

EVIDENCE AND PRACTICE CHANGING TREATMENTS IN GENITO-URINARY TUMORS

KIDNEY CANCER

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Disclosures

- Honoraria - Travel costs: Ipsen, Takeda, Bayer, Janssen, Astellas
- Advisory Boards: Janssen, Astellas, Takeda



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Summary: kidney cancer

[1] Incidence

[2] Localized RCC


- Primary treatment: the standard of care
- SBRT as primary treatment

[3] Metastatic RCC

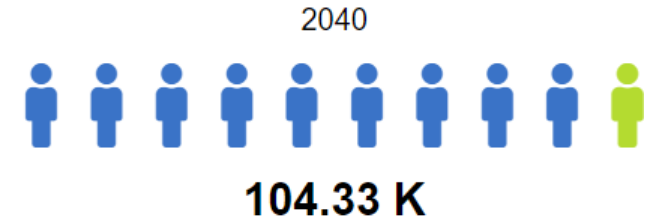
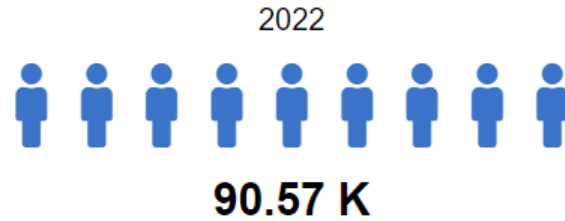
- Cytoreductive nephrectomy
- Systemic therapy
- SBRT as cytoreductive therapy
- SBRT for oligometastatic disease

[1] Incidence

Estimated incidence in 2022 and 2040

 = 10 000

EU27, Both sexes, Kidney, All ages, Baseline projected population



Relative change 15.19 %



ECIS - European Cancer Information System

Age (yrs)	Incidence 2022 (%)	Incidence 2040 (%)	Increase (%)
≤ 64	34.460 (38)	32.950 (32)	-4.39
≥ 65	56.110 (62)	71.380 (68)	27.2
≥ 75	29.430 (33)	41.360 (40)	40.5
All ages	90.570 (100)	104.330	15.19

Age (yrs)	Mortality 2022 (%)
≤ 64	6.750 (20)
≥ 65	27.020 (80)
≥ 75	18.050 (54)
All ages	33.770 (100)

[2] Localized RCC

- Primary treatment: the standard of care
- SBRT as primary treatment

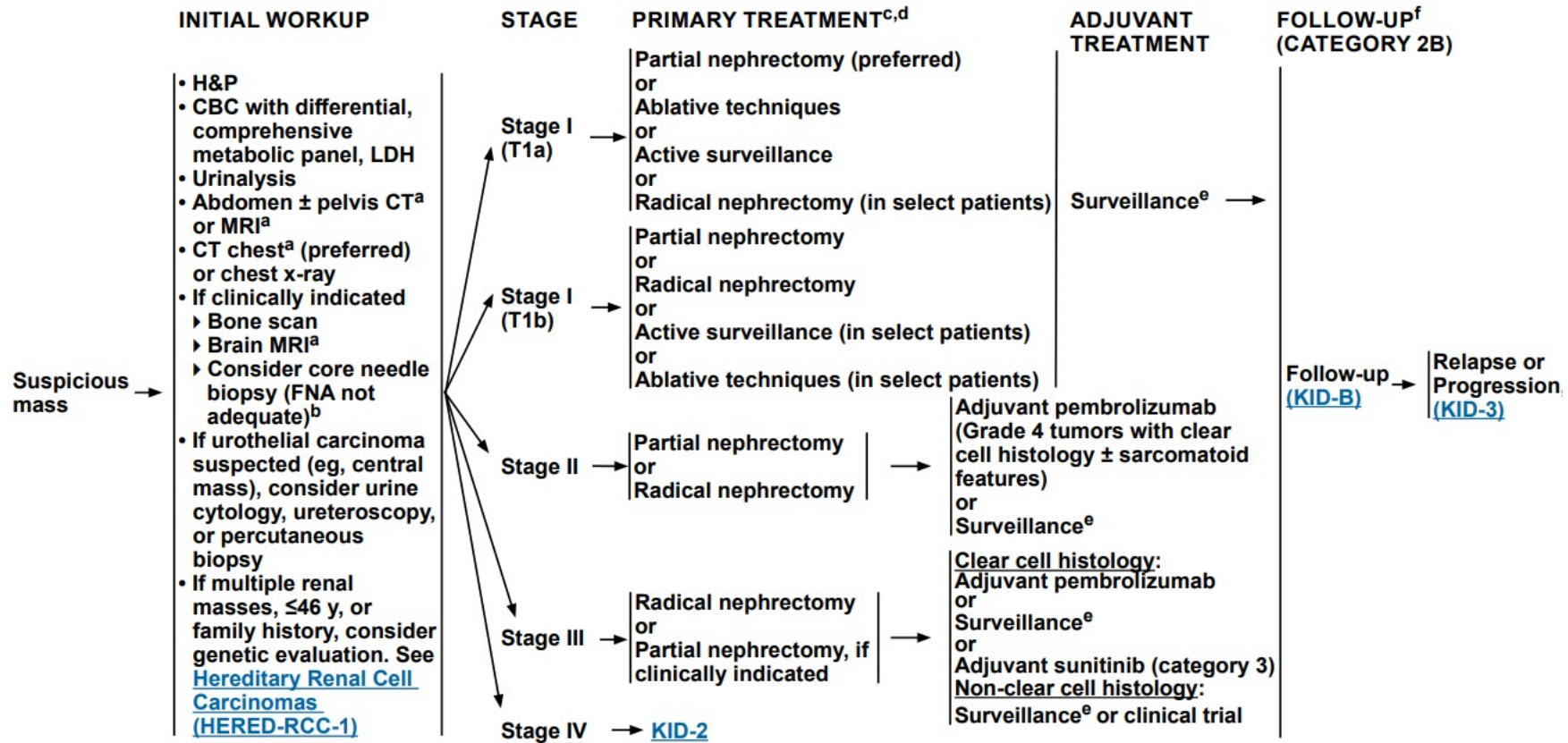
Primary treatment: the standard of care



National
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NCCN Guidelines Version 1.2024 Kidney Cancer

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SABR may be considered for medically inoperable patients with Stage I (2B) or Stage II-III (3)

Primary treatment: the standard of care
















7.1.4.3.5 Stereotactic ablative radiotherapy

Stereotactic ablative radiotherapy (SABR) has been emerging as a treatment option for medically inoperable patients with localised cT1a and cT1b tumours. Patients usually receive 26 Gy in a single fraction, three fractions of 14 Gy or five fractions of 6 Gy [406, 407]. In a systematic review of non-comparative single-arm studies with a median follow-up range of 5.8–79.2 months, the local control rate was 97.2% and the mean change in eGFR was 7.7 mL/min/1.73 m². Grade 3 or 4 toxicities occurred in 1.5% of patients. However, viable tumour cells are often seen in post-SABR biopsies, although their clinical significance remains unclear [407]. Even though early results of SABR are encouraging, more evidence from RCTs is needed [408].

SBRT as primary treatment: rationale

[1] Patient **age** and **co-morbidities**

[2] **RENAL** score [R**adius**, **E**xophytic/endophytic, **N**earness to the collecting system, **A**nterior/posterior descriptor, **L**ocation relative to the polar line]

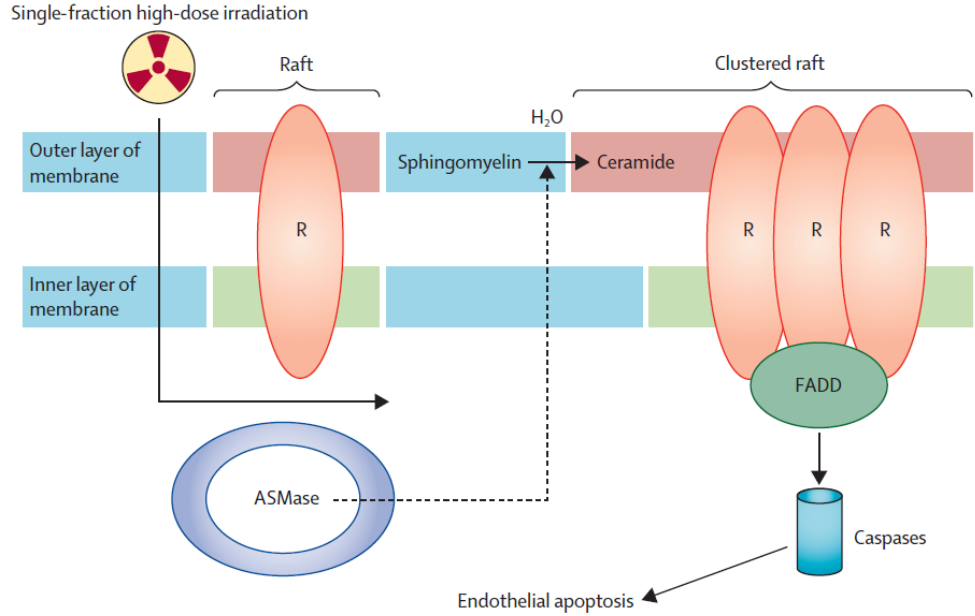
	Avoids general anaesthetic	Peri-hilar tumours	Large tumours	Non-invasive
 Surgery				
 Thermal ablation				
 SABR				

Courtesy Prof. Shankar Siva (Peter MacCallum Cancer Center, Victoria Australia)

SBRT as primary treatment: rationale

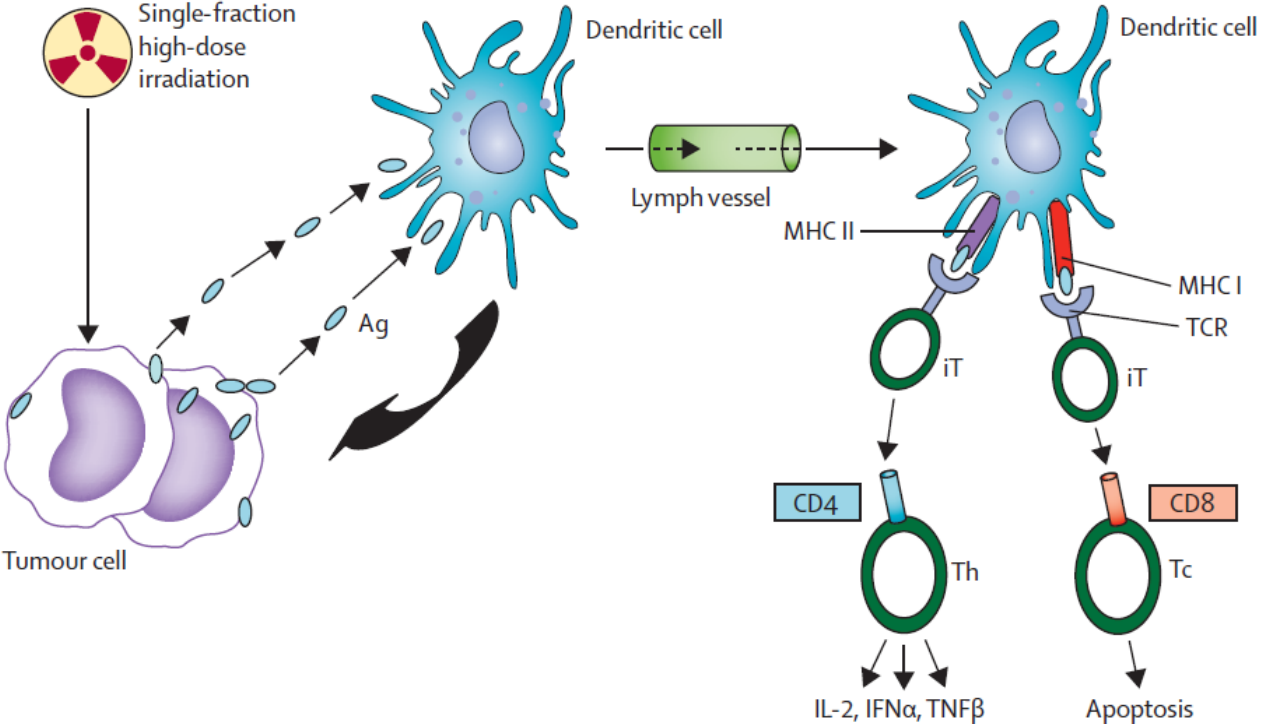
[3] Microenvironment remodeling

Endothelial damage



RCC – highly vascularised tumor

Immune system (re-)activation



RCC – highly immunogenic tumor

SBRT as primary treatment

Systematic review and meta-analysis

- 26 studies
- 11 prospective trials
- 372 pts

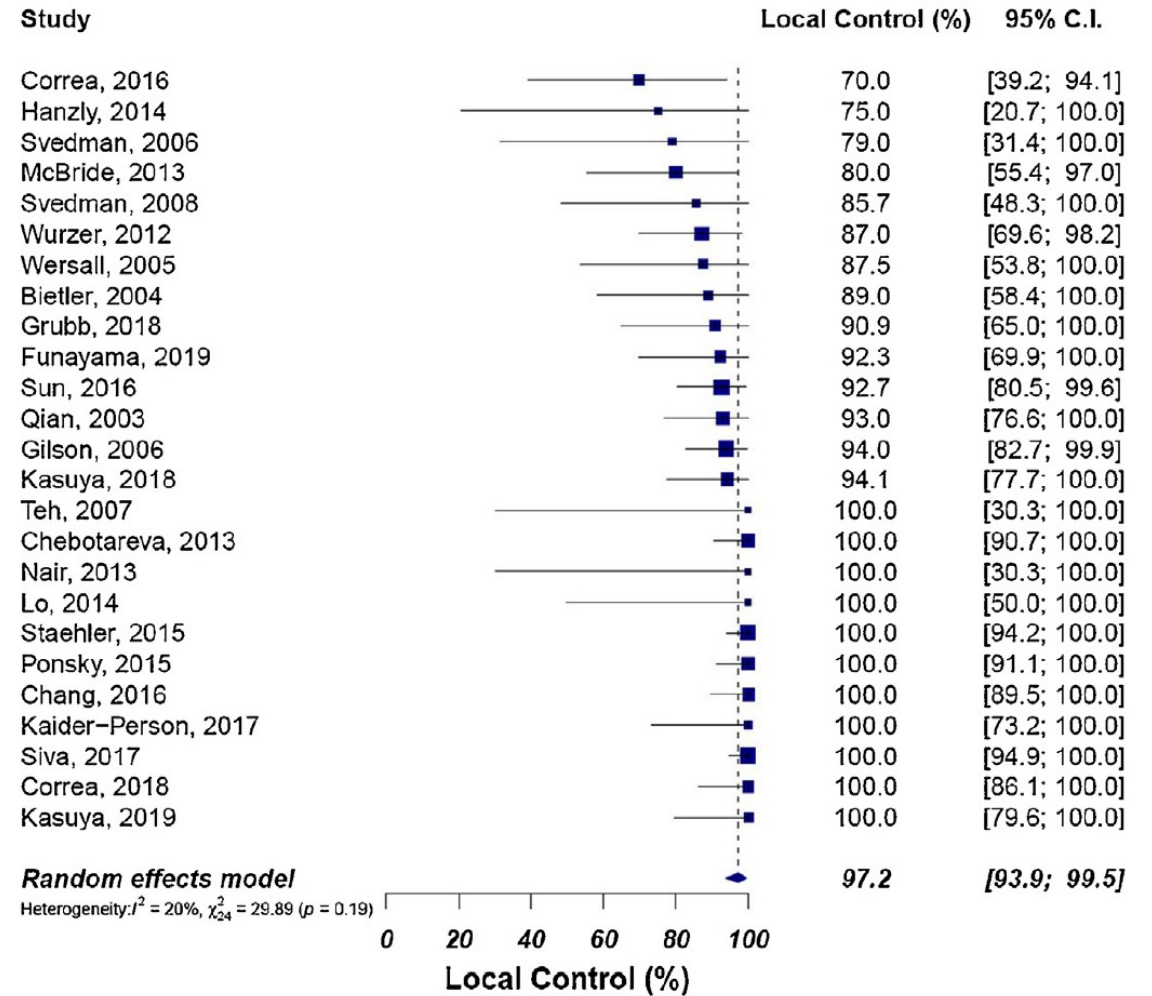
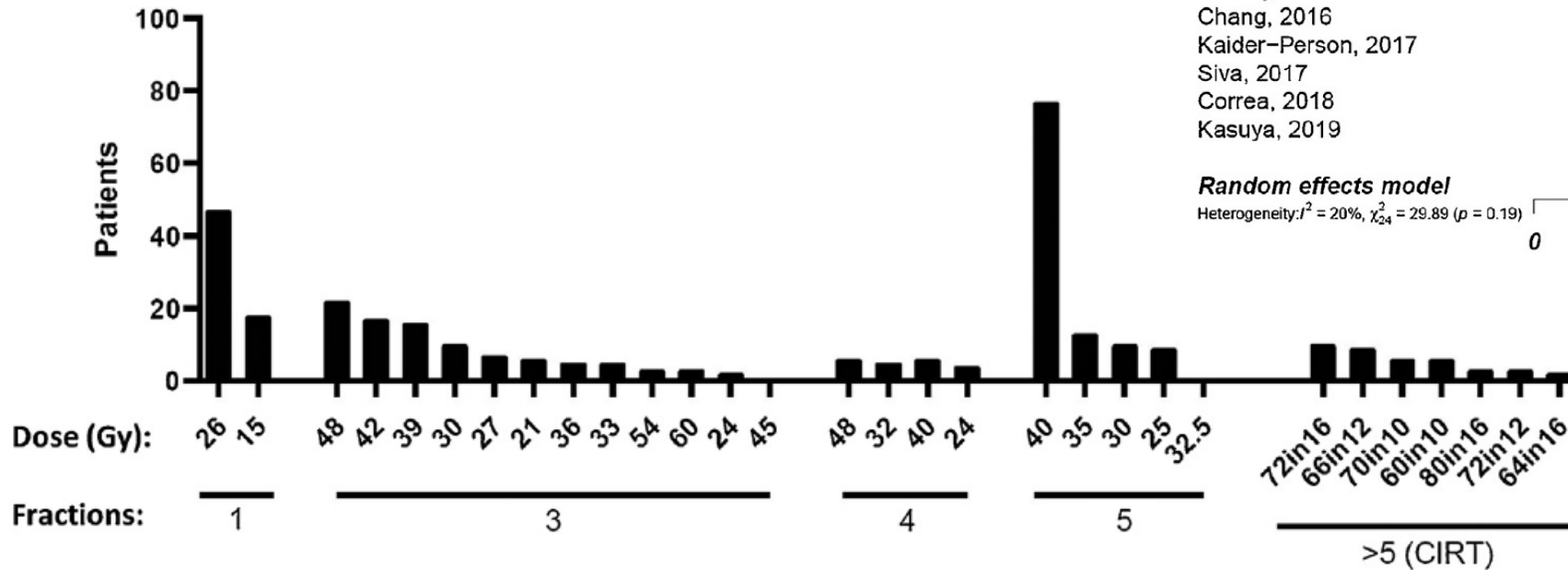
Table 1 – Published reports of stereotactic ablative radiotherapy (SABR) for primary renal cell carcinoma.

1st author (year)	Type	Study type	Patients			Treated tumors	Age (yr)	Tumor size (cm or cm ³)	Follow-Up (mo)	Dose (Gy)/ fractions	Toxicity (CTCAE)		Renal function		Local control (%)
			Total	Stage I-II	Stage III-IV						Grade 3	Grade 4	Pre-SABR eGFR (ml/min)	Post-SABR change in eGFR (ml/min)	
Qian (2003) [14]	Ab	R	20	NR	NR	27	62	367 cm ³	12	40/5	NR	NR	NR	NR	9
Beitler (2004) [15]	Ar	R	9	7	2	11	NR	4.55 cm	26.7	40/5	1 × Gastric ulcer	0	NR	NR	89
Wersall (2005) [16]	Ar	R	8	5	3	8	NR	NR	37	40/5	45% ^a	0	NR	Unchanged	87.5
Gilson (2006) [17]	Ab	R	33	NR	NR	33	62	356 cm ³	17	40/5	NR	NR	NR	NR	94
Svedman (2006) [18]	Ar	P	5	4	1	5	64	NR	52	45/3 40/4 32/4 30/2	0	0	NR	NR	80
Teh (2007) [19]	Ar	R	2	0	2	2	NR	10–200 cm ³	9	24–40/3–6	0	0	NR	Unchanged	100
Svedman (2008) [20]	Ar	R	7	1	6	7	NR	5.5 cm	49	30/3 40/4	0	0	Normal pre-SABR	Unchanged (5 pts) Cr increase (2 pts)	85.7
Wurzer (2012) [21]	Ab	R	23	23	0	23	NR	NR	37	40/5	0	0	NR	NR	87
Chebotareva (2013) [22]	Ab	R	18	0	18	18	NR	5–180 cm ³	15.5	30–52/3–4	0	0	NR	Unchanged (17 pts) Cr increase (1 pt)	100
Nair (2013) [23]	Ar	R	2	2	0	2	NR	21.3 cm ³	13	39/3	0	0	38	+6	100
McBride (2013) [24]	Ab	P	15	15	0	15	75	3.4 cm	36.7	21–48/3	0	0	55	–18	80
Lo (2014) [25]	Ar	R	3	3	0	3	83	5.0 cm	13	40/5	0	0	28.7	–6.7	100
Hanzly (2014) [26]	Ar	R	4	4	0	4	72.5	5.1 cm	21.5	15/1	0	0	NR	Unchanged	75
Ponsky (2015) [27]	Ar	P	19	19	0	19	77.6	57.9 cm ³	13.7	24–48/4	2 × CKD	1 × Duodenal ulcer	NR	NR	100
Stahler (2015) [28]	Ar	P	29	29	0	30	65.6	33.7 cm ³	28.1	26/1	0	0	76.8	–6.5	100
Chang (2016) [29]	Ar	R	16	10	6	16	73	4.0 cm	19	30–40/5	0	2 × CKD	55 ^b	–7.92 ^b	100
Correa (2018) [30]	Ar	R	11	2	9	11	79	9.5 cm	46.8	25–40/5	1 × Nausea	0	48.6	–1.5	70
Sun (2016) [31]	Ar	R	32	32	0	32	74.5	3.9 cm	18.7	21–48/3	NR	NR	NR	NR	92.7
Kaidar-Person (2017) [32]	Ar	R	6	6	0	6	68.5	5.0 cm	29.5	39/3	0	0	NR	Unchanged	100
Siva (2017) [33]	Ar	P	33	33	0	34	78	4.8 cm	24	26/1 or 42/3	1 × NS	0	54.7	–11	97
Singh (2017) [34]	Ar	P	14	0	14	14	63.9	NR	1	15/1	1 × Anemia	0	NR	NR	NR
Correa (2018) [35]	Ar	P	12	0	12	12	66.8	8.7 cm	5.8	25–35/5	2 × Fatigue, 1 × bone pain	0	89.8	–2.8	100
Grubb (2018) [36]	Ab	P	11	11	0	11	72	3.6 cm	20.4	48–60/3	1 × Pyelo.	0	NR	NR	90.9
Kasuya (2018) [37]	Ar	P	19	15	4	19	67	3.6 cm	79.2	66–80/12–16 (CIRT)	0	1 × Dermatitis; 2 × CKD	42.7	–15.6 ^b	94.1
Kasuya (2019) [39]	Ar	P	8	7	1	8	71	4.3 cm	43.1	66–72/12 (CIRT)	0	0	64.1	–10.8	100
Funayama (2019) [38]	Ar	P	13	13	0	13	72	2.28 cm	48.3	60 or 70/10 (CIRT)	0	2 × CKD	51.9	–16.8	92.3

SBRT as primary treatment

Systematic review and meta-analysis

- 26 studies
- 11 prospective trials
- 372 pts



SBRT as primary treatment

Individual patient data meta-analysis - International Radiosurgery Consortium of the Kidney (IROCK)

- Primary RCC
- Age >18
- Inoperable - declined surgery
- Follow-up at least 2 yrs
- Any performance status
- No previous local therapy
- No adjuvant or concurrent systemic therapy

Primary endpoint investigator-assessed LC per RECIST

- (2007-2018) 190 pts
- 56 (29%) had solitary kidney
- Median age 73 (IQR, 66.2-82)
- Median fu 5 yrs (IQR, 3.4-6.8)
- Median tumor diameter 4 cm (IQR, 2.8-4.9)
- Median RENAL score 7 (IQR, 5-9)
- Single fraction 81 (43%) [25 Gy/1 fr] – Multifraction 109 (57%) [42 Gy (IQR, 35-48)/2-10 frs]

SBRT as primary treatment

Individual patient data meta-analysis - IROCK

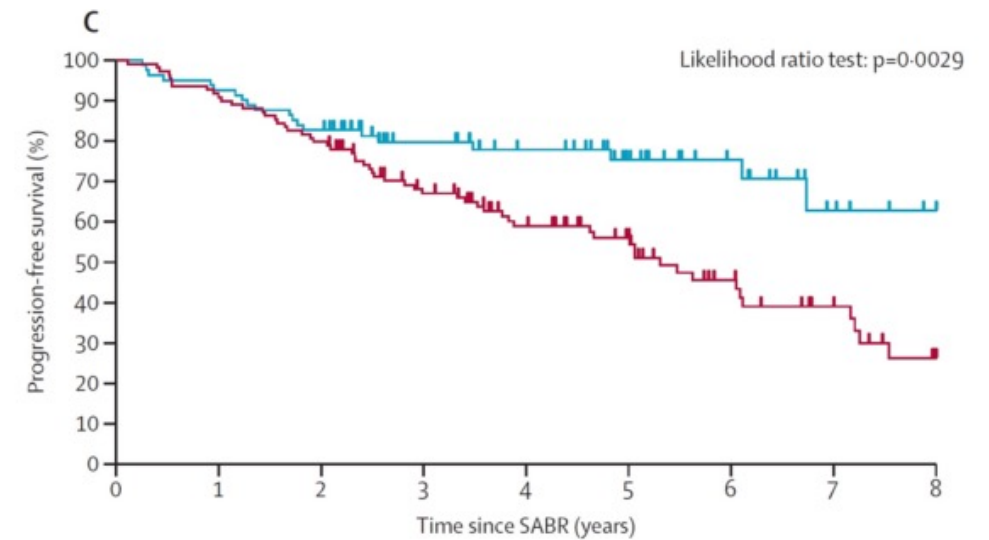
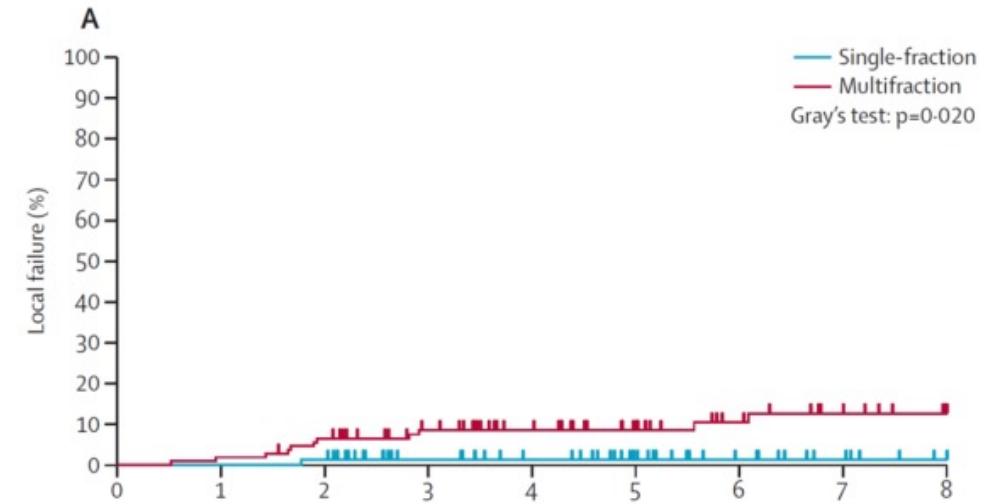
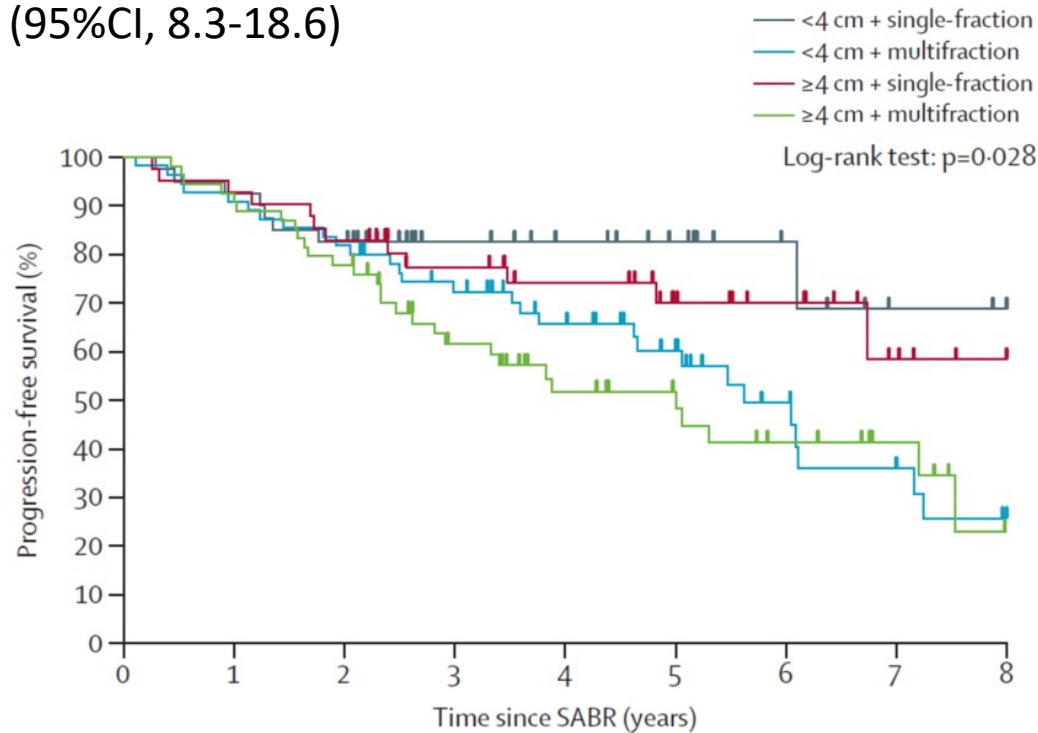
Median decrease in eGFR 14.2 ml/min (IQR, 5.4-22.5)

RENAL score > 7 was associated with a larger eGFR decrease

10/190 (5%) cancer-related deaths

5-yrs failure:

- local 5.5% (95%CI, 2.8-9.5)
- distant 10.8% (95%CI, 6.6-16.2)
- any 13% (95%CI, 8.3-18.6)



SBRT as primary treatment

Retrospective analysis - Results of SBRT for primary RCC, a multicenter retrospective series (supported by GETGUG)

16 participating centers
(Australia, France, Italy, and the Netherlands)

- Primary RCC
- Age >18
- Inoperable - declined surgery
- Follow-up at least 2 yrs
- **Any performance status**
- **No previous local therapy**
- **No adjuvant or concurrent systemic therapy**

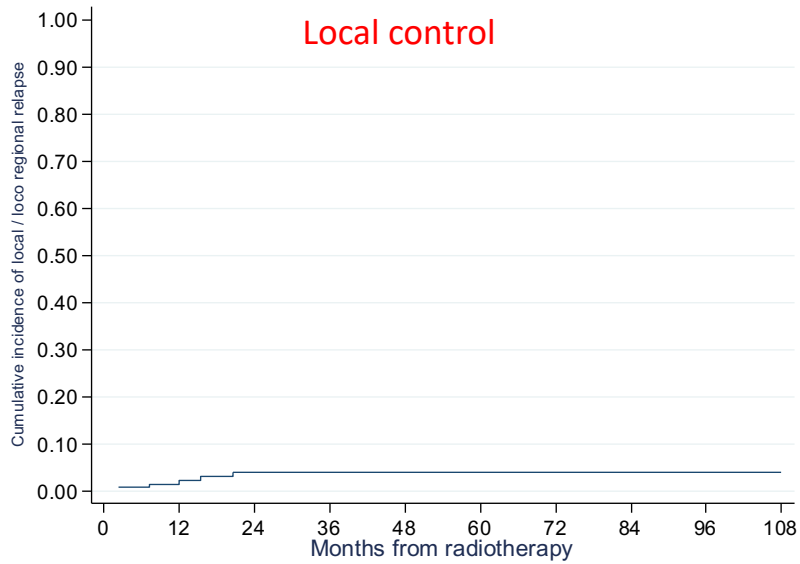
Primary endpoint investigator-assessed LC per RECIST

Secondary endpoints OS, CSS, toxicity, renal function

- (2008-2020) **145 pts**
- 56 (29%) had solitary kidney
- Median **age 76** (IQR, 67-82)
- Median fu 3.4 yrs (IQR, 2.0-6.7)
- Median **tumor diameter 4.2 cm** (IQR, 3.3-5.5)
- Median **RENAL score 8** (IQR, 5-9)

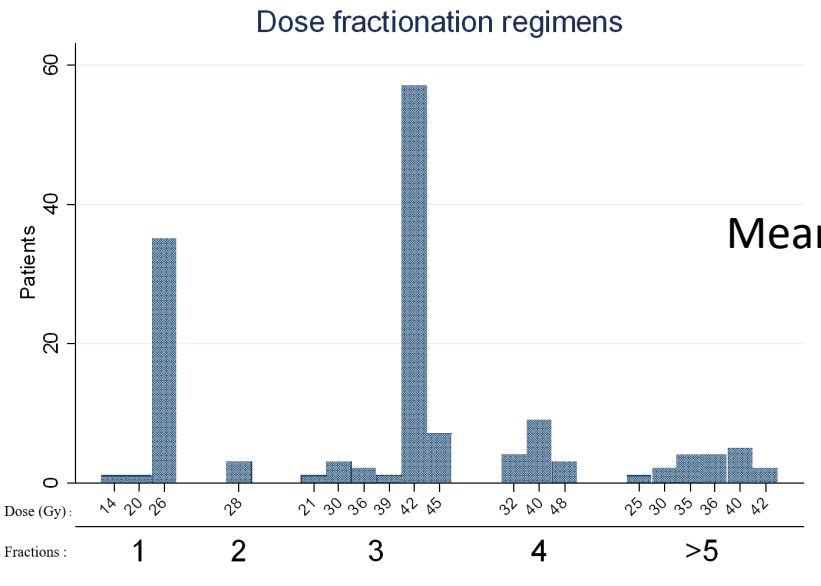
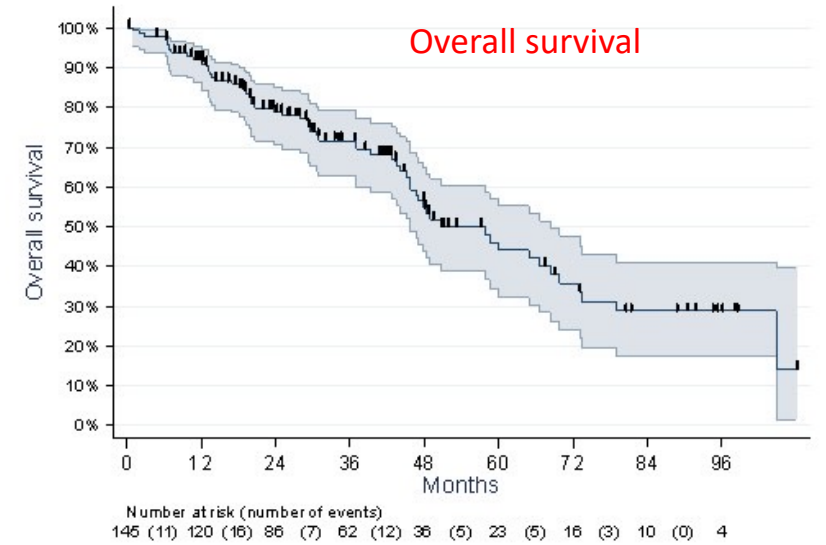
SBRT as primary treatment

Retrospective analysis - Results of SBRT for primary RCC, a multicenter retrospective series (supported by GETGUG)

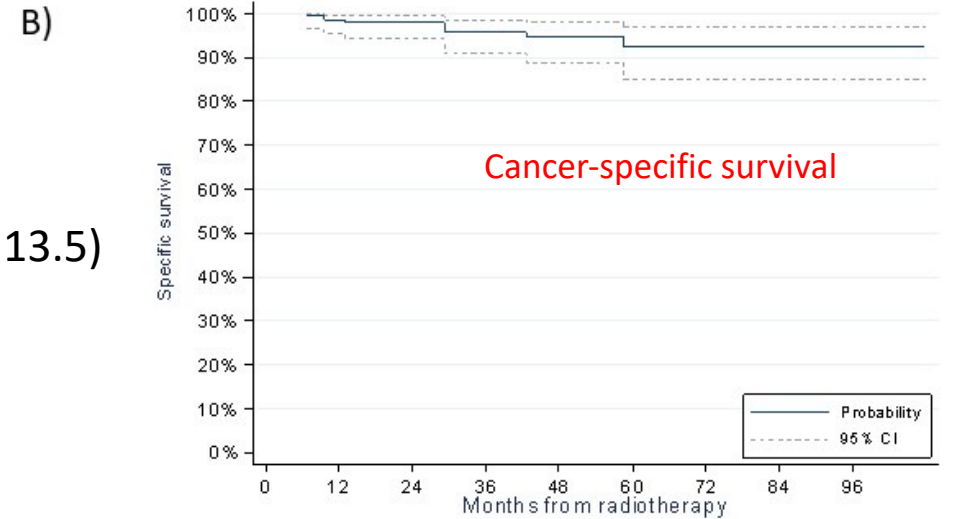


145 patients

- 5-yrs **96%** (95%CI, 92-99)
- LRFS **91%** (95%CI, 84-96)
- CSS



Mean decrease in eGFR 10 ml/min (SD 13.5)



SBRT as primary treatment

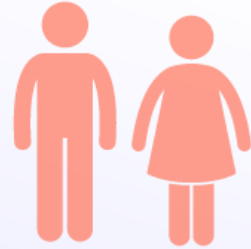
cT1 treatment options - comparison

	IROCK (cT1a-1b)	Mayo Clinic (cT1a)		
	SABR (MØ 4 cm; 190 pts)	PN (MØ 2.4 cm; 1055 pts)	RFA (MØ 1.9 cm; 175 pts)	CRYO (MØ 2.8 cm; 178 pts)
5-yrs				
LRFS	93.7% (95%CI, 88.5-96.6)	97.7% (95%CI, 96.7-98.6)	95.9% (95%CI, 92.3-99.6)	95.9% (95%CI, 92.3-99.6)
FFDF	87.3% (95%CI, 80.3-92.0)	98.0% (95%CI, 97.0-99.0)	93.9% (95%CI, 88.3-100)	100% (95%CI, 100-100)
CSS	92% (95%CI, 85.2-95.8)	99.3% (95%CI, 98.7-99.9)	95.6% (95%CI, 89.7-100)	100% (95%CI, 100-100)

SBRT as primary treatment

Phase II non-randomized trial - FASTER II

- 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*



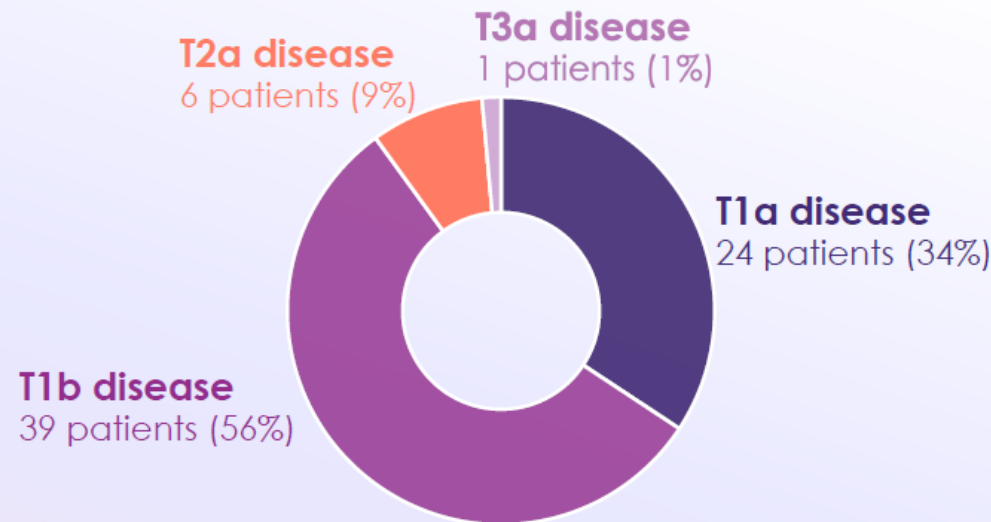
Median age: **77 years**

BMI: **32 kg/m²**

Charlson comorbidity index: **7**

70 pts

Median tumor size: 4.6 cm



∅ ≤ 4 cm - 1 x 26 Gy
∅ > 4 cm - 3 x 14 Gy

Courtesy Prof. Shankar Siva (Peter MacCallum Cancer Center, Victoria Australia)

SBRT as primary treatment

Phase II non-randomized trial - FASTRACK II

TROG 15.03
FASTRACK II
TRIAL

Clinical outcomes
at a median follow-up of 43 months



Local control rate
100%



Freedom from
distant failure
99%

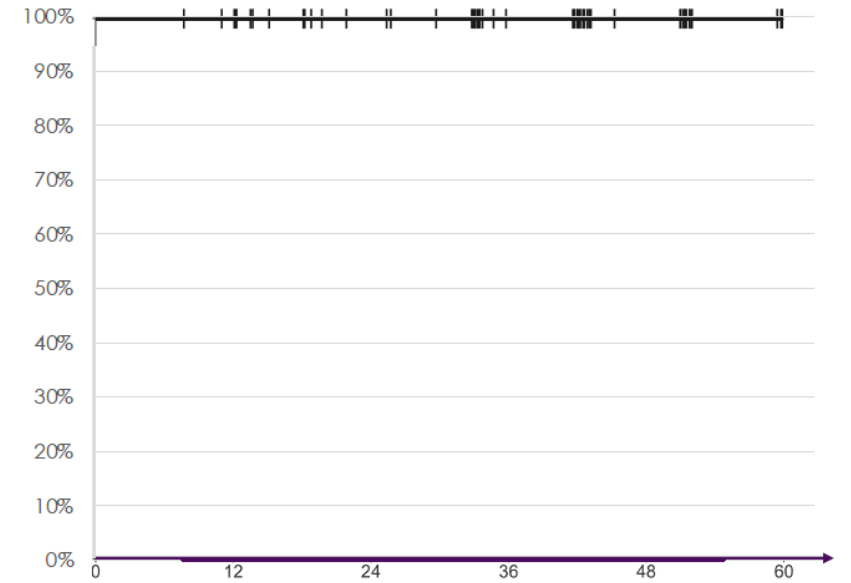


Cancer specific
survival
100%

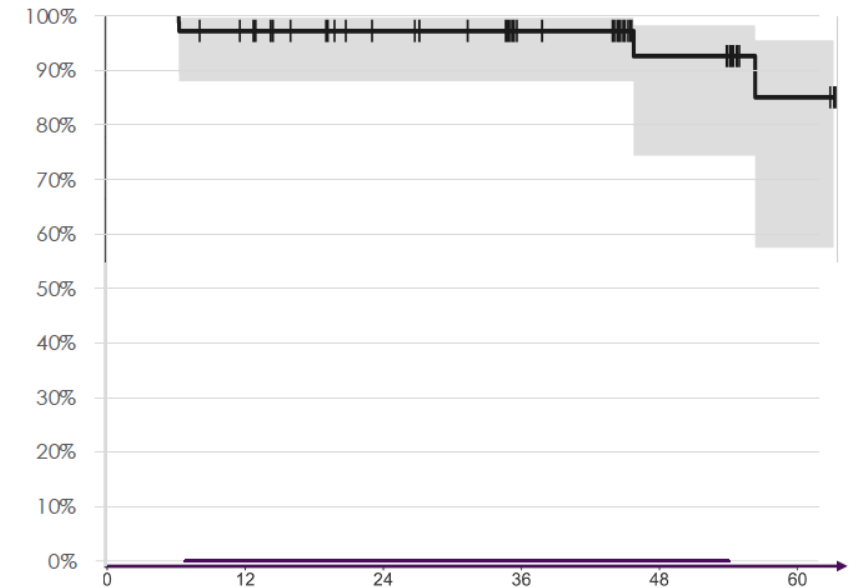


Kidney function loss
(1 patient underwent dialysis)
-14.6 mls/min

Local Control rate
(RECIST criteria)



Freedom from
distant failure



Courtesy Prof. Shankar Siva (Peter MacCallum Cancer Center, Victoria Australia)

SBRT as primary treatment

Phase II non-randomized trial - FASTRACK II

TROG 15.03
FASTRACK II
TRIAL

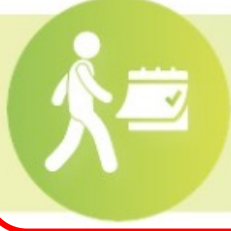
Clinical outcomes
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Local control rate
100%



Freedom from
distant failure
99%

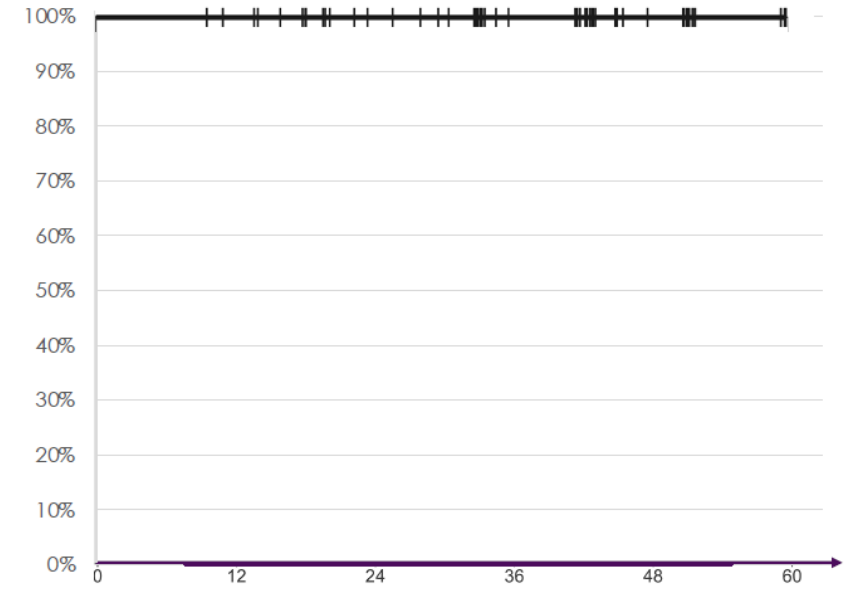


Cancer specific
survival
100%

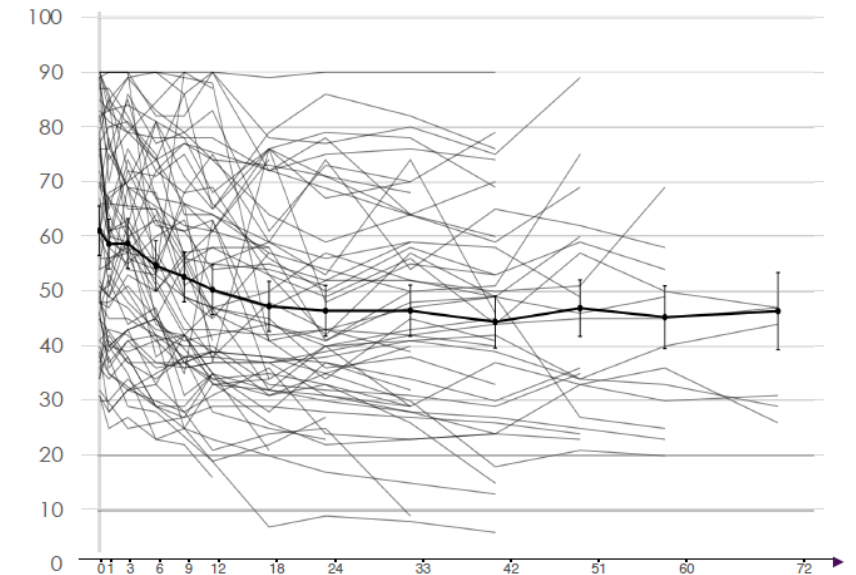


Kidney function loss
(1 patient underwent dialysis)
-14.6 mls/min

Cancer specific survival



eGFR, mLs/min (CDK-EPI)

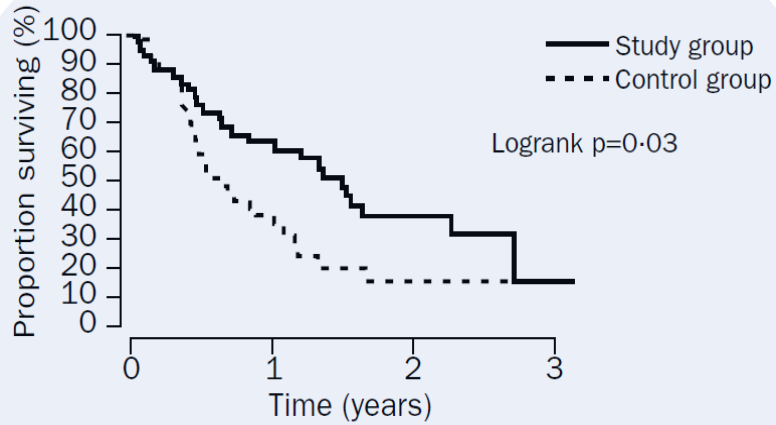


Courtesy Prof. Shankar Siva (Peter MacCallum Cancer Center, Victoria Australia)

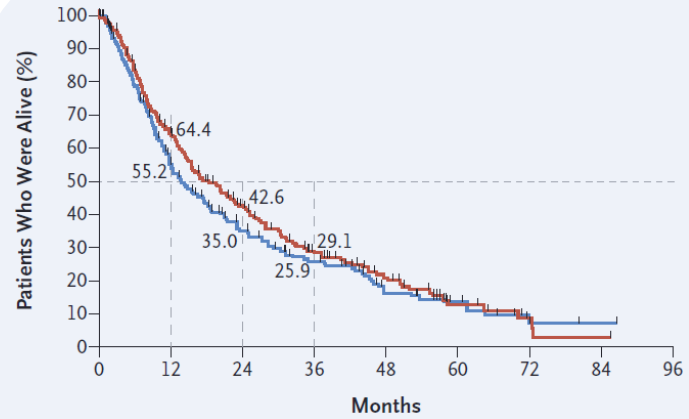
[3] Metastatic RCC

- Cytoreductive nephrectomy
- Systemic therapy
- SBRT as cytoreductive therapy
- SBRT for oligometastatic disease

Cytoreductive Nephrectomy

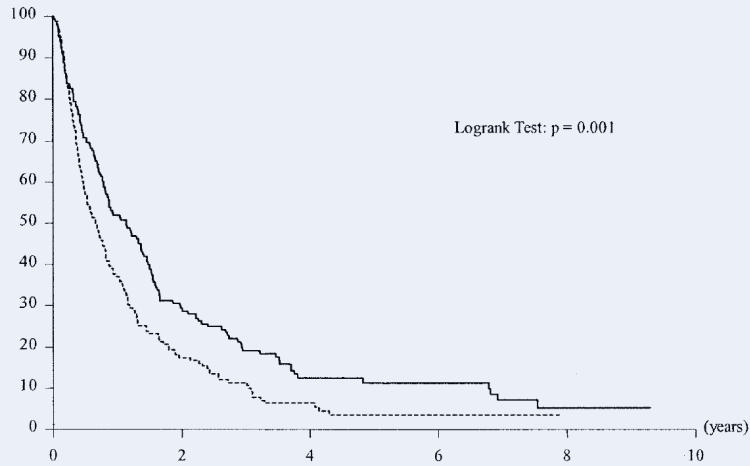


Mickisch GH, Lancet 2001



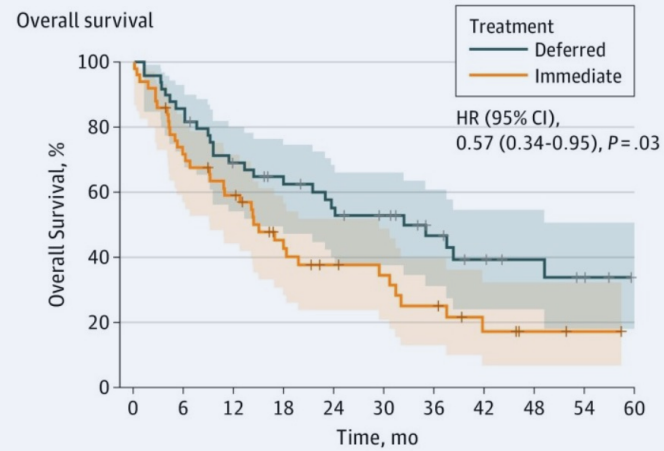
Mejean A, NEJM 2018 - CARMENA

CN + INF



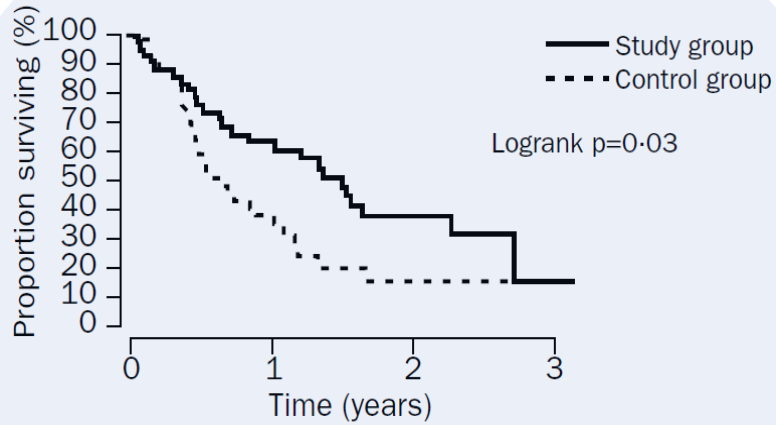
Flanigan RC, J Urol 2004

CN + TKI



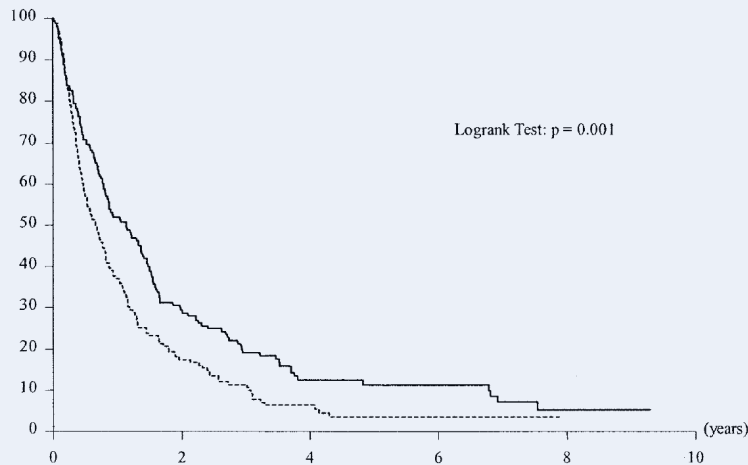
Bex A, JAMA Oncol 2019 - SURTIME

Cytoreductive Nephrectomy

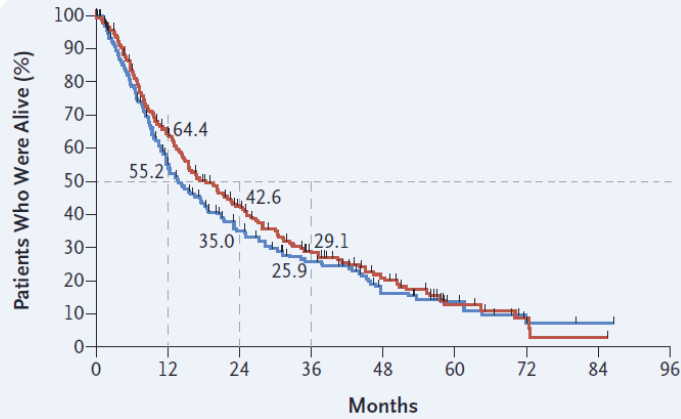


Mickisch GH, Lancet 2001

CN + INF

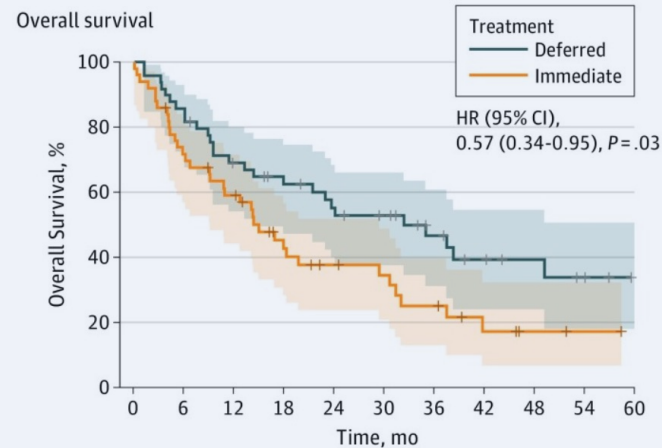


Flanigan RC, J Urol 2004



Mejean A, NEJM 2018 - CARMENA

CN + TKI



Bex A, JAMA Oncol 2019 - SURTIME

Systemic therapy

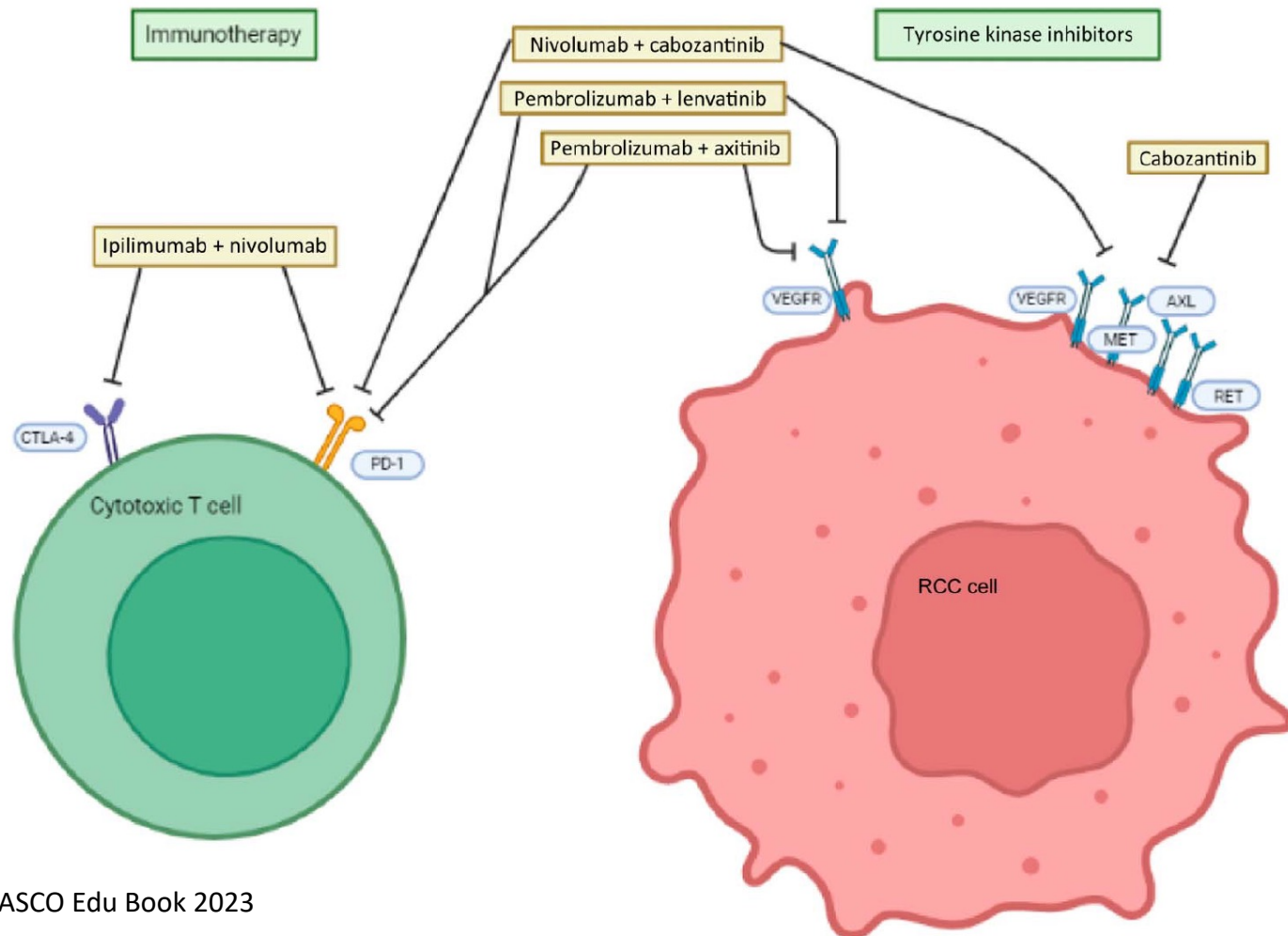
CLEAR [2019]
lenvatinib + pembrolizumab /
lenvatinib + everolimus

KEYNOTE-426 [2019]
axitinib + pembrolizumab

CHECKMATE-9ER [2021]
cabozantinib + nivolumab

CHECKMATE-214 [2018]
ipilimumab + nivolumab

Systemic therapy



sunitinib

CLEAR [2019]
lenvatinib + pembrolizumab /
lenvatinib + everolimus

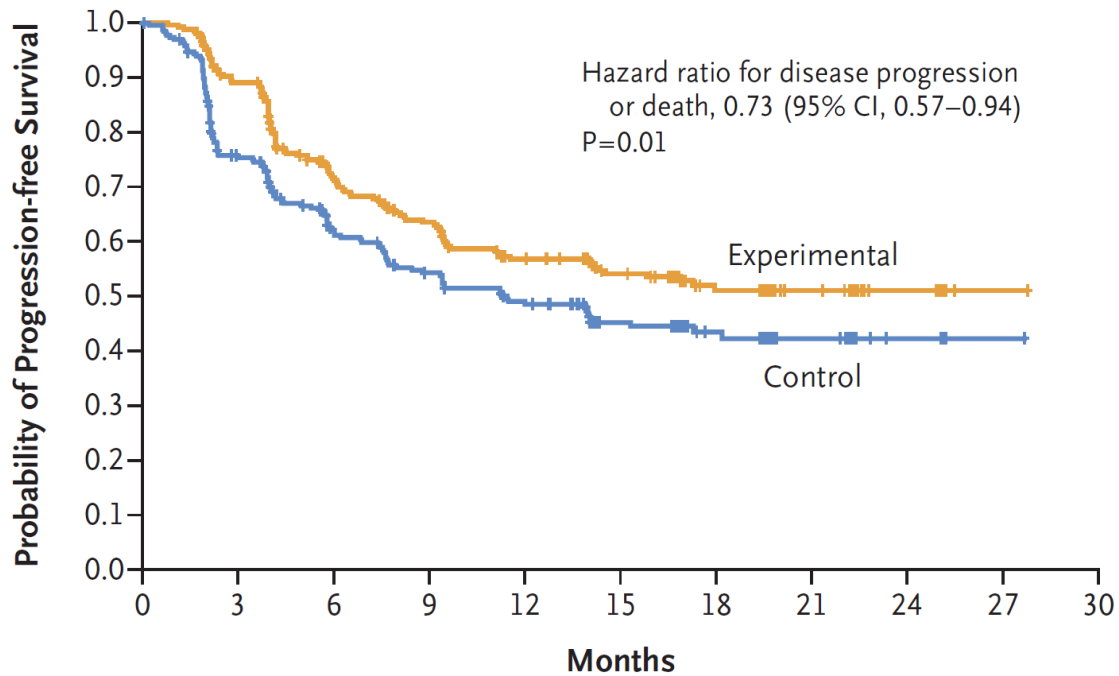
KEYNOTE-426 [2019]
axitinib + pembrolizumab

CHECKMATE-9ER [2021]
cabozantinib + nivolumab

CHECKMATE-214 [2018]
ipilimumab + nivolumab

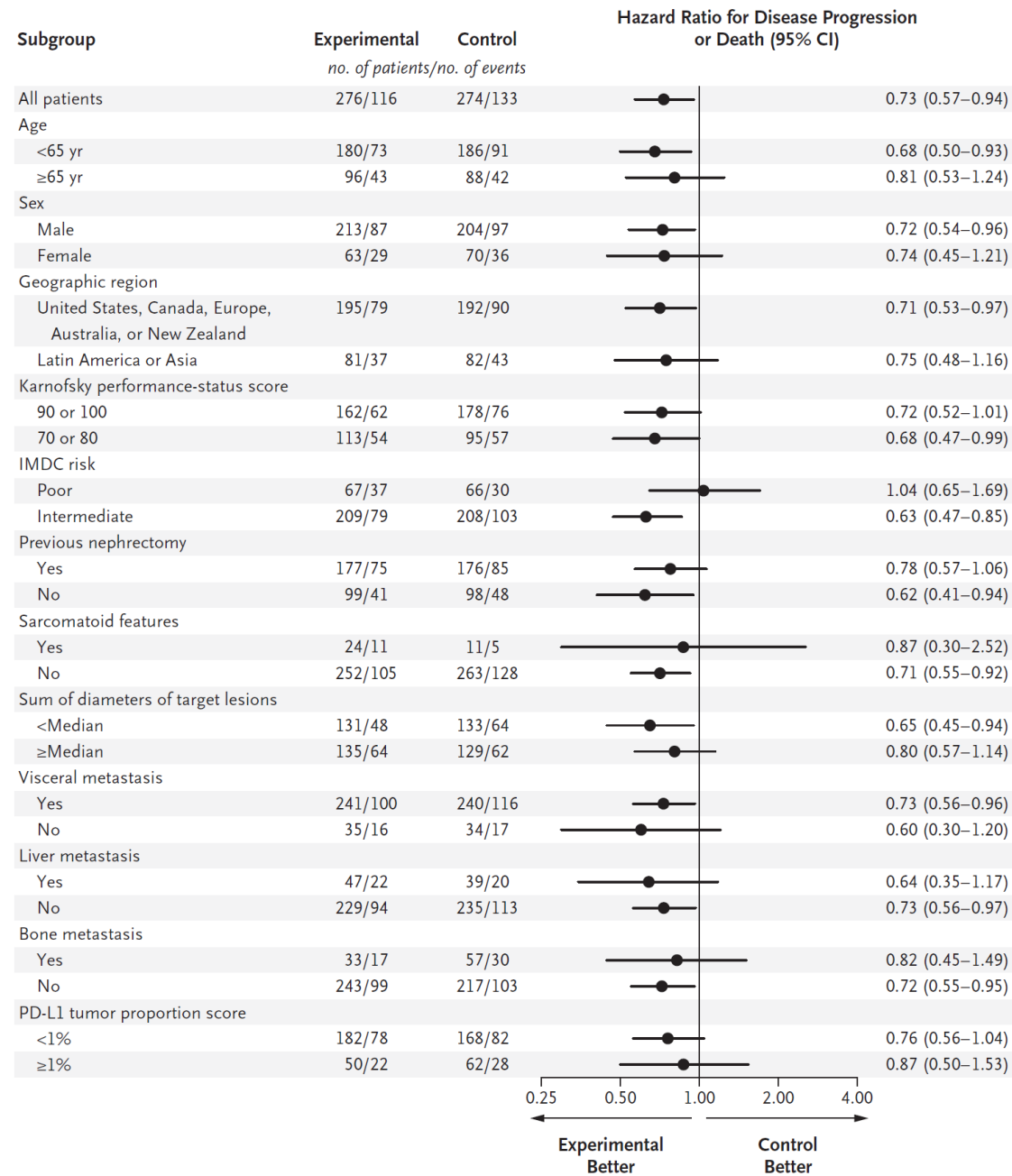
Systemic therapy

COSMIC-313 [2023]
ipilimumab + nivolumab + cabozantinib

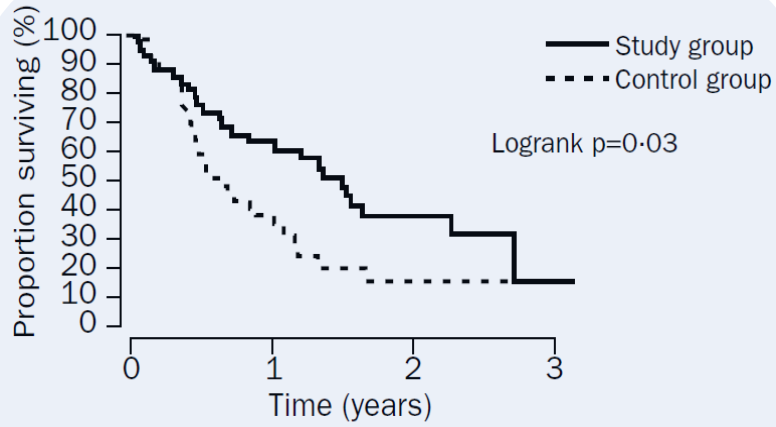


Event	Experimental (N=426)		Control (N=424)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any event	425 (100)	337 (79)	424 (100)	236 (56)

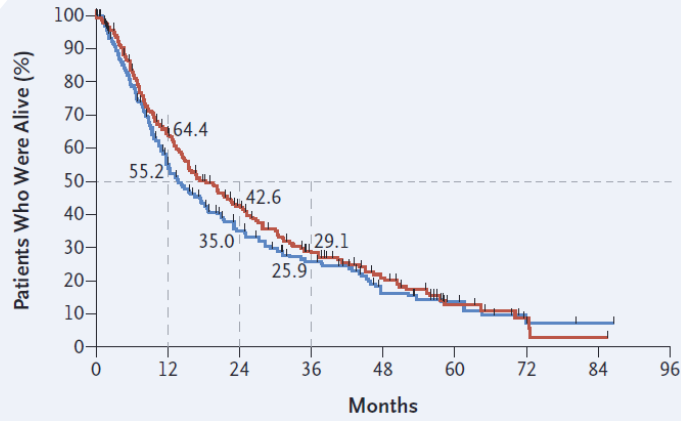
number of patients (percent)



Cytoreductive Nephrectomy

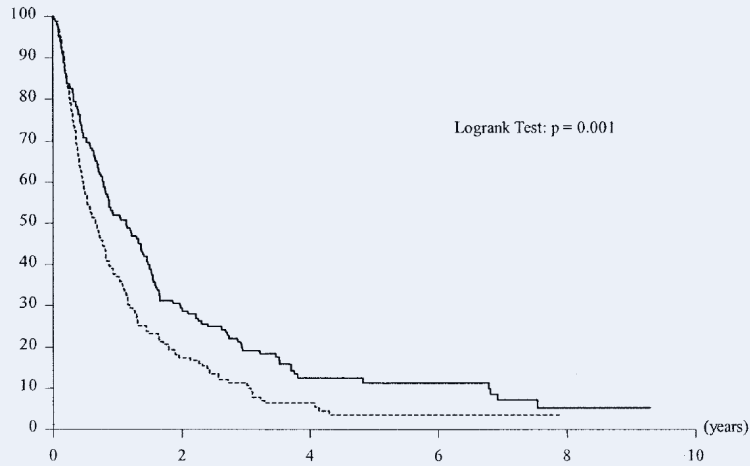


Mickisch GH, Lancet 2001



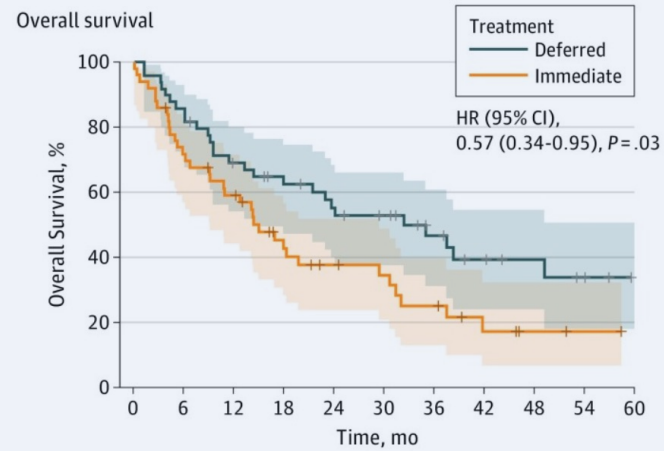
Mejean A, NEJM 2018 - CARMENA

CN + INF



Flanigan RC, J Urol 2004

CN + TKI



Bex A, JAMA Oncol 2019 - SURTIME

CN + IO/TKI

?

?

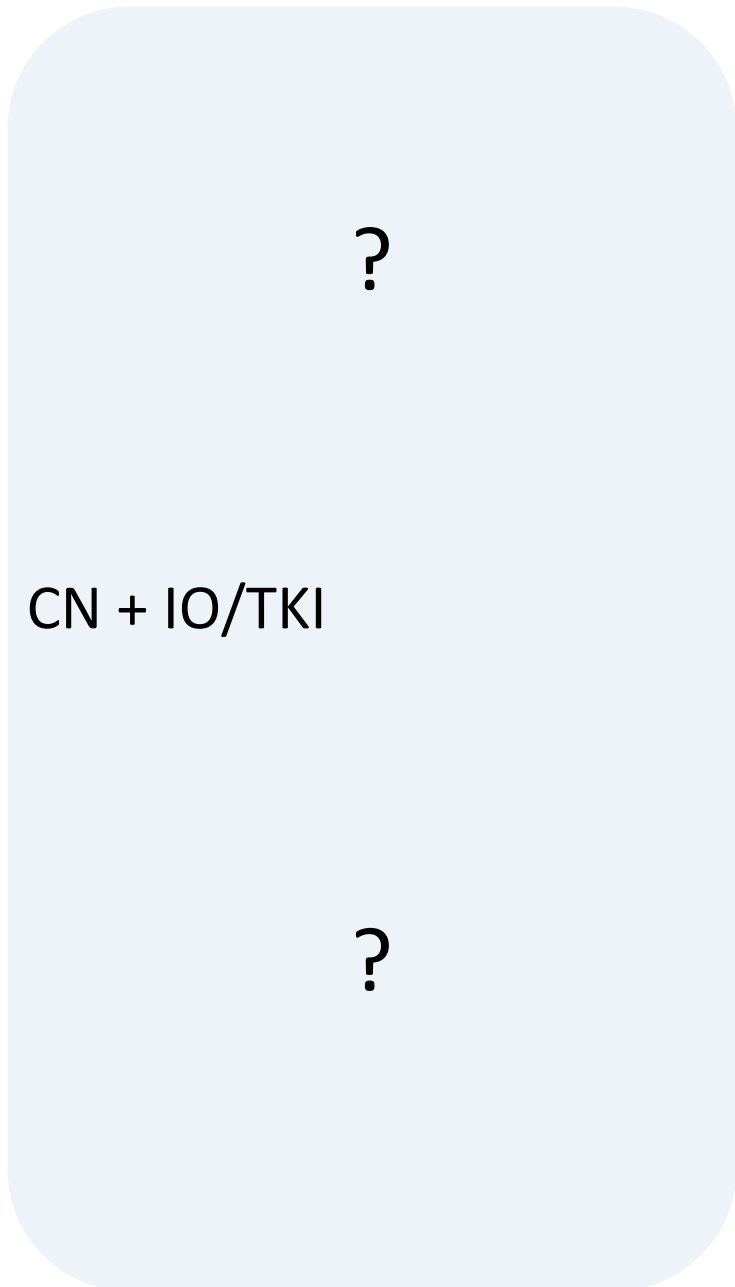
Cytoreductive Nephrectomy

JAVELIN Renal 101 [2019]
axitinib + avelumab vs sunitinib

Synchronous M1 (412 pts)

- TKI + ICI (198 pts): prior CN, 126 (64%) pts
- TKI (214 pts): prior CN, 147 (68%) pts

Prior CN vs no prior CN	HR (95%CI) PFS	HR (95%CI) OS
Avelumab + axitinib	0.79 (0.53-1.16)	0.59 (0.38-0.93)
Sunitinib	1.15 (0.77-1.70)	0.86 (0.55-1.34)



Cytoreductive Nephrectomy

IMDC real-world [2024]
IO/IO doublet or IO/TKI

Table 1 – Baseline patient characteristics by CN status

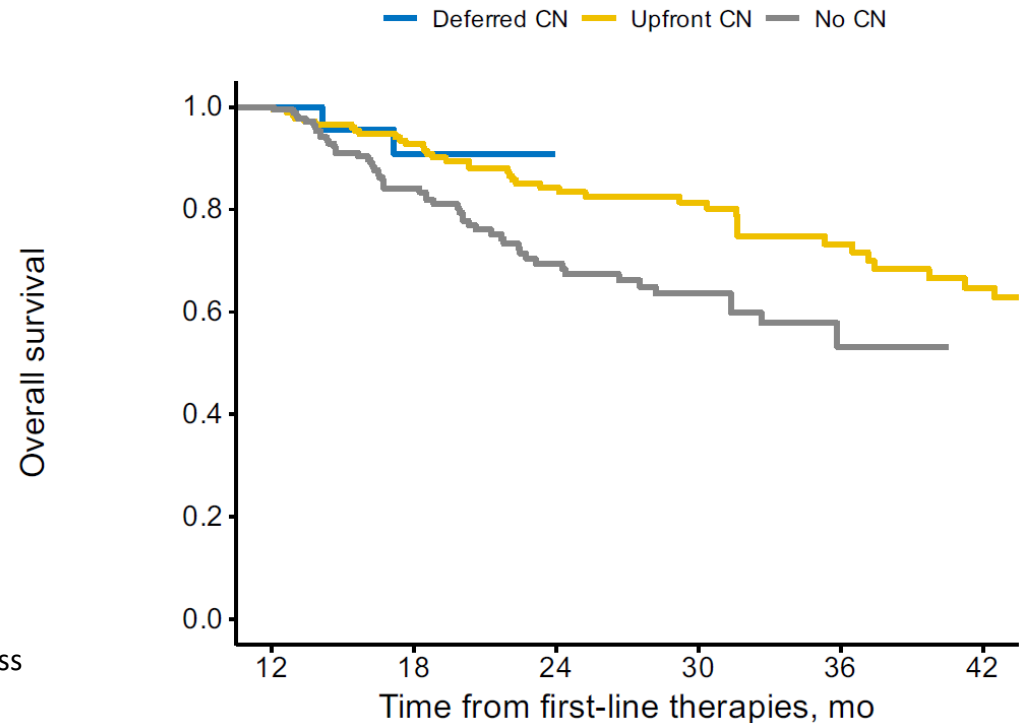
Variable	Deferred CN (N = 24)	Upfront CN (N = 182)	No CN (N = 179)	p value
Median age, yr (interquartile range)	57 (50–65)	60 (52–67)	63 (57–70)	< 0.001
Male, n/N (%)	18/24 (75)	137/182 (75)	127/179 (71)	0.6
Non-clear cell histology, n/N (%)	9/20 (45)	21/156 (14)	9/119 (7.6)	< 0.001
Sarcomatoid dedifferentiation, n/N (%)	4/15 (27)	42/147 (29)	13/107 (12)	0.004
Brain metastases, n/N (%)	2/23 (8.7)	9/173 (5.2)	14/172 (8.1)	0.5
Bone metastases, n/N (%)	6/23 (26)	41/175 (23)	77/176 (44)	< 0.001
Liver metastases, n/N (%)	1/23 (4.3)	23/173 (13)	32/172 (19)	0.14
IMDC prognostic category, n/N (%)				< 0.001
Favorable	0/19	13/168 (7.7)	3/153 (2.0)	
Intermediate	10/19 (53)	116/168 (69)	83/153 (54)	
Poor	9/19 (47)	39/168 (23)	67/153 (44)	

CN = cytoreductive nephrectomy; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium.

Treatment naive M1 (385 pts)

- IO/IO doublet: 280 pts
- IO/TKI: 105 pts

- 24 deferred CN
- 182 upfront CN
- 179 no CN



Takemura K, Eur Urol in press

Cytoreductive Nephrectomy

Ongoing phase II - III trials

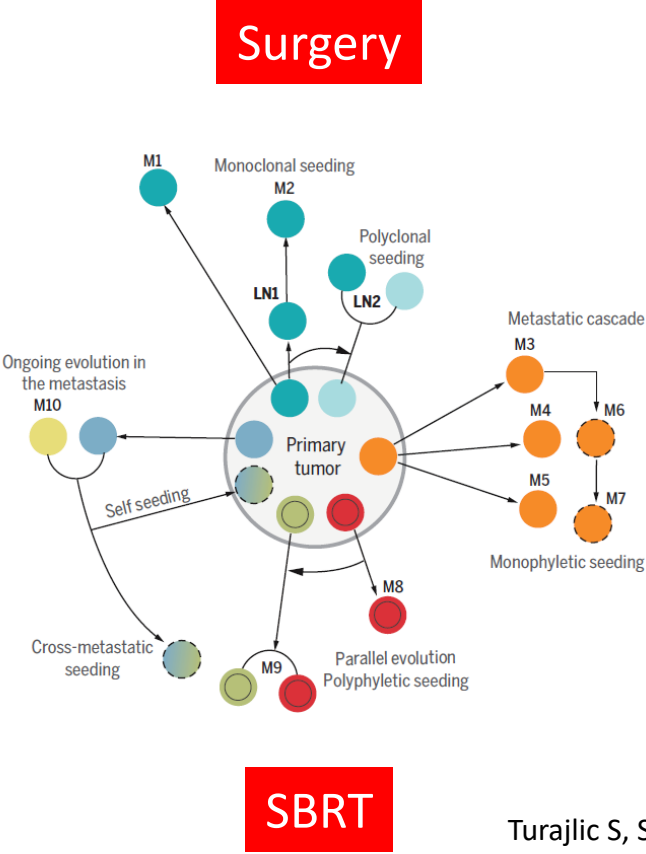
NCT04370509 ³⁶	Recruiting, estimated completion in 2025	ccRCC treated with pembrolizumab with or without axitinib for 9 weeks before nephrectomy or metastasectomy, M0, or mRCC	Primarily the impact of pembrolizumab on composition, phenotype, and function of tumor-infiltrating immune cells Secondarily efficacy, safety, and tolerability of preoperative pembrolizumab	Immunologic impact of pembrolizumab on RCC Efficacy and safety of neoadjuvant pembrolizumab with or without axitinib before CN or metastasectomy
NCT05319015 ³⁷	Recruiting, estimated completion in 2025	RCC with IVC tumor thrombus treated with lenvatinib + pembrolizumab before nephrectomy and IVC thrombectomy, M0, or mRCC	Primarily disease control rate, local and metastatic progression rate, postoperative complications	Efficacy and safety of neoadjuvant lenvatinib + pembrolizumab in patients with RCC with IVC thrombus, many of whom will have mRCC
NORDIC-SUN ³⁸	Recruiting, estimated completion in 2026	mRCC receiving doublet systemic therapy, randomly assigned to CN v no CN if resectable and 3 or less IMDC risk factors are present after 3 months of ST; reassessed for random assignment after 6 months of ST if not eligible at 3 months	Primarily OS	Assess the role for CN in mRCC with contemporary ST regimens
CYTO-KIK ³⁹	Recruiting, estimated completion in 2027	Clear cell mRCC receives cabozantinib and nivolumab for 12 weeks before nephrectomy	Primarily complete response rate Secondarily median size reduction of primary tumor, PFS, response rate, OS, surgical outcomes	Oncologic and perioperative outcome data after neoadjuvant treatment with cabozantinib + nivolumab
PROBE ⁴⁰	Recruiting, estimated completion in 2033	mRCC receiving doublet systemic therapy, randomly assigned to nephrectomy v no nephrectomy in the absence of progression at 12 weeks	Primarily OS	Assess the role for CN in mRCC with contemporary ST regimens

SBRT as cytoreductive therapy: rationale

1. Early ablation may prevent further metastatic seeding, and result in long-term freedom from disease
2. Positive impact on metastatic cross-talk
3. Trigger immune-response



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



SBRT as cytoreductive therapy

NCT05024318 - NeoAdjuvant Pembrolizumab and STereotactic Radiotherapy Prior to Nephrectomy for RCC (NAPSTER)

SABR as neoadjuvant treatment + IO in advanced or mRCC

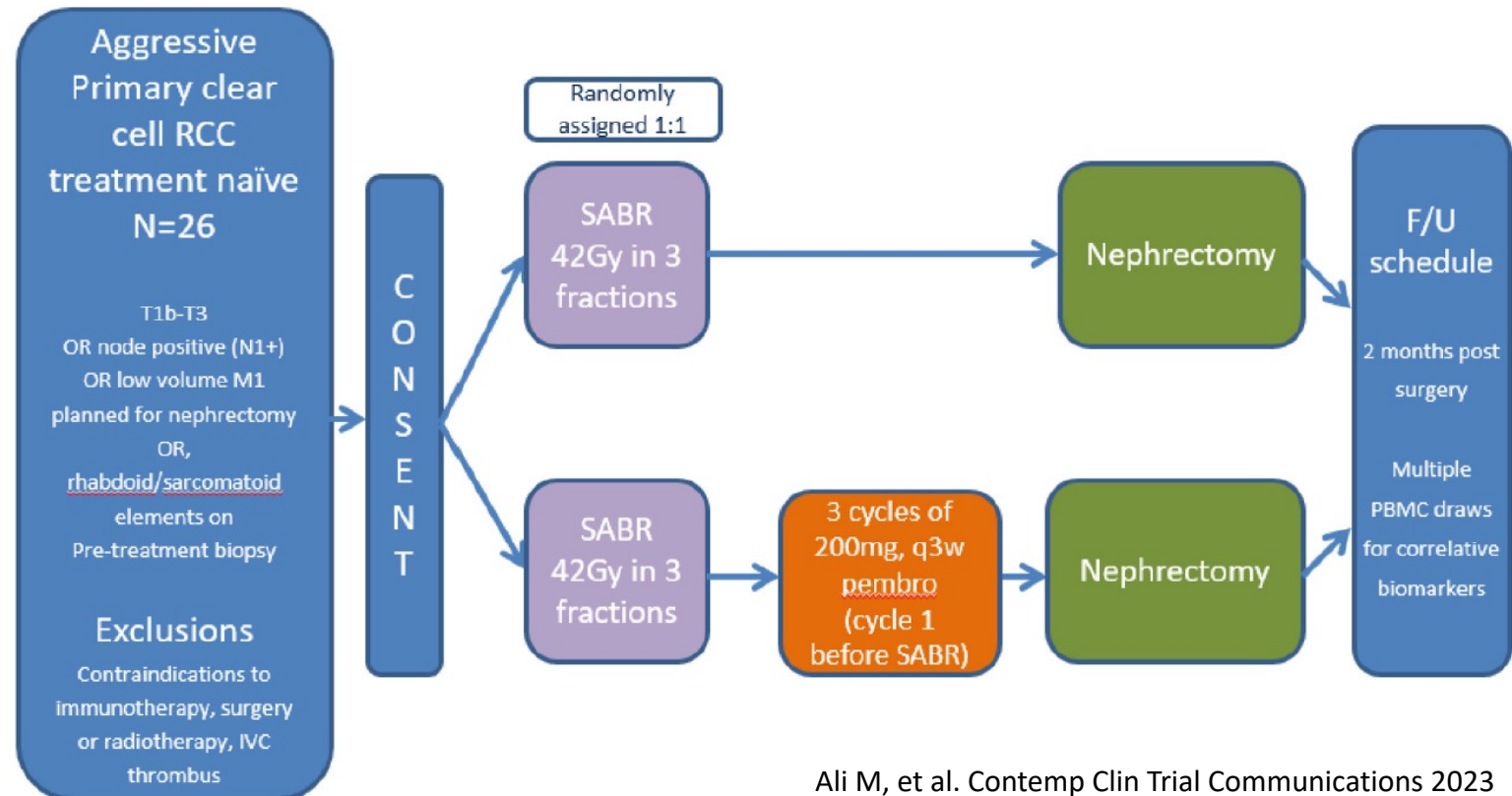
Primary endpoint:

- Major pathological response [MPR] (defined as < 10% viable cells)
- Tumoral microenvironment inflammation modifications

Secondary endpoints:

- Safety of IO+SBRT
- Association immune response - MPR
- Changes in PD-L1 PD-L2 expression in tumor

NAPSTER schema (n=26)



SBRT as cytoreductive therapy

NCT05327686 - Testing the Addition of SBRT With Immunother. for Patients With Unresectable or mRCC, SAMURAI Study

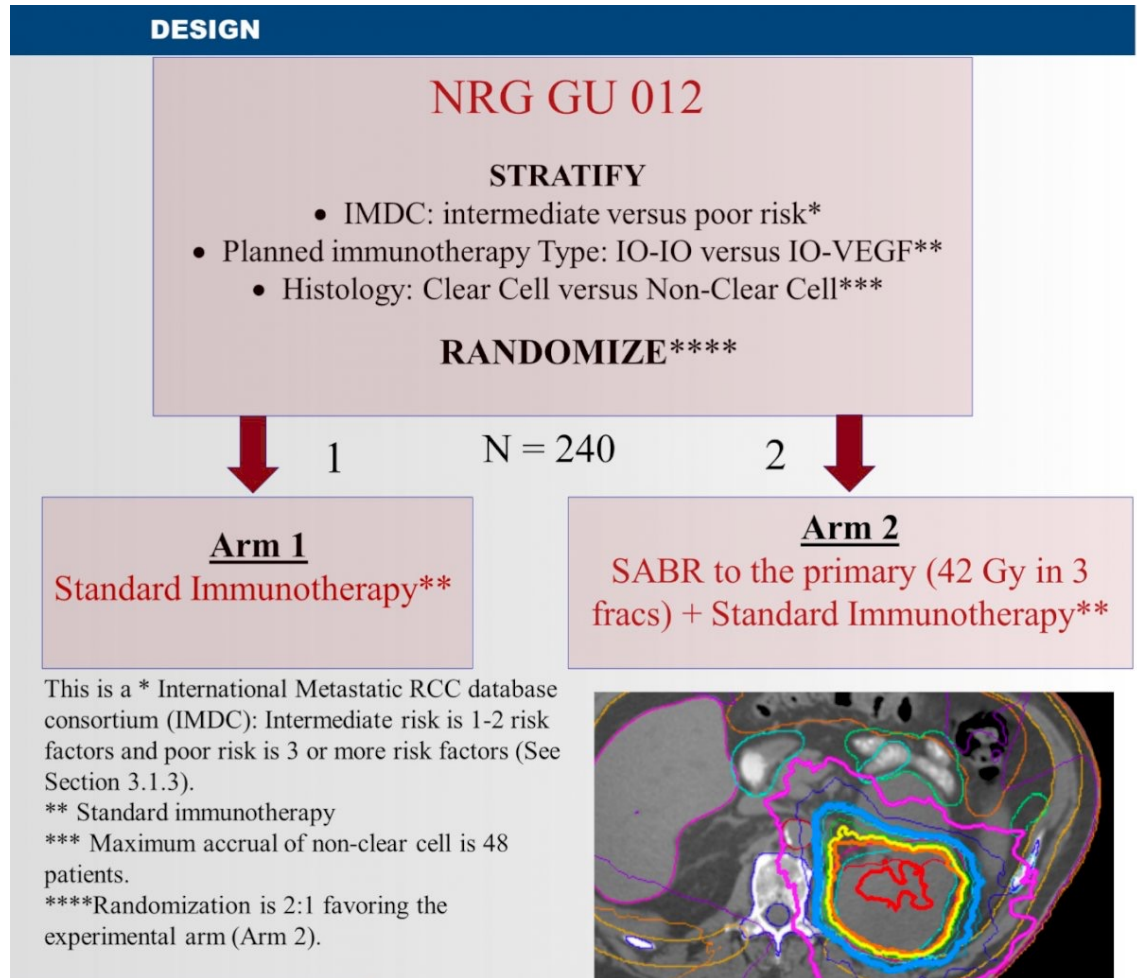
SABR as an alternative approach to treat the primary tumor in mRCC pts receiving IO, not eligible or declining surgery

Primary endpoint:

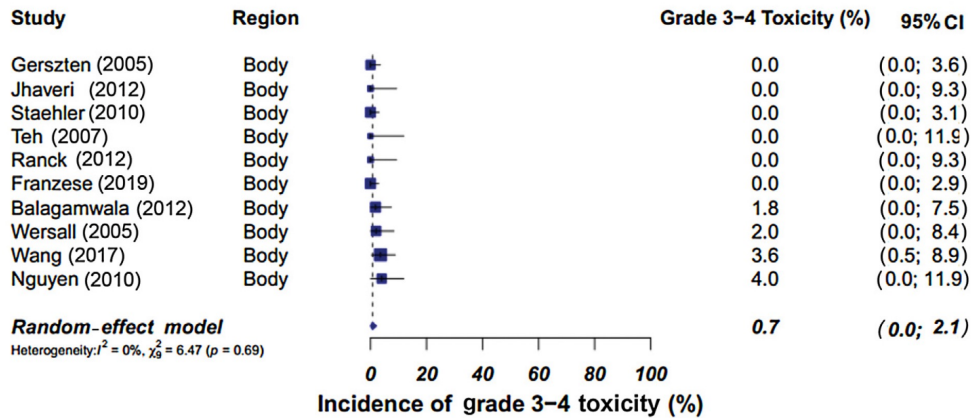
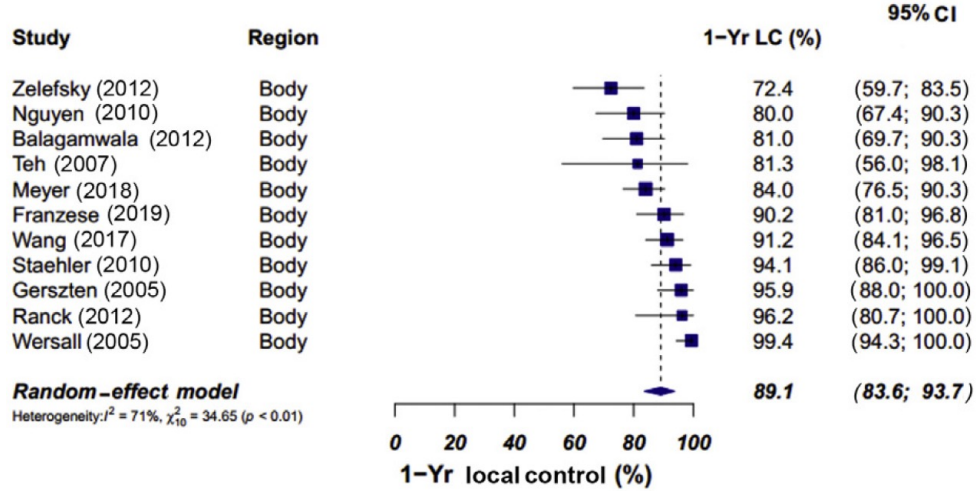
- nephrectomy and radiographic progression-free survival

Secondary endpoints:

- time to second-line therapy
- rate of cytoreductive nephrectomy
- Treatment-free survival
- overall survival



SBRT for oligometastatic disease



EA8211 SOAR (NCT 05863351) Randomized Phase III Non-inferiority Trial of SBRT vs Systemic Therapy for Oligometastatic RCC

Hypothesis:

- For Oligometastatic RCC, sequential disease control with SAbR will not be inferior to upfront systemic therapy for OS.

Co-Primary Endpoints:

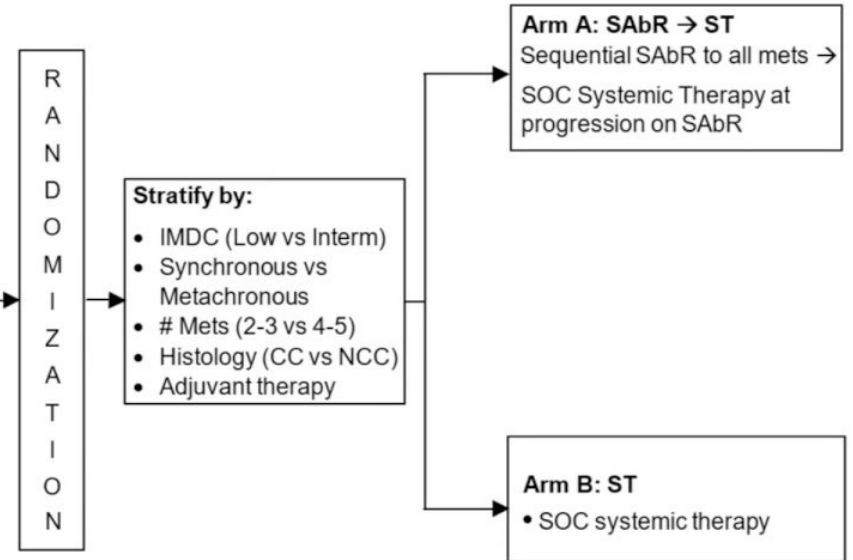
- OS: time from randomization until death from any cause (intent-to-treat)
- Gr ≥ 3 AEs

Eligibility:

- Metastatic RCC
- Primary site addressed by surgery
- No Brain metastasis
- IMDC favorable and intermediate
- Total 2-5 metastatic lesions
- All metastasis amenable to SAbR

Secondary Endpoints:

- PFS, Toxicity
- Cost-effectiveness



2023 - Localized RCC - SBRT

Population: > 70 yrs

Median:

- IROCK - 73 yrs
- GETUG - 76 yrs
- FASTER II - 77 yrs

Tumor size: ≤ 10 cm

Median:

- IROCK - 4 cm
- GETUG - 4.2 cm
- FASTER II - 4.6 cm

Treatment schedule: 26 Gy/1 fr or 42 Gy/3 frs

$\emptyset \leq 4$ cm - 1 x 26 Gy

$\emptyset > 4$ cm - 3 x 14 Gy

Decrease in eGFR: 14 ml/min

- IROCK - 14.2 ml/min
- GETUG - 10 ml/min
- FASTER II - 14.6 ml/min



2023 - Metastatic RCC

Cytoreductive nephrectomy in the IO/TKI era

Phase III trials:

- NORDIC-SUN
- PROBE

Systemic therapy

Phase III trial:

- COSMIC

SBRT as cytoreductive therapy

Phase II trials:

- NAPSTER
- SAMURAI

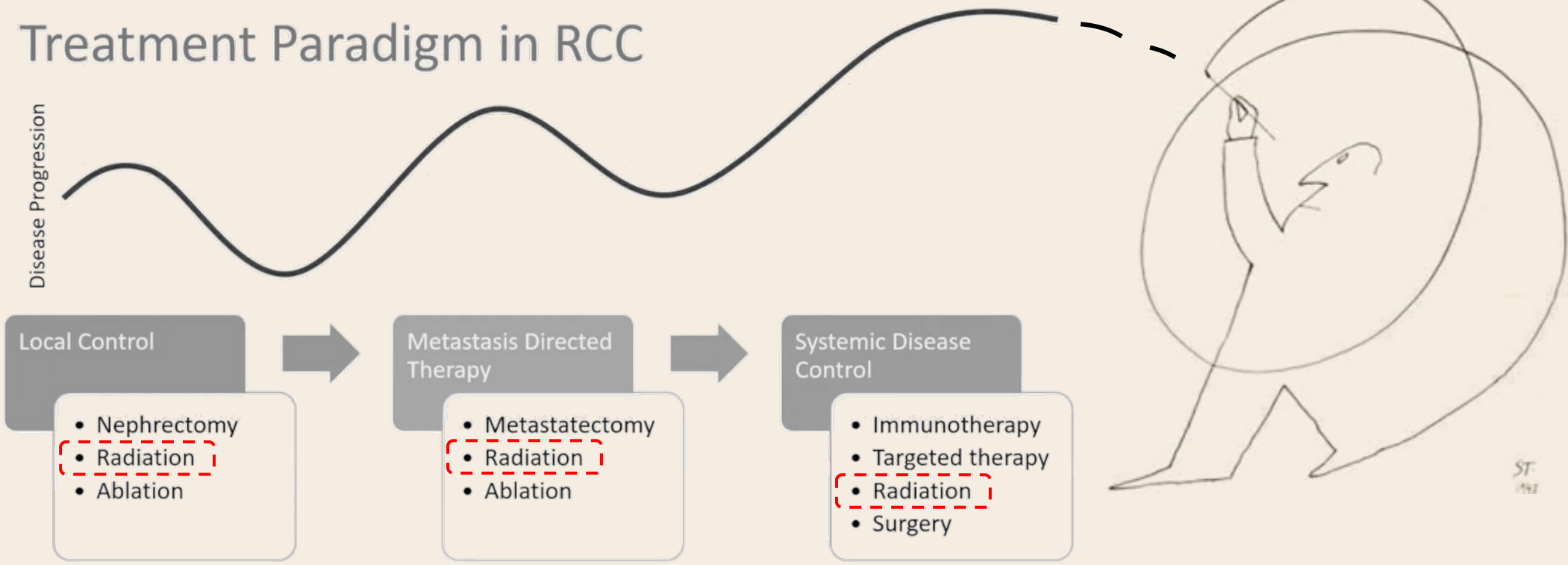
SBRT for oligometastatic disease

Phase III trial:

- SOAR



Treatment Paradigm in RCC





KIDNEY CANCER:

THIS MUST BE THE PLACE

To build more evidence FOR RADIOTHERAPY