

Advanced Flexible Bronchoscopy and Cryobiopsy for Respiratory Diseases

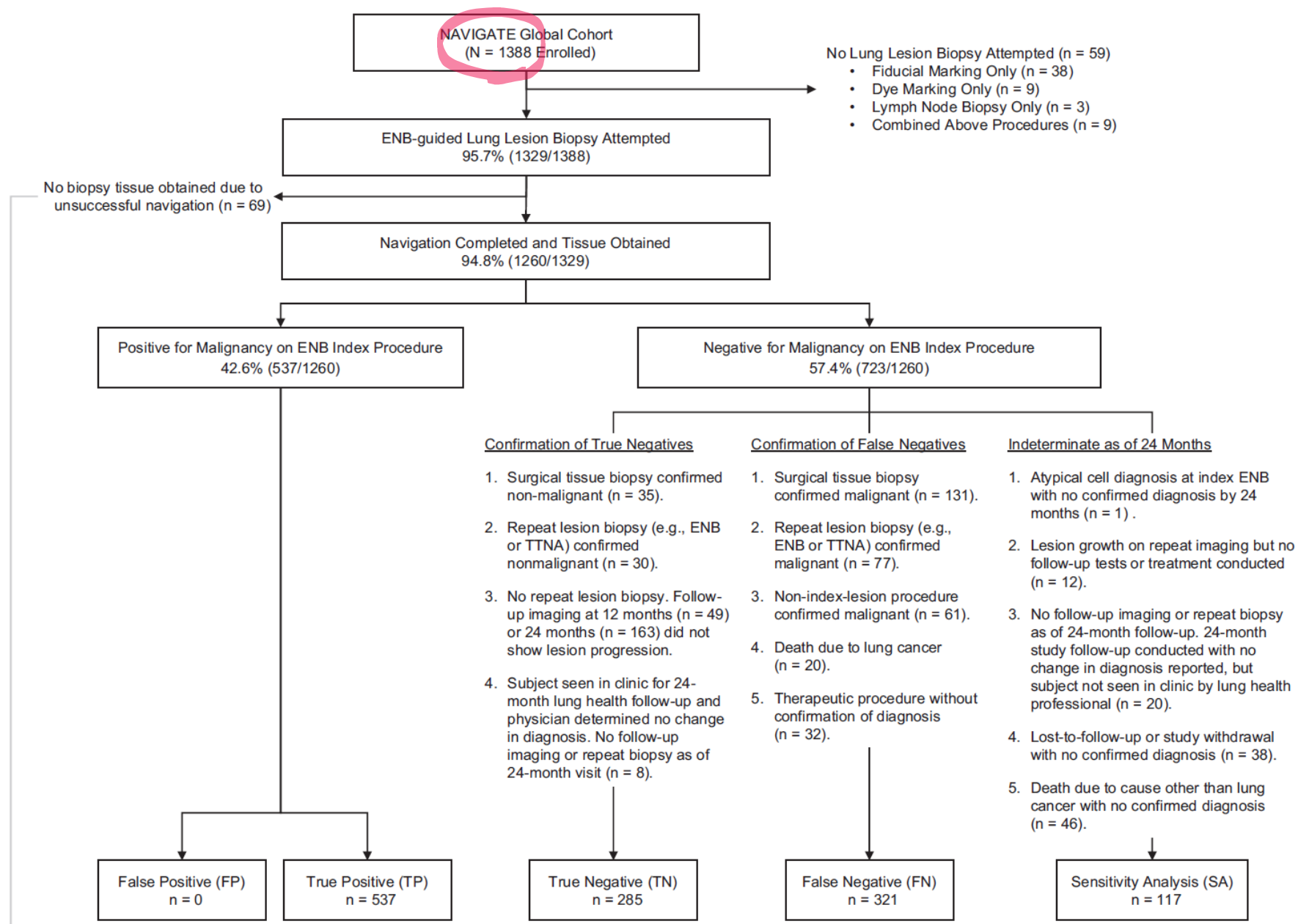
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Electromagnetic Navigation Bronchoscopy (ENB)



Diagnostic Yield (Excluding Subjects Indeterminate as of 24 months)

Calculated as (TP+TN) out of all attempted biopsies including unsuccessful navigation but excluding subjects with indeterminate follow-up:

$(537+285) / 1212 = 67.8\%$

Worst Case (TP+TN / 1329):

$(537+285) / 1329 = 61.9\%$

Best Case (TP+TN+SA / 1329):

$(537+285+117) / 1329 = 70.7\%$

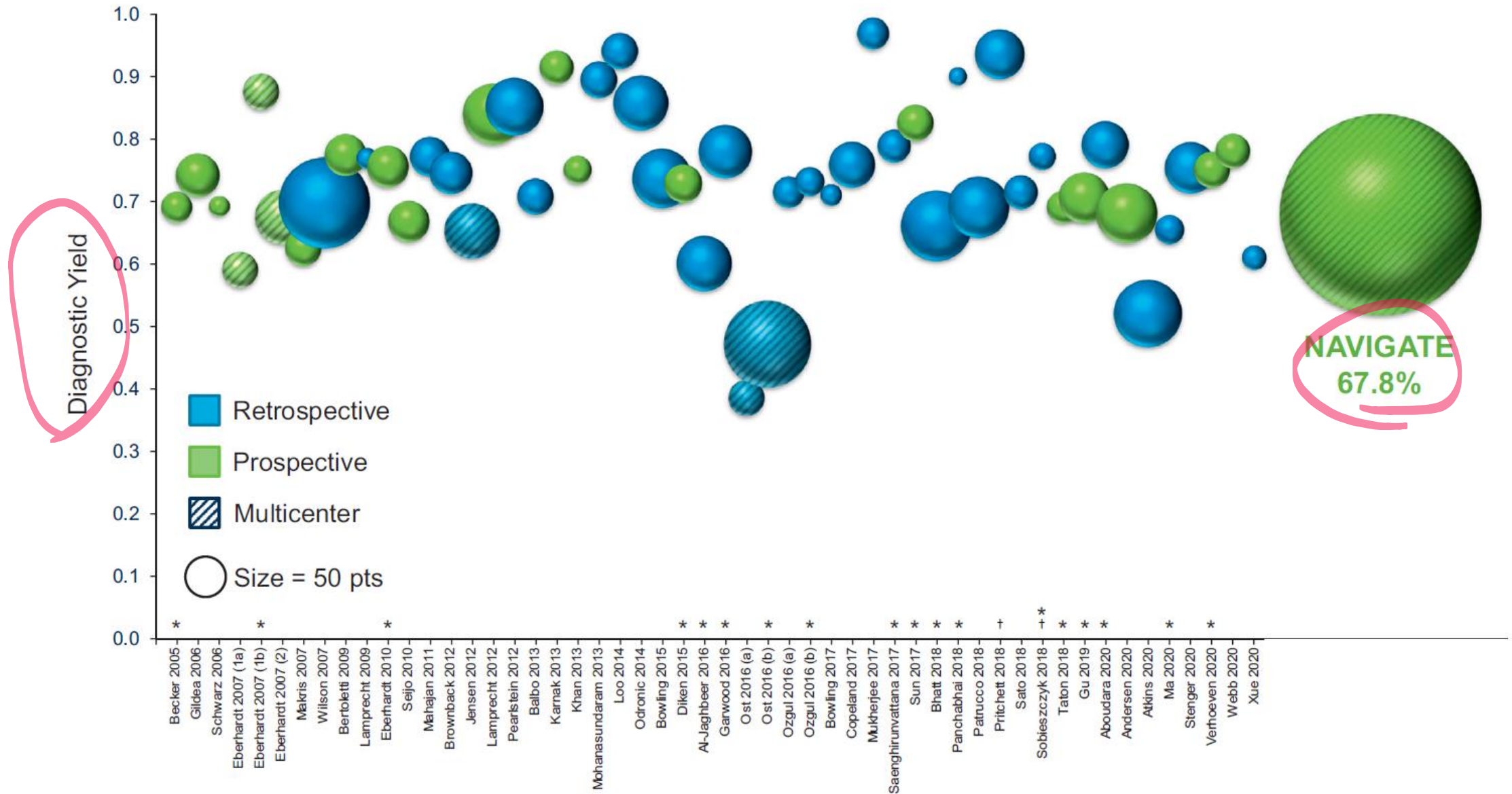


Table 1. Demographics, Procedural, and Lesion Characteristics

Baseline Variables	Global	EU Only	U.S. Only
Subject demographics	1388 subjects	175 subjects	1213 subjects
Age at consent (y)	69.0 (61.0-76.0)	69.0 (61.0-77.0)	69.0 (60.0-76.0)
Subject age \geq 65 y	64.4 (894/1388)	63.4 (111/175)	64.6 (783/1213)
Female/male	50.3/49.7	46.9/53.1	50.8/49.2
Tobacco history (current or former)	79.8 (1107/1388)	81.1 (142/175)	79.6 (965/1213)
COPD	43.3 (601/1388)	34.3 (60/175)	44.6 (541/1213)
Personal history of cancer	48.1 (667/1388)	43.4 (76/175)	48.7 (591/1213)
Family history of cancer	58.8 (816/1388)	38.3 (67/175)	61.7 (749/1213)
Procedural characteristics	1388 procedures	175 procedures	1213 procedures
General anesthesia	78.2 (1086/1388)	56.6 (99/175)	81.4 (987/1213)
Radial EBUS used during ENB	50.6 (703/1388)	4.0 (7/175)	57.4 (696/1213)
Cone-beam CT used during ENB	5.5 (77/1388)	9.7 (17/175)	4.9 (60/1213)
Fluoroscopy used during ENB ^a	85.0 (1299/1529)	41.7 (78/187)	91.0 (1221/1342)
Lesion visible on fluoroscopy ^a	59.1 (768/1299)	50.0 (39/78)	59.7 (729/1221)
Rapid on-site evaluation used ^a	61.7 (777/1260)	17.3 (29/168)	68.5 (748/1092)
Procedure planning time (min)	5.0 (5.0-10.0)	10.0 (10.0-15.0)	5.0 (4.0-9.0)
Total procedure time (min) ^b	50.0 (34.0-69.0)	40.0 (31.0-50.0)	52.0 (35.0-71.0)
ENB-specific procedure time (min) ^b	26.0 (16.0-41.0)	29.0 (21.0-40.0)	25.0 (15.0-41.0)
Operator's previous ENB experience ^c			
0-4 ENB cases per mo	16.8 (233/1388)	77.7 (136/175)	8.0 (97/1213)
5-10 ENB cases per mo	43.3 (601/1388)	21.1 (37/175)	46.5 (564/1213)
>10 ENB cases per mo	39.8 (553/1388)	0.6 (1/175)	45.5 (552/1213)

Table 1. Demographics, Procedural, and Lesion Characteristics

Baseline Variables	Global	EU Only	U.S. Only
Lung lesion characteristics in biopsy cases	1529 lesions in 1329 subjects	187 lesions in 174 subjects	1342 lesions in 1155 subjects
Lesion size (mm), median	20.0 (14.0-29.0)	18.0 (13.0-28.0)	20.0 (14.0-29.0)
Lesion size < 20 mm	49.7 (759/1528)	53.5 (100/187)	49.1 (659/1341)
≤4 mm	0.2 (3/1528)	0.0 (0/187)	0.2 (3/1341)
>4 mm to ≤8 mm	3.8 (58/1528)	5.3 (10/187)	3.6 (48/1341)
>8 mm to <20 mm	45.7 (698/1528)	48.1 (90/187)	45.3 (608/1341)
Lesion size ≥ 20 mm to <30 mm	25.7 (392/1528)	24.1 (45/187)	25.9 (347/1341)
Lesion size ≥ 30 mm to <40 mm	12.4 (189/1528)	11.8 (22/187)	12.5 (167/1341)
Lesion size ≥ 40 mm	12.3 (188/1528)	10.7 (20/187)	12.5 (168/1341)
Upper lobe lesion location	58.7 (897/1529)	62.6 (117/187)	58.1 (780/1342)
Peripheral third of the lung ^d	67.8 (1036/1529)	72.7 (136/187)	67.1 (900/1342)
Lesion distance to pleura (mm)	9.0 (0.0-20.0)	11.0 (0.0-25.0)	9.0 (1.0-20.0)
Pure to mostly ground glass ^e	6.2 (95/1523)	5.9 (11/187)	6.3 (84/1336)
Spiculated lesion border	60.4 (923/1527)	64.2 (120/187)	59.9 (803/1340)
Bronchus sign present on CT	50.8 (777/1529)	66.8 (125/187)	48.6 (652/1342)
Multiple lesions sampled	12.8 (170/1329)	6.9 (12/174)	13.7 (158/1155)
Pretest probability of malignancy > 65% (physician estimate)	61.4 (730/1188)	74.3 (139/187)	59.0 (591/1001)
Pretest probability of malignancy > 65% (calculated) ^f	52.0 (535/1029)	52.9 (64/121)	51.9 (471/908)

Table 3. Significant ($p < 0.05$) Univariate and Multivariate Predictors of Diagnostic Yield

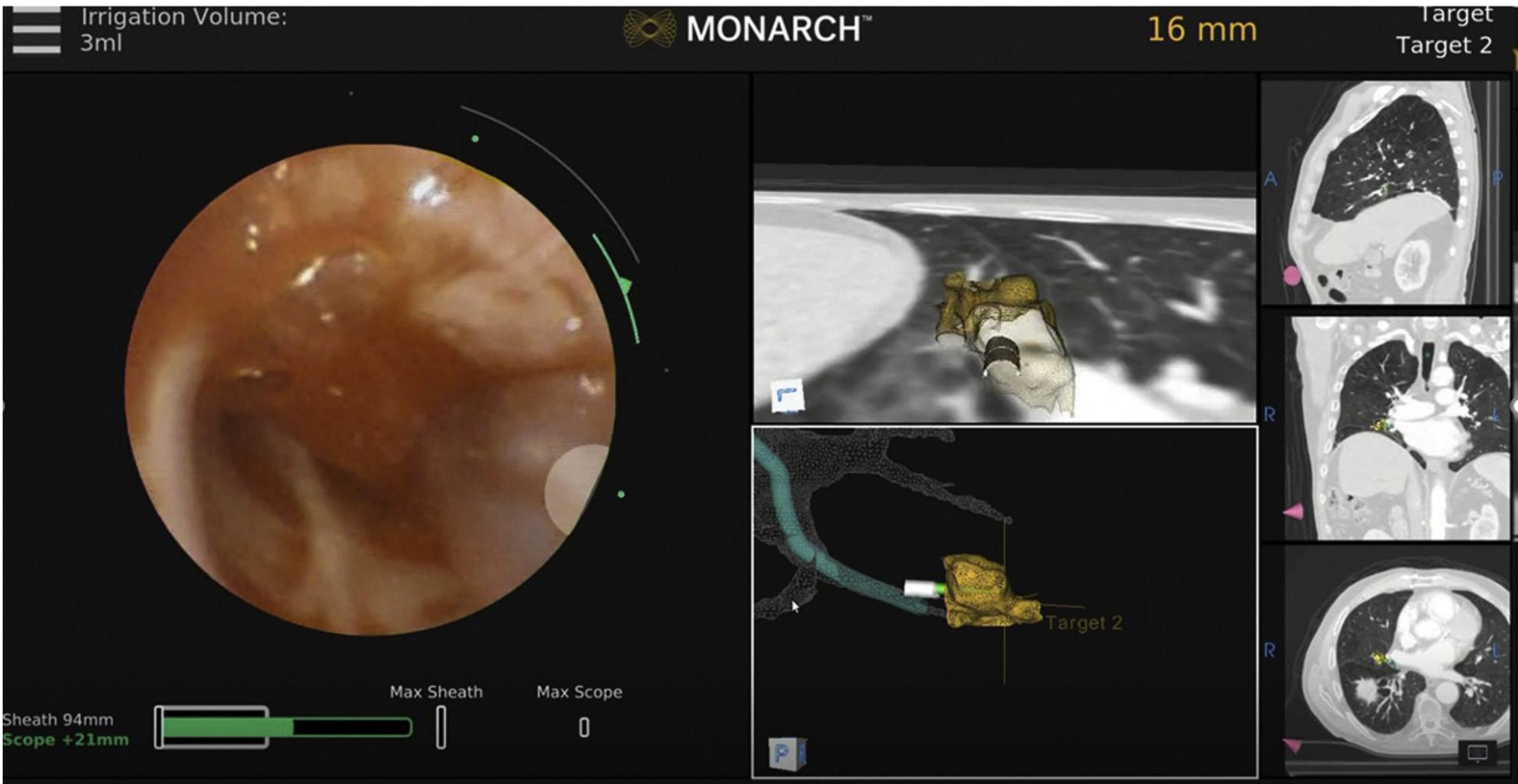
Predictors	Global (1260 Subjects)	EU Only (168 Subjects)	U.S. Only (1092 Subjects)
Significant univariate predictors of higher diagnostic yield			
Multiple lesions biopsied	1.70 (1.14-2.53)	—	1.55 (1.02-2.36)
Previous ENB Use > 10 cases/mo ^a	1.63 (1.16-2.30)	—	—
Previous ENB Use 5-10 cases/mo ^a	1.58 (1.13-2.21)	—	—
Bronchus sign present	1.62 (1.27-2.07)	2.14 (1.10-4.17)	1.69 (1.30-2.21)
Lymph nodes biopsied	1.61 (1.24-2.09)	—	1.41 (1.07-1.85)
Fluoroscopy used	1.56 (1.14-2.14)	—	—
ROSE used	1.48 (1.14-1.92)	—	—
Upper lobe location	1.48 (1.16-1.88)	—	1.51 (1.16-1.97)
Total procedure time, 30-60 min ^{b,c}	—	—	1.57 (1.18-2.10)
Significant univariate predictors of lower diagnostic yield			
Hispanic or Latino ethnicity	0.63 (0.41-0.98)	—	—
Lesion size < 20 mm	0.60 (0.47-0.76)	—	0.58 (0.45-0.76)
Personal history of cancer	0.56 (0.44-0.72)	—	0.54 (0.42-0.71)
Significant multivariate predictors of higher diagnostic yield			
Multiple lesions biopsied	2.36 (1.48-3.77)	—	2.02 (1.30-3.16)
Total procedure time < 30 min ^b	2.27 (1.42-3.65)	—	2.07 (1.30-3.28)
Total procedure time 30-60 min ^b	1.85 (1.34-2.55)	—	1.86 (1.36-2.56)
Previous ENB use 5-10 cases/mo ^{a,d}	1.68 (1.14-2.48)	—	—
Bronchus sign present	1.50 (1.13-2.00)	2.14 (1.10-4.17)	1.59 (1.18-2.13)
Lymph nodes biopsied	1.55 (1.11-2.16)	—	1.51 (1.10-2.07)
ROSE used	1.47 (1.09-2.00)	—	—
Upper lobe location	—	—	1.46 (1.10-1.93)
Significant multivariate predictors of lower diagnostic yield			
Personal history of cancer	0.58 (0.44-0.76)	—	0.56 (0.43-0.75)
Average lesion size < 20 mm	0.72 (0.54-0.95)	—	0.72 (0.54-0.96)
General anesthesia use	—	—	0.66 (0.46-0.96)

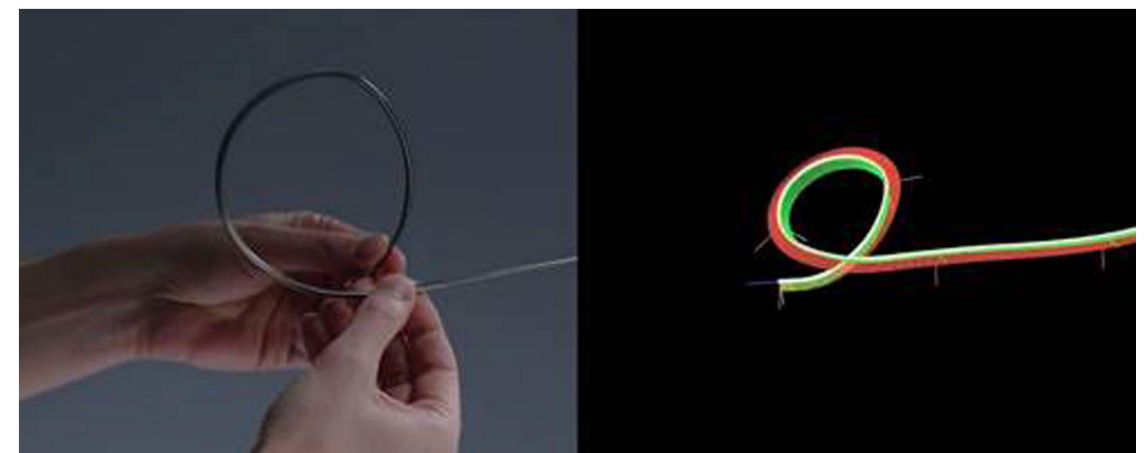
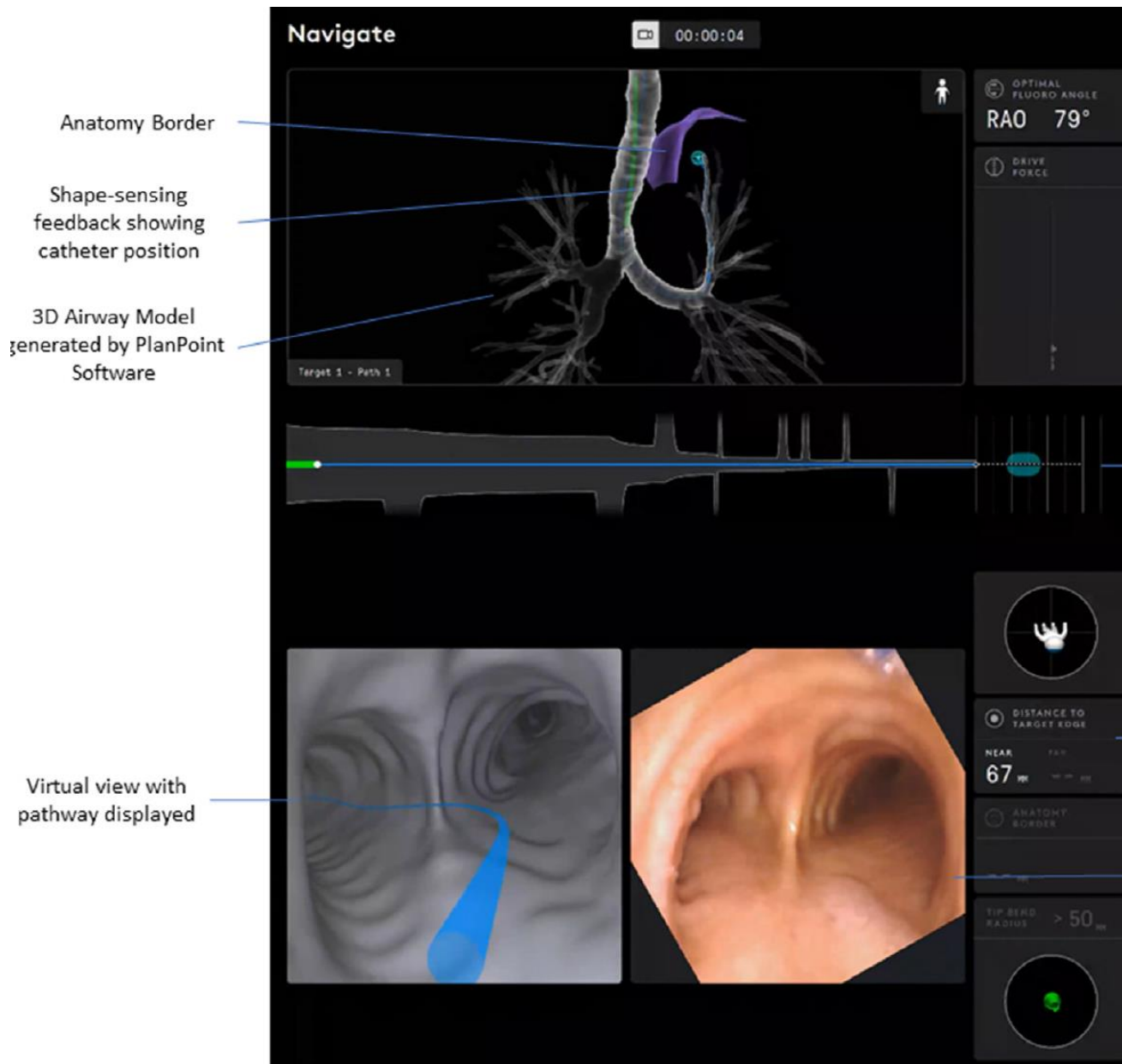
Robotic-assisted Bronchoscopy (RAB)

	<u>Monarch Robotic Bronchoscopy System</u> (Auris Health, Inc., Redwood City, CA, USA)	<u>Ion Robotic Bronchoscopy System</u> (Intuitive Surgical©, Sunnyvale, CA, USA)	<u>The Galaxy System</u> (Noah Medical, San Carlos, CA, USA)
Navigation Technology	<u>Electromagnetic Navigation</u>	<u>Shape Sensing</u>	<u>Electromagnetic with digital tomosynthesis TiLT+ Technology™</u>
Catheter Outer Diameter	Outer Sheath: 6 mm <u>Inner Scope: 4.2 mm</u>	<u>3.5 mm</u>	<u>4.0 mm</u>
Working Channel Diameter	2.1 mm	2 mm	2.1 mm
<u>Vision during Biopsy</u>	Yes	<u>No</u>	Yes
<u>Scope Reprocessing</u>	Yes	Yes	No, <u>disposable</u>
Compatibility with Cone Beam or Advanced Fluoroscopy	Yes	Yes	Yes
Therapeutic tools	Under Investigation	Under Investigation	Unclear
FDA Approval	Yes	Yes	<u>Pending</u>









View showing catheter progress towards target

Distance to Near/Far Edge of Target from catheter Tip

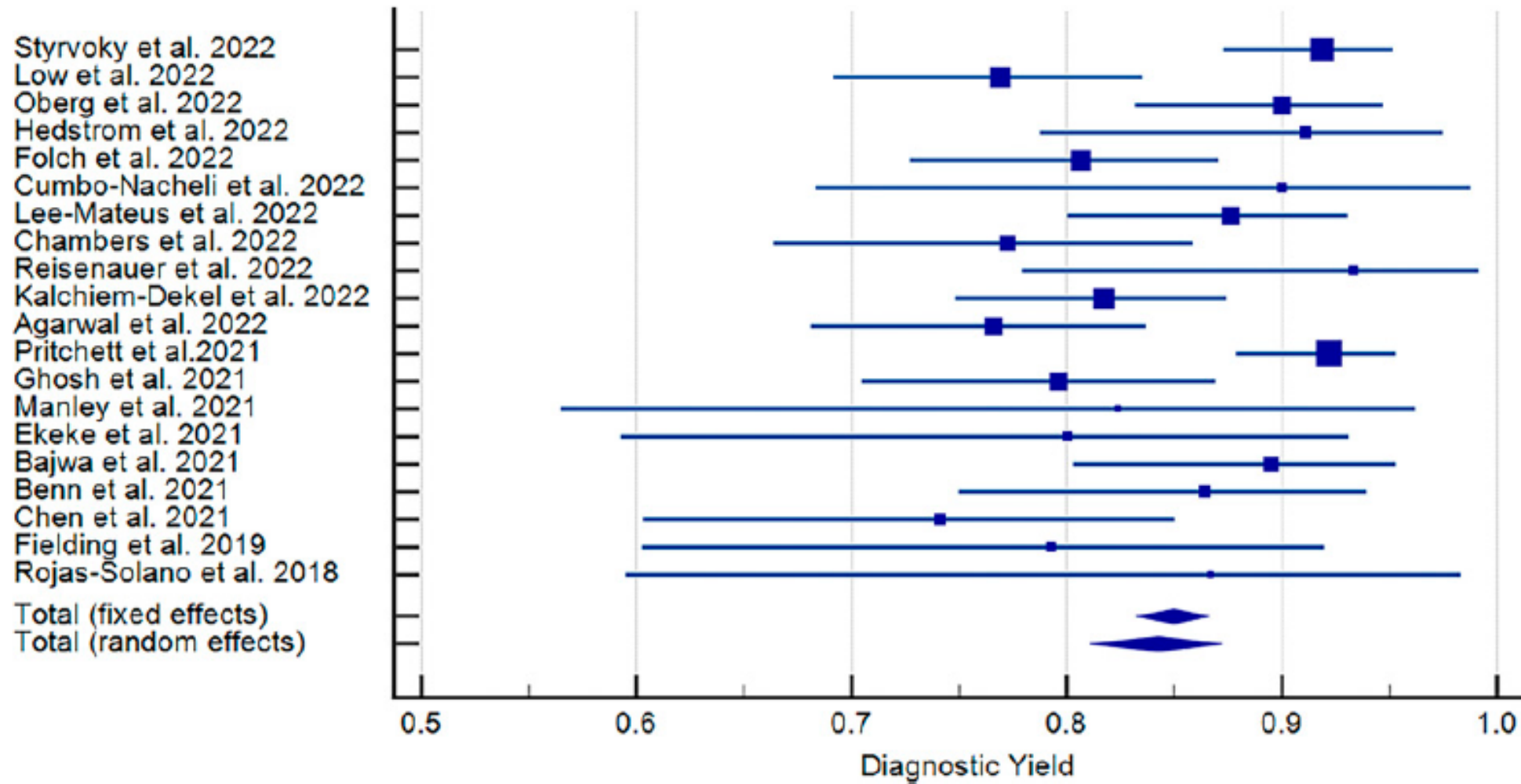
Live real-time airway view from Ion Peripheral Vision Probe

Simoff, Michael J et al. "Shape-sensing robotic-assisted bronchoscopy for pulmonary nodules: initial multicenter experience using the Ion™ Endoluminal System." *BMC pulmonary medicine* vol. 21,1 322. 16 Oct. 2021

Reisenauer, Janani et al. "Ion: Technology and Techniques for Shape-sensing Robotic-assisted Bronchoscopy." *The Annals of thoracic surgery* vol. 113,1 (2022): 308-315.

Study	Robot	Publication	Type	Time Frame	Analysis	Total Patients	Average Age (yr)	Average Size (mm)	3D Imaging	Total Lesions	Diagnosed	DY (%)
Styrvoky <i>et al.</i> (2022)	SS-RAB	Manuscript	Retro	12/2020 to 2/2022	DY and safety	198	67.1	22.6	CBCT	209	192	91.9
Low <i>et al.</i> (2022)	SS-RAB	Manuscript	Retro	11/2021 to 5/2022	DY and safety	133	64	17	No	143	110	76.9
Oberg <i>et al.</i> (2022)	SS-RAB	Manuscript	Retro	10/2021 to 8/2022	DY and safety	112	71	22	No	120	108	90
Naaman <i>et al.</i> (2022)	SS-RAB	Abstract	Pros	1/2022 to 3/2022	Safety only	11	62.9	15.8	No	12	8	66.7
Folch <i>et al.</i> (2022)	SS-RAB	Abstract	Pros	3/2019 to 5/2021	DY and safety	129	NR	16	No	129	104	80.6
Lee-Mateus <i>et al.</i> (2022)	SS-RAB	Manuscript	Retro	1/2019 to 3/2021	DY and safety	113	70	18	No	113	99	87.6
Chambers <i>et al.</i> (2022)	SS-RAB	Manuscript	Retro	9/2020 to 7/2021	DY and safety	75	65	20	O-arm	79	61	77.2
Reisenauer <i>et al.</i> (2022)	SS-RAB	Manuscript	Pros	2/2021 to 8/2021	DY and safety	30	69.3	17.5	Cios Spin	30	28	93.3
Tavakoli <i>et al.</i> (2022)	SS-RAB	Abstract	Retro	8/2020 to 12/2021	Safety only	65	NR	21.2	No	65	56	86.2
Al Taq <i>et al.</i> (2022)	SS-RAB	Abstract	Retro	NR	Safety only	20	NR	14	No	20	19	95
Kalchier-Dekel <i>et al.</i> (2022)	SS-RAB	Manuscript	Pros	10/2019 to 7-2020	DY and safety	130	69	18	Cios Spin	159	130	81.8
Ross <i>et al.</i> (2021)	SS-RAB	Abstract	Pros	8/2020 to 3/2021	Safety only	40	NR	15	No	49	43	87.8
Pritchett <i>et al.</i> (2021)	SS-RAB	Abstract	Retro	1/2020 to 4/2021	DY and safety	192	NR	15	CBCT	230	212	92.2
Ghosh <i>et al.</i> (2021)	SS-RAB	Abstract	Retro	2/2020 to 4/2021	DY and safety	95	NR	19	No	103	82	79.6
Verga <i>et al.</i> (2021)	SS-RAB	Abstract	Pros	1/2020 to 10/2020	Safety only	40	67	NR	No	57	NR	NR
Bajwa <i>et al.</i> (2021)	SS-RAB	Abstract	Retro	3/2020 to 11/2020	DY and safety	76	68.4	17	No	76	68	89.5
Benn <i>et al.</i> (2021)	SS-RAB	Manuscript	Retro	9/2019 to 6/2020	DY and safety	52	68	21.9	CBCT	59	51	86.4
Fielding <i>et al.</i> (2019)	SS-RAB	Manuscript	Pros	9/2016 to 7/2017	DY and safety	29	63.2	14.8	No	29	23	79.3
Hedstrom <i>et al.</i> (2022)	EN-RAB	Abstract	Retro	2/2021 to 11/2021	DY and safety	45	NR	16.9	AF	45	41	91.1
Cumbo-Nacheli <i>et al.</i> (2022)	EN-RAB	Manuscript	Retro	NR	DY and safety	20	70	22	CBCT	20	18	90
Agarwal <i>et al.</i> (2022)	EN-RAB	Manuscript	Retro	6/2018 to 12/2019	DY and safety	124	68	24	No	124	95	76.6
Manley <i>et al.</i> (2021)	EN-RAB	Abstract	Retro	NR	DY and safety	17	NR	NR	No	17	14	82.4
Ekeke <i>et al.</i> (2021)	EN-RAB	Manuscript	Retro	8/2020 to 2/2021	DY and safety	25	71	10-20	No	25	20	80
Chen <i>et al.</i> (2021)	EN-RAB	Manuscript	Pros	NR	DY and safety	54	67.1	23.2	No	54	40	74.1
Rojas-Solano <i>et al.</i> (2018)	EN-RAB	Manuscript	Pros	NR	DY and safety	15	67	26	No	15	13	86.7

Definition of abbreviations: 3D = three-dimensional; AF = augmented fluoroscopy; CBCT = cone-beam computed tomography; DY = diagnostic yield; EN = electromagnetic navigation; NR = not reported; Pros = prospective; RAB = robotic-assisted bronchoscopy; Retro = retrospective; SS = shape-sensing.



Diagnostic yield = 84.3%

PTX: 2.3%, CTD: 1.2%, Significant hemorrhage: 0.5%

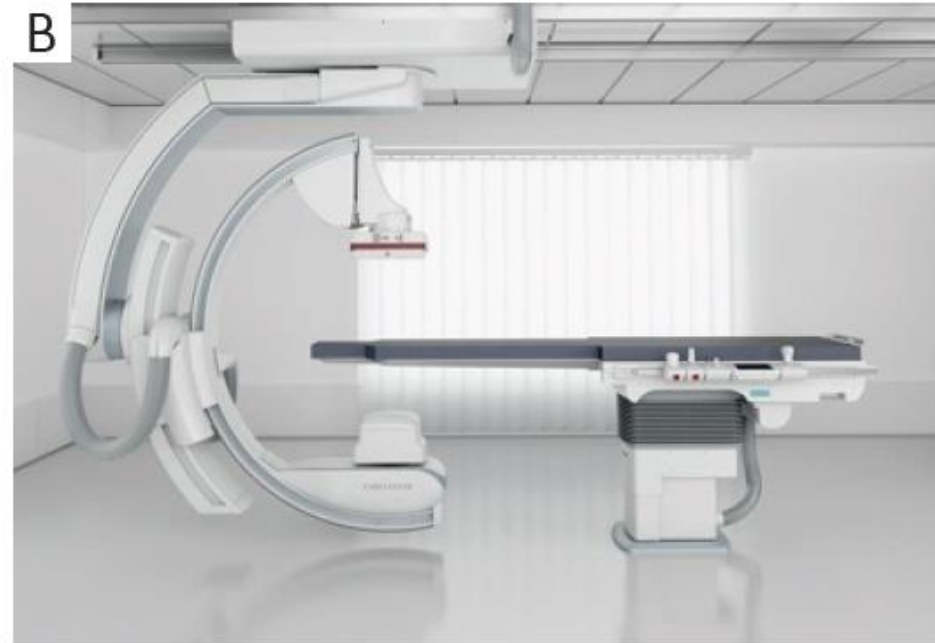
Table 4. Impact of various factors on the diagnostic yield of robotic bronchoscopy

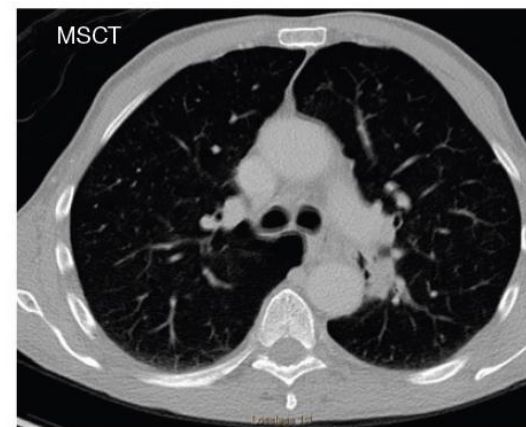
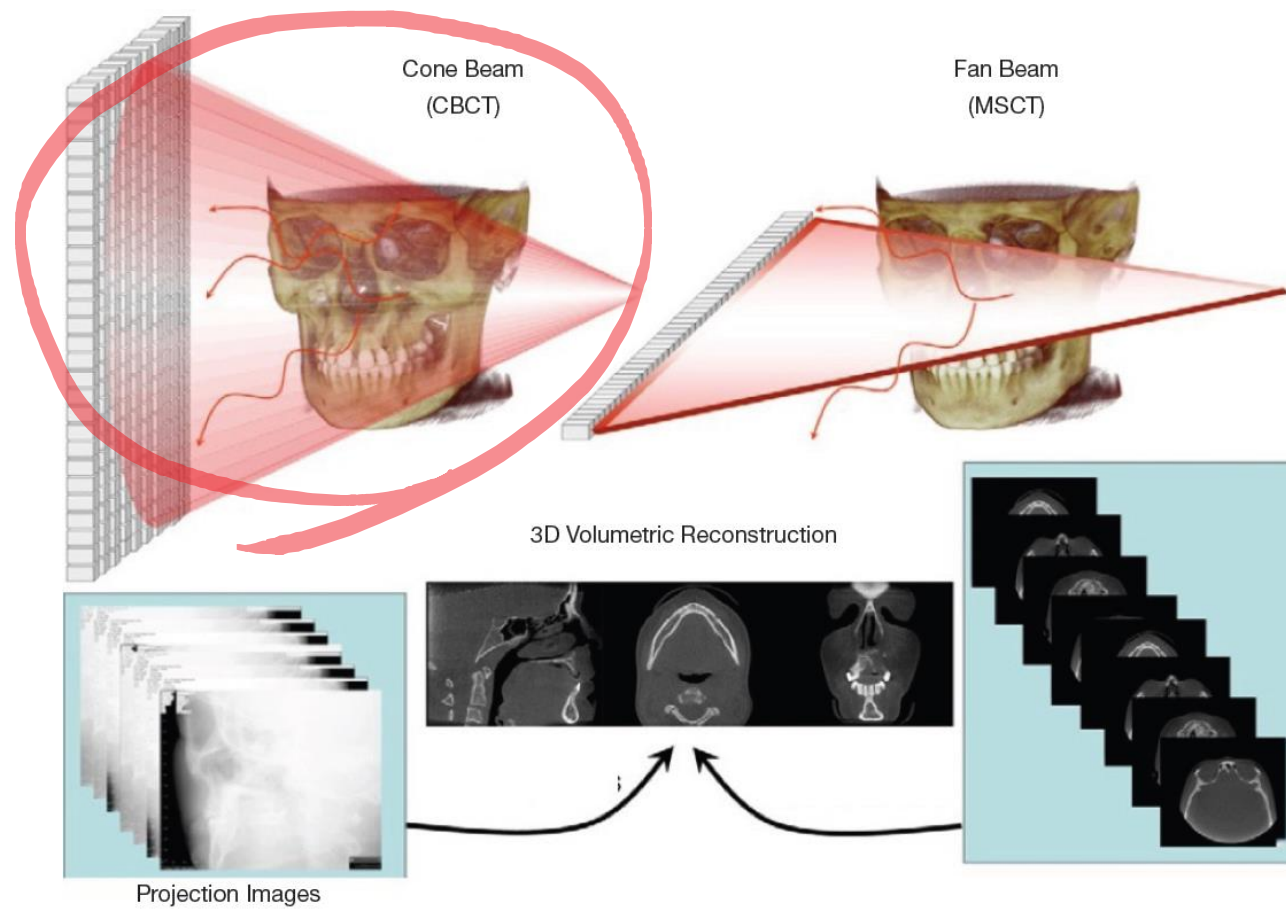
Factor	Number of Studies	OR for Diagnosis (95% CI)	P Value
Malignant vs. benign lesions	6	0.9 (0.6–1.5)	0.8
Lesion size > 2 cm vs. ≤ 2 cm	5	2.4 (1.3–4.2)	0.003
Lesion size > 3 cm vs. ≤ 3 cm	5	1.7 (0.9–3.3)	0.09
Presence vs. absence of CT-BS	5	1.6 (1.0–2.6)	0.048
Concentric vs. nonconcentric R-EBUS view	4	2.4 (1.3–4.5)	0.005
Solid vs. nonsolid lesions	3	1.1 (0.6–2.0)	0.8
Upper vs. lower lobe location	2	0.9 (0.4–2.1)	0.8
Central (two-thirds) vs. peripheral (one-third) location	2	1.2 (0.2–8.2)	0.8

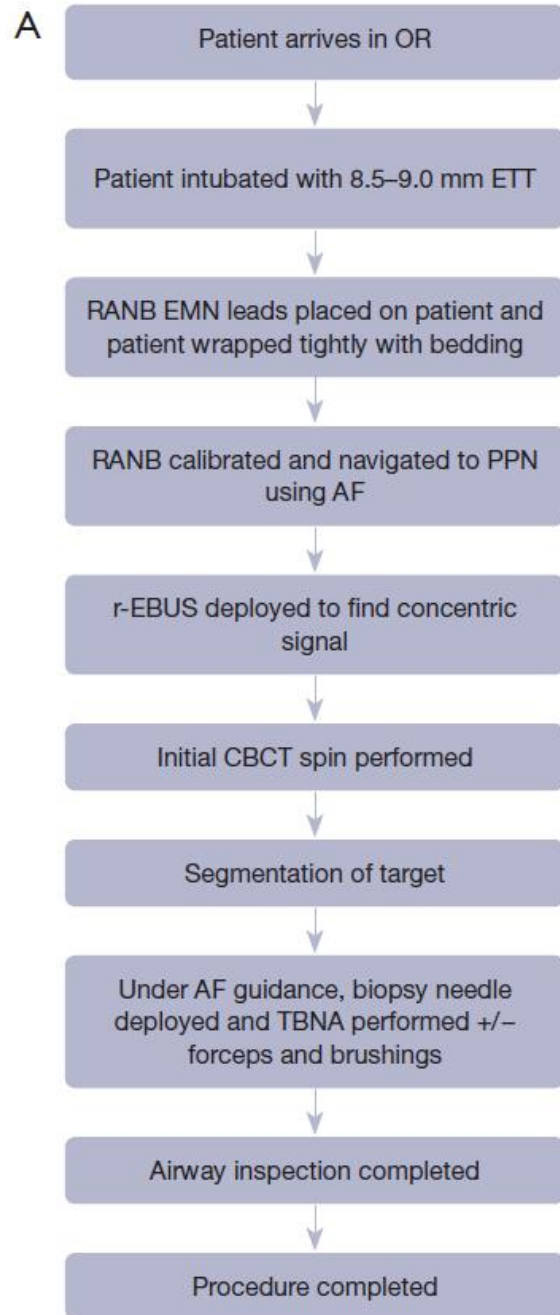
Definition of abbreviations: CI = confidence interval; CT-BS = computed tomography bronchus sign; OR = odds ratio; R-EBUS = radial endobronchial ultrasound.

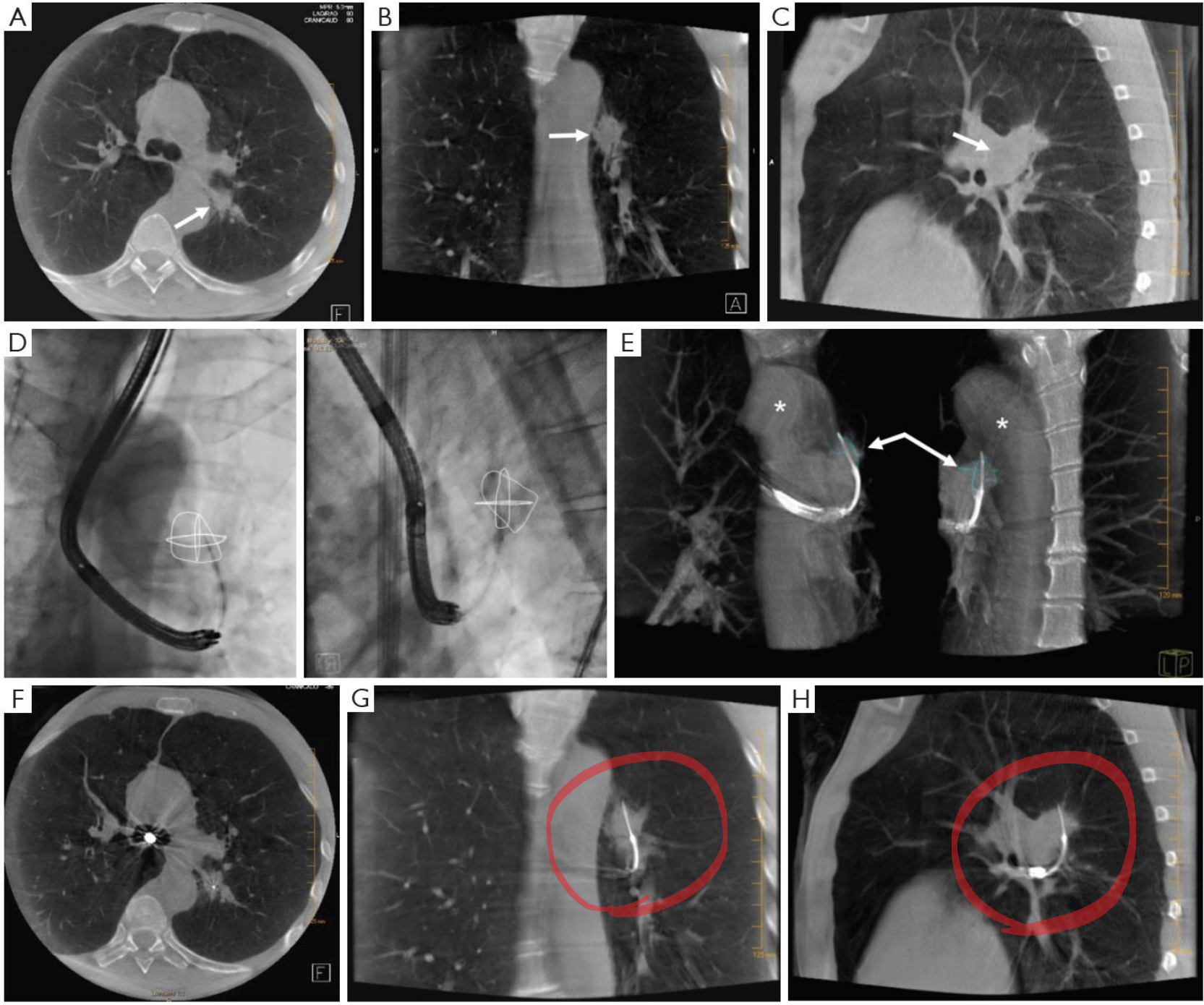
Nonconcentric R-EBUS views included both eccentric view and absence of a view. Right middle lobe and lingular lesions were added to the upper lobes. Nonsolid lesions include part-solid, ground-glass, mixed-density, and cavitory lesions. Boldface type denotes statistical significance.

Cone beam CT (CBCT)

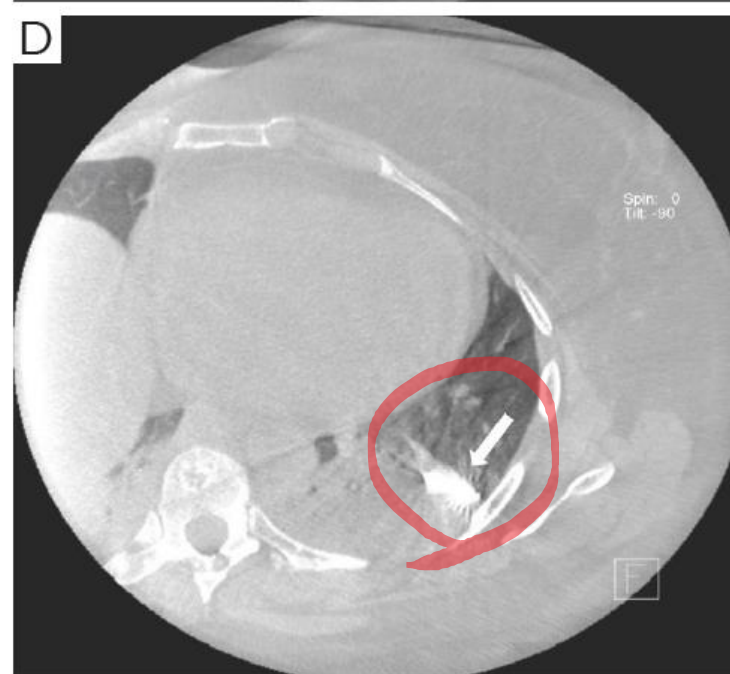
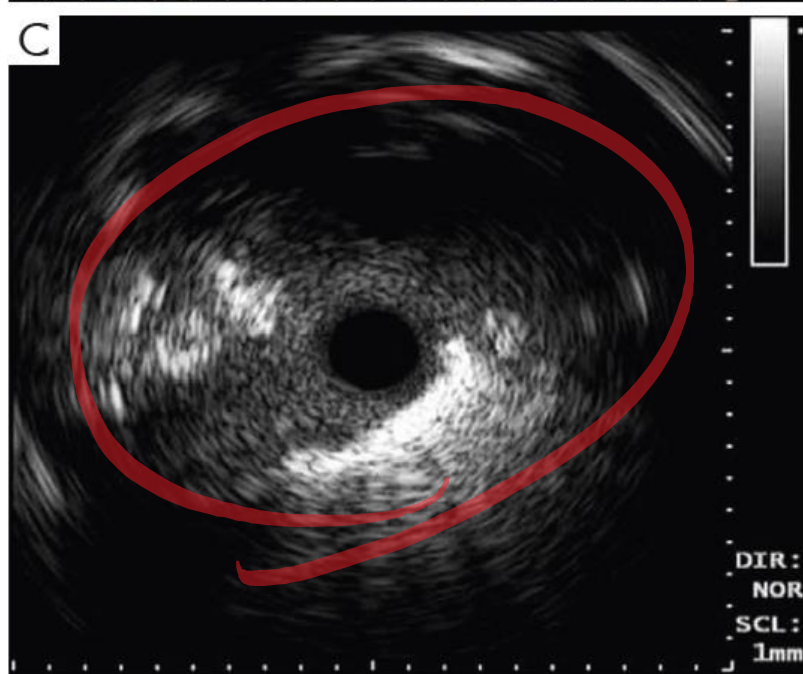
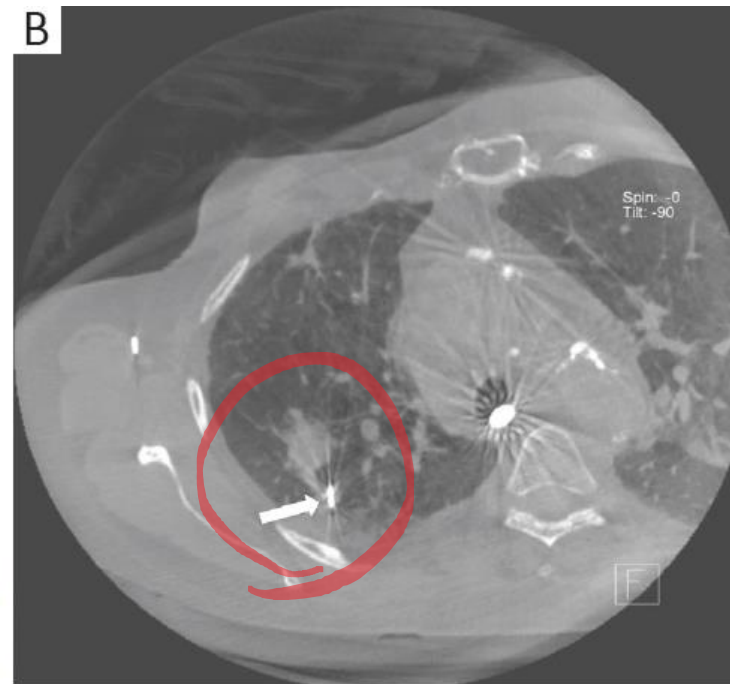
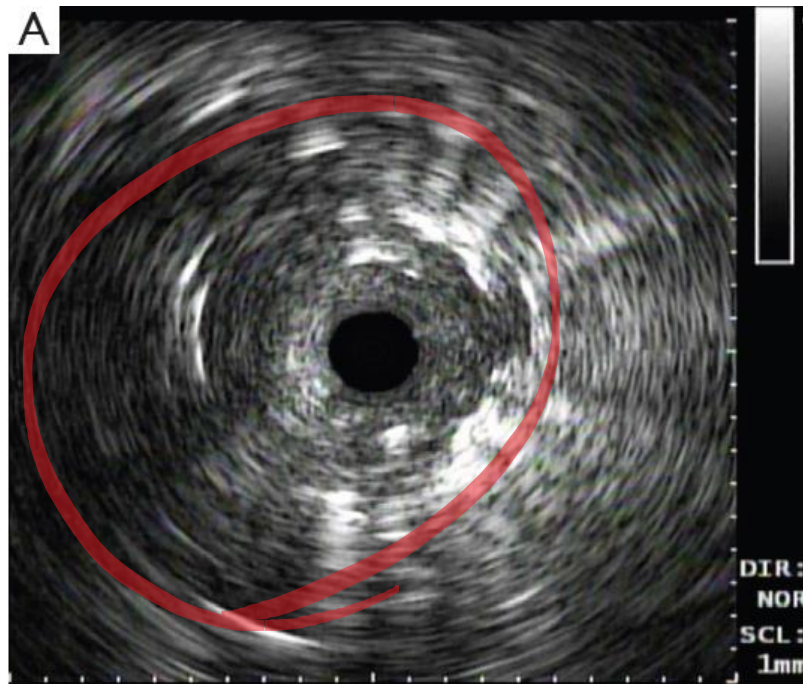








Setser R, et al. Cone beam CT imaging for bronchoscopy: a technical review. *J Thorac Dis.* 2020;12(12):7416-7428.

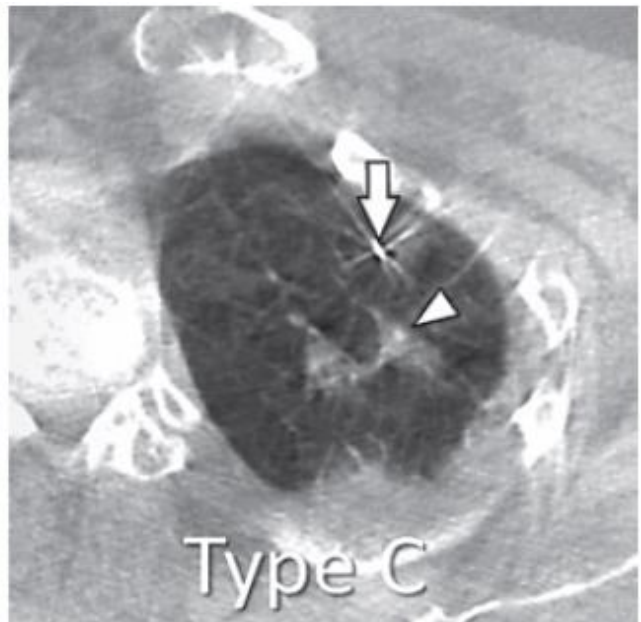
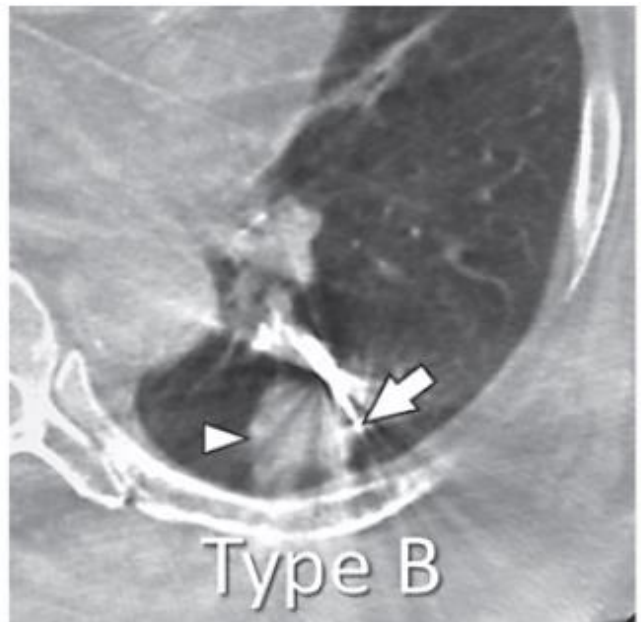
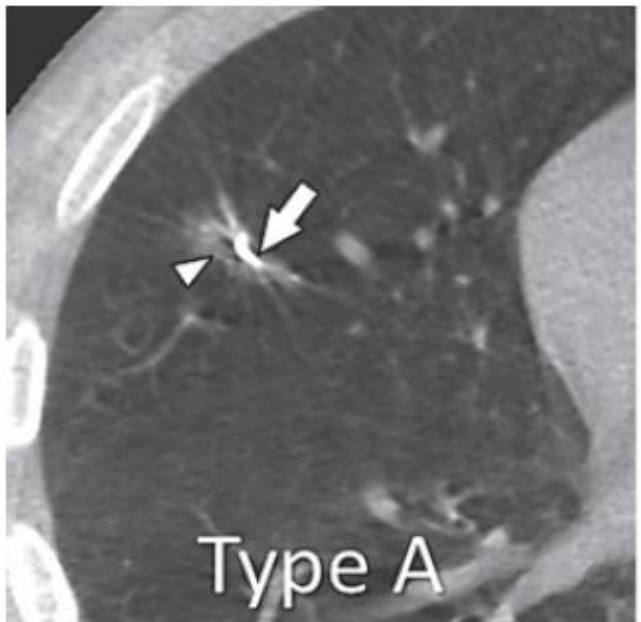
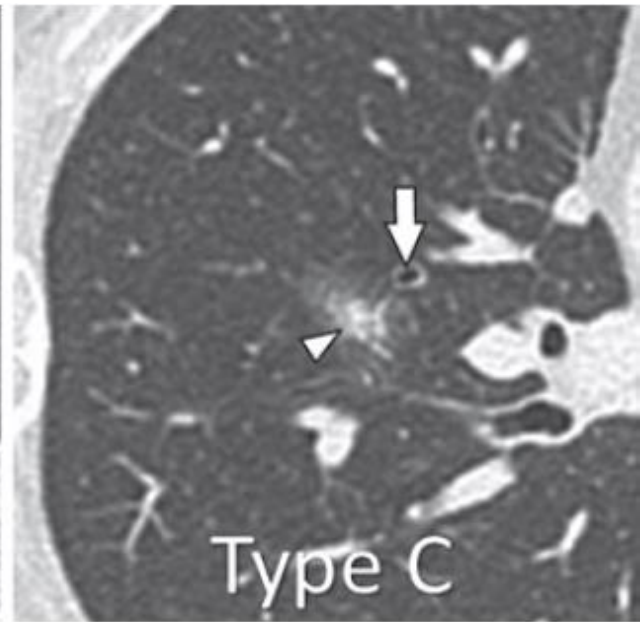
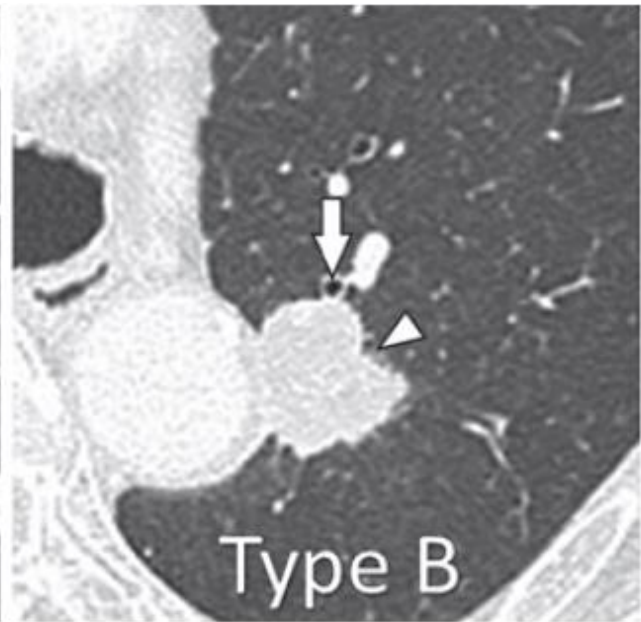
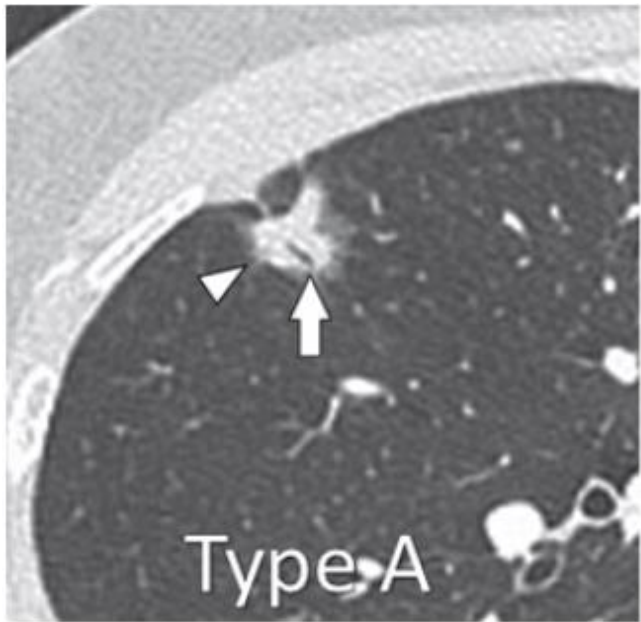


CBCT-guided bronchoscopy findings	Values, n (%)
RP-EBUS images	
Eccentric	11 [55]
Concentric	6 [30]
Inconclusive	3 [15]
RP-EBUS position per 1 st CBCT	
Contact with lesion	10 [50]
Central	5 [25]
Peripheral	5 [25]
Atelectasis	
Any	8 [40]
Obscuring target	4 [20]
<u>Pre-CBCT navigational yield</u>	
<u>Successful navigation</u>	10 [50]
Unsuccessful navigation	6 [30]
Unknown (atelectasis)	4 [20]
Post-CBCT maneuvers	
Re-navigation	6 [30]
Change of scope orientation	3 [15]
New tool/s	1 [5]

<u>Post-CBCT navigational yield</u>	
<u>Successful navigation</u>	15 [75] [¥]
Unsuccessful navigation	1 [5]
Unknown (atelectasis)	4 [20]
<u>Diagnostic yield</u>	
<u>Pre-CBCT</u>	10 [50] [*]
<u>Post-CBCT</u>	14 [70]
Bronchoscopic diagnosis	
Adenocarcinoma of the lung	8 [40]
Squamous cell carcinoma of the lung	3 [15]
MAC	1 [5]
Necrotizing pneumonia (MRSA)	1 [5]
Chronic inflammation	1 [5]

Navigation 50% → 75%

Diagnostic yield 50% → 70%



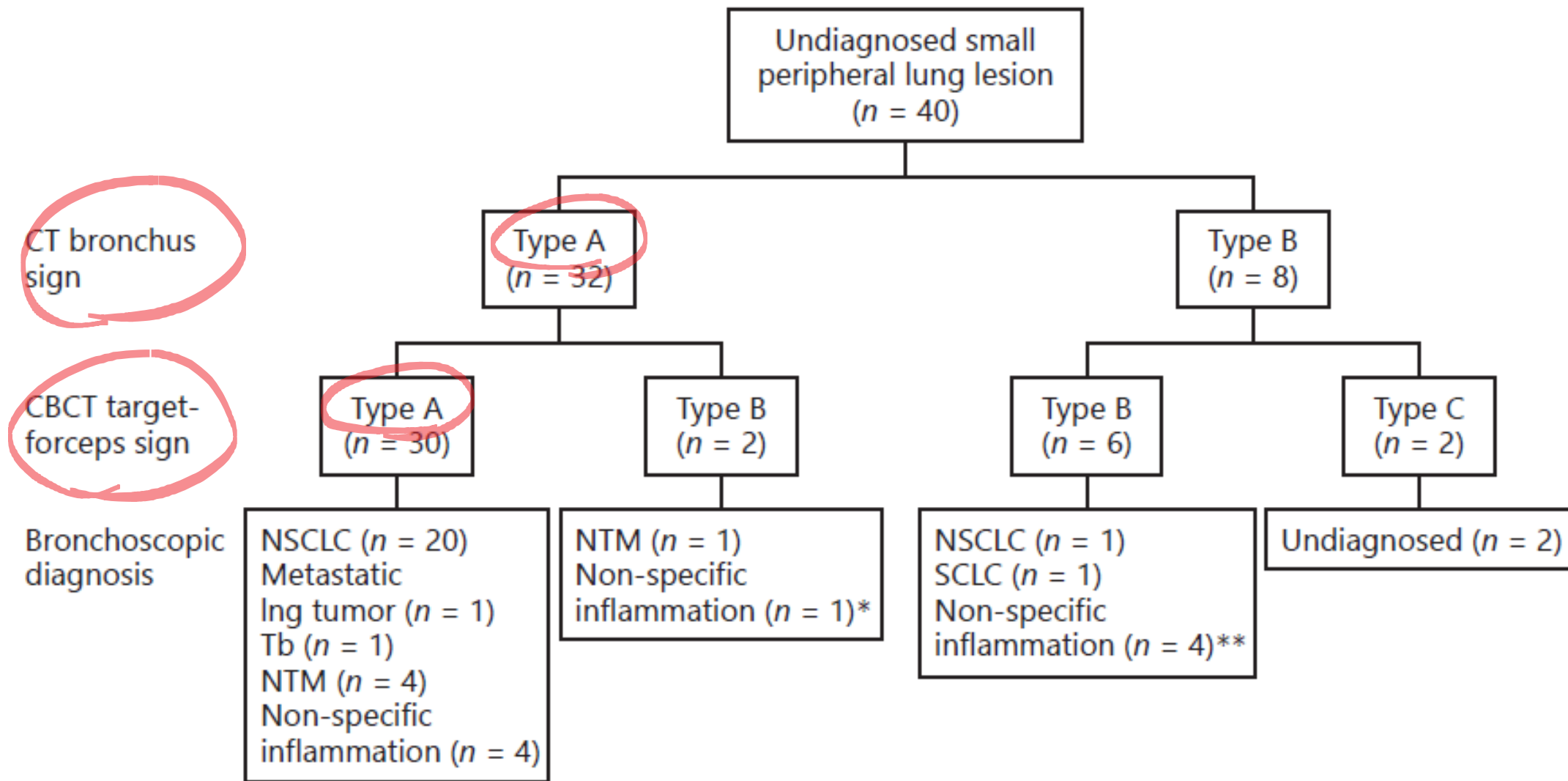



Table 2. Diagnostic yields

<u>Overall</u> , % (<i>n</i>)	90.0 (36/40)
Malignant lesion, % (<i>n</i>)	92.0 (23/25)
Benign lesion, % (<i>n</i>)	86.7 (13/15)
<u>CT bronchus sign</u> , % (<i>n</i>)	
<u>Type A</u>	96.9 (31/32)
Type B	62.5 (5/8)
<u>CBCT target-forceps sign</u> , % (<i>n</i>)	
<u>Type A</u>	100.0 (30/30)
Type B	75.0 (6/8)
Type C	0.0 (0/2)



Multimodality

Shape-Sensing Robotic-Assisted Bronchoscopy with Concurrent use of Radial Endobronchial Ultrasound and Cone Beam Computed Tomography in the Evaluation of Pulmonary Lesions

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Abstract

Purpose Lung nodules are a common radiographic finding. Non-surgical biopsy is recommended in patients with moderate or high pretest probability for malignancy. Shape-sensing robotic-assisted bronchoscopy (ssRAB) combined with radial endobronchial ultrasound (r-EBUS) and cone beam computed tomography (CBCT) is a new approach to sample pulmonary lesions. Limited data are available regarding the diagnostic accuracy of combined ssRAB with r-EBUS and CBCT.

Methods We conducted a retrospective analysis of the first 200 biopsy procedures of 209 lung lesions using ssRAB, r-EBUS, and CBCT at UT Southwestern Medical Center in Dallas, Texas. Outcomes were based on pathology interpretations of samples taken during ssRAB, clinical and radiographic follow-up, and/or additional sampling.

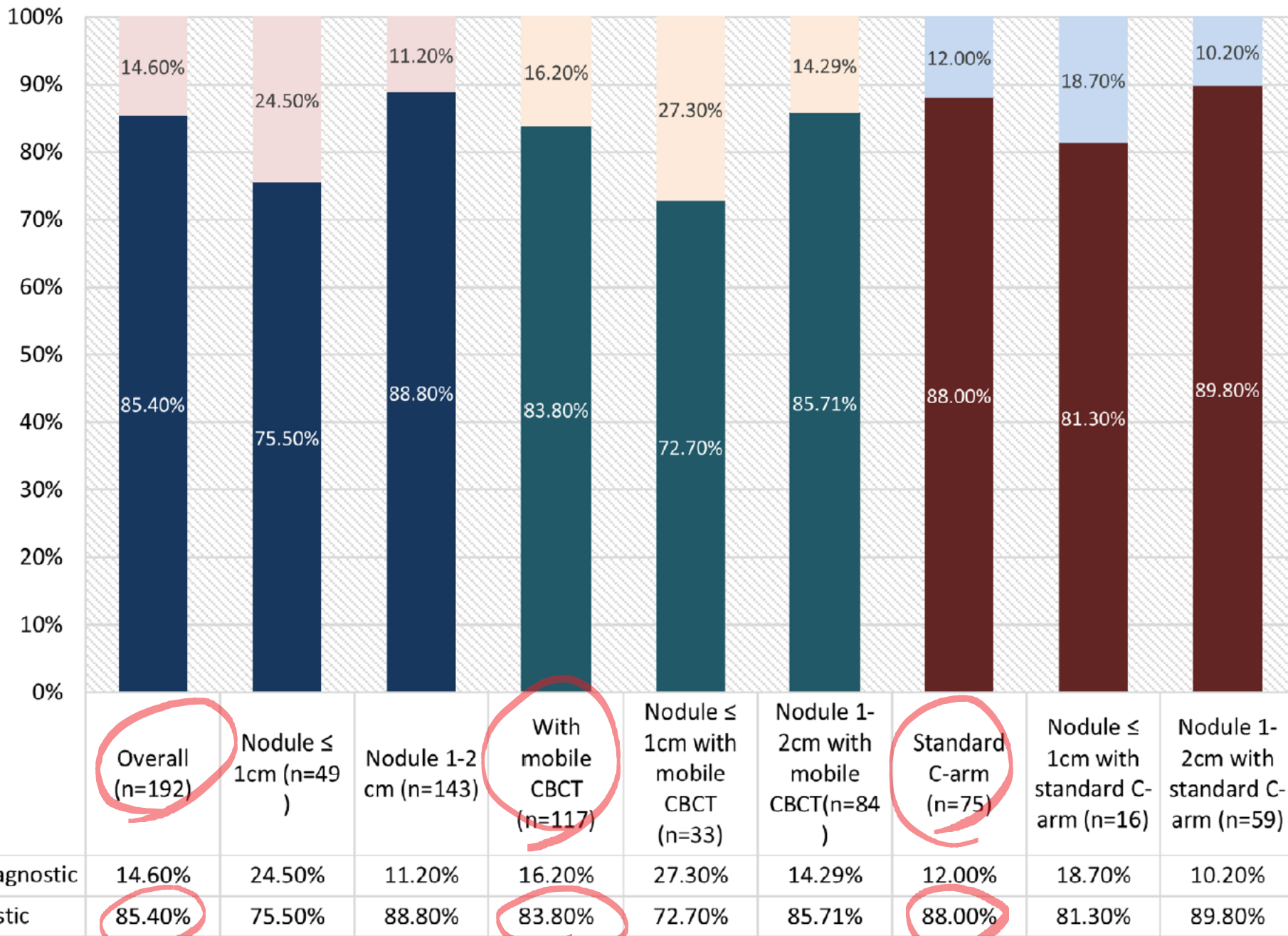
Results The mean largest lesion dimension was 22.6 ± 13.3 mm with a median of 19 mm (range 7 to 73 mm). The prevalence of malignancy in our data was 64.1%. The diagnostic accuracy of ssRAB combined with advanced imaging was 91.4% (CI 86.7–94.8%). Sensitivity was 87.3% (CI 80.5–92.4%) with a specificity of 98.7% (CI 92.8–100%). The negative and positive predictive values were 81.3% and 99.2%. The rate of non-diagnostic sampling was 11% (23/209 samples). The only complication was pneumothorax in 1% (2/200 procedures), with 0.5% requiring a chest tube.

Conclusion Our results of the combined use of ssRAB with r-EBUS and CBCT to sample pulmonary lesions suggest a high diagnostic accuracy for malignant lesions with reasonably high sensitivity and negative predictive values. The procedure is safe with a low rate of complications.

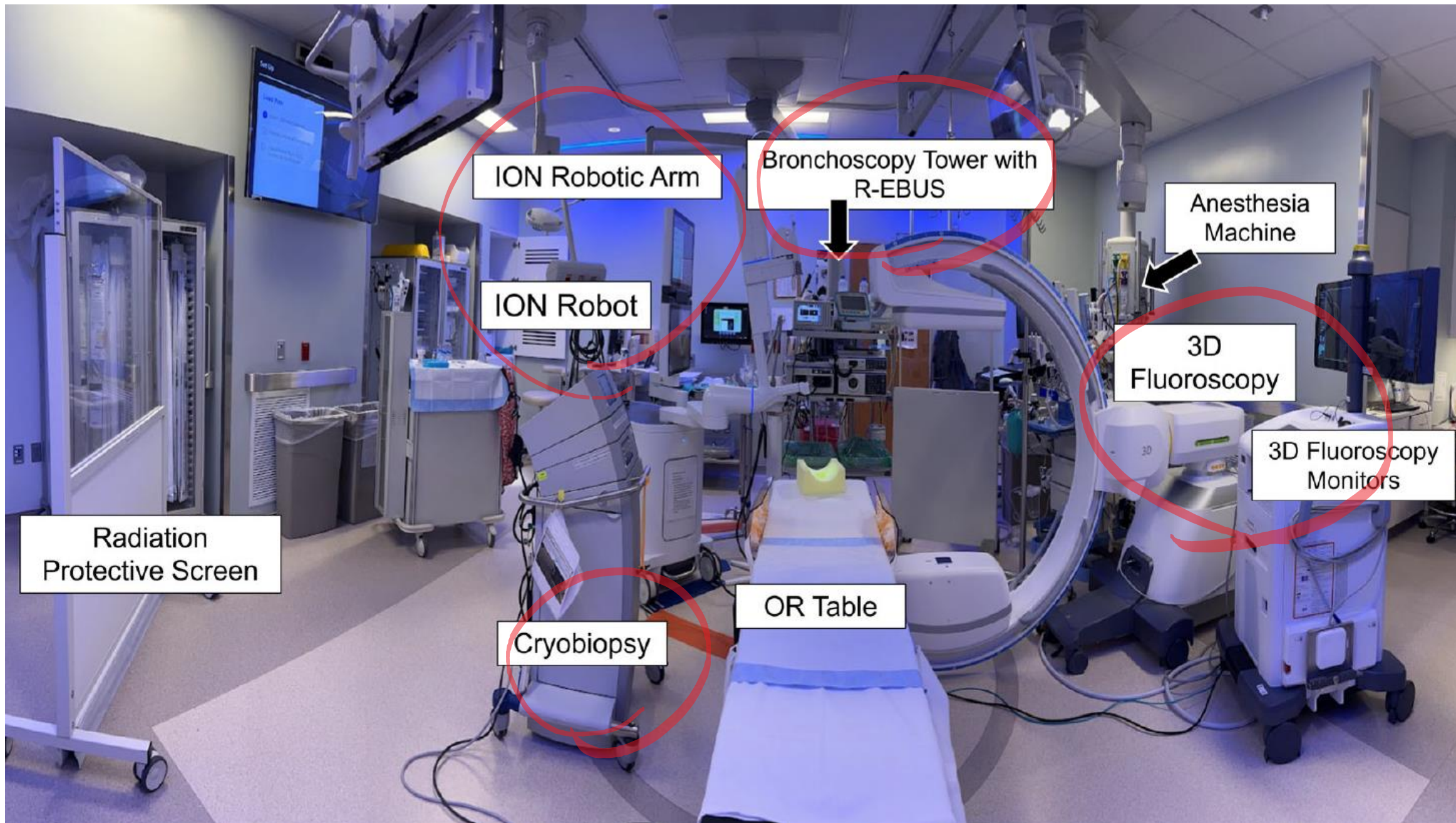
TABLE 2 Procedure details and outcomes of the overall cohort and subgroups by use of mobile CBCT or standard C-arm.

	Subgroup by mobile CBCT versus standard C-arm			<i>p</i> -value
	Overall (<i>n</i> = 192)	Mobile CBCT (<i>n</i> = 117)	Standard C-arm (<i>n</i> = 75)	
Type of lesion				
Cavitary	6 (3.1%)	4 (3.4%)	2 (2.7%)	
Cystic	3 (1.6%)	3 (2.6%)	0 (0%)	
Ground-glass	13 (6.8%)	12 (10.3%)	1 (1.3%)	0.016*
Mixed	13 (6.8%)	7 (6%)	6 (8%)	
Solid	138 (71.9%)	77 (65.8%)	61 (81.3%)	0.020*
Subsolid	19 (9.9%)	14 (12%)	5 (6.7%)	
Bronchus sign positive ^a	96 (50%)	57 (48.7%)	39 (52%)	0.657
Vessels sign positive	87 (45.3%)	54 (46.2%)	33 (44%)	0.770
Target nodule parameters				
Max size, cm	1.4 (1.1–1.7)	1.40 (1.10–1.70)	1.41 (1.20–1.80)	0.071
Min size, cm	1.08 (0.9–1.3)	1.05 (0.90–1.20)	1.10 (0.90–1.44)	0.391
Average size, cm	1.2 (1.0–1.4)	1.23 (1–1.45)	1.25 (1.05–1.55)	0.295
SUV max in PET-CT	2.8 (1.4–5.85)	2.80 (1.30–5.40)	3.45 (1.90–6.50)	0.481
Target to catheter distance (mm, <i>n</i> = 142)	2 (0–6)	2 (0–7)	0 (0–3)	0.102
Distance to pleura	1.81 (0.71–2.8)	1.95 (0.50–3)	1.70 (0.77–2.50)	0.456
Radial EBUS	190 (99%)	117 (100%)	73 (97.3%)	0.760
Cryo used	43 (22.4%)	38 (32.5%)	5 (6.7%)	<0.001***
Forceps used	80 (41.7%)	54 (46.2%)	26 (34.7%)	0.115
Brush used	14 (7.3%)	10 (8.5%)	4 (5.3%)	0.403
Bronchoalveolar lavage	109 (56.8%)	68 (58.1%)	41 (54.7%)	0.864

Diagnostic yield



Variable	Odds ratio	95% CI	p-value
Upper lobe location	1.03	0.95–1.11	0.422
Average size >1 cm	1.02	0.93–1.11	0.640
<u>Bronchus sign positive</u>	1.15	1.05–1.25	0.0019**
Vessel sign positive	1.03	0.95–1.13	0.846
Distance to pleura	0.97	0.93–1.01	0.146
Nodule in outer third	0.92	0.80–1.05	0.254
Solid nodule	1.04	0.93–1.16	0.456
Use of cryobiopsy	0.89	0.77–1.03	0.122
Use of mCBCT	1.03	0.93–1.14	0.538

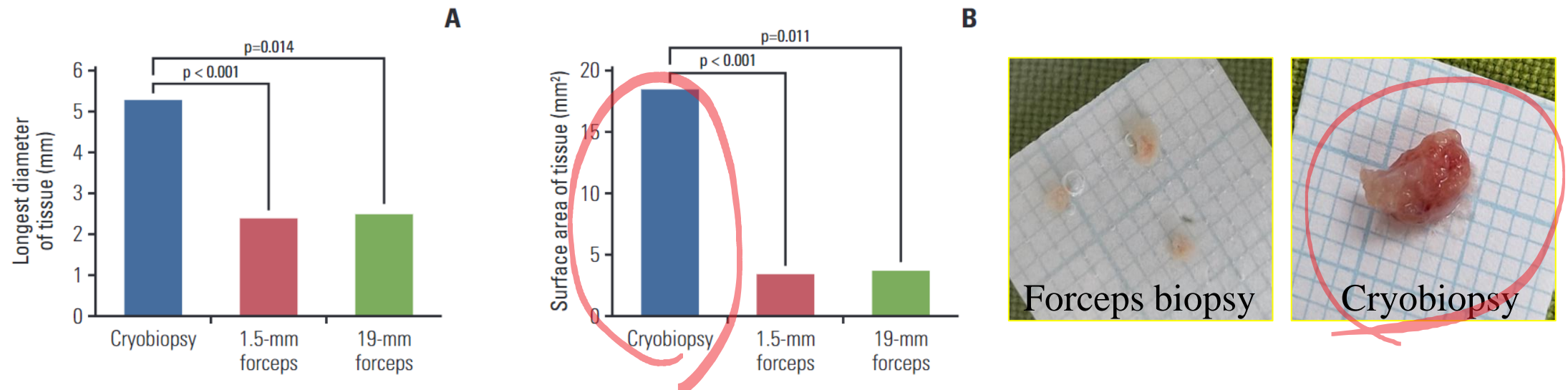


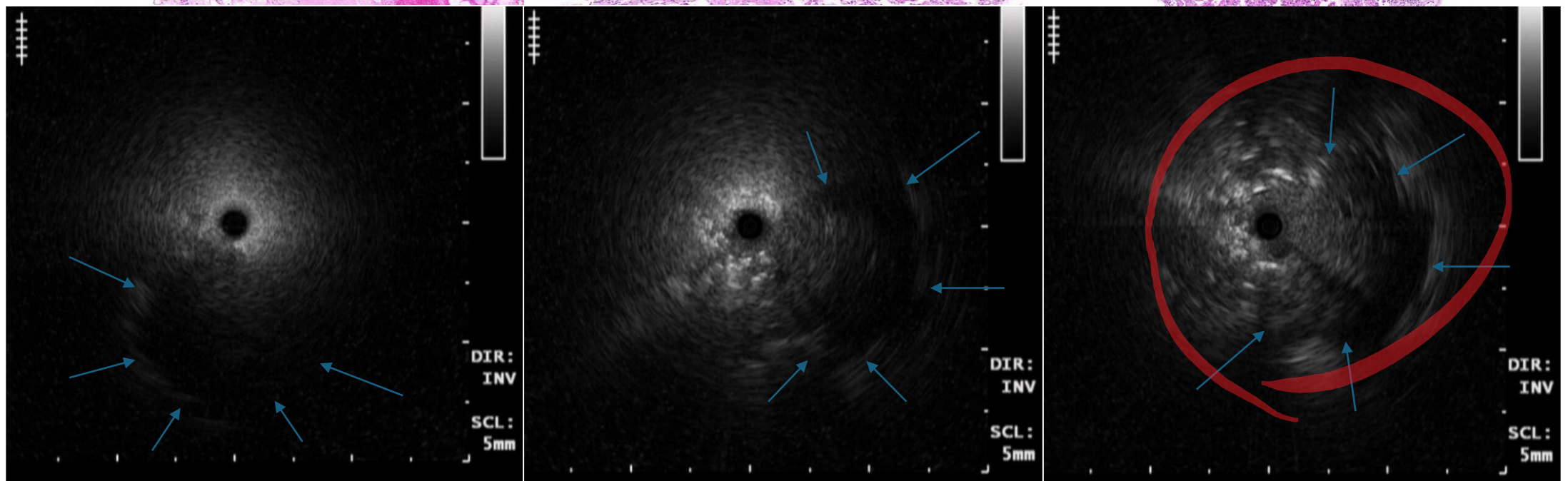
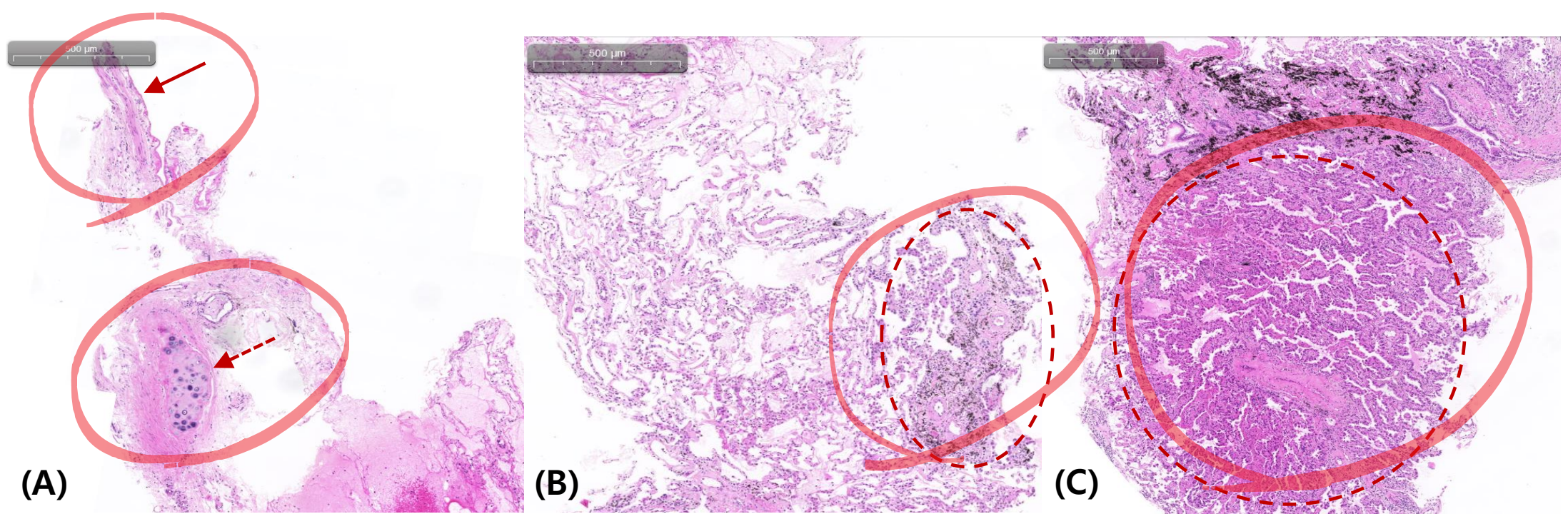
Abia-Trujillo D, et al. Mobile cone-beam computed tomography complementing shape-sensing robotic-assisted bronchoscopy in the small pulmonary nodule sampling: A multicentre experience. *Respirology*. Published online November 28, 2023.

Cryobiopsy

Transbronchial lung cryobiopsy (TBLC)

- Forceps TBLB vs. Transbronchial lung cryobiopsy (TBLC)
 - Larger tissues / Less crushing artifact
 - Additional diagnostic yield for peripheral pulmonary lesions (PPLs)
- 1.1 mm cryoprobe
 - Excellent flexibility
 - With 1.95 mm guide sheath (GS) in 2.0 mm working channel





Diagnostic yield of TBLC for PPLs

- Diagnostic yield (2021~2023): 89.9-91.5%
- Additional diagnostic yield (DY)
 - Matsumoto Y, et al. (2021) (n = 257)
 - 8.6% (81.3% → 89.9%)
 - 'Adjacent to' / 'Within': 14.9% / 3% (p = 0.001)
 - Bronchus sign (-) / (+): 15.4% / 6.3% (p = 0.011)
 - Nakai T , et al. (2022) (n = 139)
 - 76.3% (FB) / 81.3% (TBLC) / 89.9% (Total)
 - 'Adjacent to': conventional biopsy 67.4% vs. cryobiopsy 81.9% (p = 0.019)
 - 'Within': FB 94.2% (49/52) vs. cryobiopsy 84.6% (44/52) (p = 0.18)
 - Chaeuk Chung, et al. (2023) (n = 199)
 - 65.3% (FB) / 84.4% (TBLC) / 91.5% (Total)
 - 'Adjacent to' / 'Within': 29.9% / 25.2% (p = 0.003)

Ultrathin bronchoscopic cryobiopsy of peripheral pulmonary lesions

Masahide Oki¹ | Hideo Saka^{1,2} | Yoshihito Kogure¹ | Hideyuki Niwa¹ |
Arisa Yamada¹ | Atsushi Torii¹ | Chiyo Kitagawa¹

Methods: Patients with peripheral pulmonary lesions ≤ 30 mm in diameter were prospectively enrolled in the study. All patients underwent forceps biopsy followed by cryobiopsy using a 3.0-mm ultrathin bronchoscope under radial probe endobronchial ultrasound guidance, virtual bronchoscopic navigation and fluoroscopic guidance. The primary endpoint was the feasibility of cryobiopsy.

Results: In total, 50 patients with peripheral pulmonary lesions were enrolled in the study; the median longest diameter on computed tomography was 17.9 mm. Cryobiopsy was performed successfully in 49 patients (98%). Forceps biopsy, cryobiopsy and the combination of these two methods provided a specific diagnosis in 54% (27/50), 62% (31/50) and 74% (37/50) of patients, respectively. The median size of specimens obtained via cryobiopsy was significantly larger than the median size obtained via forceps biopsy (7.0 vs. 1.3 mm², respectively, $p < 0.001$). Mild bleeding during cryobiopsy occurred in 47 patients (94%). No moderate/severe bleeding or pneumothorax occurred.

Novel (Robotic-Assisted) (Cryobiopsy) for Peripheral Pulmonary Lesions

Catherine L. Oberg^{1,4} · Ryan P. Lau² · Erik E. Folch³ · Tao He¹ · Reza Ronaghi¹ · Irawan Susanto¹ · Colleen Channick¹ · Rodrigo Garcia Tome¹ · Scott Oh¹

Received: 6 September 2022 / Accepted: 26 September 2022 / Published online: 10 October 2022

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Abstract

Purpose Tissue acquisition in lung cancer is vital for multiple reasons. Primary reasons reported for molecular testing failure in lung cancer biopsy specimens include insufficient amount of tumor cells provided and inadequate tissue quality. Robotic bronchoscopy is a new tool enabling peripheral pulmonary lesion sampling; however, diagnostic yield remains imperfect possibly due to the location of nodules adjacent to or outside of the airway. The 1.1-mm cryoprobe is a novel diagnostic tool and accesses tissue in a 360-degree manner, thus potentially sampling eccentric/adjacent lesions. This study examines the diagnostic yield of the cryoprobe compared to standard needle aspiration and forceps biopsy. It additionally evaluates yield for molecular markers in cases of lung cancer.

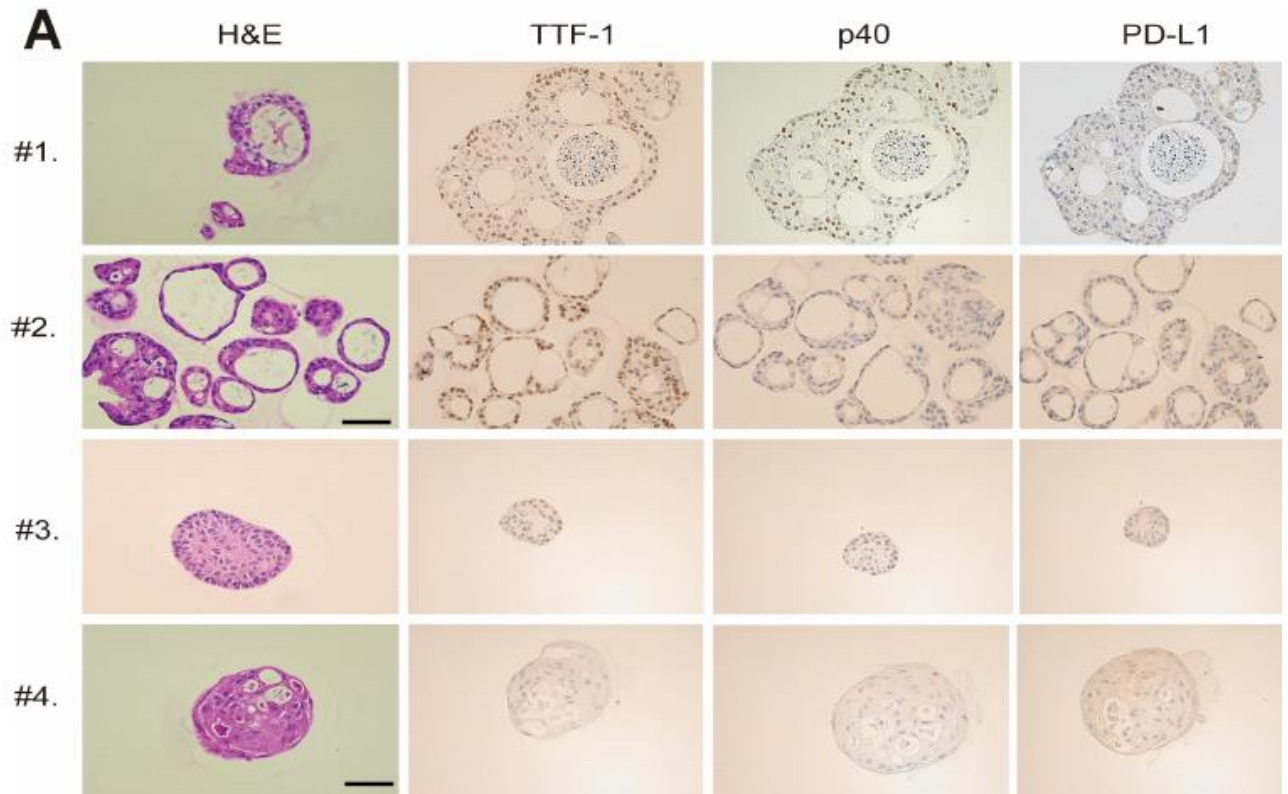
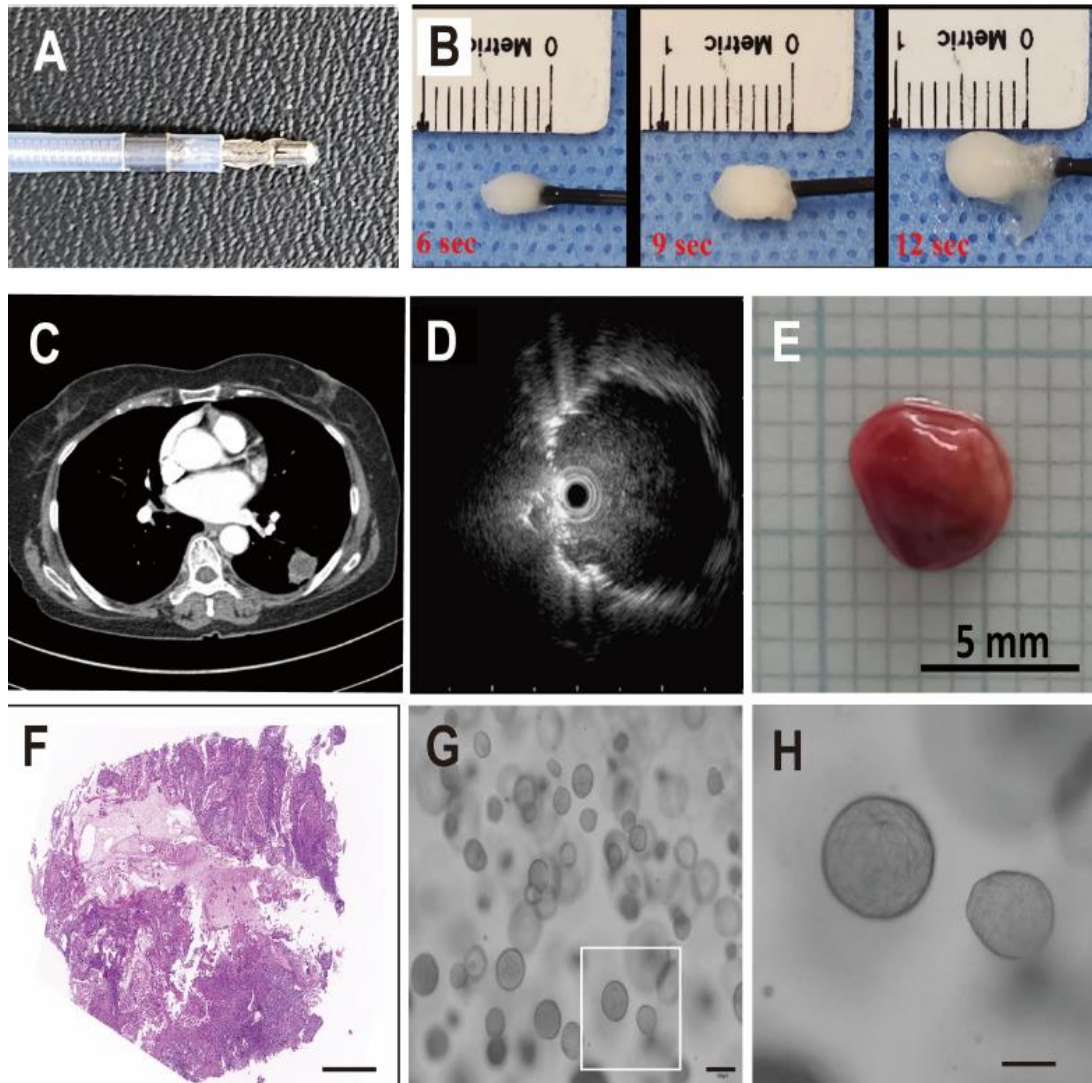
Methods This is a retrospective analysis of 112 patients with 120 peripheral pulmonary lesions biopsied via robotic bronchoscopy using needle aspirate, forceps, and cryobiopsy.

Results The overall diagnostic yield was 90%. Nearly 18% of diagnoses were made exclusively from the cryobiopsy sample. Molecular analysis was adequate on all cryobiopsy samples sent. Digital imaging software confirmed an increase in quantity and quality of samples taken via cryobiopsy compared to needle aspirate and traditional forceps biopsy.

Conclusion Using the 1.1-mm cryoprobe to biopsy PPN combined with the Ion robotic bronchoscopy system is safe, feasible, and provides more diagnostic tissue than needle aspirates or traditional forceps biopsies. The combination of cryobiopsy with robotic-assisted bronchoscopy increased diagnostic yield, likely due to its 360-degree tissue acquisition which is beneficial when targeting extraluminal lesions adjacent to the airway.

	Total (n=134)	EBUS-TBNA alone (n=134)	EBUS-TBNA plus cryobiopsy (n=134)	p value
Diagnostic yield	0.0026
No definitive diagnosis	..	24 (18%)	8 (6%)	..
Definitive diagnosis	..	110 (82%)	126 (94%)	..
Lung cancer	1.00
Any	64 (48%)	63 (47%)	63 (47%)	..
Lung, adenocarcinoma	31 (23%)	30 (22%)	30 (22%)	..
Lung, squamous cell	7 (5%)	7 (5%)	7 (5%)	..
Lung, large cell	3 (2%)	3 (2%)	3 (2%)	..
Lung, neuroendocrine	1 (1%)	1 (1%)	1 (1%)	..
Lung, small cell	22 (16%)	22 (16%)	22 (16%)	..
Other metastatic carcinoma	-
Any	5 (4%)	5 (4%)	5 (4%)	..
Breast cancer	2 (1%)	2 (1%)	2 (1%)	..
Oesophageal cancer	1 (1%)	1 (1%)	1 (1%)	..
Prostatic cancer	2 (1%)	2 (1%)	2 (1%)	..
Uncommon tumour	0.27
Any	17 (13%)	10 (7%)	13 (10%)	..
Lymphoma	10 (7%)	5 (4%)	8 (6%)	..
Neurilemmoma	1 (1%)	1 (1%)	1 (1%)	..
NUT midline carcinoma	1 (1%)	0	0	..
Seminoma	1 (1%)	1 (1%)	1 (1%)	..
Thymic carcinoma	1 (1%)	0	0	..
Thymoma	3 (2%)	3 (2%)	3 (2%)	..
Benign disorder*	0.0009
Any	48 (36%)	32 (24%)	45 (34%)	..
Pneumoconiosis	10 (7%)	9 (7%)	10 (7%)	..
Sarcoidosis	16 (12%)	12 (9%)	16 (12%)	..
Tuberculosis	19 (14%)	11 (8%)	19 (14%)	..

Fan, Ye et al. "Transbronchial needle aspiration combined with cryobiopsy in the diagnosis of mediastinal diseases: a multicentre, open-label, randomised trial." *The Lancet. Respiratory medicine* vol. 11,3 (2023): 256-264.



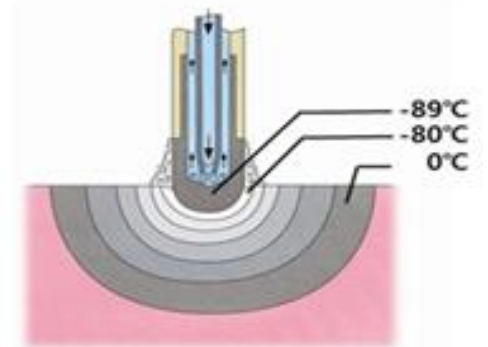
Introduction - Cryotherapy

• Cryotherapy

빠른 동결 속도(faster freeze rate)와 느린 융해 속도(slower thaw rate), 동결-융해 주기(freeze-thaw cycle)의 반복을 통하여 세포를 파괴하는 기관지 내시경 치료

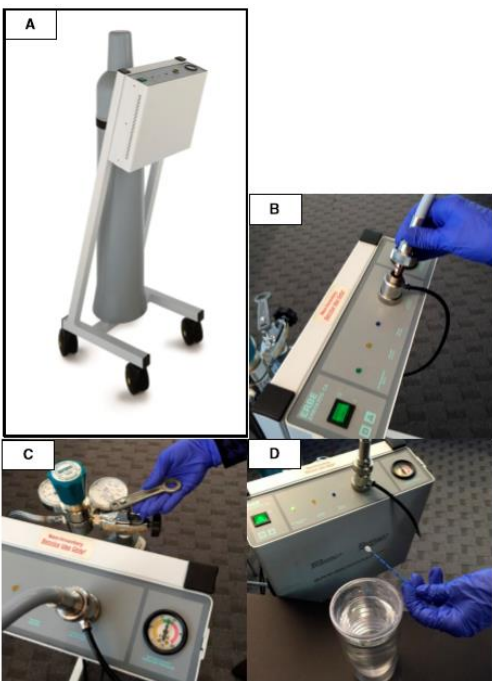
- Cryotherapy: 병변에 대해 freezing/thawing cycle을 반복하여 조직 괴사를 유도

- Cryoextraction/recannalization: cyoprobe에 냉각되어 있는 조직을 pulling out하면서 제거



Introduction - Cryotherapy

- Equipment: Cryogen + Cryomachine



	1세대(ERBECRYO)	2세대 (ERBECRYO2)
Cryogen	N ₂ O	CO ₂
Size of Probe	1.9 / 2.4 mm	1.1 / 1.7 / 2.4 mm
Thaw rate	Slow	Fast

Flexible Cryoprobe, OD 1.1 mm, length 1.15 m
(with overshooth, OD 2.6 mm, length 817 mm)
No. 20402-401

Flexible Cryoprobe, OD 1.1 mm, length 1.15 m
(with overshooth, OD 2.6 mm, length 757 mm)
No. 20402-402

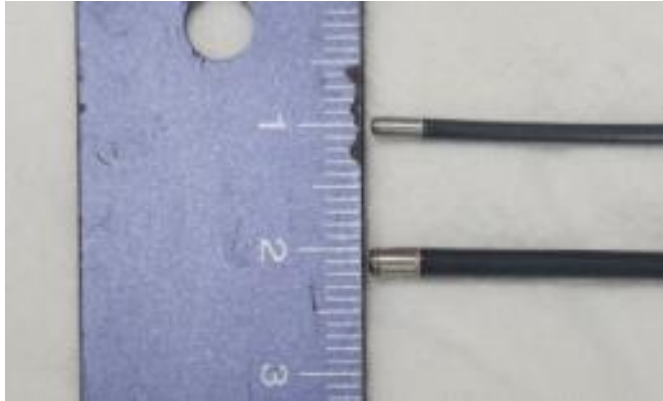
Flexible Cryoprobe, OD 1.7 mm, length 1.15 m
No. 20402-410

Flexible Cryoprobe, OD 2.4 mm, length 1.15 m
No. 20402-411



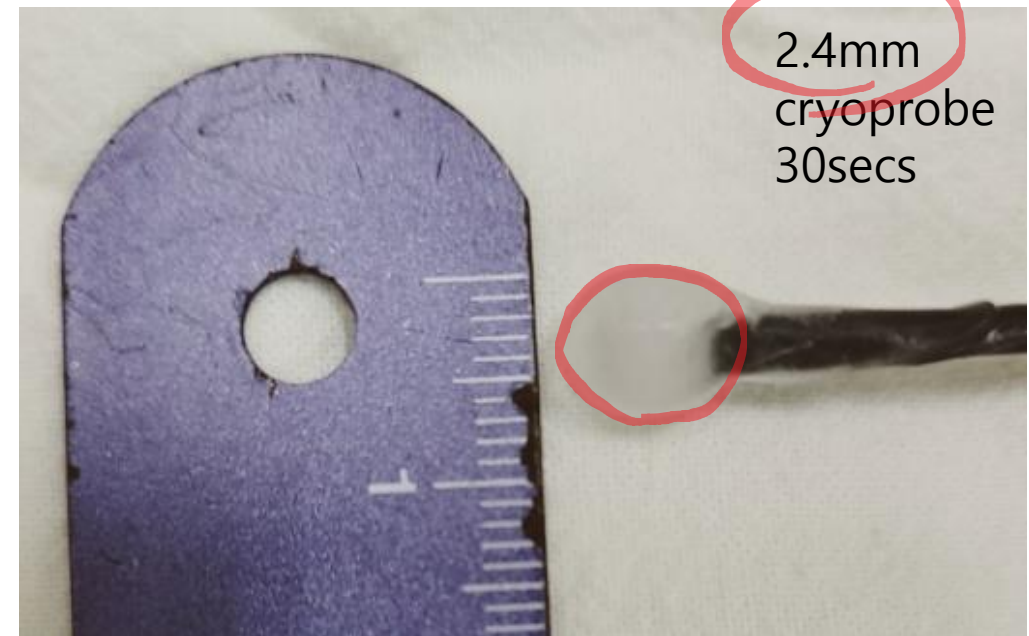
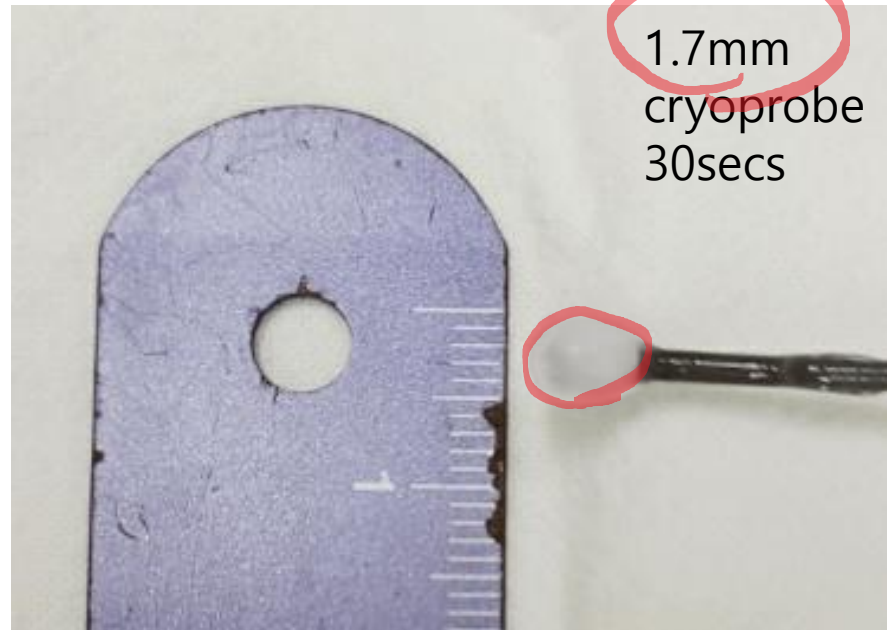
Figure 1. ERBOKRYO CA cryomachine (Erbe, Tubingen, Germany). (A) The cryogen is stored in the compressed tank held in the center of the machine. (B) The flexible cryoprobe connects the cryoprobe to the cryogen via a connection adapter. (C) The cylinder valve is then opened to allow the compressed gas to enter the machine via the transfer line. (D) The flow of cryogen is controlled using the footswitch. Depressing the pedal will allow freezing. Reprinted with permission from Erbe USA Inc.

Introduction - Cryotherapy

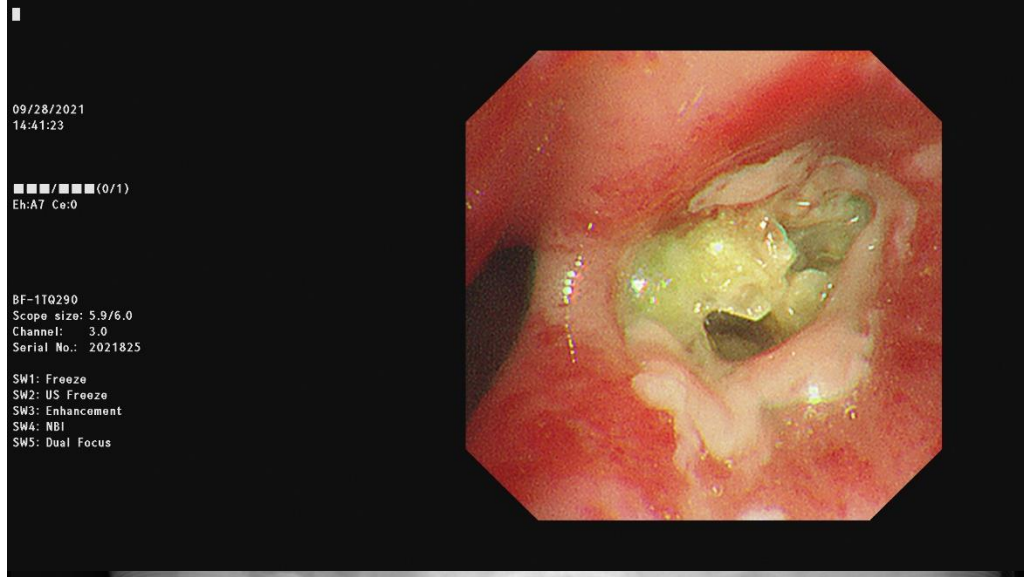
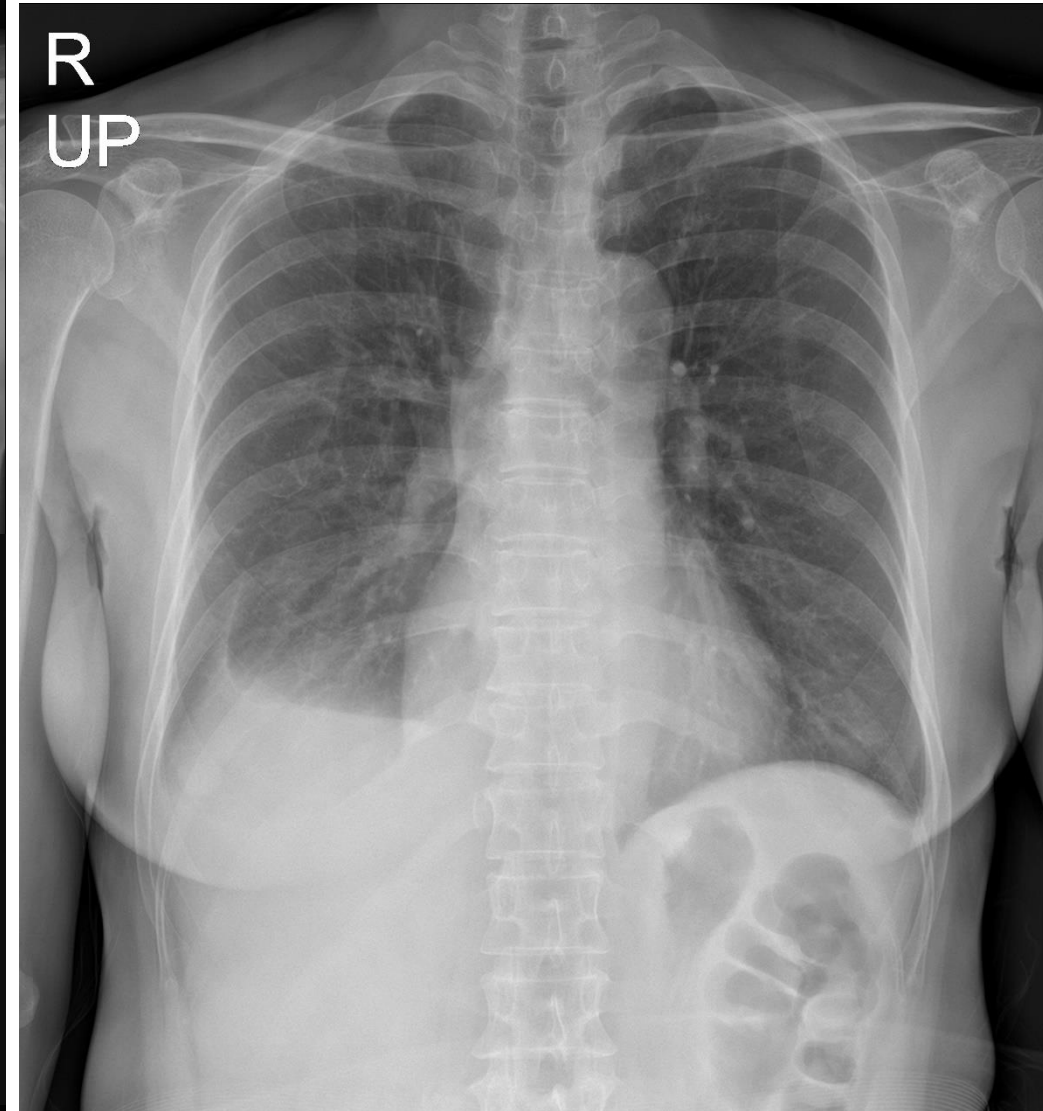


1.7mm cryoprobe

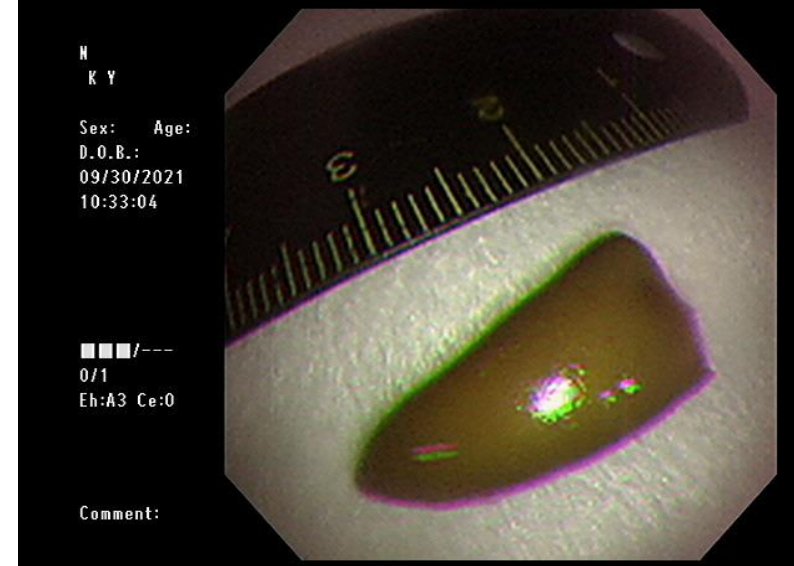
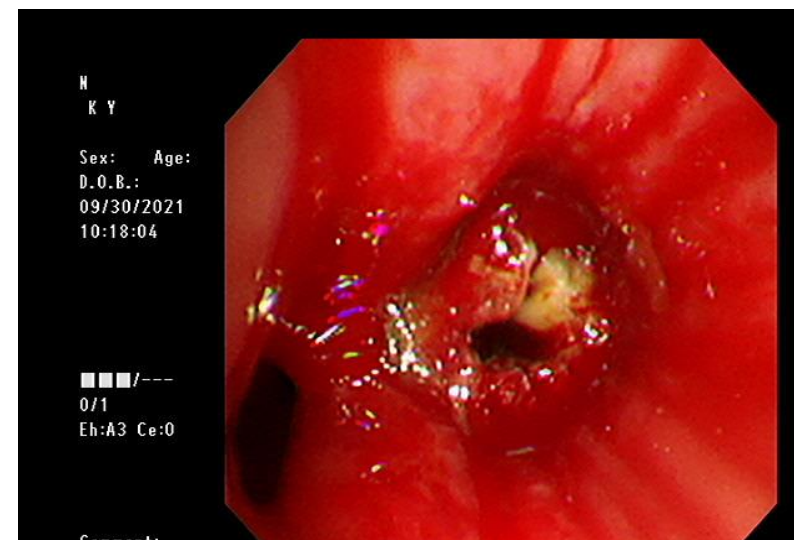
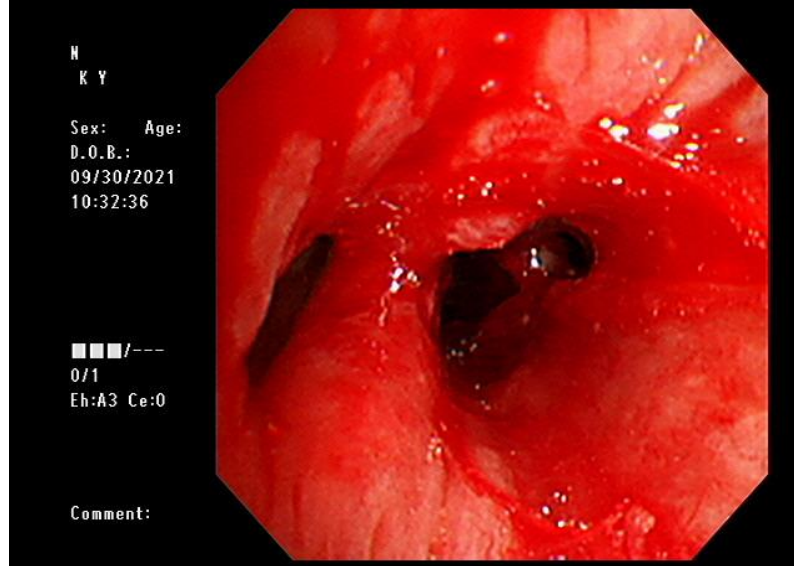
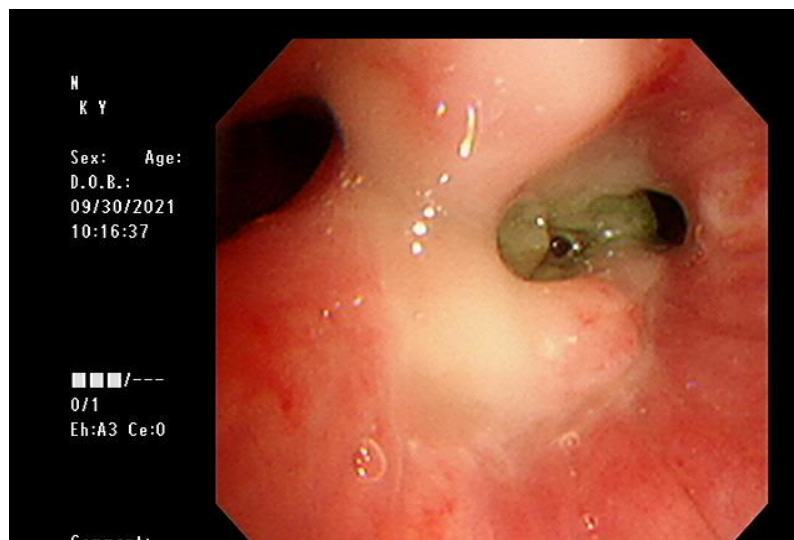
2.4mm cryoprobe



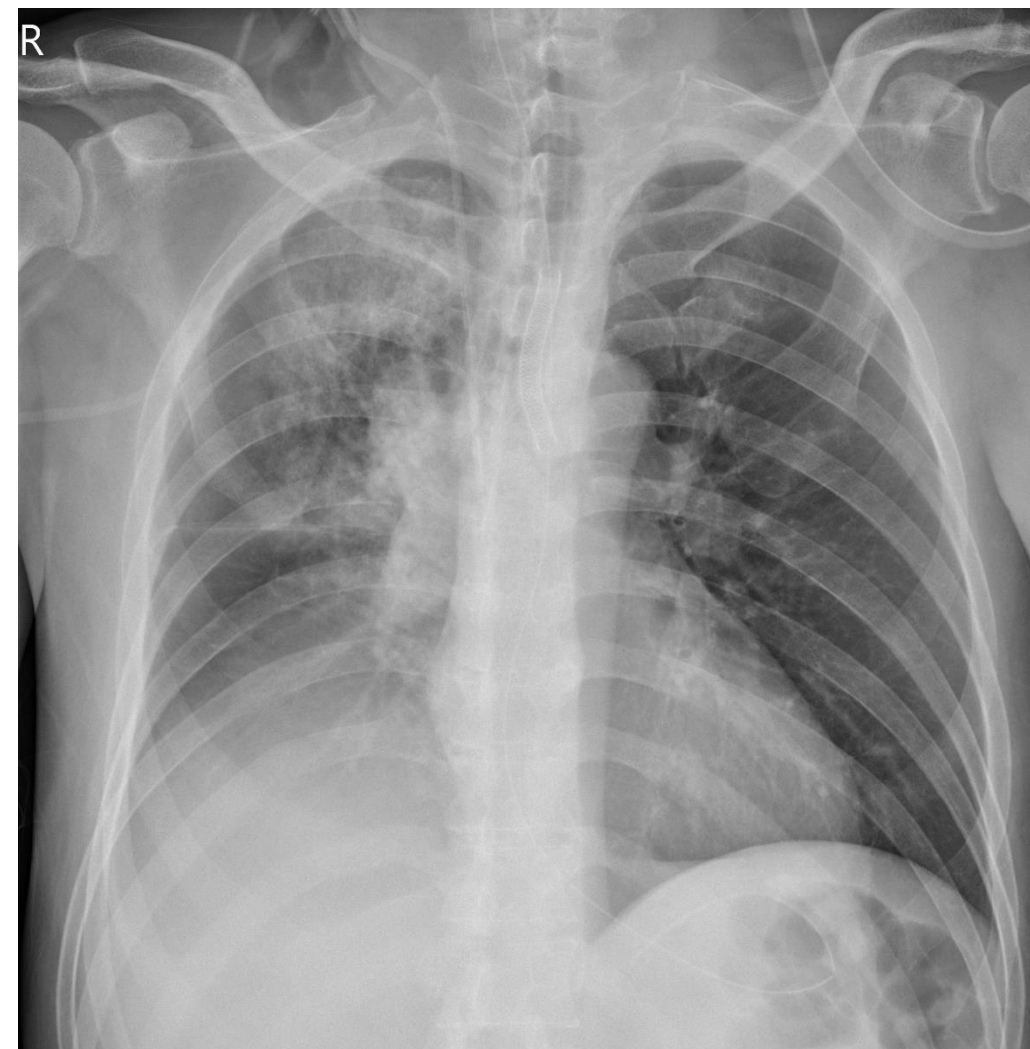
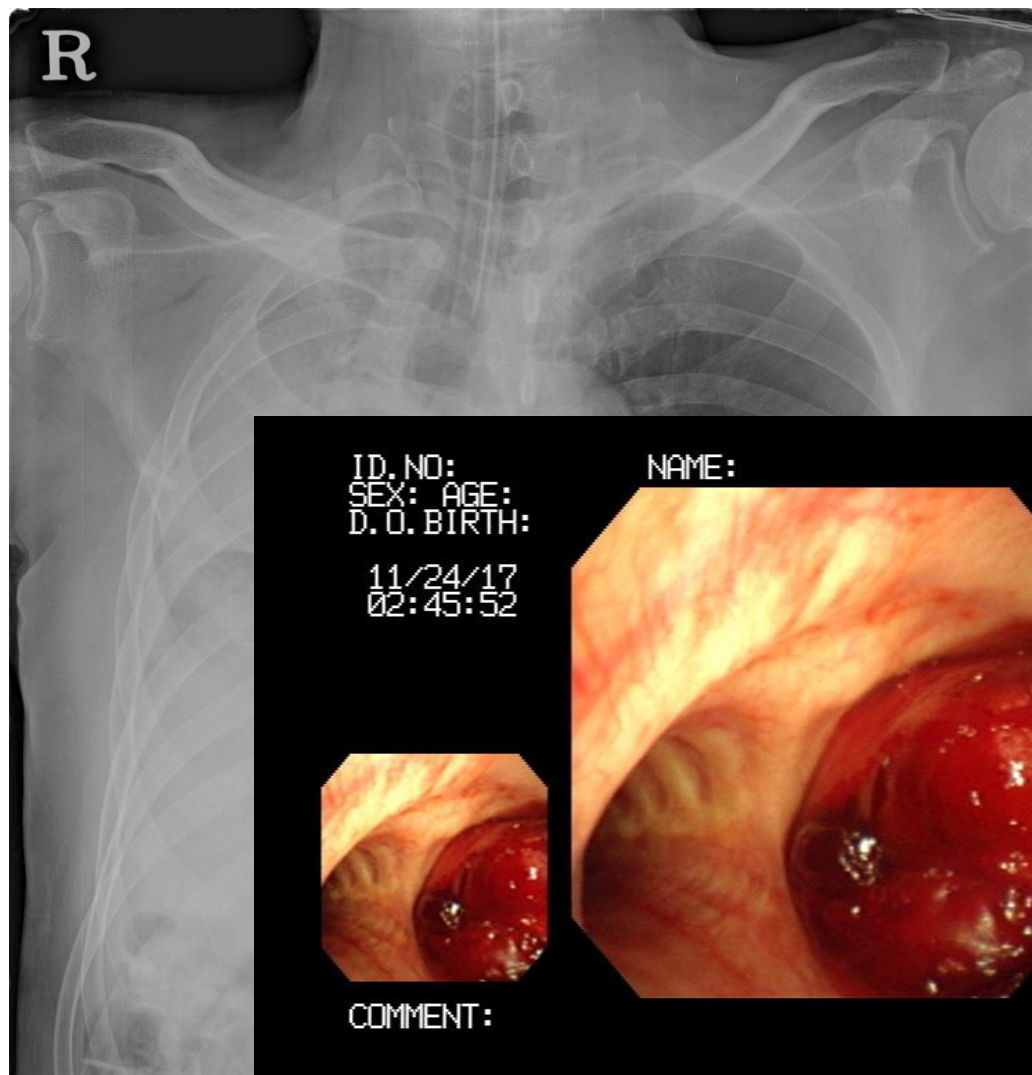
Case1 – chest PA



Case1 – Cryoextraction



Case2 – Cryoextraction



Cryotherapy for benign lesions

- Post intubation stenosis (cryotherapy alone)

INTERNAL MEDICINE

□ CASE REPORT □

Recurred Post-intubation Tracheal Stenosis Treated with Bronchoscopic Cryotherapy

Ye-Ryung Jung, Joon Taek Jeong, Myoung Kyu Lee, Sang-Ha Kim, Suk Joong Yong, Seok Jeong Lee and Won-Yeon Lee

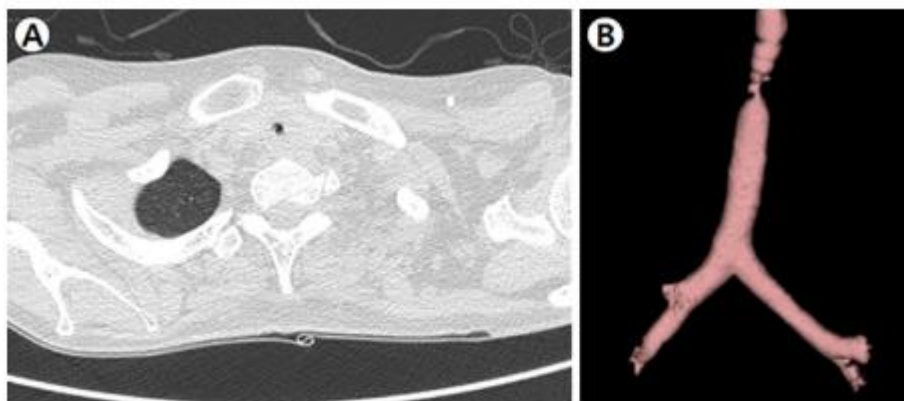
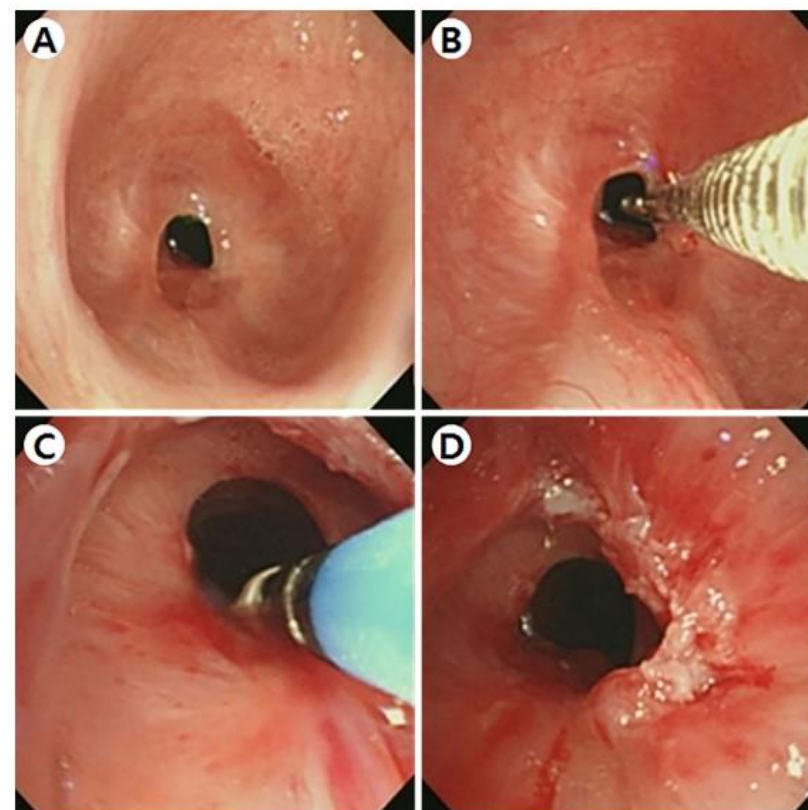


Figure 1. (A, B) Initial tracheal computed tomography shows luminal narrowing of the trachea where the narrowest diameter=3.8 mm.



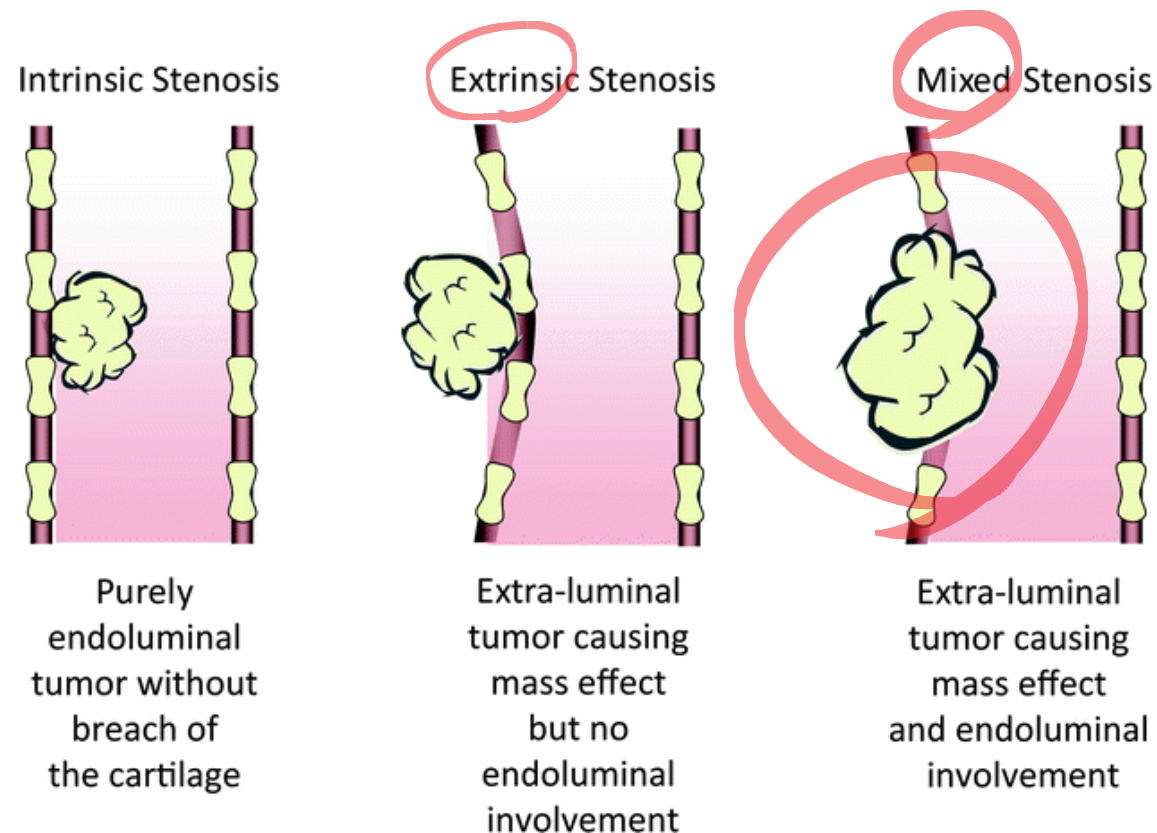
Cryotherapy in (malignant) lesions

- Treatment of superficial endobronchial malignancy
- Palliation of central airway obstruction (CAO) in advanced malignancy

Classification of MCAO

- Intrinsic (endoluminal)
- Extrinsic (extraluminal)
- **Mixed**

→ Impact on therapeutic approach

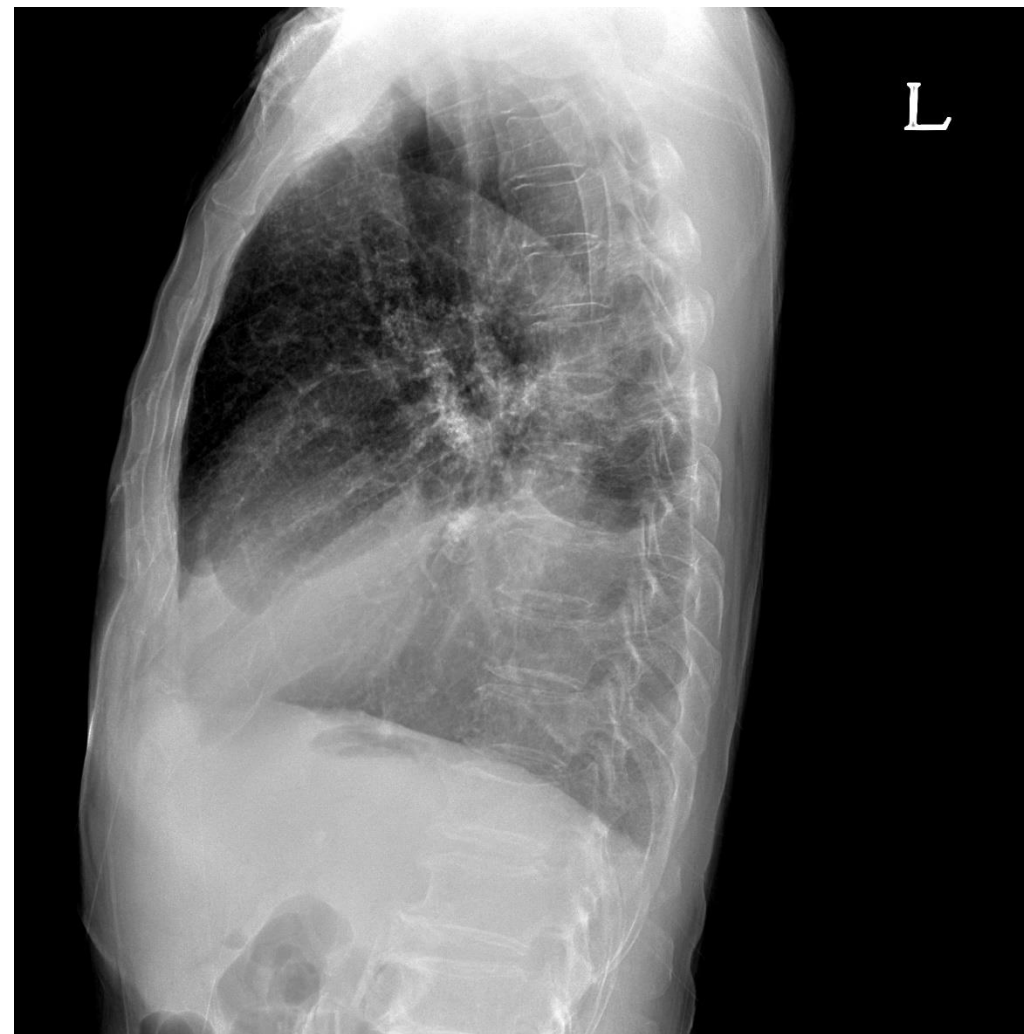
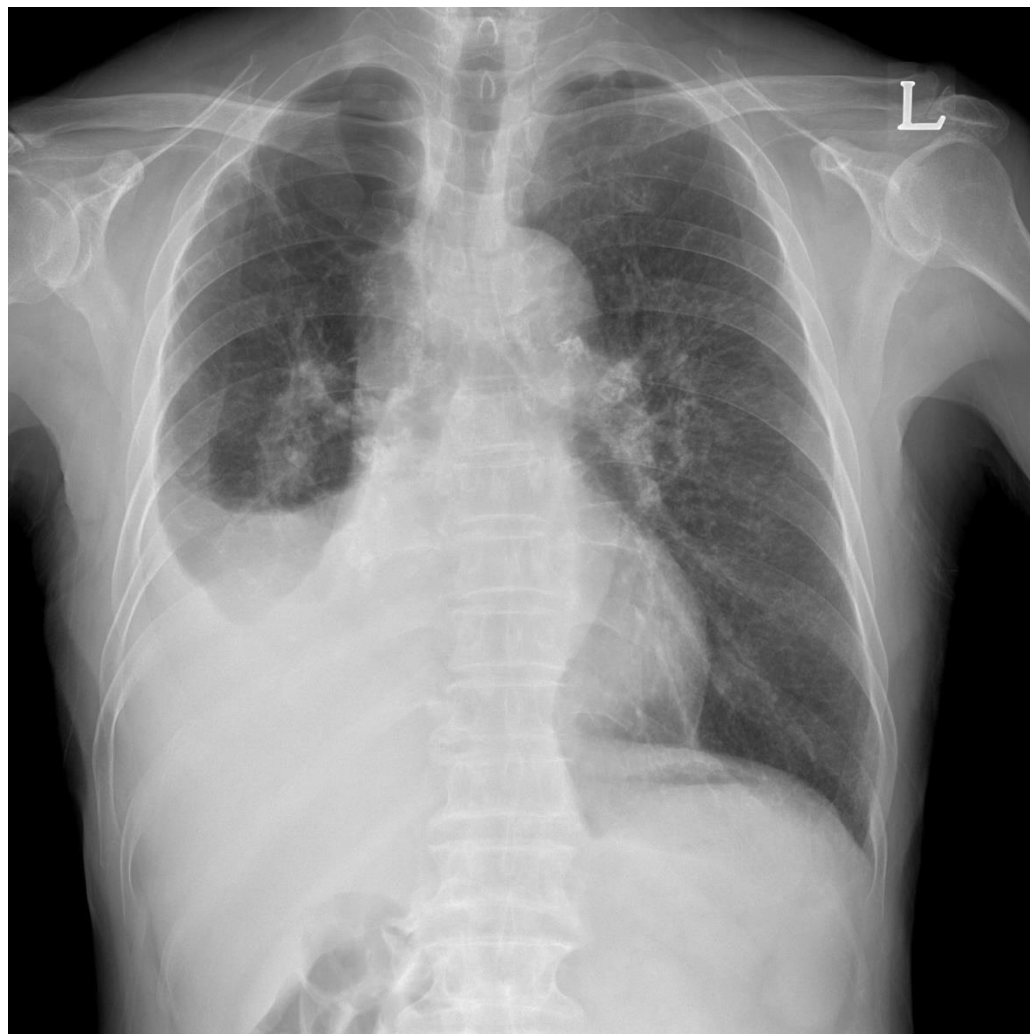


Laser & debridement	+++	-	++
Stent	±	+++	++

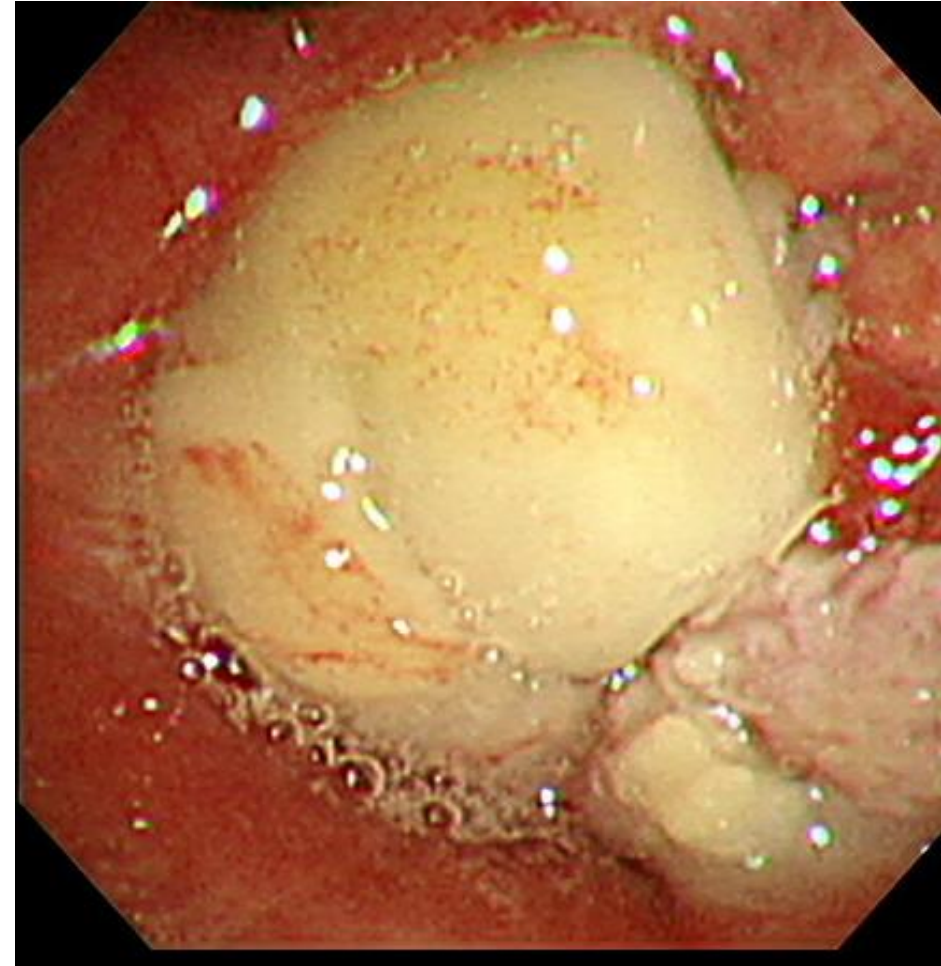
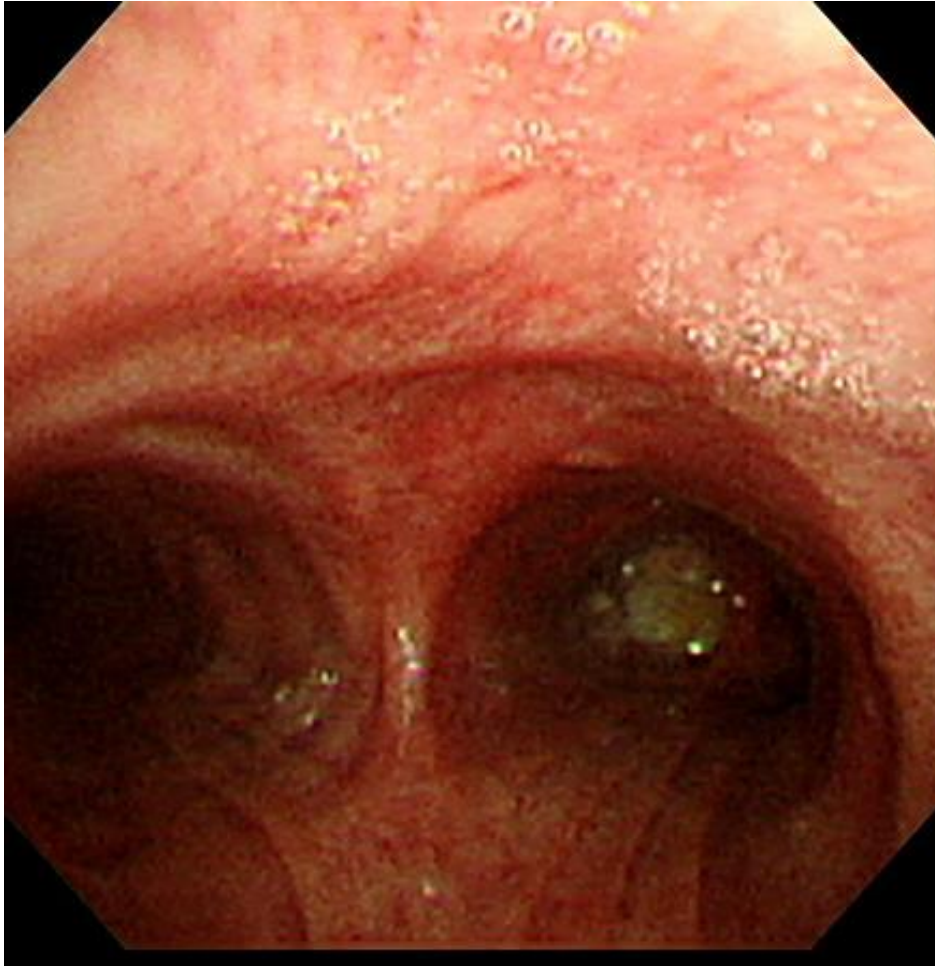
Case4 - MCAO

- 71/M, RLL atelectasis with pleural effusion
- 기저 pneumoconiosis로 연고지 병원에서 f/u 하던 분으로
- 내원 1주전 시행한 chest CT에서 RBI endobronchial mass와 RML, RLL atelectasis 소견으로 F/E위해 내원함

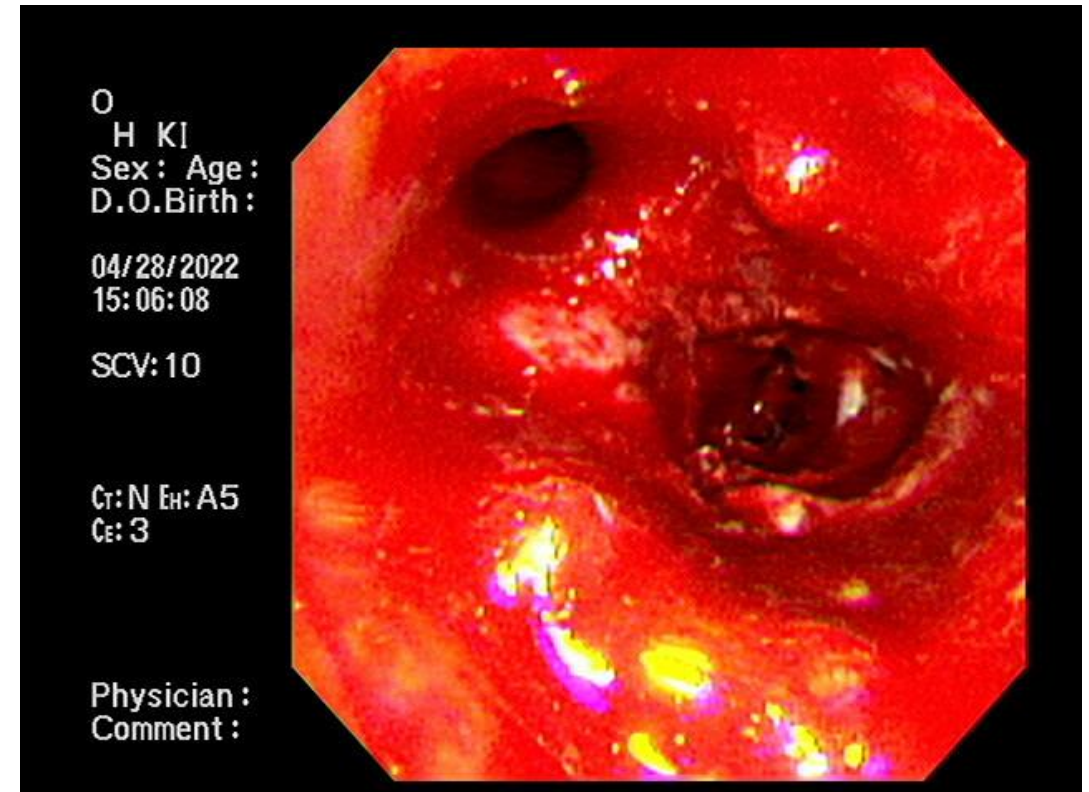
Case4 – chest PA



Case4 – Cryorecannalization



Case – cryotherapy



NSCLC, SqCC, cT3N3, PD-L1 4%
→ CCRT



Factors affecting survival in patients with endobronchial malignant mass after flexible Bronchoscopic cryotherapy: a cohort study

Fu-Tsai Chung^{1,2,3,4*}, Chun-Liang Chou^{1,2,4†}, Yu-Lun Lo², Chih-Hsi Kuo², Tsai-Yu Wang², Chun-Hwa Wang², Hung-Yu Huang^{1,2}, Horng-Chyuan Lin², Chih-Hao Chang^{1,2}, Chung-Shu Lee^{1,2}, Hao-Cheng Chen^{1,5} and Shu-Min Lin^{2*}

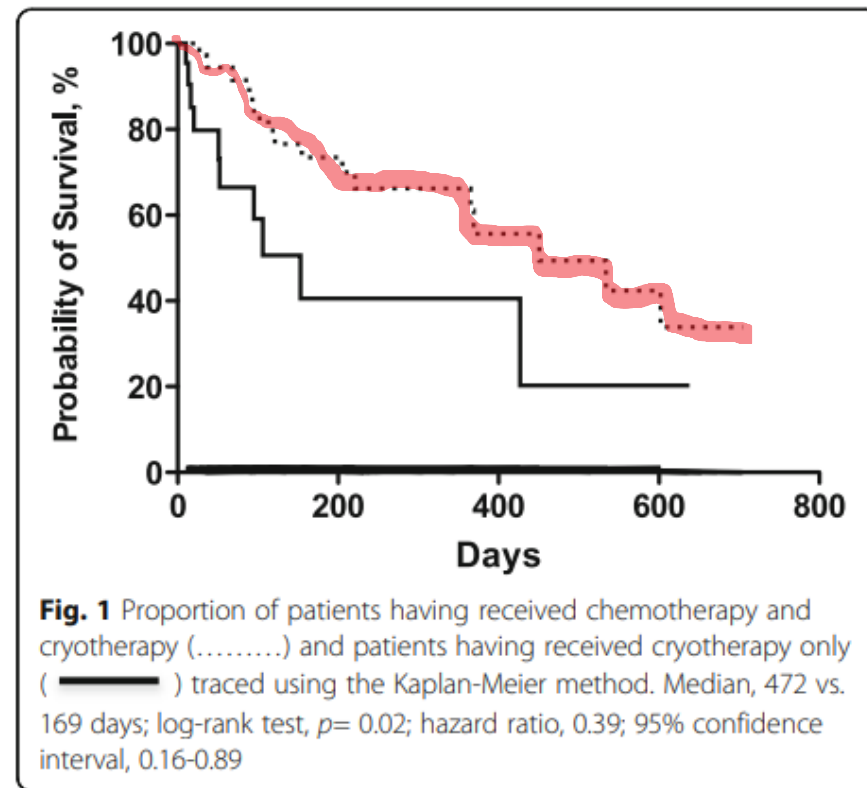


Table 4 Factors for survival, by multivariate analysis ($n = 67$)

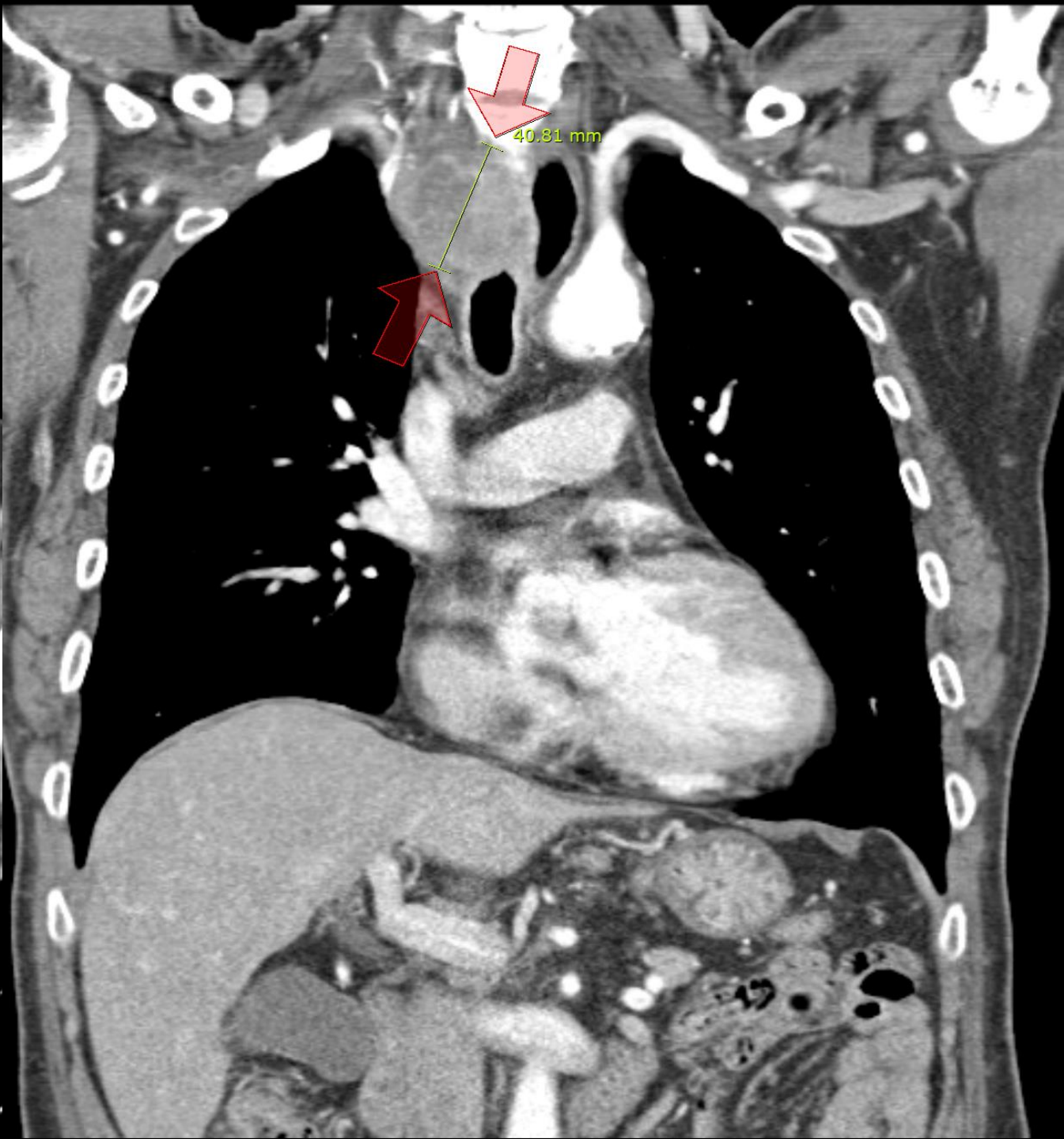
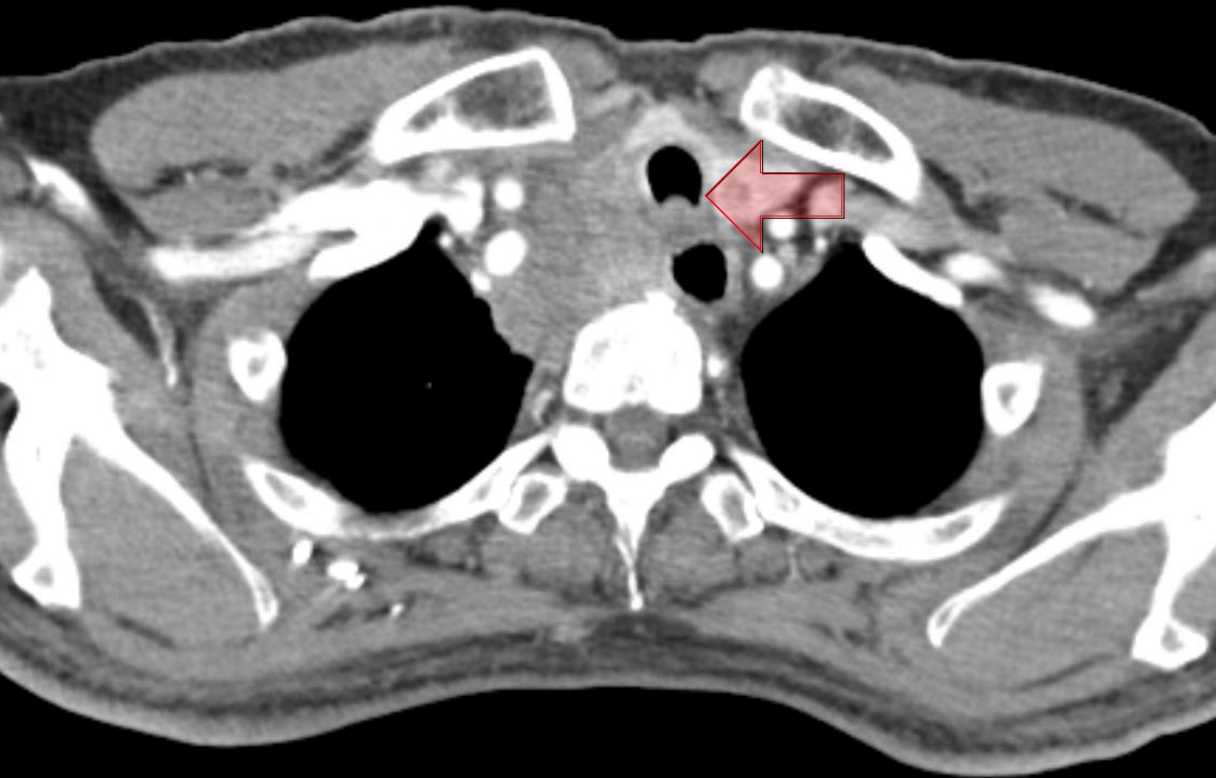
	OR	95% CI	p
Minor bleeding	1.2	0.27–5.27	0.87
Multiple procedures necessity	0.37	0.1–1.92	0.21
Symptoms relief	1.3	0.2–11.3	0.89
Performance status improved after cryotherapy*	3.7	1.2–10.7	0.03
Ability to receive further chemotherapy after cryotherapy with improvement of performance status *	4.3	1.4–13.7	0.02

Abbreviations: OR odds ratio, CI confidential interval

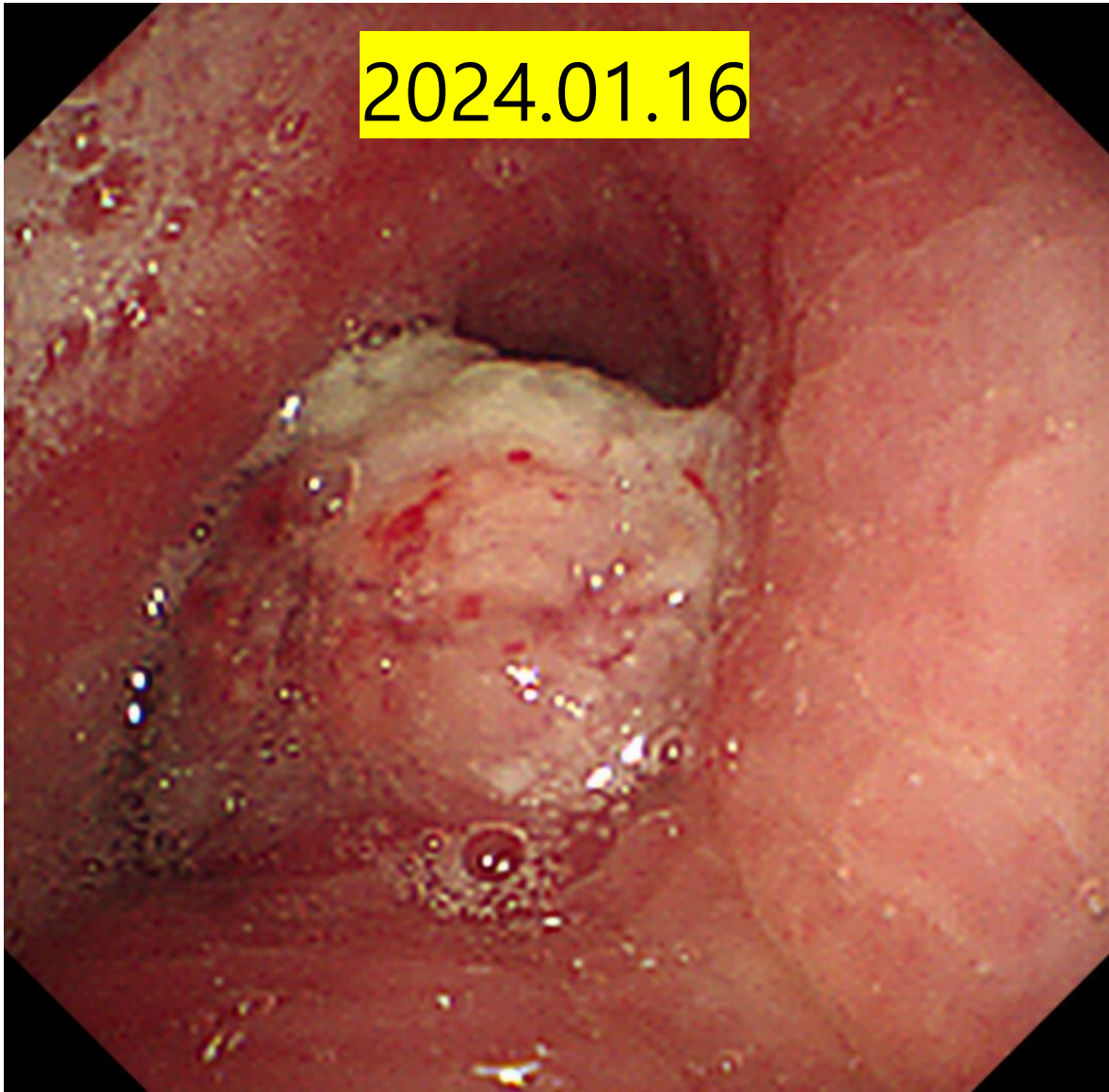
* $p < 0.05$

68/M

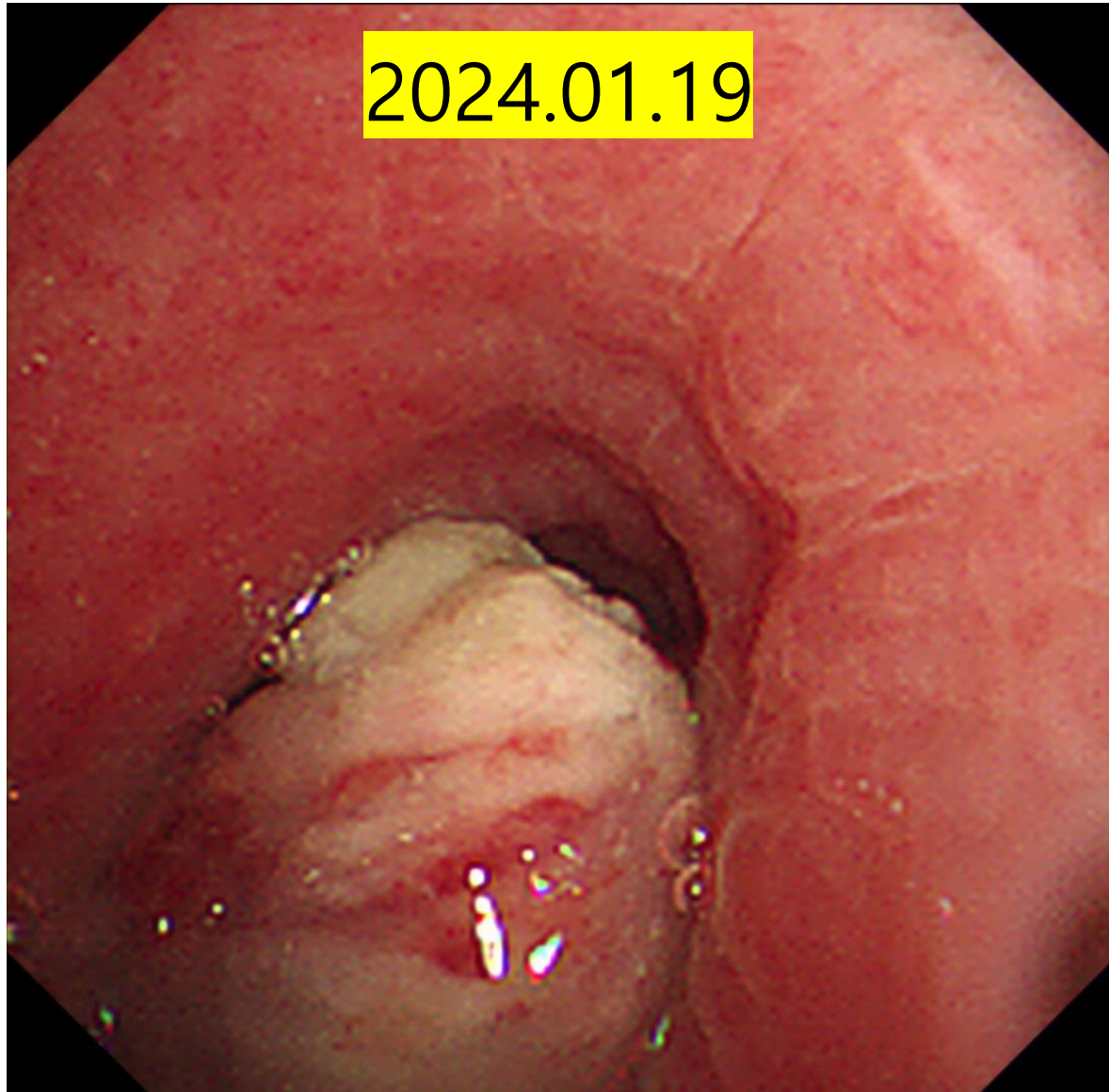
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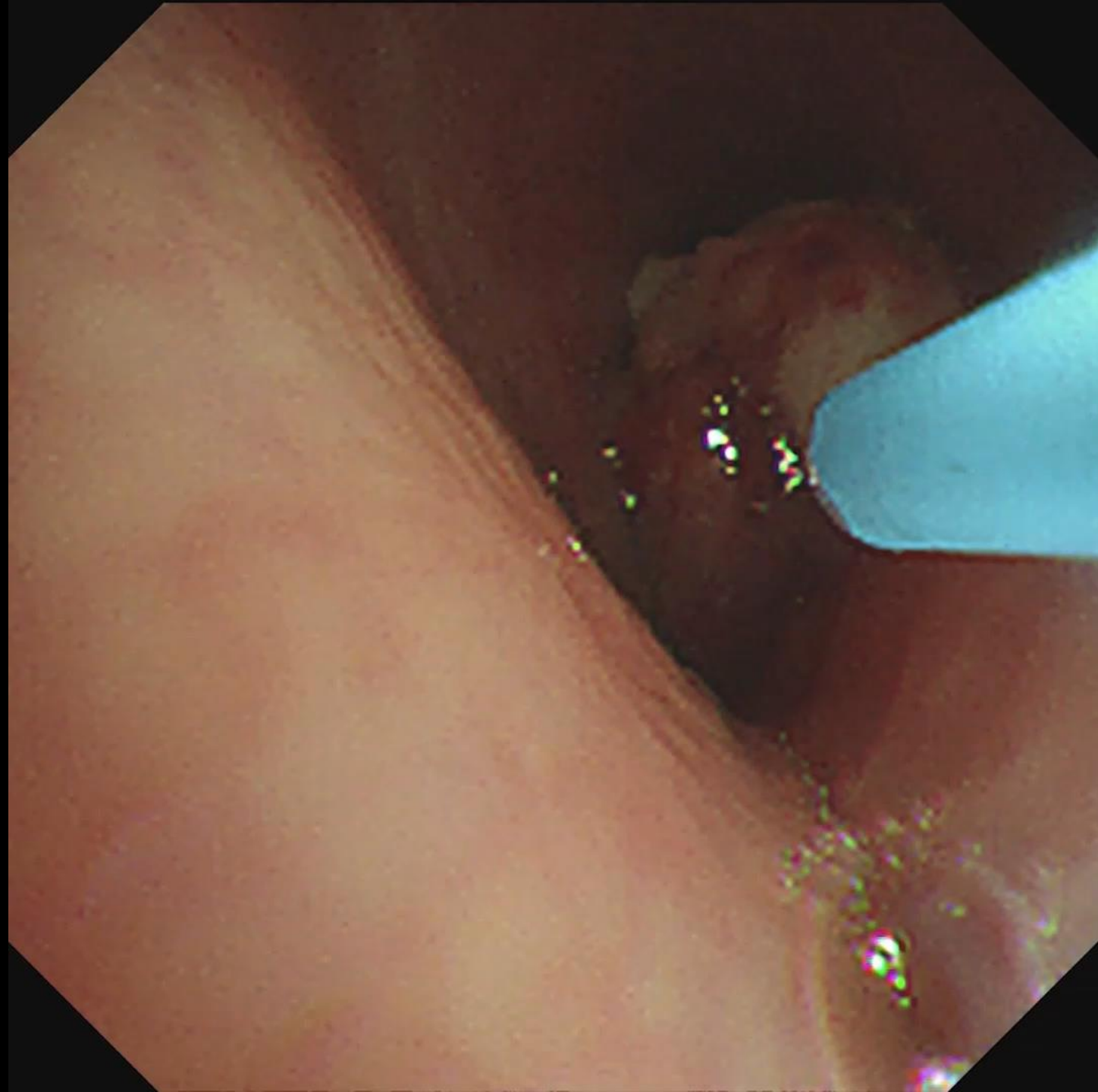


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2024.01.19





Case

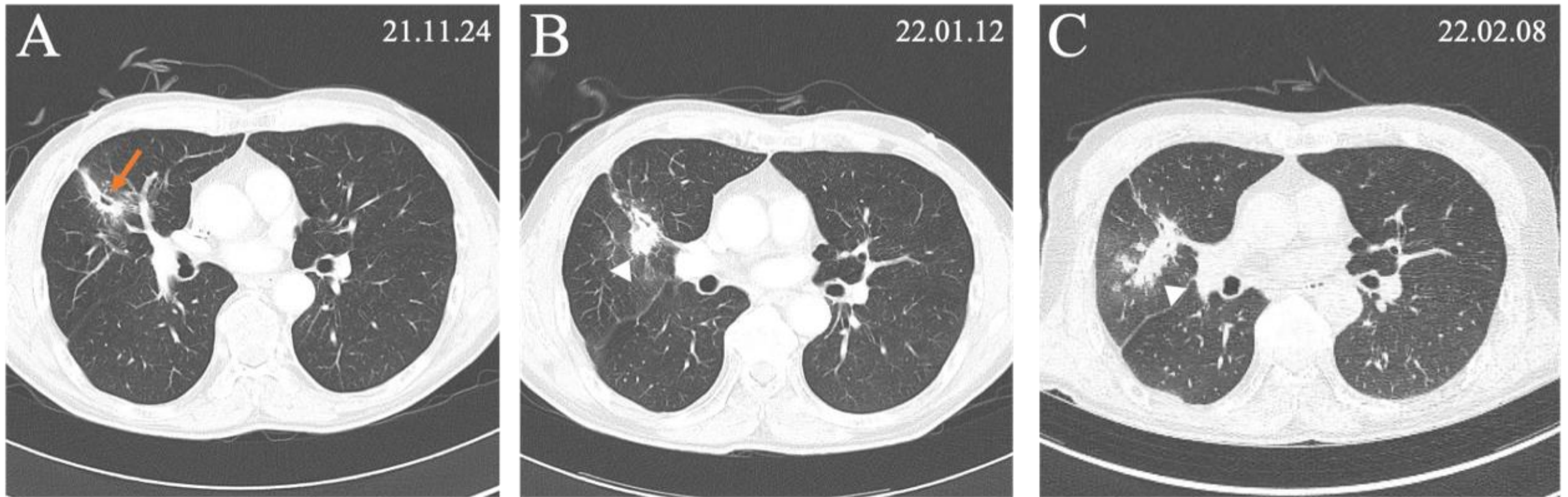
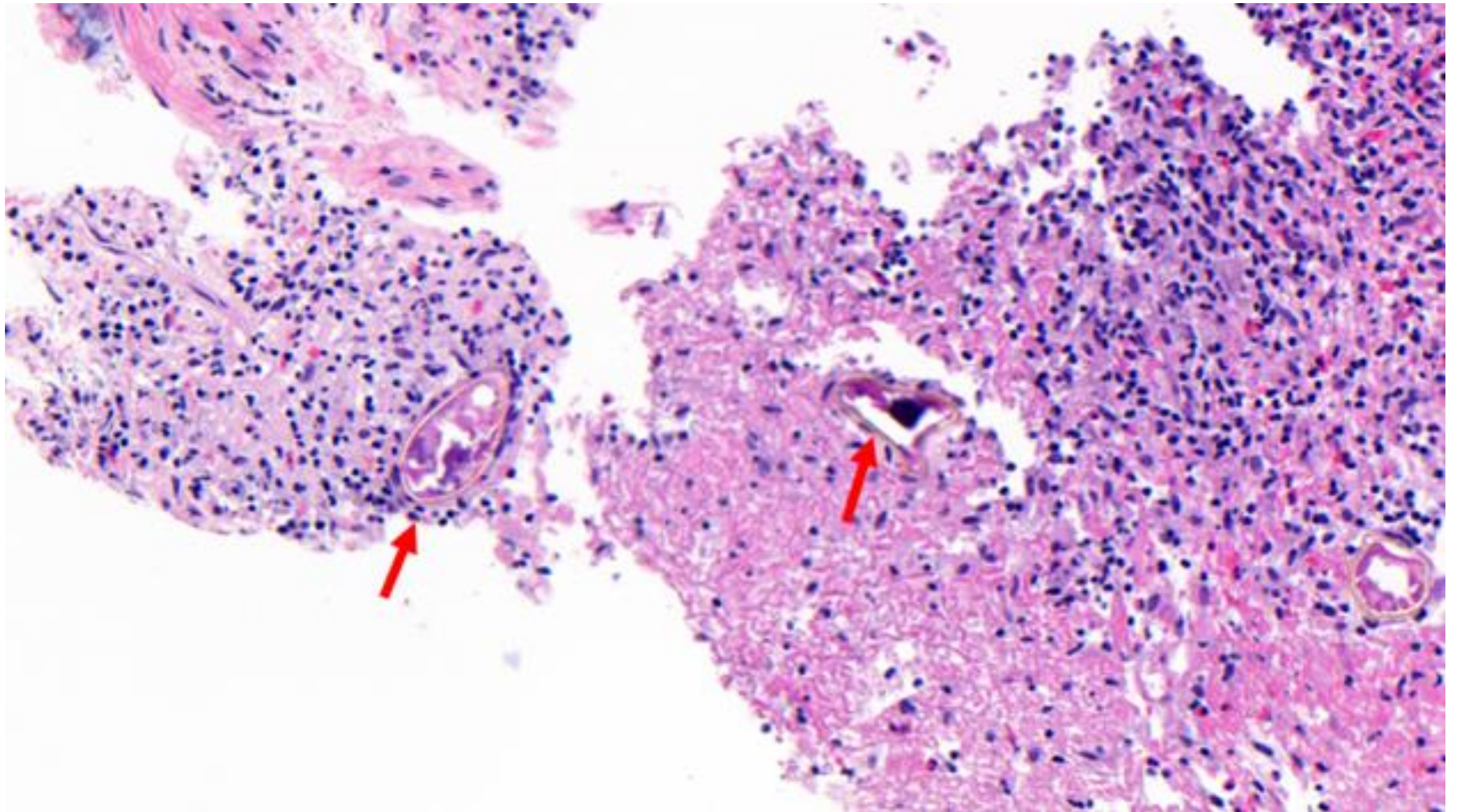
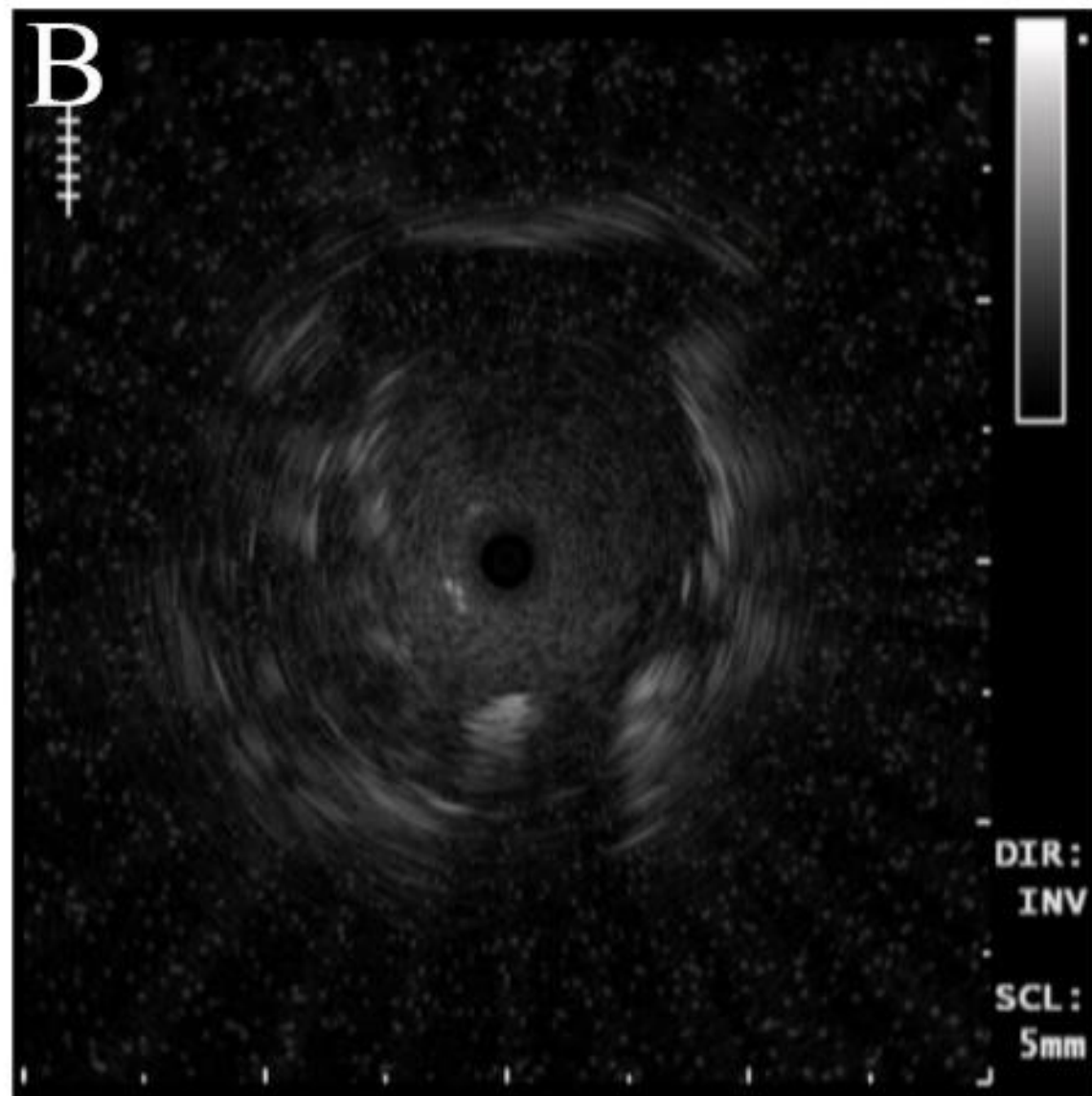
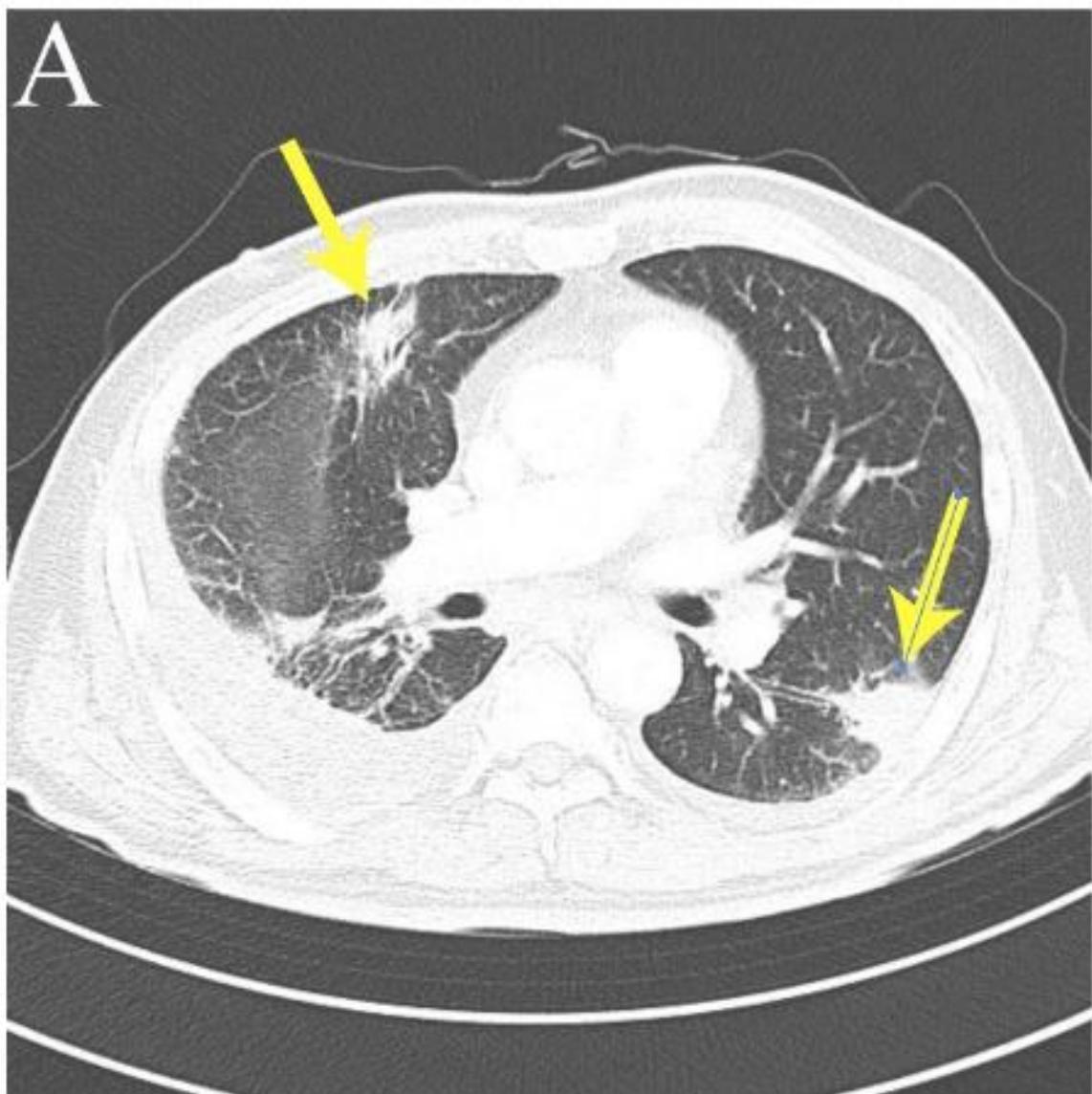
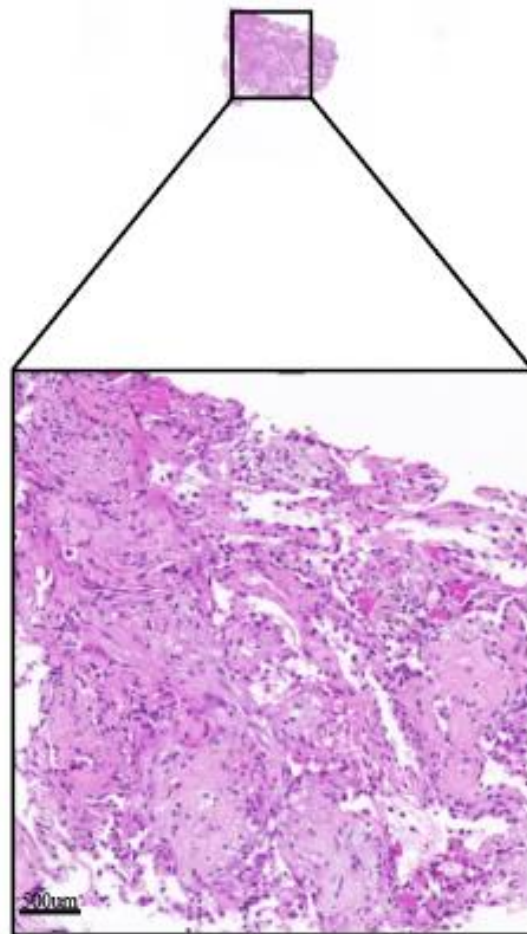


Figure 1. Serial CT findings of pulmonary paragonimiasis. (A) A transverse CT scan done initially shows 1.8cm-sized cavitary nodule of a spiculated margin with peripheral ground glass attenuation(GGA) in RML (B) A CT scan performed after 2 months demonstrates a slight decrease in the original nodule along with a new emergent 1.6cm sized nodule(arrow head). (C) A CT scan performed before biopsy shows a rapid increase in the new nodule to 4.4cm.

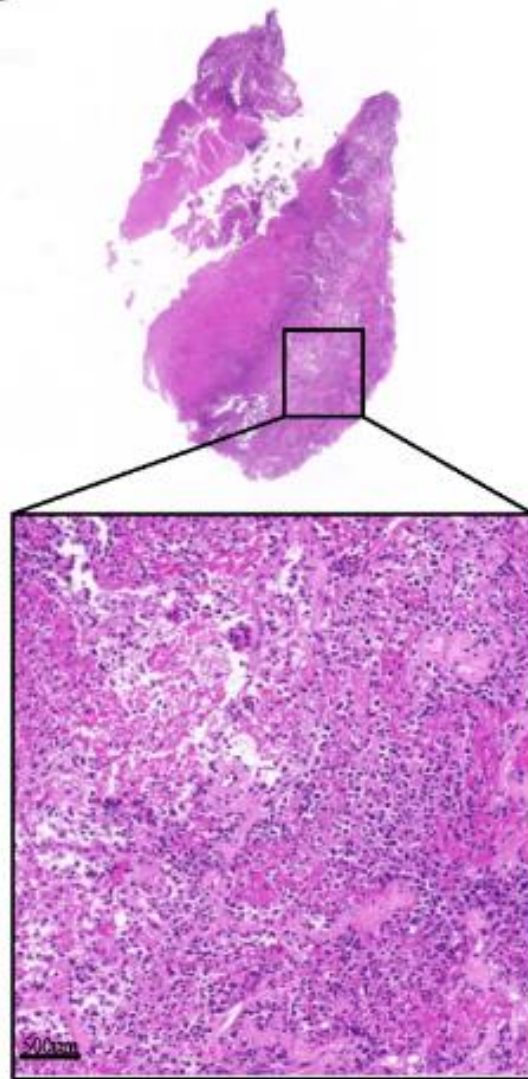




A



B



C



MPO



CD34



c-kit

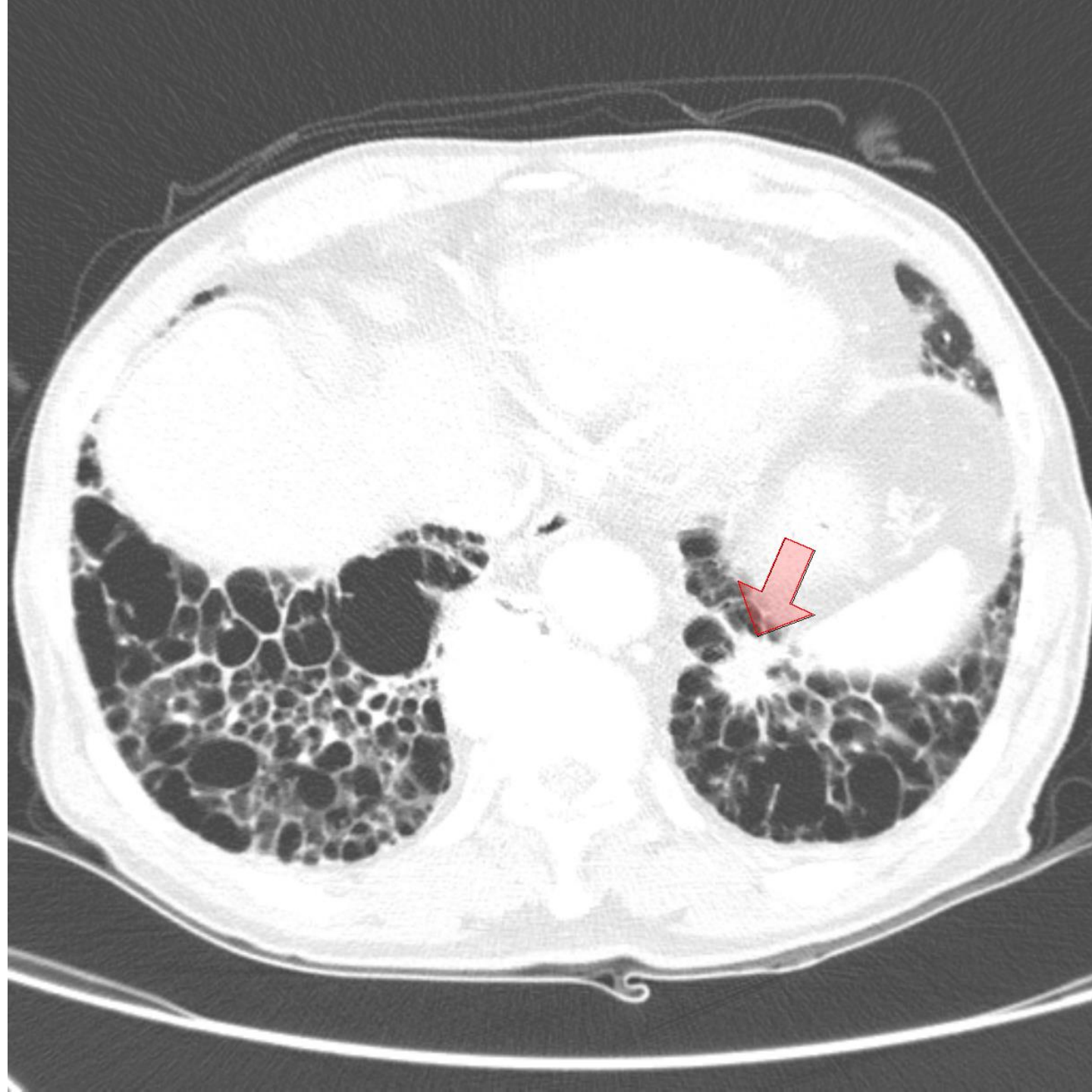


GMS

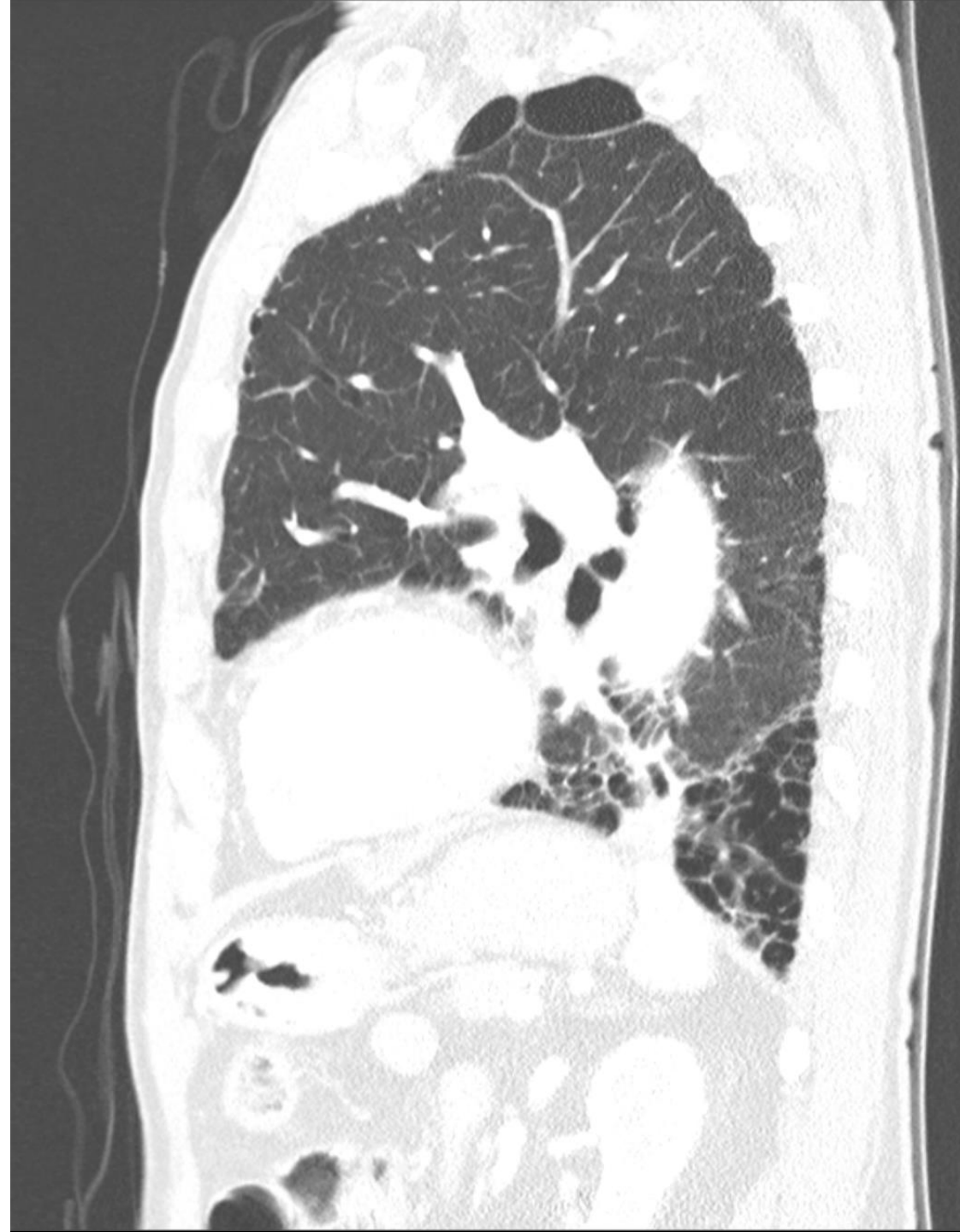
Table 1. Demographic, target lesion, procedural characteristic and outcome of overall cohort

Case	1	2	3	4	5	6	7	8	9
Demographic and target lesion characteristic									
Age, years	24	55	65	53	57	43	37	58	65
Gender	Female	Female	Female	Female	Female	Female	Female	Male	Female
Segmental location	LB2	LB4	RB8	RB4	LB9	LB8	RB4	RB9	RB4
Centrality	Middle 1/3	Middle 1/3	Middle 1/3	Middle 1/3	Inner 1/3	Inner 1/3	Inner 1/3	Middle 1/3	Inner 1/3
Size, cm	2.99	2.46	1.25	3.79	2.80	3.50	3.00	1.10	1.50
Nature	Solid	Solid	Solid	Solid	Solid	Solid	Solid	Solid	Solid
Direct Bronchus Sign	No	No	No	No	No	No	No	Yes	Yes
Procedural characteristic									
Type of EBUS	Radial	Radial	Radial	Radial	Radial	Linear	Linear	Radial	Radial
EBUS Orientation	Adjacent	Eccentric	Adjacent	Eccentric	Adjacent	Adjacent	Adjacent	Concentric	Concentric
Forceps/ needle size, mm/G	1.9 forceps	1.5 forceps	1.9 forceps	Not done	20G TBNA*	22G TBNA	22G TBNA	1.5 forceps	1.9 forceps
Forceps pass	5	8	10	Not done	Not done	3	3	6	13
Cryoprobe size, mm	1.9	Not done	1.1	1.1	1.1	1.1	1.1	1.1	Not done
Cryobiopsy pass	3	Not done	5	2	5	2	3	1	Not done
Freeze time/ pass, seconds	4.0	Not done	3.8	4.5	3.4	4.5	4.6	4	Not done
Outcome									
Forceps/ needle histology	Inflammation	PSP	Alveolar tissue	Not done	Not done	Atypical cell	Lymphocyte	PSP	PSP
Forceps conclusive	No	Yes	No	Not done	Not done	No	No	Yes	Yes
Cryobiopsy histology	Alveolar Tissue	Not done	PSP	Carcinoid	PSP	PSP	Alveolar Tissue	PSP	Not done
Cryobiopsy conclusive	No	Not done	Yes	No	Yes	Yes	No	Yes	Not done
Final diagnosis and surveillance									
Surgical resection histology	PSP	PSP	Not done	PSP	PSP	Not done	PSP	PSP	Not done
CT Surveillance	Not applicable	Not applicable	Stable	Not applicable	Not applicable	Stable	Not applicable	Not applicable	Defaulted

85/M



85/M



33333

Name :

Sex : Age :

D.O.Birth :

05 16 2022

10:21:37

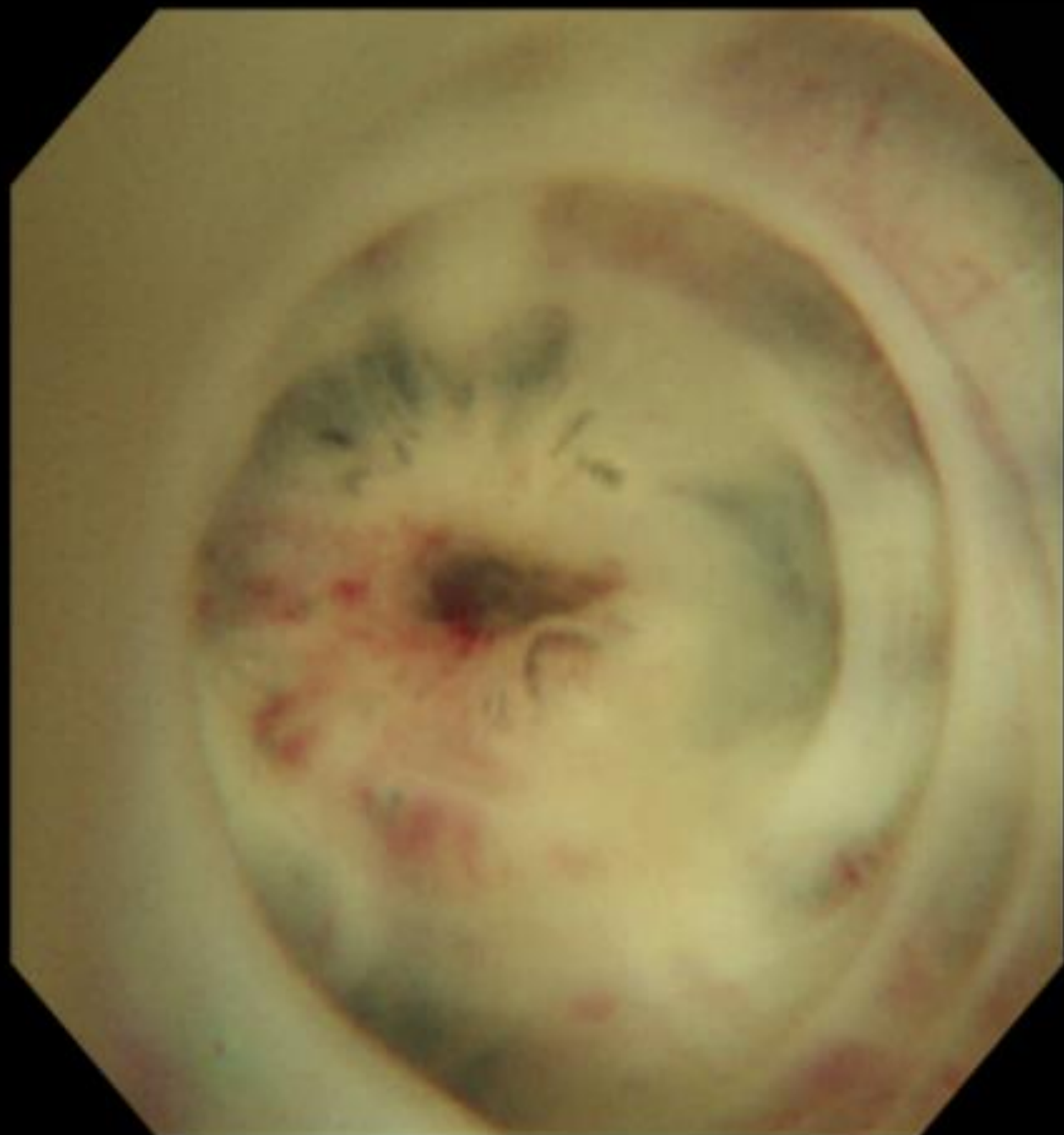
SCV:34

Ct: N Eh: A1

Ce: O

Physician :

Comment :



33333

Name : ■

Sex : Age :

D.O.Birth :

05 16 2022

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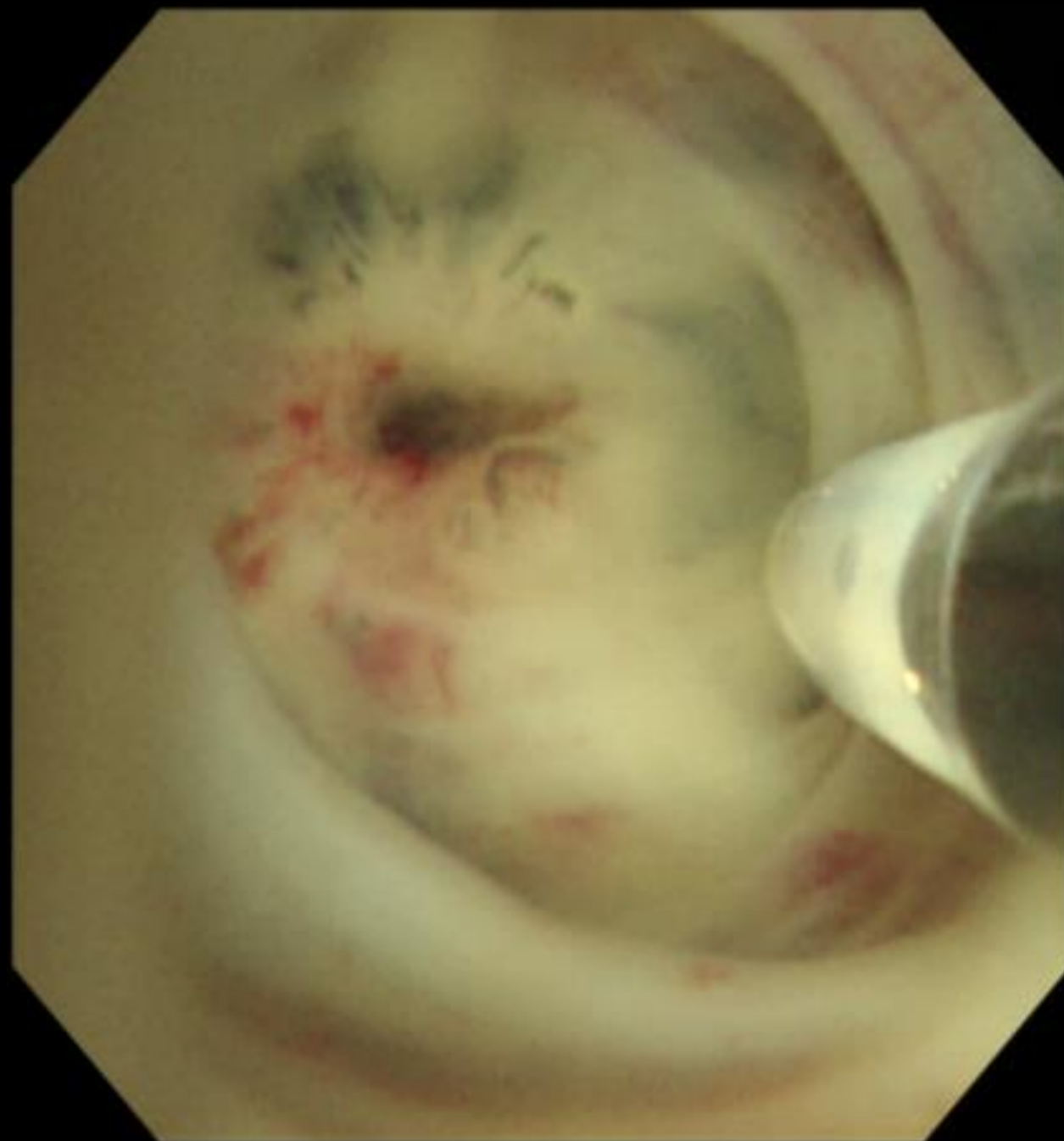
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Cr: N Eh: A1

Ce: O

Physician :

Comment :



33333

Name : ■

Sex : Age :

D.O.Birth :

05 16 2022

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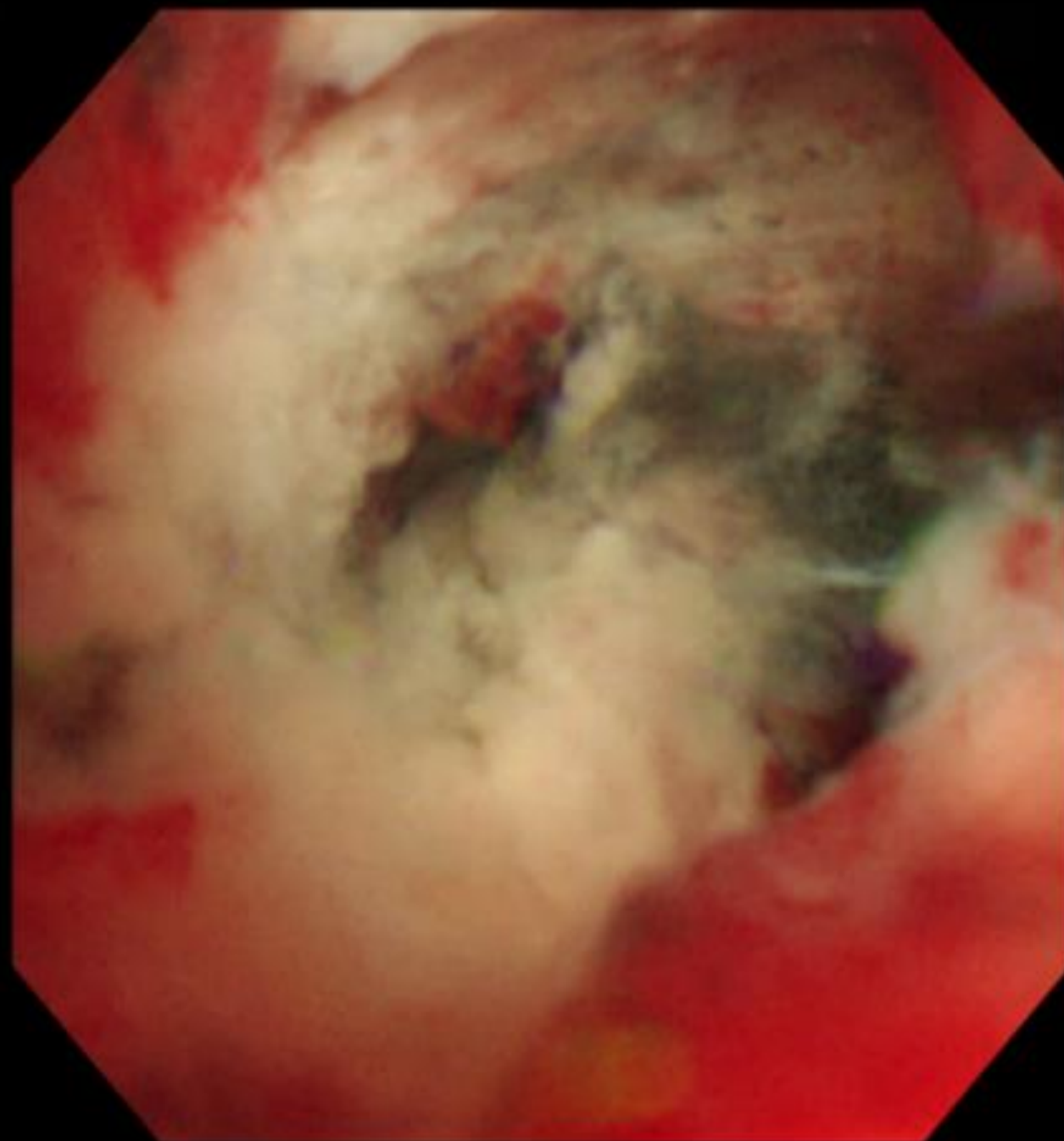
SCV:34

Cr: N Eh: A1

Ce: O

Physician :

Comment :



ID:

OLYMPUS

NAME:

AGE:

CR1

DOB:

SEX:



05/16/2022

10:37:48

20MHz 4cm

G: 9/19 I:L2

C:4/8

MEDIA

T/B:CINE REV

1/ 90

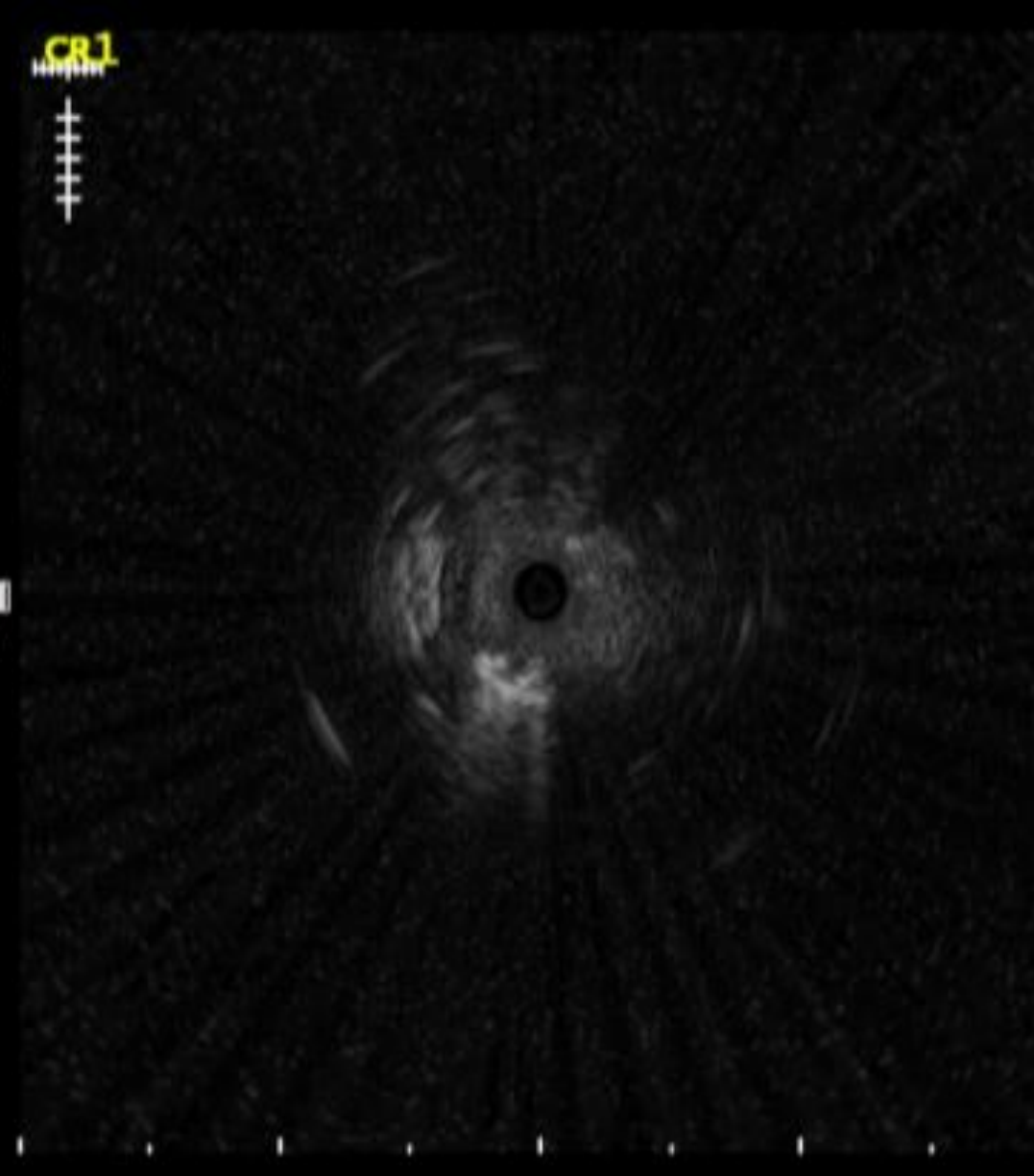
CNCT: R

DIR:

INV

SCL:

5mm

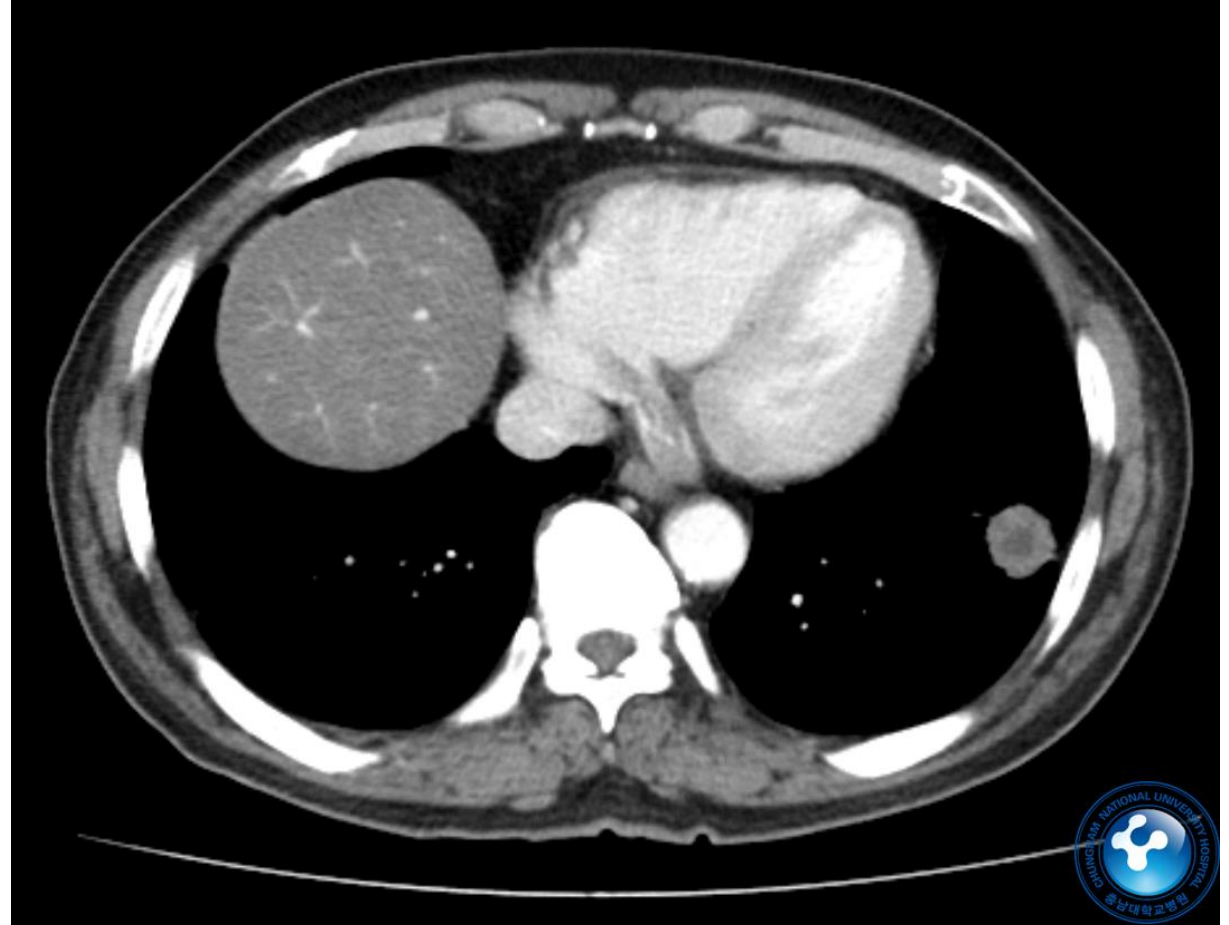
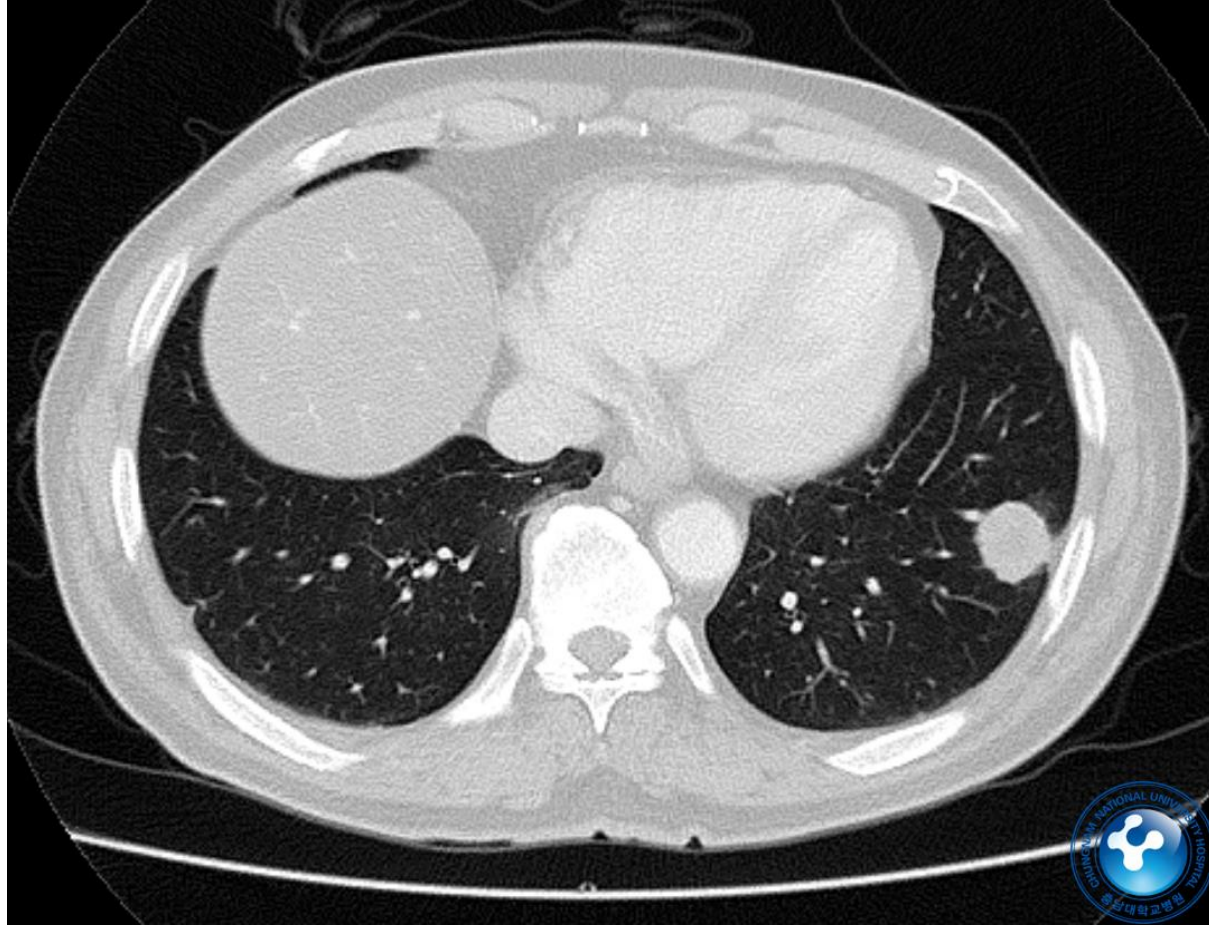


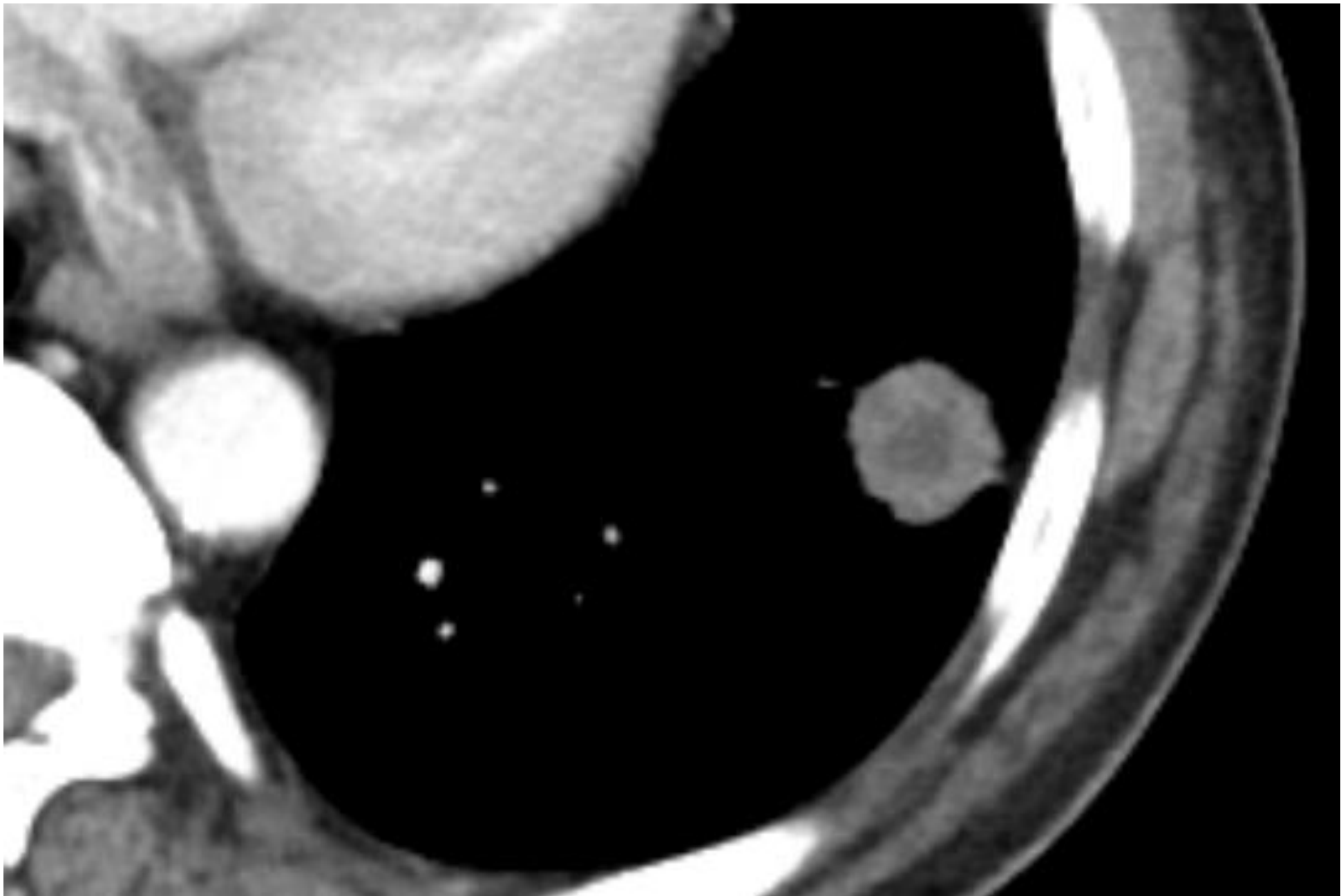
2021.12.03~2023.01.20 EBUS-TBB + Cryobiopsy in CNUH (n = 11/352)

	나이/ 성별	시술 전 진단명	크기 (mm)	위치	성상	Bronchus sign 양상	합병증	병리결과 (FB)	병리결과 (Cryo.)	최종 진단
1	68/M	IPF > CPFE	72	LUL	Solid	기관지가 병변의 말초에 접촉 후 끊김	(-)	SCLC	SCLC	SCLC
2	67/M	IPF	27	LLL	Solid	내부에서 좁아지면서 끊김	(-)	A few atypical cells	SQ	SQ
3	77/M	IPF or Fibrosing NSIP	23	LLL	Solid	기관지가 병변의 말초에 접촉 후 끊김	Mild bleeding	SCLC	SCLC	SCLC
4	65/M	IPF	15	LLL	Solid	기관지가 병변의 말초에 접촉 후 끊김	(-)	Atypical cells, suggestive of NSCLC	Adenosquamous carcinoma/N SCLC	Adenosquamous carcinoma/N SCLC
5	67/M	IPF	28	RLL	Solid	기관지가 병변의 말초에 접촉 후 끊김	Pneumonia	SCLC	SCLC	SCLC
6	87/M	IPF	23	LLL	Solid	기관지가 병변의 말초에 접촉 후 끊김	Hypoxemia (E-tube 삽입 전)	A few atypical cells, suggestive of AD	A few atypical cells, suggestive of AD	AD
7	85/M	IPF	26	RLL	Solid	내부에서 좁아지면서 끊김	Hypoxemia (E-tube 삽입 전)	NSCLC, favor SQ	NSCLC, favor SQ	SQ
8	67/M	IPF or CPFE	30	LLL	Solid	내부에서 좁아지면서 끊김	Mild bleeding Hypotension (저절로 회복)	Atypical cells, suggestive of SQ	SQ	SQ
9	81/M	CPFE > IPF	30	LLL	Solid	기관지가 병변의 말초에 접촉 후 끊김	Mild bleeding	NSCLC, favor SQ	NSCLC, favor SQ	SQ
10	70/M	IPF > CPFE	38	LLL	Solid	기관지가 병변의 말초에 접촉 후 끊김	Mild bleeding	SCLC	SCLC	SCLC
11	76/M	IPF	31	LLL	Solid	병변의 말초 경계를 스치면서 통과	Mild bleeding Hypotension (저절로 회복)	Atypical cells, suggestive of SQ	Atypical cells, suggestive of SQ	SQ

Complication Case

67/M





F1



F2



DIR:
INV
SCL:
5mm

DIR:
INV
SCL:
5mm

◎ 육안 소견

Specimen consists of three parts as follows;

No.1; Specimen labeled "C" consists of a tiny piece of soft tissue (A).

No.2; Specimen labeled "D" consists of two tiny pieces of soft tissue (B).

No.3; Specimen labeled "E" consists of a tiny piece of soft tissue (C).

◎ 병리 진단

Lung, left lower lobe, lateral segment "C", "D" and "E", cryobiopsy;
SQUAMOUS CELL CARCINOMA (A,B,C)

◆ 1차 추가진단 진단일자:2022-12-29 16:49 진단의사:박형규

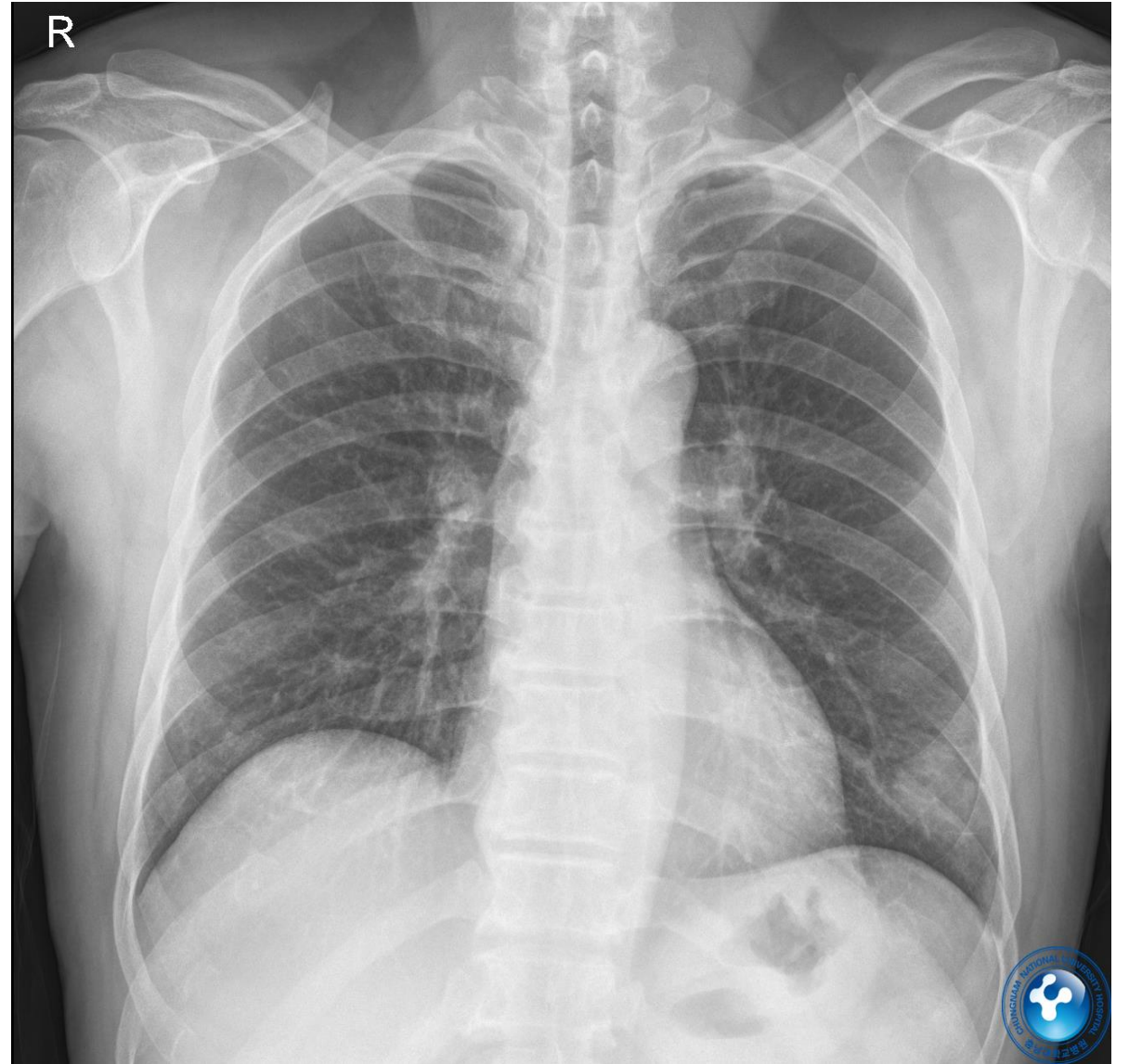
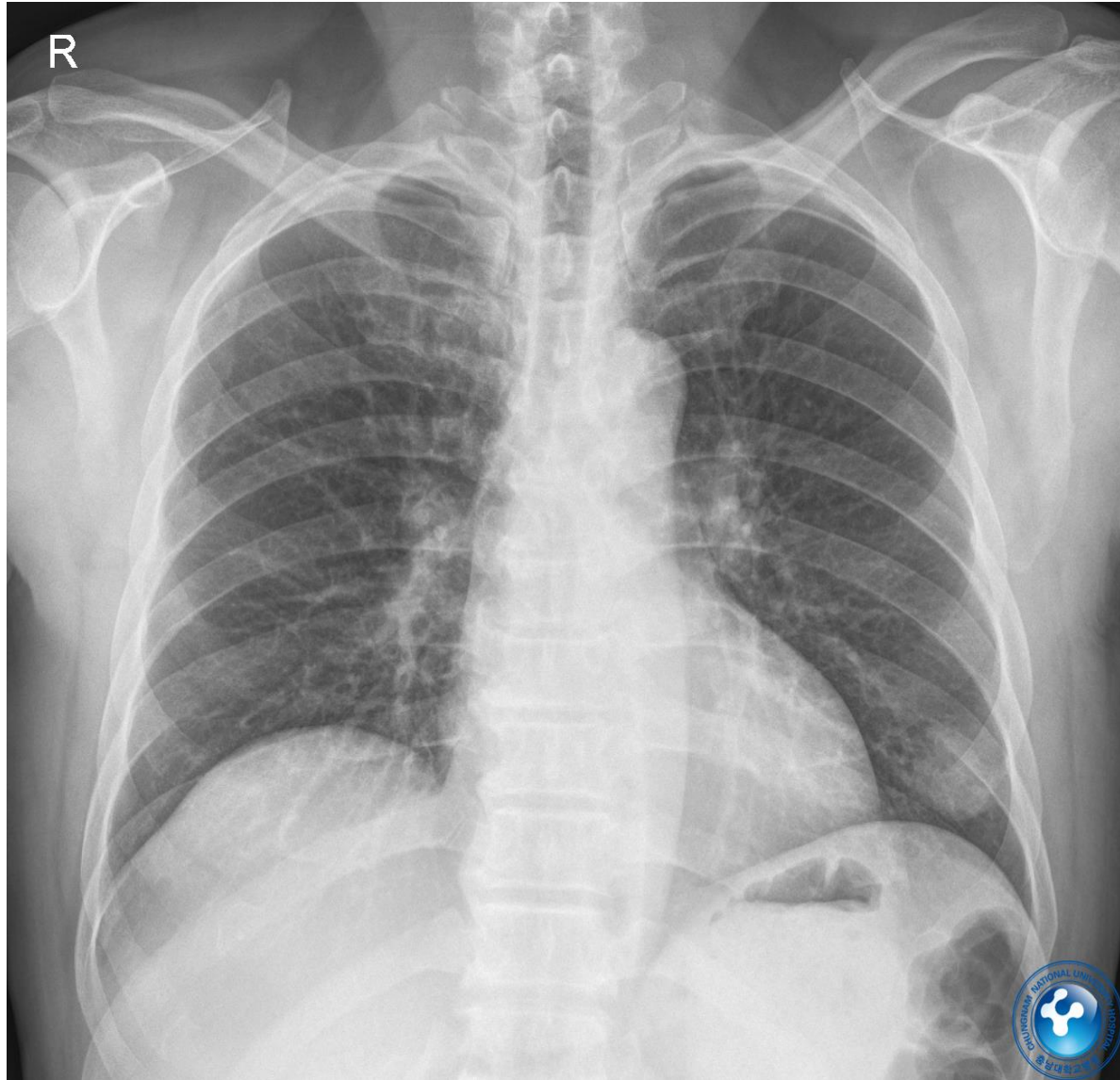
* Immunohistochemical stain results (A);

- 1) PD-L1(SP263)assay; tumor proportion score; 70 %
- 2) ALK(D5F3); negative
- 3) P40: positive
- 4) TTF-1: negative

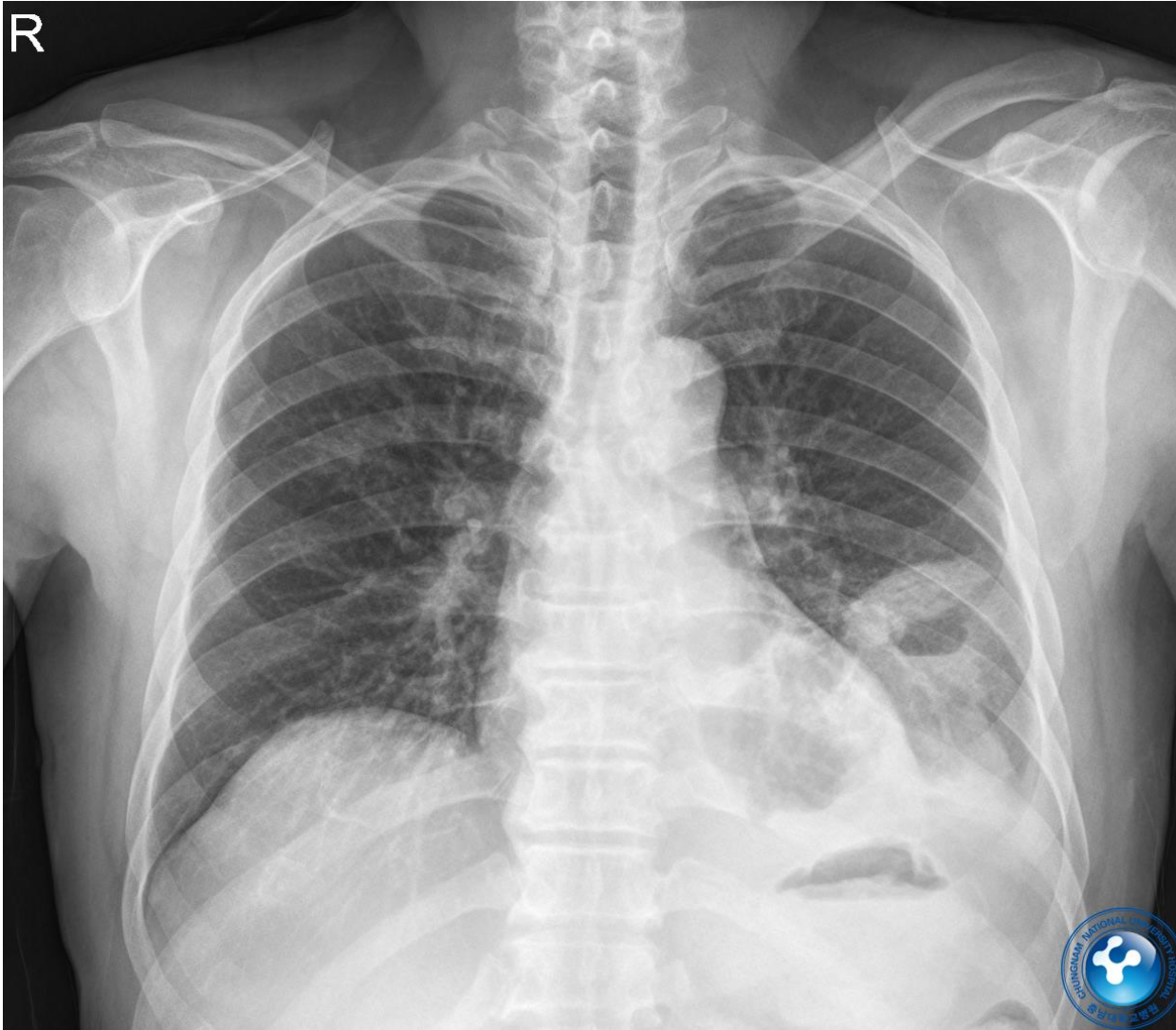
◆ 2차 추가진단 진단일자:2023-01-03 09:36 진단의사:박형규

* PD-L1 PharmDX 22C3 result (씨젠의료재단) (결과 이미지 주)
- High PD-L1 expression (Tumor Proportion Score $\geq 50\%$)



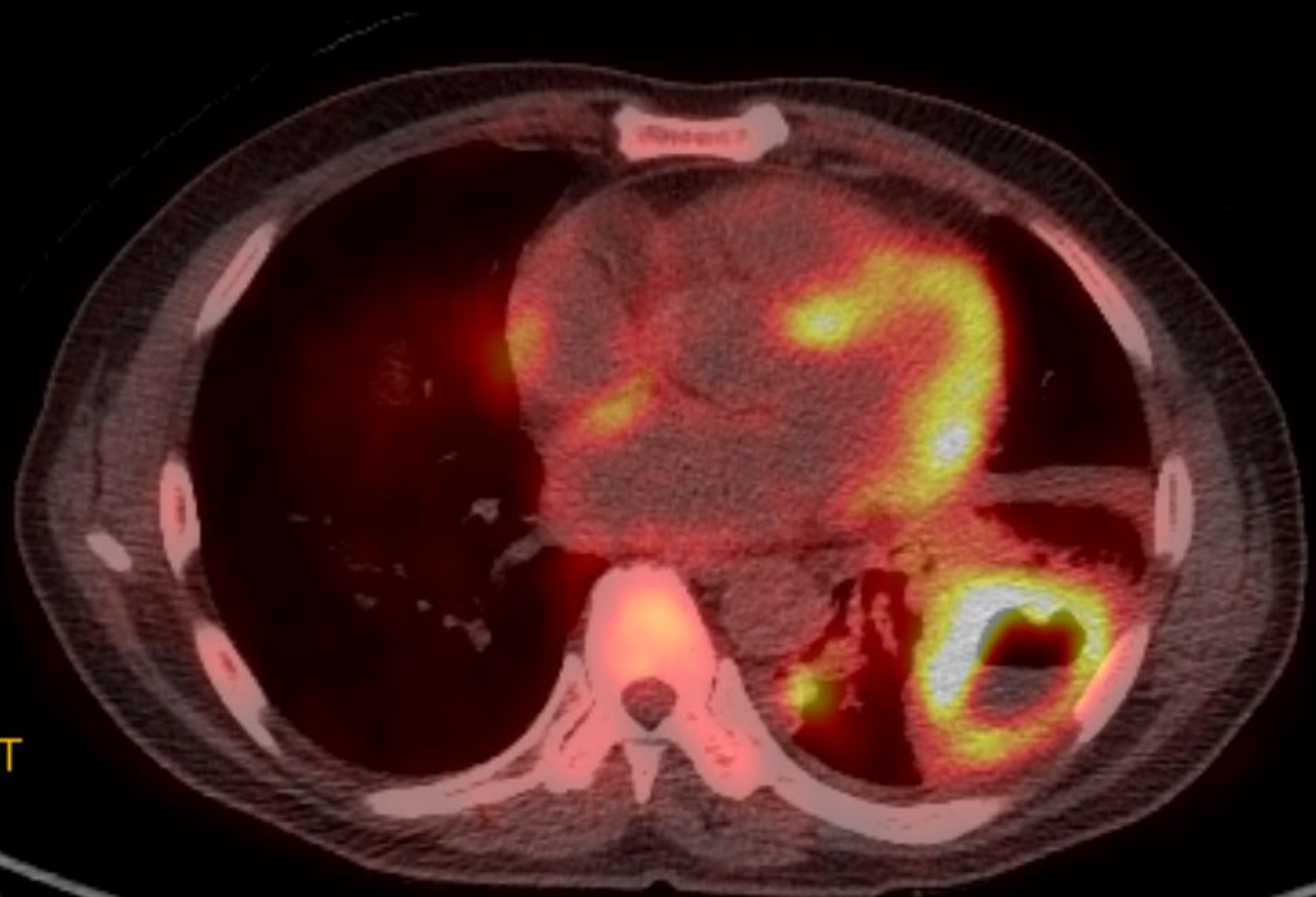
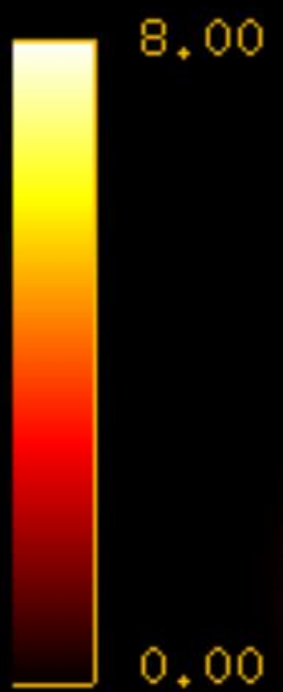


Day 16



- 조직검사 후 가슴통증이 지속된다.
- 냄새나는 농성 가래가 나온다.

DFOV 50.0 cm



50 % PET

3.3/

3.3 17.7



◎ 병 리 진 단

A - D) Lung, left lower lobe, lobectomy with lymph node dissection:

- SQUAMOUS CELL CARCINOMA, MODERATELY DIFFERENTIATED, KERATINIZING,
2.3 X 2.1 CM (A3-A5, A7-A9)

1) site: left lower lobe

2) pleura invasion: absent (superficially invades in pleural
connective tissue,

but not beyond elastic layer of
visceral pleura (PL0))

3) lymphovascular invasion: not identified

4) perineural invasion: not identified

5) lymphoplasmacytic reaction: absent

6) necrosis: PRESENT

7) bronchial resection margin: free from tumor (distance from
margin: 5.7 cm)

8) background lung: peritumoral suppurative inflammation with
abscess

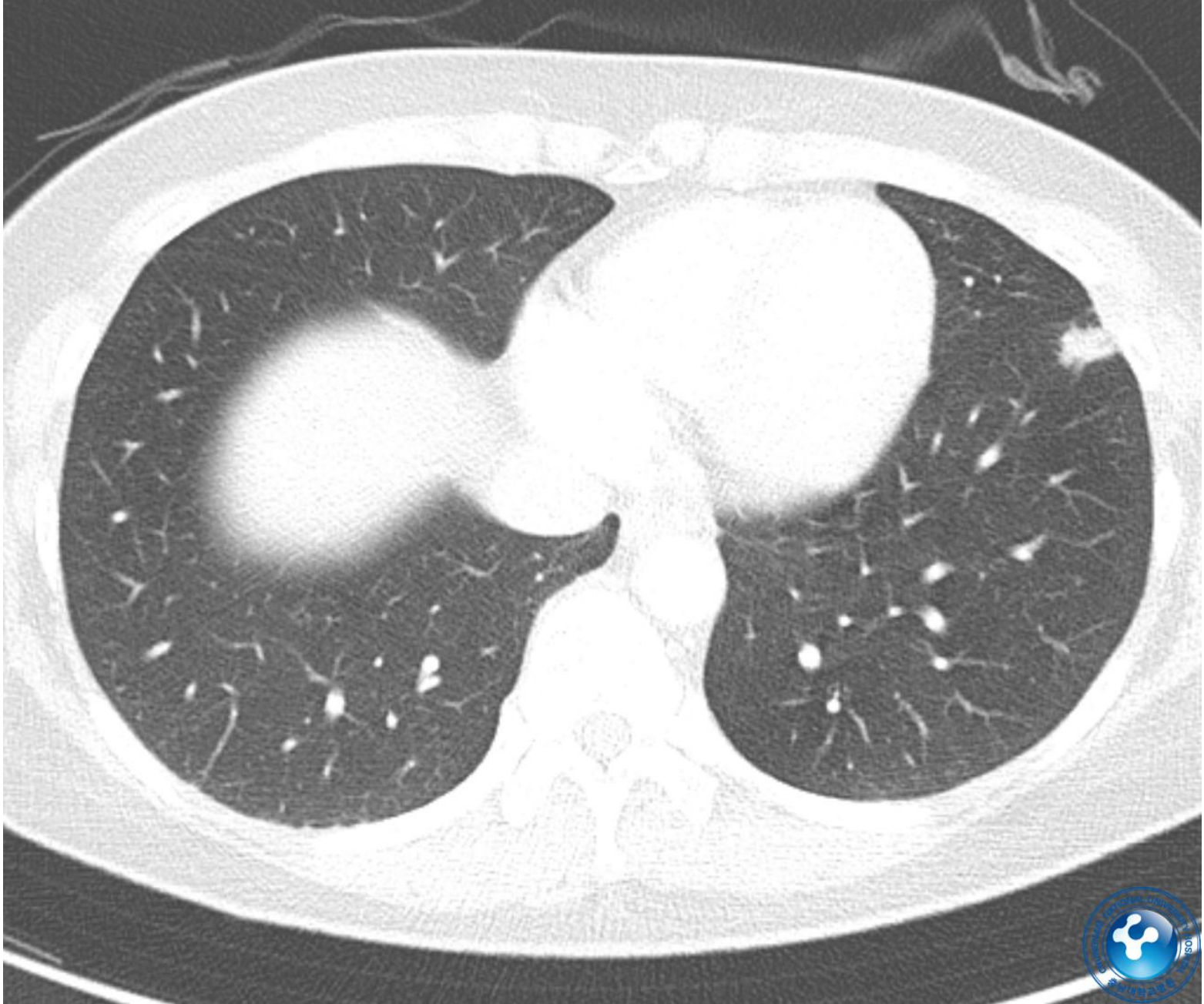
9) pT1c N0 by AJCC staging system (8th edition)

- Lymph node metastasis: absent (0/7)

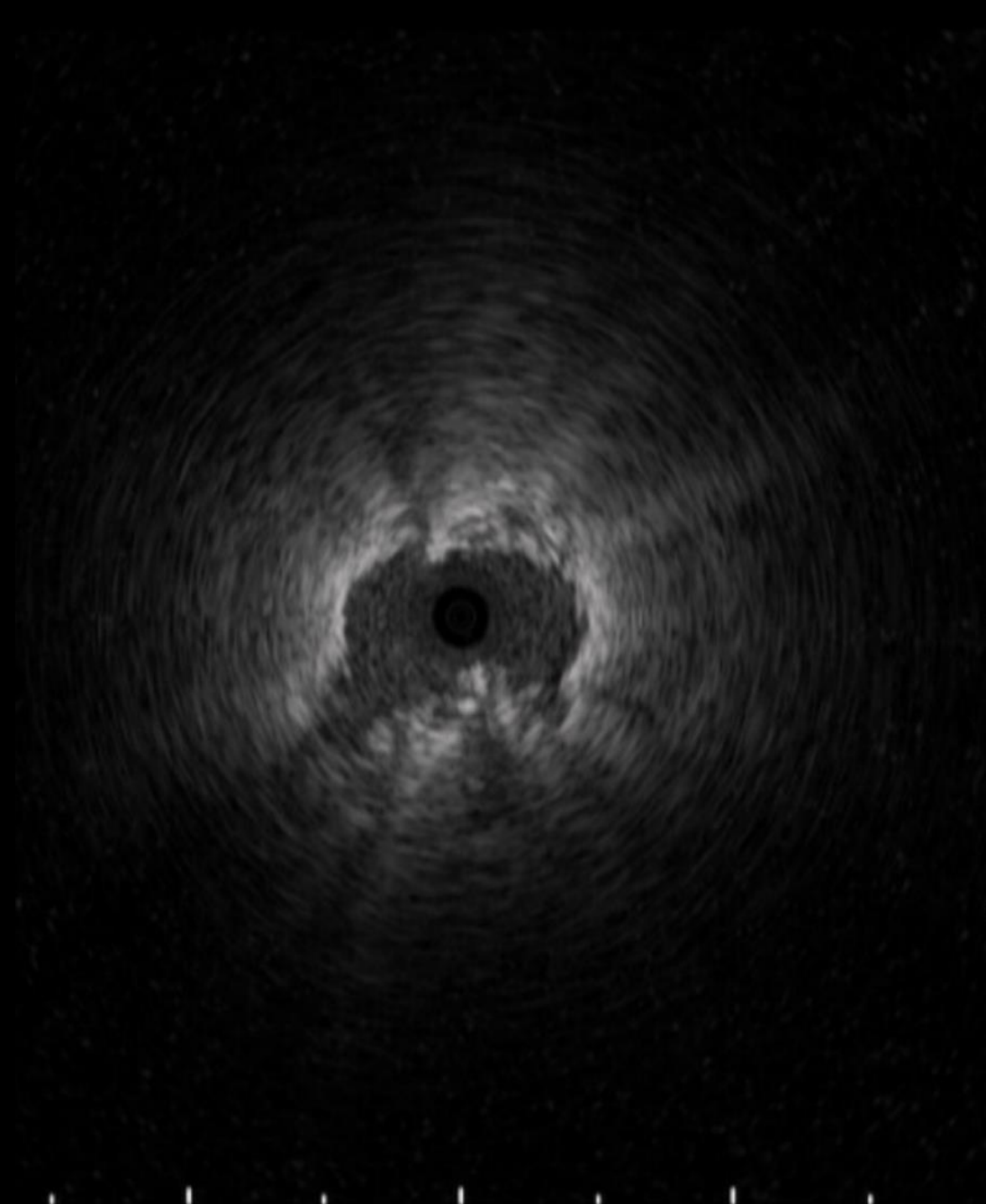
(LN 7 (B), 0/1; LN 9 (C), 0/2; LN 10 (D), 0/2; peribronchial
(A), 0/2)



46/F

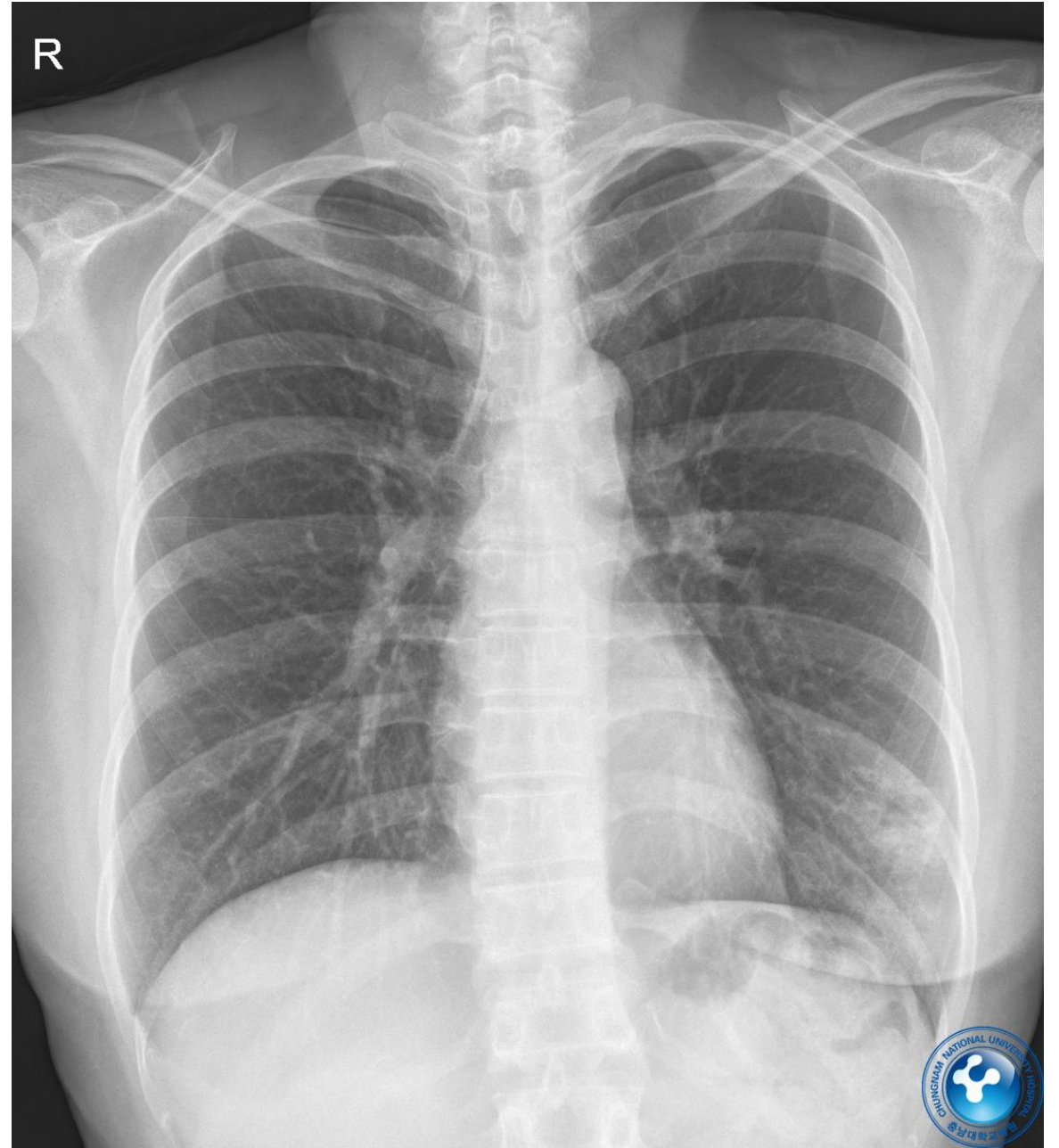
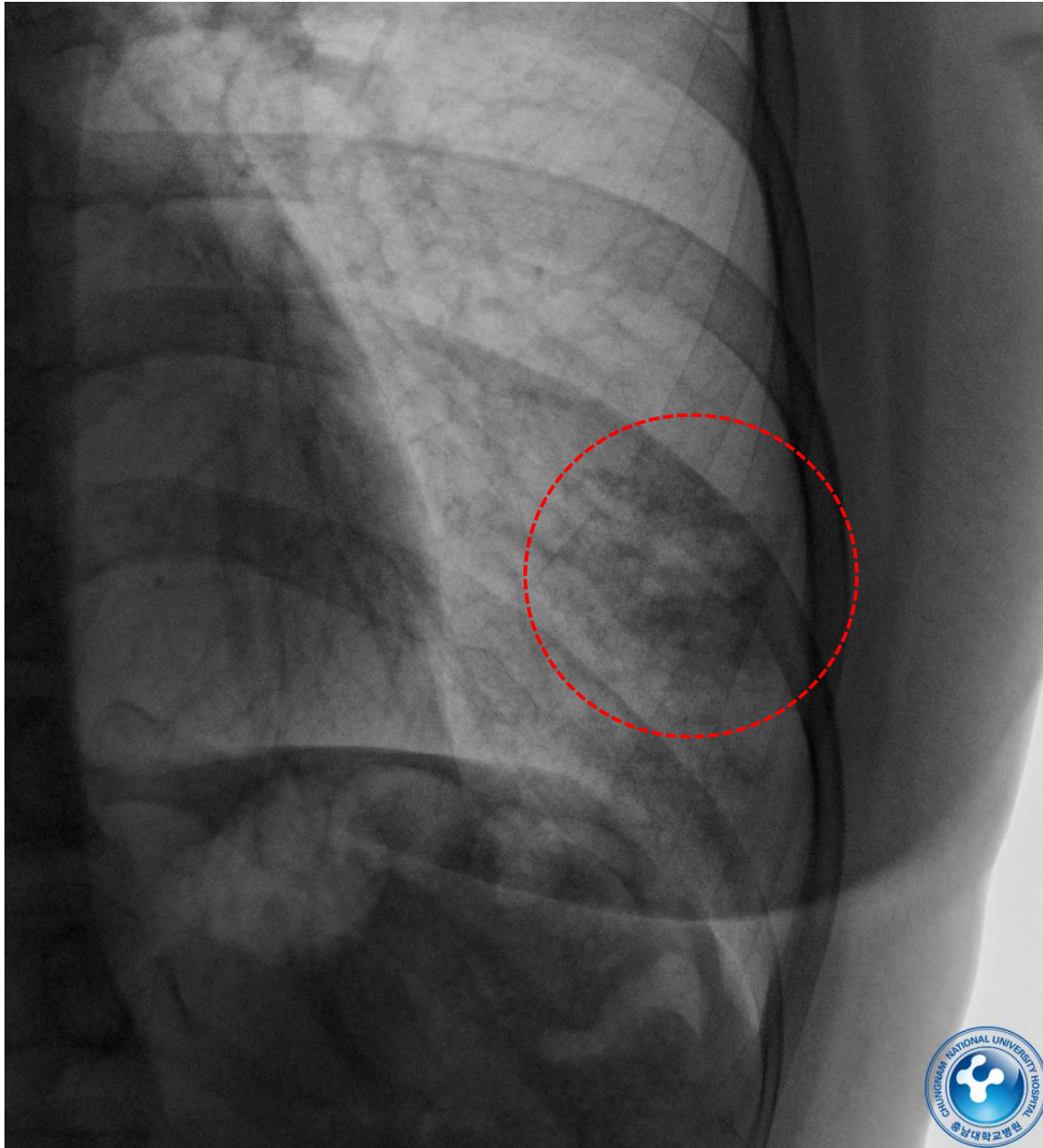


OLYMPUS



DIR:
INV





100 μ m

백선희(714B)

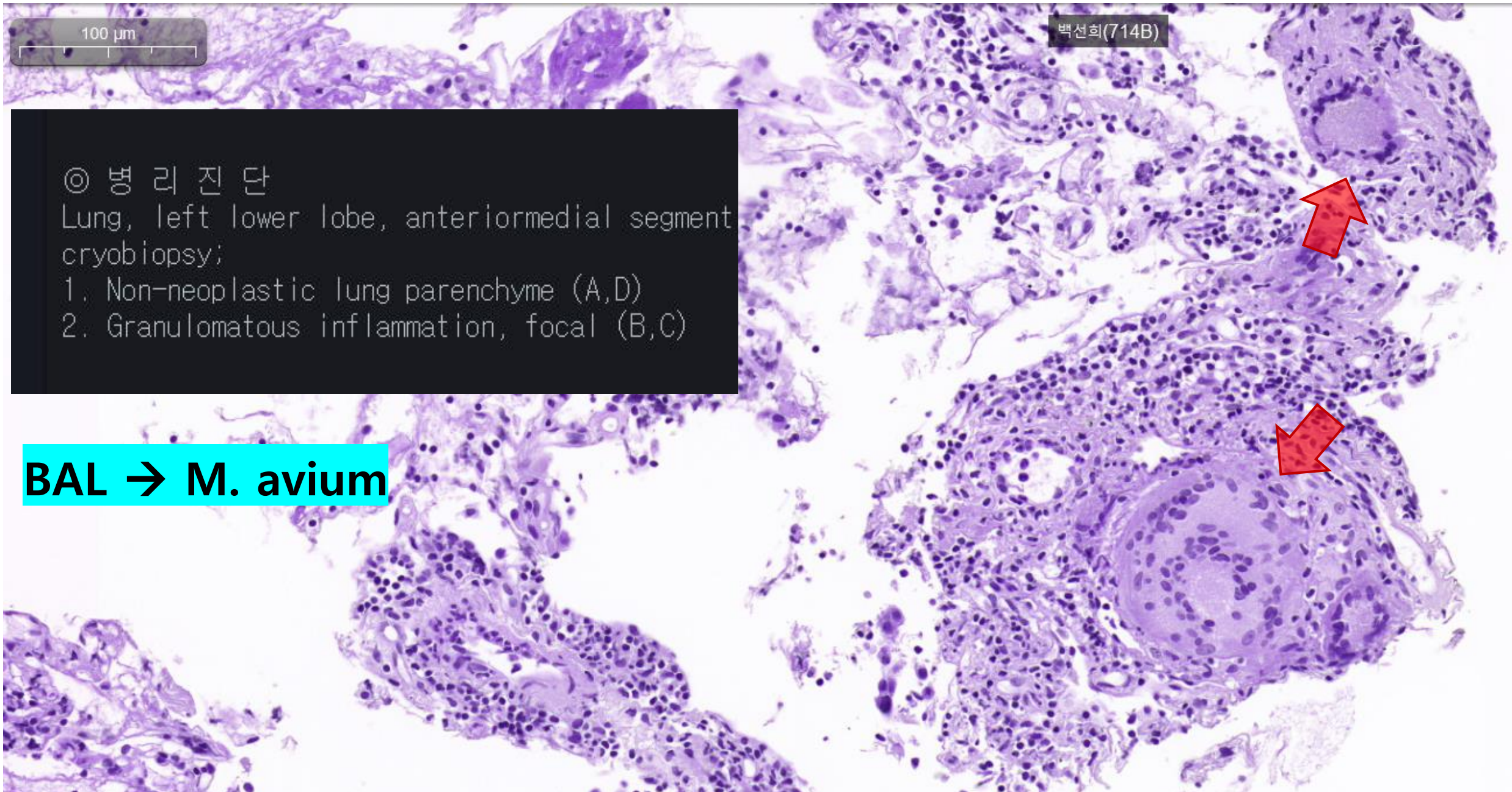
◎ 병리 진단

Lung, left lower lobe, anteriomedial segment
cryobiopsy;

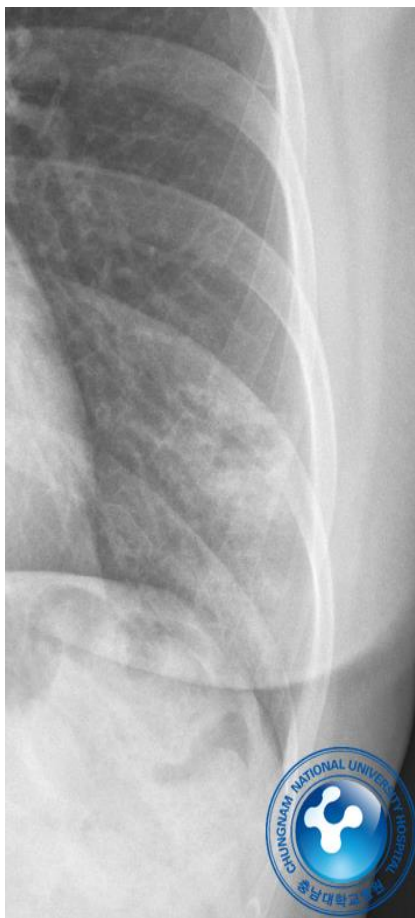
1. Non-neoplastic lung parenchyme (A,D)

2. Granulomatous inflammation, focal (B,C)

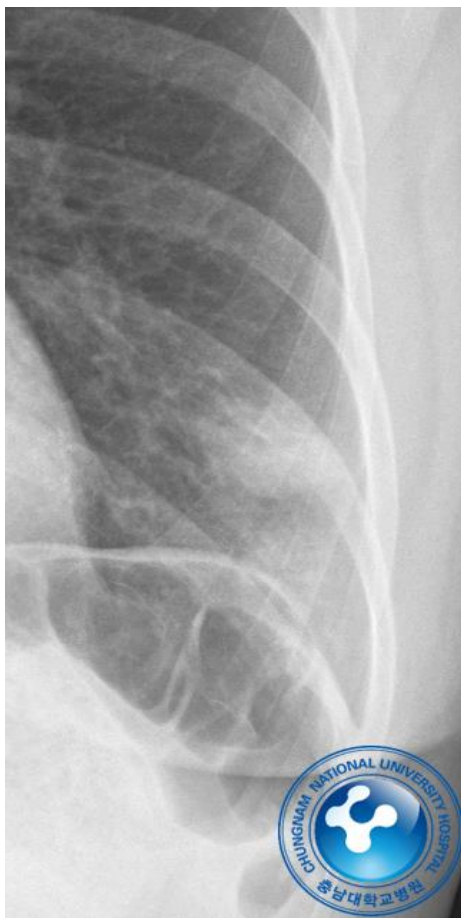
BAL \rightarrow M. avium



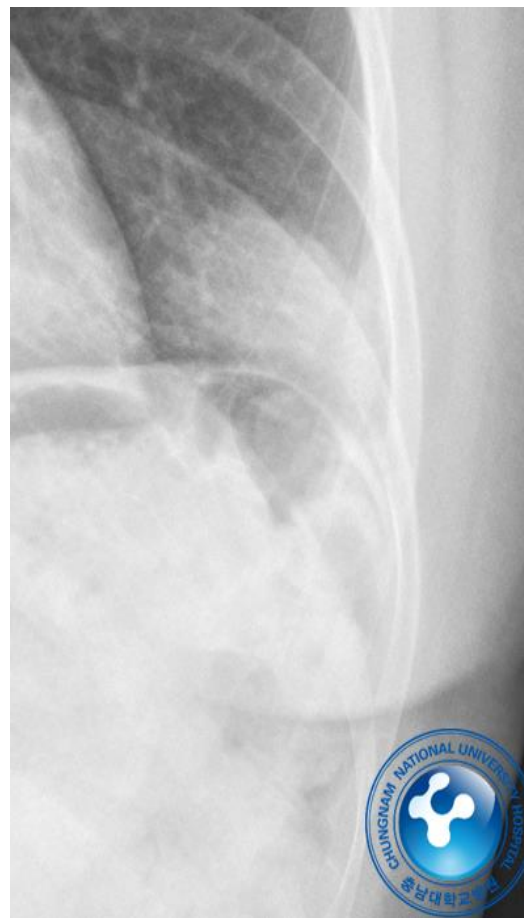
Day 2



Day 7

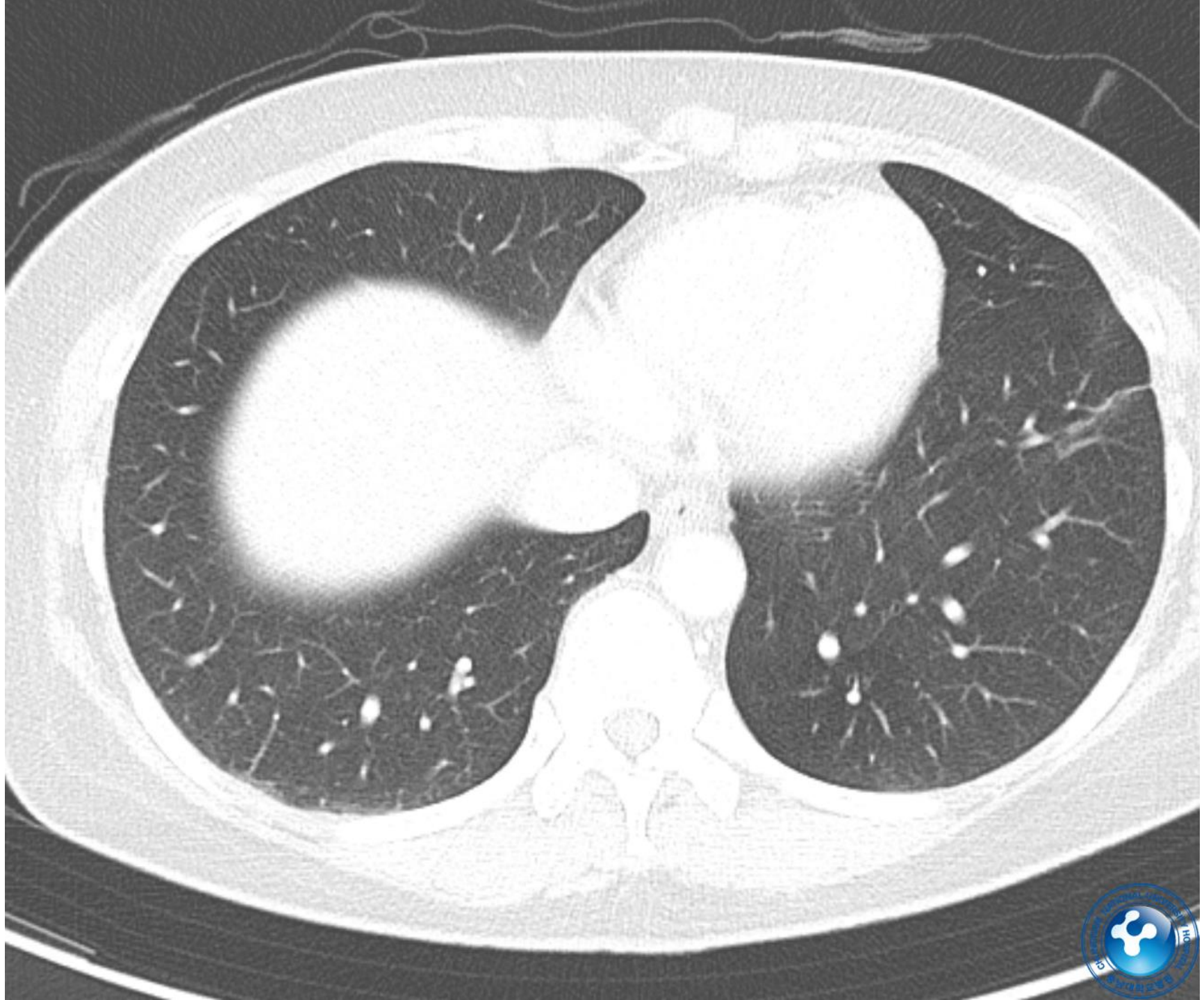


Day 14



Day 36





경청해 주셔서 감사합니다.