Radioterapia nella malattia metastatica: indicazioni nel 2018?

Filippo Alongi, MD
Associate Professor of Radiation Oncology
Chair of Radiation Oncology Department
Sacro Cuore Don Calabria Cancer Care Center,
Negrar-Verona, Italy
A CONTINUOUS CHANGING:

FROM 2D... TO 5 D?

PRECISION DEVICES TO DELIVERY SBRT/SRS

• 3D/4D target definition on CT slices
• 3D/4D dose ULTRA-conformation
• Possibility to significantly > doses/<fractions and >LC (SBRT/SABR).
• Better set-up checking (CBCT/EXAC TRAC)
• <toxicity (fit to target conformation by mMLC and rapid gradient by VMAT/IMRT/robotic approach)
LUNG SBRT:
EXPERIENCE WITH FFF BEAM ON TRUEBEAM

Planning CT  Dose distribution  Restaging CT after 3 months

50 Gy in 4 fractions with FFF
The difference in **OS** between the two groups was statistically significant in favour of **SABR**.
No significant differences in of local, regional, or distant metastasis or in **RFS** between the treatment groups.
AGENDA

• Early stage NSCLC

• Oligometastases and oligorecurrent patients
Is the same the effectiveness of SBRT for the oligometastases?
Oligometastases: the new paradigm and options for radiotherapy

A critical review

Extracranial Oligometastases: A Subset of Metastases Curable With Stereotactic Radiotherapy

Kimberly S. Corbin, Samuel Hellman, and Ralph R. Weichselbaum, University of Chicago Medical Center, Chicago, IL
**OLIGOMETASTASES:**
WHAT DEFINITION?

<table>
<thead>
<tr>
<th>Synchronous oligometastasis</th>
<th>Metachronous oligometastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>uncontrolled primary T</td>
<td>uncontrolled primary T</td>
</tr>
<tr>
<td>&lt; 2 months from cancer</td>
<td>&gt; 2 months from cancer</td>
</tr>
<tr>
<td>diagnosis</td>
<td>diagnosis</td>
</tr>
</tbody>
</table>

- **Oligorecurrence**
  - controlled primary T
  - No systemic therapy ongoing

- **Oligoprogession**
  - controlled primary T
  - Few mts in progression during systemic therapy

*Not exhaustive terminology in 2018*
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 concept of Oligometastatic disease was proposed nearly 20 years ago.

SABR is quite effective than surgery for controlling pulmunary metastases.
In the absence of randomized studies, it is necessary to compare retrospectives.
Conclusion: With limitations consisting in the retrospective observational design and different sample sizes, the results of this explorative analysis indicate that overall survival probability after SBRT is similar to surgery for the first 2 years from treatment. This finding supports the need for high-quality trials comparing different treatment modalities for lung oligometastases from CRC.
LUNG OLIGOMETASTASES: THE ROLE OF SABR

Stereotactic Ablative Radiotherapy for Pulmonary Oligometastases and Oligometastatic Lung Cancer

David Benjamin Shultz, MD, PhD,* Andrea Riccardo Filippi, MD,† Juliette Thariat, MD,‡ Francoise Mornex, MD, PhD,‡ Billy W. Loo Jr, MD, PhD,* and Umberto Ricardi, MD†

TABLE 1. Clinical Trials of Stereotactic Ablative Radiotherapy for Pulmonary Oligometastatic Disease

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Patients</th>
<th>No. of Targets</th>
<th>Radiation Dose</th>
<th>Median Follow-Up (Months)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onimaru et al.²⁷</td>
<td>20</td>
<td>32</td>
<td>48 Gy/8 fx, 60 Gy/8 fx</td>
<td>18</td>
<td>48% 2-yr OS, 69.6% 3-yr LC for 48 Gy, 100% 3-yr LC for 60 Gy</td>
</tr>
<tr>
<td>Yoon et al.²⁶</td>
<td>53</td>
<td>80</td>
<td>30 Gy/3 fx, 40 Gy/4 fx, 48 Gy/4 fx</td>
<td>14</td>
<td>70% LC for 30 Gy, 77% for 40 Gy, 90% LC for 48 Gy, 51% all 2-yr OS</td>
</tr>
<tr>
<td>Okmioff et al.²⁸</td>
<td>50</td>
<td>125</td>
<td>50 Gy/10 fx, 48 Gy/6 fx, 57 Gy/3 fx</td>
<td>18.7</td>
<td>91% 3-yr LC, 50% 2-yr OS</td>
</tr>
<tr>
<td>Norihisa et al.²⁹</td>
<td>34</td>
<td>43</td>
<td>48 Gy/4 fx</td>
<td>14</td>
<td>90% 2-yr LC, 84% 2-yr OS</td>
</tr>
<tr>
<td>Brown et al.³⁰</td>
<td>35</td>
<td>69</td>
<td>5 Gy/1 fx</td>
<td>14</td>
<td>77% crude LC, 72.5% 2-yr OS</td>
</tr>
<tr>
<td>Rusthoven et al.³¹</td>
<td>38</td>
<td>63</td>
<td>60 Gy/3 fx</td>
<td>14</td>
<td>90% 2-yr LC, 72.5% 2-yr OS</td>
</tr>
<tr>
<td>Wulf et al.³²</td>
<td>41</td>
<td>51</td>
<td>30 Gy/3 fx</td>
<td>14</td>
<td>80% 1-yr LC, 33% 2-yr OS</td>
</tr>
<tr>
<td>Ricardi et al.³³</td>
<td>61</td>
<td>77</td>
<td>45 Gy/3 fx, 26 Gy/1 fx at 80%</td>
<td>20.4</td>
<td>89% 2-yr LC, 66.5% 2-yr OS</td>
</tr>
<tr>
<td>Single Fraction SABR Only</td>
<td>30</td>
<td>71</td>
<td>12 to 30 Gy at isocenter</td>
<td>14</td>
<td>65.1% 2-yr OS</td>
</tr>
<tr>
<td>Filippi et al.³⁴</td>
<td>67</td>
<td>90</td>
<td>26 Gy at 80%</td>
<td>24</td>
<td>88.1% 2-yr LC, 70.5% 2-yr OS</td>
</tr>
</tbody>
</table>

Total doses: 24–60 Gy in 1 or 4 fr, 1–3 years LC: 70%–100%, 1–2 years OS 48%–84%
Stereotactic Ablative Radiotherapy for Pulmonary Oligometastases and Oligometastatic Lung Cancer

David Benjamin Shultz, MD, PhD,* Andrea Riccardo Filippi, MD, † Juliette Thariat, MD, ‡ Francoise Mornex, MD, PhD, ‡ Billy W. Loo Jr, MD, PhD,* and Umberto Ricardi, MD †

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Eligibility</th>
<th>Intervention</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>PulMICC38</td>
<td>Randomized phase II</td>
<td>Pulmonary metastases from colorectal cancer</td>
<td>Active monitoring vs. pulmonary metastasectomy</td>
<td>Feasibility/survival</td>
</tr>
<tr>
<td>SABR-COMET19</td>
<td>Randomized phase II</td>
<td>All treatable metastatic sites; maximum of three tumors to any single organ system; controlled primary tumor</td>
<td>Palliative-scheme radiation as clinically indicated vs. stereotactic ablative radiation to multiple sites</td>
<td>Overall survival</td>
</tr>
<tr>
<td>SAFRON II40</td>
<td>Randomized phase II</td>
<td>A maximum of three metastases to the lung from any nonhematological malignancy</td>
<td>Stereotactic multifraction SABR vs. radiosurgery</td>
<td>Toxicity</td>
</tr>
<tr>
<td>NCT01185639</td>
<td>Phase II</td>
<td>NSCLC with ≤5 metastatic sites, involving lung, liver, adrenal, or spinal lesions; if primary untreated, must have three mets</td>
<td>SBRT to affected sites, delivered in three or five fractions</td>
<td>Progression-free survival</td>
</tr>
<tr>
<td>NCT01721652</td>
<td>Randomized phase II</td>
<td>Three or less metastases from NSCLC</td>
<td>Consolidative radiotherapy and/or surgery vs. systemic therapy or observation</td>
<td>Progression-free survival</td>
</tr>
</tbody>
</table>
Based on published studies, the **patient who could benefit** most from SBRT is the patient with:

- Disease free interval $\geq 12$ months,
- Control of primary tumor,
- Small lesions,
- Limited number of lesions (up to three)
- High dose of radiation delivered (BED $> 100$ Gy).

**Salama, et al Cancer 2011**
**Wersall, et al Radiother Oncol 2005**
**Ricardi, et al Lung Cancer 2012**
Stereotactic body radiotherapy for lung oligometastases: Literature review according to PICO criteria

Filippo Alongi¹,², Rosario Mazzola¹, Vanessa Figlia¹ and Matthias Guckenberger³

In summary, SBRT allows a major benefit for lung oligometastatic patients with noncolorectal histology, DFI >24 months, when controlling the primary tumor site, small lesions, and limited number of lesions.
STEREOTACTIC BODY RT (SBRT): LUNG OLIGOMETASTASIS & PET AS PREDICTIVE

**ORIGINAL ARTICLE**

Stereotactic Ablative Radiation Therapy for Lung Oligometastases: Predictive Parameters of Early Response by $^{18}$FDG-PET/CT

Rosario Mazzola, MD, $^{a,b}$ Alba Fiorentino, MD, $^{a}$ Giaocchino Di Paola, MSc, $^{b}$ Niccolò Giai Levra, MD, $^{a}$ Francesco Ricchetti, MD, $^{a}$ Sergio Fersino, MD, $^{a}$ Umberto Tebano, MD, $^{a}$ Stefano Pasetto, MS, $^{a}$ Ruggero Ruggieri, MS, $^{a}$ Matteo Salgarello, MD, $^{a}$ Filippo Alonzi, MD $^{a}$

$^{a}$Radiation Oncology, Sacro Cuore Don Calabria Cancer Care Center, Negrar-Verona, Italy
$^{b}$Statistic Sciences Faculty, University of Palermo, Palermo, Italy
$^{c}$Radiation Oncology School, University of Padua, Padua, Italy
$^{d}$Nuclear Medicine, Sacro Cuore Don Calabria Cancer Care Center, Negrar-Verona, Italy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Local Failure (In-Field)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Distant Metastatic Progression</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Lung Metastasis Complete Response (6 mo after SABR)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>p Value</td>
<td>OR</td>
<td>95% CI</td>
<td>p Value</td>
<td>OR</td>
<td>95% CI</td>
<td>p Value</td>
<td>OR</td>
<td>95% CI</td>
<td>p Value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$SUV_{max}$ (for values $\geq 5$)</td>
<td>2.93</td>
<td>0.52-5.11</td>
<td>0.219</td>
<td>1.98</td>
<td>0.66-5.91</td>
<td>0.221</td>
<td>0.313</td>
<td>0.09-0.99</td>
<td>0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$SUV_{mean}$ (for values $\geq 5$)</td>
<td>1.06</td>
<td>0.22-5.16</td>
<td>0.936</td>
<td>1.85</td>
<td>0.61-5.68</td>
<td>0.281</td>
<td>0.237</td>
<td>0.06-0.84</td>
<td>0.026</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MTV</td>
<td>1.01</td>
<td>0.89-1.14</td>
<td>0.855</td>
<td>1.04</td>
<td>0.96-1.14</td>
<td>0.281</td>
<td>1.01</td>
<td>0.91-1.11</td>
<td>0.946</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLG</td>
<td>1.01</td>
<td>0.97-1.02</td>
<td>0.897</td>
<td>1.01</td>
<td>0.99-1.02</td>
<td>0.794</td>
<td>0.99</td>
<td>0.97-1.02</td>
<td>0.791</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Boldface indicates statistically significant p values.

SABR, stereotactic ablative radiotherapy; CI, confidence interval; $SUV_{max}$, maximum standardized fludeoxyglucose F 18 uptake value; $SUV_{mean}$, mean standardized fludeoxyglucose F 18 uptake value; MTV, metabolic tumor volume, defined as total volume with a standardized uptake value of 2.5 or greater; TLG, total lesion glycolysis.

Conclusions: In the current analysis, complete response from lung metastasis at 6 months after stereotactic body radiation therapy was significantly associated with both the maximum and mean values of pre-SABR $^{18}$FDG-PET/CT SUV. Longer-term trials are strongly advocated to improve the personalization of the monitoring of tumor response in patients with lung oligometastases and, consequently, monitoring of the cost-effectiveness of the health care.
STEREOTACTIC BODY RT (SBRT): LUNG OLIGOMETS

TRUEBEAM treatment for rectum lung central metastases

PET/CT before SBRT  60 Gy/8 fr. with FFF beams  CR @ 60 days
LUNG OLIGOPROGRESSIVE LESIONS:.. A NEW INDICATION FOR SABR???
NEW INDICATIONS:
SABR AS LOCAL CONSOLIDATIVE THERAPY?

Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study

Daniel R Gomez, George Blumenschein Jr, Jack Lee, Mike Hernandez, Rong Ye, D Ross Camidge, Robert C Doebele, Ferdinandeas Skoulidis, Laurie E Gaspar, Don L Gibbons, Jose A Karam, Brian D Kavanagh, Chad Tang, Ritsuko Komaki, Alexander V Louie, David A Palma, Anne S Tsao, Boris Sepesi, William N Williams, Jianjun Zhang, Qiuling Shi, Xin Shelley Wong, Stephen G Swisher*, John V Heymach*

* Correspondence: stephen.g.swisher@mdanderson.org (S.G. Swisher).
SABR AS LOCAL CONSOLIDATIVE THERAPY: WHICH BED?

Consolidative local therapy in oligometastatic patients

question arises: which biologically effective dose would the investigators recommend to reproduce similar findings in actual practice? In the local consolidative therapy group, patients were treated with hypofractionated regimens, as well as stereotactic body radiotherapy, without any specific details in terms of biologically effective dose or schedules of total dose or dose per fraction. Could clinicians assume that a regimen of 30 Gy in ten fractions, as often used for palliation, is as effective as ablative radiotherapy doses? If so, the real impact of the biologically effective dose and dose-effectiveness relationships should be totally revised with readers taking a more sceptical view. In the

Filippo Alonzi, Rosario Mazzola, Francesco Ricchetti
rosariomazzola@hotmail.it
Radiation Oncology, Sacro Cuore Don Calabria Cancer Care Center, Negra, Italy

Lancet Oncol 2016; 17: 1672-82
SABR AS LOCAL CONSOLIDATIVE THERAPY:
UPDATE FROM ASTRO

Consolidative local therapy in oligometastatic patients

Aggressive treatment for some stage IV lung cancer patients can dramatically improve overall survival
Adding radiation therapy or surgery to systemic therapy for stage IV lung cancer patients whose cancer has spread to a limited number of sites can extend overall survival time significantly, according to new results from a multicenter, randomized, controlled phase II study. Researchers previously reported encouraging results for progression-free survival (PFS), which were published in *Lancet Oncology* in 2016. These new results were presented as the abstract, *Local consolidative therapy (LCT) improves overall survival (OS) compared to maintenance therapy/observation in oligometastatic non-small cell lung cancer (NSCLC): Final results of a multicenter, randomized, controlled phase 2 trial* by Daniel Gomez, MD, Associate Medical Director of radiation oncology at the University of Texas MD Anderson Cancer Center in Houston.
Consolidative SABR prior to maintenance chemotherapy appeared beneficial, nearly tripling PFS in patients with limited metastatic NSCLC compared with maintenance chemotherapy alone, with no difference in toxic effects.
• Seventy-eight patients and 114 lung metastases were analyzed (oligorecurrence, oligoprogressive disease, oligopersistent disease).

• In the present experience, SBRT allowed to delay the administration of systemic treatments in several settings of lung oligometastasis.
SBRT LUNG OLIGOMETASES/OLIGOPROGRESSIVE: CONCLUSIONS

| •The perfect candidate to Local treatment in case of oligometasases is to establish |
| •Results suggest that SABR for LUNG metastases may provide durable in-field control. |
| •These outcome results appear equivalent to those achievable with surgery. |
| •In Selected oligoprogressive setting, local therapy, including SBRT could add impact on outcome compared to drug maintainence alone. |
Given systemic therapy advancements, patients live longer and approximately **20-40% of new cancer patients will develop brain metastases**.

In brain solitary metastasis, or oligometastatic setting, **SRS has been considered a primary option** as well as surgery.

For multiple metastases (>3-4), **WBRT has been considered the standard of care** and it can only increase survival between 3 and 6 months.

*Kirkpatrick et al, Neuro-oncology 2017*
NEW «CLINICAL» OPTIONS FOR INTRACRANIAL RADIOSURGERY?

WBRT is really the optimal choice for >3-4 mts??

Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study

Lancet Oncol 2014; 15: 387-95

• **M&M:** 1194 pts treated with SRS (1→10 brain mets)

• **RESULTS:** Overall survival → 2-4 BM= 5-10 BM

Interpretation: Our results suggest that stereotactic radiosurgery without WBRT in patients with five to ten brain metastases is non-inferior to that in patients with two to four brain metastases. Considering the minimal invasiveness of stereotactic radiosurgery and the fewer side-effects than with WBRT, stereotactic radiosurgery might be a suitable alternative for patients with up to ten brain metastases.

Yamamoto et al. Lancet 2014
NEW «CLINICAL» OPTIONS FOR INTRACRANIAL RADIOSURGERY

NCCN Guidelines Version 1.2018
Extensive Brain Metastases

CLINICAL PRESENTATION

- No other readily accessible tumor for biopsy
- Surgery to confirm diagnosis of CNS metastases:
  - Resection for management of mass effect or symptoms
  - Biopsy if resection not planned

WORKUP

- No other readily accessible tumor for biopsy
- Surgery to confirm diagnosis of CNS metastases:
  - Resection for management of mass effect or symptoms
  - Biopsy if resection not planned

PRIMARY TREATMENT

- See Follow-up (MU-2)

Extensive brain metastases on CT or MRI

Known history of cancer

Known history of cancer

NCCN Guidelines Index
Table of Contents
Discussion

NCCN Guidelines for Cancer Care

See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).
SRS can be considered for patients with good performance and low overall tumor volume and/or radiosensitive tumors such as melanoma. (Yamamoto M, Sznider L, et al. Stereotactic radiosurgery for patients with multiple brain metastases: A multi-institutional prospective observational study. Lancet Oncol 2014;15:387-395.)
Due to the recent LINAC technologic advancement, the choice of SRS dedicated unit is not necessarily so exclusive. Moreover LINAC offers shorter time frame for SRS (FFF, etc).

### Table 1. Difference from GK and Linac.

<table>
<thead>
<tr>
<th>Sites treated</th>
<th>GK</th>
<th>Linac</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intracranial only</td>
<td>Intracranial and extracranial</td>
</tr>
<tr>
<td>On-board image</td>
<td>No: for A, B, C, PFX models</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Yes: for Icon model</td>
<td>Frame and frameless</td>
</tr>
<tr>
<td>Immobilization</td>
<td>Frame: for A, B, C, PFX models</td>
<td>20–30 min for conical collimator</td>
</tr>
<tr>
<td></td>
<td>Frameless: for Icon model</td>
<td>10–15 min for flattening filter delivered</td>
</tr>
<tr>
<td>SRS time</td>
<td>30–60 min</td>
<td>&lt;2 min for flattening filter Free delivered</td>
</tr>
<tr>
<td>Fractionated therapy</td>
<td>Available only with GK Icon models</td>
<td>Yes</td>
</tr>
<tr>
<td>Field shaping</td>
<td>Conical collimators</td>
<td>Conical collimators and MLC</td>
</tr>
<tr>
<td>Multipurpose machine</td>
<td>Intracranial SRS only</td>
<td>SRS, SRT, 3D RT, IMRT, IGRT, electron RT, gated RT, conformal arc therapy</td>
</tr>
</tbody>
</table>

MLC: Multi-leaf collimator; GK: Gamma Knife; SRS: stereotactic radiosurgery; SRT: stereotactic radiotherapy; Linac: linear accelerator.
SRS/SFRT for multiple brain metastases: First worldwide experience and clinical results using HyperArc: EVALUATION@ 6 Months OF THE FIRST 43 PTS (246 LESIONS)

Results

PREDICTOR FACTOR for Local Control

Analysis of predictor factors for LC by histology

<table>
<thead>
<tr>
<th>Histology</th>
<th>CR</th>
<th>PR</th>
<th>SD+PD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer</td>
<td>16%</td>
<td>49%</td>
<td>35%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>30%</td>
<td>43%</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>0%</td>
<td>32%</td>
<td>68%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>18%</td>
<td>30%</td>
<td>52%</td>
<td></td>
</tr>
</tbody>
</table>
From chemotherapy to target therapies associated with radiation in the treatment of NSCLC: a durable marriage?

Filippo Alongi, Stefano Arcangeli, Sara Ramella, Niccolò Giaj-Levra, Paolo Borghetti, Rolando D’Angelillo, Francesco Ricchetti, Marta Maddalo, Rosario Mazzola, Marco Trovò, Elvio Russi & Stefano Maria Magrinion the behalf of Associazione Italiana Radioterapia Oncologica (AIRO)

In the setting of oligometastatic and oligoprogressive disease, new molecules demonstrated to be safe and effective, opening to a promising and emerging application of the best interaction between new drugs and new modalities of radiotherapy with the goal to postpone an alternative chemotherapy line, but clinical trials are necessary.
FUTURE OR....COMING SOON IN PRACTICE:

PROTON THERAPY?HEAVY IONS?

BIOLOGICAL PROFILING BEFORE RT?

WHICH INTERACTIONS WITH NEW DRUGS??