot9}$) and A498 (α/β 2·6, $BED_{2\cdot6}$), as illustrated in the appendix (p 10).[12]

Treatment-related toxic effects were defined according to the Common Terminology Criteria for Adverse Events version 4.0. Serum creatinine, urea, and estimated glomerular filtration rate (eGFR) were collected at baseline and all available follow-up timepoints post-treatment (1, 2, 3, 5, and >5 years post-treatment). eGFR was calculated from the CKD Epidemiology Collaboration equation for patients with unavailable eGFR values based on known creatinine values.[13] Patients were additionally classified as having normal renal function (eGFR ≥90 mL/min per 1·73 m²), grade 2 CKD (eGFR 60–89 mL/min per 1·73 m²), grade 3 CKD (eGFR 30–59 mL/min per 1·73 m²), grade 4 CKD (eGFR 15–29 mL/min per 1·73 m²), or end-stage renal failure (eGFR <15 mL/min per 1·73 m²). Patients with two kidneys also underwent nuclear medicine split-function renal perfusion scans (ie, renogram) to assess relative function of the affected and unaffected organs. The RENAL Nephrometry Score, consisting of (R)adius (tumour maximal diameter), (E)xophytic/endophytic properties, (N)earness of tumour to the collecting system, (A)nterior (a)/posterior (p) descriptor, and (L)ocation relative to the polar line, was used to quantify the complexity of tumours. Higher scores are associated with complex renal tumours.[14] Patients were followed up with serum creatinine measurements and CT scans (contrast-enhanced, when renal function permitted)

for primary response assessment and adverse event monitoring at the following intervals: every 3–4 months for year 1, every 3–6 months for years 2 and 3, and every 6–12 months thereafter. CT thorax–abdomen (contrast-enhanced, when possible) was used to assess distant control.[15]

Outcomes

The primary objective of this study was to assess the local efficacy of SABR for primary renal cell carcinoma, and secondary objectives were to evaluate treatment-related toxic effects, patterns of failure, survival, and renal function outcomes. Survival endpoints were progression-free survival (defined as time to local or distant failure, death, or date of last follow-up, whichever occurred first), cancer-specific survival, local failure, distant failure, and any failure. Local failure (the primary endpoint) was evaluated radiographically by the investigator based on the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 principles. Any failure was defined as local or distant failure, whichever occurred first. Renal function outcomes were based on serum creatinine and eGFR data collected at 1, 2, 3, 5, and more than 5 years post-treatment.

Statistical analysis

Baseline characteristics and post-treatment laboratory and clinical outcome data were assessed using descriptive statistics and stratified by stratification factors, which included single-fraction versus multifraction SABR, solitary versus dual kidneys, maximum tumour dimension (<4 cm *vs* ≥4 cm), and RENAL nephrometry scores (sensitivity analysis only). Comparisons by stratification factors were performed using the χ^2 test, Fisher's exact test, independent two-sample *t*-test, or Wilcoxon rank sum test, as appropriate. eGFR and CKD classification changes comparing pre-SABR and post-SABR were evaluated using the paired *t*-test and McNemar's test, respectively. Longitudinal changes in eGFR were assessed using linear mixed modelling with time as a fixed effect, stratification variables as fixed effects, and patient number as a random effect. All time-to-event endpoints (survival and patterns of failure) were calculated from the date of SABR to the date of local or distant recurrence, death due to any cause or cancer-related death, or date of the last follow-up, whichever occurred first. Kaplan-Meier estimates were generated for progression-free survival; cancer-specific survival; and freedom from local failure, distant failure, and any failure. Cumulative incidence functions and competing risk models with death as competing events were generated for local, distant, and any failure endpoints. Kaplan-Meier estimates were additionally stratified by the stratification factors and compared using the log-rank test (progression-free survival and cancer-specific survival) or Gray's test (local failure, distant failure, and any failure).

Violation of the proportional hazards assumption was evaluated using the Kolmogorov-type supremum test. If present, a time-dependent covariate was added to the model, and the p value was reported from the likelihood ratio test or Wald test (for competing risk models). Univariable and multivariable Cox proportional hazards regression was performed for progression-free survival, cancer-specific survival, any failure, local failure, and distant failure. All multivariable models were adjusted for baseline age, poor versus good performance status, solitary versus dual kidneys, maximum tumour dimension (continuous), BED_{10}, multifraction versus single-fraction SABR, and pre-SABR eGFR. Interactions were examined between (1) multifraction versus single-fraction SABR and maximum tumour dimension, and (2) pre-SABR eGFR and solitary versus dual kidneys. Additionally, the association between tumour complexity and treatment-related toxic effects of grade 2 or more was examined using logistic regression. As an exploratory analysis, we investigated the interaction between the subgroups of patients categorised by tumour size and single-fraction versus multifraction SABR. Imputation procedures were not used in this analysis to address missing data. All regression-based analyses were reported using complete case analysis only (eg, if any patient had missing data for at least one variable included in a model, then they were excluded from that particular model).

Statistical analysis was performed using SAS (version 9.4) using two-sided statistical testing at the 0·05 significance level.

Role of the funding source

There was no funding source for this study.

Results

190 patients received SABR between March 23, 2007, and Sept 20, 2018. Median follow-up was 5·0 years (IQR 3·4–6·8). Median age was 73·6 years (IQR 66·2–82·0) at time of SABR (table 1). 139 (73%) patients were men, and 51 (27%) were women. 163 (88%) of 186 patients for whom performance status information was available had good performance status. Among 128 patients with available operability details, 96 (75%) were deemed inoperable by the referring urologist, mostly for cardiovascular comorbidities (n=45, 47%) or existing or anticipated renal dysfunction (n=17, 18%). The median tumour diameter was 4·0 cm (IQR 2·8–4·9). Biopsy confirmation was attained in 157 (83%) patients; the most common histology was clear cell (n=134, 85%), followed by papillary (n=10, 6%). Of the 33 patients without histological confirmation, serial radiological enlargement was observed in 28 (85%). Baseline tumour complexity was moderate (median RENAL nephrometry scores of 7 [IQR 5–9]), and 56 (29%) patients had a solitary kidney. RENAL nephrometry distributions of high complexity score tumours are shown in the appendix (p 1). No patients received adjuvant or concurrent systemic therapy.

For the primary outcome measure, the cumulative incidence of local failure at 3 years, 5 years, and 7 years

	All patients (n=190)	Single-fraction SABR (n=81)	Multifraction SABR (n=109)	p value
Age at SABR, years	73·6 (66·2–82·0)	71·1 (61·8–78·7)	76·9 (68·3–83·8)	0·0004
Sex	..	..	..	0·36
Male	139 (73%)	62 (77%)	77 (71%)	..
Female	51 (27%)	19 (23%)	32 (29%)	..
Performance status	..	..	..	0·0069
Good (ECOG 0–1 or KPS ≥70%)	163/186 (88%)	77/81 (95%)	86/105 (82%)	..
Poor (ECOG 2–4 or KPS <70%)	23/186 (12%)	4/81 (5%)	19/105 (18%)	..
Medically inoperable	96/128 (75%)	19/19 (100%)	77/109 (71%)	0·0035
Solitary versus dual kidneys	..	..	..	<0·0001
Solitary kidney	56 (29%)	42 (52%)	14 (13%)	..
Dual kidneys	134 (71%)	39 (48%)	95 (87%)	..
Ipsilateral (target) kidney percentage function	49·5% (45·0–54·0)	52·0% (46·0–63·0)	48·0% (43·0–54·0)	0·17
Pathological confirmation	157 (83%)	80 (99%)	77 (71%)	<0·0001
Histology type	..	..	..	<0·0001
Clear cell	134/157 (85%)	78/80 (98%)	56/77 (73%)	..
Papillary	10/157 (6%)	2/80 (2%)	8/77 (10%)	..
Chromophobe	3/157 (2%)	0	3/77 (4%)	..
Other renal cell carcinoma	10/157 (6%)	0	10/77 (13%)	..
Maximum tumour dimension, cm	4·0 (2·8–4·9)	4·0 (2·9–4·5)	3·8 (2·7–5·3)	0·48
RENAL nephrometry score	7 (5–9)	8 (6–9)	7 (5–9)	0·23
eGFR pre-SABR, mL/min per 1·73 m²	60·0 (42·0–76·0)	69·0 (56·5–78·9)	51·0 (37·0–69·0)	<0·0001
Creatinine pre-SABR, µmol/L	114·9 (88·4–141·4)	114·9 (96·8–141·4)	109·0 (83·1–150·3)	0·47
Time from diagnosis to SABR, months	4·1 (1·4–18·5)	4·7 (1·4–75·3)	3·8 (1·3–12·6)	0·10
Total dose, Gy	30·0 (25·0–42·0)	25·0 (25·0–25·0)	42·0 (35·0–48·0)	<0·0001
Number of fractions	3 (1–4)	1	4 (3–5)	..
Fraction dose, Gy	16·0 (8·0–25·0)	25·0 (25·0–25·0)	8·0 (7·0–14·0)	<0·0001
$BED_{2\cdot6}$, Gy	265·4 (193·8–268·2)	265·4 (265·4–265·4)	202·2 (163·1–268·2)	0·0002
$BED_{6\cdot9}$, Gy	115·6 (92·1–124·0)	115·6 (115·6–115·6)	112·2 (84·8–131·5)	0·35
BED_{10}, Gy	87·5 (72·0–96·0)	87·5 (87·5–87·5)	96·0 (67·2–105·6)	0·22

Data are n (%), n/N (%), or median (IQR). p values are comparing single-fraction and multifraction cohorts. SABR=stereotactic ablative body radiotherapy. ECOG=Eastern Cooperative Oncology Group. KPS=Karnofsky performance status. eGFR=estimated glomerular filtration rate. $BED_{2\cdot6}$=biological effective dose (α/β=2·6). $BED_{6\cdot9}$=biological effective dose (α/β=6·9). BED_{10}=biological effective dose (α/β=10).

Table 1: **Baseline characteristics of all patients and stratified by single-fraction versus multifraction SABR (n=190)**

with death as a competing risk was 5·5% (95% CI 2·8–9·5), 5·5% (2·8–9·5), and 8·4% (4·2–14·3), respectively. Patterns of failure analysis showed that the first failure was local only in four (2%) patients, distant only in 14 (7%) patients, and combined local and distant failure in eight (4%) patients. No failure was observed in 164 (86%) patients. 66 patients died during the follow-up period, including ten (15%) cancer-related death events. Most deaths (n=51, 77%) were from non-malignant causes, including cardiovascular (n=12, 18%), other non-cancer reasons (n=12, 18%), sepsis (n=4, 6%) renal failure (n=3, 5%), respiratory failure (n=3, 5%), acute subdural haemorrhage (n=1, 2%), liver disease (n=1, 2%), lung disease (n=1, 2%), pneumonitis (n=1, 2%), and unknown cause (n=13, 20%). Five patients died from other malignancies. Descriptive details of outcomes for patients undergoing salvage treatment for local failure are shown in the appendix (p 2). The 3-year, 5-year, and 7-year estimates for cancer-specific survival were 95·5% (95% CI 90·7–97·8), 92·0% (85·2–95·8), and 92·0% (85·2–95·8), respectively. Median cancer-specific survival was not reached (95% CI not reached to not reached). The 3-year, 5-year, and 7-year estimates for progression-free survival were 72·1% (95% CI 65·0–78·1), 63·6% (55·6–70·6), and 48·5% (38·3–57·9), respectively. Median progression-free survival was 6·7 years (95% CI 5·5–7·5). The dominant pattern of progression was distant, with the 3-year, 5-year, and 7-year estimates of freedom from distant failure being 90·5% (95% CI 84·6–94·2), 87·3% (80·3–92·0), and 81·0% (69·9–88·3), respectively. By contrast, the 3, 5, and 7-year estimates for freedom from local failure were 93·7% (95% CI 88·5–96·6), 93·7% (88·5–96·6), and 89·4% (80·0–94·5), respectively. The corresponding cumulative incidences at 3 years, 5 years, and 7 years with death as a competing risk were 5·5% (95% CI 2·8–9·5), 5·5% (2·8–9·5), and 8·4% (4·2–14·3) for local failure; 8·4% (4·9–13·1), 10·8% (6·6–16·2), and 15·0% (9·1–22·4) for distant failure; and 10·6% (6·6–15·6), 13·0% (8·3–18·6), and 18·8% (12·0–26·9) for any failure. The median times to any, local, and distant failure were not reached (95% CI not reached to not reached). Multivariable Cox proportional hazards regression analyses for progression-free survival, cancer-specific survival, local failure, and distant failure are described in the appendix (p 3). One of four patients with local progression underwent successful salvage with radical nephrectomy, whereas the remaining three were not considered for surgery due to either pre-existing medical inoperability or T4 disease, which was surgically inoperable.

Pretreatment split function nuclear medicine assessments were available for 58 (31%) patients. The median split function was 50:50 for the target to contralateral kidney ratio. Before SABR, 16 (8%) patients were classified as having normal renal function, 80 (42%) had grade 2 CKD, 74 (39%) had grade 3 CKD, and 14 (7%) had grade 4 CKD. Five (3%) patients had end-stage renal failure. CKD status before and after SABR is shown in the appendix (p 4). Pre-SABR and post-SABR CKD classification data were complete for 167 of 190 patients and remained stable for 80 (48%) of 167 patients, worsened for 78 (47%) patients, and improved for nine (5%) patients (p<0·0001). 13 (7%) patients had end-stage renal failure following SABR. Of the 96 patients with grade 2 CKD or better before SABR (eGFR ≥60 mL/min per 1·73 m²), 32 (33%) developed grade 3 CKD and two (2%) developed grade 4 CKD. The median baseline eGFR for 189 of

190 patients was 60·0 mL/min per 1·73 m² (IQR 42·0–76·0). From baseline, eGFR reduced by a median of 5·5 mL/min per 1·73 m² (IQR 0·0–14·2) at 1 year, 10·3 mL/min per 1·73 m² (3·2–18·8) at 3 years, and 14·2 mL/min per 1·73 m² (5·4–22·5) at 5 years (all p<0·0001; appendix p 5). Similarly, the median baseline creatinine was 114·9 µmol/L (IQR 88·4–141·4), and increased by a median of 17·0 µmol/L (0·0–37·1) at 1 year, 23·0 µmol/L (8·9–43·0) at 3 years, and 21·2 µmol/L (5·3–51·0) at 5 years (all p<0·0001). Seven (4%) patients (two with solitary kidneys) underwent dialysis post-SABR, and in this group, the median baseline eGFR was 33·0 mL/min per 1·73 m² (IQR 18·0–46·0), and all patients had grade 3 or worse CKD (appendix p 6).

95 (50%) patients each had tumours of maximum dimension less than 4 cm and 4 cm or more, corresponding with median sizes of 2·8 cm (IQR 2·2–3·4) and 4·9 cm (4·4–5·7), respectively. Compared with patients who had tumours smaller than 4 cm, patients with tumours 4 cm or larger were older (p=0·029), had worse performance status (p=0·0038), and received less total radiation dose (p=0·014) and BED_{10} (p=0·033). No significant differences were observed for sex, solitary versus dual kidneys, histology, or fractionation. There was no difference in cancer-specific survival (log-rank p=0·19), progression-free survival (log-rank p=0·45), local failure (Gray's p=0·60), or distant failure (Gray's p=0·17) comparing patients in these two tumour size categories (appendix p 7). Details of the proportional hazards assumption testing are summarised in the appendix (p 9). The corresponding cumulative incidences of local failure at 5 years were 4·2% (95% CI 1·4–9·7) for less than 4 cm and 6·7% (2·7–13·2) for 4 cm or more, and the corresponding 5-year estimates for freedom from local failure were 95·4% (95% CI 88·2–98·2) for less than 4 cm and 92·0% (83·0–96·4) for 4 cm or more. The relationship between RENAL nephrometry scores, treatment-related toxic effects, worsening eGFR, and local failure was examined as a sensitivity analysis. There was evidence of an association between tumour complexity and treatment-related toxic effects of grade 2 or more (odds ratio per 1 unit increase: 1·44, 95% CI 1·02–2·03; p=0·039; and odds ratio for scores >7 *vs* ≤7: 5·42, 95% CI 1·12–26·26; p=0·036). No association was observed between tumour complexity and local failure based on competing risk Cox proportional hazards regression (p=0·81). Higher tumour complexity (RENAL nephrometry score >7) was associated with larger eGFR decreases at 3 years (p=0·032) and 5 years (p=0·039), but not at 1 year (p=0·29) post-SABR.

56 (29%) patients had primary renal cell carcinoma in a solitary kidney. Compared with patients with two kidneys, patients with a solitary kidney had better performance status (p=0·019), were younger (p=0·0074), included a higher proportion of patients with clear cell histology (p=0·017), and received lower total radiation dose (p<0·0001) in fewer fractions (p<0·0001). No significant differences were observed for sex, BED_{10}, or medical inoperability. Of the patients with a solitary kidney, 42 (75%) received single-fraction SABR, and two patients underwent dialysis. Compared with patients with two kidneys, post-treatment change in eGFR was

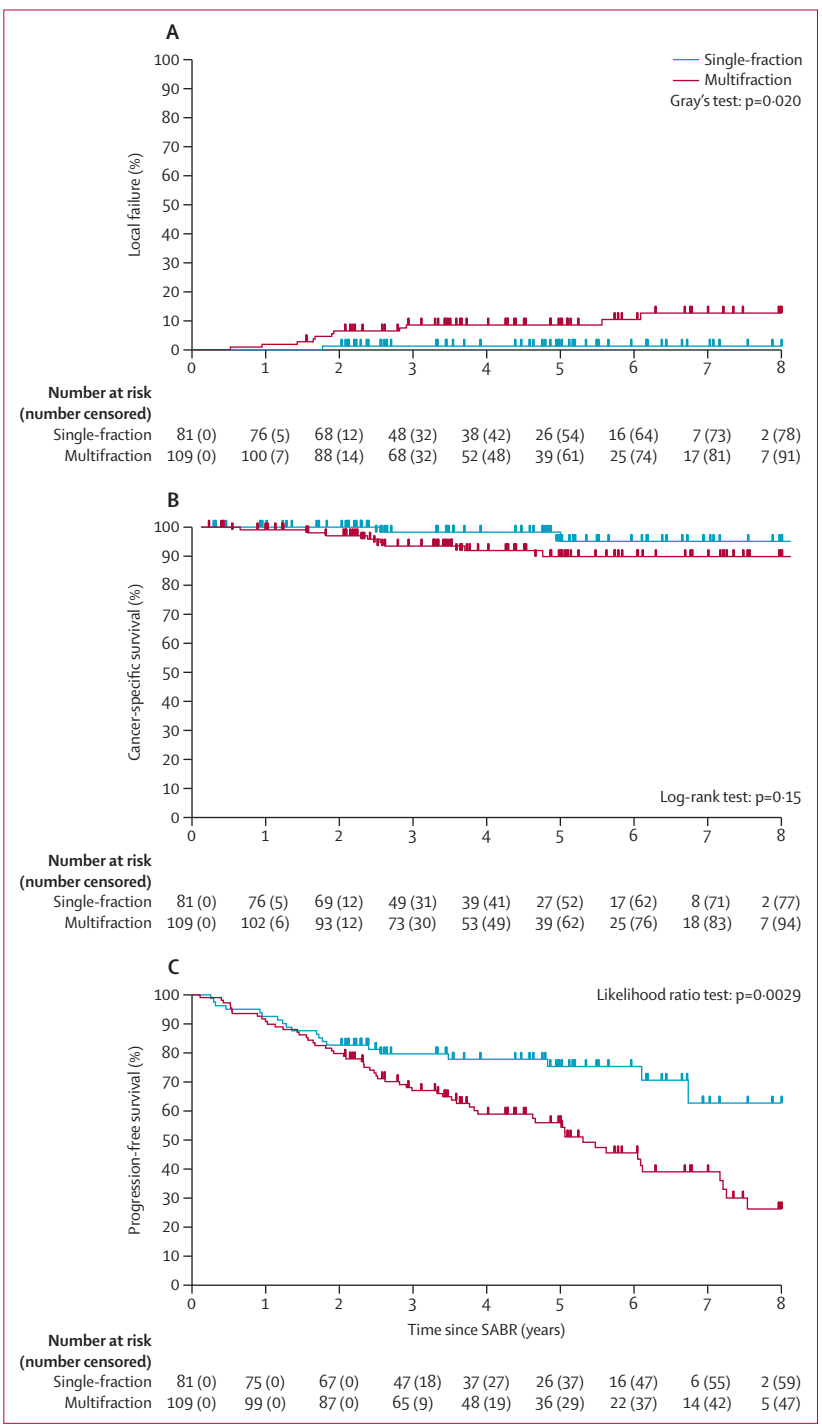

Figure 1: **Kaplan-Meier plots stratified by single-fraction versus multifraction SABR**
Plots are shown for local failure (A), cancer-specific survival (B), and progression-free survival (C). Local failure based on cumulative incidence function and competing risk model with death as competing event. Vertical dashes denote censored patients. SABR=stereotactic ablative body radiotherapy.

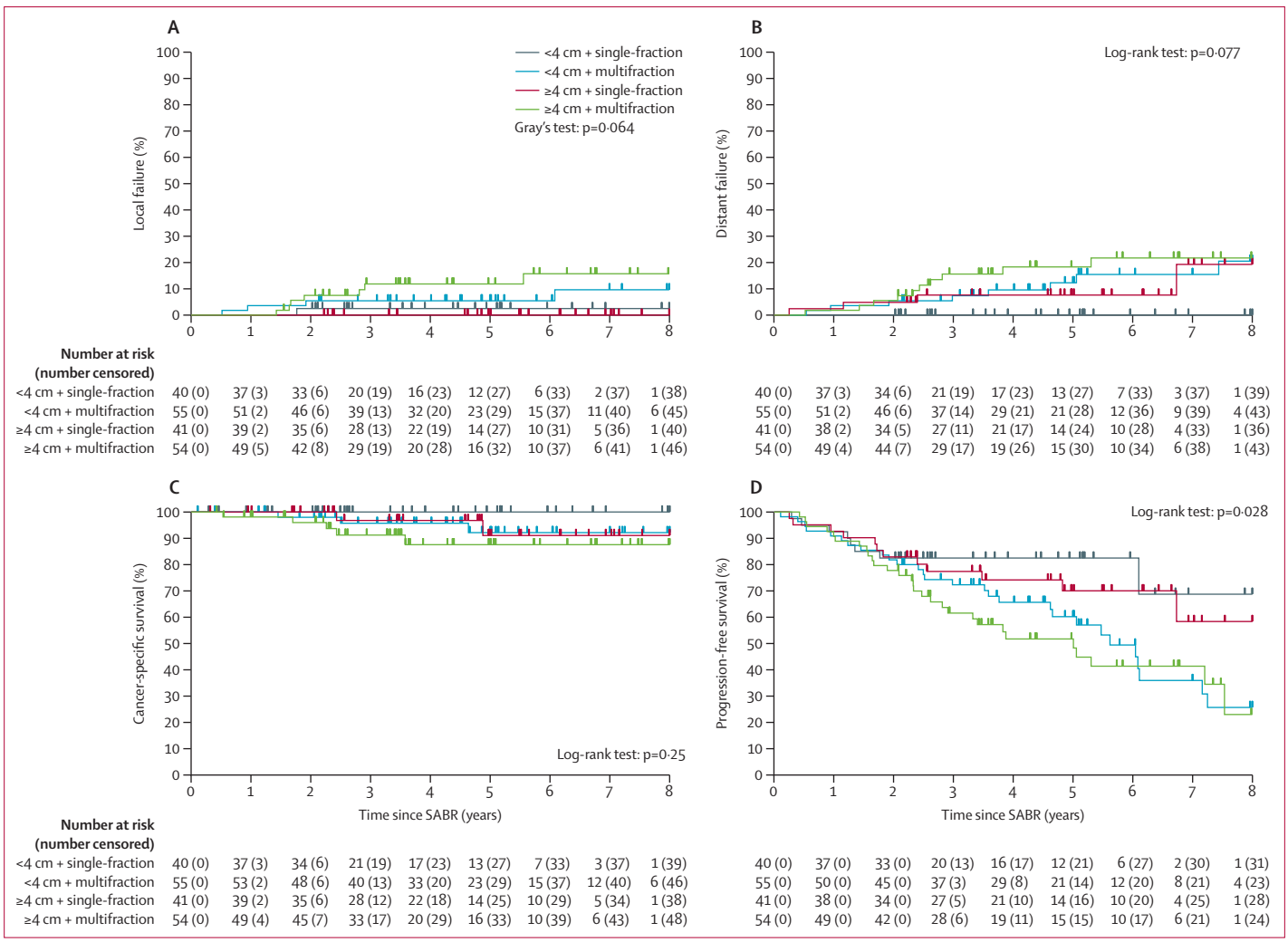

Figure 2: **Kaplan-Meier plots stratified by maximum tumour dimension (<4 cm *vs* ≥4 cm) and single-fraction versus multifraction SABR**
Plots are shown for local failure (A), distant failure (B), cancer-specific survival (C), and progression-free survival (D). Local and distant failure based on cumulative incidence function and competing risk model with death as competing event. Vertical dashes denote censored patients. SABR=stereotactic ablative body radiotherapy.

not significantly different for all the examined follow-up timepoints. There was no difference in cancer-specific survival (log-rank p=0·23), progression-free survival (log-rank p=0·65), local failure (Gray's p=0·38), or distant failure (Gray's p=0·72) between these groups (appendix p 8).

Single-fraction SABR was delivered in 81 (43%) of 190 patients, with a median dose of 25 Gy (IQR 25–25), most commonly as 25 Gy (n=52, 64%), 26 Gy (n=18, 22%), and 22 Gy (n=6, 7%). Multifraction SABR was delivered in 109 (57%) patients with a median dose of 42 Gy (IQR 35–48) in two to ten fractions over a median of 7 days (IQR 5–12). For the single-fraction group, the median BED_{10} was 87·5 Gy (IQR 87·5–87·5) versus 96·0 Gy (IQR 67·2–105·6) for multifraction SABR. No significant difference was observed in toxic effects of grade 2 or worse between single-fraction SABR (four [5%] of 81 patients) and multifraction SABR (seven [6%] of 109 patients; p=0·76). Compared with multifraction SABR, patients receiving single-fraction SABR had better performance status (p=0·0069), were younger (p=0·0004), and were more likely to have clear cell histology (p<0·0001) and a solitary kidney (p<0·0001). No significant differences were observed for sex or BED_{10}. Patients receiving single-fraction SABR were observed to have improved local failure (Gray's p=0·020) and progression-free survival (likelihood ratio test p=0·0029), but not cancer-specific survival (log-rank p=0·15) compared with those receiving multifraction SABR (figure 1). When comparing the clinical outcomes of the three lowest multifraction dose regimens ($BED_{6·9}$ <100) versus the other regimens, there were no significant differences in local failure, distant failure, cancer-specific survival, and progression-free survival. Multivariable analysis adjusting for age, performance status, solitary versus dual kidneys, maximum tumour dimension, BED_{10}, and baseline eGFR similarly identified a significantly

higher risk of local failure for multifraction SABR (hazard ratio [HR] 6·10, 95% CI 1·02–36·66; p=0·048), but not distant failure (HR 3·09, 0·65–14·62; p=0·16).

For the exploratory analysis of the interaction between the subgroups of patients categorised by tumour size and single-fraction versus multifraction SABR, we observed distinct cohorts with varying clinical outcomes. Patients who received single-fraction SABR to tumours smaller than 4 cm were observed to have the best progression-free survival (log-rank p=0·028) and cancer-specific survival (log-rank p=0·25), lowest local failure rate second to patients receiving single-fraction SABR to tumours 4 cm or larger (Gray's p=0·064), and lowest distant failure rates (Gray's p=0·077) compared with other subgroups (figure 2). However, significant differences between all subgroups were observed only for progression-free survival.

Grade 1–2 toxic effects were recorded in 70 (37%) patients; there were no grade 3 toxic effects or treatment-related deaths (table 2). One (1%) patient developed a treatment-related acute grade 4 duodenal ulcer and late grade 4 gastritis (1·4 months and 15·8 months after starting SABR, respectively). The prescription dose in this patient was 48 Gy in four fractions, with a maximum point dose to the small bowel of 54 Gy. This patient was disease-free at the last follow-up 8·8 years later.

	All patients (n=190)	Single-fraction SABR (n=81)	Multifraction SABR (n=109)
Any toxic effects			
Grade 1–2	70 (37%)	29 (36%)	41 (38%)
Grade 4	1 (1%)	0	1 (1%)
Fatigue			
Grade 1–2	51 (27%)	17 (21%)	34 (31%)
Nausea			
Grade 1–2	25 (13%)	16 (20%)	9 (8%)
Chest wall pain			
Grade 1–2	12 (6%)	5 (6%)	7 (6%)
Skin-related toxic effects			
Grade 1–2	3 (2%)	2 (2%)	1 (1%)
Gastritis			
Grade 1–2	3 (2%)	1 (1%)	2 (2%)
Grade 4	1 (1%)	0	1 (1%)
Bowel-related toxic effects			
Grade 1–2	3 (2%)	1 (1%)	2 (2%)
Grade 4	1 (1%)	0	1 (1%)

Data are n (%). There were no grade 3 toxic effects and no treatment-related deaths. SABR=stereotactic ablative body radiotherapy.

Table 2: **Toxic effects summary for all patients and by single-fraction versus multifraction SABR (n=190)**

Discussion

To our knowledge, this is the first study describing long-term (median 5 years) outcomes after SABR for primary renal cell carcinoma. In this series of 190 patients with larger renal masses (median 4·0 cm) than typically treated with thermal ablation, we observed a 5-year local failure rate of 5·5%. The 5-year cancer-specific survival rate was 92% in a predominantly medically inoperable cohort. In a population with baseline kidney dysfunction (baseline median eGFR of 60·0 mL/min per 1·73 m²), we observed a clinically acceptable decline in renal function at 5 years by a median of 14·2 mL/min per 1·73 m². We observed a significant difference in progression-free survival and local failure between single-fraction and multifraction SABR. Long-term renal function outcomes were no different between single-fraction and multifraction SABR cohorts. On multivariable analysis, we still observed a significantly higher risk of local failure for multifraction SABR than for single-fraction SABR. This finding is consistent with a previous report in oligometastatic renal cell carcinoma.[16] In that study, local progression-free survival was improved with single-fraction SABR as compared with multifraction SABR (HR 0·283, p=0·008). However, results of the single-fraction versus multiple fraction comparison should be interpreted as hypothesis-generating and are not considered definitive. Furthermore, given that the interaction testing between the subgroups of patients categorised by tumour size and single-fraction versus multifraction SABR was exploratory, these results should be interpreted with caution. This intriguing observation in the primary setting will be evaluated through a prospective randomised registry trial, with the infrastructure for the IROCK registry under development (ACSQHC-ARCR-373).

For smaller renal masses, SABR appears similar to other treatment modalities. A single-institution comparison of outcomes in T1a tumours had a median tumour size of 2·4 cm, 1·9 cm, and 2·8 cm for patients treated with partial nephrectomy, radiofrequency ablation, and cryoablation, respectively. The 5-year local recurrence-free survival rates for patients treated with partial nephrectomy, radiofrequency ablation, and cryoablation were 97·7%, 95·9%, and 95·9%, respectively.[17] By comparison, in this analysis, the tumours smaller than 4 cm had a median size of 2·8 cm and a corresponding 5-year freedom from local failure of 95·4%. Currently, more prospective clinical trial data are available for SABR[10] than for thermal ablation and partial nephrectomy. The European Association of Urology Renal Cell Carcinoma Guideline Panel published a cautionary correspondence on the limitations of studies comparing outcomes of thermal ablation, specifically, with other techniques, because of "a series of methodologically flawed SRs [systematic reviews] encompassing multiple small, highly biased, and underpowered primary studies."[18] By contrast, the current breadth of rigorously conducted prospective clinical trials of SABR includes studies investigating several populations of interest: neoadjuvant SABR for inferior vena cava thrombus,[19] neoadjuvant SABR before cytoreductive nephrectomy,[20] and as an alternative to cytoreductive nephrectomy.[21] A current

limitation of the available clinical trial data is that these data are uniformly from single-centre trials, with multi-institutional data, including the TransTasman Radiation Oncology Group (TROG 15.03) FASTRACK II trial (NCT02613819), still pending.

Comparative outcome data on partial nephrectomy and thermal ablation are lacking. Retrospective propensity score-matched studies have reported conflicting results. Uhlig and colleagues reported inferior overall survival outcomes with SABR compared with partial nephrectomy and thermal ablation among patients with stage 1 renal cell carcinoma from the National Cancer Database.[22] Patients treated with SABR were older and had larger tumour sizes than those treated with partial nephrectomy or thermal ablation. The authors have not reported the failure rates or cancer-specific survival. By contrast, a propensity score-matched analysis done in Germany compared a cohort of 70 patients undergoing partial nephrectomy and SABR in the same institution.[23] Local tumour control 9 months after either modality was 98%, with no reported difference in overall survival, cancer-specific survival, local control, and renal function outcomes. A cost-effectiveness analysis[24] performed in Canada found that over 5 years, SABR projected 4·1 quality-adjusted life years (QALYs) at CA$16 097, compared with 3·6 QALYs at CA$18 324 for radiofrequency ablation. The authors concluded that SABR appears to be cost-effective as a primary treatment for renal cell carcinoma. There are caveats to these datasets—namely, retrospective data collection and lack of randomised outcomes. In this context, the results from the RADSTER randomised trial of SABR compared with thermal ablation are awaited (NCT03811665).

Many patients with renal cell carcinoma have pre-existing CKD or risk developing CKD due to co-morbidities, such as hypertension, diabetes, or systemic vascular disease. Age, diabetes, and baseline renal function are also predictors of the development of post-treatment CKD.[25] Radical nephrectomy is associated with more pronounced renal function decline than nephron-sparing strategies (partial nephrectomy, thermal ablation, and active surveillance).[26] Despite good renal function outcomes after partial nephrectomy, the reported incidence of chronic end-stage renal disease was 4–36% in patients with a baseline eGFR of less than 60 mL/min per 1·73 m².[27] Furthermore, the higher incidence of all-cause mortality and cardiac events associated with CKD emphasises the goal of management to prevent further deterioration of renal function.[28] SABR might be considered an attractive alternative in older patients at higher risk of post-treatment end-stage renal disease due to baseline CKD and comorbidities. In this series of 190 mostly elderly patients treated with SABR, the incidence of chronic end-stage renal disease was 7% (13 patients), despite more than 50% of patients having a baseline eGFR of less than 60 mL/min per 1·73 m².

Patients with larger, medically inoperable, or technically inoperable primary renal cell carcinoma have limited curative treatment options. Radiofrequency ablation and microwave ablation have excellent oncological outcomes for masses smaller than 3 cm. Similarly, endophytic tumours near the renal pelvis are less well suited to thermal ablation,[29] as proximity to the renal pelvis is a risk factor for ureteric stricture. To date, to our knowledge, there has not been a report of ureteric stricture post-SABR. Notably, tumour complexity, as defined by RENAL nephrometry, was not predictive of clinical outcomes after SABR. We did not observe any limitations for SABR with regard to tumour location.

Significant limitations to this study need to be acknowledged. Low rates of treatment-related toxic effects might be due to under-reporting, which can occur with retrospective collection of toxicity data. Renal function-relevant diagnoses, such as diabetes and hypertension, were not captured in this database. Not all patients had pathological confirmation of renal cell carcinoma, although rates were similar to thermal ablation reports. We did not collect data for the tumour laterality or Fuhrman grade. Heterogeneity is a potential limitation, but we believe these data to be generalisable given the diversity of geography, treatment platforms, and techniques used by the institutions involved worldwide. Finally, RECIST criteria for post-SABR response assessment has limitations, but remains the most widely used system in radiation oncology.[30] At present, post-SABR renal biopsy is experimental,[30] introduces procedural risk, and is not routinely practiced across the participating institutions of this study.

In conclusion, this analysis provides mature outcome and safety data for SABR in primary renal cell carcinoma. Single-fraction SABR yielded fewer local failures than multifraction SABR. This observation should be tested in a prospective, randomised trial.

Contributors

SS, AVL, AW, RJMC, and MA contributed to conceptualisation, data curation, formal analysis, investigation, methods, project administration, resources, supervision, and writing of the manuscript (original draft, review, and editing). All remaining authors contributed to data curation, formal analysis, methods, and writing of the manuscript (original draft, review, and editing). SS, AVL, and AW (the study statistician) had full access to all the data in the study, accessed and verified the data, and vouch for the integrity of the data and the adherence to the study protocol. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

Ethics approval did not include a data sharing plan, and therefore data from the study will not be shared publicly.

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References

1 Capitanio U, Bensalah K, Bex A, et al. Epidemiology of renal cell carcinoma. *Eur Urol* 2019; **75:** 74–84.
2 Ljungberg B, Albiges L, Abu-Ghanem Y, et al. European Association of Urology guidelines on renal cell carcinoma: the 2022 update. *Eur Urol* 2022; **82:** 399–410.
3 National Comprehensive Cancer Network. Kidney cancer (version 3.022). https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf (accessed Aug 26, 2022).
4 Escudier B, Porta C, Schmidinger M, et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2019; **30:** 706–20.
5 Stewart GD, Klatte T, Cosmai L, et al. The multispeciality approach to the management of localised kidney cancer. *Lancet* 2022; **400:** 523–34.
6 Haque W, Verma V, Lewis GD, Lo SS, Butler EB, Teh BS. Utilization of radiotherapy and stereotactic body radiation therapy for renal cell cancer in the USA. *Future Oncol* 2018; **14:** 819–27.
7 Siva S, Louie AV, Warner A, et al. Pooled analysis of stereotactic ablative radiotherapy for primary renal cell carcinoma: a report from the International Radiosurgery Oncology Consortium for Kidney (IROCK). *Cancer* 2018; **124:** 934–42.
8 Siva S, Correa RJM, Warner A, et al. Stereotactic ablative radiotherapy for ≥T1b primary renal cell carcinoma: a report from the International Radiosurgery Oncology Consortium for Kidney (IROCK). *Int J Radiat Oncol Biol Phys* 2020; **108:** 941–49.
9 Correa RJM, Louie AV, Staehler M, et al. Stereotactic radiotherapy as a treatment option for renal tumors in the solitary kidney: a multicenter analysis from the IROCK. *J Urol* 2019; **201:** 1097–104.
10 Correa RJM, Louie AV, Zaorsky NG, et al. The emerging role of stereotactic ablative radiotherapy for primary renal cell carcinoma: a systematic review and meta-analysis. *Eur Urol Focus* 2019; **5:** 958–69.
11 Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol* 1989; **62:** 679–94.
12 Ning S, Trisler K, Wessels BW, Knox SJ. Radiobiologic studies of radioimmunotherapy and external beam radiotherapy in vitro and in vivo in human renal cell carcinoma xenografts. *Cancer* 1997; **80** (suppl)**:** 2519–28.
13 Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150:** 604–12.
14 Kutikov A, Uzzo RG. The R.E.N.A.L. nephrometry score: a comprehensive standardized system for quantitating renal tumor size, location and depth. *J Urol* 2009; **182:** 844–53.
15 Siva S, Ellis RJ, Ponsky L, et al. Consensus statement from the International Radiosurgery Oncology Consortium for Kidney for primary renal cell carcinoma. *Future Oncol* 2016; **12:** 637–45.
16 Zelefsky MJ, Greco C, Motzer R, et al. Tumor control outcomes after hypofractionated and single-dose stereotactic image-guided intensity-modulated radiotherapy for extracranial metastases from renal cell carcinoma. *Int J Radiat Oncol Biol Phys* 2012; **82:** 1744–48.
17 Andrews JR, Atwell T, Schmit G, et al. Oncologic outcomes following partial nephrectomy and percutaneous ablation for cT1 renal masses. *Eur Urol* 2019; **76:** 244–51.
18 Abu-Ghanem Y, Fernández-Pello S, Bex A, et al. Limitations of available studies prevent reliable comparison between tumour ablation and partial nephrectomy for patients with localised renal masses: a systematic review from the European Association of Urology Renal Cell Cancer Guideline Panel. *Eur Urol Oncol* 2020; **3:** 433–52.
19 Margulis V, Freifeld Y, Pop LM, et al. Neoadjuvant SABR for renal cell carcinoma inferior vena cava tumor thrombus—safety lead-in results of a phase 2 trial. *Int J Radiat Oncol Biol Phys* 2021; **110:** 1135–42.
20 Singh AK, Winslow TB, Kermany MH, et al. A pilot study of stereotactic body radiation therapy combined with cytoreductive nephrectomy for metastatic renal cell carcinoma. *Clin Cancer Res* 2017; **23:** 5055–65.
21 Correa RJM, Ahmad B, Warner A, et al. A prospective phase I dose-escalation trial of stereotactic ablative radiotherapy (SABR) as an alternative to cytoreductive nephrectomy for inoperable patients with metastatic renal cell carcinoma. *Radiat Oncol* 2018; **13:** 47.
22 Uhlig A, Uhlig J, Trojan L, Kim HS. Stereotactic body radiotherapy for stage I renal cell carcinoma: national treatment trends and outcomes compared to partial nephrectomy and thermal ablation. *J Vasc Interv Radiol* 2020; **31:** 564–71.
23 Staehler M, Schuler T, Spek A, et al. Propensity score-matched analysis of single fraction robotic radiosurgery versus open partial nephrectomy in renal cell carcinoma: oncological outcomes. *Cureus* 2022; **14:** e21623.
24 Donovan EK, Xie F, Louie AV, et al. Cost effectiveness analysis of radiofrequency ablation (RFA) versus stereotactic body radiotherapy (SBRT) for early stage renal cell carcinoma (RCC). *Clin Genitourin Cancer* 2022; **20:** e353–61.
25 Thompson RH, Boorjian SA, Lohse CM, et al. Radical nephrectomy for pT1a renal masses may be associated with decreased overall survival compared with partial nephrectomy. *J Urol* 2008; **179:** 468–71.
26 Patel HD, Pierorazio PM, Johnson MH, et al. Renal functional outcomes after surgery, ablation, and active surveillance of localized renal tumors: a systematic review and meta-analysis. *Clin J Am Soc Nephrol* 2017; **12:** 1057–69.
27 Lane BR, Babineau DC, Poggio ED, et al. Factors predicting renal functional outcome after partial nephrectomy. *J Urol* 2008; **180:** 2363–68.
28 Herzog CA, Asinger RW, Berger AK, et al. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2011; **80:** 572–86.
29 Tsivian M, Lyne JC, Mayes JM, Mouraviev V, Kimura M, Polascik TJ. Tumor size and endophytic growth pattern affect recurrence rates after laparoscopic renal cryoablation. *Urology* 2010; **75:** 307–10.
30 Ali M, Mooi J, Lawrentschuk N, et al. The role of stereotactic ablative body radiotherapy in renal cell carcinoma. *Eur Urol* 2022; published online July 14. https://doi.org/10.1016/j.eururo.2022.06.017.