XXII Congresso Nazionale AIRO
Roma, 17-20 Novembre 2012 .

I Sarcomi delle Parti Molli dell'adulto: Terapia Adiuvante vs Terapia Neoadiuvante

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Extremity Soft Tissue Sarcomas

Aims of Local Treatment

- Effective local control
- Limb sparing and function
- Cosmesis

Extremity Sarcoma
RT and Conservative Surgery

Randomised Trials

Amputation vs WR + post-op RT	P=0.06 (SA Ronsenberg et al., 1982)
WR + BRT vs Wide Resection	P=0.04 (PW Pisters et al., 1996)
WR + post-op RT vs Wide Resection	P=0.002 (JC Yang et al., 1998)

Extremity Soft Tissue Sarcoma
Local Treatment

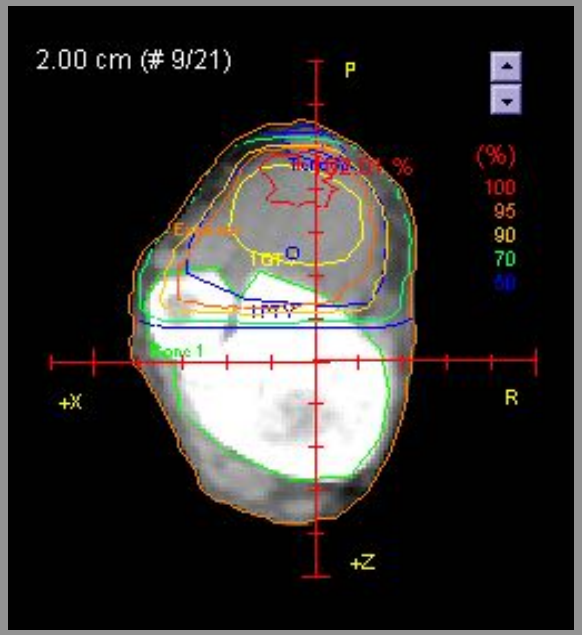
Conservative Surgery and RT

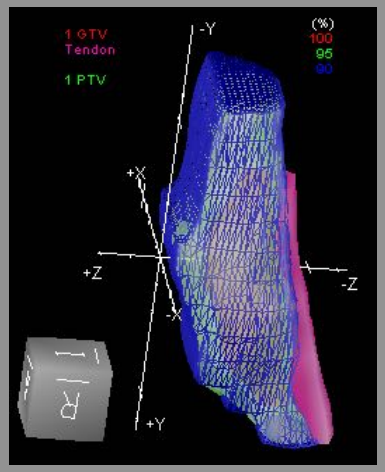
85 - 90 %

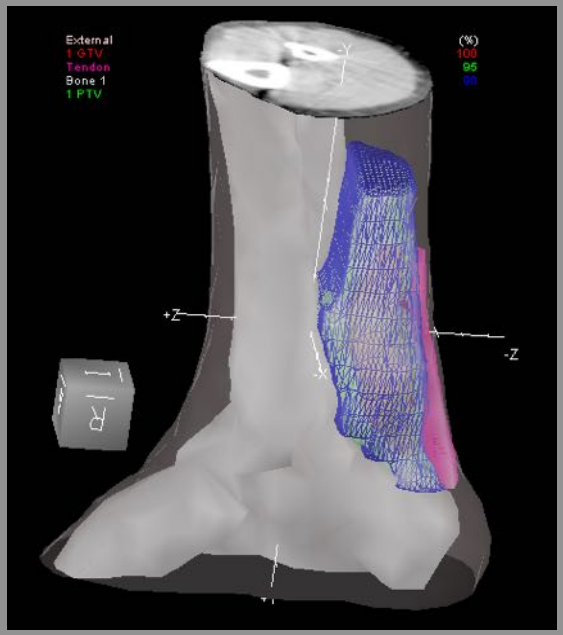
of local control

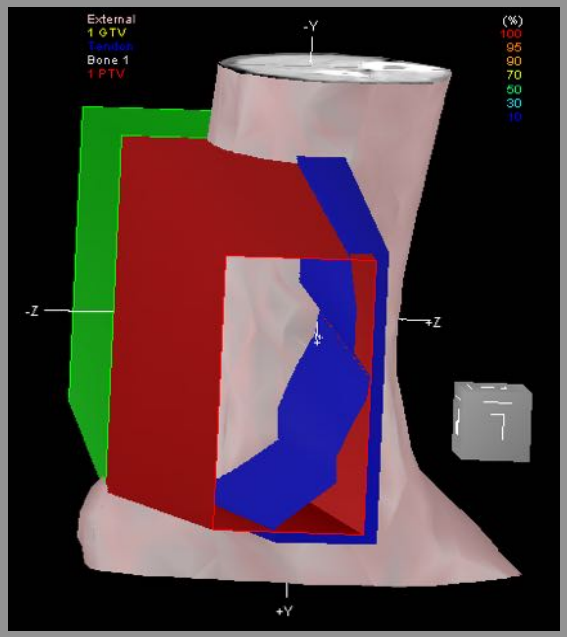
(<10% amputations)

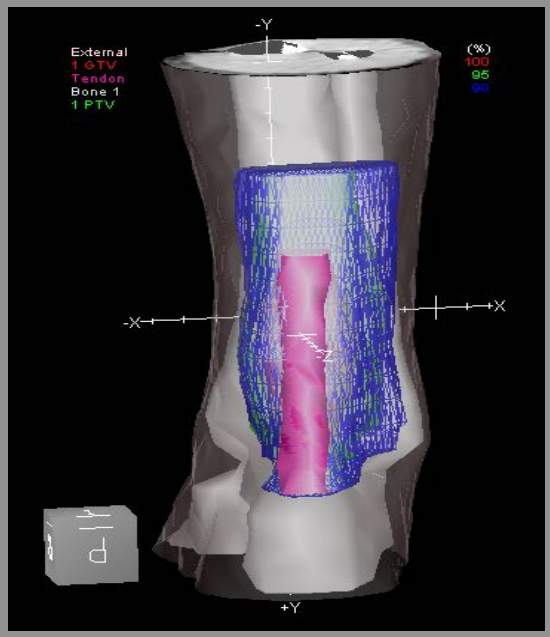
…indeed, preop RT has some potential advantages



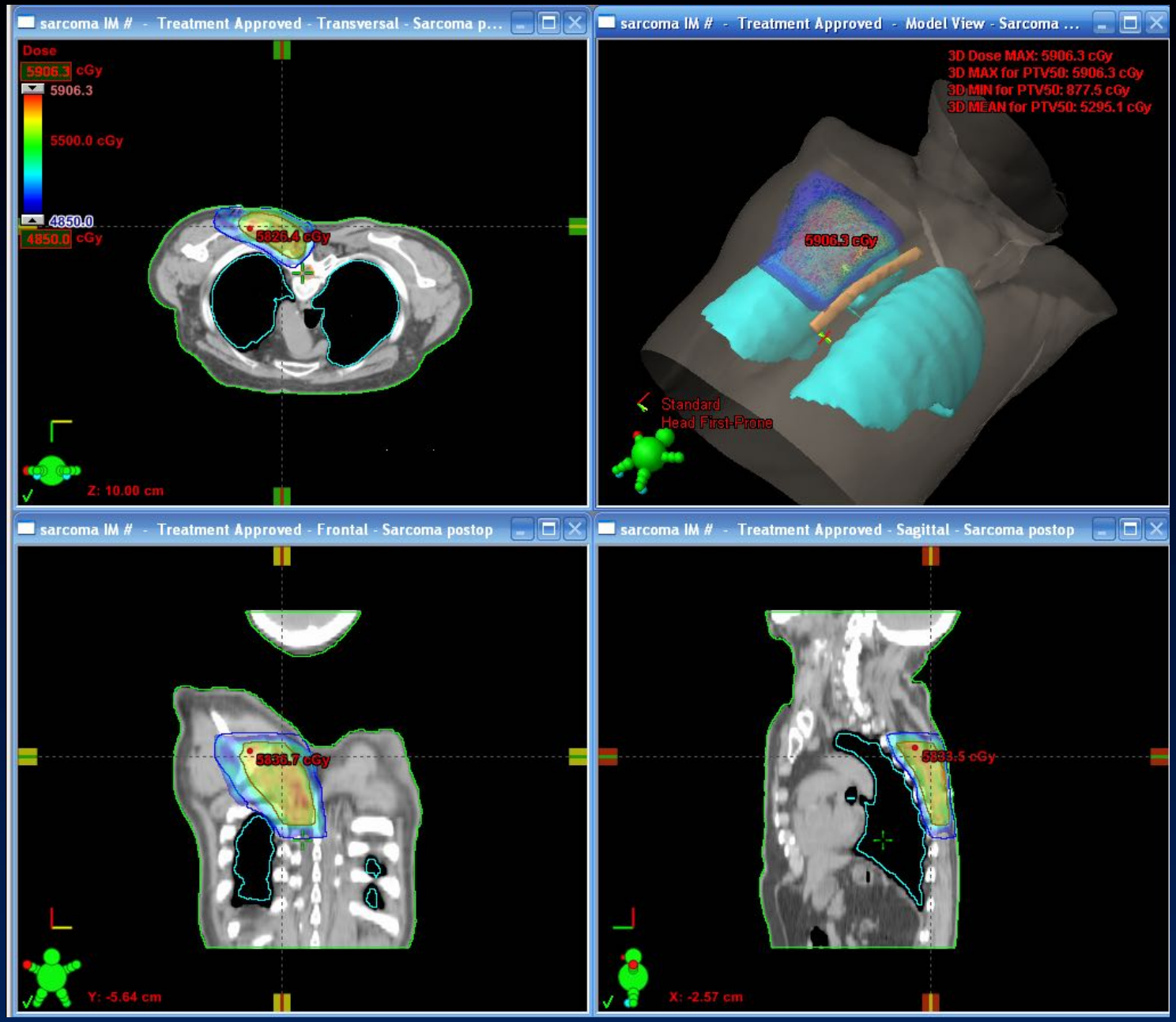








… compared to postop RT



Extremity Soft Tissue Sarcomas
Pre vs Post-op RT- Canadian SR.2 Trial

RT Modality	Early Compl.*	Late Compl.°	OS 3 yrs	
Pre-op	35%	28%	85%	p= 0.01
Post-op	17%	56%	72%	p = 0.03 p=0.048

* Major wound complications °G >=2 subcutaneous fibrosis

B. O'Sullivan et al, Lancet 2002

Adjuvant Chemotherapy for Adult Soft Tissue Sarcomas of the Extremities and Girdles: Results of the Italian Randomized Cooperative Trial

By Sergio Frustaci, Franco Gherlinzoni, Antonino De Paoli, Marco Bonetti, Alberto Azzarelli, Alessandro Comandone, Patrizia Olmi, Angela Buonadonna, Giovanni Pignatti, Enza Barbieri, Gaetano Apice, Hassan Zmerly, Diego Serraino, and Piero Picci

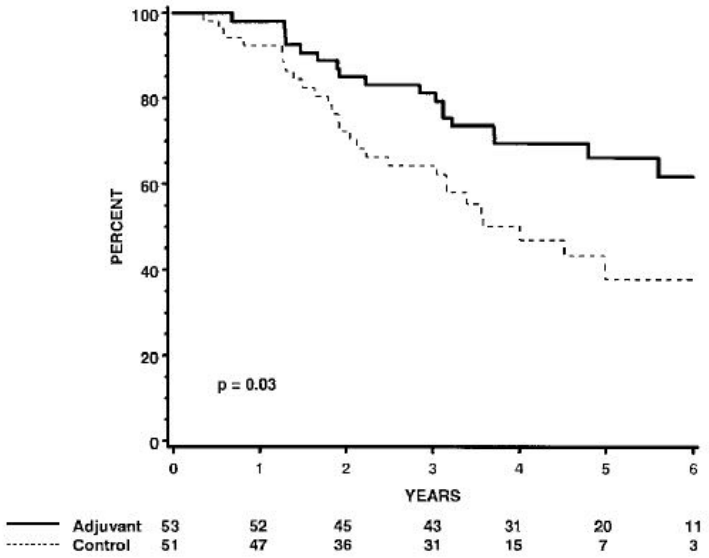


Fig 4. OS by treatment

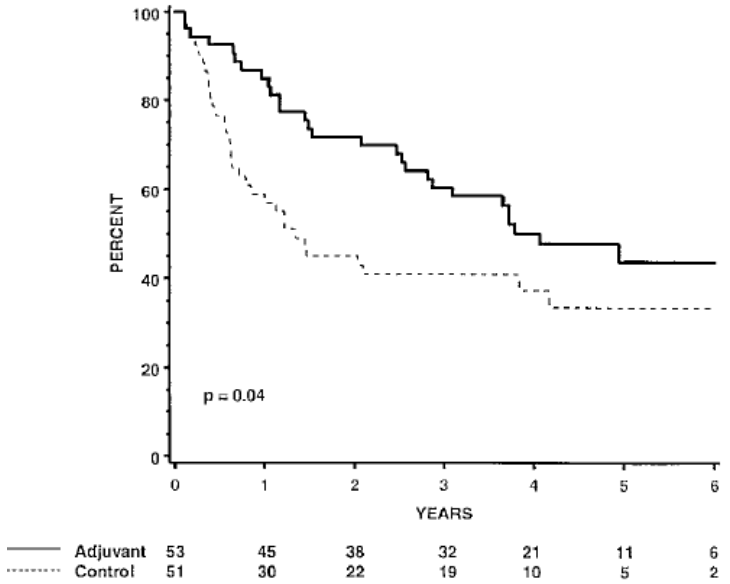


Fig 2. DFS by treatment.

Journal of Clinical Oncology, Vol 19, No 5 (March 1), 2001: pp 1238-1247

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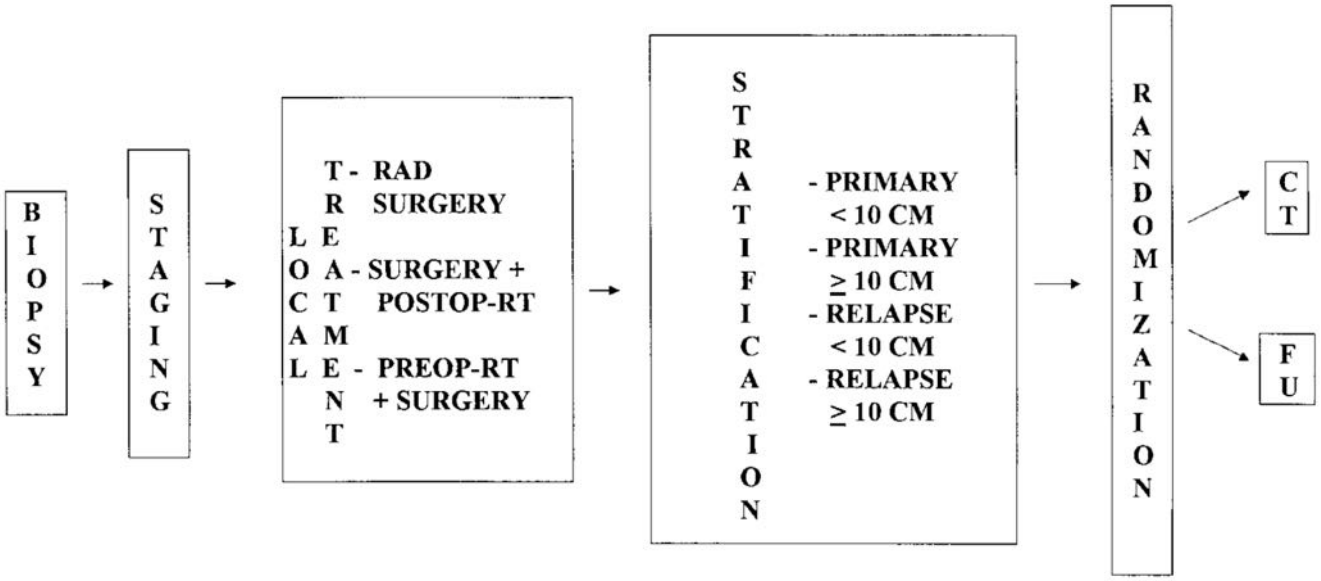

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radical surgery included an high rate of amputations

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Local treatment			
Radical surgery	20	16	36
Amputation	11	16	27
Conservative	9	0	9
Surgery + post-op RT	24	20	44
Pre-op RT + surgery	9	15	24

Journal of Clinical Oncology, Vol 19, No 5 (March 1), 2001: pp 1238-1247

Soft tissue sarcomas: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

P. G. Casali[1], L. Jost[2], S. Sleijfer[3], J. Verweij[3] & J.-Y. Blay[4]
On behalf of the ESMO Guidelines Working Group*

Data have been provided that adjuvant chemotherapy might improve, or at least delay, distant and local recurrence in high risk patients. A recent meta-analysis found a statistically significant, limited benefit in terms of both survival and relapse-free survival. However, studies are conflicting, and a final demonstration of efficacy is lacking.
It is also unknown whether it may be especially beneficial in specific subgroups.

Therefore, adjuvant chemotherapy is not standard treatment in adult-type soft tissue sarcomas, and can be proposed as an option to the high-risk individual patient (having a G2–3, deep, >5 cm tumor) for shared decision-making in conditions of uncertainty [II, C].

STS of the Limbs and Trunk Wall

ISG-GEIS Randomised Trial (High Risk)

R EPI-IFO
x 3 cycles

Local Treatment

A -- Control

B -- EPI-IFO
x 2 cycles

EPI: 60 mg/mq days 1-2
IFO: 3 gr/mq days 1-3
GSF: 300 *u*g days +9 +16

Study Coordinators: S Frustaci CRO-Aviano
A Gronchi INT-Milano
M Mercuri IOR-Bologna

G-GEIS Trial
Local Treatment Options

Favourable Presentation

EI x 3 cycles → **SURG ± RT boost**

→ 46-50 Gy ± 14-16 Gy

→ EI ↓↓↓ 22 Gy G-CSF EI ↓↓↓ 22 ± 16 G-CSF

Critical Presentation

EI ↓↓↓ G-CSF 22 Gy EI ↓↓↓ G-CSF 22 Gy EI ↓↓↓ G-CSF

SURG ± RT boost

→ Control

→ EI x 2 cycles

RT boost: IORT or BRT or 3D-CRT

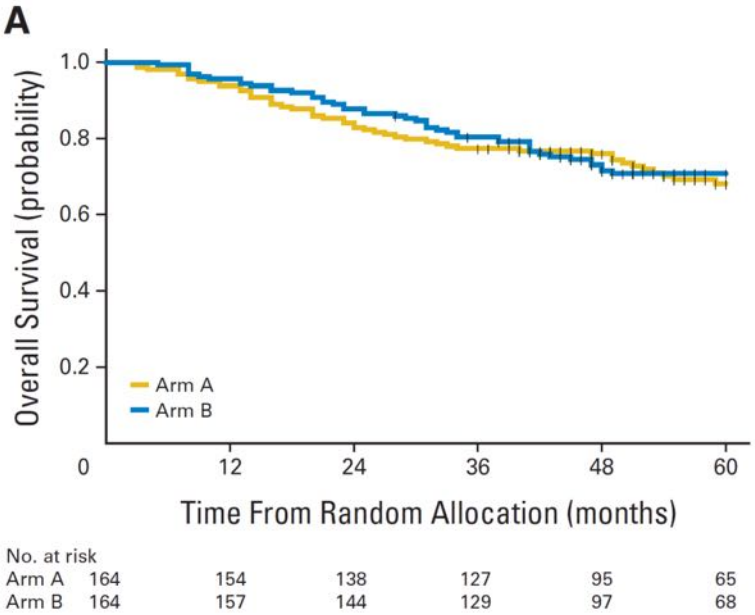
VOLUME 30 · NUMBER 8 · MARCH 10 2012

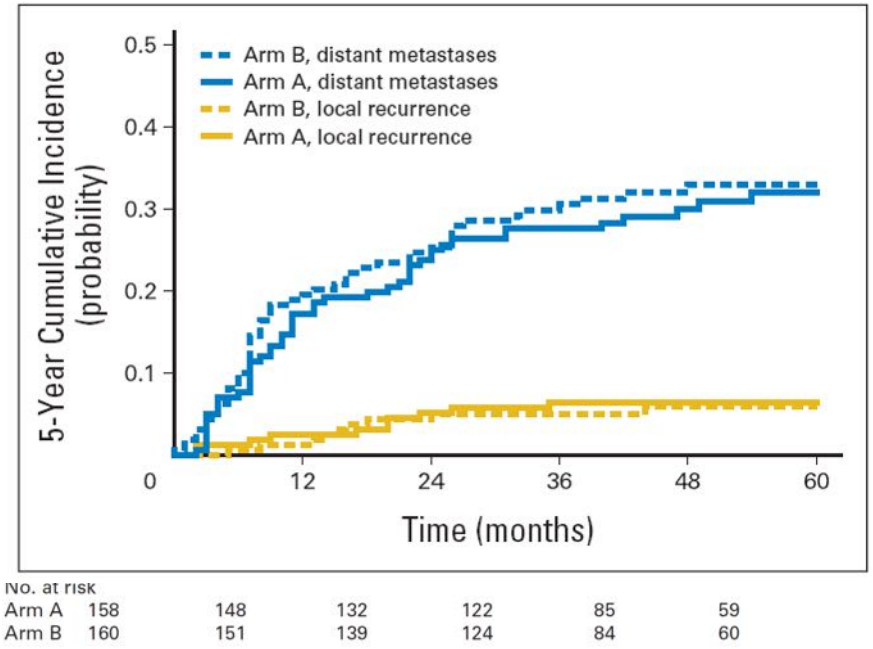
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Short, Full-Dose Adjuvant Chemotherapy in High-Risk Adult Soft Tissue Sarcomas: A Randomized Clinical Trial From the Italian Sarcoma Group and the Spanish Sarcoma Group

Alessandro Gronchi, Sergio Frustaci, Mario Mercuri, Javier Martin, Antonio Lopez-Pousa, Paolo Verderio, Lidia Mariani, Pinuccia Valagussa, Rosalba Miceli, Silvia Stacchiotti, Angelo Paolo Dei Tos, Antonino De Paoli, Alessandra Longhi, Andres Poveda, Vittorio Quagliuolo, Alessandro Comandone, Paolo Giovanni Casali, and Piero Picci





ISG-GEIS TRIAL
RADIATION THERAPY

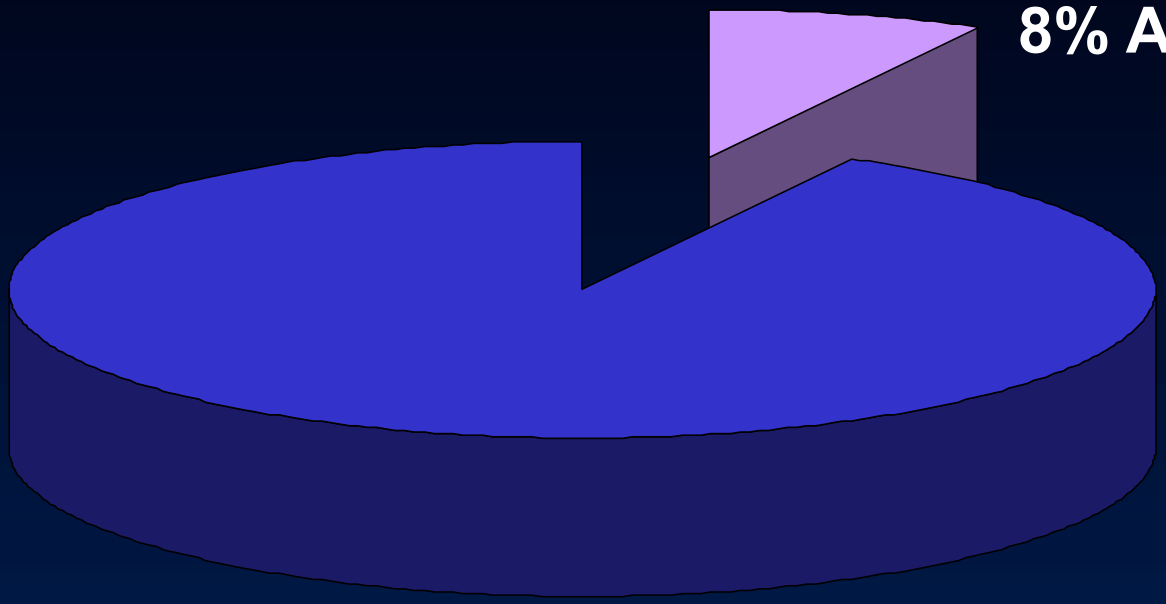
N. Patients 300/328 (91%)

Preop-RT 160 Pts (53.4%)

Postop-RT 140 Pts (46.6%)

ISG-GEIS TRIAL

Primary amputations

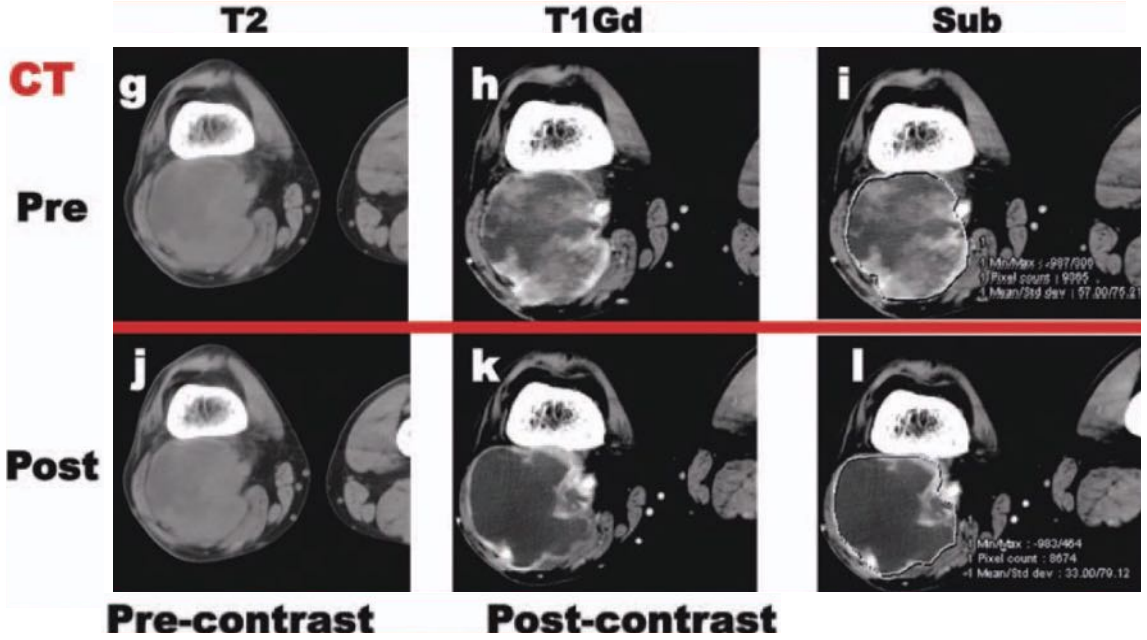


RT 300/328 pts (91%) Preop-RT 160 Pts (53.4%)

Postop-RT 140 Pts (46.6%)

Tumor Response Assessment by Modified Choi Criteria in Localized High-Risk Soft Tissue Sarcoma Treated With Chemotherapy

Silvia Stacchiotti, MD[1]; Paolo Verderio, PhD[2]; Antonella Messina, MD[3]; Carlo Morosi, MD[3]; Paola Collini, MD[4]; Antonio Llombart-Bosch, MD[5]; Javier Martin, MD[6]; Alessandro Comandone, MD[7]; Jurado Cruz, MD[8]; Andrea Ferraro, MD[9]; Giovanni Grignani, MD[10]; Sara Pizzamiglio, MSc[2]; Vittorio Quagliuolo, MD[11]; Piero Picci, MD[12]; Sergio Frustaci, MD[13]; Angelo Paolo Dei Tos, MD[14]; Paolo G. Casali, MD[1]; and Alessandro Gronchi, MD[15]



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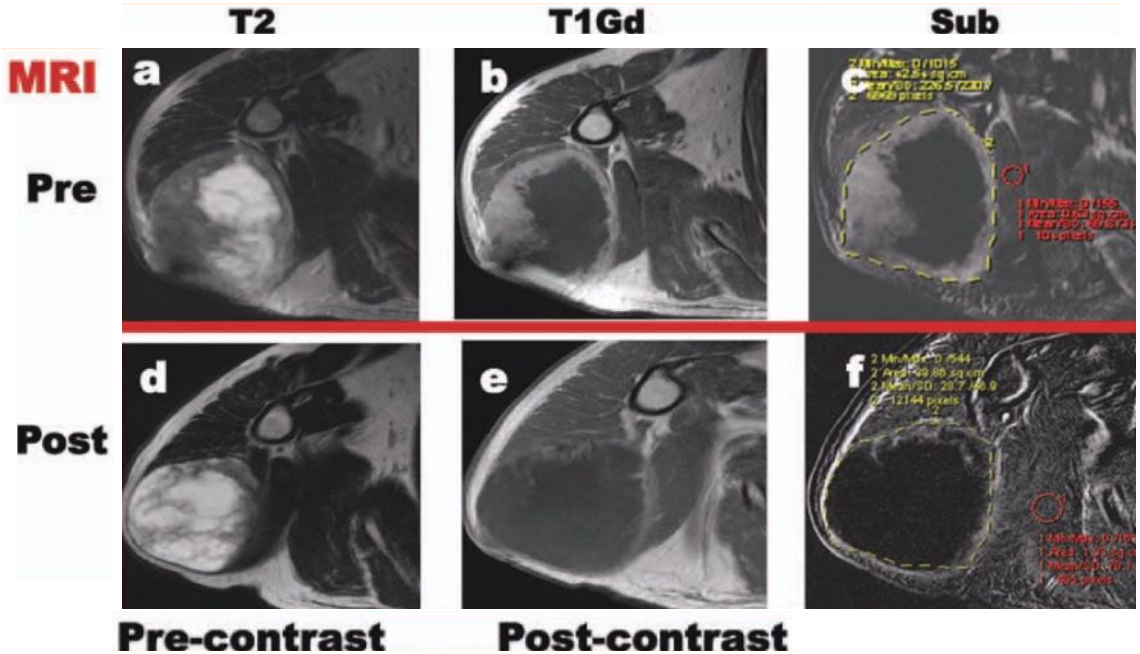


CT-related bone marrow toxicity - Protocol Compliance

Preop RT

	RT	noRT	P value
WBC G4	**53%**	**47%**	**0.5**
PLT	90% completed preop CT in both arms, independently of combination with RT		
Hb G			
TTS	70% completed postop CT in arm B (67% if RT in preop setting, 75% if not)		
TCT (months)	**1.5±0.13**	**1.5±0.18**	**0.9**

TTS: Time To Surgery

Ferrari S et al, CTOS 2012

ISG-GEIS TRIAL

Compliance to Radiation Therapy

Treatment	Pts	RT dose (Gy)	RT dose/ plannedRT(pts)
EI–S + postopRT	124	60(30-70)	109/124(88%)
EI + preopRT – S	138	44(40-50)	131/138(95%)

available data on 262/300 pts (87%)

De Paoli A et al, CTOS 2010

Early Complications (SR.2Trial criteria) data on 221/300 pts

Complication	Preop RT-CT N.Pts	Postop RT+/-CT N.Pts
Secondary operations	11	8
Readmission/prolonged hospital stay	4	3
Invasive procedure	2	3
Deep wound packing	3	1
Dressing changes >6w.	3	1
TOTAL	**23/120(20%)**	**16/101(15%)**

De Paoli A et al, CTOS 2010

Early Complications by Center data on 221/300 pts

Center	N.Pts	Complication
A	71	20%
B	70	16%
C	39	18%
D	23	17%
E	18	18%

De Paoli A et al, CTOS 2010

Preop CT-RT Toxicity

	MGH 39 pts %	RTOG 66 pts %	ISG-GEIS 160 pts %
RT(CT) compliance	83.3	89.0	91.6
G3 Acute Tox	31.0	13.0	19.0
G4 Acute Tox	48.0	78.0	53.0
Complications	29.0	11.0	20

DeLaney TF et Al – IJROBP, 2003
Kraybill WG et Al – JCO, 2006

Pre-op MAID + RT
RTOG Phase II Study 9514

N. Pts: 66; Extremity/Body W. G_2-G_3 ≥8 cm

MAID^ x 3 cycles + RT 44 Gy
SURG ± RT boost
MAID x 3 cycles

5 yrs	LDFS	78%
	DFS	56%
	OS	71%

Toxicity 78% G_4 Tox. **(hem)**
Complications 11% wound healing

3(5%) Deaths (AML)

^ Modified MAID (IFO 2.5gr/m2)

WG Kraybill, JCO 2006
WG Kraybill, Cancer 2010

Pre-op MAID + RT
MGH Phase II Study

N. Pts: 39; Extremity G_2-G_3 ≥8 cm

MAID x 3 cycles + RT 44 Gy
SURG ± RT boost
MAID x 3 cycles

5 yrs	LDFS	92% vs 86%(°)
	DFS	77% vs 42%
	OS	87% vs 58%
Toxicity		48% G_4 neutropenia
Complications		29% wound healing

(°) historical controls

TF DeLaney, IJROBP 2003

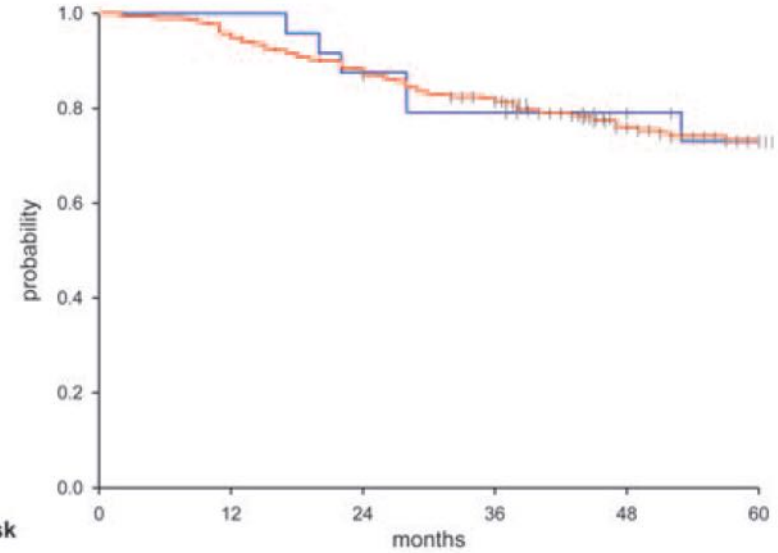
original article

Annals of Oncology 0: 1–7, 2012
doi:10.1093/annonc/mds501

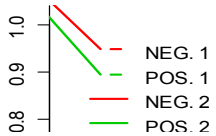
Quality of surgery and neoadjuvant combined therapy in the ISG-GEIS trial on soft tissue sarcomas of limbs and trunk wall

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]

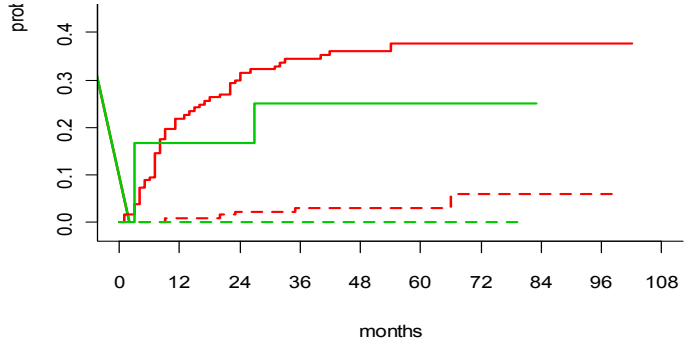
A



N. at risk						
Negative	218	209	193	174	118	82
Positive	14	24	21	19	15	12



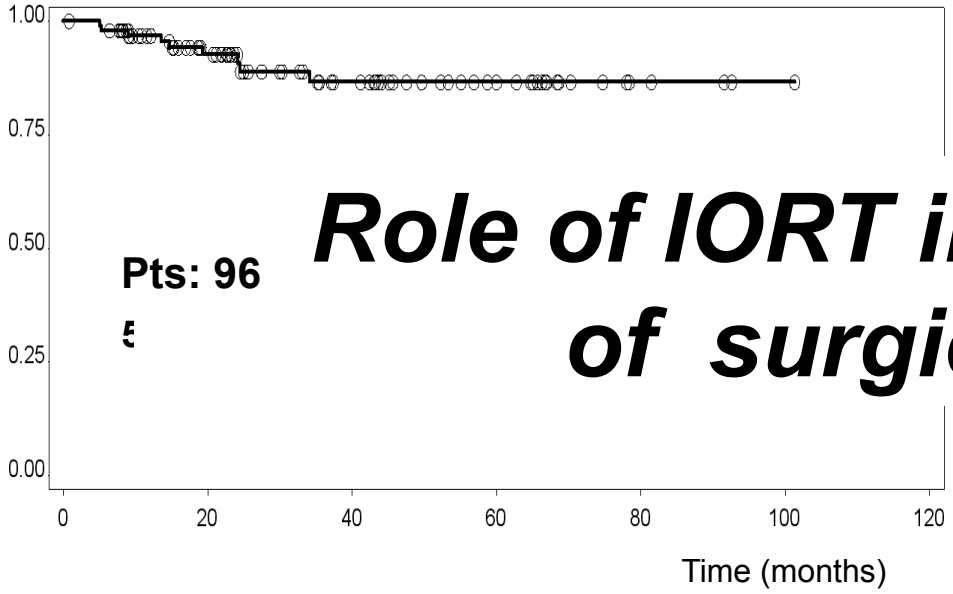
Positive margins do not affect local outcome after preop RT



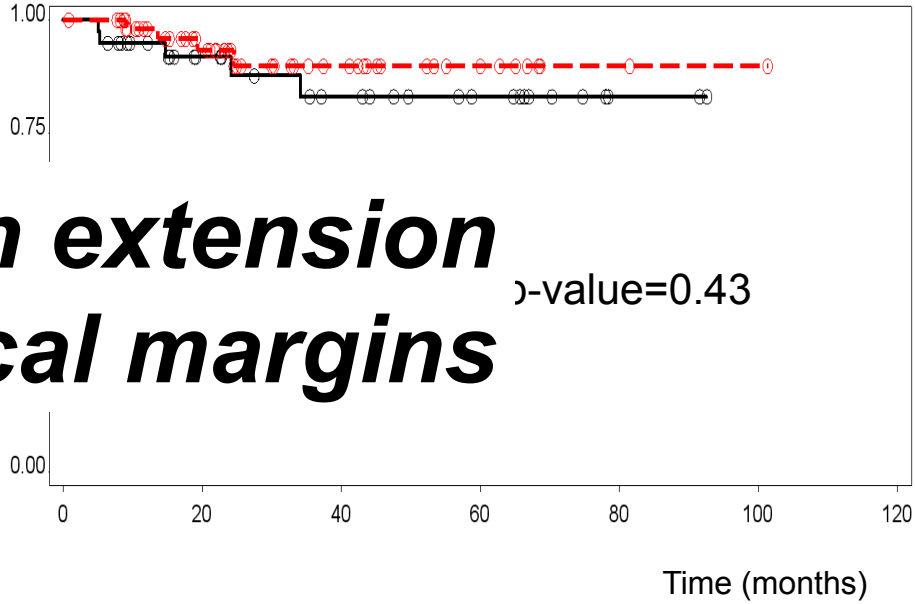
Preop RT+/-CT and IORT for Sarcoma of Extremity and S.Trunk

Local Control analysis

Local Control



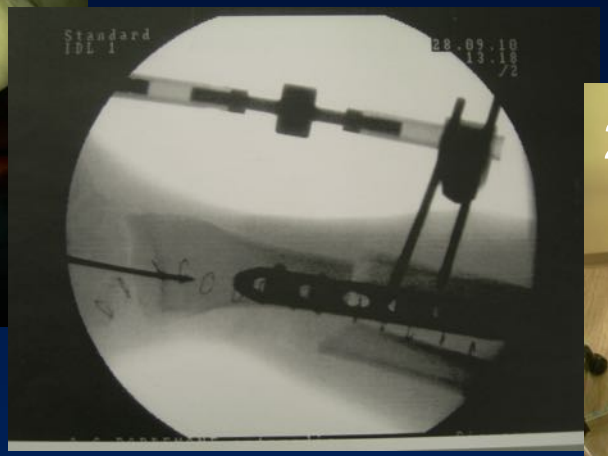
Local Control by Resection



Role of IORT in extension of surgical margins

De Paoli A et al, ISIORT 2010

Preop RT/Chemo, Resection-IORT and Surgical recontruction Strategy



CRO
Aviano

Histotype-tailored neoadjuvant CT Phase III Trial within an integrated approach

- High grade, spindle cell
- Limbs, superficial trunk
- >5 cm and/or local relapse

R

EI x 3 + Surg/RT +/- Boost

ht CT x 3 + Surg/RT +/- Boost

RT Boost: IORT
BRT
EBRT

MFH, Pleomorphic	Gem/Tax
Syn Sa	Ifx
LMS	Gem/Tax
Round Cell Lipo	ET743
MPNST	Carbo/VP

… in summary

- **Pre or Postop RT can be safely combined with full-dose of adjuvant epirubicin and ifosfamide** *(extremity/sup trunk sarcoma)*
- **Neoadjuvant CT and RT may be preferred for HR-extremity STS** (critical presentations)
- **Histoype-tailored neoadjuvant chemotherapy could be combined with new RT modalities (IMRT-IGRT/IORT) in most HR-extremity STS** *(phase I-II studies for Gem-Tax/RT are needed)*