Pulmonary Complications of Cancer Therapy

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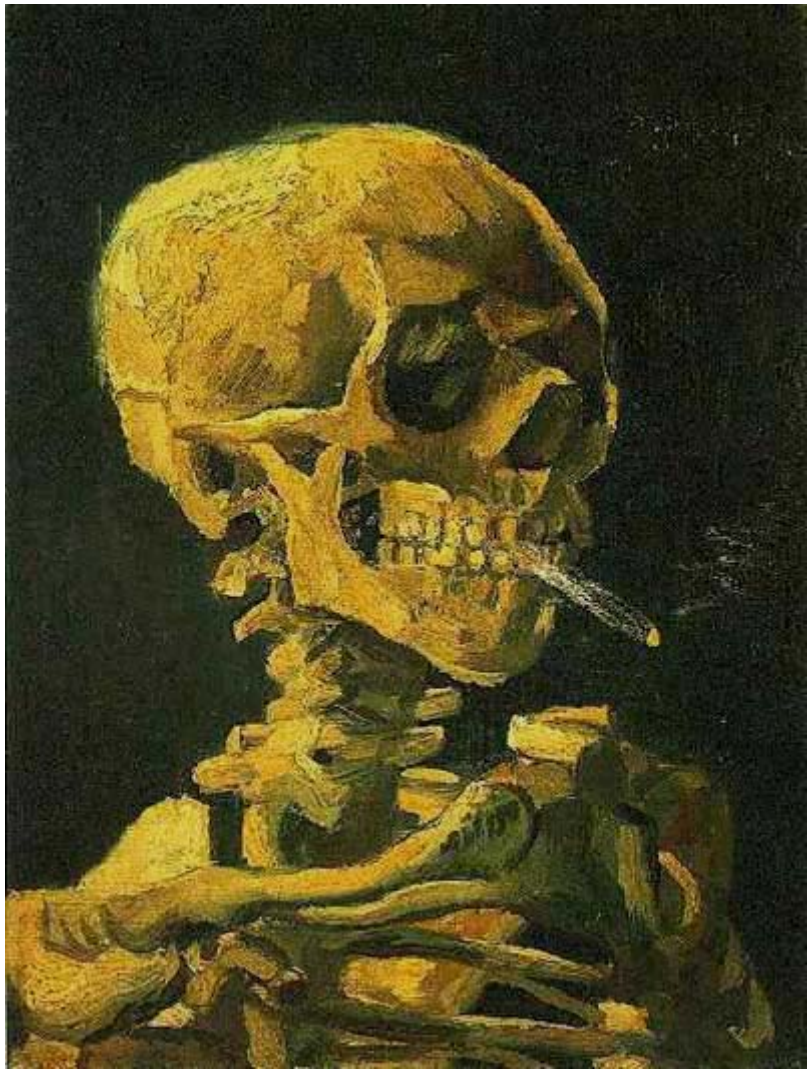
Tobacco



- About 85% of lung cancers occur in current/former smokers.
- Tobacco causes many other cancers.
  - Head & Neck
  - Bladder
  - Esophageal
  - ? Pancreas, breast

Diseases Associated with Smoking
Other than Cancer

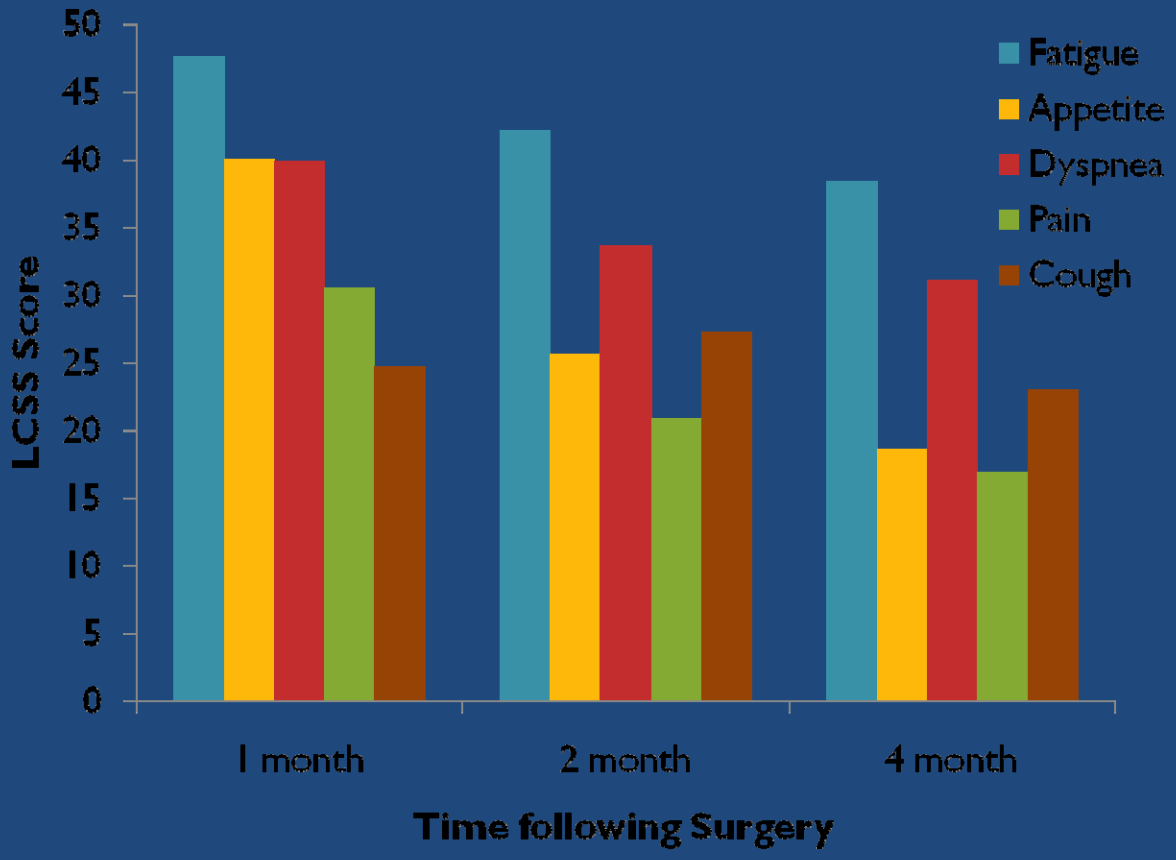
- Lung Diseases
  - COPD
- Heart Disease
  - Ischemic Heart Disease
  - Valve Disease (i.e. aortic stenosis)
  - Congestive Heart Failure
- Atherosclerosis of other organs
  - Peripheral Vascular Disease
  - Carotid Artery Stenosis, Stroke
- Osteoporosis

Lung Cancer Surgery
Symptoms after Resection

- Lung Cancer – best studied of cancer of pulmonary complications.
- Sarna et al reviewed 94 patients who had undergone lung cancer resection.
- <u>Clinical characteristics:</u>
  - 74% had lobectomy, 9% had pneumonectomy, 13% had segmentectomy/wedge resection.
  - 69% stage I.
  - <15% received neoadjuvant or adjuvant treatment.

Sarna L, et al. Am J Crit Care 2008; 17:455-67.

Lung Cancer Surgery
Symptoms after Resection



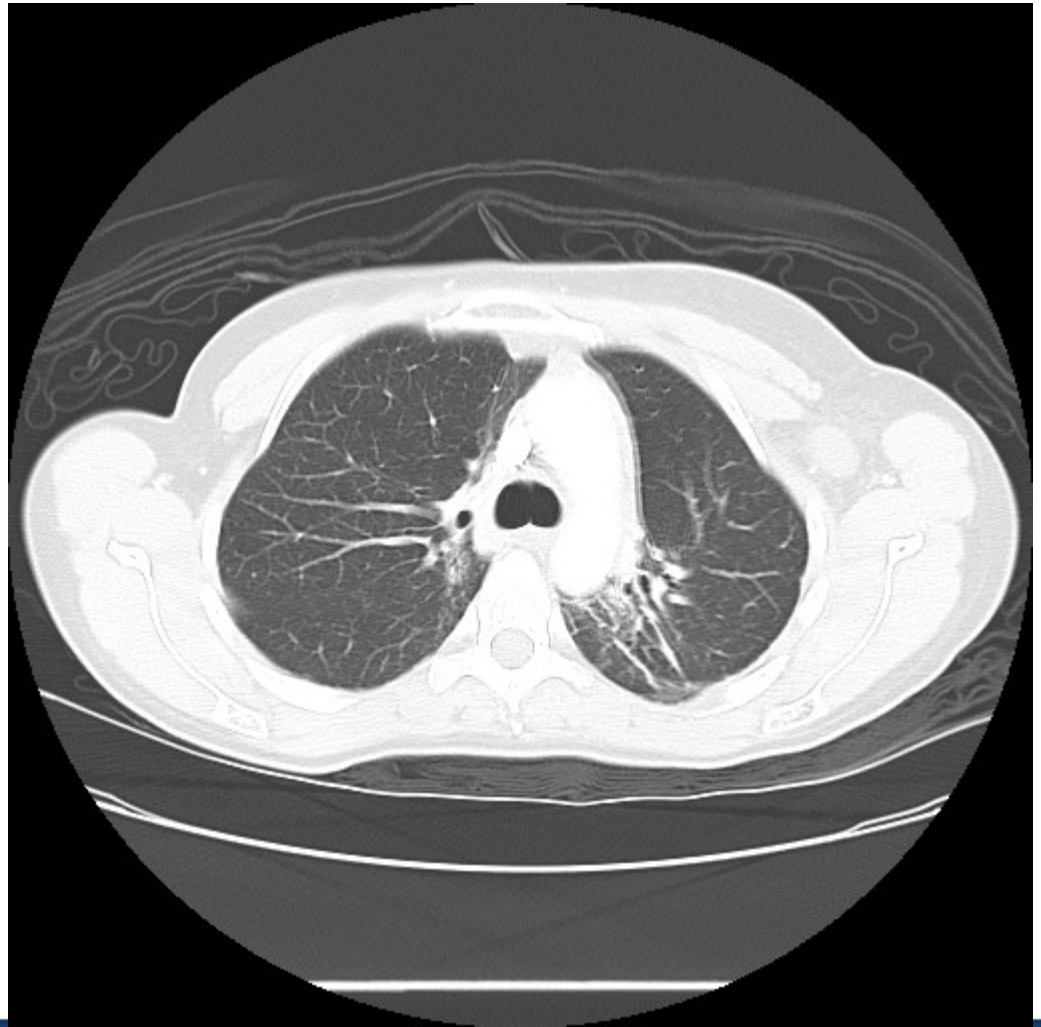
Cancer Treatments

- Radiation
- Chemotherapy
- Surgery

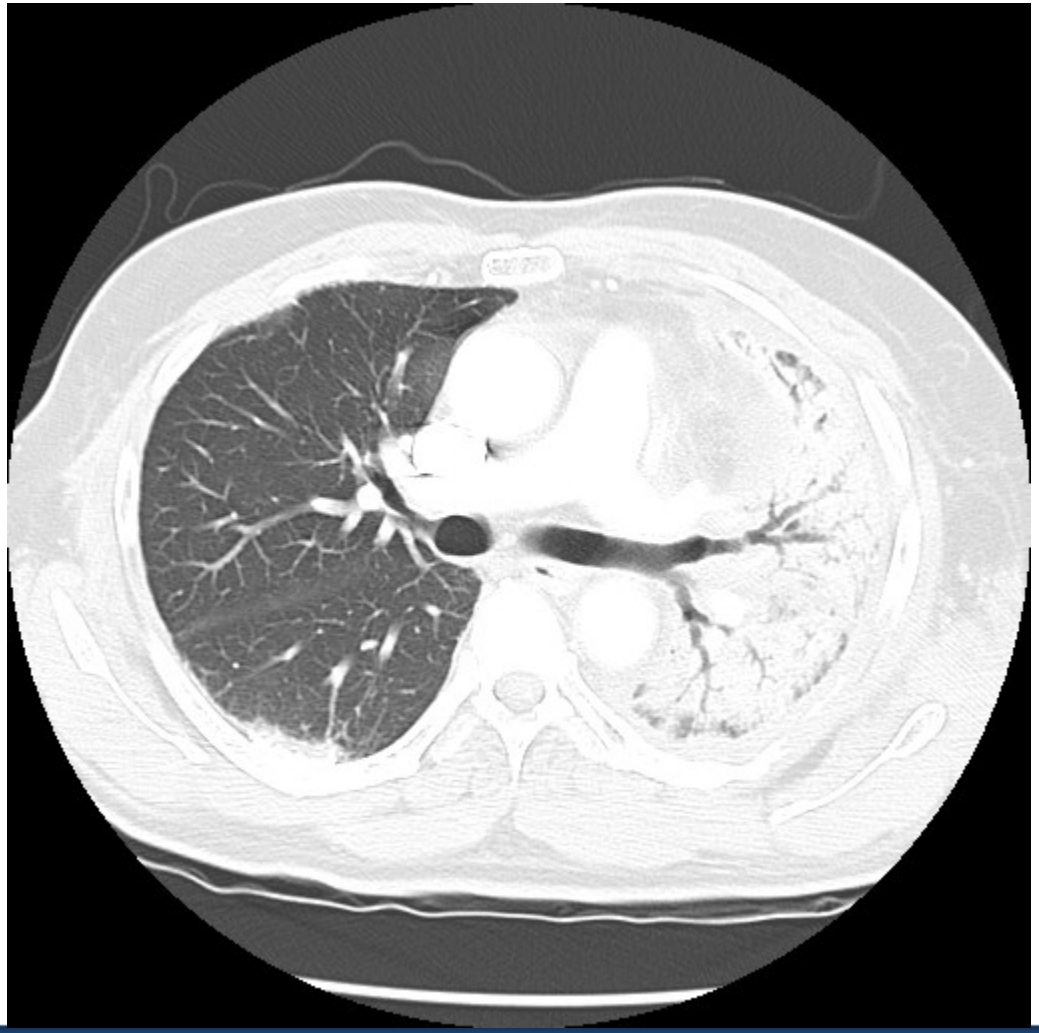
Radiation

- Regular treatments of external beam radiation – “Fry the cancer”.
- Can be used with curative intent or for emergencies.
  - Cord compression
  - SVC syndrome
  - Pain from bone metastases.
- Can affect surrounding tissues.
  - Radiation pneumonitis – usually occurs 6 weeks to 6 months following treatment.
  - BOOP

Radiation Change



Radiation Pneumonitis



Radiation Pneumonitis
Treatment

- No universal agreement regarding treatment.
- Steroids have been shown helpful in animal models.
- Prednisone 40mg
  - Taper over 1-2 months.

BOOP

Bronchiolitis

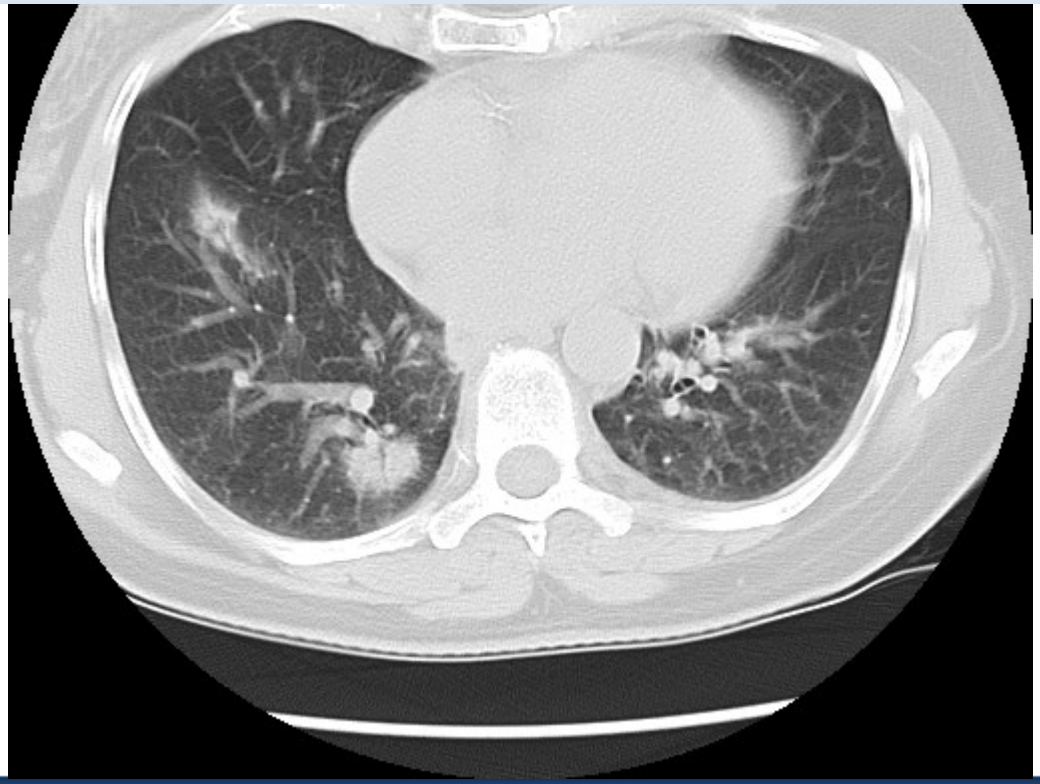
Obliterans

Organizing

Pneumonia

Radiation-Induced BOOP

- Clinical Pearl:
- Radiation pneumonitis – infiltrates within radiation field
- BOOP – infiltrates outside of radiation field



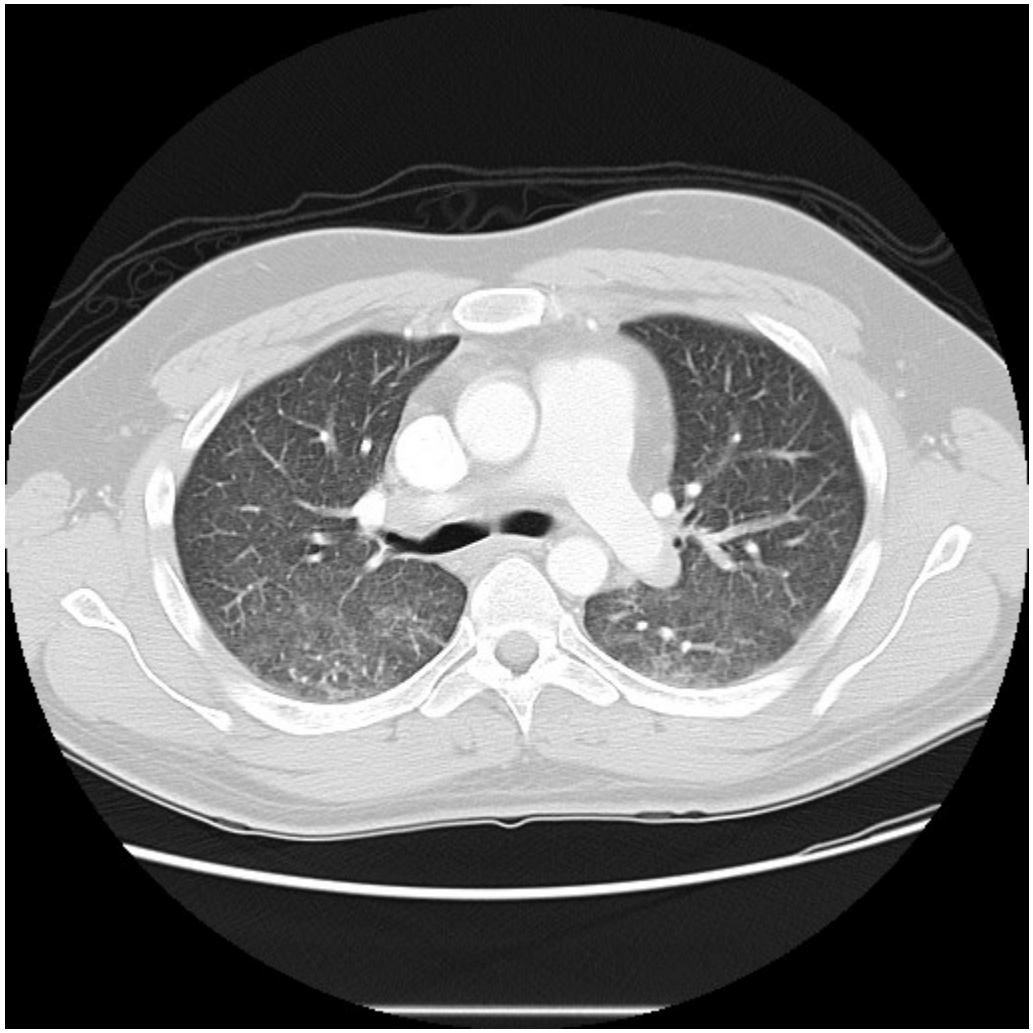
Chemotherapy

- Palliative for advanced stage disease, not amenable to curative surgery.
- Used concomitantly with surgery to improve outcomes after resection.

Chemotherapy Lung Toxicity

- Mechanism varies.
- Difficult Diagnosis - Symptom/Signs often non-specific
  - i.e. cough, fever, dyspnea, hypoxemia
  - High WBC, ESR.
- Chest imaging may show a variety of patterns
- Biopsy via bronchoscopy or surgery may be helpful, but results often non-specific.
- Rests on clinical diagnosis
- Radiation Recall Pneumonitis

Bleomycin Toxicity



Chemotherapy Lung Toxicity
Treatment

- Stop the offending drug
- Steroids

Taxane Chemotherapy

- Mechanism of action: retard normal microtubule function.
- Cells are arested in the premitotic G2 phase and fail to divide.

Taxane Chemotherapy
Adverse Reactions

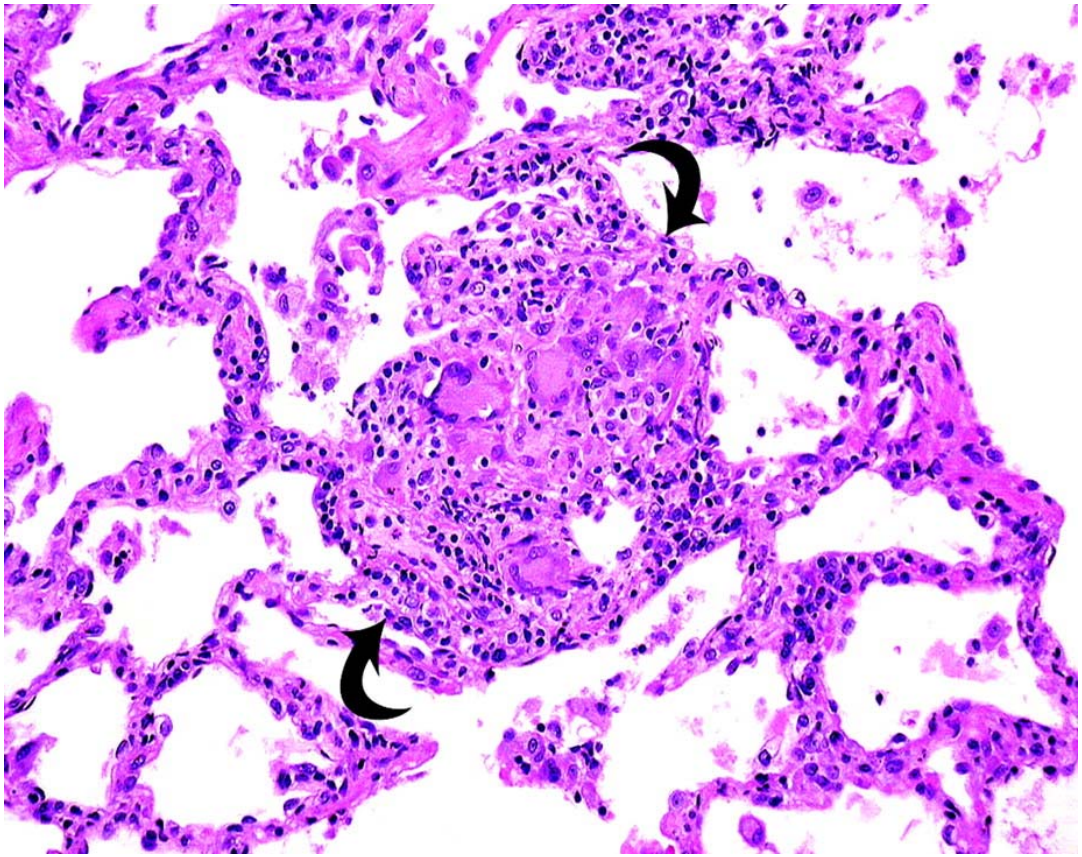
- Type I hypersensitivity: Anaphylaxis.
  - Symptoms: Dyspnea, wheezing, urticaria, rash, hypotension.
  - Up to 30%. With premedication, can be reduced to 1-3%.

- Type IV hypersensitivity: cell-mediated.
  - Bilateral pulmonary infiltrates.
  - More common with paclitaxel (Taxol)
  - Several hours to 2 weeks following administration.

Taxane Chemotherapy
Adverse Reactionsm by drug

- Paclitaxel (Taxol)
  - Pulmonary infiltrates
- Docetaxel (Taxotere)
  - Capillary leak
  - Pleural effusions

Taxol Toxicity



Taxane Chemotherapy
Radiation

- Radiosensitizer. At least one report of recall pneumonitis in a patient who had previously received radiation.

- In a report from Germany…
  - 8 of 14 patients receiving concurrent radiation and paclitaxel for NSCLC developed interstitial pneumonia.
  - Sequential therapy reduces, but does not eliminate pulmonary toxicity.

Reckzeh B, et al. J Clin Oncol 1996; 14:1071-6

Chemotherapy Lung Toxicity
Other Agents

- Bevacizumab - VEGF inhibitor
  - Hemorrhage/hemoptysis, especially in squamous cell ca.

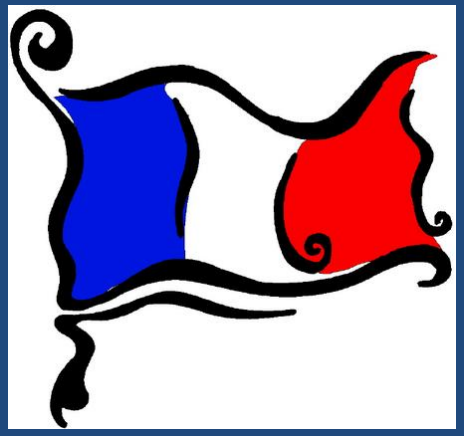
- Erlotinib – EGFR tyrosine kinase inhibitor
  - Risk 0.5-1%.
  - Bilateral pulmonary infiltrates/ground glass infiltrates.

Chemotherapy Lung Toxicity
Other Agents

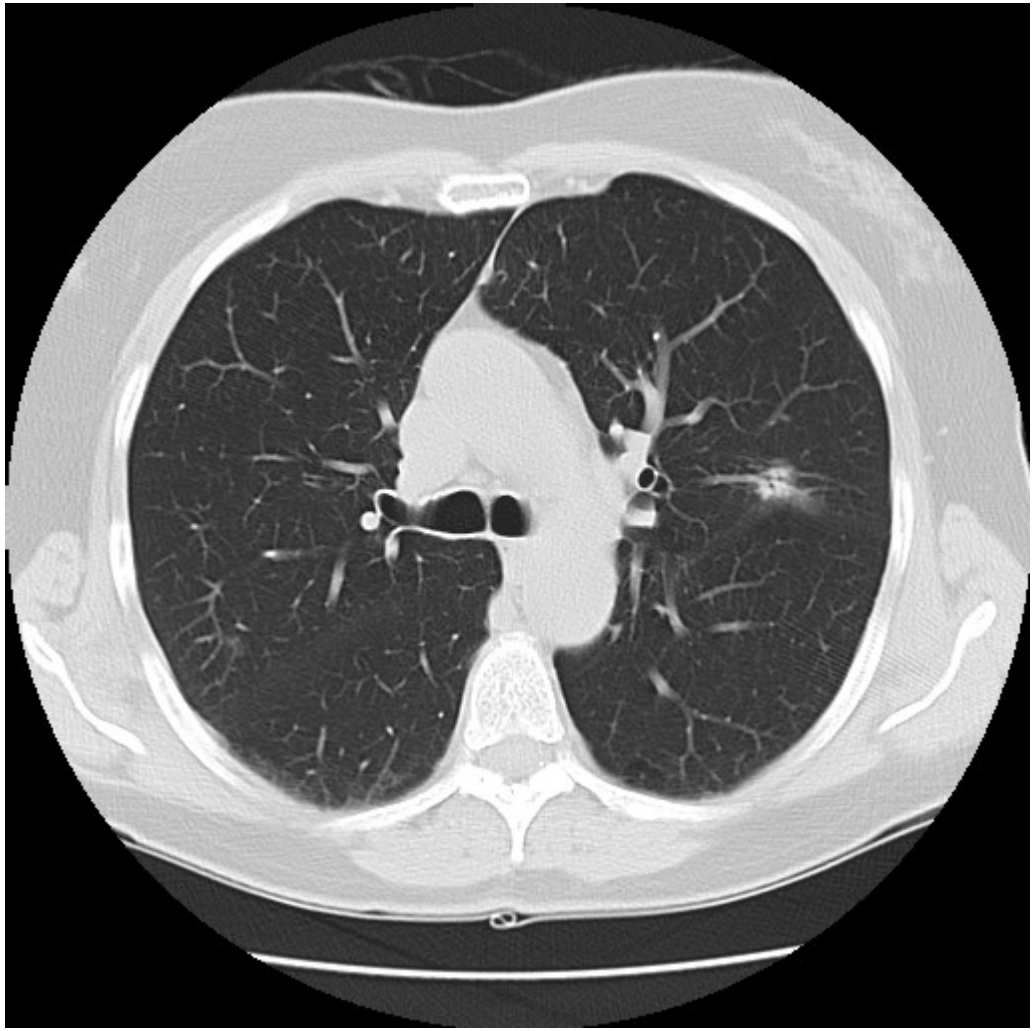
- Etoposide – used in small cell lung ca.
  - Diffuse alveolar damage and noncardiogenic edema.
  - Increases risk of radiation pneumonitis.

- Gemcitabine – non-small cell lung ca and pancreatic ca. Several pulmonary manifestations.
  - Dyspnea within hours of infusion (10%).
  - Pneumonitis:
    1. Capillary leak syndrome
    2. Diffuse alveolar damage
    3. Alveolar hemorrhage

www.pneumotox.com



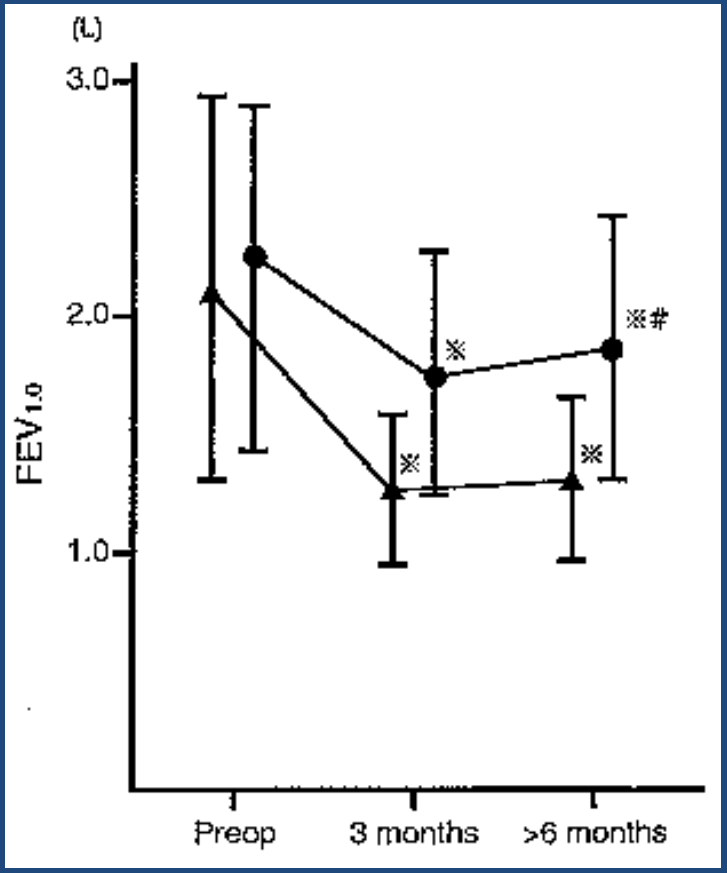
Surgery



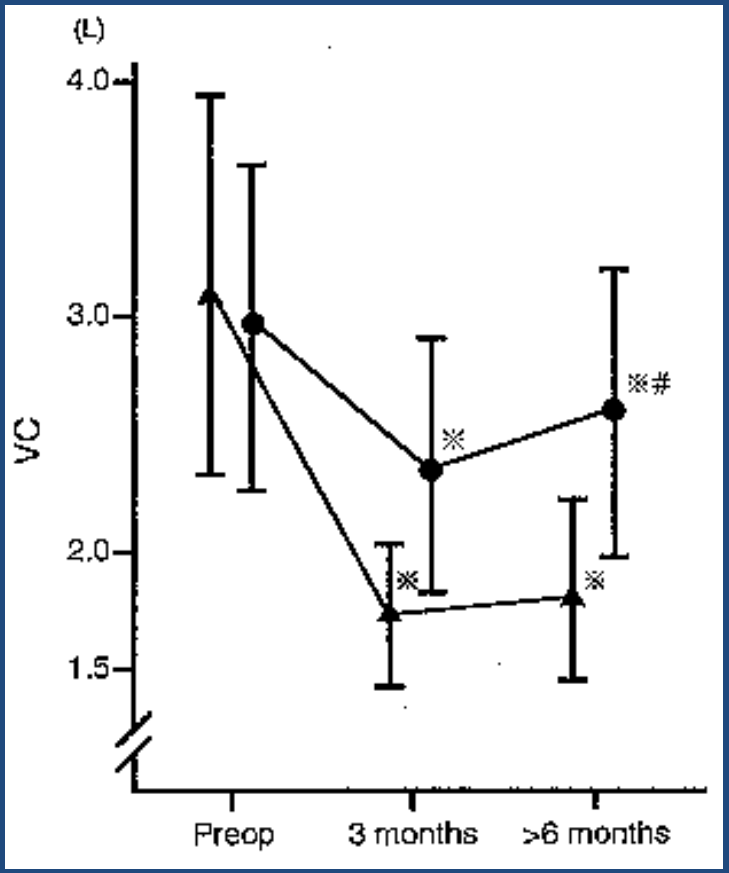
Pulmonary Function Tests

Expected Change from Surgery

FEV1



FVC



Nezu, K., et al. (1998). Chest 113(6): 1511-6.

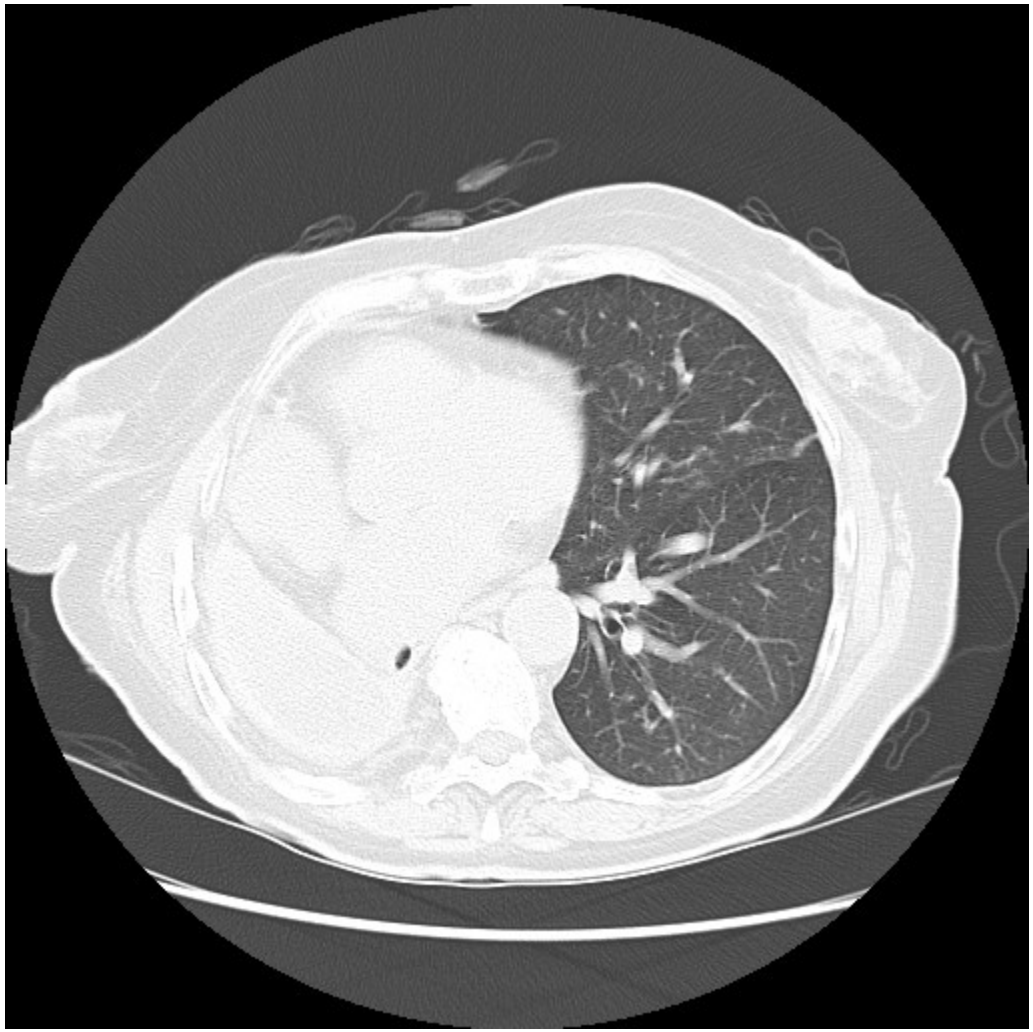
Pulmonary Function Tests

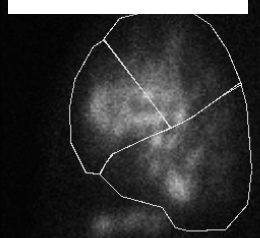
Expected Change from Surgery

	% Change 6 months postoperatively			
	Lobectomy		Pneumonectomy	
	FEV1	FVC	FEV1	FVC
Bolliger, et al. (n=68)	9	7	34	36
Larsen, et al (n=57)	8	9	23	27

Bolliger, C. T., et al. (1996). Eur Respir J 9(3): 415-21.
Larsen, K. R., et al. (1997). Ann Thorac Surg 64(4): 960-4.

Surgery





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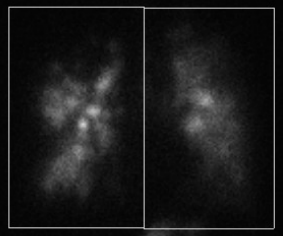
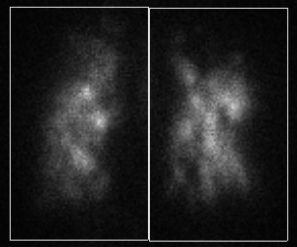
LT LATERAL

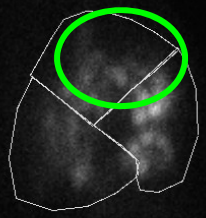




ANT VENT

POST VENT

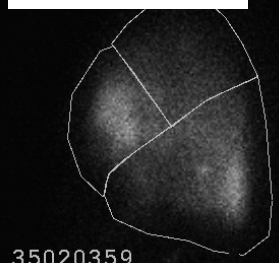
13Jun2003



RT LATERAL

LOBAR VENTILATION	(%) OF TOTAL
RT UPPER LOBE	15.74
RT MIDDLE LOBE	23.34
RT LOWER LOBE	14.65
RT LUNG TOTAL	53.7
LT UPPER LOBE	29.27
LT LOWER LOBE	17.00
LT LUNG TOTAL	46.3

MEMORIAL SLOAN KETTERING CANCER CENTER



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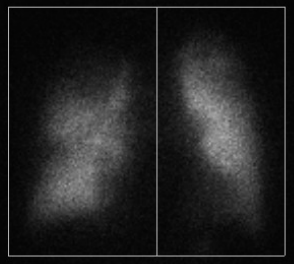
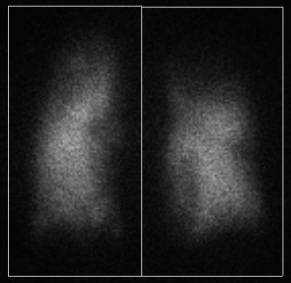
LT LATERAL





ANT PERF

POST PERF

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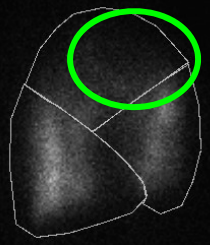


RT LATERAL

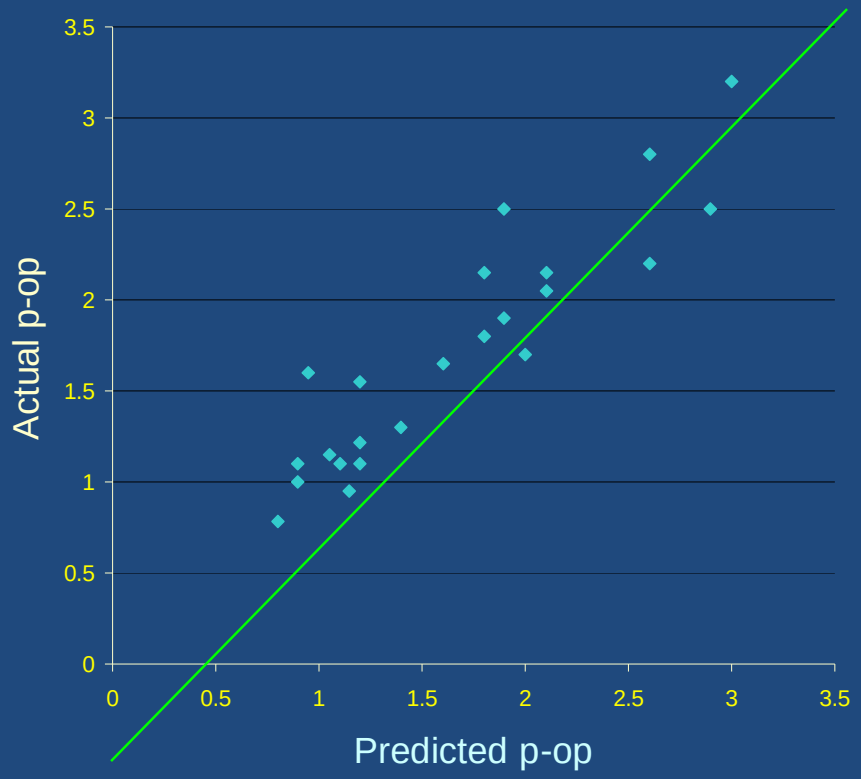
LOBAR PERFUSION	(%) OF TOTAL
RT UPPER LOBE	11.85
RT MIDDLE LOBE	15.76
RT LOWER LOBE	22.71
RT LUNG TOTAL	50.3
LT UPPER LOBE	25.00
LT LOWER LOBE	24.68
LT LUNG TOTAL	49.7

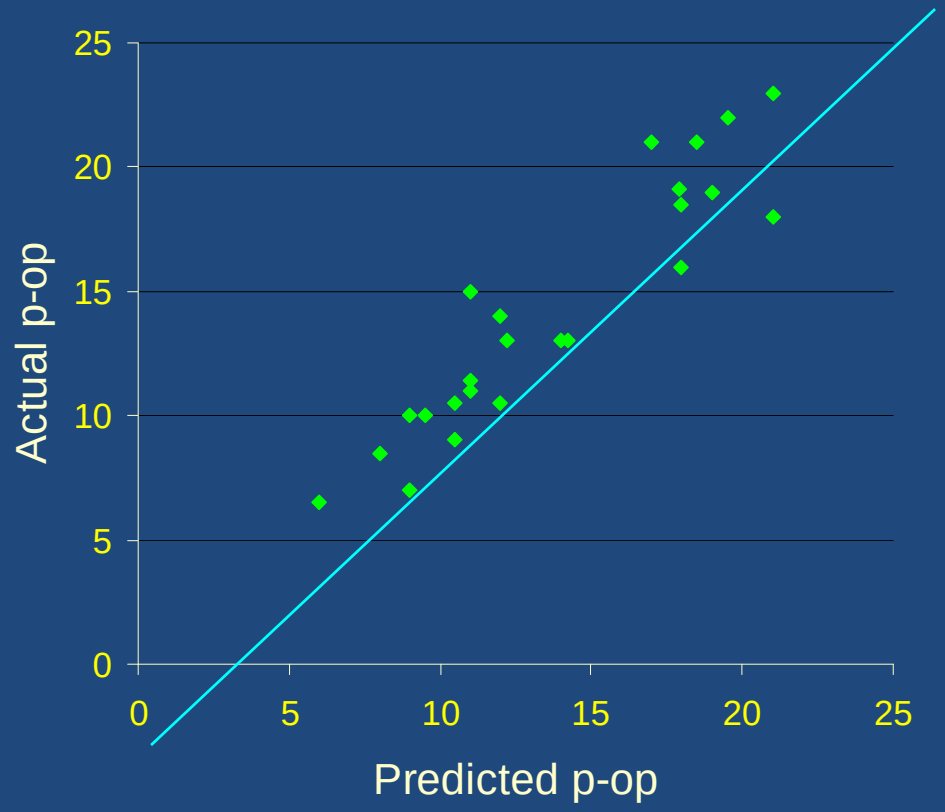
MEMORIAL SLOAN KETTERING CANCER CENTER

FEV_1

R=0.89

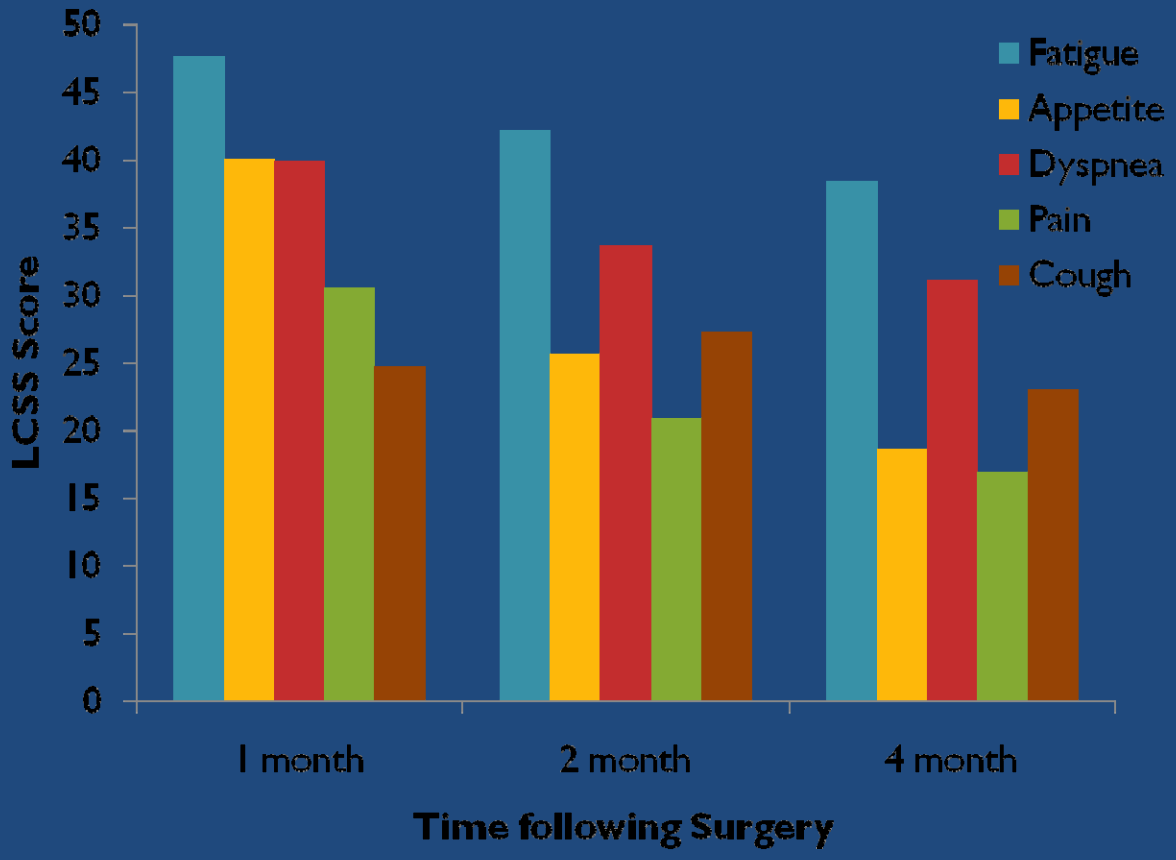
DLCO





Markos, J., et al. (1989). Am Rev Respir Dis 139(4): 902-10.

Lung Cancer Surgery
Symptoms after Resection



Long-term Lung Cancer Survivorship

- Historically, "lung cancer survivorship" considered contradiction in terms.
- Perhaps because of pessimism regarding outcomes, there has not been much research, .
  - Don't know much about chronic deficits.

- With 15-20% overall cure rate…
  - 40,000 patients annually likely to become long-term survivors.

Lung Cancer
Long-Term Respiratory Symptoms

- Sarna, 2004 studied 142 5-year minimum survivors.

Demographic characteristics	
Average Age	71 years
Diagnosis within 10 years	51%
Female gender	54%
Caucasian	83%
Education > high school	72%
Current/former smokers	85%
Medical characteristics	
Stage I	66%
Lobectomy	74%
Adenocarcinoma	59%

Sarna L, et al. Chest 2004; 125:439-45

Lung Cancer
Long-Term Respiratory Symptoms

- 66% had at least one respiratory symptom.
  - 41% had two or more symptoms

- Symptoms more likely if…
  - Exposure to first or second-hand smoke.
  - Used bronchodilators.
  - Moderate-to severe PFT abnormalities
  - More comorbid illnesses

Sarna L, et al. Chest 2004; 125:439-45

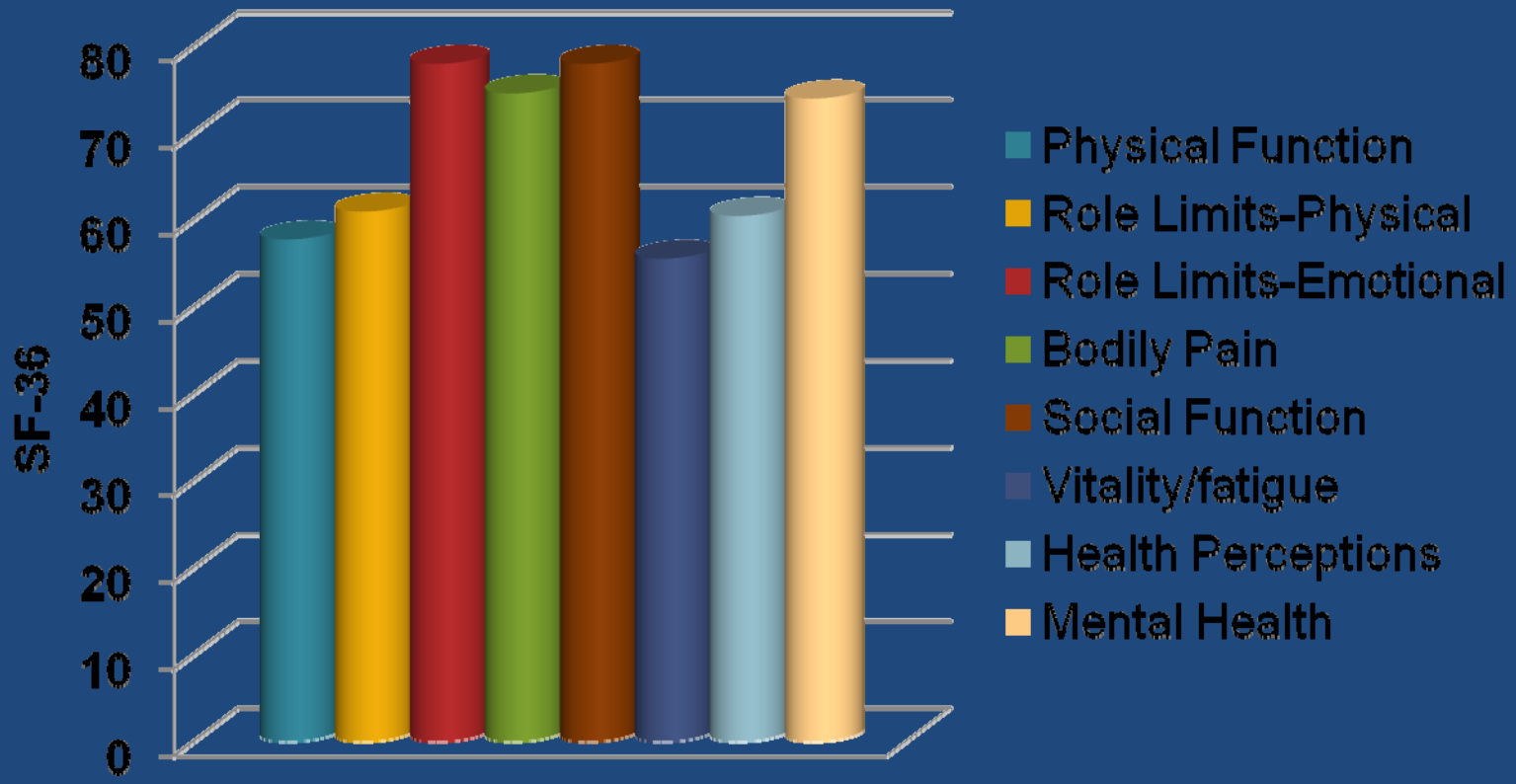
Lung Cancer
Long-Term Respiratory Symptoms

Respiratory Symptoms	No. (%)
Cough	35 (24.7)
> 4 d/wk	29 (20.4)
Morning	28 (19.7)
Day and night	33 (23.2)
> 3 mo	32 (22.5)
Phlegm	40 (28.2)
> 4 d/wk	32 (22.5)
Morning	39 (27.5)
Day and night	33 (23.2)
> 3 mo	32 (22.5)
Cough and phlegm > 3 wk in the past year	28 (19.7)
Wheezing	57 (40.1)
Wheezing with a cold	57 (40.1)
Wheezing apart from colds	43 (30.3)
Wheezing most days and nights	16 (11.3)
Short of breath in past year due to wheezing	21 (14.8)
If yes, > 2 episodes of shortness of breath	20 (95.2)
Shortness of breath	90 (63.4)
Short of breath with hurry	90 (63.4)
Walk slower than people your age because of breathlessness	55 (38.7)
Stop for breath when walking	45 (31.7)
Stop for breath every 100 yards	33 (23.2)
So breathless that can't leave house, or breathless on dressing/undressing	15 (10.6)

Sarna L, et al. Chest 2004; 125:439-45

Lung Cancer

Long-Term Quality of Life (SF-36)



MSKCC Experience

- 359 Lung Cancer Survivors, between one and six years post-treatment.

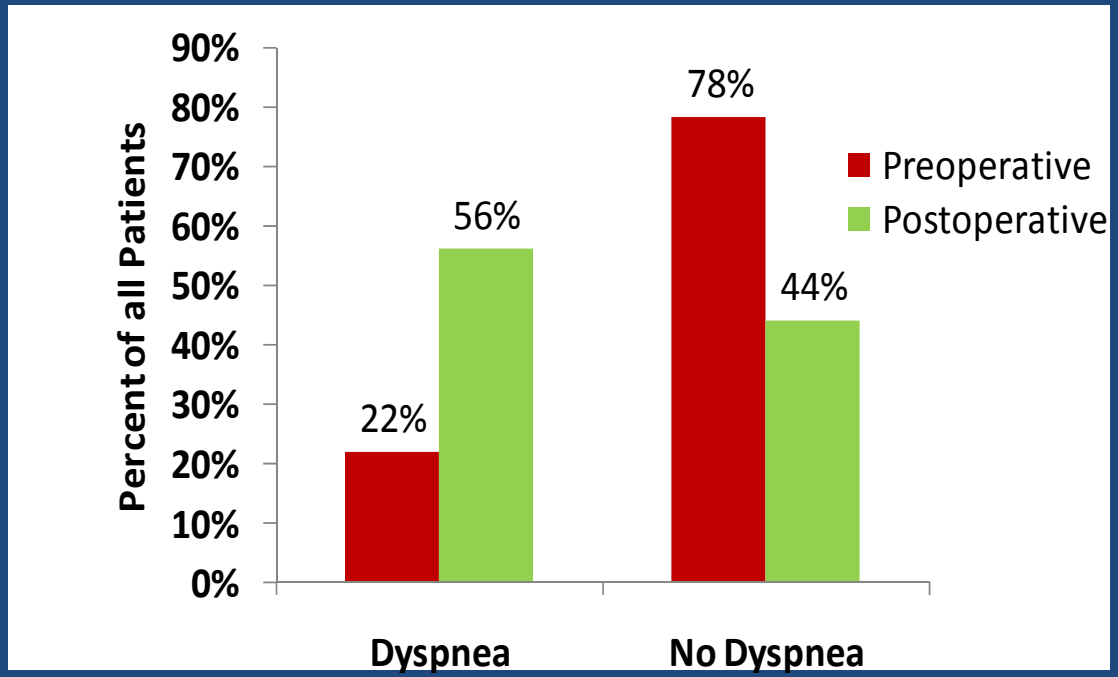
- Inclusion Criteria…
  - Prior diagnosis of stage I non-small cell lung cancer.
  - Undergone surgical resection.
  - Had no evidence of lung cancer at time of recruitment.

MSKCC Experience
Patient Characteristics

Average Age	68.9 years
Male sex (%)	130 (36.2)
Ever smokers (%)	300 (84.5)
Non-Hispanic White (%)	333 (94.7)
Stage Ia (%)	247 (69.2)
Time since surgery (years)	3.5 years
VATS only surgery	64 (18)
Number of medical comorbidities	2.5

MSKCC Experience
Dyspnea

Preoperative Dyspnea	Postoperative Dyspnea: Present	Postoperative Dyspnea: Absent	
Present	77	2	79
Absent	125	157	
	202		



MSKCC Experience
Correlates of Dyspnea

Characteristic	r	p-value
Age	0.14	0.01
Sex (Male)	-0.04	0.50
Greater than HS education	-0.15	0.01
Preoperative dyspnea	0.31	< 0.001
FEV1 %	-0.26	< 0.001
Diffusing capacity %	-0.30	< 0.001
VATS only surgery	0.01	0.88
Presence of cardiac disease	0.06	0.24
Presence of pulmonary disease	0.12	0.02
History of tobacco use	0.14	0.01
Body Mass Index	0.05	0.32
Any mins/wk moderate/strenuous physical activity (currently)	-0.29	< 0.001
Clinically significant symptoms of depression (HADS ≥8)	0.18	0.00
Clinically significant symptoms of anxiety (HADS ≥8)	0.02	0.65

MSKCC Experience
Correlates of Dyspnea

Characteristic	Odds Ratio (95% CI)	p-value
Age	1.02 (0.99 - 1.05)	0.086
Greater than HS education	0.89 (.49 – 1.60)	0.690
Preoperative dyspnea	4.71 (2.10 – 10.69)	< 0.001
FEV1% (for every 10 points)	9.9 (0.98 - 1.01)	0.359
Diffusing capacity %(for every 10 points)	9.8 (0.97 - 0.99)	0.003
Presence of pulmonary disease	0.76 (0.40 - 1.47)	0.421
History of tobacco use	1.57 (0.73 – 3.36)	0.249
Any mins/wk moderate/strenuous physical activity (currently)	0.44 (0.26 – 0.74)	0.002
Clinically significant symptoms of depression (HADS ≥8)	4.40 (1.09 – 17.79)	0.037

MSKCC Experience
Conclusions

- Dyspnea much more common among long-term survivors than previously thought (56%)
- Calls into question whether dyspnea is managed adequately over the long-term.
- Suggests intervention programs for physical activity and depression.

Currently examining other symptoms, such as fatigue.