A Beneficência
Portuguesa
de São Paulo

Programa *Team Up* da Oncologia BP



Parceria: AstraZeneca

Abordagem Prática de Nódulos Pulmonares em Vidro Fosco (Lesões Subsólidas)

Fabio José Haddad

Cirurgia Torácica e Broncoscopia

Declaração de Conflitos de Interesse

De acordo com a Norma 1595/2000 do Conselho Federal de Medicina e com a RDC 96/2008 da ANVISA, declaro que:

- Apresentações - como palestrante convidada, participo dos eventos de:

  MSD, BMS, AstraZeneca, Boehringer-Ingelheim.

- Não possuo ações de quaisquer destas companhias farmacêuticas.
- Os meus pré-requisitos para participar destas atividades são a autonomia do pensamento científico, a independência de opiniões e a liberdade de expressão.

Objetivos

1. Como avaliar imagens suspeitas e risco de câncer
2. Risco de evolução para carcinoma invasivo
3. Indicação de intervenção
4. Avaliação de lesões múltiplas
5. Importância da abordagem multidisciplinar

Pauta

1. Definições
2. Lesões suspeitas e sua evolução
3. Intervenção ou observação?
4. Lesões múltiplas: vários primários ou metástases?
5. Mensagens finais

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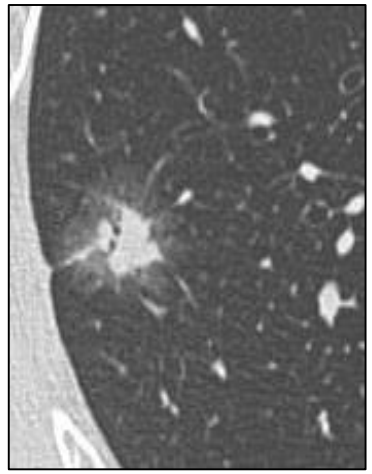
Definição: Subtipos

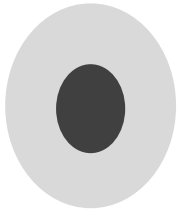


"Vidro despolido" puro



"Vidro despolido" heterogêneo





Semi-sólido

Importância

- Rastreamento ELCAP
- 223 nódulos positivos na 1ª TC
- 44 (19%) – subsólidos
- 34% destes subsólidos eram malignos
- 63% dos mistos eram adenocarcinomas

TABLE 2 **Frequency of Malignancy Found at Baseline Screening by Size and Type of Largest Nodule[a]**

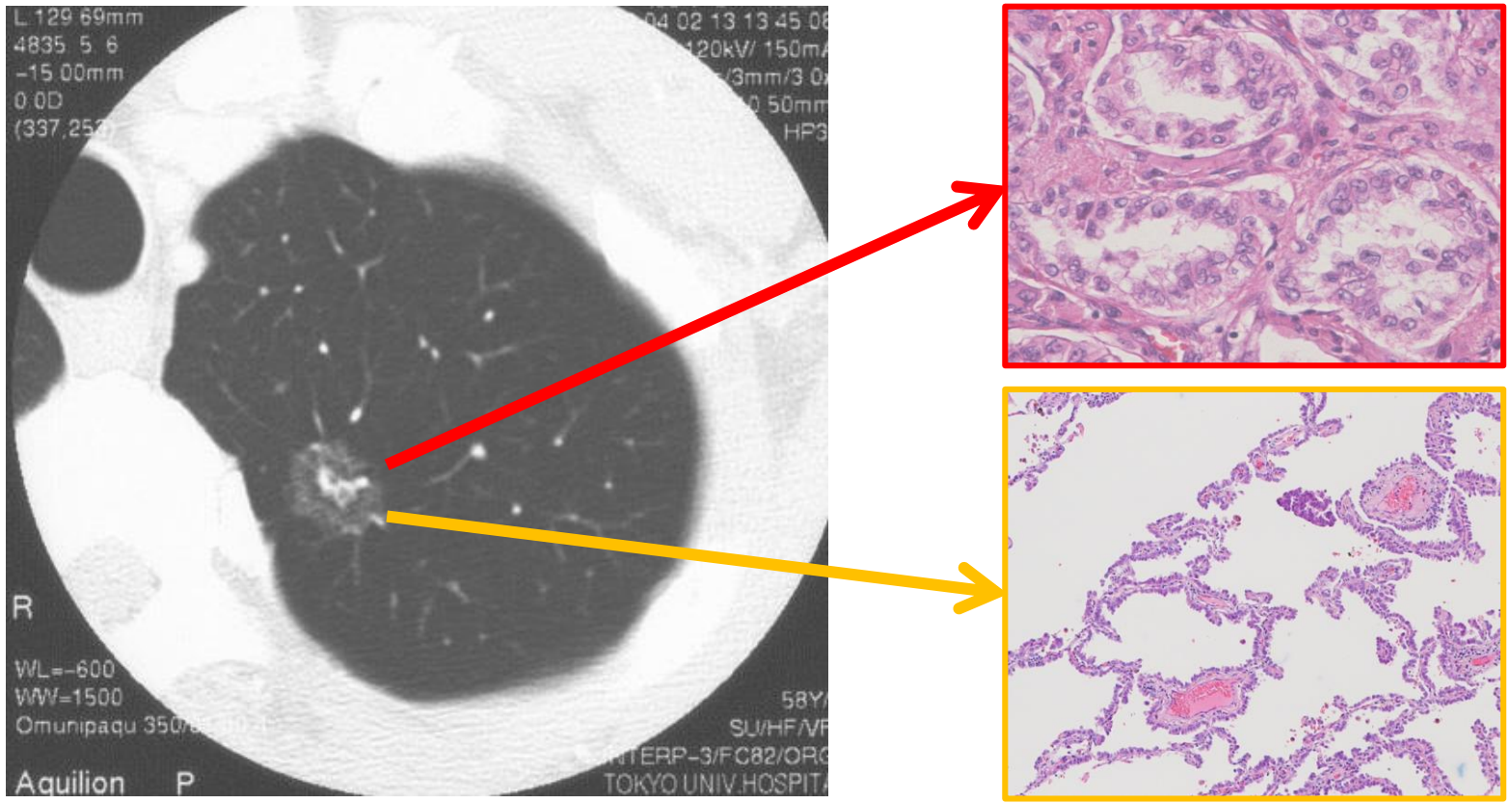
Nodule Type	Diameter (in mm) of Largest Nodule				Totals	
	2–5	6–10	11–20	21–45	Crude	Standarized[b]
Solid	1/127 (1)	7/49 (14)	4/11 (36)	2/2 (100)	14/189 (7)	32%
Partially solid	0/2 (0)	2/6 (33)	6/6 (100)	2/2 (100)	10/16 (63)	63%
Nonsolid	0/7 (0)	5/15 (33)	0/5 (0)	0/1 (0)	5/28 (18)	13%
Total	1/136 (1)	14/70 (20)	10/22 (45)	4/5 (80)	29/233 (12)	

Note.— Numbers in parentheses are percentages.

[a] Of 29 diagnosed malignancies, all but one were associated with nodules that were solitary or the largest.

[b] Standarized for size using part-solid nodules as standard (because they were smallest group).

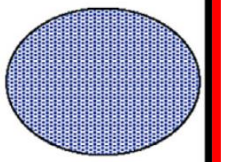
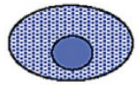
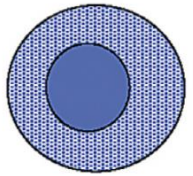
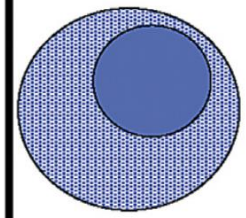
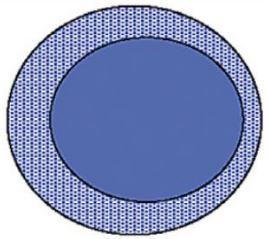
Correlação entre TC e Adenocarcinoma *in situ* ou Invasor



A opacidade em vidro fosco representa o padrão de crescimento *in situ* observado no adenocarcinoma.

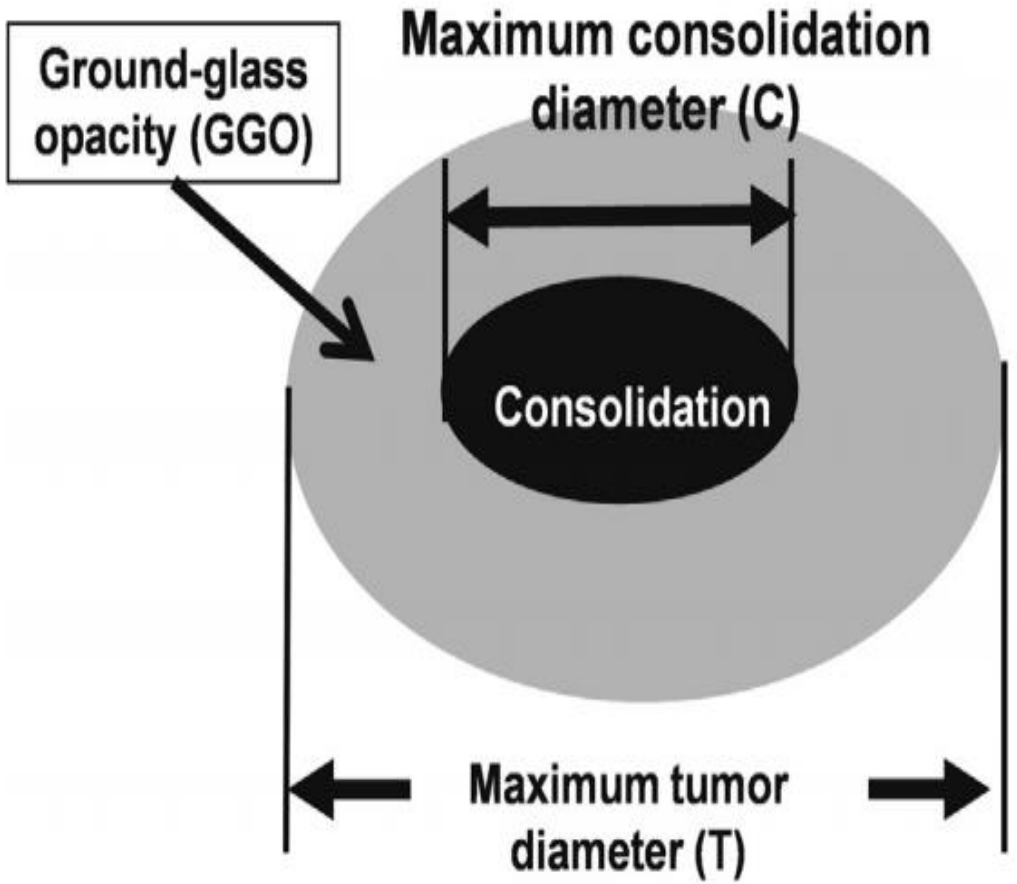
Aoki T, et al. Radiology 2001; 220: 803-809.

Correlação Clínica/Imagem com Patologia (IASLC)

cT*	CT image on HRCT						
	Solid part	0 cm	0 cm	≤0.5 cm†	0.6-1.0 cm†	1.1-2.0 cm†	2.1-3.0 cm†
	Total tumor size including GG	≤0.5 cm	0.6-3.0 cm‡‡	≤3.0 cm‡‡	0..6-3.0 cm††	1.1-3.0 cm††	2.1-3.0 cm††
	Pathologic Differential Diagnosis	AAH‡, AIS, MIA	AIS, MIA, LPA	MIA, LPA, AIS	LPA, Invasive AD, MIA	LPA, Invasive AD	Invasive AD
	Clinical Stage*		cTis‡‡	cT1mi‡‡	cT1a	cT1b	cT1c
pT	Invasive part	0 cm	0 cm	≤0.5 cm‡‡	0.6-1.0 cm†	1.1-2.0 cm†	2.1-3.0 cm†
	Total tumor size ncluding lepidic growth part	Usually ≤0.5 cm‡	≤3.0 cm‡‡	≤3.0 cm‡‡	0.6-3.0 cm††	1.1-3.0 cm††	2.1-3.0 cm††
	Pathology	AAH	AIS	MIA	Lepidic predominant AD or Invasive AD with lepidic compnent	Invasive AD with a lepidic component or lepidic predominant AD	Invasive AD with lepidic component
	Pathologic Stage		pTis‡‡	pT1mi‡‡	pT1a	pT1b	pT1c

Travis W, et al. J Thorac Oncol 2016; 11:1204-1223.

Proporção Consolidação/Tumor



C/T *ratio*

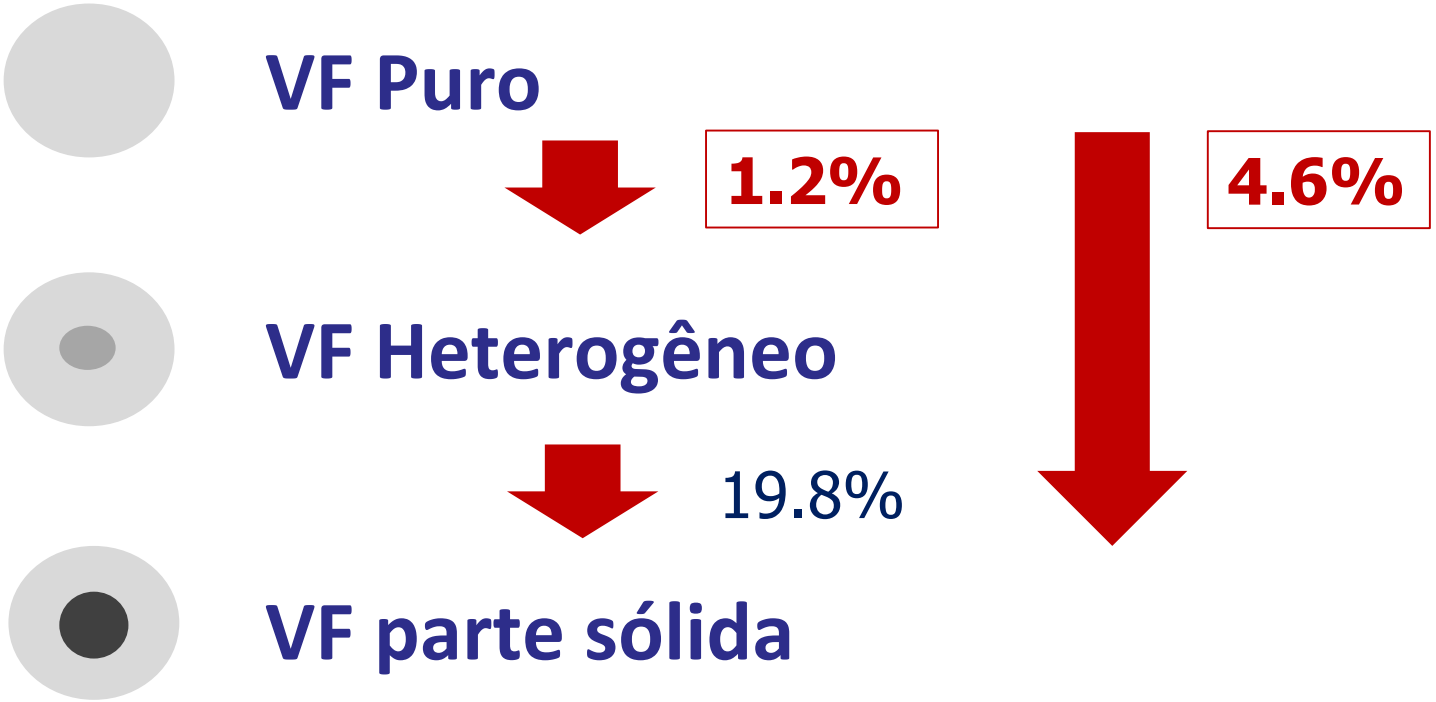
Parceria: AstraZeneca

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Lesões Subsólidas

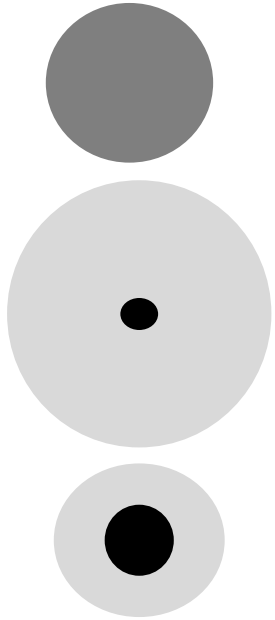
- Estudo prospectivo observacional
- N=795 pacientes com 1,229 nódulos subsólidos
- *Follow-up* mediano: 4.3 ± 2.5 anos



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Indicações de Cirurgia (no Japão)



Sólido, ≥10 mm

Parte sólido ou VF puro, ≥15 mm

Parte sólido, D <15 mm, componente sólido >5 mm

Qualquer aumento no tamanho...

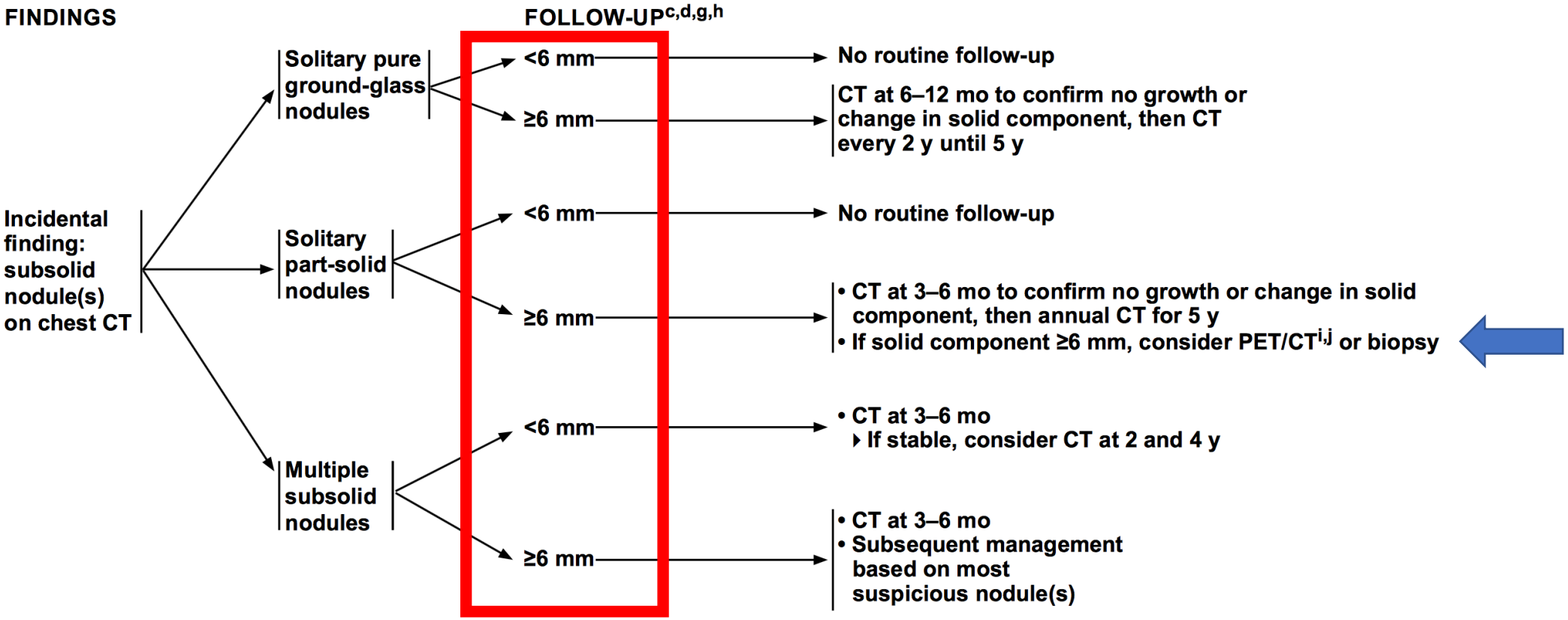
Watanabe SI, IASLC 2018.

Indicações de Cirurgia (nos EUA)

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2019
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion



Qualquer aumento no tamanho…

NCCN, version 4.2019

Indicações de Cirurgia (nos EUA)

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2019
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

Resection

- Anatomic pulmonary resection is preferred for the majority of patients with NSCLC.
- Sublobar resection - Segmentectomy and wedge resection should achieve parenchymal resection margins ≥2 cm or ≥ the size of the nodule.
- Sublobar resection should also sample appropriate N1 and N2 lymph node stations unless not technically feasible without substantially increasing the surgical risk.
- Segmentectomy (preferred) or wedge resection is appropriate in selected patients for the following reasons:
  - Poor pulmonary reserve or other major comorbidity that contraindicates lobectomy
  - Peripheral nodule[1] ≤2 cm with at least one of the following:
    - ◊ Pure AIS histology
    - ◊ Nodule has ≥50% ground-glass appearance on CT
    - ◊ Radiologic surveillance confirms a long doubling time (≥400 days)
- VATS or minimally invasive surgery (including robotic-assisted approaches) should be strongly considered for patients with no anatomic or surgical contraindications, as long as there is no compromise of standard oncologic and dissection principles of thoracic surgery.
- In high-volume centers with significant VATS experience, VATS lobectomy in selected patients results in improved early outcomes (ie, decreased pain, reduced hospital length of stay, more rapid return to function, fewer complications) without compromise of cancer outcomes.

Qualquer aumento no tamanho...

Premissa Básica:

Tratamento Cirúrgico Padrão para Câncer de Pulmão de Células Não Pequemas Localizado é

LOBECTOMIA

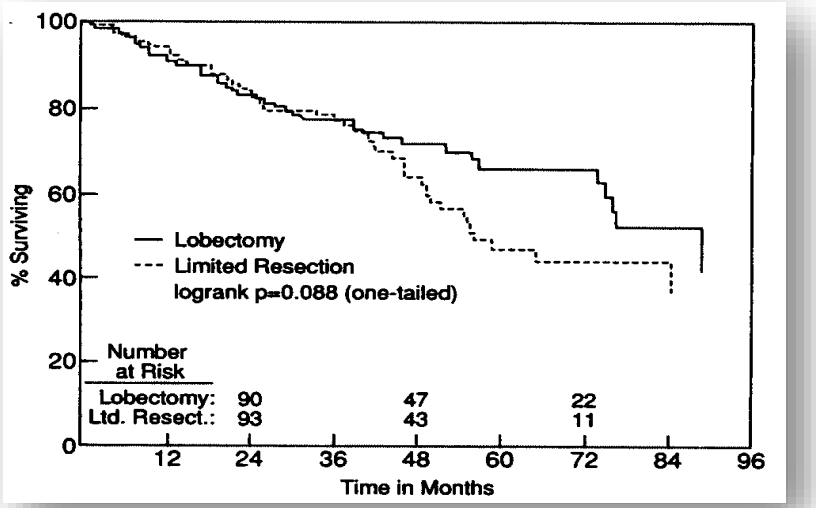
Único Estudo Randomizado: Lobectomia vs TS para T1N0



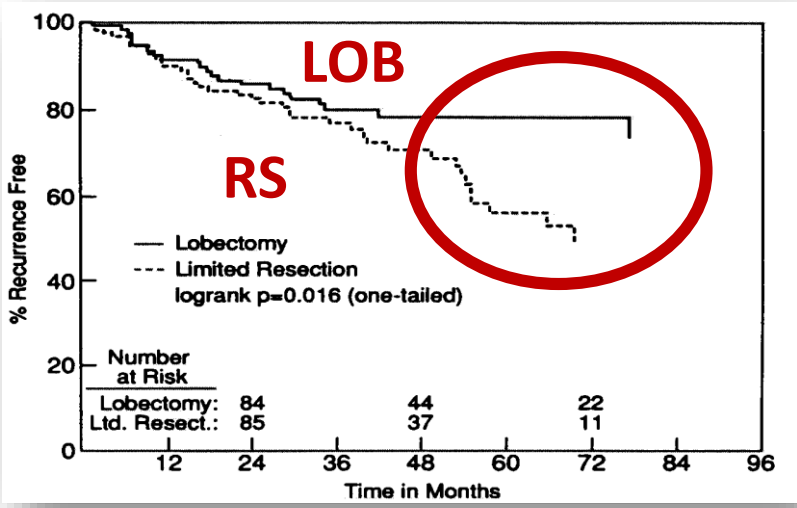
Robert Ginsberg, MD

Era pré-PET-CT
T1 < 3,0 cm
Tomógrafos menos sensíveis

OS (p=0.088)

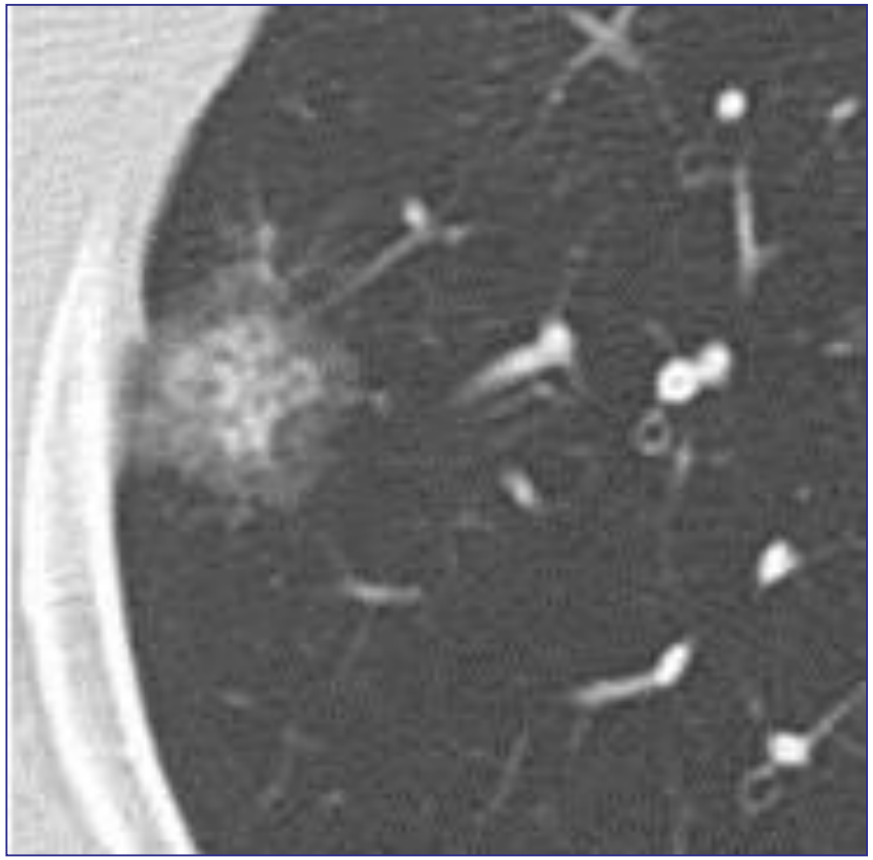


Recurrence-free survival (p=0.016)



LCSG. Ann Thorac Surg 1995; 60:615-623.

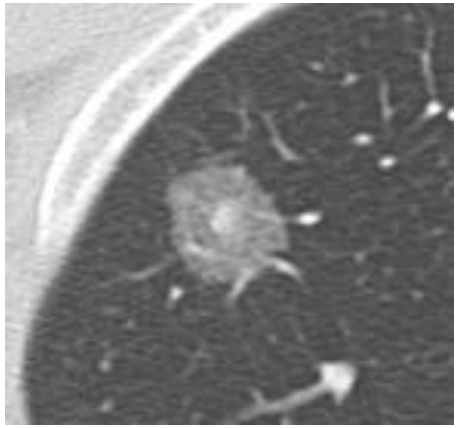
Cirurgia nos Tumores Sub-Sólidos: Lobectomia ou Sublobar?



JCOG0201:

É possível dizer se o tumor é invasivo pela TC?

- 545 adenocarcinomas ≤2 cm
- **Correlação Radiológico-Patológica no adenocarcinoma de pulmão ≤2.0 cm**
  - Lobectomia com linfadenectomia mediastinal
  - Não-invasivos: N0, sem invasão angio-linfática



C/T <0.25 foram considerados não invasivos.

(especificidade = 98.7%)

Suzuki K, et al. J Thorac Oncol 2011; 6:751-6.

Ressecção Sublobar vs Lobectomia:
Estudos de Fase III em andamento

- Japão (JCOG)
- EUA (NCI)

Jpn J Clin Oncol 2018;48:190-194;
https://clinicaltrials.gov/ct2/show/NCT00499330.

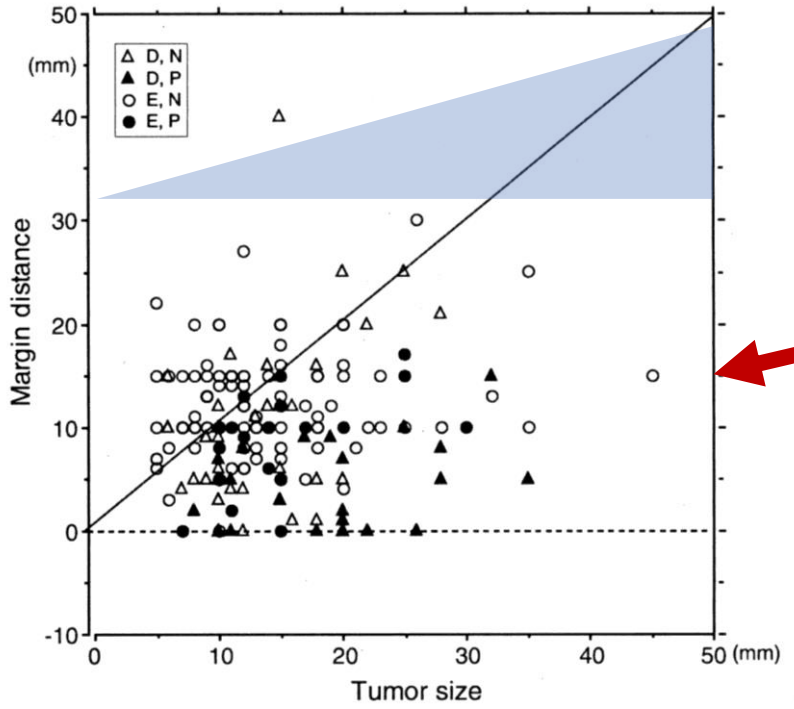
Característica mais importante da ressecção sublobar (segmentectomia):

Garantir margens livres de neoplasia

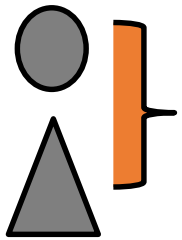
(múltiplos segmentos = lobo)

+ áreas de drenagem linfática/linfonodos

Margem adequada ≥ maior diâmetro do tumor



Casos com margem positiva



Margem < diâmetro do tumor:

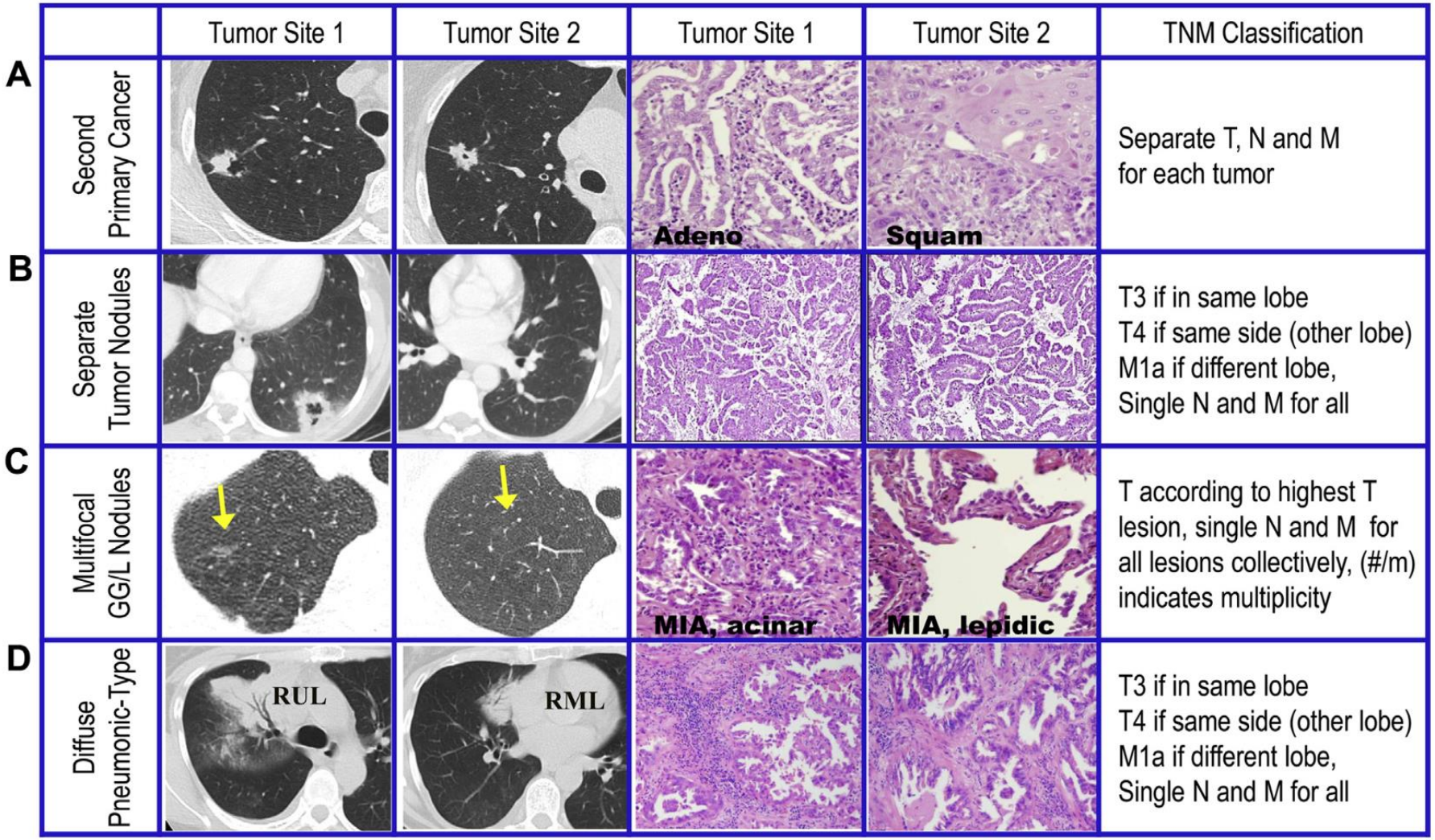
> chance de margem positiva

Sawabata N, et al. Gen Thorac Cardiovasc Surg 2013;61:9-16.

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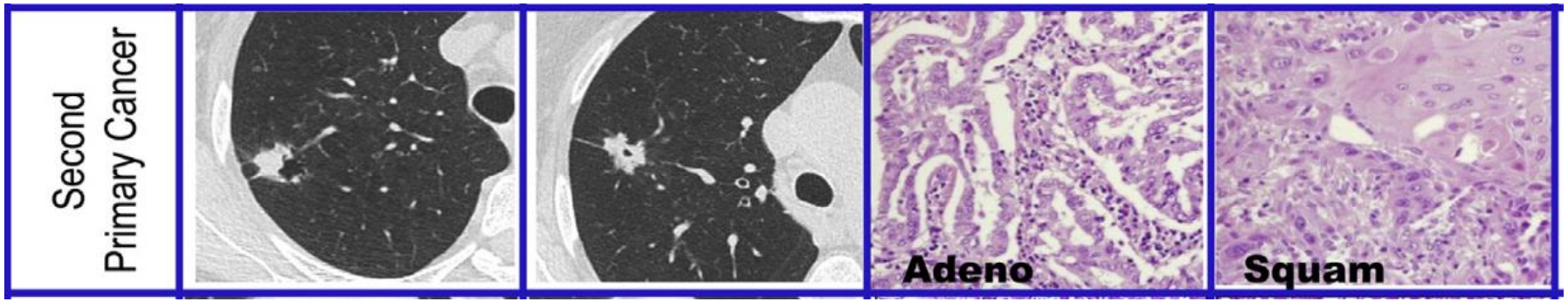
Representação esquemática da doença com múltiplos sítios pulmonares



Detterbeck FC, et al. J Thorac Oncol 2016; 11:639-650.

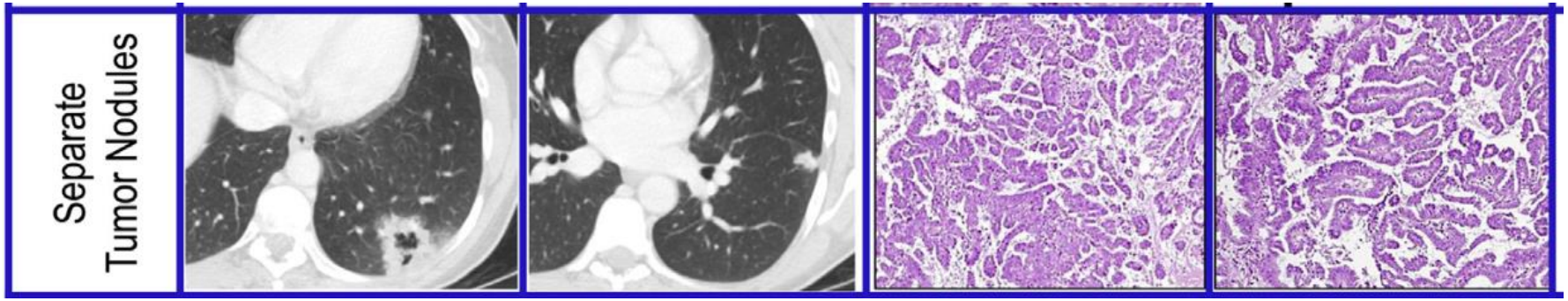
Classificação para múltiplos nódulos pulmonares IASLC 2016

- **Segundo tumor primário:**
  - Imagem: lesões distintas suspeitas para câncer de pulmão
  - Patologia: histologia ou morfologias diferentes
  - TNM: classificação separada clínica e patológica
  - Conceito: tumores não relacionados



Classificação para múltiplos nódulos pulmonares IASLC 2016

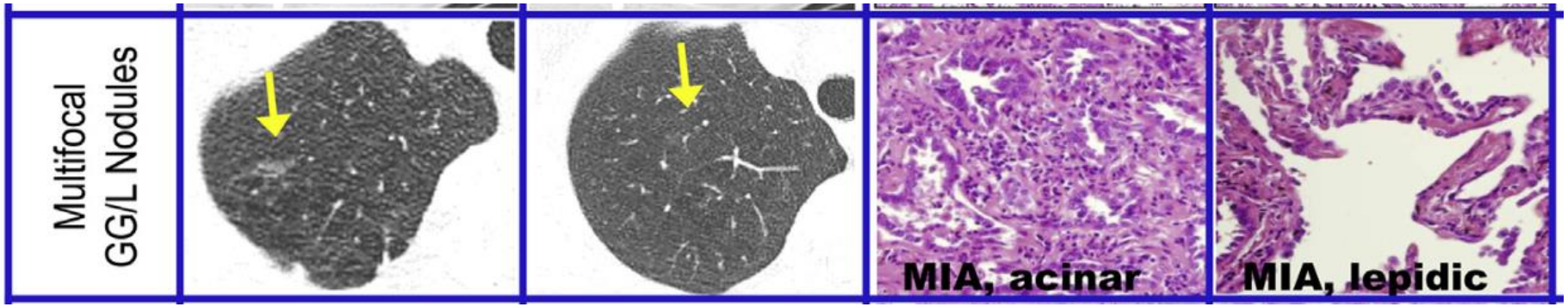
- **Tumores separados, mas relacionados:**
  - Imagem: tumor típico, sólido, nódulo separado
  - Patologia: lesões distintas, com mesmas características morfológicas (AP da peça)
  - TNM: T3, T4 ou M1a, mesmo N e M
  - Conceito: uma neoplasia, com metástase intrapulmonar



Detterbeck FC, et al. J Thorac Oncol 2016; 11:639-650.

Classificação para múltiplos nódulos pulmonares IASLC 2016

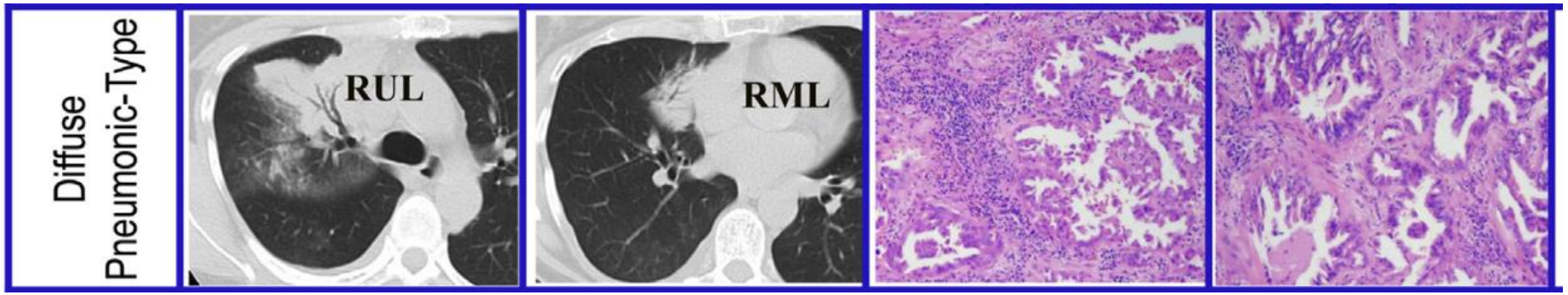
- **Doença multifocal:**
  - Imagem: múltiplas lesões em VF / Subsóldias
  - Patologia: adenocarcinomas predominantemente lepídicos
  - TNM: baseado no maior T com (#/m) – multiplicidade de nódulos, mesmo N e M
  - Conceito: tumores não relacionados, com similaridades, sincrônicos



Detterbeck FC, et al. J Thorac Oncol 2016; 11:639-650.

Classificação para múltiplos nódulos pulmonares IASLC 2016

- **Adenocarcinoma tipo pneumônico:**
  - Imagem: áreas de VF e consolidação
  - Patologia: adenocarcinomas predominantemente mucinosos, homogêneo
  - TNM: T3, T4 ou M1a, mesmo N e M
  - Conceito: uma neoplasia, acometimento pulmonar difuso ou localizado



Critérios Patológicos

- Histologia diferente
- Morfologia diferente
- CEC *in situ* em ambos
- Mesmos *breakpoints*
- Biomarcadores
- Doença nodal ou sistêmica (sim ou não)
- Discussão multidisciplinar

Pathologic criteria (i.e., after resection)
Tumors may be considered second primary tumors if
They are clearly of a different histologic type (e.g., squamous carcinoma and adenocarcinoma).
They are clearly different by a comprehensive histologic assessment.
They are squamous carcinomas that have arisen from carcinoma in situ.
Tumors may be considered to be arising from a single tumor source if
Exactly matching breakpoints are identified by comparative genomic hybridization.
Relative arguments that favor separate tumors (to be considered together with clinical factors)
Different biomarker pattern
Absence of nodal or systemic metastases
Relative arguments that favor a single tumor source (to be considered together with clinical factors)
Matching appearance on comprehensive histologic assessment
Same biomarker pattern
Significant nodal or systemic metastases

[a]A comprehensive histologic assessment is not included in clinical staging, as it requires that the entire specimen has been resected.

Detterbeck FC, et al. J Thorac Oncol 2016; 11:639-650.

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Mensagens para Levar para Casa

- ✓ Lesões subsólidas que não desaparecem com o tempo = **adenocarcinomas**
- ✓ Avaliação do **risco global do paciente** vs. Risco de evolução da lesão pulmonar
- ✓ **Evolução da lesão subsólida** pulmonar depende de tamanho, subtipo e relação S/VF (C/T):
  - VF puro
  - VF heterogêneo
  - VF com parte sólida

Mensagens para Levar para Casa

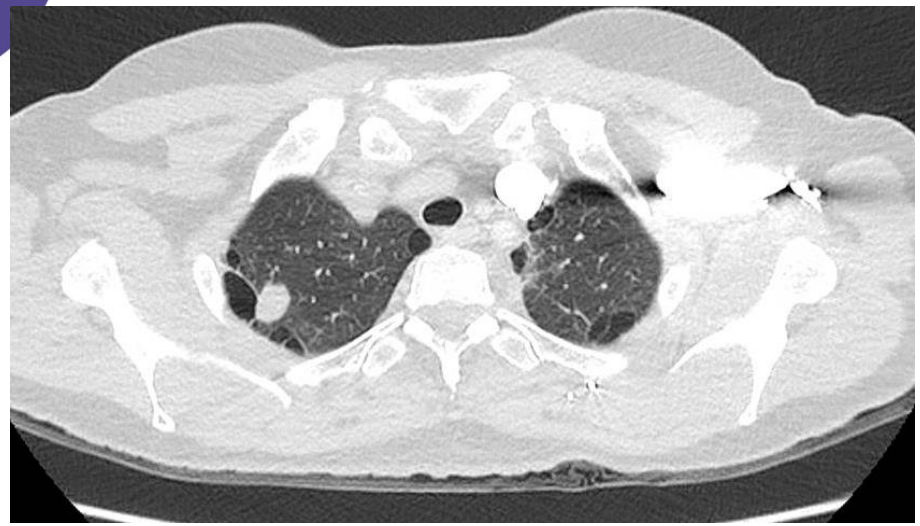
- ✓ **Indicações de intervenção:**
  - Sólido > 10 mm
  - Subsólido > 15 mm
  - VF Puro > 15 mm
  - Subsólido < 15 mm e Sólido > 5mm
- ✓ **Extensão da ressecção:**
  - Padrão: lobectomia / segmentectomia (casos anatomicamente favoráveis)
  - Estudos em andamento
  - Margem mínima = tamanho do tumor

Mensagens para Levar para Casa

- ✓ **Sublobar:**
  - < 2,0 cm – VF puro
  - Relação S/VF < 0,5 (preferencialmente segmentectomia)
  - Tempo de duplicação tumoral > 400 dias
- ✓ **Por ora, com linfadenectomia (hilar e mediastinal).**
- ✓ **Lembrar da possibilidade de novos primários**
- ✓ **Decisão multidisciplinar e com paciente**

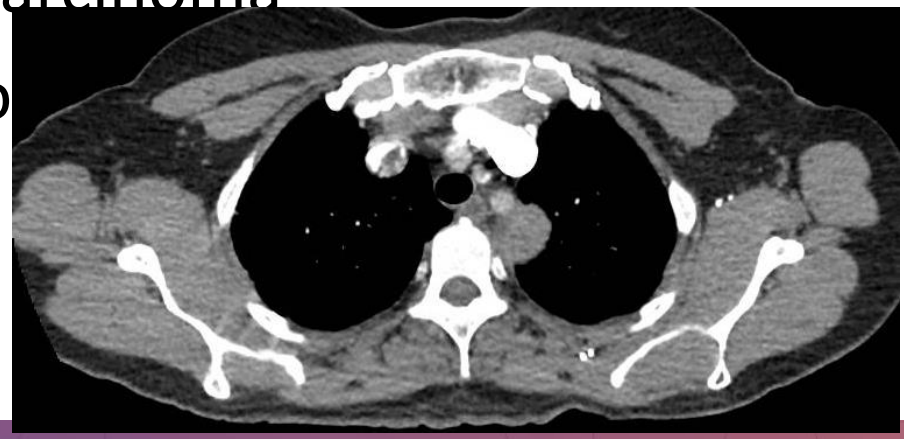

ÔNIBUS

Caso Clínico



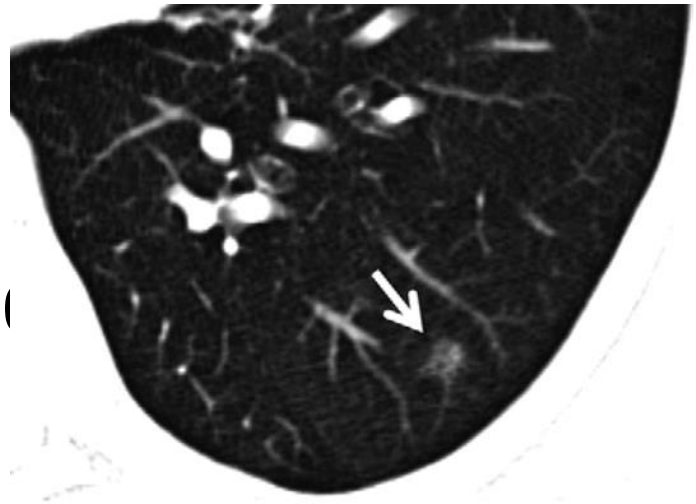


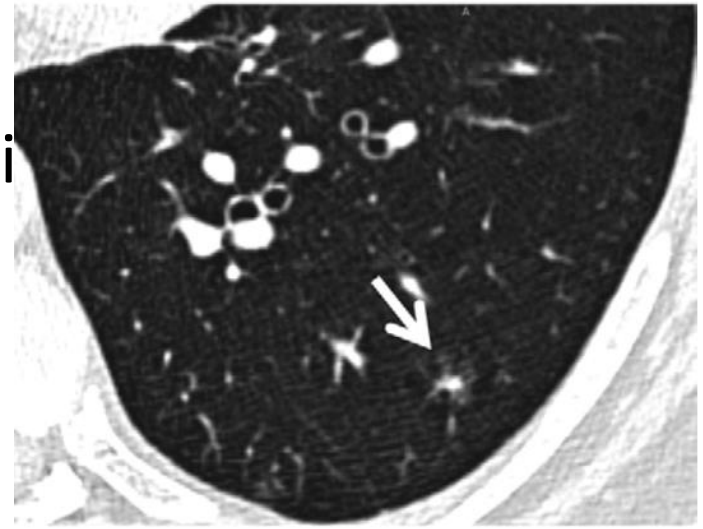
- 58 anos, ex-tabagista
- Achado incidental de nódulos pulmonares
- Biopsia de ambos = adenocarcinoma
- PET negativo no mediastino
- Sem metas a distância



Caso clínico

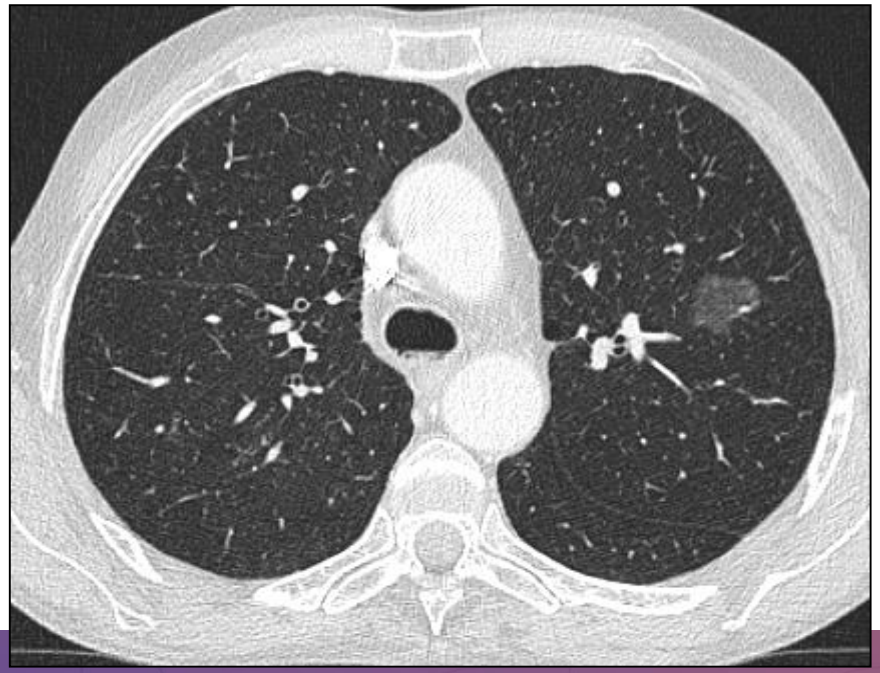
- Mulher de 55 anos, assintomática, tabagista de 3(
- Consulta com pneumologista.
- TC tórax de baixa dose (rastreamento)
- Lesão em vidro fosco de 1,0 cm em LSE
- Controle em 12 meses = 1,0 cm, componente sóli



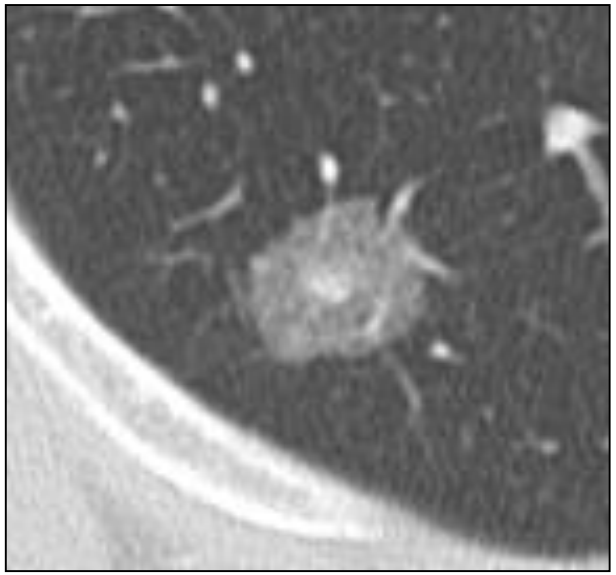


Definição

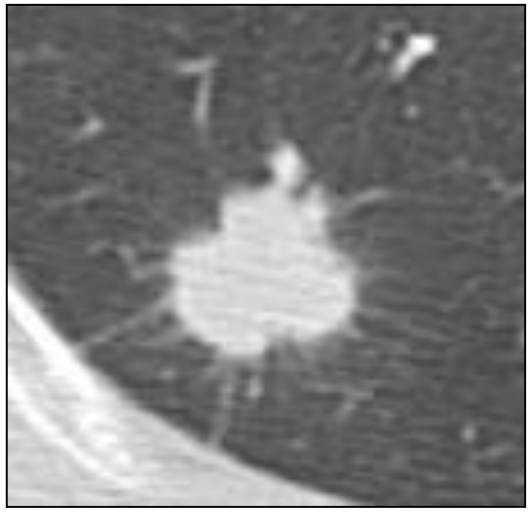
- Opacidade em “vidro despolido” (”GGO”) - puro
- Área do pulmão com atenuação aumentada, porém sem perder definição das estruturas broncovasculares
- < 3,0 cm

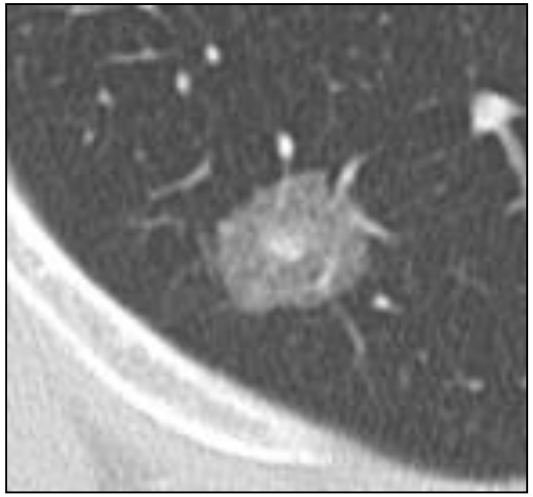


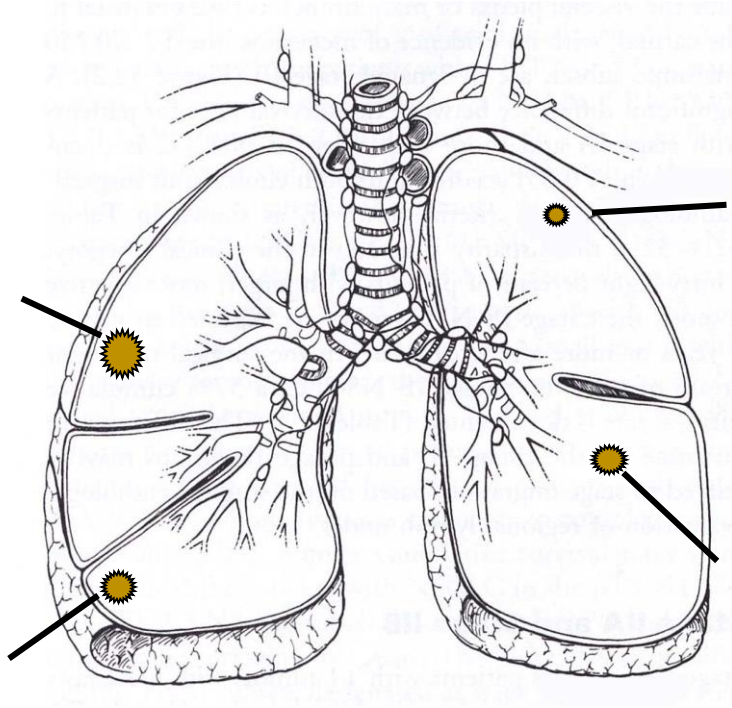
Rastreamento + Aumento do Número de Exames de Imagem (Tomografias)

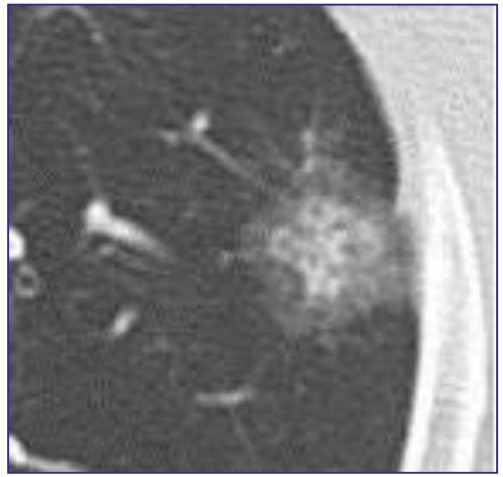


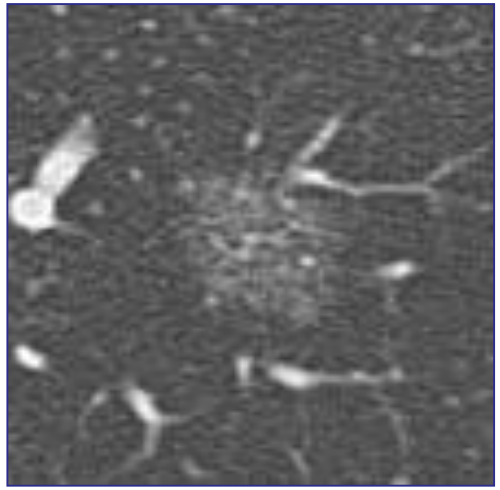
Tumores Subsólidos Pequenos











8,36% dos paciente terão um novo tumor primário em 10 anos

Han, S et al. JCO, 2017

Distinção entre dois primários

- Histologia diferente
- Aparência radiológica
- Captação no PET
- Biomarcadores
- Taxa de crescimento
- Doença nodal ou não
- Doença extratorácica ou não
- Discussão multidisciplinar

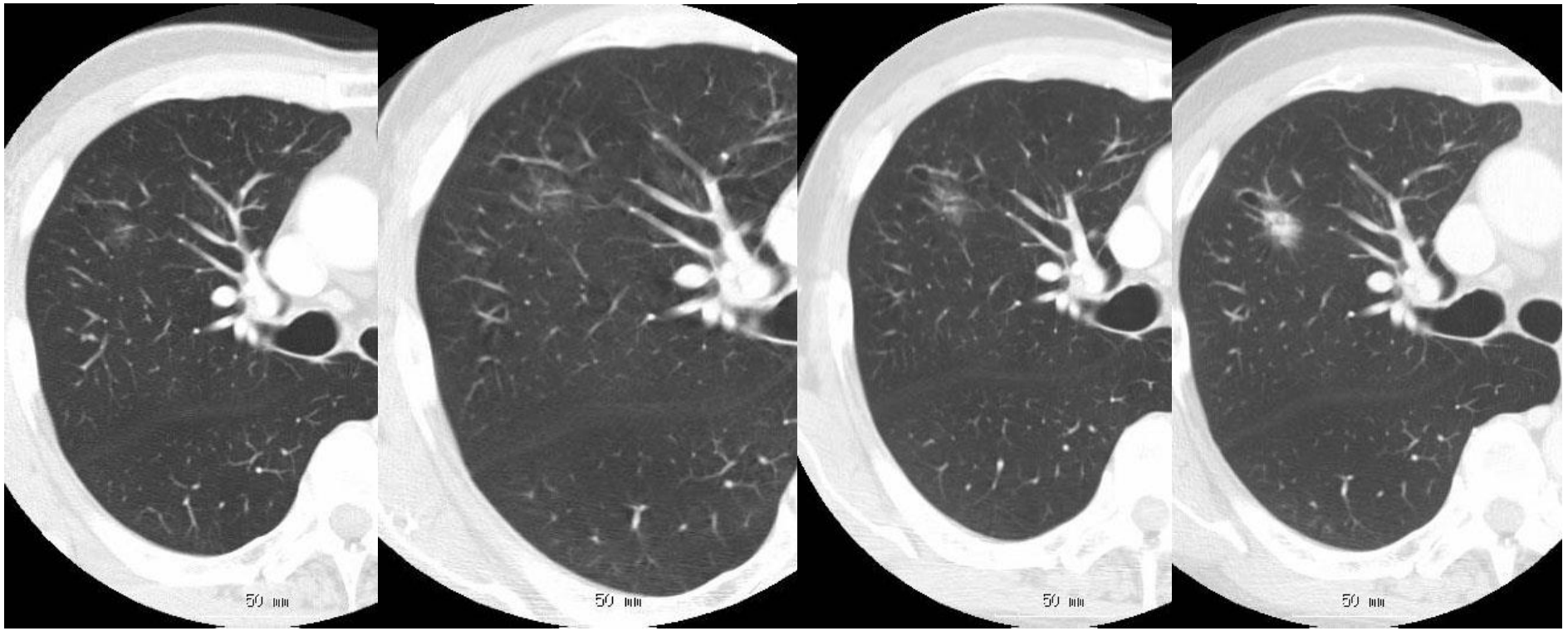
Table 1. Criteria to Distinguish Second Primary versus Related Tumors

Clinical criteria[a]
Tumors may be considered second primary tumors if They are clearly of a different histologic type (e.g., squamous carcinoma and adenocarcinoma) by biopsy.
Tumors may be considered to be arising from a single tumor source if Exactly matching breakpoints are identified by comparative genomic hybridization.
Relative arguments that favor separate tumors Different radiographic appearance or metabolic uptake Different biomarker pattern (driver gene mutations) Different rates of growth (if previous imaging is available) Absence of nodal or systemic metastases
Relative arguments that favor a single tumor source Same radiographic appearance Similar growth patterns (if previous imaging is available) Significant nodal or systemic metastases Same biomarker pattern (and same histotype)

Detterbeck FC, et al. J Thorac Oncol 2016; 11:639-650.

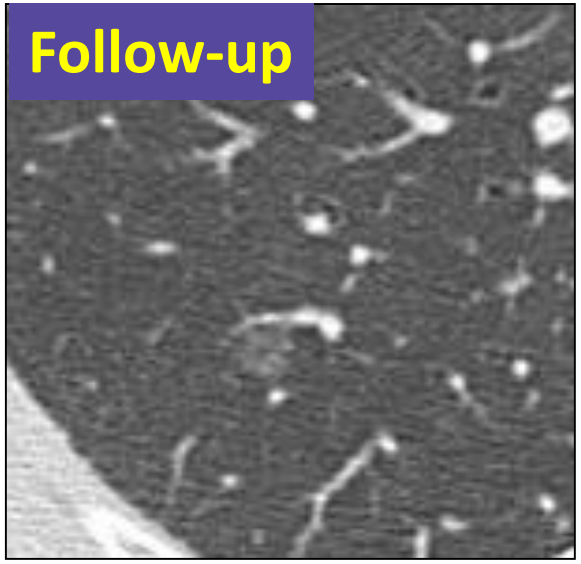
Evolução das opacidades em "vidro despolido" / Adenocarcinomas

1 ano | 2 anos | 3 anos



Os dilemas...

Follow-up



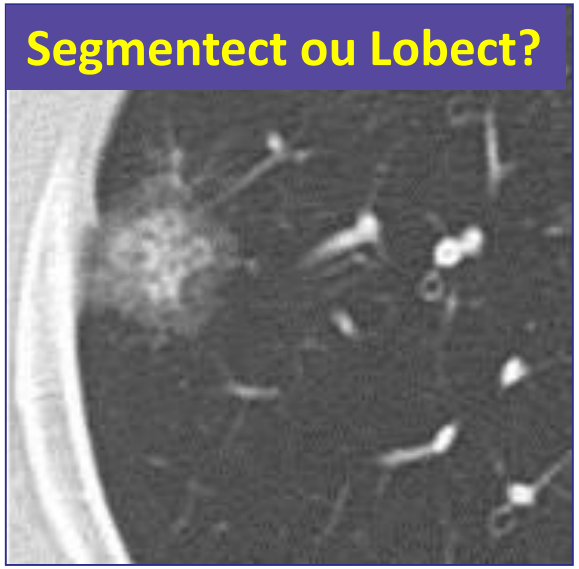
Follow-up ou Cirurgia?



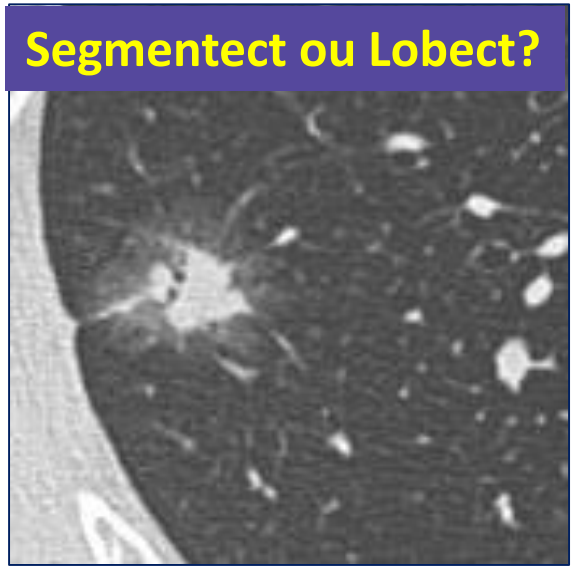
Cunha ou Segmentect?



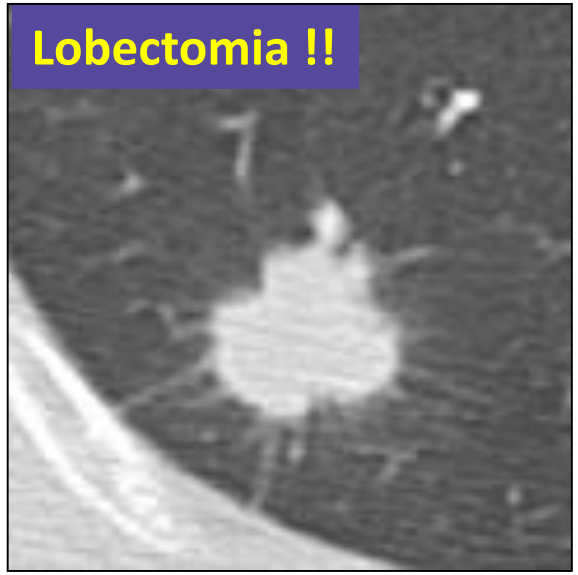
Segmentect ou Lobect?



Segmentect ou Lobect?



Lobectomia !!

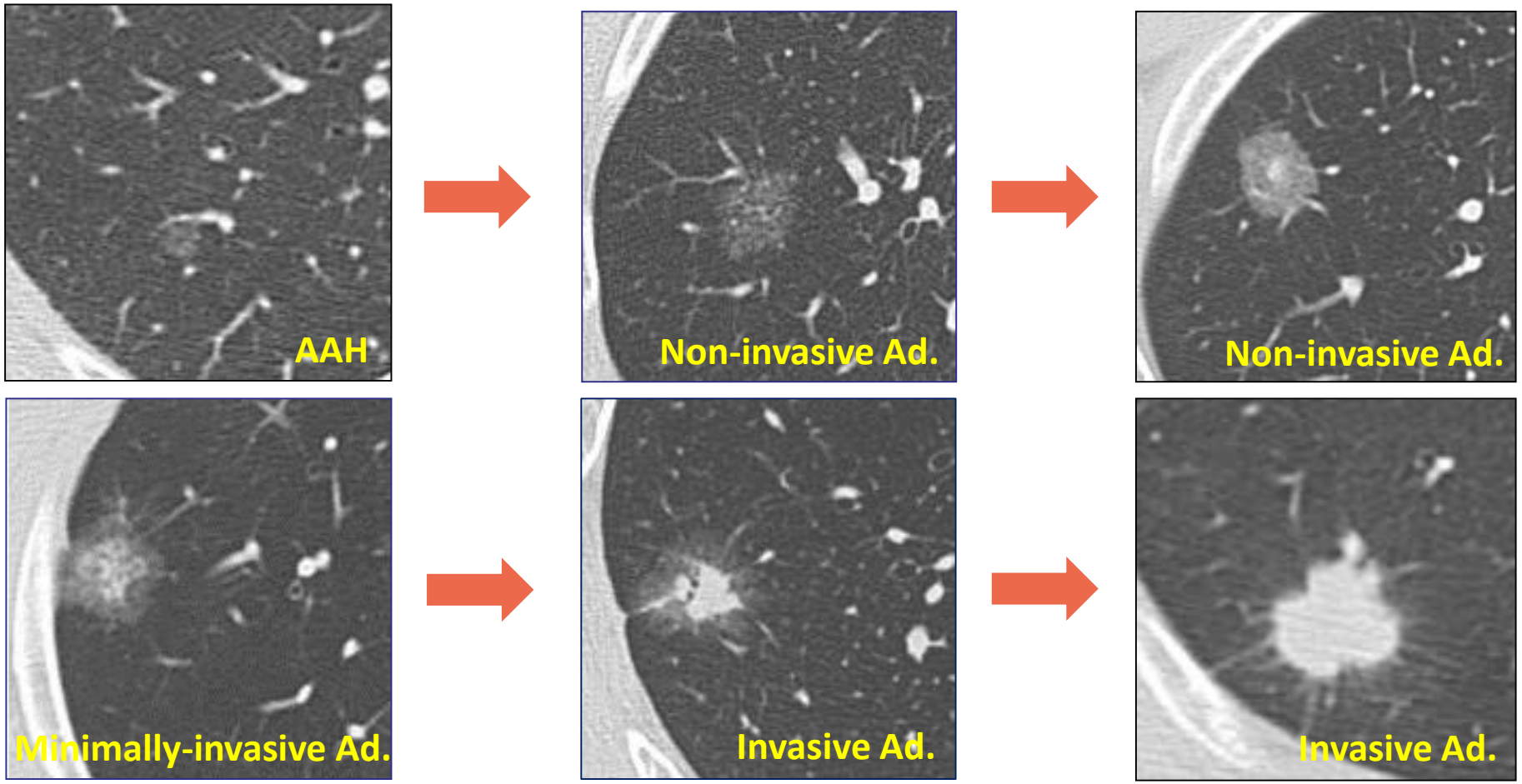


Watanabe SI, IASLC 2018.

Slides de backup

Lesões Pulmonares Subsólidas

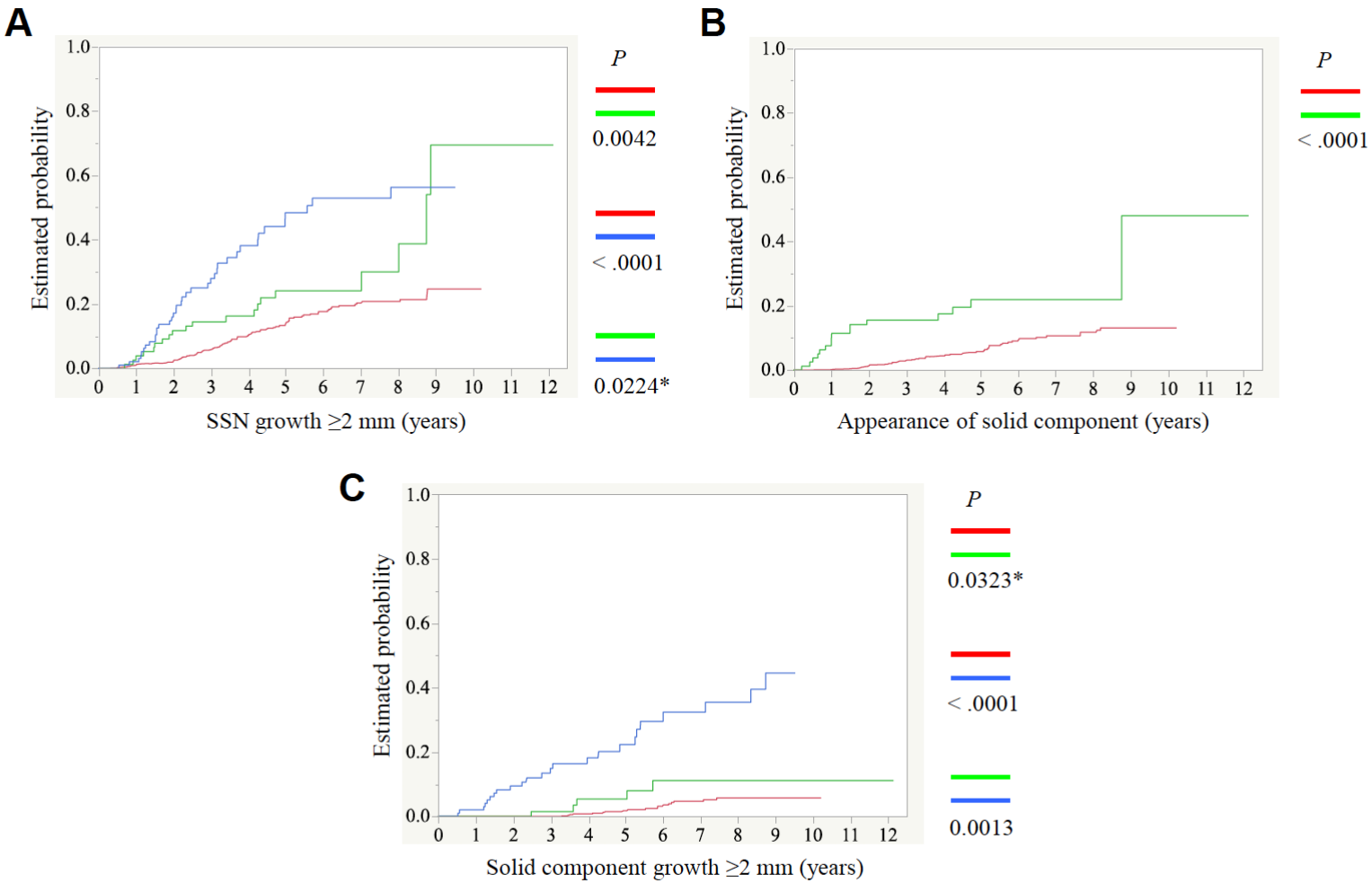
Hiperplasia Adenomatosa Atípica (AAH) → Adenocarcinoma Invasivo



Watanabe SI, IASLC 2018.

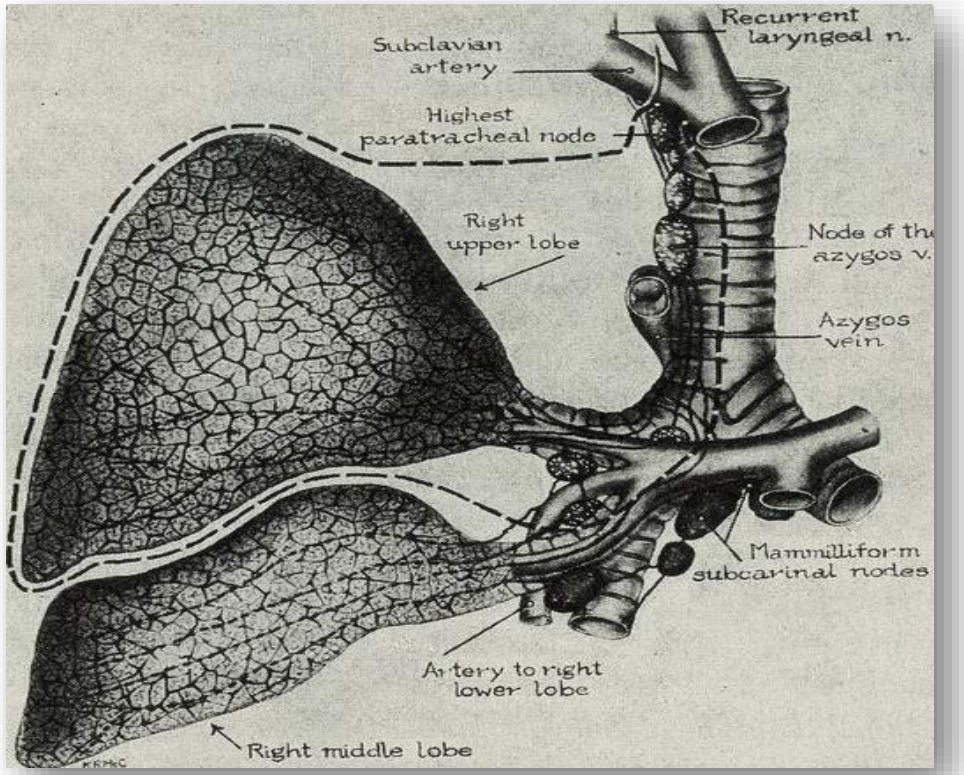
Curvas de Crescimento dos Nódulos Subsólidos

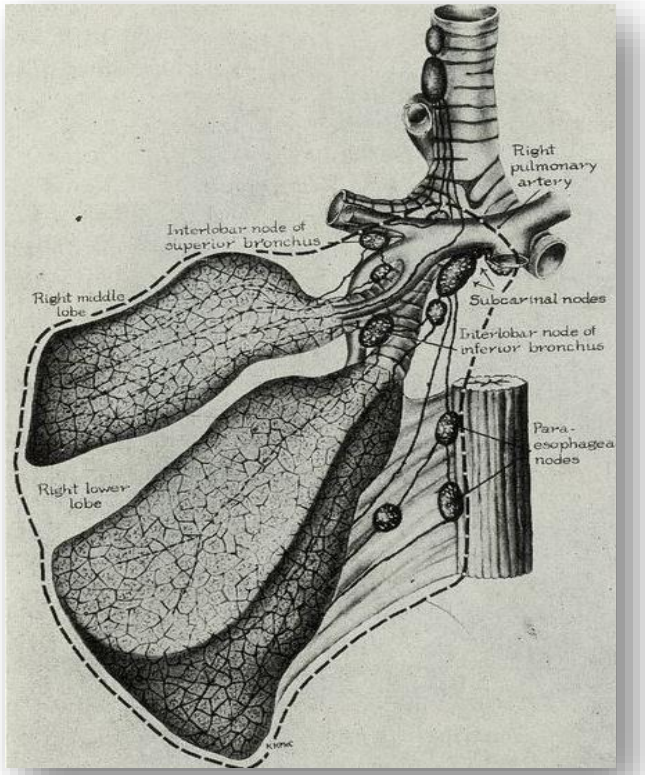
- Part-solid GGN
- Pure GGN
- Hetero GGN



Parceria: AstraZeneca

"Lobectomia Radical":
Lobectomia com Dissecção Linfonodal





Cahan WG. JTCVS 1960;39:555-572.

Segmental resection for lung cancer

A fifteen-year experience

Robert J. Jensik, M.D., L. Penfield Faber, M.D., Frank J. Milloy, M.D. (by invitation), and David O. Monson, M.D. (by invitation), Chicago, Ill.

Sobrevida em 5 anos: 56%

Taxa de recidiva local: 10%

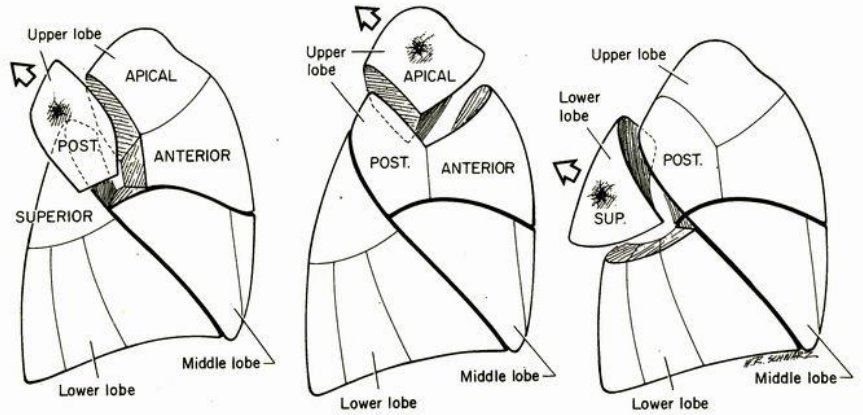


Fig. 1. Segmental resections in right lung. Upper lobe: posterior and apical. Lower lobe: superior.

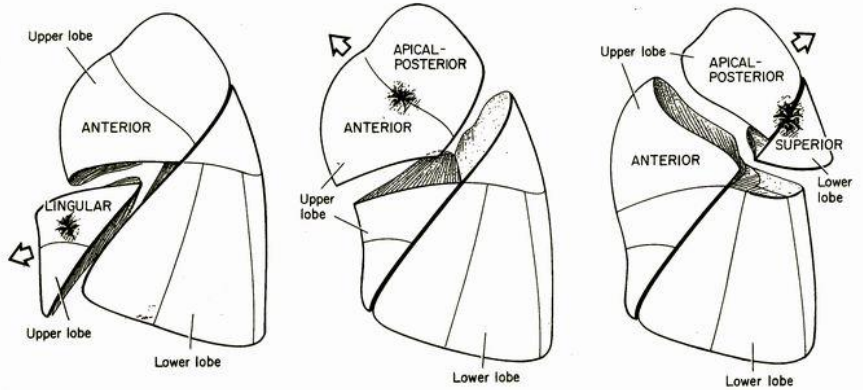
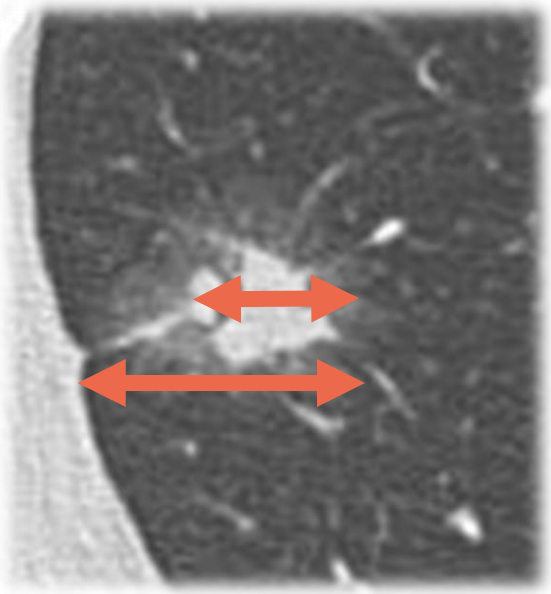


Fig. 2. Segmental resections in left lung. Upper lobe: Lingula and superior division. Combined apical posterior, left upper and superior, and left lower lobe.

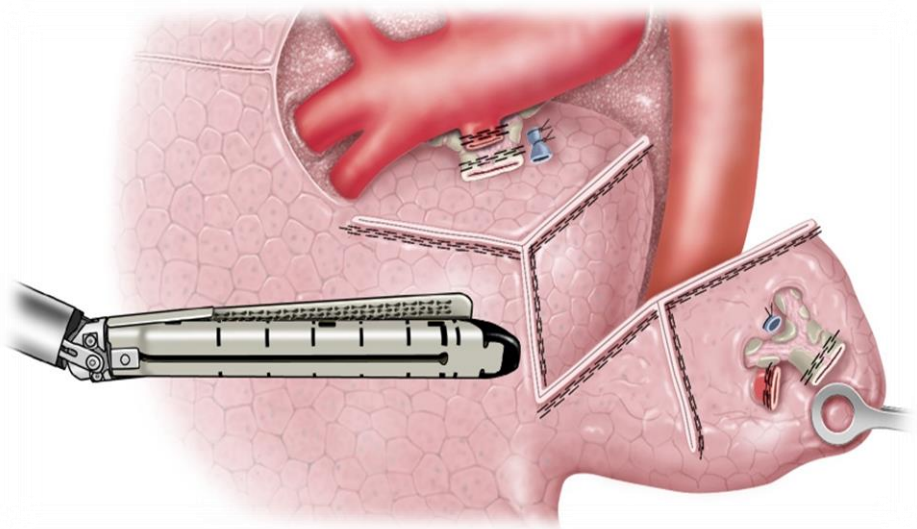
Cirurgia nos Tumores Subsólidos:
Lobectomia vs Sublobar

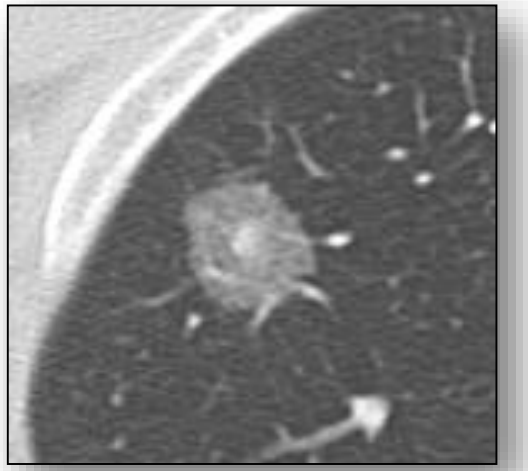
- Tipo de cirurgia baseado no tamanho e na relação consolidação/tumor (C/T)

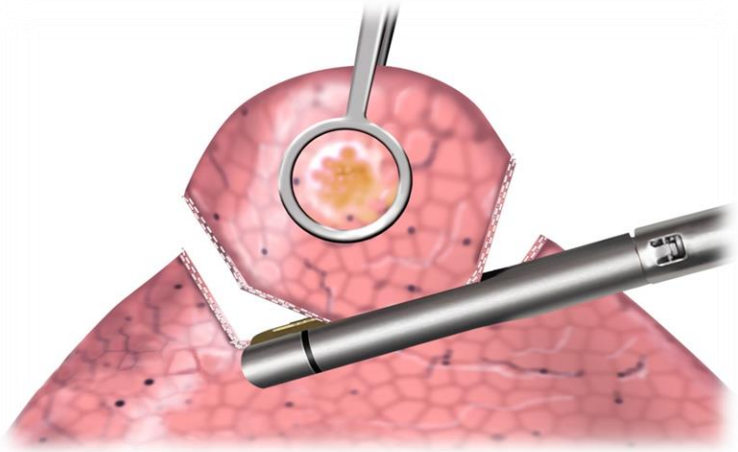


$$C/T = \frac{\text{Diâmetro Máximo da Consolidação}}{\text{Diâmetro Máximo do Tumor}}$$

Cirurgia Sublobar:
Segmentectomia vs Cunha
Ressecção Anatômica vs Não Anatômica





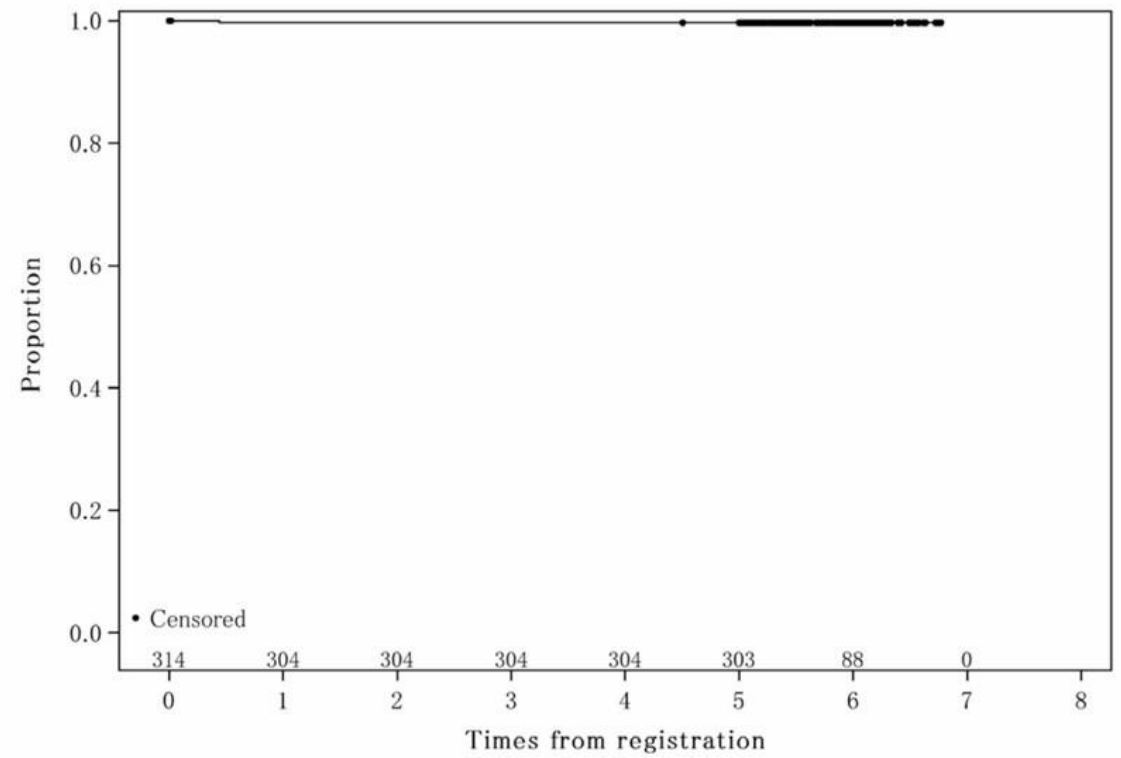


Watanabe SI, IASLC 2018.

JCOG0804

- Braço único, C/T <0,25
- Ressecção em cunha

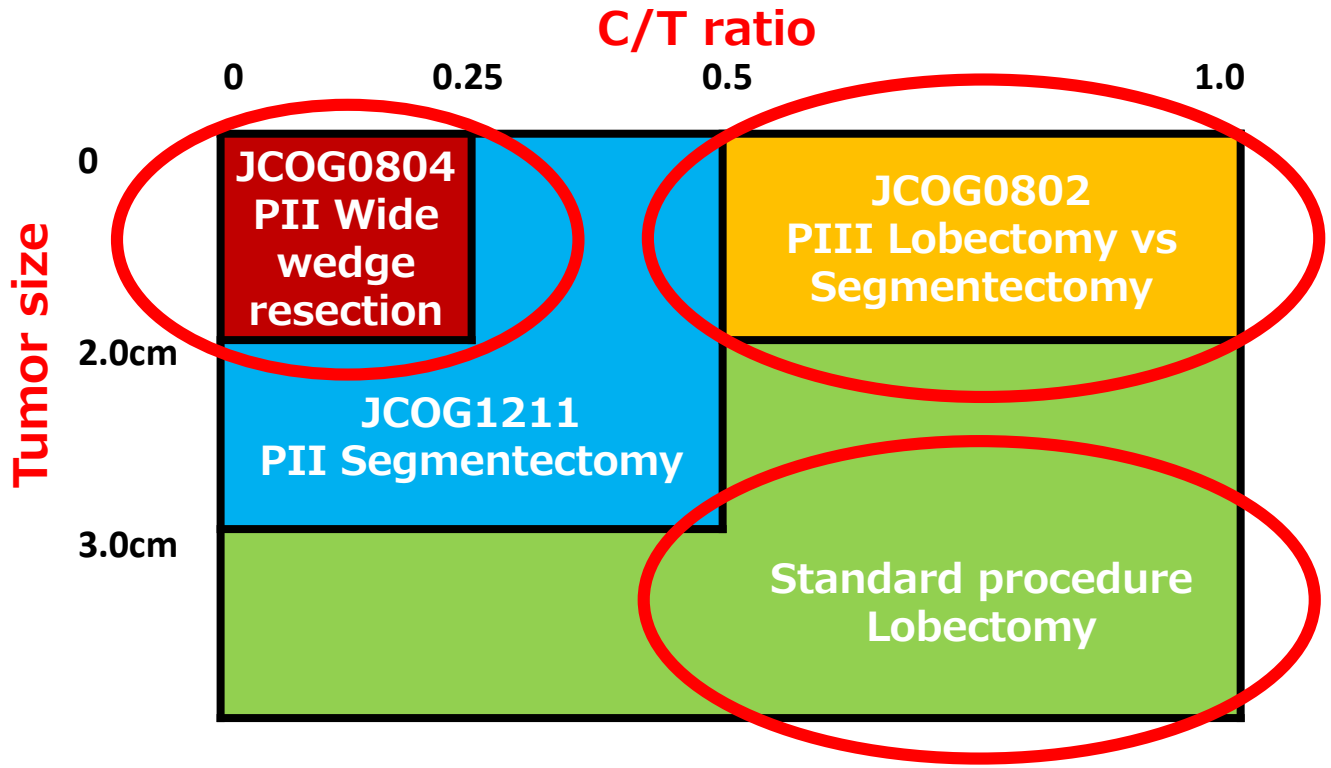
- Sobrevida livre de recorrência em 5 anos = **99.7%** (desfecho primário atingido)
- **Não houve recorrência local**.



”Non-anatomic wedge resection should be applied only for **non-invasive tumor** with C/T <0.25”.

Suzuki K, et al. ASCO 2017

Estudo Prospectivo em Andamento – Japão



JCOG
Japan Clinical Oncology Group

Watanabe SI, IASLC 2018.

Estudo Prospectivo em Andamento – EUA

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Find Studies | About Studies | Submit Studies | Resources | About Site

Home > Search Results > Study Record Detail

Save this study

Trial record **1 of 1** for: Altorki | sublobar resection | United States

Previous Study | Return to List | Next Study

Comparison of Different Types of Surgery in Treating Patients With Stage IA Non-Small Cell Lung Cancer

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

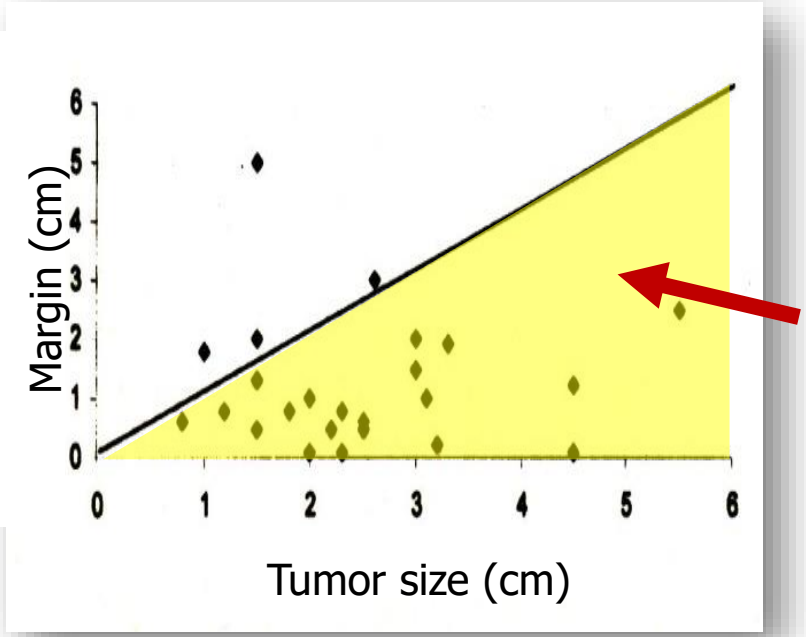
ClinicalTrials.gov Identifier: NCT00499330

Recruitment Status : Active, not recruiting
First Posted : July 11, 2007
Last Update Posted : May 28, 2018

Sponsor:
Alliance for Clinical Trials in Oncology

Collaborator:
National Cancer Institute (NCI)

O que é considerada margem adequada na ressecção sublobar?



♦ Recurrent cases after segmentectomy

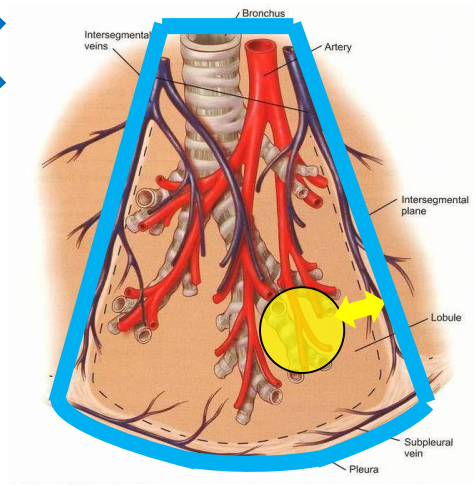
Surgical margin < tumor diameter
was associated with a higher rate of recurrence

Schuchert MJ, et al. Ann Thorac Surg 2007; 84:926-933.

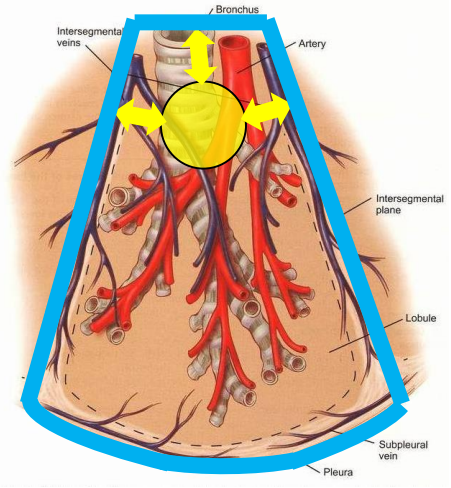
Lesões Pulmonares Subsólidas

Margem cirúrgica deve ser > diâmetro doTumor

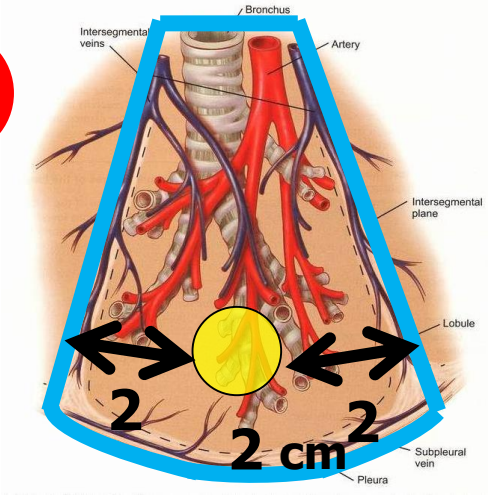
✖



✖



O



= 6 cm

Classificação para múltiplos nódulos pulmonares IASLC 2016

Table 5. Schematic Summary of Patterns of Disease and TNM Classification of Patients with Lung Cancer with Multiple Pulmonary Sites of Involvement

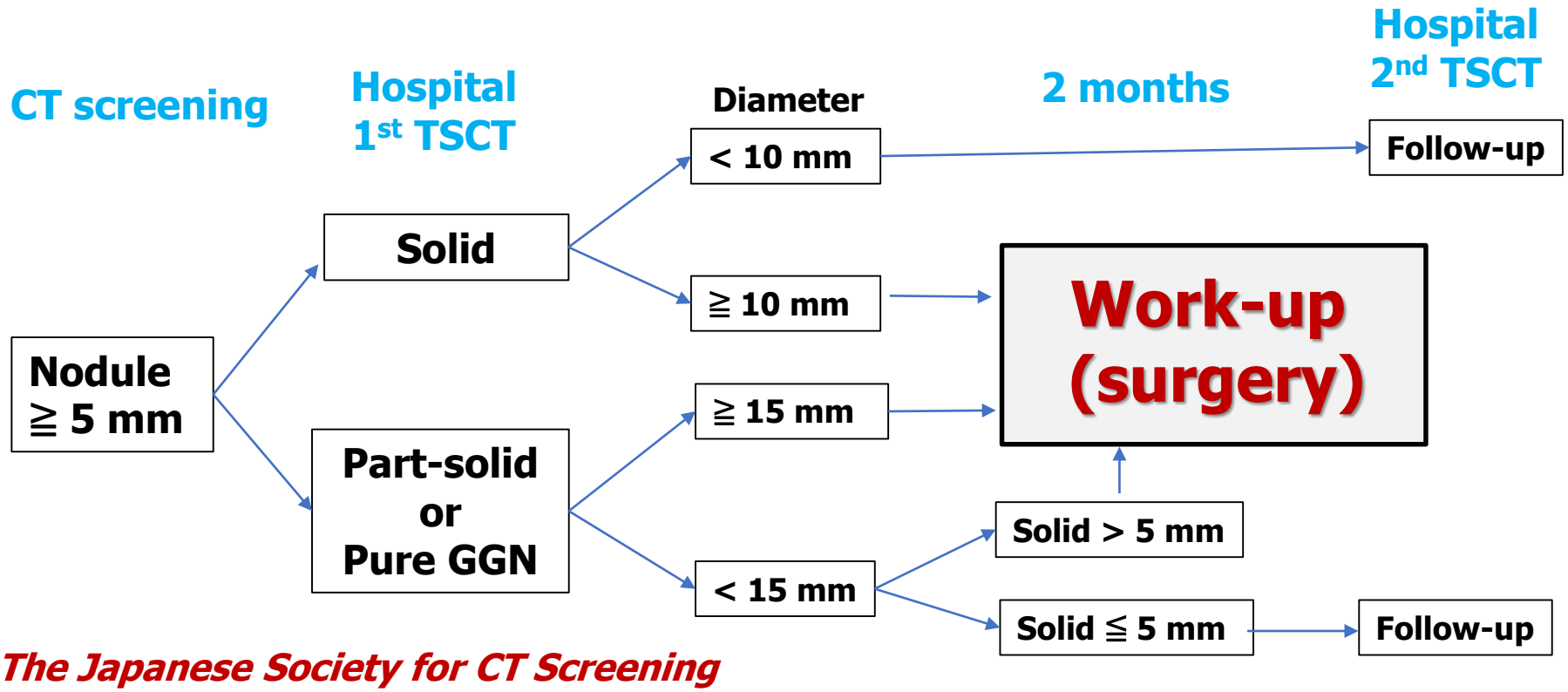
	Second Primary Lung Cancer	Multifocal GG/L Nodules	Pneumonic-Type Adenocarcinoma	Separate Tumor Nodule
Imaging features	Two or more distinct masses with imaging characteristic of lung cancer (e.g., spiculated)	Multiple ground glass or part-solid nodules	Patchy areas of ground glass and consolidation	Typical lung cancer (e.g., solid, spiculated) with separate solid nodule
Pathologic features	Different histotype or different morphologic features by comprehensive histologic assessment	Adenocarcinomas with prominent lepidic component (typically varying degrees of AIS, MIA, LPA)	Same histologic features throughout (most often invasive mucinous adenocarcinoma)	Distinct masses with the same morphologic features by comprehensive histologic assessment
TNM classification	Separate cTNM and pTNM for each cancer	T based on highest T lesion with (#/m) indicating multiplicity; single N and M	T based on size or T3 if in single lobe, T4 or M1a if in different ipsilateral or contralateral lobes; single N and M	Location of separate nodule relative to primary site determines if T3, T4, or M1a; single N and M
Conceptual view	Unrelated tumors	Separate tumors, albeit with similarities	Single tumor, diffuse pulmonary involvement	Single tumor, with intrapulmonary metastasis

AIS, adenocarcinoma in situ; c, clinical; GG/L, ground glass/lepidic; LPA, lepidic-predominant adenocarcinoma; MIA, minimally invasive adenocarcinoma; p, pathological; TNM, tumor, node, and metastasis.

Detterbeck FC, et al. J Thorac Oncol 2016; 11:639-650.

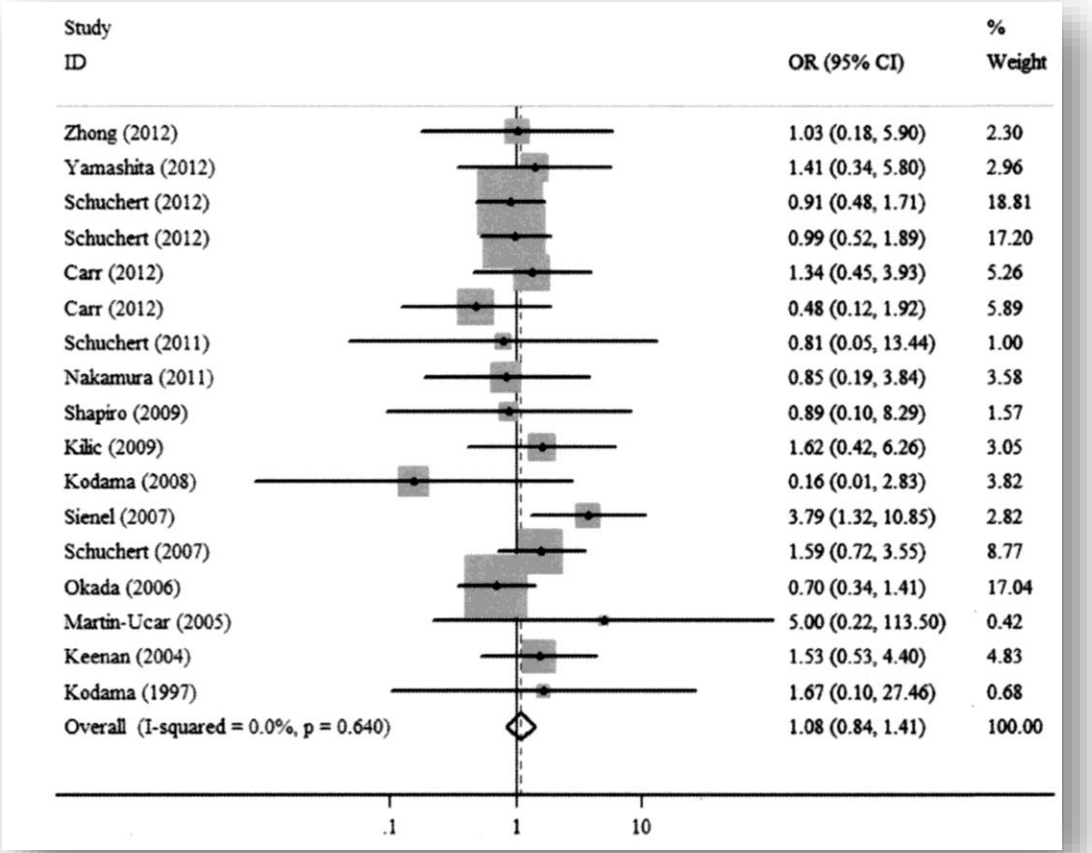
Figure 1. Representative examples of four patterns of disease that manifest multiple pulmonary sites of lung cancer. (*A*) Second primary cancers. A patient with two primary lung cancers in the RUL. CT images of each in the left two panels; corresponding microscopic images showing an adenocarcinoma and a squamous carcinoma in the next two panels. Note that most second primary cancers are of the same (not a different) histologic type. (*B*) Separate tumor nodules. A patient with a separate tumor nodule of the same histotype as the index tumor. The left panels show CT images of each lesion; the right panels show the corresponding microscopic images. (*C*) Multifocal GG/L lung cancer. A patient with multifocal GG/L tumors in the right upper lobe (who had other GG/L tumors in other lobes). Arrows point to two GG/L tumors on CT in the left two panels; the next two panels show corresponding microscopic images (both were adenocarcinoma with a prominent lepidic component, although with different other adenocarcinoma subtypes). These tumors are classified together as GG/L tumors regardless of such secondary differences. (*D*) Pneumonic-type lung cancer. A patient with pneumonic-type lung cancer (this patient also had focal sites of disease in the RLL). The left panels show CT images of the RUL and RML with the typical regional areas with a ground glass and consolidative appearance; the next panels show the corresponding microscopic images. Adeno, adenocarcinoma; CT, computed tomography; GG/L tumors, tumors with prominent ground glass (imaging) or lepidic (histologic) features; MIA, minimally invasive adenocarcinoma; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; Squam, squamous cell carcinoma.

Guidelines for the Management of Pulmonary Nodules Detected by Low-Dose CT Lung Cancer Screening



Watanabe SI, IASLC 2018.

Segmentectomy vs Lobectomy: Local Recurrence Risk – c-stage IA

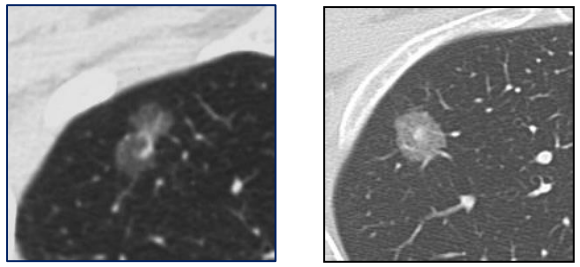


- Meta-Analysis
- 16 reports
- N= 4,658 patients
- OR=1.08 (95% CI: 0.84-1.41, p=0.54)

Zhang L, et al. Ann Thorac Surg 2015;99: 728-37.

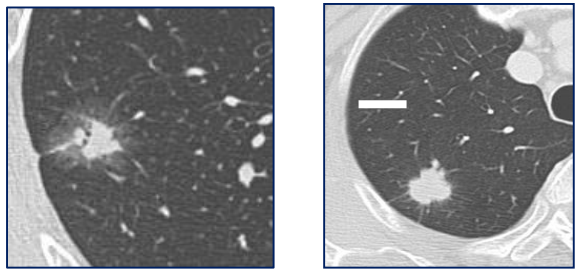
Ongoing SR Trials for Small-Sized (≤2 cm) NSCLC in Japan

JCOG0804: 0%<Solid<25%



→ **One-arm, wide wedge resection (phase II)**

JCOG0802: 50%<Solid<100%

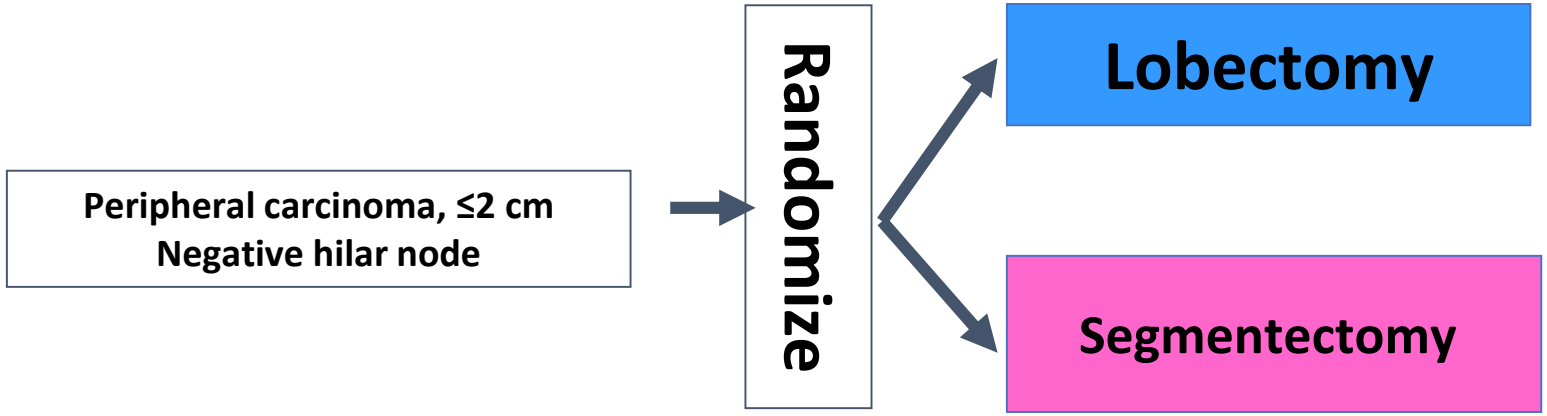


→ **Lobectomy vs. Segmentectomy (phase III)**

JCOG
Japan Clinical Oncology Group

JCOF0802

Phase III Randomized Trial between Lobectomy and Segmentectomy for Part-solid GGO – Solid disease



Non-inferiority design

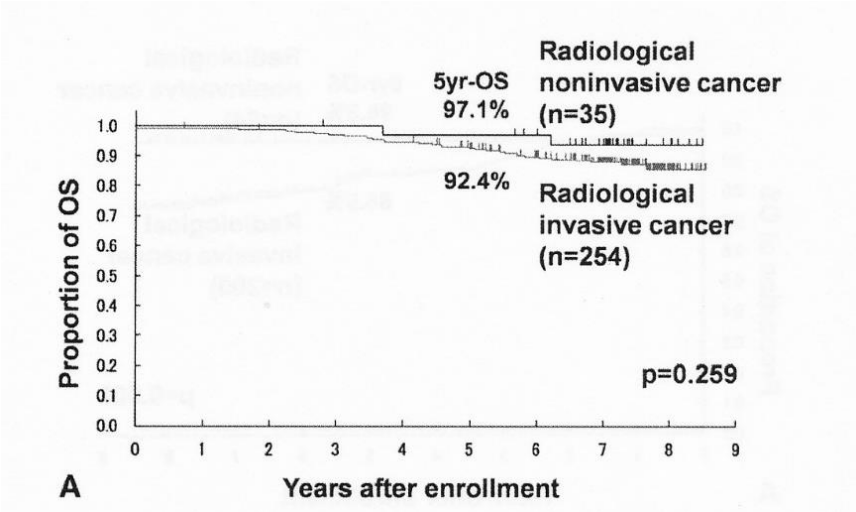
Endpoints:
Primary: OS
Secondary: pulmonary function
Sample size: 1,100

JCOG
Japan Clinical Oncology Group

Segmentectomy of the small segment (S1-3, S8-10) for solid-dominant tumor (C/T ratio >0.5) should be avoided whenever possible.

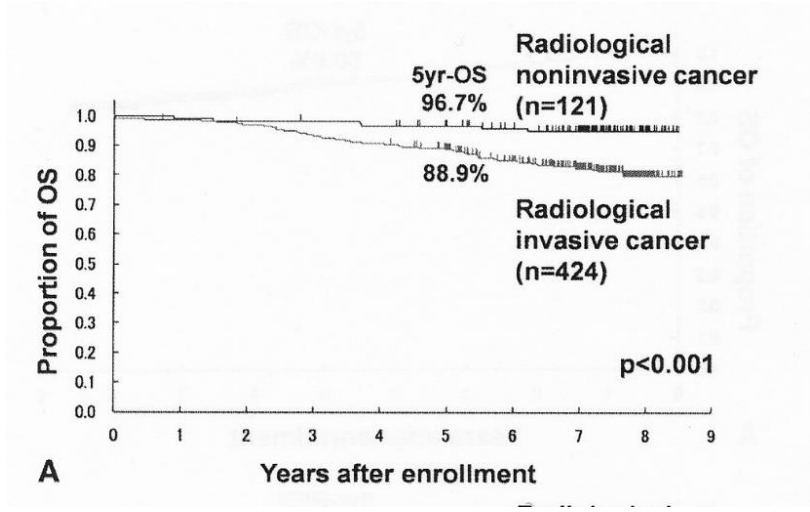
Survival Outcomes of JCOG0201

C/T ratio < 0.25, D ≤ 2cm (T1a)



5y-OS 97.1%

C/T ratio < 0.5, D ≤ 3cm (T1a + T1b)



5y-OS 96.7%

Asamura H, et al. J Thorac Cardiovasc Surg 2013; 146:24-30.

A Beneficência
Portuguesa
de São Paulo

Parceria:

AstraZeneca