Controversial Issues on N2 NSCLC

조정수

부산대학교병원 흉부외과

N2 NSCLC

- N2 metastasis means over than stage IIIA
- Mediastinal node involvement is the primary determinant for treatment in advanced NSCLC.
- N2 metastasis is locally advanced disease and curable, but remains a significant treatment challenge.

N2 NSCLC

- There is **no single treatment** paradigm appropriate for all patients.

- Many believe that a tri-modality approach using a **combination of chemotherapy, radiation, and surgery** provides the best hope for cure, but safety and success is highly dependent on **careful patient selection and meticulous treatment delivery.**

Treatment option in N2 NSCLC

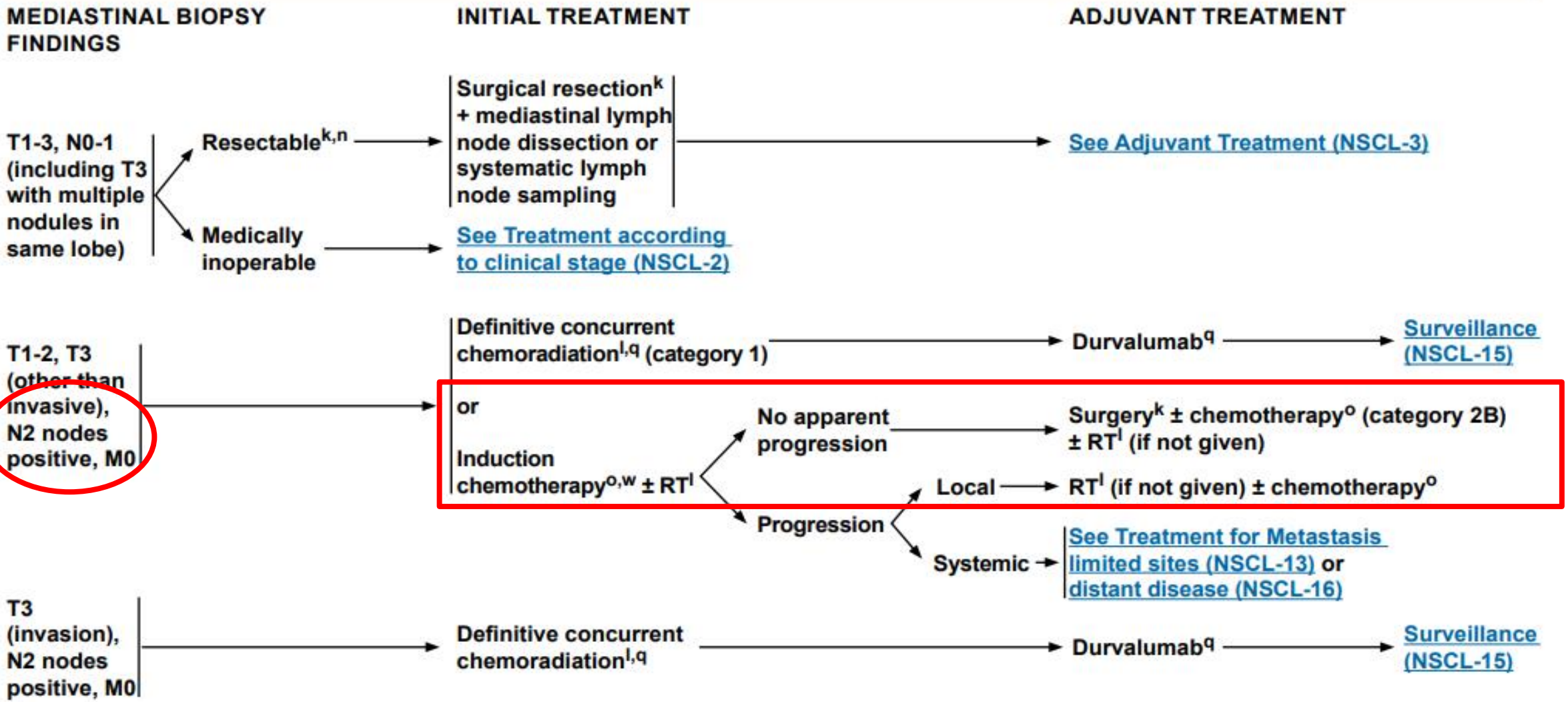
1. **Definite CCRT**
2. **Induction chemotherapy +/- RT => Surgery with chemotherapy +/- RT**
3. **Surgery with chemotherapy +/- RT**

When should surgery be performed?

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2018
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion



The role of surgery in multi-modality treatment for clinical N2-Stage IIIA remains controversial

The role for surgery is dictated by the ability to perform an R0 resection and by the extent of mediastinal node involvement.

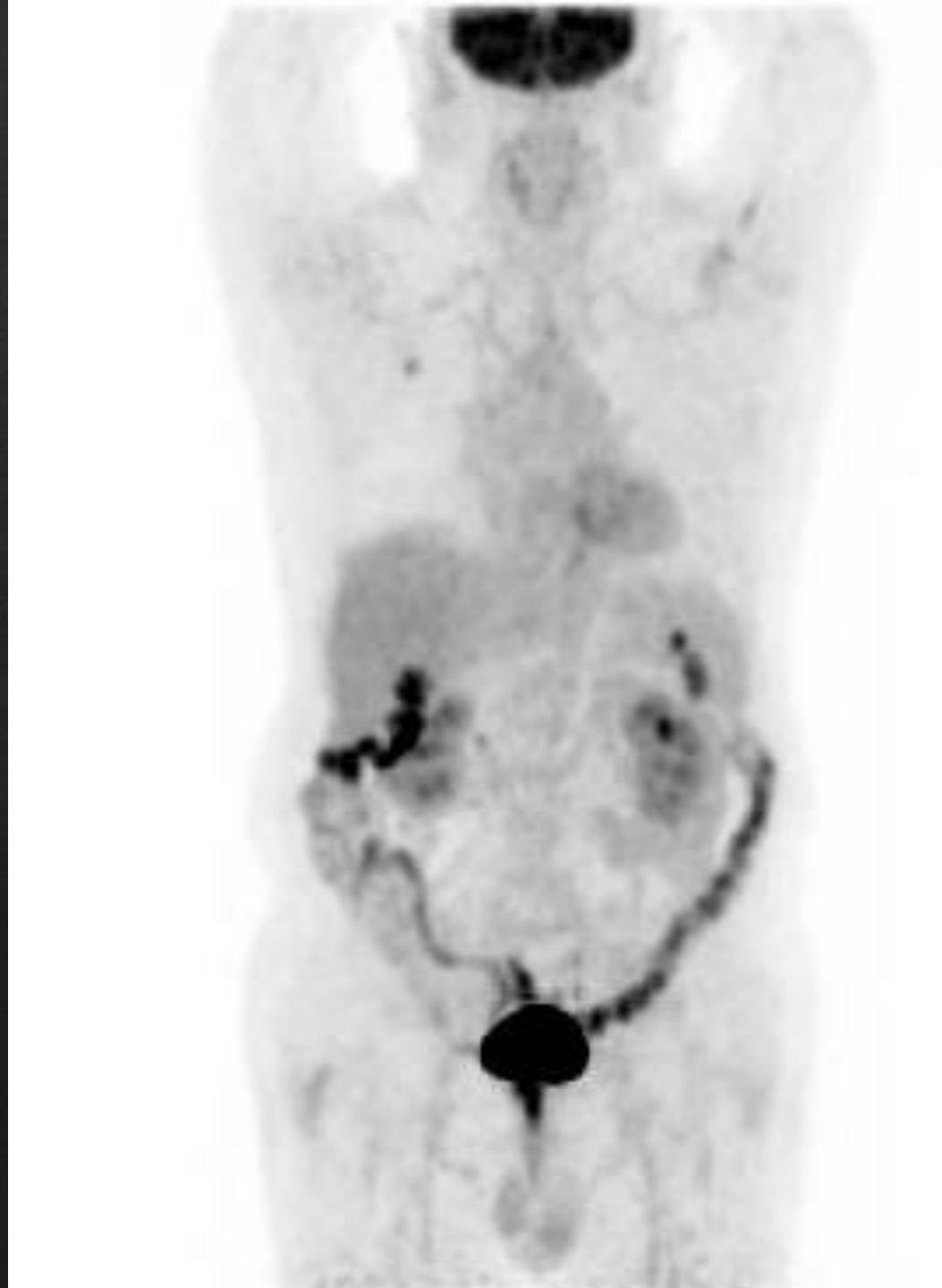
Type of mediastinal LN involvement

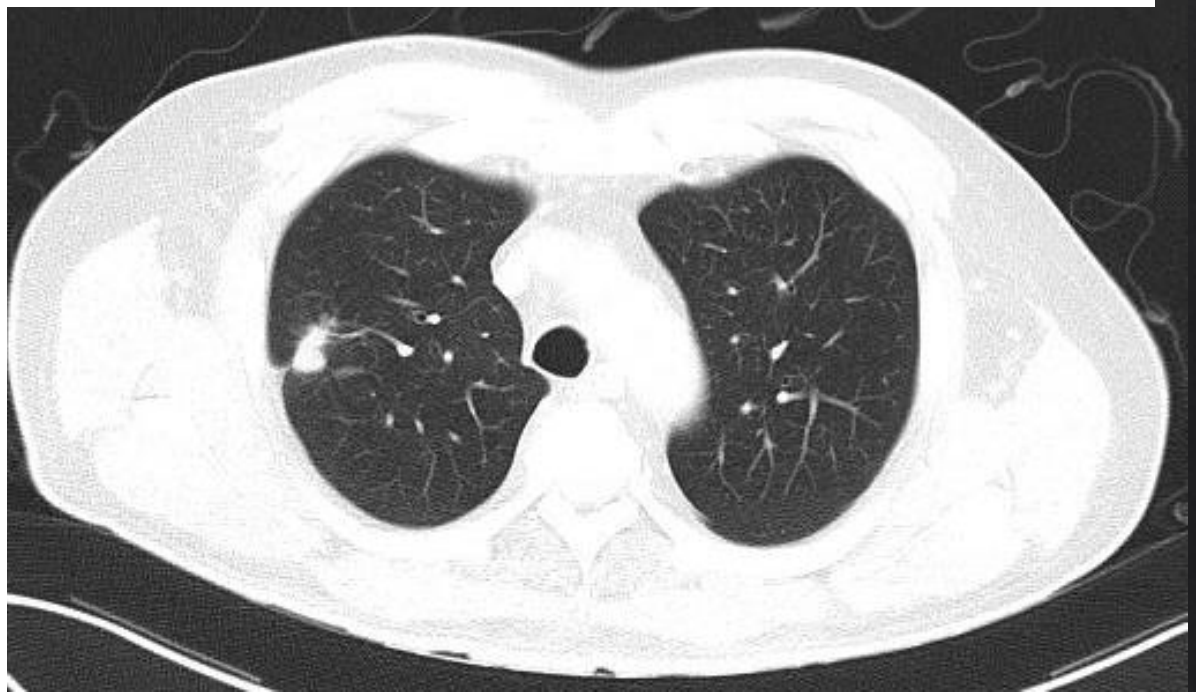
- Incidental or occult metastasis
- Single or multi-station
- Microscopic or macroscopic metastasis
- Bulky or conglomeration
- Extra-nodal
- Etc.

Incidental or occult metastasis

Case 1

- M70
- Lung cancer, RUL, adenoca, cT2aN0M0





❖ VATS RULobectomy with MLND

- Pathologic report
  - Histologic type: Adenocarcinoma, **poorly differentiated**, solid (60%) and acinar (40%) growth pattern
  - Metastasis to 3 out of 4 peribronchial lymph nodes(3/4)
  - Lymph node, #12(N1), dissection : Adenocarcinoma, metastatic (1/2).
  - Lymph node, #11(N1), dissection : Adenocarcinoma, metastatic (1/6).
  - Lymph node, #10 (N1), dissection : No tumor (0/2).
  - Lymph node, #7(N2), dissection : No tumor (0/6).
  - Lymph node, #4(N2), dissection : Adenocarcinoma, metastatic (5/6).
  - Lymph node, #2(N2), dissection : Adenocarcinoma, metastatic (3/6).
  - Lymph node, #9(N2), dissection : No tumor (0/1).

Modern Outcome and Risk Analysis of Surgically Resected Occult N2 Non-Small Cell Lung Cancer

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Background. This study was performed to assess the incidence, survival, and risk factors associated with unsuspected pathologic N2 disease in patients with resectable clinical N0-1 non-small cell lung cancer.

Methods. Between January 2002 and December 2010, 1,821 patients with clinical N0-1 non-small cell lung cancer underwent pulmonary resection and mediastinal lymph node dissection. Clinical outcomes and risk factors for pathologic N2 disease were retrospectively analyzed for this cohort.

Results. Unsuspected pathologic N2 disease was identified in 196 patients (10.8%). The most common type of resection was lobectomy (81.6%). Adjuvant therapy and multiple-station N2 were 66.6% and 36.4%, respectively ($p < 0.001$). Adenocarcinoma, clinical N1, tumor size (>3 cm), and a right middle lobe tumor were identified as independent risk factors for unsuspected multiple-station N2 disease by multivariate analysis. Incidence of unsuspected multiple-station N2 disease in low-risk classes (aggregate score, 0 to ≤2) was only 5.5%.

Conclusions. The incidence of unsuspected N2 disease in our cohort was similar to that of previous reports. Survival outcomes were favorable for unsuspected single-station N2 disease but were poor for unsuspected multiple-station N2 disease. Clinical N0-1 non-small cell

GENERAL THORACIC

Modern Outcome and Risk
Resected Occult N2 Non-Sr

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Cardiovascular Surgery, Seoul Asan Medical Center, University of U
Medicine, Graduate School of Medicine, Gachon University, Incheo

- An **overall 5-year survival rate of**
  in our present study cohort was hig
  reported previously

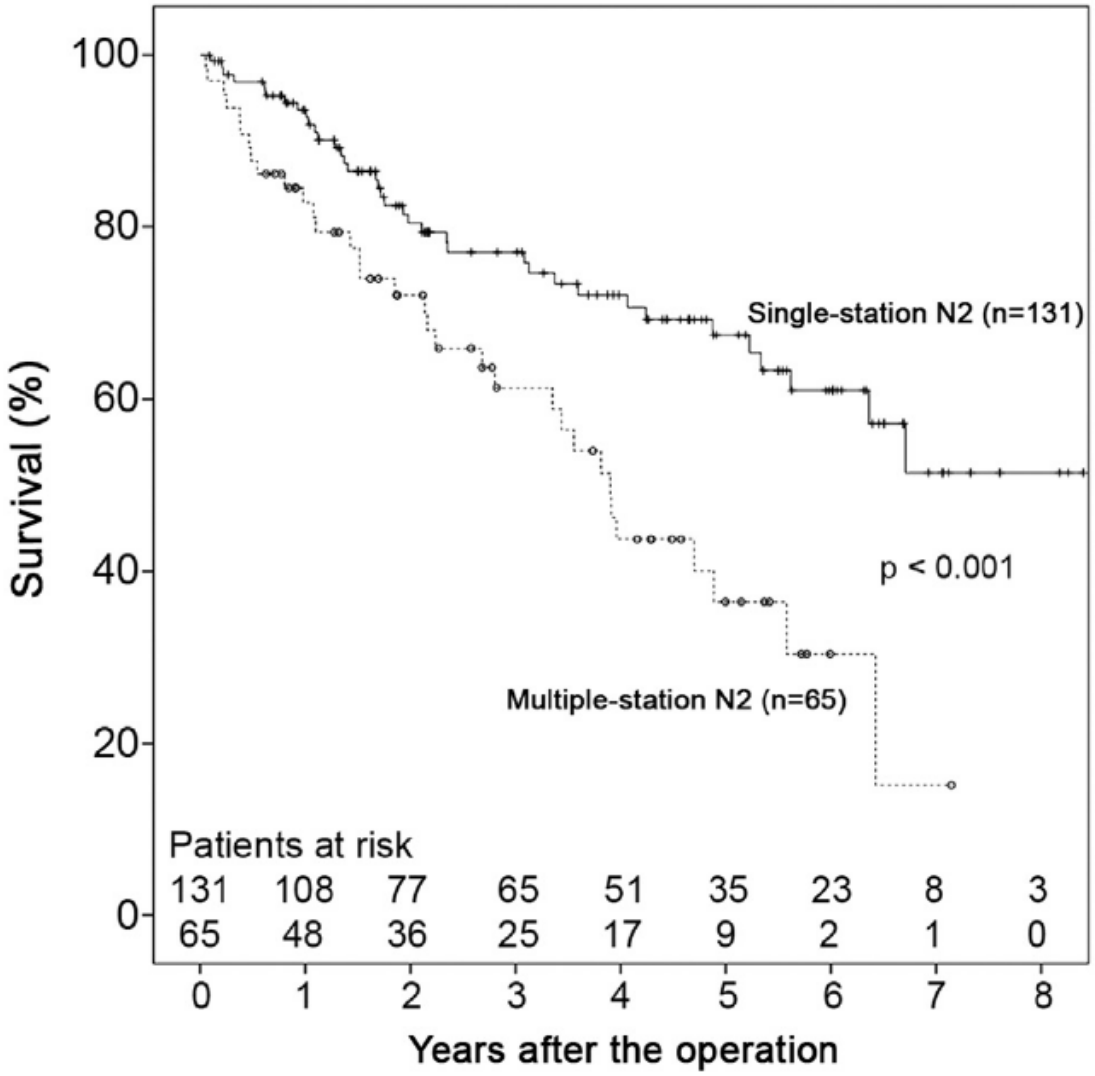

Fig 1. A comparison between patients with unsuspected single-station N2 (solid line) and those with unsuspected multiple-station N2 disease (dotted line) by Kaplan-Meier survival analysis showed the 5-year survival rates were 66.6% for patients with unsuspected single-station N2 disease and 36.4% for those with multiple-station N2 disease ($p < 0.001$).

GENERAL THORACIC

Modern Outcome and Risk Analysis of Surgically Resected Occult N2 Non-Small Cell Lung Cancer

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Table 3. Multivariate Analysis of Risk Factors for (A) Unsuspected N2 disease and (B) Unsuspected Multiple-Station N2 Disease

	Variables	Odds Ratio	95% Confidence Interval	*p* Value
(A)	Age (<70)	1.78	1.09–2.89	0.020
	Clinical N1 disease	2.86	1.96–4.17	<0.001
	Right middle lobe	1.89	1.15–3.09	0.012
	Adenocarcinoma	2.01	1.35–3.01	<0.001
	Tumor size (>3 cm)	1.59	1.14–2.22	0.006
(B)	Clinical N1 disease	3.27	1.73–6.19	<0.001
	Adenocarcinoma	5.34	2.25–12.64	<0.001
	Tumor size (>3 cm)	1.84	1.05–3.20	0.032
	Right middle lobe	2.41	1.16–5.01	0.018

Table 4. (A) Points Assigned at Individual Variables and (B) Distribution of Patients and Incidence of Unsuspected Multiple-Station N2 Disease by Class of Risk

	Variables	Points Assigned at Individual Variable
(A)	Right middle lobe	1
	Clinical N1 disease	1
	Adenocarcinoma	1.5

		Total Cohort (N = 1,821)	
		Patients	Incidence of Unsuspected Multiple-Station N2 Disease
	Risk Class	No. (%)	(n = 65) No. (%)
(B)	Class A (score 0 to ≤1)	834 (45.8)	12 (1.4)
	Class B (score 1 to ≤2)	804 (44.1)	33 (4.1)
	Class C (score 2 to ≤3)	170 (9.3)	17 (10.0)
	Class D (score 3 to ≤4)	13 (0.7)	3 (23.1)
	χ^2 *p* value	<0.0001	
	C index	0.705 (95% confidence limits, 0.64 and 0.77)	

C index = area under the receiver operating characteristic curve.

Long-term survival* of patients with pN2 lung cancer is different according to the *pattern of lymphatic spread

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

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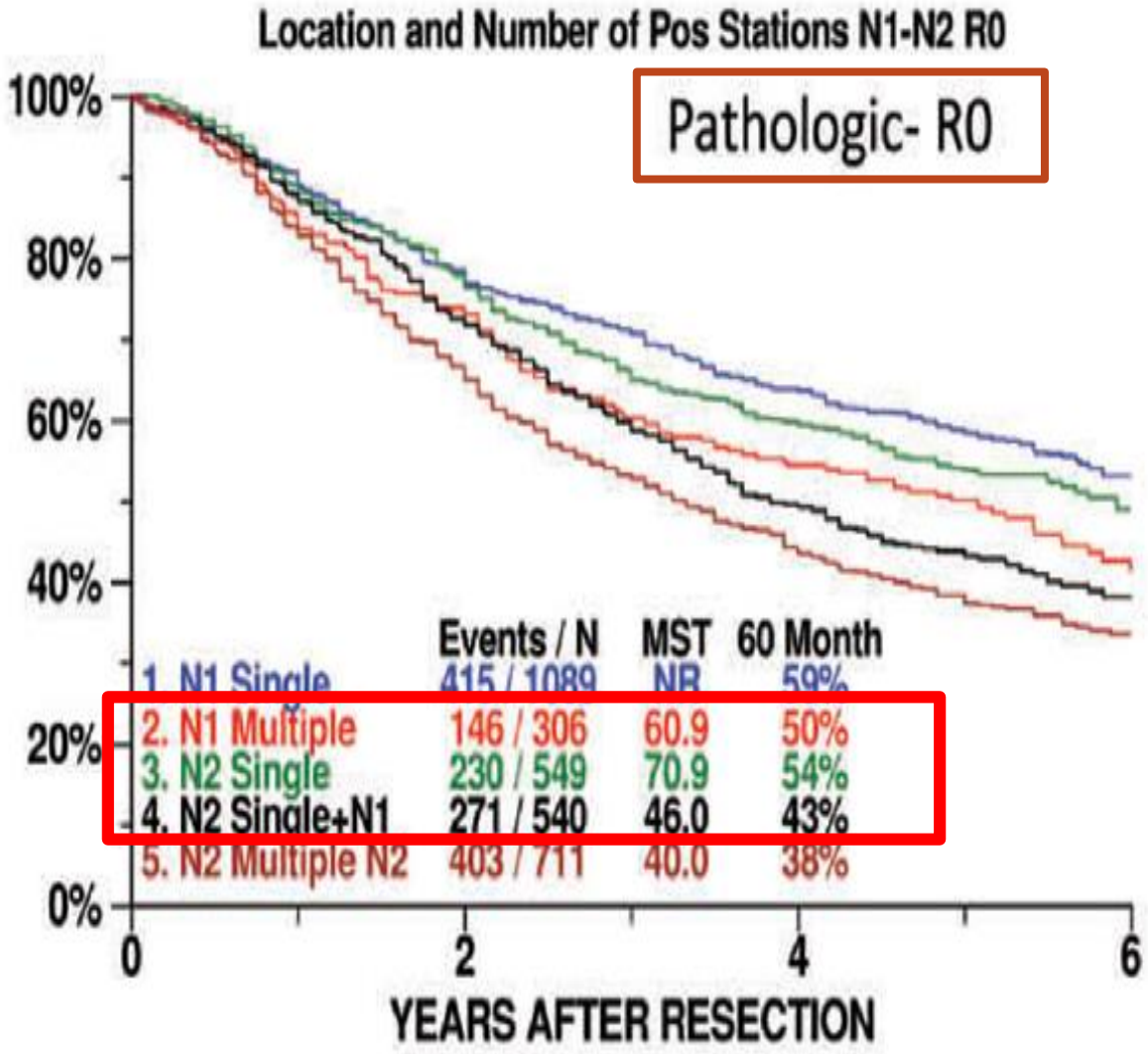
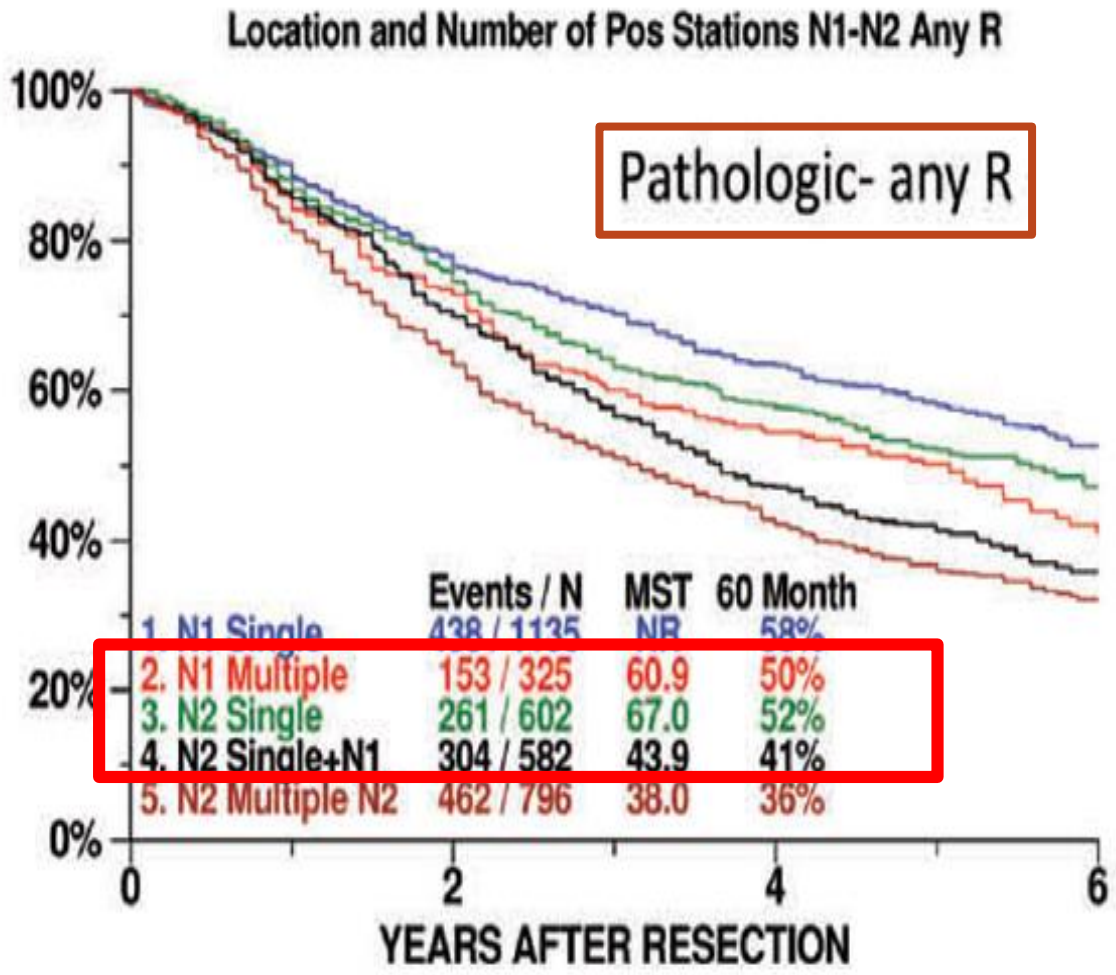


N1a vs N1b vs N2a1 vs N2a2 vs N2b Comparisons Adjusted for Histology (adeno vs others), Sex, Age 60+ , and Region. (Cox PH regression on R0 cases)		
comparison	HR	P
N1b vs N1a	1.39	0.0005
N2a1 (skip) vs N1b	0.89	0.2863
N2a2 vs N2a1 (skip)	1.35	0.0007
N2b vs N2a2	1.26	0.0028
N2a2 vs N1b	1.21	0.064

N1 Single = N1a
N1 Multiple = N1b
N2 Single N2 ("skip mets") = N2a1
N2 Single N2 + N1 = N2a2
N2 Multiple N2 = N2b

N1 Single = N1a
N1 Multiple = N1b
N2 Single N2 ("skip mets") = N2a1
N2 Single N2 + N1 = N2a2
N2 Multiple N2 = N2b



N1a vs N1b vs N2a1 vs N2a2 vs N2b Comparisons Adjusted for Histology (adeno vs others), Sex, Age 60+ , R0 Resection, and Region. (Cox PH regression on All cases)

comparison	HR	P
N1b vs N1a	1.38	0.0005
N2a1 (skip) vs N1b	0.92	0.4331
N2a2 vs N2a1 (skip)	1.37	0.0002
N2b vs N2a2	1.21	0.0117
N2a2 vs N1b	1.26	0.0197

- Additional analyses suggest that the combination of location of metastatic nodes, nN (single station versus multiple stations), and absence versus presence of skip metastasis as pN0, pN1a, pN1b, pN2a1, pN2a2, and pN2b may give a more accurate prognosis.

- This classification requires prospective evaluation before being considered for future revisions of the TNM staging system for lung cancer.

Sequence of treatment combination

- *Induction ?*
- *Surgery ?*
- *Definite CCRT ?*

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ORIGINAL ARTICLE

The N2 paradox: similar outcomes of pre- and postoperatively identified single-zone N2a positive non-small-cell lung cancer†

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Abstract

OBJECTIVES: Resection of N2a non-small-cell lung cancer (NSCLC) diagnosed preoperatively is controversial but there is support for resection of unexpected N2 disease discovered at surgery. Since the seventh TNM edition, we have intentionally resected clinical N2a disease. To validate this policy, we determined prognostic factors associated with all resected N2 disease.

METHODS: From a prospective database of 1131 consecutive patients undergoing elective resection for primary lung cancer over a period of 8 years, we identified 68 patients (35 females (51.4%), mean age 66 years, standard deviation (SD) 9 years) who had pathological N2 disease. All patients had positron emission computed tomography (CT-PET) staging and selective mediastinoscopy. A Cox-regression analysis was performed to identify prognostic factors.

RESULTS: At a median follow-up of 38.7 months (standard error 10, 95% confidence interval (CI) 19.0–58.4), the overall median survival was 22.2 months (95% CI 14.6–29.8) with 1-, 2- and 5-year survival rates of 63.3, 46.6 and 13.2%, respectively. Survival after resection of

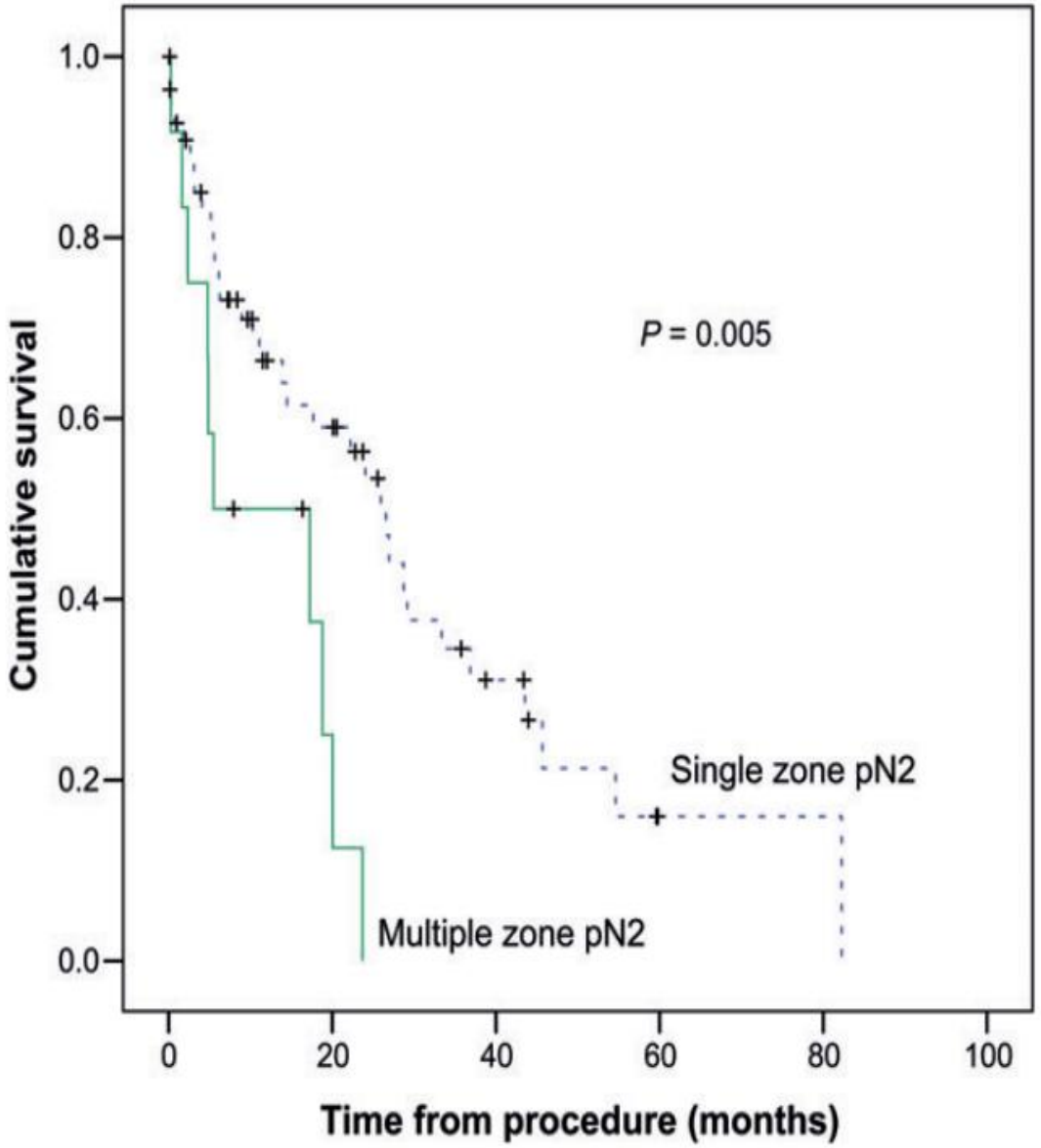
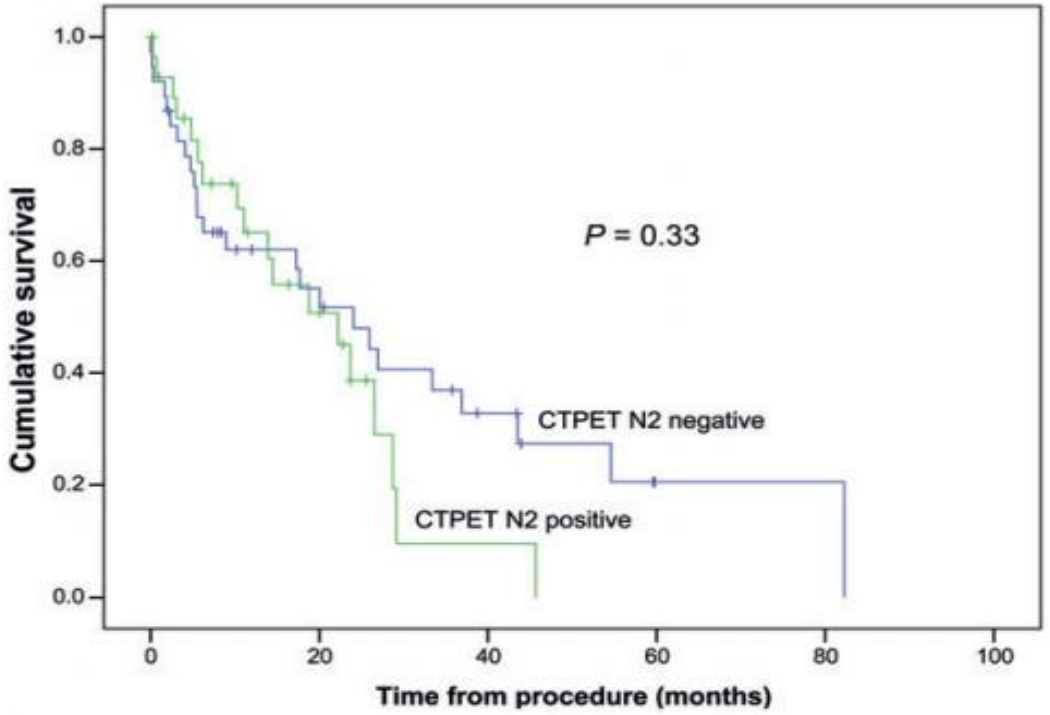


Figure 3: Overall survival by number of pN2 zones with involvement.



Number at risk

Time (months)	12	18	24	36
PET N2 negative (38)	18	15	13	8
PET N2 positive (30)	14	13	5	1

Figure 2: Overall survival of 68 resected cases of N2 NSCLC: CT-PET N2 positive group vs CT-PET N2 negative group.

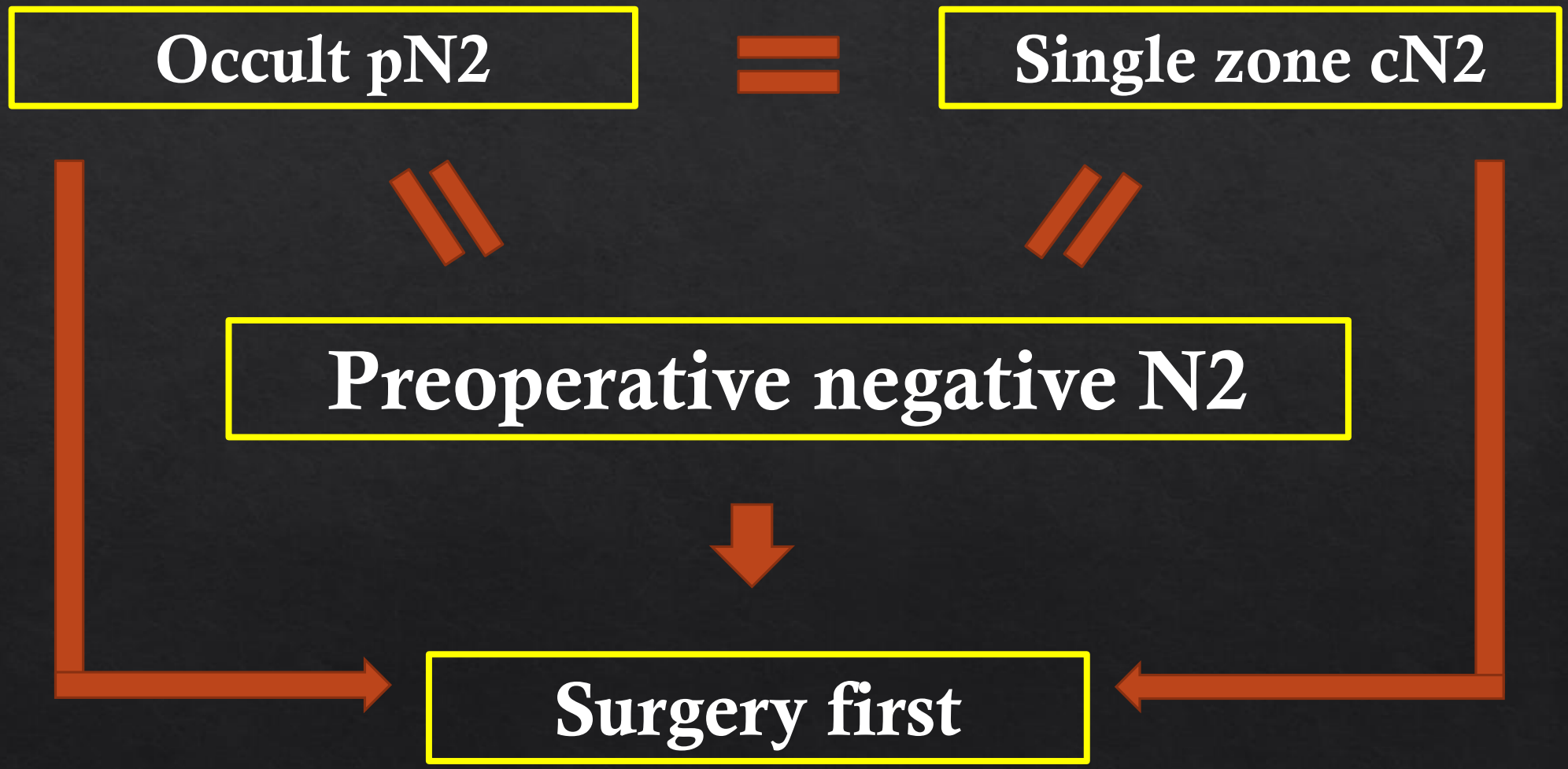
Table 3: Results of univariate analysis of overall survival

Factors	*n*	HR	95% CI	*P*-value
PET cN2	30	1.37	0.73–2.59	0.33
Multizone pN2 involvement	13	2.83	1.32–6.06	0.007
Subcarinal zone pN2	41	1.87	0.97–3.62	0.063
Lower zone pN2	6	1.40	0.49–4.02	0.52
Upper zone pN2	14	0.77	0.34–1.76	0.53
AP zone pN2	19	0.99	0.49–1.98	0.96
Adjuvant chemotherapy	23	0.42	0.22–0.83	0.012
FEV1 (<50%)	11	1.93	0.85–4.40	0.11
Pneumonectomy	15	2.70	1.36–5.35	0.005
Gender (male)	33	1.69	0.91–3.13	0.098

n: number of subjects.

Conclusion

Our results have shown no significant difference in survival between those patients with negative preoperative PET-CT who are found to have pN2 disease after resection and those who are single-zone cN2 positive before resection. Therefore, the answer to the paradox is that if the surgeon would proceed to resection for intraoperatively detected N2 disease, then he is justified to proceed to resection for preoperatively identified single-zone N2a disease. However, confirmatory mediastinoscopy should be routinely performed in this treatment schedule. Also surgery should be part of a multimodality treatment with adjuvant chemotherapy as has been demonstrated in our study.


Occult pN2
Single zone cN2
Preoperative negative N2
Surgery first

JJCO Japanese Journal of Clinical Oncology

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Surgical Outcomes after Initial Surgery for Clinical Single-station N2 Non-small-cell Lung Cancer

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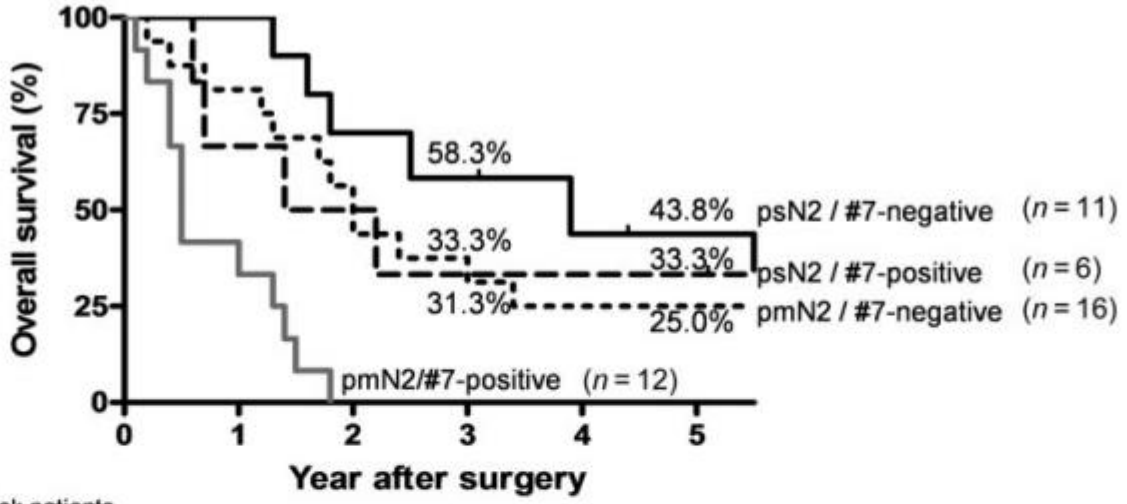
Received February 26, 2013; accepted October 9, 2013

Objective: Single-station N2 (Stage IIIA) non-small-cell lung cancer has been reported to have a relatively favorable prognosis after surgery. However, most previous studies examined surgical outcomes in N2 disease by pathologic nodal status but not by clinical nodal status. The objective of this study was to clarify the surgical outcomes in clinical single-station N2 non-small-cell lung cancer patients.

Methods: A total of 125 consecutive patients with clinical single-station N2 non-small-cell lung cancer were treated in our institution between 1992 and 2008. Among them, 97 (78%) patients

B



At-risk patients

psN2/#7-negative	11	10	6	3
psN2/#7-positive	6	5	3	3
pmN2/#7-negative	16	14	6	5
pmN2/#7-positive	12	5	0	0

Conclusion: Clinical single-station N2 status does not always correspond with pathologic true N2 status. From a prognostic point of view, initial surgery for clinical single-station N2 patients is indicated if their true single-station N2 status and negative subcarinal involvement are preoperatively confirmed.

Recommendation for Surgery first

1. **Occult**
2. **Skip metastasis without N1 i**
3. **Single station N** **ma?)**

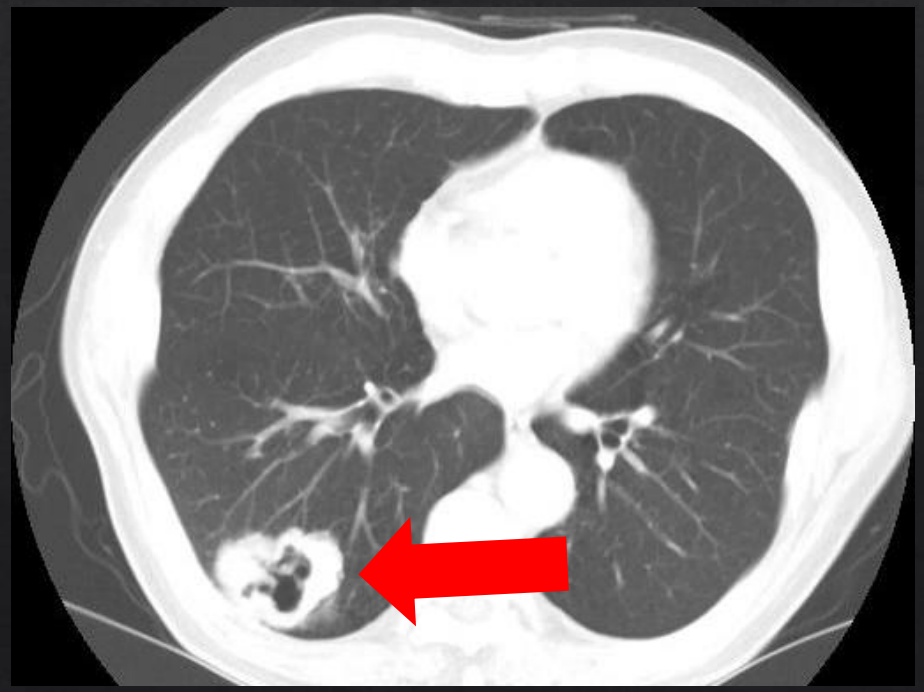
Preoperative pathologic confirmation

Surgical role in Bulky (conglomeration) or Extra-nodal (infiltrative) Single station involvement ?

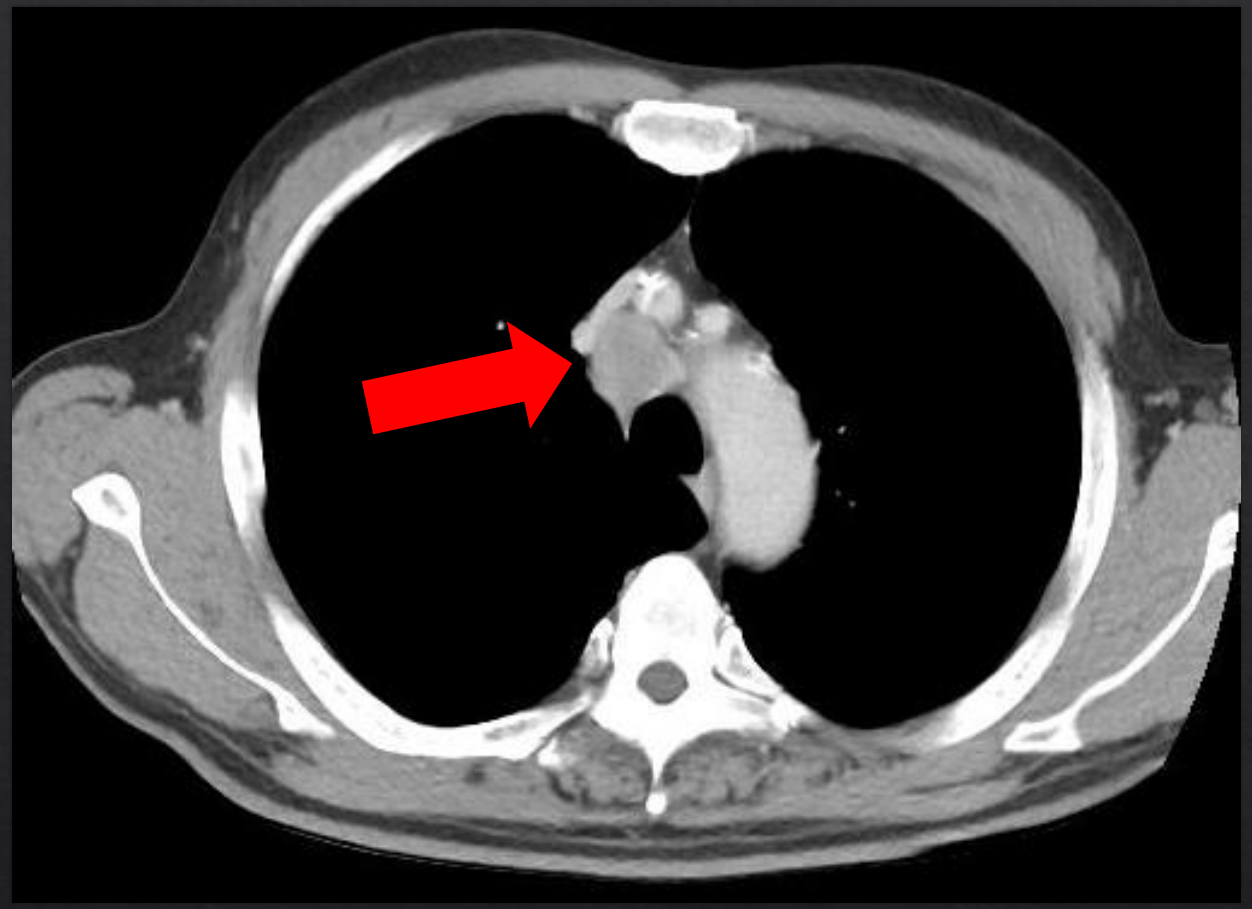
- Few positive reference
- Resectable ? or Oncologically safe?

Case 2

- M 72
- Lung cancer, SqCC, RLL, cT3N2M0



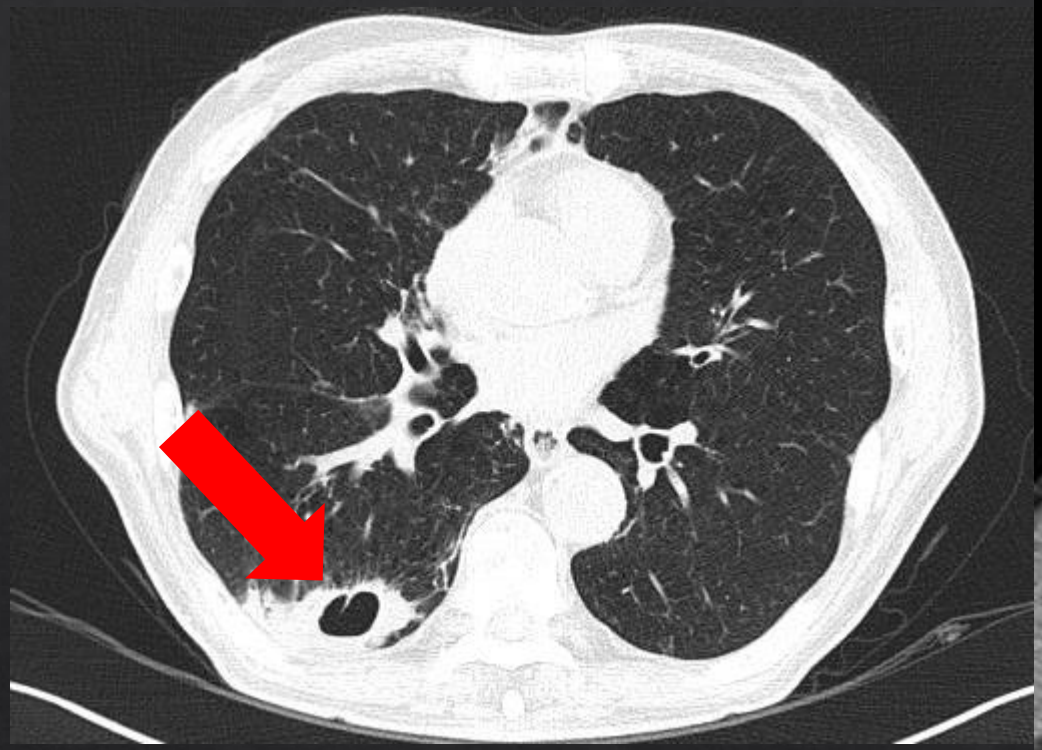
Tumor size 5.8cm

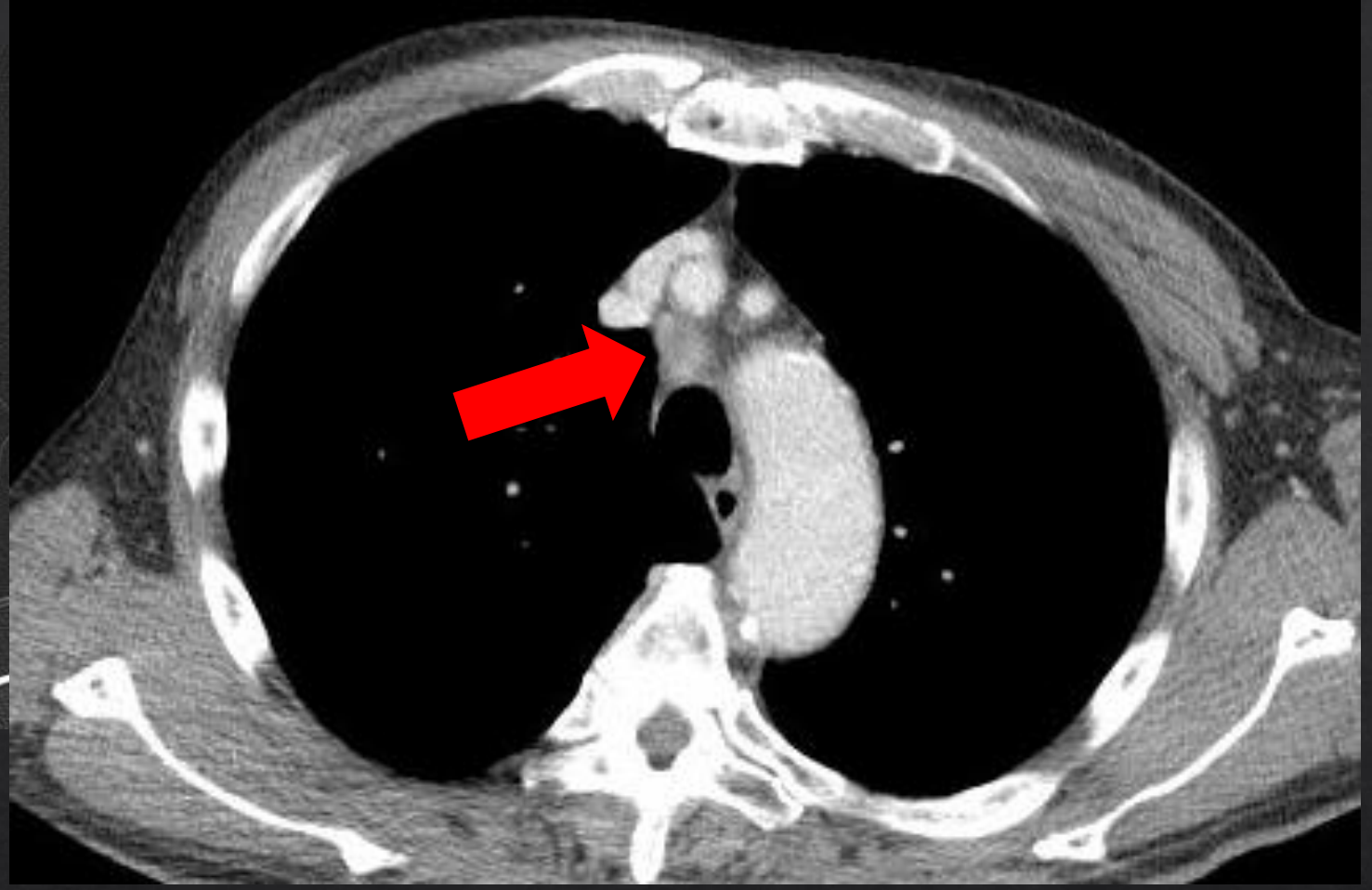


4R bulky or conglomeration

Single station

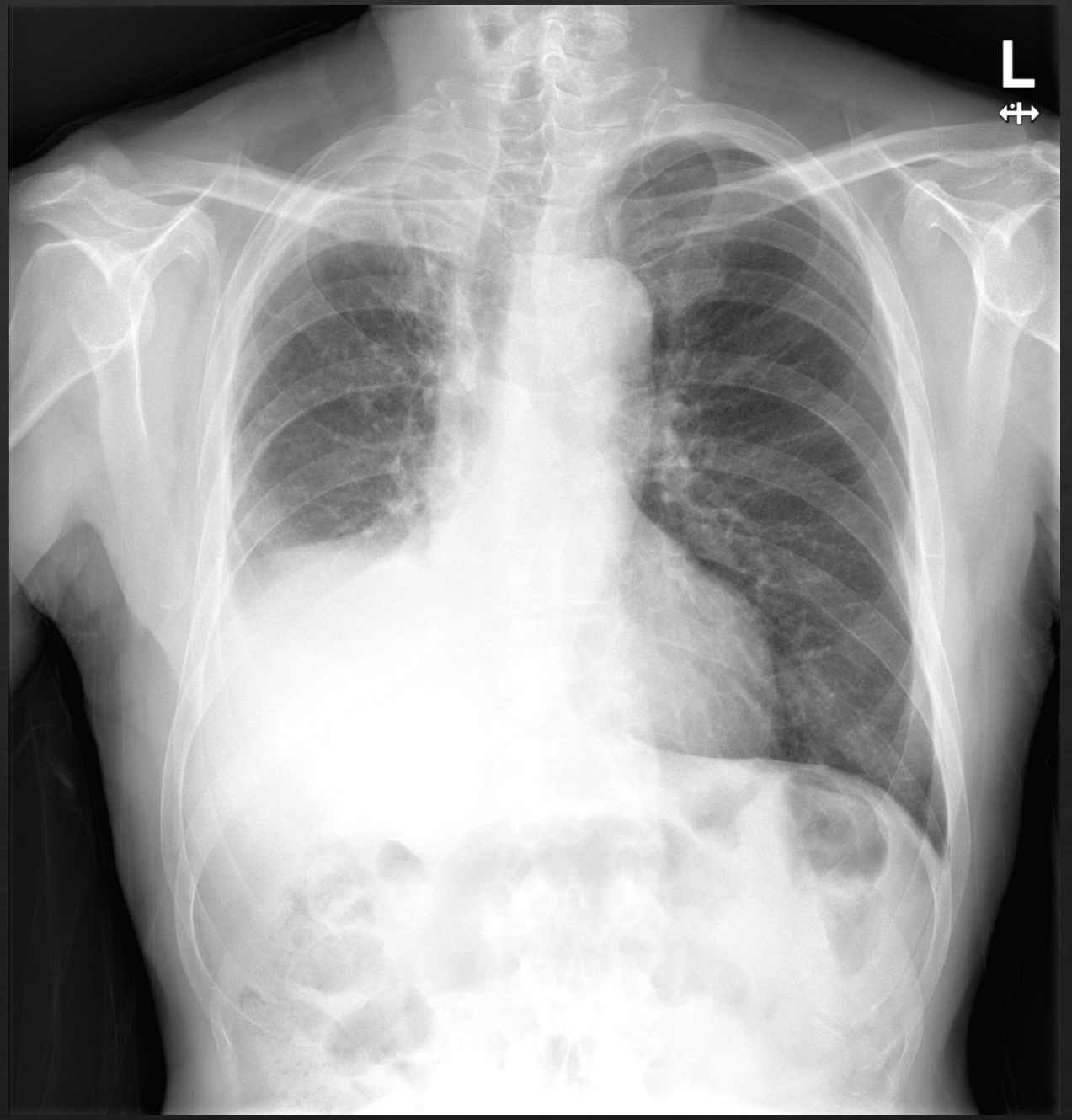
Neoadjuvant TP - CCRTx
(50-60Gy, 30 times)





VATS RLLobectomy with MLND

Adjuvant chemotherapy (TP)

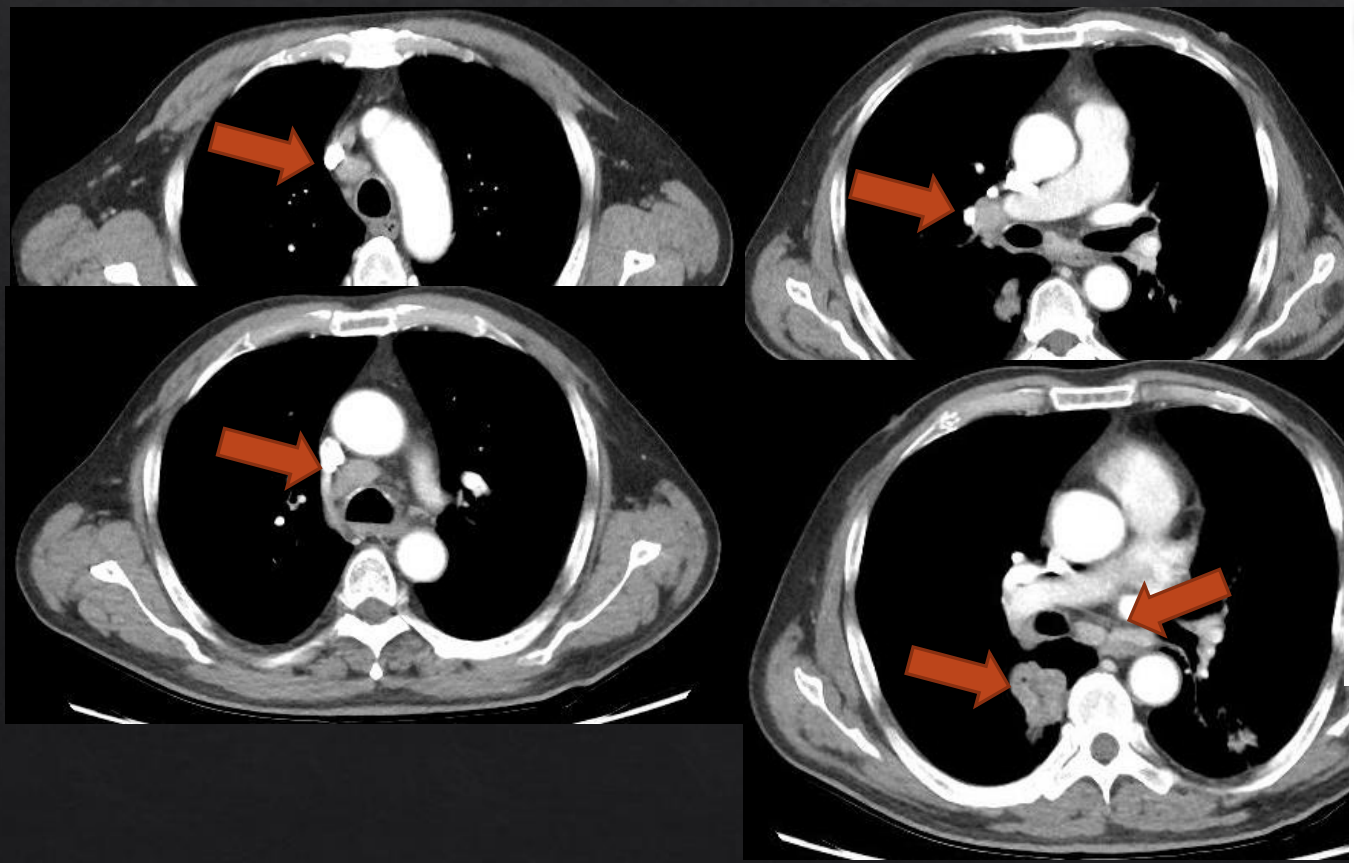


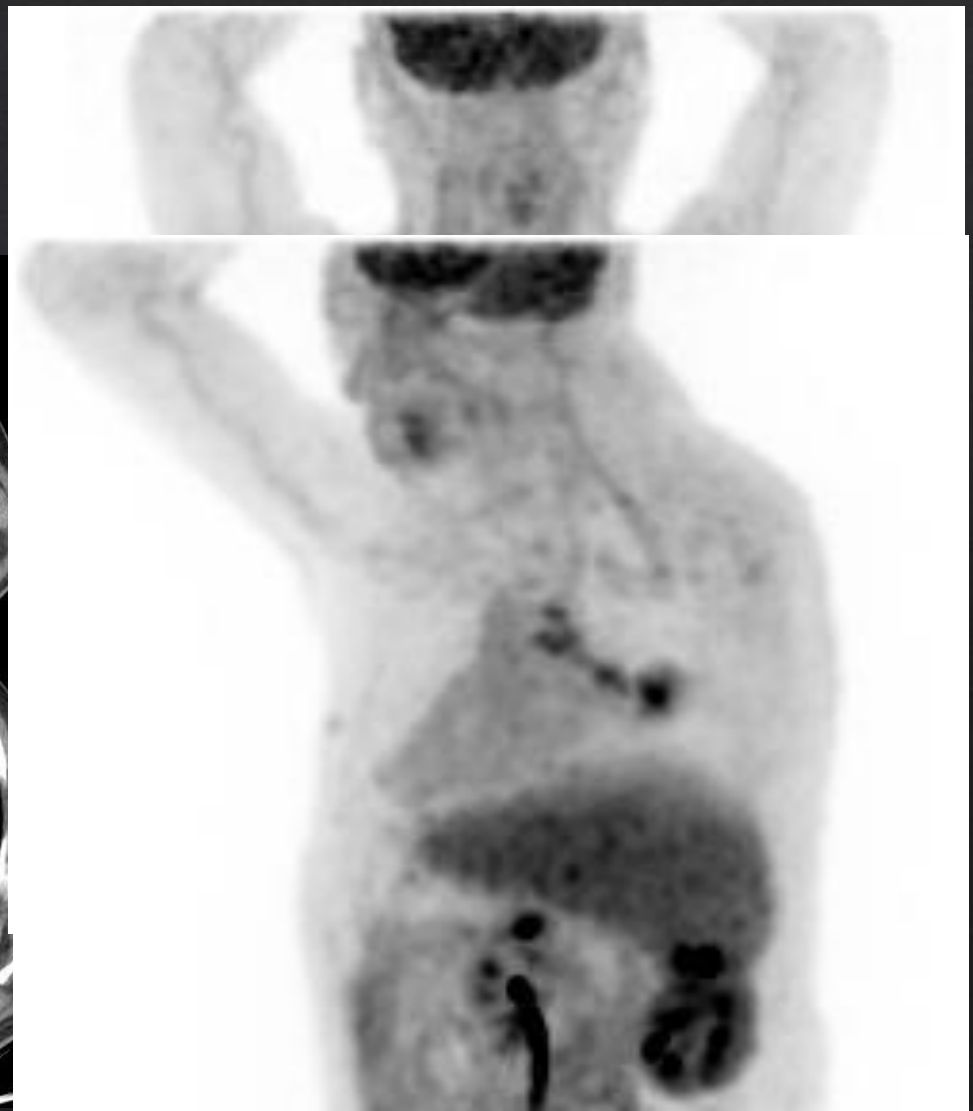
Alive with NED
(follow up duration : 30 months)

Multi-station N2 metastases

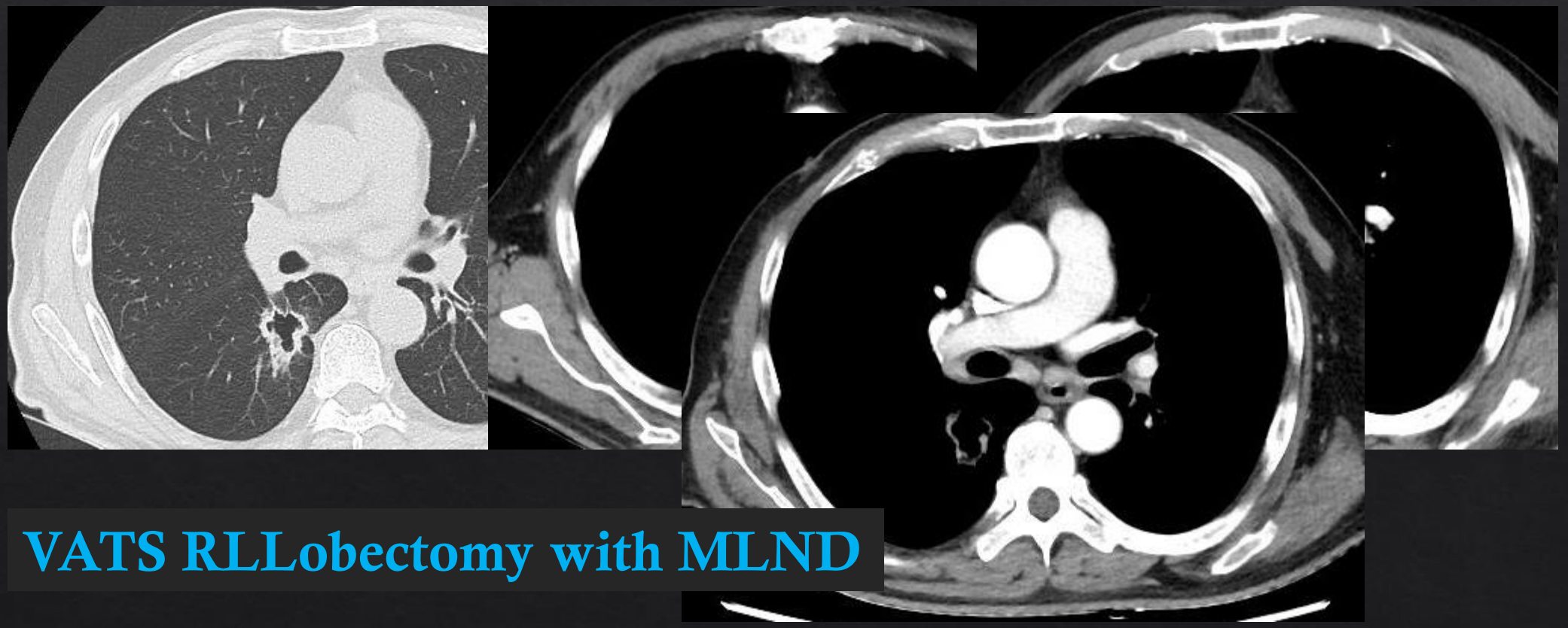
Case 3

- M 68
- Lung cancer, adenoca, RLL, ycT2aN2M0



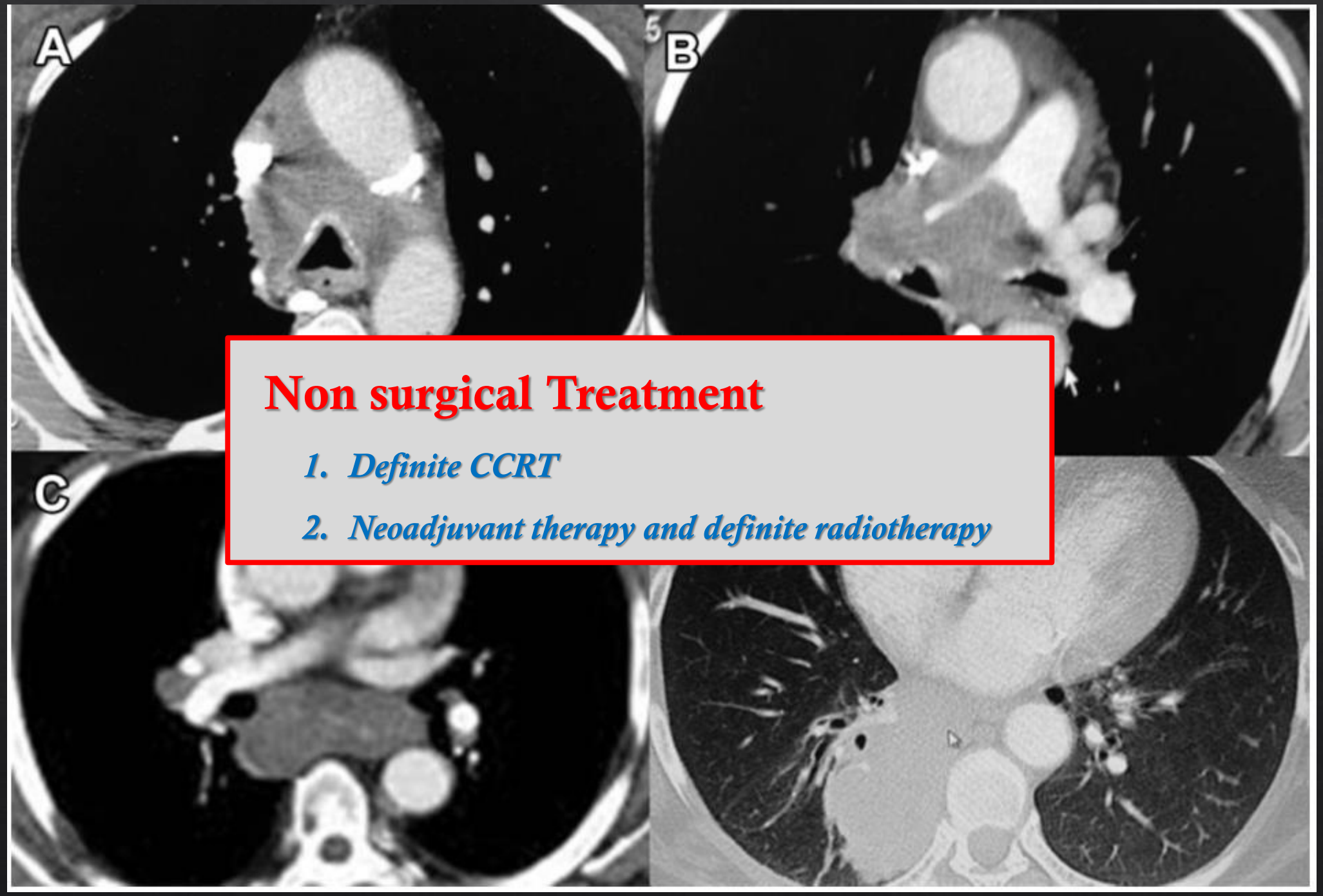


- #1 neoadjuvant gemcitabine/cisplatin 100%
- #2 neoadjuvant gemcitabine/cisplatin 80%



VATS RLLobectomy with MLND

Multi-station and infiltrative N2 metastases



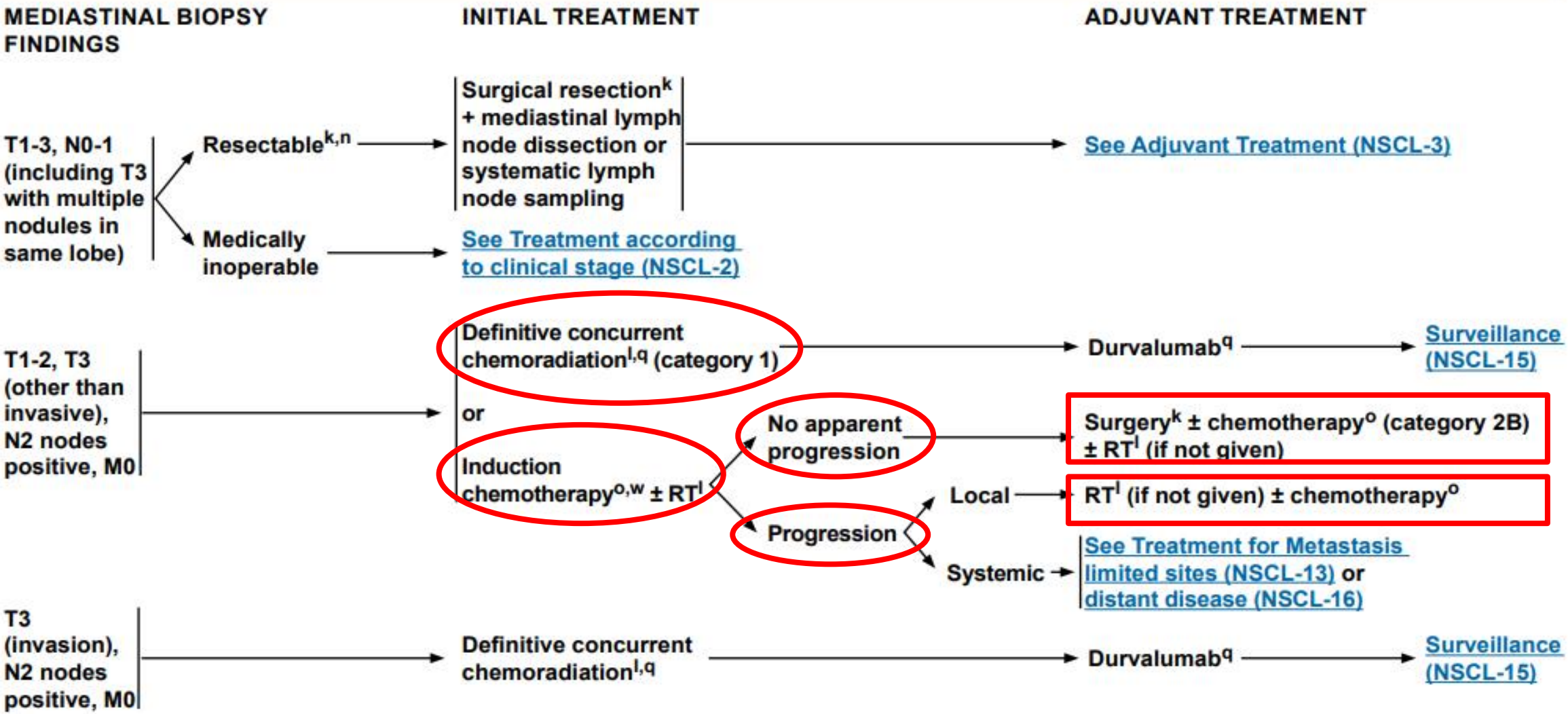
Non surgical Treatment

1. *Definite CCRT*
2. *Neoadjuvant therapy and definite radiotherapy*

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2018
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion



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SYSTEMATIC REVIEW AND META-ANALYSIS

OPEN

Is There a Survival Benefit in Patients With Stage IIIA (N2) Non-small Cell Lung Cancer Receiving Neoadjuvant Chemotherapy and/or Radiotherapy Prior to Surgical Resection

A Systematic Review and Meta-analysis

Neoadjuvant chemotherapy and/or radiotherapy prior to surgical resection do not appear to be clinically superior to neoadjuvant chemotherapy and/or radiotherapy prior to definitive radiotherapy in IIIA (N2) NSCLC patients. Neoadjuvant chemoradiotherapy does not improve survival compared to neoadjuvant chemotherapy alone.

chemotherapy and/or radiotherapy alone, or surgical resection after neoadjuvant treatment with chemotherapy and/or radiotherapy. We

But…

Improving surgical technique and instruments

- Low postoperative complication and surgical mortality
- Surgical role is changing and widening in advanced stage lung cancer

Important things are…..

Considering below…..

- ***Pattern and extent of mediastinal node involvement***
- ***Resectability***

> ***multidisciplinary discussion***

- *adequate selection of treatment modality*
- *meticulous treatment delivery*


경청해 주셔서
감사합니다