Small-Cell Lung Cancer (SCLC)

What do we know?

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Incidence and Etiology

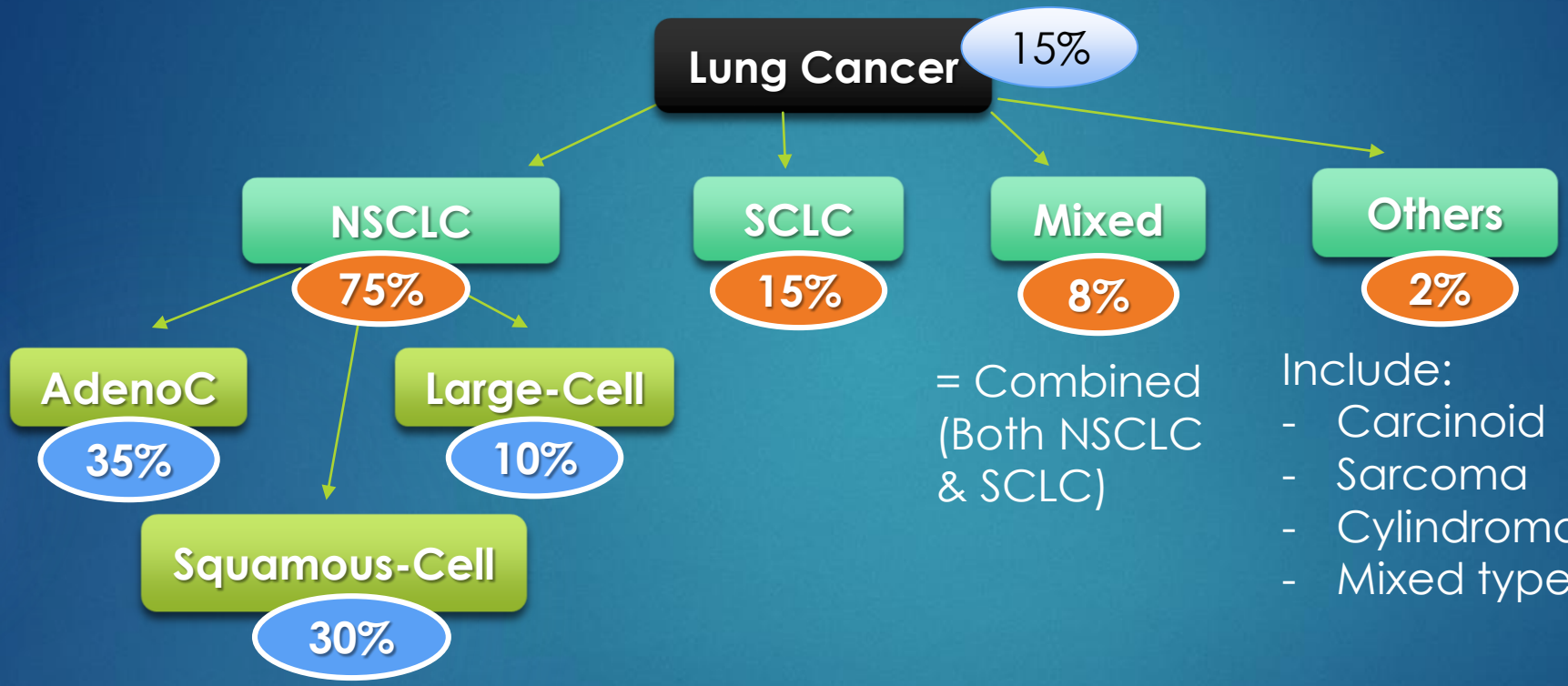
- Lung cancer is one of the most common malignancies worldwide. During 2009, approximately 219,440 of an estimated 1,449,350 **(15 %)** new cancer cases, and 1 5 9,390 of 562,340 **(28%)** total cancer deaths in the United States were attributable to lung cancer.

- **Pathological subtypes** of lung cancer generally include: NSCLC (~80% of all cases) & SCLC (~20%).

- **SCLC:** In Europe, the highest incidence rates in males are observed in Central/Eastern and Southern Europe (57 and 49 per 100,000, respectively), whereas in women the highest rates are found in Northern Europe (36 per 100,000).

- **Tobacco exposure** causes SCLC in over 95% of cases, and as a result, the incidence rates mirror smoking patterns.

Pathological Subtypes of Lung Cancer



= Combined (Both NSCLC & SCLC)

Include:
- Carcinoid
- Sarcoma
- Cylindroma
- Mixed type

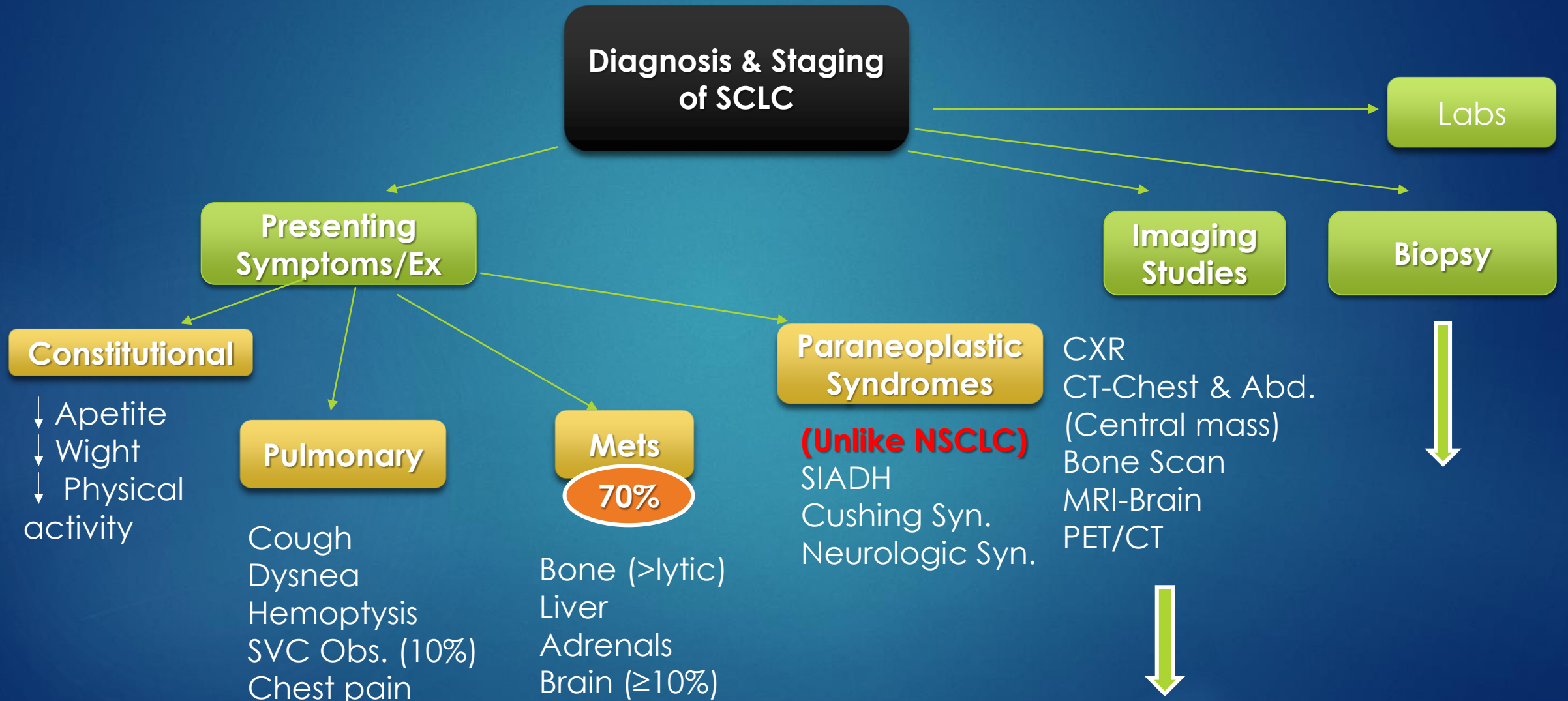
Natural History of SCLC

- SCLC originates from neuroendocrine-cell precursors and is characterized by its rapid growth, its high response rates to both chemotherapy and radiotherapy and development of treatment resistance in patients with metastatic disease.

NB

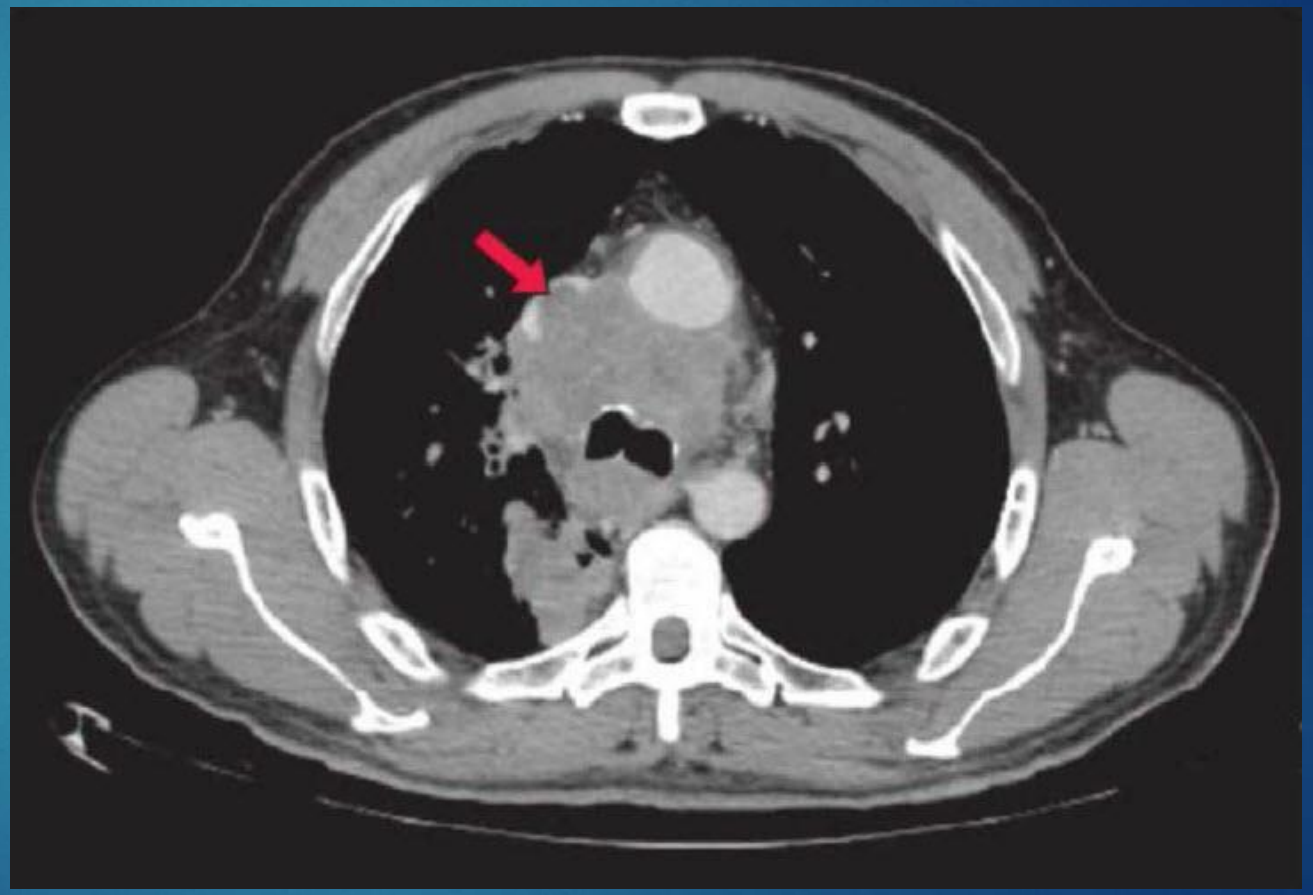
- **Neuroendocrine tumors (NET)** of the lung encompass a spectrum of tumors, including:
  - low-grade typical carcinoid
  - Intermediate grade atypical carcinoid.
  - High-grade large cell neuroendocrine carcinoma (LCNEC).
  - SCLC.

Diagnosis & Staging



Diagnosis

Fig 01
Computed tomography scan showing small cell lung cancer with an infiltrative mediastinal mass causing compression of the superior vena cava (arrow).



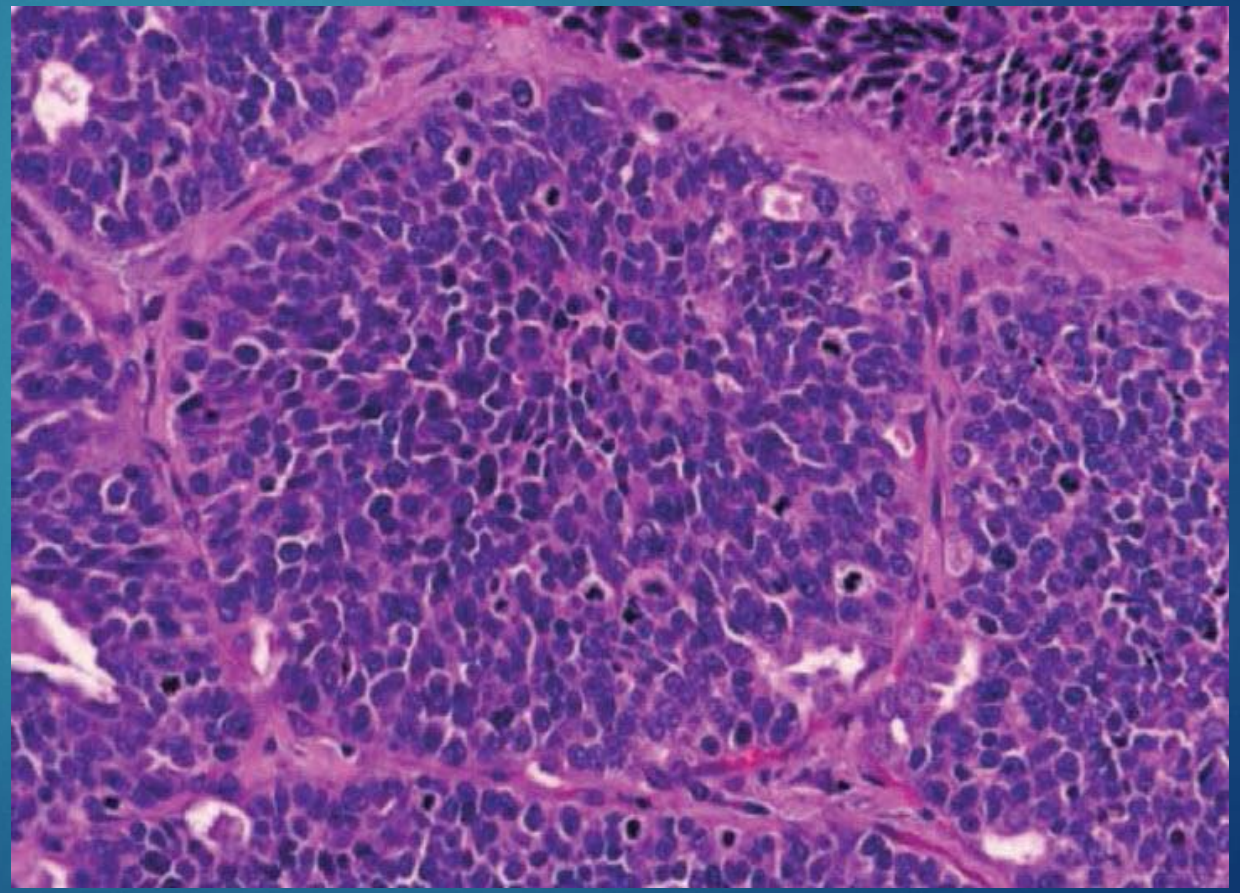
Diagnosis

Pathological diagnosis: due to its frequent central location, biopsy from the ***primary tumor*** may be best obtained by **bronchoscopy**. Other methods include Mediastinoscopy, EBUS, transthoracic needle aspiration, or even thoracoscopy. Biopsy from a ***metastatic lesion*** is preferred if its location is easily and safely accessible, this also has the advantage of pathologically staging the patient.

- **Morphology** (Based on WHO classification): Uniform round to spindled-shaped small cells, sparse cytoplasm, high mitotic index, necrotic areas.
- **IHC:** Used for diagnosis confirmation (synaptophysin, chromogranin A, CD56, thyroid transcription factor 1 and MIB-1), it **is *NOT* mandatory** but should be used in case of any doubt.

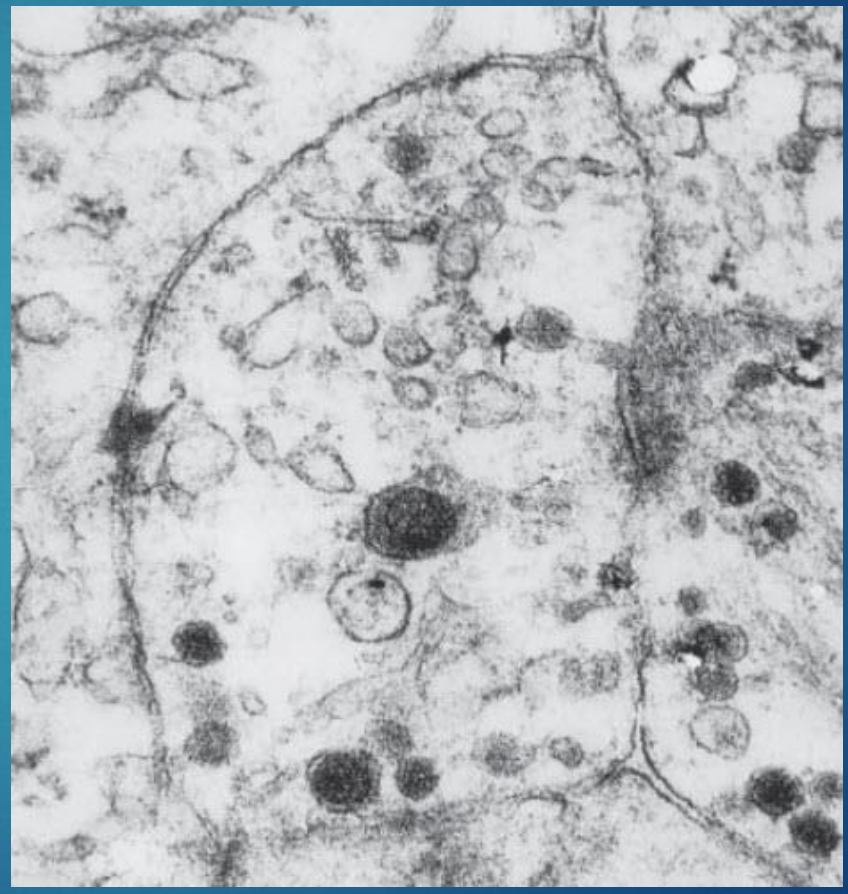
Diagnosis

Fig 2:
The tumor consists of dense sheets of small cells with scant cytoplasm, finely granular nuclear chromatin, frequent mitoses, and inconspicuous or absent nucleoli.



Diagnosis

Fig 3:
Electron microscopy appearance in SCLC. Dense neurosecretory granules are shown in cell processes (×52 250).



Staging

Limited-stage disease:
Tumor being confined to one hemithorax with regional LN mets. Including both ipsilateral and contralateral hilar, mediastinal, supraclavicular, and ipsilateral peural effusion (can be encompassed by one radiation field)

Advantage: Provides better prognostic information and more precise nodal staging, which is required for conformal radiation techniques and IMRT.

Staging

TNM Staging

TX	Positive cytology only
T1	≤3 cm
T1a	≤2 cm
T1b	>2 to 3 cm
T2	Main bronchus ≥2 cm from carina invades visceral pleura, partial atelectasis
T2a	>3–5 cm
T2b	>5–7 cm
T3	>7 cm; chest wall, diaphragm, pericardium, mediastinal pleura, main bronchus <2 cm from carina, total atelectasis, separate nodule(s) in the same lobe
T4	Mediastinum, heart, great vessels, carina, trachea, esophagus, vertebra; separate tumour nodule(s) in a different ipsilateral lobe
N1	Ipsilateral peribronchial, ipsilateral hilar
N2	Subcarinal, ipsilateral mediastinal
N3	Contralateral mediastinal or hilar, scalene or supraclavicular
M1	Distant metastasis
M1a	Separate tumour nodule(s) in a contralateral lobe; pleural nodules or malignant pleural, or pericardial effusion
M1b	Distant metastasis

Grouping

Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a,b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T1a,b	N1	M0
	T2a	N1	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a,b, T2a,b	N2	M0
	T3	N1, N2	M0
	T4	N0, N1	M0
Stage IIIB	T4	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

Limited-stage disease = T1-4, N1-3 M0
(i.e.: = non-mets disease)

Prognosis

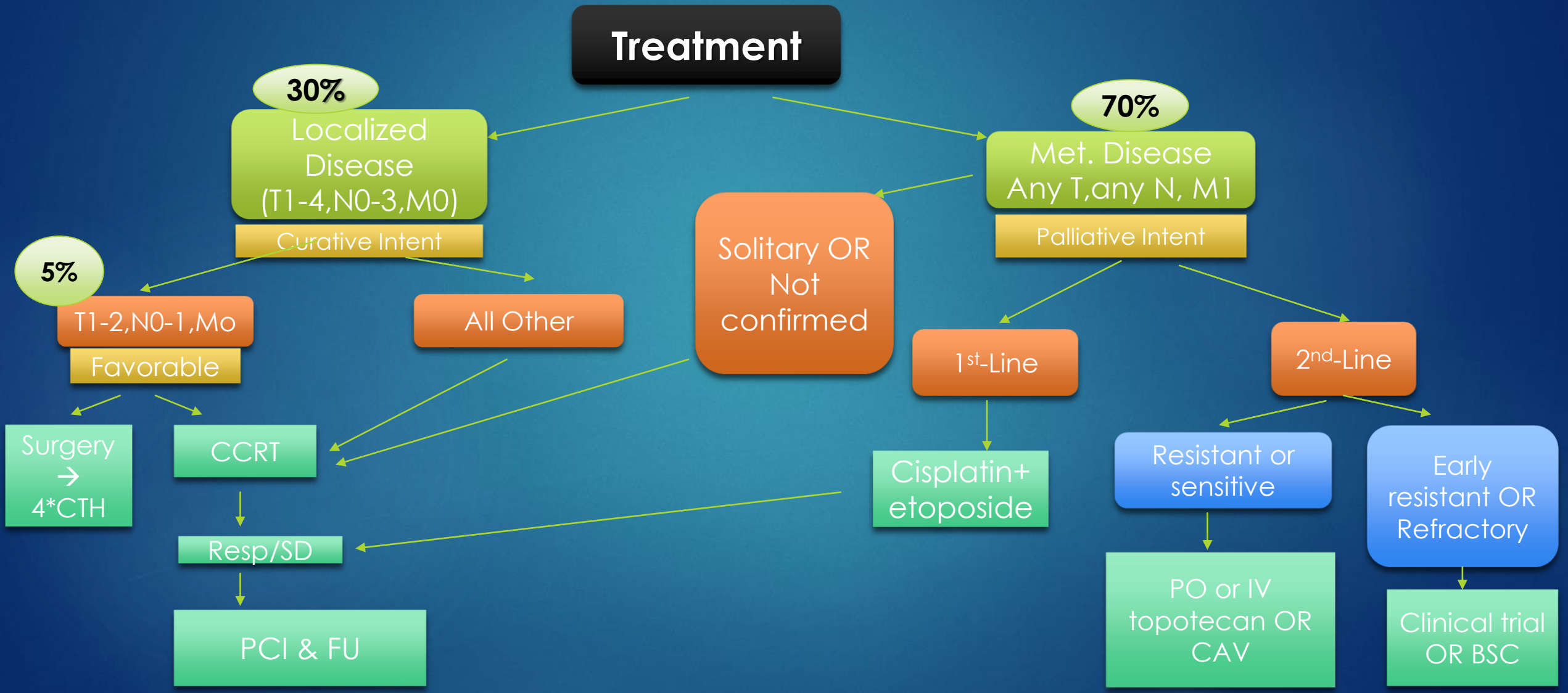
- Stage is the most important prognostic factor. **In ES disease**, **Certain metastatic sites**, such as liver, brain, bone marrow, and bone, as well as the **total number of metastatic sites** involved have been found to be of prognostic significance.

	Localized Disease (T1-4,N1-3,M0)		Met. Disease (M1)
	T1-2,N0-1	All Other	
5y OS	50%	20-25%	--------
mOS	--------	--------	< 10 months
mPFS	--------	--------	5.5 months

Prognosis

- **Paraneoplastic Cushing syndrome** has been correlated with a poor response to therapy and short survival.
- **Elevation of serum LDH** is found in 33 % to 57 % of all patients with SCLC and up to 85 % of patients with extensive-stage disease and is a strong prognostic and predictive factor. Elevation of serum LDH is associated with the presence of bone marrow involvement.
- **Serum neuron-specific enolase** (NSE): provided no additional benefit over serum LDH
- **Carcinoembryonic antigen** (CEA) has been found to predict outcome in SCLC in multiple series

Treatment


Treatment
30%
Localized Disease (T1-4,N0-3,M0)
Curative Intent
5%
T1-2,N0-1,Mo
Favorable
All Other
Surgery → 4*CTH
CCRT
Resp/SD
PCI & FU
Solitary OR Not confirmed
70%
Met. Disease Any T,any N, M1
Palliative Intent
1st-Line
Cisplatin+ etoposide
2nd-Line
Resistant or sensitive
PO or IV topotecan OR CAV
Early resistant OR Refractory
Clinical trial OR BSC

Treatment

- **Localized Disease (T1-4,N0-1,M0):**
  - **T1-2,N0-1,M0:**
    - If confirmed negative med. LN (by imaging: CT, PET/CT and biopsy with EBUS or mediastinoscopy if enlarged): Surgery → 4 Cycles of post-op CTH. Post-op RT can be administered if N1 or N2 disease was accidentally found.
    - If medically unfit for surgery: **CCRT**.
    - PCI can be given if response/SD was achieved.
  - **All Others:** If good PS → **CCRT**
    - **RT schedule**: Standard: 1.8 Gy * 25 fractions

      Accelerated: 1.5 Gy, twice daily for 30 fractions (>Survival, >Toxicity)
    - **RT volumes**: Still to be defines. Selective ENI based on pre-treatment PET/CT can replace ENI (lower nodal recurrence risk)
    - **CTH:** 4 – 6 cycles of cisplatin-etoposide (if once daily fractionation is used). Timing: Should be initiated within the first 30 days of RT (preferred: potential survival advantage) Unless patient's general condition is less than optimal, at that time CTH can be started with the 3rd cycle.
    - **PCI** can be offered if patient has good PS without DP.

Treatment

- **Met. Disease (AnyT,anyN,M1):**
  - **First-line: (RR close to 70%)**
    - **Main treatment** is: combined-CTH; cisplatin-etoposide (OS advantage compared to older regimens).
    - **Carboplatin** can replace cisplatin (Meta-analysis: same efficacy – not tested in young patients or those with localized disease, with different toxicity profile).
    - **3-drug & dose-intense regimens**: **NOT recommended** (Inconsistent results with significant toxicity)
    - **Irinotecan-platinum:** A meta-analysis showed improved OS (Not PFS) compared to the standard cisplatin-etoposide (in Asian population) with different toxicity profile. Until this moment, no regimen is superior to the standard in Western population.
    - **If etoposide is contraindicated**: RCTs showed non-inferiority of the following regimens: **Irinotecan-cisplatin**, **gemcitabine-carboplatin**, or **oral/IV topotecan-cisplatin.**
    - **Continuing CTH beyond 4-6 cycles**: **NOT recommended**, although RCTs showed small 4% OS benefit at 2years, their was considerable risk of toxicity.
    - **PCI:** Indicated if there is any response to first-line ttt with good patient's PS. Typically we give 25 Gy in 10 daily factions or 20 Gy in 5 daily fractions.
    - **CCRT: NOT recommended** even though 4 RCTs showed survival advantage when thoracic RT was added to CTH after seeing response after 3 cycles of those, and whose metastatic sites were in CR. The reason for that is the central trial was underpowered.

Treatment

- **2nd Line:**

  RRs and treatment options depend on time-to-progression (TTP) as follows:

  - **Refractory** (Not responding) and **resistant with early relapse** (TTP<6 weeks) disease: poor outcome. **Treatment options** include: clinical trial participation or BSC.
  - Resistant disease (TTP: 6 weeks to 3 months): RR is 10%
  - Sensitive disease (TTP>3 months): RR is 20%.

  Treatment options for both resistant and sensitive disease include IV or oral topotecan (better symptom control compared to BSC) OR CAV (non-inferior)

Follow Up

- **Localized Disease:**
  - **Goal of FU:** early detection of recurrence while the patient is still in a good PS.
  - **Schedule:** 3-6 monthly CT scans for 2 years with lengthening of intervals thereafter.

- **Met. Disease:**
  - **Schedule:** for patients potentially qualifying for further treatment: 2-3 monthly CT scans are recommended.

Thank You

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