肺癌手術與合併治療新進展

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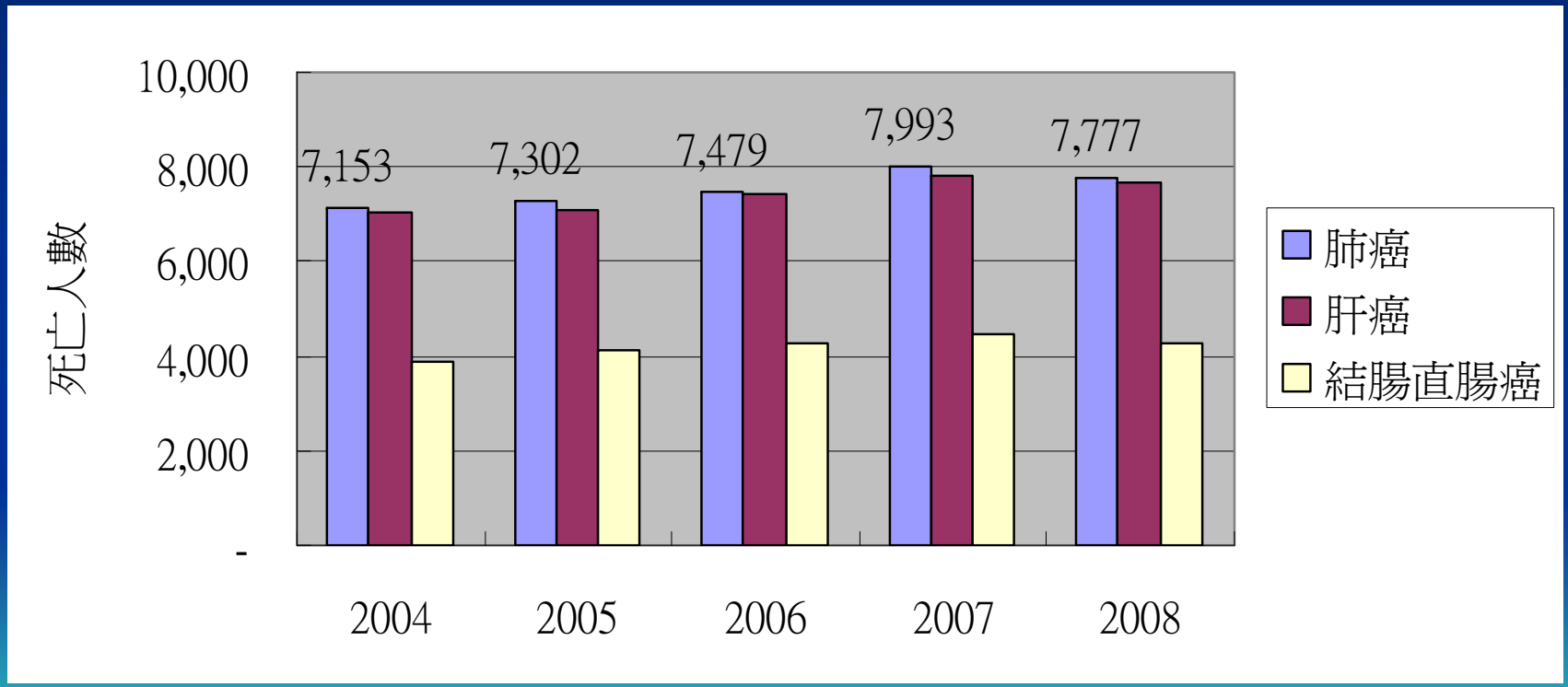
綱要

- 肺癌手術及麻醉新進展
  - 胸腔鏡肺葉切除術
  - 胸腔鏡肺節切除術
  - 免插氣管內管之胸腔鏡手術
- 合併治療新進展
  - 合併化學治療
  - 合併標靶治療

肺癌：近五年來台灣癌症死亡原因之第一名



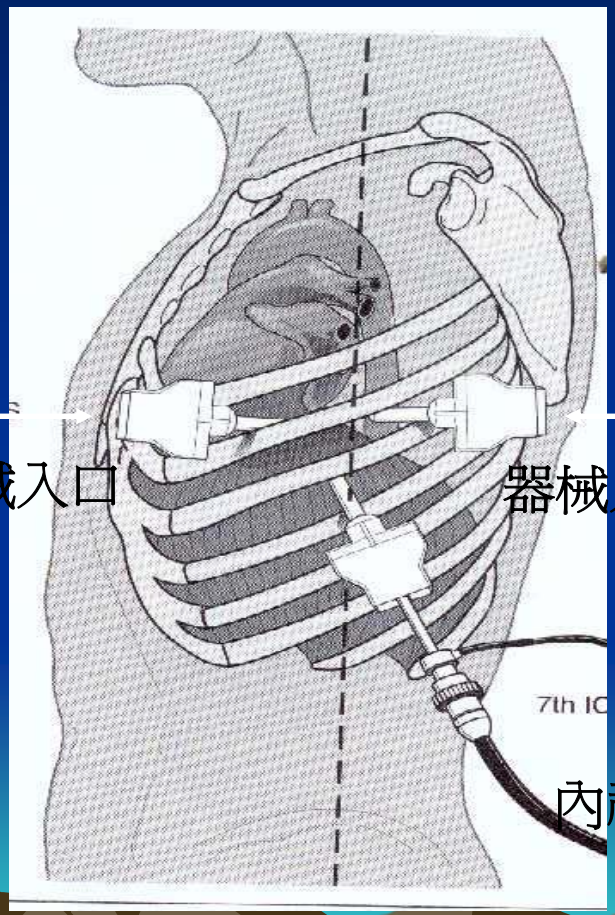
資料來源：行政院衛生署

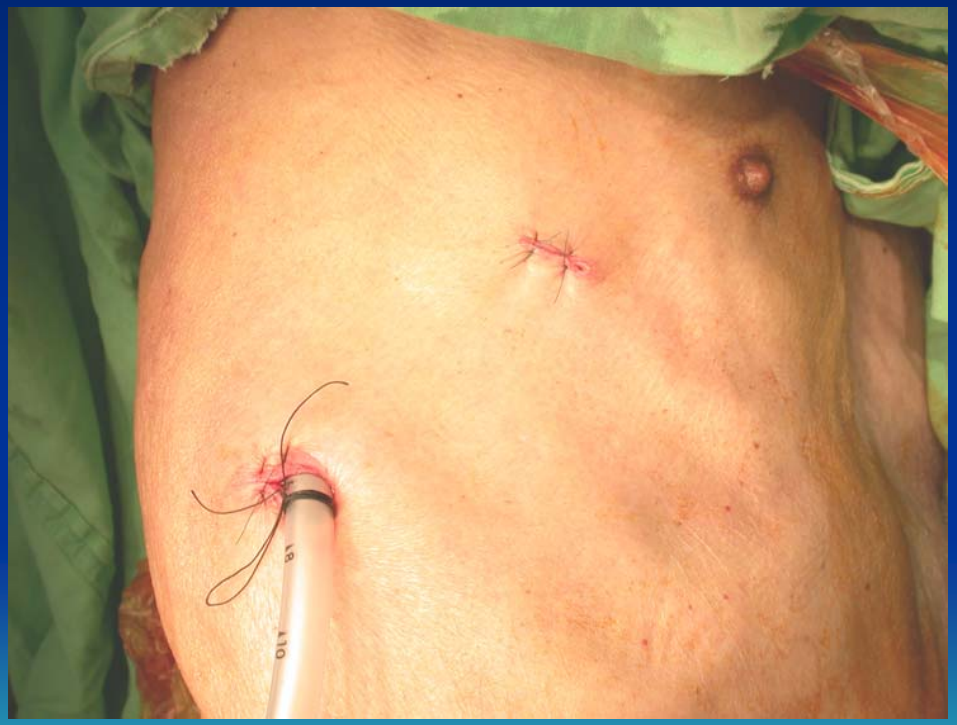
非小細胞肺癌：

- Consisting ~80% of lung cancer
- Surgery:
  - Curative resection: the best hope for cure, particularly for those with early disease

Standard Posterolateral Thoracotomy:
傷口大，恢復慢，長期疼痛比例高

胸腔鏡手術器械配置圖及傷口





胸腔鏡手術：優點

- 胸腔鏡肺葉切除術後之肺功能影響較小
- 胸腔鏡手術引發較少之發炎反應，對免疫功能較好
- 胸腔鏡肺葉切除術後長期生活品質較好

1. Kaseda S. Ann Thoracic Surg, 2000
2. Leaver HA. Eur J Clin Investi, 2000
3. Sugiura H. Surg Laparo Endo, 1999

肺葉切除術：胸腔鏡或開胸手術？

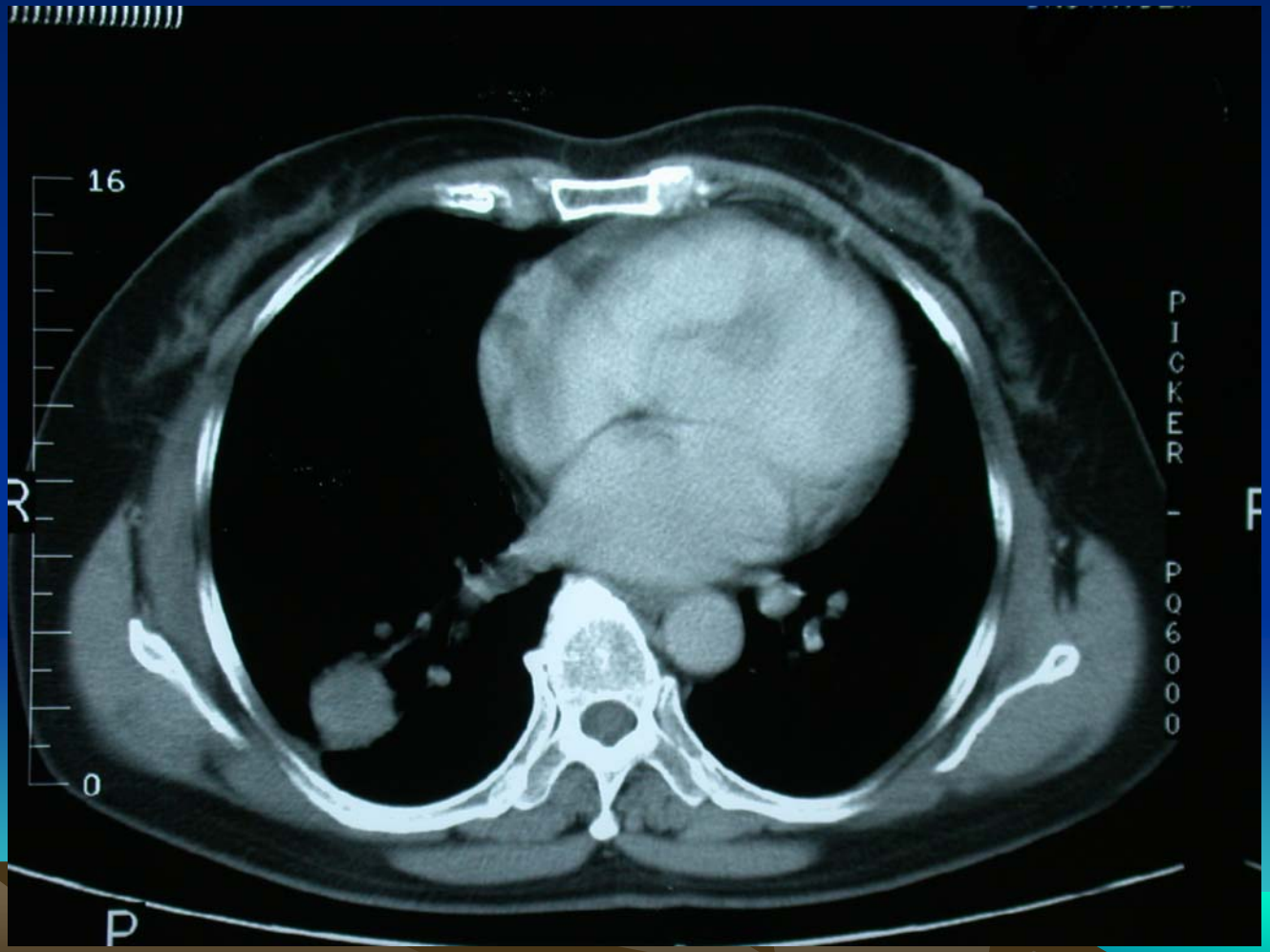
- 目前胸腔鏡肺葉切除術已經有許多醫學中心使用於肺癌之手術治療.
- 安全性：與開胸手術類似，甚至更好
- 腫瘤學方面考量(JCO 2009 meta-analysis)：
  - 局部復發率沒有差別
  - 遠處轉移率較低
  - 5年死亡率較低

Yan TD. J Clin Oncol 2009.

VATS versus Thoracotomy for Lung cancer: NTUH experience

- Retrospective study: 1997-2006
- 768 patients with lung cancer undergoing curative resection at NTUH
- 344 patients were excluded
  - stage III and IV
  - tumor size > 5 cm,
  - undergoing wedge resection, sleeve lobectomy or pneumonectomy.
- Only 424 patients undergoing lobectomy or bilobectomy were included for analysis.

65y/o female, RLL lung adenocarcinoma

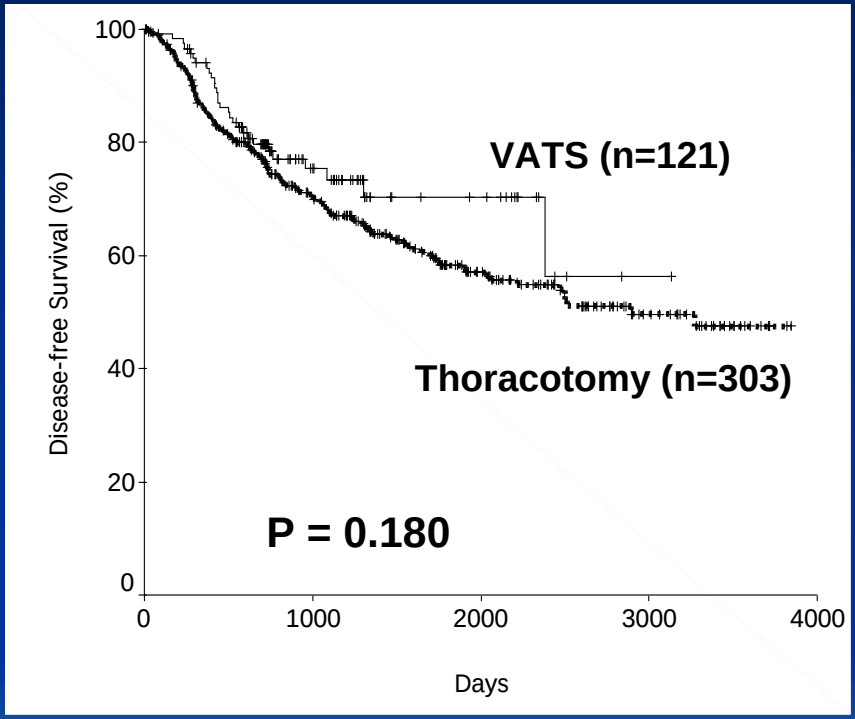


RLL VATS Lobectomy

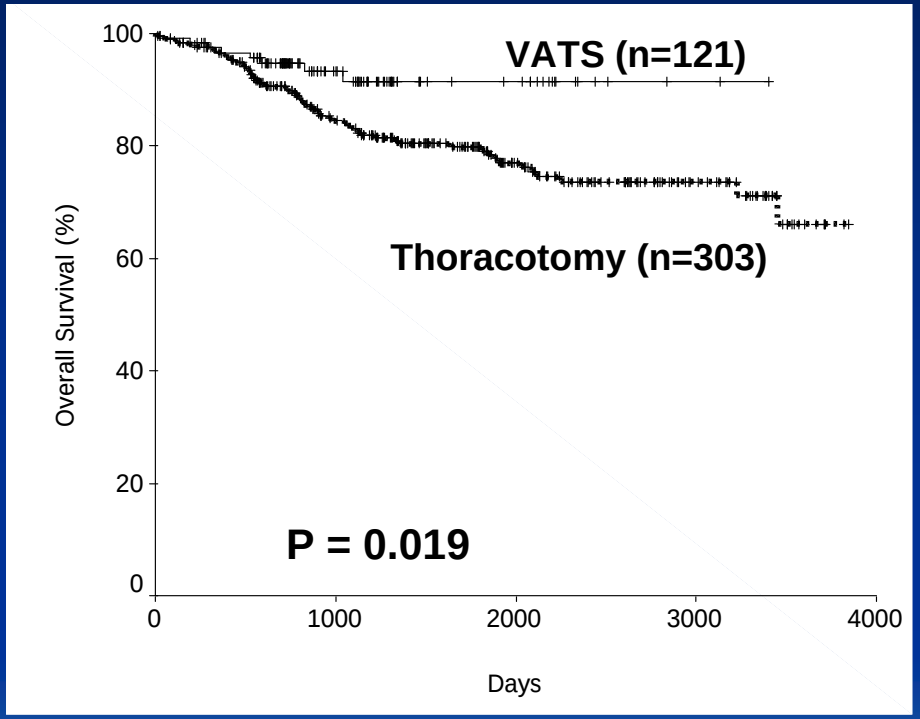
Table 1. Demographic data (1997-2006)

	VATS (n=121)	Thoracotomy (n=303)	p value
Sex (male)	47 (39%)	167(55%)	0.003
Age (years)	64.5 ± 11.8	64.4 ± 10.5	0.304
Tumor size (cm)	2.7 ± 1.0	3.0 ± 1.1	0.002
Cell type			0.032
Adenocarcinoma	99 (82%)	215 (71%)	
Squamous carcinoma	15 (12%)	72 (24%)	
Others	7 (6%)	16 (5%)	
Clinical staging			
Ia	67 (55%)	116 (38%)	0.013
Ib	42 (35%)	137 (45%)	
IIa	3 (3%)	15 (5%)	
IIb	9 (7%)	35 (12%)	
Procedure			0.003
Lobectomy	120 (99%)	280 (92%)	
Bilobectomy	1 (1%)	23 (8%)	
Operation Mortality	0 (0%)	3 (1%)	0.263

VATS = video-assisted thoracic surgery



Disease-free survival



Overall survival

Multivariate analysis of factors affecting disease-free survival (424 patients)

	Relative Risk	Confidence Interval	p value
Sex (female vs male)	0.707	0.497-1.006	0.054
Age (≤65y vs >65y)	0.628	0.450-0.877	0.006
Cell type (Adenoca vs others)	1.576	1.054-2.355	0.027
Clinical staging (I vs II)	3.281	2.243-4.799	<0.001
Operation (lobectomy vs bilobectomy)	0.707	0.376-1.328	0.281
Approach (thoracotomy vs VATS)	1.142	0.0.747-1.745	0.540

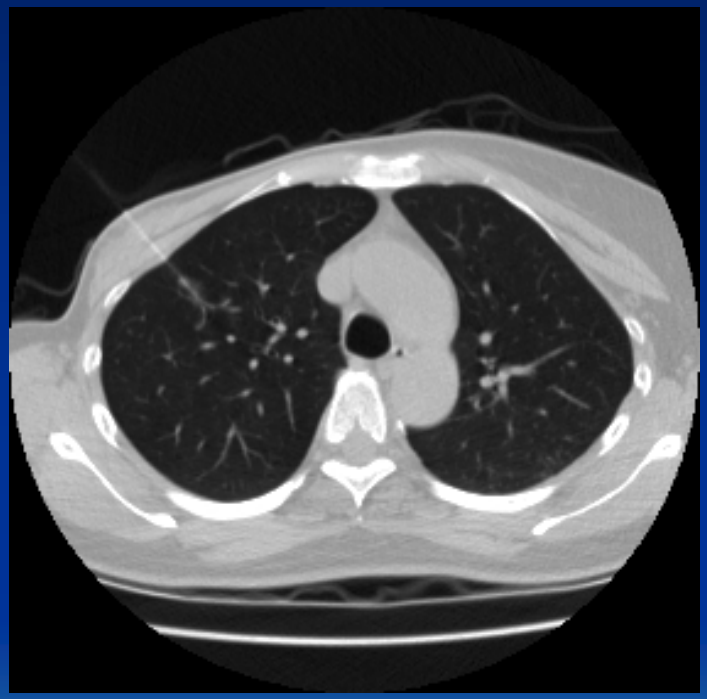
1. Old age, adenocarcinoma, and advanced stage are associated with poor disease-free survival.
2. Operation method and approach method: not correlated with disease-free survival.

Conclusion and Discussion

- VATS lobectomy is a safe alternative to posterolateral thoracotomy in treating lung cancer patients
  - Comparable complication and mortality rates
- Long-term survival: unclear by multivariate analysis
- Further prospective studies are required

62 歲女性，胸部電腦斷層發現0.7公分結節，是否一定要接受肺葉切除？

52歲女性, right lung small nodule



Needle localization with a hook-wire system

Needle localization

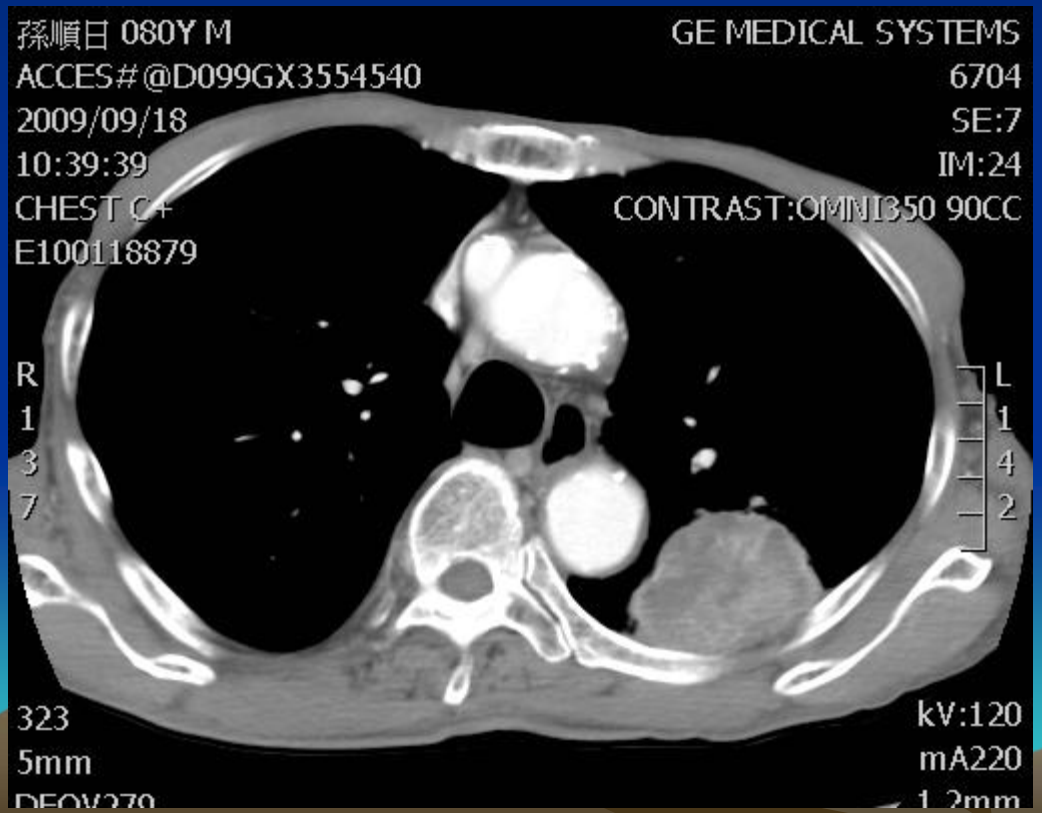
VATS sublobar resection for lung cancer

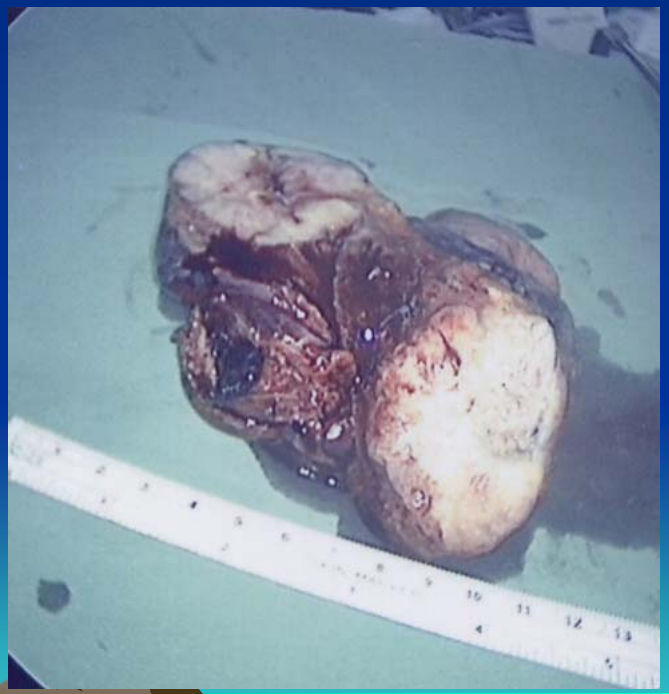
- Including wedge resection or segmentectomy
- Similar overall and disease-free survival in large retrospective studies
- Indications:
  - Tumor size < 2cm, especially for BAC
  - With prior resection
  - Old patients with poor pulmonary reserve

Bilfinger TV. Curr Opin Pulm Med 2008

VATS segmentectomy

80歲男性
CAD 心導管支架置放術後
須最近二月體重減輕8公斤





免氣管插管之胸腔鏡手術
Non-intubated thoracoscopic surgery

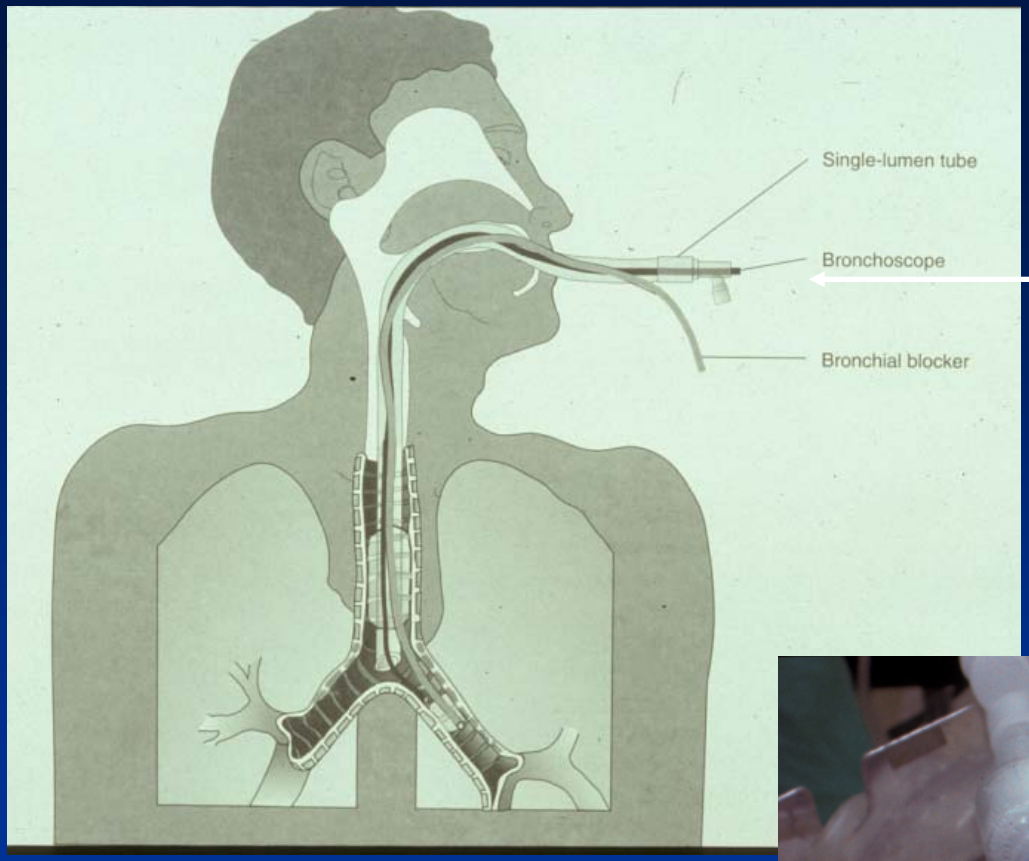
傳統胸腔手術之麻醉

- General anesthesia with muscle paralysis
- Endotracheal intubation with one lung ventilation

-> 醫師輕鬆，病患危險增加：

  - Increased risk of pneumonia
  - Impaired cardiac performance
  - Barotrauma by ventilator
  - Pulmonary atelectasis
  - Intubation-related complication

胸腔手術之麻醉及插管



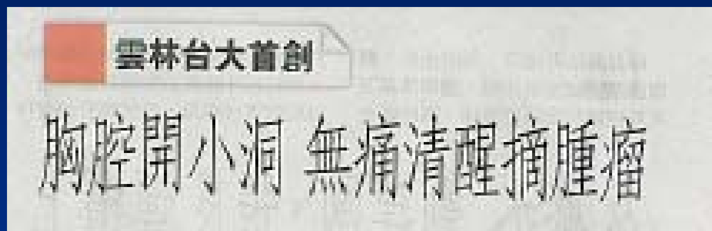
Double lumen endotracheal tube

Advantages of non-intubated thoracic surgery with epidural anesthesia

- Effect on cardiovascular system
  - Improved myocardial blood flow
  - Improved LV function
  - Reduced heart rate and arrhythmia
- Effect on lung function
  - Intact cough ability immediate after op
  - Improved post-op lung function
- Effect in patients with COPD
  - Decreased bronchospasm
  - Decreased respiratory complications

Mineo TC. Eur J Cardiothorac Surg. 2007

Non-intubated (Awake) thoracoscopic surgery



雲林台大首創

胸腔開小洞 無痛清醒摘腫瘤

迷你胸腔鏡手術

切除肺腫瘤 全程醒著看

無痛開胸 病患清醒傷口小

開口僅0.3公分 麻醉風險低

邊開邊聊天

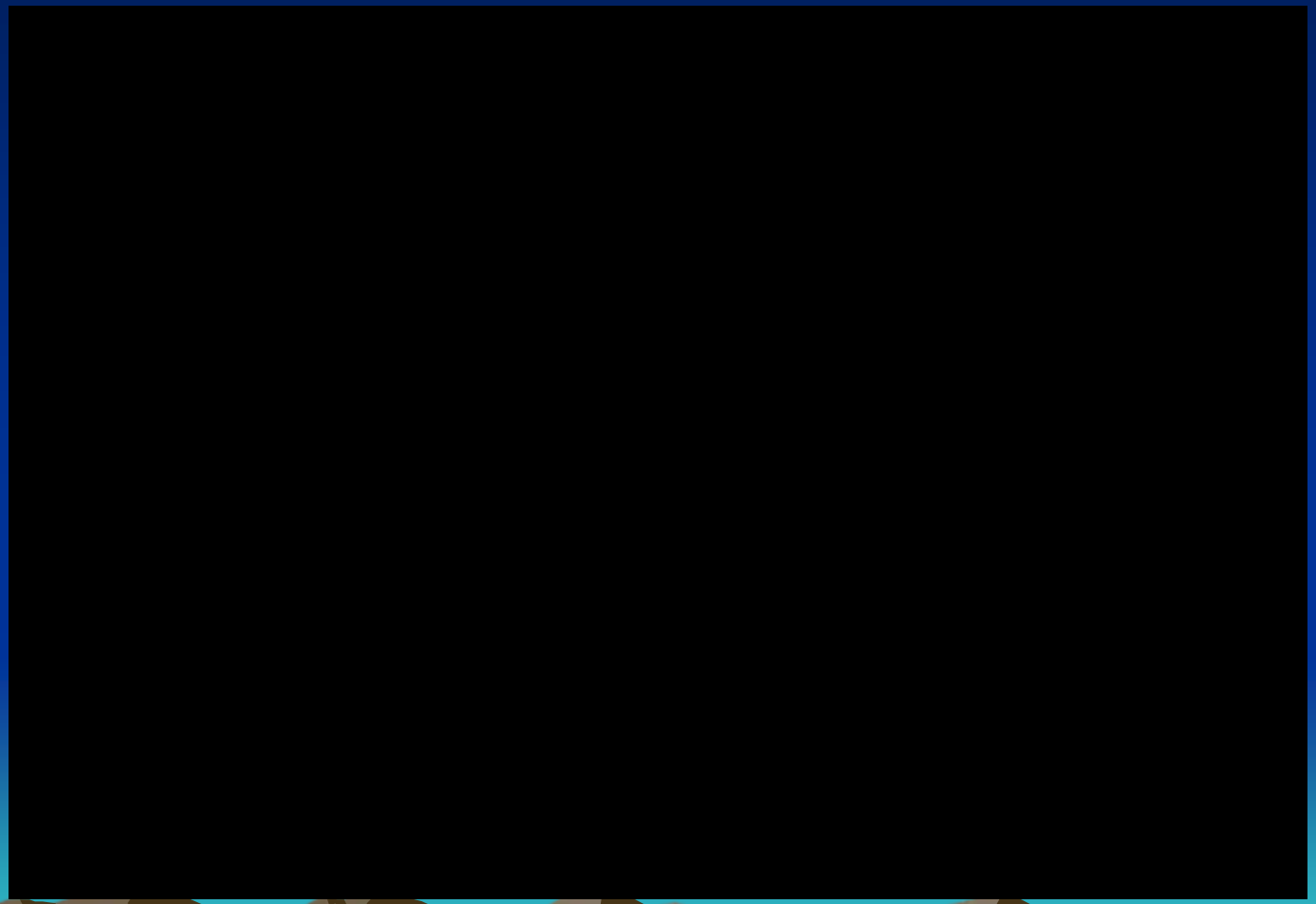
傷口不留痕

台大首創

健保也有給付

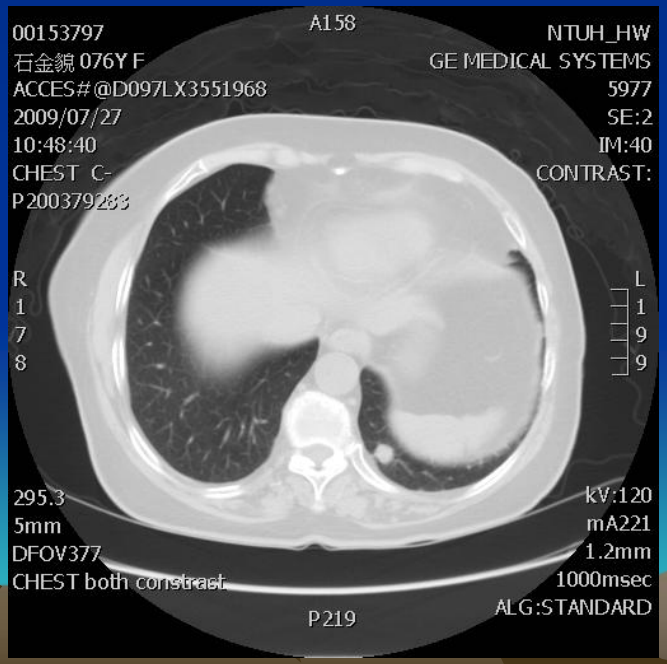
時間不能拖久

手術錄影帶:

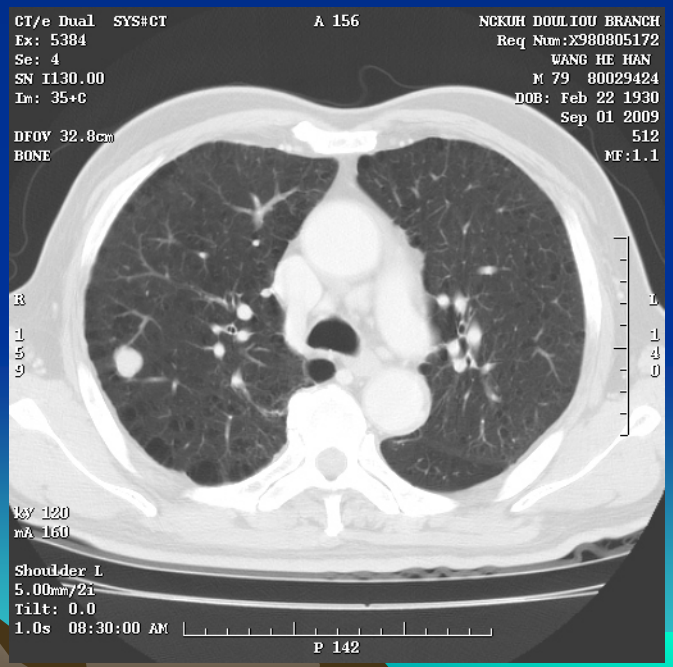


免氣管插管之迷你胸腔鏡切除肺腫瘤

76歲女性，大腸癌術後
左下肺1公分腫瘤



81歲男性, COPD
雙側肺腫瘤，無診斷



胸椎硬腦膜外麻醉 + 傷口局部麻醉
（沒有氣管插管）

病人術後恢復良好

- 術後病患可以自行移床，可馬上進食
- 術後第一天拔除胸管
- 術後第二天出院
- 術後2-3天可恢復正常生活作息

Non-intubated thoracoscopic surgery: NTUH experience

- VATS wedge resection: 18 cases
- VATS lobectomy: 9 cases
- VATS segmentectomy: 1 cases
- No major complications, no mortality

免氣管插管胸腔鏡手術總結

- 未來的世界是老年人的世界
  - 體力不好、心臟不好、呼吸功能不好、手術併發症比例高
- 不僅開刀方式要微創，麻醉方式也要微創
  - General anesthesia with endotracheal intubation決不是每一台胸腔手術的必然選擇
- 未來主流：Target anesthesia and minimal invasive approach: Non-intubated thoracoscopic surgery

Multimodality Approach in Patients with Stage-III Resectable Non-Small Cell Lung Cancer:

Literature Review and the Experience of

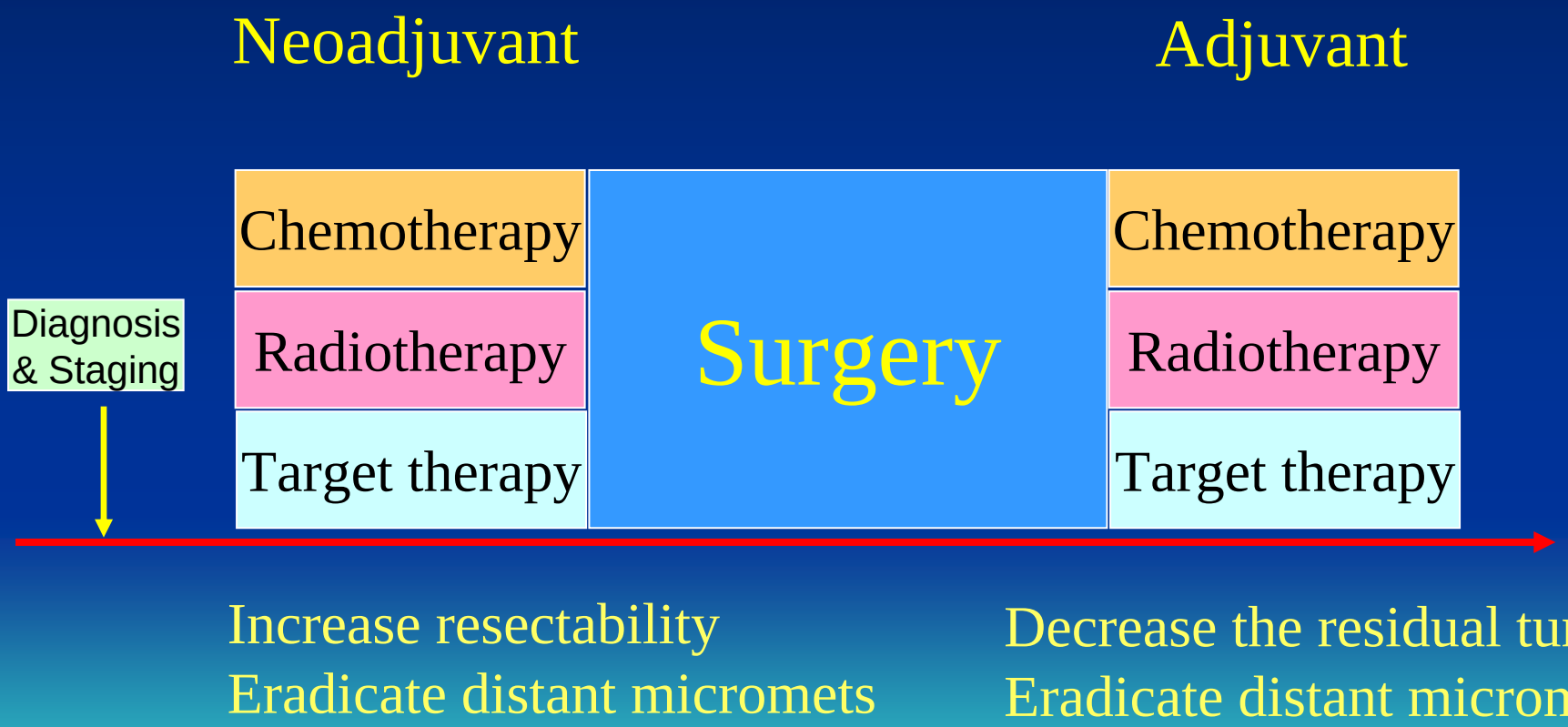
National Taiwan University Hospital

Stage III Resectable Disease:

- Disappointing long-term outcome by "surgery only" approach
  - Pre-op positive mediastinal nodes: 5% 5-y survival
  - Intra-operative multilevel nodal involvement: 11% 5-y survival
  - Distant metastasis in 80% of cases with relapse
- Systemic treatment with combined modality for better control of both local and disseminated diseases is indicated

Andre F, JCO 2000;18:2981

Multimodality Approach for Stage III Resectable NSCLC



Theoretical Advantage of Neo-adjuvant Chemotherapy

- Better compliance & all patients eligible (many don't receive adjuvant CT after surgery)
- Reduce tumor burden
  - Downstages: Mediastinal lymph node clearance
  - More complete resection
- Earliest treatment of micro-metastatic disease

Randomized Trials of Neoadjuvant Therapy in IIIA NSCLC

	Stage	No. of patients	Regimen	MS (months)	5-yr SR (%)	Hazard *P* value
Pass et al. (1992)	IIIA	14	Surgery	16	12	0.80
		13	CT+surgery	29	30	NS
Roth et al. (1994)	IIIA	32	Surgery	11	14	0.78
		28	CT+surgery	64	36	<0.05
Rosell et al. (1994)	IIIA	30	Surgery	8	0	0.75
		29	CT+surgery	26	25	<0.05
Depeirre et al. (2002)	IB-IIIA	119	Surgery	26	NA	0.82
		101	CT+surgery	37	NA	0.15

Concerns: 1. Positive results: only small patient numbers

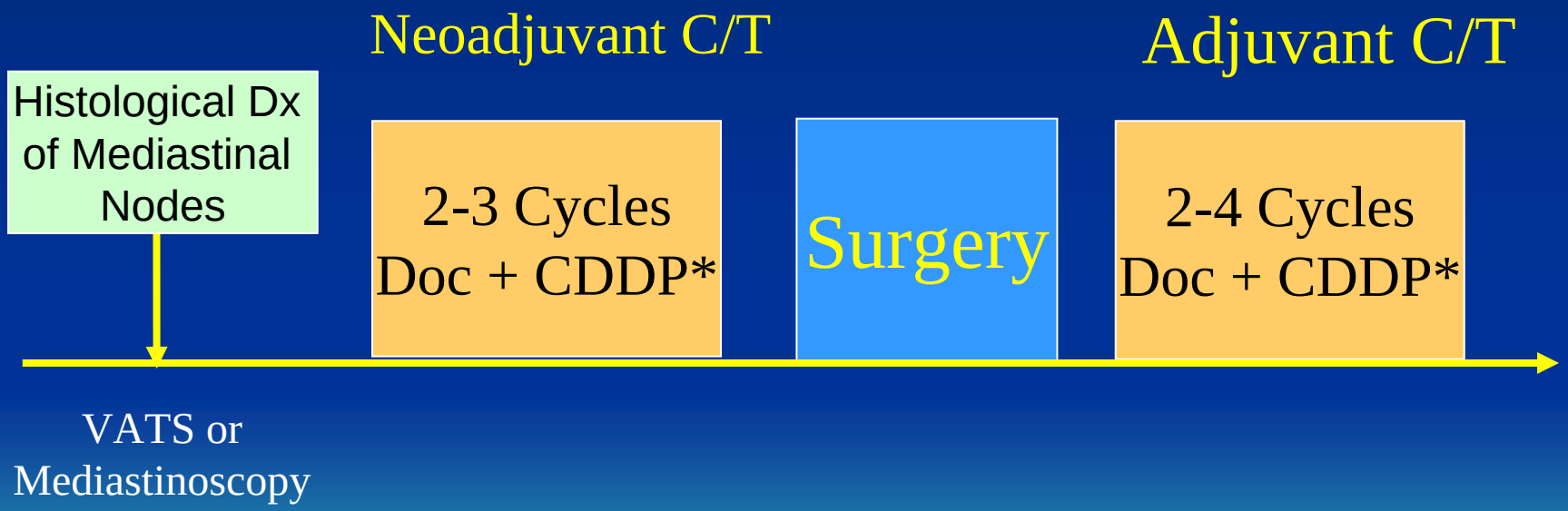
2. Most trials stop earlier because positive results of adjuvant C/T

Neoadjuvant Chemotherapy with Docetaxel-Cisplatin in N2 NSCLC: Results of a Prospective Study in NTUH

Jin-Hsing Chen, Muzo Wu, Chih-Hsin Yang, Fu-Chang Hu, Jin-Yuan Shih, Kuan-Yuh Chen, CC Ho MD, ZZ Lin, Chong-Jen Yu, Yuan-Chi Lee

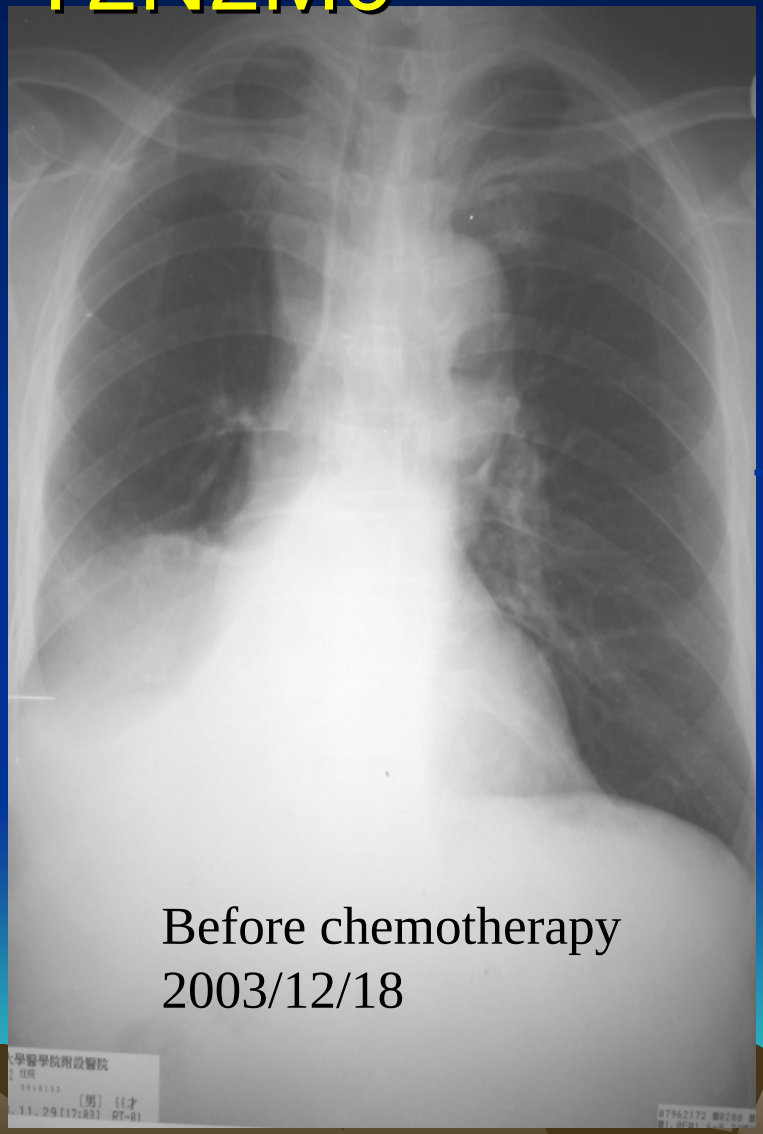
Study Protocol (2003-2005):

Inclusion criteria:
Patients with resectable N2 NSCLC (stage IIIA or IIIB)

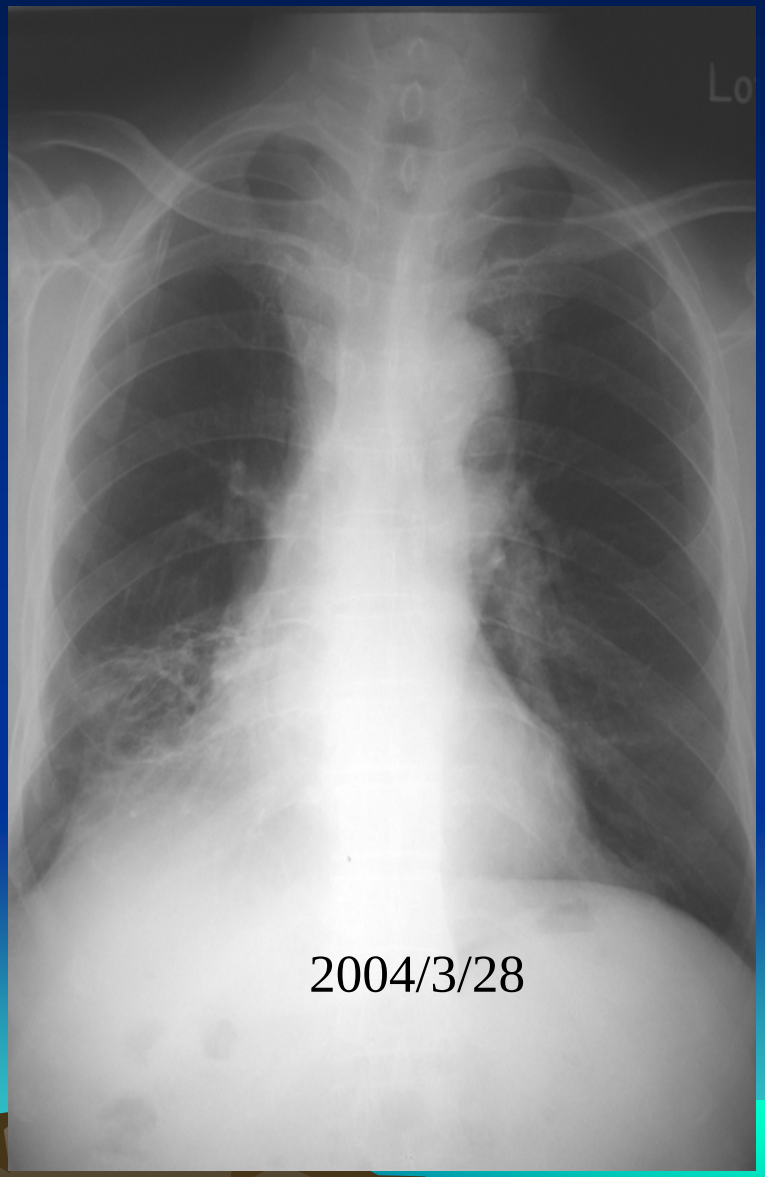


*Doc (36 mg/m2, d1,8,15,29,36,43), CDDP (70 mg/m2, d15,43) before and after surgery

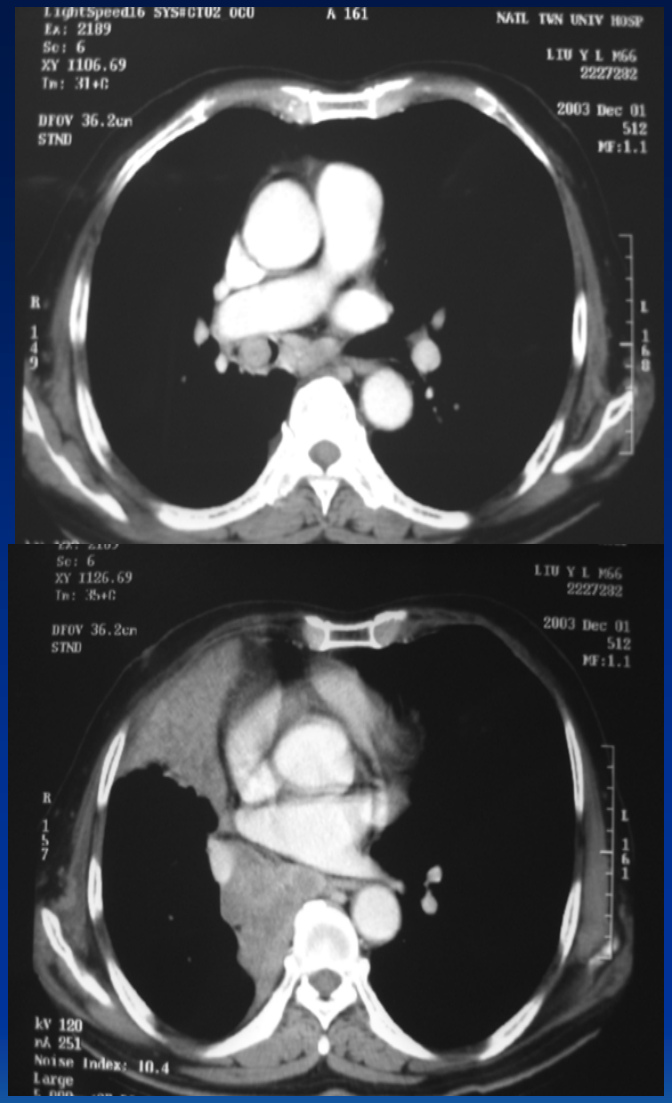
57y/o M, SqCC, T2N2M0



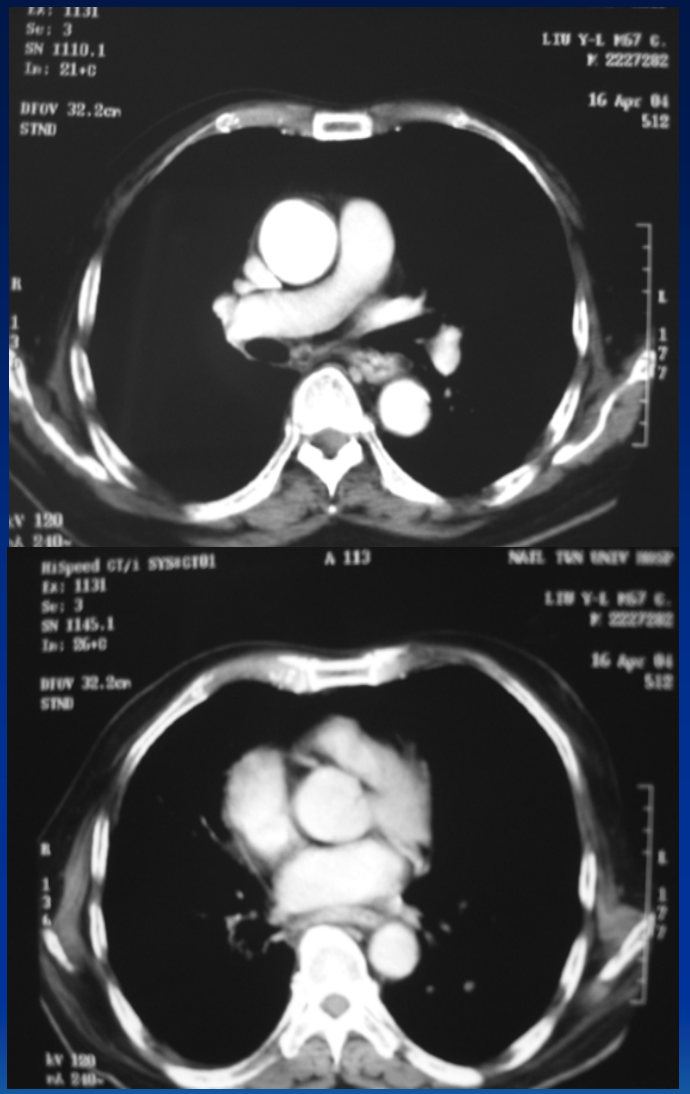
Before chemotherapy
2003/12/18



2004/3/28

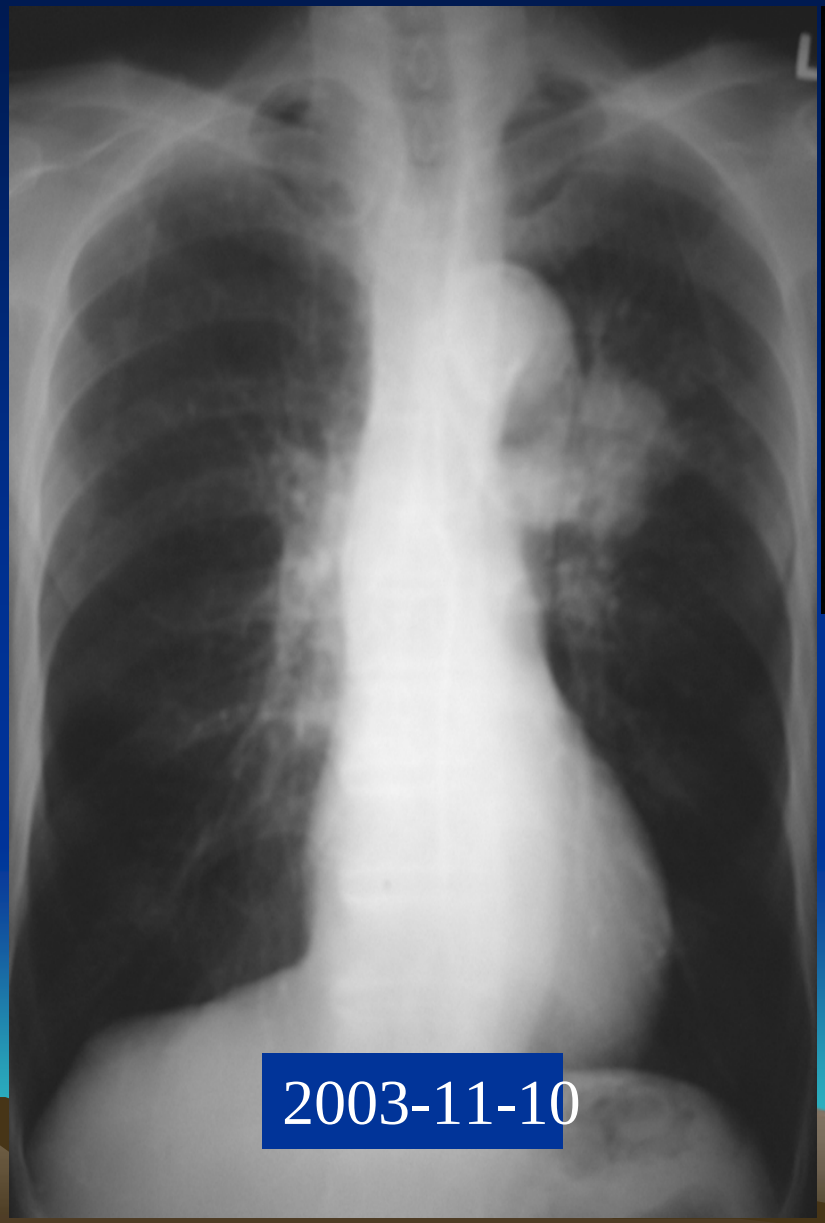


Before neoadjuvant C/T

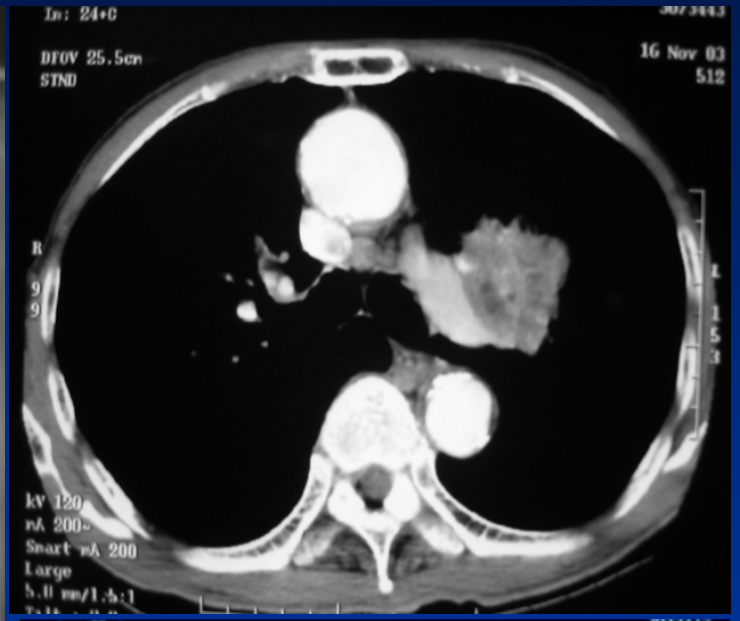


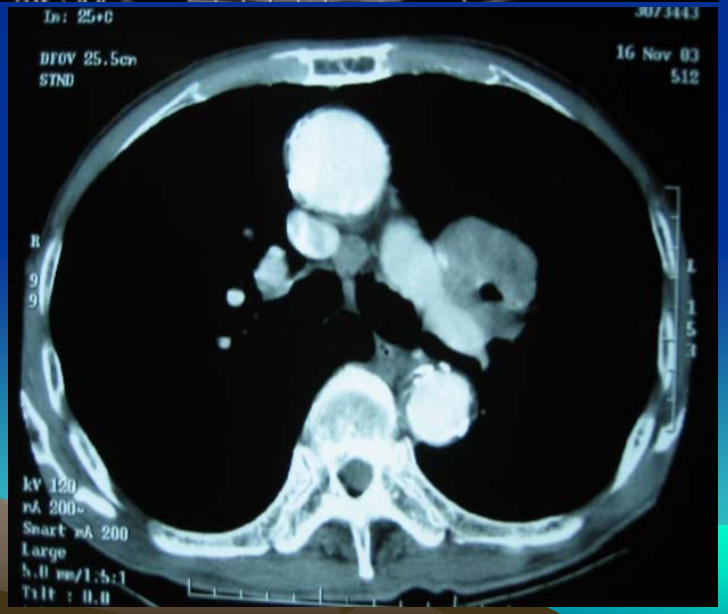
After neoadjuvant C/T

78 y/o man, T3-4N2M0. FEV1 1.02L, FEV1% 48.6%



2003-11-10

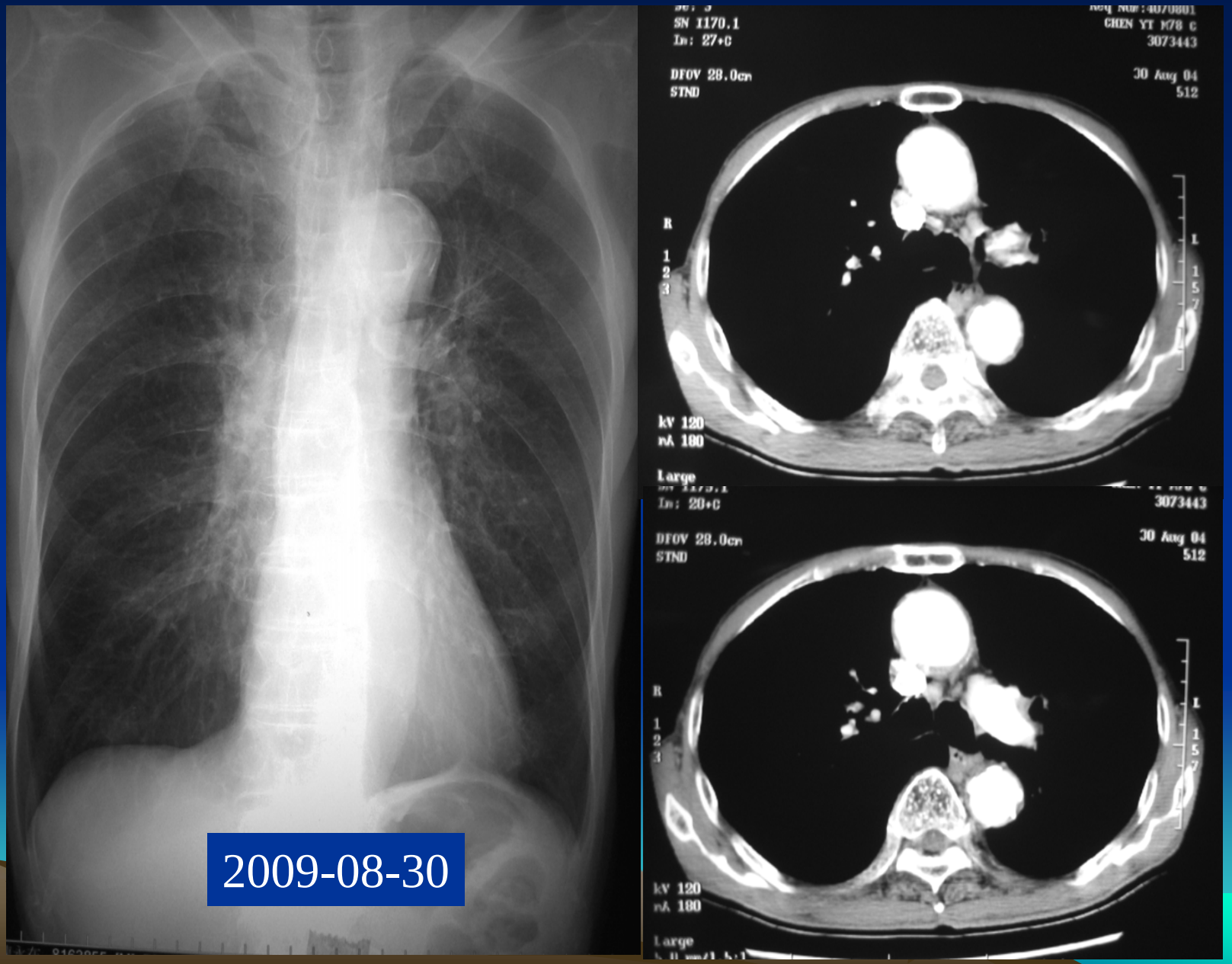




After 3 cycles of Doc/Cis. Surgeon hesitates. Give 3 more cycles

2004-01-29

Complete 6 cycles of Doc/Cis. FEV1 1.30L, FEV1% 55.8%



Neoadjuvant C/T + Surgery + Adjuvant C/T with Docetaxel+Cisplatin, NTUH (2004-2005)

- Results (39 patients)
  - Overall response rate: 69.3%
  - Surgery performed in 35 patients (89.7%)
    - No operation mortality or major morbidity
  - Median follow-up: 49 months
  - Recurrence: 62.9%
  - 3 year overall survival: 75.9%
  - univariate analysis: early recurrences were correlated with female gender (p=0.024), age < 60 years (p=0.044), adenocarcinomas (p=0.005), and increased number of residual metastatic lymph nodes (p=0.022).
  - Multivariate analysis: adenocarcinoma was the strongest factor for early recurrences over squamous cell carcinoma (p=0.0242).

Conclusions (2003-2005) :

- Combination of neoadjuvant C/T + surgery +/- adjuvant C/T with Doc+CDDP provides a safe and feasible alternative for stage III NSCLC patients
- 3-year overall survival: satisfactory
- Adenocarcinoma was an independent factor for early recurrences over squamous cell carcinoma

Adjuvant Chemotherapy for Lung Cancer

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

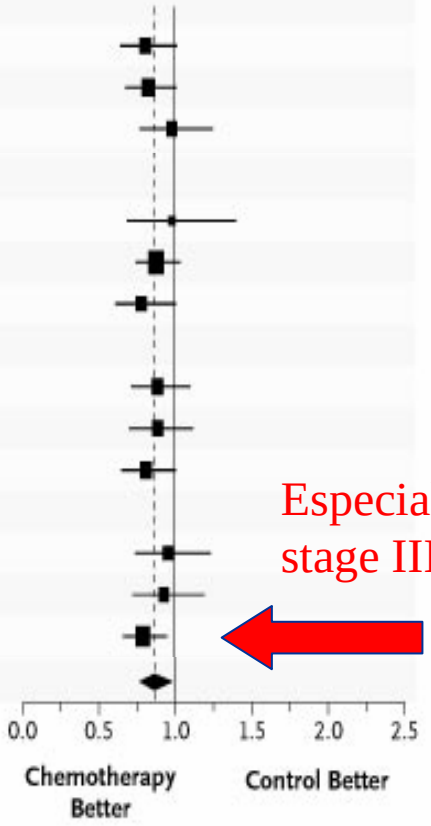
Adjuvant Chemotherapy for Lung Cancer — A New Standard of Care

Ronald H. Blum, M.D.

IALT Trial (1867 patients):

Cisplatin-based adjuvant C/T improves survival with completely resected NSCLC

Covariate	Chemotherapy Group	Control Group	P Value for Interaction	P Value for Trend
	No. of deaths/No. of patients			
Age			0.46	0.26
<55 yr	141/314	163/316		
55–64 yr	181/355	214/386		
>64 yr	147/263	127/233		
Tumor stage			0.57	0.32
1	67/169	59/151		
2	282/570	314/603		
3 or 4	120/193	131/181		
Nodal status			0.80	0.56
0	164/423	174/427		
1	144/271	155/267		
2	161/238	175/241		
Stage			0.41	0.21
I	115/333	122/348		
II	123/230	126/222		
III	231/369	256/365		
Total	469/932	504/935		



Especially for stage III patients

(IALT. NEJM 2004;350:351)

結論：Cisplatin-based adjuvant C/T is suggested for stage II and III disease

TABLE 1. Overall Survival Benefit in Adjuvant Chemotherapy Trials by Stage and Duration of Follow-Up

	IALT[4]		CALGB[40]		JBR.10[5]		ANITA[3]
Follow-up (yr)	4.7	7.5	4	6.2	5.2	9.3	6.3
Overall survival benefit by stage							
IB HR			0.62 ($p = 0.03$)	0.83 ($p = 0.12$)	0.94 ($p = 0.79$)	1.03 ($p = 0.87$)	1.14 (p = NS)
II HR	*0.86 ($p = 0.03$)	*0.91 ($p = 0.10$)			0.59 ($p < 0.01$)	0.68 ($p = 0.01$)	0.67 ($p < 0.05$)
IIIA HR							0.60 ($p < 0.05$)

Stage distribution by study: IALT: IA (10%), IB (27%), II (25%), and III (39%); CALGB: IB (100%); JBR.10: IB (45%), II (55%); and ANITA: IB (36%), II (24%), III (39%).
*Stage-specific outcomes not reported in IALT. Pooled results for all stages shown here.
IALT, International Adjuvant Lung Trial; CALGB, Cancer and Leukemia Group B, HR, hazard ratio.

Goodgame B. J Thorac Oncol 2009.

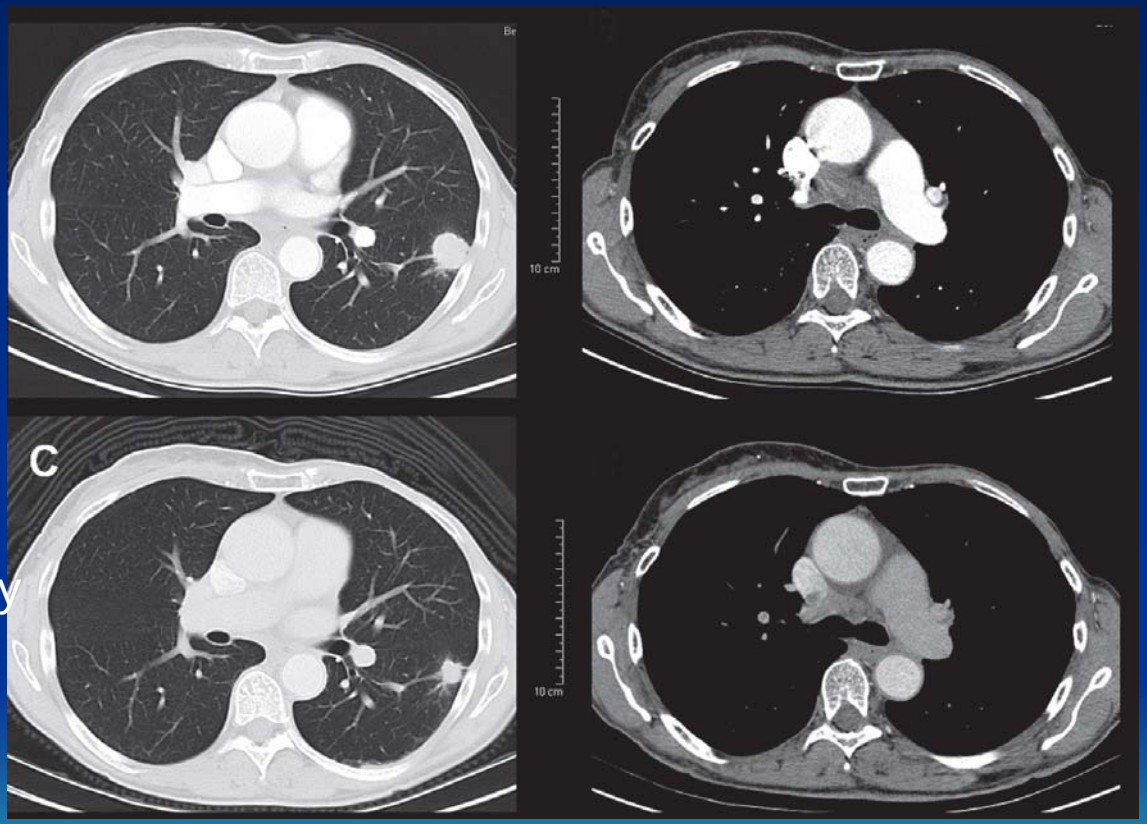
The role of target therapy in neoadjuvant or adjuvant for lung ca: unclear

TARGETS	TARGETED AGENTS
EGFR family	Erlotinib, gefitinib
Angiogenesis	Bevacizumab, ZD2171
Farnesyltransferase	Ionafrmib
Histone deacetylase	LAQ824, CI994
mTOR	RAD001, AP23573
COX2	Celecoxib
.....	

Neoadjuvant (Induction) Erlotinib Response in Stage IIIA Non – Small-Cell Lung Cancer

67 y/o female
Adenocarcinoma
Stage IIIA (T1N2M0)
EGFR mutation analysis:
Exon 19 deletion

OP: LLL B6 segmentectomy
+ LN dissection



Before Erlotibib

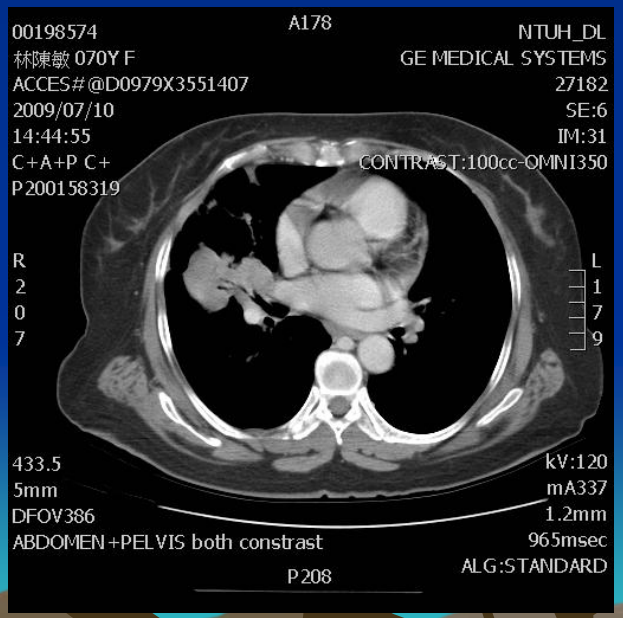
After Erlotibib

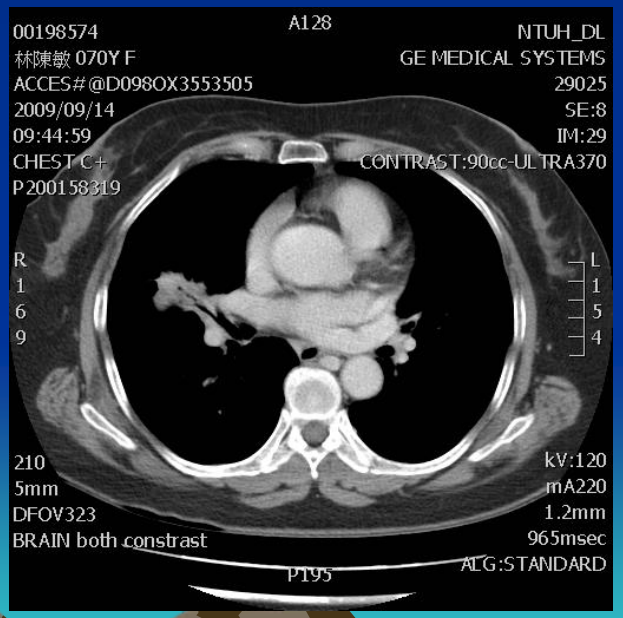
J Clin Oncol 2008

Neoadjuvant (Induction) Gefitinib Response in Locally advanced Lung Cancer

70 y/o female, COPD, FEV1 = 0.96L, 55% of prediction
Adenocarcinoma occupyting the right hilum,
pneumonectomy is indicated for complete resection
EGFR mutation analysis: Exon 21 mutation

OP: Right middle lobectomy + LN dissection



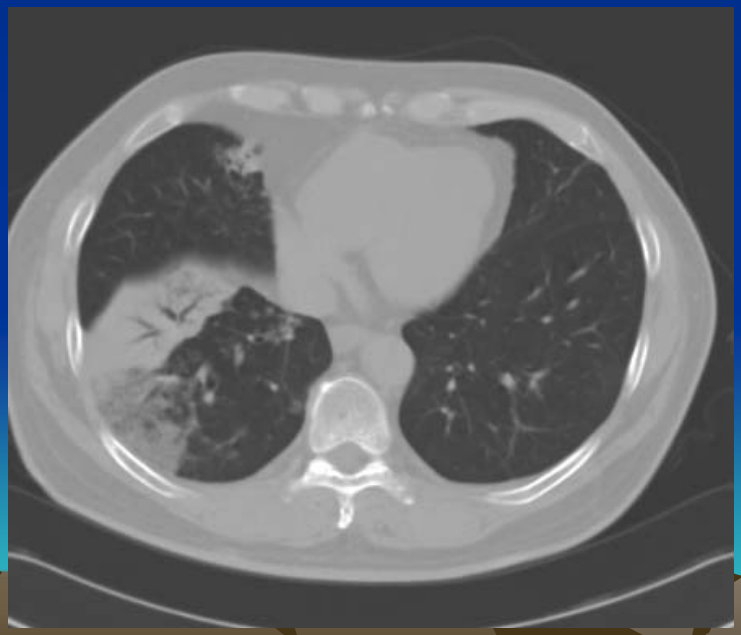


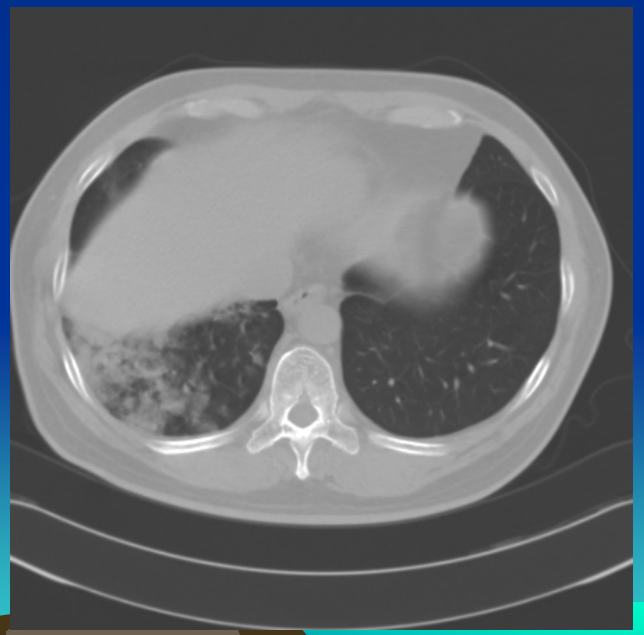
Before Gefitinib

After Gefitinib

Adjuvant Erlotinib in Advanced Non – Small-Cell Lung Cancer

- 54 y/o male, RCC s/p right nephrectomy
- Adenocarcinoma with BAC pattern occupying the RML and RLL
- OP: Right middle wedge resection + RLL lobectomy + LN dissection
- Pathology: Mediastinal LN metastasis, T2N2M1, stage IV
- No recurrence for 14 months after operation





肺癌手術與合併治療趨勢

- Minimally invasive surgical approaches and procedures
- Minimally invasive anesthesia
- Adjuvant therapy if ≥ stage II
- Personalized treatment
  - 考量身體狀況、年齡、肺功能 (balance between radicality and life quality)
  - 基因檢測及對藥物之反應

臺大雲林分院
肺癌國際學術研討會
2010年3月27日
竭誠歡迎您的參與