State-of-the-art in local disease

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Disclosure slide

- **Consulting or Advisory Role**
  - ✓PharmaMar, GSK, Novartis, Amgen, Bayer
- **Speakers' Bureau**
  - ✓PharmaMar

AGENDA

1) The role of MTD

2) SURGERY: The mainstay of local treatment

3) ADJUVANT THERAPIES:

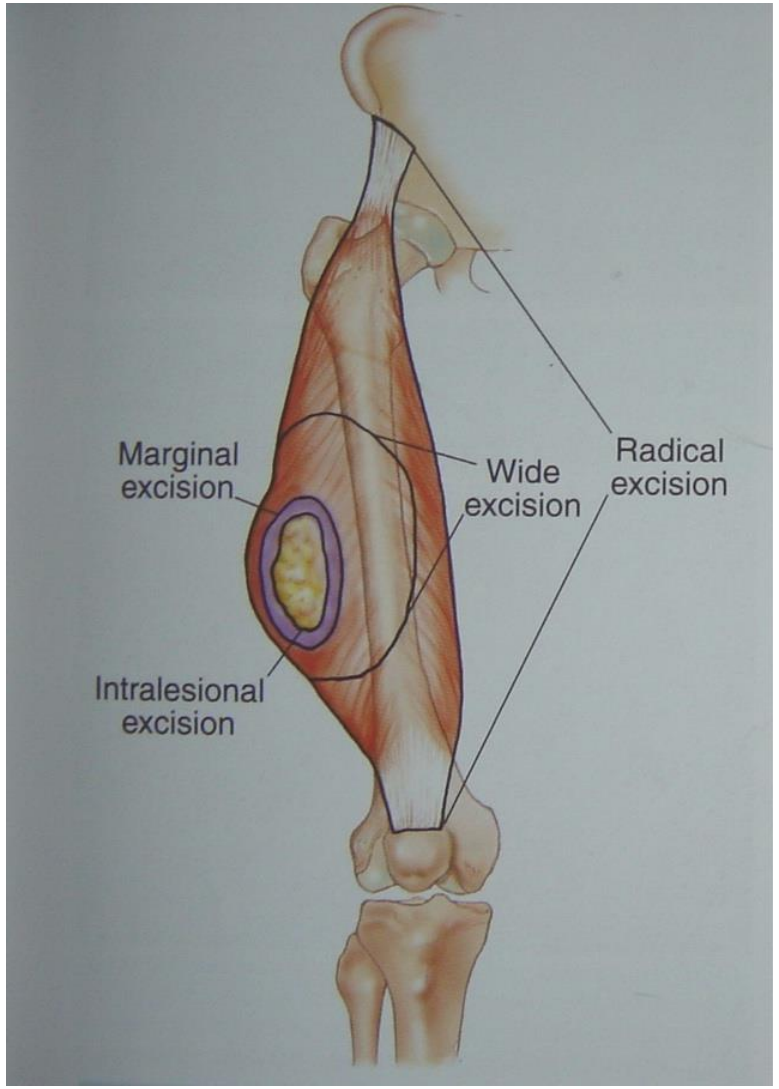
   - RADIATION THERAPY
   - CHEMOTHERAPY

Enneking Classification of Surgical Margins

RESECTABLE

LOCAL RECURRENCE RISK

OPERABLE



LIMB FUNCTION

DISTANT M1 RISK

LONG-TERM EFFECTS

SURGERY: THE THERAPEUTIC MAINSTAY

TERRIBLE LOOP IN REAL LIFE

GP

Referral delayed

GS

Positive Margins

MO

Over-treated

P

RAD

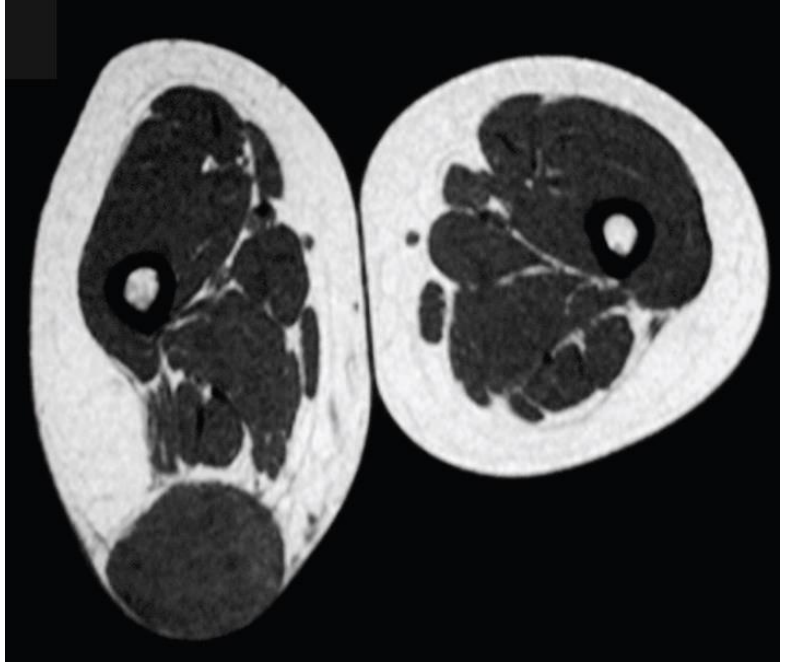
RT

Blind-treated

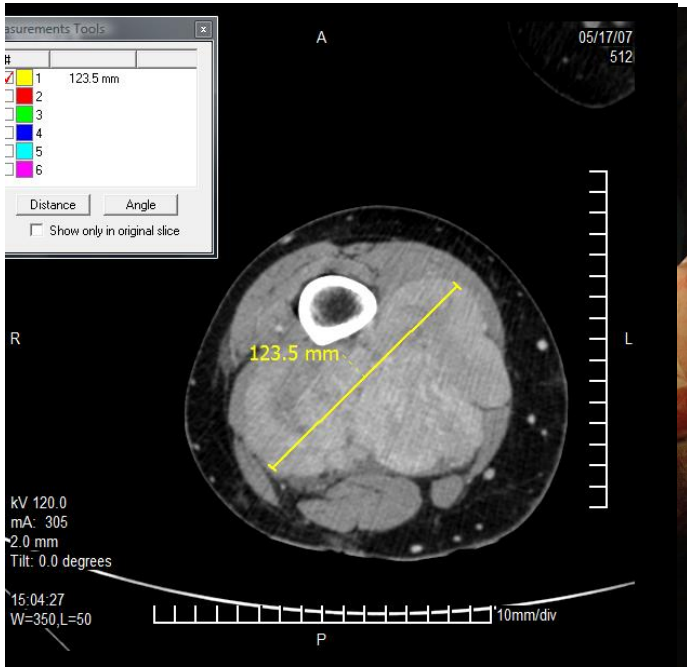
OS

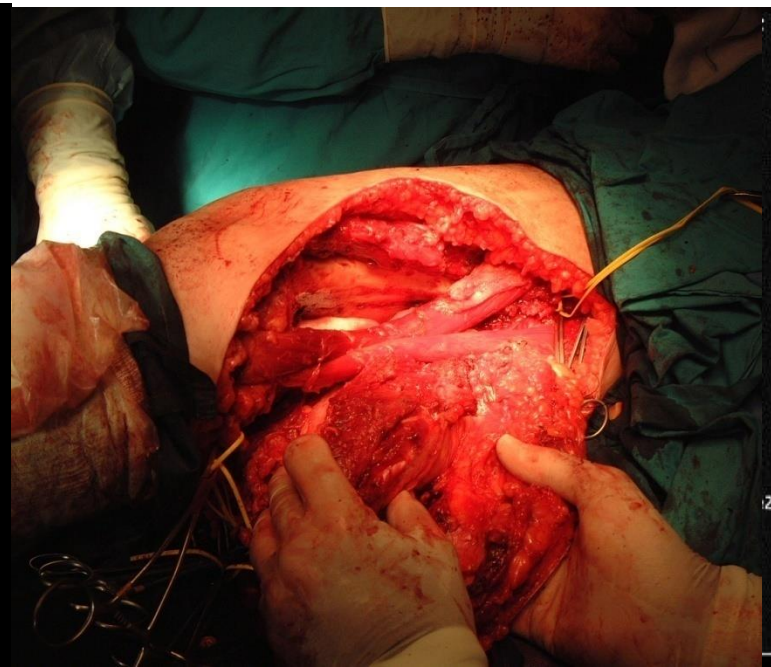
Loss of function

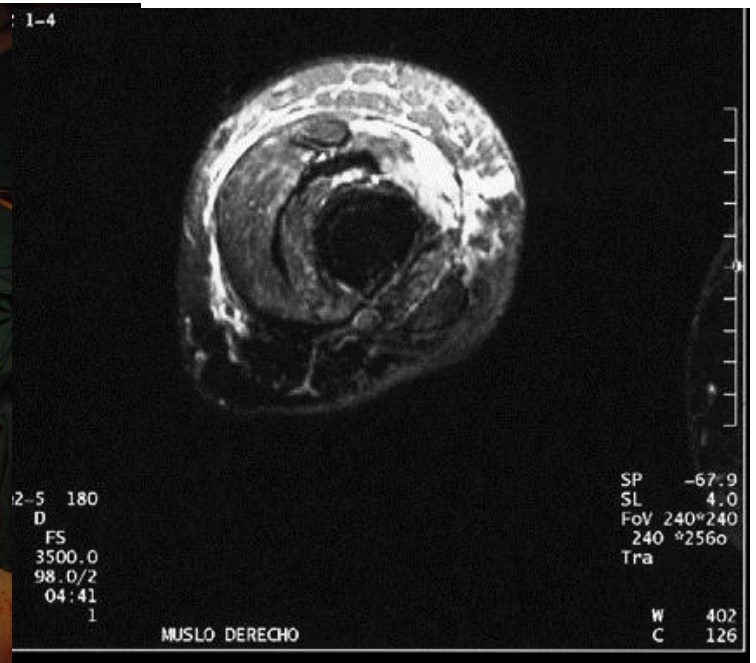
PHISIO



Adequate biopsy: first step of good surgery







Planned surgery: Why not in STS?

Unplanned surgeries

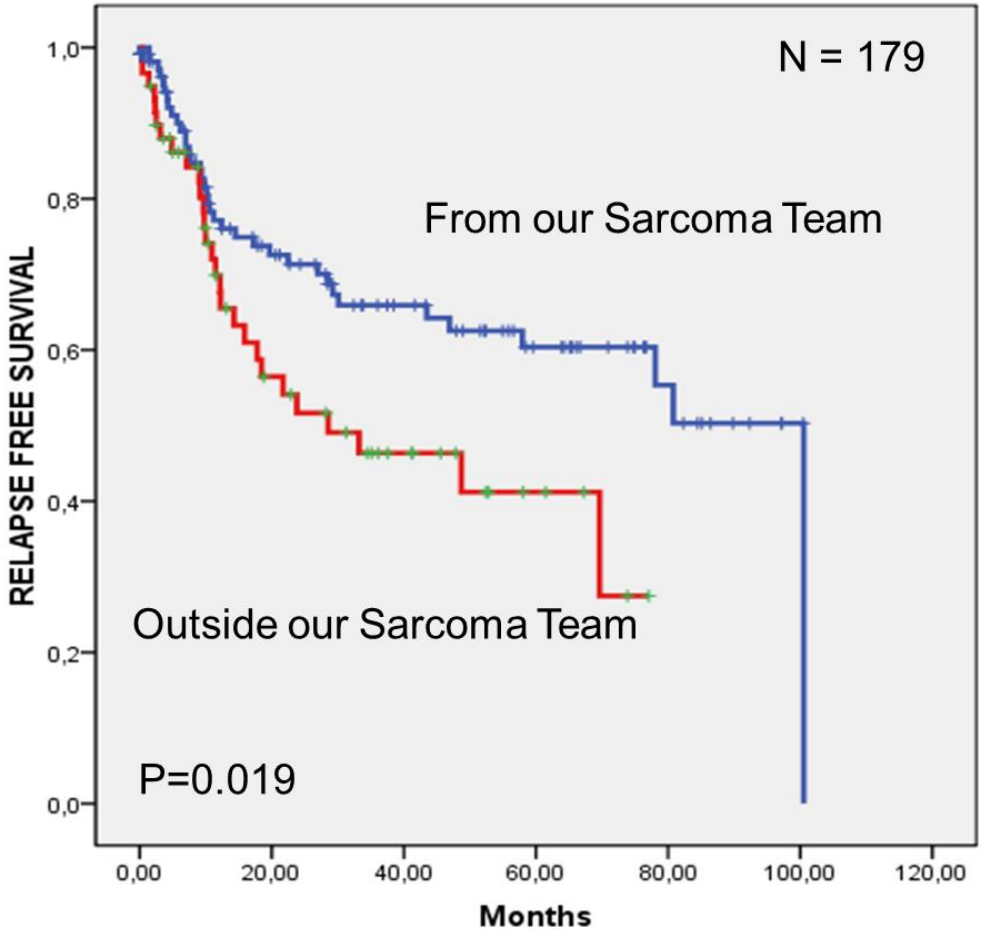
- UNDERESTIMATED
- EXCISIONAL BIOPSY
- INADEQUATE INCISION
- PSEUDOCAPSULE

Alert Signs*

- Recent Growth
- Mass > 5 cm
- Deep (attached mass)

(*) Johnson CJ et al. Clinical features of soft tissue sarcomas. Ann R Coll Surg Engl. 2001;83:203–5.

Origin of biopsy and imaging matters



RFS according to the origin of the biopsy

Preoperative MRI/CT	Negative margins	Positive margins	Total
Yes	72 (77.4%)	21 (22.6%)	93
No	22 (53.7%)	19 (46.3%)	41
Total	94 (70.1%)	40 (29.9%)	134 (100%)

p = 0.006

Correlation between MRI/CT before surgery with surgical margin status

Reference Centers (MTD teams in sarcoma)

Study	Year	Objectives	n	Results	Advise?
Bhanghu et al. (UK)	2004	Specialist Center vs General Hospital	263	RFS 5a: 39% vs 19% OS: HR 0,59 in HRisk	Centralisation improves LC and OS in some.
Paszat et al. (Canada)	2002	Search a surrogate for expertise centers after a population based case series	1467	Risk for die: x1.4 and for amputation x3 if no treated in SC in the first 3 m	Advisable to refer patients with STS within first 3 m
Ray-Coquard et al. (France)	2004	To assess the conformity of medical practice to CG	100	Presurgery MDT and management in SC: predicted conformity and better LC	Treatment strategy within MDT: improves clinical outcome
Bauer et al. (Sweden)	2001	Report from Scandinavian Registry	1851	CT/MRI preS: 35 vs 80% Wide margin: 11 vs 66% LR: 0.7 vs 0.2	Improving outcome with referring policies
Wiklund et al. (Finland)	1996	Compare results after an MDT fo STS	134	LR: 48 vs 13% DFS: 36 vs 69%	Improved results are seen in that institution with that MDT

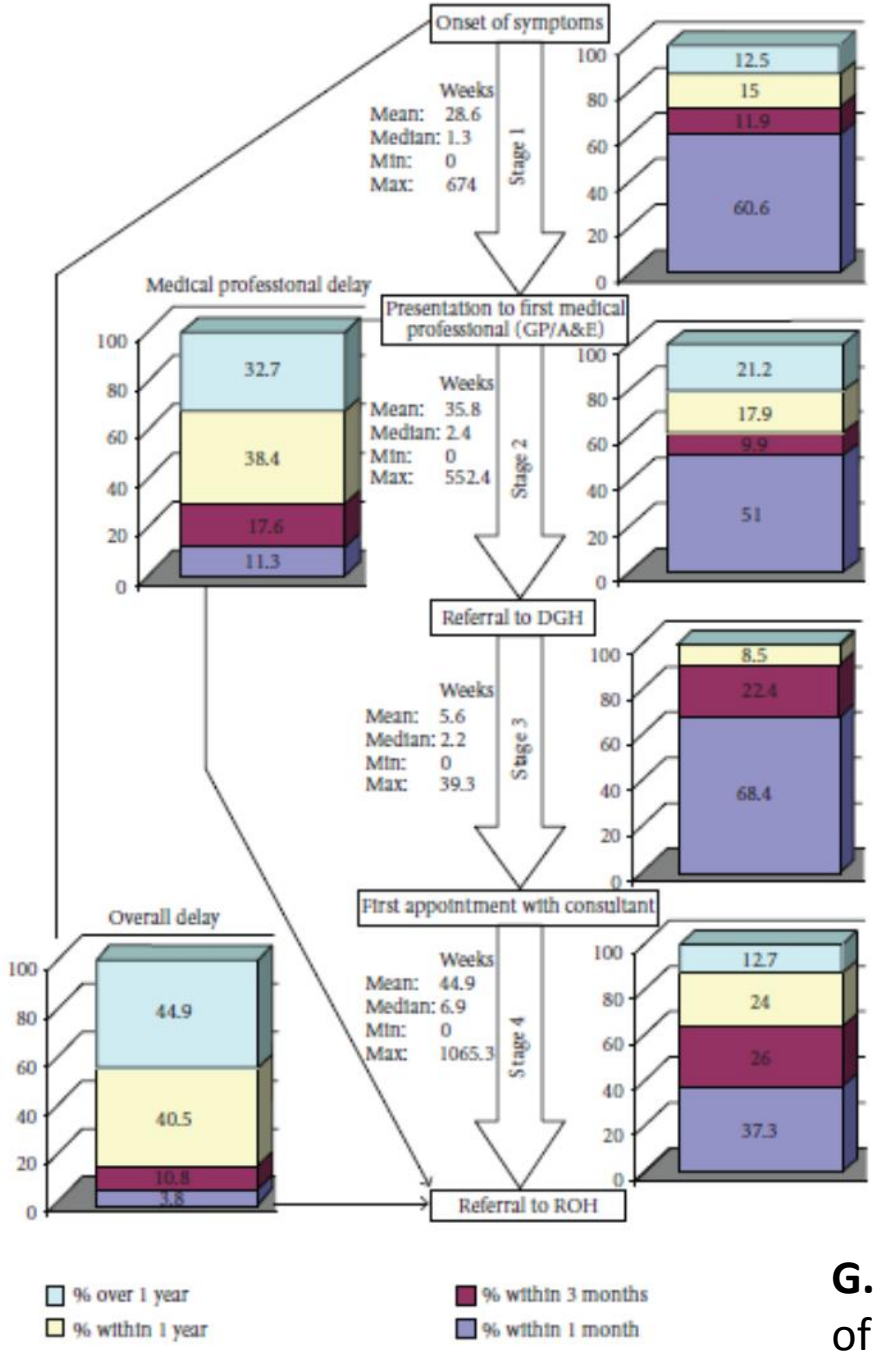


FIGURE 3: Flow chart of delay.

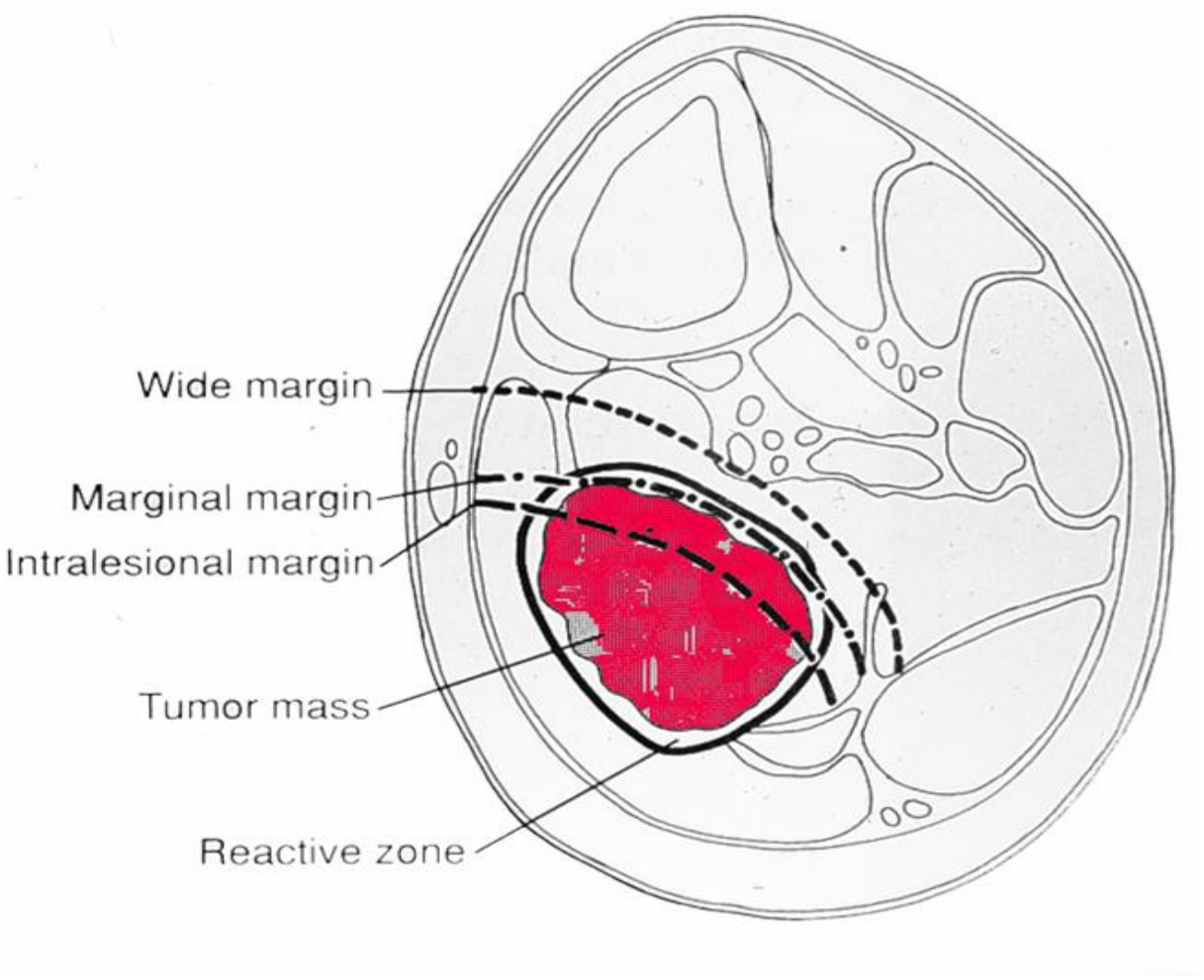
Medical professionals contributed to longest delay

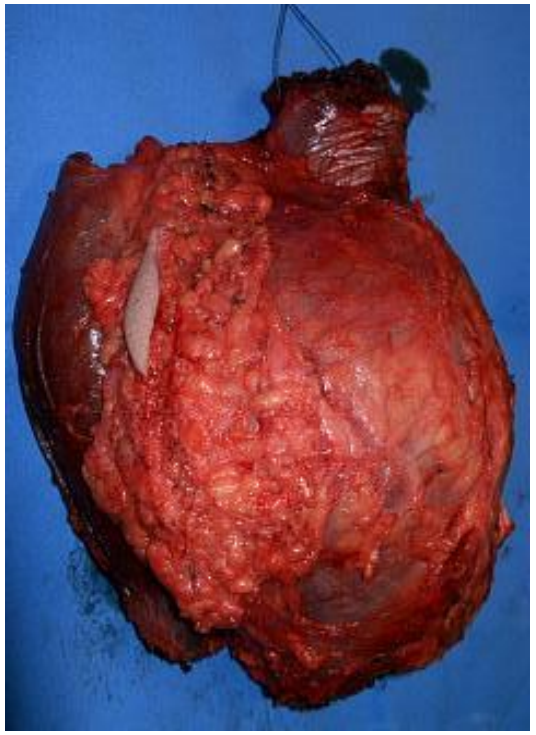
G. D. Johnson, G. Smith, A. Dramis, and R. J. Grimer, "Delays in Referral of Soft Tissue Sarcomas," Sarcoma, vol. 2008, Article ID 378574, 7 pages, 2008. doi:10.1155/2008/378574

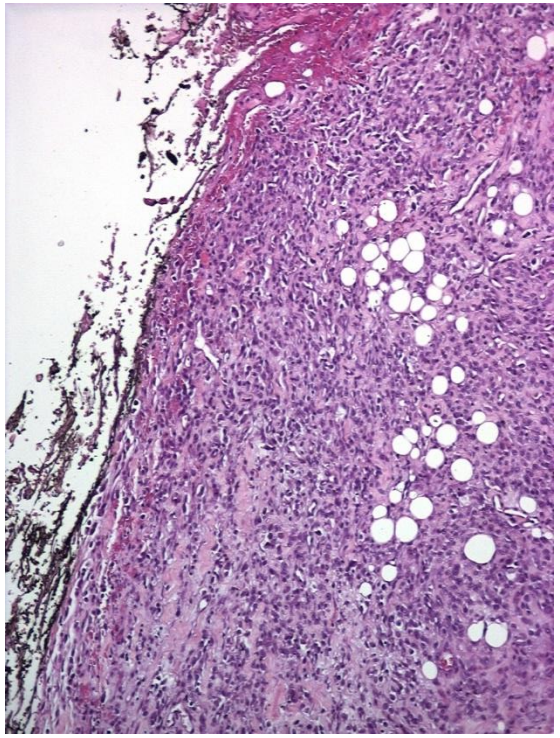
General rules of Surgery in STS

- ✓ Goal of surgery is achieving a negative margin while preserving limb function
- ✓ What constitutes an appropriate margin is a matter of debate
- ✓ Margins of resection should be personalized to
    - Individual needs of patient, reflecting functional preferences
    - Sarcoma “needs” histology/grade, reflecting differences in tumor biology.

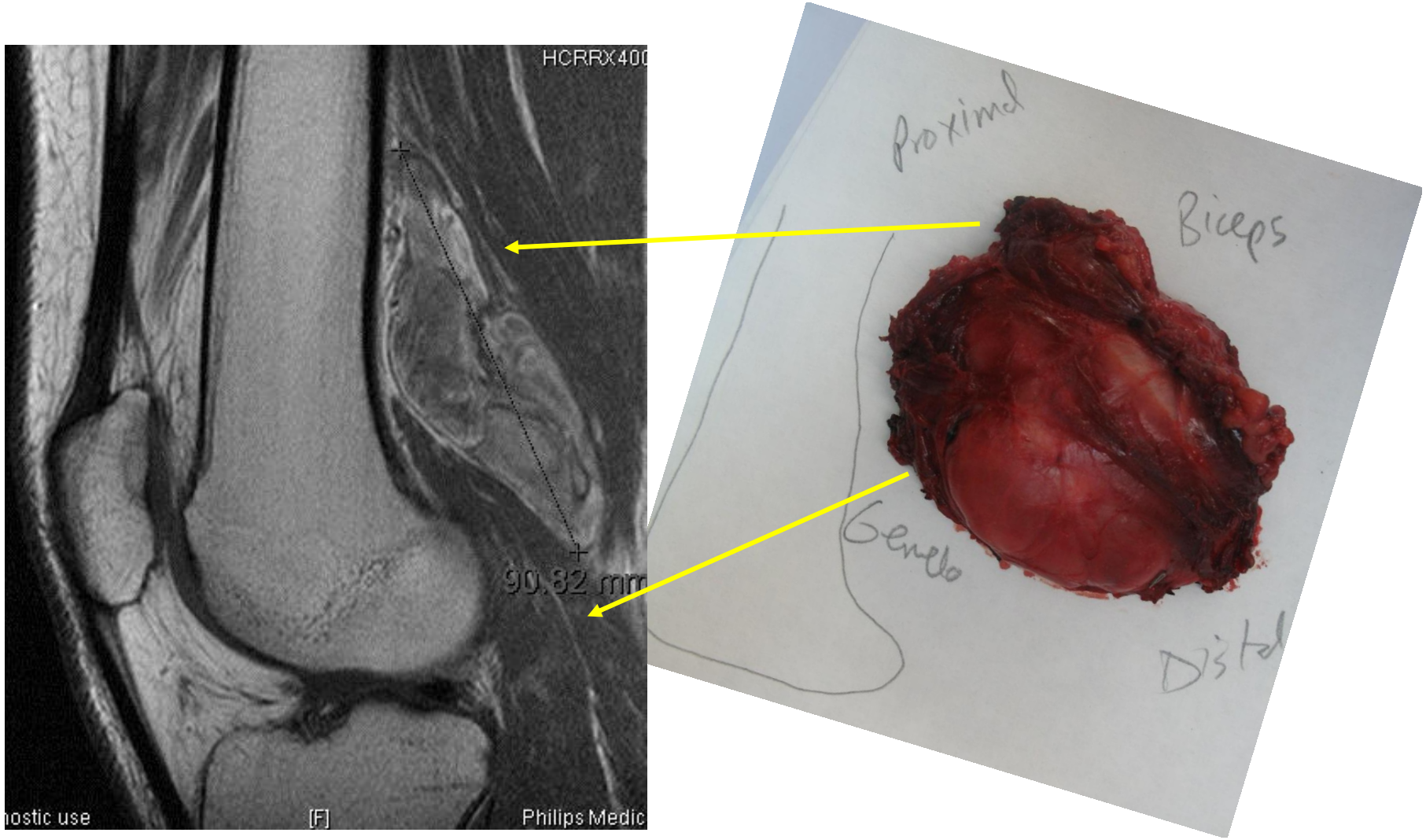
Main surgical principle: to avoid positive margins







Microscopic margins interpretation: Well oriented surgical specimen

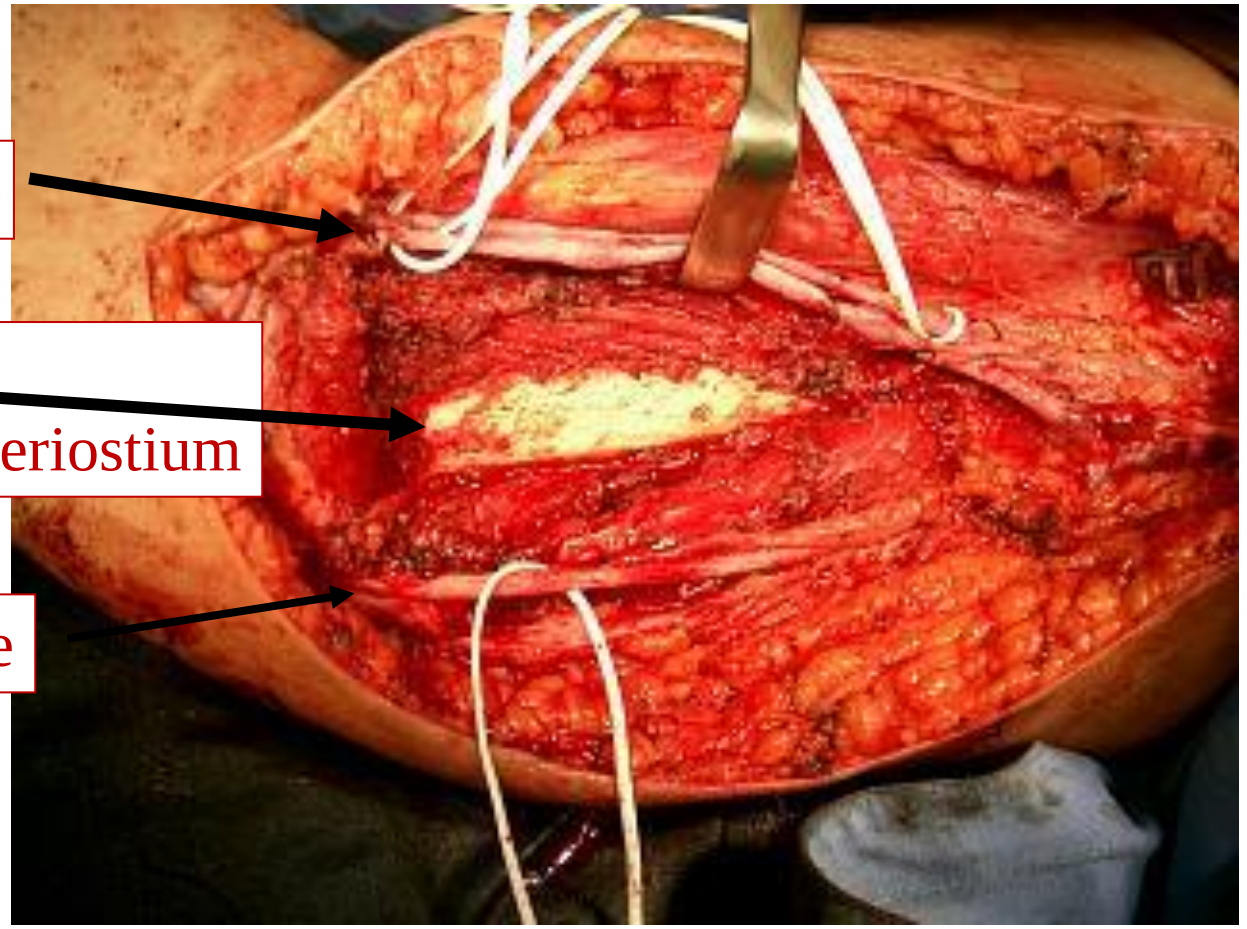


SURGICAL BED

Radial nerve

Humerus.
Resection of periostium

Cubital nerve



Natural barriers resection: still wide resection

- **Close to nerves**
  - **Epineurium Resection**
- **Close to vessels**
  - **Adventicia Resection**
  - **Vessels Resection and by-pass**
- **Close to bone (Bone scan +)**
  - **Periostium Resection**
  - **Bone Resection**
- **Close to skin**
  - **Skin graft**

HELP

RESECTION:
•VASCULAR SURGEON

RECONSTRUCTION
•PLASTIC SURGEON

The impact of Margins

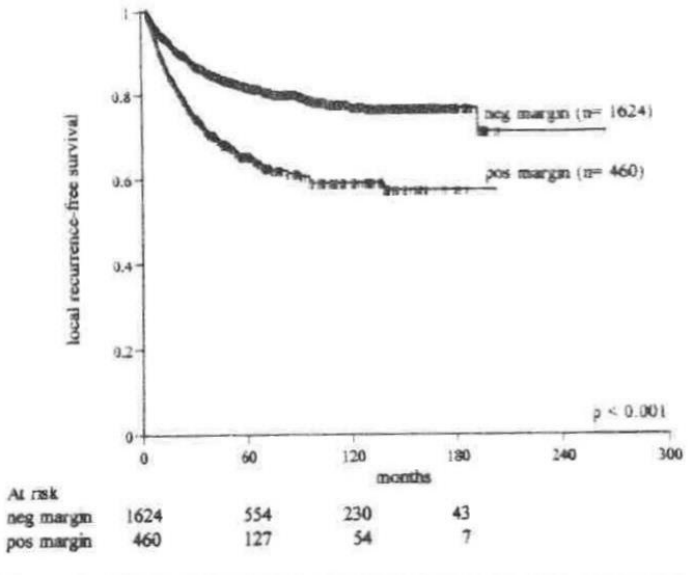
Study	Time period	N	Follow-up (months)	LR rate		DR rate		OS rate	
				Margin+	Margin-	Margin+	Margin-	Margin+	Margin-
Zagars et al	1960-1999	666	139	36%	12%	25%	28%	69%	75%
Stodajadinovic et al	1982-2000	2084	50	35%	18%	32%	24%	70%	80%
Gronchi et al	1985-2005	997	85	26%	10%	20%	21%	71%	84%
Trovik et al	1986-1991	559	89	36%	18%	28%	28%	NR	NR

Analysis of the Prognostic Significance of Microscopic Margins in 2,084 Localized Primary Adult Soft Tissue Sarcomas

Alexander Stojadinovic, MD,* Denis H. Y. Leung, PhD,† Axel Hoos, MD, PhD,* David P. Jaques, MD,*
Jonathan J. Lewis, MD, PhD, and * Murray F. Brennan, MD*

*From the Departments of *Surgery and †Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, New York*

LR



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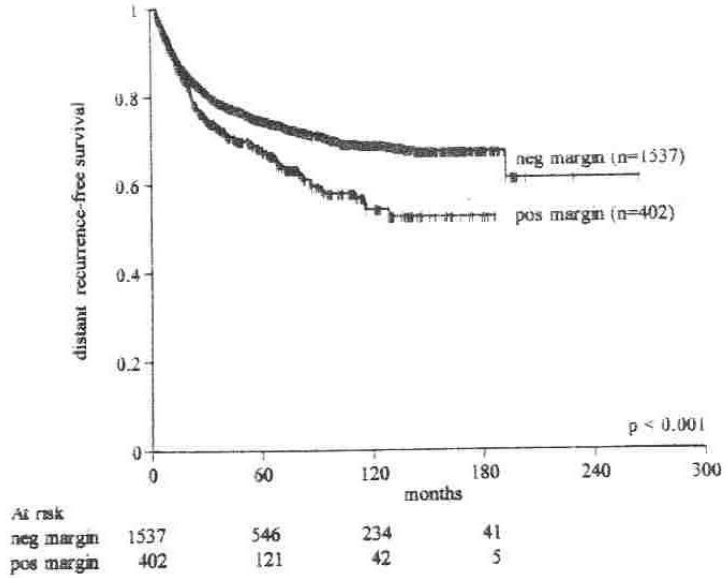

A Stojadinovic , Ann Surg 2002, 235: 424-34

VOLUME 23 · NUMBER 1 · JANUARY 1 2005

JOURNAL OF CLINICAL ONCOLOGY

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A. Gronchi, P.G. Casali, L. Mariani, R. Miceli, M. Fiore, S. Lo Vullo, R. Bertulli, P. Collini, L. Lozza, P. Olmi, and J. Rosai

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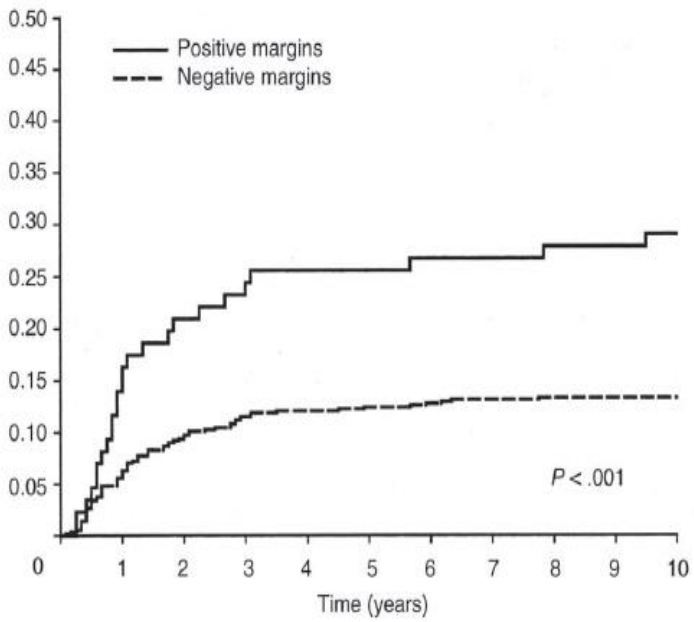

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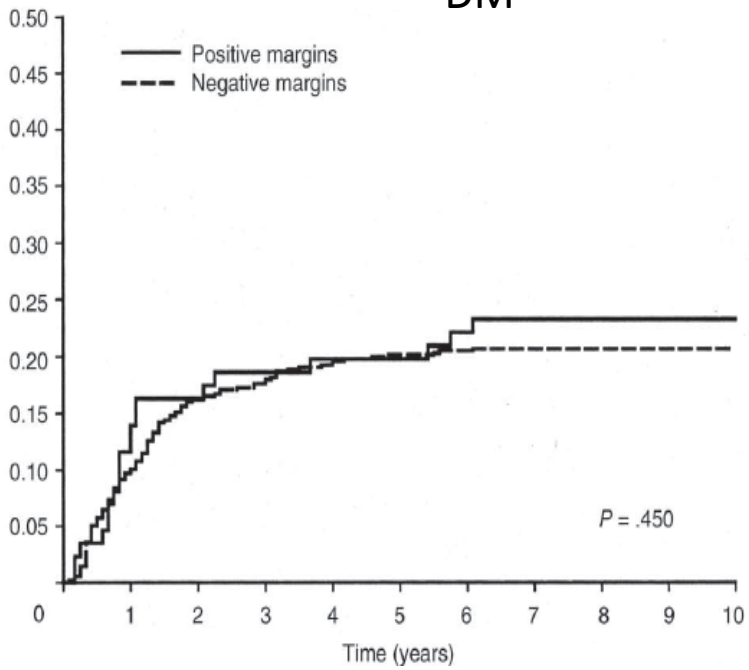


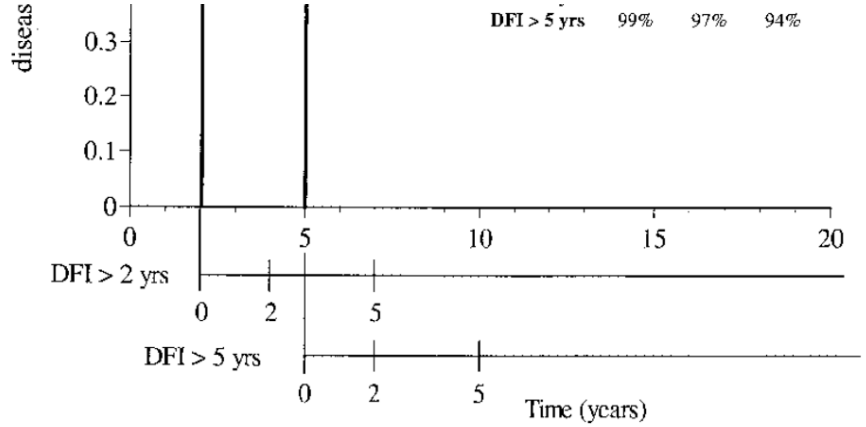
Primary Adult Soft Tissue Sarcoma: Time-Dependent Influence of Prognostic Variables

By Alexander Stojadinovic, Denis H.Y. Leung, Peter Allen, Jonathan J. Lewis, David P. Jaques, and Murray F. Brennan

J Clin Oncol 20:4344-4352. © 2002

biology governs early tumor-related mortality

microscopic resection margins influence late outcome.



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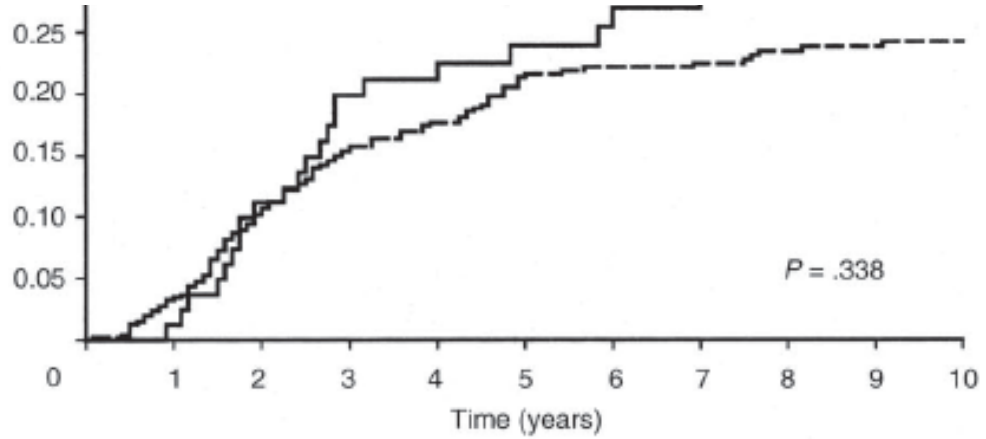
Mortality

HR 1.8 after the 5th year



Remarks in Surgery

Planned positive margins

- If Local recurrence rates are not worse
- Consider preoperative radiation therapy

Deliberate marginal excision

- For low grade, indolent sarcomas, prioritize function and quality of life

Extended margins

- Histologies with microscopic extensions
- Review imaging to determine extent of surgery and radiation field

Amputation

- Limb residual function is poor

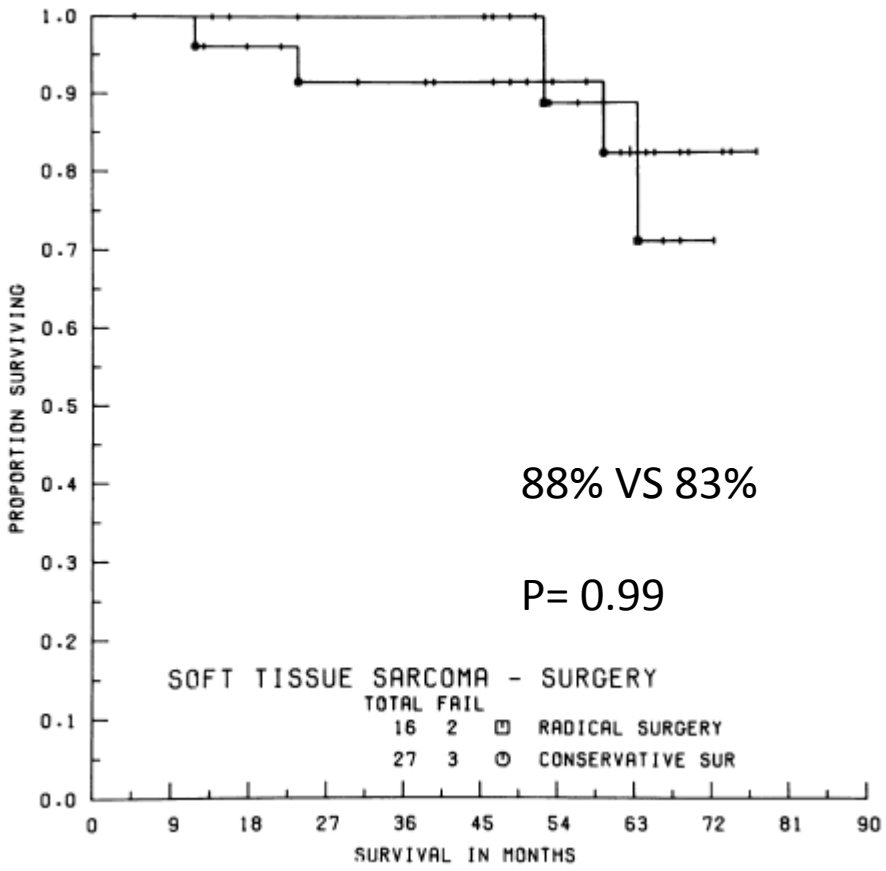
General rules of Radiation Therapy in STS

- ✓ Local control of adequate Limb Sparing + RTP is similar to Amputation
- ✓ Radiation therapy significantly improves local control (not survival)
- ✓ Doubtful in low risk for local recurrence: Low grade (with good surgery) or superficial tumors.

Milestones of Radiation Therapy in STS

Amputation vs Limb sparing+RTP

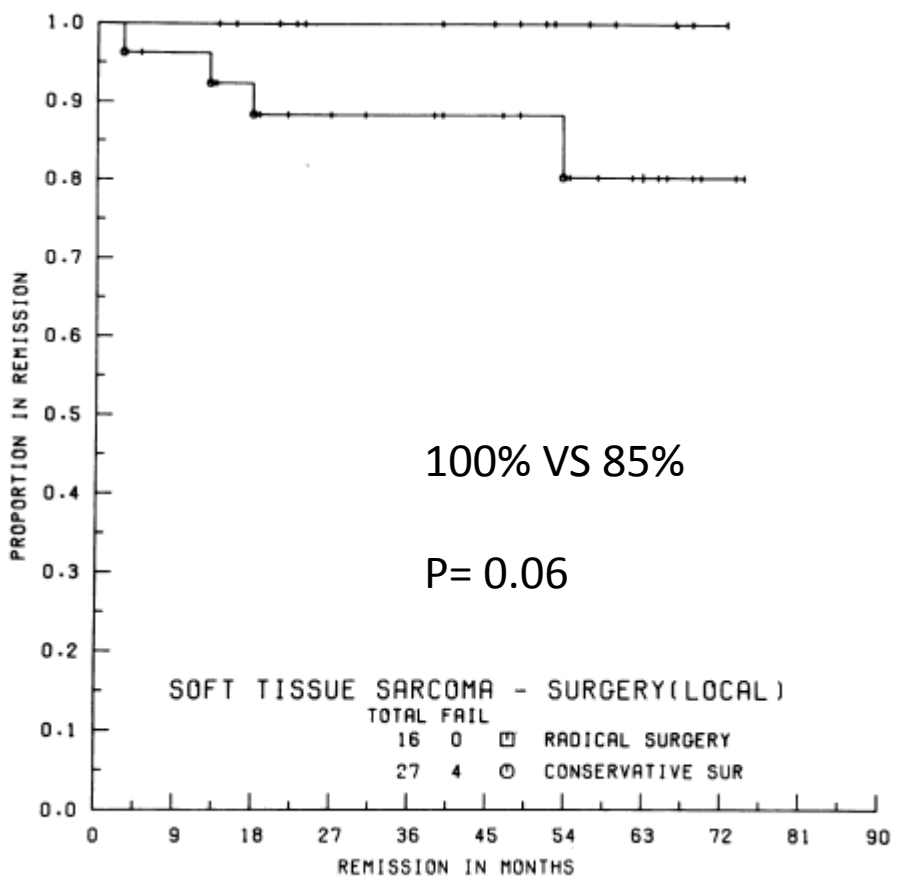
Randomized 2:1
N=43



88% VS 83%

P= 0.99

OS



100% VS 85%

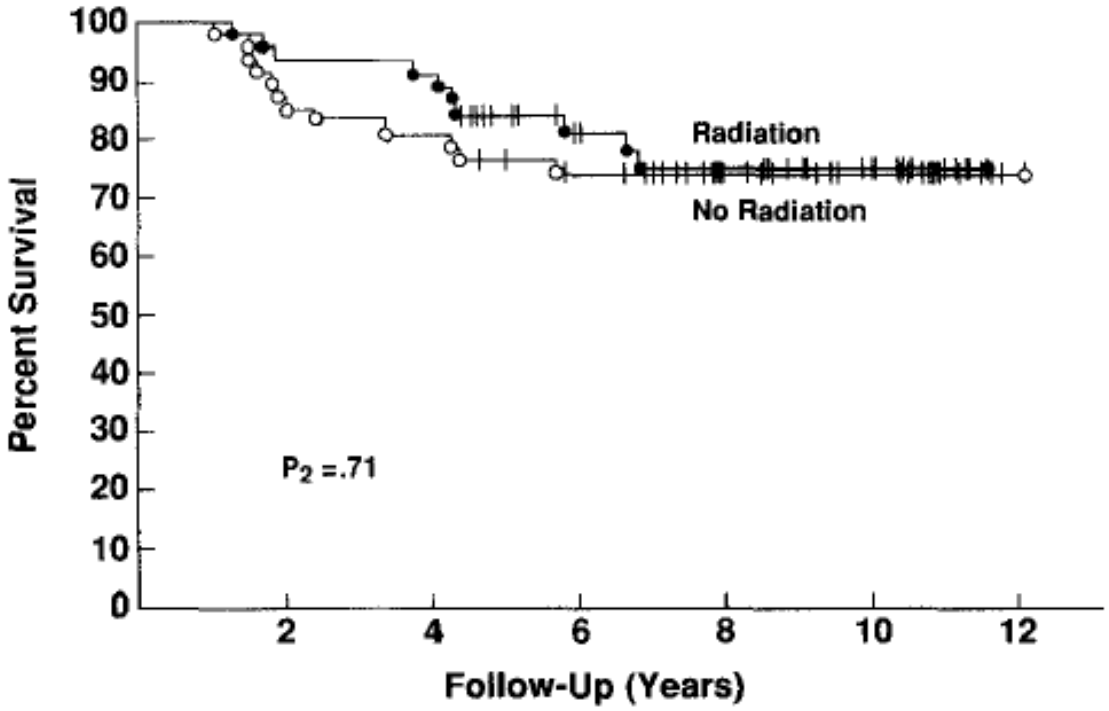
P= 0.06

LR

Rosenberg SA. *Annals of Surgery*. 1982;196(3):305-315.

Limb sparing vs Limb sparing+EBRT

Randomized N=91 High grade



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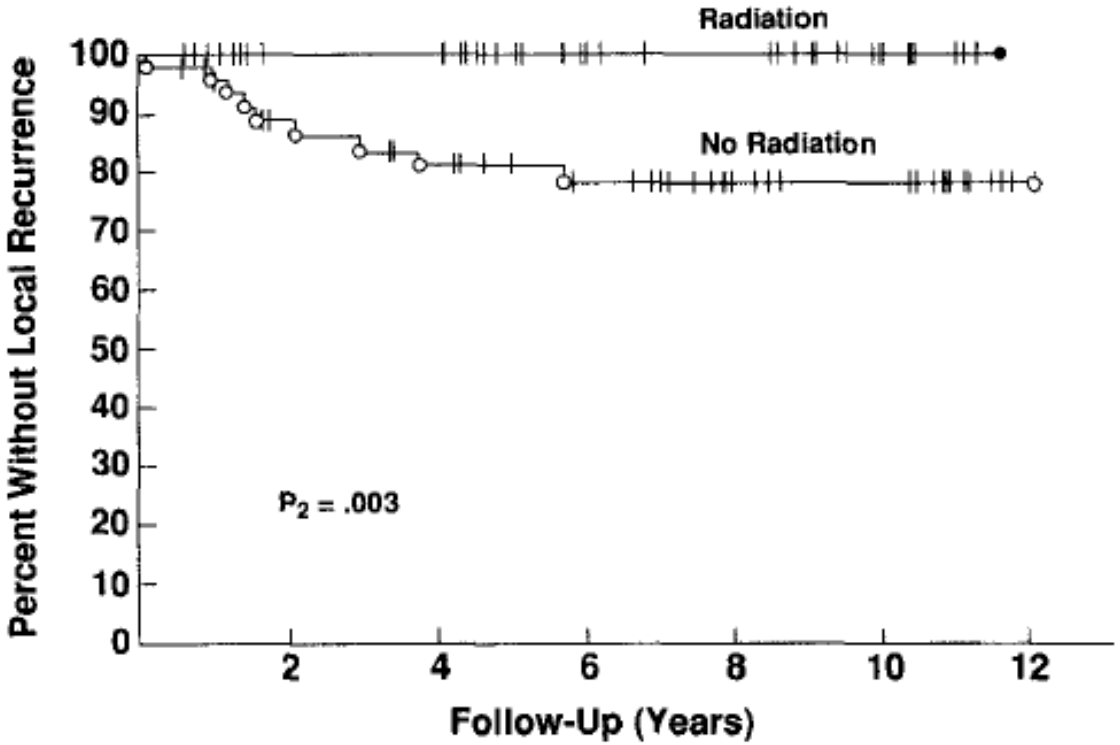
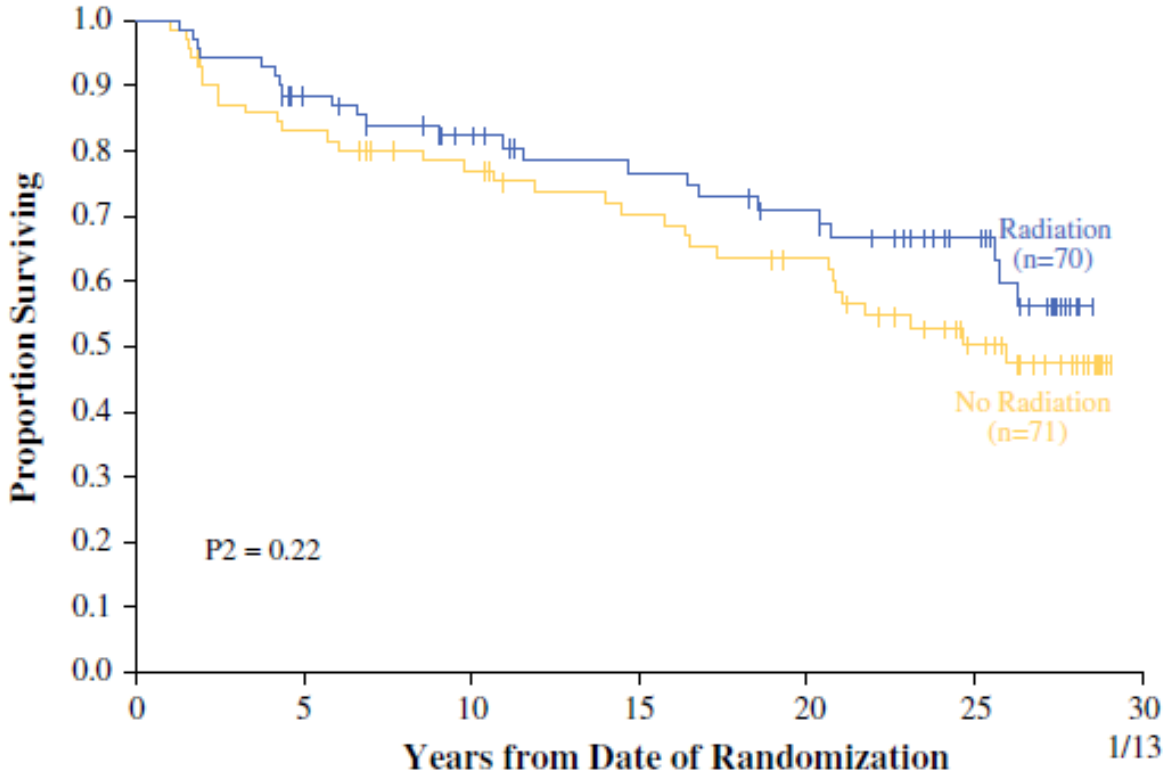


LR

Yang JC, J Clin Oncol1998 Jan;16(1):197-203.

Limb sparing vs Limb sparing+ EBRT

UPDATED N=141

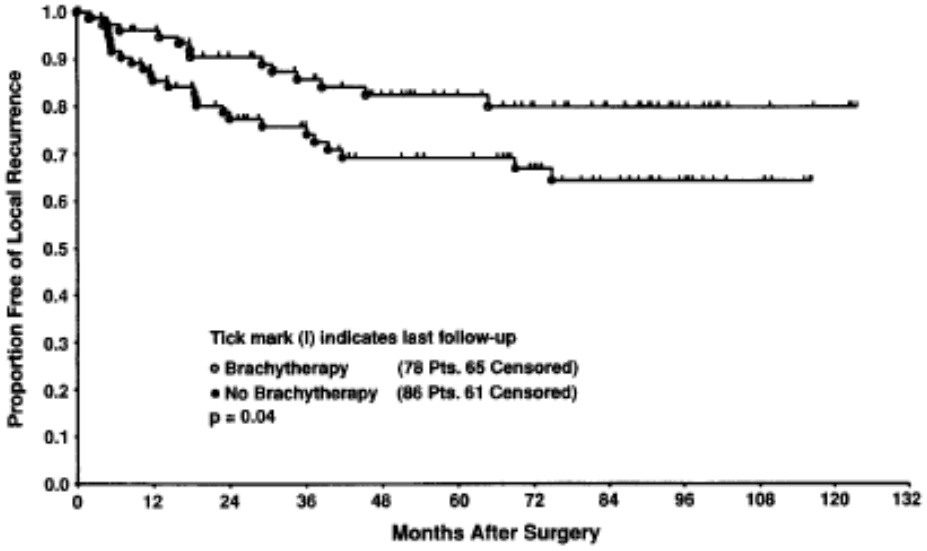


OS

Beane JD et al, Ann Srug Oncol 2014 Aug;21(8):2484-9.

Limb sparing vs Limb sparing + Brachytherapy

Randomized N=164



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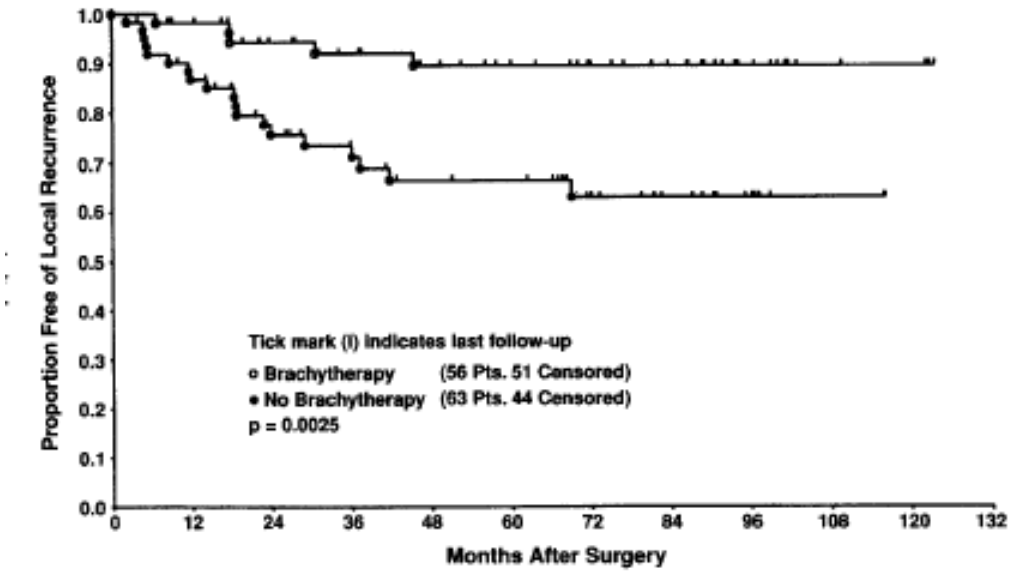


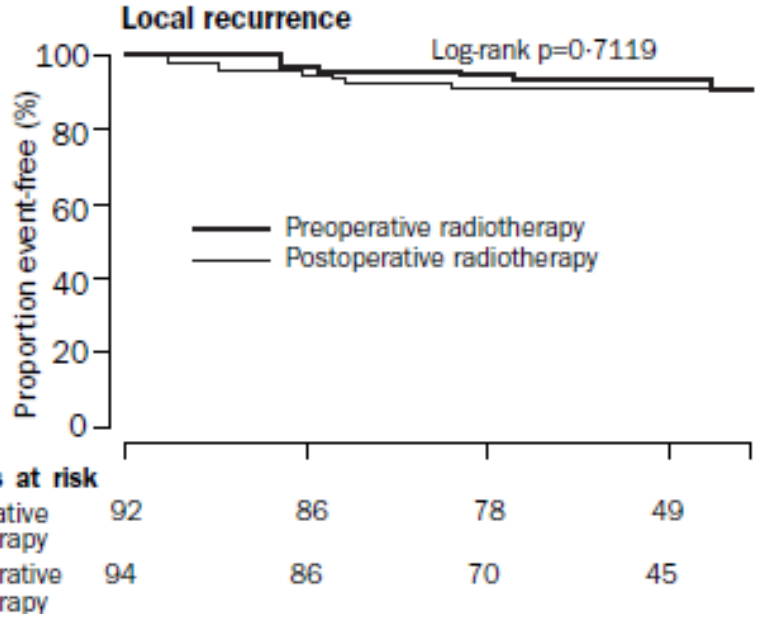
LR in high grade tumors

Pisters et al. J Clin Oncol 1996 Mar;14(3):859-68.

PreOperative vs PostOperative EBRT

	Preoperative (n=88)	Postoperative (n=94)
Wound complications*		
Yes	31 (35%)	16 (17%)
Secondary operation for wound repair	14 (45%)	5 (31%)
Invasive procedure for wound management†	5 (16%)	4 (25%)
Deep wound packing deep to dermis in area of wound at least 2 cm with or without prolonged dressings >6 weeks from wound breakdown‡	11 (35%)	7 (44%)
Readmission for wound care§	1 (3%)	0
No complications	57 (65%)	78 (83%)

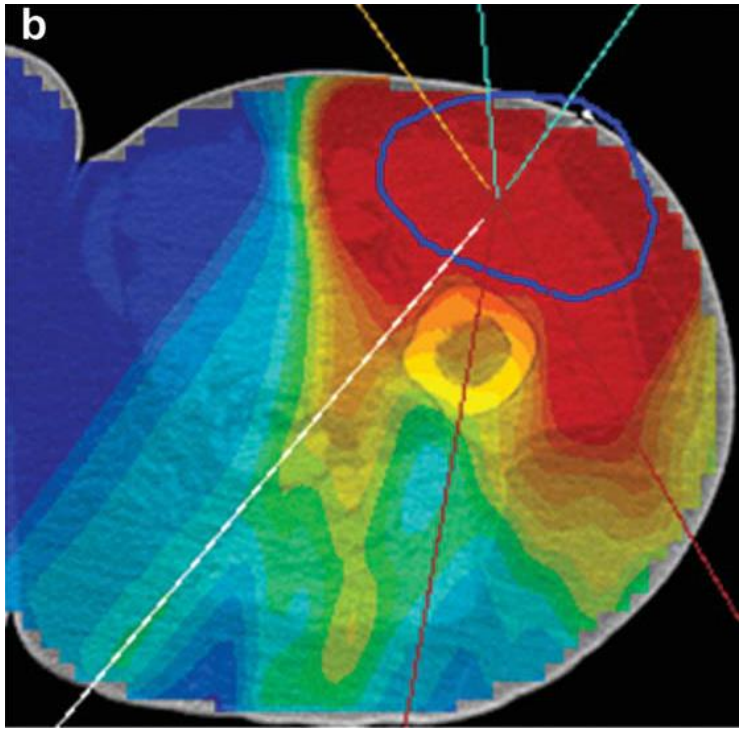
*p=0·01 for yes *vs* no. †Without secondary operation. ‡Without secondary operation or invasive procedure. §Without secondary operation, invasive procedure, deep wound packing, or prolonged dressing.

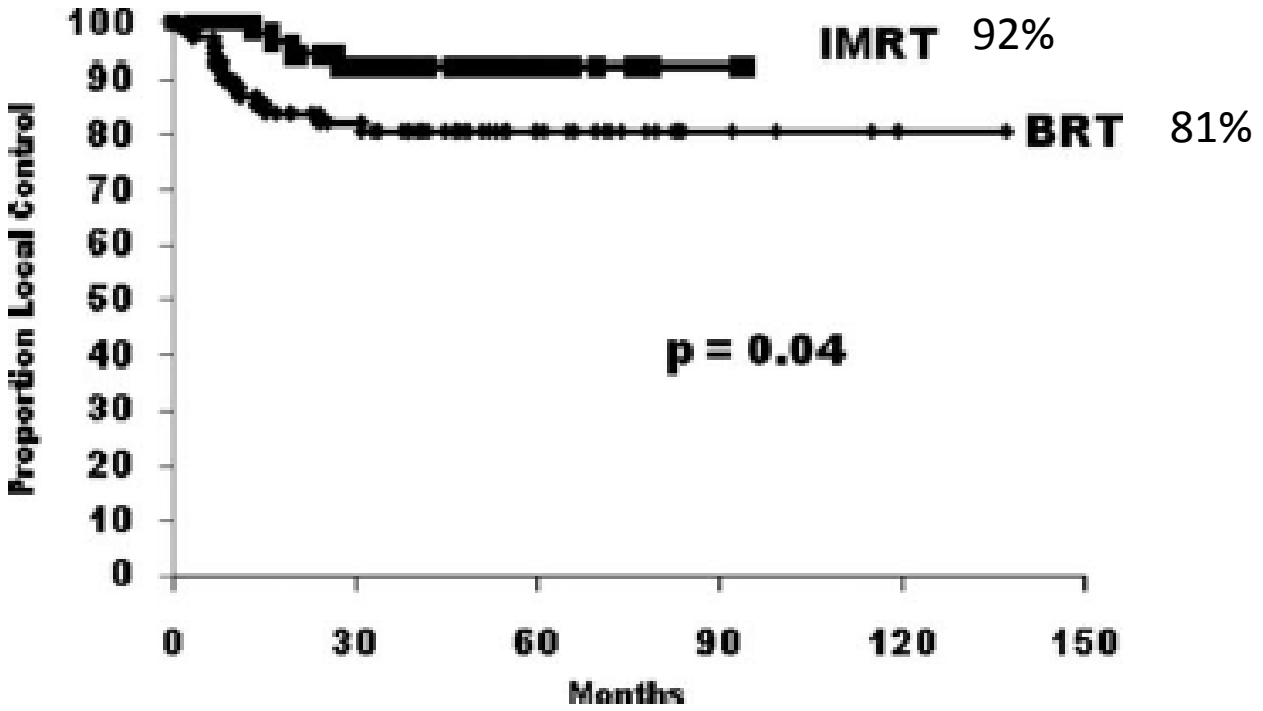


O' Sullivan et al. et al. Lancet, 2002 Jun 29;359(9325):2235-41.

IMRT vs Brachytherapy

N= 134





- **High grade**
- **Limb sparing**
- **Limbs**

Wound complications:

19% IMRT vs 11% Brachytherapy

Remarks in Radiation Therapy

Local Control

- Limb sparing + RTP → Local control rates of more than 80%

Radiation therapy modality

- No direct comparison between brachytherapy and EBRT
- Indirect comparison: better LC with IMRT
- IMRT can offer fewer number of secondary side effects

Radiation timing

- More acute toxicity for preoperative
- More late toxicity for postoperative?

General rules of perioperative Chemo in STS

- ✓ Still a controversial issue
- ✓ According to meta-analysis: 7% of absolute benefit in Limbs
- ✓ Adequate selection is needed:
  - High risk population
  - Full dose scheme

Cox Multivariate Analysis for Metastasis-free Survival (n= 1199)

Factor	No. patients	Relative Risk	95% CI	p
Grade				
1	154	1		
2	492	3.12	1.83-5.35	3.2×10^{-5}
3	553	7.81	4.63-13.17	1.1×10^{-14}
Tumor Size				
< 5 cm	260	1		
5-9 cm	415	1.5	1.11-2.09	0.01
≥ 10 cm	524	2.02	1.47-2.76	1.2×10^{-5}
Neurovascular involvement				
No	985	1		
Yes	214	1.5	1.21-1.89	0.0003
Tumor Depth				
Superficial	165	1		
Deep	1034	1.47	1.00-2.18	0.048

J M Coindre, Cancer 2001, 91: 1914-26

5-Year Metastasis free survival in the main histologic types

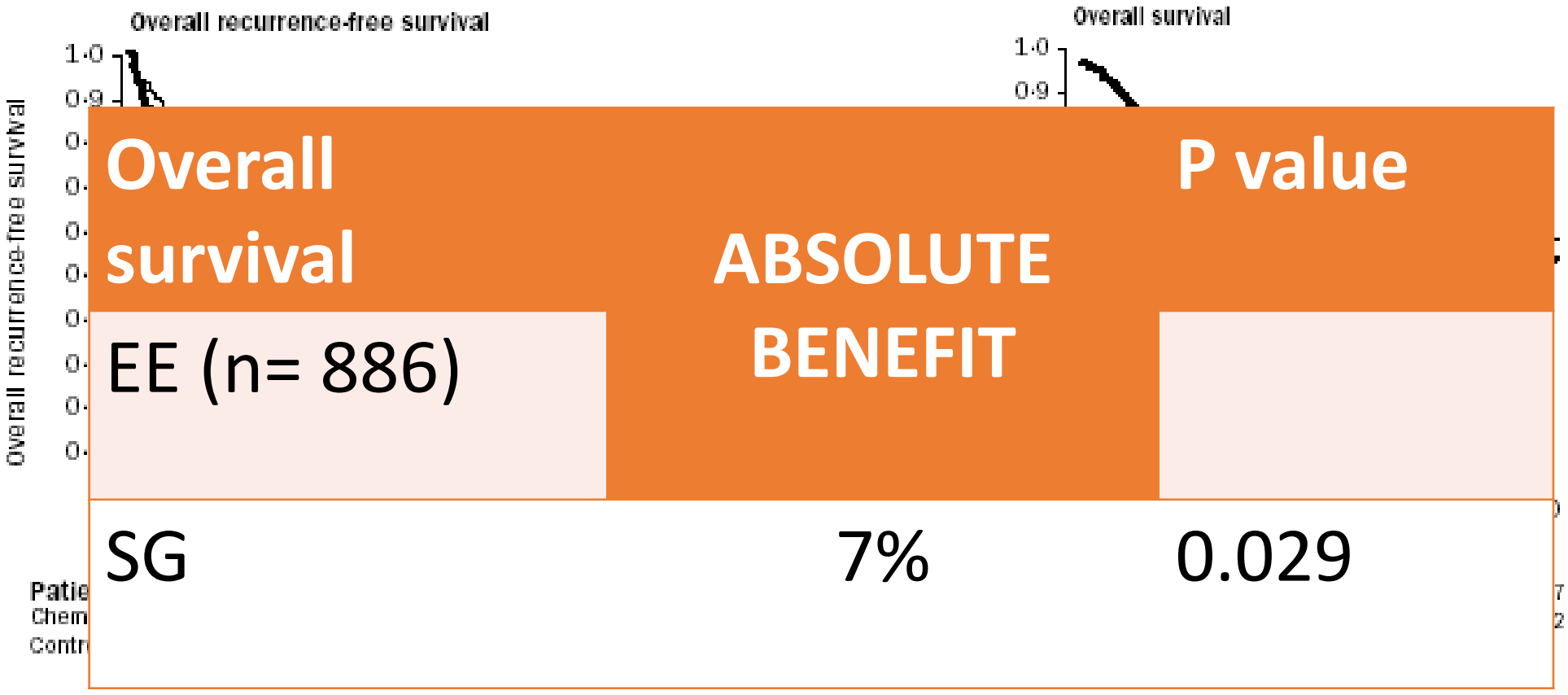
Factors	UPS	LIPOS.	LEIOM.	SYNOV.	MPNST	UNCLASS.
Tumor Size	p= 0.005	p=0.0061	p=0.0001	p=0.0104	p=0.67	p=0.053
<5 cm	88.2 (78)	92.6 (14)	88.0 (41)	66.8 (39)	61.2 (12)	72.4 (21)
5-9 cm	65.4 (117)	94.7 (39)	52.7 (48)	56.3 (54)	57.6 (28)	58.2 (49)
≥ 10 cm	53.6 (147)	72.8 (130)	41.2 (59)	27.3 (26)	44.5 (29)	34.5 (66)
Tumor Depth	p=0.0043	p= 0.07	p=0.0002	p=0.0407	nd	p=0.042
Superficial	82.2 (69)	100 (11)	86.0 (35)	100 (5)		78.6 (14)
Depth	60.7 (279)	77.8 (177)	50.9 (112)	50.6 (120)		46.0 (125)
Grade	p< 0.0001	p<0.0001	p=0.002	p=<0.0001	p=0.33	p<0.0001
1	89.8 (33)	93.8 (85)	92.9 (16)	--	77.8 (5)	82.0 (18)
2	76.5 (160)	71.6 (71)	66.6 (65)	74.8 (56)	56.1 (26)	69.0 (75)
3	48.1 (156)	58.7 (32)	44.7 (67)	35.1 (69)	52.1 (41)	36.5 (65)

J M Coindre, Cancer 2001, 91: 1914-26

Multivariate analysis (Overall Survival)				
	GRADE 2 (N=625)		GRADE 3 (N=627)	
	HR (95% IC)	p	HR (95% IC)	p
AGE > 51 años	2.1 (1.6-2.8)	< 0.0001	1.6 (1.2-2.1)	0.0002
TUMOR > 5 cm	1.8 (1.3-2.5)	0.0003	1.6 (1.2-2.2)	0.003
Local superficial	NS		0.6 (0.4-0.9)	0.02
Neurovascular involvement	1.9 (1.3-2.6)	0.0001	1.5 (1.1-2.1)	0.003
Adyuvant Chemo	0.8 (0.6-1.1)	0.15	0.6 (0.5-0.8)	0.0002

A Italiano , Ann Surg 2002, 235: 424-34

Sarcoma Meta-analysis Collaboration
(Lancet, 350:1647-54, 1997)



Overall survival	ABSOLUTE BENEFIT	P value
EE (n= 886)		
SG	7%	0.029

Endpoint	results		Absol benefit	P value
	Treatm.	Control		
RFS	55%	45%	10%	0.0001

Endpoint	results		Absol benefit	P value
	Treatm.	Control		
OS	54%	50%	4%	0.12

Criticism of first generation trials

- Inadequate patient selection:
  - Heterogeneous population: Different grade, stage; locations; depth; surgical margins; staging
- Inadequate drug selection:
  - Only 3% of patients had received Ifosfamide
  - Low dose-intensity for anthracyclines

SECOND GENERATION TRIALS: Anthracyclines+Ifosfamide

GROUP	SCHEME	TIME INTERVAL	D.I. (mg/m2/s)
NCI 92	ADR 70 IFOS 4	4 W X 5	ADR 17.5 IFOS 1000
EORTC 62931	ADR 75 IFOS 5	3 W X 5	ADR 25 IFOS 1667
RTOG 9514	ADR 20 D1-3 IFOS 2,5 D1-3 DTIC 225 D1-3	3 W X2 +4	ADR 20 IFOS 2500 DTIC 225
ITALY (Frustaci et. al)	EPI 60 D1-2 IFOS 1,8 D1-5	3W X 5	EPI 40 IFOS 3000

Systematic Meta-analysis

(Includes 2nd generation trials)

RELATIVE RISK 95% CI FOR LR, DR, OR, OS								
	LOCAL RECURRENCE		DISTANT RECURRENCE		OVERALL RECURRENCE		OVERALL SURVIVAL	
	RR	95%IC	RR	95%IC	RR	95%IC	RR	95%IC
DOXO	0.75	0.56-1.01	0.69	0.56-0.86	0.75	0.56-0.86	0.84	0.68-1.03
DOXO+IFOS	0.66	0.39-1.12	0.61	0.41-0.92	0.61	0.41-0.92	0.56	0.36-0.85
ALL	0.73	0.56-0.94	0.67	0.56-0.82	0.67	0.56-0.82	0.77	0.64-0.93
	5%	NTT 25	10%	NTT 10	10%	NTT 10	6%	NTT 17

Cancer, 113: 573-581. 2008

ISG FIRST TRIAL: EPI+IFOS
G3, deep, > 5 cm

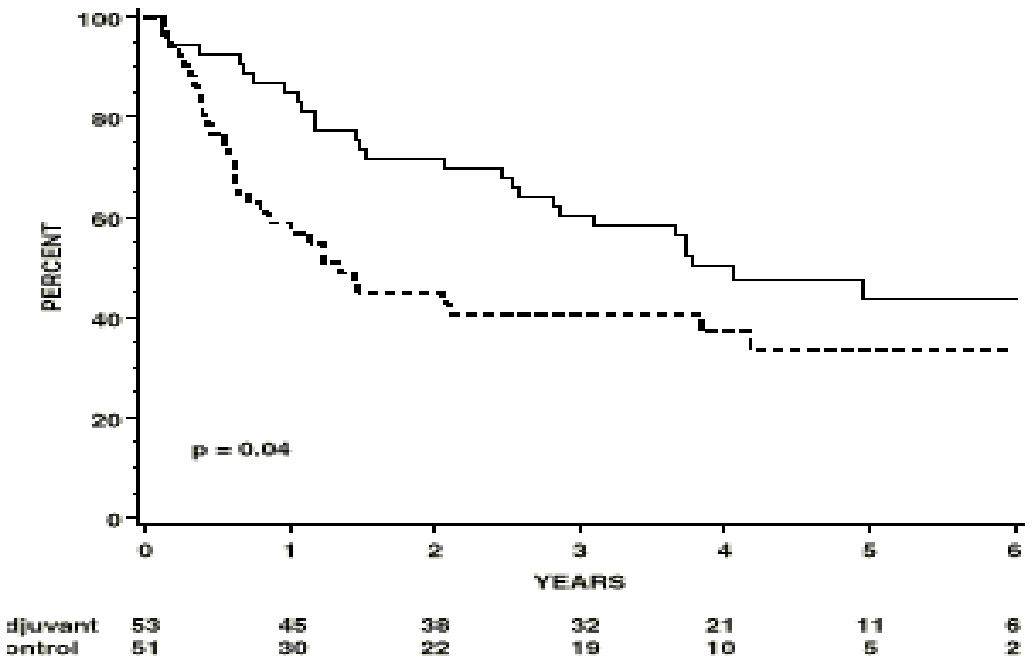


Figure 2. Disease-free Survival by Treatment

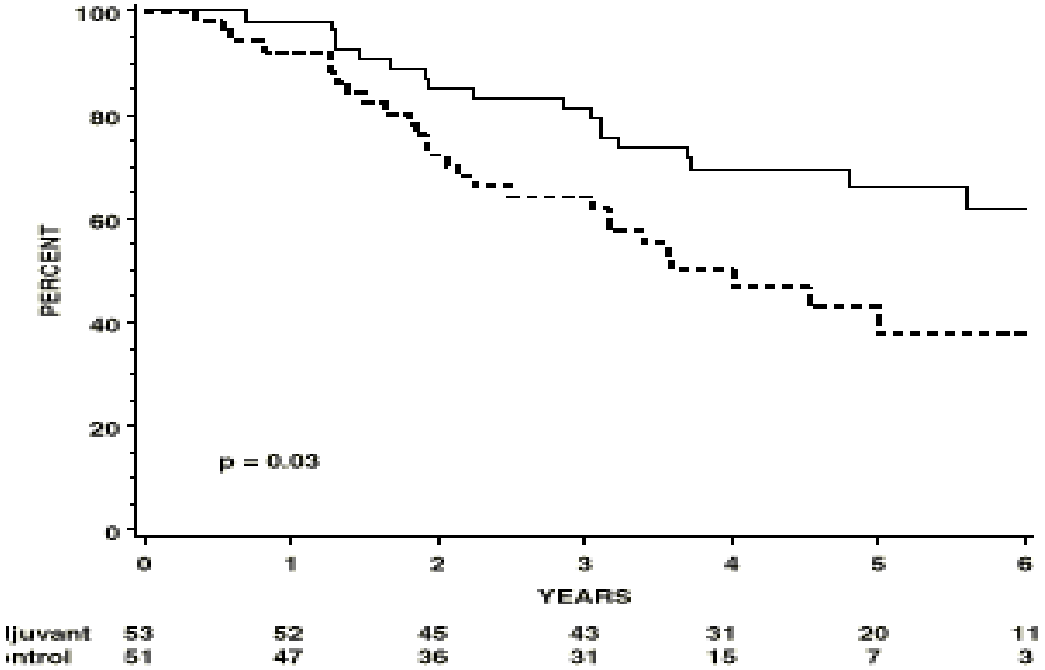


Figure 4. Overall Survival by Treatment

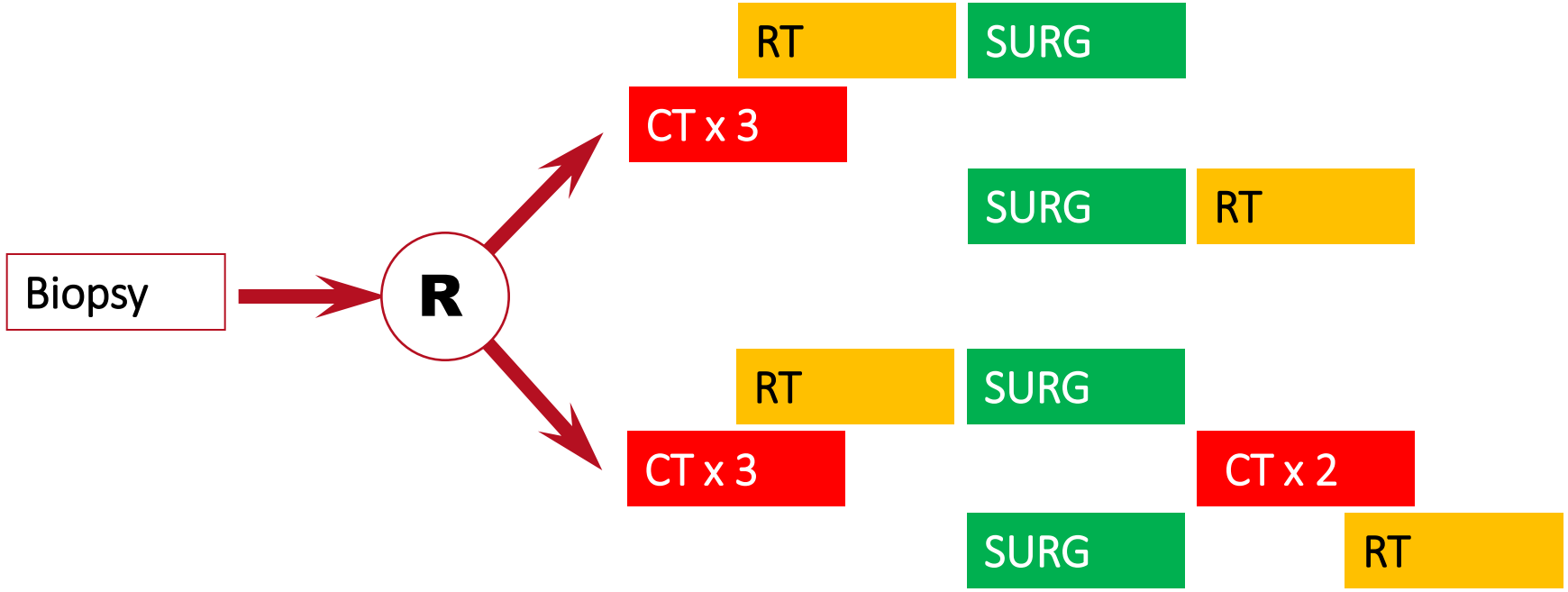
P=0.04

Median F.U.=59 m
Minimum F.U.=36 m

P = 0.03

S. Frustaci et al, JCO, 2001, Vol. 19, 5

ISG Second TRIAL: EPI+IFOS
G3, deep, > 5 cm



A. Gronchi, J Clin Oncol 30:850-856. 2012

ISG First & Second TRIAL
Equivalent OS

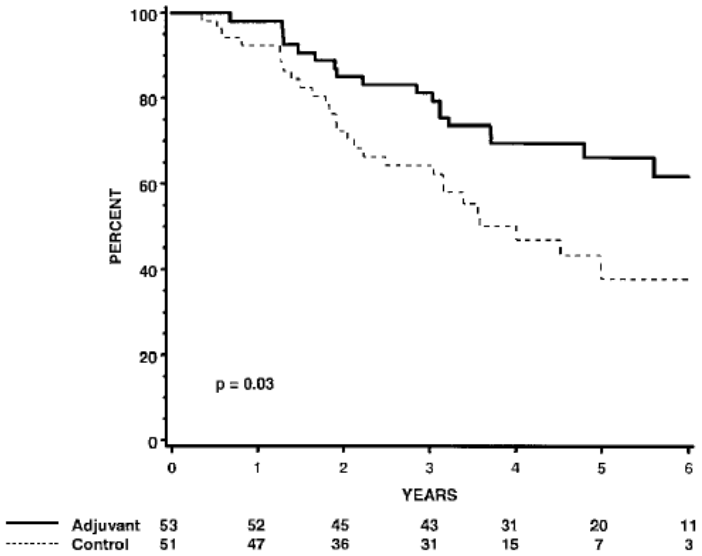
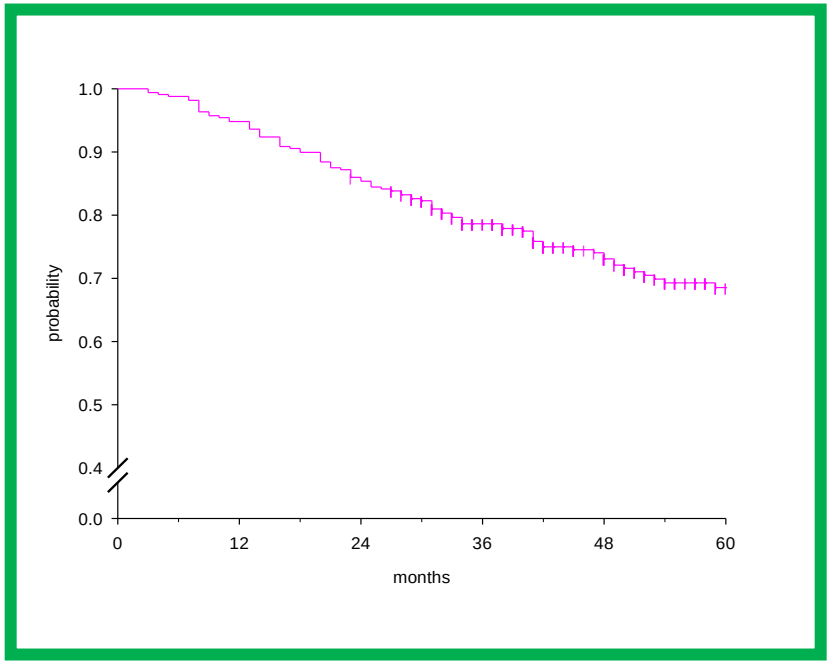
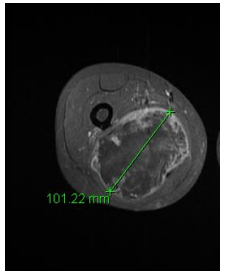
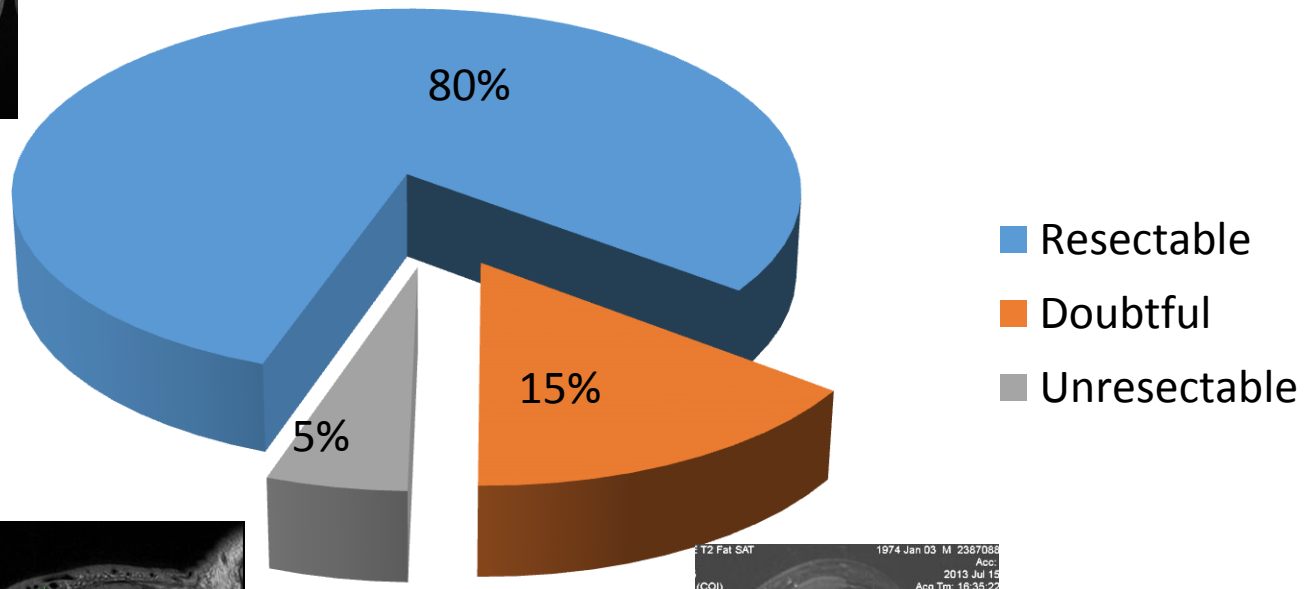


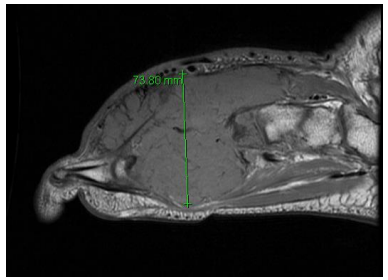
Fig 4. OS by treatment

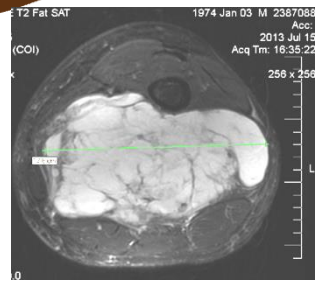


Neo-Adjuvant chemotherapy:
Does it improve resectability?

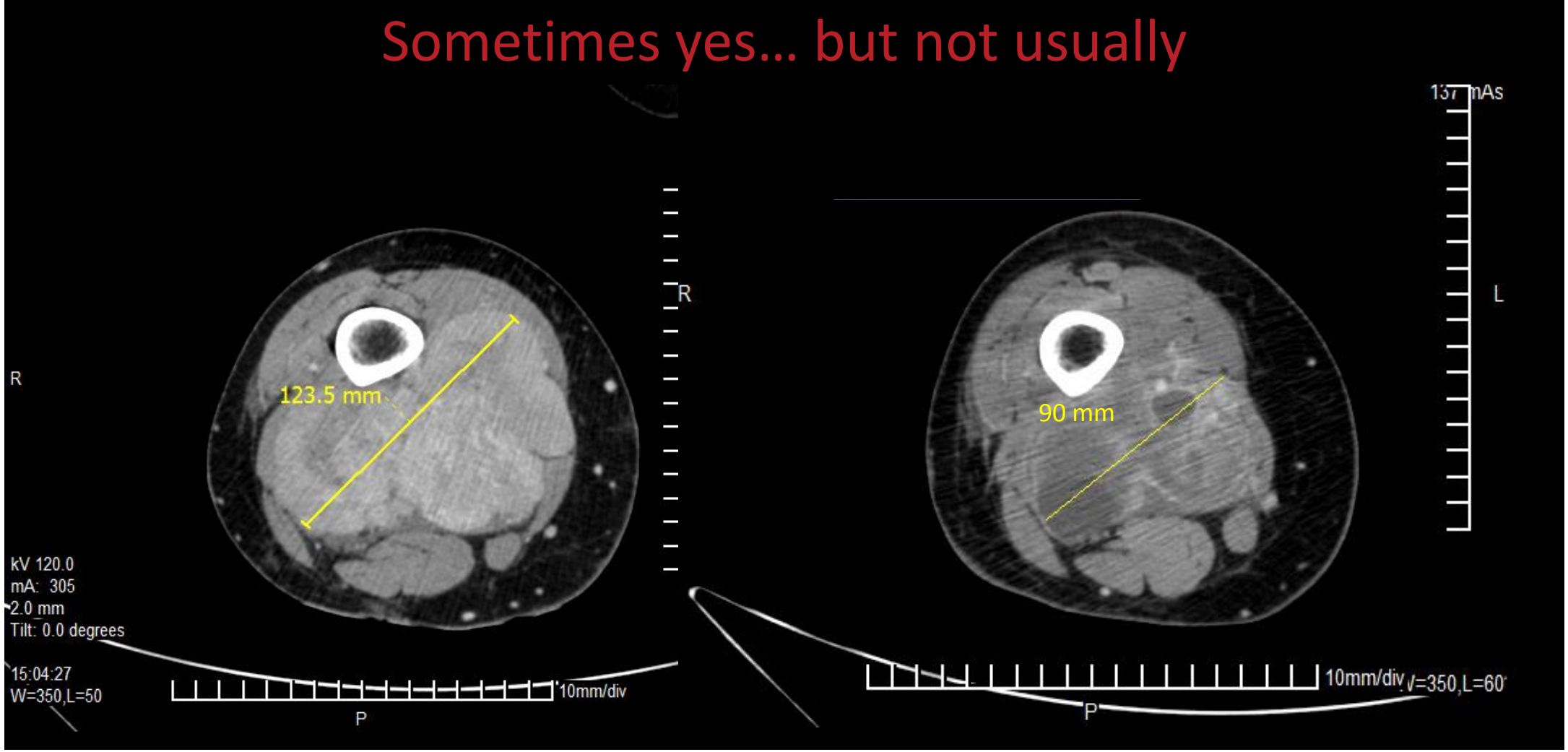








Sometimes yes… but not usually



3 courses CT (E.I.) + RT (50 Gy)

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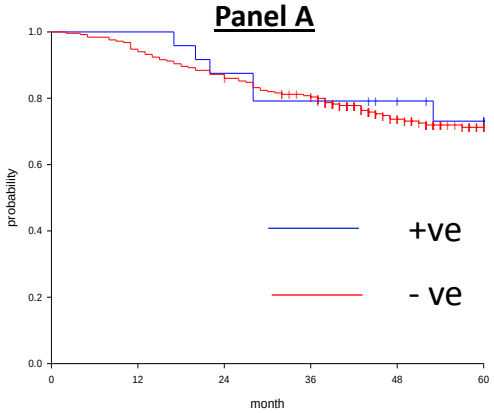
PROSPECTIVE

Quality of surgery and neoadjuvant combined therapy in the ISG-GEIS trial on soft tissue sarcomas of limbs and trunk wall

A. Gronchi[1*], P. Verderio[2], A. De Paoli[3], A. Ferraro[4], O. Tendero[5], J. Majò[6], J. Martin[5], A. Comandone[7], G. Grignani[8], S. Pizzamiglio[2], V. Quagliuolo[9], P. Picci[10], S. Frustaci[11], A. P. Dei Tos[12], E. Palassini[13], S. Stacchiotti[13], S. Ferrari[14], M. Fiore[2] & P. G. Casali[13]

5-year OS



With Neo-adjuvant Chemo-RTP the impact of positive margins seems to be prevented

Neoadjuvant studies: some benefits

Author	Scheme	Patients	RTP timing	Study nature	Clinical benefit
Mahmaud	Doxo + ifosf x 4-6	G2-3 borderline resectable	Post Surgery	Retrospective N=97	Local control Trends DFS
Grobmayer	Doxo 75 + Ifos 6-9 x 3	G2-3; ≥ 5 cm; deep	no	Retrospective N=74	DSS in ≥ 10 cm
Delaney	MAID X 3	G2-3; ≥ 8 cm	Pre	Retrospective N=48	Distal M1* and OS*
Gortzak	Doxo 50 + Ifos 5 x 3	"High risk"	Post (some)	Prospective N= 150	No
Italiano	Doxo 50-60+ Ifos 6-7 g x 3	G2-3;	Post	Retrospective N=60	No
Curtis	Several: Doxo+Ifos; MAID…	ST II/III	Pre/Post	Prospective N=112	OS in > 5 cm
Gronchi	Epi 120 + Ifos 9	G3; ≥ 5 cm; deep	Pre/Post	Prospective N=252	In +ve Surgical margins

(*) Confirmed with long-term follow-up

Remarks in Systemic Therapy

- Co-adjuvant chemotherapy could be advisable if:
  - Localized high risk STS limbs/trunk wall
  - Full doses anthracycline+ifosfamide
  - Individualizing decision-making process
- Neo-adjuvant chemotherapy better than adjuvant:
  - If can be anticipated R1 margins
  - More prognostic information (Radiological and Molecular)
  - We need to gain more knowledge (prospective clinical trials)

THANK YOU

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