SH01: Highlights of the Previous Day Session

Surgery

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DISCLOSURE

- Honorarium, lecture fee:

  AstraZeneca KK, Eli Lilly Japan, Boehringer-Ingelheim Japan, Daiichi-Sankyo, Chugai Pharmaceutical CO.,LTD,

  Taiho Pharma, Teijin Pharma, MSD, Ono Pharmaceutical CO.,LTD, Johnson & Johnson Japan, Covidien Japan

- Research grant:

  Boehringer-Ingelheim Japan

No conflict related to this presentation

My selection: Surgical topics

among presentations from OA1, OA6, OA7, MA01, MA05, MA07

- OA06.03: Sublobar resection is equivalent to Lobectomy for Screen detected Lung Cancer

- OA06.02: VATS vs. Thoracotomy for Non-small Cell Lung Cancer: Oncological Outcome of a randomized Trial (*from statistical point of view*)

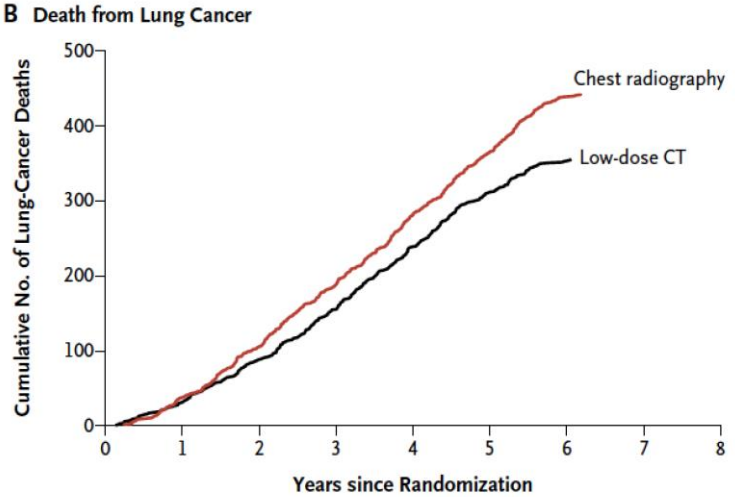
OA06.03

Sublobar resection is equivalent to lobectomy for screen detected lung cancer

Brendon Stiles, MD
Department of Cardiothoracic Surgery
Weill Cornell Medicine / NewYork-Presbyterian

The National Lung Screening Trial (NLST)

- **Results reported in 2011, CMS coverage 2015**
- **Demonstrated 20% reduction in lung cancer related mortality**
- CT screening has increased the detection of “very early” (<2cm) NSCLC.
- **Role of sublobar resection in screen detected cancers not well explored**
- Still several years away from results of JCOG 0802 and CALGB 140503.



N ENGL J MED 365;5 NEJM.ORG AUGUST 4, 2011

Methods

NIH NATIONAL CANCER INSTITUTE Cancer Data Access System

- Retrospective, unplanned analysis
- **NLST dataset obtained and reviewed for patients who underwent surgical resection for confirmed lung cancer: 1,029 patients (1.9% of NLST cohort)**

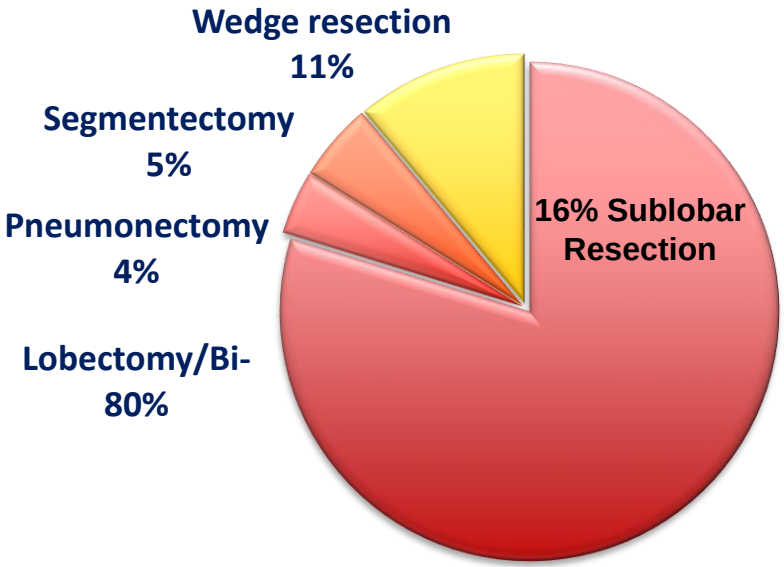
- **Outcomes of interest:**
  - **Proportion of patients undergoing sublobar resection**
  - **Overall survival**
  - **Cancer-specific survival**

- **Specifically analyzed within propensity matched cohorts for effect of extent of resection**

Patient population

Characteristics of Surgical Patients		Number (n=1,029)	Percentage / IQR
Median age		**63**	**IQR 59-68**
Gender	*Male*	**593**	**58%**
	Female	**436**	**42%**
Race	*White*	**946**	**92%**
	Black	**45**	**4%**
	Asian	**21**	**2%**
Smoking pack years (median)		**57**	**IQR 45-80**
Stage (n=1019)	*Stage IA/IB*	**564 / 186**	**55% / 18%**
	Stage II / III / IV	**113 / 126 / 30**	**11% / 12% / 3%**
Histology (Adenocarcinoma)		**568**	**55%**

Extent of resection: NLST



Study (year)	Number	% SLR
STS GTSD (2012-2014)	17,153	19.8%
NCDB (Stage I, 2004-2013)	76,623	20%
SEER-Medicare (IA< 2cm; 2007-2012)	3,986	31%

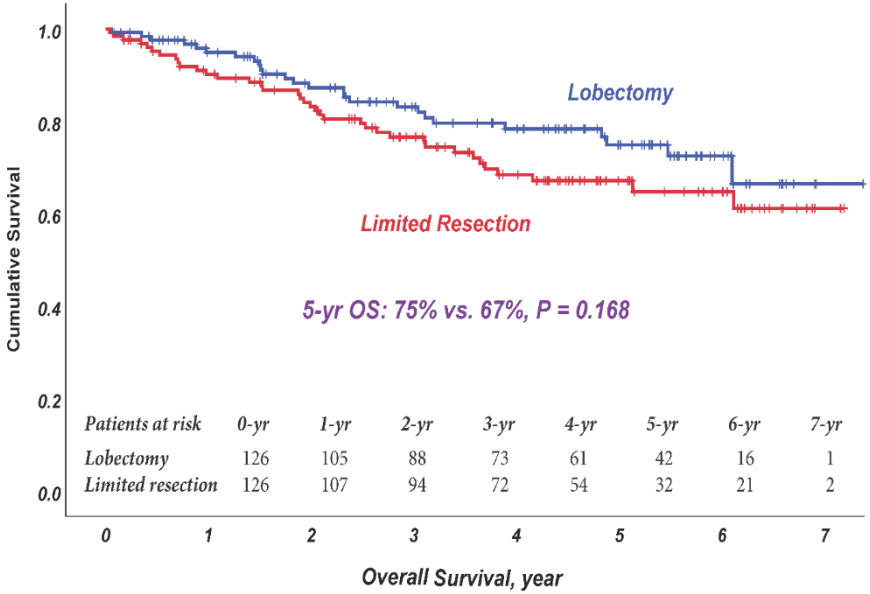
Patients characteristics

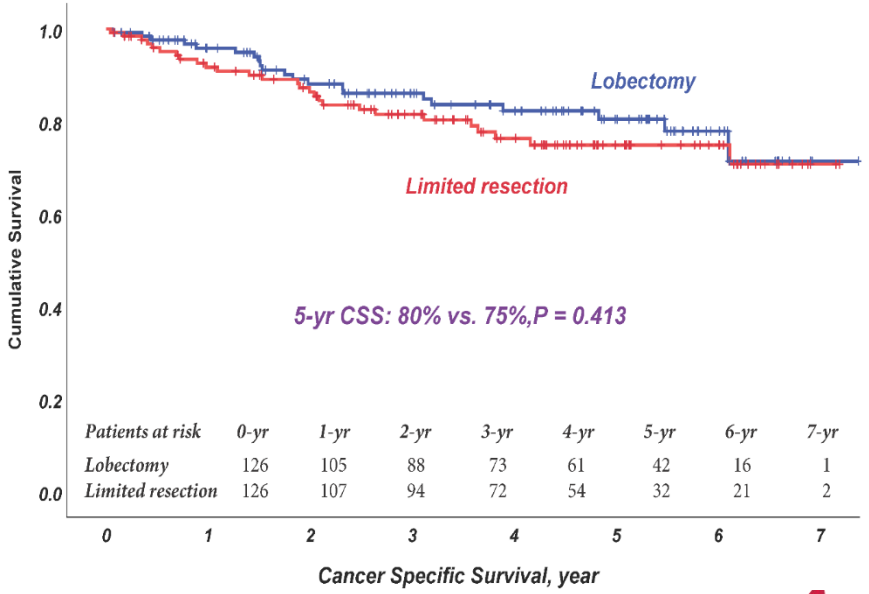
	Lobectomy (n=821)	SLR (n=166)	P value
Age	61 (58-64)	64 (59-68)	0.066
Gender (Male)	485 (59%)	78 (47%)	0.004
Race (White)	755 (93.3%)	151 (93.8%)	0.258
Histology (Adenocarcinoma)	456 (55.5%)	100 (60.2%)	0.490
Tumor size, cm (Median)	2 (1.4-3)	1.5 (1.1-2.2)	<0.001
Stage I	613 (75.2%)	129 (79.6%)	0.001
VATS Approach (n=897)	236 (31%)	67 (49%)	<0.001
LN Dissection	758 (92%)	91 (55%)	<0.001
Post-operative Complications	266 (32.4%)	37 (22.3%)	0.010

Propensity Matched Patients: Characteristics

	Lobectomy (n=126)	SLR (n=126) 47 segments, 79 wedges	P value
Age, year	64 (60-68)	64 (60-70)	0.610
Gender (Female)	68 (54%)	65 (52%)	0.705
Race (White)	122 (97%)	119 (94%)	0.355
Pulmonary comorbidity	39 (31%)	35 (28%)	0.580
Cardiovascular comorbidity	18 (14%)	22 (17.5%)	0.490
cStage I	106 (84%)	109 (86.5%)	0.593
Tumor size	1.5 (1-2.1)	1.5 (1.1-2.2)	0.636
Histology (Adenocarcinoma)	78 (62%)	80 (63.5%)	0.881
Hospital volume (≥ 44 cases)	64 (51%)	58 (46%)	0.449
Approach (VATS)	58 (46%)	61 (48%)	0.705

NLST: Propensity matched analysis of lobectomy vs. SLR (n=126 each)





Conclusion by authors

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Cancer Data Access System

- For patients with screen detected lung cancer, the use of SLR decreases perioperative morbidity compared to lobectomy

- SLR confers equivalent survival to lobectomy in patients with screen detected cancers

- The use of SLR for screen detected lung cancer should therefore be strongly considered

NLST
National Lung Screening Trial
NATIONAL CANCER INSTITUTE

strength

- utilizes large dataset from the NLST
- 5 year f/u available
- 55% stage IA (18% stage IB)
- Propensity matched analysis added

weakness

- retrospective & unplanned analyses
- decision for sublobar resection based on complex interplay of
  - tumor location
  - tumor/consolidation size
  - histological subtype

- JCOG and CALGB trials will address definitively

JCOG0802/WJOG4607L; Phase III Randomized Trial between Lobectomy and Limited Resection for Part-solid GGO – Solid T1a disease

Non-inferiority design

UMIN-CTR (UMIN000002317)

PI: Asamura H. (JCOG) & Okada M (WJOG)

Peripheral carcinoma, <=2 cm Negative hilar node

→ Randomize

Lobectomy N=554

From Aug. 2009 to Oct. 2014

Segmentectomy N=552

Stratified factors;
Institute, Gender,
Histology (Ad vs, Non-ad),
Solid or non-solid

Endpoints:
Primary: OS
Secondary: pulmonary function, RFS, safety, etc
Sample size: 1,100

JCOG Japan Clinical Oncology Group

Suzuki K, et al. AATS 2017

WJOG

CALGB/ ALLIANCE 140503-Intergroup; Phase III Randomized Trial between Lobectomy and Sublobar Resection for Small-sized carcinoma

Non-inferiority design

PI: Altorki N

Peripheral carcinoma, <=2 cm
Negative hilar node
Without pure GGO

Stratified factors;
Tumor size,
Histology,
Smoking status

Randomize

Lobectomy N=357

From Jun. 2007 to Mar. 2017

Sublobar resection (segmentectomy/ wedge) N=340

Endpoints
Primary: DFS
Secondary: OS, Rate of loco-regional and systemic recurrence, pulmonary function
Sample size: 908⇒692

Altorki NK, et al AATS2018

Conclusions in JCOG0802 / CALGB140503 at the moment

- In these large, multicenter trials, there were no significant differences in mortality and morbidity between lobar and sub-lobar resection in physically and functionally fit patients with clinical T1aN0 NSCLC.
- The low overall 30/90 day mortality and morbidity reflect modern day standards for perioperative outcomes in the surgical treatment of early stage NSCLC.

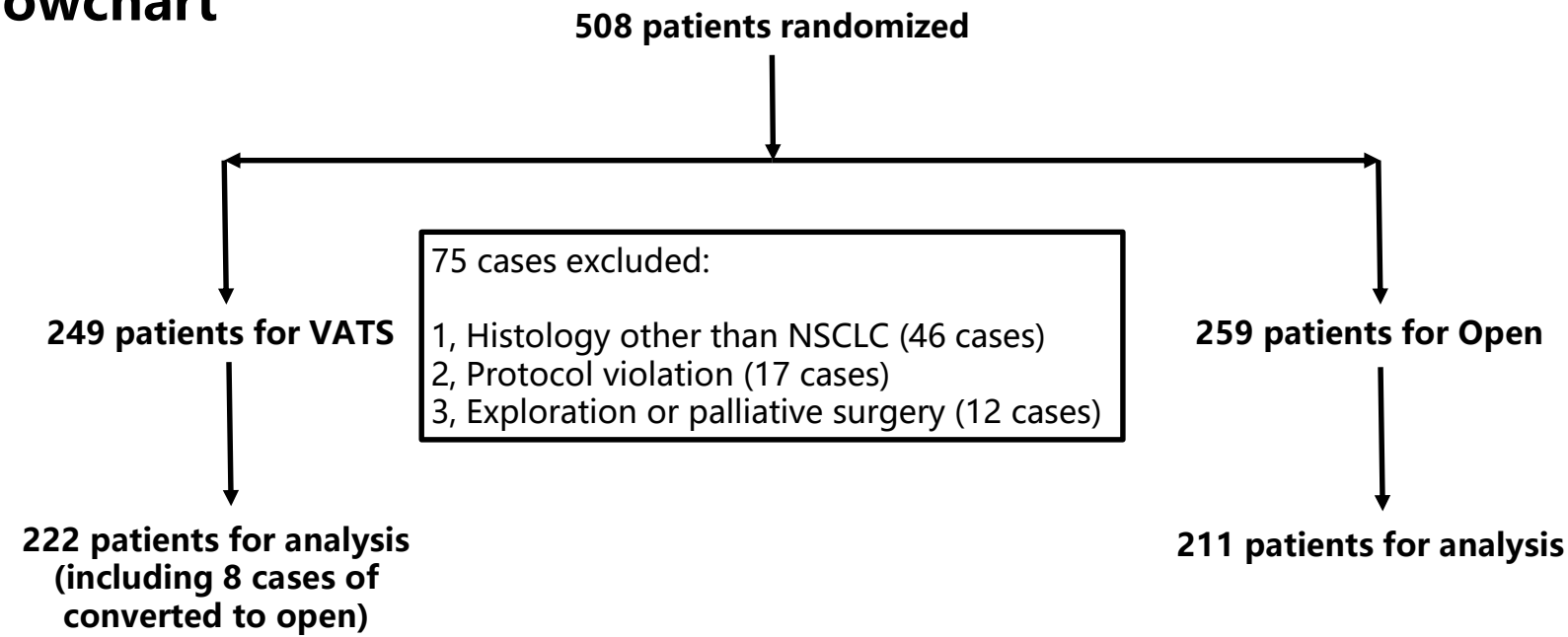
Suzuki K, et al. AATS 2017
Altorki NK, et al AATS2018

OA06.02

Video-Assisted Thoracoscopic Surgery vs. Thoracotomy for Non-Small Cell Lung Cancer: Oncologic Outcome of a Randomized Trial

Dongrong Situ, Hao Long, Qunyou Tan, Qingquan Luo, Zheng Wang, Gening Jiang, Tiehua Rong

Flowchart


508 patients randomized
249 patients for VATS
75 cases excluded:
1, Histology other than NSCLC (46 cases)
2, Protocol violation (17 cases)
3, Exploration or palliative surgery (12 cases)
259 patients for Open
222 patients for analysis (including 8 cases of converted to open)
211 patients for analysis

Methods

- Randomization and masking

1. Randomized in a 1:1 ratio into VATS and thoracotomy lobectomy groups
2. Neither patients nor any investigators were masked to treatment allocation

- Sample size : >190 cases in each group

1. Non-inferiority design
2. alpha level=0.05, beta level=0.10, non-inferiority margin = 20%
3. for a difference of a 92% 5-year OS of stage IA NSCLC in thoracotomy group versus a 82% in VATS group (from literatures)
4. aimed to enroll >400 patients to allow pre/post-randomization exclusions.

This statistical consideration was enough?

- Ex. JCOG0802; Planned sample size is 1,100

One-sided alpha of 5%, power of 80%, non-inferiority margin of 5% assuming 5-year OS of 90%.

- If the authors have assumed equivalent oncologic outcomes between open and VATS derived from retrospective studies, the setting of 10% difference for 5YS was not reasonable. In fact, the authors have selected the non-inferiority design.
- If the non-inferiority margin is set at -20%, HR will be about 4. This means the instantaneous death rate by VATS will four times, compared with open.
- In my idea; if one-sided alpha of 5%, power of 80% and non-inferiority margin of 5% assuming 5-year OS of 92% (HR: 1, Non-inferiority margin: 1.67) are set, total 918 cases will be required.
- It leads to the correct settings are correct conclusion. Investigators must have smooth relations with skillful statisticians.

Take Home Message

- The retrospective study has demonstrated that sublobar resection confers equivalent survival to lobectomy in patients with screen detected cancers. But, definitive decision for this issue should be addressed after concluding the results of both CALGB study and JCOG/WJOG one.

- Although a surgical RCT randomizing between 2 distinctly different operations is very challenging due to patient perceptions (and sometimes physician bias), a prospective RCT should be carried out to observe the manners, especially hypothesis and statistical considerations.

Back up

Predictors of surgical morbidity and mortality in the entire cohort

Independent variables	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age in years	1.02 (0.99-1.05)	0.077	1.02 (0.99-1.05)	0.125
Male Gender	1.32 (1.01-1.73)	0.044	1.20 (0.89-1.62)	0.229
Smoking pack/year	1.01 (1.002-1.01)	0.005	1.01 (1.001-1.01)	0.020
Pulmonary comorbidity	1.28 (0.96-1.07)	0.099	1.34 (0.98-1.82)	0.064
VATS approach (vs. thoracotomy)	0.71 (0.52-0.96)	0.024	0.76 (0.56-1.04)	0.091
Sublobar resection (vs. lobectomy)	0.60 (0.40-0.89)	0.011	0.59 (0.38-0.94)	0.024

Survival of the entire group