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Optimal assessment of an additional lung nodule in a patient with potential for cure.

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Introduction ‘additional nodule’

Assessment / treatment of suspected lung cancer with additional pulmonary nodule = a challenge !

- Biologic nature is largely speculative.

  - Benign *vs.* Metastatic *vs.* Synchronous cancer

- Literature is equivocal.

  - Selection bias : surgical literature series
  - Terminology : satellite *vs.* additional nodule
  - Identification : on imaging *vs.* on pathology
  - Nodule = rounded-irregular opacity, well-poorly defined measuring up to 3cm in greatest diameter

Incidence ‘additional nodule’

Resectable lung cancer on CT scan with

additional **solid** pulmonary nodule(s)

= 15-26% of patients

(Yuan Eur Radiol 2003;13:2447 - Keogan Clin Radiol 1993;48:94 - Ruppert Lung Cancer 2011;74:233)

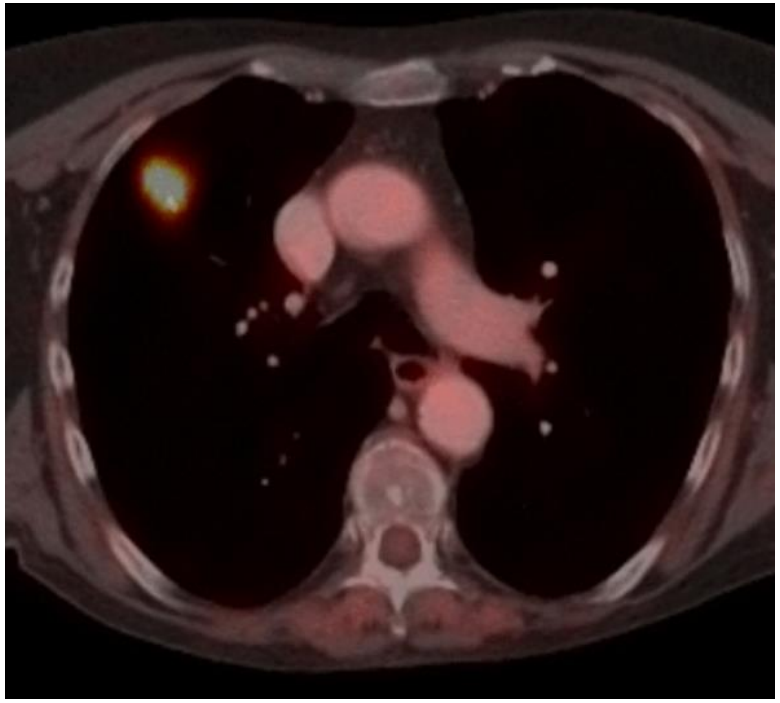
→ majority = benign

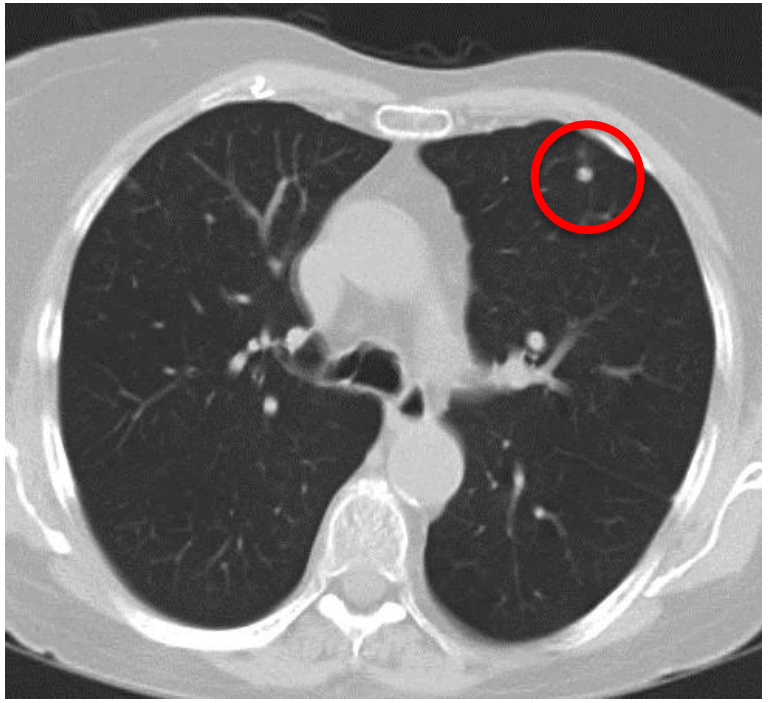
→ up to 8% = malignant

(Yuan Eur Radiol 2003;13:2447 - Kunitoh Cancer 1992;70:1876 - Shen Chest 2007;132 - Ruppert Lung Cancer 2011;74:233)

Presentation ‘additional nodule’

1. **Typical solid cancer & additional small solid nodule.**

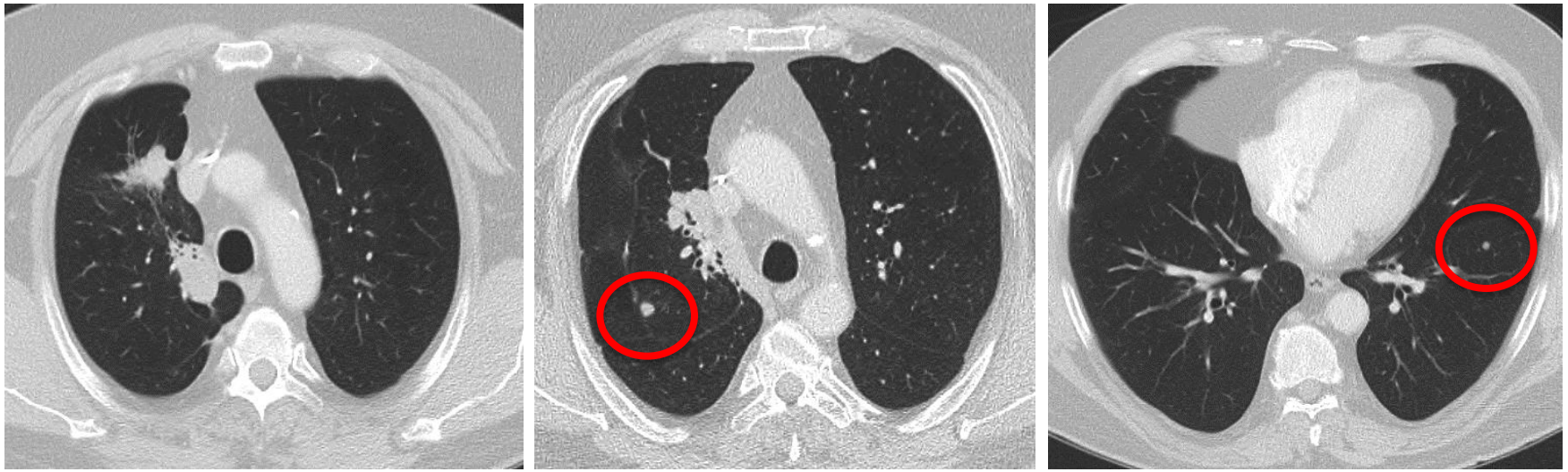




MDTB decision : suspected lung cancer RUL cT1aN0M0

Presentation ‘additional nodule’

1. Typical solid cancer & additional small solid nodule.

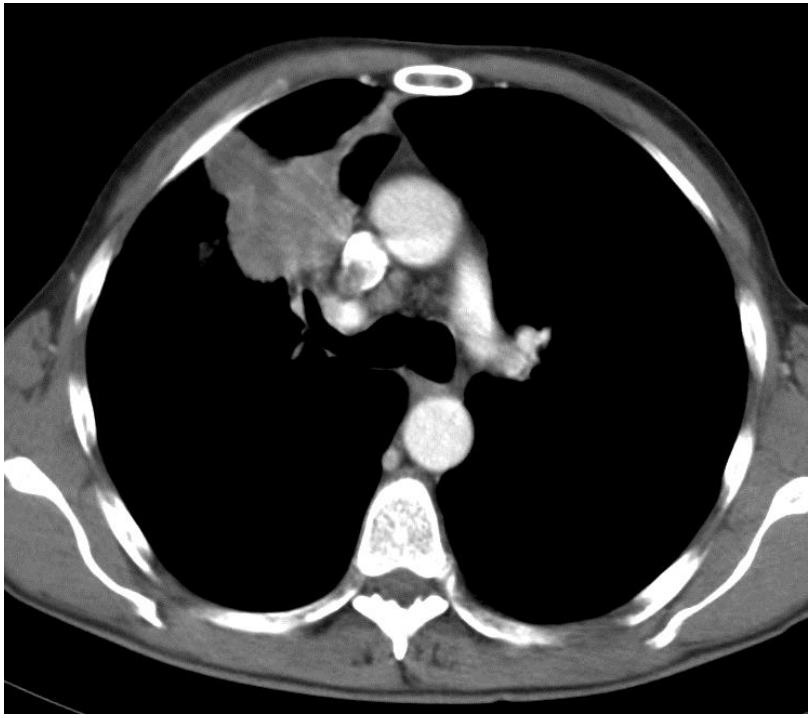


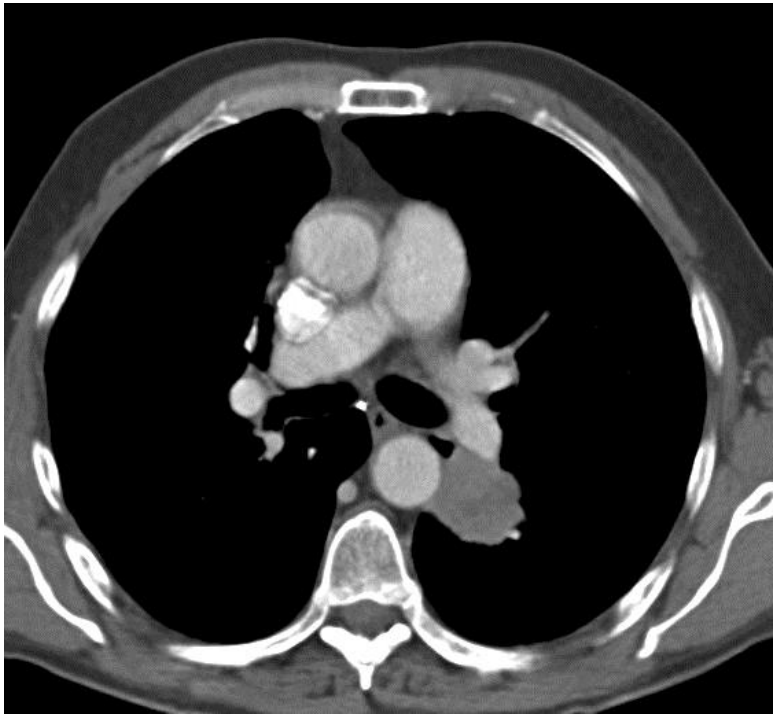
Known for >4 years with EGFR-Mt lungadenocarcinoma RUL treated with EGFR-TKI and (2012) SBRT of RUL for oligoprogression

MDTB : lungadenocarcinoma RUL cT3N0M1a(LLL: new & FDG avid)

Presentation ‘additional nodule’

2. Typical solid cancer and additional solid cancer.



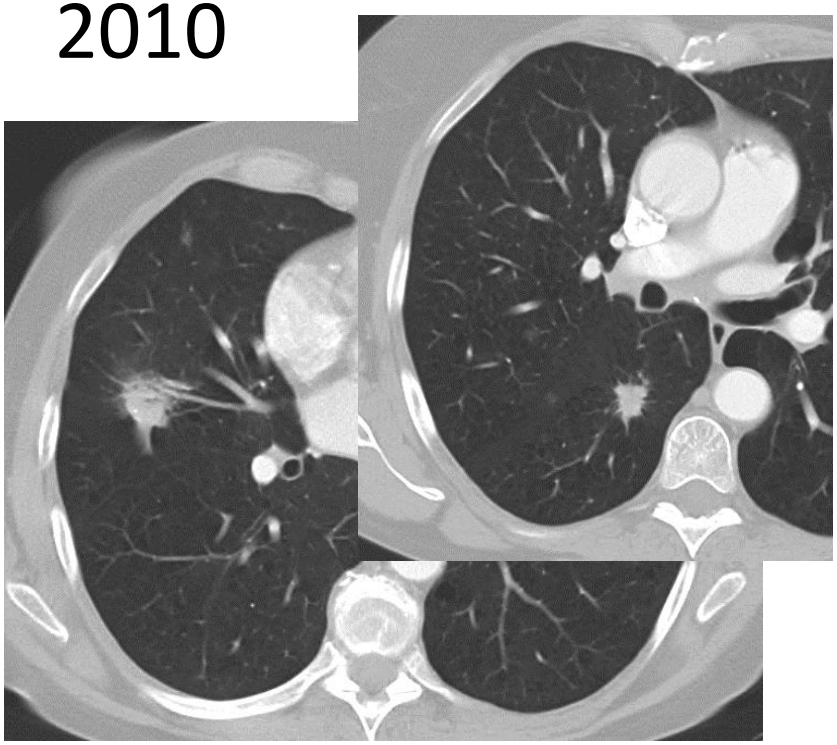


MDTB : SqCCa RUL cT2bN0M0 & SqCCa apex LLL cT2aN0M0

Presentation ‘additional nodule’

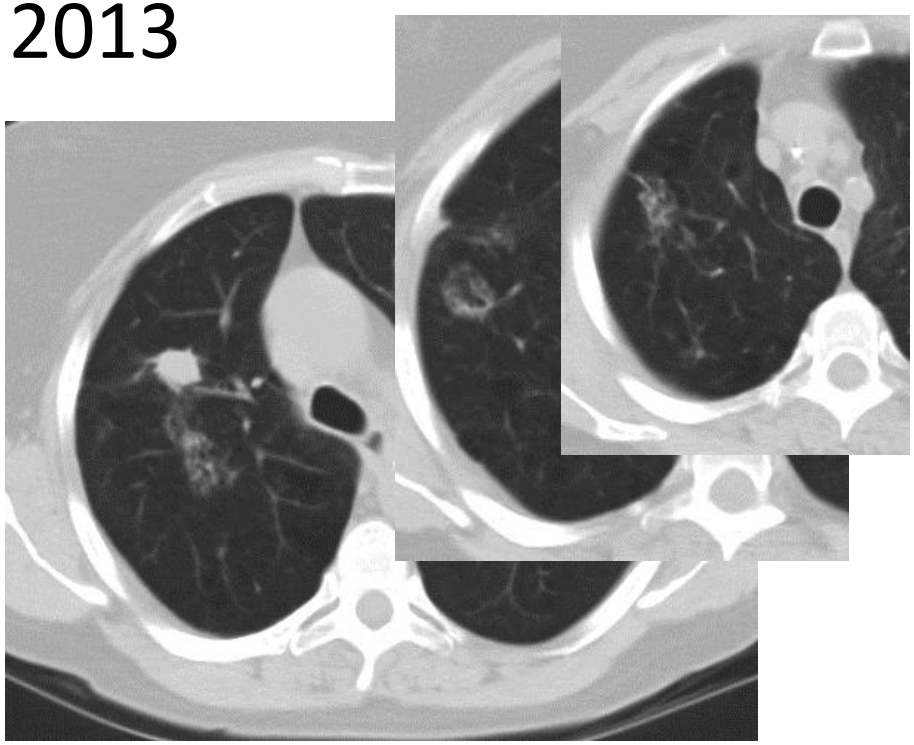
3. Lung cancer with additional (semisolid) GGO.

2010



Semisolid WD invasive adCa RML &
Solid MD adenoCa RLL pT1a(2)N0M0

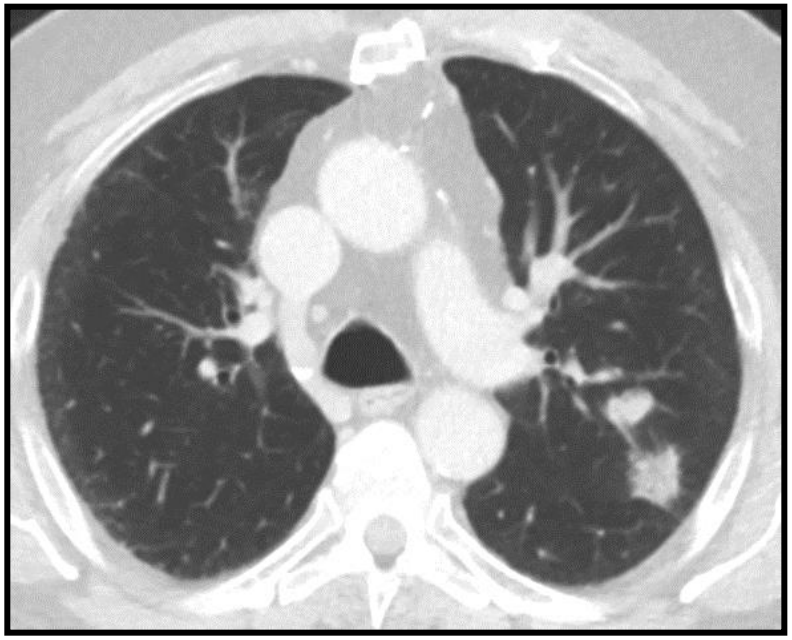
2013



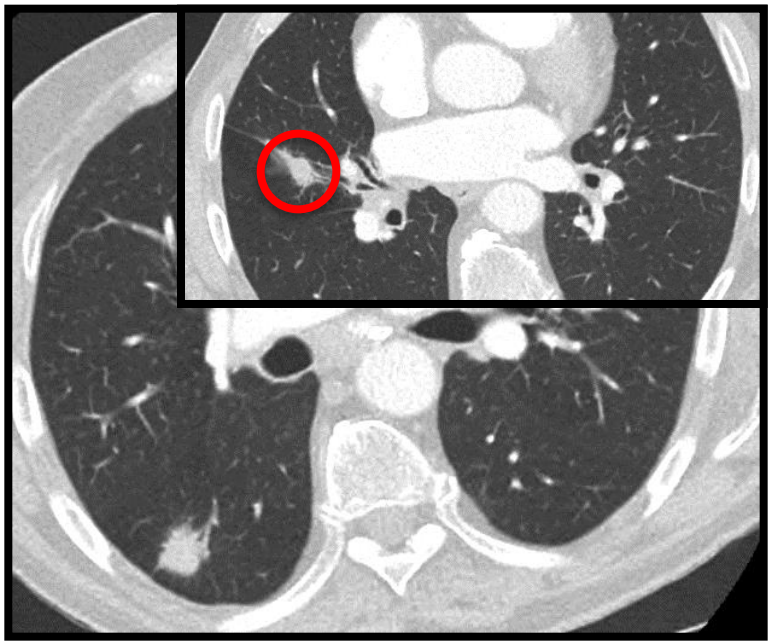
adenoCa RUL rcT1b(4)N0M0

Presentation ‘additional nodule’

4. Typical lung cancer with additional solid nodule.



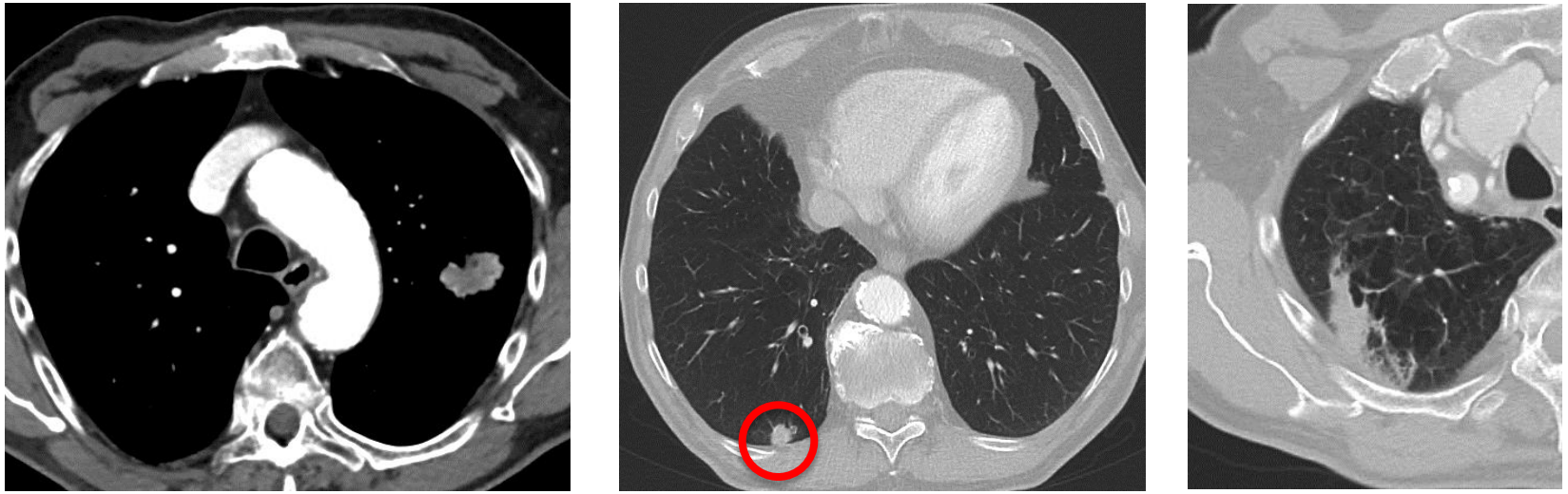
SqCCa LUL c**T3**(same lobe)N0M0



SCLC RLL c**T4**(RML)N2M0

Presentation ‘additional nodule’

4. Typical lung cancer with additional solid nodule.



Lungadenocarcinoma LUL cT1bN0**M1a**(RLL: 14mm and FDG avid)

- Bonchoscopy with EBUS-MP TBLB and CT-TTP RLL
- Videomediastinoscopy : negative in 4 MLN stations

Presentation ‘additional nodule’

Presentation ‘additional nodule’ on CT	Outcome category	Staging nomenclature
Typical solid cancer & additional small solid nodule	very likely benign *or* to be explored	cTanyNany M0/1a
Typical solid cancer & additional typical solid cancer	synchronous disease (SPLC) 1.5% incidence	2 separate cTNM
Lung cancer (±GGO) & additional (semisolid) GGO lesion(s)	pattern of multifocal disease (MFLC)	cT(m)NM with NM applying to all T(m) (T : lungs = one organ)
Typical solid cancer & additional solid nodule	same histology - LC with add nodule	cT3(same lobe) cT4(diff lobe ipsi lung) cM1a(other lung)

Clonality of ‘additional nodule’

- Current understanding of ability to distinguish between ‘second primry’ and ‘metastatic’.

  - **Martini & Melamed**
  - 50 cases
  - 18 synchronous – 32 metachr.
  - Mostly squam cell carcinoma

Synchronous Lung Tumors

Anatomic Location	Identical Histology	Different Histology
Same segment	Metastasis	Synchronous primary
Different Segment	Metastasis: cancer in shared lymph basin or systemic metastasis or no CIS	Synchronous primary
	Synchronous primary: no cancer in shared lymph basin and no systemic metastasis and CIS	Synchronous primary

Abbreviation: CIS, carcinoma in situ.
Data from Martini N, Melamed MR. Multiple primary lung cancers. J Thorac Cardiovasc Surg 1975;70:606–12.

= for clinical decision making

= not for definitive proof of origin

Clonality of 'additional nodule'

- Current understanding of ability to distinguish between 'second primry' and 'metastatic'.

- **Detterbeck F**, et al. **ACCP**

  Chest 2003;123:248.

  - histology and location
  - timing
  - nodal disease

= for clinical decision making

= not for definitive proof of origin

Multiple primary lung cancers

- Same histology, anatomically separated
  - Cancers in different lobes and no N2,3 involvement and no systematic metastases
- Same histology, temporally separated
  - ≥4-y interval between cancers and no systemic metastases from either cancer
- Different histology
  - Different histologic type or different molecular genetic characteristics or arising separately from foci of carcinoma in situ

Hematogenously spread pulmonary metastases

- Same histology and multiple systemic metastases
- Same histology, in different lobes, and presence of N2,3 involvement, or <2-y interval

Clonality of 'additional nodule'

- Current understanding of clonality :

  - data set : 20 patients / 24 'pairs' of tumours

  - data set : 76% of cases were pairs of adenocarcinoma

	'primaries'	'metastases'
Clinocopathologic criteria by Martini & Melamed	21	3
Genomics (array CGH, multiplex mutation analysis)*	14	8
Comprehensive histologic assessment**	16	8

* 2 unaccessable ; ** Comprehensive histologic assessment = cytologic features, patterns of stroma, necrosis, growth pattern, variants, …)

Histology (CHA) matched with genomics in 91%

→ histology may be almost as good as genomics.

Girard N, Travis W, et al. Am J Surg Pathol 2009.

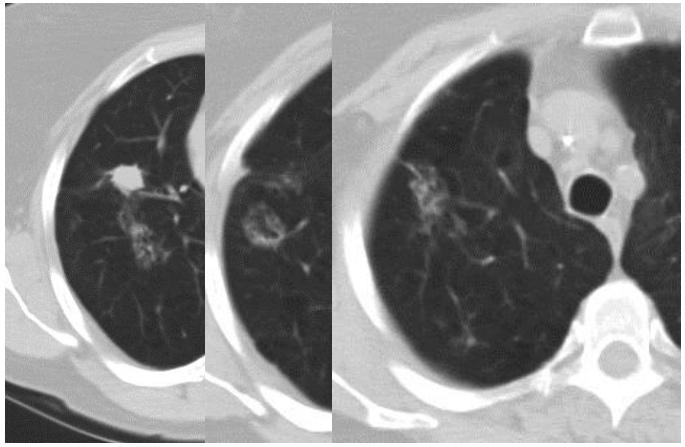
Clonality of ‘additional nodule’

- Multiple separate foci with genetic similarity, or mutant clones which migrate with variable progression, or both ?
- **“Multifocal” AdenoCa**

  Independent synch. prim. disease

  Lepidic predominant invasive non-mucinous adenocarcinoma

  (formerly nonmucinous BAC)



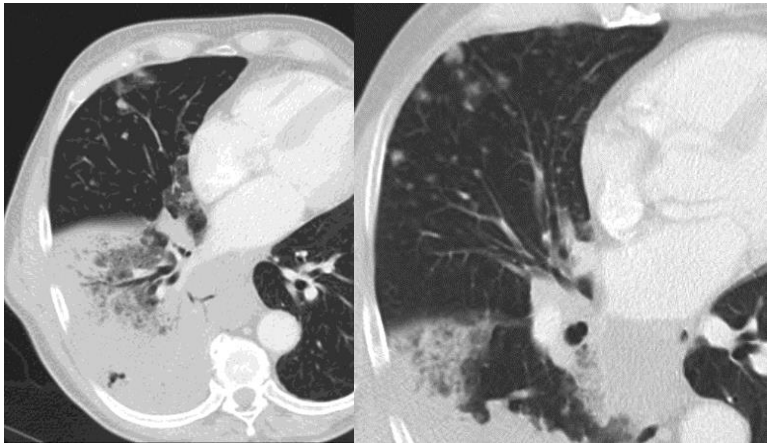
“Multifocal” AdenoCa

Intrapulm. aerogeous spread primary

Genetic similarity of lesions = stage IV

Invasive mucinous adenocacrinoma

(formerly mucinous BAC)



Evaluation of T3 add nodule same lobe

- Following assessment should be carried out :
  - integrated PET/CT : to exclude M1b
  - CT/MRI brain : to exclude M1b
  - invasive mediastinal nodal staging

Literature data on resected T3 :

up to 50% preop not detected

30% pN2 disease

nearly 100% R0-resection rate

average 5-yr survival rate :

- center series : 37 %
- registries : 27 %

First Author	No. of Patients	% with Multiple Nodules	Continent	% Survival 2-Year	% Survival 5-Year
Nagai[165]	316	-	Asia	46	27
Okumura[166]	152	-	Asia	52	34
Okada[151]	51	-	Asia	52	30
Yano[167]	39	-	Asia	57	36
Shimizu[168]	37	-	Asia	41	27
Osaki[152]	36	-	Asia	46	27
Watanabe[153]	24 [a]	-	Asia	36	22
Lee [113]	23	-	Asia	-	30
Yoshino[169]	22	-	Asia	34	34
Fukuse[170]	20	12	Asia	58	37
Ruffini[154]	50	-	Europe	-	28
Oliaro[172]	39	49	Europe	49	20
Trousse[155]	35	-	Europe	-	52
Terzi[156]	32	-	Europe	70	42
Port[172]	53	19	N. Am	73	48
Pennathur[157]	51	-	N. Am	-	26
Rao[158]	35	-	N. Am	-	57
Battafarano[116]	27	-	N. Am	70	(66) [b]
Bryant[159]	26	-	N. Am	75	57
Average [c]				**54**	**37**
Registry Database Studies [d]					
IASLC[160]	363	-	Global	50	28
CCR[161]	422	-	N. Am	40	23
SEER[162]	633	-	N. Am	44	35
SEER[163]	2,285	-	N. Am	43	24

Kozower et al. Chest 2013;143:e369s.

Impact of PET/CT on TNM staging

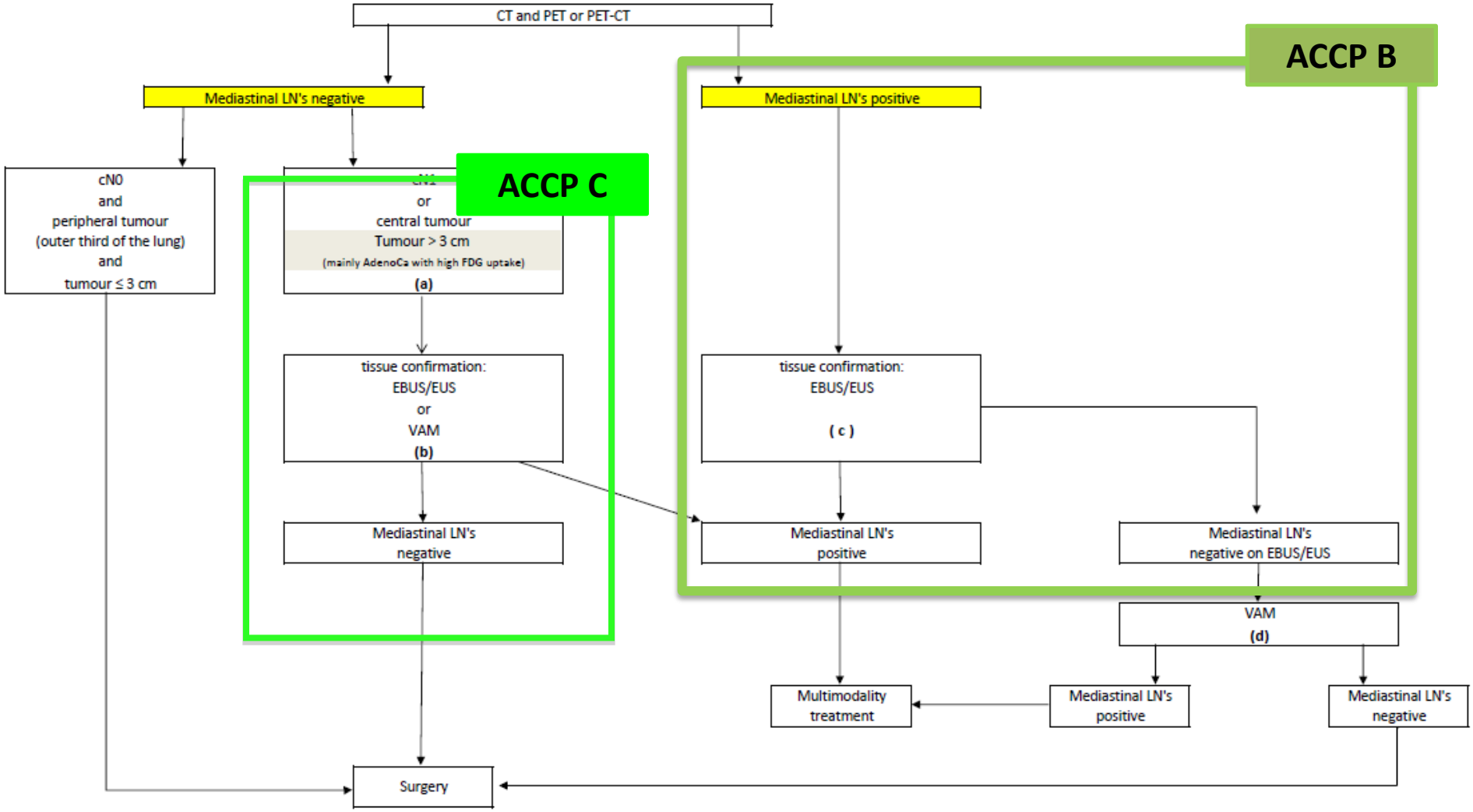
Study	Year	N	Population	Study question	Comparison	Findings
Fischer et al.	2009	189	Resectable Stage I-III NSCLC	Number of 'futile thoracotomies'	CS -> S PET-CT -> S	52% vs. 35% (*P*=0.05)
Maziak et al.	2009	337	Resectable stage I-IIIA NSCLC	Proportion in whom correct upstaging	CS -> S PET-CT -> S	7% vs. 14% (*P*=0.046)
Ung et al.	2009	310	Unresectable Stage III NSCLC	Proportion in whom correct upstaging	CS -> RT PET-CT -> RT	3% vs. 15%. (*P*=0.0002)
Yi et al.	2013	300	Resectable Stage I-IIIA NSCLC	Proportion in whom correct upstaging	PET-CT -> S MRI-PET -> S	22% vs. 26% (*P*=0.43)

Impact of PET/CT on TNM staging

Study	Year	N	Stage I-II	PET impact	Stage IV
Fischer et al.	2009	189	33%	- 17% futile thoracotomies	+ 11%
Maziak et al.	2009	337	90%	+ 7 % correct overall upstaging	+ 4%
Ung et al.	2009	310	0%	+ 12% correct overall upstaging	+ 10%
Yi et al.	2013	300	97%	NR	+ 9-13%

Fischer et al. NEJM 2009;361:32. Maziak et al. Ann Intern Med 2009;151:221. Ung et al. J Clin Oncol 2009;27:15s(7548). Yi et al. Cancer 2013;119:1784-91.

ESTS mediastinal nodal staging algorithm



De Leyn et al. Eur J Cardiothorac Surg 2014;45:787.

Mediastinoscopy vs Endosonography for Mediastinal Nodal Staging of Lung Cancer

A Randomized Trial

	SS	ES+SS	*p*-Value
	N=118	N=123	
N2/N3 detected ; n (%)	41 (35)	62 (50)	0.02
Sensitivity, % (95% CI)	**79 (66-88)**	**94 (85-98)**	**0.02**
NPV, % (95% CI)	86 (76-92)	93 (84-97)	0.18

	SS	ES	*p*-Value
Sensitivity, % (95% CI)	**79 (66-88)**	**85 (74-92)**	**0.47**
NPV, % (95% CI)	86 (76-92)	85 (75-92)	0.99
complications	6%	1%	0.03

Annema et al. JAMA 2010;304:2245.

ASTER 2 (selected ACCP C).

	ES N=100	**ES+SS** N=100
N2/N3 detected ; n	10	17
Sensitivity* (95% CI)	**0.38 (0.18-0.57)**	**0.73 (0.55-0.91)**
NPV (95% CI)	**0.81 (0.71-0.91)**	**0.91 (0.83-0.98)**
NLR (95% CI)	**0.18 (0.13-0.27)**	**0.09 (0.04-0.17)**

*based on multiple imputation analysis

Dooms et al. Chest 2014; Epub ahead of print.

Evaluation of T4 different lobe same lung

- Following assessment should be carried out :
  - integrated PET/CT : to exclude M1b
  - CT/MRI brain : to exclude M1b
  - invasive mediastinal nodal staging

"Presumed metastasis"

average 5-yr survival rate for

resected T4 disease :

- center series : 19 %
- IASLC registry : 22 %

nearly 100% R0-resection rate

First Author	No. of Patients	% Survival	
		2-Year	5-Year
Nagai[165]	129	42	22
Okumura[166]	48	31	11
Okada[107]	38	49	23
Ruffini[154]	36	-	28
Oliaro[171]	35	49	10
Lee[118]	26	42	31
Fukuse[170]	21	41	0
Tung[164]	20	40	28
Average		**42**	**19**
Registry Database Studie.			
IASLC[160]	180	40	22
CCR[161]	745	(26)[a]	(9)[a]
SEER[162]	3,010	(18)[a]	(7)[a]
SEER[163]	3,019	(26)[a]	(8)[a]

Kozower et al. Chest 2013;143:e369s.

Evaluation of T4 different lobe same lung

- Following assessment should be carried out :
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  - CT/MRI brain : to exclude M1b
  - invasive mediastinal nodal staging

"Presumed metastasis"

worse survival if multiple nodules

worse survival if N2 :

- SEER database : N2 up to 66 %
- Nagai et al : 5-yr survival 10 %

worse survival if **unresected** disease

- CCR/SEER : 5-yr survival <10 %

First Author	No. of Patients	% Survival 2-Year	% Survival 5-Year
Nagai[165]	129	42	22
Okumura[166]	48	31	11
Okada[107]	38	49	23
Ruffini[154]	36	-	28
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Kozower et al. Chest 2013;143:e369s.

Evaluation of add nodule M1a other lung

When to biopsy the M1a additional nodule other lung ?

- **No, when benign features on CT scan.**

Table 1 Features of benign nodules.

High specificity
- Calcification (diffuse, popcorn, central, and laminated)
- Internal fat
- Polygonal (all surfaces concave or straight unless in contact with a pleural surface)
- Ovoid (coffee-bean shaped), flat, or tubular
- Clustering of subcentimetre nodules in an isolated lung segment

Low specificity
- Solid with no ground glass components
- Subpleural
- Punctate calcification

Table 2 Features suggestive of intrapulmonary lymph nodes.

Size
- Commonly 3–6 mm (may be <12 mm)

Location
- Subpleural or within 15 mm of pleural surface
- Predominantly lower-zone distribution

Shape
- Subpleural intrapulmonary lymph nodess to be corrected: half-moon
- Intraparenchymal: coffee-bean or angular if small

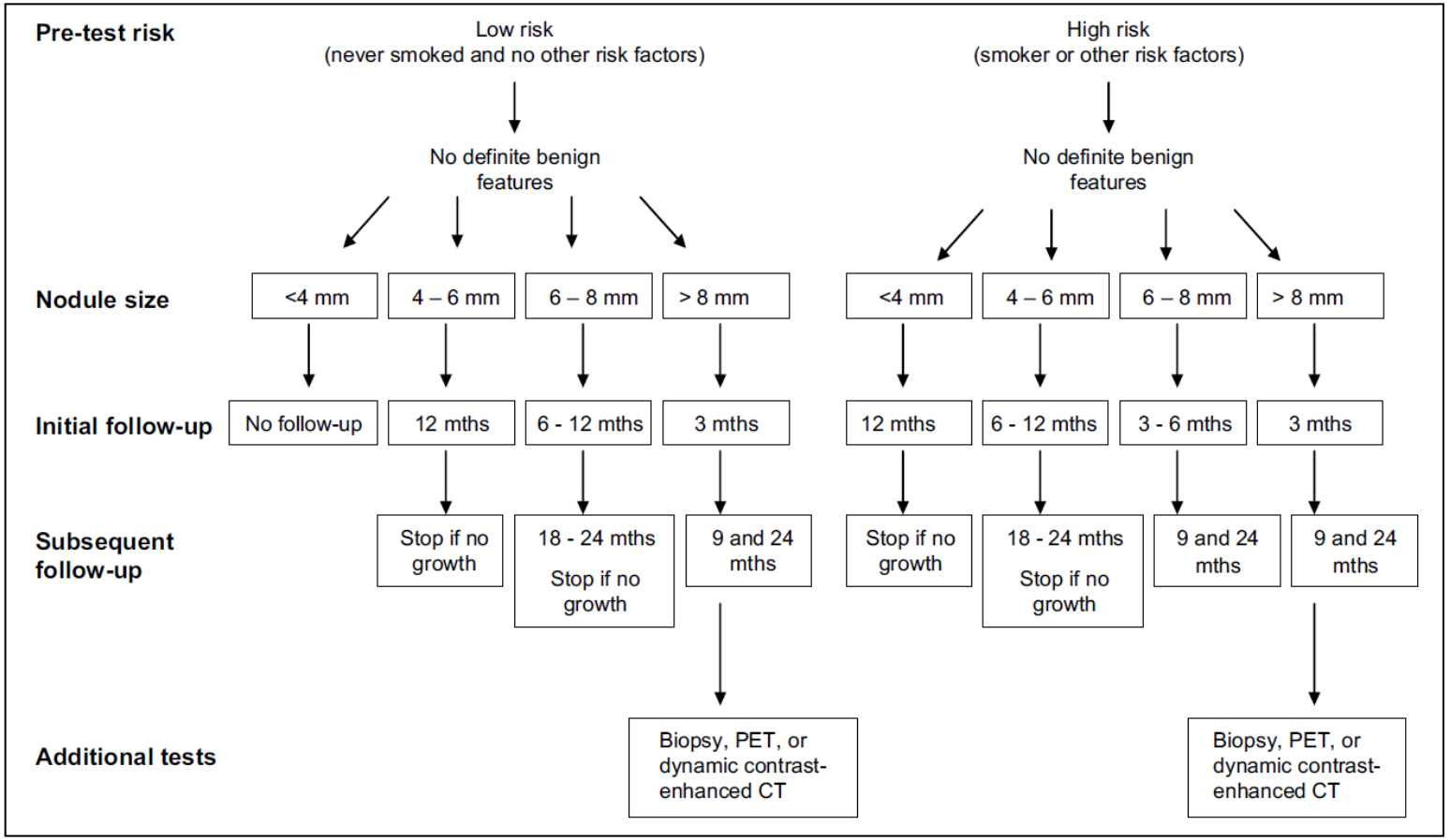
Ancillary features
- Linear connection to pleural surface (interlobular septum)

Edey and Hanssell. Clinical Radiology 2009;64:872.

Evaluation of add nodule M1a other lung

When to biopsy the M1a additional nodule other lung ?

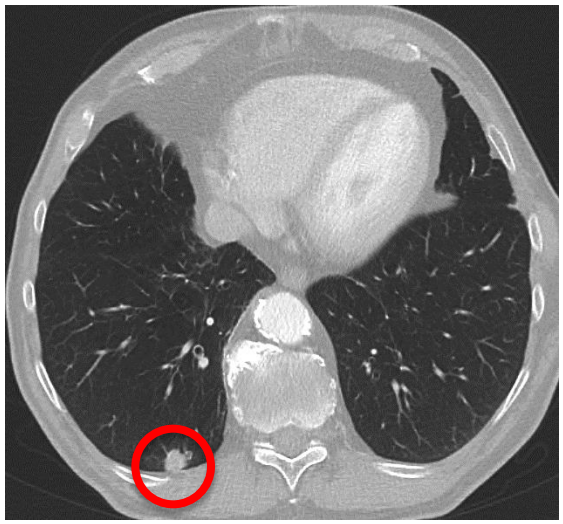
- **No, when FU recommended for small solid nodule (Fleischner).**

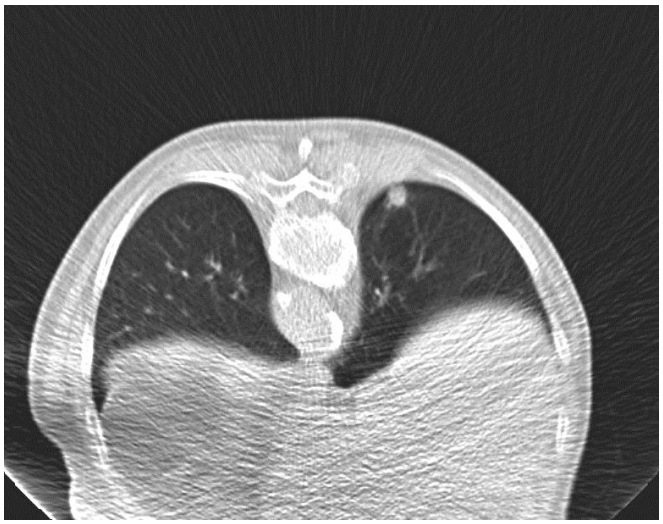


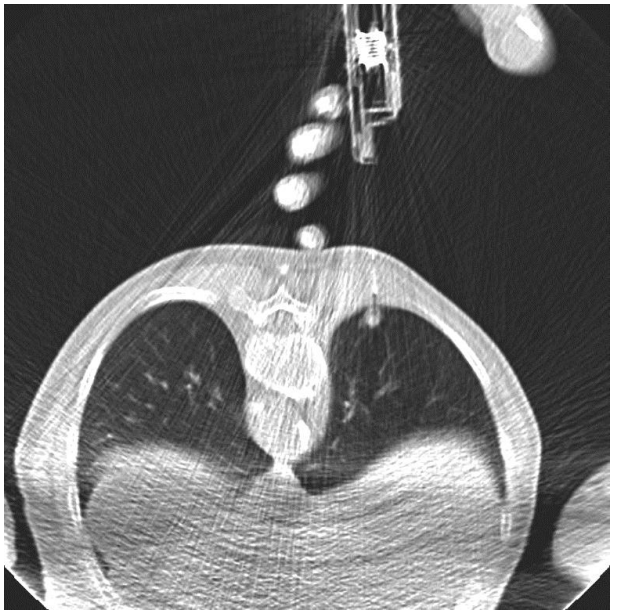
Evaluation of add nodule M1a other lung

When to biopsy the M1a additional nodule other lung ?

- No, when benign features on CT scan.
- No, when FU recommended for small solid nodule.
- **No, when minimal invasive surgery planned and feasible.**
- **Yes, when SBRT planned.**







Evaluation of add nodule M1a other lung

- Careful clinical and radiological assessment
  - for distant metastases : integrated PET/CT, CT/MRI brain
  - for mediastinal node metastases : invasive nodal staging

In absence of mediastinal nodal disease “synchrounous LC”

5-yr survival rate 38% ; 50% same histology

De Leyn et al. Eur J Cardiothorac Surg 2008;34:1215.

In presence of mediastinal nodal disease “metastatic spread”

Study	No. of patients	% Resected	% pN2	% 5-year Survival		
				All	Same histol	diff histol
SEER[163]	5,382	6	53	**3**	-	-
CCR[161]	1,148	8	-	**2-6**[a]	-	-
IASLC[160]	362	2	-	**3**	-	-

Kozower et al. Chest 2013;143:e369s.

Evaluation of multifocal lung cancer (MFLC)

- Recognise these patients according to clinical features !
- Decreased propensity for nodal/systemic spread, but increased propensity for additional pulmonary foci (GGO).
- Careful preop clinical and radiologic evaluation.
- Careful clinical and nodal evaluation at the time of resection.
- Careful pathologic assessment of T-factor (AIS/MIA/INV).

First Author	No. of patients	Median F/U (mo)	% pN2	% Surg Treated	% Multi-focal	CT appearance (% GGO)			% BAC Histology		% 5-y Survival
						Solid	Mixed	Pure	Mixed	Pure	
Casali[201]	40	48	-	100	15	-	-	-	-	100	64
Ebright[202]	100	86	-	100	29	-	-	-	53	47	74
Carretta[137]	26	82	-	100	55	71	26	7	10	40	92
Nakata[180]	31	28	6	100	84	28	43	29	69[a]	31	93
Mun[203]	29	46	0	100	93	0	100	0	29[b]	71	100
Roberts[192]	14	60	0	100	100	-	-	-	14	57	64
Kim[178]	23	40	0	44	100	0	100	0	26[b]	69	100
Average									34	59	**84**

Kozower et al. Chest 2013;143:e369s.

Evaluation of pts considered to have SPLC

- Careful clinical and radiological assessment :
  - for distant metastases : integrated PET/CT, CT/MRI brain
  - for mediastinal node metastases : mediastinoscopy

First Author	No.	% incidental[a]	% resected	% limited resection[b]	% Operative mortality	% 5-year Survival		
						All	Resected	pI
Synchronous								
Finley[120]	175	42	(100)[c]	27	1	52	52	64[d]
Trousse[194]	125	-	(100)[c]	14	11	34	34	-
Riquet[114]	118	-	(100)[c]	16	5	26	26	-
Rostad[113]	94	79	(100)[c]	16	9	33	33	-
Chang[133]	92	-	(100)[c]	11	1	35	35	-
Van Rens[138]	85	32	(100)[c]	13	14	20	20	23
Fabian[139]	67	-	(100)[c]	60	2	53	53	89
van Bodegom[101]	64	-	50	34	-	-	-	24[e]
Voltolini [140]	50	-	>90	65	7	31	34	-
Shah[49]	47		(100)[c]	41	2	29	29	90
De Leyn[112]	36	-	(100)[c]	72	3	38	38	-
Deschamps[103]	36	42	(100)[c]	21	6	-	16	-
Vansteenkiste[146]	35	-	(100)[c]	23	9	33	33	-
Rosengart[104]	33	-	91	33	-	44	-	-
Jung[142]	32	3	(100)[c]	53[f]	9	61	61	31
Ferguson[147]	28	18	68	47	0	0	0	0
Okada[107]	28	39	(96)[c]	7	0	70	-	79[e]
Kocaturk[143]	26		92	38	8	50	50	-
Antakli[108]	26	19	92	42	-	5	12	-
Ribet[109]	24	-	63	40	4			
Average		**34**	**79**	**34**	**5**	**36**	**33**	**51**

Kozower et al. Chest 2013;143:e369s.

Conclusions.

Optimal assessment of additional lung nodule in LC :

- **Does matter** : in 15-26% of pts, but malignant in up to 8%.
- Most **current evidence** based on surgical series – IASLC.
- Categories based on **clinical** feature(s).
- Comprehensive **histologic** subtyping/profiling when biopsied.
- Role of genomic profiling not yet defined.
- **Invasive mediastinal** staging should be performed.
- **PET**/CT should be performed for more accurate M1b staging.

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Thank you for your attention !

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