Definition of oligometastatic NSCLC in the context of innovative treatments

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Disclosures

Nothing to disclose

Oligometastatic disease: a recent history

The term «**oligometastases**» was firts intraduced in 1995 by Hellman and Weichselbaum to describe a particular subgroup of patients that suffered from a single metastasis

or the systemic hypotheses. The systemic hypothesis is binary: metastases either do or do not exist. If present, even if microscopic, they are extensive and widespread. The contiguous hypothesis considers systemic metastases to occur only after nodal disease; but when they occur, they are also blood borne, extensive, and widespread.

From considerations of these theories of cancer dissemination, in the light of the emerging information on the multistep nature of cancer progression, we propose the existence of a clinical significant state of *oligometastases*. For certain tumors, the anatomy and physiology may limit or concentrate these metastases to a single or a limited number of organs. The likelihood of the oligometastatic state should correlate with the biology of tumor progression, rough clinical surrogates of which, for many tumors, might be primary tumor size and grade. Metastasizing

An attractive consequence of the presence of a clinically significant oligometastatic state is that some patients so affected should be amenable to a curative therapeutic strategy. The occasional success of surgical excision or radiation ablation of one or a small number of pulmonary, hepatic, or even brain metastases is evidence of a limited form of the oligometastatic state. The complete resection

Acceptance of this new paradigm for neoplastic pathogenesis and the resulting clinical relevance of the oligometastastic state requires the use of the most sophisticated diagnostic and therapeutic techniques. This paradigm em-

S. Hellman, R.R. Weichselbaum, JCO 1995 - Editorial

Oligometastatic Breast Cancer: biological & clinical definition

new biological and clinical concept

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-
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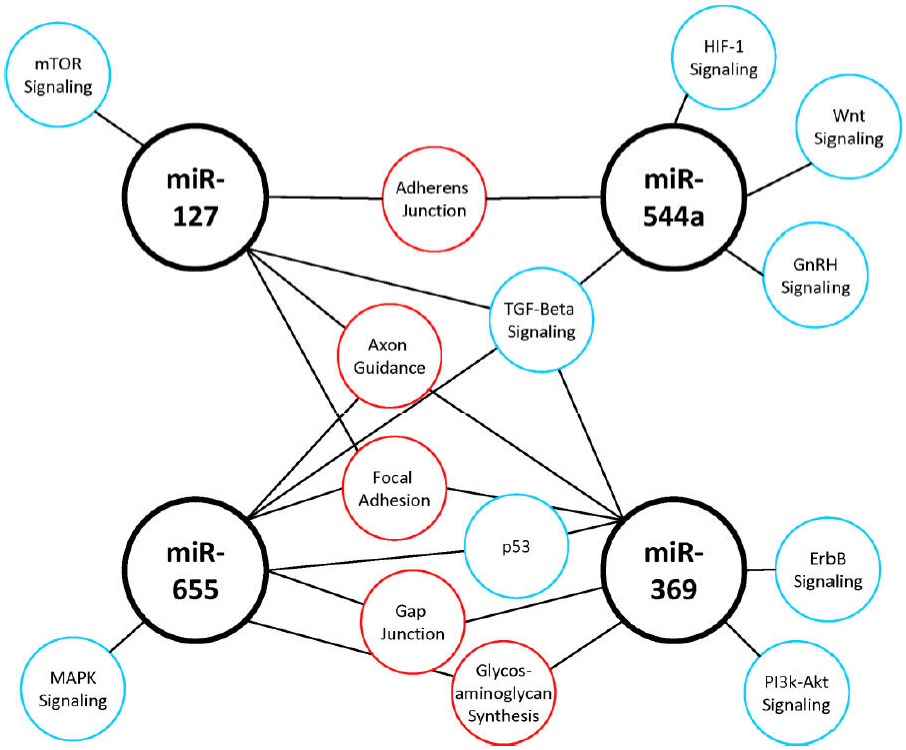
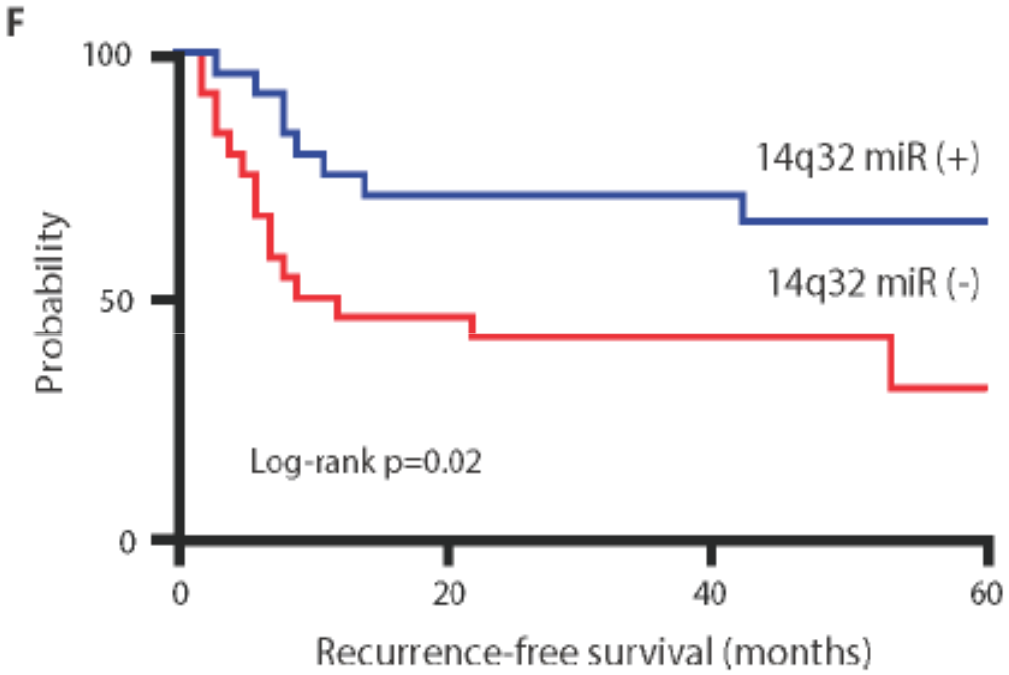
Rationale for "curative intent" of OligoMetastatic Cancer:
to prevent further clonal evolution that could lead to the acquisition of full potential of widespread metastases

Weichselbaum and Hellmann, JCO 1995 and NRCO 2011

Molecular basis of Oligometastatic Disease to Lung





miR-127-5p, miR-544a, and miR-655-3p encoded in the 14q32 microRNA cluster.
These miR co-regulate pathways related to adhesion, invasion, motility and intracellular signaling

Uppal A et al , Oncotarget 2015

Oligometastatic disease: an open issue

- **Lack of univocal definition**
  - *ESMO*: «…mostly defined as at maximum 5 metastatic lesions in the body»
  - *NCCN*: «…isolated or limited metastatic disease»

- **Heterogeneous group of NSCLCs**
  - Synchronous *vs* metachronous oligometastases
  - Different sites: brain, adrenal, contralateral lung
  - Different treatment options: surgery, stereotactic body radiotherapy (SBRT)

- **Lack of clinical trials:**

  few data mainly from retrospective analyses of small series

- **Clinical practice**:

  oligometastatic NSCLC is often defined as a limited disease in the chest with secondary lesions amenable to radical intent treatment (i.e. 1 to 3 metastases in no more than 2 sites) → single center expertise

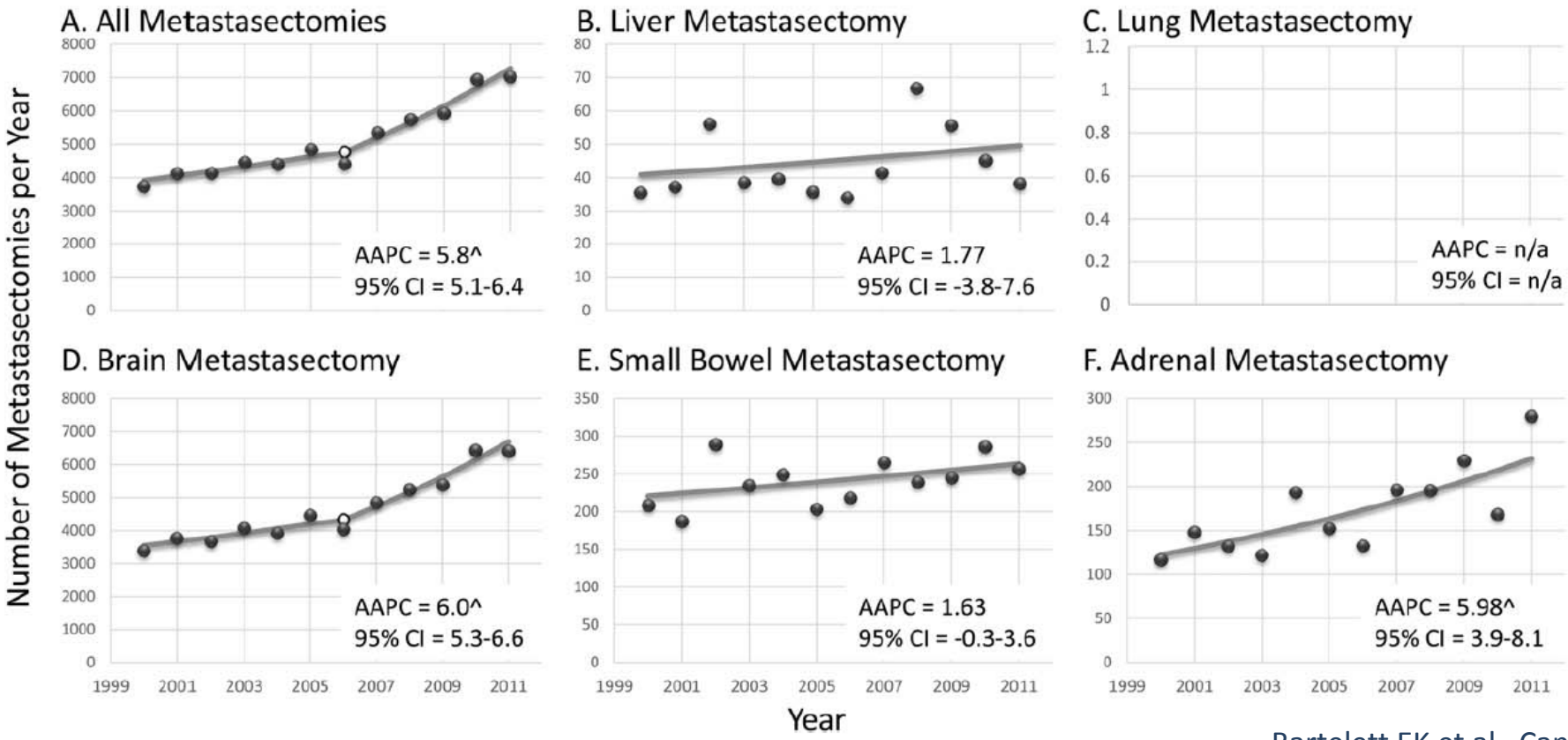
Oligometastatic disease…an increasingly frequent issue

- Improved imaging (role of PET-CT/FDG)
- Increased availability of locoregional treatments (radiofrequency, stereotactic radiotherapy, vertebroplasty, minimally invasive surgery)
- Availability of more efficacious systemic treatments (targeted therapies for oncogene addicted NSCLC, immunotherapy)
- Multidisciplinary approach

Metastasectomy rate for lung cancer over time

Metastasectomy for cancer types: colorectal 87,407; lung 58,245; breast 26,271; melanoma 20,298

Lung cancer



Bartelett EK et al , Cancer 2015

Prevalence of oligometastatic NSCLC

- Few data
- Limited restrospective series
- Different definition
- Dynamic concept

Prevalence of oligometastatic NSCLC

- ~ 7% of stage IV NSCLCs have single site metastasis (either synchronous or metachronous)

- ~ 50% of patients who develop metastasis after radical lung cancer treatment (1-3 metastatic sites)

Ettinghausen SE et al, JCO 1991
Pfannschmidt J et al, Lung Cancer 2010
Torok et al, Clin Lung Cancer 2017

The oligometastatic concept in Lung cancer

1 - Timing

2 - Number

3 - Sites

4 - Molecular dysregulation

5 – Available evidence

The oligometastatic concept in Lung cancer

Local and systemic treatment: a complex relationship

SYSTEMIC TREATMENT

- Reduced tumor burden and local invasivity

- Potential complications limiting feasibility of local treatment

LOCAL TREATMENTS

- Reduction of tumor burden

- Alteration of immune response

- Potential complications affecting systemic treatment

The oligometastatic concept in Lung cancer

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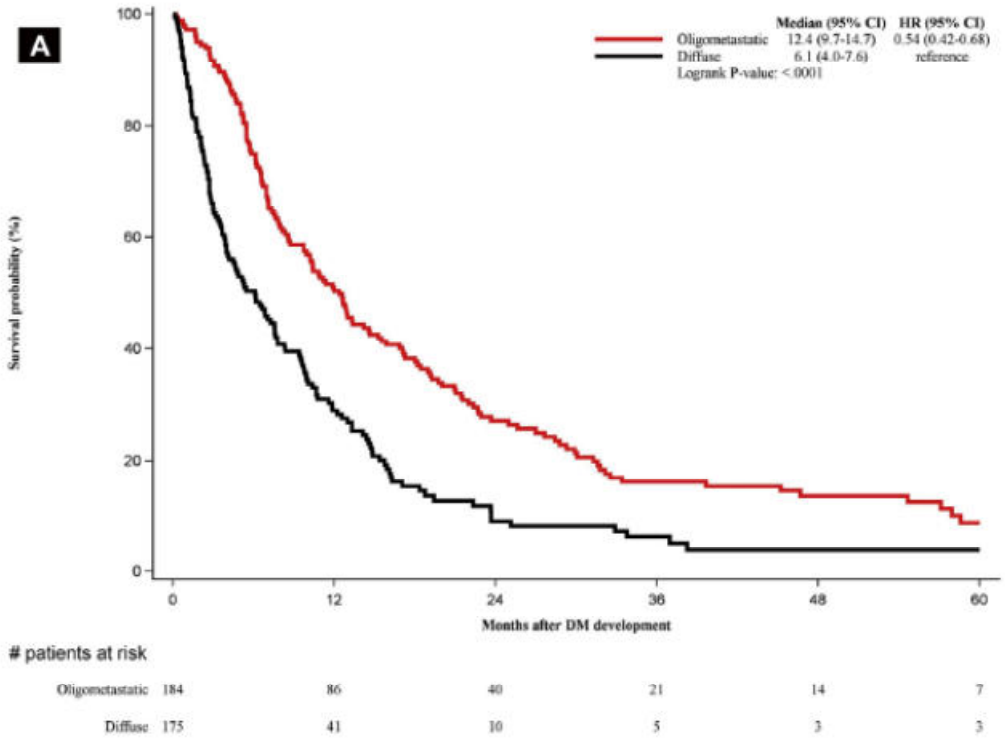
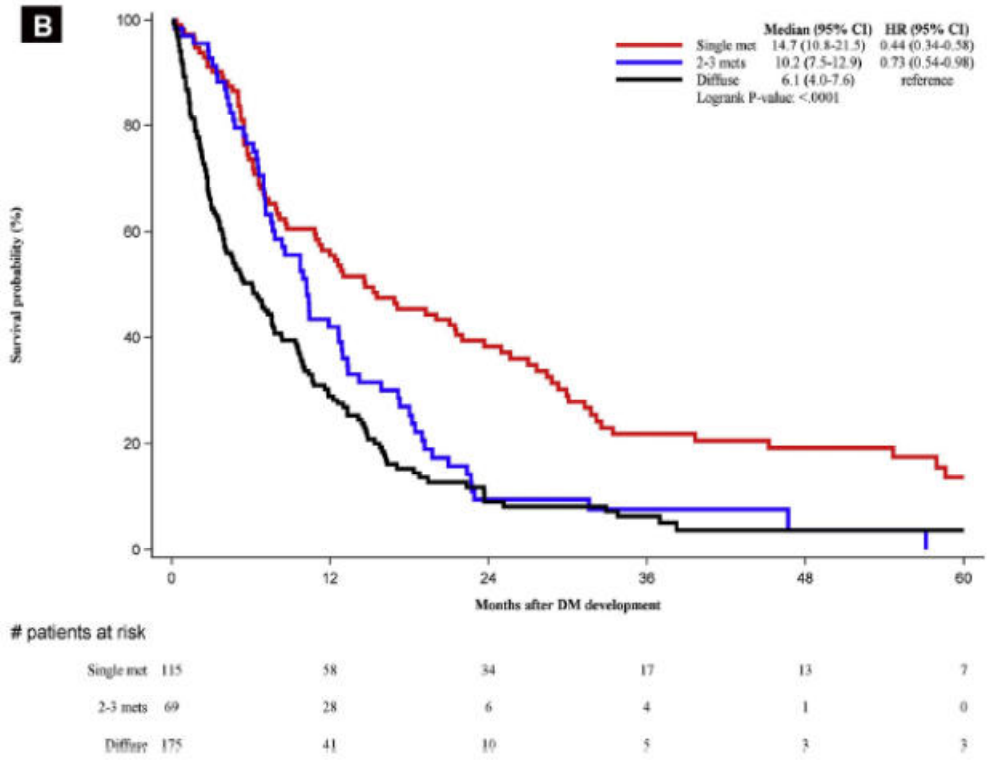
Diffuse vs Oligo-metastasis: a different disease

Diffuse vs Oligometastatic



1 vs 2-3 vs diffuse



Torok et al, Clin Lung Cancer 2017

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Prognosis classification: number & sites count!!

Favourable	Relatively favourable	Relatively unfavourable	Unfavourable
Oligo-recurrence 1-2 lesions & 1 site (brain or adrenal gland)	**Oligo-recurrence** 3-5 lesions & 1 site (brain or adrenal gland)		> 5 sites (polymetastases)
	Synchronous oligometastasis 1-2 lesions & 1 site (brain or adrenal gland)	**Synchronous oligometastasis** 3-5 lesions& 1 site (brain or adrenal gland)	> 5 sites (polymetastases)

Adapted from Niibe et al, Pulm Med 2013

Diffuse vs Oligo-metastasis: a different disease?

1-3 sites

Site	DM Pattern			Total (n = 368)	*P* Value[a]
	Unknown (n = 9)	Diffuse (n = 175)	Oligometastatic (n = 184)		
Brain	6 (66.7)	46 (26.3)	56 (30.4)	108 (29.3)	.4136
Lung	2 (22.2)	73 (41.7)	41 (22.3)	116 (31.5)	< .0001
Pleural	0 (0.0)	28 (16.0)	0 (0.0)	28 (7.6)	< .0001
Adrenal	0 (0.0)	27 (15.4)	26 (14.1)	53 (14.4)	.7673
Liver	2 (22.2)	48 (27.4)	17 (9.2)	67 (18.2)	< .0001
Lymph	0 (0.0)	26 (14.9)	19 (10.3)	45 (12.2)	.2060
Bone	1 (11.1)	79 (45.1)	39 (21.2)	119 (32.3)	< .0001
Other	1 (11.1)	18 (10.3)	18 (9.8)	37 (10.1)	.9999

Retrospective data collection (n=368)

Torok et al, Clin Lung Cancer 2017

Brain

- Most frequent oligometastatic site
- Local brain treatment is an accepted first therapeutic approach
- No differences between synchronous and metachronous metastases
- Median OS ranges from 7-24 mos. (significantly better in case of NO disease)
- Multiple available approaches:
  - ✓Surgery plus WBRT
  - ✓WBRT plus SRS
  - ✓SRS alone (≤ 4 lesions, ≤ 3 cm in diameter)

Getman V et al, Eur J Cardiothorac Surg 2004; Mintz AH et al, Cancer 1996; Andrews DW et al, Lancet 2004; Aoyama H et al, JAMA 2006; Endo C et al, Ann Thorc Surg 2014

Adrenal

- 1.6 - 4% of metastatic NSCLC: single adrenal metastasis
- Up to 50% benign adenoma at histologic examination
- Ipsilateral vs contralateral :
  5-year survival rate 83% vs 0% in small series

Ettinghausen SE et al, JCO 1991
Kim HK et al, Lung Cancer 2007
Raz DJ et al, Ann Thorac Surg 2011

Lung

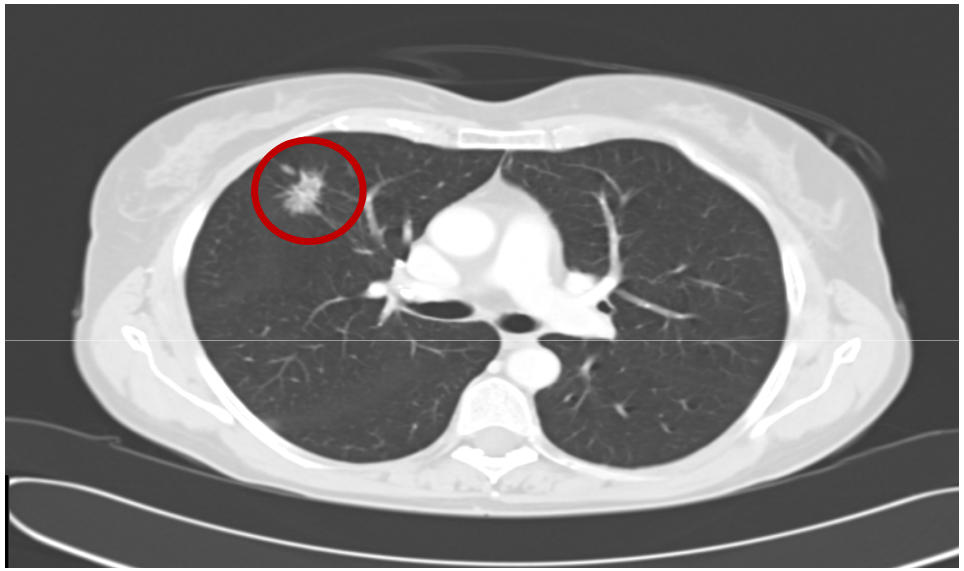
- Synchronous vs metachronous
- Ipsilateral vs contralateral
- Differential diagnosis of multiple primary tumors
  (in this case a curative-intent treatment is recommended)

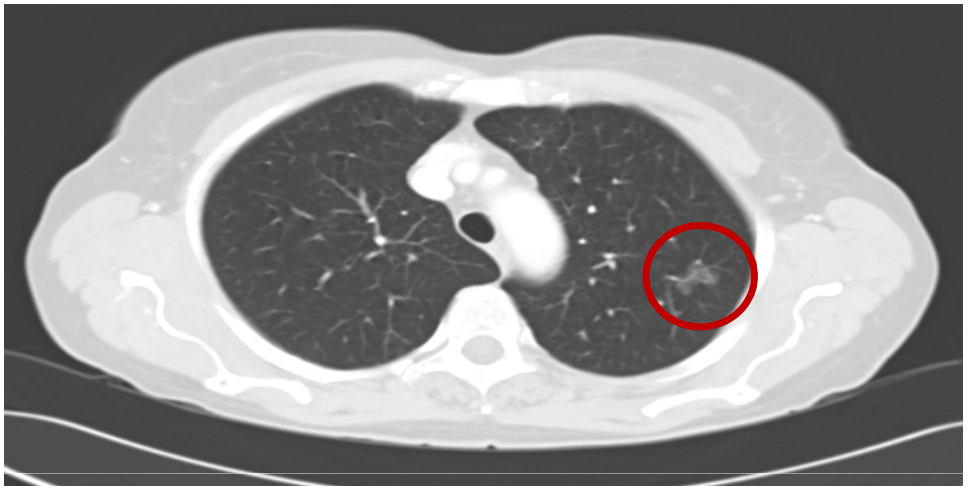
Endo C et al, Ann Thorc Surg 2014
Loukeri A, Clin Lung Cancer 2015

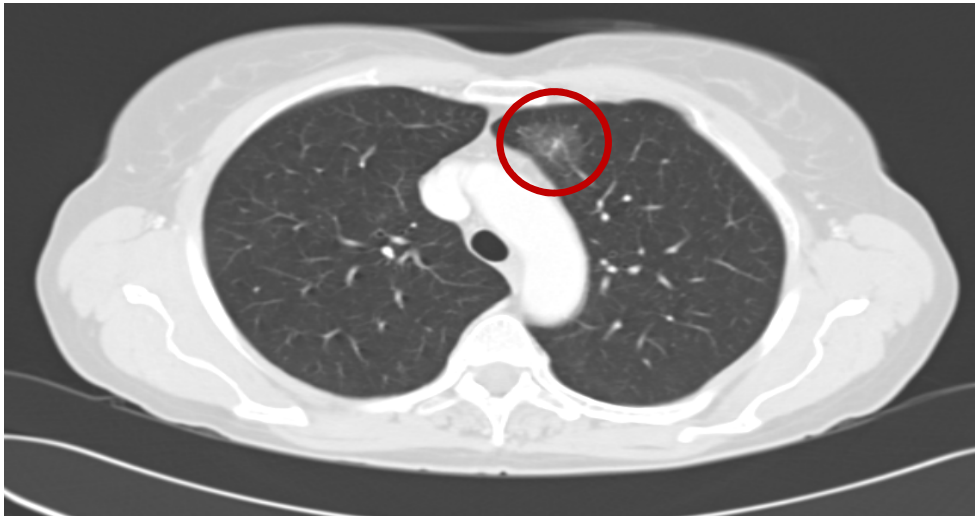
Synchronous lung metastasis or multiple lung tumors?

- ✓ **Imaging**: timing of evolution
- ✓ **Pathology**: subtypes distribution
- ✓ **Molecular profiling**: driver mutations

Synchronous lung metastasis or multiple lung tumors? IMAGING

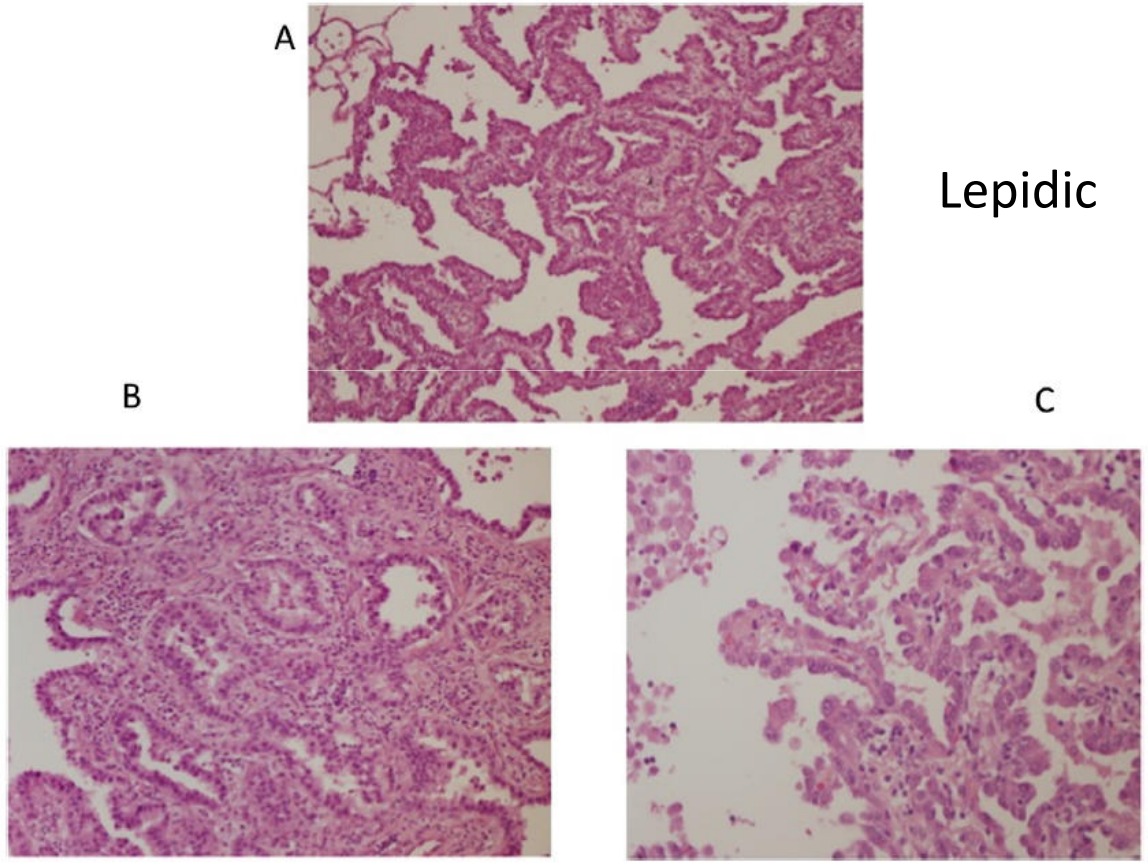






Bonanno L et al, Lung Cancer 2016

Synchronous lung metastasis or independent multiple tumors? PATHOLOGY



Lepidic

Acinar

Papillary

Bonanno L et al, Lung Cancer 2016

Synchronous lung metastasis or independent multiple tumors? MOLECULAR PROFILING

Table 1
Pattern of EGFR mutations in multiple adenocarcinoma lesions.
from the same patient by pyrosequencing

Site	Prevalent morphology	EGFR-Pyrosequencing	Tumor cells percentage	Mutated allele frequency
Middle lobe	Lepidic	Exon 19 DelE746A750	70%	NA
Left upper lobe #1	Acinar	Exon 21 L858R	70%	8%
Left upper lobe #2	Papillary	Wild-type	70%	NA
Liver metastasis	Acinar	Exon 21 L858R	30%	18%
Liver progression	Acinar	Exon 21 L858R	45%	15%

NA: not available. The percentage of mutated allele may not be evaluated for exon 19 deletions with pyrosequencing.

Table 2
Results of NGS analysis.

Right Middle Lobe Nodule		Left Upper Lobe Nodule #1		Left Upper Lobe Nodule #2		Liver Metastasis	
Variant	Mutant allele Fraction	Variant	Mutant allele Fraction	Variant	Mutant allele Fraction	Variant	Mutant allele Fraction
EPHA3 (p.P422S)	0.11						
		PIK3CA (p.E542 K)	0.10			PIK3CA (p.E542 K)	0.32
EGFR (p. delE745-A750)	0.84						
		EGFR (p.L858R)	0.33			EGFR (p.L858R)	0.40
MET (p.G198D)	0.14						
		TP53 (p.R280T)	0.17			TP53 (p.R280T)	0.38
				PTEN (p.L182 V)	0.12		

NGS libraries were run on MiSeq (Illumina). Only variants found in > 10% of the reads (mutant allele fraction) and coverage > 600 reads are reported. The colors highlight identical mutations found in different tumor samples.

Bonanno L et al, Lung Cancer 2016

Bone

- 27% of patients with single site metastasis
- Median survival: 12.1 m
- 57 patients undergoing surgery on primary lesions and
  - Bone surgery/fixation plus radiotherapy (median OS 13.9 mos.)
  vs
  - Radiotherapy alone (median OS 11.6 mos.)

"SINGLE-SITE BONE INVOLVEMENT IS LIKELY TO BE EXCLUDED FROM OLIGOMETASTATIC CONCEPT"

Xu Q et al, Clin Transl Oncol 2013

Nodal involvement

Prospective observational study-1

- cT1-2 cN0-1
- 1-3 synchronous or metachronous resectable metastatic lesions (single organ)
- 34 patients (17 pts synchronous brain, 12 pts syn/meta lung, 5 pta sync/meta others)
- 20 patients with complete resection of primary & metastatic site
- 5 y OS: 44.7% (similar to stage IIA/IIB disease)

Selected patients without nodal involvement undergoing radical-intent local treatment on primary tumor and 1-3 metastasis could have similar outcome to locally advanced disease

Endo C et al, Ann Thorac Surg 2014

Nodal involvement

Prospective observational study-2

- cT1-3 c N0-2
- 23 patients
- Solitary synchronous and resectable metastasis
- Platinum-based induction CT → resection of all remaining sites of disease
- Median OS: 11 mos.

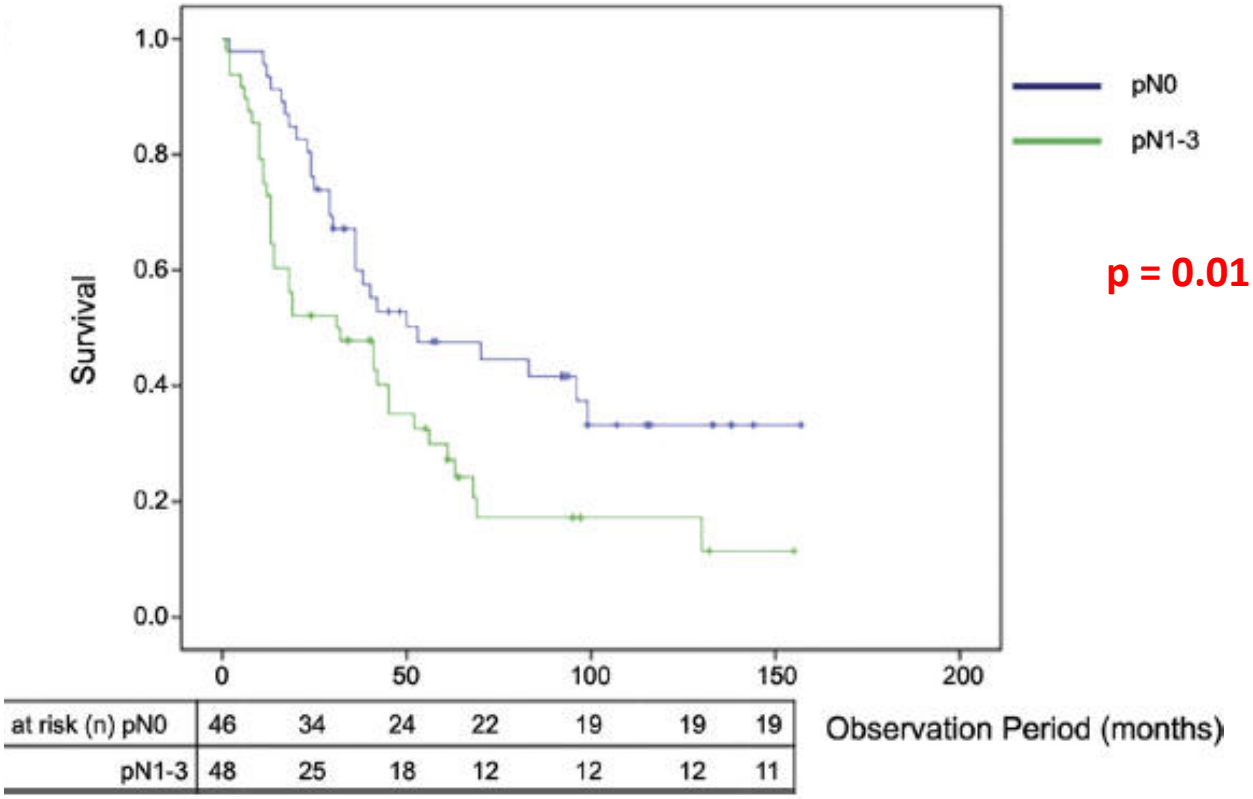
Selected patients with nodal involvement undergoing radical-intent local treatment on primary tumor and single metastasis had similar outcome to metastastic patients

Downey RJ et al, Lung Cancer 2002

Nodal involvement

Retrospective study

- n = 99
- N0 46.5%
- N+ 48.5%
- Nx 5%



at risk (n) pN0	46	34	24	22	19	19	19
pN1-3	48	25	18	12	12	12	11

p = 0.011

Tonnies M et al, Ann Thor Surgery 2014

The oligometastatic concept in Lung cancer

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Prognosis

- Indolent biological phenotype
  - molecular dysregulations
  - targeted agents
  - immunotherapy
- Efficacy of local treatments
  - surgical & radiotherapy expertise
  - technologies
- Number and sites of metastasis
  - single vs multiple
  - N2 involvement
  - brain & adrenal vs others
  - lung

The oligometastatic concept in Lung cancer

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Limited evidence of efficacy (does not mean lack of efficacy…)

- Data from retrospective case series & prospective observational studies
- Heterogeneity of treatments
- One meta-analysis
- Few data from a small prospective trial

Retrospective studies (> 20 pts, from 2000)

Author	No of patients	Oligometastatic site	5-year survival (%)
Getman et al, 2004	65	Brain	19
Billing et al, 2001	28	Brain	21
Bonnette et al, 2001	103	Brain	11
Furak et al, 2005	65	Brain	19
Strong et al, 2007	94	Adrenal	29
Mercier et al, 2005	23	Adrenal	23
Porte et al, 2001	43	Adrenal	12
Pham et al, 2001	78	Adrenal	40
Raz et al, 2011	20	Adrenal	34
Tanvetyanon et al, 2008	114	Adrenal	25
Yano et al, 2010	138	Brain, adrenal, lung	38.7
Congedo et al, 2012	53	Various sites	23.5
Tonnies et al, 2014	99	Various sites	38

Prospective studies (> 20 pts, from 2000)

Author	No of patients	Oligometastatic site	5-year survival (%)
Xu et al, 2013	213	Various sites	4.5
Endo et al, 2014	34	Brain, adrenal, lung	44.7
Downey et al, 2002	23	Various sites	20
De Ruysscher et al, 2012	39	Various sites	3-y 17.5

Metanalysis

- **49 articles , 84% retrospective series, 2176 NSCLC patients**
- **60.3% brain mets only, 24% mixed mets, 10.6 % adrenal mets only, 5% lung mets only**
- **53.6% solitary mets, 31.2% 1-3 mets, 15.2% 1-5 mets**
- **39.1% synchronous only, 13% metachronous only, 47.8% sync or metachronous**
- **Surgical metastasectomy (55%), SRS, SABR (45%), Conventional RT (1 study)**

Location of oligometastases		No. patients (*n*)	MS range (months)	Overall MS (months)
Brain	Status of primary lung tumor			
All patients	Controlled or uncontrolled	1436	5.9–52	13.6
All patients	Controlled	1082	6.8–52	19.7
Solitary Metastasis	Controlled or uncontrolled	294	5.9–52	9.3
Solitary Metastasis	Controlled	215	6.2–52	19.7
Mixed	Controlled (all)	431	13–30.9	20
Adrenal	Controlled (all)	190	11–21	17
Lung (one study only)	Controlled (all)	76	40	n/a

- **great heterogeneity of outcome: median OS 15 mos (range 6-52 mos)**
- **main prognostic factors: control of primary site , N0 and DFS> 6-12 mos.**

Ashworth et al, Lung Cancer 2013

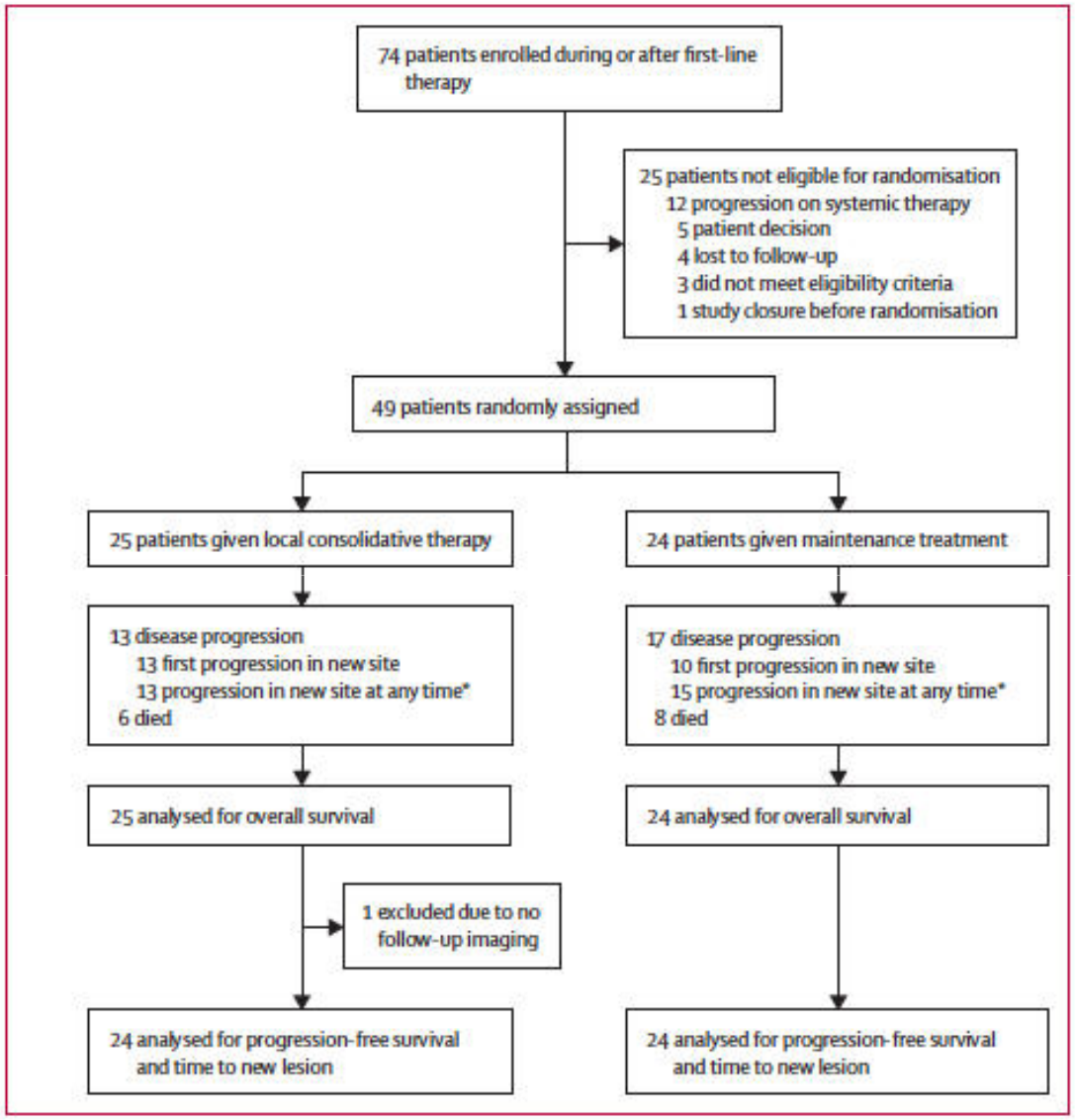
Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study

Daniel R Gomez, George R Blumenschein Jr, J Jack Lee, Mike Hernandez, Rong Ye, D Ross Camidge, Robert C Doebele, Ferdinandos Skoulidis, Laurie E Gaspar, Don L Gibbons, Jose A Karam, Brian D Kavanagh, Chad Tang, Ritsuko Komaki, Alexander V Louie, David A Palma, Anne S Tsao, Boris Sepesi, William N William, Jianjun Zhang, Qiuling Shi, Xin Shelley Wang, Stephen G Swisher*, John V Heymach*

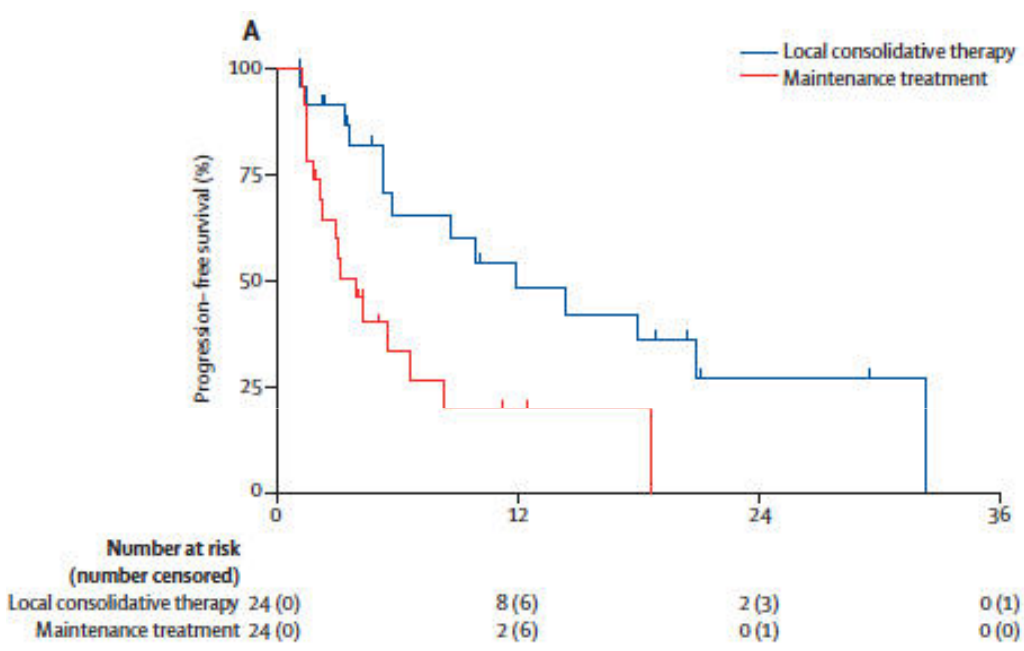
Lancet Oncol 2016; 17: 1672–82

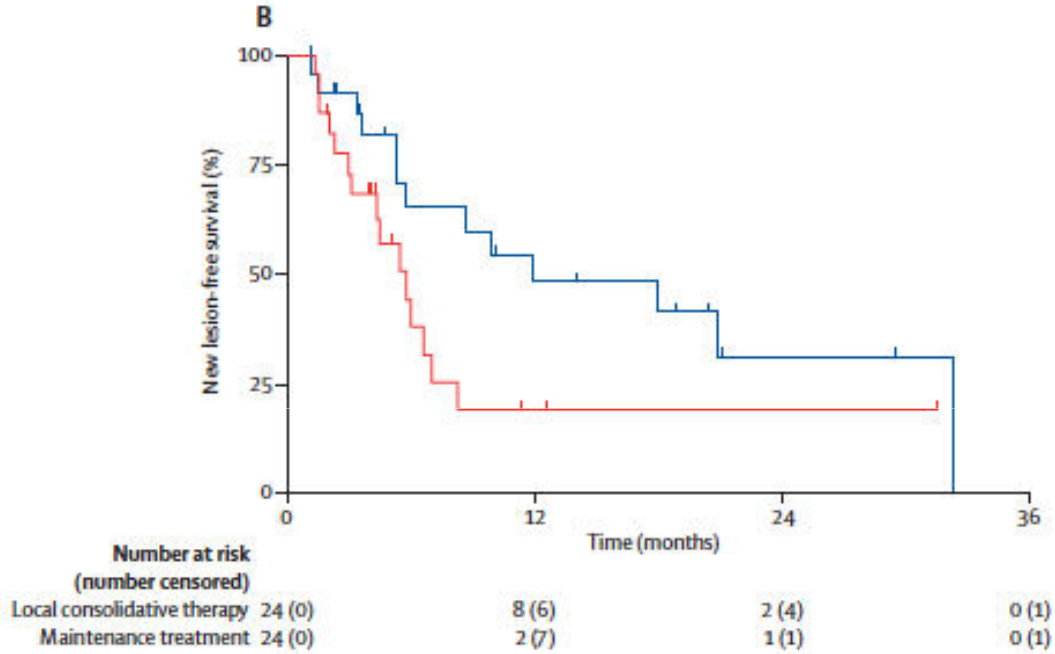
CONSOLIDATIVE LOCAL TREATMENTS

Primary lung lesion: RT, SABR, Surgery
Metastatic sites: RT, SABR,ChemoRx+RT



Randomized phase II trial of consolidation therapy in NSCLC





Median PFS: 11.9 (6-21) vs 3.9 (2-7) m; HR: 0.35

- ✓ **Progression was mainly systemic**
- ✓ **Only type of treatment and EGFR/ALK status affected PFS with statistical significance**

Gomez DR et al, Lancet Oncol 2016

Evidence to guide our decisions

- Mainly limited retrospective data
- Heterogeneity of treatments
- One meta-analysis
- Very little prospective trial

MULTIDISCIPLINARY EVALUATION
PERSONALIZED APPROACH
PROSPECTIVE OBSERVATION

Thoracic Oncology Padova proposal

Prospective observational trial of oligometastatic NSCLC with molecular characterization before and after systemic treatment

maximum of 3 metastasis in two sites
N0-1 or single station (non-bulky) N2

SYSTEMIC TREATMENT
(Upfront Surgery or RadioSurgery in case of Brain Mets)

RADICAL-INTENT LOCO-REGIONAL THERAPY (Lung & Metastases)

Conte PF, Rea F