

Early Detection of Lung Cancer
and
management of the high risk patient

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Faculty Disclosure

Dr. Loewen has indicated that he does not have
any relevant financial relationships or
affiliations that may have a direct bearing on
the subject matter of this CME activity

- Lung Cancer Overview and
Risk assessment
 - Detection strategies
 - New therapies

Overview
and risk assessment

Trends in Lung Cancer Incidence

- World wide incidence is 3,000,000 and rising
- Most common cancer in the world
- Leading cause of cancer death in men and in women with 28% total cancer mortality in the US, and 17% worldwide.

Lung Cancer trends: 2009 statistics

- About 219,440 new cases of lung cancer will be diagnosed (116,090 among men and 103,350 among women).
- There will be an estimated 159,390 deaths from lung cancer (88,900 among men and 70,490 among women), accounting for about 28% of all cancer deaths.

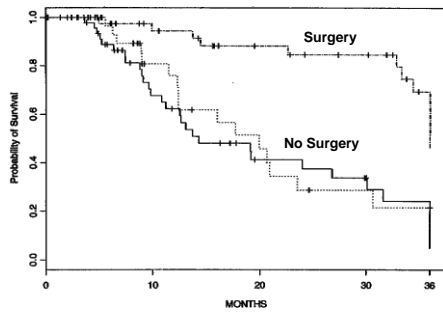
American Cancer Society 2009

Natural history of Early Lung Cancer

- Of 128 patients diagnosed with early stage lung cancer
- 49 patients received no cancer treatment, 36 patients received radiation therapy only, and 43 patients were treated with primary surgery.
- Median \pm SD survival time following surgery was 46.2 \pm 3.15 months; Median survival for no treatment was 14.2 \pm 2.37 months ($p = 3.2 \times 10^{-6}$);
- Median survival for radiotherapy alone was 19.9 \pm 5.6 months ($p = 0.0005$).
- Cause of death was cancer in 53% of untreated patients and 43% for those receiving radiotherapy.

McGarry RC Chest 2002

Survival from time of diagnosis for patients with stage I or II NSCLC by treatment modality



©2002 by American College of Chest Physicians

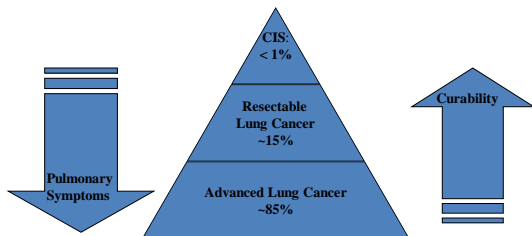


Tumor Doubling time and Survival

- Retrospective study of 149 stage I lung cancer with >2 CT scans
- 32% of invasive lung cancer cases showed no growth at > 1 year
- Survival is worse in fast growing tumors ($p=0.002$) and also worse for non-adenocarcinoma ($p < 0.05$)
- Elderly patients more likely to have slow-growing tumors ($p = 0.047$)

Jennings SG Radiology 2006

Lung Cancer: the rationale for early detection



Lung Cancer risk factors	Relative Risk	Population Frequency
Active Cigarette Smoking (>20PY)	10.0	30%
Passive Cigarette Smoking (>40-80PY)	1.2	90%
Asbestos Exposure	15.1	?
COPD (FEV1<70%)	7.0	3-13%
Diet (Fruits and Vegetables >5 servings/day)	0.5	33%
Selenium (>0.63 µg/g)	0.5	20%
Family History (Parent/Child/Sib)	2.4	4-10%

Risk Assessment for lung cancer risk

- Cancer: Prior Malignancy
- Asbestos: Occupational
- Smoking > 20 pack/year
- Emphysema: COPD
- Also, consider *family history*, *age > 50*, other exposures
- Radiation in cancer survivors

Theoretical drawbacks of CT screening

- Radiation carcinogenesis
- screening & consequent diagnostic tests: CT, PET
 - Additional minimally invasive procedures
 - Percutaneous Lung FNA
 - Bronchoscopy
 - VATS Thoracotomy for benign disease
- Potential post-operative morbidity & mortality

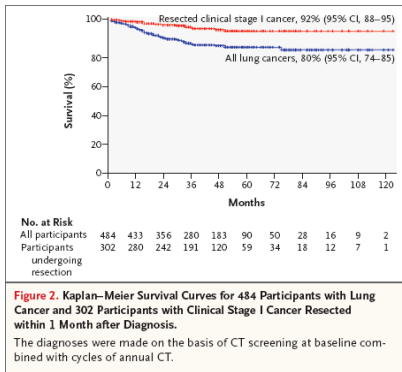
Risk of Cancer from X-ray and CT

- CXR @ 0.033 mSv = INCREMENTAL RISK OF 0.00017% (1/600,000)
- CT @ 2.2 mSv = INCREMENTAL RISK OF 0.011% (1/9,000; 67/600,000)
- ASSUMING AN INCREMENTAL CANCER MORTALITY RISK OF 5% / Sv, AND A LINEAR, NO THRESHOLD, DOSE RELATIONSHIP, YIELDS
 - CXR @ 0.033 mSv = INCREMENTAL RISK OF 0.00017% (1/600,000)
 - CT @ 2.2 mSv = INCREMENTAL RISK OF 0.011% (1/9,000; 67/600,000)
 - *Might find early lung cancer in 117/9000*

Is there an acceptable percentage?

I-ELCAP Henschke NEJM 2006

- 31,567 asymptomatic persons at risk for lung cancer using low-dose CT from 1993 through 2005
- Screening resulted in a diagnosis of lung cancer in 484 participants. Of these participants, 412 (85%) had clinical stage I lung cancer, and the *estimated* 10-year survival rate was 88% in this subgroup.
- The 8 participants with clinical stage I cancer who did not receive treatment died within 5 years after diagnosis



I-ELCAP Investigators. NEJM 2006; 355:1763-1771.

Criticisms of I-ELCAP data

- Estimated 10 year survival data
- Median FU of 3.3 years
- No lung cancer-specific mortality data
- ? Overdiagnosis bias
- Benign pulmonary nodules

CT screening and Lung Cancer

Bach JAMA 2007

- 3246 asymptomatic current or former smokers screened for lung cancer beginning in 1998 in 3 academic medical centers in the United States and Italy with follow-up for a median of 3.9 years.
- 144 individuals diagnosed with lung cancer compared with 44.5 expected cases.

CT screening and projected mortality Bach JAMA 2007

- There were 109 individuals who had a lung resection compared with 10.9 expected cases.
- But there was no evidence of a decline in the number of diagnoses of advanced lung cancers (42 individuals compared with 33.4 expected cases) or deaths from lung cancer (38 deaths due to lung cancer observed and 38.8 expected).

Ongoing screening trials: the jury is still out

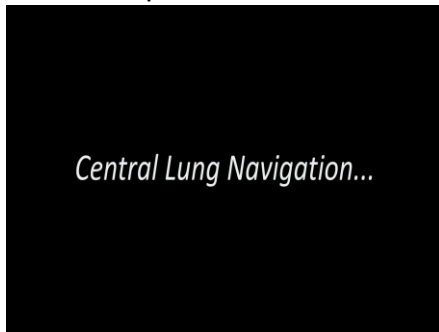
- **NLST**: 50,000 smokers in a a 200 million\$ federally-funded randomized lung cancer screening trial; randomized to CT versus chest X-ray yearly for 3 years, and are followed for 10 years. Endpoint is mortality; closes in 2009.
- **DANTE**: 2400 patients LDCT vs no screening; closes 2010
- **NELSON**: 16,000 former or current smokers randomized to CT vs no screening; closes 2015

Managing the high risk patient with a Solitary Pulmonary Nodule

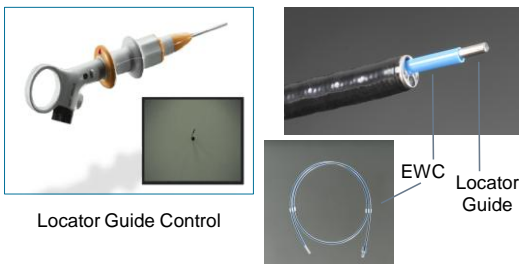
NLST protocol for Pulmonary Nodules

- Nodules >10mm:
 - PET CT or
 - enhanced CT or
 - Low dose follow up CT in 3 months:
- If nodule enhances >15 HU or if is FDG avid (SUV >2.5) or if nodule enlarges, then TTNB, bronchoscopy, or VATS biopsy
- Nodules 4-9mm: repeat CT in 4-6 months

SuperDimension

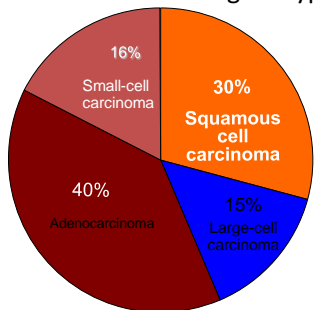


Navigational Bronchoscopy



Diagnosis of selected pulmonary nodules
Real-time CT images for guidance during biopsy

LUNG CANCER: histological types



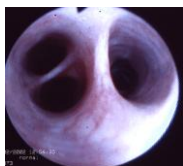
Numbers do not sum to 100% because of differences in diagnostic criteria.

Ginsberg RJ, et al. *Cancer: Principles and Practices of Oncology*. 5th ed. 1997:858-911

Central versus Peripheral lung cancer



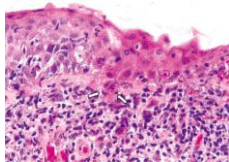
- Screen-detected lung cancers are usually small peripheral adenocarcinomas.
 - Early central lung cancers (squamous cell) detected with bronchoscopy may not be seen on spiral CT.
 - Upper endoscopy and colonoscopy are routinely used for primary screening.
- Sensitivity of sputum cytology is disappointing



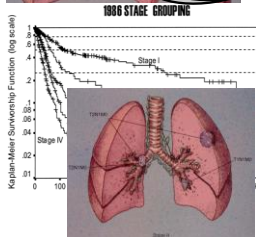
Central Lung Cancer in perspective

- Squamous cell is the 2nd most common form of lung cancer in North America and Japan; most common form of lung cancer in Europe
- If 172,000 new cases of lung cancer are identified; then ~43,000 cases of squamous cell lung cancer will be diagnosed.

What is early Central lung cancer?



- T0 (or *tis*) = **Carcinoma-in-situ**
- Microinvasive squamous cell lung cancer is: **T1**
- Radiographically Occult lung cancer is (usually): **T1**
- Of 1561 lung cancer cases seen at RPCI since 1998, 25% were squamous cell carcinoma, 0.4% were carcinoma in situ and 0.4% were microinvasive carcinoma

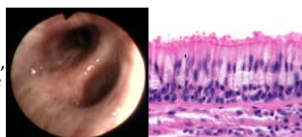


Buccheri Chest 2000

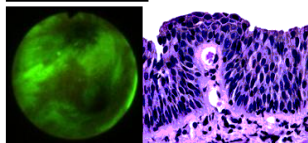
Stage	TNM System		
I M0	T1	N0	
IB M0	T2	N0	
IIA M0	T1	N1	
IIB M0	T2	N1	
M0	T3	N0	
IIIA M0	T3	N1	
M0	T1-3	N2	
IIIB M0	T4	N0-2	
M0	T1-4	N3	
IV M1	T1-4	N1-3	

Autofluorescence bronchoscopy and preinvasive bronchial epithelial lesions

Normal epithelium: ciliated columnar cells, basal cells, and basement membrane



CIS/Squamous dysplasia: columnar size and shape altered; epithelial architecture regresses, Mitotic figures, pleomorphism



Early stage lung cancer

- A 63 year old white male with COPD and a history of stage 1 nslc status post RUL wedge resection with 2 years NED presented with a change in his cough habit.
- Physical examination was negative, and chest radiograph was unchanged from previous studies.

“white light” image

“blue light” image

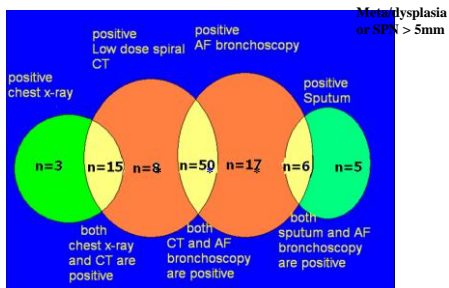


Bimodality Surveillance in high-risk patients

Loewen Thorax 2006

- 169 symptomatic high-risk patients with >2 risk factors for lung cancer underwent AF bronchoscopy and LD spiral CT of the chest.
- 7% (13) prevalence cancers were identified; 25% (3) were squamous cell.
- 3 lung cancers were identified only with AF bronchoscopy, and 9 lung cancers were identified with LDST.
- AF bronchoscopy identified premalignant changes in 66% of patients.

Bimodality Screening:
Surrogate Endpoint Comparison



Pan-Canadian Trial:

Early Detection of Lung Cancer

- Estimated Enrollment: 2500
- Study Start Date: September 2008
- Estimated Primary Completion Date: March 2013
- Modalities: spiral CT scan at baseline and then at 1 and 2 years; autofluorescence bronchoscopy

What should we do for high risk patients?

- "Lung cancer screening is not recommended"
---2003 ACCP statement
- "In high-risk patients, physicians may decide to have these screening tests done on an individual basis"
--- 2003 ACS statement



Two kinds of Early Detection strategies

Surveillance:

Close observation of a person or group, especially one under suspicion

Screening:

The examination of a group of usually asymptomatic individuals to detect those with a high probability of having or developing a given disease

Stedman's Medical Dictionary 2002

Screening vs Case-finding discussion with the at-risk patient

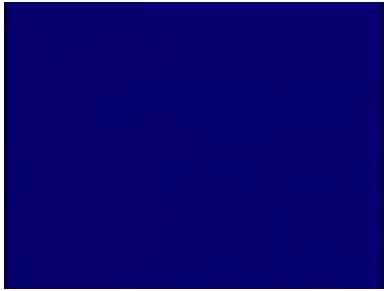
- Risks of CT include expense, stress, radiation exposure and false positive pulmonary nodules.
- Benefits include the detection of earlier disease and higher survival rates.
- What is the patient's risk? (CASE)

canine scent detection

- A food reward-based method of training: 5 ordinary household dogs were trained to distinguish, by scent alone, exhaled breath samples of 55 lung and 31 breast cancer patients from those of 83 healthy controls.
- The dogs' ability to distinguish cancer patients from controls was then tested using breath samples from subjects not previously encountered by the dogs
- Overall sensitivity of canine scent detection compared to biopsy-confirmed conventional diagnosis was 0.99 (95% confidence interval [CI], 0.99, 1.00) and overall specificity 0.99 (95% CI, 0.96, 1.00).

MuCulloch M 2006

PDT for early lung cancer
Carcinoma in Situ, Left Upper Lobe



What about patients with early
peripheral lung cancers?

Advantages of VATS

- Shorter hospital stay
- Shorter chest tube duration
 - 1-2 days
- Earlier return to full activities
- Less pain
- Faster recovery for high risk and frail patients
- Epidural less duration or no epidural
- Less use of analgesics
- Less sleep disturbances
- Lower incidence of post thoracotomy pain syndrome
- Most patients off all pain meds by POD # 7

ACSOG Trial: RF ablation

- **ACOSOG Z4033, L**, A phase II study of radiofrequency **ablation** (RFA) in high-risk patients with non-small cell **lung cancer**, 3 cm or smaller
- **PROJECTED ACCRUAL**: A total of 55 patients will be accrued for this study; projected closure in August 2010.
- A radiofrequency electrode is placed by CT guidance into the target tumor. Patients undergo radiofrequency ablation (RFA) directly to the tumor for up to 12 minutes to obtain an intratumoral temperature > 60°C. Patients may receive 3 RFA treatments (a total of 36 minutes) to obtain the target temperature. Patients undergo fludeoxyglucose F18 positron emission tomography within 24-96 hours after the final treatment.
- After completion of study treatment, patients are followed every 3 months for 1 year and then every 6 months for 1 year.

Stereotactic Body Radiotherapy (SBRT) (‘Cyberknife’)



- Multiple beams of radiation are delivered to the tumor through a robotic platform
- Gold fiducial markers are placed at the tumor borders.

SBRT: IGRT, and Hypofractionation



- Image-guided Radiotherapy; may be gated to respiration
- SBRT
Hypofractionation:
50Gy in 5 fractions;
60Gy in 3 fractions – provides higher biological doses
- Not useful with nodal disease

SBRT for lung cancer

Grills IS J Clin Oncol 2010

- In a non-randomized trial, 124 patients with T1-2N0 NSCLC underwent either wedge resection (n = 69) or image-guided lung SBRT (n = 58) All were ineligible for anatomic lobectomy
- SBRT was volumetrically prescribed as 48 (T1) or 60 (T2) Gy in four to five fractions. Median follow-up is 2.5 years
- SBRT reduced the risk of local recurrence (LR), 4% versus 20% for wedge (P = .07). Overall survival (OS) was higher with wedge but cause-specific survival (CSS) was identical

What about patients with early *peripheral* lung cancers?

- VATS Wedge resection or segmentectomy
- Cyberknife with gold fiducials
- CT-guided RFA or cryoablation

RFA, VATS, or Cyberknife: which one?

- VATS resection is often preferred since it is the most established strategy
- Exercise VO2 and nuclear perfusion studies can identify operable patients
- Noninvasive modalities have similar and promising results in early single-armed trials, and comparison trials are in progress.
