

TREATMENT OF OLIGOMETASTATIC NSCLC: SURGERY VS RADIOTHERAPY AFTER SYSTEMIC TREATMENT



Prof. Lorenzo Spaggiari
Division of Thoracic Surgery
European Institute of Oncology
Department of Oncology and Hemato-oncology (DIPO)
University of Milan, Italy



THE PAST

Distant metastatic involvement was considered to be a state of disseminated disease with a very poor median survivals of 8–11 months and 5-year OS of 4–6%

No loco-regional control of the disease



THE PRESENT

The concept of oligometastatic disease emerged representing patients with only a few or “oligo” metastases

loco-regional control of the disease play a role

J Clin Oncol 1995



THE FUTURE

What will the future of oligometastatic disease in the era of biological drugs and immunotherapy?

?

Adjuvant local control (surgery/radiotherapy?)



Lung Cancer TNM 8th edition

- M1a Separate tumor nodule(s) in a contralateral lobe
- M1b Single extrathoracic metastasis
- M1c Multiple extrathoracic metastasis

Median survival (p<0.001)
 M1a 22.5 months
 M1b 17.8 months
 M1c 13.6 months



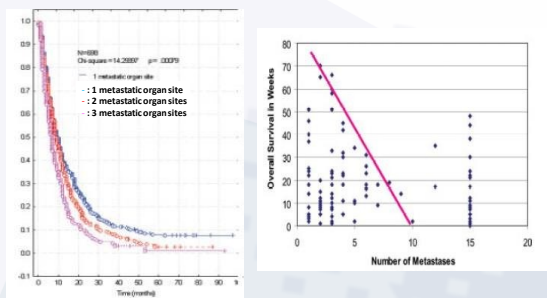
WHAT IS OLIGOMETASTASIS ?

- Intermediate state in-between patients without distant metastases and those with multiple metastatic involvement in one or more distant organs
- Different cut-off numbers of metastases: <3 or <5
- Different definition: oligometastatic primary vs oligo-recurrence vs oligoprogression



Oligometastatic NSCLC

→ Different cut-off



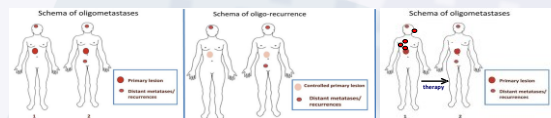
Courtesy of J. Vansteenkiste (ELCC 2016)



Oligometastatic NSCLC

→ Different definition

- 'oligometastases' = diagnosed with oligometastatic disease
 - 'oligo-recurrence' = relapsed oligometastatic disease
 - 'oligoprogression' = status after cytoreductive therapy
- cohorts probably have different prognoses



Courtesy of J. Vansteenkiste (ELCC 2016)



Oligometastatic NSCLC

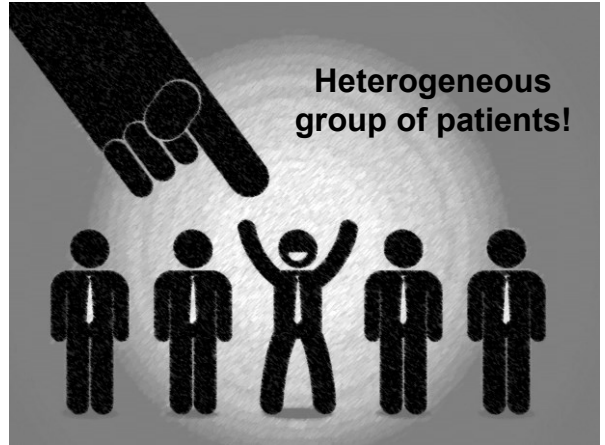
→ Different approach

Clinical classification of oligometastatic NSCLC

Categories	Characteristics	Description
Type I	Very limited oligometastatic disease	Patients with up to three metastatic lesions amenable to local aggressive treatment (LAT) with a controlled NSCLC
Type II	Synchronous oligometastatic disease	Patients with up to five metastatic lesions amenable to LAT at NSCLC diagnosis
Type III	Oligorecurrence	Patients with the appearance of up to five metastatic lesions amenable to LAT with a controlled NSCLC
Type IV	Oligoprogession	Patients with the appearance of up to five lesions during an adjuvant protocol
Type V	Residual oligometastatic disease	Patients with previous diffuse metastatic disease and residual lesions after chemo-radiotherapy

NSCLC, non-small cell lung cancer.

Local aggressive treatment



PROGNOSTIC FACTORS

Highly significant

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

Ashworth, Lung Cancer 2013



PROGNOSTIC FACTORS

Moderately significant

- extracranial mets worst than 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, Lung Cancer 2013



PROGNOSTIC FACTORS

Occasionally significant

- histology (adenocarcinoma better)
- age (<50; <70)
- perioperative chemotherapy (vs no chemo)
- number of metastases
- primary T stage
- synchronous worst than metachronous

Ashworth, Lung Cancer 2013



An Individual Patient Data Metaanalysis of Outcomes and Prognostic Factors After Treatment of Oligometastatic Non-Small-Cell Lung Cancer

Ashworth, Clinical Lung Cancer 2014

Review involving 49 publications and 2,176 NSCLC

1-5 synchronous or metachronous metastases treated with surgical metastasectomy, stereotactic radiotherapy or radical EBRT and curative treatment of the primary lung cancer

Results: Median OS was 26 months, 1-year OS 70.2%, and 5-year OS 29.4%. Surgery was the most commonly used treatment for the primary tumor (635 patients [83.9%]) and metastases (339 patients [62.3%]). Factors predictive of OS were: synchronous versus metachronous metastases ($P < .001$), N-stage ($P = .002$), and adenocarcinoma histology ($P = .036$); the model remained

- **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%)

Median OS 26 months
1-year OS 70.2%
5-year OS 29.4%



WHY SHOULD WE TREAT STAGE IV NSCLC ?

After first-line therapy, **progressive disease** is more likely to **occur at sites of disease present at baseline**, rather than in new sites

Patients with stage IV NSCLC but with **limited number of metastases** could benefit from ablation of these metastases (surgery or radiotherapy) for consolidation

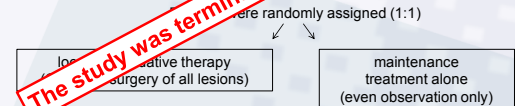


Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study

Daniel R Gomez, George R Blumenschein Jr, J Jack Lee, Mike Hernandez, Rong Yu, D Ross Camidge, Robert C D'Amico, Ferdinando L...

Lancet Oncol 2016

Multicenter, randomized, controlled, phase 2 study of 100 patients from three hospitals had histological confirmation of stage IV NSCLC (3 metastatic lesions) after first-line systemic therapy and no disease progression before randomization.



Interpretation Local consolidative therapy with or without maintenance therapy for patients with three or fewer metastases from NSCLC that did not progress after initial systemic therapy improved progression-free survival compared with maintenance therapy alone. These findings suggest that aggressive local therapy should be further explored in phase 3 trials as a standard treatment option in this clinical scenario.

The study was terminated early after 49 patients

Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up*

Novello, Ann Onc 2016

Treatment of oligometastatic disease

- Stage IV patients with one to three synchronous metastases at diagnosis may experience long-term DFS following systemic therapy and radical local treatment (high-dose radiotherapy or surgery) [III, B]. Because of limited evidence, inclusion in clinical trials is preferred.
- Stage IV patients with limited metachronous metastases may be treated with a radical local treatment and may experience long-term DFS [III, B]. However, this is based only on retrospective data.
- Solitary lesions in the contralateral lung should, in most cases, be considered as synchronous secondary primary tumours and, if possible, treated with radical intent [IV, B].
- In patients with driver mutations for whom active systemic therapies are available, the use of ablative therapies such as SABR or surgery is likely to increase. However, there is limited prospective data to support this policy [IV, C].

N. Martini, MSKCC 1979

HOW SHOULD WE TREAT NSCLC METASTASIS?

- Induction chemotherapy
- Primary tumor → always surgery, RT?
- Metastasis → Surgery? RT?



Patchell et al. 1999: prospective randomized trial
→ single brain metastases (77% of whom had NSCLC) underwent surgery or conventional WBRT. OS significantly better in the surgery group (40 vs 15 weeks; P<.01).

Bonnette et al. 2001: retrospective study
103 patients underwent lung resection and synchronous brain metastases from NSCLC. OS was 56% at 1 year and 11% at 5 years

Collaud et al. 2012: retrospective study
29 patients underwent lung resection and local treatment of synchronous metastasis (brain, lung, adrenal). OS was 65% at 1 year and 36% at 5 years, and their median survival was 20.5 months.

Congedo et al. 2012: retrospective study
53 patients with oligometastatic disease treated primarily with surgery (in 42 patients). OS was 73.1% at 1 year and 24% at 5 years, with a median survival of 19 months

Radical treatment of synchronous oligometastatic non-small cell lung carcinoma (NSCLC): Patient outcomes and prognostic factors

Gwendolyn H.M.J. Griffioen^{a,*}, Daniel Toguri^b, Max Dahele^a, Andrew Warner^b, Patricia F. de Haan^a, George B. Rodrigues^b, Ben J. Slotman^a, Brian P. Yaremko^b, Suresh Senan^a, David A. Palma^b

Lung Cancer 2013

Objective: Metastatic non-small cell lung carcinoma (NSCLC) generally carries a poor prognosis, and systemic therapy is the mainstay of treatment. However, extended survival has been reported in patients presenting with a limited number of metastases, termed oligometastatic disease. We retrospectively reviewed the outcomes of such patients treated at two centers.

Materials and methods: From September 1999-July 2012, a total of 61 patients with 1-3 synchronous metastases, who were treated with radical intent to all sites of disease, were identified from records of two cancer centers. Treatment was considered radical if it involved surgical resection and/or delivery of radiation doses $\geq 13 \times 3$ Gy.

Results: Besides the primary tumor, 50 patients had a solitary metastasis, 9 had two metastases, and 2 had three metastases. Locations of metastases included the brain (n = 36), bone (n = 11), adrenal (n = 4), contralateral lung (n = 4), extra-thoracic lymph nodes (n = 4), skin (n = 2) and colon (n = 1). Only one patient had metastases in two different organs. Median follow-up was 26.1 months (m), median overall survival (OS) was 13.5 m, median progression free survival (PFS) was 6.6 m, and median survival after first progression (SAFP) was 8.3 m. The 1- and 2-year OS were 54% and 38%, respectively. Significant predictors of improved OS were: smaller radiotherapy planning target volume (PTV) (p = 0.004), and surgery for the primary lung tumor (p < 0.001). Factors associated with improved SAFP included surgery for the primary lung tumor, absence of brain metastases, and absence of bone metastases. No significant differences in outcomes were observed between the two centers.

Conclusion: Radical treatment of selected NSCLC patients presenting with 1-3 synchronous metastases can result in favorable 2-year survival. Favorable outcomes were associated with intra-thoracic disease status: patients with small radiotherapy treatment volumes or resected disease had the best OS. Future prospective clinical trials, ideally randomized, should evaluate radical treatment strategies in such patients.



WHEN SHOULD WE TREAT NSCLC METASTASIS?

- **Brain lesions** → single, not brainstem lesions or lesions within eloquent brain
- **Bone or spine** → high morbidity
- Limited number of **liver lesions**
- Ipsilateral or contralateral **lung** → respiratory function
- **Adrenal** metastases → minimally invasive approach



Synchronous metastasis

→ Indication for surgery

Primary tumor resectable
1 metastasis in 1 organ
Not lymph node metastasis



INDUCTION CHEMOTHERAPY

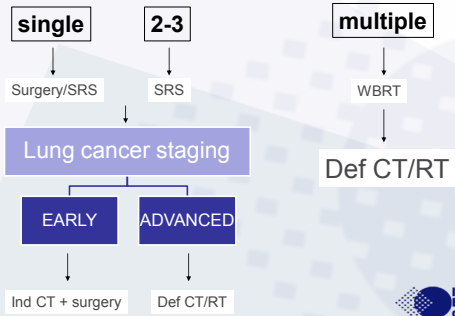
PRIMARY TUMOR RESECTION

LOCAL TREATMENT FOR METASTASIS



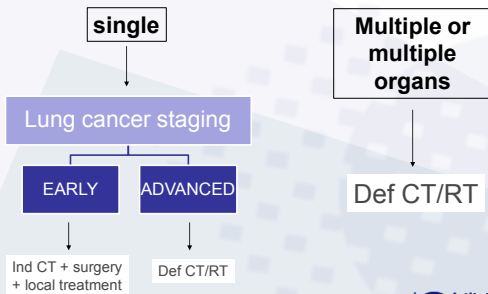
Synchronous metastasis

→ Intracranial metastasis



Synchronous metastasis

→ Extracranial metastasis



Metachronous metastasis

Primary tumor controlled

2-3 metastasis

Local ablative treatment



Personal experience

Oligometastatic Non-Small Cell Lung Cancer: A Multidisciplinary Approach in the Positron Emission Tomographic Scan Era

Tommaso M. De Pas, MD, Filippo de Braud, MD, Gianpietro Catalano, MD, Carlo Putzu, MD, Giulia Veronesi, MD, Francesco Leo, MD, Fiero G. Solli, MD, Daniela Brambilla, PhD, Giovanni Pagani, MD, and Lorenza Spaggiari, MD, PhD
New Drug Development Unit, Department of Medicine, Radiotherapy Division, Thoracic Surgery Division, and Nuclear Medicine Division, European Institute of Oncology, and University of Milan, School of Medicine, Milan, Italy

Background. We have assessed the survival rate of patients with non-small cell lung cancer and synchronous hematogenous solitary metastasis identified with complete staging workup, including total body (18F)fluorodeoxyglucose positron emission tomography scan, and treated with a multidisciplinary approach.

Methods. We examined the database of all patients who underwent surgery for primary non-small cell lung cancer in our institute. The criteria required for inclusion in this analysis were diagnosis of non-small cell lung cancer with synchronous hematogenous solitary metastasis by staging workup with total body computed tomography scan and brain magnetic resonance if indicated, total body positron emission tomography scan, radical surgery for the primary tumor, local treatment of the solitary metastasis, and systemic chemotherapy administration.

Results. We analyzed the data from 1,509 patients treated from January 2005 to December 2005. 89 (5.9%) satisfied the selection criteria. The median overall survival was 30 months, and the median time to progression was 20 months; 6 patients were alive at the time of analysis, with a median follow-up of 30 months. Four patients were tumor progression-free after 1, 16, 23, and 32 months from the start of their treatment.

Conclusions. The presentation of non-small cell lung cancer with a synchronous hematogenous solitary metastasis identified by (18F)fluorodeoxyglucose positron emission tomography requiring complete staging workup is extremely rare. This subset of patients can achieve long-term survival with a multidisciplinary treatment approach.

J Clin Oncol 25:2074-2079. © 2007 by The Society of Thoracic Surgeons

NSCLC who are erroneously diagnosed with single

INVITED COMMENTARY

The article by de Pas and colleagues [1] describes the management of stage IV lung cancer with a solitary metastasis in the positron-emission tomographic scan era. Previous studies have reported that whole-body positron-emission tomography (PET) for lung cancer staging detected occult distal metastases in 6% to 37% of patients for whom conventional clinical methods failed to identify [2, 3]. Indeed the incidence of patients with synchronous solitary metastatic deposits evaluated by conventional work-up and PET is small. For this highly selective subset of 39 of a total of 1,509 patients, the investigators found a potential for long-term survival after a multidisciplinary treatment approach including local complete resection of the primary lung cancer. In

goes through at some point. We are surprised by the literature in not considering the negative prognosis of patients with stage IV non-small cell lung cancer, but an individualized indication for a subset of patients with singular metastatic lesions suggests that surgical resection in a multidisciplinary treatment approach may be beneficial and can achieve prolonged survival.

Few investigators have reported patients who have undergone a curative treatment regimen for oligometastatic lung cancer. The rarity of solitary metastatic disease in patients who are candidates for surgical resection of the primary lung cancer makes it unlikely for larger randomized prospective trials to compare different treatment regimens. The absence of prognostic factors that could predict survival benefit makes it impossible to prospectively identify the subgroup of patients who would benefit from an aggressive treatment regimen. For

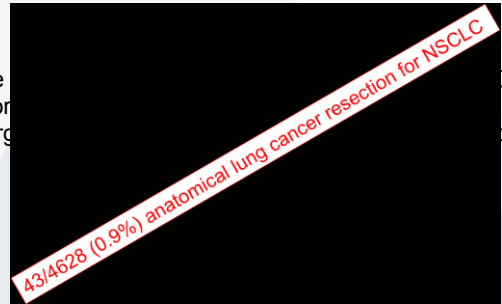
© 2007 by The Society of Thoracic Surgeons
Published by Elsevier Inc.



OUR EXPERIENCE

January 1998 - December 2016

We
for
surg



OUR EXPERIENCE

January 1998 - December 2016

43 patients

All patients had distant metastasis synchronous

Number of metastasis		
Single DM	37	86%
≥ DM	6	14%

Metastasis treatment		
Before Lung surgery	34	79%
Post Lung surgery (4 had both treatments)	13	30%

Type of surgery		
Lobectomy	37	86%
Segmentectomy	1	2.3%
Pneumonectomy	5	11.7%

Postoperative Complications		
None	34	79.1%
At least one	9	20.9%

Histology		
Adenocarcinoma	38	88.4%

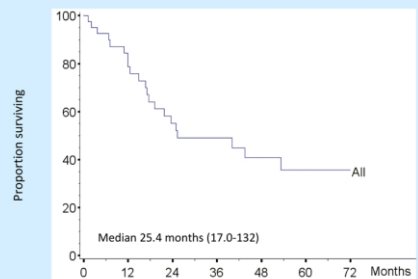
FA	7	16.3%
Anemia	1	2.3%
Pneumonia/ARDS	3	6.8%

Pathological Lymphnodes		
N1 positive	7	16.3%
N2 positive	17	39.5%

30-days mortality	0	0%
-------------------	---	----

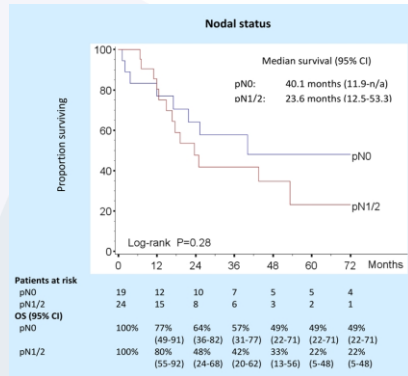
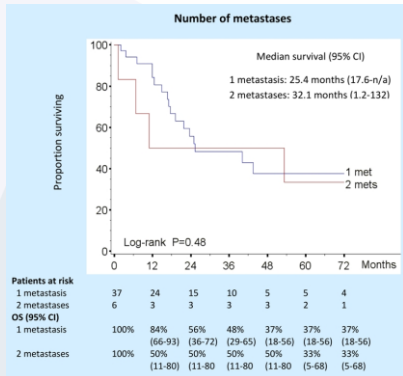


The median OS was 25.4 (17-132) months



Patients at risk	43	27	18	13	8	7	5
Overall Survival (95% CI)	100	79% (62-89)	55% (37-70)	49% (32-64)	41% (23-57)	35% (19-53)	35% (19-53)





CONCLUSIONS

1 metastasis in 1 organ
 Not lymph node involvement
 Primary tumor resectable
 Chemotherapy first

