The Lung Cancer Patient in 2011 – Not the Marlboro Man

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MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

Outline

Epidemiology
Staging and Patterns of Spread
Clinical Presentation
Treatments

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Leading Cancer Sites, Cases 2008

Estimated New Cases*

Male		Female	
Prostate	186,320 (25%)	Breast	182,460 (26%)
Lung & bronchus	114,690 (15%)	Lung & bronchus	100,330 (14%)
Colon & rectum	77,250 (10%)	Colon & rectum	71,560 (10%)
Urinary bladder	51,230 (7%)	Uterine corpus	40,100 (6%)
Non-Hodgkin lymphoma	35,450 (5%)	Non-Hodgkin lymphoma	30,670 (4%)
Melanoma of the skin	34,950 (5%)	Thyroid	28,410 (4%)
Kidney & renal pelvis	33,130 (4%)	Melanoma of the skin	27,530 (4%)
Oral cavity & pharynx	25,310 (3%)	Ovary	21,650 (3%)
Leukemia	25,180 (3%)	Kidney & renal pelvis	21,260 (3%)
Pancreas	18,770 (3%)	Leukemia	19,090 (3%)
All sites	745,180 (100%)	All sites	692,000 (100%)

*Excludes basal and squamous cell skin cancers and in situ carcinoma except urinary bladder.

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Leading Sites of Cancer Deaths 2008

Estimated Deaths

Male		Female	
Lung & bronchus	90,810 (31%)	Lung & bronchus	71,030 (26%)
Prostate	28,660 (10%)	Breast	40,480 (15%)
Colon & rectum	24,260 (8%)	Colon & rectum	25,700 (9%)
Pancreas	17,500 (6%)	Pancreas	16,790 (6%)
Liver & intrahepatic bile duct	12,570 (4%)	Ovary	15,520 (6%)
Leukemia	12,460 (4%)	Non-Hodgkin lymphoma	9,370 (3%)
Esophagus	11,250 (4%)	Leukemia	9,250 (3%)
Urinary bladder	9,950 (3%)	Uterine corpus	7,470 (3%)
Non-Hodgkin lymphoma	9,790 (3%)	Liver & intrahepatic bile duct	5,840 (2%)
Kidney & renal pelvis	8,100 (3%)	Brain & other nervous system	5,650 (2%)
All sites	294,120 (100%)	All sites	271,530 (100%)

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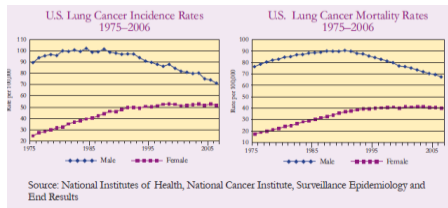
Lung Cancer



Source: National Institutes of Health, National Cancer Institute, Surveillance Epidemiology and End Results

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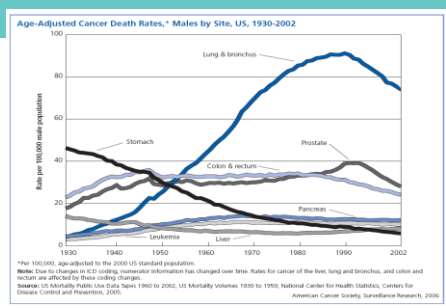

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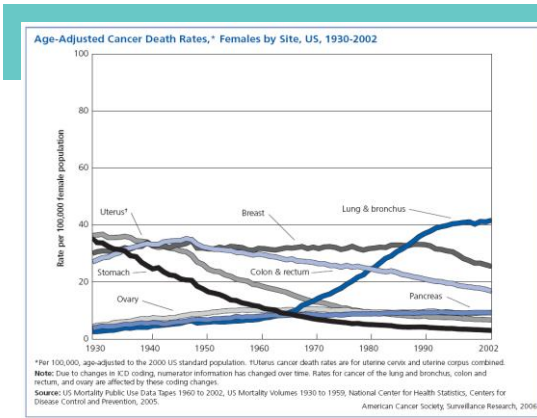

Smoking

- Lung cancer develops 20-30 years after exposure to tobacco carcinogens
- In 2011, about 23% of men smoke (decrease of 50% since 1960s), 18% of women smoke (decrease of 25% since 1960s)

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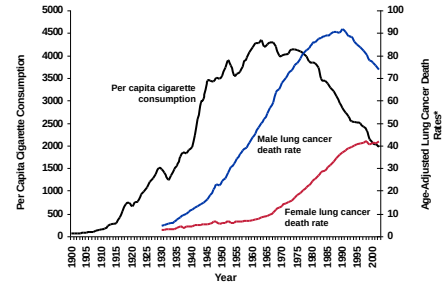
Tobacco Use in the U.S.



*Age-adjusted to 2000 US standard population.
Source: Death rates: US Mortality Public Use Tapes, 1960-2002, US Mortality Volumes, 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2005. Cigarette consumption: US Department of Agriculture, 1900-2002.

Cigarette smoking and lung cancer

Intensity	RR
Non smokers	1.0
1-9 cigarettes/day	3-5
40+ cigarettes/day	18-27
Duration	
Non smokers	1.0
15 yrs smoking	3-5
25 yrs smoking	5-8

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Cigarette smoke carcinogens

Carcinogen class	Compound	Amount in mainstream cigarette smoke, ng/cigarette‡	Sidestream/ mainstream ratio§	Representative lung tumorigenicity in species‖
Polycyclic aromatic hydrocarbons	Benzo[*a*]pyrene	20–40	2.5–3.5	Mouse, rat, hamster
	Benzo[*b*]fluoranthane	4–22		Rat
	Benzo[*j*]fluoranthane	6–21		Rat
	Benzo[*k*]fluoranthane	6–12		Rat
	Dibenzo[*a*,*j*]pyrene	1.7–3.2		Hamster
	Indeno[1,2,3-*cd*]pyrene	4–20		Rat
	Dibenz[*a*,*h*]anthracene	4		Mouse
	5-Methylchrysene	0.6		Mouse
Asz-arenes	Dibenz[*a*,*h*]acridine	0.1		Rat
	7H-Dibenzo[*c*,*g*]carbazole	0.7		Hamster
N-Nitrosamines	*N*-Nitrosodiethylamine	ND–2.8	<40	Hamster
	4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	80–770	1–4	Mouse, rat, hamster
Miscellaneous organic compounds	1,3-Butadiene	20–70 × 10^3		Mouse
	Ethyl carbamate	20–38		Mouse
Inorganic compounds	Nickel	0–510	13–30	Rat
	Chromium	0.2–500		Rat
	Cadmium	0–6670	7.2	Rat
	Polonium-210	0.03–1.0 pCi	1.0–4.0	Hamster
	Arsenic	0–1400		None¶
	Hydrazine	24–43		Mouse

JNCI 1999; 91: 1194-1210

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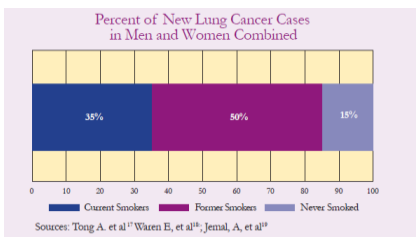
Not all related to smoking..



Sources: Tong A. et al[17] Waren E, et al[18]; Jemal, A, et al[19]

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Non-smokers and lung cancer

- Approx 20-30,000 new cases of lung cancer among non-smokers
- One in 5 women diagnosed with lung cancer have never smoked
- One in 12 men diagnosed with lung cancer have never smoked

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Women

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Women

- Women who have never smoked appear to be at greater risk for developing lung cancer than men who have never smoked.
- Women tend to develop lung cancer at younger ages than men.
- Women are more likely than men to be diagnosed in early stages of lung cancer.
- Women are likely to live longer than men after treatment for the disease.

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Women

- Incidence of Lung cancer has increased six-fold in the last 30 years
- Smoking-
  - Social marketing
  - "Flavoring" cigarettes with menthol
- Hormones- estrogen
- Estrogen Replacement Therapy

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Estrogen

- Studies have found a possible connection between hormones such as *estrogen* and lung cancer development, particularly adenocarcinoma.
- In both men and women, estrogen primarily helps regulate certain functions of the reproductive system, but also is involved in other non-reproductive functions such as cell division and growth.
- Researchers believe estrogen can directly or indirectly promote lung cancer by triggering *estrogen receptors* that are present on non-small lung cancer cells, causing these cells to grow and spread in the lungs.

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Hormone Replacement Therapy

- Women's Health Initiative
- 5 years of combined HRT use and another 3 years of follow-up off the drugs
- risk of *developing* lung cancer was not significantly higher in women taking HRT than in the women who took the placebo
- BUT women who took HRT had an increased risk of dying from lung cancer, especially non-small cell lung cancer
- Some other, less rigorous studies have also looked at a possible link between combined HRT and the risk of lung cancer diagnosis, but the results have been mixed.

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Other Causes- Men and Women

- Asbestos
- Radon
- Arsenic, chromium, nickel, beryllium, cadmium
- DNA mutation

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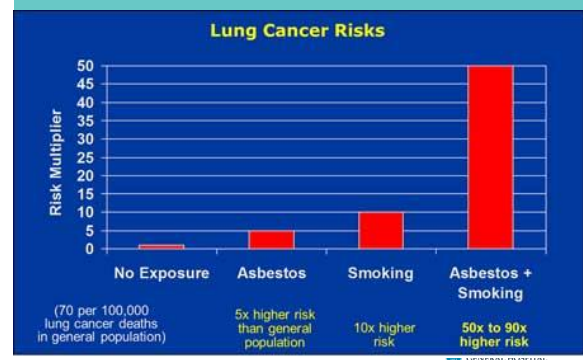
Asbestos

- Exposure associated with many workplace settings- construction, shipyards, railroads, mines, manufacturing plants, auto body repair
- Asbestos exposure in schools, public buildings if damaged
- Can take 10-40 years until symptoms occur
- No “safe” amount of exposure has been recommended



Radon

- Radon is a Class A carcinogen.
- radon is a naturally occurring, colourless, odourless, highly toxic gas
- Radon may seep into your home and, when trapped indoors, may become a serious health hazard
- One in every 15 homes in the US has high radon levels
- The only way to know how much radon you have in your home is to get your home tested

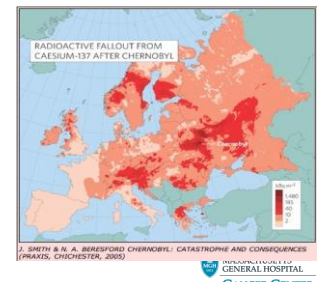
Chernobyl Disaster

April 26, 1986, explosions at of the nuclear power plant at Chernobyl Ukraine, Soviet Union

The nuclear disaster at Chernobyl has produced the biggest group of cancers ever from a single incident

Average morbidity rates for all cancers increased by 39.8%

Thyroid Cancer risk most increased Followed by leukemia, lymphoma, Breast and lung cancer



World Trade Center, NY 9/11

- Asbestos was a major material used in the construction of the World Trade Center
- World Trade Center Health Registry tracking health of more than 71,000 people

September 11, 2000

- **statistics show that cancer rates among those who worked in trade center rubble are in line with rates among the general public.**
- **Three major research efforts tracking the health of ground zero responders have so far failed to turn up evidence linking any type of cancer to the dust.**
- **However, risk of cancer will continue to unfold for the next 1-2 decades.**

DNA Mutations

Gene	Amino acid/cDNA residue	Result
APC	R1114 - 3340C	Wild Type
APC	Q1338 - 4012C	Wild Type
APC	R1450 - 4348C	Wild Type
APC	T1556fs - 4666_4667insA	Wild Type
BRAF	V600 - 1798G	Wild Type
BRAF	V600 - 1799T	Wild Type
CTNNB1(Beta-Catenin)	D32 - 94G	Wild Type
CTNNB1(Beta-Catenin)	D32 - 95A	Wild Type
CTNNB1(Beta-Catenin)	S33 - 98C	Wild Type
CTNNB1(Beta-Catenin)	G34 - 101G	Wild Type
CTNNB1(Beta-Catenin)	S37 - 109T	Wild Type
CTNNB1(Beta-Catenin)	S37 - 110C	Wild Type
CTNNB1(Beta-Catenin)	T41 ? 121A	Wild Type
CTNNB1(Beta-Catenin)	T41 - 122C	Wild Type
CTNNB1(Beta-Catenin)	S45 - 133T	Wild Type
CTNNB1(Beta-Catenin)	S45 - 134C	Wild Type
EGFR	G719 - 2155G	Wild Type
EGFR	T790 - 2369C	Wild Type
EGFR	L858 ? 2573T	Wild Type
EGFR	E746_A750 - 2235_2249del	Mutant
EGFR	E746_A750 - 2236_2250del	Wild Type
EGFR	Exon 19 deletions	Mutant
FLT3	D835 - 2503G	Wild Type
JAK2	V617 - 1849G	Wild Type
KIT	D816 - 2447A	Wild Type
KRAS	G12 - 34G	Wild Type
KRAS	G12 - 35G	Wild Type
KRAS	G13 - 37G	Wild Type
KRAS	G13 - 38G	Wild Type

NOTCH1	L1575 - 4724T	Wild Type
NOTCH1	L1601 - 4802T	Wild Type
NRAS	G12 - 34G	Wild Type
NRAS	G12 - 35G	Wild Type
NRAS	G13 - 37G	Wild Type
NRAS	G13 - 38G	Wild Type
NRAS	Q61 - 181C	Wild Type
NRAS	Q61 - 182A	Wild Type
NRAS	Q61 - 183A	Wild Type
PIK3CA	R88 - 263G	Wild Type
PIK3CA	E542 - 1624G	Wild Type
PIK3CA	E545 - 1633G	Wild Type
PIK3CA	Q546 - 1638C	Wild Type
PIK3CA	Q546 - 1637A	Wild Type
PIK3CA	H1047 - 3139C	Wild Type
PIK3CA	H1047 - 3140A	Wild Type
PIK3CA	G1049 - 3145G	Wild Type
PTEN	R130 ? 388C	Wild Type
PTEN	R173 - 517C	Wild Type
PTEN	R233 - 697C	Wild Type
PTEN	K267fs - 800delA	Wild Type
TP53	R175 - 524G	Wild Type
TP53	G245 - 733G	Wild Type
TP53	R248 - 742C	Wild Type
TP53	R248 - 743G	Wild Type
TP53	R273 - 817C	Wild Type
TP53	R273 - 818G	Wild Type
TP53	R306 - 916C	Wild Type

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- What is it? *Tissue diagnosis*
- Where is it? *Staging*

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Lung Cancer Histologies

- Non-small cell lung cancer (87%)
  - Adenocarcinoma
  - Squamous cell carcinoma
  - Large cell carcinoma
  - BAC
  - NSCLC NOS
- Small cell lung cancer (13%)

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Staging and Patterns of Spread

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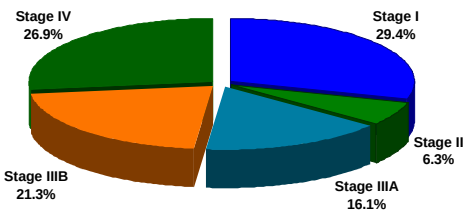
US Incidence of NSCLC by Stage



- 48.2% of new patients with NSCLC are diagnosed with late stage (IIIB and IV) disease

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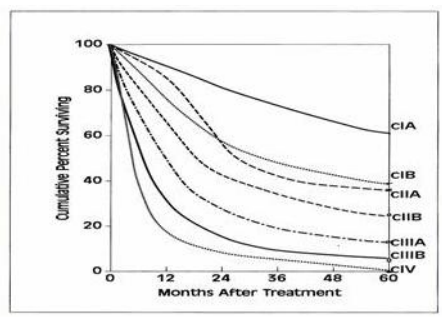
Survival by Stage for NSCLC



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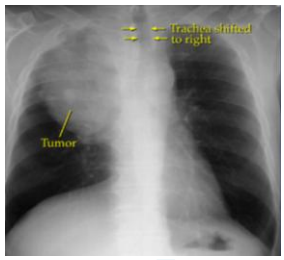
Screening???



Lung Cancer Screening

- CT scan and CXR are the only tools
- Goal would be to find lung cancer earlier
  - 70 % of patients with stage I lung cancer live 5 years
  - CT scans are effective at detecting stage I lung cancer
- Screening incidentally decreases smoking- 23% of patients that go through screening quit!

Screening- Cons

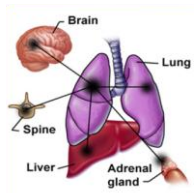
- Who should be screened?
- Critics argue that screening may increase survival time (the period between diagnosis and death), because a tumor is detected earlier, without reducing death rates from the disease
- repeated exposure to CT scans over a period of years may result in high levels of radiation exposure
- some nodules detected through screening may not become clinically significant, causing patients unnecessary risk, anxiety, cost and intervention.

Clinical Presentation

Clinical Presentation – Local Symptoms

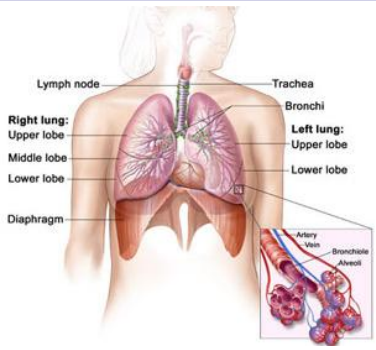
Cough	45-75%
Dyspnea	30-40%
Hemoptysis	25-50%
Chest pain	25-50%
Hoarseness	2-20%

Clinical Presentation – Systemic Symptoms

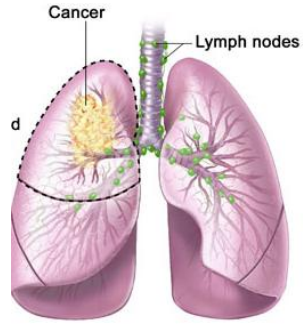


- Brain
  - Headache
  - Nausea/vomiting
  - Seizures
  - Confusion
- Bone
  - Pain
  - Cord compression
  - Compression fracture/pathologic fracture
- Liver
  - Jaundice
  - Nausea

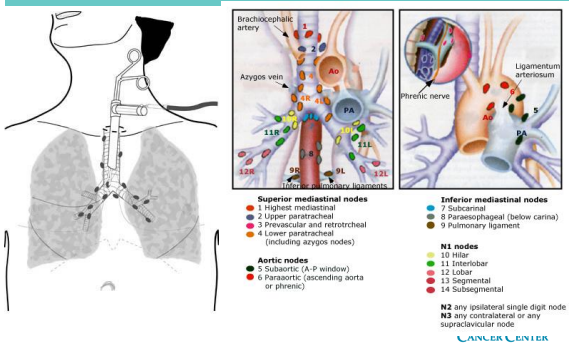
Patterns of Spread: Local



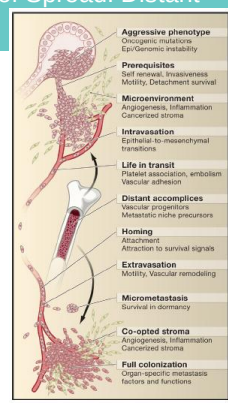
Patterns of Spread: Lymphatic



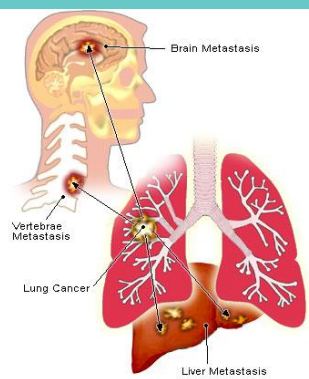
Surgical staging of lymph nodes



Patterns of Spread: Distant



Cell 2006; 127: 679-95



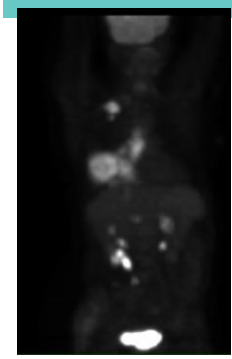
Pleural Effusion

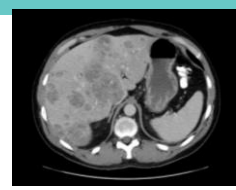
- Fluid in lung (s)
- Patient usually with shortness of breath
- Fluid can have cancer cells
- Removed with “Tap” Thoracentesis or pleuredesis

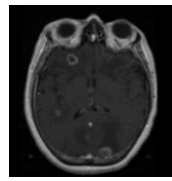
Staging Studies

- Chest CT with liver and adrenal cuts
- Brain imaging
- PET scan
- Bone scan
- Mediastinoscopy
  - Cervical mediastinoscopy
  - Chamberlain

Stage IV Non-small Cell Lung Cancer







Paraneoplastic syndromes

Anorexia, cachexia, weight loss

Hypercoagulability

Hypercalcemia

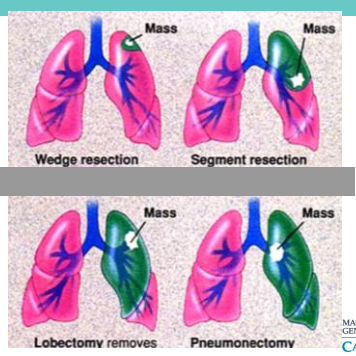
Hyponatremia – ADH production

Cushing's syndrome – ectopic ACTH production

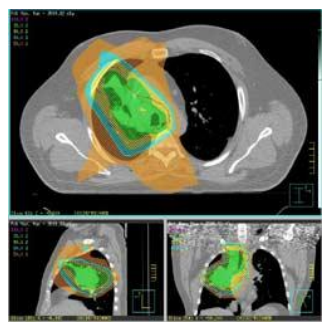
Neurologic and dermatologic syndromes

Treatments

Surgical Options in Lung Cancer



Radiation



Chemotherapy

- Standard cytotoxic chemotherapy (act broadly to kill all fast-growing cells — killing malignant and healthy cells)
- Targeted therapy (block the production of proteins that make cancers grow)
- Clinical trials
  - Standard chemotherapy
  - Targeted therapy
  - Combination of standard and targeted therapy

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Metastatic Lung Cancer

Not curable

Median survival of 8-10 months and a 1 year survival of 30-40%.

Use of chemotherapy for advanced NSCLC has become standard of care.

There have been a number of trials comparing chemotherapy v BSC which have demonstrated both a survival and quality of life advantage.

Goals are to prolong survival and palliate symptoms to improve quality of life

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Standard Chemotherapy- First line

Stratification Variables
Performance status: 0 or 1 vs. 2
Weight loss in previous 6 mo: <5% vs. >5%
Disease stage: IIIB vs. IV or recurrent disease
Presence or absence of brain metastases

Regimens
Cisplatin plus paclitaxel
paclitaxel, 135 mg/m² over 24-hr period on day 1
cisplatin, 75 mg/m² on day 2
3-wk cycle
Cisplatin plus gemcitabine
gemcitabine, 1000 mg/m² on days 1, 8, and 15
cisplatin, 100 mg/m² on day 1
4-wk cycle
Cisplatin plus docetaxel
docetaxel, 75 mg/m² on day 1
cisplatin, 75 mg/m² on day 1
3-wk cycle
Carboplatin plus paclitaxel
paclitaxel, 225 mg/m² over 3-hr period on day 1
carboplatin, AUC 6.0 mg/ml/min on day 1
3-wk cycle

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Standard Chemotherapy

	Response rate	Median survival	1 year survival
Cis/tax	21%	7.8	31%
Cis/gem	22%	8.1	36%
Cis/taxotere	17%	7.4	31%
Carbo/tax	17%	8.1	33%

Schiller, NEJM, 2002

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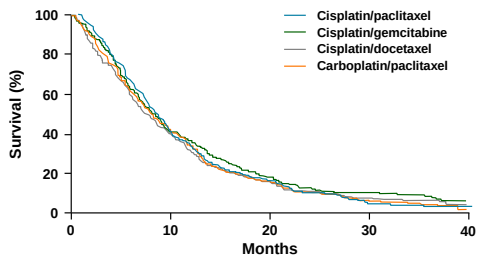
Doublet Regimens



ECOG 1594 demonstrated no clear difference between various doublet chemotherapy combinations

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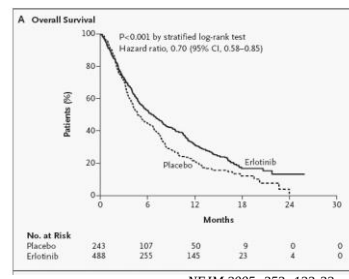
Erlotinib in previously treated NSCLC



NEJM 2005; 353: 123-32

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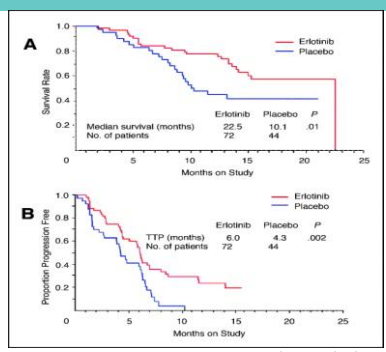
TRIBUTE: never smoker sub-group



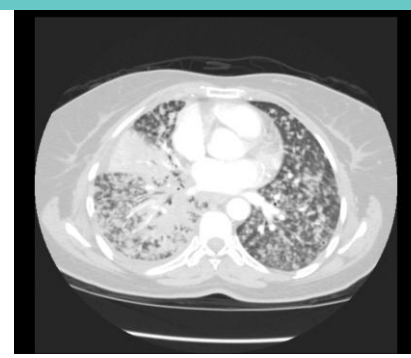
Herbst, R. S. et al. J Clin Oncol; 23:5892-5899 2005

Erlotinib

- Targeted agent
- Pill- take daily at home
- Side effects- rash, diarrhea
- 10-15% patients with great response
  - Women, non-smokers, Asian ethnicity, adenocarcinoma (BAC)
- 20% patient with stable disease

Typical Erlotinib Rash

49 year old never-smoker



After two months on erlotinib

Predictors of response to Erlotinib

- Clinical
  - Female
  - Never smokers
  - Adenocarcinoma
  - Asian
- Pathological
  - Mutation in the EGFR gene

Crizotinib

- works by blocking the anaplastic lymphoma kinase (ALK) protein, a genetic abnormality believed to promote tumor growth found in about 5% of non-small-cell lung cancer patients
- The abnormality is most common in nonsmokers and younger patients

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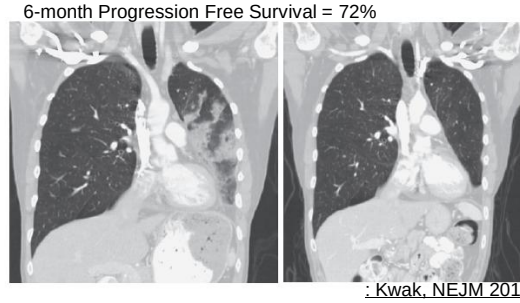
Crizotinib

Overall Response Rate 57%
Stable disease 33%
6-month Progression Free Survival = 72%



: Kwak, NEJM 2010

Crizotinib

- Not yet FDA approved
- Pill form- taken BID
- Side effects include visual disturbances, peripheral edema, nausea, vomiting, diarrhea, constipation

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Problems with Targeted Therapies

- ? Patient compliance
- Cost
- Resistance

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Summary

- Lung cancer is the leading cause of cancer-related mortality in the United States
- Vast majority of cases are related to cigarette smoking
- Clinical presentation of lung cancer is related to signs and symptoms from local extension and distant metastases
- New directions in treatment include targeted therapies and tailoring chemotherapies to individual profiles

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