Lung Cancer

Cytogenetics

- **Kras mutations:** predicts primary resistance to EGFR TKIs & poor prognosis
- **EGFR mutations:** predicts good response to EGFR TKIs

*Kras and EGFR mutations are *mutually exclusive*

Risk factors

- **Tobacco:** 85-90% of lung cancer deaths, 10-20x higher risk than non-smokers (males > females)
  - ↓Risk after 2-3 years after quitting → risk declines steadily over next 10 years
- **Asbestos:** 6x ↑risk, synergistic with smoking
- **Radon gas & ionizing radiation:** 2nd leading cause
- **Occupational & environmental exposure:** petroleum, nickel, arsenic, chromates, haloethers, polycyclic aromatic hydrocarbons, vinyl chloride
- **Diet:** ↓β carotene, ↓Vit E
- **Coexisting lung disease:** pulmonary fibrosis (14x ↑risk), emphysema
- **Genetic disposition:** first degree relatives, polymorphisms

Preventative screening

- **CXR:** not shown to have benefit in trials
- **Sprial CT scans:** highly sensitive but high rate of false positives (50% benign nodules)
  - Low dose CT appropriate for elderly heavy smokers (>55 y/o, smoking ≥30 packs/year)

Chemoprevention

- Several trials studied the role of *β carotene* in primary prevention
  - **ATBC:** β carotene caused significant ↑lung cancer incidence & mortality in male smokers
  - **CARET:** β carotene + retinyl palmitate → ↑lung cancer incidence in male & female smokers
  - **Physician's Health Study:** β carotene had no effect on lung cancer incidence

Clinical Presentation

- **Primary tumor in lung:** cough, dyspnea, hemoptysis, hoarseness, dysphagia, stridor, wheezing, chest/shoulder/arm pain, superior vena cava obstruction, pleural effusion, phrenic nerve palsy
- **Metastases:** neurological dysfunction, bone pain, liver dysfunction, spinal cord compression
- **Paraneoplastic syndromes**: occur at sites away from primary tumor or metastases caused by production of biologically active substances (e.g. SIADH, hypercalcemia, ectopic Cushing's, hypercoaguable state, Eaton-Lambert)

Diagnosis

- **History & physical:** weight loss, performance status, smoking history
- **Labs:** electrolytes, LFTs
- **Radiographic imaging:** CT scan, PET scan (for diagnosis & staging), bone scan (for metastases)
- **Tissue sampling:** sputum cytology, bronchoscopy, transthoracic needle biopsy, thoracentesis, immunohistochemical staining, molecular studies, biomarker analysis

Pathology: types of lung cancer

SCLC | Small Cell Lung Cancer	NSCLC | Non-Small Cell Lung Cancer
Classical small cell carcinoma	Non-squamous cell cancer • Adenocarcinoma • Large cell carcinoma
Large cell neuroendocrine cancer	Squamous cell cancer (epidermoid)
Combined (predominantly SCLC + occasional NSCL)	

	Small cell lung cancer	Non-small cell lung cancer
Severity	Most aggressive, high mortality	Slower growing
Smoking	Clear relationship	Non-squamous: least related Squamous: clear relationship, dose-related effect
Paraneoplastic syndromes	Common	
Radiation	Highly sensitive	Moderately sensitive
Chemotherapy	Highly sensitive, doublet therapy is superior	Low sensitivity to conventional chemo
Targeted tx		Yes
Surgery	No established role	Established role
Staging	*Veterans Admin*: limited vs. extensive stage *AJCC*: TNM staging	TNM staging

SCLC | Small Cell Lung Cancer

	SCLC: Limited Stage	SCLC: Extensive Stage
Definition	Confined to ipsilateral hemithorax, can be encompassed within a radiation field	Beyond ipsilateral hemithorax, including malignant pleural or pericardial effusion or hematogenous metastases
Poor prognostic factors	Poor PS (3-4), extensive stage, weight loss, bulky disease markers (e.g. LDH)	
Favorable prognostic factors	Female, <70 y/o, normal LDH, stage I	Good PS (0-2), younger age, normal LDH, normal SCr, single metastatic site
Treatment goal	Cure	Palliative
Chemotherapy	E+P: etoposide + cisplatin x 4-6 cycles q21 days	Platinum-based regimen: Platinum deriv + topo isomerase inhibitor: mix & match • *Platinums:* cisplatin or carboplatin (↓nephrotox) • *Topo*: etoposide (topo II) or irinotecan (topo I)
Other therapy	Concurrent radiation therapy	Prophylactic cranial irradiation (PCI): brain metastases, after adjuvant chemo with complete resection, not recommended if poor PS or altered mental status
Median survival	16-22 months	5 weeks without treatment

Salvage therapy

Relapse	Clinical trial preferred
Relapse <2-3 months PS 0-2	Ifosfamide, paclitaxel, docetaxel, gemcitabine, irinotecan, topotecan
Relapse <6 months	Topotecan PO or IV Irinotecan, paclitaxel, docetaxel, etoposide PO, vinorelbine, gemcitabine CAV: cyclophosphamide + doxorubicin + vincristine
Relapse >6 months	Repeat original regimen

NSCLC | Non-Small Cell Lung Cancer

Non-squamous NSCLC		Squamous NSCLC
Adenocarcinoma	**Large cell carcinoma**	**Squamous cell (epidermoid) carcinoma**

• 37-47% of NSCLC
• Periphery of lung
• Most common in non-smokers
• Increasing incidence in women
• Linked to EGFR activating mutations
• Categories:
  ○ AIS: adenocarcinoma in situ
  ○ MIA: minimally invasive adenocarcinoma
  ○ Invasive adenocarcinoma
  ○ Variants of invasive adenocarcinoma
• Excellent survival if resected: AIS & MIS
	• 10-18% of NSCLC
	• Periphery of lung
	• Common: bulky tumors, metastases
		• 25-32% of NSCLC
		• Center of chest: tracheobronchial tree
		• Clear relationship to smoking
		• Slower growing
		• Better prognosis than adenocarcinoma

Prognostic factors

- **Favorable:** early stage, good PS (0-2), no significant weight loss <5%, females
- **Biomarkers**
  - **EGFR:** exon 19 deletion or exon 21 mutation → predicts benefit from EGFR-TKI therapy
  - **Kras:** oncogene mutation → lack benefit from platinum/vinorelbine or EGFR-TKI therapy
  - **ELM4-ALK:** fusion oncogene gene rearrangements → resistant to EGFR-TKIs (testing for ELK recommended)
    - **Crizotinib** (Xalkori)
      - Indication: patients with ALK gene-positive NSCLC, with locally advanced or metastatic disease
      - Dose: 250mg po BID
      - Dose modifications: renal (not studied in CrCl ≤30), hematological (grade 3 & 4 toxicities), hepatic (↑LFTs), QTc prolongation
      - Warnings: hepatotoxicity, pneumonitis, QTc prolongation
      - Interactions: CYP3A4, pregnancy category D
  - **ERCC1:** ↑ERCC1 levels → poor response to platinum therapy but overall better survival
  - **RRM1**: ↑expression → poor response to gemcitabine

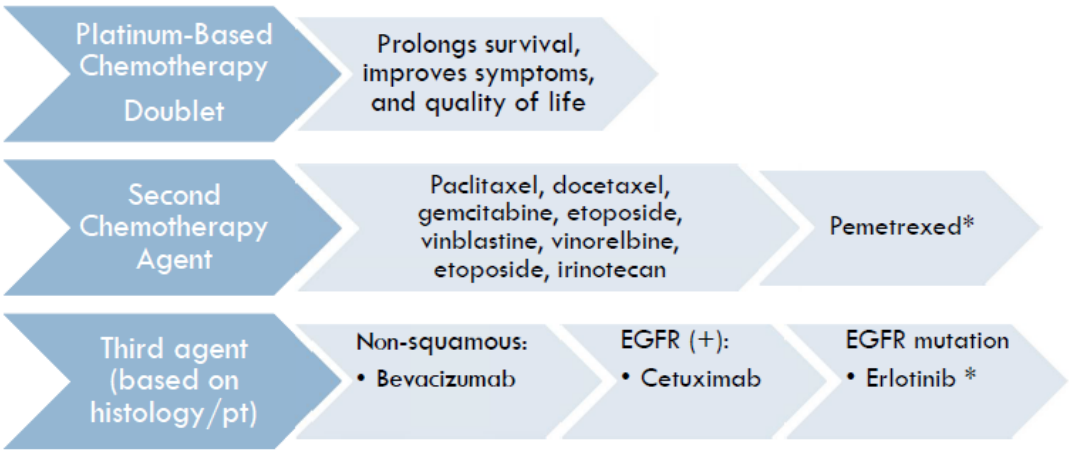
Adjuvant chemotherapy

- **Goals:** curative intent (stage I-IIIB) vs. palliation (stage IV)
- **Cisplatin-based therapy x 4 cycles**
  - Cisplatin + [pick one: vinorelbine, etoposide, docetaxel, gemcitabine, pemetrexed, paclitaxel]
  - Indication: resected stage II and IIIA
  - Common toxicities: grade 3 & 4 toxicities
  - Age considerations: not studied in ≥74 y/o

Treatment of unresectable or advanced disease (stage IIIB or IV)

- **Cytotoxic chemo:** PS 3-4 do not benefit (exception: erlotinib for patients with EGFR pos mutation)
- **Platinum-based chemo:** recommended for all eligible patients

EGFR pos	--*First line:* erlotinib or gefitinib
ELM4-ALK pos	--*First or second line:* crizotinib
EGFR neg + ALK neg + nonsquamous	--Carboplatin/paclitaxel + bevacizumab --Cisplatin/pemetrexed ± bevacizumab --[Cisplatin or carboplatin] in combo with [pemetrexed & docetaxel or gemcitabine or paclitaxel --Cisplatin/vinorelbine ± cetuximab
EGFR neg + ALK neg + squamous	--[Cisplatin or carboplatin] in combo with [docetaxel or gemcitabine or paclitaxel] --Cispalin/vinorelbine ± cetuximab



- **First line agents:** bevacizumab, cetuximab, pemetrexed, gemcitabine
    - **Pemetrexed vs. gemcitabine:** pemetrexed had less toxicities and superior efficacy than gemcitabine when combined with cisplatin in non-squamous
    - **Bevacizumab criteria:** non-squamous, no history of hemoptysis, EGFR mutation neg or unknown, caution with thrombocytopenia due to ↑bleeding risk
      Cetuximab: used for EGFR pos, used resulted in no brain metastases, but more grade 3 & 4 toxicities
- **Second line:** single agent chemo (docetaxel, pemetrexed, erlotinib)
    - **Erlotinib:** for EGFR mutation pos regardless of PS, for locally advanced or metastatic NSCLC after failure of at least 1 prior chemo regimen
- **Third line:** erlotinib