Treatment of oligometastatic NSCLC

Jarosław Kuźdżał

Department of Thoracic Surgery
Jagiellonian University Collegium Medicum,
John Paul II Hospital, Cracow
No conflict of interest to disclose regarding this presentation

Jarosław Kużdżał
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
New idea?

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

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 *
Does it exist?

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>
<th></th>
<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>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>IA1</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIIB</td>
<td>IVA</td>
<td>IVA</td>
<td>IVB</td>
</tr>
<tr>
<td>T1b</td>
<td>IA2</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIIB</td>
<td>IVA</td>
<td>IVA</td>
<td>IVB</td>
</tr>
<tr>
<td>T1c</td>
<td>IA3</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIIB</td>
<td>IVA</td>
<td>IVA</td>
<td>IVB</td>
</tr>
<tr>
<td>T2a</td>
<td>IB</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIIB</td>
<td>IVA</td>
<td>IVA</td>
<td>IVB</td>
</tr>
<tr>
<td>T2b</td>
<td>IIA</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIIB</td>
<td>IVA</td>
<td>IVA</td>
<td>IVB</td>
</tr>
<tr>
<td>T3</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIIB</td>
<td>IIIC</td>
<td>IVA</td>
<td>IVA</td>
<td>IVB</td>
</tr>
<tr>
<td>T4</td>
<td>IIIA</td>
<td>IIIA</td>
<td>IIIB</td>
<td>IIIC</td>
<td>IVA</td>
<td>IVA</td>
<td>IVB</td>
</tr>
</tbody>
</table>
# Lung Cancer TNM 8th edition


<table>
<thead>
<tr>
<th>Stage</th>
<th>Events/N</th>
<th>MST</th>
<th>24 months</th>
<th>60 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA1</td>
<td>68/781</td>
<td>NR</td>
<td>97%</td>
<td>92%</td>
</tr>
<tr>
<td>IA2</td>
<td>505/3105</td>
<td>NR</td>
<td>94%</td>
<td>83%</td>
</tr>
<tr>
<td>IA3</td>
<td>546/2417</td>
<td>NR</td>
<td>90%</td>
<td>77%</td>
</tr>
<tr>
<td>IB</td>
<td>560/1928</td>
<td>NR</td>
<td>87%</td>
<td>68%</td>
</tr>
<tr>
<td>IIA</td>
<td>215/585</td>
<td>NR</td>
<td>79%</td>
<td>60%</td>
</tr>
<tr>
<td>IIB</td>
<td>605/1453</td>
<td>66.0</td>
<td>72%</td>
<td>53%</td>
</tr>
<tr>
<td>IIIA</td>
<td>2052/3200</td>
<td>29.3</td>
<td>55%</td>
<td>36%</td>
</tr>
<tr>
<td>IIIB</td>
<td>1551/2140</td>
<td>19.0</td>
<td>44%</td>
<td>26%</td>
</tr>
<tr>
<td>IIIC</td>
<td>831/986</td>
<td>12.6</td>
<td>24%</td>
<td>13%</td>
</tr>
<tr>
<td>IVA</td>
<td>336/484</td>
<td>11.5</td>
<td>23%</td>
<td>10%</td>
</tr>
<tr>
<td>IVB</td>
<td>328/398</td>
<td>6.0</td>
<td>10%</td>
<td>0%</td>
</tr>
</tbody>
</table>
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?
Evidence – general remarks

- poor quality of scientific data
- mainly observational studies
- only two RCT and two metaanalyses
- majority are retrospective case series
- however: significant increase in the number of papers: 59 published in 2018
Evidence - RCT

- Multicentre, phase 2 RCT
- St IV NSCLC patients with ≤3 mets
- First-line therapy (chemo, EGFr or ALK inhibitors)
- randomisation 1:1
  - local consolidative therapy (surgery or RTH)
  - maintenance treatment

Gomez et al., Lancet Oncology 2016
Evidence – RCT cont.

• median PFS was:
  - in the consolidation group was 11.9 months
  - in the maintenance group - 3.9 months

• The study was terminated due to these results by the Data Safety Monitoring Committee at the MD Anderson

• No deaths, no grade 4 adverse effects

Gomez et al., Lancet Oncology 2016
Evidence – RCT cont.

- single-institution, small RCT
- oligometastatic NSCLC (≤5 mets), no EGFR-targetable or ALK-targetable mutations, PR or SD after induction chemotherapy
- maintenance chemotherapy alone vs SBRT + maintenance chemotherapy

Iyengar P et al. JAMA Oncol 2018
Evidence – RCT cont.

- 29 patients:
  - 14 in the intervention arm
  - 15 patients in the control arm
- PFS: 9.7 months vs 3.5 months ($p = 0.01$)
  - the accrual was terminated after an interim analysis

Iyengar P et al. JAMA Oncol 2018
Evidence – RCT cont.

- two ongoing RCTs on SBRT in oligometastatic NSCLC:
  - STOP trial (NCT02756793)
  - HALT (NCT03256981)
Evidence – propensity analysis

- multicentre study, propensity score analysis
- 180 NSCLC patients treated 2000-2016
- ≤4 mets (brain or adrenal)
- intervention group: local ablative therapy (surgery or SBRT)
- control: standard CTH ± local palliative treatment

Frost N et al., Lung Cancer, 2018
Evidence – propensity analysis cont.

• progression-free survival:
  - 25.1 vs. 8.2 months
  - HR: 0.30; 95% CI, 0.21-0.43; p < 0.001

• overall survival:
  - 60.4 vs. 22.5 months
  - HR: 0.42; 95% CI, 0.28-0.62; p < 0.001

• Prognostic factors: T1a, N0-2, AC, ECOG-PS 0-1

Frost N et al., Lung Cancer, 2018
Evidence – retrospective controlled study

- 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
Evidence – retrospective controlled study

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

Gray et al., Lung Cancer 2014
Evidence – systematic review

- median OS: 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)
Evidence – systematic review cont.

• highly significant predictive factors for OS
  - 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
Evidence – systematic review cont.

- moderately significant predictive factors for OS
  - 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
Evidence - systematic review cont.

• occasionally predictive factors for OS
  - 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
Evidence - metaanalysis

- 757 NSCLC patients, controlled primary
- 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
Evidence – metaanalysis cont.

• Prognostic factors in 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
Evidence – metaanalysis cont.

• 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
Evidence – metaanalysis cont.

OS and PFS according to risk groups

Ashworth et al., Clin Lung Cancer 2014
Evidence - metaanalysis

- Effect of ATT (surgery or radiotherapy with a total >40 Gy)
- NSCLC patients, 1-5 synchronous mets
- impact of ATT on OS
- 7 retrospective cohort studies, 668 patients
- 34% received ATT

Li D. et al. J Thorac Dis, 2017
Evidence – metaanalysis cont.

• significant improvement of OS (HR, 0.48; 95% CI, 0.39–0.60; P<0.00001)
• also in subgroup analysis for single organ mets, solitary brain mets and less advanced primary
• pooled survival rates at 1, 2, 3 and 4 years:
  74.9%, 52.1%, 23.0% and 12.6%
  vs 32.3%, 13.7%, 3.7%, and 2.0%

Li D. et al. J Thorac Dis, 2017
Curative-intent treatment options

• complete resection/radical RTH of the primary tumour

    AND

• treatment of all metastatic sites
  (surgical metastasectomy, SBRT, RFA)

    AND

• systemic therapy
Lung mets - strategy

- contralateral metastasis or second primary?
- which one is metastasis?
- sequence: primary first or metastasis first?
- for metastasis: surgery or SBRT?
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

ACCP 2013 guidelines (contralateral lobe)

• in patients with a contralateral lobe tumor nodule(s), 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, **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)

- in patients with a *synchronous* presentation, resection of the primary tumor and the metastasis is recommended (Grade 1C)
- in patients with *metachronous* presentation, resection of an isolated adrenal metastasis is recommended (Grade 1C)
- In patients who have undergone a curative resection of an adrenal metastasis, *adjuvant* chemotherapy is suggested (Grade 2B)
Synchronous primary or metastasis?

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

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martini and Melamed criteria to define multiple primary NSCLC (adapted from [23]).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Synchronous multiple tumors</th>
<th>Tumor location</th>
<th>Same histology</th>
<th>Different histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same segment</td>
<td>Metastasis</td>
<td>Origin from carcinoma in situ, and no carcinoma in lymphatics common to both, and no systematic metastasis: multiple primary</td>
<td>Multiple primary</td>
</tr>
<tr>
<td>Different segment</td>
<td></td>
<td>No carcinoma in situ, or carcinoma in lymphatics common to both, or systemic metastasis: metastasis</td>
<td>Multiple primary</td>
</tr>
</tbody>
</table>

<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>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2 years</td>
<td>Same lobe</td>
<td>Multiple primary</td>
<td>Multiple primary</td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>Different lobe</td>
<td>Metastasis</td>
<td>Multiple primary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No carcinoma in lymphatics common to both, and no systematic metastasis: multiple primary</td>
<td>Multiple primary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carcinoma in lymphatics common to both, or systemic metastasis: metastasis</td>
<td>Multiple primary</td>
</tr>
</tbody>
</table>
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 minority of stage IV 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 – **confirmed survival benefit**!

• 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 oligometastatic 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
Certainly,

There are many issues concerning treatment of oligometastatic lung cancer that are not clear...

but,
“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!