

Challenges in the diagnosis and treatment of drug-susceptible tuberculosis: case-based problem solving

경북의대 이재희

Treatment of DS-TB: simple?

2. 감수성결핵의 치료

권고요약

- 감수성결핵 치료의 표준처방은 2HRZE/4HR이다. 약제감수성검사 결과 이소니아지드 및 리팜핀에 감수성 결핵으로 확인된 경우에는 에탐부톨을 중단할 수 있다(IIb).
- 감수성결핵 환자에서 치료 시작 시 흉부X선에서 공동이 있고, 치료 2개월 후 시행한 객담 배양이 양성인 경우에는 유지 치료 기간의 연장을 고려할 수 있다(IIb).



MDR/RR-TB 의 치료

나. 치료의 일반 원칙

권고요약

- 분자생물학적 약제감수성검사서 리팜핀 내성 유전자 변이가 확인되면 다제내성결핵 처방으로 치료를 시작한다(IIa).
- 효과적인 치료법과 약제를 선정하기 위해 과거 결핵 치료력과 약제감수성검사 결과를 동시에 고려해야 한다(IIIa).
- 적극적인 부작용 관리, 치료 과정에 대한 모니터링, 적절한 환자 관리가 병행되어야 한다(IIIa).
- 다제내성결핵 치료는 치료 경험이 많은 전문가에게 의뢰할 것을 권고한다(IIIa).

가. 퀴놀론 감수성 다제내성결핵

권고요약

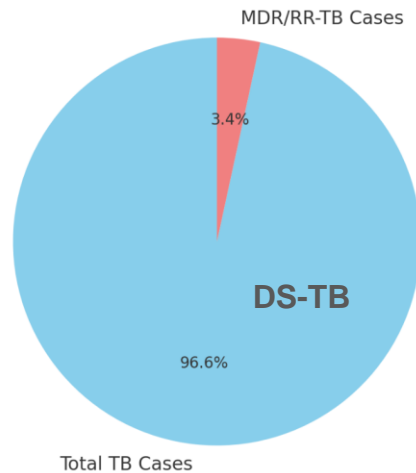
- 6개월 BPaLM 요법^a 또는 9개월 MDR-END 요법^b을 사용하는 것을 권고한다(IA).
 - 18-20개월 장기요법은 6개월 BPaLM 요법^a 또는 9개월 MDR-END 요법^b에 적합하지 않은 환자에게 사용하는 것을 권고한다(IA).
- ^a 베다퀼린[B], 프레토마니드[Pa], 리네졸리드[L], 목시플록사신[M]
^b 레보플록사신, 델라마니드, 리네졸리드, 피라진아미드

나. 퀴놀론 내성 다제내성결핵

권고요약

- 6개월 BPaL 요법^a을 사용하는 것을 권고한다(IIa).
 - 18-20개월 장기요법은 6개월 BPaL 요법^a에 적합하지 않은 환자에게 사용하는 것을 권고한다(IIa).
- ^a 베다퀼린[B], 프레토마니드[Pa], 리네졸리드[L]

Tuberculosis Cases in South Korea (2023)

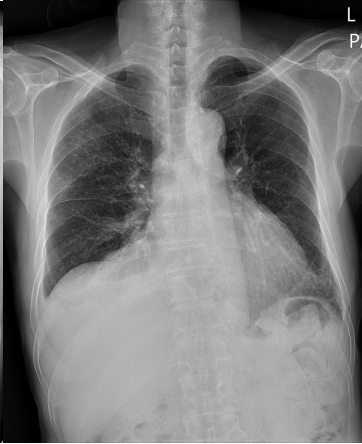


Contents

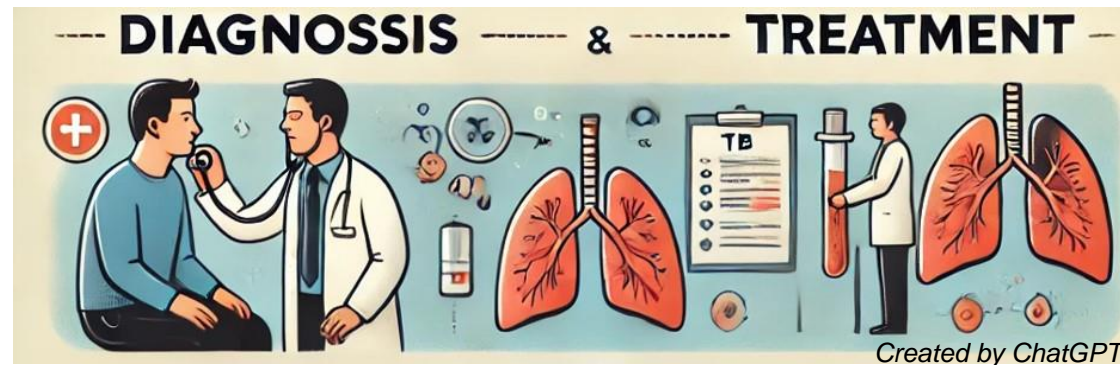
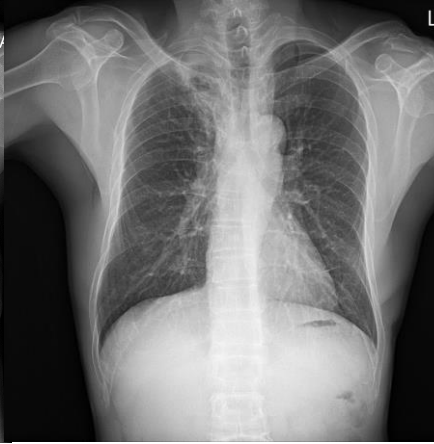
Case #1



Case #2



Case #3

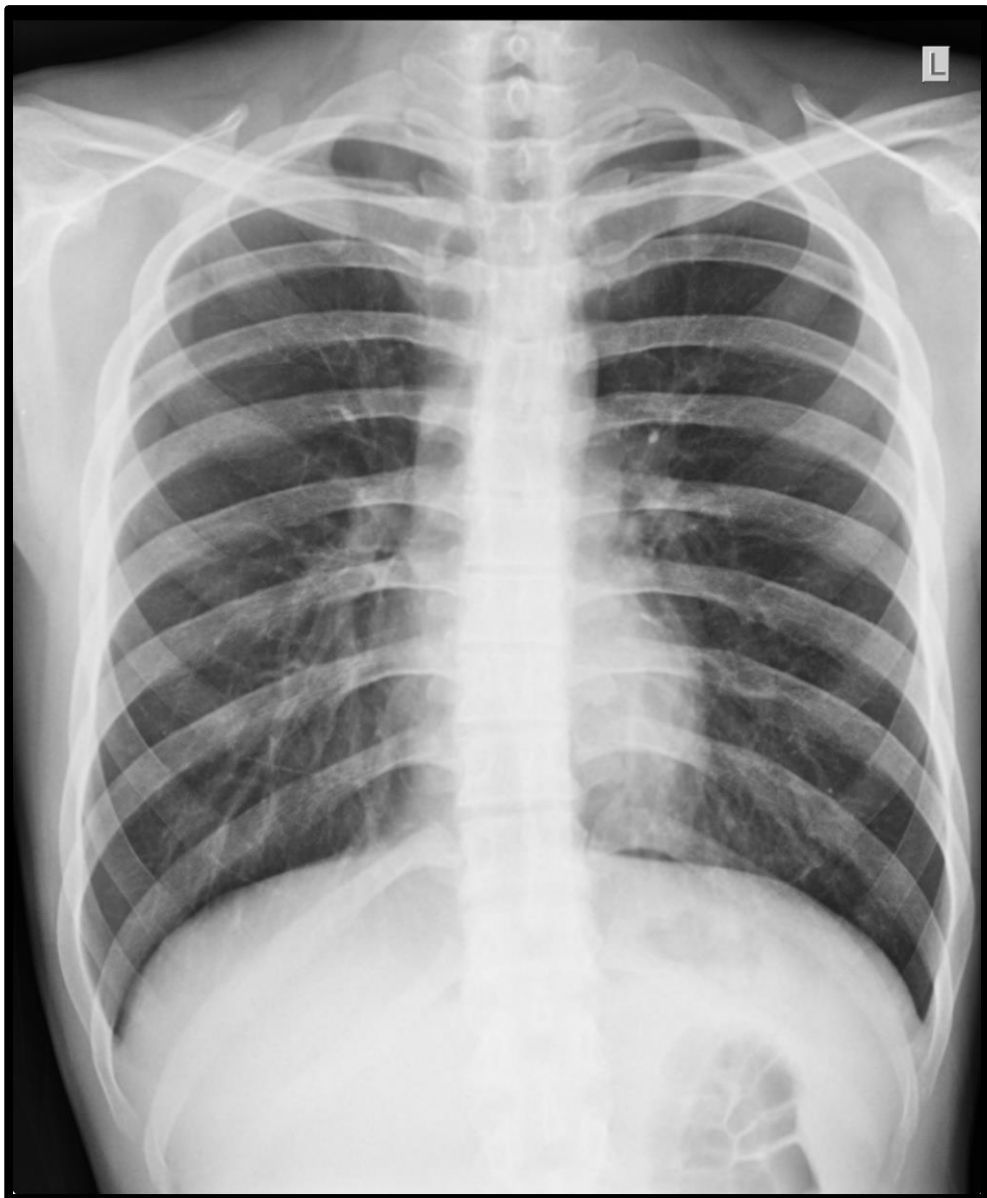


Case 1: 24/M

- Incidentally found CXR abnormality
- Mild sputum since starting smoking
- Current smoker (1PPD for 8y)



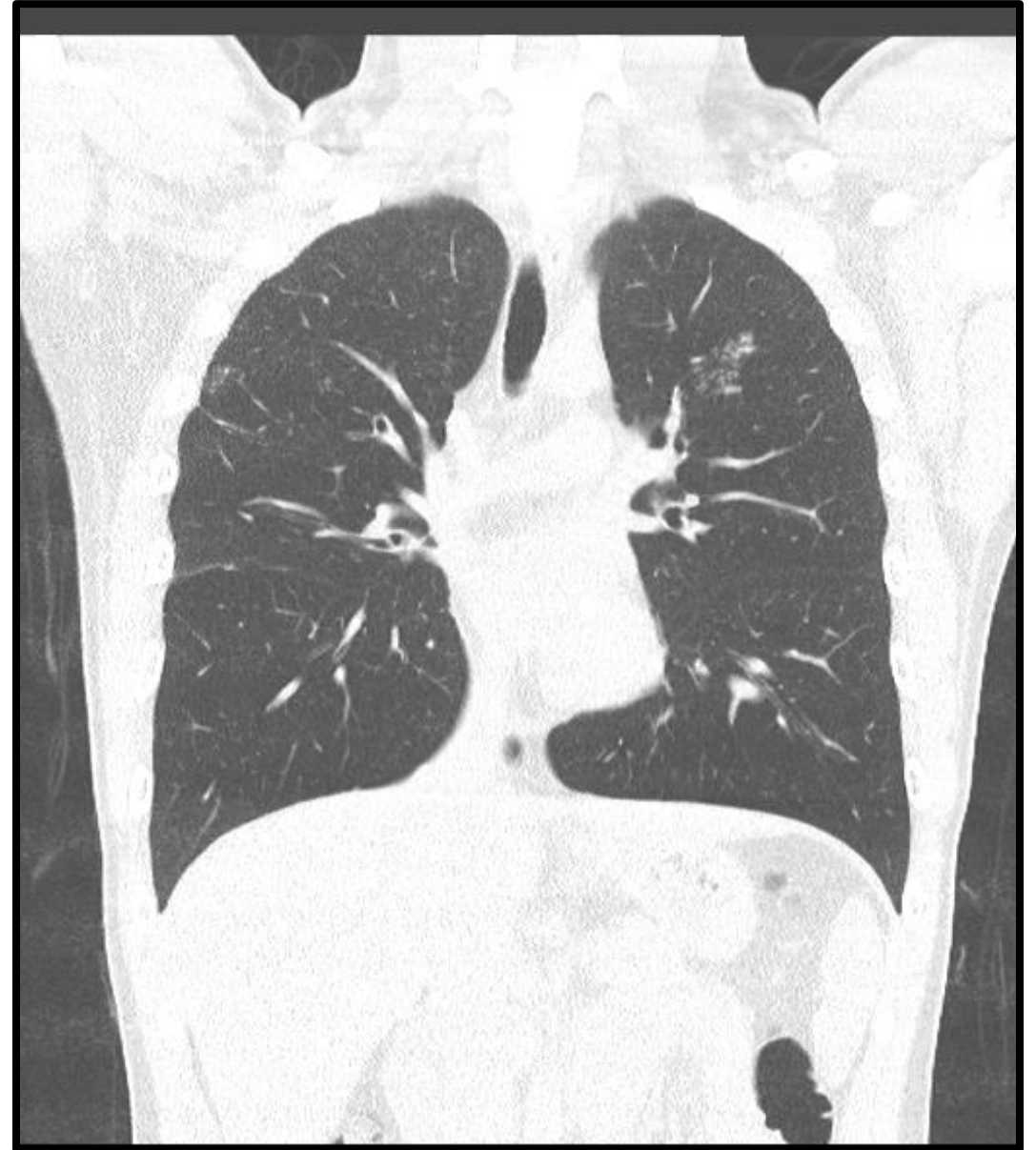
4 years ago



Present



Initial Chest CT



Case 1: 24/M

- Sputum AFB smear (-)/Xpert MTB/RIF assay (-)
- Bronchial aspirate AFB smear (-)/Xpert MTB/RIF assay (-)
- Blood IGRA (+)

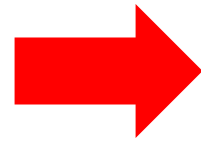
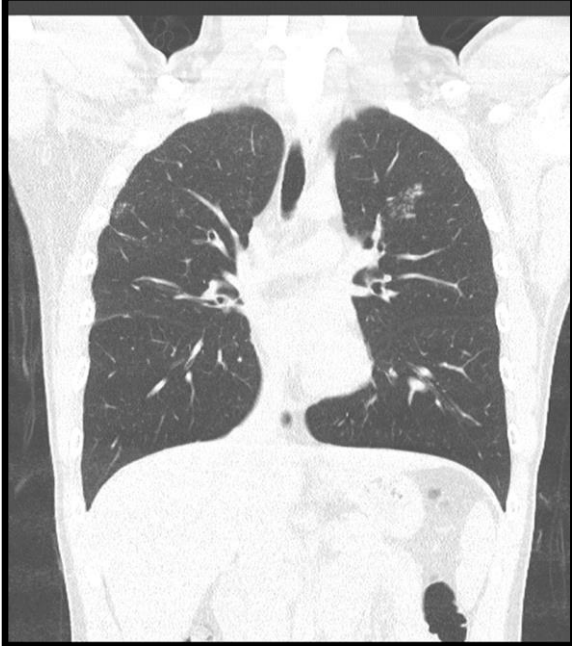
Q: what action should be taken next ?

1. Initiate anti-tuberculosis treatment (HRZE)
2. Initiate TB preventive therapy (R or HR or H)
3. Wait for the culture results
4. None of the above

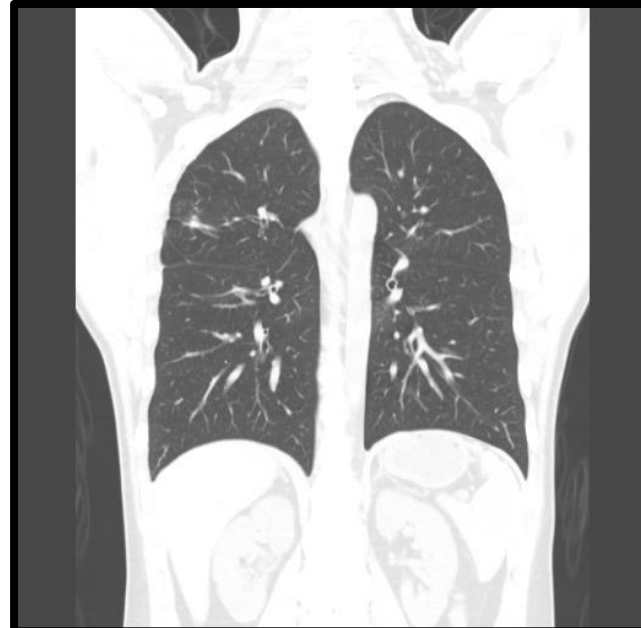
Vote 1



Initial Dx



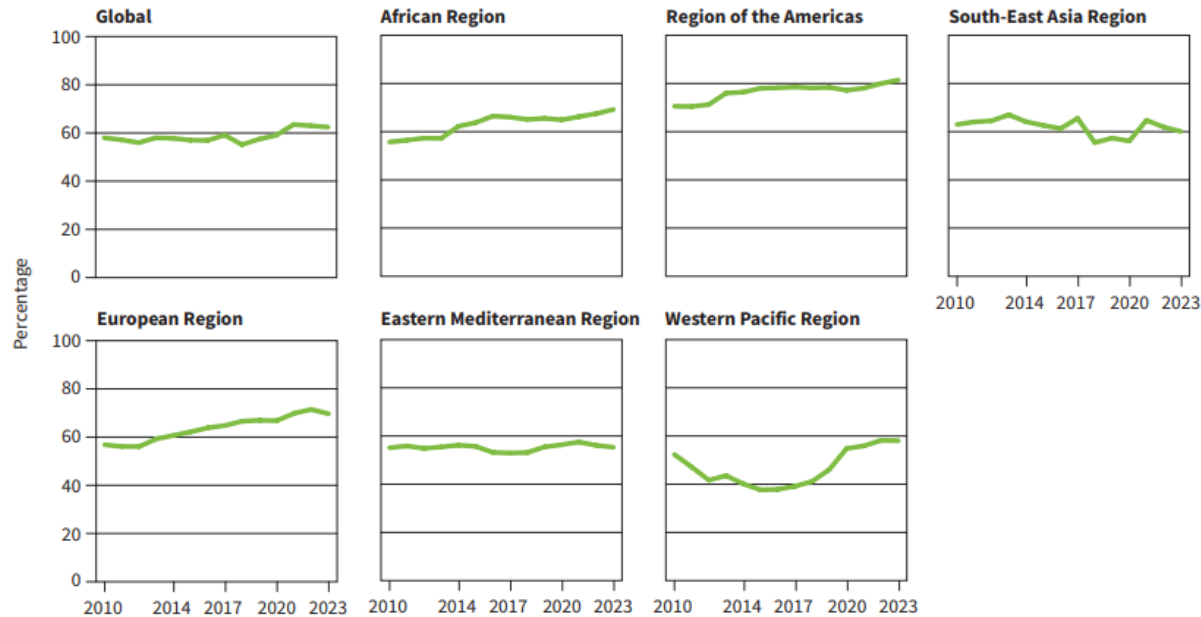
At 2nd mo of anti-TB Tx



Sputum & BA
- MTB culture (-)

Proportion of culture-negative pulmonary TB

Percentage of people newly diagnosed with pulmonary TB who were bacteriologically confirmed, globally and for WHO regions,^a 2010–2023



Global tuberculosis report 2024

Min et al. *BMC Pulm Med* (2020) 20:316
<https://doi.org/10.1186/s12890-020-01351-z>

BMC Pulmonary Medicine

RESEARCH ARTICLE

Open Access

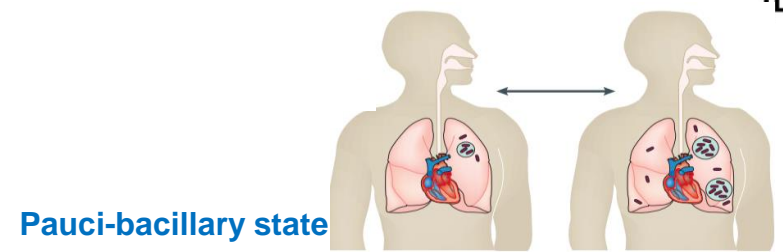
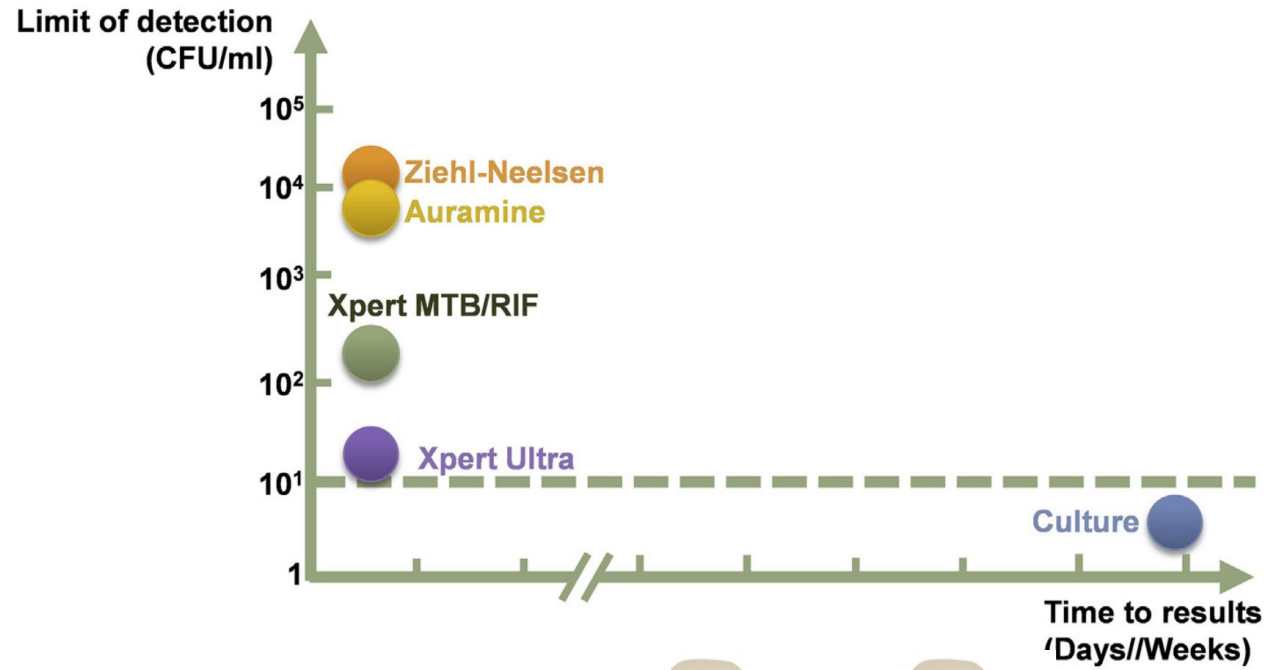
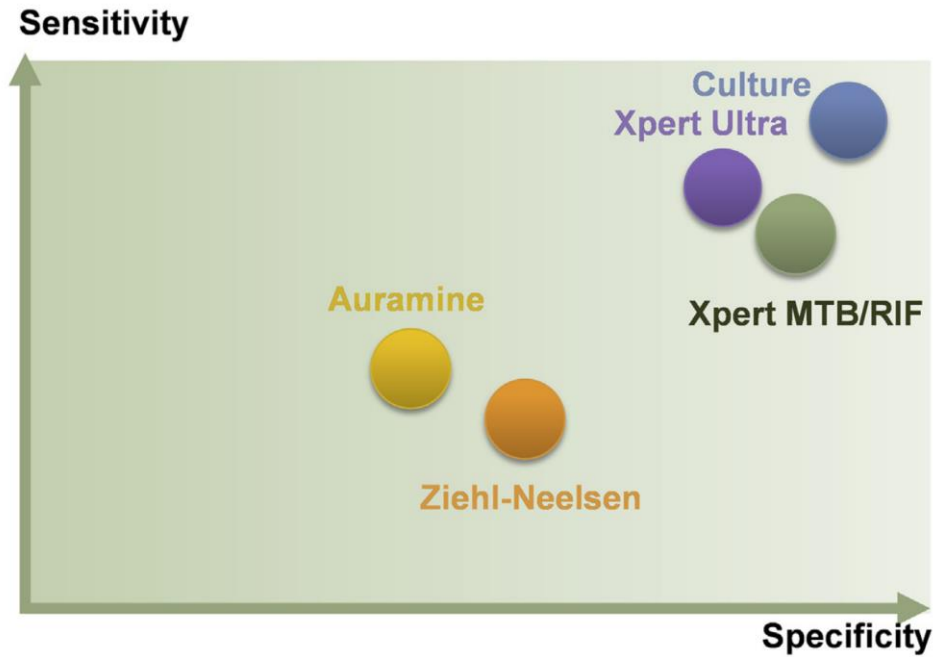


Clinical profiles of subclinical disease among pulmonary tuberculosis patients: a prospective cohort study in South Korea

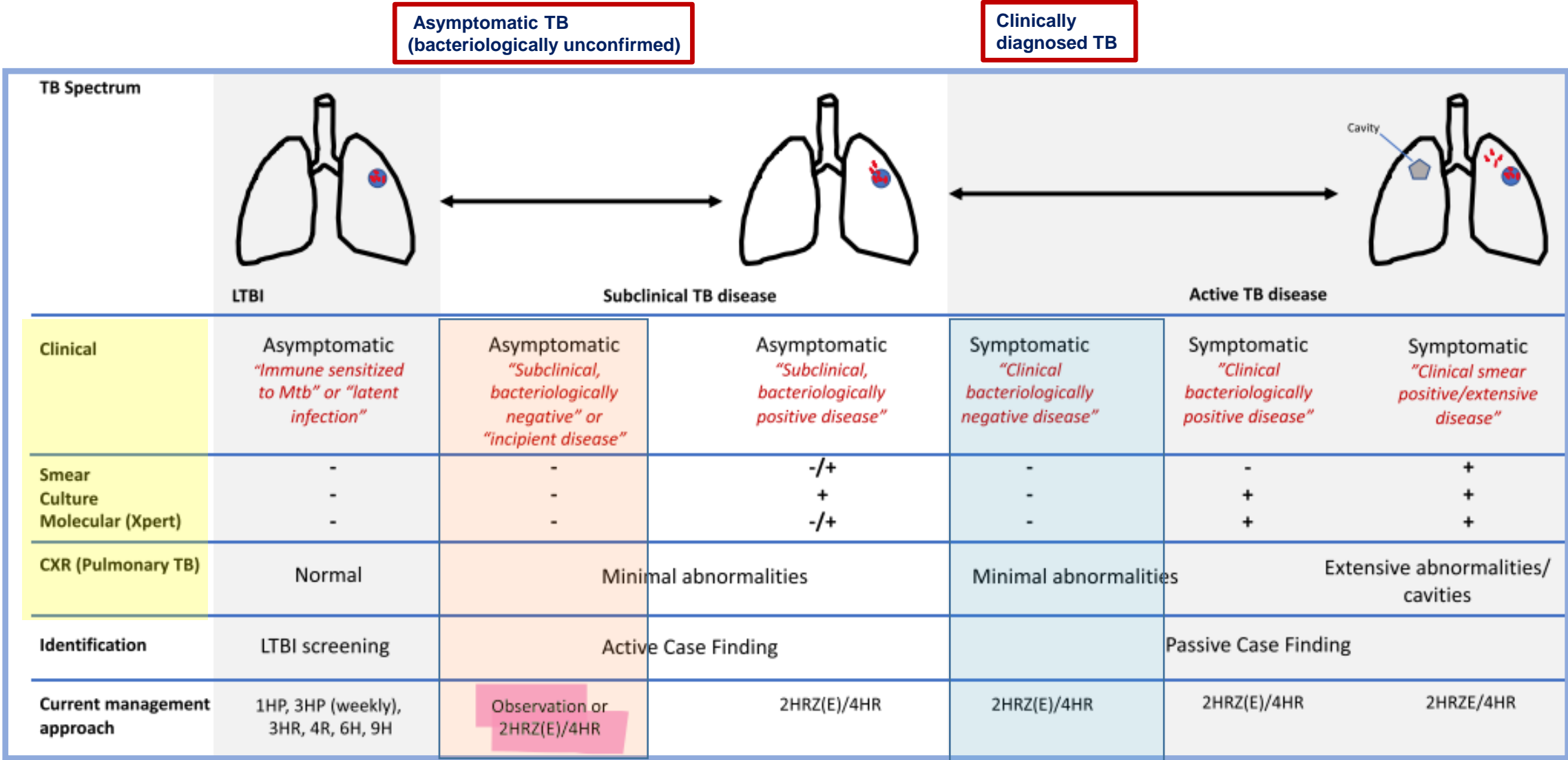
Jinsoo Min¹, Chaeuk Chung², Sung Soo Jung², Hye Kyeong Park³, Sung-Soon Lee³ and Ki Man Lee^{4,5*}

31% (95% CI, 26.9-35.8%)

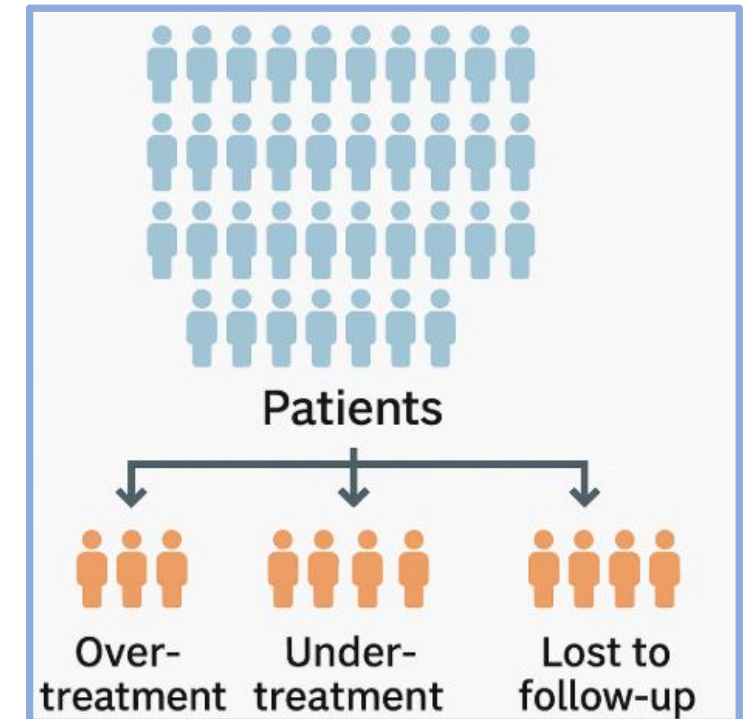
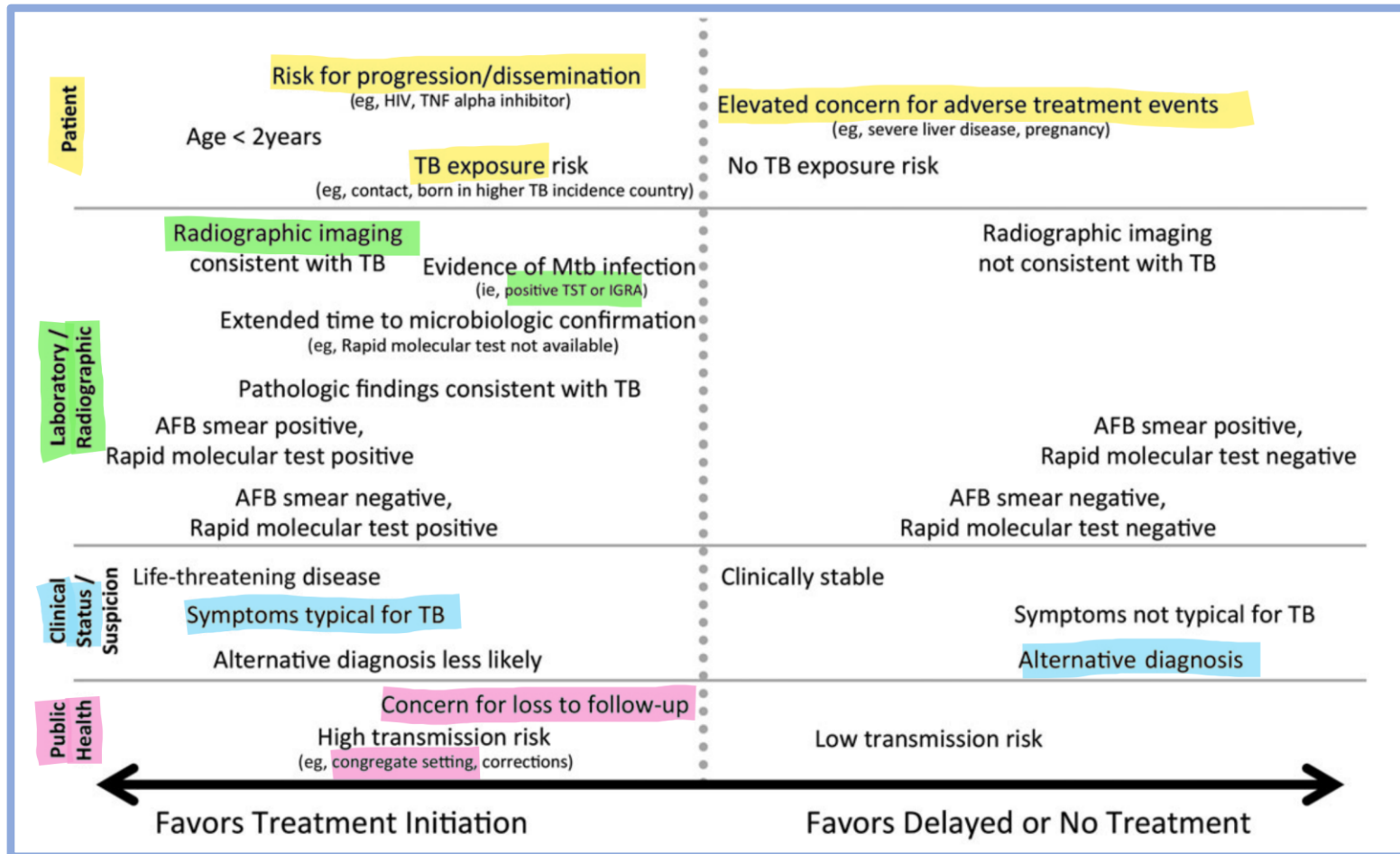
Diagnostic performance of microbial tests for TB



Current diagnostic and treatment approaches across the spectrum



Factors to be considered in deciding to initiate empirical TB Tx prior to microbiologic confirmation



The natural history of untreated pulmonary tuberculosis in adults: a systematic review and meta-analysis

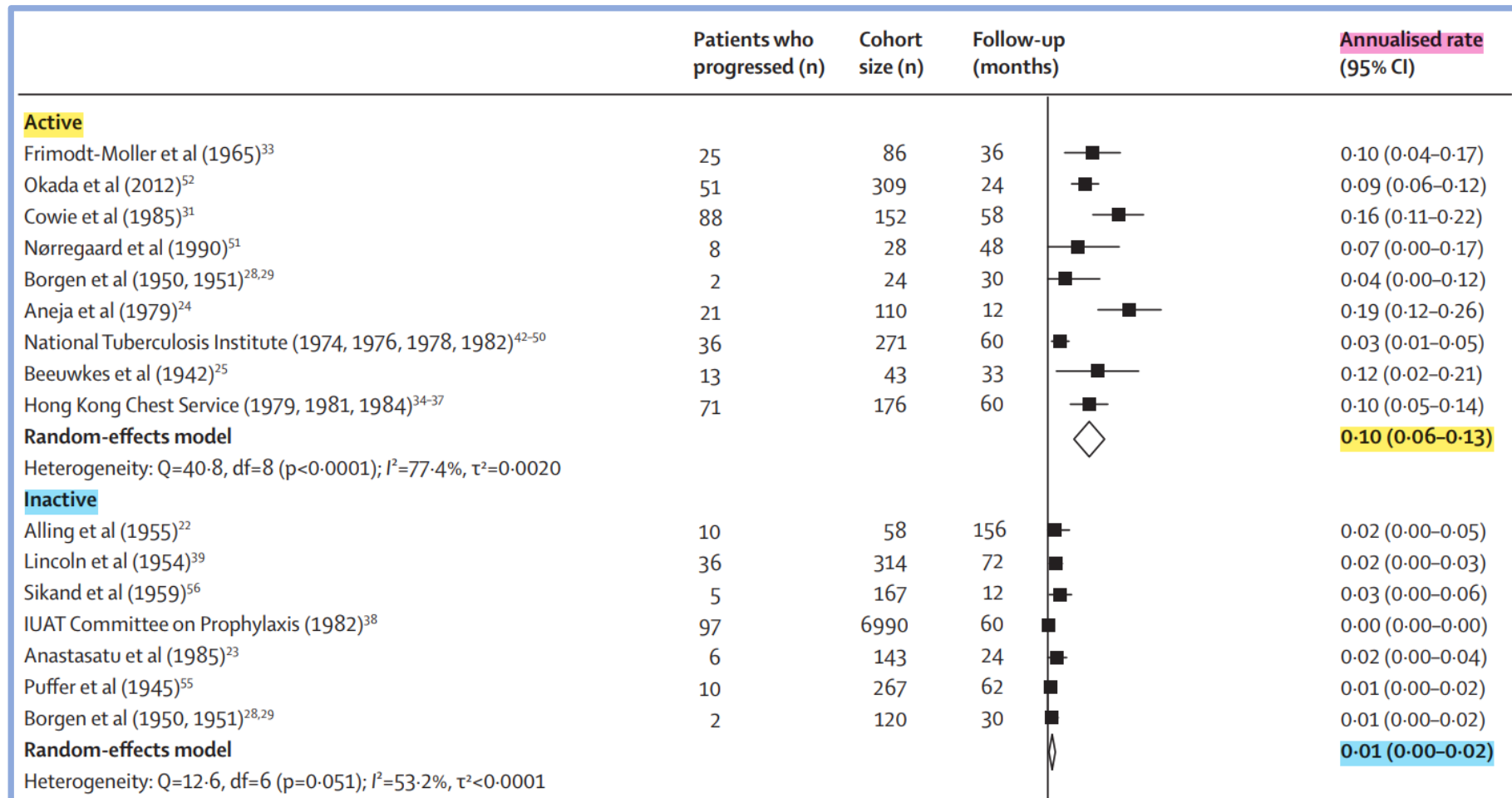


Bianca Sossen*, Alexandra S Richards*, Torben Heinsohn, Beatrice Frascella, Federica Balzarini, Aurea Oradini-Alacreu, Anna Odone, Ewelina Rogozinska, Brit Häcker, Frank Cobelens, Katharina Kranzer, Rein M G J Houben†, Hanif Esmail†

Stages of tuberculosis disease can be delineated by radiology, microbiology, and symptoms, but transitions between *Lancet Respir Med* 2023;

Inactive tuberculosis	Inactive tuberculosis	Active tuberculosis: culture negative	Active tuberculosis
<p>Discrete fibrotic scar or linear opacity Discrete linear or reticular opacity within the lung with or without volume loss</p>			<p>Infiltrate or consolidation Opacification of airspaces within the lung parenchyma</p>
<p>Discrete non-calcified nodule(s) One or more nodular opacities with distinct borders and no airspace consolidation</p>			<p>Cavitary lesion Lucency within the lung parenchyma that might be surrounded by airspace consolidation</p>
<p>Other findings suggestive of previous tuberculosis eg, upper lobe bronchiectasis</p>			<p>Nodule with poorly defined margins Round opacity within the lung parenchyma</p>
			<p>Pleural effusion Presence of fluid within the pleural space</p>
			<p>Hilar or mediastinal lymphadenopathy Enlargement of lymph nodes within the hila, mediastinum, or both</p>
			<p>Miliary nodules Nodules measuring 1–2 mm in size distributed throughout the lung parenchyma</p>

Transition rates from bacteriologically negative to positive disease



The same treatment approach for culture-positive & culture-negative pulmonary TB?

2. 감수성결핵의 치료

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- 감수성결핵 치료의 표준처방은 2HRZE/4HR이다. 약제감수성검사 결과 이소니아지드 및 리팜핀에 감수성 결핵으로 확인된 경우에는 에탐부톨을 중단할 수 있다(IIb).
- 감수성결핵 환자에서 치료 시작 시 흉부X선에서 공동이 있고, 치료 2개월 후 시행한 객담 배양이 양성인 경우에는 유지 치료 기간의 연장을 고려할 수 있다(IIb).

Clinical Trial > Br J Dis Chest. 1984 Oct;78(4):330-6.

A controlled trial of 6 months' chemotherapy in pulmonary tuberculosis. Final report: results during the 36 months after the end of chemotherapy and beyond. British Thoracic Society

Inclusion criteria: sputum AFB smear (+)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 10, 2022 VOL. 386 NO. 10

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

A. Turkova, G.H. Wills, E. Wobudeya, C. Chabala, M. Palmer, A. Kinikar, S. Hissar, L. Choo, P. Musoke, V. Mulenga, V. Mave, B. Joseph, K. LeBeau, M.J. Thomason, R.B. Mboizi, M. Kapasa, M.M. van der Zalm, P. Raichur, P.K. Bhavani, H. McIlerron, A.-M. Demers, R. Aarnoutse, J. Love-Koh, J.A. Seddon, S.B. Welch, S.M. Graham, A.C. Hesselting, D.M. Gibb, and A.M. Crook, for the SHINE Trial Team*

있다. 세균학적 검사와 흉부X선 검사가 시행된 소아청소년 환자에서 다음 조건을 모두 만족하는 약제 감수성 결핵의 경우 **2HRZ(E)/2HR 단축 치료요법**을 적용할 수 있음을 제시하였다.

- 3개월 이상 16세 미만 소아청소년
- 흉부X선에서 비중증 결핵 소견 : 기도 폐쇄가 없는 흉곽내 림프절 결핵, 공동이 없고 좁쌀 결핵 형태가 아닌 한쪽 폐엽에 국한된 결핵, 또는 단순 결핵성 흉수
- 객담 도말검사 음성 또는 Xpert MTB/RIF 검사 음성/미량(trace)
- 입원을 요하지 않는 경미한 증상

Treatment of culture-negative pulmonary TB

Clinical Infectious Diseases Advance Access published August 10, 2016

IDSA GUIDELINE



Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis

Payam Nahid,¹ Susan E. Dorman,² Narges Alipanah,¹ Pennan M. Barry,³ Jan L. Brozek,⁴ Adithya Cattamanchi,¹ Lelia H. Chaisson,¹ Richard E. Chaisson,² Charles L. Daley,⁵ Malgosia Grzemska,⁶ Julie M. Higashi,⁷ Christine S. Ho,⁸ Philip C. Hopewell,¹ Sal Richard Menzies,¹⁰ Cynthia Merrifield,¹ Masahiro Narita,¹² Rick O'Brien,¹³ Charles A. Peloquin,¹⁴ Ann Giovanni Sotgiu,¹⁷ Jeffrey R. Starke,¹⁸ Giovanni Battista Migliori,¹¹ and Andrew Vernon⁹

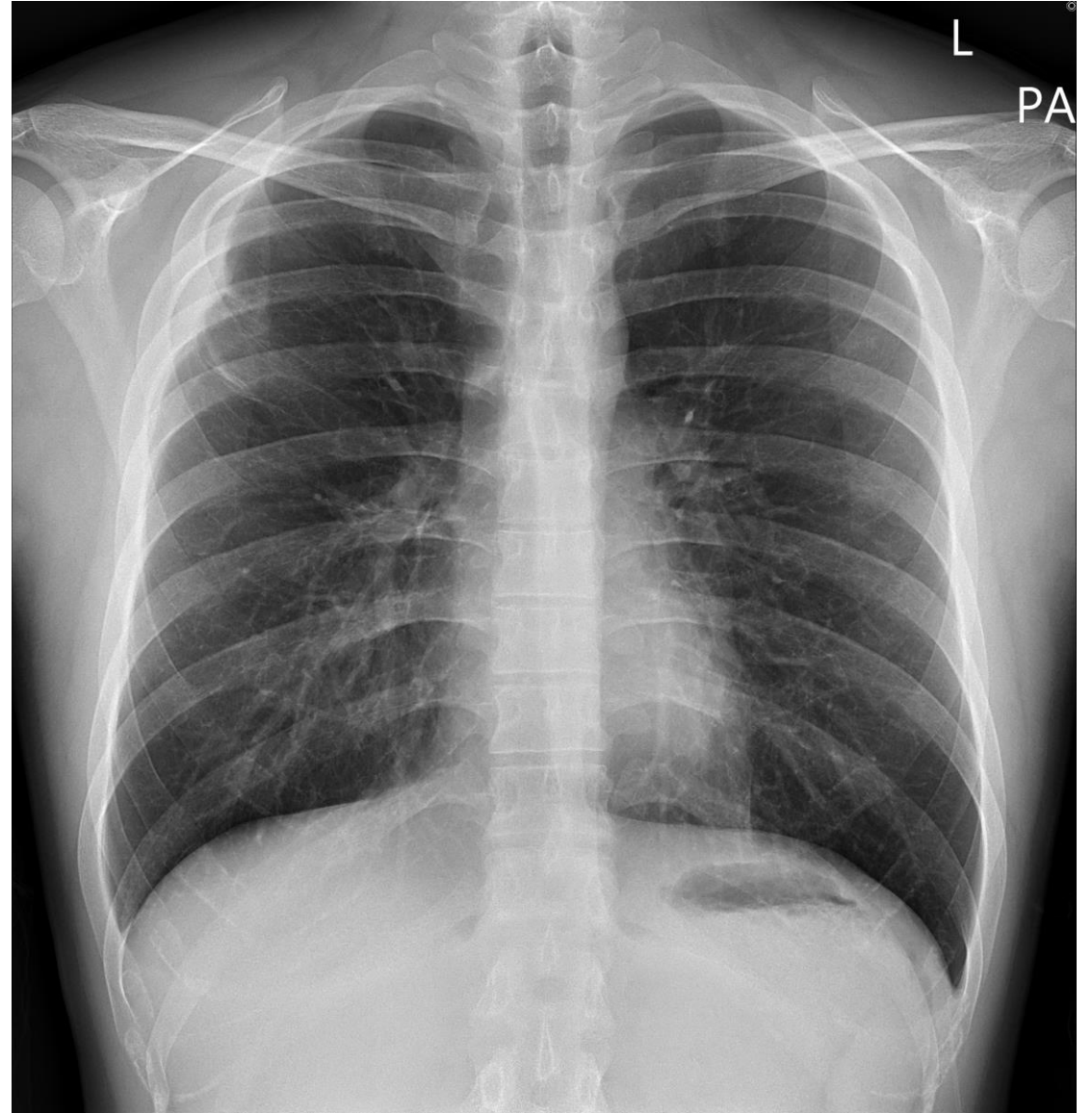
Recommendation 9: We suggest that a 4-month treatment regimen is adequate for treatment of HIV-uninfected adult patients with AFB smear- and culture-negative pulmonary tuberculosis (*conditional recommendation; very low certainty in the evidence*).

Hope for the development of a shorter, less toxic treatment regimen

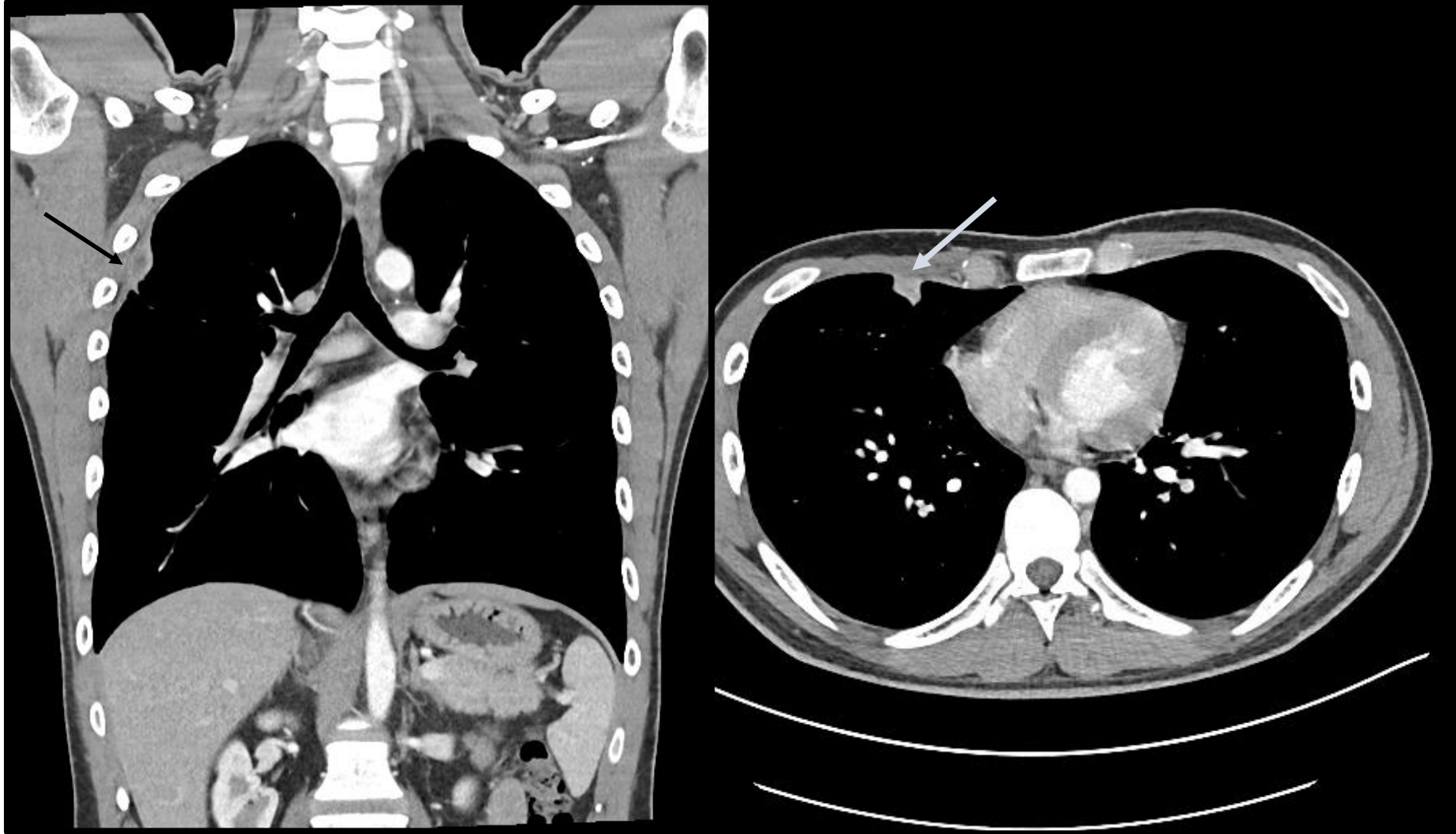
At 2nd mo of anti-TB Tx



At 4th mo of anti-TB Tx



At 4th mo of anti-TB Tx



- Pleuritic chest pain, mild
- Sputum
 - AFB smear (-)
 - Xpert MTB/RIF assay (-)

Q: what action should be taken next ?

1. Keep anti-tuberculosis treatment (HRE)
2. Keep anti-TB treatment & add corticosteroids
3. Perform a biopsy
4. None of the above

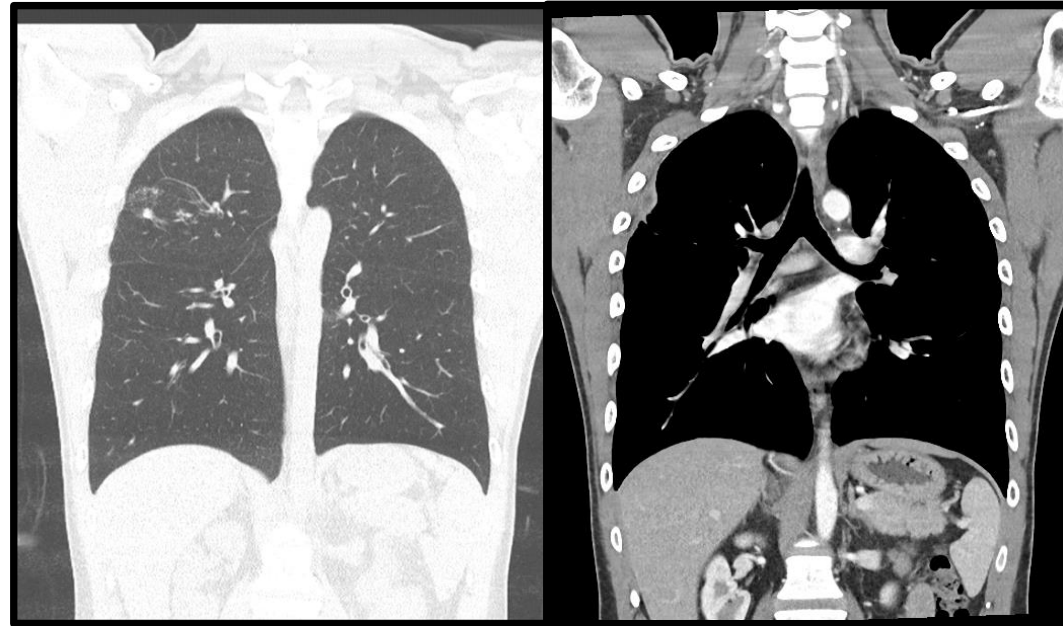
Vote 2



Differential diagnosis

Initial

At 4th mo of anti-TB Tx



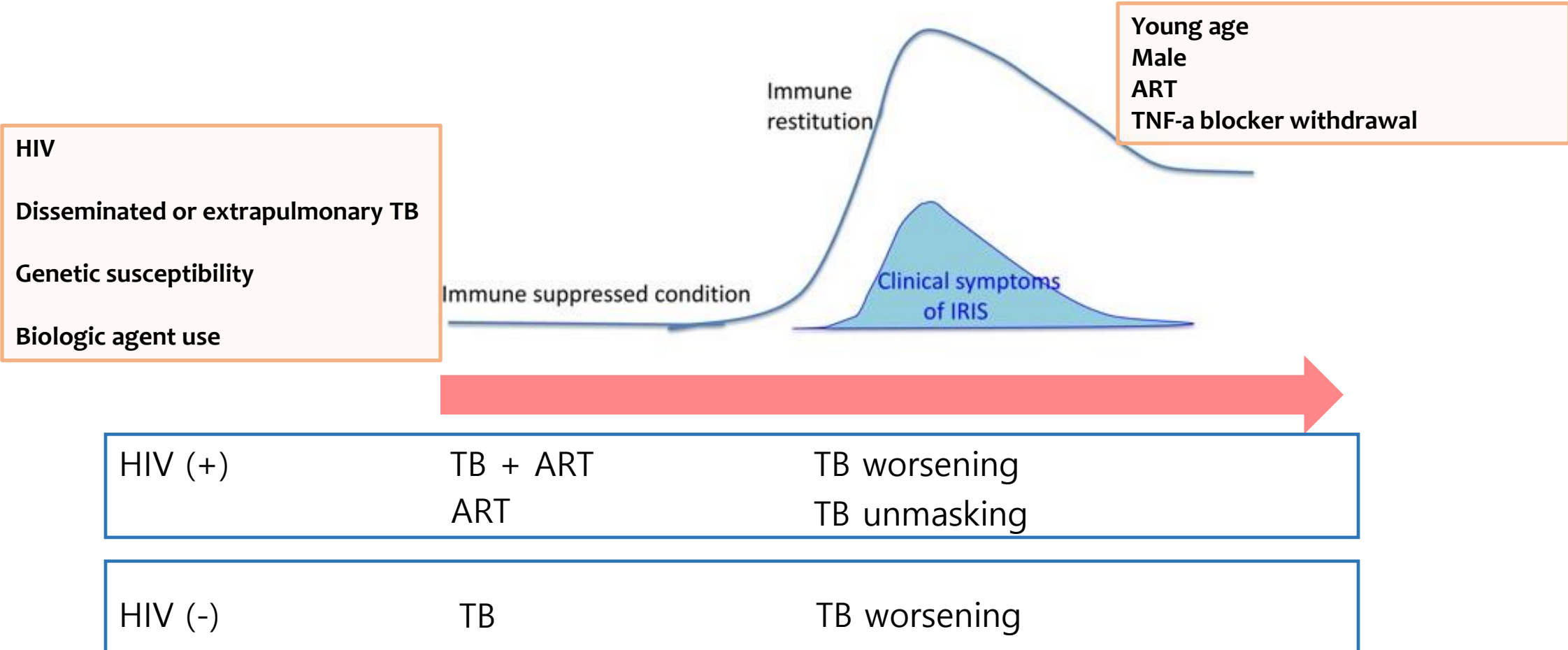
- Incorrect initial diagnosis (NTM, pneumonia, nonspecific bronchiolitis etc.)?
- DR-TB?
- Non-compliance to TB drugs?

- New disease other than TB?

TB- paradoxical response (TB-immune reconstitution inflammatory syndrome)

- Worsening of **pre-existing TB lesions** or development of **new lesions** after effective anti-TB treatment
- Criteria
 - 1) **initial response** to anti-tuberculosis treatments
 - 2) paradoxical **deterioration** of TB-related symptoms and/or radiological findings
 - 3) **exclusion of alternative explanations** for clinical deterioration such as **drug resistance, poor adherence, drug side effects and other infections**

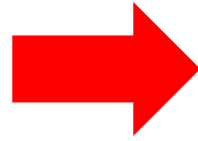
TB-Immune reconstitution inflammatory syndrome



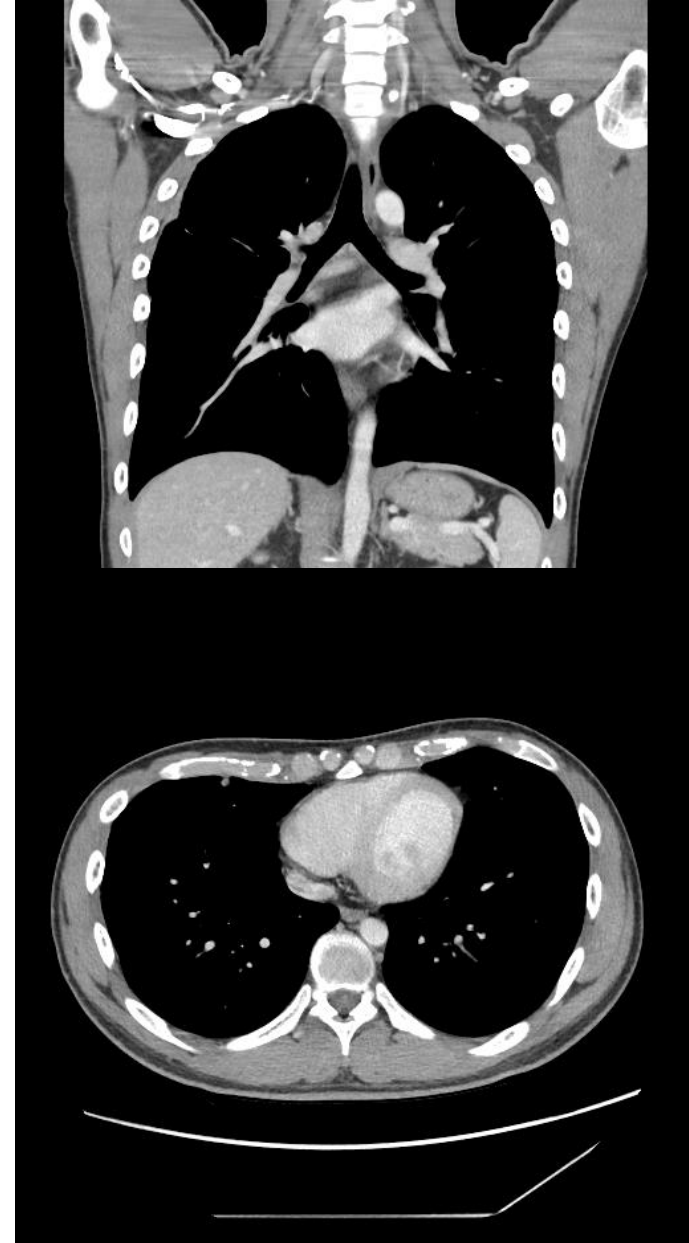
Diagnosis and treatment of TB-IRIS

- Exclusive diagnosis
 - CT/PET-CT or Bx (malignancy)
 - Microbiologic test (bacteria, fungus, **DR-TB**)
- No standard treatment
 - Clinical improvement of most patients in 2-3 mo following anti-TB treatment
 - Corticosteroids (symptomatic enlarging intracranial tuberculoma, endobronchial obstruction)

At 4th mo of anti-TB Tx

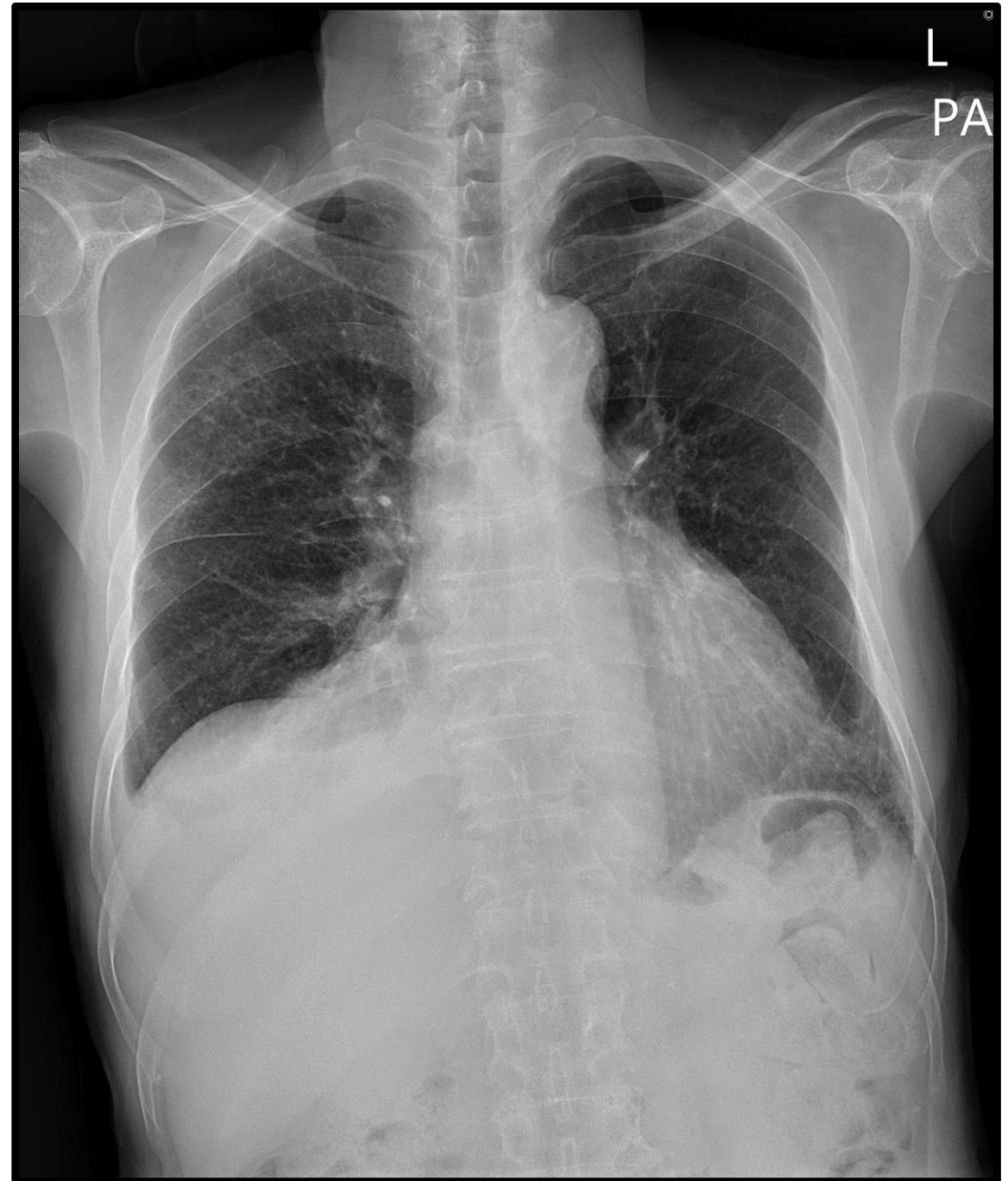


At 6th mo of anti-TB Tx

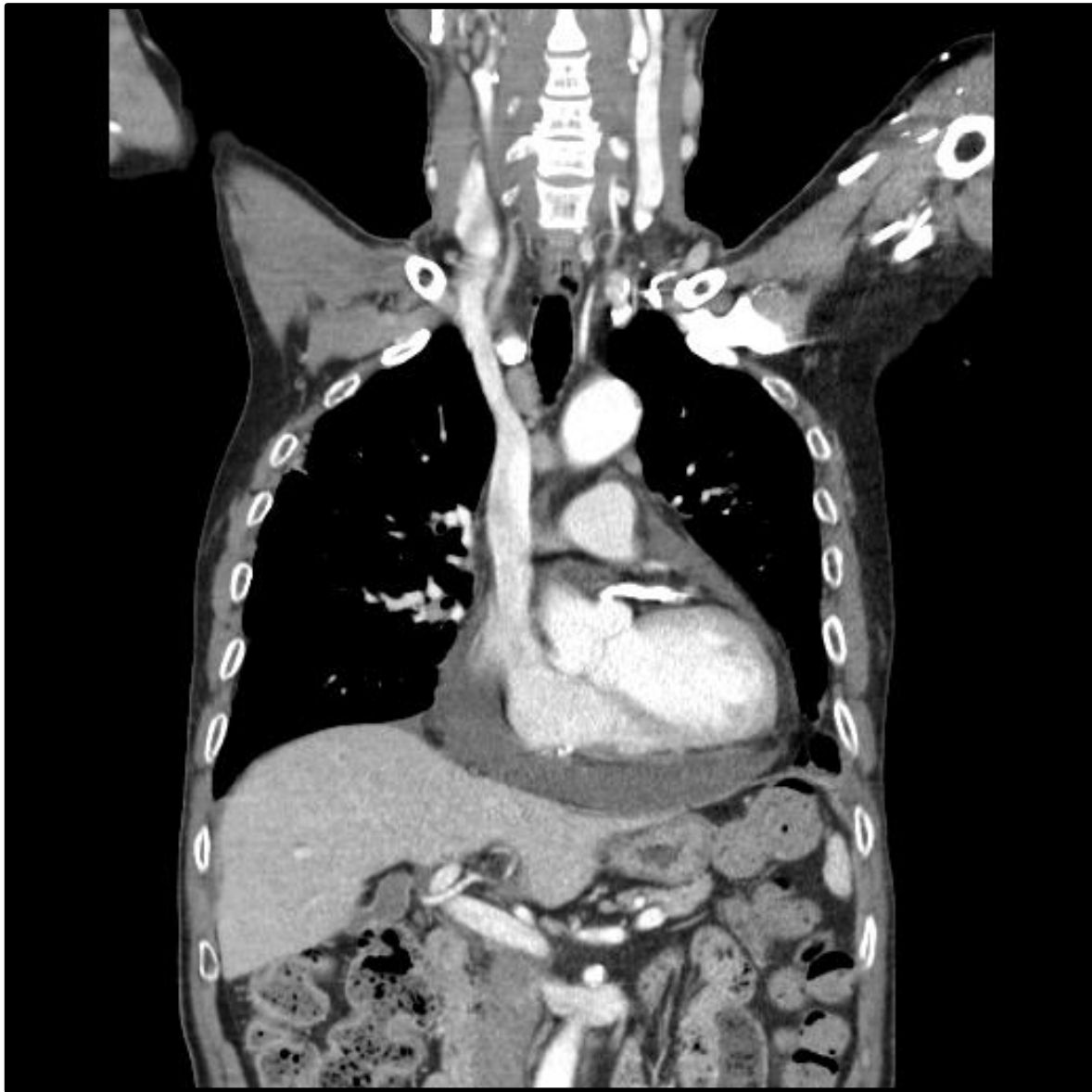


Case 2: 80/M

- DOE for 4 mo
- Muroid sputum, scant
- DM/Parkinson's disease (+/+)
- Ex-smoker (quit 15y ago, 40PYs)



Initial Chest CT



Case 2: 80/M

- Diagnostic thoracentesis
 - Straw color fluid
 - pH 7.46, **C/C 1,748 (MNL 99.4%)**
 - **Protein 5.9 g/dL**, LDH 174 U/L, Glc 125 mg/dL
 - **ADA 50 IU/L**
 - CEA 1.8 ng/mL
 - AFB smear (-)/Xpert MTB/RIF assay (-)

- Serum protein 7.4 g/dL, LDH 171 U/L
- Blood IGRA (-)
- ANA (-)/IgG4 2,606 mg/L (Ref, 30-2,010 mg/L)
- Sputum AFB smear (-)/Xpert MTB/RIF assay (-)

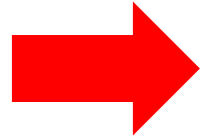
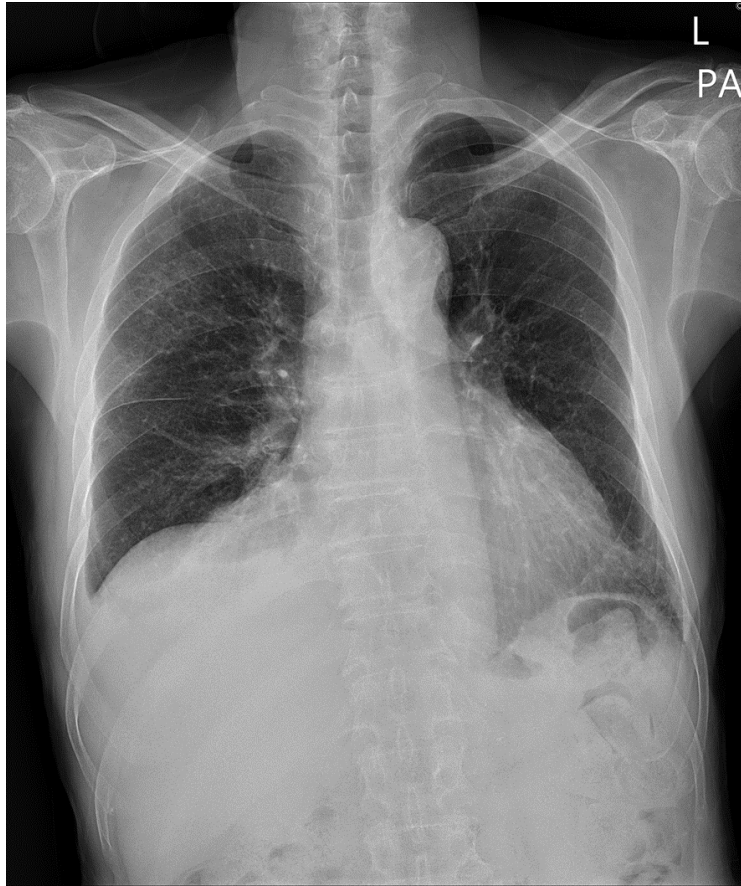
Q: what action should be taken next ?

1. **Initiate anti-tuberculosis treatment (HRZE)**
2. **Wait for the culture results**
3. **Perform a pleural biopsy**
4. **None of the above**

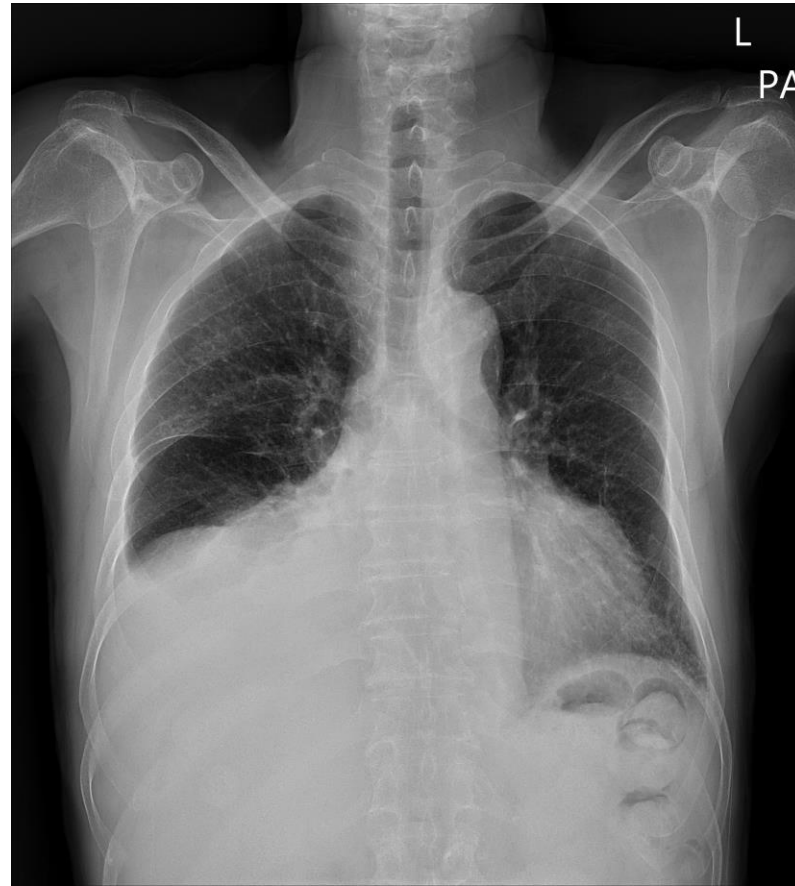
Vote 3



Initial Dx



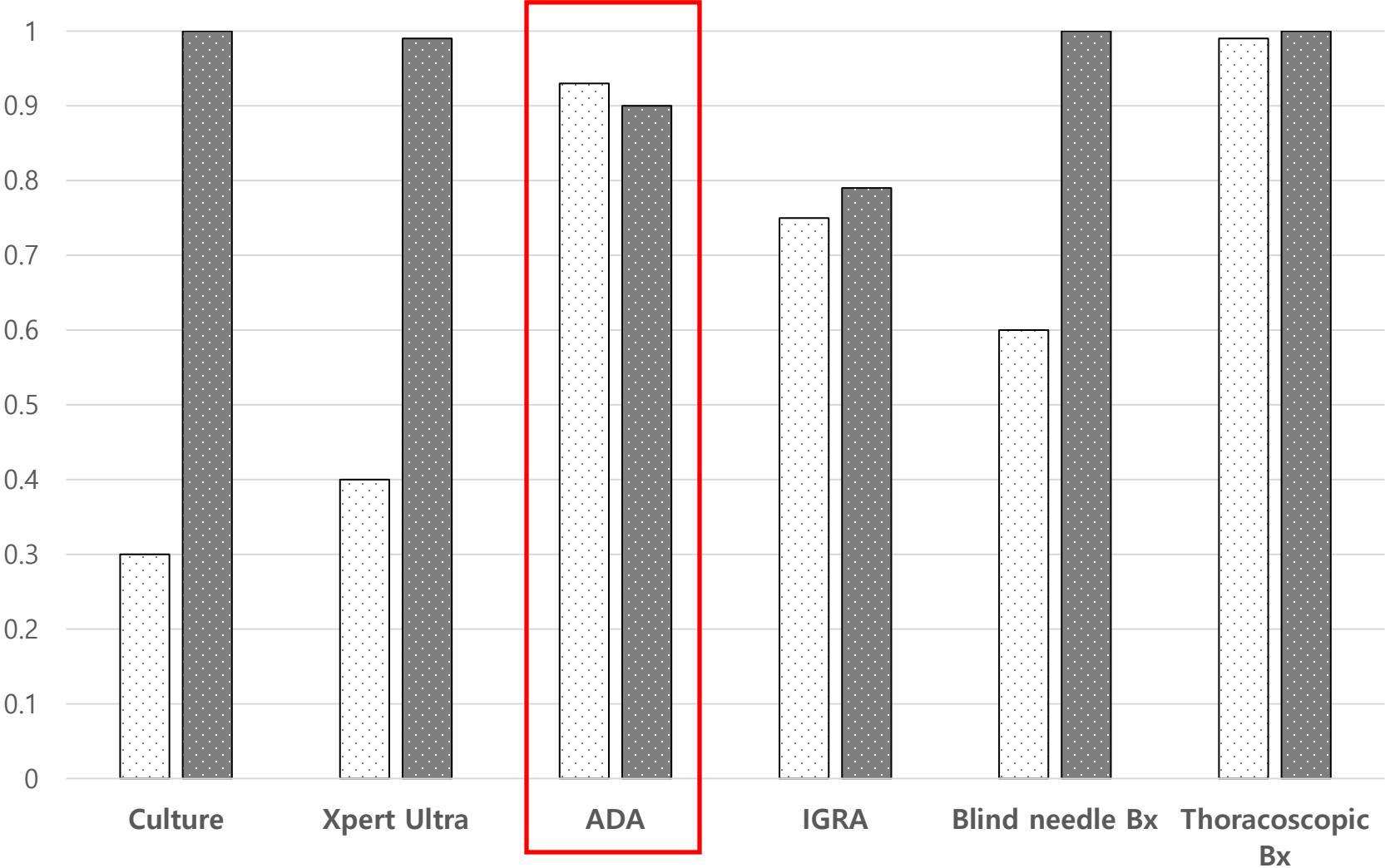
At 2nd mo of anti-TB Tx



Sputum & pleural fluid:

MTB culture (-)

Performance of diagnostic tests for TB pleural effusions



□ Sensitivity ■ Specificity

Diagnosis of TB pleural effusions

권고요약

- 일측성 흉수를 동반한 모든 환자에서 결핵성 흉막염의 가능성을 의심해야 한다(III B).
- 결핵성 흉막염이 의심되는 환자에서도 적극적으로 객담 도말 및 배양검사를 시행해야 한다 (II A).
- 림프구가 우세 염증세포인 삼출성 흉수에서 흉수 adenosine deaminase (ADA) >40 IU/L이고, ADA가 증가할 수 있는 다른 동반 질환이 없다면 결핵성 흉수의 가능성이 크다 (II A).

PF ADA > 40IU/L

TB pleural effusion

Malignant pleural effusion

Parapneumonic effusion, Empyema

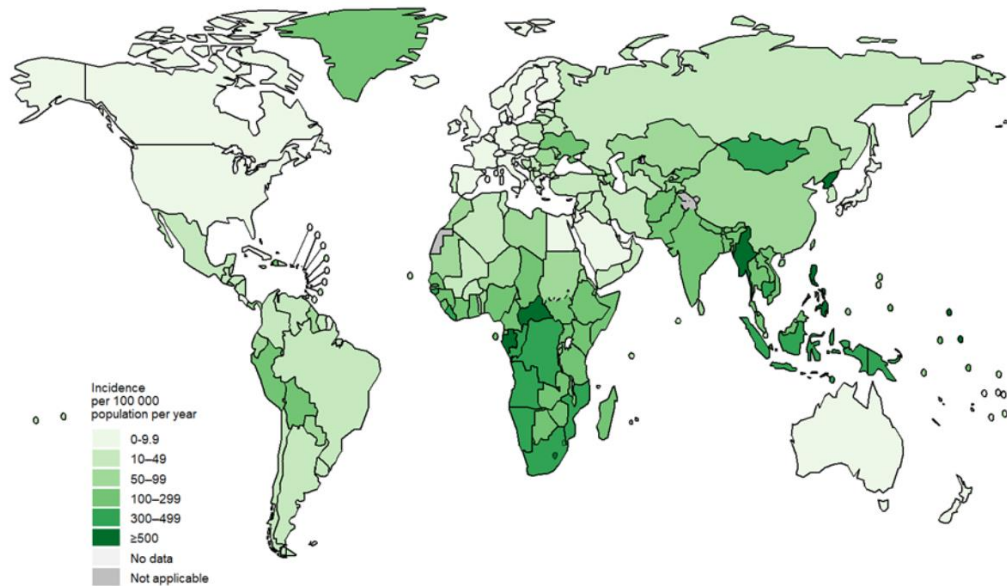
RA-pleural effusion

IgG4-related pleural effusion

Others

Diagnostic performance of pleural fluid adenosine deaminase: pretest probability

Fig. 1.1.3 Estimated TB incidence rates, 2023



High TB prevalence settings

Clinical suspicion of TB infection

Lymphocyte-dominant exudate with
ADA > 40 IU/L



PPV 98% for diagnosing TPE

Low TB prevalence settings

No TB exposure history

Lymphocyte-dominant exudate with
ADA < 30 (40) IU/L

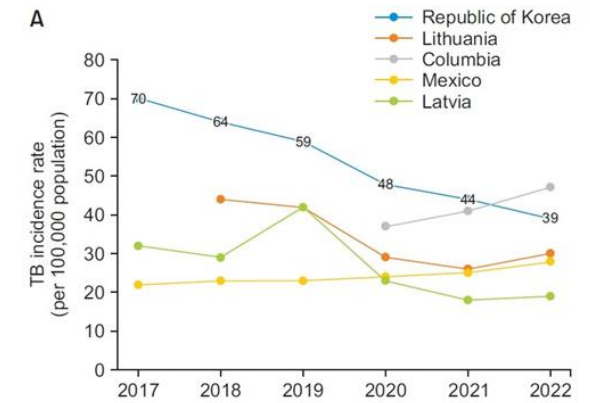


NPV 98% for ruling out TPE

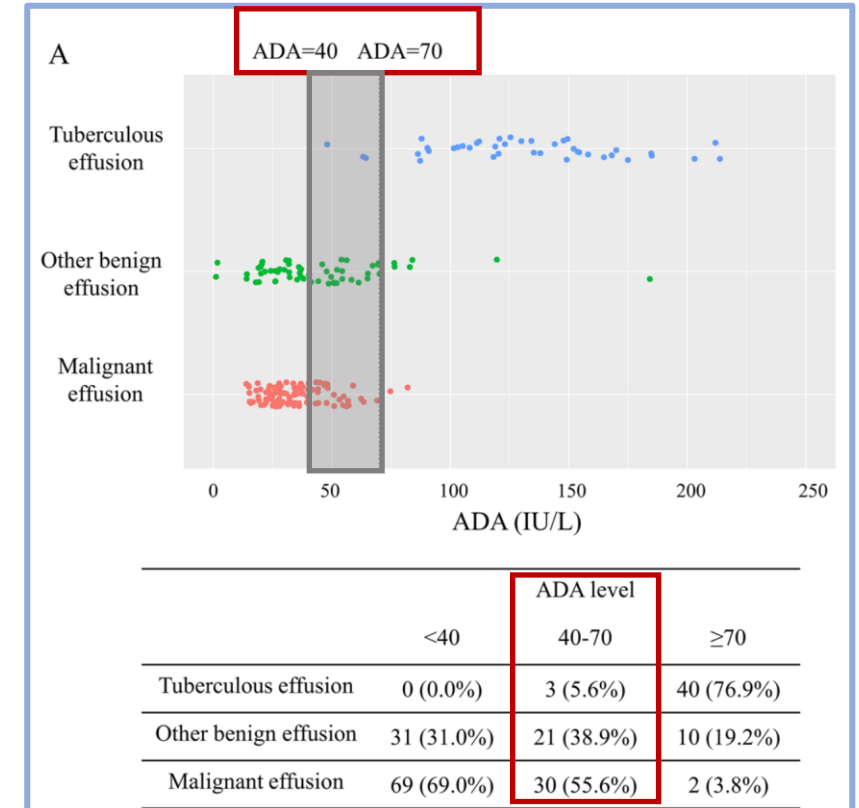
Role of ADA for diagnosis of TPE

- TB-epidemiologic status changes in South Korea

- Patients who underwent MT
- **2015-2020**
- TPE (n=52), MPE (n=156), Other benign effusion (n=84)



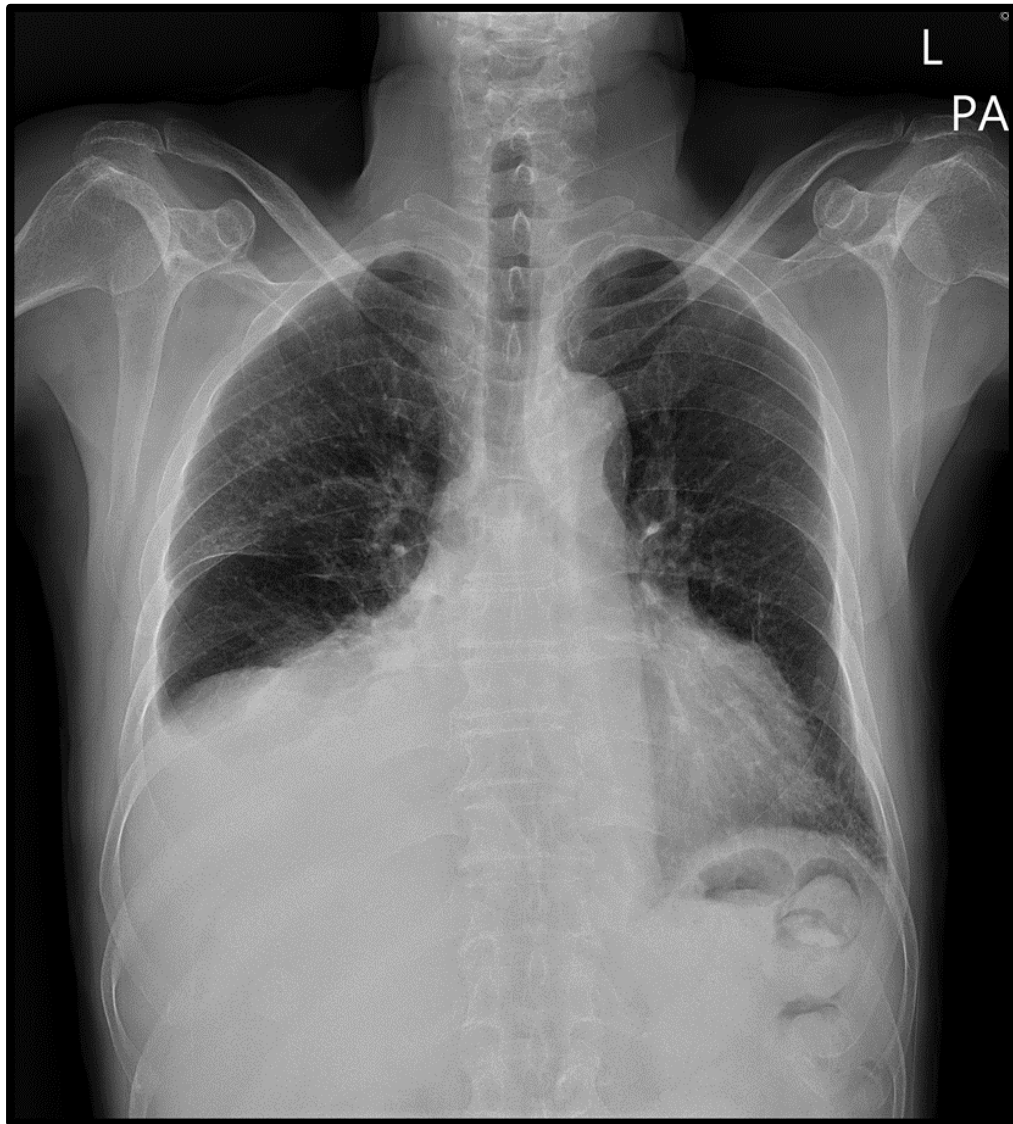
	TPE	Non-TPE	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Lymphocyte dominant pleural effusion^a						
Current cutoff: 40 IU/L						
ADA ≥ 40	43	63	1.00 (0.92–1.00)	0.61 (0.53–0.69)	0.41 (0.31–0.51)	1.00 (0.96–1.00)
ADA < 40	0	100				
Raised cutoff: 70 IU/L						
ADA ≥ 70	40	12	0.93 (0.81–0.99)	0.93 (0.87–0.96)	0.77 (0.63–0.87)	0.98 (0.94–1.00)
ADA < 70	3	151				
Best cutoff: 84 IU/L						
ADA ≥ 84	40	5	0.93 (0.81–0.99)	0.97 (0.93–0.99)	0.89 (0.76–0.96)	0.98 (0.95–1.00)
ADA < 84	3	158				



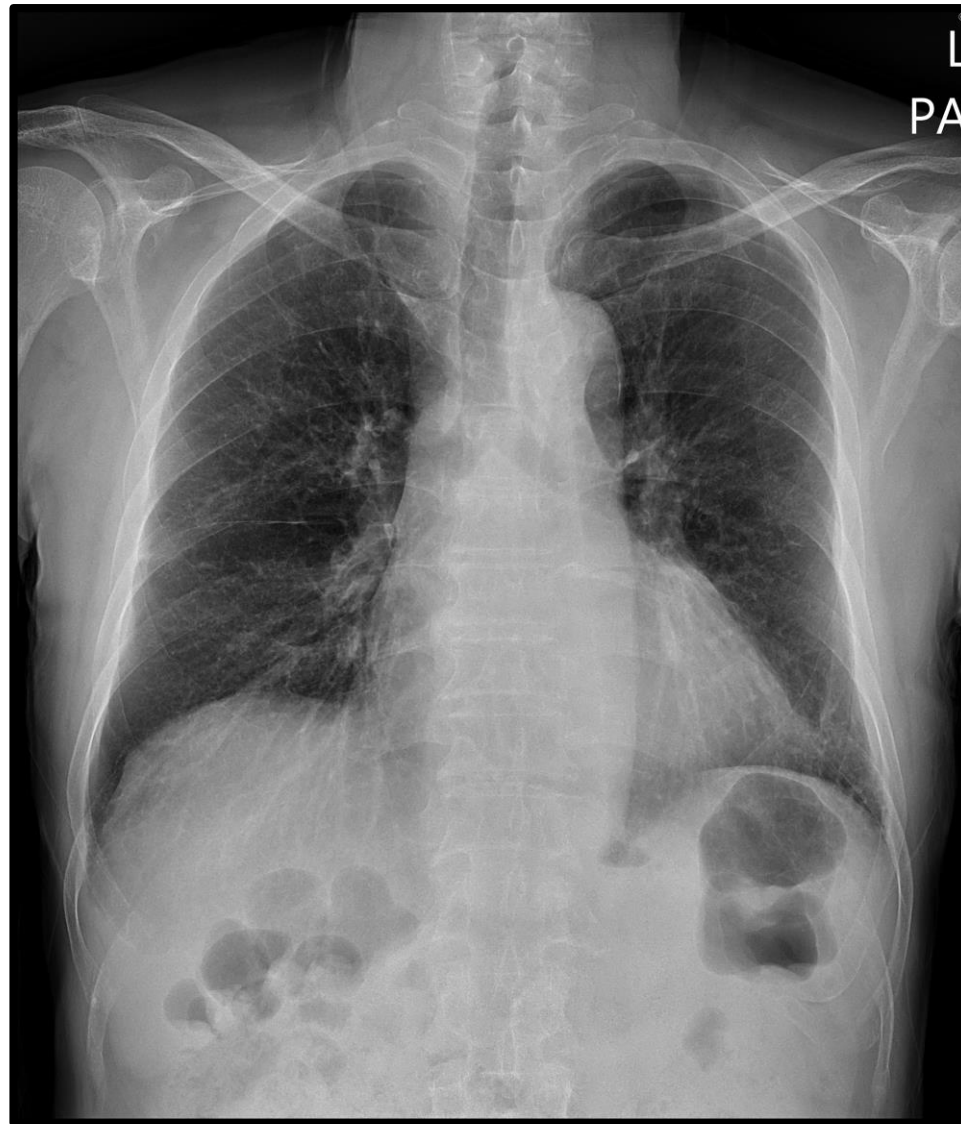
Case 2: 80/M

- Pleural biopsy (VATS)
 - Pleural tissue Xpert MTB/RIF assay (-)
 - Pleural tissue AFB smear (-)
 - Histologic report: **chronic inflammation with a few IgG4-positive cells**
 - Pleural tissue MTB culture (-)
- **Serum IgG4 3,557 mg/L** (Ref, 30-2,010 mg/L)

At 2nd mo of anti-TB Tx

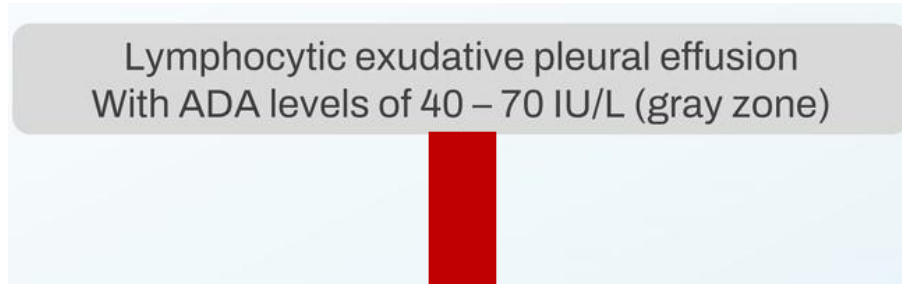
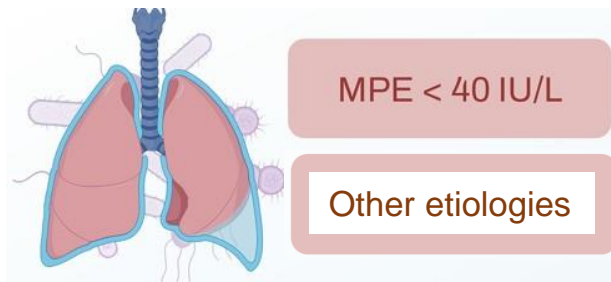


After 2-mo of prednisolone Tx

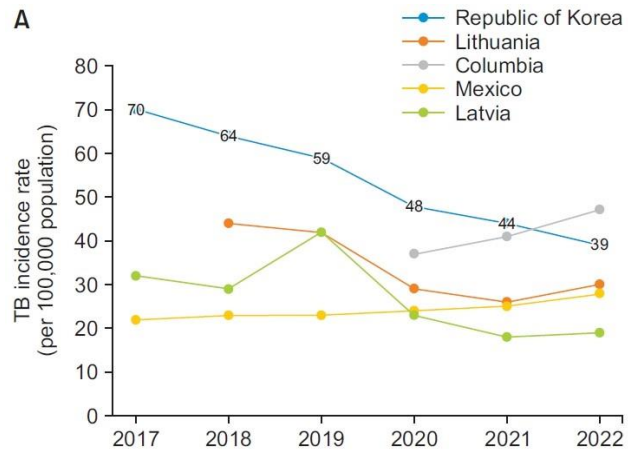


Role of ADA for diagnosis of TPE

- TB-epidemiologic status changes in South Korea



Further evaluation & differentiation with diseases other than TB

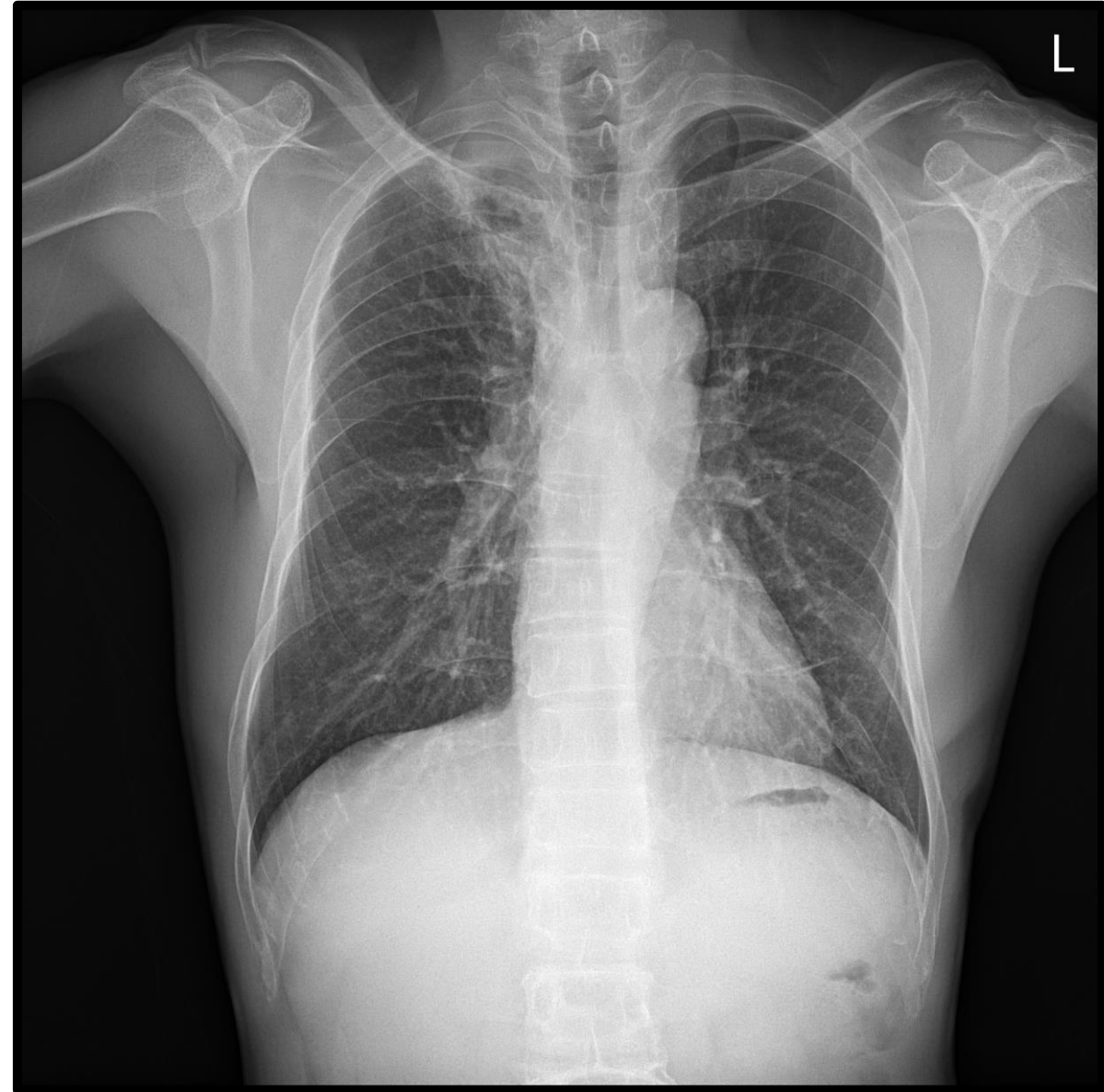


- PF ADA > 40IU/L**
- Malignant pleural effusion
 - RA-pleural effusion
 - IgG4-related pleural effusion
 - Others

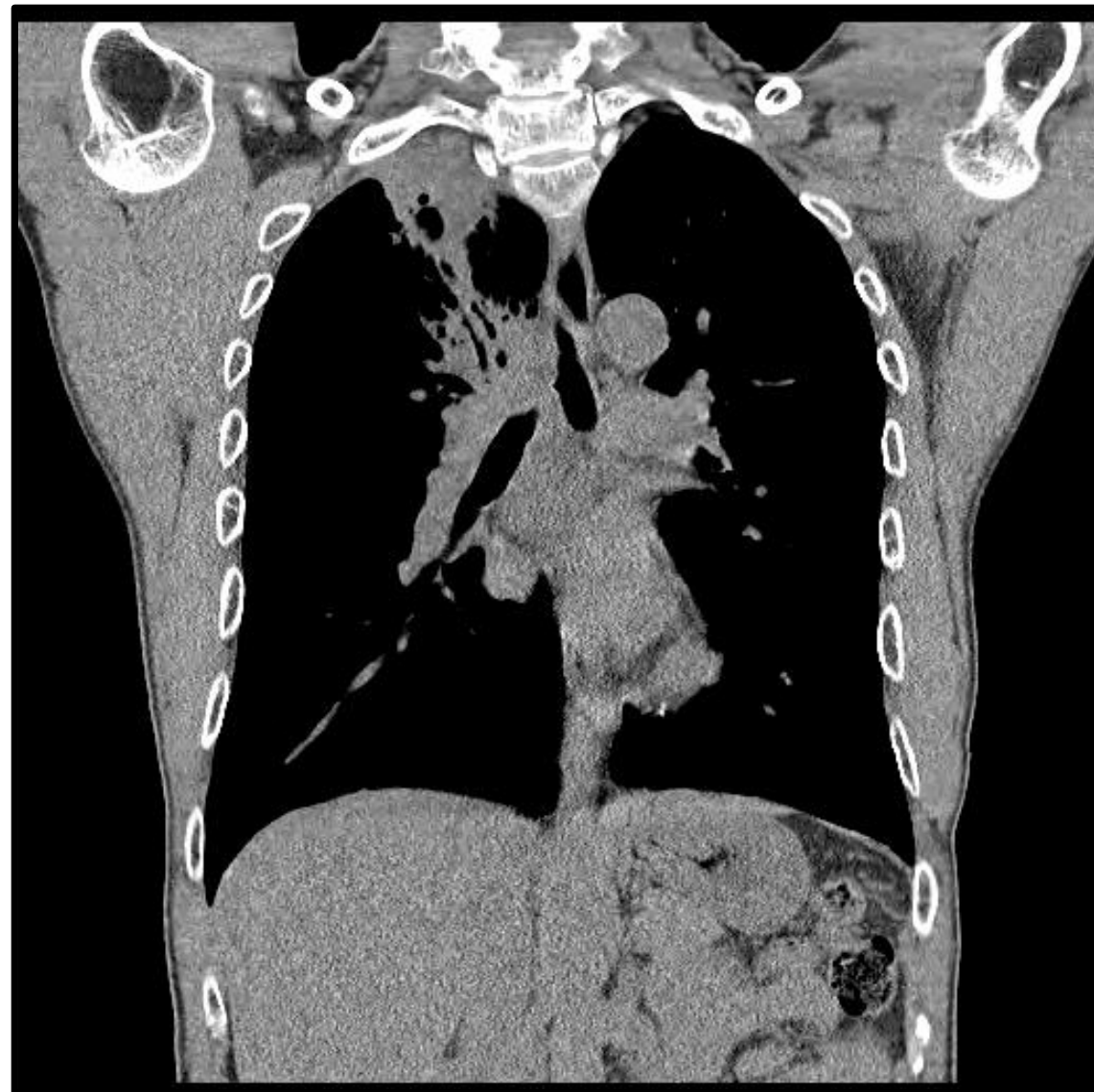
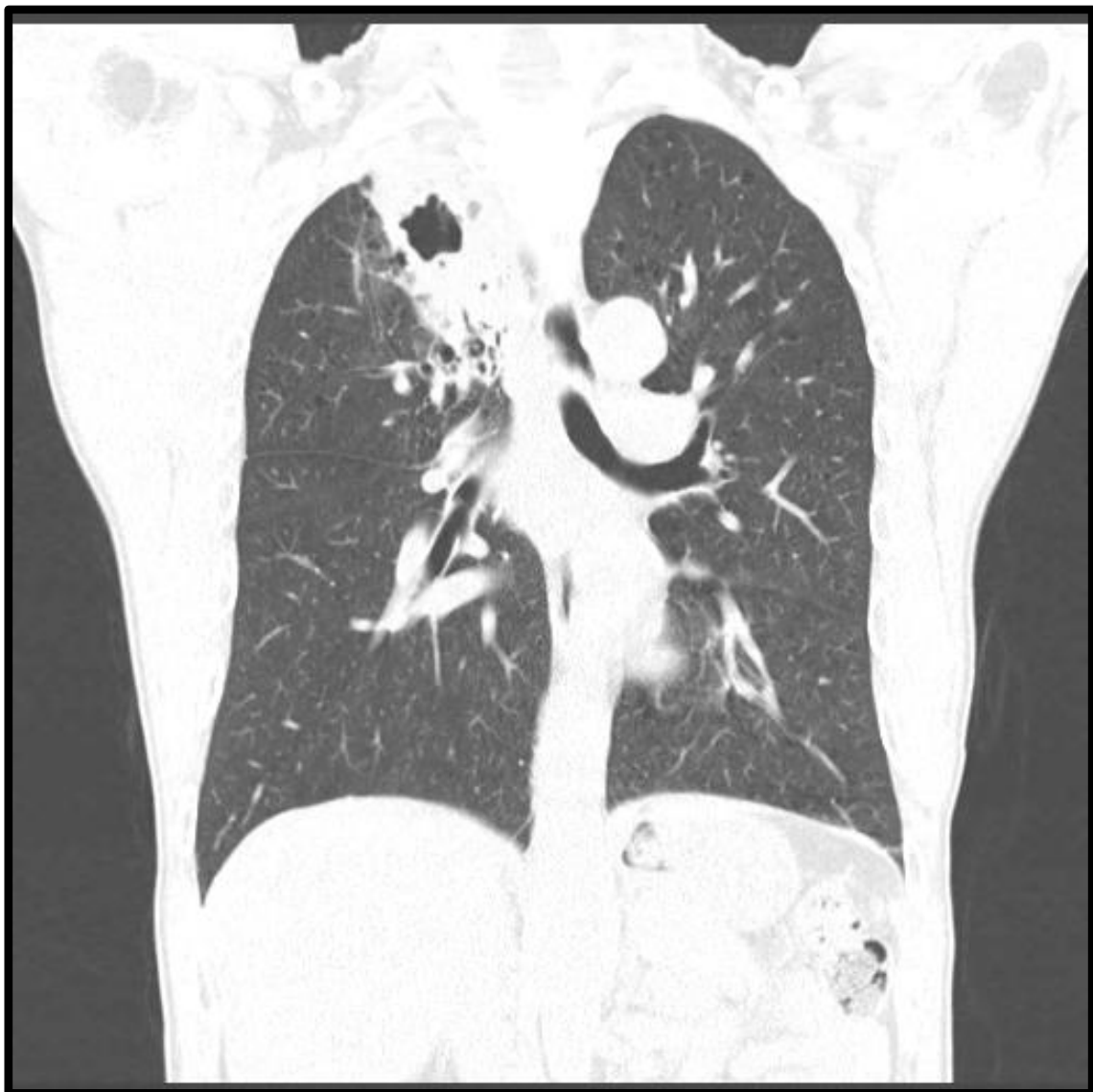
Case 3: 55/M

- Right chest discomfort for 2 mo
- Current smoker (1PPD for 35y)

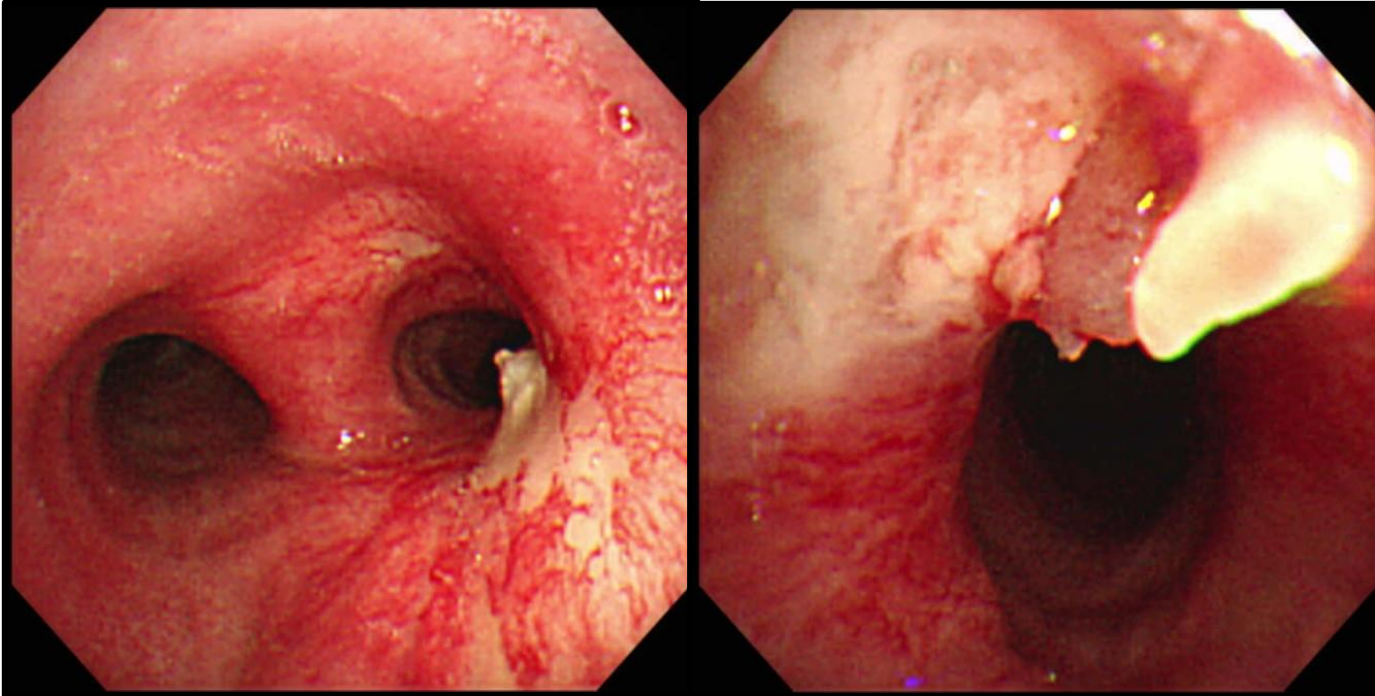
Initial CXR (4 mo ago, LMC)



Initial Chest CT (4 mo ago, LMC)



Initial bronchoscopy (4 mo ago, LMC)



- Bronchial aspirate
 - AFB smear/TB-PCR (4+/+)
 - cytology: atypical cells
- Bronchoscopic biopsy
 - chronic inflammation

Q: what action should be taken next ?

1. Initiate anti-tuberculosis treatment (HRZE) & re-assessment
2. Repeated bronchoscopic biopsy
3. Perform PET/CT scan
4. None of the above

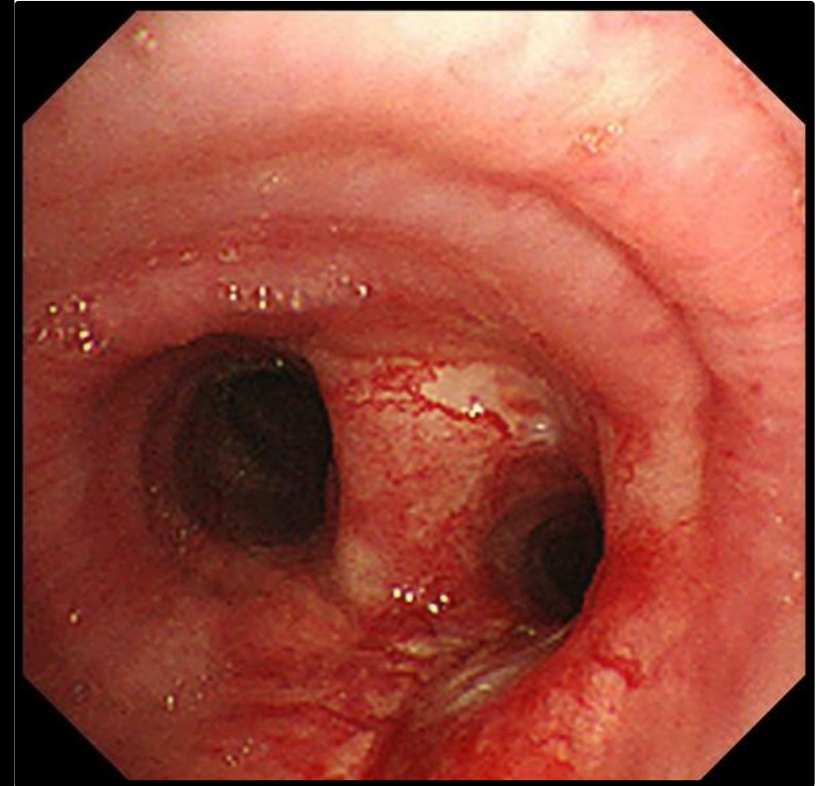
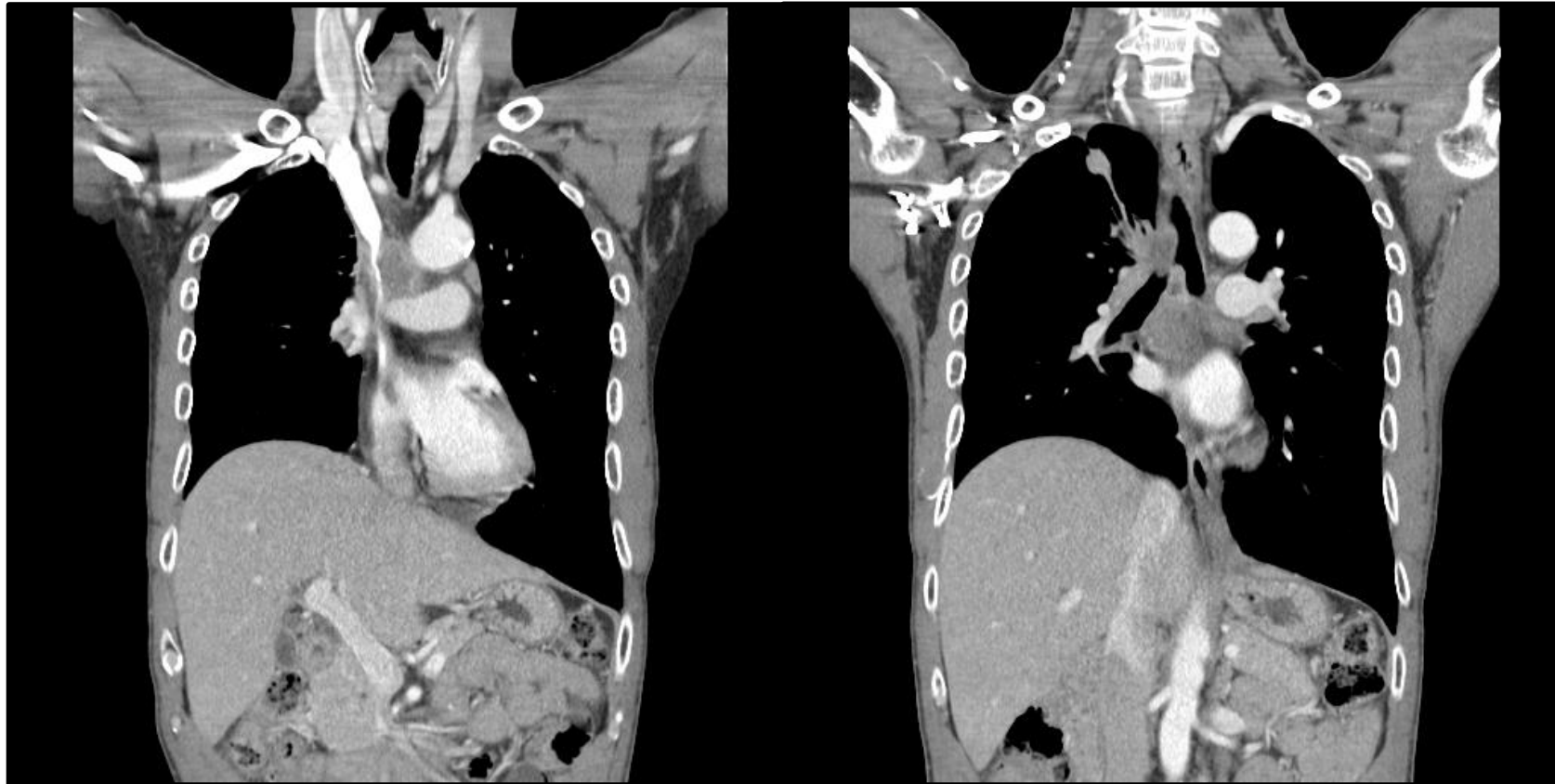
Vote 4



Case 3: 55/M

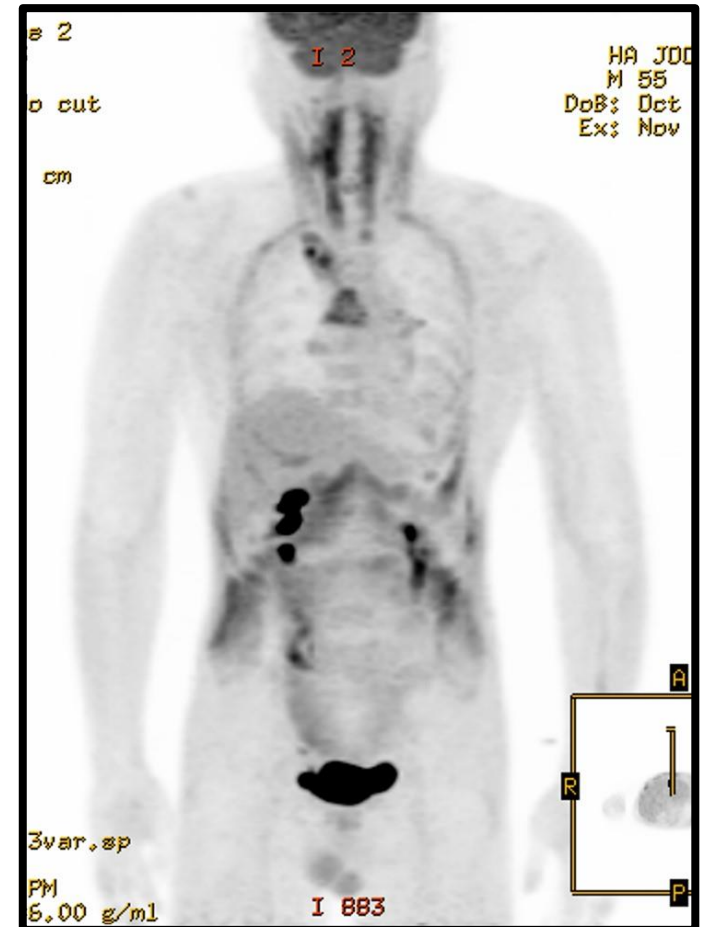
- HRZE taken
- Bronchial aspirate culture: MTB growth (DS)
- **Persistent chest pain even after 4 months of anti-TB treatment**
- Facial swelling & neck vein distension for the past month

Chest CT (At 4th mo of anti-TB Tx)

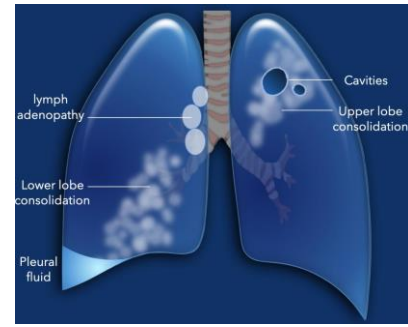


Case 3: 55/M

- Bronchial aspirate AFB smear (-)/Xpert MTB/RIF (+/-)
- Bronchial aspirate cytology: atypical cells
- **Bronchoscopic Bx: ADC**
- **ADC of lung, cT4N2M0**
 - EGFR/ALK/ROS1/K-RAS/PD-L1 (-/-/-/-/50%, TC2/IC1)



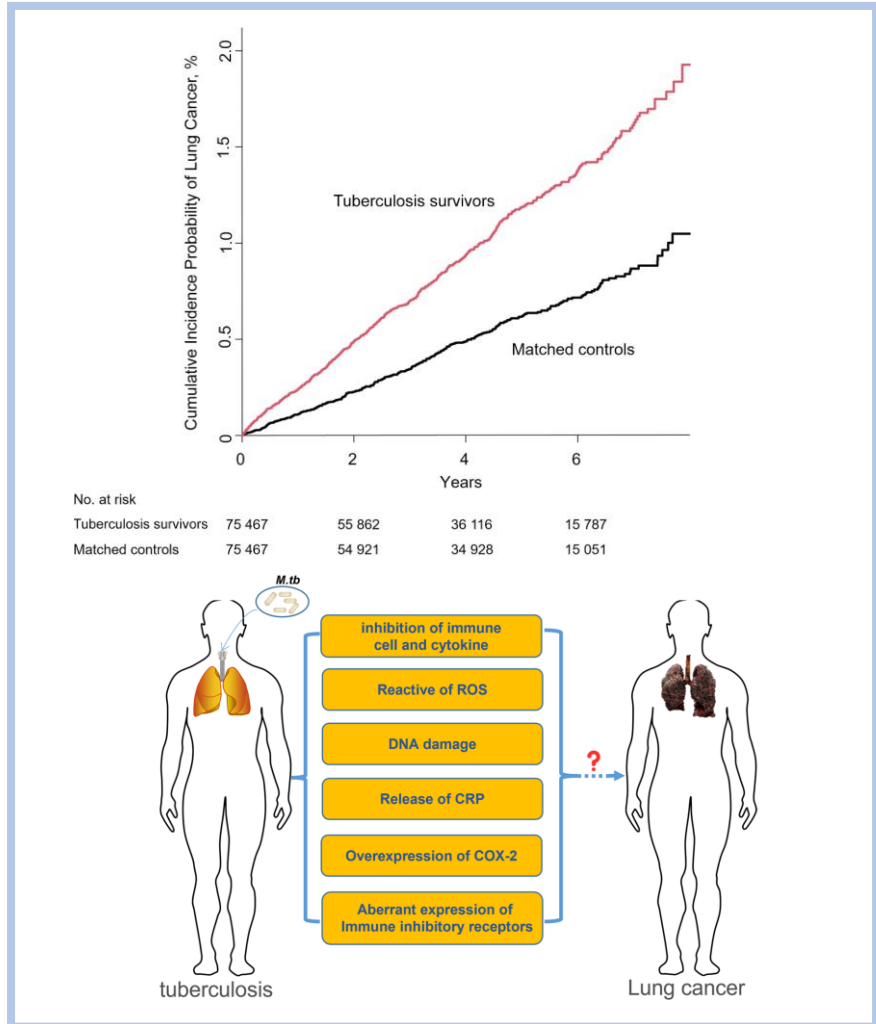
Co-existent TB and lung cancer



The radiology assistant: Imaging findings in TB

TB increases lung cancer risk

- prevalence: 2-4%



Lung cancer increases TB risk

Taiwanese population based study

Malignancy, primary location	N (% of total)	Person-year	Event	Rate*	SIR# (95% C.I.)
Total	1,105,009 (100.00)	6383055.73	19,906	312	1.31 (1.30–1.33)
Head and neck	85,950 (7.78)	521311.01	1,990	382	2.58 (2.37–2.80)
Digestive	394,258 (35.68)	1981200.05	5,990	302	1.50 (1.39–1.61)
Respiratory	131,116 (11.87)	543125.91	4,842	892	5.45 (4.92–5.97)

Shu et al. Scientific Reports 2019

Moon et al. Clinical Infectious Diseases 2023

Qin et al. Infectious Agents and Cancer 2022

Coexisting Bronchogenic Carcinoma and Pulmonary Tuberculosis in the Same Lobe: Radiologic Findings and Clinical Significance

Young Il Kim, MD¹
Jin Mo Goo, MD¹
Hyea Young Kim, MD²
Jae Woo Song, MD³
Jung-Gi Im, MD¹

Objective: Bronchogenic carcinoma can mimic or be masked by pulmonary tuberculosis (TB), and the aim of this study was to describe the radiologic findings and clinical significance of bronchogenic carcinoma and pulmonary TB which coexist in the same lobe.

Korean J Radiol 2001

- N= 51
- Location: upper lobes (82%), cavitation (10%), mediastinal LNE (82%)
- \geq Stage IIIB (61%)
- 21 patients with serial chest X-rays prior to diagnosis of lung cancer: delay in diagnosing lung cancer [mean **11.7 mo** (range, 1-24 mo)]



Careful follow-up (CT) is essential in the care of patients whose symptoms show little improvement despite anti-TB therapy

Timing of radiologic response of TB

- Retrospective study: Suspected PTB (n=267)
- Changes between baseline and 1- & 2- month CXR findings

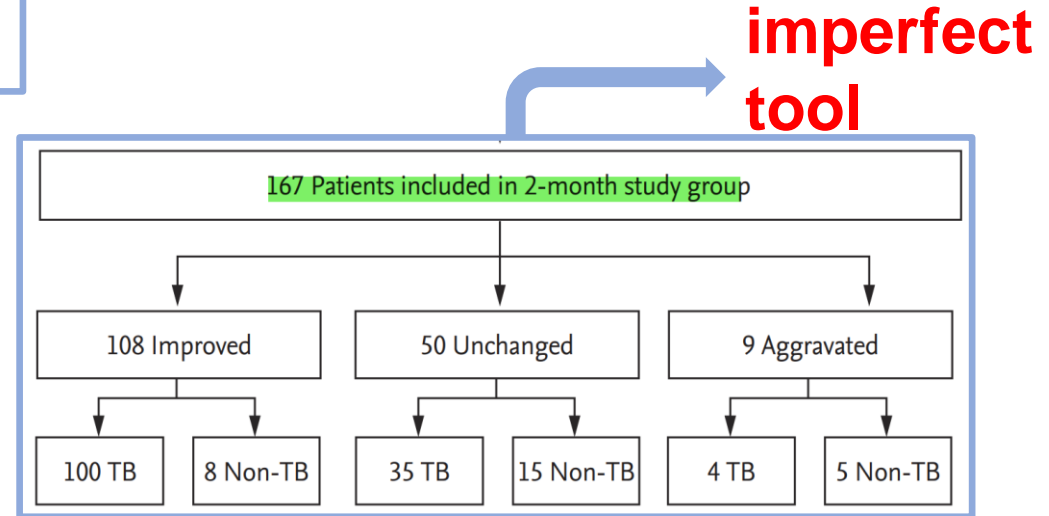
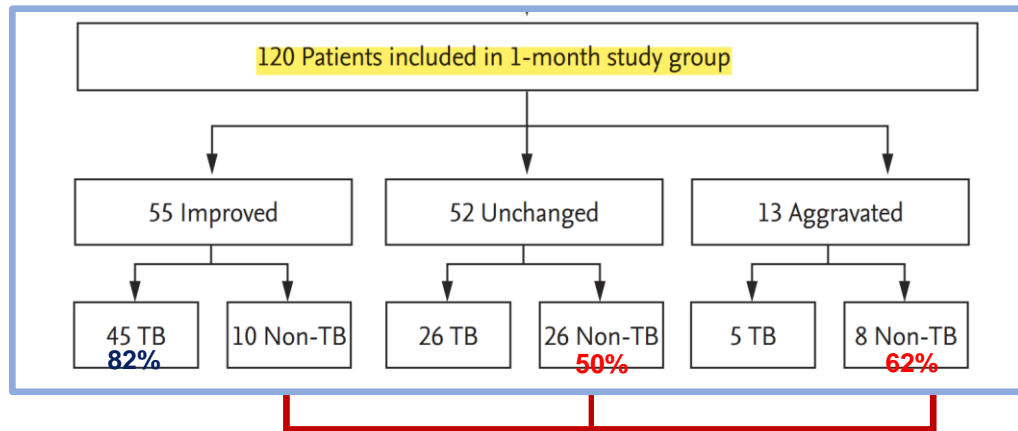
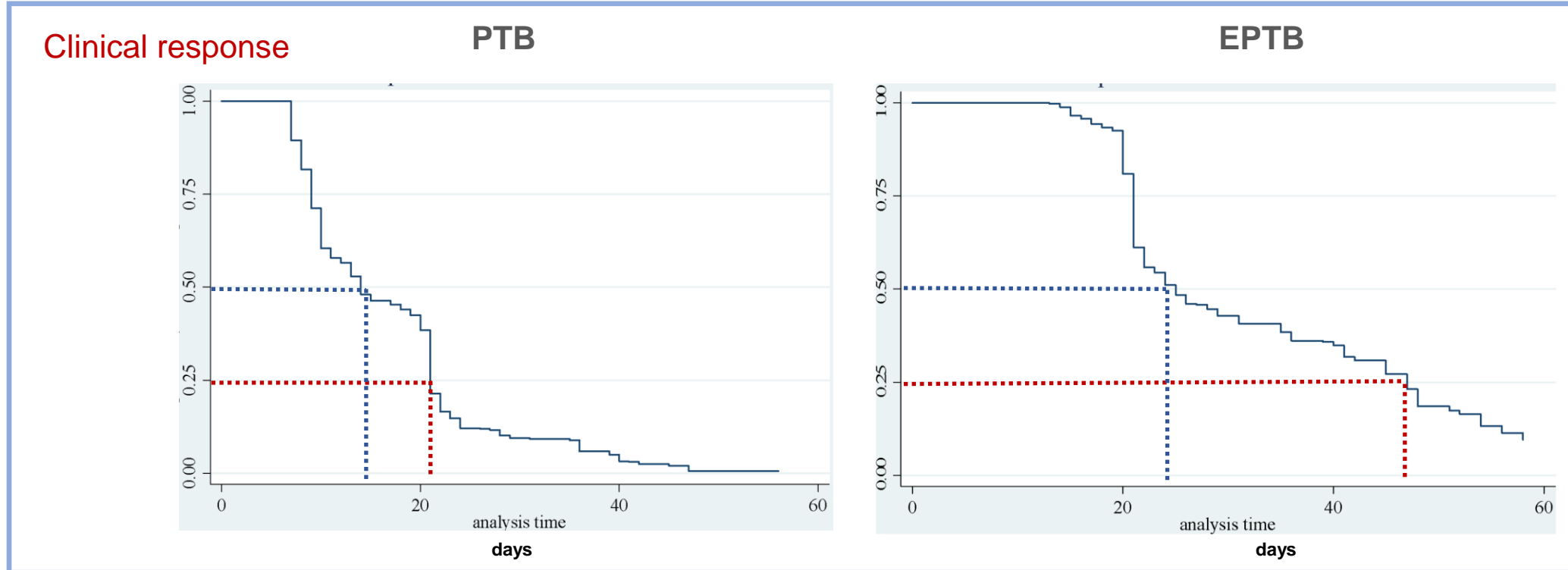


Table 3. Detailed diagnoses of 44 patients in the 1-month group with non-tuberculosis as the final diagnosis

Variable	Total (n = 44)	Improved (n = 10)	Unchanged (n = 26)	Aggravated (n = 8)
Nontuberculous mycobacteria	16	6	9	1
Malignancy	14	0	8	6
Granuloma ^a	4	0	4	0
Sarcoidosis	2	1	1	0
Organizing pneumonia	2	1	1	0
Bacterial pneumonia	1	0	1	0
Diffuse panbronchiolitis	1	1	0	0
Castleman's disease	1	0	1	0
Fungal pneumonia	1	0	0	1
Necrotizing pneumonia	1	0	1	0
Non-specific inflammation	1	1	0	0

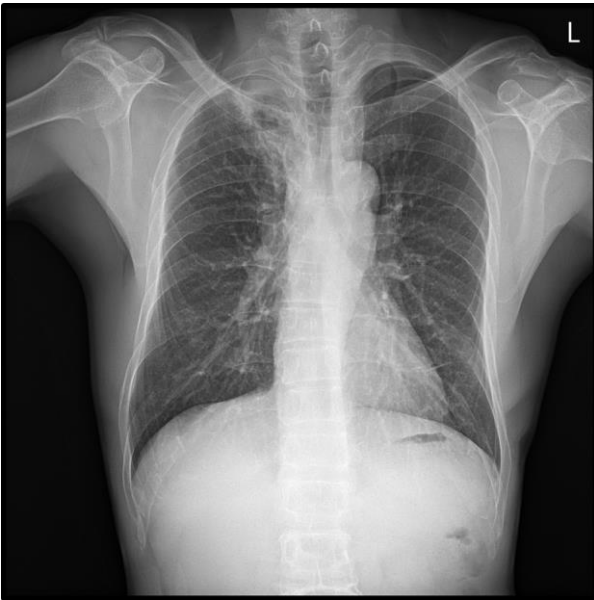
Timing of clinical response of TB

- Prospective cohort study: PTB (n=804) & EPTB (n=804)
- Clinical response – **resolution of the initial symptoms and sign**
- DOT



Co-existent TB and lung cancer

- Suspicion of lung cancer => Dx of PTB



Clinical & radiologic findings strongly suggestive of lung cancer



- Anti-TB treatment
- Repeat biopsy
- PET/CT scan

Anti-TB treatment



- Close follow-up
 - re-evaluation in **1mo**(clinical response & CT)

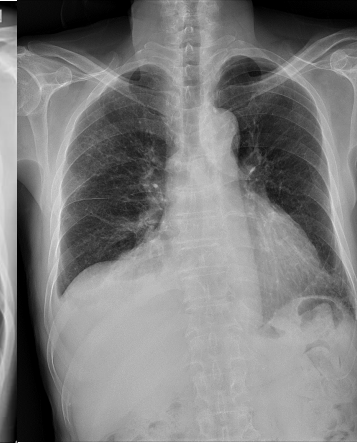
Summary

- Culture-negative PTB
- TB-paradoxical response
- ADA for diagnosis of TPE
- Missed combined lung cancer

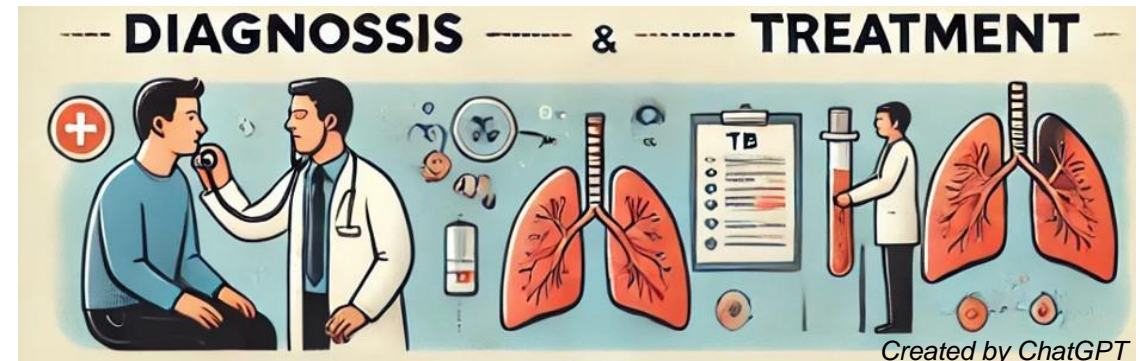
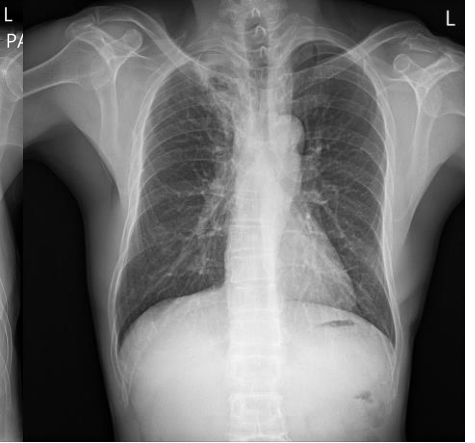
Case #1



Case #2



Case #3



경청해주셔서 감사합니다