



Local recurrence after treatment of extremity soft tissue sarcoma may kill patients



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Background

- What is the prognostic meaning of local recurrence
- What is the prognostic meaning of positive surgical margins

- What is the prognostic meaning of local recurrence

Annals of Surgical Oncology, 4(1): 1-12
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Presidential Address
The Enigma of Local Recurrence

Murray F. Brennan, MD
President, The Society of Surgical Oncology



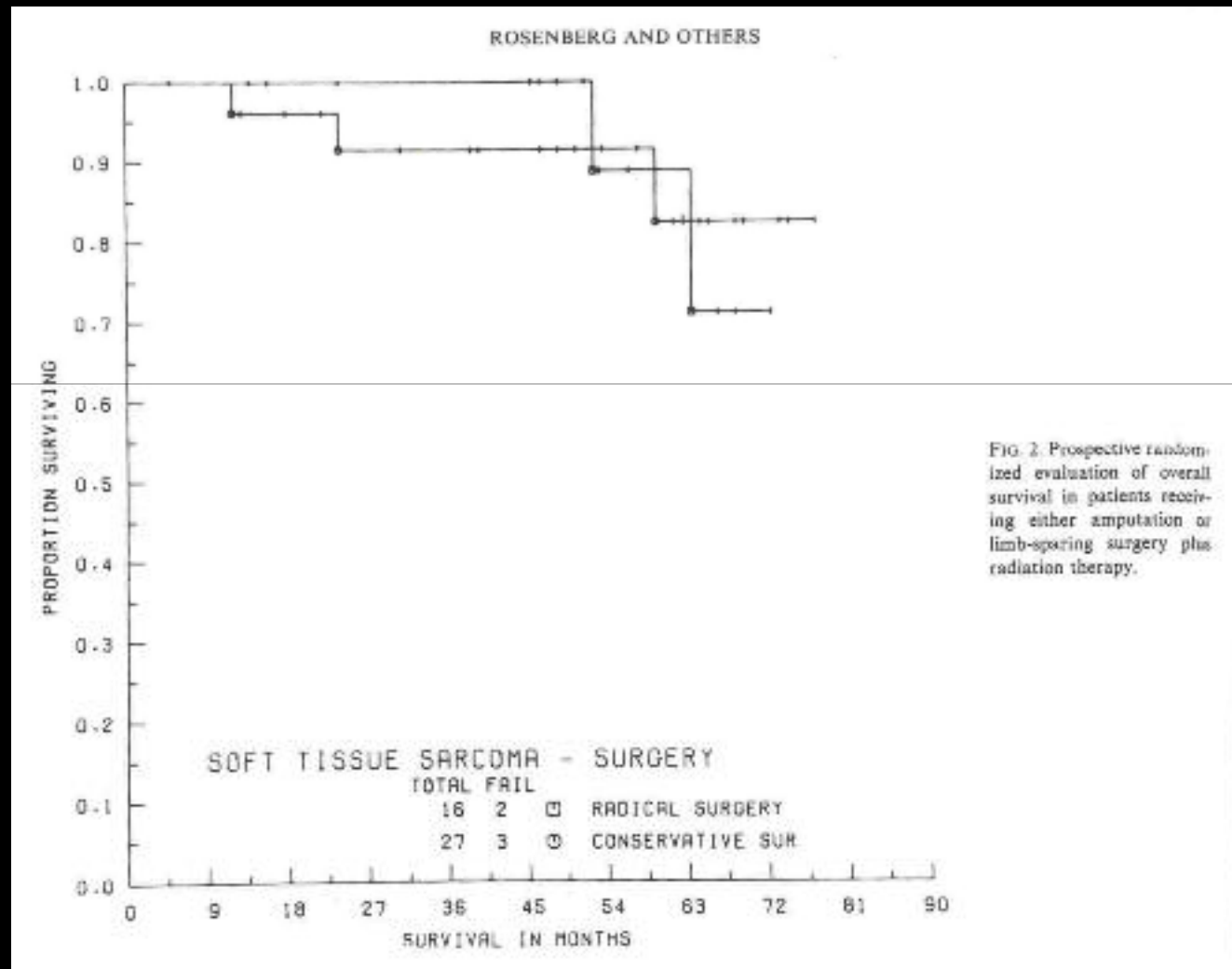
Annals of Surgical Oncology 14(5):1528-1529
DOI: 10.1245/s10434-006-9340-1

Editorial Review

**Local Recurrence in Soft Tissue Sarcoma: More About the
Tumor, Less About the Surgeon**

Murray F. Brennan, MD

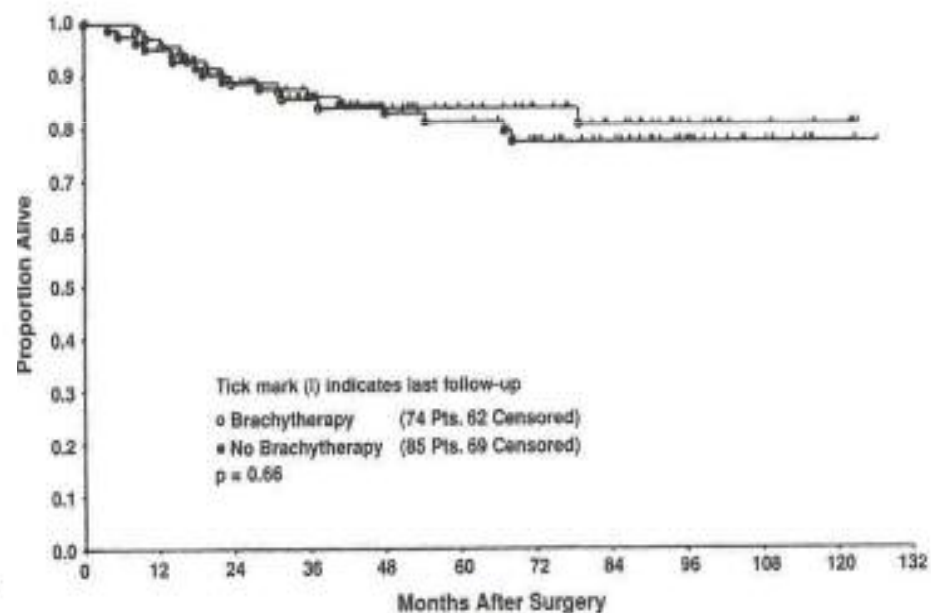
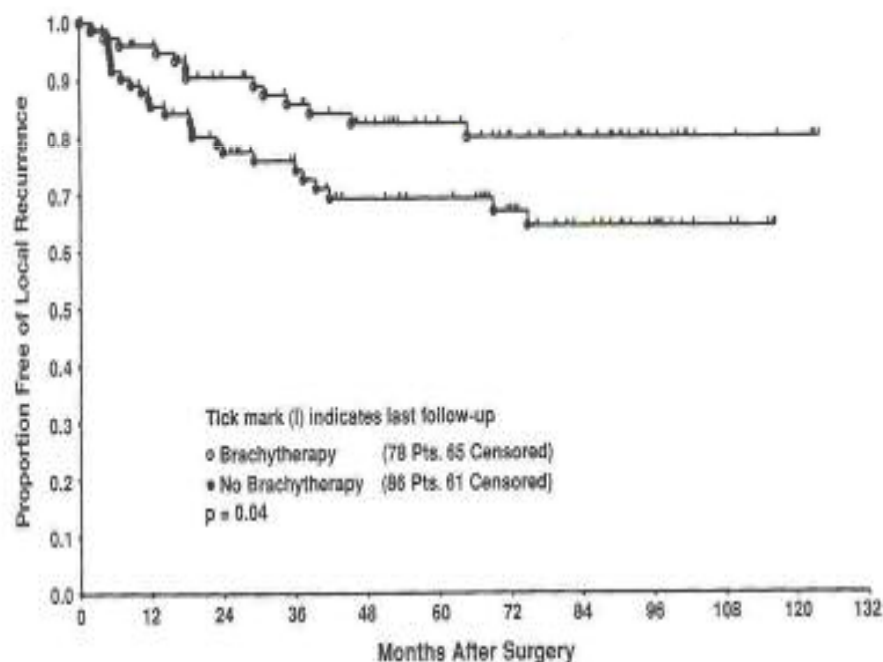
Rosenberg et al. : 43 pts. (NCI) Ann Surg, 1982.



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

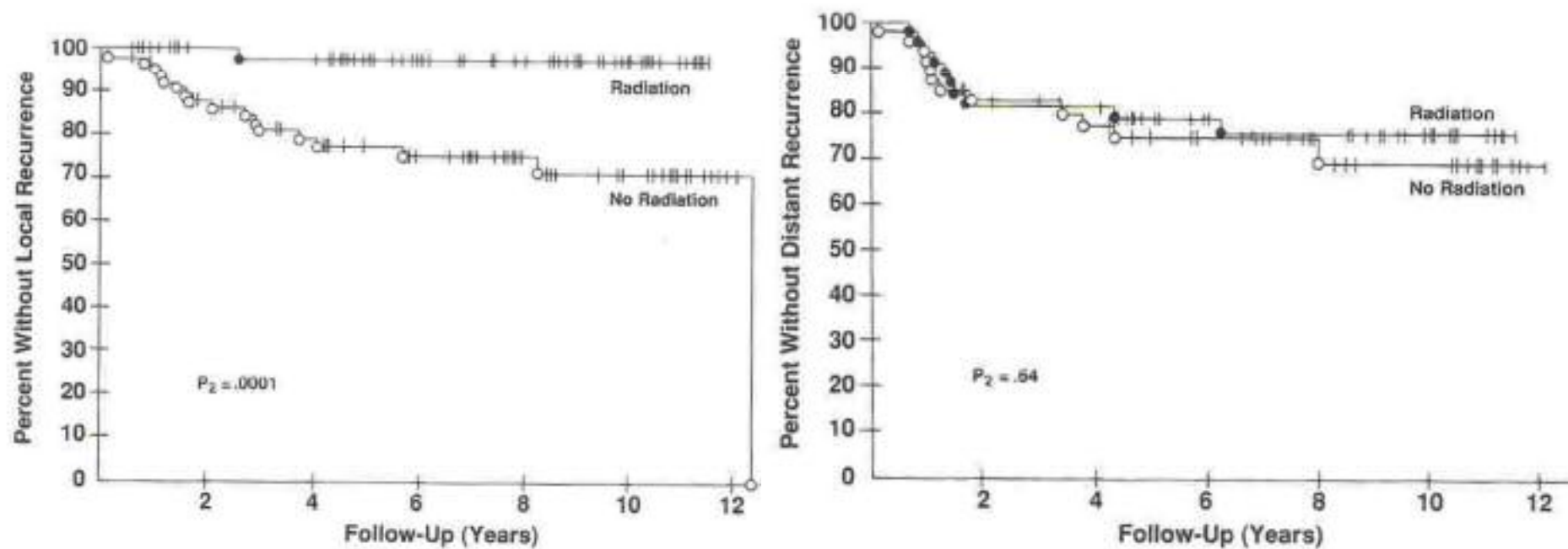
Journal of Clinical Oncology, Vol 14, No 3 (March), 1996: pp 859-868



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

Journal of Clinical Oncology, Vol 16, No 1 (January), 1998: pp 197-203



**LR seems
not to be able to kill the patient**

**LR is a marker of tumor
aggressiveness**

Is there any difference whether it follows adequate or inadequate surgery ?

Extremity Soft Tissue Sarcoma: Adding to the Prognostic Meaning of Local Failure

Alessandro Gronchi, MD,¹ Rosalba Miceli, PhD,² Marco Fiore, MD,¹ Paola Collini, MD,³

Risk of death

3.7 for LR after optimal surgery

1.8 for LR after suboptimal surgery

Cat
Pha
Pha
Tun
Tun
Dep

Histotype: neurofibroma, syringoma, schwannoma (liposarcomas)	1.27	.89–2.10	.090	2.37	1.31–2.00	.001	1.74	.93–2.13	.029
Histotype: other (liposarcomas)	1.70	1.11–2.59		1.69	1.05–2.70		1.74	1.16–2.63	
Grade: 2 (1)	3.56	1.85–6.84	<.001 ^a	1.78	1.13–2.78	.013 ^a	3.31	1.85–5.90	<.001 ^a
Grade: 3 (1)	6.18	3.28–11.66		1.13	.72–1.80		5.07	2.87–8.96	
Margin status: positive (negative)	1.25	.89–1.75	.194	2.60	1.82–3.70	<.001	1.27	.91–1.78	.157
RT: yes (no)	.91	.69–1.19	.492	.66	.47–.92	.013	1.00	.77–1.30	.988
CT: yes (no)	1.58	1.17–2.13	.003	.67	.43–1.05	.080	1.54	1.15–2.06	.003

HR, hazard ratio; CI, 95% confidence interval; *P*, *P* value at Wald test; PR-P, postrelapse phase in patients treated at Istituto Nazionale dei Tumori for primary disease; PR-R, postrelapse phase in patients with recurrent disease previously treated elsewhere; RT, radiotherapy; CT, chemotherapy.

^a Overall Wald test.

What is the prognostic meaning of inadequate surgery (+ margins)

- Does inadequate surgery kills any patients ?
- If so, how does it happen ?



PERGAMON

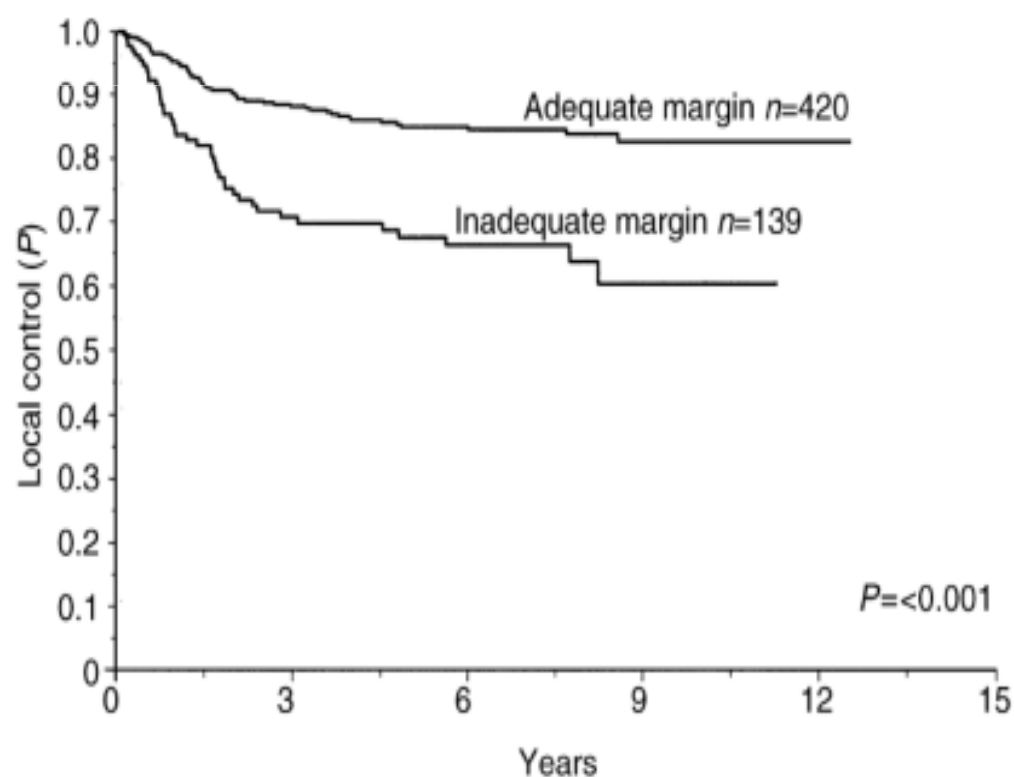
European Journal of Cancer 36 (2000) 710-716

European
Journal of
Cancer

www.ejconline.com

Surgical margins, local recurrence and metastasis in soft tissue sarcomas: 559 surgically-treated patients from the Scandinavian Sarcoma Group Register

C.S. Trovik^{a,*}, H.C.F. Bauer^b, T.A. Alvegård^c, H. Anderson^d, C. Blomqvist^e,
Ö. Berlin^f, P. Gustafson^g, G. Sæter^h, A. Wallöeⁱ

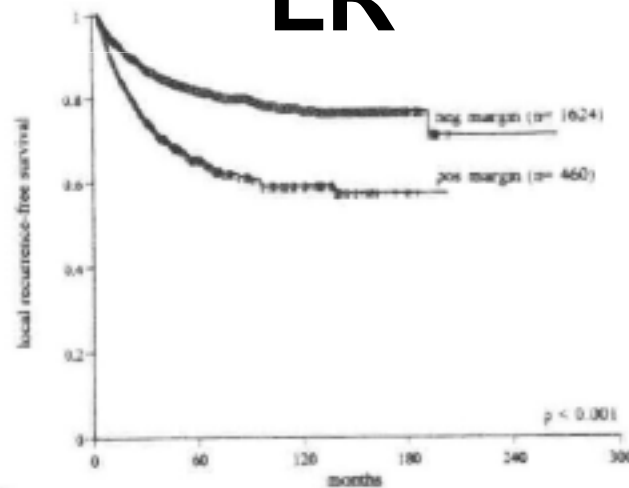


Analysis of the Prognostic Significance of Microscopic Margins in 2,084 Localized Primary Adult Soft Tissue Sarcomas

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*

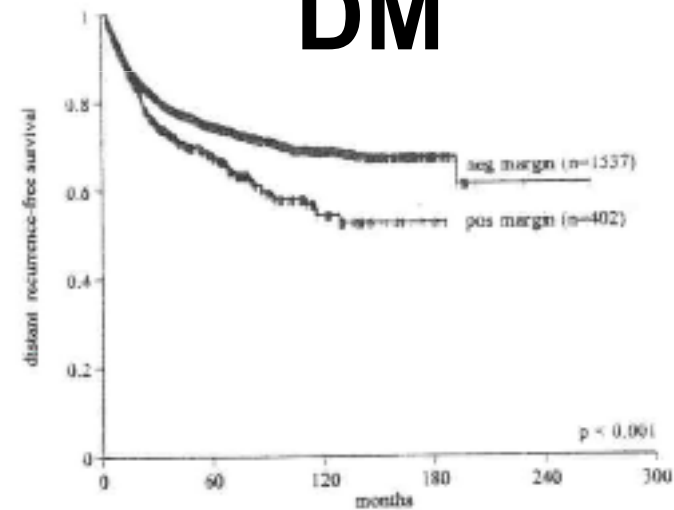
From the Departments of *Surgery and †Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, New York

LR



At risk	0	60	120	180
neg margin	1624	554	230	43
pos margin	460	127	54	7

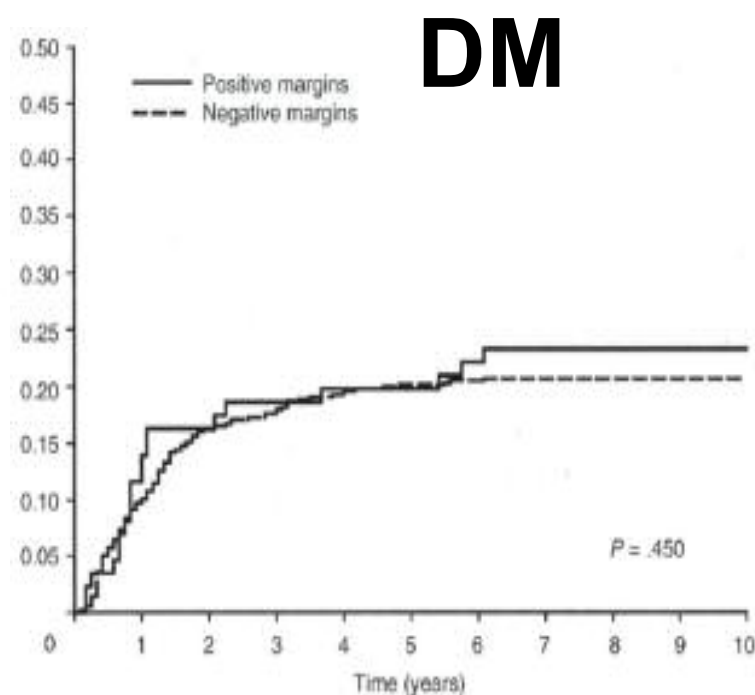
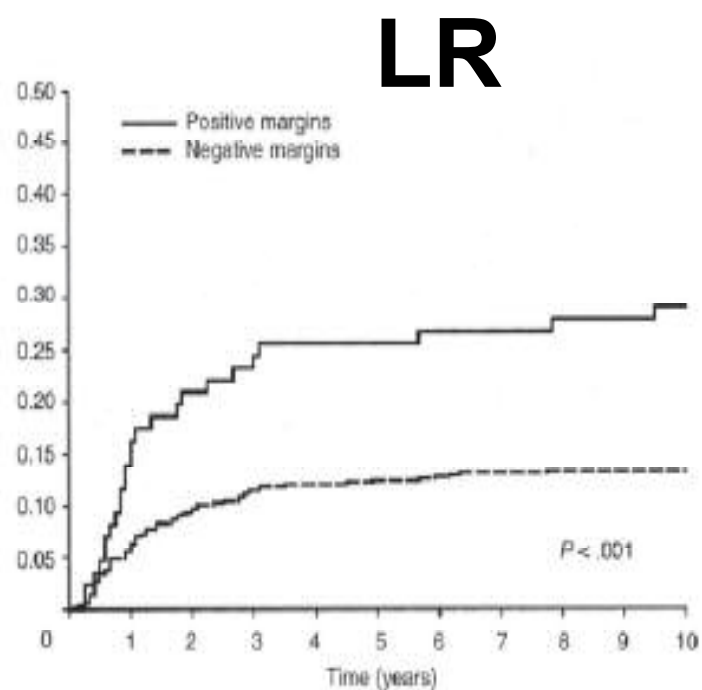
DM



At risk	0	60	120	180
neg margin	1537	546	234	41
pos margin	402	121	42	5

Status of Surgical Margins and Prognosis in Adult Soft Tissue Sarcomas of the Extremities: A Series of Patients Treated at a Single Institution

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



Prognostic Factors for Patients with Localized Soft-Tissue Sarcoma Treated with Conservation Surgery and Radiation Therapy

An Analysis of 1225 Patients

CANCER May 15, 2003 / Volume 97 / Number 10

Gunar K. Zagars, M.D.¹

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Shreyaskumar R. Patel, M.D.³

Robert S. Benjamin, M.D.³

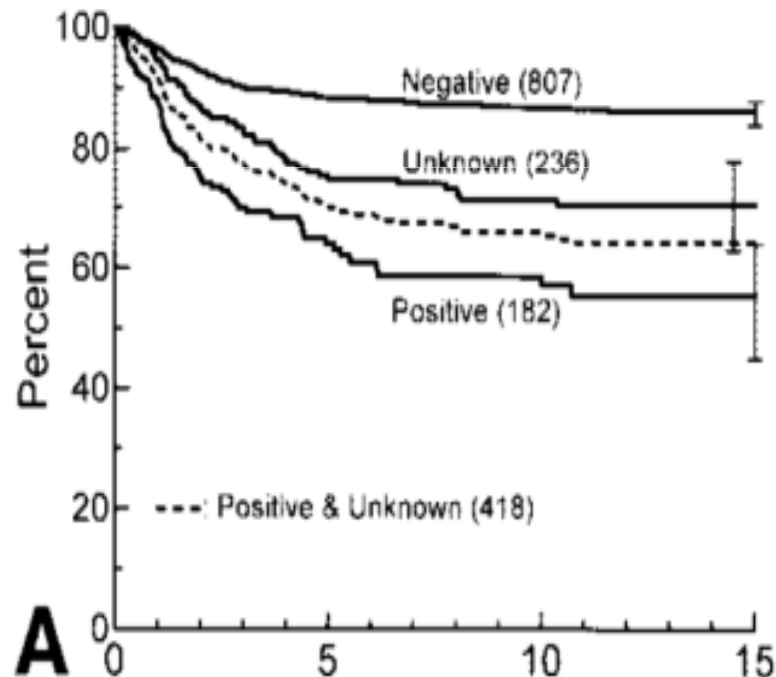
Harry L. Evans, M.D.⁴

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² Department of Surgical Oncology, University of Texas M. D. Anderson Cancer Center, Houston, Texas.

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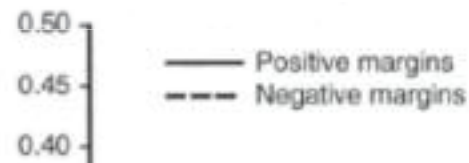
⁴ Department of Pathology, University of Texas M. D. Anderson Cancer Center, Houston, Texas.



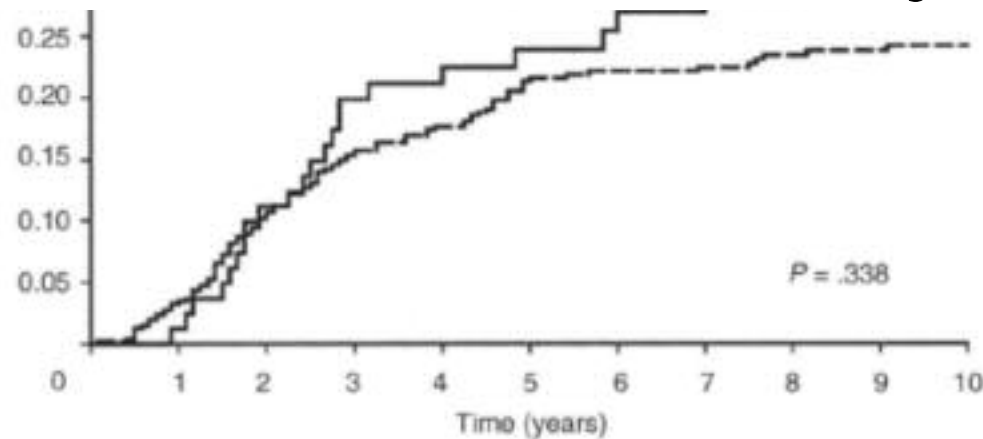
Status of Surgical Margins and Prognosis in Adult Soft Tissue Sarcomas of the Extremities: A Series of Patients Treated at a Single Institution

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Mortality



HR 1.8 after the 5th year



Inadequate surgery may be associated to a poorer prognosis

- **How could it happen... ?**

Extremity Soft Tissue Sarcoma in a Series of Patients Treated at a Single Institution

The Local Control Directly Impacts Survival

Alessandro Gronchi, MD, Salvatore Lo Vullo, BSc,† Chiara Colombo, MD,* Paola Collini, MD,‡ Silvia Stacchiotti, MD,§ Luigi Mariani, MD,† Marco Fiore, MD,* and Paolo Giovanni Casali, MD§*

(Ann Surg 2010;251: 512–517)

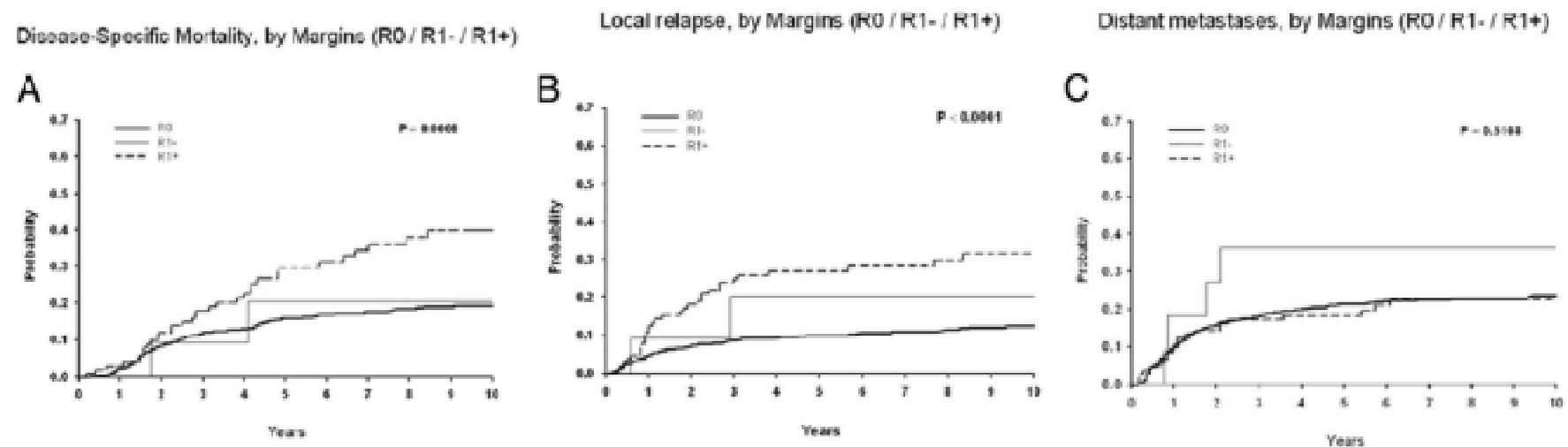
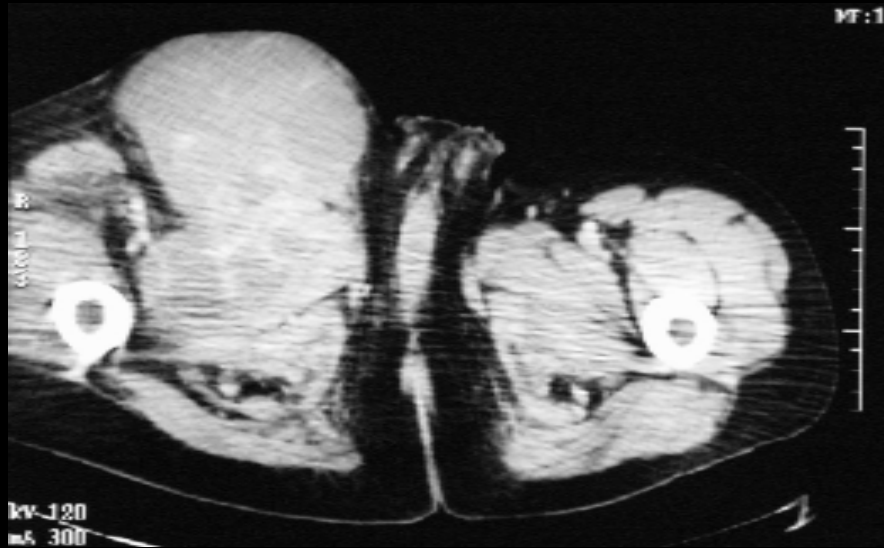


FIGURE 1. Disease specific mortality (panel A), crude cumulative incidence of local recurrence (panel B), crude cumulative incidence of distant metastases (panel C) according to margin status (R0, R1 negative, R1 positive).

Why a better surgery (negative microscopic margins) translated into a survival benefit ?

- 20% of the R1 patients who died of disease, did so for loco-regional recurrence without any distant disease.



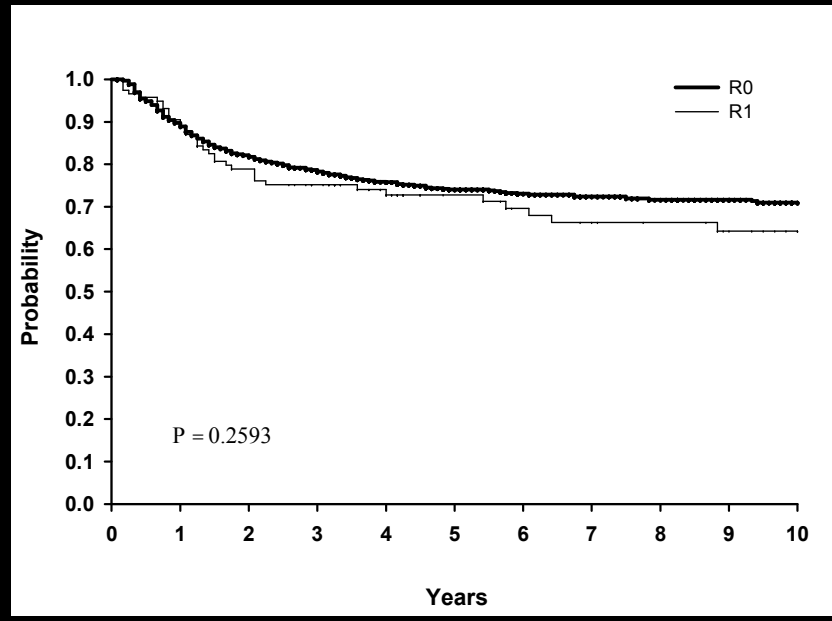
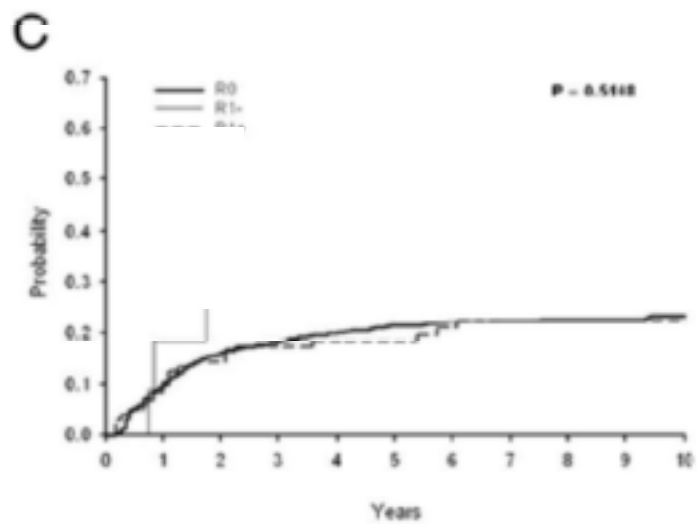
+ margins → LR → Death

**Indeed it fortunately
happens not so often in
ESTS**

Why a better surgery (negative microscopic margins) translated into a survival benefit ?

- was inadequate surgery able to give rise to local recurrence that eventually gave rise to distant metastases and killed the patient ?**

Distant metastases, by Margins (R0 / R1- / R1+)



+ margins → LR → DM → Death

**Positive margins have a higher risk
of death also through the distant
spread occurred after an otherwise
avoidable LR**

We further explored this finding even in another very recent retrospective analysis carried out at our institution on...

1987 - 2007

1094 pts



1987-1991

192

1992-1997

252

1998-2002

274

2003-2007

376

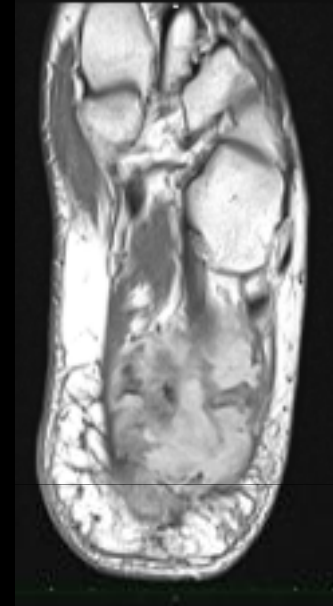
excluding...



DFSP



WD LIPO



DESMOID

Localized Extremity Soft Tissue Sarcoma: Improved Knowledge With Unchanged Survival Over Time

By Jürgen Weitz, Christina R. Antonescu, and Murray F. Brennan

Table 8. Summary of Multivariate Analysis of Prognostic Factors

Factor	Distant Recurrence- Free Survival	Local Recurrence- Free Survival	Relapse- Free Survival	Disease- Specific Survival
Age > 50 years	—	—	—	—
Recurrent sarcoma	—	—	—	—
Size > 5 cm	—	—	—	—
Deep location	—			—
High grade	—		—	—
Proximal position				—
Histology				
Fibrosarcoma		—		
Leiomyosarcoma	—		—	—
Positive microscopic margin	—	—	—	—
Time period of treatment				

NOTE. Minus symbols indicate an independent adverse prognostic factor, and blank fields indicate a nonindependent prognostic factor.

Similarities of prognostic factors in the 4 time periods

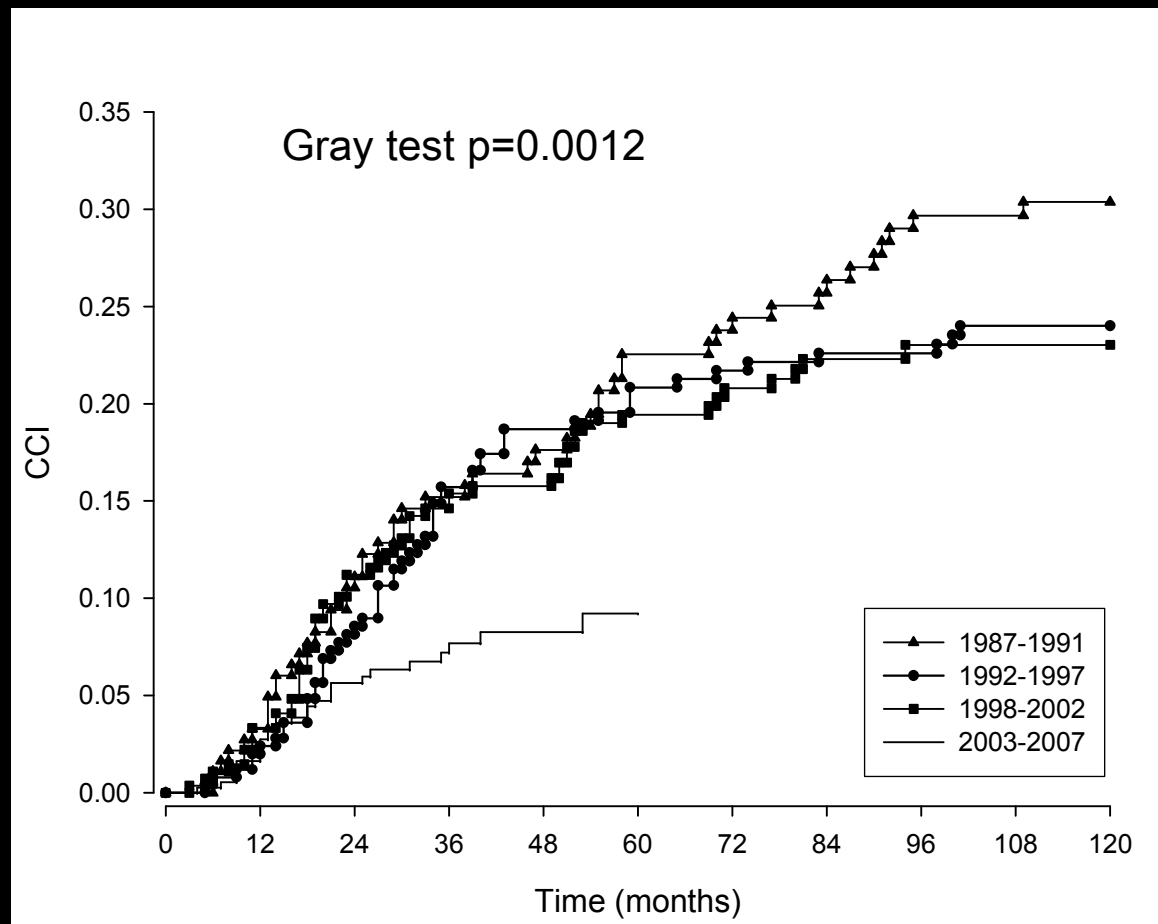
- **Age and gender distribution**
- **Median size**
- **Site of origin**
- **Histological subtype**

Differences of prognostic factors in the 4 time periods

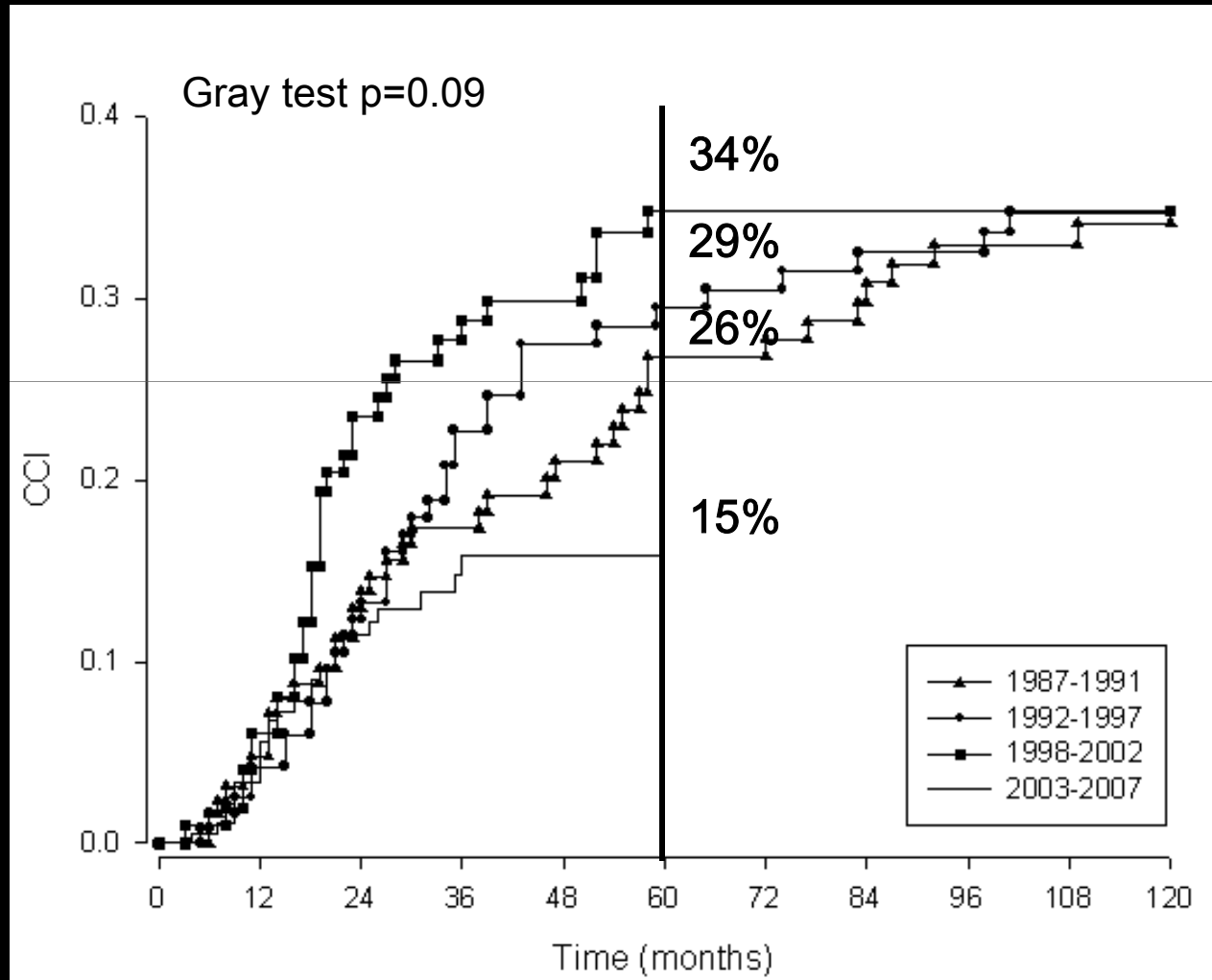
- **Depth (higher rate of deep tumors in the first 2 periods)**
- **Grade (higher rate of grade III tumors in the 1° period)**
- **N° of amputation (decreased from the 1° to 4° period)**
- **+ margins (decreased from 1° to 4° period)**
- **Administration of CT-RT (both as independent procedure but mostly as combined preop treatment, never given before the 4° period)**

1094 Primary ESTS

Sarcoma specific mortality

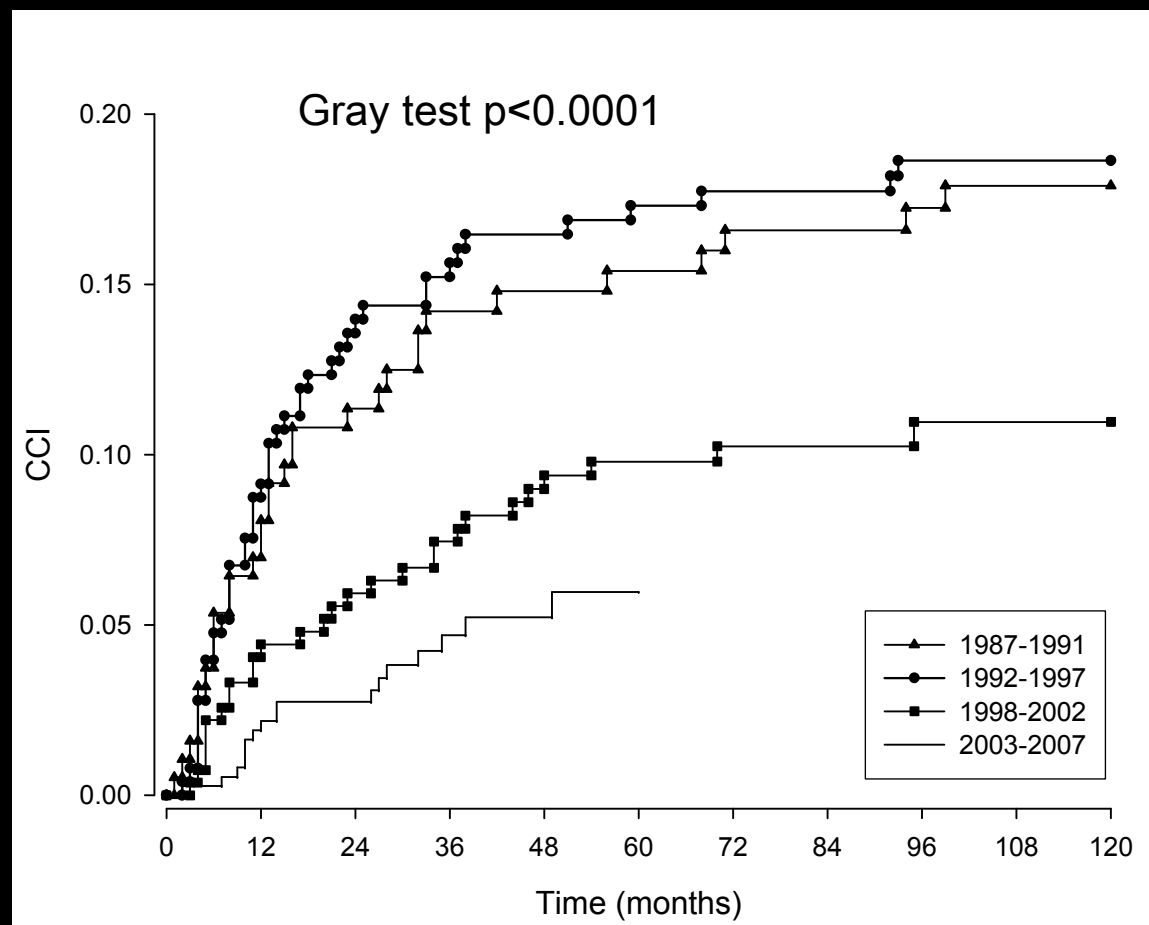


Sarcoma specific mortality – only GIII



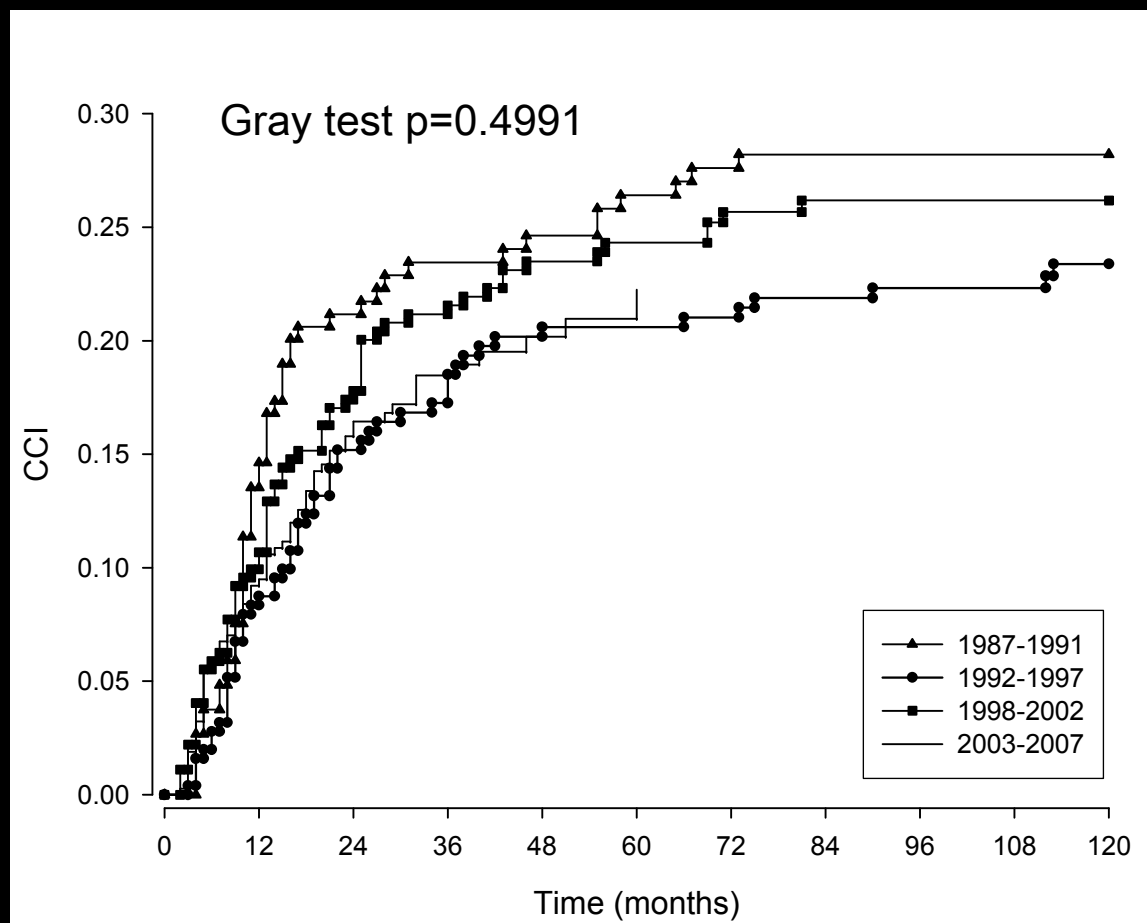
1094 Primary STS

CCI for Local Recurrence

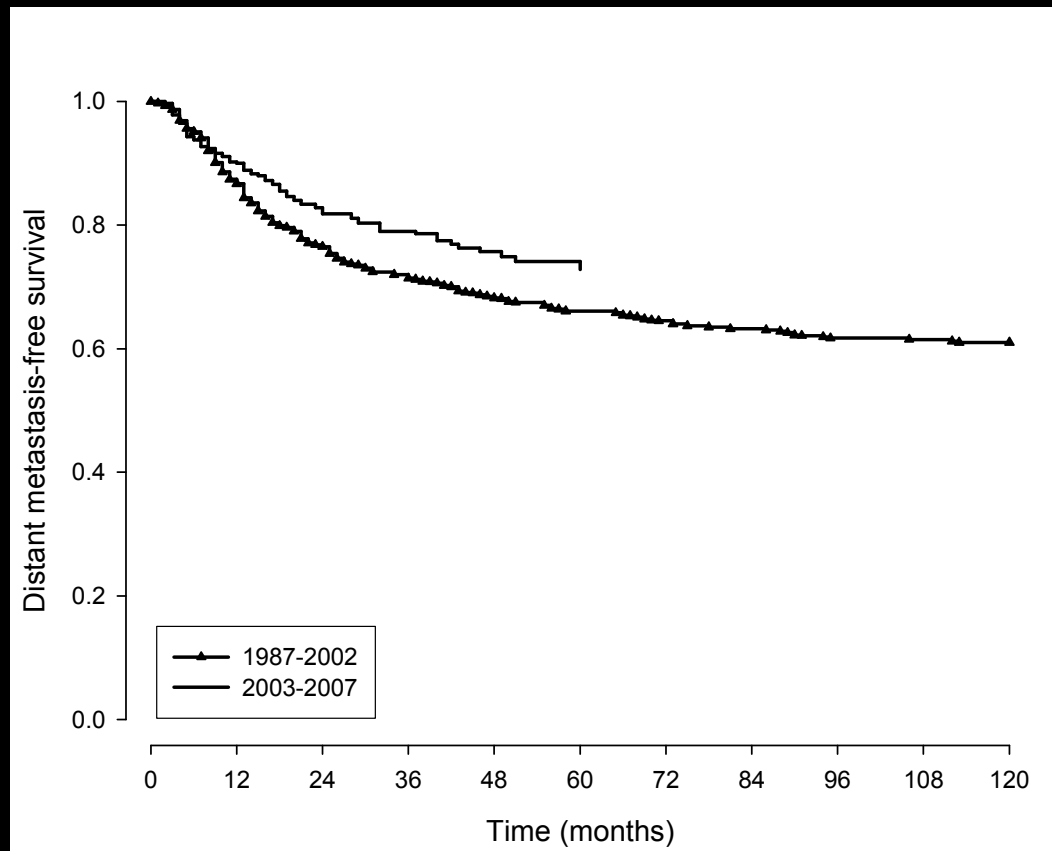


1094 Primary STS

CCI for Distant Metastasis



Metastases free survival



**An improvement in local control –
whatever has made it – was
associated to an improvement in
distant recurrence (7%) and
survival**

In brief

- Local recurrence is bad.
- If it occurs after adequate surgery, it reflects tumor biology. It is associated to a high risk of death (at least 3 times the original one), but a causative effect on metastatic spread is very unlikely to be in place.
- If it occurs after inadequate surgery, it may both be caused by it or reflect tumor biology. It is associated to a less high risk of death (not more than 1.5-2 times the original one), but the effect on survival could be in place also through the occurrence of
 - inoperable locoregional recurrence in critical sites
 - distant spread after local recurrence, that could have been avoided if local recurrence had not occurred
- Every effort should be made to keep the local control in the 90% range, maintaining a very low amputation rate, through multidisciplinary approaches...

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