



@\_ShankarSiva

# SABR for Primary RCC



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# DISCLOSURES

- Research Funding to Institution
  - Varian Industries
  - Merck-Sharp-Dohme
  - Bayer Pharmaceuticals
- Speaker Honoraria / Advisory Board
  - Astra Zeneca
  - Telix Pharmaceuticals
- AI images
  - Mid-Journey™

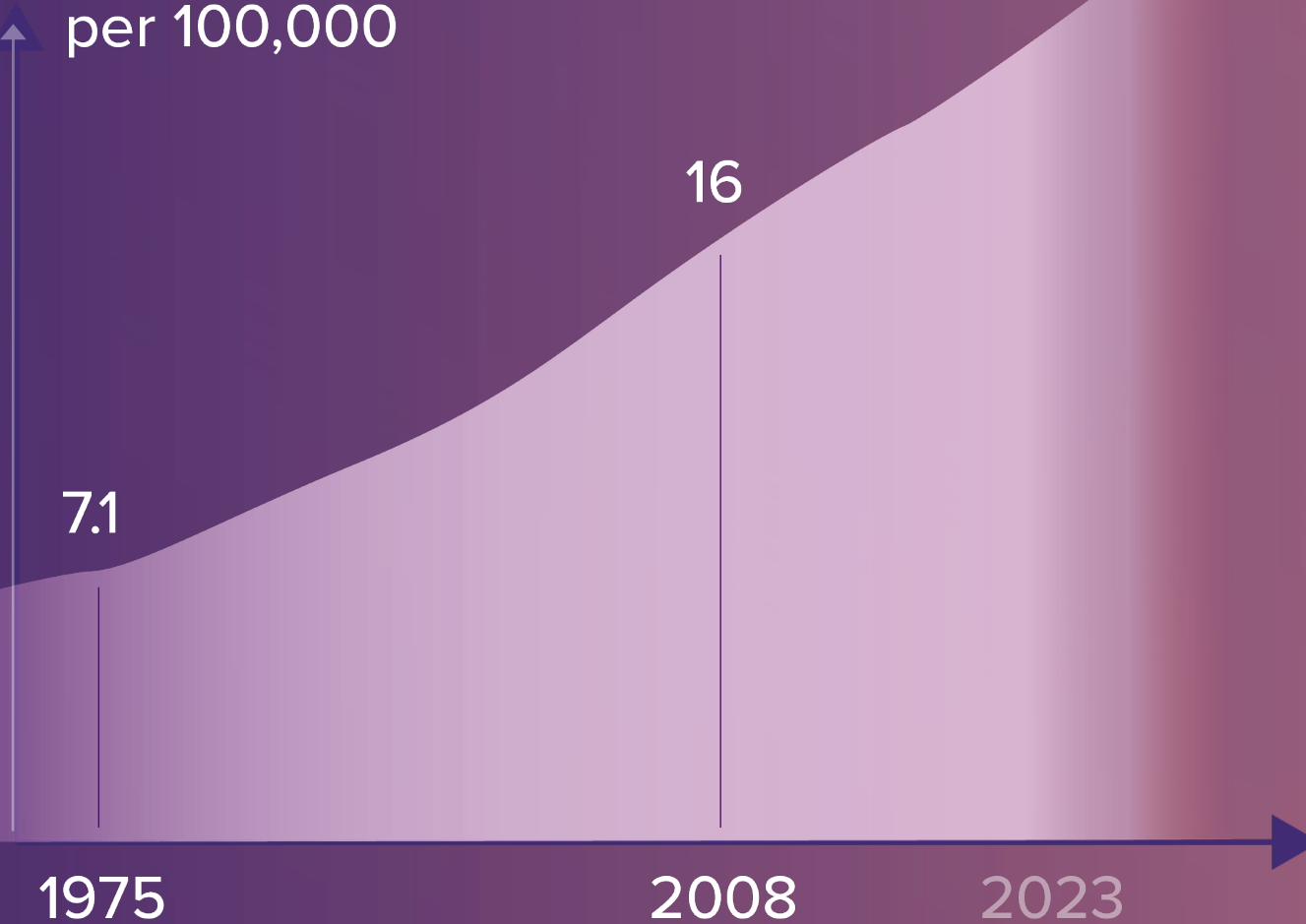


# BACKGROUND: Worldwide increase of RCC



Incidence of  
kidney cancer  
per 100,000

Most rapidly increasing in >70s age group<sup>1</sup>

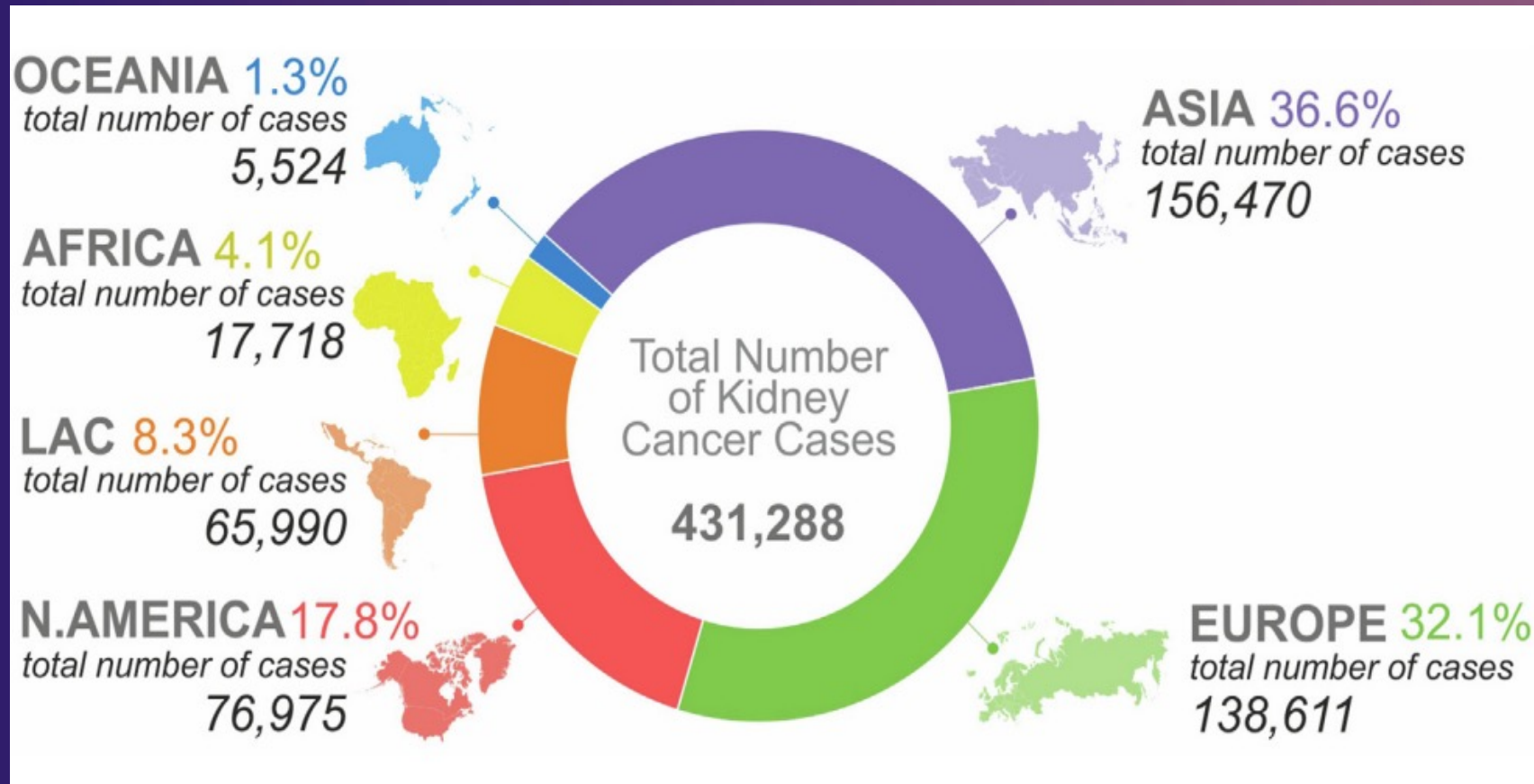


1. Hsieh, J et al. Nat Rev Dis Pri. 2017 Mar 9;3:17009.

# BACKGROUND: Worldwide increase of RCC

Incidence increasing in **N. America, Europe, Asia**<sup>1</sup>

Elderly patients at **greater risk of cancer-specific mortality** (up to 3.8-fold)<sup>2</sup>



1. Bukavina, L et al. *Eur Urol.* 2022. In Press; 2. Sun, M et al. *Eur Urol.* 2011;60:1152-9.

# The Current Standard of Care

**Surgery is the standard of care (ideally nephron sparing).**

**There are limited curative options inoperable patients**



Partial Nephrectomy



# Standard of Care: (Partial) Nephrectomy



Surgery

Avoids general anaesthetic

Peri-hilar tumours

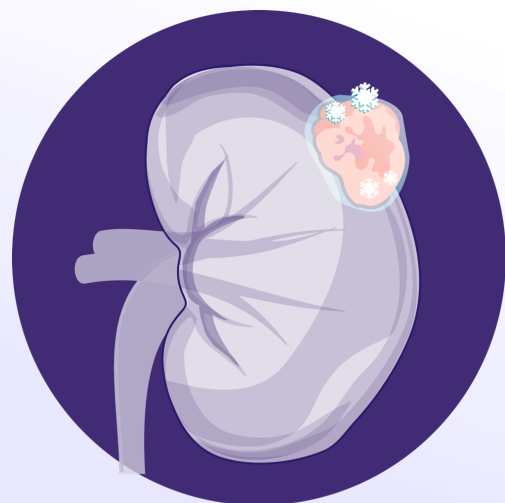
Large tumours

Non-invasive





# Thermal ablation



cryoablation

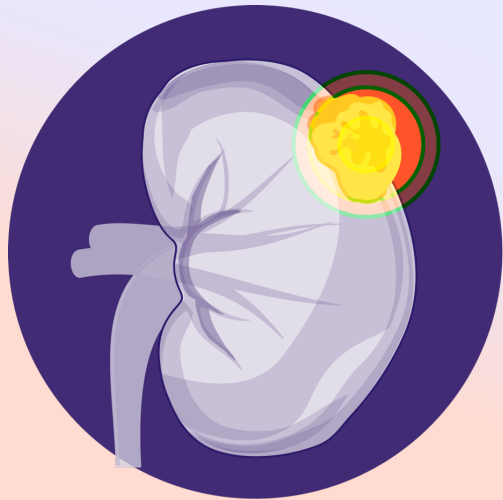
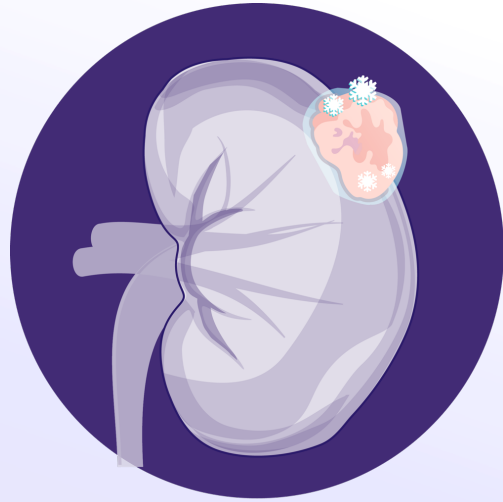


Radiofrequency ablation  
(RFA) or Microwave  
ablation (MWA)

Thermal ablation is an alternative intervention, but is limited by:

- reduced efficacy when  $>3-3.5\text{cm}$
- increased complications for large masses
- a general anaesthetic is often required for cryotherapy

# Cryotherapy, Microwave, Radiofrequency Ablation



Thermal  
ablation

Avoids general  
anaesthetic

Peri-hilar tumours

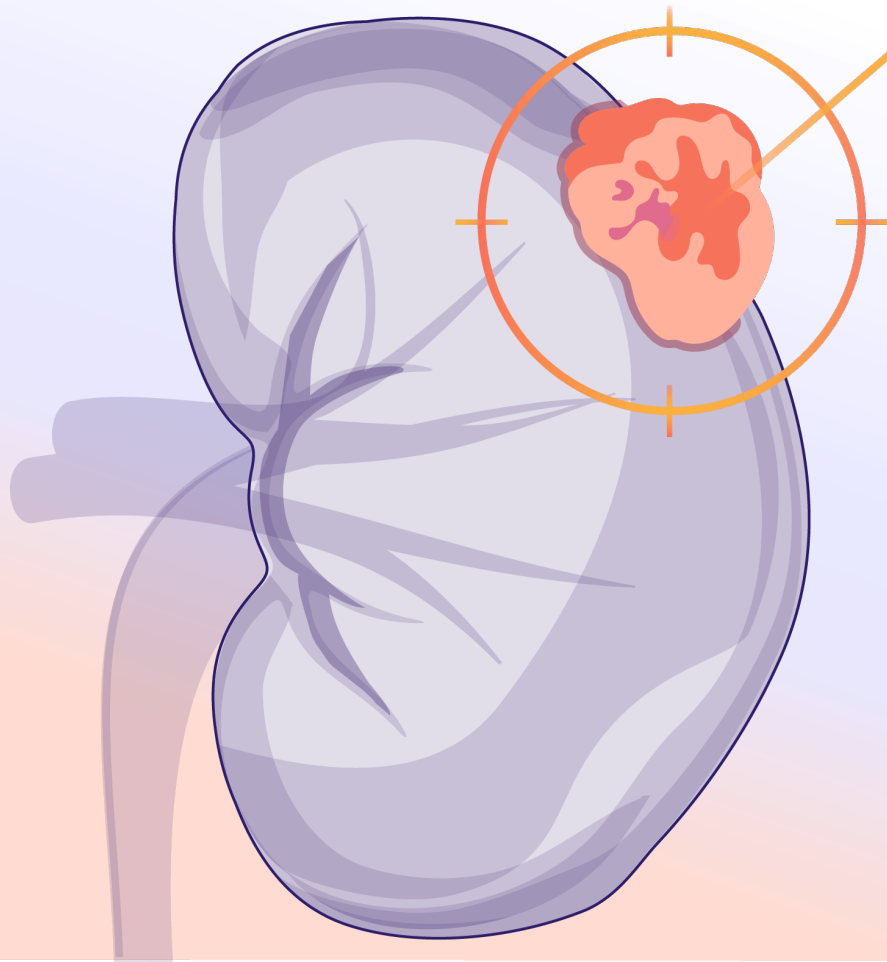
Large tumours

Non-invasive





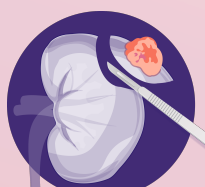




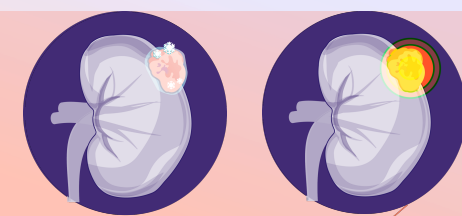




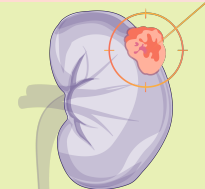




# A new option: SABR



**SABR**

**is an emerging  
non-invasive treatment  
option for patients  
unsuitable for surgery.**

# SABR as an alternative may tick all the boxes

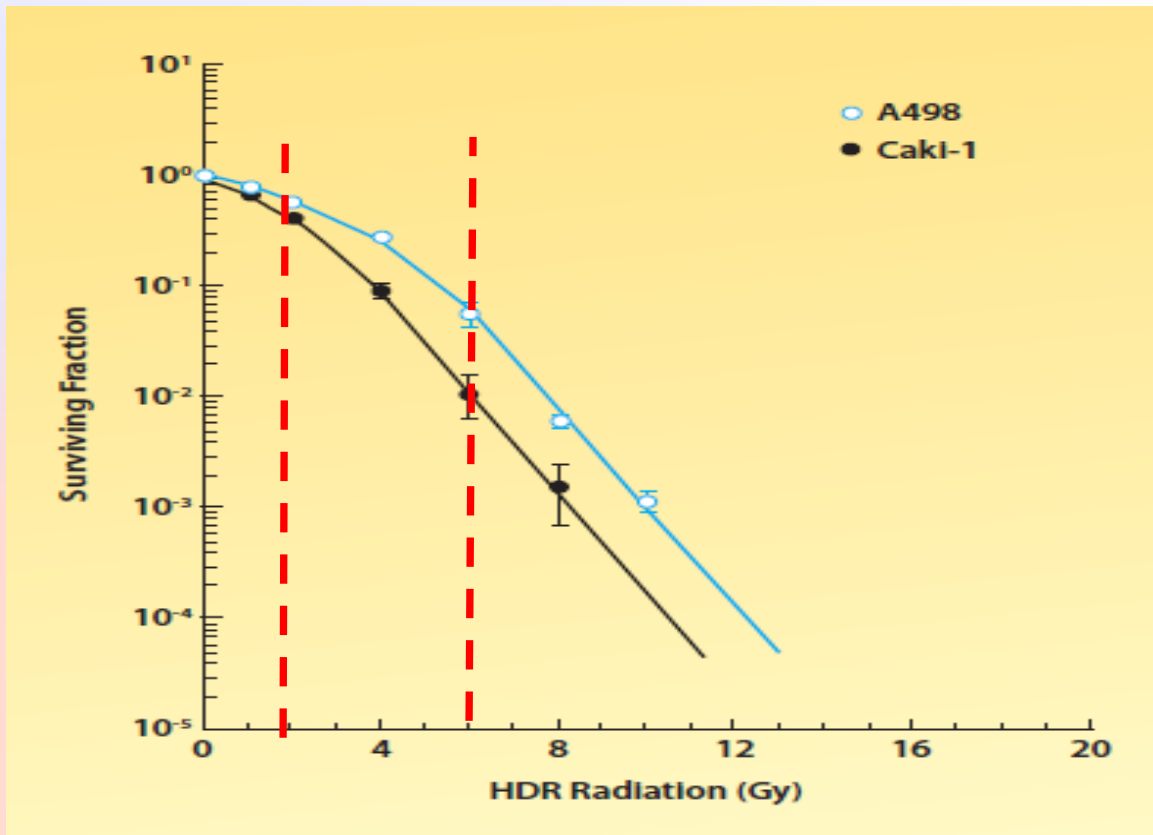
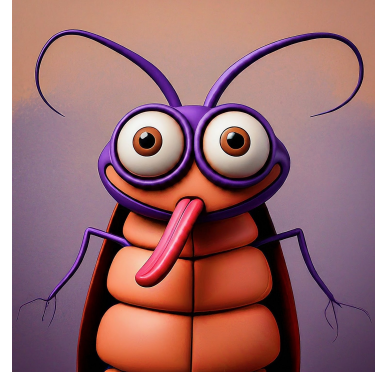
	Avoids general anaesthetic	Peri-hilar tumours	Large tumours	Non-invasive
 Surgery				
 Thermal ablation				
 SABR				

... but is RCC radioresistant?



# ... but is RCC radioresistant?

- Considered resistant to conventional RT
- Stanford – clonogenic assay with 2 clones

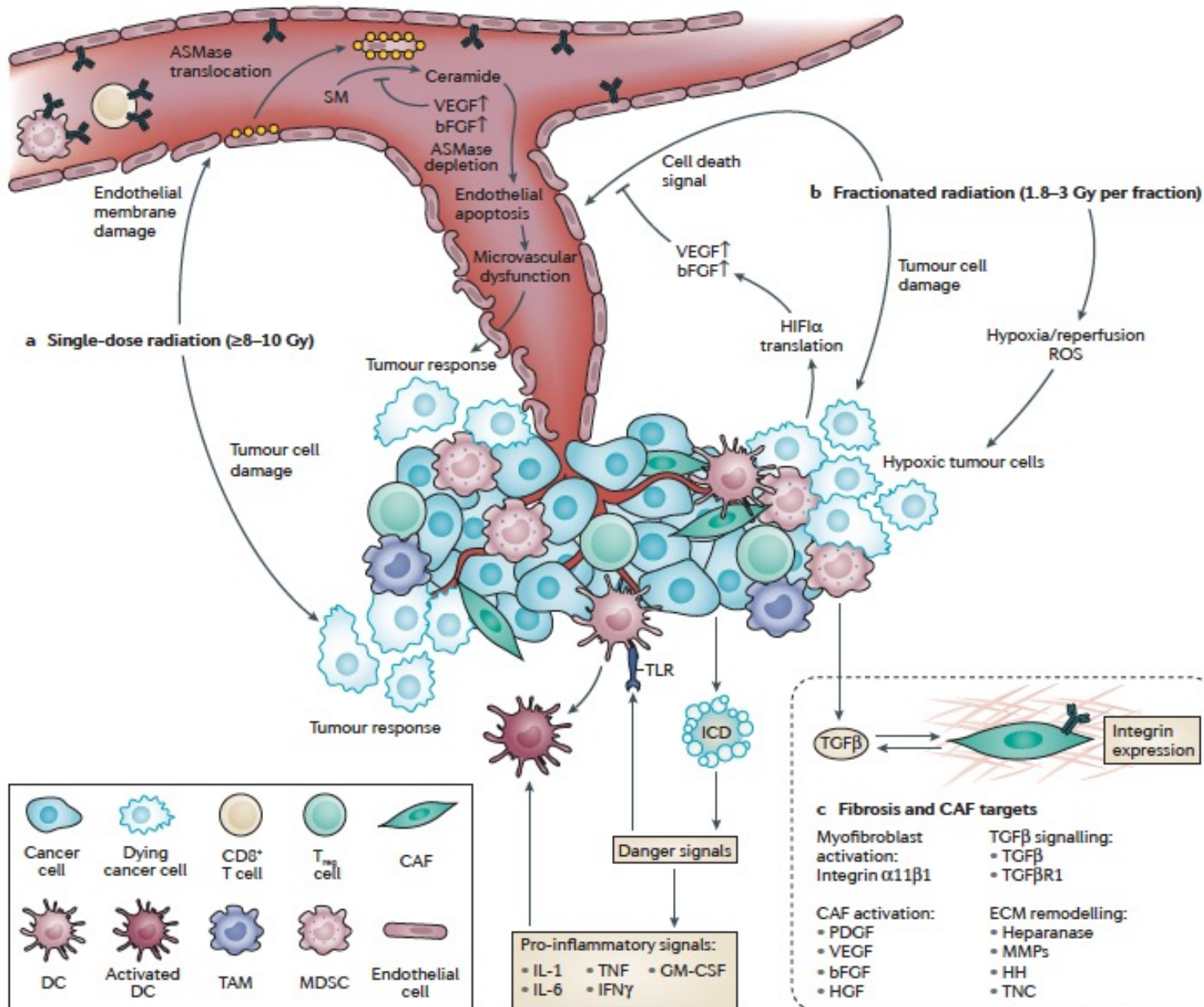


- Small fraction cell kill at doses of 2Gy
- Logarithmic cell kill at doses  $> 6$  Gy



# Different Mechanism of cell kill with high-dose radiation (SABR)

- endothelial apoptosis
- ceramide / sphingomyelinase induced cell death
- pro-inflammatory signalling for adaptive immunity





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# FASTRACK II

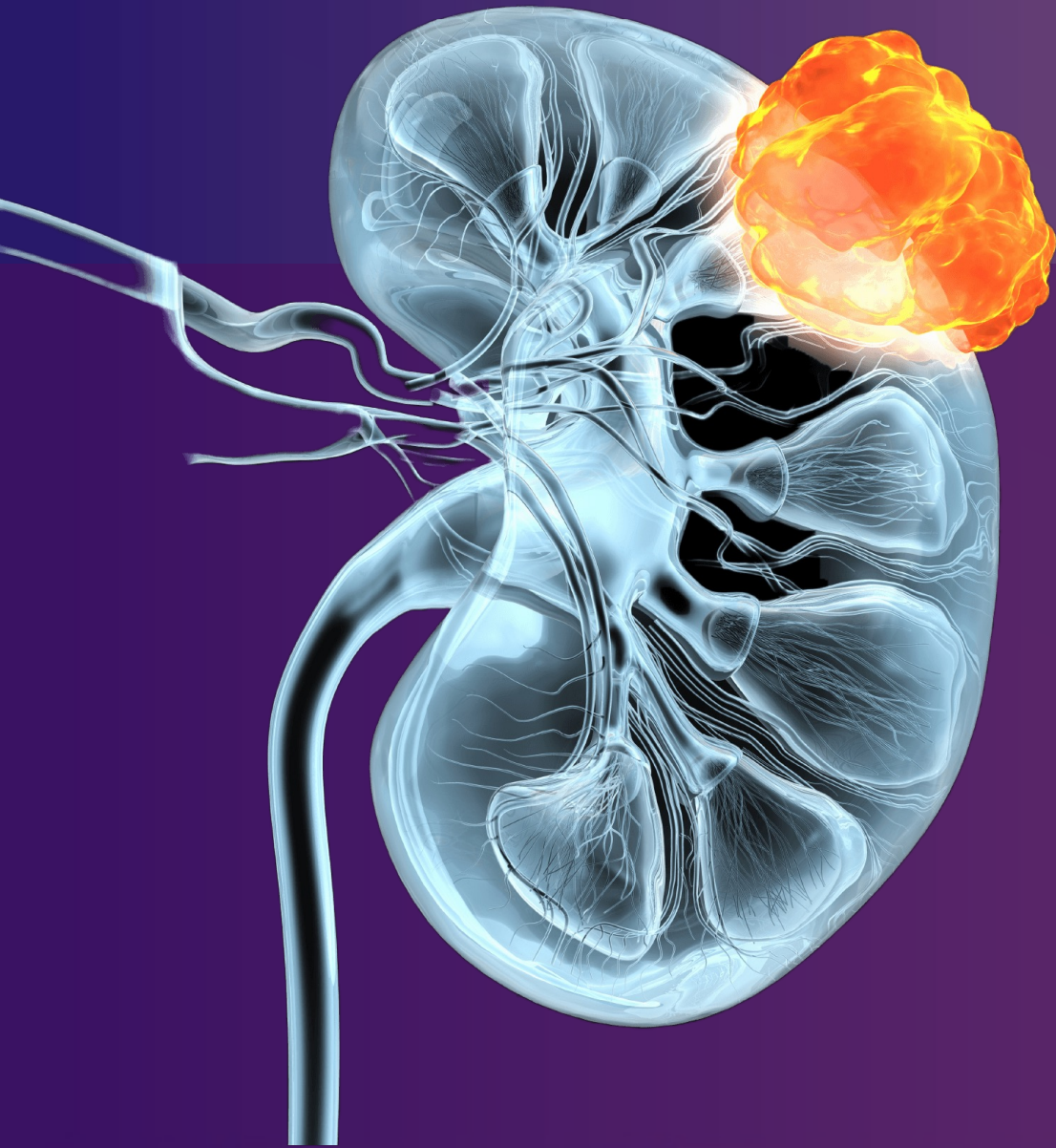
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## TRIAL

Focal Ablative Stereotactic  
Radiotherapy for Cancers of the Kidney

*Shankar Siva, Peter MacCallum Cancer Centre*





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# FASTRACK II

TRIAL

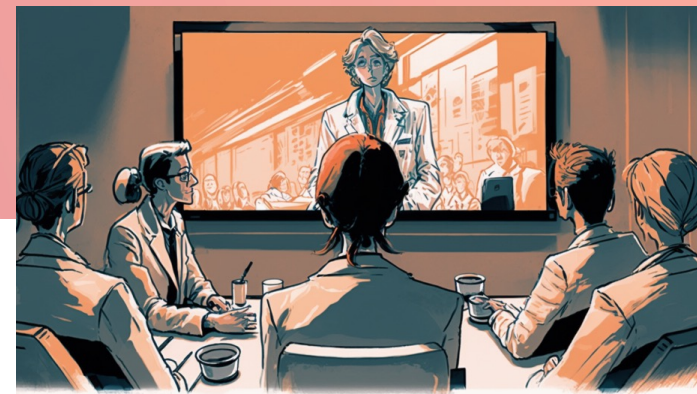
METHODS:

*First multicentre phase II  
trial of non-surgical  
therapy for primary RCC*

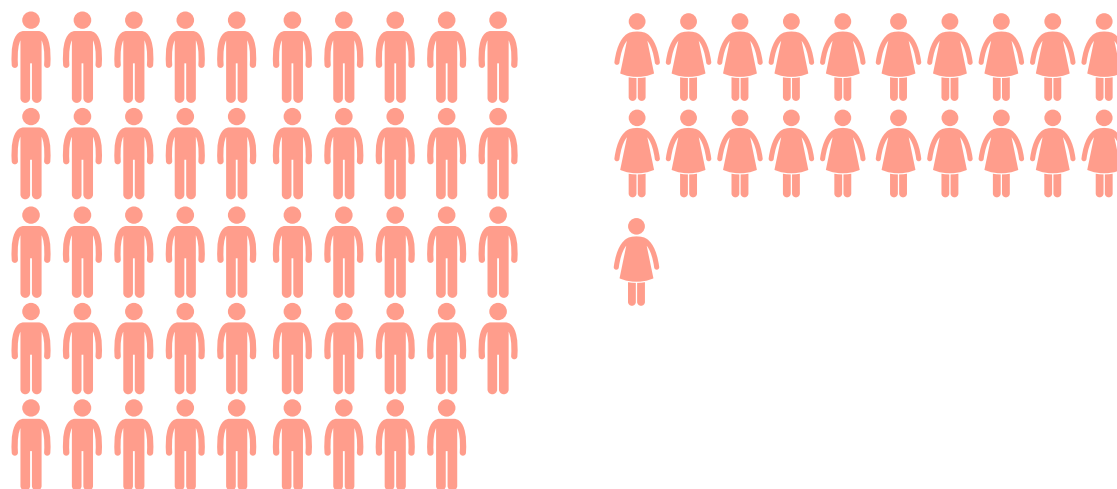
TROG 15.03

# FASTRACK II TRIAL

## TROG/ANZUP collaboration



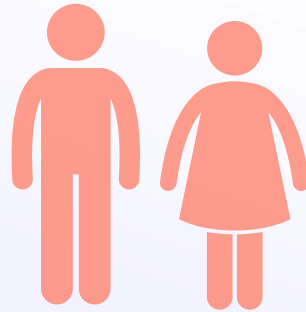
**70 patients**  
Recruited between  
Jul. 2016 and Feb. 2020





## Key Eligibility and Patient Characteristics

- Biopsy-confirmed RCC with a single lesion in kidney
- Medically inoperable or high-risk for surgery
- Multidisciplinary decision that active treatment is warranted
- eGFR > 30mls/min
- *Tumour not abutting bowel*
- *Tumour maximum size not larger than 10cm*

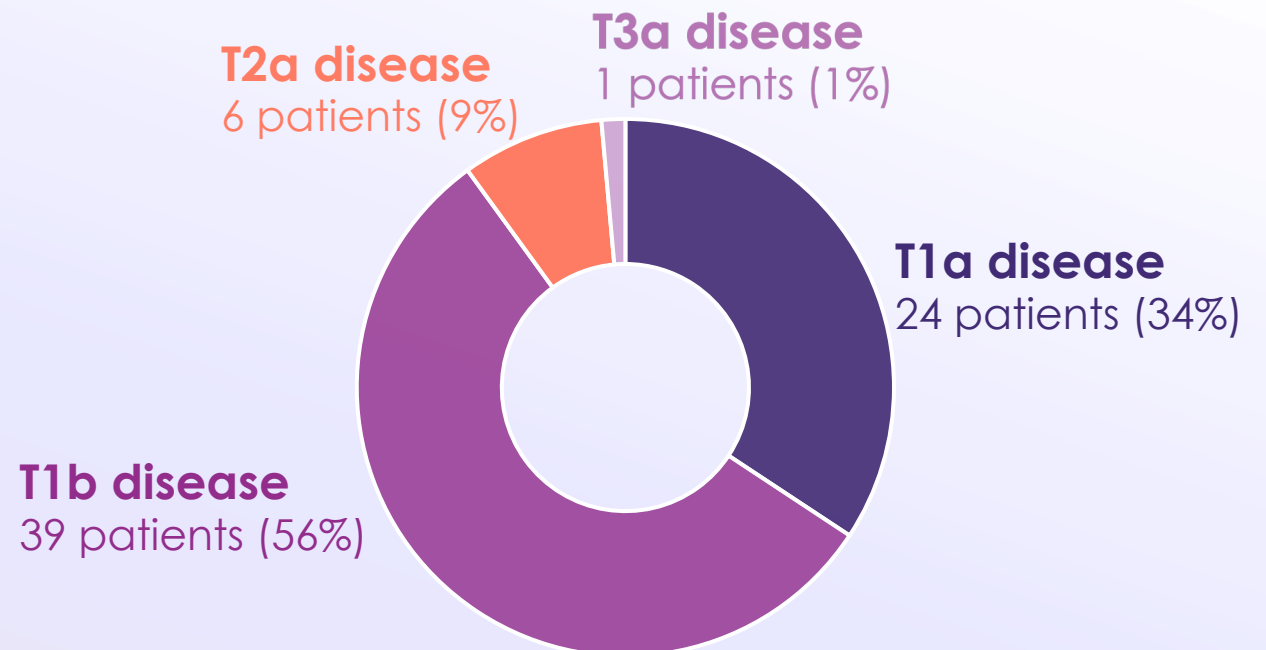


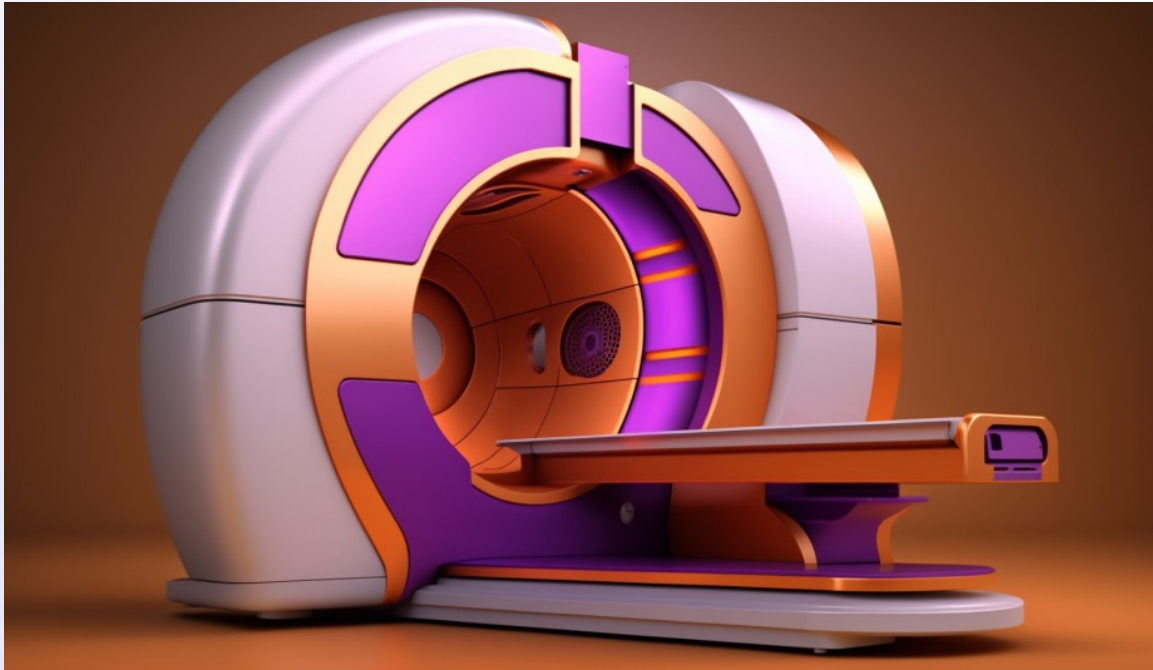
Median age: **77 years**

BMI: **32 kg/m<sup>2</sup>**

Charlson comorbidity index: **7**

Serial growth after initial surveillance: **70%**





**Single fraction  
(26Gy)**

for tumours  $\leq 4$  cm



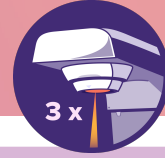
**3 fractions  
(42Gy)**

for tumours  $> 4$  cm

### Prescription methodology:

- ITV to PTV = 5 mm isotropic expansion
- 99% of the PTV to be covered by 100% of the dose ( $D_{99PTV} = 100\%$ )
- peak dose ( $D_{Max}$ ) between 125-143%

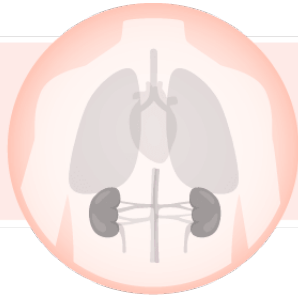
# Baseline Characteristics



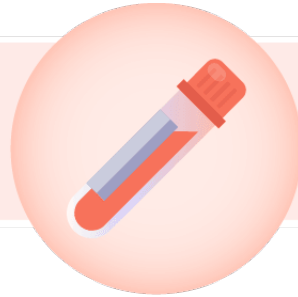
Treatment characteristic	26GY/1# (n = 23)	42GY/3# (n = 47)	Total (n = 70)
<b>Age, years</b>			
Median [range]	<b>73</b> [47 - 87]	<b>78</b> [57 - 91]	<b>77</b> [47 - 91]
<b>Gender, n (%)</b>			
Male	<b>14</b> (61%)	<b>35</b> (74%)	<b>49</b> (70%)
Female	<b>9</b> (39%)	<b>12</b> (26%)	<b>21</b> (30%)
<b>Tumour location, n (%)</b>			
Left	<b>12</b> (52%)	<b>19</b> (40%)	<b>31</b> (44%)
Right	<b>11</b> (48%)	<b>28</b> (60%)	<b>39</b> (56%)
<b>Tumour maximal dimension, mm</b>			
Median [range]	<b>33</b> [15 - 39]	<b>53</b> [40 - 89]	<b>46</b> [15 - 89]
<b>R.E.N.A.L. complexity score</b>			
Median [range]	<b>7</b> [4 - 10]	<b>9</b> [5 - 11]	<b>8</b> [4 - 11]
<b>ECOG, n (%)</b>			
0	<b>7</b> (30%)	<b>19</b> (40%)	<b>26</b> (37%)
1	<b>9</b> (39%)	<b>22</b> (47%)	<b>31</b> (44%)
2	<b>7</b> (30%)	<b>6</b> (13%)	<b>13</b> (19%)
<b>Charlson comorbidity index</b>			
Median [range]	<b>6</b> [3 - 12]	<b>8</b> [3 - 12]	<b>7</b> [3 - 12]

## Schedule of Assessments over 5 years

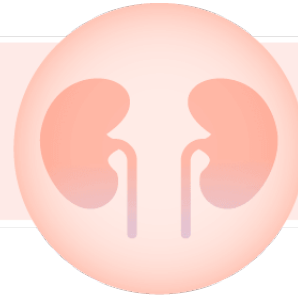
### Assessment



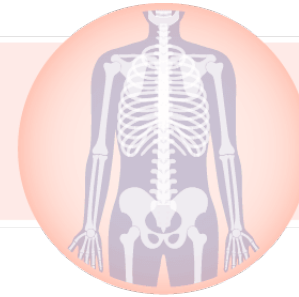
CT (Thorax, Abdomen)



eGFR (CKD-EPI)



Split renal function test & calculated GFR



Whole body bone scan



Assessment	CT (Thorax, Abdomen)	eGFR (CKD-EPI)	Split renal function test & calculated GFR	Whole body bone scan
Baseline	✓	✓	✓	✓
Year 1	At 6, 9 & 12 months	3 monthly	Annually	
Year 2	6 monthly	6 monthly		
...until Year 5	9 monthly	9 monthly		
5+ years	Annually	Annually		
At progression	✓	✓	✓	✓

Data cut-off:  
18 / 08 / 2023

## Radiotherapy Quality Assurance Program



### Site benchmarking activity

- **95.9%** compliance at initial submission
- **99.4%** compliance after resubmission

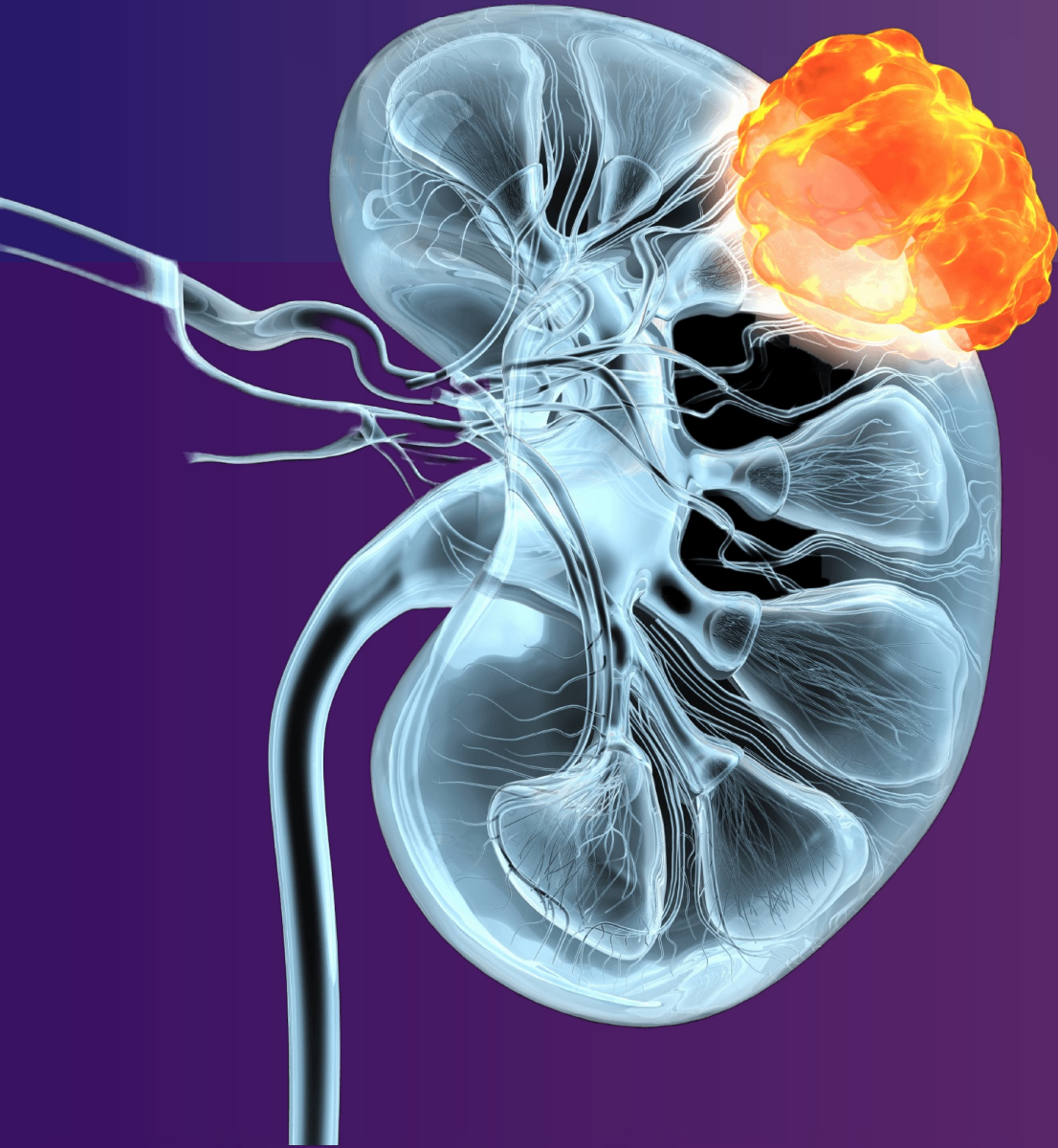
- **Pre-treatment real-time QA:**  
2119 compliance variables  
assessed (~30 per patient)
- **At initial review:**  
9 major protocol violations noted  
in 7 cases (10.0%)
- **After resubmission:**  
number of cases with major  
variations reduced to 3 (4.3%)

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# FASTRACK II

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TRIAL

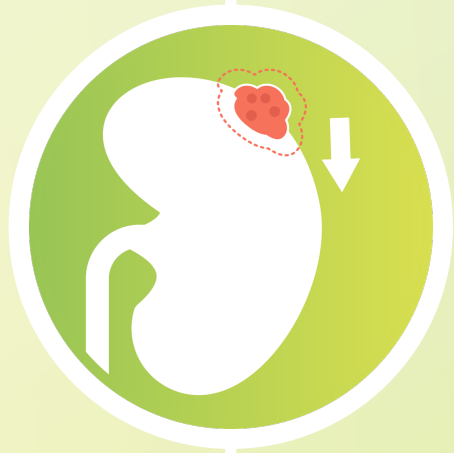


## Clinical Outcomes

at a median follow-up of **43 months**

## Clinical outcomes

at a median follow-up of 43 months



### Local control rate

# 100%



Freedom from distant failure

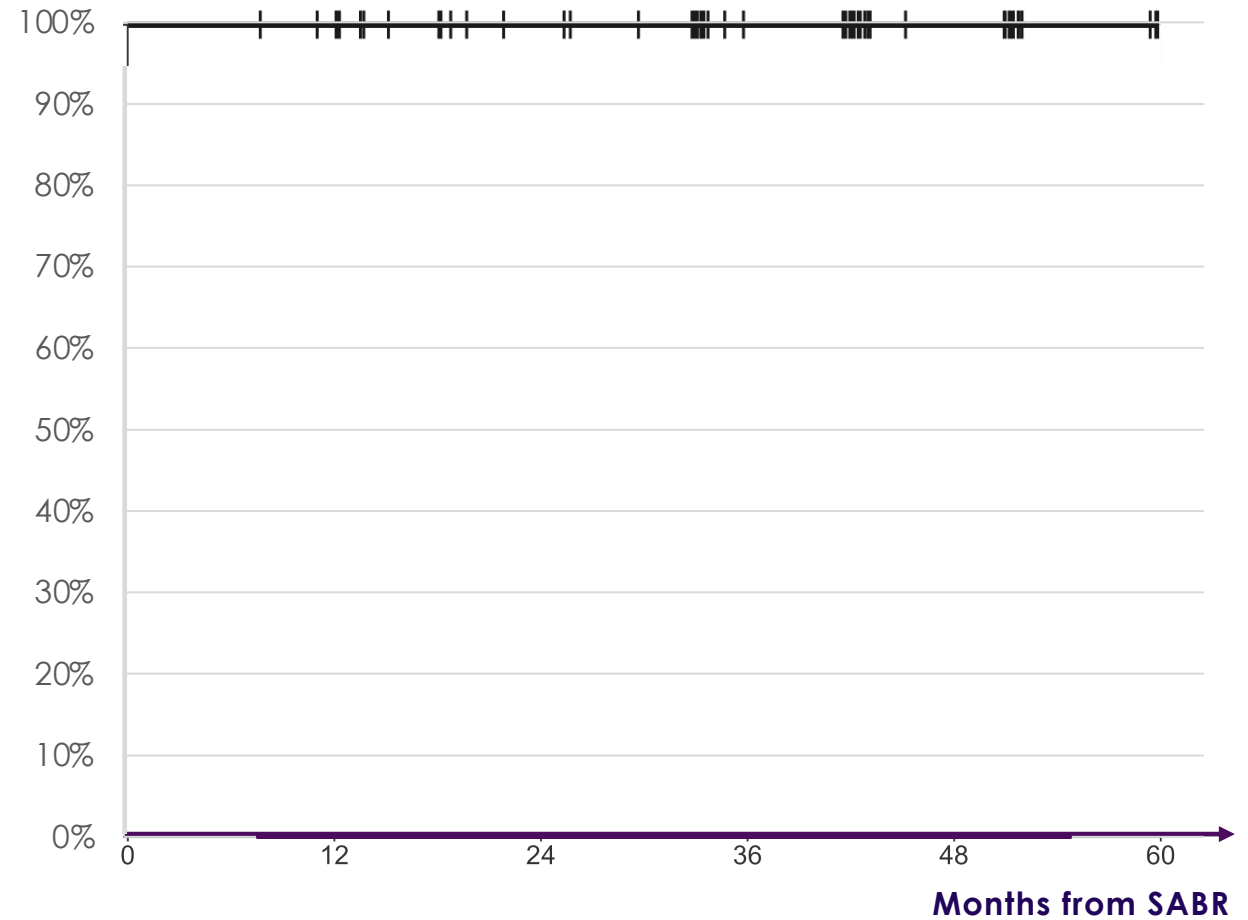


Cancer specific survival



Kidney function loss

### Local Control rate (RECIST criteria)



## Clinical outcomes

at a median follow-up of 43 months



Local control rate



Freedom from distant failure at 3 yrs **97%**

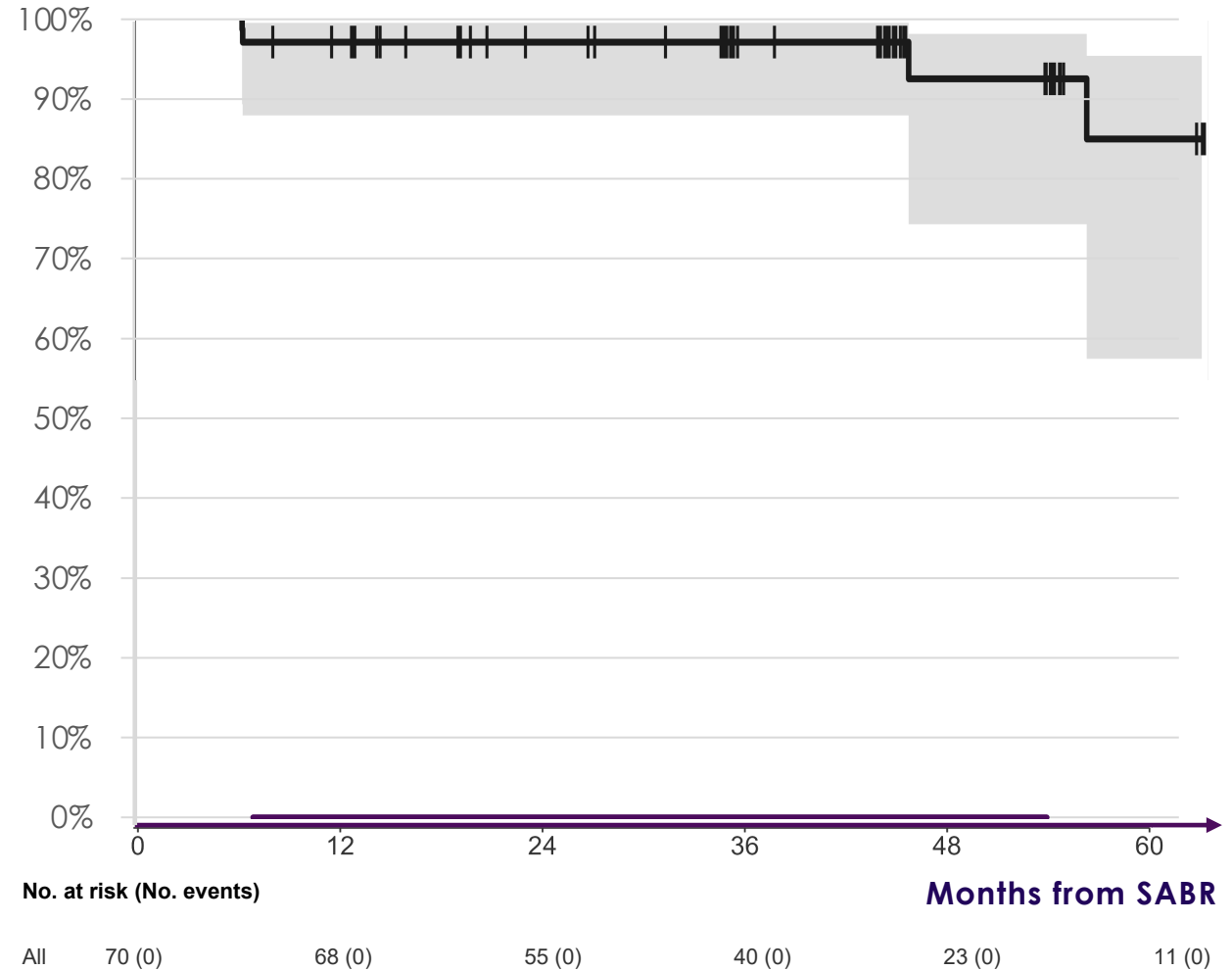


Cancer specific survival



Kidney function loss

### Freedom from distant failure





## Clinical outcomes

at a median follow-up of 43 months



Local control rate



Freedom from distant failure



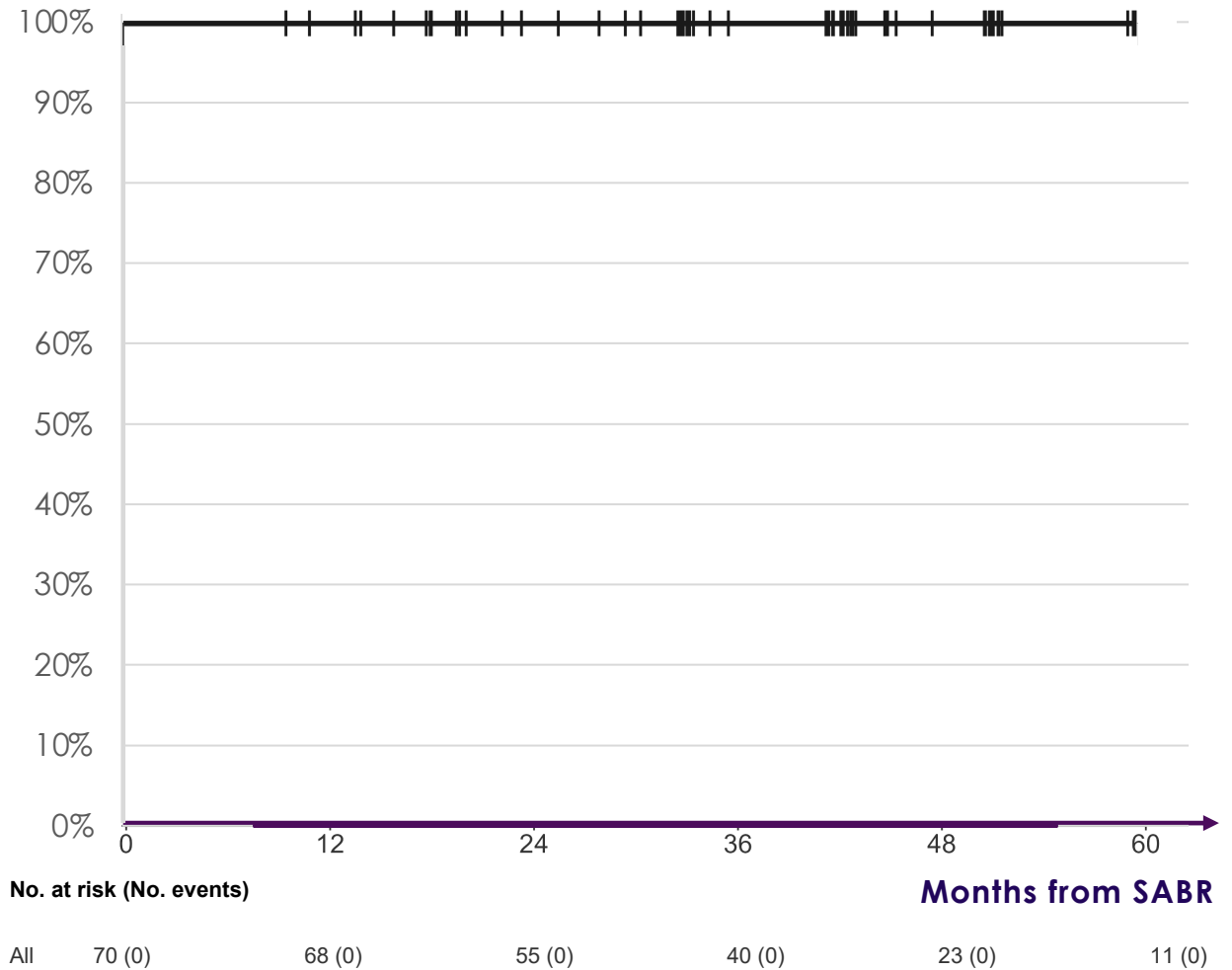
### Cancer specific survival

# 100%



Kidney function loss

### Cancer specific survival



## Clinical outcomes

at a median follow-up of 43 months



Local  
control rate



Freedom from  
distant failure



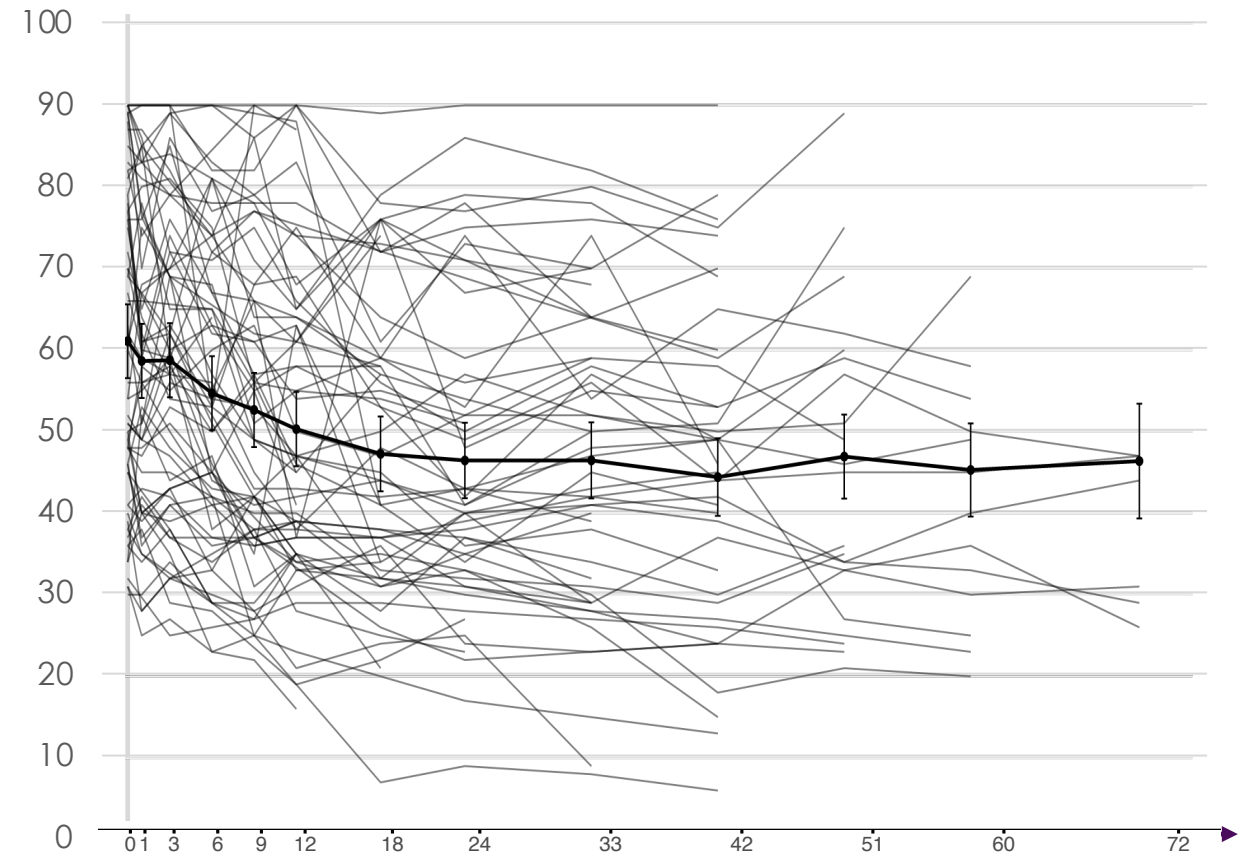
Cancer specific  
survival



**Kidney  
function loss**  
**-14.6** mls/min

One patient underwent  
dialysis; 59mm central  
tumour and baseline eGFR  
of 34mls/min.

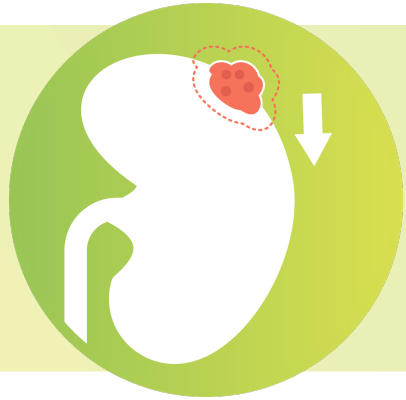
### eGFR, mLs/min (CDK-EPI)



Months from treatment commencement

## Clinical outcomes

at a median follow-up of 43 months



Local control rate

**100%**



Freedom from distant failure

**97%**



Cancer specific survival

**100%**



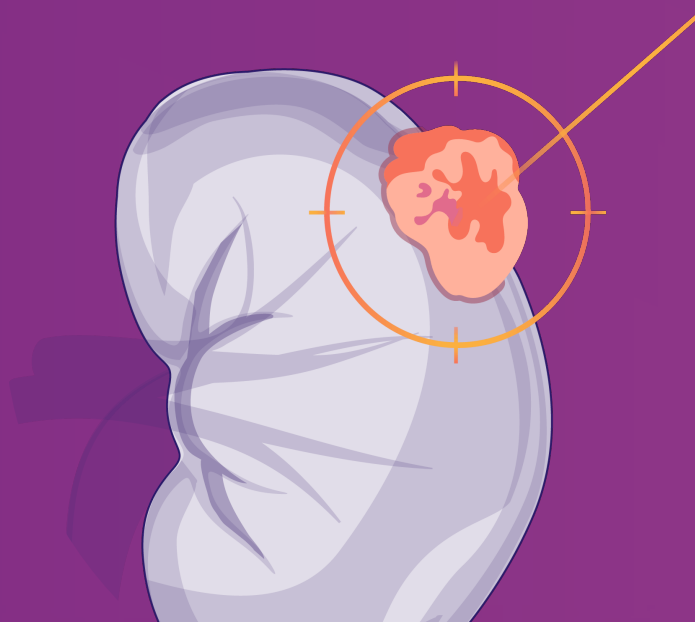
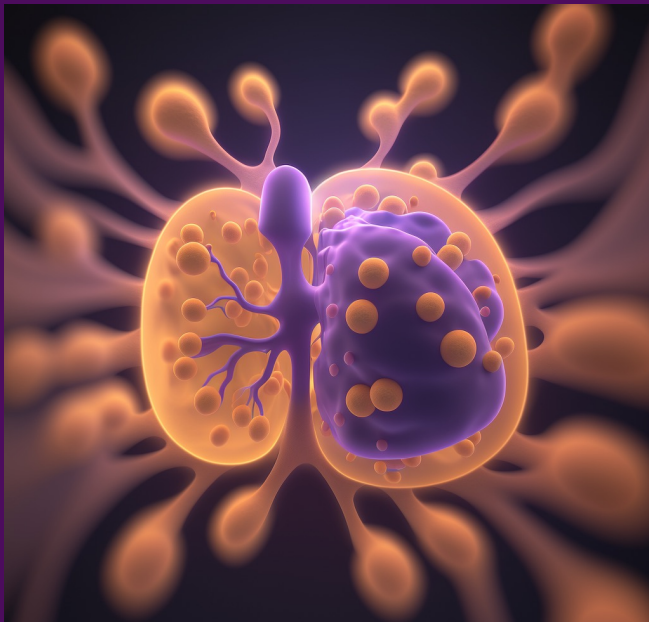
Kidney function loss  
(1 patient underwent dialysis)

**-14.6** mls/min

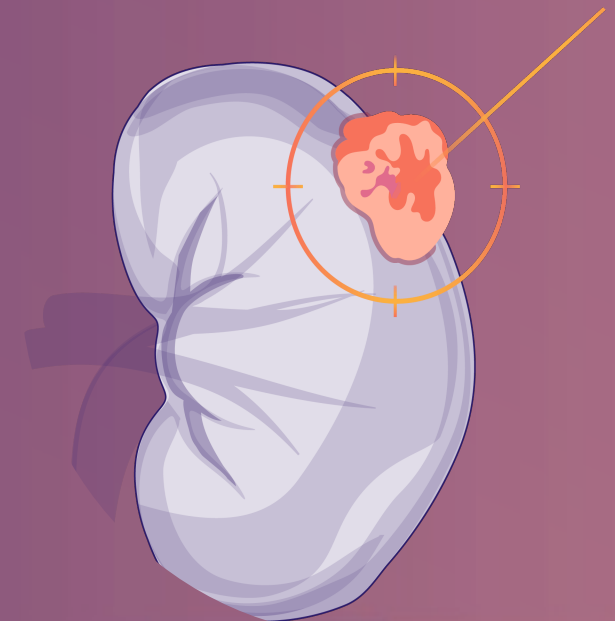
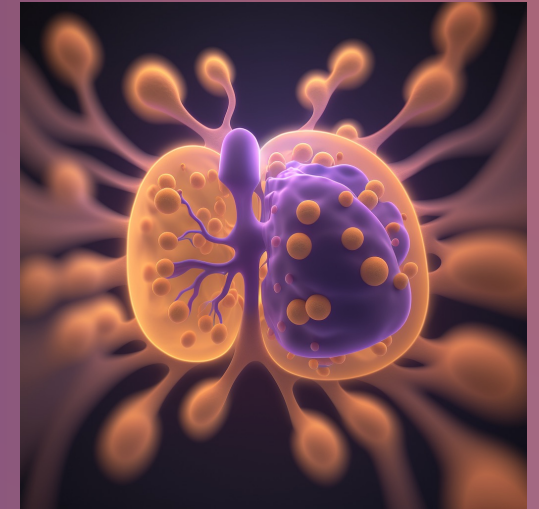
TROG 15.03 FASTRACK II is the first multicentre trial of a definitive non-surgical therapy for primary RCC.

Median tumour size of 4.6cm larger than that of EORTC [3.0cm] and Brazilian [3.5cm] randomized trials of RN vs PN.

Observed excellent efficacy is likely attributable to potent biological dose and rigorous quality control.



- Despite larger median size [4.6cm] than RCTs of surgery, renal function loss is comparable to PN
- No G4/G5 tox, but G3 SABR tox in n=7 (10%)
  - Mainly transient pain (3%) or N&V (4%).
  - Prophylactic antiemetics or steroids were not mandated but should be considered.
- Tumours were larger and more complex than could be reasonably treated with Thermal Ablation.

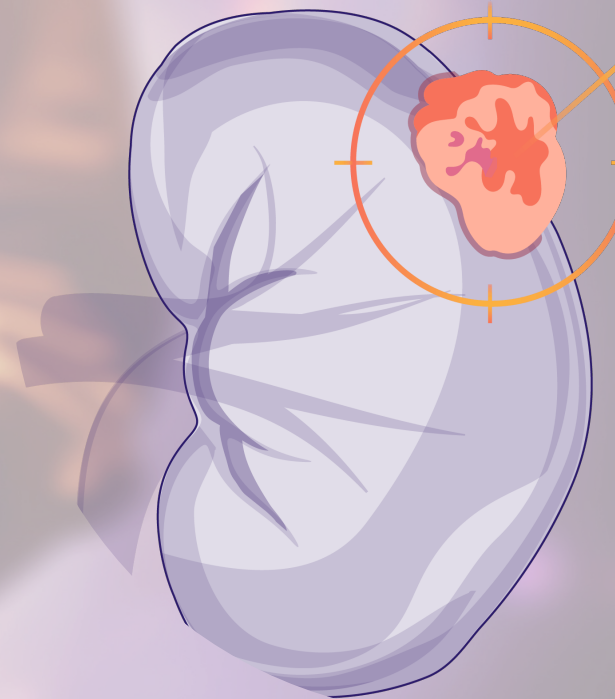


## Conclusions



# SABR is effective in primary RCC.

- Exceptional cancer control rates
- No cancer-related deaths
- Modest side effect profile and renal function decline after treatment



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# FASTRACK II TRIAL



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

Shankar Siva, Mathias Bressel, Mark Sidhom, Swetha Sridharan, Ben G L Vanneste, Ryan Davey, Rebecca Montgomery, Jeremy Ruben, Farshad Foroudi, Braden Higgs, Charles Lin, Avi Raman, Nicholas Hardcastle, Michael S Hofman, Richard De Abreu Lourenco, Mark Shaw, Pascal Mancuso, Daniel Moon, Lih-Ming Wong, Nathan Lawrentschuk, Simon Wood, Nicholas R Brook, Tomas Kron, Jarad Martin, David Pryor, together with the FASTRACK II Investigator Group\*



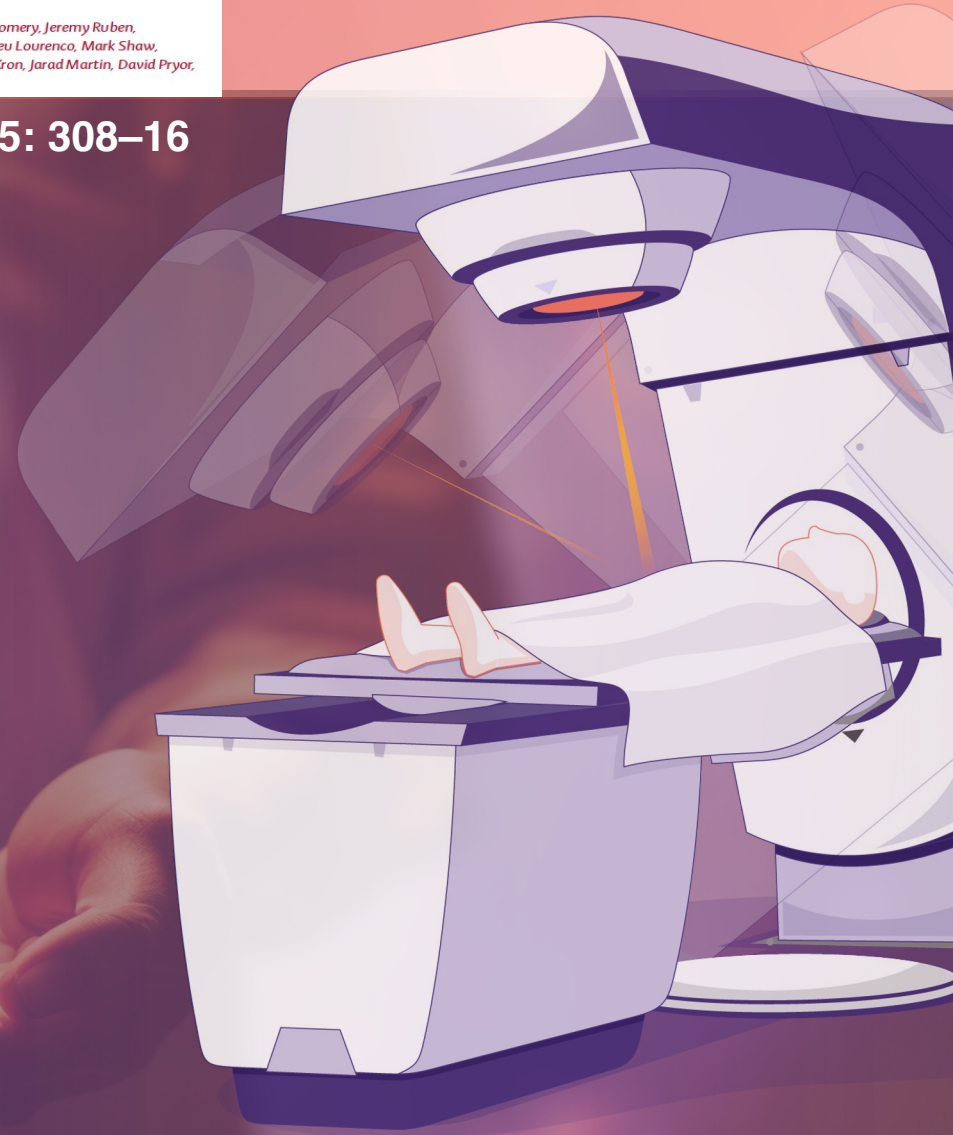
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*Lancet Oncol* 2024; 25: 308–16



**SABR is a new standard of care for primary kidney cancer not suited to surgery.**

These outcomes support the design of a future randomised clinical trial of SABR versus surgery for primary RCC.



**Background**  
The incidence of Renal Cell Carcinoma (RCC) has been steadily increasing worldwide, particularly in the age group over 70.

**Surgery** has been the standard treatment. However, for patients medically inoperable due to advanced age or comorbidities, there are limited curative treatment options.

**Thermal ablation** is an alternative intervention for small tumours (physically < 3cm), but it has limited efficacy and increased complications for larger masses.

**Stereotactic Ablative Body Radiotherapy (SABR)** is an emerging non-invasive treatment option for patients who are unsuitable for surgery.

Treatment	Local control	Freedom from distant failure	Cancer specific survival	Kidney function loss
Surgery	✓	✓	✓	✗
Thermal ablation	✓	✗	✗	✗
SABR	✓	✓	✓	✓

**The trial**

**70 patients** of median age 77 years were recruited between Jul. 2016 and Feb. 2020. (49 men / 21 women)

5 centres in the Netherlands, 7 centres in Australia. Intergroup collaborative trial TROG/ANZUP.

**Inclusion criteria:**

- Biopsy confirmed diagnosis of primary RCC with a single lesion within a kidney
- ECOG performance < 2
- Medically inoperable or high-risk for surgery

**Median tumour size (range): 4.6cm (3.7-5.8)**

- Single fraction (20Gy)** for tumours < 4 cm. Median size (SD): 3.2cm (1.3-5.4) (23 patients)
- 3 fractions (42Gy)** for tumours > 4 cm. Median size (SD): 5.3cm (4.4-6.0) (47 patients)

**Assessment:** CT (Thorax, Abdomen), sGFR (CKD-EPI), Split renal function test & calculated GFR, Whole body bone scan.

Timepoint	CT (Thorax, Abdomen)	sGFR (CKD-EPI)	Split renal function test & calculated GFR	Whole body bone scan
Baseline	✓	✓	✓	✓
Year 1	At 6, 9 & 12 months	3 monthly	✓	✓
Year 2	6 monthly	6 monthly	✓	✓
Year 5	9 monthly	9 monthly	Annually	✓
5+ years	Annually	Annually	✓	✓
At progression	✓	✓	✓	✓

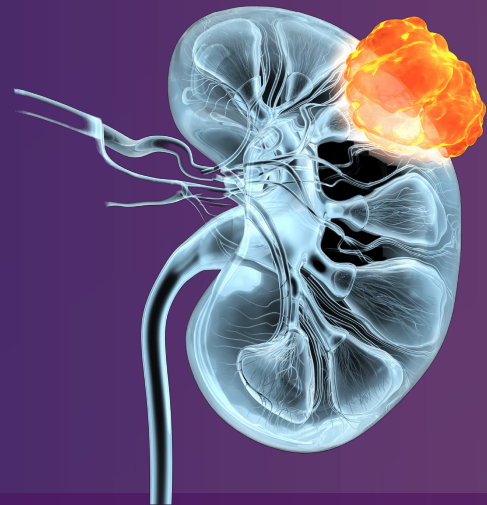
**Data cut-off: 18/08/2023**

**Clinical outcomes at a median follow-up of 43 months**

**SABR treatment was effective for all patients.** We observed exceptional cancer control rates, no cancer-related deaths, and an acceptable side-effect profile and renal function after treatment.

- Local control rate **100%**
- Freedom from distant failure **99%**
- Cancer specific survival **100%**
- Kidney function loss (a single patient underwent dialysis) **-14.6 ml/min**

**Interpretation**  
SABR is a new standard of care for primary kidney cancer not suited to surgery. These outcomes support the design of a future randomised clinical trial of SABR versus surgery for primary RCC.



# TROG 15.03 FASTRACK II TRIAL

Thank you



Trial Management Committee: David Pryor, Jeremy Ruben, Farshad Foroudi, Braden Higgs, Nathan Lawrentschuk, Mathias Bressel, Alex Car, Swetha Sridharan, Mark Sidhom, Ben Vanneste (MAASTRO)

Physics: Tomas Kron, Nick Hardcastle

Radiotherapy: Daniel Pham, Brent Chesson, Andrew Lim

Nuclear Medicine: Michael Hofman, Jason Callahan, Price Jackson

Imaging: Arian Lasocki, Eddie Lau, Bimal Kumar, James Korte

TROG: Bec Montgomery, Alisha Moore, Olivia Cook, Ryan Davey

1. Subramanian, Venkatesh K, Singh S, et al. Epidemiology of renal cell carcinoma: 2020 update. *Urol Oncol* 2023;31:238-246.  
2. Miller JL, Poretsky AP, Sigmundson S, et al. Renal cell carcinoma. *Nat Rev Dis Prim* 2017;7:17075.



# Are these findings consistent with literature?

Articles

*Lancet Oncology 2022 Dec;23(12):1508-1516.*




## **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)**

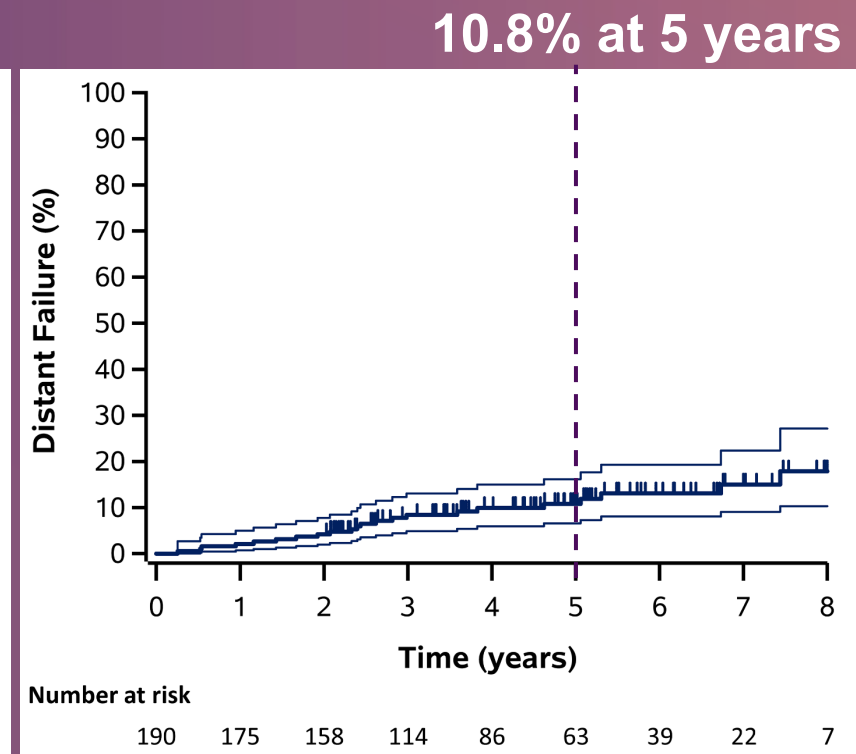
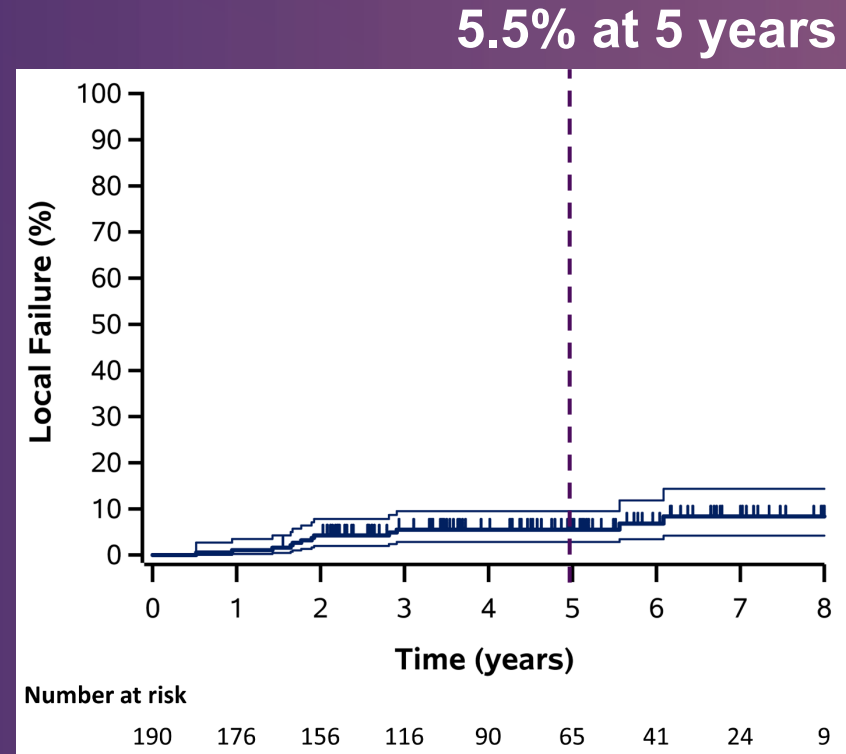
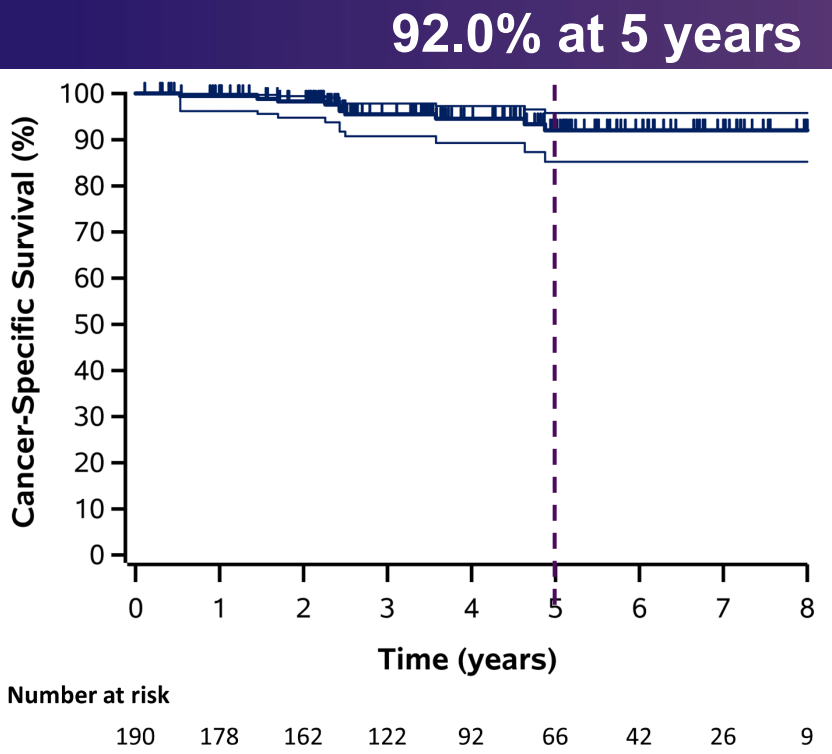
*Shankar Siva, Muhammad Ali, Rohann J M Correa, Alexander Muacevic, Lee Ponsky, Rodney J Ellis, Simon S Lo, Hiroshi Onishi, Anand Swaminath, Mark McLaughlin, Scott C Morgan, Fabio L Cury, Bin S Teh, Anand Mahadevan, Irving D Kaplan, William Chu, William Grubb, Raquibul Hannan, Michael Staehler, Andrew Warner, Alexander V Louie*

**iROCK**



# IROCK 5-year outcomes

- In 190 patients, the median follow-up was 5.0 years (95%CI: 4.58-5.24 years)
- Mean tumour size = 4.2 cm, mean baseline eGFR = 58.9 mLs/min
-  eGFR 13.5 mLs/min @ 5-yrs , despite 56 patients (29.5%) having a solitary kidney



# ROLE OF POST SABR BIOPSY

## Stereotactic Radiotherapy for Renal Cell Carcinoma: The Fallacy of (False) Positive Post-treatment Biopsy?

Rohann J.M. Correa<sup>a</sup>, Sree Appu<sup>b,c</sup>, Shankar Siva<sup>c,\*</sup> *Eur Urol* 2023 **84**(3): 287-288

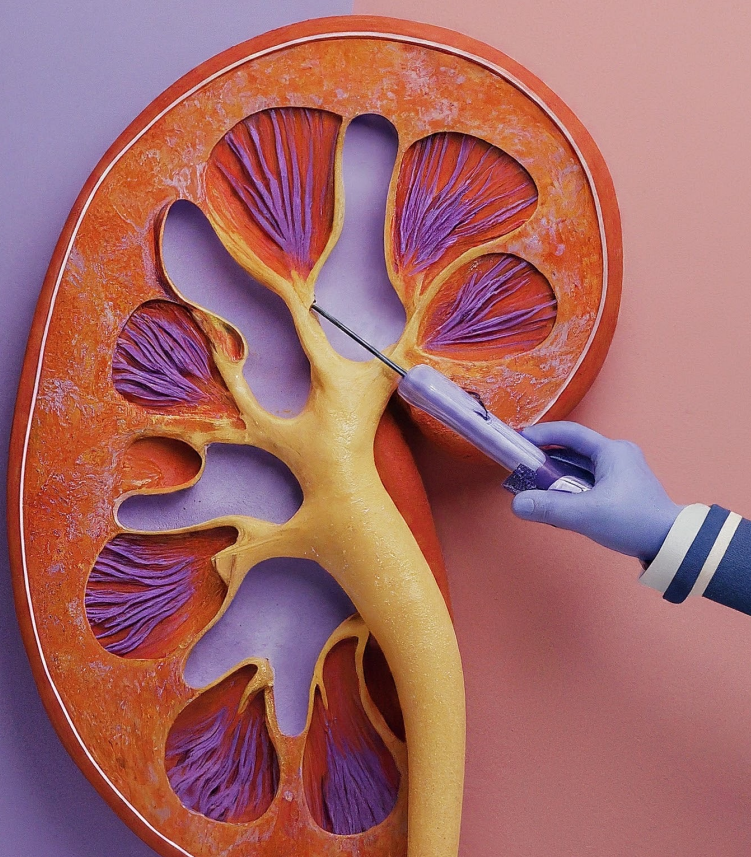
*“Owing to the potential to mislead, post-radiotherapy biopsy or surgical dissection has been discarded in the treatment paradigm for many other malignancies treated with radical radiotherapy.”*

- Abandoned in head and neck cancer, lung cancer, cervical cancer, prostate cancer – post-treatment biopsy does not correlate to outcomes
- Hannan et al.<sup>1</sup> reduced cellularity, Ki67 index, transcriptomic engagement of senescence and apoptotic pathways
- Tang et al.<sup>2</sup> LC 92%, but 57% “positive” biopsy at 3 mo... though Ki67 only 6%.
- Grubb et al.<sup>3</sup> “positive” biopsy at 6 months despite phase I dose escalation to 60Gy/3#

<sup>1</sup>Hannan R et al *Eur Urol.* 2023 Sep;84(3)

<sup>2</sup>Tang et al. *Lancet Oncol* 2021;22:1732–9

<sup>3</sup>Grubb W et al. *Radiother Oncol* 2021;155:138–43.



# In context: Prospective Trials of SABR for Primary RCC

\*Siva, S., A. V. Louie, R. Kotecha, et al 2024 [The Lancet Oncology](#) 25(1): e18-e28.



*At start 2024, there are over a dozen prospective trials versus zero for thermal ablation!*

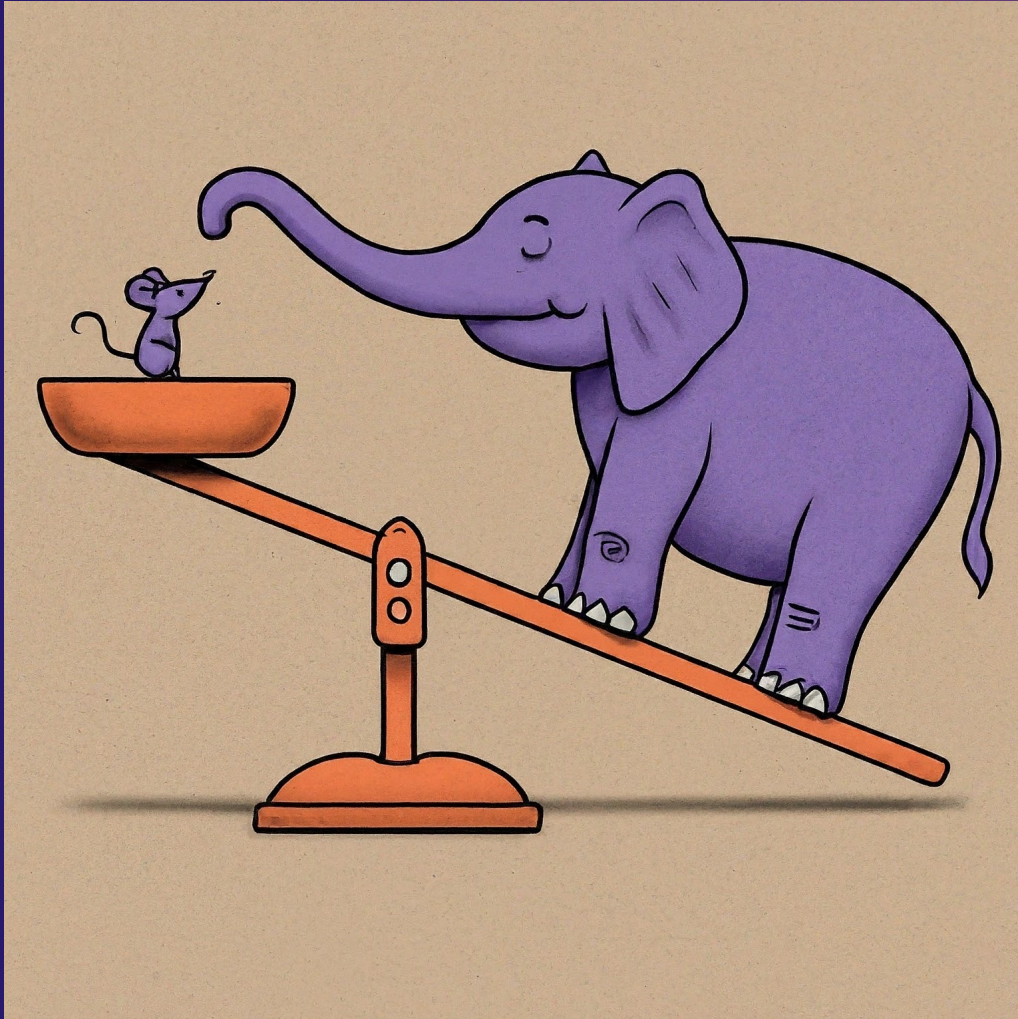
1 <sup>st</sup> Author, Year	Patients	Confirmed via biopsy rate (%)	Tumor Size (median, cm; unless stated)	Follow-Up (months)	Dose & Fractions	OS (median)	Local Control (%)	Pre-SABR Renal Function			Change in eGFR (mLs/min)
								Gr. 1-2	Gr. 3	Gr. 4-5	
Svedman, 2006[28]	5	NR	NR	52	45Gy in 3 40Gy in 4 32Gy in 4 30Gy in 2	NR	80	NR	0	0	NR
McBride, 2013[6]	15	NR	3.4	36.7	21-48Gy in 3	NR	80	46.7	0	0	-18
Staehler, 2015[34]	29	100%	33.7 cm <sup>3</sup>	28.1	26Gy in 1	2-yr 84%	100	20	0	0	-6.5
Ponsky, 2015[14]	19	95%	57.9 cm <sup>3</sup>	13.7	24-48Gy in 4	2-yr 72% 3-yr 72%	100	11.5	10.5	5.3	NR
Siva, 2017[7]	33	92%	4.8	24	26Gy in 1 or 42Gy in 3	2-yr 92%	97	79	3	0	-11
Singh, 2017[37]*	14	100	NR	1	15Gy in 1	NR	NR	62.5	6	0	NR
Correa, 2018[38]	12	100%	8.7	5.8	25-35Gy in 5	NR	100	66.7	25	0	-9.9
Kasuya, 2019[40]	8	25%	4.3	43.1	66-72Gy in 12 (CIRT)	NR	100	75	0	0	-10.8
Funayama, 2019[41]	13	NR	2.28	48.3	60 or 70 Gy in 10	3-yr 71.3%	92.3	15.4	0	0	-16.7
Grubb, 2021[8]	11	100%	3.7	34.3	48,54,60Gy in 3	3-yr 75.8% 5-yr 55.7%	90	63.6	9.1	0	-7
Kirste, 2022[47]	7	NR	2.8	43	50Gy in 5 (1 pt had 60Gy in 8)	86%	100	43	0	0	-7.1
Lapierre, 2023[48]	13	100%	3.3	23	32, 40 or 48 Gy in 4, or 40Gy in 5	NR	100	41.7	0	0	-5.9
Hannan, 2023[9]	16	100%	3.2	36	36 Gy in 3 (63%) OR 40Gy in 5	3-yr 79%	94	50	0	0	-12.1

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## COMPARING EVIDENCE TO THERMAL ABLATION



- *At the start of 2024, there are over a dozen prospective trials versus zero for thermal ablation!*
- *265 patients enrolled in robust clinical trials*
- *Efficacy comparable to (retrospective) TA results, but zero retreatment rates*
- *Nephron sparing with renal function loss comparable to partial nephrectomy*

# CONCLUSIONS

- SABR has the most robust evidence for non-surgical patients.
- Over a dozen prospective clinical trials with consistently excellent oncological outcomes and nephron preservation.
- Efficacy of thermal ablation reduces  $> 3\text{cm}$  in size and locations close to the ureter, renal pelvis, or vessels - SABR has a broader scope and utility than TA.
- An RCT of SABR versus surgery is warranted.

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*Thank you for your attention!*

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