Stereotactic ablative body radiotherapy for primary kidney cancer (TROG 15.03 FASTRACK II): a non-randomised phase 2 trial

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Summary

Background Stereotactic ablative body radiotherapy (SABR) is a novel non-invasive alternative for patients with primary renal cell cancer who do not undergo surgical resection. The FASTRACK II clinical trial investigated the efficacy of SABR for primary renal cell cancer in a phase 2 trial.

Methods This international, non-randomised, phase 2 study was conducted in seven centres in Australia and one centre in the Netherlands. Eligible patients aged 18 years or older had biopsy-confirmed diagnosis of primary renal cell cancer, with only a single lesion; were medically inoperable, were at high risk of complications from surgery, or declined surgery; and had an Eastern Cooperative Oncology Group performance status of 0–2. A multidisciplinary decision that active treatment was warranted was required. Key exclusion criteria were a pre-treatment estimated glomerular filtration rate of less than 30 mL/min per 1·73 m², previous systemic therapies for renal cell cancer, previous high-dose radiotherapy to an overlapping region, tumours larger than 10 cm, and direct contact of the renal cell cancer with the bowel. Patients received either a single fraction SABR of 26 Gy for tumours 4 cm or less in maximum diameter, or 42 Gy in three fractions for tumours more than 4 cm to 10 cm in maximum diameter. The primary endpoint was local control, defined as no progression of the primary renal cell cancer, as evaluated by the investigator per Response Evaluation Criteria in Solid Tumours (version 1.1). Assuming a 1-year local control of 90%, the null hypothesis of 80% or less was considered not to be worthy of proceeding to a future randomised controlled trial. All patients who commenced trial treatment were included in the primary outcome analysis. This trial is registered with ClinicalTrials.gov, NCT02613819, and has completed accrual.

Findings Between July 28, 2016, and Feb 27, 2020, 70 patients were enrolled and initiated treatment. Median age was 77 years (IQR 70–82). Before enrolment, 49 (70%) of 70 patients had documented serial growth on initial surveillance imaging. 49 (70%) of 70 patients were male and 21 (30%) were female. Median tumour size was 4·6 cm (IQR 3·7–5·5). All patients enrolled had T1–T2a and N0–N1 disease. 23 patients received single-fraction SABR of 26 Gy and 47 received 42 Gy in three fractions. Median follow-up was 43 months (IQR 38–60). Local control at 12 months from treatment commencement was 100% (p<0·0001). Seven (10%) patients had grade 3 treatment-related adverse events, with no grade 4 adverse events observed. Grade 3 treatment-related adverse events were nausea and vomiting (three [4%] patients), abdominal, flank, or tumour pain (four [6%]), colonic obstruction (two [3%]), and diarrhoea (one [1%]). No treatment-related or cancer-related deaths occurred.

Interpretation To our knowledge, this is the first multicentre prospective clinical trial of non-surgical definitive therapy in patients with primary renal cell cancer. In a cohort with predominantly T1b or larger disease, SABR was an effective treatment strategy with no observed local failures or cancer-related deaths. We observed an acceptable side-effect profile and renal function after SABR. These outcomes support the design of a future randomised trial of SABR versus surgery for primary renal cell cancer.

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Introduction

The incidence of kidney cancer has been steadily increasing in the Americas, Asia, and Europe. The first worldwide age-standardised rate reported for kidney cancer was 7·1 per 100 000 people in 1975, steadily increasing to 16 per 100 000 people in 2008.[1] In 2017, renal cell carcinoma accounted for 393 000 yearly incident cases, 138 500 yearly deaths, and 3·3 million disability-adjusted life-years globally.[2] The greatest rise in incidence has been observed in the age group of 70 years or older.[3] Although active surveillance can be a reasonable option for indolent, small renal masses,

Research in context

Evidence before this study

Renal cell carcinoma is perceived to be a radioresistant disease. Surgery is the preferred treatment for a primary renal cell cancer in patients who are medically operable and with resectable tumours; however, many older patients have comorbidities that preclude them from surgical intervention. Although percutaneous thermal ablation has been described as an alternative intervention for small renal masses, this technique has several technical limitations and there is an absence of published clinical trial evidence to support its use. Therefore, patients with primary renal cell cancer who are medically inoperable or at high risk of surgical complications, particularly those with larger renal masses, have limited curative treatment options. It is in this context that stereotactic ablative body radiotherapy (SABR) is emerging as a novel, non-invasive curative treatment option for primary renal cell cancer. We searched PubMed and Embase for research articles published in English between Jan 1, 1995, and April 5, 2023, with the search string: ("radiotherapy" OR "radiation therapy" OR "stereotactic" OR "cyberknife" OR "sabr" OR "sbrt") AND ("Kidney neoplasms" OR "kidney neoplasm" OR "renal neoplasms" OR "kidney cancer" OR "renal cell carcinoma" OR ""carcinoma, renal cell" OR "renal cell cancer" OR "renal adenocarcinoma") AND (english[Filter]). Although several retrospective studies, systematic reviews, and meta-analyses of SABR for primary renal cell cancer have been published, prospective clinical trial evidence for SABR so far has been confined to small, single-centre trials.

Added value of this study

To our knowledge, TROG 15.03 FASTRACK II is the first multicentre clinical trial of a non-surgical definitive therapy for primary renal cell cancer. This non-randomised trial enrolled patients with medically inoperable or technically high-risk primary renal cell cancer across eight centres in Australia and the Netherlands. Despite a larger average tumour size (4·6 cm) than in many pre-existing prospective trials of surgery or SABR in primary renal cell cancer, there were no local treatment failures observed and no patients died from cancer during the study period. Few treatment-related toxicities and limited renal function decline were noted. Notably, the tumours that were treated were larger and more complex than could be expected to be effectively treated with thermal ablation approaches.

Implications of all the available evidence

Taken together, the results of FASTRACK II along with previous single-centre clinical trials support SABR as a therapeutic option for patients with inoperable or high-risk primary renal cell cancer. Renal function preservation and the associated toxicity profile appears acceptable. The observed exceptional oncological outcomes justify the design of a randomised controlled trial of surgery versus SABR for patients with primary renal cell cancer.

older patients diagnosed with renal tumours have up to 3·8 times lower cancer-specific survival rates than younger patients.[4] Surgery is the standard of care for patients with primary renal cell carcinoma. Surgery involves the removal of either the entire kidney and surrounding tissues (radical nephrectomy) or the tumour plus a margin (nephron-sparing surgery). However, older patients might have medical comorbidities that might exclude surgical extirpation and, in particular, nephron-sparing surgery.

In this context, percutaneous thermal ablation has been described as an alternative intervention for small renal masses (T1a tumours). The efficacy of thermal ablation is reduced, and the rate of complications increased when renal cell cancers are larger than about 3–3·5 cm or are in spatial proximity to the renal hilum or proximal ureters.[5,6] It is an invasive procedure performed either with local or under general anaesthesia. Furthermore, although widely available, thermal ablation is limited by operator-dependent expertise and by the absence of any published clinical trial evidence to support its use. Thus, patients with renal cell cancer who are not suitable for percutaneous thermal ablation or have T1b or larger tumours (>4 cm) that are not medically operable have limited curative treatment options. Therefore, this non-surgical population is in need of an effective treatment alternative.

Stereotactic ablative body radiotherapy (SABR) is a novel, non-invasive curative treatment option for patients with primary renal cell cancer. In contrast to thermal ablation, SABR is feasible for both T1a and T1b or greater tumours. Several small single-centre prospective trials of SABR have shown promising safety and efficacy in patients with primary renal cell cancer unsuited to surgery.[7–15] We aimed to build on the TransTasman Radiation Oncology Group (TROG)'s initial single-centre, phase 1 FASTRACK trial, using the same treatment methodology as previously published,[9] by investigating the efficacy of SABR in a multicentre, international clinical trial setting. The targeted population were not suited to active surveillance or surgery and therefore had limited curative alternatives.

Methods

Study design and participants

TROG 15.03 FASTRACK II, a non-randomised phase 2 trial, was conducted by TROG, in collaboration with the Australian and New Zealand Urogenital and Prostate Cancer Trials Group, in seven centres in Australia and one centre in the Netherlands (appendix p 79). The study population was patients aged 18 years or older with a biopsy-confirmed solitary primary renal cell cancer who were medically inoperable or technically at high risk of

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See Online for appendix

complications from surgery or declined surgery. Key inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 and a multidisciplinary decision that active treatment was warranted. Key exclusion criteria were a pre-treatment estimated glomerular filtration rate (eGFR) of less than 30 mL/min per 1·73 m² calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, receipt of previous systemic therapies for renal cell cancer, previous high-dose radiotherapy to an overlapping region, maximum tumour diameter larger than 10 cm, and direct contact of the renal cell cancer with the bowel. Patients with untreated previous malignancy or previous malignancy within 2 years of screening were excluded, as were patients with a horseshoe kidney or visceral or bony metastatic disease. Sex was recorded in the electronic medical records. Data on race and ethnicity were not collected.

The study underwent independent human ethics review board approval, and all patients provided written informed consent. The trial was performed in accordance with the principles of the Declaration of Helsinki. The protocol is available in the appendix.

Procedures

The intervention was SABR, with one of two fractionation schedules selected based on tumour size: a single fraction of 26 Gy was used for tumours 4 cm or less in maximum diameter, or 42 Gy in three fractions for tumours more than 4 cm to 10 cm in maximum diameter. All participants were immobilised using, at a minimum, a half-body vacuum immobilisation device. A four-dimensional CT scan in the treatment position was used to account for respiratory motion. Target volumes accounting for respiratory motion and setup uncertainty were defined as an internal target volume taking into consideration the total tumour excursion through respiration, with a 5 mm isotropic expansion from internal target volume to the planning target volume. The investigational treatment was prescribed to the covering isodose, ensuring that 99% of the planning target volume was covered by 100% of the dose. When doses to organs at risk could not be respected while achieving this level of coverage, an alternative was 95% coverage of the planning target volume with 100% of the dose. The peak dose was between 125% and 143%. For fractionated treatment schedules, treatment fractions were delivered on non-consecutive days (about 48 h apart).

Safety was evaluated using Common Toxicity Criteria for Adverse Events (CTCAE; version 4.03) and was summarised as the worst grade per adverse event. Patients were followed up at 4 weeks and at 3 months after treatment commencement for clinical assessments and blood tests (full blood count, urea and electrolytes, and eGFR calculated with the CKD-EPI equation). Subsequently, chest and abdomen CT, blood tests, and clinical assessments were performed at 6 months, 9 months, 12 months, 18 months, 24 months, 33 months, 42 months, 51 months, and 60 months from treatment commencement, and annually thereafter (figure 1). Investigators assessed the imaging scans. An optional split renal function nuclear medicine scan was collected at 12 months, 24 months, 42 months, and 60 months using technetium-99m DMSA (2,3 dimercaptosuccinic acid) single photon emission CT or CT and GFR calculated with chromium-51 EDTA (edetic acid). A whole-body bone scan and CT scans of the chest and abdomen were performed at baseline and at progression.

All participating sites underwent SABR benchmarking activities before site activation, and all patients underwent real-time radiotherapy peer review before treatment delivery. Radiotherapy treatment plans were submitted before treatment and were reviewed by a radiation oncologist and a medical physicist or radiation therapist (appendix pp 5–13, 18–19). The treatment plan review included target and critical organ segmentation, motion management, and treatment plan dosimetry. In a subset of patients, treatment plan review was supplemented with knowledge-based planning to determine whether the dose to critical organs could be reduced.[16]

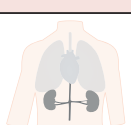
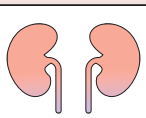
	Assessment			
	 CT (thorax, abdomen)	 eGFR (CKD-EPI equation)	 Split renal function test and calculated GFR (nuclear medicine)	 Whole-body bone scan
Baseline	✓	✓	✓	✓
Year 1	3 monthly	3 monthly	Annually	..
Year 2	6 monthly	6 monthly	Annually	..
Up to year 5	9 monthly	9 monthly	42 months, 60 months	..
After 5 years	Annually	Annually	Annually	..
At progression	✓	✓	..	✓

Figure 1: **Schedule of assessments**
CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration. GFR=glomerular filtration rate. eGFR=estimated GFR.

Outcomes

The primary endpoint of the study was local control (also referred to as freedom from local progression), measured from the date of commencement of SABR to first evidence of local progression (assessed by local investigators per Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1), censored at the last tumour assessment. Secondary endpoints were overall survival (defined as the time from the date of treatment commencement to the date of death from any cause);

cancer-specific survival (defined as the time from the date of treatment commencement to the date of cancer-related death, with death from any other cause considered as a competing event); freedom from distant failure (defined as the time from the date of treatment commencement to the date of first documented distant progression, with death considered as a censoring event); safety assessed using CTCAE (version 4.03); and renal function changes over time measured using serum creatinine, eGFR by the CKI-EPI equation, and split function and calculated GFR on nuclear medicine testing. A prespecified exploratory analysis was to investigate the impact of clinical and demographic factors on the 12-month eGFR. Prespecified exploratory outcomes of imaging biomarkers of MRI and cost-effectiveness of SABR compared with extirpative and ablative therapies are not included in this primary analysis because data are not yet mature.

Statistical analysis

The sample size of 70 patients was chosen to provide sufficiently narrow CIs for clinical outcomes. If up to 15% of participants dropped out before 1 year and assuming the freedom from local progression at 1 year was 90%, the corresponding two-sided 95% CI would be 79–96%. With 70 patients, this trial would have more than 80% power to reject the null hypothesis of an undesirable local control rate of 80% or less at 1 year if the true local control was 90% with 0·1 alpha and up to 15% of participants dropped out before 1 year. The Kaplan–Meier method was used to estimate time-to-event endpoints. Estimates are provided alongside 95% CIs derived using the log–log transformation. A one-sided test was used to generate the p value, but two-sided 95% CIs are reported. Median follow-up was estimated using the reverse Kaplan–Meier method. Withdrawal of consent, loss to follow-up, and close out dates were censoring events for all Kaplan–Meier analysis. Death due to any cause was a censoring event for local failure and distant failure. Non-cancer-related deaths were censoring events for cancer-specific survival. The maximum toxicity grade per patient of each adverse event and treatment relatedness were tabulated.

Change over time in renal function was described using linear mixed models with time as a fixed effect and patients as a random effect. A prespecified exploratory analysis of the impact of clinical and demographic factors on the 12-month eGFR was assessed using a linear model. The following variables were considered: RENAL nephrometry score, radiotherapy dose to ipsilateral kidney, age, hypertension, diabetes, baseline eGFR, tumour size, BMI, and smoking status. All variables were included in the multivariable model. All statistical

For the **RENAL score** see https://www.mdcalc.com/calc/3908/renal-nephrometry-score

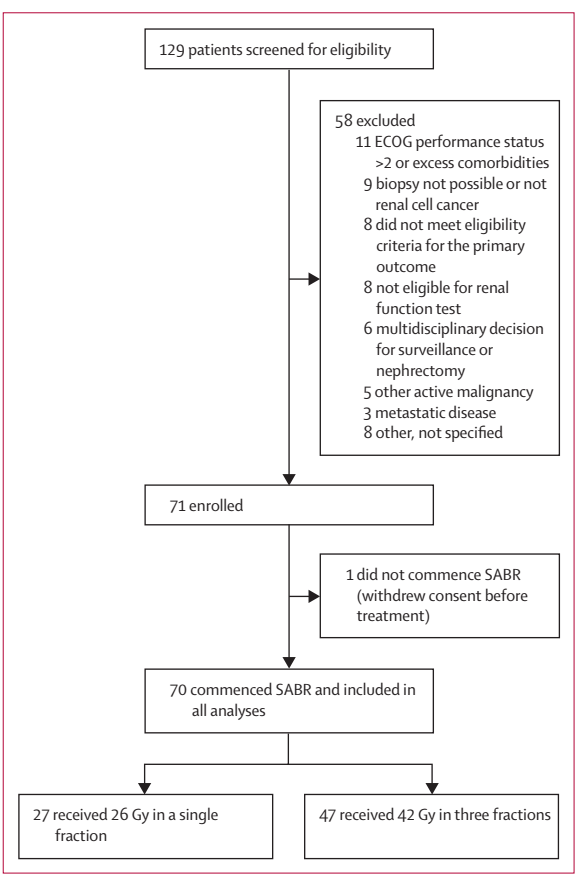


Figure 2: **Trial profile**
ECOG=Eastern Cooperative Oncolgy Group. SABR=stereotactic ablative body radiotherapy.

	Single-fraction 26 Gy group (n=23)	Three-fraction 42 Gy group (n=47)
Age, years	73 (66–80)	78 (71–82)
Sex		
Male	14 (61%)	35 (74%)
Female	9 (39%)	12 (26%)
ECOG performance status		
0	7 (30%)	19 (40%)
1	9 (39%)	22 (47%)
2	7 (30%)	6 (13%)
Tumour location		
Left	12 (52%)	19 (40%)
Right	11 (48%)	28 (60%)
Tumour maximal dimension, cm	3·3 (3·0–3·6)	5·3 (4·6–6·0)
Tumour volume, mL	16 (11–19)	58 (42–88)
RENAL score	7 (6–8)	9 (8–10)
RENAL complexity group		
Low	4 (17%)	17 (36%)
Moderate	9 (39%)	4 (9%)
High	10 (43%)	26 (55%)
Charlson comorbidity index	6 (5–6)	8 (6–9)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. SABR=stereotactic ablative radiotherapy.

Table 1: **Baseline patient characteristics, displayed per SABR treatment**

analyses were performed in R (version 4.3.1) and were prespecified in the protocol and statistical analysis plan. The analysis population for primary and all secondary endpoints was all patients who commenced trial treatment. This study was prospectively registered with ClinicalTrials.gov, NCT02613819.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between July 28, 2016, and Feb 27, 2020, 129 patients were screened, 71 patients were enrolled, and 70 patients commenced trial treatment (one patient withdrew consent before treatment; figure 2; appendix p 3). The analysis cutoff date was Aug 16, 2023, and included all primary and secondary outcomes of the protocol. Before enrolment, 49 (70%) of 70 patients had documented serial growth on initial surveillance imaging. 49 (70%) were male. Median tumour size was 4·6 cm (IQR 3·7–5·5). Median age was 77 years (IQR 70–82), median BMI was 32 kg/m² (27–38), and the median Charlson comorbidity index was 7 (5–8). The median RENAL score was 8 (IQR 4–11). Baseline comorbidities included hypertension in 56 (80%) patients, diabetes in 31 (44%) patients, and ischaemic heart disease in 27 (39%) patients. Smoking status was missing for one (1%) patient, eight (11%) were current smokers, and 34 (49%) were past smokers. ECOG performance status was 0 in 26 (37%), 1 in 31 (44%), and 2 in 13 (19%) patients. 24 (34%) patients had T1a disease, 39 (56%) had T1b disease, six (9%) had T2a disease, and one (1%) with T3a disease. One (1%) patient had nodal involvement (N1). Patient histology was clear cell (49 [70%] patients), papillary (12 [17%]), chromophobe (three [4%]), oncocytic carcinoma (one [1%]), and renal cell cancer not otherwise specified (five [7%]). Table 1 describes the baseline patient characteristics by SABR treatment.

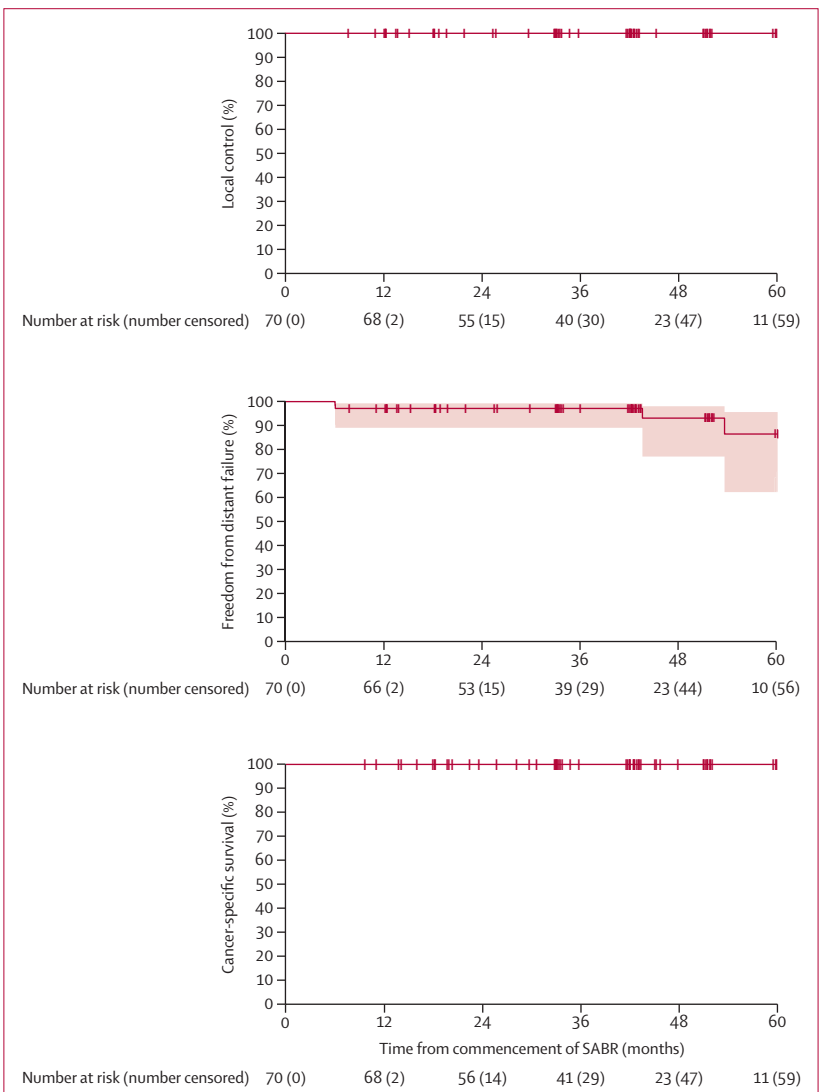


Figure 3: **Kaplan–Meier curves for local control (A), freedom from distant failure (B), and cancer-specific survival (C)**
Shaded areas represent 95% CIs. SABR=stereotactic ablative body radiotherapy.

Site benchmarking across eight sites resulted in 96% protocol compliance at initial submission, and 99% compliance after final review if resubmission was required (appendix pp 5–6). At pre-treatment central review, 2119 protocol compliance variables were assessed (about 30 per patient). At initial review, nine major protocol violations were noted for seven (10%) of the 70 patients, and in total nine (13%) patient cases were resubmitted after reviewer feedback (appendix pp 7–9). Three (4%) further patient cases were resubmitted based on recommendations on dose optimisation (n=2) and motion management (n=1). After resubmission, the number of patients with major variations was reduced to three (4%). Treatment was delivered as planned in 67 (96%) patients, with replanning required in one patient (adaptive replanning after the first fraction due to change in bowel position), and treatment interrupted in two patients due to intratumoural haemorrhage and tumour bleeding. All patients were treated on conventional linear accelerators; technical treatment characteristics are supplied in the appendix (pp 10–11). Post-treatment metrics review of dose, number of fractions, imaging schedule, and timing of radiotherapy demonstrated 95% compliance across 345 variables, and no major protocol variations were noted (appendix pp 12–13, and planned dose metrics provided in the appendix p 4).

The median follow-up was 43 months (IQR 38–60). For the primary endpoint assessment, local control at 12 months from treatment commencement was 100% (p<0·0001; figure 3A). There were no local failures observed during the trial. Cancer-specific survival was

also 100%. Freedom from distant failure at 12 months and 36 months from treatment commencement was 97% (95% CI 89–99; figure 3B). Overall survival was 99% (95% CI 90–100) at 12 months and 82% (70–89) at 36 months from treatment commencement (figure 3C).

Baseline mean eGFR was 61·1 mL/min per 1·73 m² (95% CI 56·5 to 65·6) and changed by –10·8 mL/min per 1·73 m² (–13·1 to –8·5) at 12 months from treatment commencement, by –14·6 mL/min per 1·73 m² (–17·1 to –12·1) at 24 months from treatment commencement, and plateaued thereafter (figure 4A; appendix p 14). The 24-month estimate for eGFR was 46·5 mL/min per 1·73 m² (95% CI 41·8 to 51·1). Split function for the ipsilateral kidney at baseline was 50% (95% CI 47 to 53; appendix p 15). The split function estimate was 36% (95% CI 33 to 39) at 12 months from treatment commencement and 33% (30 to 37) at 24 months from treatment commencement for the ipsilateral kidney. Again, a plateau was noted from 24 months onwards. In a prespecified multivariable analysis of predictors of renal function at 12 months, only baseline eGFR had an association with subsequent decline, with an average reduction of 8·4 mL/min per 1·73 m² at 12 months per 10 mL/min per 1·73 m² lower baseline eGFR (p<0·0001; appendix p 16). One patient underwent dialysis. The patient had a 5·9 cm central tumour, with a baseline eGFR of 34 mL/min per 1·73 m² and 12-month eGFR of 19 mL/min per 1·73 m², and at 18 months required dialysis with an eGFR of 7 mL/min per 1·73 m². Tumour size changes are depicted in the appendix (p 17).

Seven (10%) of 70 patients sustained one or more grade 3 treatment-related adverse events (table 2). Grade 3 adverse events that were designated possibly, probably, or definitely related to treatment were nausea and vomiting (three [4%] patients), abdominal, flank, or tumour pain (four [6%]), colonic obstruction (two [3%]), and diarrhoea (one [1%]). 52 (74%) patients had a grade 1–2 treatment-related adverse event, and 11 (16%) patients did not report any treatment-related adverse events. No grade 4 treatment-related adverse events occurred, and no treatment-related or cancer-related deaths occurred.

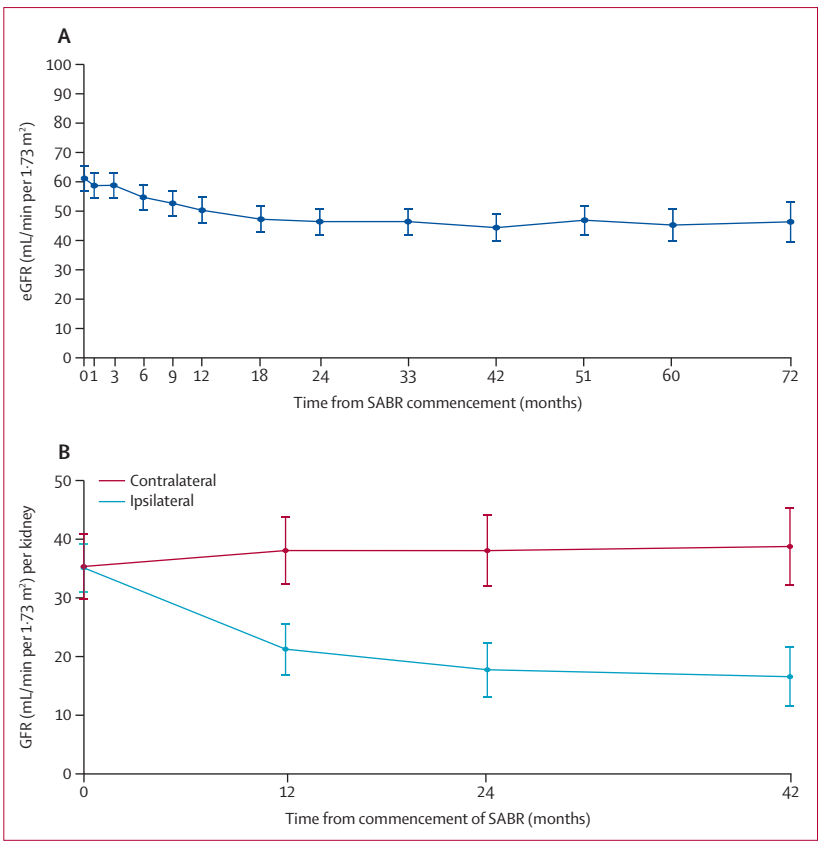


Figure 4: **Renal function outcomes**
(A) eGFR estimates (calculated with the Chronic Kidney Disease Epidemiology Collaboration equation) and 95% CIs from linear mixed model. (B) Absolute ipsilateral and contralateral kidney function, with 95% CIs derived using technetium-99m DMSA (2,3 dimercaptosuccinic acid) single photon emission CT or CT and GFR calculated with chromium-51 EDTA (edetic acid) nuclear medicine assessments. GFR=glomerular filtration rate. eGFR=estimated GFR.

Discussion

FASTRACK II, to our knowledge, is the only multicentre clinical trial of a curative non-surgical therapy for primary renal cell cancer. All participants had tumours that were inoperable and not suitable for active surveillance or watchful waiting. The majority of participants had cT1b or enlarging tumours on surveillance (median size 4·6 cm [IQR 3·7–5·5]), which were all confirmed by biopsy, and 70% had radiological enlargement on surveillance before enrolment, and patients had a life expectancy where cancer relapse and related mortality were a relevant concern. We observed a 100% rate of local control and cancer-specific survival during the trial. These findings are concordant with previous small single-centre clinical trials.[7–15] These trials observed local control rates ranging from 93% to 100%. Similarly, a recent multicentre individual patient data meta-analysis of 190 patients with a median tumour diameter of 4·0 cm (IQR 2·8–4·9) reported a cumulative incidence of local failure at 5 years of 5·5% (95% CI 2·8–9·5), and cancer-specific survival of 92·0% (85·2–95·8).[19] The observed toxicity profile in this study was clinically acceptable, with no treatment-related grade 4 adverse events or deaths observed. Grade 3 treatment-related adverse events occurred in seven (10%) patients, comprising mainly transient abdominal or flank pain (4%) or nausea and vomiting (4%). Prophylactic antiemetics or steroids were not mandated on study but should be considered.

Several cohort series of thermal ablation in primary renal cell cancer have been published. A systematic review of cohort series of thermal ablation in T1b tumours reported a primary successful ablation rate of 86%, and a grade 3 or worse Clavien–Dindo complication rate of 10%.[20] In context, 66% of the patients in FASTRACK II had T1b disease. The participants enrolled on this trial typically had primary renal cell tumours that

	Grade 1	Grade 2	Grade 3
Any adverse event*	34 (49%)	18 (26%)	7 (10%)
Vomiting	1 (1%)	0	2 (3%)
Abdominal pain	0	0	2 (3%)
Colonic obstruction	0	0	2 (3%)
Flank pain	22 (31%)	9 (13%	1 (1%)
Nausea	18	2 (3%)	1 (1%)
Diarrhoea	5	1 (1%)	1 (1%)
Tumour pain	0	0	1 (1%)
Elevated creatinine	0	2 (3%)	0
Fatigue	32 (46%)	11 (16%	0
Gastritis	6	1 (1%)	0
Colitis	0	1 (1%)	0
Thromboembolic event	0	1 (1%)	0
Dermatitis	5 (7%)	0	0
Haematuria	5 (7%)	0	0
Chest wall pain	2 (3%)	0	0
Duodenal ulcer	1 (1%)	0	0
Elevated C-reactive protein	1 (1%)	0	0
Fracture	1 (1%)	0	0

Data are n (%). Adverse events were graded according to Common Terminology Criteria for Adverse Events (version 4.03). No grade 4 treatment-related adverse events or deaths occurred. *Number of patients whose worst adverse event was grade 1, 2, or 3.

Table 2: **Adverse events related to treatment in 70 participants**

were larger (median diameter 4·6 cm) and more complex (median RENAL score 8) than can be expected to be effectively treated with thermal ablation approaches.[5,6,21] There were no observed differences in oncological outcomes between single-fraction and three-fraction SABR schedules; however, direct comparisons are not advisable because the fractionation schedules represented two different populations. Fractionation was selected based on size (≥T1b tumours were treated with three fractions, whereas single fraction treatments were reserved for the smaller T1a cohort).

The cohort enrolled in FASTRACK II had significant pre-existing chronic disease, with a baseline mean eGFR of 61·1 mL/min per 1·73 m². Comparisons to expected outcomes with surgical approaches are difficult; the burden of comorbidities in this non-surgical patient cohort are themselves known to contribute to worsening chronic kidney disease over time.[22] The decline in renal function in FASTRACK II plateaued after 2 years, indicating a reversion to the background rate of decline due to chronic kidney disease factors after an initial drop secondary to SABR, a pattern that has been previously observed.[19] Furthermore, some studies have shown lower preoperative eGFR association with poorer eGFR after partial or radical nephrectomy.[23,24] The randomised EORTC trial of partial nephrectomy versus radical nephrectomy enrolled patients with a median tumour size of 3·0 cm, of whom 91·9% had normal renal function at baseline. The mean eGFR (1 year after surgery) was 66·8 mL/min per 1·73 m² (95% CI 64·6–68·9) in the partial nephrectomy group and 52·7 mL/min per 1·73 m² (50·8–54·5) in the radical nephrectomy group, a difference of 14·1 mL/min per 1·73 m².[25] The baseline eGFR was not reported, but 93% of randomly assigned patients had baseline creatinine less than 1·25 times the upper limit of normal. Similarly, in a randomised trial of laparoscopic partial nephrectomy versus open partial nephrectomy in Brazil among patients with a median tumour size of 3·5 cm, the median baseline eGFR in the two groups was 85·2 mL/min per 1·73 m² versus 87·3 mL/min per 1·73 m² and dropped by 4·5 mL/min per 1·73 m² versus 9·7 mL/min per 1·73 m² by 1 year.[26] Five local recurrences and four distant recurrences were reported. 103 patients undergoing robotic partial nephrectomy in a multicentre prospective trial in Japan showed a lower baseline eGFR of 73·2 mL/min per 1·73 m² compared with the EORTC and Brazilian studies, and observed a mean drop of GFR of 10 mL/min per 1·73 m² at 1 year, with a mean tumour diameter of 2·7 cm.[27] 5-year relapse-free survival was 92·8% (95% CI 85·5–96·5).[27] In the context of worse baseline renal function (mean eGFR 61·1 mL/min per 1·73 m²) and larger tumours (median 4·6 cm) compared with the previously mentioned surgical trials, the observed mean decline in eGFR of 10·8 mL/min per 1·73 m² at 1 year in TROG 15.03 FASTRACK II is similar to the expected decline with partial nephrectomy. Similarly, we report only a single patient undergoing dialysis at 18 months after treatment, who had a 5·9 cm centrally located tumour and a baseline eGFR of 34 mL/min per 1·73 m². In a large multicentre cohort study of patients in the Canadian Kidney Cancer information system, the incidence of post-surgery dialysis or chronic kidney disease stage 5 with partial nephrectomy was 0·6% in patients with stage 1–2 chronic kidney disease at baseline and 2·2% in patients with baseline stage 3 chronic kidney disease.[23] We also observed an increase in the contralateral kidney function in the trial cohort, presumably as a compensatory response to SABR. This observation needs further validation in future studies.

The primary objective of this study was met, and there were no local treatment failures observed by the cutoff date. These exceptional cancer control rates could be partially attributed to the rigorous conduct of trial quality assurance procedures. For example, post-hoc analysis of the TROG 02.02 phase 3 trial showed a 20% overall survival impact from high-quality radiotherapy delivery.[28] Similarly, the PROCLAIM phase 3 trial study showed that sites enrolling multiple patients with radiotherapy protocol violations had a lower median overall survival (21·1 months [95% CI 16·0–26·8] *vs* 29·8 months [24·7–32·9]).[29] In the current trial, all patients underwent real-time case peer review of treatment volumes, and dosimetric plan review to monitor adherence to the protocol. Furthermore, the dose and fractionation schedules were selected based on

putative radiobiological equivalence from the two common human renal cell carcinoma cell lines, Caki-1 and A498. The trial prescription methodology mandated optimal target coverage while respecting surrounding organ tolerance (99% of volume to receive the prescription dose). The protocol dose constraints can be found in the appendix; inclusive of a recommended modification to the original protocol to include a 3 mm planning organ at risk volume expansion on hollow organ viscus. Notably, no recommendation was made to contour or constrain for the renal pelvis, vessels, or proximal ureter. To date, RECIST remain the most robust method of assessing progression following radiotherapy. Post-treatment tumour responses evolve over years, and, in contrast to ablative therapy, persistent enhancement following radiotherapy is common and not correlated with risk of subsequent progression in renal cell cancer.

The limitations of this study should be recognised. In comparison to prospective trials of surgery, FASTRACK II has a smaller sample size and less mature follow-up. The study did not have a control group, so it was not possible to assess whether SABR is superior, inferior, or similar to other treatment options. Definitions of operability or technically high risk might vary between multidisciplinary teams. The excellent oncological outcomes after SABR for primary renal cell cancer observed with this multicentre clinical trial are concordant with those reported in the prospective and retrospective literature.[30] Given the absence of other potentially curative options for inoperable patients with larger tumours or a location not amenable to thermal ablation, SABR can be considered a proven modality. Furthermore, given the increasing incidence of renal cell cancer, the non-invasive nature of SABR and demonstrated efficacy, we propose that the findings of FASTRACK II should be considered for escalation to a randomised controlled trial of surgery versus SABR as the primary treatment modality in operable patients. In the future, the aim would be to determine the optimal individualised treatment approach as part of a collaborative decision-making process involving patients.

Contributors

SS and DP were responsible for conceptualisation of the study. SS, DP, MB, MSH, and RDA developed the methodology. SS supervised the projects executions and acquired funding. RD, RM, NH, MH, and TK conducted validation and quality assurance assessments. MSi, SS, BV, JR, FF, BH, CL, AR, MSh, PM, DM, L-MW, NL, SW, NB, JM, and DP provided resources including recruitment of patients, collection of data, and project administration at their sites. RD and RM were responsible for overall project administration. SS, DP, and MB prepared the initial draft of the manuscript. SS and MB verified the data. All authors had full access to all data in the study, reviewed the final manuscript and take responsibility for the decision to submit the study for publication.

Declaration of interests

SS declares salary support from Cancer Council Victoria via the Colebatch Fellowship; grants or contracts from Varian, Bayer Pharmaceuticals, and Merck Sharp Dohme; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from AstraZeneca, Varian, and Roche Pharmaceuticals; a leadership or fiduciary role on the American Society of Radiation Oncology Science Council, Advanced Radiotherapy Techniques committee of the International Association for the Study of Lung Cancer, and Board of Directors of the Radiosurgery Society during the past 36 months. NH declares research grant funding from Varian to the institution for the current study; research funding from RefleXion; and consulting fees from SeeTreat Medical during the past 36 months. MSH declares research grants or contracts from Prostate Cancer Foundation, National Health and Medical Research Council (Australia), Movember, US Department of Defence, Medical Research Future Fund (Australia), Bayer, th ePeter MacCallum Foundation, Isotopia, and the Australian Nuclear Science and Technology Organisation; consulting fees from Merck Sharp & Dohme and Novartis; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Janssen, Novartis, AstraZeneca, and Astellas; a leadership or fiduciary role with Australian Friends of Sheba; and other financial or non-financial interests in the Peter MacCallum Cancer Centre and the University of Melbourne during the past 36 months. RDL declares research grant funding from Varian to the institution for the current study. TK declares support to attend meetings or travel from Chioda company to attend the International Workshop on Ionising Radiation Monitoring, Japan, as an invited speaker; and a leadership or fiduciary role on the board of Medical Physics for World Benefits during the past 36 months. All other authors declare no competing interests.

Data sharing

The data generated from this study will not be uploaded to a public repository due to privacy and consent restrictions. De-identified data will be made available to researchers on reasonable request to the corresponding author, subject to a data sharing agreement.

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