Treatment of oligometastatic NSCLC

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New idea?

14 NSCLC patients with solitary extrathoracic metastasis (lymph nodes, skeletal muscle, bone, and small bowel)

Oligometastatic concept

• the term ‘oligometastasis’ has been proposed by Hellman and Weichselbaum (J Clin Oncol, 1995)
• it was defined as an intermediate stage between locally advanced and widely disseminated disease
• lung tumour, no evidence of lymph node involvement, and limited distant metastasis
Confusing terminology

- oligometastatic primary vs oligorecurrence?
- different cut-off numbers of metastases are used: 1, 1-2, 1-5
- metastasis on 1 distant organ? In 2? In 3?
- negative vs positive mediastinal lymph nodes?
Does it exist?

Is there an oligometastatic state in non-small cell lung cancer? A systematic review of the literature

Allison Ashworth. George Rodrigues. Gabriel Boldt. David Palma*

Yes, it does!
Lung Cancer TNM 8th edition

• M1a  Separate tumor nodule(s) in a contralateral lobe
• M1b  Single extrathoracic metastasis
• M1c  Multiple extrathoracic metastasis
## Lung Cancer TNM 8th edition

<table>
<thead>
<tr>
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<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
<th>M1a any N</th>
<th>M1b any N</th>
<th>M1c any N</th>
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<td>IVA</td>
<td>IVA</td>
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Location

- contralateral lung
- brain
- adrenal gland
- bone
- other?
Curative-intent treatment options

• complete resection of the primary tumour AND
• surgical metastasectomy ± chemotherapy OR
• stereotactic ablative radiotherapy ± chemotherapy OR
• radiofrequency ablation ± chemotherapy
Lung mets – staged thoracotomoy

• currently the most often use approach
• sequence: wedge resection or segmentectomy for mets first, lobectomy or bilobectomy for the primary second
• low morbidity and mortality of 0-2.5%

Pfannschmidt et al., Ann Thorac Surg 2007
Brain mets

• 66 pts with sync brain-only (SBO) mets (1-4)
• Aggressive Thoracic Treatment (ATT), incl. surgery and CTH/RCT
• 2-Y OS 54% - 5-Y OS 29%
• MST 26 months (ATT) vs. 10 months (non ATT)

Gray et al., Lung Cancer 2014
Brain mets

- aggressive management in NSCLC patients with SBO is associated with improved survival

Gray et al., Lung Cancer 2014
Brain mets - strategy

• sequence: primary first or metastasis first?
• surgery or stereotactic radiosurgery: depending on anatomic relationship and number of mets
• complications and mortality
Adrenal mets - strategy

• metastasis or incidentaloma – need of confirmation
• sequence: primary first?
• laparoscopic adrenalectomy: mortality <1% and morbidity – 6%, used for smaller tumours and associated with less complications, shorter hospital stay and smaller blood loss

Evidence

- poor quality of scientific data
- only observational studies
- 84% are retrospective case series
- only 2 out of 49 studies were prospective (uncontrolled) series

Ashworth et al. Lung Cancer 2013
Survival

• overall median: 18.8 months (range: 5.9-52)  
  Ashworth et al., Lung Cancer 2013

• in the general stage IV population the overall median survival is 7-11 months
OS predictive factors

- highly significant
  - controlled primary tumour (curative treatment vs palliative or no treatment)
  - N status (N0 vs N+; N0-1 vs N2-3)
  - DFI (1 year for brain mets, 6 months for adrenal mets)

Ashworth et al., Lung Cancer 2013
OS predictive factors

• moderately significant
  - extracranial mets (vs brain mets only)
  - use of PET-CT (vs CT alone)
  - primary tumour size (1-3 vs 3-5 vs >5 cm)
  - type of pulmonary resection (lobectomy vs pneumonectomy)

Ashworth et al., Lung Cancer 2013
OS predictive factors

- occasionally significant
  - histology (adenocarcinoma vs other)
  - age (<50; <70)
  - perioperative chemotherapy (vs no chemo)
  - number of metastases (1 vs >1 for lung mets, 1 vs 2-3 vs 4-6 for brain mets)
  - primary T stage
  - synchronous vs metachronous

Ashworth et al., Lung Cancer 2013
Survival (controlled primary)

- metaanalysis, 757 NSCLC patients, 1-5 synchronous or metachronous metastases treated with surgical metastasectomy, stereotactic radiotherapy or radical EBRT and curative treatment of the primary lung cancer
- median OS – 26 months
- 1-year OS 70.2%
- 5-year OS 29.4%

Ashworth et al., Clin Lung Cancer 2014
OS predictive factors (controlled primary)

- metachronous versus synchronous metastases ($p < 0.001$)
- N-stage ($p = 0.002$)
- adenocarcinoma histology ($p = 0.036$)

Ashworth et al., Clin Lung Cancer 2014
Risk groups

- low-risk: metachronous metastases (5-year OS, 47.8%)
- intermediate risk: synchronous metastases and N0 disease (5-year OS, 36.2%)
- high risk, synchronous metastases and N1/N2 disease (5-year OS, 13.8%)

Ashworth et al., Clin Lung Cancer 2014
OS and PFS according to risk groups

Ashworth et al., Clin Lung Cancer 2014
in patients with a contralateral lobe tumor nodule(s), it is suggested that evaluation of extrathoracic metastases (eg, PET and brain MRI/CT) and invasive evaluation to rule out mediastinal node involvement should be carried out (Grade 2C).

if negative, resection of each lesion is suggested, provided the patient has adequate pulmonary reserve (Grade 2C).
ACCP 2013 guidelines (isolated brain met)

- if considered for curative treatment, invasive mediastinal staging and either whole-body PET or abdominal CT plus bone scan are suggested (Grade 2C)
- if negative, and primary tumour completely resected, resection or radiosurgical ablation of brain metastasis is recommended (Grade 1C)
- after that, adjuvant whole-brain radiotherapy is suggested (Grade 2B) plus adjuvant chemo.
ACCP 2013 guidelines (isolated adrenal met)

• if considered for curative-intent surgical resection, invasive mediastinal staging and head CT/MRI plus either whole-body PET or abdominal CT plus bone scan are suggested (Grade 2C)

• in patients with a synchronous resectable N0,1 NSCLC and no other sites of metastases, resection of the primary tumor and the metastasis is recommended (Grade 1C)
ACCP 2013 guidelines (isolated adrenal met)

• in patients with no other sites of metastases and a previously completely resected primary NSCLC (*metachronous* presentation), resection of an isolated adrenal metastasis is recommended (Grade 1C)

• In patients who have undergone a curative resection of an isolated adrenal metastasis, adjuvant chemotherapy is suggested (Grade 2B)
Synchronous primary or metastasis?

- Martini and Melamed criteria – 4 decades old, but still in use

| Table 1 |
|-----------------|-----------------|-----------------|
| Martini and Melamed criteria to define multiple primary NSCLC (adapted from [23]). |

<table>
<thead>
<tr>
<th>Tumor location</th>
<th>Same histology</th>
<th>Different histology</th>
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<tbody>
<tr>
<td>Same segment</td>
<td>Metastasis&lt;br&gt;Origin from carcinoma in situ, and no carcinoma in lymphatics common to both, and no systematic metastasis: multiple primary&lt;br&gt;No carcinoma in situ, or carcinoma in lymphatics common to both, or systemic metastasis: metastasis</td>
<td>Multiple primary</td>
</tr>
<tr>
<td>Different segment</td>
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<td>Multiple primary</td>
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<table>
<thead>
<tr>
<th>Metachronous multiple tumors</th>
<th>Location</th>
<th>Same histology</th>
<th>Different histology or arising separately from foci of carcinoma in situ</th>
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<tr>
<td>Interval between cancers</td>
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<tr>
<td>≥2 years</td>
<td>Same lobe</td>
<td>Multiple primary&lt;br&gt;Metastasis&lt;br&gt;No carcinoma in lymphatics common to both, and no systemic metastasis: multiple primary&lt;br&gt;Carcinoma in lymphatics common to both, or systemic metastasis: metastasis</td>
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<td>&lt;2 years</td>
<td>Different lobe</td>
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Martini and Melamed, J Thorac Cardiovasc Surg 1975
Synchronous primary or metastasis?

Genomic profiling and comprehensive histological analysis improves differentiation

Martini-Melamed criteria were incorrect in 32% of patients

Synchronous primary or metastasis?

discrimination of multiple primary lung cancers from intrapulmonary metastasis based on the expression of four cancer-related proteins: p53, p16, p27, and C-erbB2

Ono et al, Cancer, 2009
Synchronous primary or metastasis?

- despite this progress, uncertainty is common
What we know

- there are patients with NSCLC distant metastases, who can be cured!!!
- it is possible in a small minority of patients
- we are unable to precisely determine, in whom it is possible
- there are factors (controlled primary, metachronous mets, long DFI, N0 status,) known to be associated with better chance of cure or longer survival
What we know - cont.

• in these carefully selected patients, there is no reason to deny aggressive, multimodal, curative-intent treatment, aimed at both: primary tumour and metastasis

• we have to cooperate!!! (oncologists, radiation oncologists, surgeons, pathologists)

• in these low-risk patients, overall survival >40% can be expected
What we can expect

• increasing number of patients with oligometastatic NSCLC, due to better diagnostics
• more efficient tests enabling differentiation between multiple primary tumours and mets
• better selection of truly oligometastastic disease, thus improved patients selection
• implementation of new drugs into the multimodal treatment regimens
Questions to be answered

• Molecular and genetic mechanisms determining the oligometastatic spread
• Optimal follow-up strategy aimed at early detection of oligometastatic recurrence
• Distinguishing between true oligometastatic state and occult widespread dissemination
• Proper selection and sequence of elements of the multimodal treatment
• Prevention of treatment-related complications
There are many issues concerning treatment of oligometastatic lung cancer that are not clear...
• “lack of ‘clarity’ should not translate into a lack of intervention as long as the morbidity of the intervention is reasonable”

E. Vallieres
Thank you for your attention!