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SPECIAL CONTRIBUTION

The Current Status and Future Direction of Surgical Treatments for Lung Cancer

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KEY WORDS —— Lung cancer, Surgery, Limited resection, Minimally invasive surgical technique, Multimodality therapy

Surgery has long been a mainstay in the management of lung cancer, particularly non-small cell lung cancer (NSCLC). However, the role of surgery has evolved during the past 20 years as a result of several factors including the increasing use of multimodality therapy, the earlier detection of disease through CT scan screening and the development of minimally invasive surgical techniques. The rapidly expanding understanding of the molecular features of lung cancer is also beginning to influence surgical resection for NSCLC.

Surgical resection remains the principal treatment for Stage I NSCLC but the frequent detection of very small tumors (2 cm or less in size) through CT screening has led surgeons to question whether lobectomy, long the standard of care, is required for such very early stage disease. The risk of recurrence after resection of very early NSCLC (especially adenocarcinomas) appears to be related to tumor histology as well as tumor size. Several clinical trials in Japan and North America are underway to try to determine whether limited resections (wedge resection or segmentectomy) may be adequate for these small tumors. In addition, an international project is in progress to redefine the pathological classification of lung adenocarcinomas in a way that more closely aligns this with clinical features and prognosis. This new classification will facilitate future trials testing the use of surgery and adjuvant therapies in early stage NSCLC. Emerging knowledge about the relationships between key molecular abnormalities (e.g. EGFR mutations), tumor behavior and clinical outcome are also beginning to influence the use of surgery and the approach to resection.

The advent of minimally invasive surgical techniques (e.g. VATS lobectomy and robotically-assisted resections) has radically altered approaches to the resection of NSCLC. Large retrospective studies now clearly indicate that well performed VATS resections with systematic lymph node dissection are oncologically equivalent to thoracotomy and resection. Immediate postoperative results (length of hospital stay, postoperative pain, etc.) appear superior for VATS. It is as yet unclear whether robotic assistance enhances the results of VATS and this requires further study. However, VATS resections are now widely accepted as a standard approach to the surgical management of early stage NSCLC.

Conversely, the increasing use of multimodality therapy has expanded the role of surgical resection for locally advanced NSCLC. Key examples of this are the routine use of resection after induction chemo or chemoradiotherapy for patients with stage IIIA (N2) disease and patients with T3 or T4 superior sulcus NSCLC (Pancoast tumors). Whereas 20 years ago surgery for such patients would have been considered unusual or investigational, recent clinical trials have established multimodality therapy including surgery, as a standard of care in properly selected cases. Newer techniques of extended resection that permit complete removal (R0 resection) of locally advanced NSCLC that invade adjacent structures such as the spine and the great vessels have expanded the role of surgery in the routine manage-

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※第 50 回日本肺癌学会総会招請講演 1.

ment of such tumors.

An emerging area of controversy and of clinical investigation is the relative benefit of surgery versus stereotactic radiotherapy (SBRT) or ablative techniques such as radiofrequency ablation (RFA) in the treatment of small-sized lung cancers. Recent data suggest that SBRT for tumors measuring 3 cm or less in size can successfully achieve local control of disease in 85% or more of NSCLC at 3-5 years. These data emanate primarily from the use of SBRT in patients who are not candidates for surgery because of their overall medical condition but raise the question of whether better risk patients should also be treated with radiotherapy rather than surgery. Future clinical trials need to address this question. The role of RFA is less well defined at present making it primarily a technique for local palliation in inoperable patients.

The role of surgery in small cell lung cancer (SCLC) remains limited. Resection is appropriate for patients who have locally recurrent tumors or who develop second primary lung cancers (usually NSCLC) after definitive chemoradiotherapy for early stage SCLC.

Thus, while surgery remains a mainstay of the treatment of NSCLC, its role is constantly evolving and is influenced by changes in the other therapies for this disease as well as emerging knowledge of tumor biology.

和訳：

伊豫田明[1]・吉村博邦[1]・佐藤之俊[1]・早川和重[2]

索引用語 —— 肺癌，手術，縮小手術，低侵襲手術手技，集学的治療

はじめに

このたび，第50回日本肺癌学会総会の招請講演のために米国 Memorial Sloan-Kettering Cancer Center の Valerie W. Rusch 先生が来日され，“The Current Status and Future Direction of Surgical Treatments for Lung Cancer”（肺癌の外科的治療法の現状と今後の展望）という演題名にて御講演をいただいた．貴重な講演であり，本学会会員の後学のために講演内容の日本語での要旨と御使用スライドの学会誌への掲載をお願いしたところ快諾されたため，Rusch 先生に送っていただいたスライド原稿に英文要旨の和訳を加え，提示する．

講演要旨

肺癌とりわけ非小細胞肺癌の治療では，長い間外科的療法が中心であった．しかし，集学的治療の導入拡大，CT スキャンを用いたスクリーニングによる病変の早期発見，低侵襲手術手技の進歩など，種々の要素により最近20年間で外科的療法の役割は進展している．肺癌の分子レベルの特徴に関する知見が急速に拡充したことも，非小細胞肺癌に対する外科的切除に影響を与えている．

I 期非小細胞肺癌に対して外科的切除が主たる治療法であることは変わらないが，CT スクリーニングによって2 cm 以下の小型肺癌が高頻度に発見されるようになり，そのような非常に早期の肺癌に対して，長年標準手術であった肺葉切除が必要なのか，外科医は疑問をいだき始めた．非常に早期の非小細胞肺癌（特に腺癌）の切除後の再発リスクは，腫瘍径だけでなく組織型にも関係していると思われる．小型肺癌に対して縮小手術（楔状切除もしくは区域切除）が適切か否かを確認するため，日本と北米でいくつかの臨床試験が行われている．さらに，肺腺癌の臨床的な特徴と予後に密接に関連付けられるように，肺腺癌の病理分類を再定義する国際プロジェクトが進行中である．この肺腺癌の新しい分類によって，早期の非小細胞肺癌に対する外科治療や補助療法を用いた今後の試験が実施し易くなるであろう．EGFR 遺伝子変異などの重要な分子異常や，腫瘍の病態，臨床的な特徴の関連についての新たな知見が得られていることも，外科治療や肺切除への取り組みに影響を与えている．

胸腔鏡下肺葉切除術やロボット支援切除などの低侵襲手術手技が用いられるようになったことで，非小細胞肺癌に対する外科切除の取り組み方は根本的に変わった．系統的リンパ節郭清を伴った胸腔鏡下手術の施術例が，腫瘍学的に開胸手術と同等の成績をもたらすことを，大規模な後ろ向き試験は明確に示している．入院期間や術後疼痛などの，術後早期の問題を比較すると，胸腔鏡手術に優位性があると思われる．現時点では，ロボット補助技術の採用が，胸腔鏡下手術の成績をさらに改善するかどうかは，明らかでない．これについてはさらなる研究が必要である．しかしながら，現在胸腔鏡下切除は早期非小細胞肺癌に対する外科治療の標準的方法として，広く受け入れられている．

一方，集学的治療を多く行うようになると，局所進行肺癌に対する外科治療の重要性が増大する．その主要な例は，ステージ IIIA（N2）と T3 もしくは T4 肺尖部肺癌（パンコースト腫瘍）患者に対して，導入化学療法あるいは化学放射線療法後に定型的な外科的切除を行うことである．20年前には，このような患者に対する手術は例外的とか研究的なものと考えられていたが，外科手術を含めた集学的治療が対象症例の標準的治療法となることが，近年の臨床試験によって証明された．脊椎や大血管などの隣接臓器に浸潤する局所進行非小細胞肺癌を完全除去するために拡大切除（R0 切除）を行う新しい技術では，これらの腫瘍の定型的治療法として外科手術の役割はさらに大きい．

小型肺癌の治療における外科手術と，体幹部定位放射線治療（SBRT）もしくはラジオ波焼灼治療法（RFA）の利点の比較が，議論の対象となっており，また臨床研究の課題となっている．最近のデータでは，SBRT は3～5年の時点で，非小細胞肺癌の3 cm 以下の腫瘍に対して85% 以上の局所制御の達成が可能であると報告されている．これらのデータは本来，全身状態が悪く手術適応にならない患者に SBRT を用いた結果に由来しているが，状態の悪くない患者においても，外科手術ではなく放射線治療を行うべきかどうかという問題を提起している．今後，臨床試験でこの問題に取り組む必要がある．

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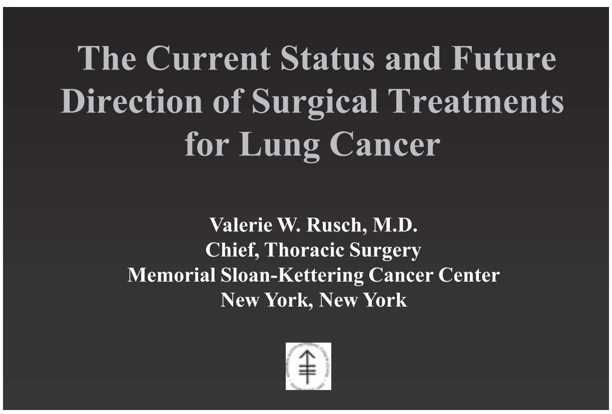
RFA は，主として手術不能の患者に対する局所緩和の技術ではあるが，現時点ではその役割は明確になっていない．

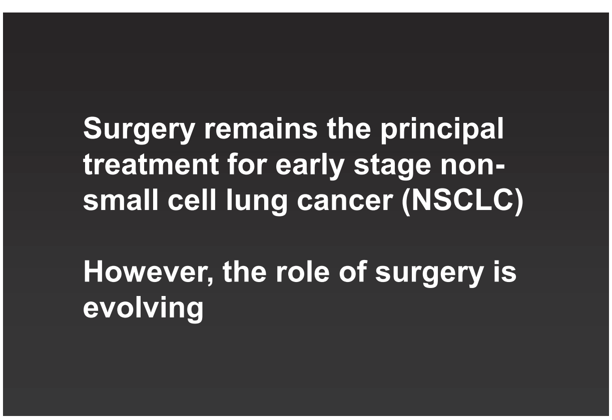
小細胞肺癌における外科手術の役割は相変わらず限られている．切除の適応となるのは，局所的な再発腫瘍，あるいは早期小細胞肺癌に対する根治的化学放射線療法後に第 2 原発性肺癌（通常非小細胞肺癌）が生じた症例である．

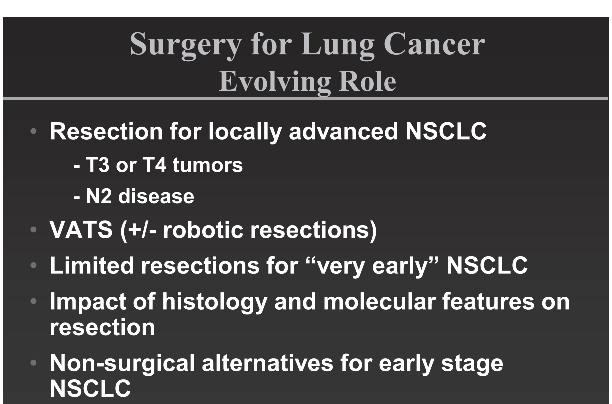
このように外科手術は非小細胞肺癌の治療の主役であるばかりでなく，腫瘍生物学的知見の新たな出現や，この疾患に対する他の治療方法の変化の影響を受けて，その役割はたえず進展し，変わっていくものである．

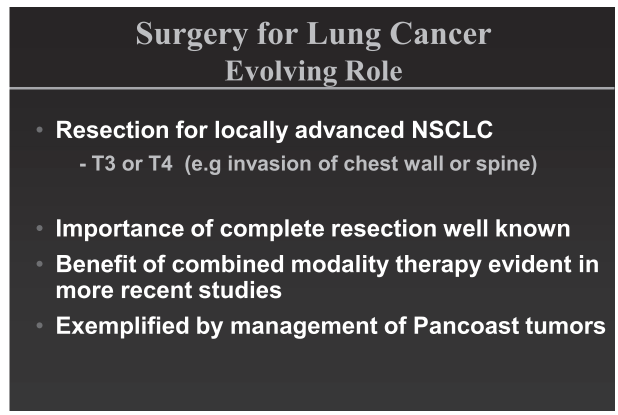
謝辞：第 50 回日本肺癌学会総会・招請講演 1 の要旨とスライド原稿を特別寄稿として掲載させていただくことを快諾された Valerie W. Rusch 先生，ならびに学会誌「肺癌」への掲載を快くお引き受けいただいた編集委員長の田村友秀先生に心より感謝申し上げます〔第 50 回日本肺癌学会会長早川和重（北里大学医学部放射線科学）〕．

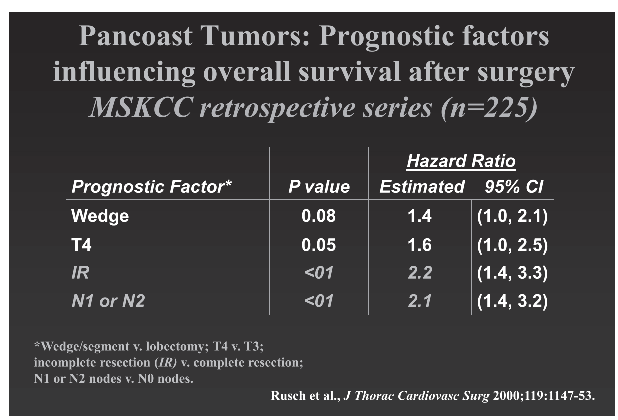
講演スライド

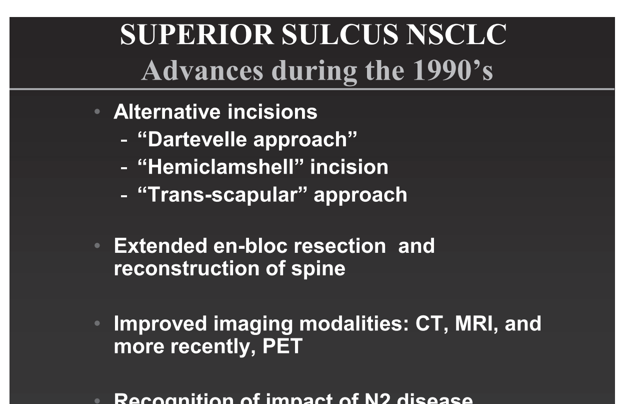












SWOG 9416 (INT 0160) Schema

T3-4, N0-1, M0 NSCLC of the superior sulcus
(n = 110)
↓
2 cycles cisplatin + etoposide
RT (45 Gy,5 weeks)
↓
Repeat Extent of Disease Evaluation
N = 102 (92%)
↓
CR, PR or Stable
↓
Surgical Resection
N=83 (75%)

Rusch et al. *JCO* 2007;25:313-318.

Other ChemoRT + Surgery Series for Pancoast Tumors

Author (Yr)	# Pts	Induction Rx	R0 (%)	5 yr OS
Marra (2007)	31	C+E /P + 45Gy	94%	46%
de Perrot (2008)	44	C+E + 45Gy	89%	59%
Pourel (2008)	107	C+E + 45 Gy (3D)	90%	40%*
Kunitoh (2008) **	76	MVP +45 Gy (split)	89%	56%

C = cisplatin
E = etoposide
M= mitomycin
V = vinblastine

* 3 yr OS ** *JCOG Trial 9806*

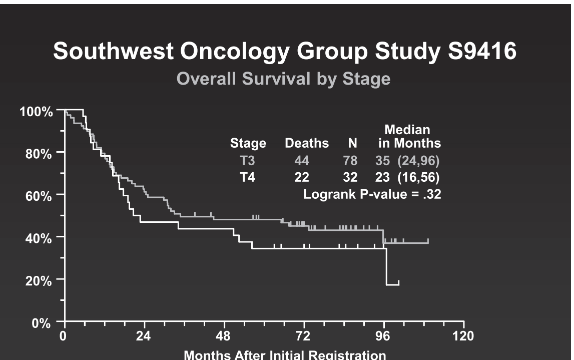
SWOG 9416 (INT 0160): Surgical Resection Data

Completeness of Resection	No. Pts.	% All Pts
Surgically complete (R0, R1)	76	91.6
T3	55/60	92.0
T4	21/23	91.0
Pathologically complete (R0)	75	90.4
T3	55/60	91.3
T4	20/23	87.0

Rusch et al. *JCO* 2007;25:313-318.

Surgery for Lung Cancer Evolving Role

- **Resection for locally advanced NSCLC**
  - N2 disease
- **During the past 20 years many studies show survival benefit for induction / adjuvant chemo**
- **Role of surgery (versus RT) controversial**
- **Clearest comparison provided by North American intergroup trial**



Rusch et al. *JCO* 2007;25:313-318.

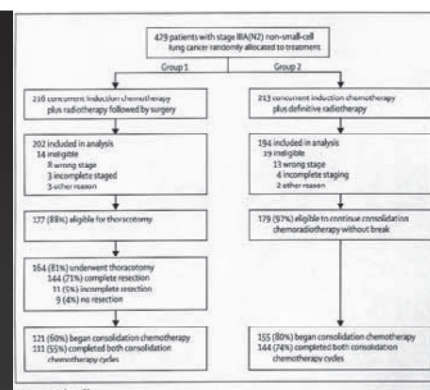
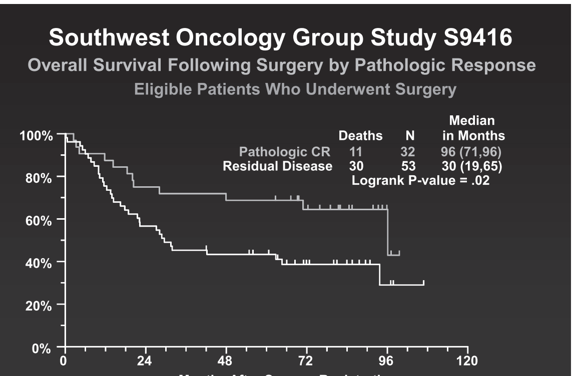
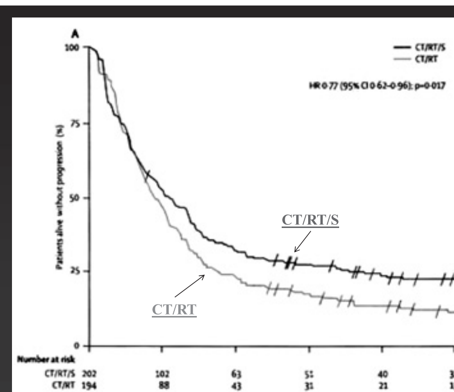


Figure 1: Trial profile
N2=ipsilateral mediastinal nodal metastases.

Albain et al. *Lancet* 2009;374:379-86.

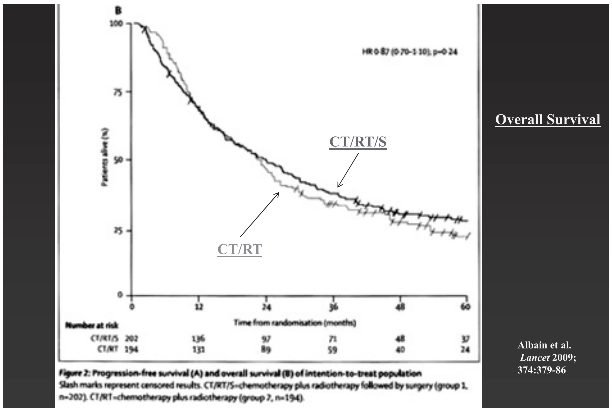


Rusch et al. *JCO* 2007;25:313-318.



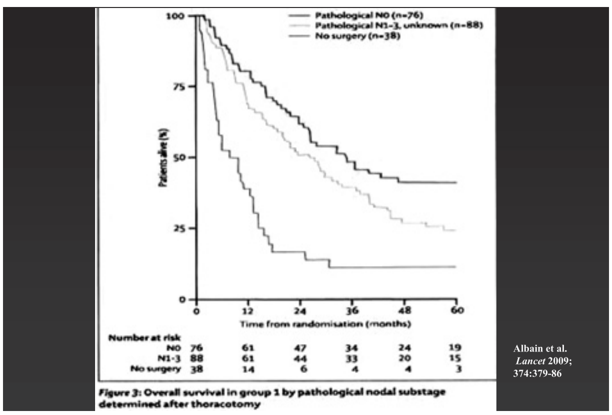
Progression – free survival

Albain et al. *Lancet* 2009; 374:379-86



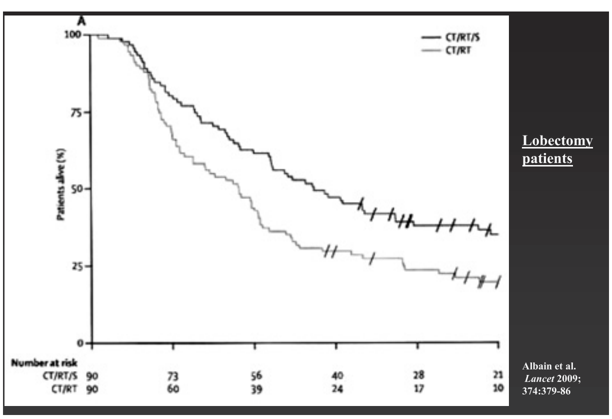
Surgery for Lung Cancer
Evolving Role: Intergroup Trial

- Progression-free survival improved with surgery
- No overall survival benefit was shown in this study for the addition of surgery to chemoRT
- Many factors including the numbers of patients entered may have influenced these results
- Overall survival significantly better in subset analysis for patients who had lobectomy



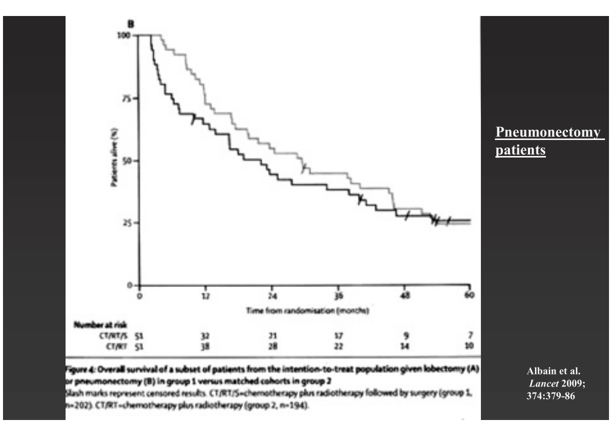
Surgery for Locally Advanced NSCLC (T3-4, N2)
Evolving Role: Summary

- Use of combined modality Rx (chemo +/-RT) has:
  - extended indications for surgery
  - improved local control (T3-4)
  - improved overall survival (N2)



Surgery for Lung Cancer
Evolving Role

- Resection for locally advanced NSCLC
  - T3 or T4 tumors
  - N2 disease
- VATS (+/- robotic resections)
- Limited resections for "very early" NSCLC
- Impact of histology and molecular features on resection
- Non-surgical alternatives for early stage NSCLC



Minimally Invasive Thoracic Surgery
Potential Benefits of VATS Lobectomy

- Improved tolerance in high risk patients (elderly, poor lung function)
- Faster recovery ⟶ better ability to receive postop therapy (chemo)
- Improved quality of life
- Diminished chronic post-thoracotomy pain

VATS Lobectomy
Variability in Technique

- Survey of 33 general thoracic surgeons worldwide know to perform VATS lobectomy
- 70% used rib spreader at some point
- 48% employed > 6 cm utility incision
- 46% looked through the utility incision either primarily or when necessary

Yim, Landreneau, et al. Ann Thorac Surg 1998;66:1155-8

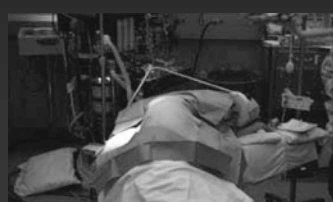
VATS Lobectomy
Pain and Lung Function

- VATS better in terms of acute pain and postop pulmonary function
- No difference reported in long-term rates of post-thoracotomy pain
- Two prospective studies of found early differences in lung function resolved at >1 year

Nakata M et al. Ann Thorac Surg 2000; 70:938
Giudicelli R et al. Ann Thorac Surg 1994; 58:712

VATS Lobectomy
Approach at MSKCC

- Three incisions
- 4 cm non-rib spreading utility incision
- Individual dissection and ligation of hilar structures
- Clinical stage I NSCLC



Minimally Invasive Thoracic Surgery
MSKCC VATS Lobectomy Experience

- Began performing VATS lobectomy for clinical stage I NSCLC in May 2002
- 7/9 staff perform VATS lobectomy using 3-incision, non-rib spreading technique
- Perform approximately 120 VATS lobectomies/year currently (~20-25% lobes)

Minimally Invasive Thoracic Surgery
VATS versus Thoracotomy

			OR (min)		CT (days)		LOS (days)	
Author	Year	n	VATS	Thor	VATS	Thor	VATS	Thor
Nagahiro	2001	13	250	186	3.6	3.8	n/a	n/a
Demmy	1999	23	229	215	4.0	8.3	5.3	12.2
Ohbuchi	1998	35	217	195	5.3	7.6	15.0	24.0
Walker	1996	70	135	n/a	n/a	n/a	7.0	n/a
Kirby*	1995	25	161	175	4.6	6.5	7.1	8.3
Giudicelli	1994	44	133	110	8.0	10.0	12.0	15.0
Landreneau	1993	81	n/a	n/a	n/a	n/a	5.0	7.5

*Randomized

Minimally Invasive Thoracic Surgery
MSKCC VATS Lobectomy Experience

- Retrospective case control series comparing outcomes of VATS vs. thoracotomy lobectomy
- May 2002 to August 2007: 741 patients resected for clinical stage I (328 VATS, 413 thoracotomy)
- Perioperative data compared between groups

Flores RM, Park BJ, et al. JThCvS in press

VATS Lobectomy for Early Stage NSCLC

Study	Patient No.	Lesion Size	Survival 5-year
McKenna et al.	1100	NS	76%
Watanabe et al.	221	<4 cm	92%
Oniatis et al.	492	NS	85% (2-year)
Lewis et al.	214	3.4 cm	83%
Yim et al.	214	<5 cm	93%

Nguyen et al. *Cancer Treat Rev* 2008;34:719-727

Minimally Invasive Thoracic Surgery
MSKCC VATS Lobectomy Experience

Variable	VATS Lobectomy n=328	Thoracotomy n=413	p value
FEV1 % predicted	92	88	0.050
Complications	73 (22%)	128 (31%)	0.010
LOS (days)	5	7	0.001
5-year survival (adjusted)	78%	76%	0.080

Flores RM, Park BJ, et al. JThCvS in press

Minimally Invasive Thoracic Surgery
VATS Lobectomy in Elderly Patients

- Retrospective case-control series
- From May 2002 to December 31, 2005, all patients ≥ 70 years that underwent lobectomy for NSCLC by VATS or thoracotomy matched for age, sex, clinical stage and co-morbidities
- Groups compared for postoperative incidence and grade of complications

Cattaneo S, Park B, et al. Ann Thorac Surg 2008;85:231-236

VATS Lobectomy in Elderly Patients
Perioperative Results

Characteristics	THOR (N=82)	VATS (N=82)	p-value
LOS, days (range)	6 (2-27)	5 (2-20)	< 0.001
Complications, n (%)	37 (45)	23 (28)	0.04
Death, n (%)	3 (3.6)	0 (0)	0.10

Cattaneo S, Park B, et al. Ann Thorac Surg 2008;85:231-236

VATS Lobectomy in Elderly Patients
Severity of complications

	THOR (N=82)	VATS (N=82)	p-value
Number, n (%)			
0	45 (55)	58 (70)	0.014
1	23 (28)	16 (20)	
2	8 (10)	8 (10)	
≥ 3	6 (7)	0 (0)	
Max grade, n (%)			
0	45 (55)	58 (70)	0.007
1	6 (7)	4 (5)	
2	25 (31)	20 (25)	
≥ 3	6 (7)	0 (0)	

Cattaneo S, Park B, et al. Ann Thorac Surg 2008;85:231-236

VATS Lobectomy in Elderly Patients
Complication Types

Type, n (%)	THOR (N=82)	VATS (N=82)	p-value
None	45 (55)	59 (72)	0.04
Pulmonary	27 (33)	12 (15)	0.01
Cardiac	19 (23)	14 (17)	0.44
Genitourinary	5 (6)	2 (2)	
Gastrointestinal	4 (5)	0 (0)	
Infectious	4 (5)	1 (1)	
Neurologic	1 (1)	3 (4)	
Other	2 (2)	0 (0)	

Cattaneo S, Park B, et al. Ann Thorac Surg 2008;85:231-236

VATS Lobectomy
Impact on Adjuvant Chemotherapy

- Retrospective, unmatched review of 100 consecutive patients that underwent lobectomy by VATS or thoracotomy followed by adjuvant chemotherapy
- Groups compared for time to chemo, % planned chemo received, dose delay or reduction and peri-treatment outcomes

Peterson R et al. Ann Thorac Surg 2007;83:1245-50

VATS Lobectomy
Impact on Adjuvant Chemotherapy

Table 5. Adjuvant Chemotherapy Compliance After Lobectomy by Surgical Approach

Compliance[a]	Thoracoscopy n = 57 (%)	Thoracotomy n = 43 (%)	p Value
Time to initiation of chemo (days)	58 ± 31	54 ± 35	0.277
Percentage of planned regimen received	88% ± 24%	89% ± 19%	0.835
Pts with delayed chemotherapy doses	10 (18)	25 (58)	<0.001
Pts with reduced chemotherapy doses	15 (26)	21 (49)	0.020
>75% of total planned regimen[b]	35 (61)	17 (40)	0.030
Toxicity grade ≥2	29 (51)	24 (56)	0.624
Toxicity grade ≥3	7 (12)	9 (21)	0.243

[a] Data presented means ± standard deviation, or as n (%). [b] Without delay or dose reduction.

Peterson R et al. Ann Thorac Surg 2007;83:1245-50

VATS Lobectomy
Conclusions

- Describes a variety of operative approaches
- Technically feasible and safe
- Fewer complications, especially respiratory in early postoperative period
- Overall survival similar to lobectomy via thoracotomy for early stage NSCLC
- May be particularly beneficial for high risk patients (COPD, elderly)

VATS Lobectomy
Future Directions

- Standardization of technique
- ?? Prospective comparisons of thoracotomy vs. VATS lobectomy
- Prospective quality of life studies
- Additional data on long-term cancer outcome
- Evaluation of robotically- assisted versus standard VATS

Surgery for Lung Cancer
Evolving Role

- Resection for locally advanced NSCLC
  - T3 or T4 tumors
  - N2 disease
- VATS (+/- robotic resections)
- Limited resections for “very early” NSCLC
- Impact of histology and molecular features on resection
- Non-surgical alternatives for early stage NSCLC

T,N,M Categories and Stage Groupings: 7th edition of staging system

Sixth Edition T/M Descriptor	7th Edition T/M	N0	N1	N2	N3
T1 (≤2 cm)	T1a	IA	IIA	IIIA	IIIB
T1 (>2-3 cm)	T1b	IA	IIA	IIIA	IIIB
T2 (≤5 cm)	T2a	IB	IIA	IIIA	IIIB
T2 (>5-7 cm)	T2b	IIA	IIB	IIIA	IIIB
T2 (>7 cm)	T3	IIB	IIIA	IIIA	IIIB
T3 invasion		IIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)		IIB	IIIA	IIIA	IIIB
T4 (extension)	T4	IIIA	IIIA	IIIB	IIIB
M1 (ipsilateral lung)		IIIA	IIIA	IIIB	IIIB
T4 (pleural effusion)	M1a	IV	IV	IV	IV
M1 (contralateral lung)		IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV

Cells in pink indicate changes from the 6th edition

From Goldstraw et al., *J Thorac Oncol* 2007;8:706-714.

Lobectomy vs. Limited Resection for T1N0 NSCLC : LCSG trial 821

267 Pts. randomized

247 Pts. Eligible for analysis

Peripheral carcinoma on CXR, <=3 cm Negative hilar node → Randomize → Lobectomy / Limited resection

Endpoints:
Primary: OS
Secondary: pulmonary function
Sample size: 80 deaths and 70 recurrences to occur with a power of .90 to detect a 1.8 fold difference in median survival

Ann Thorac Surg 1995; 60: 615-23

Limited Resection for NSCLC: JCOG 0802/WJCOG 4607L trial*

Peripheral NSCLC ≤ 2 cm in size
Stage Ia by CT; “invasive” by CT**

randomize

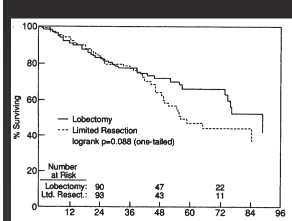
lobectomy | segmentectomy

*planned accrual=1100, 1° endpoint=OS

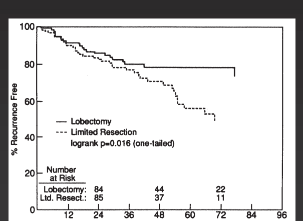
**>25% appears solid by CT scan

Lobectomy vs. Limited Resection for T1N0 NSCLC: LCSG Trial 821

Time to Death (p=0.088)



Time to Recurrence (p=0.016)



Ann Thorac Surg 1995; 60: 615-23

Limited Resection for NSCLC: CALGB trial 140503*

Peripheral NSCLC ≤ 2 cm in size
Stage Ia by CT; No “pure GGO”

randomize

lobectomy VATS or open | wedge resection or segmentectomy

*planned accrual=1297, 1° endpoint=OS

Lobectomy vs. Limited Resection for T1N0 NSCLC LCSG Trial 821

CONCLUSION:

Lobectomy with SLN sampling/dissection should remain the standard surgical treatment for T1N0 NSCLC.

Ann Thorac Surg 1995; 60: 615-23

Surgery for Lung Cancer
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IASLC/ATS/ERS ADENOCARCINOMA
MULTIDISCIPLINARY PANEL
MARCH 12-13, 2009 (In Situ Wine Toast)

TENTATIVE PROPOSAL IASLC/ATS/ERS ADENOCARCINOMA CLASSIFICATION

INVASIVE ADENOCARCINOMA
- **Lepidic pattern predominant (formerly non-mucinous BAC pattern)**
- **Acinar pattern predominant**
- **Papillary pattern predominant**
- **Micropapillary pattern, predominant**
- **Solid pattern predominant**

(In explanatory notes, recommend semiquantitative assessment of patterns in 5-10% increments)

TENTATIVE PROPOSAL IASLC/ATS/ERS ADENOCARCINOMA CLASSIFICATION

- **PREINVASIVE LESIONS**
  - **ATYPICAL ADENOMATOUS HYPERPLASIA**
  - **ADENOCARCINOMA IN SITU (formerly BAC pattern) ***
    - **non-mucinous**
    - **mucinous**
- **MINIMALLY INVASIVE ADENOCARCINOMA (a lepidic predominant tumor with <=5mm or <10% invasion – definition being refined)**
- **INVASIVE ADENOCARCINOMA**

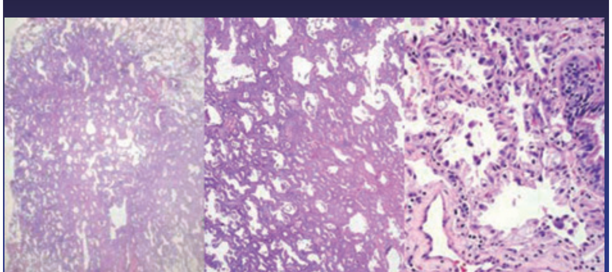
* Size should be specified. In well sampled tumors adenocarcinoma in situ is independent of size; extensive sampling is needed to exclude invasion, particularly in larger tumors

WHAT ARE SOME IMPLICATIONS OF THIS CLASSIFICATION FOR

PATHOLOGIC STAGING

OF ADENOCARCINOMA?

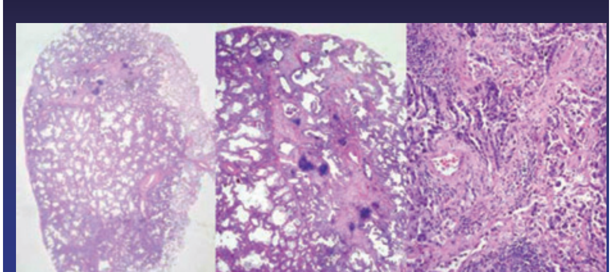
ADENOCARCINOMA IN SITU



POTENTIAL IMPACT OF NEW ADENOCARCINOMA CLASSIFICATION ON STAGING
SIZE T-FACTOR

- <u>PATHOLOGIC STAGE</u>: **By recording the percent BAC and other invasive components, the tumor size for staging may be adjusted to only the size of the invasive component (i.e. a 2.0 cm tumor with 50% AC in situ – is now regarded as 1.0 cm size)**
- <u>CLINICAL STAGE</u>: **By CT scan the size of a part solid tumor may be measured only by the diameter of the solid component – not the GGO**

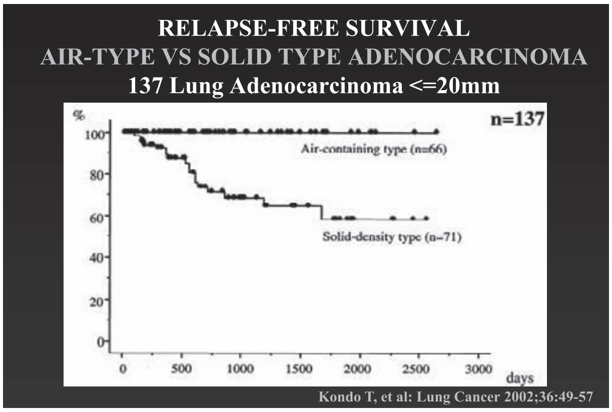
MINIMALLY INVASIVE
ADENOCARCINOMA



WHAT ARE SOME IMPLICATIONS OF THIS CLASSIFICATION FOR

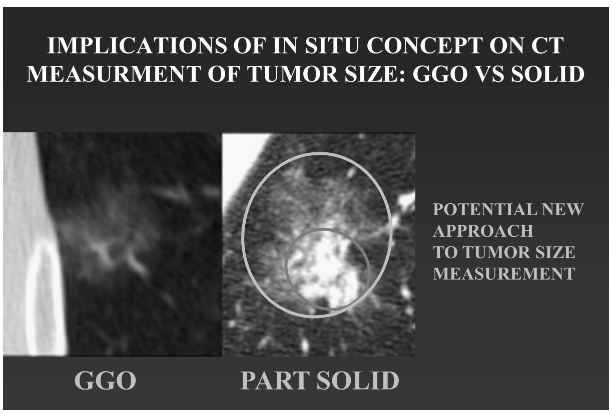
CLINICAL STAGING
(BY CT SCAN)

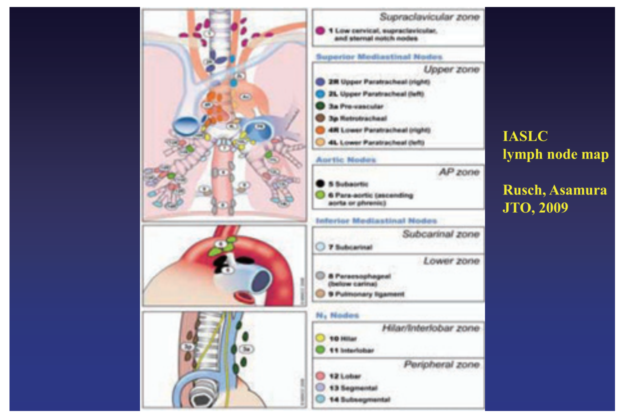
OF ADENOCARCINOMA?



Surgery for Lung Cancer
Clinical Implications of Mutations

- Mutations appear to be both ***predictive*** (of response to chemotherapy) and ***prognostic*** (of overall survival)
- Mutations associated with level of tobacco exposure and also with tumor histology
- In future, treatment selection including type of operation, may be based not just on TNM stage but also on histology and molecular profile
- Additional studies correlating mutations to overall survival are needed





Surgery for Lung Cancer
Key Molecular Abnormalities*

- **KRAS mutations**
  - smoking- related; associated with poor prognosis
- **EGFR mutations**
  - never/ mild smokers; most frequently in women; associated with good prognosis
- **EML4-ALK translocations**
  - never/ mild smokers; more men than women; younger patients; associated with acinar histology

* all are mutually exclusive

Marks et al JTO 2008;3:111-116
Shaw et al JCO 2009;27:4247-4253
Horn, Pao JCO 2009;27:4232-4235

Surgery for Lung Cancer
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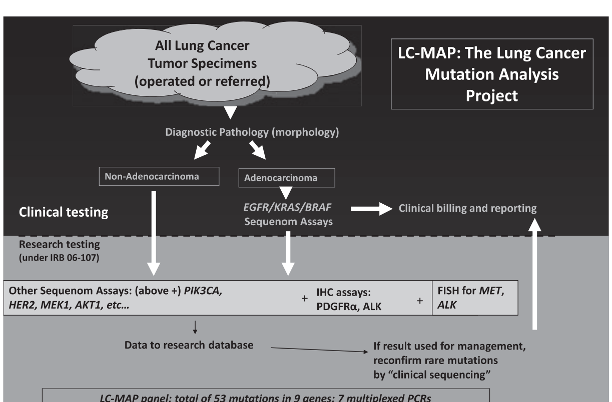
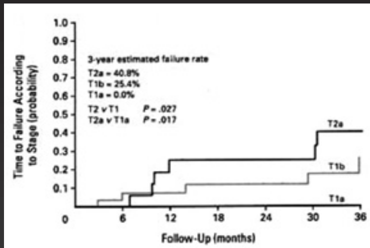


SBRT in Patients with Early Stage NSCLC
Biologic Equivalent dose of 100 Gy or more

Study	Patient No.	Tumor Size	Local Control	Survival
Lagerwaard et al.	206	<6 cm	97%	64% (2-Y)
Onishi et al.	257	2.8 cm	86%	42% (5-Y)
Timmerman et al.	70	NS	95%	52% (2-Y)
Hoopes et al.	58	12 cc 2.8 cm	74%	48% (3-Y)
Takeda et al.	50	<10 cm	92%	NS

Nguyen et al. *Cancer Treat Rev* 2008;34:719-727

SBRT in Inoperable Stage I NSCLC: Time to Failure according to Stage



T-stage		PD+	PD-	Censored	Total
T1a*	No.	0	5	6	11
T1 ≤ 2 cm†	Median, months	–	40.5	31.7	
T1b*	No.	5	7	17	29
T1 > 2 ≤ 2 cm†	Median, months	13.9	37.9	22.9	
T2a*	No.	6	7	4	17
T2 > 3 ≤ 5 cm†	Median, months	11.0	39.4	11.6	

Baumann et al.
J Clin Oncol 2009;
27:3290-3296

Surgery for Lung Cancer
Evolving Role: Summary

- Integration of surgery with chemo +/- RT important for locally advanced lung cancers
- Increasingly well defined role for minimally invasive techniques (e.g. VATS lobectomy)
- Emerging influence of molecular abnormalities on treatment
- Need for further study of tumor histology and mutations in relationship to surgical options
- Need for further study of non-surgical options

Non-Surgical Treatments for Lung Cancer
RFA

- Relative to SBRT, less data to support RFA
- Reported series are retrospective and include both lung cancers and metastases
- Variable techniques
- Variable methods of staging and follow-up
- Requires standardization and further study
- Currently, last treatment option for local control

Zhu et al Ann. Surg. Oncol. 2008; 15(6) 1765-74