Pure and part-solid GGNs, Is early surgical treatment needed?

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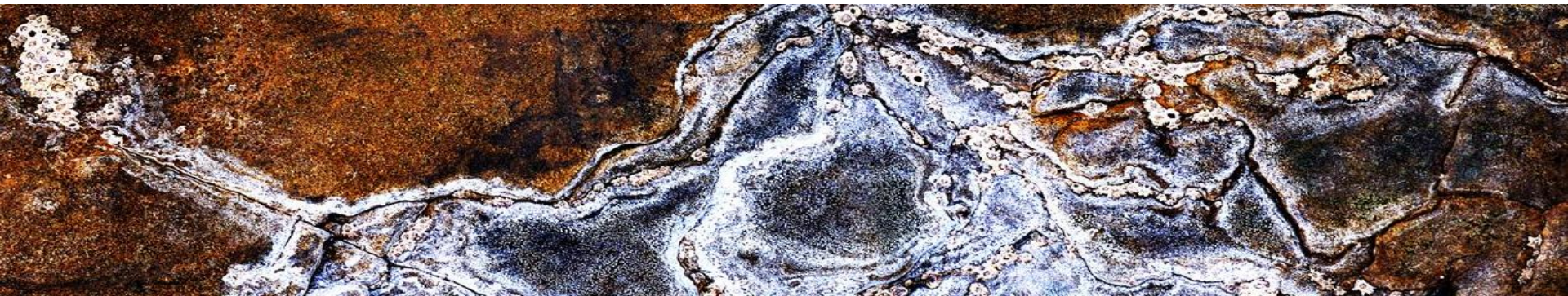
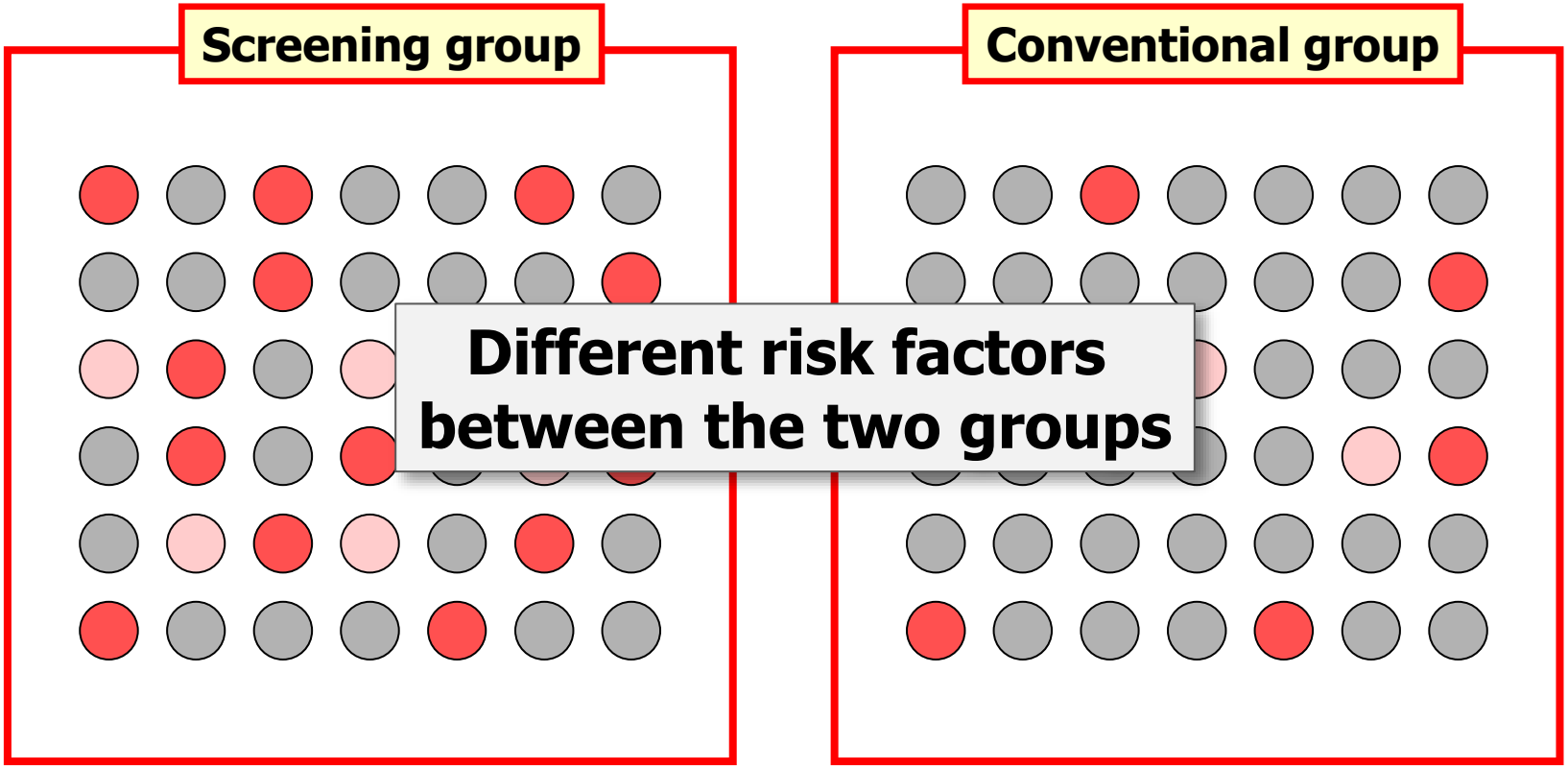
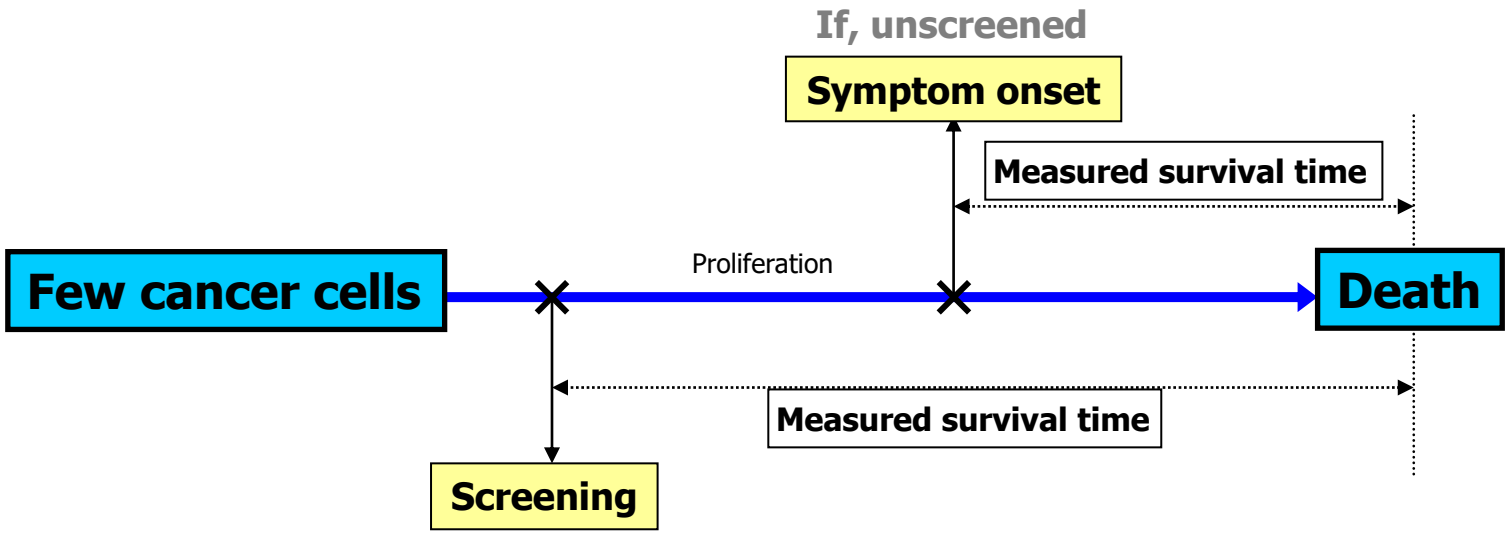


Selection bias



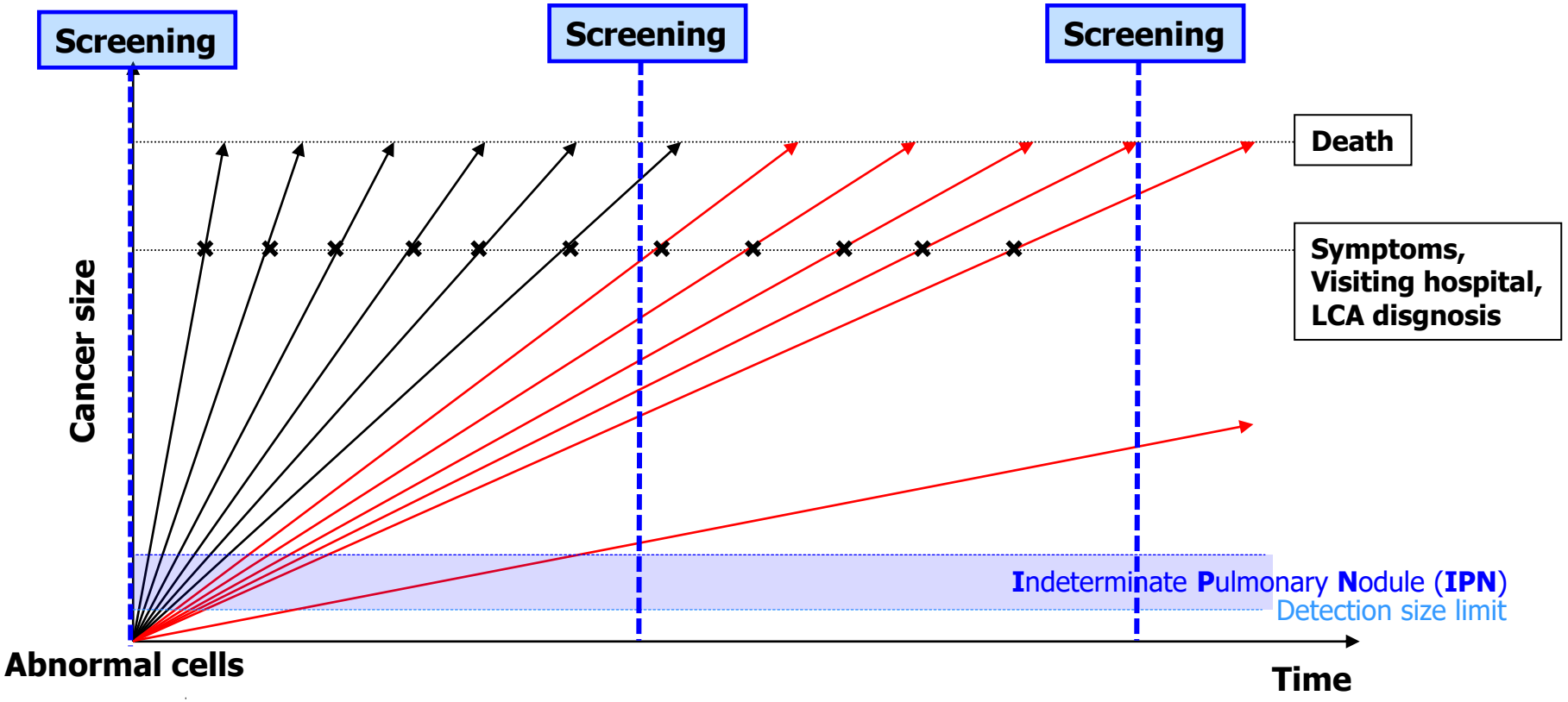
Studies have shown that people who attend screening tend to be healthier than those who do not. This has been called the "**healthy screenee effect**"

Lead time bias



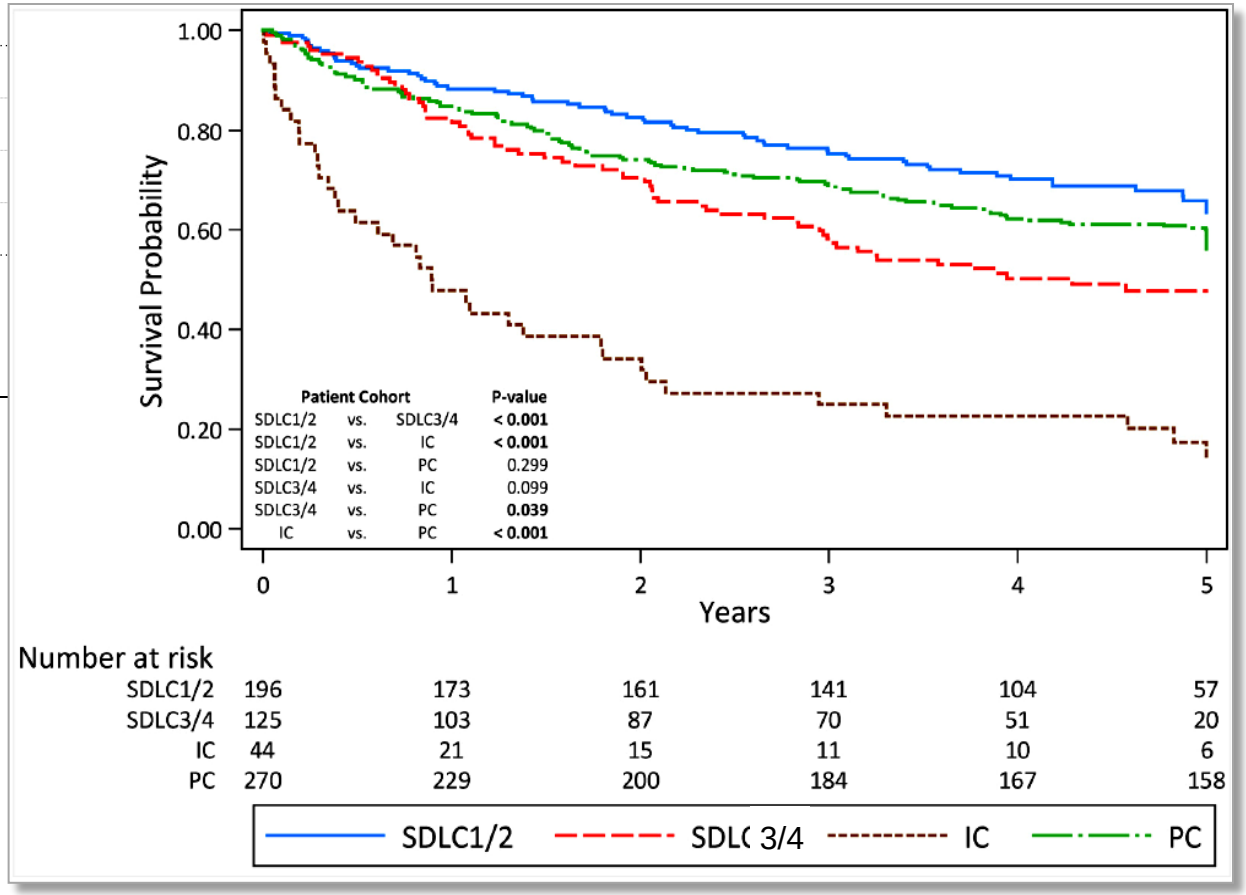
Length time bias

"Screening에서 진단되는 폐암은 상대적으로 성장속도가 느린 것들이다"



Differences in patient outcomes of Prevalence, Interval, and Screen-Detected Lung Cancers in the CT arm of the NLST

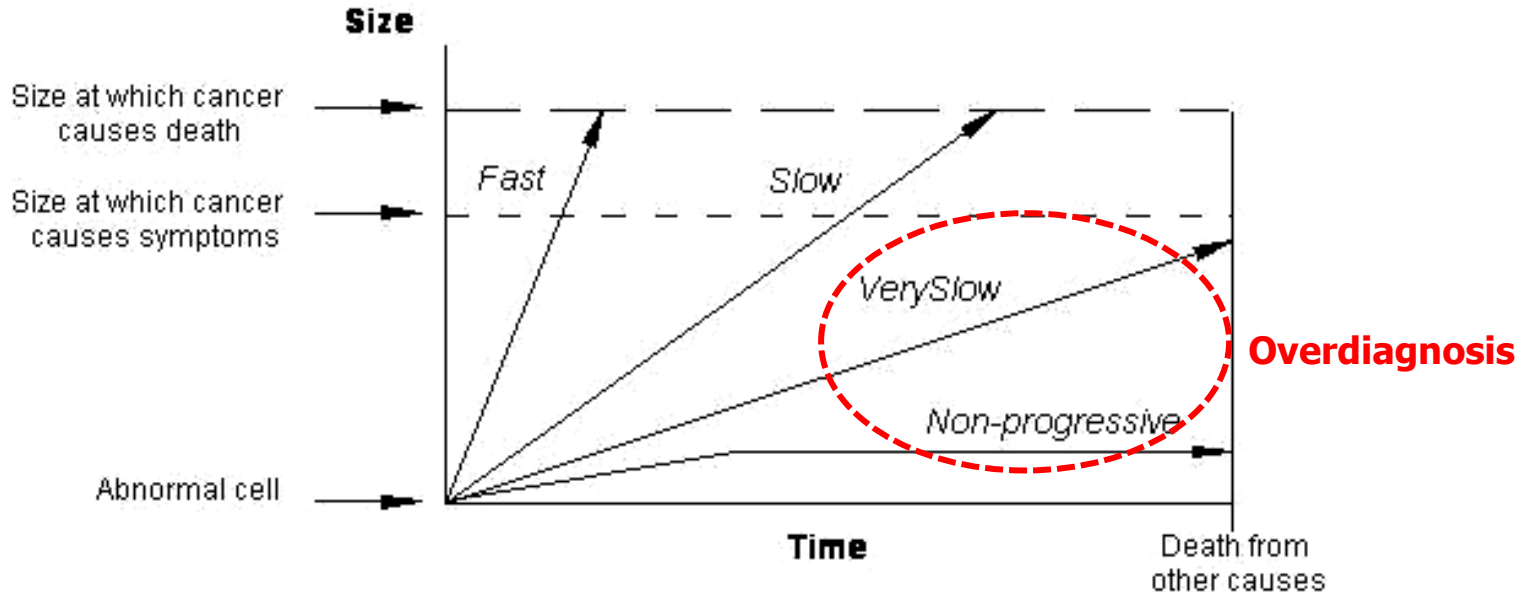
Definition		T0	T1	T2
Prevalence LC				
Screen-**D**etected **LC**	**SDLC1**			
	SDLC2			
	SDLC3			
	SDLC4			
Interval LC				



Schabath MB, et al. PLoS One. 2016;11:e0159880

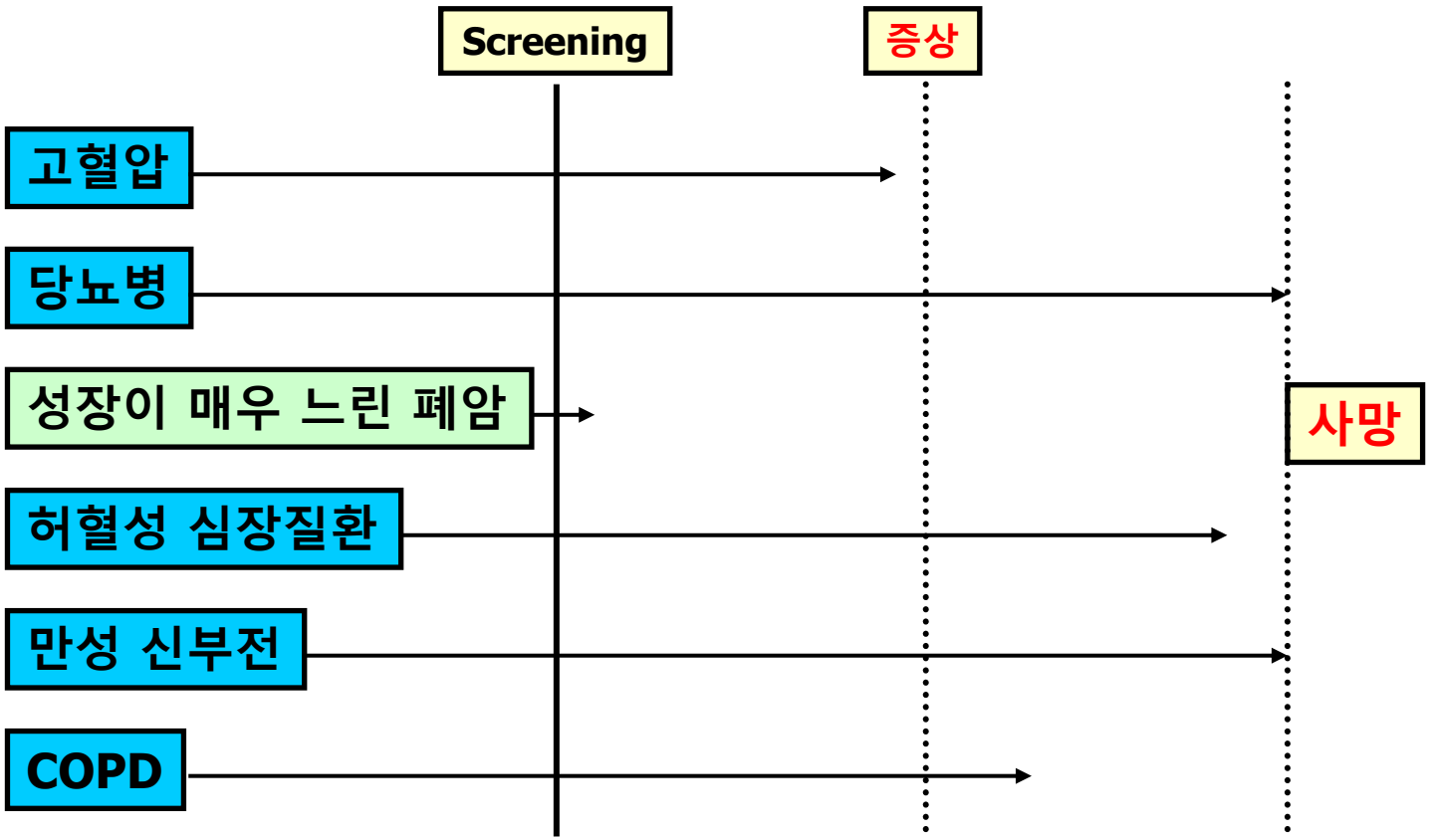
Overdiagnosis bias

Overdiagnosis is the diagnosis of "disease" that will **never cause symptoms** **or** **death** **during a patient's ordinarily expected lifetime.**



Welch HG, et al. J Natl Cancer Inst. 2010;102:605-13
https://commons.wikimedia.org/wiki/File:Overdiagnosis1.jpg

Overdiagnosis bias



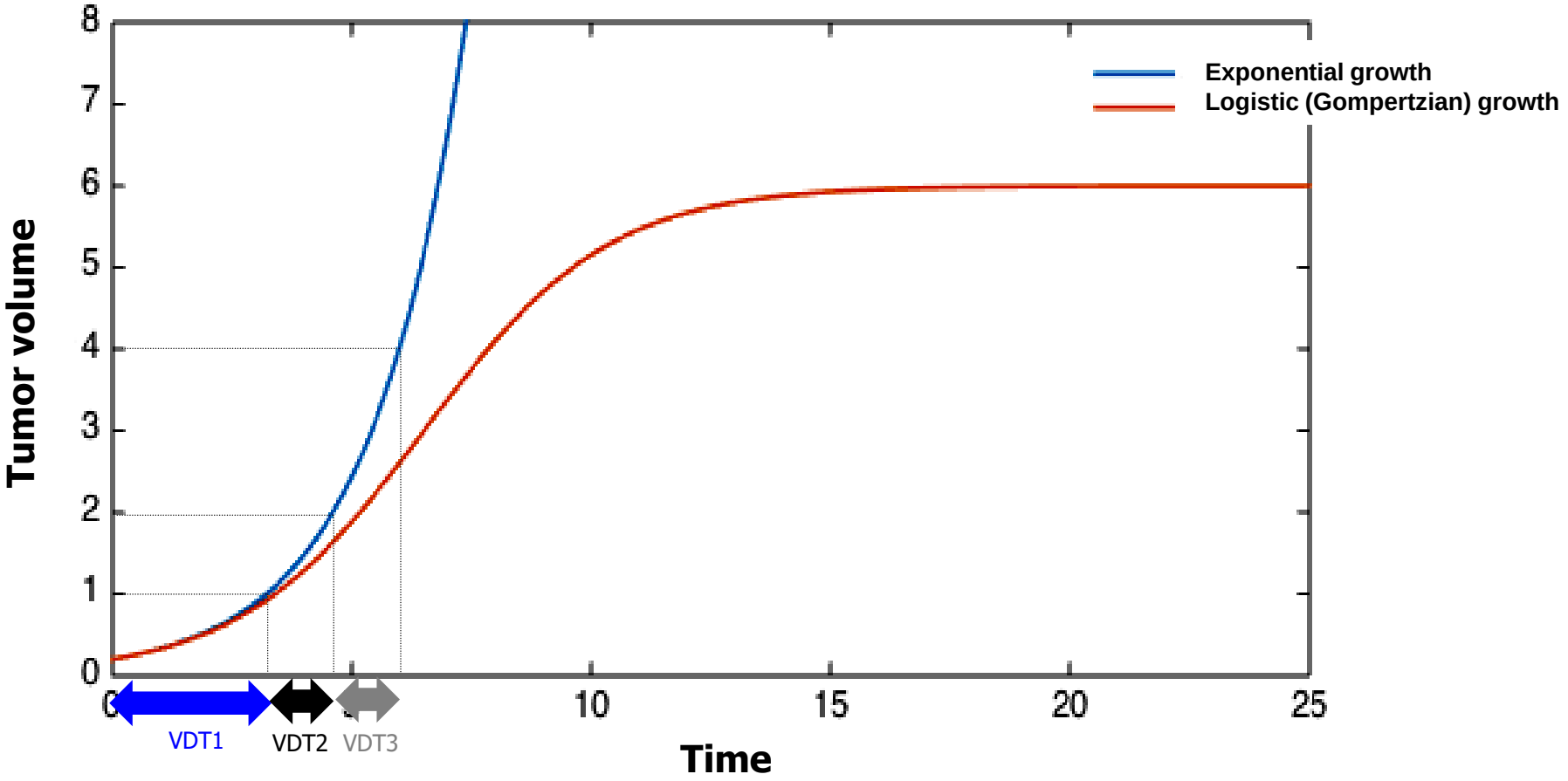
Growth rate (Doubling time)

Doubling time	Time required for a nodule to **double in volume**
	Volume doubling = **26% increase in diameter**
	The predictive value for benignity of 2-year stability = 65%*
	Doubling time of many malignant lesions are between 30-400 days
Exceptions of 2-year stability rule	
	Low-grade malignancy: typical carcinoid tumor
	Adenocarcinoma in situ (AIS)
	Very small lung nodule
Technical problem in the measurement of small nodule	
	High resolution CT
	3D volumetric software

*Yankelevitz DF, Henschke CI. AJR Am J Roentgenol. 1997;168:325-8

Cancer cell growth model

Exponential vs. Gompertzian growth model



Volume-doubling time of pulmonary nodules with ground glass opacity at multidetector CT

Retrospective analysis of **47 GGO nodules** detected by thin-section helical CT in Japan
Assessment with **computer-aided 3D-volumetry**

	AAH	BAC	AC
Nodules (patients)	13 (9)	22 (20)	12 (10)
Patient sex			
Male	6	6	3
Female	7	16	9
Mean age (year)	58.8 ± 13.1	63.9 ± 9.0	67.4 ± 6.1
GGO subtype			
Pure-GGO	13	14	1
Mixed-GGO	0	8	11
Mean maximum diameter (mm)	10.1 ± 3.2	13.3 ± 5.6	13.4 ± 4.6
Mean CT attenuation (HU)	−614.5 ± 98.4	−611.4 ± 123.0	−323.3 ± 210.7
Mean interval between two CT scans (days)	331.6 ± 436.9	123.9 ± 118.5	85.9 ± 39.8

AAH, atypical adenomatous hyperplasia; BAC, bronchioloalveolar carcinoma; AC, adenocarcinoma.

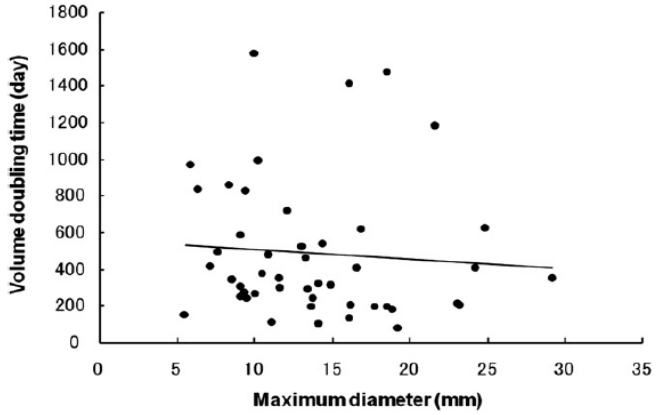


Figure 5. Graph showing the correlation between the volume-doubling time (VDT) and the maximum diameter of ground glass opacity (GGO) nodules on the initial computed tomography scan. No correlation was found (r = -0.19, P = .19).

	Volume doubling time (VDT)	
AAH	859.2 ± 428.9 **days**	2.35 ± 1.18 **years**
BAC	421.2 ± 228.4 **days**	1.15 ± 0.63 **years**
AC	202.1 ± 84.3 **days**	0.55 ± 0.23 **years**
pGGN	628.5 ± 404.2 **days**	1.72 ± 1.11 **years**
psGGN	276.9 ± 155.9 **days**	0.76 ± 0.42 **years**

Oda S, et al. Acad Radiol. 2011;18:63-9

Overdiagnosis in low-dose computed tomography screening for lung cancer

Study objective is to estimate overdiagnosis in the **N**ational **L**ung **S**creening **T**rial (**NLST**)

	Overdiagnosis, [95% CI] $P_S = \frac{\Delta \text{ LC patients (LDCT- CXR)}}{\text{LDCT screen detected LC patients}}$	Mean sojourn time **Pre-clinical phase**
All lung cancers	**18.5%** [5.4-30.6]	
All NSCLC, + BAC, + NOS	22.5% [9.7-34.3]	
All NSCLC, **- BAC**, + NOS	**11.7%** [-3.7-25.6]	3.6 yr [3.0-4.3]
BAC only	**78.9%** [62.2-93.5]	32.1 yr [17.3-270-7]

Patz EF Jr, et al. JAMA Intern Med. 2014;174:269-74

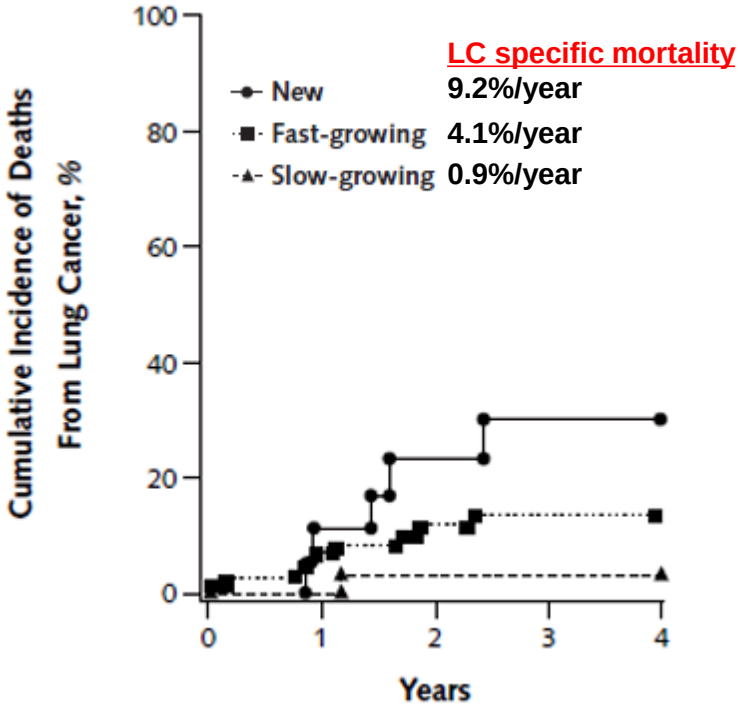
Estimating overdiagnosis in LDCT screening for lung cancer: COSMOS study

Nonrandomized single-center study in Italy, in 2004~2005; **N=5,203 (79.2% of adherence)**
Age ≥ 50 yr, smoking ≥ 20PY, current or ex-smoker (stop-smoking <10 years)
Annual LDCT for 5 years, structured follow-up schedule for patients with positive findings (≥5.1mm)

Cancer	**N**		mVDT*	**Case definition** by VDT	
Prevalent	55				
Incident	120	19	52d	**New**	
		70	223d	**Fast** growing	<400d
		18	495d	**Slow** growing	400~600d
		13	987d	**Indolent**	≥600d

*mVDT, median volume doubling time

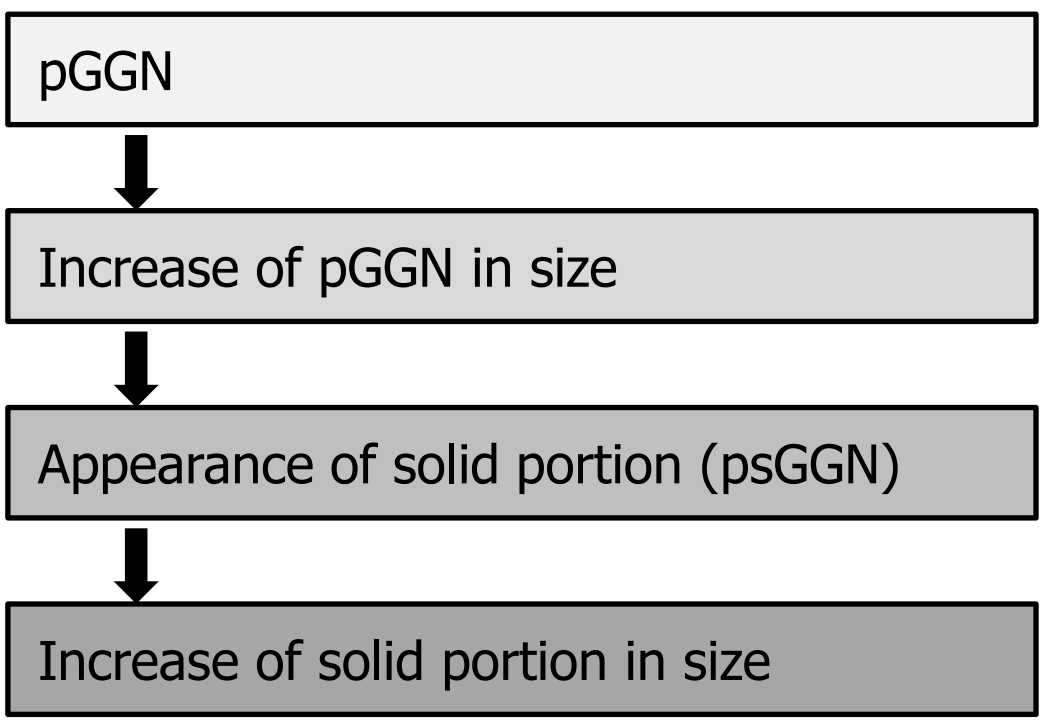
Overdiagnosis rate ≈ (18+13)/120 = **25.8%**

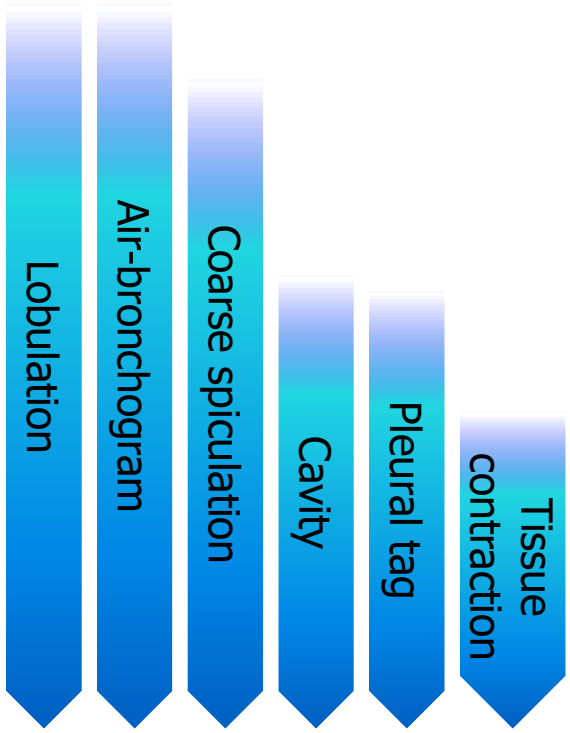


Veronesi G, et al. Ann Intern Med. 2012;157:776-84

CT findings and progression of small peripheral lung neoplasms having a replacement growth pattern

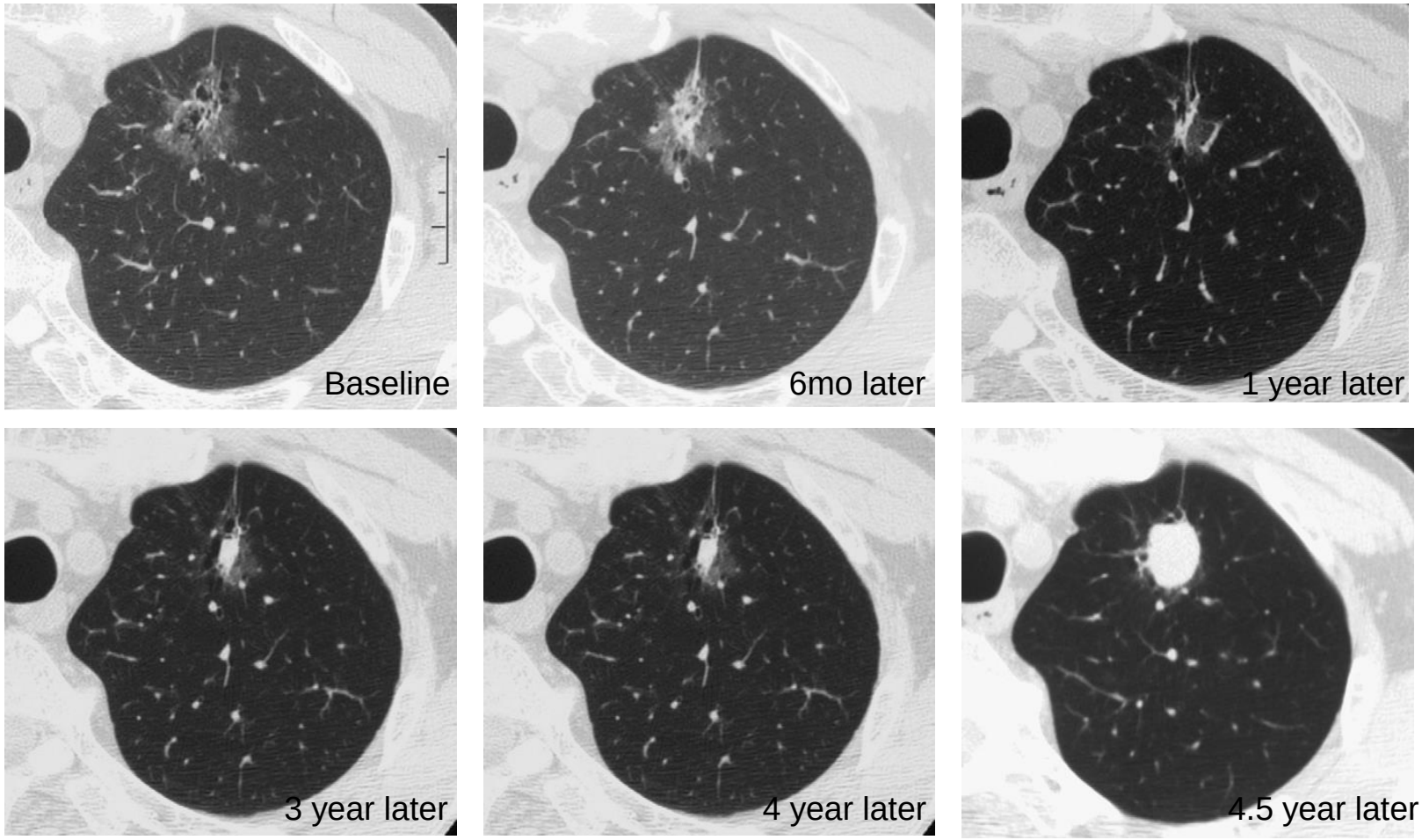
N = 62
GGN ≤ 20mm in serial chest CT
Pathologic confirmation
Retrospective analysis



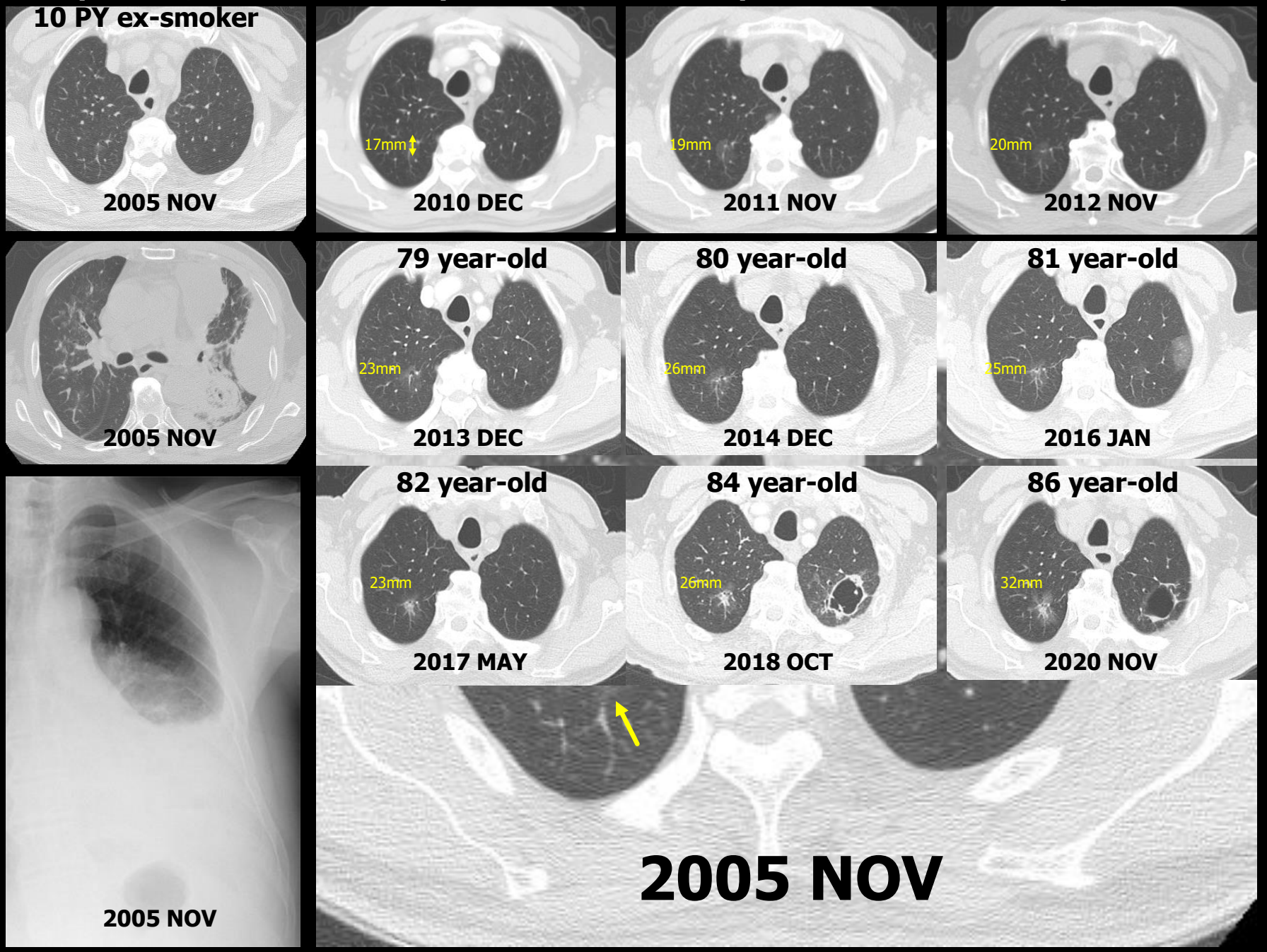


Takashima S, et al. AJR Am J Roentgenol. 2003;180:817-26

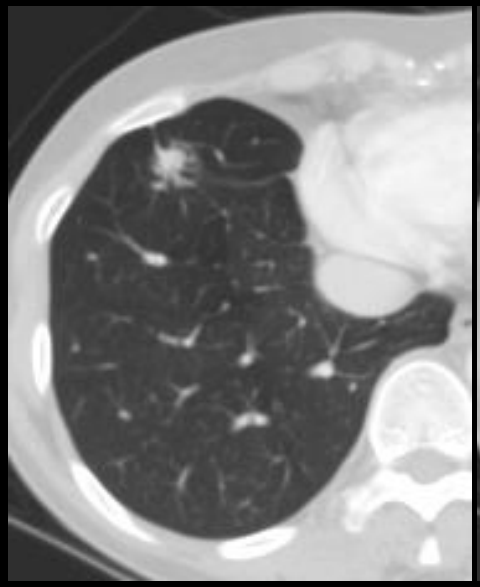
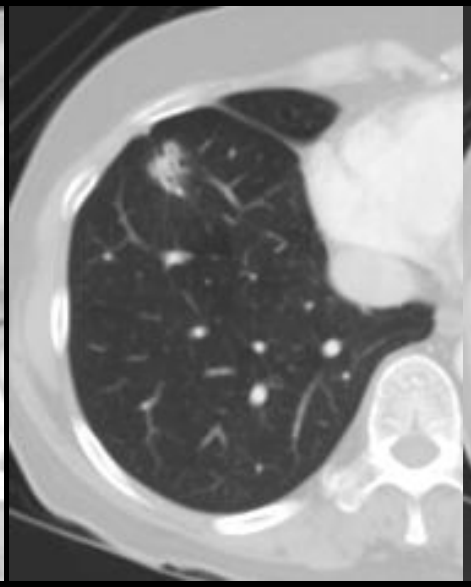
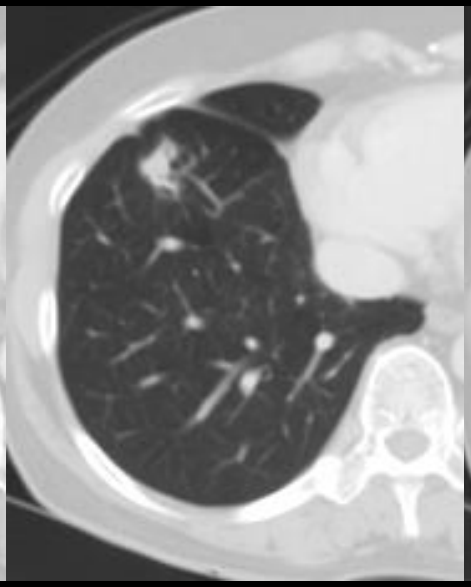
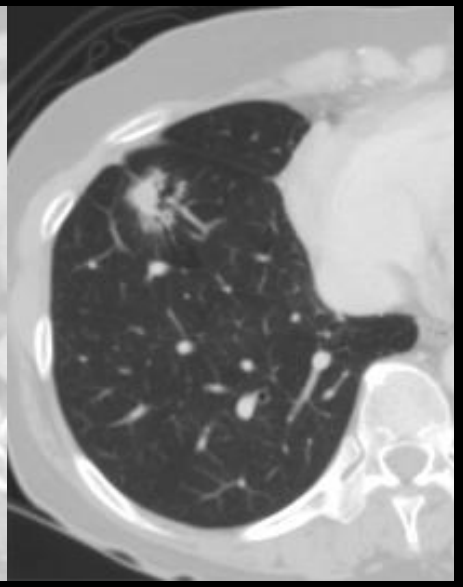
Stepwise progression from GGO towards invasive adenocarcinoma



Soda H, et al. Lung Cancer 2008;60:298-301


71 year-old, male
10 PY ex-smoker
2005 NOV
76 year-old
17mm
2010 DEC
77 year-old
19mm
2011 NOV
78 year-old
20mm
2012 NOV
2005 NOV
79 year-old
23mm
2013 DEC
80 year-old
26mm
2014 DEC
81 year-old
25mm
2016 JAN
2005 NOV
82 year-old
23mm
2017 MAY
84 year-old
26mm
2018 OCT
86 year-old
32mm
2020 NOV
2005 NOV

F/56, Incidentally detected lung nodule during breast cancer surgery

First detection #53 mo ago	#32 mo ago	#9 mo ago	At diagnosis
			
Small lobulated nodule Post-inflammatory change or lung cancer rec) Close F/U and PCNA, if necessary	No interval change	No interval change	Slightly increased size → R/O Lung cancer

ADC, RLLobectomy
pT1bN0M0, Stage IA

Long term follow-up of small pulmonary GGNs stable for 3 years: Implications of the proper follow-up period and risk factors for subsequent growth

453 GGNs (438 pGGNs and 15 mGGNs) in **218 patients**, year 2003-2015 from Bundang SNUH, Korea
Inclusion: After the initial 3-yr F/U, ① at least 5-yr F/U CT from the initial CT, ② op. for persistent GGN
Exclusion: Transient, resection or GGN growth within the initial 3 years, and systemic chemotherapy cases

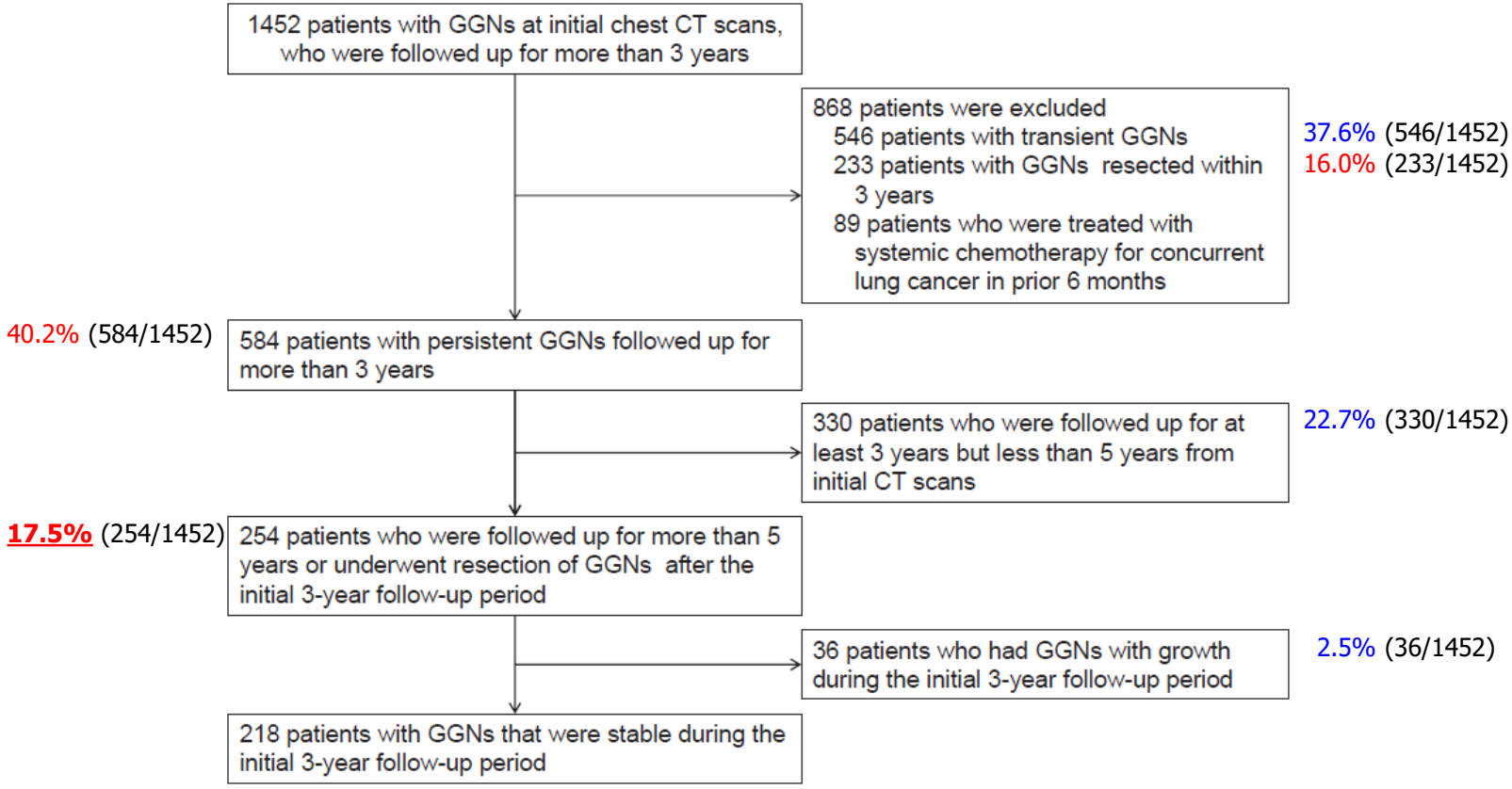


Figure 1. Flowchart of the study patients. GGN, ground-glass nodule; CT, computed tomography.

Cho J, et al. J Thorac Oncol. 2016;11:1453-9

Long term follow-up of small pulmonary GGNs stable for 3 years: Implications of the proper follow-up period and risk factors for subsequent growth

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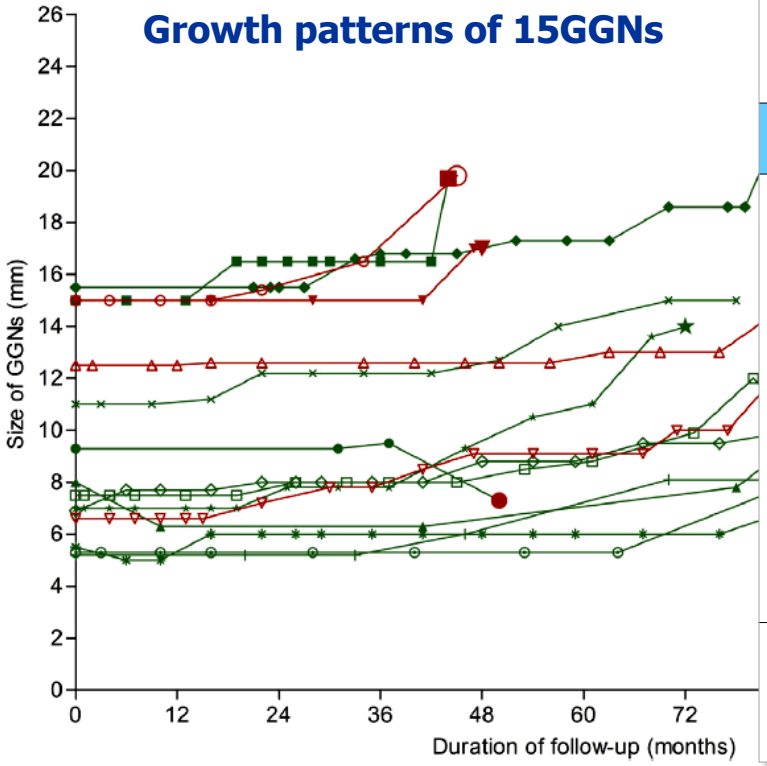
Inclusion: After the initial 3-yr F/U, ① at least 5-yr F/U CT from the initial CT, ② op. for persistent GGN
Exclusion: Transient, resection or GGN growth within the initial 3 years, and systemic chemotherapy cases
In **14**/218(**6.4%**) patients, **15**/453(**3.3%**) GGNs showed subsequent growth, median follow-up of 6.4 years



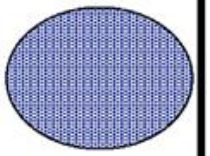
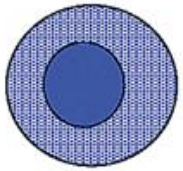
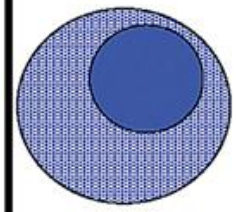
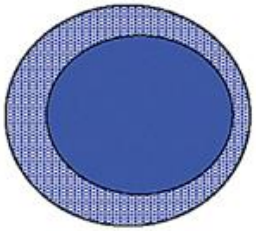
❖ **Risk factors*** of subsequent **growth†** **of GGNs**
that had been stable during the initial 3 years

Variables	aOR	95% CI	P-value
Age ≥ 65	5.51	[1.46-20.90]	0.012
History of **LCa**	6.44	[1.73-24.00]	0.006
Initial size ≥ 8mm	5.74	[1.58-20.92]	0.008
psGGN	16.58	[2.04-134.70]	0.009
Air bronchogram	5.83	[1.41-24.19]	0.015
Bubble lucency	9.88	[0.67-146.14]	0.096
Spiculated margin	4.36	[0.18-103.35]	0.362

* Multivariate analysis
† Definition of growth: GGN growth ≥2mm, solid part growth ≥2mm, or emerging new solid component in pGGN

Cho J, et al. J Thorac Oncol. 2016;11:1453-9

The IASLC lung cancer staging project: proposals for coding T categories for subsolid nodules in the 8th edition of the TNM classification

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					compnent	predominant AD	
	Pathologic Stage		pTis‡‡	pT1mi‡‡	pT1a	pT1b	pT1c

If, **pGGN > 3cm ➡ cT1a**
If, **psGGN** (total size **> 3cm**) ➡**T1a**, **T1b**, **T1c** depending on **solid part**

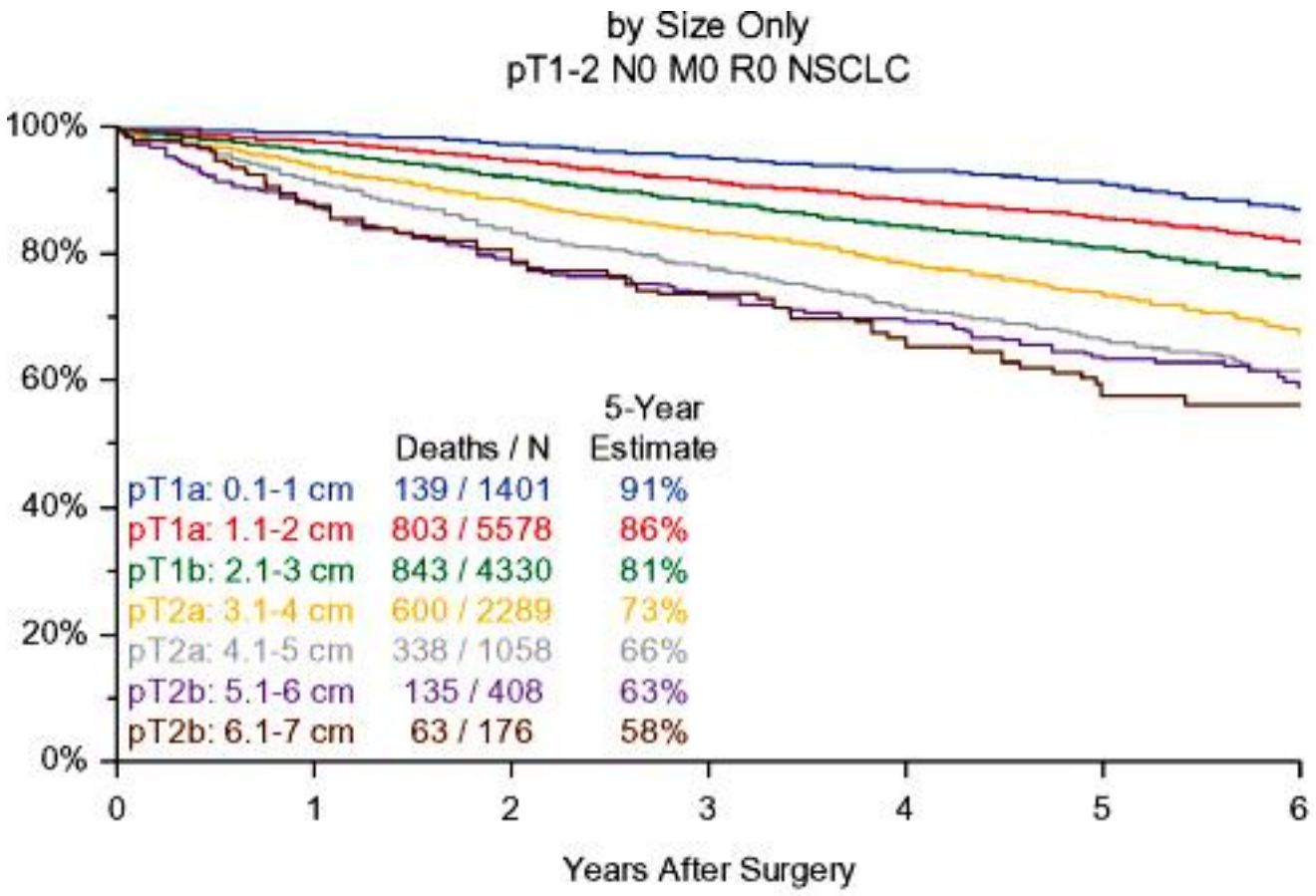
Recommendation for CT measurement

① For all measurements, use a **lung window setting**.
② **For staging**, only the **long axis dimension** of the **solid component** is used
③ Currently, **no consensus** about part-solid lesions with **several** solid components

Travis WD, et al. J Thorac Oncol. 2016;11:1204-23

The IASLC Lung Cancer Staging Project

Proposals for the revisions of the T descriptors in the 8th edition of the TNM classification for lung cancer

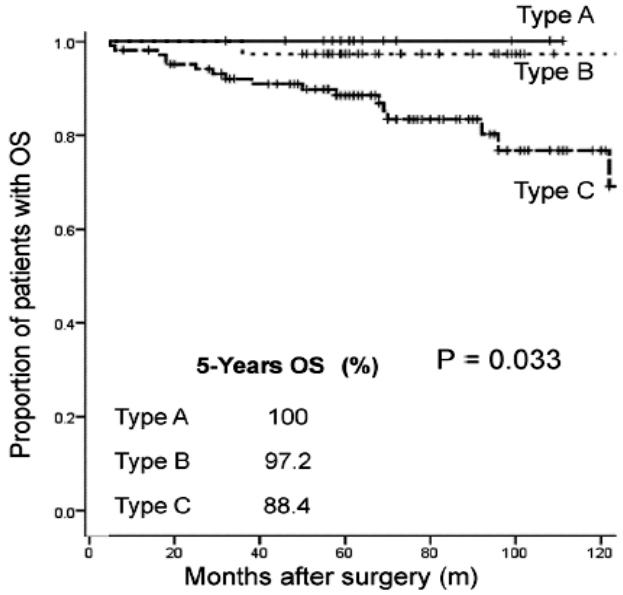


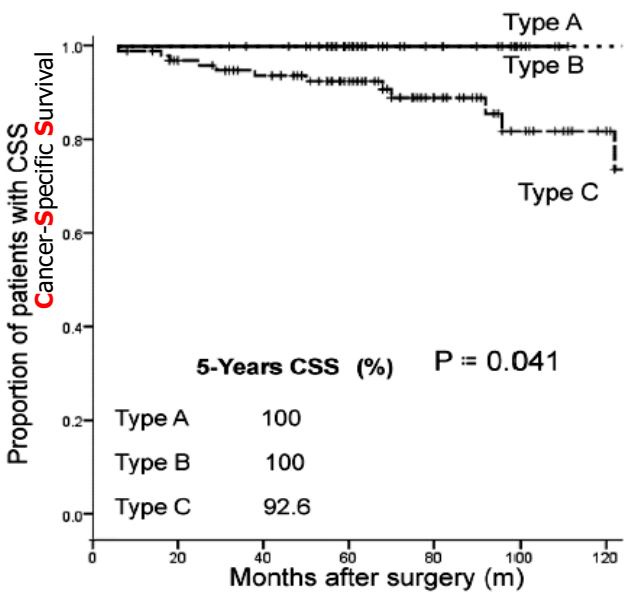
Rami-Porta R, et al. J Thorac Oncol. 2015;10:990-1003

Clinical features of GGO-dominant lung cancer exceeding 3.0 cm in the whole tumor size

160 surgically resected cancers with GGO >3.0 cm on CT, year 2002-2012 from NCC of Japan
CTR = consolidation/tumor ratio

	Type A (N=16) 0 < **CTR** ≤ 0.25	**Type B** (N=37) 0.25 < **CTR** ≤ 0.5	**Type C** (N=107) 0.5 < **CTR** < 1.0	P-value
Tumor size	4.2cm (3.1-6.0)	3.7cm (3.1-6.0)	4.0cm (3.1-6.3)	0.087
Solid part size	**0.7**cm (0.45-1.1)	**1.3**cm (1.0-2.4)	**3.4**cm (2.0-5.4)	<0.0001
L/N metastasis	0%	0%	32%	<0.0001
Vascular invasion	0%	16%	55%	<0.0001
Pleural invasion	0%	0%	34%	<0.0001





Suzuki S, et al. Ann Thorac Surg. 2018;105:1499–506

Limited resection (Sub-lobar resection)

- Segmental (preferred) or wedge resection
- Also sample appropriate N1 and N2 lymph node stations
- Resection margin ≥ 2cm or ≥ the size of nodule

- **<u>Indication for sub-lobar resection</u>**

  Poor pulmonary reserve or other major co-morbidity

  Peripheral nodule **≤ 2cm** with **at least one** of the following
  - ► Pure adenocarcinoma in situ (AIS)
  - ► Nodule has **≥ 50% GGO** on CT
  - ► Radiological long doubling time (≥ 400 days)

NCCN Practice Guidelines for Non-small-cell Lung Cancer v.2.2021

Clinical consideration before surgery of GGN

- **Age**
- **Performance**, co-morbidity, reserved lung function
- **Features of GGN**: total size, solid part size, multiplicity
- **Stage**, especially lymph node status
- **Volume doubling time**