Systemic treatment in isolated lung metastases of STS: state of the art

Axel Le Cesne
Gustave Roussy, Villejuif, France

ESMO, 28th of September 2014
Isolated lung metastases in STS
ESMO 2012 recommendations

1) Metachronous resectable lung metastases without extrapulmonary disease are managed with surgery, if complete excision of all lesions is feasible.
Comments: for a surgeon excision of all lesions is always/often feasible… …whatever the number of mets…(until 250, Treasure et al, BJM 2013)

2) Chemotherapy may be added to surgery as an option. Chemotherapy is preferably given before surgery, in order to assess tumor response and thus modulate the length of treatment.
Comments: if medical oncologists see the patients in first!
Poor responders to CT are not in the published surgical series… …biais in the interpretation of results
Isolated lung metastases
impact of « sarcoma » tumor boards

Lurkin A et al, BMC Cancer 2010

Advanced disease in STS: The decision-making is complex, depending on diverse presentations and histologies, and should always be multidisciplinary
21\textsuperscript{st} century: to understand our mistakes and sarcoma complexity

At least 50 histological subtypes, multiple primary sites, size, grade, age…

100 patients with isolated lung metastases included in retrospective surgical/medical series

= 100 different diseases!!

\textit{Courtesy of G. Demetri}
STS – Adjuvant CT
EORTC 62931

Relapse free survival

Grade 2 and some grade 1 STS

Grade 3

Observation
Adjuvant

P. Woll, Lancet Oncol 2012
Post-metastasis survival in extremity STS: Prognostic factors

Gpe A: low grade/metastasectomy

Gpe B: low grade/ no metastasectomy, DFI ≥ 1 yr

Gpe C: low grade / no Metastasectomy, DFI < 1 yr

Gpe D: High grade / no Metastasectomy, DFI < 1 yr

Advanced STS: A “potentially curable” disease for oncologist…?

5 years OS: 8% of all pts included in clinical trials (majority of women/PS0/grade1)  Blay et al, EJC 2004

5 years OS: 15% (Thames Cancer Registry)

81/1888 patients considered in CR after 1st chemotherapy line (4.3%)
Isolated lung metastases: a “curable” disease for surgeons!

- The words « cure » or « curative » are used in 7/18 surgery reports and in NICE guidance (National Institute for Health and Clinical Excellence) for metastatic soft tissue sarcoma!

- 5 years overall survival in all series: 20 to 50%
  30% in S. Kang et al, EJC 2014

20 to 50% of all pts with advanced STS seen in Oncology Department ??

« In the absence of control data, quantifying the difference in survival among patients who have metastasectomy, and attributing it to metastasectomy rather than selection for metastasectomy, is bad science »
“A randomized controlled trial is necessary if we are to see the signal from the noise in this area of clinical practice”  
(T. Treasure et al, BMJ 2013)
STUDY 62933: DESIGN
Study coordinator: A. van Geel, Rotterdam

Closed after inclusion of 37/340 patients in 4 years!

Metastatic soft tissue sarcoma
< 6 lung metastases
no extra-pulmonary disease
metastasectomy feasible

Randomization
Insitution choice - high or low* dose
to be applied to all patients

No neo-adjuvant chemotherapy

DOXO 75 mg/m^2 d1 (50 mg/m^2)*
IFOS 5 g/m^2 d1
G-CSF 150 ug/m^2 d3 to 13 (none)*
3 cycles / q 3 wks

DOXO 75 mg/m^2 d1 (50 mg/m^2)*
IFOS 5 g/m^2 d1
G-CSF 150 ug/m^2 d3 to 13 (none)*
2 cycles / q 3 wks if CR/PR before surgery
Multi-agent chemotherapy with adequate-dose anthracyclines plus ifosfamide may be the treatment of choice, especially when a tumor response is felt to be able to give an advantage and patient performance status is good.
## Advanced STS Poly- vs monoCT

<table>
<thead>
<tr>
<th>Authors</th>
<th>Schedule</th>
<th>N</th>
<th>OR</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muss</td>
<td>A/AC</td>
<td>104</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Omura</td>
<td>A/AD</td>
<td>146</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Borden</td>
<td>A/AD</td>
<td>186</td>
<td>AD = 30%</td>
<td>(p = 0.02)</td>
</tr>
<tr>
<td>Lerner</td>
<td>A/AD</td>
<td>66</td>
<td>AD : 44%</td>
<td>(leiomyo S)</td>
</tr>
<tr>
<td>Santoro</td>
<td>A/AI/CYVADIC</td>
<td>449</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Borden</td>
<td>A/AVd</td>
<td>295</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Edmonson</td>
<td>A/AI/APM</td>
<td>262</td>
<td>AI = 34%</td>
<td>(p = 0.03)</td>
</tr>
<tr>
<td>Antman</td>
<td>AD/MAID</td>
<td>340</td>
<td>MAID : 32%</td>
<td>(p = 0.002)</td>
</tr>
<tr>
<td>Judson</td>
<td>A/AI</td>
<td>415</td>
<td>AI: 26%</td>
<td>(p = 0.0006)</td>
</tr>
</tbody>
</table>
Overall survival by treatment

Overall Logrank test: p=0.129

The impact of surgery of residual lung mets after an adapted polyCT should be apparent if the rate of pts with resectable isolated lung metastases was high!

S. Sleijfer et al, 2009

Judson et al, LO 2014
General treatment algorithm in STS

1\textsuperscript{st}-line chemotherapy
- Anthracyclins

2\textsuperscript{nd}-line chemotherapy
- Ifosfamide

3\textsuperscript{rd}-line and beyond
- Trabectedin (Europe)
- Pazopanib
- gemcitabine + docetaxel (US)

CURE

LOCAL DISEASE
- Surgery ± RT+/- CT

50-60%

LOCAL RELAPSE
- Surgery ± RT+/- CT

80-90%

METASTASES

Paliative

LOCAl RELAPSE AND METASTASES
- Isolated lung mets “Curative”? 10-20%

- Anthracycline-based multi-agent chemotherapy

- Trabectedin (Europe)
- Pazopanib
- gemcitabine + docetaxel (US)
- Clinical trials

Surgery
Isolated lung metastases
Selection of patients with CT

Surgery alone: 41
CT then surgery: 52

Both histological and radiological responses to pre-operative CT seems to be prognostic in STS pats undergoing complete pulmonary metastasectomy

Pre-operative CT «selects»
Good/poor candidates for surgery

N = 93

Radiological response

- PR
- SD
- PD

Cumulative survival

Progression-free survival

Time (months)

p = 0.02
Induction CT in STS

If the decision is made to use CT as upfront treatment, it may well be used preoperatively, at least in part. A local benefit may be gained, facilitating surgery.

Rate of nonPD 94%
Rate of R0 82%

N = 80
CR  57%
PR  32%
SD  5%
PD  6%

Ruiz et al, EJC 2011
Isolated lung metastases of STS in 2014

« Take home messages »

- **The first step:** no surgery, no emergency (metachronous mets = synchronous infra-clinical mets!)
- **The second step:** pluridisplinary discussion in a « sarcoma » tumor board
- **The third step:** strategy depending of mets evolution after two consecutive CT scan (size and number)

<table>
<thead>
<tr>
<th>Increase in size, not in number (gde 1-2)</th>
<th>Planned Surgery</th>
<th>« Adjuvant » CT if naive pts?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in both size and number (gde 3)</td>
<td>Systemic treatments</td>
<td>Planned Surgery in responders?</td>
</tr>
</tbody>
</table>

Majority of tumors will be seen in « sarcoma » tumor boards! Registry at diagnosis of lung metastases!
Isolated lung metastases of STS
« initial surveillance »

D1

Increase in size, not in number

2-3 months later

No systemic treatment

Planned Surgery/locoregional approaches
Isolated lung metastases of STS
« initial surveillance »

D1

Increase in both size and number

Systemic treatments

2-3 months later

Planned Surgery in responders?
# Future of CT in isolated lung mets in front line?
## Active drug/regimen in 2014

<table>
<thead>
<tr>
<th>Histological subtype</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dedifferenciated Liposarcoma</td>
<td>Doxorubicin +/-Ifosfamide</td>
</tr>
<tr>
<td>Myxoid liposarcoma</td>
<td>Trabectedine +/-Doxorubicin</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>Uterine leiomyosarcoma</td>
<td>Gemcitabine + Docetaxel</td>
</tr>
<tr>
<td></td>
<td>Doxorubicine + Trabectedine</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>Doxorubicin + Dacarbazine</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin + Trabectedine</td>
</tr>
<tr>
<td>Synovialosarcoma</td>
<td>Ifosfamide</td>
</tr>
<tr>
<td>DFSP</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Giant Cell Tumor</td>
<td>Denosumab</td>
</tr>
</tbody>
</table>

Planned surgery in responders...first step of personalized treatment!
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Questions/Discussions

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