



Lung Cancer Clinical and Biological Correlation


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Objectives


- Review lung cancer presentation/risk factors
- Review molecular and clinical staging
- Discuss less invasive trends
- Targeted therapy



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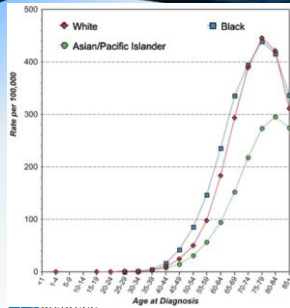
History and Risk Factors

- Typically Males in 6th or 7th Decade
 - Prognosis worse if presents < 50
- High Risk Occupations/Activities
 - Uranium Miner-- especially smokers
 - Radon (other miners) 1.5 – 4x / 100 months
 - 21,000 lung cancer deaths per year
 - Chlormethyl ether workers
 - Cigarette Smoking, benzopyrene
 - Asbestos exposure- synergistic with smoking


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Lung cancer Rates by Age/Race



•Genes & Cancer 2012
3(7-8) 467-480

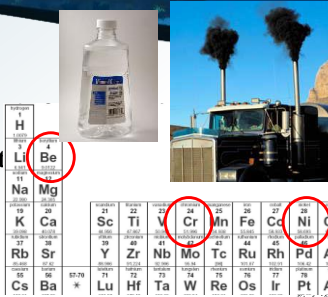


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Other Risk Factors

- Beryllium
- Chromium
- Nickel
- Diesel exhaust
- Mineral oil
- Silica
- Vinyl chloride



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Demographics 2017

New cases
222,250

Deaths
155,870

Males		Females	
Prostate	161,360 19%	Breast	252,710 30%
Lung & bronchus	116,990 14%	Lung & bronchus	105,510 12%
Colon & rectum	71,420 9%	Colon & rectum	64,010 8%
Urinary bladder	60,490 7%	Uterine corpus	61,380 7%
Melanoma of the skin	52,170 6%	Thyroid	42,470 5%
Kidney & renal pelvis	40,610 5%	Melanoma of the skin	34,940 4%
Non-Hodgkin lymphoma	40,080 5%	Non-Hodgkin lymphoma	32,160 4%
Leukemia	36,290 4%	Leukemia	25,540 3%
Oral cavity & pharynx	35,720 4%	Pancreas	25,700 3%
Liver & intrahepatic bile duct	29,200 3%	Kidney & renal pelvis	23,380 3%
All Sites	836,150 100%	All Sites	852,630 100%

•Cancer Facts and Figures 2017, www.cancer.org



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Symptoms-Intrathoracic

- **Pulmonary**
 - Cough - 75%
 - Hemoptysis - 33% (range 6 - 52%)
 - Dyspnea - 60%
 - Fever - 22%
 - Chest pain - 50%
- **Extra Pulmonary**
 - Pleural effusion - Poor prognosis
 - Recurrent Nerve - Hoarseness 1-8%
 - SVC Syndrome - 5%
 - Dysphagia 1-5%



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Symptoms-Extrathoracic

- **Extra Thoracic**
 - Hypertrophic pulm. osteoarthropathy 4-12%
 - Synovitis- resolves with tumor resection
 - Cervical Lymph Node Mets - 15-20%
 - Bone Pain 1-2%
 - CNS Sx 3-6%
- **Non-specific**
 - Weight loss 60%
 - Weakness
- **Hormonal**
 - Oat cell Cushing
 - ADH Adeno or poorly diff
 - Parathormone, Hypercalcemia SCCA



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History and Physical

- Asymptomatic - 10%
- Others
 - Neuromyopathies (Eaton-Lambert) Oat Cell
 - Dermatoses
 - Vascular
 - Hematologic



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Overall Results

- 95% mortality in 1yr if untreated
- Overall survival in all patients 17% 5yrs
- 5yr survival 25-35% for surgically resectable patients
- Females do slightly better
 - 53 vs 46% Early stage
 - 17 vs 14% All stages



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The relative risk of 1 ppd Smoking is ?

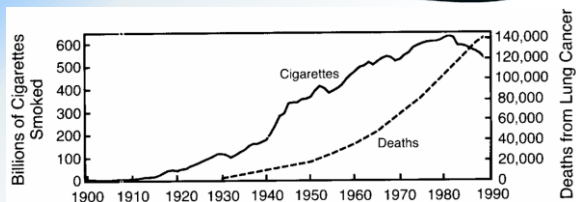
- A. 5 x non-smokers
- B. 10 x
- C. 20 x
- D. 30 x
- E. 70 x



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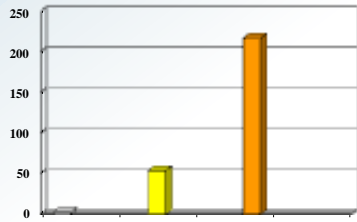
Smoking and Lung CA



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Incidence (per 100,000)



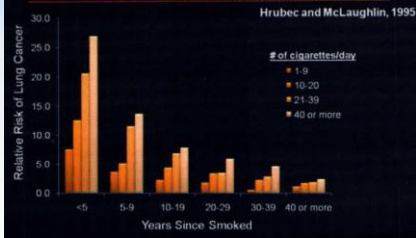
Non-Smoke 1 PPD 2 PPD

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Smoking and Lung CA

Risk of Lung Cancer Continues, But Declines, Over Time Since Quitting

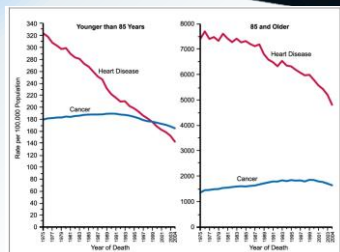


•Int J Cancer. 1995 Jan 17;60(2):190-3

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Smoking and Lung CA

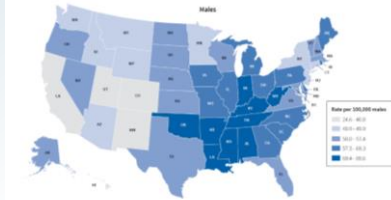


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Geographic Variation

Figure 5. Geographic Patterns in Lung Cancer Death Rates* by State, US, 2010-2014



Cancer Facts and Figures 2017, www.cancer.org

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Oncogenesis and Smoking

- Chromosome
 - 3p, 5q, 9p, 13q, 17p
- Increased neuroendocrine cells
 - Chronic bronchitis
 - Emphysema
 - Bronchiectasis
 - Hypoxia
 - Nitrosamines



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Low Smoking Exposure

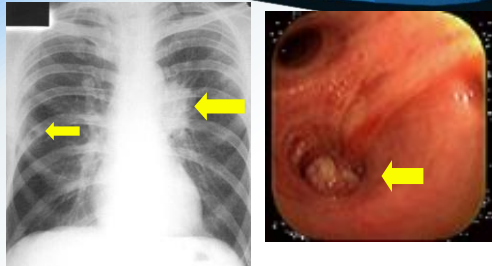
- Mutations TK domain of EGFR
- Adenocarcinomas
- Well Differentiated
- Women > Men
- Non-smokers



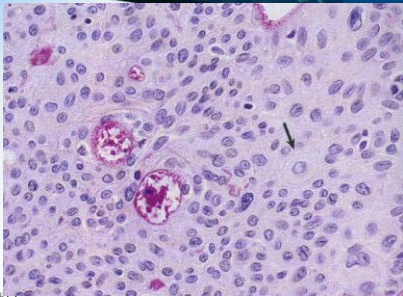
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VATS for Diagnosis & Staging Lung Cancer



Squamous Cell Carcinoma

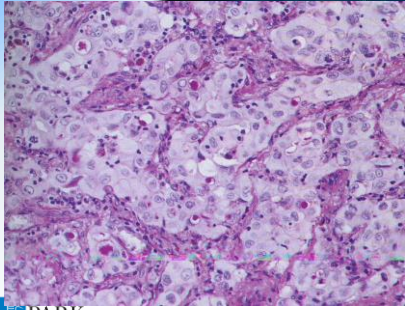


Pathology

- SCCA - about 40%, formally most common
 - Prolonged smoking
 - Central - 2/3
 - Frequent mets to hilar, mediastinal, and supraclavicular lymph nodes
 - Less frequently to brain/bone than adeno
 - Tend to be large



Adenocarcinoma



- Acinar (Berry) Pattern, most common

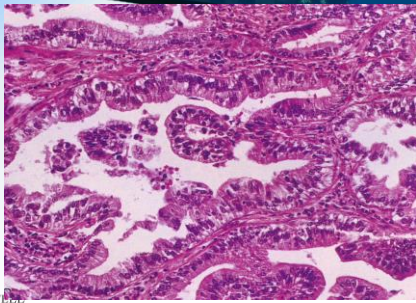


Pathology

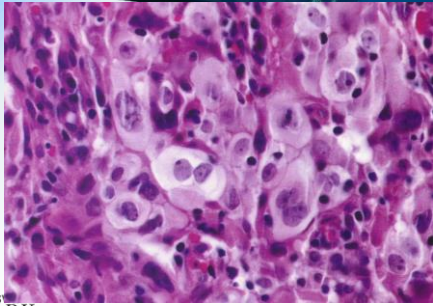
- Adeno CA - About 45%, Most common histology
 - Peripheral
 - More common in females
 - Tend to met to liver, brain, bone, adrenals, lymph nodes



Bronchoalveolar Carcinoma



Large Cell Carcinoma



Primary Lung Cancer

Parameter

Incidence

Sex

Age(yr)

Location

Growth

Curability

• **NSCLC**

• >80% of Lung Ca

• M:F = 2:1

• 60s

• AdenoCA, peripheral-
Epidermoid, central

• Variable, 40% slow

• Good for Stage 1; poor for
advanced

• **SCLC**

• <20% of Lung
Ca

• M:F = 2:1

• 60s

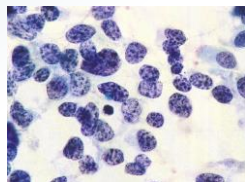
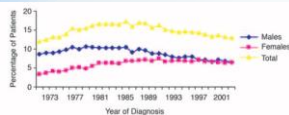
• Mostly central

• Usually rapid

• Usually
advanced and
poor



Small Cell Carcinoma



Growth factors

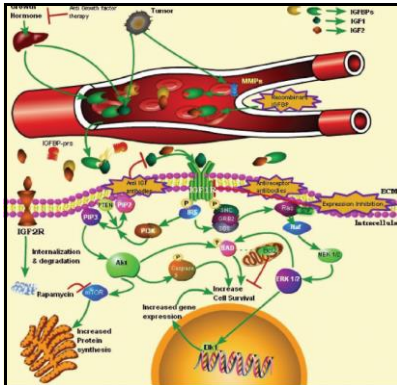
- **Gastrin release peptide**
 - Carcinoid to SCLC
 - **Neuromedin**
 - **Bombesin**
 - 30% SCLC, 5% NSCLC
 - **Arginine vasopressin**
 - Only SCLC
- Also increased receptors



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Insulin-like GF



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Oncogenes, -myc

- **c-,n-,l-**
- **Common in 20-25% SCLC**
- **only 10% c-myc NSCLC**
- **Worse survival**
- **Can be a mosaic in same tumor**



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Tumor Suppressor Genes

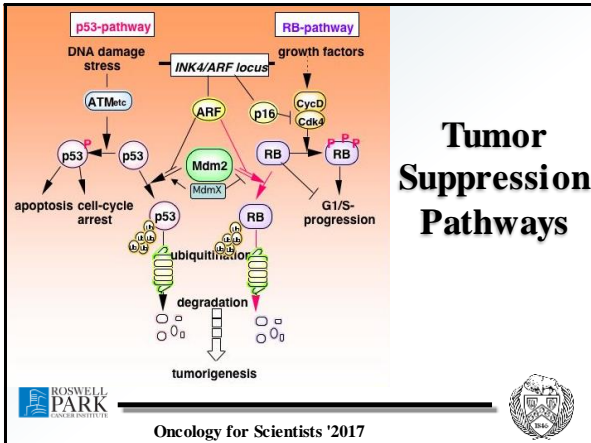
- **Chromosome 3p**
 - Segment loss early in carcinogenesis – All histologic types.
 - 70-80% have deletions
 - Correlates with histo for NSCLC
 - More losses in Squamous
 - Transfer of 3p stops carcinogenesis
 - **3p14 FHIT (fragile histidine triad)**



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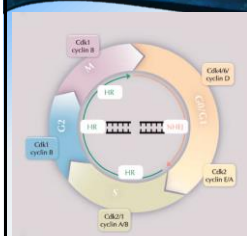
Tumor Suppression Pathways



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Other Cell Cycle Genes



Mitotic/cyclin inhibitors. NHE1, non-homologous HR, homologous recombination.

- **p16 - aka INK4 α**
 - Cyclin D1-Rb cell cycle pathway
 - Inactivated in >40% NSCLC
- **Cyclin D1**
 - Overexpressed in 25-60% NSCLC
- **Cyclin E**
 - SCCA > Adeno.ca



• J Thorac Oncol. 2015;10: S1–S63

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Tumor Suppressor Genes Retinoblastoma - Rb

- Rb protein absent in large cell neuroendocrine
- 70-80% SCLC
 - Transfer slows tumor
- 24-40 % NSCLC
 - No survival significance



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Tumor Suppressor Genes Tp53

- Most common Cancer mutation
- 75% SCLC, 50% NSCLC
- > 500 mutations
- Diversity of mutation higher in lung Ca compared to other malignancies
 - G:C → T:C rather than
 - G:C → A:T
- Correlates with quantity of cigs

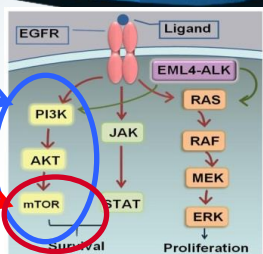


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Tumor Suppressor Genes Other

- PTEN
- *LKB1* (also known as STK11)



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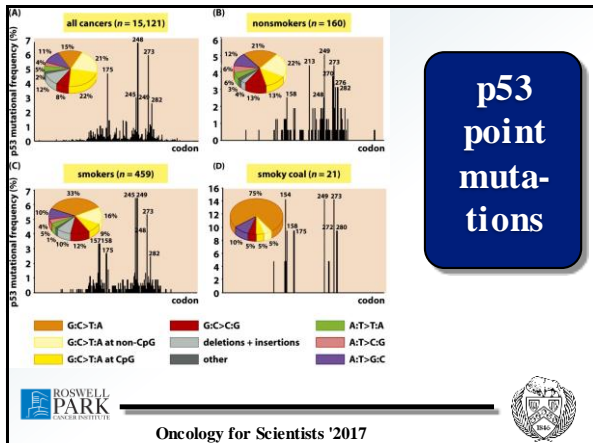
Tumor Suppressor Genes Other

- **Reduced by 3p21 deletion**
 - *RASSF1A, FUS1, SEMA3B, and SEMA3F*
- **Reduced by Promoter Hypermethylation**
 - *p16INK4a, MGMT, DAPK, RASSF1A, FHIT, and TIMP3*



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Receptor Tyrosine Kinase

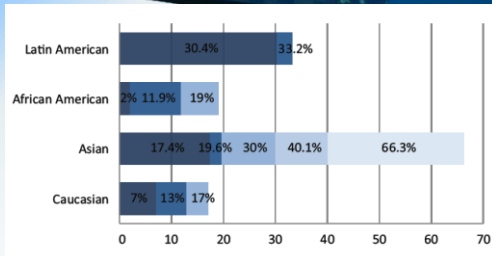
- ErbB-1 to 4 receptor aka HER
- EGFR (HER1) Overexpression
 - Small Cell 0-5%
 - Adeno & Lrg Cell 40-60%
 - Squamous 60-85%
- But EGFR Mutations Rare in Squamous



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EGFR Mutations By Race

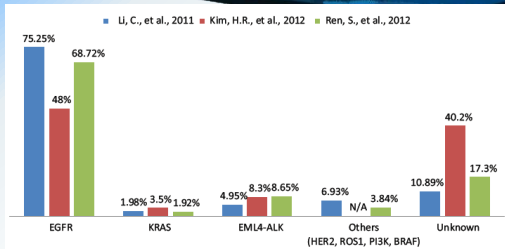


Genes & Cancer 3(7-8) 467-480

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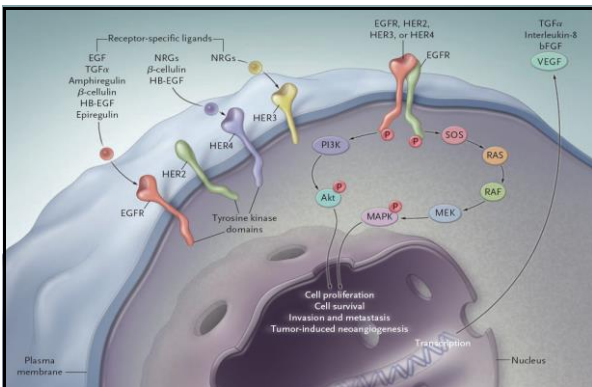
EGFR Mutations in Asian Never Smoker with Adenocarcinoma



Genes & Cancer 2012 3(7-8) 467-480

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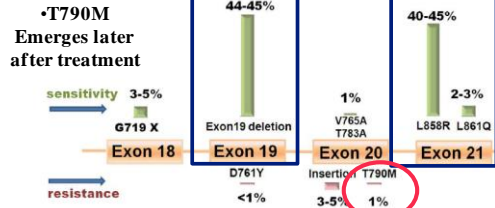


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Frequency of EGFR Mutations and Effect on Therapy

One of most common actionable genes



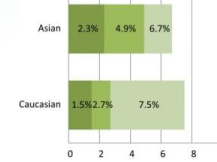
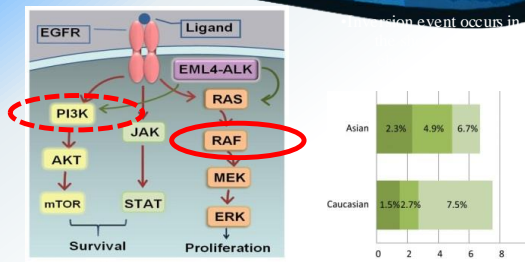
•T790M Emerges later after treatment

Roswell Park Cancer Institute
Int. J. Mol. Sci. 2012, 13, 11471-11496
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EML4/ALK fusion gene

One of most common actionable genes



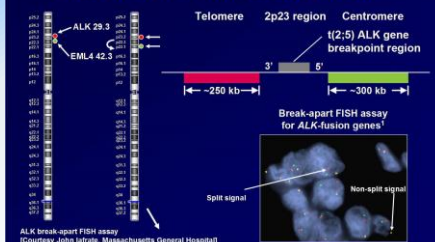
Roswell Park Cancer Institute
Int. J. Mol. Sci. 2012, 13, 11471-11496
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EML4/ALK fusion gene

One of most common actionable genes

FISH Assay for ALK Rearrangement*



*Assay is positive if rearrangements can be detected in ≥15% of cells
 *Shaw AT et al. J Clin Oncol 2009;27:4247-4253

Roswell Park Cancer Institute
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Oncogenes, k-ras

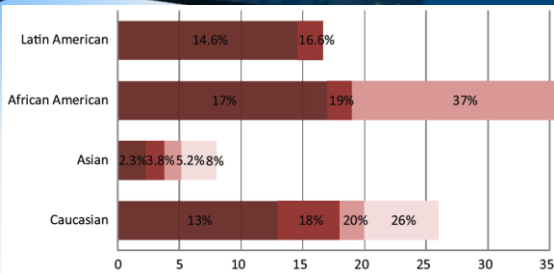
- h-, k-, n-
 - k most common 90%
- mutation in 20% NSCLC
 - 25-40% adenoca
 - 9% Squamous
- 0% SCLC
- **Reduced survival**
- **Smoking increases k-ras**
- **Precedes mets**
- **Blocks EGFR therapy**
- **Rare to occur with EGFR mutation**



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Kras Mutation by Race

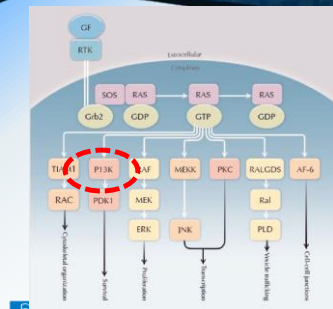


Genes & Cancer 2012 3(7-8)467-480

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KRAS Mutant (12p12.1)



- **Mutations increase intrinsic GTP activity which drives multiple pathways**
- *J Thorac Oncol.* 2015;10: S1-S63



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Telomerase

- **Activity**
 - benign lung pathology - 6.1%
 - Lung cancer - 69.5%
- **High levels and telomere attrition correlate**
 - with advanced stage
 - **With poor prognosis**



Increased Survival

Higher Expressions of

- Bcl-2
- a-catenin
- c-catenin
- FHIT
- ERCC1
- RANIES
- p16

Lower Expression of

- MCM2



Decreased Survival

•Ann Surg Oncol (2012) 19:669–676

Higher Expressions of

- p18Sc-erbB2* (HER2/neu)
- Ki-67
- Cyclin A
- Cyclin B1
- Cyclin E
- VEGF
- HGF/Met
- Carbonic anhydrase IX
- MMP-2, MMP-9
- PTEN
- EGFR with increased HER2-neu
- MUC1/SP-A ratio
- PCNA
- BRCA1

Lower Expression of

- E-cadherin
- p16^{INK4A}
- p27^{Kip}
- β -catenin

Mutations of

- KRAS codon 12
- P53



Lung Chemotherapy Predictors if Increased

•Ann Surg Oncol (2012) 19:669–676

Sensitivity/Benefit	Chemotherapy	Resistance
DYRK2	Cisplatin	ERCC1, BRCA1
	Etoposide, Bleomycin	BRCA1
BRCA1	Paclitaxel	Class III beta tubulin
BRCA1, MDR1 polymorphism	Vinorelbine	
hENT1	Gemcitabine	RRM1, dCK



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EGFR Inhibitor Effectiveness

Higher Expressions Increases Response

- pEGFR, pAKT, pSTAT3
- ERBB3
- High serum SP-D levels

Higher Expression Decreases Response

- pErk

Mutations of

- EGFR and copy number (Enhance)
- KRAS (Resistance)



•Ann Surg Oncol (2012) 19:669–676

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Miscellaneous predictors of survival

- Microvessel count
- MMP (matrix metalloproteinases)
- Urokinase plasminogen activator
- rtPCR assay for CEA in lymph nodes (upstages in 50%)
- Histologic Patterns
- Radiographic (CT) Image analysis



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Women and Lung Cancer

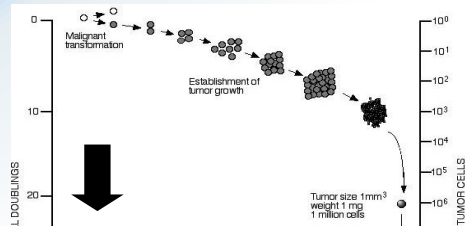
- higher level of female lung cytochrome P4501A1 (CYP1A1) gene expression → bulky DNA adducts
- decreased DNA repair capacity
- increased K-ras gene mutations
- novel estrogen receptor beta



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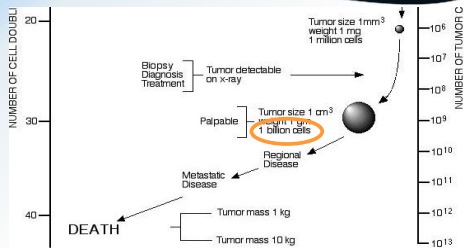
Tumor Growth I Stepwise Model



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Tumor Growth II Stepwise model



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Nodule Size and Cancer Risk

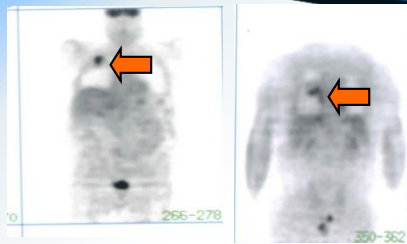
- ≤ 2 cm - 43%
- > 2 cm - 80%
- > 3 cm - $> 90\%$



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PET Scan Imaging



- 97% Sensitive
- 78% Specific
- > 1 cm



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Market Expansion in Lung Nodules

Entry Criteria for the NLST

Parameter	Criterion
Eligibility	
	Age 55-74 years
	30 or more pack-years of cigarette smoking history (pack-years = packs per day \times years smoked)
	Former smokers: quit smoking within the previous 15 years
	Ability to lie on the back with arms raised over the head
	Signed informed consent form



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NLST Schema Screening Study

•N=53,500
•Randomized

•Low Dose CT
•Annual x 2

→

•354 Deaths

•Chest
Roentgenogram
•Annual x 2

→

•442 Deaths

•20% MORTALITY Reduction

•Radiology: Volume 258: Number 1—January 2011

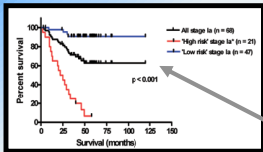
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Duke Multivariate Model

Factor	Action	Women	Men & SqCA	Adeno Ca
P53	Apoptosis	***		*
Factor viii	Angiogenesis	*		*
Erb-b2	Growth regulation		*	
CD-44	Adhesion	*		*
Rb	Cell cycle	*		

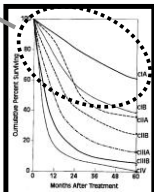
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Survival by Stages



Percent survival vs Survival (months)

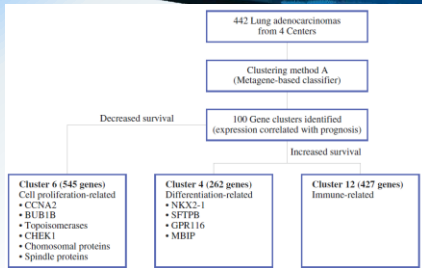
•Gene Expression Array, Potti, NEJM 2006



Cumulative fraction survival vs Months After Treatment

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Metagene Systems



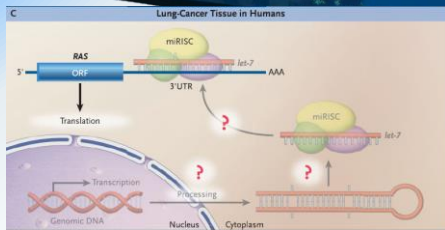
•Ann Surg Oncol (2012) 19:669–676



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MicroRNA in Lung Cancer



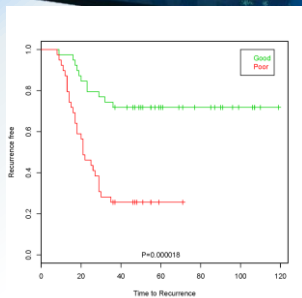
N ENGL J MED 352:3 WWW.NEJM.ORG JUNE 9, 2005



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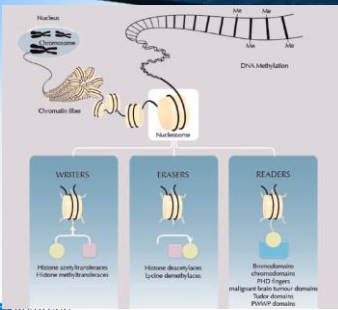
MicroRNA in Lung Cancer



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Epigenetic Therapy of Lung Cancer



• *J Thorac Oncol.*
2015;10: S1–S63

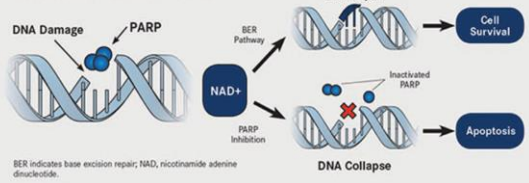


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DNA Repair

PARP Mechanism and Inhibition



• Poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP)
• 17 protein family aiding DNA repair.

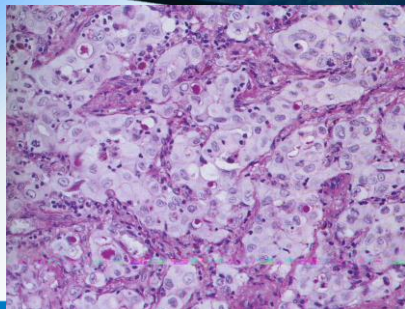
• *J Thorac Oncol.*
2015;10: S1–S63



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Adenocarcinoma



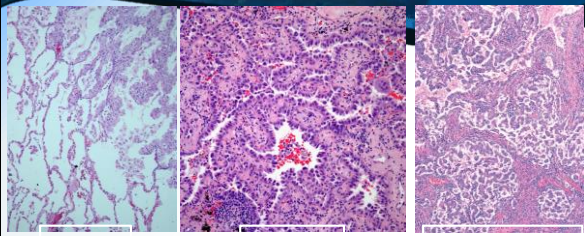
• Acinar (Berry) Pattern, most common



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Histology Risk Adenocarcinoma Classification



•Lepidic •Papillary •Micropapillary

→ Worse prognosis

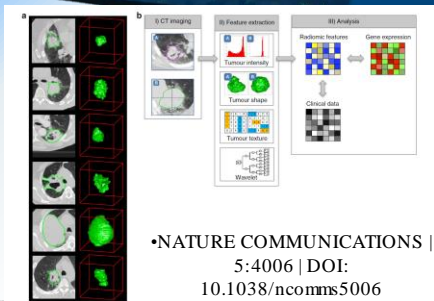
•Other types: Acinar and Solid



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“Radiomics”



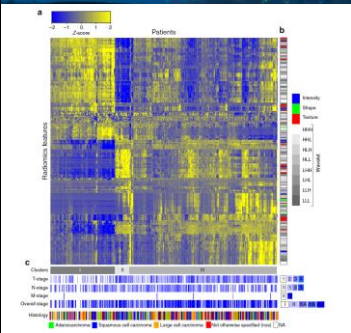
•NATURE COMMUNICATIONS | 5:4006 | DOI: 10.1038/ncomms5006



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“Radiomics”



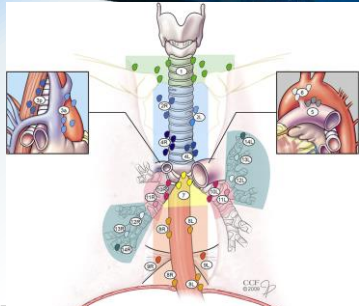
•NATURE COMMUNICATIONS | 5:4006 | DOI: 10.1038/ncomms5006



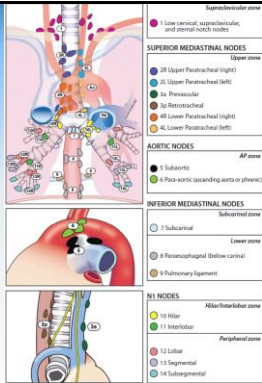
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N Status



Lymph Nodes



Mediastinoscopy

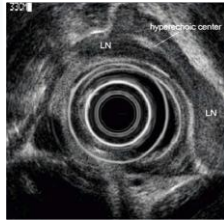


Competing/Complementary Staging Technology

- EBUS



- EUS



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Navigational Bronchoscopy

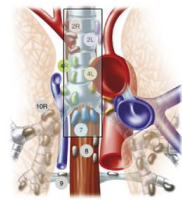


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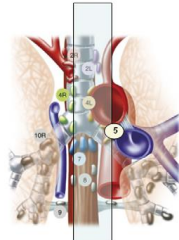


Various Surgical Staging Methods Comparative Anatomic Access

Cervical mediastinoscopy
EBUS-TBNA



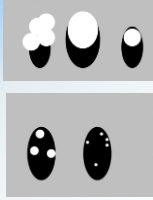
EUS-FNA



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Limitation of FNA (EUS) EUS-FNA sensitivity



	N	True positive	False negative	Sensitivity (%)
LN size				
Normal	59	7	9	43.8
Enlarged	49	25	7	75
Bulky disease	12	11	1	91.7
Tumour location				
Right	64	16	16	50
Left	46	23	1	95.6
Lymph node station				
7	96	29	7	80.6
5/6	35	15	4	78.9
4R	66	5	16	23.8
4L	49	3	9	25



Sur J Cardiothoracic Surgery 33 (2008) 1124–1128



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Nodal Status



- NX- Can't Assess
- N0- No regional nodes**
- N1- Peribronchial**
- N2- Ipsilateral mediastinal
- N3- Contralateral mediastinal



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Nodal Status



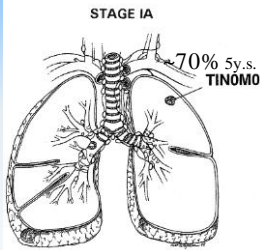
- NX- Can't Assess
- N0- No regional nodes
- N1- Peribronchial
- N2- Ipsilateral mediastinal**
- N3- Contralateral mediastinal



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Stage I Tumors < 30 % of presentations



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Minimally Invasive Lobectomy

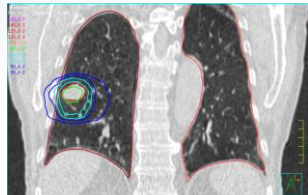
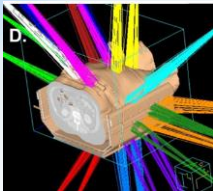


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Minimally Invasive Stereotactic Ablative Radiotherapy

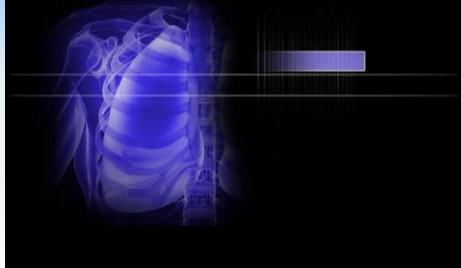
SAbR



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VAT S Right Middle Lobectomy



More Surgical Videos



- http://www.ctsnet.org/sections/video/section/videos/2013_video-atlas-thoroscopic-lobectomy.html



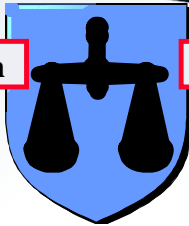
Minimal residual disease in "Early Stage" NSCLC Patients

- 38% of patients have a Positive pleural lavage
 - 34 vs 69% 4 yr survival
- 21% of patients positive bone marrow cytokeratin staining
- 10% histologically negative lymph node have positive cytokeratin



Dormancy of Micrometastases

Proliferation



Apoptosis

Angiogenesis suppression



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“Excisional surgery for cancer cure: therapy at a cost”

-Coffey, et al, Lancet Oncology, 2003

- Circulating tumor cells
- LPS
- Inflammatory cytokines
- Immunosuppression



Minimal Residual Disease

Accelerated systemic/local recurrence



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“Excisional surgery for cancer cure: therapy at a cost”

-Coffey, et al, Lancet Oncology, 2003

- > 100 reports of adverse effects of blood transfusions
- Multiple surgical trials with disease progression after resection
- Lacy, et al trial, Stage III laparoscopic colectomy did better than open colectomy, Lancet 2002.

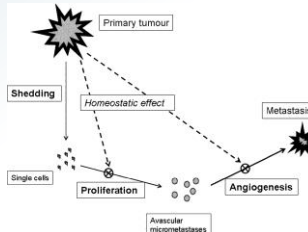


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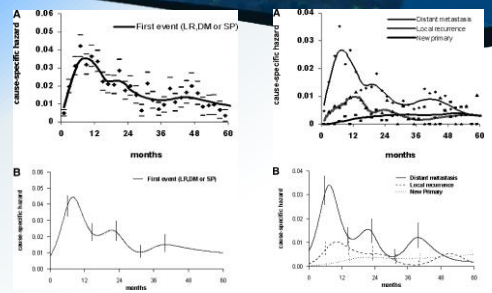
“Air Got to the Tumor”

Demicheli, *J Thorac Oncol.* 2012;7: 723–730



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Recurrence Dynamics

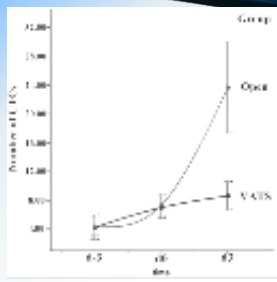


Demicheli, *J Thorac Oncol.* 2012;7: 723–730



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Circulating Tumor Cells



The increase in number of CTCs		
Group	d3 to d0	d3 to d3
VATS (n = 43)	1,363 ± 2,924	2,181 ± 2,962
Open (n = 36)	1,500 ± 2,315	9,666 ± 15,641
t	-0.204	-2.688
p	0.329	0.015

Huang, et al, *Thorac Cardiovasc Surg* 2016;64:515–519



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~55% 5y.s.

T2a **T2b**

**Stage I Tumors
< 30 % of presentations**

Tumour: >3 cm, <5 cm

Tumour <5 cm, invasion of the visceral pleura

Tumour involves main bronchus, 2 cm or more distal to carina

Associated atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

Tumour: >5 cm, <7 cm (with or without other T2 descriptors)

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Impaired Survival of Larger Tumors

	Deaths / N	MST	5-Year NR	77%
pT1, <=2cm	492/ 1816	113	71%	
pT1, >2-3 cm	582/ 1653	81	58%	
pT2, <=5 cm	1311/ 2822	56	49%	
pT2, >5-7 cm	461/ 825	29	35%	
pT3, > 7 cm	240/ 364	36	41%	

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Limited Stage Small Cell Carcinoma

- Generally treated as systemic disease
- NCCN guidelines support resection of T1-2, N0, M0 tumors followed by chemo

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T3
Chest wall invasion, including
Processus transversus without invasion
of vertebral body or spinal canal,
encasement of the subcarinal
vessels, or unequivocal
involvement of the
superior branches
of the bronchial tree
(S3 or above)
Invasion of
parietal pleura
over the
mediastinum
Tumour > 7 cm
Reticular nests of
parietal
pericardium
invasion
Diaphragmatic
invasion
Additional
tumour
nodules in
the lobe of
the primary
Tumour in the main
bronchus less than 2
cm from the carina
(without involvement
of the carina and/or
associated atelectasis or
obstructive pneumonitis
of the entire lung)

N1

**Stage II Tumors
10-20 % of
presentations**

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Cause-Specific Mortality and Morbidity in Stage I Lung Cancer by Age

> 75

< 65

Legend: Lung cancer-specific CID (blue), Noncancer-specific CID (yellow)

Time From Surgery (years)

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Eguchi, et al, JCO 2017 Jan 20;35(3):281-290

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NSQIP Analysis 2005-2012 Mortality by Age Favoring VATS

Age Group	Odds Ratio	95% CI	p Value
65-69 years	2.72	1.00-9.46	0.039
70-74 years	4.41	1.28-23.42	0.008
75-80 years	1.60	0.50-5.95	0.450

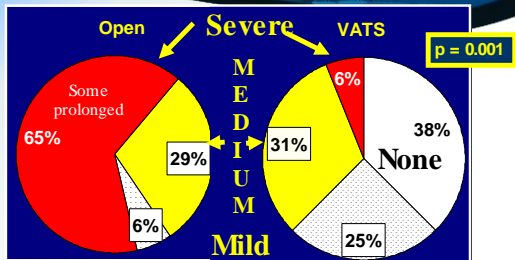
Legend: VATS (blue), Open (red)

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Bravo-Iñiguez, et al, Ann Thorac Surg 2016;101:541-6

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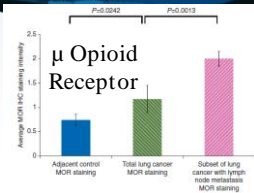
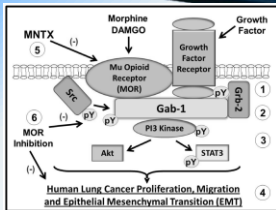
Pain 3 Weeks Postop



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Opioid and Cancer



Lennon, et al, PLoS One. 2014 Mar 24;9(3):e91577

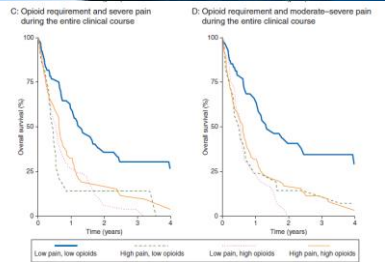
Singleton, et al, Br J Anaesth. 2014 Jul;113 Suppl 1:i103-8



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Opioid and Cancer



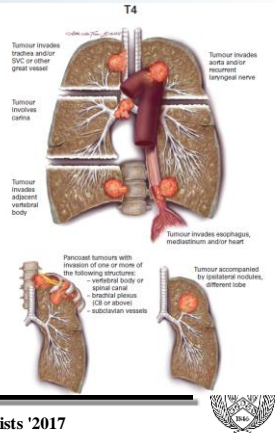
Singleton, et al, Br J Anaesth. 2014 Jul;113 Suppl 1:i103-8



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**Stage III
Tumors
35% of
presentations**



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TNM System

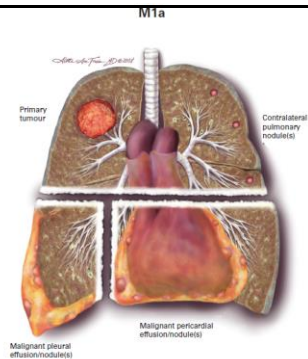
- M0 No distant metastasis
- M1 Distant metastasis
 - M1a Separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or malignant pleural or pericardial effusion
 - M1b Distant metastasis



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Lung Staging

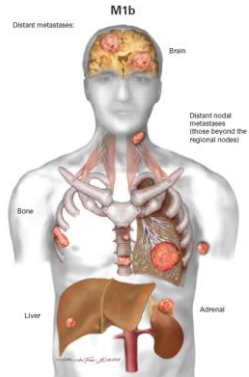


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Lung Staging - Mets

- Lymph Nodes 96%
- Bones 48%
- Adrenals 40%
- Liver 41%
- Kidneys 19%
- Heart 15%
- Opposite lung 13%



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VATS Views



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Surgical Contraindications

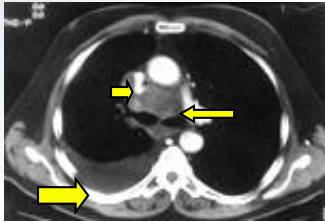
- Inadequate cardiopulmonary reserve
- Malignant pleural effusion
- Recurrent laryngeal nerve paralysis
- Small cell carcinoma
- Contralateral lymph node mets
- Distant mets



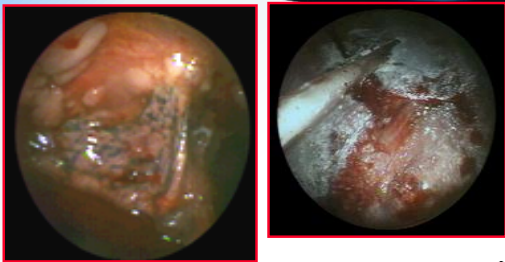
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CT Scan – IIB/IVA Disease

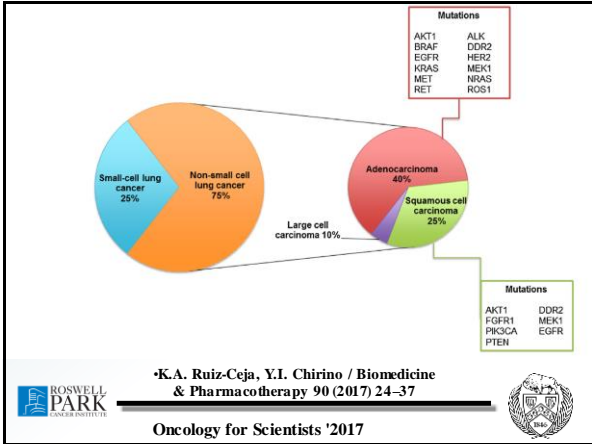


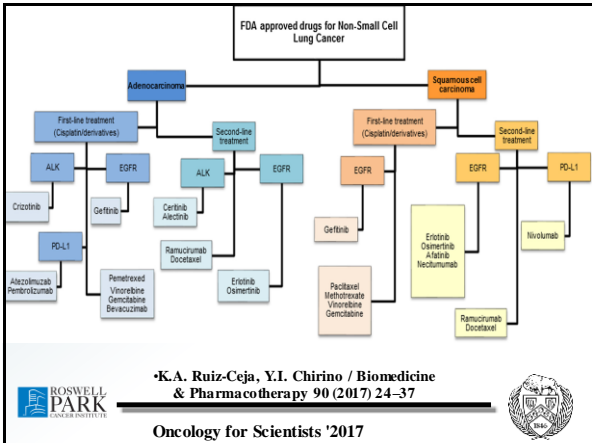
Talc Rx for Malignant Effusions

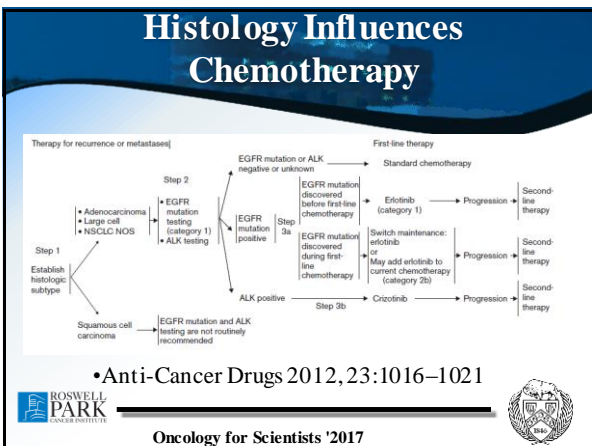


PleurX Catheter









Histology related therapy

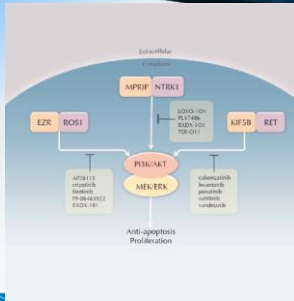
ADENOCARCINOMA	SQUAMIOUS	SLCC
EGFR mutation	PIK3CA mutation	PTEN loss
ALK rearrangement	FGFR1 amplification	FGFR1 amplification
ROS1 rearrangement	FGFR2/3 mutation	
BRAF mutation	FGFR3 rearrangement	
PIK3CA mutation	DDR2 mutation	
RET rearrangement		
KRAS mutation		
HER2 mutation		
MET amplification		

• *J Thorac Oncol.* 2015;10: S1–S63

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Histology related therapy



• *J Thorac Oncol.* 2015;10: S1–S63

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OmniSeq Target™ for Lung Cancer

OmniSeq Target™ for Lung Cancer

• **NYS CLEP Approved**

• Predicts response to targeted therapies for 15 lung cancer associated genes

• **Mutations** – 205 known actionable variants

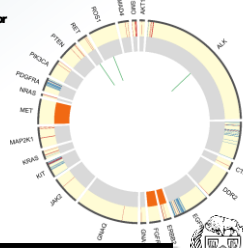
• AKT1, ALK, BRAF, CTNNB1, DDR2, EGFR, ERBB2 (HER2), KRAS, MAP2K1 (MEK1), NRAS, PIK3CA, PTEN, RET

• **Translocation**

• ALK, RET, ROS1

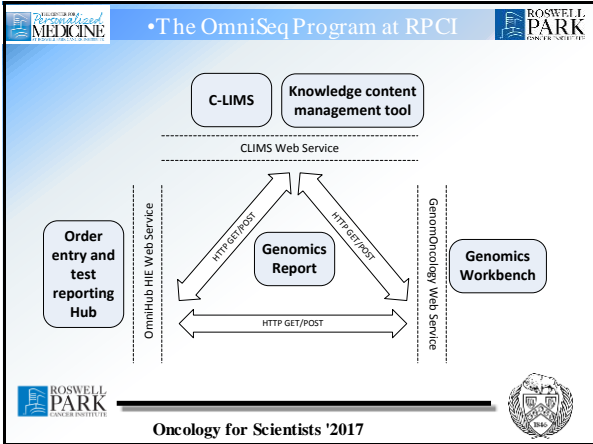
• **Amplification**

• ERBB2 (HER2), EGFR1, MET



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OmniSeq Target™ for Lung Cancer

•Summary Report •Mutation Report •Translocation Report •Copy Number Report

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OmniSeq Target™ for Lung Cancer

•Link to My Cancer Genome

•State of the art reporting to the ordering physician:

- Integration with the EHR
- Link to knowledge resources within the EHR
- Failed testing completely reported
- Pending confirmation updates

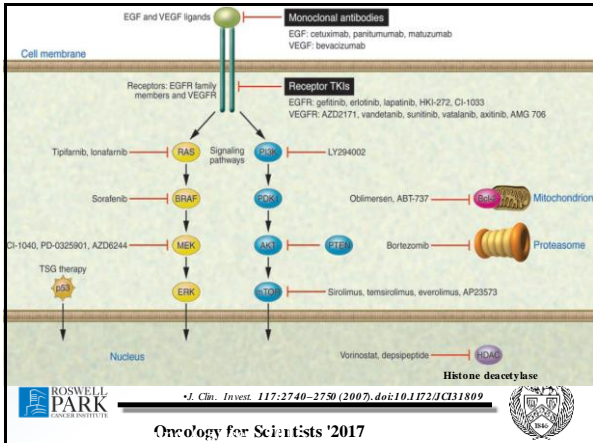
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Thank you!!!



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New Cancer Drugs

Suffix	Meaning	Example
-ib	Inhibitor	Imatinib
-momab	Mouse antibodies	ibritumomab
-ximab	Chimeric antibodies	rituximab
-zumab	Humanized antibodies	trastuzumab
-umab	Fully human antibodies	adalimumab



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Disclosures



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