Preop chemo/RT in Soft Tissue Sarcoma

Alessandro Gronchi
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The use of (neo)adjuvant chemo in STS
Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data
Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data

6% absolute improvement in LRFS
10% absolute improvement in DMFS
4% absolute improvement in OS
• 1568 patients
• Median FU 9.4 yrs

• 67% “High” grade
• 16% > 10 cm
• Any site (extremities and girdle 60%; uterine sarcoma 17%)
• Any histologies (30% affected by “other” histologies)
• Doxorubicine alone or in combination with other drugs

• 10% absolute improvement in DM
A Systematic Meta-Analysis of Randomized Controlled Trials of Adjuvant Chemotherapy for Localized Resectable Soft-Tissue Sarcoma

5% absolute improvement in LRFS
10% absolute improvement in DMFS
11% absolute improvement in OS

BACKGROUND. The use of adjuvant chemotherapy in treat adults with localized resectable soft-tissue sarcoma remains controversial. The objective of this sys-

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Adjuvant chemotherapy with doxorubicin, ifosfamide, and lenograstim for resected soft-tissue sarcoma (EORTC 62931): a multicentre randomised controlled trial

Penella J Woll, Peter Reichardt, Axel Le Cesne, Sylvie Bonvalot, Alberto Azzarelli, Harald J Hoekstra, Michael Leahy, Frits Van Coevorden, Jaap Verweij, Pancras C W Hogendoorn, Monia Quali, Sandrine Marreaud, Vivien H C Bramwell, Peter Hohenberger, for the EORTC Soft Tissue and Bone Sarcoma Group and the NCIC Clinical Trials Group Sarcoma Disease Site Committee

• 1995-2003
• 351 patients
• Median FU 8 yrs

• G2 and G3 (G3 = 46% after central path review)
• Any size (median 8 cm)
• Any site (extremity and girdle: 278, 80%)
• Any histologies: 90 patients affected by “other” histotypes + DD liposarcoma in the Liposarcoma group
• Doxo 75mg/sqm + Ifo 5g/sqm
• A trend for better RFS/OS in larger tumors and G3
Adjuvant chemotherapy with doxorubicin, ifosfamide, and lenogastim for resected soft-tissue sarcoma (EORTC 62931): a multicentre randomised controlled trial

Penella J Woll, Peter Reichardt, Axel Le Cesne, Sylvie Bonvalot, Alberto Azzarelli, Harald J Hoekstra, Michael Leahy, Frits Van Cauwenberge, Jaap Verweij, Pancras C W Hogendoorn, Monia Qualli, Sandrine Marraud, Vivien H C Bramwell, Peter Hohenberger, for the EORTC Soft Tissue and Bone Sarcoma Group and the NCIC Clinical Trials Group Sarcoma Disease Site Committee

<table>
<thead>
<tr>
<th>Events/patients</th>
<th>Statistics</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>O-E</td>
</tr>
<tr>
<td>Adjuvant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMAC⁹</td>
<td>328/767</td>
<td>-20.4</td>
</tr>
<tr>
<td>Fakhrai et al 2010¹¹</td>
<td>12/31</td>
<td>0</td>
</tr>
<tr>
<td>Petrioli et al 2002¹⁴</td>
<td>13/45</td>
<td>-5.4</td>
</tr>
<tr>
<td>Frustaci et al 2003¹³</td>
<td>22/53</td>
<td>-7.3</td>
</tr>
<tr>
<td>62931</td>
<td>68/175</td>
<td>-3.1</td>
</tr>
<tr>
<td>Total</td>
<td>443/1071 (41.4%)</td>
<td>-36.2</td>
</tr>
</tbody>
</table>

Test for heterogeneity χ²=4.84, df=4, p>0.1

Favours adjuvant Favours control

• 1995-2003
• 351 patients
• Median FU 8 yrs

• Loose inclusion criteria
• Histologic subtype not considered
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 Scacchiotti, Cécile 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 3: Distant metastases nomogram
Median predicted OS (pr-OS):
72% (IQR 57-83%)
The impact of chemotherapy on survival of patients with extremity and trunk wall soft tissue sarcoma: revisiting the results of the EORTC-STBSG 62931 randomised trial

Sandro Pasquali a,*, Sara Pizzamiglio a, Nathan Touati a, Saskia Litte i b, Sandrine Marreaud c, Bernd Kasper d, Hans Gelderblom e, Silvia Staicu iott f, Ian Judson g, Angelo P. Del To s h, Paolo Verderio a, Paolo G. Casali i, Gabriele Penella J. Wolf i, Alessandro Gronchi a,*,* on behalf of the EORTC – Soft Tissue and Bone Sarcoma Group

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b Unit of Biodeformative and Reconstructive, Department of Applied Research and Technological Development, Fondazione IRCCS Istituto Nazionale Del Tumore, Milan, Italy
c European Organization for Research and Treatment of Cancer (EORTC), Brussels
d University of Wroclaw, Medical University, Surgical Oncology – Thoracic Centre, Sarcoma Unit, Wroclaw, Poland
e University of Clinical Oncology, Ludwig University Medical Center, Lindau, Bavaria, Germany
f Department of Clinical Oncology, Linköping University, Medical Centre, Linköping, Sweden

Median predicted OS (pr-OS): 72% (IQR 57-83%)

Low pr-OS (adj vs Obs) HR 0.50 (0.28-0.90)
High pr-OS (adj vs Obs) HR 1.20 (0.75-1.91)

LOW < 60%
HIGH >60%

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KEYWORDS
Soft tissue sarcoma; Adjuvant; Chemotherapy;

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A benefit in the high risk population is possible if chemotherapy is given at full doses

epiADM 120 mg/m² + IFX 9 g/m² q 21 days

*Journal of Clinical Oncology, Vol 19, No 5 (March 1), 2001: pp 1238-1247*
• 1992-1996
• 104 patients
• Median FU 5 yrs

• G3
• Size > 5 cm (median 10 cm)
• Only extremity and girdle
• Selected histologies: 8 patients affected by “other” histotypes
• Epidoxo 120mg/sqm + Ifo 9g/sqm
• A better RFS/OS
which is “maintained” even at a long FU….

Median FU 90 months

**Fig. 1.** Overall survival of 104 randomized patients.

**Fig. 2.** Overall survival in patients initiating adjuvant chemotherapy versus control.

Oncology 2003;65(suppl 2):80–84
• 1992-1996
• 104 patients
• Median FU 5 yrs

• Stricht inclusion criteria
• Histologic subtype not included
Overall Survival
However the dose intensity of the last 2 cycles was significantly reduced

<table>
<thead>
<tr>
<th>Table 2. Median and Average Relative Dose-Intensity (DI) (%)</th>
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<tbody>
<tr>
<td>Dose-Intensity (%)</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>EPI</td>
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<tr>
<td>Median</td>
</tr>
<tr>
<td>Range</td>
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<td>IFO</td>
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<tr>
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<tr>
<td>Range</td>
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<tr>
<td>ARDI</td>
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<tr>
<td>Median</td>
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<tr>
<td>Range</td>
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</tbody>
</table>

Abbreviation: ARDI, average relative dose-intensity.
• Can we obtain the same benefit at a lower “price”?

• Why don’t we give chemotherapy in the neoadjuvant setting, so that we start with the treatment, which addresses the systemic risk?
ISG – STS - GEIS 0101

- high grade
- deeply seated
- >5 cm

\[ epiADM+IFX \times 3^* \rightarrow \text{Surgery + RT} \]

\[ epiADM+IFX \times 3^* \rightarrow \text{Surgery + RT} \rightarrow epiADM+IFX \times 2 \]

\* epiADM 120 mg/m² + IFX 9 g/m² q 21 days

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Short, full-dose adjuvant chemotherapy (CT) in high-risk adult soft tissue sarcomas (STS): long-term follow-up of a randomized clinical trial from the Italian Sarcoma Group and the Spanish Sarcoma Group.

Median FU 10 yrs

ISG – STS 1001

Group 1

histology-tailored chemo x 3 → Surgery + RT

MLPS: Trabectedin 1.3 mg/m² q 21 days
LMS: GEM 1800 mg/m² + DTIC 500 mg/m² q 14 days
UPS: GEM 900 mg/m² day 1-8 + TAX 75 mg/m² q 21 days
Synovial Sa: HD-IFX 14 g/m² over 14 days q 28 days
MPNST: IFX 9g/m² + Etoposide 450 mg/m² q 21 days

epiADM+IFX x 3 → Surgery + RT

epiADM 120 mg/m²+ IFX 9g/m² q 21 days

- high grade
- deep seated
- >5 cm

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• 2011-2016
• 287 patients
• Median FU 52

• G3
• Size > 5 cm (median 11 cm)
• Only extremity and girdle
• Only 5 histologic subtypes
• Epidoxo 120mg/sqm + Ifo 9g/sqm X 3 vs histology tailored regimens
The first study which included histologic subtype

<table>
<thead>
<tr>
<th>Subtype</th>
<th>MLPS</th>
<th>LMS</th>
<th>UPS</th>
<th>Synov Sa</th>
<th>MPNST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count</td>
<td>65 (23%)</td>
<td>28 (10%)</td>
<td>97 (34%)</td>
<td>70 (24%)</td>
<td>27 (9%)</td>
</tr>
<tr>
<td>HT</td>
<td>28 (10%)</td>
<td>16 (6%)</td>
<td>52 (18%)</td>
<td>34 (12%)</td>
<td>12 (4%)</td>
</tr>
<tr>
<td>S</td>
<td>37 (13%)</td>
<td>12 (4%)</td>
<td>45 (16%)</td>
<td>36 (12%)</td>
<td>15 (5%)</td>
</tr>
</tbody>
</table>
The importance of histologic subtype

Incidence of DM

Time (months)

Probability

LMS
SS
UPS
PLPS
MLPS
MFS
MPNST
VS
Other

Lancet Oncol 2016; 17(5):671-80
3rd Futility Analysis

Median FU: 12.34 months (IQ range: 25.45)

Lancet Oncol 2017; 18:812-822
Final analysis

Median FU: 51.75 months (IQ 28.03)
The projection of the DFS of the HT arm was similar to the no Tx arm of the 1st ISG trial.
... but infact it was not Disease-free Survival
The outcome of HT chemo proved to be better than initially projected.
DFS of the E(A)I arm of the 3 consecutive studies were consistent.
OS of the E(A)I arm of the 3 consecutive studies were consistent.
S chemotherapy was associated with an absolute benefit averaging 10% for both DFS and OS.

This may be the least added value of neoadjuvant chemotherapy per se in high-risk STS.
Median predicted pr-OS: 63% (IQR 50-72%)
Median observed OS: 72% (IQR 57-83%)

Median FU: 51.75 months (IQR 28.03)
Of note, in the lower risk group (@Sarculator predicted OS ≥ 60%) the difference between the 2 treatment arms was almost nil.

**Predicted OS ≥ 60% (median 70%)**

**DISEASE FREE SURVIVAL**

HR: 1.01 (95%CI 0.61, 1.67; p=0.958)

**OVERALL SURVIVAL**

HR: 1.51 (95%CI 0.75, 3.05; p=0.248)
while, in the higher risk group (@Sarculator predicted OS < 60%) a wider difference between the 2 treatment arms was observed.

**Predicted OS < 60% (median 46%)**

**DISEASE FREE SURVIVAL**

@Sarculator < 60

- Standard CT
- Histotype-tailored CT
- Standard CT-censored
- Histotype-tailored CT-censored

HR: 1.47 (95%CI 0.92, 2.37; p=0.109)

**OVERALL SURVIVAL**

@Sarculator < 60

- Standard CT
- Histotype-tailored CT
- Standard CT-censored
- Histotype-tailored CT-censored

HR: 1.91 (95%CI 1.00, 3.66; p=0.0498)
Is (neo)adjuvant chemotherapy a standard for every high risk STS?
Is (neo)adjuvant chemotherapy a standard for every high risk STS?

- Undifferentiated Pleomorphic Sarcoma
- Leiomyosarcoma
- Synovial Sarcoma
- Malignant Peripheral Nerve Sheath Tumor
- High grade Myxoid Liposarcoma (A/E.I. or Trabectedin?)

80% high risk STS of the extremities and trunk wall
Is (neo)adjuvant chemotherapy a standard for every high risk STS?
The higher the risk the higher the benefit against systemic spread with a **cut-off at 40%** with the available therapies.
Is (neo)adjuvant concurrent chemo-RT possible?
High grade Myxoid Liposarcoma
The Significance of a Marginal Excision After Preoperative Radiation Therapy for Soft Tissue Sarcoma of the Extremity

Roi Dagan, MD; Daniel J. Indelicato, MD; Lisa McGee, MD; Christopher G. Morris, MS; Jessica M. Kirwan, MA; Jacquelyn Knapi, MD; John Reith, MD; Mark T. Scarborough, MD; C. Parker Gibbs, MD; Robert B. Marcus, Jr, MD; and Robert A. Zlotecki, MD, PhD

Marginal margins do not affect local outcome after preop RT
The Effect of the Setting of a Positive Surgical Margin in Soft Tissue Sarcoma

Patrick W. O'Donnell, MD, PhD1,2,3; Anthony M. Griffin, MS1,2; William C. Eward, DVM, MD1,2,3; Amir Sternheim, MD1,2,3; Charles N. Catton, MD4; Peter W. Chung, MD4; Brian O'Sullivan, MD4; Peter C. Ferguson, MD1,2,3; and Jay S. Wunder, MD1,2,3

A planned positive margin on a critical structure is not improved by its resection, if adequate RT is delivered.
Quality of surgery and neoadjuvant combined therapy in the ISG-GEIS trial on soft tissue sarcomas of limbs and trunk wall

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

Positive margins do not affect local outcome after preop CT-RT
Anthracycline/Ifosfamide + RT

- Response rate ($\downarrow$ max diameter $\geq 10\%$): 50%
  - CT alone: 45%
  - CT-RT: 50%
- Progression rate: 6%
  - CT alone: 7%
  - CT-RT: 6%
A glance into the future
Concurrent RT and trabectedin in MLPS
Neoad Pembro + RT in DD LPS and UPS

Randomized Phase II Design

Grade 2 – 3 UPS or LPS, >5 cm

Screening & Consent

Eligible patients

STRATIFY: • Grade

RANDOMIZE

Group 1 (Standard of Care)

Group 2 (Experimental)

Group 1: Standard of Care Arm

Image-guided XRT (50 Gy/25 fractions) 4-6 wk Surgery Follow up

Group 2: Experimental Arm

Image-guided XRT (50 Gy/25 fractions) 4-6 wk Surgery Adjuvant pembrolizumab (200 mg Q3 week; up to 14 cycles for 1 yr total therapy)

Pembrolizumab 200 mg Q3 wk

Follow up

SARC 032
... the next study...

Preop RT → Surgery

epiADM+IFX x 3* + RT → Surgery

- high grade
- Extremity/trunk wall
- >5 cm
- Sarculator <40% risk of death

*epiADM 120 mg/m² + IFX 9 g/m² q 21 days

MLPS
LMS
UPS
Synovial Sa
MPNST
MFS
PLPS
... the next study...

epiADM+IFX x 3* → Surgery + RT

epiADM+IFX x 3* + RT → Surgery

*epiADM 120 mg/m2 + IFX 9 g/m2 q 21 days

- high grade
- Extremity/trunk wall
- >5 cm
- Sarcculator >40% risk of death

LMS
UPS
Synovial Sa
MPNST
MFS
PLPS
... the next study...

- epiADM+IFX ± RT x 3* → Surgery
  
*epiADM 120 mg/m² + IFX 9 g/m² q 21 days

- epiADM+IFX x 3* ± RT → Surgery → histology tailored chemo X 3

- high grade
- Extremity/trunk wall
- >5 cm
- Sarculator >40% risk of death

MLPS: Trabectedin 1.3 mg/m² q 21 days
LMS: GEM 1800 mg/m² + DTIC 500 mg/m² q 14 days
UPS: GEM 900 mg/m² day 1-8 + TAX 75 mg/m² q 21 days
Synovial Sa: EI X 3
MPNST: EI X 3
... the next study...

epiADM+IFX + RT x 3* → Surgery

*epiADM 120 mg/m2 + IFX 9 g/m2 q 21 days

«DoPe» x 3 + RT → Surgery → Pe X 1 yr

- high grade
- Extremity/trunk wall
- >5 cm
- Sarculator >40% risk of death
In RPS: STRASS 2

G3 LPS

R

SURGERY ONLY

PREOP ADM/IFO + SURGERY

LMS

R

SURGERY ONLY

PREOP ADM/DTIC + SURGERY
Statistical design

• Type I error 2 sided: p 0.05
• Power 85%
• HR: 0.6 (H0 36.3%, H1 54.4%)
• N. events: 140
• N. patients: 250
EORTC and TARPSWG networks
A glance into the future
RPS

G1-G2 LPS
- SURGERY ONLY
- PREOP RT + SURGERY

G3 LPS
- SURGERY ONLY
- PREOP ADM/IFO + SURGERY

LMS
- SURGERY ONLY
- PREOP ADM/DTIC + SURGERY

All RPS not
- INVESTIGATOR/PATIENT’S CHOICE

TARSTS cohort d

STRASS 2

RESAR