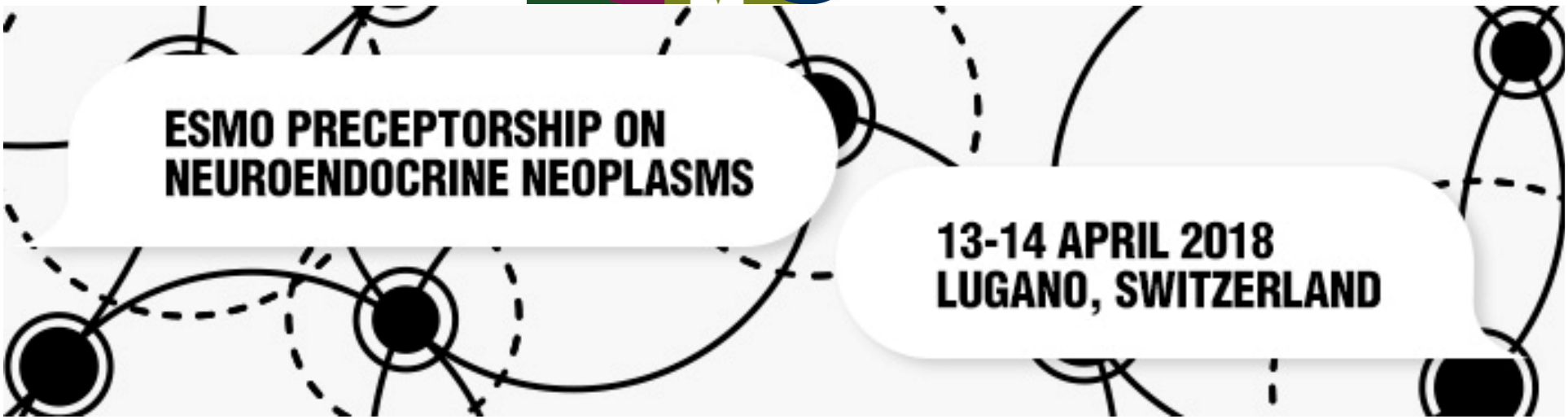
Session 5 – Lung NEN

Principles of diagnostic work-up and therapy

Aviral Singh MD, MSc
THERANOSTICS Center for Molecular Radiotherapy & Molecular Imaging
ENETS Center of Excellence, Zentralklinik Bad Berka, Germany

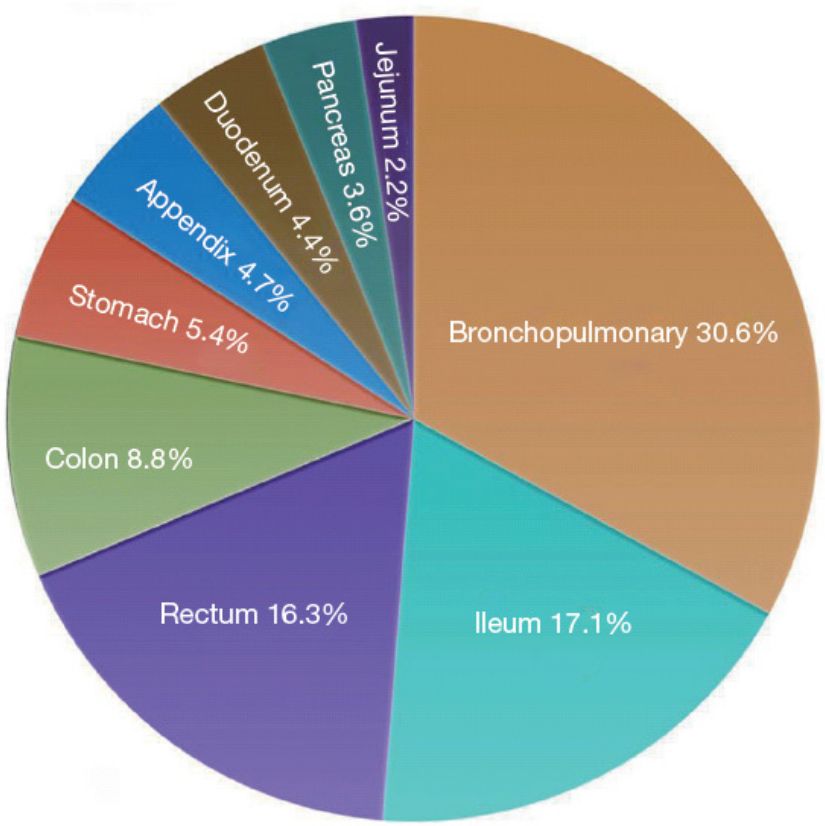
ESMO
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE



Disclosure Statement

No disclosures

Background – Lung / BP NEN



BP NETs arise from respiratory neuroendocrine cells.

Represent ~20% of all lung neoplasia and ~30% of all NETs.

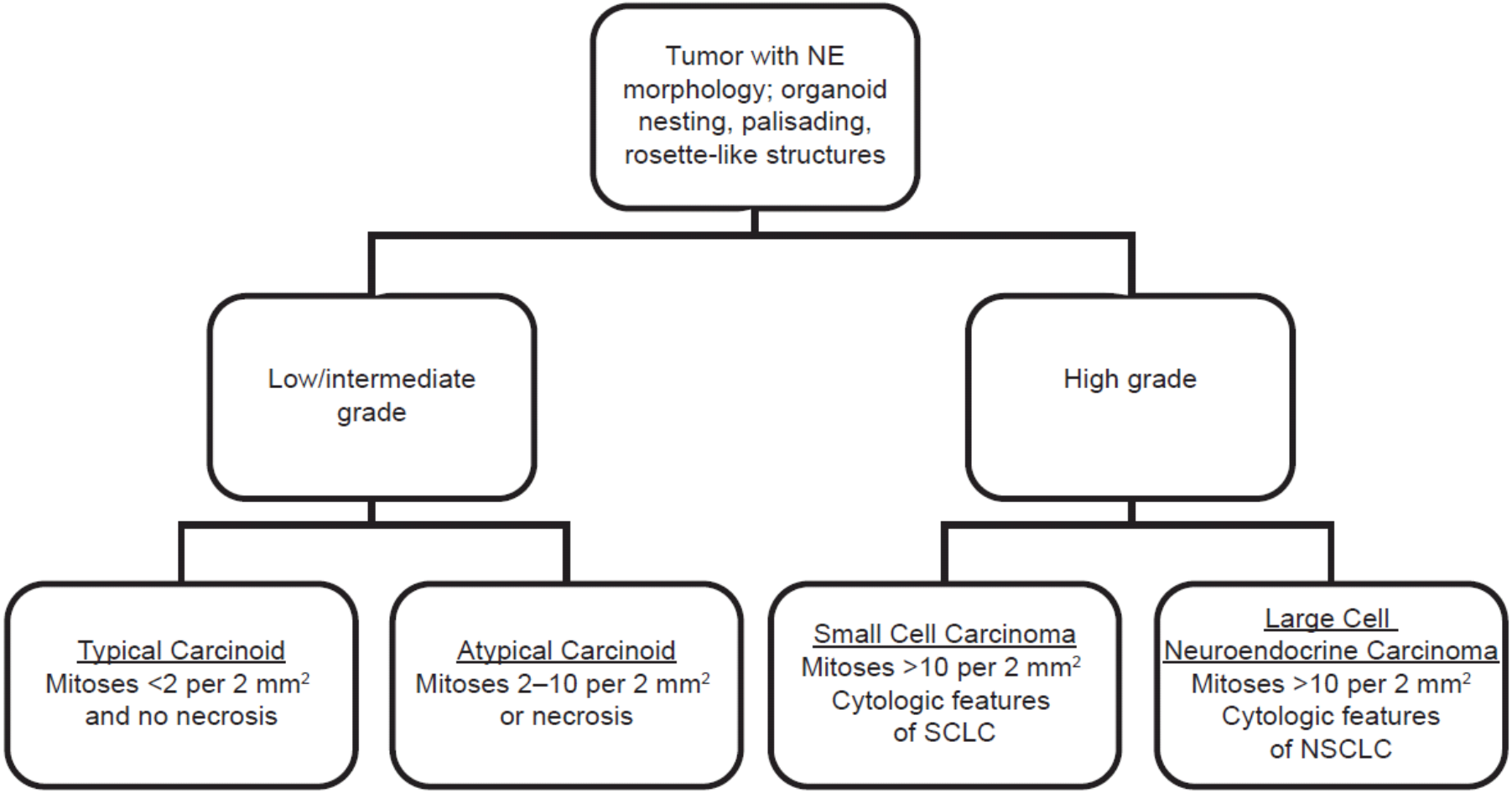
BP-NETs may present with cough, hemoptysis, and obstructive pneumonia but this depends on their site, size, and growth pattern.

Often identified incidentally on chest radiology.

Less than 5% exhibit hormonally-related symptoms such as carcinoid syndrome, Cushing, acromegaly, or SIADH.

Bodei et al. J Thorac Dis 2017;9(Suppl 15):S1511-S1523

Morphologic criteria for distinguishing lung NEN

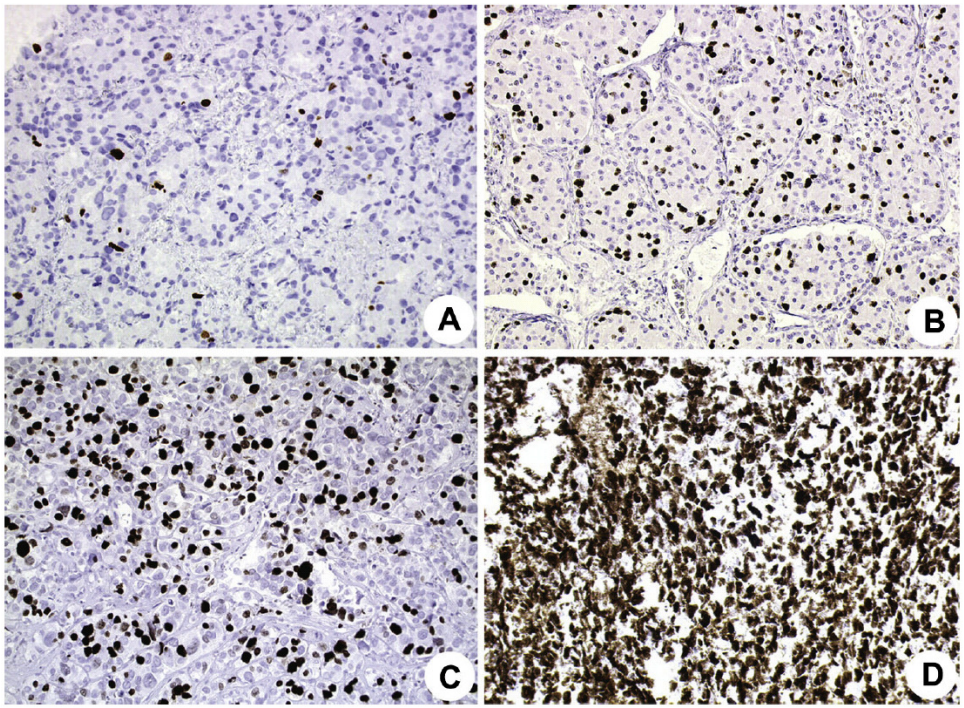


Tumors with neuroendocrine morphology are divided into the four subtypes primarily according to the number of mitoses and presence or absence of necrosis.

Hendifar et al. J Thoracic OnCol. 2017

Ki-67 index labeling distribution in the four subtypes of Lung NEN

Typical Carcinoid (TC)



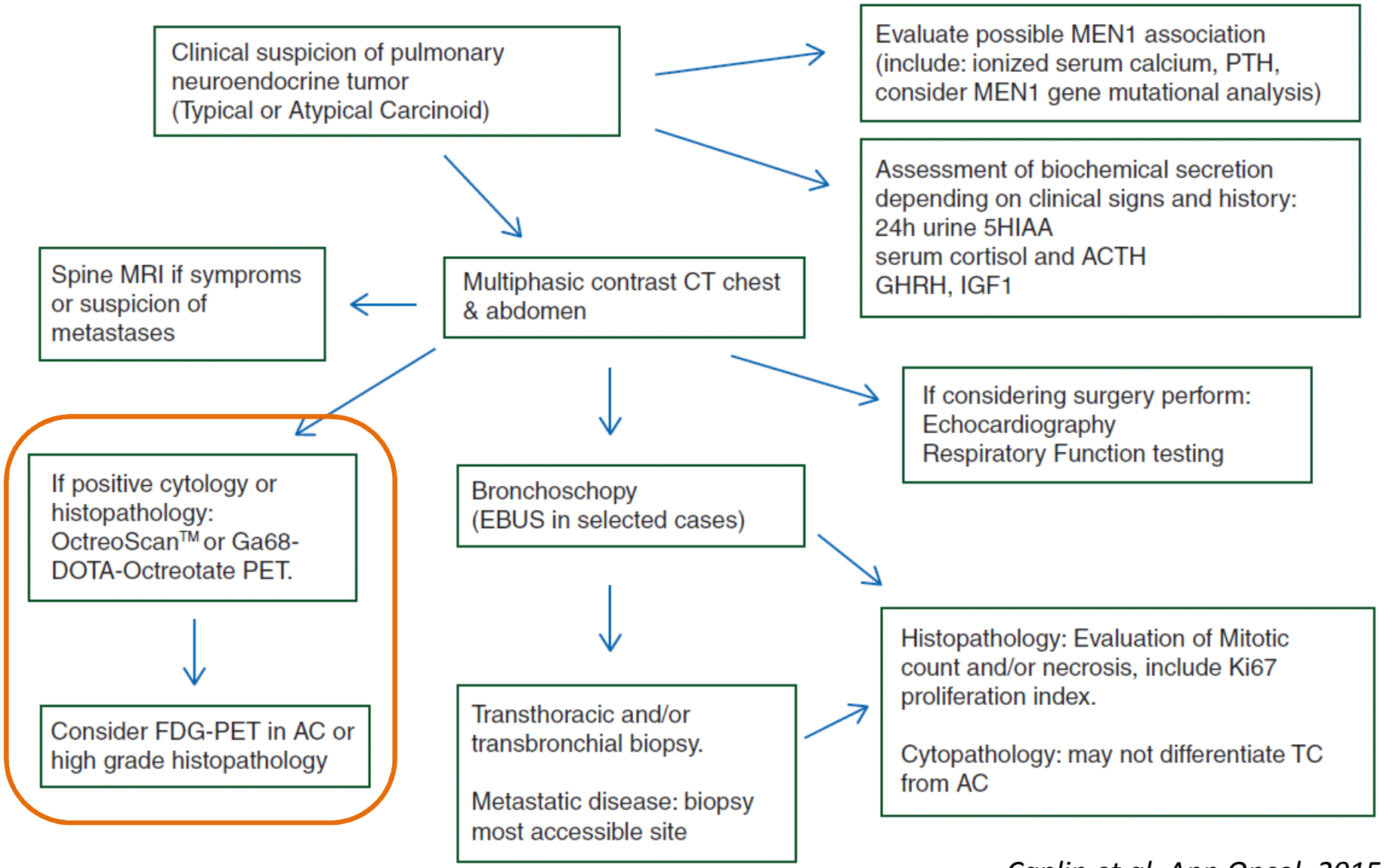
Atypical Carcinoid (AC)

Large Cell Neuroendocrine Carcinoma (LCNEC)

Small Cell Lung Cancer (SCLC)

Hendifar et al. J Thoracic OnCol. 2017

European Neuroendocrine Tumor Society (ENETS) algorithm for the diagnosis of Pulmonary NET – Role of Nuclear Medicine



Caplin et al. Ann Oncol. 2015

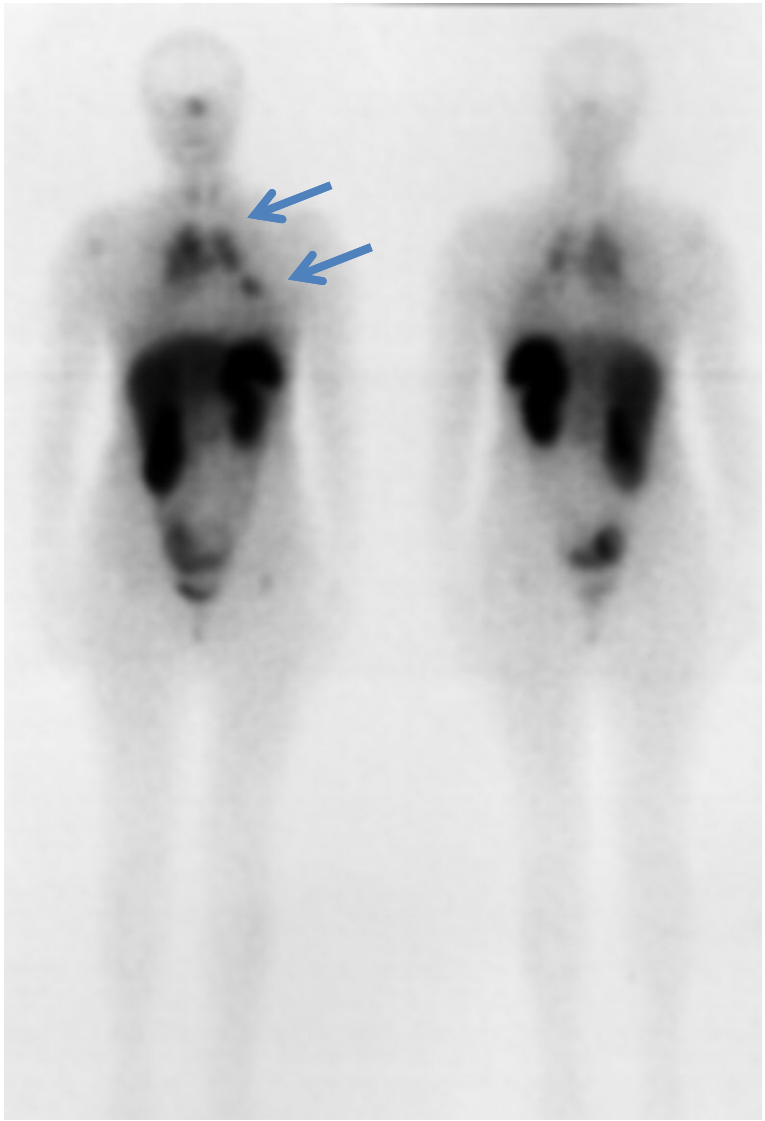
ENETS Consensus Recommendations for the Standards of Care in Neuroendocrine Neoplasms: Follow-Up and Documentation

Table 1. Tumor-specific recommendations for follow-up (in most cases life-long)

Organ	Status	F-U	Every	CgA	Markers[a]	Endoscopy	CT/MRI/US[b]	SRI[c]	FDG-PET	Comments
Bronchopulmonary										
Typical	resected	yes	6–12 m	yes	5-HIAA[d] relevant tumor hormones[d]	bronchoscopy[m] 5–10 y	6–12 m	12–36 m[e]		EBUS may be required if recurrence is suspected
Typical	residual tumor or metastases	yes	3–6 m	yes	5-HIAA[d] relevant tumor hormones[d]	bronchoscopy[m] 5–10 y	3–6 m	12–36 m[e]	12–24 m[l]	EBUS may be required if progression is suspected
Atypical	resected	yes	3–6 m	yes	5-HIAA[d] relevant tumor hormones[d]	bronchoscopy[m] 1–3 y	(3)–6 m	12–24 m[e,f]	12–24 m[l]	EBUS may be required if recurrence is suspected
Atypical	residual tumor or metastases	yes	3 m	yes	5-HIAA[d] relevant tumor hormones[d]	bronchoscopy[m] 1–3 y	3–6 m	12–24 m[e,f]	12–24 m[l]	EBUS may be required if progression is suspected
LCNEC poorly diff.	resected/ nonresected	yes	2–3 m	yes[d]	NSE[d] relevant tumor hormones[d]	bronchoscopy[m] if symptoms	2–3 m	12–24 m[e,f]	12–24 m[l]	bronchoscopy indicated if rebiopsy, argon-beam or bronchial stent is required; EBUS may be required if recurrence or progression is suspected
Thymic										
Typical	resected/ residual tumor or metastases	yes	6–12 m	yes	relevant tumor hormones[d]		6–12 m	12–36 m[e,f]	12–36 m[e,f]	
Atypical	resected/ residual tumor or metastases	yes	3–6 m	yes	relevant tumor hormones[d]		3–6 m	12–24 m[e,f]	6–24 m[e,f]	
Poorly diff.	resected/ nonresected	yes	2–3 m	yes[d]	relevant tumor hormones[d]		3–6 m	12–24 m[e,6]	6–24 m[e,f]	

Knigge et al. Neuroendocrinology. 2017

SSTR scintigraphy in Lung NEN

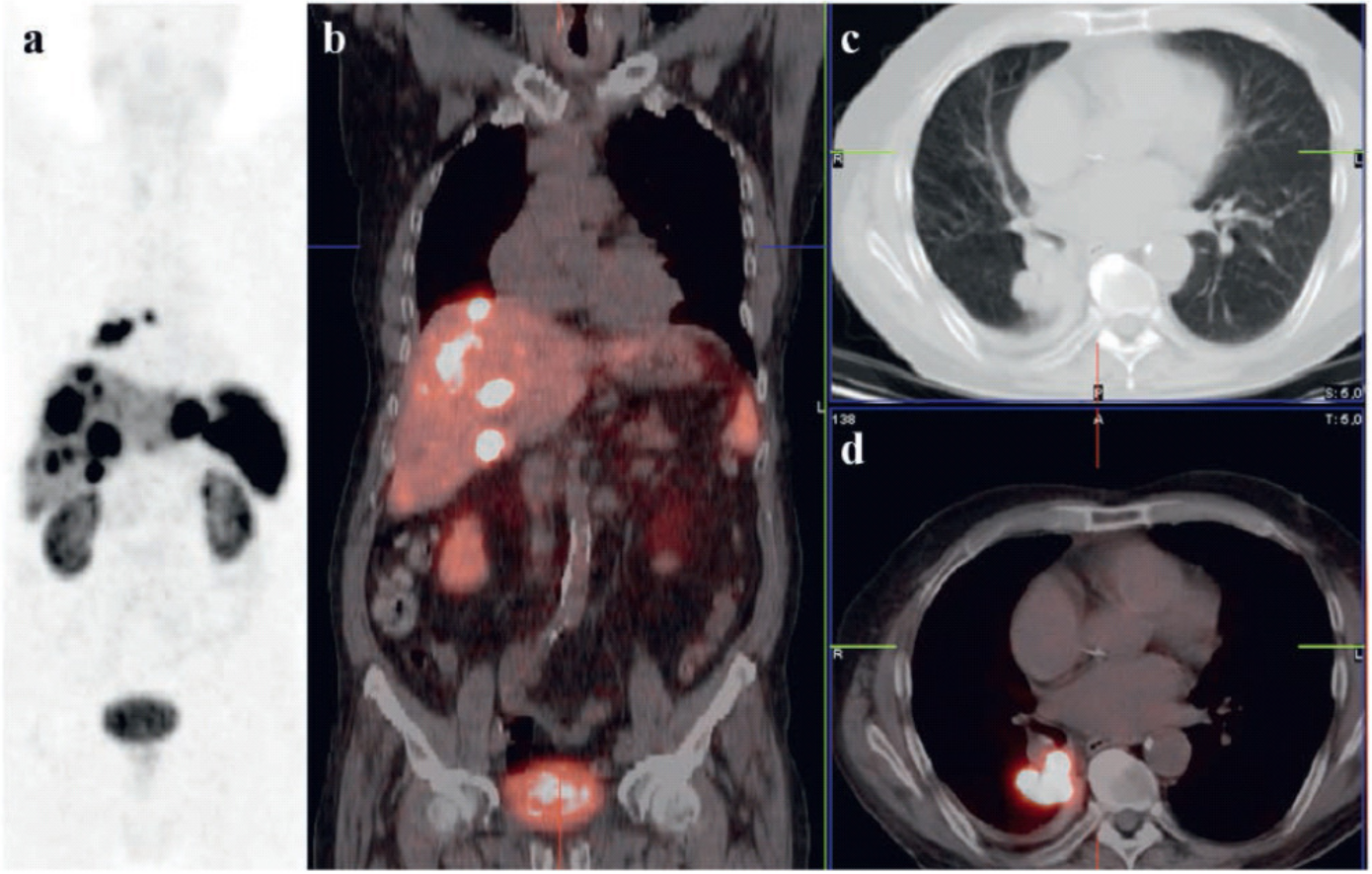


Anterior Posterior

SSTR scintigraphy with ^{111}In-pentetreotide (AP views) showing multiple foci in mediastinum and a new lesion in the left lung.

Patient previously treated with chemotherapy and hormone therapy for a lung carcinoid .

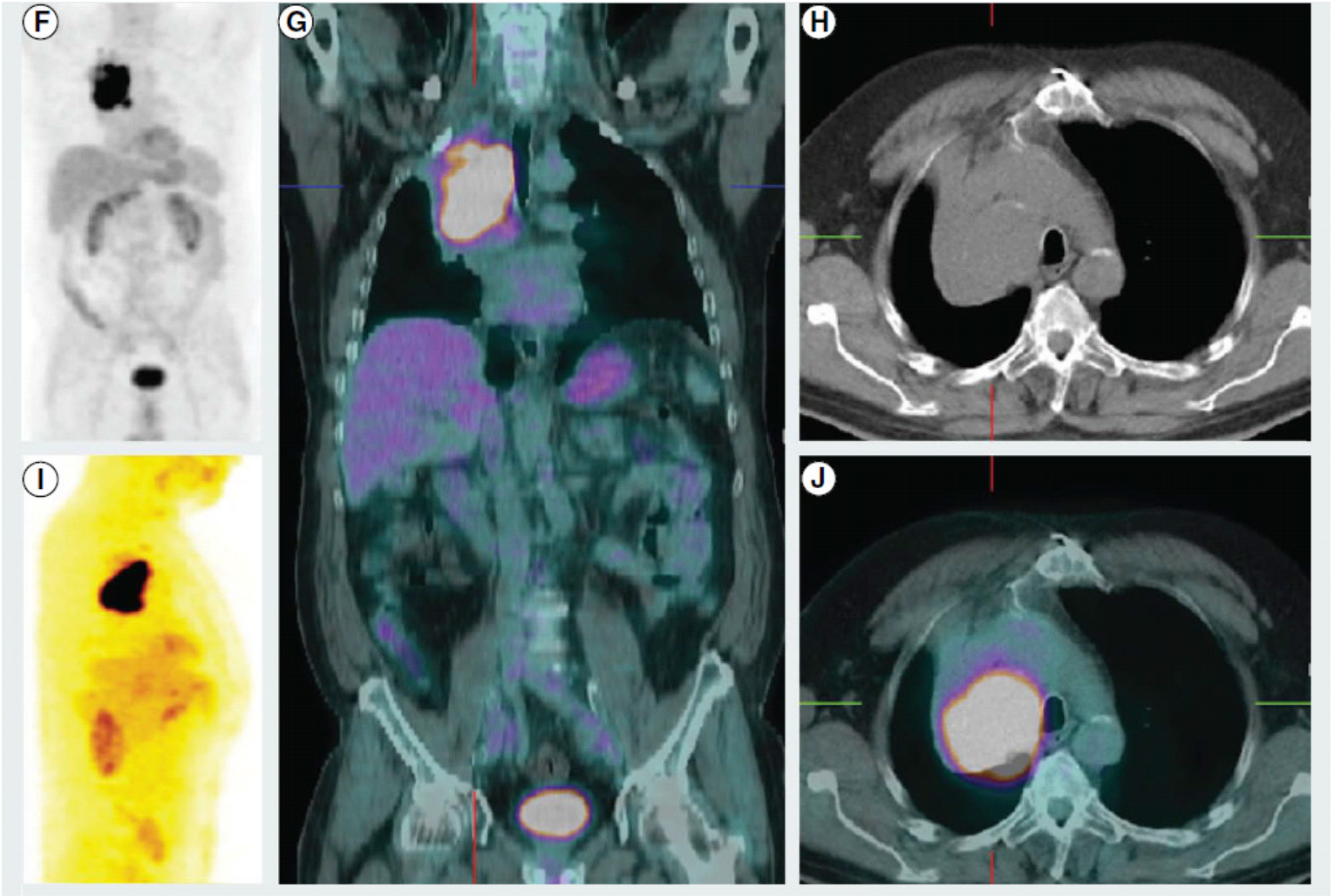
Ga-68 DOTANOC PET/CT in Lung NEN



69M, NEC of RML with mediastinal and hepatic metastases.
Initially treated with platin-based chemothrapy, interferon, lantreotide, then with STZ and doxorubicin. PD on restaging.
Ga-68 DOTANOC PET/CT demonstrated SSTR expression in primary as well as metastases. Received Lu-177 DOTATOC PRRT, resulting in PR.

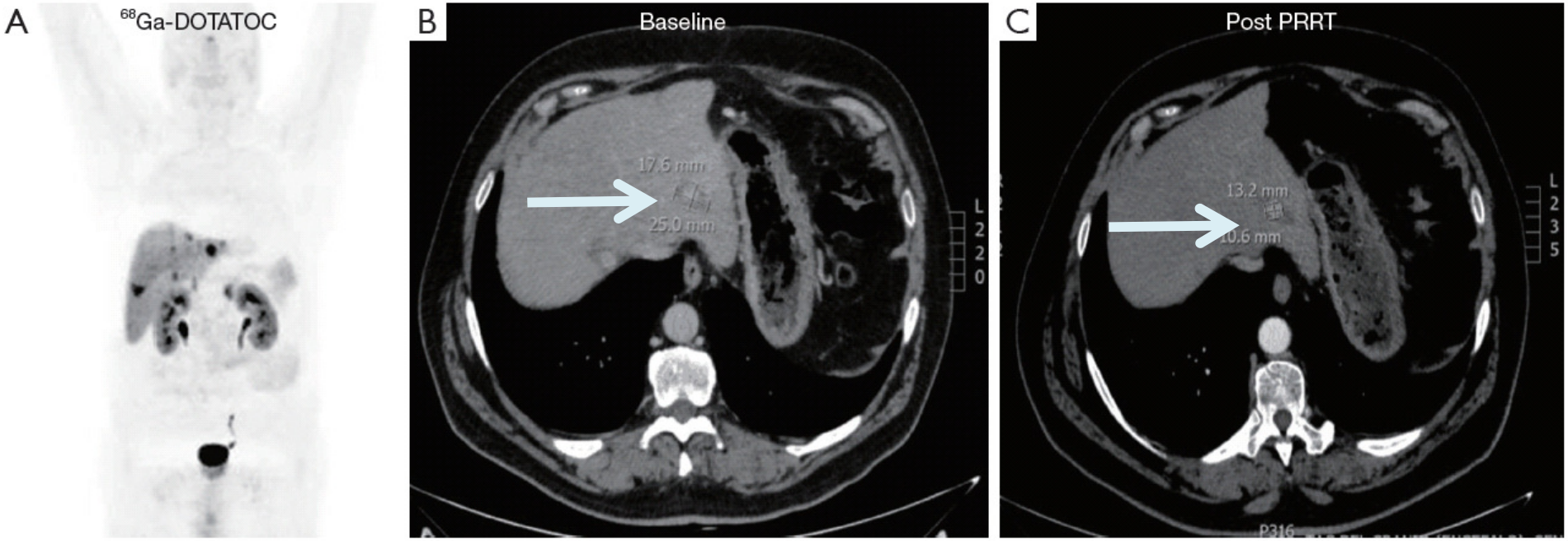
Hoersch et al. Oncol Res Treat 2014;37:266–276

F-18 FDG PET/CT in Atypical Carcinoid



56 y.o. with RUL atypical carcinoid.
Hypermetobolic mass with central RUL bronchus obstruction.

Assessment of response to PRRT



Maximum intensity projection image

Liver CT, axial image

Liver CT, axial image

Baseline

NELM from AC = 17.6 mm x 25.0 mm

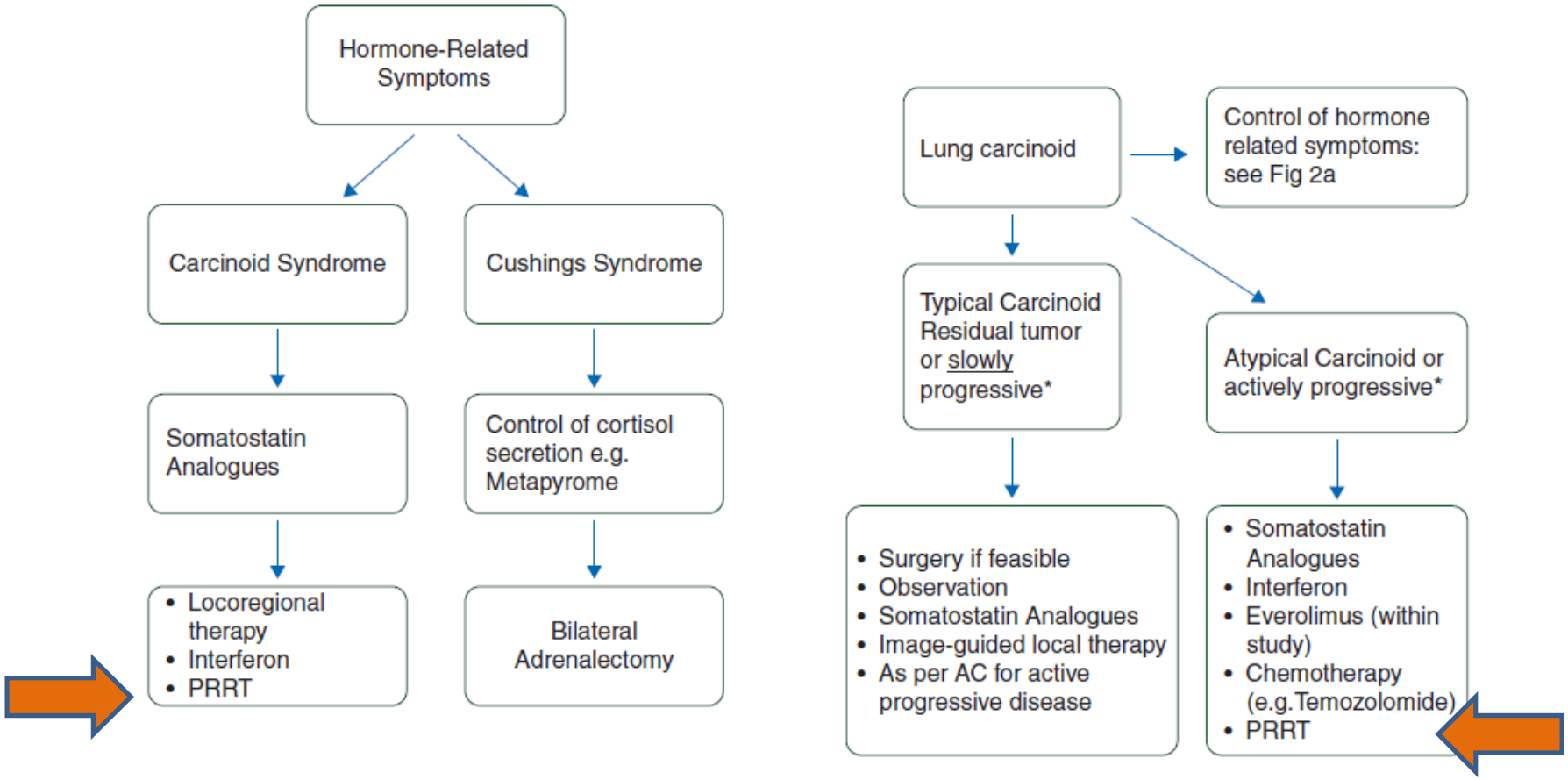
Post- PRRT (27.8 GBq)

NELM from AC = 13.2 mm x 10.6 mm

Patient with liver metastases from an atypical carcinoid.
Previously treated with surgery and SSA.
Ga-68 DOTATOC PET/CT shows elevated SSR expression in the tumor lesions.
Treated with Lu-177 DOTATATE (cumulative activity 27.8 GBq).
Objective response on f/u CT scan.

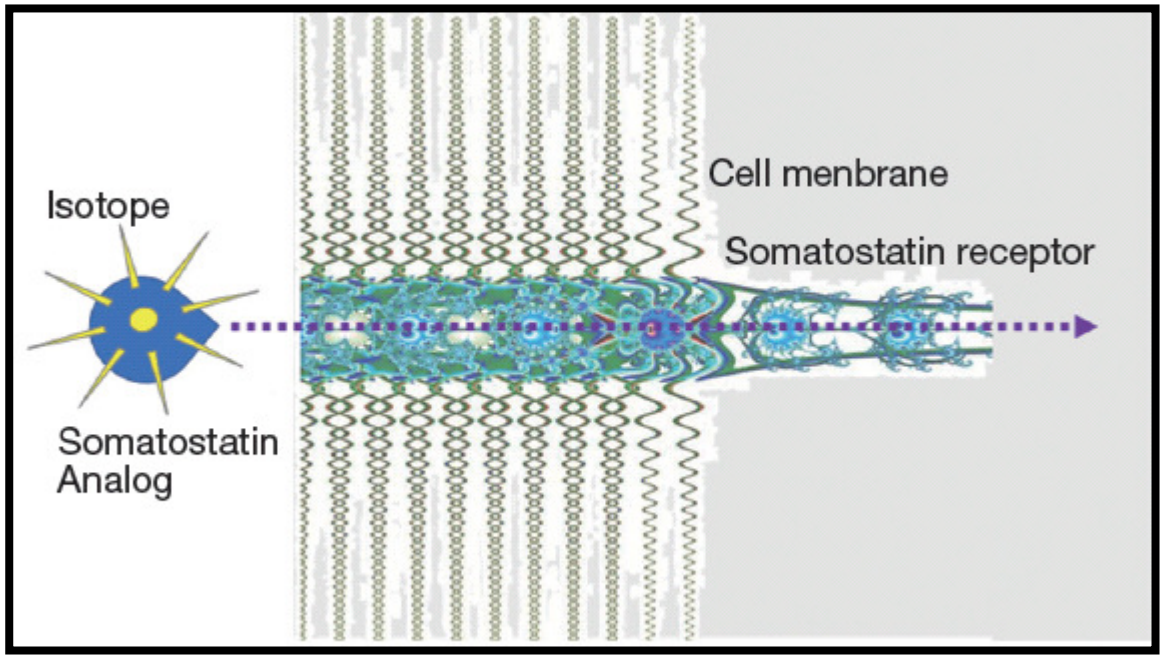
Bodei et al. J Thorac Dis 2017.

ENETS Recommendations for the Control of Hormone-Related Symptoms and Tumor Growth



Caplin et al. Ann Oncol. 2015

Mechanism of effectiveness of PRRT



Somatostatin analog linked to the isotope binds to the membrane somatostatin receptor.

The radiopeptide/somatostatin receptor complex is internalized.

Radioactivity is imparted into the intracellular compartment of the NET cell, where it exerts its action in proximity to the nucleus.

Bodei et al. J Thorac Dis. 2017

VOLUME 29 · NUMBER 17 · JUNE 10 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Response, Survival, and Long-Term Toxicity After Therapy With the Radiolabeled Somatostatin Analogue [^{90}Y-DOTA]-TOC in Metastasized Neuroendocrine Cancers

Anna Imhof, Philippe Brunner, Nicolas Marincek, Matthias Briel, Christian Schindler, Helmut Rasch, Helmut R. Mäcke, Christoph Rochlitz, Jan Müller-Brand, and Martin A. Walter

Baseline characteristics and spectrum of outcome of PRRT with Y-90 DOTATOC in Thoracic-NEN

Characteristic	Patients		Morphologic Response		Biochemical Response		Clinical Response		Mean Survival	95% CI
	No.	%	No.	%	No.	%	No.	%		
Histology										
Carcinoids	479	43.2								
Thymus	8		3	37.5	2	25.0	2	25.0	37	19 to 56
Bronchus	84		24	28.6	11	13.1	32	38.1	40	31 to 50
Small-cell lung cancer	12		1	8.3	0	0	4	33.3	21	0 to 47

Efficacy of Lu-177 DOTATATE in BP-NETS

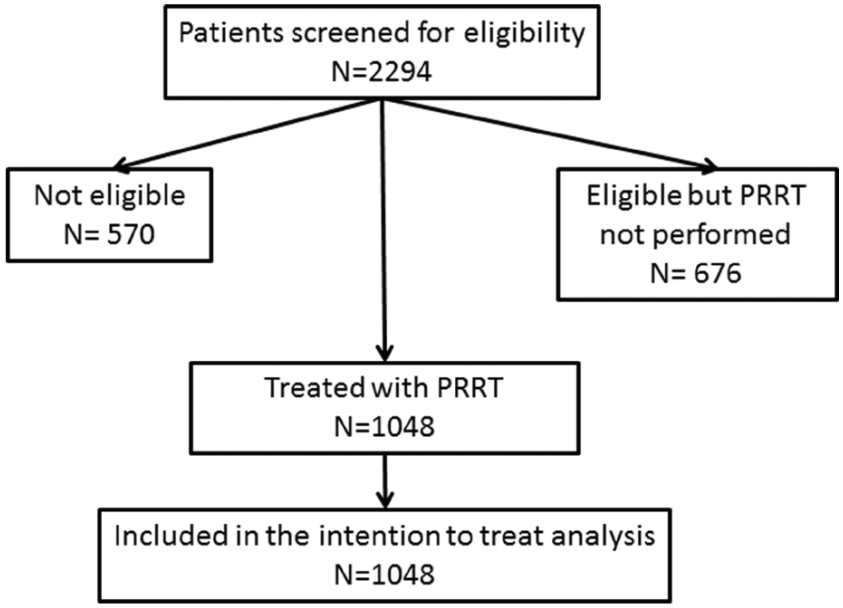
Non-controlled studies

Schedule	Pts	Best response	PFS	TTP	OS	Authors
^{90}Y-DOTATOC (11 GBq); ^{177}Lu-DOTATATE (21GBq) ; ^{90}Y-TOC+^{177}Lu-TATE (7+13 GBq)	114	18% PR+MR 29% PR+MR 38% PR+MR	23 mo 31 mo 31 mo	-	46 mo >110 mo 61 mo	Mariniello 2015
27 GBq in 4 cycles	22	27% PR	27 mo	-	42 mo	Sabet 2017
22.2-29.6 GBq in 4 cycles	23	30% CR+PR	20 mo	25 mo	52 mo	Brabander 2017

PRRT with ^{177}Lu-DOTATATE is a favorable therapeutic option in patients with broncho-pulmonary NETs with objective responses and impact on survival parameters.

Results and adverse events of personalized peptide receptor radionuclide therapy with ^{90}Yttrium and ^{177}Lutetium in 1048 patients with neuroendocrine neoplasms

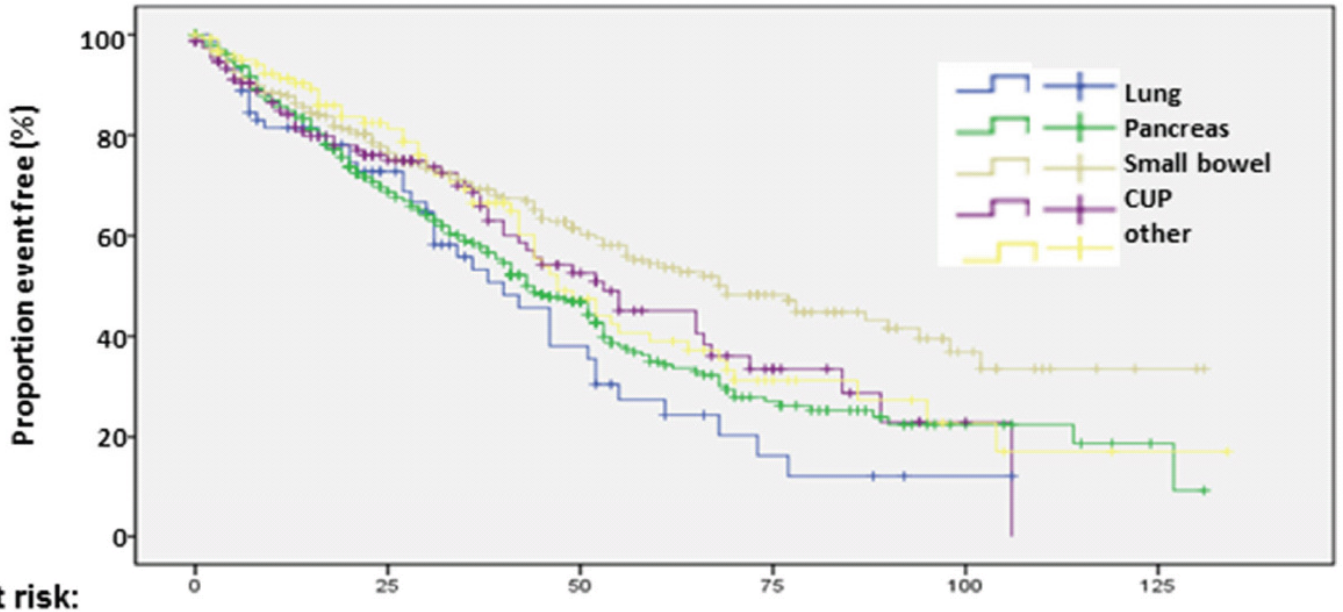
Richard P. Baum[1], Harshad R. Kulkarni[1], Aviral Singh[1], Daniel Kaemmerer[2], Dirk Mueller[1], Vikas Prasad[3], Merten Hommann[2], Franz C. Robiller[4], Karin Niepsch[1], Holger Franz[5], Arthur Jochems[6], Philippe Lambin[6,7] and Dieter Hörsch[8]



Primary tumors were localized in pancreas (384, 36.6%), small intestine (315, 30.1%), lung (75, 7.2%), colon and rectum (52, 5.0%), duodenum (22, 2.1%), thymus and mediastinum (16, 1.5%), stomach (15, 1.4%), caecum and appendix (5, 0.5%), others (13, 1.2%), and CUP (151, 14.4%).

(Epub, ahead of print).

Median OS 40 months in Lung NEN following PRRT



Number at risk:						
Total	1048	561	262	103	28	5
Bronchial / Lung	75	37	15	4	1	0
Pancreas	384	202	95	32	9	2
Small bowel	315	185	91	45	12	2
CUP	151	72	32	11	2	0
Other	123	65	29	11	4	1

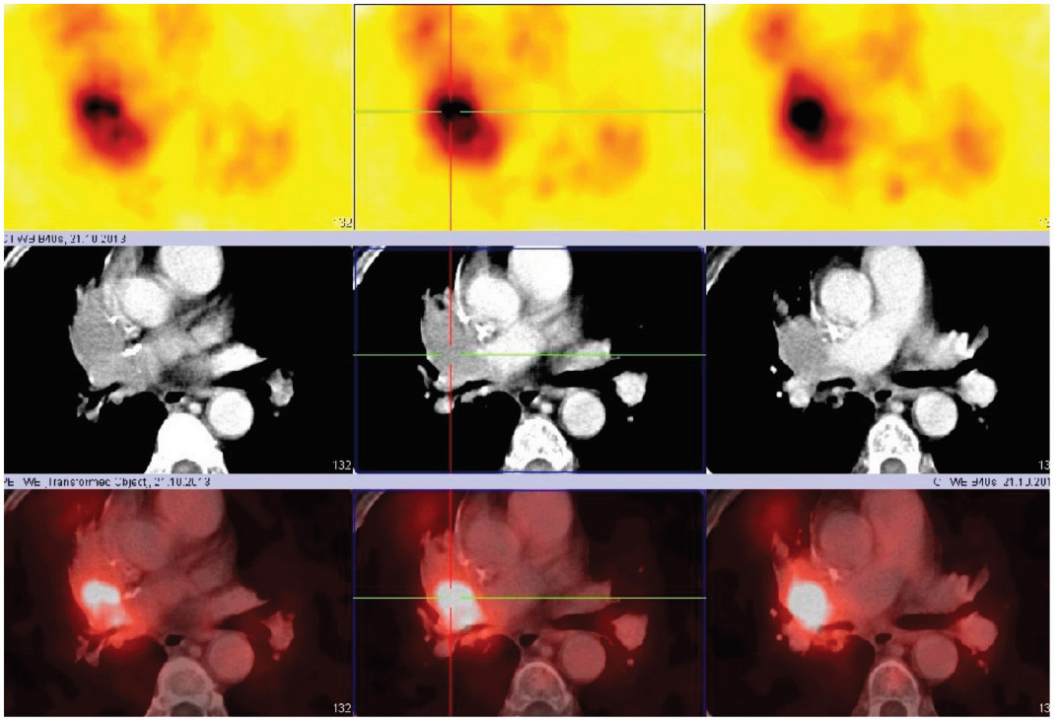
Figure 4: Kaplan-Meier plots of overall survival according to number of previous therapies **(A)** and primary tumors **(B)**.

Baum et al Oncotarget. 2017. (Epub, ahead of print).

Differential expression and prognostic value of the chemokine receptor CXCR4 in bronchopulmonary neuroendocrine neoplasms

Daniel Kaemmerer[1,*], Christiane Reimann[2,*], Elisa Specht[2], Ralph M. Wirtz[3], Manal Sayeg[4], Richard P. Baum[5], Stefan Schulz[2] and Amelie Lupp[2]

December 30, 2014

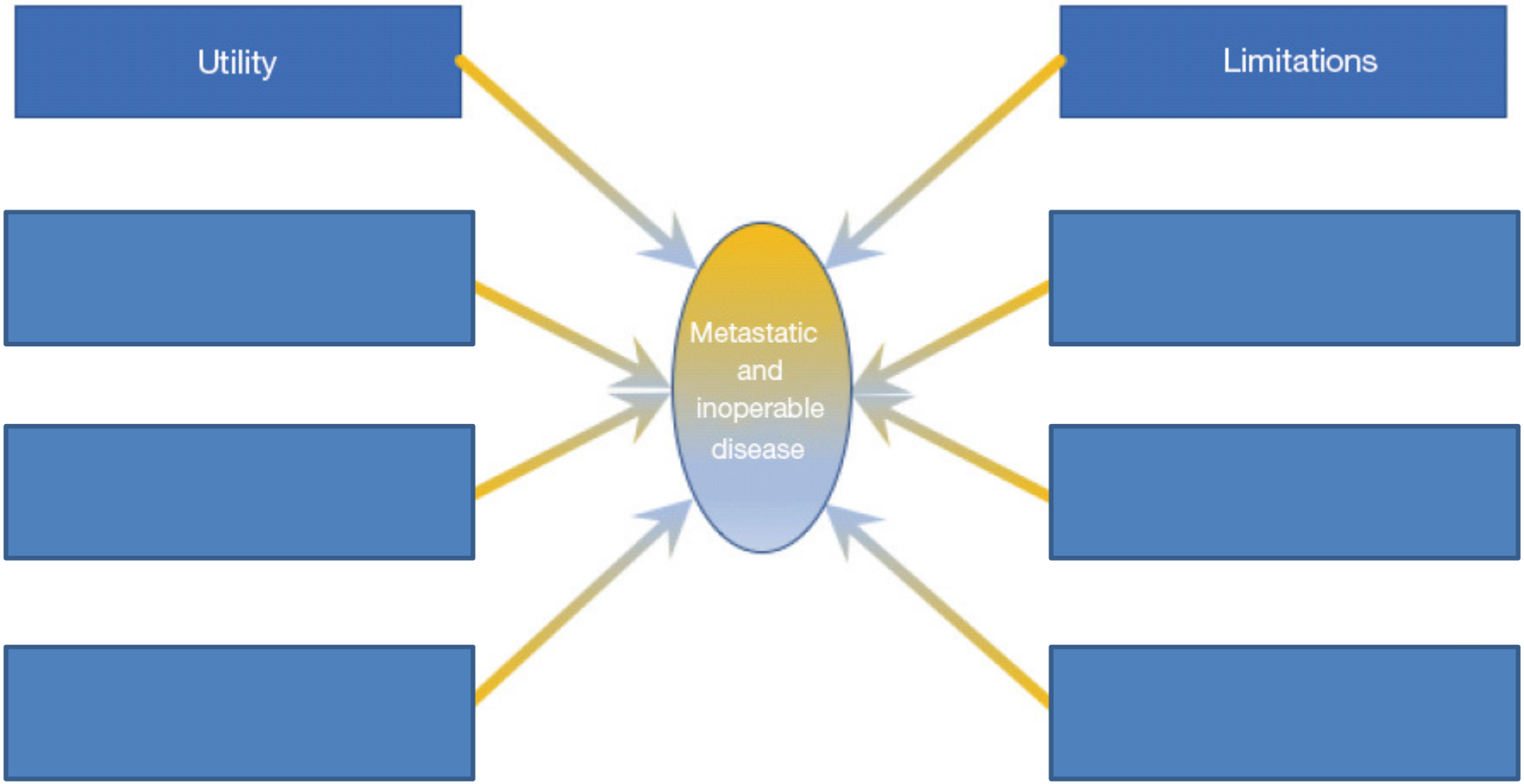


^{68}Ga-CPCR4-2 PET/CT (transverse images)

Local recurrence of a centrally localized SCLC

Upper panel: PET scan, middle panel: CT scan, lower panel: PET + CT fusion image

Summary - utility and limitations of PRRT in Lung-NEN



Adapted from Bodei et al. J Thorac Dis 2017.

Thank you for your attention

Potential role of CXCR4 in SCLC

Introduction: For many tumors, the overexpression of the chemokine receptor CXCR4 is associated with increased malignancy and poor patient outcomes. However, comprehensive data for neuroendocrine neoplasms of the lung are still lacking.

Methods: CXCR4 expression was evaluated in a panel of bronchopulmonary neuroendocrine neoplasms (BP-NEN) comprising typical carcinoids (n = 26), atypical carcinoids (n = 30), and small cell lung cancers (SCLC, n = 34). Samples were analyzed by immunohistochemistry using the novel monoclonal rabbit anti-human CXCR4 antibody UMB-2 and by qRT-PCR. The expression was correlated with clinical data and overall patient survival.

Results: CXCR4 was predominantly localized at the plasma membrane of the tumor cells. CXCR4 was expressed with a high intensity in almost all of the 30 SCLC samples. In contrast, it was detected infrequently and with low intensity in the typical carcinoid and atypical carcinoid samples. There was a significant correlation between the immunohistochemistry and qRT-PCR data. Additionally, there was a significant negative relationship between CXCR4 expression and overall survival.

Conclusions: With increasing malignancy, BP-NEN clearly differ in the extent of CXCR4 expression. As in other tumor entities, CXCR4 overexpression significantly correlates with negative patient outcome. Due to its particular high expression rate in SCLC, CXCR4 may serve as a promising new target for diagnostic and pharmacological intervention as well as for peptide receptor-based radionuclide therapy.

Kaemmerer et al. Oncotarget. 2014.