10th IELCART Meeting, October 30, 2020
Disclosures

- I am a named inventor on a number of patents and patent applications relating to the evaluation of pulmonary nodules on CT scans of the chest which are owned by Cornell Research Foundation (CRF).
- As of April 2009, I signed away any financial benefit including royalties and any other proceeds related to the patents or patent applications owned by CRF.
- I am the President of the Early Diagnosis and Treatment Research Foundation.
Thoracic Surgery for Lung Cancer
Preserve Lung Tissue, Minimize Complications

1883
First pulmonary resection in Gdansk
- Later Sauerbruch, von Miculicz, Brauer, others in Germany
- US: surgeons at Rockefeller Institute and Mount Sinai in NY, Mount Zion in San Francisco, Philadelphia, Mayo Clinic.

1962
Resolved by a retrospective review of two clinics

1995
Ginsburg Report

2007 US CALGB 140503
2009 Japan JCOG/WJOG 0802

2020
Japanese and US randomized trials - ongoing

Pneumonectomy vs. Lobectomy

Standard of care

Pneumonectomy vs. Lobectomy

~60 yrs. later, lobectomy still the standard of care

Lobectomy vs. Sublobar resection

Radiation Therapy for Early Lung Cancer (SBRT)
Preserve Lung Tissue, Minimize Complications

Late 1990s
First used for early stage lung cancer in Japan

Early 2000s
First used in US

Matched Analyses of Surgery vs. SBRT

2010
RTOG 0236 reported in JAMA w. local control of over 90%

2008 ROSEL; STARS
2011 ACOSOG Z4099 / RTOG 1012

Pooled analysis of two failed trials

2015
SBRT was better tolerated and had better overall survival, but underpowered.

2017
VALOR trial is underway
Will hopefully elucidate the role of surgery and SBRT

• Tough to interpret due to selection bias
• Showed similar local control but better survival with surgery

Compare surgery to SBRT, but failed due to lack of accrual

Improving technology: safer and more accurate treatment

Lung Cancer Stage Distribution by Year: NSCLC Planning Adjuvant/Neoadjuvant Trials

Mount Sinai Registry: Early Stage vs. Late Stage
Initiative for Early Lung Cancer Research on Treatment: IELCART

- Reduce lung cancer deaths by early detection and diagnosis of small, early stage lung cancers followed by optimal treatment, including watchful waiting cases.

- Call by the Institute of Medicine in 2007 to develop treatment assessments based on information obtained in the context of clinical care.

Key components of IELCART cohort study:

- Ensure that we capture all relevant patients
  - recruit patients with clinical stage I lung cancer with a maximum tumor diameter of ≤40 mm, who will undergo surgery, radiation, watchful waiting, or any other treatment.

- Usual care treatment as offered by the treating physicians at each institution
  - no consent is needed for the treatment, consent only to store patient data and images.

- Carefully document short-term and long-term follow-up results
  - Pre- and post-treatment and then every year for 10 years, or until death.

Intake Process

Treating physicians identified patients with T1-2N0M0 NSCLC

Study Coordinator recruit potential candidates

NO

Retrospective comparison of outcomes among refusers and non-refusers

YES

Enrolled

- Patient Consent
- Data collection forms
- CT scans
- Background
- Pre-treatment
  - Physician
  - Patients

Follow up Process

Enrolled

Radiation (SBRT)

Surgery with/without MLND

Sublobar resection (Segment/Wedge)

Lobectomy

Watchful waiting

Radiation

Data collection forms
- Post-treatment radiation oncologist
- Post-treatment Patients
- QoL questionnaires

Surgery

Data collection forms
- Post-treatment Surgeon
- Post-treatment Patients
- QoL questionnaires

Watchful waiting

Data collection forms
- QoL questionnaires

Primary Outcome Measures: Survival, Recurrence

Short term outcomes
- Quality of life
- Surgical outcomes: Modification to plan, other abnormalities
- SBRT outcomes
- Survival
- Treatment-related complications

Long term outcomes
- Quality of life
- Tumor recurrence
- Survival

INITIATIVE FOR EARLY LUNG CANCER RESEARCH ON TREATMENT (IELCART): started in 2016

PIs: Thoracic Surgery, Radiology, Statistics, Epidemiology, Percutaneous Interventional Procedures

Raja M. Flores, MD
Claudia I. Henschke PhD, MD
Emanuela Taioli MD, PhD
David F. Yankelevitz, MD

IELCART: development of protocol

- Meta-analysis of studies comparing lobectomy vs. sublobar resection
  - Inconclusive results

- Quality of life
  - Sparse information for early lung cancer
  - Development needed for appropriate Q of L instruments

- Importance of surgical margin and how to measure it

Participating IELCART Sites

Vassar Brothers Medical Center
Stony Brook University Hospital
Upstate Medical University
Northwell Health
Mount Sinai Hospital
Beth Israel Lahey Health
Lahey Hospital & Medical Center
NYU Langone Medical Center
The Valley Hospital
Valley Health System
Swedish Medical Center
Erasmus MC
Universitair Medisch Centrum Rotterdam

7 IELCART Workshops 2015-6 and 3 IELCART Conferences 2015-6
IELCART: Enrolled 1,263 cases (as of 9/2020)

Participating Sites (8)
- MSHS: 5 hospitals
- SUNY Upstate, Syracuse, NY
- New York University, NYC
- Vassar Brothers, Poughkeepsie, NY
- Northwell Health System, NYC and Long Island
- Erasmus Univ. Med. Center, Rotterdam, Netherlands
- Lahey Clinic, Boston, MA
- Medical University of Gdansk, Gdansk, Poland

7 IELCART Workshops 2015-6 and 3 IELCART Conferences 2015-6
IELC ART Mount Sinai Hospital Surgeons

Raja M. Flores MD
Andrew J. Kaufman MD
Daniel G. NICASTRI MD
Andrea Wolf, MD

Dong-Seok Dan Lee, MD
Ardeshir Hakami-Kermani, MD
Kimberly J. Song, MD
RADIOTherapy
Treatment of Lung Cancer

IELC ART Mount Sinai Radiotherapists

Kenneth Rosenzweig, MD
Pinaki Dutta, MD, PhD
IELCART Participating PIs

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Leslie Kohman, MD
Cliff Connery, MD
Henry Tannous, MD
Adam Bograd, MD
Witold Rzyman, MD
Robert Dziedzic, MD
Alexander P.W.M. Maat, MD
Robert Korst, MD
Syed Quadri, MD
Paul Lee, MD
Mount Sinai IELCART Team

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Artit Jirapatnakul, PhD
Qiang Cai MD
Yeqing Zhu MD
Natthaya Triphuridet MD

Nan You MS
Sydney Kantor BA
Jeffrey Zhu MPH
Huiwen “Samme” Chan MPH and MBA
Shana Adler BS
First monograph.
Formation and background of IELCART: 2014-2016
and History of Thoracic Surgery by Fred Grannis Jr MD

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Individualized CT screening depends on indicators of risk e.g., current smokers, former smokers, never smokers

I-ELCAP

100+ investigators
78 institutions in 10 countries
82,000+ participants

Study design
Screening protocol
Pathology protocol
Regimen of screening

Determines lung cancer size, stage, cure rate

Computer Analytics
Conferences @ 6 months
Continuous Quality Improvement
Publications 300+

Nodule growth and detection
Mediastinal masses
Emphysema
Coronary Artery Ca++
Breast Diseases

Israel
Switzerland
Spain
Italy

NY-ELCAP

Roswell Park
UNY-Upstate
SUNY-Downstate
SUNY-Stonybrook
Mount Sinai
NY Medical
Long Island Jewish
Our Lady of Mercy
MSKCC

NYELCAP

Coronary Artery Ca++
Breast Diseases

NEJM 2006; 170:684-8; Radiology 2007; 243:239-49
Common IELCART Management System based on ELCAP Management System™

1992
Original system was created for the initial 1,000 screening participants
C. Henschke

2000
System was upgraded to web-based system for I-ELCAP
C. Henschke together with A.P. Reeves, Electrical Engineer at Cornell University

2016
Created the Biopsy Registry
Created multi-institutional IELCART data and imaging prospective cohort registry

2019
It has been updated and translated into open source management system
Provided to the VA by a grant from Bristol Myers Squibb Foundation

Now available as an open source system to the world

Reeves et al. Radiology Nov 27 2001;
Henschke et al. Oncology 2020; PMID 31365749
& J Thorac Imaging 2020; PMID 32520848
IELCART Research Topics

Projects

<table>
<thead>
<tr>
<th>Clinical staging criteria</th>
<th>Surgical decision making</th>
<th>Comparison of treatment approaches</th>
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<tbody>
<tr>
<td></td>
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<td>Surgical resection (Sublobar vs. Lobectomy)</td>
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<tr>
<td>Risk factors for recurrence</td>
<td>Never smokers</td>
<td>Surgery vs. Radiotherapy</td>
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<tr>
<td></td>
<td>~25% of IELCART cases</td>
<td>Quality of life</td>
</tr>
<tr>
<td></td>
<td>work in progress</td>
<td>Complications</td>
</tr>
<tr>
<td></td>
<td>0% 100%</td>
<td>Long Term Survival</td>
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</table>

Surgical Decision Making

To explore factors associated with sublobar resection (vs. lobectomy) for patients with clinical stage I lung cancer and

To formulate surgeons’ knowledge about surgical treatment options (limited resection vs. lobectomy) into probability function.

RESULTS:

- Great inter-surgeons variability
- Nodule size and location are the most important factors for surgical decision making
- Surgical decision making based on experts’ knowledge can be translated into a probability function
Patient Survey

3. Did you get a second option about your treatment?

- Yes: 33%
- No: 67%
4. Did you get information about lung cancer treatment from any of the following other sources?

- Internet: 41%
- No other sources: 37%
- Family/friends: 25%
- Medical literature: 17%
- Family or friend who is a physician: 15%
- Other: 9%
Q1. Did the pre-treatment discussion prepare you for how you would feel after treatment?

- Very well, 837, 86%
- Moderate well, 108, 11%
- Not well, 33, 3%

If ‘not well’ or ‘moderately well’, what area should have been discussed more fully?

- Post treatment pain
- Recovery time
- Quality of life after treatment
- Post treatment medications and exercises
- Possibility of a change in plan by the surgeon during surgery
- Other
- Cost

In summary: Surgeons prepared patients very well, with only 121(14%) exceptions.
Patient and Surgeon Perspectives

Did the pre-treatment discussion prepare you for how you would feel after treatment?

**Patient’s perspective**
- Not well, 33, 3%
- Moderate well, 108, 11%
- Very well, 837, 86%

**Surgeon’s perspective**
- Not well, 33, 3%
- Moderate well, 96, 11%
- Very well, 801, 89%
2. Did your physician present any options to assist you with navigating list post-treatment, such as information on support groups?

3. Did your physician have you meet with a nurse navigator or social worker?

4. Did you believe that your physician answered most of your post-treatment questions?
Physician Survey

- Before treatment
- After treatment
Q3. Which of the following were the most important factors in recommending that particular surgery to this particular patient:

- Location of the nodule: 79%
- Size of the nodule: 69%
- Ability to have a parenchymal neg margin: 35%
- Patient functional status/co-morbidities: 22%
- CT consistency of the nodule: 21%
- Other (PET, no tissue confirmation, etc): 20%
- Ability to perform min. invasive resection: 16%
- Patient's age: 15%
- Ability to have bronch/ven/art neg margin: 14%
- Preop percutaneous/bronchoscopic biopsy: 12%
- Patient preference for a given operation: 9%
- Presence of multiple nodules: 6%
- Patient's size: 4%
- Patient's family's preference: 3%
Comparison of initial choices and final surgical procedure performed

Final decision before surgery

- Sublobar: 31%
- Lobectomy: 48%
- Pneumonectomy: 2%
- More than 1 choice: 7%
- Other: 3%

Actual surgery performed

- Lobectomy: 50%
- Pneumonectomy: 1%
- Sublobar: 37%
- Segmentectomy: 10%
- More than 1 choice: 7%
- Other: 2%

IELCART Workshops 2015-6 and 9 IELCART Conferences 2015-9
Quality of Life

Sparse literature on early stage lung cancer

QoL questionnaire

• before and 1-2 and 6 mos after Rx
• then every year for 10 years

Quality of Life: Surgery vs. SBRT

184 patients (28 SBRT; 156 surgery) in SEER-MHOS 1998-2014

- Significant decline in PCS score from baseline to follow-up in both surgery ($\Delta PCS=-4.81$, $p<0.0001$) and radiotherapy ($\Delta PCS=-5.6$, $p=0.014$) patients
- MCS score declined from baseline to follow-up after treatment with surgery only ($\Delta MCS=-2.96$, $p=0.0003$) or radiotherapy only ($\Delta MCS=-1.86$, $p=0.29$)
- Surgical patients had higher baseline PCS and MCS scores than SBRT patients
- No significant difference in the change over time between the two treatment options for PCS or MCS

*Adjusted for age at diagnosis, gender, race, education, smoking status, completion of survey by proxy, and presence of relevant comorbidities.
Quality of Life after Surgery for Stage IA NSCLC

Sublobar resection (SL) vs. Lobectomy (L)

During the 1st post-operative year, SL patients had better physical health (PMS) and lung cancer symptoms (LCS) but lower mental health (MCS).

The first two postoperative months showed the most significant change which suggests targeting postoperative intervention during that time might be beneficial.

QoL scores were lower for women than for men, but only significantly worse for lung cancer symptoms (FACT-LCS) and anxiety (PHQ-4).
Mind-body intervention for early stage lung cancer surgical patients

The **Stress Management and Resilience Training (SMART;** Park et al., 2013) is a Comprehensive mind-body intervention designed to improve mental and physical health QoL and normalize HPA axis functioning.

Pilot the 8-week SMART intervention among 20 Mount Sinai Health System patients to determine feasibility, satisfaction, and acceptability for use with RCT of early-stage lung cancer post-surgical patients.

Schwartz R. Funded pilot
Staging

- Separate staging for solid and subsolid cancers
- Pre-surgical assessment of mediastinal lymph nodes
- Value of PET scans for lymph node metastases

Yip et al. J Thorac Oncol 2019; 14: 890-902
Tumor diameter (HR=1.1) and PAI (HR=3.2) were significant independent risk factors for risk of dying of lung cancer.

However, when including clinical, CT and pathologic findings in the final multivariable Cox regression, PAI was no longer a significant prognostic indicator (p = 0.19).
Kaplan-Meier Survival for pN0M0 NSCLC ≤ 30mm Subsolid Cancers (n=163): Angiolympathic (PAI) and pleural (PVI) Inv.

- One death (1/163): in patient w/ part-solid nodule (15mm solid component)

> Lung cancer survival for patients With subsolid nodules = 99.1%

Lung cancer specific survival

<table>
<thead>
<tr>
<th>Time (month)</th>
<th>Invasion</th>
<th>None</th>
<th>PAI only</th>
<th>VPI only</th>
</tr>
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<tr>
<td>0</td>
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<td>250</td>
<td>175</td>
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<td>177</td>
<td>178</td>
</tr>
</tbody>
</table>

Log-rank p=0.96

Nodule consistency, p<0.0001

- No Invasion
- VPI or PAI Invasion

Subsolid (n=163) Solid (n=336)

# of patients

Yip et al. J Thorac Oncol 2019; 14: 890-902
Kaplan-Meier Survival for pN0M0 NSCLC ≤ 30mm:

**Bottom Line:** Nodule consistency on CT was a more significant prognostic indicator than either PAI or VPI.
Assessment of Mediastinal Lymph Node Metastases in Stage IA NSCLC using CT and PET

For the 212 patients with solid cancers,

None of the 51 patients with nonsolid or part-solid cancers had mediastinal LN metastases

Treatment

Assessments

Length of stay
Major complications
Frequency of oxygen use after discharge
New primaries
Recurrence: local, mediastinal, distant
Long term consequences

IELCART Investigators. Work in progress
Lobar vs. sublobar surgical treatment

335 patients w/ clinical stage I NSCLC manifesting as a solid nodule

Both 10-year K-M survival analysis and Cox proportional hazard regression found no significant difference in lung cancer-specific survival.

Flores et al. J Thorac Cardiovasc Surg 2014; 147: 1619-26
Survival After Treatment for NSCLCs ≤ 30 mm
Surgery vs. Radiotherapy

Buckstein et al. 2014

Radiation Rx alone: 92% (95% CI: 76%-100%)
Surgery alone: 90% (95% CI: 87%-94%)

n = 10
n = 376

Berlin et al. 2019

Surgery alone: 95% (95% CI: 93%-97%)
Radiation alone: 90% (95% CI: 85%-100%)

n = 24
n = 702
Post-surgical change in Lung Volume

Statistically significant changes in volumes and masses can be quantified using a fully automated computer algorithm.

Jirapatnakul et al. Work in progress
Hiatal Hernia

- Post-surgical patients had a significantly higher incidence of hiatal hernia than matched non-surgical controls (24.4% vs. 4.6%, P <0.0001)

- Further analysis showed post-surgical patients were 8.1 times more likely to develop hiatal hemias (OR=8.1, 95% CI: 2.3-28.8)

- More frequent after lower lobe than upper lobe lobectomy (29.3% vs 20.0%; P=0.24)

- More frequent after right-sided as compared with left-sided lobectomy (23.5% vs 22.0%; P=0.85)

IELCART Investigators. Work in progress
PERSONALIZED LUNG CANCER RISK PREDICTION

Clinical Factors
- Demographics,
- Smoking History,
- Comorbidities,
- Exposures
  (SHTS, environmental, occupational)

Imaging

Genetics / Pathology

C-G-I Models

IELCART Investigators. Work in progress
AI for Lung Cancer: detection, diagnosis and prognostication


IELCART Investigators. Work in progress
AI Collaborative Investigations

- AP Reeves
  - Vision and Image Analysis (VIA) Laboratory at Cornell University, Ithaca NY
- M. Giger and S. Armado
  - Maryellen Giger Laboratory, Department of Radiology, University of Chicago
- G. Tourassi and G. Agasthya
  - Oak Ridge National Laboratory
Table of Contents

TBD:
An important historical summary
Future Personalized Lung Cancer Care