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IORT in Soft-tissue Sarcoma

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Disclosure

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Guidelines

Intraoperative radiation therapy (IORT) for soft tissue sarcoma – ESTRO IORT Task Force/ACROP recommendations

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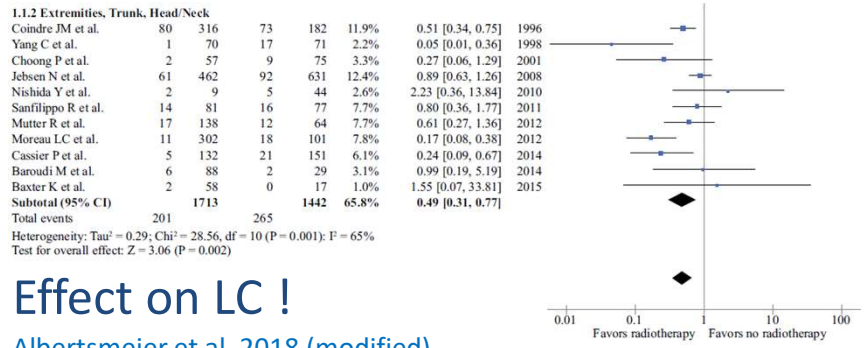
General role of RT in STS – Extremity (until 2020)

Rosenberg et al. 1982, n=43, randomized
wide excision + RT = Amputation (OS)

Yang et al. 1998, n=141, randomized
wide excision + RT > wide excision (LC)

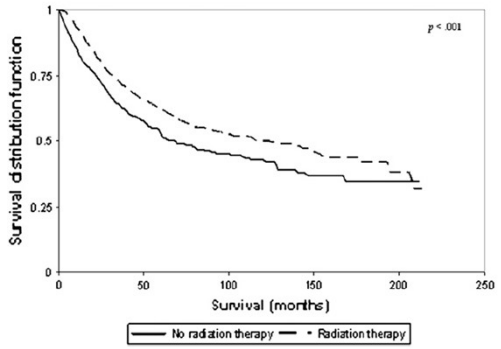
Albertsmeier et al. 2018, n=3958, metaanalysis
OP + RT > OP (LC)

Koshy et al. 2010, n=6960, population-based
OP + RT > OP (OS, high grade)



Effect on LC !

Albertsmeier et al. 2018 (modified)



Effect on OS ?
(high grade STS)

Koshy et al. 2010

RT improves at least LC !

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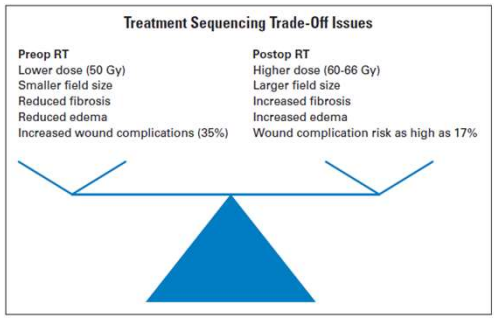
General role of RT in STS – Extremity (until 2020)

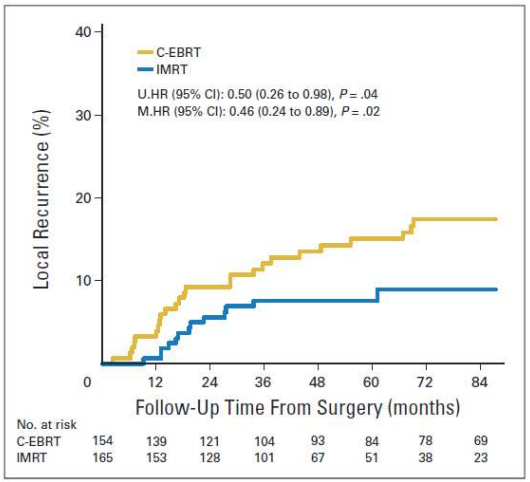
Benefit depends on RF, Jebsen et al., n=1093 trial
Most important: close/pos. margin, high grade

Preop. vs Postop. RT, O´Sullivan et al. 2002, Davis et al. 2005, n=190, randomized (postop. boost if R1 !)
LC/DFS: no difference
wound complication: favors postop. RT
acute and **late** toxicity: favors preop. RT

IMRT vs 3D-RT, Folkert et al, n=319 , retrospective
LC and Tox. favors IMRT



Pisters et al. 2007



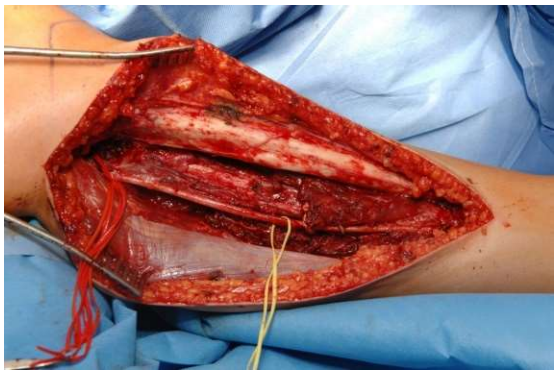
Folkert et al. 2014

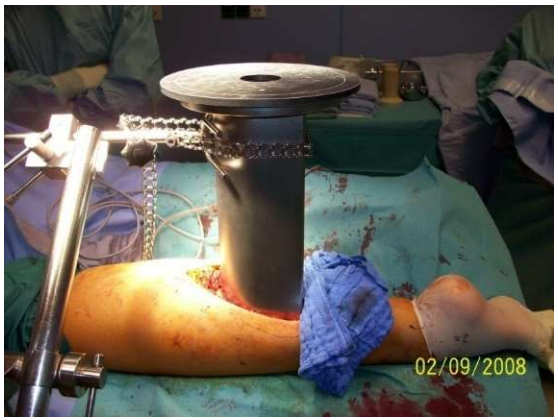
Outcome depends on risk profile, timing, technique and field size

Rationale for IORT – extremity STS (until 2020)

Dose escalation for high risk patients
e.g. anticipated close/pos. margin

Favorable compared to EBRT boost:
- smaller safety margins (no motion)
- smaller volume (deep tumor bed only)
- Higher biologically effect (single dose)





Improved LC/similar toxicity
Similar LC/less toxicity

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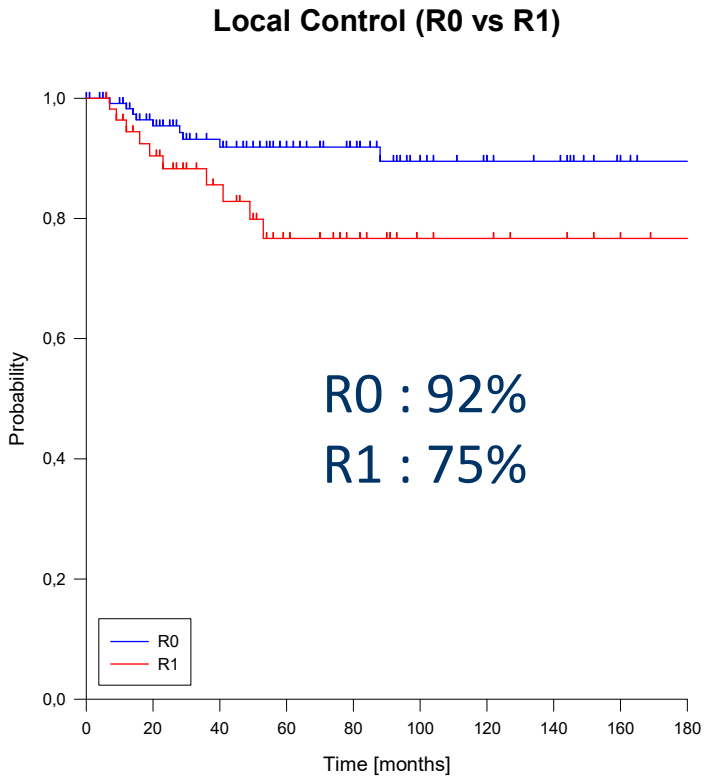
Roeder et al. 2015

- n=183, f/u 78 mo
- unfavorable tumors
  (40% > 10 cm, 64% G3, 32% R1, 22% recurrent)
- IOERT 15 Gy + EBRT 45 Gy
- 5y-LC : 86%, 5y-OS : 77%
- postop. compl.: 19%
- late tox: 20% (8% neuropathy, 6% bone necrosis)
- excellent/good functionality 83 %



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Roeder et al. 2014

- NEO-WTS subgroup analysis
- N=34, med. f/u 48 mo
- > 5cm, G2-3
- 4x EIA + OP + IOERT + EBRT + 4x EIA

5-yr LC : 97%

5-yr OS : 79%

- wound complication 20%, severe late tox 18%
- limb preservation 94%, good funct. 81%

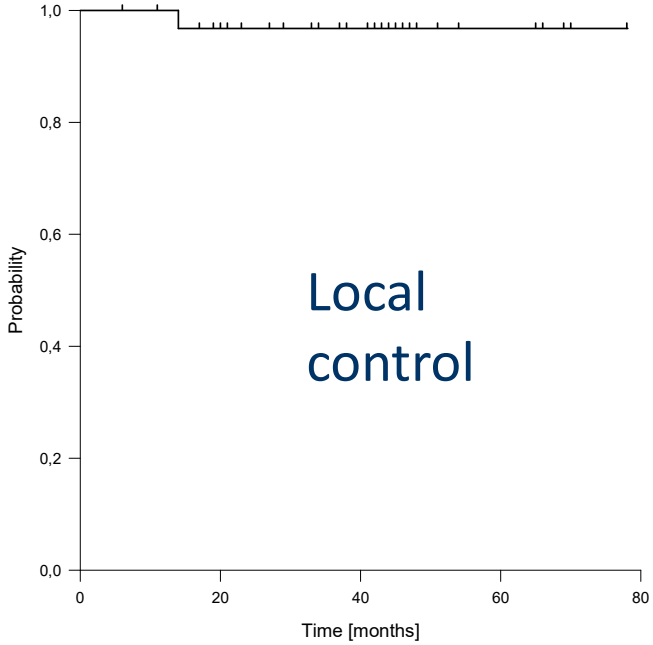

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Table 1
Published IORT series in extremity STS.

								EBRT		IORT								
Author	Year	Period	Type	*n*	f/u	PD	R0	EBRT	Dose	IORT	Tech.	Dose	5y-LC	5y-OS	LP	FO	Toxicity	Comments
Carbo-Laso et al. [26]	2017	1995–2003	r, sc	39	158	85	n.r.	85	45	100	e⁻	10	82	64	82	n.r.	AT3+:13%, LT3+:12% (N:8%, F:5%)	
Roeder et al. [27]	2015	1991–2011	r, sc	183	64	78	68	100	45	100	e⁻	15	86	71	95	83	LT:20% (NP3+:8%, F:6%)	
Tinkle et al. [28]	2015	2000–2011	r, sc	26	35	0	54	42	52*4	100	e⁻	15	58	50	81*11	77	AT3+:23%, LT3+:31%	rec. only, 58% prior EBRT
Roeder et al. [29]	2014	2005–2010	p, sc	34	43	100	88	100	46	91	e⁻	15	97	79	94	81	LT3:18% (N:12%, N3:3%, BN:3%)	phase II, all received CHT
Calvo et al. [30]	2014	1986–2012	r, mc	159	53	100	84	100	45	100	e⁻	12.5	82	72	94*11	n.r.	AT3+:14%, LT3+:10% (N3+:4%)	
Call et al. [31]	2014	1990–2009	r, sc	61	71	87	82	100	50.4	100	e⁻	7.5–20	91	72	97	n.r.	NP3:2%, BN:2%	upper extremity only
Tran et al. [32]	2005	1995–2001	r, sc	17	23	94	65	76	50.3	100	e⁻	12.5	86*7	78*7	n.r.	n.r.	n.r.	
Oertel et al. [33]	2006	1991–2004	r, sc	153	33	62	49*1	100	45	100	e⁻	15	83*8	83*8	90	86	AT2+:23%, LT2+:17% (NP2+:5%)	8% GRD, 16% MD
Kretzler et al. [34]	2003	1989–1999	r, sc	28	52′	39	61	89	50.6*5	100	e⁻/HDR	14.5*5*6	84	66	n.r.	59	LT3+: 24% (N3:5%, F:10%)	
Azinovic et al. [35]	2003	1986–1994	r, sc	45	93	58	87	80	30–60	100	e⁻	15	80*9	64*9	88	77	N:16% (25%*12), BN:2%, F:4%	
Rachbauer et al. [36]	2003	1996–2002	r, sc	39	24	95	n.r.*2	100	50	100	HDR	12–15*6	100*10	82*10	100	100	N:0%, F:0%	10% non-extremity tumours
Edmonson et al. [37]	2001	1994–1997	p, sc	39	70	100	n.r.*3	97	45	97	e⁻/HDR	10–20	90*9	80	95	n.r.	F:3%	phase II, all received CHT
van Kampen et al. [38]	2001	1991–1997	r, sc	68	n.r.	71	n.r.	78	40	100	e⁻	15	88	70	n.r.	n.r.	N3:2%, F:4%, Fi:23%, Fi3+:6%	fi rel. to IOERT volume*13

year: year of publication, period: study period, type: study type, r: retrospective, p: prospective, sc: single centre, mc: multi centre, n:number of patients, f/u: median follow-up in months, n.r.: not reported, PD: primary disease (%), R0: microscopic clear resection margin (%), EBRT: patients receiving external-beam RT (%), EBRT dose: median EBRT dose in Gy, IORT: patients receiving intraoperative RT (%), tech.: IORT technique, e-: electrons, HDR: high dose-rate brachytherapy, IORT dose: median IORT dose in Gy, 5y-LC: actuarial 5-year local control rate (%), 5y-OS: actuarial 5-year overall survival (%), LP: limb preservation rate (%), FO: good functional outcome (%), ATx: acute toxicity grade x, LTx: late toxicity grade x, N: neuropathy all grades, Nx: neuropathy grade x, F: fracture, BN: bone necrosis (without fracture), Fi: fibrosis, Fix: fibrosis grade x, CHT: chemotherapy, GRD: gross residual disease, MD: metastatic disease, rec.: recurrences, rel.: related, *1: modified R0 definition (1 cm free margin), *2: all marginal, *3: 38% marginal, *4: in patients without prior EBRT (no RE-EBRT performed), *5: mean, *6: prescribed to applicator surface in HDR patients, *7: 3-year rate, *8: in initially non-metastatic patients, *9: crude rate, *10: 2-year rate, *11: actuarial 5-year amputation free survival, *12: if nerve included into IORT area, *13: toxicity analysis based on 53patents receiving IORT + EBRT.

Roeder et al. 2020

General role of RT in STS – retroperitoneal (until 2020)

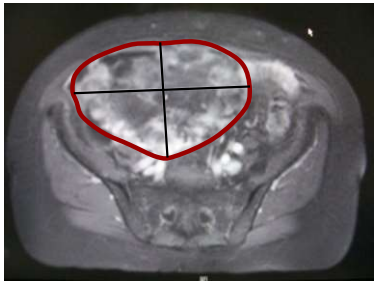
strong rationale based on extremity data (small surgical margins, if any), but

No randomized data, conflicting retrospective/population-based data

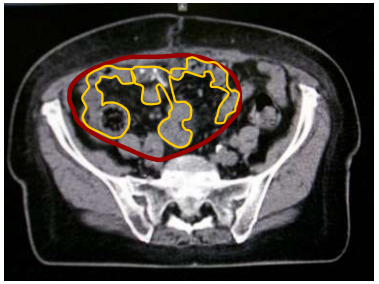
No general agreement on indication for RT:
usually at least >5cm, high grade, but if RT:

Preoperative RT clearly favored
(less total dose, improved coverage,
less dose to OAR (small bowel), less toxicity)

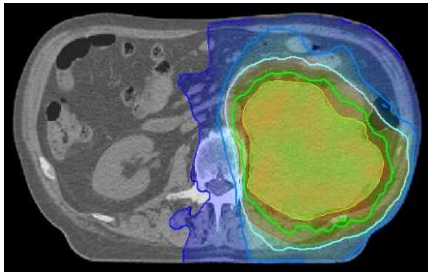
IMRT clearly favored
(improved coverage, less dose to OAR)



Preop. MRI



Postop. Planning CT



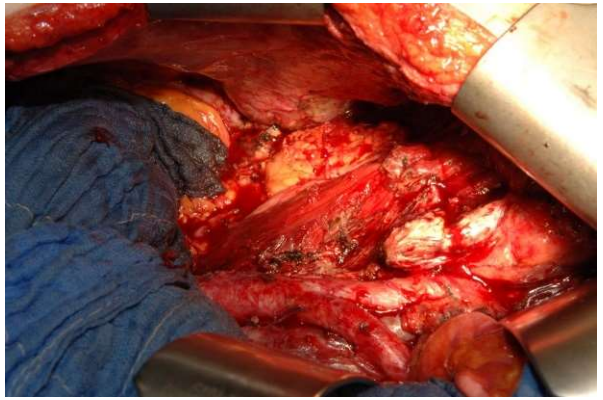
Treatment plan
preop. VMAT

Rationale for IOERT – retroperitoneal STS (until 2020)

Enabling Dose escalation compared to EBRT

Favorable features:

- surgical relocation of OAR (small bowel)
- small safety margins (no motion)
- small volume (deep tumor bed only)
- high biological effect (single dose)



Improved LC and OS ?

Role of IOERT – retroperitoneal STS (until 2020)

Retro-WTS trial (Roeder et al. 2014)

- prospective single arm trial
- n=27/37, interim analysis (med. f/u 33 mo)
- primary/recurrent: 85%/15%
- grading (1/2/3): 18%/52%/30%
- R0: 22%, R1: 74%, R2: 4%

5-yr-LC: 72% (all pts.)

5-yr-LC: 88% (primary only)

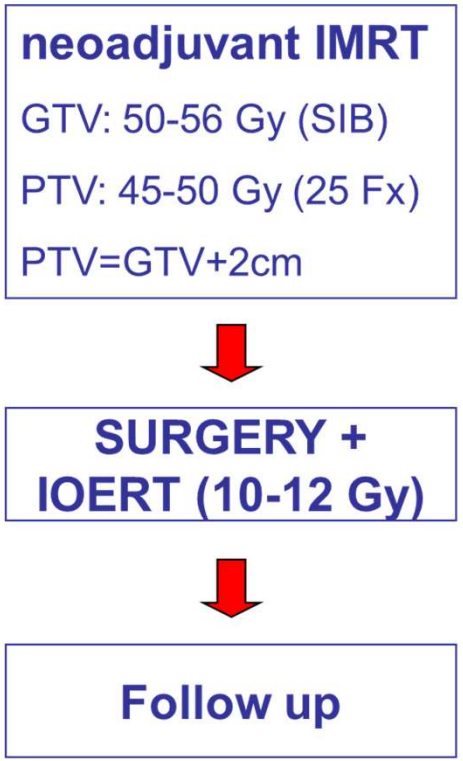


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Table 2
published IORT series in retroperitoneal STS.

								EBRT			IORT						
Author	Year	Period	Type	*n*	f/u	PD	GTR	pre.	post.	Dose	IORT	Tech.	Dose	5y-LC	5y-OS	Toxicity	Comments
Wang et al. [48]	2017	1988–2013	SEER	352*1	n.r.	n.r.	n.r.	14*4	87*4	n.r.	0		n.r.	n.r.	55*12	n.r.	OS EBRT +/−IORT sig.
				15*1				0	0		100	e−			34*12		OS IORT +/−EBRT sig.
				13*1				100		100	e−			87*12			
Hull et al. [49]	2017	2003–2013	r, sc	46	53	85	98	100*4	15*4	50.4	35	e−	10	86*6	81	PC3+:22%	
Kelly et al. [50]	2015	2003–2011	r, mc	32	37	100	97	94	6	50	47	e−	10	91	93*13	PC3 + 12%	LC S+/−RT sig.
				172	39	100	100	0	0		0			65	85	PC3+:5%	
Stucky et al. [51]	2014	1996–2011	r, sc	37	45	64	89	95	0	45	100	e−	10–20	89	60	AT3: 3%, AT2:31% (N2:16%)	LC +/−RT sig.
				26				0	0		0			46	60	n.r.	
Roeder et al. [25]	2014	2007–2013	p, sc	27	33	85	96	100	0	45–55*5	85	e−	12	72	74	AT3+:15%, PC3+:33%, LT3+:6%	
Gronchi et al. [52]	2014	2003–2010	p, mc	83	58	76	95	100	0	50.4	18	e−	12	63*6*7	59	PC3+:21%, HT:27%, NV:11%*14	
Sweeting et al. [53]	2013	2001–2009	r, sc	18	43	72	100	94	0	45–50.4	100	e−	12.5	64	72	PC3+:17%,	
Yoon et al. [54]	2010	2003–2008	r, sc	28	33	71	89	79*4	29*4	50	43	e−	10–12	90*11	87*11	PC3+:29%, LT3+:14%	
Dziewirski et al. [55]	2010	1998–2006	r, sc	84	40	23	88	0	40	50	68	HDR	20	65*7*8	50*7*8	RS:18%, LT3+:18%*15 (N3+:6%)	LC/OS IORT +/−EBRT sig.
Pezner et al. [56]	2011	1990–2008	r, sc	33	49	67	94	0	100	26–60	61	e−	10–20	67	55	AT3+:9%, LT3+:21%	
Zagar et al. [57]	2008	2000–2008	r, sc	31	19	77	84	61	39	59.4	52	e−	11	77*10	70*10	AT3+:10%, LT3+:55% (GI3+:19%)	
Caudle et al. [58]	2007	1994–2004	r, sc	14	19	64	93	100	0	45	36	e−	12.5	50*7*10	74*10	AT3+:7%, PC3+:36%	
Ballo et al. [59]	2007	1960–2003	r, sc	18	47	73	100	60	40	45–66	100	e−	15	51	n.r.	RT3+:2%	
				63			100				0			46	n.r.		
Dziewirski et al. [60]	2006	1998–2004	r, sc	46	20	9	100	0	52	50	52	HDR	20	51	55	RS: 22%	
Pawlik et al. [61]	2006	1996–2002	p, mc	72	40	75	95	100	0	45	39	e−	15	60*7	61*7	n.r.	
Pierie et al. [62]	2006	1973–1998	r, sc	14*2	27	100	100	100	0	40–50	100	e−	10–20	n.r.	77	LT3+:29% (N3+:21%)	
				27*2		100	100	100	0	40–50	0			n.r.	45	LR3+:4%	
Krempien et al. [16]	2006	1991–2004	r, sc	67	30	39	82	0	67	45	100	e−	15	40	64	AT2+:20%, LT3+:21%	
Bobin et al. [63]	2004	1988–2001	r, sc	24	53	21	92	29	63	45–50	100	e−	15	46*6	56	LT3+: 8% (N3: 8%)	
De Paoli et al. [64]	2003	1999–2003	r, sc	30	27	50	63	100	0	50.4	77	e−	15	73*6	n.r.	LT3+: 10% (N3+:6%)	
Gilbeau et al. [65]	2002	1990–2000	r, sc	45	53	100	96	0	93	49	38	e−	15	40	60	AT3+:7%, LT3+:4% (N2:18%)	
Petersen et al. [18]	2002	1981–1995	r, sc	87	42	49	83	75*4	28*4	47.6	100	e−	15	59	48	GI3 + 18%, F3: 9%, N3:10%, UO:5%	
Gieschen et al. [66]	2001	1980–1996	r, sc	16	38	78	100	100	0	45–50.4	100	e−	10–20	83	74	LT3+:25% (N3+:12%)	OS +/− IORT sig.
				13			100	100	0	45	0			61	30	n.r.	
Alektiar et al. [67]	2000	1992–1996	r, sc	32	33	37	94	0	78	45–50	75	HDR	12–15	62	45	BO3+:18%, F3+:6%, N2:6%	
Bussières et al. [68]	1996	1991–1994	r, sc	19	17	74	79	5	63	50	100	e−	17	76*10	60*10	PC3+:21%, LT3+:11%	
Sindelar et al. [20]	1993	1980–1985	p, sc, ran	15	96	n.r.*3	100	0	100	35–40	100	e−	20	60*6	45*12	AE:7%, CE:13%, F:0%, N3+:47%	LC +/−IORT sig.
				20			100	0	100	50–55	0			20*6	52*12	AE:60%, CE:50%, F:25%, N3+:0%	AE, CE, N IORT +/− sig
Gunderson et al. [69]	1993	n.r.	r, sc	20	min. 15	50	55	30	70	45–60.4	100	e−	15	85*6	49	AT3+:10%, LTR3+:20% (N3+:5%)	
Willett et al. [70]	1991	1981–1989	r, sc	20	38	70	85	95	5	40–50	60	e−	10–20	81*9	71*6	LT3+:15% (N3+:10%, UO3+:10%)	
Kinsella et al. [71]	1988	1980–1985	p, sc, ran	15	min. 15	n.r.*3	100	0	100	35–40	100	e−	20	55	38	AE:7%, CE:13%, F:0%, N:27%	LC +/−IORT sig
				20			100	0	100	50–55	0			30	50	AE:60%, CE:35%, F:30%, N:5%	AE, CE, F +/−IORT sig

year: year of publication, period: study period, n.r.: not reported, type: study type, r: retrospective, p: prospective, sc: single centre, mc: multi centre, ran: randomized, n: number of patients, f/u: median follow-up in months, min.: minimum, PD: primary disease (%), GTR: gross total resection (%), EBRT: external-beam RT, pre.: patients receiving preoperative EBRT (%), post.: patients receiving postoperative EBRT (%), dose: median EBRT dose in Gy, IORT: intraoperative RT, IORT(lower line):patients receiving IORT (%), tech.: technique of IORT, e-: electrons, HDR: high-dose rate brachytherapy, dose: median IORT dose in Gy, 5y-LC: actuarial 5-year local control rate, 5y-OS: actuarial 5-year overall survival rate, AT: acute toxicity all grades, ATx: acute toxicity grade x, LT: late toxicity all grades, LTx: late toxicity grade x, RS: re-surgery, PC: postoperative complications all grades, PCx: postoperative complications grade x, UO: ureteral obstruction all grades, UOx: ureteral obstruction grade x, N: neuropathy all grades, Nx: neuropathy grade x, AE: acute enteritis all grades, CE: chronic enteritis all grades, F: fistula all grades, Fx: fistula grade x, BO: bowel obstruction all grades, Box: bowel obstruction grade x, GI: gastrointestinal all grades, GIx: gastrointestinal grade x, RT: radiation therapy associated all grades, RTx: RT associated grade x, HT: hematological all grades, HTx: hematological grade x, NV: nausea/vomiting all grades, NVx: nausea/vomiting grade x, *1: liposarcoma subgroup only, *2: only irradiated patients, *3: stratified according to primary vs recurrent disease, *4: some patients received pre- and postoperative EBRT, *5: simultaneous-integrated boost, *6: crude rate, *7: in patients with GTR, *8: in patients with IORT, *9: 4-year rate, *10: 2-year rate, *11: 3-year rate, *12: median OS in months, *13: disease specific survival, *14: preoperative chemoradiation, *15: IORT + EBRT.

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Comparative series +/- IOERT

author	year	type	n	f/u	PD	GTR	preop RT	postop RT	IOERT	5-year LC	5-year OS	
Sindelar	1993	p, sc, ran	15 20	96	n.r.	100% 100%	none none	100% (35-40 Gy) 100% (50-55 Gy)	100% none	60% (crude) 20% (crude)	45 mo (med OS) 52 mo (med OS)	favors IOERT
Gieschen	2001	sc, r	16 13	38	78%	100% 100%	100% 100%	none none	100% none	83% 61%	74% 30%	favors IOERT
Pierie	2006	sc, r	14 27	27	100% 100%	100% 100%	100% 100%	none none	100% none	n.r. n.r.	77% 45%	favors IOERT
Ballo	2007	sc, r	18 63	47	73%	100% 100%	60% 60%	none none	100% none	51% 46%	n.r. n.r.	no sig. diff.
Stucky	2014	sc, r	37 26	45	64%	89%	95% none	none none	100% none	89% 46%	60% 60%	favors IOERT
Kelly	2015	mc, r	32 172	45	100% 100%	97% 100%	94% none	6% none	47% none	91% 65%	93% (DSS) 85% (DSS)	favors RT
Wang	2017	SEER	13 352 15	n.r.	n.r.	n.r.	100% 14% none	none 87% none	100% none 100%	n.r. n.r. n.r.	87% 55% 34%	favors IOERT

Prof. Dr. F. Roeder
08.11.2024

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New Developments (RT in STS – Extremity)

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Preop. RT with moderate hypofractionation (HYPORT-STS)

Single centre phase 2 (MD Anderson)
N=120, med postop. f/u 20 mo
Preop. RT 42.75 Gy in 15 Fx (SD 2.85 Gy)
Primary endpoint: major wound complication
Comparison: preop arm NCIC trial (35%)

Results:
Major wound complication rate 31%
Acute toxicity grade 3+: 0%
Late toxicity grade 3+: 2%
crude LR rate: 5%

	All patients (n=120)
Major wound complication	37 (31%)
Secondary operation for wound repair	12 (10%)
Invasive procedure for wound management without secondary operation	16 (13%)
Deep wound packing of an area of wound at least 2 cm in length with or without prolonged dressing	2 (2%)
Readmission to hospital for wound care	7 (6%)
No major wound complication	83 (69%)

Data are n (%).

Table 2: Type and frequency of major wound complications by 120 days

Ashleigh Guadagnolo et al. 2022

→ Moderate hypofractionation seems feasible

SCOPES trial ongoing
randomized phase II
Preop EBRT:
14x3 Gy vs 25x 2 Gy

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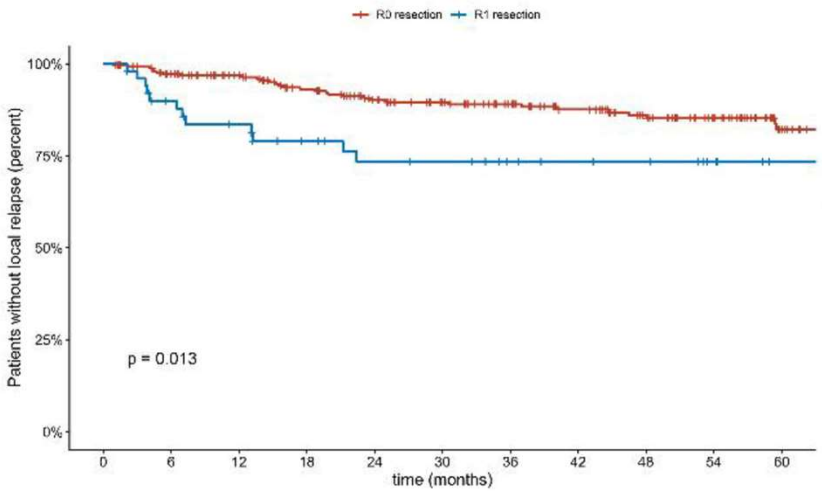
Preop. RT with ultra-hypofractionation

Single centre prospective
N=311, med f/u 57 mo
Preop. RT 5x5 Gy, surgery after 2-4 days
Primary endpoint: LRFS (LC)

Results:
R0-resection rate: 84%
Wound complication (diff. def.): 24%
Late toxicity: 9%

5-year LC: 81%
5-year OS: 63%



LC according to resection margin

Kosela-Paterczyk et al. 2021

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Preop. RT with ultra-hypofractionation

author	year	type	n	f/u	preop RT	time to S	R0	LC	OS	WC	late tox.	amp.
Kosela-Paterczyk	2021	pro.	311	57	5 x 5 Gy (cons.)	< 1 wk	84%	86%	63%	24%	overall 9%	n.r.
Spalek	2021	phase II	46	24	5 x 5 Gy (cons.)	6-8 wks	72%	93%	67%	34%	n.r.	7%
Silva	2021	phase II	18	29	5 x 5 Gy (cons.)	6 wks	83%	94%	95%	33%	Gr. 3+: 6%	n.r.
Kalbasi	2020	phase II	52	29	5 x 6 Gy (cons.)	2-6 wks	n.r.	94%	n.r.	32%	Gr. 3: 0%	n.r.
Mayo	2023	retro	22	25	5 x 6 Gy (cons.)	< 1 wk	82%	100%	77%	41%	Gr. 2+: 18%	n.r.
Bedi	2021	phase II	32	36	7 x 5 Gy (EOD)	4-6 wks	91%	100%	83%	25%	Gr. 3: 13%	n.r.
Parsai	2020	retro	16	11	5 x 5.5-8 Gy (cons. or EOD)	< 1 wk	63%	100%	n.r.	31%	Gr.3+: 0%	n.r.
Kubicek	2022	phase II	16	57	5x 7-8 Gy (EOD)	4-8 wks	75%	93%	n.r.	20%	Gr. 3+: 7%	n.r.
Leite	2021	phase II	25	21	5 x 8 Gy (EOD)	> 4 wks	96%	96%	n.r.	28%	Gr. 3: 8%	16% (all tox.)
Curry	2024	MA	786	n.r.	5 x 5-8 Gy (cons. or EOD)	n.r.	85%	92%	78%	30% (gr. 2+)	fibrosis Gr.2+: 6%	n.r.
Kao	2023	MA	477	n.r.	5 x 5-8 Gy (cons. or EOD)	n.r.	87%	96%	86%	30%	n.r.	n.r.

Ultra-hypofractionation seems feasible, but similar efficient and equitoxic ?

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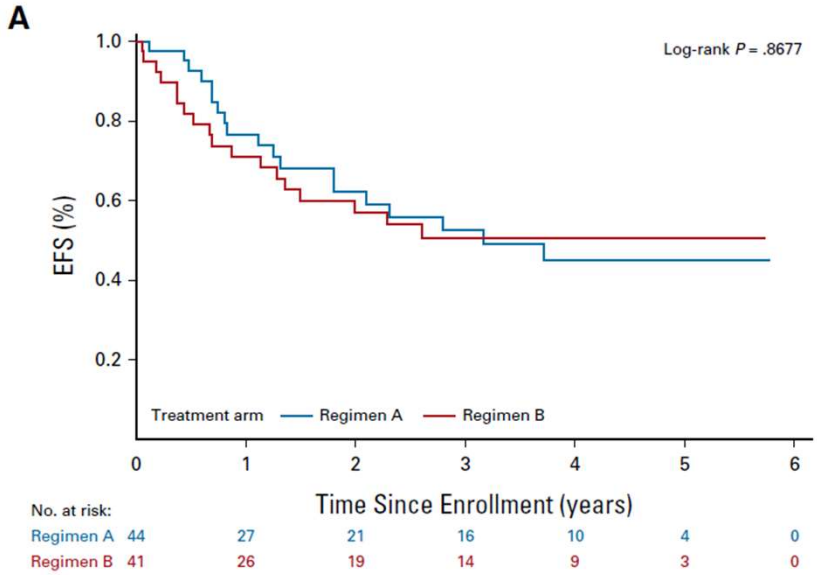
Renaissance of chemoradiation ?

Pazopanib and (C)RT – ARST 1321 trial

Phase II, children/adults, non-Rhabdo STS
N=81 (58), median f/u 40 mo
Neoadj. Ifo/Doxo + RT +/- Pazopanib + adj. CHT
Primary endpoint: near pCR (> 90% necrosis)

near-pCR: 58% vs 22% (sig.)
Acute Tox Gr 3+: sig. higher with Pazopanib

3y-EFS 53% vs 51% (n.s.)
3y-OS 76% vs 65% (n.s.)



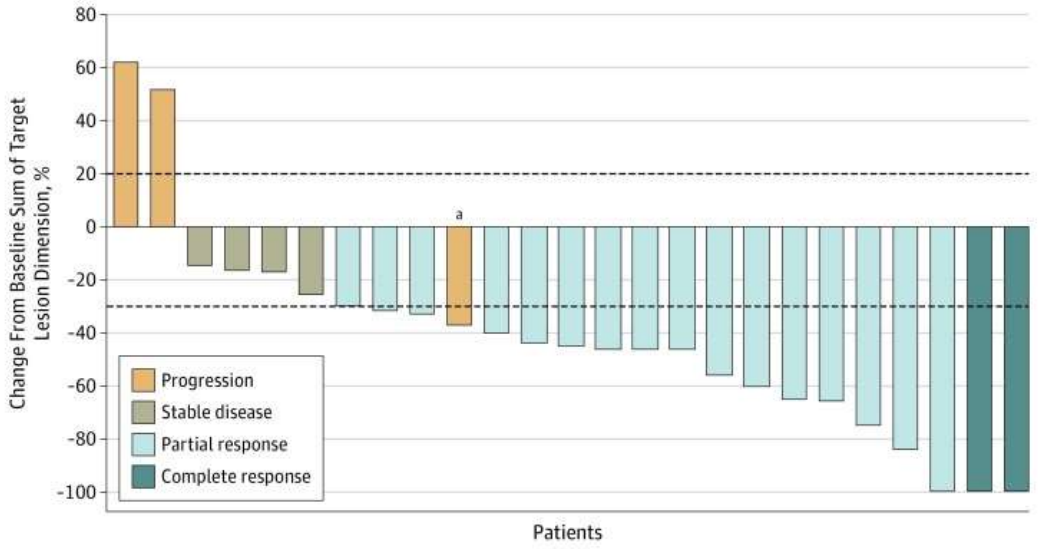
Weiss et al. 2020, 2023

Renaissance of chemoradiation ?

Trabectedin and RT – TRASTs trial

Phase I/II, n=45, med f/u 14 mo
Advanced or metastatic STS
Trabectedin + low dose RT
(30 Gy/10 Fx)

MTD 1.5 mg/m2
ORR 72% (local), 60% (central)



high response rate, useful in localized disease ?

Martin-Broto et al. 2020

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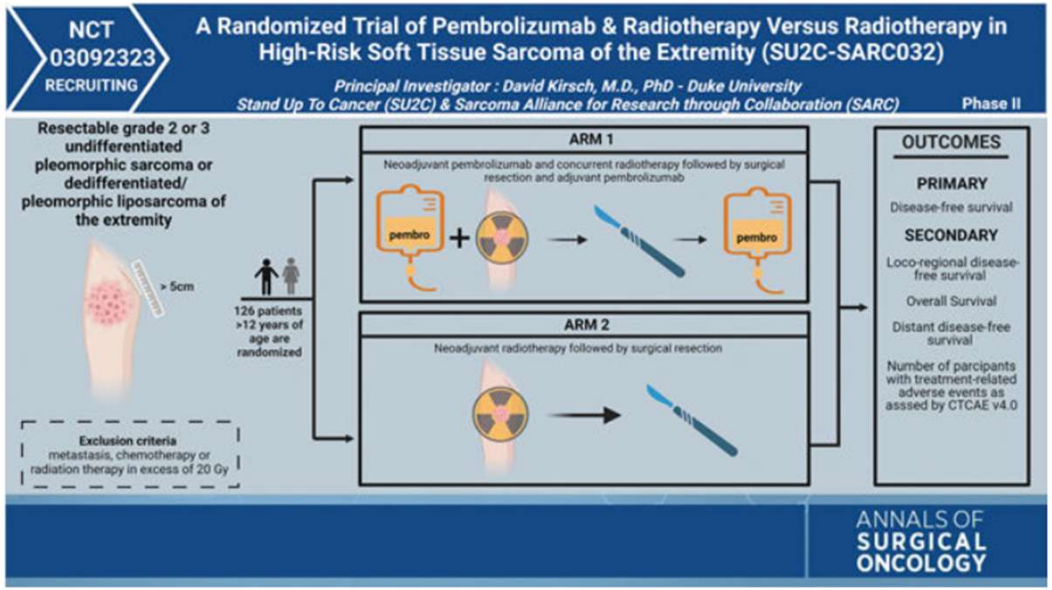
Renaissance of chemoradiation ?

Pembrolizumab and RT – SARC 032 trial

Phase II, n=143, med. f/u 24 mo
UPS 85%, grade 3 64%
Pembro before, during and after RT

2y-DFS 70% vs 53% (sig.)
Benefit limited to grade 3

2y-LRFS, DDFS, OS n.s.
GR 3+ Tox 52% vs 26% (sig.)



Saif et al. 2023, Mowery et al. ASCO 2024

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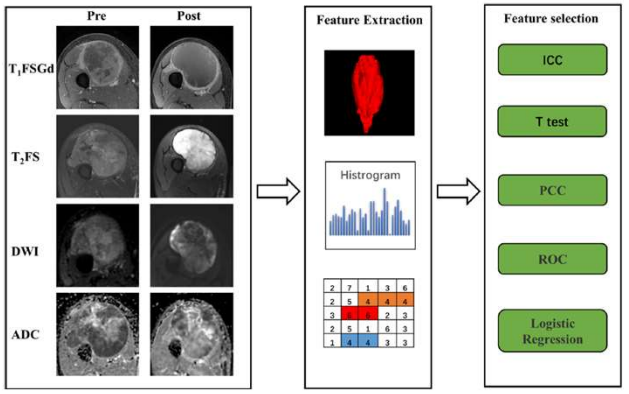
Response based treatment ?

European Radiology (2023) 33:3984–3994
https://doi.org/10.1007/s00330-022-09362-6

Predicting pathological complete response of neoadjuvant radiotherapy and targeted therapy for soft tissue sarcoma by whole-tumor texture analysis of multisequence MRI imaging

Lei Miao[1] · Ying Cao[2] · LiJing Zuo[2] · HongTu Zhang[3] · ChangYuan Guo[3] · ZhaoYang Yang[3] · Zhuo Shi[1] · JiuMing Jiang[1] · ShuLian Wang[2] · YeXiong Li[2] · YanMei Wang[4] · LiZhi Xie[5] · Meng Li[1] · NingNing Lu[2]



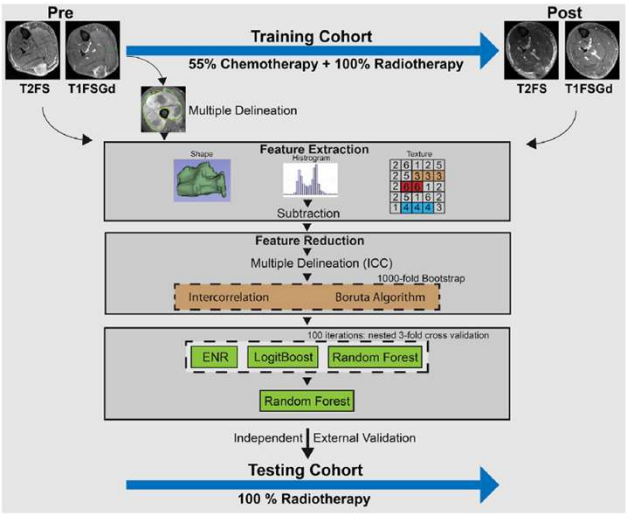
Miao et al. 2023

Contents lists available at ScienceDirect
Radiotherapy and Oncology
journal homepage: www.thegreenjournal.com

Original Article

MRI-based delta-radiomics predicts pathologic complete response in high-grade soft-tissue sarcoma patients treated with neoadjuvant therapy

Jan C. Peeken[a,b,c,d,e,*], Rebecca Asadpour[a], Katja Specht[f], Eleanor Y. Chen[g], Olena Klymenko[a], Victor Akinkuoroye[a], Daniel S. Hippe[h], Matthew B Spraker[i], Stephanie K. Schaub[d], Hendrik Dapper[a], Carolin Knebel[j], Nina A. Mayr[d], Alexandra S. Gersing[k], Henry C. Woodruff[e,l], Philippe Lambin[e,l], Matthew J. Nyflot[d,m,1], Stephanie E. Combs[a,b,c,1]



Peeken et al. 2021

Delta radiomics predict pCR

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Response based treatment ?

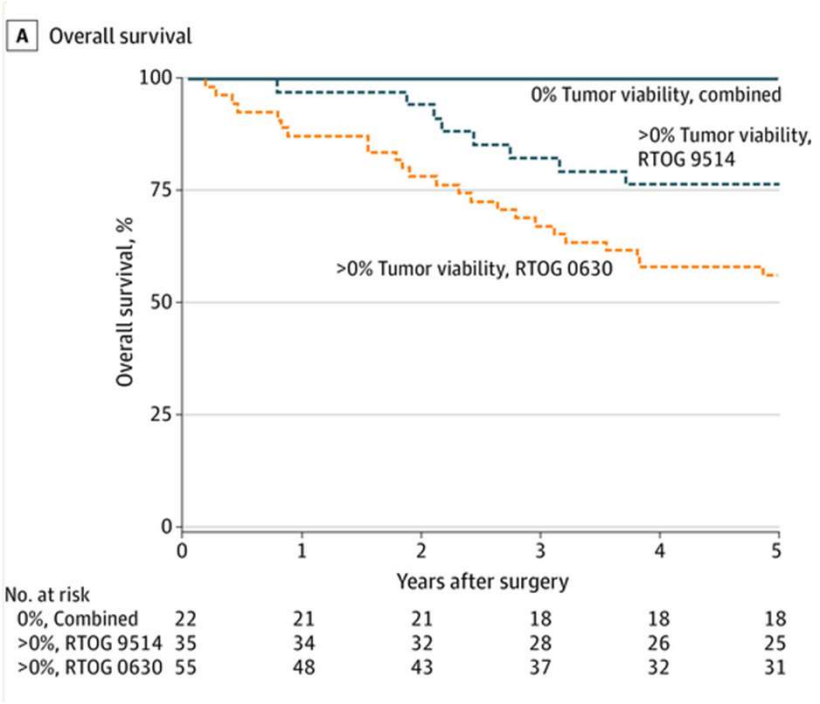
Combined analysis RTOG 9514 and 0630

RTOG 9514: neoadjuvant MAID with interdigitated RT
RTOG 0630: neodjuvant IMRT with reduced target volume

N=143
pCR: 28% (RTOG 9514) vs 19% (RTOG 0630)

5-year OS: 100% (pCR)
77% (no pCR RTOG 9514)
56% (no pCR RTOG 0630)

5-year LF: 0% (pCR)
12% (no pCR RTOG 9514)
9% (no pCR RTOG 0630)



Wang et al. 2023

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pCR/Response associated with outcome ?

Table 1
Published studies of the impact of pCR on clinical outcomes (enrolled > 50 patients).

First Author, Year [reference]	Type Design	N patients	Preoperative treatment	Pathological response rate	Significant impact on DFS (Yes/No)	Significant impact on OS (Yes/No)
Andreou, 2015 [17]	Retrospective (monocentric)	53	CT	32% (<10% viable tumor cells)	Yes (event-free survival)	Yes (disease specific survival)
Menendez, 2007 [19]	Retrospective (monocentric)	82	CT	39% (≥95% necrosis)	No	No
Eilber, 2001 [20]	Retrospective (monocentric)	496	CRT	14% (≥95% necrosis)	Yes	Yes
Mullen, 2014 [18]	Retrospective (monocentric)	113	CT or RT	44% (≥95% necrosis)	No	No (OS and disease-specific survival)
Gannon, 2019 [13]	Retrospective (monocentric)	162	RT or CRT	54% (≥10% necrosis)	Yes, but inversely correlated (≥10% necrosis predicted worse DMFS, and PFS on univariate analysis, and DMFS and PFS on multivariate analysis)	Yes, but inversely correlated (≥10% necrosis predicted worse OS on univariate analysis)
Cates, 2019 [12]	Retrospective (monocentric)	143	CT, RT or CRT	NA	Yes, but inversely correlated (Increasing necrosis, and fibrosis, is associated with decreased DFS)	No
Vaynrub, 2015 [16]	Retrospective (monocentric)	207	CT, RT or CRT	25% (≥90% necrosis)	Yes (DFS and RFS)	No
Salah, 2018 [15]	Meta-analysis	1663	CT, RT, CRT, or limb perfusion	NA	Yes	Yes
Bonvalot, 2020 present study	Retrospective (multicentric)	330	CT, RT, or CRT	22% (≤5% viable cells or ≥95% necrosis/fibrosis	Yes	Yes

Abbreviations: CRT, chemotherapy + radiation therapy; CT, chemotherapy; DFS, disease-free survival; DMS, distant metastasis-free survival; pCR, pathological complete response; RT, radiation therapy; OS, overall survival. NA, not available.

Bonvalot et al. 2021

Conflicting results !

- diff. definition of pCR
- Effect depending on neoadj. treatment (RT vs CT vs CRT) ?

Schaefer et al. 2017
EORTC response score not assoc. with outcome !

Hyalinization/fibrosis: OS ⇧

Necrosis: OS ⇩

Prof. Dr. F. Roeder
08.11.2024

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New Developments (RT in STS – Retroperitoneum)

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STRASS – Study design

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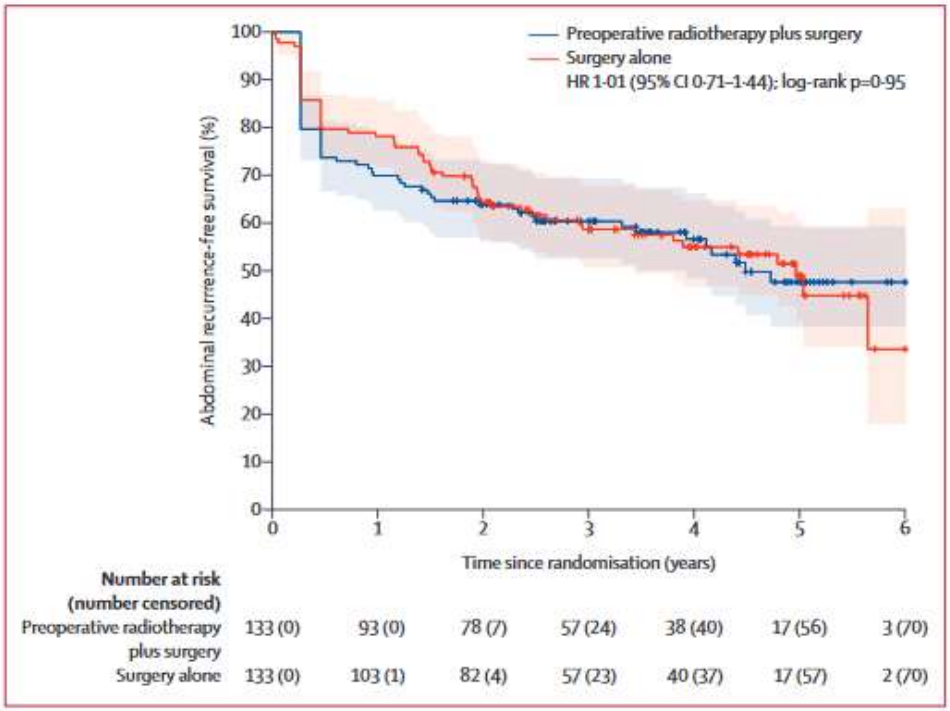
STRASS – primary endpoint ARFS (ITT)

Preop RT 3y-ARFS: 60 %
Surgery 3y-ARFS: 59%

main critics:
- design (time intervals)
- primary endpoint
- target volume
- RT interuptions
- included pts.
- interpretation



Bonvalot et al. 2020

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STRASS – patient characteristics

	OP	RT + OP	Total
Histology			
- wd-LPS	32%	35%	33%
- dd-LPS	41%	38%	40%
- other LPS	3%	1%	2%
- Leiomyosarcoma	17%	12%	14%
- other/missing	8%	14%	11%
Grading			
- G1	32%	33%	33%
- G2	29%	35%	32%
- G3	14%	9%	12%
- not evaluable/missing	25%	23%	24%

LPS 75%

few G3 many missing

Bonvalot et al. ASCO 2019, Bonvalot et al. 2020

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Type of events	OP (61 events)	RT + OP (60 events)	
Progression during RT	0	19 (32%)	15/19 GTR
Not operated	5	6	
Not resectable/operable (e.g. ASA3)	1	4	all OP
Peritoneal sarcomatosis at surgery	7	5	
Local recurrence after GTR	39 (64%)	17 (28%)	
Death	9	9	

→ IDMC sensitivity analysis: local progression during RT or medically unfit not counted if GTR

Bonvalot et al. ASCO 2019, Bonvalot et al. 2020

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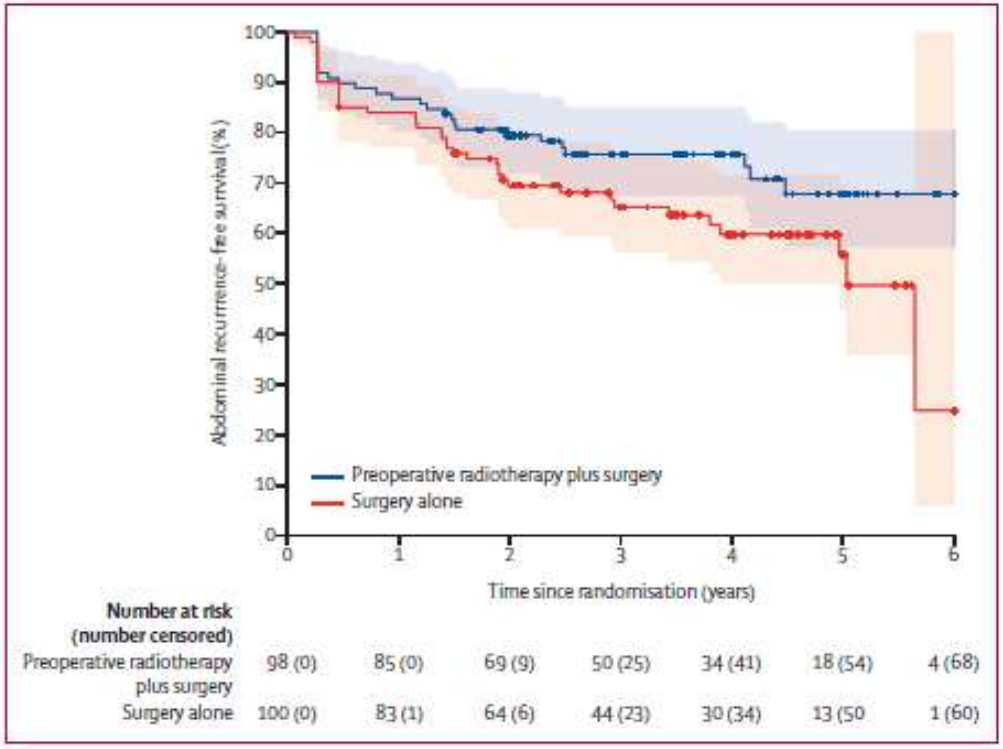
STRASS – second sensitivity analysis ARFS

(local progression or medically unfit for surgery during RT not an event if GTR)

all histologies:
Preop RT 3y ARFS: 72%
Surgery 3y ARFS: 60%

Liposarcoma only:
Preop RT 3y-ARFS: 76 %
Surgery 3y-ARFS: 65%

sig. favors preop RT



Bonvalot et al. 2020

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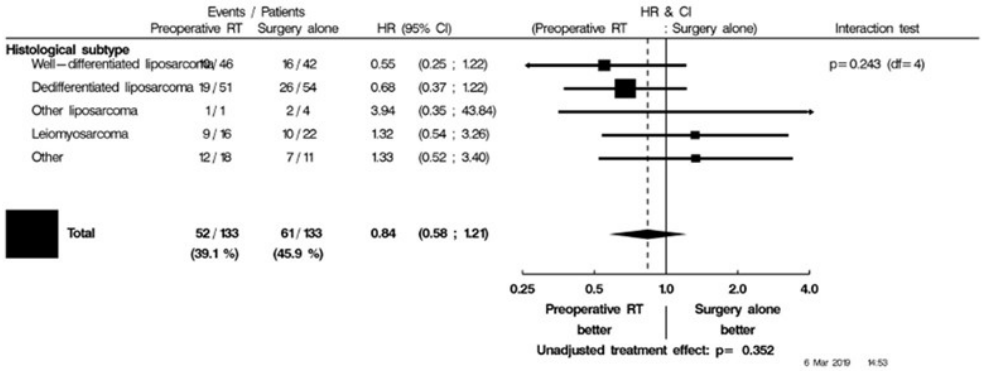
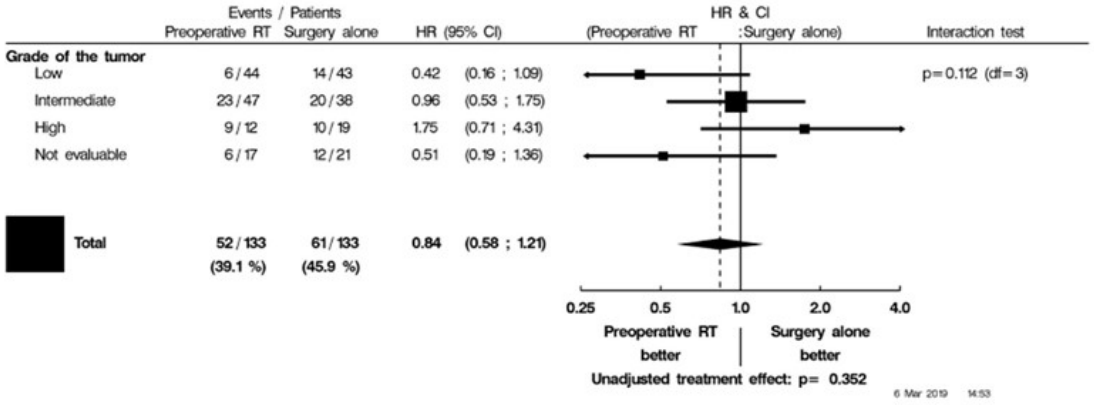
STRASS – sensitivity analysis ARFS (histology, grading)



favors RT in wd-LPS and dd-LPS



favors RT in G1 and not evaluable

Bonvalot et al. 2019 ASCO

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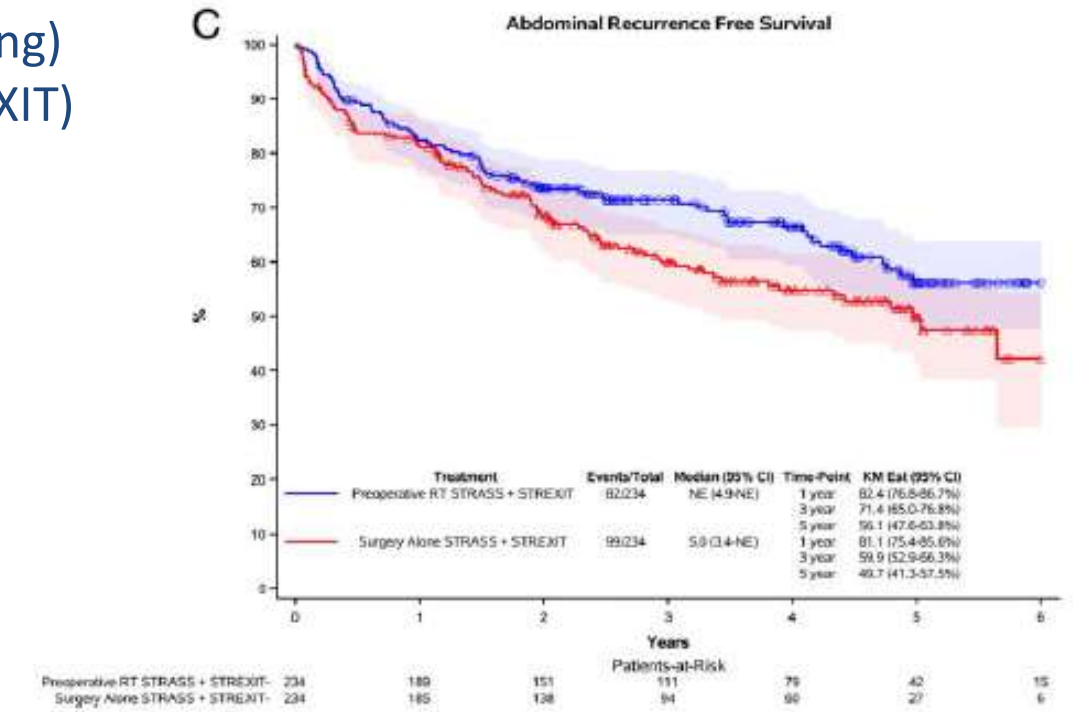
STREXIT – off protocol pts. in STRASS centers during STRASS recruiting time

n=727 (surgery 620, RT+ surgery 107)
n=202 (after propensity score matching)
n=468 pooled cohort (STRASS + STREXIT)

ARFS defined as
- R2 resection
- abdominal recurrence
- death of any cause

3y-ARFS:
STRASS: 66% vs 59%
STREXIT: 78% vs 62%
pooled: 71% vs 60%



Callegaro et al. 2022

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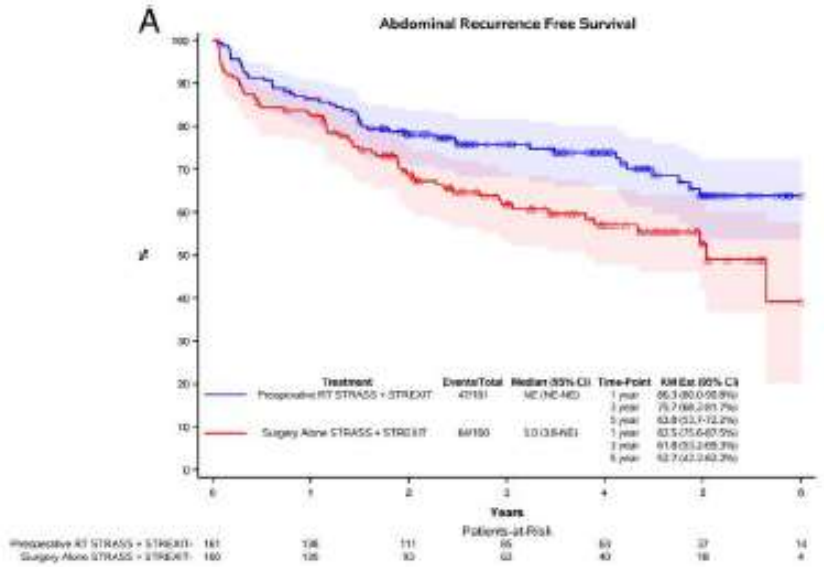
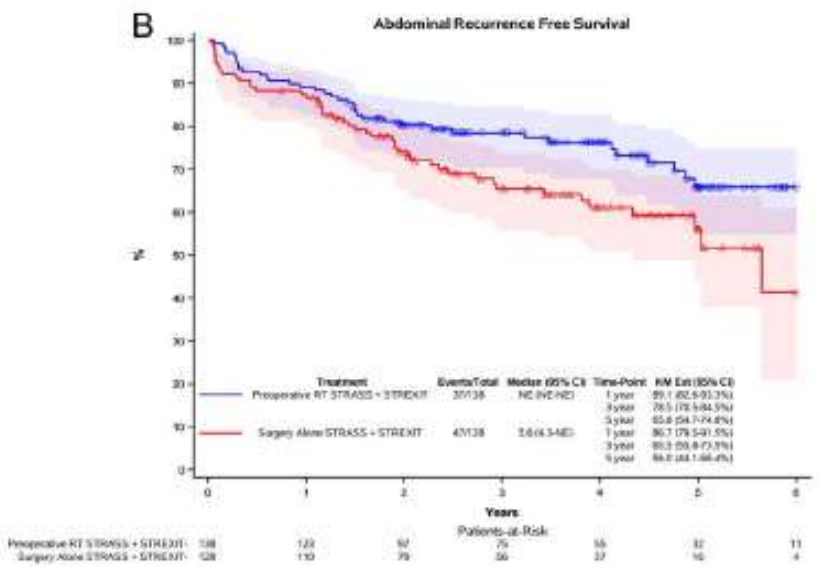
STREXIT – pooled cohort subgroups



all LPS



WD-LPS and DD LPS G1-2

Callegaro et al. 2022

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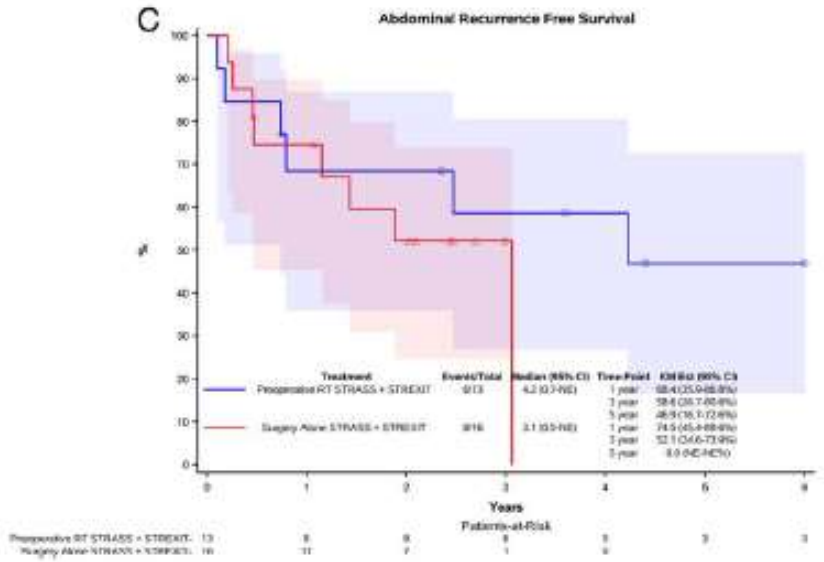
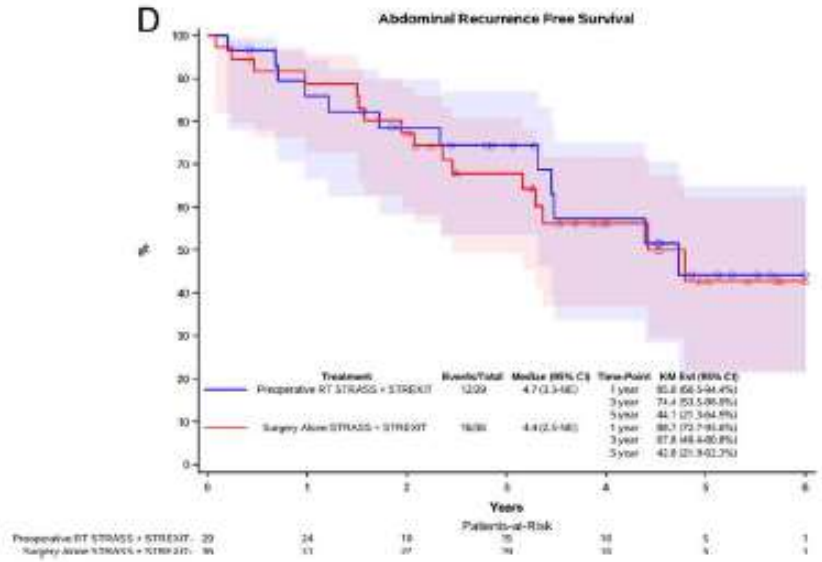
STREXIT – pooled cohort subgroups



DD-LPS G3



Leiomyosarcoma

Callegaro et al. 2022

STRASS/STREXIT– summary

complex study endpoint in STRASS (ARFS): difficult to interpret
different results with more usual definition of ARFS

„Less-debatable“ results

- Preop RT (IMRT) is safe with acceptable additional morbidity (data not shown)
- Preop RT did not improve overall survival
- Preop RT reduces true local recurrences after GTR
- Preop RT improved ARFS in WD-LPS and DD-LPS G1/2

„More-Debatable“ results

- No benefit/detrimental effect of preop RT in Non-LPS or G3 DD-LPS
- analyses clearly underpowered
- probably true for Leiomyosarcoma (supported by other data)

New Developments (RT in STS – general)

Histology driven approaches

STRASS/STREXIT: benefit of RT certain only for WD-LPS, DD-PLS G1-2

SARC 032: included only UPS, myxofibrosarcoma and LPS

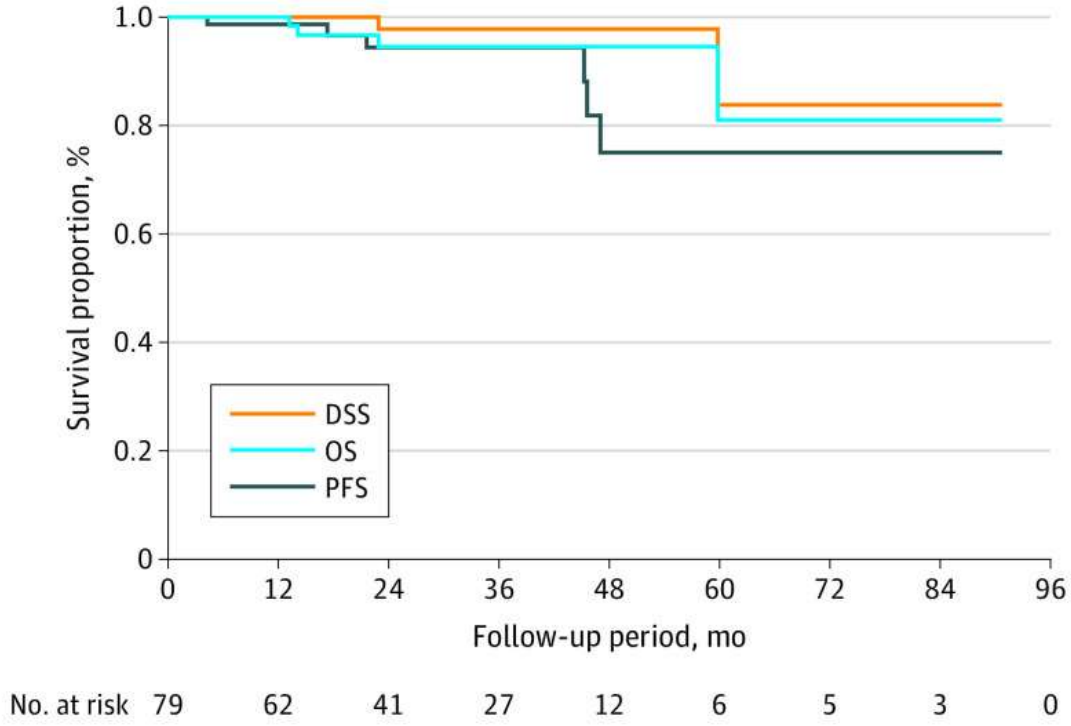
DOREMY: dose reduction in preop. RT of myxoid liposarcoma

DOREMY trial

- Phase II, n=79, med f/u 25 mo
- preop RT 18x2 Gy (36 Gy)
  -> surgery if curative
- primary endpoint:
  percentage of major pathological responses (< 50% viable cells)

Result:

- Surgery n=77 (two mets)
- Major response: 70/77 (91%)
- LC: 100% (in all surgical pts.)
- 3y-OS 95%



Lansu et al. 2020

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08.11.2024

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New Developments in IORT

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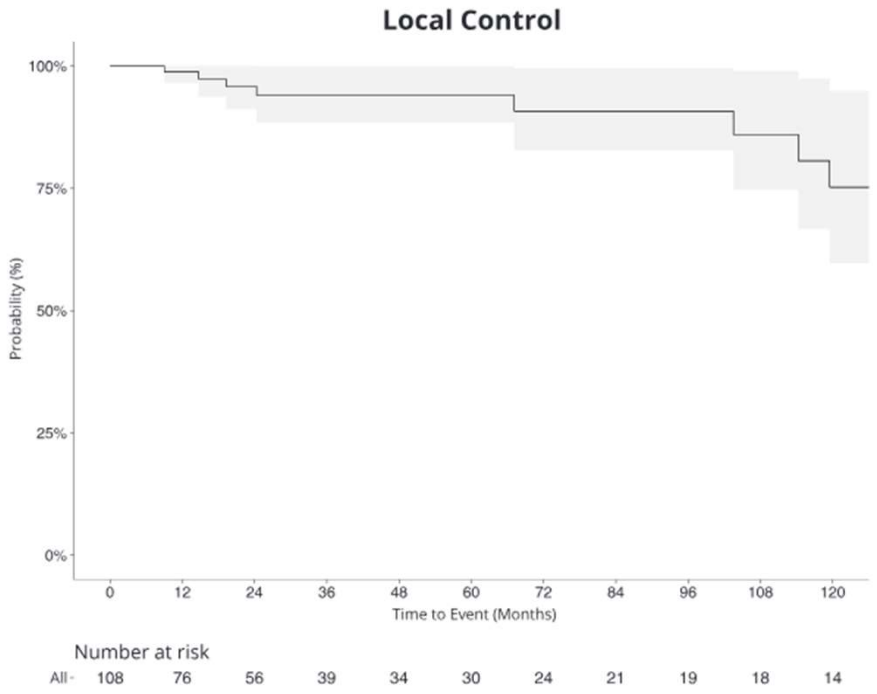
More retrospective evidence for preop. EBRT + IOERT in extr. STS

Mayo series 2022
n=108, med f/u 25 mo, R0: 89%
IOERT only if surgeon anticipated CM or R+
Median preop. EBRT dose: 50 Gy
Median IOERT dose: 12.5 Gy

5-year LC 94%, EFS: 75%, OS 64%
Limb preservation rate: 97%

Wound complications: 40%
Grade 3+ late Tox: ≤ 11%



Laughlin et al. 2022

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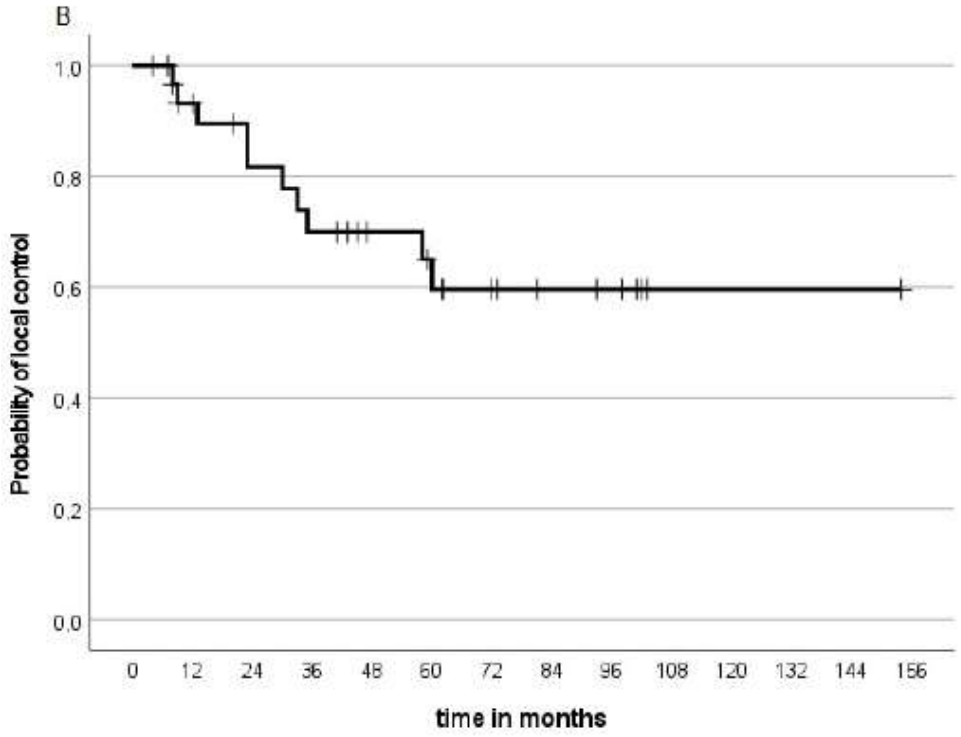
Some disappointing prospective results with IOERT in retro. STS

Retro WTS – „final“ results

- prospective single arm trial
- n=37, 2007-2017, med. f/u: 61 months
- histology: lipo 70%, leio 24%
- primary/recurrent: 84% / 16%
- surgery: 95%
- R0: 20%, R1: 69%, R2: 3%, Rx: 9%

5y-LC: 60% (rec. worse)

5yr-DC: 65% (leiomyosarcoma worse)



Seidensaal et al. 2023

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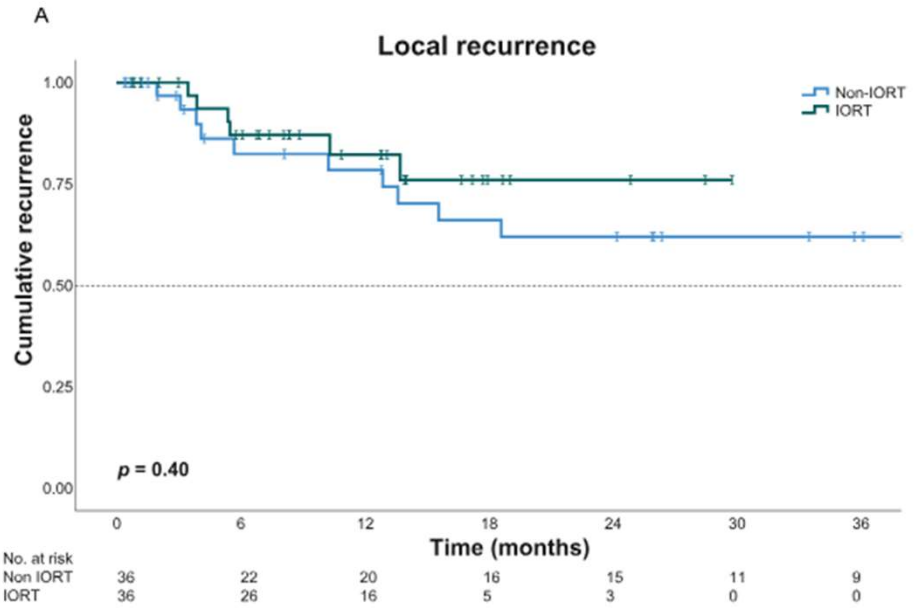
More retrospective evidence for IOERT in retro. STS

Mor et al. 2023
propensity matched 36:36 pts.
IOERT (median 15 Gy) vs no IOERT
primary/rec: 56%/44%

2y-LRFS: 76% vs 60% (n.s.)
Organ resected weighted score 0:
53% vs 8% (sig.)



Improved organ preservation with IOERT

Mor et al. 2023

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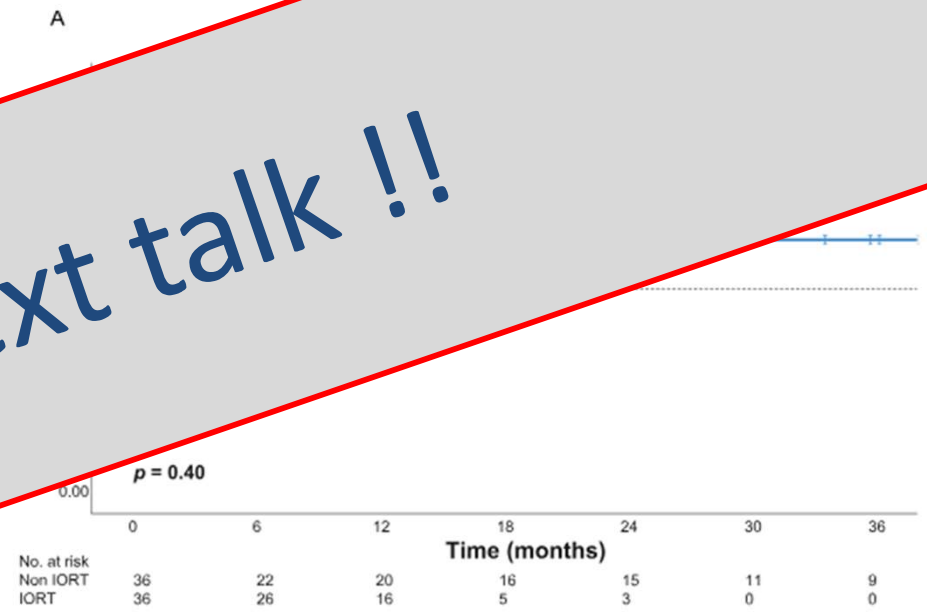
More retrospective evidence for preop EBRT + IOERT i… S

Mor et al. 2023
propensity matched 36:36 pts.
IOERT (median 15 Gy) vs no IOERT
primary/rec: 56%/44%

2y-LRFS: 7…
…
…
…
…vation with IOERT



See next talk !!

Mor et al. 2023

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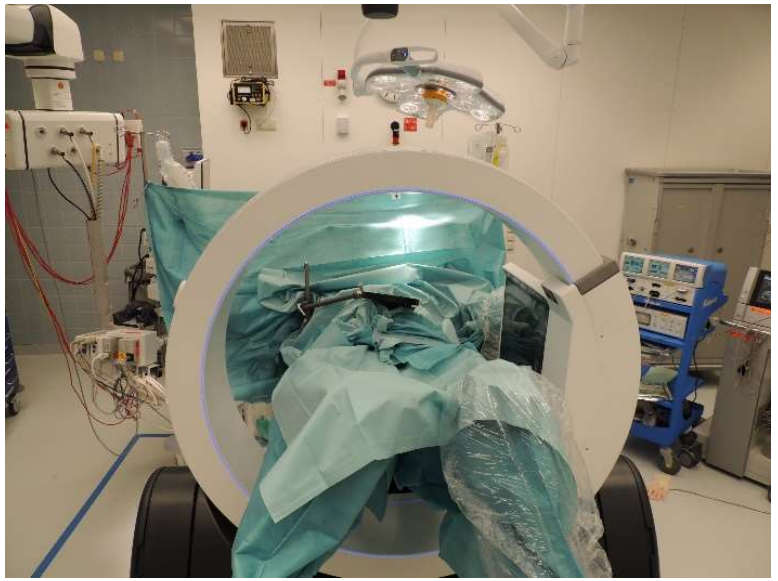
Image-Guided IOERT



Salzburg IOERT Suite (Imagingring for intraoperative 3D-Imaging and Treatment Planning)

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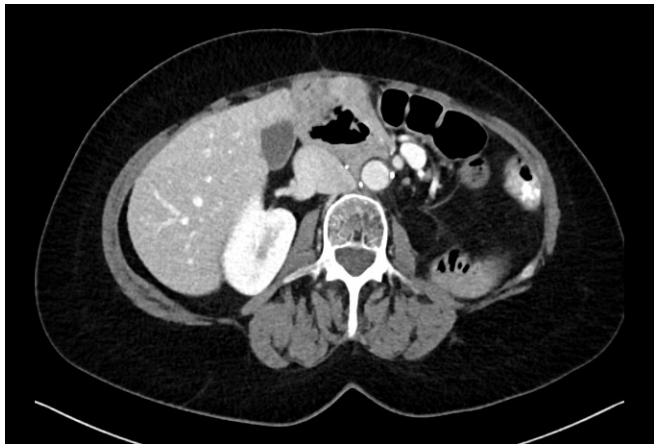
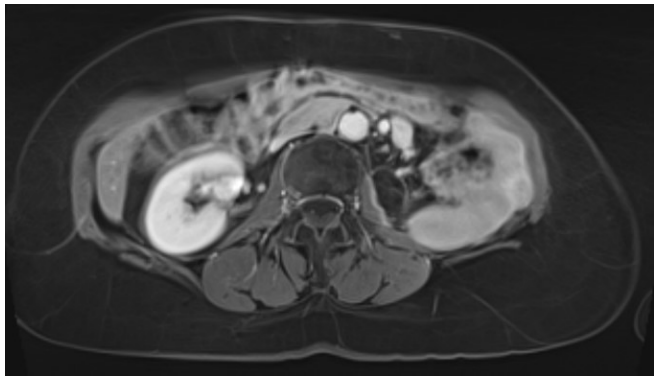
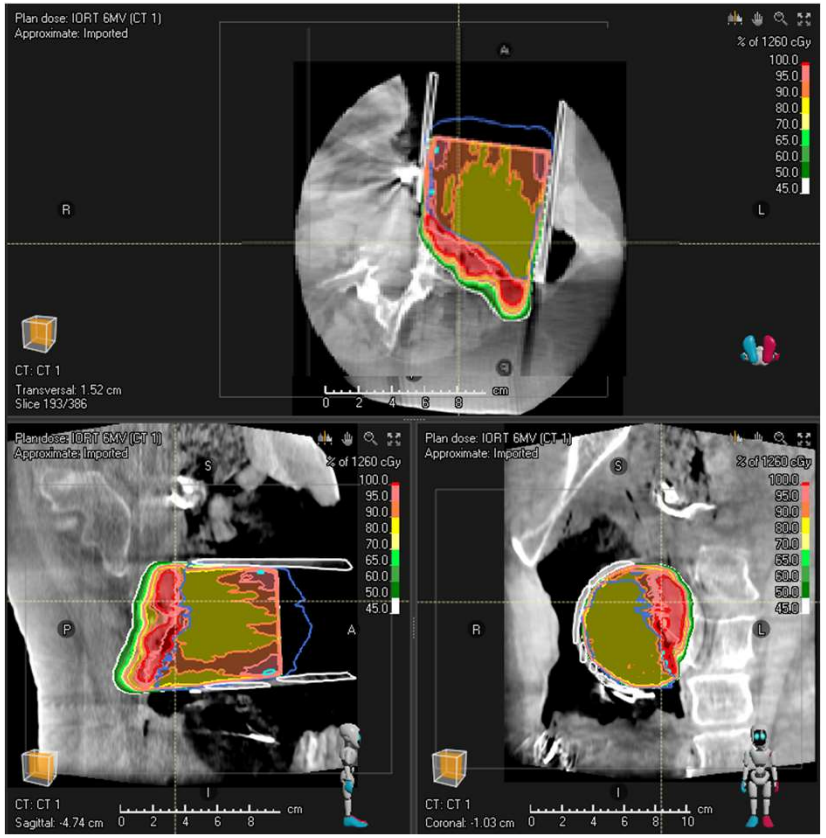
Image-Guided IOERT – example recurrent STS







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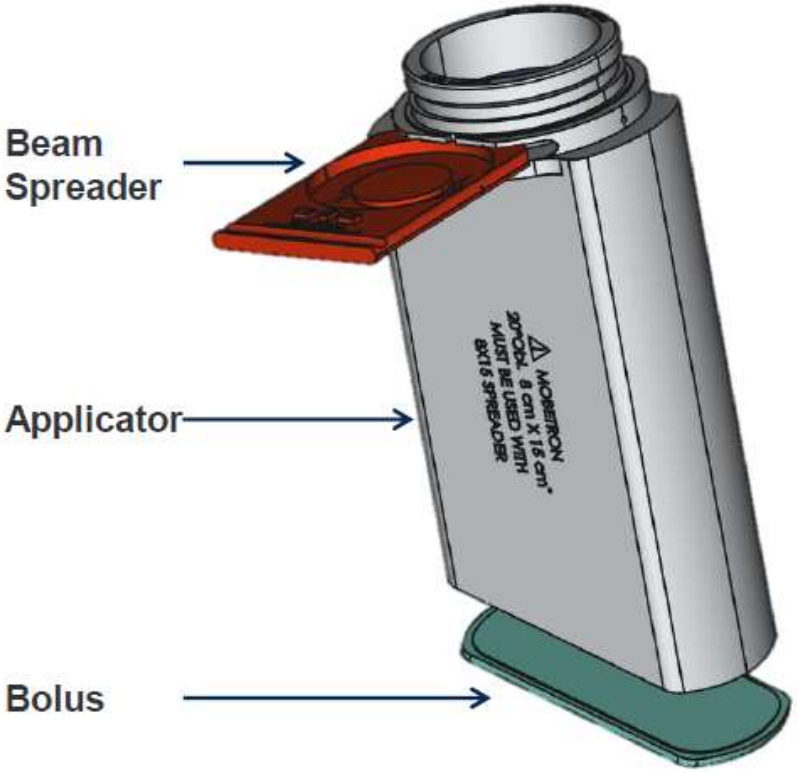
Sarcoma applicators

- non-circle shapes
- diff. lengths and widths
- for extremity tumors

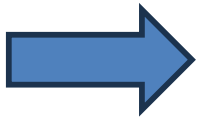


Intraop product sheet

Summary

Role of RT in STS is changing rapidly

- (ultra)-hypofractionation
- Chemo(immune)radiation with new agents ?
- Response based tailored treatment ?
- Omission of RT based on histology/Grading ?



Role of IORT has to be newly defined

Extremity STS:

IORT still valuable option:

- if anticipated close/positive margin after preop EBRT (function preservation !)
- if recurrent disease combined with moderate preop Re-EBRT (limb preservation !)

IORT after (ultra)-hypofractionated EBRT ?

- No trials or data so far
- 5 x 5 Gy + IORT vs 5 x 8 Gy (functionality/toxicity ?)
- Combine with response- tailored approach ?

➡ **Need for trials !**

Retroperitoneal STS:

IORT still valuable option:

- if anticipated close or positive margin after preop EBRT (organ preservation !)
- if recurrent disease combined with moderate preop Re-EBRT
- at least in certain histologies like WD-LPS or DD-LPS Grade 1/2

Technical developments will enable
- better understanding of dose distributions and dose prescription
- correctness of target volume definition (compared to pattern of failure)

➡ **Need for trials !**


Thank you !