SBRT in Oligometastasis Lung / Liver: Available Evidences
Flow of Presentation:

- Definition
- Biology of oligometastatic disease
- Best available evidence
- Role of stereotactic ablative radiotherapy (SABR)
- Future directions
- Take-home messages
Definition:

• No consensus.

• 1995 - Hellman & Weichselbaum (JCO)

• Patients with a limited number of clinically detectable metastatic disease.

• Hypothetic transitional state between localised and widespread disease

Oligometastasis

• Metastatic state with limited burden

• 1 to 5 metastasis
Oligometastases is the state in which the patient shows distant relapse in only a limited number of regions.
Oligo-recurrence has a primary site of the cancer controlled, meaning that all gross recurrent or metastatic sites could be treated using local therapy.
SAME ORGAN VS DISTANT ORGAN

Lung cancer oligometastatic to other organs vs. Oligometastasis to lung
Synchronous oligometastasis

≤5 metastatic or recurrent lesions in the presence of active primary lesions

Oligometastatic disease is detected at the time of diagnosis of the primary tumor, therefore there is an active primary tumor
Metachronous oligometastatic disease

Definition:
After period initial disease-free interval, new presentation of oligo-metastases
BIOLOGY OF OLIGOMETASTASIS

Oligometastatic *Versus* Systemic disease: Key-factors

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<thead>
<tr>
<th></th>
<th>Oligometastatic disease</th>
<th>Systemic disease</th>
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<tbody>
<tr>
<td><strong>Primary tumour</strong></td>
<td>Favourable microenvironment</td>
<td>Poor conditions creating undifferentiated aggressive clones</td>
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<tr>
<td><strong>Seed (migrating cells)</strong></td>
<td>Sloughed cancer cells</td>
<td>Actively migrating cells</td>
</tr>
<tr>
<td><strong>Soils (target organs)</strong></td>
<td>In hospitable target organs (trap)</td>
<td>Hospitable target organs</td>
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Conclusion:

- OMD can be defined as 1–5 metastatic lesions.
- Controlled primary tumor is optional.
- All metastatic sites must be safely treatable.
- Patient selection for SBRT/curative intent MDRT holds the key.
A systematic literature review focused on curative intent MDRT
Common endpoints: PFS, OS, LC, QOL & Toxicity reported
Uncommon endpoints as deferral of systemic therapy and cost were endorsed
High-resolution imaging to assess and confirm OMD is crucial, including brain imaging when indicated

Conclusion:
Based on available data, OMD can be defined as 1–5 metastatic lesions, a controlled primary tumor being optional, but where all metastatic sites must be safely treatable
More data are needed to define the optimal patient selection for SBRT/ curative intent MDRT for OMD
Treatment for Oligometastatic disease:

- Chemotherapy
- Targeted therapy
- Immunotherapy
- Radiotherapy
- Surgery
SABR is commonly used in:

- Lung
- Liver
- Spine
- Prostate
LUNG

Prevalence of OMD in stage IV NSCLC has been estimated to range between 25% and 50%.
Lung metastasis is most common in OMD

In OMD small number of metastatic lesions limited to an organ

Considered for curative treatment because long term survival can be expected

Aggressive local t/t to metastases in OMD increases the patients disease-free interval

In previous previous years for lung metastasis surgery is the primary of choice (Metastatectomy)

Surgery requires:
- Good PS
- Good CVS function
- Good Respiratory functions
Local Ablative Therapy in Oligometastatic NSCLC

Questions to be addressed before applying LAT?

Q-1: What defines OMD in NSCLC?

- OMD is defined by the presence of limited number of metastases (between 1 and 5) on appropriate imaging studies.
- As per, ESTRO-ASTRO consensus document proposed a definition of 1-5 metastases) with the primary tumor controlled and all metastatic sites amenable to safe t/t.

Q-2: Who is the appropriate patient for LAT?

- No biomarker to define OMD and to select appropriate NSCLC patients for LAT. (Nomograms and other predictive models have been proposed)
Local Ablative Therapy in Oligometastatic NSCLC

Q-3: Which is the most appropriate technique of Radiation therapy?

• Most evidence supports an SABR.
• Other approaches:
  • Conventionally fractionated RT
  • Moderately hypofractionation
  • Lower dose regimens that may stimulate the immune system.
  • Most studies pre-immunotherapy, high-level evidence remains unavailable.
• Patients with targetable mutations or in patients undergoing t/t with immune checkpoint inhibitors (ICIs). (When to give TAT?)

Q-4: What is the appropriate time to treat OMD by LAT?

• We don”t know the optimal timing of delivering LAT in relationship to systemic therapy.
How to treat OMD?

What to treat in OMD?

- TREAT PRIMARY
- TREAT MET SITES
- TREAT BOTH

SBRT

RFA

SURGERY

BRACHYTHERAPY

INTRA ARTERIAL EMBOLIZATION

COMBINING WITH IMMUNOTHERAPY
Role of SABR in Oligometastatic NSCLC

Medical comorbidities & anatomical location decides the role of Surgery.

Local therapies like RT (SABR) evolved as a treatment for lung mets.

SBRT to be integrated in OMD when surgery not feasible

SBRT can offer curative treatment of OMD in Lungs

SBRT is non invasive.
Why SBRT:

- Non-invasive
- Precise
- Rapid dose fall off
- Maximum normal tissue sparing
- Potential reduction of the deleterious effect of tumor proliferation
- More lethal damage to DNA and less sublethal damage
- Ablative radiotherapy doses (i.e., those that destroy all living tissue in an area) need to have a higher biologically effective dose (BED)
Radiobiological advantages of SBRT

• Greater potential cell kill

• Engaging of sphingomyelin based endothelial mechanism of tumor control related to the high dose per fraction.

• Higher radiation doses overcomes hypoxic microenvironments found in metastases
Role of Sphingolipids:

- Structural molecules of cell membrane
- Maintains barrier function & fluidity
- Also regulates biological processes
  - Growth
  - Proliferation
  - Migration
  - Invasion or metastases by controlling signaling functions in cancer cell signal transduction network
Sphingolipids are responsible for tumor proliferation, progression, and metastasis.

SBRT action on Sphingolipids:
- High-dose per fraction radiotherapy
- Endothelial membrane alterations
- Inducing sphingomyelin mediated endothelial apoptosis
- Microvasculature dysfunction
- Tumor cell death
Other actions:
1) Ionizing radiation induces ceramide induced cytochrome C release into tumor cytoplasm
   → Apoptosis
2) High-dose per fraction radiotherapy
   → Induces antigen presentation within the tumor stroma
      → Facilitate cytotoxic T-cell therapy
      → Stromal targeting
Patient selection for SABR to Lung in OMD:

- Primary Tumor Histology
- Node negative
- Female
- KPS
- Control of primary tumor
- Size of largest metastasis
- Number of metastasis

Prognostic factors:
- Number of metastases
- Response to first-line systemic therapy
- CNS mets
- Intrathoracic nodal status
- EGFR/ALK mutation status.
Let's see the Evidence
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


- Phase II & Randomized study
- ≤3 metastases who did not progress on standard frontline systemic therapy with maintenance therapy/observation
- 49 Patients
- OS & PFS evaluated
- 2 arms

Conclusion:
In patients with oligometastatic NSCLC that did not progress after front-line systemic therapy, LCT prolonged PFS and OS relative to MT/O.
Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non-Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study

**Conclusion:**

In patients with oligometastatic NSCLC that did not progress after front-line systemic therapy, LCT prolonged PFS and OS relative to MT/O.
Meta analysis
• 757 Patients
• 1 to 5 synchronous or metachronous metastases treated with surgical metastectomy, SRS/EBRT
• OS & PFS evaluated
• 38% of patients received RT

Conclusion:
• Significant OS / PFS benefits were observed in metastasis directed local therapy in NSCLC patients with OMD.
34 patients with 43 oligometastatic lung tumors
• Lung - 15, colorectum - 9, H & N - 5, Kidney - 3, Breast – 1 & Bone - 1
• Tumor diameter < 3 cm (91%), max – 4cm
• At 2 years:
  • OS – 84.3
  • Local Relapse free rate – 90%
  • PFS - 34.8%
• No local progression was observed in tumors irradiated with 60 Gy

Conclusion:
• SBRT for oligometastatic lung tumors was comparable to Surgical metastasectomy
• SBRT could be an effective treatment of pulmonary oligometastases.
29 patients
EGFR & ALK negative patients
1-5 synchronous oligometastasis
Induction therapy given to all patients
2 arms: Control arm & SABR arm
PFS: 9.7 vs 3.7 months

Doses:
- 21 - 27 Gy in single fraction
- 26.5 – 33 Gy in 3 fraction schedule
- 30 – 37.5 Gy in 5 fraction schedule

Conclusion:
Consolidative SABR prior to maintenance chemotherapy appeared beneficial, nearly tripling PFS in patients with limited metastatic NSCLC compared with maintenance chemotherapy alone
No difference in toxicity.
Stereotactic body radiotherapy (SBRT) in lung oligometastatic patients: role of local treatments

Pierina Navarria, Anna Maria Ascolese, Stefano Tomatis, Luca Cozzi, Fiorenza De Rose, Pietro Mancosu, Filippo Alongi, Elena Clerici, Francesca Lobefalo, Angelo Tozzi, Giacomo Reggiori, Antonella Fogliata and Marta Scorsetti

- 76 patients & 118 lung lesions treated
- SBRT performed in
  - Controlled primary tumor
  - Long-term to disease progression.
  - Number of metastatic sites ≤ 5
- Dose: 48 Gy to 60 Gy.
- Median follow up – 20 months

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<th>1 Year (%)</th>
<th>2 Years (%)</th>
<th>3 Years (%)</th>
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<tbody>
<tr>
<td>Local Control</td>
<td>95</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>OS</td>
<td>84.1</td>
<td>73</td>
<td>73</td>
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Conclusion: SBRT is feasible with promising results in terms of local control, survival and toxicity
Open-label, multi-centric (10 centres in Canada, Australia, Scotland and Netherlands).

2012-2016

1\textsuperscript{st} trial to directly test the oligometastatic paradigm, i.e. OS after Ablative vs Palliative t/t

Initial results- 13 month improvement of OS in test arm.
Stereotactic Body Radiotherapy for Patients with Lung Oligometastatic Disease: A Five-Year Systematic Review

Guillaume Virbel, Clara Le Fèvre, Georges Noël and Delphine Antoni

- 5 years systematic review
- 2015 to 2020 published data analyzed
- 18 studies included (Retrospective studies)
- 1191 patients
- 1705 metastases were irradiated
- Diameter of tumor – 7mm to 124mm

Conclusions:
- SBRT is an efficient and well-tolerated treatment for lung metastases in oligometastatis
- Optimal treatment schedule is not definite.
- BED > 100 Gy, appear to be appropriate to obtain a LC comparable with that of surgery.
<table>
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<tr>
<th>Metastases to the liver are common</th>
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<tr>
<td>Colorectal cancers commonly metastasize to the liver</td>
</tr>
<tr>
<td>Long-term survival is possible after metastatectomy.</td>
</tr>
<tr>
<td>Metastasectomy remains the gold standard for resectable liver metastases</td>
</tr>
<tr>
<td>Many patients are not candidates for surgical resection</td>
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<tr>
<td>Non-invasive techniques such as liver SBRT is an option.</td>
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<tr>
<td>SBRT is a recognized tool for ablation of liver metastases.</td>
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<td>SBRT is an option for unresectable disease and for medically inoperable patients</td>
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Phase II study on stereotactic body radiotherapy of colorectal metastases

Morten Hoyer, Henrik Roed, Anders Traberg Hansen, Lars Ohlhuus, Jørgen Petersen, Hanne Nellemann

64 patients, 1999 - 2003
1-6 metastases (maximum diameter of the largest tumor < 6 cm)
Radical resection of the primary tumor & metastases had to be determined to be inoperable
141 metastases were treated (Liver mets 44)
Dose: 15 Gy x 3fr within 5-8 days
Tumor specific local control 79% at 2 years

Conclusion:
- Promising local control for patients with CRC metastases primarily in the liver and lungs treated with SBRT
- Re-treatment of new lesions was possible and in general, the toxicity of the treatment was moderate
2013

61 patients were enrolled with 76 liver metastases
- 1-3 unresectable liver metastases with max diameter < 6 cm
- 34% of patients had stable extrahepatic disease
- Dose: 75 Gy in 3 fractions
- Primary end-point: In-field local control.
- Secondary end-points: Toxicity and survival
- 1-year in-field LC was 94%

Conclusion:
SBRT for unresectable liver metastases is an effective, safe, therapeutic option, with excellent local control and a low t/t toxicity.
DOSE:

• 15 Gy x 3 fractions given in 5-8 days

• 30-37.5 Gy in 3 fractions

• 36 Gy to 60 Gy in 3 fractions

• 75 Gy in 3 fractions
Pooled analysis
65 patients with 102 lesions treated from August 2003 to May 2009
1 - 4 lesions & Received 1 - 6 fractions of SBRT
Radiological imaging 3 months post-treatment

Conclusion:
• 3-fraction regimen of SBRT of prescription dose of 48 Gy should be considered, if normal tissue constraints allow
• Patients without active extrahepatic disease have better OS than patients with active extrahepatic disease
70 patients with 103 colorectal liver metastases
45 to 60 Gy in 3 to 4 fractions

**Conclusion:**
- Longer local control can be expected if higher doses are used
- SBRT of liver metastases derived from colorectal cancer offers a locally effective treatment without significant complications

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<tr>
<th>Group</th>
<th>Dose (Gy)</th>
<th>Local Control (%)</th>
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<tbody>
<tr>
<td>Group 1</td>
<td><code>&lt;= 80</code></td>
<td>52</td>
</tr>
<tr>
<td>Group 2</td>
<td>100 - 112</td>
<td>83</td>
</tr>
<tr>
<td>Group 3</td>
<td><code>&gt;= 132</code></td>
<td>89</td>
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Non colorectal Liver metastases
Stereotactic body radiation therapy for melanoma and renal cell carcinoma: impact of single fraction equivalent dose on local control

2011

Michelle A Stinauer, Brian D Kavanagh, Tracey E Schefter, Rene Gonzalez, Thomas Flaig, Karl Lewis,

- RCC – 13 patients, 25 lesions
- Melanoma – 17 patients, 28 lesions
- LC defined pathologically by negative biopsy or radiographically by lack of tumor enlargement on CT or stable/declining standardized uptake value (SUV) on PET scan

SBRT dose regimen was converted to the single fraction equivalent dose (SFED) to characterize the dose-control relationship using a logistic tumor control probability (TCP) model.

The actuarial rate of LC at 24 months was 100% for SFED ≥45 Gy v 54% for SFED <45 Gy.

Conclusion:
An aggressive SBRT regimen with SFED ≥ 45 Gy is effective for controlling metastatic melanoma and RCC

TCP modeling indicated that to achieve ≥90% 2 yr LC in a 3 fraction regimen, a prescription dose of at least 48 Gy is required.
Radiosensitivity Differences Between Liver Metastases Based on Primary Histology Suggest Implications for Clinical Outcomes After Stereotactic Body Radiation Therapy

Conclusion:

This study suggests that primary histology may be an important factor to consider in SBRT radiation dose selection.

Dose
50-60Gy / 5 fr
FUTURE DIRECTIONS

Immunotherapy with SBRT

• Anti-PD-1/PD-L1 therapy
• Anti-CTLA-4
• IFN- Gamma
Radiation therapy to convert cancers

Into an “in situ tumor vaccine” by inducing release of antigens during cancer cell death

promoting proinflammatory signals within and out of the radiation field

creating positive microenvironmental changes

Stimulate the innate immune system to activate tumor specific T cells and enhance cancer infiltrations

• This augments the effectiveness of Immunotherapy
• 79 patients
• 3 patients only received SBRT
• Patients included in the analysis were treated with SBRT and at least one cycle of pembrolizumab

**SBRT**
- 30 to 50 Gy in 3 to 5 fractions
• Most (94.5%) of patients received SBRT to two metastases

**Median follow-up for toxicity** was 5.5 months (interquartile range, 3.3 to 8.1 months)

**Median OS** - 9.6 months & **Median PFS** - 3.1 months

**Conclusion:**
Multisite SBRT followed by pembrolizumab was well tolerated with acceptable toxicity.
Thank You