Lung cancer

Lung cancer basics

Incidence:

- A worldwide epidemic :
- More than 1 million new cases per year and more than 900,000 deaths annually.
- Overall mortality rate from lung cancer has risen markedly over the past century.
- In United states of America:
- 2010 statistics per American cancer society cancer facts and figures: 2010

- 2010 statistics per American cancer society cancer facts and figures: 2010

	Estimated new cases			Estimated deaths		
	Total	Males	Females	Total	Males	Females
USA	222,520	116,750	105,770	157,300	86,220	71,080
Michigan	8,150			5,830		

  - About 85% are non small cell and about 15% are small cell lung cancer
  - The incidence is declining in men from 1984 to 2006 data
  - The incidence is reaching a plateau in women after years of increase
  - Lung cancer accounts for more deaths than any other cancer in both men and women
  - The mortality rate from lung cancer in American men declined from 1990 to 2006 reflecting a decrease in smoking prevalence among men since the 1950s.
  - Lung cancer mortality has been stable after years of increase for American women.

Risk factors:

- Tobacco: Most important risk factor. Risk increases with quantity of cigarettes and duration of smoking.
- Asbestos (with tobacco)
- occupational or environmental exposure to secondhand smoke
- Radon, asbestos
- Certain metals (chromium, cadmium, arsenic)
- Ionizing radiation
- Air pollution,
- A history of tuberculosis
- Genetic susceptibility plays a contributing role in the development of lung cancer, especially in those who develop the disease at a younger age.

Prevention strategy:

- Avoid tobacco exposure
- Chemoprevention options are not yet successful

Symptoms / signs: Most patients with lung cancer present with new signs or symptoms.

- New or worsening cough is the most common symptom.
- Hemoptysis
- Dyspnea.
- Chest pain (pleuritic)
- Weight loss, loss of appetite.
- Symptoms of metastatic disease such as bone pain
- Common presentations
- Signs of post obstructive pneumonitis: productive cough, or fever, more common in patients with centrally located tumors.
- Pleuritic chest pain or nonproductive cough more common in patients with peripheral lesions.
- Hoarseness of voice suggests vocal cord paralysis with entrapment of the recurrent laryngeal nerve. It is seen more often on the left than the right side because of the longer course of the left nerve around the aorta.
- Swelling of the face and most often the right arm may occur owing to the superior vena cava syndrome.
- Pan coast syndrome :
    - Seen with apical tumors.
    - Symptoms are
        - Shoulder pain
        - Lower brachial plexopathy
        - Horner's syndrome
            - Unilateral constricted pupil
            - Facial dryness
            - Ptosis caused by damaged sympathetic nerves.
- Patients with pleural or pericardial effusions may present with dyspnea, cough, and chest pain.
- Paraneoplastic syndromes
- Adenocarcinoma and large-cell carcinoma, often are present in the peripheral lung and are indicated by pleural effusions or signs or symptoms of metastatic disease.
- Some patients present asymptomatically with an incidental lung lesion on radiograph or CT scan of the chest.

General observations about histologic patterns:

Squamous cell

- Central location
- 95% Smokers
- 60% Metastases
- Hypercalcemia
- Conversely, squamous cell carcinoma, the non–small-cell lung cancer most associated with smoking, is decreasing in incidence.
- In general, squamous cell carcinoma tends to occur centrally with endobronchial lesions, and more than half the time with no evidence of metastases on staging tests; however, subclinical metastases often exist.

Adenocarcinoma

- Peripheral location
- 50% Smokers, 50% non smokers
- 80% Metastases
- Hypercoagulability

- Hypertrophic pulmonary osteoarthropathy
- More older nonsmokers and women
- Half of patients with adenocarcinoma of the lung have never smoked, and the rapid rise in incidence of this type of cancer in the past 20 years may reflect the aging of the population.
- The use of filtered cigarettes may result in smaller smoke particles entering into smaller airways with a resulting increased incidence of adenocarcinoma in peripheral pulmonary sites.

Bronchioloalveolar cell carcinoma

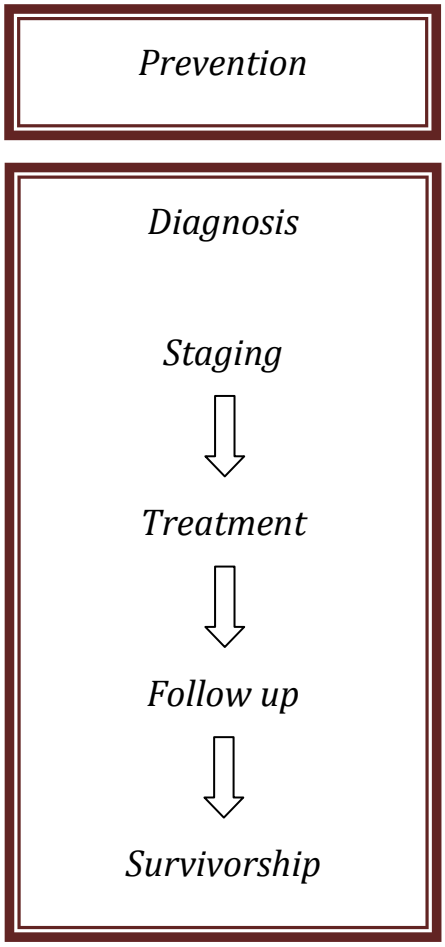
- Subtype of adenocarcinoma
- Nonsmokers
- Usually female
- Often bilateral, diffuse, multi-focal
- Infiltrates or multiple nodules
- Multifocal recurrence
- Sensitive to epidermal growth factor receptor inhibition
- Slow growth
- Late metastases outside of lung
- Bronchioloalveolar cell carcinoma, which represents 20% of cases of adenocarcinoma
- A distinct clinico-pathologic presentation

Large-cell

- Peripheral location
- 90% Smokers
- 80% Metastases

Small-cell

- Central location
- Almost 100% smokers
- Almost 100% metastases
- Eaton-Lambert syndrome
- SIADH
- Ectopic ACTH



Screening for lung cancer: controversial

- Screening for early lung cancer detection has not yet been proven to reduce mortality.
- Detection by chest x-ray, analysis of cells in sputum, and fiber-optic examination of the bronchial passages has shown limited effectiveness in reducing lung cancer deaths.
- Newer tests, such as low-dose spiral computed tomography (CT) scans and molecular markers in sputum, have produced promising results in detecting lung cancers at earlier, more operable stages in high-risk patients, but have not yet been shown to reduce lung cancer deaths.
- There are considerable risks associated with lung biopsy and surgery that must be considered when evaluating the risks and benefits of screening.
- The National Lung Screening Trial is a clinical trial to assess whether screening individuals at high risk for lung cancer with spiral CT or standard chest x-ray can prevent lung cancer deaths. Launched in 2002, results from the study are expected by 2010-2011.

- Summary of screening: Screening tests, such as spiral CT scans, have not yet been found to reduce lung cancer mortality .
- Look for updated information on Medline: Data is evolving.

Diagnosis confirmation:

- A biopsy is necessary.

Methods of diagnosis:

- A bronchoscopy: Centrally located pulmonary tumors :
- CT guided biopsy: for peripheral lesions.
- Video thoracoscopy.
- Sputum cytology.
- A lymph node biopsy,
- A mediastinoscopy or an anterior mediastinotomy.
- Pleural fluid cytology.
- Biopsy of metastatic site: Any histologically confirmed findings of non–small-cell lung cancer metastasis by CT, PET, or bone scan would preclude resection.

Non–small-cell lung cancer

Non–small-cell lung cancer : three distinct histological types

- Squamous cell carcinoma (epidermoid)
- Adenocarcinoma (including the slow-growing, often diffuse bronchioloalveolar cell subtype)
- Large-cell carcinoma
- These histological types of lung cancer are classified together as Non small cell lung cancer on a clinical basis.
- They are all potentially cured by localized disease resection.
- They respond only modestly to chemotherapy.
- Radiation therapy can provide local tumor control in many patients with locally unresectable disease.
- Cure is rare in unresectable disease.

Non–small-cell lung cancer Staging studies / staging work up:

- Staging is important in the selection of therapy in patients with non–small-cell lung cancer.
- Clinical staging includes:
  - A complete physical examination: Look for signs of spread
  - CT scan of the chest and abdomen (frequent metastases are found in the adrenal gland)
  - A bone scan
  - A CT scan or MRI of the head.
  - PET scan: Look for updated information on Medline: Data is evolving.
    - A positron emission tomography (PET) as a separate study or combined with CT scan (PET/CT fusion scan), when available; A positive PET scan finding that correlates with findings of the CT scan, such as mediastinal lymph node involvement beyond the primary lesion, suggests distant metastases and unresectability.

- PET scans are used routinely in the staging process to identify patients who may qualify for surgical resection, although their impact on actual outcomes is unproven.
- PET scans may detect lesions unseen by other radiologic tests, but two trials have reported contradictory results on whether PET scans reduce needless thoracotomy
- Patients with false-positive PET scan findings may be denied potential cure by surgery; however, the high rate of subclinical metastases in all patients with early-stage disease lessens the impact of false-positive results.

Staging of Non–small-cell Lung Cancer

- See detailed AJCC system for updated information
- Early-Stage Disease (Stage I or II)
- Bordered by lung or visceral pleura
  - 2 cm or more distal to the carina
  - No invasion of mediastinal lymph nodes
  - Can include locally advanced invasion of chest wall (including superior sulcus), diaphragm, parietal pleura, or pericardium
- Regionally Advanced Disease (Stage III)
  - Mediastinal involvement
- Distant Metastases (Stage IV)

Treatment of Non-Small-Cell Lung Cancer

- Clinical trial participation is appropriate for eligible patients.

Stage I resectable disease

- Surgery is the treatment of choice for patients with early-stage (stage I) non–small-cell lung cancer.
- Five years after resection, approximately 50% to 70% of patients with stage I non–small-cell lung cancer (no hilar lymph node involvement) are recurrence free
- Use of adjuvant (postoperative) chemotherapy for patients with early-stage disease and represent a new standard of care.
  - Three large randomized studies have shown that in patients with early-stage (stage IB and II) non–small-cell lung cancer, treatment after surgery with chemotherapy consisting of combination Paclitaxel and Carboplatin or Cisplatin with Etoposide or Vinorelbine improves absolute overall survival by 4% to 15% at 5 years
  - Use of adjuvant radiotherapy in patients with early-stage non–small-cell lung cancer has not been found to confer a survival benefit, and may be associated with increased mortality in this setting.

Stage II resectable disease

- Surgery is the treatment of choice for patients with early-stage (stage II) non–small-cell lung cancer.
- Five years after resection, approximately 20% to 40% of patients with stage II disease (hilar lymph node involvement) are recurrence free
- Use of adjuvant (postoperative) chemotherapy for patients with early-stage disease and represent a new standard of care.

  - Three large randomized studies have shown that in patients with early-stage (stage IB and II) non–small-cell lung cancer, treatment after surgery with chemotherapy consisting of combination Paclitaxel and Carboplatin or Cisplatin with Etoposide or Vinorelbine improves absolute overall survival by 4% to 15% at 5 years
  - Use of adjuvant radiotherapy in patients with early-stage non–small-cell lung cancer has not been found to confer a survival benefit, and may be associated with increased mortality in this setting.

Patients with stage III disease (Usually with mediastinal lymphadenopathy)

- Multi-modality therapy is strongly recommended based on clinical data.
- 5-year survival rate of 2% to 15%, depending on the extent of mediastinal disease.
- Chemo-RT is better than RT alone for stage III: A meta-analysis of 11 randomized trials showed that, Cisplatin-based combination chemotherapy plus radiation therapy yielded a 10% relative reduction in the risk for mortality, compared with radiation therapy alone.
- Concurrent chemotherapy and radiation therapy is better than sequential chemotherapy followed by radiation.
- Neo-adjuvant chemotherapy is used before surgery, in patients with potentially resectable disease (that is, those with minimal mediastinal lymph node involvement),
- An optimal sequence of chemotherapy, radiation therapy, and surgical resection is under study.
- Superior sulcus tumors are a special sub group of stage III disease in which local invasion causes pain in the shoulder or brachial plexus. Five-year survival rates of 20% have been reported for selected studies in which radiation therapy, surgery, or both were used.

Patients with stage IV disease: with distant metastases. See an update at the end of presentation.

- Median survival of untreated patients: 6- to 8-months.
- Must assess performance status prior to treatment decision.
- Palliative Chemotherapy is generally offered only to patients whose performance status is good (patients who are not bedbound during the day).
- A Modest overall survival benefits (10 to 20 weeks more compared to the median survival of untreated patients) have been shown only in good performance status patients.
- Cisplatin based therapy is considered standard of care. Several platinum combinations are equivalent. The type of platinum-based combination chemotherapy used has not had an effect on efficacy of treatment.
- Combinations are better than single agent which is better than best supportive care in randomized clinical trials.
- Second- or third-line chemotherapy has been used for patients with recurrent disease. Prospective randomized trials have shown a small survival advantage (median survival, 8 weeks) with the use of Docetaxel or Pemetrexed; however, radiotherapy in this setting is not helpful and may increase mortality.
- Patients with stage 4 non–small-cell lung cancer and poor performance status, do not usually derive any benefit from chemotherapy and should be managed with supportive or palliative care.
- Bronchioloalveolar cell carcinoma subgroup:
  - Seems particularly sensitive to epidermal growth factor receptor inhibition; among 90 patients with advanced disease, approximately 20% had a major response and 30% stable disease with oral Gefitinib.
  - Tyrosine kinase inhibitors represent a new therapeutic advance for patients with non–small-cell lung cancer.

  - For patients with recurrence of metastatic disease, Erlotinib has conferred a small overall survival advantage (median survival, 8 weeks).
  - Up to 50% of patients with bronchioloalveolar cell carcinoma have sustained response or stability with Gefitinib.
  - A subgroup of patients has specific mutations in the epidermal growth factor receptor gene, which causes increased growth-factor signaling, conferring a rapid and dramatic clinical response to the tyrosine kinase inhibitor Gefitinib.

Bronchial obstruction:

- Radiation therapy may be palliative for patients with symptomatic local involvement, such as tracheal or bronchial compression, bony metastases, hemoptysis, or superior vena cava syndrome.
- In some instances, endobronchial laser therapy, cryotherapy, or implantation of radioactive seeds may shrink obstructing lesions in the proximal bronchus.
- Expandable metal stents inserted bronchoscopically into the tracheobronchial tree can improve pulmonary function in patients with extrinsic bronchial tumor compression.

Special situations:

- Monthly intravenous bisphosphonate therapy with Pamidronate or Zoledronate decreases skeletal-related events for patients with bony metastases.
- A solitary brain metastasis with no evidence of extra cranial tumor
- Patients who have relapses after resection of primary non–small-cell lung cancer as manifested by a solitary brain metastasis with no evidence of extra cranial tumor may have prolonged disease-free survival after surgical excision and postoperative whole-brain radiation therapy compared with those who receive radiation therapy alone.
- Subsequent tumor recurrence in the brain can be palliated with further surgery or with stereotactic radio surgery.

- Pleural effusion:
  - Thoracocentesis and pleurodesis
  - Patients with malignant pleural effusions do not benefit from radiotherapy
  - Palliative chemotherapy for palliation alone may be offered.

A second primary tumor.

- Patients who have relapses in the form of a solitary pulmonary nodule usually have a second primary tumor.
- Subsequent resection of this new lesion plus adjuvant chemotherapy may result in long-term survival in selected patients.

Survival: American cancer society data (2010 update)

- The 5-year survival rate for all stages combined is only 16%.
- The 5-year survival rate is 53% for cases detected when the disease is still localized, but only 15% of lung cancers are diagnosed at this early stage.
- The 5-year survival for small cell lung cancer (6%) is lower than that for non-small cell (17%).
- The 1-year relative survival for lung cancer increased from 35% in 1975-1979 to 42% in 2002-2005, largely due to improvements in surgical techniques and combined therapies.

Treatment of Non-Small-Cell Lung Cancer: Summary:

- Stage I

    - Surgery and adjuvant chemotherapy for selected
    - Curative intent
    - Stage I: 50% to 70% long-term disease-free survival

- Stage II
    - Surgery and adjuvant chemotherapy
    - Curative intent
    - Stage II: 20% to 40% long-term disease-free survival

- Stage III
    - Mediastinal involvement
    - Chemotherapy and radiotherapy in stage III: 5% to 20% long-term disease-free survival
    - In selected patients, chemotherapy followed by surgery

- Stage IV
    - Distant metastases
    - Chemotherapy for good performance status patients
    - Palliative intent

Small-cell lung cancer

Small-cell lung cancer

- Small-cell lung cancer accounts for approximately 15% of all cases of lung cancer
- Almost always associated with tobacco use.
- Small cell lung cancer is considered a systemic disease: Almost all patients have disseminated disease on initial presentation, with most having evidence of metastatic disease on CT scan.
- Even patients who present with localized disease almost always have concurrent micro metastases.
- Small-cell lung cancer has a much more aggressive clinical course than the other histological types.
- Small-cell lung cancer is much more responsive to chemotherapy and radiotherapy than the other histological types, but the cure rate remains low.

Staging for SCLC:

- Limited stage:
    - Localized disease that can be encompassed within a radiation therapy port, usually with confinement to one hemothorax lymph node, the mediastinum, and supraclavicular lymph nodes.
    - About 30% of patients with small-cell lung cancer have limited-stage disease.
    - Most 2-year disease-free survivors have limited-stage disease at presentation.
    - Median survival: 16 to 24 months.
- Extensive stage:
    - Tumor beyond the confines of a radiation port.
    - Median survival is only 8 to12 months.
    - Long-term disease-free survival is rare.

Staging studies for SCLC:

- Most staging studies are noninvasive (staging does not change need for chemotherapy).

- A CT scan of the chest and abdomen up to adrenals.
- A CT or MRI of the head (3% to 7% of patients have asymptomatic brain metastases at presentation).
- A radionuclide bone scan.
- Bone marrow biopsies are not required in these patients.
- PET scans can identify the presence of limited-stage disease and help define radiation ports.

Special Considerations prior to treatment:

- Incidentally detected small lesions: Patients who can undergo complete resection before chemotherapy have an even better prognosis than those who cannot, but this scenario is rare. Some of these patients may actually have atypical carcinoid or well-differentiated neuroendocrine tumors, which are much less likely to metastasize but can nevertheless be histologically mistaken for small-cell lung cancer.
- Those with central nervous system or liver metastases have the worst prognosis.

Treatment for SCLC:

- Good prognostic factors:
  - Limited-stage disease
  - Female sex
  - Good performance status.
- Main treatment for patients with small-cell lung cancer is palliative systemic therapy.
- Clinical trial participation is appropriate for eligible patients.
- For patients with limited-stage small-cell lung cancer:
  - Chemotherapy + chest radiation is standard of care.
  - Two meta-analyses :
  - Chemo-RT is better than chemotherapy alone.
  - A 5% absolute improvement in 3-year survival rates favoring chemotherapy and radiation therapy compared with chemotherapy alone.
  - The current standard treatment :
    - Cisplatin and Etoposide with chest radiation therapy during the first two to three cycles of chemotherapy.
    - A median survival of 18 to 24 months
    - A 2-year survival likelihood of 40% to 50%.
    - Modern regimens: less than 3% treatment-related mortality.
  - Superior vena cava syndrome at initial presentation: Chemotherapy, with or without radiation therapy, is appropriate
- Prophylactic cranial irradiation (PCI) should be considered for patients who have a complete remission after chemo-chest RT.
  - A meta-analysis of seven randomized trials evaluating PCI in patients with a complete response:
    - Showed decreased brain involvement
    - Improved disease-free and overall survival (15% to 21% increased survival compared with untreated patients) at 3 years.
    - Patients who undergo PCI for SCLC and who survive for more than 2 years from start of therapy experience a decline in neuropsychological function. The degree of this impairment is controversial.
- For patients with extensive-stage small-cell lung cancer:

- Patients with extensive-stage disease and poor performance status (that is, those who are usually bedbound) may derive significant short-term palliative benefit and improved survival from chemotherapy.
- Combination palliative chemotherapy
  - Combination palliative chemotherapy alone may result in a 70% to 85% response rate and a 20% to 30% complete response rate.
  - Median survival is 8 to 12 months, with survival beyond 2 years rare.
  - Most of these chemotherapeutic regimens are platinum-based, consisting of Cisplatin and Etoposide or Carboplatin and Etoposide.
- Monthly intravenous bisphosphonate administration with Pamidronate or Zoledronate decreases skeletal-related events for patients with bony metastases.
- Prophylactic cranial irradiation can be considered for complete responders with extensive-stage disease to reduce the 60% actuarial risk for developing brain metastases within 2 years.
- For patients with extensive-stage disease and very poor performance status often caused by advanced age and co morbid conditions, single-agent intravenous or oral agents can provide palliation.
- Clinical trials are underway to identify new systemic options, particularly targeted therapies, for patients with extensive-stage disease.
- In the past 30 years, no incremental prolongation of survival has been noted in those with extensive-stage disease since the first use of combination chemotherapy.

Recurrent SCLC:

- Survival is short after small-cell lung cancer recurrence.
- Patients who are primarily resistant to therapy or have received many chemotherapeutic regimens rarely respond to more therapy.
- Those who respond to initial chemotherapy and have a relapse longer than 6 months after the end of treatment are more likely to respond to additional chemotherapy than non-responders.
- No one drug or regimen is considered standard in this setting.

Risk of second primary lung tumors:

- Long-term survivors of small-cell lung cancer with no recurrence beyond 5 years usually have limited-stage disease at presentation.
- Beyond 5 years, most subsequent mortality is attributable to second primary lung tumors, often of distinct histological type.
- Retrospective analyses suggest that continued smoking might increase the risk for a second primary lung tumor after successful treatment of small-cell lung cancer.
- Counsel all patients about smoking cessation.

Summary for SCLC:

- Chemotherapy improves median survival in patients with small-cell lung cancer (SCLC) substantially compared with surgery or radiotherapy alone.
- Patients with extensive-stage SCLC and poor performance status may derive significant short-term palliative benefit and improved survival from chemotherapy.
- Chemotherapy plus radiation results in a 5% absolute improvement in 3-year survival in patients with limited-stage SCLC compared with chemotherapy alone.

- Prophylactic cranial irradiation is an option for complete responders with extensive-stage SCLC to reduce the risk for brain metastases.
- Continued smoking may increase the risk for a second primary lung tumor after successful treatment of small-cell lung cancer.
- Overall, 10% of patients with small-cell lung cancer are disease free 2 years after completion of chemotherapy.
- By 10 years, half of these "long-term survivors" die of small-cell cancer recurrence or a new non–small-cell lung cancer.

Solitary Pulmonary Nodule

Solitary Pulmonary Nodule

- Although most patients with pulmonary nodules require either a diagnostic biopsy or a plan for observation, some highly selected may require no further follow-up.

- Comparison of Benign and Malignant Features of a Solitary Pulmonary Nodule

    - Benign Features
        - Younger age
        - No tobacco use
        - <1 cm size
        - Regular border
        - Increased density on CT scan
        - Low or absent uptake on PET scan
        - Doubling time >1 year
        - Benign pattern of calcification

    - Malignant Features
        - Older age
        - Tobacco use
        - >1 cm size
        - Irregular border
        - Lower density on CT scan
        - Increased uptake on PET scan
        - Doubling time <1 year
        - Malignant patterns of calcification

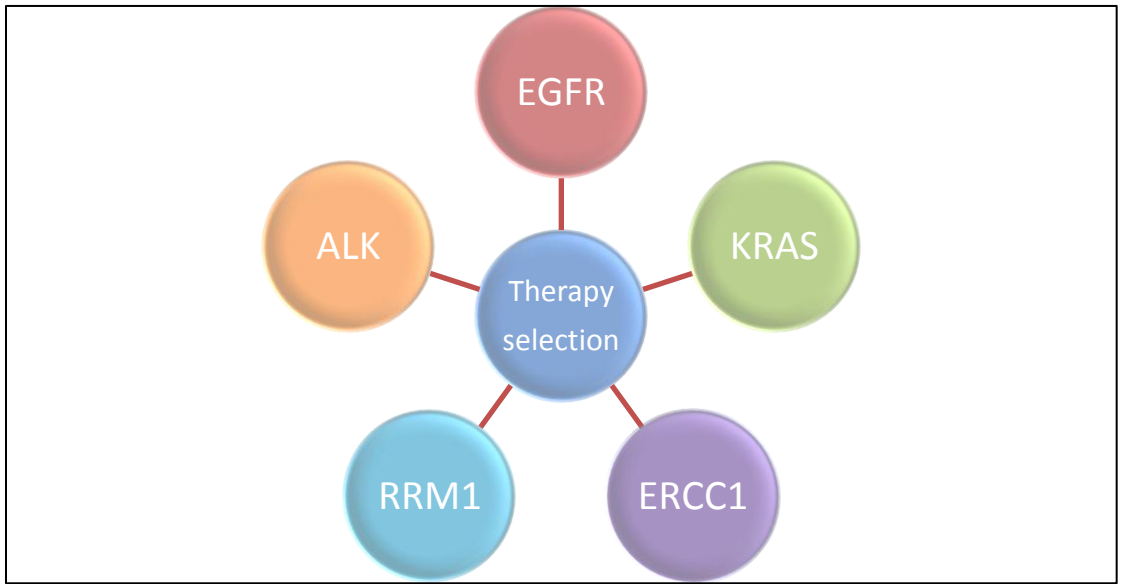
- A biopsy should be performed in patients with pulmonary nodule/s suspicious for malignancy based on clinical signs or context (with a higher pretest probability for malignancy).
- What is the best diagnostic approach for the evaluation of and precise labeling criteria for suspicious solitary pulmonary nodule: Controversial
    - A direct surgical resection
    - Needle biopsy:
        - A needle biopsy can yield false-negative results.
        - Percutaneous needle biopsy followed by other staging studies allows for assessment of resectability.

- Pulmonary nodules most likely to be benign based on clinical signs or context (with a lower pretest probability for malignancy) should be monitored by follow-up serial CT scans of the chest to assess interval growth.
- A sample monitoring schedule is 3 to 4 months for the first CT scan, 6 to 8 months for the second CT scan, and a third scan at 1 year.

2014 update -
Individualized therapy based on molecular markers in stage 4 Non small cell lung cancer
Please note that at this time the role of markers is limited to therapy selection only in stage 4 non squamous non small carcinoma specifically adenocarcinoma of lung. (as of 2014 - not for stages I-III and not for squamous cell)

Potential molecular markers for therapy selection

- EGFR Exon 19 mutations in adenocarcinoma
- EML4-ALK mutations
- RRM1 may predict Gemcitabine sensitivity
- ERCC1 may predict platinum resistance
- Multiple gene expression assays are in development



EGFR mutations

- *EGFR* mutations and over expression activates signaling pathways leading to cell growth and cell survival
- Exon 19 deletions and L 858R point mutations are common
- Seen in 10-15% Caucasians (higher in Asians up to 40%)
- T790M mutation indicates resistance to first generation EGFR inhibitors
- EGFR inhibitors (Gefitinib and Erlotinib or Afatinib) may benefit selected patients with *EGFR* mutations

- Patients with *EGFR* mutations particularly those from East Asia, females, never smokers, and those with adenocarcinoma may benefit from EGFR tyrosine kinase inhibitors as an alternative to first- or second-line chemotherapy.
- Median PFS was significantly longer in Erlotinib-treated patients than in those treated with chemotherapy (13 vs 4.6 months in Chinese study)

Cetuximab

- Activity of Cetuximab (anti EGFR antibody) seems to be independent of EGFR mutations
- Currently EGFR mutation status is not used to decide Cetuximab eligibility

KRAS mutations

- Seen in up to 30% Caucasians (less in Asians)
- Mutated KRAS stimulates pathways downstream to EGFR pathways
- Predicts resistance to EGFR inhibitors
- Seen more in smokers
- Associated with poorer prognosis

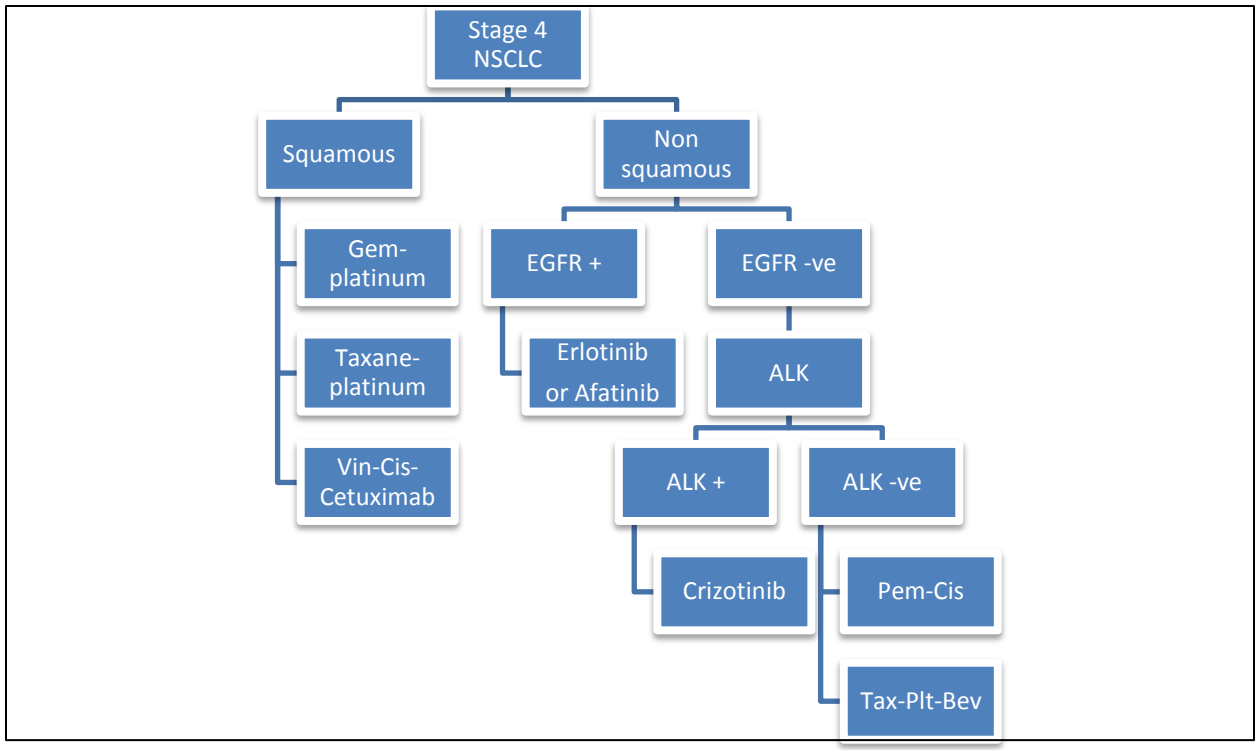
EML4-ALK mutations

- ALK mutations are generally seen in EGFR negative and KRAS negative tumors
- Generally seen in younger patients, adenocarcinoma histology and never smokers
- Crizotinib (ALK TKI) helpful for patients whose tumors have mutated ALK – over 50% response rates seen in early trials
- Predicts resistance to EGFR inhibitors

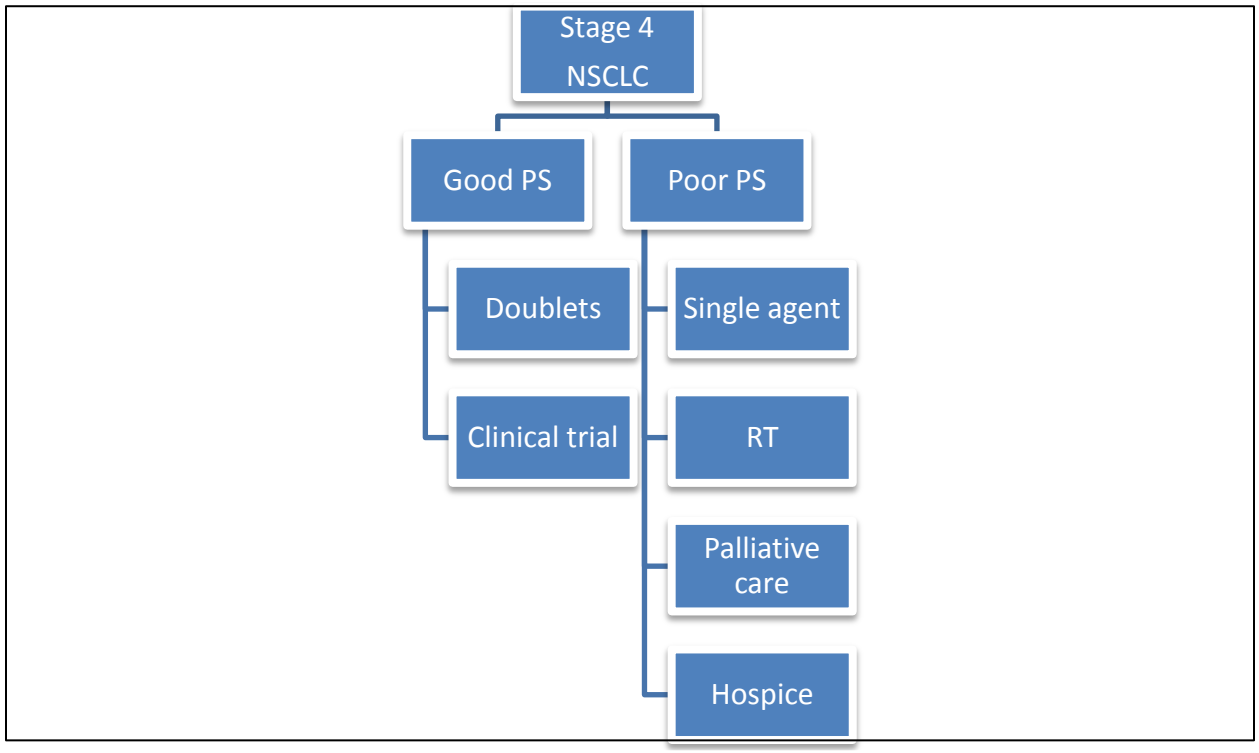
Clinical correlation: How accurate

- Even though certain characteristics are associated with certain mutations, only molecular testing can reliably detect genetic mutations
- Reflex testing
    - Timely and resource saving and protocol driven for consistency
    - Automatic testing for EGFR for all non squamous samples
    - ALK testing for EGFR negative tumors
    - Some labs start with KRAS → if negative than EGFR assay and if negative → than ALK assay
- NCCN Clinical Practice Guidelines 2012
    - Recommend EGFR and ALK mutation testing all recurrent or metastatic Adenocarcinoma, large-cell carcinoma, and NSCLC NOS.
    - Do not recommend routine biomarker testing of pure squamous cell carcinoma

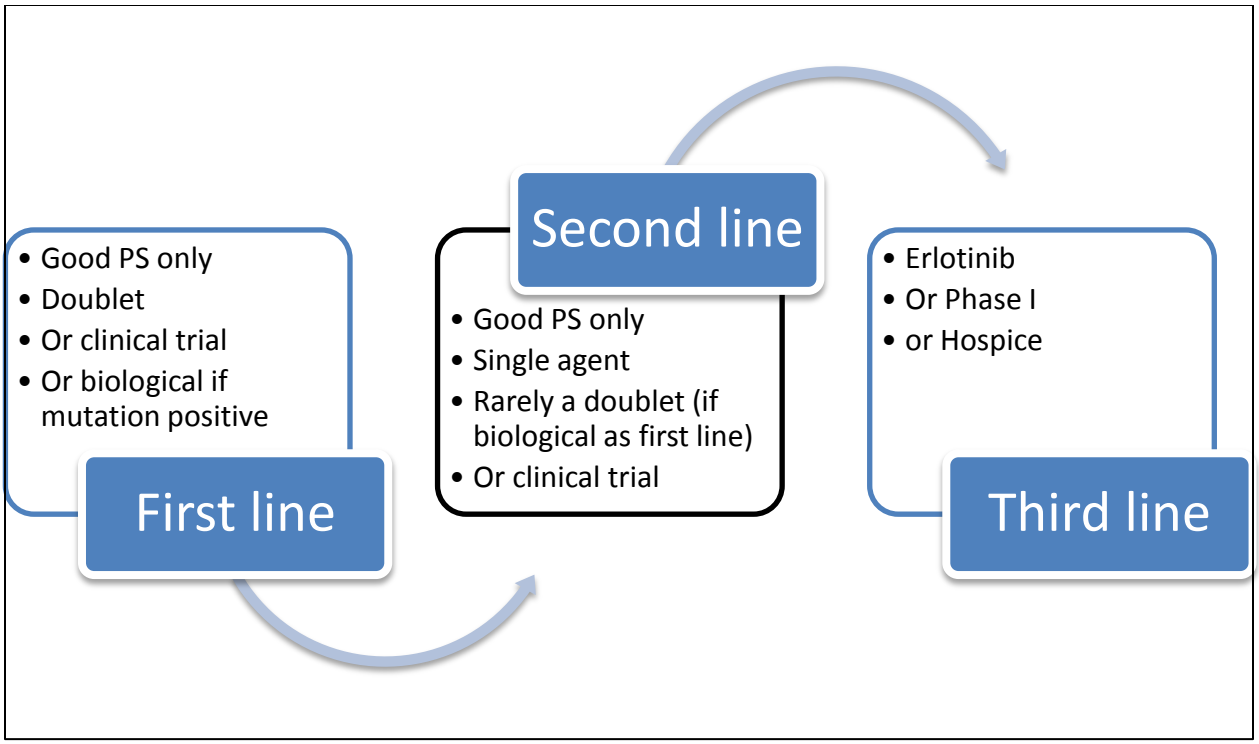
Example of Histology based therapy in actual clinical practice



Example of Performance Status (P)S based therapy



Example of sequential therapy


First line
• Good PS only
• Doublet
• Or clinical trial
• Or biological if mutation positive
Second line
• Good PS only
• Single agent
• Rarely a doublet (if biological as first line)
• Or clinical trial
Third line
• Erlotinib
• Or Phase I
• or Hospice