

Stereotactic Radiation for Localized Kidney Cancer

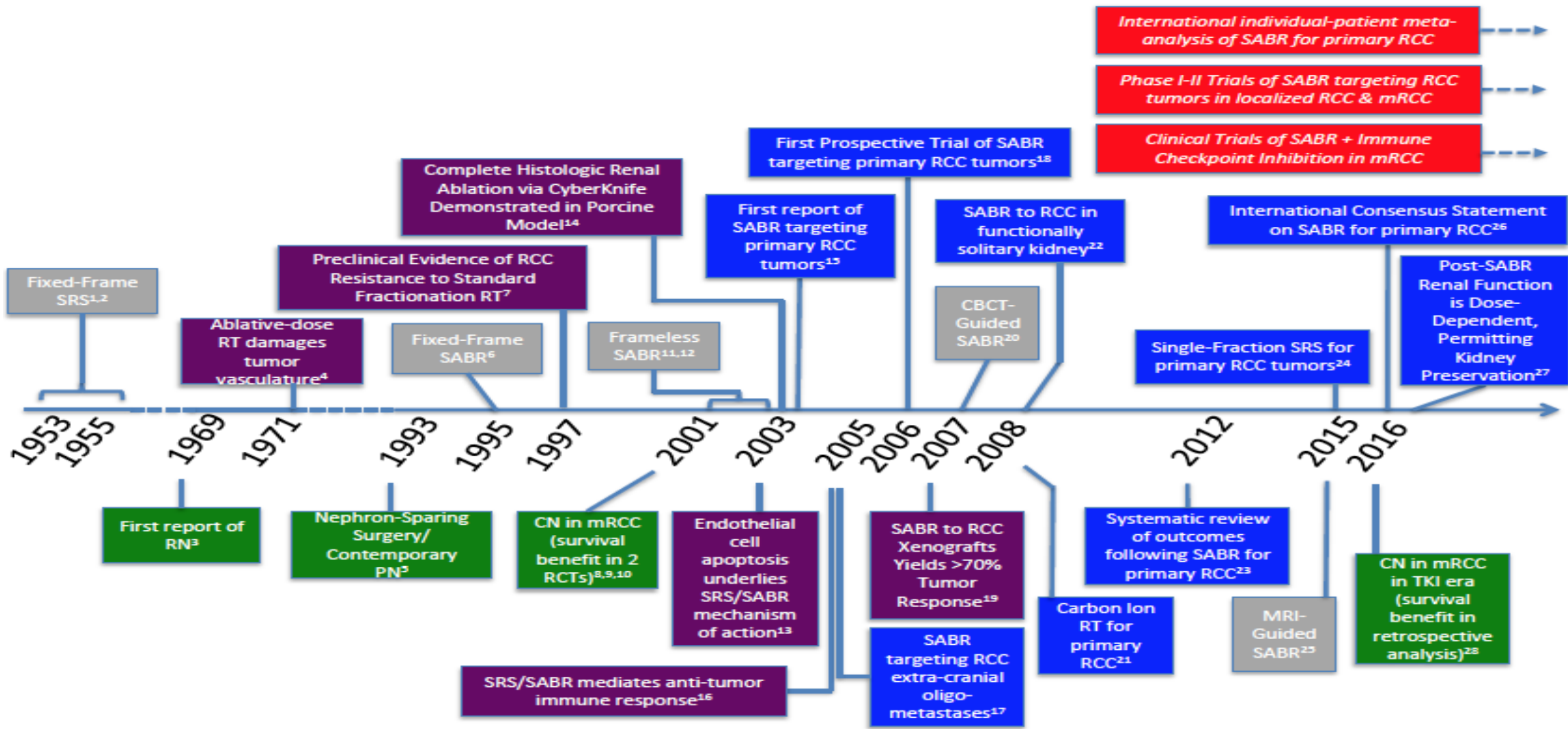
CKCF
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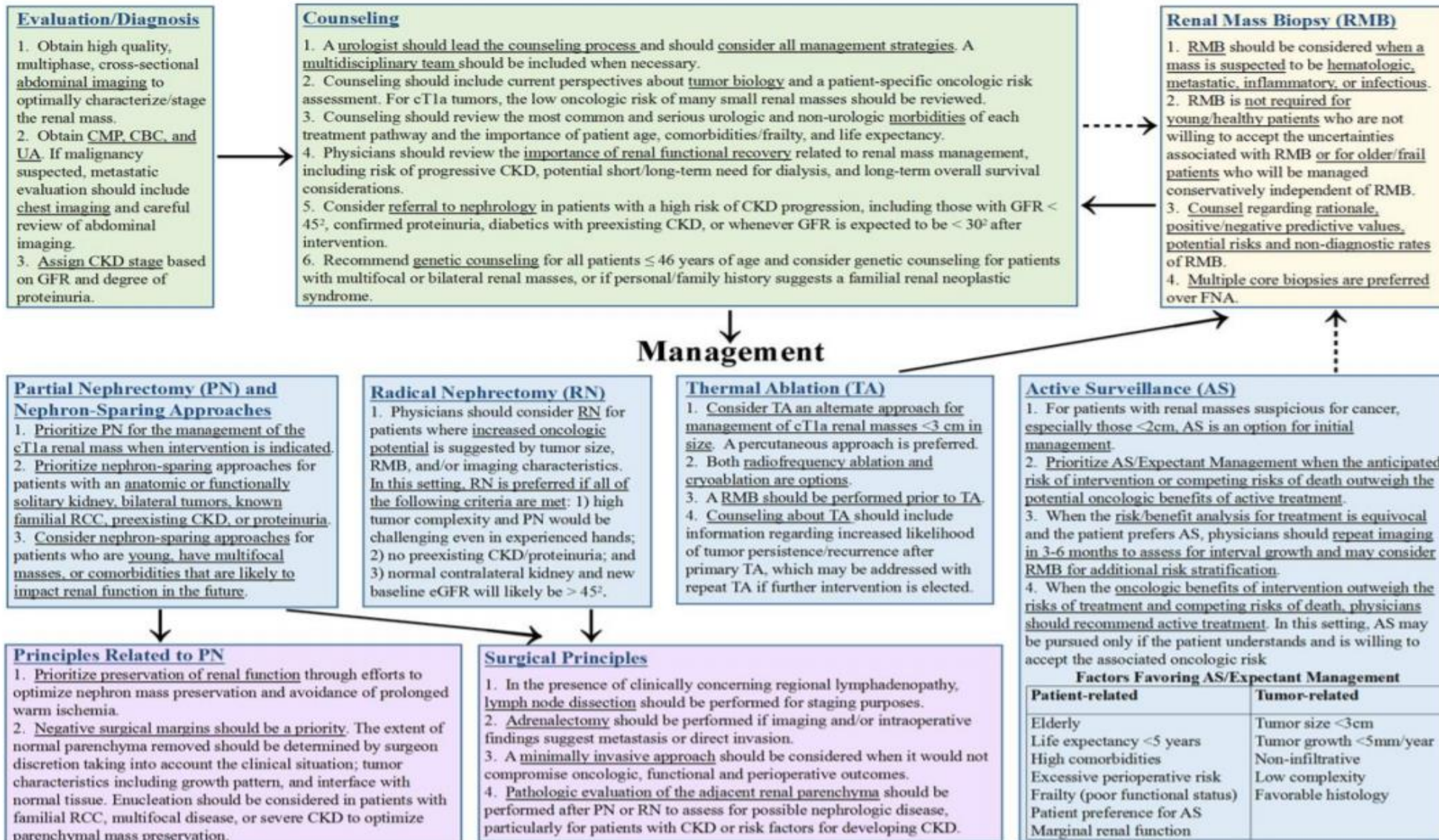


Disclosures

- AstraZeneca – Advisory Board (lung cancer, outside scope of this work)
- Accuray – Educational Grant (breast cancer and palliative RT, outside scope of this work)



Renal Mass and Localized Renal Cancer¹



1. Focus is on clinically localized renal masses suspicious for RCC in adults, including solid enhanced tumors and Bosniak 3 and 4 complex cystic lesions. 2. ml/min/1.73m².

Recommendations	Strength rating
Offer surgery to achieve cure in localised renal cell cancer.	Strong
Offer partial nephrectomy to patients with T1 tumours.	Strong
Do not perform ipsilateral adrenalectomy if there is no clinical evidence of invasion of the adrenal gland.	Strong
Consider an extended lymph node dissection in patients with adverse clinical features including a large diameter of the primary tumour.	Weak
Offer embolisation in patients unfit for surgery presenting with massive haematuria or flank pain.	Weak

Recommendations	Strength rating
Offer laparoscopic radical nephrectomy to patients with T2 tumours and localised masses not treatable by partial nephrectomy.	Strong
Do not perform minimally invasive radical nephrectomy in patients with T1 tumours for whom a partial nephrectomy is feasible by any approach, including open.	Strong
Do not perform minimally invasive surgery if this approach may compromise oncological, functional and peri-operative outcomes.	Strong

Recommendation	Strength rating
Offer active surveillance, radiofrequency ablation and cryoablation to elderly and/or comorbid patients with small renal masses.	Weak

How do we



join the conversation?

SBRT (Stereotactic Body Radiation Therapy)

~~“RCC is a radioresistant malignancy”~~

Comparison of conventional RT and SBRT in RCC

Characteristic	Conventional RT	SBRT
Total radiation dose	45–50 Gy	30–45 Gy
Dose per fraction	1.8–2 Gy	6–12 Gy
No. fractions	25–30	3–5
Total treatment duration	5–6 weeks	1–2 weeks
Treatment time per fraction	5–10 minutes	15–45 minutes
Maximum dose in tumour	95–105% of prescription dose	100–140% of prescription dose
Image guidance used	Occasionally	Routinely
Indications		
Primary RCC	Minimal	Emerging
Adjuvant therapy	Uncommon, no survival benefit	Not studied
Neoadjuvant/pre-surgical therapy	None	Possible
Metastatic disease	Palliative	Radical (oligometastases)
Limitations		
Technical	Inability to dose escalate due to bowel/kidney tolerance	Challenging when in close proximity to GI structures
Outcomes	No survival benefit in adjuvant setting	Although good local control in primary setting, need long term follow-up

RT: radiotherapy; SBRT: stereotactic body radiotherapy; RCC: renal cell carcinoma; Gy: Gray

High dose per fraction kills kidney cancer cells

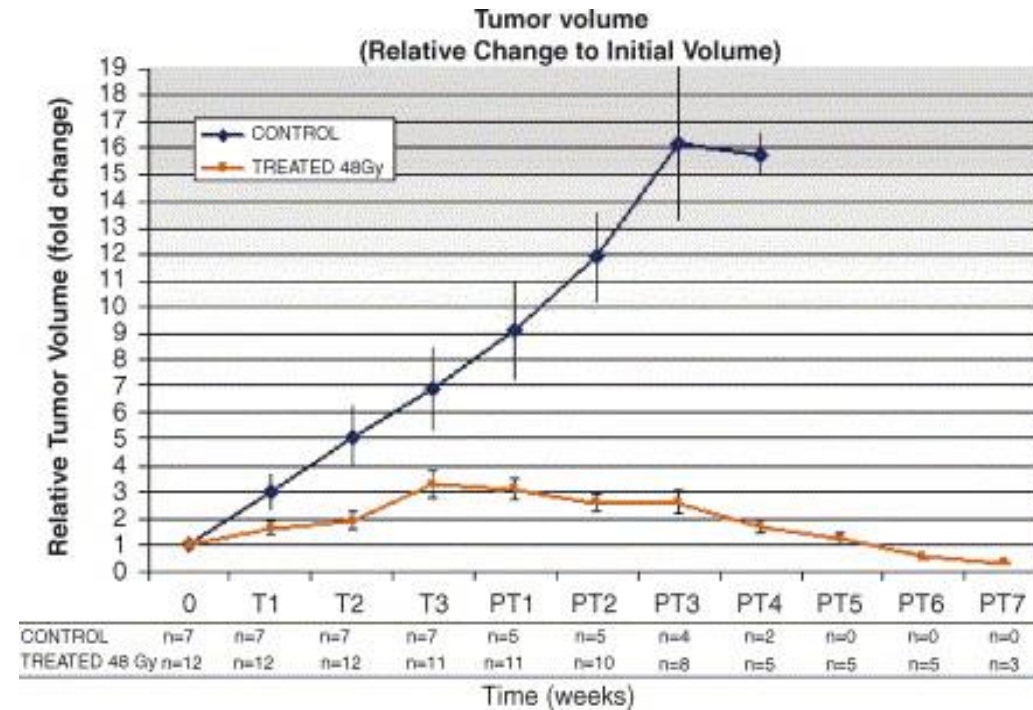
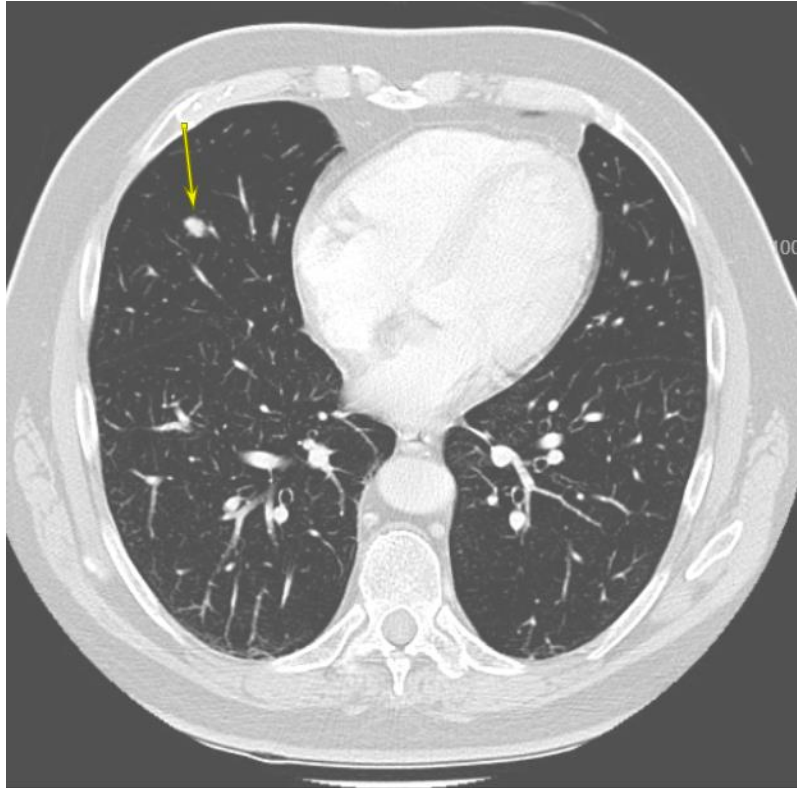


Table 1. Radiobiological Parameters of In Vitro Survival Curves of Human RCC Cell Lines

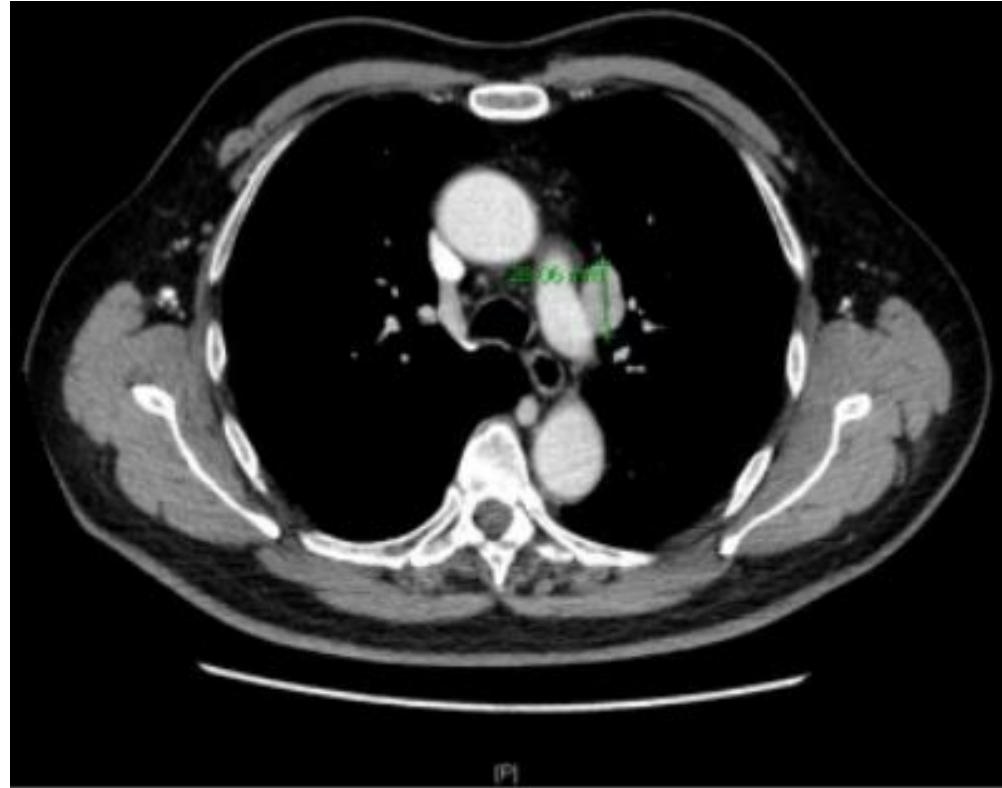
	LQ ^a			SHMT ^b			
	α	β	α/β	n	$D0$	Dq	SF2 ^c
<i>HDR irradiation</i>							
Caki-1	0.39 ± 0.02	0.057 ± 0.005	6.92 ± 0.2	5.13 ± 1.09	1.01 ± 0.09	1.60 ± 0.08	0.37 ± 0.03
A498	0.15 ± 0.05	0.057 ± 0.003	2.60 ± 0.9	23.00 ± 8.97	1.04 ± 0.04	3.15 ± 0.31	0.60 ± 0.07

“Prostate Cancer-Like”

April 2013



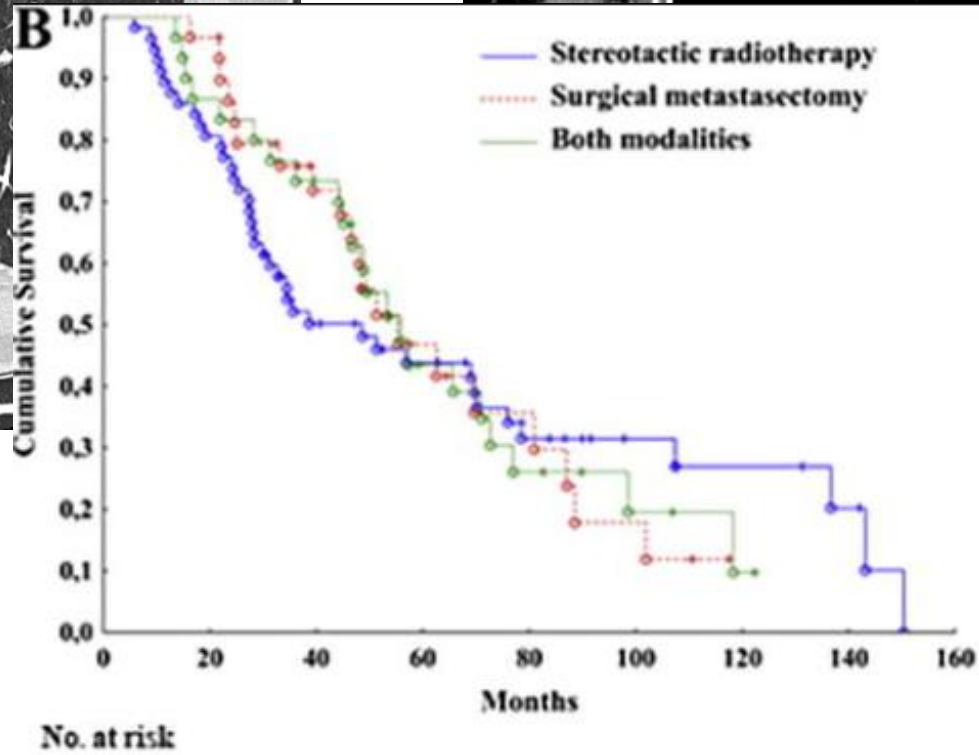
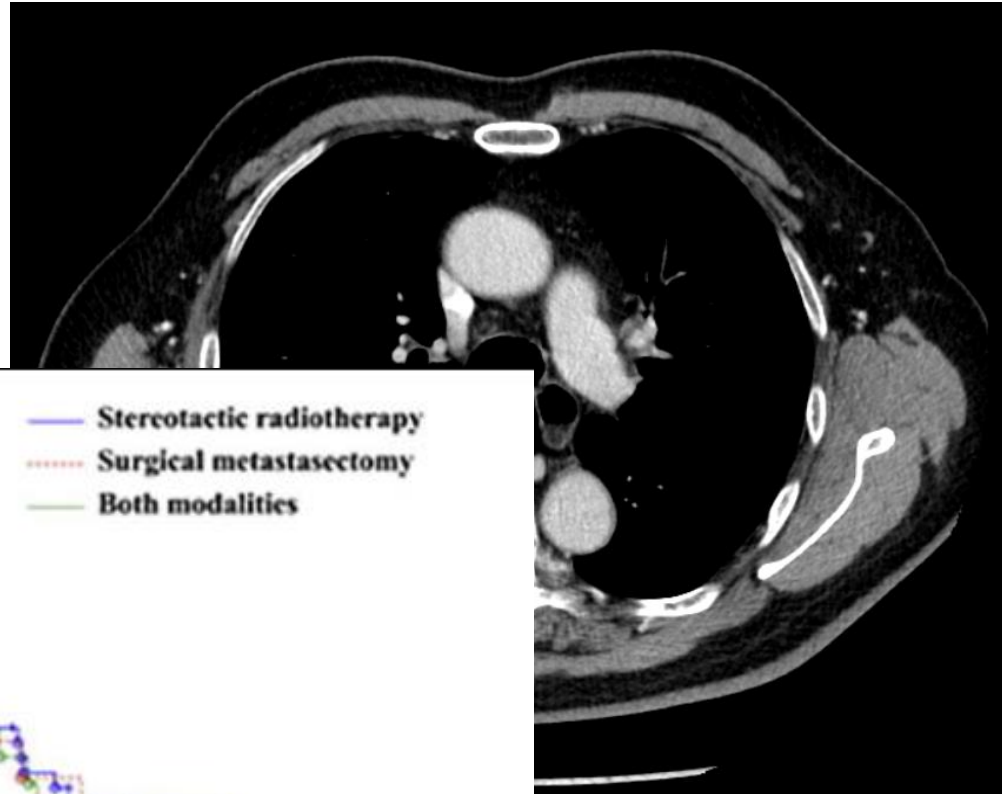
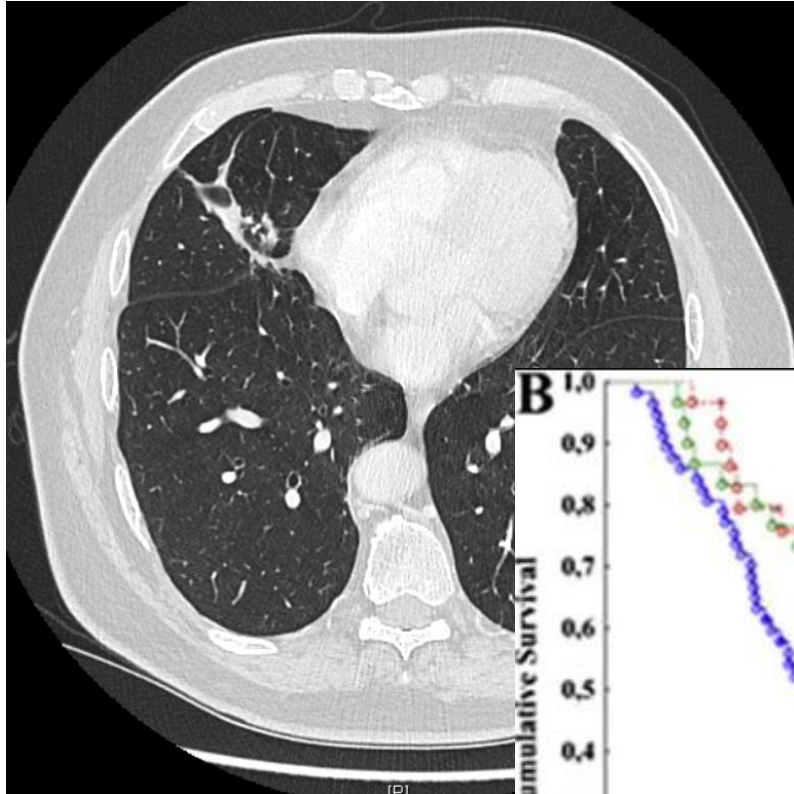
April 2015



65 yo man w/ oligometastatic clear cell RCC post nephrectomy 2011

Jan 2019

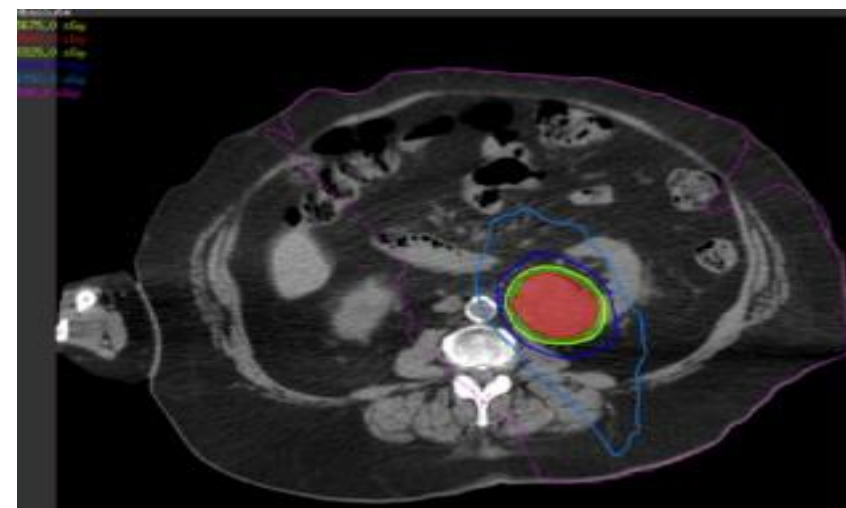
Jan 2019



Individual patient data meta-analysis of SBRT kidney: A report from the International Radiosurgery Oncology Consortium for Kidney (IROCK)

Shankar Siva, Alexander Muacevic, Michael Staehler, Andrew Warner, Senthilkumar Gandhidasan, Lee Ponsky, Rodney Ellis, Irving Kaplan, Anand Mahadevan, William Chu, Hiroshi Onishi, Simon S. Lo, Bin Teh, Anand Swaminath, Rohann Correa, Alexander V. Louie

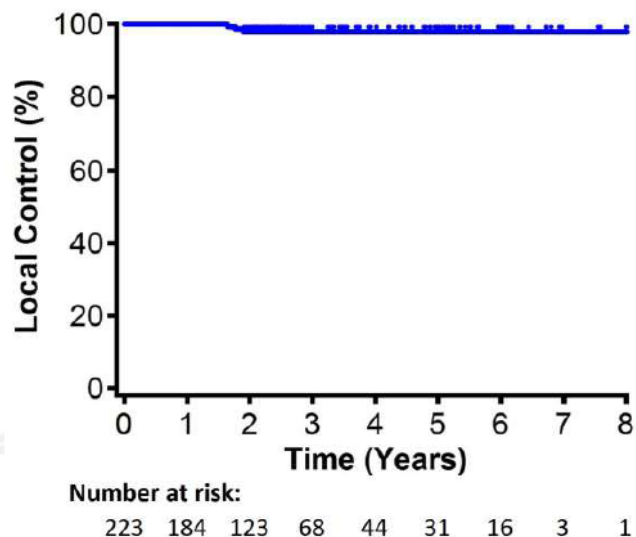
Characteristic	N	All Patients (n=223)	1 Fraction (n=118)	> 1 Fraction (n=105)	p-value
Age at SABR – mean ± SD	223	72.0 ± 11.8	69.0 ± 11.9	75.3 ± 10.9	< 0.001
Male – n(%)	223	155 (69.5)	82 (69.5)	73 (69.5)	0.996
Good Performance Status (ECOG 0-1 or KPS ≥ 70) – n(%)	223	195 (87.4)	114 (96.6)	81 (77.1)	< 0.001
Pathological Confirmation – n(%)	223	189 (84.8)	116 (98.3)	73 (69.5)	< 0.001
Histology Type – n(%)					
Clear Cell	189	163 (86.2)	114 (97.4)	49 (68.1)	< 0.001
Papillary		9 (4.8)	2 (1.7)	7 (9.7)	
Chromophobe		2 (1.1)	–	2 (2.8)	
Other Renal Cell Carcinoma		11 (5.8)	–	11 (15.3)	
Urothelial		4 (2.1)	1 (0.9)	3 (4.2)	
Maximum Diameter (mm) – mean ± SD	223	43.6 ± 27.7	37.1 ± 10.6	50.9 ± 37.6	0.009
eGFR Pre-SABR (mL/min) – mean ± SD	220	59.9 ± 21.9	66.4 ± 20.6	52.6 ± 21.2	< 0.001



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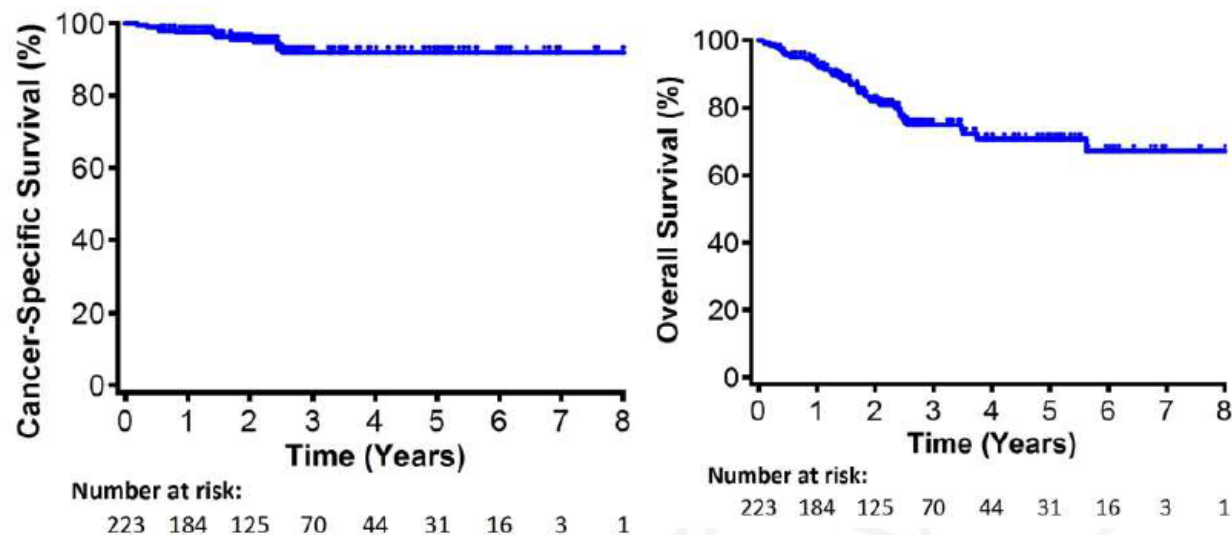
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Overall Cohort: Local Control



- 3 local failures (1.4%) all within 2 years
- Local Control at 2- and 4-years was 97.8%

Survival Outcomes



- 16 patients had distant disease failure (7.2%)
- Cancer Specific Survival at 2 and 4-years was 95.7% and 91.9%
- Overall Survival at 2 and 4-years was 82.1% and 70.7%

Comparison to Other Options – AS?

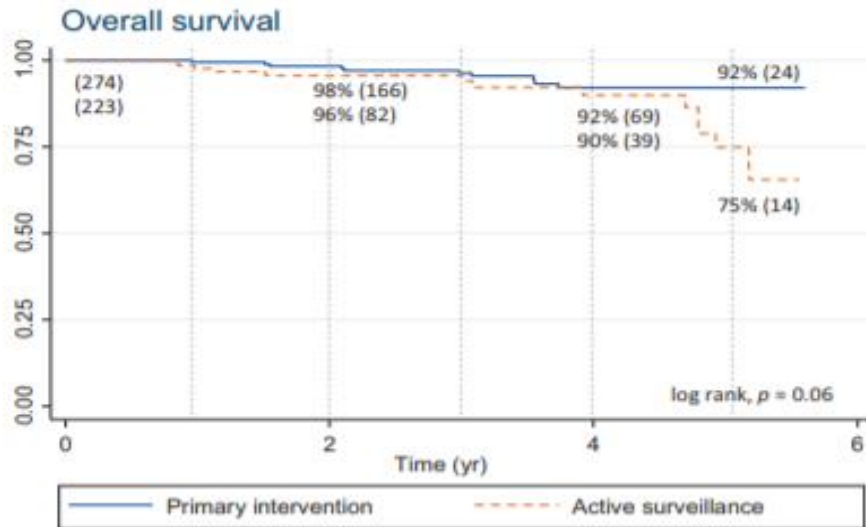


Fig. 2 – Overall survival for patients undergoing primary intervention or active surveillance in the Delayed Intervention and Surveillance for Small Renal Mass (DISSRM) registry.

Table 3. Comparison of Clinical and Cross-Sectional Imaging Characteristics in Patients who Did Not Progress to Metastasis (Pooled Cohort Series Data) and Patients who Demonstrated Evidence of Progression (Case Series Data) During Periods of Observation

Characteristic	No.	Nonprogressors		Progressors		P
		Mean±SD: Median (Range)	No.	Mean±SD: Median (Range)		
Age, y	230	66.6±12.3: 69 (35-88)	9	75.1±9.1: 78.0 (54.0-84.0)		.03
Initial MTD, cm	281	2.3±1.3: 2.0 (0.2-12.0)	16	4.3±2.1: 3.1 (2.0-8.8)		<.001
Initial ETV, cm ³	281	15.1±60.3: 4.3 (0.004-903.7)	16	66.3±100.0: 15.2 (4.3-363.0)		<.001
Final MTD, cm	249	3.0±1.6: 2.7 (0.9-15.0)	14	5.9±2.1: 5.9 (3.1-10.7)		<.001
Final ETV, cm ³	281	29.0±109.8: 10.3 (0.3-1765.1)	14	132.1±170.9: 87.9 (13.4-653.0)		<.001
Linear growth rate, cm/y	249	0.4±0.3: 0.25 (-1.4-2.47)	13	0.80±0.7: 0.65 (0.1-2.72)		<.001
Volumetric growth rate, cm ³ /y	281	6.2±27.5: 1.6 (-20.0-430.7)	14	27.1±24.9: 19.1 (4.8-84.4)		<.001
Time under AS, mo	281	33.3±22.6: 27.0 (5.3-156.0)	17	40.2±31.2: 29.0 (9.0-132.0)		.47

Abbreviations: AS, active surveillance; ETV, estimated tumor volume; MTD, maximum linear tumor dimension; SD, standard deviation.

Characteristic	Overall N=69	No mets N=46	Mets N=23	p
	Mean (SD)			
Age years (range 56–92)	75.5 (8)	76.6 (8.3)	73.2 (6.8)	0.1023
eGFR, ml/min/1.73m ² (range 6– >120)	57.5 (23)	60.4 (20.3)	51 (27.6)	0.14
Tumour size, cm (range 4–17.6)	5.7 (2.2)	5.25 (1.41)	6.5 (3.1)	0.024
Growth rate, cm/year (range 0.33–2.57)	0.82 (1.2)	0.67 (1.1)	1.13 (1.2)	0.12
Followup, months (range 6–118)	28.4 (28)	30.4 (32)	24.8 (21.7)	0.44

24% metastatic rate in all patients
0.82 cm/year growth rate in all patients

Compared to 7.2% metastatic rate (IROCK)

Comparison to Other Options – TA?

TABLE 2: Achievement of Complete Necrosis and Number of Ablation Sessions to Achieve Complete Necrosis Based on Tumor Size

Tumor Size (cm)	No. (%) of Tumors with Complete Necrosis	No. (%) of Tumors with Complete Necrosis After		
		One Ablation Session	Two Ablation Sessions	Three Ablation Sessions
≤ 3	52/52 (100)	48/52 (92)	4/52 (8)	NA
3–5	36/39 (92)	19/36 (53)	16/36 (44)	1/36 (3)
> 5	2/8 (25)	0/2 (0)	1/2 (50)	1/2 (50)

Note—One patient was excluded from this analysis because enhancement could not be used as a measure of necrosis. NA = not applicable.

- Other potential limitations to RFA
 - Heat sink
 - Increased risk in central/hilar/bowel adjacent tumours
 - Cryoablation – similar outcomes to RFA
 - For 3-5 cm masses – 2nd ablations often required

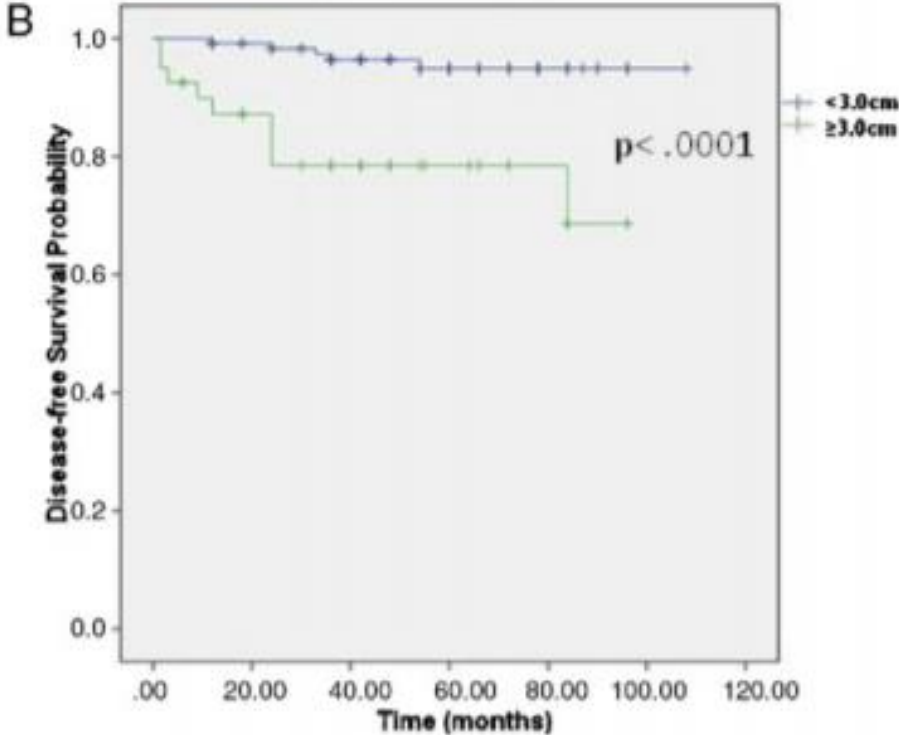


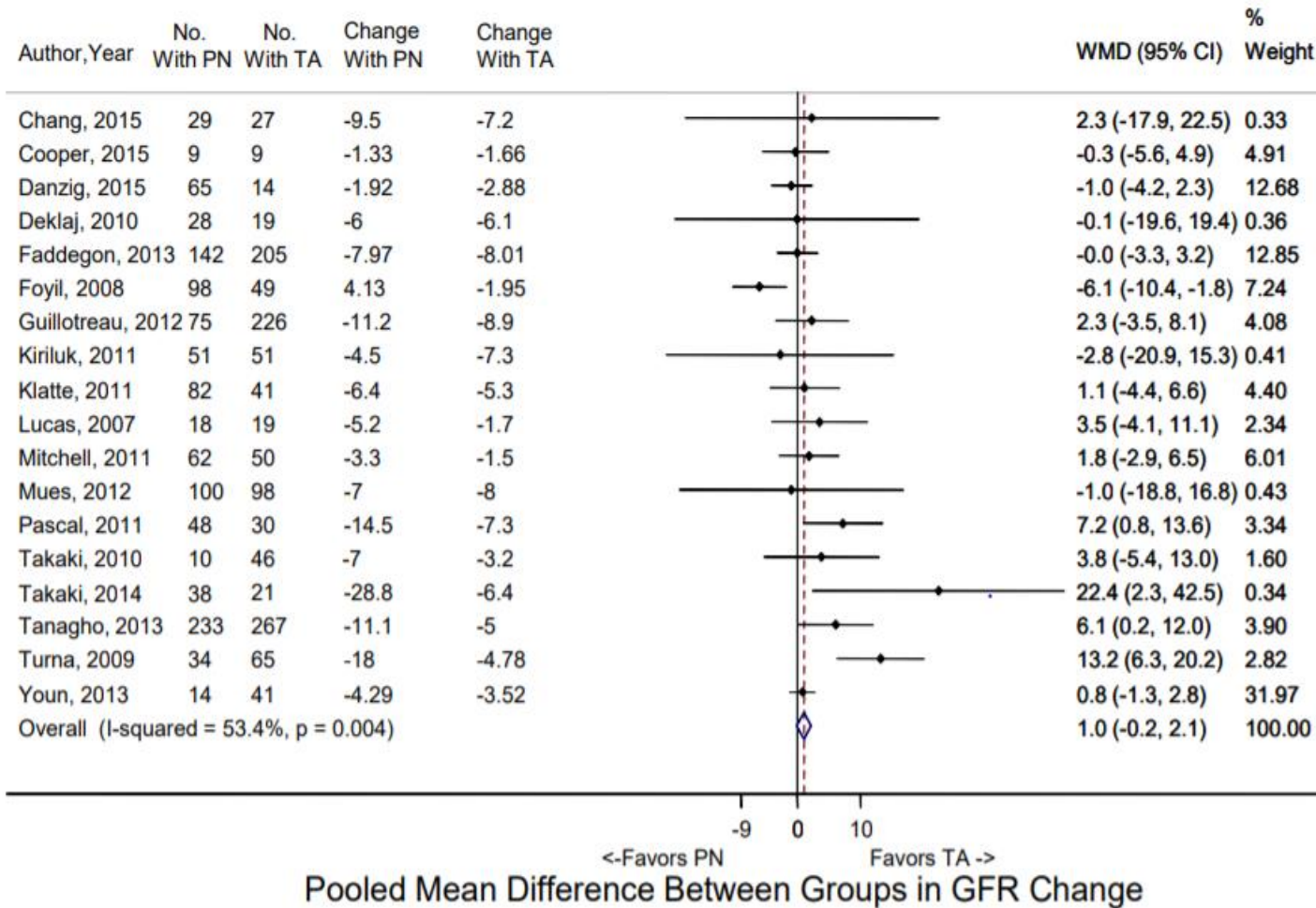
Figure 2: Advantages and Disadvantages of SABR for Primary RCC.

Advantages	Disadvantages
Outpatient treatment	Limited pathologic assessment
Safe & minimally toxic	Limited prospective evidence
Promising local control rates	Lower limit of renal function pre-SABR remains undefined
No definite size limitation	Optimal dose and fractionation regimen remains undefined
Not limited by tumour location	Ideal treatment response assessment modality not yet established
May stimulate anti-tumour immunity	Very stringent technical and quality assurance requirements
Suitable for surgically unresectable tumours	Requirement of intensive training of the whole RT team
Feasible in a functionally solitary kidney	Challenging to assess response on post-treatment imaging

Points of Discussion Regarding SBRT in 2019 (before thinking about CER)

- Risks of kidney toxicity/renal preservation especially in larger renal masses
 - Compared to TA and/or PN?
- RMB post SBRT – if/when to do?
 - Is there a correct time? 1 year? 2 years? Never?
 - Are there other metrics we can use to determine SBRT effectiveness?
 - Growth kinetics
- Quality of Life preservation
- Moving prospectively forward

Renal Function post kidney SBRT



Mean change post SBRT -9.0 mL/min

Median tumour size 4 cm (1 – 13 cm)

Active Surveillance ~ -3 mL/min

Surgery ~ -6 to -22 mL/min

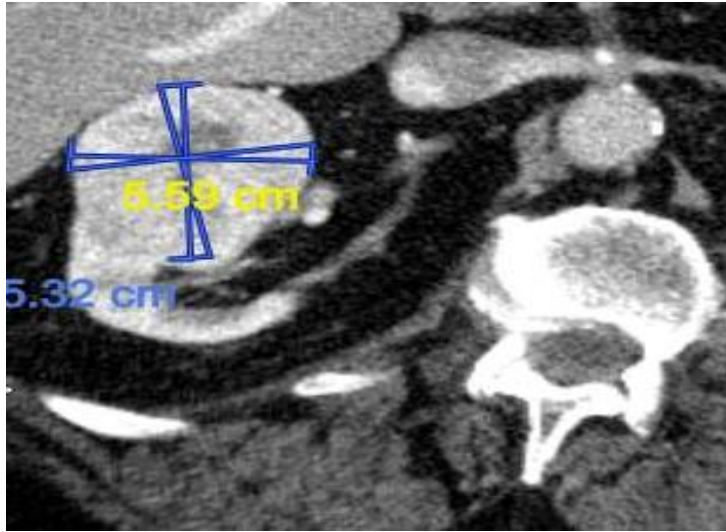
RFA ~ -3 to -7 mL/min

SBRT (IROCK) ~ -5.5 mL/min

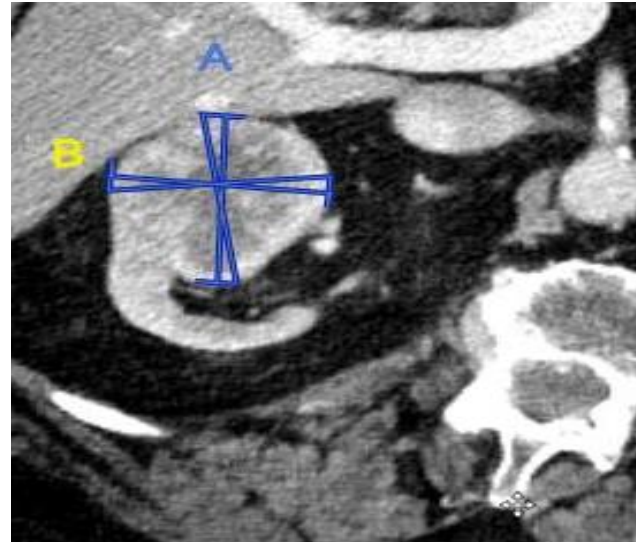
eGFR = estimated glomerular filtration rate; No. = number; PN = partial nephrectomy; RN = radical nephrectomy; TA = thermal ablation; WMD = weighted mean difference
 Note: The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval.

RMB post kidney SBRT?

- Current practice is to measure local control using renal-protocol CT and/or MRI



Pre-SBRT



12 months post SBRT

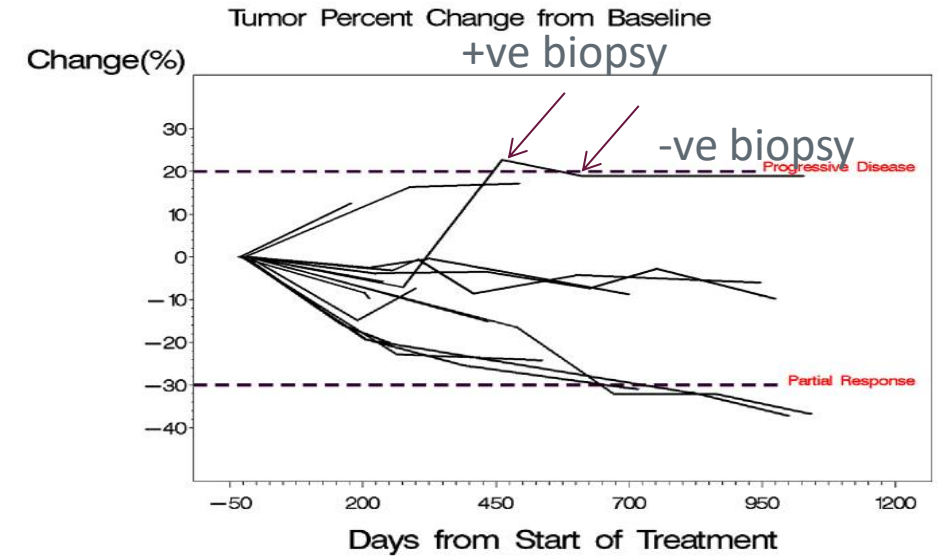


Fig. 1. Individual profiles of tumor response based on RECIST (version 1.1).

- Is stable (or better) disease enough to demonstrate good local control, or is biopsy needed?
- Mechanism of action is mediated by slow tumour kill (as compared to immediate kill using TA techniques)
- BUT, persistent enhancement should be viewed with cautious optimism and ongoing surveillance is needed!
- However, there is no consistent data to support using RMB post SBRT, and at what time interval
- One study (Ponsky et al) had a 64% positive biopsy rate at 6 months post SBRT (likely too soon) – positive biopsy did not correlate with long term control – similar story to prostate cancer

RMB post kidney SBRT?

- Using growth kinetics instead as a marker?

TABLE 2: Total Growth Rates of Renal Tumors for Linear Dimensions and Volume Before and After Stereotactic Body Radiotherapy Treatment

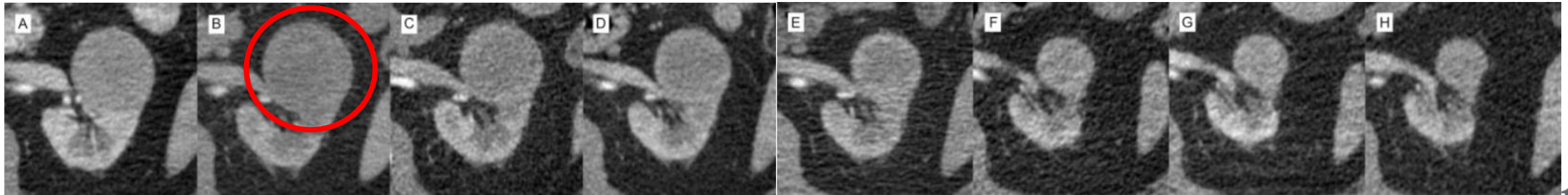
Linear Dimensions and Volume of Renal Tumors	Total Growth Rate		Mean Reduction in Total Growth Rate	p
	Mean ± SD	Median		
Dimension 1 (transverse), cm/y			0.72	<0.0001
Pretreatment	0.67 ± 1.24	0.38		
Posttreatment	-0.35 ± 0.52	-0.30		
Dimension 2 (AP), cm/y			0.69	<0.0001
Pretreatment	0.69 ± 1.54	0.40		
Posttreatment	-0.37 ± 0.68	-0.35		
Dimension 3 (CC), cm/y			0.90	<0.0001
Pretreatment	0.67 ± 1.02	0.44		
Posttreatment	-0.39 ± 0.68	-0.30		
Volume, cm ³ /y			12.79	0.002
Pretreatment	21.21 ± 75.6	4.63		
Posttreatment	-5.35 ± 15.2	-2.96		

Note—Statistically significant reductions in total growth rate were observed for each of the three measured dimensions and for tumor volume. AP = anteroposterior, CC = craniocaudal.

Table 3. Patient Characteristics.

Number	Age	Sex	Tumor Size (mm)	Laterality	PS	Operability	Past History of Nephrectomy	Dose (Gy)/Fraction	Prescription Point	Follow-Up Months	Response	Months Before PR
1	72	M	18	R	0	High-risk operable	Yes	60/10	PTV-D95	108	PR	29.5
2	79	M	19	R	0	Inoperable	Yes	70/10	Isocenter	16	SD	—
3	78	M	25	L	1	High-risk operable	Yes	60/10	Isocenter	44	PR	17.5
4	60	M	26	R	0	High-risk operable	No	60/10	ITV-D95	29	SD	—
5	73	M	19	L	0	High-risk operable	No	70/10	ITV-D95	104	PR	34.9
6	61	M	28	L	1	High-risk operable	Yes	70/10	ITV-D95	90	PR	24.7
7	78	M	16	R	2	High-risk operable	No	70/10	PTV-D95	28	SD	—
8	77	M	9	L	1	High-risk operable	No	70/10	PTV-D95	61	PR	22.9
9	59	F	10	R	1	Operable	No	60/10	PTV-D95	49	SD	—
10	67	F	18	L	0	Inoperable	Yes	70/10	PTV-D95	46	PR	11.6
11	65	M	35	L	0	High-risk operable	No	70/10	PTV-D95	25	PD	—
12	65	M	30	L	0	High-risk operable	Yes	60/10	PTV-D95	17	SD	—
13	81	F	43	R	1	Inoperable	No	60/10	PTV-D95	11	PR	17.4

- Be wary of pseudoprogression!



Quality of Life post kidney SBRT

Patient	PF-B	PF-1	PF-3	FA-B	FA-1	FA-3	NV-B	NV-1	NV-3	EF-B	EF-1	EF-3	DY-B	DY-1	DY-3	AP-B	AP-1	AP-3	GQ-B	GQ-1	GQ-3
B-1	-3.5			-4.6			2.0			-6.9			-2			0			2.9		
p-value	.377			.331			.668			.089			.750			1			.455		
B-3	6.7			-1.9			9.7			-4.9			-2.8			11.1			5.6		
p-value	.225			.655			.206			.339			.723			.166			.266		

Patient	FACT-B	FACT-1	FACT-3	EQSCORE-B	EQSCORE-1	EQSCORE-3	EQVAS-B	EQVAS-1	EQVAS-3
B-1	-3.0			-0.045			-0.81		
p-value	.128			.074			.821		
B-3	-2.1			0.028			-4.2		
p-value	.509			.554			.356		

	Immediate Intervention							Active Surveillance						
	N	SF12	(Range)	MCS	(Range)	PCS	(Range)	N	SF12	(Range)	MCS	(Range)	PCS	(Range)
Enrollment	200	100.7	(47.9-117.4)	52.8	(11.4-69.7)	49.5	(20.1-64.8)	70	94.4	(47.9-114.7)	52.4	(22.8-66.5)	42.8	(20.5-58.3)
6 months	143	105.7	(50.7-117.4)	55.5	(13.5-69.3)	50.2	(21.7-63.5)	55	95.8	(62.7-116)	55.9	(37.4-65.5)	39.1	(12.9-57.9)
1 year	122	106.0	(51.5-117.4)	56.3	(17.5-66.4)	50.8	(21.4-64.2)	39	97.2	(65-114.7)	55.1	(22.6-64.8)	42.0	(21.7-57.2)
2 year	78	104.25	(54.8-117.4)	56.45	(20.8-66.9)	48.2	(20.8-61.7)	27	95.4	(71.2-114.7)	53.8	(33.4-62.9)	42.2	(22.5-57.9)
3 year	30	102.4	(55.8-114.7)	55.95	(24.2-63.8)	47.2	(18.7-58.9)	14	68.9	(66.1-107.3)	58.65	(34.7-68.4)	40.9	(16.5-57.5)

Summary of Kidney SBRT in 2019

- Large retrospective series have demonstrated excellent local control and long term survival
 - Evident especially in large renal masses, and in elderly/infirm patients
 - Be careful regarding pseudoprogression – be patient!
 - Renal function changes very similar to that of PN and/or TA (and we are treating bigger lesions!)
 - Early QOL similar to that of AS
- Questions still exist regarding optimal assessment of local control
 - When/if to do RMB?
 - Wait at least 1 year post treatment, as early biopsy may not correlate to long term control
 - Other ways to assess efficacy
 - Look at growth kinetics (even in RECIST stable lesions)
 - Novel imaging modalities (PSMA PET? DCE MRI?)
- Moving SBRT to the next frontier (and into the guidelines)
 - Need prospective studies for both small and large renal masses
 - RADSTER (Hamilton)
 - AQuOS-II (Sunnybrook/Hamilton)
 - Exploit the potential immunogenicity of SBRT and “abscopal effect”
 - CYTO-SHRINK (Hamilton)

Need Uro-Oncology Champions to help create interest and drive research

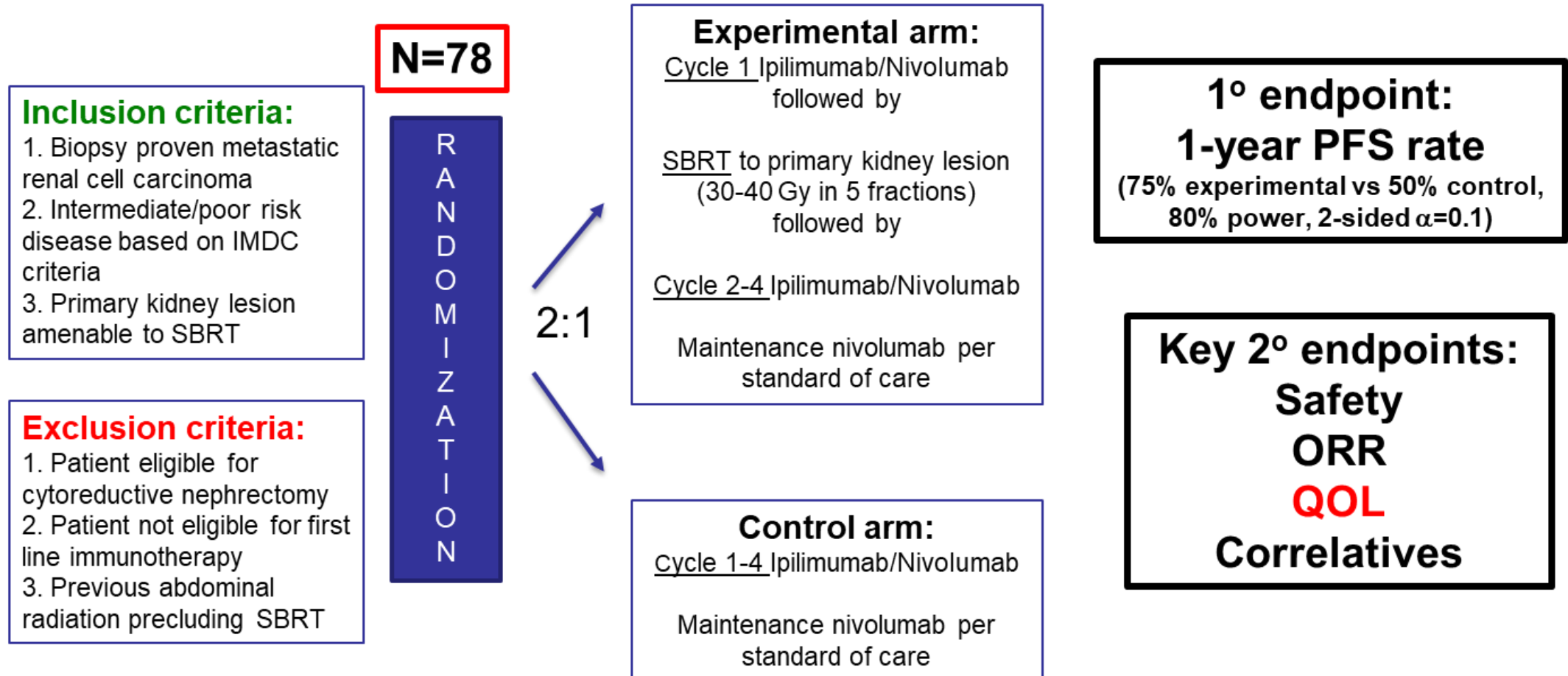
RADSTER (Kapoor PI, Mironov, Swaminath)

- Feasibility RCT of SBRT versus RFA for SRM (< 4 cm)
 - Single session RFA versus single fraction (25 Gy) SBRT
- Primary outcomes are feasibility, toxicity, and disease control
 - Biopsy mandated at 1 year post intervention
 - Secondary Outcomes
 - Disease-free survival
 - Renal eGFR changes
 - Tumor volume changes post intervention
 - QOL
- Plan to randomize 24 patients within the next year
 - Basis for larger trial (if appropriate) comparing these two modalities in future

AQuOS-II (Chu/Swaminath PI) – KCRNC funded

- Multicentre Canadian Phase II trial of SBRT for large (>4 cm) renal masses
 - Fractionated SBRT 30-40 Gy/5 fractions
 - Builds upon initial pilot study (AQuOS-I) at Sunnybrook/Hamilton (30 patients in 3.5 years)
- Primary outcomes are local control and QOL
 - Using standard imaging techniques (will look at growth kinetics post tx)
 - Secondary Outcomes
 - Disease-free survival
 - Renal eGFR changes
 - QOL
- Plan to accrue 46 additional patients within the next 2-3 years
 - Basis for larger trial (if appropriate) comparing SBRT to AS
 - Potential outcomes – reduced rate of delayed intervention, growth rate

CYTOSHRINK – Swaminath/Lalani/Hotte Co-PIs





Thanks!

Questions?

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