

# DEGRO 2023 – Refresher Sarkome

Klinik für Strahlentherapie

22.06.2023 - Nina Schmidt-Hegemann



## Erklärung zu möglichen Interessenskonflikten:

### **Berater- und Gutachtertätigkeiten**

Nein

### **Honorare**

Nein

### **Forschungsfinanzierung**

Nein

### **Eigentümerinteressen (Patent, Urheberrecht, Verkaufslizenz)**

Nein

### **Geschäftsanteile, Aktien, Fonds**

Nein



Rothermundt C, et al.; Writing committee on behalf of CSSS panellists. Controversies in the management of patients with soft tissue sarcoma: Recommendations of the Conference on State of Science in Sarcoma 2022. Eur J Cancer. 2023

## Overview

- Incidence
- Histopathology
- Natural history
- Clinical evaluation & diagnostic workup
- Staging

## Literature Review & Treatment Approach

- Extremity & trunk STS
- Retroperitoneal STS

An intraoperative photograph showing a surgical dissection of a soft tissue mass. The mass is white and lobulated, surrounded by red muscle and vascularized connective tissue. A hand is visible on the left side of the frame, providing scale. A green box with the word 'Incidence' is overlaid on the bottom left of the image.

## Incidence

- Soft tissue sarcomas (STSs) = 80 Entitäten analog WHO
- Selten – Inzidenz 4-5/100 000/Jahr in Europa
  - <1% aller Tumore
  - 15-20% aller pädiatrischer Tumore
- **CAVE:** Anbindung an Zentren für alle Pat. mit ungeklärter tiefer Weichteilmasse oder oberflächiger Weichteilläsion mit einem Durchmesser von  $\geq 3$  cm – Hausärzte!!!

- Sporadic (most common)
- Genetic alterations
  - NF-1
  - RB
  - Li Fraumeni
  - Familial polyposis
- Radiation
- Chronic edema  
Stewart-Treves Syndrome
- Environmental
  - Vinyl chloride
  - Phenoxyacetic acid
  - Arsenic
- Burns, foreign implants, scars (rare)

# Histopathology

➤ >100 different histologic subtypes

Pleomorphic Sarcoma

Liposarcoma

Leiomyosarcoma

MPNST

Synovial Sarcoma

= 75% of STS cases

Angiosarcoma

Rhabdomyosarcoma

Myxofibrosarcoma

Desmoid Tumor

Synovial sarcoma

GIST

Solitary Fibrous Tumor

Fibrosarcoma

Osteosarcoma

Ewing sarcoma

## Natural History

- Along longitudinal tissue planes
- Within compartment
- Compresses/distorts adjacent soft tissues
- Tumor can be well beyond mass



- Lymph node involvement uncommon (5%)

Exception: "CARE" (15-20%)

- Clear cell sarcoma
- Angiosarcoma
- Rhabdomyosarcoma
- Epithelioid sarcoma

- Distant spread commonly to lungs

- 10% at diagnosis

- Myxoid liposarcoma: Spine & extrapulmonary metastases (obtain whole body MRI)

- Brain MRI alveolar STS, clear cell sarcoma & Angiosarcoma

## Extremity

- Enlarging painless mass
- Functional limitations
- Symptoms associated with compression of local structures
- Pain

## Retroperitoneal

- Incidentally discovered
- GI symptoms
- Pain
- Neurologic symptoms
- Musculoskeletal symptoms

## Extremity

- X-ray
- MRI
- CT chest
- CT abdomen-pelvis if tumor involves groin
- PET

## Retroperitoneal

- CT abdomen-pelvis
- MRI for evaluation of muscle invasion or neural foramina Invasion
- CT chest
- PET

## Prätherapeutische histopathologische Sicherung

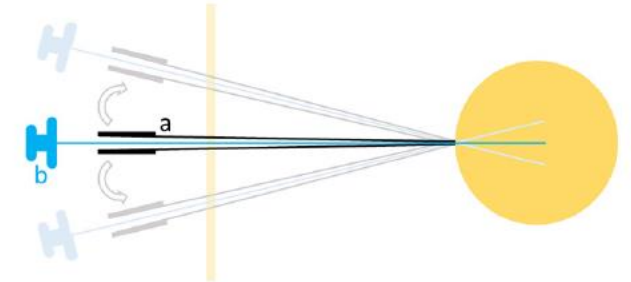
### Indikation – Planung - Durchführung

#### Rechtfertigung: Abhängigkeit von Therapieentscheidungen von der Histopathologie

- Wahl des OP-Verfahrens
- Indikation einer neoadjuvanten Therapie (Systemtherapie, Strahlentherapie)

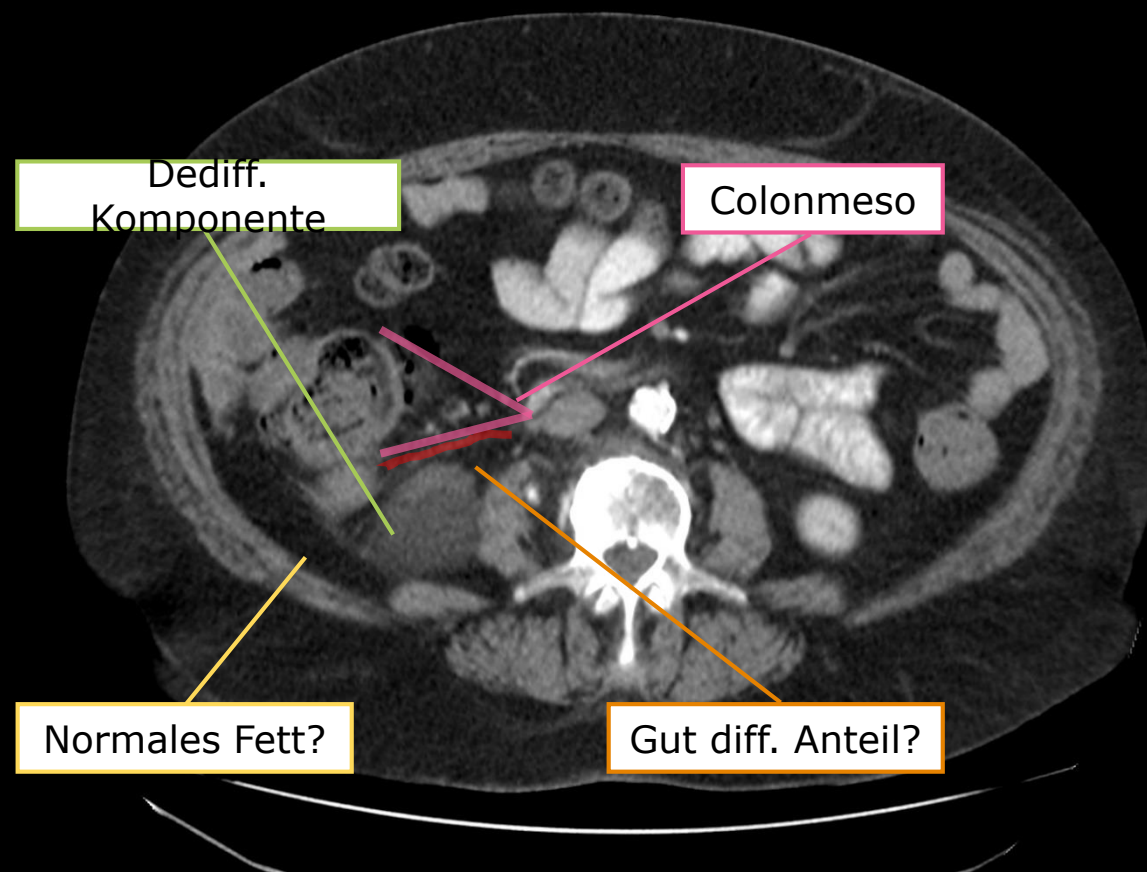
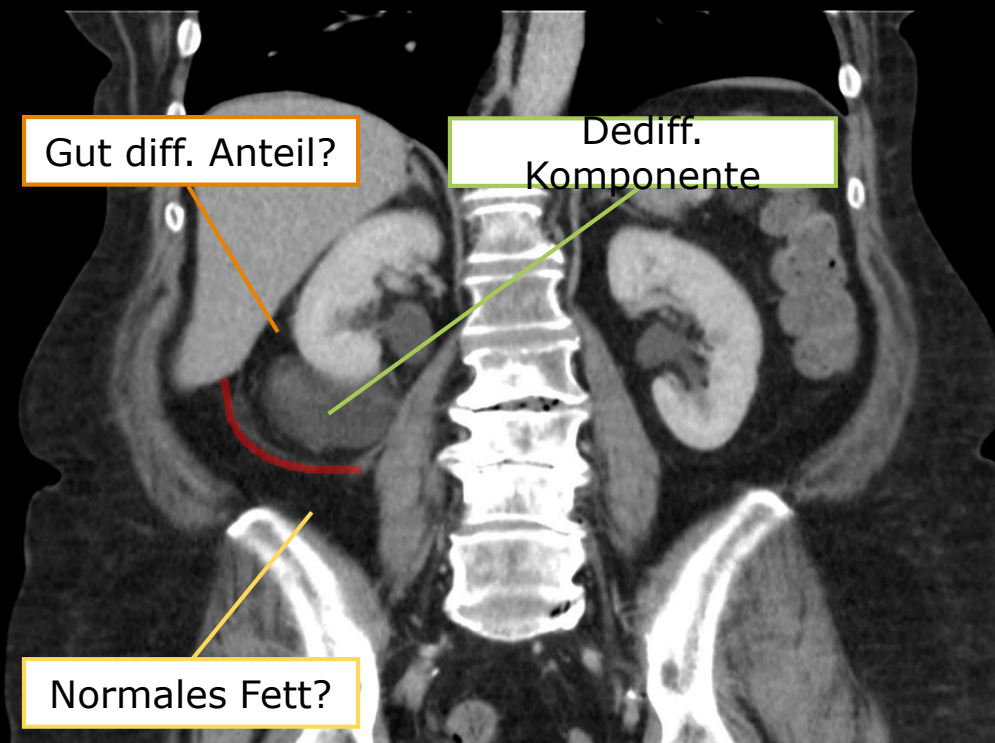
#### Durchführung

- CT-gesteuert
- Koaxial-Nadel: quasi kein Risiko für Impfmastasen
- Nicht trans-peritoneal: von dorsal
- Heterogener Tumor: Punktion der dedifferenzierten Komponente
- Planung ambulant, wenn fernab von Risikostrukturen punktiert wurde
- Kontroll-CT
- Bei Op Mitentfernen des Biopsiekanals/der Narbe außer bei retroperitonealen STS



Wang J, et al. (2018); Chin Clin Oncol 7 (4): 39

# Biopsie - Dedifferenziertes Liposarkom



# Pathologie

- Soft Tissue and Bone Tumours

WHO Classification of Tumours, 5th Edition, Volume 3

WHO Classification of Tumours Editorial Board

2020

- Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) Grading System validiert und prädiktiv für undifferentiertes, pleomorphes Sarkome, Leiomyosarkome, Liposarkome u. Synovialsarkome
  - > 3 Malignitätsgrade (G1-G3) in Abhängigkeit von Differenzierung, Nekrose und Mitoserate
  - > CAVE: Grading nur vor CTX/RTX möglich!
  - > High-risk STS: a deep-seated tumour, >5 cm in size and G3
- Postop: R0 vs. R1 vs. R2
- Postop: R0 – Doku des minimalen Resektionsrandes

# Staging

**Table 1. Staging Systems for Soft Tissue Sarcoma of the Extremity or Trunk**

Staging System	Description
<b>AJCC 7th edition<sup>a</sup></b>	
T1a	Tumor ≤5 cm in greatest dimension, superficial
T1b	Tumor ≤5 cm in greatest dimension, deep
T2a	Tumor >5 cm in greatest dimension, superficial
T2b	Tumor >5 cm in greatest dimension, deep
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M0	No distant metastasis
M1	Distant metastasis
<b>Stage groups</b>	
Stage IA	T1a/b; N0; M0; G1
Stage IB	T2a/b; N0; M0; G1
Stage IIA	T1a/b; N0; M0; G2/3
Stage IIB	T2a/b; N0; M0; G2
Stage III	T2a/b; N0; M0; G3
	Any T; N1; M0; any G
Stage IV	Any T; Any N; M1; any G
<b>AJCC 8th edition<sup>b</sup></b>	
T1	Tumor ≤5 cm in greatest dimension
T2	Tumor >5 cm and ≤10 cm in greatest dimension
T3	Tumor >10 cm and ≤15 cm in greatest dimension
T4	Tumor >15 cm in greatest dimension
N0	No regional lymph node metastasis or unknown lymph node status
N1	Regional lymph node metastasis
M0	No distant metastasis
M1	Distant metastasis
<b>Stage groups</b>	
Stage IA	T1; N0; M0; G1
Stage IB	T2, T3, T4; N0; M0; G1
Stage II	T1; N0; M0; G2/3
Stage IIIA	T2; N0; M0; G2/3
Stage IIIB	T3, T4; N0; M0; G2/3
Stage IV	Any T; N1; M0; any G
	Any T; any N; M1; any G

## Development and external validation of two nomograms to predict overall survival and occurrence of distant metastases in adults after surgical resection of localised soft-tissue sarcomas of the extremities: a retrospective analysis



Dario Callegaro, Rosalba Miceli, Sylvie Bonvalot, Peter Ferguson, Dirk C Strauss, Antonin Levy, Anthony Griffin, Andrew J Hayes, Silvia Stacchiotti, Cecile Le Pechoux, Myles J Smith, Marco Fiore, Angelo P Dei Tos, Henry G Smith, Luigi Mariani, Jay S Wunder, Raphael E Pollock, Paolo G Casali, Alessandro Gronchi

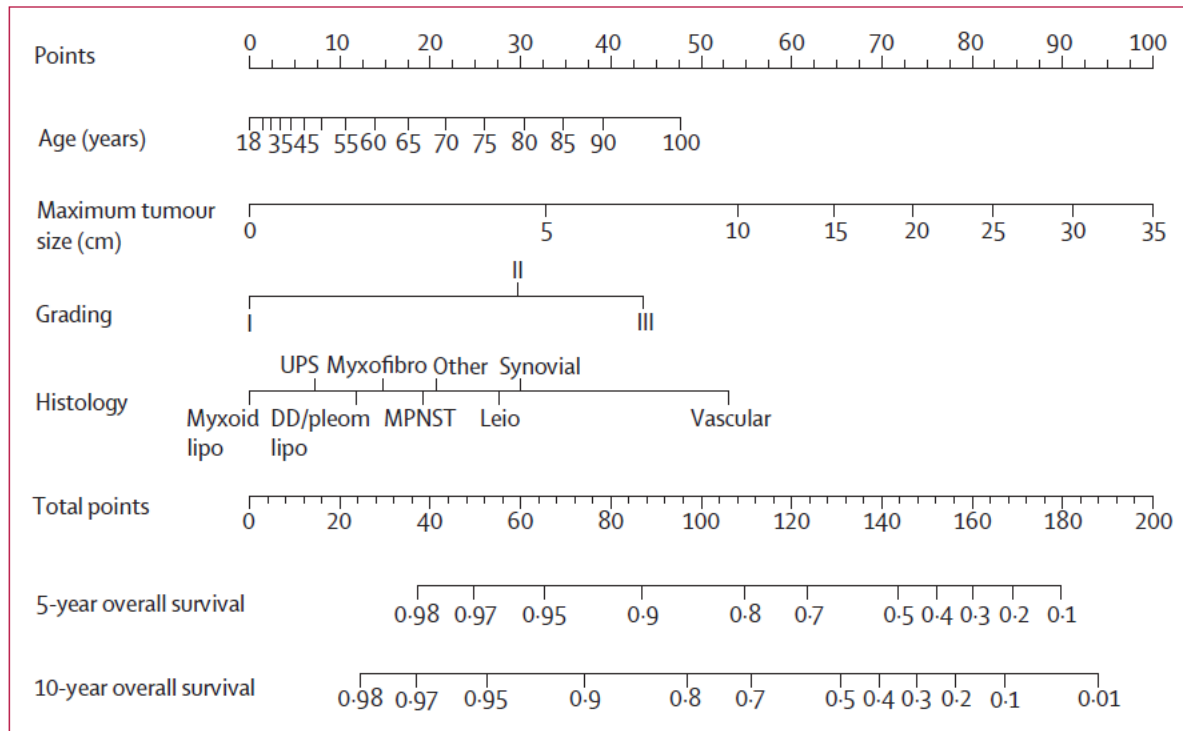
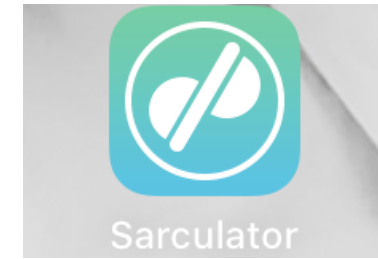


Figure 1: Overall survival nomogram

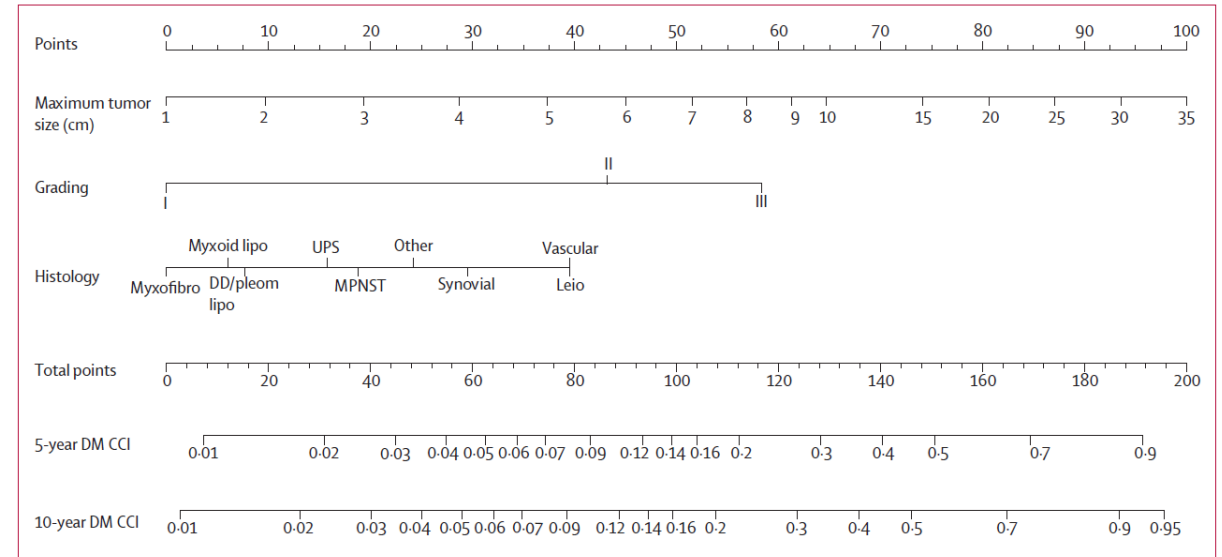


Figure 3: Distant metastases nomogram



# A prediction model for treatment decisions in high-grade extremity soft-tissue sarcomas: Personalised sarcoma care (PERSARC)



Veroniek M. van Praag<sup>a,1</sup>, Anja J. Rueten-Budde<sup>b,1</sup>, Lee M. Jeys<sup>c</sup>, Minna K. Laitinen<sup>c</sup>, Rob Pollock<sup>d</sup>, Will Aston<sup>d</sup>, Jos A. van der Hage<sup>e</sup>, P.D. Sander Dijkstra<sup>a</sup>, Peter C. Ferguson<sup>f</sup>, Anthony M. Griffin<sup>f</sup>, Julie J. Willeumier<sup>a</sup>, Jay S. Wunder<sup>f</sup>, Michiel A.J. van de Sande<sup>a,\*,2</sup>, Marta Fiocco<sup>b,g,2</sup>

## 766 ESTS patients who underwent surgery

Table 4. Fine and Gray model for local recurrence. Subdistribution hazard ratio (sHR) along with 95% confidence interval (n = 766).

	sHR	95% CI	p-Value
<b>Age</b>	1.051	0.942–1.184	0.337
<b>Size</b>	1.031	1.001–1.063	0.042
<b>Depth<sup>a</sup></b>			0.559
Deep	1.000		
Superficial	0.907	0.536–1.535	
Deep and superficial	0.563	0.198–1.604	
<b>Histology</b>			0.864
Myxofibrosarcoma	1.000		
MPNST	1.079	0.580–2.009	
Synovial sarcoma	0.779	0.379–1.602	
Spindle cell sarcoma	0.979	0.570–1.681	
MFH/UPS	1.096	0.557–2.156	
<b>Margin</b>			<0.001
0 mm	1.000		
0.1–2 mm	0.635	0.406–0.992	
>2 mm	0.282	0.159–0.500	
<b>RT</b>			0.010
No RT	1.000		
Neoadjuvant	0.312	0.146–0.668	
Adjuvant	0.700	0.417–1.175	

Table 2. Multivariate Cox model for overall survival: hazard ratio (HR) along with 95% confidence interval (n = 766).

	HR	95% CI	p-Value
<b>Age</b>	1.195	1.116–1.268	<0.001
<b>Size</b>	1.068	1.052–1.085	<0.001
<b>Depth<sup>a</sup></b>			0.377
Deep	1.000		
Superficial	0.813	0.591–1.117	
Deep and superficial	1.110	0.736–1.674	
<b>Histology</b>			0.492
Myxofibrosarcoma	1.000		
MPNST	1.422	0.989–2.044	
Synovial sarcoma	1.261	0.869–1.831	
Spindle cell sarcoma	1.211	0.884–1.661	
MFH/UPS	1.293	0.890–1.876	
<b>Margin</b>			0.080
0 mm	1.000		
0.1–2 mm	0.786	0.599–1.033	
>2 mm	0.711	0.524–0.964	
<b>RT</b>			<0.001
No RT	1.000		
Neoadjuvant	0.548	0.399–0.753	
Adjuvant	0.638	0.486–0.837	

Welkom bij  
VALUE-PERSARC

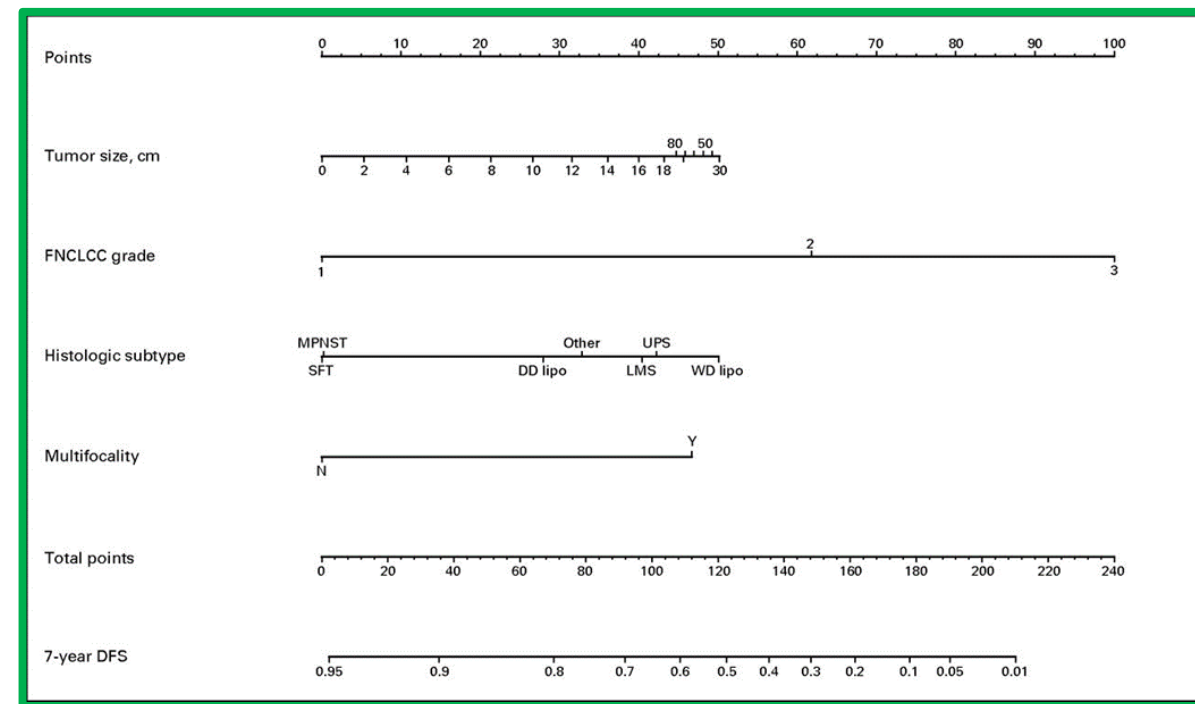
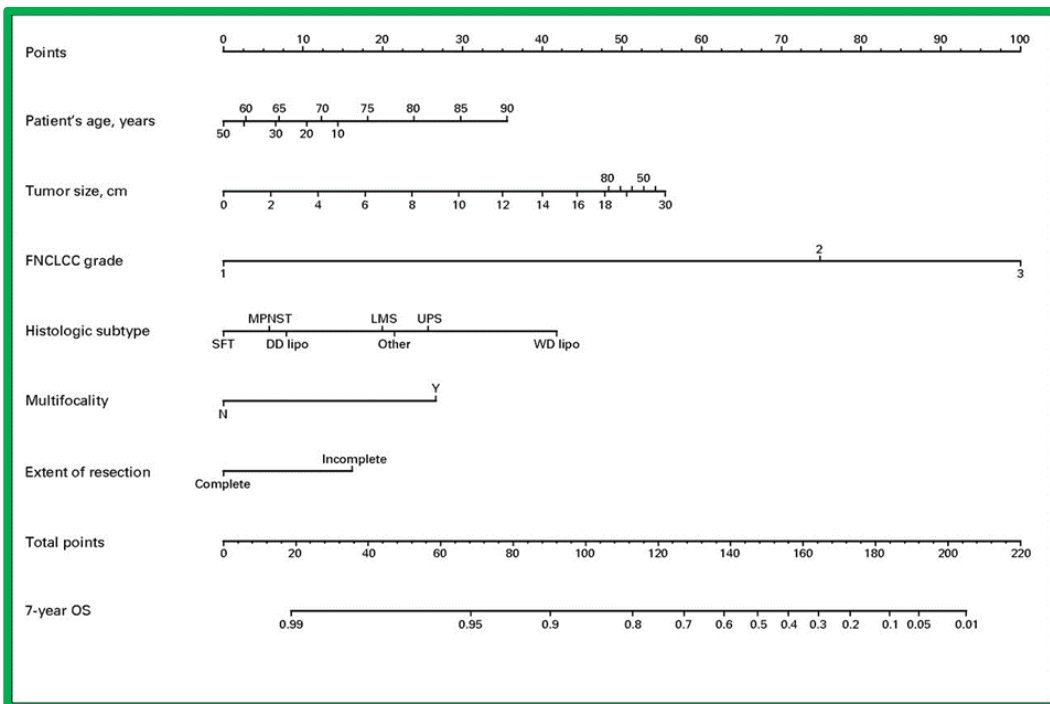
PERSONALIZED SARCOMA CARE



App versie: 3.0

## Outcome Prediction in Primary Resected Retroperitoneal Soft Tissue Sarcoma: Histology-Specific Overall Survival and Disease-Free Survival Nomograms Built on Major Sarcoma Center Data Sets

Alessandro Gronchi, Rosalba Miceli, Elizabeth Shurell, Fritz C. Eilber, Frederick R. Eilber, Daniel A. Anaya, Michael W. Kattan, Charles Honoré, Dina C. Lev, Chiara Colombo, Sylvie Bonvalot, Luigi Mariani, and Raphael E. Pollock




- 523 pts
- median follow-up of 45 months (22 - 72 months)

# Extremity & Trunk STS

# RARE Tumors -> Multidisciplinary Care by Sarcoma Specialists

## Improved survival for extremity soft tissue sarcoma treated in high-volume facilities

Tyler Abarca BS<sup>1</sup> | Yubo Gao PhD<sup>2</sup> | Varun Monga MD<sup>3</sup> | Munir R. Tanas MD<sup>4</sup> | Mohammed M. Milhem MBBS<sup>3</sup> | Benjamin J. Miller MD, MS<sup>5</sup> 

- NCDB: propensity score analysis of pts with non-met. STS treated in high- and low-volume centers (2437 pts each)

**TABLE 3** Univariate comparison of 2-, 5-, and 10-year survival between low and high volume centers

	2-year (95%CI)	5-year (95%CI)	10-year (95%CI)
Low-volume	84.0 (82.5-85.5)	68.1 (66.0-70.2)	53.3 (50.0-56.6)
High-volume	87.0 (85.6-88.4)	72.7 (70.6-74.7)	57.6 (54.1-61.1)
P-value	0.003	0.001	0.001

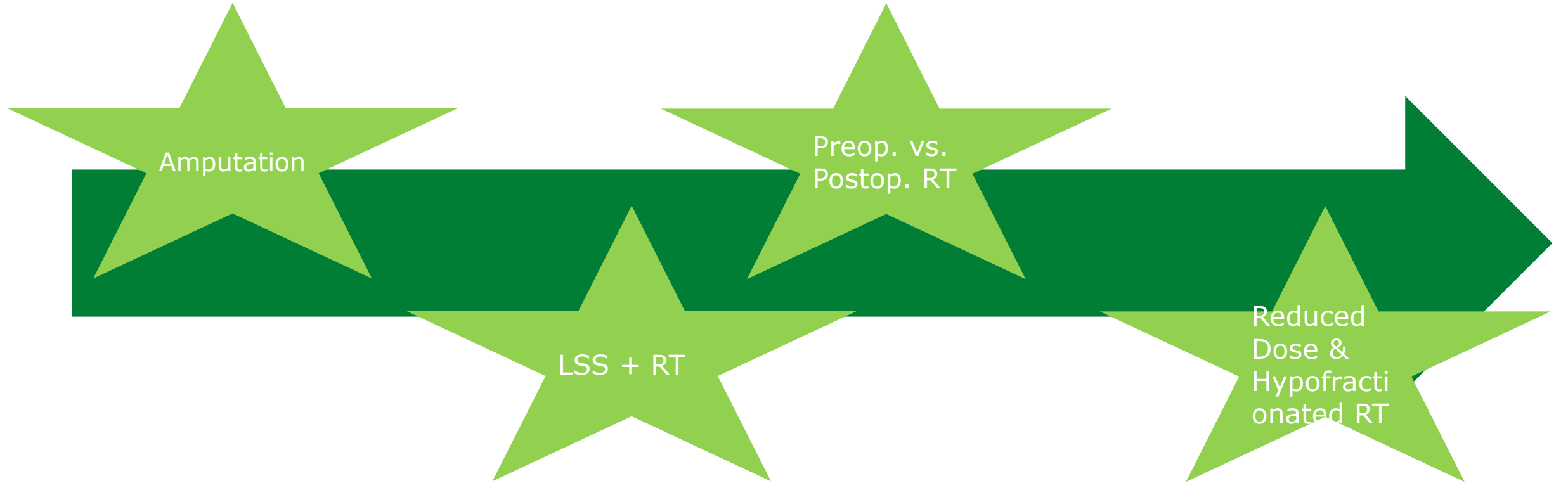
# Treatment Evolution

Amputation

Preop. vs.  
Postop. RT

LSS + RT

Reduced  
Dose &  
Hypofractionated RT



## Historisch ... 3 randomisierte Studien

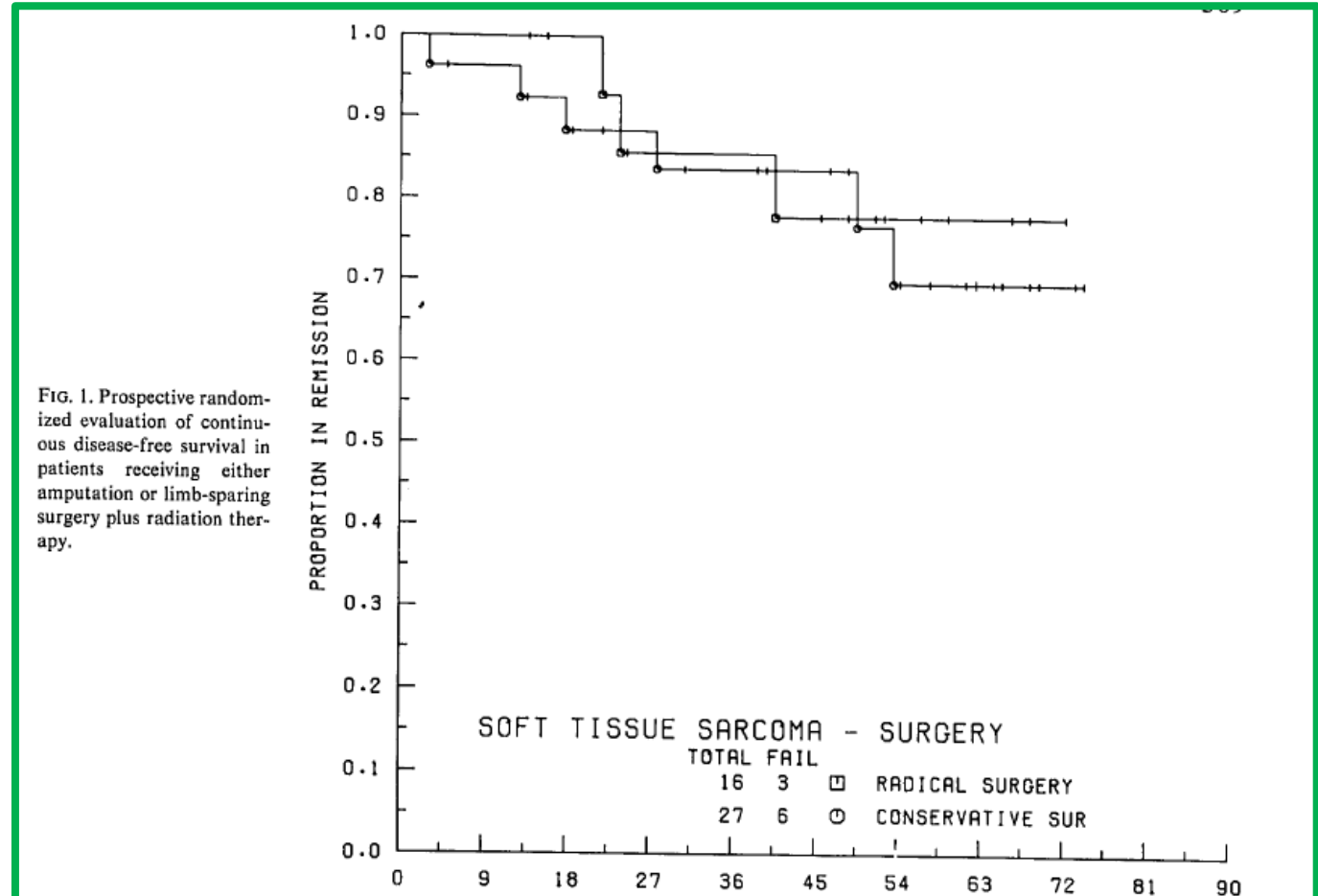
### *The Treatment of Soft-tissue Sarcomas of the Extremities*

*Prospective Randomized Evaluations of (1) Limb-sparing Surgery Plus Radiation Therapy Compared with Amputation and (2) the Role of Adjuvant Chemotherapy*

Rosenberg et al. Ann surg 1982

43 Pat. mit hochgradigen Extremitäten STS randomisiert zw. Amputation und Extremitäten Erhalt + adj. RT (50Gy + 10-20Gy)

- 4 LR in Extremitätenerhaltgruppe vs. 0 in der Amputationsgruppe
- kein Unterschied im DFS oder OS
- sign. Einfluss des Resektionsstatus auf LC



# Randomized Prospective Study of the Benefit of Adjuvant Radiation Therapy in the Treatment of Soft Tissue Sarcomas of the Extremity

By James C. Yang, Alfred E. Chang, Alan R. Baker, William F. Sindelar, David N. Danforth, Suzanne L. Topalian, Thomas DeLaney, Eli Glatstein, Seth M. Steinberg, Maria J. Merino, and Steven A. Rosenberg

JCO 1998

- Randomisierte Studie für Weichteilsarkome der Extremitäten
- Design: Extremitätenerhaltende OP (+ Chemo bei G3) und Randomisation + EBRT
- RT senkt Lokalrezidivrate, hat aber keinen signifikanten Einfluss auf OS und Fernmetastasierung
- schlechtere Gelenkfunktion nach RT (Alte Technik !)

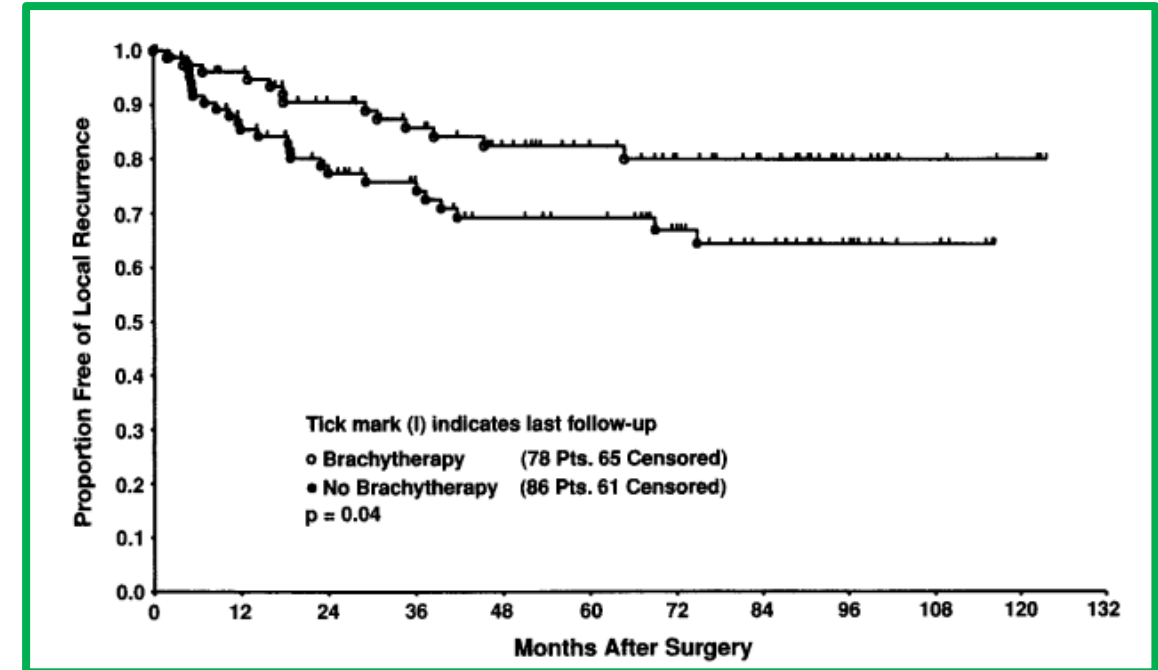
Entität	Lokalrez. ohne RT	Lokalrez. mit RT	Signifikanz
Hochmaligne STS (+ adj. Chemo)	22%	0%	p=0,0028
Niedrigmaligne STS (keine Chemo)	33%	4%	p=0,016

# Long-Term Results of a Prospective Randomized Trial of Adjuvant Brachytherapy in Soft Tissue Sarcoma

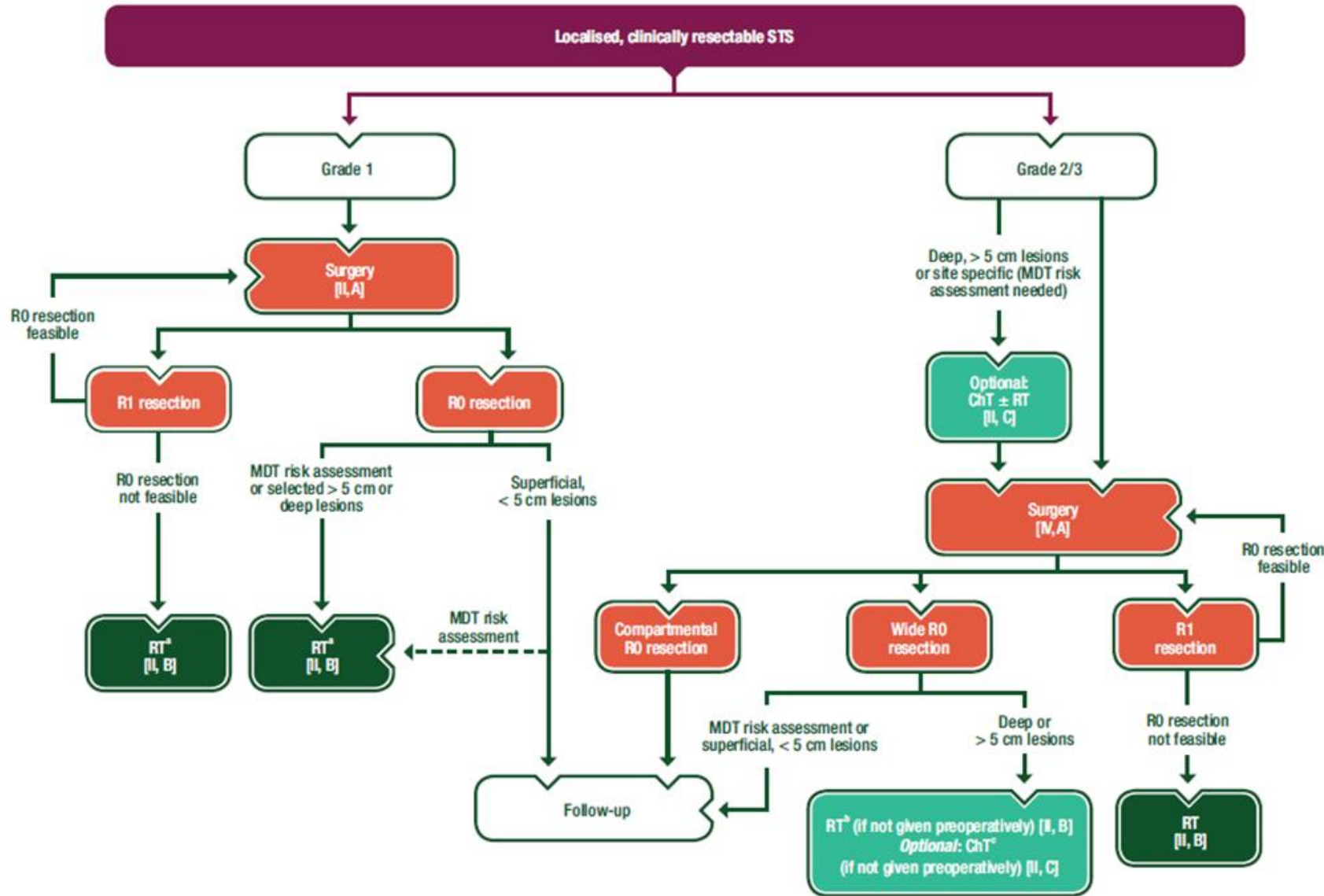
By Peter W.T. Pisters, Louis B. Harrison, Denis H.Y. Leung, James M. Woodruff, Ephraim S. Casper, and Murray F. Brennan

J Clin Oncol 1996

- 164 Pat. randomisiert für adjuvante Brachytx oder keine Brachytx nach kompletter Resektion von STS der Extremität oder des oberflächlichen Rumpfes
- Brachytx = iridium-192 Implantat (42 - 45 Gy über 4 - 6 Tagen)
- 5 Jahre-LC 82% vs. 69% zu Gunsten Brachytx ( $p = 0.04$ )
- Hochgradige Läsionen: LC 89% vs. 66% ( $p = 0.0025$ )
- Niedriggradige Läsionen: kein Einfluss auf LC ( $p = 0.49$ )
- Kein Einfluss auf distante Kontrolle/Überleben!







**Figure 1.** Management of localised, clinically resectable STS.

<sup>a</sup>RT can be omitted in selected cases; *optional*: isolated limb perfusion in highly selected cases.

<sup>b</sup>RT can be omitted in selected deep cases and added in selected superficial cases; to be administered preoperatively if problematic postoperatively.

<sup>c</sup>Extremity and superficial trunk, G3, deep, > 5 cm.

ChT, chemotherapy; MDT, multidisciplinary team; R0, no tumour at the margin; R1, microscopic tumour at the margin; RT, radiotherapy; STS, soft tissue sarcoma.

## Surgery Alone Considered

- Primarily for superficial tumors, <5 cm, treated with wide R0 resection
- Local recurrence (LR): <15%
- Survival: >90%

## Radiation Indications

- Positive margins
- LR s/p prior surgery alone (with re-resection)
- Location not amenable to salvage surgery

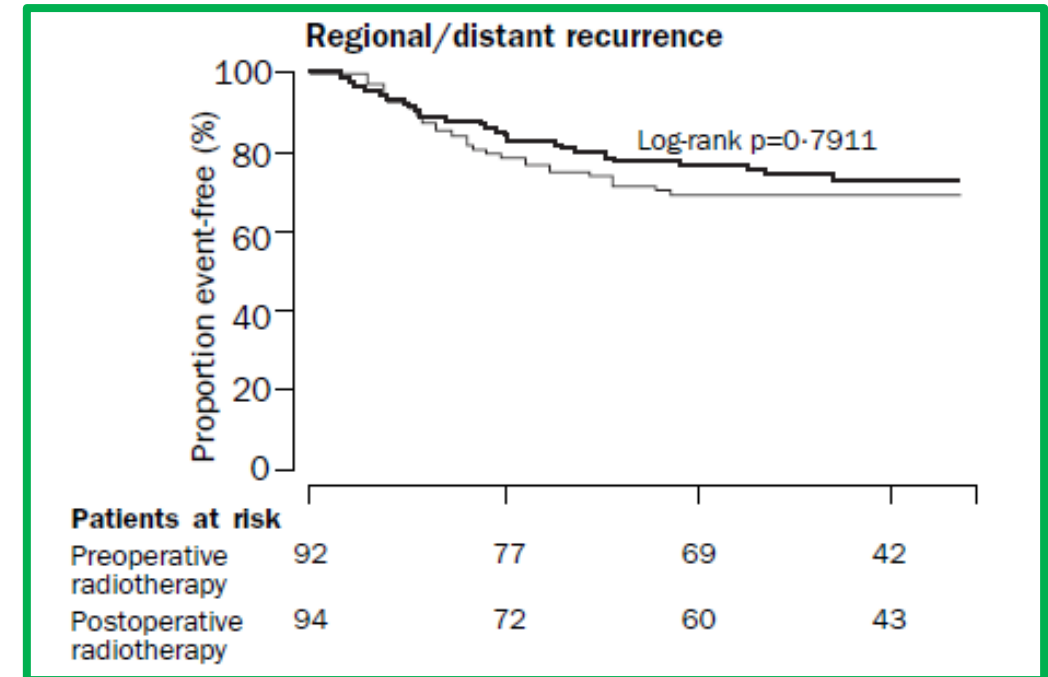
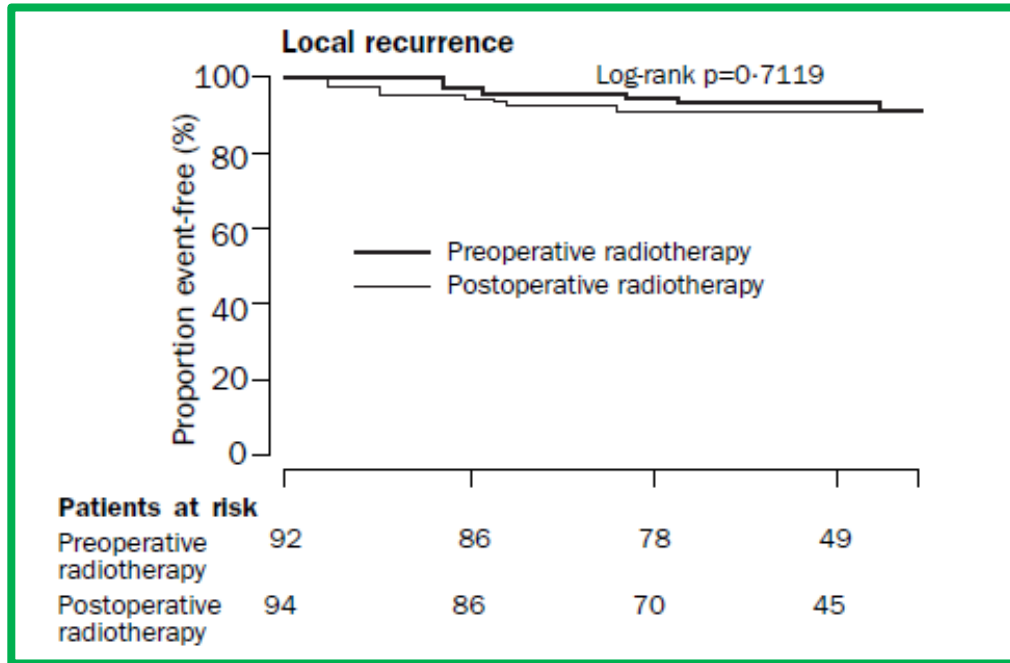
## High Grade (Grade 2 & 3) STS Treatment

- Limb salvage surgery (LSS) + RT
- LR <15%
- Survival varies by size and grade

**Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial**

Brian O'Sullivan, Aileen M Davis, Robert Turcotte, Robert Bell, Charles Catton, Pierre Chabot, Jay Wunder, Rita Kandel, Karen Goddard, Anna Sadura, Joseph Pater, Benny Zee

- Präop (50 Gy) vs. Postop (66 Gy)
- Median f-u 3.3 years
- wound complications 35% in preop. vs. 17% in postop. group
- No sign. Diff. in LC, DC



## Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma

Aileen M. Davis<sup>a,j,\*</sup>, Brian O'Sullivan<sup>b,j</sup>, Robert Turcotte<sup>c</sup>, Robert Bell<sup>b,d,j</sup>, Charles Catton<sup>b,j</sup>, Pierre Chabot<sup>e</sup>, Jay Wunder<sup>b,d,j</sup>, Alex Hammond<sup>f</sup>, Veronique Benk<sup>g</sup>, Rita Kandel<sup>d,j</sup>, Karen Goddard<sup>h</sup>, Carolyn Freeman<sup>c</sup>, Anna Sadura<sup>i</sup>, Benny Zee<sup>i</sup>, Andrew Day<sup>i</sup>, Dongsheng Tu<sup>i</sup>, Joseph Pater<sup>i</sup>,  
A Canadian Sarcoma Group and NCI Canada Clinical Trials Group Randomized Trial

- grade  $\geq 2$  fibrosis: 48.2% in postop. vs. 31.5% in preop. arm (P=0.07)
- Edema: 23.2% in postop. vs. 15.1%
- joint stiffness: 23.2% in postop. vs. 17.8%
  
- Field size predictive of greater rates of fibrosis (P=0.002) and joint stiffness (P=0.006) and marginally predictive of edema (P=0.06)!

Field size matters!

- Vascular involvement
- Joint involvement
- Tissue planes
- E.g., adjacent bone; removal of periosteum?; need for fixation?
- Functional loss
- Need for plastic surgery

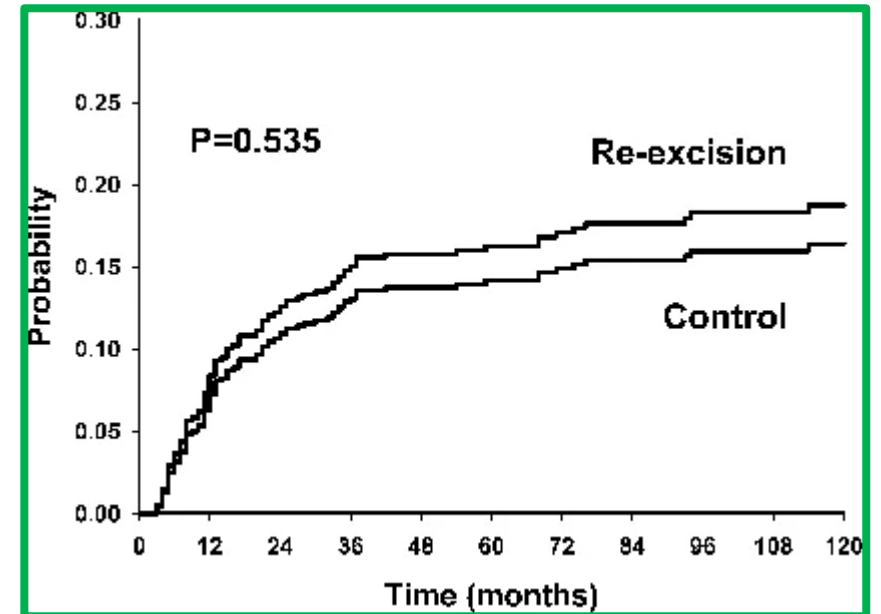
## Inadvertent Excisions

- Common phenomena
- Generally smaller and subcutaneous tumors
- Inappropriate skin incision common
- Residual disease in 24-74% of cases
- Treatment is LSS + RT, i.e. like a de novo diagnosis
- Similar local control and survival to those with primary management

## Prognostic Effect of Re-Excision in Adult Soft Tissue Sarcoma of the Extremity

Marco Fiore, MD,<sup>1</sup> Paolo G. Casali, MD,<sup>2</sup> Rosalba Miceli, PhD,<sup>3</sup>  
Luigi Mariani, MD,<sup>3</sup> Rossella Bertulli, MD,<sup>2</sup> Laura Lozza, MD,<sup>4</sup> Paola Collini, MD,<sup>5</sup>  
Patrizia Olmi, MD,<sup>4</sup> Chiara Mussi, MD,<sup>1</sup> and Alessandro Gronchi, MD<sup>1</sup>

- 597 adult pts with primary extremity STS
- 318 pts referred after unplanned excisions, 279 with primary resection
- 10-year incidences in re-excised and primarily operated pts: local relapse 18.7% vs. 16.4% ( $P = .535$ ), metastasis 17.6% vs. 20.2% ( $P = .541$ ) for, mortality 20.4% vs. 22.4% ( $P = .645$ )
- In pts with re-excision, R1 resection sign. prognostic effect on multivariable analysis for distant metastases ( $P = .002$ ).

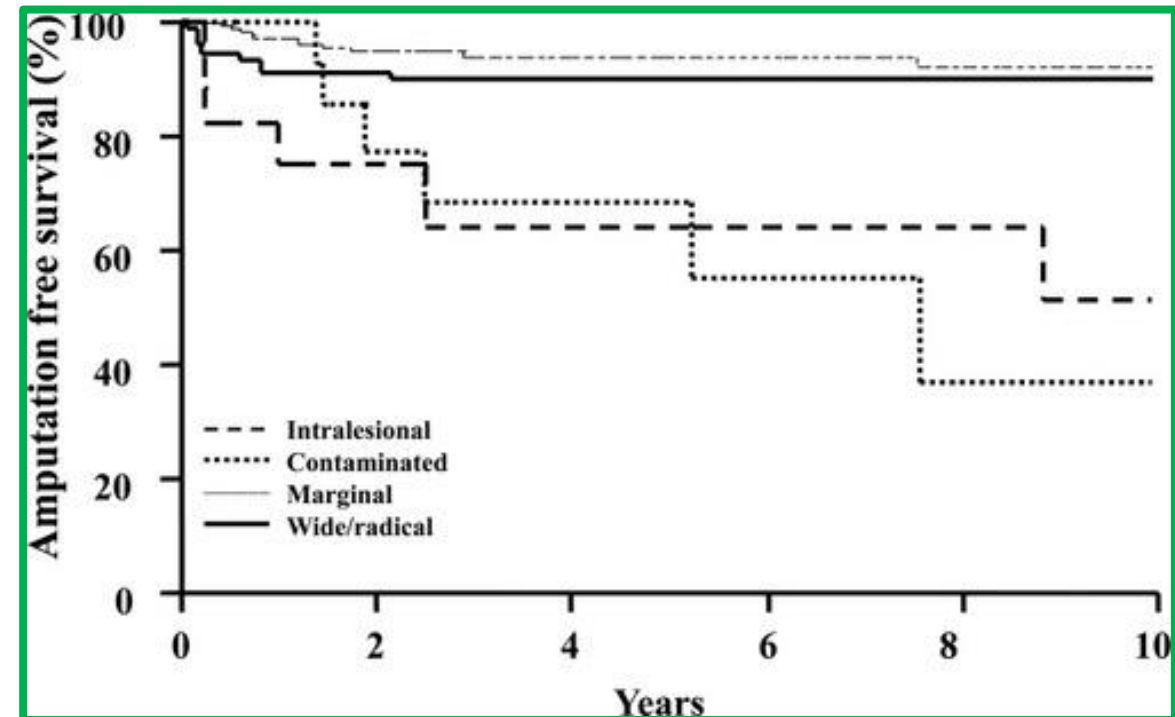




# The Significance of a Marginal Excision After Preoperative Radiation Therapy for Soft Tissue Sarcoma of the Extremity

Roi Dagan, MD<sup>1</sup>; Daniel J. Indelicato, MD<sup>1,4</sup>; Lisa McGee, MD<sup>1</sup>; Christopher G. Morris, MS<sup>1</sup>; Jessica M. Kirwan, MA<sup>1</sup>; Jacquelyn Knapik, MD<sup>2</sup>; John Reith, MD<sup>2</sup>; Mark T. Scarborough, MD<sup>3</sup>; C. Parker Gibbs, MD<sup>3</sup>; Robert B. Marcus, Jr, MD<sup>4</sup>; and Robert A. Zlotecki, MD, PhD<sup>1</sup>

- 317 pts with nonmetastatic extremity STS
- median f-u 4.7 years (8.3 years for living patients)
- median tumor size 10 cm (range, 2-36 cm)
- 86% high grade
- median RT dose 50.4 Gy (range, 12.5-57.6 Gy)
- Margins: wide/radical (n = 105), marginal (n = 179), contaminated (n = 15), positive (n = 17), or unknown (n = 1)
- 5-y. CSS and OS 62% 59%
- 5-y. LC and AFS 93% and 89%
- AFS by margin status 64%, 83%, 97%, and 92% for positive, contaminated, marginal, and wide/radical margins (P<.005)
- Marginal excision following preoperative RT resulted in equivalent LC and AFS compared with wide/radical margins.



## Innovative Preoperative RT Strategies

- Preoperative RT preferred for most situations
- Local control outcomes are excellent for most extremity STS
  - <15% LF
  - Acceptable toxicities and functional outcomes
- **How can we advance local therapies?**
  - RT dose deintensification
  - Hypofractionation
  - smaller field size?

# Preoperative RT Dose Deintensification

- Myxoid liposarcoma most radiosensitive STS subtype
  - <5% local failure rate
  - Tumor volumes shrinks during or after RT

JAMA Oncology | Original Investigation

## Dose Reduction of Preoperative Radiotherapy in Myxoid Liposarcoma A Nonrandomized Controlled Trial

- pts with nonmetastatic, biopsy-proven and translocation-confirmed myxoid liposarcoma of the extremity or trunk
- 36 Gy in once-daily 2-Gy + surgical resection after  $\geq 4$  weeks
- Extensive pathological treatment response: 91%
- LC 100%
- 17% wound complication requiring intervention
- 14% grade  $\geq 2$  toxic effects
- deintensification of preop. RT effective and oncologically safe

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 $\geq 2$ toxic effect	R0	WC	LC	
DOREMY trial	77 <sup>a</sup>	Prospective	All	18 × 2 Gy	14	94	17	100	2.1
O'Sullivan et al, <sup>8</sup> 2002; Davis et al, <sup>9</sup> 2005	88 <sup>a</sup>	Prospective	Preoperative group, various histological subtypes	25 × 2 Gy	37	84	35	92 <sup>b</sup>	3.3
Lansu et al, <sup>10</sup> 2019	32 <sup>c</sup>	Retrospective	Myxoid liposarcoma subgroup	25 × 2 Gy	NA	91	38	97	5
Chung et al, <sup>7</sup> 2009	88 <sup>d</sup>	Retrospective	Myxoid liposarcoma subgroup	25 × 2 Gy	NA	81	NA	98	5
O'Sullivan et al, <sup>34</sup> 2013	59 <sup>e</sup>	Prospective	All, various histological subtypes	25 × 2 Gy	24	93	31	93 <sup>b</sup>	4
Wang et al, <sup>35</sup> 2015 (RTOG-0630 trial)	57 <sup>f</sup>	Prospective	All, various histological subtypes	25 × 2 Gy	11	76	36	89	2

# Hypofractionated Preoperative RT

Preoperative hypofractionated radiotherapy in the treatment of localized soft tissue sarcomas

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<sup>b</sup>Department of Epidemiology, Institute of Mother and Child, Warsaw, Poland

- 272 pts with STS of the extremities or trunk wall
- 25/5fx = EQD2 40 Gy
- median follow up 35 months
- 3-year OS 72%
- 3-year local recurrences 19.1 %
- acute toxicity 32.4%
- late toxicity 14.7%

higher dose



better local control?

# Hypofractionated Preoperative RT

## Articles

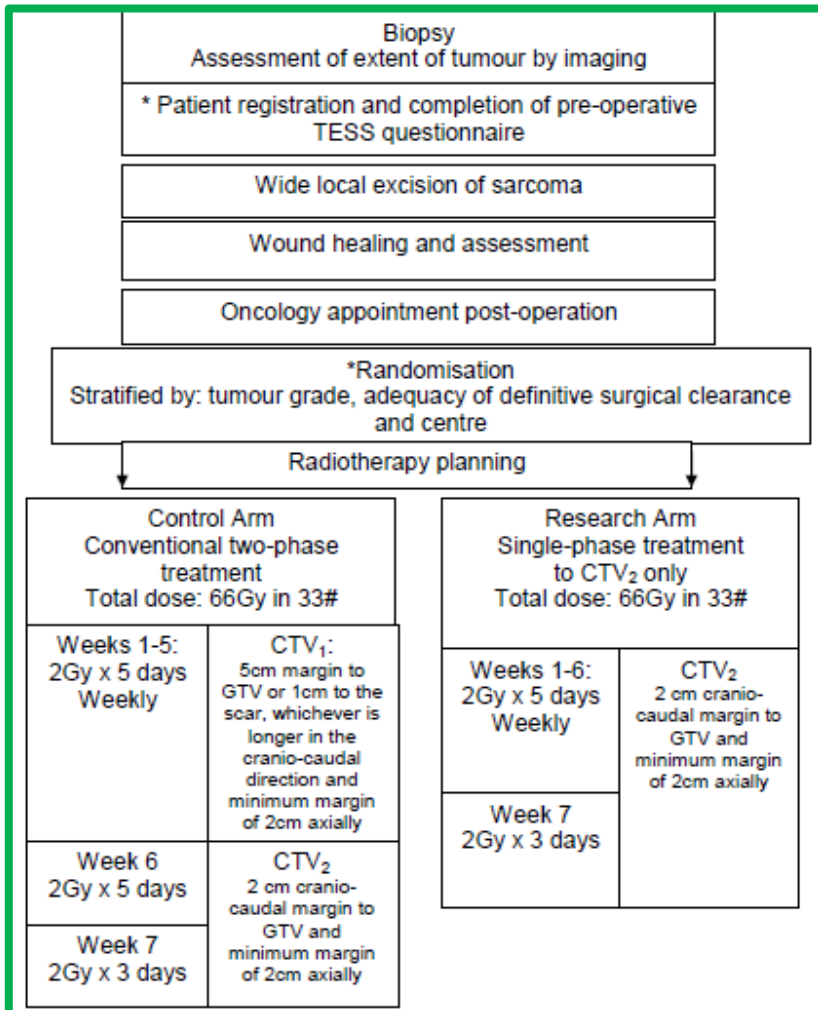
Hypofractionated, 3-week, preoperative radiotherapy for patients with soft tissue sarcomas (HYPORT-STS): a single-centre, open-label, single-arm, phase 2 trial

Prof B Ashleigh Guadagnolo MD<sup>a</sup>  , Roland L Bassett MS<sup>b</sup>, Devarati Mitra MD<sup>a</sup>,

- Preop. RT 42.75 Gy/15 fractions/2.85 Gy/day for 3 weeks (five fractions per week)
- 120 pts with non-metastatic STS of the extremities or superficial trunk
- median postop. follow-up 24 months
- 31% major wound complication after surgery
- No acute radiation toxicity
- 3% late radiation toxicity ( $\geq 6$  months post-surgery) of at least grade 3
- Local control 93% at 2.5 yr
- OS 91% at 2 yr
- Results on long-term oncological, late toxicity, and functional outcomes are awaited.

# Vortex Trial: A Randomized Controlled Multicenter Phase 3 Trial of Volume of Postoperative Radiation Therapy Given to Adult Patients With Extremity Soft Tissue Sarcoma (STS)

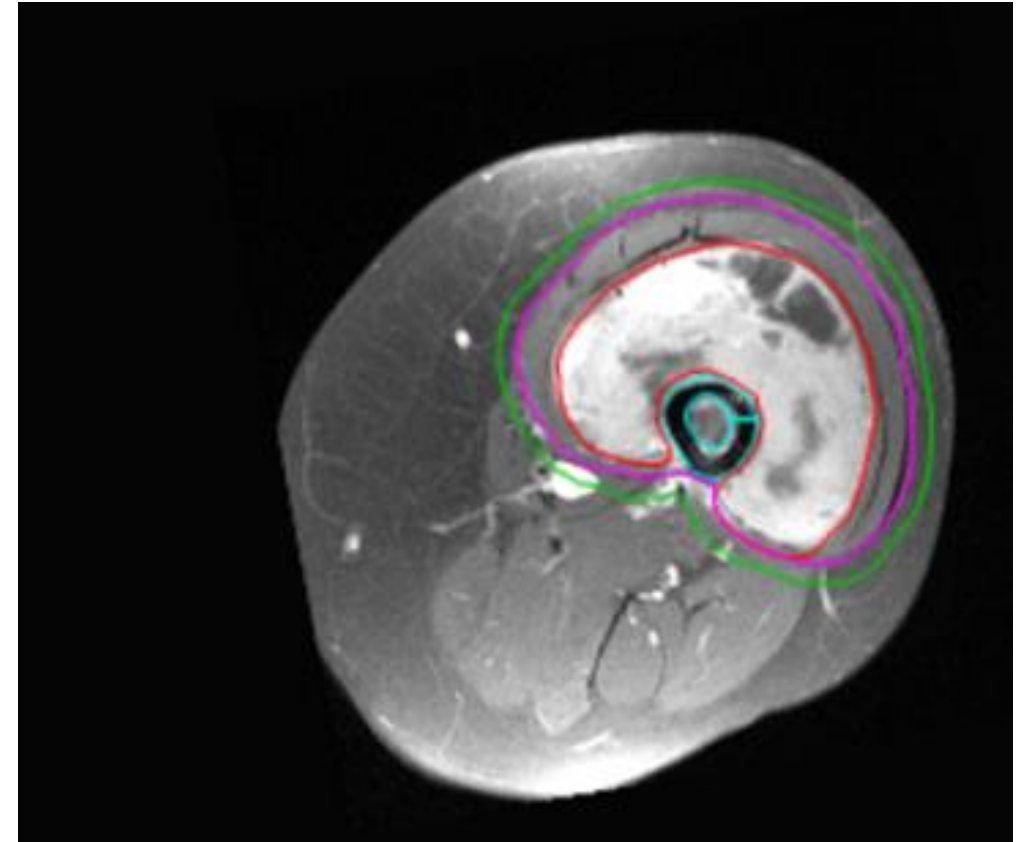
M.H. Robinson • P. Gaunt • R. Grimer • ... C.M.L. West • K. Venables • L. Billingham • [Show all authors](#)



- 216 pts randomized
- no sign. difference in 2 years limb function
- no sign. difference in 5-year LC or OS
- no sign. Difference in late radiation toxicity grade 2+

# RT Treatment Principles: Simulation

- Custom immobilization
- Soft tissue reproducibility
- Fixation to prevent rotation
- Soft tissue contact with immobilization device
- Avoid
  - Lower extremity: Contralateral extremity
  - Upper extremity: Torso, head
- Ensure patient comfort
- MRI with contrast in treatment position



## Preoperative RT

Preoperative RT

- 50 Gy in 25 fx
- Hypofractionation on trial or in certain circumstances where conventional fractionation is not possible
- Discuss with patient the absence of long term-follow up data

## Postoperative RT

Exulcerant tumor, extremely painful tumor, or high risk of wound complications

Initial volume: 45 – 50 Gy

Boost: 16 - 20 Gy

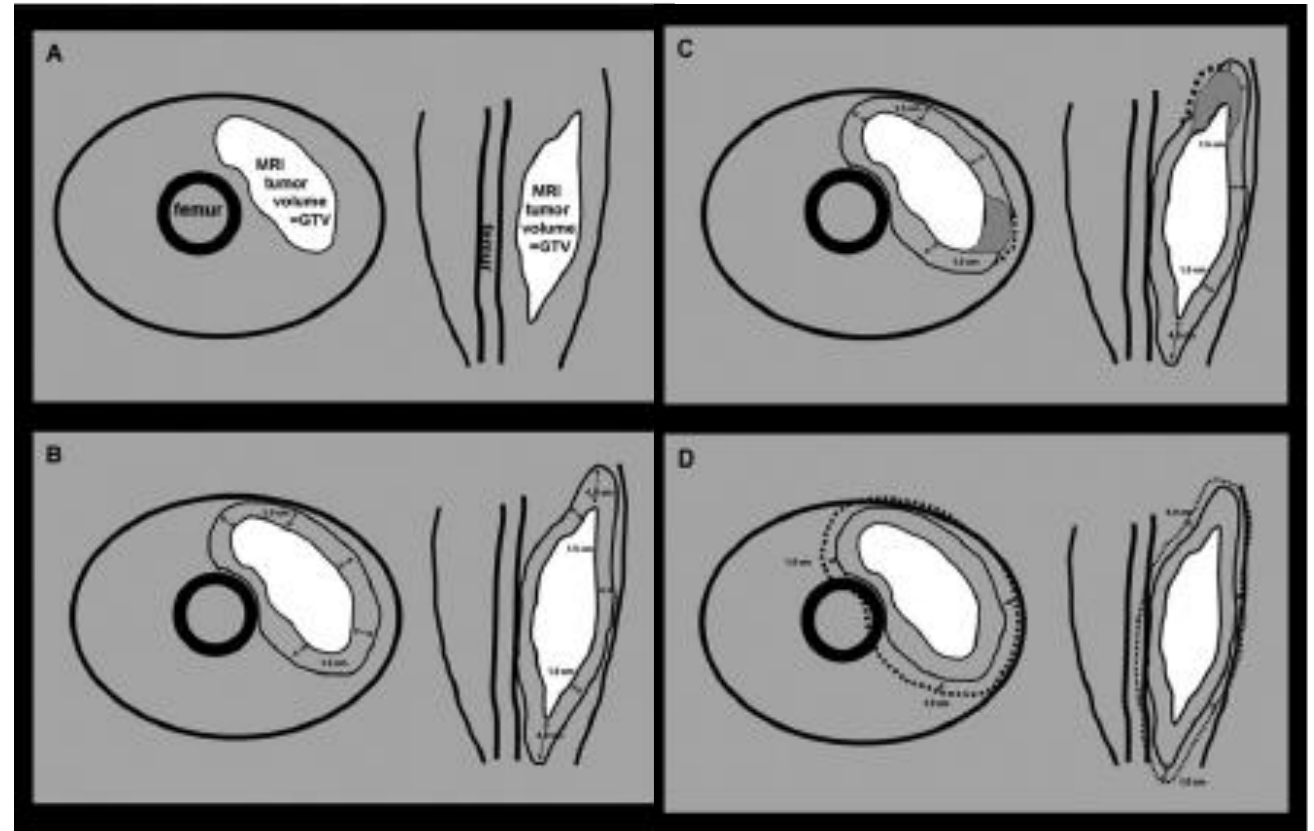
Total dose: 60-68 Gy (1.8-2 Gy/fx)

\*Negative margins: 64 Gy (60-66 Gy)

\*Positive margins: 66-68 Gy



- GTV: From T1 contrast images
- CTV: Along direction of muscle fibers, path of least resistance, anatomically constrained (bone, compartment, etc.)
  - Longitudinal: 3-4 cm
  - Radial: 1.5 cm
  - CTV should include all peritumoral edema (T2 image)
- PTV: 0.5 – 1.0 cm



## Significant Reduction of Late Toxicities in Patients With Extremity Sarcoma Treated With Image-Guided Radiation Therapy to a Reduced Target Volume: Results of Radiation Therapy Oncology Group RTOG-0630 Trial

*Dian Wang, Qiang Zhang, Burton L. Eisenberg, John M. Kane, X. Allen Li, David Lucas, Ivy A. Petersen, Thomas F. DeLaney, Carolyn R. Freeman, Steven E. Finkelstein, Ying J. Hitchcock, Manpreet Bedi, Anurag K. Singh, George Dundas, and David G. Kirsch*

- 79 pts
- median f.-u. 3.6 years
- IMRT 75%
- 5 LR - all in field
- 2yr late toxicities: 10.5% at least one grade 2 toxicity vs. 37% of pts inbCAN-NCIC-SR2: Phase III Randomized Study of Pre- vs Postoperative Radiotherapy in Curable Extremity Soft Tissue Sarcoma) trial receiving preop. RT without IGRT (P= 0.001)

-> sign. reduction of late toxicities  
-> long-term outcome awaited

GTV = MRI T1 plus contrast images.

CTV GTV & adjacent tissue at risk for microscopic extension

- intermediate - high-grade tumors  $\geq 8$  cm

CTV = GTV + 3 cm margins in the longitudinally to include edema (MRI T2) & radially 1.5 cm

- low-grade tumors or  $< 8$  cm

CTV = GTV + 2 cm margins longitudinally & radially 1 cm

- CTV expanded to cover suspicious edema & constrained by anatomic barriers, including fascia, bone, or compartment

PTV = CTV + 5 mm

Radiation avoidance structures:

- longitudinal strip of skin and subcutaneous tissue of an extremity  $\leq 50\%$  received 20 Gy
- no bolus
- $<50\%$  of a weight-bearing bone within the radiation field received 50 Gy except when the tumor invaded bone, circumferential involvement of tumor around more than a quarter of the bone, or when the bone was to be resected at surgery

## • Initial Volume

- Operative bed
- Fuse preop MRI with CT
- Postoperative changes, surgical clips, scar, and drain sites

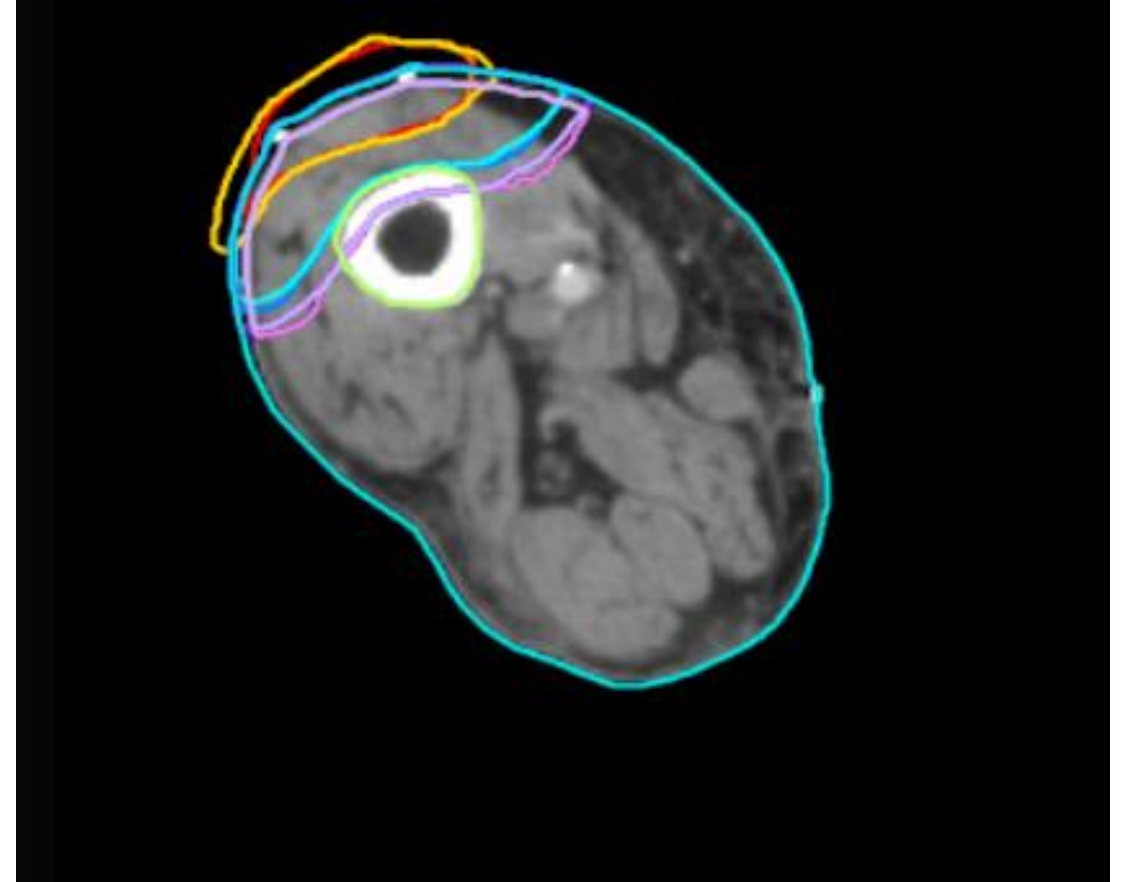
## • CTV

- Longitudinal: 3-4 cm
- Radial: 1.5 cm

## • Boost Volume

- Longitudinal: 2 cm
- Radial: 1.5 cm

## • PTV: 0.5 – 1.0 cm



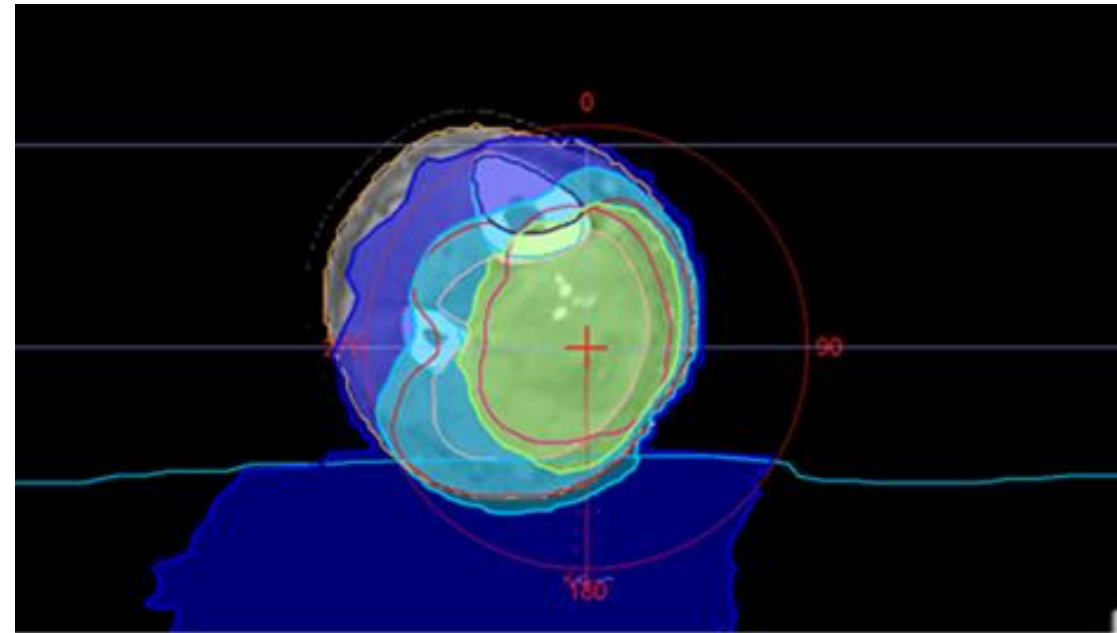
- 3D and IMRT used
- Important to spare strip of skin
- Femur: to lower risk of path. fx and periosteal stripping
  - mean dose <37Gy, V40<64%, max dose <59Gy (Dickie et al IJROBP 2009)
  - limit slices of 50Gy encompassing entire femur (Bishop et al PRO 2016)
- Joint:  
V50 <50% to preserve synovial function

## IMRT advantages

- Decrease dose to normal tissues (bone, soft tissue)
- Increase conformity

## IMRT disadvantages

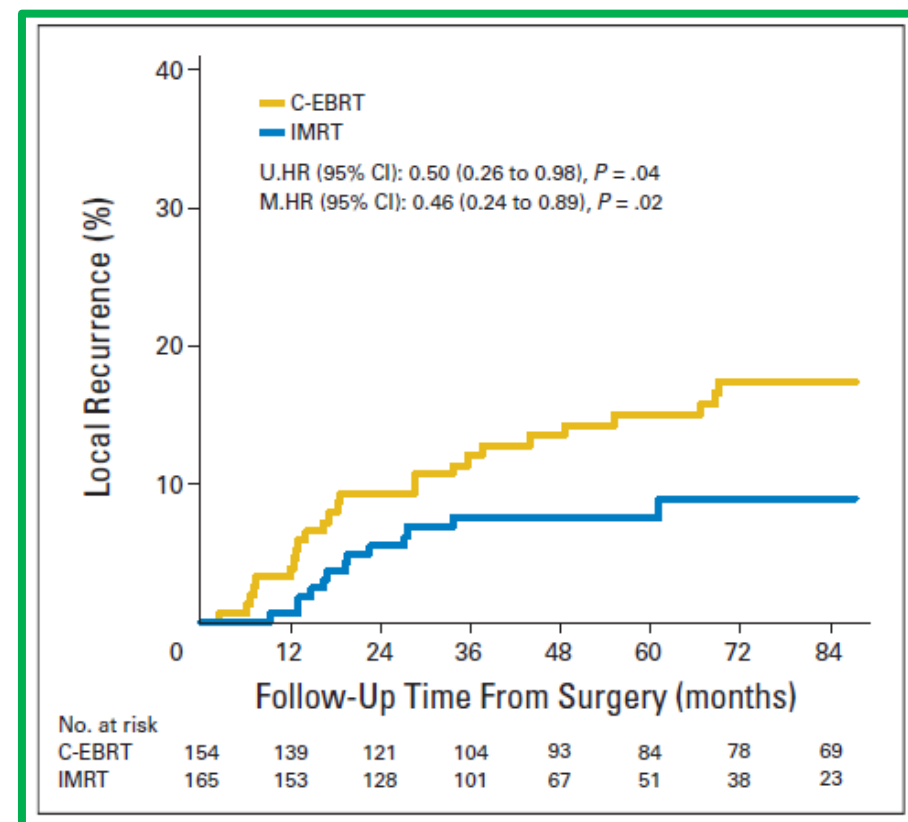
- Higher dose to full circumference of limb
- Cost
- Potential dose to other parts of body (head with proximal upper extremity STS treatment)
- Proximal thigh tumors - IMRT advantageous (spare genitals)



## Comparison of Local Recurrence With Conventional and Intensity-Modulated Radiation Therapy for Primary Soft-Tissue Sarcomas of the Extremity

Michael R. Folkert, Samuel Singer, Murray F. Brennan, Deborah Kuk, Li-Xuan Qin, Wendy K. Kobayashi, Aimee M. Crago, and Kaled M. Alekhtiar

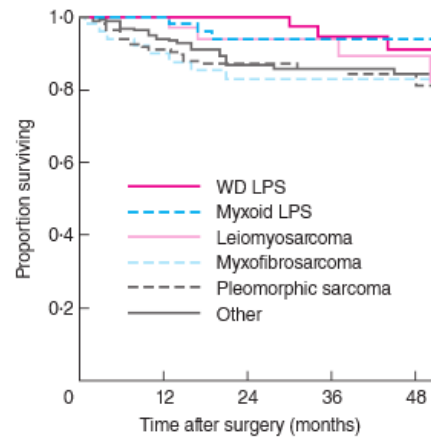
- 319 pts with ary nonmetastatic extremity STS
- limb-sparing surgery + adj. RT
- cEBRT (154 pts) and IMRT (165 pts)
- median f.-u. 58 months
- MVA: IMRT = sign. independent predictor of reduced LR (hazard ratio = 0.46; 95% CI, 0.24 to 0.89; P = .02).



# Patterns of disease relapse in primary extremity soft-tissue sarcoma

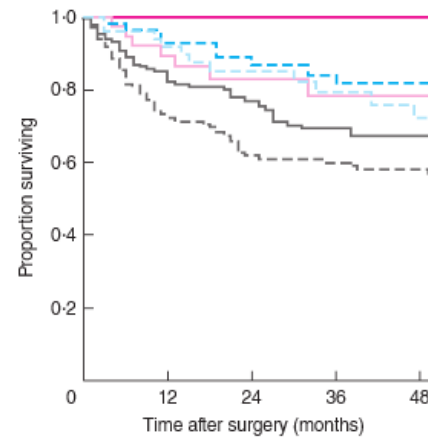
H. G. Smith, N. Memos, J. M. Thomas, M. J. F. Smith, D. C. Strauss and A. J. Hayes

BJS 2016



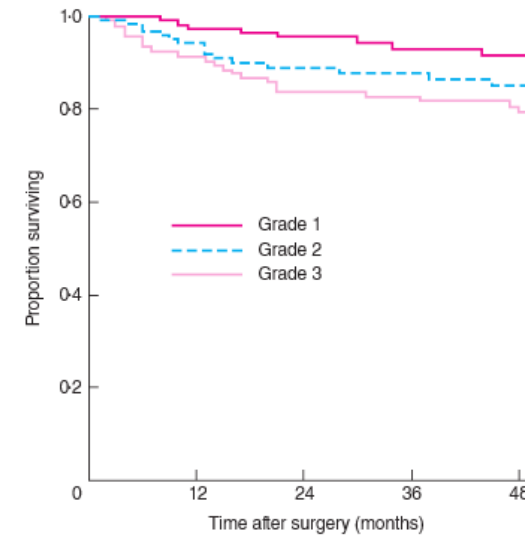
No. at risk	0	12	24	36	48
WD LPS	63	55	41	29	23
Myxoid LPS	62	51	41	37	32
Leiomyosarcoma	39	34	23	19	13
Myxofibrosarcoma	54	40	29	22	16
Pleomorphic sarcoma	169	123	88	64	50
Other	169	131	95	75	56

**a** Local recurrence-free survival



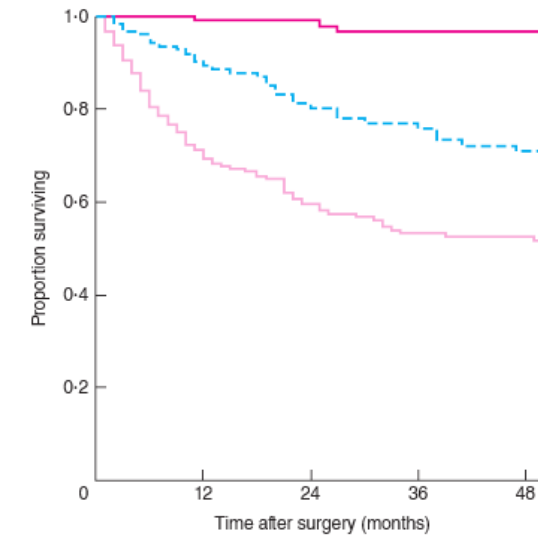
No. at risk	0	12	24	36	48
WD LPS	63	55	41	31	26
Myxoid LPS	62	49	38	33	28
Leiomyosarcoma	39	34	21	16	12
Myxofibrosarcoma	54	42	31	25	19
Pleomorphic sarcoma	169	106	74	61	50
Other	169	126	94	71	54

**b** Distant metastasis-free survival



No. at risk	0	12	24	36	48
Grade 1	132	113	88	66	53
Grade 2	132	110	86	67	49
Grade 3	230	164	106	84	64

**a** Local recurrence-free survival



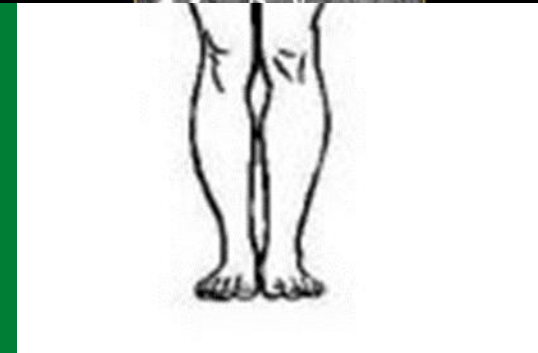
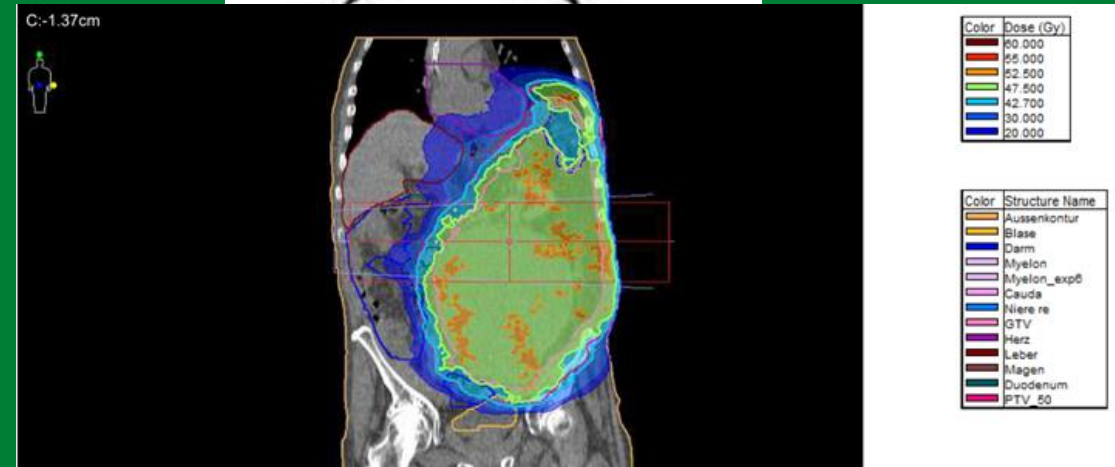
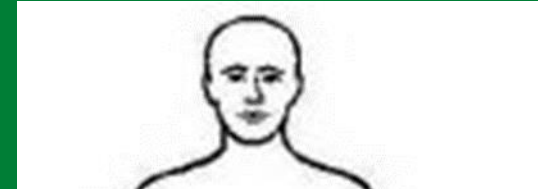
No. at risk	0	12	24	36	48
Grade 1	132	115	90	68	57
Grade 2	132	106	80	66	50
Grade 3	230	140	92	72	60

**b** Distant metastasis-free survival

## Patientselektion für präop. RT abhängig von verschiedenen Faktoren...

- 1) Resektabilität**
- 2) Resektionsrand**
- 3) Erhöhung der lokalen Kontrolle durch RT?**
- 4) Spricht das Sarkom auf eine RT an?**
- 5) Früh- und Spättox.**
- 6) Stellt die postop. Bestrahlung eine sinnvolle Alternative dar?**
- 7) Wundkomplikationen**
- 8) Risiko für Metastasen und Zeit bis zur Metastasierung**





# Retroperitoneal STS

# Overview

- Common histologies:
  - Liposarcoma (60%)
  - Leiomyosarcoma (20%)
- Patterns of failure:
  - Predominately LR: 50-80%
  - Distant recurrence to lung and liver
- Poor outcomes:
  - 5-year overall survival: 30-60%
- Level I evidence
- STRASS Study = 1. randomised study
- retrospektive: Nussbaum et al. Lancet, 2016 & Zhou et al. Arch Surg, 2010
- Contouring: Baldini et al. Red Journal 2015
- Guidelines: Management of primary retroperitoneal sarcoma (RPS) in the adult: a consensus approach from the Trans-Atlantic RPS Working Group. Ann Surg Oncol 2015

## Surgery

- Resectable to R0?
- Proximity to critical organs, major neurovascular structures
- Functional loss

## RT

- Large tumor size
- Normal tissue sensitivities
- Kidney resection plans?/Kidney function status?
- Postoperative RT dose exceeds bowel tolerance
- Patient's GI symptoms

## Treatment Approach

- Surgery = only curative treatment
- Role of RT has been criticized for many years
  - If RT, preop. RT preferred
    - Advantages: Tumor identifiable, tumor displaces bowel, margin improvement, lower radiation dose (50 Gy)
- Postoperative RT: Discouraged
  - Rarely can achieve adequate therapeutic dose (60-66 Gy) because bowel falls into treatment area, normal tissue dose constraints below prescription dose, higher GI toxicity

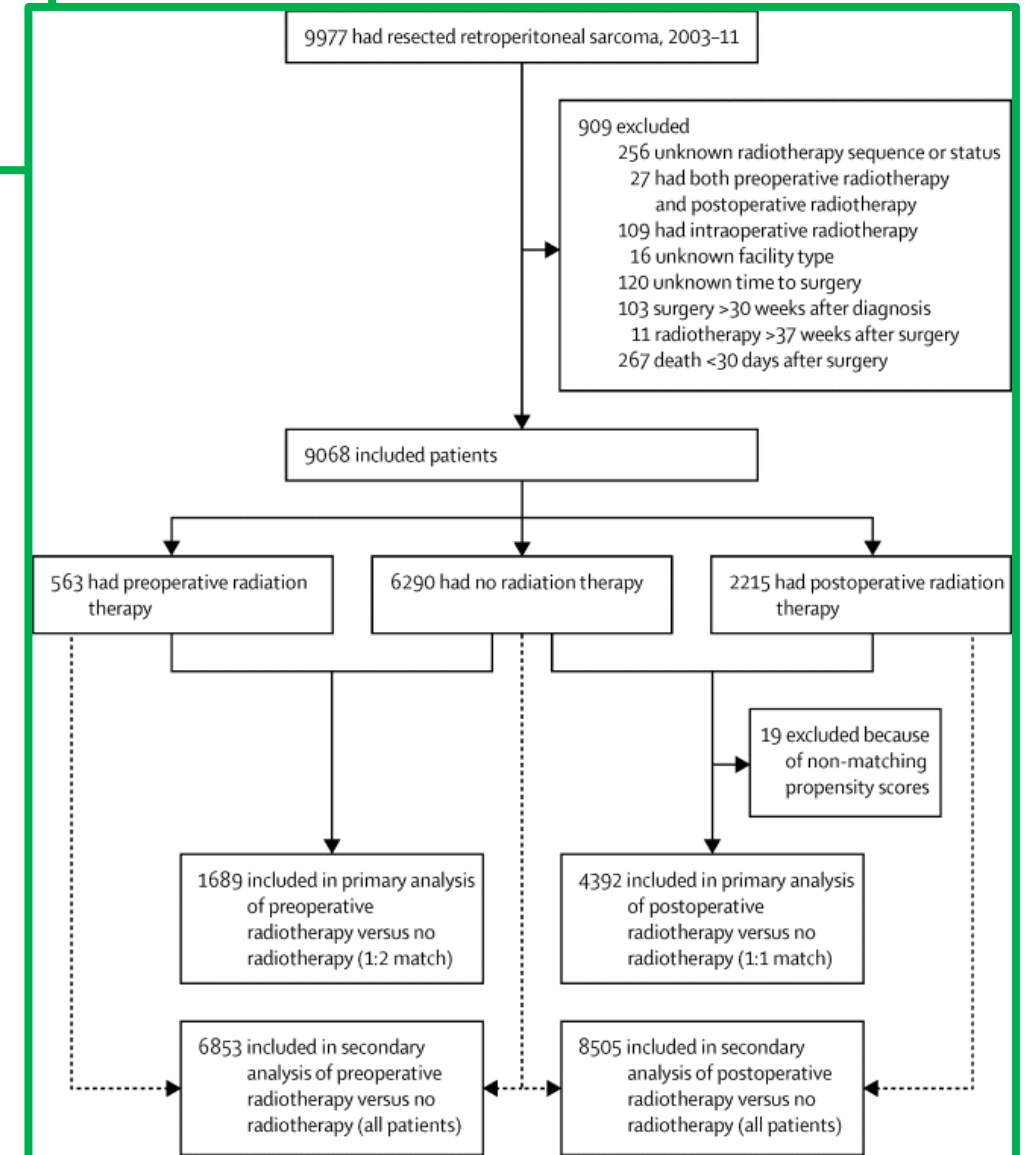


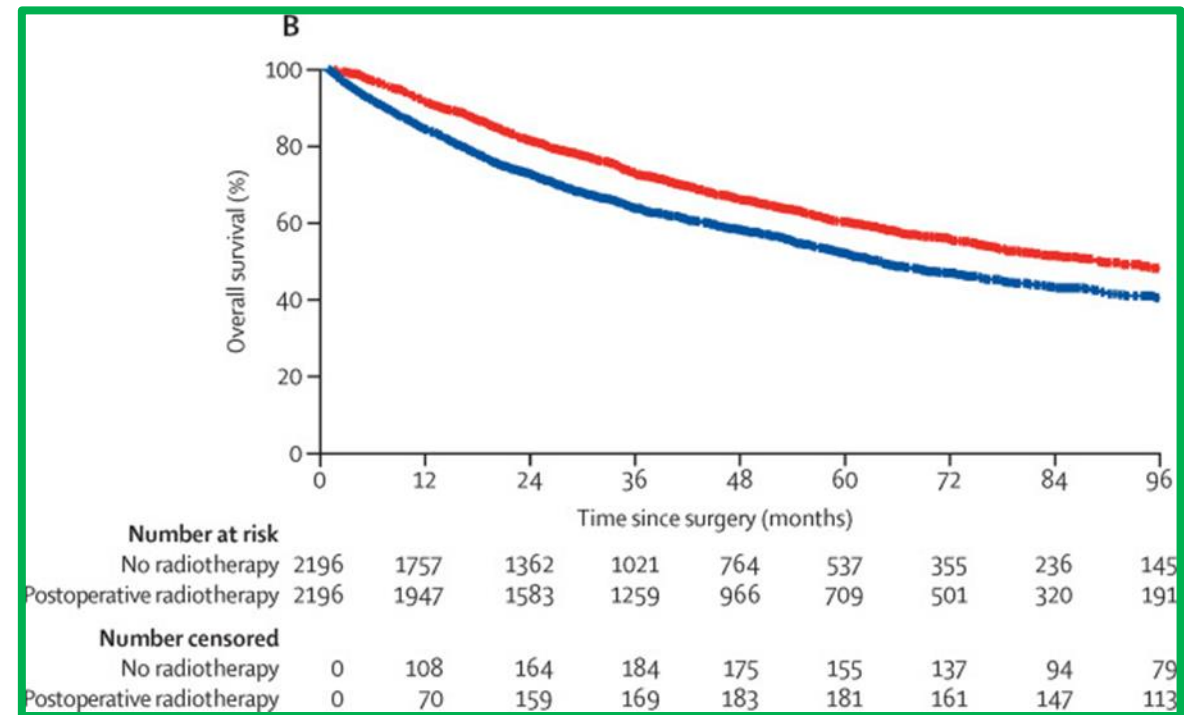
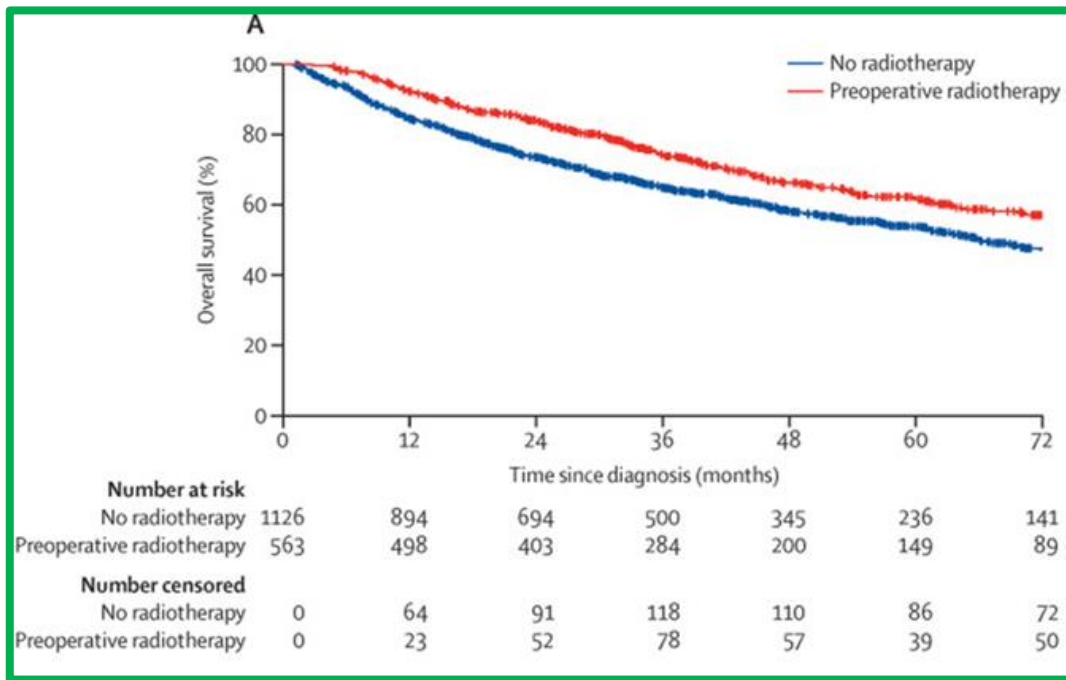
# Preoperative or postoperative radiotherapy versus surgery alone for retroperitoneal sarcoma: a case-control, propensity score-matched analysis of a nationwide clinical oncology database

Daniel P Nussbaum, Christel N Rushing, Whitney O Lane, Diana M Cardona, David G Kirsch, Bercedis L Peterson, Dan G Blazer 3rd

Lancet 2016

- National Cancer Data Base
- 2003 - 2011
- 9068 pat.: 563 pat. preop. RT, 2215 postop. RT, & 6290 sx alone





- Median f.-u.: 42 months preop RT vs. 43 sx alone
- Median OS: 110 months preop RT vs. 66 sx alone
- Median f.-u.: 54 months postop RT vs. 47 sx alone
- Median OS: 89 months postop RT vs. 64 sx alone
- Preop. RT (HR 0.70, 95% CI 0.59-0.82;  $p < 0.0001$ ) and postop. RT (HR 0.78, 0.71-0.85;  $p < 0.0001$ ) sign. associated with improved OS compared with sx alone!

	Preoperative radiotherapy vs no radiotherapy	Postoperative radiotherapy vs no radiotherapy
Use of radiotherapy	0.67 (0.57-0.78); p<0.0001	0.77 (0.71-0.83); p<0.0001
Age per 5 years	1.15 (1.13-1.17); p<0.0001	1.14 (1.12-1.15); p<0.0001
Male sex	1.11 (1.02-1.20); p=0.013	1.11 (1.03-1.19); p=0.0069
Charlson/Deyo comorbidity score		
0	1	1
1	1.22 (1.10-1.34); p=0.0001	1.20 (1.09-1.31); p=0.0002
≥2	1.70 (1.44-2.02); p<0.0001	1.61 (1.38-1.88); p<0.0001
Income above median*	0.91 (0.84-0.98); p=0.015	0.88 (0.82-0.95); p=0.0004
Patient was insured	0.76 (0.59-0.97); p=0.025	0.75 (0.61-0.92); p=0.0068
Tumour size per 5 cm	1.07 (1.05-1.08); p<0.0001	1.06 (1.05-1.07); p<0.0001
Histology		
Leiomyosarcoma	1	1
Low-grade liposarcoma	0.56 (0.49-0.65); p<0.0001	0.55 (0.48-0.63); p<0.0001
Intermediate-grade liposarcoma	0.78 (0.64-0.95); p=0.015	0.78 (0.65-0.93); p=0.0058
High-grade liposarcoma	0.90 (0.80-1.02); p=0.11	0.89 (0.80-0.99); p=0.038
Haemangiosarcoma	2.02 (1.49-2.75); p<0.0001	2.10 (1.62-2.72); p<0.0001
Malignant fibrous histiocytoma	1.25 (1.06-1.48); p=0.0075	1.23 (1.07-1.42); p=0.0041
Malignant peripheral nerve sheath tumour	1.77 (1.29-2.43); p=0.0005	1.78 (1.41-2.27); p<0.0001
Fibrosarcoma	0.70 (0.49-0.98); p=0.040	0.87 (0.65-1.17); p=0.35
Spindle cell sarcoma	1.23 (1.00-1.51); p=0.050	1.34 (1.11-1.61); p=0.0023
Giant cell sarcoma	1.31 (1.08-1.59); p=0.0073	1.50 (1.26-1.78); p<0.0001
Sarcoma, not otherwise specified	1.16 (0.98-1.36); p=0.088	1.21 (1.05-1.41); p=0.011
Grade		
1	1	1
2	1.20 (1.04-1.40); p=0.017	1.17 (0.99-1.38); p=0.071
3	2.16 (1.92-2.44); p<0.0001	2.13 (1.86-2.43); p<0.0001
Extent of resection		
Radical	–	1
Local excision	–	0.95 (0.87-1.04); p=0.28
Simple resection	–	1.12 (1.03-1.22); p=0.011
Positive surgical margins	NA	1.51 (1.39-1.64); p<0.0001

Data are HR (95% CI); p value, unless otherwise specified. NA=not applicable (variable not included in initial model).

\*Income was based on zip code of patient residence at time of diagnosis.

**Table 3: Hazard ratios for predictors of overall survival (unmatched complete datasets)**

## Matched pair analysis :-)



Ozzy Osbourne

- Male
- Born in 1948
- Raised in the UK
- Married twice
- Lives in a castle
- Wealthy & famous



Charles III

- Male
- Born in 1948
- Raised in the UK
- Married twice
- Lives in a castle
- Wealthy & famous



# Variability in Patterns of Recurrence After Resection of Primary Retroperitoneal Sarcoma (RPS)

*A Report on 1007 Patients From the Multi-institutional Collaborative RPS Working Group*

Alessandro Gronchi, MD,\* Dirk C. Strauss, MD,† Rosalba Miceli, MD, PhD,‡ Sylvie Bonvalot, MD, PhD,§ Carol J. Swallow, MD,¶ Peter Hohenberger, MD,|| Frits Van Coevorden, MD,\*\* Piotr Rutkowski, MD,†† Dario Callegaro, MD,\* Andrew J. Hayes, MD, PhD,† Charles Honoré, MD,§ Mark Fairweather, MD,‡‡ Amanda Cannell, MD,¶¶ Jens Jakob, MD,|| Rick L. Haas, MD,§§ Milena Szacht, MD,†† Marco Fiore, MD,\* Paolo G. Casali, MD,¶¶ Raphael E. Pollock, MD, PhD,||| and Chandrajit P. Raut, MD††

Ann surg 2016

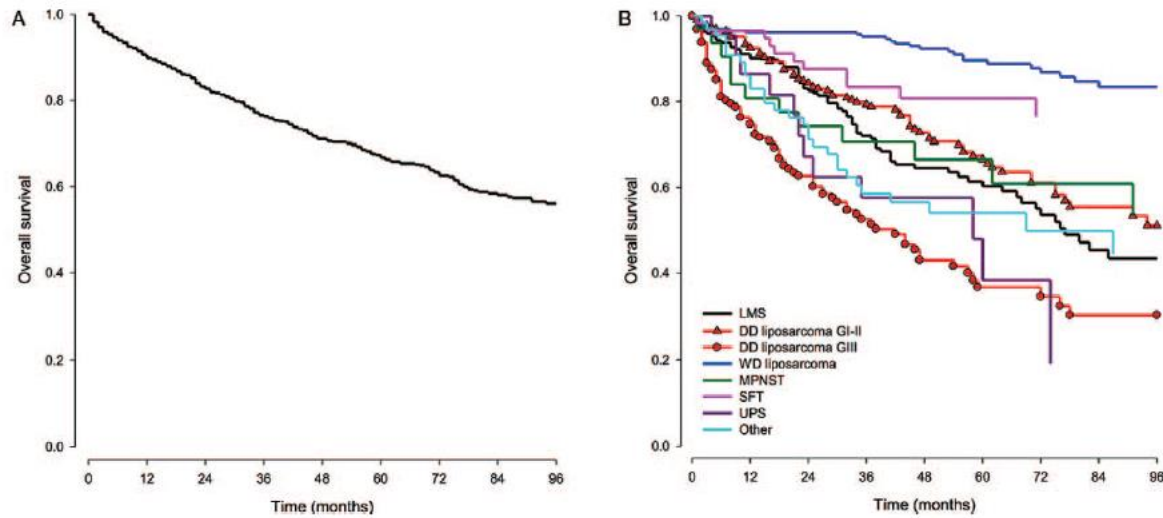
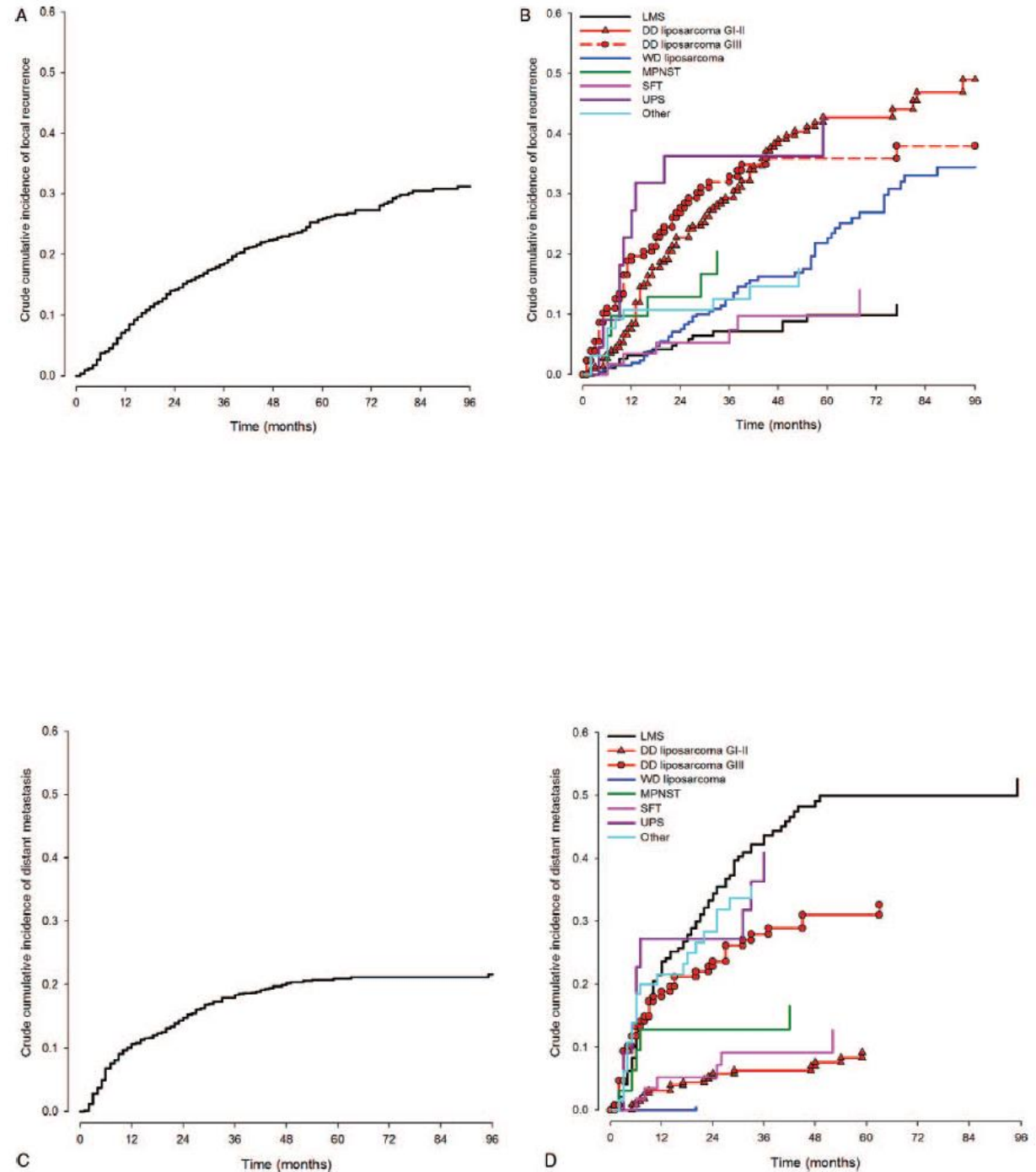


FIGURE 1. Panel A, Overall survival curve in the whole series. Panel B, Overall survival curves according to histological subtype.



Preoperative radiotherapy plus surgery versus surgery alone  
for patients with primary retroperitoneal sarcoma  
(EORTC-62092: STRASS): a multicentre, open-label,  
randomised, phase 3 trial



Sylvie Bonvalot, Alessandro Gronchi, Cécile Le Péchoux, Carol J Swallow, Dirk Strauss, Pierre Meeus, Frits van Coevorden, Stephan Stoldt, Eberhard Stoeckle, Piotr Rutkowski, Marco Rastrelli, Chandrajit P Raut, Daphne Hompes, Antonino De Paoli, Claudia Sangalli, Charles Honoré, Peter Chung, Aisha Miah, Jean Yves Bloy, Marco Fiore, Jean-Jacques Stelmes, Angelo P Dei Tos, Elizabeth H Baldini, Saskia Litière, Sandrine Marreaud, Hans Gelderblom, Rick L Haas

- 266 pts, primary diagnosis
- 74% liposarcoma

RANDOMISATION

- Sx only vs. preop. RT + sx

- Median dose: 50.4 Gy

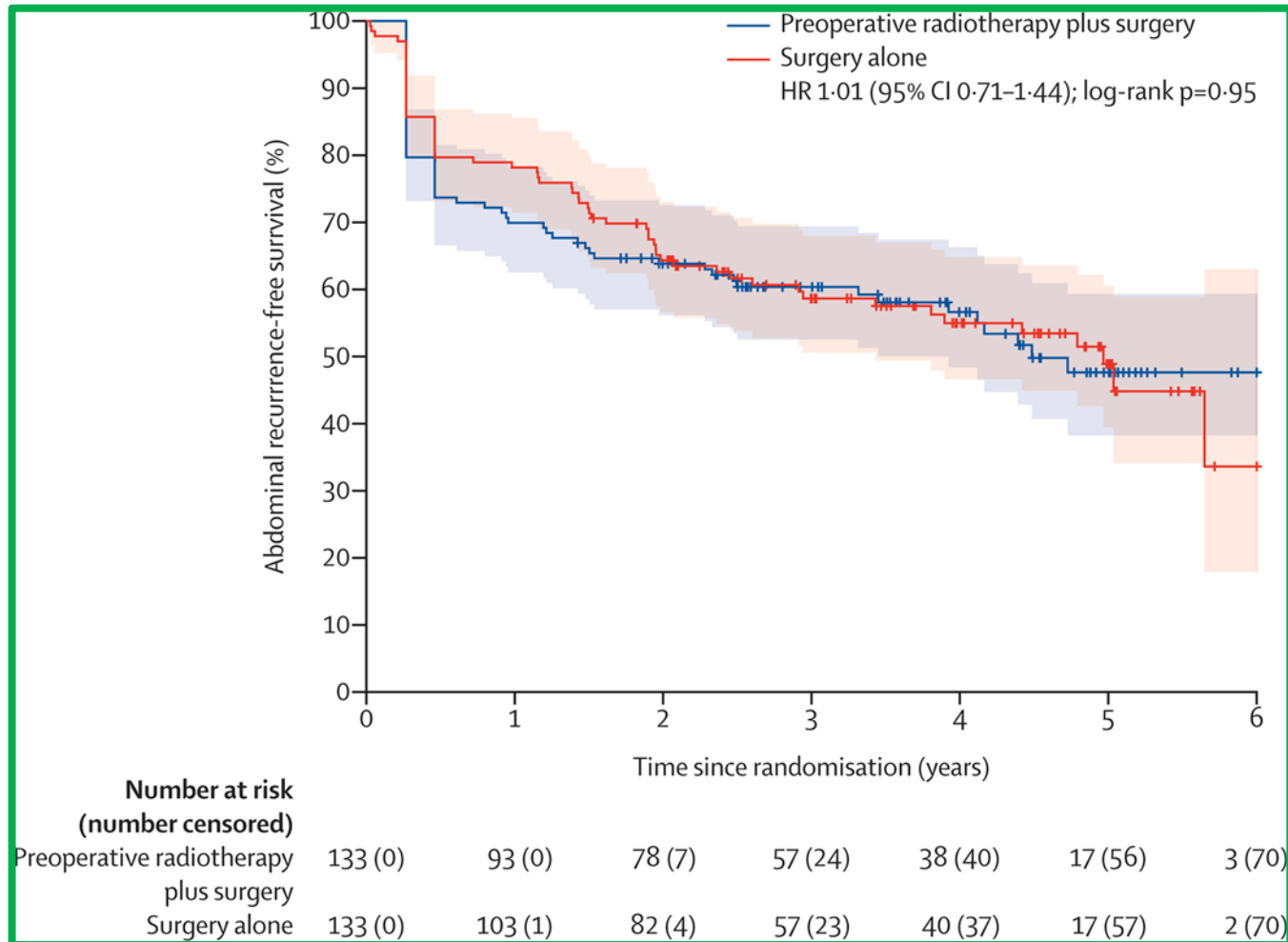
Prim. endpoint: Abdominal recurrence free survival (ARFS)

- Progressive disease
- Tumor or patient becomes inoperable during RT
- Macroscopically incomplete resection
- Peritoneal sarcomatosis at time of surgery
- LR

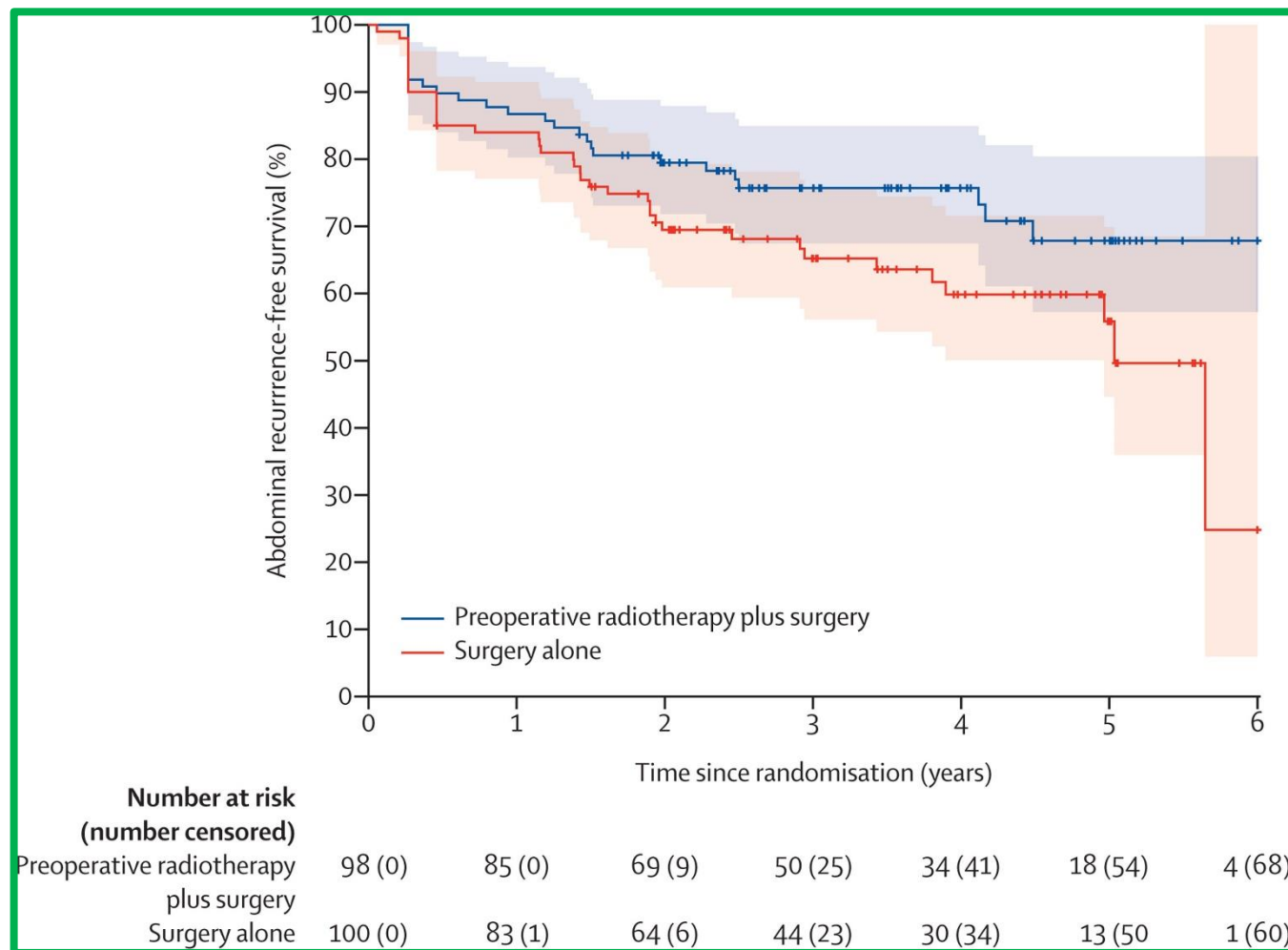
	Surgery alone group (n=133)	Preoperative radiotherapy plus surgery group (n=133)
Age (years)	61 (53-67)	61 (52-68)
Sex		
Female	66 (50%)	62 (47%)
Male	67 (50%)	71 (53%)
WHO performance status		
0	100 (75%)	110 (83%)
1	33 (25%)	22 (17%)
2	0	1 (<1%)
Pre-operation biopsy		
Imaging-guided	123 (92%)	119 (89%)
Surgical	10 (8%)	12 (9%)
Missing	0	2 (2%)
Tumour size (mm)	167 (124-210)	160 (111-210)
Histological subtype		
All liposarcoma subtypes	100 (75%)	98 (74%)
Well-differentiated liposarcoma	42 (32%)	46 (35%)
De-differentiated liposarcoma	54 (41%)	51 (38%)
Other liposarcoma	4 (3%)	1 (<1%)
Leiomyosarcoma	22 (17%)	16 (12%)
Other	11 (8%)	18 (14%)
Data missing	0	1 (<1%)
Tumour grade at biopsy		
Low	43 (32%)	44 (33%)
Intermediate	38 (29%)	47 (35%)
High	19 (14%)	12 (9%)
Not evaluable	21 (16%)	17 (13%)
Data missing	12 (9%)	13 (10%)

Data are median (IQR) or n (%).

**Table 1: Baseline characteristics**



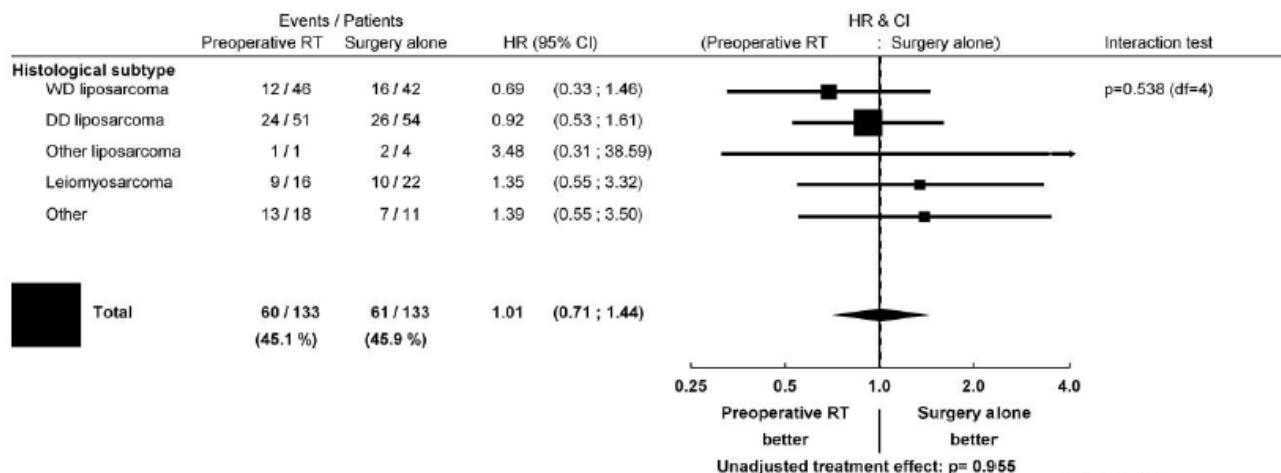
- Median f.-u.: 43.1 months
- ARFS: 61 in sx arm vs. 60 in RT + sx arm
- 3-y. ARFS 58.7% in sx vs. 60.4% in RT + sx arm
- BUT: twice as many local rec. in sx vs. RT + sx arm (39 vs. 17)
- No sign. diff. in MFS 68.2% in sx vs. 68.3% in RT + sx
- No sign. diff. in 5y-OS 79.4% in Op vs. 76.7% in RT + Op



### Pts with liposarcoma

- ARFS: 39 pts with sx vs. 26 pts with RT + sx
- 3-y. ARFS 65.2% in sx vs. 75.7% in RT + sx arm (HR = 0.62, 95% CI 0.38-1.02)
- Local recurrences 30 in sx vs. 11 in RT + sx arm

## Abdominal recurrence free survival (primary)



### ➤ RT benefit:

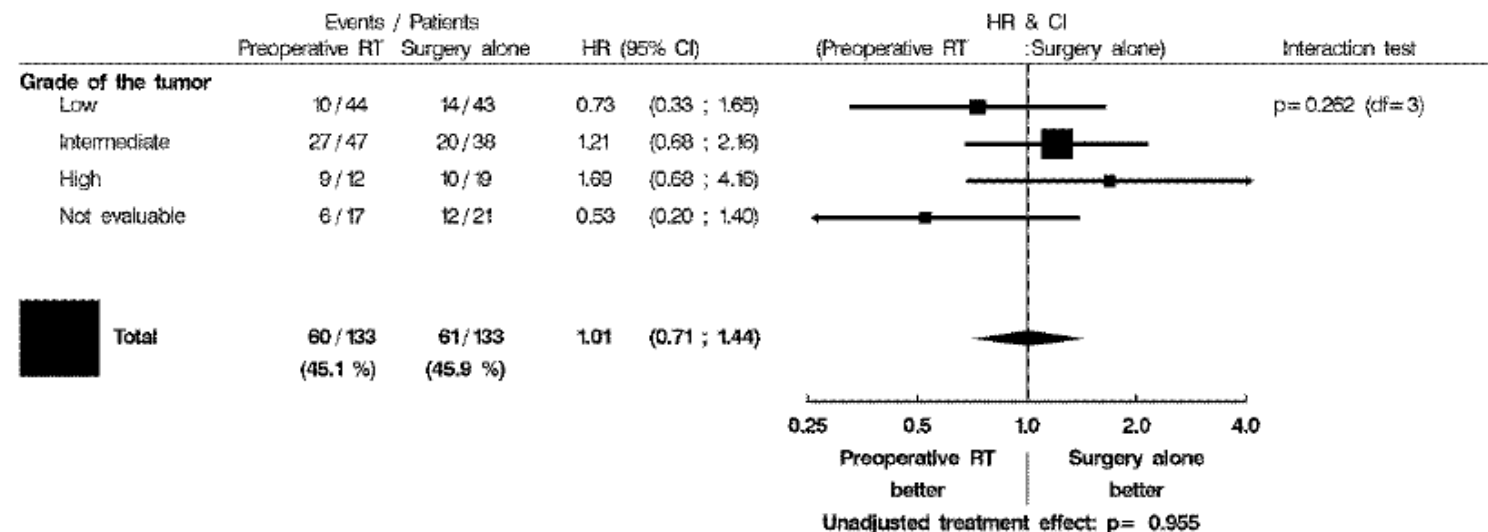
Liposarcome & low grade RPS

### ➤ No RT benefit:

Leiomyosarcoma & high grade RPS

CAVE: unplanned subgroup analysis!!!

## Abdominal recurrence free survival (primary)



## Serious adverse events

- 30 (24%) pts in RT + sx group vs. 13 (10%) pts sx alone group
- One (1%) pat in RT + sx group vs. none in the sx alone group died
  
- Authors' interpretation:
  - *"Preoperative radiotherapy should not be considered as standard of care treatment for retroperitoneal sarcoma."*

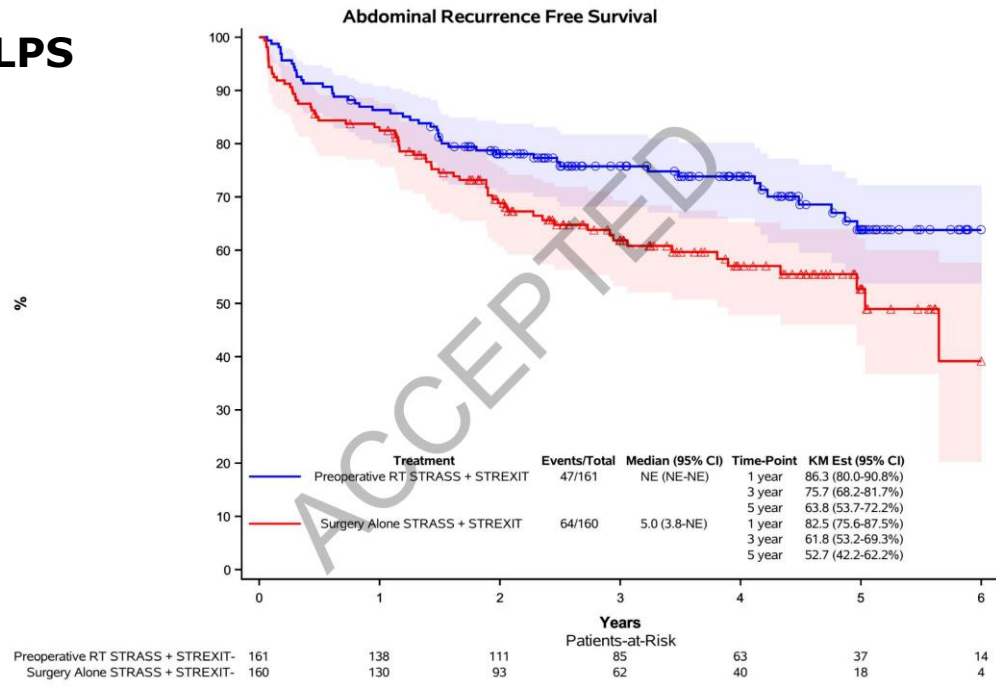


## STRASS vs. STREXIT

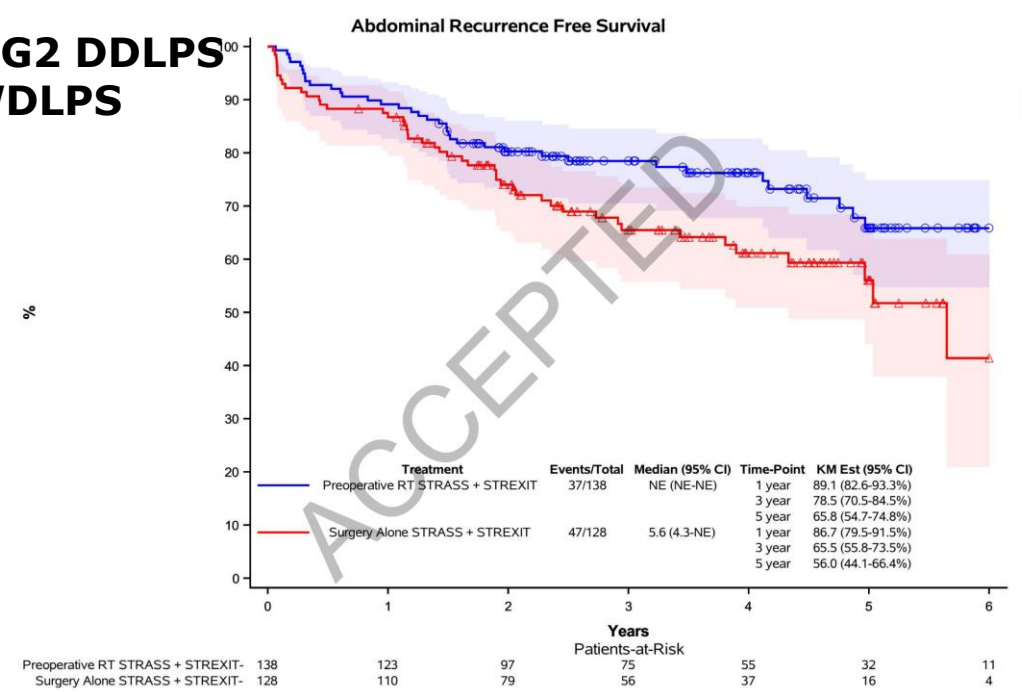
- STRASS 266 pts
- STREXIT 831 pts (727 after excluding pts with preop. CTX, 202 after 1:1 PS-matching)
- RT associated with better ARFS in pts with liposarcoma [N=321, HR, 0.61; 95% CI, 0.42–0.89]
- BENEFIT in pts with well-diff. liposarcoma and G1-2 dediff. liposarcoma (HR, 0.63; 95% CI, 0.40–0.97)
- No benefit in G3 DDLPS and leiomyosarcoma pts
- No association between RT and OS/DMFS



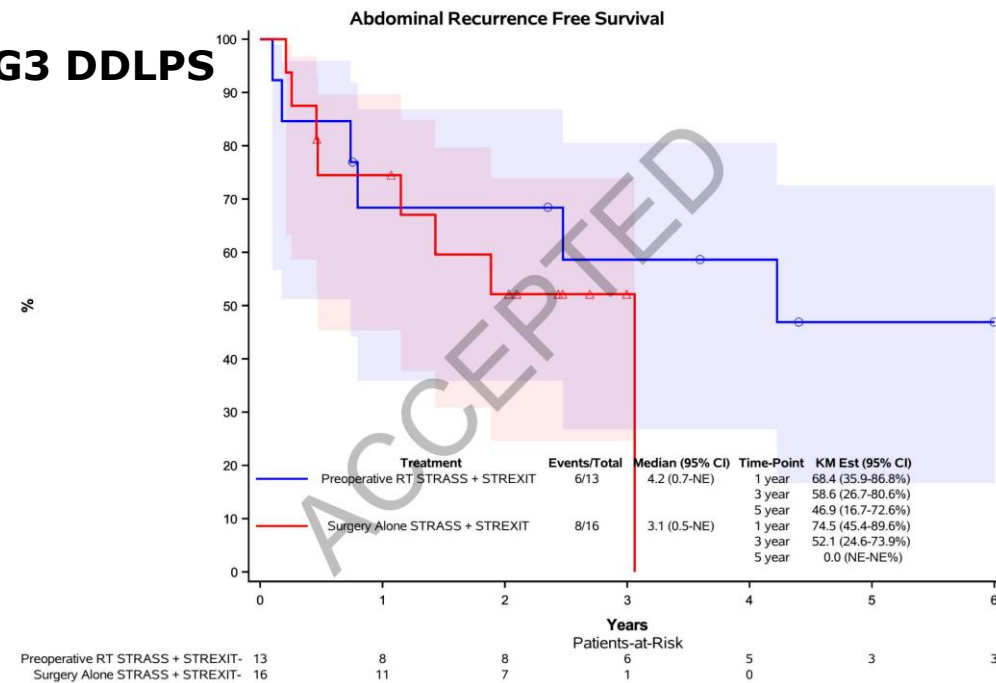
# LPS



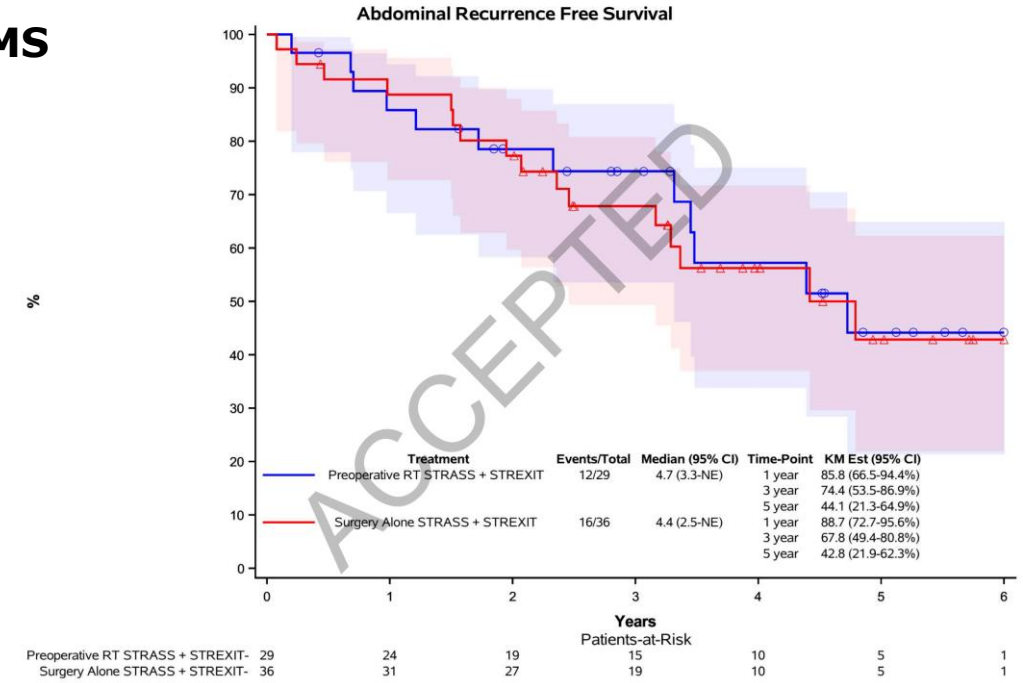
# G1/G2 DDLPS + WDLPS



# G3 DDLPS



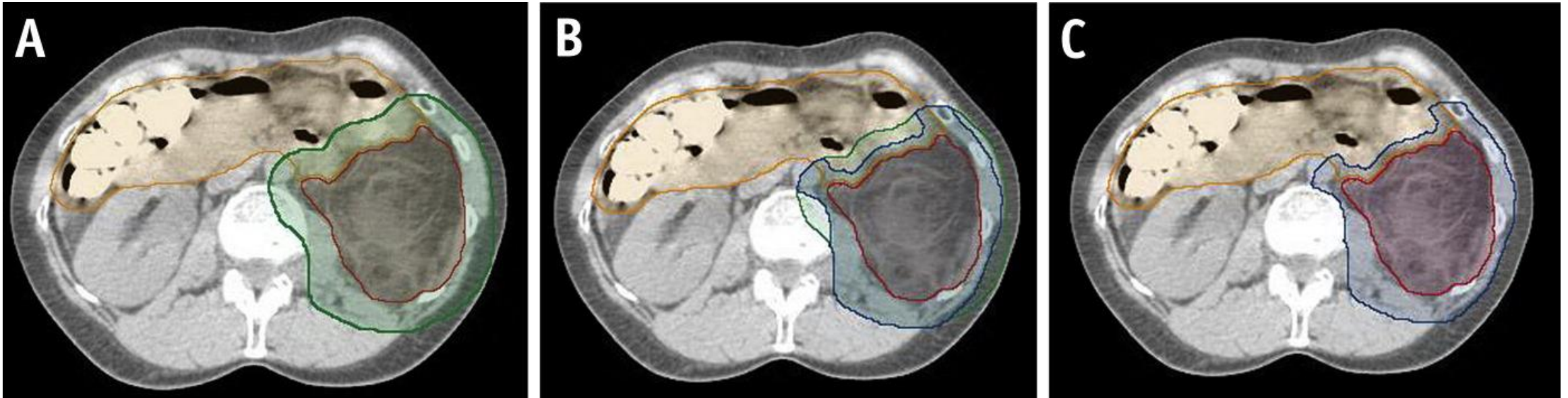
# LMS





# Treatment Guidelines

- IV contrast
- 4D scan for tumors superior to iliac brim
- For psoas muscle invasion, fuse MRI
- iGTV = GTV incorporating 4D motion
- CTV: 1.5 cm longitudinal and radial expansion
- 0 cm expansion at liver, bone, and kidney
- 0.5 cm expansion at bowel interfaces
- If tumor extends into inguinal canal, add 3 cm distally
- PTV: 0.5 -1.2 cm expansion depending on IGRT



- De novo diagnosis
  - Multidisciplinary discussion: Evaluate surgical margins, probability of tumor recurrence
  - Preoperative RT likely beneficial for liposarcoma histology (WDLPS, G1 DDLPS, G2 DDLPS)
- Recurrent diagnosis
  - Consider preoperative RT
- Preoperative RT: 50 Gy / 25 fx or 50.4 Gy / 28 fx
- Consider SIB to high-risk margins

**LMU KLINIKUM**

Gemeinsam. Fürsorglich. Wegweisend.

**Thank you**

**For your attention!**



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