The evidence for and against neoadjuvant chemotherapy in localized STS

Axel Le Cesne
Gustave Roussy, Villejuif
French Sarcoma Group
EORTC, CTOS
Académie de Médecine

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Localized resectable STS

Adjuvant CT?

For who??

Male 30-60 yrs
Extremity
5-10 cm
High grade

Which hystotype?
Only for R1?
Margins unknown?

Adjuvant chemotherapy should never be intended to rescue inadequate surgery

Tierney et al, Lancet 1997
Le Cesne et al, Annals of Oncol 2014
Meta-analysis of adjuvant CT for soft tissue sarcoma

On source data meta-analysis
14 trials, 1568 patients (1973-1990)

Overall Survival: HR: 0.91 (NS)
Local relapse: HR: 0.74 (p = 0.024)

If adjuvant CT improves local control….
….better before surgery than postoperatively!

Tierney et al, Lancet (1997); 350: 1647-54
**Adjuvant CT in STS**

**Frustaci S et al.**  
*JCO* 2001

**Sarcoma Meta-analysis.**  
*Lancet* 1997

**EORTC 62931**  
Woll, LO 2012

5-yr overall survival: 40 to 60%

R0 resection in adjuvant series: 50 to 60%
R0 resection: prerequisite for cure!

Figure 1. Local recurrence-free probability according to resection type.

Stoeckle E, et al. EJSO 2006; 32: 1242-48

Primary endpoint for each localized STS: R0 en bloc resection!
R2/R1 resection: prerequisite for relapse/death?
Patients whose primary surgery was performed in Netsarc centers had R0, R1, R2 surgery in 49%, 27%, 7% vs 24%, 31%, 21% in centers outside Netsarc (p<0.000001)
If the decision is made to use CT as upfront treatment, it may well be used preoperatively. A local benefit may be gained, facilitating surgery.

Multi agent CT with adequate dose anthracyclines plus ifosfamide is the treatment of choice.
FULL-DOSE NEOADJUVANT ANTHRACYCLINE+IFOSFAMIDE CHEMOTHERAPY IS ASSOCIATED WITH A RFS AND OS BENEFIT IN LOCALIZED HIGH-RISK ADULT STS OF THE EXTREMITIES AND TRUNK WALL: INTERIM ANALYSIS OF A PROSPECTIVE RANDOMIZED TRIAL.

Gronchi A; Ferrari S; Quagliuolo V; Martin Broto J; Lopez Pousa A; Grignani G; Ferraresi V; Basso U; Blay JY; Tendero O; Valverde C; Rutkowski P; Merlo FD; Fontana V; Marchesi E; Ledesma P; Dei Tos AP; Bagué S; Coindre JM; Morosi C; Stacchiotti S; Donati DM, Palassini E; Palmerini E; De Sanctis R; Picci P; Bruzzi P and Casali PG
Standard versus histotype-tailored CT

ISG-STS 1001

Homogeneous group of STS
Grade III, adult type STS
Extremities and trunk wall
Size ≥ 5 cm

Hypothesis: HT CT reduces by 30% the risk of relapse (40 to 27%, HR: 0.66)
N random = 350, 500 registered
Analysis: 150 events (relapses or deaths) with interim analysis for futility (IDMC)
ISG-STS 1001 - Results

N = 287 ® pts

RFS

P=0.004

62%

38%

OS

P=0.033

89%

64%
Induction CT in STS
Response rate with anthrac + ifosfamide

Very few PD during CT: no lost of chance for the vast majority of patients

Ruiz et al, EJC 2011
Gronchi et al, ESMO 2016
Induction CT in STS
Response rate with anthrac + ifosfamide

N = 80

Rate of R0
92%

Locally advanced STS

Rate of R0
90%

Resectable STS

N = 121

High level of R0 resection, pre-requisite for a better outcome in STS

Ruiz et al, EJC 2011

Gronchi et al, ESMO 2016
Evolution of PFS overtime with EI regimen in the adjuvant and neoadjuvant setting in high grade STS of extremity

Results mean: increasing the rate of R0 with neoadjuvant CT could have an impact on PFS in localized operable STS of extremity
1) Three cycles of HT-CT regimen: a «placebo» control arm.....

2) Three cy of EI in neoadjuvant setting > 5 cy in adjuvant means better to achieved a R0 resection after CT than received 5 adjuvant cycles after a R1 resection...
RFS by histology subtype – Histological response

**Phase II trial - trabectedin in resectable MLPS  N = 23**

4 pCR, 10 pPR, no clinical PD

*A. Gronchi et al, Annals of Oncol 2011*

**Phase II trial - AI regimen - GR**

*R. Ruiz et al, EJC 2011*
Is neoadjuvant chemotherapy in resectable STS a new standard of care?

Evidence for neoadjuvant CT:

- « Facilitate » surgery: « planed » surgery vs « unplanned » one
- High level of R0 resection, pre-requisite for a better outcome in STS
- Very few PD during CT (3%) : no lost of chance for the vast majority of patients
- Validation of routine practice in referral center using neoadjuvant full dose since a few decades in « marginally » operable STS patients
- Rigorous selection of patients (50-70% risk of relapse, use of a « sarcomator algorythm »?)
- Translational studies for precision medicine programs in large/referral centers with techniques used to identify new actionable targets (Moscato, MOST, MultiSarc….)
- Impact of MTB in the decision making in referral centers dedicated to STS (NetSarc, ESMO 2016)
## Sarcoma reference networks (2009-2014)

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<th>Surgery inside Netsarc</th>
<th>Surgery outside NetSarc</th>
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<tbody>
<tr>
<td><strong>Radiology before treatment</strong></td>
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<tr>
<td>Yes</td>
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<td>No</td>
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<td><strong>Biopsy before surgery</strong></td>
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<td><strong>Discussion in MTB</strong></td>
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<td>Before surgery</td>
<td>56%</td>
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<tr>
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<td><strong>First discussion in MTB</strong></td>
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<tr>
<td>Before surgery</td>
<td>54%</td>
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<td>After surgery</td>
<td>48%</td>
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### Sarcomas / GIST / desmoïds

- 2011 N=2386
- 2012 N=2772
- 2013 N=3006
- 2014 N=3247

### Rechute

- Avant chirurgie: 41%
- Après chirurgie: 47%
- Rechute: 45%

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Is neoadjuvant chemotherapy in resectable STS a new standard of care?

Evidence against neoadjuvant CT/ Limits

• Not indicated in all extremity high grade STS (<50% risk of relapse?) where a R0 resection is a « easy » achievement with free tumor margins. Discussion in MTB!!
• Optimal management of pts with early PD under CT at first tumor evaluation (after 2 cycles)? : RT, ILPs, local hyperthermia, salvage CT, amputation?
• Selection of histotype based on early predictive factors of sensitivity/resistance to anthracyclins/alkylating agents has to be defined!
• Quality of induction CT no equivalent to quality of surgery!! Induction CT has to be performed in referral centers qualified for surgery of these diseases +++
• Optimal duration of induction CT in « responding » patients? How many cycles of EI?
Late responders to first line chemotherapy (AI) for advanced or metastatic soft tissue sarcoma have a longer survival than early responders.

M. Van Glabbeke, A. Le Cesne, ASCO 2000
Neoadjuvant chemotherapy in resectable STS
Could we do better?

- Mandatory: histological response related to favorable outcome?? (as OS/PNET)
- If yes: development of new strategies based on histological responses
  - EI/AI plus RT
  - EI/AI plus targeted therapies (olaratumab….)
  - EI/AI vs ILPs vs RT…
  - New histotype tailored CT in other histological subtypes of STS
  - ……
- Having in mind that tumor control and metastases could not be predicted by the same factors…. 
Surgery is the standard treatment of all patients with an adult type, localized STS. It must be carried out by a surgeon specifically trained in the treatment of this disease [III, A]. The standard surgical procedure is a wide excision with negative margins (R0).

Addition from Dr Le Cesne: patient has to be alive before surgery!
The increase in tumor control should be balanced against toxicity

“Primum non nocere”

Hippocrates
If your lump is bigger than a golf ball and growing, think Sarcoma and think neoadjuvant CT!

R. Nandra a,*, J. Forsberg b, R. Grimer a

a Bone Tumor Service, The Royal Orthopaedic Hospital, Bristol Road South, Birmingham B31 2AP, United Kingdom

b Section of Orthopaedics and Sports Medicine, Department of Molecular Medicine and Surgery, Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden

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Abstract

Aim: Only 1 in 100 of primary care consultations regarding new soft tissue lumps (STL) are malignant and are susceptible to a delay in diagnosis. We aimed to generate a Bayesian Belief Network to estimate the likelihood of malignancy in patients to facilitate the initial evaluation of a STL and improve timing and quality of referrals to specialist treatment centres.

Methods: We evaluated all patients referred with a new STL between 1996 and 2007. Variables investigated focused on patient factors, symptoms and STL characteristics. Relevant data was extracted and coded for statistical analysis.

Results: 3018 patients with a STL were assessed, of which 1563 (52%) were benign and 1455 (48%) malignant. The features most conditionally associated with the outcome of interest (Benign or Malignant) are referred to as first-degree associates, and are increasing size, age, size of the lump, and duration of symptoms, in that order. On cross validation, this model demonstrated an AUC of 0.77 (95% CI, 0.75–0.79).

Conclusions: For the first time, we have described the hierarchal relationship between factors and created an aide memoire, larger than a golf ball and growing, to trigger referral to tertiary tumor units. Importantly, we found pain to be a poor discriminatory factor. We hope our findings will lead to greater awareness and earlier diagnosis of STL.

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Keywords: Golf ball; Sarcoma; Nomogram; Soft tissue lump; Bayesian belief network
Thank you