Les carcinoïdes broncho-pulmonaires

Pr. Nicolas Girard

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Liens d'intérêt

- Recherche clinique:
- GlaxoSmithKline
- Hoffmann-La Roche
- Eli-Lilly
- MSD
- Servier

- Symposium:
- Amgen
- Astra-Zeneca
- BMS
- Boehringer-Ingelheim
- Hoffmann-La Roche
- Eli-Lilly

- Consultation:
- Astra-Zeneca
- BMS
- Boehringer-Ingelheim
- Clovis
- Hoffman-La Roche
- Novartis
- Eli-Lilly
- Pfizer
- Teva

- Hospitalité:
- Boehringer-Ingelheim
- Chiesi
- Novartis
- Hoffman-La Roche
- Pfizer

Les carcinoïdes broncho-pulmonaires

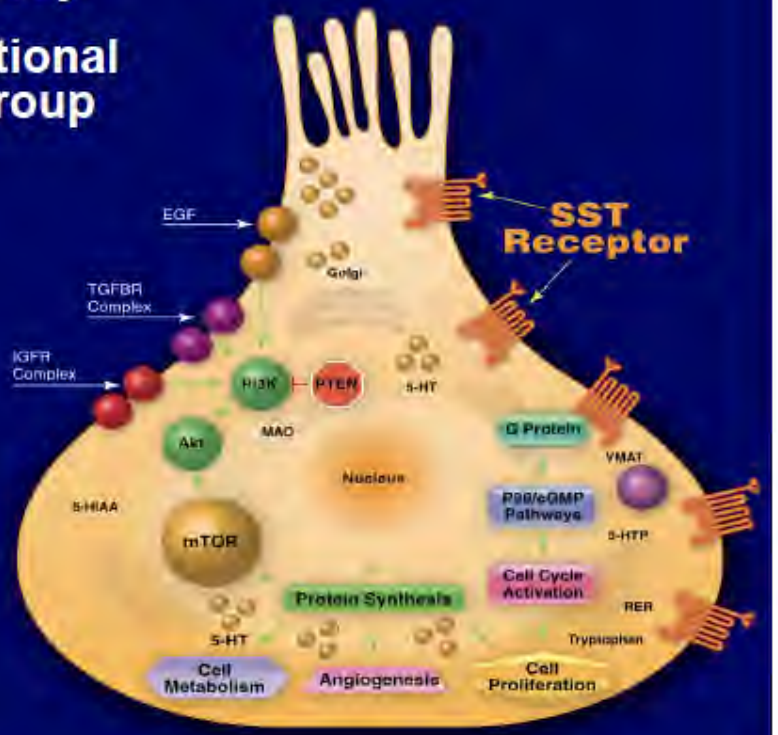
Les carcinoïdes broncho-pulmonaires

Les tumeurs carcinoïdes

Les tumeurs neuro-endocrines

Neuroendocrine Tumors (NETs): A Diverse Group of Malignancies, a Clinical Challenge

- Neuroendocrine cells: migrated from the neural crest to the gut endoderm, from multipotent stem cells
- Tumors arising from enterochromaffin cells located in neuroendocrine tissue throughout the body
- NETs present with functional and nonfunctional symptoms and include a heterogeneous group of neoplasms[1,2]
  - Multiple endocrine neoplasia (MEN)de, type 1 and type 2/medullary thyroid carcinoma
  - Gastroenteropancrtic neuroendocrine tumors (GEP-NETs)
  - Islet cell tumors
  - Pheochromocytoma/paraganglioma
  - Poorly differentiated/small cell/atypical lung carcinoid
  - Small cell carcinoma of the lung
  - Merkel cell carcinoma

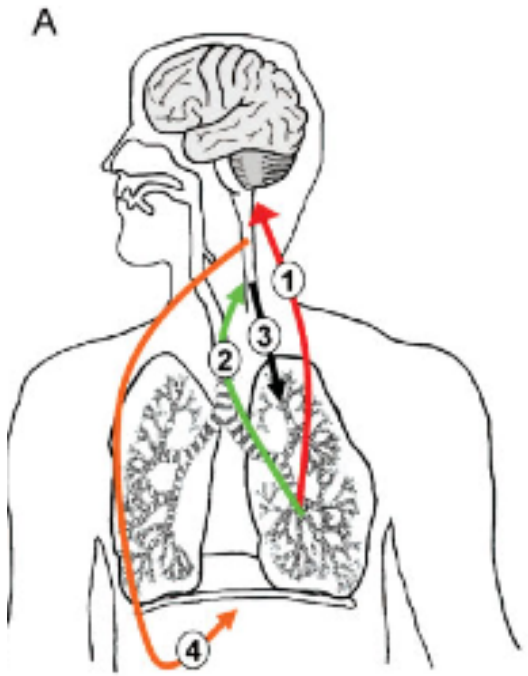


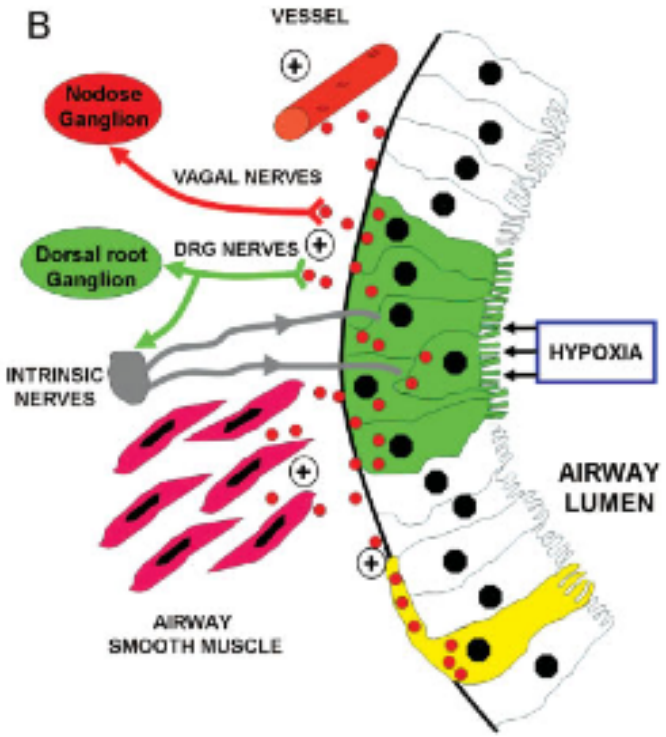
Les tumeurs neuro-endocrines pulmonaires

- Cellules de Kulchitsky

- Capteurs système nerveux végétatif
  - Contrôle de la ventilation
  - Contrôle de la circulation
  - Chemo- et mécanorécepteurs
- Rôle dans le développement

- Capacité à métaboliser la L-DOPA et le 5-hydroxytryptophane





Les carcinoïdes broncho-pulmonaires

Les tumeurs carcinoïdes

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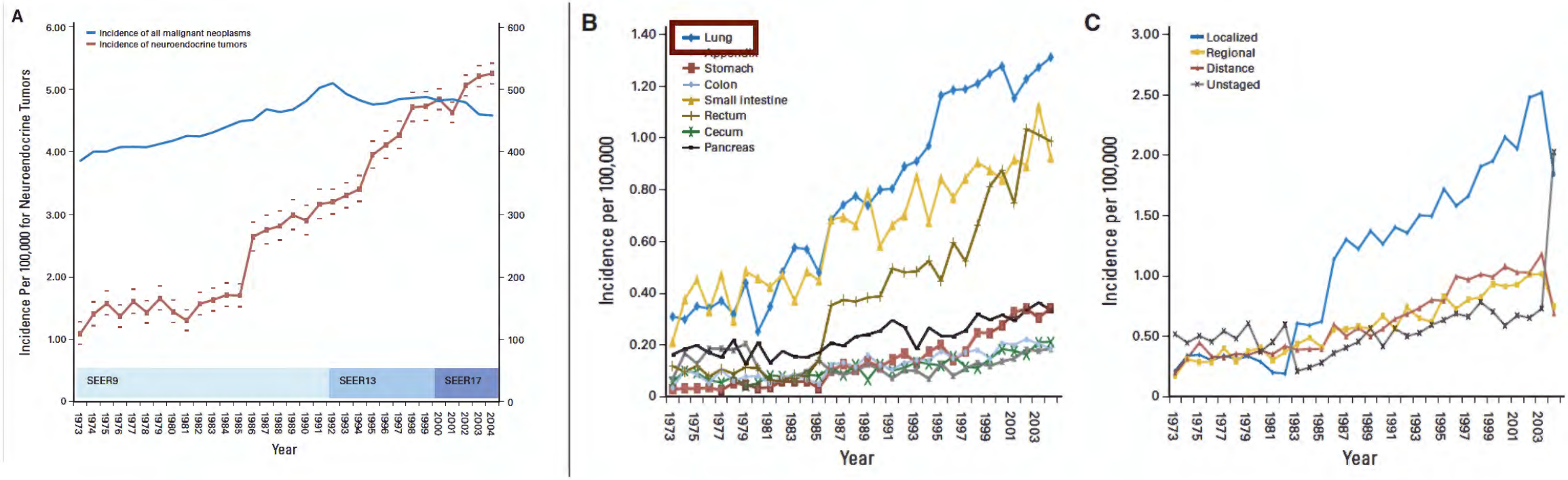

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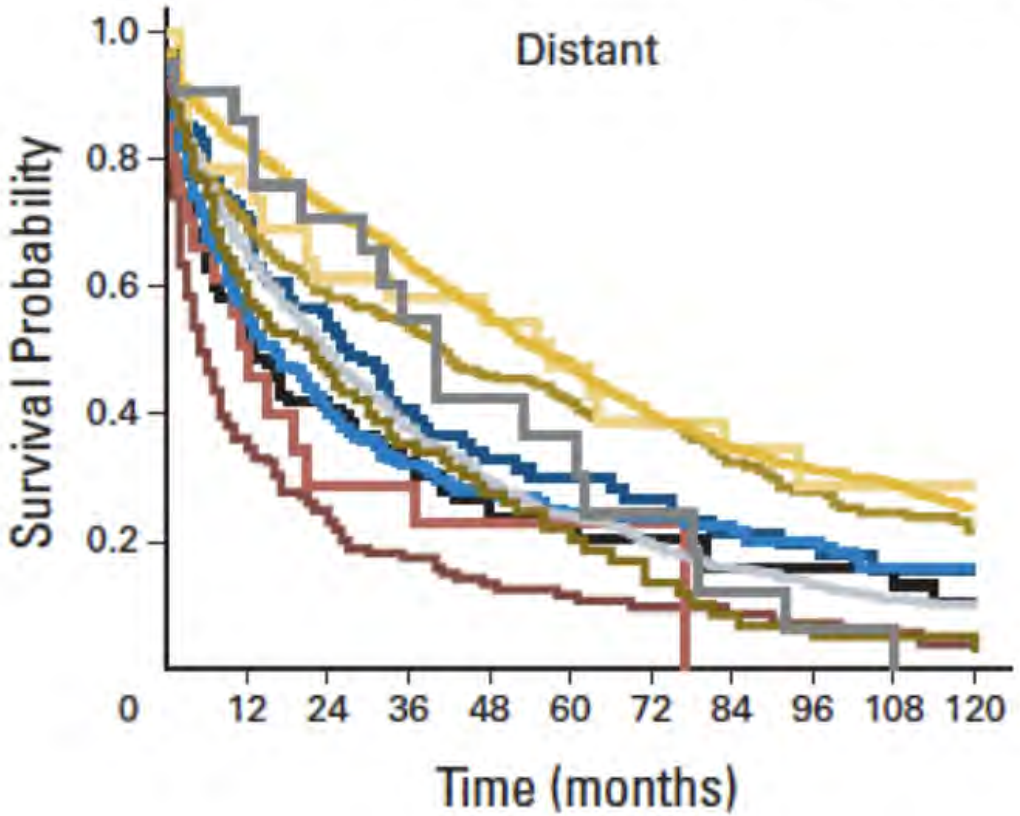

		Median Survival (months)		
Color	Site	Localized	Regional	Distant
	Appendix	>360	>360	27
	Cecum	135	107	41
	Colon	261	36	5
	Duodenum	107	101	57
	Gastric	154	71	13
	Liver	50	14	12
	Lung	227	154	16
	Pancreas	136	77	24
	Rectum	290	90	22
	Small bowel	111	105	56
	Thymus	110	68	40

Les carcinoïdes broncho-pulmonaires

Les tumeurs carcinoïdes

Anatomie pathologique

Classification des tumeurs neuro-endocrines pulmonaires

WHO 2004	Typical carcinoid	Atypical carcinoid	Large cell neuroendocrine carcinoma	Small cell neuro-endocrine carcinoma
Differentiation	Well	Well	Poor	Poor
Cell size			>20 µm	< 20 µm
Necrosis	Absent	Possible, focal	Jsual, extensive	Frequent
Mitotic index	< 2 mitoses /10 HPF (2 mm²)	2 – 10 mitoses /10 HPF (2 mm²)	> 10 mitoses /10 HPF (2 mm²)	> 10 mitoses /10 HPF (2 mm²)

Mots-clés : Carcinoid, Atypical carcinoid, Small cell carcinoma, Large cell neuroendocrine carcinoma, Mitoses

Survival Analysis of 200 Pulmonary Neuroendocrine Tumors With Clarification of Criteria for Atypical Carcinoid and Its Separation From Typical Carcinoid

Travis, William D. M.D.; Rush, Walter M.D.; Flieder, Douglas B. M.D.; Falk, Roni M.S.; Fleming, Marian V. J.D., M.D.; [illegible] Anthony A. M.D.; Koss, Michael N. M.D.

WHO 2004	Typical carcinoid
Differentiation	Well
Cell size	
Necrosis	Absent
Mitotic index	< 2 mitoses /10 HPF (2 mm²)

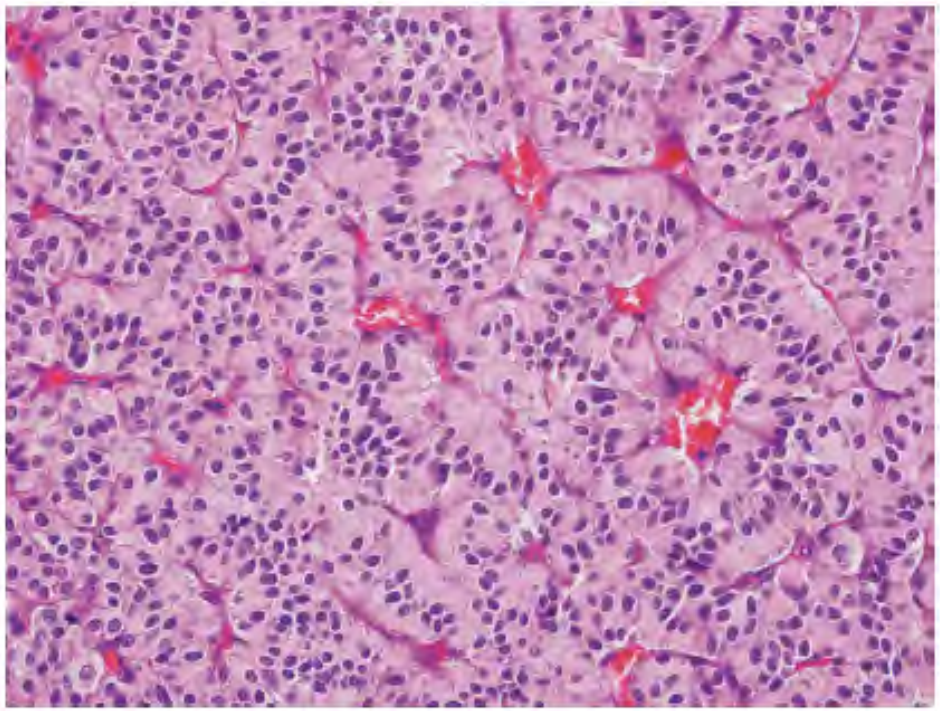

Figure. 1. Typical carcinoid. This tumor shows an organoid nesting pattern with a prominent vascular stroma. The tumor cells are uniform with a moderate amount of eosinophilic cytoplasm and finely granular nuclear chromatin. No necrosis or mitoses are seen.

Am J Surg Pathol 1998; 22:934

Mots-clés : Carcinoid, Atypical carcinoid, Small cell carcinoma, Large cell neuroendocrine carcinoma, Mitoses

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WHO 2004	Typical carcinoid	Atypical carcinoid
Differentiation	Well	Well
Cell size		
Necrosis	Absent	Possible, focal
Mitotic index	< 2 mitoses /10 HPF (2 mm²)	2 – 10 mitoses /10 HPF (2 mm²)

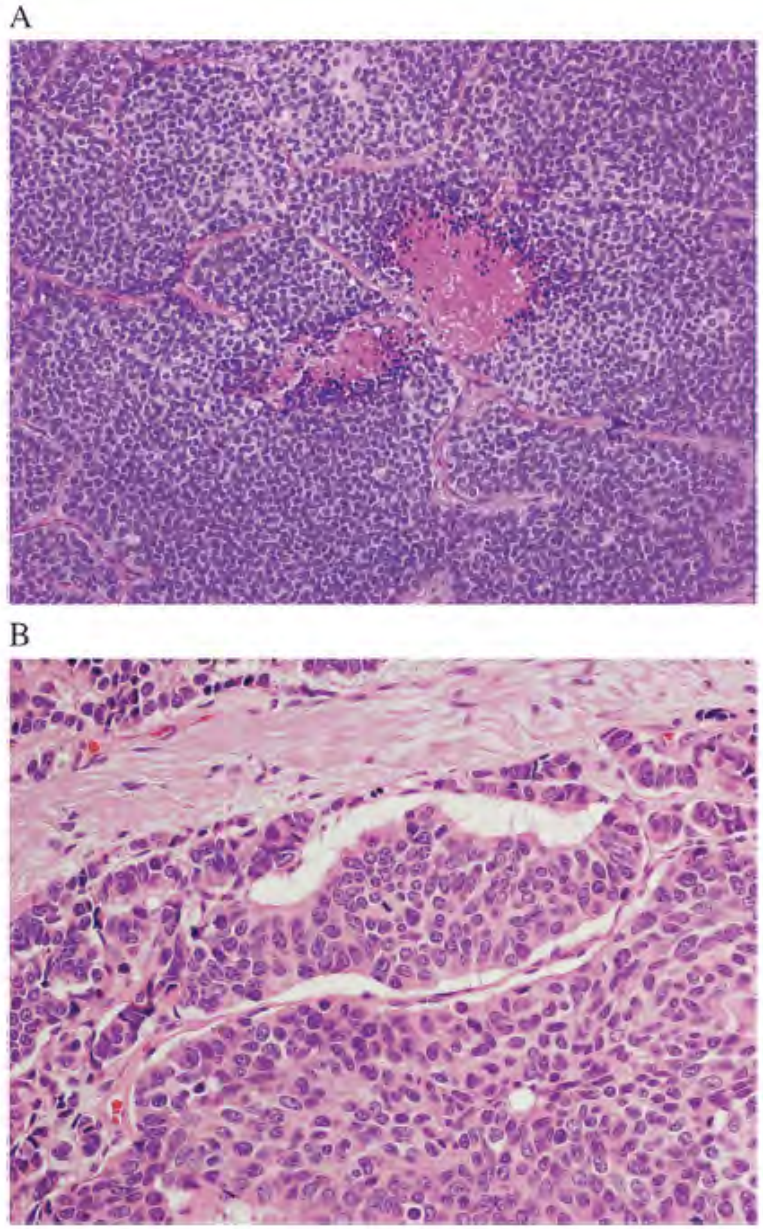

Figure. 2. (A) Atypical carcinoid. This tumor shows a punctate focus necrosis within sheets and nests of carcinoid tumor cells. (B) There is a single mitosis (center) in one tumor cell. The cells have finely granular nuclear chromatin.

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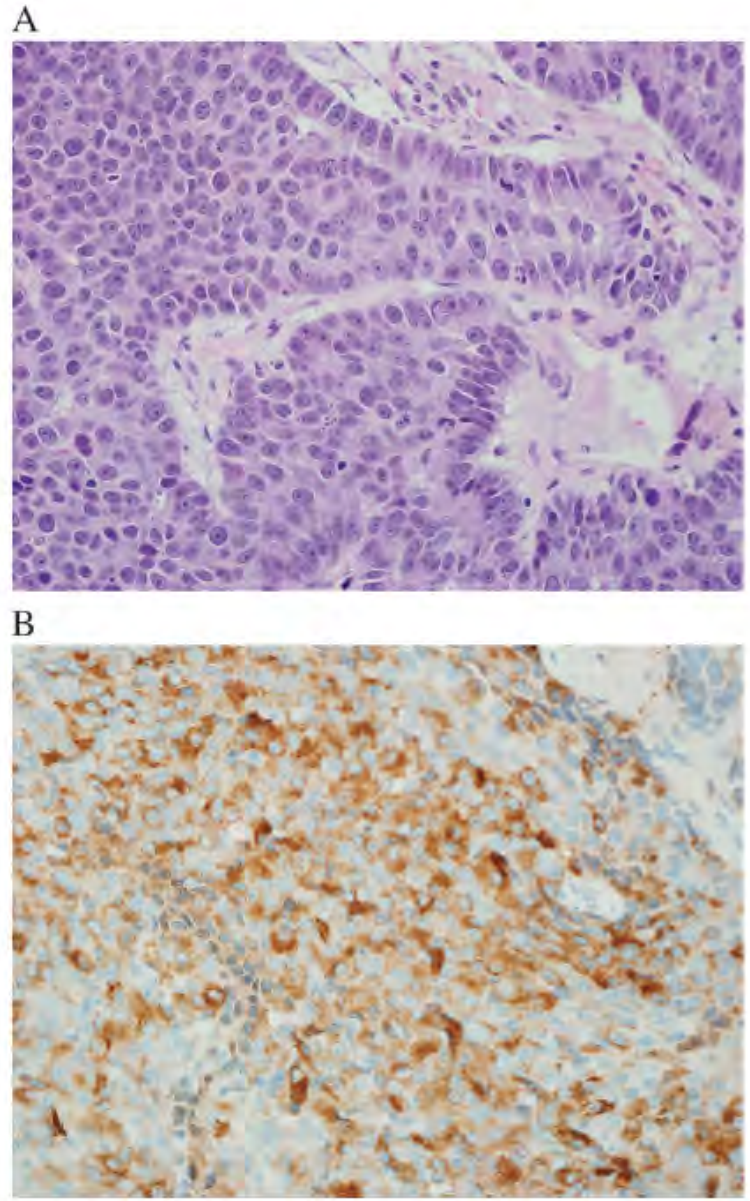

Figure. 3. Large-cell neuroendocrine carcinoma. (A) The tumor grows in sheets with prominent peripheral palisading and vague rosette-like structures. Several mitoses are seen. The tumor cells have abundant cytoplasm, prominent nucleoli. (B) Chromogranin strongly stains the tumor cells.

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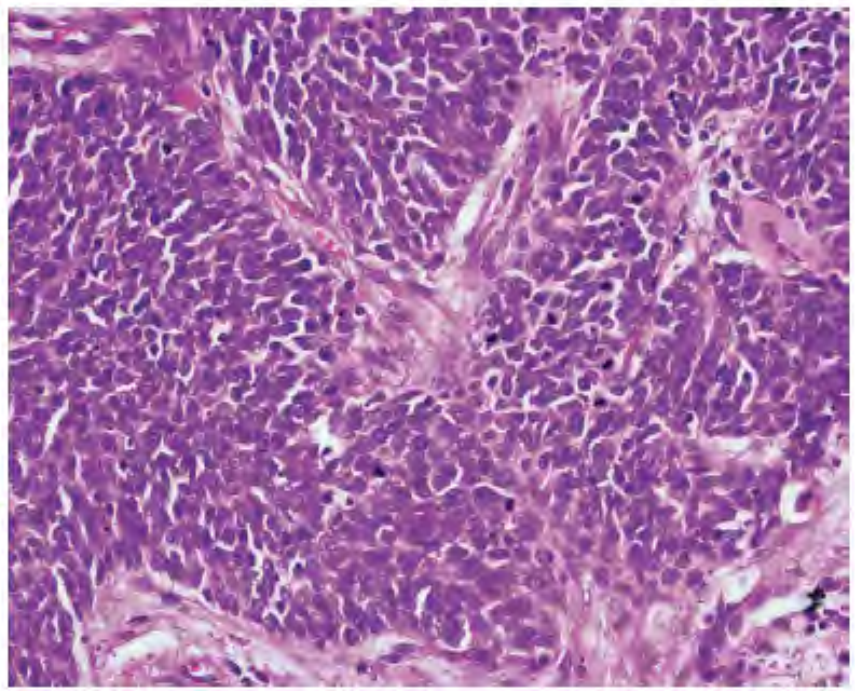

. 4. Small-cell carcinoma. This tumor consists of dense sheets of ells with scant cytoplasm, finely granular nuclear chromatin, frequent s; nucleoli are inconspicuous or absent.

Am J Surg Pathol 1998; 22:934

Mots-clés : Carcinoid, Atypical carcinoid, Small cell carcinoma, Large cell neuroendocrine carcinoma, Mitoses

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Marker	Positive rate (%)
NSE	18/19 (94.7)
Chromogranin A	19/19 (100)
Leu-7	17/19 (89.5)
Synaptophysin	16/19 (84.2)

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Mots-clés : Carcinoid, Atypical carcinoid, Small cell carcinoma, Large cell neuroendocrine carcinoma, Mitoses

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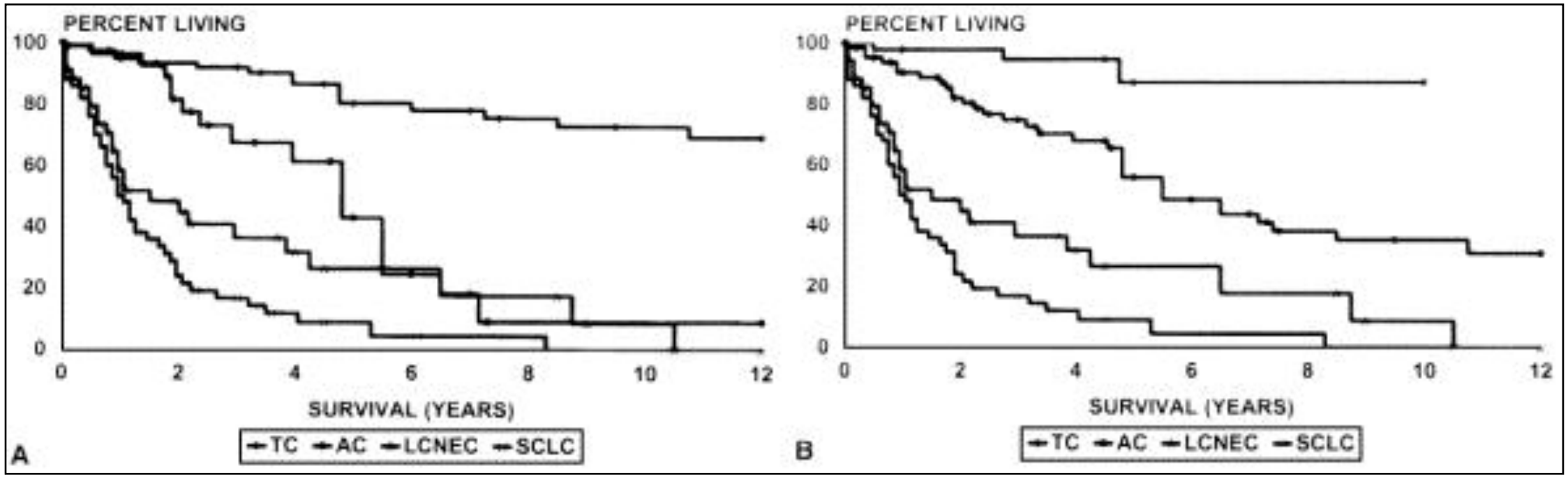
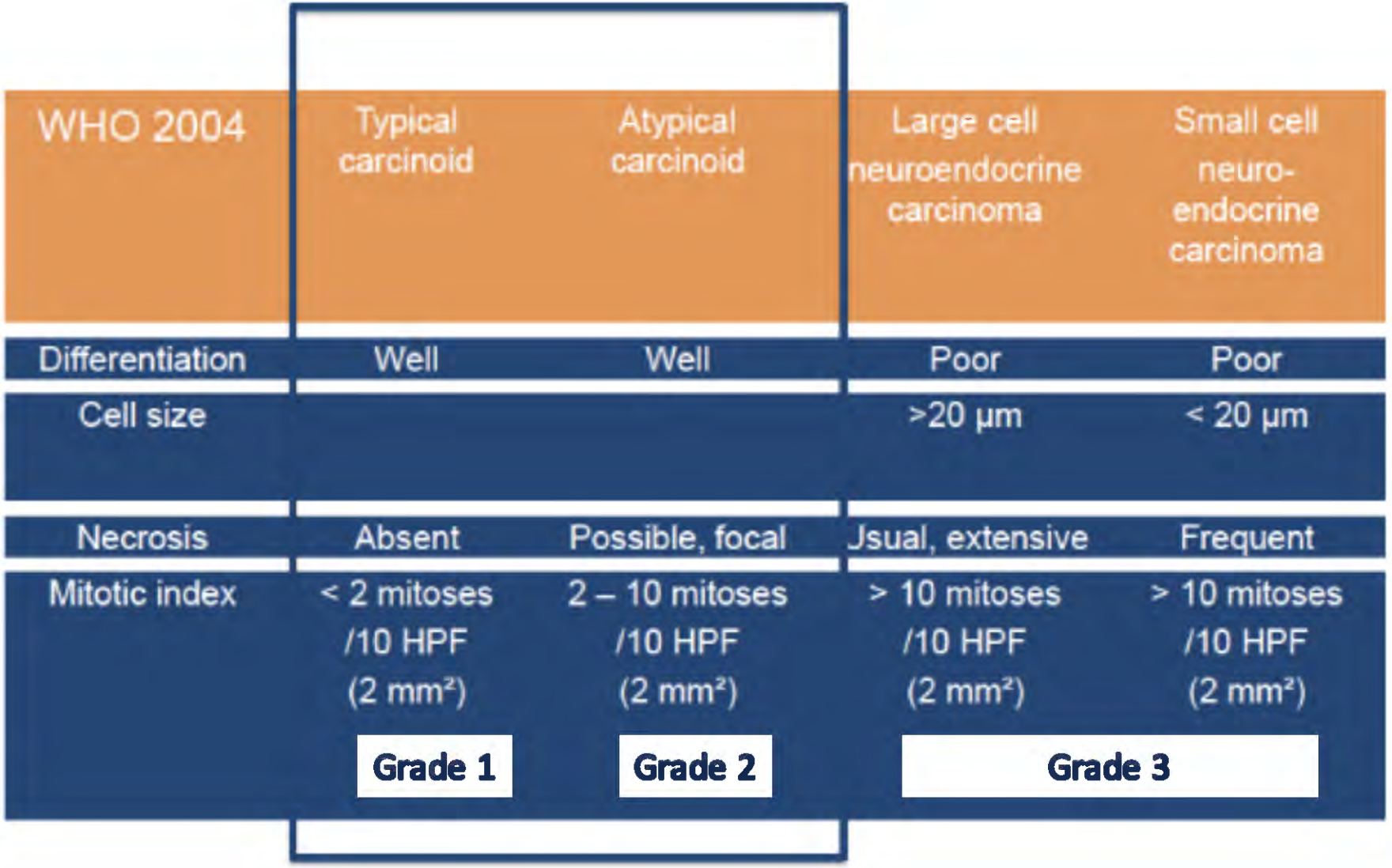
Histologie = grade?



Am J Surg Pathol 1998; 22:934

Classification des tumeurs neuro-endocrines pulmonaires



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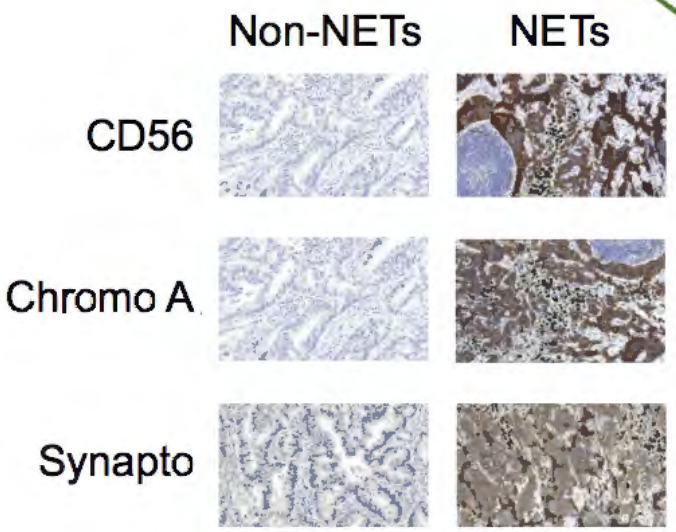
	Grade 1	Grade 2	Grade 3	

Classification des tumeurs neuro-endocrines pulmonaires

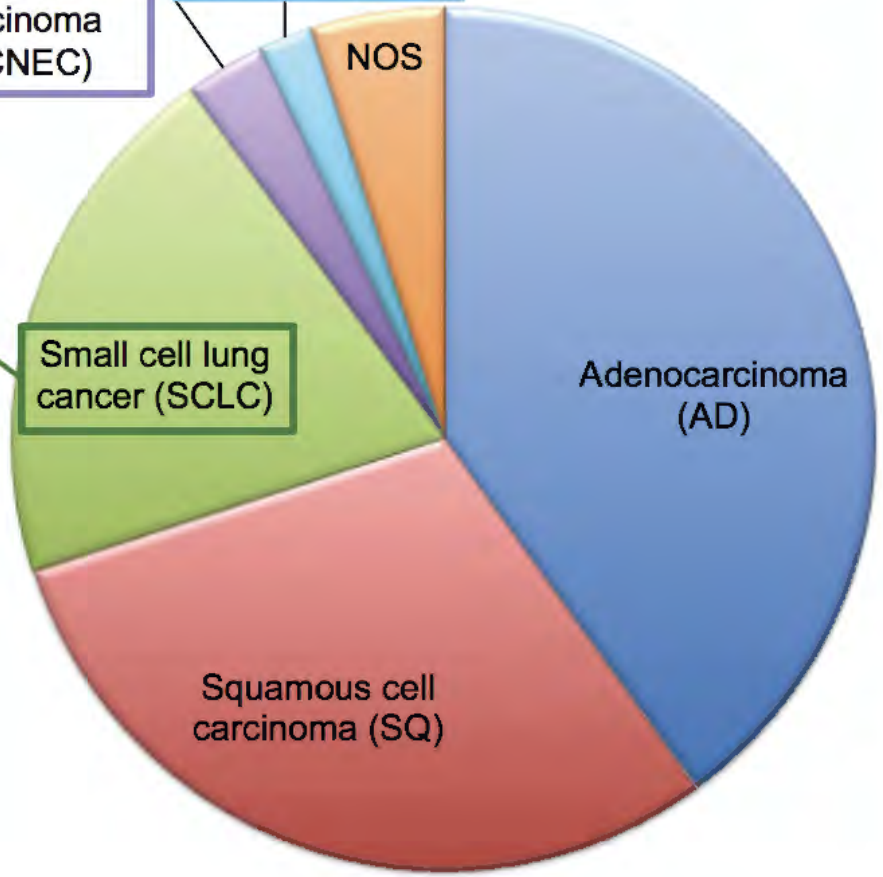
- Poorly differentiated
- Bad prognosis
- Heavy smokers
- SCLC → relapse chemoresistant

- Highly differentiated
- Good prognosis
- Surgical resection



International Agency for Research on Cancer

World Health Organization



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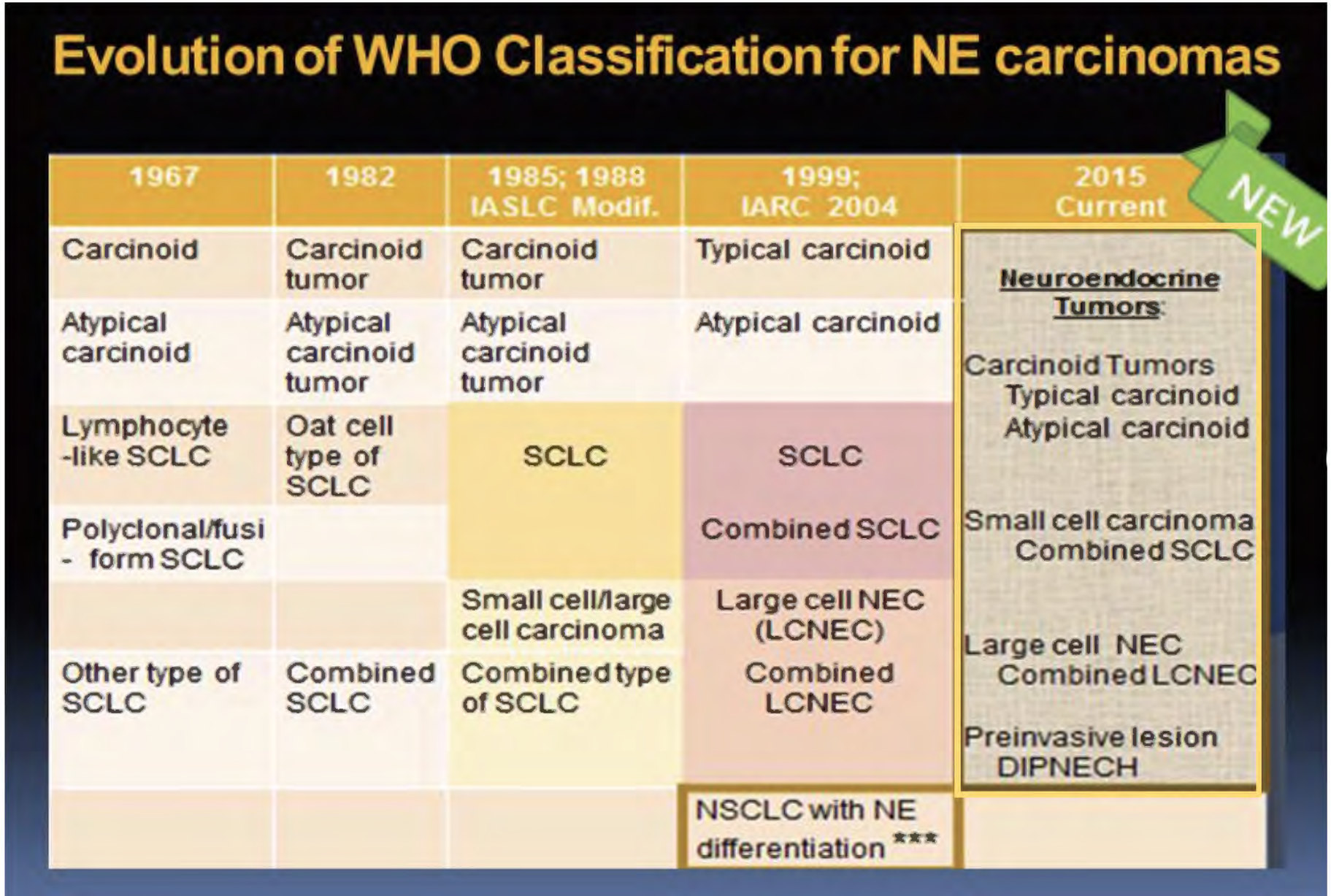


TNE pulmonaires : faut-il changer la nomenclature ? (1)

- La classification actuelle est celle de l'OMS 2004, basée sur l'histologie
  la classification 2015 sera inchangée pour la nomenclature

Classification OMS 2004 et 2015

Dénomination	Tumeurs malignes pulmonaires (%)	Malignité
Carcinoïde typique	2	Faible
Carcinoïde atypique	0,2	Intermédiaire
Carcinome neuroendocrine à grandes cellules	3	Élevée
Carcinome neuroendocrine à petites cellules	15	

- **Faut-il une classification basée sur le grade comme dans les TNE digestives ?**
- Les TNE pulmonaires sont réparties en 3 catégories plutôt que 4
  - Plan épidémiologique
  - Plan clinique
  - Plan évolutif

G1 si 2 ou 3 variables N1
G2 si 2 ou 3 variables N2
G3 si 2 ou 3 variables N3

Proposition de classification basée sur la prolifération et la nécrose

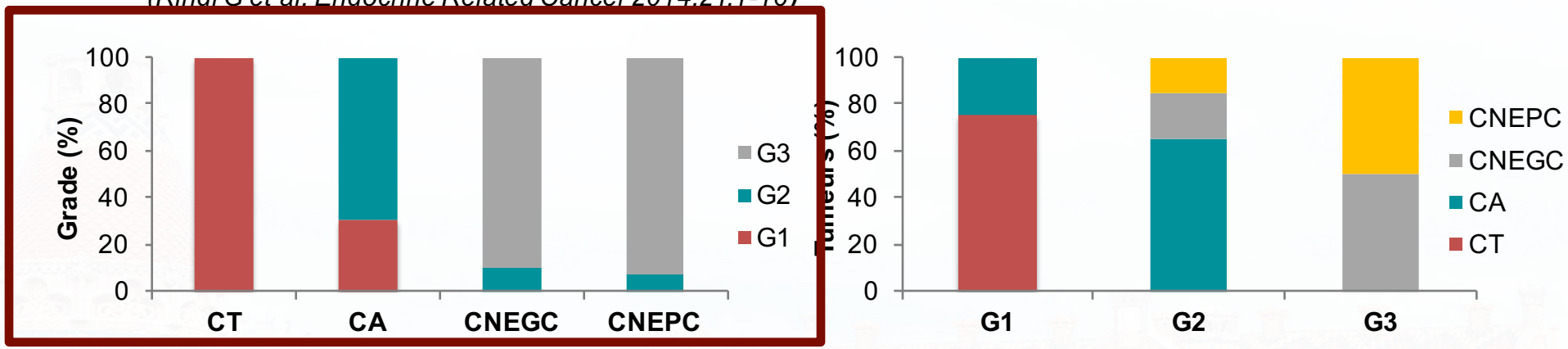
	Variable					
	Index mitotique		Ki67		Nécrose	
G1	2	N1	< 4 %	N1	Non	N1
G2	> 2 - 47	N2	4-25 %	N2	< 10 %	N2
G3	> 47	N3	≥ 25 %	N3	> 10 %	N3

ENETS 2015 - D'après Pelosi G et al., Session 7 actualisé

TNE pulmonaires : faut-il changer la nomenclature ? (2)

- 348 tumeurs : 105 carcinoïdes typiques (CT), 75 carcinoïdes atypiques (CA), 86 carcinomes neuroendocrines à grandes cellules (CNEGC) et 82 carcinomes neuroendocrines à petites cellules CNEPC

(Rindi G et al. Endocrine Related Cancer 2014;21:1-16)



- Nécessité d'intégrer le grade aux autres facteurs
  - Grade 1 (bien différenciée, de bas grade) : CT ou CA
  - Grade 2 (bien ou moyennement différenciée, grade intermédiaire) : CA, parfois CNEGC et quelques cas de CPC
  - Grade 3 (moyennement à non différencié, haut grade) : CNEGC ou CPC, mais aussi quelques rares cas de CA

➜ **Une classification basée sur le grade permettrait de mieux évaluer l'agressivité tumorale pour guider le traitement**

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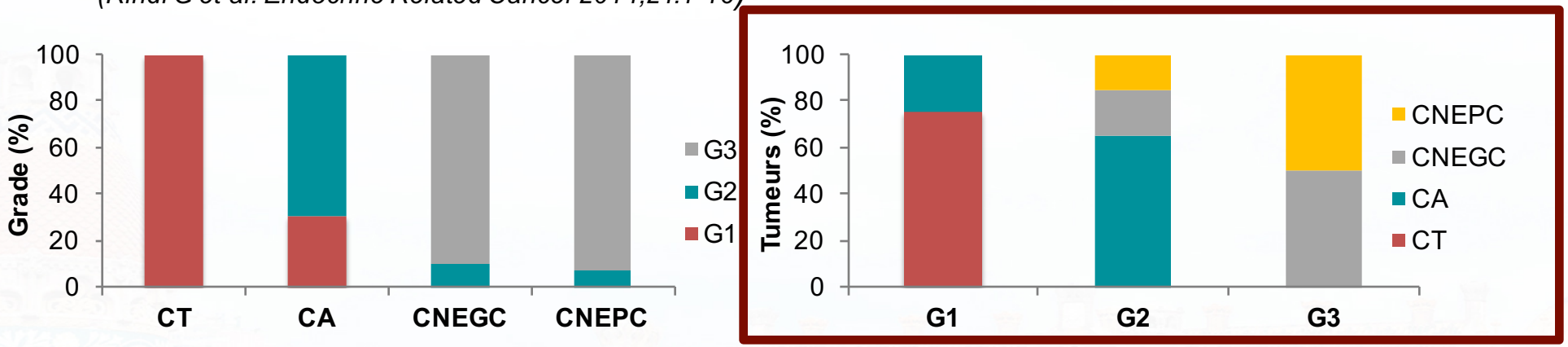

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Classification des tumeurs neuro-endocrines pulmonaires

Evolution of WHO Classification for NE carcinomas

NEW

1967	1982	1985; 1988 IASLC Modif.	1999; IARC 2004	2015 Current
Carcinoid	Carcinoid tumor	Carcinoid tumor	Typical carcinoid	**Neuroendocrine Tumors**: Carcinoid Tumors Typical carcinoid Atypical carcinoid
Atypical carcinoid	Atypical carcinoid tumor	Atypical carcinoid tumor	Atypical carcinoid	
Lymphocyte -like SCLC	Oat cell type of SCLC	SCLC	SCLC	
Polyclonal/fusi - form SCLC			Combined SCLC	Small cell carcinoma Combined SCLC
		Small cell/large cell carcinoma	Large cell NEC (LCNEC)	
Other type of SCLC	Combined SCLC	Combined type of SCLC	Combined LCNEC	Large cell NEC Combined LCNEC
				Preinvasive lesion DIPNECH
			NSCLC with NE differentiation ***	

Diffuse Idiopathic Pulmonary Endocrine Cell Hyperplasia (DIPNECH)

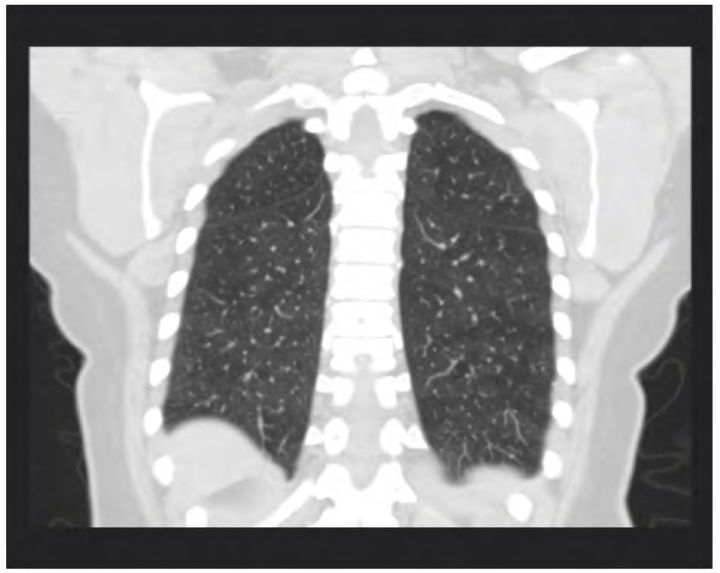
- Nodules pulmonaires multiples
  < 5mm

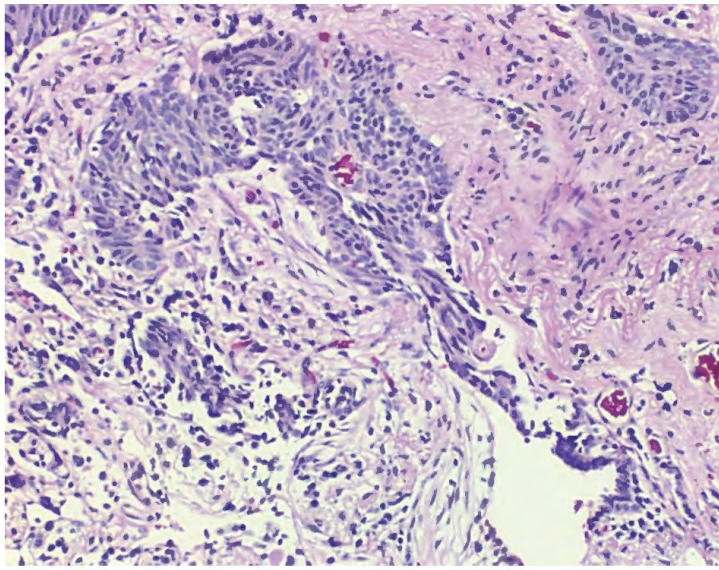
- Trouble Ventilatoire obstructif dans
  50% des cas

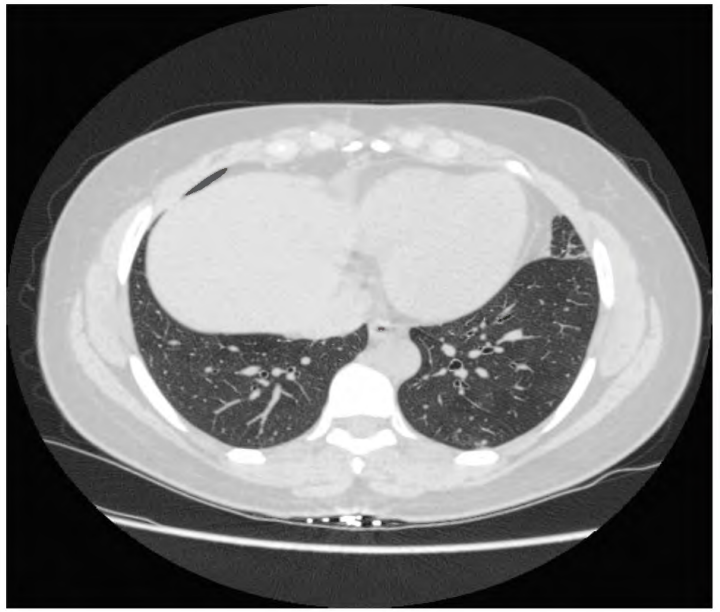
- Foci de cellules neuro-endocrines

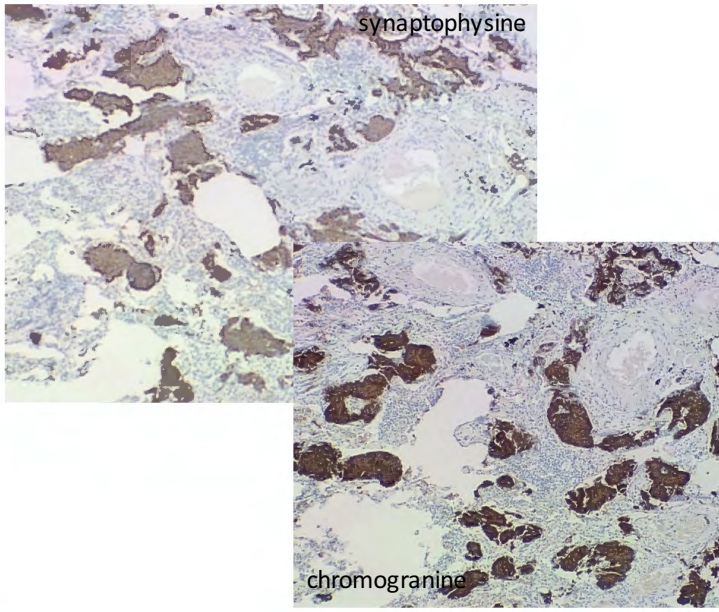
- Expression de chromogranine et
  synaptophysine

- Condition pré-tumorale?
- Mais aussi observée en cas de
  bronchiolite, PID, vie en altitude









Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia

A Systematic Overview

Adrienne A. Nassar[1], Dawn E. Jaroszewski[2], Richard A. Helmers[3], Thomas V. Colby[4], Bhavesh M. Patel[5], and Farouk Mookadam[6]

[1]Division of Internal Medicine, Department of Medicine; [2]Division of Cardiothoracic Surgery, Department of Surgery; [3]Division of Pulmonary Medicine, Department of Medicine; [4]Department of Laboratory Medicine and Pathology; [5]Department of Critical Care; and [6]Division of Cardiovascular Diseases, Department of Medicine, Mayo Clinic, Scottsdale, Arizona

Table 1 Clinical features of patients with diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

Clinical features	Group 1 (n=9) (Symptomatic)	Group 2 (n=10) (Asymptomatic)	Overall (n=19)
Male : female (n=19)	2 : 7	2 : 8	4 : 15
Smoking history (n=17) (never: ex-smoker : current)	5 : 2 : 1	7 : 2 : 0	12 : 4 : 1
Mean age at onset (years)	49.1 (31–67)	NA	
Presenting complaints:			
Cough	4/9	0/10	4/19
Increasing dyspnoea	6/9	0/10	6/19
Pleuritic chest pain	2/9	0/10	2/19
Haemoptysis	1/9	1/10*	2/19
Asymptomatic	0/9	9/10*	9/19*
Previous malignancy	0/9	8/10	8/19
History of asthma	3/9	2/10	5/19
Lung function (n=16; obstructive : mixed : normal)	5 : 3: 0	3: 0: 5	8 : 3: 5
Mean duration of illness before diagnosis (years)	8.6	NA	8.6
Bronchoalveolar lavage	Lymphocytosis 2/2	–	Lymphocytosis 2/2
Treatment†			
Steroids	2/6	0/8	2/14
Watch and wait	3/6	4/8	7/14
Follow-up			
Clinically stable (alive with disease)	5/7 (range 1–12 years, mean 5.8 years)	6/7 (range 0.2–2.2 years, mean 1.0 year)	11/14
Clinical deterioration	1/7	0/7	1/14
Died of DIPNECH	1/7‡	0/7	0/14
Died of other disease	0/7	1/7§	1/14

Table 3 Histopathological features in cases of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

Histopathological features	Group 1	Group 2	Total
Neuroendocrine cell hyperplasia	9/9	10/10	19/19
Tumourlets	9/9	10/10	19/19
Typical carcinoid	4/9	5/10	9/19
Atypical carcinoid	0/9	3/10	3/19
Bronchiolitis	9/9	10/10	19/19
Obliterative bronchiolitis	7/9	7/10	14/19
Peribronchial fibrosis	6/9	8/10	14/19
Bronchiolectasis	4/9	1/10	5/19
Mucus plugging	5/9	4/10	9/19
TTF-1 staining of NEH/TL cells	5/5	6/6	11/11
TTF-1 staining of TC	N/A	3/3	3/3
TTF-1 staining of AC	N/A	2/2	2/2

AC, atypical carcinoid; NE, neuroendocrine; NEH, neuroendocrine cell hyperplasia; TC, typical carcinoid; TL, tumourlet; TTF-1, thyroid transcription factor-1.

Table 2 Imaging data on high-resolution computed tomography

CT findings	Group 1*	Group 2†	Total
Presence of nodules	4/6	7/7	10/13
Airway dilatation	2/6	1/7	3/13
Bronchial wall thickening	2/6	0/7	2/13
Air trapping ± mosaicism	4/6	1/7	5/13
Atelectasis	1/6	0/7	1/13
Normal	1/6	0/7	1/13

*One other patient had a chest radiograph only, which showed a single nodule.
†One other patient had a chest radiograph only, which showed multiple nodules.

Les carcinoïdes broncho-pulmonaires

Les tumeurs carcinoïdes

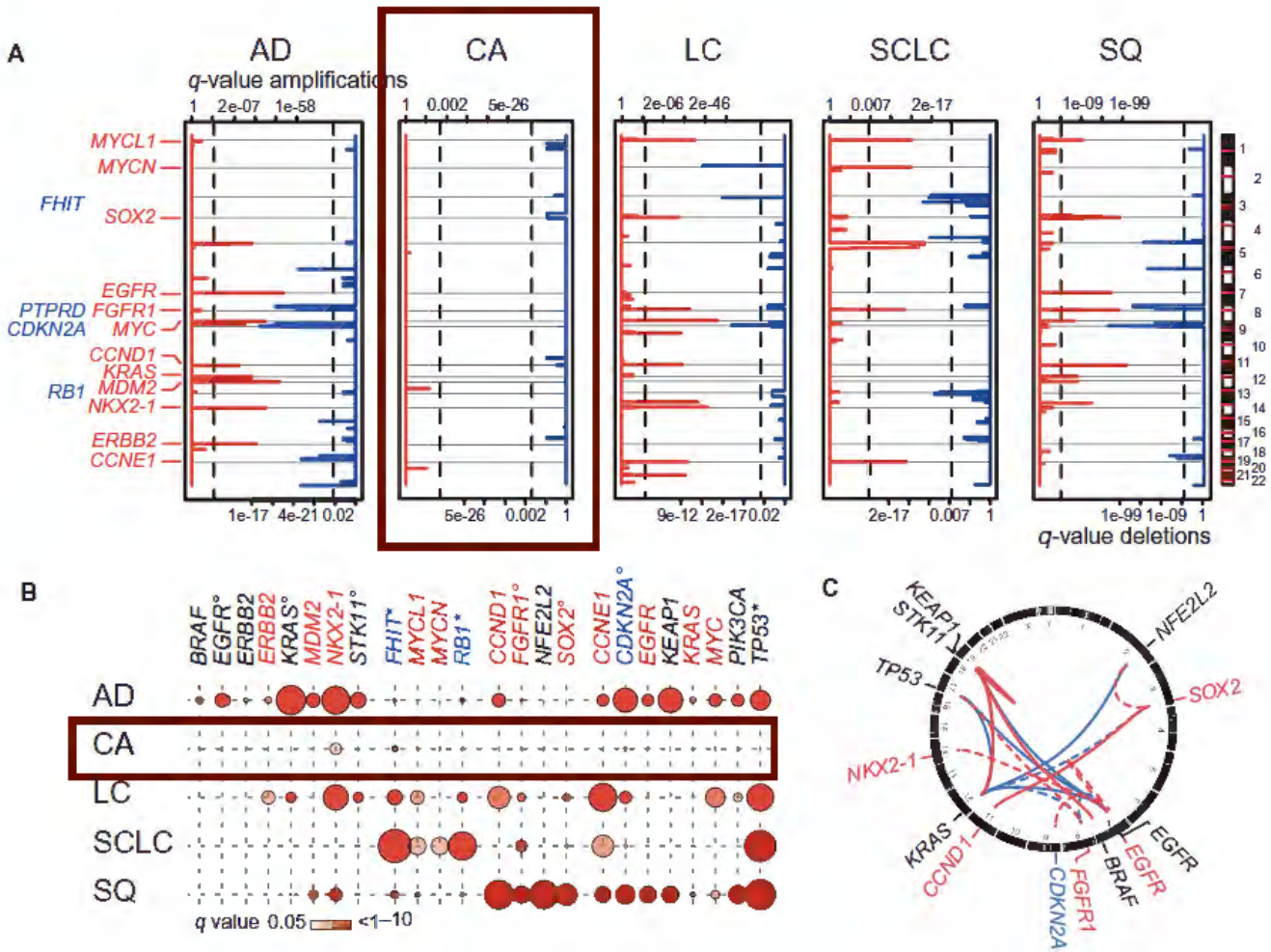
Anatomie pathologique

CANCER

A Genomics-Based Classification of Human Lung Tumors

The Clinical Lung Cancer Genome Project (CLCGP) and Network Genomic Medicine (NGM)*†

We characterized genome alterations in 1255
to identify genetically defined and clinically r
oncogenic genome alteration potentially am
personalized treatment approaches that are a
of genomic alterations existed between and
tomorphological diagnosis. Immunohistoche
The reassignment eliminated almost all case
relevant alterations. Prospective testing of o
patients enabled a genome-based diagnosis
reassignments of large cell lung cancer, and
mutant or *ALK*-rearranged cancers. Thus, our f
based diagnosis of lung cancer.



Sci transla Med 2013;5: 209ra153

nature COMMUNICATIONS

ARTICLE

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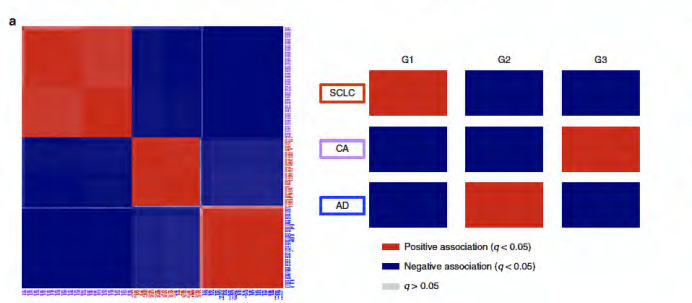
DOI: 10.1038/ncomms4518

Frequent mutations in chromatin-remodelling genes in pulmonary carcinoids

Lynnette Fernandez-Cuesta[1,*], Martin Peifer[1,2,*], Xin Lu[1], Ruping Sun[3], Luka Ozretić[4], Danila
Thomas Zander[1,6,7], Frauke Leenders[1,5], Julie George[1], Christian Müller[1], Ilona Dahmen[1], Be
Graziella B , Viktor Achter
Peter M. S stugun[15,16], Ås
Steinar Soll avin M. Wright
Zoe Waine l P.A. Davies[23]
Iver Peters William D. Trav
Martin Vin 5,7] & Roman K



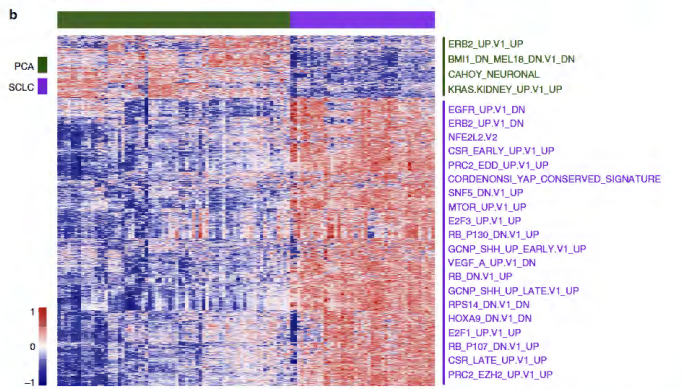
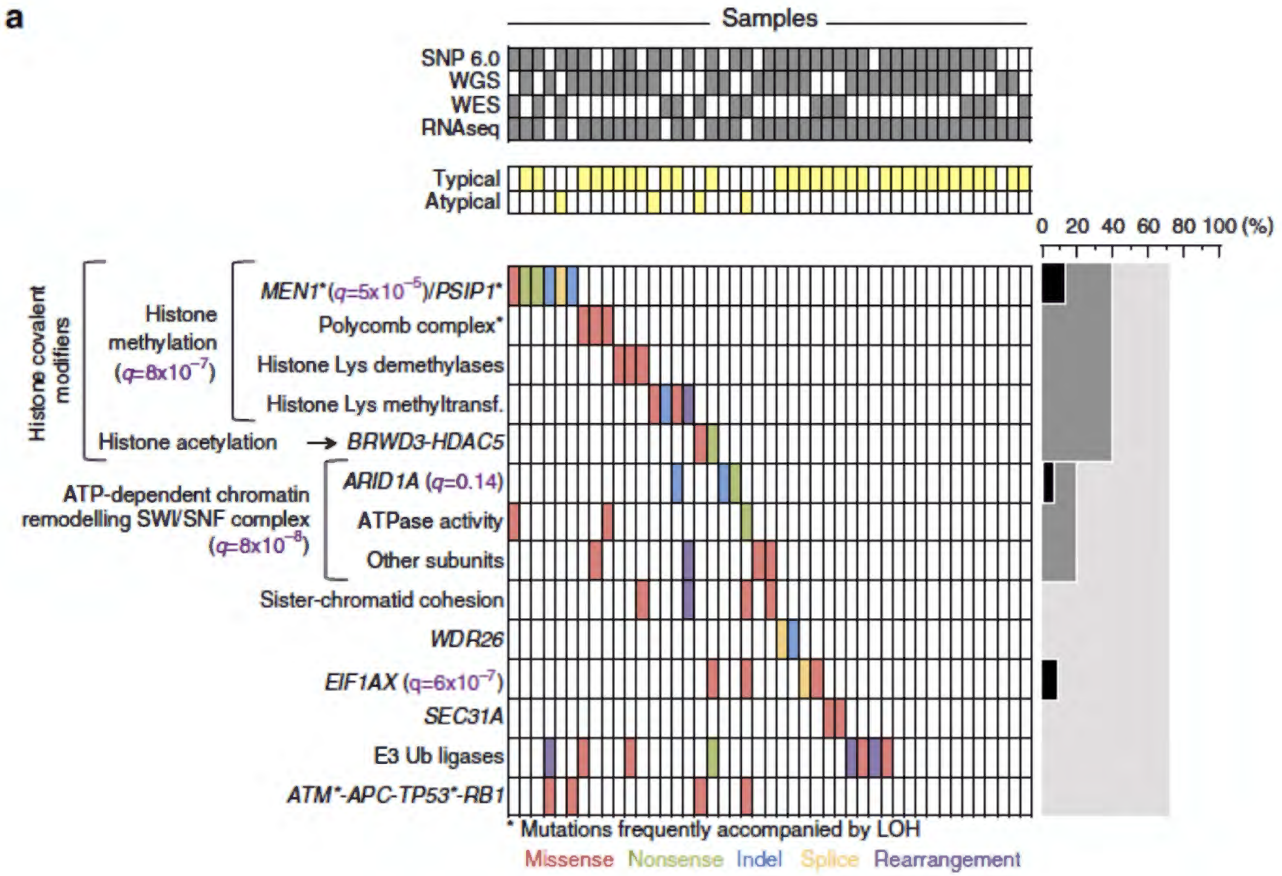


Figure 3 | Expression data analysis of pulmonary carcinois based on RNAseq data. (**a**) Consensus k-means clustering[32,33] using RNAseq expression data of 49 adenocarcinomas (AD, in blue), 43 small-cell lung cancer (SCLC, in red) and 69 pulmonary carcinoids (PCA, in purple) identified three groups using the clustering module from GenePattern[31] and consensus CDF[32,33] (left panel). The significance of the clustering was evaluated by using SigClust[34] with a $P < 0.0001$. Fisher's exact test[35] was used to check associations between the clusters and the histological subtypes (right panel). (**b**) Gene set enrichment analysis[21] for SCLC versus PCA using RNAseq expression data. Low gene expression is indicated in blue and high expression, in red. On the right side are given the altered pathways in PCA (green) and SCLC (purple).



Les carcinoïdes broncho-pulmonaires

Les tumeurs carcinoïdes

Anatomie pathologique

Stadification

The IASLC Lung Cancer Staging Project

Proposals for the Inclusion of Broncho-Pulmonary Carcinoid Tu in the Forthcoming (Seventh) Edition of the TNM Classificatio Lung Cancer

William D. Travis, MD, Dorothy J. Giroux, MS,† Kari Chansky, MS,† John Crowley, PhD Hisao Asamura, MD,‡ Elisabeth Brambilla, MD, PhD,§ James Jett, MD,‖ Catherine Kenned Ramon Rami-Porta, MD,# Valerie W. Rusch, MD,** and Peter Goldstraw, MB, FRCS,†† on behalf of the International Staging Committee and Participating Institutions*

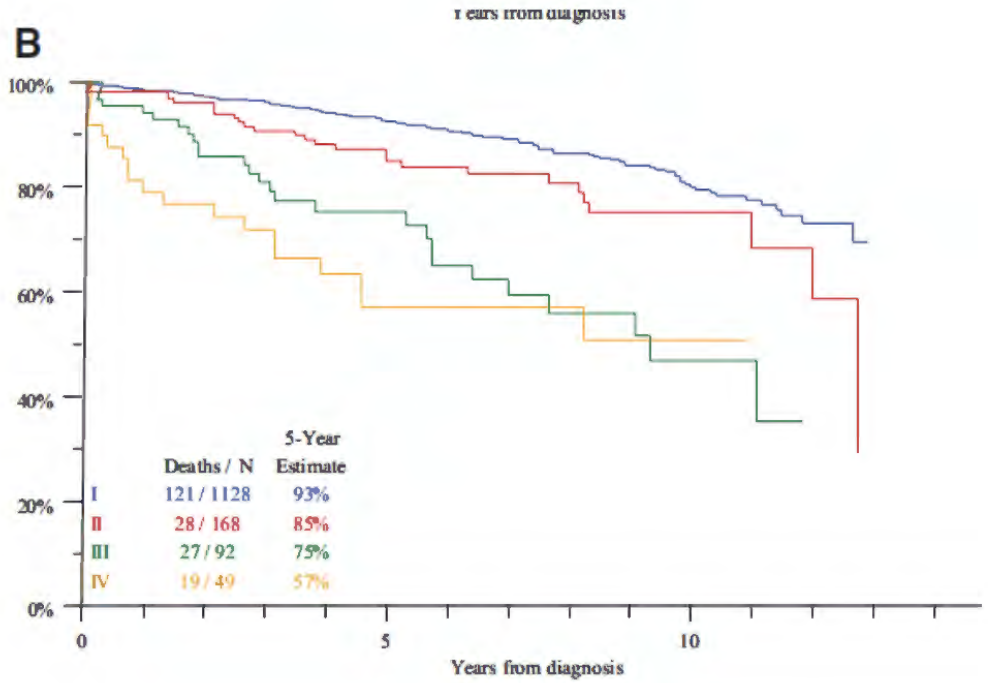
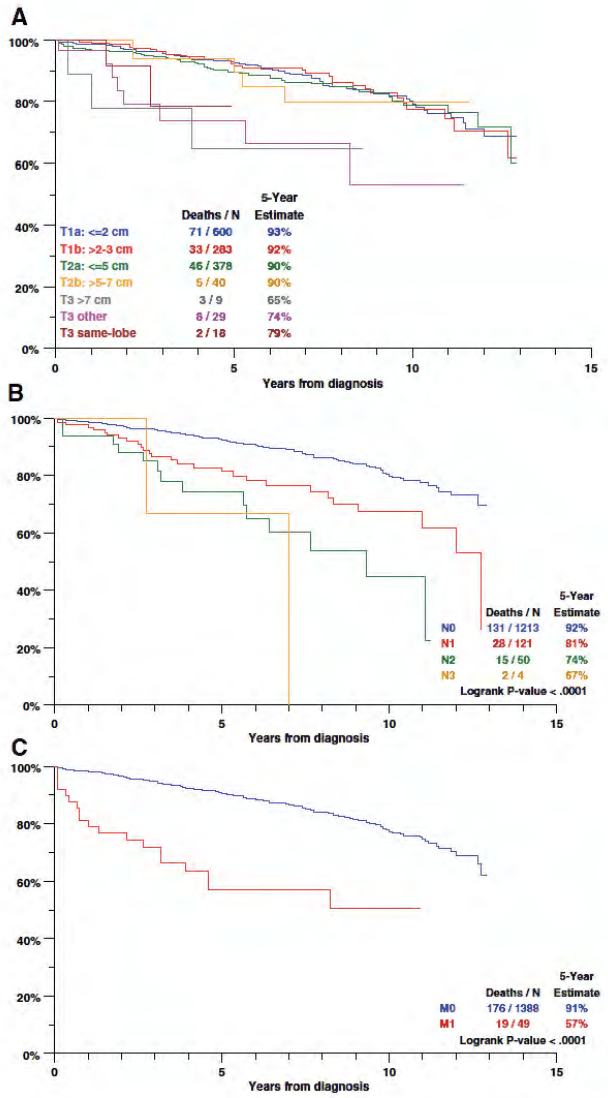


TABLE 3. IASLC Proposed Staging or IASLC Carcinoid Database, Pathologic Stage by pTM-Descriptor and pN

		pN-Category		
Total	**Total**	**N0**	**N1**	**N2**
	392	350	29	13
IA Total stage 1A	267	267		
T1a T1a: ≤2 cm	154	154		
T1b T1b: >2–3cm	72	72		
T1x T1x, no size	41	41		
IB Total stage 1B	56	56		
T2a T2a: ≤5 cm	56	56		
IIA Total stage IIA	37	10	27	
T1a T1a: ≤2 cm	8		8	
T1b T1b: >2–3 cm	8		8	
T1x T1x, no size	1		1	
T2a T2a: ≤5 cm	10		10	
T2b T2b: >5–7 cm	10	10		
IIB Total stage IIB	18	17	1	
T2b T2b: >5–7 cm	1		1	
T3 T3: >7 cm	1	1		
T3 by invasion	9	9		
T3 by same-lobe nodules	7	7		
IIIA Total stage IIIA	13	0	1	12
T1a T1a: ≤2 cm	2		2	
T1b T1b: >2–3 cm	1			1
T2a T2a: ≤5 cm	5			5
T2b T2b: >5–7 cm	1			1
T3 T3: >7 cm	1		1	0
T3 by invasion	3		0	3
IV Total stage IV	1	0	0	1
M1b Distant metastasis	1	0	0	1

IASLC, International Association for the Study of Lung Cancer.



J Thorac Oncol 2008;3:1213

Les carcinoïdes broncho-pulmonaires

Les tumeurs carcinoïdes

Anatomie pathologique

Stadification

Evaluation pré-thérapeutique

Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids

M. E. Caplin[1*], E. Baudin[2], P. Ferolla[3], P. Filosso[4], M. Garcia-Yuste[5], E. Lim[6], K. Oberg[7], G. Pelosi[8], A. Perren[9], R. E. Rossi[1,10] & W. D. Travis[11] the ENETS consensus conference participants[†]

[1]Neuroendocrine Tumour Unit, Royal Free Hospita
Roussy, Université Paris Sud, Villejuif Cedex, Franc
Surgery, University of Torino, Torino, Italy; [5]Depart

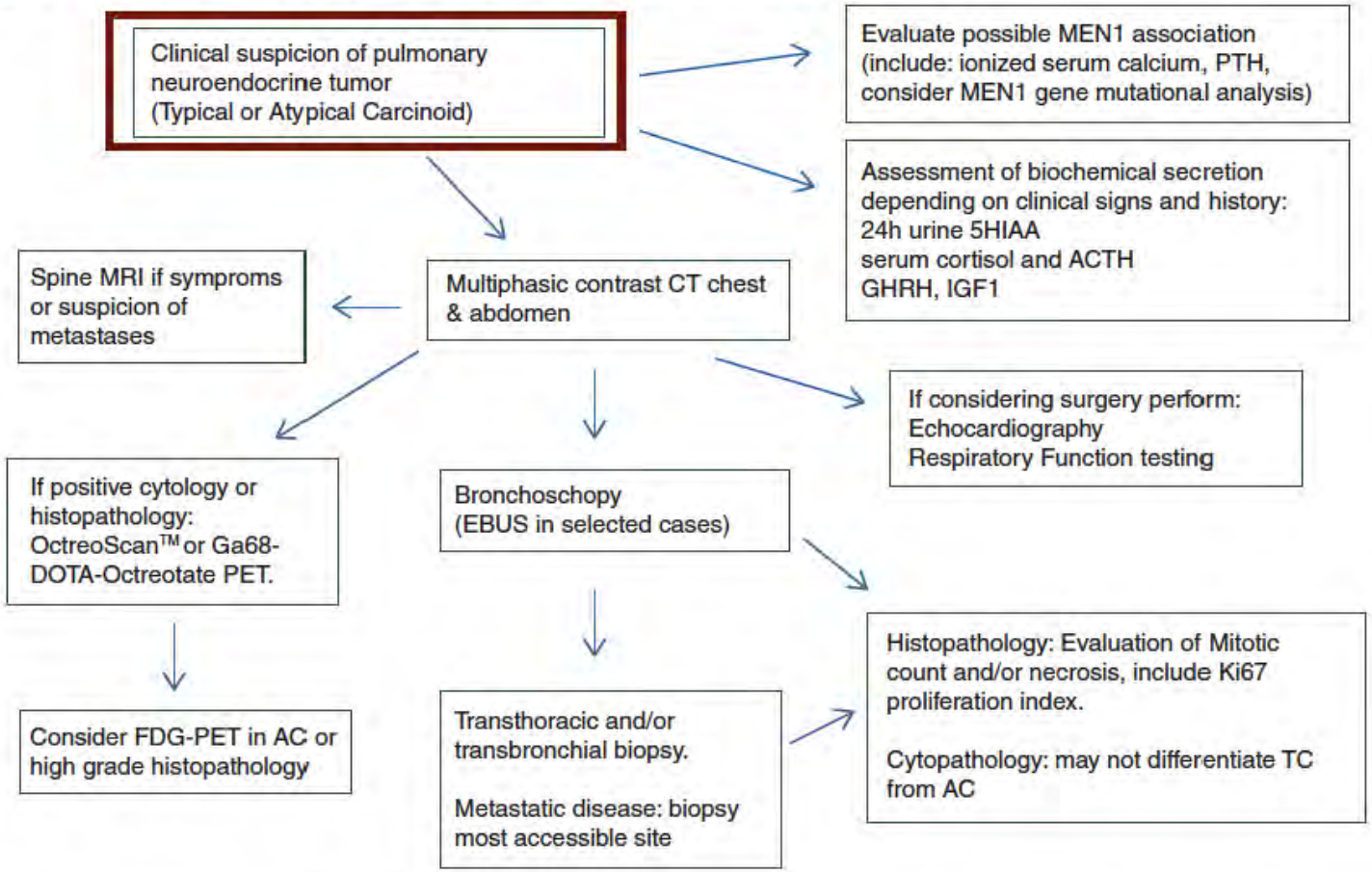


Figure 1. Algorithm for diagnosis of pulmonary neuroendocrine tumor.

Clinical Presentation and Evaluation of Neuroendocrine Tumors of the Lung

Frank C. Detterbeck, MD

KEYWORDS

• Carcinoid tumors • Bronchopulmonary carcinoid tumors • Neuroendocrine tumors
• Clinical presentation

- Symptomes liés à la localisation tumorale
  - toux, hémoptysie, infections
- Sd sécrétoire (1% au diagnostic, 5% dans le suivi)
  - diarrhée, flush, bronchospasme,
  - sécrétion du métabolite sérotonine 5-HIAA
- Sd de Cushing (6%)
  - sécrétion d'ACTH

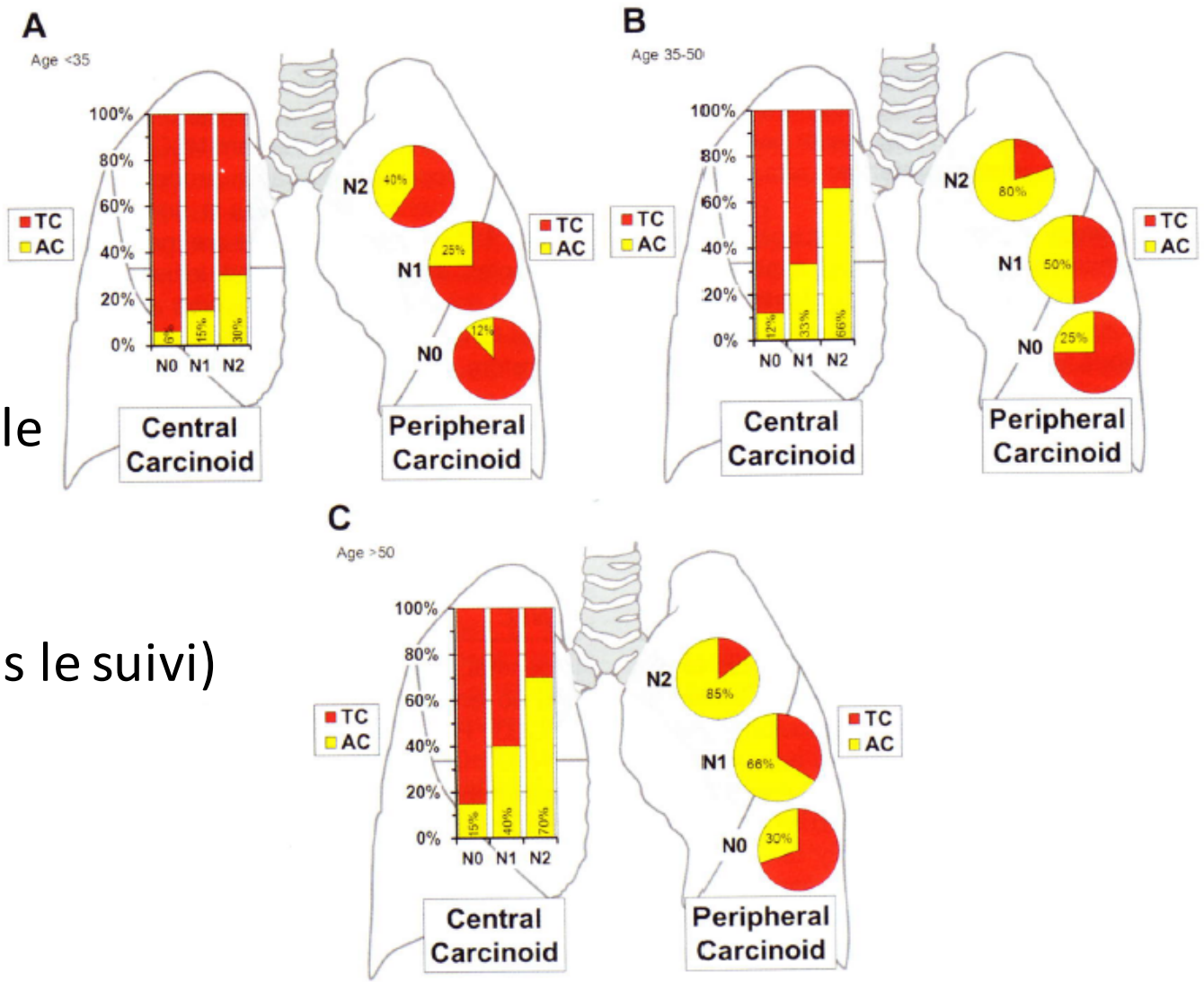


Fig. 2. Estimated proportion of TC and AC tumors among bronchopulmonary carcinoids by location and pathologic nodal status. (*A*) Age <35. (*B*) Age 35–50. (*C*) Age >50. Results are a rough estimate based on age distribution, proportion of TC versus AC tumors, and rate of node involvement.

Thorac Surg Clin 2014;24:267

Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids

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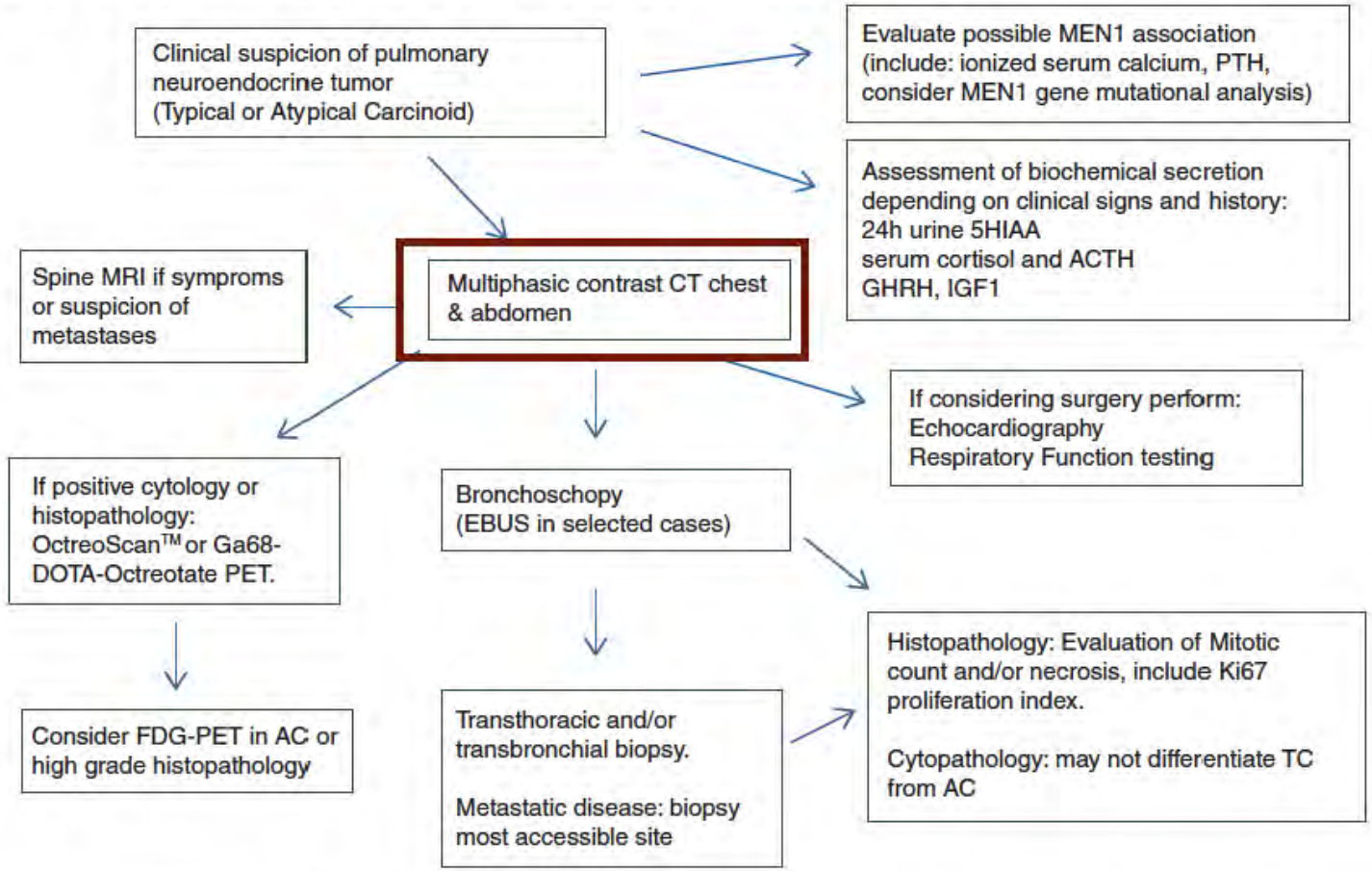
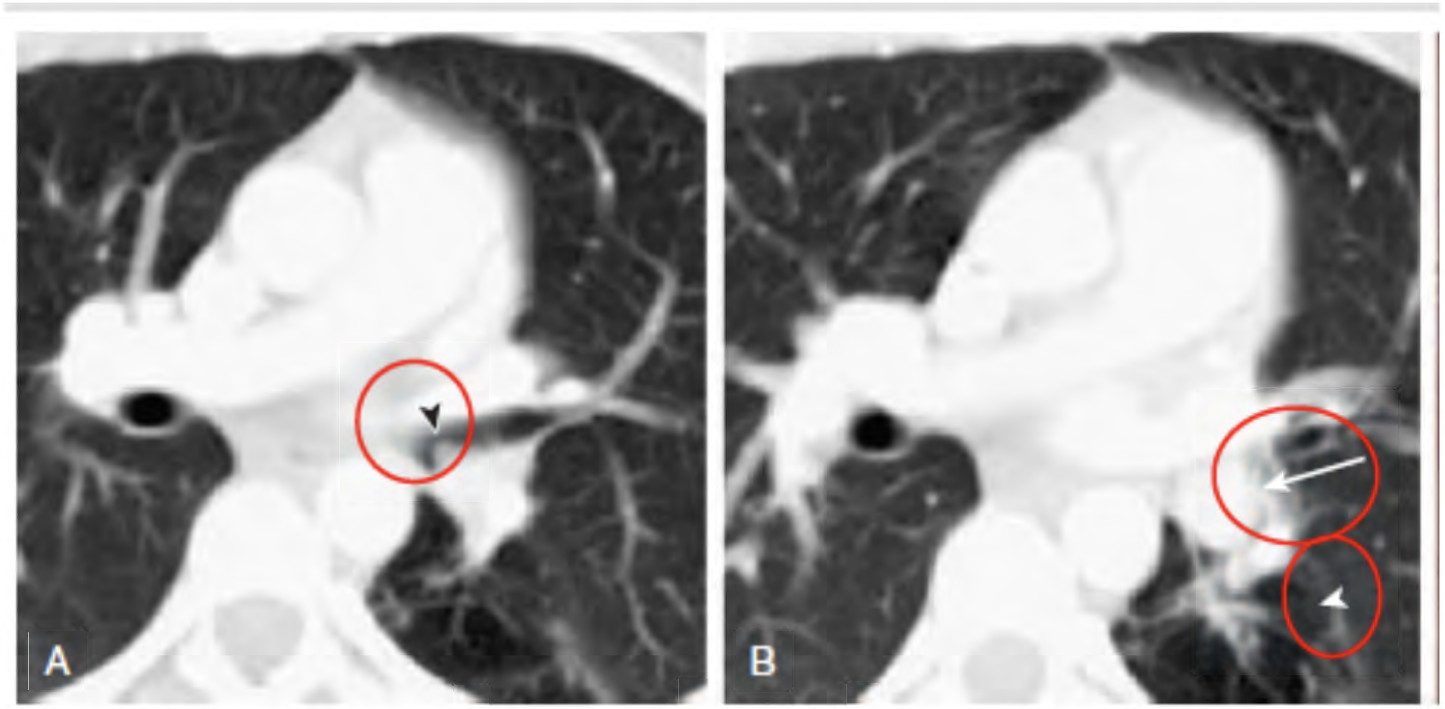


Figure 1. Algorithm for diagnosis of pulmonary neuroendocrine tumor.

Aspects tomodensitométriques et endoscopiques



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M. E. Caplin[1*], E. Baudin[2], P. Ferolla[3], P. Filosso[4], M. Garcia-Yuste[5], E. Lim[6], K. Oberg[7], G. Pelosi[8], A. Perren[9], R. E. Rossi[1,10] & W. D. Travis[11] the ENETS consensus conference participants[†]

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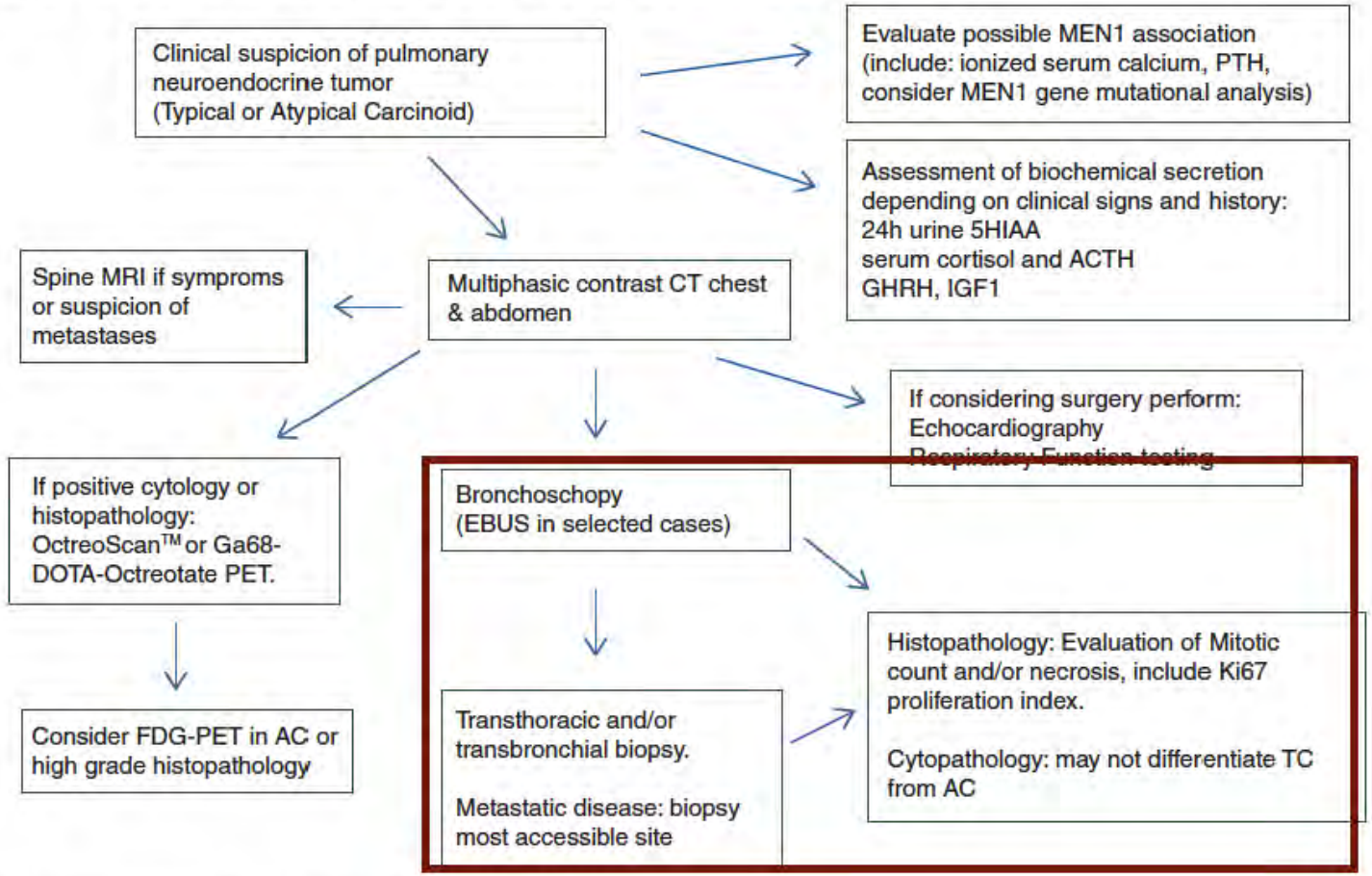


Figure 1. Algorithm for diagnosis of pulmonary neuroendocrine tumor.

Aspects tomodensitométriques et endoscopiques

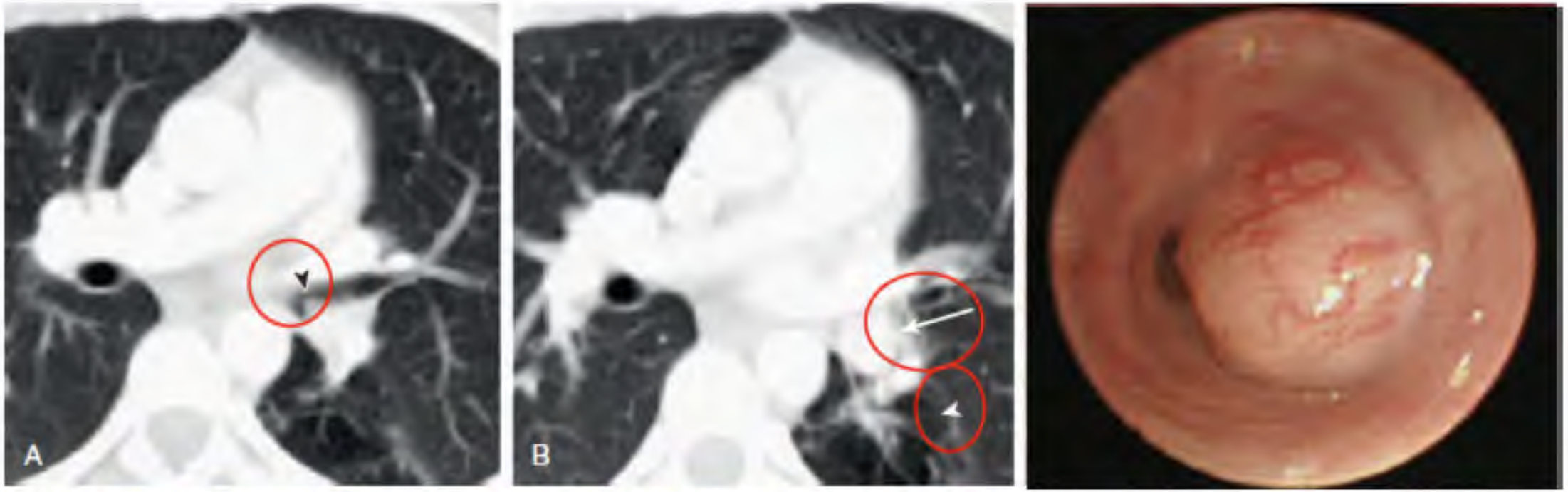


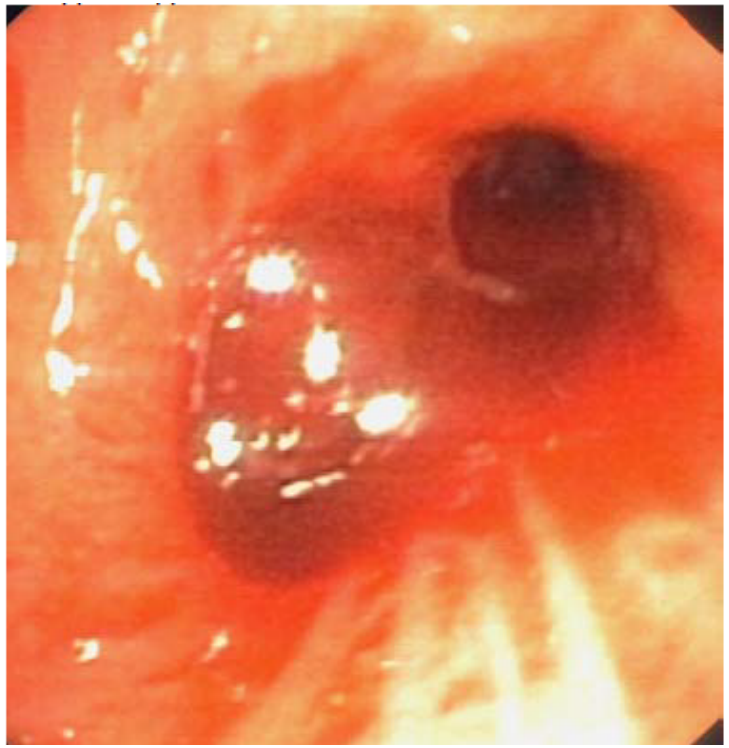
Figure 54-2 "Typical" carcinoid tumor: "iceberg-like" endobronchial mass. **A** and **B,** Axial chest CT displayed in lung windows in a 32-year-old woman with recurrent pneumonia shows complete obstruction of the left lower lobe bronchus (**B,** *arrow*), with a small portion of tumor protruding into the left mainstem bronchus (**A,** *arrowhead*), in a manner analogous to the small portion of an iceberg that protrudes above the ocean water. Left lower lobe postobstructive air trapping (**B,** *arrowhead*) is present, which confirms an airway origin for the lesion. **C,** Bronchoscopic image shows the left lower lobe lesion protruding into the left mainstem bronchus.

Aspects endoscopiques

- Risque de saignement: 0,3% décès
- S'y préparer: épinéphrine

- Rôle de la bronchoscopie rigide et du laser?

- Thoracotomie d'emblée?



Diagnostic histo-pathologique sur petites biopsies?

- Diagnostic de carcinoïde: 70% des cas

- Risque d'erreur diagnostique: 10% des cas
  - Carcinome à petites cellules
  - Carcinome épidermoïde

- Différentiation entre carcinoïde typique et atypique: 40% des cas

Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids

M. E. Caplin[1*], E. Baudin[2], P. Ferolla[3], P. Filosso[4], M. Garcia-Yuste[5], E. Lim[6], K. Oberg[7], G. Pelosi[8], A. Perren[9], R. E. Rossi[1,10] & W. D. Travis[11] the ENETS consensus conference participants[†]

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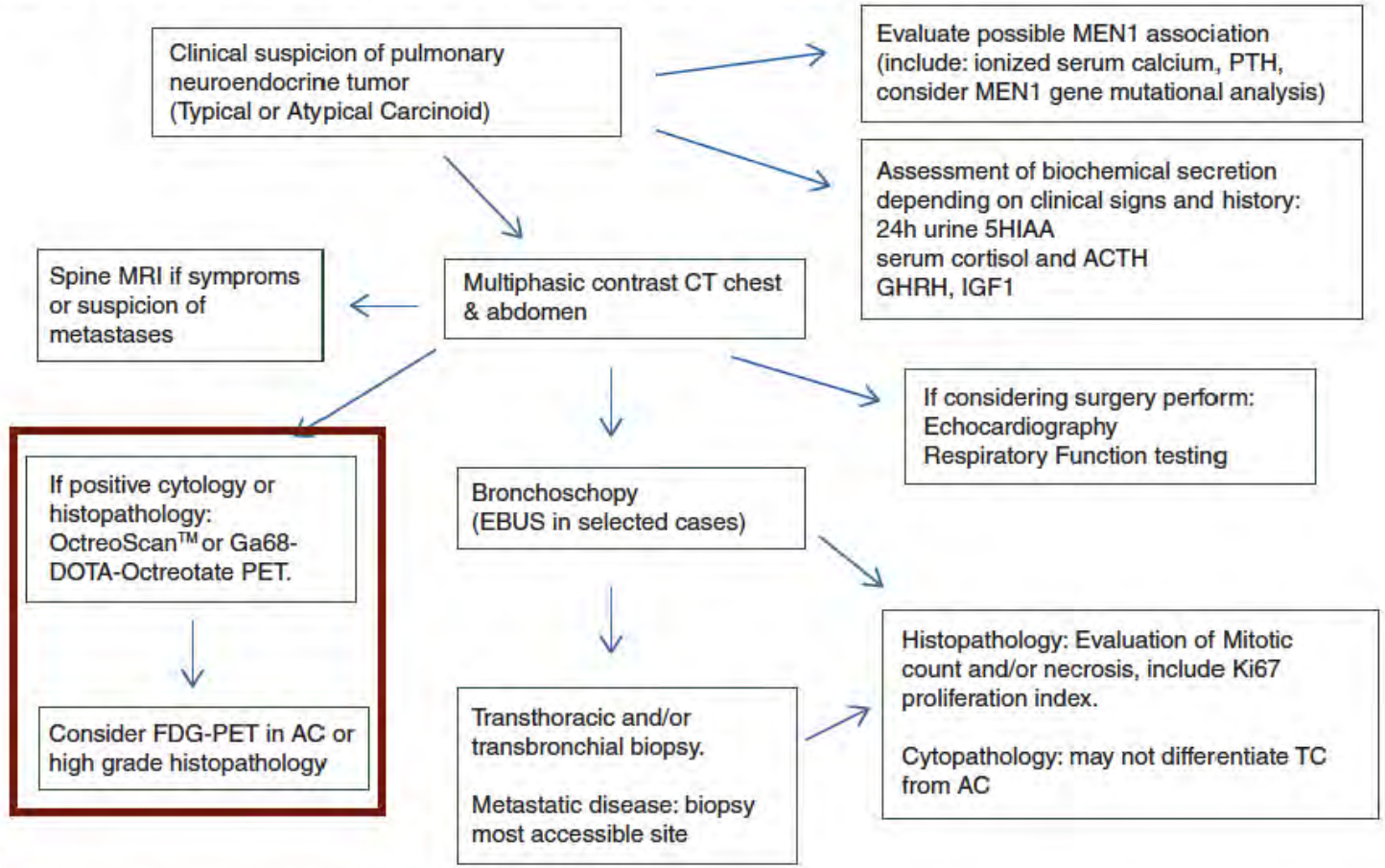


Figure 1. Algorithm for diagnosis of pulmonary neuroendocrine tumor.

Evaluation scintigraphique

- **OCTREOSCAN: Indium 111–DTPA–pentetreotide**

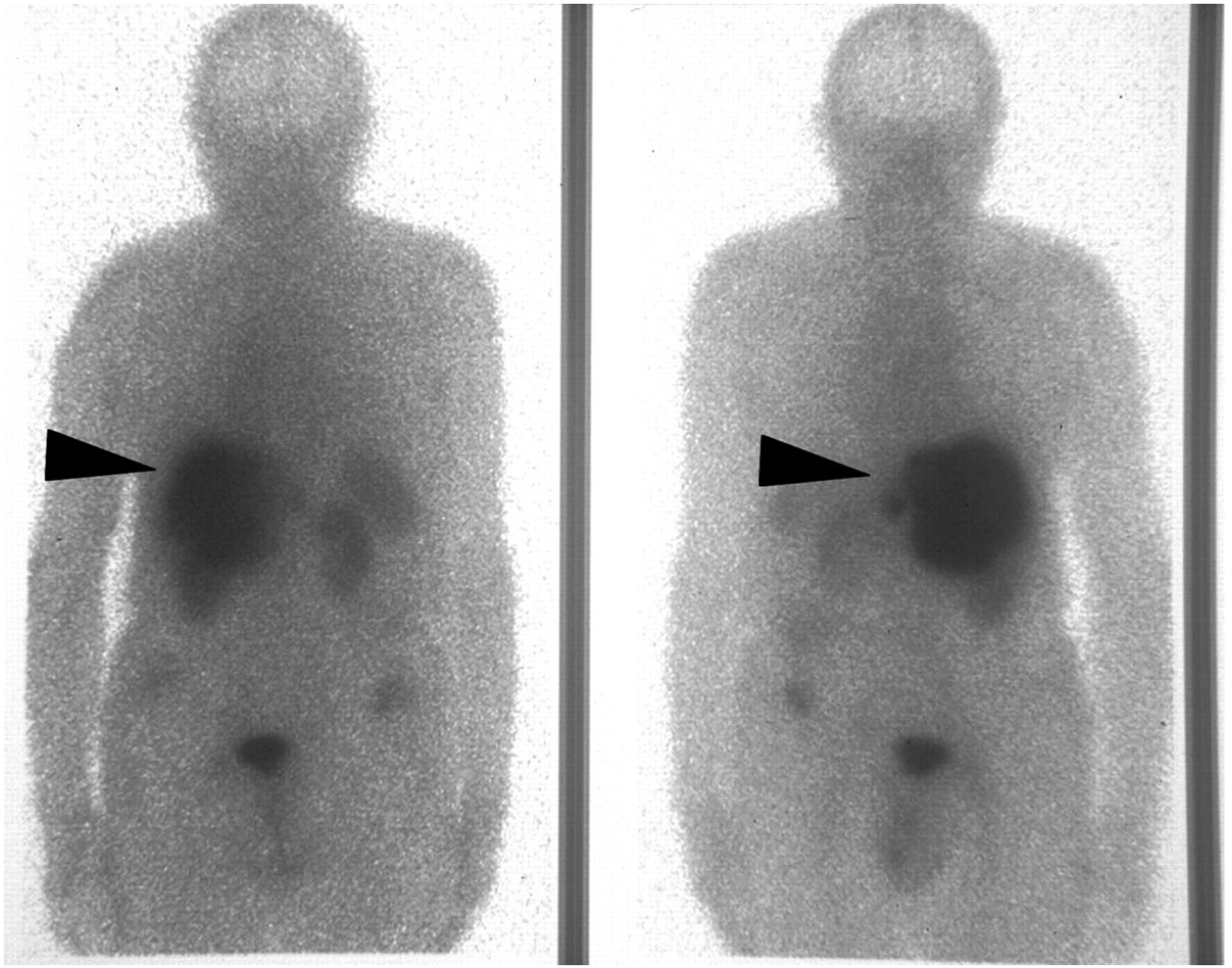
  - Caméra 2 dimensions

  - Sensibilité 80-90%
  - Spécificité faible

  - Seuil de détection 15mm

  - Prédiction de l'efficacité des analogues de la somatostatine?

  - Prédiction de l'efficacité de la radiothérapie métabolique



Evaluation scintigraphique

- **18-FDG PET**

  - Caméra 3 dimensions

  - Seuil de détection 8 mm

Carcinoïdes typiques: faux négatifs = sensibilité faible

Functional Imaging Evaluation in the Detection, Diagnosis, ar Histologic Differentiati Pulmonary Neuroendocr Tumors

Filippo Lococo, MD[a,*], Giorgio Treglia, MD[b], Alfredo Cesario, MD[c], Massimiliano Paci, MD[a], Angelina Filice, MD[d], Annibale Versari, MD[d], Pier Luigi Filosso, MD[e]

Table 1
Literature overview: ^{18}F FDG-PET scan in the evaluation of pulmonary carcinoids

Author, Year	Number of Subjects	Histology	Detection Rate (%)
Wartski et al,[11] 2004	2	1 TC, 1 AC	100
Kruger et al,[12] 2006	15	12 TCs, 1 AC	54
Daniels et al,[13] 2007	16	11 TCs, 5 ATs	75
Chong et al,[9] 2007	7	2TCs, 5 ACs	86
Kayani et al,[14] 2009	13	11 TCs, 2 ACs	69
Jindal et al,[15] 2011	20	13 TCs, 7 ACs	70
Stefani et al,[16] 2013	25	24 TCs, 1 AC	48 (positive result if SUVmax >2.5) 96 (positive result if SUVmax >1.5)

Thorac Surg Clin 2014;24:285

AUDIT, RESEARCH AND GUIDELINE UPDATE

Test performance of PET-CT for mediastinal lymph node staging of pulmonary carcinoid tumours

Holly A Pattenden,[1] Maria Leung,[1] Emma Beddow,[1] Michael Dusmet,[1] Andrew G Nicholson,[1,2] Michael Shackcloth,[3] Saifullah Mohamed,[4] Adnan Darr,[4] Babu Naidu,[4] Swetha Iyer,[5] Adrian Marchbank,[5] Amy Greenwood,[6] Doug West,[6] Felice Granato,[7] Alan Kirk,[7] Priyadharshanan Ariyaratnam,[8] Mahmoud Loubani,[8] Eric Lim,[1,2] on behalf of the UK Thoracic Surgery Collaborative

For our primary outcome, the calculated sensitivity and specificity of ^{18}FDG PET-CT to identify mediastinal (N2) lymph node disease were 33% (95% CI 4% to 78%) and 94% (89% to 97%), respectively.

Table 1 Baseline characteristics

Sample size (n)	247
Mean age, years (SD)	61 (15)
Males, n (%)	84 (34)
Mean tumour max size, mm (SD)	26 (15)
Stage, n (%)	
IA	129 (56)
IB	50 (22)
IIA	24 (10)
IIB	11 (5)
IIIA	16 (7)
IIIB or IV	0
Histology, n (%)	
Typical carcinoid	217 (88)
Atypical carcinoid	30 (12)
Mean FDG PET-CT SUV max (SD)	
Typical carcinoid	4.6 (3.8)
Atypical carcinoid	6.1 (4.4)
Surgical procedure, n (%)	
No resection	2 (1)
Wedge resection	19 (8)
Segmentectomy	5 (2)
Lobectomy	208 (84)
Pneumonectomy	13 (5)
Contingency table results, n	
PET-CT positive/pathology positive	2
PET-CT positive/pathology negative	13
PET-CT negative/pathology positive	4
PET-CT negative/pathology negative	188

Thorax 2015;70:379

Evaluation scintigraphique

- **68Ga-DOTA-peptides PET**

  - Caméra 3 dimensions

  - Seuil de détection 8 mm

  - Traceur spécifique des récepteurs SSRTs (2, 3, 5)

  - Indépendant du métabolisme cellulaire

  - Sensibilité et spécificité optimales

  - En cours de déploiement en France

Functional Imaging Evaluation in the Detection, Diagnosis, Histologic Differentia Pulmonary Neuroend Tumors

Filippo Lococo, MD[a,*], Giorgio Treglia, MD[b], Alfredo Cesario, MD[c], Massimiliano Paci, MD[a], Angelina Filice, MD[d], Annibale Versari, MD[d], Pier Luigi Filosso, MD[e]

Table 2
Literature overview: ^{68}Ga DOTA-peptides PET scan in the evaluation of pulmonary carcinoids

Author, Year	Number of Subjects	Histology	Detection Rate (%)
Hofman et al,[25] 2001	2[a]	N/A	100
Koukouraki et al,[26] 2006	2[a]	N/A	100[b]
Kumar et al,[27] 2009	3	3 TCs	100
Ambrosini et al,[28] 2009	11	N/A	82
Kayani et al,[14] 2009	13[c]	11 TCs 2 ACs	100
Jindal et al,[15] 2011	20	13 TCs 7 ACs	95
Venkitaraman et al,[29] 2014	26	21 TCs 5 AC	96

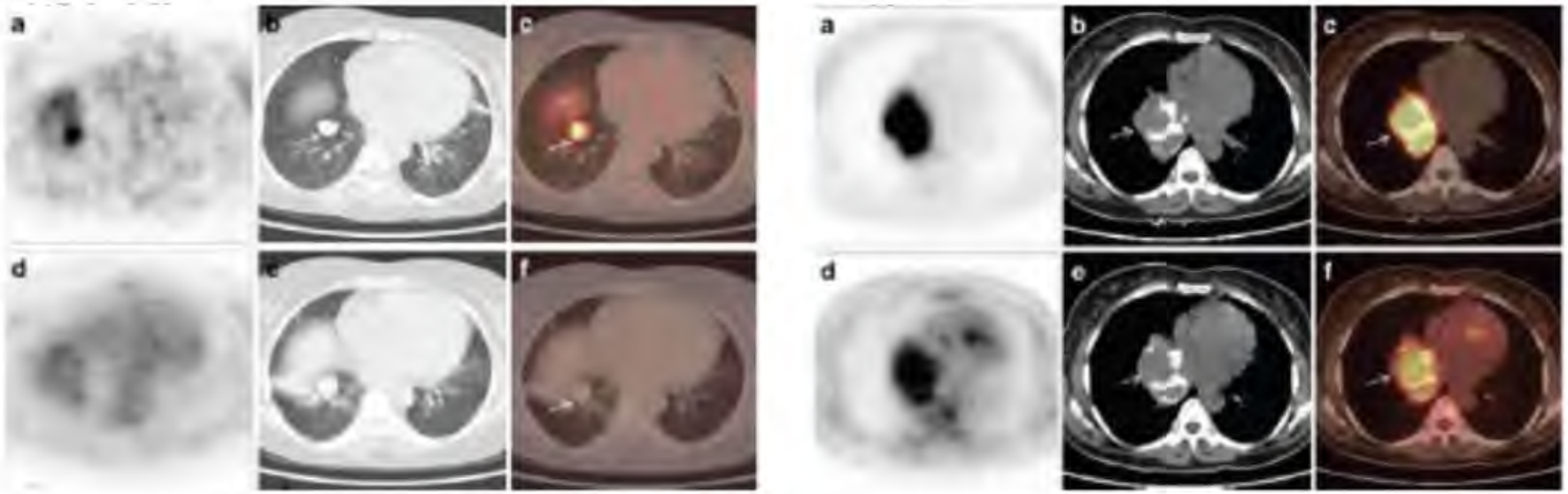
Thorac Surg Clin 2014;24:285

Eur J Nucl Med Mol Imaging (2014) 41:856–864
DOI 10.1007/s00259-013-2659-5

ORIGINAL ARTICLE

Role of ^{68}Ga-DOTATOC PET/CT in initial evaluation of patients with suspected bronchopulmonary carcinoid

Balasubramanian Venkitaraman · Sellam Karunanithi · Arvind Kumar · G. C. Khil



Histology	Range of tumour size (long axis, cm)	Range of SUV_{max} on ^{18}F-FDG PET/CT	Range of SUV_{max} on ^{68}Ga-DOTATOC PET/CT
Typical carcinoid (21)	1–7	0.74–12.80 (mean 2.88)	3.58–55 (mean 21.50)
Atypical carcinoid (5)	1.8–7	2.4–8.45 (mean 4.37)	1.1–32.5 (mean 15.43)

Modern Pathology (2007) 20, 1172–1182

www.modernpathology.org

Somatostatin receptor type 2A immunohistochemistry in neuroendocrine tumors: a proposal of scoring system correlated with somatostatin receptor scintigraphy

Marco Volante[1], Maria Pia Brizzi[1], Antongiulio Faggiano[2], Stefano La Rosa[3], Ida Rapa[1], Anna Ferrero[1], Gelsomina Mansueto[4], Luisella Righi[1], Silvana Garancini[5], Carlo Capella[3]

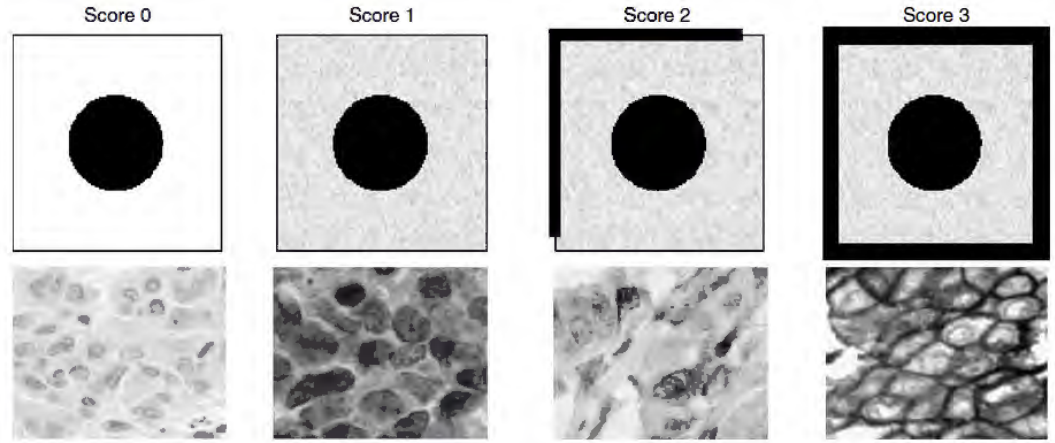


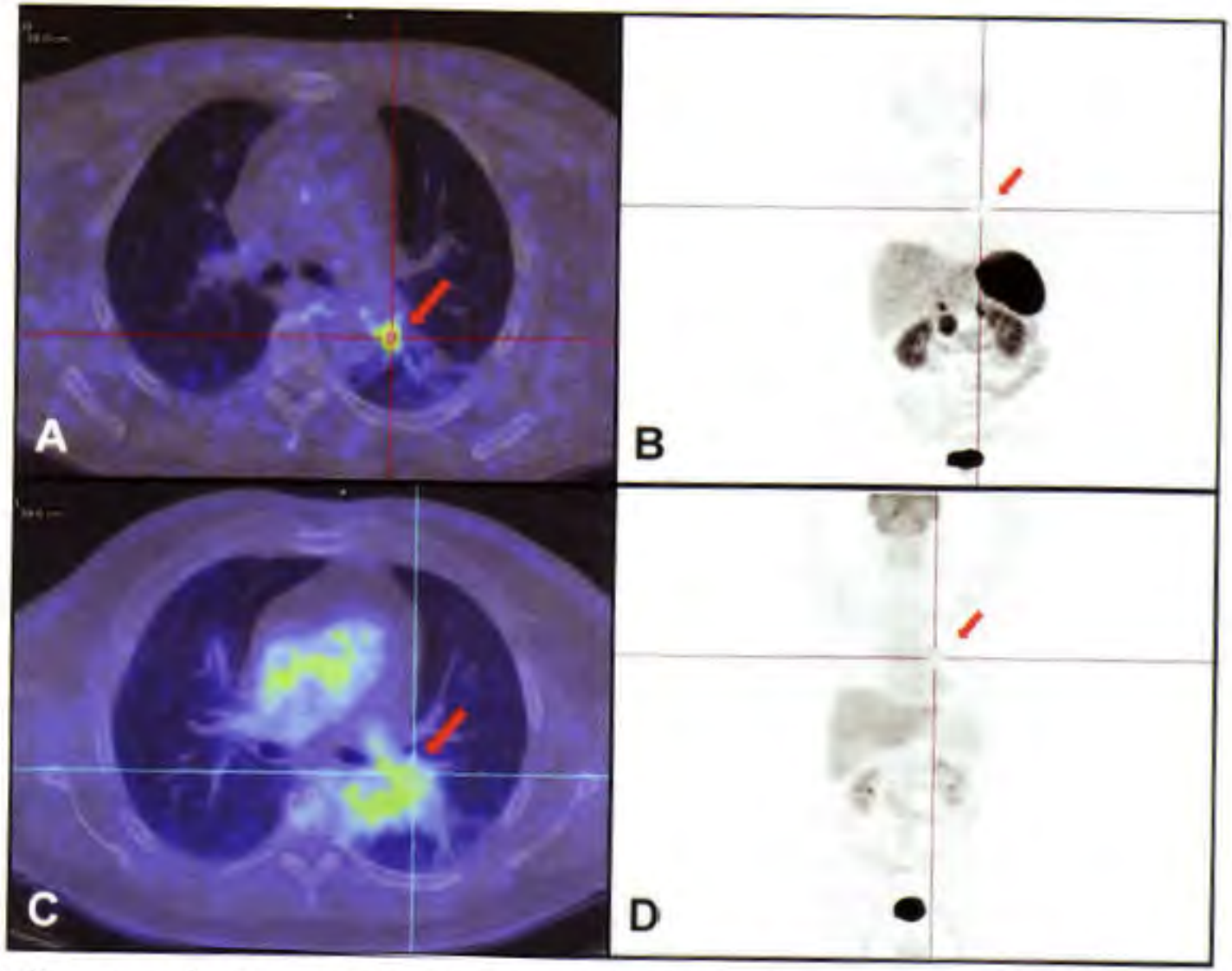
Table 1 Somatostatin receptors expression in 107 neuroendocrine tumors

	Somatostatin receptor type 2A (scores 2 and 3)	*Somatostatin receptor type 3*	*Somatostatin receptor type 5*
WD NET/NEC (70 cases)	79%	44%	71%
PD NEC (18 cases)	44%	17%	28%
Others (19 cases)	21%	53%	74%

18-FDG PET vs. 68Ga-DOTA PET

68Ga-DOTA PET

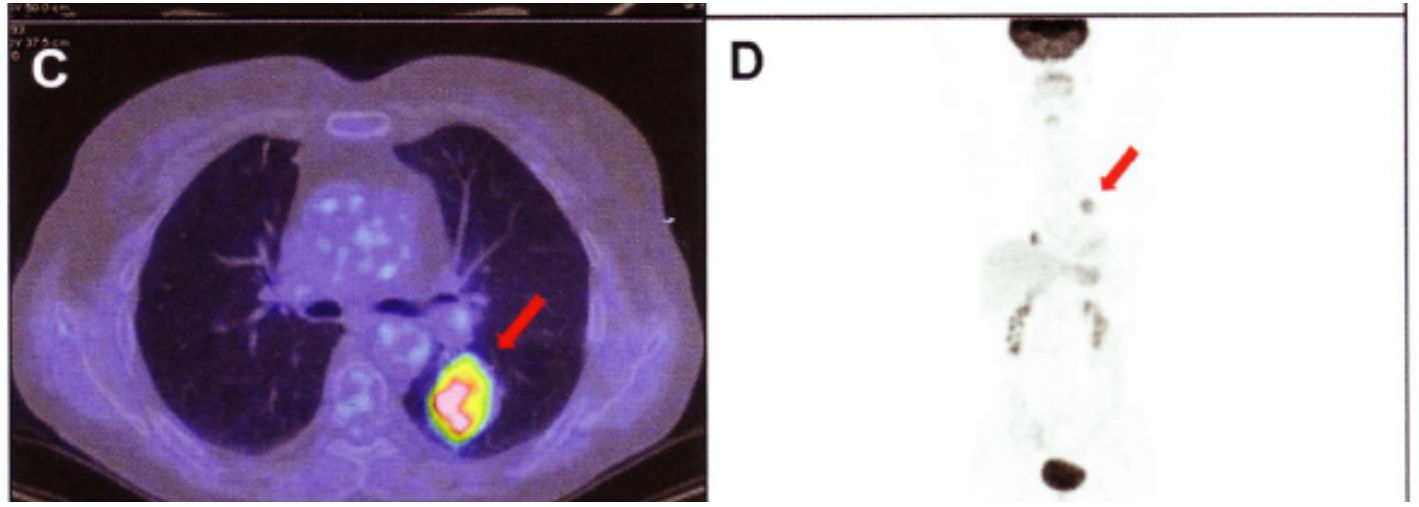
18-FDG PET



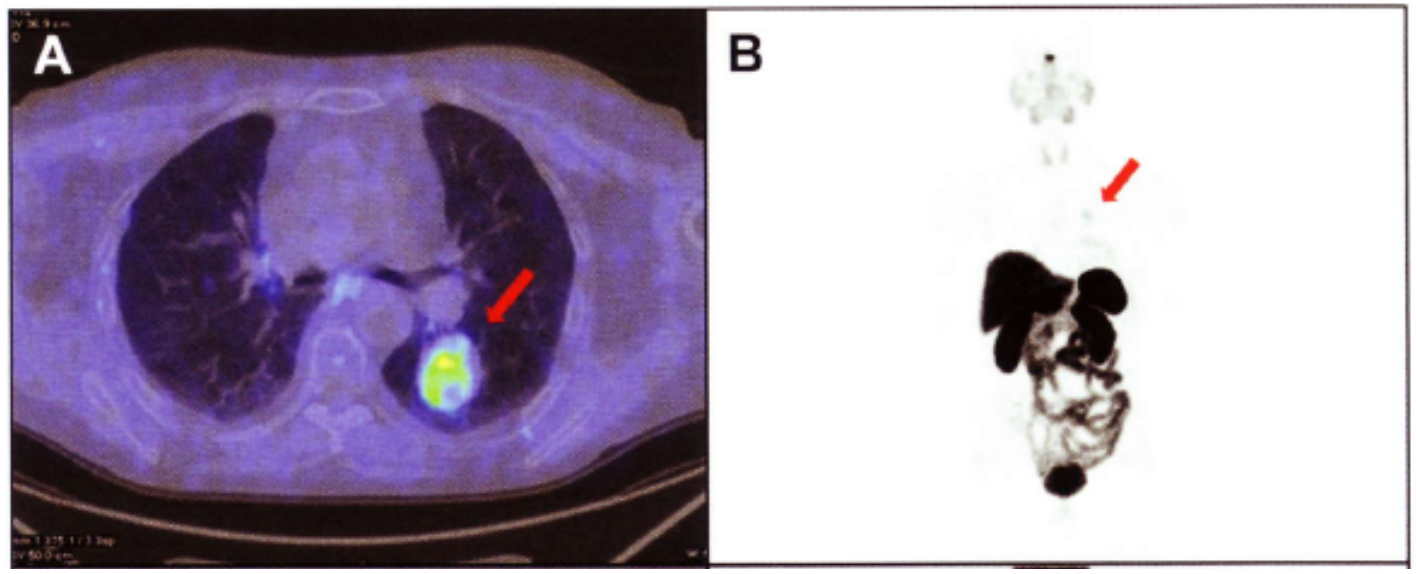
. 1. Metabolic pattern for TC, in CT (*A*, *C*) and in PET scans (*B*, *D*). Increased uptake of radiolabeled somatotin analogues (*A*, *B*) and low or absent uptake of ^{18}F FDG (*C*, *D*). *Red arrows* indicate the lesion. (*Courtesy*

18-FDG PET vs. 68Ga-DOTA PET

68Ga-DOTA PET



18-FDG PET



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Surgery, University of Torino, Torino, Italy; [5]Depart

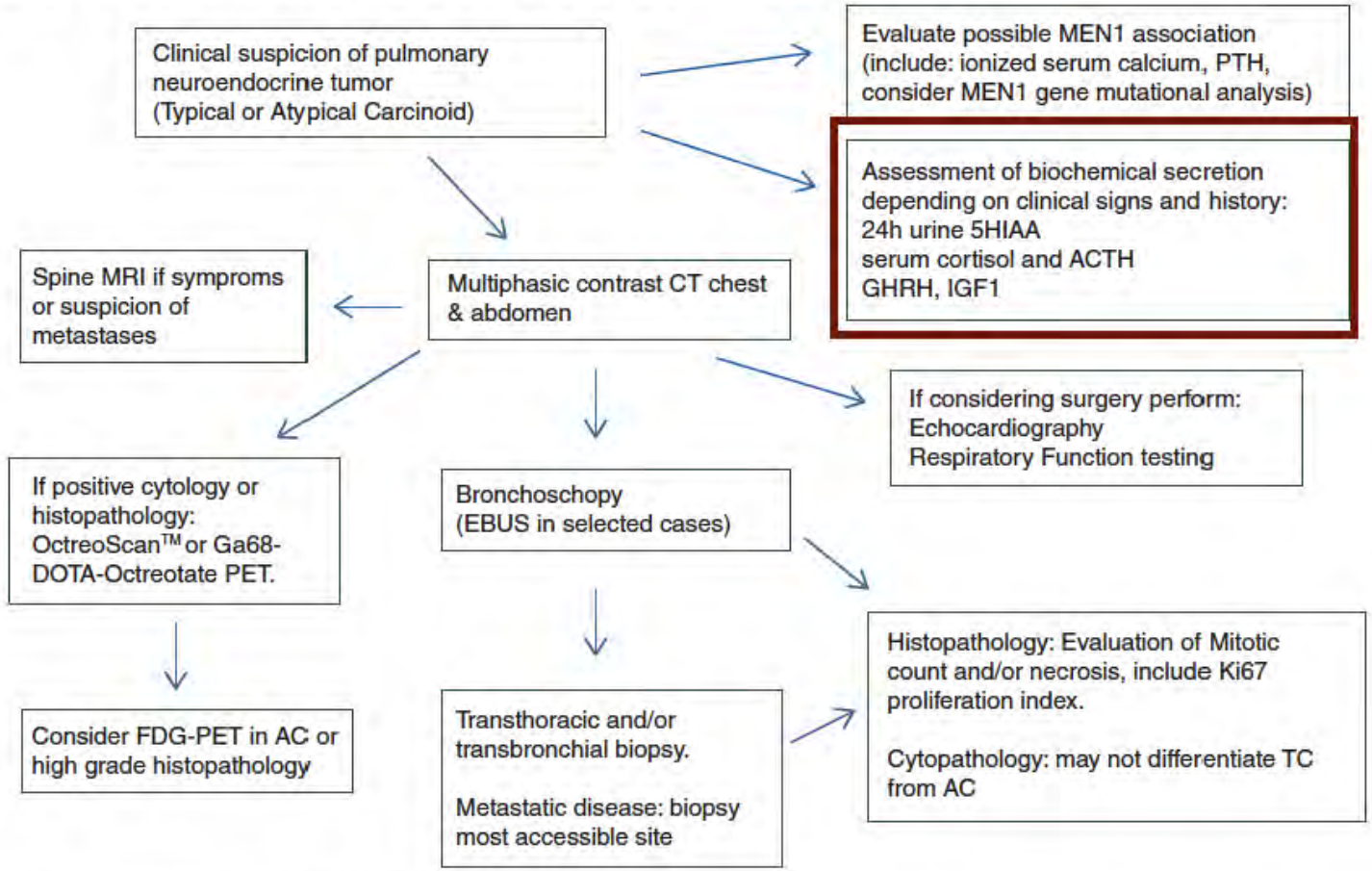
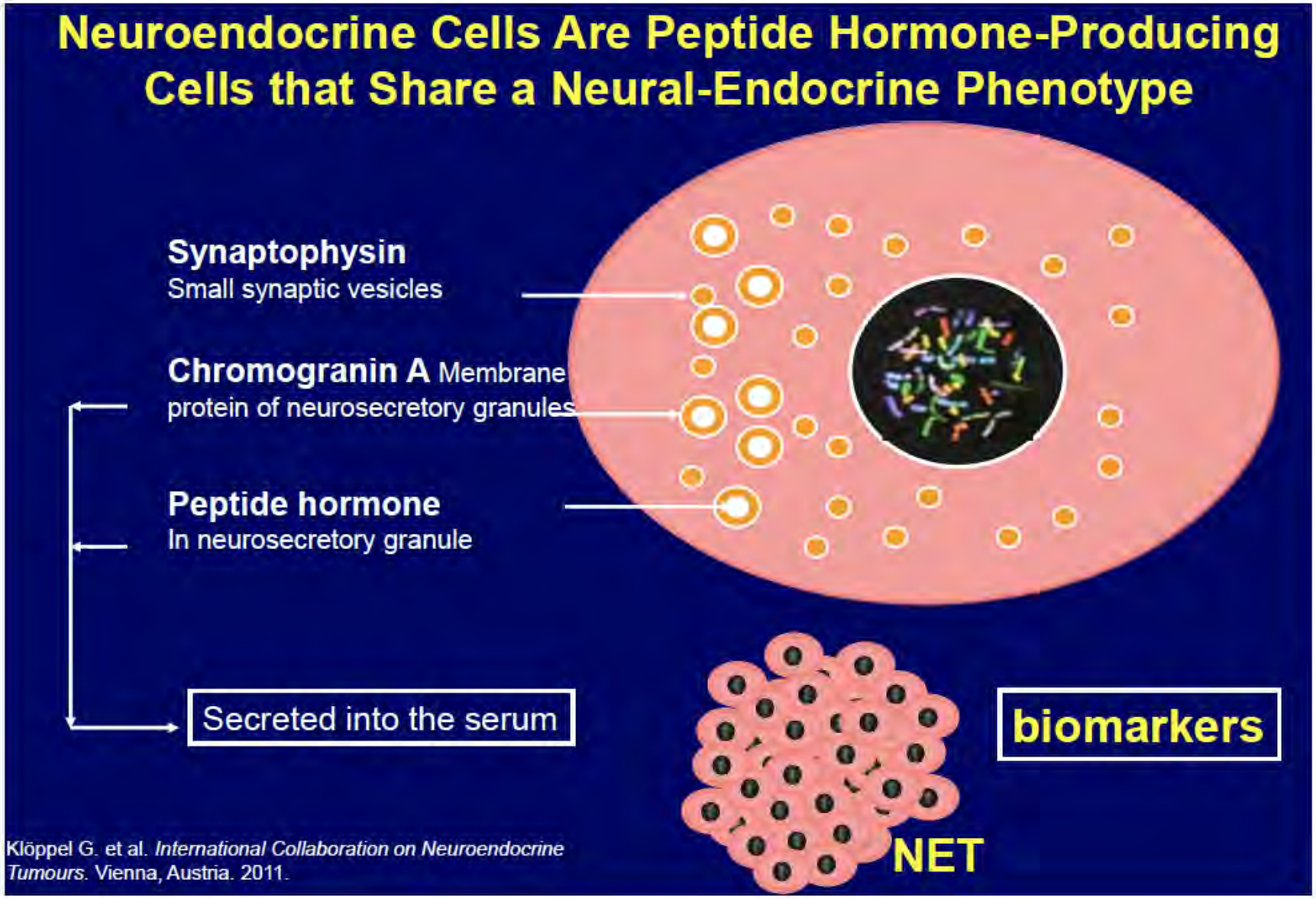


Figure 1. Algorithm for diagnosis of pulmonary neuroendocrine tumor.

Bilan biologique

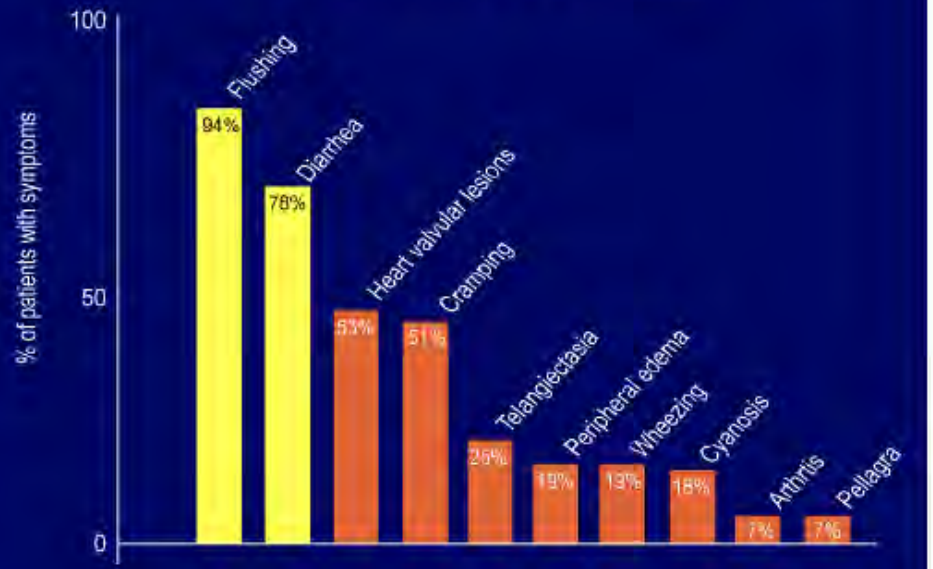


Bilan biologique

Carcinoid Syndrome

- Occurs in approximately 8% to 35% of patients with NETs and occurs mostly in cases of patients with hepatic metastases[1]
- Consequence of vasoactive peptides such as serotonin, histamine, or tachykinins released into the circulation[2,3]
- Manifested by episodic flushing, wheezing, diarrhea, and, potentially, the eventual development of carcinoid heart disease[2,3]

Percentage of patients with symptoms of carcinoid syndrome[4]



1. Rorstad O. *J Surg Oncol*. 2005; 89:151-60.
2. Modlin IM, Kidd M, Latich I, Zikusoka MN, Shapiro MD. *Gastroenterology*. 2005;128:1717-1751.
3. Vinik A, Moattari AR. *Dig Dis Sci*. 1989;34(3 Suppl):14S-27S.
4. Creutzfeldt W. *World J Surg*. 1996;20:126-131.

Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids

M. E. Caplin[1*], E. Baudin[2], P. Ferolla[3], P. Filosso[4], M. Garcia-Yuste[5], E. Lim[6], K. Oberg[7], G. Pelosi[8], A. Perren[9], R. E. Rossi[1,10] & W. D. Travis[11] the ENETS consensus conference participants[†]

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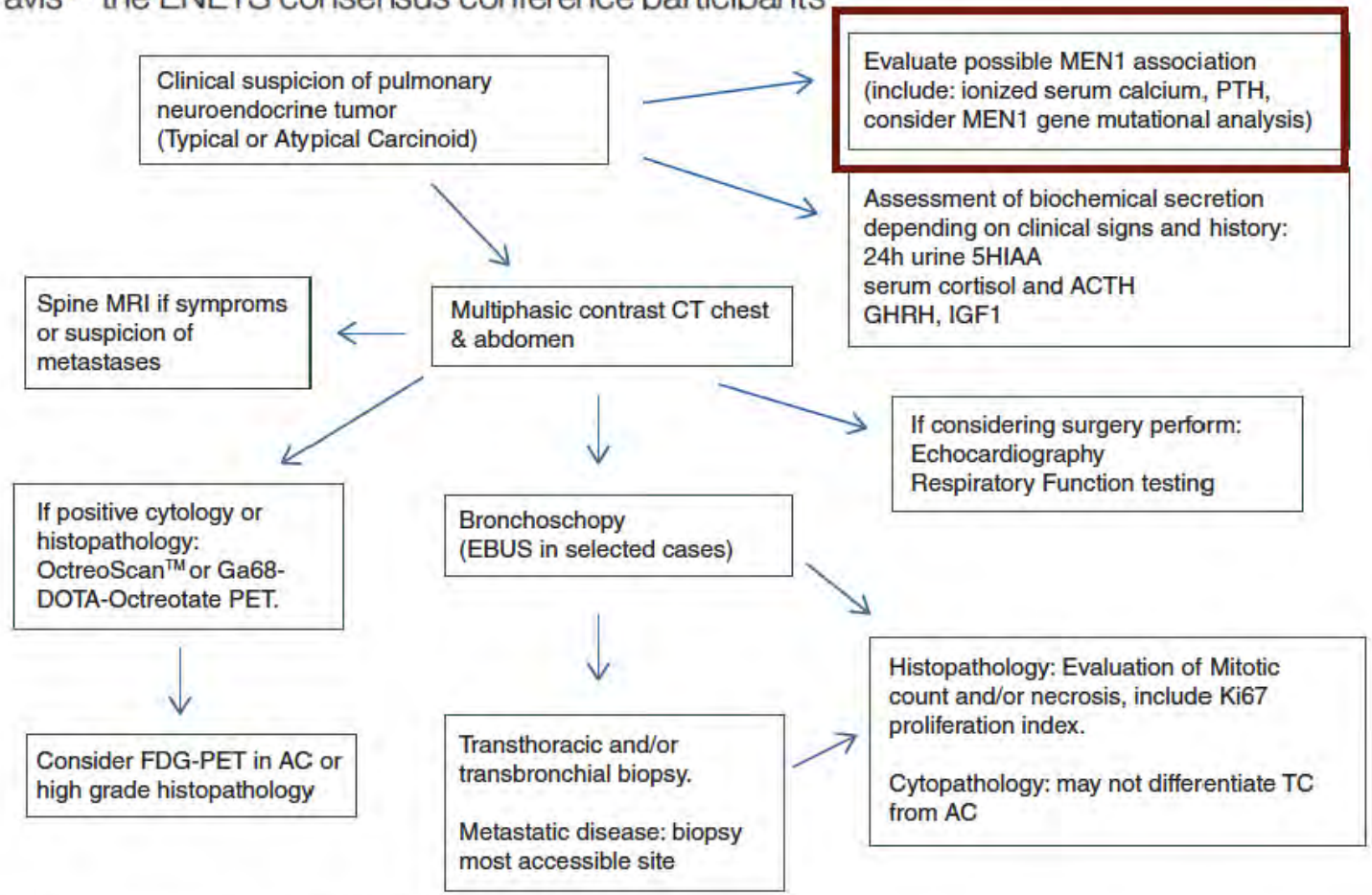

Figure 1. Algorithm for diagnosis of pulmonary neuroendocrine tumor.

Ne pas oublier la consultation d'oncogénétique

Dépistage Génétique **Cas Index :**

Diagnostic d'une TNE Héréditaire

↓

Dépistage Familial

↙ Apparentés Sains à Ecarter de la Surveillance

↓

Apparentés Génétiquement à Risque

↓

Bilan Lésionnel : Dépistage des Lésions du Syndrome

↙ Protocole de Surveillance Biologique et Morphologique

↓ Traitement Précoce des Lésions Détectées

Thyroidectomie Prophylactique des NEM2 : Reco INCa 2009

Conseil Génétique, Diagnostic Pré natal

Rapport INCa 2006

Les carcinoïdes broncho-pulmonaires

Les tumeurs carcinoïdes

Anatomie pathologique

Stadification

Evaluation pré-thérapeutique

Traitement des tumeurs localisées

Traitement initial des carcinoïdes de stade T1-4 N0-2 M0

- **Principes de la chirurgie thoracique**

Traitement initial des carcinoïdes de stade T1-4 N0-2 M0

- **Principes de la chirurgie thoracique**

- Carcinoïdes typiques:

- tumeur centrale: résection anastomose
- tumeur périphérique: lobectomie, segmentectomie, pneumonectomie
- curage ganglionnaire systématique

Interactive CardioVascular and Thoracic Surgery 17 (2013) 291–295
doi:10.1093/icvts/ivt154 Advance Access publication 28 April 2013

Pure bronchoplastic resections of the bronchus without pulmonary resection for endobronchial carcinoid tumours†

Kai Nowak[a,b,*], Wolfram Karenovics[a,c], Andrew G. Nicholson[d,e], Simon Jordan[a] and Michael Dusmet[a]

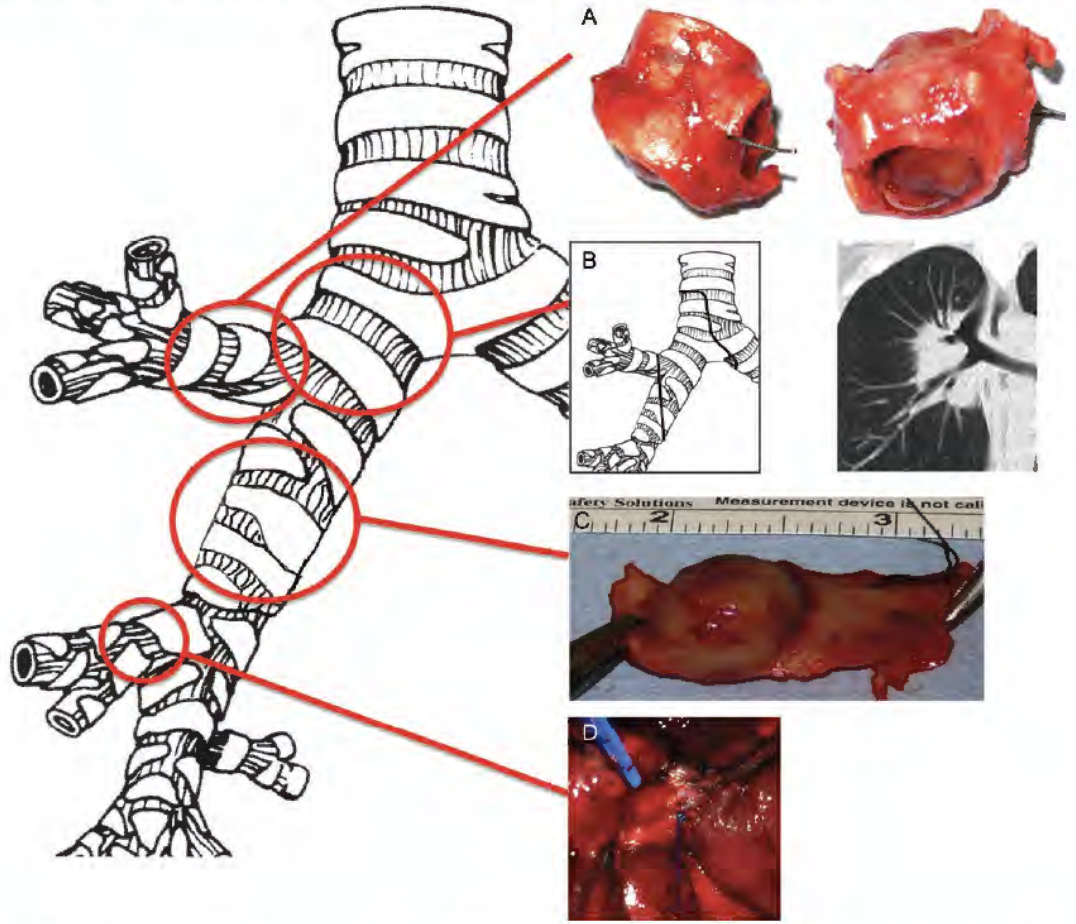

Figure 1: Right-sided parenchyma-sparing bronchial sleeve resection types for endobronchial carcinoids. (**A**) Upper lobe division bronchial sleeve resection. (**B**) Central carinal and right main bronchial sleeve. (**C**) Bronchus intermedius sleeve resection. (**D**) Sleeve resection of the middle lobe bronchus.

Traitement initial des carcinoïdes de stade T1-4 N0-2 M0

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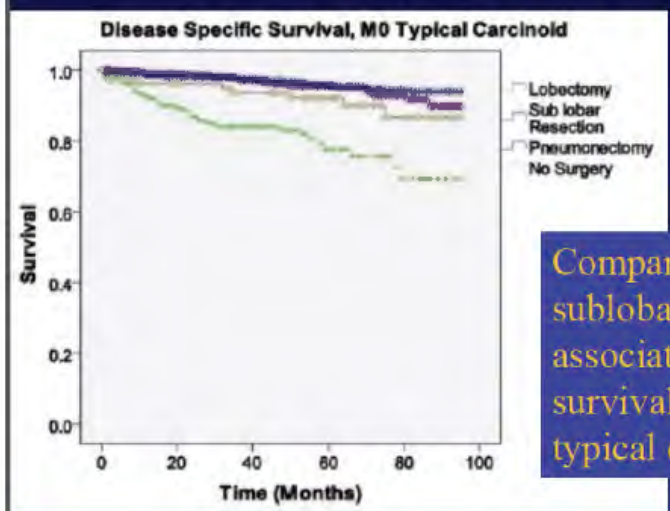
Interactive CardioVascular and Thoracic Surgery 16 (2013) 858-864
doi:10.1093/icvts/ivt067 Advance Access publication 6 March 2013

Is sublobar resection equivalent to lobectomy for surgical management of peripheral carcinoid?

Jonathan Afoke, Carol Tan, Ian Hunt and Mustafa Zakkar*

tabulated. A literature search showed that there is a good prognosis after resection of lung carcinoid with the 10-year disease-free survival rate ranging between 77 and 94%, and suggested that sub-lobar resection of a typical carcinoid did not compromise the long-term survival. The proportion of peripheral tumours ranged between 22.6 and 100% and the proportion of patients with a preoperative diagnosis of carcinoid ranged between 51.9 and 86.7%, with many series not providing either or both of these data. As a result, a lobectomy or greater resection was necessary on anatomical or diagnostic grounds and led to a low number of sub-lobar resections. Owing

Limited resection



Compared with lobectomy, sublobar resection is associated with noninferior survival in patients with typical carcinoid of the lung.

Fox M, et al. Am J Surg 2013;205:200-8

Traitement initial des carcinoïdes de stade T1-4 N0-2 M0

- **Principes de la chirurgie thoracique**

- Carcinoïdes typiques:

- tumeur centrale: résection anastomose
- tumeur périphérique: lobectomie, segmentectomie, pneumonectomie
- curage ganglionnaire systématique

- Carcinoïdes atypiques:

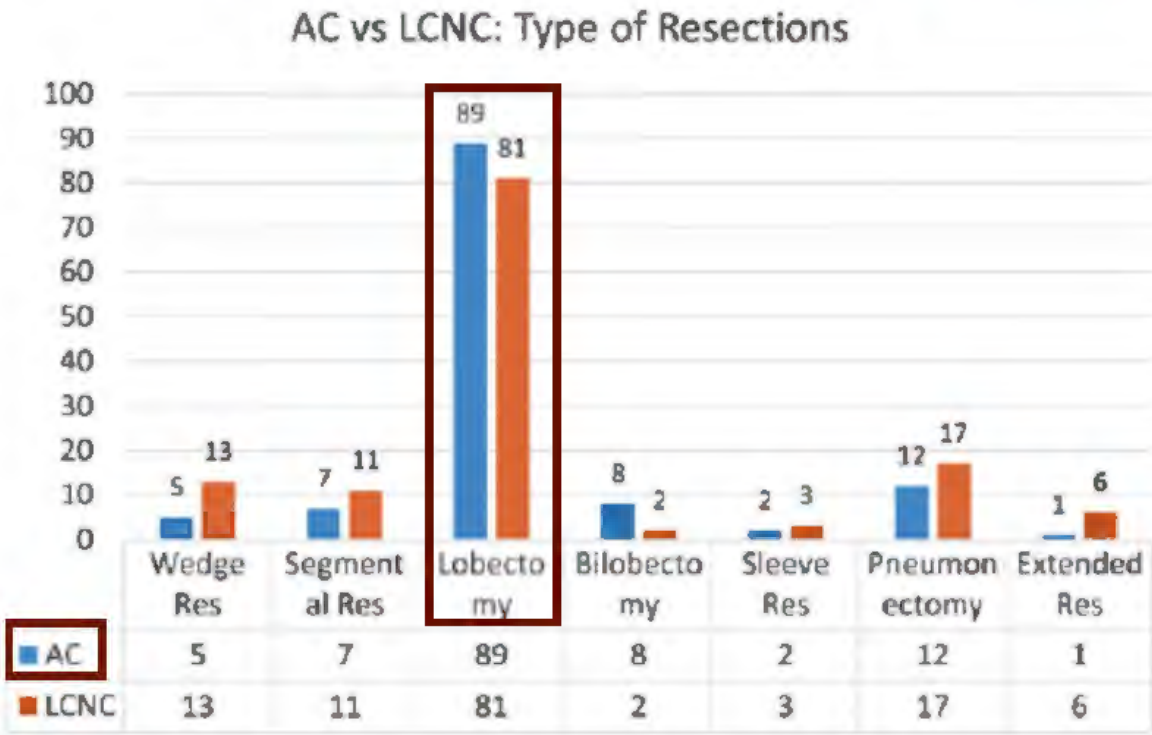
- tumeur centrale: résection anastomose?, lobectomie, pneumonectomie
- tumeur périphérique: lobectomie, segmentectomie, pneumonectomie
- curage ganglionnaire systématique

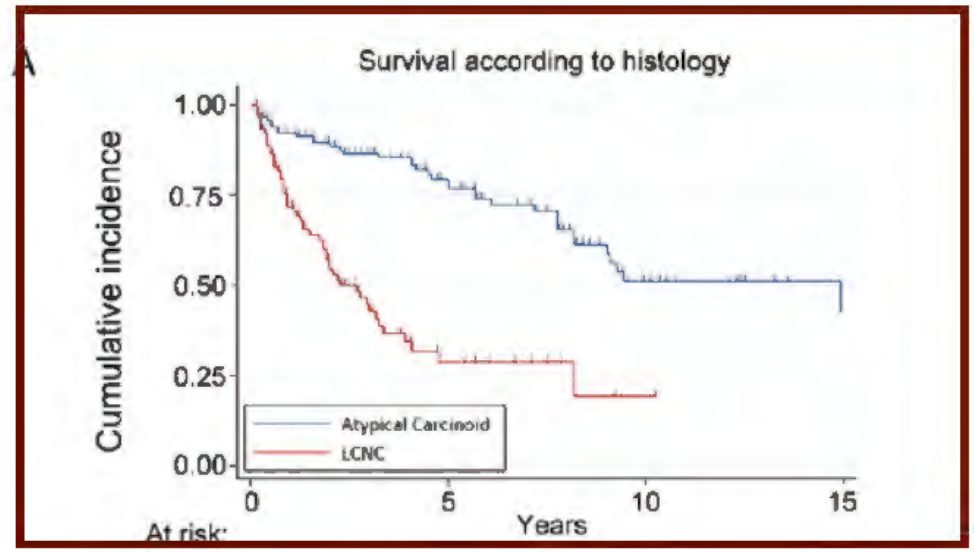
- Interprétation des sections congelées circonspecte

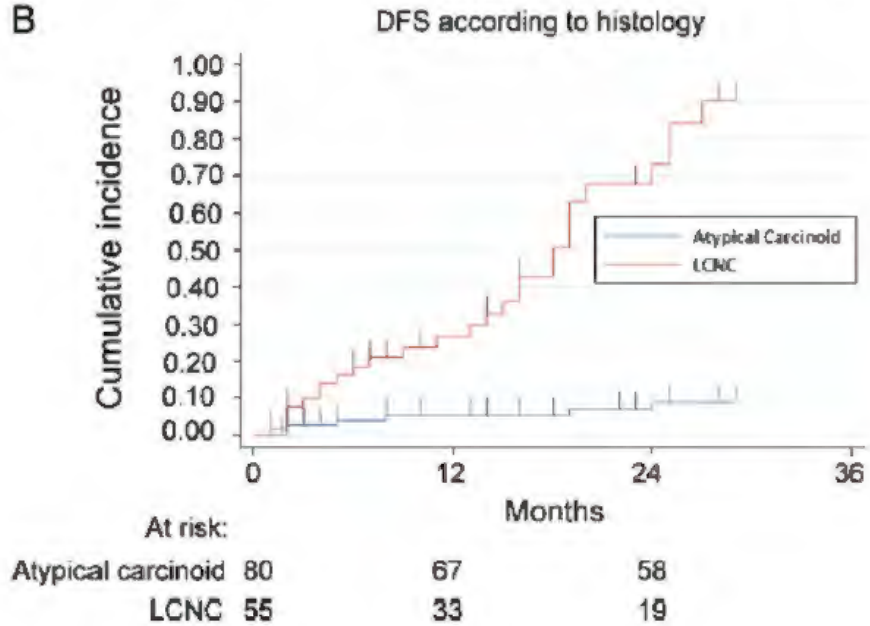
European Journal of Cardio-Thoracic Surgery (2014) 1–10
doi:10.1093/ejcts/ezu404

Clinical management of atypical carcinoid and large-cell neuroendocrine carcinoma: a multicentre study on behalf of the European Society of Thoracic Surgeons (ESTS) Neuroendocrine Tumours of the Lung Working Group†

Pier Luigi Filosso[a,*], Ottavio Rena[b], Francesco Guerrera[a], Paula Moreno Casado[c], Dariusz Sagan[d], Federico Raveglia[e], Alessandro Brunelli[f,†], Stefan Welter[g], Lucile Gust[h], Cecilia Pompili[f,†], Caterina Casadio[b], Giulia Bora[a], Antonio Alvarez[c], Wojciech Zaluska[i], Alessandro Baisi[e], Christian Roesel[g] and Pascal Alexandre Thomas[h], the ESTS NETs-WG Steering Committee



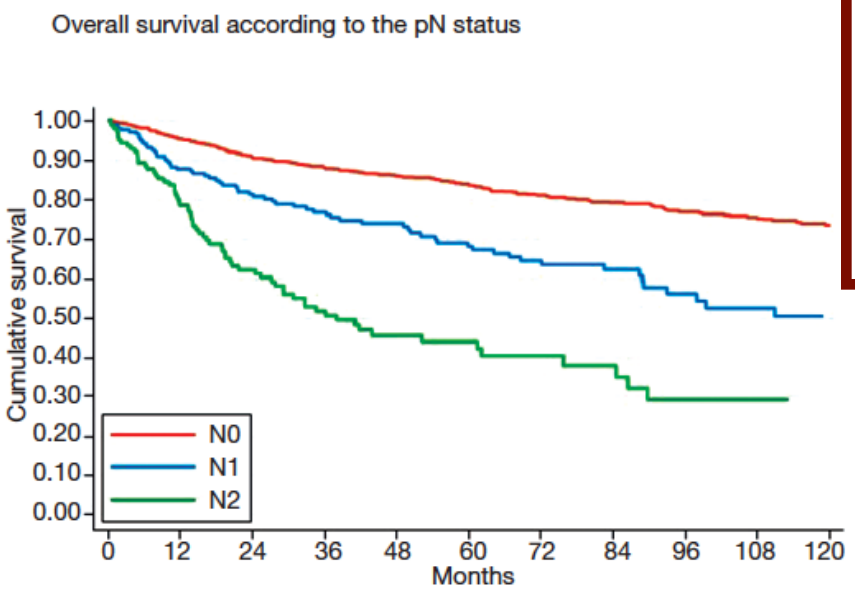


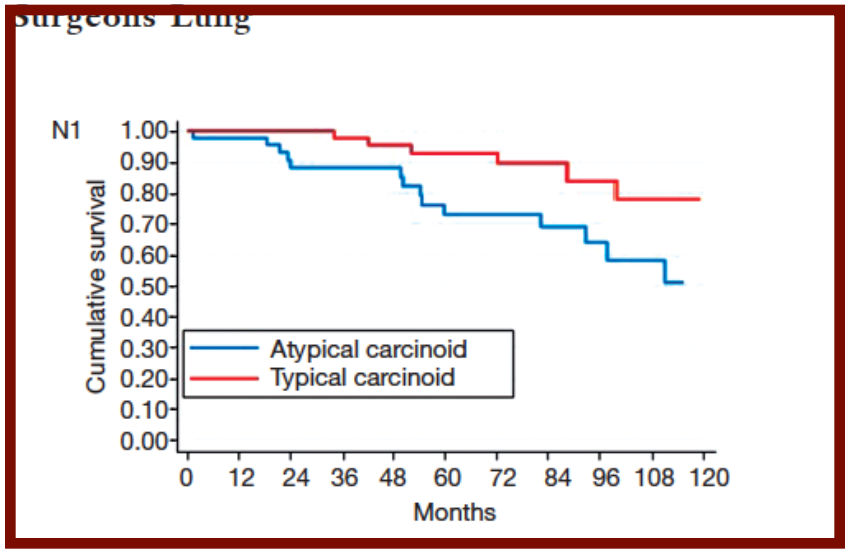


Multidisciplinary management of advanced lung neuroendocrine tumors

Pier Luigi Filosso[1], Piero Ferolla[2], Francesco Guerrera[1], Enrico Ruffini[1], William D. Travis[3], Giulio Rossi[4], Paolo Olivo Lausi[1], Alberto Oliaro[1]; the European Society of Thoracic Surgeons Lung Neuroendocrine Tumors Working-Group Steering Committee[5]

[1]Department of Thoracic Surgery, Uni
Tumors, Umbria Regional Cancer Ne
USA; [4]Unit of Pathology, Azienda Os
Neuroendocrine Tumors of the Lung V
Correspondence to: Pier Luigi Filosso, M
3 10126 Torino, Italy. Email: pierluigi.f





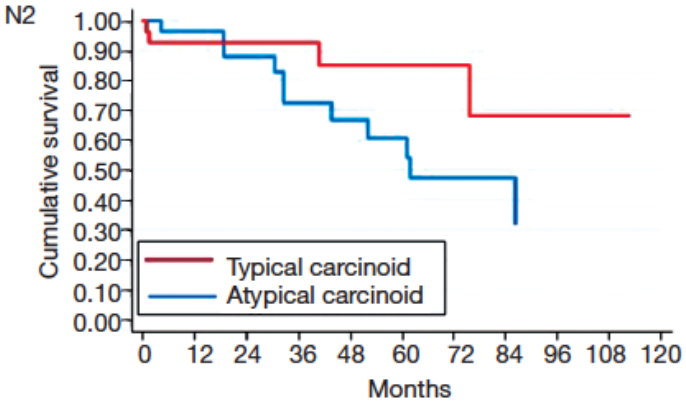


Figure 3 Bronchial carcinoids overall survival (OS) according to the lymph-nodal involvement.

European Journal of Cardio-Thoracic Surgery Advance Access published January 5, 2015

European Journal of Cardio-Thoracic Surgery (2015) 1–7
doi:10.1093/ejcts/ezu495

ORIGINAL ARTICLE

Cite this article as: Filosso PL, Guerrera F, Evangelista A, Welter S, Thomas P, Casado PM *et al*. Prognostic model of survival for typical bronchial carcinoid tumours: analysis of 1109 patients on behalf of the European Society of Thoracic Surgeons (ESTS) Neuroendocrine Tumours Working Group. Eur J Cardiothorac Surg 2015; doi:10.1093/ejcts/ezu495.

THORACIC

Prognostic model of survival for typical bronchial carcinoid tumours: analysis of 1109 patients on behalf of the European Society of Thoracic Surgeons (ESTS) Neuroendocrine Tumours Working Group†

Pier Luigi Filosso[a,*], Francesco Guerrera[a], Andrea Evangelista[b], Stefan Welter[c], Pascal Thomas[d], Paula Moreno Casado[e], Erino Angelo Rendina[f], Federico Venuta[f], Luca Ampollini[g], Alessandro Brunelli[h], Franco Stella[i], Mario Nosotti[j], Federico Raveglia[k], Valentina Larocca[l], Ottavio Rena[m], Stefano Margaritora[n], Francesco Ardissone[o], William D. Travis[p], Inderpal Sarkaria[q] and Dariusz Sagan[r], the ESTS

Table 3: Predictors of overall survival using Cox proportional hazard models ($n = 1109$)

	Age as continuous		Age as categorical			
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	Coefficient	Score
Age as continuous, (per 1 year increase)	1.07 (1.05–1.09)	<0.001	–	–	–	–
Age as categorical						
<55 (Ref.)	–	–	1	–	–	0
55–64	–	–	2.54 (1.15–5.59)	0.021	0.931	1
65–74	–	–	4.18 (1.99–8.79)	<0.001	1.431	2
≥75	–	–	10.36 (4.66–23.03)	<0.001	2.338	3
Male	2.18 (1.39–3.43)	0.001	2.2 (1.4–3.47)	0.001	0.790	1
Previous malignancy	1.88 (1.16–3.05)	0.010	1.95 (1.2–3.16)	0.007	0.669	1
Peripheral tumour	1.89 (0.78–4.59)	0.142	2.05 (0.88–4.81)	0.091	0.719	1
pTNM						
I (Ref.)	1	–	1	–	–	0
II	2.19 (1.13–4.21)	0.019	2.1 (1.09–4.04)	0.026	0.743	1
III	3.77 (1.56–9.13)	0.003	3.74 (1.55–9.02)	0.003	1.320	2
ECOG PS						
0	1	–	1	–	–	0
1–2	2.04 (1.1–3.76)	0.023	2.05 (1.11–3.8)	0.023	0.718	1
≥3	3.49 (0.32–38.7)	0.300	4.16 (0.34–50.87)	0.255	1.425	2
C-statistics						
Original sample	0.836		0.822			
Optimism-corrected	0.806		0.795			

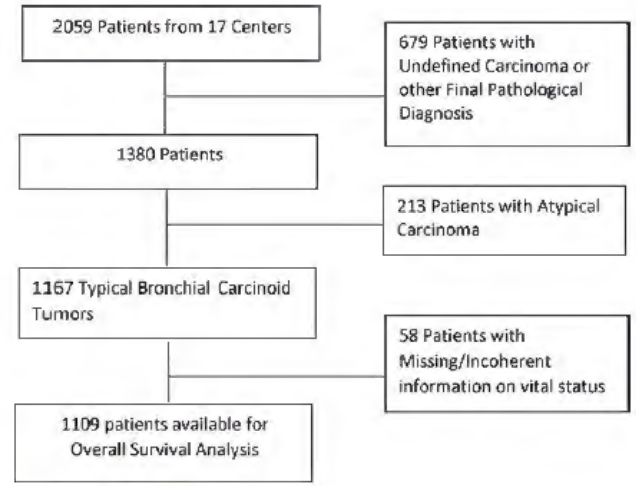


Figure 1: Study flow chart.

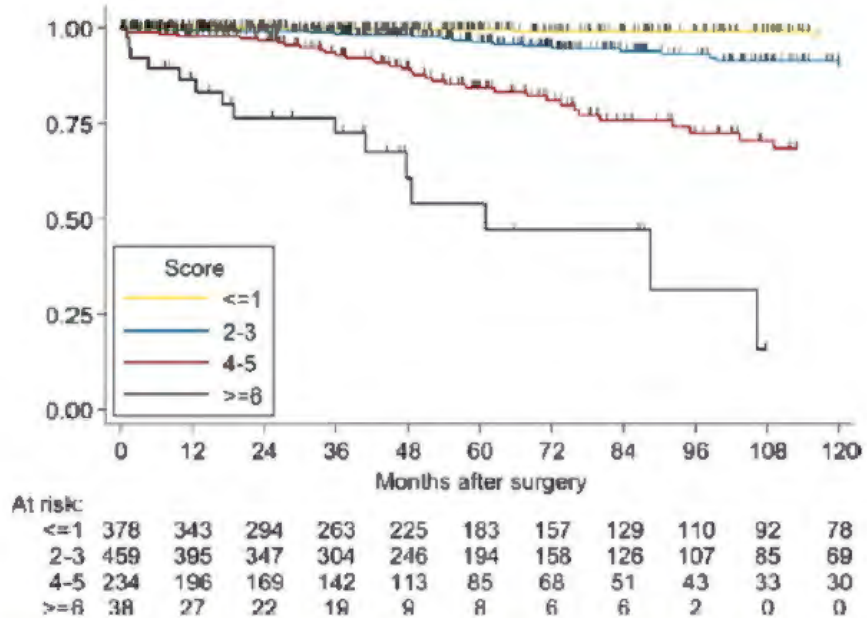


Figure 5: Overall survival Kaplan–Meier estimates by additive risk score. Data points represent censoring times.

Traitement adjuvant?
Carcinoïdes typiques

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016
Lung Neuroendocrine Tumors

NCCN Guidelines Index
SCLC Table of Contents
Discussion

Low-Grade Lung Neuroendocrine Carcinoma (Typical Carcinoid)

CLINICAL STAGE[e]	PRIMARY TREATMENT	SURVEILLANCE
Stage I-II	Surgery: Lobectomy or other anatomic resection[f] + mediastinal lymph node dissection or sampling	Follow-up every 6–12 mo post-treatment up to 10 y • H&P • Chest CT annually • Biochemical evaluation, as clinically indicated
Stage IIIA, Surgical candidate	Surgery: Lobectomy or other anatomic resection[f] + mediastinal lymph node dissection or sampling	
Stage IIIA, Not surgical candidate	Cisplatin/etoposide[g] + RT[h]	
Stage IIIB (except T4 due to multiple lung nodules)	Cisplatin/etoposide[g] + RT[h]	
Stage IIIB (T4 due to multiple lung nodules) or stage IV	Consider observation for asymptomatic, low-bulk disease or Systemic therapy[g]	

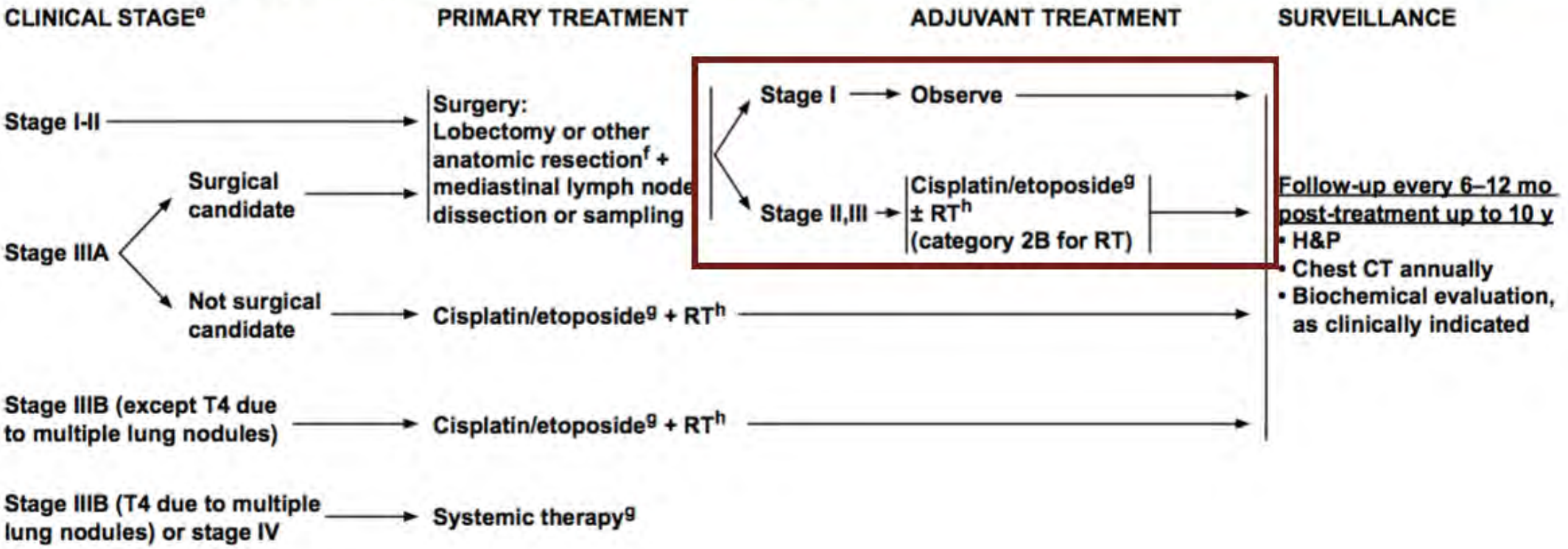
Traitement adjuvant?
Carcinoïdes atypiques

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016
Lung Neuroendocrine Tumors

NCCN Guidelines Index
SCLC Table of Contents
Discussion

Intermediate-Grade Lung Neuroendocrine Carcinoma (Atypical Carcinoid)



Les carcinoïdes broncho-pulmonaires

Les tumeurs carcinoïdes

Anatomie pathologique

Stadification

Evaluation pré-thérapeutique

Traitement des tumeurs localisées

Traitement initial des carcinoïdes de stade T1-4 N0-2 M0

- **Alternatives à la chirurgie thoracique**

- Carcinoïdes typiques:

- tumeur centrale: traitements endobronchiques
- tumeur périphérique: stéréotaxie, radiofréquence

- Carcinoïdes atypiques:

- radiothérapie, stéréotaxie, radiofréquence

Les carcinoïdes broncho-pulmonaires

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Evaluation pré-thérapeutique

Traitement des tumeurs localisées

Traitement des tumeurs avancées

VOLUME 26 · NUMBER 18 · JUNE 20 2008

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

One Hundred Years After "Carcinoid": Epidemiology of and Prognostic Factors for Neuroendocrine Tumors in 35,825 Cases in the United States

James C. Yao, Manal Hassan, Alexandria Phan, Cecile Dagohoy, Colleen Leary, Jeannette E. Mares, Eddie K. Abdalla, Jason B. Fleming, Jean-Nicolas Vauthey, Asif Rashid, and Douglas B. Evans

Table 4. Survival Analysis of Patients with Well-Differentiated to Moderately Differentiated NETs: Actuarial Survival by Disease Stage and Primary Tumor Site in Patients With G1/G2 NETs Diagnosed From 1988 to 2004

Primary Tumor Site	Localized				Regional				Distant			
	Median Survival (months)	Survival Rate (%)			Median Survival (months)	Survival Rate (%)			Median Survival (months)	Survival Rate (%)		
		3-Year	5-Year	10-Year		3-Year	5-Year	10-Year		3-Year	5-Year	10-Year
Thymus	92	93	93	52	68	78	65	49	40	62	32	0
Lung	NR	89	84	70	151	77	72	56	17	34	27	15
Pancreas	NR	83	79	58	111	73	62	46	27	42	27	11
Liver	47	64	43	—	14	32	27	—	12	34	26	0
Gastric	163	80	73	56	76	75	65	43	13	33	25	9
Duodenum	112	80	68	48	69	75	55	44	57	60	46	27
Jejunum/ileum	115	73	65	49	107	83	71	46	65	70	54	30
Cecum	135	74	68	55	107	78	71	44	55	61	48	23
Colon	NR	90	85	74	52	60	46	33	7	20	14	6
Rectum	NR	94	90	80	90	74	62	47	26	37	24	3
Appendix	NR	93	88	72	NR	86	78	67	31	42	25	11

Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids

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[1]Neuroendocrine Tumour Unit, Royal Free Hospital, London, UK; [2]Department of Nuclear Medicine, Endocrine Cancer and Interventional Radiology, Institut Gustave Roussy, Université Paris Sud, Villejuif Cedex, France; [3]NET Center, Umbria Regional Cancer Network, Università degli Studi di Perugia, Perugia; [4]Department of Thoracic Surgery, University of Torino, Torino, Italy; [5]Department of Thoracic Surgery, University Clinic Hospital, Valladolid, Spain; [6]Imperial College and The Academic Division of

Fréquence des métastases hépatiques

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Traitement similaire à celui des tumeurs neuro-endocrines digestives

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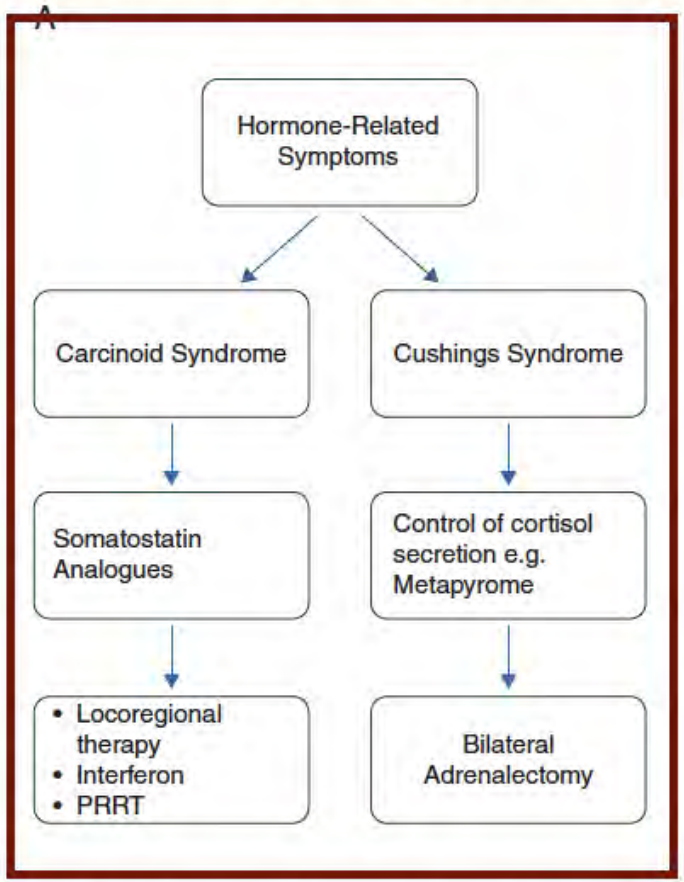

Figure 2. (A) ENETS recommendations for the control of hormone-related symptoms and tumor growth. *Progression is defined according to RECIST cri

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Traitement similaire à celui des tumeurs neuro-endocrines digestives

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Fréquence des métastases hépatiques

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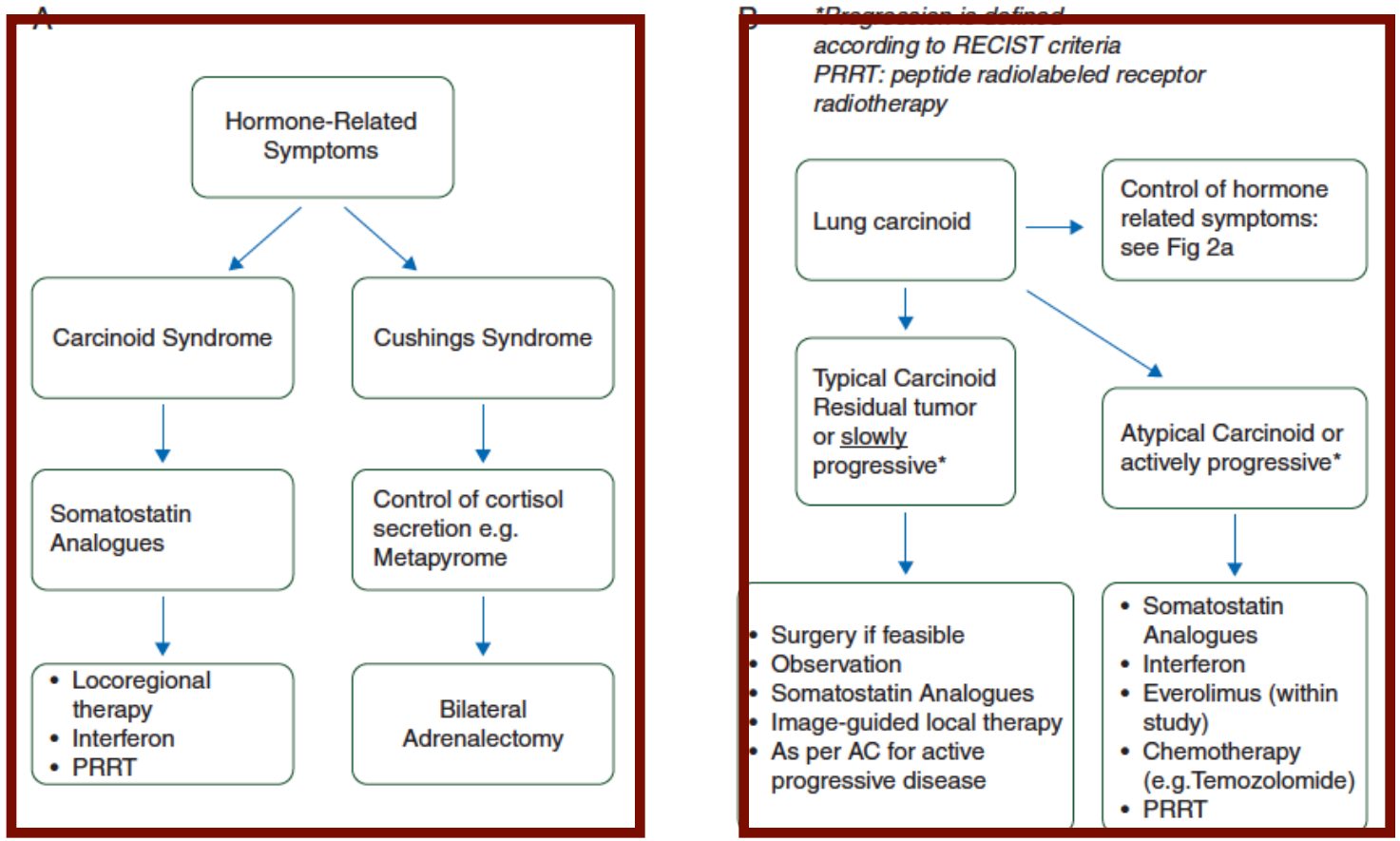
Traitement similaire à celui des tumeurs neuro-endocrines digestives



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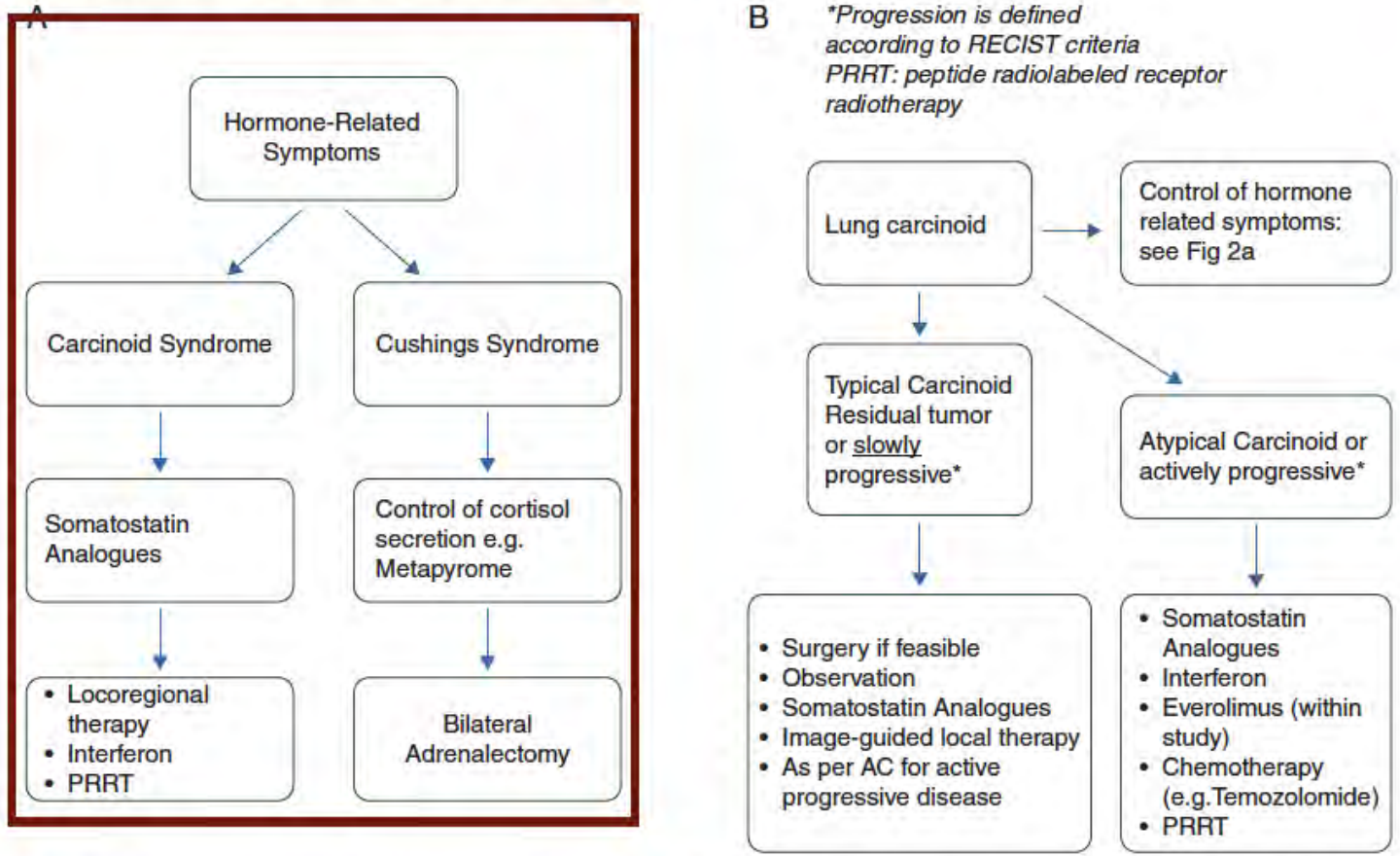

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Fréquence des métastases hépatiques

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Traitement similaire à celui des tumeurs neuro-endocrines digestives

Contrôle du syndrome sécrétoire

- Le syndrome sécrétoire est rare dans les tumeurs carcinoïdes pulmonaires (10%-15% vs. 30% dans les tumeurs digestives)

- Il est plus fréquent dans les carcinoïdes atypiques

- Traitement : analogues de la somatostatine
  - Traitement initial sous cutané: octreotide ou sandostatine 50-200 microgx2/j
  - Relais par sandostatine (octreotide LAR) LP ou somatuline (lanréotide) 20-50 mg/28j

- Traitements symptomatiques possibles, y compris corticoïdes

- Attention aux B2-mimétiques

Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids

M. E. Caplin[1*], E. Baudin[2], P. Ferolla[3], P. Filosso[4], M. Garcia-Yuste[5], E. Lim[6], K. Oberg[7], G. Pelosi[8], A. Perren[9], R. E. Rossi[1,10] & W. D. Travis[11] the ENETS consensus conference participants[†]

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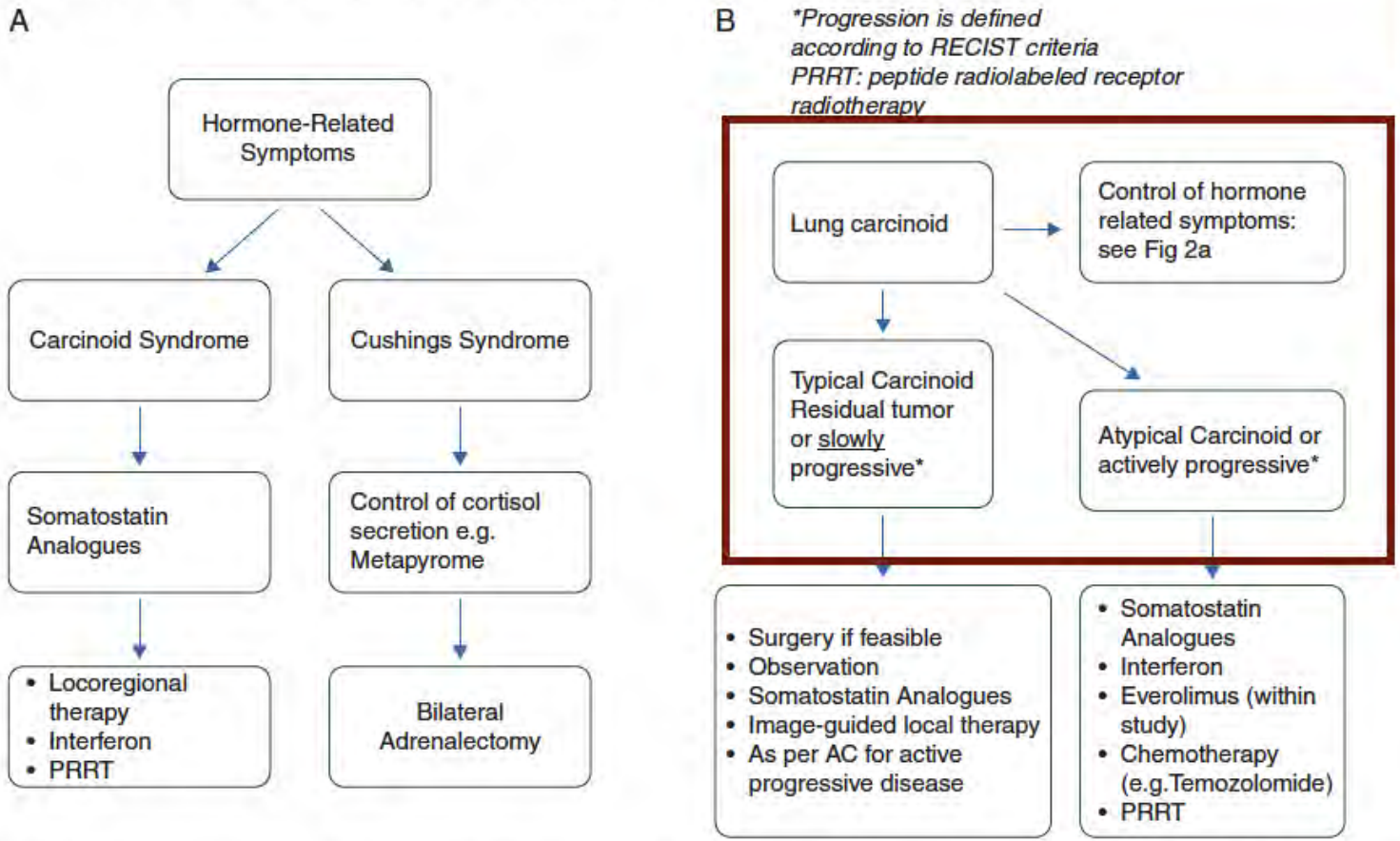

Figure 2. (A) ENETS recommendations for the control of hormone-related symptoms. (B) ENETS recommendations for the control of hormone-related symptoms and tumor growth. *Progression is defined according to RECIST criteria. PRRYT: peptide radiolabeled receptor radiotherapy.

Fréquence des métastases hépatiques

=

Traitement similaire à celui des tumeurs neuro-endocrines digestives

Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids

G1

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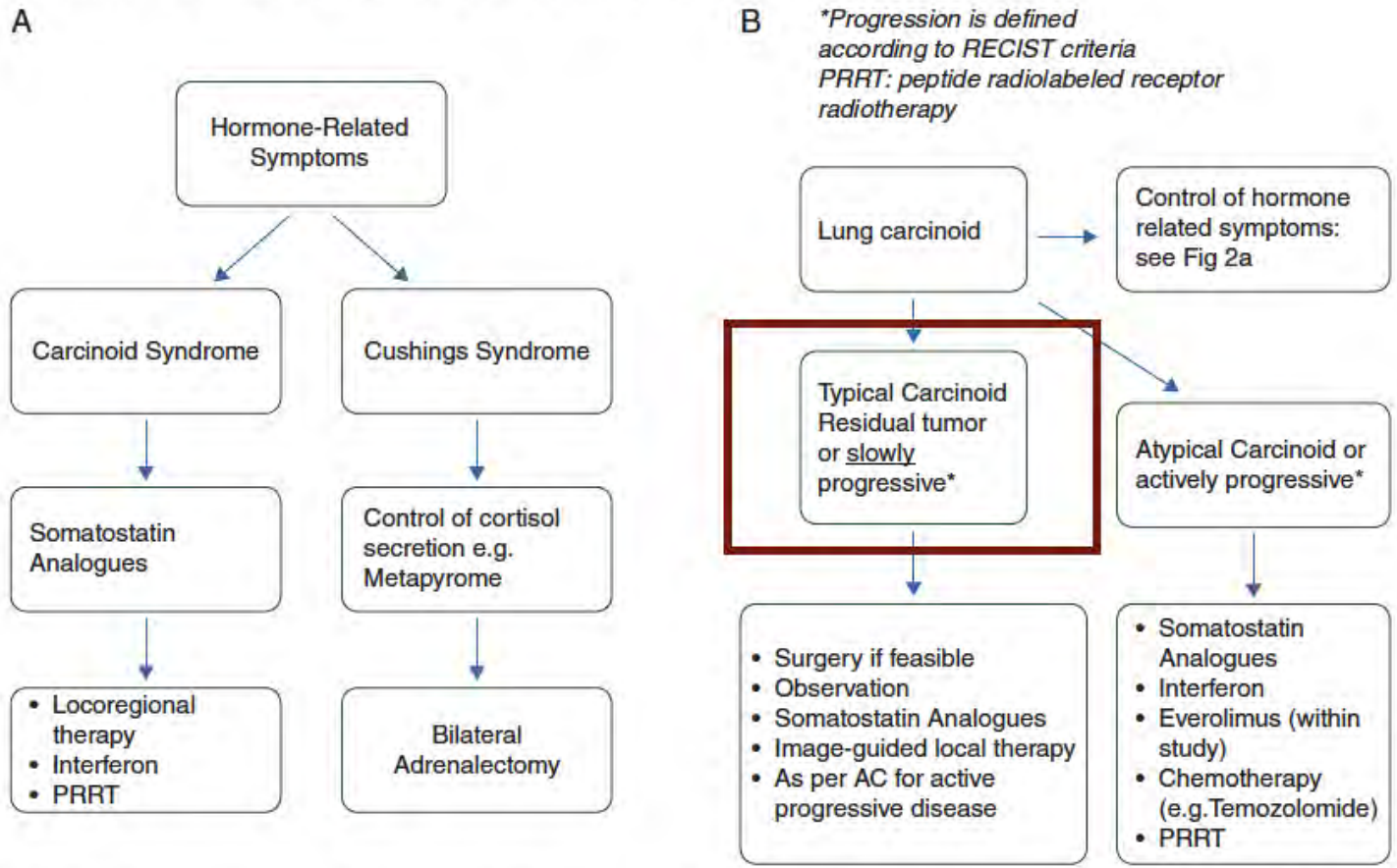

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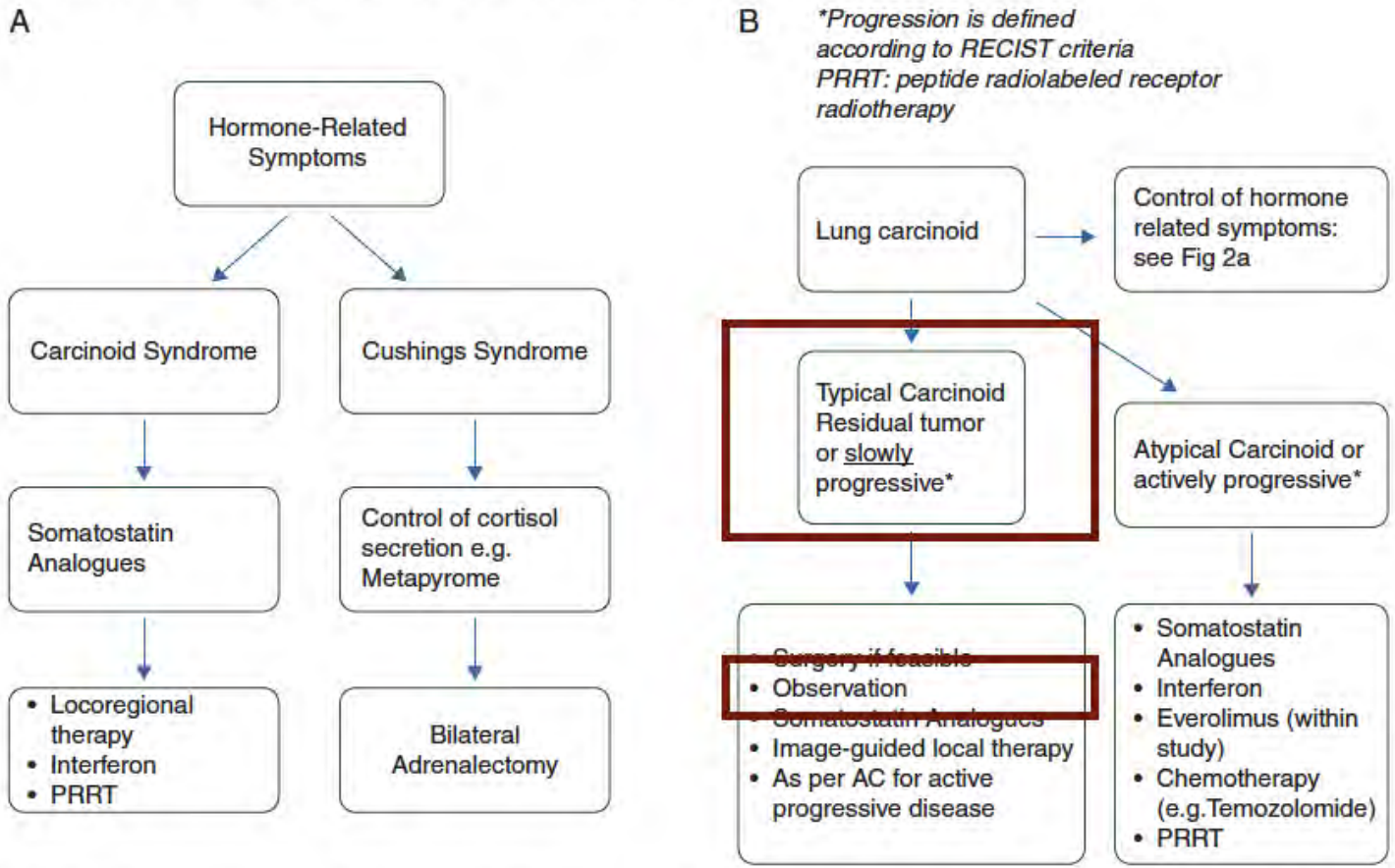

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Observation

- Evolution lente
- Volume tumoral faible

- Patients asymptomatiques
- Absence de risque de complication locorégionale

- Index de prolifération faible (grade 1: carcinoides typiques)

- Compliance et compréhension

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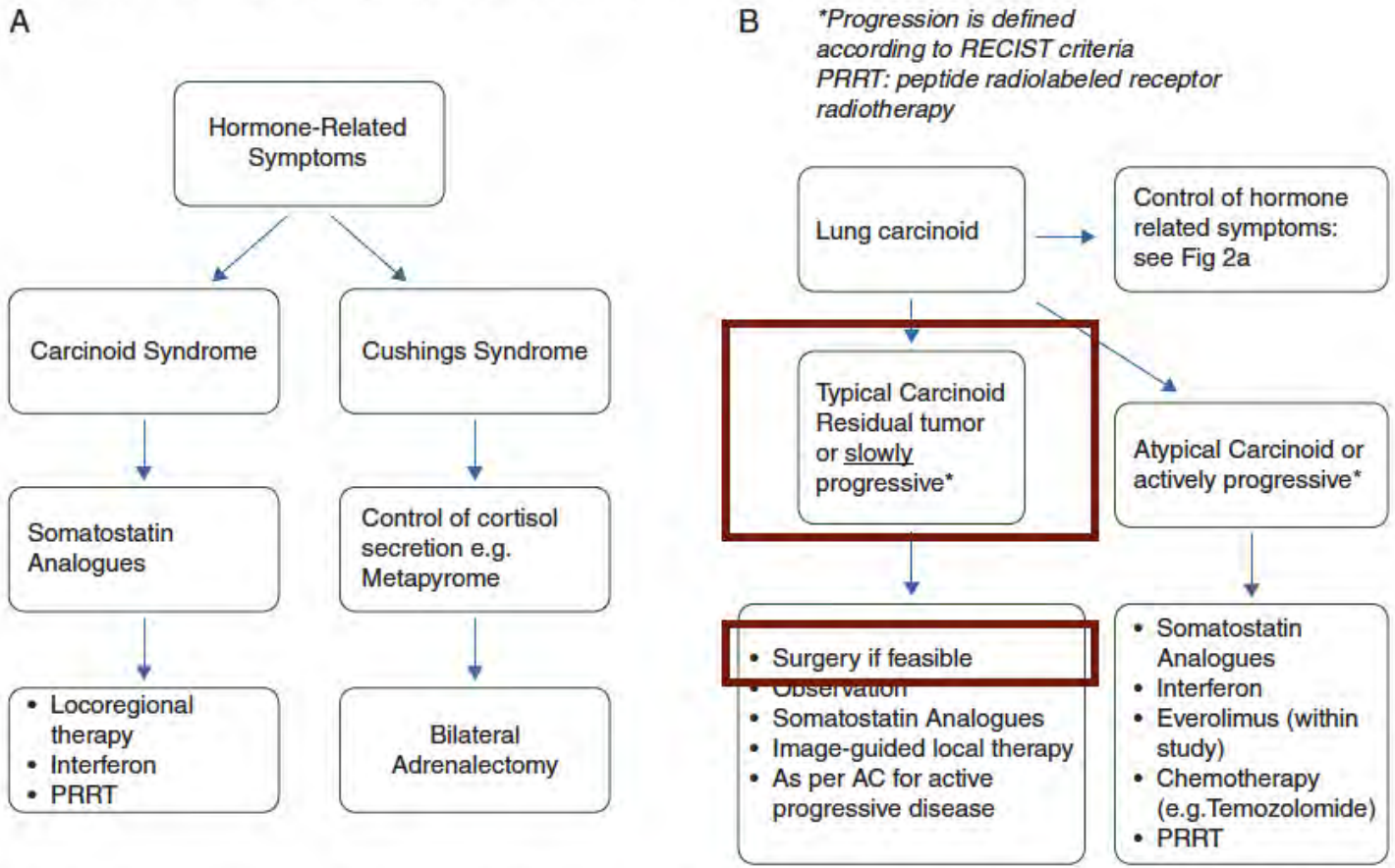

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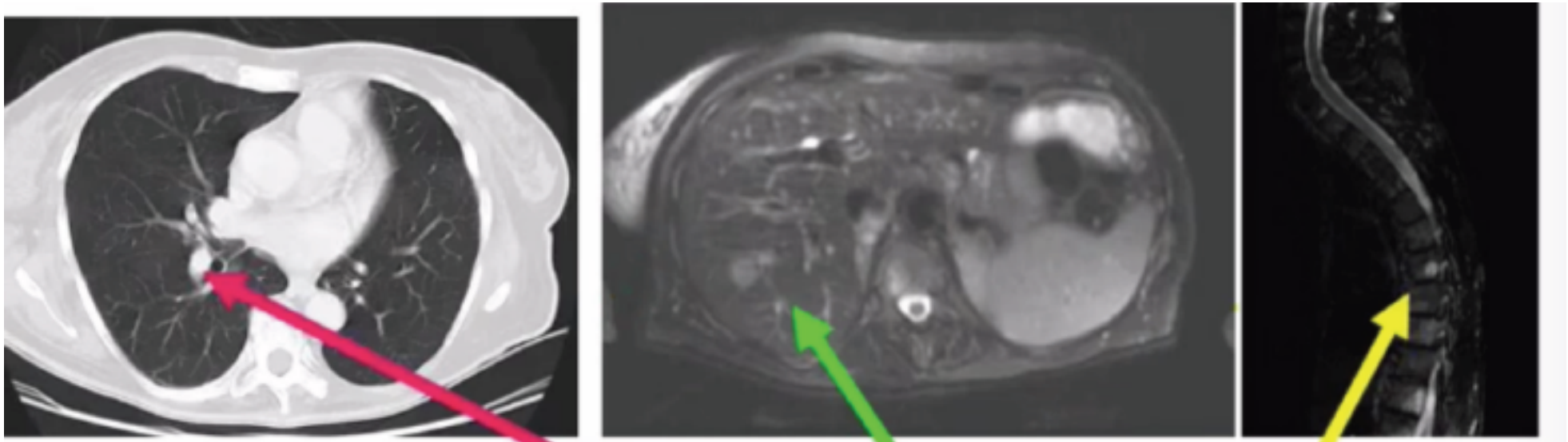
Traitements loco-régionaux

- Peuvent être proposés en cas de lésions multiples si progression lente
- Après traitement par analogues?



RCP dédiée

Mortalité <3%

Chirurgie
RT
Radiofrequence, cryoablation
Cimentoplastie

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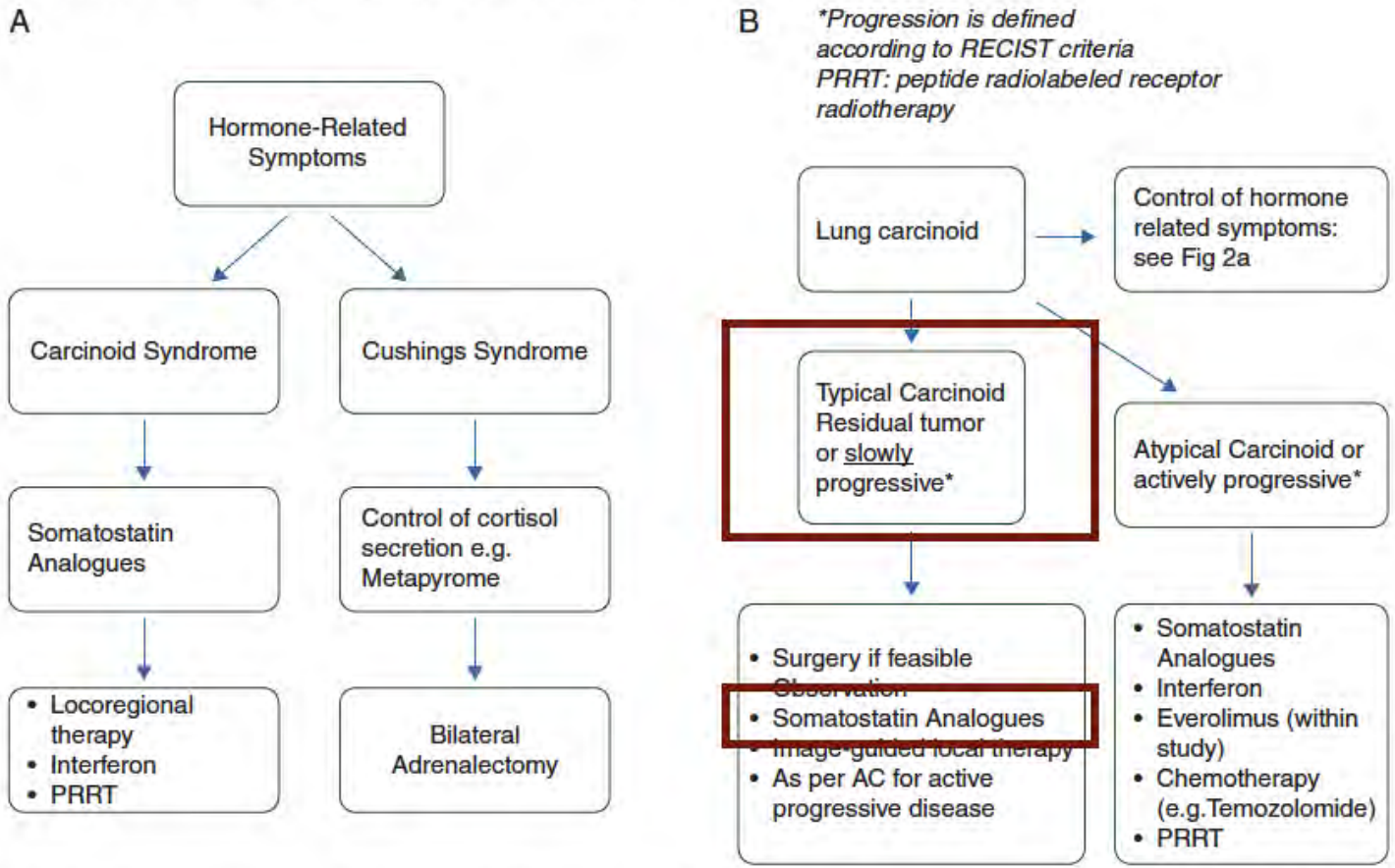

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Analogues de la somatostatine: essai PROMID

VOLUME 27 · NUMBER 28 · OCTOBER 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors: A Report From the PROMID Study Group

Anja Rinke, Hans-Helge Müller, Carmen Schade-Brittinger, Klaus-Jochen Klose, Peter Barth, Matthias Wied, Christina Mayer, Behnaz Aminossadati, Ulrich-Frank Pape, Michael Bläker, Jan Harder, Christian Arnold, Thomas Gress, and Rudolf Arnold

Table 1. Baseline Patient Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	Octreotide LAR (n = 42)		Placebo (n = 43)		Total (N = 85)		
	No. of Patients	%	No. of Patients	%	No. of Patients	%	*P*
Carcinoid syndrome	17	40.5	16	37.2	33	38.8	.8256
Resection of primary tumor	29	69.1	27	62.8	56	65.9	.6487
Ki-67 up to 2%	41	97.6	40	93.0	81	95.3	.6160
Octreoscan							.8806
Positive	32	76.2	31	72.1	63	74.1	
Negative	4	9.5	6	14.0	10	11.8	

Tumeurs sécrétantes: 40%
Octreoscan positif: 75%

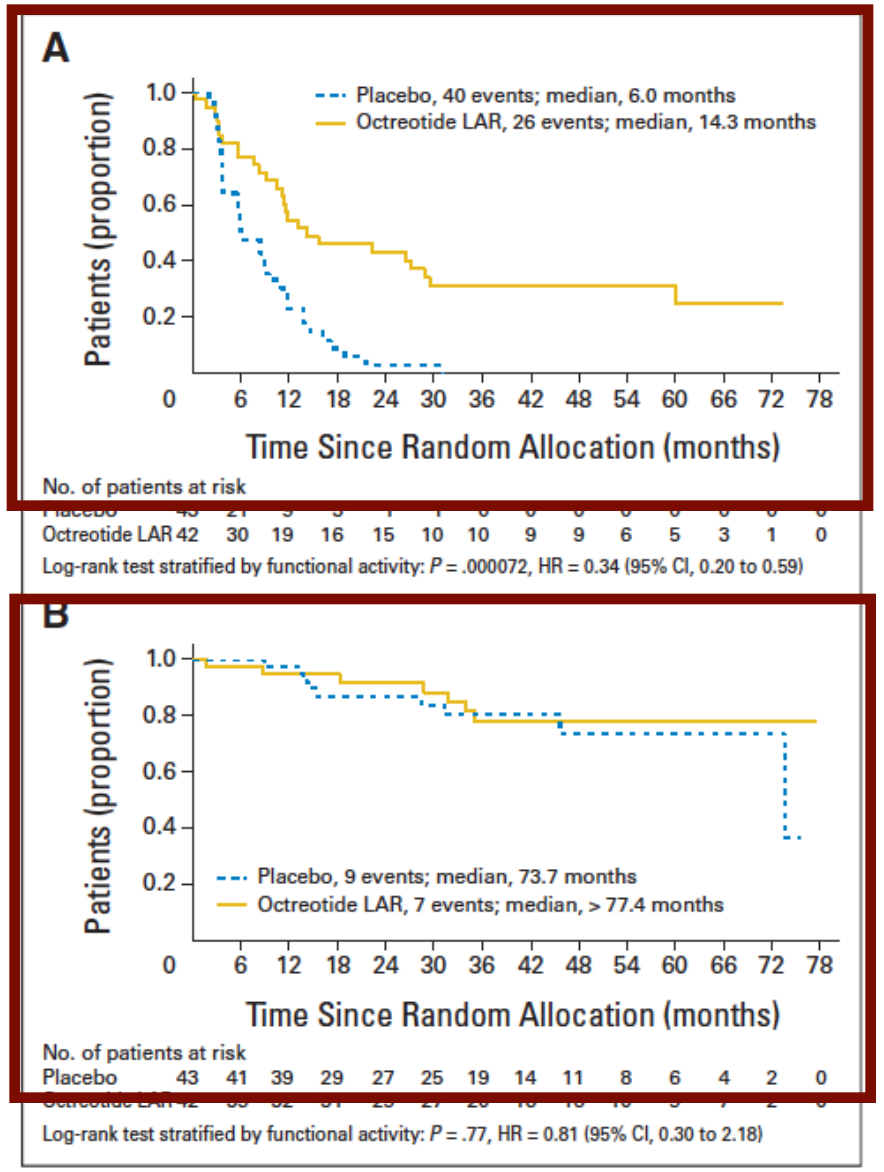


Fig 2. (A) Conservative intent-to-treat analysis of time to progression or tumor-related death. (B) Intent-to-treat analysis of overall survival. HR, hazard ratio.

Analogues de la somatostatine: essai CLARINET

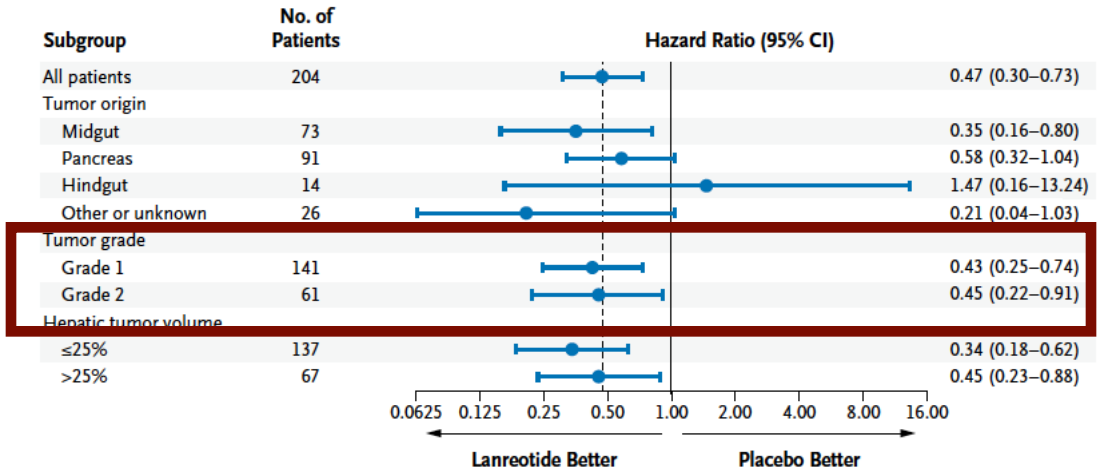
ORIGINAL ARTICLE

Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors

Martyn E. Caplin, D.M., Marianne Pavel, M.D., Jarosław B. Ćwikła, M.D., Ph.D., Alexandria T. Phan, M.D., Markus Raderer, M.D., Eva Sedláčková, M.D., Guillaume Cadiot, M.D., Ph.D., Edward M. Wolin, M.D., Jaume Capdevila, M.D., Lucy Wall, M.D., Guido Rindi, M.D., Ph.D., Alison Langley, M.Sc., Séverine Martinez, B.Sc., Joëlle Blumberg, M.D.,

Table 1. Baseline Demographic and Disease Characteristics of the Patients (Intention-to-Treat Population).*

Variable	Lanreotide (N=101)	Placebo (N=103)
Tumor grade — no. (%)‡		
1: Ki-67 0–2%	69 (68)	72 (70)
2: Ki-67 3–10%	32 (32)	29 (28)
Data missing	0	2 (2)



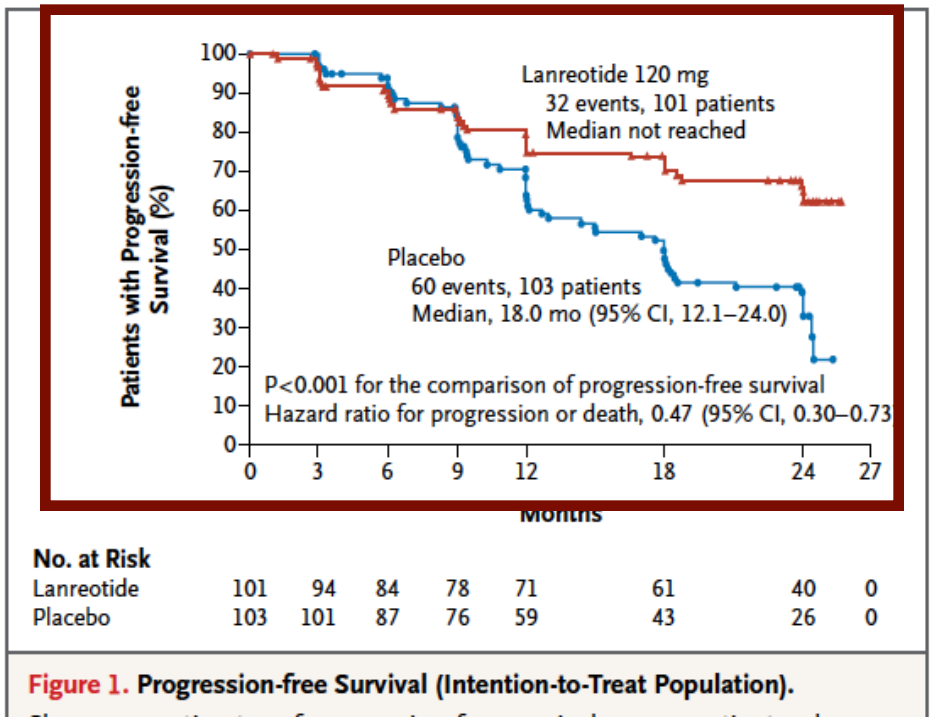


Figure 1. Progression-free Survival (Intention-to-Treat Population).

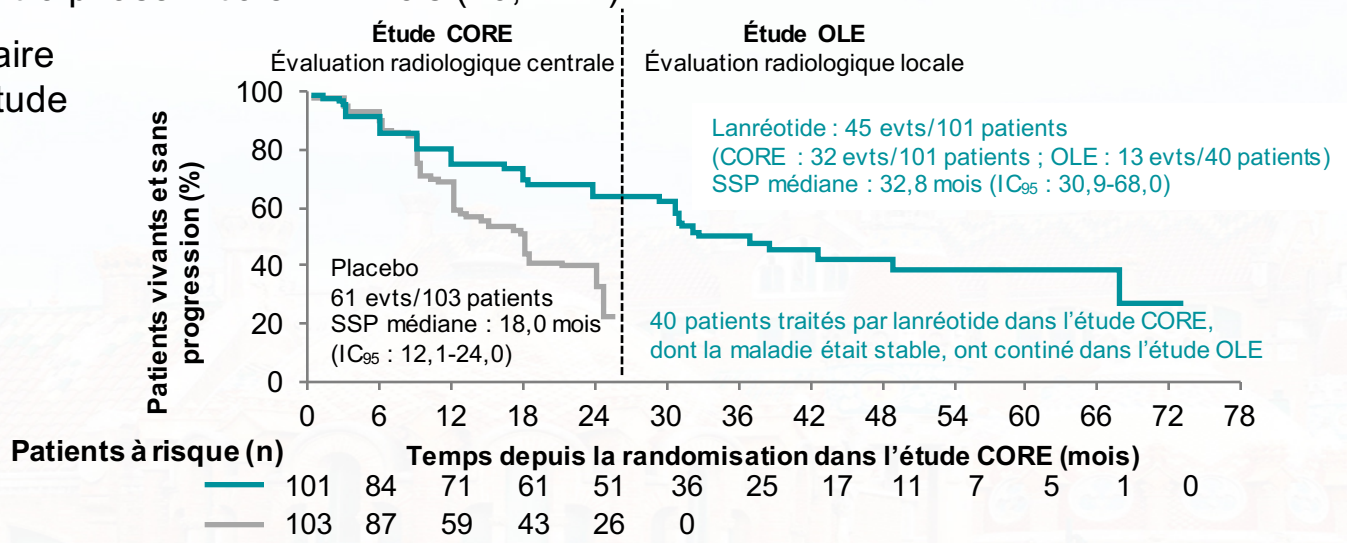
Tumeurs non sécrétantes
Octreoscan positif

Diarrhea	26 (26)
Abdominal pain	14 (14)
Cholelithiasis	10 (10)
Flatulence	8 (8)
Injection-site pain	7 (7)
Nausea	7 (7)
Vomiting	7 (7)
Headache	5 (5)
Lethargy	5 (5)
Hyperglycemia	5 (5)
Decreased level of pancreatic enzymes	5 (5)

Résultats actualisés de l'étude CLARINET

Phase d'extension en ouvert

- Inclusion des patients de l'étude CLARINET si maladie stable ou progression (bras placebo uniquement), lors de la visite finale
- Traitement de tous les patients par lanréotide Autogel® 120 mg/mois
- SSP médiane des patients initialement sous lanréotide : 32,8 mois (IC_{95} : 30,9-68,0)
- Délai médian jusqu'à 2e progression des patients initialement sous placebo ayant progressé pendant la phase initiale : 14 mois (10,1-NA)
- Profil de tolérance similaire à celui observé dans l'étude initiale



➜ **Confirmation des données de l'étude CLARINET et activité anti-tumorale chez les patients ayant progressé sous placebo, et traités par lanréotide**

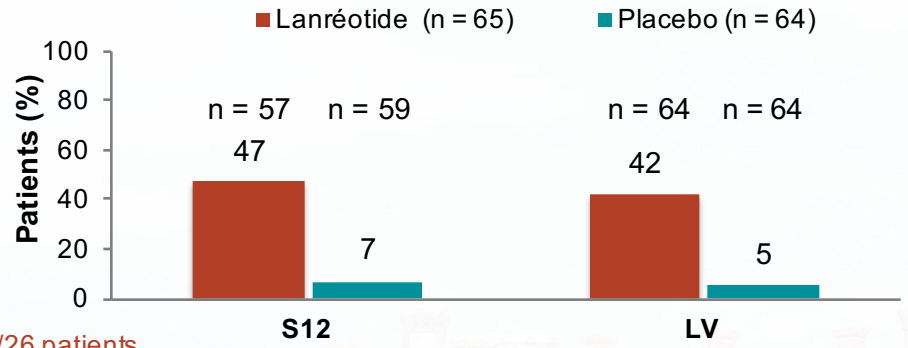
ENETS 2015 - D'après Caplin ME et al., Poster K2 actualisé

Chromogranine A (CgA) : facteur prédictif de réponse au traitement par lanréotide 120 mg

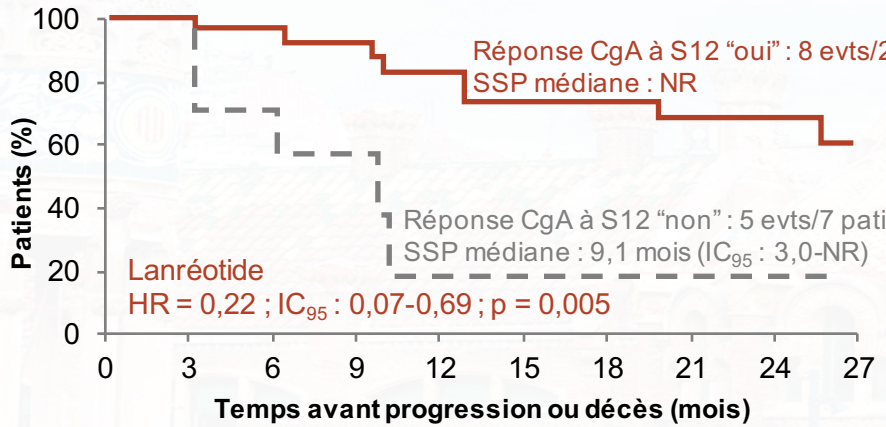
Analyse des données de l'étude CLARINET

- Réduction plus importante des taux de CgA sous lanréotide que sous placebo
- Les pourcentages de patients avec diminution de la CgA ≥ 30 % et ≥ 50 % étaient plus importants en cas de stabilisation qu'en cas de progression

Pourcentages de patients avec diminution ≥ 50% de la CgA à S12 et à la visite finale



SSP en fonction de la réponse CgA à S12*



N1/N2	26/7	26/7	23/4	21/3	18/1	15/1	15/1	14/1	10/1	0/0
C1/E1		0/0	2/1	3/2	4/4	5/6	5/6	5/7	9/7	18/8
C2/E2		0/0	0/3	1/3	1/5	1/5	1/5	1/5	1/5	2/5

- SSP significativement + longue en cas de réponse CgA précoce dans le bras lanréotide

* Diminution ≥ 30 % ou normalisation

➜ **Une diminution précoce de la CgA sous traitement par lanréotide pourrait être prédictive de la réponse au traitement**

ENETS 2015 - D'après Caplin ME et al., Poster K4 actualisé

Expression des récepteurs de la somatostatine

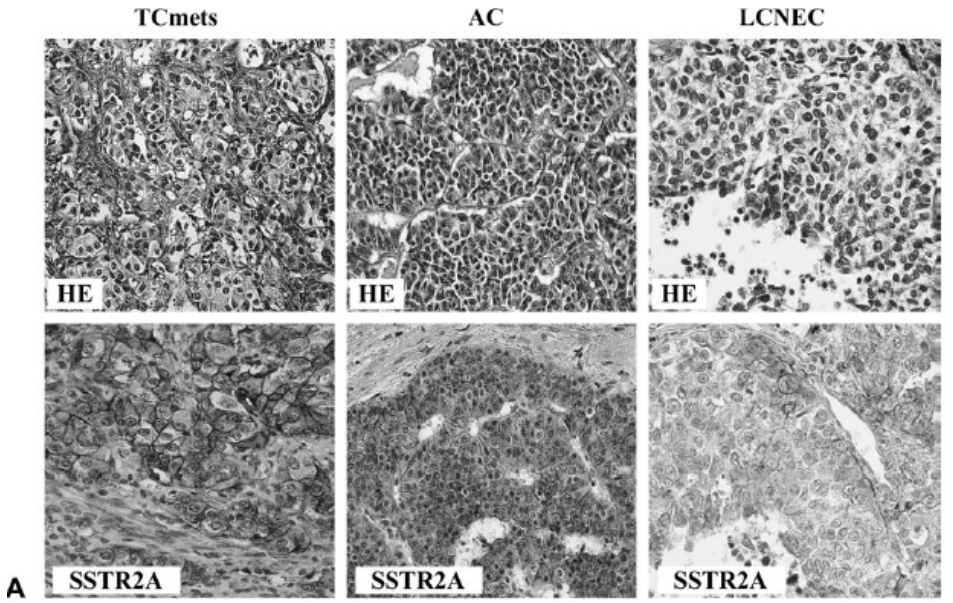
original article

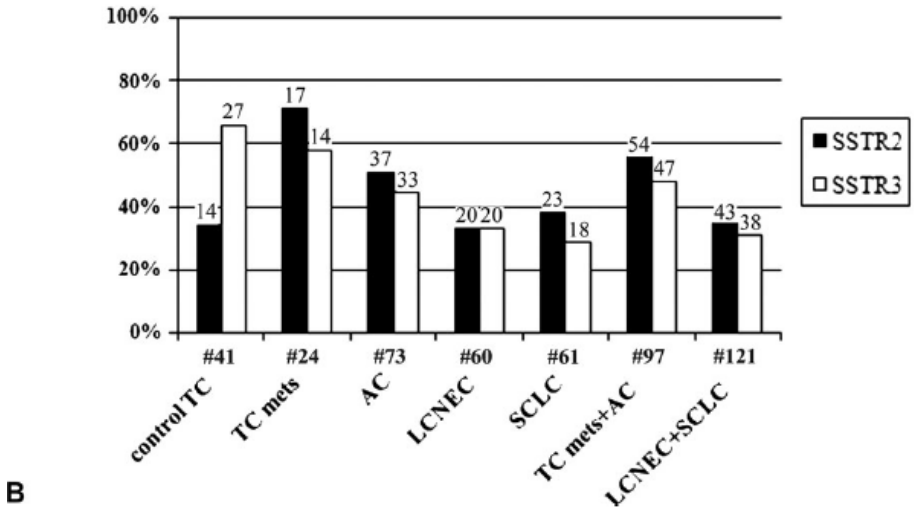
Annals of Oncology 21: 548–555, 2010
doi:10.1093/annonc/mdp334
Published online 16 September 2009

Somatostatin receptor tissue distribution in lung neuroendocrine tumours: a clinicopathologic and immunohistochemical study of 218 'clinically aggressive' cases

L. Righi[1]*, M. Volante[1], V. Tavaglione[1], A. Billè[2], L. Daniele[3], T. Angusti[4], F. Inzani[5], G. Pelosi[6], G. Rindi[5] & M. Papotti[1]

Expression plus fréquente dans les carcinoïdes typiques?



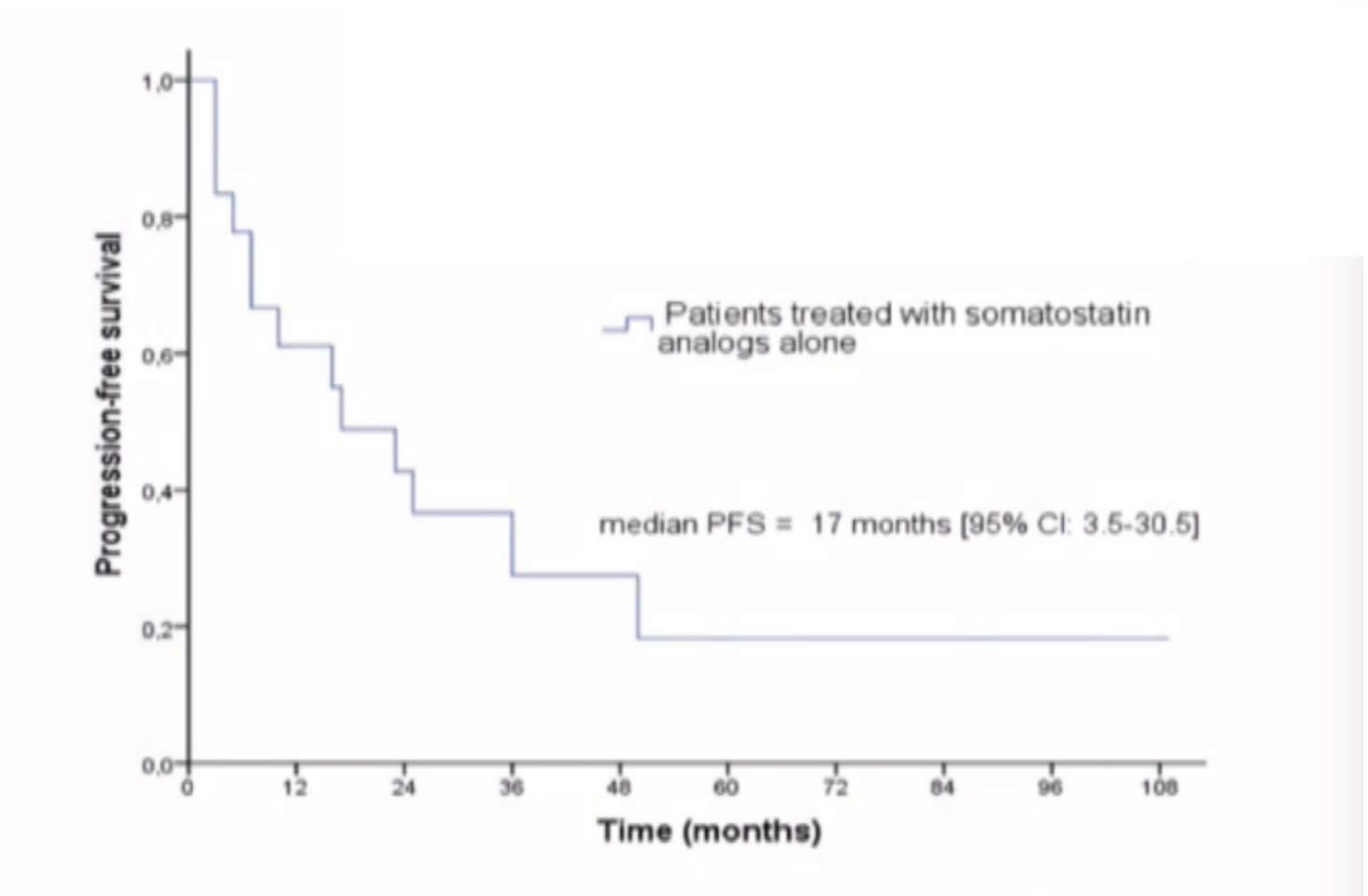


Righi et al. Ann Oncol 2009;21:548

Analogues de la somatostatine: cohorte IGR

- 18 patients, 9 typiques, 9 atypiques
- 12 patients progresseurs avant traitement

- PFS 17 mois pour la cohorte globale
- PFS: 50 mois pour les typiques
  17 mois pour les atypiques



Fekhi et al. ESMO 2011

Dans les carcinoïdes bronchiques:

Analogues de la somatostatine (sandostatine LP ou somatuline LP):

- Tumeurs sécrétantes
  - traitement du syndrome sécrétoire
  - traitement anti-tumoral: tumeur de grade 1 ou 2 (typique ou atypique)

- Tumeurs non sécrétantes
  - traitement anti-tumoral: tumeur de grade 1 ou 2 (typique ou atypique) si octreoscan positif

- Pas d'indication en adjuvant

Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids

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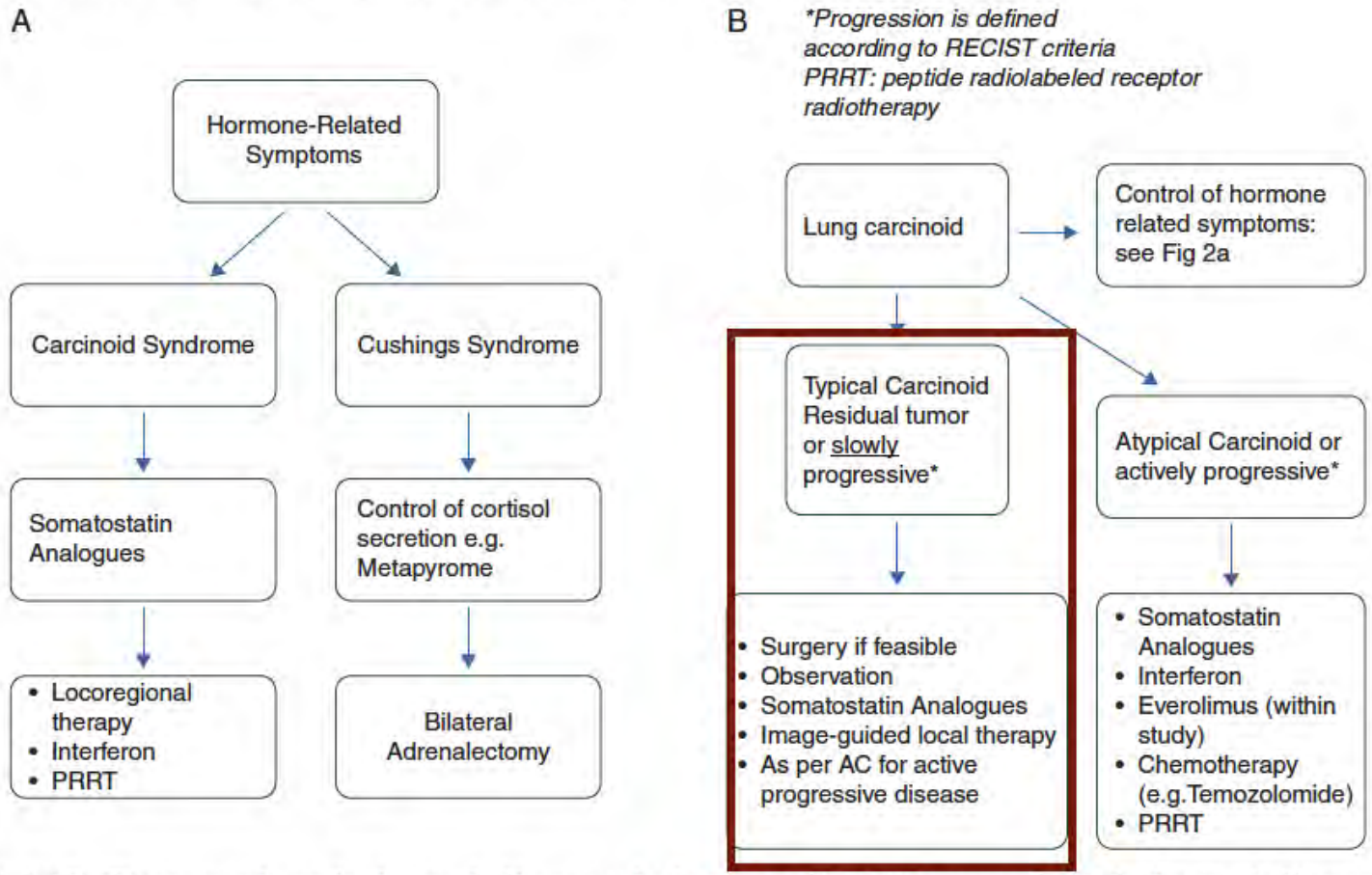

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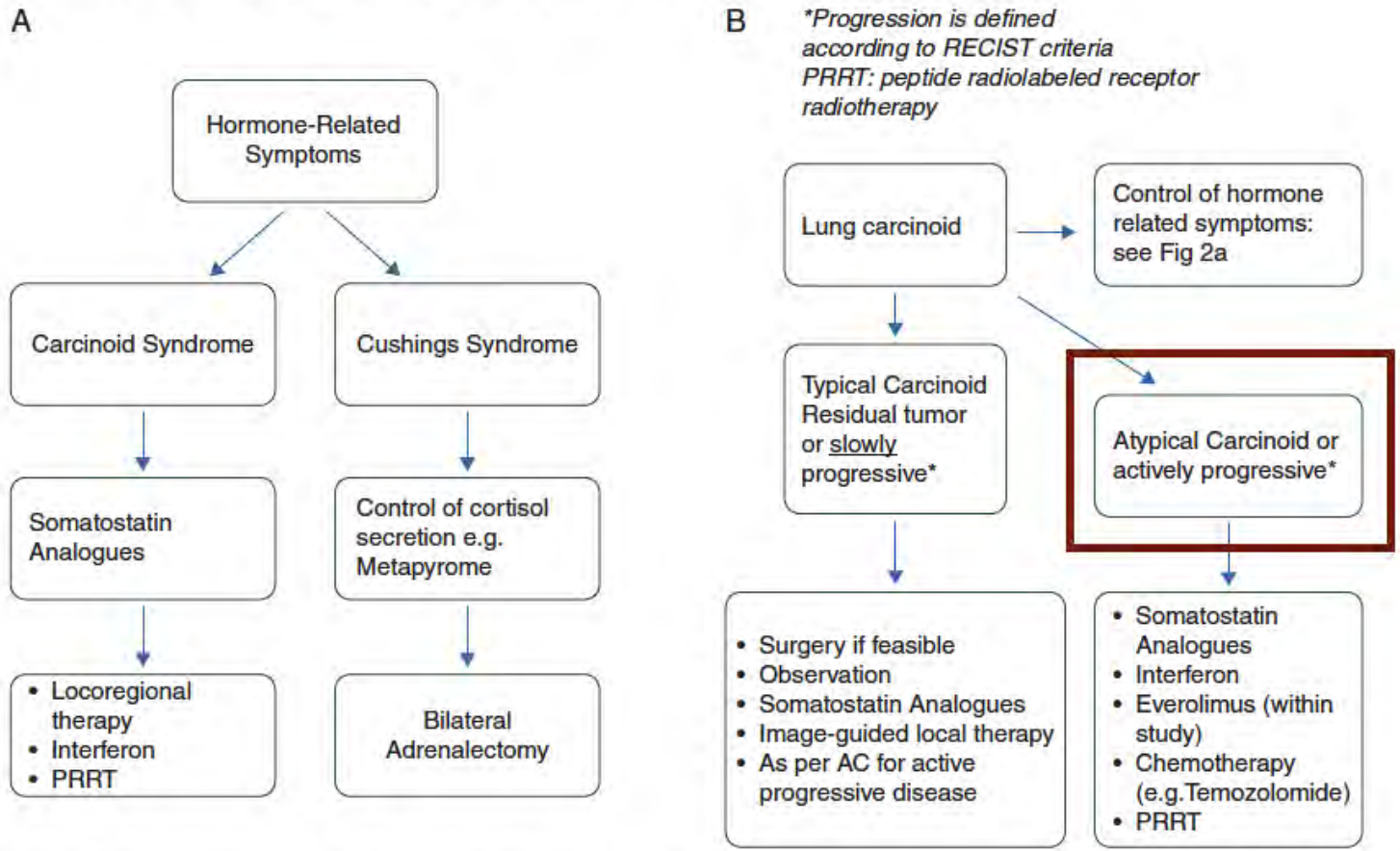

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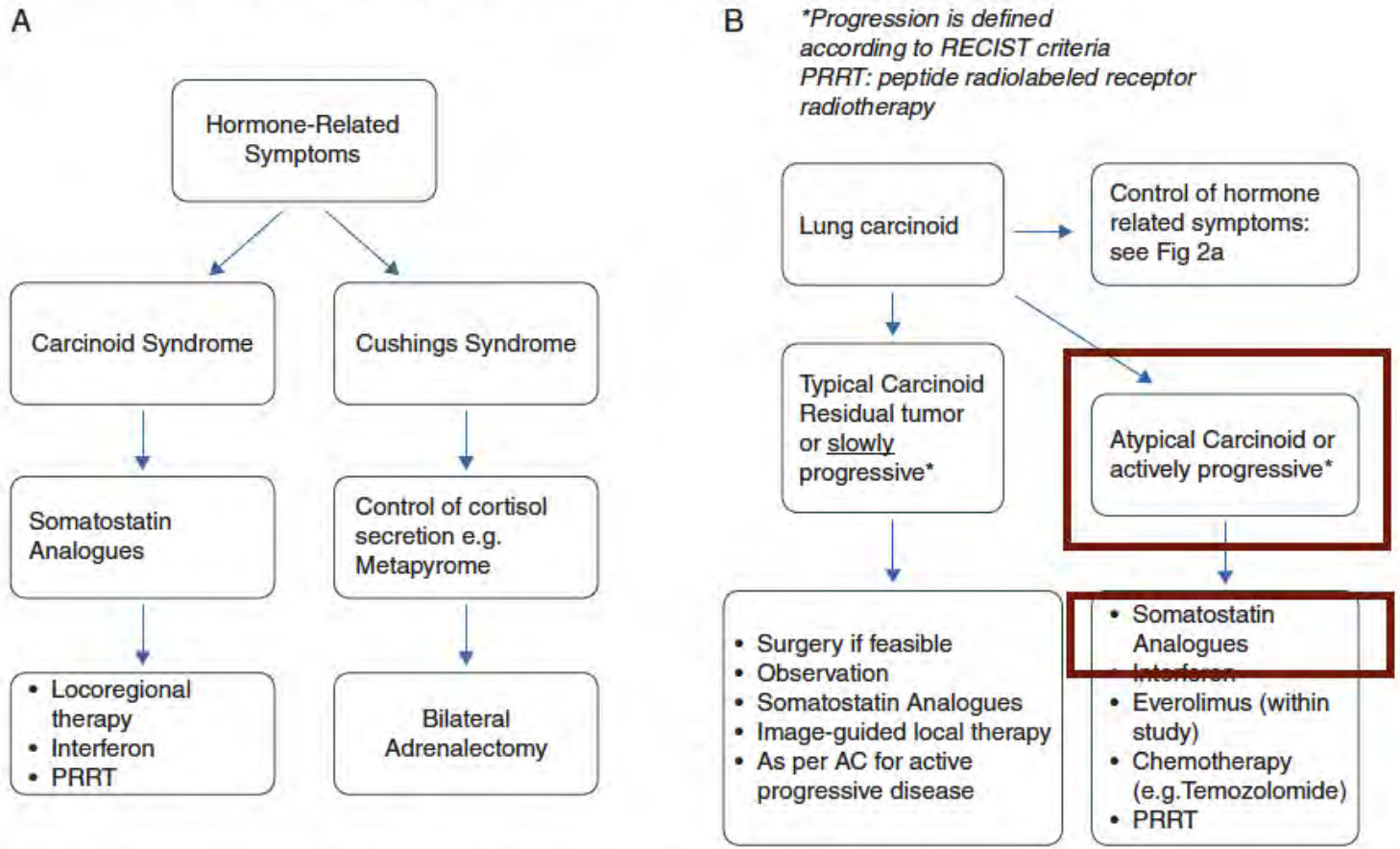

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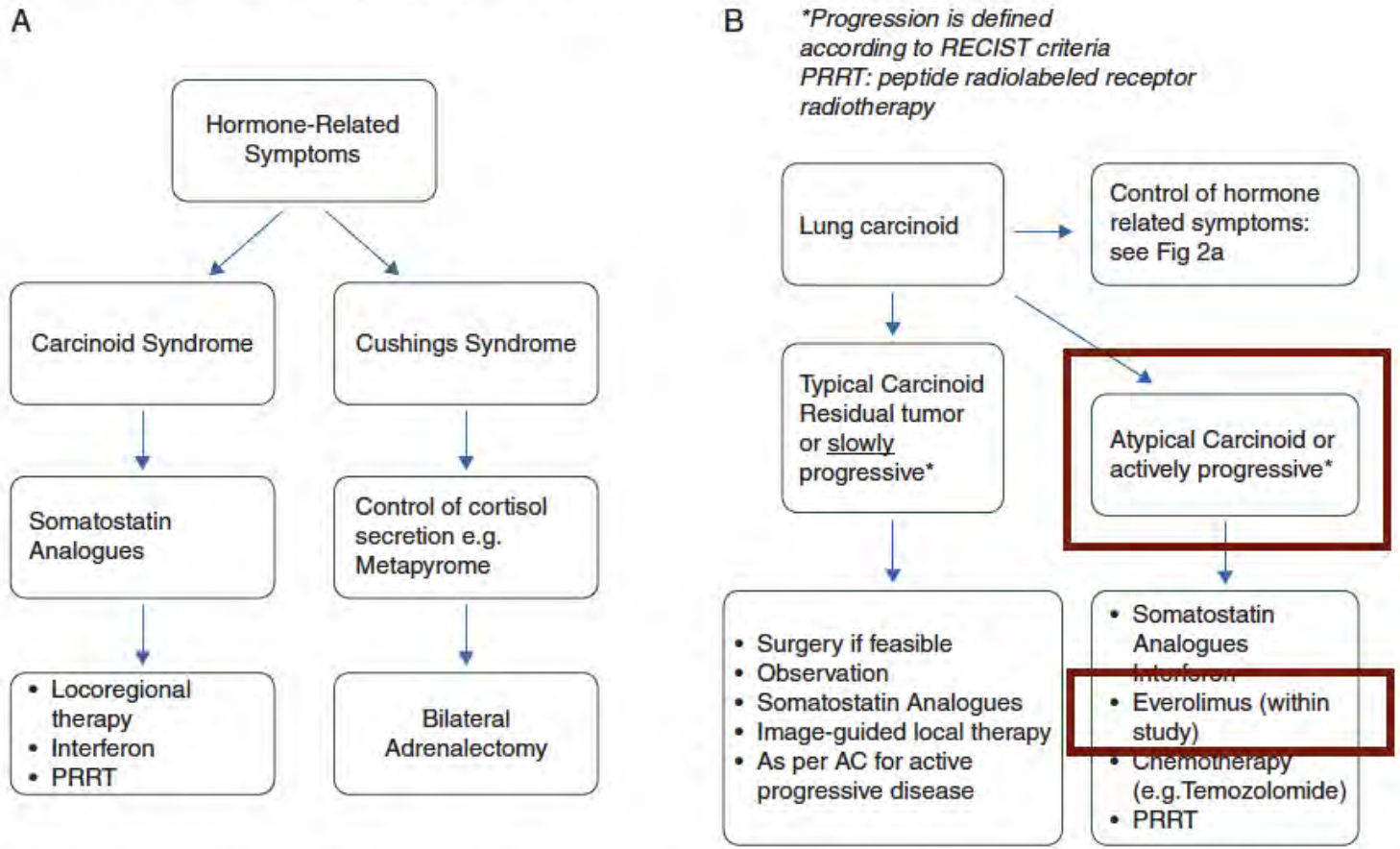

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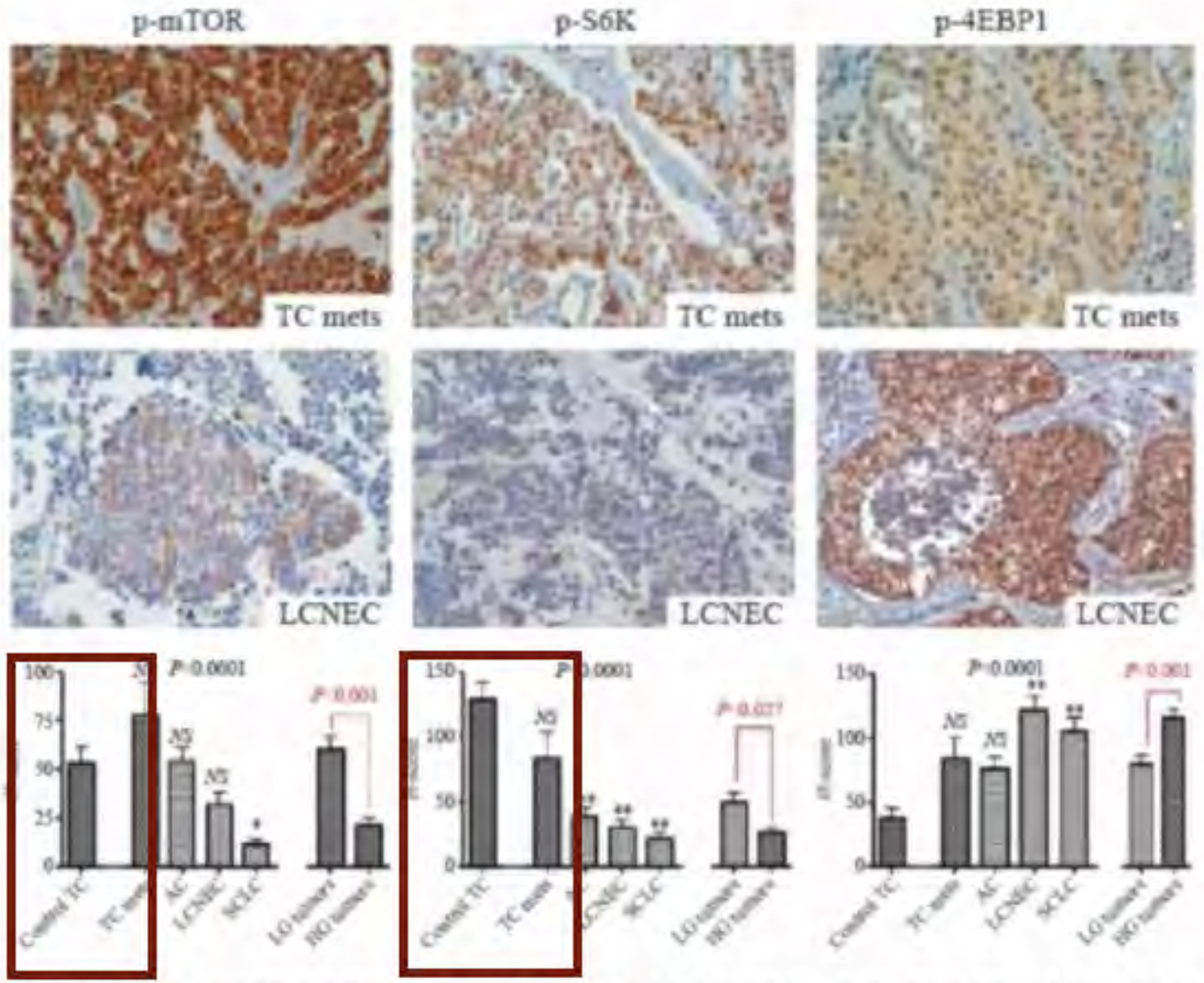
La voie mTor est activée dans les tumeurs carcinoïdes



Righi L, et al . Endocr Relat Cancer. 2010;17(4):977-87. Ali G et al., Exp Ther Med. 2011 2(5):787-792

Tumeurs carcinoïdes avancées
Everolimus: RADIANT-2

Tumeurs sécrétantes

Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study

Marianne E Pavel, John D Hainsworth, Eric Baudin, Marc Peeters, Dieter Hörsch, Robert E Winkler, Judith Klimovsky, David Lebwohl, Valentine Jehl, Edward M Wolin, Kjell Öberg, Eric Van Cutsem, James C Yao, for the RADIANT-2 Study Group

11; 378: 2005–12

Summary
Background

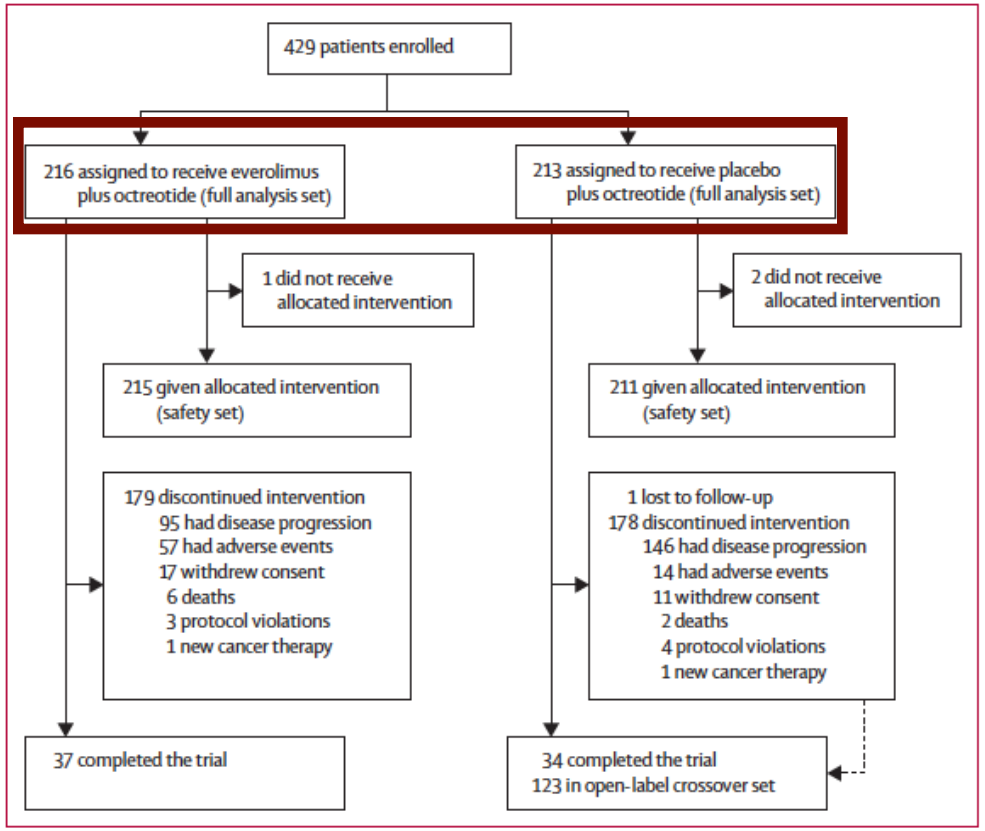


Figure 1: Trial profile

	Everolimus plus octreotide LAR group (n=216)	Placebo plus octreotide LAR group (n=213)
Median age, years (range)	60 (22–83)	60 (27–81)
Number of women	119 (55%)	89 (42%)
Number of men	97 (45%)	124 (58%)
WHO performance status*		
0	118 (55%)	140 (66%)
1	84 (39%)	62 (29%)
2	14 (6%)	10 (5%)
Primary site of cancer		
Small intestine	111 (51%)	113 (53%)
Lung	33 (15%)	11 (5%)
Colon	14 (6%)	14 (7%)
Pancreas	11 (5%)	15 (7%)
Liver	7 (3%)	11 (5%)
Other	40 (19%)	48 (23%)
Missing	0	1 (0·5%)
Histological grade		
Well differentiated	166 (77%)	175 (82%)
Moderately differentiated	36 (17%)	30 (14%)
Poorly differentiated	1 (0·5%)	1 (0·5%)
Unknown	11 (5%)	6 (3%)
Missing	0	1 (0·5%)
Current tumour-related symptoms†	170 (79%)	172 (81%)
Organ type involved‡		
Liver	198 (92%)	196 (92%)
Lymph nodes	80 (37%)	85 (40%)
Lung	64 (30%)	52 (24%)
Bone	35 (16%)	24 (11%)
Other	103 (48%)	103 (48%)

Tumeurs carcinoïdes avancées
Everolimus: RADIANT-2

Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated wi

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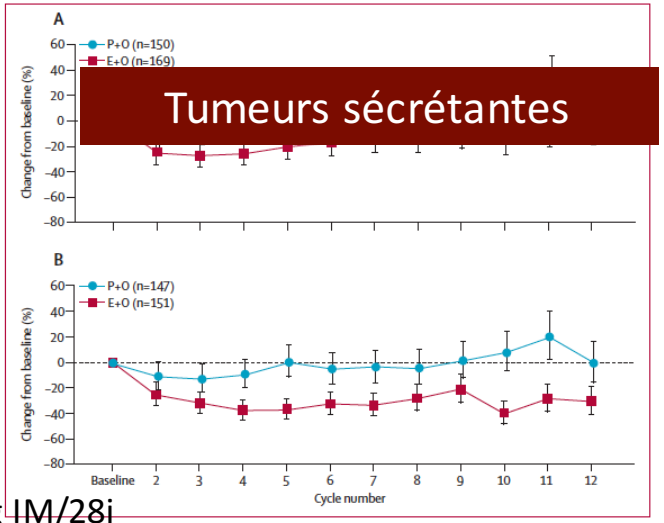
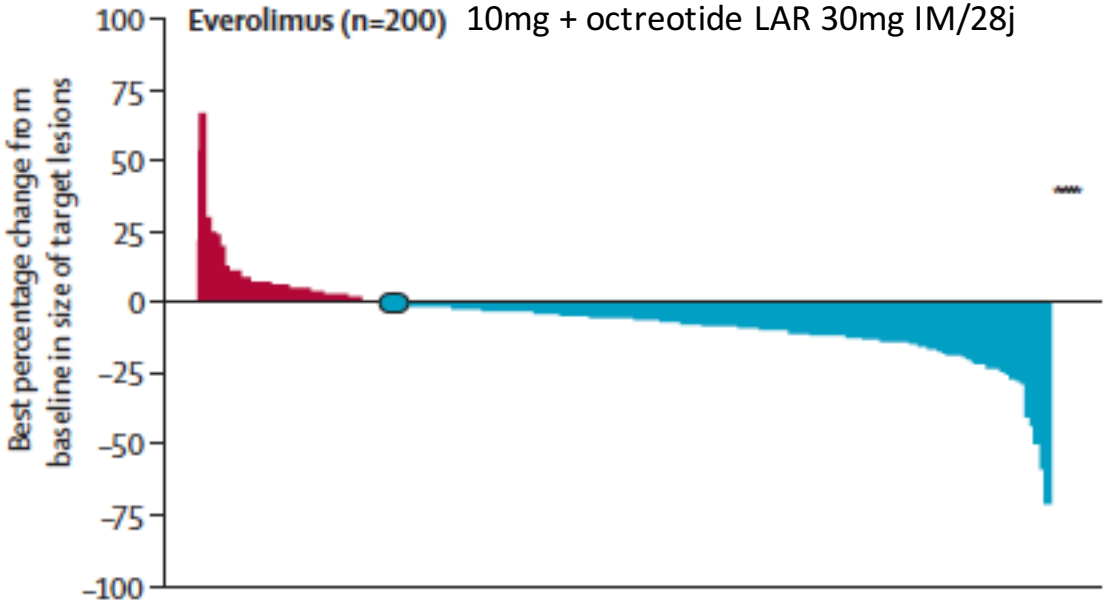
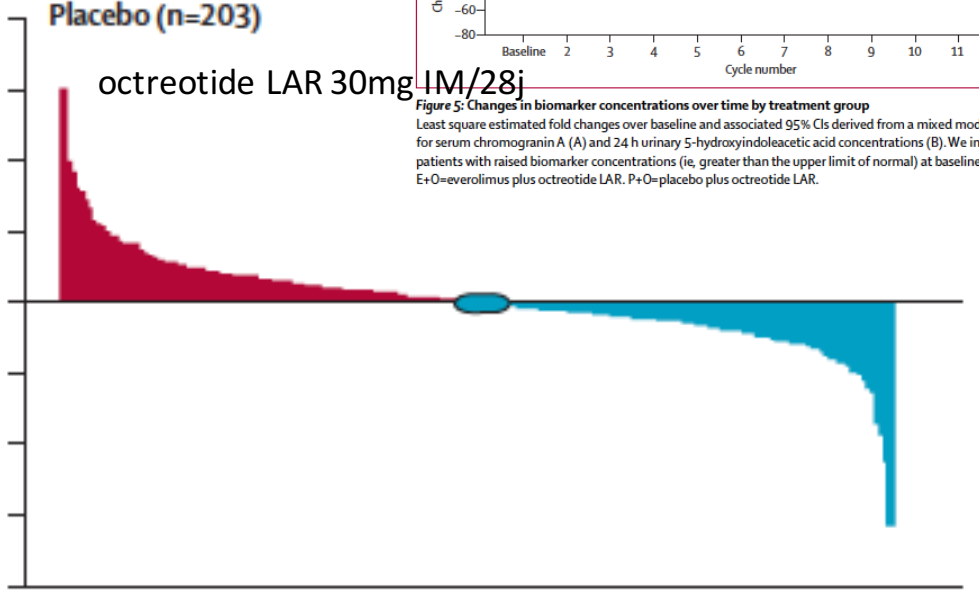


Tumeurs sécrétantes

Figure 5: **Changes in biomarker concentrations over time by treatment group**
Least square estimated fold changes over baseline and associated 95% CIs derived from a mixed model are shown for serum chromogranin A (A) and 24 h urinary 5-hydroxyindoleacetic acid concentrations (B). We include only patients with raised biomarker concentrations (ie, greater than the upper limit of normal) at baseline.
E+O=everolimus plus octreotide LAR. P+O=placebo plus octreotide LAR.



10mg + octreotide LAR 30mg IM/28j



octreotide LAR 30mg IM/28j

	E+O	P+O
Increase in size of target lesions from baseline	43 (22%)	94 (46%)
No change in size of target lesions from baseline	3 (2%)	10 (5%)
Decrease in size of target lesions from baseline	150 (75%)	91 (45%)
Change in size of target lesion was available but contradicted by overall lesion response of progressive disease	4 (2%)	8 (4%)

Figure 4: **Best percentage change from baseline in size of target lesion**

Tumeurs carcinoïdes avancées
Everolimus: RADIANT-2

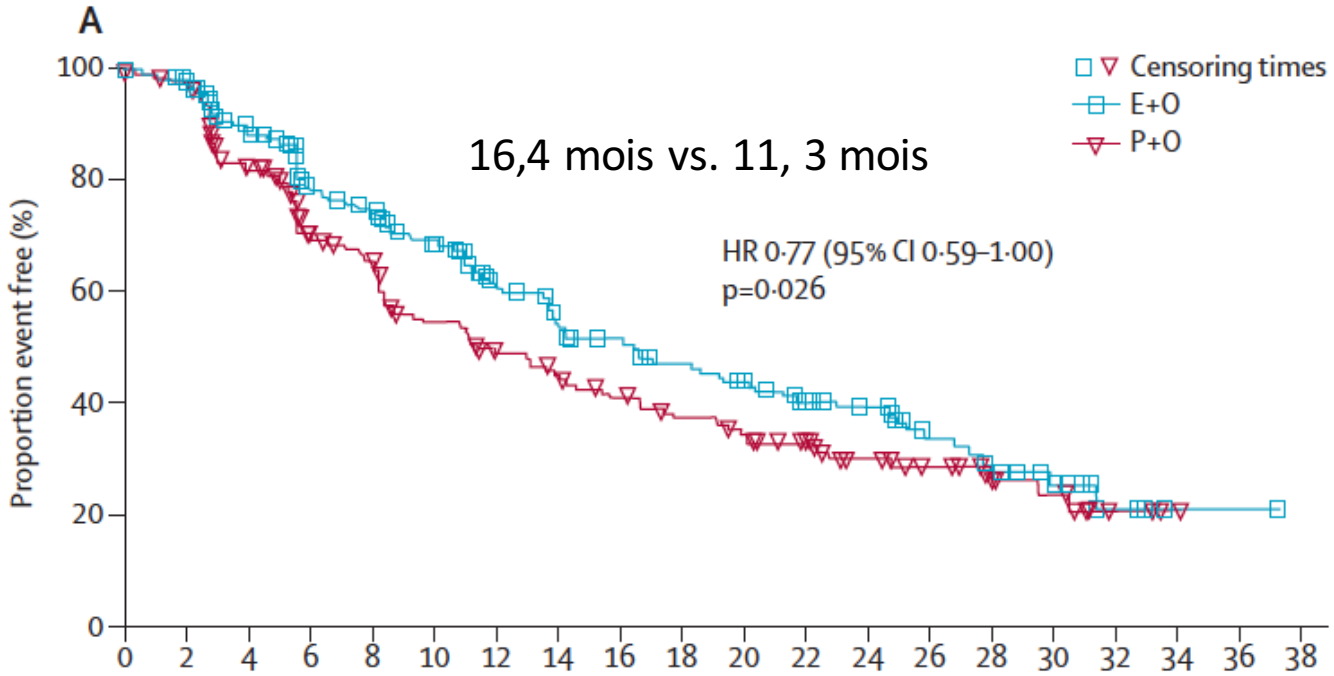
Tumeurs sécrétantes

Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study

Marianne E Pavel, John D Hainsworth, Eric Baudin, Marc Peeters, Dieter Hörsch, Robert E Winkler, Judith Klimovsky, David Lebwohl, Valentine Jehl, Edward M Wolin, Kjell Öberg, Eric Van Cutsem, James C Yao, for the RADIANT-2 Study Group

Summary

Background Everolimus, an oral inhibitor of the mammalian target of rapamycin (mTOR), has shown antitumour *Lancet* 2011; 378: 2005–12



	Everolimus plus octreotide LAR group (n=215)		Placebo plus octreotide LAR group (n=211)	
	All grades	Grades 3 and 4	All grades	Grades 3 and 4
Stomatitis*	133 (62%)	14 (7%)	29 (14%)	0
Rash	80 (37%)	2 (1%)	26 (12%)	0
Fatigue	67 (31%)	14 (7%)	49 (23%)	6 (3%)
Diarrhoea	59 (27%)	13 (6%)	33 (16%)	5 (2%)
Nausea	42 (20%)	1 (0·5%)	34 (16%)	2 (1%)
Infections†	42 (20%)	11 (5%)	13 (6%)	1 (0·5%)
Dysgeusia	36 (17%)	1 (0·5%)	7 (3%)	0
Anaemia	33 (15%)	3 (1%)	10 (5%)	0
Decreased weight	32 (15%)	1 (0·5%)	7 (3%)	0
Thrombocytopenia	30 (14%)	10 (5%)	0	0
Decreased appetite	29 (13%)	0	13 (6%)	0
Peripheral oedema	28 (13%)	0	7 (3%)	0
Hyperglycaemia	26 (12%)	11 (5%)	4 (2%)	1 (0·5%)
Dyspnoea	26 (12%)	4 (2%)	3 (1%)	0
Pulmonary events‡	25 (12%)	5 (2%)	0	0
Vomiting	23 (11%)	1 (0·5%)	11 (5%)	1 (0·5%)
Pruritus	23 (11%)	0	8 (4%)	0
Asthenia	22 (10%)	2 (1%)	14 (7%)	1 (0·5%)

*Includes stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration. †Includes all infections. ‡Includes pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis.

Table 2: **Drug-related adverse events in at least 10% of patients (safety set)**

Tumeurs carcinoïdes avancées
Everolimus: RADIANT-2

Tumeurs sécrétantes

CHEST Original Research
LUNG CANCER

Everolimus Plus Octreotide Long-Acting Repeatable in Patients With Advanced Lung Neuroendocrine Tumors

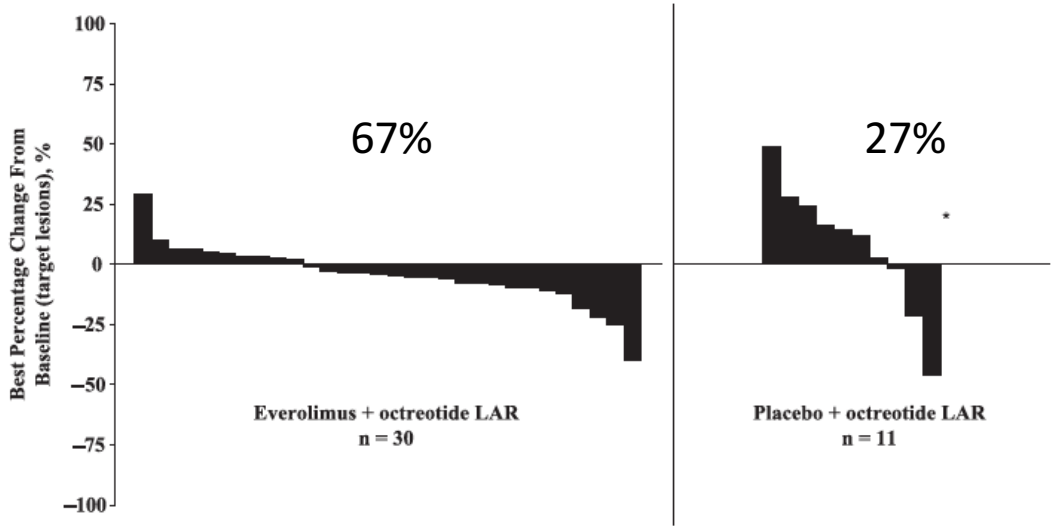
Analysis of the Phase 3, Randomized, Placebo-Controlled RADIANT-2 Study

Nicola Fazio, MD; Dan Granberg, MD, PhD; Ashley Grossman, MD; Stephen Saletan, MD; Judith Klimovsky, MD; Ashok Panneerselvam, PhD; and Edward M. Wolin, MD

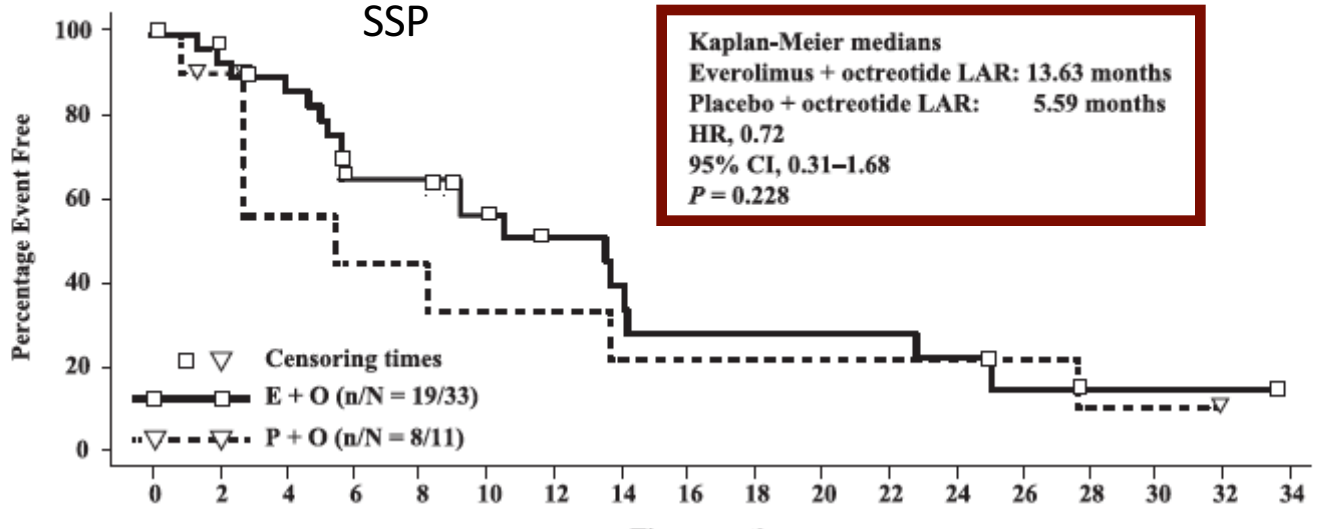
Table 1—*Baseline Demographics and Disease Characteristics*

Characteristics	Everolimus + Octreotide LAR (n = 33)	Placebo + Octreotide LAR[a]
Age, y		
<65	19 (57.6)	9 (81.8)
≥65	14 (42.4)	2 (18.2)
Sex		
Male	20 (60.6)	7 (63.6)
Female	13 (39.4)	4 (36.4)
White	33 (100)	11 (100)
Region		
Europe	19 (57.6)	6 (54.5)
United States	12 (36.4)	5 (45.5)
Other	2 (6.1)	0 (0)
Time since initial diagnosis, mo		
≤6	4 (12.1)	4 (36.4)
>6-≤24	4 (12.1)	1 (9.1)
>24-≤60	10 (30.3)	1 (9.1)
>60	15 (45.5)	5 (45.5)
Histologic grade		
Well differentiated	25 (75.8)	8 (72.7)
Moderately differentiated	6 (18.2)	3 (27.3)
Unknown	2 (6.1)	0 (0)
WHO performance status		
0	15 (45.5)	7 (63.6)
1	17 (51.5)	3 (27.3)
2	1 (3.0)	1 (9.1)
[illegible]	[illegible]	[illegible]
Other previous, systemic, antitumor therapy	16 (48.5)	4 (36.4)
Chemotherapy	13 (39.4)	4 (36.4)
Immunotherapy	4 (12.1)	1 (9.1)
Targeted therapy	5 (15.2)	1 (9.1)
Other	3 (9.1)	2 (18.2)
Organs involved		
1	6 (18.2)	2 (18.2)
2	9 (27.3)	2 (18.2)
≥3	18 (54.5)	7 (63.6)
History of diarrhea, flushing, or both	31 (93.9)	11 (100)
History of diarrhea	27 (81.8)	8 (72.7)
History of flushing	25 (75.8)	8 (72.7)

Data given as No. (%) unless otherwise indicated. LAR = long-acting repeatable; WHO = World Health Organization.
[a]Data missing for two patients in the placebo plus octreotide LAR group.



SSP



Tumeurs carcinoïdes avancées
Everolimus: RAMSETE

Tumeurs non sécrétantes

An open-label, single-arm, multicenter, phase II study conducted in 16 European sites (ClinicalTrials.gov number NCT00688623)

Patients with advanced nonsyndromic, nonpancreatic NET

(ITT/safety population, N = 73; PP population, N = 60)

- Radiologic progression within 12 months before study entry
- Measurable disease at baseline (RECIST criteria, version 1.0)
- ECOG PS of 0-2
- Life expectancy ≥6 months
- Previous treatment with ≤3 systemic treatments allowed

→

Everolimus 10 mg/day orally

- Each cycle comprised 28 days of consecutive treatment with everolimus

Triphasic CT or MRI performed at baseline and every 12 weeks

→

Patients continued treatment until

- Tumor progression
- Occurrence of unacceptable toxicity
- Death
- Discontinuation due to any other reason

Primary Endpoint
- ORR as per RECIST by central radiologic review

Secondary Endpoints
- Disease control rate, PFS, OS, Sa

Follow-up: Every 28 days (after the last dose of everolimus) for AEs and SAEs; every 12 weeks for radiologic assessment

	Lung, Thymic, Bronchial, or Mediastinal n = 22
Median age, years (range)	56.5 (30.0-75.0)
Male/female sex, n (%)	7 (32)/15 (68)
Histologic grade, n (%)	
Well differentiated	9 (41)
Moderately differentiated	13 (59)
Ki67 ≥10%, n (%)	10 (63)

AE, adverse event; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; MRI, magnetic resonance imaging; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PP, per protocol; PS, performance status; RECIST, Response Evalu Criteria in Solid Tumors; SAE, serious adverse event.

Pavel, et al. ESMO 2012

Tumeurs carcinoïdes avancées
Everolimus: RAMSETE

Tumeurs non sécrétantes

Best Overall Response by Primary Tumor Origin in Per Protocol Population

	Lung, Thymic, Bronchial, or Mediastinal n = 19		Small Bowel, Rectum, and Others n = 28		Unknown n = 13	
	Central Radiologic Review	Local Investigator Review	Central Radiologic Review	Local Investigator Review	Central Radiologic Review	Local Investigator Review
CR, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PR, n (%)	0 (0)	0 (0)	0 (0)	2 (7)	0 (0)	1 (8)
SD, n (%)	12 (63)	12 (63)	12 (43)	18 (64)	9 (69)	9 (69)
PD, n (%)	7 (37)	6 (32)	16 (57)	7 (25)	4 (31)	3 (23)
Unknown, n (%)	0 (0)	1 (5)	0 (0)	1 (4)	0 (0)	0 (0)
ORR, n (%)	0 (0)	0 (0)	0 (0)	2 (7)	0 (0)	1 (8)
DCR (CR+PR+SD), n (%)	12 (63)	12 (63)	12 (43)	20 (71)	9 (69)	10 (77)

Pavel, et al. ESMO 2012

Tumeurs carcinoïdes avancées
Everolimus: RADIANT-4

Tumeurs non sécrétantes

TNE pulmonaires ou digestives (G1/G2), bien différenciées, avancées, progressives, non fonctionnelles (n = 302)

- Absence de syndrome carcinoïde (présent ou historique)
- Maladie avancée histologiquement prouvée
- Inclusion dans les 6 mois suivant la progression radiologique

2:1

R

- Evérolimus 10 mg/day (n = 205)
- Placebo (n = 97)

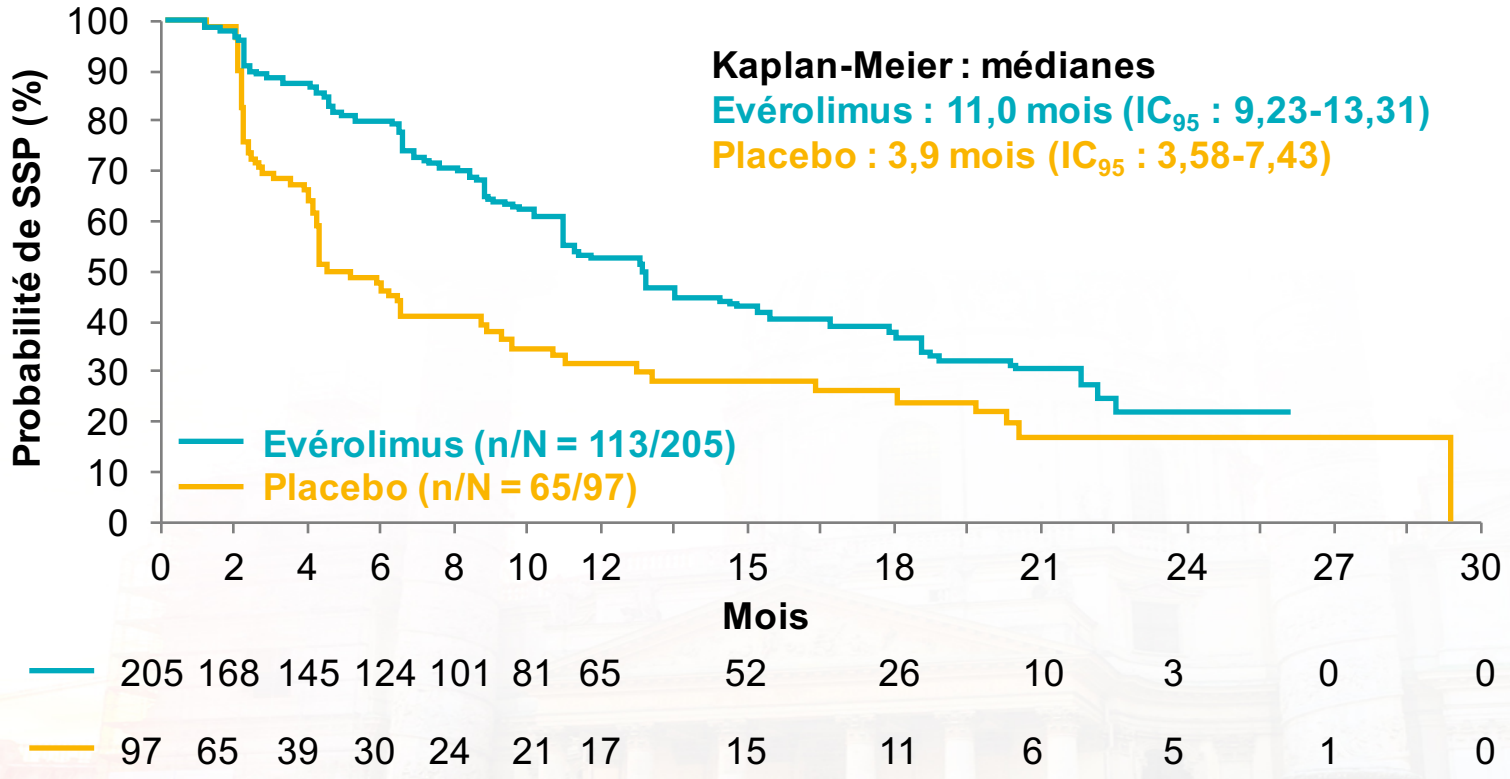
Traitement jusqu'à progression, toxicité inacceptable ou sortie volontaire du patient

- **Objectif(s) :**
  - **Principal : SSP (central)**
  - **Secondaires +++ : SG**
  - **Secondaires (autres) : RO, durée de la RO, tolérance, qualité de vie (FACT-G), PS, NSE/CgA, cinétique**
- **Stratification :**
  - **Traitement antérieur par analogue d ela somatostatine (oui versus non)**
  - **Origine de la tumeur (stratum A versus B)**
  - **PS (0 versus 1)**

ESMO 2015 - D'après Yao JC et al., LBA5, actualisé

Tumeurs carcinoïdes avancées
Everolimus: RADIANT-4

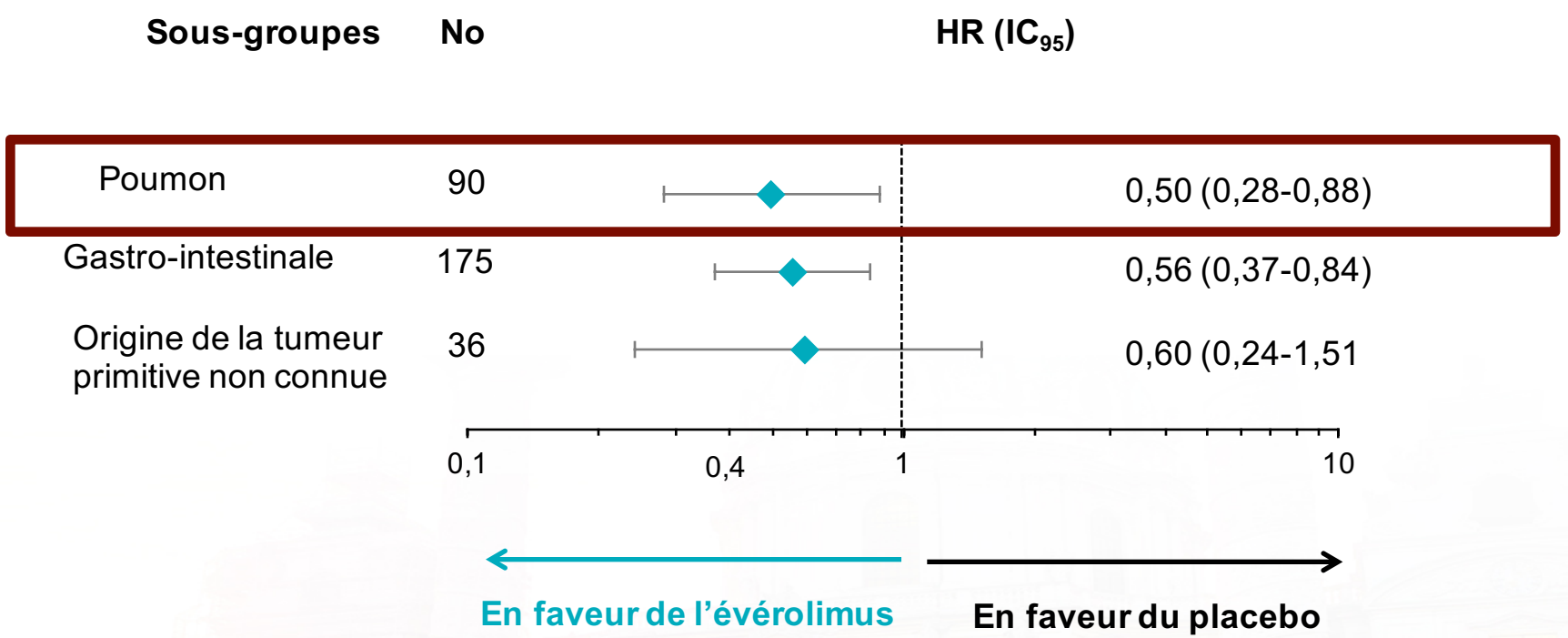
- **Réduction de 52 % du risque relatif de progression ou de décès avec l'évérolimus vs placebo**
- **HR = 0,48 (IC_{95} : 0,35-0,67) ; p < 0,00001**



ESMO 2015 - D'après Yao JC et al., LBA5, actualisé

Tumeurs carcinoïdes avancées
Everolimus: RADIANT-4

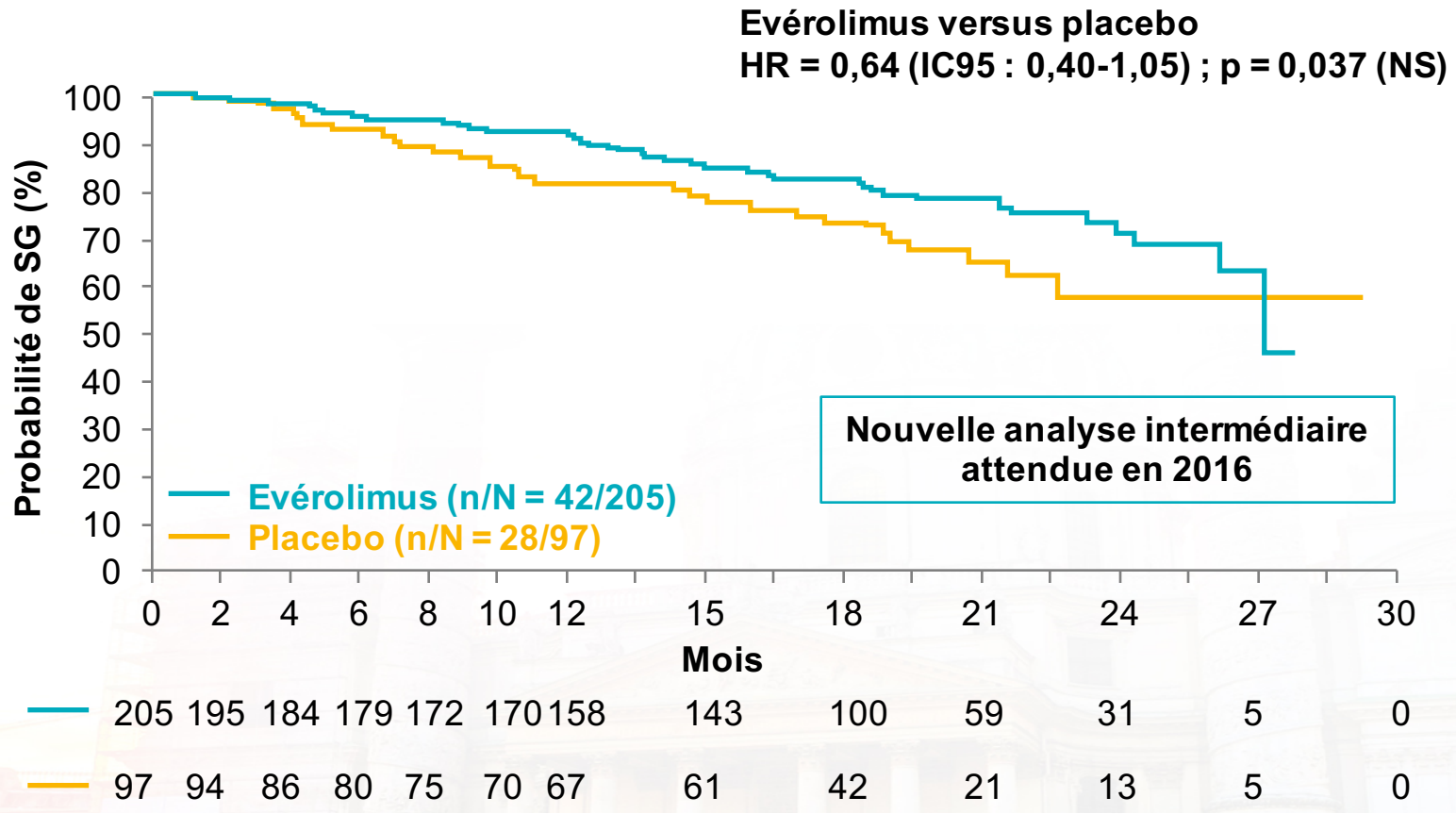
Tumeurs non sécrétantes



ESMO 2015 - D'après Yao JC et al., LBA5, actualisé

Tumeurs carcinoïdes avancées
Everolimus: RADIANT-4

- **Première analyse intermédiaire de la SG réalisée après 37% d'évènements : en faveur du bras Evérolimus**



ESMO 2015 - D'après Yao JC et al., LBA5, actualisé

Dans les carcinoïdes bronchiques:

Everolimus :

- Tumeurs sécrétantes
  - traitement de seconde ligne après échec d'analogues de la somatostatine pour les carcinoïdes typiques (grade 1) et atypiques (grade 2), en poursuivant les analogues

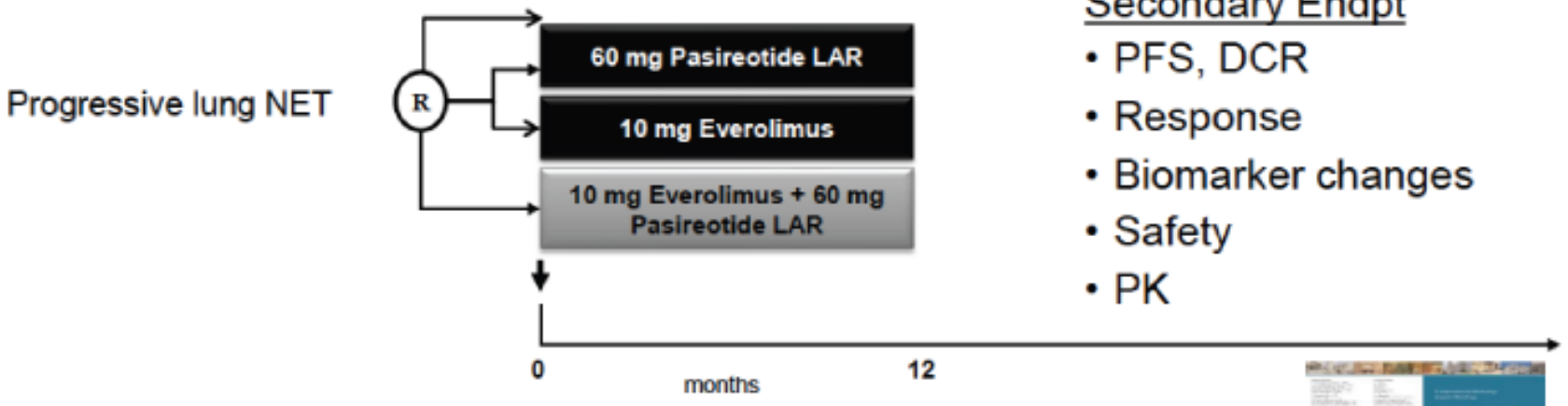
- Tumeurs non sécrétantes
  - traitement de seconde ligne après échec d'analogues si octreoscan positif
  - traitement de première ligne si octreoscan négatif?

- Pas d'indication en adjuvant

Quelle stratégie?

LUNA: Phase II Study in lung NET

- Advanced metastatic or inoperable lung or thymic NET Randomized multicenter phase II study
- 112 patients in 3 arms (28/arm)



Primary EndPt

- Proportion of pts. progression free at 12 months

Secondary Endpt

- PFS, DCR
- Response
- Biomarker changes
- Safety
- PK

Pasireotide
Analogue de sst 1, 2, 3, 5

Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids

M. E. Caplin[1*], E. Baudin[2], P. Ferolla[3], P. Filosso[4], M. Garcia-Yuste[5], E. Lim[6], K. Oberg[7], G. Pelosi[8], A. Perren[9], R. E. Rossi[1,10] & W. D. Travis[11] the ENETS consensus conference participants[†]

[1]Neuroendocrine Tumour Unit, Royal Free Hc
Roussy, Université Paris Sud, Villejuif Cedex, I
Surgery, University of Torino, Torino, Italy; [5]De

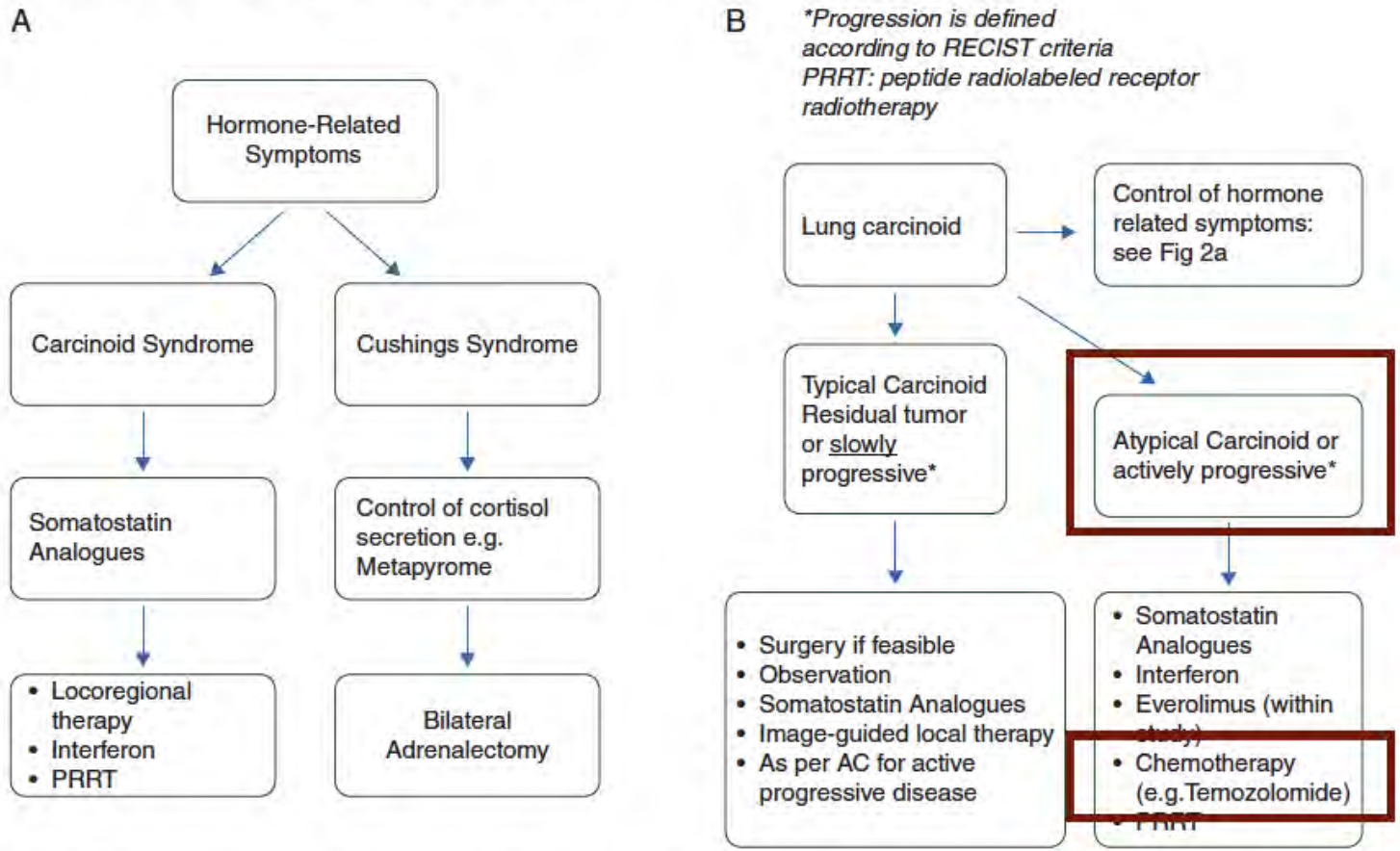


Figure 2. (A) ENETS recommendations for the control of hormone-related symptoms. (B) ENETS recommendations for the control of hormone-related symptoms and tumor growth. *Progression is defined according to RECIST criteria. PRRYT: peptide radiolabeled receptor radiotherapy.

Tumeurs carcinoïdes avancées
Chimiothérapie

Regimen	Tumor Type	No. of Patients	PR/CR (%)	Median PFS (months)	Median OS (months)	Study (year)
STZ + doxorubicin	PNET	16	6	NA	NA	Cheng (1999)[21]
Dacarbazine	Carc	56	16	NA	20	Bukowski (1994)[22]
Dacarbazine	Carc	7	14	NA	NA	Ritzel (1995)[23]
FU + IFN-α	Carc/PNET	24	21	8	23	Andreyev (1995)[24]
Mitoxantrone	Carc/PNET	30	7	NA	16	Neijt (1995)[25]
Paclixatel	Carc/PNET	24	4	3	18	Ansell (2001)[26]
STZ + FU + doxorubicin	PNET	84	39	18	37	Kouvaraki (2004)[27]
Doxorubicin + FU	Carc	85	13	5	16	Sun (2005)[28]
STZ + FU	Carc	78	15	5	24	Sun (2005)[28]
Irinotecan + FU	Carc/PNET	20	5	5	15	Ducreux (2006)[29]
Oxaliplatin + capecitabine	Well-differentiated NET	27	30	NA	40	Bajetta et al (2007)[30]

Kwekkeboom et al. J Clin Oncol 26:2124

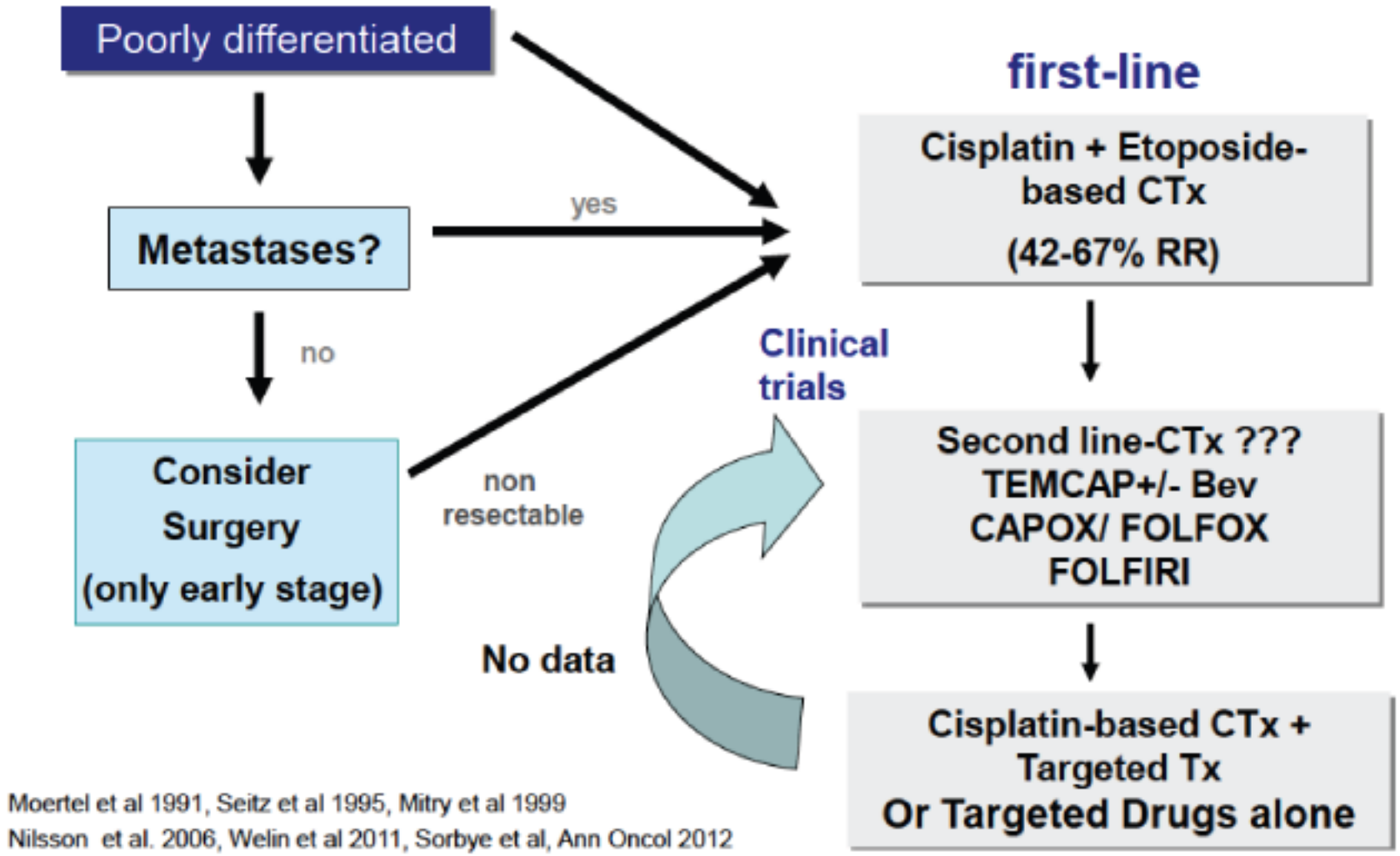
Tumeurs carcinoïdes avancées
Platine et etoposide

Study	Number	Primary		OR	Duration months
Moertel, 1991	27	Mixed		7%	4-6
Mitry, 1999	12	Mixed		9%	8
Fjallskog, Granberg, 2000	18	Bronchial-thymus		39%	9
Wirth, 2004	15	Bronchial		20%	11-102

Tumeurs carcinoïdes avancées
Temozolomide

Authors (n)	TMZ Regimen	Pancreas (n)	Ileum (n)	Bronchial (n)	Others (n)
Ekeblad S 2007 (36)	100-200 mg/m2 5d	8% (12)	_	31% (13)	0 PR (11)
Kulke M 2009 (89)	Various	34% (53)	0 (19)	13% (8)	0 (17)
Maire F NE 2009 (21)	150-200 mg/m2 5d	25 % (4)	0 (10)	-	0 (7)
Lindhom ENETS 2011 (23)	100-200 mg/m2 5d	-	-	17% (23)	-

Tumeurs carcinoïdes avancées
Algorithme de chimiothérapie



Moertel et al 1991, Seitz et al 1995, Mitry et al 1999
Nilsson et al. 2006, Welin et al 2011, Sorbye et al, Ann Oncol 2012

Pavel. ESMO 2014

Tumeurs carcinoïdes bronchiques avancées
Chimiothérapie en pratique

Lung Cancer (2004) 44, 213–220

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Outcome of patients with pulmonary carcinoid tumors receiving chemotherapy or chemoradiotherapy

Lori J. Wirth[a,b,c,*], Mark R. Carter[d], Pasi A. Jänne[a,b,c], Bruce E. Johnson[a,b,c]

Table 2 Patient response and survival

Patient	Final histology	Stage	Treatment	Response	Survival (months)	Cause of death
1	TC	IV	EP/CAV	PR	102	N/A
2	TC	IB	EP + TRT	SD	60+	Alive
			EP	CR		
3	TC	IV	PAC/CPT-11	SD	10	PD
4	TC	IIIA	EC	SD	10+	Alive
			EP	PD		
5	TC	IV	DOC	PD	6	PD
6	TC	IV	EC	SD	10+	Alive
7	TC	IB	EP	SD	6+	Alive
8	TC	IV	EC	PD	11	Pneumonia
9	AC	IIIA	EP + PAC, then EP + TRT	SD	10+	Alive
10	AC	IIIA	EP + TRT	SD	8+	Alive
11	AC	IIIB	DOC/CPT-11	SD	15+	Alive
12	AC	IV	EC	PD	23	PD
13	AC	IV	EP + PAC	PR	11	N/A
			EP	SD		
14	AC	IV	C/PAC	SD	20	N/A
			EC	PD		
15	AC	IIIB	PAC + TRT	PR	84	N/A
16	AC	IV	DOC	PD	20	N/A
17	AC	IV	EC	SD	15+	Alive
18	AC	IV	EC	allergy	9+	Alive
			P/CPT-11	PD		

Abbreviations: TC, typical carcinoid; AC, atypical carcinoid; PR, partial response; CR, complete response; SD, stable disease; PD, progressive disease; N/A, not available; DOC, docetaxel; E, etoposide; P, cisplatin; CAV, cyclophosphamide, doxorubicin and vincristine; C, carboplatin; PAC, paclitaxel; CPT-11, irinotecan; TRT, thoracic radiotherapy.

GEMOX et FOLFOX dans les carcinoïdes pulmonaires

- Analyse rétrospective de 42 patients atteints d'un carcinoïde pulmonaire métastatique, traités par GEMOX (n = 21) ou FOLFOX (n = 21)
- Carcinoïde typique (20 %) ; carcinoïde atypique (54 %) ; non précisé (26 %)
- 79 % progressifs avant de débuter la chimiothérapie
- Traitement en 1re ligne (19 %), 2e ligne (33 %) ou au delà de la 2e ligne (47 %)

	FOLFOX	GEMOX	Tous
Patients (n)	21	21	42
Nombre médian de cycles (range)	7 (1-12)	7 (4-11)	7 (1-12)
RO, n (%)	3 (14)	4 (19)	7 (17)
SD, n (%)	13 (62)	16 (76)	29 (69)
PD, n (%)	3 (14)	1 (5)	4 (9)
Not available, n (%)	2 (9)	0 (0)	2 (5)
SSP médiane, mois (IC)	14 (0-27)	17 (7-27)	14 (7-21)
SG médiane, mois (IC)	30 (13-45)	41 (9-62)	35 (21-49)

➜ **Le traitement par GEMOX ou FOLFOX semble prometteur dans les carcinoïdes pulmonaires**

ENETS 2015 - D'après Walter T et al. Poster J12 actualisé

Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids

M. E. Caplin[1*], E. Baudin[2], P. Ferolla[3], P. Filosso[4], M. Garcia-Yuste[5], E. Lim[6], K. Oberg[7], G. Pelosi[8], A. Perren[9], R. E. Rossi[1,10] & W. D. Travis[11] the ENETS consensus conference participants[†]

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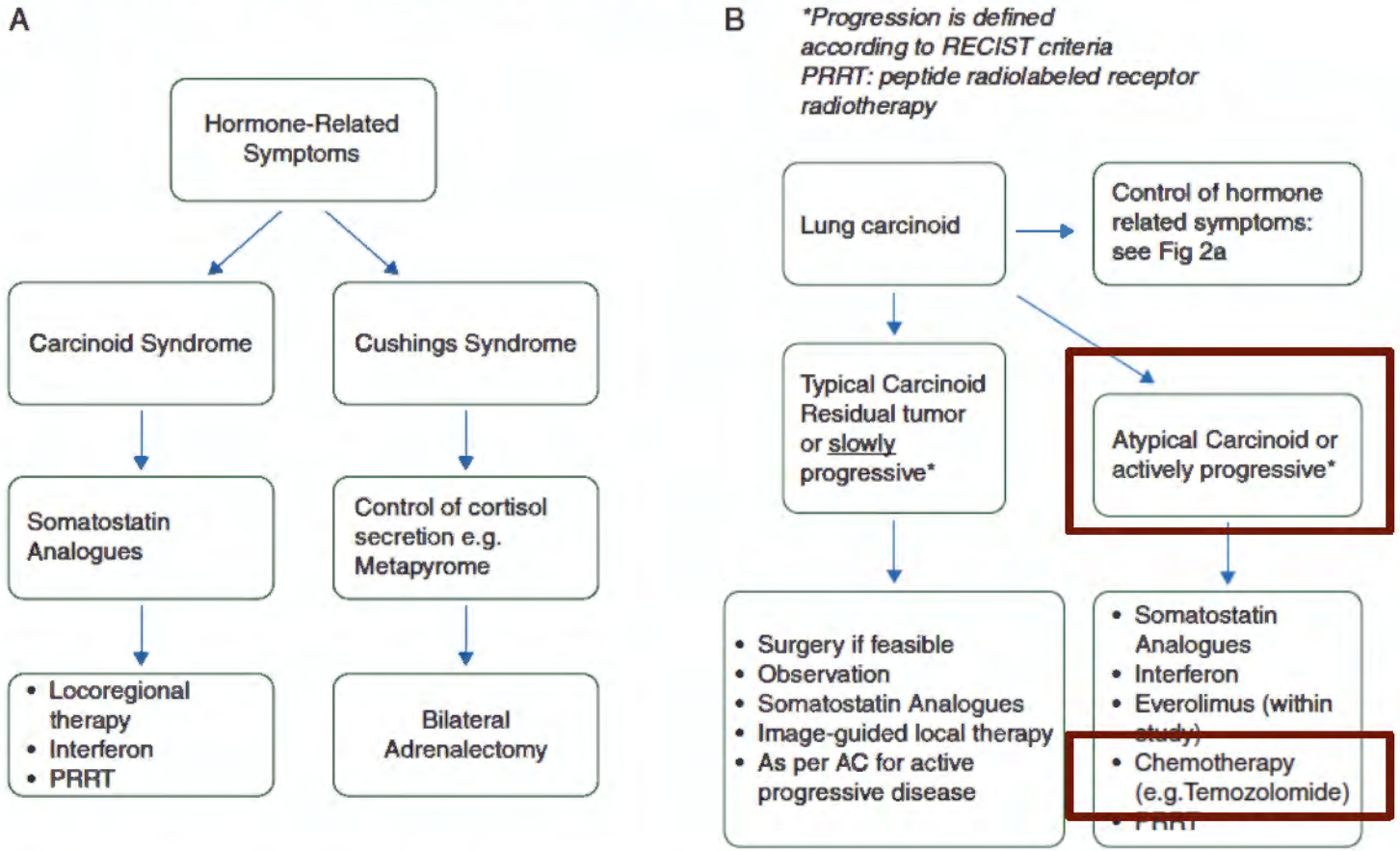
Surgery, University of Torino, Torino, Italy; [5]D



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Sunitinib Malate for the Treatment of Pancreatic Neuroendocrine Tumors

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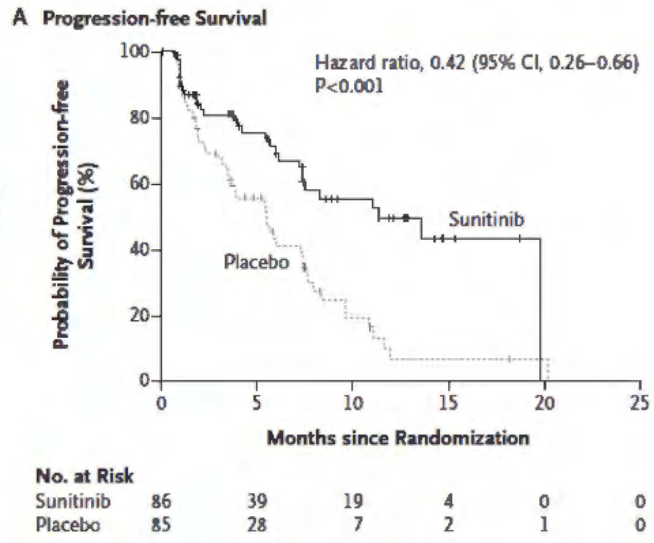
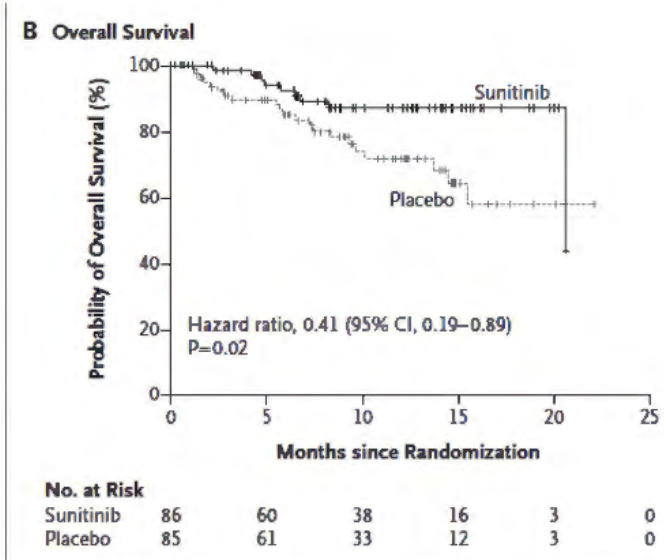
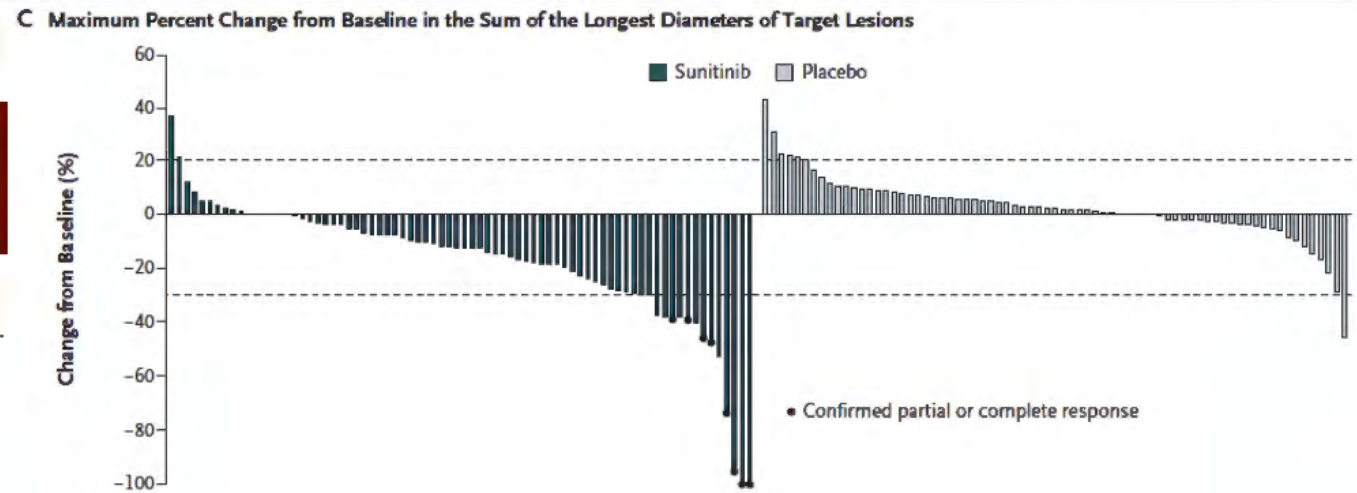




Objective tumor response		
Best observed RECIST response — no. (%)		
Complete response	2 (2)	0
Partial response	6 (7)	0
Stable disease	54 (63)	51 (60)
Progressive disease	12 (14)	23 (27)
Could not be evaluated	12 (14)	11 (13)
Objective response rate — %	9.3	0



A multi-institutional, phase II open-label study of ganitumab (AMG 479) in advanced carcinoid and pancreatic neuroendocrine tumors

J R Strosberg, J A Chan[1], D P Ryan[2], J A Meyerhardt[1], C S Fuchs[1], T Abrams[1], E Regan[1], R Brady[1], J Weber, T Campos, L K Kvols and M H Kulke[1]

Correspondence should be addressed

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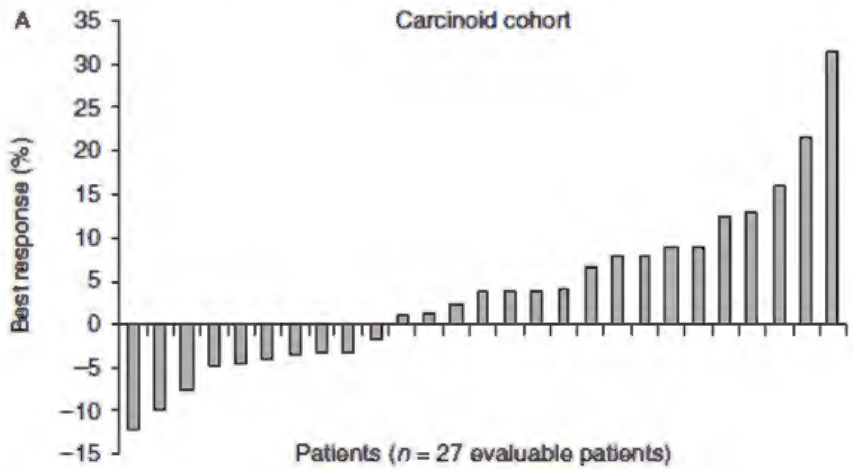

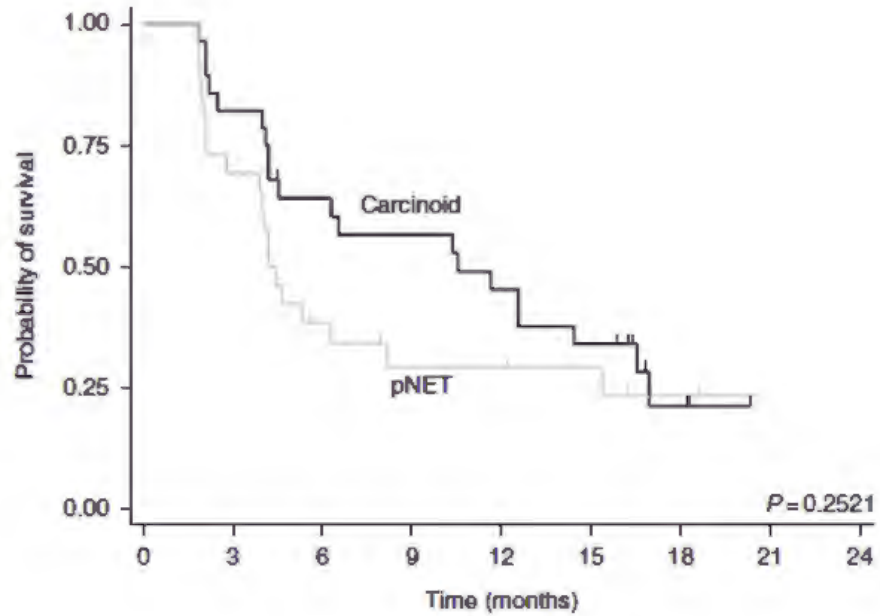

Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids

M. E. Caplin[1*], E. Baudin[2], P. Ferolla[3], P. Filosso[4], M. Garcia-Yuste[5], E. Lim[6], K. Oberg[7], G. Pelosi[8], A. Perren[9], R. E. Rossi[1,10] & W. D. Travis[11] the ENETS consensus conference participants[†]

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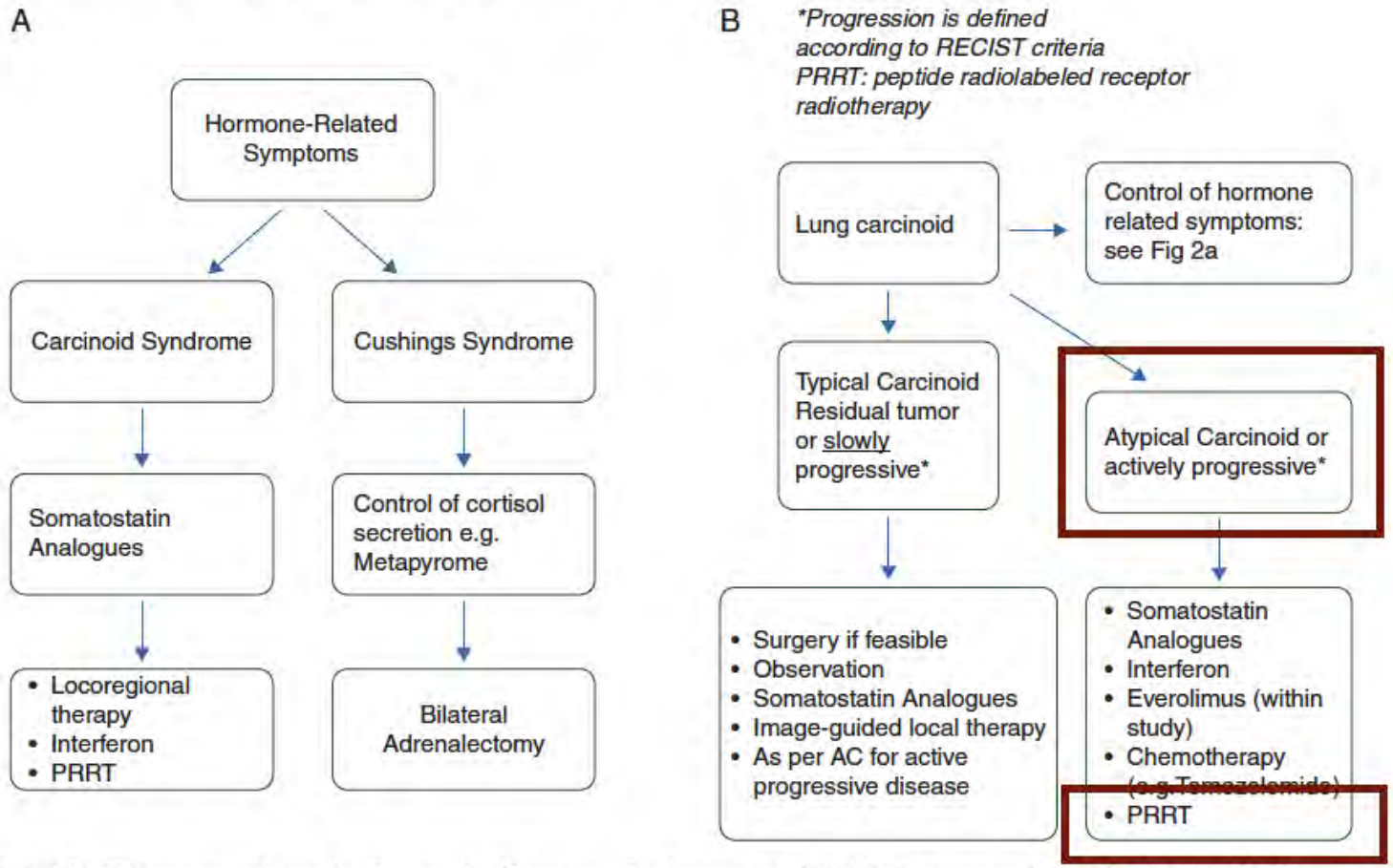
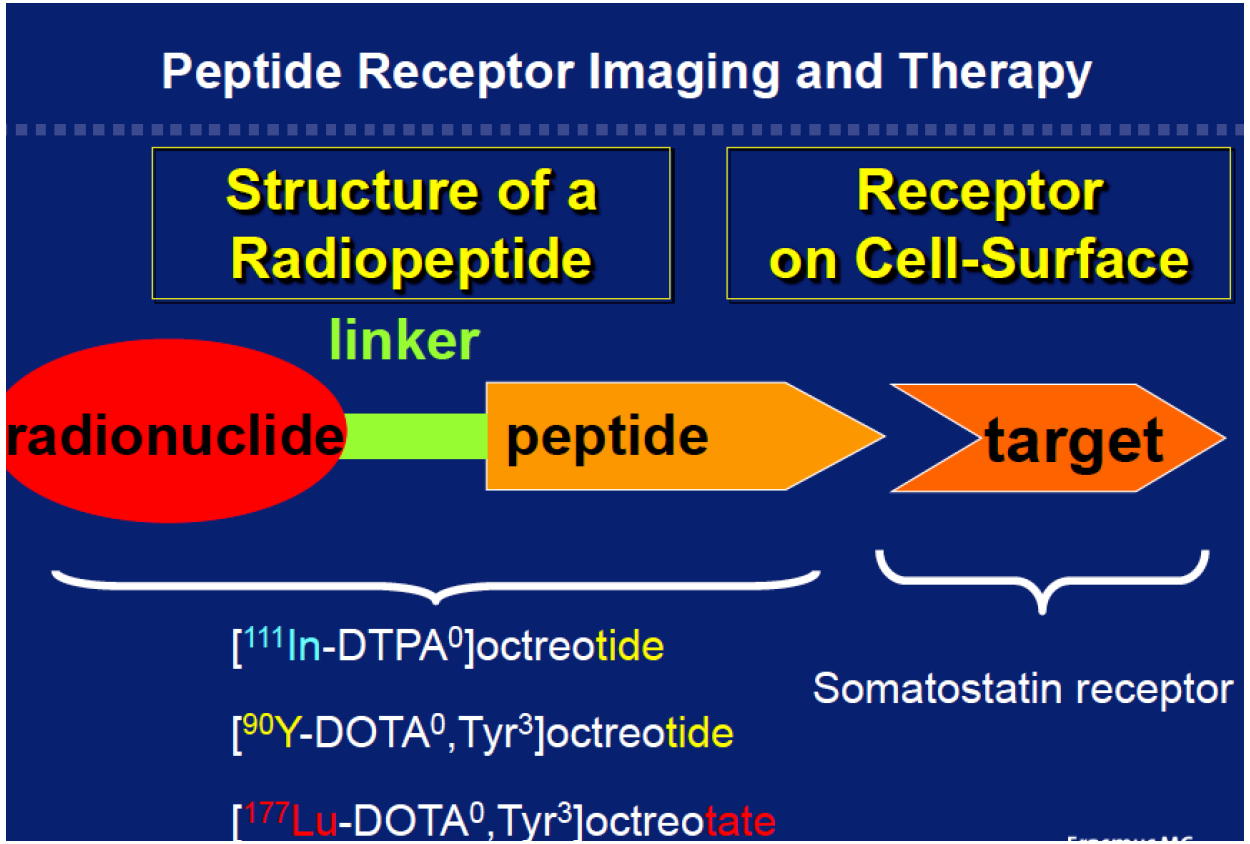
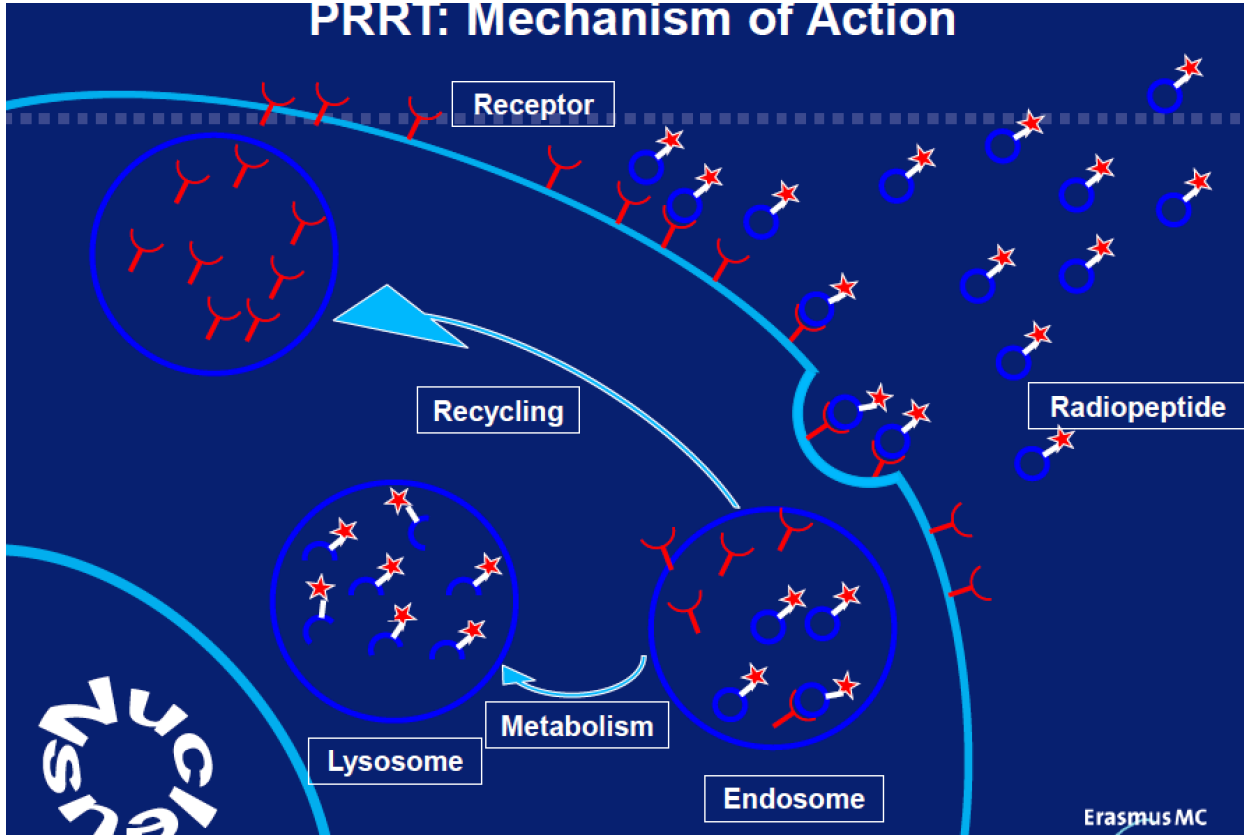


Figure 2. (A) ENETS recommendations for the control of hormone-related symptoms. (B) ENETS recommendations for the control of hormone-related symptoms and tumor growth. *Progression is defined according to RECIST criteria. PRRYT: peptide radiolabeled receptor radiotherapy.

Tumeurs carcinoïdes avancées
Radiothérapie métabolique





Tumeurs carcinoïdes avancées
Radiothérapie métabolique

Indications:

- Tumeurs avancées, non opérables, métastatiques
- Hypermétabolisme en octreoscan, supérieur au tissu hépatique
- Pas de traitement antérieur par radiothérapie métabolique
- Hémogramme et fonction hépatique normaux

En pratique:

- Service de médecine nucléaire
- Bale, Rotterdam
- Anti-émétiques, perfusion de 30 min, hospitalisation 1 nuit

Plusieurs traceurs:

- [^{111}In-DTPA^{0}]octreotide
- [^{90}Y-DOTA^{0},Tyr^{3}]octreotide
- [^{90}Y-DOTA^{0}]lanreotide
- [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate
- [^{177}Lu-DOTA^{0},Tyr^{3}]octreotide
- [^{90}Y-DOTA^{0},Tyr^{3}]octreotate

Tumeurs carcinoïdes avancées
Radiothérapie métabolique

PRRT: Adverse events

- ^{90}Y-DOTATOC: Renal insufficiency in 1-3.5% (3 studies); MDS in 2% of patients (1 study).
- ^{90}Y-DOTATOC: Renal insufficiency in 9% in 1 study; not all had amino acid protection; poor baseline kidney function not excluded.
- ^{177}Lu-DOTA-Octreotate: Renal insufficiency in 0.5%; MDS in 1% in 1 study.
- ^{177}Lu-DOTA-Octreotate update in 279 Dutch patients (long follow-up): 2 renal insufficiencies; 2 Leukemias (1 CML, 1 AML); 4 MDS; 1 pancytopenia > 6mo (2 bone marrow biopsies: no MDS). 9/279 = 3%

Tumeurs carcinoïdes avancées
Radiothérapie métabolique

PRRT in GEPNET Patients: Tumor Response

Center	Ligand	Patients	CR+PR
Rotterdam (Valkema 2002)	[^{111}In-DTPA^{0}]octreotide	26	0%
New Orleans (Anthony 2002)	[^{111}In-DTPA^{0}]octreotide	26	8%
Milan (Bodei 2003)	[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	21	29%
Basel (Waldherr 2001/2)	[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	74	24%
Basel (Waldherr 2002)	[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	33	33%
Multicenter (Valkema 2006)	[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	58	9%
Multicenter (Bushnell 2010)	[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	90	4%
Copenhagen (Pfeifer 2011)	[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	53	23%
Warsaw (Cwikla 2010)	[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	58	23%
Rotterdam (Kwekkeboom 2008)	[^{177}Lu-DOTA^{0},Tyr^{3}]octreotate	310	29%
Gothenburg (Sward 2010)	[^{177}Lu-DOTA^{0},Tyr^{3}]octreotate	26	38%
Lund (Garkavij 2010)	[^{177}Lu-DOTA^{0},Tyr^{3}]octreotate	12	17%
Milan (Bodei 2011)	[^{177}Lu-DOTA^{0},Tyr^{3}]octreotate	42	31%

Erasmus M

Kwekkeboom WCLC 2013

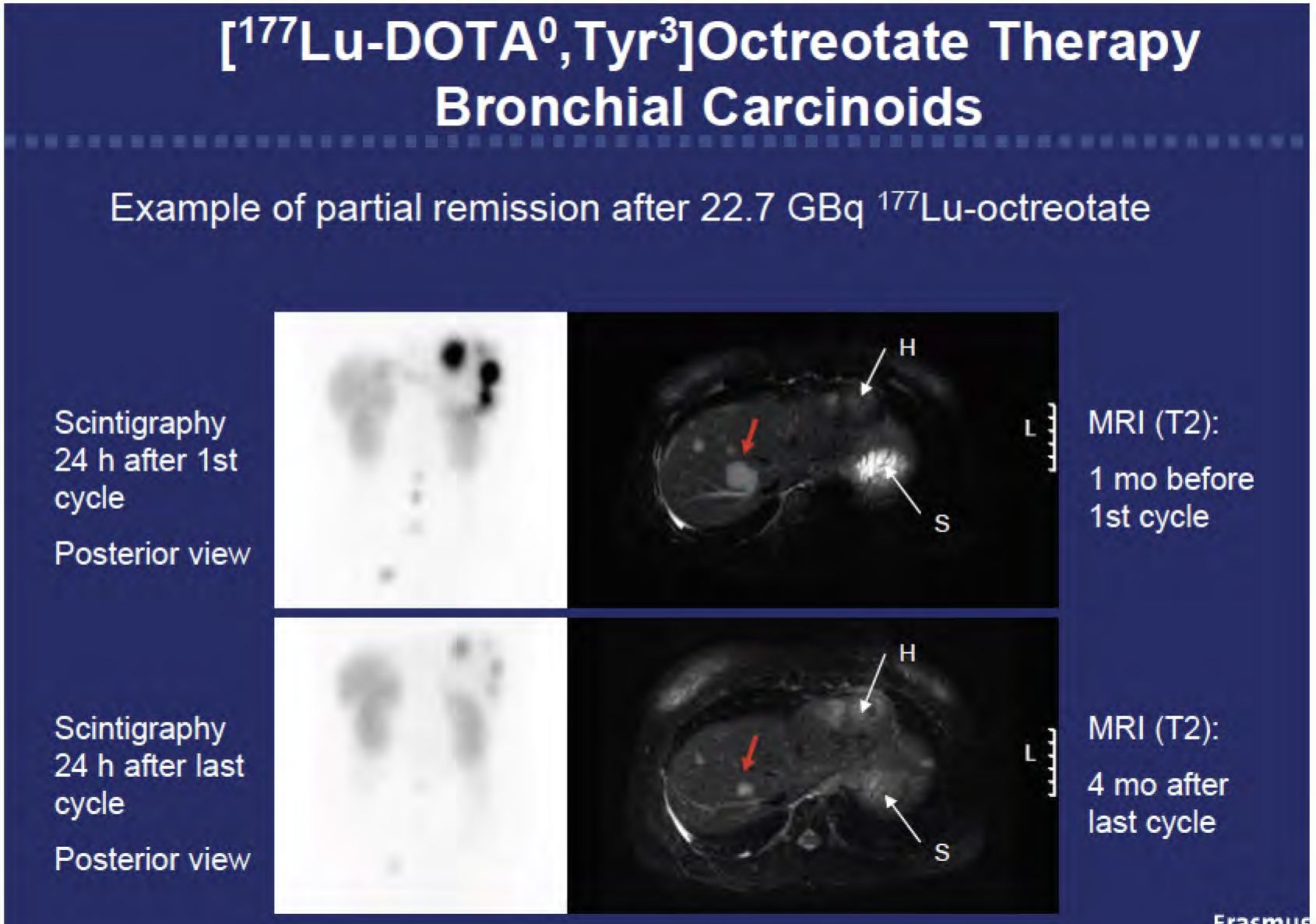
Tumeurs carcinoïdes avancées
Radiothérapie métabolique

PRRT in GEPNET Patients: Survival Data

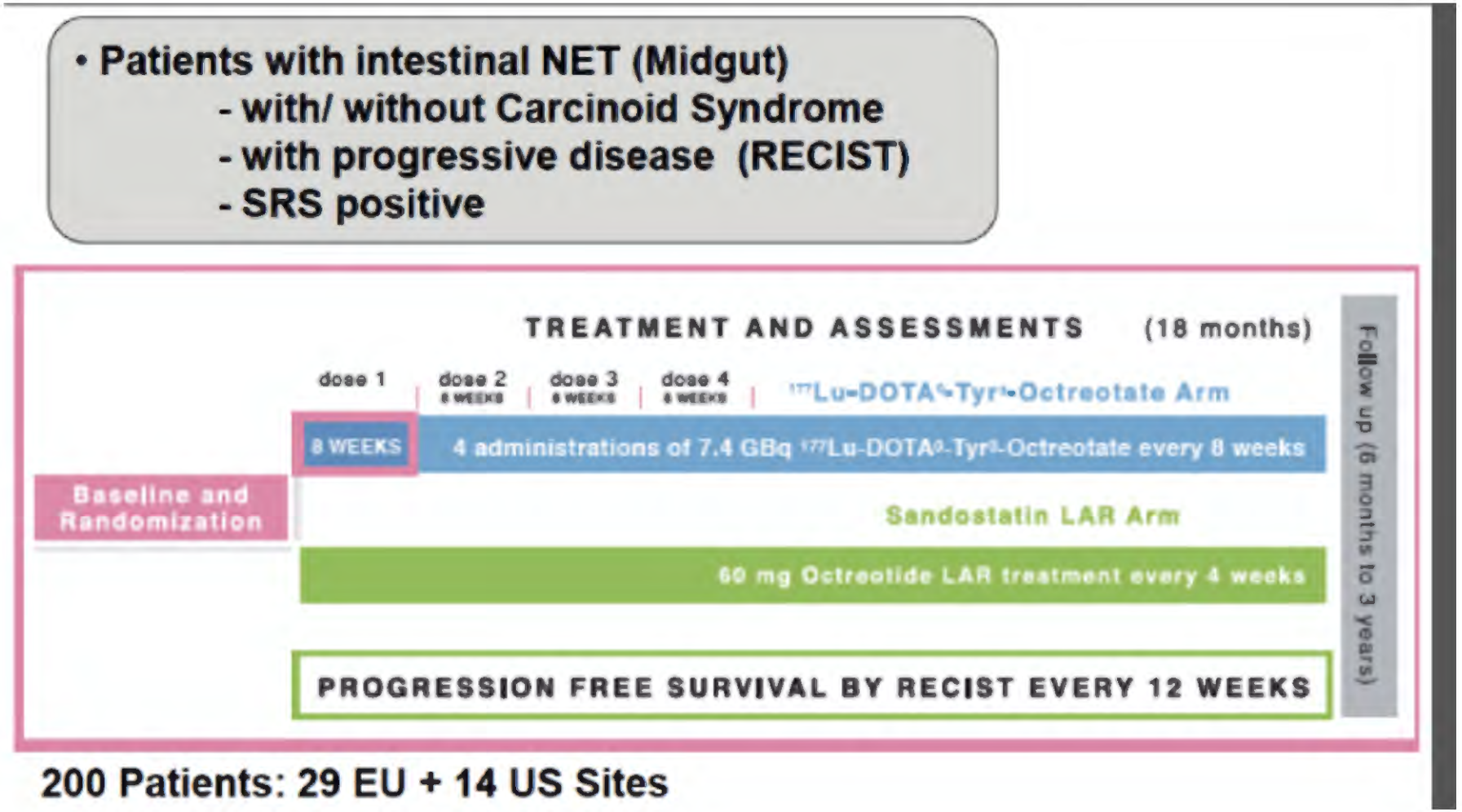
Center	Ligand	Patients	Liver Mets	PFS (mo)	OS (mo)
Multicenter (Valkema 2006)	^{90}Y-DOTATOC	58	-	29	37
Multicenter (Bushnell 2010)	^{90}Y-DOTATOC	90	72%	16	27
Copenhagen (Pfeifer 2011)	^{90}Y-DOTATOC	53	87%	29	-
Warsaw (Cwikla 2010)	^{90}Y-DOTATOC	58	85%	17	22
Rotterdam (Kwekkeboom 2008)	^{177}Lu-octreotate	310	89%	33	46

Kwekkeboom WCLC 2013

Tumeurs carcinoïdes avancées
Radiothérapie métabolique



Tumeurs carcinoïdes avancées
Radiothérapie métabolique: AAA trial



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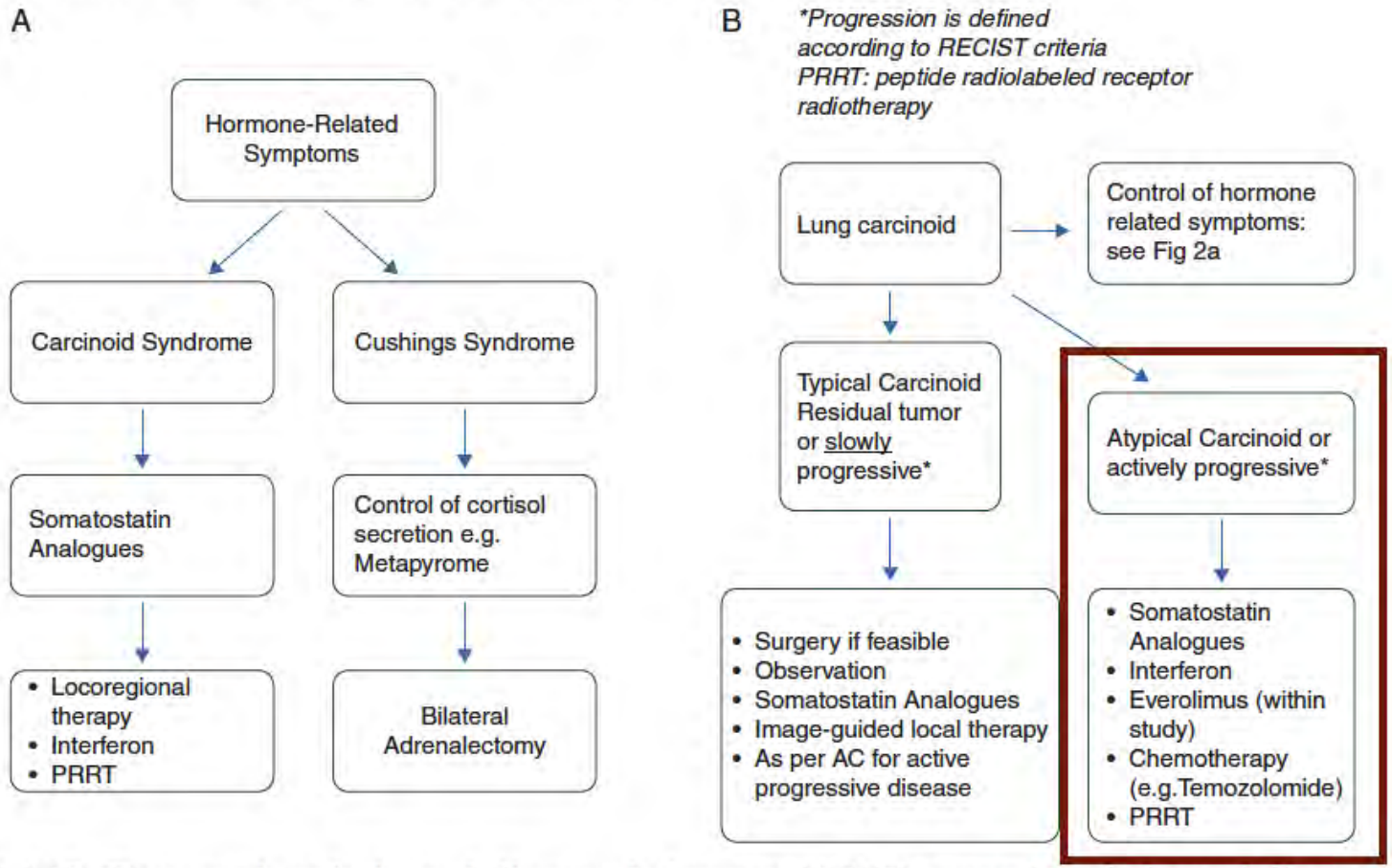

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Les carcinoïdes broncho-pulmonaires

Les tumeurs carcinoïdes

Anatomie pathologique

Stadification

Evaluation pré-thérapeutique

Traitement des tumeurs localisées

Traitement des tumeurs avancées

Réseau RENATEN

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