Evidence and practice changing treatments in radioresistant tumors (Melanoma, Kidney, Sarcoma)

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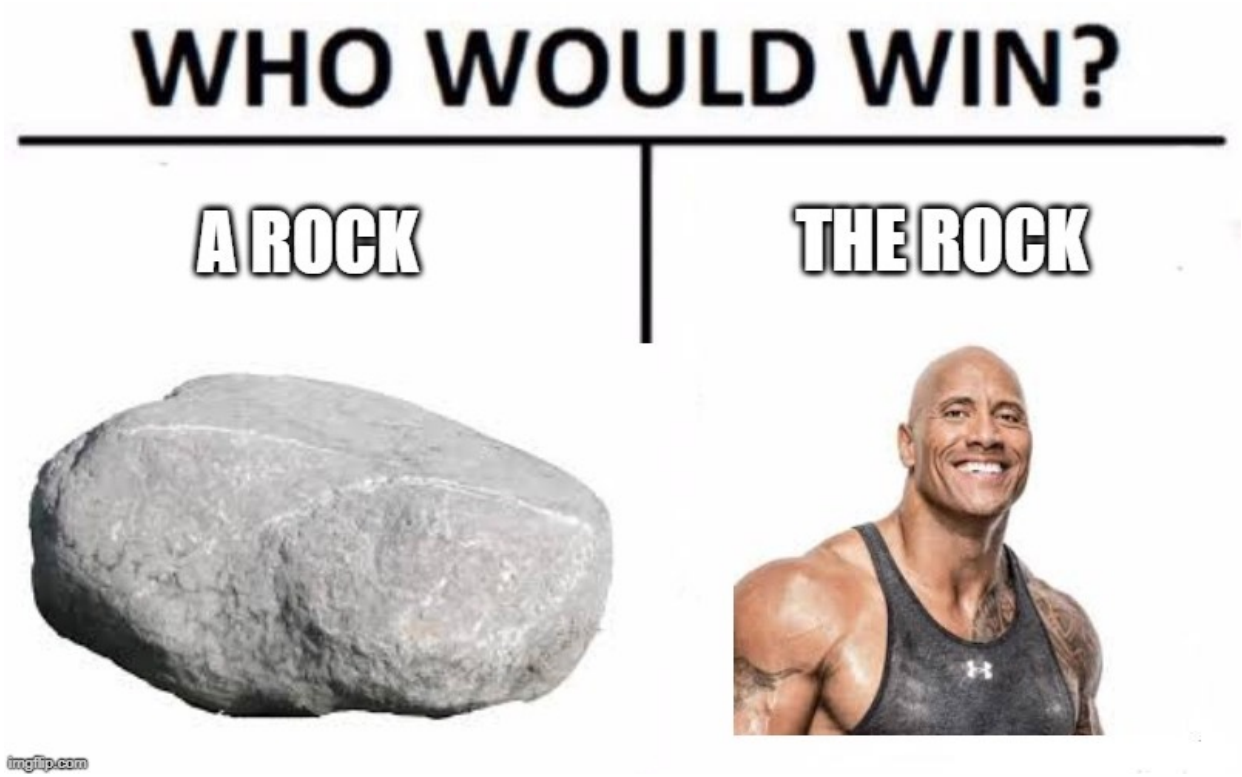
Azienda Ospedaliero Universitaria Careggi

Firenze

No COI to disclose

2022 IN REVIEW: RENAL CANCER



IROCK

THE LANCET Oncology

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

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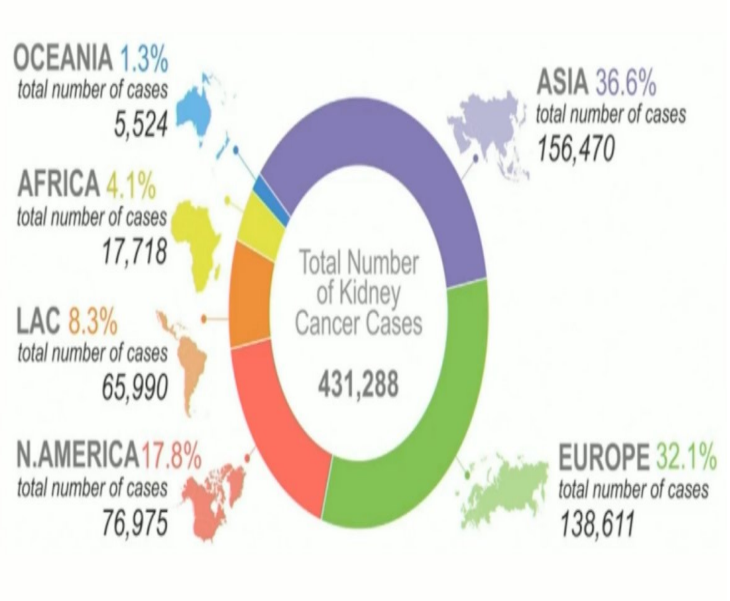
- RCC unsuitable for surgery : few curative treatment options

→ Thermal ablation: ↘ efficacy if > 3 cm or near collecting system

- Unmet medical need

→ Increasing incidence in the elderly population (>70 yrs)

→ Elderly patients x3.8 of cancer mortality due to frailty precluding medical interventions



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- Pooled data from 12 institutions from IROCK

→ M1 disease and/or upper tract urothelial carcinoma were excluded

→ minimum eligible follow-up was ≥ 2 years

- Data analysis

→ Local failure was investigator defined using RECIST 1.1.

→ Patterns of failure were described using a cumulative incidence function with death as competing event.

→ Toxicity was described using CTCAE v4.0.

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- 190 patients

→ Median follow-up was 5.0 years (95% CI 4.6 – 5.2 years)

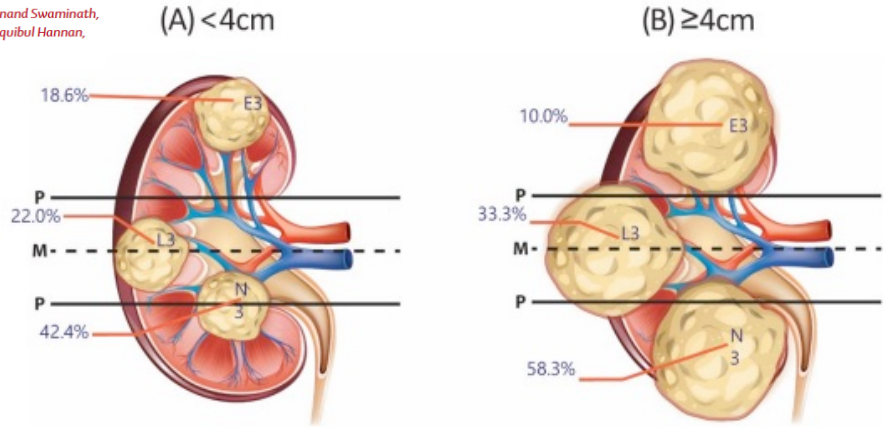
→ Median age 74 yrs (IQR: 66-82)

→ ECOG 0-1 or KPS ≥ 70%): 87.6%

→ Mean ± SD tumor diameter was 4.2 ± 2.2 cm (NB 50%≥ T1b)

→ Mainly inoperable due to CV comorbidities (46.9%).

→ Mean ± SD eGFR 58.9 ± 22.6 mL/min (NB 28% <45 mL/min)



Characteristic	Patients (n=190)
Age (years) – median (IQR)	73.6 (66.2, 82.0)
Male – n (%)	139 (73.2)
Good performance status (ECOG 0-1 or KPS ≥ 70) – n (%)	163 (87.6)
Medically inoperable – n (% of evaluable)	96 (75.0)
Pathological confirmation – n (%)	157 (82.6)
Maximum dimension (cm) – mean ± SD	4.2 (±2.2)
Solitary kidney	56 (29.5)

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- Cyberknife-based (RTTT, n=4) or Linac-based (Gating or Abdominal compression, n=8)
- GTV=CTV in all cases, median PTV:+5mm (0-7)
- Median BED10: 87.5 Gy (range 33.5-180.0).
- No patients received adjuvant or concurrent systemic therapy

Dose (Gy) / fractions[2]	$BED_{2.6}$ (Gy)	$BED_{6.9}$ (Gy)
24/1	245·54	107·48
25/1	265·38	115·58
26/1	286·00	123·97
36/3	202·15	98·61
42/3	268·15	127·22
35/5	102·31	60·36
40/5	163·08	86·38
60/10	290·77	146·96
70/10	258·46	141·01

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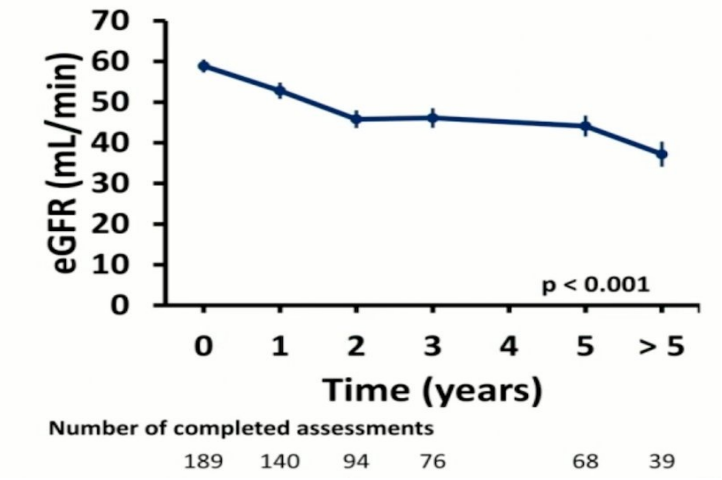
- Mean ± SD eGFR decreased by

→ -10.8 ± 16.6 mL/min at 3 yrs

→ -13.5 ± 14.9 mL/min at 5 yrs.



- 7 patients (3.7%) required dialysis (mean +/- SD baseline eGFR of 28.1 +/- 14.9 mL/min)
- 70 (36.8%) had a grade 1-2 toxicity
- 1 (0.5%) had a grade 4 gastrointestinal toxicity (at 1.4 months) and a grade 4 bowel toxicity (at 15.8 months; the patient is alive at 8.8 years without disease).

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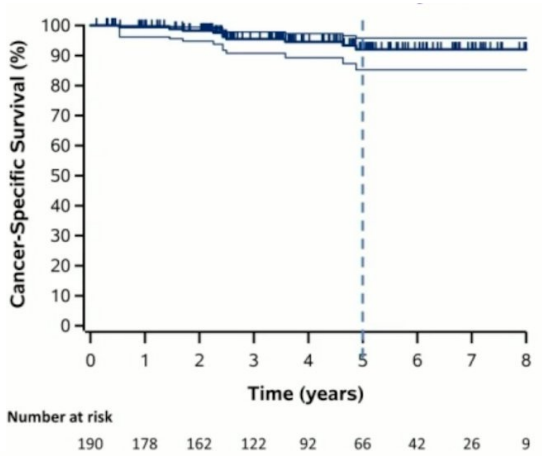
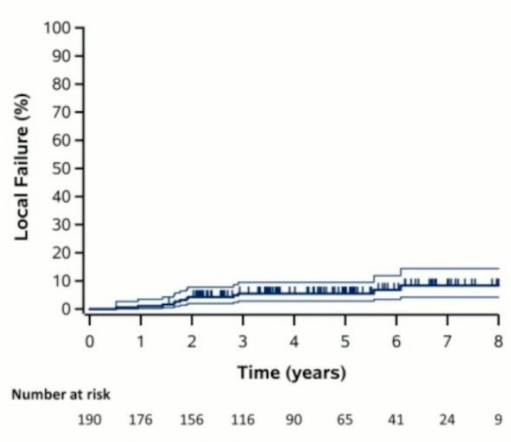
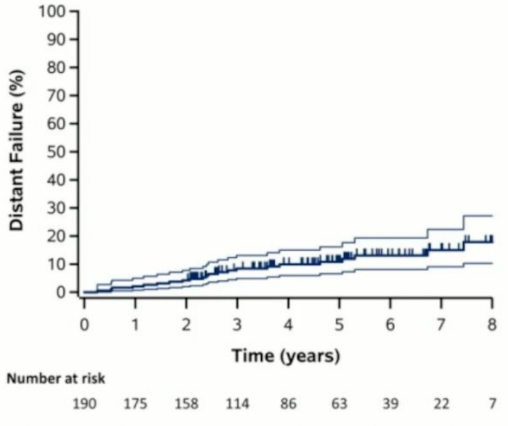
- CSS: 95.5% at 3 yrs and 92.0% at 5 yrs
- PFS: 72.1% at 3 yrs and 63.6% at 5 yrs
- Local, distant and any failure at 5 years were 5.5%, 10.8% and 13.0%







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- Increasing tumor size associated with inferior

→ CSS (HR per 1 cm increase: 1.41, 95% CI 1.15-1.71; p < 0.001)

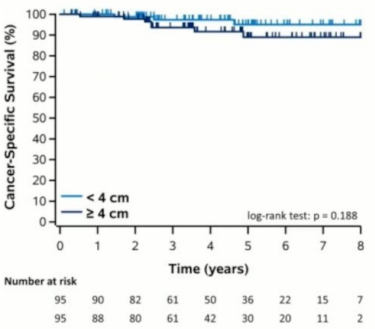
→ PFS (HR 1.10, 95% CI 1.01-1.19; p = 0.030)

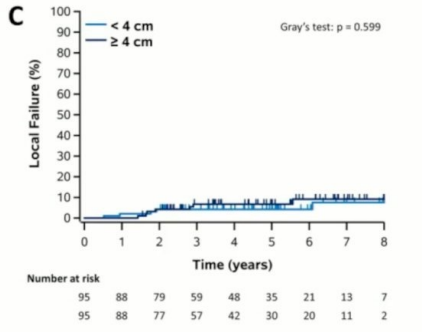
→ LC (HR 1.15, 95% CI 1.10-1.32; p = 0.056).

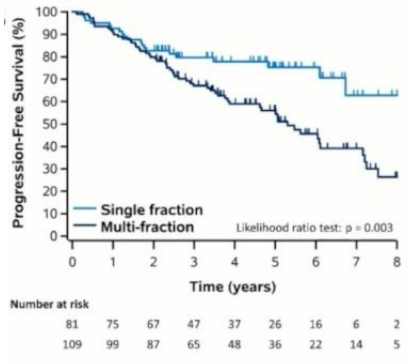
- No difference in CSS, PFS or LC in T1a versus T1b+
- 25-26 Gy/1#:

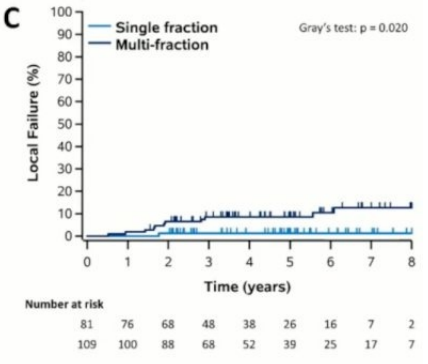
→ decreased LF(Gray's p = 0.020) and PFS (log-rank p = 0.004)

→ No differences in CSS (p = 0.153)









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- Concluding Remarks

→ 94,5% LC compares positively with partial nephrectomy, RFA, and cryoablation

→ Larger masses (mean 4.2 cm) than those typically treated with thermal ablation

→ Clinically acceptable decline of renal function at 5 years by a mean 13.5 mL/min

→ Inconclusive role of fractionation

→ Prospective IROCK registry planned

2022 IN REVIEW: SARCOMA

- Conventionally fractionated, 5-week preoperative RT has been the standard of care for STS
- Increased interest in hypofractionated and ultra-hypofractionated approaches
- Most available studies used preoperative doses that were not radiobiologically equivalent to standard conventional dosing

Author	No.	Dose/Fraction	Median FUP (mo)	RT→Surgery Time	CT	R0 Resection	Wound Complication*	≥G2 Fibrosis	LC@ y	OS@ y
Kosela-Paterczyk et al	272	25 Gy/5 fx	35	3-7 d	Yes	78.7%	32.4%	3.7%	81% @ 3 y	72% @ 5 y
Kalbasi et al	52	30 Gy/5 fx	29	2-6 wk	No	82%	32.0%	11%	94.3% @ 2 y	NR
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Ryan et al	25	28 Gy/8 fx	24	4-5 wk	Yes	88%	20%	NR	88% @ 2 y	84% @ 2 y
Pennington et al	116	28Gy/8 fx	71	2-3 wk	Yes	93%	10%	NR	89% @ 3 y	82% @ 3 y

THE LANCET Oncology

Hypofractionated, 3-week, preoperative radiotherapy for patients with soft tissue sarcomas (HYPORT-STS): a single-centre, open-label, single-arm, phase 2 trial

B Ashleigh Guadagnolo, Roland L Bassett, Devarati Mitra, Ahsan Farooqi, Caroline Hempel, Courtney Dorber, Tiara Willis, Wei-Lien Wang, Ravin Ratan, Neeta Somaiah, Robert S Benjamin, Keila E Torres, Kelly K Hunt, Christopher P Scally, Emily Z Keung, Robert L Satcher, Justin E Bird, Patrick P Lin, Bryan S Moon, Valerae O Lewis, Christina L Roland, Andrew J Bishop

- Single-centre, open-label, single-arm, phase 2 trial
- Non-metastatic STS of the extremities or superficial trunk eligible for preop RT
- Primary endpoint : major wound complication within 120 days of surgery

→ reintervention for wound treatment or invasive procedures for wound care

→ deep wound packing to an area of wound measuring at least 2 cm in length

→ prolonged dressing changes or wet dressings for longer than 4 weeks

→ repeat surgery for revision of a split thickness skin graft

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- 42,75 Gy in 15 fractions of 2,85 Gy/day for 3 weeks (5 fractions per week)
- Equivalent to 50 Gy/25#/2 Gy assuming α/β of 3-5 for STS
- CTV according to guidelines (MRI-based GTV + 1.5cm radial and 3cm CC expansion)
- Dosimetric constraints for organs-at-risk

Weight-bearing bone	D65%<35Gy Mean Dose <30,5 Gy
Joint	D50%<42,75 Gy
Femur Head	D50%<38 Gy
Skin Corridor	Dmax <17 Gy

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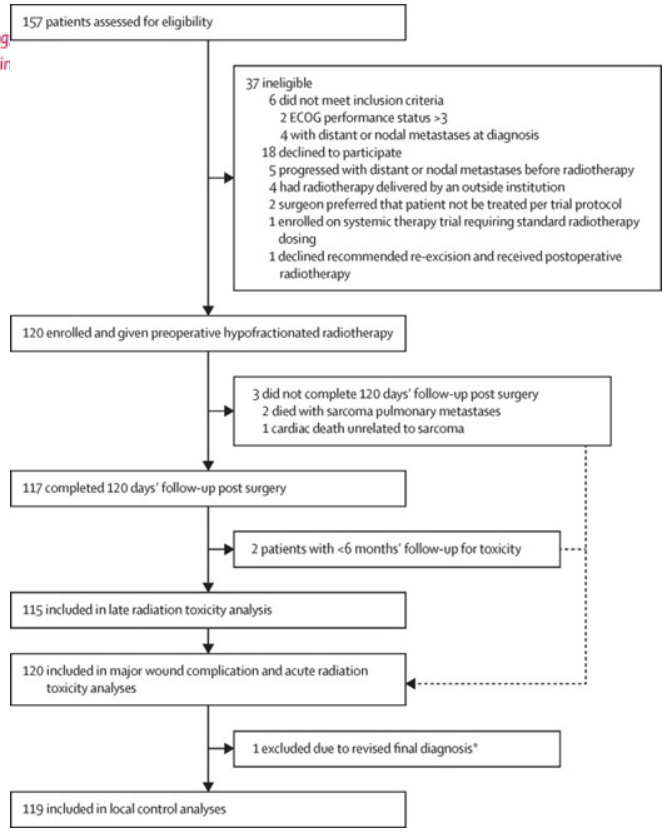
- 119 patients
- All patients completed RT in median 20 days (IQR 18–21)
- Neoadjuvant CT in 30% (n=36)
- Surgery at a median interval of 5·7 weeks (IQR 4·6–6·4)
- Median follow-up 24 months (IQR 17–30).



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- 6 (5%) patients had developed a local relapse at a median time of 16 months (IQR 7–17)
- No acute toxicity of grade 3 or worse
- 45 (38%) had a wound complication of any severity (major in 31%).
- No predictors at MV analysis
- Four (3%) late radiation toxicity (≥6 months post-surgery)

→ femur fractures (n=2)

→ lymphoedema (n=1)

→ skin ulceration (n=1)

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- Concluding Remarks

→ 31% major wound complications versus 35% (historical control) in CFRT

→ Similar LC rates

→ No differences in acute toxicity

Scientific Article

Is 5 the New 25? Long-Term Oncologic Outcomes From a Phase II, Prospective, 5-Fraction Preoperative Radiation Therapy Trial in Patients With Localized Soft Tissue Sarcoma

advances in radiation oncology
www.advancesradonc.org

Meena Bedi, MD,[a,1,*] Reena Singh, MD,[b] John A. Charlson, MD,[c] Tracy Kelly, MD,[a] Candice Johnstone, MD, MPH,[a] Adam Wooldridge, MD, MPH,[d] Donald A. Hackbarth, MD,[d] Nicole Moore, BS, CCRP,[e] John C. Neilson, MD,[d] and David M. King, MD[d]

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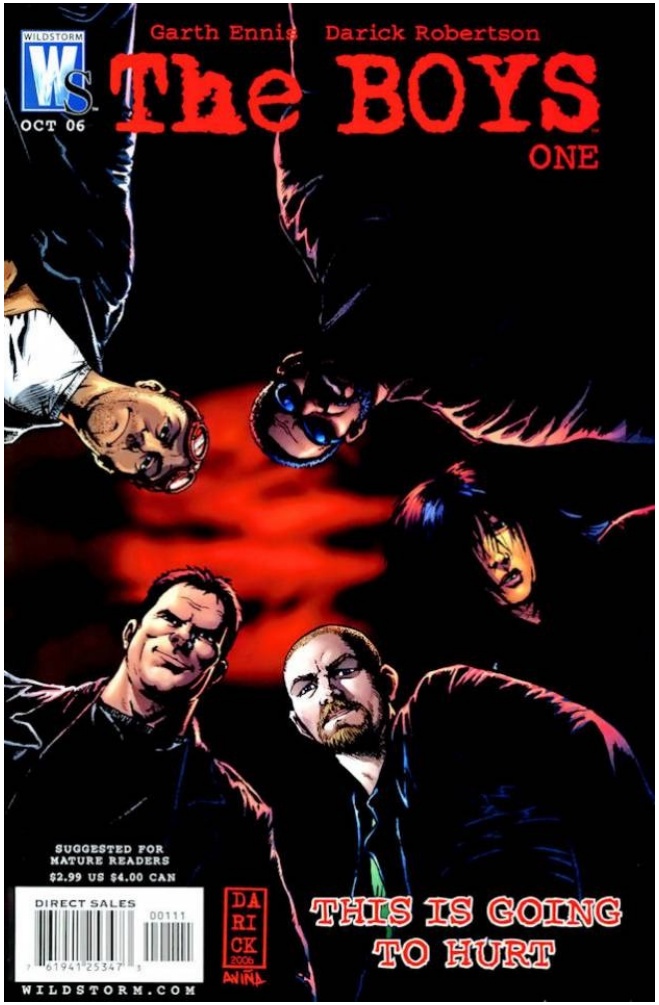

Local Control Outcomes Using Stereotactic Body Radiation Therapy or Surgical Resection for Metastatic Sarcoma

Paulina M. Gutkin, BS,* Rie von Eyben, MS,† Alexander Chin, MD, MBA,† Sarah S. Donaldson, MD,† Justin Oh, MD,† Alice Jiang, BS,† Kristen N. Ganjoo, MD,‡ Raffi S. Avedian, MD,§ Matías Bruzoni, MD,‖ Robert J. Steffner, MD,§ Everett J. Moding, MD, PhD,† and Susan M. Hiniker, MD†

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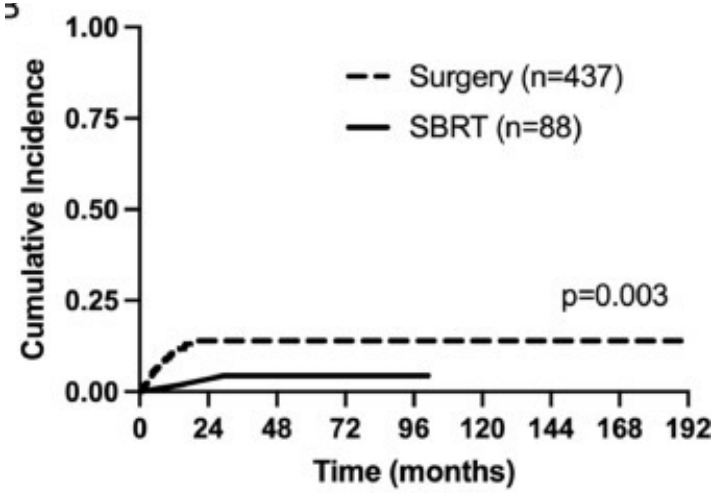

- SBRT demonstrated an excellent LR of 1.7% at 2 years.
- Among surgically resected,14.8% LR was observed at 2 years.

Stereotactic Body Radiation Therapy for Lung Metastases From Sarcoma in Oligometastatic Patients: A Phase 2 Study

Pierina Navarria, MD,* Davide Baldaccini, MD,* Elena Clerici, MD,* Beatrice Marini, MD,* Luca Cozzi, PhD,* Davide Franceschini, MD,* Alexia Francesca Bertuzzi, MD,† Vittorio Quagliuolo, MD,§ Valter Torri, MD,‖ Piergiuseppe Colombo, MD,¶ Ciro Franzese, MD,*† Luisa Bellu, MD,* and Marta Scorsetti, MD*†

International Journal of Radiation Oncology Biology • Physics

- Single-centre, open-label, single-arm, phase 2 trial
- Metastatic STS patients

→ up to 4 lung metastases (LMs)

→ ≤5 cm in diameter

→ unsuitable for surgery

- Primary Endpoint: 1-yr LC

Peripheral lesions ≤10 mm, and.	30 Gy/1 fraction
Peripheral lesions 11 to 20 mm	60 Gy/3 fractions
Peripheral lesions >20 mm	48 Gy/4 fractions
Central lesions	60 Gy/8 fractions

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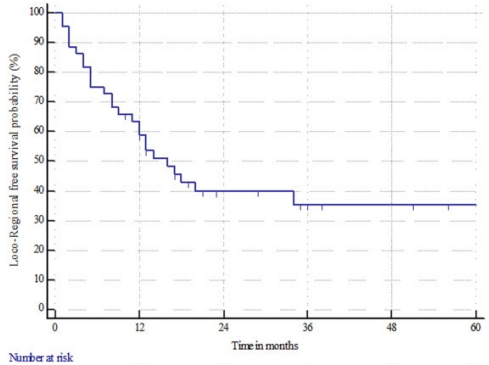
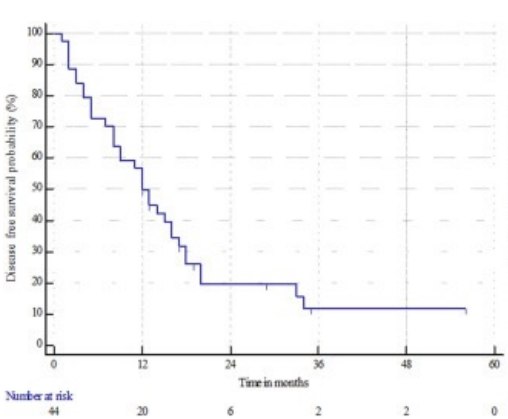
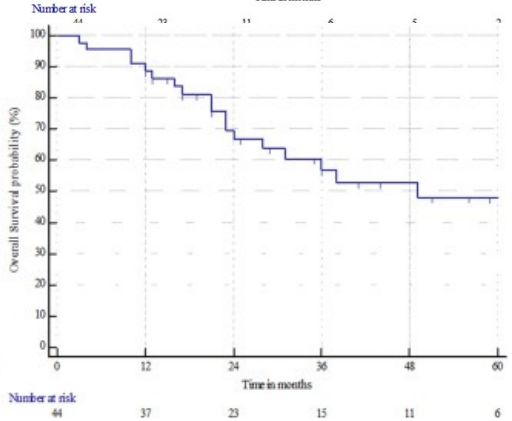
International Journal of Radiation Oncology Biology • Physics

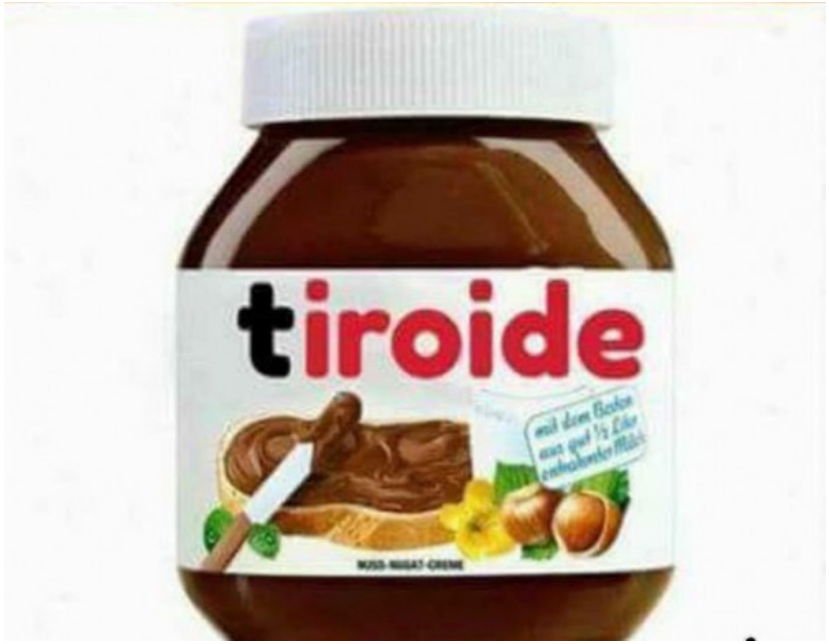
- 44 patients with a total of 71 LMs were enrolled
- 1yr LC 98.5% ± 1.4%, reaching the primary aim
- Median DFS 12 months (95% CI, 8-16 months
- Median OS 49 months (95% CI, 24-49 months)
- Survival affected by age, grade of primary sarcoma, interval time from diagnosis to occurrence of LMs, and number of LM







2022 IN REVIEW: ATC



THE LANCET Oncology

Radiotherapy and paclitaxel plus pazopanib or placebo in anaplastic thyroid cancer (NRG/RTOG 0912): a randomised, double-blind, placebo-controlled, multicentre, phase 2 trial

Eric J Sherman, Jonathan Harris, Keith C Bible, Ping Xia, Ronald A Ghossein, Christine H Chung, Nadeem Riaz, G Brandon Gunn, Robert L Foote, Sue S Yom, Stuart J Wong, Shlomo A Koyfman, Michael F Dzeda, David A Clump, Saad A Khan, Manisha H Shah, Kevin Redmond, Pedro A Torres-Saavedra, Quynh-Thu Le, Nancy Y Lee

- Multicentre, double-blind, 2 arms, randomized phase 2 trial
- ATC, any TNM
- Concurrent weekly paclitaxel(50 mg/m^2) and IMRT (66Gy/33#) + pazopanib (300 mg/die)
- Primary endpoint : OS (HR 0.65)
- Required accrual 79 pts (71 events)

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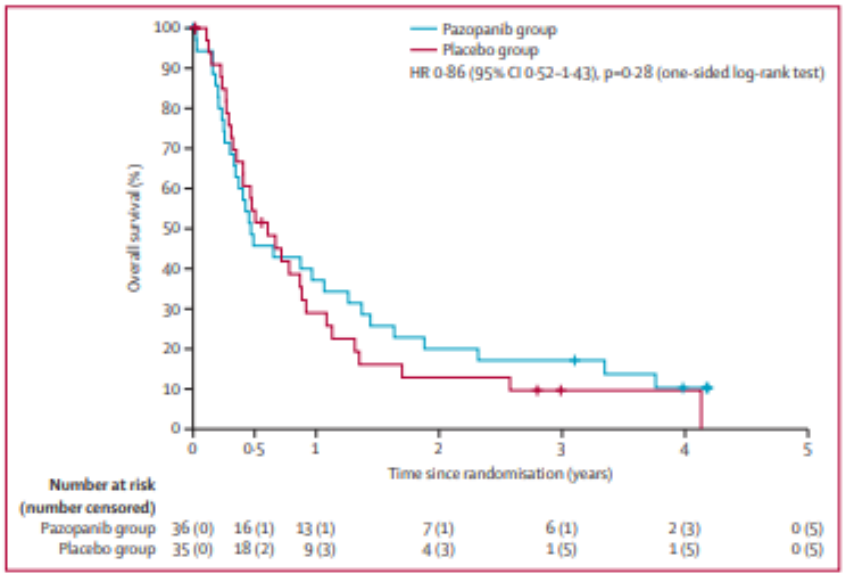
- 71 patients enrolled (Exp: 35 vs Ctrl: 36), M1: 26 patients
- Safety run-in: no SAE in 9 patients
- Median FUP 2.9 years (IQR 0·002–4·0)
- Median OS Exp 5·7 months (95% CI 4·0–12·8) vs Ctrl 7·3 months (4·3–10·6) p=0·28).
- At MV only M stage correlate with OS (HR [M1 or MX vs M0] 2·73, 95% CI 1·49–5·00; p=0·0011)
- No proven benefit in M0 subset or prior surgery



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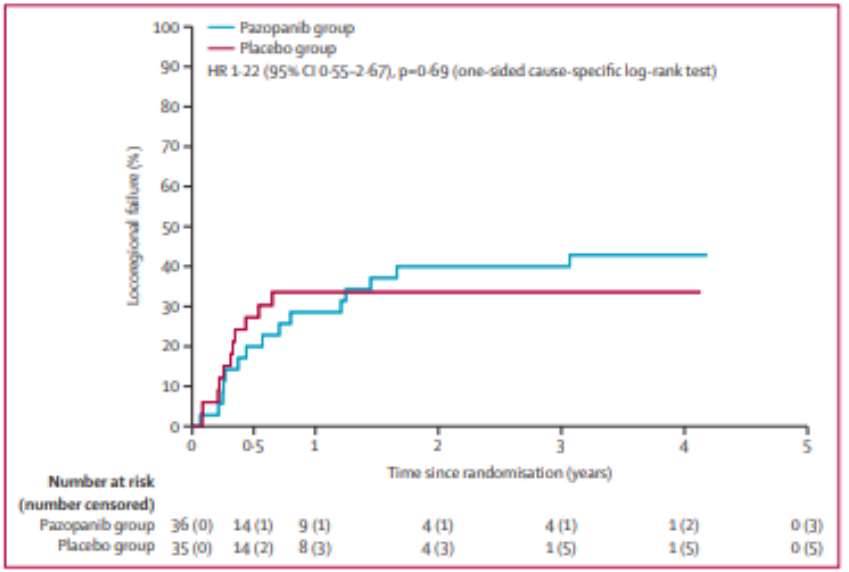
- No difference in 1yr LR: Exp 28,6% vs Ctrl 33% (NS)
- No difference in G3-5 SAE: Exp 88,9 vs Ctrl 85,3%
- Mostly G3-5 liver enzyme increase (22% vs 0%) and leucoopenia (19% vs 0%) found more frequently in Exp vs Ctrl



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- Concluding Remarks

→ Underpowered to show a smaller treatment effect

→ Optimistic drop-off rate (10 >>20%)

→ Potential OS benefit may be limited to patients with M0 disease after 6 months

→ High toxicity rate in both arms due to frail population

→ Outdated drug

2022 IN REVIEW: MISCELLANEOUS

International Journal of Radiation Oncology Biology • Physics

Dose-Escalated 2-Fraction Spine Stereotactic Body Radiation Therapy: 28 Gy Versus 24 Gy in 2 Daily Fractions

K. Liang Zeng, MD,* Ahmed Abugarib, MD,*† Hany Soliman, MD,* Sten Myrehaug, MD,* Zain A. Husain, MD,* Jay Detsky, MD, PhD,* Mark Ruschin, PhD,* Aliaksandr Karotki, PhD,* Eshetu G. Atenafu, MSc,‡ Jeremie Larouche, MD,§ Mikki Campbell, BSc,* Pejman Maralani, MD,‖ Arjun Sahgal, MD,* and Chia-Lin Tseng, MDCM*

- Identification of appropriate spine SBRT schedule (24 Gy or 28 Gy in 2 fractions)
- Prospective database of 482 patients and 942 vertebral segments treated with spine SBRT
- Radioresistant histotypes accounted for 31% (n=148) of patients

→ renal cell carcinoma, colorectal cancer, melanoma, sarcoma, or thyroid origin

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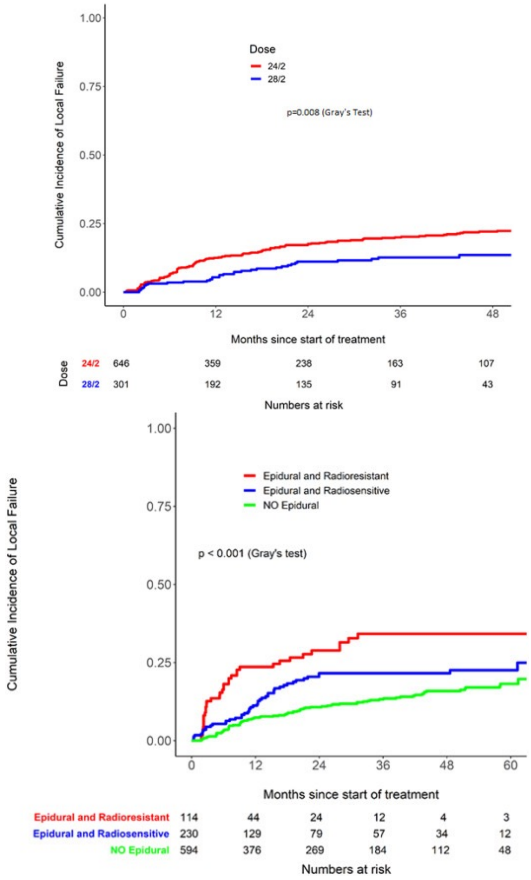
- Superior LC in 28 vs 24 Gy (P = .008)
- On multivariable analysis increased LF in

→ 24 Gy (hazard ratio [HR], 1.525; 95%CI, 1.039-2.238; P = .031)

→ paraspinal disease extension (HR, 1.422; 95%CI, 1.010-2.002; P = .044)

→ epidural extension in either radioresistant or radiosensitive histologies (HR, 2.117 and 1.227, respectively; P = .003)

- No correlation between dose level and VCF



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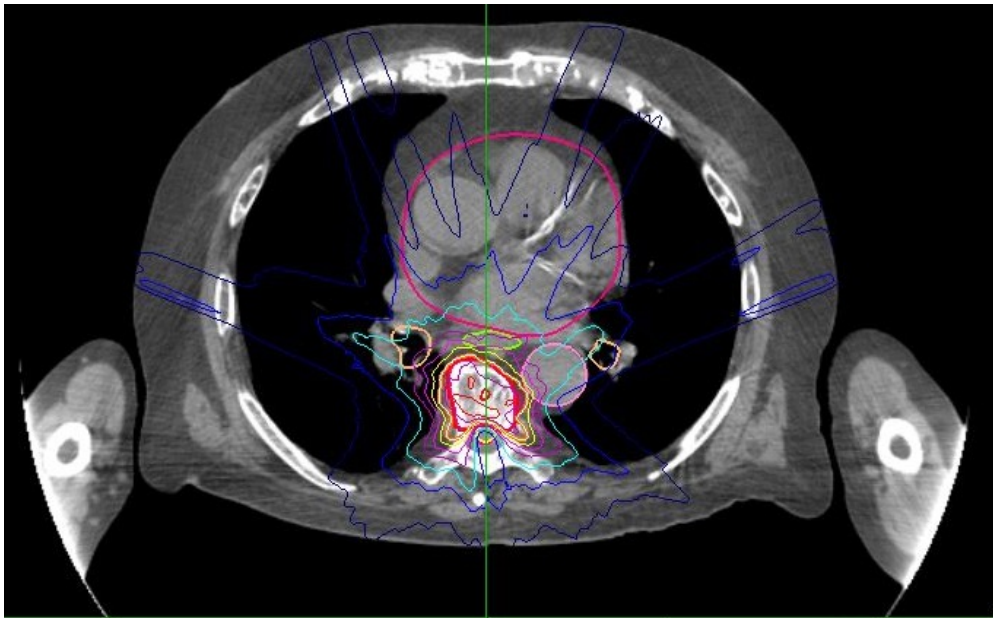
- Concluding remarks

→ RR histology non significant per se, but a significant interaction with epidural disease

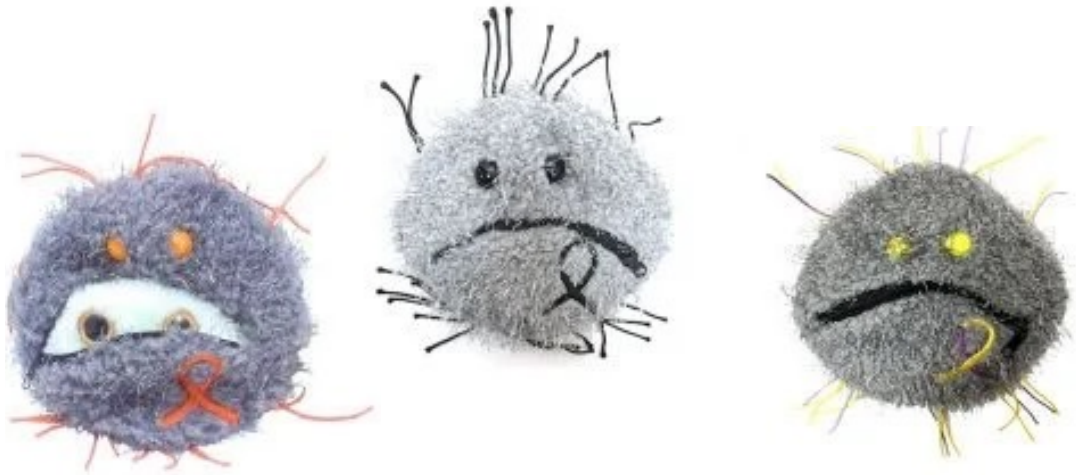
→ In patients with epidural disease, ++RR, consideration should be made for dose escalation to 28 Gy in 2 fractions



	Name	Dose (cGy)	Dose (%)	Volume (cm³)	Volume (%)
	PTV	3000	**69.0**	41.24	96.
	PRVcord	2070	47.6	**0.03**	0.
	Spinal Cord	1682	38.7	**0.03**	0.
	Esophagus	2332	53.6	**0.03**	0.
	Proximal Bronchus	2542	58.5	**0.03**	0.

	Name	Dose (cGy)	Dose (%)	Volume (cm³)	Volume (%)
	PTV	**2800**	70.0	40.35	9
	PRVcord	1741	43.5	**0.03**	
	Spinal Cord	1409	35.2	**0.03**	
	Esophagus	2147	53.7	**0.03**	
	Proximal Bronchus	1938	48.5	**0.03**	
	PTV	**2600**	65.0	41.54	9

Thank you for your attention!



See you at ESTRO 2023