

CASE

 건국대학교병원 내과 R2 이경언

54/F

Chief Complaint

Polyarthralgia
(Onset : 2 months ago)

Present Illness

상기 54세 여환 특이 과거력 없는 분으로 내원 2개월 전부터 발생한 양측 무릎, 발목, 팔꿈치의 통증 및 최근 2주전부터 기침, 호흡곤란, 두통 동반되어 본원 류마티스 내과 경유 하여 내원함.

- **Past Medical History**

DM / HTN / Tbc / Hepatitis (- /- / - / -)

- **Family history**

- (-)

- **Social history**

- Alcohol : 월 1회
- Smoking : Ex-smoker (2YA) 2.5 PY

- **Medication**

- Antitussive, NSAID

Review of System

General

General weakness (-)
Dizziness (-)

Fatigue (-)
Weight loss (-)

HEENT

Headaches (+)
Epistaxis (-)

Sore throat (-)
Hoarseness (-)

Respiratory

Hemoptysis (-)
Sputum (-)

Cough (+)
Dyspnea (+)

Cardiovascular

Chest pain (-)
Palpitation (-)

Syncope (-)

Gastrointestinal

Diarrhea (-)
Hematochezia (-)

Constipation (-)
Melena (-)

Musculoskeletal

Polyarthralgia (+)

Physical Examination

Initial Vital sign 113/72 mmHg - 88 회/분 - 20 회/분 - 36.8°C

General Not so ill - looking, Alert mentality

HEENT
Anicteric sclera (-)
Pale conjunctivae (-)
Palpable LN enlargement (-)
Neck vein engorgement (-)

Thorax
Normal chest contour, symmetric expansion
Clear breathing sound without crackle
No wheezing
Regular heart beat without murmur

Abdomen
Soft & flat abdomen
Normoactive bowel sound
Tenderness (-), rebound tenderness (-)
No palpable mass

Back & Extremity
No pretibial pitting edema
No CVA tenderness

Initial Laboratory Findings

CBC

WBC **12980** /mm³
(N 83.4%, L 10.5%, M 5.7%, E 0.2%, B 0.2%)
Hb **11.8** g/dL, Hct 35.4%
PLT **480,000** /mm³

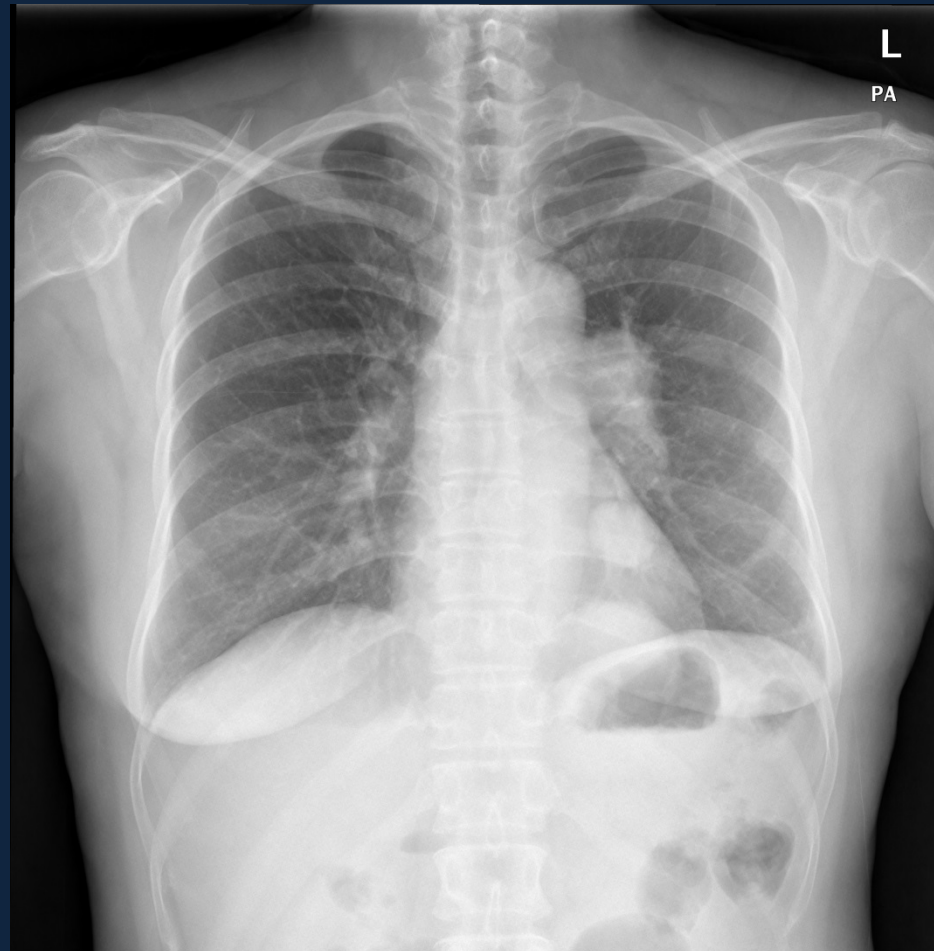
Chemistry

T.Bil	0.3	(mg/dL)
AST/ALT	15/10	(IU/L)
Albumin/Globulin	3.2/3.5	(g/dL)
BUN/Cr	13.8/0.65	(mg/dL)
CRP	6.42	(mg/dL)
LDH	592	(IU/L)

Electrolyte

Na/K/Cl/tCO2	140/3.7/105/23	(mEq/L)
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Chest Radiography



Initial Assessment & Plan

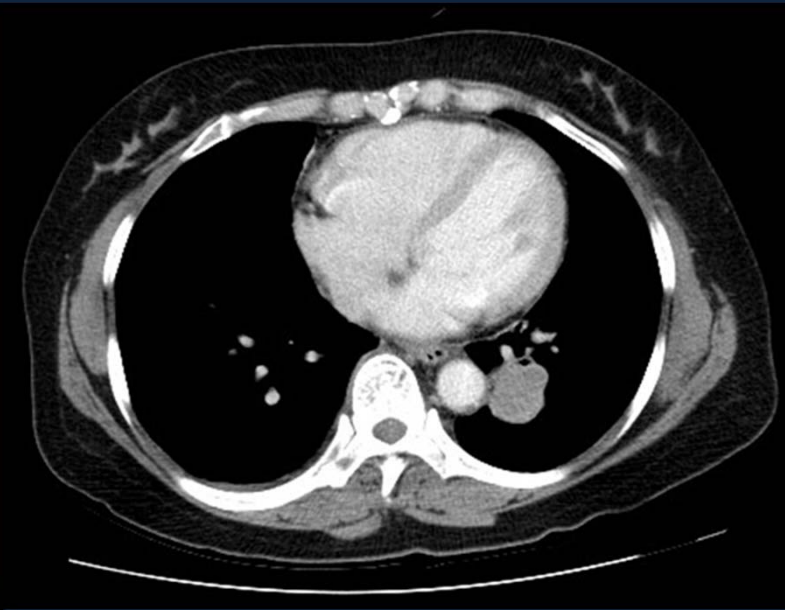
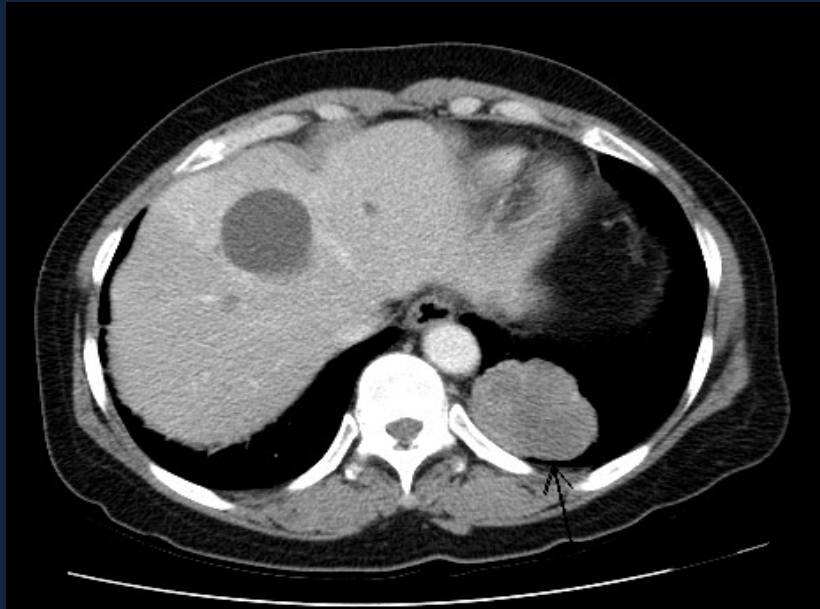
Assessment>

- #1. r/o Lung cancer, LLL
- #2. r/o Paraneoplastic arthropathy
 - r/o Rheumatoid arthritis
 - r/o OA

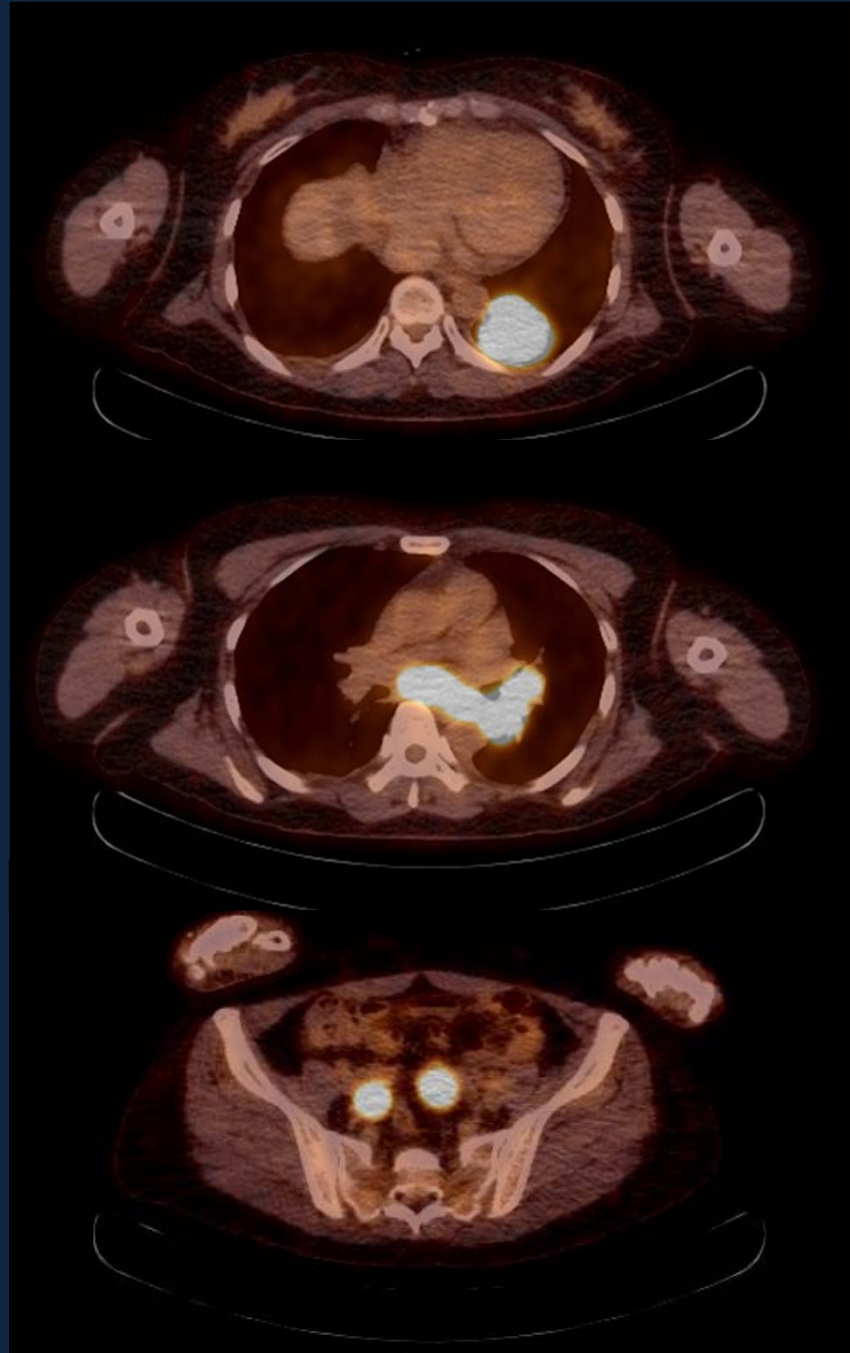
Diagnostic plan>

- #1. Imaging
 - Chest CT (+)
 - PET-CT
 - Brain MRI
 - Tissue sampling
 - CT-guided PCNB (percutaneous needle biopsy)
 - Bronchoscopy
- #2. Serologic test(RF, Anti-CCP Ab, ANA, C3/C4)
 - X-ray

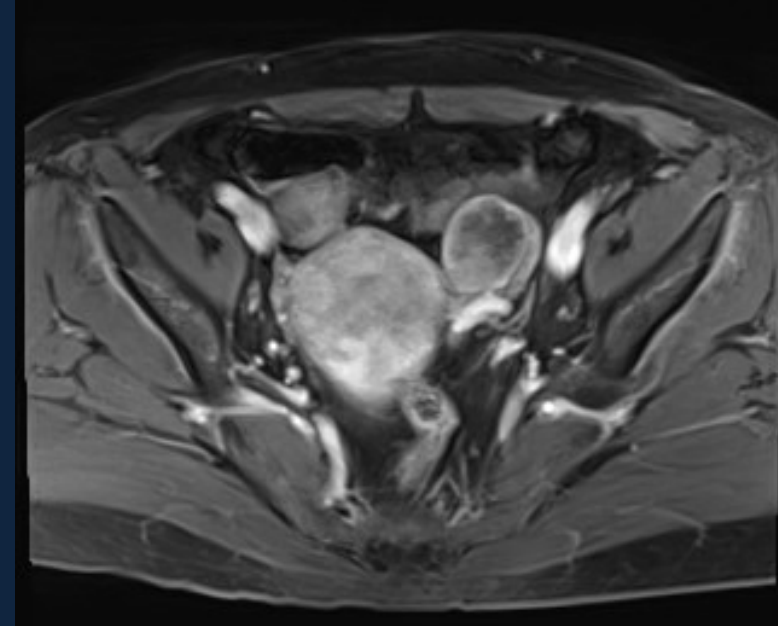
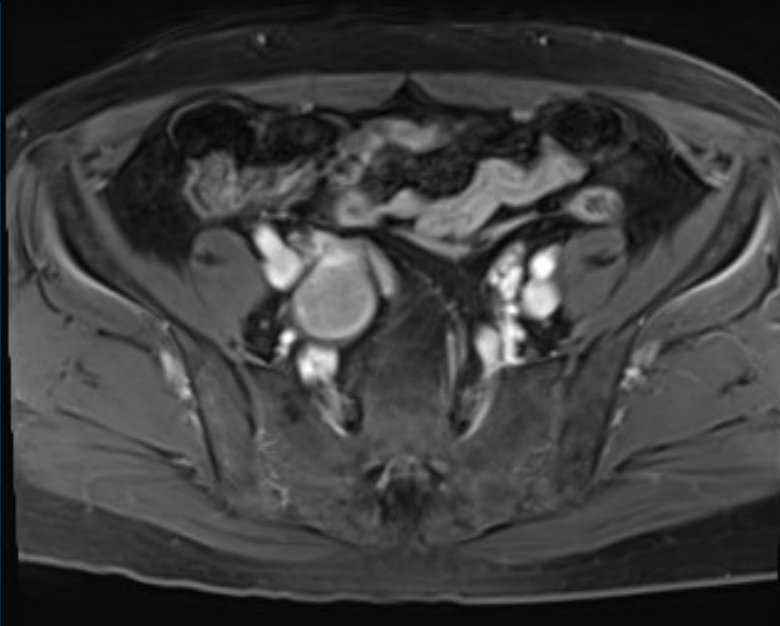
Chest CT



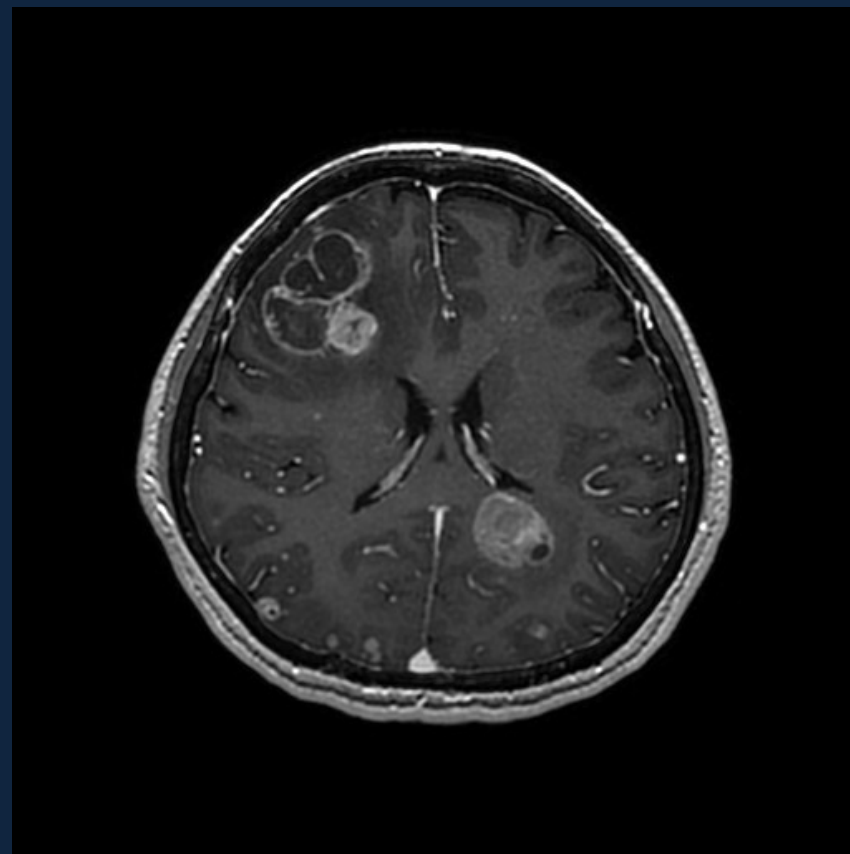
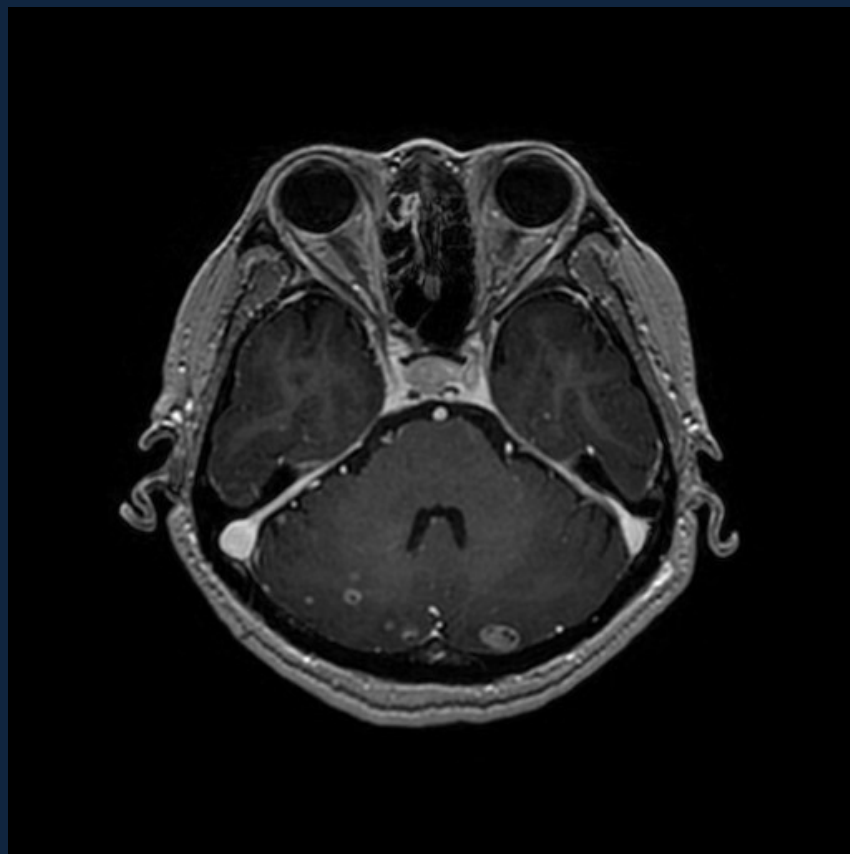
PET-CT



Abdomen CT & MRI

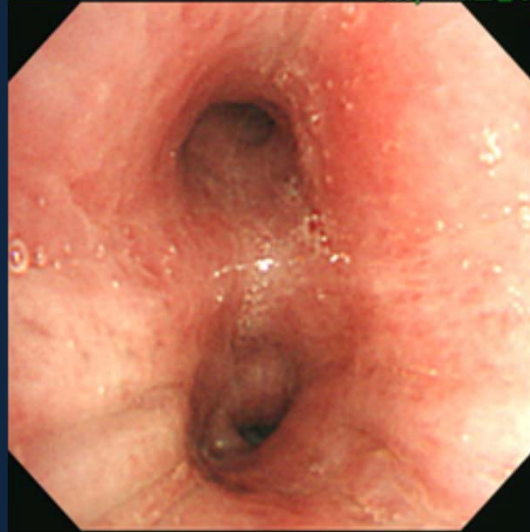


Brain MRI

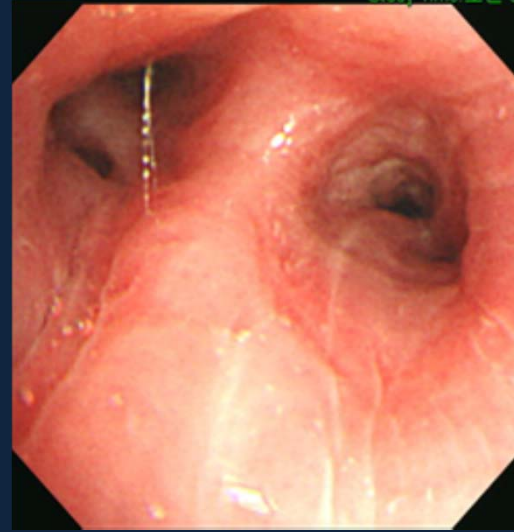


Bronchoscopy

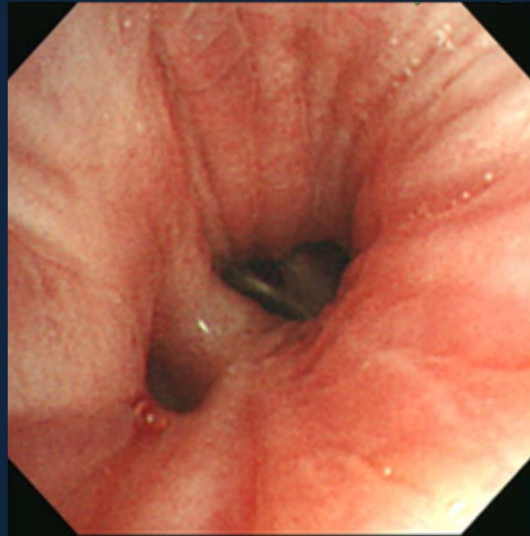
Left main



LUL



LLL



LLL
posterobasal
segment



Bronchoscopy

- Bronchial Washing
 - No malignant cells seen
- LLL, Posterobasal segment, Bronchoscopic Bx.
 - Chronic nonspecific inflammation, mild

PCNB

Lung, lower, left, needle biopsy

NONSMALL CELL CARCINOMA, favor ADENOCARCINOMA

In view of **ALK immunostaining strong positivity**, ALK translocation study is recommended.

[DIAGNOSIS]

Lung, lower, left, needle biopsy:

NONSMALL CELL CARCINOMA

[SPECIAL & IMMUNOHISTOCHEMICAL STAIN]

ALK [A01] : positive

CK 5/6 [A01] : negative

EGFR [A01] : negative

P63 [A01] : negative

TTF-1 [A01] : weak positive

Thymidylate Synthase [A01] : positive

Napsin A [A01] : negative

Alcian blue pH 2.5 [A01] : negative

- FISH for ALK translocation : Positive

- EGFR gene mutation study

Exon 18 : No Mutation (Wild type)

Exon 19 : No Mutation, No deletion (Wild type)

Exon 20 : No Mutation, No insertion (Wild type)

Exon 21 : No Mutation (Wild type)

- K-ras gene mutation study

Codon 12 : No Mutation (Wild type)

Codon 13 : No Mutation (Wild type)

Codon 61 : No Mutation (Wild type)

2013.11.29 HD #11

A>

#1. NSCLC, Adenocarcinoma, T3N2M1b stage IV

Female and Ex smoker (2YA) 2.5PY

Wt loss (-)

PS ECOG 0

Comorbidity : (-)

#2. Paraneoplastic arthropathy

– RF 5 IU/ml, Anti-CCP Ab 1.48 U/ml, ANA negative

P>

1st-line #1 Alimta/cisplatin

Palliative RT to whole brain, 3000cGy/10fxs (2013.12.2~2013.12.13)

2013.12.09. HD#21

1st-line #1 Alimta/cisplatin D11

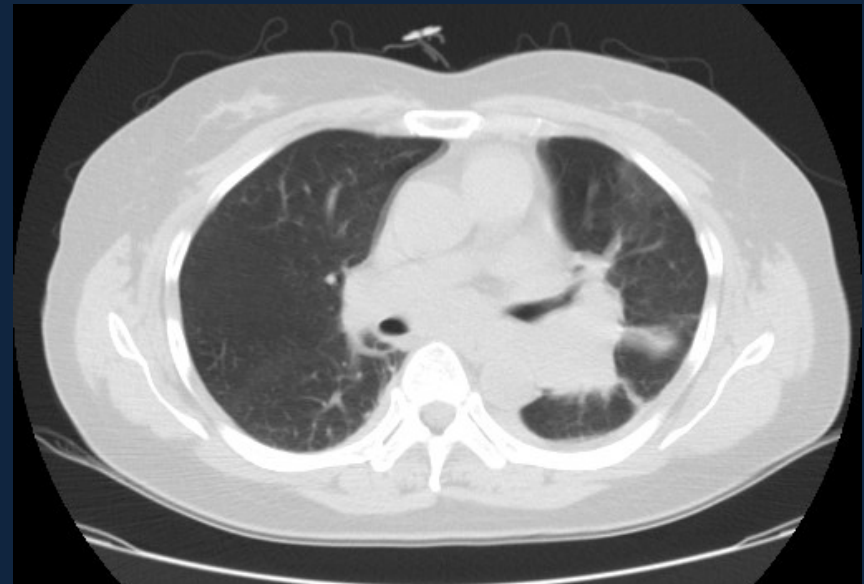
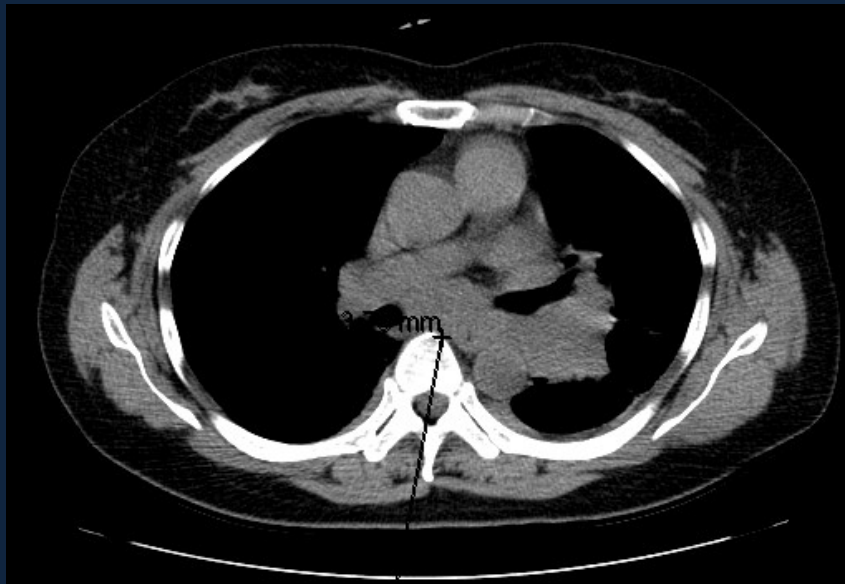
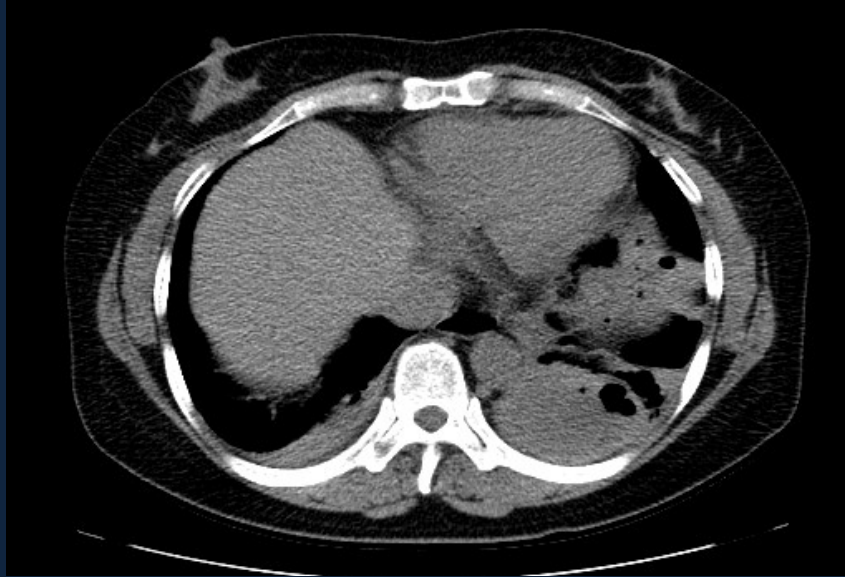
S> Lt. pleuritic chest pain, Cough, Fever

O> WBC 9890 $\Rightarrow\Rightarrow$ 14950

CRP 1.97 $\Rightarrow\Rightarrow$ 22.85

HRCT

HRCT



2013.12.09. HD#21

A>

- #1. NSCLC, adenocarcinoma, T3N2M1 stage IV
Progressive Disease
- #2. Pneumonia

P>

- #1. Recommend Crizotinib
2nd-line Tarceva (erlotinib) 으로 변경
Palliative RT to LLL mass, 3500cGy/14fxs
(2013.12.12~14.01.03)
- #2. Piperacillin-Tazobactam

2013.12.24 #HD 35

2nd line Erlotinib D16

S> Both leg pitting edema

O> D-Dimer 2.20 ug/ml

A>#1. r/o DVT

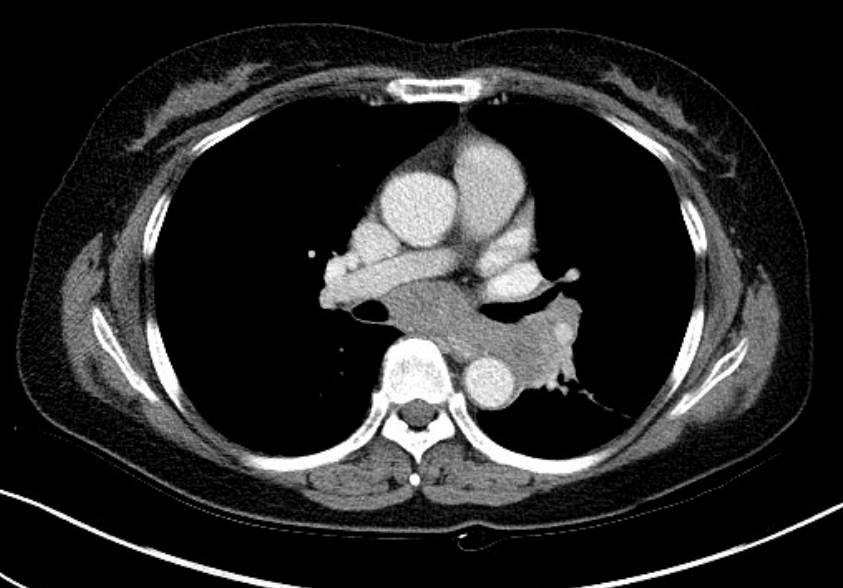
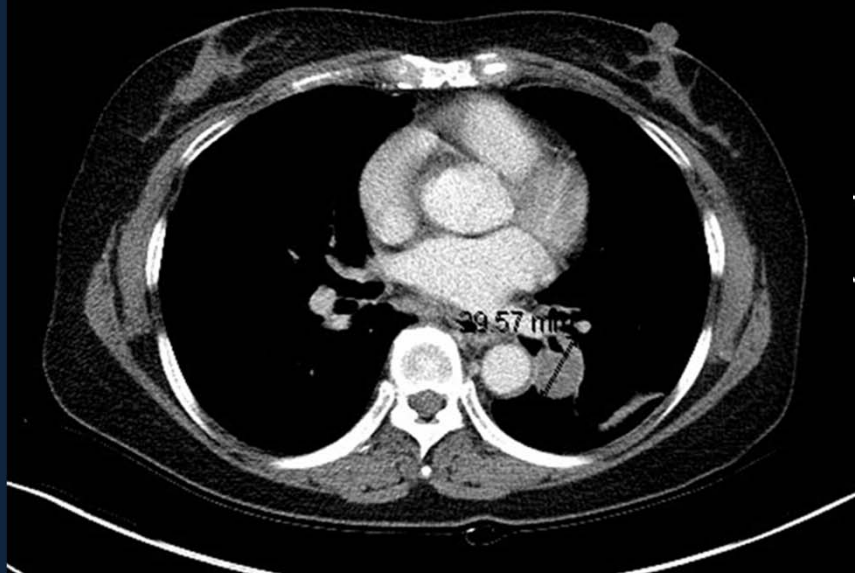
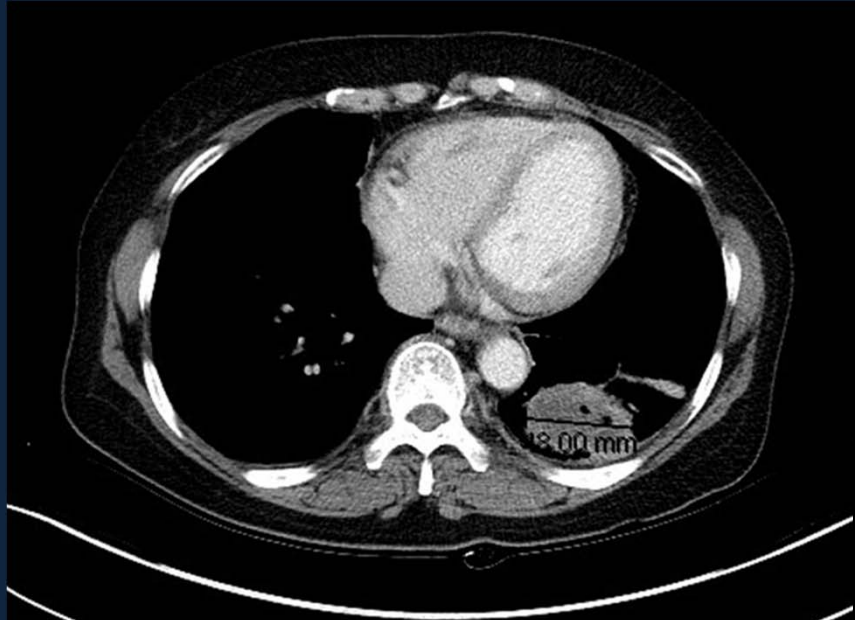
#2. NSCLC

P> Low extremity embolism CT (+)

Low extremity CT (+)



Chest CT



2013.12.30 #HD 41

Laparoscopic both salpingo-oopherectomy

Ovary, both, salpingo-oophorectomy:

METASTATIC ADENOCARCINOMA, from lung

size: right 5.7 x 3.0 x 2.5 cm

left 5.5 x 3.8 x 3.7 cm

ALK : Positive in the tumor cells

TTF-1 : Weak positive

Napsin A : Negative

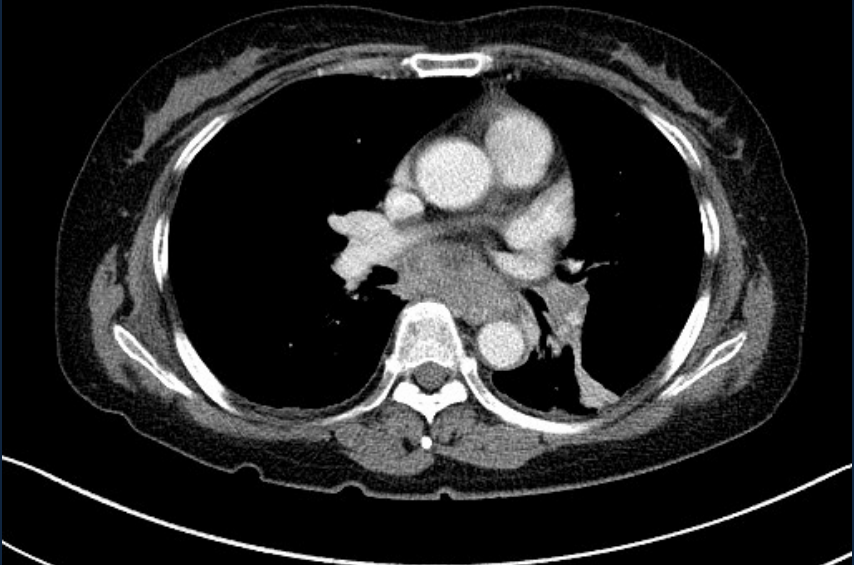
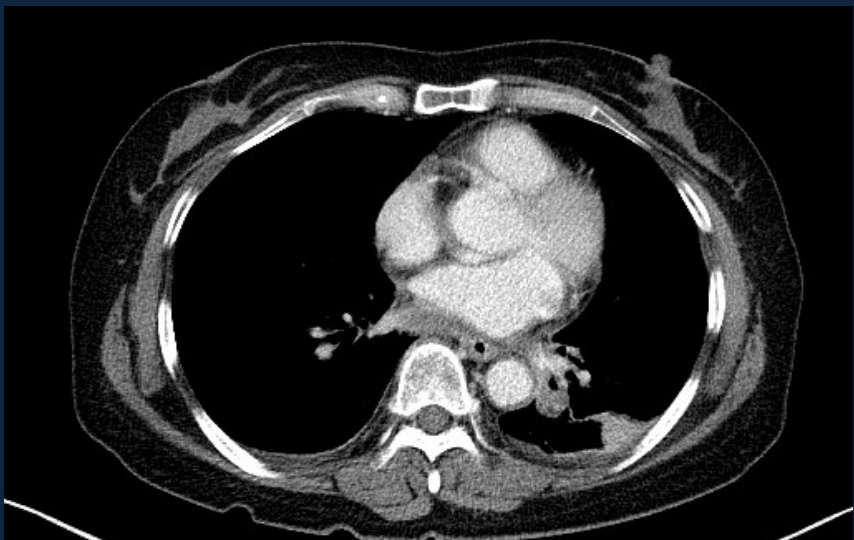
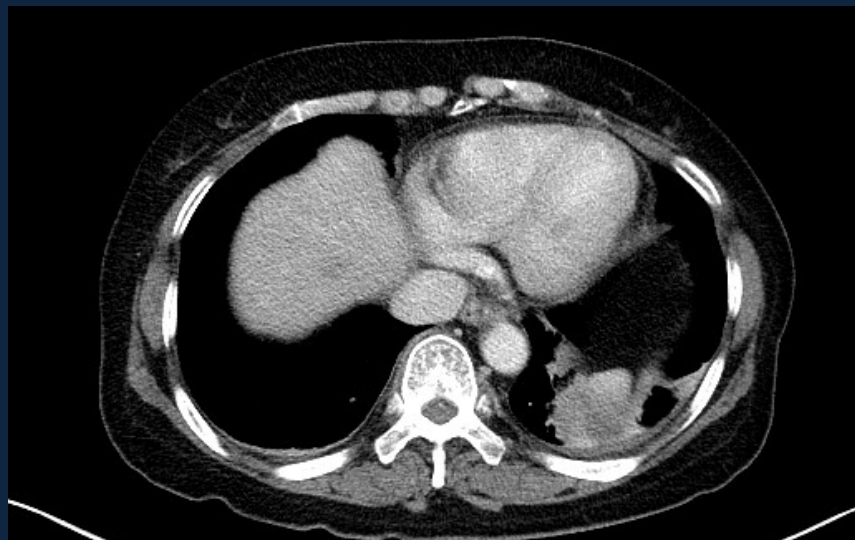
FISH for ALK translocation : Positive (2014.1.24)

2014.01.22 #HD 64

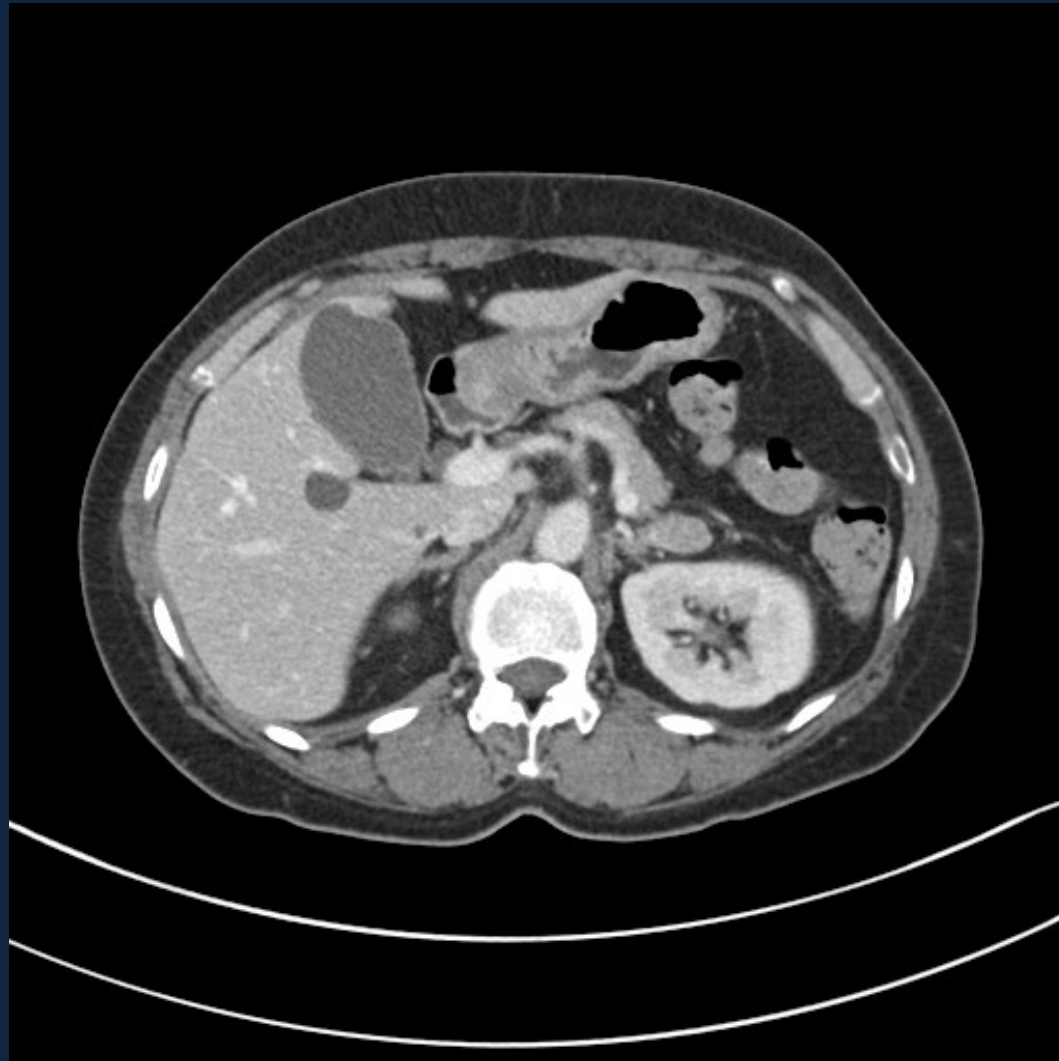
- S> Palliative RT to LLL : 2013.12.12~2014.01.03
- Palliative RT to brain : 2013.12.2~2013.12.13
- D/C Erlotinib d/t drug eruption
: 2013.12.9 ~2014.1.1

- O> Response evaluation

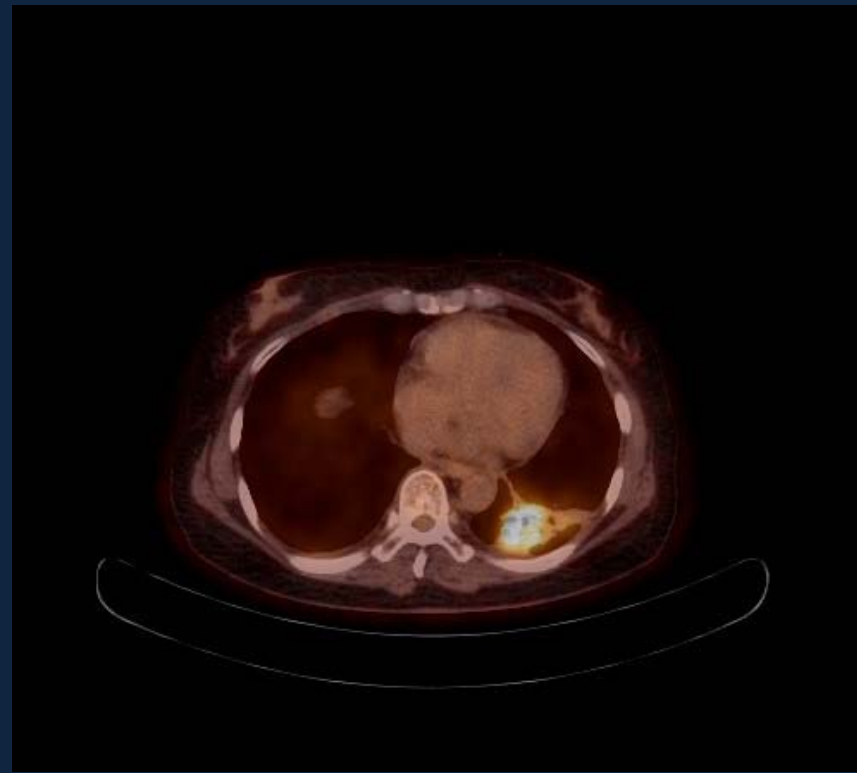
Chest CT



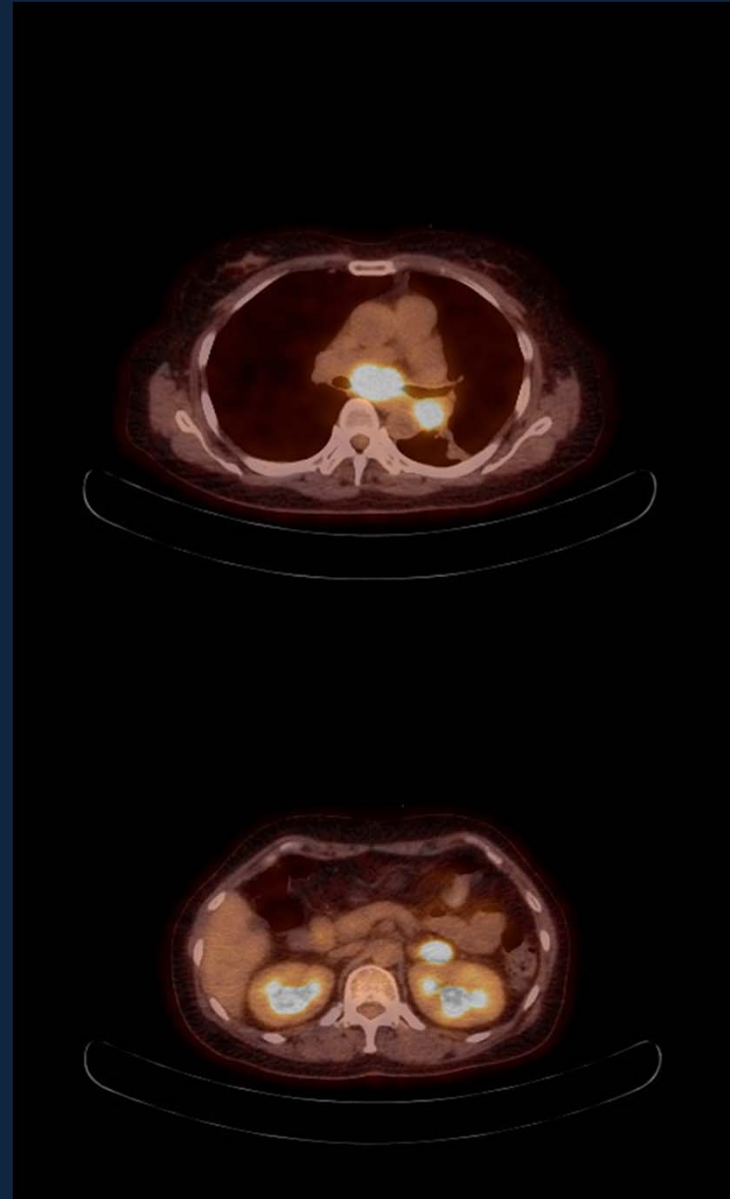
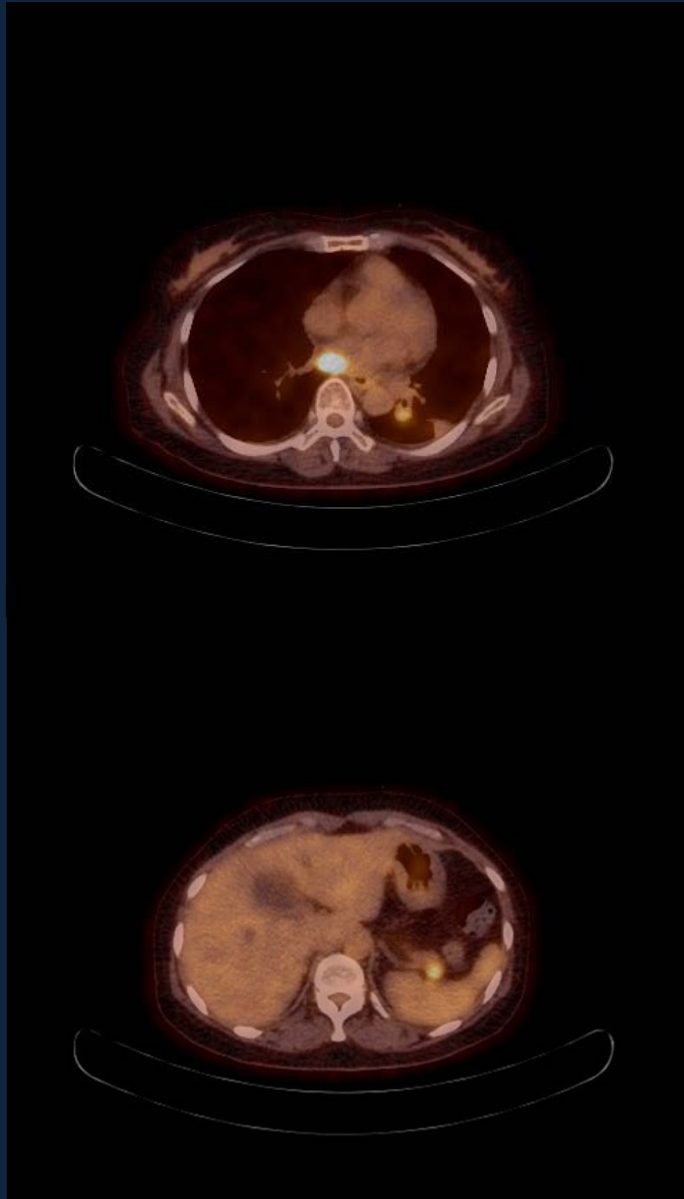
Abdomen CT



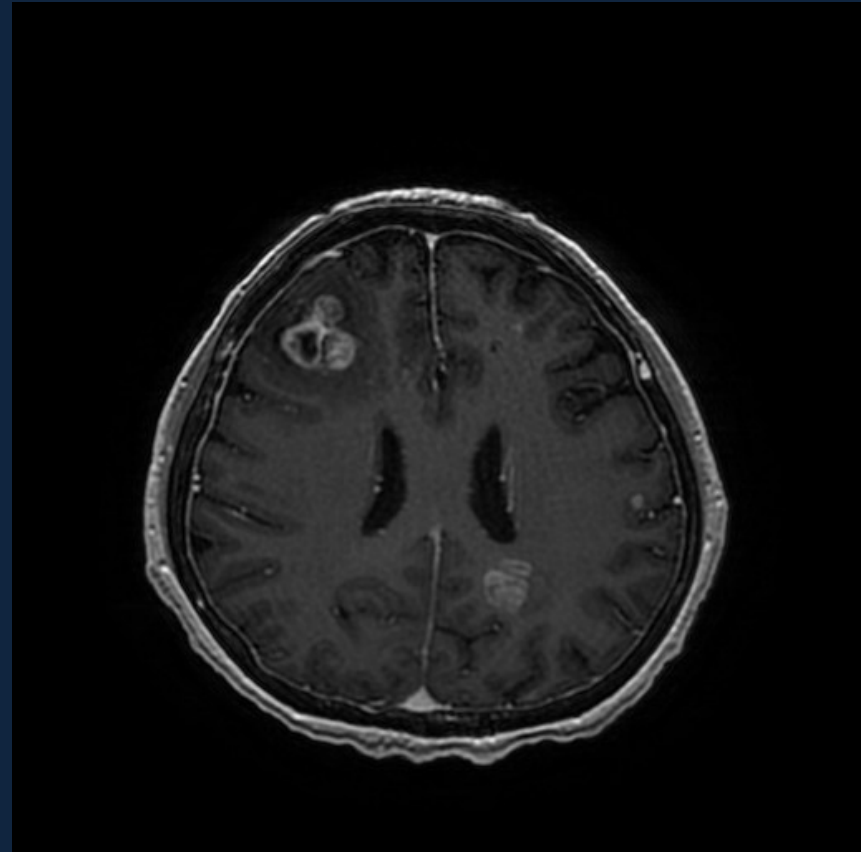
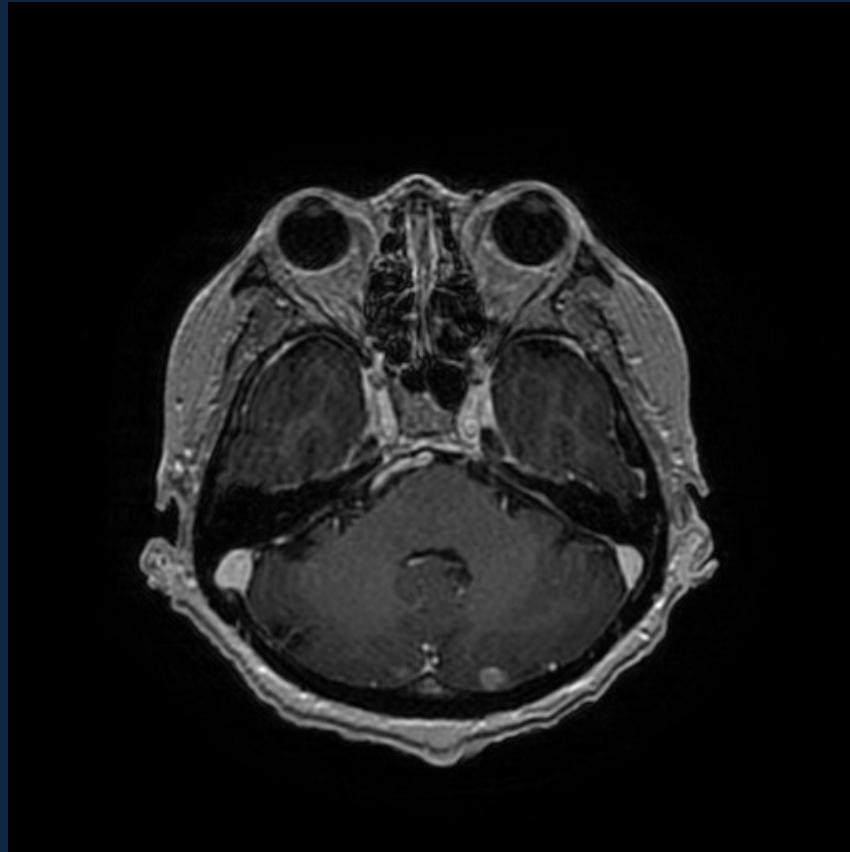
PET-CT



PET-CT



Brain MRI



2014.01.28 #HD 70

A> NSCLC, Adenocarcinoma, T3N2M1b stage IV
Progressive disease

P> Recommend Crizotinib
3rd line Gemcitabin/carboplatin 으로 변경

Summary

- Adenocarcinoma, T3N2M1b, stage IV
- ALK positive

- 1st line Alimta/ Cisplatin
- 2nd line Erlotinib, palliative radiation therapy
- 3rd line Gemcitabine/ Carboplatin
- Consider crizotinib

Review

EML4-ALK non-small cell lung cancer
Ovarian metastasis from lung cancer

Introduction

- Fusion of the anaplastic lymphoma kinase (ALK) with the echinoderm microtubule-associated protein-like 4 (EML4)
- Inversion on the short arm of Chromosome 2 [Inv(2)(p21p23)]
 - Identified in 2007 in Japanese non-small cell lung cancers
 - 5% of all NSCLC
 - Over 70,000 patients/year, worldwide

Clinical and molecular features of EML4-ALK NSCLC

1. Age of onset

Relatively younger, median age : 52 (range 21-82 yrs)

2. Smoking history

Never/former light (≤ 10 PY, quit ≥ 1 yr ago)

3. Outcomes with current NSCLC therapies

(Response rate, time to progression, overall survival)

Platinum-based chemotherapy : Similar

EGFR tyrosine kinase based therapy : Ineffective

4. Morphologic profile of ALK-rearranged NSCLC

Adenocarcinoma : 97% (acinar ; Asian, signet-ring cell ; Western)

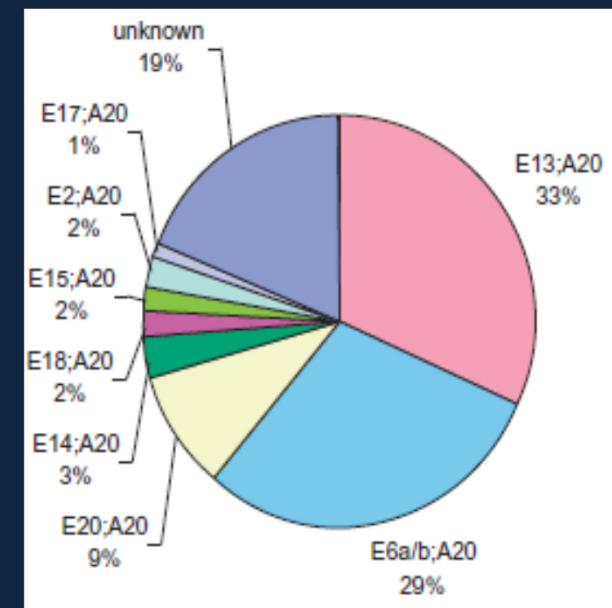
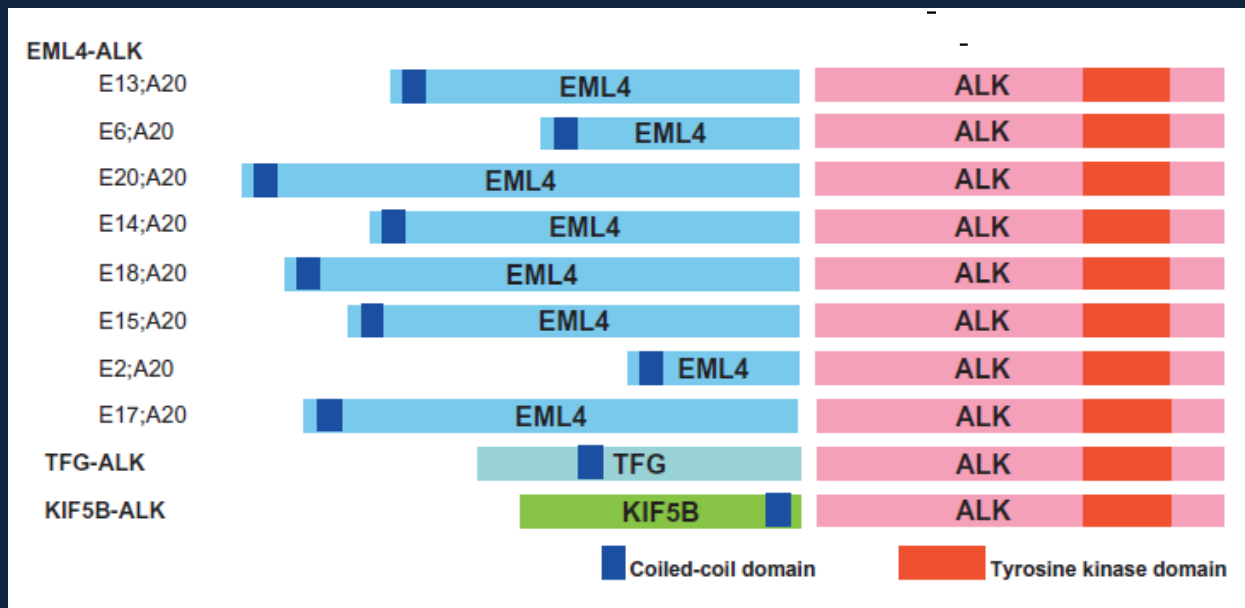
Abundant intracellular mucin & small, marginalised nuclei

Clinical and molecular features of EML4-ALK NSCLC

5. Variants of EML4-ALK and non-EML4 translocation partners

At least 11 variants

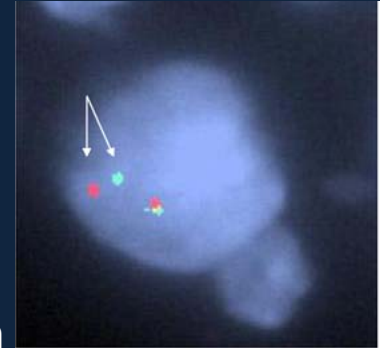
E13;A20 (33%) & E6a/b;A20 (29%) : m/c



Diagnosis of EML4-ALK NSCLC

1. FISH

- Gold standard assay
- Chromosome 2 : ALK gene , EML4 gene
 - Inversion : Orange and green signal break, Not inversion : Fusion
 - Positive : Break \geq 15%, Negative : Only fusion, Equivocal
- More specific and sensitivity
- Commercially available probe set (ALK-rearranged ALCLs)
- Not distinguish between the different EML-ALK fusion variants

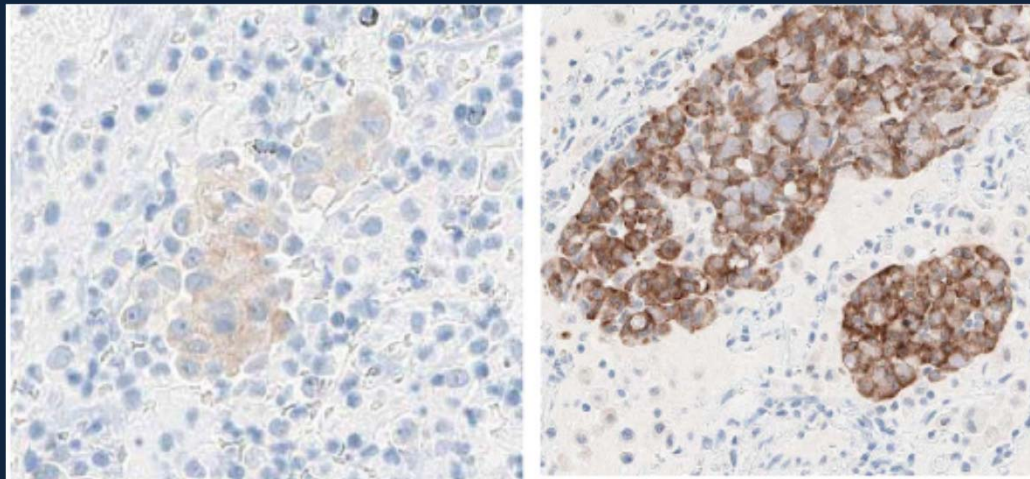


2. PCR

- Rapid, extreme sensitivity
- Multiplexed : variant EML4-ALK fusions
RNA extracted from formalin-fixed paraffin embedded (FFPE) tissue → highly degraded

3. Immunohistochemical (IHC) analysis

- Assay for tumor-specific antigen expression
- Novel antibodies for detecting ALK protein expression in FFPE (formalin-fixed paraffin embedded)
 - Highly sensitive and specific
 - Rapidly screen for patients harbouring an ALK translocation
 - Only approved test to diagnose ALK-positive NSCLC (U.S.A.)
: FISH



IHC analysis for ALK using the D5F3(Cell signaling Technology) Ab

ALK-targeted therapy in NSCLC

- **Crizotinib**
 - Orally bioavailable ALK inhibitor
 - Preferred as the initial therapy
 - G1-S phase cell cycle arrest & Induction of apoptosis
 - Phase 1 study : May 2006
- **Efficacy** : Crizotinib versus chemotherapy in advanced ALK-positive lung cancer (median follow-up of 12 months)
 - progression-free survival(Primary end point) : median 7.7 vs. 3.0 months
 - Response rate (radiologic review) : 65 versus 20 %
 - Median time to response : 6.3 vs. 12.6 weeks
 - Duration : 32 vs. 24 weeks
 - overall survival (median 20.3 vs. 22.8 months) : No significant difference
 - Subsequent treatment since 64 % of chemotherapy-treated patients had crossed over to crizotinib after progressing on chemotherapy

- **Toxicity**

- Visual disturbance , photophobia, blurred vision
- GI side effect : nausea, vomiting, diarrhea
- Hepatotoxicity
- Pneumonitis (1.6%)
- Cardiotoxicity : bradycardia, QT prolongation

Other approaches

- **Chemotherapy**

- Similar level of activity in ALK-positive patients with NSCLC compared to those with ALK-negative disease
- pemetrexed or a pemetrexed-based regimen : preferred
- ALK positive NSCLC (121) vs. ALK negative, EGFR-mutation negative (266)
 - Pemetrexed combined with either cisplatin or carboplatin
 - Significant Improvement in progression-free survival

- **EGFR tyrosine kinase inhibitors**

- No clinical responses to EGFR TKI (Erlotinib, Gefitinib)
- Similar response rate and time to survival : Wild type (EGFR & ALK (-))

Oncogene Status - Patterns of Metastatic Spread

- Method
 - University of Colorado
 - June 2008 ~ May 2011
 - Retrospective, Total 209 patients
 - NSCLC, stage IV (classified by TNM 7th edition)
 - Triple test (EGFR, KRAS, ALK gene rearrangement)
 - More than 1 positive result ⇒ Excluded
 - Classification
 - NSCLC histology, age at metastatic diagnosis, sex, smoking status, presence of metastatic disease

Results

Table 1. Characteristics of Patients

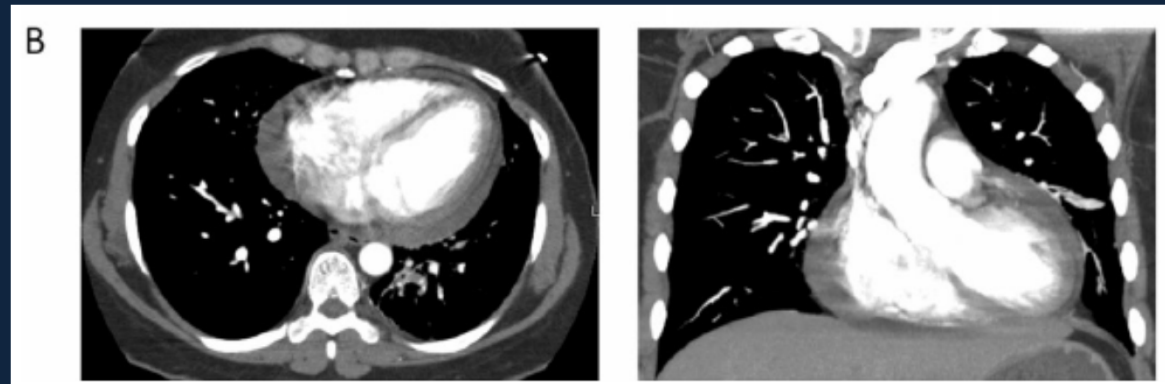
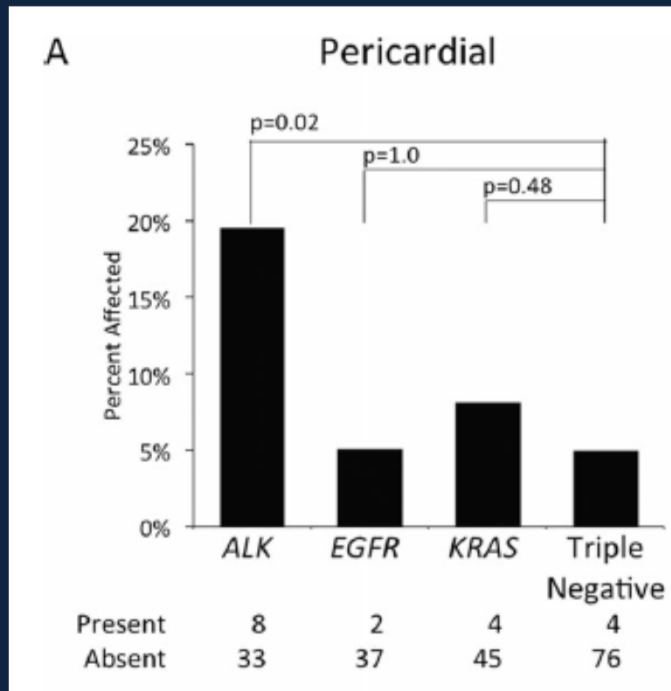
Characteristic	Molecular Cohort				Total
	ALK+	EGFR+	KRAS+	Triple Negative	
Total	41 (20)	39 (19)	49 (23)	80 (38)	209
Histology					
Adenocarcinoma	38 (93)	37 (95)	47 (96)	78 (98)	200 (96)
Large cell	1 (2)	0	2 (4)	0	5 (2)
Not otherwise specified	2 (5)	2 (5)	0	2 (3)	6 (3)
Staging					
Stage IV at diagnosis	35 (85)	28 (72)	39 (80)	63 (79)	165 (79)
Recurrent disease	6 (15)	11 (28)	10 (20)	17 (21)	44 (21)
Smoking history					
Never (<100 cigarettes)	31 (76)	22 (56)	6 ^a (12)	25 (31)	84 (40)
Light (≤10 pack-y)	5 (12)	5 (13)	1 (2)	9 (11)	20 (10)
Current/former	5 (12)	12 (31)	42 (86)	46 (58)	105 (50)
Mean pack-y	22.6	43.9	46.2	39.8	42
Sex					
Male	21 (51)	10 (26)	14 (29)	38 (48)	83 (40)
Female	20 (49)	29 (74)	35 (71)	42 (52)	126 (60)
Median age, years (range) ^b	51 (21-78)	62 (45-78)	59.5 (32-82)	62 (41-82)	59 (21-82)

ALK indicates anaplastic lymphoma kinase tyrosine kinase receptor; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma viral oncogene.

^a Includes 1 pipe smoker.

^b Age at diagnosis of metastatic disease.

Metastatic spread to the pericardium



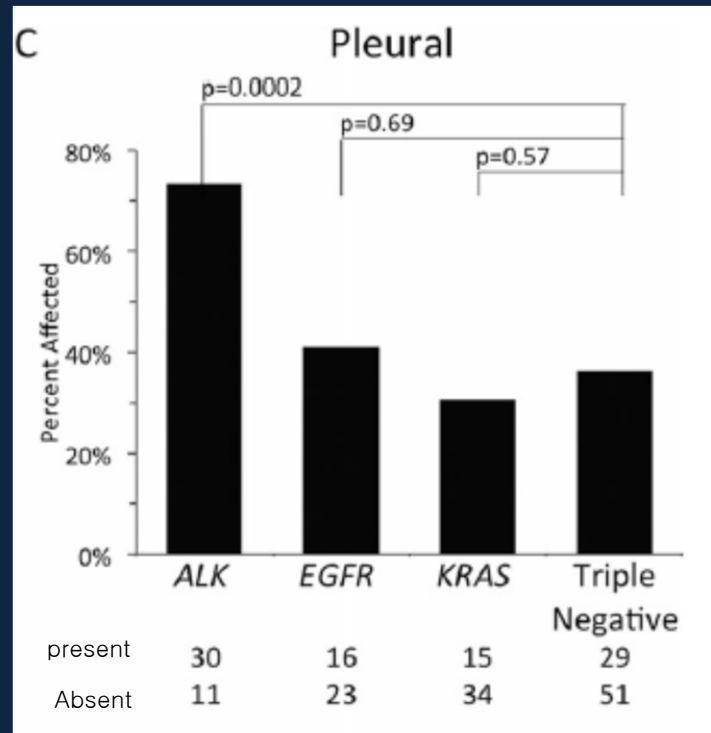
Triple negative vs.

ALK (OR = 4.61; 95% CI = 1.30, 16.37; P = .02)

EGFR (OR = 1.03; 95% CI = 0.18, 5.87; P = 1.0)

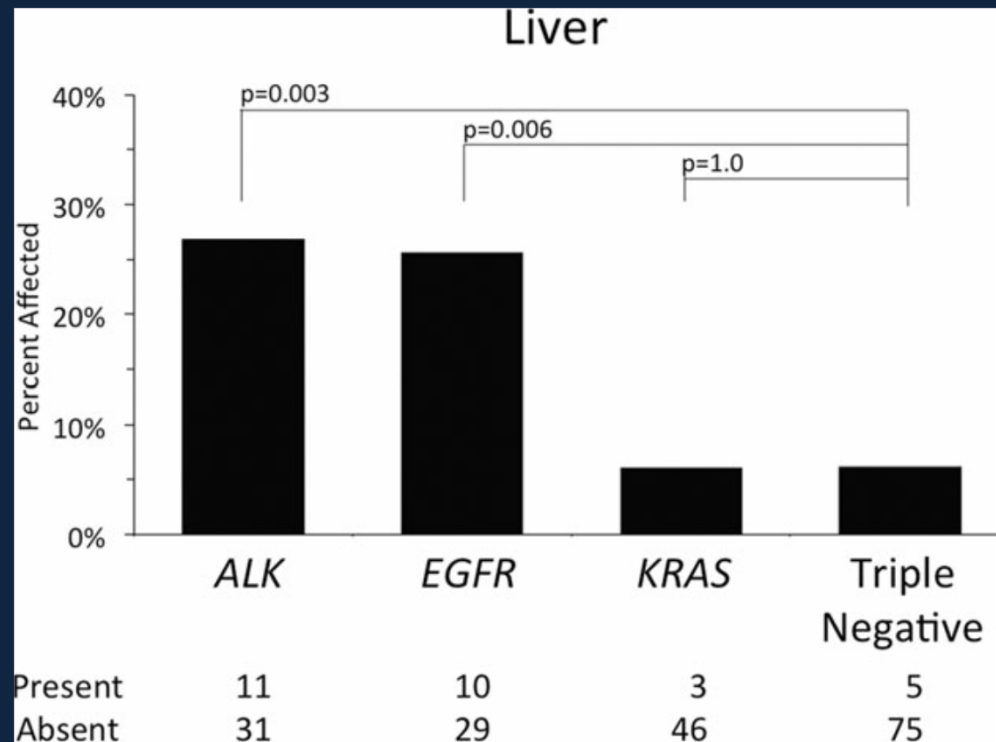
KRAS (OR = 1.69; 95% CI = 0.40, 7.09; P = .48)

Metastatic spread to the pleura



- Pleural disease : 43% (90/209)
- Triple negative vs.
ALK (OR = 4.80; 95% CI= 2.10, 10.97; P < .001)
EGFR (OR = 1.22; 95% CI = 0.56, 2.68; P = .69)
KRAS (OR = 0.78; 95% CI = 0.36, 1.66; P = .57)

Metastatic spread to the liver

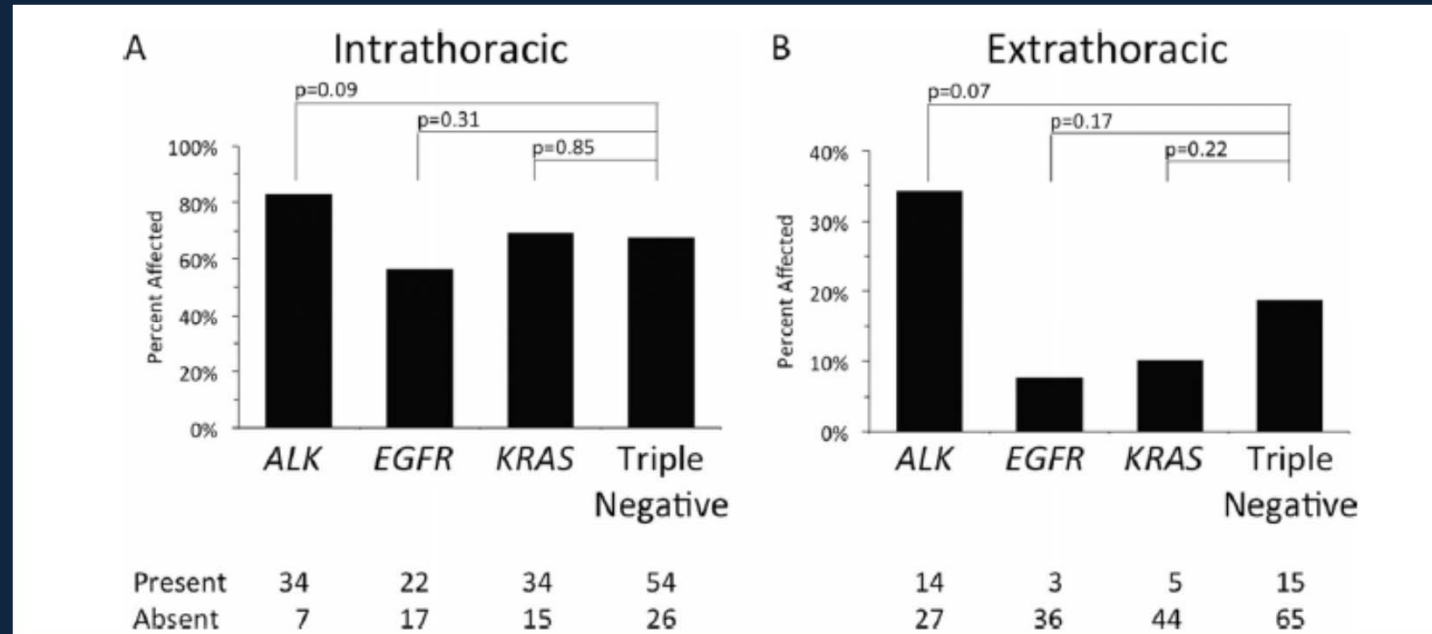


- Liver metastasis (vs. triple negative cohort)

ALK : (OR = 5.50; 95% CI = 1.76, 17.18; P = .003)

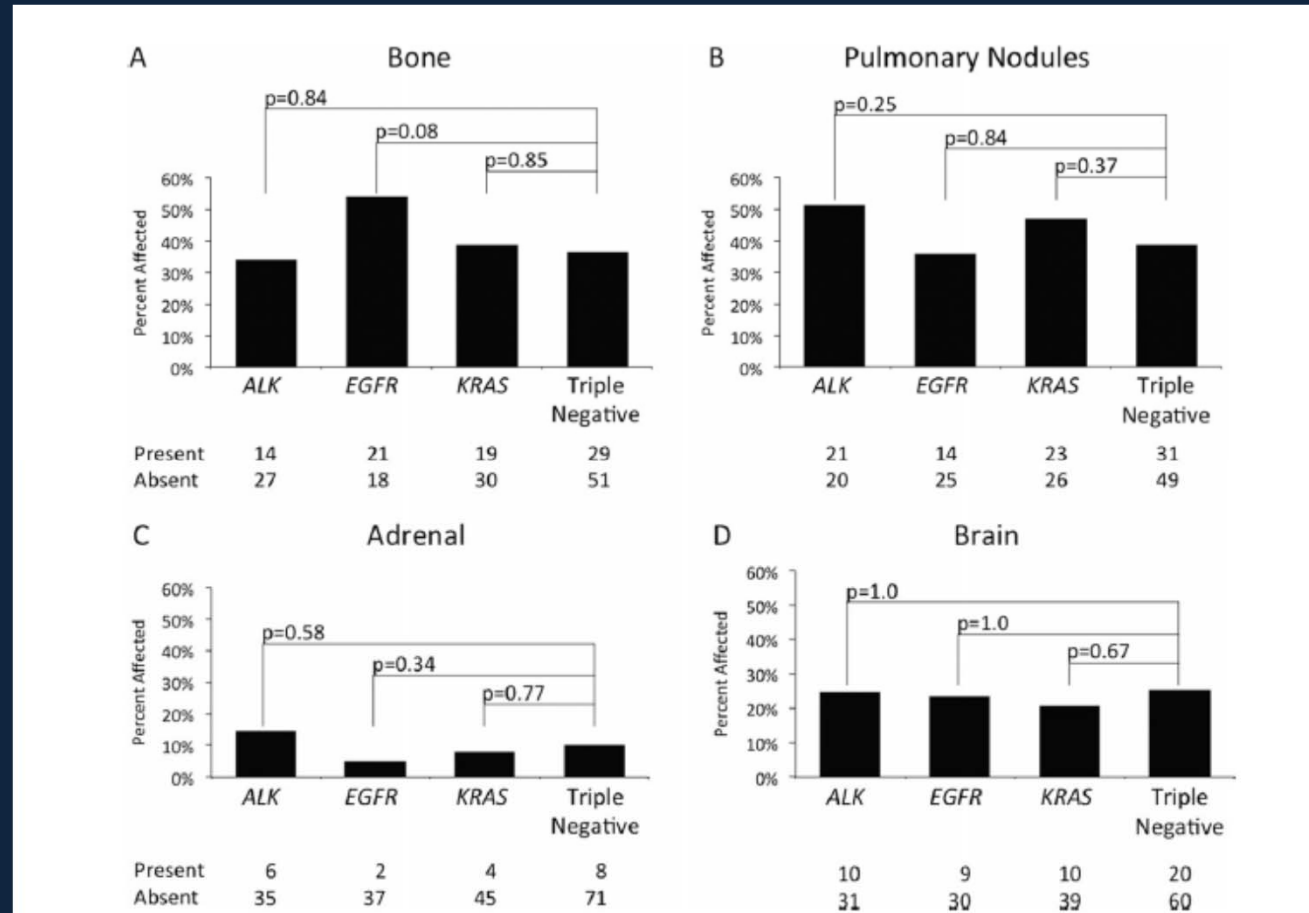
EGFR : (OR= 5.17; 95% CI= 1.63, 16.43; P =.006)

Metastatic spread to the LN



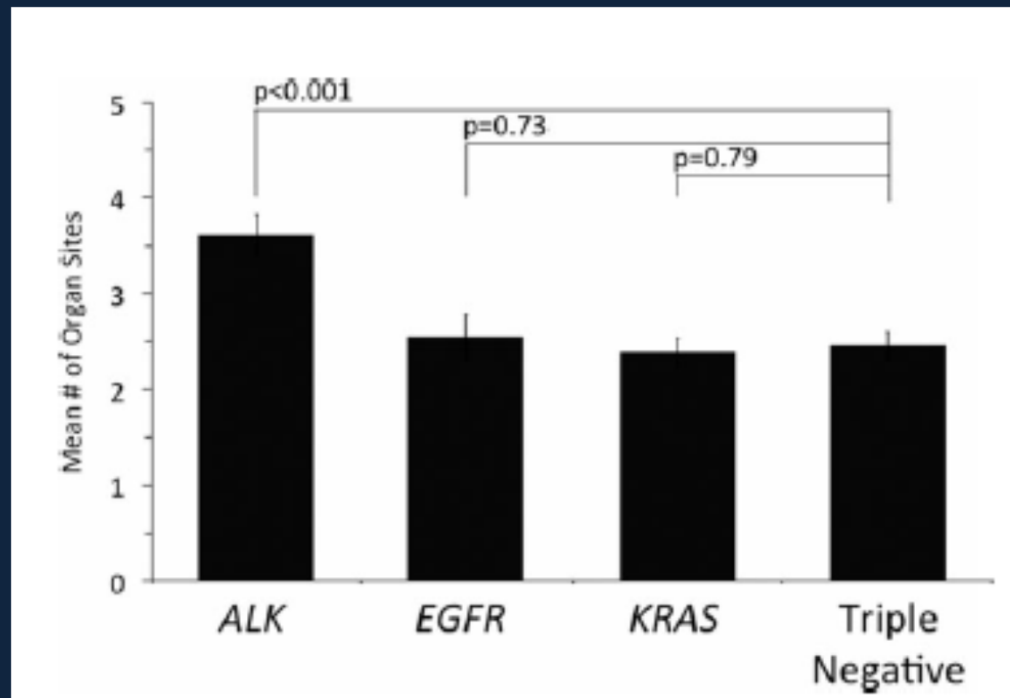
- Intrathoracic LN : 69% (144/209)
- Extrathoracic LN : 18% (37/209)
- ALK rearrangement vs. triple negative cohort spread to intrathoracic LN (OR =2.34; 95% CI = 0.92, 5.98; P = .09) & extrathoracic LN (OR =2.25; 95% CI = 0.96, 5.29; P =.07)

Metastatic spread to adrenal, bone or brain



No significant predilection

Number of metastatic disease sites



Triple negative cohort (mean = 2.5 sites) VS.

EGFR (mean = 2.5 sites, $P = .79$)

KRAS mutation cohorts (mean = 2.4 sites, $P = .72$)

ALK-positive cohort (mean = 3.6 sites, $P < .0001$)

Ovary metastasis

- Metastatic ovarian tumors
 - approximately 10-30% of all ovarian cancer
- The common primary sites
 - Colon, stomach, appendix, breast and pancreas
 - Gastric cancer (m/c, in korea)
- Lung cancer
 - 0.3~0.4% of metastatic ovarian tumors

Lung carcinoma metastatic to the ovary

- 32 cases, 26~76 years (mean, 47 years)
- History of prior lung cancer : 53% (17/32)
- Synchronously occurred : 31% (10/32)
- Detected before the lung cancer : 16% (5/32)

- Small cell lung cancer : 44% (14/32)
- Adenocarcinoma : 34% (11/32)
- Large cell carcinoma : 16% (5/32)
- Squamous cell carcinoma : 3% (1/32)

Summary

- EML4-ALK NSCLC represents a unique subset of NSCLC patients for whom ALK inhibitors may represent a very effective therapeutic strategy
- Crizotinib is superior to standard chemotherapy in patients with advanced NSCLC with ALK rearrangement.
- Dominant molecular oncogenes in NSCLC are associated with different biological behaviors manifesting as distinct patterns of metastatic spread at the time of diagnosis
 - Specific genetic pathways that mediate the sites of cancer metastasis