“PAZIENTE OLIGOMETASTATICO: OUTCOME A CONFRONTO”

“SUCCESSIVI TRATTAMENTI RADIO-ONCOLOGICI?”

FILIPPO ALONGI

ISTITUTO CLINICO HUMANITAS, ROZZANO-MI

filippo.alongi@humanitas.it

XXII CONGRESSO NAZIONALE AIRO-18nov-ROMA
The term "oligometastases" was first described by Hellman and Weichselbaum in 1995 as "...a less advanced state of metastatic disease amenable to and potentially curable with local therapy".

*Hellman S, Weichselbaum RR: JCO, 1995*

The term "oligometastases" is usually used for five or fewer metastatic lesions.


Often, this clinical situation has a slow rate of progression, justifying focal treatments.
For several anatomical sites, **surgical resection** of metastases prolongs survival in selected patients.

*Rubin P, et al. Semin Radiat Oncol, 2006*

For example, **surgical resection** is the standard choice for patients with oligometastatic lung cancer.

Unfortunately the benefits of resection and appropriate **selection criteria** in patients who develop metastasis are still poorly defined.

• The primary end point of **SBRT** is to achieve local control of targeted tumor deposits with ablation doses.

• In general SBRT for oligometastases should follow the same philosophy relating to indications for surgical metastasectomy.

• As smaller foci of metastases are found, high conformal radiation may well prove *less invasive and more/equal effective* than surgery, decreasing morbidity and delivering ablative treatment more economically on an outpatient basis.

*Alongi F et al. Critical Rev Oncol Hematol, 2012*
• In terms of **Radiobiology, SBRT** may add a novel mechanism of radiation-induced damage.

• At higher doses per fraction (**ablative doses**), emerging data suggest that, in addition to direct cytotoxicity, a different mechanism involving microvascular damage begins to have a substantial effect on the tumor cell kill.


Targeting the tumor vasculature for obliteration with high-dose radiation may be beneficial for tumor control.

*Fuks and Kolesnick, Cancer Cell 2005*
In primary NSCLC, when ablative doses are used, the survival rate for SBRT is potentially comparable to that for surgery.
Lung metastases probably represent the paradigm of the potential benefit achievable by SBRT, which is able to produce high rates of tumor control with very limited toxicity.

For isolated or a few lung metastases the local control probability at 1 year is in the range of 70%–100%.

Ricardi et al, Lung cancer 2011; Okunieff, Acta oncologica 2006

In most series, the prescribed biologically effective doses (BED) are 100 Gy, with several fractionation schedules and different delivery techniques.

Table 1. Outcomes of stereotactic body radiation therapy for lung metastases from selected trials

<table>
<thead>
<tr>
<th>Study</th>
<th>n of patients</th>
<th>Median dose/n of fractions</th>
<th>Median (range) follow-up, mos</th>
<th>Local control rate</th>
<th>Overall survival</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onimaru et al. [5]</td>
<td>45</td>
<td>48 Gy/8; 60 Gy/8</td>
<td>18 (2–44)</td>
<td>3-yr, 69.6% for 48 Gy, 100% for 60 Gy</td>
<td>2-yr, 47.1%</td>
<td>Grade 5, 1 (2.2%)</td>
</tr>
<tr>
<td>Wulf et al. [32]</td>
<td>27</td>
<td>30 Gy/3; 36 Gy/3</td>
<td>13–17</td>
<td>2-yr, 71%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yoon et al. [71]</td>
<td>53</td>
<td>30 Gy/3; 40 Gy/4; 48 Gy/4</td>
<td>14 (4–56)</td>
<td>70% for 30 Gy, 77% for 40 Gy, 100% for 48 Gy</td>
<td>1-yr, 48%; 2-yr, 21%</td>
<td>Grade 3, 1 (3.7%); Grade 5, 1 (3.7%) Grade ≥2, 0%</td>
</tr>
<tr>
<td>Okunieff et al. [18]</td>
<td>50</td>
<td>50 Gy/10; 48 Gy/6; 57 Gy/3</td>
<td>18.7 (3.7–60.9)</td>
<td>3-yr, 91%</td>
<td>2-yr, 50%</td>
<td>Grade 2, 6.1%</td>
</tr>
<tr>
<td>Norihisa et al. [6]</td>
<td>34</td>
<td>48 Gy/4; 60 Gy/5</td>
<td>27 (10–80)</td>
<td>2-yr, 90%</td>
<td>2-yr, 84%</td>
<td>Grade 2, 4 (12%); Grade 3, 2%</td>
</tr>
<tr>
<td>Brown et al. [72]</td>
<td>35</td>
<td>5 Gy/1 to 60 Gy/4</td>
<td>18 (2–41)</td>
<td>Crude, 77%</td>
<td>2-yr, 72.5%</td>
<td>Grade 3–4, 1 (2.8%)</td>
</tr>
<tr>
<td>Rusthoven et al. [14]</td>
<td>38</td>
<td>60 Gy/3</td>
<td>15.4 (6–48)</td>
<td>2-yr, 96%</td>
<td>2-yr, 39%</td>
<td>No grade 4</td>
</tr>
<tr>
<td>Ricardi et al. [17]</td>
<td>61</td>
<td>45 Gy/3; 26 Gy/1</td>
<td>20.4 (3–77)</td>
<td>2-yr, 89%</td>
<td>2-yr, 66.5%</td>
<td>Grade 3, 3 (8%); Grade 3, 1 (1.6%)</td>
</tr>
</tbody>
</table>
• It is difficult to properly evaluate survival estimates using SBRT for lung metastases and compare with metastasectomy historical data because there is:

- an absence of randomized trials and because most of the phase I–II studies included patients with widely variable clinical characteristics.

- a bias in selection: most patients referred for SBRT are judged to be inoperable because of medical comorbidities that are able to significantly affect their OS outcome.


• RFA (radiofrequency ablation) could be a reasonable competitor but data are few and preliminary.
SBRT treatment for rectum bilateral lung metastases: **48 Gy / 4 fract.** (TrueBeam FFF beams)

CR @ PET/TC after 6 months
• The liver is one of the most common sites of metastatic spread from colorectal cancer (CRC).

• Surgical resection of limited liver metastases can result in long-term survival in selected patients.

• Surgery is technically difficult and only 10–20% of metastatic colorectal cancer patients are candidates for surgical resection

*Altendorf-Hofmann et al, Surg Oncol Clin N Am 2003*

---

**What kind of ablative options are available today for the remaining 80-90%?**

• Cryotherapy, laser-induced thermotherapy, and high-intensity focal ultrasounds have some grade of invasiveness and are currently limited to smaller tumors (commonly <3 cm) and far away from critical structures.

*de Meijer et al, Ann surg 2009*
Multi-Institutional Phase I/II Trial of Stereotactic Body Radiation Therapy for Liver Metastases

Kyle E. Rusthoven, Brian D. Kavanagh, Higimia Cardenes, Volker W. Stieber, Stuart H. Burri, Steven J. Feigenberg, Mark A. Chidel, Thomas J. Pugh, Wilbur Franklin, Madeleine Kane, Laurie E. Gaspar, and Tracey E. Schefter
## Table 2. Summary of recent prospective trials with stereotactic body radiation therapy for liver metastases

<table>
<thead>
<tr>
<th>Study</th>
<th>n of patients</th>
<th>Median dose/n of fractions</th>
<th>Median follow-up, mos</th>
<th>Local control rate</th>
<th>Overall survival</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herfarth et al. [37, 38]</td>
<td>33</td>
<td>14–26 Gy/1, prescribed to 80%</td>
<td>18</td>
<td>Crude, 78%; 6-mo, 75%; 12-mo, 71%; 18-mo, 67%</td>
<td>1-yr, 72%</td>
<td>Radiation-induced liver disease: 0%</td>
</tr>
<tr>
<td>Hoyer et al. [39]</td>
<td>44</td>
<td>45 Gy/3, prescribed to 95%</td>
<td>4.3 yrs</td>
<td>86%</td>
<td>24-mo, 38%</td>
<td>--</td>
</tr>
<tr>
<td>Kavanagh et al. [40]</td>
<td>36</td>
<td>60 Gy/3</td>
<td>19</td>
<td>18-mo, 93%</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Lee et al. [42]</td>
<td>70</td>
<td>27.7–60.0 Gy/6, prescribed to isodose line covering PTV (median, 41.4 Gy)</td>
<td>10.8 for 68 assessable patients</td>
<td>1-yr, 71%</td>
<td>18-mo, 47%</td>
<td>Late grade 4 and 5 toxic effects, 2.9% and 1.5%, respectively</td>
</tr>
<tr>
<td>Méndez Romero et al. [43]</td>
<td>14</td>
<td>37.5 Gy/3, prescribed to 65%</td>
<td>12.9</td>
<td>Crude, 94%; 1-yr, 100%; 2-yr, 86%</td>
<td>1-yr, 85%; 2-yr, 62%</td>
<td>Grade ≥4 toxic effects, 0%</td>
</tr>
<tr>
<td>Rusthoven et al. [44]</td>
<td>47</td>
<td>12–20 Gy/3, prescribed to isodose line covering PTV</td>
<td>16</td>
<td>1-yr, 95%; 2-yr, 92%</td>
<td>2-yr, 30%</td>
<td>Grade 4 toxic effects, 0%</td>
</tr>
<tr>
<td>Goodman et al. [45]</td>
<td>26</td>
<td>18–30 Gy/1, prescribed to 80%</td>
<td>17.3</td>
<td>1-yr, 61.8%; 2-yr, 49.4%</td>
<td>1-yr, 61.8%; 2-yr, 49.4%</td>
<td>Late grade 2 gastrointestinal toxic effects, 2 of 26 patients</td>
</tr>
<tr>
<td>Rule et al. [46]</td>
<td>27</td>
<td>30–60 Gy/5</td>
<td>20</td>
<td>2-yr, 56%, 89%, and 100% for the 30-Gy, 50-Gy, and 60-Gy cohorts, respectively</td>
<td>--</td>
<td>Grade ≥3 toxic effects, 0%</td>
</tr>
</tbody>
</table>

Abbreviation: PTV, planning target volume.
**INCLUSION CRITERIA**

- Inoperable or medically unsuitable for resection
- Maximum tumour diameter < 6cm
- \( \leq \) 3 discrete lesions
- Performance status 0-2
- Good compliance to treatment

<table>
<thead>
<tr>
<th>Dose/reduction</th>
<th>Dose/fraction</th>
<th>Number fractions</th>
<th>Median dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard dose</strong></td>
<td>25Gy</td>
<td>3</td>
<td>75 Gy</td>
</tr>
<tr>
<td><strong>Dose reduction 10%</strong></td>
<td>22.5 Gy</td>
<td>3</td>
<td>67.5 Gy</td>
</tr>
<tr>
<td><strong>Dose reduction 20%</strong></td>
<td>20.63 Gy</td>
<td>3</td>
<td>61.89 Gy</td>
</tr>
<tr>
<td><strong>Dose reduction 30%</strong></td>
<td>18.75 Gy</td>
<td>3</td>
<td>56.25 Gy</td>
</tr>
</tbody>
</table>

*Scorsetti et al, ASTRO 2012 Annual meeting, Boston*
Humanitas protocol in LIVER OLIGOMTS

• From February 2010 and September 2011, 61 patients (74 lesions)
• Acute toxicity was limited: 26% G2 transient transaminase elevations definitively returned to baseline.
• No RILD. No major (grade 4 or 5) late toxicity.
• Median FU: 12 months (2-26)
• Actuarial LC at 6, 12 and 22 months were 100%, 94.0% and 90.6%
• Median OS rate was 19 months

<table>
<thead>
<tr>
<th>In field-response</th>
<th>Lesions (N= 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RC</td>
<td>36 (47.4%)</td>
</tr>
<tr>
<td>RP</td>
<td>16 (21.0%)</td>
</tr>
<tr>
<td>SD</td>
<td>20 (26.3%)</td>
</tr>
<tr>
<td>PD</td>
<td>4 (5.3%)</td>
</tr>
</tbody>
</table>

LOCAL CONTROL: 94.7% (72 of 76)

Scorsetti et al, ASTRO 2012 Annual meeting, Boston
SBRT: Dose: 25 Gy x 3; 10FFF; DR 2400.

PET pre

RapidArc
1 isocentre
2 arcs
Jaw tracking

PET after 6 months

MU: 3174 + 3004
BOT: 170s
• Few published data exist on the local control rate using conventional RT in the context of isolated or limited lymph node metastases.

• SBRT does not replace chemotherapy but rather can augment its effects on focal areas of gross disease as well as metastatic lymph nodes.

Choi et al. IJROBP 2009;
Scorsetti et al, Acta Oncol 2011

• Because small volumes are irradiated for metastatic lymph nodes, dose escalation might result in better efficacy without prohibitive toxicity.
The poorer disease-free survival rates observed in several series may be explained by the substantial differences in the patient populations (primary tumor behavior; the burden of microscopic systemic disease outside the irradiated target, etc).

Scorsetti et al, Acta Oncol 2011; Bignardi et al, IJROBP 2011
SBRT: Dose: 7.5 Gy x 6; 10FFF; DR 2400.

Abdominal LN metastases (primary gastric adenocarcinoma)

RC@PET after 60 days
- **Adrenal gland metastases** can occur as a result of various types of extra-adrenal primary cancers, although the most frequent primary tumor is non-small cell lung cancer (NSCLC).

- Longer median survival and OS times have been demonstrated with resection of clinically isolated adrenal metastases.

Several criticisms could arise regarding the lack of clear data on local control and on dose fractionation.

Nevertheless, the good tolerability and the promising clinical results should stimulate the scientific community to further design clinical studies with the aim of optimizing local control and evaluating a potential PFS benefit.

<table>
<thead>
<tr>
<th>Study</th>
<th>n of patients</th>
<th>Median dose/n of fractions</th>
<th>Median (range) follow-up, mos</th>
<th>Local control rate</th>
<th>Overall survival</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casamassima et al. [26]</td>
<td>48</td>
<td>36 Gy/3</td>
<td>16.2 (3–63)</td>
<td>1–2 yrs, 90%</td>
<td>1-yr, 39.7%; 2-yr, 14.5%</td>
<td>1 case of grade II adrenal insufficiency</td>
</tr>
<tr>
<td>Chawla et al. [24]</td>
<td>30</td>
<td>40 Gy/10</td>
<td>9.8 (3.2–28.3)</td>
<td>1-yr, 55%</td>
<td>1-yr, 44%; 2-yr, 25%</td>
<td>Mild grade 1 fatigue and nausea, “common”</td>
</tr>
<tr>
<td>Oshiro et al. [25]</td>
<td>19</td>
<td>45 Gy/10</td>
<td>11.5 (5.4–87.8)</td>
<td>Objective response rate, 68%</td>
<td>1-yr, 56%; 2-yr, 33%; 3-yr, 22%</td>
<td>1 grade 2 duodenal ulcer</td>
</tr>
<tr>
<td>Holy et al. [54]</td>
<td>18</td>
<td>20 Gy/5 or 40 Gy/8</td>
<td>21</td>
<td>Objective response rate, 77%</td>
<td>Median, 23 mos</td>
<td>–</td>
</tr>
<tr>
<td>Torok et al. [55]</td>
<td>7</td>
<td>16 Gy/1 or 27/3</td>
<td>14 (1–60)</td>
<td>1-yr, 63%</td>
<td>Median, 8 mos</td>
<td>–</td>
</tr>
</tbody>
</table>
• *Spinal radiosurgery* has been proven to be an option in the treatment of spinal metastases in properly selected patients, even though only retrospective and phase I–II studies are available.

• Local control based on imaging and/or pain control is achieved in 80% of presentations.

• SBRT can also be safely applied in the postoperative setting, with the intent of reducing the extent of surgery (which can be limited to epidural decompression and fixation).

• There are several dose prescription schedules and total doses or doses per fraction, making direct comparison difficult, with a follow-up time globally of a few months.

• The predominant pattern of failure after SBRT for spinal metastases is characteristic of the procedure because the principle of SBRT is to treat only the target region, and areas close to the spinal cord are frequently underdosed.

Table 5. Summary of published trials of stereotactic body radiation therapy for spinal metastases

<table>
<thead>
<tr>
<th>Study</th>
<th>n of patients</th>
<th>Median dose/ n of fractions</th>
<th>Median follow-up, mos</th>
<th>Local control rate</th>
<th>Pain response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yamada et al. [73]</td>
<td>93</td>
<td>24 Gy/1</td>
<td>15</td>
<td>15-mo, 90% (imaging)</td>
<td>NS</td>
</tr>
<tr>
<td>Ryu et al. [74]</td>
<td>49</td>
<td>10–16 Gy/1</td>
<td>6.4</td>
<td>93% (imaging and pain)</td>
<td>85%</td>
</tr>
<tr>
<td>Sahgal et al. [56]</td>
<td>14</td>
<td>24 Gy/3</td>
<td>9</td>
<td>78% (imaging and/or pain)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>24 Gy/3</td>
<td>7</td>
<td>92% (imaging and/or pain)</td>
<td>NS</td>
</tr>
<tr>
<td>Nguyen et al. [75]</td>
<td>48</td>
<td>30 Gy/5</td>
<td>13.1</td>
<td>78% (imaging)</td>
<td>52%</td>
</tr>
<tr>
<td>Tsai et al. [76]</td>
<td>69</td>
<td>15.5 Gy/2</td>
<td>10</td>
<td>10-mo, 96.8% (imaging)</td>
<td>Improved pain control, 88%</td>
</tr>
<tr>
<td>Chang et al. [58]</td>
<td>63</td>
<td>30 Gy/5</td>
<td>21.3</td>
<td>77% (imaging)</td>
<td>Narcotic use declined 60% to 36%</td>
</tr>
<tr>
<td>Gibbs et al. [77]</td>
<td>74</td>
<td>14–25 Gy/1–5</td>
<td>9</td>
<td>NS</td>
<td>Clinical benefit, 84%</td>
</tr>
<tr>
<td>Gerstzen et al. [78]</td>
<td>393</td>
<td>20 Gy/1</td>
<td>21</td>
<td>88% (imaging)</td>
<td>Clinical benefit, 86%</td>
</tr>
</tbody>
</table>

Abbreviation: NS, not significant.
SBRT and Systemic Therapy: TIMING?

A single-institution study of stereotactic body radiotherapy for patients with unresectable visceral pulmonary or hepatic oligometastases


- The number of previous chemotherapy regimens administered or progression while receiving chemotherapy significantly correlates with a higher risk of failure after SBRT in 90 patients treated for oligometastases in Lung and Liver.

- One hypothesis that could explain this finding could be that the previous chemotherapy regimens, received by the patients, selected tumoral clones with a lower sensitivity to radiation, even if no study has been published to prove it.

- This suggests that SBRT should perhaps be used as a local treatment for metastases *before* the administration of several systemic therapies.

*Lartigau et al, Radiation Oncology 2012.*
CONCLUSIONS

• From preliminary published results, thanks to the more extensive prescription of SBRT and SABR, the role of radiation therapy for metastatic disease has evolved from palliating symptoms to a potentially curative purpose, as shown in specific patient settings, including promising data from oligometastases.

  Thariat et al. Bull Cancer, 2010
  Timmerman et al JCO, 2007
  Lartigau Et al, Radiat oncol 2012

• In the subgroup of patients with a solitary metastasis, investigating SBRT dose escalation in order to optimize local control may be worthwhile.

• For cases with more than one metastasis, especially if more than one organ is involved, the selection criteria for SBRT should be evaluated with extreme attention to life expectancy and toxicity.
OPEN ISSUES

• what is the real cutoff between pure palliative and hypothetical curative intent therapy in oligometastatic patients,

• (b) what is the correct timing with chemotherapy,

• (c) what is the optimal target and how can the radiation oncologist define it as best as possible considering the risk for other potential microscopic foci of disease?

• Considering the high propensity for distant progression in these patients, the combination of novel drugs and SBRT needs to be deeply explored.

• With this background and rationale, prospective trials of high-dose SBRT should be proposed to definitively assess its role in selected oligometastatic cancer patients.

An international randomized phase II controlled trial called Comprehensive Treatment of Oligometastatic Tumors is currently accruing patients...
THANK YOU