

# CARCINOID TUMOURS IN LUNG

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# PULMONARY CARCINOID TUMOR

- Pulmonary carcinoid tumor, also termed well-differentiated neuroendocrine tumor, is a pulmonary neuroendocrine epithelial neoplasm.
- It is uncommon, making up approximately 2% of primary lung neoplasms.
- The neoplasm arises in both men and women throughout life, with a peak incidence in the 5th decade.

# EPIDEMIOLOGY

- < 1% of all lung cancers and 2% of resected lung tumors (Histopathology 2018;72:142)
- More frequently in :
- Patients aged < 60 years
- Female
- Caucasian

# RISK FACTORS

- Family history
- Mutation in MEN1 gene
- Unrelated to smoking (Arch Pathol Lab Med 2010;134:1628)

# SITES

- Anywhere from the trachea to the distal bronchioles
- Central airways (85%), mostly main and lobar bronchi > peripheral airways (15%) (Cancer 2008;113:5)
- Central
  - Most common type, usually slow growing, associated with obstruction, infection, hemorrhage
  - Usually adults but also most common lung tumor of children
  - 5% metastasize, usually to regional lymph nodes
  - Rarely distant osteoblastic metastases to bone
  - 10 year survival 70%
  - Cytology often negative since tumor is covered by mucosa

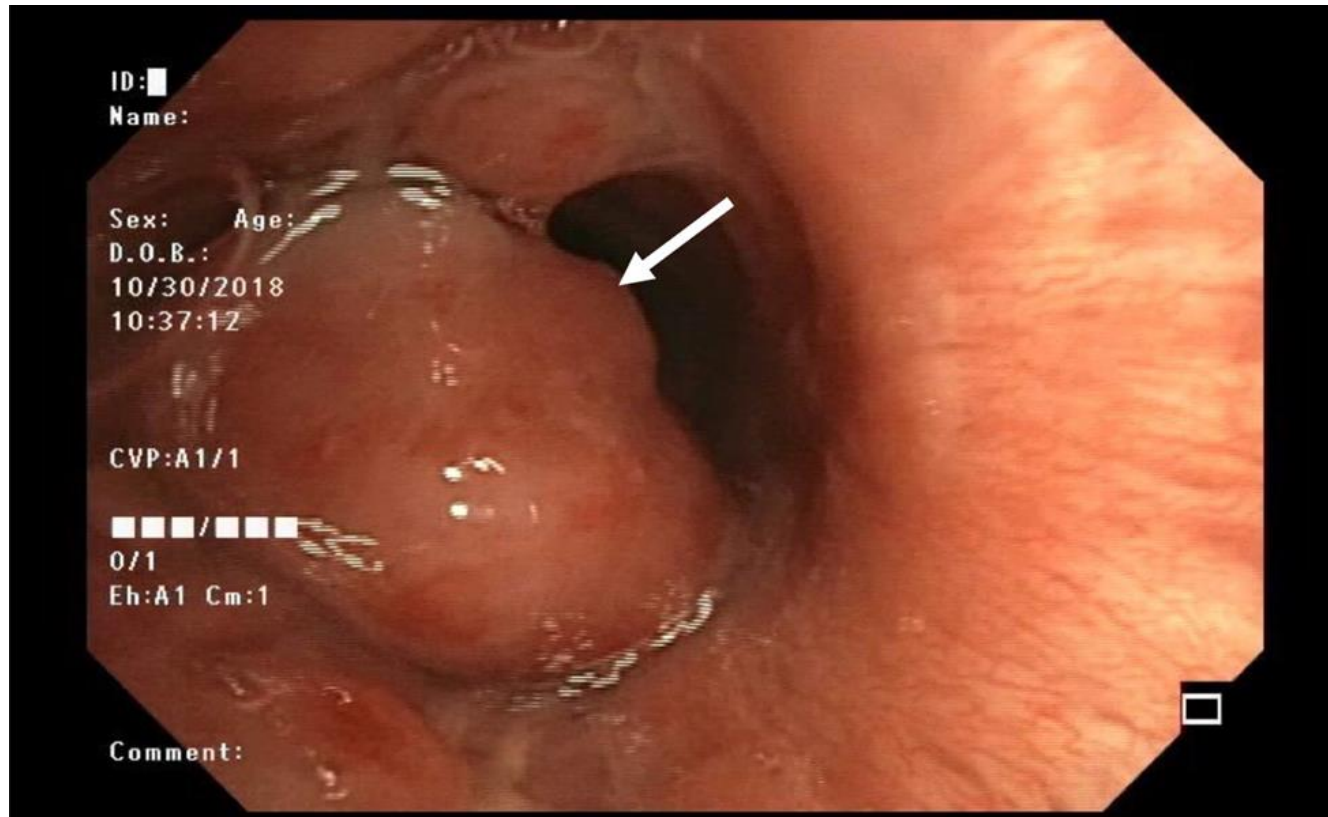
# PERIPHERAL

- Arise in peripheral lung, often beneath the pleura
- Usually asymptomatic and incidental
- Excellent prognosis
- Rare nodal metastases are usually cured by excision

# CLINICAL FEATURES

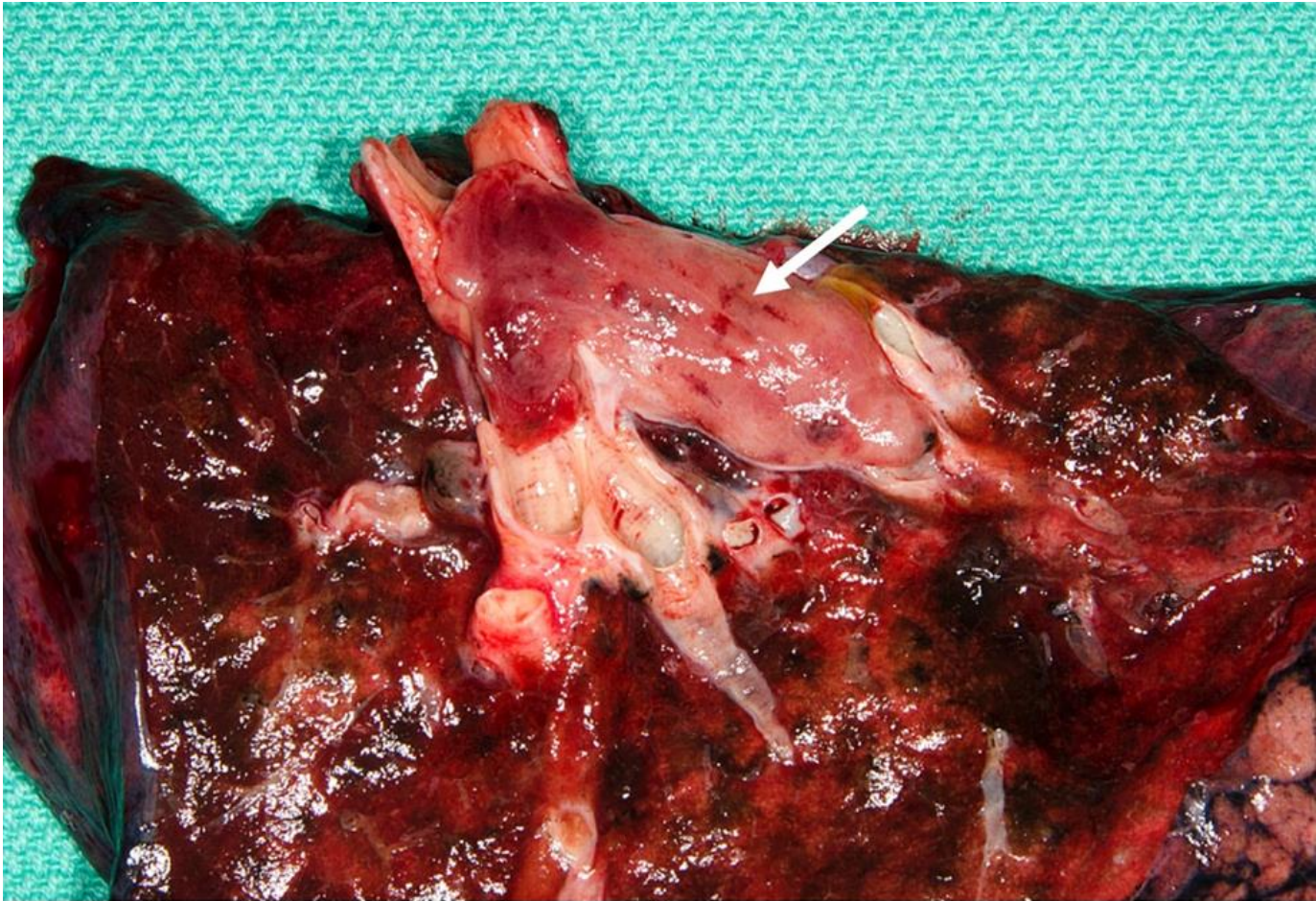
- Mostly due to tumor location (Chest 2017;151:1141)
- Peripheral carcinoids are commonly asymptomatic.
- Centrally located carcinoids may present with dyspnea, cough, wheezing, hemoptysis, recurrent infection and pneumonia due to airway obstruction
- Paraneoplastic syndromes are uncommon and usually present in the setting of liver metastases (CMAJ 2017;189:E398),
- Carcinoid syndrome (< 2%): flushing, diarrhea, valvular disease, Cushing syndrome (4%), Other rare endocrine syndromes.

# BRONCHOSCOPY



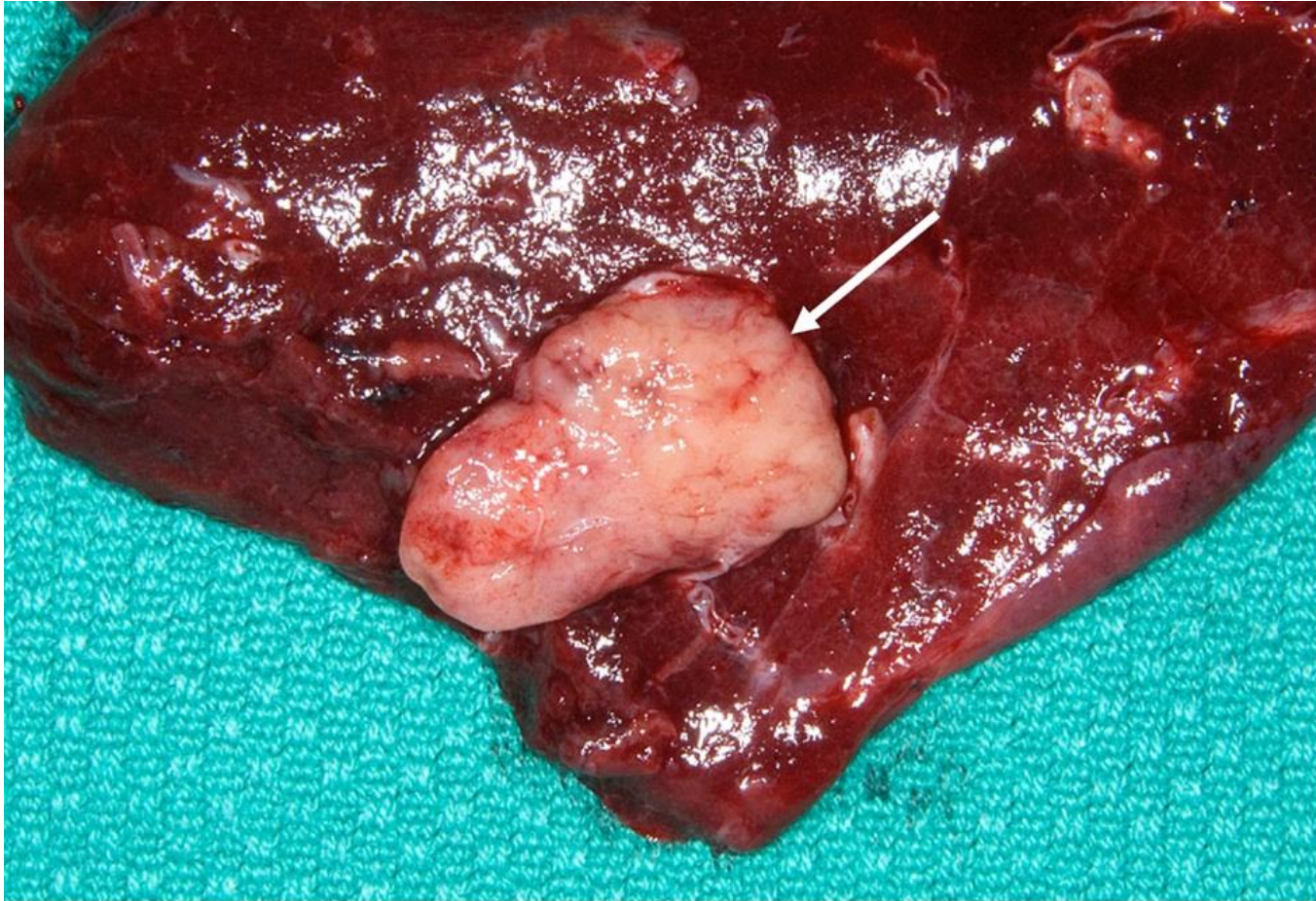
Bronchoscopy showing an endobronchial atypical carcinoid (arrow) occluding at least 50% of the lumen





Gross image of a lobectomy with a well circumscribed, flesh colored endobronchial carcinoid tumor (arrow)





Gross image of a well circumscribed, flesh colored peripheral carcinoid tumor (arrow)



**Carcinoid tumor: this large polypoid tumor completely obstructs the lumen of a lobar bronchus with resulting severe, diffuse bronchiectasis distal to the obstruction**

# Radiology Imaging

- Lobulated and well circumscribed nodule implicating major bronchi
- Obstruction signs (atelectasis, bronchiectasis) can be seen (AJR Am J Roentgenol 2011;197:1073)
- Positron emission tomography (PET) scan: low to moderate uptake (mean standardized uptake value [SUV]: 3.4)

# DIAGNOSIS

Diagnosis of carcinoid can be made on biopsy or cytology specimen but the distinction between typical and atypical carcinoid usually requires a surgical specimen, unless necrosis or mitoses are seen (Ann Oncol 2015;26:1604)



# DIAGNOSTICS WORKUP

## **Clinical history**

- Presence of functioning syndrome
- Presence of obstructive syndrome
- Family or personal history of MEN-1 syndrome

## **Pathology**

- WHO 2015 classification
- Multiple synchronous primaries; DIPNECH features
- Specification of node dissection (e.g. number, station)
- Resection status

## **Biochemistry**

- Biochemical: K, Ca, glucose
- Chromogranin A<sup>a</sup>
- In syndromic patients: 24 h-urine-5-HIAA, serum cortisol, ACTH, 24 h-urine-free cortisol, serum GHRH, IGF-1<sup>a</sup>

## **Imaging**

- TNM staging according to the 8th UICC edition: chest/abdomen CT with i.v. contrast (liver MRI)
- <sup>68</sup>Ga-DOTA SSA PET-CT or <sup>111</sup>In-DTPA scintigraphy if not available
- Consider FDG-PET-CT in AC or high-grade histopathology or negative SRI
- Whole spine, brain MRI if symptoms
- Bronchoscopy
- Transthoracic echocardiography if CS
- Tumour growth rate (radiological) over 2-3 months in non-resectable asymptomatic TC or low-grade AC

## **If considering surgery, carry out:**

- Transthoracic echocardiography<sup>b</sup>
- Respiratory function tests
- Bronchoscopy
- Mediastinoscopy (or EBUS)<sup>c</sup>

## **Genetic screening**

- MEN-1 germline testing when suspected

# HISTOPATHOLOGY

- Gross description
- Well circumscribed, round to oval tan colored tumors (Travis: WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart, 4th Edition, 2015)
- Localization:
- Frequently in bronchial lumen, sessile or pedunculated with partial or complete obstruction of the lumen
- Peripheral tumors may not be evidently located in airways
- Size range: 0.5 - 9.5 cm

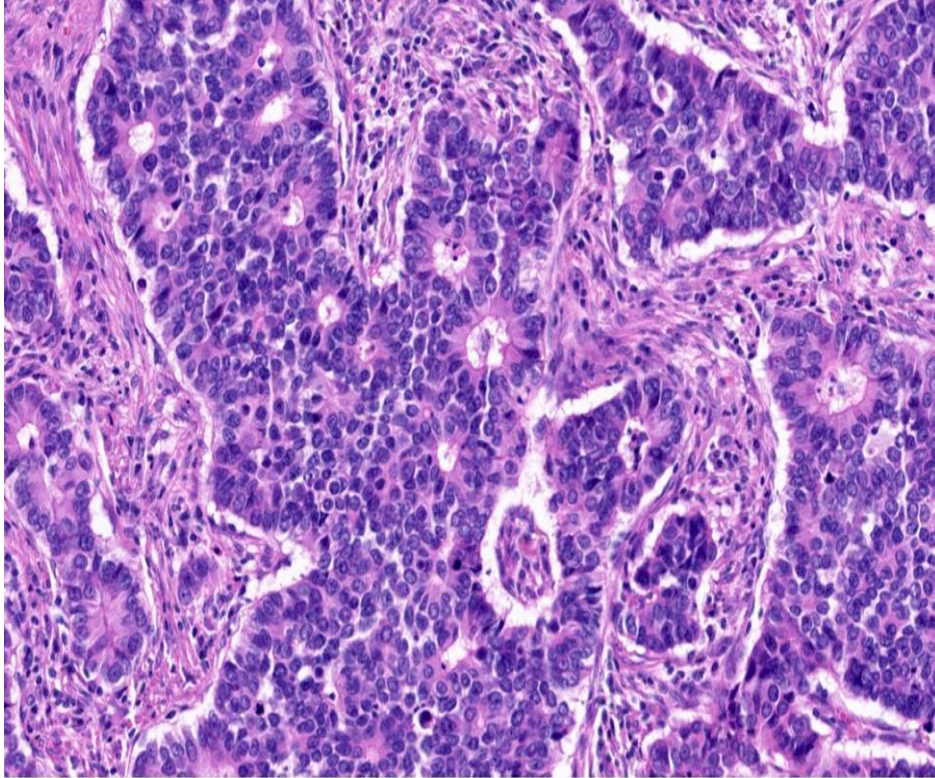
# HISTOPATHOLOGY

- Pulmonary carcinoids further divided into typical and atypical carcinoids
- Classification is based on
  - mitotic count per 2 mm<sup>2</sup>
  - presence / absence of necrosis
- (Ki67 proliferative index is currently not recommended to distinguish between typical and atypical carcinoids)

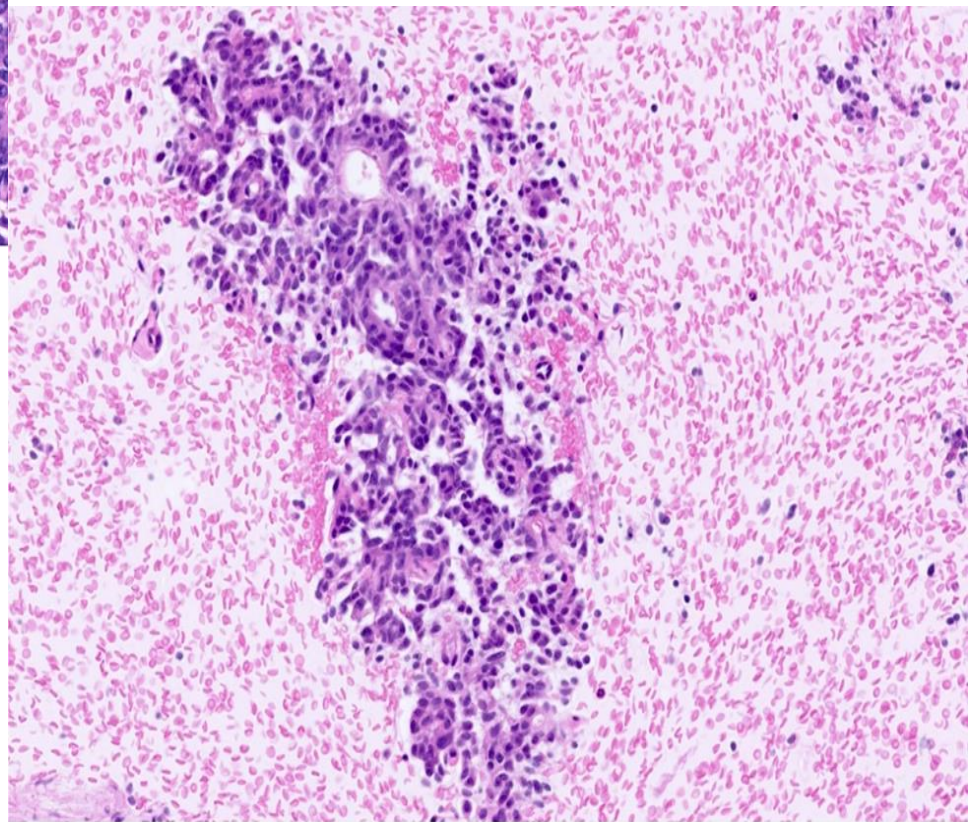


# MICROSCOPIC DESCRIPTION

- Diagnostic criteria (Travis: WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart, 4th Edition, 2015)
- Neuroendocrine tumor with size  $> 5$  mm with  $< 2$  mitoses/ $2 \text{ mm}^2$  and absence of necrosis
- Neuroendocrine growth pattern (organoid, trabecular, rosette formation, nested) or pseudoglandular, follicular and papillary growth
- Tumor cells are uniform with a polygonal shape, round to oval nuclei with salt and pepper chromatin and inconspicuous nucleoli, along with moderate to abundant eosinophilic cytoplasm
- Spindle cells and clear cell features can be seen
- Stroma is fine and highly vascularized; hyalinization, cartilage or bone formation are possible



Pulmonary carcinoid tumor showing rosettes (H&E, 200x)



Fragments of tumor with rosette structures can be seen on cell block (H&E, 200x)





Contributed by Jijgee Munkhdelger, M.D.,  
Ph.D. and Andrey Bychkov, M.D., Ph.D.

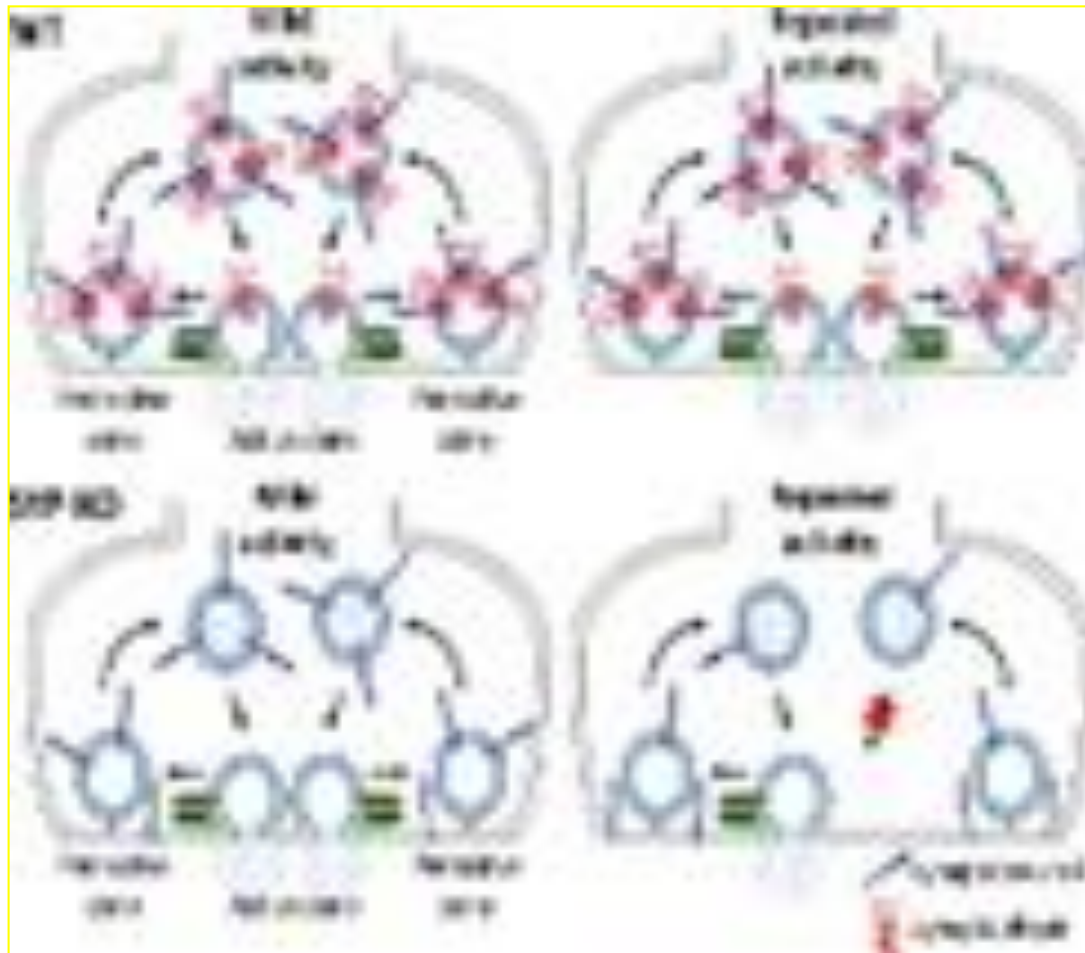


# POSITIVE STAINS

- Chromogranin, synaptophysin, CD56: diffusely and strongly positive
- Pancytokeratins: positive, useful to distinguish from paraganglioma Ki67: typical and atypical carcinoid < 20%, useful to discriminate between high grade neuroendocrine tumors (small cell carcinoma and large cell neuroendocrine carcinoma), in particular on small or crushed biopsies
- Utility not proven to differentiate between typical and atypical carcinoid (Virchows Arch 2017;470:153)

- TTF1: useful marker of pulmonary lineage in typical and atypical carcinoids but only positive in < 50% of cases
- TTF1+ carcinoids are more commonly seen in peripheral lesions and staining is commonly focal and weak (Hum Pathol 2004;35:825)
- Rb: preserved in the vast majority of pulmonary carcinoids

# An integral membrane protein of small synaptic vesicles in brain and endocrine cells



## ICD coding

- ICD-10: D3A.090 - Benign carcinoid tumor of the bronchus and lung
- ICD-O: 8240 / 3 - Typical carcinoid

# PROGNOSTIC FACTORS

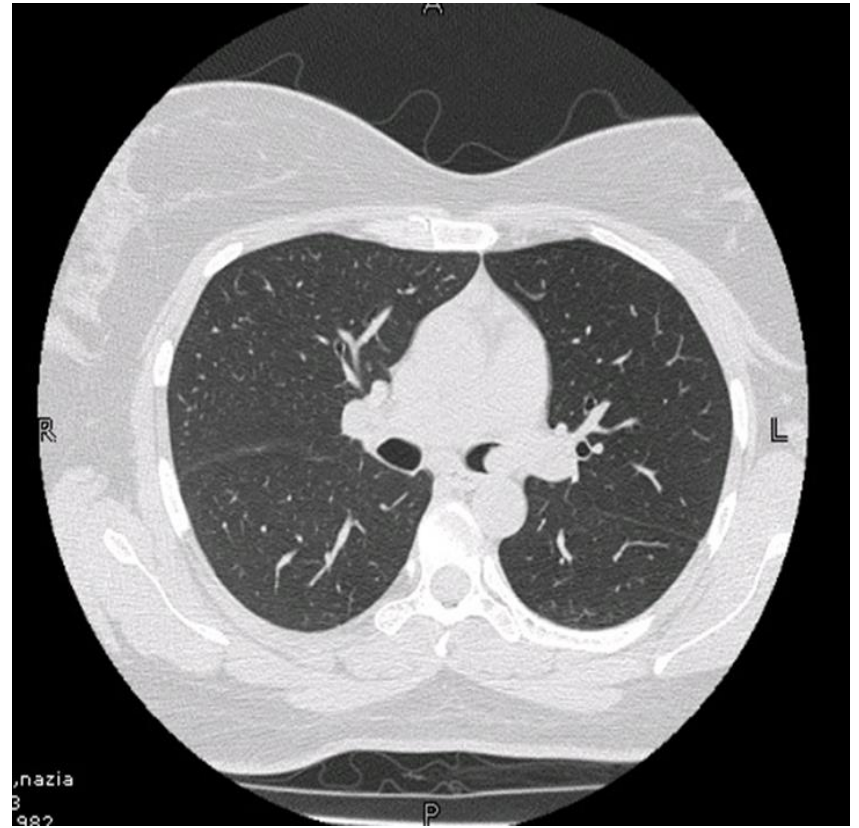
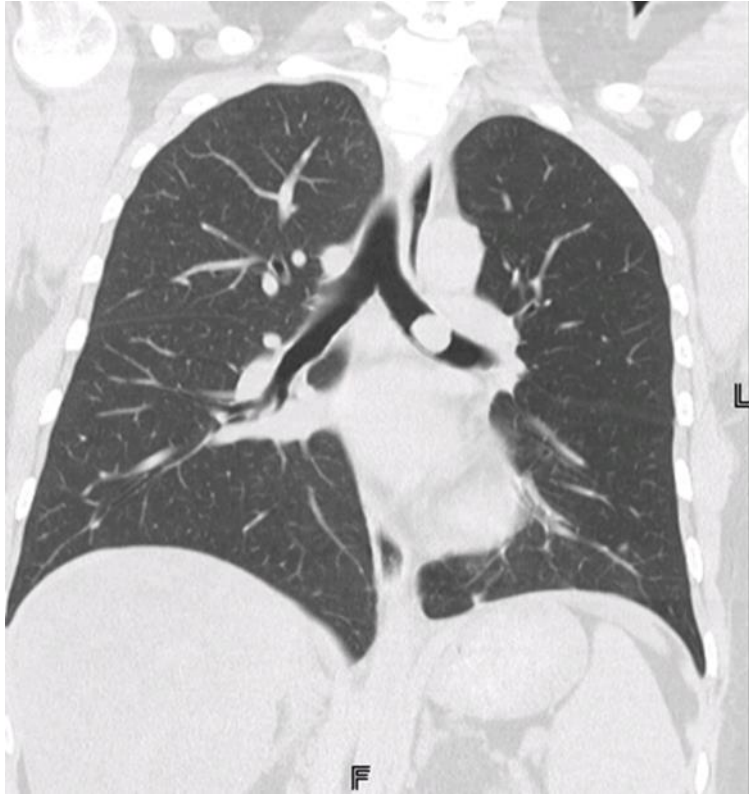
- 5 year survival: 90%
- Lymph node metastasis: 9%
- Distant metastases at time of diagnosis: 3 - 5%, mainly liver and bone
- TNM staging
- Spread through air spaces: presence linked to a worse prognosis
- Ki67 immunostaining: utility remains controversial (Arch Pathol Lab Med 2018;142:947)



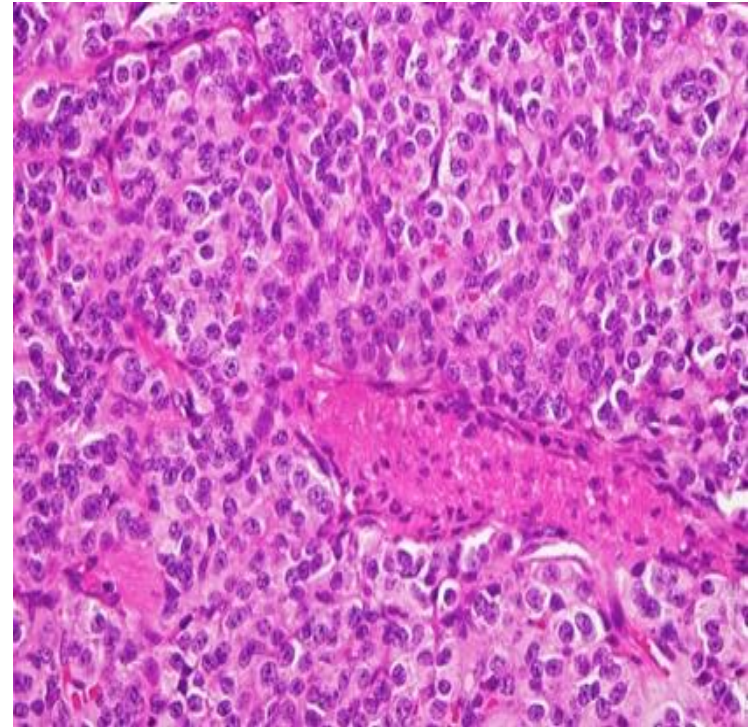
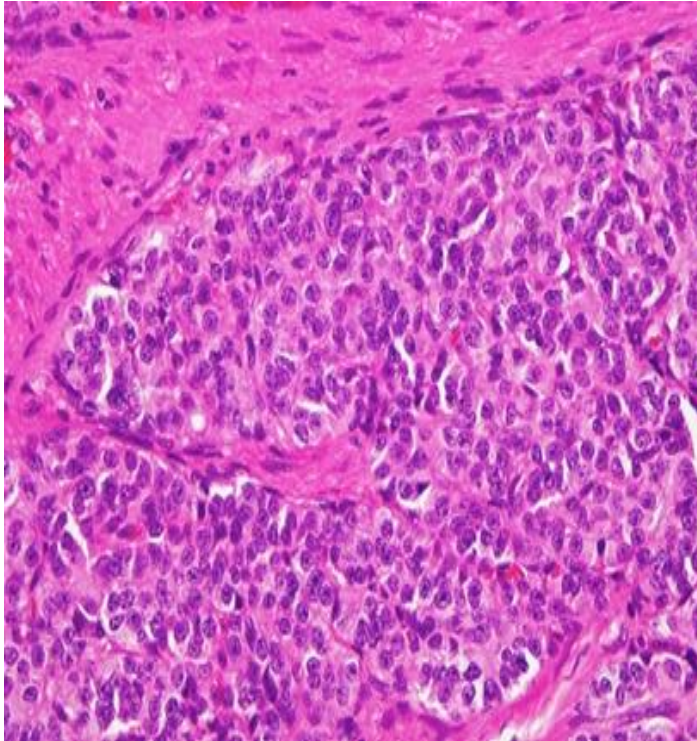
- Increase in plasma chromogranin A can be used but has limited specificity (Ann Oncol 2015;26:1604)

# CASE

- A 36 year old woman presented with hemoptysis and fever for 2 weeks. High resolution CT showed a well defined, rounded, high attenuation endobronchial lesion arising from the posterosuperior wall of the Left main bronchus. A biopsy was performed.

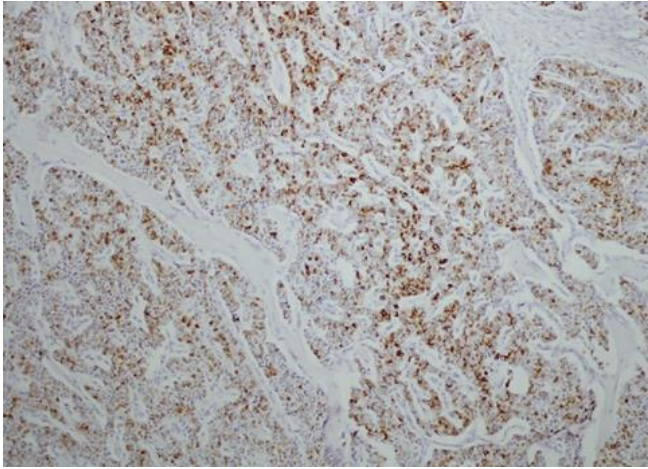


# What is your diagnosis?

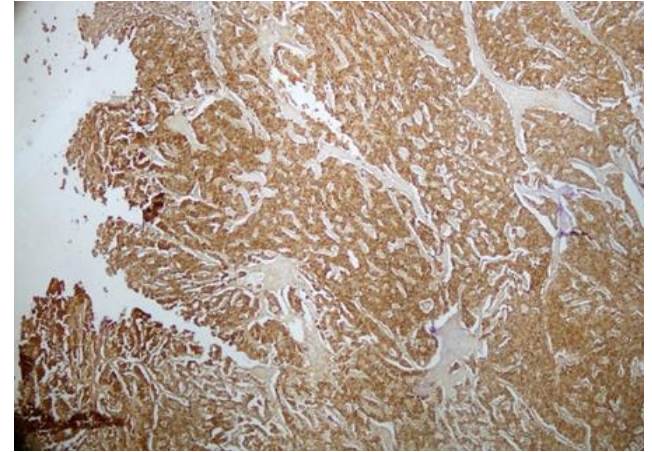




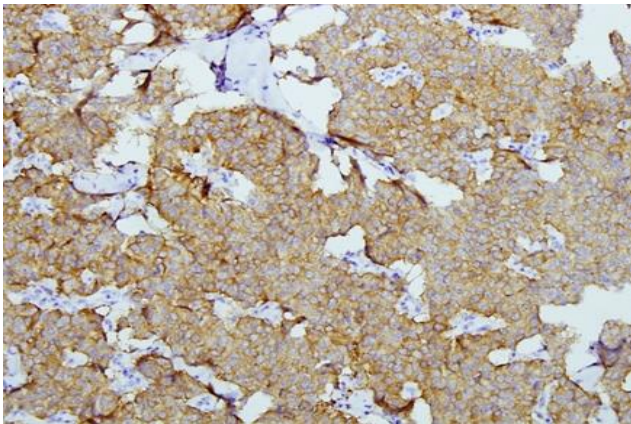
# IHC



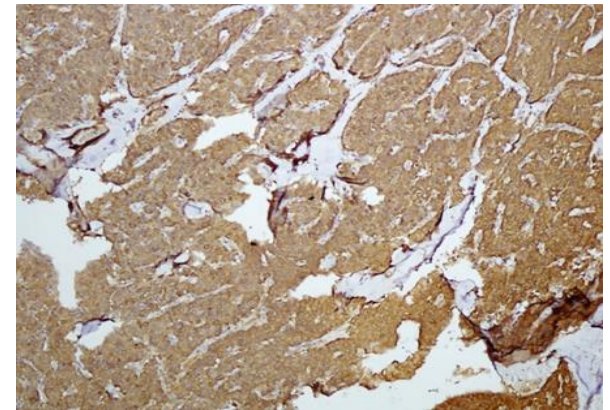
**AE1-AE3**



**Chromogranin**



**Synaptophysin**



**NSE**

# DIFFERENTIAL DIAGNOSIS

- other neuroendocrine lung tumors, including
  - tumorlet (less than 5 mm),
  - metastatic carcinoid from the GI tract or elsewhere,
  - atypical carcinoid (2-10 mitotic figures/HPF, necrosis, often atypia or pleomorphism),
  - large cell neuroendocrine carcinoma small cell neuroendocrine carcinoma (atypia, pleomorphism, mitotic figures, necrosis).
- 
- Tumors with a pseudoglandular pattern may resemble adenocarcinoma (marked atypia throughout).

# Local/locoregional disease treatment

- Control of a functioning syndrome must be considered before any invasive therapeutic intervention
- The surgical approach depends on tumour size, location and preoperative biopsy specimen assessment

- Anatomic pulmonary resection (e.g. segmentectomy,
- lobectomy, bilobectomy, pneumonectomy)
- Lymph node resection (with a minimum of six nodal stations)
- Three hilar and three mediastinal also including subcarinal station as recommended by the European Society of Thoracic Surgery for non-small-cell lung cancer is the preferred extent of resection .
- Indeed, wedge resection may increase the risk of tumour recurrences, especially in N-positive TC or intermediate-grade ACs



- Frozen sections of bronchial and vascular margins are recommended to rule out tumour involvement of resection margins, a condition that consequently imposes a greater pulmonary resection.
- Lymph node dissection is recommended as lymph node metastases may be observed in up to 27% of TCs and in up to 47% of ACs, and lymph node resection influences the prognosis and the modality of follow-up.

Lung carcinoid - UICC TNM stage I-III

Anatomic resection  
and LN dissection<sup>a</sup> [IV, B]

TC

Observation

AC

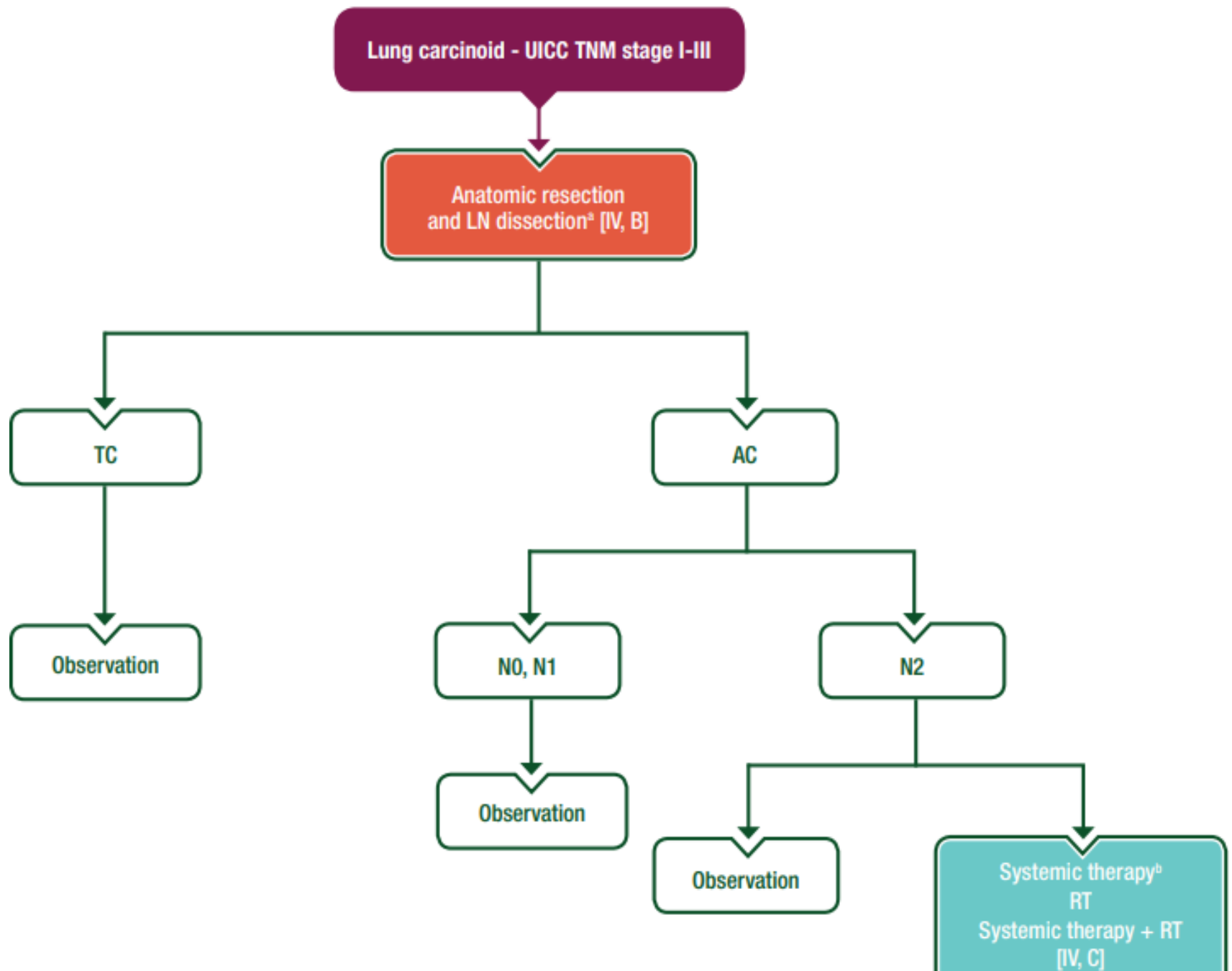
N0, N1

Observation

N2

Observation

Systemic therapy<sup>b</sup>  
RT  
Systemic therapy + RT  
[IV, C]



- No routine adjuvant therapy is recommended in LCs
- However, cytotoxic ChT (dacarbazine/temozolomide- or oxaliplatin-based ChT)
- RT may be considered in selected fit patients with a particularly high risk of relapse (i.e. AC N2) after multidisciplinary discussion
- Watchful follow-up may be considered in asymptomatic patients with slowly radiologically progressing LCs

- Annual echocardiography screening in case of CS or increased 5-HIAA levels is recommended
- SSAs are recommended as first-line therapy for CS
- Short-acting SSAs given intravenously are recommended in perioperative treatment
- In patients with refractory CS, a variety of options exist but there is no consensus on the best strategy, due to the lack of specific LC studies
- Metyrapone and/or ketoconazole are recommended as first-line therapy for CuS
- In patients with refractory CuS, early bilateral adrenalectomy should be considered
- SSAs are recommended for other functional syndromes such as acromegaly or hypercalcaemia

# ANTI-TUMOUR MANAGEMENT

- Locoregional therapy including surgery.
- Palliative surgery or radiofrequency ablation (RFA) or cryoablation or endobronchial treatment (EBT) of the primary tumour are occasionally considered in cases of advanced disease at risk of local events or refractory CS

- Multiple locoregional therapies including **surgery, combined or not with SSAs**, are recommended to decrease the tumour burden, to control hormonal secretions and to prevent local complications, as a first-line therapeutic approach in patients with advanced slowly progressing LC

# SYSTEMIC ANTI-TUMOUR THERAPY

Systemic anti-tumour therapies of patients with advanced LC :

- **SSAs**
- **ChT**
- **everolimus**
- **peptide receptor radionuclide therapy (PRRT)**
- **Interferon-a (IFNa).**

- **SSAs Octreotide**

[long-acting release (LAR) 30 mg] and lanreotide (120 mg) are m/c used Both showed antiproliferative activity and gains in time to progression or progression-free survival (PFS) in placebo-controlled, phase III trials

- ☐ SSAs are recommended first-line treatment in patients
- ☐ with TC and/or slowly progressing advanced SRIpositive LC and ThC



# TARGETED THERAPIES

- RADIANT-4 trial

## EVEROLIMUS

- delayed tumour progression while preserving overall health-related QoL.<sup>80</sup> Everolimus has been reported to be potentially effective also in a post hoc analysis of the RADIANT-2 trial regarding a subgroup of LC associated with a history of CS.
- Everolimus is recommended either as first line in case of AC or, second-line post-SSA, in patients with TC and or progressive advanced LCs and ThCs

# CHEMOTHERAPY

- Due to better tolerance and convenience, we recommend **Dacarbazine/Temozolomide** based ChT as first line are recommended in advanced LC patients refractory or intolerant to everolimus therapy
- Platinum-based ChT as second-line options in patients with progressive advanced LC . Among platinum-based agents, **OXALIPLATIN-BASED** is recommended by the majority of the panel.

# **PRRT (peptide receptor radionuclide therapy )/ IFNa**

(based on positive uptake at SRI on all RECISTevaluable targets) as alternative second-line (in case of uncontrolled CS) or mainly third-line therapy (beyond SSAs and or everolimus) in morphologically progressive or high tumour burden advanced LC and ThCs is recommended.

Metastatic lung or thymic carcinoid<sup>a</sup>

TC  
or slowly progressive carcinoids

Observation  
SSAs [IV, C]  
Locoregional therapies including surgery [V, B]

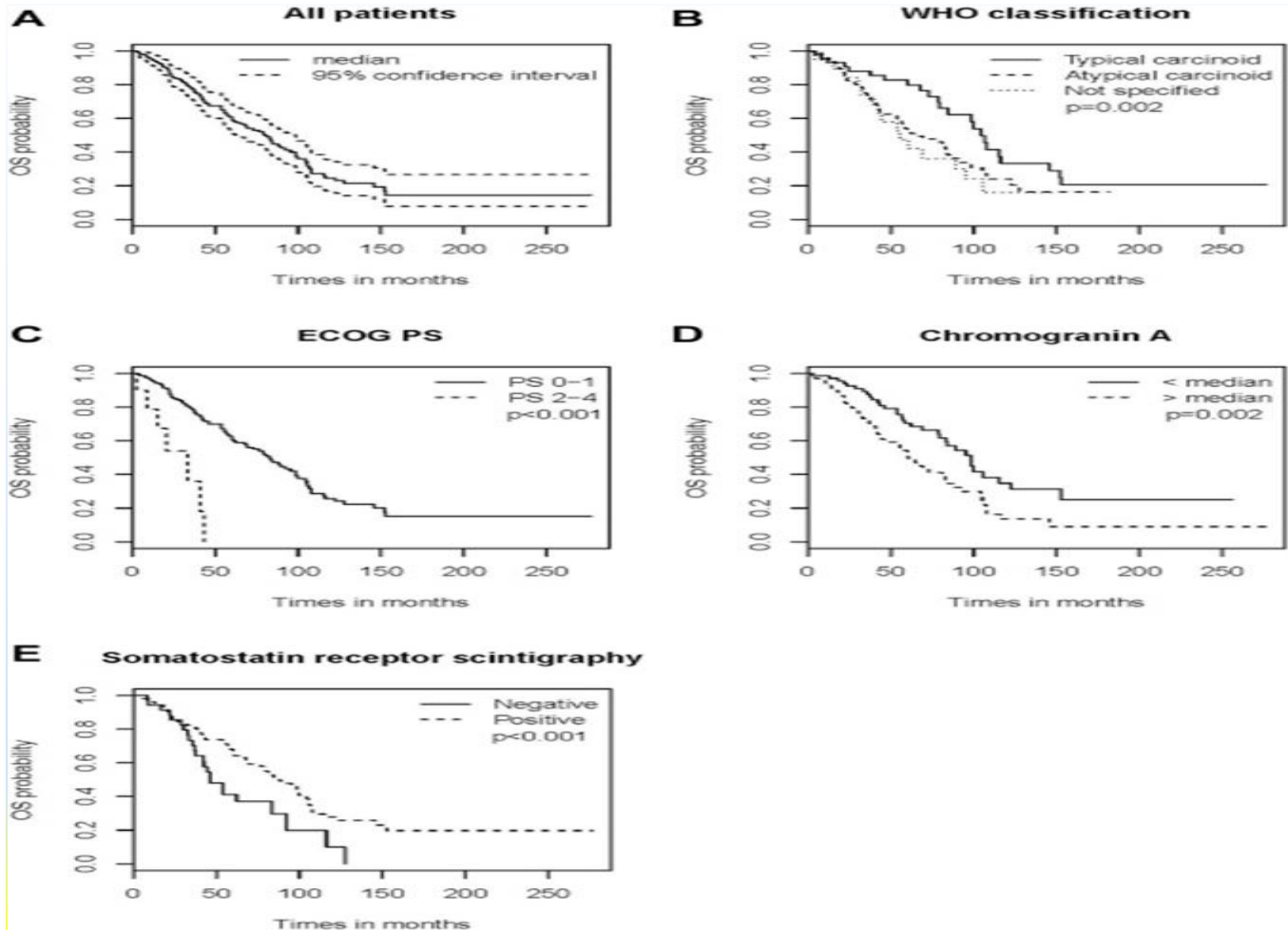
AC<sup>b</sup>  
or significantly progressive carcinoids  
or post-SSA therapy

Everolimus<sup>c</sup> [II, B]  
Temozolomide-based ChT [IV, C]<sup>d</sup>

PPRT<sup>e</sup> [IV, B]  
IFN- $\alpha$ <sup>f</sup> [IV, B]  
Platinum-based ChT<sup>d</sup> [IV, C]

# Characterization, Prognosis, and Treatment of Patients With Metastatic Lung Carcinoid Tumors

Patrick Robelin, MD Julien Hadoux, MD Julien Forestier, MD . Journal of thoracic oncology .  
VOLUME 14, ISSUE 6, P993-1002, JUNE 01, 2019

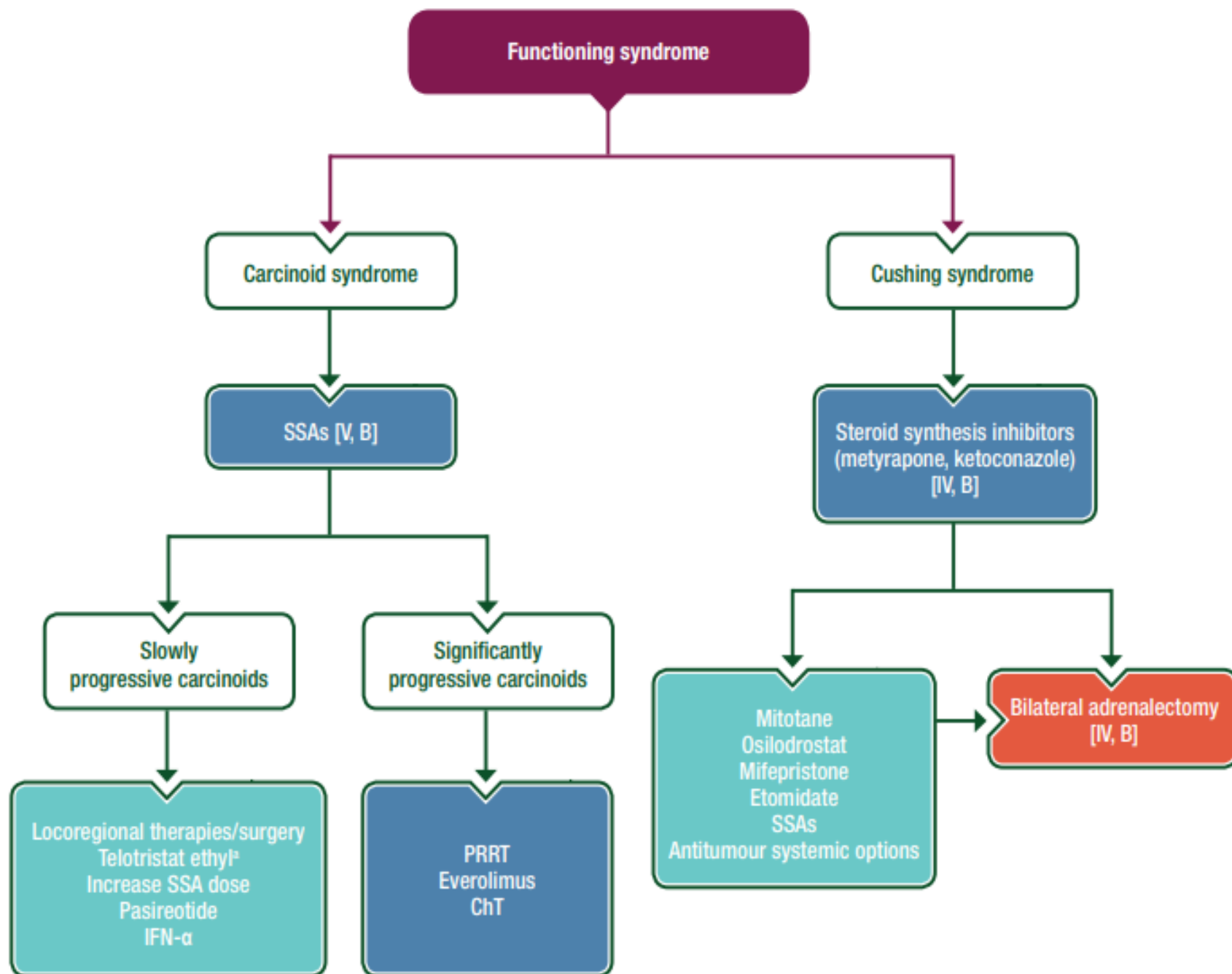


FOLLOW-UP, LONG-TERM  
IMPLICATIONS AND  
SURVIVORSHIP



- Follow-up for LC should be life-long, since recurrences remain very common over time.
- After radical resection of LC, life-long follow-up with low radiation imaging procedures and increasing interval of time, adjusted to prognostic factors, is recommended.
- In patients with advanced tumours, morphological follow-up is recommended every 2-12 months depending on WHO histology, tumour growth rate and control of functioning syndrome

Patients with disseminated disease may benefit from affiliation to specialised palliative care units concerning pain treatment, psychosocial impact and rehabilitation



# THANK YOU

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