# LUNG NENs
# MAIN STREAM IN DIAGNOSIS AND TREATMENT

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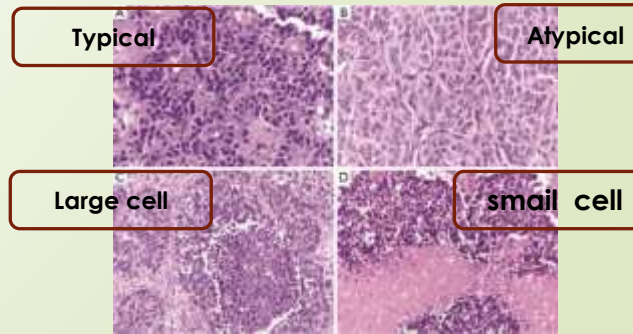
# Introduction

- Pulmonary carcinoids (PC)= LUNG NENs
- Epithelial tumors display features well-differentiated neuroendocrine neoplasms >>endocrine morphology & expression of neuroendocrine markers chromogranin A , synaptophysin
- Represent 1–2% of pulmonary neoplasms and approximately 25% of all NETs
- There growing evidence NETs anatomic subgroups have different biology different responses to treatment

  >>>>>> should be investigated as separate entities in clinical trials

# Classification of lung NETs

- A subject of considerable controversy, multiple competing classification schemes
- NETs arising in the lung characterized by strikingly different biologic behavior
- low-grade (typical) lung NETs, majority of tumors, are well-differentiated, slowly growing neoplasms that rarely metastasize to extrathoracic structures
- Intermediate-grade (atypical) lung NETs is intermediate between low-grade (typical) NETs and SCLC/large cell NEC
- High-grade (poorly differentiated) neuroendocrine carcinomas (NECs), small cell lung cancer (SCLC) & large cell NEC, aggressive behavior, rapid tumor growth, early distant dissemination



## 2015 WHO criteria for the diagnosis of pulmonary neuroendocrine tumors

| Tumor type | Criteria |
|---|---|
| Typical carcinoid | Carcinoid morphology and <2 mitoses/2 $mm^2$ (10 HPFs), lacking necrosis and >0.5 cm |
| Atypical carcinoid | Carcinoid morphology with 2 to 10 mitoses/2 $mm^2$ (10 HPFs) or necrosis (often punctuate) |
| 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: large 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; and |
| | Positive immunohistochemical staining for one or more NE markers (other than neuron-specific enolase) and/or NE granules by electron microscopy |
| Small cell neuroendocrine carcinoma | Small size (generally less than the diameter of three resting lymphocytes); |
| | Scant cytoplasm; |
| | Nuclei: finely granular nuclear chromatin, absent or faint nucleoli; |
| | High mitotic rate: >11 mitoses/2 $mm^2$ (10 HPFs), median of 80/2 $mm^2$ (10 HPFs); and |
| | Frequent necrosis, often in large zones |

HPF: high-power field; NSCLC: non-small cell lung carcinoma; NE: neuroendocrine.

# Presenting signs and symptoms

- Majority of tumors arise in the proximal airways, symptomatic (obstructing tumor mass / bleeding hypervascularity) cough / wheeze, hemoptysis, chest pain, / recurrent pneumonia
- Due to misdiagnosis, the diagnosis of a lung neuroendocrine tumor (NET) is often delayed, and patients may receive several courses of antibiotics to treat recurrent pneumonia before the tumor is diagnosed
- On chest radiograph, tumors appear as round or ovoid opacities that range in size from 2 to 5 cm and may be associated with a hilar or perihilar mass
- One-fourth of cases present in the periphery as an asymptomatic solitary pulmonary nodule
- These tumors are frequently discovered on a routine chest radiograph, most commonly as a solitary pulmonary nodule

# Clinical syndromes

- Related to peptide production
- Features of carcinoid syndrome atypical due to secretion of histamine metabolites symptoms include lacrimation, wheeze, sweating
- Semiology a purple-red flush, potentially covering the entire body, which can be intense and prolonged in duration as opposed to the more red and patchier flushing seen midgut NETs which typically does not last as long and predominates on the face and upper trunk
- Carcinoid syndrome may occur in the absence of liver metastases as vasoactive peptides directly drain into the left heart, making mitral and aortic valves first exposed to dysfunction as a consequence
- Cushing's syndrome — Approximately 1 - 2 %lung NETs (both typical and atypical tumors) due to ectopic production of adrenocorticotropic hormone (ACTH), some data suggest that ACTH-producing lung NETs behave more aggressively than do hormonally quiescent tumors
- Acromegaly — Acromegaly from ectopic production of growth hormone-releasing hormone (GHRH) or insulin-like growth factor 1 (IGF-1) is a rare manifestation of lung NETs

# DIAGNOSIS-Biochemistry&Others

- Renal function, potassium, calcium, glucose, and plasma
- Chromogranin A  marker of tumor burden but appears to have poor specificity and sensitivity
- 24-h u-5HIAA in syndromic patients
- Serum cortisol, ACTH, 24-h urine free cortisol, serum GHRH, IGF-1
- The NETest, a PCR-based 51-mRNA marker signature,has recently been suggested to be a more sensitive and specific test for the detection of Lung NETs and identifying  progressive disease ,but needs to be validated in prospective studies and in a large population of  patients
- Molecular characterization of NET s, although further studies are needed

  Molecular studies have demonstrated frequent alterations in the chromatin remodelling genes,

  MEN1,  PSIP1, and ARID1A, & in inactivating mutations in TP53 and RB1 in Lung Nets

# DIAGNOSIS-Imaging

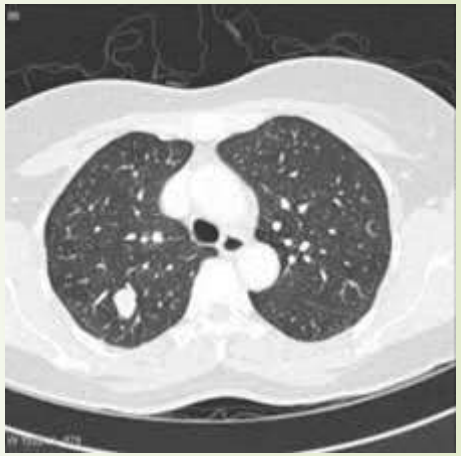
- Multiphasic contrast-enhanced CT chest and abdomen
- Dynamic contrast-enhanced MRI liver
- 68Ga-DOTA somatostatin analogue PET/CT
- Consider 18F-FDG PET/CT in atypical carcinoids or high grade
- Whole-spine MRI if symptoms
- Bronchoscopy
- EBUS in selected cases

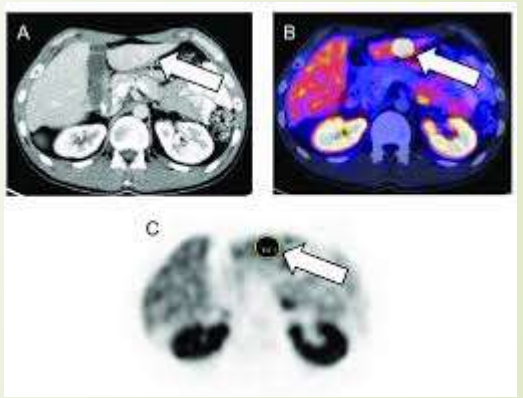
*If considering surgery perform*

- – Transthoracic echocardiography
- – Respiratory function tests

*Genetic screening*

MEN1 germline testing when suspected





# Treatment

- Low-grade (typical) lung NETs seldom metastasize and have an excellent prognosis, even when regional lymph nodes are involved
- intermediate-grade (atypical) lung NETs have a higher likelihood of metastases and a worse prognosis, particularly if mediastinal nodes are involved
- For patients with either low- or intermediate-grade resectable lung NET whose medical condition pulmonary reserve will tolerate >>>>>**surgical resection including mediastinal lymph node sampling / dissection** (presence of mediastinal lymph node metastases does not preclude cure)
- For most patients, for curative end point endobronchial resection is suboptimal method and best reserved for palliative treatment of patients with central airway occlusion who are poor surgical candidates

# Treatment

- Patients **slowly progressive, metastatic disease** , somatostatin-receptor-positive >>>>>> therapy with SSA for disease control
- **Carcinoid syndrome** ( relatively uncommon, occur both in patients with locoregional / disseminated disease)
- Patients with locoregional lung NETs producing carcinoid syndrome >>>>Surgical resection preferred strategy
- Unresectable lung NETs >>>>>>Initiation of long-acting somatostatin analog (SSA) therapy either octreotide or lanreotide
- Treatment options for patients with symptoms of carcinoid syndrome that do not respond to SSA therapy
- Ablative treatments for liver metastases
- Systemic antiproliferative therapy with cytotoxic agents
- Peptide receptor RT (for patients with somatostatin-receptor-positive advanced disease)
- Tryptophan hydroxylase inhibitor telotristat.

# Treatment

- Patients with progressive or disseminated disease SSA refractory, everolimus is an option. although the RADIANT 4 trial excluded concomitant SSA use, combination of everolimus with an SSA is safe and commonly prescribed in patients with gastrointestinal NETs.
- In cases, everolimus may be an appropriate first-line option (eg, for patients with tumors that are somatostatin receptor negative on somatostatin receptor imaging)
- Patients with initially rapidly progressive disease, and/or for those whose tumors progress while receiving everolimus or who are intolerant of everolimus, cytotoxic chemotherapy is a reasonable approach(cisplatin- or carboplatin-based chemotherapy )
- Patients with highly aggressive atypical lung NETs, temozolomide-based chemotherapy for patients with more indolent, typical or atypical lung NETs, although the level of evidence supporting use of these drugs in this setting is low
- Another option for treatment of somatostatin-receptor-positive advanced disease, is peptide receptor radioligand therapy
- RT can provide useful pain relief for patients with bone metastases
- Participation in a clinical trial is appropriate for patients with progressive lung NETs during any line of therapy.