I-ELCAP

International Early Lung Cancer Action Program

IELCART

Initiative for Early Lung Cancer Research on Treatment

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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

2009 Japan JCOG/WJOG 0802

2007 US CALGB 140503

2020 Japanese and US randomized trials - *ongoing*

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

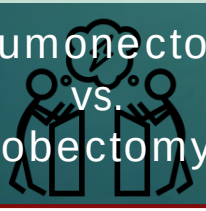
Standard of care

PNEUMONECTOMY

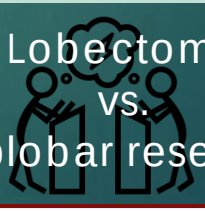
LOBECTOMY

CONTROVERSY

Pneumonectomy vs. Lobectomy



Lobectomy vs. Sublobar resection



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Shimkin MB, Connelly RR, Marcus SC, Cutler SJ.
J Thorac Cardiovasc Surg. 1962; 44:503-19

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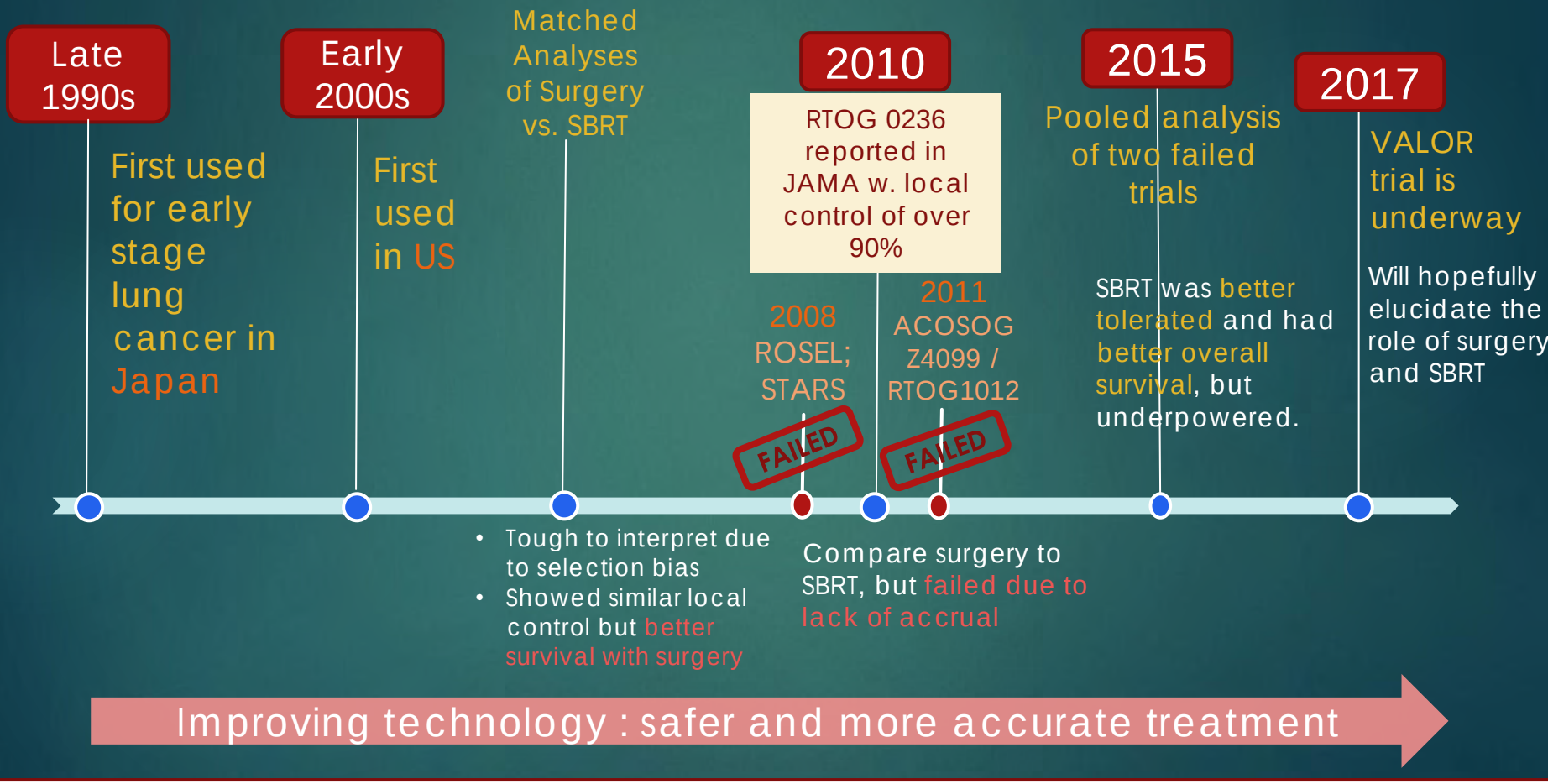
Radiation Therapy for Early Lung Cancer (SBRT)

Preserve Lung Tissue, Minimize Complications



Improving technology : safer and more accurate treatment

Fernando HC et al. J Thorac Cardiovasc Surg 2012;144:S35-38; Trial of Either Surgery or Stereotactic Radiotherapy for Early Stage IA Lung Cancer (ROSEL) https://clinicaltrials.gov/ct2/show/NCT00687986;
Randomized study to compare CyberKnife to surgical resection in Stage I NSCLC(STAR) https://clinicaltrials.gov/ct2/show/NCT00840749;
Chang JY et al. Lancet Oncol 2015; 16:630-7.

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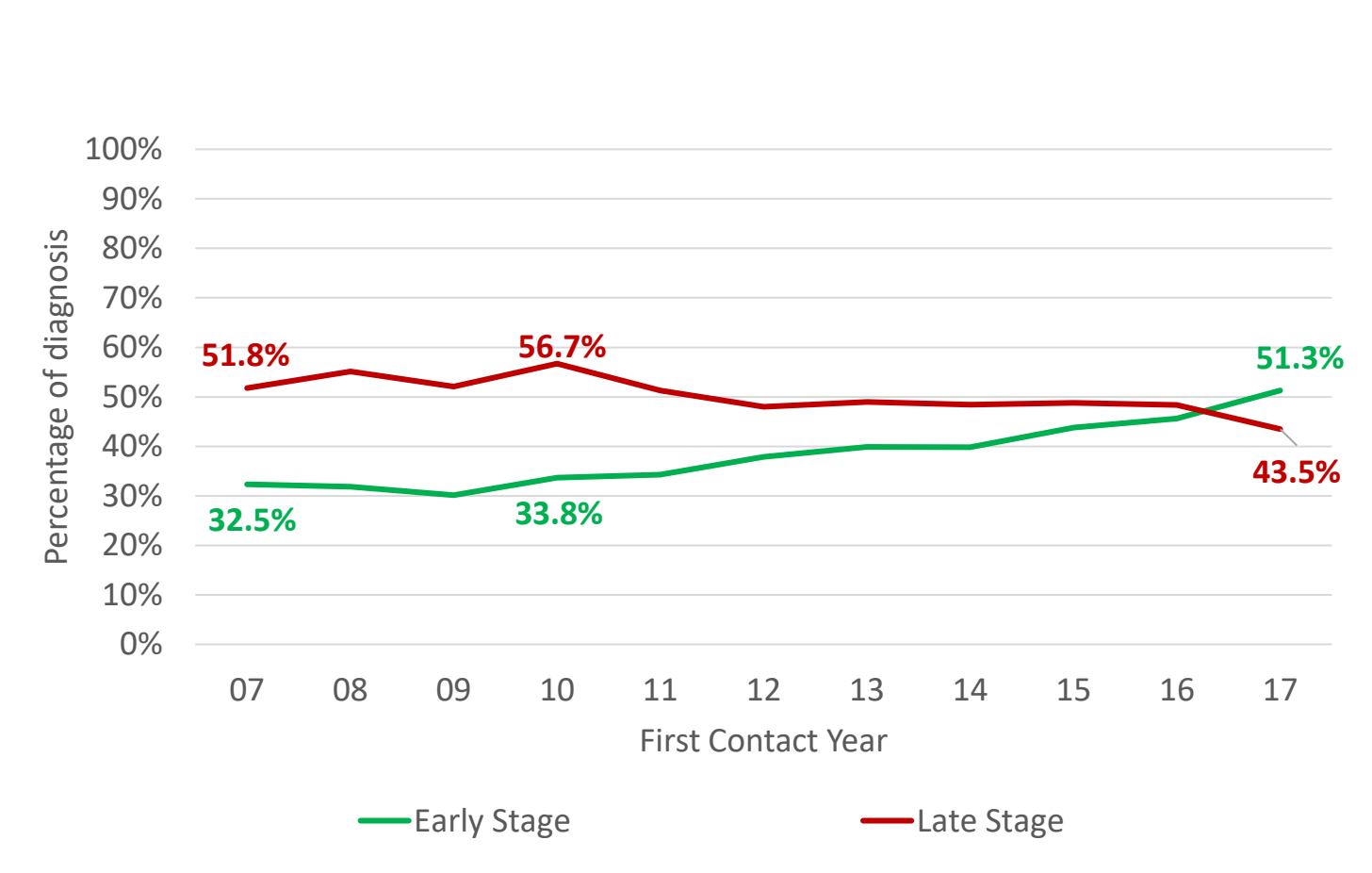
Lung Cancer Stage Distribution by Year: NSCLC Planning Adjuvant/Neoadjuvant Trials



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

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Olsen L, Aisner D, McGinnis J. The learning healthcare system: workshop summary of the Institute of Medicine Roundtable on evidence-based medicine. National Academy Press (US) 2007: 4-10

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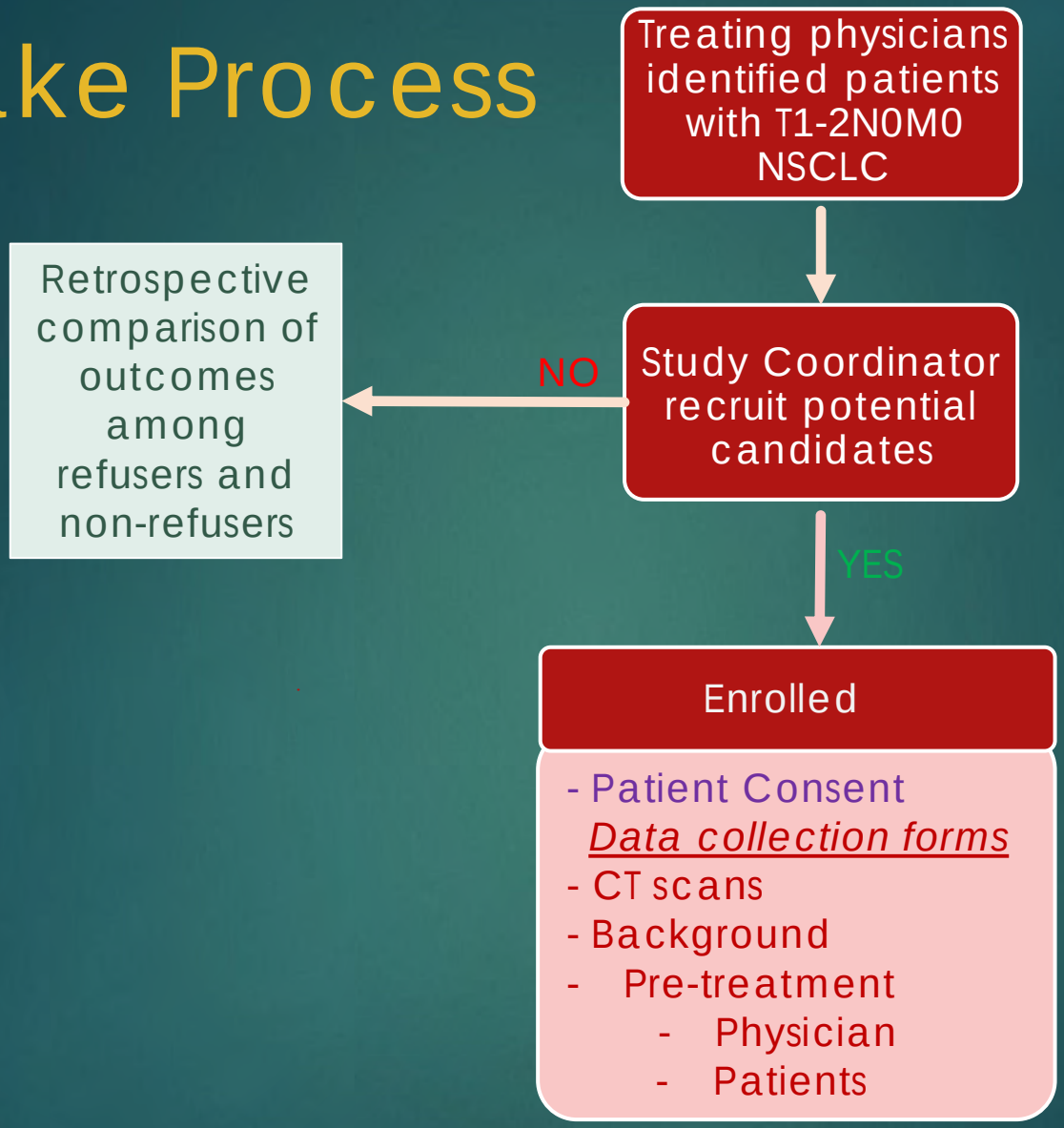
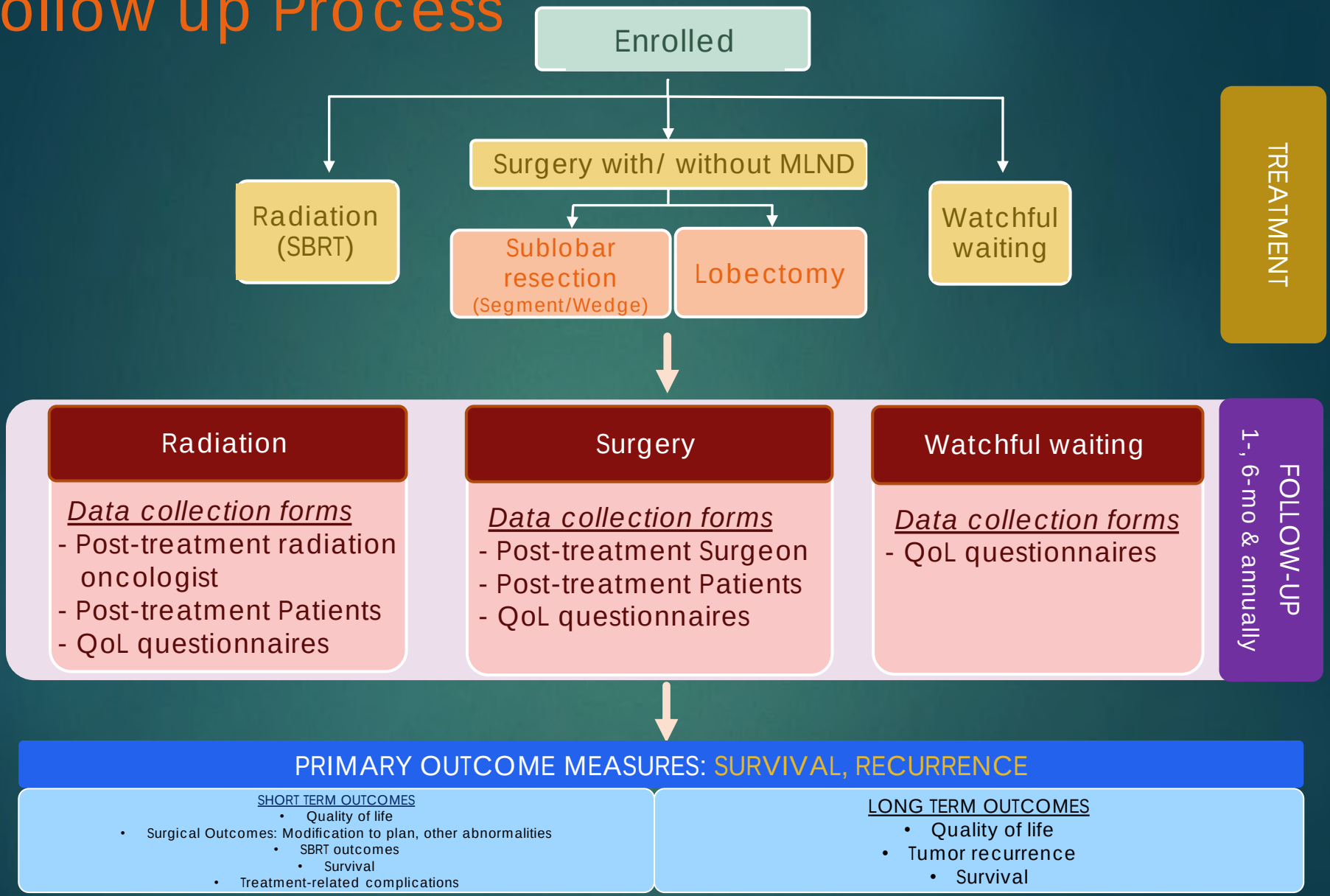
Intake Process



Flores et al. J Thorac Oncol. 2018; 13:946-57

Follow up Process



Flores et al. J Thorac Oncol. 2018; 13:946-57

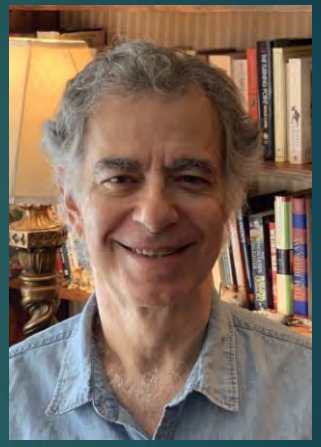
INITIATIVE FOR EARLY LUNG CANCER RESEARCH ON TREATMENT (IELCART):

started in 2016

Raja M. Flores, MD

Claudia I. Henschke
PhD, MD

Emanuela Taioli
MD, PhD



David F. Yankelevitz, MD

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

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Flores et al. J Thorac Oncol. 2018; 13:946-57

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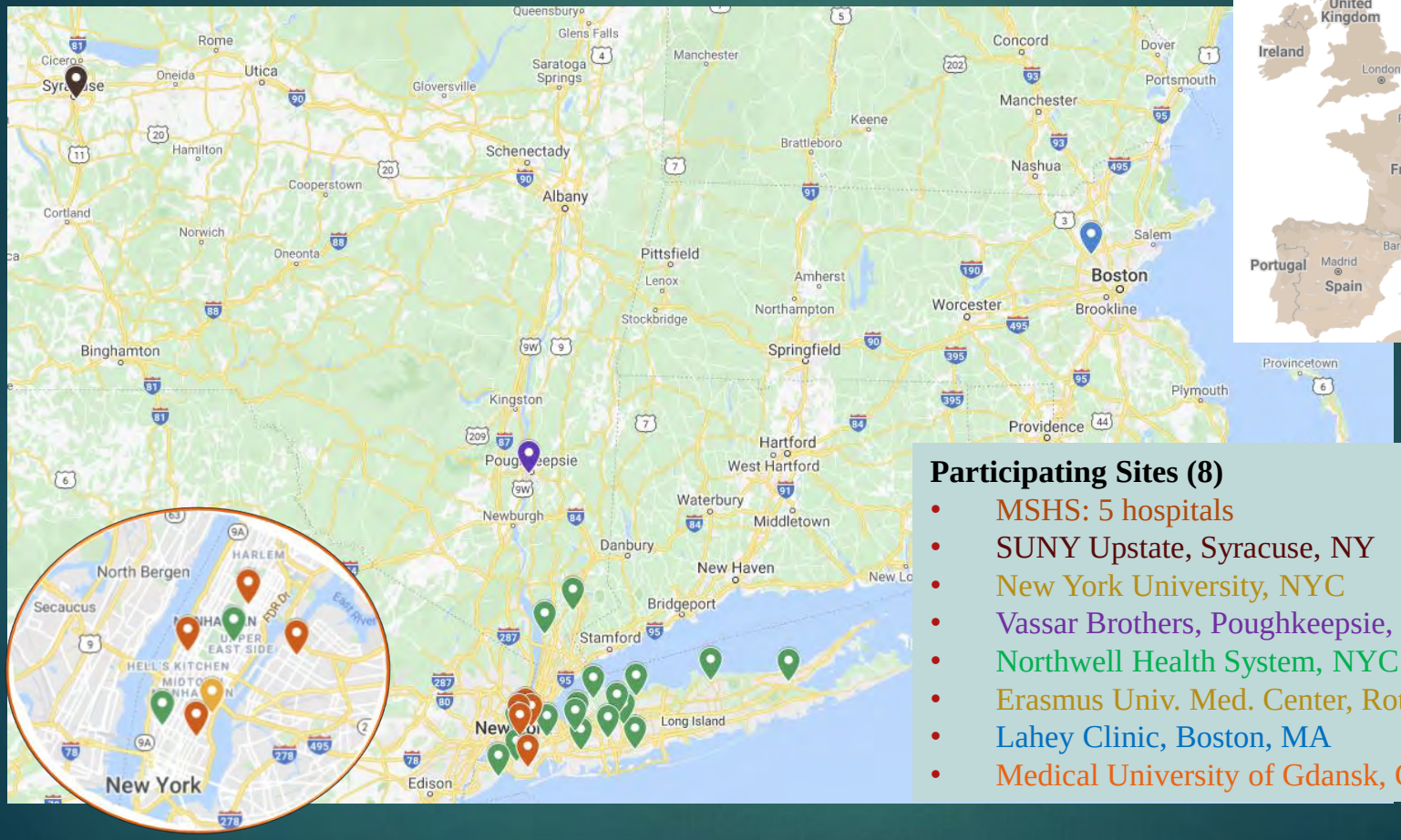
IELCART: development of protocol

- 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

Taioli et al. J Thorac Oncol 2016; 11:400-6; Schwartz et al. J Comm Support Oncol 2016; 14: 37-44; Yip et al. Cancer Invest. 2018; 36: 122-6; Wolf et al. Ann Thor Surg 2017; 104:1171-8; Flores et al. J Cardiovasc Surg 2014; 147:1619-26; Buckstein M et al. J Rad. Oncol 2014: 3: 153-7

Participating IELCART Sites

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

I-ELCAP International Early Lung Cancer Action Program

7 IELCART Workshops 2015-6 and
3 IELCART Conferences 2015-6

IELCART Initiative for Early Lung Cancer Research on Treatment

IELCART 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

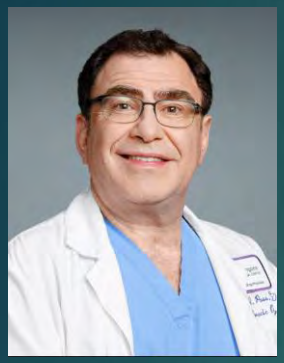
RADIOTHERAPY
Treatment of Lung Cancer

IELCART Mount Sinai Radiotherapists

Kenneth Rosenzweig, MD

Pinaki Dutta, MD, PhD

IELCART Participating PIs



Harvey Pass, MD

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

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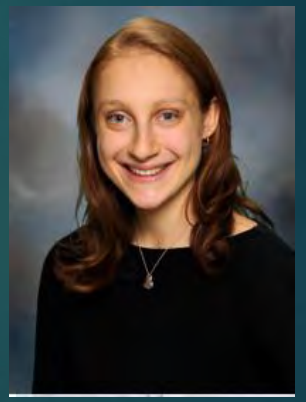
Huiwen “Samme” Chan MPH and MBA



Shana Adler BS

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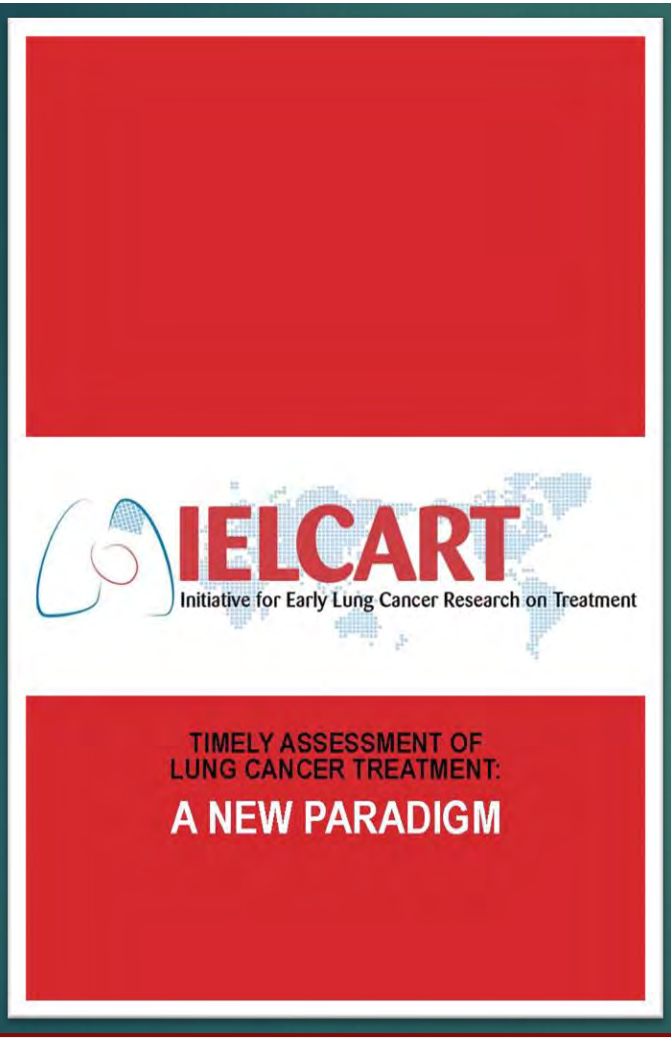
IELCART Initiative for Early Lung Cancer Research on Treatment

First monograph.
Formation and background of IELCART: 2014-2016 and History of Thoracic Surgery by Fred Grannis Jr MD



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ISBN: 978-0-46-477881-3

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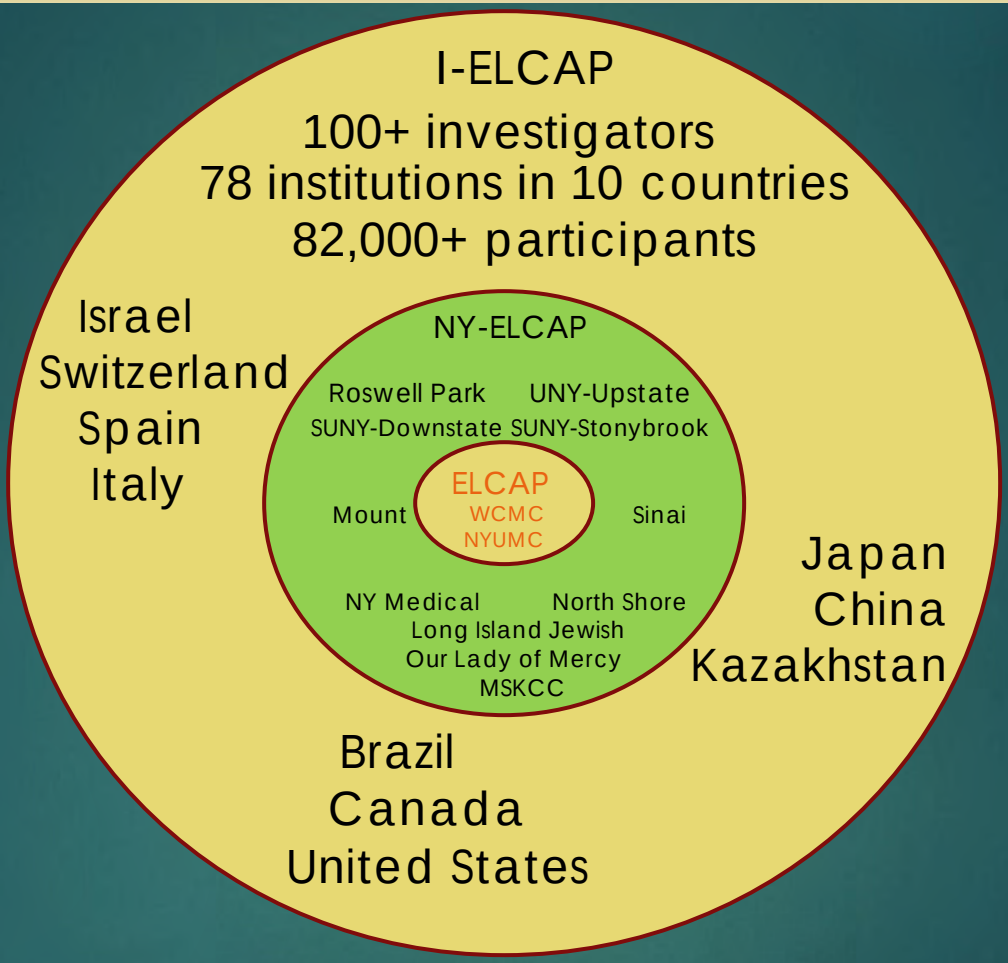
Individualized CT screening depends on indicators of risk
e.g., current smokers, former smokers, never smokers



- Study design
- Screening protocol
- Pathology protocol
- Regimen of screening
- Determines lung cancer size, stage, cure rate
- Nodule growth and detection
- Mediastinal masses
- Emphysema
- Coronary Artery Ca++
- Breast Diseases
- Computer Analytics
- Conferences @ 6 months
- Continuous Quality Improvement
- Publications 300+

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Clin Imaging 1994; 18:16-20; Lancet 1999; 354: 99-105
NEJM 2006; 170:684-8; Radiology 2007; 243:239-49

IELCART Initiative for Early Lung Cancer Research on Treatment

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 a *open source system* to the world

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

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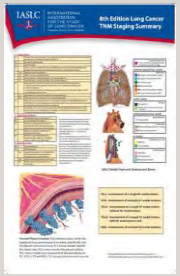
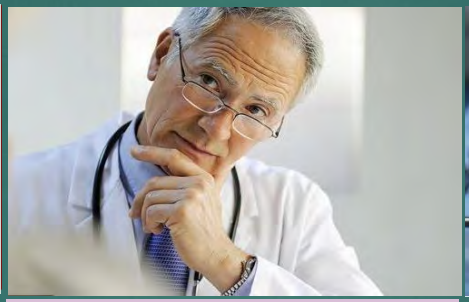
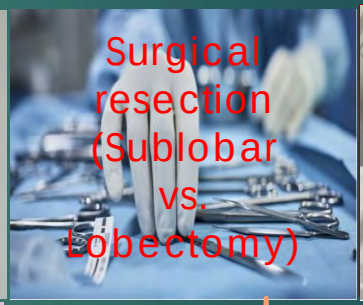
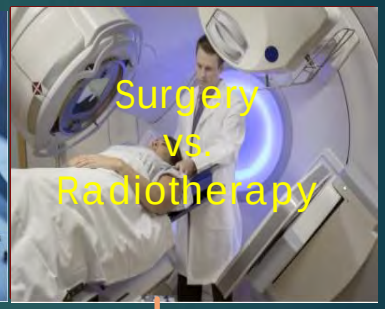
IELCART Research Topics

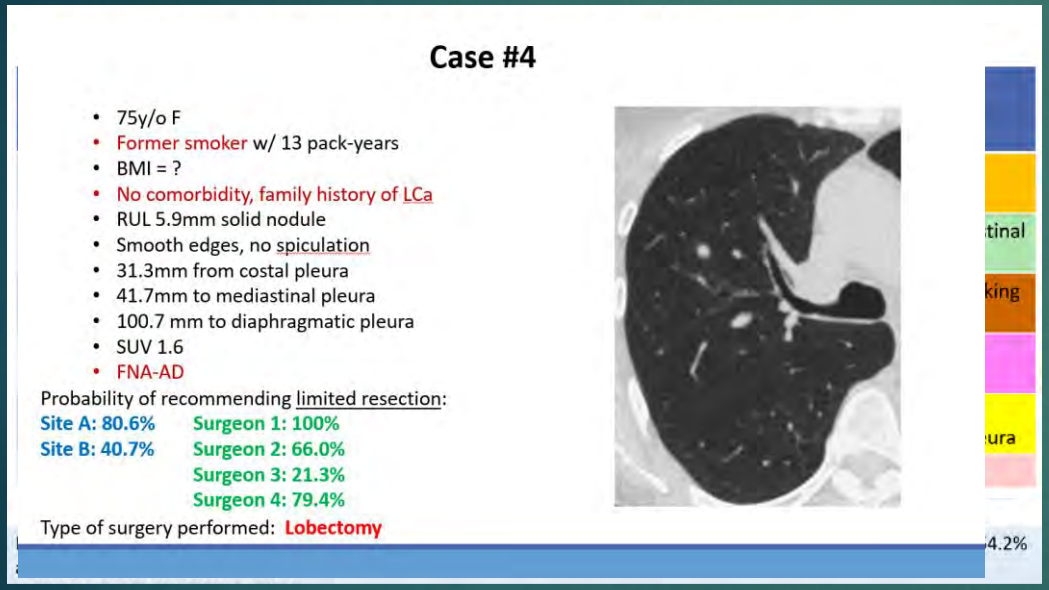
Projects

Clinical staging criteria	Surgical decision making	Comparison of treatment approaches
		 
Risk factors for recurrence	Never smokers	Quality of life Complications Long Term Survival
		

Flores et al. J Thorac Oncol. 2018; 13:946-57

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

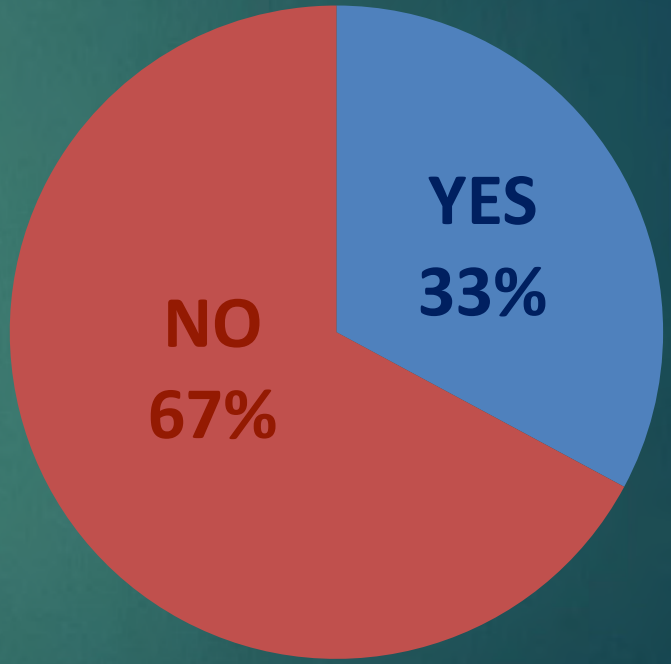
Patient Survey

Pre-treatment:
- Background form
- Pre-treatment patient form
- Quality of life questionnaire

Post-treatment:
- Post-treatment patient form
- Quality of life questionnaire

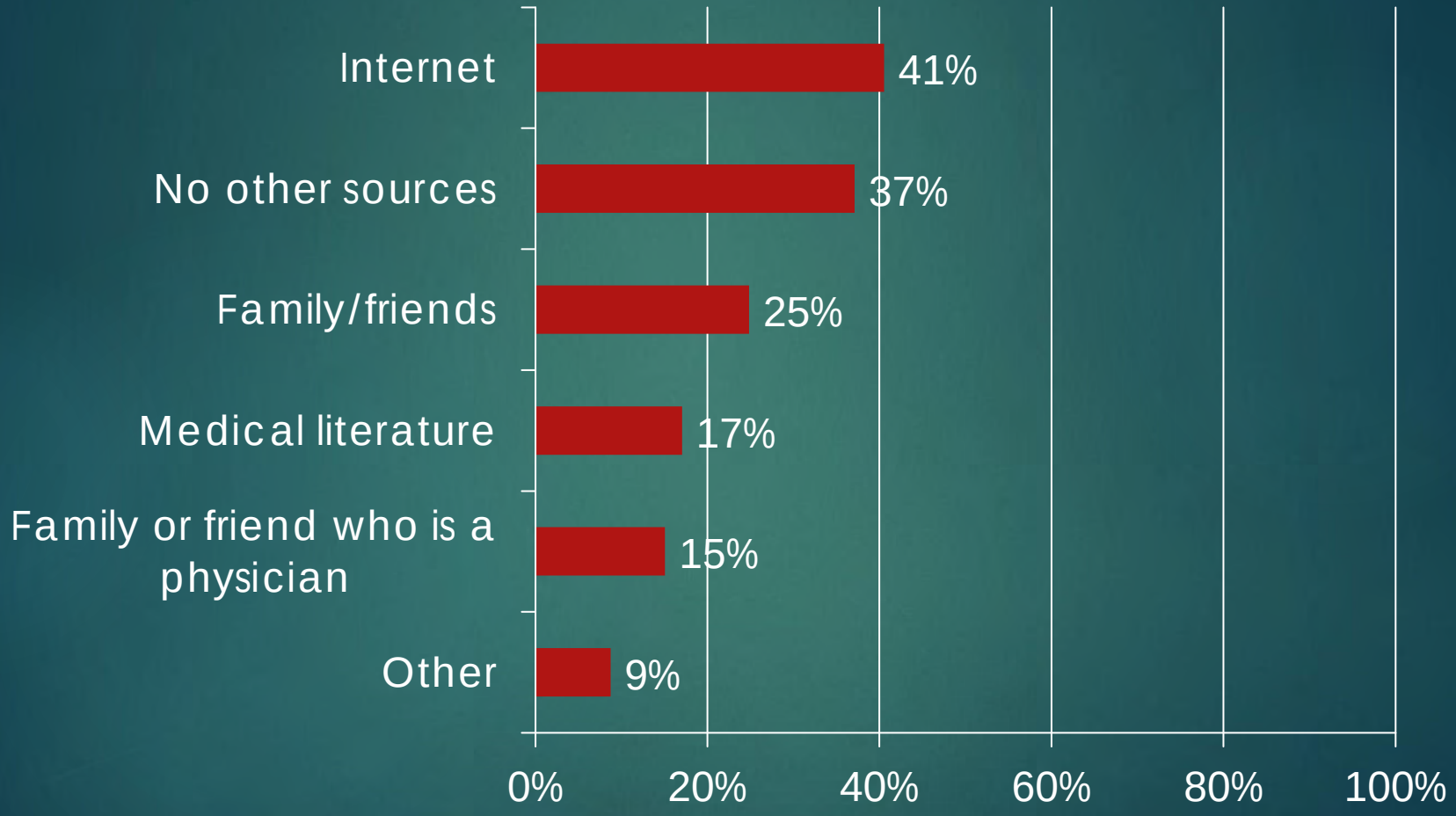
Each Follow-up:
- Follow-up form
- Quality of life questionnaire

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



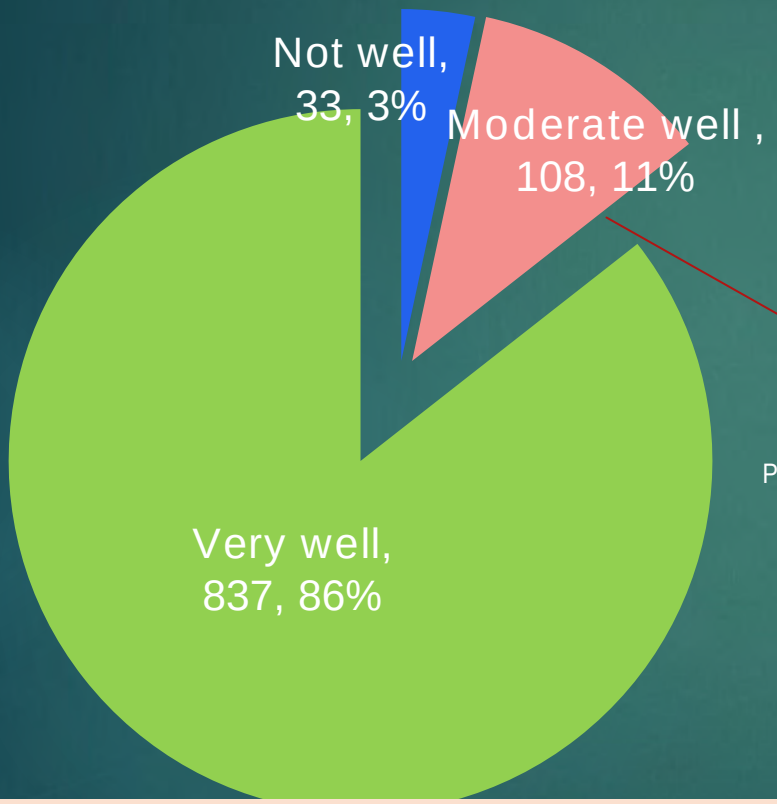
Patient Pre-Treatment Questionnaire

4. Did you get information about lung cancer treatment from any of the following other sources?

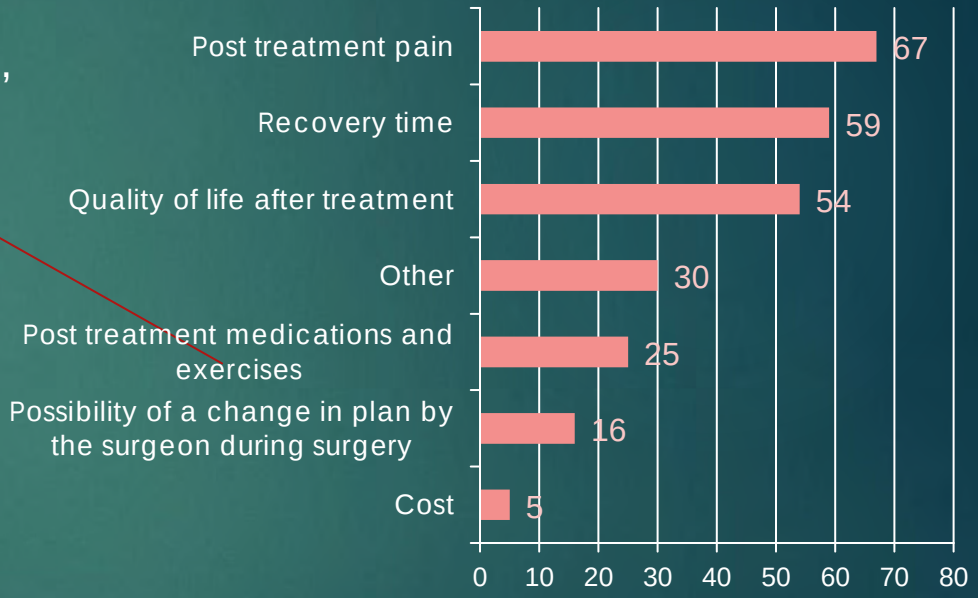


Patient Post-Treatment Questionnaire

Q1. Did the pre-treatment discussion prepare you for how you would feel after treatment?



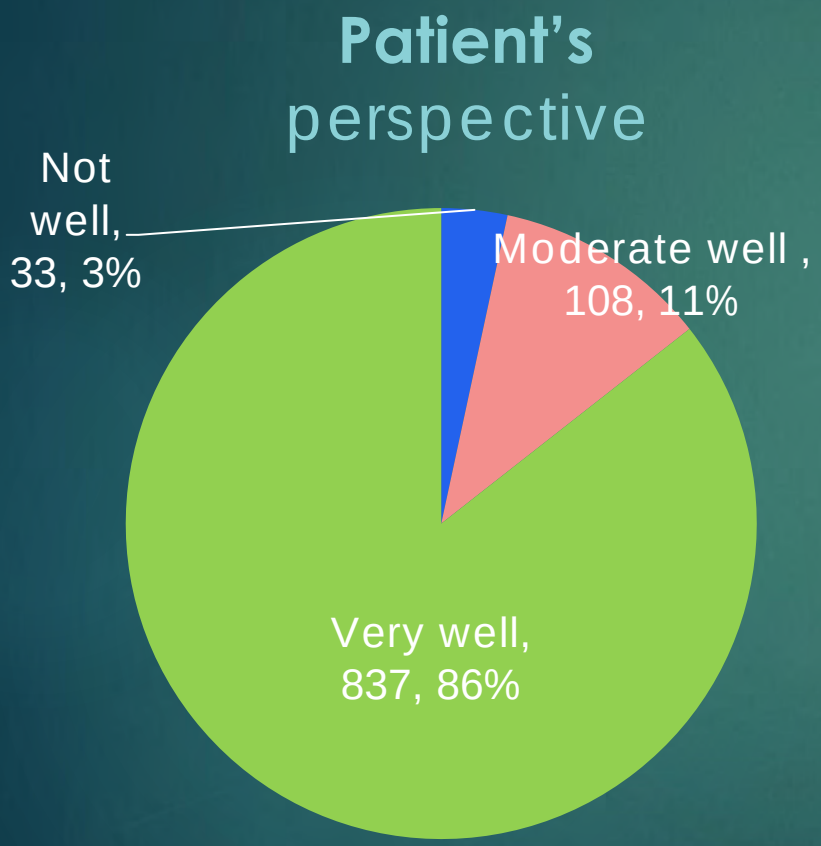
If 'not well' or 'moderately well', what area should have been discussed more fully?

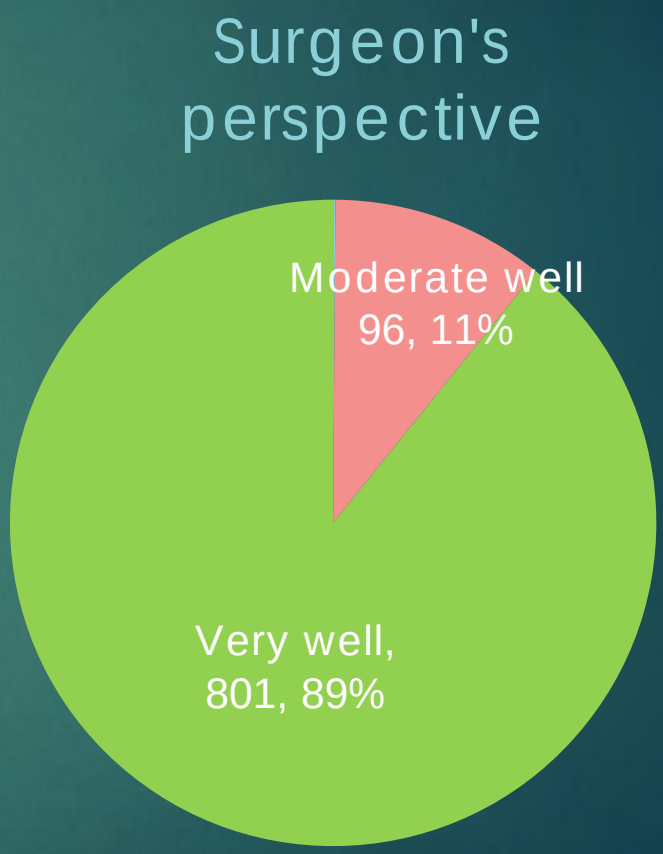


In summary: Surgeons prepared patients very well, with only 121(14%) exceptions.

Patient and Surgeon Perspectives

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





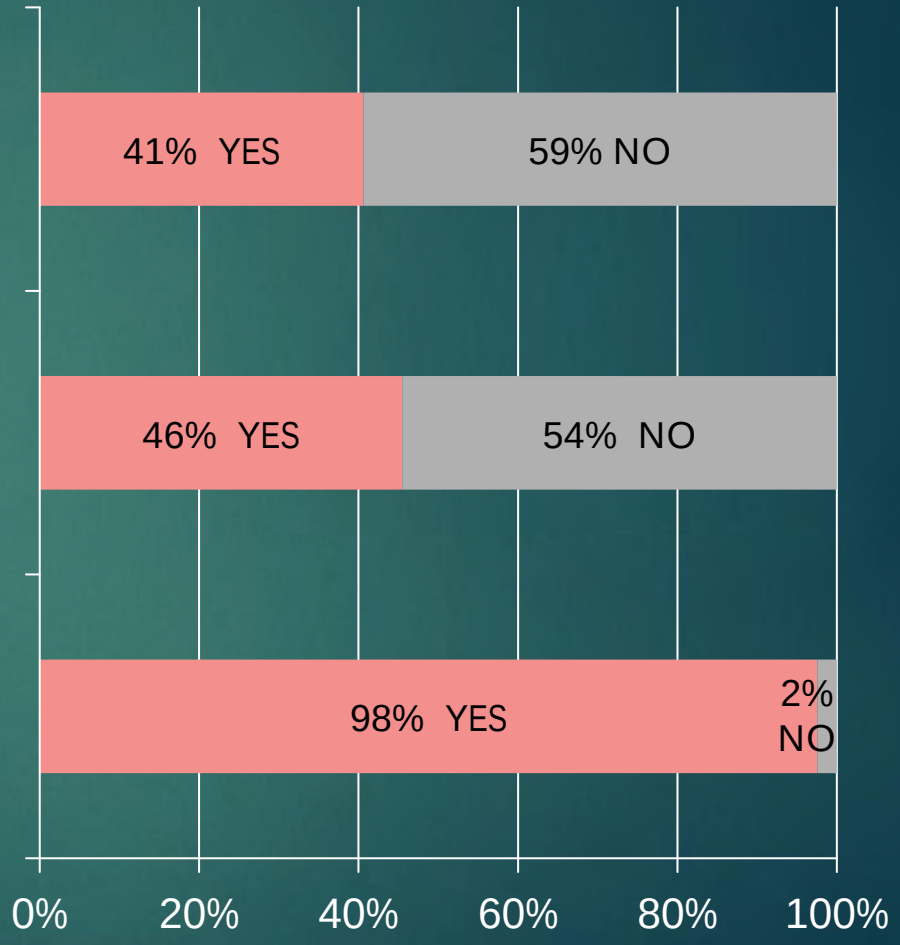
Patient Post-Treatment Questionnaire

Post-surgical support group or social worker recommendations?

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 pos-treatment questions?

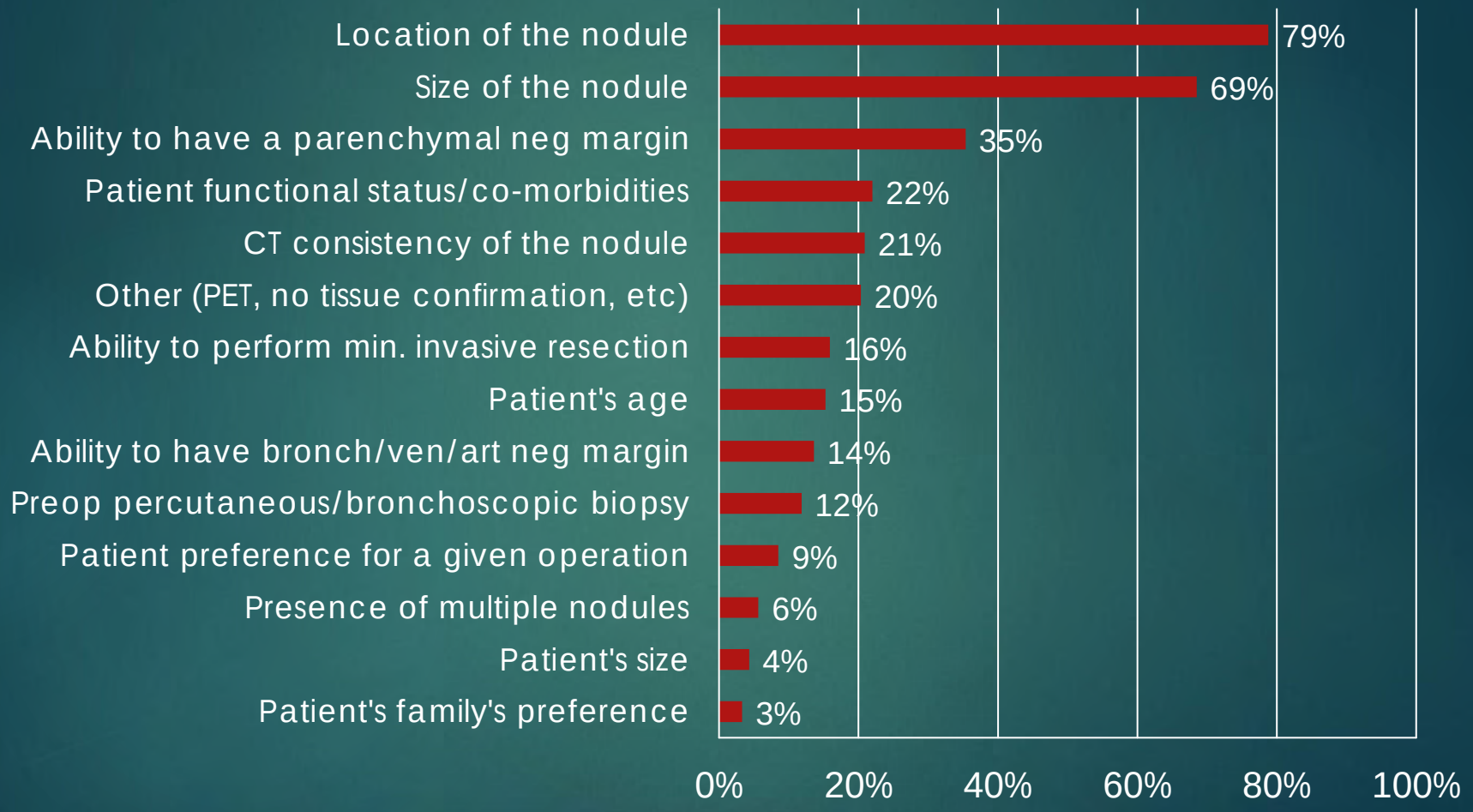


Physician Survey

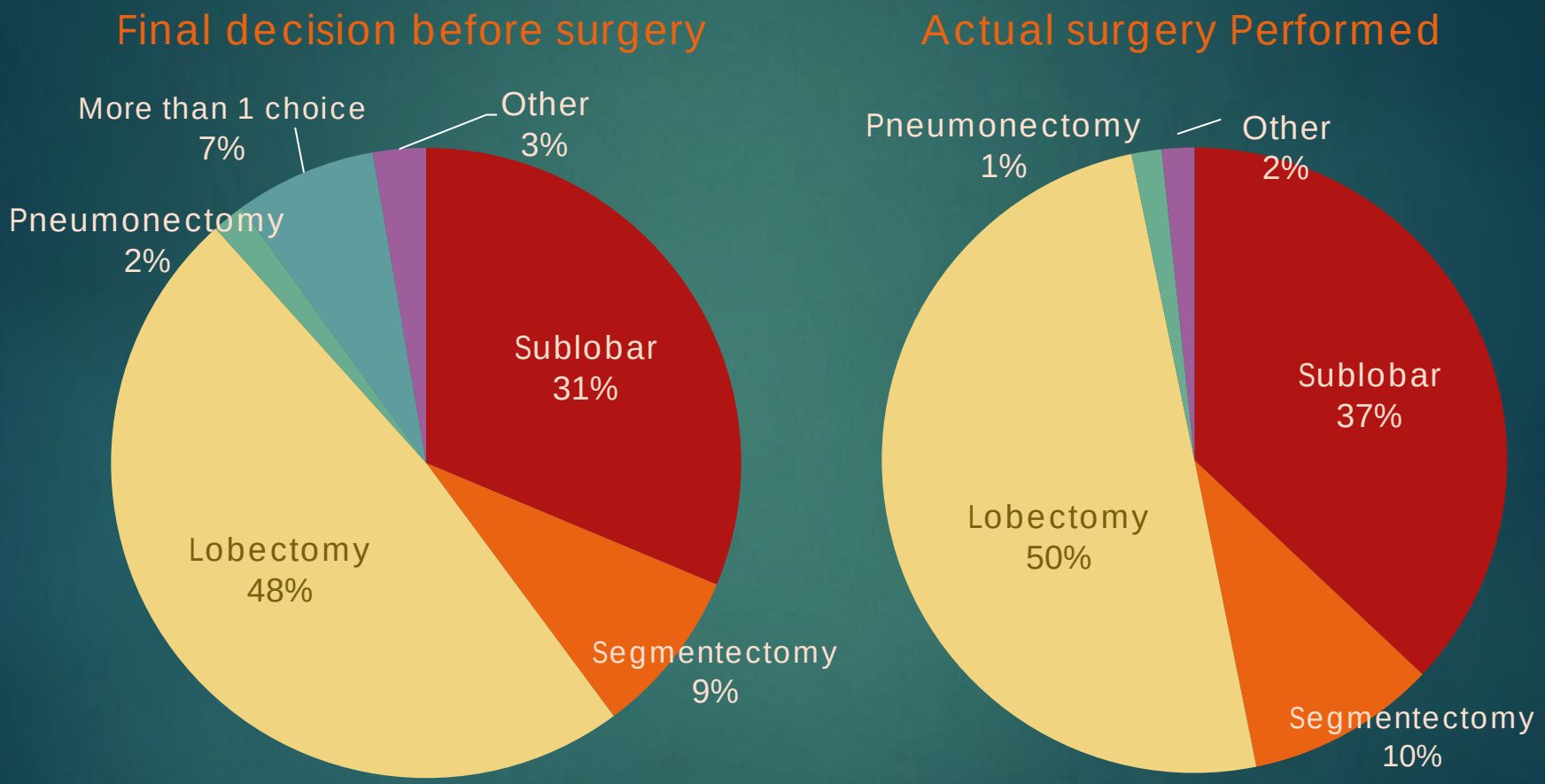
- Before treatment
- After treatment

Surgeon Pre-Surgery Questionnaire

Q3. Which of the following were the most important factors in recommending that particular surgery to this particular patient



Comparison of initial choices and final surgical procedure performed



Quality of Life

Sparse literature on early stage lung cancer

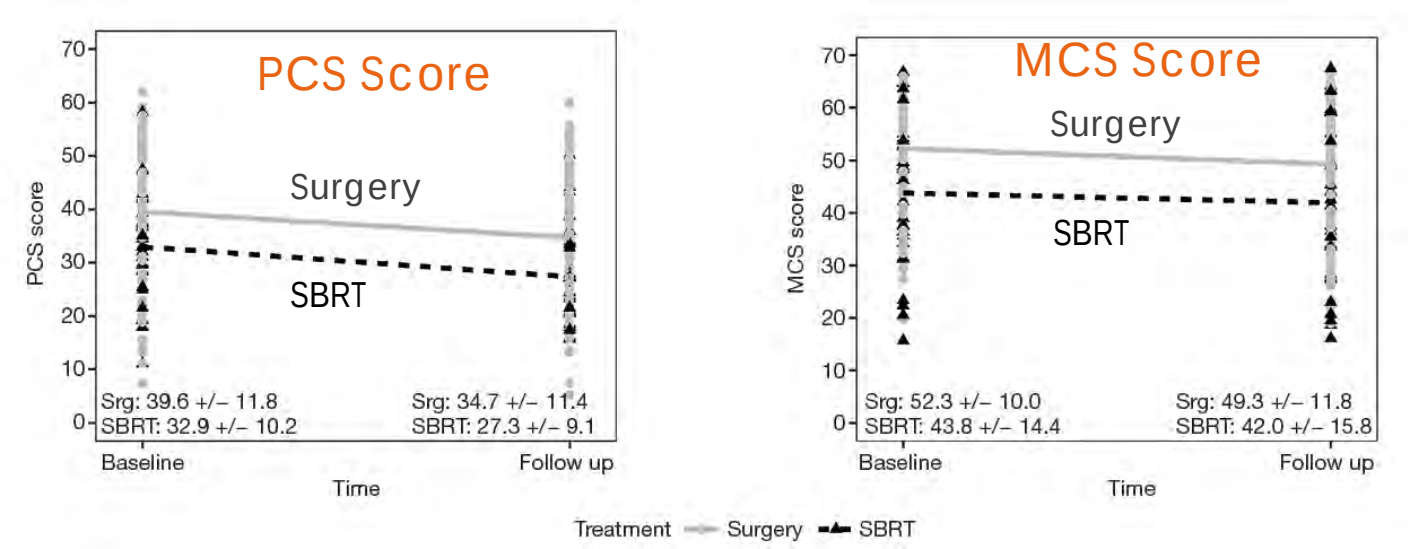
QoL questionnaire

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

Schwartz et al. J Surg Oncol 2017; 115: 173-80
Yip et al. Cancer Invest. 2018; 36: 122-6

Quality of Life: Surgery vs. SBRT

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



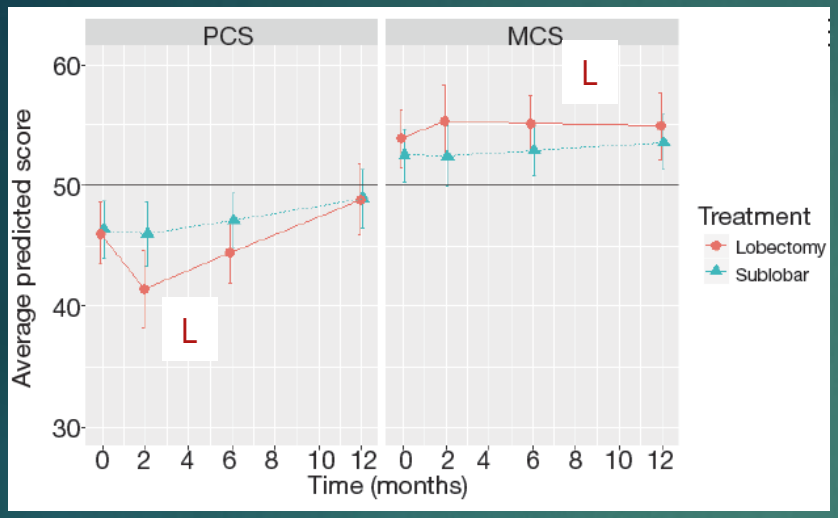
- Significant decline in PCS score from baseline to follow-up in both surgery (ΔPCS=-4.81, p<0.0001) and radiotherapy (ΔPCS=-5.6, p=0.014) patients
- MCS score declined from baseline to follow-up after treatment with surgery only (ΔMCS=-2.96, p=0.0003) or radiotherapy only (ΔMCS=-1.86, p=0.29)
- Surgical 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

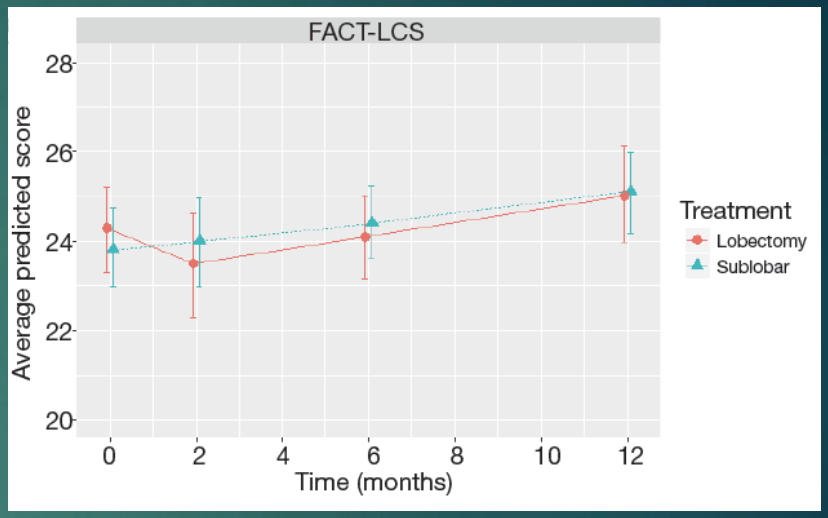
*Adjusted for age at diagnosis, gender, race, education, smoking status, completion of survey by proxy, and presence of relevant comorbidities.

Schwartz et al. J Thorac Dis 2019; 11:154-161

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).

Schwartz et al. Future Oncol 2018; 14: 151-63
Fevrier et al. J Thorac Dis 2020; 12: 3488-99

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

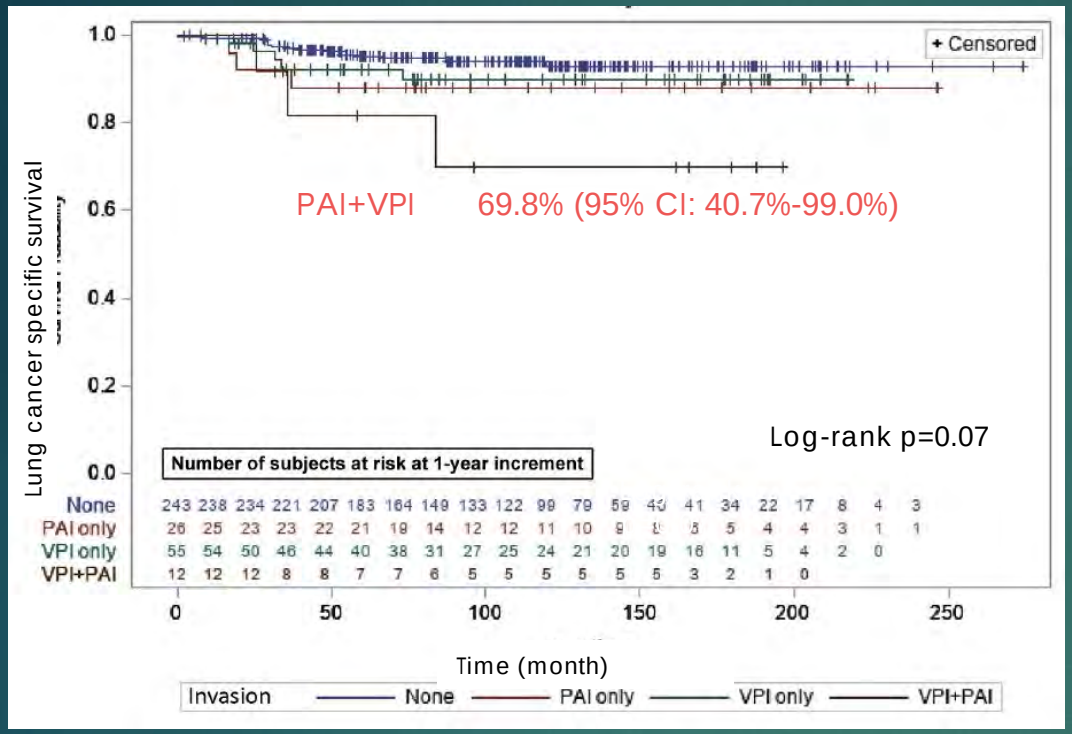
- Pilot the 8-week SMART intervention among 20 Mount Sinai Health System patients to determine feasibility, satisfaction, and acceptability for use with RCT of early-stage lung cancer post-surgical patients

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
Wang et al. Clin Imaging 2020; 68:61-7

Kaplan-Meier Survival for pN0M0 NSCLC ≤ 30mm Solid Cancers (n=336): Angiolymphatic (PAI) and pleural (PVI) invasion

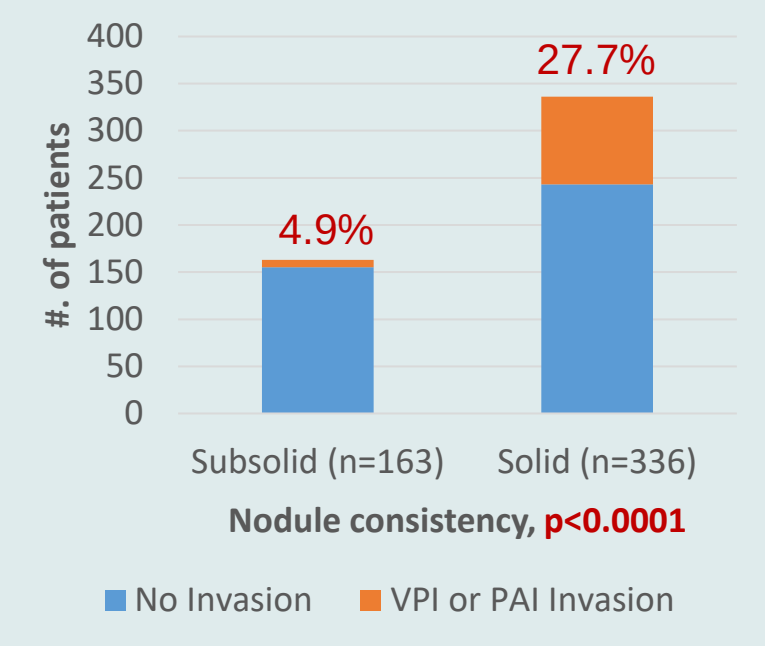


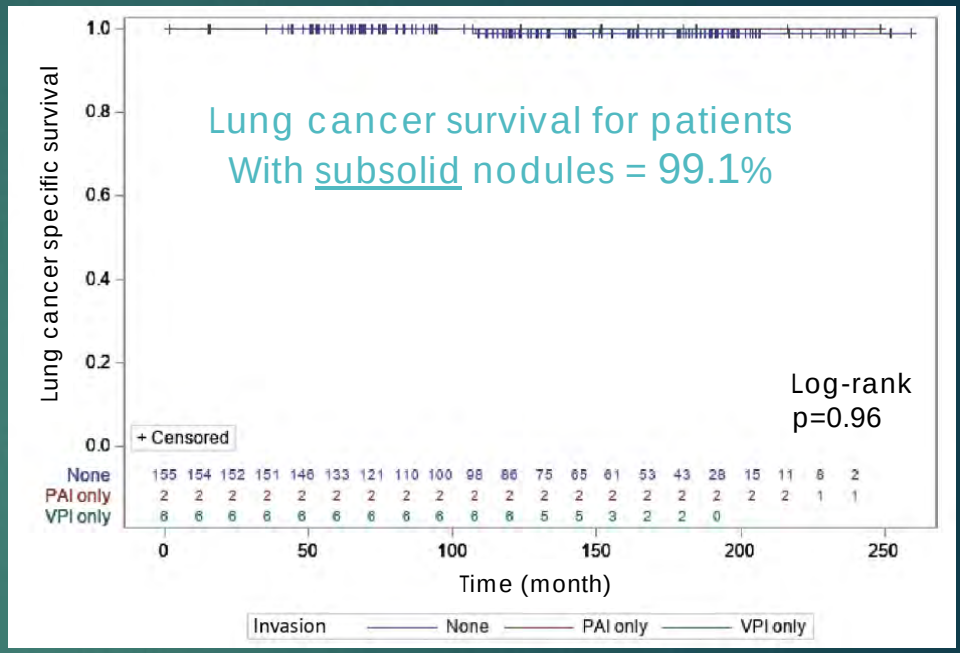
None	93.0% (95% CI: 87.9%-94.6%)
VPI alone	89.8% (95% CI: 81.3%-98.3%)
PAI alone	88.0% (95% CI: 75.3%-100.0%)

- 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)

Yip et al. J Thorac Oncol 2019; 14: 890-902

Kaplan-Meier Survival for pN0M0 NSCLC ≤ 30mm Subsolid Cancers (n=163): Angiolymphatic (PAI) and pleural (PVI) Inv.





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

Yip et al. J Thorac Oncol 2019; 14: 890-902

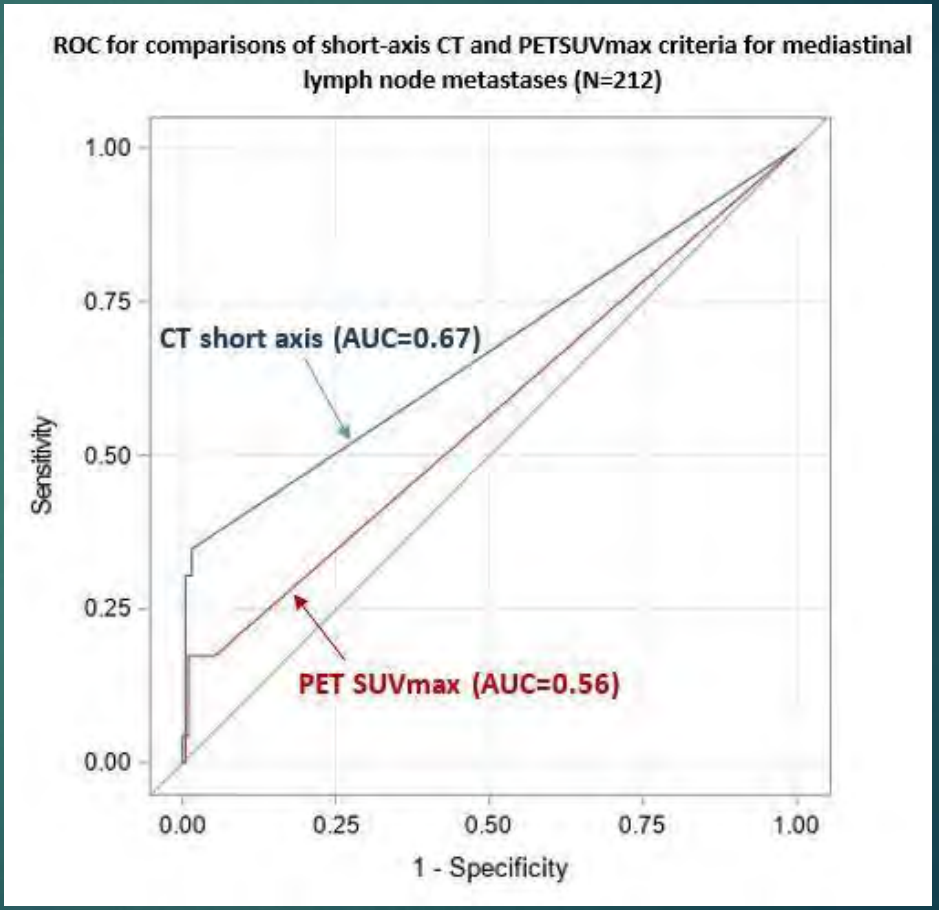
Kaplan-Meier Survival for **pN0M0 NSCLC ≤ 30mm:**

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

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

For the 212 patients with solid cancers,



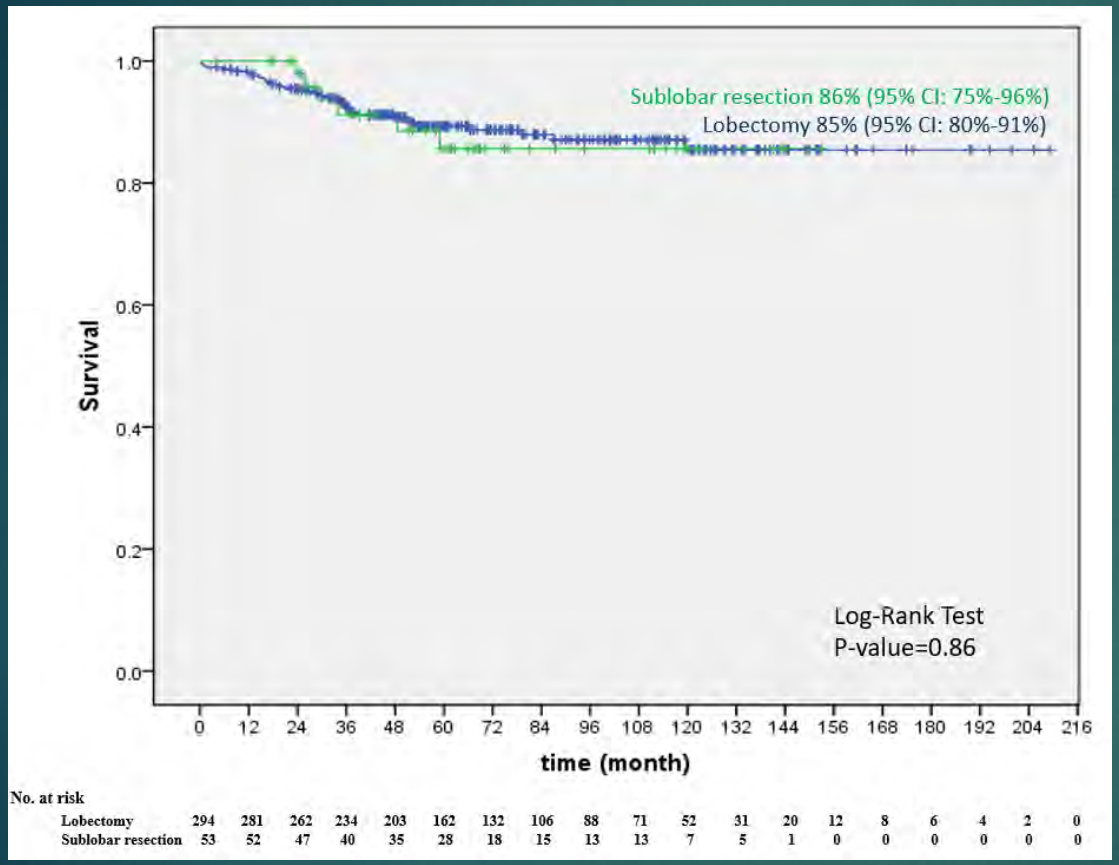
Wang et al. Clin Imaging 2020; 68: 61-7

Treatment Assessments

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

Lobar vs. sublobar surgical treatment

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



Both 10-year K-M survival analysis

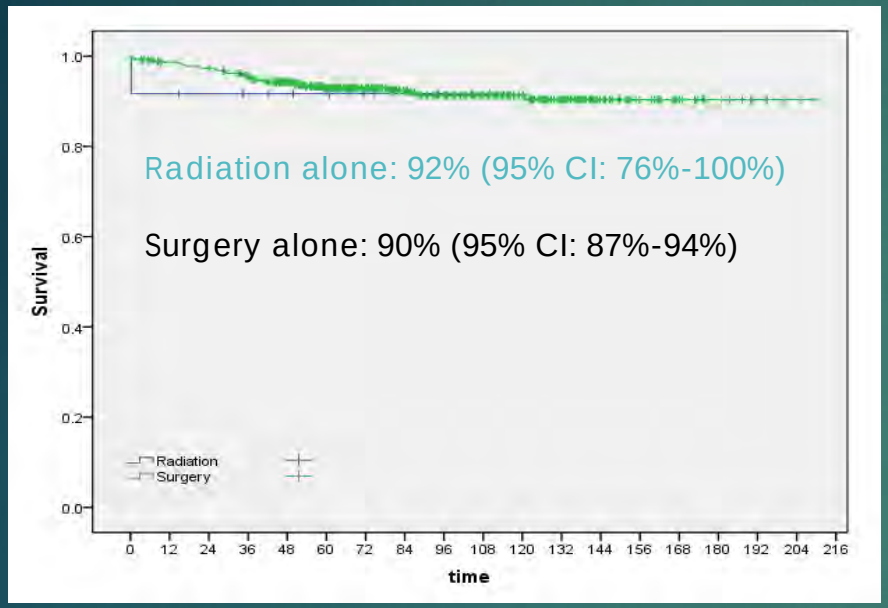
and

Cox proportional hazard regression

found no significant difference in lung cancer-specific survival

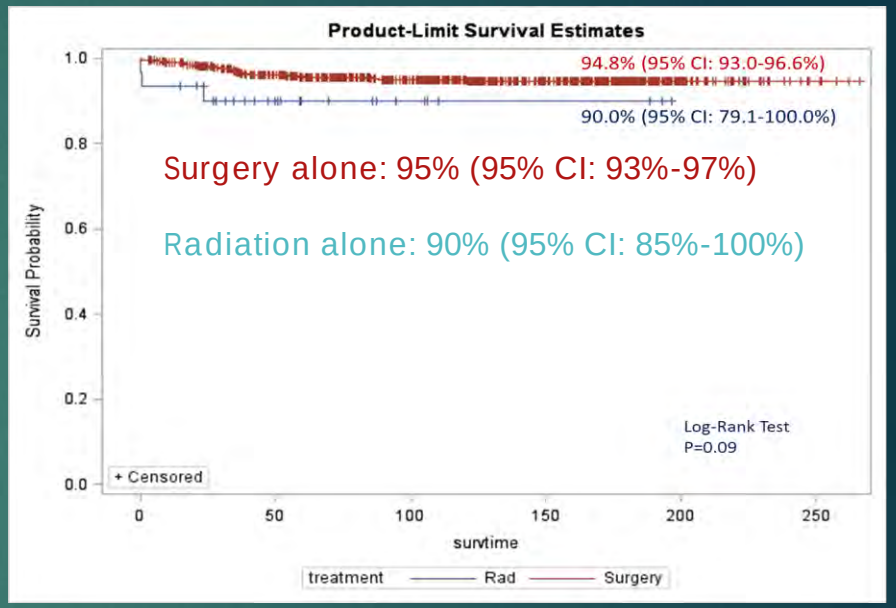
Altorki et al. J Thorac Cardiovasc Surg 2014; 147: 754-62
Flores et al. J Thorac Cardiovasc Surg 2014; 147: 1619-26
Buckstein M et al. J Rad. Oncol 2014: 3: 153-7

Survival After Treatment for NSCLCs <= 30 mm
Surgery vs. Radiotherapy



Radiation alone: 92% (95% CI: 76%-100%)

Surgery alone: 90% (95% CI: 87%-94%)



Surgery alone: 95% (95% CI: 93%-97%)

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

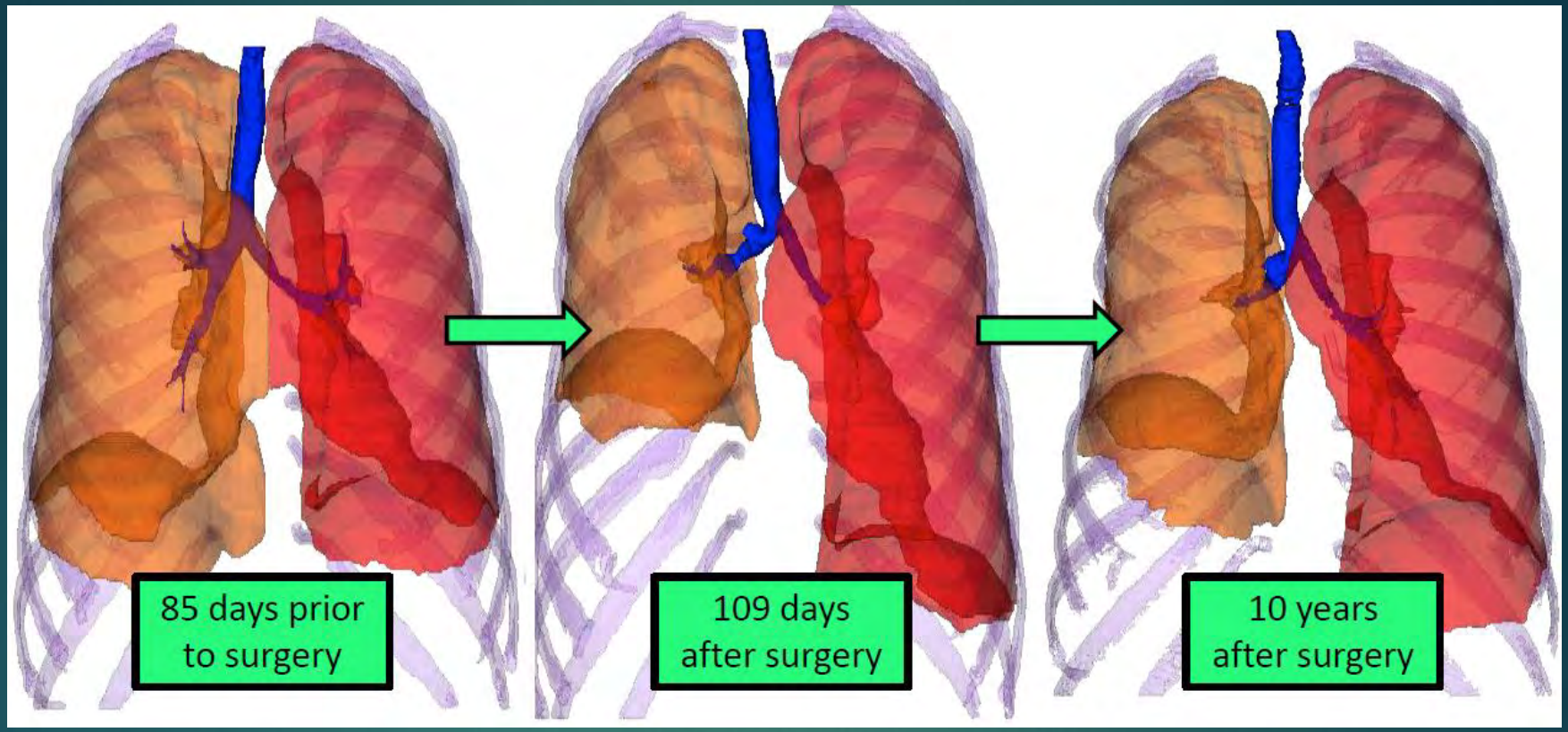
Buckstein et al. 2014

Berlin et al. 2019

n = 10	Radiation Rx alone	n = 24
n = 376	Surgery alone	n = 702

Buckstein M et al. J Rad. Oncol 2014: 3: 153-7
Berlin et al. Int J Radiat Oncol Biol Phy 2019; 104:122-6

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 hernias (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)

C-G-I Models

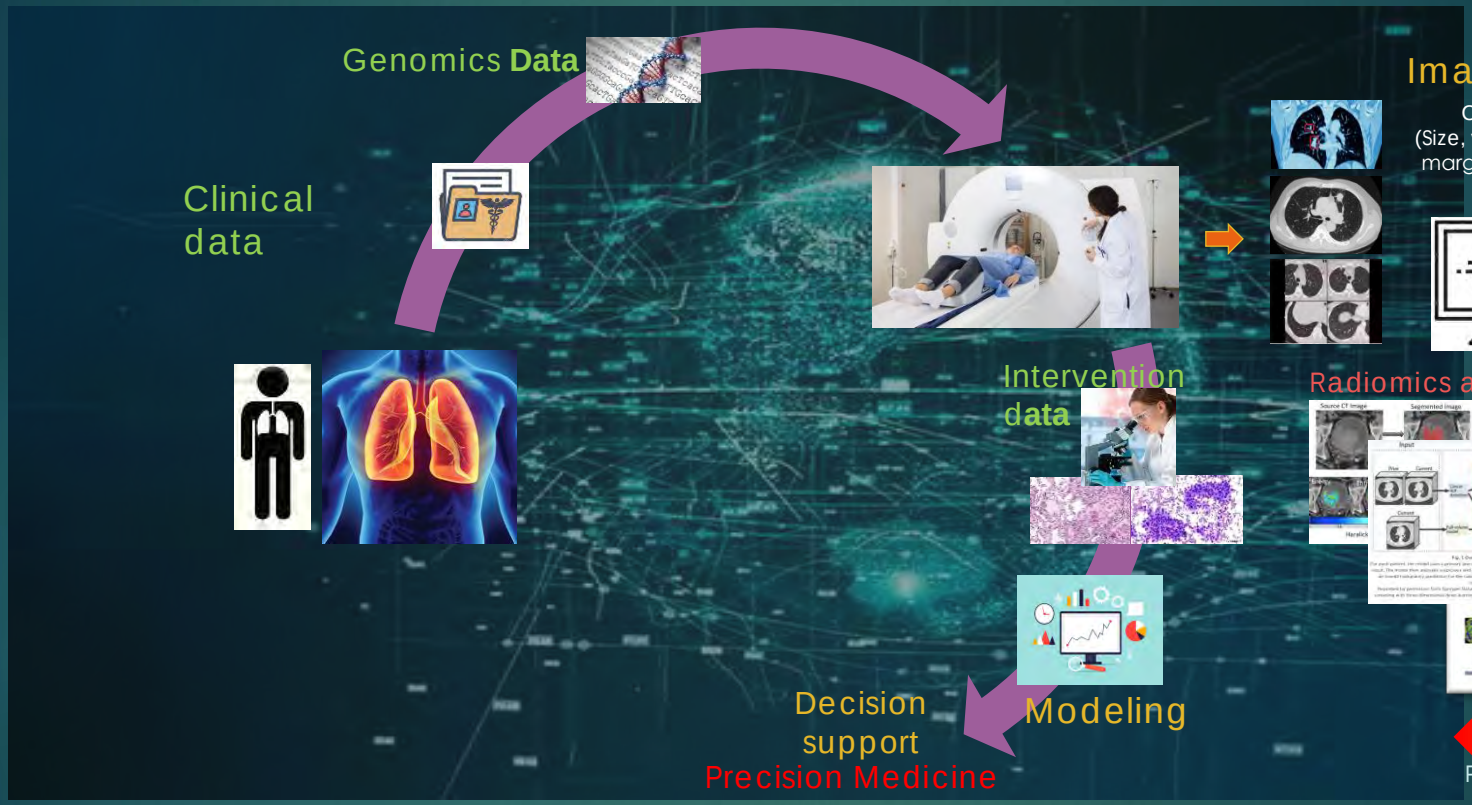
Clinical Factors
Demographics,
Smoking History,
Comorbidities,
Exposures
(SHTS, environmental, occupational)

Genetics /
Pathology

Imaging

PERSONALIZED
LUNG CANCER
RISK PREDICTION
RECURRENCE
SURVIVAL

AI for Lung Cancer: detection, diagnosis and prognostication

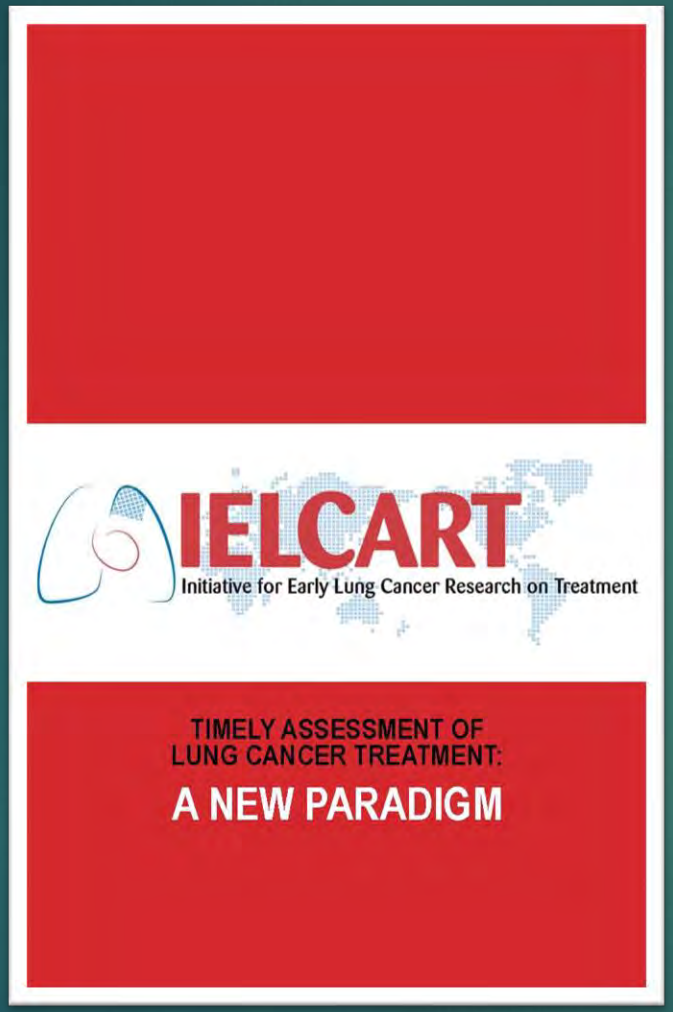


Henschke CI et al. 1996-7: Neural Networks for Radiology; 2019-2020: Jirapatnakul A et al. & Fuhrman et al.

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

Second monograph: 2017-2020



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TBD:
An important historical summary

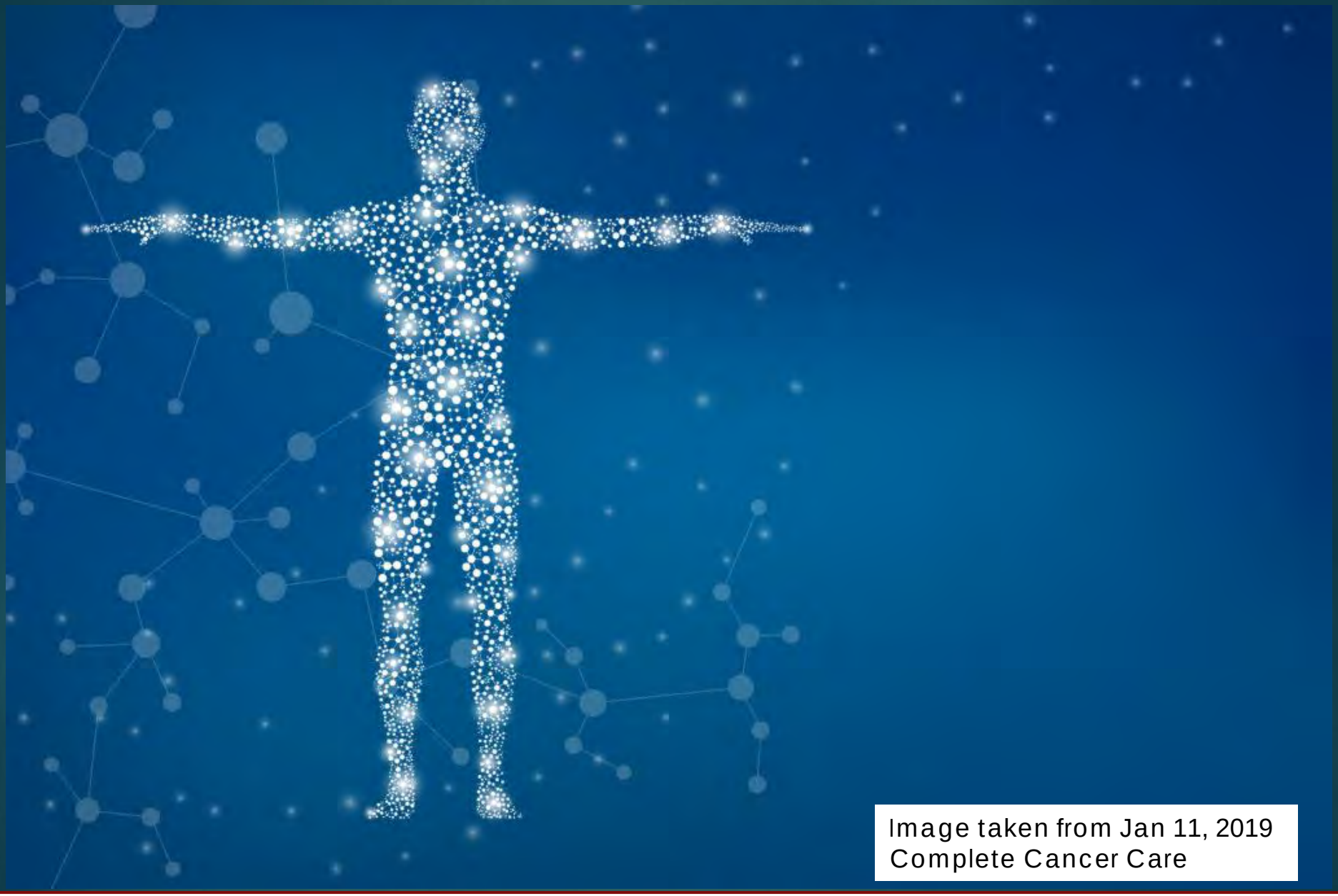

Image taken from Jan 11, 2019
Complete Cancer Care