Surgery for early stage NSCLC

Ugo Pastorino, Thoracic Surgery
Istituto Nazionale Tumori, Milan
Lung cancer stage at diagnosis

NIH SEER 2017

- Local (I): 16%
- Regional (II-III): 22%
- Metastatic (IV): 56%
Lung cancer survival by stage

Local: 56%
Regional: 29%
Metastatic: 5%

Overall survival:
- 14% (1990-94)
- 20% (2007-13)
Lung cancer survival in Europe

EUROCare Registries

8% 13%

78-85 90-94 99-07

male female total

IARC Pub 1995; 132
Ann Onc 2003; 14:128
Eur J Can 2015; 51:2242
SURGICAL OUTCOME FOR EARLY LC: REAL WORLD DATA

**Italy**
- 30-day mortality overall, number
- 5-yr survival overall

**EU / USA**
- 30-day mortality overall, volume
- 5-yr survival overall, number, stage surgery vs RT, volume
Thirty-day mortality and five-year survival in thoracic surgery: “real-world” assessment of outcomes from a single-institution audit

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\(^4\) Anesthesiology Department, Fondazione Policlinico Universitario “La Sapienza”, Rome - Italy
\(^5\) Medical Directorate, Fonden - Italy

<table>
<thead>
<tr>
<th>Database</th>
<th>Period</th>
<th>Deaths</th>
<th>30-day Mortality</th>
<th>5-year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTM</td>
<td>2003-2015</td>
<td>2,636</td>
<td>1.2%</td>
<td>1.1%</td>
</tr>
<tr>
<td>ESTS</td>
<td>2007-2015</td>
<td>47,960</td>
<td>2.7%</td>
<td>2.3%</td>
</tr>
<tr>
<td>STS</td>
<td>2002-2008</td>
<td>18,800</td>
<td>2.2%</td>
<td></td>
</tr>
<tr>
<td>EPITOR</td>
<td>2005-2010</td>
<td>19,556</td>
<td>7.4%</td>
<td>6.1%</td>
</tr>
</tbody>
</table>
Thirty-day mortality after surgery: “real-world” experience from a single-institution audit

Anna Cantarutti¹, Carlotta Galeone², Giovanni Felicetti³, Vincenzo Mazzaferr⁴, Gustavo Galmozzi⁵, Giovanni Gazzaniga⁷

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² Department of Clinical Sciences and Community Health, Fondazione IRCCS Istituto Nazionale dei Tumori - Italy
³ Thoracic Surgery Unit, Fondazione IRCCS Istituto Nazionale dei Tumori - Italy
⁴ Medical Directorate, Fondazione IRCCS Istituto Nazionale dei Tumori - Italy
⁵ Anesthesiology Department, Fondazione IRCCS Istituto Nazionale dei Tumori - Italy
⁶ General Surgery Department, Fondazione IRCCS Istituto Nazionale dei Tumori - Italy
⁷ Scientific Director, Fondazione IRCCS Istituto Nazionale dei Tumori - Italy
EARLY LC RESECTION:

STS DB 2015

2005: 18%
2011: 46%

USA

VATS LOBECTOMY IN SURGICAL DATA BASES

ESTS DB 2015

2010: 4%
2014: 22%

EUROPE
ROBOT vs 2D VATS

+ 3D vs 2D
  magnification
  rotation

- number of ports
  time
  costs
Use and Outcomes of Minimally Invasive Lobectomy for Stage I Non-Small Cell Lung Cancer in the National Cancer Data Base

Chi-Fu Jeffrey Yang, MD, Zhifei Sun, MD, Paul J. Speicher, MD, MHS, Shakir M. Saud, MA, Brian C. Gulack, MD, Matthew G. Hartwig, MD, David H. Harpole Jr, MD, Mark W. Onaitis, MD, Betty C. Tong, MD, Thomas A. D’Amico, MD, and Mark F. Berry, MD, MHS

Results—Of 30,040 lobectomies, 7,824 were VATS and 2,025 were robotic.

Conclusions—In this population-based analysis, MIS (VATS and robotic) lobectomy was used in the minority of patients for stage I non-small cell lung cancer. MIS lobectomy was associated with shorter length of hospital stay and was not associated with increased perioperative mortality, compromised nodal evaluation, or reduced short-term survival when compared with the open

Robotic-Assisted, Video-Assisted Thoracoscopic and Open Lobectomy: Propensity-Matched Analysis of Recent Premier Data

Daniel S. Oh, MD, Rishindra M. Reddy, MD, Madhu Lalitha Gorrepati, MD, Shilpa Mehendale, MS, MBA, and Michael F. Reed, MD

Conclusions. Robotic-assisted lobectomy was associated with improved outcomes for certain perioperative clinical variables, including shorter length of stay and lower complication rates. It was also associated with a lower conversion rate to OL compared with VL.

(Ann Thorac Surg 2017;104:1733–40) © 2017 by The Society of Thoracic Surgeons

Shiyou Wei¹,³†, Minghao Chen²†, Nan Chen¹,³ and Lunxu Liu¹,³*

Conclusions: RATS lobectomy is a feasible and safe technique and can achieve an equivalent short-term surgical efficacy when compared with VATS, but its cost effectiveness also should be taken into consideration.
MINIMALLY INVASIVE APPROACH: LOBE / SEGMENT + 3N1 / 3N2 ND

> 90% MuscleSparing  \[\rightarrow\]  45% MuscleSparing

45% VATS

LDCTdetected: 75% VATS
MINIMALLY INVASIVE LOBECTOMY: PRESENT INTM TECHNIQUE

3D VATS lobe / segment

uni – biportal
SURGERY FOR EARLY LC: IS LOBECTOMY MANDATORY?

Survival Following Lobectomy and Limited Resection for the Treatment of Stage I Non-small Cell Lung Cancer ≤ 1 cm in Size

A Review of SEER Data

Conclusions: Limited resection and lobectomy may lead to equivalent survival rates among patients with stage I NSCLC tumors ≤ 1 cm in size. If confirmed in prospective studies, limited resection may be preferable for the treatment of small tumors because it may be associated with fewer complications and better postoperative lung function.

CHEST 2011; 139(3):491–496
Intra-operative mediastinal staging: evidence from RCTs

➢ in order to be suitable for randomization, all patients had to prove node negative at frozen section of four nodal stations:

2R, 4R, 7, 10R or 5, 6, 7, 10L

➢ a procedure that far exceeds the level of routine intraoperative mediastinal node investigations in most centers, outside clinical trials

Darling GE, J Thorac Cardio Vasc Surg. 2011; 141:662

negative results of ACOSOG trial

1,023 patients
**Intra-operative staging: SEER data**

24,273 stage I NSCLC

lymphadenectomy = increased 5-year overall survival from 41.6% to 58.4% (P<.0001)

with a two-fold increase of 10-year survival in patients with > 21 resected nodes compared with 0 nodes

Varlotto JM, Cancer 2009;115:851
Intra-operative mediastinal staging either MLNS or systematic sampling should include:

- 2R, 4R, 7,
- 10, 11, 12 R
- 5, 6, 7,
- 10, 11, 12 L

**MANAGEMENT OF EARLY LC: MLNS OR SAMPLING IS MANDATORY**
<table>
<thead>
<tr>
<th><strong>LDCT SCREENING &amp; SURGERY: EXPECTED OUTCOME</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>positive</strong></td>
</tr>
<tr>
<td>1. higher resectability</td>
</tr>
<tr>
<td>2. higher % stage I</td>
</tr>
<tr>
<td>3. minimal invasion (VATS/RATS)</td>
</tr>
<tr>
<td>4. lesser morbidity / mortality</td>
</tr>
<tr>
<td>5. better 5-yr survival</td>
</tr>
<tr>
<td><strong>negative</strong></td>
</tr>
<tr>
<td>1. overdiagnosis / overtreatment</td>
</tr>
<tr>
<td>2. costs</td>
</tr>
</tbody>
</table>
### 15 YEARS OF LDCT SCREENING: BASELINE DETECTION RATES & FREQUENCY OF STAGE I

<table>
<thead>
<tr>
<th></th>
<th>screened</th>
<th>pos LDCT</th>
<th>LC</th>
<th>stage I</th>
</tr>
</thead>
<tbody>
<tr>
<td>non RCT</td>
<td>16</td>
<td>71,935</td>
<td>21%</td>
<td>1.0%</td>
</tr>
<tr>
<td>all RCTs</td>
<td>8</td>
<td>44,629</td>
<td>23%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

> 115,000 smokers enrolled  
LC = 1 / 20 - 25 of positive LDCT

LC = 1 / 20 - 25 of positive LDCT
Long-Term Surveillance of Ground-Glass Nodules
Evidence from the MILD Trial


* Azienda Ospedaliero-Universitaria di Padova, Padova, Italy. † ERSU Foundation, Padova, Italy. ‡ Azienda Ospedaliero-Universitaria di Padova, Padova, Italy.

J Thor Oncol 7:1541, 2012
Outcomes of lung cancers manifesting as nonsolid nodules

Rowena Yip\textsuperscript{a,}\textsuperscript{*}, Andrea Wolf\textsuperscript{b}, Kathleen Tam\textsuperscript{a}, Emanuela Taioli\textsuperscript{c}, Ingram Olkin\textsuperscript{d}, Raja M. Flores\textsuperscript{b}, David F. Yankelevitz\textsuperscript{a}, Claudia I. Henschke\textsuperscript{a}

a median follow up of 18–51 months. All NSNs were Stage I adenocarcinoma without pathologic nodal involvement upon resection, except for one case in which the NSN progressed to become part-solid nodule after 6 years of follow-up. The five-year lung cancer-specific survival rate was 100%. These findings suggest an indolent course for lung cancers manifesting as NSNs.
Natural History of Pulmonary Subsolid Nodules: A Prospective Multicenter Study

Ryutaro Kakinuma, MD, PhD, a,b,c,∗ Masayuki Noguchi, MD, PhD, d Kazuto Ashizawa, MD, PhD, e Keiko k

Conclusion: This study revealed the frequencies and periods of development from PGGNs and HGGNs into part-solid nodules. Invasive adenocarcinomas were diagnosed only among the part-solid nodules, corresponding to 1% of all 1229 SSNs.
sified nodules from the test set (DLCST). Each row depicts nodules from one class
ACTIVE SURVEILLANCE OF GGNs: UPDATE OF MILD 2017

384 subjects with subsolid nodules (GGNs)
4 – fold detection rate by Cyrrus CAD
followed by LDCT for 10 years

4 (1%) progressed to stage Ia ADC (years 8 - 10)

18 (4.7%) developed LC in other sites
3 (0.8%) died for other causes

active surveillance is safe and effective, with long F-U
SCREENING & SURGERY: VALUE OF BLOOD MARKERS

- Identify higher risk individuals
- Select candidates as upfront test
- Define intensity and duration of LDCT
- Reduce LDCT false positive rate
- Target LC therapy
- Focus primary prevention
Clinical Utility of a Plasma-Based miRNA Signature Classifier Within Computed Tomography Lung Cancer Screening: A Correlative MILD Trial Study

false positive rate  = 4% vs. 96.4% in NLST

J Clin Oncol 2014;32:768
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>NLST 2011</td>
<td></td>
<td>24%</td>
</tr>
<tr>
<td>NELSON 2009</td>
<td></td>
<td>27%</td>
</tr>
<tr>
<td>DLCST 2012</td>
<td></td>
<td>32%</td>
</tr>
<tr>
<td>LUSI 2012</td>
<td></td>
<td>29%</td>
</tr>
<tr>
<td>DANTE 2009</td>
<td></td>
<td>24%</td>
</tr>
<tr>
<td>MILD 2012</td>
<td></td>
<td>8%</td>
</tr>
<tr>
<td>bioMILD 2016</td>
<td></td>
<td>4%</td>
</tr>
</tbody>
</table>
Clinical Utility of a Plasma-Based miRNA Signature Classifier Within Computed Tomography Lung Cancer Screening: A Correlative MILD Trial Study

Overall Survival (N=77)

Overall Survival (Stage I cases N=45)
EARLY LC SURGERY: **BIOMARKERS VALIDATION**

- CAD radiomic (texture, density, size, shape)
- Pulmonary damage (FEV1, lung density)
- CRP levels & inflammatory markers
- Blood & tissue immune markers
- Circulating DNA & miRNAs
- Proteomic & metabolomic
Inflammatory status and lung function predict mortality in lung cancer screening participants

Cumulative Probability of Lung Cancer Death

- high CRP & low FEV1
- low CRP & high FEV1

Eur J Can Prev 2017a
Baseline and postoperative factors predict mortality in 1750 LC patients with complete resection from 2003 to 2015.
stage I

never smokers
Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial

Paul M Ridker, Jean G MacFadyen, Tom Thuren, Brendan M Everett, Peter Libby*, Robert J Glynn*, on behalf of the CANTOS Trial Group†

Summary
Background Inflammation in the tumour microenvironment mediated by interleukin 1β is hypothesised to have a major role in cancer invasiveness, progression, and metastases. We did an additional analysis in the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS), a randomised trial of the role of interleukin-1β inhibition in atherosclerosis, with the aim of establishing whether inhibition of a major product of the Nod-like receptor protein 3 (NLRP3) inflammasome with canakinumab might alter cancer incidence.

\[ p<0.0001; p<0.0001 \text{ for trend across groups}. \] Lung cancer mortality was significantly less common in the canakinumab 300 mg group than in the placebo group (HR 0.23 [95% CI 0.10–0.54]; \( p=0.0002 \)) and in the pooled canakinumab population than in the placebo group (\( p=0.0002 \text{ for trend across groups} \)). Fatal infections or sepsis were significantly
Defining the biological basis of phenotypes in lung cancer

Radiomic approaches permit noninvasive assessment of both molecular and clinical characteristics of tumors, and therefore have the potential to advance clinical decision-making by systematically analyzing standard-of-care medical images.

Dana-Farber Cancer Institute, Boston
Research Institute GROW, Maastricht
Lee Moffitt Cancer Center Institute, Tampa
Institut de recherches cliniques de Montreal
Princess Margaret Cancer Centre, Toronto

Grossmann et al. eLife 2017;6:e23421. DOI: 10.7554/eLife.23421
LDCT SCREENING IN EUROPE: CRITICAL ISSUES

- results of Nelson trial
- who should be screened
- how often
- best diagnostic work-up
- competing risks of death
- real value of blood & other biomarkers
- impact on primary prevention
Cause of Death review NELSON trial

Cause of Death review

266 completed medical files

Dutch deceased NELSON participants

✓ Diagnosed with lung cancer during the study
✓ Lung cancer as CoD death certificate

Blinded towards study arm
Blinded towards patients identity

Comparison with official Dutch death certificates

Linkage with Statistics Netherlands

UPbestWCLC2017
LDCT SCREENING: POTENTIAL CANDIDATES IN EUROPE

- EU population > 500 millions
- current smokers > 100 millions
- aged 55 – 75 > 20 millions
- ≥ 30 pack/yrs > 10 millions
- western EU > 7 millions

SOURCE: WHO REPORT ON TOBACCO EPIDEMIC 2017 - http://www.who.int/tobacco/surveillance
Changes in Treatment Patterns: SEER data

- 32,249 stage IA NSCLC
- Definitive RT Increased from 13% to 29% (P<.0001) from 2004 to 2012
- Better survival for RT or surgery
- Similar survival for RT and surgery

Haque W, AJCO 2016 epub
SBRT vs SURGERY: SBRT THE FIRST CHOICE?

3D VATS vs SURGERY: SBRT THE FIRST CHOICE?

SITE MATTERS
SURGERY FOR EARLY STAGE LC: NEW PROSPECTS

- more selective / more biologically targeted
- less invasive in most patients
- safer in high-risk individuals
- postoperative mortality \( \leq 1\% \)
- benign resections \( \leq 10\% \)
- avoidable for indolent disease
- adjuvant / chemoprevention for higher risk