

The best approach to oligometastatic NSCLC

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Definition

- 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
- different cut-off numbers of metastases are used: 1, 1-2, 1-5

Mechanisms - anatomical

- Direct lymphatic drainage to the thoracic duct
Riquet et al., Surg Radiol Anat 1988, Riquet et al., Ann Thorac Surg 2002
- Lymphatic pathways from the lungs to the abdominal lymph nodes
Riquet et al., Surg Radiol Anat 1988

Mechanisms - molecular

- loss of cellular adhesion
- entry to circulation
- survival in circulation
- entry to destination organ
- colonisation and growth in destination organ

Mechanism – genetic factors

- initiation genes – provide selective biological advantage increasing metastatic potential of primary tumour cells
- progression genes – provide specific features enabling settlement in distant organs
- virulence genes – provide advantage in growth in the micro-environment of the target organ

Gupta and Massague, Cell, 2006

Location

- contralateral lung
- brain
- adrenal gland

Curative-intent treatment options

- Complete resection of the primary tumour

AND

- surgical metastasectomy \pm chemotherapy

OR

- stereotactic ablative radiotherapy \pm chemotherapy

OR

- radiofrequency ablation \pm chemotherapy

Lung mets – staged thoracotomy

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

Pfannschmidt et al., Ann Thorac Surg 2007

Brain mets - strategy

- Sequence: primary first or metastasis first?
- Surgery or stereotactic radiosurgery: depending on anatomic relationship and number of mets
- Complications: surgery - 7%, SRS - 25%
- Mortality: surgery 0-3%, SRS – 1.8%

Al-Shamy, J Neurooncol 2009, Mussi, J Thorac Cardiovasc Surg 1996

Adrenal mets - strategy

- Metastasis or incidentaloma – need of confirmation
- Sequence: primary fist?
- Laparoscopic adrenalectomy: mortality <1% and morbidity – 6%, used for smaller tumours and associated with less complications, shorter hospital stay and smaller blood loss

Thompson, Surgery 1997, Arenas et al., World J Surg 2014

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)
- median in patients with controlled primary tumour: 19 months (range: 6.2-52)

Ashworth et al., Lung Cancer 2013

- In the general stage IV population the overall median survival is 7-11 months

Ramalingam, Oncologist 2008

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

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%)

Niibe-Onishi-Chang risk groups

- Favourable:
 - oligorecurrence 1 or 2 (brain and adrenal)
- Relatively favourable:
 - oligorecurrence 3-5 (brain and adrenal)
 - sync-oligometastases 1 or 2 (brain and adrenal)

Niibe et al., Pulm Med 2013

Niibe-Onishi-Chang Risk groups (cont)

- Relatively unfavourable
 - 3-5 (brain, adrenal gland, others)
 - sync-oligometastases 3 to 5 (brain and adrenal)
- Unfavourable
 - >5 or polymetastases

ACCP 2013 guidelines (contralateral lobe)

- 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

Martini and Melamed, J Thorac Cardiovasc Surg 1975

- Genomic profiling and comprehensive histological analysis improves differentiation

Girard et al., Clin Cancer Res 2009, Am J Surg Pathol 2009

- Despite this progress, uncertainty is common

Synchronous primary or metastasis?

- 31 patients, 5-year OS - 34% (Trousse et al., J Thorac Cardiovasc Surg 2007)
- 57 patients, 5-year OS - 38% (De Leyn et al., Eur J Cardiothorac Surg 2008)
- 19 patients, 5-year OS - 76% (Mun et al., Ann Thorac Surg 2007)

What we know

- There are patients with NSCLC metastases, who can be cured
- We are unable to determine, in whom it is possible
- There are factors, known to be associated with better chance of cure or longer survival
- in these favourable cases, aggressive multimodal treatment should be used

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

Thank you for your attention!

