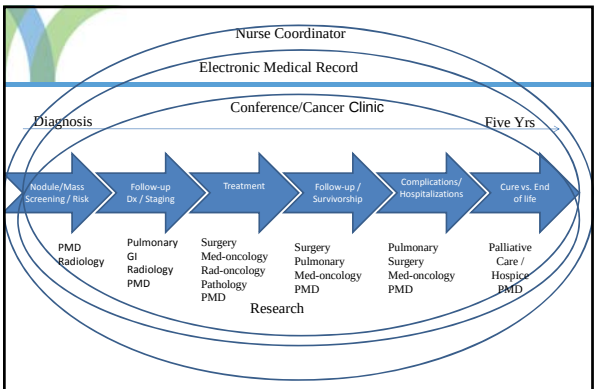
LUNG CANCER

Lee Kamman, MD
United Lung and Sleep Clinic



"More women die annually of lung cancer than breast cancer but it is not a women's issue. Far more Americans die of lung cancer than AIDS, but lung cancer victims are not viewed as victims and have no Advocacy group."

Timothy C. Kennedy, MD
1997

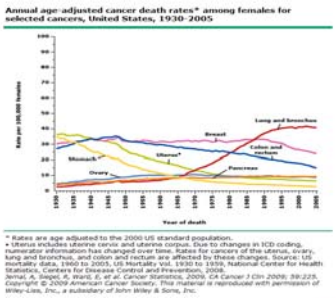
"except for smoking cessation efforts, there is no public strategy for this disease. In fact, of increasing incidence of new cases (170,000/year), 100 million current and ex-smokers at risk, an unchanging 87% mortality rate and a 6% cause of death by Americans, there is no strategy, and, in fact, little research funding for the epidemic."

Timothy C. Kennedy, MD
1997

- In 1900 there were less than 80 cases of primary lung cancer recorded in the medical literature.
- In 1912 Adler wrote monograph on lung cancer and apologized for writing a book on such a rare disease.

Lung Cancer Projections

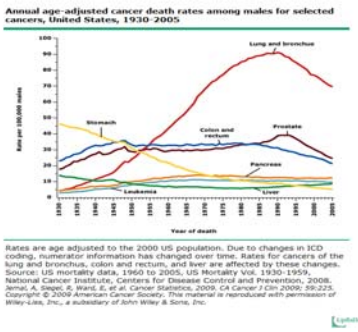
- 2008 Worldwide:
  - 1,600,000 new cases
  - 1,380,000 deaths
- 2014 United States:
  - 224,200 new cases
  - 159,300 deaths



Estimated cancer deaths for United States women in in 2012

Site	Number of deaths	Percent of cancer deaths
Lung	72,590	26 percent
Breast	39,510	14 percent
Colon and rectum	25,220	9 percent
Leukemia and lymphomas	19,180	7 percent
Ovary	15,500	6 percent

Data from: Siegel R, et al. CA-Cancer Journal for Clinicians 2012; 62:10.

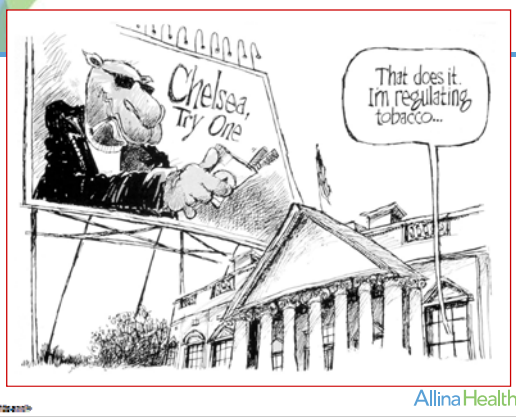


Cigarette Ads are Aimed at Young Women's Interests and Values

- Independence and liberation
- Popularity
- Beauty and glamour
- Weight

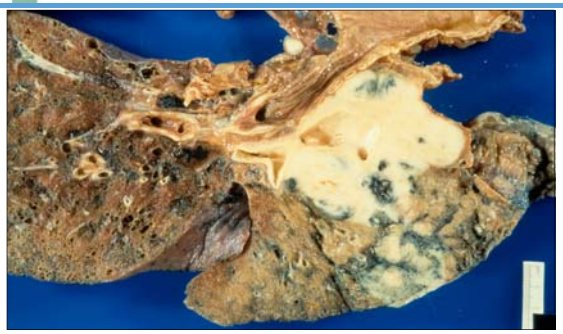
It is becoming increasingly clear that women have an enhanced susceptibility… which results in an increased risk for lung cancer compared to men.

Risch et al. *Am J Epid*, 1993; p 138
Sand and Wynder, *J Natl Cancer Inst*. 1996; p 88
Chen et al. *ARRD*, 1991, p 143



Master Settlement (NEJM 8/16/2001)

- Tobacco industry agreed to pay states $206 billion over 25 years, to respect limits on advertising and to fund public education
- Reality
  - Shifted resources to areas not restricted by the settlement
  - Many states are not using the money as was intended
- Legislation is needed to empower the FDA to:
  - Reduce tobacco use by young persons
  - Encourage and help adults to quit
  - Reduce the harm caused by present products
  - Broaden authority over tobacco marketing



The World Health Organization classification for primary lung cancer recognizes four major histologic cell types:

1. Adenocarcinoma (including bronchioloalveolar carcinoma) — 38%
2. Squamous cell carcinoma – 20%
3. Large cell carcinoma – 5%
4. Small cell carcinoma -13%

•Other non-small cell carcinomas, which cannot be further classified -18%
•Other -6%

***The relative incidence of adenocarcinoma has risen dramatically, and there has been a corresponding decrease in the incidence of other types of NSCLC and SCLC. The increased incidence of adenocarcinoma is thought to be due to the introduction of low-tar filter cigarettes in the 1960s, although this relationship is unproven.*

TABLE 1. IASLC/ATS/ERS Classification of Lung Adenocarcinoma in Resection Specimens

Preinvasive lesions
Atypical adenomatous hyperplasia
Adenocarcinoma in situ (≤3 cm formerly BAC)
Nonmucinous
Mucinous
Mixed mucinous/nonmucinous
Minimally invasive adenocarcinoma (≤3 cm lepidic predominant tumor with ≤5 mm invasion)
Nonmucinous
Mucinous
Mixed mucinous/nonmucinous
Invasive adenocarcinoma
Lepidic predominant (formerly nonmucinous BAC pattern, with >5 mm invasion)
Acinar predominant
Papillary predominant
Micropapillary predominant
Solid predominant with mucin production
Variants of invasive adenocarcinoma
Invasive mucinous adenocarcinoma (formerly mucinous BAC)
Colloid
Fetal (low and high grade)
Enteric

BAC, bronchioloalveolar carcinoma; IASLC, International Association for the Study of Lung Cancer; ATS, American Thoracic Society; ERS, European Respiratory Society.

Etiology (Beyond Cigarettes)

1. Cigars- 5 cigars about equal to 1 pack of cigarettes
2. Pipe- about the same as cigars
3. Recreational drugs- relationship not well established
4. Genetics- determines host susceptibility
   - Individual's responsiveness to treatment
   - Increased role if 1st degree family member had lung cancer, especially if under age 60

Etiology

5. Diet- decrease role if rich in fruits, vegetables and flavonoids (dark chocolate, red wine)
6. COPD and pulmonary fibrosis
7. Environmental tobacco smoke- slight increase
8. Biomass and wood smoke- slight increase
9. Air Pollution- probably some increase risk

Etiology

10. Occupation:
    a) Asbestos
    b) Arsenic
    c) beryllium
    d) cadmium
    e) chromium
    f) Nickel
11. Radon/Uranium
12. Gender: non-smokers with lung cancer more likely to be women

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Initial Symptoms of Bronchogenic Carcinoma in Patients Seen at M.D. Anderson Hospital

Symptoms	Occurrence %
Cough	21
Hemoptysis	21
Chest pain	16
Dyspnea	12
Extra thoracic pain	6
Anorexia and weight loss	5
Cervical mass	5
Fatigue	3
Superior vena cava obstruction	3
Hoarseness	3
Central nervous system symptoms	3
Shoulder pain	2
Clubbing of fingers	1

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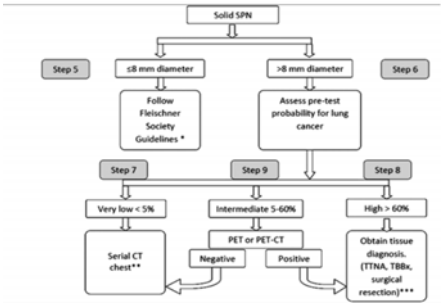
Algorithm for Management of Solid Pulmonary Nodule



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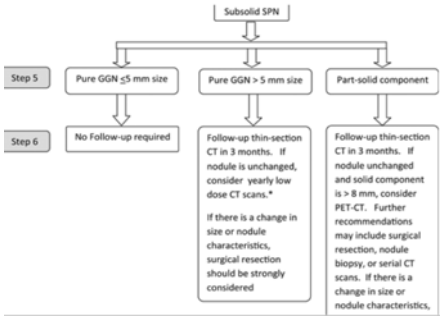
Algorithm for Management of Subsolid Pulmonary Nodule



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FLEISCHNER SOCIETY RECOMMENDATIONS FOR FOLLOW-UP OF SMALL LUNG NODULES DETECTED INCIDENTALLY ON CT (PATIENTS ≥ 35 YEARS OF AGE)

NODULE SIZE	LOW-RISK PATIENT	HIGH-RISK PATIENT
≤ 4 mm	No follow-up needed	• CT at 12 months • If stable, no further follow-up
>4 – 6 mm	• CT at 12 months • If stable, no further follow-up	• Initial CT at 6-12 months • If stable, repeat CT at 18-24 months
>6 – 8 mm	• Initial CT at 6-12 months • If stable, repeat CT at 18-24 months	• Initial CT at 3-6 months • If stable, repeat CT at 9-12 months and 24 months
> 8 mm	• CT at 3, 9, and 24 months • Consider PET or biopsy	• CT at 3, 9, and 24 months • Consider PET or biopsy

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Fleischner Society Guidelines

LOW RISK = minimal or absent history of smoking or other known risk factors.
HIGH RISK = history of smoking or other known risk factors.
KNOWN RISK FACTORS: history of lung cancer in first-degree relative; exposure to asbestos, radon, or uranium.

- NOTE: nonsolid, partially solid, or ground-glass nodules may require longer follow-up to exclude indolent adenocarcinoma
- NOTE: guidelines do NOT apply to the following groups:
  - known or suspected cancer outside of the lungs
  - patients younger than 35 years of age
  - patients with unexplained fever

SOURCE: MacMahon H, Austin JHM, Gamsu G, et al. Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society. *Radiology* 2005; 237: 395-400.

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Endobronchial Ultrasound (EBUS)

Gomez and Silvestri: Endobronchial Ultrasound for Lung Cancer

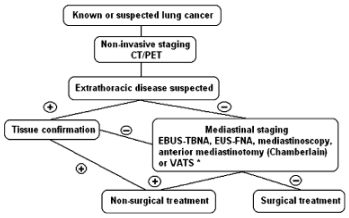

Figure 6. Proposed algorithm for lung cancer staging. CT = computed tomography; EBUS-TBNA = endobronchial ultrasound-fine needle aspiration; EUS-FNA = endoscopic ultrasound-fine needle aspiration; PET = positron emission tomography. * Based on local expertise and lymph node location; negative needle techniques should be followed by surgical staging.

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Definitions for TNM Descriptors

Descriptors	Definitions	Subgroups*
T	**Primary tumor**	
T0	No primary tumor	
T1	Tumor ≤ 3 cm,† surrounded by lung or visceral pleura, not more proximal than the lobar bronchus	
T1a	Tumor ≤ 2 cm†	T1a
T1b	Tumor > 2 but ≤ 3 cm†	T1b
T2	Tumor > 3 but ≤ 7 cm† or tumor with any of the following‡:	
	Invades visceral pleura, involves main bronchus ≥ 2 cm distal to the carina, atelectasis/obstructive pneumonia extending to hilum but not involving the entire lung	
T2a	Tumor > 3 but ≤ 5 cm†	T2a
T2b	Tumor > 5 but ≤ 7 cm†	T2b
T3	Tumor > 7 cm;	T3
	or directly invading chest wall, diaphragm, phrenic nerve, mediastinal pleura, or parietal pericardium;	T3
	or tumor in the main bronchus < 2 cm distal to the carina‡;	T3
	or atelectasis/obstructive pneumonitis of entire lung;	T3
	or separate tumor nodules in the same lobe	T3
T4	Tumor of any size with invasion of heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina;	T4
	or separate tumor nodules in a different ipsilateral lobe	T4
N	**Regional lymph nodes**	
N0	No regional node metastasis	

Figure 1. [Sections 2.0, 3.0, 6.2] Definitions for TNM descriptors. Adapted with permission from Detterbeck et al.[13]
*These subgroup labels are not defined in the IASLC publications[7,10] but are added here to facilitate a clear discussion.

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From: The Stage Classification of Lung CancerStage Classification of Lung Cancer: Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines
Chest. 2013;143(5_suppl):e191S-e210S. doi:10.1378/chest.12-2354

T/M	Subgroup	N0	N1	N2	N3
T1	T1a	Ia	IIa	IIIa	IIIb
	T1b	Ia	IIa	IIIa	IIIb
T2	T2a	Ib	IIa	IIIa	IIIb
	T2b	IIa	IIb	IIIa	IIIb
T3	T3 (>7 cm)	IIb	IIIa	IIIa	IIIb
	T3 (invasion)	IIb	IIIa	IIIa	IIIb
	T3 (satellite)	IIb	IIIa	IIIa	IIIb
T4	T4 (invasion)	IIIa	IIIa	IIIb	IIIb
	T4 (ipsilateral satellite)	IIIa	IIIa	IIIb	IIIb
M1	M1a (Contra-lateral)	IV	IV	IV	IV
	M1a (Pl Dissem)	IV	IV	IV	IV
	M1b	IV	IV	IV	IV

Figure Legend:
[Section 5.0] Stage groups according to TNM descriptor and subgroups. Reproduced with permission from Detterbeck et al.[13]

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Treatment for Non-Small Cell Stage I- 50% 5 Year Survival

- A. Surgery- Preferably minimally invasive
  - i) Lobectomy
  - ii) Sub lobar
  - iii) Sleeve resection
  - iv) Lymph node dissection

B. Radiation
  - i) Stereotactic (SBRT)
  - ii) Cyber Knife
  - iii) External Beam (EBRT)
  - iv) RFA

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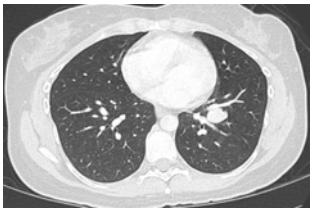
L. R.

- 36 year-old never smoker presents with complaint of hemoptysis
- 9/14/12- CT Chest reveals a LLL mass measuring 3.3 x 2 x 2.2 cm



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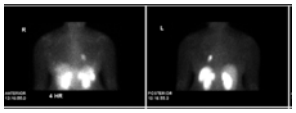
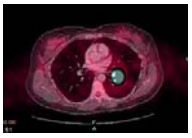
9/20/12- Octreotide Scan shows LLL nodule to be somatostatin-avid, consistent with carcinoid tumor





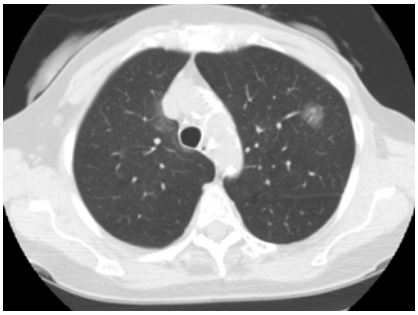
10/1/12- Left thoracotomy, left lower lobectomy with mediastinal lymph node dissection

- Well-differentiated endobronchial neuroendocrine carcinoma (typical carcinoid)
- Final TNM: pT1aN0M0
- Stage: IA
- No additional treatment necessary

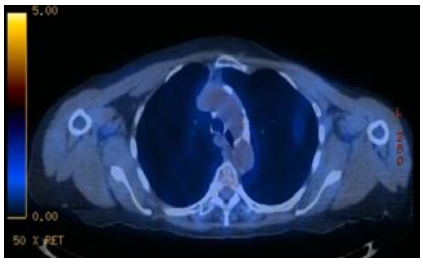
M. G.

- 84 year-old former smoker with history of stage IA breast cancer treated with SBRT and finding of incidental pulmonary nodule in July 2013 onCT chest completed for esophageal reflux and shortness of breath

7/18/13- CT chest with findings of a 1.8 x 1.4-cm ground-glass nodule left upper lobe. Nodule measured 11 mm in 2007



8/2/13- PET demonstrates SUV 1.2 associated with the LUL nodule



7/30/13- CT guided biopsy of LUL nodule

- Suspicious for well-differentiated adenocarcinoma
- FEV1 74%
- Patient declines surgical resection
- 8/15/13-8/21/13- SBRT

SBRT

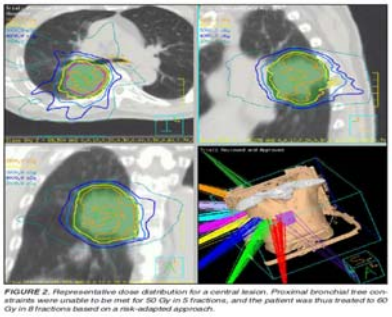


FIGURE 2. Representative dose distribution for a central lesion. Proximal bronchial tree constraints were unable to be met for 50 Gy in 5 fractions, and the patient was thus treated to 60 Gy in 8 fractions based on a risk-adapted approach.

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C. S.

- 83 year-old former 90 pack year smoker (quit in 2001) followed since January 2013 for incidental finding of a 9 mm pulmonary nodule

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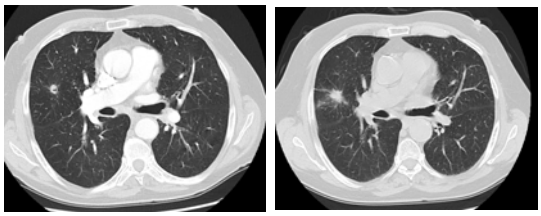
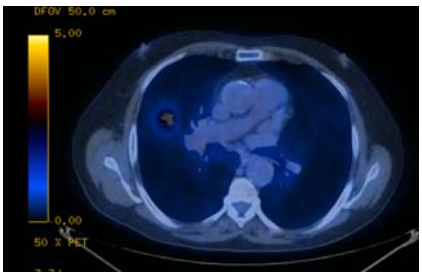
9 mm to 1.4 x 1.3

1/25/13- CT chest, abdomen **7/28/14- CT chest**



8/13/14 PET demonstrates SUV 2.7 associated with the RUL nodule



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- 8/15/14- Case presented at Multidisciplinary Lung Conference
  - Biopsy considered risky due to close proximity of nodule to blood vessels and possibility of pneumothorax
  - Recommend continued surveillance vs. biopsy vs. SBRT without confirmed diagnosis
- Patient and his family decided on SBRT

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Stage II- 30% 5 Year Survival

A. Surgery

i) Lobectomy
ii) Pneumonectomy
iii) Adjuvant chemotherapy

B. Chemotherapy

C. EBRT

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Stage IIIA- 14% 5 Year Survival

- Present at Multidisciplinary Lung Conference
- Generally combined chemo/radiation therapy
- Re-evaluate for surgery

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L. H.

- 60 year-old female smoker who was being evaluated for spine surgery when a lung abnormality was noted on MRI.

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12/26/13- CT chest shows a left lung mass and some adenopathy.

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12/26/13 CT Chest

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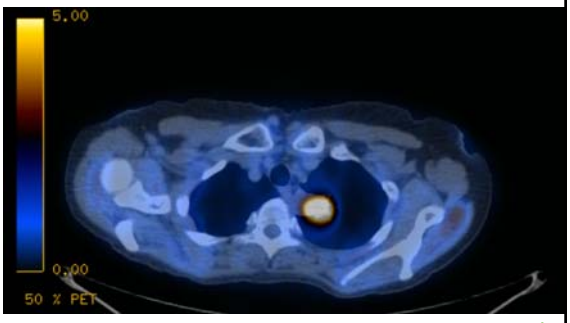
12/30/13- PET confirms evidence for primary LUL lung cancer with metastasis to AP window and subaortic lymph nodes



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12/30/13 PET

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L. H.

- 12/30/13- PNC Consult
- 12/30/13- FEV1 75% of predicted
- 1/2/14- Case presented at Multidisciplinary Lung Conference with recommendations to proceed with MRI brain and surgical biopsy station 5 AP window LN
- 1/6/14- MRI brain negative for metastatic disease

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Non-small cell carcinoma, favor poorly differentiated adenocarcinoma of the lung

- 1/30/14- Left anterior mediastinotomy with biopsy of AP window lymphadenopathy.
- ALK and EGFR negative
- 2/26/14- Concurrent radiation and cisplatinum/etoposide
- 4/9/14- Completion of radiation

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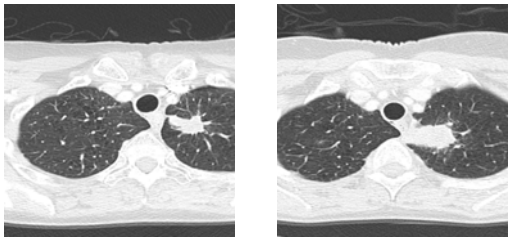
5/19/14- Restaging CT CAP (Left)



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Further Recommendations?

- 5/22/14- Case presented at Multidisciplinary Lung Conference with recommendations to proceed with left upper lobectomy
- 7/10/14- Left thoracotomy, left upper lobectomy with mediastinal lymph node dissection.

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Final Pathology

1. Necrotizing granulomatous inflammation with no residual adenocarcinoma, forming a 3.2 x 2.7 x 1.7 cm area, consistent with complete pathologic response

Final TNM: ypT0N0M0
2012 stage: Stage 0

2. Separate minimally invasive adenocarcinoma, forming a1.2 x 1.0 x 0.8 cm mass, located 2.0 cm from the necrotic previously treated tumor

Final TNM: pT1aN0M0
2012 stage: IA

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Stage IIIB- 5% 5 Year Survival

- Chemotherapy plus EBRT
- EBRT alone

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Stage IV- 1% 5 Year Survival

- Combination chemotherapy
- Maintenance chemotherapy
- Targeted therapy

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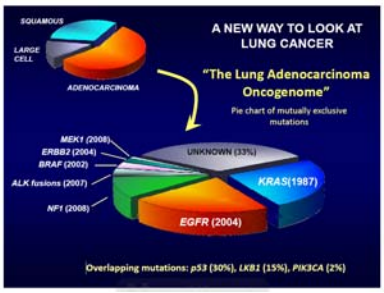
Adenocarcinoma Mutations



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EML4-ALK Oncogene (FISH)

1. Minimal smoking history
2. Younger age
3. Adenocarcinoma (acinar)
4. Respond to ALK targeted inhibitors (crizotinib)

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P. L.

- 47 year-old healthy male never smoker presented to primary care with complaints of cough, shortness of breath and chest pressure.

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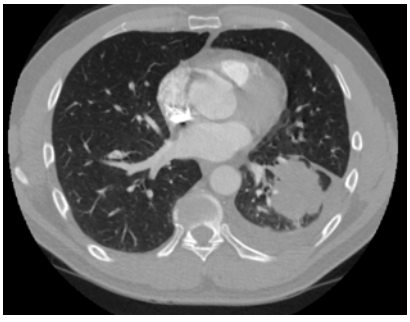
6/12/14- CT Chest PE Study shows a 4.7 x 4.8 cm mass left lower lobe



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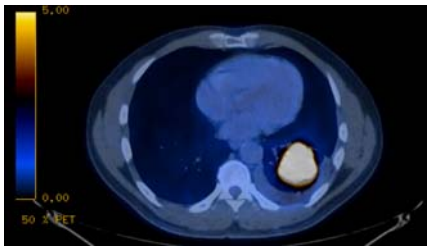
6/17/14- PET with hypermetabolic left lower lobe lesion



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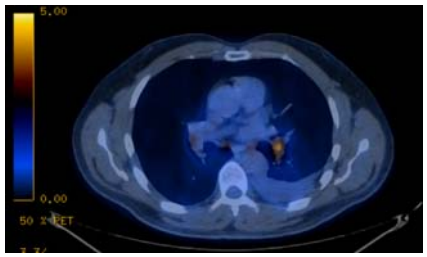
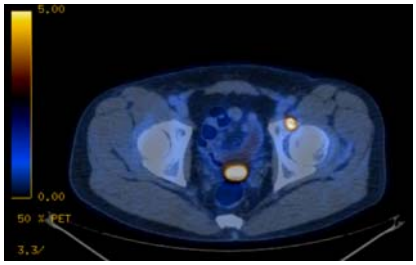
Hypermetabolic bilateral hilar and mediastinal adenopathy



Hypermetabolic bone lesions



7/1/14- EBUS Station 7 LN

- Poorly differentiated nonsmall cell carcinoma consistent with pulmonary adenocarcinoma
- ALK positive
- Treated with Crizotinib

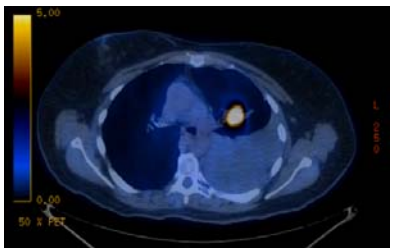
EGFR Mutation

1. Adenocarcinoma
2. Women
3. Non-smokers
4. Asian
5. Respond to erlotinib and gefitinib

R. F.

- 59 year-old healthy female never smoker, missionary from Costa Rica presents with complaints of 3-4 weeks of increasing shortness of breath and fatigue
- 3/5/14-CT Chest shows large left pleural effusion and a left mid lung mass
- 3/5/14-Thoracentesis with pleural fluid demonstrating non-small cell carcinoma
- Patient returns to MN for further work-up

3/13/14- PET with hypermetabolic LUL mass with evidence of left hilar, left supraclavicular and retroperitoneal LN metastases



3/14/14- Left VATS Talc Pleuradesis with biopsies of parietal pleura

- Final pathology reveals adenocarcinoma consistent with pulmonary primary
- EGFR mutation detected
- Treated with Tarceva

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ROS 1
Reactive Oxygen Species 1

1. Light or never smokers
2. Chromosomal rearrangement of the gene encoding Ros 1
3. Crizotinib (NEJM 9/27/14)

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J. J.

- 65 year old remote former smoker (14 pack years, quit in 1977) presented in April 2012 with complaints of persistent, increasing cough over several months
- 6/6/12- Bronch shows malignant cells consistent with adenocarcinoma of the lung
- 7/31/12- Left lower lobectomy, pathological stage IIIA (pT3, pN1, M0)
- EGFR, ALK negative

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J. J.

- 8/25/14- One dose cisplatin and Navelbine tolerated poorly due to nausea and vomiting which aggravated his post operative pain. Patient declined further adjuvant chemo
- 1/7/13- CT CAP shows nearly confluent, rounded ground glass densities in the LUL progressing from previous imaging

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J. J.

- 1/17/13- Completion left pneumonectomy
- 3/26/13- 5/28/13- Six cycles of adjuvant carboplatin/Taxol

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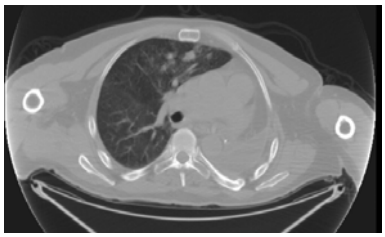
8/18/14- CT chest shows increasing ground glass density in the RUL



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J. J.

- 8/21/14- Case presented at Multidisciplinary Lung Conference with recommendations to proceed with PET
- 8/26/14- PET demonstrates SUV of 1.5 associated with slowly progressing groundglass infiltrates in the right lung

Allina Health

J. J.

- 8/28/14- Case presented at Multidisciplinary Lung Conference with recommendation to proceed with Bronch in order to rule out infection
- 9/5/14- RUL BAL positive for malignant cells, consistent with recurrent lung adenocarcinoma
- Tissue sent for mutation testing panel and reveals a ROS 1 mutation
- Treated with Crizotinib

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PD- L1

- Over-expressed in tumor cells
- Interferes with the body's anticancer immune response
- Allows tumor to grow

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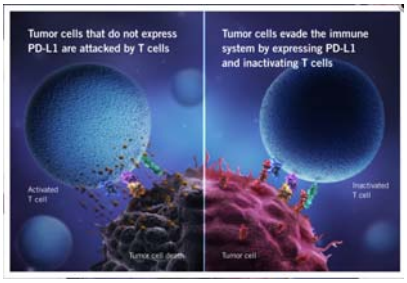
PD-L1



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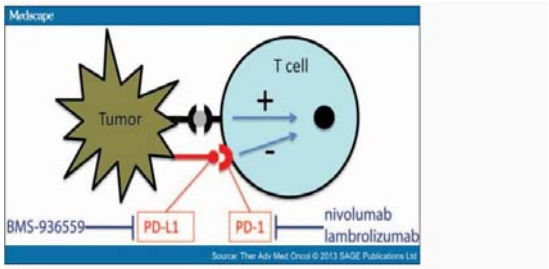

Figure 2.

The PD-1/PD-L1 axis and antibodies in development. T cells interact with tumor cells in peripheral tissues. Tumor cells can present antigen to the T-cell receptor, resulting in a stimulatory signal to the T cell (+). Tumor cells may also express PD-L1, which interacts with PD-1 on activated T cells, and results in inhibition (–) of the antitumor T-cell response.

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Ancillary Therapy

- Radiologically Occult Lung Cancer – usually squamous
  - Hematoporphyrin derivatives are concentrated by cancer cells and produce cytoloxic effects by producing oxygen radicals
- Advanced or Recurrent Obstructive Airway Lesions
  - Laser – YAG
    - Lesion no responsive to other therapy
    - Not totally obstructing
    - Functional lung tissue beyond the lesion
  - Brachytherapy
  - Stents – used when airway is extrinsically compressed by tumor

Allina Health

Treatment for Small Cell

- Limited stage- Single Radiation Field
  - Chemotherapy: platinum plus etoposide
  - Concurrent thoraci radiation therapy
- Extensive stage
  - Carboplatinum and Etoposide
- Prophylactic Cranial Irradiation
  a) Decrease CNS metastases
  b) Improve survival

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5 Year Survival Rates for Small Cell

- Stage I- 31%
- Stage II- 19%
- Stage III- 8%
- Stage IV- 2%

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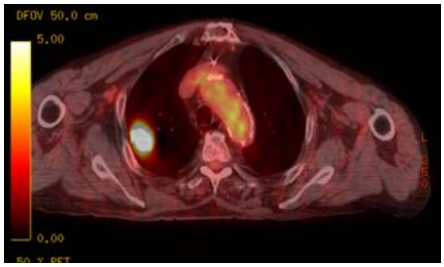
Limited Stage SCLC



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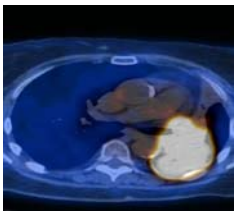
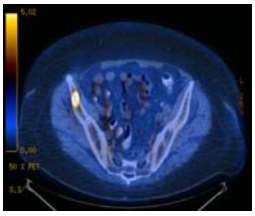
Extensive Stage SCLC





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Research Links Red Wine to Healthier Lungs

WINE & HEALTH

Two recent health studies may let red wine drinkers breathe easier.

Research in Spain has found that drinking red wine may reduce one's risk of lung cancer. Other alcoholic beverages showed no benefit, according to the study, published in the journal *Thorax*.

The researchers studied 282 hospital patients—mostly men ages 50 to 70—and categorized them by the type of alcohol they primarily drank. Of the patients, 118 had lung cancer; the rest served as the control group.

After adjusting for factors such as smoking, the scientists determined the median risk for lung cancer associated with each serving of alcohol. Compared with nondrinkers, red-wine drinkers' risk decreased 13 percent with each glass consumed per day. Beer drinkers' risk was similar to that of nondrinkers, spirits drinkers showed a 3 percent greater risk for each glass per day, and white-wine drinkers showed a 20 percent greater risk with each glass. This contradicts an earlier finding that white wine was linked to good lung health.

The authors noted that the smaller number of subjects who drank white wine versus red could have skewed the results. But they believe the difference may largely be due to red wine's higher levels of polyphenols, such as resveratrol.

Resveratrol may one day be given to people with stubborn lung ailments, said researchers at Imperial College London in England. In lab trials, the compound stopped inflammation in human lung cells, the team reported in the American Journal of *Physiology-Lung Cellular and Molecular Physiology*.

Coauthor Louise Donnelly said resveratrol switches off inflammatory genes present in asthmatics and people with chronic bronchitis and emphysema. While you can't drink enough red wine to have this effect, you may someday see a resveratrol inhaler.

—Jacob Gaffney

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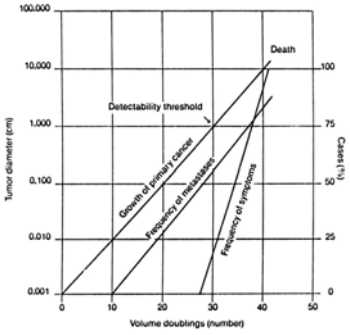
Neoplasms of the Lungs



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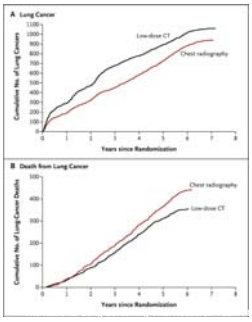

SEER 5 Year Survival

Malignancy	1975-1980	1990-1995	2005-2010
Lung	12.5	14	18
Breast	74	86	91
Colon-Rectal	51	60	65
Ovarian	37	41	45
Cervix	69	72	70
Pancreas	3	4	7
Esophageal	5	12	20
Kidney	50	61	74

“Is there anyone out there ‘cause it’s getting harder and harder and harder to breathe.”

Maroon 5

What is Needed?
A Change in Our Culture

- Recognize we have a health problem that is near epidemic proportions
- Take whatever steps are necessary to dissuade people from beginning to smoke, especially for teens
- Provide opportunities and incentives for smokers to quit
- Provide research money for:
  - Screening
  - New treatment modalities
- Provide support for those with lung cancer

“Those who cannot remember the past are condemned to repeat it.”

George Santayana,
(1863-1952)

The End

- Questions?