SMALL CELL LUNG CANCER

Introduction

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Small cell lung cancer comes under the neuroendocrine spectrum of tumors.

2021 WHO classification of lung :

Sl no.	Types	Features
1.	Typical carcinoid	Carcinoid morphology and <2 mitoses/2 mm^2 (10 HPFs), lacking necrosis and >0.5 cm.
2.	Atypical carcinoid	Carcinoid morphology with 2 to 10 mitoses/2 mm^2 (10 HPFs) or necrosis (often punctuate)
3.	Large cell neuroendocrine carcinoma	• Neuroendocrine morphology (organoid nesting palisading rosettes, trabeculae). • High mitotic rate > 10/2 mm^2 (10 HPFs), median of 70/2 mm^2. • Necrosis (often large zones). • Cytologic features of a NSCLC[illegible] cell size, low nuclear to cytoplasmic ratio, vesicular or fine chromatin, and/or frequent nucleoli; some tumors have fine nuclear chromatin and lack nucleoli but qualify as NSCLC because of large cell size and abundant cytoplasm. • Positive immunohistochemical staining for one or more NE markers (other than neuron-specific enolase) and/or NE granules by electron microscopy.
4.	Small cell lung cancer	

Classification and grading criteria for neuroendocrine neoplasms of the gastrointestinal tract and hepatobiliary

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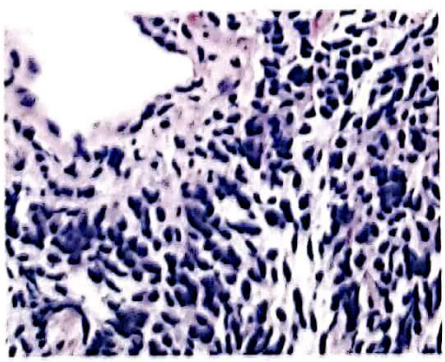
organs, WHO 2019 :

Terminology	Differentiation	Grade	Mitotic rate* (mitoses/2 mm²)	Ki-67 Index* (percent)
NET, G1	Well differentiated	Low	<2	<3
NET, G2	Well differentiated	Intermediate	2 to 20	3 to 20
NET, G3	Well differentiated	High	>20	>20
NEC, small cell type (SCNEC)	Poorly differentiated	High[Δ]	>20	>20
NEC, large cell type (LCNEC)	Poorly differentiated	High[Δ]	>20	>20
MiNEN	Well or poorly differentiated[¶]	Variable[¶]	Variable[¶]	Variable[¶]

- For determining grade of GI and heaptobiliary tumors : mitotic rate and Ki 67 is used.
- For lung tumors only mitosis is used.

Histopathological examination :

- Small blue malignant cells.
- Cells twice the size of resting lymphocytes.
- No distinct nucleoli.
- Finely dispersed chromatin.
- Differentiating points from LCNEC : large cells.
- Nuclear moulding is characteristic.] High grade tumors
- Crush artifacts.]
- Concept of combined SCLC : Coexistence of NSCLC, m/c with squamous cell cancer, treat as SCLC.
- NSCLC : Evolution is 14% into SCLC.



Association of smoking with SCLC is important.
98 % of SCLC are smokers, 2% in non smokers.

Immunohistochemistry :

- EMA and CK positive.
- 80% of SCLC are thyroid transcription factor (TTF I) positive (in adenocarcinoma lung and thyroid tumors).
- Synaptophysin/chromogranin/CD56 or NCAM : The NE markers.
- Ki 67 : 80 to 100.
- > 11 mitoses at least, usually more than 80/10 hpf.

Molecular pathogenesis :

- p53 mutation is the most common, 75 to 98 %.
- Rb gene mutation and myc mutation .
- Driver mutations seen in NSCLC are absent.

Presentation :

- mc symptom of SCLC : Fatigue.
- Large central mass with hilar and mediastinal nodes.
- SVC syndrome seen in 10% of patients at diagnosis.
- Brain mets seen in 18% of cases at diagnosis.
- Bone/liver/adrenal, normal ALP with lytic mets is characteristic.

Paraneoplastic syndromes 00:29:26

Paraneoplastic SIADH :

- 75 % of tumour related SIADH is due to SCLC.
- Euvolemic hyponatremia : Hypoosmolality, hyperosmolar urine; Urine Na > 40 mEq/L.
- most SCLC : ADH is high, but only 10% meet criteria for SIADH and 5% only have symptomatic SIADH.
- Is a bad prognostic factor.
- Both SCC and SCLC (also GI/GU/ovary/HNSCC/olfactory neuroblastoma).

Paraneoplastic cushing's syndrome :

- 50% SCLC have high ACTH but only 5% have cushing syndrome.

- Bad prognostic factor.
- Gene involved : POMC.

Ectopic ACTH secretion :

- SCLC.
- Adenocarcinoma lung.
- SCC lung.
- Bronchial carcinoid.
- MTC.
- Pancreatic islet tumours.
- Phaeochromocytoma.

Ectopic CRH :

- Carcinoids.
- Lung tumors.
- Prostate tumors.
- Islet tumours.

Neurologic paraneoplastic syndromes :

- Limbic encephalitis.
- Subacute cerebellar degeneration, presenting as ataxia.
- GI pseudoobstruction.
- Autonomic neuropathy.
- Subacute sensory neuropathy.
- Onconeural antibody : Anti Hu or ANNA I and antiCV2 or anti CRMP5.

Other paraneoplastic syndromes :

- SCLC and Ca breast can cause stiff person syndrome, onconeural antibody : Anti amphiphysin.
- Opsoclonus myoclonus syndrome : Anti Ri or anti ANNA2 (also in breast).
- Retinopathy (CAR) : Recoverin antibody (anti bipolar cell).
- Limbic encephalitis/seizures : Anti GABAb receptor.
- Anti yo (CA1) is NOT associated with SCLC.

Lambert Eaton myasthenic syndrome (LEMS) :

- Onconeural antibody : Presynaptic voltage gated

calcium channel.

- Can be non paraneoplastic also.
- Features : Proximal myopathy, autonomic neuropathy, oculobulbar palsy, lost DTR.
- Ptosis : m/c cranial nerve finding.
- Myopathy : Symmetric and proximal.
- Recovery of DTR and power on brief muscle activation : post exercise facilitation.

Work up of LEMS :

- Gold standard : High frequency repetitive nerve stimulation shows at least 100% increase in CAMP.
- Antibody levels in serum.
- Nerve conduction studies.
- EMG.
- Single fibre EMG in selected cases.

Treatment options for neurologic paraneoplastic syndromes :

- Plasma exchange.
- IVIG.
- Steroids.
- Cyclophosphamide.
- Tacrolimus.
- Amifampridine : Relieves LEMS symptoms; prolongs nerve terminal depolarisation.
- Rituximab (anti CD20 antibody).

Staging

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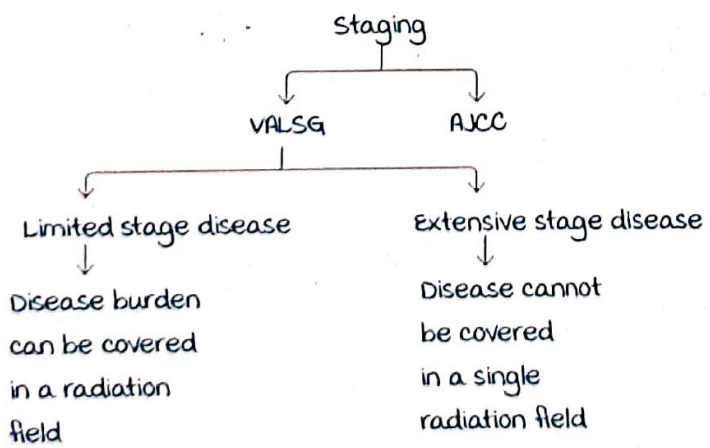

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Feedback

- 1/3 rd will have limited stage disease.
- T1-4 N1-3 M0 is limited stage except when locoregional disease is extensive that can't be covered in a radiational field, come under extensive stage disease.

Staging investigations :

- PET-CT is always preferred.
- Bone scan with CT thorax and abdomen, if PET CT is not done.
- MRI brain : mandatory at baseline.
- Sampling of pleural effusion, if significant.
- Bone marrow biopsy is not routinely recommended.

TNM staging :

T1	Tumor ≤3 cm in greatest dimension surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more
T1a(mi)	Minimally invasive adenocarcinoma[f]
T1a	Tumor ≤1 cm in greatest dimension[a]
T1b	Tumor >1 cm but ≤2 cm in greatest dimension[a]
T1c	Tumor >2 cm but ≤3 cm in greatest dimension[a]
T2	Tumor >3 cm but ≤5 cm or tumor with any of the following features:[b] • Involves main bronchus regardless of distance from the carina but without involvement of the carina • Invades visceral pleura • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung
T3	Tumor >5 cm but ≤7 cm in greatest dimension or associated with separate tumor nodule(s) in the same lobe as the primary tumor or directly invades any of the following structures: chest wall (including the parietal pleura and superior sulcus tumors), phrenic nerve, parietal pericardium
T4	Tumor >7 cm in greatest dimension or associated with separate tumor nodule(s) in a different ipsilateral lobe than that of the primary tumor or invades any of the following structures: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, and carina
N: Regional lymph node involvement	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M: Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis present
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion[g]
M1b	Single extrathoracic metastasis[h]
M1c	Multiple extrathoracic metastases in one or more organs

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Treatment

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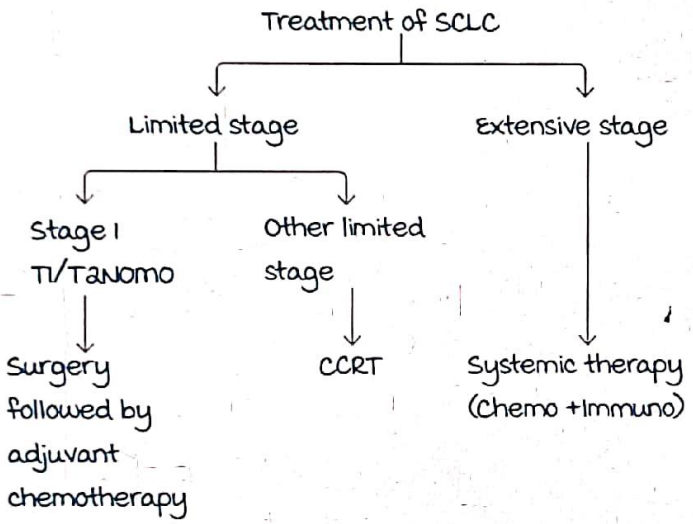

Surgery and adjuvant treatment in limited stage disease :

- T1–T2 N0 M0 : Surgery if medically fit.
- Thorough staging including thoracoscopy to rule out nodal mets is mandatory.
- Sugery : Lobectomy plus mediastinal node dissection.
- Adjuvant chemotherapy is mandatory.
  - Cisplatin + Etoposide (4–6 cycles).
  - Carboplatin + Etoposide.
- Role of adjuvant RT only in :
  - R1 (microscopic disease left behind)/R2 (macroscopic disease left behind).
  - Pathological node positivity.
  - Surgical margin positivity.

Non surgical cases of limited stage SCLC like :

1. Node positive disease.
2. T3 or T4 disease.
3. Stage I but medically inoperable.

CCRT : Standard of care (cisplatin/carboplatin + etoposide)
RT is started with second line of chemotherapy.
No role for immunotherapy in limited stage SCLC first line.

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Radiotherapy doses :

- 60 to 70 Gy in fractions of 2 Gy (old).
- 45 Gy in twice daily fractions over three weeks : current standard (accelerated hyperfractionation).

Prophylactic cranial irradiation (PCI) : To reduce chances of brain mets in clinical course.
Indications : Patients who achieved partial/complete response to CCRT.

Extensive stage SCLC :
Standard of care : Chemotherapy + immunotherapy.

- Carboplatin + etoposide + durvalumab/atezolizumab > pembrolizumab .
- No role for concurrent chemoradiation.
- Carboplatin = cisplatin here.
- Platinum + irinotecan acceptable, instead of etoposide.

Thoracic irradiation after systemic therapy, indications : Good response to initial therapy with residual disease in thoracic cavity.
Prophylactic cranial irradiation (PCI) :

- Indications : patients who achieved partial response to initial therapy.
- If not fit, followed up by periodic MRI brain for mets.

management of brain mets :

- Asymptomatic : Protocol treatment of systemic therapy.
- Symptomatic : Whole brain radiotherapy → protocol treatment of systemic therapy.

If immunotherapy contraindications like autoimmune disorders present, then chemotherapy alone can be given.
Relapse :

Platinum sensitive relapse	Refractory relapse
more than 3 months after therapy	Less than 3 months of therapy
Platinum included in regimen	Platinum not used again

For treatment, 6 month cut off is taken.

Platinum refractory relapse within 6 months :

- Lurbinectidin : Alkylating agent.
- Topotecan. ┐
- Irinotecan. ┘ India

After 6 months :

- Rechallenge with same regimen.
- Can add immunotherapy to chemotherapy, if not used in the first line setting.
- If not fit for platinum again, use lurbinectidin or irinotecan.
- Can use pembrolizumab as single agent in 3rd line if immunotherapy not employed thus far only setting immunotherapy without chemo is indicated.

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