Role Of Radiotherapy In Oligo metastatic lung cancer (NSCLC)

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54 years male diagnosed c/o of adenocarcinoma right lung with liver, lung and bone metastases

<table>
<thead>
<tr>
<th>Stage</th>
<th>IV</th>
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<tbody>
<tr>
<td>Treatment</td>
<td>Palliative chemotherapy ± Radiotherapy to bone metastases</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Poor</td>
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</tbody>
</table>
Oligometastases (OMD):

- “Oligos”: Few; “Metastasis”: removal from one place to another
- Postulated in 1995 by Hellman and Weichselbaum
- Special category of stage IV cancer
- Reduced tendency to widespread dissemination
- Hallmark- limited number of metastatic deposits (intermediate metastatic state)
Oligometastases: Definition

Current gold standard to diagnose oligometastases relies on **number of metastases** and **metastatic sites** and determine whether they are amenable to local treatment, with the aim to prolong survival.
EORTC-LCG consensus statement(2019): “a radical treatment that may modify the disease course (leading to long-term disease control) is technically feasible for all tumor sites with acceptable toxicity”

It does not / cannot account for tumor markers, genomic signatures and micro environmental factors that have a strong influence on the clinical course of the disease

- $^{18}$F-FDG PET–computed tomography and brain imaging are mandatory

- Diffuse serosal (meningeal, pleural, pericardial, and mesenteric) or bone marrow metastases are excluded
Oligometastases: Classification

- Metastatic disease
  - Oligometastatic
    - Induced oligometastatic
    - De-novo oligometastatic
      - Synchronous oligometastatic
      - Metachronous oligometastatic
- Polymetastatic
  - Post treatment

Temporality of oligomets
Response of oligometas to treatment

- Oligometastatic
  - Oligorecurrent
  - Oligopersistent
  - Oligoprogessive
Oligorecurrent

Radical treatment

LOCALISED DISEASE

OLIGORECURRENCE
Oligopersistent

Systemic treatment

OLIGOMETASTASES

OLIGOPERSISTENT
Oligoprogression
Oligometastases: How frequent?

25-50% of NSCLC patients have Oligometastases at presentation

Organs involved:

- Bones (35.5%)
- Brain (25%)
- Adrenal gland (20%)
- Liver (12%)
- Skin, lymph nodes, or peritoneum (7.5%)
Oligometastases: Staging

- 18F-FDG PET-CT

- MRI brain

- Pathological confirmation of 1 metastasis is required unless risk outweighs benefit

- Solitary metastasis:
  - Solitary liver metastasis: MRI scan of liver
  - solitary pleural metastasis thoracoscopy and dedicated biopsies
Oligometastases NSCLC: Poor prognostic factors

- Synchronous lesions
- More nodal involvement
- Squamous cell histology
- Poor performance status
- Shorter interval from initial diagnosis to metastatic development
- Metastases to > one organ
- Extrapulmonary metastases
Oligometastases NSCLC: Management

- **Systemic therapy**
  - Chemotherapy/targeted therapy
  - Immunotherapy

- **Local therapy**
  - Surgery
  - Radiotherapy
    - EBRT
    - Brachytherapy
  - Radiofrequency ablation
  - Intra arterial embolization
  - Cryoablation
Oligometastases: Biological Rationale of Local Ablative therapy

Metastatic cascade

Linear progression model
- Late emergence of metastatic subclones
- Low degree of genetic divergence

Parallel progression model
- Early emergence of metastatic subclones
- High degree of genetic divergence

LAT prevent emergence of new metastasis and progression to disseminated metastasis

Intratumoral heterogeneity of primary tumor and metastasis

Disseminated metastases

Yang-Gun Suh et al E roj 2019
LAT may prevent emergence of new metastasis-competent clone
Oligometastases: Mechanism of local ablative therapies

• Reduced overall disease burden through direct cytoreduction

• Induces more systemic treatment-sensitive proliferative phase of surviving clonogens in the target lesion

• Curbs cancer growth and metastases, delaying progression due to emergence of treatment-resistant clonogens

• Enhances antitumor immune-mediated effect by promoting cancer antigen presentation and lymphocytic tumor infiltration: Abscopal effect
Oligometastatic NSCLC: Sequence of therapy

• Unclear and highly debated

• **Upfront LAT**: prevent more aggressive subclones from originating in anyone of the detectable disease sites

• **Upfront systemic therapy**: allows for response assessment before considering LAT
Oligometastatic NSCLC: Upfront LAT approach
Oligometastatic NSCLC: Upfront Systemic chemotherapy approach

Systemic therapy → No progression → LAT → Change Systemic therapy...

Progression
Oligometastases: Surgery

• Surgical treatment has been the main modality historically

• Surgery has the attributes of being:
  • Diagnostic: pathologic confirmation of metastatic disease
  • Therapeutic: eliminating tumor and/or alleviating tumor-related symptoms

• Approximately 55% of all patients receive surgical treatment
  • Brain oligometas: 5-year OS rates 20%
  • Adrenal oligometas: 5-year OS rates 20-30%
Oligometastases: Radiotherapy

• Technical advancements in computing power, diagnostic imaging, and motion management → dramatic improvements in the planning and delivery of radiation treatments

• Non-invasive, well-tolerated and fewer interruptions to systemic therapy

• Intracranial and extracranial metastases

• Techniques
  • SRS/SBRT/ SABR and conventional techniques
  • Brachytherapy
Oligometastases: Why SBRT

• Better technology

• Ablative dose with limited number of fractions

• No delay in systemic therapy

• Good number of studies

• SABR for metastatic lesions in various sites has shown good local control rates (70% to 100%)

• Acceptable treatment-related toxicities
Oligometastases: Should SABR replace surgery?

• No RCTs have compared SABR with surgical resection

• Limited data available comparing surgery with SABR support a position of equipoise between the two treatments

• Choice of SABR versus surgery should be personalized, determined by various factors including patient preferences and clinical scenario
Oligometastases: Patient selection for local treatment

Selection of most effective method for local treatment of oligometastases depends on:

- **Patient-related factors**
  - Age
  - Performance status
  - Organ function
  - Patient preferences

- **Tumour-related factors**
  - Location
  - Size
  - Proximity to vessels/critical organs

- **Treatment-related factors**
  - Availability of expertise
  - Cost
  - Waiting list
Metastatic sites treatable with stereotactic radiotherapy

Brain
Spine
Lung
Liver
Adrenal gland
Lymph nodes
Bone
Oligometastases NSCLC: Target to be treated

A. Primary

B. Metastases

C. Both
## Oligometastases: Radiotherapy doses

<table>
<thead>
<tr>
<th>Site</th>
<th>Dose</th>
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<tbody>
<tr>
<td>Brain</td>
<td>• 18-24 Gy (single fr)</td>
</tr>
<tr>
<td></td>
<td>• 27-30Gy/3-5 fr</td>
</tr>
<tr>
<td>Lung</td>
<td>• Peripheral lesions &lt;2 cm: 60 Gy in 3 fr</td>
</tr>
<tr>
<td></td>
<td>• Peripheral lesions 2 -5 cm:48Gy in 4 fr</td>
</tr>
<tr>
<td></td>
<td>• Central lesions: 60 Gy in 8 fr</td>
</tr>
<tr>
<td></td>
<td>• 45 Gy in 15 fr</td>
</tr>
<tr>
<td>Adrenal</td>
<td>• 42 Gy in 6 fr</td>
</tr>
<tr>
<td></td>
<td>• 20–40 Gy in 5 fr</td>
</tr>
<tr>
<td>Liver</td>
<td>• 30–60 Gy in 3 fr</td>
</tr>
<tr>
<td></td>
<td>• 50 Gy in 5 fr</td>
</tr>
<tr>
<td>Bone</td>
<td>• 18 to 24Gy (single fr)</td>
</tr>
<tr>
<td></td>
<td>• 24-27Gy in 2 or 3 fr</td>
</tr>
<tr>
<td></td>
<td>• 30-35Gy in 5 fr</td>
</tr>
</tbody>
</table>
## Oligometastases NSCLC: Summary of studies of radiation therapy

<table>
<thead>
<tr>
<th>Trial (yr and design)</th>
<th>Patients (Mets per patient)</th>
<th>RT technique</th>
<th>Definitive thoracic therapy / Systemic therapy</th>
<th>Median progression free survival (months)</th>
<th>Overall survival (OS)</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gomez et al (2016) P</td>
<td>49 (≤3)</td>
<td>Various</td>
<td>Yes /All received induction chemo</td>
<td>11.9 (LCT) vs 3.9 (no LCT)</td>
<td>Median OS not reached</td>
<td>20 vs 8.3% G3</td>
</tr>
<tr>
<td>Iyengar et al. (2014) P</td>
<td>24 (≤6)</td>
<td>SBRT</td>
<td>NA / All progressed through 1st line chemo, all received erlotinib</td>
<td>14.7</td>
<td>Median 20.4 months</td>
<td>2 G3 RT-related toxicities</td>
</tr>
<tr>
<td>Griffioen et al. (2013) R</td>
<td>61 (≤3)</td>
<td>Various</td>
<td>Yes / 84% chemo</td>
<td>6.6</td>
<td>2 years 38%</td>
<td>6.6% G3</td>
</tr>
<tr>
<td>Cheruvu et al. (2011) R</td>
<td>96 (≤8)</td>
<td>SBRT</td>
<td>NA /70% chemo</td>
<td>NA</td>
<td>2 years 25% (oligorecurrence) vs 43% (de novo oligometastases)</td>
<td>NA</td>
</tr>
<tr>
<td>Hasselle et al. (2012) R</td>
<td>25 (≤5)</td>
<td>SRS/ SBRT</td>
<td>NA / 76% prior to SBRT</td>
<td>7.6</td>
<td>1 year 81.1%</td>
<td>8% G3</td>
</tr>
<tr>
<td>SABR COMET trial: (2020) P</td>
<td>99 (≤5)</td>
<td>Standard-of-care:(arm 1),SOC plus SABR (arm 2)</td>
<td>5-year PFS rate was not reached in arm 1 and 17.3% in arm 2</td>
<td>5-year OS :17.7% -arm 1 versus 42.3% - arm 2</td>
<td>no Gr 2-5 adverse events, no differences in QOL between arms</td>
<td></td>
</tr>
</tbody>
</table>
**Oligometastases NSCLC: Brachytherapy**

- Limited data available

<table>
<thead>
<tr>
<th>Study (pts)</th>
<th>NSCLC pts</th>
<th>Site</th>
<th>Technique</th>
<th>Dose</th>
<th>Toxicity</th>
<th>Median follow up (months)</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walter F (106) 2021</td>
<td>5</td>
<td>Liver</td>
<td>Catheters</td>
<td>20 Gy</td>
<td>2 pts</td>
<td>9</td>
<td>76.3% 1 yr</td>
</tr>
<tr>
<td>Wang (53) 2020</td>
<td>25</td>
<td>Mixed</td>
<td>$^{125}$ Iodine seeds</td>
<td>100-140 Gy</td>
<td>4 pts</td>
<td>13</td>
<td>12.8 m</td>
</tr>
</tbody>
</table>
## Oligometastatic NSCLC: Ongoing trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Arms</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OMEGA (Phase 3)</strong></td>
<td>Standard treatment plus local ablative therapy (surgery and/ or radiotherapy) or to standard treatment alone</td>
<td>Overall survival</td>
</tr>
<tr>
<td><strong>SARON (Phase 3)</strong></td>
<td>Efficacy and safety of SABR in addition to chemotherapy compared to standard treatment alone</td>
<td>OS/PFS/QOL/Toxicity/ Local control</td>
</tr>
<tr>
<td><strong>HALT (Phase 3)</strong></td>
<td>SBRT plus TKI compared to TKI alone beyond oligo-progression in patients with oncogene-driven NSCLC</td>
<td>PFS/OS/toxicity/pattern of disease progression</td>
</tr>
<tr>
<td><strong>OITROLC (Phase 3)</strong></td>
<td>Upfront chemo plus concurrent radiotherapy to the primary and all metastatic sites versus a consolidative approach after two cycles of induction chemotherapy</td>
<td>Response rate / toxicity / QOL</td>
</tr>
</tbody>
</table>
Conclusions

• Oligometastatic NSCLC is a broad spectrum disease, with a variable prognosis

• Biology & behaviour of “intermediate state” of metastatic disease not fully understood

• Consensus definition has now been developed for NSCLC

• SBRT provides an attractive ablative option because it is well tolerated

• Additional studies are required for improved patient selection, optimal treatment schedule, and to define treatment related toxicities
Thank You