Lung Cancer Introductory Lecture

General Info: Lung Cancer

General Information:

50% occur age > 65

Standard Screening:

Age 50-80
20 pack-year history
Current or former smoker (within 15 years)

Annual low-dose CT

Clinical Risk Factors:

Smoking
- 80-90% of lung cancer is smoking- related
- 10-15% of smokers get lung cancer

Other exposures
- Asbestos, chemicals, radon

Medical Conditions
- COPD
- Age

Types of Lung Cancer

1. Non-Small Cell Lung Cancer = NSCLC

- Adenocarcinoma
- Squamous

2. Large Cell Lung Cancer = LCLC

* Distinct entity between NSCLC and SCLC
  Treated more like SCLC

3. Small Cell Lung Cancer = SCLC

spectrum of pulmonary neuroendocrine tumors (NET)

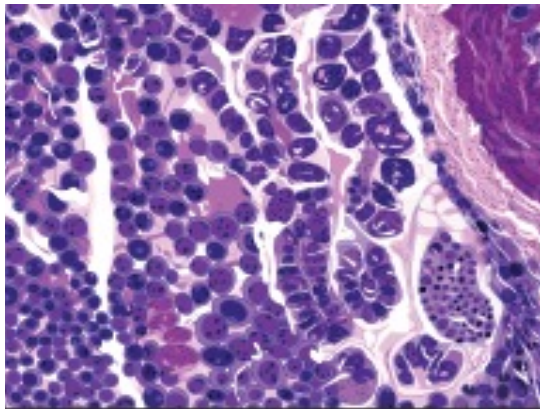
- Carcinoid — low-grade NET
- Atypical — intermediate-grade NET
- Small Cell — high-grade NET

increasing grade

Lung Cancer Pathology

Lung Primary IHC: CK7+/CK20-

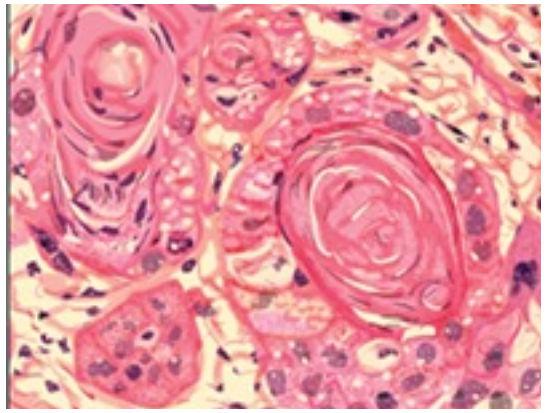
Adenocarcinoma



Histology: glandular cells

IHC:
TTF+
Napsin+

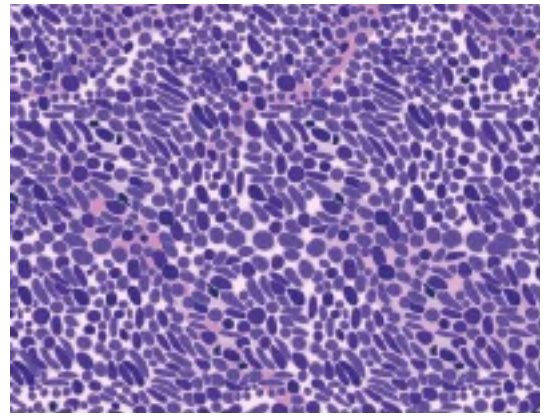
Squamous



Histology: keratin pearls

IHC:
P40+
P63+

Small Cell



Histology: small, round blue monotonous sheets of cells

IHC:
Synaptophysin+
Chromogranin+
CD56+

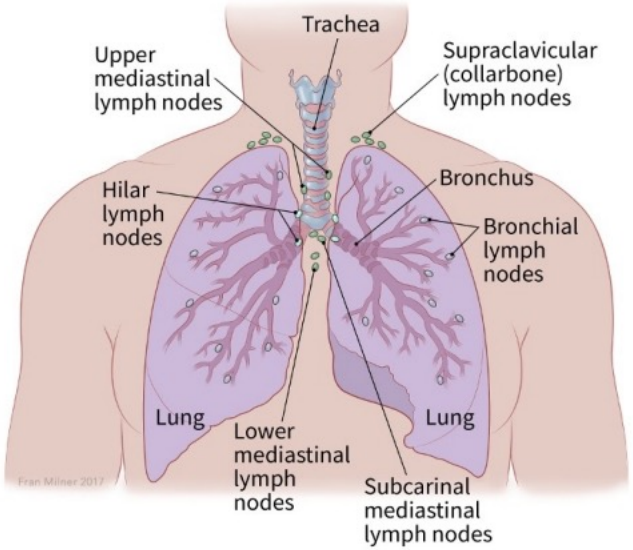
Lung Cancer Staging & Prognosis

NSCLC Staging

NSCLC T Sizes:
T1: 0-3 cm
T2: 3-5 cm
T3: 5-7 cm; multiple nodules same lobe
T4: > 7 cm; ipsilateral multi-lobular nodules

NSCLC LN:
N1: Lobar/hilar
N2: Ipsilateral Mediastinal/subcarinal
N3: Contralateral Mediastinal/supraclavicular

Rough Staging Guide NSCLC:
Stage I: T1-T2, N0, M0
Stage II: T1-3, N0-1, M0
Stage III: T1-4, N0-3, M0
Stage IV: M+ (includes Pleural and Pericardial effusions)



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Work Up for Stage II+

PET-CT
Brain MRI

SCLC Staging

Limited (LS-SCLC)
Confined within a radiation field

Extensive (ES-SCLC)
Extends beyond a radiation field

Lung Cancer Staging & Prognosis

SCLC is MORE aggressive than NSCLC

NSCLC 5Y Overall Survival by Stage: *Rough Guide*

- Stage I = 60-70%
- Stage II = 40-50%
- Stage III = 20-30%
- Stage IV = <10%

NSCLC vs. SCLC

SCLC is very aggressive.
OS for ES-SCLC is weeks-months.

Clinical Pearl

Chemotherapy interferes with cell division and affects rapidly dividing cells more than slowly dividing cells *THUS*

Chemotherapy works very well on rapidly dividing SCLC cells; however, cancer will return quickly and often be insensitive to prior therapies

Non-Small Cell Lung Cancer

NSCLC Early Lung Cancer Treatment

Very Early Stage (Stage I-II)

* Very Early Stage = Tumor < 4-5 cm
  Node negative

Surgical Resection (lobectomy) +
Observation

Resectable Early Stage (Stage II-IIIA)

* Resectable = non-bulky hilar LN or single station mediastinal LN

Surgical Resection (lobectomy) +
Neoadjuvant or Adjuvant chemotherapy
Maintenance TKI or IO

Locally Advanced Unresectable (Stage IIIB-IIIC)

ChemoRT +
Maintenance Durvalumab

NSCLC Early Lung Cancer Treatment

Resectable Early Stage

Surgery + Chemotherapy
+/- TKI
+/- IO

Chemotherapy Regimens

Platinum Doublet [4 cycles]

* Cis preferred for curative-intent (more toxic)

Cisplatin + **Pemetrexed (non-squamous)**
Gemcitabine (squamous)
Docetaxel/Taxotere (squamous)

Maintenance Therapy

EGFR+ (exon 19del, exon21 L858R) = Osimertinib x3Y
PDL1+ (EGFR/ALK-) = Atezolizumab x1Y
Any PDL1 (EGFR/ALK-) = Pembrolizumab x 1Y

Chemo Ineligible

EGFR+ = Osimertinib
PDL1+ = Pembrolizumab

Important Side Effects:

Cisplatin → neuropathy, nephrotoxicity, ototoxicity
Pemetrexed → mucositis (needs B12/folate ppx)
Taxanes → neuropathy
All → myelosuppression, alopecia (exception pemetrexed)

NSCLC Early Lung Cancer Treatment

Locally Advanced Unresectable

ChemoRT + Durvalumab

Chemotherapy Regimens

Platinum Doublet [4 cycles]

Cisplatin +

Pemetrexed (non-squamous)
Paclitaxel/Taxol (squamous or adeno)
Etoposide (squamous or adeno)

Maintenance Therapy
Any PDL1: Durvalumab x1Y

Important Side Effects:

Cisplatin → neuropathy, nephrotoxicity, ototoxicity
Pemetrexed → mucositis (needs B12/folate ppx)
Taxanes → neuropathy
All → myelosuppression, alopecia (exception pemetrexed)

NSCLC Early Lung Cancer Treatment: Special Subtypes

Pancoast Tumors

Definition: tumors located at lung apex (superior sulcus)
Often invade chest wall, ribs

Potential Symptoms:

- Horner's (miosis, ptosis, anhidrosis)
- Shoulder pain
- Ulnar neuropathy
- Muscle weakness/wasting

Management:
Neoadjuvant chemoRT → surgical resection → chemo

Neuroendocrine Tumors

Low-Grade NET (Carcinoid)

Surgery + Observation

Intermediate-Grade NET (Atypical)

Surgery + Observation or ChemoRT

High-Grade NET (Small Cell)

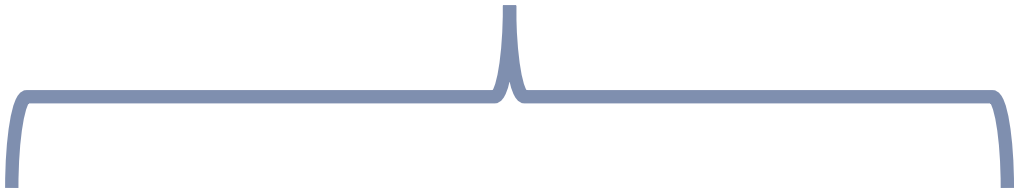
ChemoRT LS-SCLC

Metastatic NSCLC Treatment Approach

1. Identify if genetic driver mutation present

Driver mutations are most often found in NSCLC non-smokers

* Send for sequencing in all stage IV adenocarcinoma
* Send for sequencing in stage IV squamous if non-smoker



Driver Mutation Present

→ **Targeted Molecular Therapy**

No Driver Mutation

→ **Immunotherapy +/- Chemotherapy**

Metastatic NSCLC Treatment: Driver Mutation Present

Driver Mutation	Front Line Therapy	Other Targeted Agents
EGFR Several Muts Exon 19del, Exon 21 L858R, S768I, L861Q, G719X	Osimertinib, Dacomitinib	Erlotinib, Gefitinib, Afatinib
EGFR Exon 20 Ins Mut	Amivantamab, Mobocertinib	
ALK Rearrangement	Alectinib, Brigatinib, Lorlatinib	Crizotinib, Ceritinib
ROS1 Rearrangement	Crizotinib, Entrectanib	Ceritinib, Lorlatinib
BRAF V600E	Dabrafenib + Trametinib	Dabrafenib, Vemurafenib
MET Exon 14 Skip Mut	Capmatinib, Tepotinib	Crizotinib
RET Rearrangement	Selpercatinib, Pralsetinib	Cabozantinib, Vadentinib
KRAS G12C Mut	Sotorasib *2nd line	Adagrasib
NTRK 1/2/3 Gene Fusion	Larotrectinib, Entrectanib	
ERBB2/HER2 Mut	Trastuzumab Deruxtecan/Enhertu 2nd line	Trastuzumab Emtansine/TDM1

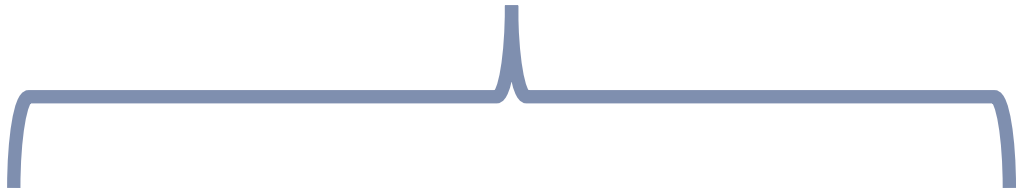
POD on TARGETED AGENT:

- Re-biopsy, consider conversion to SCLC or drug-resistant mutation
- If no other targeted therapy, switch to chemotherapy. Patients with driver mutations are less responsive to immunotherapy (exception KRAS, BRAF)

Metastatic NSCLC Treatment Approach

1. Identify if genetic driver mutation present

2. Check PDL1 biopsy staining



Driver Mutation Present

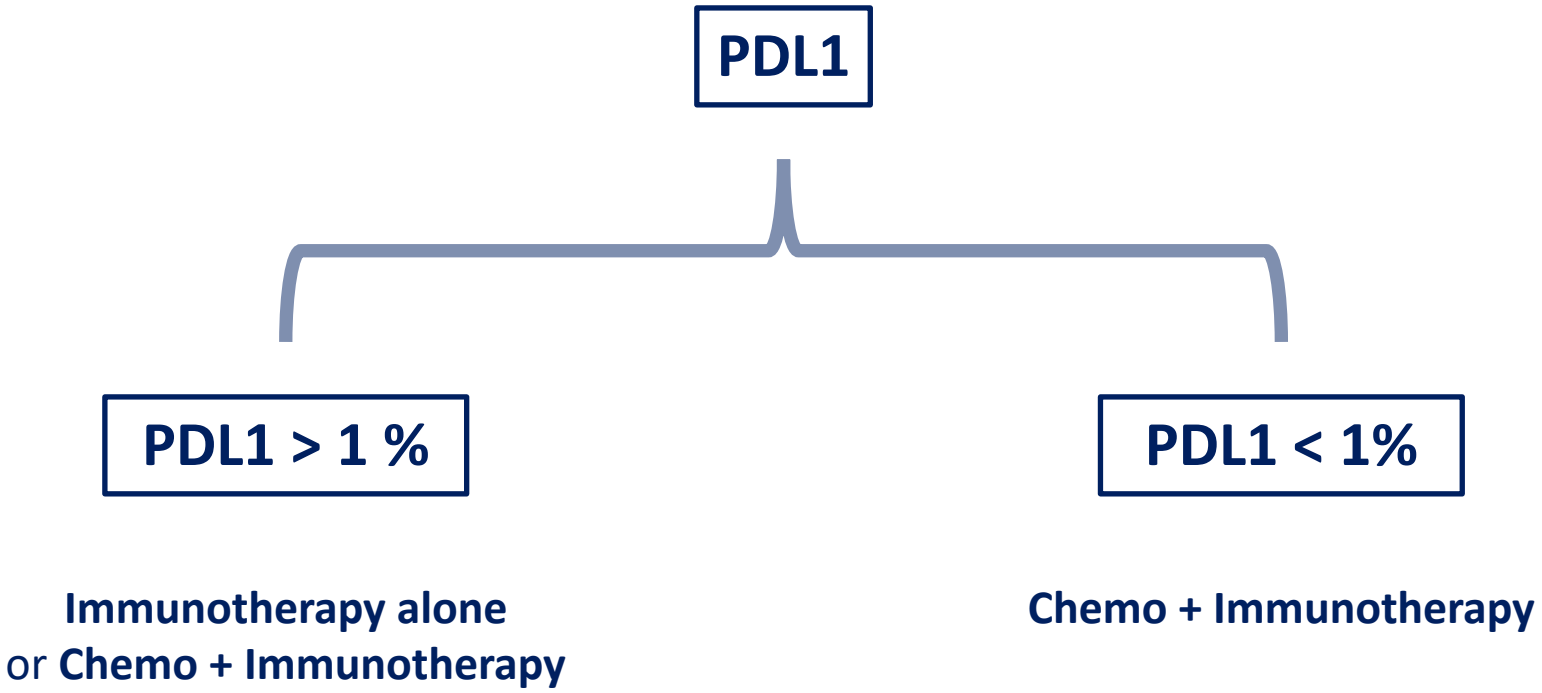
→ Targeted Molecular Therapy

No Driver Mutation

→ Immunotherapy +/- Chemotherapy

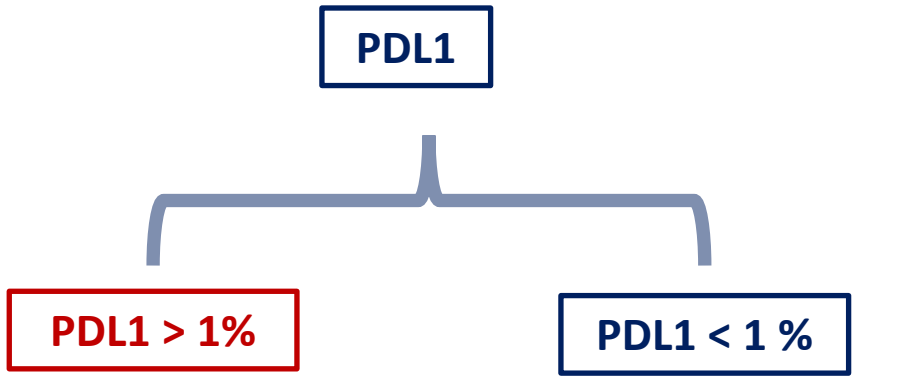
Metastatic NSCLC Treatment: No Driver Mutation

Chemotherapy or Immunotherapy



Metastatic NSCLC Treatment: No Driver Mutation

Chemotherapy or Immunotherapy



Immunotherapy
or **Chemo + Immunotherapy**

Chemo + Immunotherapy

Immunotherapy Regimens: Checkpoint Inhibitors (CPI)

PDL1 >1%	**PDL1 >50%**	
Pembrolizumab	Pembrolizumab	Atezolizumab
Nivolumab/Ipilimumab	Nivo/Ipi	Cemiplimab

Immunotherapy Management

PMH: whether to use CPI

Autoimmune Disease/Transplant: Consider withholding CPI
Immunosuppressants: Consider discontinuing prior to CPI

Pseudo-Progression Phenomenon

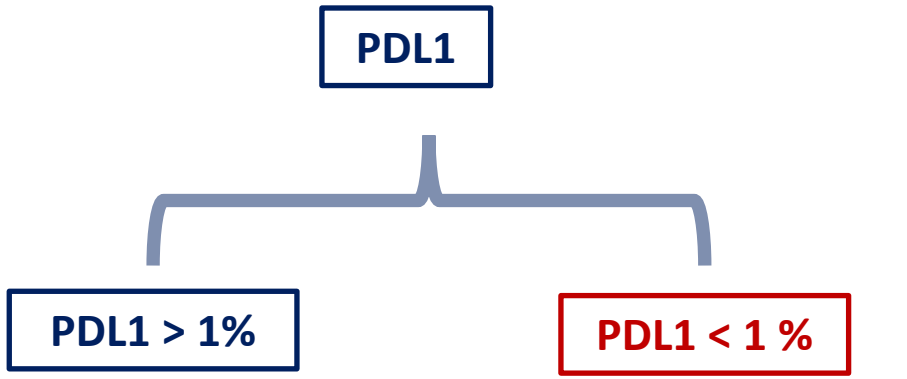
Radiographic Flair: usually occurs within approx. 1-3 months, commonly in areas of prior cancer

IRAE: Immune Related Adverse Events

IRAE: dermatitis, colitis, hepatitis, thyroiditis, any “itis”
Timing: can occur anytime
Management = hold therapy, steroids, immunosuppressants
**based on IRAE grade: graded 1 (mild) - 4 (severe)*

Metastatic NSCLC Treatment: No Driver Mutation

Chemotherapy or Immunotherapy



Immunotherapy
or **Chemo + Immunotherapy**

Chemo + Immunotherapy

Chemotherapy Regimens

Platinum Doublet +/- CPI

* Carbo preferred for palliative intent (less toxic)

Carboplatin +

Pemetrexed (non-squamous)
Nab-Paclitaxel/Abraxane (squamous)
Paclitaxel/Taxol (squamous)

CPI = ex: Pembrolizumab

Maintenance:
Consider ongoing maintenance, often IO +/- pemetrexed or bevacizumab

Important Side Effects:

Carboplatin → neuropathy, nephrotoxicity, ototoxicity
Pemetrexed → mucositis (needs B12/folate ppx)
Paclitaxel → neuropathy
All → myelosuppression, alopecia (exception pemetrexed)

Metastatic NSCLC Treatment: No Driver Mutation

Oligometastatic Disease

Consider oligometastectomy if:

- CNS
- Adrenal

2nd Line/POD

- Nivolumab
- Atezolizumab
- Pembrolizumab
- Docetaxel +/- Ramucirumab
- Gemcitabine
- Nab-paclitaxel/Abraxane
- Platinum doublet + Necitumab
- Afatinib (non-EGFR squamous, if POD on platinum)

Metastatic NSCLC Treatment Paradigm

1. Sequence if Driver Mutation

Driver Mutation Present

→ **Targeted Molecular Therapy**

EGFR:	Osimertinib
ALK:	Alectinib, Brigatinib, Lorlatinib
ROS:	Crizotinib, Entrectanib
BRAF:	Dabrafenib/Trametinib
MET:	Capmatinib
RET:	Selpercatinib
KRAS:	Sotorasib 2nd line
HER2:	Enhertu 2nd line

No Driver Mutation

2. Stain for PDL1

PDL1 > 1%

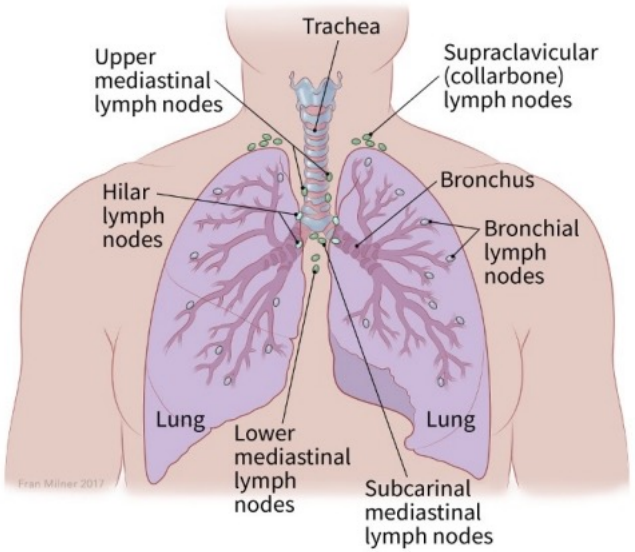
→ **CPI monotherapy**
→ **Carboplatin Doublet + CPI**

PDL1 < 1%

→ **Carboplatin Doublet + CPI**

Small Cell Lung Cancer

SCLC Staging



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SCLC Staging
requires mediastinal staging

SCLC Staging

Limited (LS-SCLC)
Confined within a radiation field

→ Ipsilateral hemothorax
→ Ipsilateral supraclavicular LN
→ Contralateral mediastinal LN

Extensive (ES-SCLC)
Extends beyond a radiation field

→ Pleural, pericardial effusions
→ Contralateral hilar/supraclavicular = controversial

SCLC Treatment Paradigm

Limited Stage SCLC

Within a radiation field
→ ChemoRT (sequential or concurrent RT)

→ rarely if very early stage (T1-T2N0)
Surgery + Chemo

Extensive Stage SCLC

NOT within a radiation field
→ Chemotherapy + Immunotherapy

Chemotherapy Regimens

LS-SCLC: Platinum Doublet [4 cycles]

Cisplatin + Etoposide

ES-SCLC: Platinum Doublet + CPI

Carboplatin + Etoposide
+ Atezolizumab or Durvalumab

* Cisplatin if LS-SCLC, curative intent
* Carboplatin if ES-SCLC, no curative intent

Important Side Effects:

Carboplatin → neuropathy, nephrotoxicity, ototoxicity
All → myelosuppression, alopecia
CPI → dermatitis, colitis, hepatitis, thyroiditis, any “itis”

SCLC Treatment Paradigm

PCI: prophylactic cranial irradiation

Consider in LS-SCLC: CAN improve OS, chance of cure
Consider in ES-SCLC: does NOT improve OS, no chance of cure

→ *typically*: no PCI for ES-SCLC

2nd Line/POD

- Clinical Trial
- Topotecan
- Lurbinectidin
- Other single agent chemo or IO

Mesothelioma

Mesothelioma

Histologic Types:

Epithelioid
Often better prognosis

Mixed: Epithelioid + Sarcomatoid

Sarcomatoid
Often worse prognosis

Clinical Risks:

Age
Asbestos exposure
Radon exposure
Prior RT

Genetic Risks:

BRCA
MET (Sarcomatoid type)

Mesothelioma

Resectable: Stage I-IIIA

Tumor: **pleura +/- lung parenchyma, diaphragm**

Nodes: **ipsilateral hilar, mediastinal**

Unresectable: Stage IIIB+

Tumor: **+/- chest wall, bone, contralateral pleura, mediastinal organs, pericardium, peritoneum**

Nodes: **contralateral mediastinal, supraclavicular**

Early Stage & Resectable

Stage I-IIIA, Epithelioid or Biphasic

Neoadjuvant chemo → surgery +/- RT

1) Neoadjuvant Platinum/Pemetrexed
2) Pleurectomy/Decortication
3) Consider adjuvant RT

Advanced Stage & Unresectable

Stage IIIB+ Epithelioid, Biphasic or Sarcomatoid

Chemotherapy **(works better for epithelioid)**
Platinum/Pemetrexed +/- Bevacizumab

Immunotherapy **(preferred in sarcomatoid, biphasic; works well in epithelioid)**
Nivolumab/Ipilimumab

Lung Cancer Reference Handout

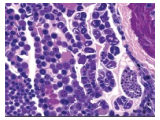
Lung Cancer Dx

1. Non-Small Cell Lung Cancer = NSCLC

Adenocarcinoma

Histology: glandular cells

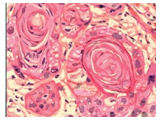
IHC:
TTF+
Napsin+



Squamous

Histology: keratin pearls

IHC:
P40+
P63+



2. Large Cell Lung Cancer = LCLC

*** Distinct subtype between NSCLC and SCLC**

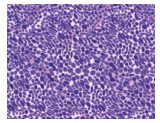
3. Small Cell Lung Cancer = SCLC

- **Carcinoid** low-grade NET
- **Atypical** intermediate-grade NET
- **Small Cell** high-grade NET

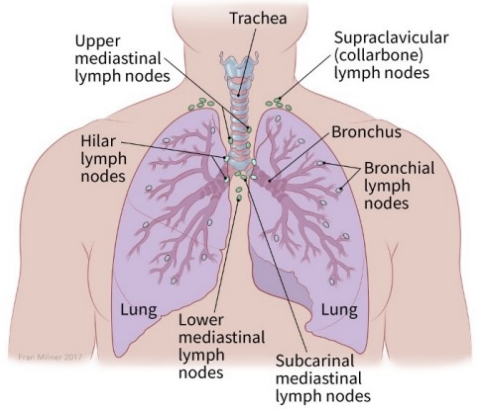
pulmonary NETs

Histology: small, round blue monotonous sheets

IHC:
Synaptophysin+
Chromogranin+
CD56+



Lung Cancer Staging



NSCLC Staging

Rough Staging Guide NSCLC:
Stage I: T1-T2, N0, M0
Stage II: T1-3, N0-1, M0
Stage III: T1-4, N0-3, M0
Stage IV: M+ (malignant effusions)

NSCLC T Sizes:
T1: 0-3 cm
T2: 3-5 cm
T3: 5-7 cm; multiple nodules same lobe
T4: > 7 cm; ipsilateral multi-lobular nodules

NSCLC N Status:
(N1) Lobar/hilar
(N2) Mediastinal/subcarinal
(N3) Contralateral/supraclavicular

SCLC Staging

Limited (LS-SCLC)
Confined to a radiation field

Extensive (ES-SCLC)
Extends beyond a radiation field

SCLC Tx

Limited Stage SCLC

Ipsilateral Hemothorax: within a radiation field
→ ChemoRT +/- PCI
* Rarely surgery + chemo (T1-T2N0)

LS-SCLC: Platinum Doublet
Cisplatin + Etoposide

Extensive Stage SCLC

NOT within a radiation field
→ Chemotherapy + CPI

ES-SCLC: Platinum Doublet + CPI
Carboplatin + Etoposide
+ Atezolizumab or Durvalumab

Mesothelioma Tx

Resectable, Stage I-IIIA

Epithelioid, Biphasic

Neoadjuvant chemo → surgery +/- RT
1) Neoadjuvant Platinum/Pemetrexed
2) Pleurectomy/Decortication
3) Consider adjuvant RT

Unresectable (Stage IIIB+)

Epithelioid, Biphasic, Sarcomatoid

Chemotherapy
Platinum/Pemetrexed +/- Bevacizumab
Immunotherapy
Nivolumab/Ipilimumab

Early Stage NSCLC Lung Cancer Tx

Very Early Stage (Stage I-II)

Very Early Stage = Tumor < 4-5 cm, node negative

Surgical Resection (Lobectomy) + Observation

Resectable Early Stage (Stage II-IIIA)

Resectable = non-bulky hilar LN, single station mediastinal LN

Surgical Resection + Neoadjuvant or Adjuvant Platinum Doublet

EGFR+ = Osimertinib x3Y
PDL1+ = Atezolizumab x1Y
PDL1- = Pembrolizumab x1Y

Locally Advanced Unresectable (Stage IIIB-IIIC)

ChemoRT (Platinum Doublet) + Durvalumab x 1Y

Neoadjuvant/Adjuvant/ChemoRT Chemotherapy Regimens

Platinum Doublet — **Cisplatin** +
- **Pemetrexed (non-squamous)**
- **Gemcitabine (squamous)**
- **Docetaxel (squamous)**
- **Etoposide (chemoRT)**
- **Paclitaxel/Taxol (chemoRT)**

Important Side Effects:
- **Platins** → neuropathy, nephrotoxicity, ototoxicity
- **Pemetrexed** → mucositis (need B12/folate ppx)
- **Taxanes** → neuropathy
- **All** → myelosuppression, alopecia
- **CPI** → dermatitis, colitis, hepatitis, thyroiditis, any "itis"

Metastatic NSCLC Lung Cancer Tx

1. Sequence if Driver Mutation

- **Driver Mutation Present**
  - → **Targeted Molecular Therapy**
    - **EGFR:** Osimertinib
    - **ALK:** Alectinib, Brigatinib, Lorlatinib
    - **ROS:** Crizotinib, Entrectanib
    - **BRAF:** Dabrafenib/Trametinib
    - **MET:** Capmatinib
    - **RET:** Selpercatinib
    - **KRAS:** Sotorasib 2nd line
    - **HER2:** Enhertu 2nd line
- **No Driver Mutation**
  - **2. Stain for PDL1**
    - **PDL1 > 1%**
      - → **CPI monotherapy**
      - → **Carbo Doublet + CPI**
    - **PDL1 < 1%**
      - → **Carbo Doublet + CPI**

Immunotherapy: Checkpoint Inhibitors (CPI)

PDL1 >1%	PDL1 >50%	
Pembrolizumab	Pembrolizumab	Atezolizumab
Nivolumab/Ipilimumab	Nivo/Ipi	Cemiplimab

Carbo Doublet + CPI

Carboplatin + **Pemetrexed (non-squamous)**
Nab-Paclitaxel/Abraxane (squamous)
Paclitaxel/Taxol (squamous)

Maintenance
Consider maintenance IO
+/- Pemetrexed or Bevacizumab

+ CPI = ex: Pembrolizumab