Radiotherapie bei Sarkomen

Ärztefortbildung 28. November 2024

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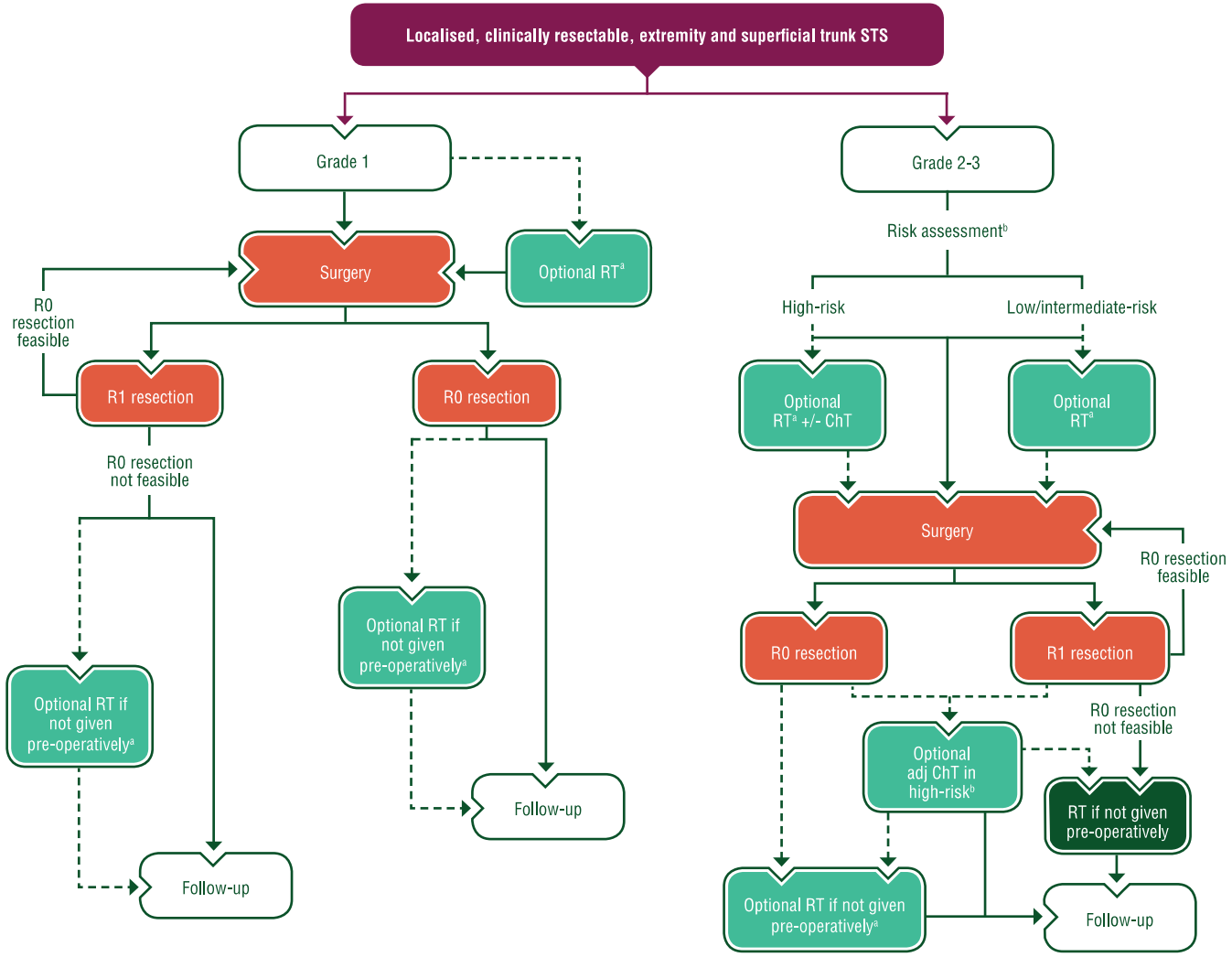
ESMO Leitlinien von Extremitäten-Sarkomen



Gronchi et al. (ESMO / EURACAN / GENTURIS) Annals of Oncology 2021, Vol 32, Issue 11.

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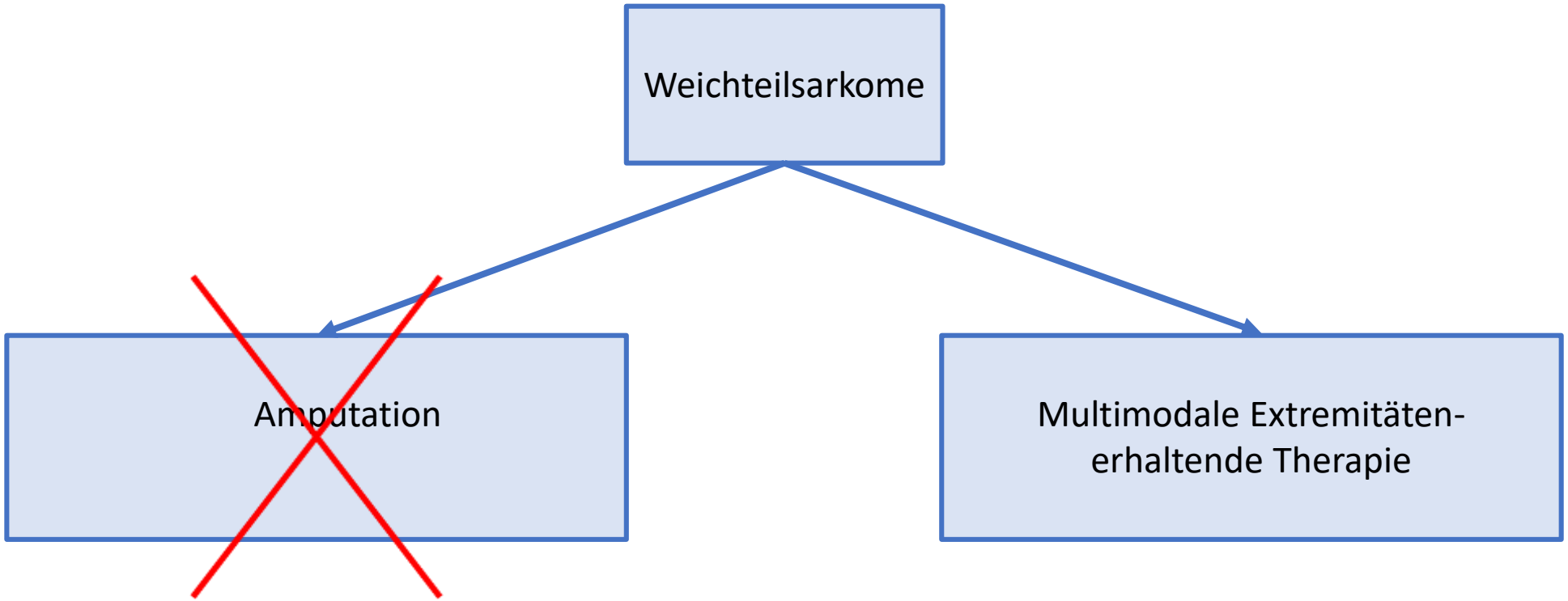
Evolution des Management von Extremitäten-Sarkomen



Lokale Kontrolle bei Extremitäten-Sarkomen

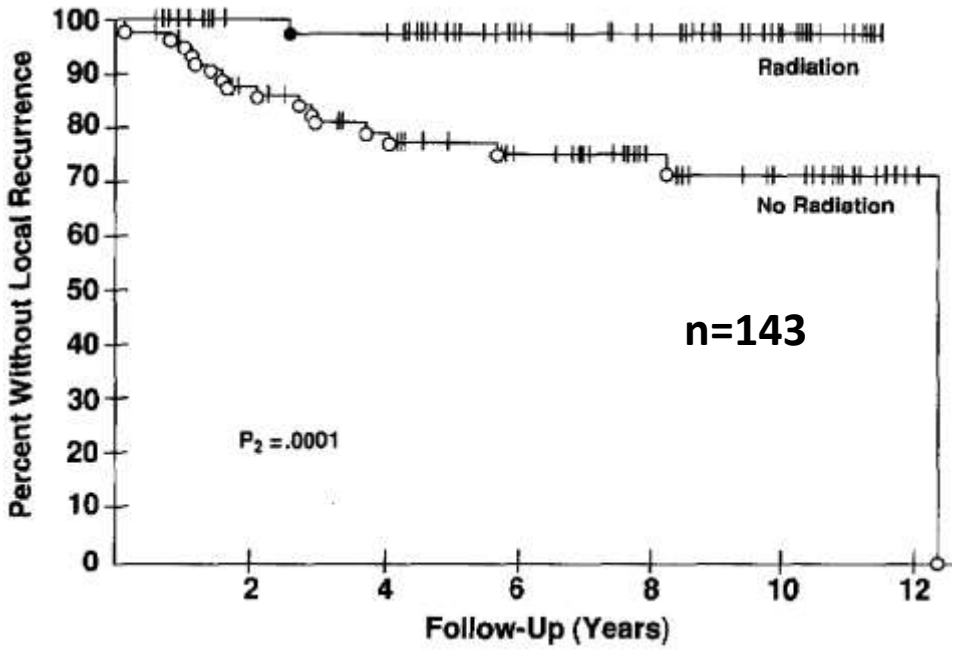
Yang et al., J Clin Oncol 1998;16:197-203

- Randomisierung
  - RT postoperative
    - 25 x 1.8 Gy = 45 Gy, Boost 10 x 1.8 Gy = 18 Gy,
    - insgesamt 63 Gy
  - keine RT

- **n=143**

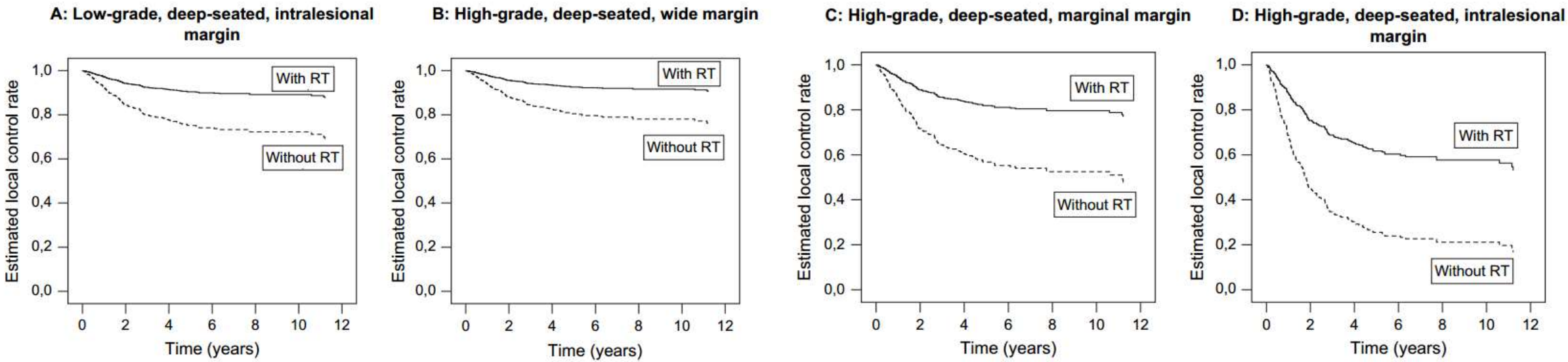
- high-grade: 4 Zyklen Chemotherapie

lokale Kontrolle, alle Patienten



Yang et al., J Clin Oncol 1998;16:197-203

Lokale Kontrolle bei Extremitäten-Sarkomen



Die Radiotherapie verbessert die lokale Kontrolle unabhängig vom chirurgischen Margin und Grading

Jebsen et al. Int. J. Radiation Oncology Biol. Phys., Vol. 71, No. 4, pp. 1196–1203, 2008

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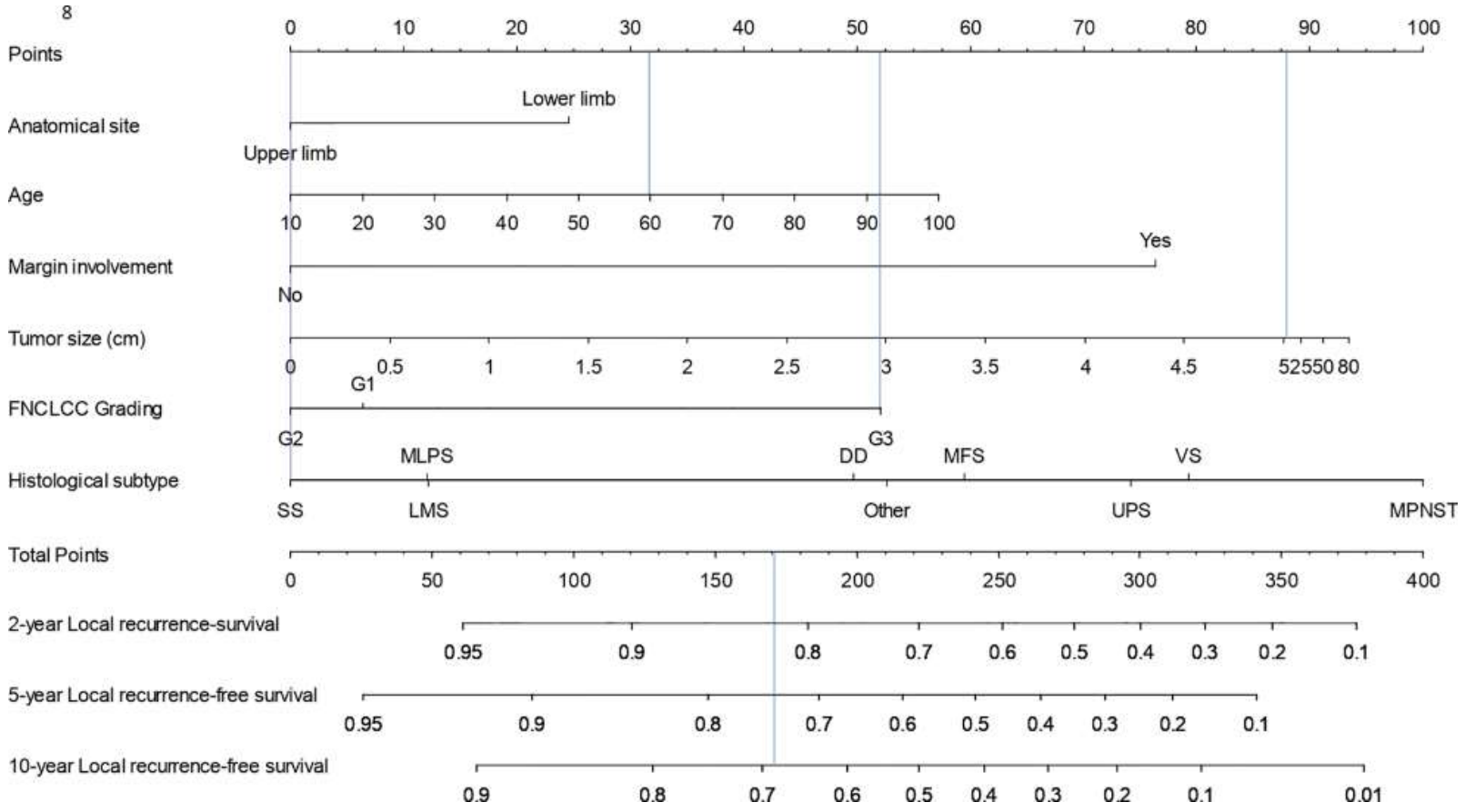
Nomogramm für Lokalrezidiv-Wahrscheinlichkeit bei Extremitäten-Weichteilsarkomen



De Sanctis et al. (2022) Front. Oncol. 12:941896.

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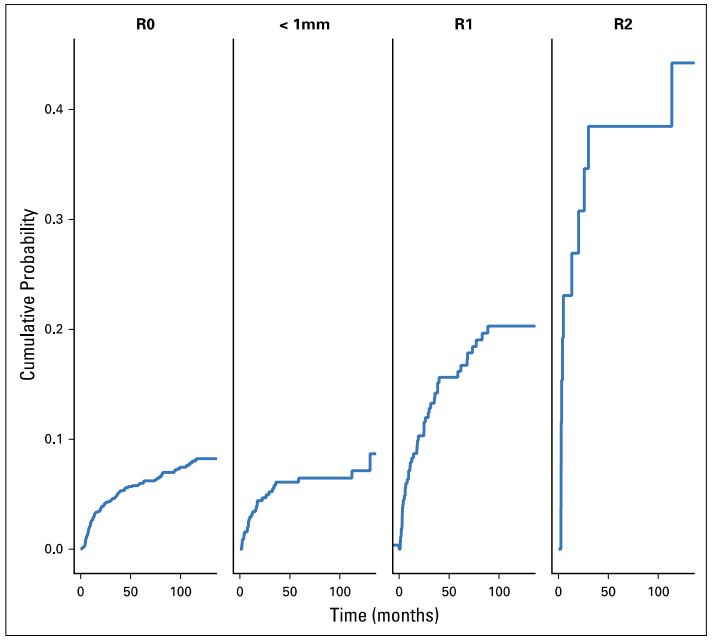
Resektionsmargin und Rezidivrisiko bei Extremitäten-Sarkomen

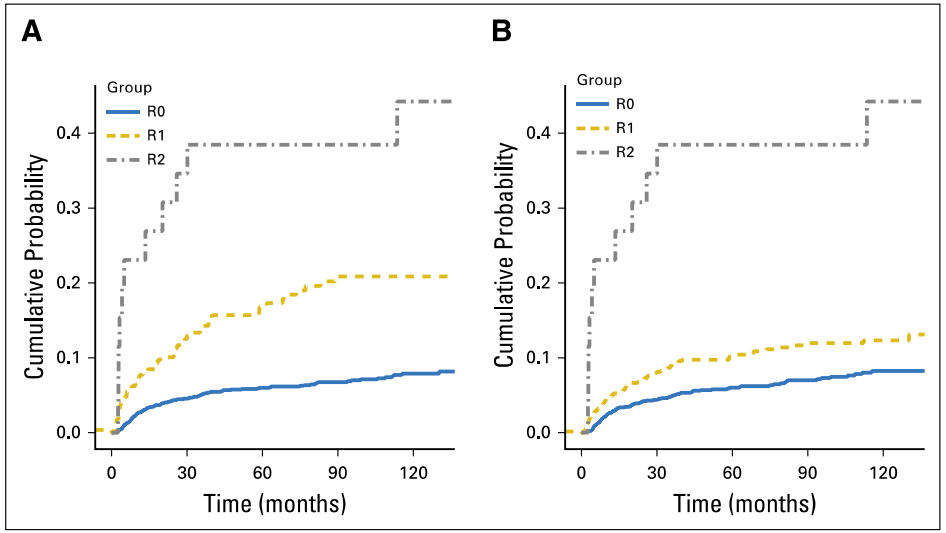
Lokalrezidivrisiko



Kumulatives Lokalrezidivrisiko

R-Klassifikation

R+1mm Klassifikation



Eine R+1mm Klassifikation reduziert den Lokalrezidivrisiko-Unterschied zu R0

Somit ist ein R0 <1mm Margin adäquat im multimodalen Behandlungssetting

Gundle et al. J Clin Oncol 2018. 36:704-709

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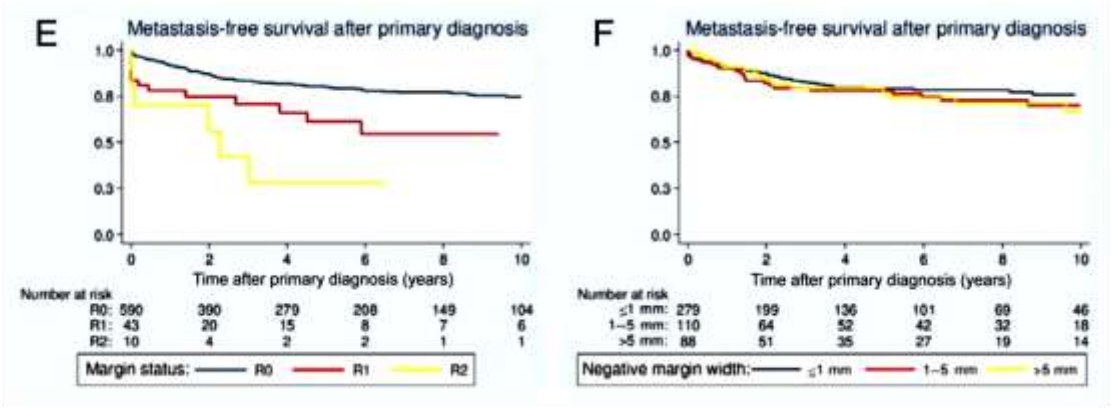
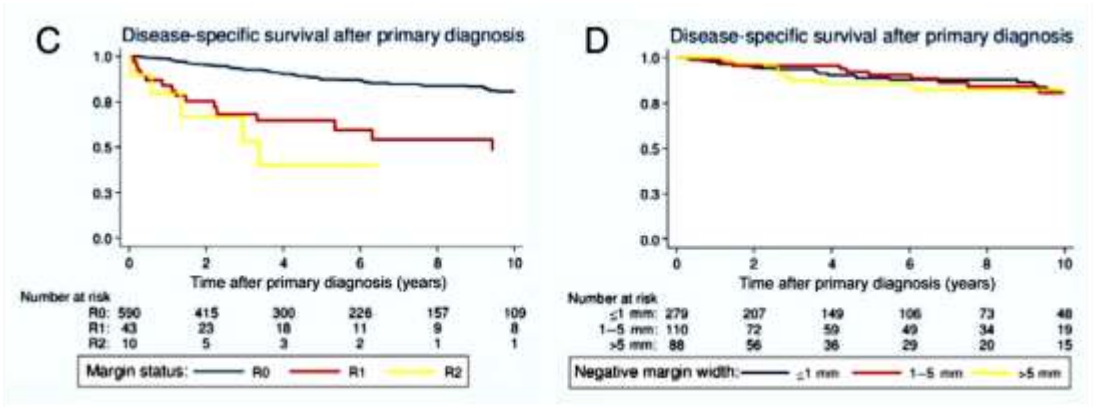
Resektionsmargin und Rezidivrisiko / Überlebenbei Extremitäten-Sarkomen

Metastasenfreies Überleben



Krankheitsfreies Überleben



Rezidivfreies Überleben

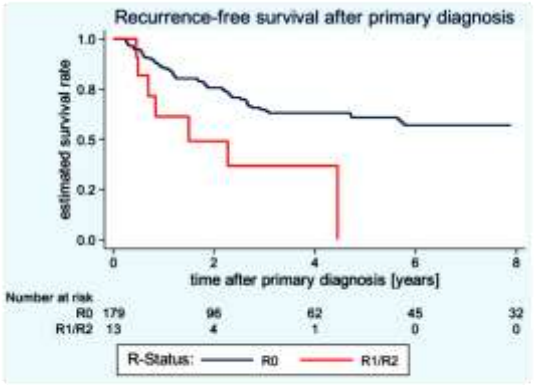


Figure 1. Estimated local recurrence-free survival (LRFS) curves after primary diagnosis according to margin status.

Gesamt-Überleben

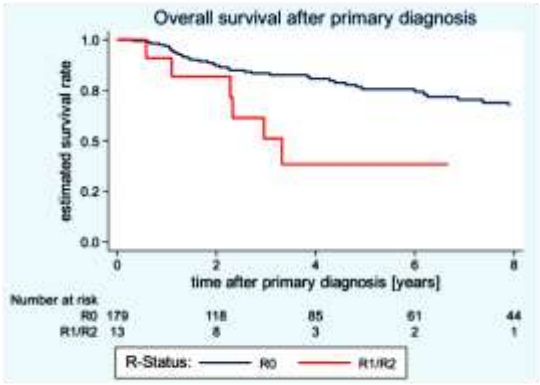


Figure 2. Estimated overall survival (OS) curves after primary diagnosis according to margin status.

Mikroskopisch negative Margins (no ink on tumor) sind assoziiert mit:

- Besserer lokaler Kontrolle, metastasenfreiem Überleben, Krankheitsfreiem Überleben und Gesamtüberleben

Harati et al. The Oncologist 2017;22:1400–1410

Goertz et al. Cancers 2020, 12, 362

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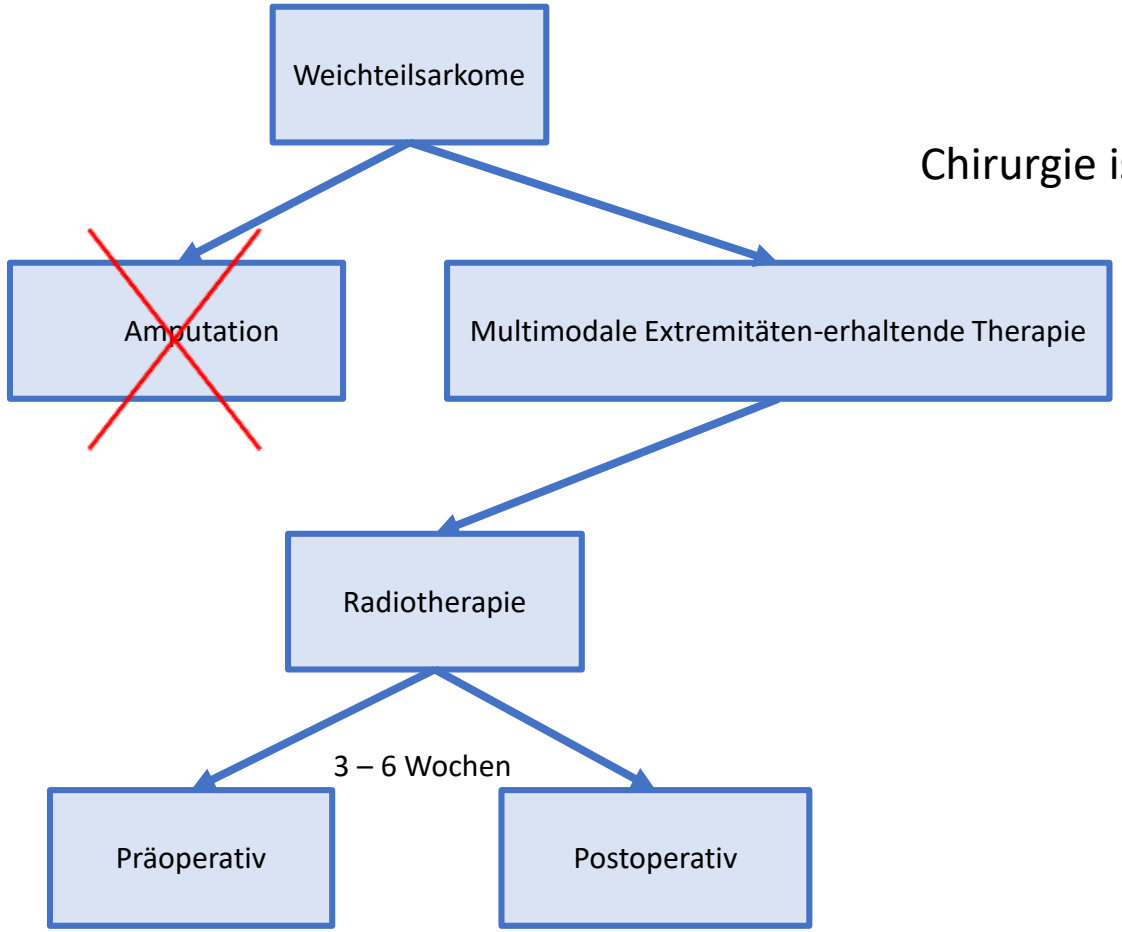

Chirurgie ist das Hauptstandbein der Sarkomtherapie

OP nicht später als 8 Wochen

Die Radiotherapie kompensiert nicht für eine schlechte Chirurgie sondern soll eine optimale Chirurgie ermöglichen

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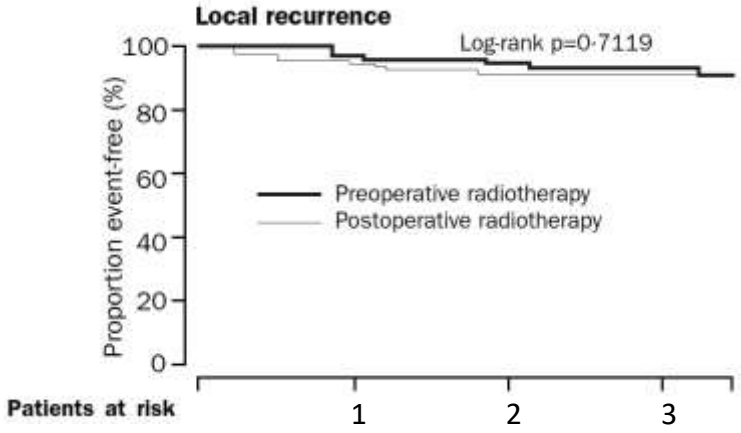
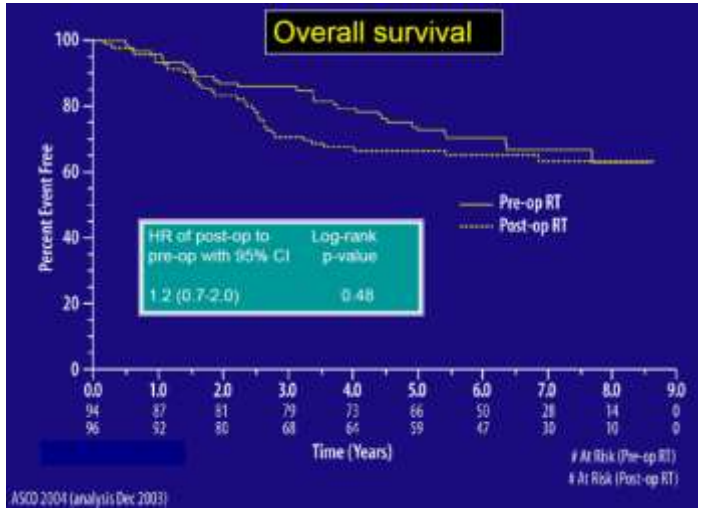
Präop. Radiotherapie bei Extremitäten-Sarkomen

O'Sullivan et al., Lancet 2002;359:2235-41

- präoperative vs postoperative RT
- primärer Endpunkt = **Wundkomplikationen, n=182**
- präoperative RT
  - 25 x 2 Gy = 50 Gy, 5 f pro Woche
- postoperative RT
  - 25 x 2 Gy = 50 Gy, 5 f pro Woche
  - 8-10 x 2 Gy = 16-20 Gy, 5 f pro Woche





O'Sullivan Lancet 110:817-22; 2002; JCO 22(14S):9007; 2004

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Präop. Vs. Postop. Radiotherapie bei Weichteilsarkomen

	preoperative RT	postoperative RT
Total radiation dose[1]	50 Gy[2]	60-68 Gy
Target volume	↓	↑
Tumor shrinkage[1,3]	possible	-
Local control[4]	↑?	↓?
reversibel: Hauttoxizität	↓	↑
reversibel: Wound complications	↑	↓
irreversibel: Fibrosis	↓	↑
irreversibel: Edema	↓	↑
irreversibel: Joint Stiffness	↓	↑
Functional outcome	↑	↓

36% vs 68%

35% vs 17%

Grade >2	Pre-op	Post-op	
Fibrosis	31.5%	48.2%	P = 0.07
Edema	15.1%	23.2%	NS
Joint stiffness	17.8%	23.2%	NS

Roeder F. *Cancers* **2020**, *12*(11), 3242

Davis AM RadiotherOncol. 2005;75:48-53.

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Einfluss des Resektionsmargins bei Extremitäten-Sarkomen

	Negative	Positive	p-value
Preop EBRT[1]	91%	62%	0.005
BRT[2]	86%	74%	0.04
Postop EBRT[3]	79%	57%	0.07

1:Tanabe; Cancer 1994, 2:Alektiar; ASO 2002, 3: Suit, JCO 1988.

Die Resektion eines Sarkoms kann erleichtert werden nach einer präoperativen Bestrahlung.

Das Sarkom kann schrumpfen
Die Pseudokapsel kann dicker und azellulär werden

Die preoperative Radiotherapie ist mit R0 Resektion und verbessertem Überleben assoziiert (NCDB Analyse)

Positive Margins sind ein negative prognostischer Faktor

Wenn eine R0-Resektion unwahrscheinlich scheint, ist eine preoperative Strahlentherapie indiziert, um die R0-Resektion zu erleichtern.

Gingrich et al. Ann Surg Oncol (2017) 24:3252–3263

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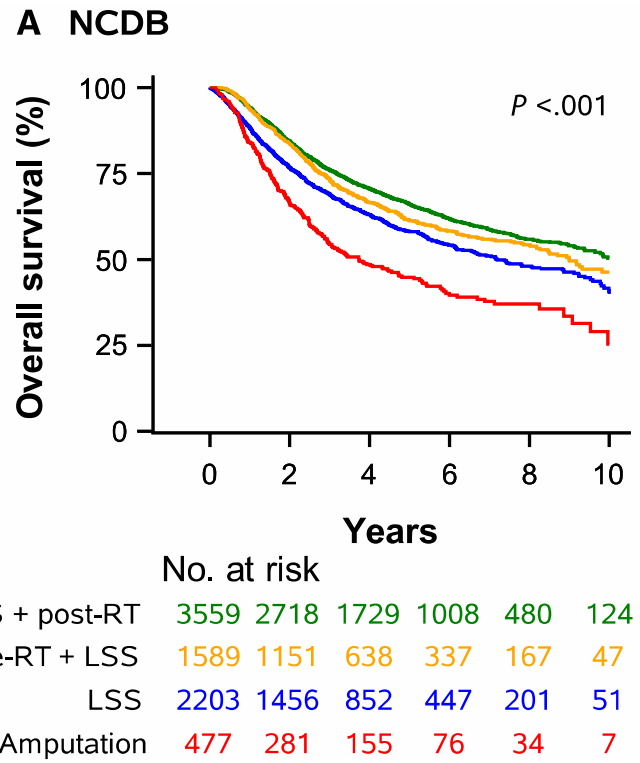
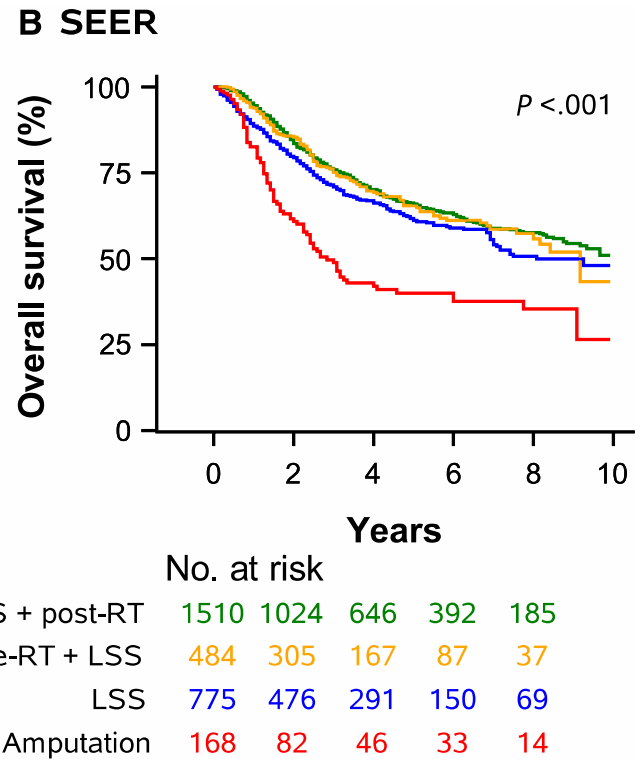
Überleben bei Extremitäten-Sarkomen

National Cancer Database (NCDB) und SEER:
High-grade, stage II-III E-STS

- Amputation
- Limb-sparing surgery
- Präoperative Radiotherapie
- Postoperative Radiotherapie





Präoperative und postoperative Radiotherapie verbesserten das OS und die Sarkom-Mortalität

Ramey et al. *Cancer Medicine.* 2018;7:4228–4239

Rezidiv-Lokalisation bei Extremitäten-Sarkomen

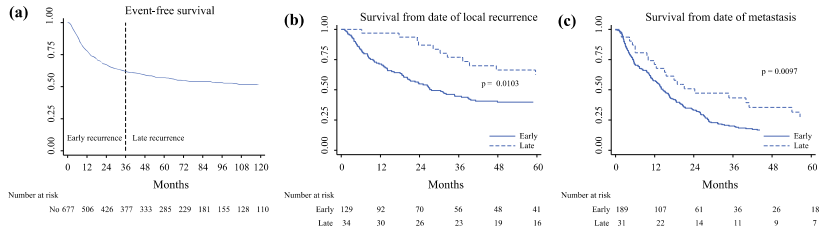


FIG. 1 **a** Event-free survival from date of diagnosis of soft tissue sarcoma. **b** Survival in months from date of local recurrence for early and late recurrence (log-rank test). **c** Survival in months from date of metastatic disease for early and late recurrence (log-rank test)

	< 3 Jahre	> 3 Jahre	Gesamt
	677	377	
Lokalrezidiv	60 / 250 (24%)	23 / 55 (42%)	83 / 305 (27%)
Metastasen	121 / 250 (48%)	21 / 55 (38%)	142 / 305 (47%)
Kombination	69 / 250 (28%)	11 / 55 (20%)	80 / 305 (26%)
total	250 / 677 (37%)	55 / 677 (8%)	305 / 677 (45%)
Tod ohne Sarkom	50		

65 – 84% der Lokalrezdive sind in-field Rezidive

Von Konow et al. Ann Surg Oncol (2021) 28:7891–7902

Roohani 2023 Advances in Radiation Oncology

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Radiotherapie und Resektabilität bei Extremitäten-Sarkomen

Table 2
Influence of preoperative radiotherapy on minimal distance to critical structures.

Low-grade tumors (G1) *n = 17*			
Minimal distance to [mm]:	Before radiotherapy	After radiotherapy	*P* =
Vessel	8.21 [0–51.30]	7.89 [0–32.70]	0.25
Nerve	2.25 [0–10.30]	4.19 [0–32.70]	0.74
Bone	3.81 [0–17.20]	5.97 [0–24.60]	0.32
Skin	9.63 [0–26]	10.30 [4.6–26.20]	0.81
High-grade tumors (G2/3) *n = 34*			
Minimal distance to [mm]:	Before radiotherapy	After radiotherapy	*P* =
Vessel	13.63 [0–85]	13.67 [0–77.10]	0.83
Nerve	6.20 [0–44.50]	7.51 [0–48.60]	0.11
Bone	4.27 [0–22]	3.15 [0–18.80]	**0.018**
Skin	12.11 [0–30.10]	9.2 [0–32.10]	**0.020**

Subgroup of tumors showing a volume decrease after preoperative radiotherapy *n = 19*			
Minimal distance to [mm]:	Before radiotherapy	After radiotherapy	*P* =
Vessel	4.64 [0–39.70]	7.52 [0–40.10]	0.26
Nerve	1.06 [0–10.30]	4.97 [0–32.70]	0.26
Bone	3.80 [0–18]	5.74 [0–24.60]	0.26
Skin	11.51 [0–30.10]	11.79 [4.7–26.2]	0.49
Subgroup of all myxoid liposarcomas tumors showing a volume decrease after preoperative radiotherapy *n = 12*			
Minimal distance to [mm]:	Before radiotherapy	After radiotherapy	*P* =
Vessel	1.09 [0–12.1]	5.23 [0–32.70]	**0.045**
Nerve	0.78 [0–5.4]	4.42 [0–32.70]	0.08
Bone	3.21 [0–17]	6.81 [0–24.60]	0.10
Skin	8.66 [0–20]	11.24 [4.7–26.2]	0.25

Table 3
Analysis of tumor volume.

	Low-grade STS (G1) (n = 17)	High-grade STS (G2/3) (n = 34)
Mean volume before radiotherapy [cm^3]	497.76 [25–1132]	382.03 [9–1801]
Mean Volume after radiotherapy [cm^3]	347.12 [7–1134]	530.71 [14–1581]
P =	**0.028**	**0.011**
Median difference of volume [cm^3]	−51	+40
Median difference of volume (%)	−23	+23

Die präoperative Strahlentherapie vergrössert den Abstand zu Gefässen bei myxoiden Liposarkomen.

Sarkome mit Volumenverminderung unter Bestrahlung haben ebenfalls grössere Abstände zu Nevern / Gefässen.

Der Strahlen-Effekt auf das Sarkom-Volumen variiert beträchtlich unter den Sarkomtypen, wobei die myxoiden Liposarkome immer kleiner wurden.

Kaiser et al. Surgical Oncology 39 (2021) 101668

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Strahlensensibilität von Weichteilsarkomen

Historisch

Radiosensitive

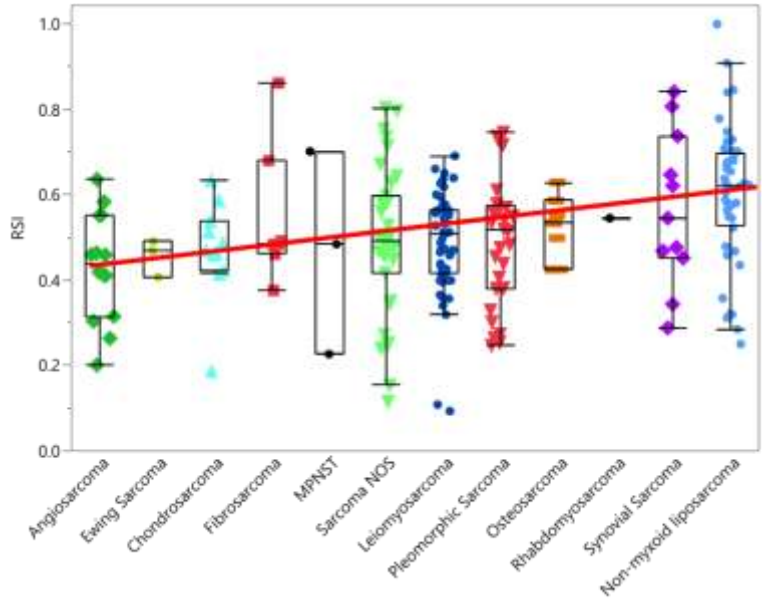
- Myxoid liposarcoma – dramatic response to RT
  - McGill 50 patients, evaluated response to RT
  - <1% for high grade sarcomas
  - 13.8% non-myxoid low grade sarcomas
  - 82.1% myxoid liposarcomas
- Ewing Sarcoma
- Rhabdomyosarcomas

- “RMS-like tumours” (Synovial Sarcoma, soft tissue Ewing tumours (including pPNET), and undifferentiated sarcoma) should principally be treated similar to RMS (CWS-guidance).

Radioresistant

- Leiomyosarcoma (50% PR; uterus LMS: no 5y survial) – consider surgery
- Fibrosarcoma (RT + razoxane)
- Synovial sarcoma (chemosensitive)
- Undifferentiated pleomorphic sarcoma
- Chondrosarcoma
- Osteosarcoma

Genomic Radiosensitivitäts-Index



Weichteilsarkome sind generell strahlenresistent,
Die Strahlensensibilität ist hetereogen

Sarkomzellen haben eine tiefe α-β ratio (−0.5–5.4)

Yang et al. Translational Oncology 14 (2021) 101165
Haas et al. Radiation Research 196, 23–30 (2021)

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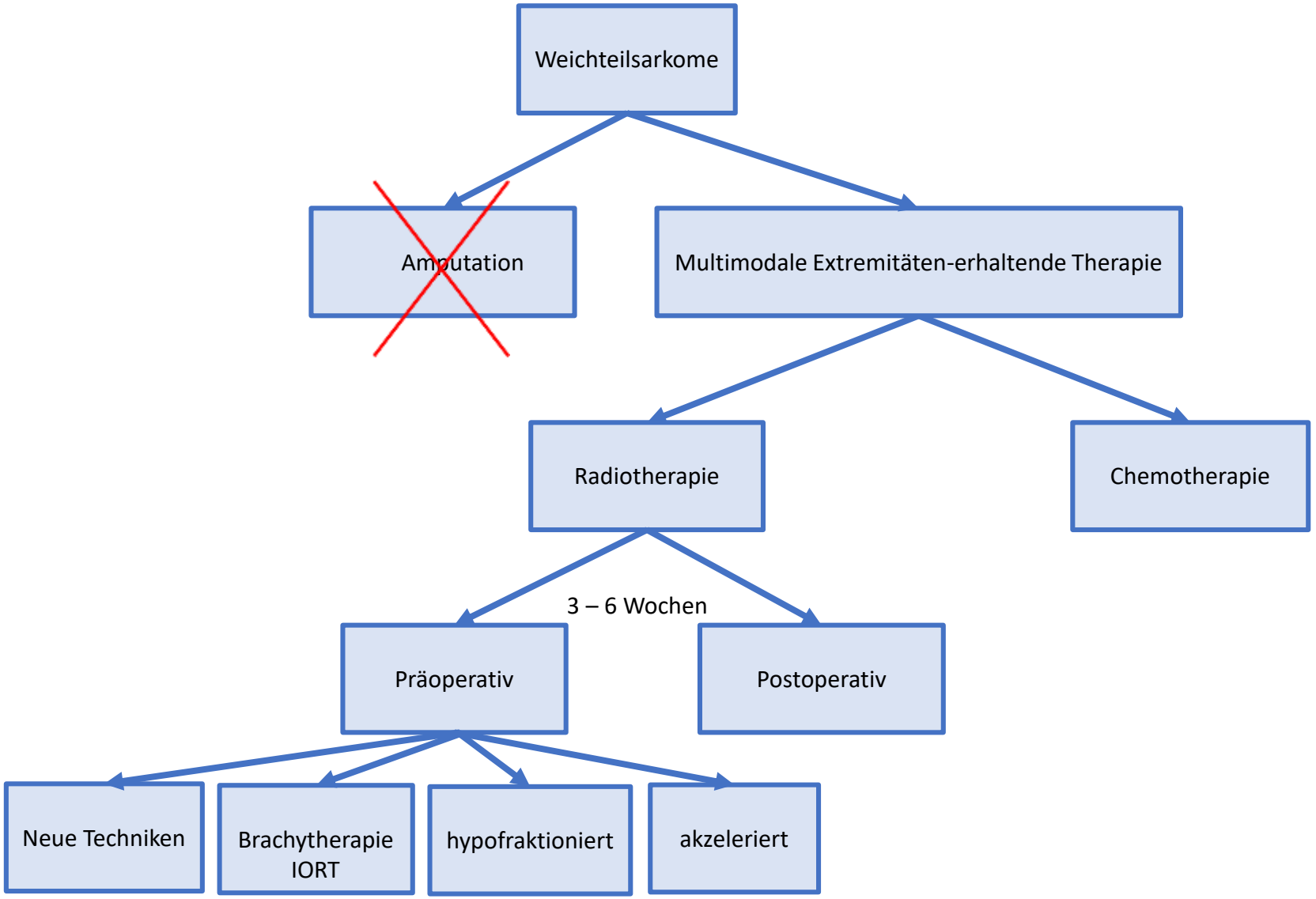

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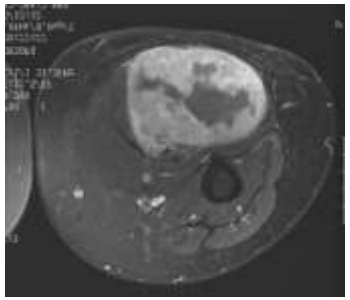
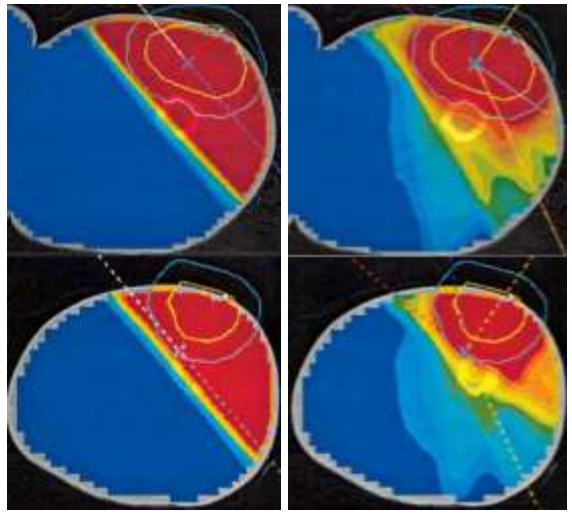
Moderne Strahlentherapie von Extremitäten-Sarkomen

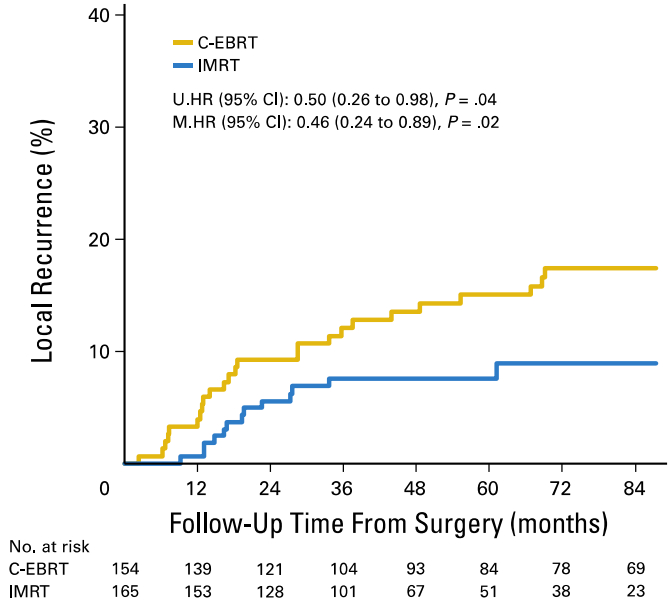
3D-CRT vs. IMRT / VMAT





Isodoses
Red 100%
Light blue 20-30%

Lokalkontrolle



Toxizität

Table 3. Grade ≥ 2 Toxicity Comparison Between Conventional RT and IMRT

	Overall		Conventional RT		IMRT		
Toxicity	No.	%	No.	%	No.	%	*P*
Wound complications							
Noninfected	28	8.8	14	9.1	14	8.5	1.0
Infected	30	9.4	13	8.4	17	10.3	.70
Radiation dermatitis	127	39.8	75	48.7	52	31.5	.002
Fracture	22	6.9	14	9.1	8	4.8	.18
Nerve damage*	7	2.6	2	1.6	5	3.5	.45
Joint stiffness	41	12.9	17	11	24	14.5	.40
Edema	36	11.3	23	14.9	13	7.9	.05

- IMRT ist mit weniger Lokalrezidiven assoziiert verglichen mit 3D-CRT für Weichteilsarkome der Extremitäten
- IMRT verringert die Toxizität (Oedem, Dermatitis, Fibrose, Frakturen, Gelenkssteifigkeit)

Hong et al. IJROBP 2004

Folkert et al. 2014. J Clin Oncol 32:3236-3241.

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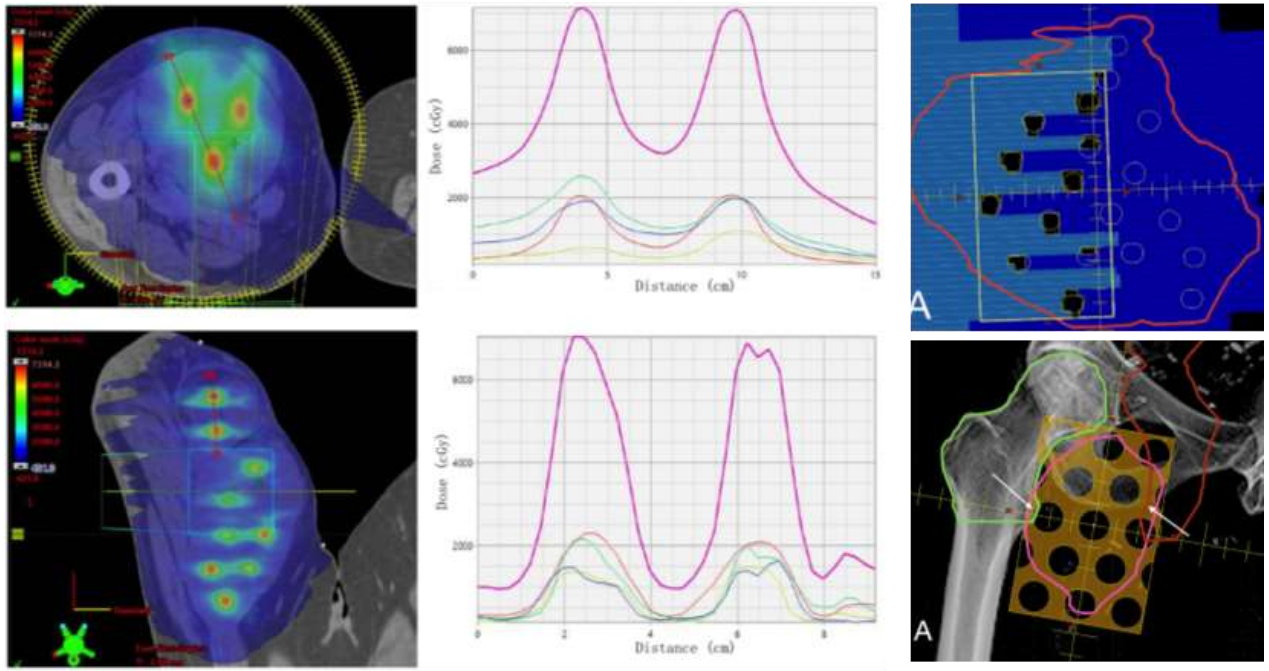
Experimentelle Bestrahlungs-Techniken von Extremitäten-Sarkomen

Simultan-Integrierter Boost (SIB)

Bryant et al. Advances in Radiation Oncology (2024) 9, 101447

Lattice Approach

Spatially fractionated radiation therapy (SFRT) Behandlung mit entweder brass grid oder volumetric modulated arc therapy (VMAT).



Grams et al. Physica Medica 111 (2023) 102616

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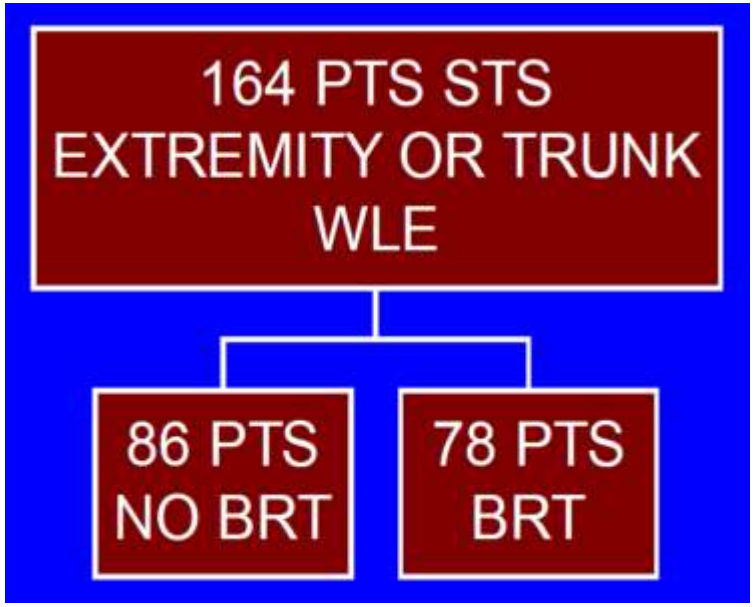
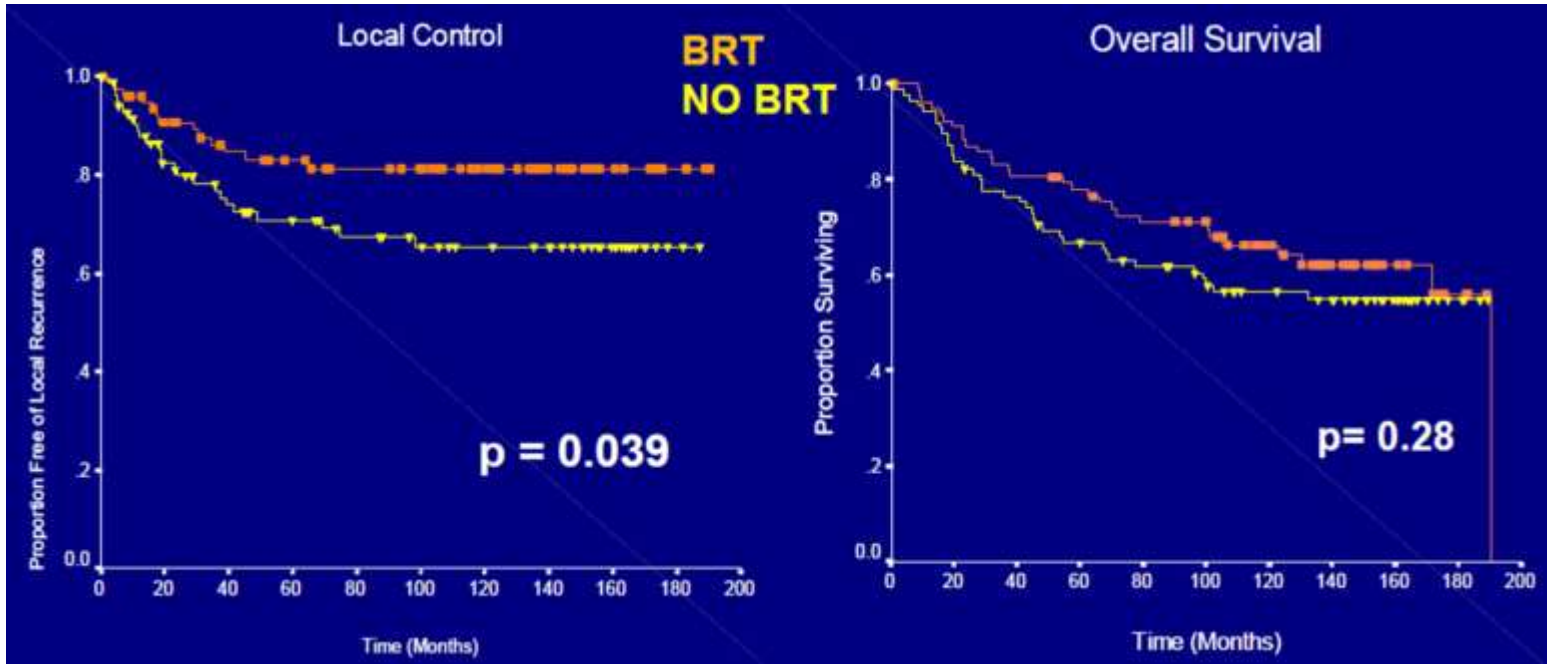
Brachytherapie bei high-grade Extremitäten-Sarkomen

MSKCC Brachytherapy Trial





Harrison, IJROBP 1993, Pisters et al JCO 1996

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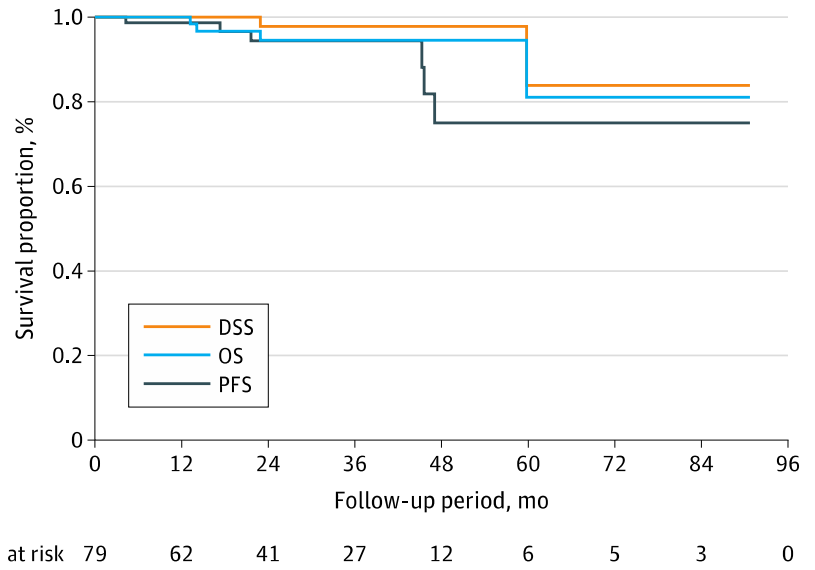
De-Escalation bei Myxoiden Liposarkomen

DOREMY Studie

- Prospective, single-group, Phase 2 non-randomized kontrollierte Studie
- 9 Zentren in Europa und den USA
- 36 Gy / 2-Gy tgl. gefolgt von Resektion 4 Wochen später



Characteristic	No. (%)			P value
	Total (n = 79)	Pathological treatment effect[a]		
		≥50% (n = 70)	<50% (n = 7)	
Surgical margins				.004
Negative	72 (94)	68 (97)	4 (57)	
Positive	5 (6)	2 (3)	3 (43)	

Table 3. Overview of the Most Relevant Studies on Morbidity and Local Control After Preoperative Radiotherapy in Soft-Tissue Sarcomas

Source	No. of patients	Design	Subgroup	Preoperative RT regimen	Rate, %				Follow-up, y
					Grade ≥2 toxic effect	R0	WC	LC	
DOREMY trial	77[a]	Prospective	All	18 × 2 Gy	14	94	17	100	2.1
O'Sullivan et al,[8] 2002; Davis et al,[9] 2005	88[a]	Prospective	Preoperative group, various histological subtypes	25 × 2 Gy	37	84	35	92[b]	3.3

- De-Escalation ist effektiv, onkologisch sicher und assoziiert mit weniger Morbidität verglichen mit historischen Kontrollen
- De-Escalation ist eine akzeptable Alternative bei Myxoiden Liposarkomen

Lansa et al. JAMA Oncol. 2021;7(1):e205865.

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Hypofraktionierte Bestrahlung bei Weichteilsarkomen

Study (year)	N	Design	Dose	Fractions	Post-op boost (% patients)	$EqD2_4$	Chemotherapy	Overall survival	Local control	Necrosis >90%	Necrosis >95%	Necrosis 100%	Necrosis Median	R1	Time to surgery	1° limb-sparing
O'Sullivan et al[3] (2002) *Pre-Op	88	Phase III RCT MC	50 Gy	25	16-20G/8-10 (11.3%)	50 Gy	None	~90% @ 3 y	~96%@2 y	-	-	-	-	16%	3-6 wk	98%
Ryan et al[23] (2008)	25	Phase II MC	28 Gy	8	12Gy/6 (12%)	35 Gy	Concomitant (EI)	84%@2 y	88%@2 y	-	40%	4%	80% (10%-100%)	12%	3 wk	91%
Meyer et al[24] (2013)	16	Phase I SC	28 Gy	8	12Gy/6 (6.25%)	35 Gy	Concomitant (EI + sorafenib)	100%	100%	-	44%	-	10%-100%	6.25%	NR	100%
Koseła-Paterczyk et al[18] (2014)	272	Phase II SC	25 Gy	5	30Gy/15 (7.7%)	37.5 Gy	Optional Pre-Op (22.4%)	72% @3 y 60% @5 y	81%@3 y	-	-	-	-	21.3%	3-7 d	100%
Kubicek et al[25] (2018)	15	Prospective + phase II (N = 8) SC	35-40 Gy	5 Alt days	-	64-80 Gy	Optional Pre-Op (21.4%)	100%@1 y	100% @1 y 1 failure @15 mo	-	-	-	-	-	5 wk (4-12)	100%
Lu et al[26] (2018)	76	Phase II (N =25) + petrospective SC	28 Gy	8	12Gy/6 (11%)	35 Gy	Concomitant (EI)	70.4%@5 y	87.2%@5 y	38%	32%	-	-	11%	2-3 wk	93%
Koseła-Paterczyk et al[27] (2020)	29	Phase II SC	25 Gy	5	-	37.5 Gy	None	~87.5%@2 y	100%	33.3%†	3.7%†	3.70%	-	7.4%	7 wk (5-10)	100%
Kalbasi et al[28] (2020)	53	Phase II SC	30 Gy	5	-	50 Gy	Optional adjuvant (12%)	92%@2 y	94%@2 y	-	-	4%	44.2%* (0%-100%)	18%	4 wk (2-8)	100%
Gobo Silva et al[29] (2021)	18	Phase II SC	25 Gy	5	16Gy/8 (11%)	37.5 Gy	Concomitant (AI)	92%@2 y	91%@2 y	33%†	33%†	33%	70%	17%	6 wk (2.4-15.7)	94%
Koseła-Paterczyk et al[17] (2021)	311	Phase II SC	25 Gy	5	30Gy/10 (5.8%)	37.5 Gy	Optional Pre-Op (AI/AD) (30%)	63%@5 y	81%@5 y	-	-	-	-	16.4%	2-4 d	100%
Leite et al[30] (2021)	25	Phase II SC	40 Gy	5 Alt days	-	80 Gy	Optional Pre-OPp (AI) (20%)	~85%@2 y	100%@2 y	32%	20%	8%	65% (0-100)	4%	8.5 wk (4-13)	100%
Novikov et al[31] (2021)	14	Prospective observation SC	35 Gy	5	All Patients 50Gy/25	64 Gy	None	-	100% ~1 y	0%	0%	0%	50% (0%-80%)	0%	3 wk (1-4.5)	100%
Spałek et al[32] (2021)	46	Phase II SC	25 Gy	5	30-40Gy/15-20 (6.52%)	37.5 Gy	Concomitant (AI)	67%@2 y 53%@3 y	67%@2 y	34.2%†	24.4%†	9.8%	80%†	19.5%	6-8 wk	93%
Bedi et al[33] (2022)	32	Phase II SC	35 Gy	5 Alt days	-	64.17 Gy	Optional Pre-Op (AI) (31.5%)	94.4%@3 y	100%@3 y	12.7%	-	-	37.5%	9%	6 wk (3-7.5)	97%
Guadagnolo et al[34] (2022)	120	Phase II SC	42.75 Gy	15	-	48.81 Gy	Optional Pre-Op (30%)	~90%@2 y	93% @30 mo	-	-	-	-	10%	5.7 wk (4.6-6.4)	100%

Joyce et al. Int J Radiation Oncol Biol Phys, pp. 1–15, 2024

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Hypofraktionierte Bestrahlung bei Weichteilsarkomen

Study (year)	N	WC major
O'Sullivan et al[3] (2002) *Pre-Op	88	35%
Wang et al[22] (2015)	71	36.6%
Ryan et al[23] (2008)	25	20%*
Meyer et al[24] (2013)	16	38%*
Koseła-Paterczyk et al[18] (2014)	272	32.4%*
Kubicek et al[25] (2018)	13	28.5%
Lu et al[26] (2018)	76	32%*
Koseła-Paterczyk et al[27] (2020)	29	27.5%
Kalbasi et al[28] (2020)	53	32%
Gobo Silva et al[29] (2021)	18	33%
Koseła-Paterczyk et al[17] (2021)	311	24%*
Leite et al[30] (2021)	25	28%*
Novikov et al[31] (2021)	14	14%
Spałek et al[32] (2021)	46	34%
Bedi et al[33] (2022)	32	25%
Guadagnolo et al[34] (2022)	120	31%

Study (year)	N	Fibrosis	Joint stiffness	Edema	Bone
O'Sullivan et al[3] (2002) *Pre-OP	88	≥G2: 31.5%	≥G2: 17.8%	≥G2: 15.1%	-
Wang et al[22] (2015)*	79	≥G2 5.3%	≥G2: 3.5%	≥G2:5.3 %	-
Koseła-Paterczyk et al[18] (2014)	272	G1/2: 3.7% G3: 1 Patient	-	9.2% (<G3)	2.6% N = 7 fracture
Dincbas et al[35,†] (2014)	60	≥G2: 31.7%	≥G2: 13%		N = 2 osteonecrosis
Koseła-Paterczyk et al[27] (2020)	29	G1/2: 6.8%	-	G1/2: 6.8%	-
Kalbasi et al[28] (2020)	53	G1: 24% G2: 11%	G1: 11% G2: 11%	G1: 4% G2: 4%	-
Gobo Silva et al[29] (2021)	18	G1:50% G2: 6%	G1: 16% G2: 6% G3: 6% G4: 6%	G1: 11% G2: 11%	6% N = 1 fracture
Koseła-Paterczyk et al[17] (2021)	311	<1%	-	2.5%	1% N = 3 fracture
Leite et al[30] (2021)	25	G1: 34.7% G2: 4.3%	13%	G1: 21.7% G2: 4.3%	4.3% N = 1 fracture
Bedi et al[33] (2022)	32	G1: 34.7% G2: 21.7% G3: 13%	-	-	3% N = 1 fracture
Guadagnolo et al[34] (2022)	120	G1: 24% G2: 3%	G1: 21% G2: 0%	G1:12% G2: 2% G3: 1%	1.7% N = 2 fracture
Mayo et al[36,†] (2023)	22	≥G2: 18%	≥G2: 5%	≥G2: 5%	5% N = 1 fracture

- Evidenz unterstützt die Hypofraktionierung als sicher und effektiv in der neoadjuvanten Therapie on STS.
- Laufende Studien: 25 x 2 Gy = 50 Gy vs. 15 x 2.85 Gy = 42.75 Gy (EQD2 48.8 Gy), 14 x 3 Gy = 42 Gy EQD2 49 Gy), 5 x 5.5 Gy = 27.5 Gy (EQD2 43.5 Gy)

Joyce et al. Int J Radiation Oncol Biol Phys, pp. 1–15, 2024

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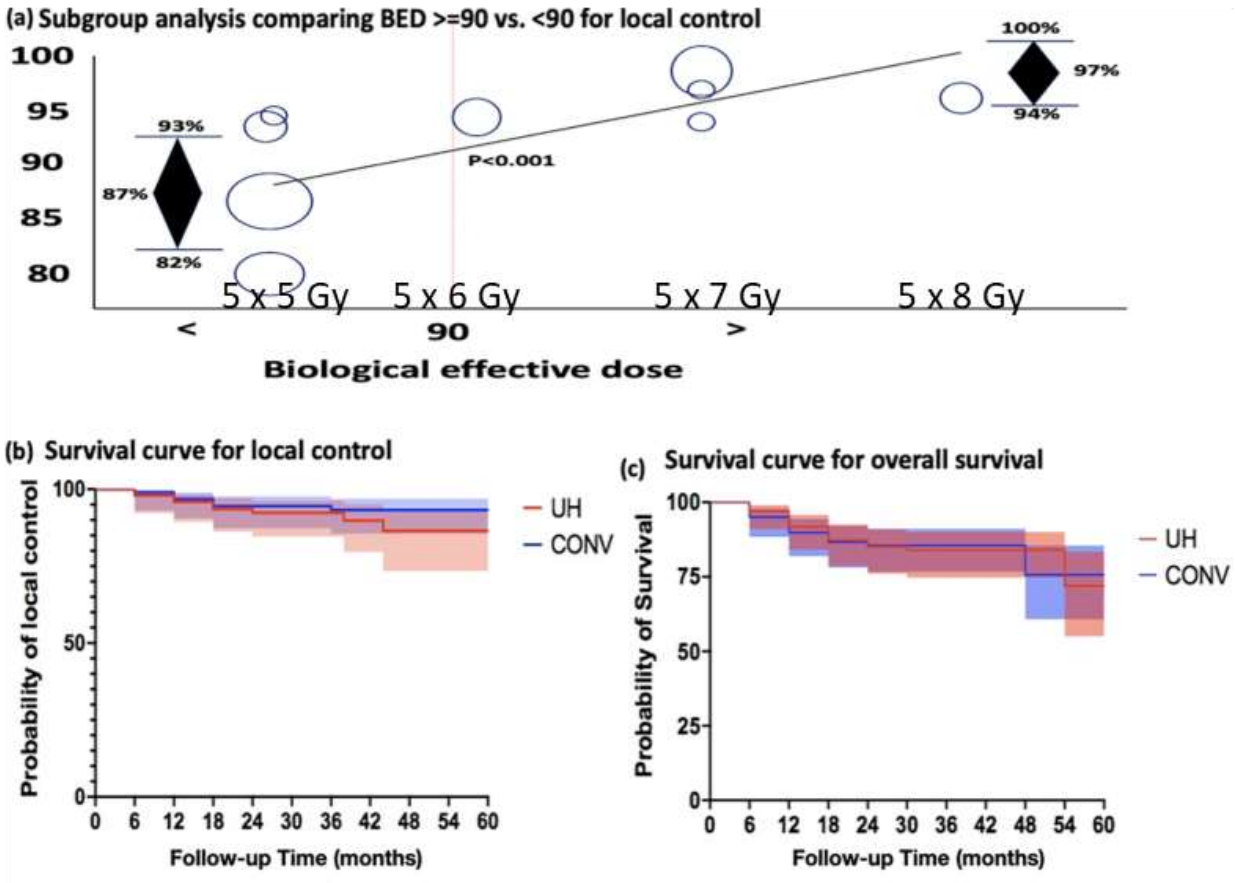
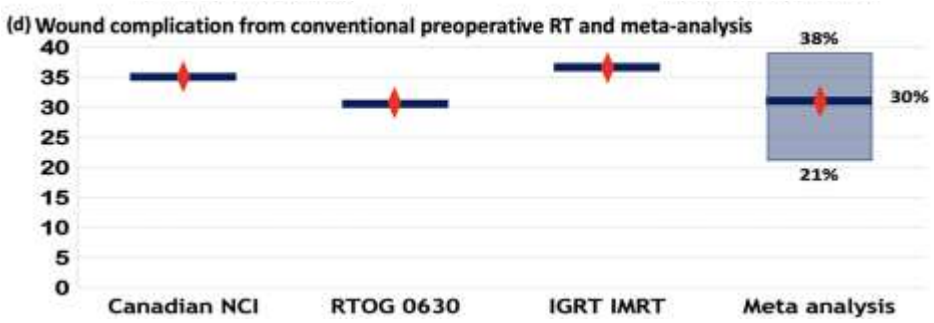
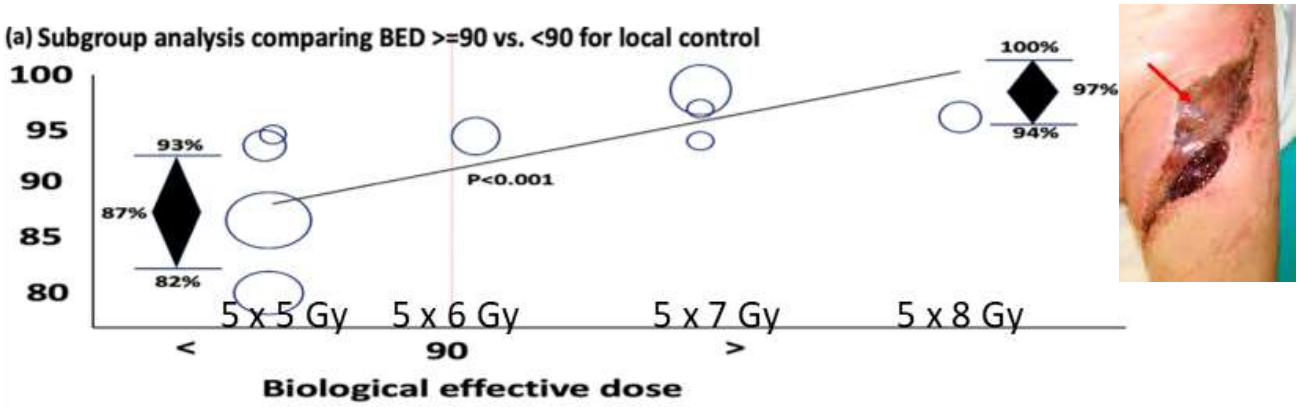
Hypofraktionierte Bestrahlung Meta-Analyse
Ist 5 die Neue 25?

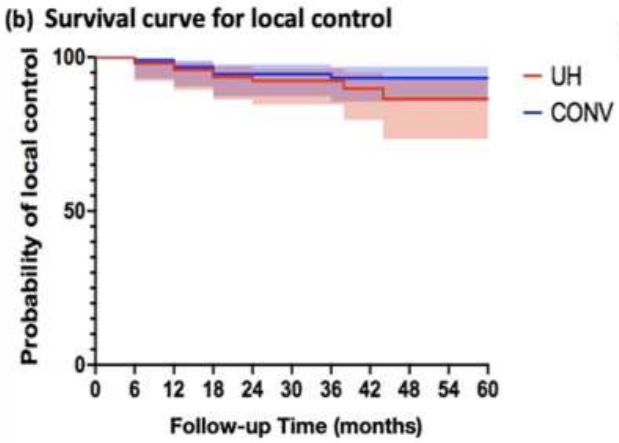


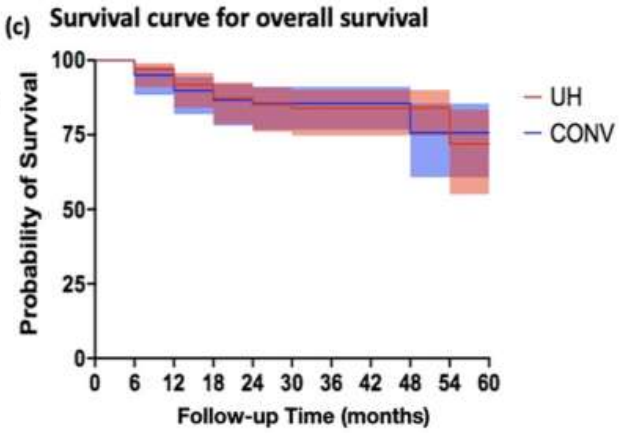


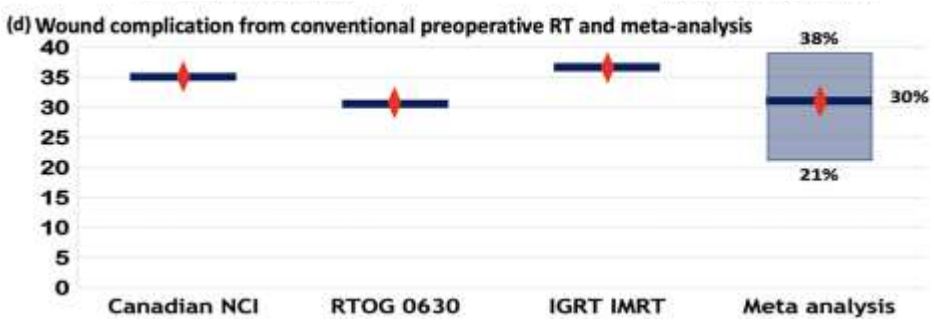
Cury et al. Radiotherapy and Oncology 190 (2024) 109935

Hypofraktionierte Bestrahlung Meta-Analyse
Ist 5 die Neue 25?



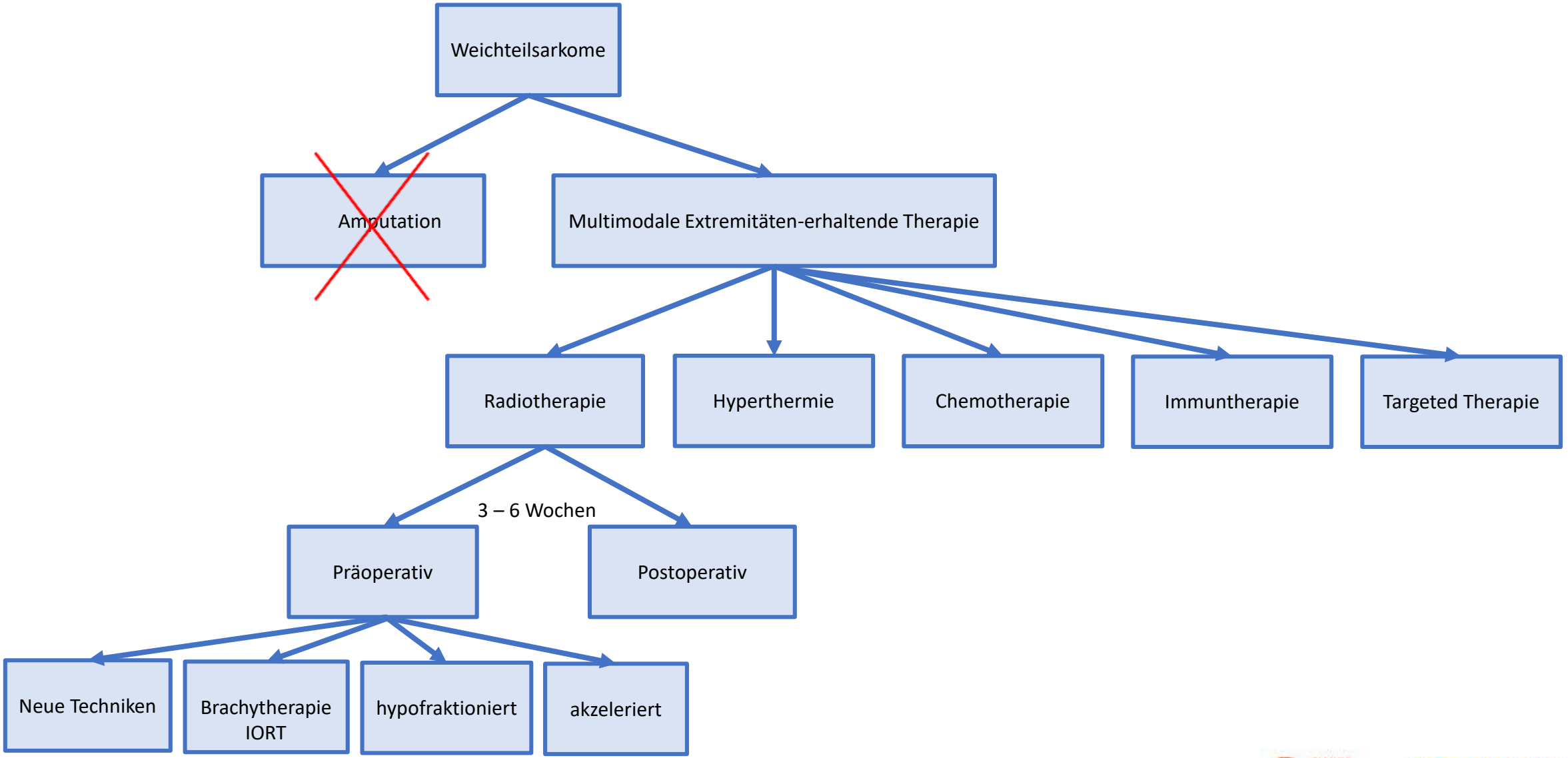






Cury et al. Radiotherapy and Oncology 190 (2024) 109935

Evolution des Management von Extremitäten-Sarkomen



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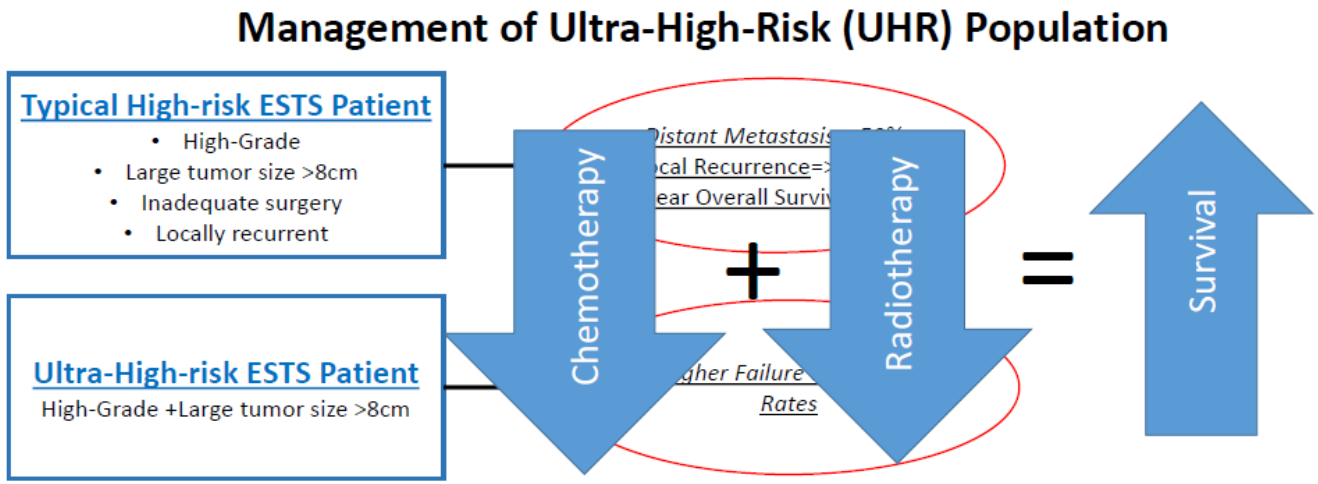
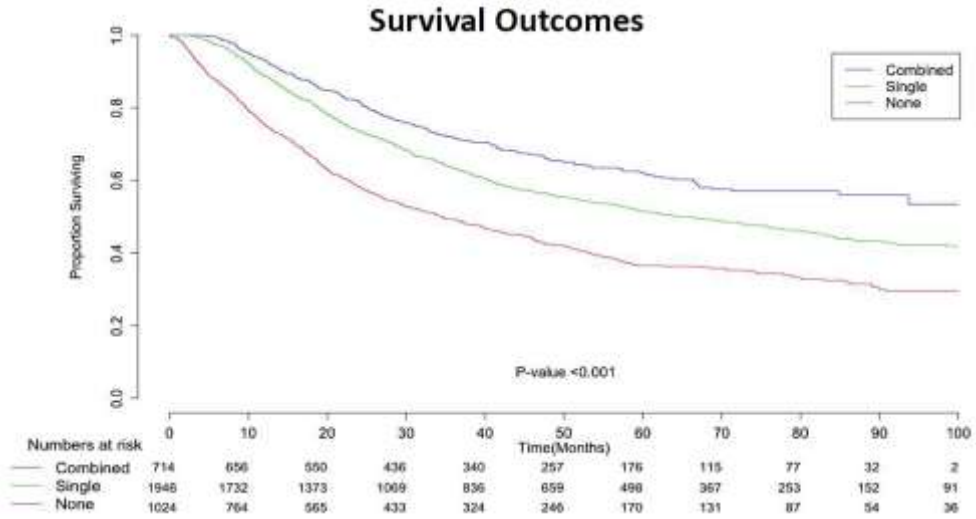
Bestrahlung mit Chemotherapie bei high-risk Weichteilsarkomen





National Database Study ASTRO 2016

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Bestrahlung mit Chemotherapie bei high-risk Weichteilsarkomen

Table 3. Novel neoadjuvant radiochemotherapy regimens in soft tissue sarcomas.

Authors and Type of Study	N	Radiotherapy Regimen	Chemotherapy Regimen	Hematology Toxicity	Local Control @Years	Overall Survival @Years
Temple et al. 1997 prospective cohort [73]	42	10 × 3 Gy	Concurrent ADM	not reported	97% @5y	65% @5y
Edmonson et al. 2002 phase II clinical trial [74]	39	25 × 1.8 Gy	Concurrent IMAP	G3+ 77%	92% @5y	80% @5y
DeLaney et al. 2003 phase II clinical trial [75]	48	22 × 2 Gy	Interdigitated MAID	febrile neutropenia 25%	92% @5y	84% @5y
Kraybill et al. 2006 phase II clinical trial [76]	64	22 × 2 Gy	Interdigitated MAID	G4 83%	90% @3y	75% @3y
Ryan et al. 2008 phase II clinical trial [77]	25	8 × 3.5 Gy	Concurrent EPI+IFO	G4 84%	88% @2y	84% @2y
MacDermed et al. 2010 retrospective cohort [78]	34	8 × 3.5 Gy	Concurrent IFO	G4 53%	89% @5y	45% @5y
Hong et al. 2013 retrospective cohort [79]	66	22 × 2 Gy	Interdigitated MAID	febrile neutropenia 10%	91% @5y	86% @5y
Spalek et al. 2019 phase II clinical trial [57]	30	5 × 5 Gy	Interdigitated AI	G3+ [1] @26%	97% @1y	67% @2y. 53% @3y

[1] Only grade 3 or higher toxicities that caused chemotherapy dose reduction or withdrawal; abbreviations: ADM—doxorubicin; AI—doxorubicin, ifosfamide; EPI—epirubicin; FN—febrile neutropenia; G—grade; IFO—ifosfamide; IMAP—ifosfamide, mitomycin, doxorubicin, cisplatin; MAID—mesna, doxorubicin, ifosfamide, dacarbazine; N—number of patients.

RTOG 9514

Spalek et al. Cancers 2020, 12, 2061

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Bestrahlung mit interdigitierter Chemo (AI) bei high-risk Weichteilsarkomen

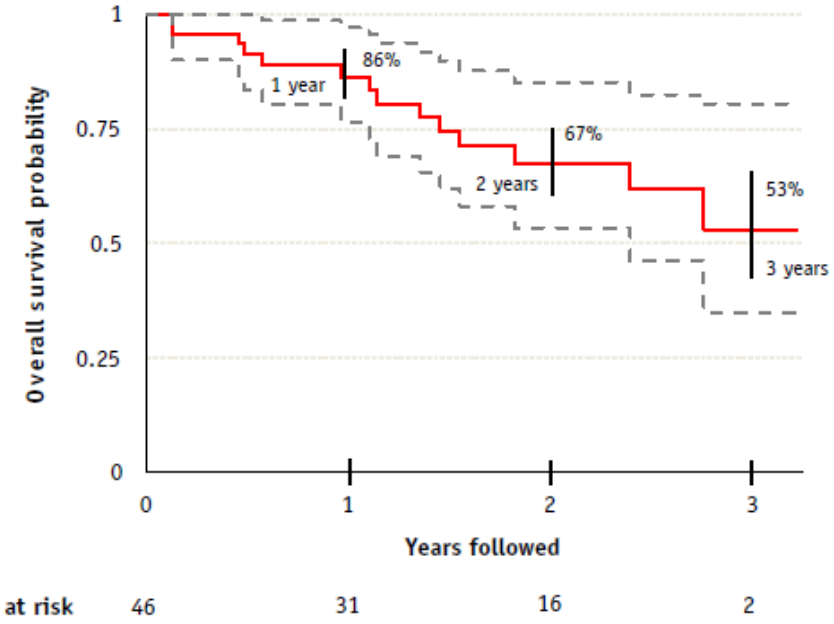
Phase 2 Studie

46 Patienten

Tumor pathology, n (%)	
Undifferentiated pleomorphic sarcoma	22 (48)
Myxofibrosarcoma	9 (20)
Myxoid liposarcoma	3 (7)
Dedifferentiated liposarcoma	2 (4)
Malignant peripheral nerve sheath tumor	2 (4)
Leiomyosarcoma	2 (4)
Undifferentiated round cell sarcoma	2 (4)
Undifferentiated epithelioid sarcoma	1 (2)
Synovial sarcoma	1 (2)
Malignant tenosynovial giant cell tumor	1 (2)
Pleomorphic liposarcoma	1 (2)

Table 2 Characteristics of the patients who underwent en bloc resection stratified by the achieved resection margin

Characteristics	R0	Non-R0	*P* value
No. of patients	33	8	
Grade, n (%)			
2	15 (46)	1 (13)	.19
3	18 (54)	7 (87)	
Tumor site, n (%)			
Trunk wall	8 (24)	2 (25)	.97
Arm/shoulder	2 (6)	0	
Forearm	3 (9)	1 (13)	
Thigh/buttock	16 (49)	4 (50)	
Calf	4 (12)	1 (13)	
Median largest tumor dimension (IQR), cm	17.5 (12.2-20.0)	14.5 (10.3-17.5)	.374
Median GTV (IQR), cm^3	814.1 (371.2-2330.4)	677.1 (156.3-1616.6)	.43
Median CTV (IQR), cm^3	2850.5 (1511.4-5604.8)	2281.9 (1058.4-3774.4)	.34
Near pCR, n (%)*			
Yes	9 (27)	1 (13)	.679
No	24 (73)	7 (87)	
Pathologic response grade, n (%)			
A	4 (12)	0	.606
B	5 (15)	1 (13)	
C	4 (12)	0 (0)	
D	15 (46)	5 (63)	
E	5 (15)	2 (25)	



Preoperative Chemotherapie mit AI kombiniert mit hypofraktionierter Strahlentherapie 5 x 5 Gy ist eine vielversprechende Methode für das Management von marginal-resektablen Weichteilsarkomen.

Ein solches Protokoll führt zu einer hohen Rate an R0-Extremitätenerhaltenden / konservativen Operation.

Spalek et al. Int J Radiation Oncol Biol Phys, Vol. 110, No. 4, pp. 1053e1063, 2021

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Akzelerierte Bestrahlung mit interdigitierter Chemo bei Weichteilsarkomen

Scandinavian Sarcoma Group study

20 Patienten mit high-grade, locally advanced and deep STS

Tumour size (cm)	
Median	13
Range	7–17
Histopathological subtype	
Undifferentiated pleomorphic sarcoma	10
Pleomorphic liposarcoma	1
Leiomyosarcoma	1
Synovial sarcoma	6
Malignant peripheral nerve sheath tumor	1
Myxofibrosarcoma	1

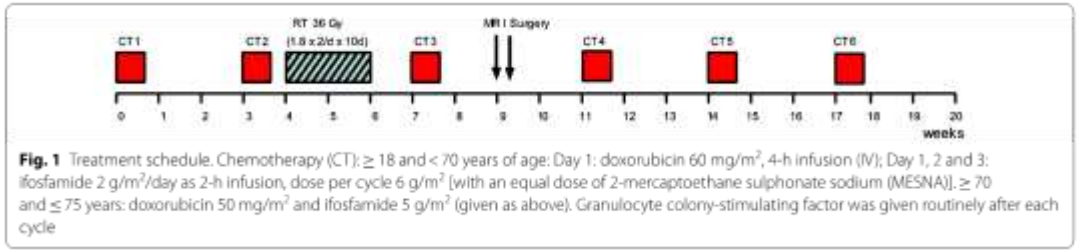
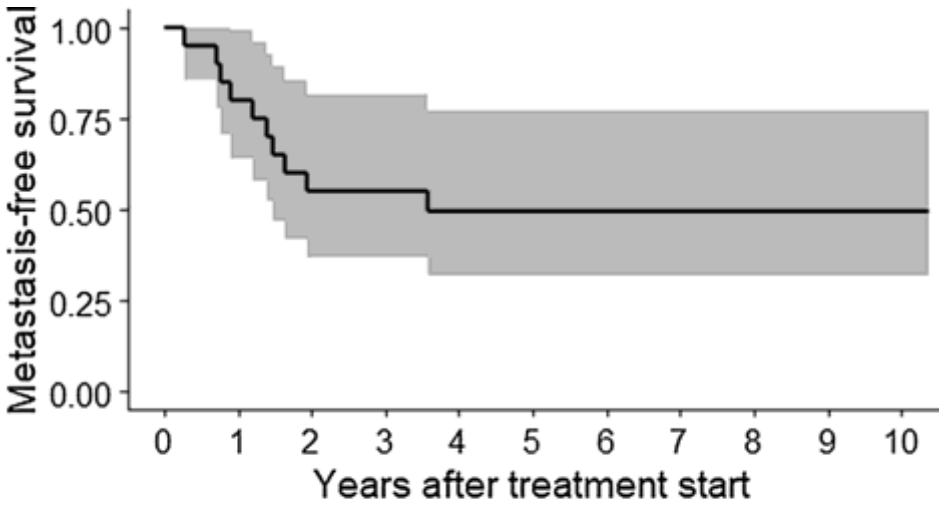
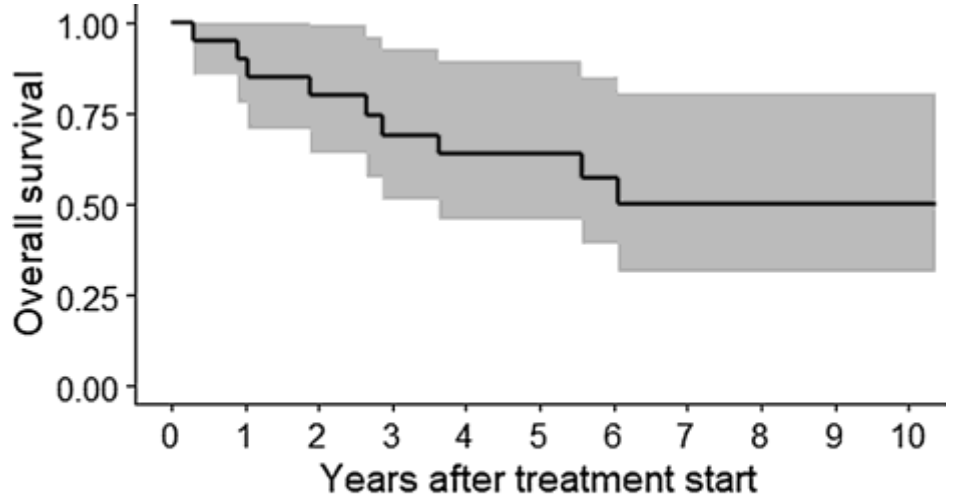


Fig. 1 Treatment schedule. Chemotherapy (CT): ≥ 18 and < 70 years of age: Day 1: doxorubicin 60 mg/m², 4-h infusion (IV); Day 1, 2 and 3: ifosfamide 2 g/m²/day as 2-h infusion, dose per cycle 6 g/m² (with an equal dose of 2-mercaptoethane sulphonate sodium (MESNA)). ≥ 70 and ≤ 75 years: doxorubicin 50 mg/m² and ifosfamide 5 g/m² (given as above). Granulocyte colony-stimulating factor was given routinely after each cycle

- 0 Patienten hatten präoperativ eine Progression
- 3 Patienten mit Lokalrezidiv, wobei 2 bereits Lungenmetastasen hatten
- 11 Patienten (55%) hatten Wundheilungsstörung (temporary in 8 and persistent in 3).





Hall et al. Clin Sarcoma Res (2020) 10:22

Bestrahlung mit Chemotherapie (Trabectidin) bei Weichteilsarkomen

Phase II Studie

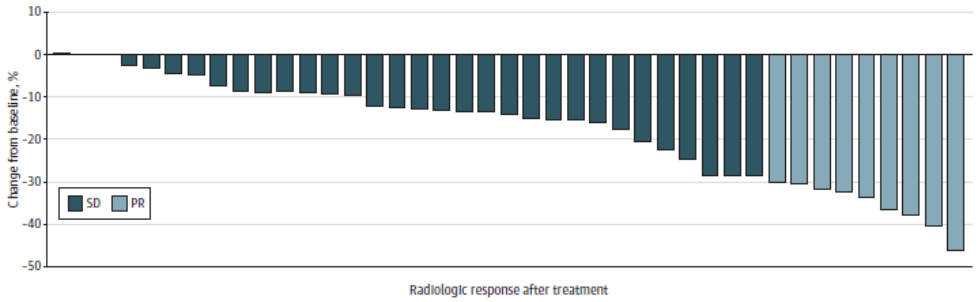
46 Patienten

Myxoide Liposarkome

45 Gy / 1.8 Gy
Trabectidin 1.5 mg/m^2

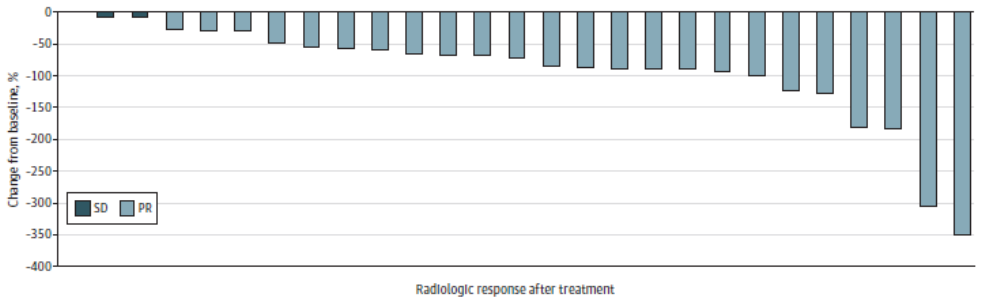
Trabectedin hemmt TC-NER, welches DNA-Schäden erkennt und Repaeraturprozesse in Gang setzt

Figure 1. Waterfall Plot of Radiologic Response After Treatment by Response Evaluation Criteria in Solid Tumors (RECIST Central Assessment)



PR indicates partial response; SD, stable disease.

Figure 2. Waterfall Plot of Radiologic Response After Treatment by Choi Criteria



PR indicates partial response; SD, stable disease.

- Die Kombination von Bestrahlung mit Trabectidin wurde gut toleriert und war effektiv
- Die pathologische Response war aber unter < 70% nach RECIST

Sanfilippo et al. JAMA Oncol. 2023;9(5):656-663

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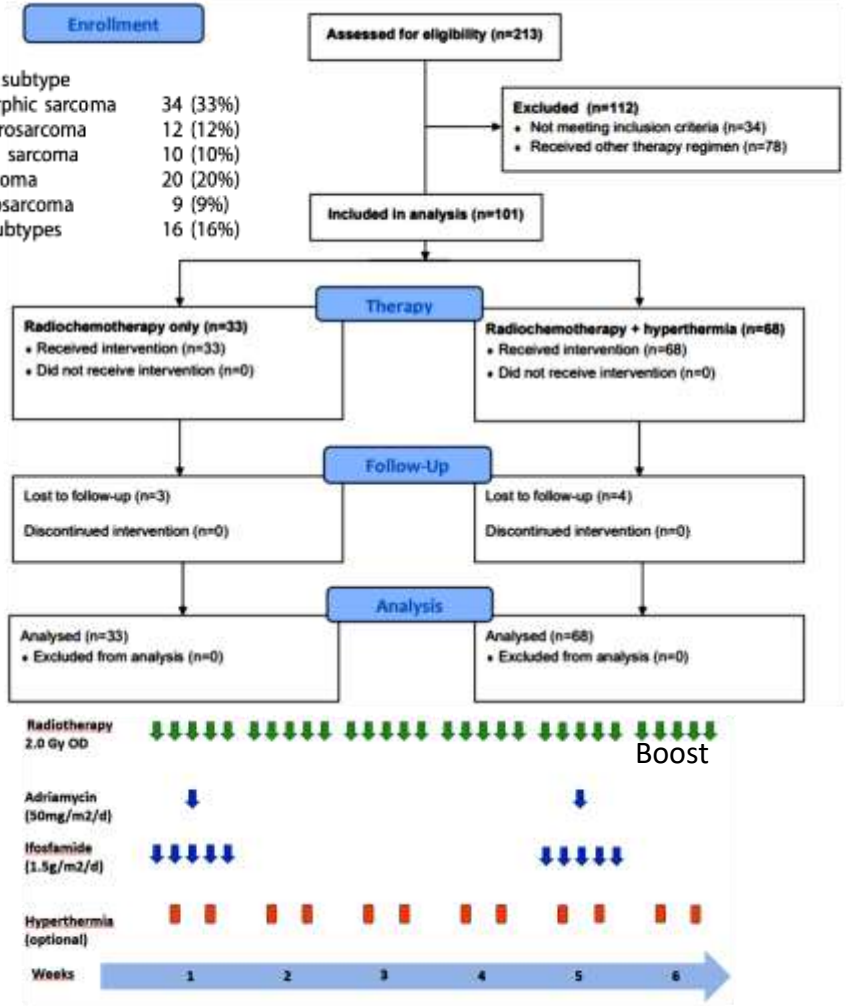
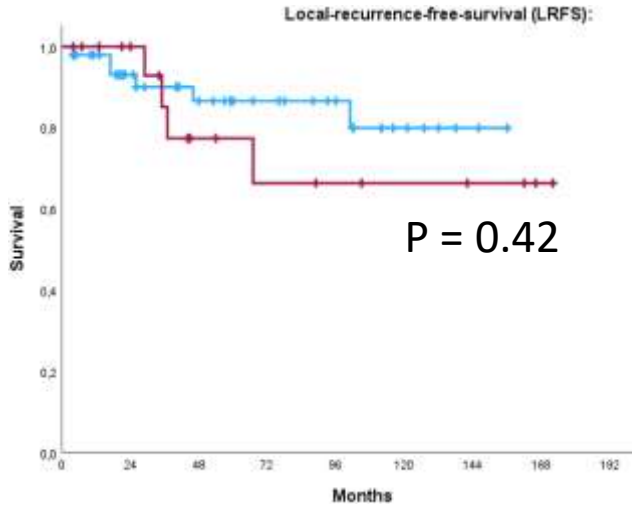
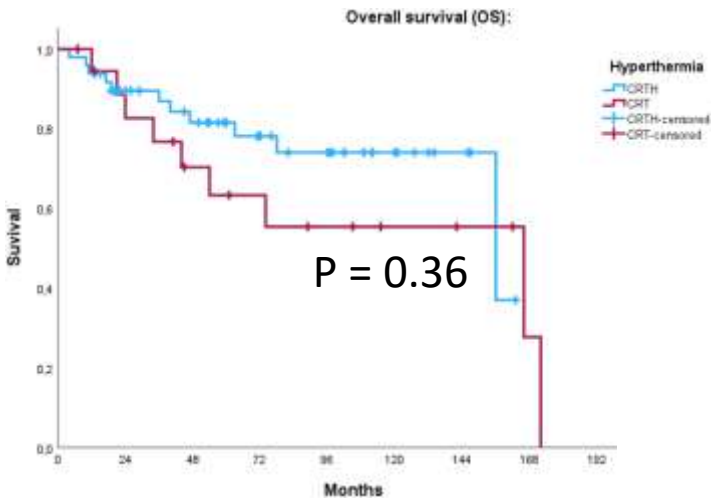
Radiochemotherapie / Hyperthermie bei Weichteilsarkomen

Histological subtype

Pleomorphic sarcoma	34 (33%)
Myxofibrosarcoma	12 (12%)
Synovial sarcoma	10 (10%)
Liposarcoma	20 (20%)
Leiomyosarcoma	9 (9%)
Other subtypes	16 (16%)







Postoperative complications	
Wound complications	22 (22%)
Infection	7 (7%)
Seroma	8 (8%)
Persistent pain	5 (5%)

Both CRT and CRTH are well tolerated with an expected rate of wound complications. The results suggest that adding hyperthermia may improve tumor response.

Willner et al. Int Journal of Hyperthermia, 2023, Vol. 40, No. 1, 2248424

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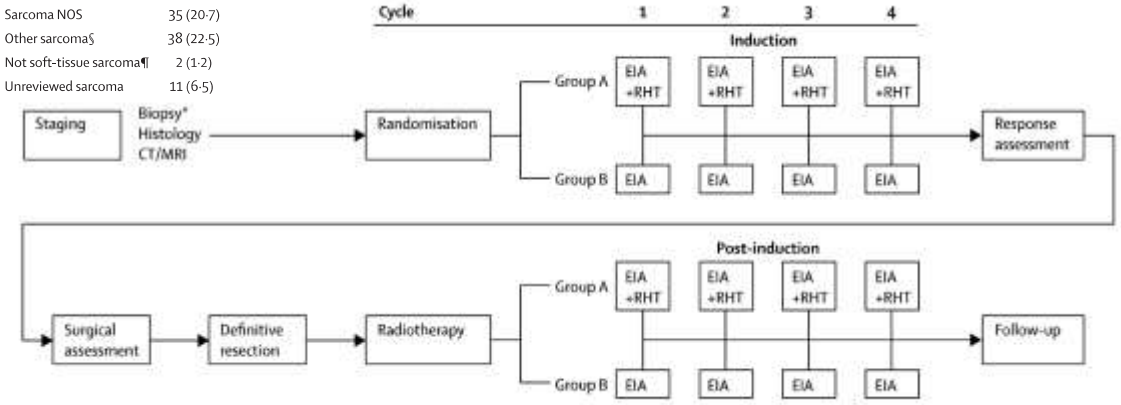
Chemo / Hyperthermie und Radiotherapie bei Weichteilsarkomen

EORTC-STBSG Phase III Studie
341 Patienten

Liposarcoma‡	31 (18·3)
Leiomyosacoma	27 (16·0)
Synovial sarcoma	25 (14·8)
Sarcoma NOS	35 (20·7)
Other sarcoma§	38 (22·5)
Not soft-tissue sarcoma¶	2 (1·2)
Unreviewed sarcoma	11 (6·5)



Response to induction therapy†		
No measurable disease	51 (30·2)	46 (26·7)
Measurable disease	118 (69·8)	126 (73·3)
Complete response (n [%])	3 (2·5)	1 (0·8)
Partial response (n [%])	31 (26·3)	15 (11·9)
Stable disease (n [%])	66 (55·9)	73 (57·9)
Progressive disease (n [%])	8 (6·8)	26 (20·6)
Could not be evaluated (n [%])	10 (8·5)	11 (8·7)
Overall response (%)	34 (28·8)	16 (12·7)

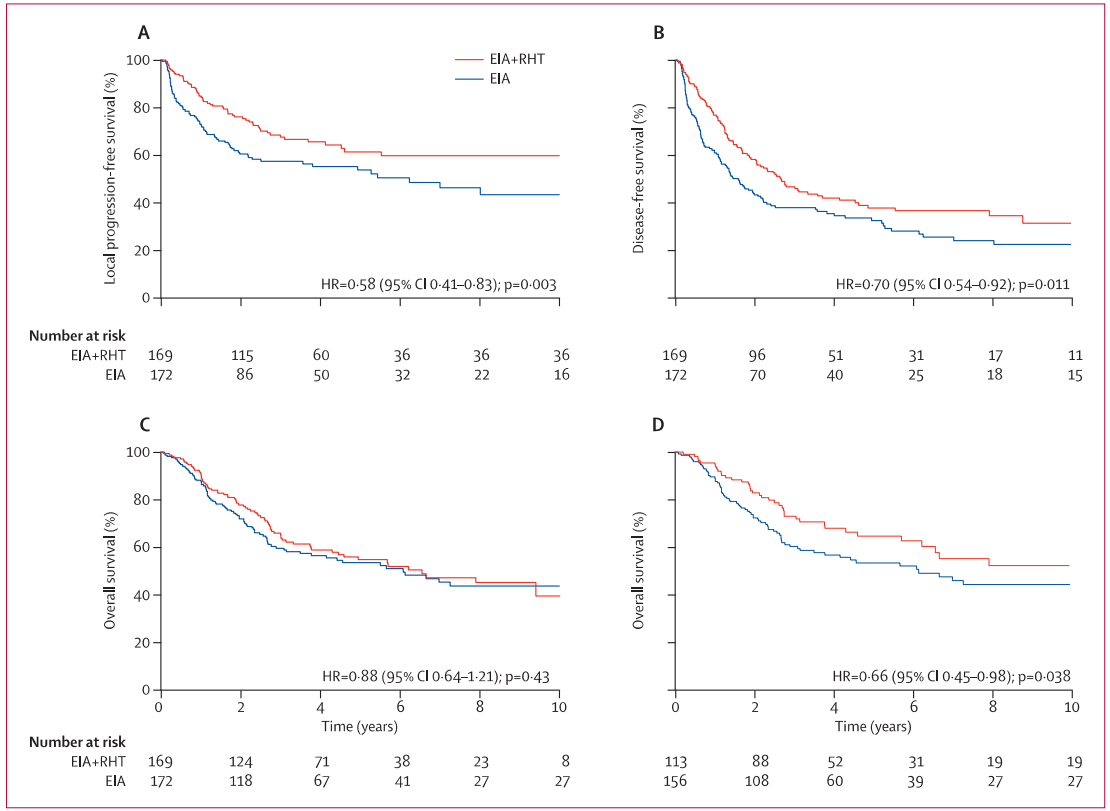


Figure 3: **Kaplan-Meier estimates of local progression-free survival (A), disease-free survival (B), and overall survival in all patients randomly allocated treatment (C), and overall survival in the per-protocol-induction population (D)**
EIA=etoposide+ifosfamide+doxorubicin. RHT=regional hyperthermia.

Issels et al. Lancet Oncol 2010; 11: 561–70

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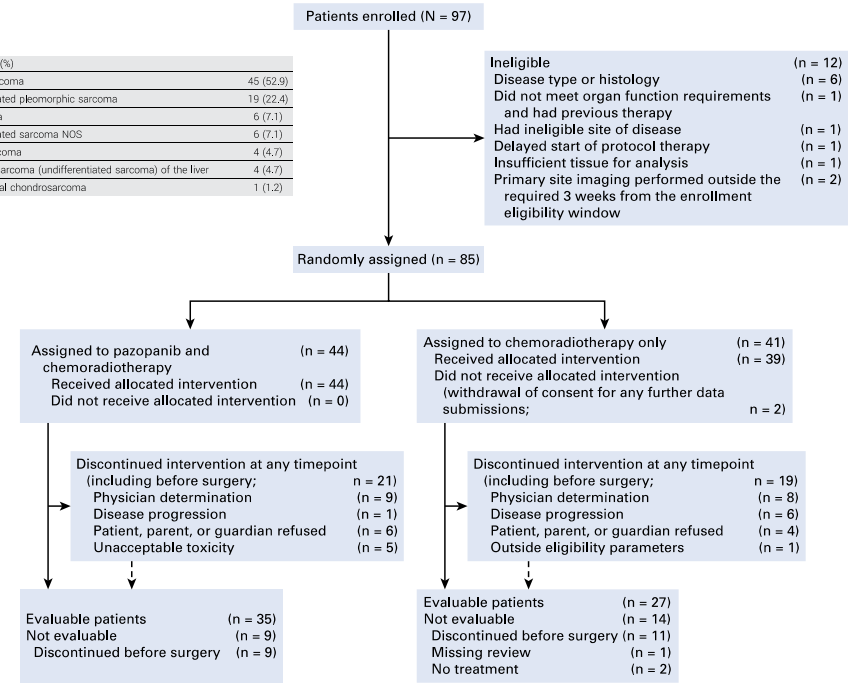
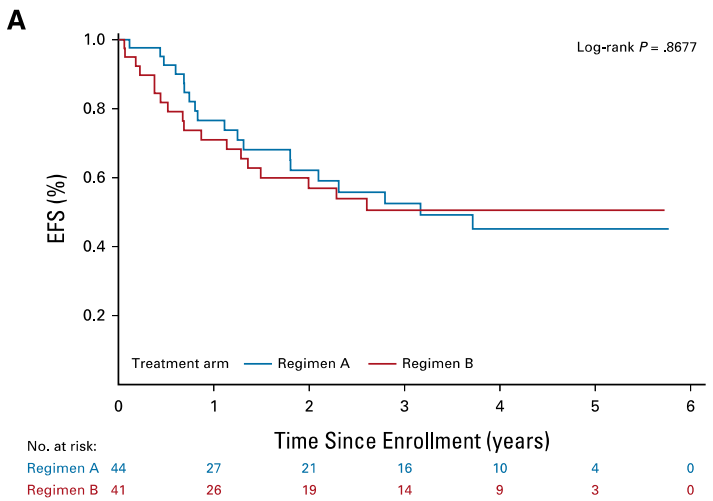
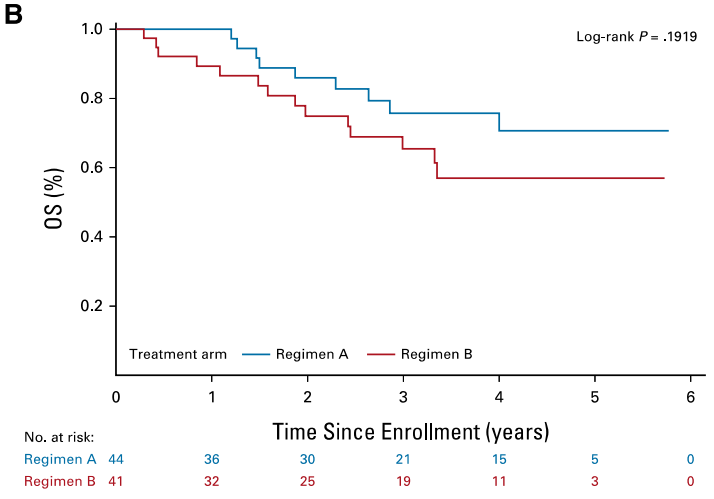
Bestrahlung mit Targeted Therapie (Pazopanib) bei Weichteilsarkomen

ARST1321 phase II study
Children's Oncology Group and NRG Oncology

Histology, No. (%)	
Synovial sarcoma	45 (52.9)
Undifferentiated pleomorphic sarcoma	19 (22.4)
Liposarcoma	6 (7.1)
Undifferentiated sarcoma NOS	6 (7.1)
Leiomyosarcoma	4 (4.7)
Embryonal sarcoma (undifferentiated sarcoma) of the liver	4 (4.7)
Mesenchymal chondrosarcoma	1 (1.2)



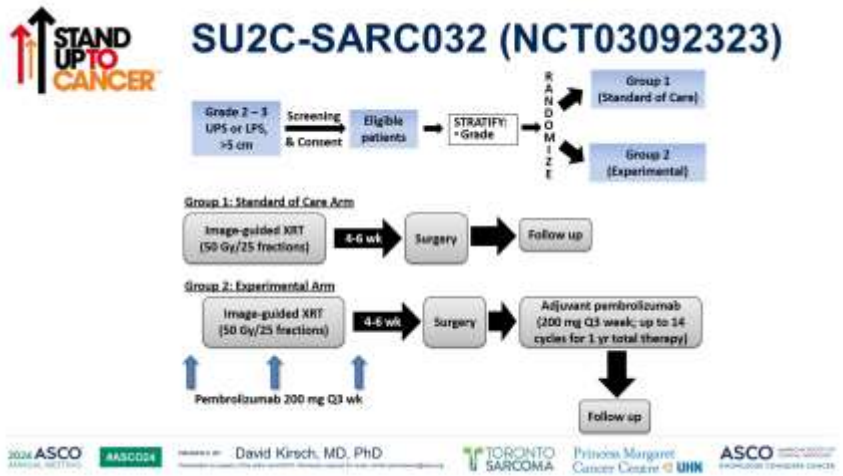




Obwohl die pCR Rate mit Pazopanib höher war, waren das EFS und OS nicht signifikant besser

Weiss et al. J Clin Oncol 2023, 41:4842-4848

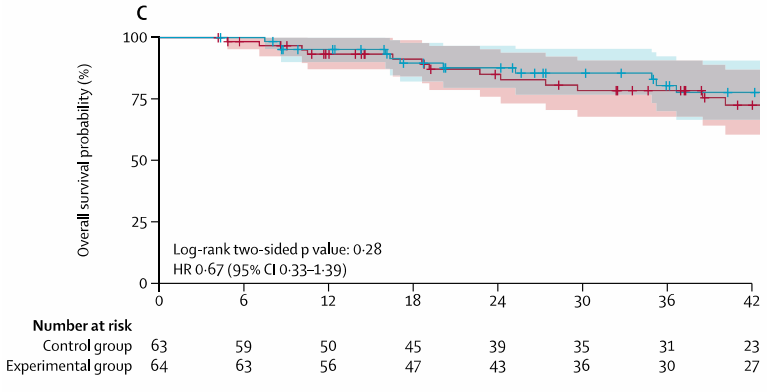
Bestrahlung mit Immunotherapie bei high-risk Weichteilsarkomen



Open-label, randomised clinical trial

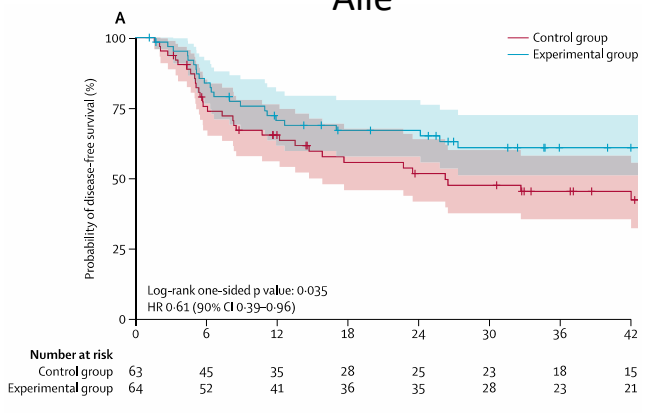
- 143 Patienten
- Grade 2-3, Stage III

Sarcoma histologic subtype at initial diagnosis		
Dedifferentiated liposarcoma	4 (6%)	4 (6%)
Pleomorphic liposarcoma	5 (8%)	0
Myxofibrosarcoma	6 (10%)	7 (11%)
Undifferentiated pleomorphic sarcoma	48 (76%)	53 (83%)

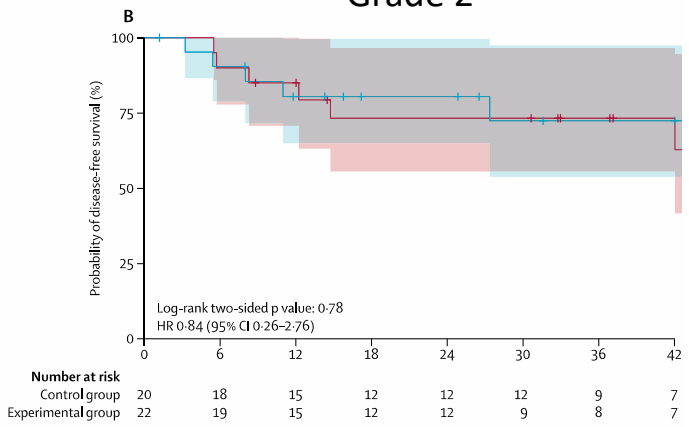


Krankheitsfreies Überleben

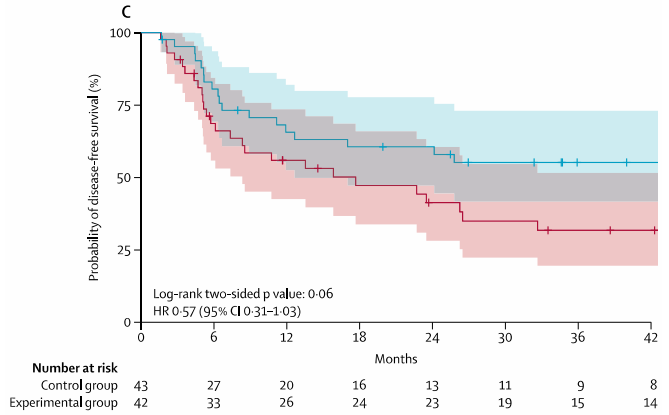
Alle



Grade 2



Grade 3



SU2C-SARC032 etabliert Pembrolizumab als neue Systemtherapie-Option bei Stage III undifferenzierte pleomorphe Sarkome und Liposarkome (grade 2 or 3) der Extremitäten.

Mowery et al. Lancet 2024; 404: 2053–64

SWISS SARCOMA NETWORK

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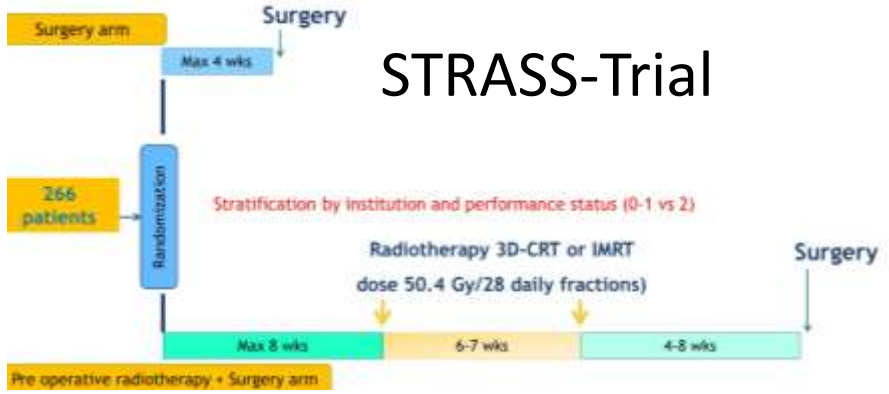
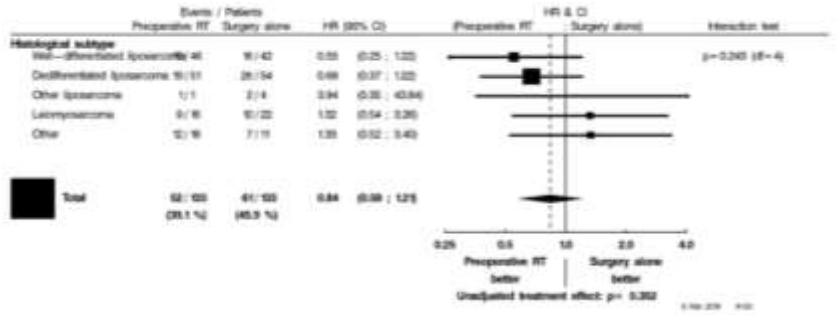
Bestrahlung bei retroperitonealen Sarkomen

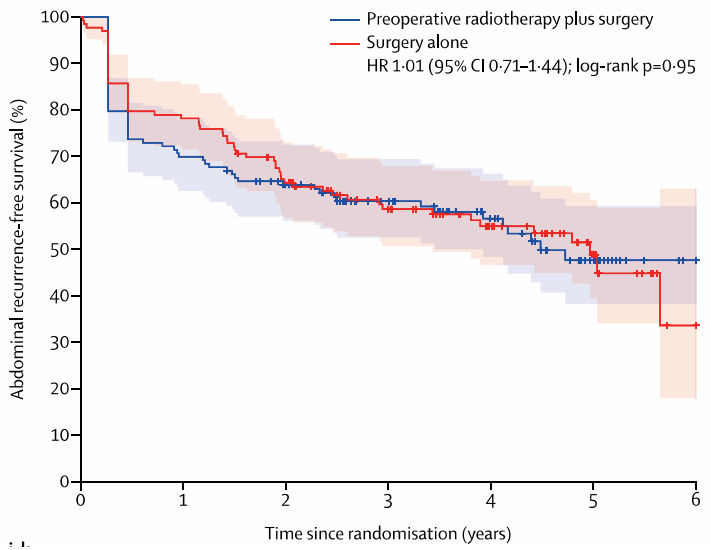


STRASS-Trial

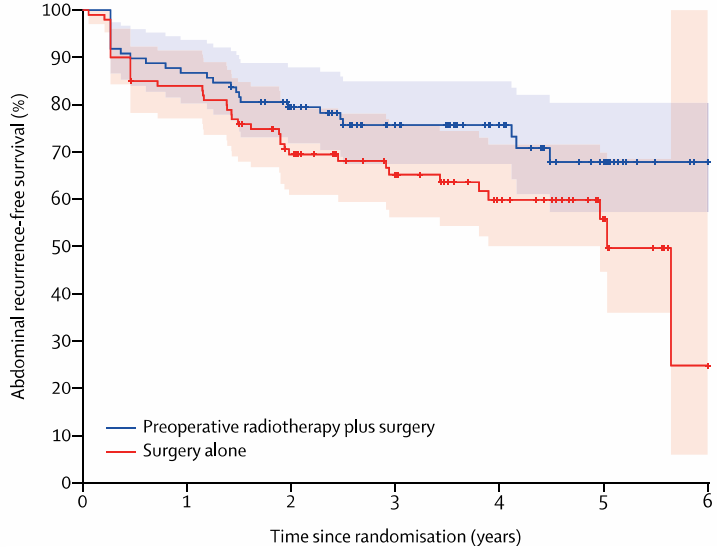
Histological subtype				
Well-differentiated liposarcoma	42 (31.6)	46 (34.8)	88 (33.1)	75%
Dedifferentiated liposarcoma	54 (40.6)	51 (38.3)	105 (39.5)	
Other liposarcoma	4 (3.0)	1 (0.8)	5 (1.9)	
Leiomyosarcoma	22 (16.5)	16 (12.0)	38 (14.3)	
Other	11 (8.3)	18 (13.5)	29 (10.9)	
Missing	0 (0.0)	1 (0.8)	1 (0.4)	
Grade				
Low	43 (32.3)	44 (33.1)	87 (32.7)	
Intermediate	38 (28.6)	47 (35.3)	85 (32.0)	
High	19 (14.3)	12 (9.0)	31 (11.7)	
Not evaluable	21 (15.8)	17 (12.8)	36 (14.3)	24%
Missing	12 (9.0)	13 (9.8)	25 (9.4)	



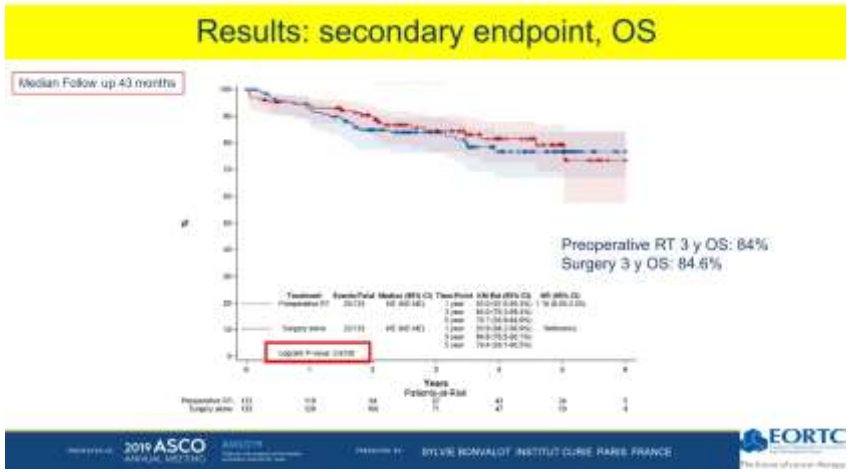
Alle



Liposarcoma Subgroup



Results: secondary endpoint, OS



Bonvalot et al. Lancet Oncol 2020; 21: 1366–77

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Danke

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