【2016 대한흉부종양외과학회 학술대회】

Radiologic Evaluation of LN in Lung Cancer (PET/CT)

아주대병원 핵의학과

이 수 진

PET/CT with F-18 fluorodeoxyglucose (FDG) is routinely recommended for staging work-up in the patients with lung cancer. The status of mediastinal or hilar LNs is the most important factors to determine TNM stage in lung cancer with localized or regional stage.

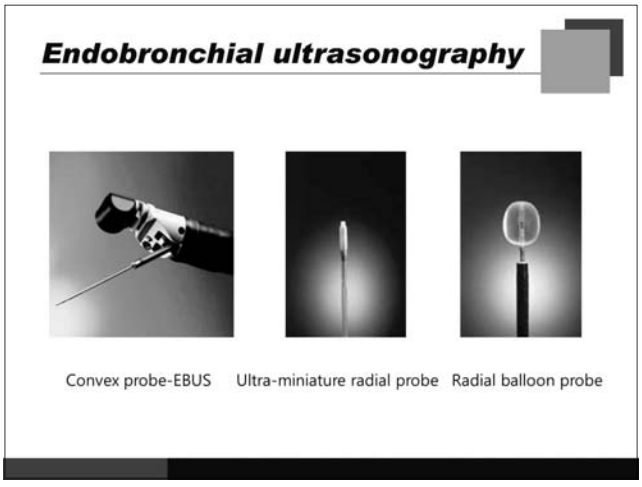
Previous studies have reported that FDG PET/CT shows low sensitivity and high specificity for nodal staging in lung cancer. One reason for false-negative findings is the insufficient resolution of PET for detecting microscopic lymph node metastasis. In addition, partial volume effect is one of the important factors in false negatives for small-sized LNs. One of the main reasons for false-positives is reactive lymph nodes containing inflammatory or granulomatous tissue with increased metabolic activity. It has been reported that tuberculosis, sarcoidosis, lung empyema, eosinophilic lung disease, aspergillosis, and other infections show high FDG uptake. The pattern of bilateral symmetric FDG uptake of mediastinal and hilar LNs with or without calcification is often encountered in our clinical practice. Nuclear medicine physicians can classify the uptake pattern as benign. However, metastatic LNs can be hidden among the concurrent infection or inflammation, which might be one of low sensitivity of PET/CT for nodal staging.

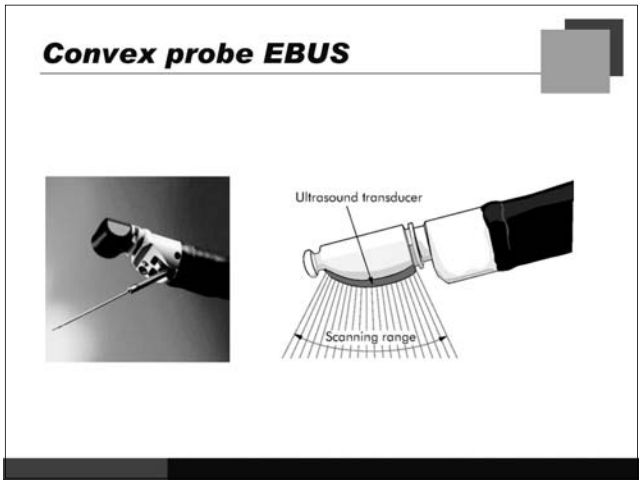
In this section, some cases are introduced to show the usefulness and limitations of FDG PET/CT for nodal staging. In addition, the current imaging techniques to overcome these limitations are also discussed.

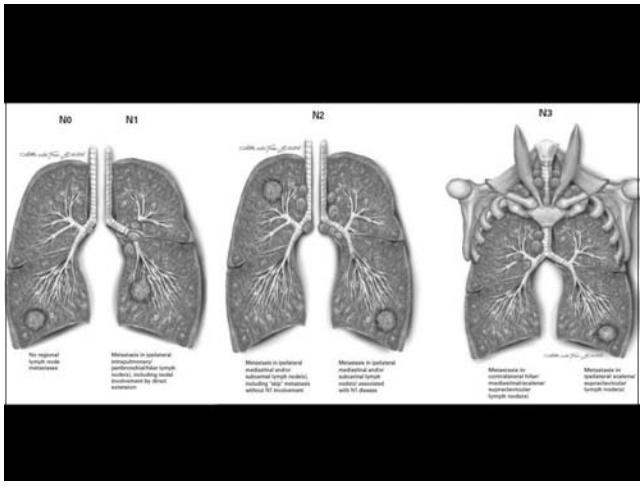
Endobronchial Sonography for Mediastinal Node Metastasis

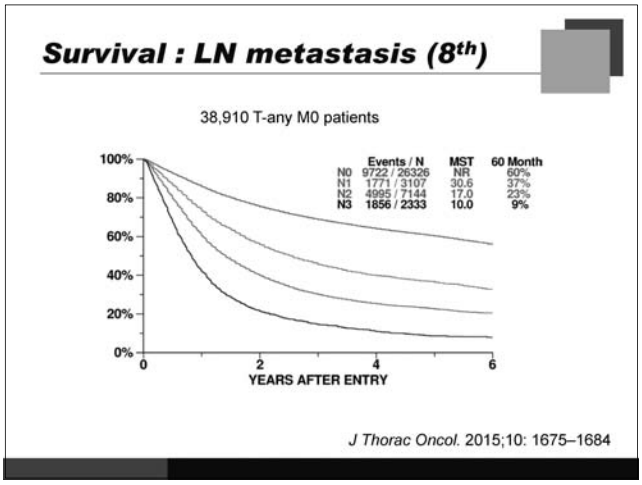
Division of Pulmonary and Critical Care Medicine, Department of Medicine,
Samsung Medical Center, Sungkyunkwan University School of Medicine

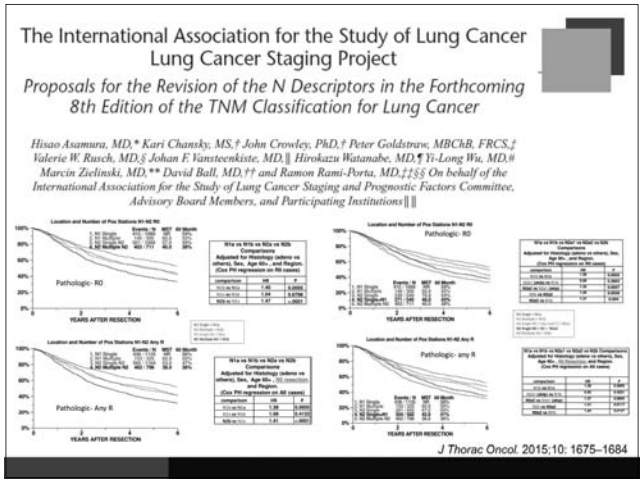
Kyung Jong Lee, MD

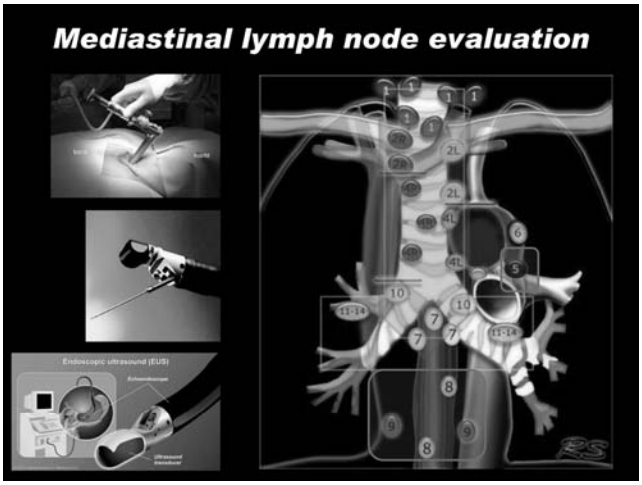


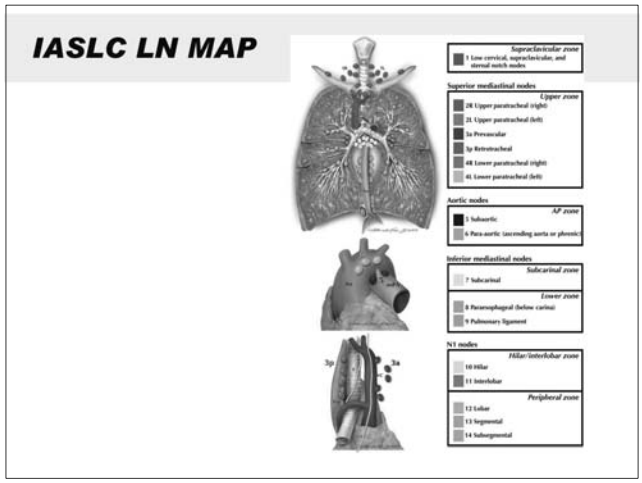


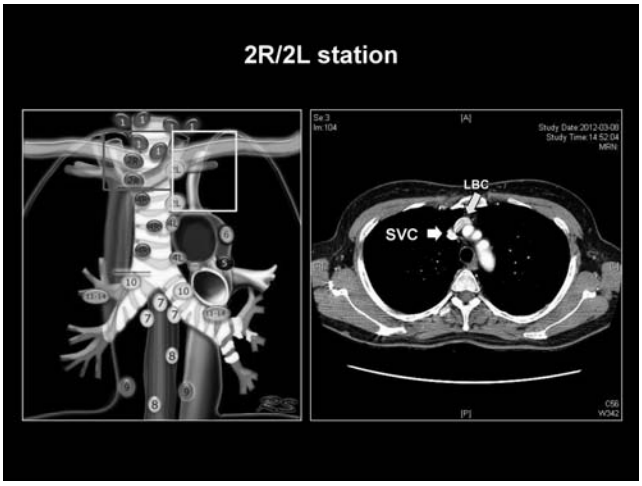


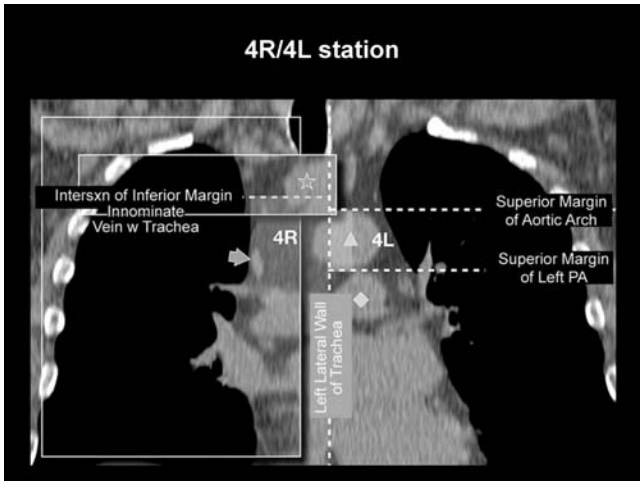


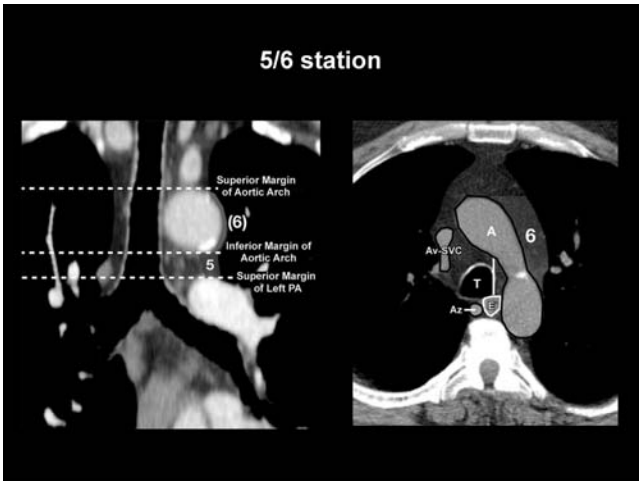

The International Association for the Study of Lung Cancer
Lung Cancer Staging Project
Proposals for the Revision of the N Descriptors in the Forthcoming 8th Edition of the TNM Classification for Lung Cancer
Hisao Asamura, MD,* Kari Chansky, MS,† John Crowley, PhD,† Peter Goldstraw, MBChB, FRCS,‡ Valerie W. Rusch, MD,§ Johan F. Vansteenkiste, MD,‖ Hirokazu Watanabe, MD,¶ Yi-Long Wu, MD,# Marcin Zielinski, MD,** David Ball, MD,†† and Ramon Rami-Porta, MD,‡‡§§ On behalf of the International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee, Advisory Board Members, and Participating Institutions‖‖
Pathologic- N0
Pathologic- any N
YEARS AFTER RESECTION
J Thorac Oncol. 2015;10: 1675–1684

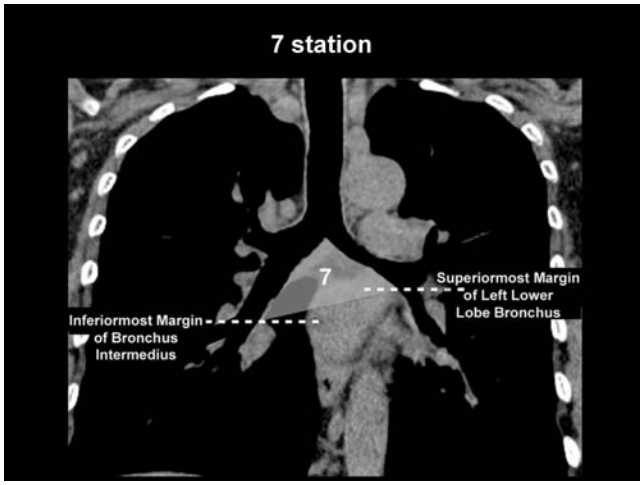

Mediastinal lymph node evaluation
Endoscopic ultrasound (EUS)

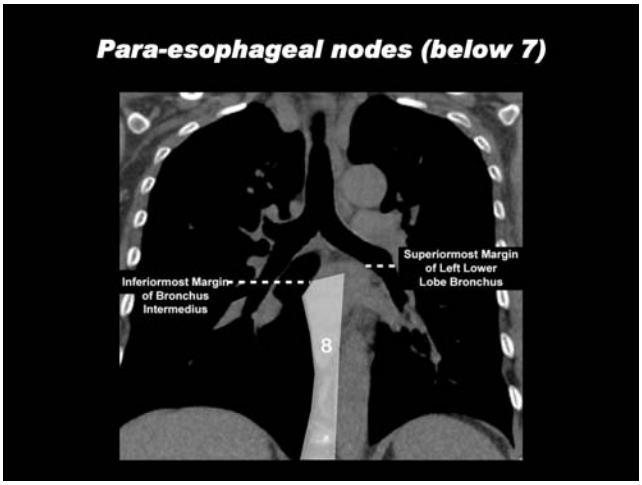

IASLC LN MAP
Supraclavicular zone
1 Low cervical, supraclavicular, and sternal notch nodes
Superior mediastinal nodes
Upper zone
2R Upper paratracheal (right)
2L Upper paratracheal (left)
3a Prevascular
3p Retrotracheal
4R Lower paratracheal (right)
4L Lower paratracheal (left)
Aortic nodes
AP zone
5 Subaortic
6 Para-aortic (ascending aorta or phrenic)
Inferior mediastinal nodes
Subcarinal zone
7 Subcarinal
Lower zone
8 Paraesophageal (below carina)
9 Pulmonary ligament
N1 nodes
Hilar/interlobar zone
10 Hilar
11 Interlobar
Peripheral zone
12 Lobar
13 Segmental
14 Subsegmental

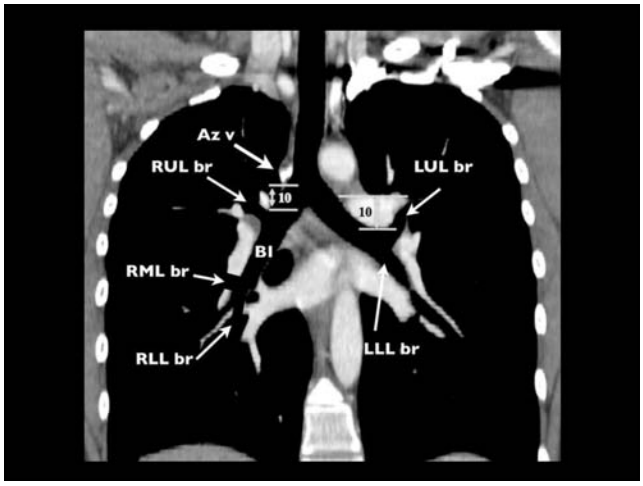

2R/2L station
LBC
SVC

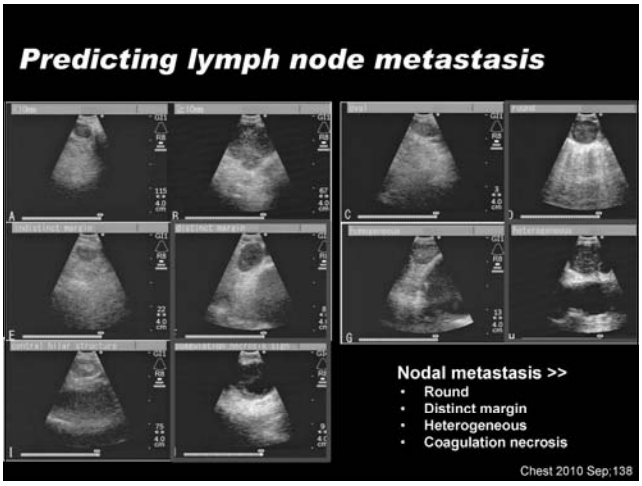

4R/4L station
Intersxn of Inferior Margin Innominate Vein w Trachea
4R
4L
Superior Margin of Aortic Arch
Superior Margin of Left PA
Left Lateral Wall of Trachea

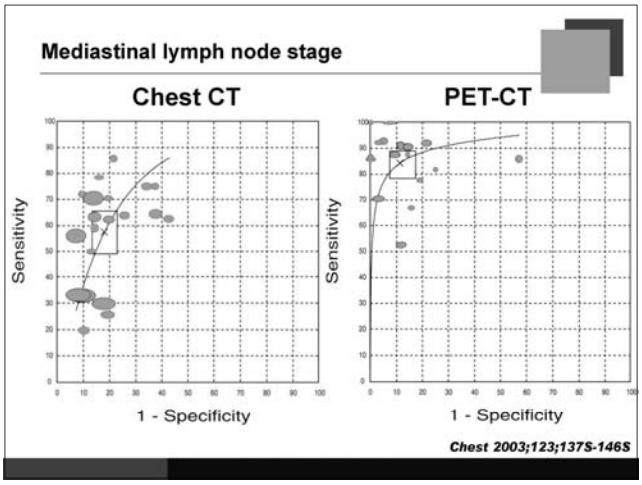

5/6 station
Superior Margin of Aortic Arch
(6)
Inferior Margin of Aortic Arch
5
Superior Margin of Left PA
A
6
Av-SVC
T
Az

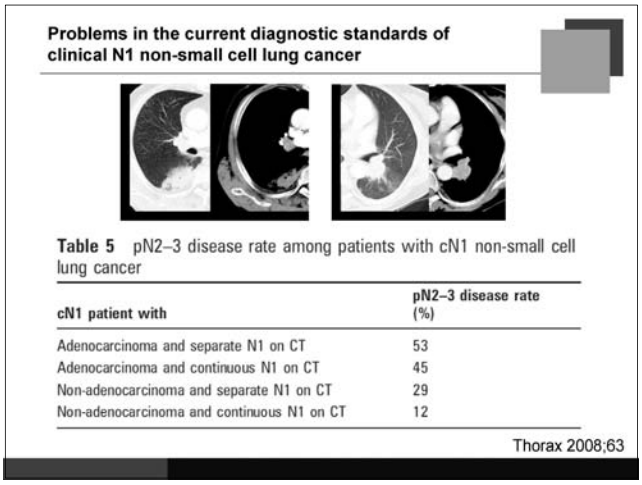

7 station
7
Superiormost Margin
of Left Lower
Lobe Bronchus
Inferiormost Margin
of Bronchus
Intermedius


Para-esophageal nodes (below 7)
Superiormost Margin
of Left Lower
Lobe Bronchus
Inferiormost Margin
of Bronchus
Intermedius
8


Az v
RUL br
10
LUL br
10
BI
RML br
RLL br
LLL br


Predicting lymph node metastasis
Nodal metastasis >>
Round
Distinct margin
Heterogeneous
Coagulation necrosis
Chest 2010 Sep;138


Mediastinal lymph node stage
Chest CT
PET-CT
Sensitivity
Sensitivity
1 - Specificity
1 - Specificity
Chest 2003;123;137S-146S


Problems in the current diagnostic standards of
clinical N1 non-small cell lung cancer
Table 5 pN2–3 disease rate among patients with cN1 non-small cell lung cancer
cN1 patient with
pN2–3 disease rate (%)
Adenocarcinoma and separate N1 on CT 53
Adenocarcinoma and continuous N1 on CT 45
Non-adenocarcinoma and separate N1 on CT 29
Non-adenocarcinoma and continuous N1 on CT 12
Thorax 2008;63

EBUS-TBNA of lymph nodes in the radiologically normal mediastinum on chest CT

* Chest CT : < 10 mm lymph node; sample range : 5-10 mm size LN

Location	Biopsied nodes	Nodes positive for cancer	Surgically confirmed diagnoses
2r	13	5 (38)	6 (46)
2l	16	2 (13)	2 (13)
4r	17	2 (12)	2 (12)
4l	17	3 (18)	3 (18)
7	13	1 (8)	1 (8)
10r	12	3 (25)	3 (25)
10l	10	1 (10)	1 (10)
11r	10	1 (10)	2 (20)
11l	11	4 (36)	4 (36)
Total	119	22 (19)	24 (20)

20%

19%

ERJ November 1, 2006 vol. 28 no. 5 910-914

FN after PET-CT in cI stage NSCLC

Abstract

OBJECTIVES: To assess the false-negative (FN) rate of positron emission tomography (PET)-chest computed tomography (CT) scan in clinical non-central cIA and cIB non-small-cell lung cancer (NSCLC) for mediastinal staging.

METHODS: Between January 2007 and December 2010, 402 patients with potentially operable NSCLC were assessed by thoracic CT scan and 18-fluoro-2-deoxy-o-glucose PET-CT for mediastinal staging and to detect extrathoracic metastases, of which 153 surgically treated patients (79 cIA and 74 cIB cases) were prospectively included in the study. Central tumours were excluded on the basis of CT scan criteria, defined as contact with the intrapulmonary main bronchi, pulmonary veins or the origin of the first segmental branches. CT scan was considered negative if lymph nodes were <1 cm at the smaller diameter. 18FDG PET-CT was considered negative when the high maximum standard uptake value (SUV_{max}) was <2.5. Non-invasive surgical staging was carried out in this group, and curative resection plus systematic mediastinal dissection was performed except in the event of unexpected oncological contraindication.

RESULTS: Composite non-invasive staging (CT scan, PET-CT) showed a negative predictive value (NPV) of 92% (CI 83.6–96.8) in the cIA group and 85% (CI 74–92) in the cIB group. There were 6 of 79 (7.6%) false-negatives (FNs) in cIA and 11 of 74 (14.8%) in cIB. Multilevel pN2 were detected in four cases, all of them in the cIB group. The most frequently involved N2 was subcarinal (two cases) in cIA and right lower paratracheal (R4) and seven (five cases) in cIB. Occult (pN2) lymph nodes were more frequent in tumour sizes ≥5 cm (pT2b, nine cases, four FNs, $P = 0.03$), pN1, adenocarcinoma [excluding minimally invasive adenocarcinoma (MIA) and lepidic predominant growth (LPA)] ($P = 0.029$) and female patients, but no other risk factors for mediastinal metastases were identified (age, clinical stage, tumour location, central or peripheral, $P > 0.05$). Multilevel pN2 was significantly more frequent in the cIB group ($P < 0.03$). In pT ≤ 1 cm (T1a), NPV was significantly better (NPV = 100%, $P < 0.05$) than the other subgroups studied (IA > 1 cm and IB).

CONCLUSIONS: Composite results for non-invasive mediastinal staging (CT scan, PET-CT) showed 11% of FNs in cI stage (7.6% in non-central cIA and 14.8% in cIB). In tumours ≤1 cm, NPV makes surgical staging unnecessary. In women with adenocarcinoma and non-central cIB, however, the high FN rate makes invasive staging necessary, particularly in pT2b to decrease the incidence of unexpected pN2 in thoracotomy.

European Journal of Cardio-Thoracic Surgery 42 (2012)

False negative of PET-CT

- Rate : 8-18% (pooled incidence)
- PET-CT negative adenocarcinoma
- Incidence of pN2 disease in cN0-1 patients 11%

Eur J Cardiothorac Surg 2016

Results of CP-EBUS

Table 3—*Diagnostic Values of Integrated PET/CT Scanning and EBUS-TBNA in the Detection of Mediastinal Metastases*

Patient Groups and Procedures	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Accuracy, %
Total (n = 117)					
PET/CT scan	70.0	59.5	37.5	85.2	62.4
EBUS-TBNA	90.0	100	100	96.7	97.4
p Value	0.052	< 0.001	< 0.001	0.011	< 0.001
Adenocarcinoma (n = 55)					
PET/CT scan	70.0	60.0	50.0	77.8	63.6
EBUS-TBNA	90.0	100	100	94.6	96.4
p Value	0.114	< 0.001	< 0.001	0.044	< 0.001
Squamous cell carcinoma (n = 53)					
PET/CT scan	85.7	56.5	23.1	96.3	60.4
EBUS-TBNA	85.7	100	100	97.9	98.1
p Value	1.0	< 0.001	< 0.001	0.689	< 0.001

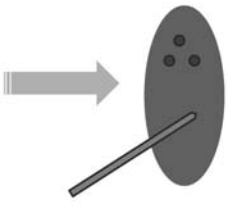
CHEST 2009; 135:1280–1287

EBUS가 Mediastinoscopy 대체가능한가?

TABLE 5. Patients with false-negative results of mediastinal staging

Patient	Nodal station	Diameter of nodes short/long axis (mm)	Description of case
Staged incorrectly by both EBUS and mediastinoscopy			
1	4R	5/10	4R positive on final pathology
2	6	15/18	6 positive on final surgical staging
3	5	5/5	5, 6 positive on final surgical staging
	6	10/12	
4	5	5/5	5 positive on final surgical staging
Staged incorrectly by EBUS			
1	7	3/8	Micrometastasis
2	4L	3/3	Micrometastasis, not sampled by EBUS
3	2R	3/3	Not sampled by EBUS
4	2R	5/10	N3 lymph node not sampled by EBUS
5	4R	3/8	Micrometastasis
6	7	12/15	Micrometastasis, PET negative
Staged incorrectly by mediastinoscopy			
1	4L	12/18	Enlarged and hard node on mediastinoscopy
2	4L	5/8	Grossly normal on mediastinoscopy
3	4R	15/18	Enlarged node on mediastinoscopy
4	7	5/5	Grossly normal on mediastinoscopy
5	4L	3/5	4R (N2) positive, 4L (N3) negative on mediastinoscopy
6	7	10/12	Grossly normal on mediastinoscopy
7	4L	3/3	2R, 4R (N2) positive, 4L (N3) negative on mediastinoscopy

EBUS, Endobronchial ultrasound; *PET*, positron emission tomography.



J Thorac Cardiovasc Surg 2011;142:1393-400

EBUS vs Mediastinoscopy at SMC

TABLE 3. Diagnostic Performance of EBUS-TBNA and Mediastinoscopy on a Per-Person Basis ($n = 127$)

	EBUS-TBNA	Mediastinoscopy	p Value
Sensitivity	66/75 (88.0) [80.6–95.4]	61/75 (81.3) [72.5–90.2]	0.0039
Specificity	52/52 (100) [100–100]	52/52 (100) [100–100]	NA
Accuracy	118/127 (92.9) [88.5–97.4]	113/127 (89.0) [83.5–94.4]	0.0001
PPV	66/66 (100) [100–100]	61/61 (100) [100–100]	NA
NPV	52/61 (85.2) [76.3–94.1]	52/66 (78.8) [68.9–88.7]	0.0018

Data are presented as numbers/total numbers (%) [with 95% confidence intervals].
EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; NA, not applicable; NPV, negative predictive value; PPV, positive predictive value.

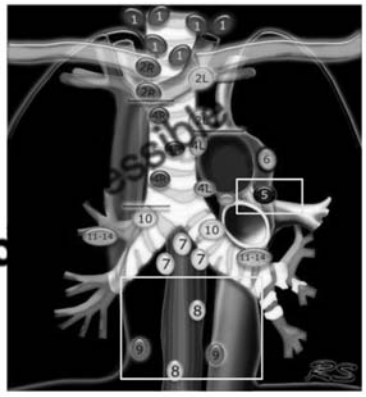
TABLE 4. Diagnostic Sensitivities of EBUS-TBNA and Mediastinoscopy on an Individual Lymph Nodal Station Basis

	EBUS-TBNA	Mediastinoscopy	p Value
2R ($n = 67$)	10/18 (55.6) [32.6–78.5]	11/18 (61.1) [38.6–83.6]	0.8243
2L ($n = 12$)	0/3 (0) [0–0]	3/3 (100) [100–100]	0.0833
4R ($n = 125$)	34/41 (82.9) [71.4–94.4]	33/41 (80.5) [68.4–92.6]	0.1668
4L ($n = 111$)	17/21 (81.0) [64.2–97.7]	15/21 (52.4) [31.0–73.7]	0.0270
7 ($n = 126$)	33/40 (82.5) [70.7–94.3]	30/40 (75.0) [61.6–88.4]	0.0614

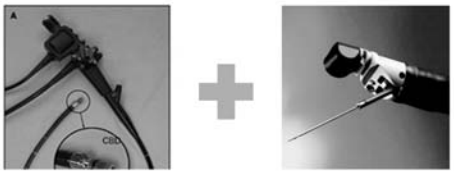
EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration.

Journal of Thoracic Oncology,February 2015

Limitation of EBUS

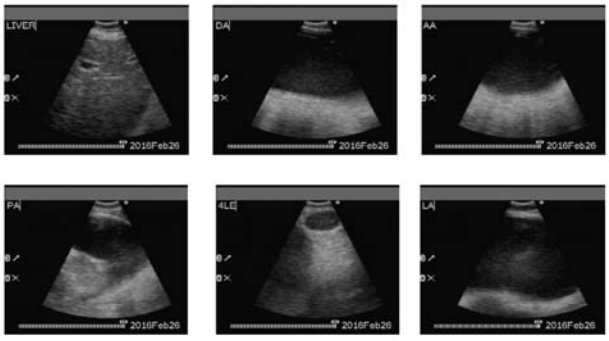


Combination of EUS-FNA and EBUS-TBNA



- **Limitation of this combination procedure**
  - Expert endoscopist
  - Expenesive equipment
  - Incresed medical costs
  - Delayed time for stage work-up

Landmark of EUS using EBUS scope



JAMA Mediastinoscopy vs Endosonography for Mediastinal Nodal Staging of Lung Cancer

A Randomized Trial

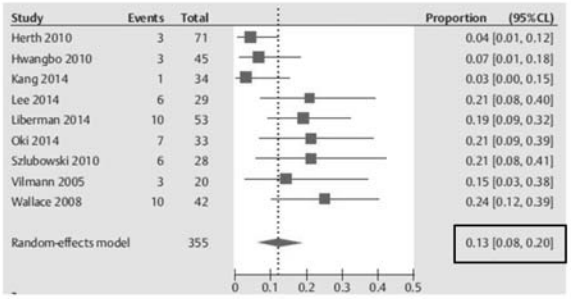
Table 2. Diagnostic Performance[a]

Nodal Invasion, N2/N3	No./Total No. (%) [95% Confidence Interval] Surgical Staging (n = 118)	Endosonography and Surgical Staging (n = 123)	*P* Value
Sensitivity	41/52 (79) [66-88]	62/66 (94) [85-98]	.02
Negative predictive value	66/77 (86) [76-92]	57/61 (93) [84-97]	.18

Combined endosonography and surgical staging reduced unnecessary thoracotomies from 18% to 7%
Negative endosonography results : 20 % lymph node metastasis
Adding a confirmatory mediastinoscopy → missed nodal metastasis to 5%

JAMA. 2010;304(20):2245-2252

Increase in sensitivity of 13 % (95 %CI 8 %–20 %) for the combined approach compared with EBUS-TBNA alone



Endoscopy 2015; 47: 545–559

Combined endobronchial and esophageal endosonography for the diagnosis and staging of lung cancer: European Society of Gastrointestinal Endoscopy (ESGE) Guideline, in cooperation with the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS)

ESGE ERS EUROPEAN RESPIRATORY SOCIETY every breath counts

For mediastinal nodal staging in patients with suspected or proven non-small-cell lung cancer (NSCLC) with abnormal mediastinal and/or hilar nodes at CT and/or PET, endosonography is recommended over surgical staging as the initial procedure.

The combination of EBUS-TBNA and endoscopic EUS-FNA or EUS-B-FNA scope, is preferred over either test alone

For mediastinal nodal staging in patients with suspected or proven non-small-cell peripheral lung cancer without mediastinal involvement at CT or CT-PET, we suggest that EBUS-TBNA and/or EUS-(B)-FNA should be performed before therapy, provided that one or more of the following conditions is present:
(i) enlarged or fluorodeoxyglucose (FDG)-PET-avid ipsilateral hilar nodes;
(ii) primary tumor without FDG uptake;
(iii) tumor size ≥3cm

Endoscopy 2015; 47: 545–559

Interpretation of false negative outcomes

Lymph node scoring system for predicting malignancy in patients no found malignancy by EBUS-TBNA

	0	1	2
Echogenicity	Homogeneous		Heterogeneous
SUV	≤4	>4	
Lymph SUV%	≤40	41-60	>60

- Total score : 0~5
- Low risk : 0-1 ➡ NPV 97.9%
- High risk ≥ 2

JTO 2015

Endosonography for lung cancer staging: predictors for false-negative outcomes

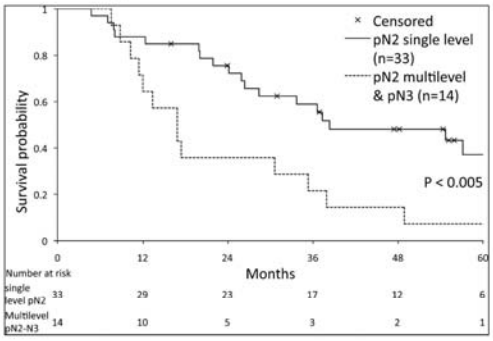
Mehrdad Tale
Johannes Nab

Predicted probabilities of false negative endosonography results

	EBUS	EUS	EUS/EBUS
Peripheral tumor, no nodal enlargement on CT, PET N0/N1	0.04253	0.032	0.00987
Peripheral tumor, nodal enlargement on CT, PET N0/N1	0.12542	0.078	0.04656
Peripheral tumor, no nodal enlargement on CT, PET N2/N3	0.15611	0.119	0.06959
Central tumor, no nodal enlargement on CT, PET N0/N1	0.14059	0.131	0.03423
Peripheral tumor, nodal enlargement on CT, PET N2/N3	0.37393	0.255	0.26823
Central tumor, nodal enlargement on CT, PET N0/N1	0.34562	0.277	0.14798
Central tumor, no nodal enlargement on CT, PET N2/N3	0.40523	0.377	0.21012
Central tumor, nodal enlargement on CT, PET N2/N3	0.68748	0.606	0.56589

Kaplan–Meier survival curve: single versus multilevel persistent N2 disease

After induction therapy



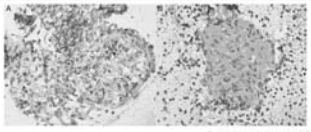
Decaluwé H et al. Eur J Cardiothorac Surg 2009;36:433-439

Comparison between endobronchial ultrasound-guided transbronchial needle aspiration and ^{18}F-fluorodeoxyglucose positron emission tomography in the diagnosis of postoperative nodal recurrence in patients with lung cancer

Takayoshi Yamamoto[a], Yuichi Sakairi[a], Takahiro Nakajima[a,*], Hidemi Suzuki[a], Tetsuzo Tagawa[a], Takekazu Iwata[a], Teruaki Mizobuchi[a], Shigetoshi Yoshida[a], Yukio Nakatani[b] and Ichiro Yoshino[a]

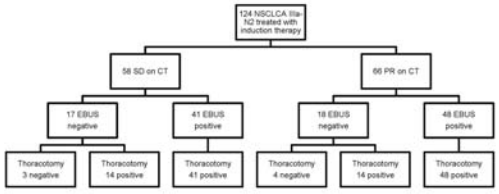
Table 3: Pathological results of EBUS-TBNA and FDG-PET

n = 40	EBUS-TBNA (+)	EBUS-TBNA (-)
FDG-PET (+)	23	14
FDG-PET (-)	1	2



European Journal of Cardio-Thoracic Surgery 47 (2015)

Endobronchial Ultrasound With Transbronchial Needle Aspiration for Restaging the Mediastinum in Lung Cancer



Criteria	Tumor response outcome (%)	
	PR (n=66)	SD (n=58)
Sensitivity	77	75
Specificity	100	100
PPV	100	100
NPV	22	18
Accuracy	79	76

J Clin Oncol. 2007

The Efficacy of Restaging Endobronchial Ultrasound in Patients With Non-Small Cell Lung Cancer After Preoperative Therapy

Neoadjuvant therapy
- Chemoradiation 31 (97%)
- Chemotherapy only 1 (3%)

Performance of Endobronchial Ultrasound as a Restaging Tool

Results of EBUS	Results of Surgery		
	Positive	Negative	
Positive	True positive N = 3	False positive N = 0	PPV 100%
Negative	False negative N = 3	True negative N = 21	NPV 88%
	Sensitivity = 50%	Specificity = 100%	Accuracy = 89%

Ann Thorac Surg. 2014 Sep

Comparison for restaging

Restaging after induction theray of lung cancer

		n	Sensitivity(%)	Specificity(%)	Accuracy(%)
PET	8 trials	380	59	85	
MES	3 trials	204	71	100	81
EBUS	2 trials	185	67-76	86-100	77-80

Summary

- EBUS ; The first choice of mediastinal staging in lung cancer
- Combination of EBUS & EBUS using EBUS scope showed better diagnostic performance
- Indication of EBUS
  - abnormal mediastinal and/or hilar nodes at CT and/or PET
  - In case if normal mediastinum at CT and PET,
    1) hilar node enlargement or abnormal PET uptake in N1
    2) primary tumor > 3cm
    3) no uptake of primary tumor
- Restaging by EBUS revealed acceptable diagnostic accuracy

Pattern of LN Metastasis

서울대학교 의과대학 보라매병원 흉부외과

성 용 원

Pathology of LN Metastasis

연세대학교 의과대학 세브란스병원 병리과

심 효 섭

폐암 환자의 수술 검체에서 림프절 전이 여부를 판정하기 위한 병리학적 검사 방법은 다른 암종의 림프절 처리 방식과 동일하다. 흉부외과에서 각 위치 별로 림프절을 따로 보내주면, 각 위치에 따라서 각각 블록 및 슬라이드를 제작하여 검색을 시행한다. 검색 후 병리의사는 병리 보고서를 작성하며, 일반적으로 각 위치 별 림프절의 총 개수와 그 중에서 전이가 발견된 림프절의 수, 그리고 전이 종양의 크기 및 림프절 바깥의 연부조직으로의 침윤 여부를 기록하고 있다.

림프절 전이와 관련된 병리과 진단 영역에서 최근에 연구되고 토론되고 있는 주제는 크게 2가지가 있으며, 본 발표에서는 이에 대한 내용을 요약하여 토론하고자 한다.

1. Intrapulmonary lymph node retrieval in pathologic examination of resected lung cancer

앞서 기술된 대로, 림프절의 병리학적 검사는 흉부외과에서 이미 구분되어 보내온 림프절 검체에 의존한다. 그러나, 절제된 폐 검체 내에도 N1 림프절이 다수 존재하며 이를 현미경 검색에 포함시키기 위해서는 주의 깊은 병리학적 육안 검사 (gross examination)가 필요하다.

Ramirez RA 등은 폐암 수술 검체의 육안 검사를 통상적인 방법 (routine pathologic examination; RPE)과 림프절 검출을 높이기 위한 특화된 방법 (special pathologic examination; SPE)으로 구분하여 총 73명의 환자 검체에서 시행한 결과를 보고하였다[1]. SPE 방법은 통상적인 육안 검색 후에 남은 검체를 3-5 mm 간격으로 절개하여 림프절과 유사한 조직을 모두 발라내고 이를 슬라이드로 제작하여 현미경으로 검색하는 방법이었다. 그 결과, 90%의 검체에서 추가적으로 림프절이 발견되었고, 추가로 발견된 림프절의 11%에서 전이가 발견되었다. SPE 방법을 통하여 8명 (11%)의 환자에서 최종 병리학적 병기가 변경되었는데, 그 중 6명은 림프절 전이가 추가로 발견되었기 때문이며, 2명은 추가 종양 결절이 발견되었기 때문이었다. 이렇게 추가로 발견된 림프절 전이가 환자의 예후에 어떤 영향을 미치는 지에 대한 결과는 존재하지 않아 SPE 방법의 궁극적인 임상적 의의는 아직 미정이라고 할 수 있다. 그러나, 폐 수술 검체 내에 존재하는 림프절에 대하여 병리학적 검사 과정이 충분히 이루어져야 함을 잘 보여주고 결과라고 할 수 있다.

2. Occult micrometastases in lymph nodes

현재 사용하고 있는 AJCC Cancer Staging 7판은 림프절 미세 전이와 관련하여 다음과 같이 기술하고 있다[2].

Isolated tumor cells (ITC)는 단일 암세포(single tumor cells) 또는 0.2 mm 이하의 작은 무리(small clusters)를 의미한다. 이는 보통 면역조직화학 염색이나 분자 검사에서 발견되며, N0로 명기하도록 기술되어 있다. 즉, 면역조직화학 염색 및 분자 검사 결과에 따라 각각 pN0(i-)/pN(i+) 또는 pN0(mol-)/pN0(mol+)로 표기하는 것이다. 현 병기 시스템에서 미세 전이의 정의가 명확하게 나와 있지 않으나 상기 내용을 근거로 한다면, 0.2mm 이상의 전이는 전이의 위치에 따라 N1 또는 N2가 될 것임을 시사한다.

병기 설정에서 미세 전이가 하나의 인자로 잘 반영되어 있는 암종은 유방암이다. 유방암의 병기 설정에서 isolated tumor cell의 정의는 폐암에서의 정의와 비슷하다. 즉, 0.2 mm 이하의 작은 무리, 또는 단일 세포, 또는 200개 미만으로 구성된 세포 무리로

정의한다. 0.2 mm를 초과하거나 200이상의 세포로 구성되어 있으나 2.0 mm 이하인 경우를 micrometastasis로 정의한다.

이러한 기준에 비추어 볼 때 폐암 환자에서 통상적으로 발견되는 림프절 전이암의 크기는 2.0mm를 초과하는 경우가 대부분이다. 2.0 mm 미만의 전이 여부를 확실하게 감별하기 위해서는 앞서 기술되어 있듯이 면역조직화학 염색이나 분자학적 검사를 시행하여야 한다.

이러한 미세 전이의 임상적 의의에 대하여 여러 연구 결과가 보고 되었다. ACOSOG Z0040 Trial 에서는 면역조직화학 염색으로 발견된 림프절 occult metastasis가 불량 예후인자임을 보고하였다[3]. 최근에 보고된 CALGB 9761 연구에서는 N2 림프절에 면역조직화 염색으로 발견된 occult metastasis가 불량 예후인자였으며, N1 림프절의 전이는 예후와 상관이 없었다[4].

이상의 결과를 종합하면, 통상적인 H&E 검색으로 발견되지 않는 미세 전이가 존재하며, 이러한 미세 전이가 면역조직화학 염색에서 확인되었을 때 환자의 예후가 불량하였으므로, 향후 이러한 미세 전이의 병기 반영 여부와 이에 따라 추가 항암치료의 적응증이 될 수 있을지에 대한 검증 작업이 필요하다. 이와 더불어 미세 전이 유무를 검출하기 위한 면역조직화학 염색이 표준지침으로 자리잡기 위해서는 추가로 시행하는 염색에 대한 수가 산정에 대해서 논의가 필요할 것으로 사료된다.

References

1. Ramirez RA, Wang CG, Miller LE, Adair CA, Berry A, Yu X, et al. Incomplete intrapulmonary lymph node retrieval after routine pathologic examination of resected lung cancer. J Clin Oncol 2012;30:2823-8.
2. AJCC cancer staging manual. 7th ed. New York: Springer, 2010.
3. Rusch VW, Hawes D, Decker PA, Martin SE, Abati A, Landreneau RJ, et al. Occult metastases in lymph nodes predict survival in resectable non-small-cell lung cancer: report of the ACOSOG Z0040 trial. J Clin Oncol 2011;29:4313-9.
4. Martin LW, D'Cunha J, Wang X, Herzan D, Gu L, Abraham N, et al. Detection of Occult Micrometastases in Patients With Clinical Stage I Non-Small-Cell Lung Cancer: A Prospective Analysis of Mature Results of CALGB 9761 (Alliance). J Clin Oncol 2016;34:1484-91.

Surgical Technique of Lymph Node Dissection

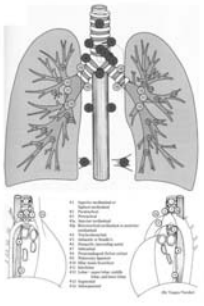
Department of Thoracic and Cardiovascular Surgery,
Ajou University School of Medicine, Suwon, Korea

Seong Yong Park, MD, PhD

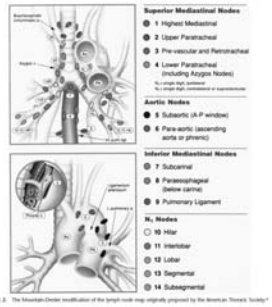
Ageda

- Lymph node map
- Surgical anatomy of mediastinal lymph node dissection
- Techniques and Surgical video

Lymph node map

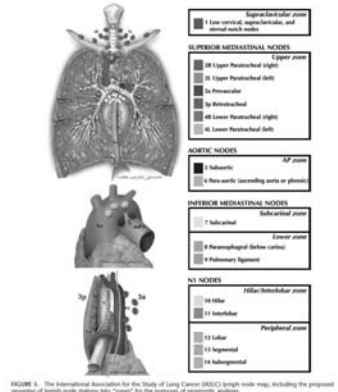


Naruke lymph node map (1978)



Mountain-Dresler lymph node map (MD-ATS map, 1997)

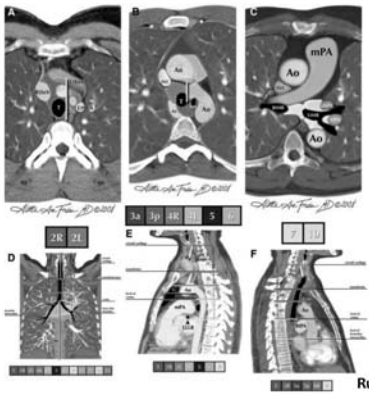
IASLC lymph node map



- Proposed at 2009 with 7th AJCC TNM stage

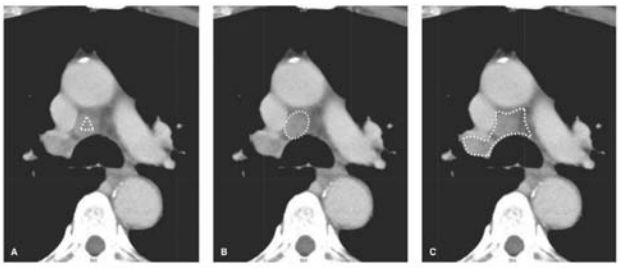
Rusch et al. JTO 2009

IASLC lymph node map

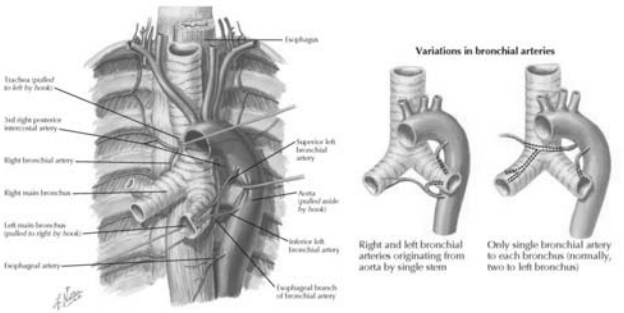


Rusch et al. JTO 2009

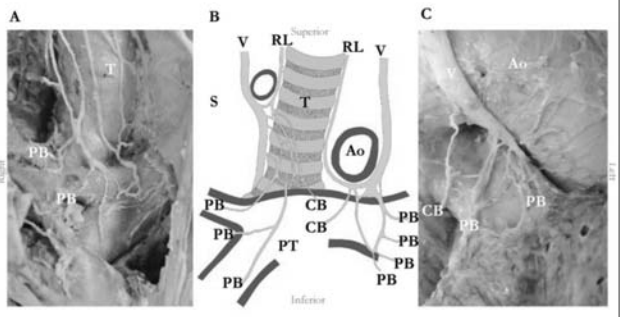
Biopsy vs. Sampling vs. Dissection



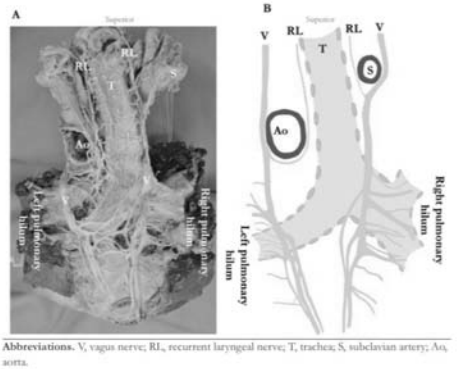
Bronchial artery

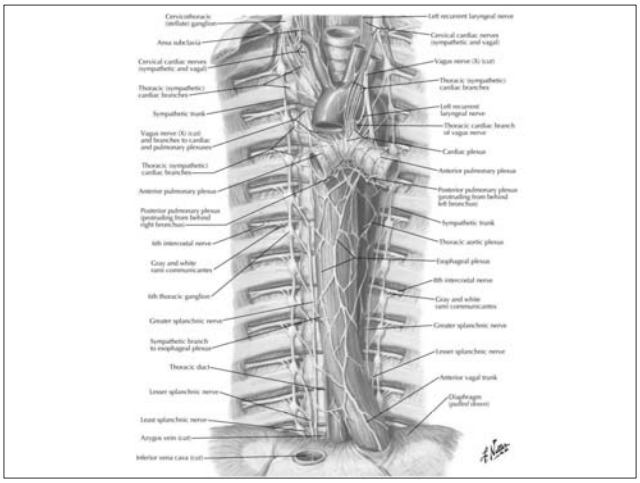


Vagus nerve

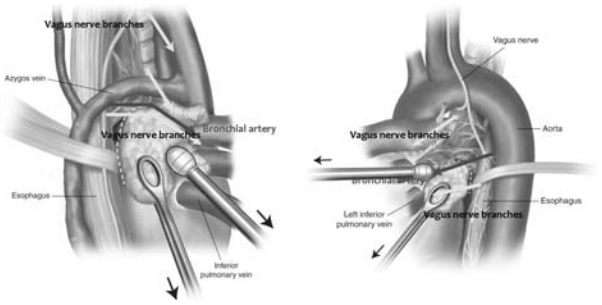


Vagus nerve

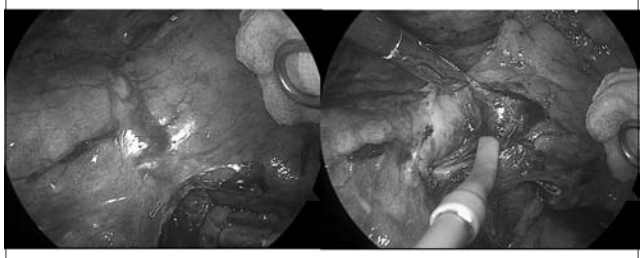




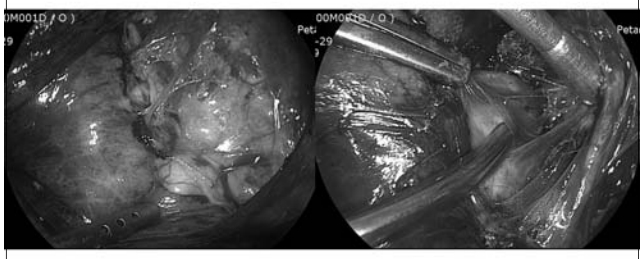
Clinical anatomy



Visceral pleura



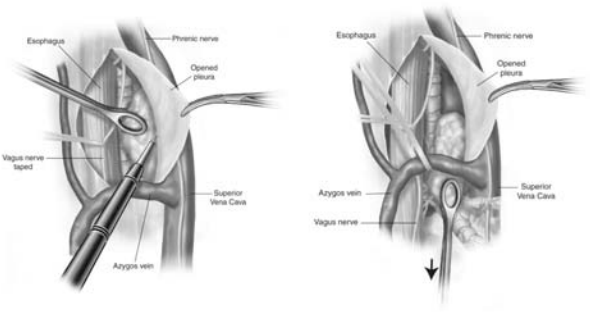
Calcified anthracotic LN



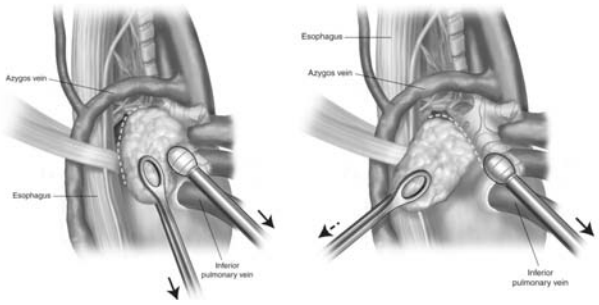
Types of approaches for MLND

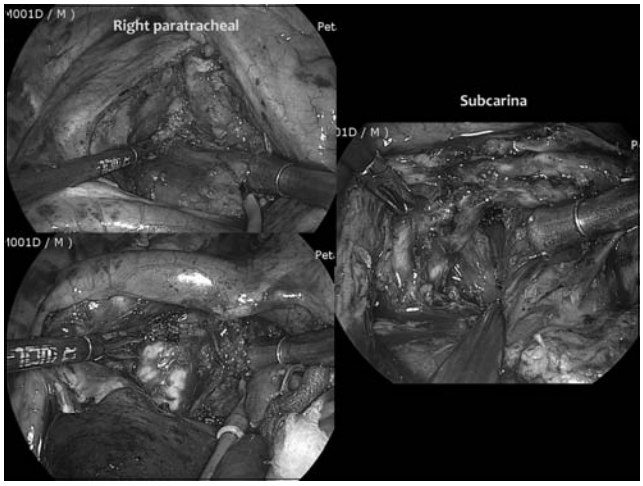
- Right side approach
- Left side approach
- Sternotomy
- TELMA (transcervical extended mediastinal lymphadenectomy), VAMLA
  - For staging purpose or for dissection of contralateral lymph nodes (N3)

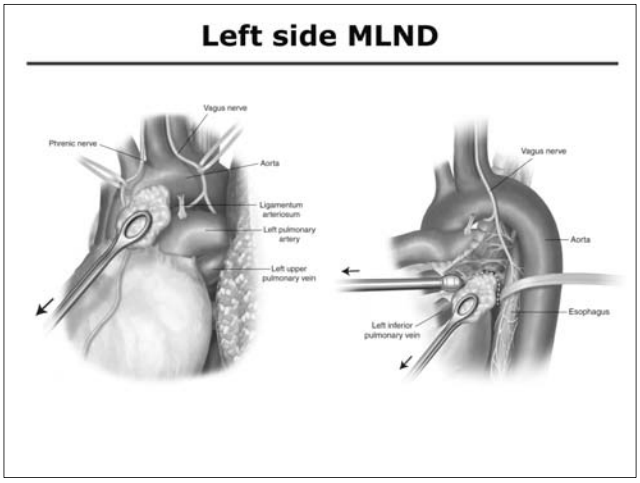
Right side MLND – paratracheal

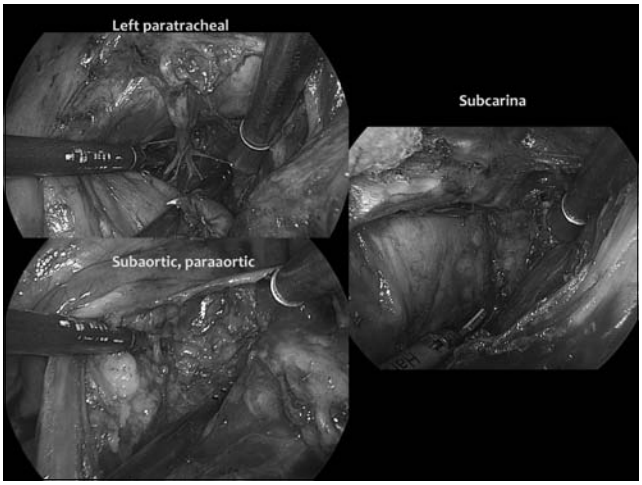


Right side MLND - subcarina






Left side MLND
Vagus nerve
Phrenic nerve
Aorta
Ligamentum arteriosum
Left pulmonary artery
Left upper pulmonary vein
Vagus nerve
Aorta
Esophagus
Left inferior pulmonary vein


Left paratracheal
Subcarina
Subaortic, paraaortic


Thank you for attention!!!

LN Dissection in Metastatic Lung Cancer from Other Organs

Seoul National University Bundang Hospital

Sukki Cho

Since the first pulmonary metastasectomy (PM) was performed in 1882, it is now generally agreed that overall survival can be improved by PM in highly selected patients. Much has been focused on prognostic indicators for patients undergoing PM including the cell type of the primary tumor, time interval between primary tumor resection and the identification of metastasis, number, and the completeness of PM. However, very little attention has been paid to the influence of lymph node (LN) metastasis on outcomes after PM.

Despite mediastinal LN dissection being a widely accepted standard in primary lung cancer, its role of PM has not been well-defined. One of the reasons for this is the infrequency with which mediastinal LN dissection was performed. The International Registry of Lung Metastases found only a 5% of incidence of LN metastases in 5206 patients, however, only 4.6% having mediastinal LN dissection among 5206 patients. Generally the incidence of metastatic LN involvement ranged from 14.3% to 29.8%.

Recent studies have investigated the prognostic significance of metastatic LN after PM. In most of these studies, 5-year survival ranges from 25-50% of negative LN metastasis, in contrast, 5-year survival ranges from 0 to 24% of positive LN metastasis. Pfannschmidt et al found that in patients with colorectal cancer, median survival after PM in patients with hilar LN metastases alone was 21 months versus 15 months for patients in whom mediastinal LN were involved. Murthy et al. demonstrated that in patients having PM for renal cell carcinoma, an increasing number of involved LN was associated with an incremental risk of death.

Whether mediastinal LN dissection during PM has a positive therapeutic effect is unknown although there appears to be little doubt that positive LN during PM portends worse prognosis. However, most studies recommend complete mediastinal LN dissection at the time of PM to define the patients' prognosis and to guide adjuvant therapy.

Radiation Therapy for LN Metastasis

성균관대학교 의과대학 삼성서울병원 방사선종양학과

노 재 명

본 발표에서는 N2-3 병기 비소세포폐암에서 방사선치료가 포함되는 combined treatment가 이루어지는 상황 들에 관해 논하고자 한다. 크게 Clinical, Pathological, Recurrent N2 disease에 대한 문헌 고찰과 IMRT, proton therapy 등의 modern radiotherapy technique을 중심으로 하였다.

1. Radiotherapy for N2 disease

① Clinical N2-IIIA disease: Definitive CCRT or Neoadjuvant CCRT + Surgery

NCCN guideline에서는 definitive concurrent chemoradiation (CCRT)을 category 1으로 제시하고 있다. Definitive CCRT vs. sequential chemoradiotherapy를 비교한 6개 연구(1205명)의 meta-analysis에서 3년 생존율 23.8% vs. 18.1%, 3년 locoregional progression rate 28.1% vs. 34.1% 로 우수한 성적을 보였는데[1], 이들 연구는 1988-2003년에 걸쳐 치료를 받은 환자를 대상으로 하여 최근에 치료를 받은 환자들에 비해 전체적인 성적은 좋지 않은 편이다. 한편, 2008-2012년에 치료가 진행된 PROCLAIM study의 3년 생존율은 37-40%였으며[2], 2007-2011년에 치료가 진행된 RTOG 0617 trial의 2년 생존율은 44.6-57.6%였다[3].

N2-IIIA disease에서 induction chemo±radiotherapy (RT) 후에 수술적 치료를 고려할 수도 있는데, 이를 definitive CCRT와 비교한 연구에서 survival에 유의한 차이가 없었지만 수술적 방법으로 lobectomy를 받은 경우 생존율이 향상되는 결과를 보여, lobectomy candidate에서는 trimodality therapy가 고려될 수 있다[4,5]. 이와 관련된 내용이 2015년 ASCO - ASTRO practice guideline에서 아래와 같이 기술되어 있다[6].

- Patients with resectable stage III NSCLC should be managed by a multidisciplinary team that uses best surgical judgment. The best candidates for preoperative chemoradiotherapy have preoperatively planned lobectomy (as opposed to pneumonectomy), no weight loss, female sex, and only one involved nodal station.

② Pathological N2 disease: Postoperative RT + Chemotherapy

수술 전 병기는 cN0-1이었지만 수술 후 N2 disease가 발견된 경우 postoperative RT (PORT)가 권장된다. pN0-1의 경우 PORT가 hazardous하다는 보고가 많으나, pN2에서는 PORT를 통해 survival이 향상되는 것으로 알려져 있으며, 이는 선형가속기를 이용한 현대 방사선치료를 받은 경우 더욱 뚜렷하다[7-10]. 다만 sequential chemotherapy + RT의 순서로 시행하는 것을 NCCN guideline 및 2015년 ASCO - ASTRO practice guideline에서 권장하고 있으며[6], R1-2 resection의 경우 postoperative CCRT를 고려할 수 있는 것으로 되어 있다.

- Postoperative radiotherapy may be recommended for patients with complete resection of N2 disease to improve local control, but should be delivered sequentially after adjuvant chemotherapy.
- Postoperative radiotherapy is recommended for patients with incomplete resection (microscopic or gross positive mar-

gin, or gross residual disease), to be given either concurrently or sequentially with chemotherapy.

③ Recurrent N2 disease: Salvage RT or CCRT

최초 치료 후 mediastinal recurrence가 발생한 경우 resection이 여의치 않다면 curative aim의 high-dose RT±Chemotharpy를 시행해 볼 수 있다. 이 때 median survival 10-20개월의 성적이 다양하게 보고 되고 있으며, disease-free interval 이 1년 이상으로 긴 경우 좀더 우수한 치료 성적을 기대할 수 있다[11]. NCCN guideline에서는 prior RT를 받은 경우 systemic therapy를 권장하고 있지만, 이전에 RT를 받았다 하더라도 IMRT/proton 등의 technique을 이용하면 안전하고 효과적인 re-RT가 가능하다 [12].

2. Modern Radiotherapy Technique

① 방사선치료의 목적은 tumor control을 극대화하면서 부작용을 최소화하는 것이다.

20세기에 주로 이루어지던 2차원 방사선치료에서는 landmark에 기반한 넓은 범위를 치료함에 따라 target miss의 가능성과 정상조직에 불필요한 방사선이 조사될 가능성이 모두 존재하여, 이러한 목적을 달성하는 데 충분하지 못 하였다. CT-simulation을 기반으로 하는 3차원 입체조형 방사선치료(3-dimensional conformal radiotherapy, 3D-CRT)는 정확하게 target volume을 delineation하여 최적의 선량분포를 만들어 낼 수 있어 현대 방사선치료의 최소 필수조건으로 제시된다. 또한 PET-CT가 보편화 됨에 따라 elective nodal irradiation을 하지 않고 involved-field에만 고선량을 조사할 수 있게 되었으며, 환자의 호흡에 따른 움직임을 반영한 4D-simulation을 통해 더욱 정확한 치료가 가능하게 되었다.

② IMRT (Intensity-modulated radiotherapy, 세기조절방사선치료)

N2-3 병기 폐암에 대한 근치적 목적의 방사선치료를 할 때 60 Gy 이상의 선량이 권장되는데, 척수의 견딤선량은 45-50 Gy 이며 mean lung dose의 제한은 20 Gy 이하이다. 식도 역시 방사선을 많이 받게 되면 severe esophagitis 및 장기적으로 esophageal stenosis 등의 부작용을 겪게 되는데, lower lobe primary tumor 에 SCN involvement가 있는 N3-IIIB disease 처럼 병변의 범위가 큰 경우 3D-CRT로는 “tumor control 극대화와 부작용 최소화”의 두 마리 토끼를 동시에 잡기가 매우 어려우며, 이를 가능하게 한 것이 IMRT이다.

IMRT는 다양한 각도에서 세기가 다른 여러 층의 방사선을 조사하는 방법으로, 표적에 정확하게dose painting이 가능하며 폐, 식도, 척수, 심장 등에 조사되는 선량을 일정 수준 이하로 제한할 수 있다. 폐암에 대한 IMRT 치료 성적은 MDACC 등의 기관에서 주로 stage III 환자를 대상으로 하여 그 결과를 보고하였으며, 3D-CRT를 받는 환자에 비해 더 큰 범위의 병변을 치료함에도 불구하고 폐/식도의 부작용은 크게 증가하지 않으며, 치료 성적은 대등하게 나오는 것으로 되어 있다 [13-15]. 이는 삼성서울병원의 경험에서도 유사하게 나타났으며, 다만 early dissemination을 보이는 환자를 선별하고 이에 대한 효과적인 systemic therapeutic strategy를 강구할 필요는 있다 [16].

③ Proton therapy (양성자치료)

Proton beam은 Bragg Peak라는 특징적인 physical property를 가지며, 이를 통해 X-ray에 비해 lung, heart 등의 normal tissue를 좀 더 sparing할 수 있어 방사선치료 관련 독성을 감소시킬 수 있다. 이러한 특성이 survival benefit으로 연결되는 지에 대해서는 아직 충분히 밝혀지지는 않은 상태인데, MDACC의 치료성적에서도 치료 관련 부작용은 낮게 나타난 반면 survival outcome은 기존 X-선 치료 성적에 비해 뚜렷하게 우수하지는 못 하였다 [17]. Stage II-IIIB 환자에서 Proton CRT vs. X-ray 3D-CRT or IMRT를 비교하는 RTOG 1308 3상 연구 등이 진행되고 있으며, 이러한 연구를 통해 양성자치료의 효과에 대한 evidence가 좀 더 축적될 필요가 있다.

References

1. Auperin A, Le Pechoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 2010;28:2181-90.
2. Senan S, Brade A, Wang LH, et al. PROCLAIM: Randomized Phase III Trial of Pemetrexed-Cisplatin or Etoposide-Cisplatin Plus Thoracic Radiation Therapy Followed by Consolidation Chemotherapy in Locally Advanced Nonsquamous Non-Small-Cell Lung Cancer. J Clin Oncol 2016;34:953-62.
3. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. The Lancet Oncology 2015;16:187-99.
4. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. The Lancet 2009;374:379-86.
5. Koshy M, Fedewa SA, Malik R, et al. Improved survival associated with neoadjuvant chemoradiation in patients with clinical stage IIIA(N2) non-small-cell lung cancer. J Thorac Oncol 2013;8:915-22.
6. Bezjak A, Temin S, Franklin G, et al. Definitive and Adjuvant Radiotherapy in Locally Advanced Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Evidence-Based Clinical Practice Guideline. J Clin Oncol 2015;33:2100-5.
7. Billiet C, Decaluwe H, Peeters S, et al. Modern post-operative radiotherapy for stage III non-small cell lung cancer may improve local control and survival: a meta-analysis. Radiother Oncol 2014;110:3-8.
8. Douillard JY, Rosell R, De Lena M, et al. Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non-small-cell lung cancer treated with adjuvant chemotherapy: the adjuvant Navelbine International Trialist Association (ANITA) Randomized Trial. Int J Radiat Oncol Biol Phys 2008;72:695-701.
9. Lally BE, Zelterman D, Colasanto JM, Haffty BG, Detterbeck FC, Wilson LD. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. J Clin Oncol 2006;24:2998-3006.
10. Patel SH, Ma Y, Wernicke AG, Nori D, Chao KS, Parashar B. Evidence supporting contemporary post-operative radiation therapy (PORT) using linear accelerators in N2 lung cancer. Lung Cancer 2014;84:156-60.
11. Bae SH, Ahn YC, Nam H, et al. High dose involved field radiation therapy as salvage for loco-regional recurrence of non-small cell lung cancer. Yonsei Med J 2012;53:1120-7.
12. McAvoy SA, Ciura KT, Rineer JM, et al. Feasibility of proton beam therapy for reirradiation of locoregionally recurrent non-small cell lung cancer. Radiother Oncol 2013;109:38-44.
13. Sura S, Gupta V, Yorke E, Jackson A, Amols H, Rosenzweig KE. Intensity-modulated radiation therapy (IMRT) for inoperable non-small cell lung cancer: the Memorial Sloan-Kettering Cancer Center (MSKCC) experience. Radiother Oncol 2008;87:17-23.
14. Liao ZX, Komaki RR, Thames HD, Jr., et al. Influence of technologic advances on outcomes in patients with unresectable, locally advanced non-small-cell lung cancer receiving concomitant chemoradiotherapy. Int J Radiat Oncol Biol Phys 2010;76:775-81.
15. Jiang ZQ, Yang K, Komaki R, et al. Long-term clinical outcome of intensity-modulated radiotherapy for inoperable non-small cell lung cancer: the MD Anderson experience. Int J Radiat Oncol Biol Phys 2012;83:332-9.
16. Noh JM, Kim JM, Ahn YC, et al. Effect of Radiation Therapy Techniques on Outcome in N3-positive IIIB Non-small Cell Lung Cancer Treated with Concurrent Chemoradiotherapy. Cancer Res Treat 2016;48:106-14.
17. Nguyen QN, Ly NB, Komaki R, et al. Long-term outcomes after proton therapy, with concurrent chemotherapy, for stage II-III inoperable non-small cell lung cancer. Radiother Oncol 2015;115:367-72.

Chemotherapy for LN Metastasis

Department of Oncology, University of Ulsan College of Medicine,
Asan Medical Center, Seoul, Korea

Dae Ho Lee, MD, PhD

Reasons to Favor Neo-Adjuvant Chemotherapy

☐ control **potential distant metastatic disease** at earliest time point

☐ facilitate less extensive surgery or render inoperable tumor operable

☐ evaluate biological effects of conventional or novel agents with visible results

☐ improve drug delivery and patient tolerance in preoperative setting

Reasons to Favor Neo-Adjuvant Chemotherapy

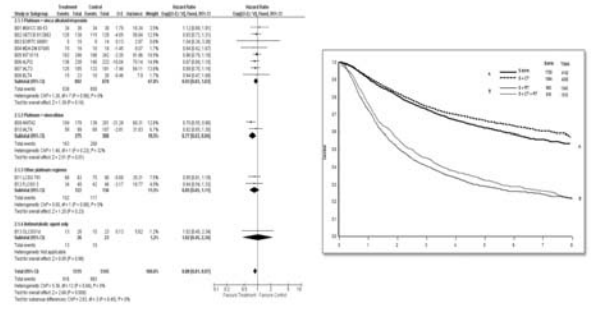
☑ control **potential distant metastatic disease** at earliest time point

☐ facilitate less extensive surgery or render inoperable tumor operable

☐ evaluate biological effects of conventional or novel agents with visible results

☐ improve drug delivery and patient tolerance in preoperative setting

Stage I-IIIA NSCLC_Adjuvant Chemotherapy

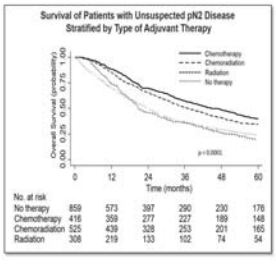


❖ **Combined HR was 0.88 (95% CI, 0.81-0.97, p=0.009), favoring adjuvant chemotherapy, from 29% to 33% @ 5-YSR.**

NSCLC Meta-analysis Collaborative Group. Lancet 2014;383:1561

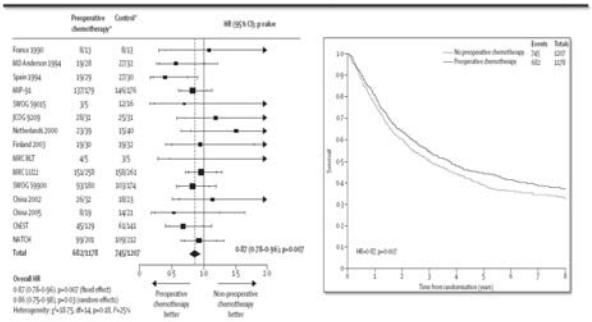
Lobectomy when Unsuspected pN2?

- Of 46,746 patients who underwent lobectomy as primary therapy for cT1-3 N0-1 NSCLC, **2,108 (4.5%)** patients had **pN2 disease** with **5-YSR of 29%**
- **5-YSR was 24%** for no therapy, while that was 40% for adjuvant chemotherapy **(HR, 0.63; 95% CI: 0.53-0.76; p < 0.001)**, 34% for chemoradiotherapy **(HR, 0.65; 95% CI: 0.53-0.80; p < 0.001)**, 19% for radiotherapy (Hazard Ratio [HR], 1.04; 95% CI: 0.78-1.38; p=0.78).
- There was no difference in 5-YSR between **suspected N2 patients** (cT1-3 N2 NSCLC) and **unsuspected pN2 patients** that received adjuvant chemotherapy or chemoradiotherapy (43% vs 44%, p = 0.63).



Yang CJ et al. National Cancer Data Base Analysis. 2015 AATS Annual Meeting

Stage I-IIIA NSCLC_Neo-Adjuvant Chemotherapy



❖ Combined HR was 0.87 (95% CI, 0.78-0.96, p=0.007), favoring neo-adjuvant chemotherapy, from 45% to 50% @ 5-YSR.

NSCLC Meta-analysis Collaborative Group. Lancet 2014;383:1561

Reasons to Favor Neo-Adjuvant Chemotherapy

☐ control **potential distant metastatic disease** at earliest time point:
unlikely

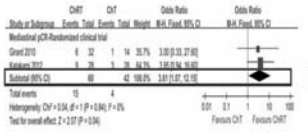
☑ facilitate **less extensive surgery** or render inoperable tumor operable

☐ evaluate biological effects of conventional or novel agents with visible results

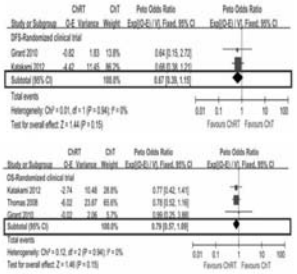
☐ improve drug delivery and patient tolerance in preoperative setting

Neo-adjuvant Chemo *vs.* Chemoradiotherapy

Mediastinal Downstaging (pCR)



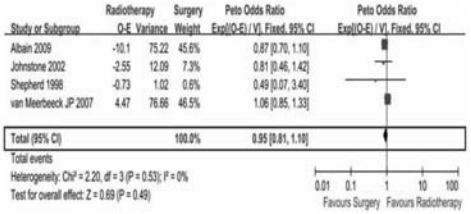
Survival Outcome



Significant 15% increase in pCR in stage IIIA (N2) NSCLC after neoadjuvant chemoradiotherapy compared to neoadjuvant chemotherapy prior surgery. But,
no difference in survival outcome.

Xu Y et al. Medicine 2015;94:e879

Neo-adjuvant followed by Surgery *vs.* Radiotherapy



No significant difference in survival outcome in stage IIIA (N2)

- between surgery and radiotherapy (**HR 0.95; 95% CI 0.81–1.10; *P*=0.49**)
- following neoadjuvant chemotherapy or chemoradiotherapy
- after pathological proof of N2 based on endobronchial ultrasound-guided procedures, mediastinoscopy, or thoracoscopic procedures.

Xu Y et al. Medicine 2015;94:e879

Reasons to Favor Neo-Adjuvant Chemotherapy

☐ control **potential distant metastatic disease** at earliest time point

☐facilitate **less extensive surgery** or render inoperable tumor operable:
unlikely

☑ evaluate **biological effects** of conventional or novel agents with visible results

☐ improve drug delivery and patient tolerance in preoperative setting

Stage I-IIIA NSCLC_Neo-Adjuvant

Effect of Preoperative Chemotherapy by Pre-specified Trial Group

Trial Group	# of Trials	# of Death/Patients	HR (95% CI), p value	Heterogeneity, p value
Schedule (Interaction p= 0.32)				
Preoperative Only	10	1045/1883	0.90 (0.80-1.02), 0.09	0.10
Pre & postoperative for responders	5	382/502	0.78 (0.64-0.95), 0.02	0.62
Number of cycles (Interaction p =0.74)				
2 cycles	6	418/576	0.89 (0.74-1.08), 0.25	0.39
3 cycles	8	1002/1799	0.85 (0.74-0.96), 0.01	0.10
Regimen (Interaction p= 0.79 (all trials), 0.62 (platinum only trials))				
Non-platinum singlet	1	38/62	0.95 (0.50-1.79), 0.87	NA
Platinum+2nd generation doublet	2	68/83	1.08 (0.66-1.76)	0.42
Platinum+2nd generation triplet	5	475/611	0.83 (0.69-1.00),0.05	0.01
Platinum+3rd generation doublet	6	801/1540	0.85 (0.74-0.97), 0.02	0.57
Cisplatin vs. Carboplati, n (Interaction p=0.48)				
Cisplatin-based	7	830/1289	0.83 (0.72-0.95), 0.01	0.08
Carbopaltin-based	5	492/905	0.90 (0.75-1.07), 0.23	0.88

NSCLC Meta-analysis Collaborative Group. Lancet 2014;383:1561

Reasons to Favor Neo-Adjuvant Chemotherapy

☐ control **potential distant metastatic disease** at earliest time point

☐ facilitate **less extensive surgery** or render inoperable tumor operable

☐ evaluate **biological effects** of conventional or novel agents with visible results: **likely**

☑ improve drug delivery and patient tolerance in preoperative setting

Adjuvant Therapy: Compliance?

Study	Planned	Obtained	Compliance	Survival Gain Planned/Obtained
ALPI (2003)	1300	1209	69%	7% (5y)/3% (5y)
BLT (2004)	4000	381	64%	5% (5y) /0% (1y)
IALT (2004)	3300	1867	74%	5% (5y)/4% (5y)
BR10 (2005)	450	482	65%	10% (3y)/15%(3y)
ANITA (2005)	800	840	76%	10% (2y)/5.1% (2y)

Neo-Adjuvant Therapy: Impact on Surgery?

	EORTC 08941 (stage IIIN2)	INT0139 (stage IIIAN2)	GLCCG (stage IIIA/B)	
Treatment	CT→ S vs. RT	CT/RT→ CT/RT vs. S	CT→CT/R →S	CT →S
No. of Pts (Randomized)	579 (332)	396	264	260
Surgical Resection/Allocated (N)	154/167	164/177	142/202	154/226
% uni-/bi- lobectomy	38	59	56	55
% pneumonectomy	47	33	35	35
Surgical mortality (%)	4	7.9	9.2	4.5
% uni-/bi- lobectomy	0	1	7.5	2.4
% pneumonectomy	7	26	14.0	5.4

Reasons to Favor Neo-Adjuvant Chemotherapy

☐ control **potential distant metastatic disease** at earliest time point

☐ facilitate **less extensive surgery** or render inoperable tumor operable

☐ evaluate **biological effects** of conventional or novel agents with visible results

☑ improve drug delivery and patient tolerance in preoperative setting:

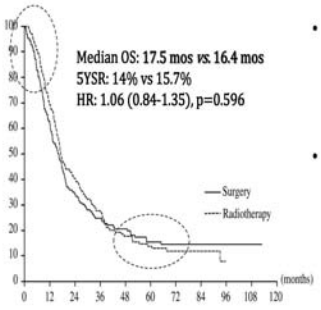
Likely but

So what?

Stage IIIA (N2)_Multimodality Treatment

Study	Key Eligibility
EORTC 08941 van Meerbeeck JP et al 2007	• Pathologic proof of unresectable stage IIIA-N2 (Neither PET nor MRI brain) - **Unresectability**; 1) any N2 involvement by a nonsquamous carcinoma; 2) in case of squamous cell carcinoma, any N2 nodal involvement exceeding level 4R for a right-sided tumor and level 5 and 6 for a left-sided tumor. - **N2 found only at thoracotomy after a negative staging mediastinoscopy** was **not** necessarily considered to be **unresectable.**
INT0139/RTOG9309 Albain KS et al 2009	• Pathologic proof of Stage IIIA-pN2 - Biopsy of ipsilateral mediastinal nodes visible on radiographs: N2 - Biopsy of contralateral mediastinal nodes >1 cm on the CT scan: N3 • Potentially technically resectable.
German LCCG Thomas M et al. 2008	• **Assessment of** mediastinal lymph nodes by mediastinoscopy (occasionally by thoracoscopy, thoracotomy, or needle biopsy) was mandatory • Stage IIIA (T1–3 N2 M0 or central T3 N0–1 M0) or stage IIIB (T4 N1–3 M0 or T1–4 N3 M0) • Tumor involving the superior vena cava, left atrium, carina, distant trachea, or the great vessels was resectable T4 while T4 tumor invading the heart, oesophagus, or vertebra, or involving supraclavicular LN were not eligible.

Stage IIIA pN2_EORTC 08941

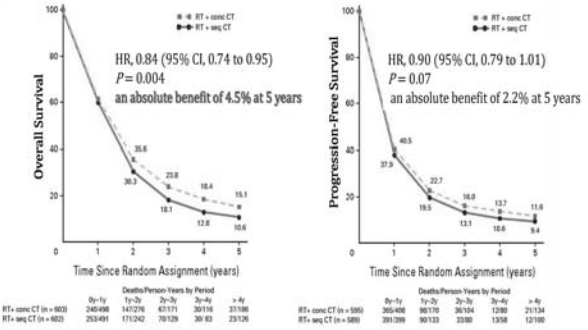


- Out of eligible 579 patients with median OS of 15.4 mo, 332 patients were randomly assigned with an ORR of 61%.
- For responders to induction chemotherapy, subsequent surgery did not improve overall or progression-free survival compared with radiation therapy.

Induction Chemotherapy vs Sequential Chemoradiotherapy

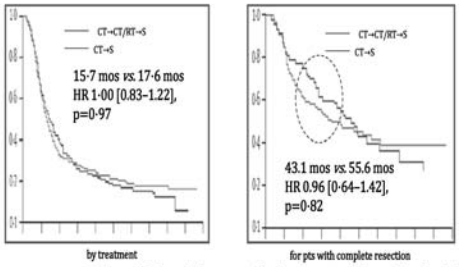
van Meereeck JP et al. JNCI 2007;99:442

Concurrent vs Sequential Chemoradiotherapy



Auperin A et al. J Clin Oncol 2010;28:2181

Stage IIIA (N2)_GLCCG



Induction treatment with additional chemoradiation increased mediastinal down-staging but did not improve survival.

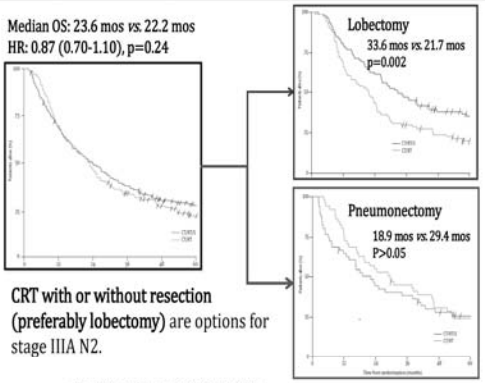
More intensive induction treatment before Surgery? Mortality!

Thomas M et al. Lancet Oncol 2008;9:636

Stage IIIA (N2)_Multimodality Treatment

	EORTC 08941 (stage IIIN2)	INT0139 (stage IIIAN2)	GLCCG (stage IIIA/B)	
Treatment	CT→ S vs. RT	CT/RT→ CT/RT vs. S	CT→CT/R →S	CT →S
No. of Pts (Randomized)	579 (332)	396	264	260
Surgical Resection/Allocated (N)	154/167	164/177	142/202	154/226
% uni-/bi- lobectomy	38	59	56	55
% pneumonectomy	47	33	35	35
Surgical mortality (%)	4	7.9	9.2	4.5
% uni-/bi- lobectomy	0	1	7.5	2.4
% pneumonectomy	7	26	14.0	5.4

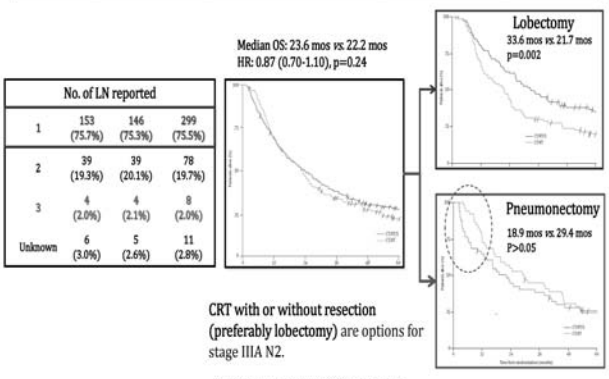
Stage IIIA (N2)_INT0139/RTOG9309



CRT with or without resection (preferably lobectomy) are options for stage IIIA N2.

Albain K, et al. Lancet 2009; 374: 379

Stage IIIA (N2)_INT0139/RTOG9309



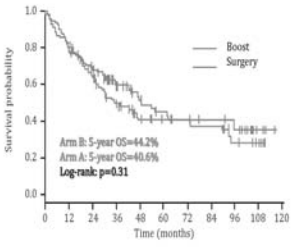
No. of LN reported			
1	153 (75.7%)	146 (75.3%)	299 (75.5%)
2	39 (19.3%)	39 (20.1%)	78 (19.7%)
3	4 (2.0%)	4 (2.1%)	8 (2.0%)
Unknown	6 (3.0%)	5 (2.6%)	11 (2.8%)

CRT with or without resection (preferably lobectomy) are options for stage IIIA N2.

Albain K, et al. Lancet 2009; 374: 379

Stage IIIA (N2)_ESPATUE

- Induction Therapy (n=246): Induction chemotherapy (Pac/CDDP) followed by Concurrent CRT (45Gy, Vin/CDDP)
- Then, Boost Therapy: Surgery (n=81) vs Definitive Concurrent CRT (65~71Gy) (n=80)
- There was no difference in terms of overall survival.

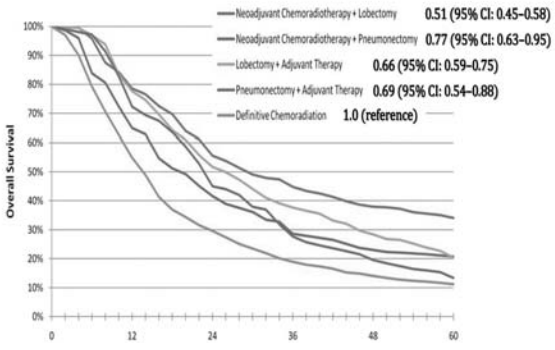


After More Intensive Induction Treatment, surgery vs CCRT?

Eberhardt WEE et al. J Clin Oncol 2014;32 (suppl 5): abstr 7510

The ball is in your court but...

Trimodality is Better in Stage III-N2



Koshy et al. J Thorac Oncol 2013;8:915-922