Innovative combination of targeted agents with radiotherapy in soft tissue sarcomas.

ESMO 2014

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Department of Radiotherapy, The Netherlands Cancer Institute Amsterdam
Disclosure

Investigator Initiated Research Grant GSK, but GSK had no part in the design nor the conduct of my studies
Role of RT in STS ??

Role of RT “in general” in STS

Arguments for postoperative RT

Arguments for preoperative RT

What dose ?

When not to irradiate at all

Interaction with targeted therapy
Role of RT “in general” in STS

There are not so many prospective randomized clinical trials performed in the past!
Role of RT “in general” in STS

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Now running: EORTC 62092 / 22092 for RPS
### Role of RT “in general” in STS

<table>
<thead>
<tr>
<th>Ref</th>
<th>LC-RT (5yr)</th>
<th>LC+RT (5yr)</th>
<th>OS (5yr)</th>
<th>comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pisters 1996</td>
<td>All: 69%</td>
<td>All: 82% (p=0.04)</td>
<td>81-84%</td>
<td>Brachytherapy had no impact on local control in patients with low-grade lesions.</td>
</tr>
<tr>
<td>n= 164</td>
<td>High grade: 66%</td>
<td>High grade: 89% (p=0.0025)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yang 1998</td>
<td>High grade: 78%</td>
<td>High grade: 100% (p= 0.003)</td>
<td>75%</td>
<td>High grade patients also received chemotherapy.</td>
</tr>
<tr>
<td>n= 141</td>
<td>Low grade: 6/19 failures</td>
<td>Low grade: 1/22 failures (p= 0.067)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O'Sullivan 2002</td>
<td>Pre-op RT 92%</td>
<td>Post-op RT 93%</td>
<td>68% at 7yrs</td>
<td>Due to wound complications prematurely closed</td>
</tr>
</tbody>
</table>
Arguments for postoperative RT
Arguments for postoperative RT

Many centers apply RT after surgery.

Reasons:
- full pathology report on a heterogeneous sarcoma mass,
- unaffected by prior RT
- less wound complications
Arguments for postoperative RT

Surgery followed by external beam RT.

=> large fields

=> more joints in field.

=> late functional toxicity

Because of the scar
Arguments for preoperative RT

NCIC SR-2 trial: 50Gy preoperative RT versus 66Gy postoperative.

Study prematurely closed due to more postoperative morbidity in the pre-op arm.

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<tr>
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<tr>
<td>med FU</td>
<td>postop</td>
<td>pre-op</td>
</tr>
<tr>
<td>alive</td>
<td>3,3 yr</td>
<td></td>
</tr>
<tr>
<td>local control</td>
<td>94%</td>
<td>96%</td>
</tr>
<tr>
<td>(+) margins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(-) margins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>early tox</td>
<td>17%</td>
<td>p=0.01</td>
</tr>
<tr>
<td>late tox</td>
<td>26%</td>
<td>20%</td>
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(grade III = fibrosis, Graad IV = necrosis)
Arguments for preoperative RT

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Arguments for preoperative RT

NCIC SR-2 trial: 50Gy preoperative RT versus 66Gy postoperative RT.

Conclusion:

at longer FU preoperative RT as “good” as postoperative RT (efficacy)

at longer FU preoperative RT “better” than postop (toxicity)
What dose?

Conventional RT in non-hematological diseases

46-50Gy for microscopic disease

66-70Gy boost for macroscopic disease
What dose?

Conventional RT in non-hematological diseases

46-50Gy for microscopic disease

66-70Gy boost for macroscopic disease
What dose?

Also the Canadian NCIC SR-2 dose levels; 50Gy versus 66Gy
The dose in myxoid liposarcomas (MLS)

4 studies of MLS show volume reduction during preoperative RT
Pitson et al 2004
Engström et al 2007
de Vreeze et al 2008 (NKI-AVL)
Betgen et al 2013 (NKI-AVL)

Vasculature ???
Radiation response in MLS after 25 x 2 Gy
Radiation response in MLS after 25 x 2 Gy

Radiation response in MLS after 18 x 2 Gy
Interaction with targeted therapy

Issues to address:

1. The total dose to deliver
2. The fraction size to deliver the total dose with
3. Interactions with sensitizers
Interaction with targeted therapy (1)

Is 50 Gy total dose the Holy Grail in STS management?
Interaction with targeted therapy (2)

Why 2 Gy per fraction for all STS subtypes without systemic treatment?
Interaction with targeted therapy (2)

Why 2 Gy per fraction for all STS subtypes without systemic treatment?

In “carcinomas”; interaction with conventional chemotherapy smart molecules

=> increased local control
=> sometimes increased OS
=> be it at the cost of increased acute / temporary toxicity
Interaction with targeted therapy (2)

Why 2 Gy per fraction for all STS subtypes without systemic treatment?

In “carcinomas”; interaction with conventional chemotherapy smart molecules

=> increased local control
=> sometimes increased OS
=> be it at the cost of increased acute / temporary toxicity

But what about STS?
Interaction with targeted therapy (3)

PDQ search:

Jean-Yves Blay, Lyon, France    Sunitinib
David Thomas, Australia        Sunitinib
Robert Canter, California, USA Sorafenib
Yen-Lin Chen, Boston, USA      Bevacizumab
Rick Haas, Amsterdam NL        Pazopanib
Sylvie Bonvalot, Paris, France nanoparticles
### Interaction with targeted therapy versus RT alone

#### Necrosis induction by preoperative RT in ESTS

<table>
<thead>
<tr>
<th>Setting</th>
<th>Author</th>
<th>Journal</th>
<th>regimen</th>
<th>n</th>
<th>% necrosis in % of patients</th>
<th>remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT only</td>
<td>Canter</td>
<td>Ann Surg Oncol 2010</td>
<td>RT</td>
<td>25</td>
<td>Median 30% ≥ 95% in 8% ≥ 80% in &lt;20%</td>
<td>In pCR patients DRFS improves (ns)</td>
</tr>
<tr>
<td></td>
<td>Shah</td>
<td>Anticancer Res 2012</td>
<td>RT</td>
<td>30</td>
<td>Median 35% ≥ 95% in 10%</td>
<td></td>
</tr>
<tr>
<td>RT + conventional chemotherapy</td>
<td>Kraybill</td>
<td>JCO 2006</td>
<td>RT interdigitated in MAID</td>
<td>59</td>
<td>≥ 95% in 27%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ryan</td>
<td>Cancer 2008</td>
<td>Al + RT</td>
<td>25</td>
<td>≥ 95% in 40%</td>
<td></td>
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<tr>
<td></td>
<td>MacDermed</td>
<td>Red J 2010</td>
<td>I + RT</td>
<td>34</td>
<td>&gt; 90% in 50% ≥ 95% in 11.8%</td>
<td>In pCR patients DRFS improves (p =0.02)</td>
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<tr>
<td>“Biologicals”</td>
<td>Yoon</td>
<td>Red J 2011</td>
<td>Avastin + RT</td>
<td>20</td>
<td>≥ 80% in 45% &gt; 95% in 20%</td>
<td></td>
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<td>Canter</td>
<td>Ann Surg Oncol 2014</td>
<td>Sorafenib + RT</td>
<td>8</td>
<td>≥ 95% in 38%</td>
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<tr>
<td>PASART-1</td>
<td>Haas</td>
<td>Red J ...</td>
<td>Pazopanib + RT</td>
<td>8</td>
<td>≥ 50% in 87.5% ≥ 95% in 50%</td>
<td></td>
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<tr>
<td>Nanoparticles</td>
<td>Bonvalot</td>
<td>ASCO / CTOS</td>
<td>NP + RT</td>
<td>20</td>
<td>&gt;90% in 18% average pathological response 74%</td>
<td>At 10% injection =&gt; average tumor volume reduction 49%</td>
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## Interaction with targeted therapy versus RT alone

### Necrosis induction by preoperative RT in ESTS; \( \geq 95\% \) necrosis

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Interaction with targeted therapy

A clinical meaningful necrosis induction (pCR; defined as ≥ 90% / ≥ 95% necrosis) may result in an increase in local control and DRFS
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Thanks for the invitation

Aurora Borealis
March 2014, Lapland