Problematic Cases of Pathologic Diagnosis with Suspected Lung Cancer

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엄중섭

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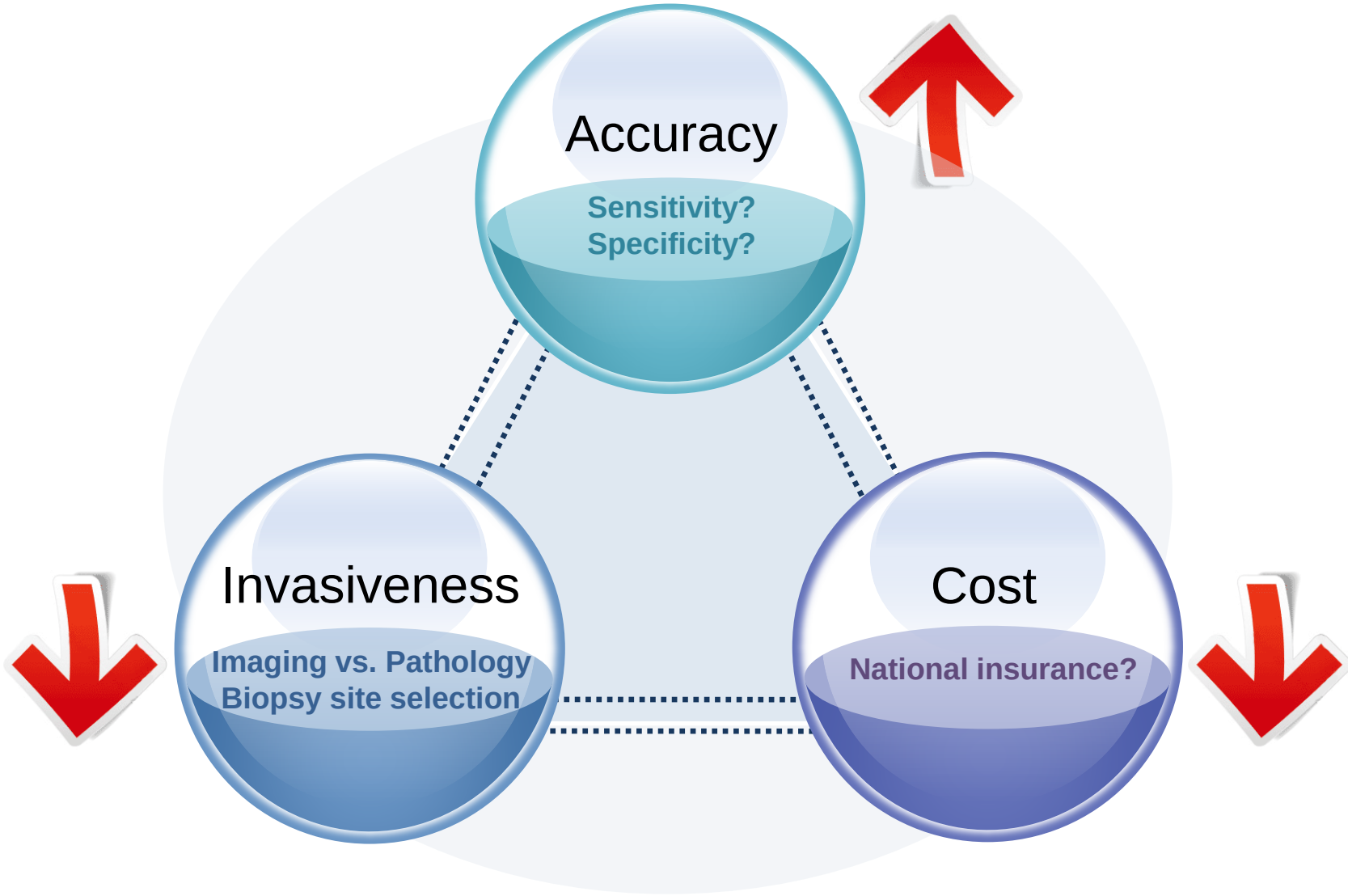
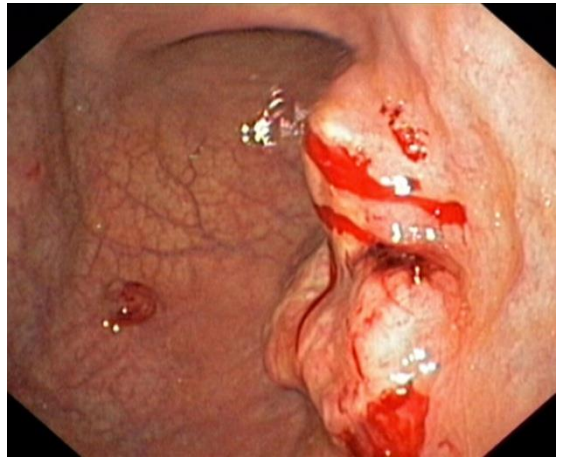
– Limitation of small biopsy in lung cancer

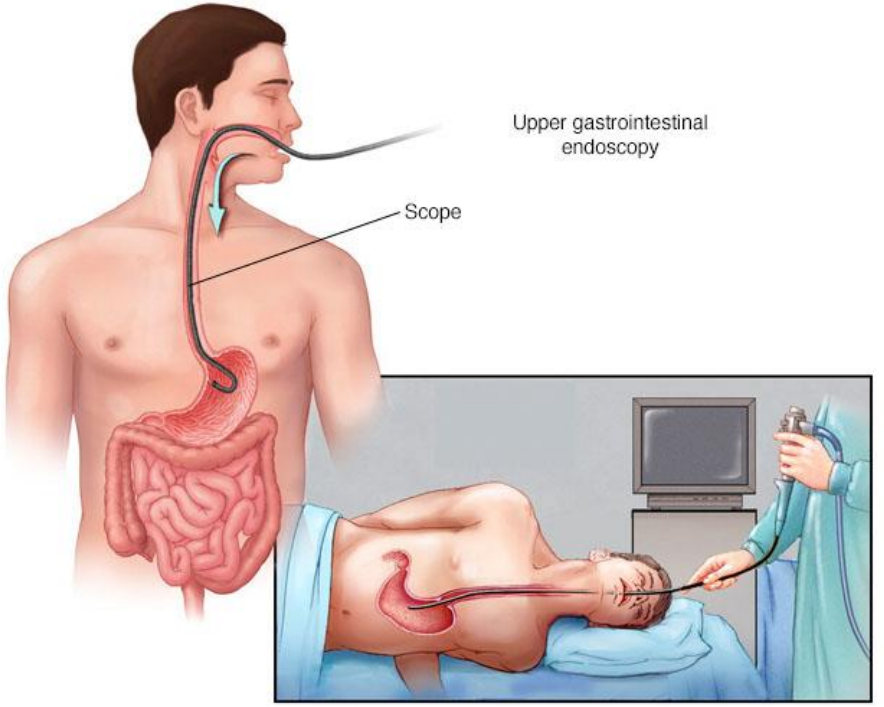
Best procedure for the pathological diagnosis?



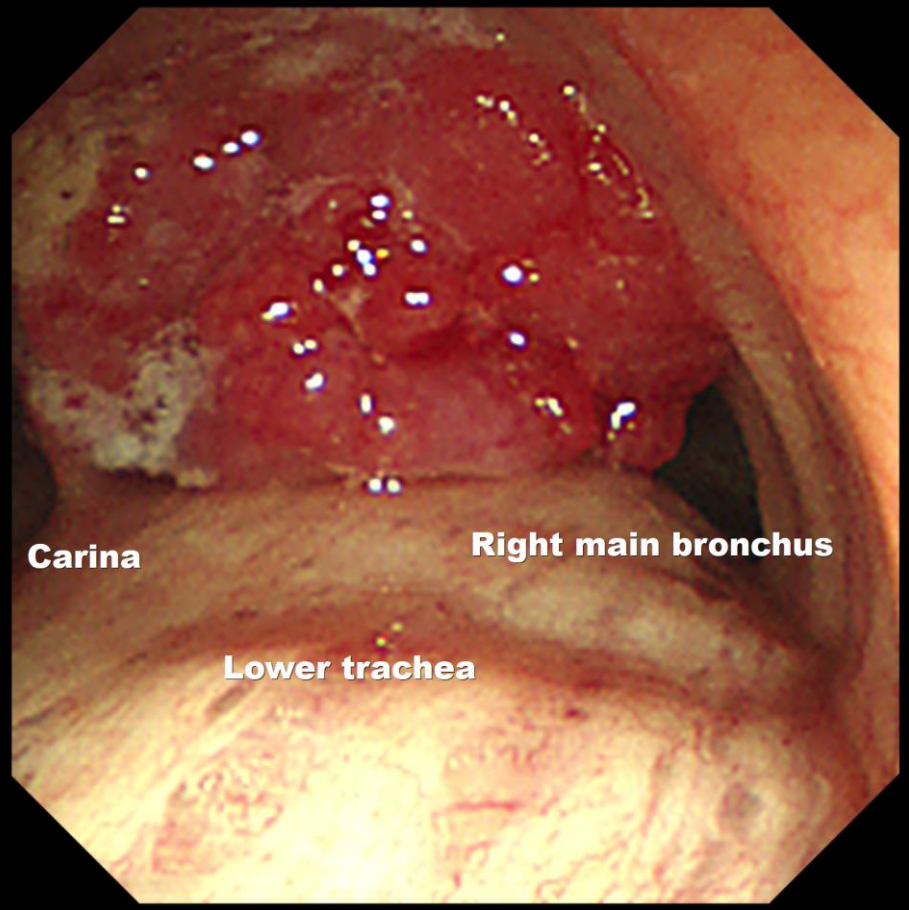


위암

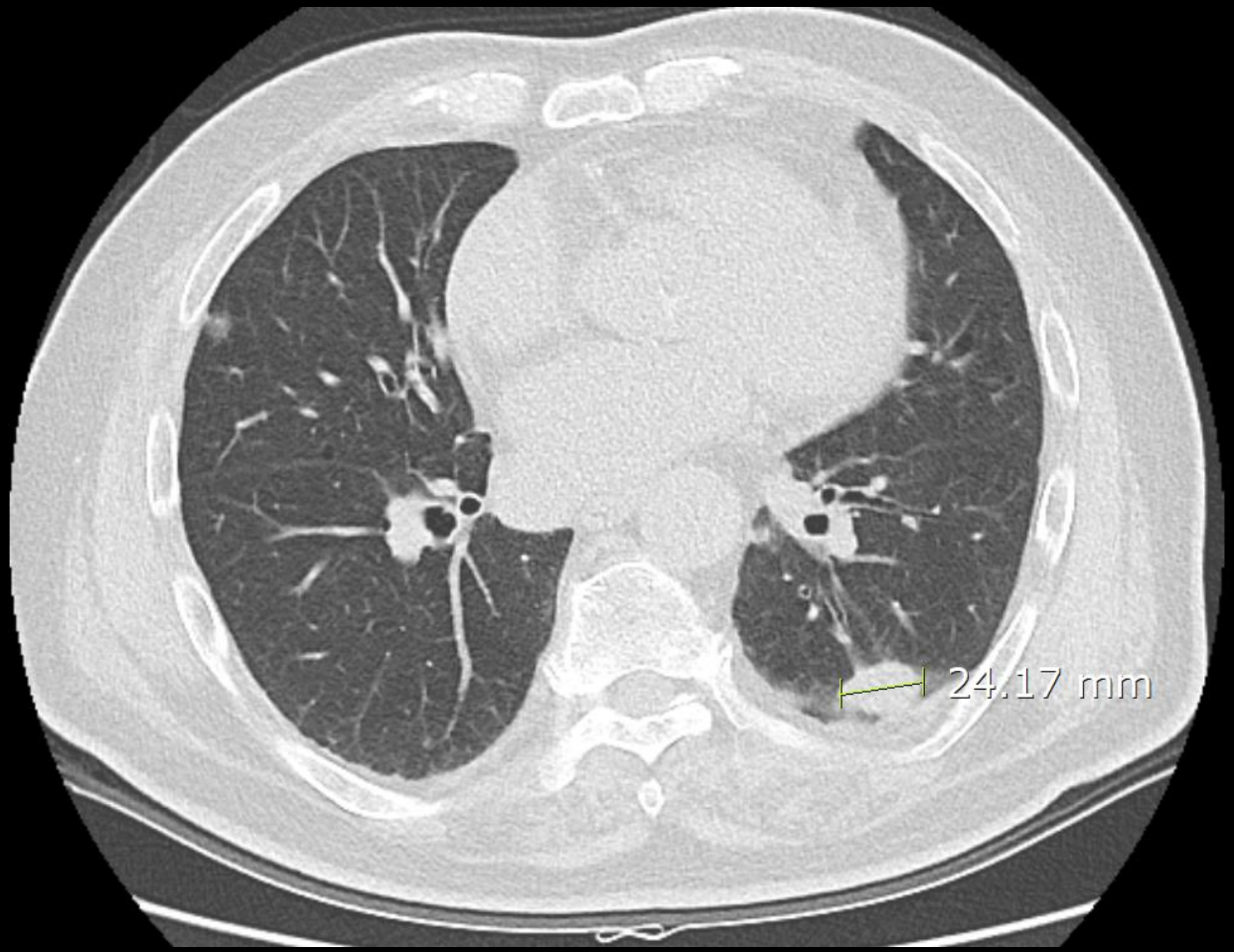
대장암



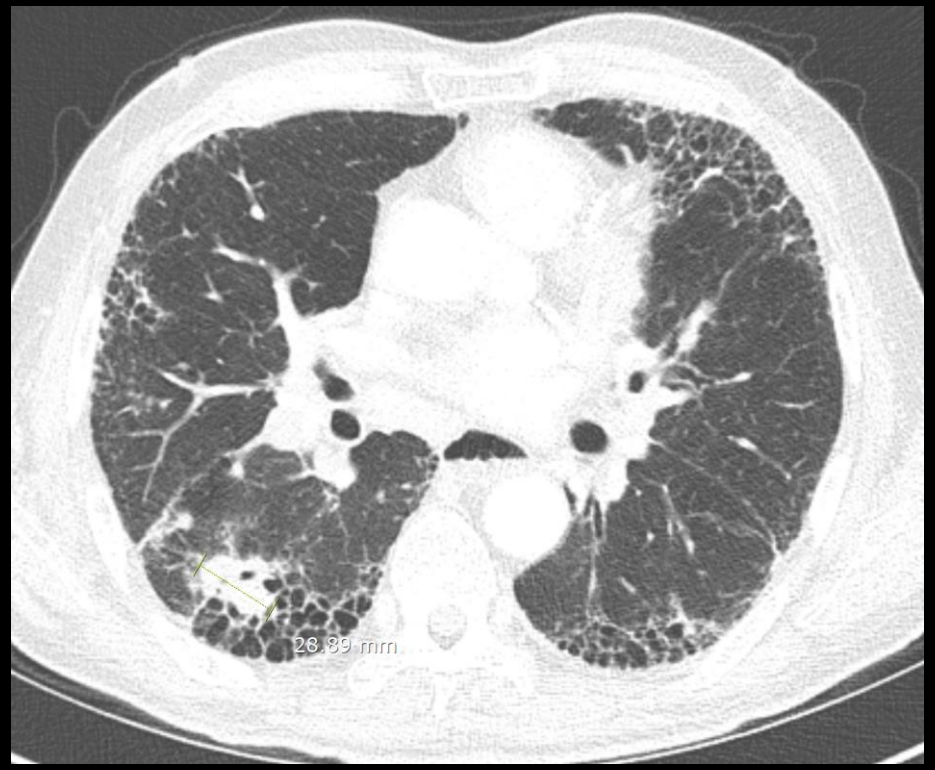
Easy cases for bronchoscopy or EBUS



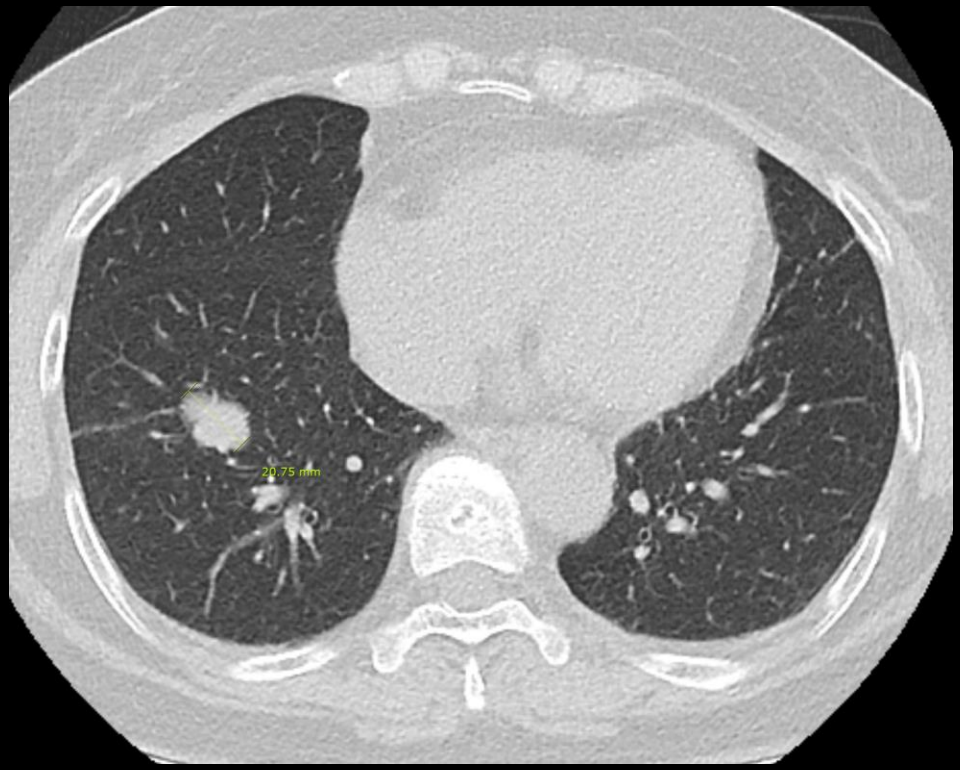
Easy case for surgical diagnosis



Difficult cases for diagnosis



Peripheral lesion with structural destruction



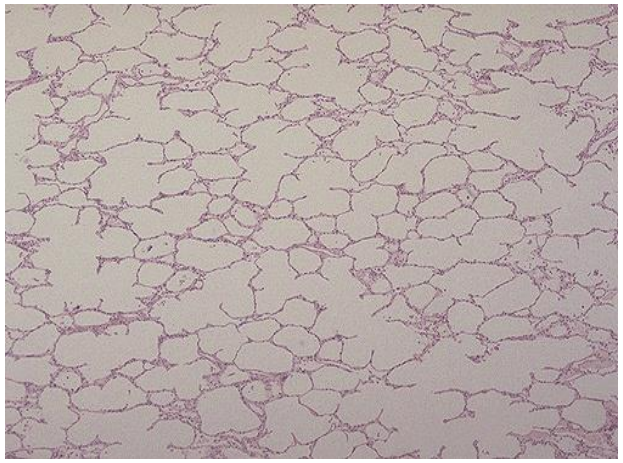
Central lesion

Problems in Pathological Diagnosis
– Problematic cases in early lung cancer

	Potential benefit	Potential harms
Surgical wedge resection	▪ Prompt, definite diagnosis ▪ Proceed to lobectomy if frozen reveals malignancy	▪ Complications – Pneumonia: 1-8% – Persistent air leak: 3-5% – Death: 0.5% ▪ Unnecessary surgery if nodule is benign
CT guided needle lung biopsy (PCNA)	▪ Diagnostic yields ≤ 15 mm: ~70-80% > 15 mm: ~90%	▪ Complications – Bleeding: 1% – Any pneumothorax: 15% – Pneumothorax with chest tube: 7% – Death: < 1% ▪ False negative: 10-30%
Peripheral bronchoscopy	▪ Diagnostic yields Fluoroscope-guide: ~30% EBUS, ENB, VBN: 60-90%	▪ Complications – Bleeding: 2-5% – Any pneumothorax: 2-4% – Death: < 1% ▪ False negative: 30-70%

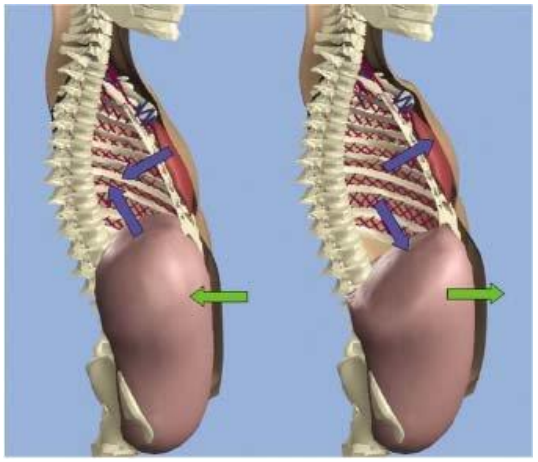
Chest. 2013 May;143(5 Suppl):7S-37S.

Hurdles in real clinical practice

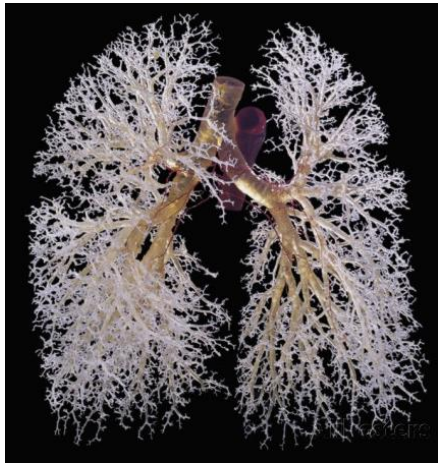


Airspace in Lung

Lung destruction



Respiratory movements



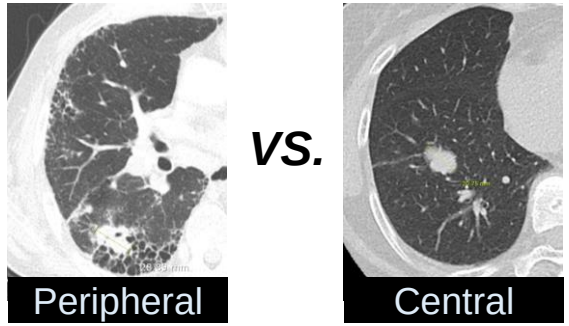
Complex anatomical structures

Respir Res. 2019 Aug 6;20(1):177.

Factors influencing biopsy

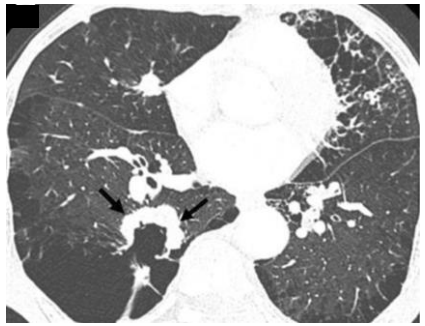
Location of adenocarcinoma	Percentage
Central	35%
Peripheral	65%

Radiology. 2018 Dec;289(3):831-840.



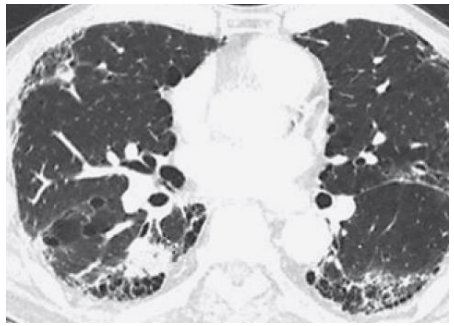
Presence of emphysema in lung cancer	Percentage
With COPD	76%
Without COPD	27%

AJR Am J Roentgenol. 2015 Sep;205(3):540-5.
Respir Res. 2019 Aug 6;20(1):177.



ILD incidences in lung cancer	Percentage
Korea (1 study)	2%
Japan (11 studies)	5−24%
European countries (4 studies)	2−5%

J Thorac Dis. 2018 Aug;10(6): 3829-3844.
Respiration. 2021 Nov 19;1-7.



Complication following invasive procedure

- Retrospective cohort analysis of Veterans (N = 82,641)
- Subjects: Veterans with invasive procedure after LCS (n = 1,741)

Variables	Odds ratio	95% CI
Thoracic surgery	**7.70**	5.48-10.81
Number of non-thoracic surgery procedures	**1.49**	1.15-1.92
Comorbidities		
Chronic obstructive pulmonary disease	1.17	0.87-1.58
Dementia	**3.91**	1.79-8.52
Interstitial lung disease	0.29	0.10-0.88

Invasive procedure = bronchoscopy, transthoracic needle biopsy, mediastinoscopy, or lung resection.
LCS = lung cancer screening.

Chest. 2022 Feb: S0012-3692(22)00397-X

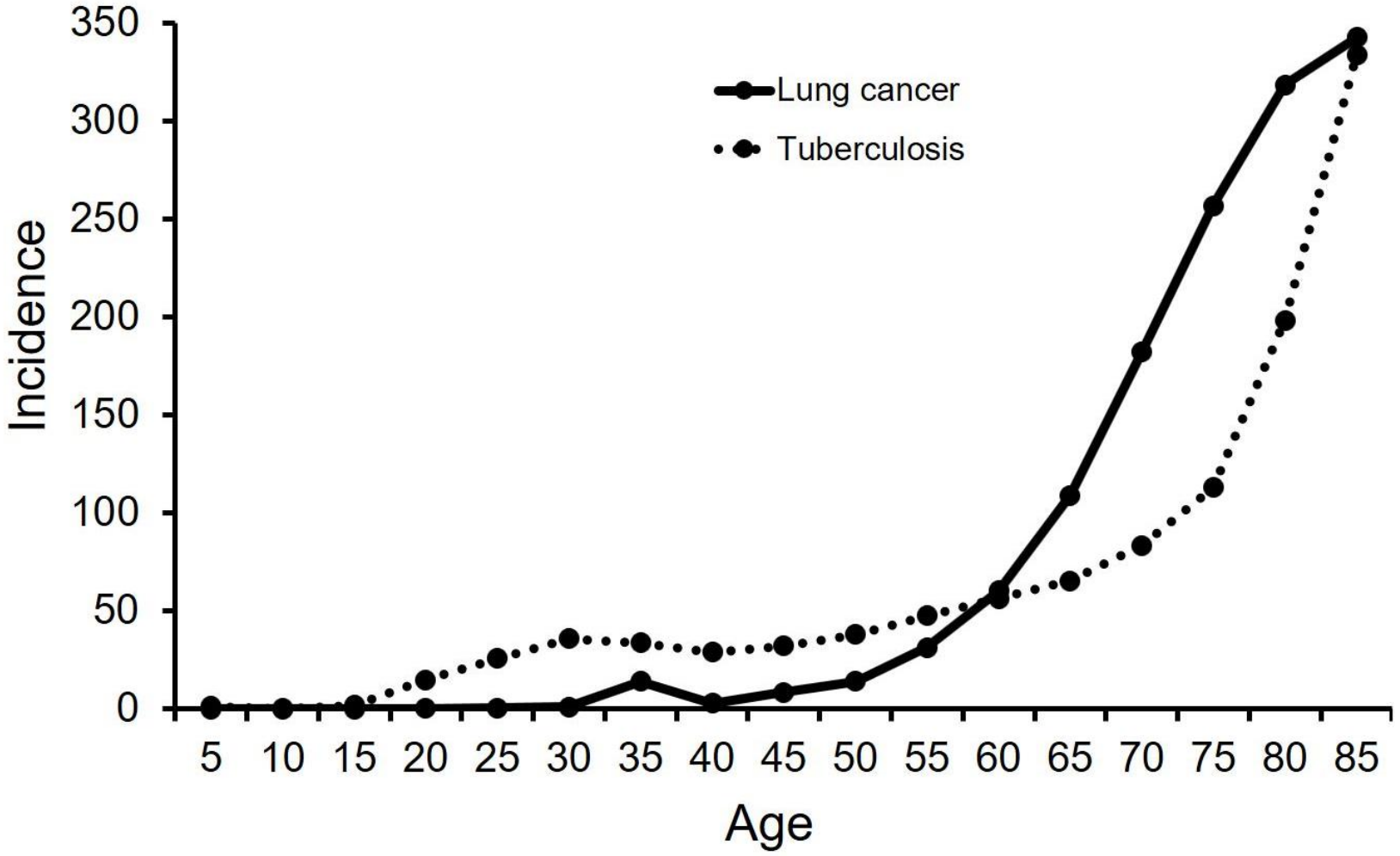
Complications after PCNA

- Cross-section study in USA (N = 15,865)
- Objective: To determine risks for complications after PCNA

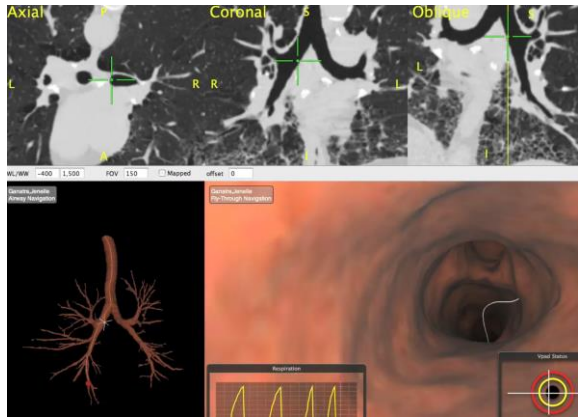
Comorbid condition	Odds ratio for complication (95% CI)		
	Hemorrhage (n = 163, 1%)	Any pneumothorax (n = 2381, 15%)	Pneumothorax requiring chest tube (n = 1047, 7%)
Ever smoker	1.13 (0.78−1.63)	1.37 (1.23−1.54)	1.50 (1.26−1.77)
COPD	1.61 (1.08−2.39)	1.88 (1.69−2.09)	2.52 (2.16−2.95)
Pleural effusion	6.32 (4.18−9.55)	1.04 (0.83−1.29)	1.09 (0.81−1.47)

Ann Intern Med. 2011 Aug 2;155(3):137-44.

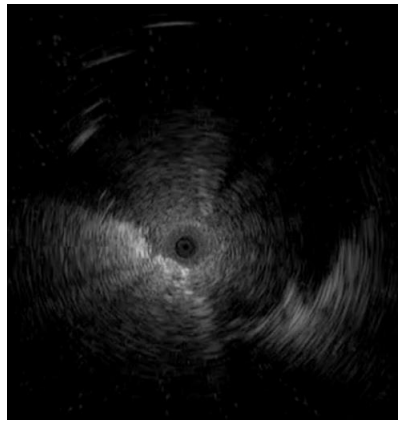
Age distribution in lung cancer patients



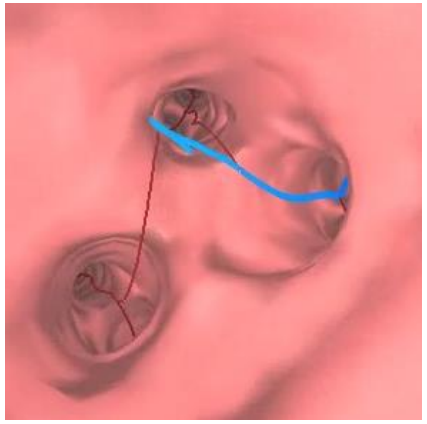
PLoS One. 2021 Jan 28;16(1):e0246371.



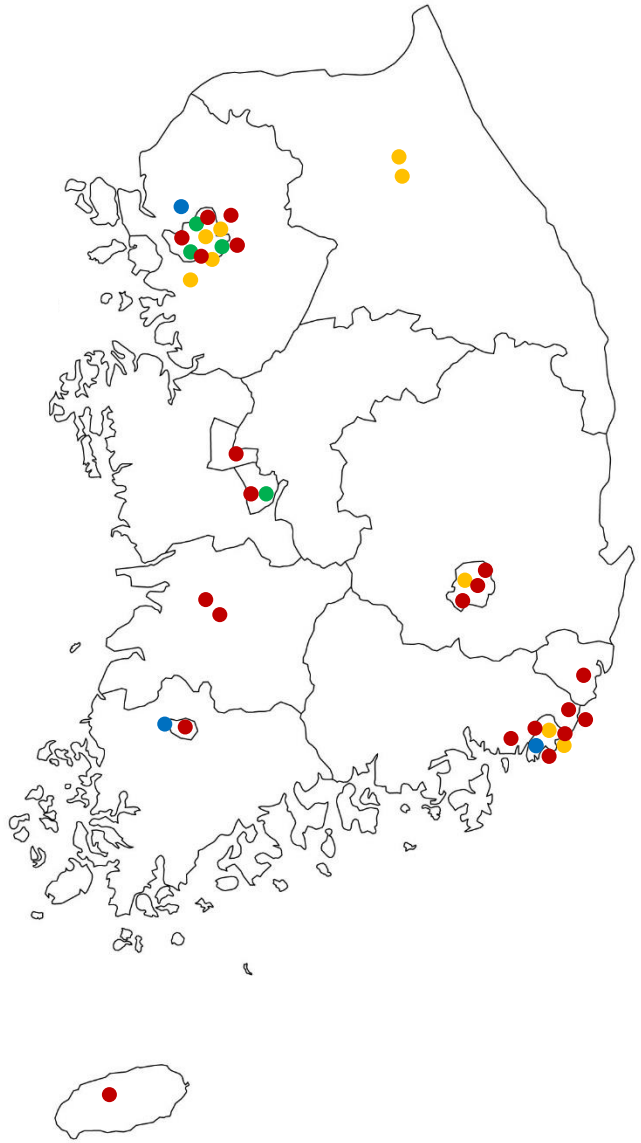
- ENB



- RP-EBUS

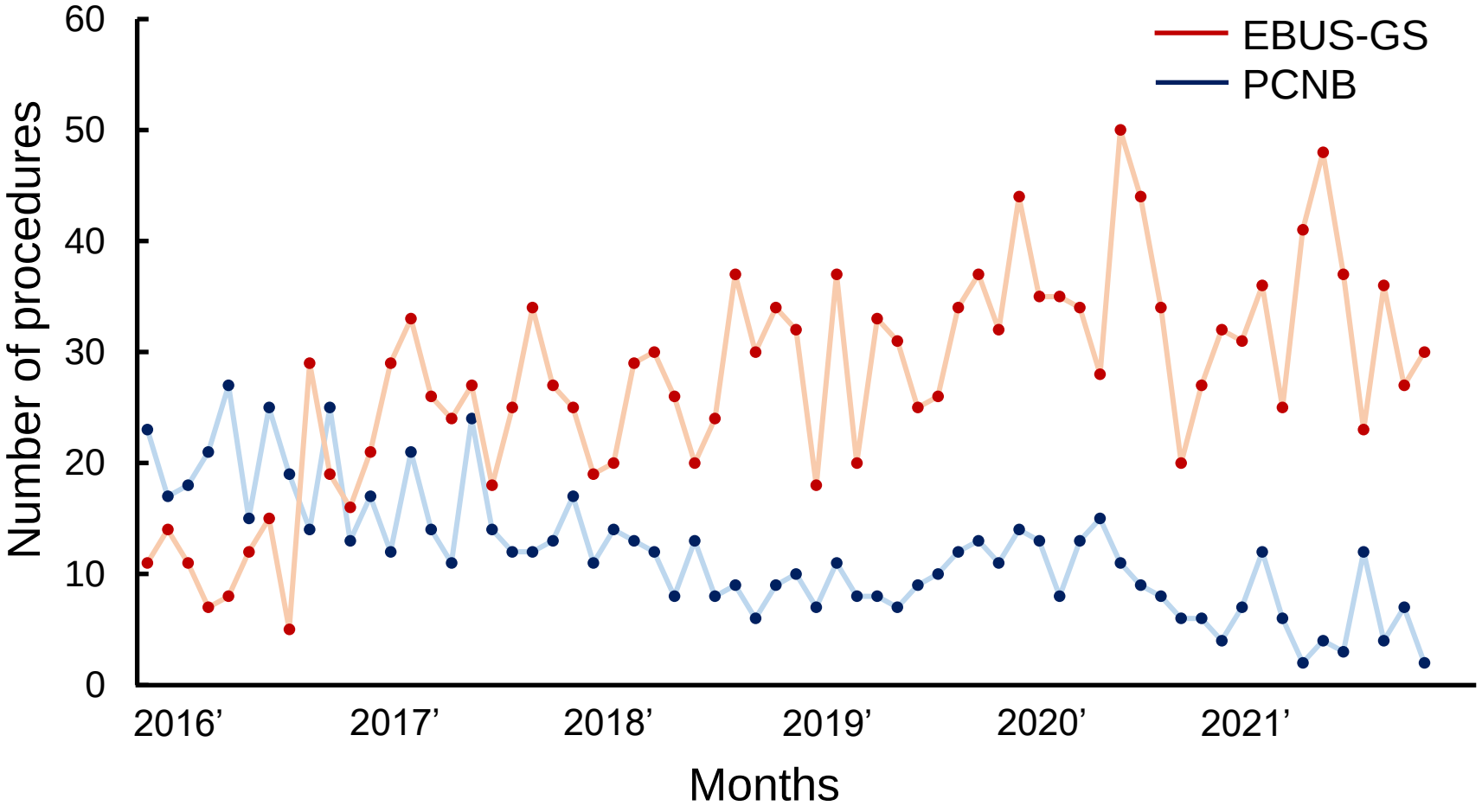


- VBN

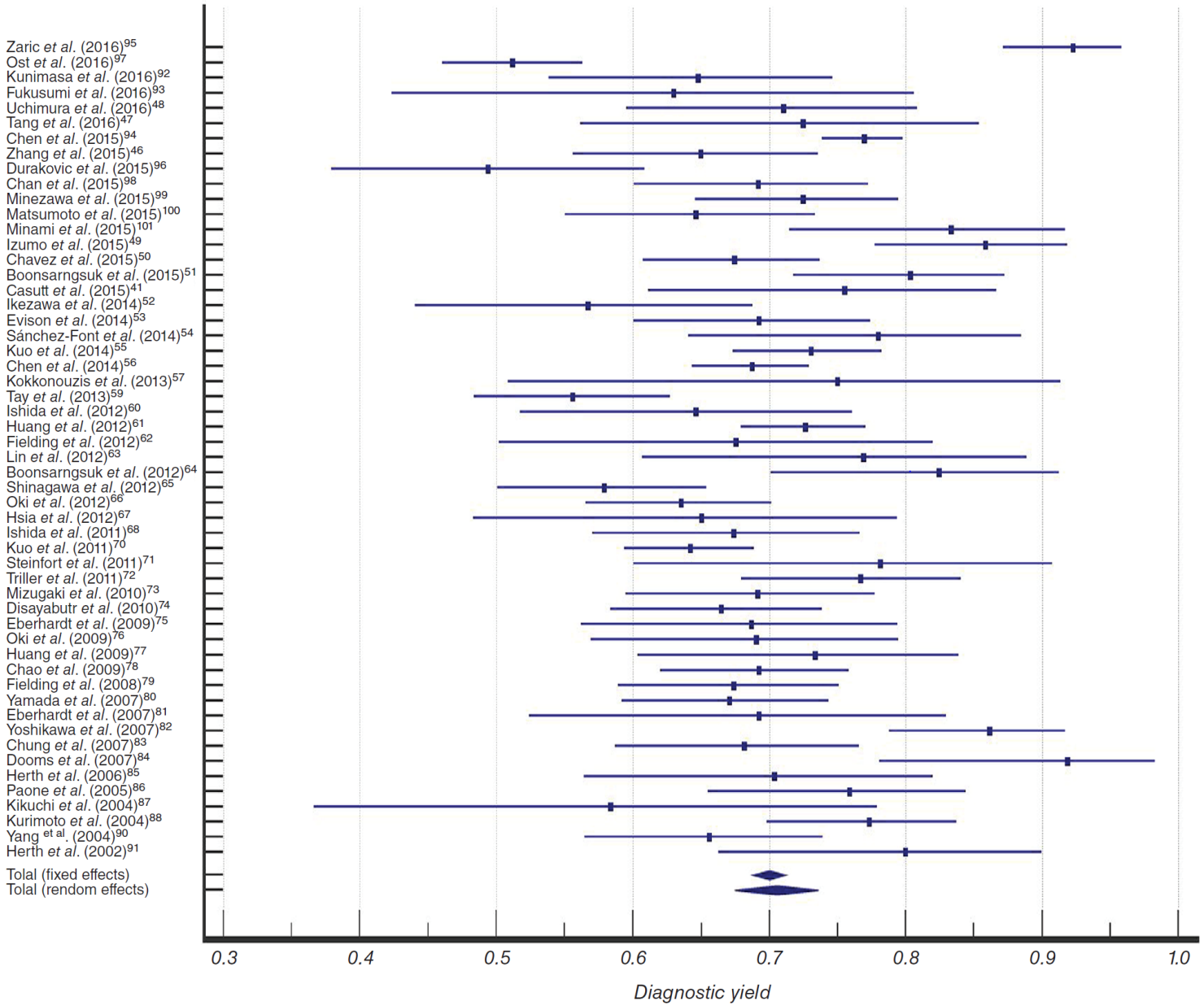


- Radial probe EBUS
- VBN – Lung Point®
- ENB – SuperDimension®
- ENB – SPiNDrive®

Changes in number of procedures



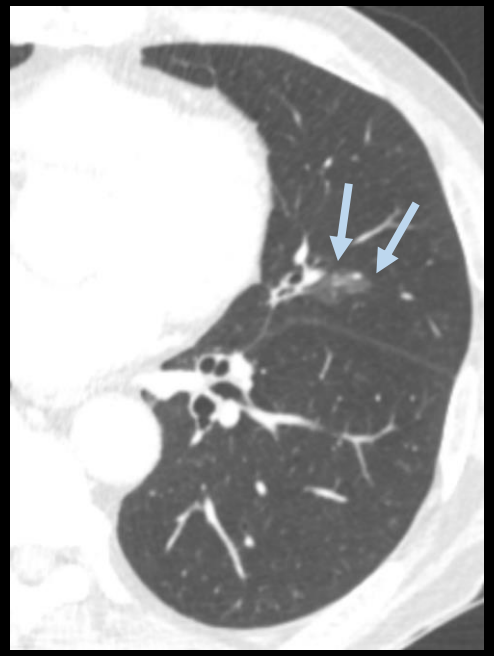
Trends in Pusan National University Hospital



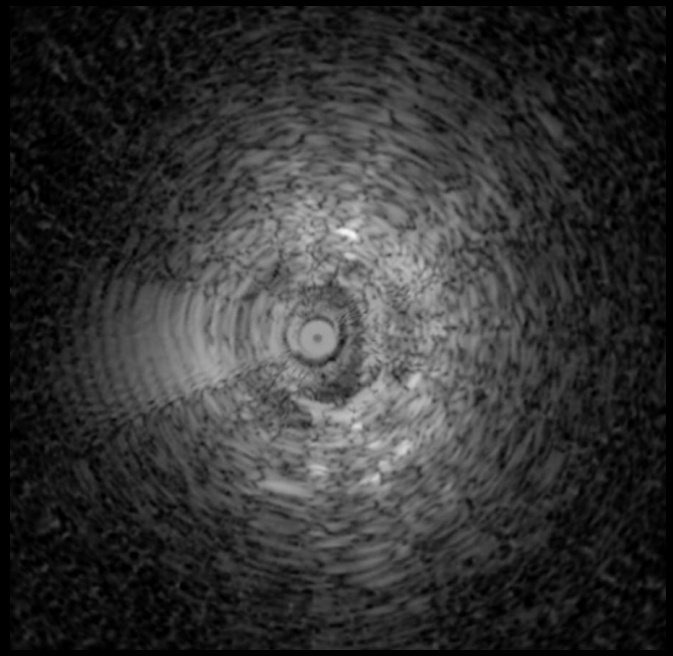
Respirology. 2017 Apr;22(3):443-453.

Case 1

- Male, 79 years old
- Never smoker



Chest CT



Radial probe EBUS

CONCLUSION

1. No change of 2.4cm sized pure GGO nodule at LUL lingular segment.
   --> DDx. 1) AIS/MIA
   2) Nonspecific inflammatory fibrosis.
2. N change of 1.0cm sized GGO nodule in RUL.
3. No change of multiple calcified and non-calcified nodules in both lung.
4. Small nodule in left thyroid gland.
5. 2.0cm sized nodule in left adrenal gland.
6. Aorta and cononary artery calcification.

진단

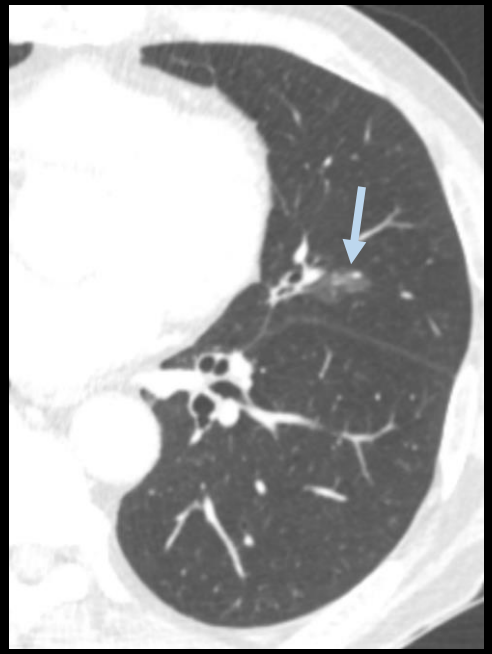
Lung, lingular division, inferior segment #1~4, left, EBUS-TBLB :
A few atypical pneumocytes(see NOTE).

?

Immunohistochemistry in section
TTF-1(+)
p63(-)

Note : Clinico-pathologic correlation is recommended.
Intradepartment consultation was done.

Case 1



2019.11
Chest CT

2020.02
Chest CT

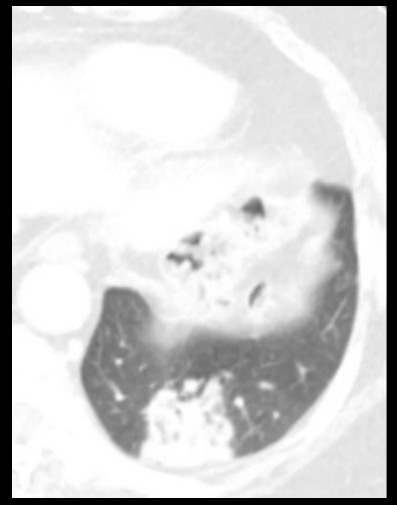
2020.8
Chest CT

2021.12
Chest CT

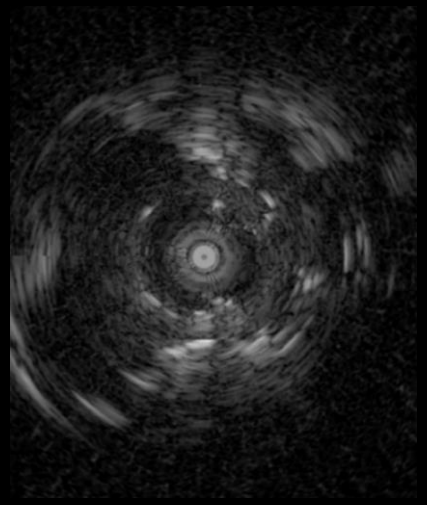
Non-small cell lung cancer
(TTF-1 focal positive, P40 positive)

Case 2

- Male, 62 years old
- Never smoker



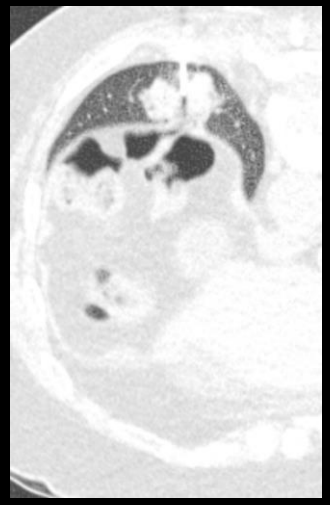
Initial chest CT



Radial EBUS

⬇

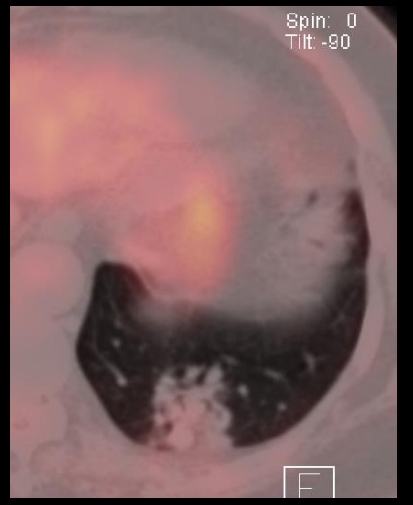
Chronic inflammation



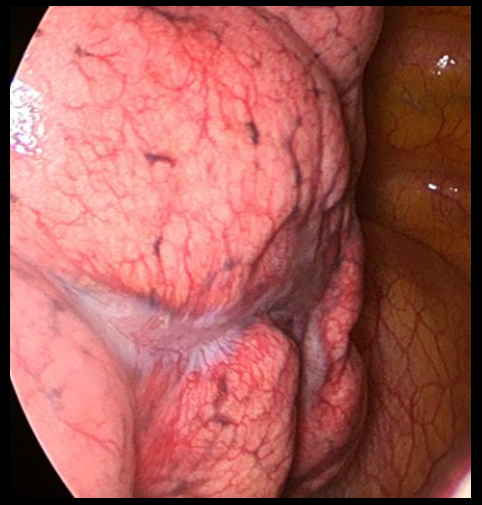
PCNA

⬇

Scanty cellularity



PET



VATS

⬇

Chronic organizing pneumonia

Failed PCNA and its final diagnosis – US data

Final diagnosis (N =122)	Percentage
Benign	64%
Malignancy	
Primary lung cancer	**28%**
Metastasis	4%
Lymphoproliferative disease	4%

Korean J Radiol. 2019 Nov;20(11):1515-1526.

Failed PCNA and its final diagnosis – Chinese data

Final diagnosis (N = 40)		RP-EBUS (n = 28)	PCNA (n = 12)
Malignant	Adenocarcinoma	39%	42%
	Large cell carcinoma	7%	8%
	Adenocarcinoma	4%	0%
	Metastatic carcinoma	4%	8%
	Total	**54%**	**58%**
Benign	Tuberculosis	25%	25%
	Fungal infection	11%	0%
	Orgnanic pneumonia	7%	8%
	Harmatoma	4%	0%
	Infected cyst	0%	8%
	Total	**46%**	**44%**

Oncotarget. 2018 Jan 4;9(19):15122-15131.

Which way is better?

	Yields	Limitations	Favorable location	Unfavorable factors
PCNA	90%	Complications	Peripheral lesion, especially presence of pleural contract	Central lesion, Lower lobar location, Lung destruction
Transbronchial biopsy • RP-EBUS • ENB	70~80%	Medical resources, Affordability	Both central and peripheral lesions	Negative bronchus sign

Korean J Radiol. 2019 Nov;20(11):1515-1526.
Chest. 2009 Dec;136(6):1612-1617.
Thorac Cancer. 2020 May;11(5):1191-1201.
Chest. 2019 Nov;156(5):954-964.
Respirology. 2017 Apr;22(3):443-453.
Chest. 2020 Oct;158(4):1753-1769.

Problems in Molecular Diagnosis
– Problematic cases in advanced lung cancer

Targeted therapy or Immunotherapy for NSCLC

TARGETED THERAPY OR IMMUNOTHERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]

EGFR Exon 19* Deletion or *L858R
- First-line therapy
  - Afatinib[1]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6]
  - Erlotinib + ramucirumab[7]
  - Erlotinib + bevacizumab[c] (nonsquamous)[8]
- Subsequent therapy
  - Osimertinib[9]

EGFR S768I, L861Q,* and/or *G719X

First-line therapy
- Afatinib[1,10]
- Erlotinib[2]
- Dacomitinib[3]
- Gefitinib[4,5]
- Osimertinib[6,11]

Subsequent therapy
- Osimertinib[9]

***EGFR Exon 20* Insertion Mutation Positive**
- Subsequent therapy
  - Amivantamab-vmjw[12]
  - Mobocertinib[13]

***KRAS G12C* Mutation Positive**
- Subsequent therapy
  - Sotorasib[14]

***ALK* Rearrangement Positive**
- First-line therapy
  - Alectinib[15,16]
  - Brigatinib[17]
  - Ceritinib[18]
  - Crizotinib[15,19]
  - Lorlatinib[20]
- Subsequent therapy
  - Alectinib[21,22]
  - Brigatinib[23]
  - Ceritinib[24]
  - Lorlatinib[25]

***ROS1* Rearrangement Positive**
- First-line therapy
  - Ceritinib[24]
  - Crizotinib[27]
  - Entrectinib[28]
- Subsequent therapy
  - Lorlatinib[29]
  - Entrectinib[28]

***BRAF* V600E Mutation Positive**
- First-line therapy
  - Dabrafenib/trametinib[30,31]
  - Dabrafenib[30]
  - Vemurafenib
- Subsequent therapy
  - Dabrafenib/trametinib[31,32]

***NTRK1/2/3* Gene Fusion Positive**
- First-line/Subsequent therapy
  - Larotrectinib[33]
  - Entrectinib[34]

***MET* Exon 14 Skipping Mutation**
- First-line therapy/Subsequent therapy
  - Capmatinib[35]
  - Crizotinib[36]
  - Tepotinib[37]

***RET* Rearrangement Positive**
- First-line therapy/Subsequent therapy
  - Selpercatinib[38]
  - Pralsetinib[39]
  - Cabozantinib[40,41]

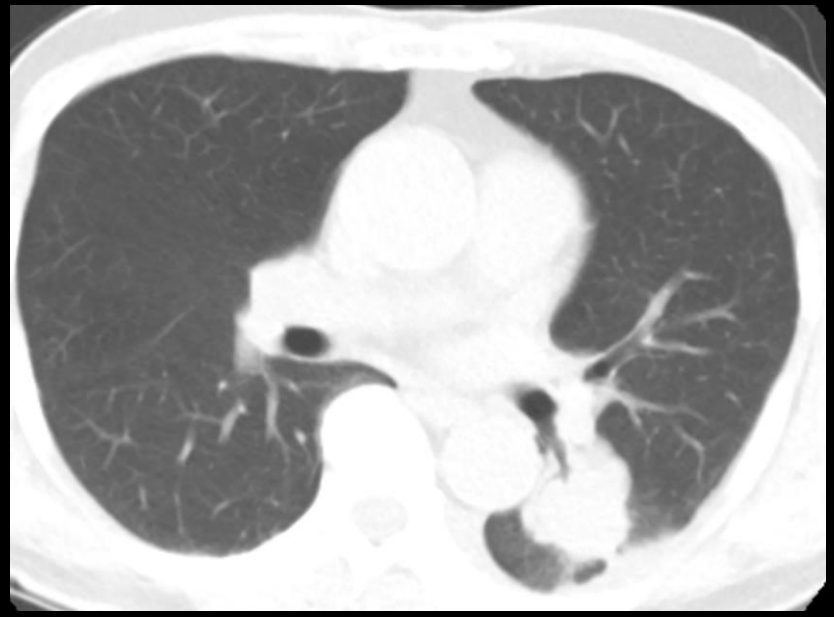
PD-L1 ≥1%
- First-line therapy[d]
  - Pembrolizumab[42-44]
  - (Carboplatin or cisplatin)/pemetrexed/ pembrolizumab (nonsquamous)[45,46]
  - Carboplatin/paclitaxel/bevacizumab[c]/ atezolizumab (nonsquamous)[47]
  - Carboplatin/(paclitaxel or albumin-bound paclitaxel)/pembrolizumab (squamous)[48]
  - Carboplatin/albumin-bound paclitaxel/ atezolizumab (nonsquamous)[48]
  - Nivolumab/ipilimumab[49]
  - Nivolumab/ipilimumab/pemetrexed/ (carboplatin or cisplatin) (nonsquamous)[50]
  - Nivolumab/ipilimumab/paclitaxel/carboplatin (squamous)[50]

PD-L1 ≥50% (in addition to above)
- First-line therapy[d]
  - Atezolizumab[51]
  - Cemiplimab-rwlc[52]

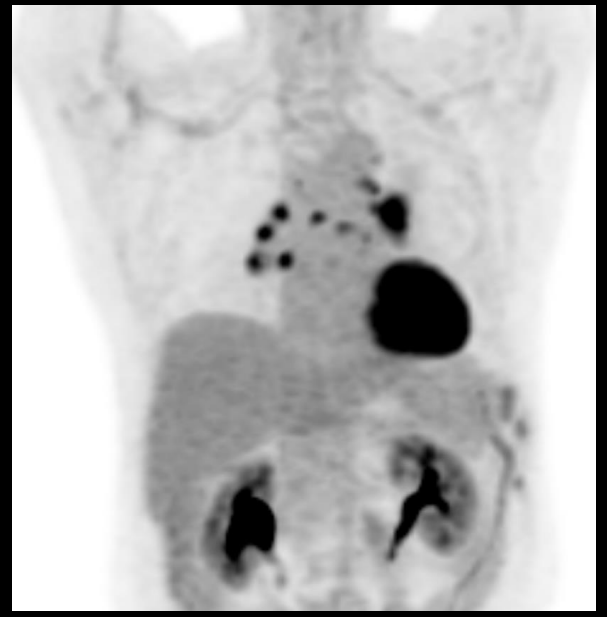
NSCLC NCCN guidelines Version 2.2022

Case 3

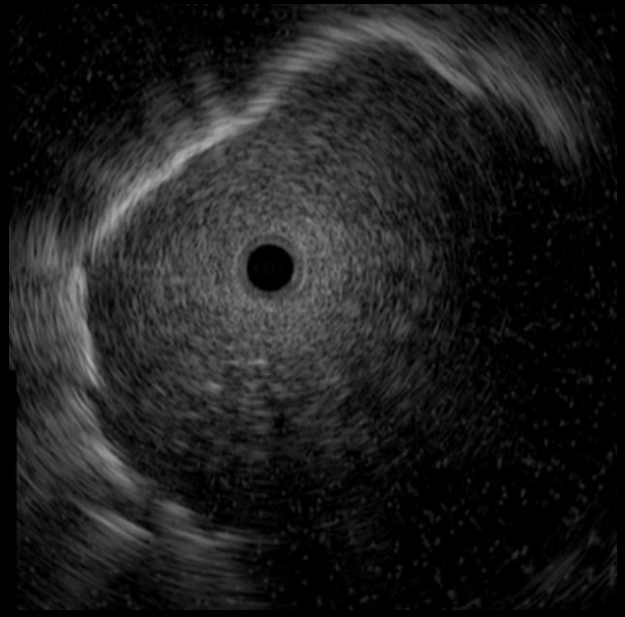
- Male, 75 years old
- Never smoker



Chest CT



PET



Radial probe EBUS

Case 3

육안소견

Submitted are 3 parts.
1. Left, lower lobe #1~2: fragments of brownish white soft tissue, 0.4x0.4cm in size(the largest). Blocked in toto, Slide A.
2. Left, lower lobe #3~4: 2 fragments of brownish white soft tissue, 0.4x0.3cm in size(the largest). Blocked in toto, Slide B.
3. Left, lower lobe #5~6: 2 fragments of brownish white soft tissue, 0.4x0.3cm in size(the largest). Blocked in toto, Slide C.

PA 이은지 | 육안검사의 이소정 | 전사자 강지혜

진단

Lung, lower lobe, #1~2, left, EBUS-TBLB :
Adenocarcinoma, suggestive of primary in the lung.
Lung, lower lobe, #3~4, left, EBUS-TBLB :
Adenocarcinoma, suggestive of primary in the lung.
Lung, lower lobe, #5~6, left, EBUS-TBLB :
Adenocarcinoma, suggestive of primary in the lung.

Immunohistochemistry in section A
TTF-1, Napsin A: positive
ALK, p63: negative
PD-L1: pending

NOTE: The result of EGFR mutation and ALK gene study (section B) will follow.

[ADDENDUM 20171017]
Immunohistochemistry
PD-L1 22C3 (Dako) Tumor Proportion Score: 10% (low expression)

[addendum 20171214]
Immunohistochemistry
PD-L1 SP263 (Ventana) Tumor Expression: 20%

분자병리검사보고서

검사항목: EGFR mutation

검체종류 : Lung　　채취방법 : FFPE biopsy
외과병리번호 : S17-28958 B　　외과병리 진단: Adenocarcinoma

결과:
< EGFR Mutation Analysis Report >
Lung, lower lobe, #3~4, left, EBUS-TBLB :
Negative for EGFR oncogene mutation at exons 18, 19, 20 and 21.

-Test information
Specimen : Genomic DNA isolated from FFPE tissue (S17-28958 B)
Analyzed gene : Human EGFR on Chromosome 7p11.2 (Exon 18-21)
Method : PNA-clamp method
Instrument : CFX96 RT-PCR System (Bio-Rad)
DNA Preparation:
Maxwell(R) 16 FFPE Plus LEV DNA Purification Kit for IVD (AX1860)
Reagent: PNAClamp (TM) EGFR Mutation Detection Kit

- Interpretation
EGFR 유전자의 주요 돌연변이 부위를 분석한 결과, 돌연변이가 검출되지 않았습니다.

NOTE) Lung, lower lobe, #3~4, left, EBUS-TBLB :
Adenocarcinoma, suggestive of primary in the lung.

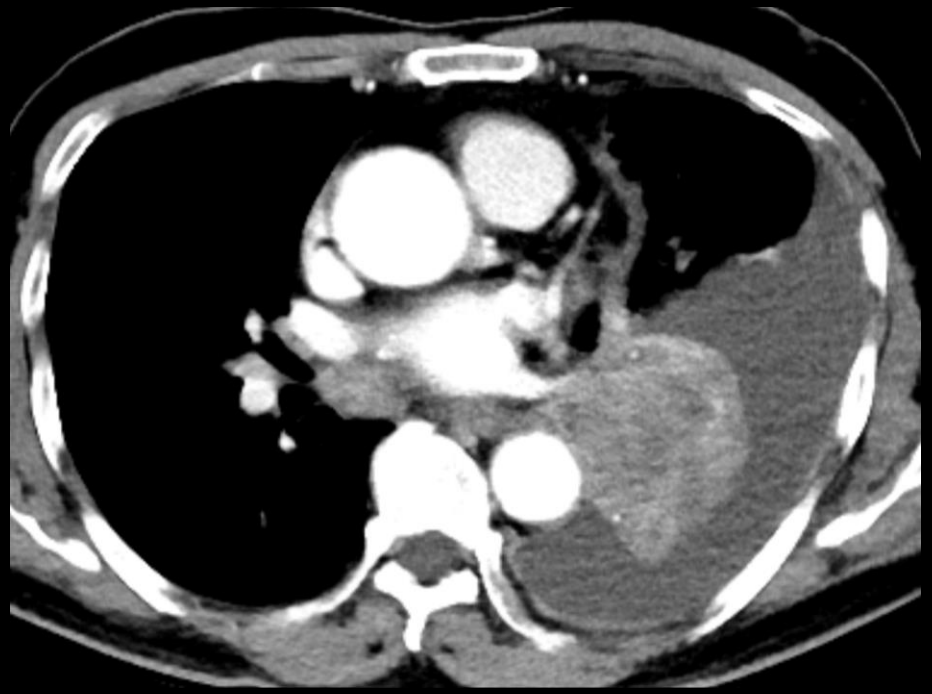
Case 3

- Stage IV lung adenocarcinoma
- Pleural seeding metastasis
- EGFR mutation negative, ALK IHC negative
- PD-L1 SP263: 20%, PD-L1 22C3: 10%

- 2017.10~2018.01 1st line pemetrexed/cisplatin
- 2018.01~2018.05 pemetrexed maintenance
- 2018.06~2019.12 2nd line nivolumab

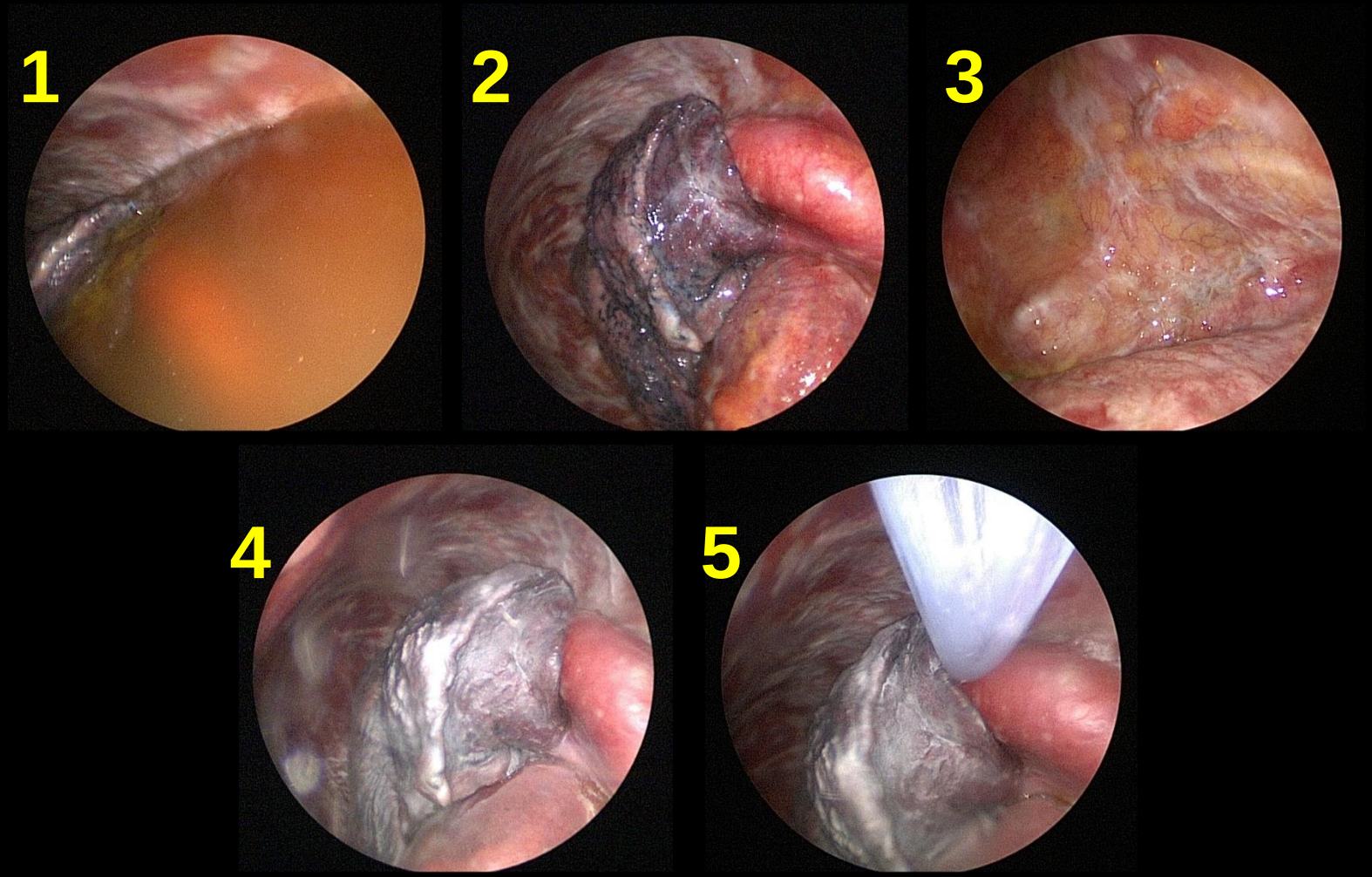
Case 3

2017.09
Chest CT
– Initial presentation



2019.12
Chest CT
– PD after 2nd line
Nivolumab

Case 3



2020.01 Medical thoracoscopy

Case 3

진단

Soft tissue, pleura, #1, left, medical thoracoscopic biopsy :
Adenocarcinoma, suggestive of primary in the lung.

Soft tissue, pleura, #2, left, medical thoracoscopic biopsy :
Adenocarcinoma, suggestive of primary in the lung.

<Immunohistochemistry>
ALK(-)

진단

분자병리검사보고서

검사항목: EGFR mutation
검체종류 : FFPE, Pleura
병리번호 : S20-00745 B
병리 진단: Adenocarcinoma, suggestive of primary in the lung

결과:
< EGFR Mutation Analysis Report >
Soft tissue, pleura, #2, left, medical thoracoscopic biopsy :
POSITIVE FOR EGFR ONCOGENE MUTATION as deletion mutation at exon 19

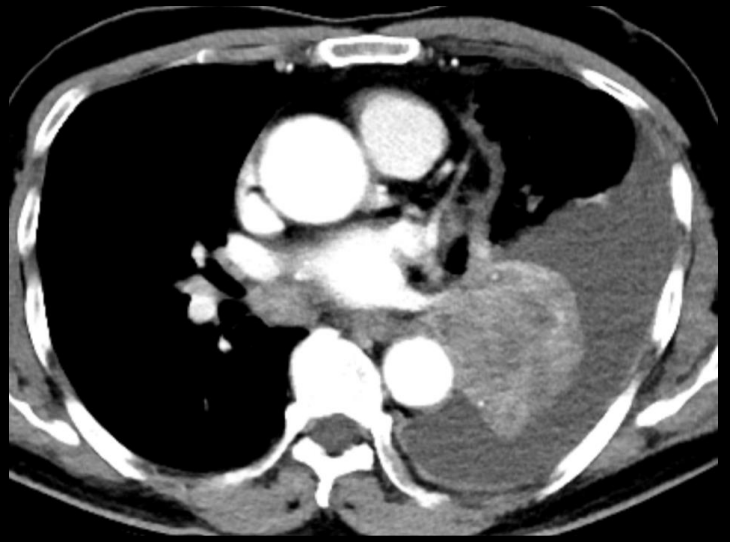
-Test information
Specimen : Genomic DNA isolated from FFPE tissue (S20-00745 B)
Analyzed gene : Human EGFR on Chromosome 7p11.2 (Exon 18-21)
Method : PANAMutyperTM R EGFR method(Melting curve analysis)
Instrument : CFX96 RT-PCR System (Bio-Rad)
DNA Preparation: Maxwell(R) 16 FFPE Plus LEV DNA Purification Kit for IVD (AX1860)
Reagent: PANAMutyperTM R EGFR Mutation Detection Kit

- Interpretation
EGFR 유전자의 주요 돌연변이 부위를 분석한 결과, exon 19 (deletion mutation) 에서 돌연변이가 검출되었습니다.

NOTE) Soft tissue, pleura, #2, left, medical thoracoscopic biopsy :
Adenocarcinoma, suggestive of primary in the lung.

Case 3

2017.09
Chest CT
– Initial presentation



2019.12
Chest CT
– PD after 2nd line
Nivolumab

2020.07
Chest CT
– 6 month after
Erlotinib treatment

Case 3

- 2017.10~2018.01 1st line pemetrexed/cisplatin
- 2018.01~2018.05 pemetrexed maintenance
- 2018.06~2019.12 2nd line nivolumab

- 2020.01 Medical thoracoscopy: EGFR mutation positive
- 2020.01~2021.06 3rd line erlotinib
- 2021.07~2021.08 4th line gemcitabine/carboplatin
- 2021.10~ 5th line lazertinib

EGFR mutations in Primary vs. Metastatic tumors

Metastatic lesions	**Primary tumor**	
	EGFR+	EGFR-
EGFR+	35%	2%
EGFR-	4%	59%

Concordance of EGFR mutations in the same patients

J Thorac Oncol. 2013 Jul;8(7):823-59.

Concordances of driver mutations

- Retrospective study at PNUH between 2015 and 2017
- Study subjects: 91 patients with early stage lung cancer
- Small biopsy sample (EBUS-GS) vs. Surgical specimen

	Specimens		**Correlation analysis**		
	EBUS-GS	Surgery	Agreement rate	Kappa coefficient	*P*-value
EGFR mutation detected*	35/91 (38%)	38/91 (42%)	97%	0.931	< 0.001
ALK FISH positive	5/91 (5%)	5/91 (5%)	100%	1.000	< 0.001

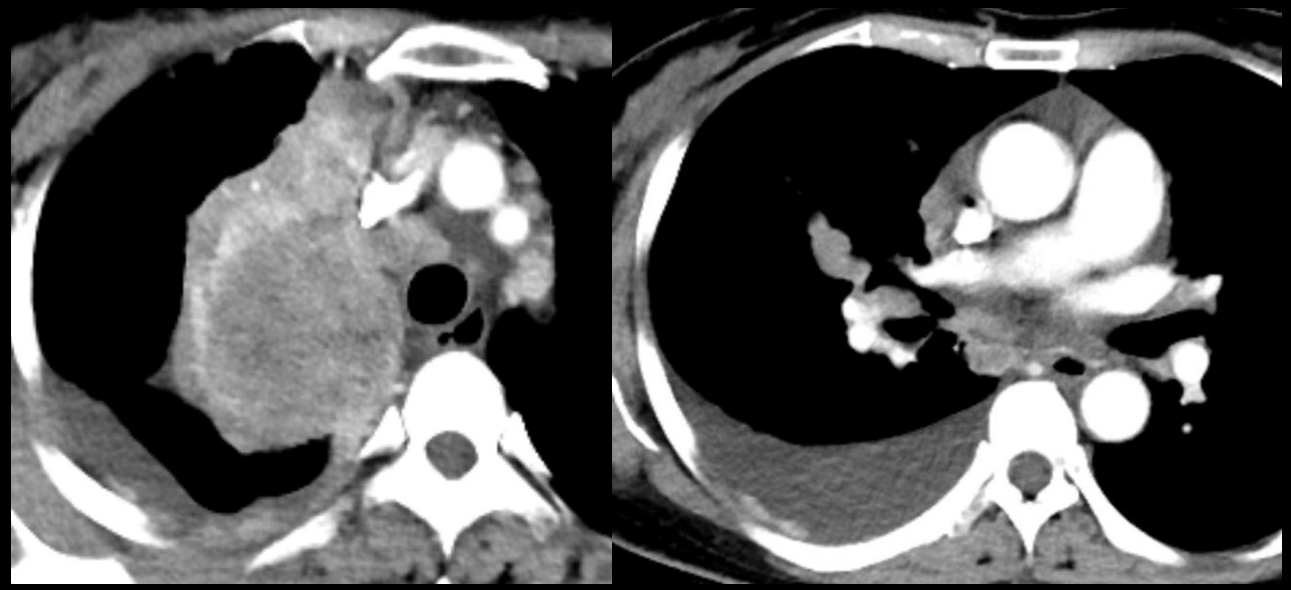
*PNA clamp

PLoS One. 2019 Feb 26;14(2):e0212672.

Case 4

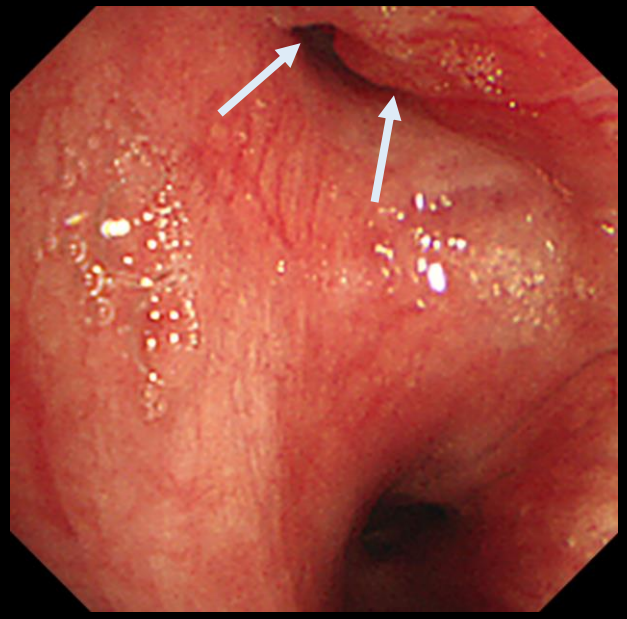
- Female, 54 years old
- Never smoker
- Chief complaints: dyspnea, weight loss

Chest X-ray



Chest CT scan

Case 4



Bronchoscopy

↓

Adenocarcinoma
ALK IHC positive

EBUS-TBNA

↓

Adenocarcinoma

Case 4

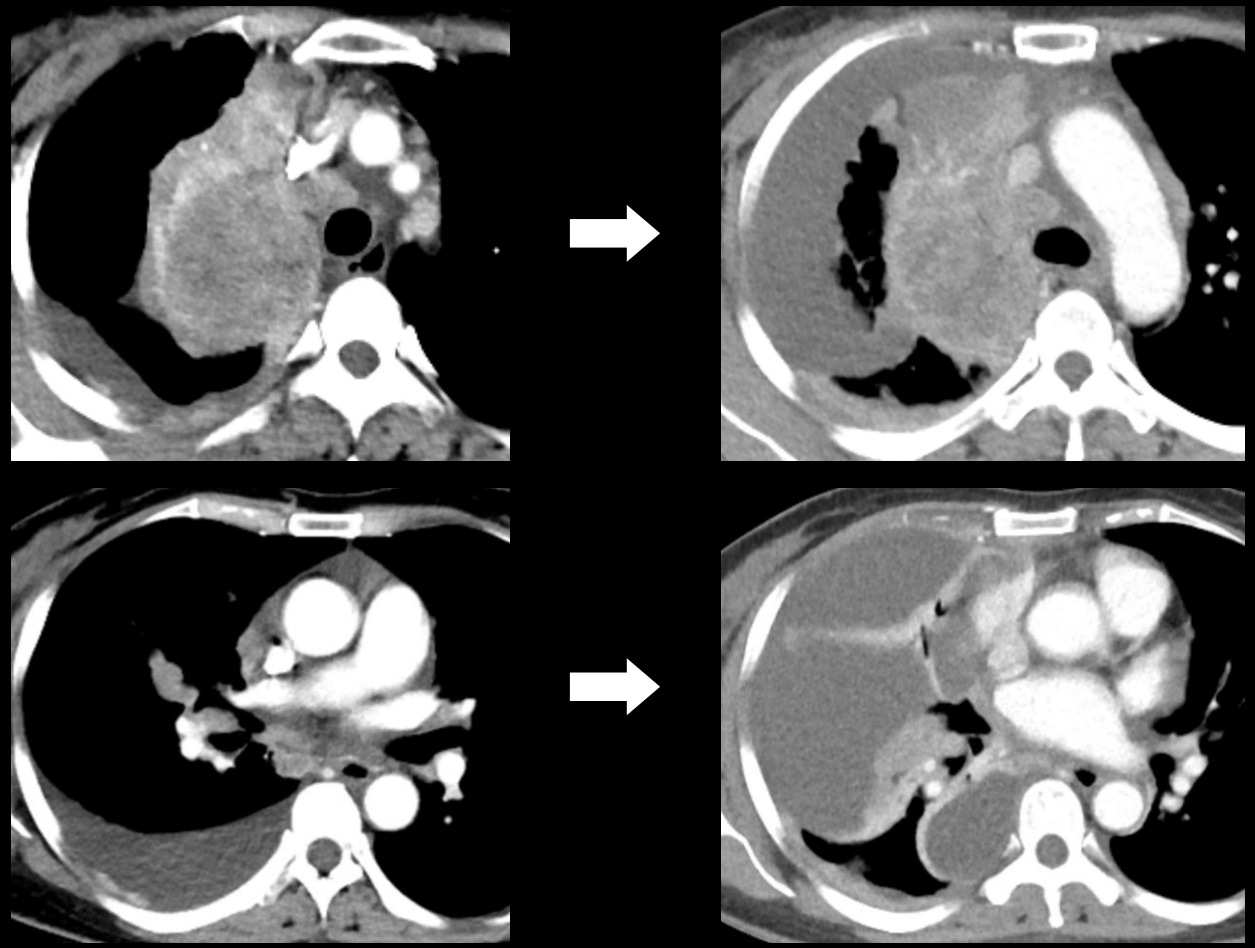
- Stage IV lung adenocarcinoma, ALK IHC positive
- Malignant pleural effusion, spine metastasis
- 2020.01~ alectinib

Case 4

2020.01
Chest X-ray

2020.02
Chest X-ray

Case 4



2020.01
Chest CT

2020.02
Chest CT

Case 4

의뢰서 내용	검사명	EGFR Mutyper(파라핀 블록)
	채취부위	Right upper lobe mass
	임상진단	R/O lung cancer
	기타	
조직/세포 병리번호		

진단

분자병리검사보고서

검사항목: EGFR mutation
검체종류 : FFPE, Lung
병리번호 : S20-01394
병리 진단: Adenocarcinoma, suggestive of primary in the lung

결과:
< EGFR Mutation Analysis Report >
Lung, upper lobe, right, EBUS-TBNA :
POSITIVE FOR EGFR ONCOGENE MUTATION as p.L858R at exon 21

-Test information
Specimen : Genomic DNA isolated from FFPE tissue (S20-01394)
Analyzed gene : Human EGFR on Chromosome 7p11.2 (Exon 18-21)
Method : PANAMutyperTM R EGFR method(Melting curve analysis)
Instrument : CFX96 RT-PCR System (Bio-Rad)
DNA Preparation: Maxwell(R) 16 FFPE Plus LEV DNA Purification Kit for IVD (AX1860)
Reagent: PANAMutyperTM R EGFR Mutation Detection Kit

- Interpretation
EGFR 유전자의 주요 돌연변이 부위를 분석한 결과, exon 21 (p.L858R) 에서 돌연변이가 검출되었습니다.

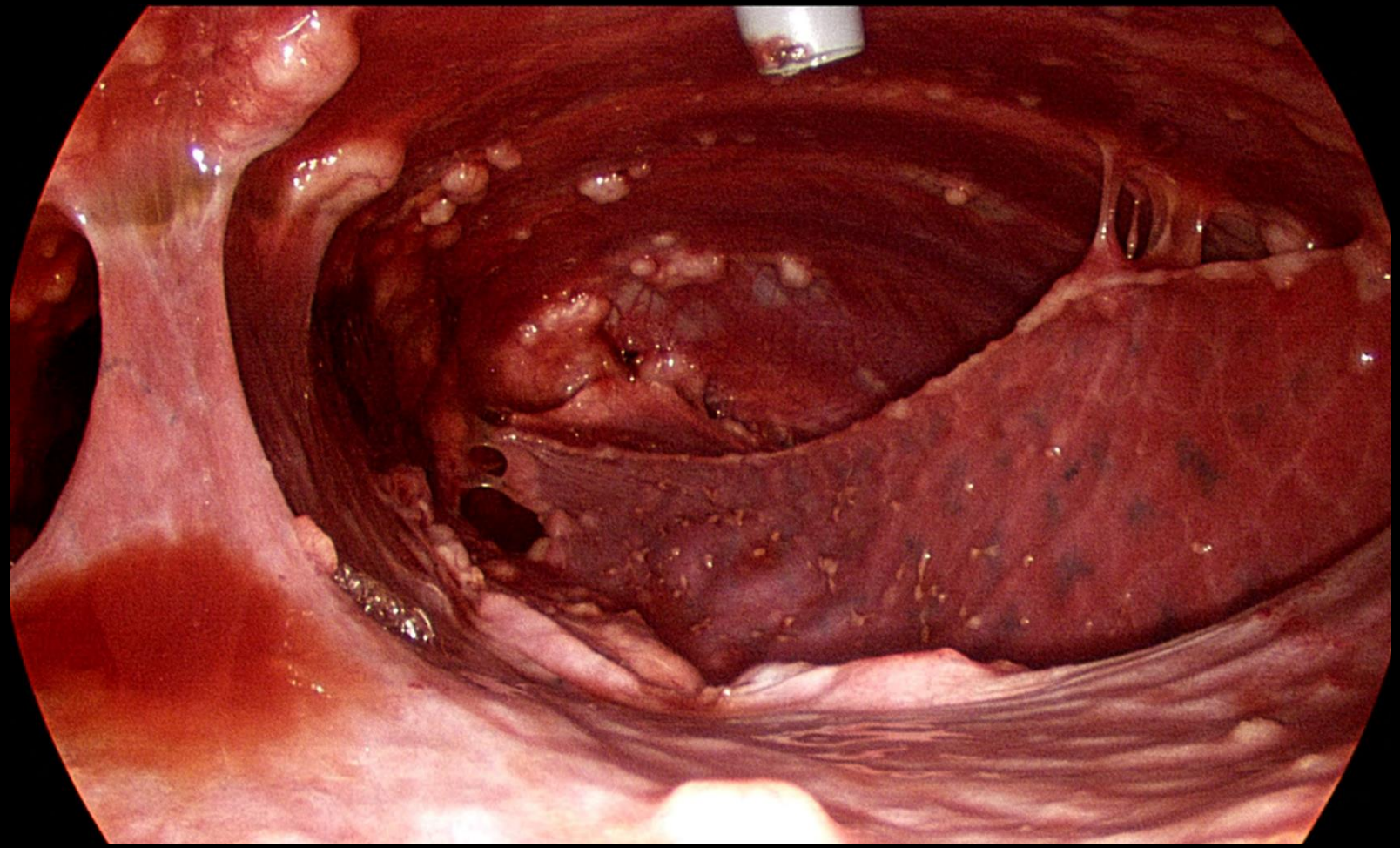
NOTE) Lung, upper lobe, right, EBUS-TBNA :
Adenocarcinoma, suggestive of primary in the lung.

- Comment
EGFR(epidermal growth factor receptor)은 epidermal growth factor를 인지하여 세포 내 여러 신호전달 기작의 스위치 역할을 하는 타이로신 카이나제(TK) 를 만들어내는 구조로서, EGFR 유전자는 과발현, 증폭, 돌연변이의 3가지 기전에 의해 암유전자의 기능을 수행하는 것으로 알려져 있습니다.
비소세포폐암과 연관된 EGFR 유전자 돌연변이는 exon 18-21에서 발생하며, gefitinib 및 erlotinib 등의 치료약제에 좋은 반응을 보이는 것으로 알려져 있으나 T790M과 같은 내성 돌연변이의 경우 초기의 치료반응 이후 이차저항성(acquired resistance)을 보일 수 있습니다.
본 검사는 검체에서 추출한 DNA로 PANAMutyperTM R EGFR 와 정량중합효소연쇄반응(real time PCR) 기법을 이용하여 EGFR exon 18-21의 흔한 돌연변이 47종에 대하여 DNA 염기서열을 분석하는 방법으로 적은 양의 검체로(1ng/㎕) 1% 미만의 돌연변이도 검출이 가능한 민감도가 높은 검사입니다. 다만 임상적 중요성이 잘 알려지지 않은 드문 돌연변이나 일부 exon 19의 deletion 돌연변이는 발견되지 않을 수도 있

Case 4

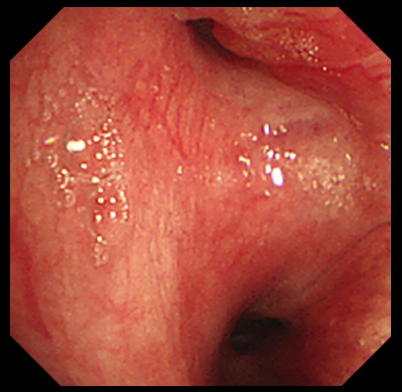
- Stage IV lung adenocarcinoma, ALK IHC positive
- Malignant pleural effusion, spine metastasis
- 2020.01~2020.02 alectinib
- 2020.02~ gefitinib

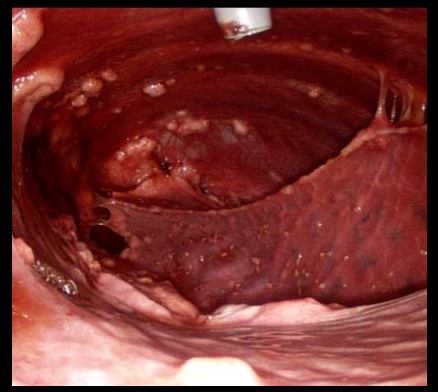
Case 4



2020.02 VATS adhesiolysis with pleurodesis

Case 4





ALK FISH

NGS

진단

ALK GENE translocation FISH TEST

[General Information]
- Specimen site : Lung
- Pathologic diagnosis : Adenocarcinoma
- Sample : Unstained slides x4, H&E slide x1

[ALK FISH evaluation results]
- The number of cells scored : 60
- Distinct two break-apart signals : 7 (11.7%)
- Isolated red yellow : 3 (5.0%)
- Fused yellow signals : 50 (83.3%)
- Isolated green signals : 0 (0%)

[SUMMARY]
: The result of ALK-rearrangement : Positive

GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
EGFR - L858R	Afatinib 1	none
	Dacomitinib 1	
	Erlotinib 1	
	Gefitinib 1	
10 Trials *see p. 22*	Osimertinib 1	
ERBB2 - amplification	Afatinib	Ado-trastuzumab emtansine
	Dacomitinib	Fam-trastuzumab deruxtecan
		Lapatinib
		Neratinib
10 Trials *see p. 24*		Pertuzumab
		Trastuzumab
MET - H1094R - subclonal	Crizotinib	Cabozantinib
9 Trials *see p. 26*		
MYC - amplification	none	none
6 Trials *see p. 28*		

NCCN category

Case 4

2020.01
Chest CT
– Initial presentation

2020.02
Chest CT
– 1 month after
Alectinib

2020.04
Chest CT
– 2 month after
Gefitinib

Concordance between ALK IHC and ALK FISH

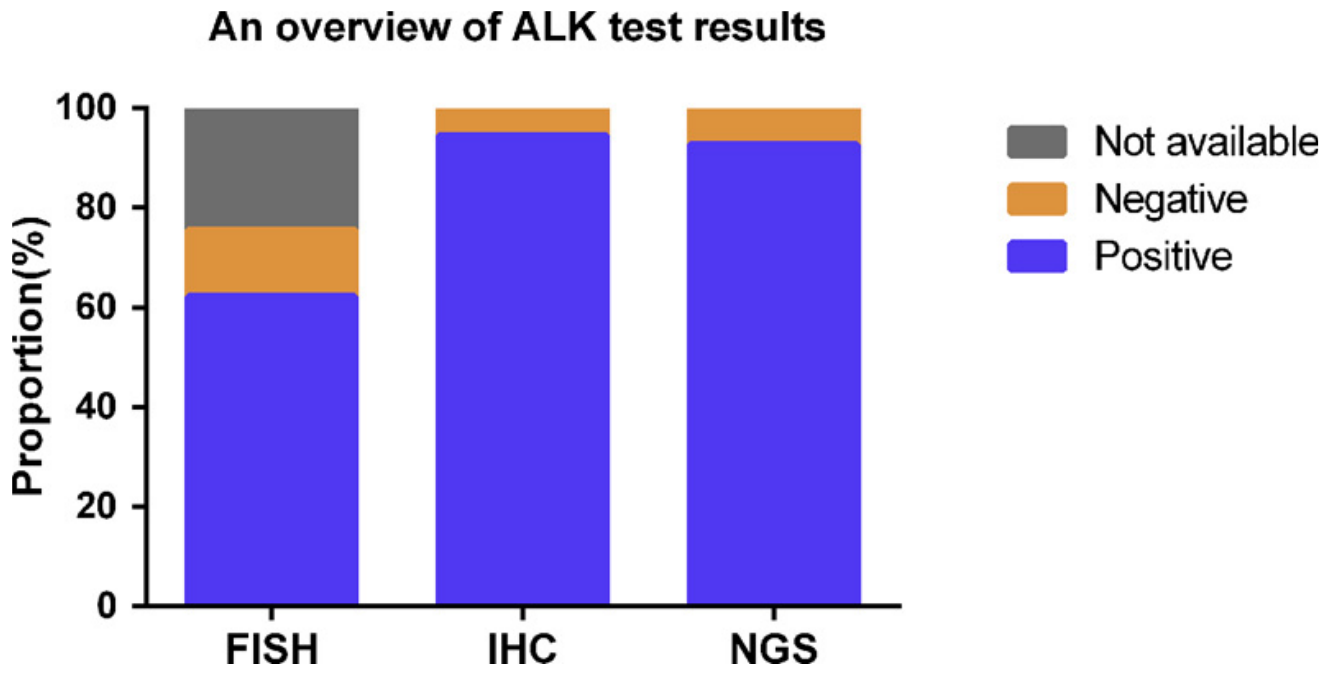
- Blind review of 103 NSCLC specimen (48 ALK FISH-positive cases)
- Overall agreement in 7 pathologists
- ALK IHC vs. ALK FISH

Results		ALK FISH Positive	ALK FISH Negative	Sensitivity	Specificity	Accuracy
ALK IHC	Positive	40%	3%	90%	95%	93%
	Negative	5%	52%			

J Thorac Oncol. 2014 May;9(5):631-8.

Concordance between ALK IHC and ALK FISH

- ALK FISH *vs*. ALK IHC *vs*. NGS
- Study patients: 55 ALK positive patient confirmed by at least one test



Lung Cancer . 2019 May;131:62-68.

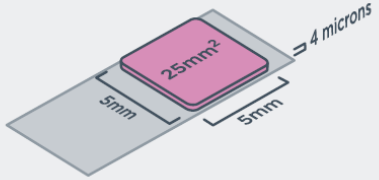
NGS sample requirements

1 검체 크기

FFPE 블록 또는 적어도 11개 비염색 슬라이드

양전하(positively charged) 슬라이드를 이용하며, 4-5 마이크론 두께의 절편은 **고온 처리하지 않음**

2 표면적 및 부피

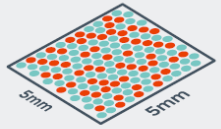


3 종양 핵 비율

종양 핵 비율(Percent tumor nuclei, %TN) = 종양 세포 수를 핵이 있는 모든 세포의 총 수로 나눈 값.

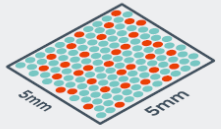
참고: 종양이 차지하는 조직 면적은 종양 핵 비율과 동일하지 않습니다.

최적 (≥35%)



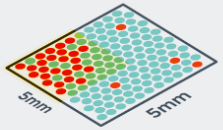
유핵 종양 세포는 35:100 이상 비율로 정사각형 전체에 걸쳐 분산되어 있습니다.

검사 가능 (20%–35%)



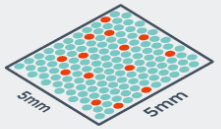
유핵 종양 세포는 1:5 이상의 비율로 정사각형 전체에 걸쳐 분산되어 있습니다.

차선 (<20%)



전체 비율이 20:100 미만으로 세포가 희소하게 분포되어 있지만 종양 세포가 군집화를 이루고 있습니다.

종양 세포를 포함하는 면적을 선택적으로 이용할 경우 (enrichment) 잠재적으로 검사 가능합니다.



유핵 종양 세포는 1:5 미만의 비율로 정사각형 전체에 걸쳐 분산되어 있습니다. 종양 세포를 포함하는 면적을 선택적으로 이용할 수 없습니다.

표본은 Foundation Medicine에서 검토한 후 검사 가능한 경우 주문 담당 의사의 동의를 받아 검사를 진행할 수 있습니다.

유핵 종양 세포
유핵 비종양 세포

From Foundation Medicine

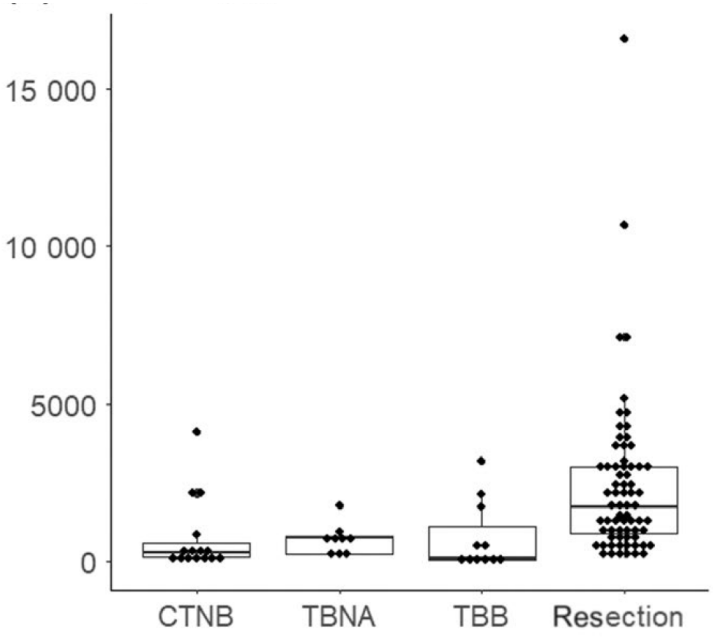
Suitability of bronchoscopic samples for NGS

	EBUS-GS (small GS)	EBUS-GS (large GS)	EBB	EBUS-TBNA
Tumor concentration ≥ 30%	56%	52%	64%	36%
Tissue surface area ≥ 1 mm^2	48%	79%	79%	N/A

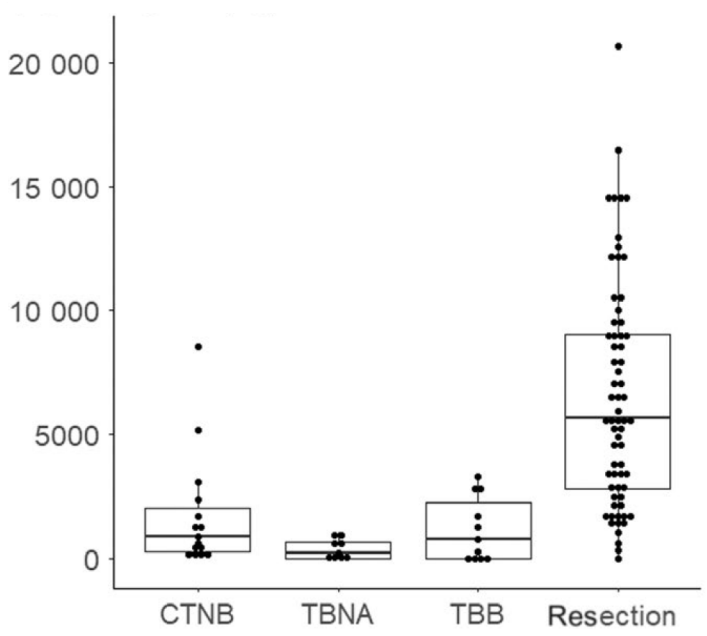
EBUS-GS = endobronchial ultrasound using guide sheath.
EBB = endobronchial biopsy.
EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration.

Diagnostics (Basel). 2021 Feb 25;11(3):391.

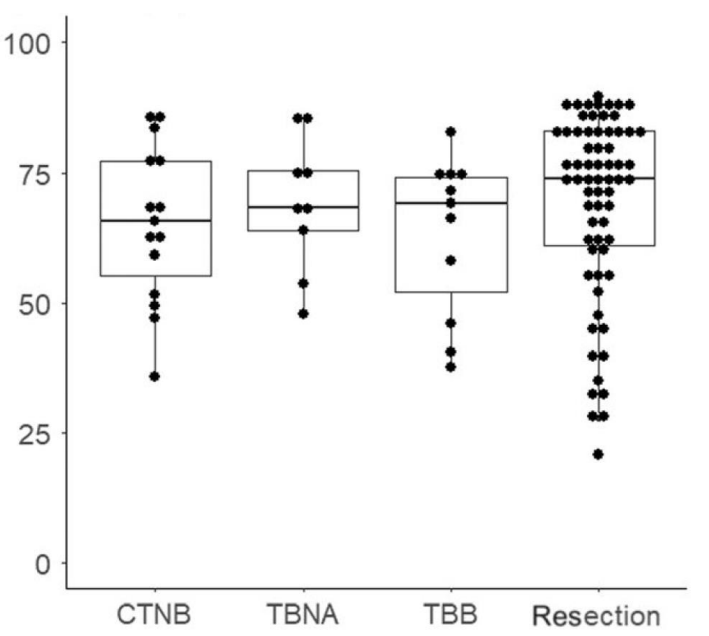
Small bronchoscopic biopsy for NGS



DNA yield



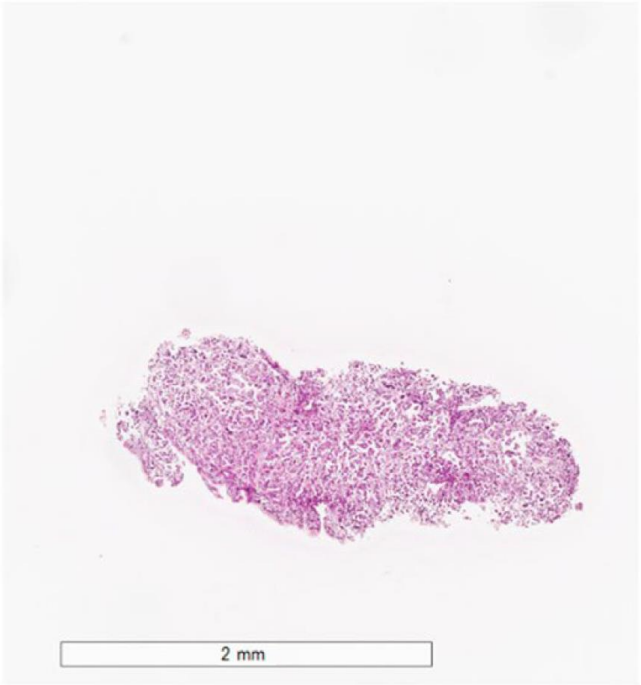
RNA yield



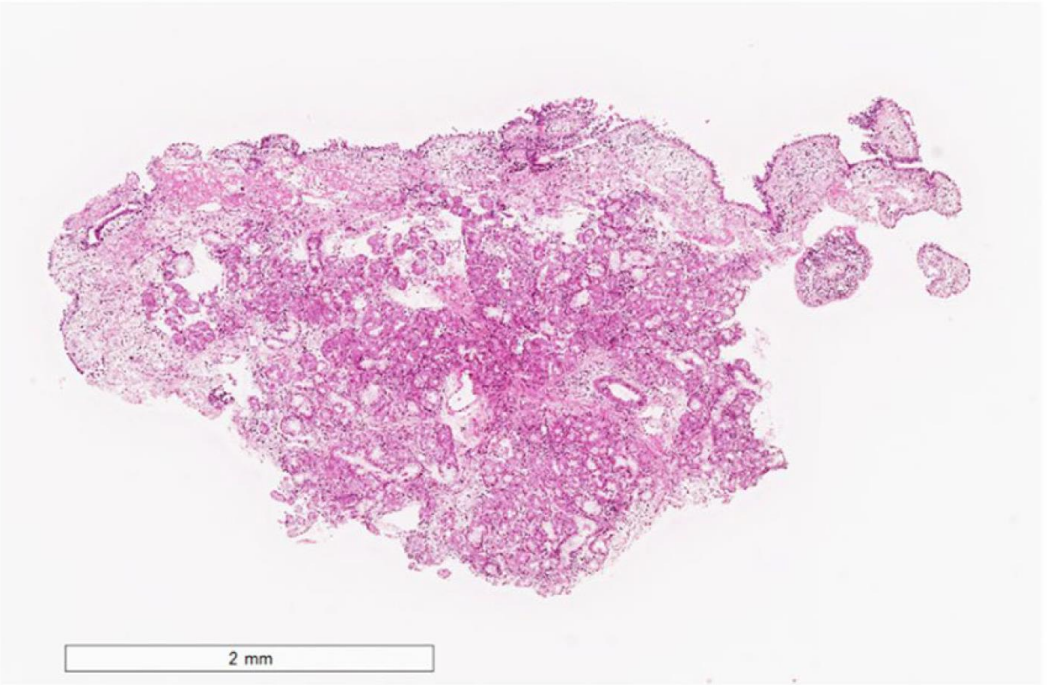
DV200 index

Cancer Sci. 2019 Aug;110(8):2652-2657.

Transbronchial cryobiopsy for precision medicine



Forceps biopsy



Cryobiopsy

Cancer Sci. 2020 Jul;111(7):2488-2498.

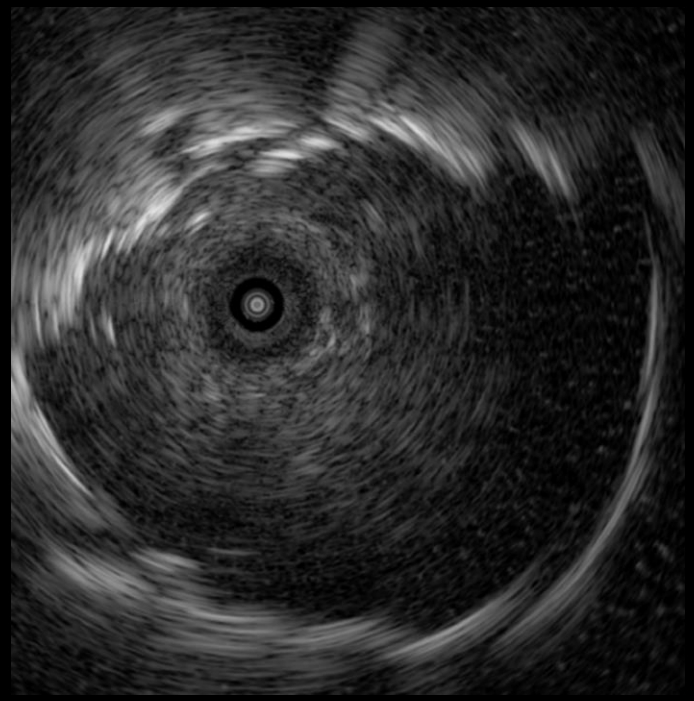
Transbronchial cryobiopsy for precision medicine

	1.9 mm-sized cryoprobe	Common forceps	*P*-value
Median sample size	15 mm^2	2 mm^2	< 0.01
Median DNA amount	1.6 μg	0.6 μg	0.02
Median DNA integrity number	3.1	2.4	< 0.01
Median RNA amount	0.6 μg	0.2 μg	< 0.01
Median RNA integrity number	2.1	2.2	0.07
Successful whole-exome sequencing	90%	15%	< 0.01
Successful RNA sequencing	75%	10%	< 0.01

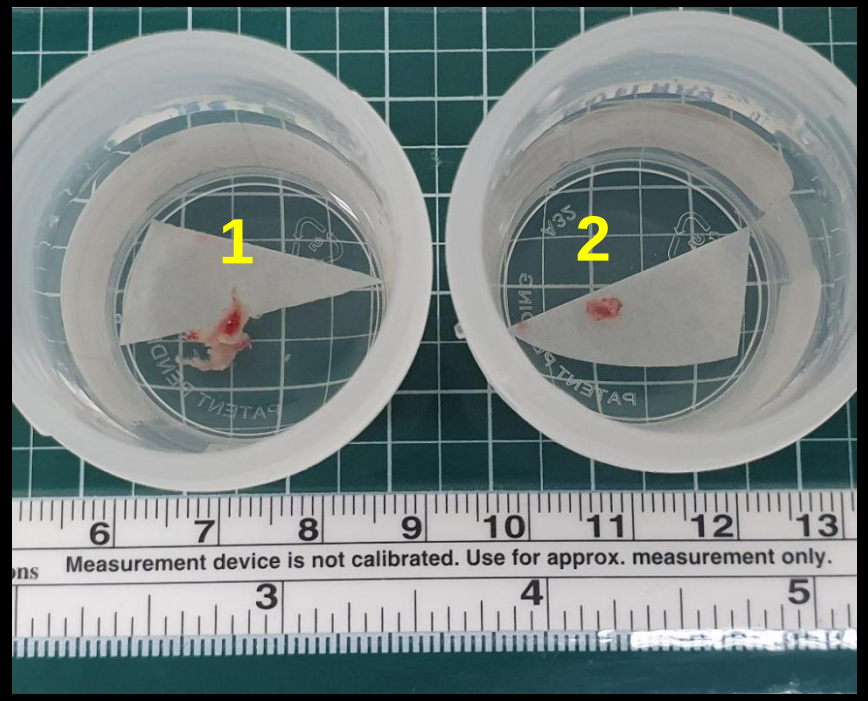
Cancer Sci. 2020 Jul;111(7):2488-2498.

Case 5

Chest CT scan



Radial probe EBUS

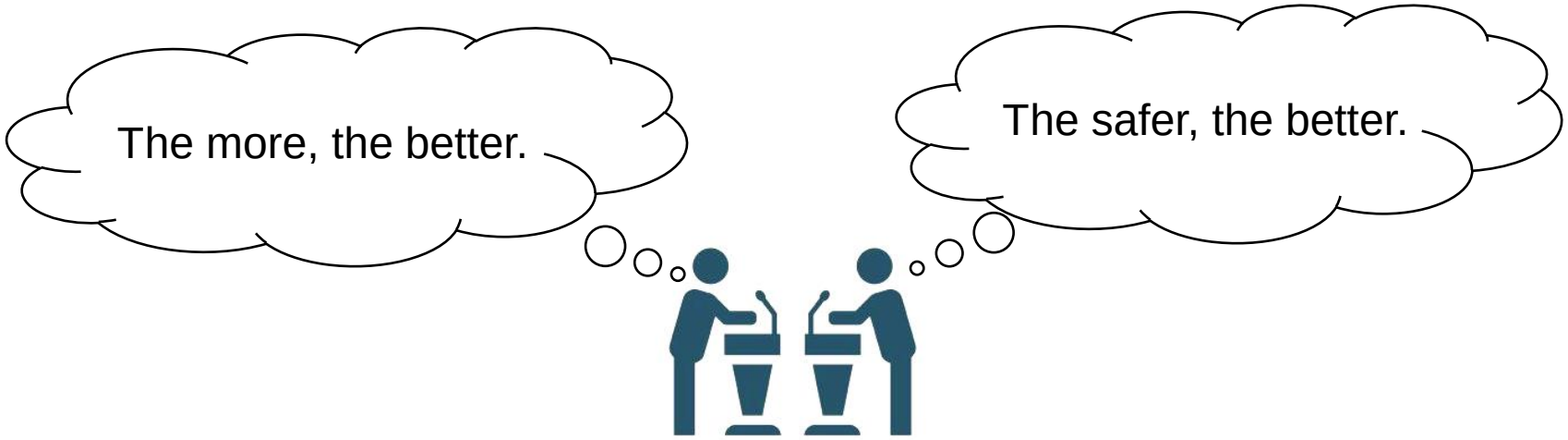


Cryobiopsy samples

1 – Squamous cell carcinoma, 1.3x0.7 cm in size
2 – Squamous cell carcinoma, 0.4x0.3 cm in size

NGS – Tissue volume *vs*. Safety

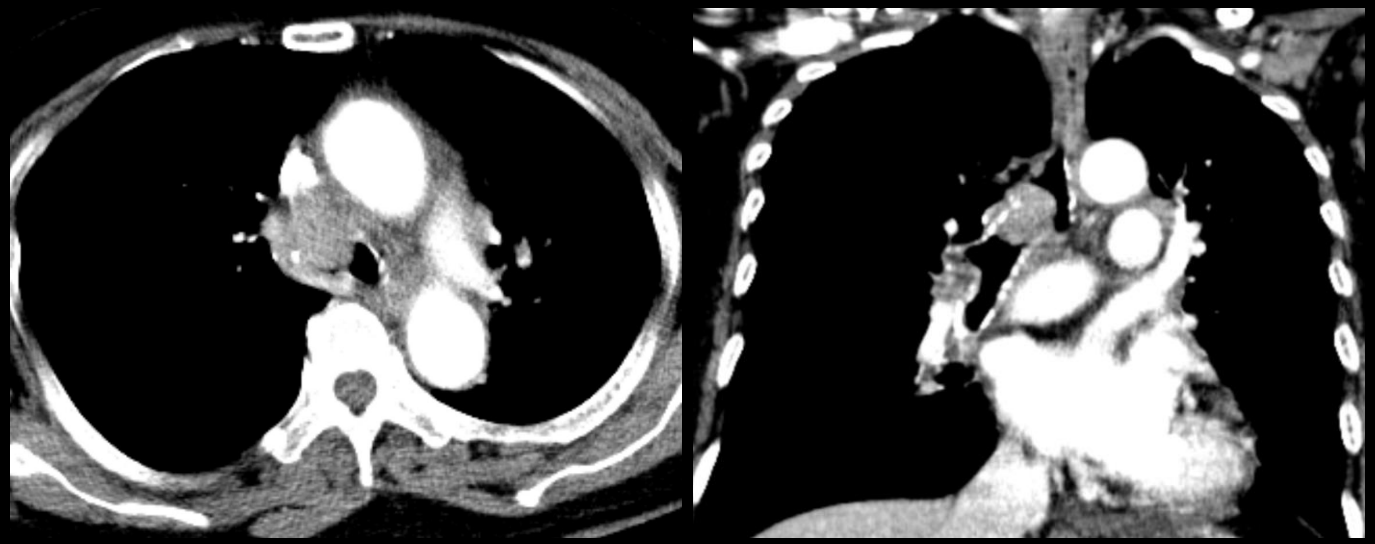
EBUS-TBNA or TBB, PCNA < Cryobiopsy < Medical thoracoscopy < Endobronchial biopsy



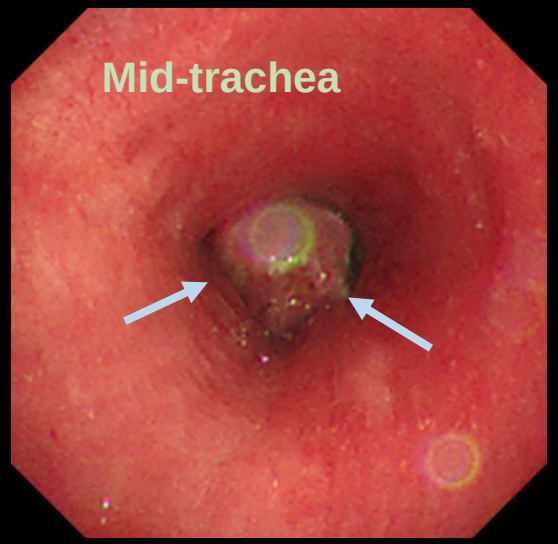
Benign diseases mimicking lung cancer
or
Lung cancer mimicking benign disease

Case 6

- Female, 79 years old
- Never smoker
- Chief complaints: progressive dyspnea



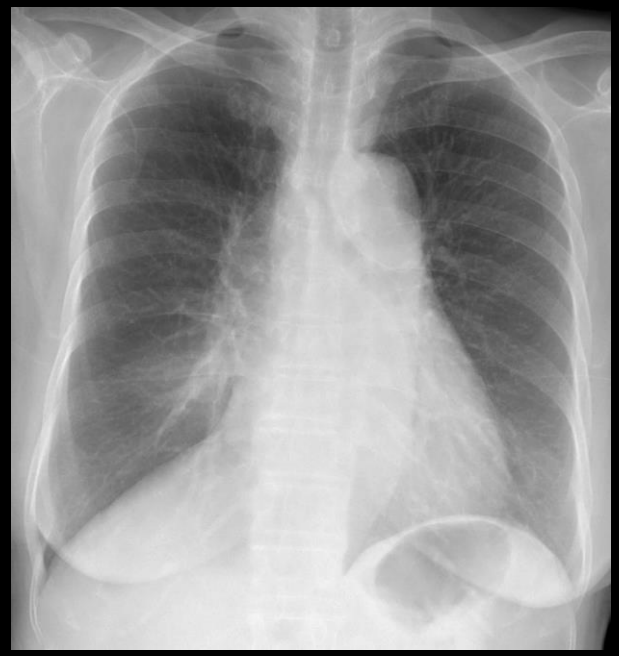
Chest CT scan



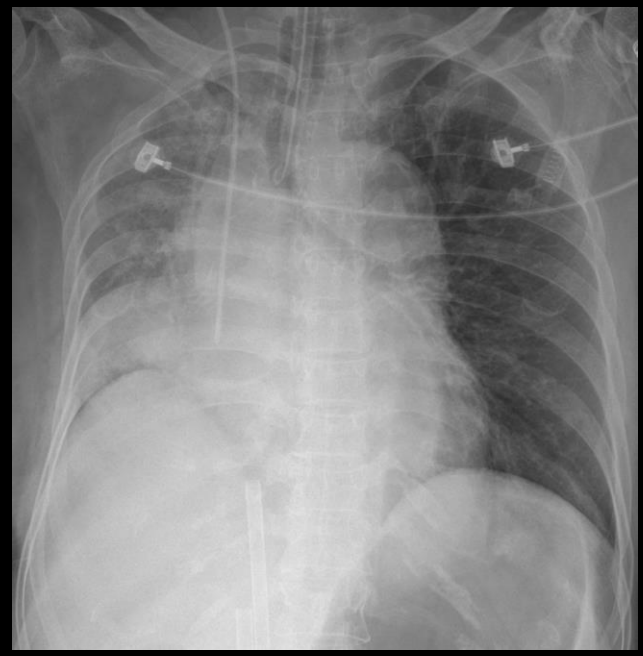
Bronchoscopy

Case 6

- Initial impression: Malignant mass in the central airway
- Plan: Rigid bronchoscopy



Admission day



After CPR and ECMO

Case 6

육안소견

A product of trachea: 3.2g in weight and 2.0x1.3x1.1cm in dimensions(the largest). Sections are blocked in toto, Slides A to D.

PA 최희진 | 육안검사의 정호진 | 전사자 오혜민 | 저장

진단

Lung, trachea, rigid bronchoscopic biopsy :
1.Chronic granulomatous inflammation with necrosis.
2. extensive squamous metaplasia

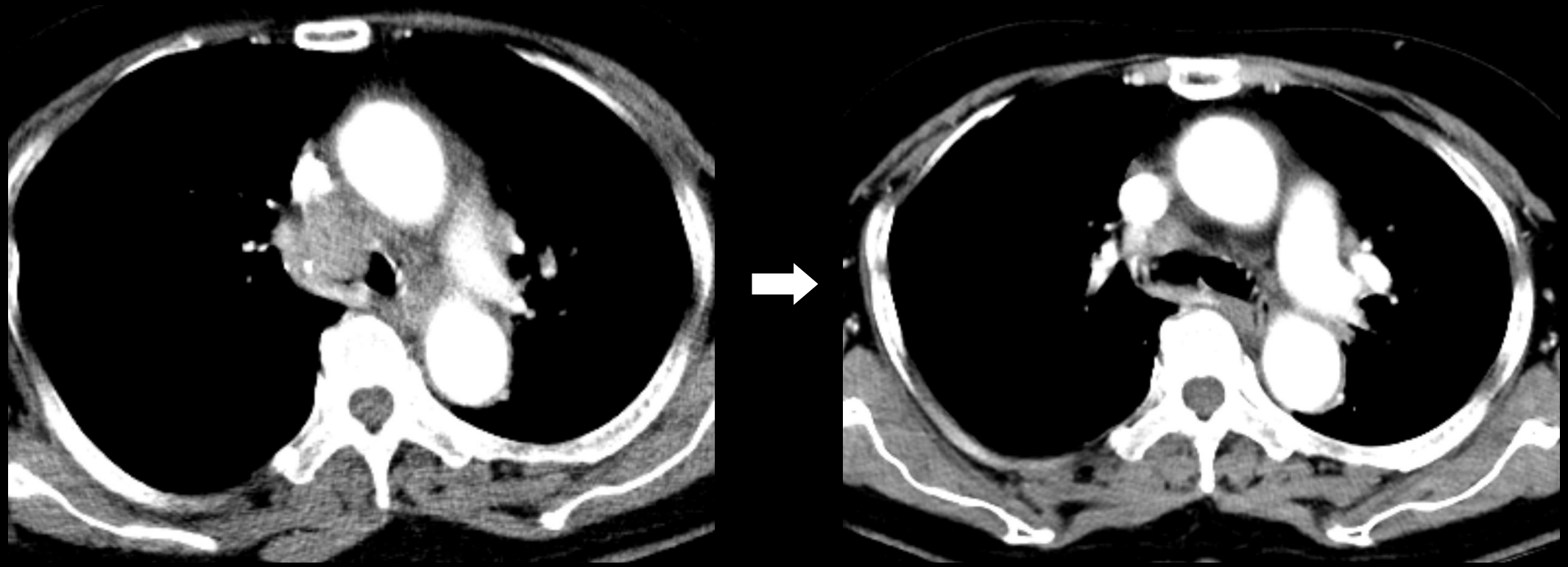
NOTE: The result of Tb-PCR will follow.

결과:

검사항목	검사방법	결 과
M. tuberculosis	Nested PCR	

Lung, trachea, rigid bronchoscopic biopsy :
POSITIVE for Mycobacterium tuberculosis.

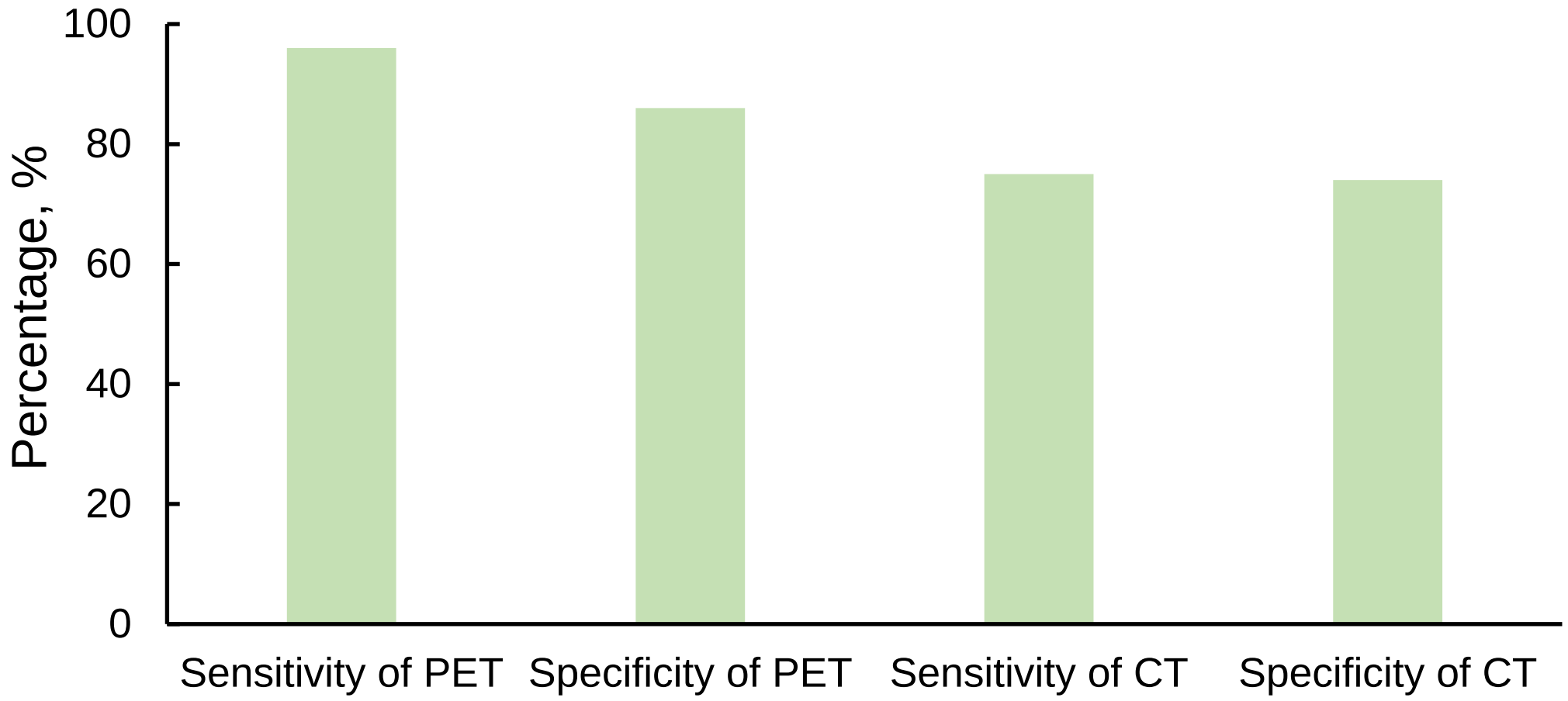
Case 6



Before rigid bronchoscopy

After rigid bronchoscopy +
anti-TB treatment 1 months

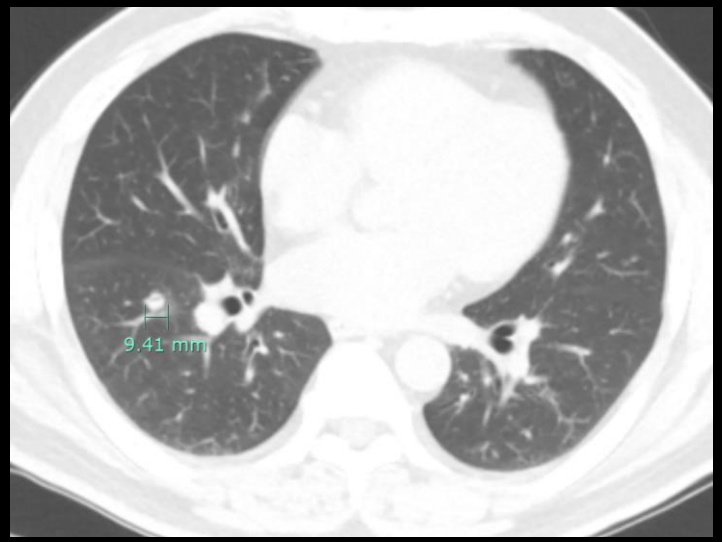
Performance of CT and PET scans

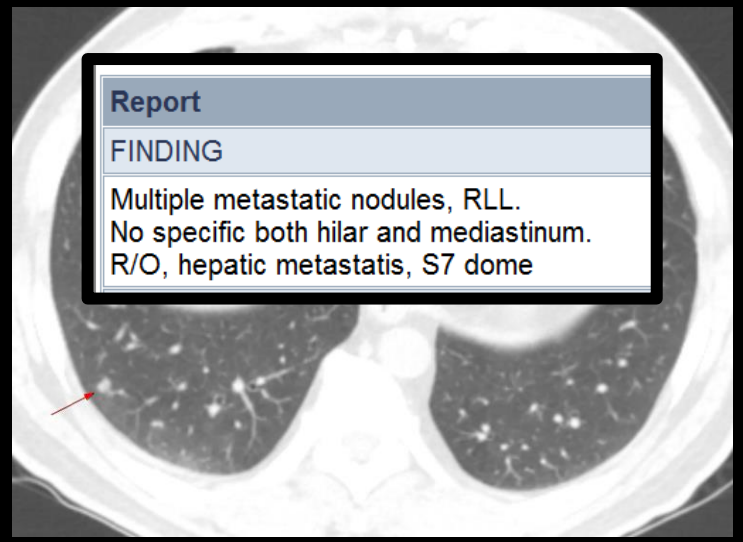


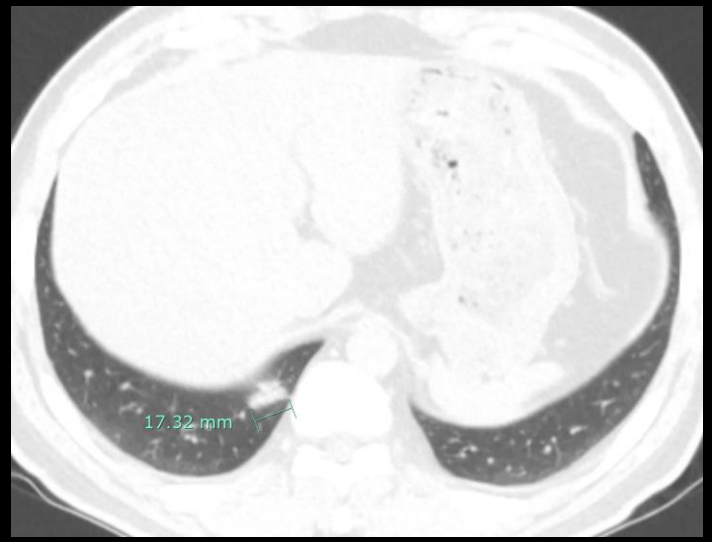
JAMA. 2014 Sep 24;312(12):1227-36.
Clin Radiol. 2019 Jan;74(1):67-75.

Case 7

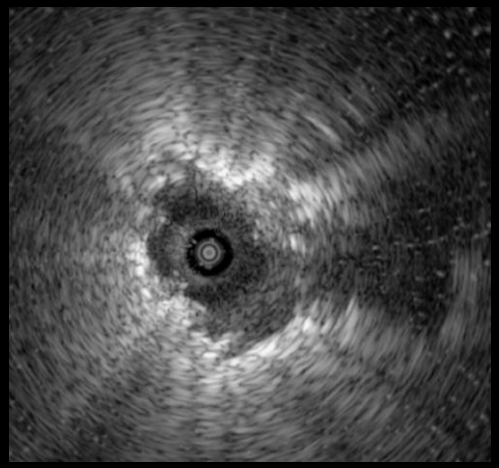
- Male, 53 years old
- Current smoker without underlying disease
- Chief complaints: lung nodules on abdomen CT







Case 7



Radial probe EBUS

Fluoroscopy

진단

```
Lung, lower lobe, posterobasal segment #1~2, right, EBUS-TBLB :
   - Fungal yeast-like foreign organisms, identified (see note)
   - No definite evidence of malignancy.
Lung, lower lobe, posterobasal segment #3, right, EBUS-TBLB :
   - Fungal yeast-like foreign organisms, identified (see note)
   - No definite evidence of malignancy.
```

처방일자	그룹명	검사명	결과	이전결과	R	P	D	참고치	단위	검
2020-09-18		진균 배양	Cryptococcus neoformans							20

Histologic findings in suspected lung neoplasm

Histologic diagnosis (N = 2903)	Percentage
Malignancy	93.3%
Infection	1.3%
Benign lesion	0.4%
Non-specific findings	5%

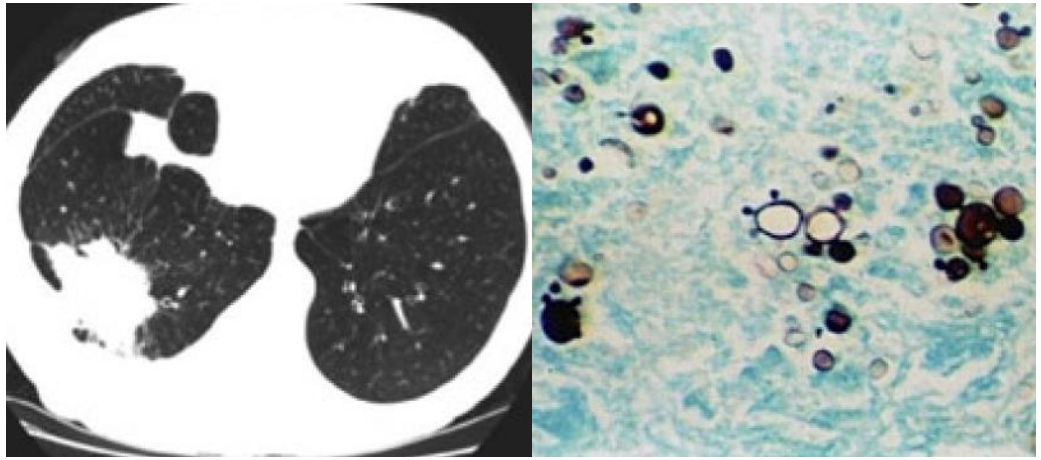
Support Care Cancer. 1997 Mar;5(2):90-3.

Pulmonary infections mimicking cancer

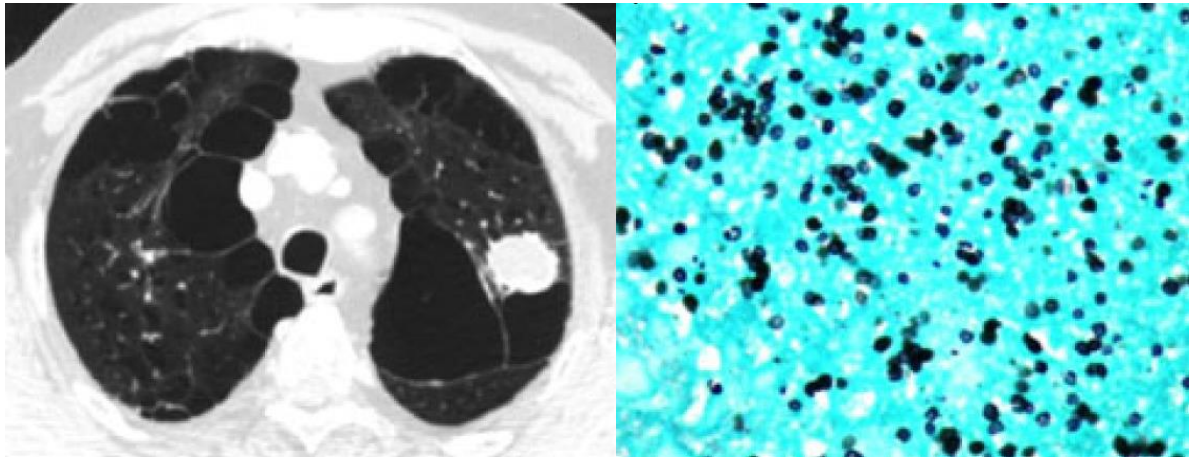
Type of infection (n = 37)	Number (%)
Fungal	**17 (46%)**
Histoplasma capsulatum	8
Coccidioides immitis	6
Cryptococcus neoformans	2
Aspergillus fumigatus	1
Mycobacterial	**10 (27%)**
Mycobacterium tuberculosis	9
NTM	1

Type of infection (n = 37)	Number (%)
Bacterial	**8 (22%)**
Pseudomonas spp.	3
Fusobacterium spp.	2
a-Hemolytic streptococci	2
Staphylococcus aureus	1
Enteobacter cloaceae	1
Parasitic	**2 (5%)**

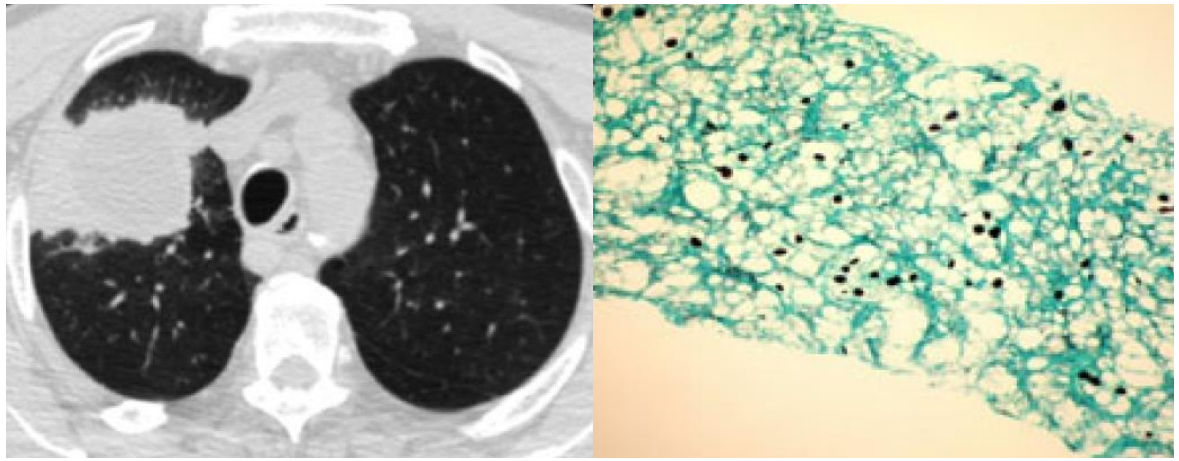
Support Care Cancer. 1997 Mar;5(2):90-3.



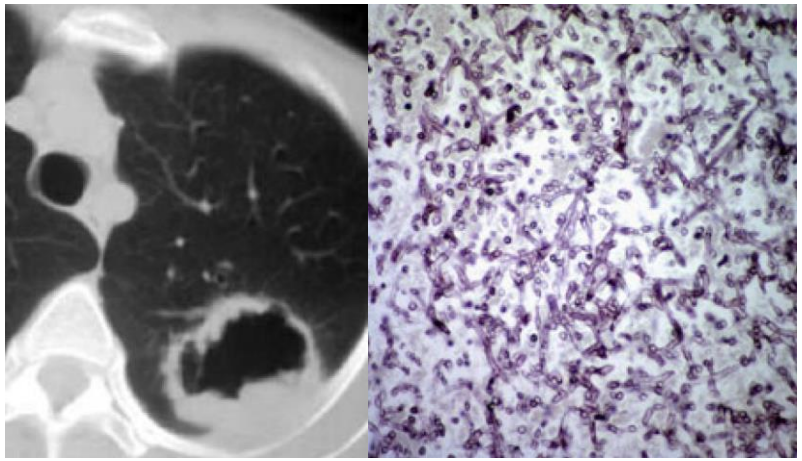
Paracoccidioides brasiliensis



Histoplasma capsulatum



Cryptococcus neoformans



Aspergillus fumigates

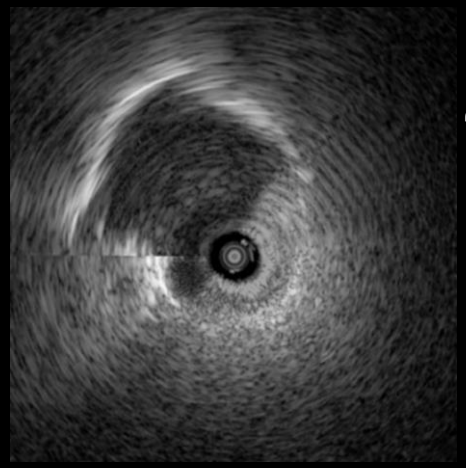
Mycoses. 2014 Apr;57(4):197-208.

Case 8

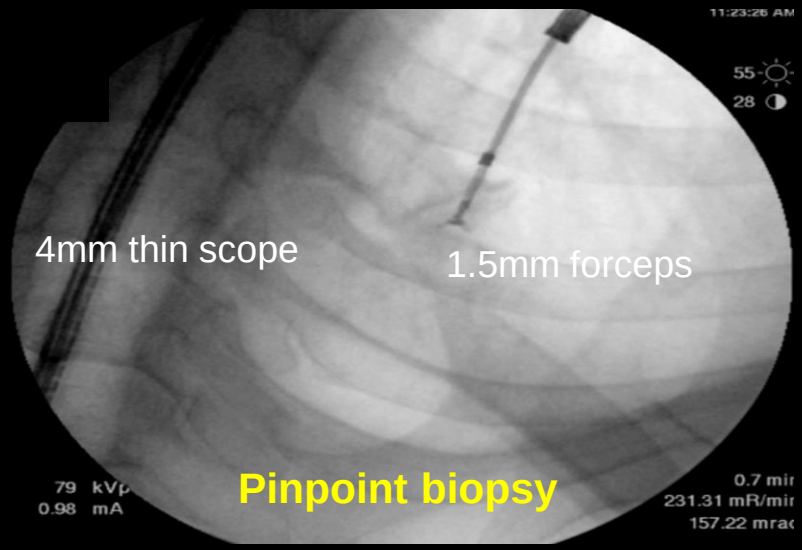
- Male, 60 years old
- 40 PYs current smoker without underlying disease
- Chief complaints: lung nodule found in routine checkup

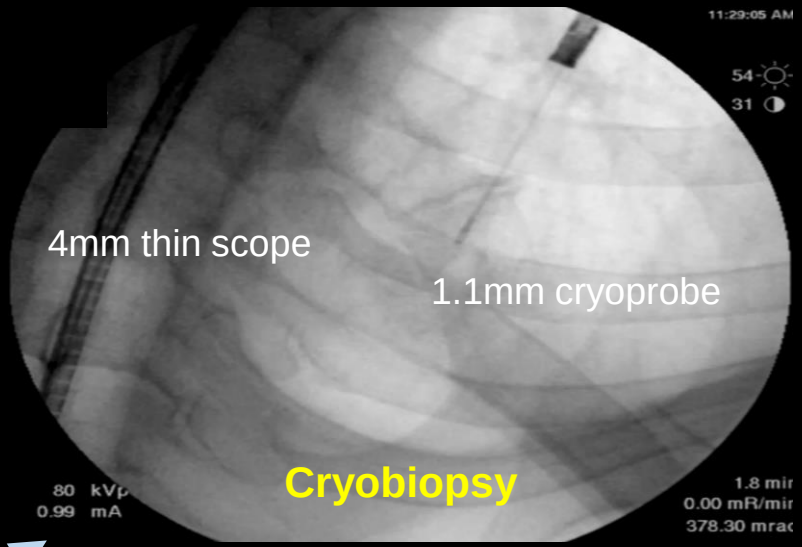
Chest CT

Case 8

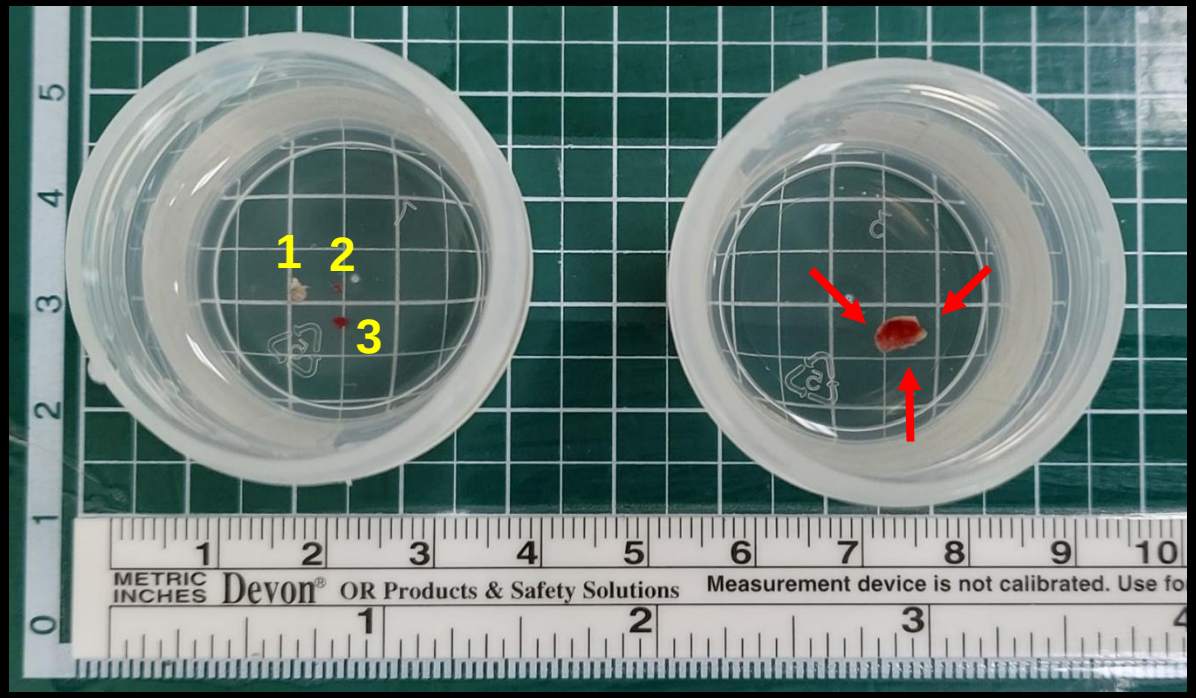


‘Adjacent to’ image on radial probe EBUS





Case 8



Pinpoint biopsy → Cryobipsy

Chronic inflammation

Chronic granulomatous inflammation with necrosis

Tissue TB-PCR positive

Prevalence of TB in PLL

Authors	Year	Region	Desinge	No. of lesion	TB
Herth et al.	2002	Germany	Prospective	50	4%
Shirakawa et al.	2004	Japan	Prospective	50	4%
Kurimoto et al.	2004	Japan	Prospective	150	8%
Herth et al.	2006	Germany	Prospective	54	11%
Huang et al.	2009	Taiwan	Retrospective	83	6%
Tamiya et al.	2013	Japan	Prospective	68	4%
Oki et al.	2015	Japan	Prospective	305	4%

PLoS One. 2021 Jan 28;16(1):e0246371.

Etiology of PLL in Korea

Diagnosis using radial probe EBUS (N = 970)	No. (%)
Lung cancer	71.4%
Pulmonary tuberculosis	3.2%
NTM lung disease	1.0%
Organizing pneumonia	1.0%
Fungal disease	0.6%
Metastasis from colon cancer	0.5%
Metastasis from breast cancer	0.4%

PLoS One. 2021 Jan 28;16(1):e0246371.

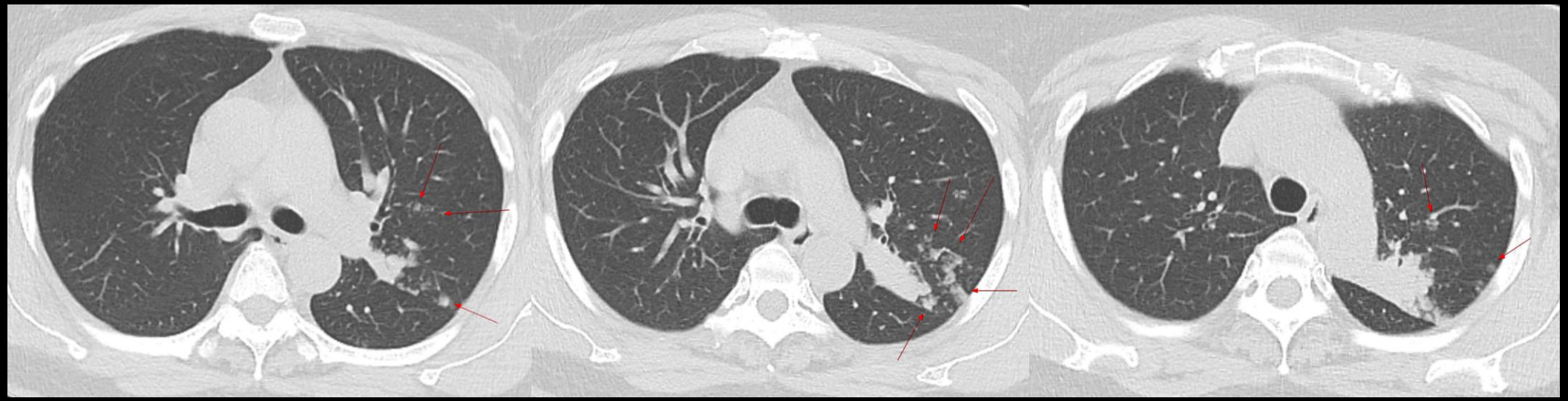
Factors associated with TB

Variables	Odds ration (95% CI)	*P*-value
Age (per year)	0.951 (0.924−0.978)	0.001
Difference in HU between pre- and post-enhancement image	0.976 (0.955−0.996)	0.022
Concentric cavitation	5.211 (1.447−18.759)	0.012
Satellite centrilobular nodule	22.925 (10.556−49.785)	< 0.001

PLoS One. 2021 Jan 28;16(1):e0246371.

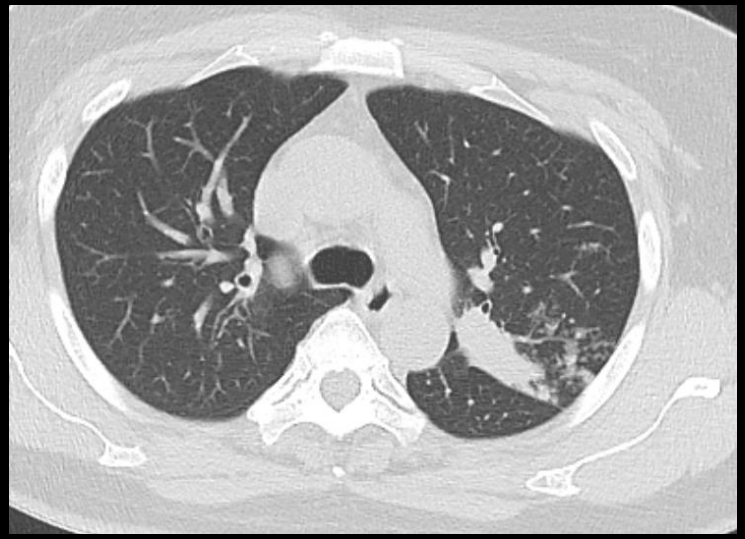
Case 9

- Female, 51 years old
- Never smoker without underlying disease
- Chief complaints: incidental lung nodules

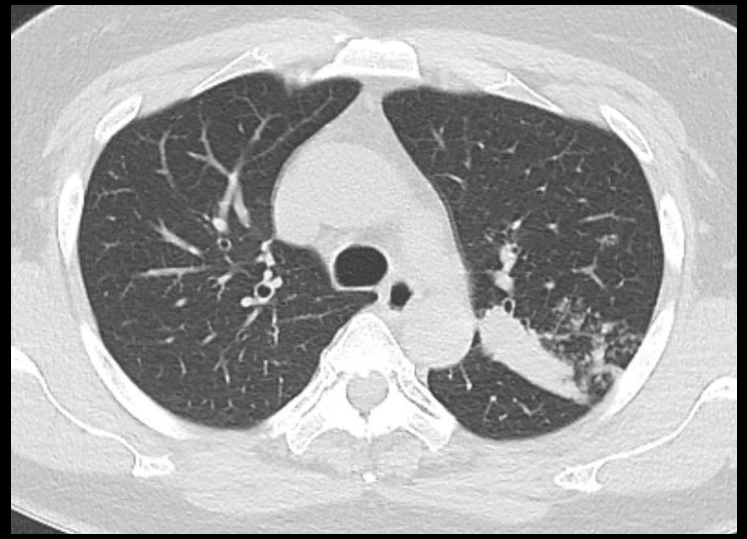


Chest CT at initial presentation

Case 9



Initial CT



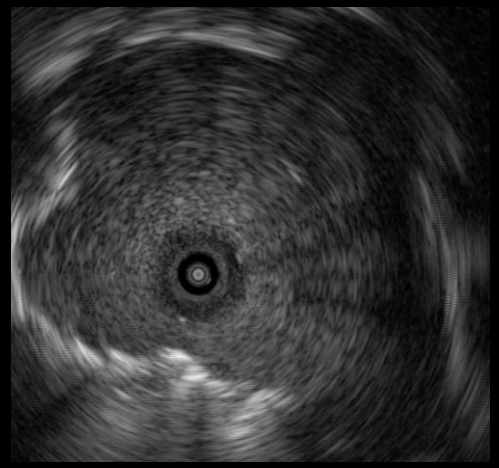
1 month after antibiotics

진단

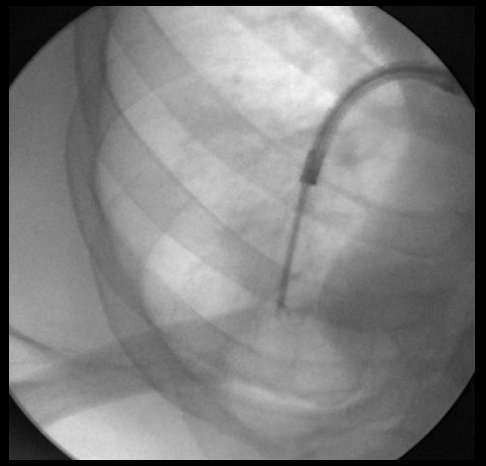
Lung, upper lobe, left, bronchial washing, smear:
   Atypical
   Atypical epithelial cells, suspicious of adenocarcinoma.

NOTE: Cell block was done.

Case 9



Radial probe EBUS



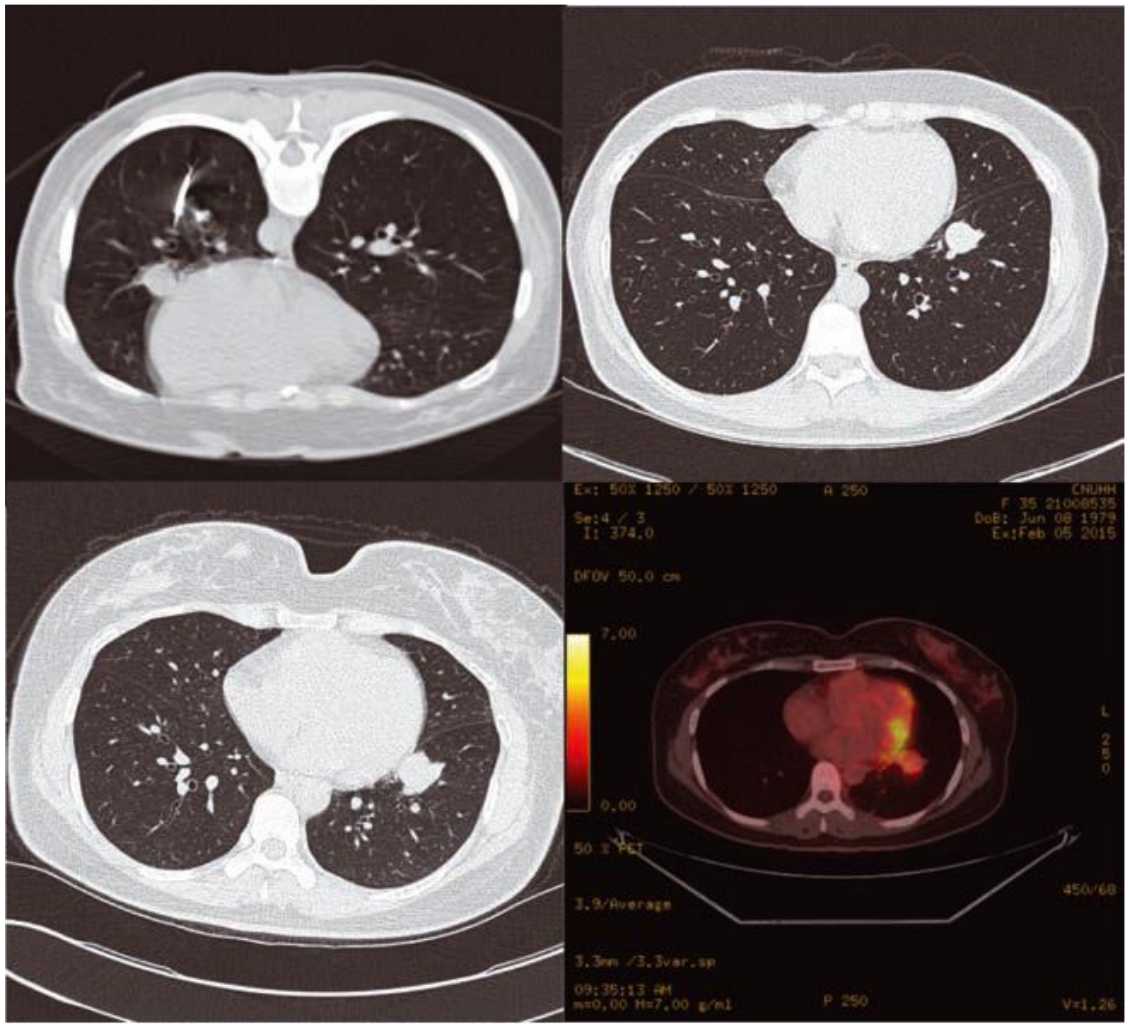
Fluoroscopy

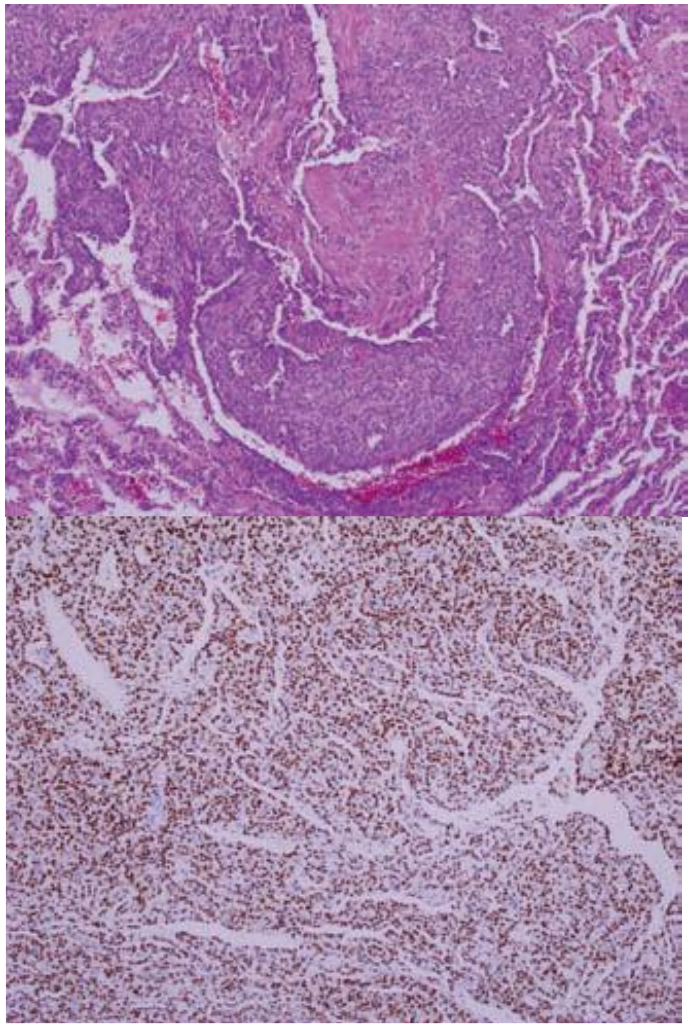
진단

Lung, upper division, apicoposterior segment #1~5, left, EBUS-TBLB :
Non-small cell carcinoma, favor adenocarcinoma.
Lung, upper division, apicoposterior segment #6~10, left, EBUS-TBLB :
Non-small cell carcinoma, favor adenocarcinoma.

Immunohistochemistry (B)
panCK, TTF-1: positive
p40: negative
Ki-67 index: <5%
ALK (D5F3 CDx Ventana): positive
PD-L1 SP263 (Ventana) Tumor Expression: 50%.

Pulmonary sclerosing pneumocytoma





Thorac Cancer. 2016 Jul;7(4):508-11.

Wolf in sheep’s clothing

Summary

- **Successful pathologic diagnosis**
  - Surgery vs. PCNA vs. Bronchoscopy
  - Factors influencing biopsy (ex. CT findings, patient's characteristic)
  - Possible complications?
  - False negative results in lung cancer patients? Careful F/U plan!
  - Diseases mimicking lung cancer or Lung cancer mimicking disease

- **Successful molecular diagnosis**
  - Possible false negative results of each driver mutation
  - Rebiopsy?
  - NGS using appropriate tissue samples

경청해 주셔서 감사합니다!

도움주신 분들

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부산대병원 호흡기내과 김수한 교수님

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