1st AP STATE CONFERENCE ON NEUROENDOCRINE TUMORS

Date: **8th APRIL 2018**
Venue: **Dolphin Hotel Visakhapatnam**

DON'T FORGET THAT "ZEBRA" EXISTS! APPREHENSION LEADS TO SOLUTION

Mahatma Gandhi
Cancer Hospital & Research Institute
MVP Colony, Vizag, Andhra Pradesh

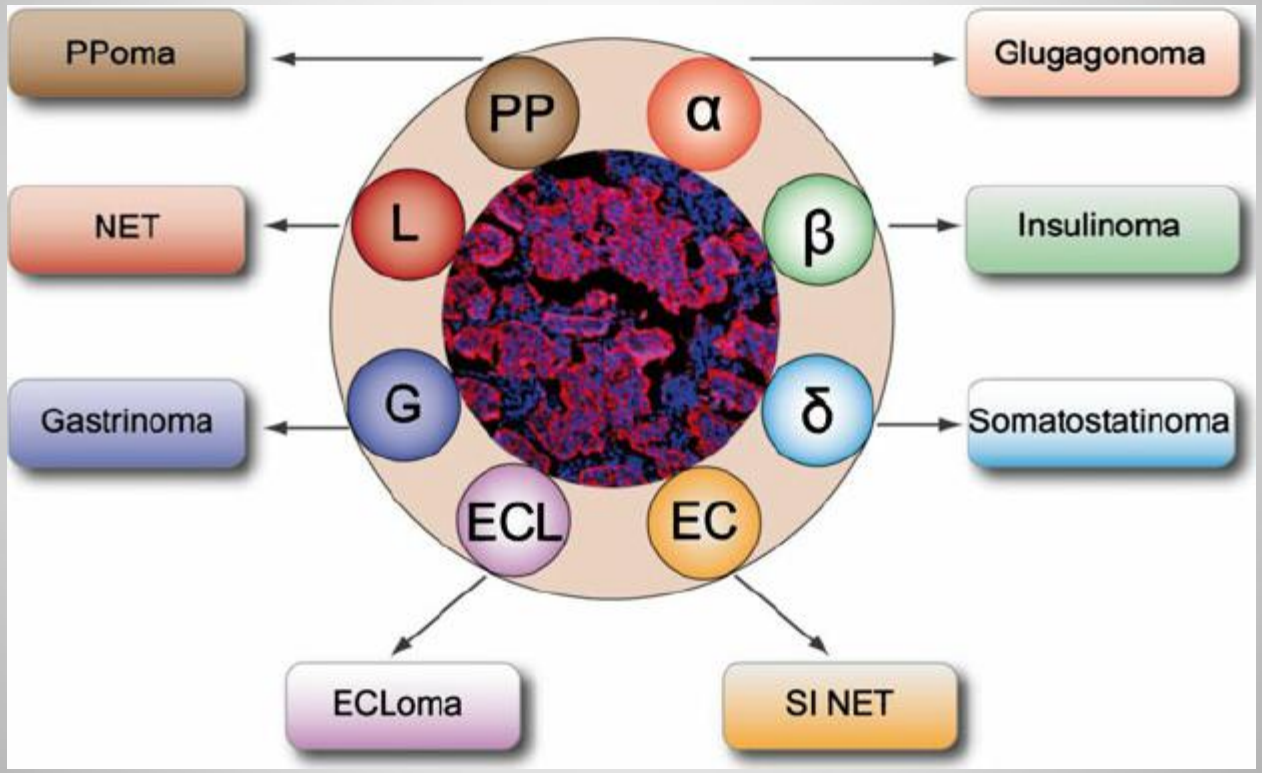
SUPPORTING PARTNER

ANMPI

Different Neuroendocrine Cell Types

Location	Cell type	Peptides Secreted
Entire GI tract	*Delta (D), Enterochromaffin (EC), Ghrelin (Gr), Vasoactive intestinal paptide (VIP)*	*Somatostatin (D)* *Serotonin/substance P/guanylin/melatonin (EC)* *Ghrelin (Gr), VIP*
Gastric fundus	*Enterochromaffin-like (ECL)*	*Histamine*
Gastric antrum & duodenum	*Gastrin (G)*	*Gastrin*
Duodenum	*I, Motilin (M), Secretin (S)*	*CCK, Motilin, Secretin*
Duodenum/jejunum	*K*	*GIP*
Small intestine	*L, Neurotensin (N)*	*GLP-1, PYY, NPY, Neurotensin*
Stomach: fundus and antrum	*X*	*Amylin*
Pancreas	*Alpha, Beta, Delta, Pancreatic Polypeptide (PP)*	*Glucagon, Insulin, Somatostatin, PP*

14 types of NE cells



Epidemiology: Seer database of 64971patients

- Incidence and prevalence of _NETs_are steadily rising
- Possibly due to better detection of early-stage disease and stage migration
- 6.4-fold increase in age-adjusted annual incidence: from 1.09 in 1973 to 6.98 in 2012,
- Prevalence increased from 0.006% in 1993 to 0.048% in 2012 ($P < .001$).
- Especially in older age group

A Dasari ***Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States***
JAMA Oncol. 2017;3(10):1335-1342

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New WHO 2017 classification for pancreatic NETs

	Mitotic index	MIB1 index
WD NET G1	≤2%	**< 3%**
WD NET G2	3-20%	3-20%
WD NET G3	>20%	>20%
PD NEC G3 Small cell and Large cell	>20%	>20%
MiNEN		

RADIOLOGICAL IMAGING

General Imaging Considerations for NETs

A BIG Noooo….

- Single /dual slice CT
- Only Plain study
- Manual injection of contrast
- Positive oral contrast agent
- Only venous phase imaging
- Single plane imaging

I'm happy if…

- MDCT
- Always a contrast study (If not contraindicated)
- Power / Pressure injector
- Negative oral contrast agent
- Multiphase imaging
- Multiplanar reconstructions

CT Imaging protocol

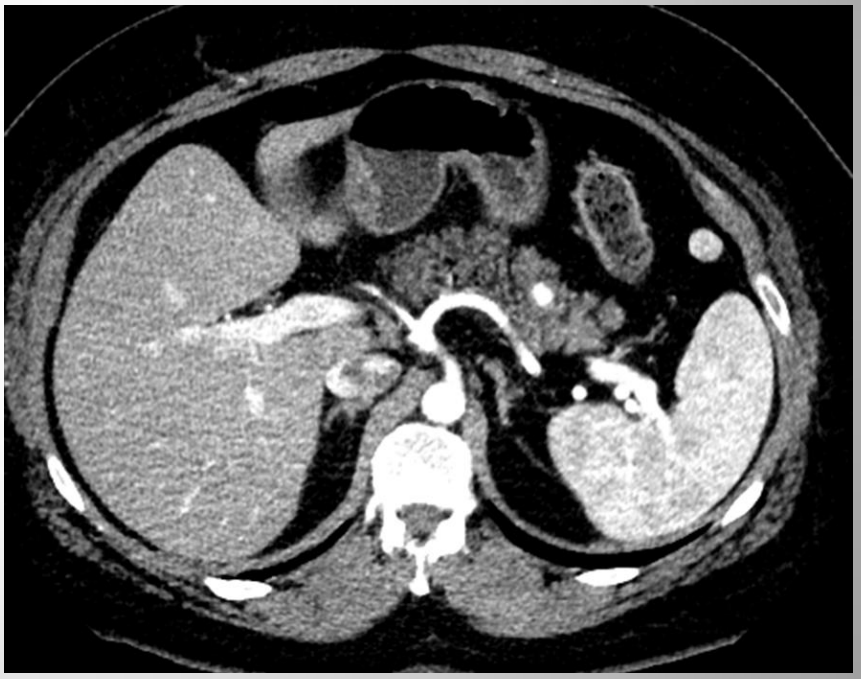
- Triphasic examination consisting of an initial non-contrast phase followed by arterial and portal venous phases.
- 1-2.5 mm collimation using helical technique
- A neutral contrast agent, such as water, as oral contrast
- Multiplanar reconstructions

MR Imaging protocol

- Combination of T1- and T2 W sequences and dynamic pre & postcontrast volumetric T1 W sequences with fat saturation.
- Should include an arterial and more delayed phases of imaging
- Overall sensitivity and specificity of 80% and 100%, respectively for pancreatic tumors

Functioning tumors

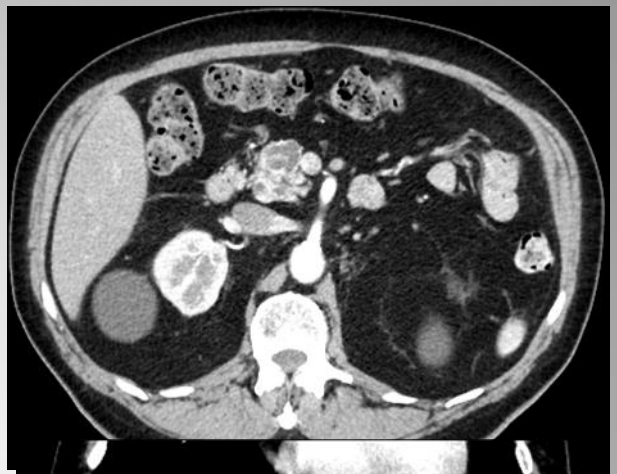
- Usually produce symptoms and syndromes earlier
- Detected and resected earlier; typically small (1–2 cm) homogeneous tumors.
- Such tumors are not metastatic and are not locally invasive at the time of diagnosis.

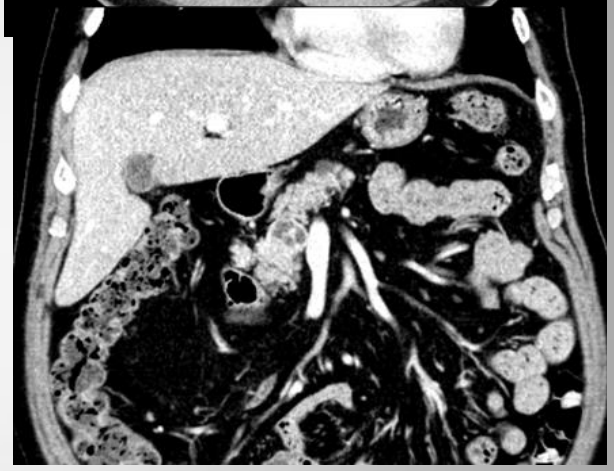


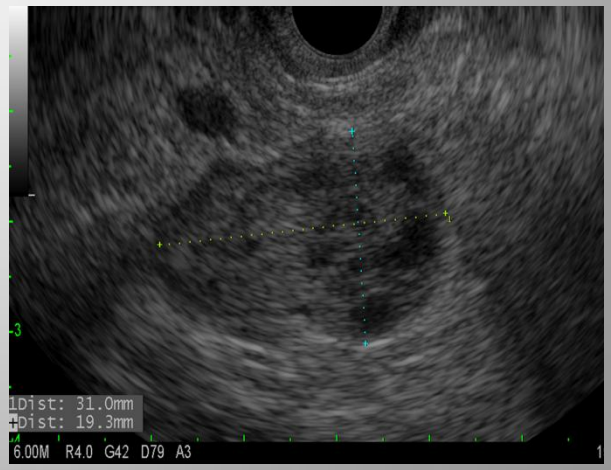
1.2 cm panc NT WHO grade 1

Nonfunctioning

- Typically larger (several centimeters) & heterogeneous
- commonly contain calcification, necrosis, & cystic changes
- Local invasion, vascular invasion, and distant metastases







Pheochromocytoma- The 10% Tumor

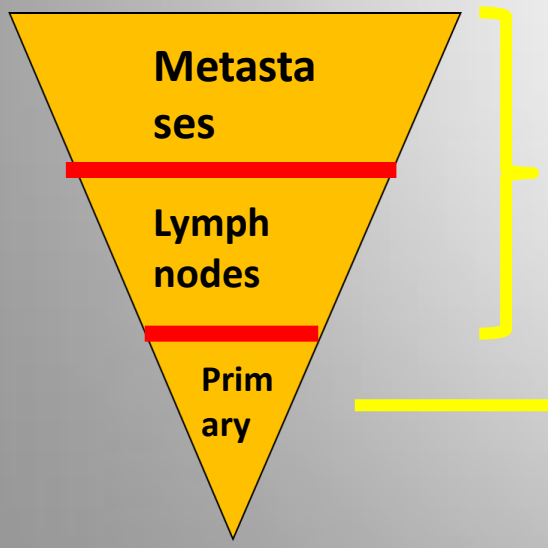
- High signal intensity on T2-w imaging, best appreciated on fat sat
- Typically heterogeneous
- The ***spurious*** light bulb sign on T2-w imaging
- Misdiagnosis of pheochromocytoma in up to 35% of cases
- Fat signal is key in differentiating from adenomas on CT & MRI

FUNCTIONAL IMAGING – NUCLEAR MEDICINE

IMAGING IN NET

- CT – first modality of investigation .
- Usually a three phase CT is done.

Then Why Functional Imaging ?



CT is good

Functional imaging is needed

Functional imaging modalities –

- **Detects primary**
- **Accurate staging – additional metastatic sites.**
- To differentiate well differentiated tumors from poorly differentiated tumors depending on their positivity of **SSTR (Somatostatin receptor) or glycolytic metabolism** and thus provide **prognostic information.**

Functional Imaging in NET

- SRS receptor imaging
  - ^{111}In – Octreotide
  - ^{99m}Tc- Hynic TOC
  - ^{68}Ga-DOTA PET/CT
- ^{18}F- FDG PET/CT

SSTR Imaging

- SRS imaging is based on high affinity of radiolabeled somatostatin analogs for tissues expressing SSTR.

Radionuclide	Linker + Peptide	Affinity to SSTR subtype
^{68}Ga	DOTATATE	SSTR 2
^{68}Ga	DOTATOC	SSTR 2, 5
^{68}Ga	DOTANOC	SSTR 2, 3, 5

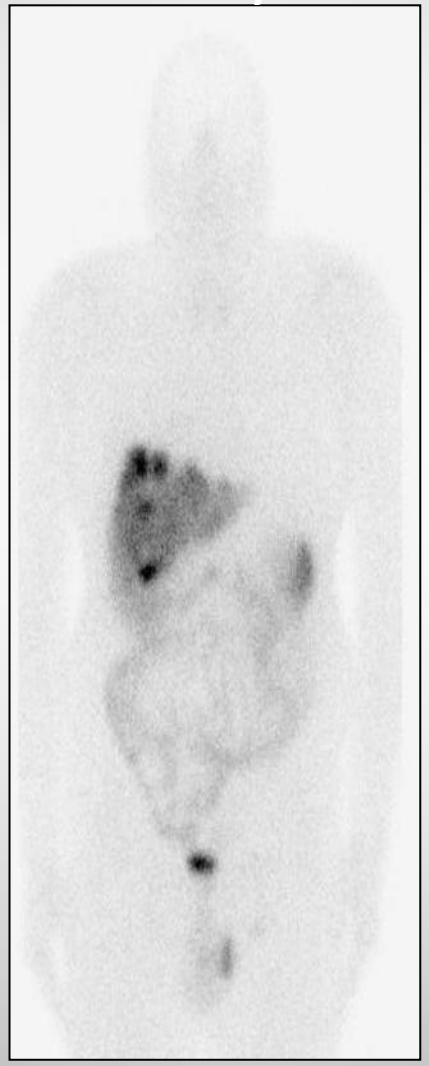
Recommendations for the use of SRS imaging

- To localize the **primary tumor** in patients with biochemical suspicion of NET/known metastatic NET
- Confirm the **diagnosis of NET** in patients with anatomic lesions that are suspicious for NET
- Exclude more **advanced disease** prior to surgical intervention
- As a **prelude to PRRT** – to identify patients who are likely to benefit from octreotide hormonal therapy or PRRT.

$^{111}In/^{99m}Tc$ based SRS Imaging (Gamma camera, SPECT with or without CT)

- ^{111}In DTPA octreotide (Octreoscan)
- Half-life - 68 hrs.
- Imaging at 24 and 48 h.

99mTc Hynic TOC



99mTc HYNIC TOC

- Half life – 6 hrs.
- Imaging at 1 hr.
  - Less expensive
  - Readily available.
  - Better imaging characteristics.
  - Faster tumor visualization

Octreotide Imaging

	Sensitivity
GNET	86- 88%.
pNET	60 to 90% .

Sensitivity of SRS is lower in –

- **lesions <1 cm** - beyond its resolution
- **Insulinomas** (sensitivity <50%) - due to the reduced expression of SSTR-2 in these pNET

^{68}Ga DOTA peptide PET/CT Imaging

^{68}Ga DOTA peptides	Octreotide imaging (^{111}In)
Short half life 68min - faster imaging	Long half life – longer imaging time
Generator produced-in house – on demand production	Cyclotron produced
Lower radiation dose	Higher radiation dose
Better spatial resolution - <5mm lesions can be visualized	Spatial resolution is low
Quantitative	Not quantitative

Eur J Nucl Med 2007; 34: 982– 993.

^{68}Ga DOTA peptide PET/CT Imaging

Accuracy

- A recent meta-analysis of 22 studies, >2000 patients,

	Sensitivity	Specificity	ROC curve
^{68}Ga-DOTA PET	93%	95%	0.98 (95 % CI 0.95 – 1.0)

Eur J Nucl Med Mol Imaging 2013;40(11):1770–1780

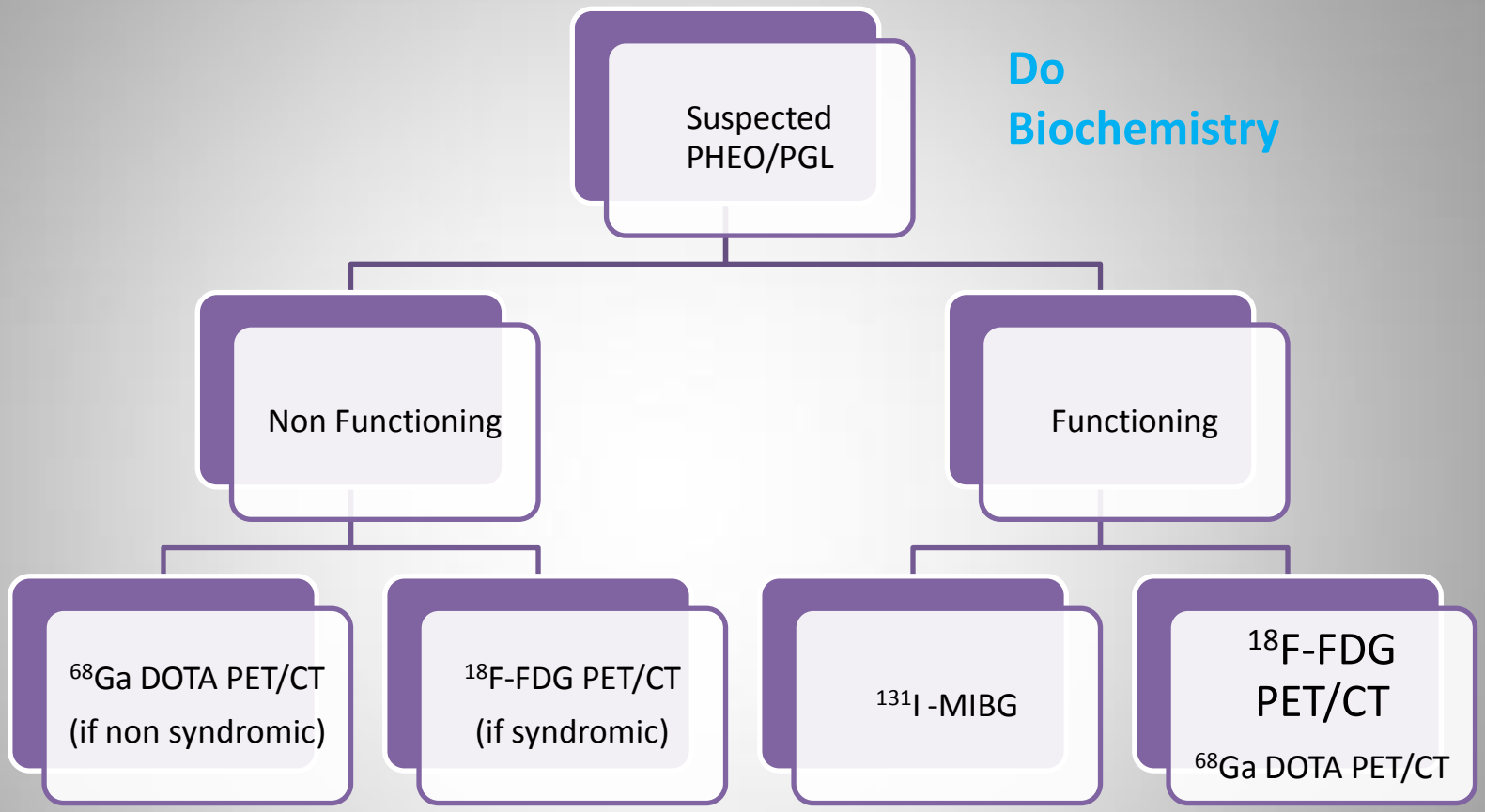
Impact on management - SSTR PET/CT

Study	No. pf patients	Tracer	Impact on Management
Ambrosini et al 2010	90	DOTA-NOC	50% change in stage or therapy modification
Srirajaskanthan et al 2010	41	DOTA-TATE	Inter-modality change 71%
Frilling et al 2011	52	DOTA-TOC	Change in Rx decision 60%
Naswa et al 2011	109	DOTA-NOC	Inter-modality change 19%
Ruf et al 2010	64	DOTA-TOC	Inter-modality change 38%
Hofman et al 2012	59	DOTA-TATE	Inter-modality change 47% Intra-modality change 10%

Selective use of FDG PET/CT with SSTR PET/CT
▪ Ki 67 > 5%
▪ Poorly differentiated NET/NEC
▪ Suspicious lesions with no uptake on SSTR PET/CT
▪ Clinical or radiological progression - within <6 months despite Ki < 5%

Imaging techniques for localization and staging of HNPGLs

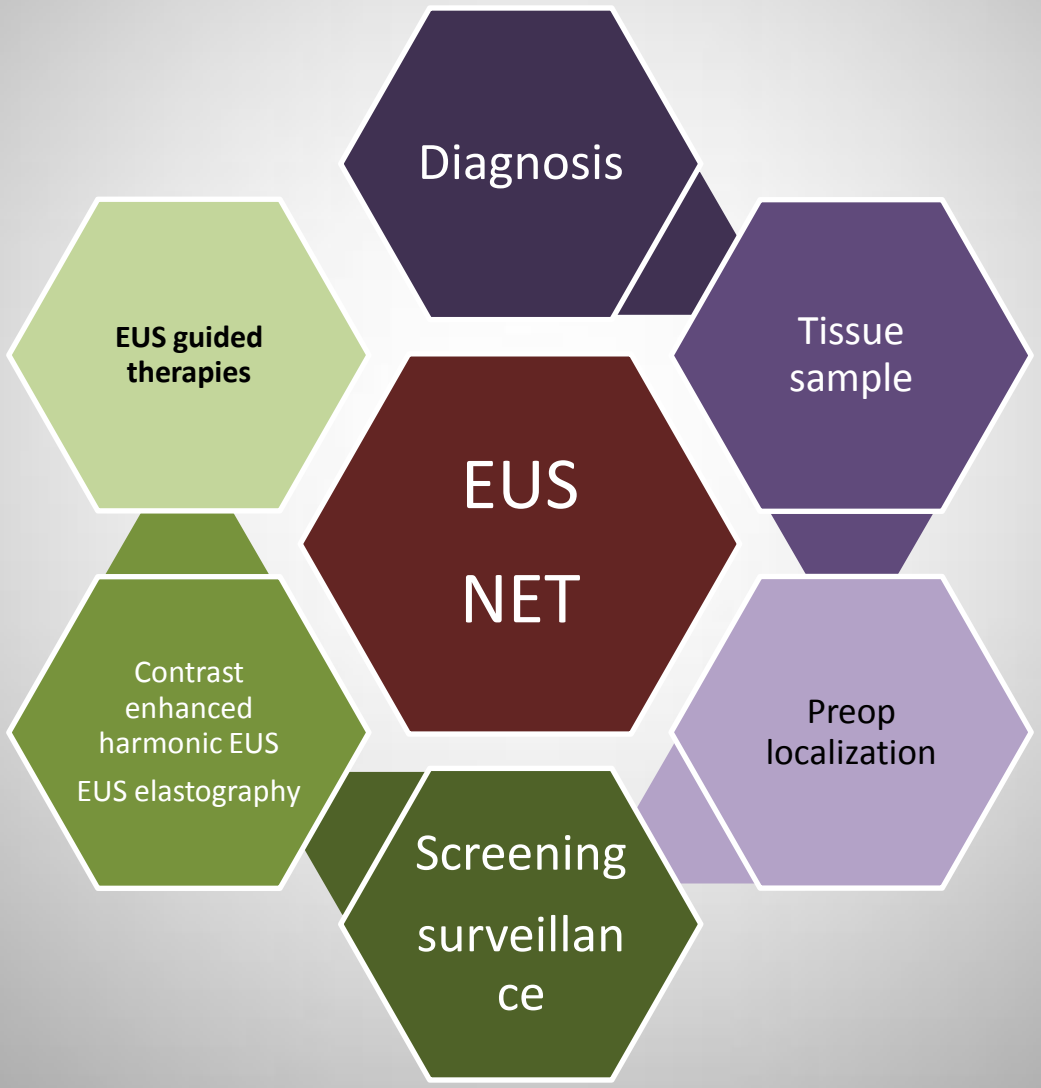
MODALITY	SN %	SP %
CT	80-90	90
MRI	80-90	90
18F-DOPA PET/CT	>90	>95
68GA-DOTA PET/CT	>90	90
18F-FDG	80	80-90
MIBG	18-50	


Suspected PHEO/PGL
Do Biochemistry
Non Functioning
Functioning
68Ga DOTA PET/CT (if non syndromic)
18F-FDG PET/CT (if syndromic)
131I -MIBG
18F-FDG PET/CT
68Ga DOTA PET/CT

Take home message……

- GI NET – Functional imaging helps to differentiate between well and poorly differentiated tumors
  - ✓ G1 – 68Ga DOTA study.
  - ✓ G2 – Both 68Ga and FDG
  - ✓ G3 – FDG would suffice
- Broncho pulmonary carcinoid –
  - ✓ DOTA ….if DOTA is negative --- FDG study
- PGL/Pheo-
  - ✓ Non functional – DOTA PET (if nonsyndromic)…….FDG PET (if syndromic)
  - ✓ Functional – MIBG (for primary and prelude to MIBG therapy) and FDG/DOTA – for additional metastatic sites.

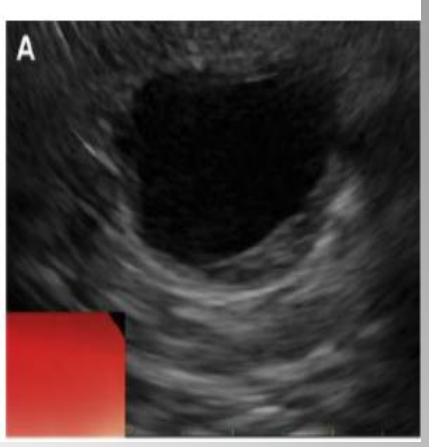
Role of EUS in NET



EUS in NET
Morphological Features

- Round, well-demarcated, homogenous, hypoechoic lesions with smooth margins
  - Rarely isoechoic and hyperechoic with irregular margins.
- Features of malignancy
  - Iso/hyperechogenicity, vascular invasion, PD obstruction
- Majority are solid lesions

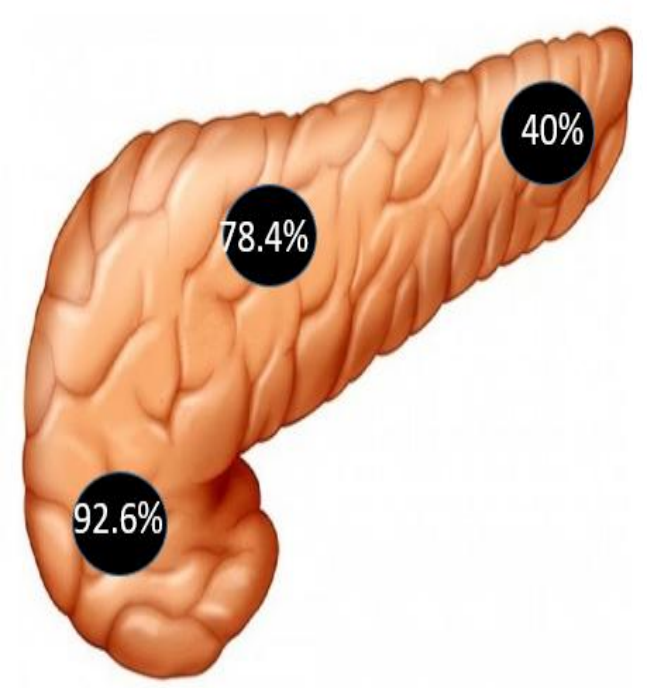
Cystic NET



- 8 to 21%
- Thin wall with variable degree of focal or concentric wall thickening
- Unilocular, septated, multicystic, mixed solid-cystic lesion
- More often asymptomatic
- Associated with VHL, MEN-1
- 2 x larger than their solid counterparts
- 81%- nonfunctional
- Closely resemble pancreatic cysts
- Target the wall of cyst on EUS/FNAC
- Nonviscous fluid with low CEA

Rustagi et al. J Clin Gastroenterol 2014

Diagnostic EUS Insulino



- 90% occur in pancreas
- <2 cms
- EUS is the best
- Combined with hormone
- Detection rates: 79-94%

Anderson MA et al. Gastro 2000
Gouya H et al. AJR Am J Roentgenol. 2003
Ardengh JC et al. Gastrointest Endosc. 2000
Sotoudehmanesh R et al. Endocrine 2007

Diagnostic EUS Gastrinomas

- Pooled sensitivity: 84.5%
- Pooled specificity: 95.3%

Pancreatic gastrinomas (50%)

- 11-50% detection rates

Extrapancreatic gastrinomas (50%)

- Detects metastatic node detection
- Careful endoscopic examination of the duodenal wall

Rustagi T et al. J Clin Gastroenterol 2014

EUS
Liver/Nodal Mets in pNET

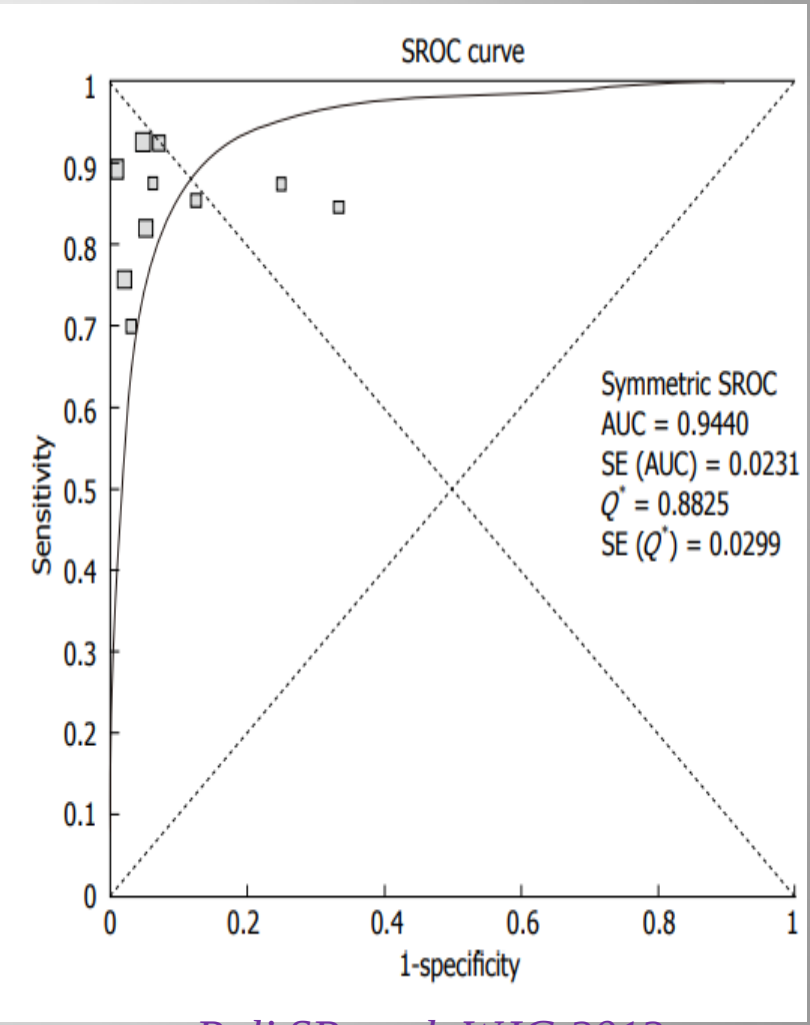
- Metastatic PNETs are more likely to be located in both lobes, have >2 lesions visible on EUS and have larger undetected masses on CT

- Picks up undetected nodal metastases on EUS

Atiq M et al. Dig Dis Sci 2012
O'Neil JM et al. GIE 2007 (abstract)

Diagnostic EUS NET

- Pooled sensitivity: 88%
- Pooled specificity: 98%
- S ROC: 0.94



Puli SR et al. WJG 2013

EUS
NET

Advantage

- As small as 2-5 mm
- Synchronous lesions, multifocal lesions – 9%

Pitfalls

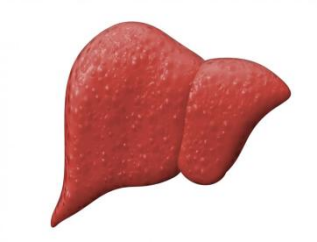
- Isoechoic appearance
- Pedunculated lesions at the pancreatic tail
- Low body mass index

Kann PH et al. Eur J Endocrinol. 2003
Kann PH et al. Eur J Endocrinol. 2007

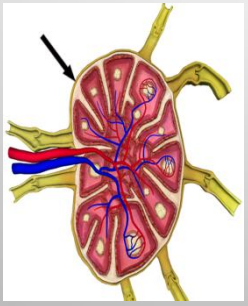
EUS FNAC
Performance in NET

- Sensitivity: 61%-84%
- Specificity: 92.5%
- FNAC can obtain material for IHC studies in 70% cases
- Onsite cytology evaluation will increase the yield from 80% to 91%

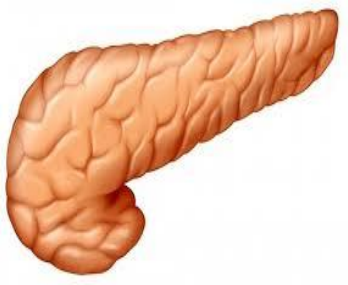
2-3 passes



2-5 passes



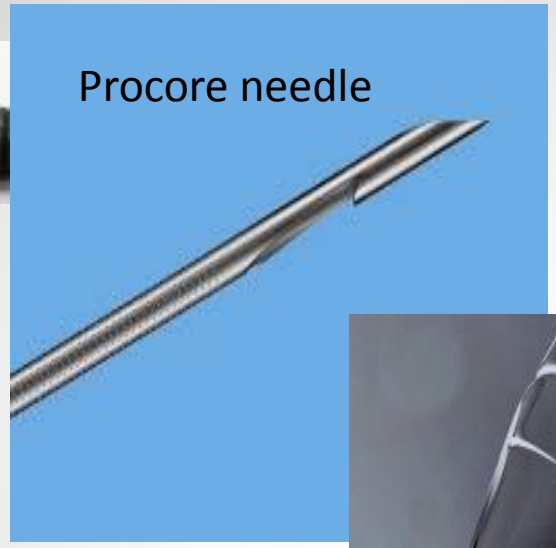
5-7 passes

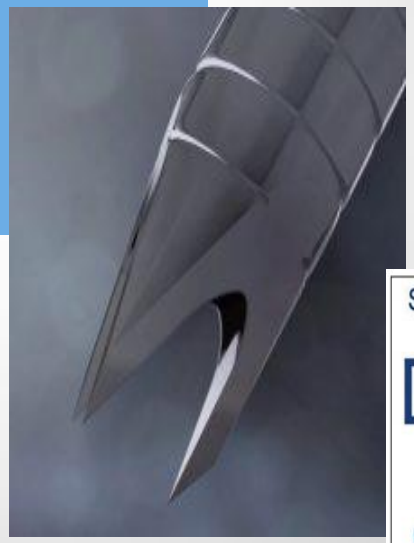


Pais SA et al. GIE 2010
Pais SA et al. GIE 2007 (abstract)
Atiq M et al. Dig Dis Sci 2012

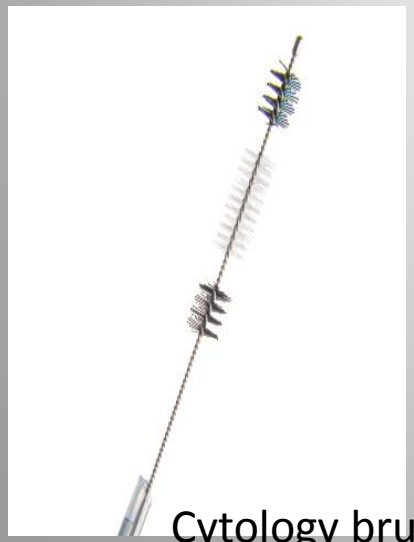
EUS Guided Tissue Acquisition

FNAC needle



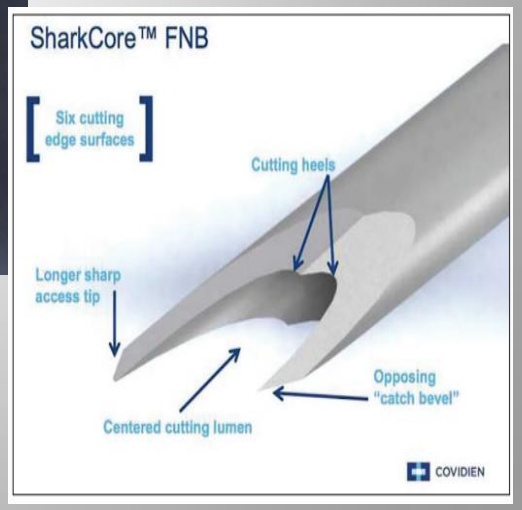


Acquire needle



Cytology brush
Cystic NET

Shark Core needle

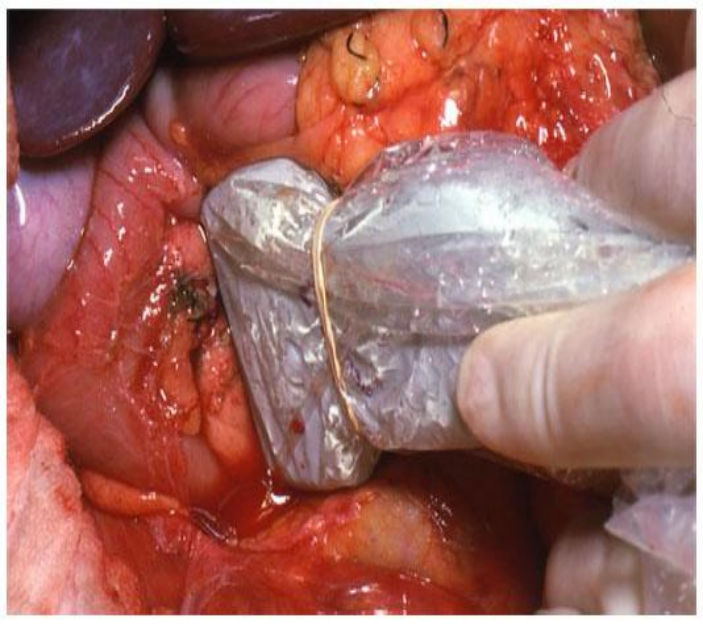


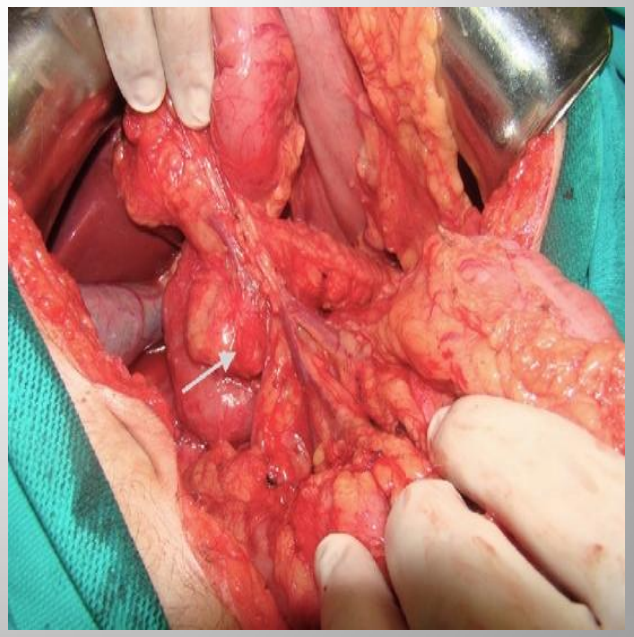
Preoperative EUS

- Identify multifocal lesions missed on CT
- Identify candidates for enucleation rather than extensive pancreatectomy
- Differentiating adenocarcinoma from NET and alter the surgical choice

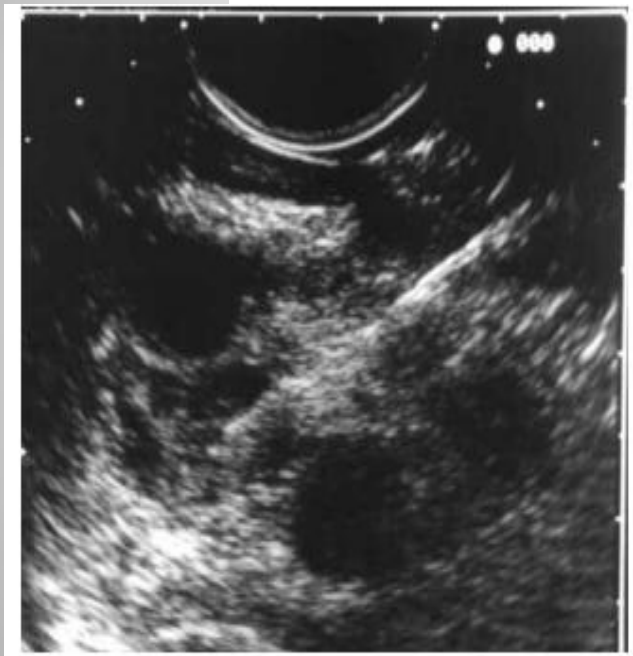
Improving Intraoperative Localization

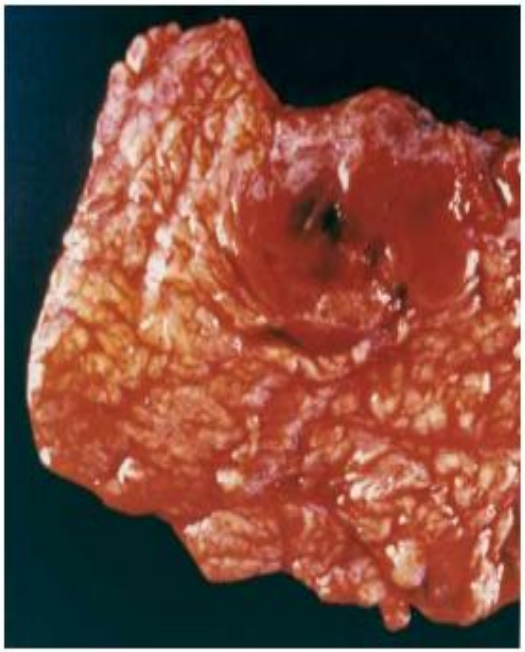
- Time consuming intraoperative palpation and intraoperative ultrasound
- Risk of splenic artery injury
- Not possible during laparoscopic surgery





EUS Tattooing
EUS guided Fiducial Marking

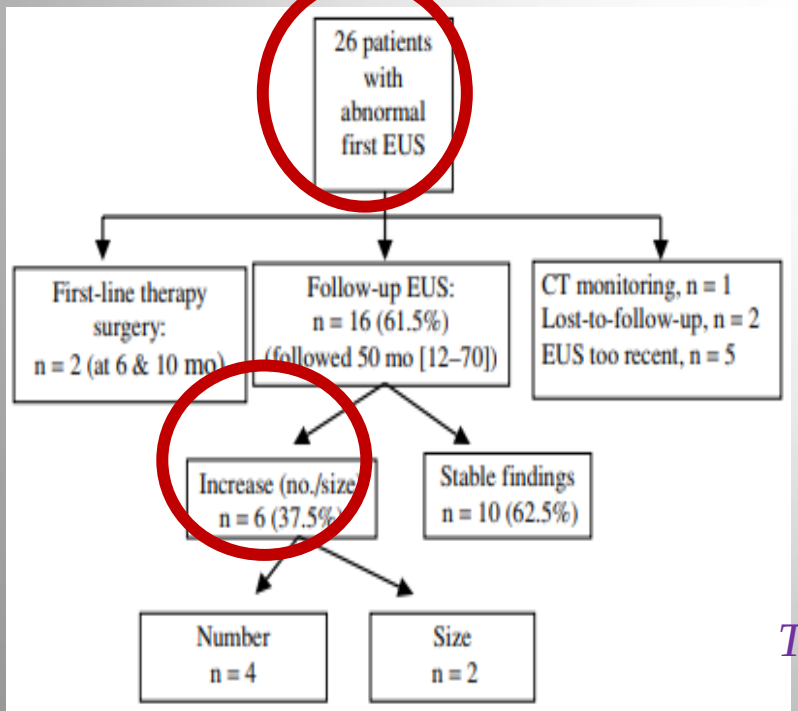




Gress FG et al. GIE 2002
Newman NA et al. Surgery 2010
Zografos GN et al. Hormones 2005

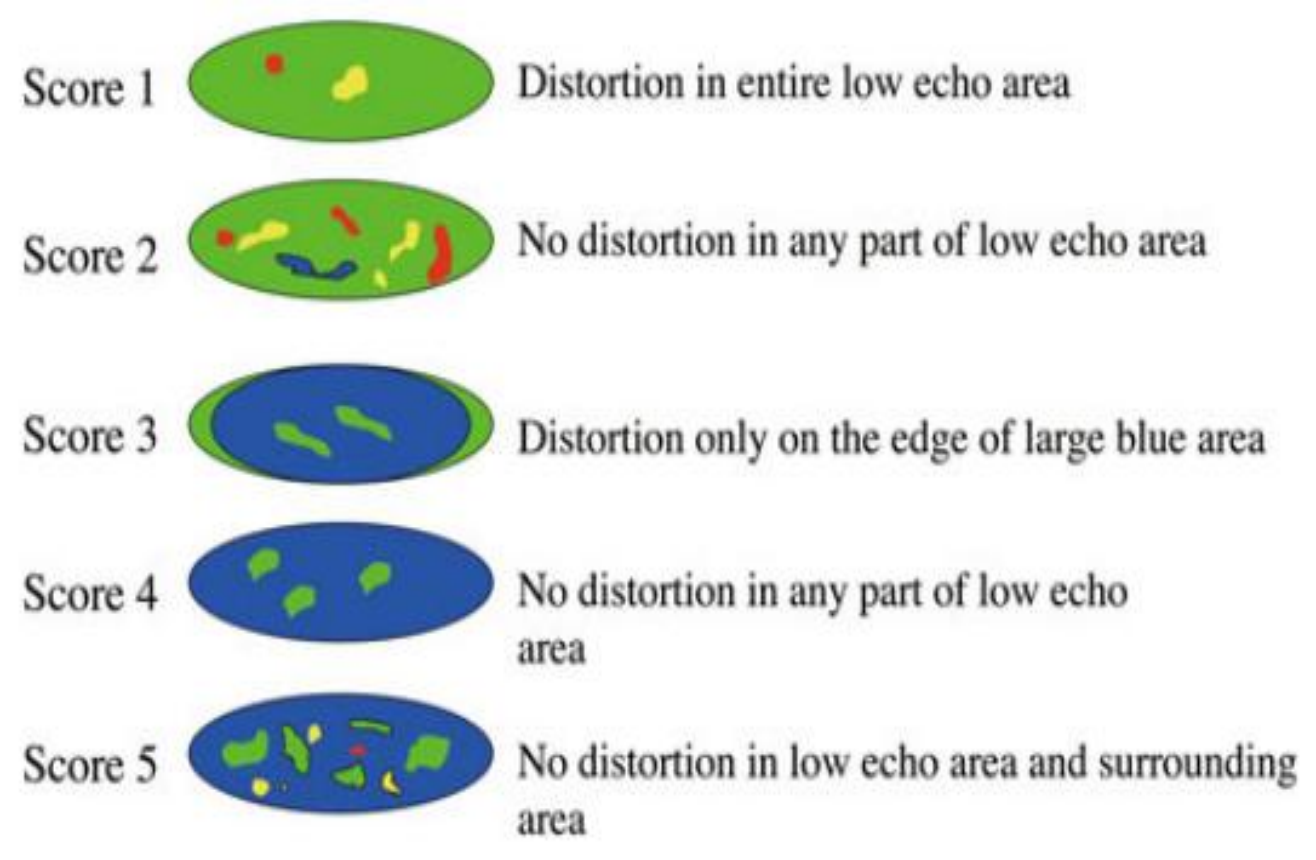
EUS Screening/Surveillance – MEN 1

- 54.9% in otherwise asymptomatic patients
- Median of 3 tumors
- Median size 6mm
- 37.5% had progression on followup EUS



Thomas-Marques L. Am J Gastroenterol 2006

EUS Elastography
Qualitative Scoring - NETs

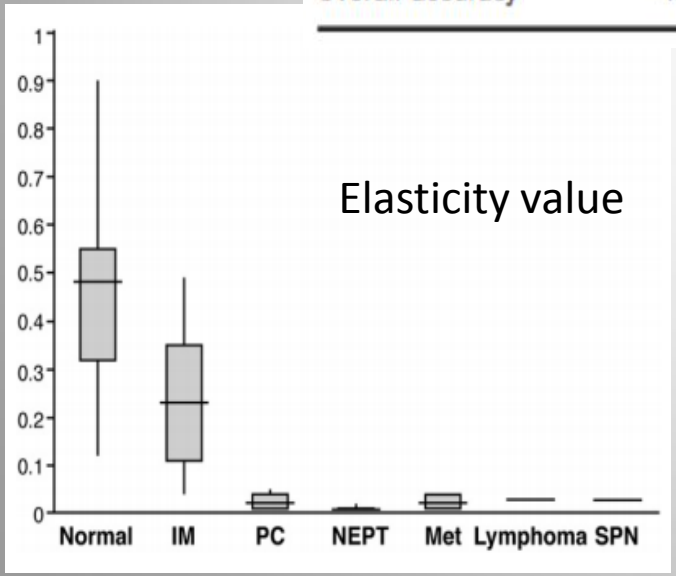


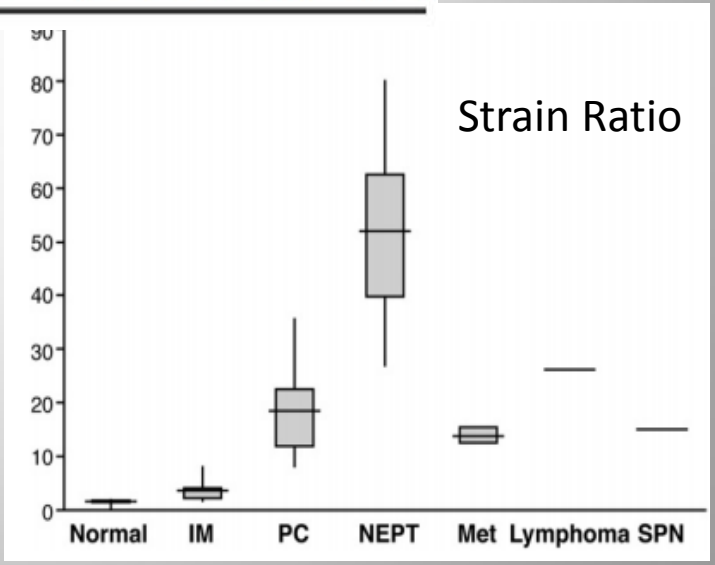
Giovannini elasticity scores

Itokawa F et al. J Gastroenterol 2011

EUS Elastography Quantitative Scoring NET

	Neuroendocrine tumor vs pancreatic adenocarcinoma	
	Strain ratio (cut-off level, 26.63)	Elasticity of pancreatic mass (cut-off level, 0.01)
Sensitivity	6/6 (100%; 91.7%–100%)	5/6 (83.3%; 45.2%–100%)
Specificity	43/49 (87.8%; 77.6%–100%)	30/49 (61.2%; 46.6%–75.1%)
Positive predictive value	6/12 (50.0%; 17.5%–82.5%)	5/24 (20.8%; 2.5%–39.2%)
Negative predictive value	43/43 (100%; 98.8%–100%)	30/31 (96.8%; 88.9%–100%)
Overall accuracy	49/55 (89.1%; 79.9%–98.2%)	35/55 (63.6%; 50.0%–77.3%)



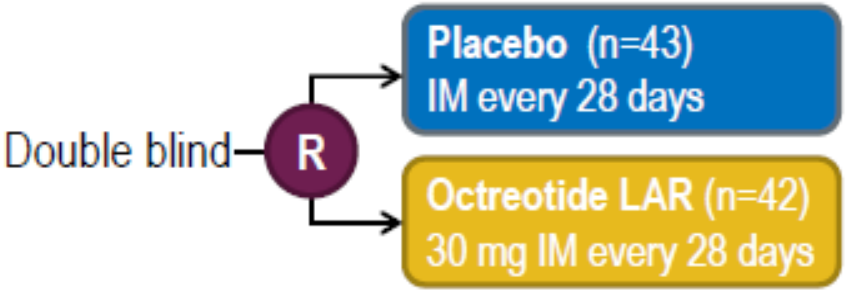


Iglesias- Garcia J et al. Gastroenterol 2010

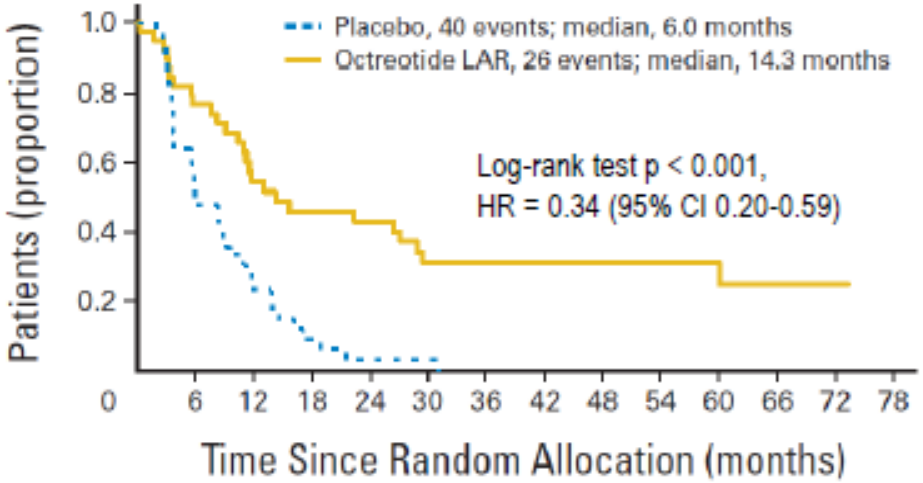
Anti – Tumour Medical therapy for Neuroendocrine Tumours

PROMID: OCTREOTIDE LAR - PHASE 3

- Patients with:
  - Treatment-naïve
  - Well differentiated (95% Ki-67 ≤2%)
  - Metastatic mid-gut NETs



- Primary endpoint:
  Time to tumour progression



No. of patients at risk

Placebo	43	21	9	3	1	1	0	0	0	0	0	0	0	0
Octreotide LAR	42	30	19	16	15	10	10	9	9	6	5	3	1	0

Octreotide LAR significantly lengthens time to tumour progression compared with placebo in patients with functionally active and inactive metastatic midgut NETs

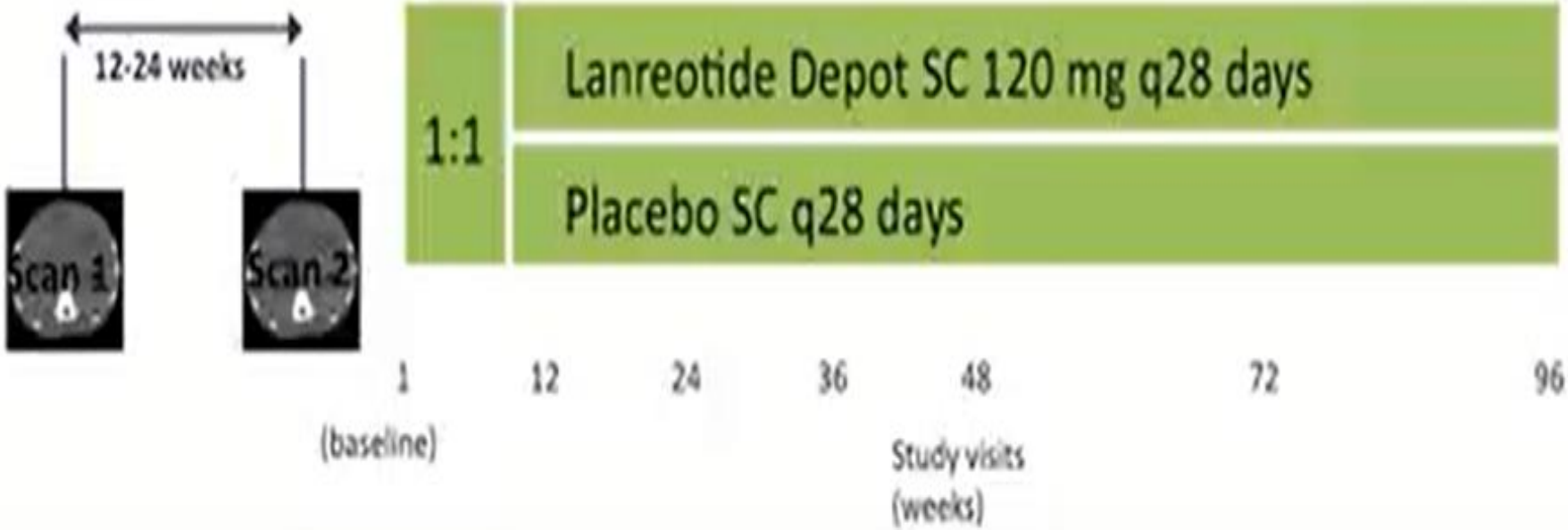
CLARINET : Study Design

JULY 17, 2014 371;3
The NEW ENGLAND JOURNAL of MEDICINE

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., and Philippe Ruszniewski, M.D., Ph.D., for the CLARINET Investigators*

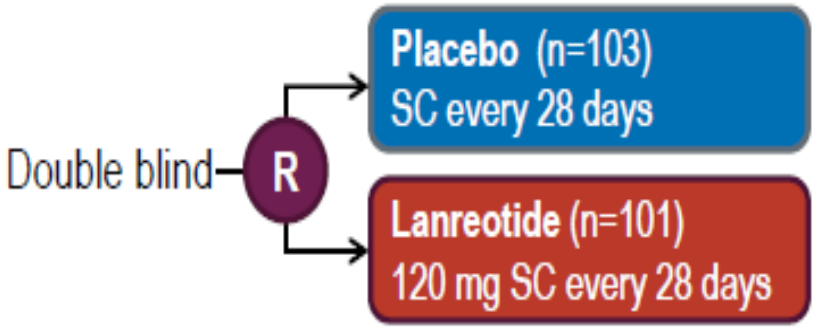
Study design:	Phase 3, 96-week, randomized, double-blind, placebo-controlled, multicenter study (14 countries: the US, India, and 12 European countries)
Population:	N=204 adults with well- or moderately differentiated, metastatic, and/or locally advanced unresectable GEP-NETs, and Ki-67 <10%
Treatments:	Lanreotide Depot 120 mg (fixed dose) vs placebo every 28 days

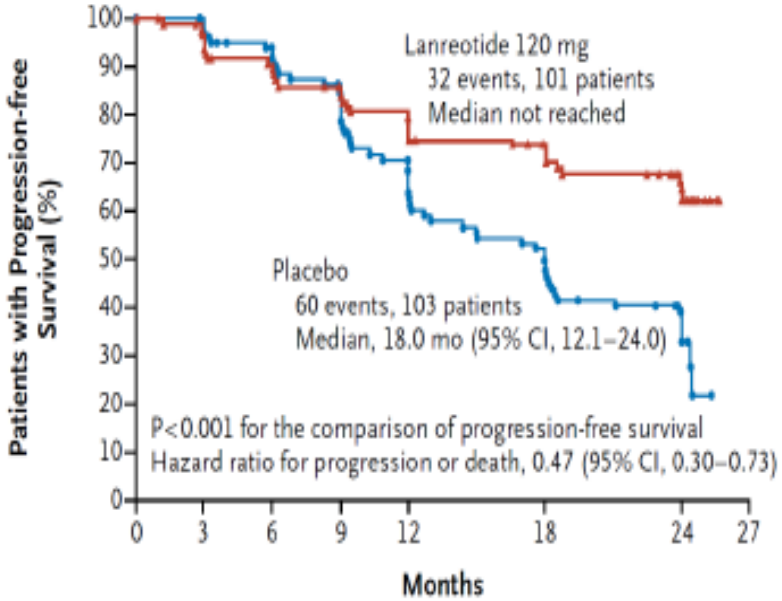


- Tumours originated in pancreas, mid-gut, hindgut or of unknown origin
- 96% no tumour progression in 3-6 months before randomisation
- 84% patients had no previous treatment
- Well differentiated (Ki-67<10%)

- Primary endpoint: Progression-free survival (PFS)

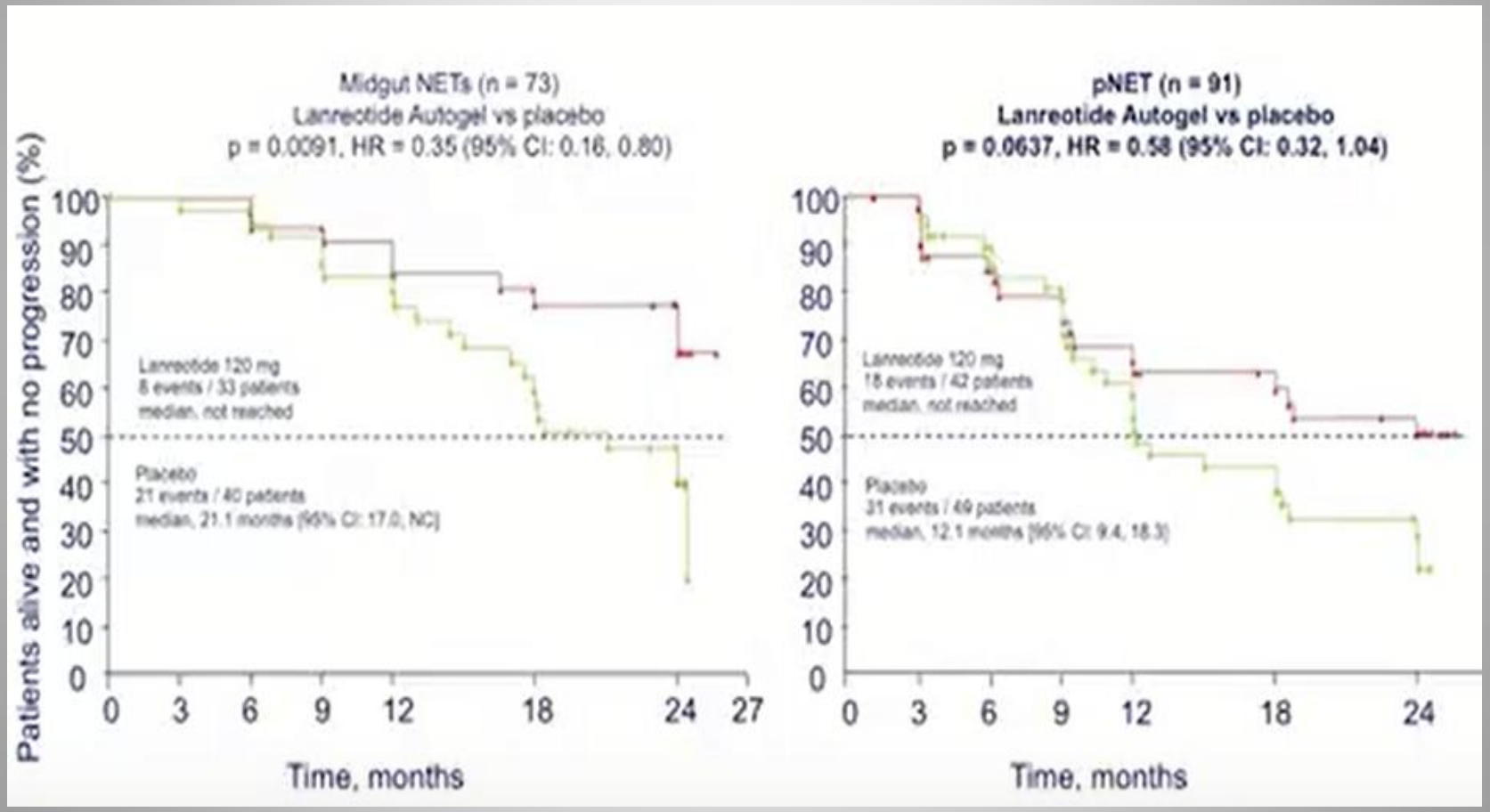
Lanreotide is associated with significantly prolonged PFS among patients with metastatic enteropancreatic NETs (Grade 1 or 2)





No. at Risk								
Lanreotide	101	94	84	78	71	61	40	0
Placebo	103	101	87	76	59	43	26	0

Subgroup analysis : Midgut & pNET



So, Where do SSA fit in ?

- SSA active as antiproliferative agents in a heterogeneous group of GEP-NETs
- HR for PFS similar Octreotide Vs Lanreotide
- Anti-proliferative effects appears to be strongest in mid-gut NETs.
- Observation may be appropriate in asymptomatic patients.

So, Where do SSA fit in?

- Appropriate 1st line agent in most WD NETs

✓ Low proliferation> high proliferation

✓ Low volume > high volume?

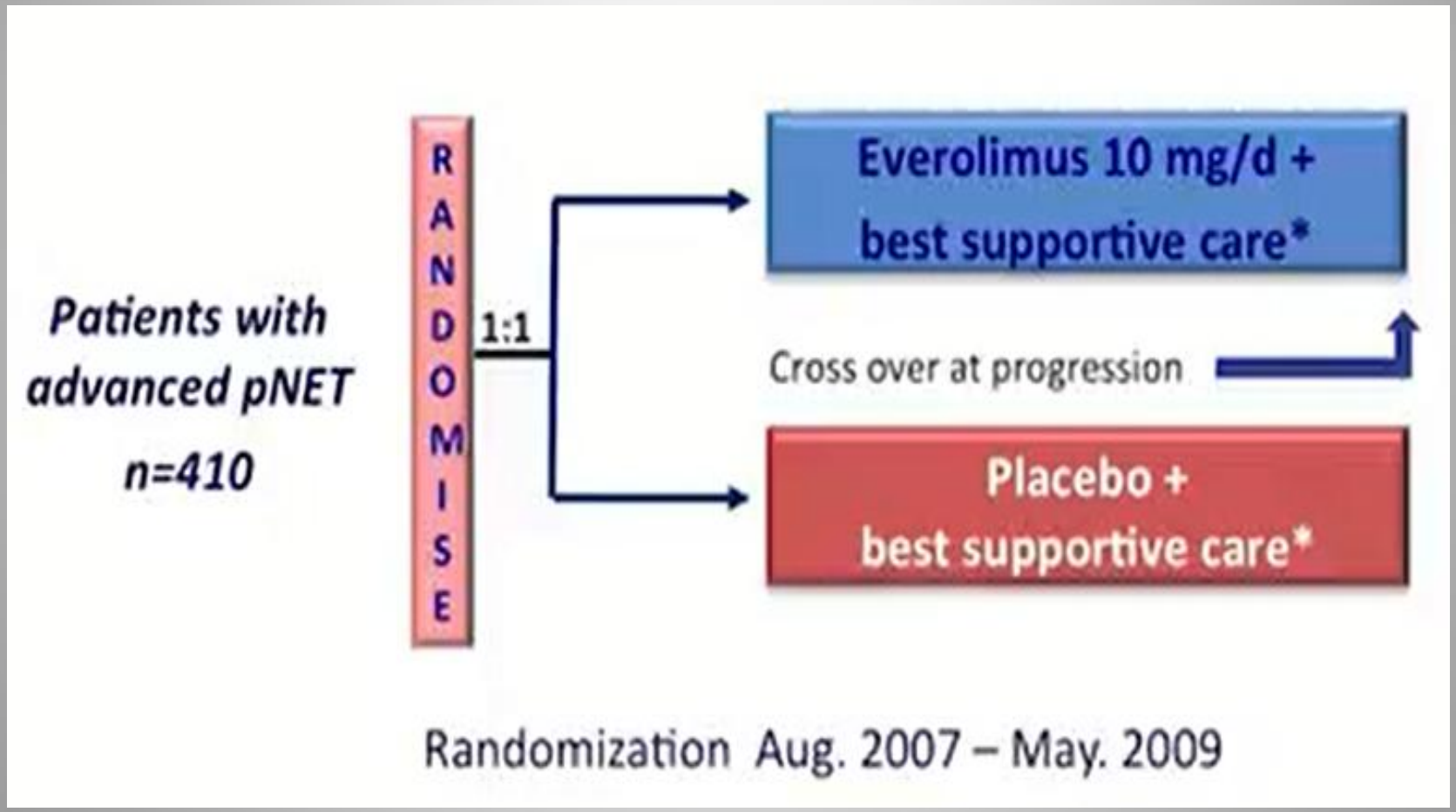
✓ Slow growing > fast growing

✓ Midgut> non mid gut

✓ SRS + >>> SRS neg

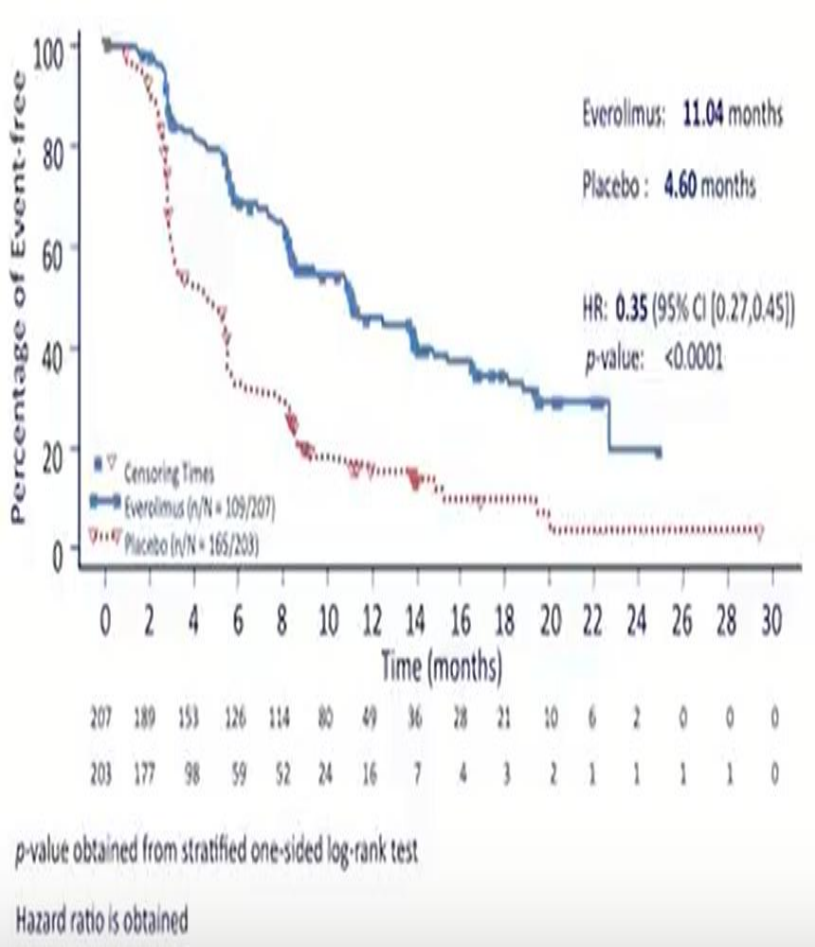
- Functioning and Non functioning

RADIANT 3: Ph –III trial advanced pNET

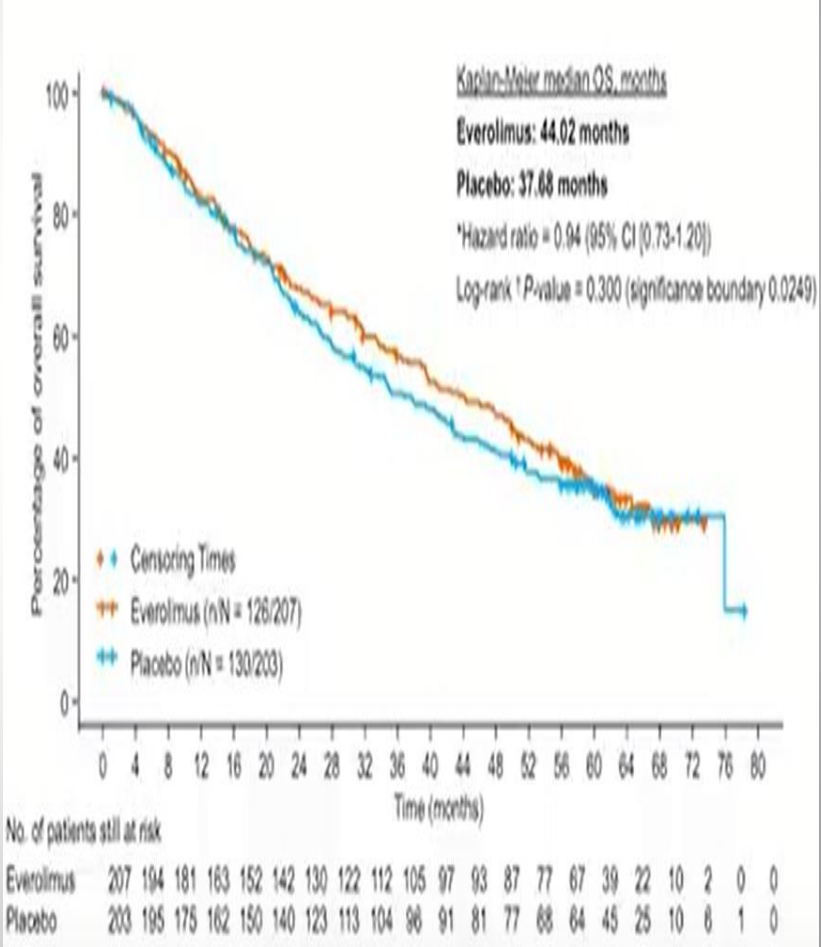


RADIANT -3: Results

PFS



OS



RADIANT -4 : Study Design

Patients with well-differentiated (G1/G2), advanced, progressive, nonfunctional NET of lung or GI origin (N=302)

- Absence of active or any history of carcinoid syndrome
- Pathologically confirmed advanced disease
- Radiologic disease progression in ≤ 6 months

RANDOMIZE 2:1

- Everolimus 10 mg/day N=205
- Placebo N=97

Treated until PD, intolerable AE, or consent withdrawal

Endpoints:

- **Primary:** PFS (central)
- **Key Secondary:** OS
- **Secondary:** ORR, DCR, safety, HRQoL (FACT-G), WHO PS, NSE/CgA, PK

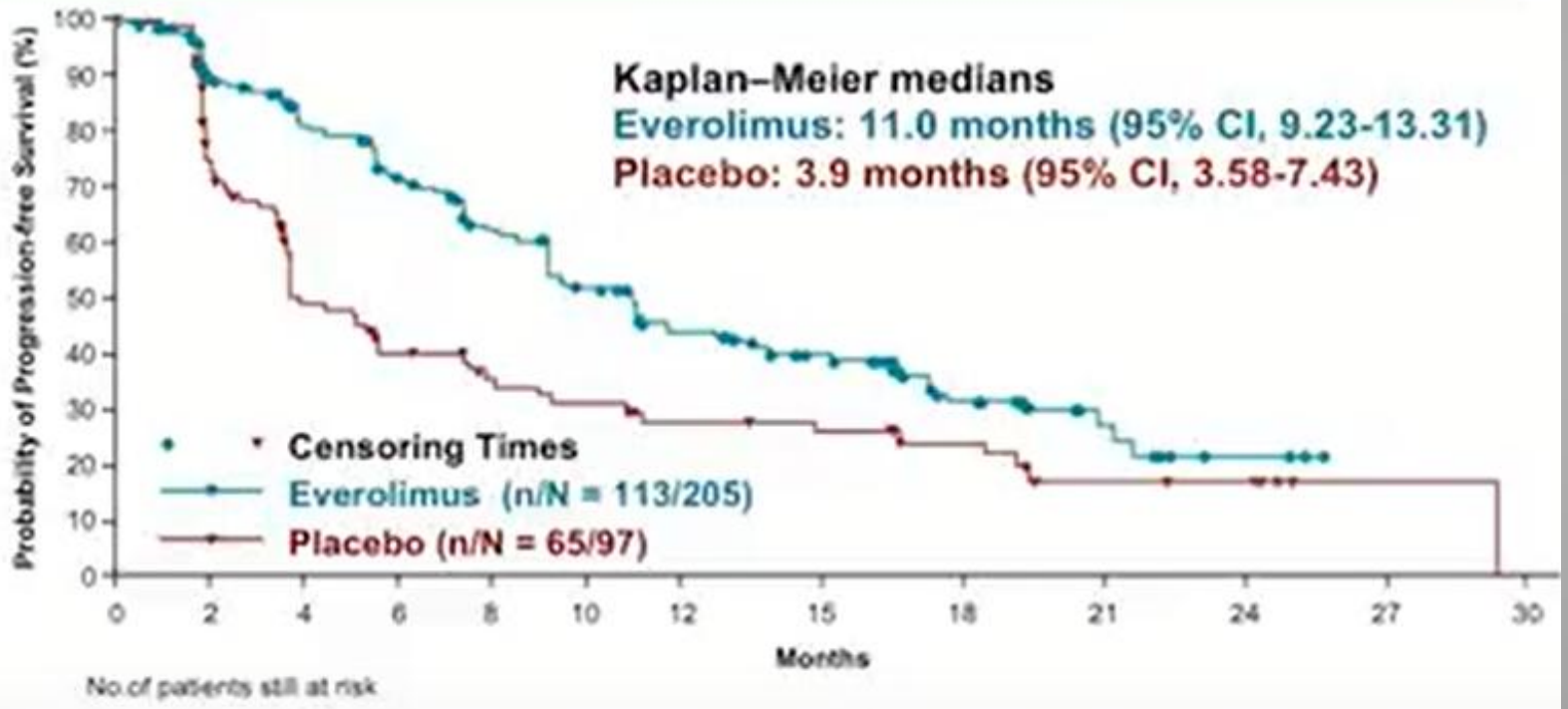
Stratified by:

- Prior SSA treatment (yes vs. no)
- Tumor origin (stratum A vs. B)*
- WHO PS (0 vs. 1)

PFS by Central review : Primary end point

52% reduction in the relative risk of progression or death with everolimus vs placebo

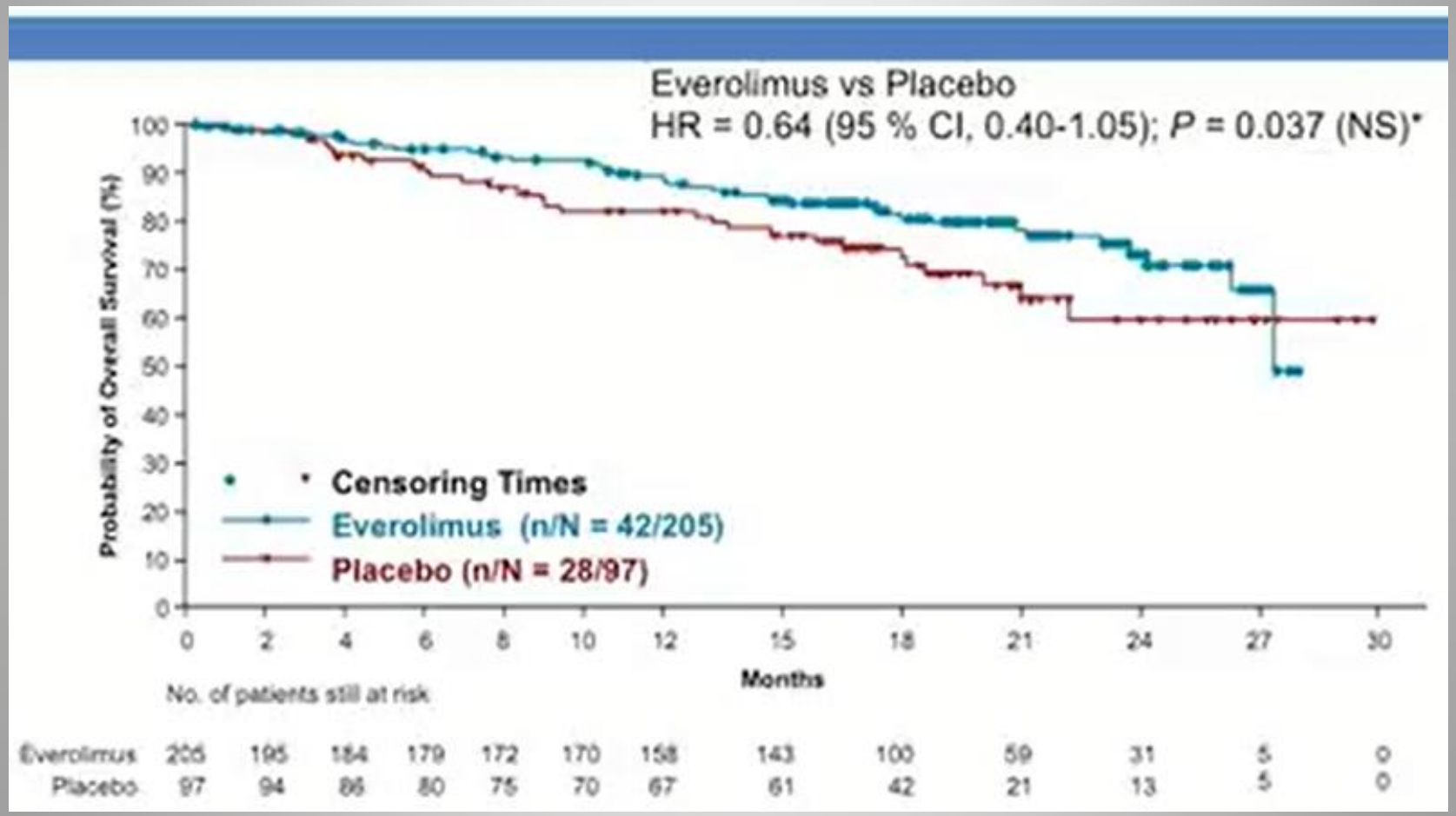
HR = 0.48 (95% CI, 0.35-0.67); *P* < 0.00001



No.of patients still at risk

Everolimus	205	168	145	124	101	81	65	52	26	10	3	0	0
Placebo	97	65	39	30	24	21	17	15	11	6	5	1	0

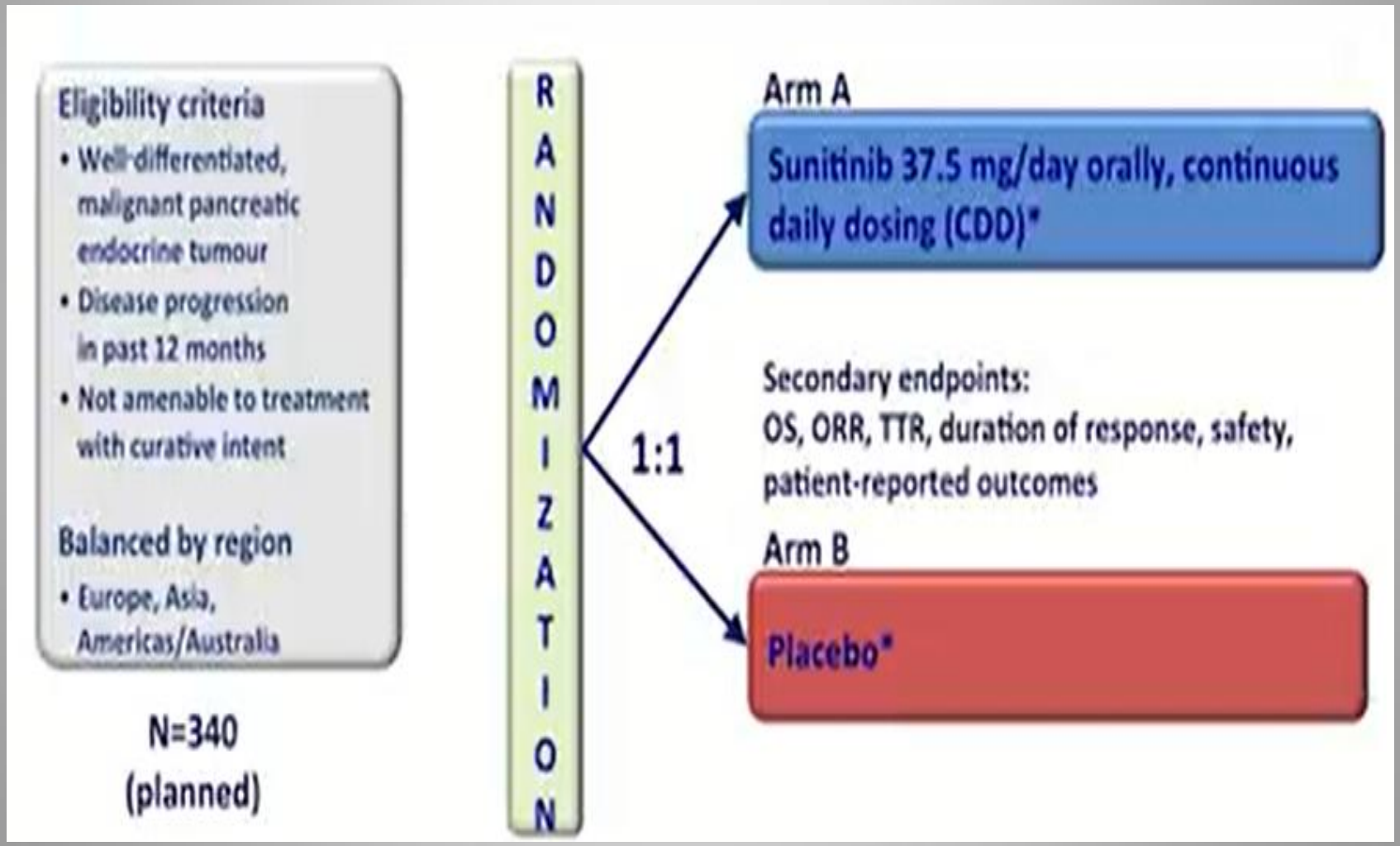
Interim OS results



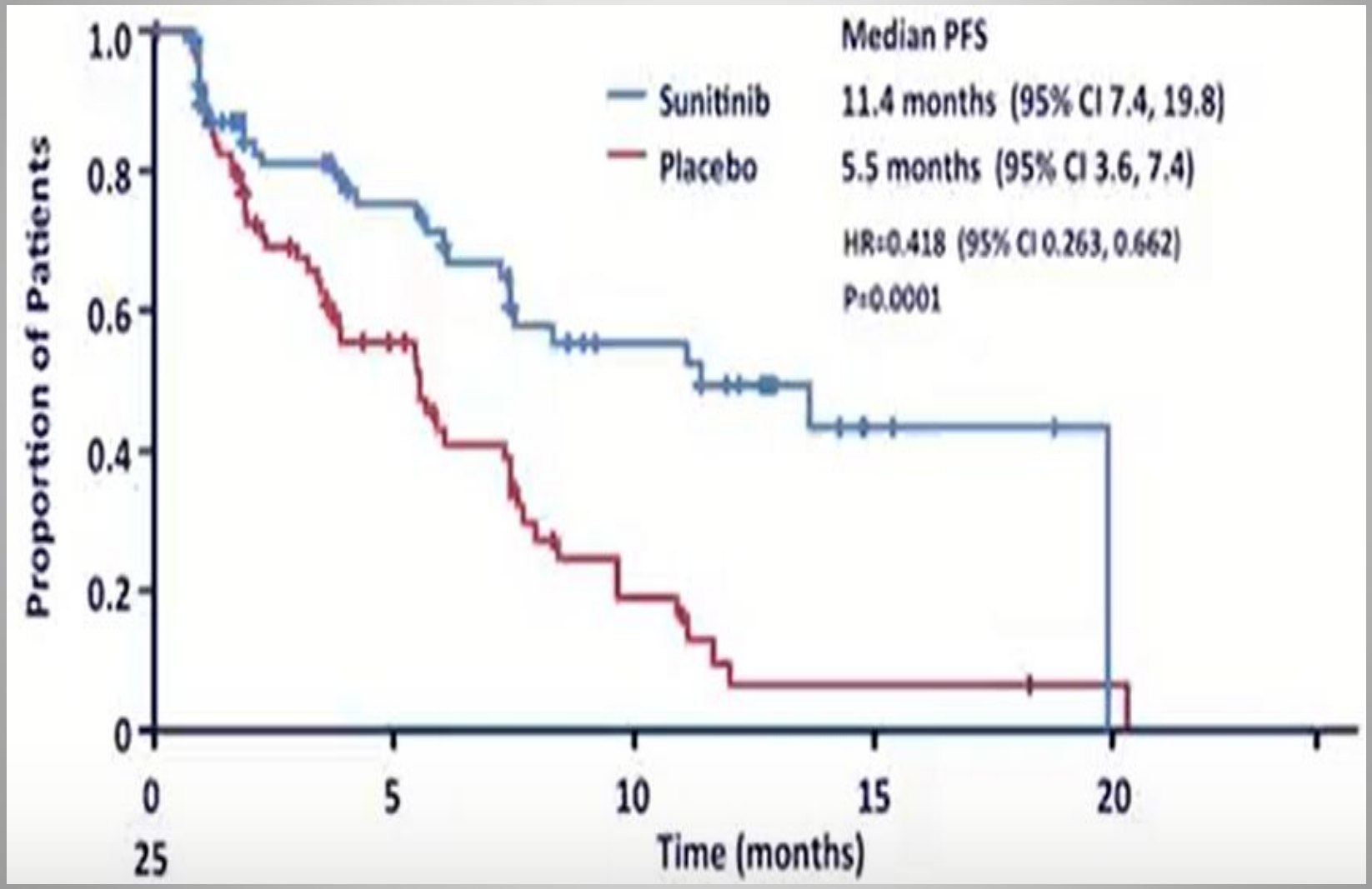
So, where does EVEROLIMUS fit in ?

- Active in a heterogeneous population of GEP-NETs.
- May be more active in Non-midgut Vs Midgut.
- SE profile may be challenging: need to select patients with clinically significant disease progression.
- Frail , elderly require vigilant monitoring. Consider low starting doses.

Sunitinib: Ph-III trial Sunitinib Vs Placebo in progressive pNETs



PFS


Median PFS
Sunitinib
11.4 months (95% CI 7.4, 19.8)
Placebo
5.5 months (95% CI 3.6, 7.4)
HR=0.418 (95% CI 0.263, 0.662)
P=0.0001
Proportion of Patients
1.0
0.8
0.6
0.4
0.2
0
0
5
10
15
20
25
Time (months)

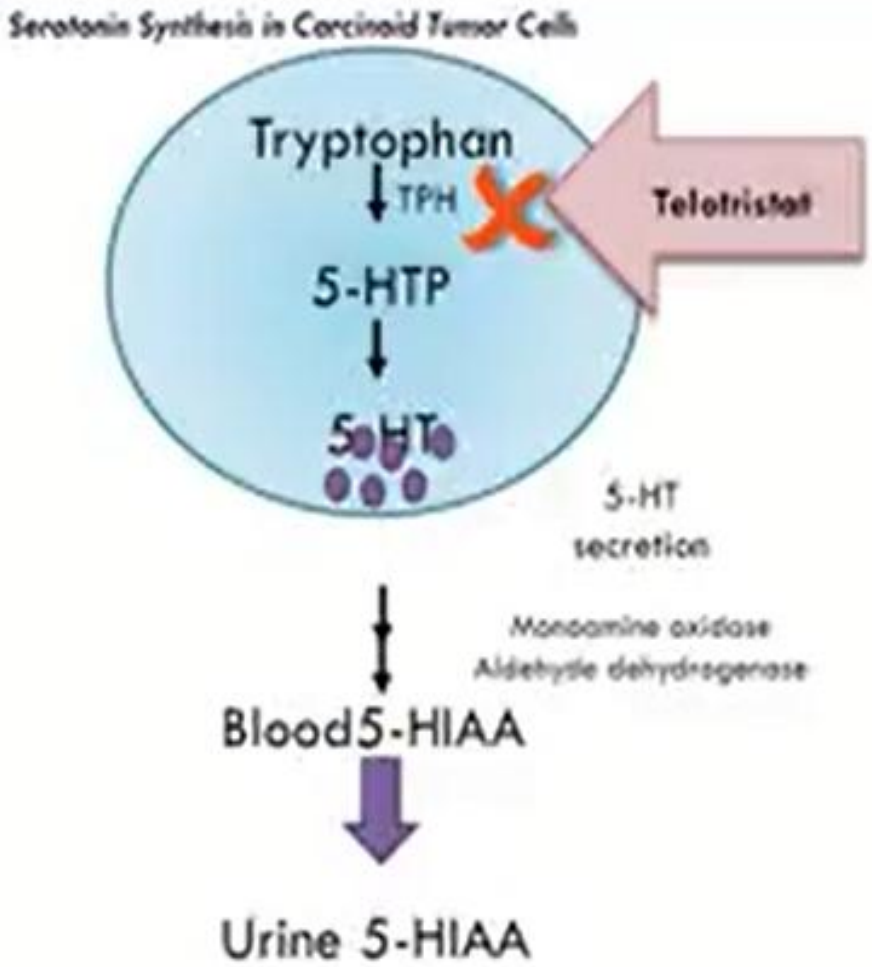
Sunitinib Vs Everolimus: pNET How to choose?

Comorbidity	Favors sunitinib	Favors everolimus
Hypertension		✓
Cardiovascular disease		✓
Bleeding diathesis		✓
Risk of perforation/fistula		✓
Diabetes	✓	
Underlying lung disease	✓	

Where do temozolamide based regimens fit in?

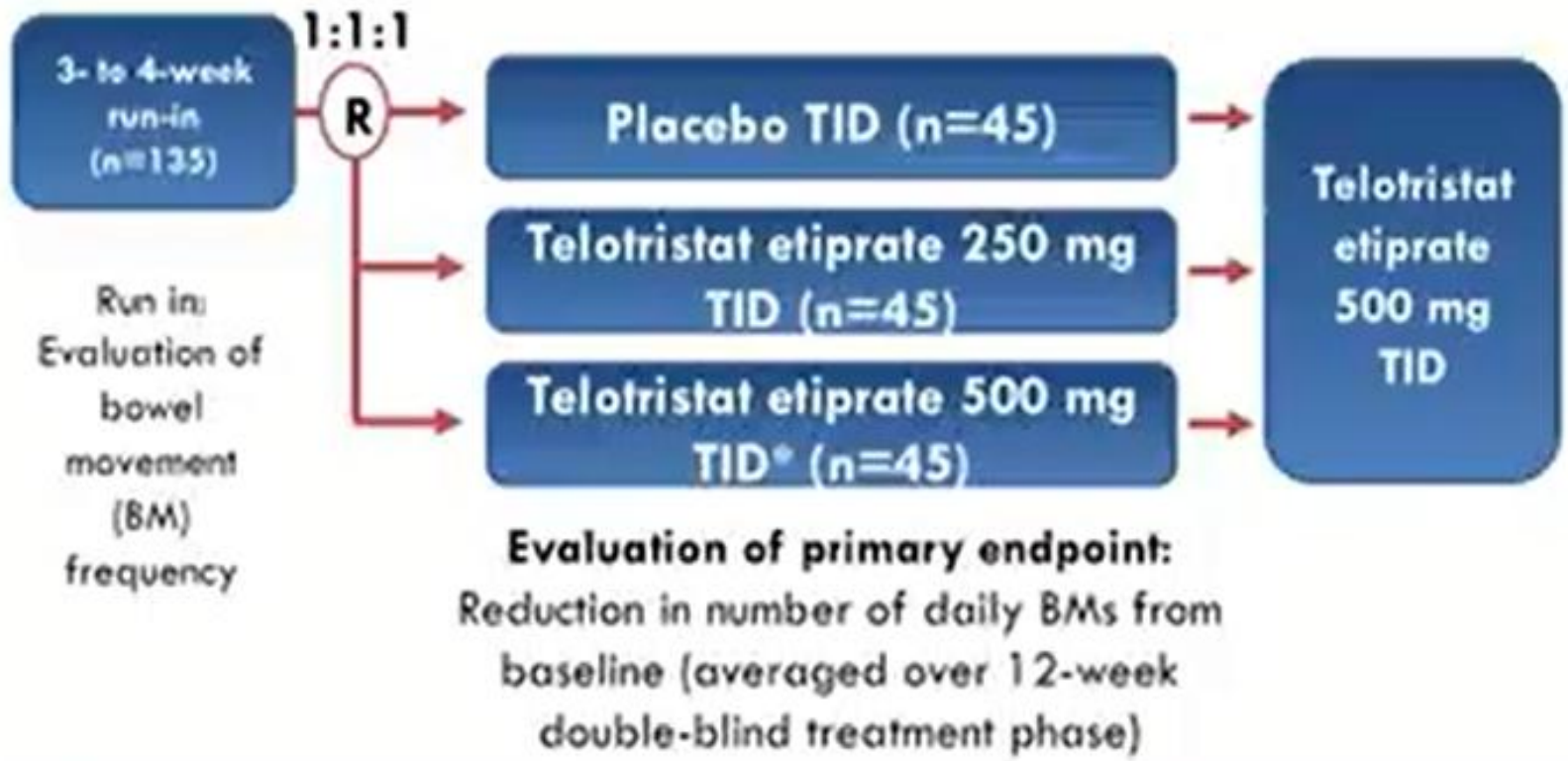
- Pancreatic NET> foregut/Lung NET> midgut NET
- Intermediate/High grade> low grade
- Fast growing> slow growing
- High tumour burden > Low burden
- Symptomatic > Non symptomatic
- MGMT deficient respond better?

Telotristat: Tryptophan hydroxylase inhibitor (TPH inhibitor)



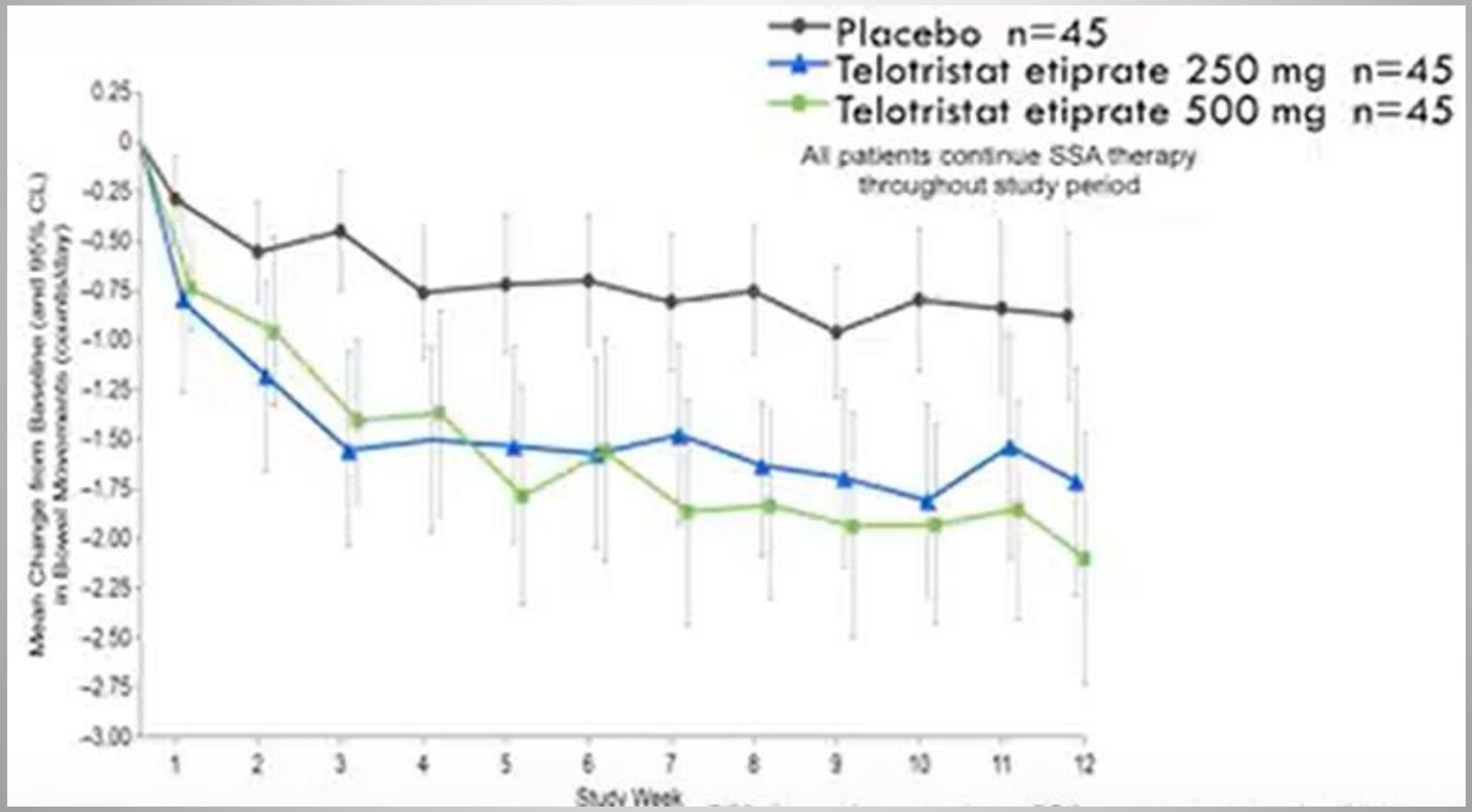
- Telotristat etiprate is a novel oral inhibitor of TPH, the rate-limiting enzyme in serotonin biosynthesis[1]
- Two early-stage clinical studies of telotristat etiprate demonstrated a favorable safety profile and evidence of clinical activity in carcinoid syndrome[2,3]
- Both preclinical and clinical studies suggested that telotristat etiprate is associated with minimal CNS activity[1-3]

TELESTAR : Ph -3, RCT



All patients required to be on SSA at enrollment and continue SSA therapy throughout study period

Reduction in daily Bowel movements



Surgical Management of Gastro-Entero-Pancreatic NETs

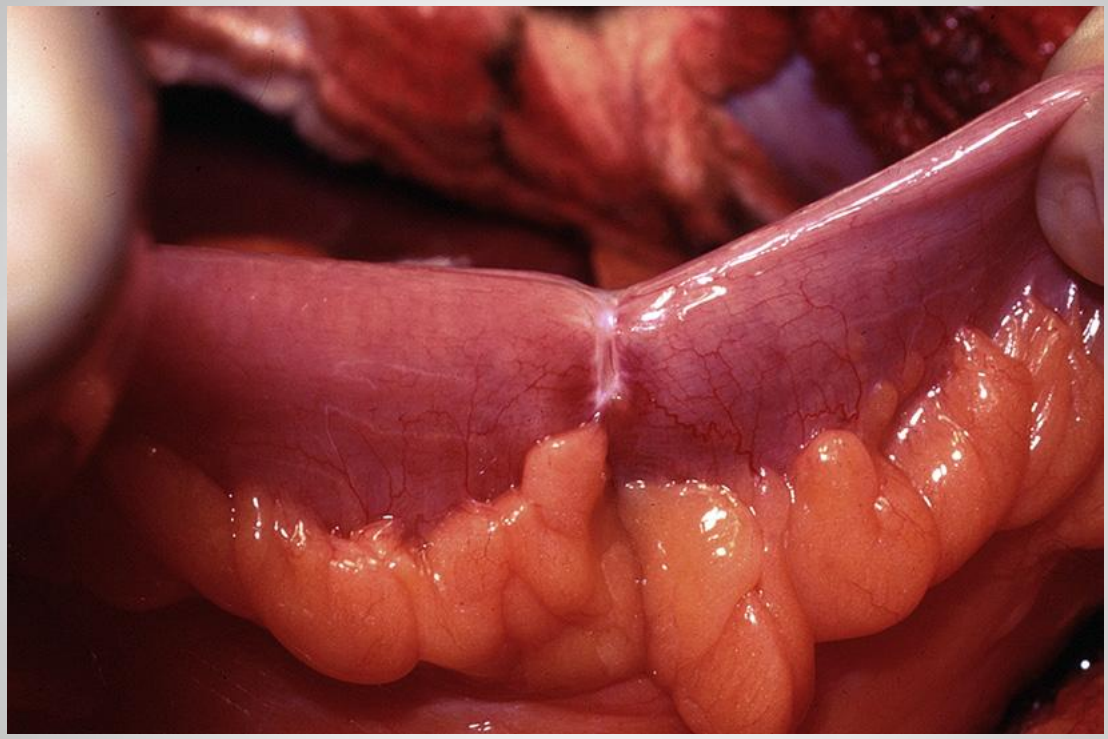
pNETs

- Goal of surgery – Maximal parenchyma preservation
- Enucleation (preferred)
- Central pancreatectomy
- Standard resections (large lesions, nodal disease)
  - Pancreatico-duodenectomy,
  - Distal pancreatico-splenectomy,
  - Distal pancreatectomy

EUS – distance btw duct and tumor

Disease	Localized	Regional	Distant		
Stage	**I/II**	**III**	**IV**		
TNM	T1–3N0M0	T4N0M0 T1–4N1M0		TxNxM1	
Surgical treatment	**Radical** resection		**Radical** resection **with curative intent**	**Palliative** resection	**No** resection
	Local radical open (or in selected pts) laparoscopic resection* of • primary tumor(s)** • lymph nodes (dissection along the superior mesenteric root)		Local radical open resection of • primary tumor(s) • lymph nodes (dissection along the superior mesenteric root) in combination with: • mets (liver)	Local radical open (in selected pts) laparoscopic resection of • primary tumor(s) • lymph nodes (dissection along the superior mesenteric root)	Due to: • local inoperability • comorbidity
Aim	Free from tumor		Free from tumor	• To avoid local complications (obstruction, bleeding etc.) • To possibly improve prognosis*	

Specific issues with SB- NENs



Small lesions, - intra-op palpation – best modality
(VCE and CT enteroclysis) – fare worse
Multiple tumors (20%)

Appendiceal NETs

- Usually asymptomatic
- Do not have "carcinoid" symptoms
- Usually G1-G2

Early tumors – Appendicectomy

- <1 cm
- Invasion upto subserosa
- Mesoappendix free
- Tip lesions (70%)
- Margins free

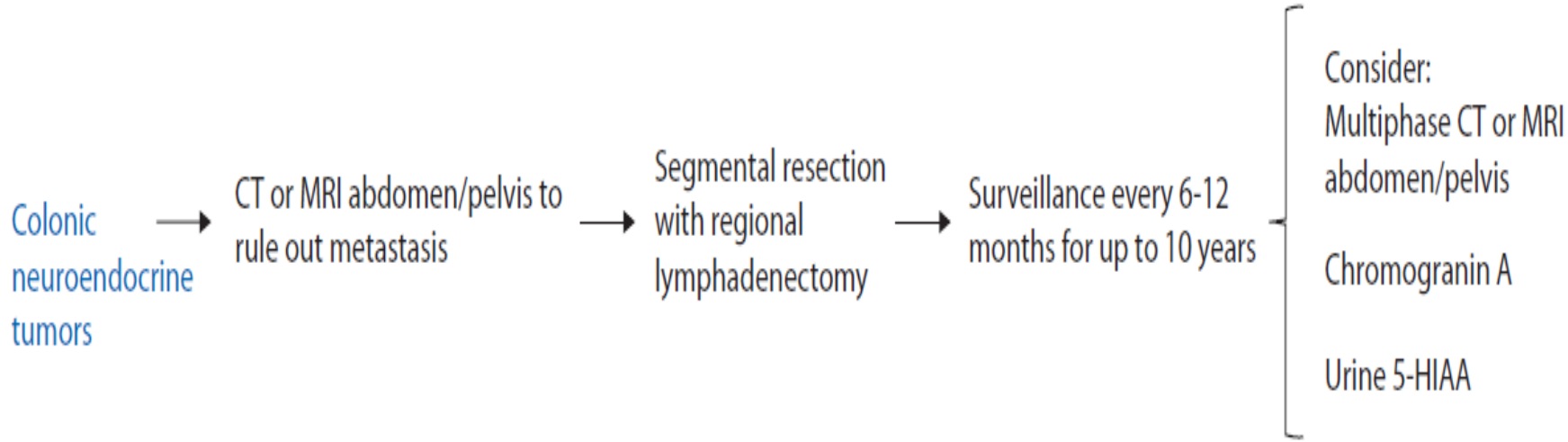
Locally advanced tumors –radical right hemicolectomy

- > 1-2 cm
- Serosal involvement
- >3mm infiltration of mesoappendix
- Base involved
- Suspicious nodes
- 40% risk of mets

Appendiceal NETs

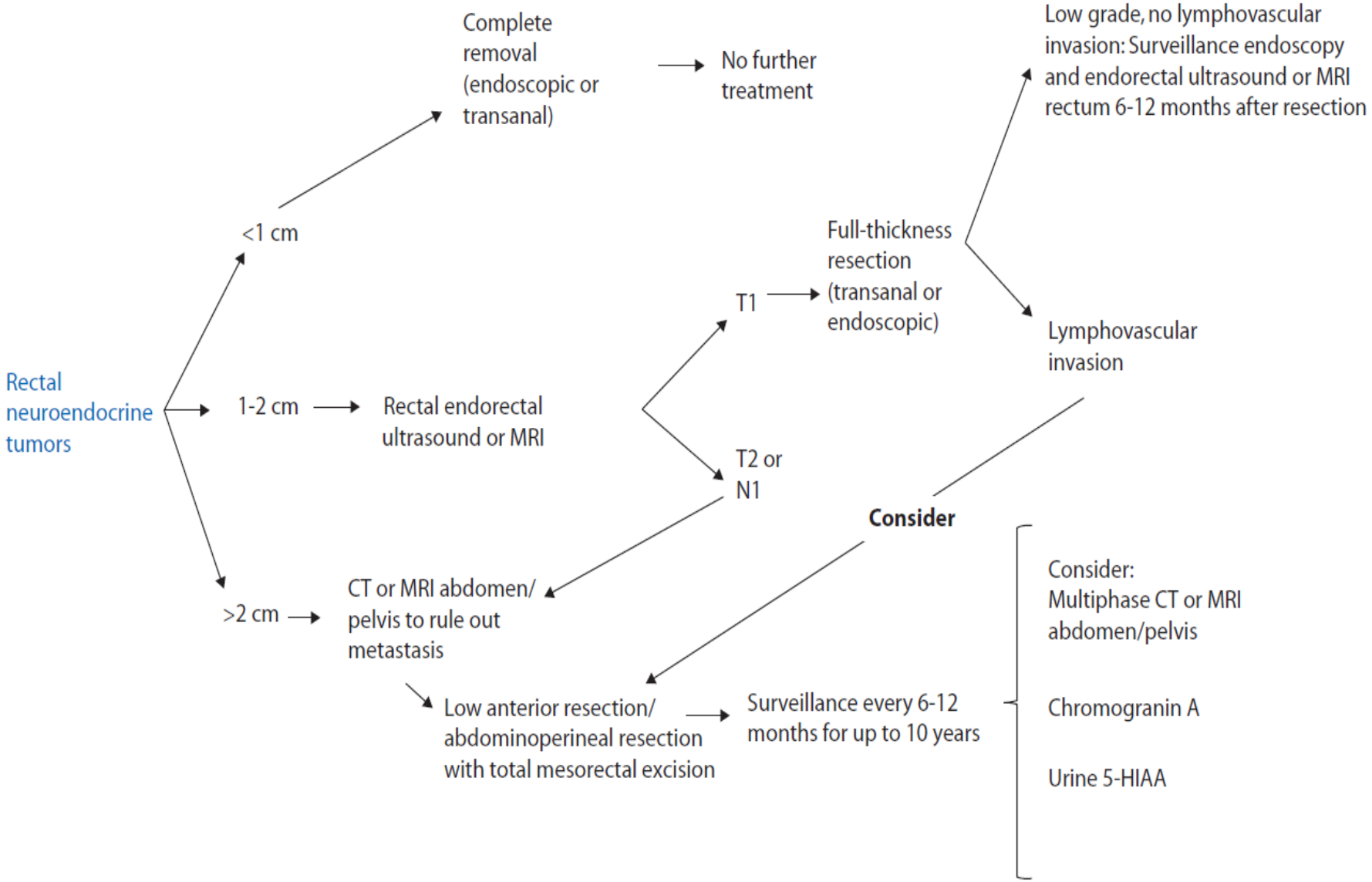
- G3 lesions – treat like AdenoCa
- Incidentally detected after appendicectomy
  - Imaging (CT/MRI + SR PET-CT)
  - Suspicion of mets / high risk features on HPE – radical colectomy

Colon NETs



Resection of primary in high grade colorectal NENs with or without metastases does not result in improved prognosis (median survival 13 months). – Similar to SCLC

Rectal NETS


Rectal neuroendocrine tumors
<1 cm
Complete removal (endoscopic or transanal)
No further treatment
1-2 cm
Rectal endorectal ultrasound or MRI
T1
Full-thickness resection (transanal or endoscopic)
Low grade, no lymphovascular invasion: Surveillance endoscopy and endorectal ultrasound or MRI rectum 6-12 months after resection
Lymphovascular invasion
T2 or N1
>2 cm
CT or MRI abdomen/ pelvis to rule out metastasis
Consider
Low anterior resection/ abdominoperineal resection with total mesorectal excision
Surveillance every 6-12 months for up to 10 years
Consider:
Multiphase CT or MRI abdomen/pelvis
Chromogranin A
Urine 5-HIAA

Liver metastases

- Patterns of involvement:
  - single metastasis of any size (type 1)
  - isolated metastatic bulk accompanied by smaller deposits, with both liver lobes always involved (type 2)
  - Disseminated metastatic spread, with both liver lobes always involved, single lesion of varying size, and virtually no normal liver parenchyma (type 3)

Liver metastases

- Type I – Surgery vs RFA
- Type III – if criteria are met – liver transplantation

- Type II - Palliative cytoredutive surgery
  - Combination of Surgery/RFA/systemic treatment
  - Two staged procedures (Primary resection + Portal vein ligation -> liver surgery , ALPPS)
  - 90% debulking – improve survival (60% vs 30%)

Liver metastases

- Milan criteria for liver transplantation in NETs:
  - i) well-differentiated NETs (Ki67 < 5%);
  - ii) portosystemic tumor drainage;
  - iii) patient age < 55 years;
  - iv) stable disease for at least 6 months;
  - v) pre-transplant R0 primary tumor resection;
  - vi) hepatic tumor involvement < 50% of the liver volume; and
  - vii) absence of extra-hepatic disease

Cholecystectomy

- Prophylactic cholecystectomy in all patients undergoing surgery

- Why?
  - Cholestasis and cholecystitis risk with SSAs
  - Biliary necrosis due to TACE/TARE

To summarise the role of surgery

- Curative intent – early stage
- Cytoreductive intent – good prognostic metastatic lesions (small bowel, appendix,pancreatic esp)
- Palliative intent -(bleeding, obstruction, perforation, hormonal symptoms);

Mahatma Gandhi
Cancer Hospital &
Research Institute

PRRT
Peptide Receptor Radionuclide Therapy

Therapeutic Nuclides

Gamma

- 111 In: 2.8 days
- Auger Electrons
- Short path length
- Relatively high LET

Beta

- 177 Lu : 6.7 days, 490 kev
- 90 Y : 2.7 days, 2.2Mev

Alpha

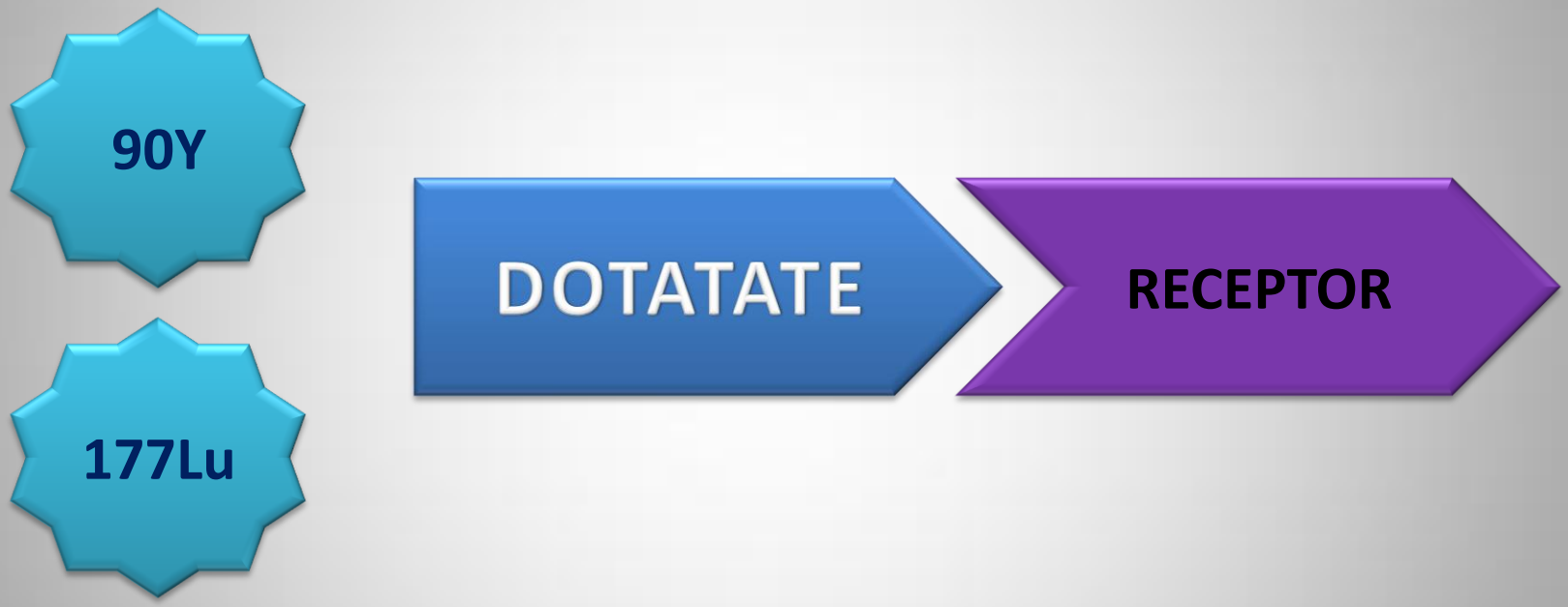
- Ac 225
- Bi 213
- Very High LET
- Short path length

Comparison of [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate and [^{177}Lu-DOTA^{0}, Tyr^{3}]octreotide: which peptide is preferable for PRRT?

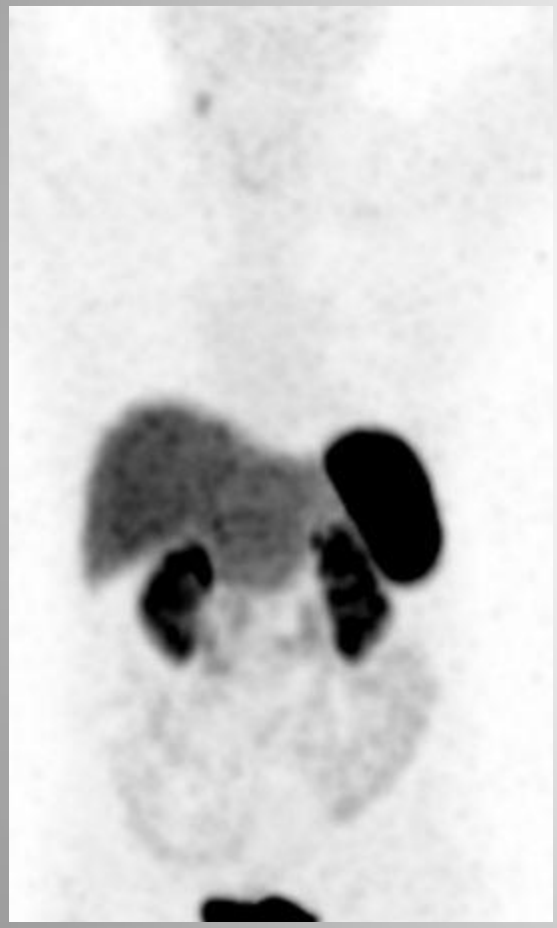
J. P. Esser[1, 2], E. P. Krenning[1], J. J. M. Teunissen[1], P. P. M. Kooij[1], A. L. H. van Gameren[1], W. H. Bakker[1], D. J. Kwekkeboom[1]

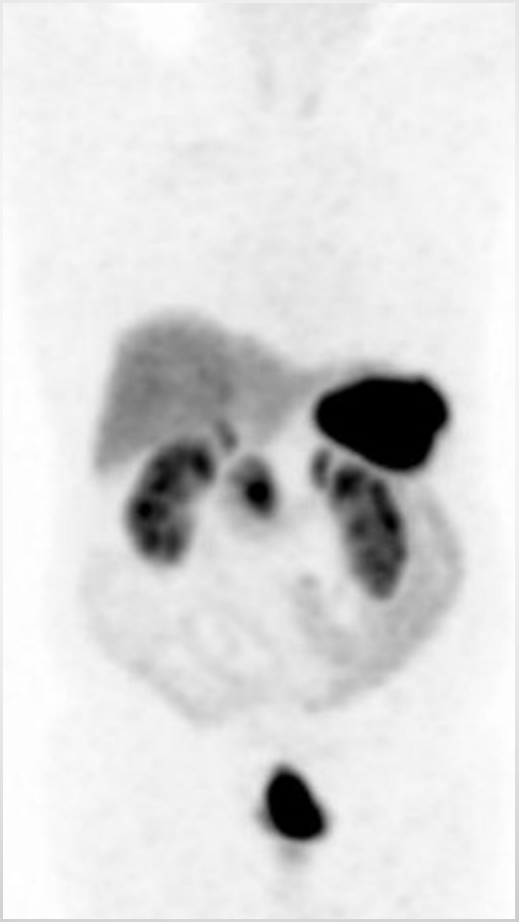
Results: All patients had longer residence times in spleen, kidneys and tumours after use of ^{177}Lu-DOTATATE (p=0.016 in each case). Comparing ^{177}Lu-DOTATATE with ^{177}Lu-DOTATOC, the mean residence time ratio was 2.1 for tumour, 1.5 for spleen and 1.4 for kidneys. Dose-limiting factors for PRRT are bone marrow and/or kidney dose. Although the residence time for kidneys was longer when using ^{177}Lu-DOTATATE, the mean administered dose to tumours would still be advantageous by a factor of 1.5, assuming a fixed maximum kidney dose is reached. Plasma radioactivity after ^{177}Lu-DOTATATE was comparable to that after ^{177}Lu-DOTATOC. Urinary excretion of radioactivity was comparable during the first 6 h; thereafter there was a significant advantage for ^{177}Lu-DOTATOC.

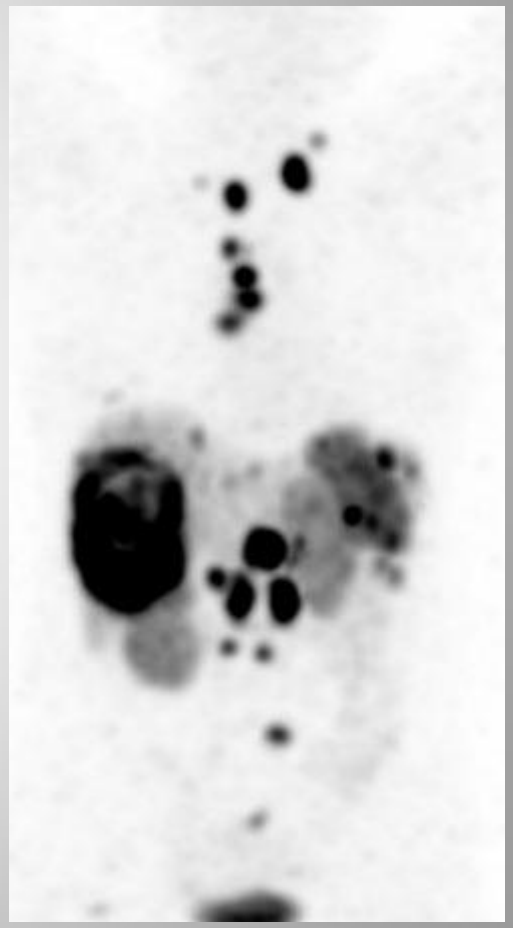
Eur J Nucl Med Mol Imaging (2006) 33:1346–1351

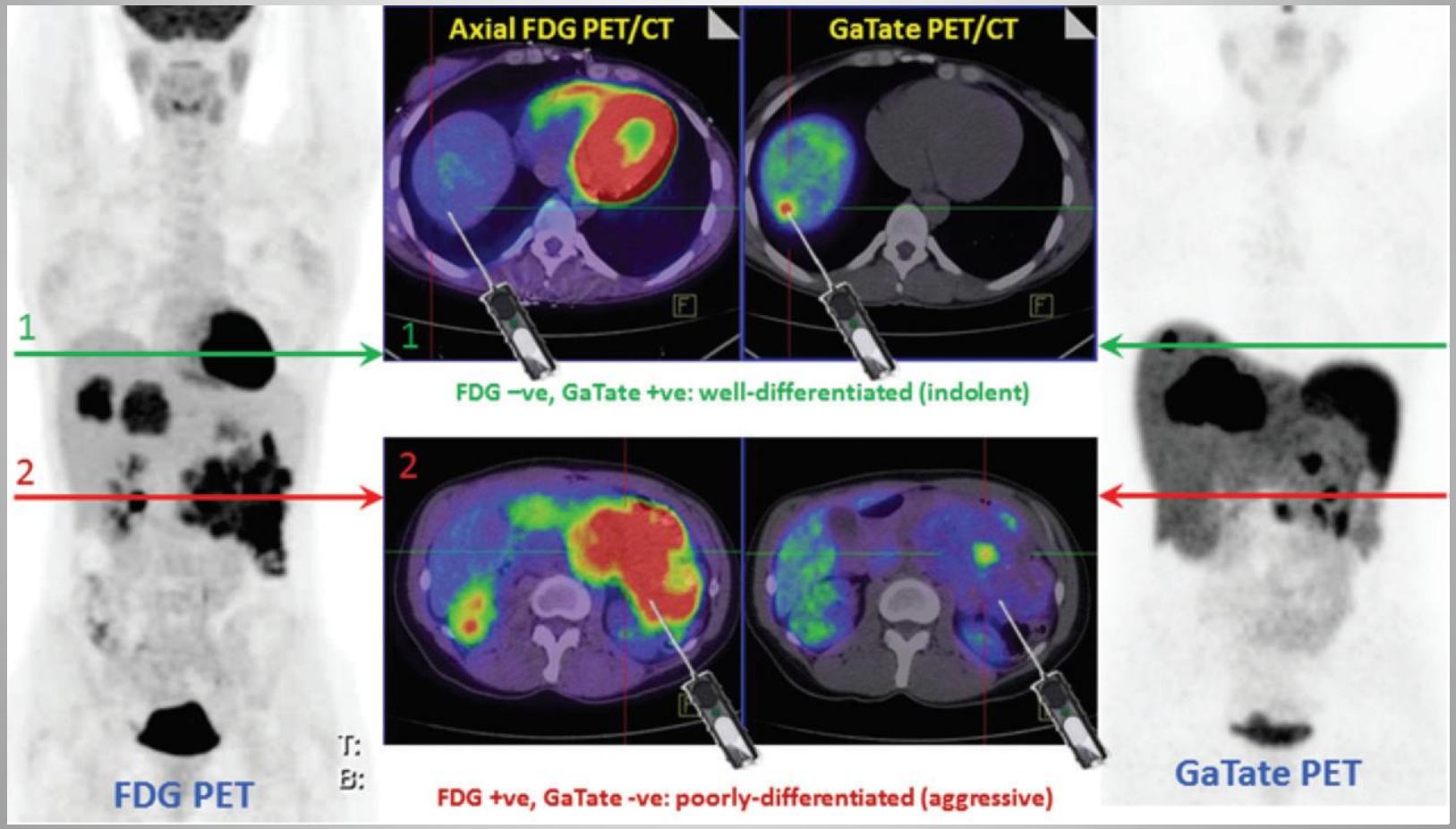

90Y
177Lu
DOTATATE
RECEPTOR

Prerequisite – SSR Expression









Hofman et al | RG • Volume 35 Number 2

PRRT

- Prerequisite :
  - Demonstrate Expression of SSR
  - Krenning Grade 3 / 4

- Contra-indications:
  - Pregnancy
  - Acute illness
- Relative CI:
  - Renal Failure
  - WBC<3,000/µl, with absolute neutrophil count <1,000/µl
  - PLT <75,000/µl
  - RBC < 3000000/ µl

Renal Protection

- Aminoacid infusion
- Gelofusine
- 25g Lysine and 25 g arginine in 1 – 2 litres
- Infused starting 30 minutes prior to RP injection and continued for total 4 hours

Octreotide withdrawal

- 4-6 weeks for long acting
- 24 hours for short acting

RP administration

- 177Lu – 150 t0 200mCi
- 90 Y – 100mCi / m^2
- 98% Radiochemichal purity
- 100 to 200 µg Peptide
- Specific activity
  - 177 Lu - specific activity of 37 to 74 MBq (1–2 mCi) 177Lu per microgram of precursor
  - 90Y – 35mCi / µg
- Time interval – 6-8weeks Total 3-5 cycles
- Combined 90Y and 177Lu / Sequential treatment
- Children : 5-10mCi/kg

SIDE EFFECTS - ACUTE

- Nausea, Vomiting
- Hyperkaliemia, Metabolic Acidosis
- Hepatotoxicity
- Hematological
  - Transient
  - Platelets
  - 10-12% 90Y
  - 2-3% 177Lu
- Hormonal Crisis <1%

SIDE EFFECTS - CHRONIC

- Renal Toxicity:
  - More with 90 Yttrium despite renal protection
- Marrow Toxicity

J Nucl Med. 2018 Mar;59(3):452-458. doi: 10.2967/jnumed.117.189712. Epub 2017 Aug 3.

Persistent Hematologic Dysfunction after Peptide Receptor Radionuclide Therapy with 177Lu-DOTATATE: Incidence, Course, and Predicting Factors in Patients with Gastroenteropancreatic Neuroendocrine Tumors.

Bergsma H[1], van Lom K[2], Raaijmakers MHGP[2], Konijnenberg M[3], Kam BLBLR[3], Teunissen JJM[3], de Herder WW[4], Krenning EP[3], Kwekkeboom DJ[3].

- MDS and Leukimias and Aplastic anemia do occur
- Up to 4% of patients
- Median time to development if ~41 months

Treatment With the Radiolabeled Somatostatin Analog [^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate: Toxicity, Efficacy, and Survival

J Clin Oncol 26:2124-2130. © 2008

Results

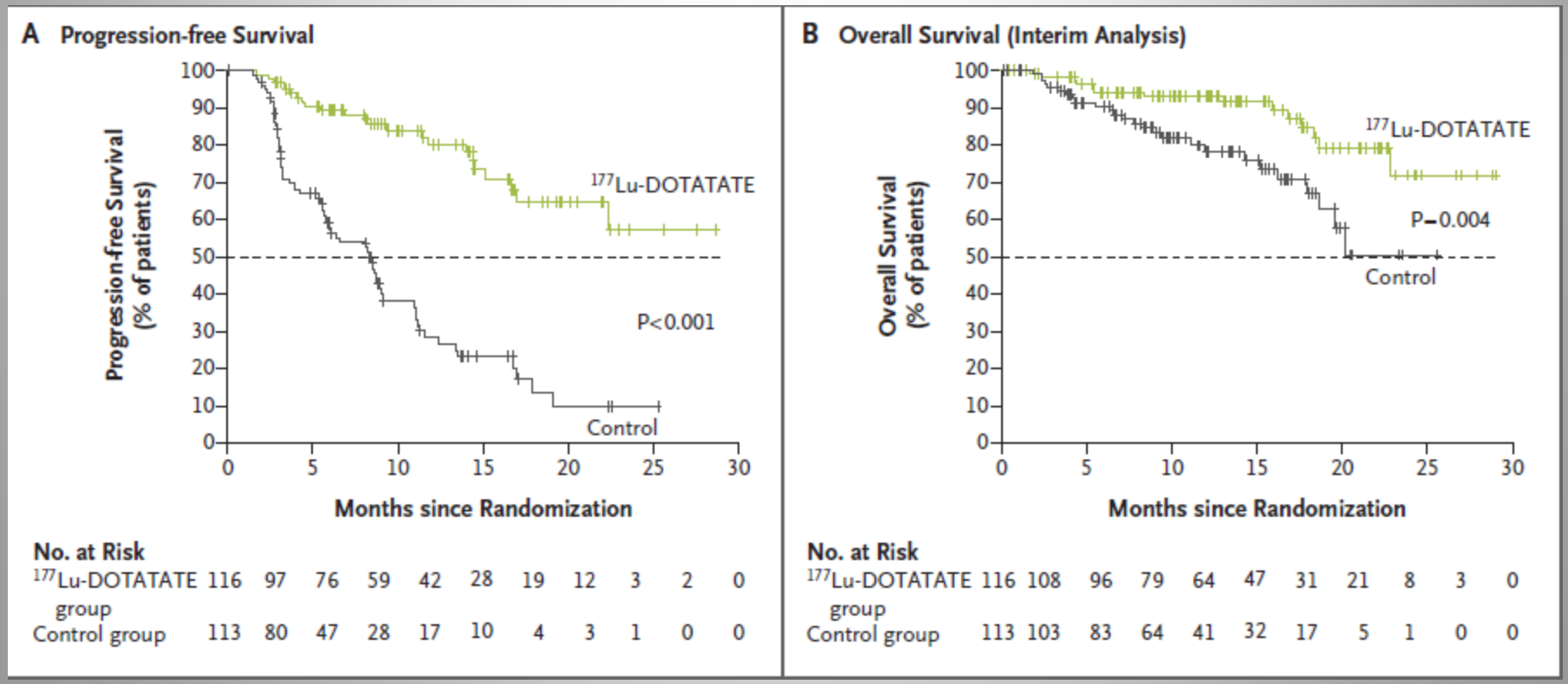
Any hematologic toxicity grade 3 or 4 occurred after 3.6% of administrations. Serious adverse events that were likely attributable to the treatment were myelodysplastic syndrome in three patients, and temporary, nonfatal, liver toxicity in two patients. Complete and partial tumor remissions occurred in 2% and 28% of 310 GEPNET patients, respectively. Minor tumor response (decrease in size > 25% and < 50%) occurred in 16%. Median time to progression was 40 months. Median OS from start of treatment was 46 months, median OS from diagnosis was 128 months. Compared with historical controls, there was a survival benefit of 40 to 72 months from diagnosis.

Conclusion

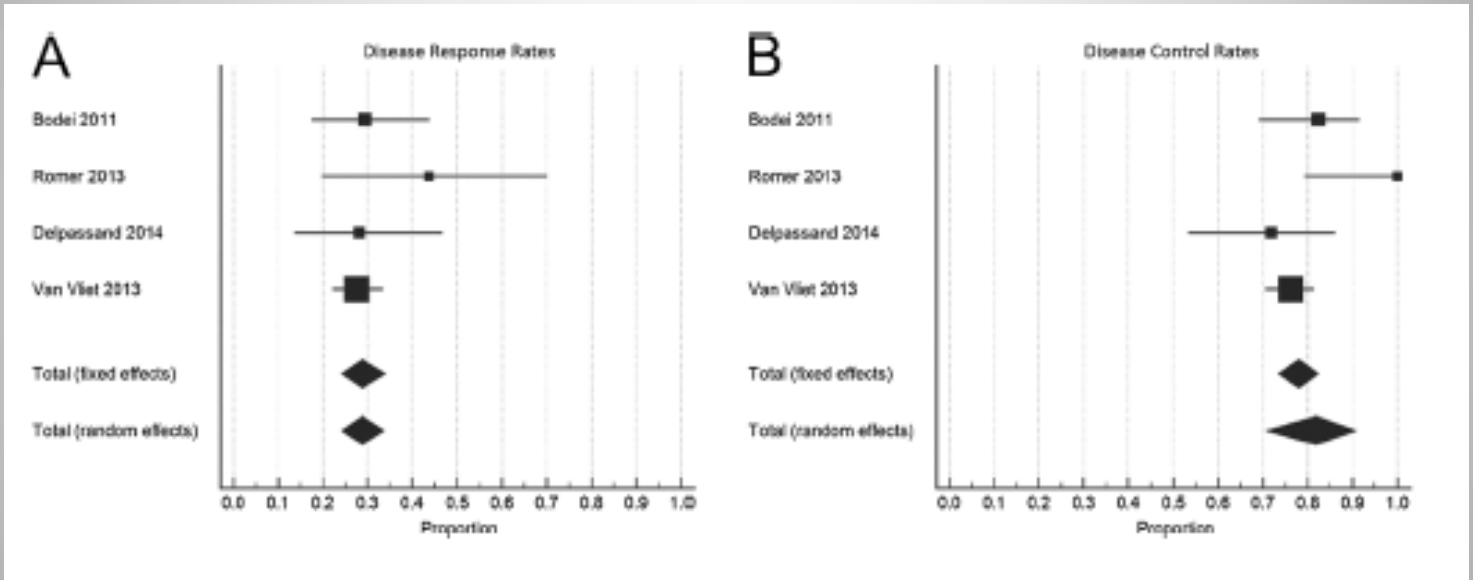
Treatment with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate has few adverse effects. Tumor response rates and progression-free survival compare favorably to the limited number of alternative treatment modalities. Compared with historical controls, there is a benefit in OS from time of diagnosis of several years.

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srirajaskanthan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators*



Disease Control – Imaging Response



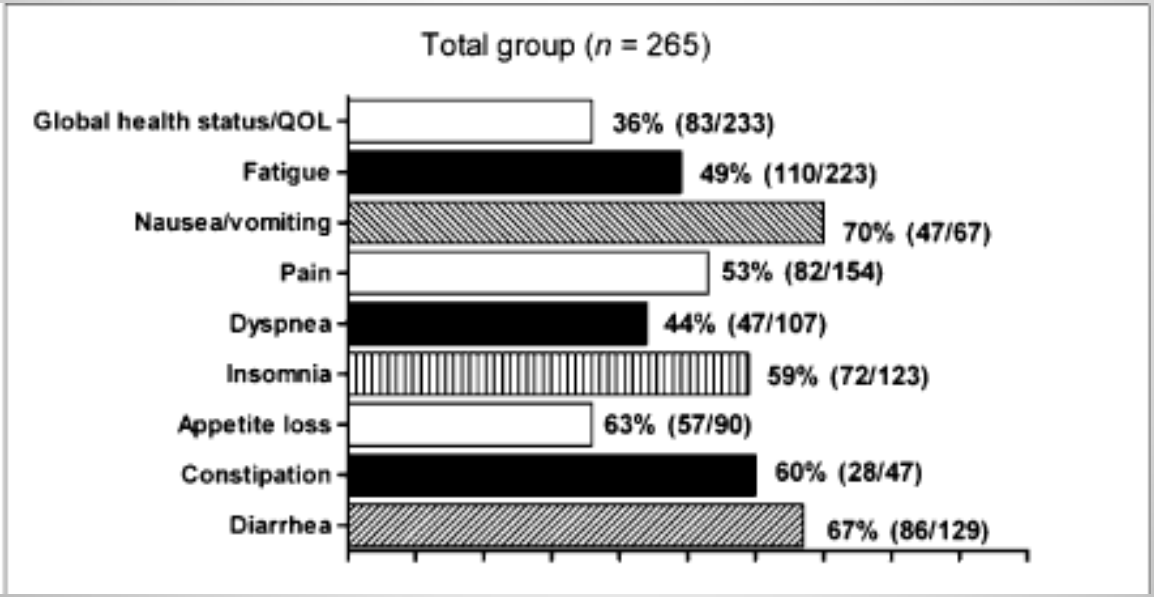
The efficacy of ^{177}Lu-labelled peptide receptor radionuclide therapy in patients with neuroendocrine tumours: a meta-analysis

Eur J Nucl Med Mol Imaging (2015) 42: 1964–1970

Quality of Life in 265 Patients with Gastroenteropancreatic or Bronchial Neuroendocrine Tumors Treated with [^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate

Saima Khan, Eric P. Krenning, Martijn van Essen, Boen L. Kam, Jaap J. Teunissen, and Dik J. Kwekkeboom

J Nucl Med 2011; 52:1361–1368



PRCRT – Peptide receptor Chemo RT

- N = 52
- Progressive disease despite prior treatments
- Median PFS 48 months
- Median OS not reached
- 30% objective imaging response (CR and PR)

Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-014-2906-4

ORIGINAL ARTICLE

Favourable outcomes of ^{177}Lu-octreotate peptide receptor chemoradionuclide therapy in patients with FDG-avid neuroendocrine tumours

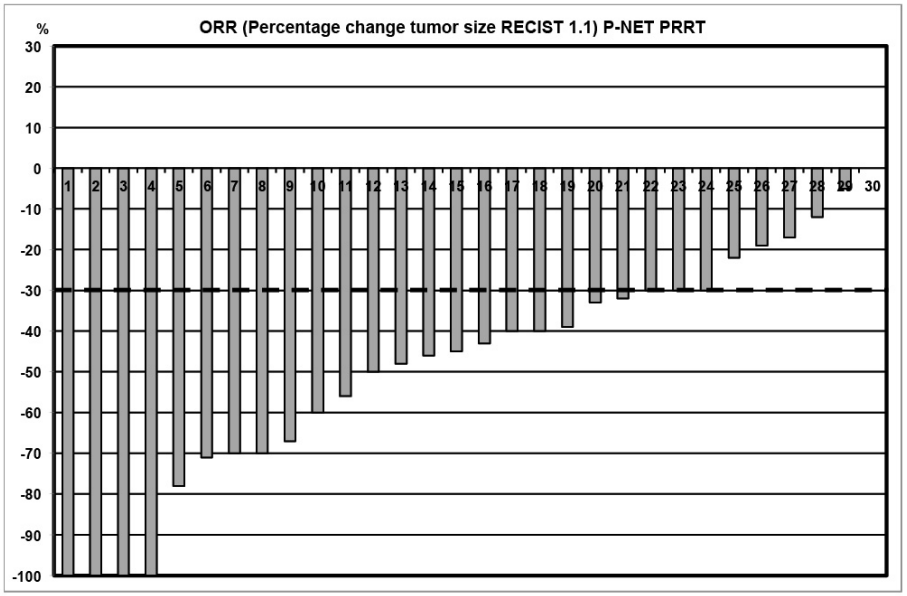
Raghava Kashyap · Michael S. Hofman ·
Michael Michael · Grace Kong · Timothy Akhurst ·
Peter Eu · Diana Zannino · Rodney J. Hicks

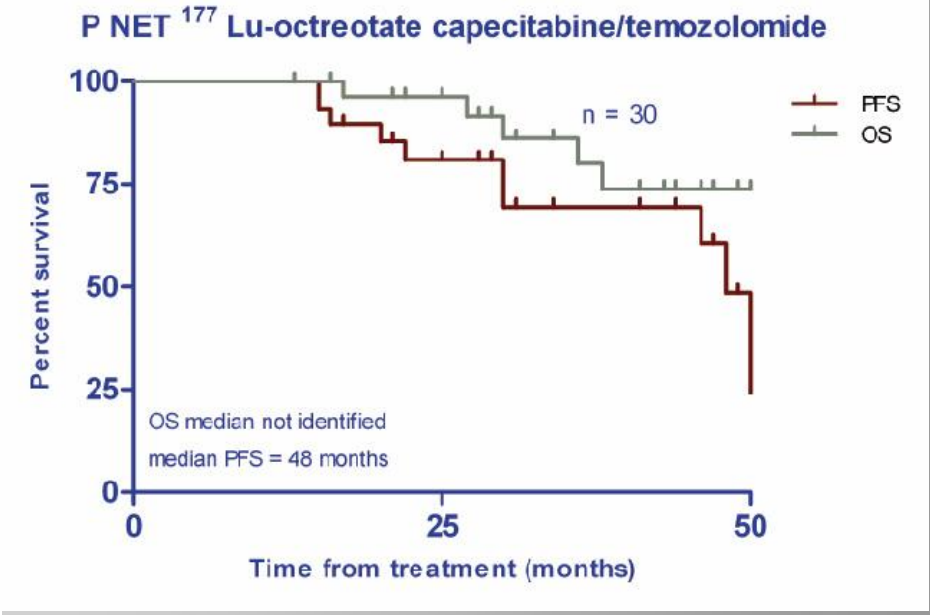
Neuroendocrinology. 2016;103(5):432-9. doi: 10.1159/000434723. Epub 2015 Jun 10.

Pancreatic Neuroendocrine Tumor Control: Durable Objective Response to Combination 177Lu-Octreotate-Capecitabine-Temozolomide Radiopeptide Chemotherapy.

Claringbold PG, Turner JH.

- Progressive Gr 1 and 2 NET
- Capecitabine at 1,500 mg/m2 and 5 days of temozolomide at 200 mg/m2.
- N = 30





Neoadjuvant Treatment of Nonfunctioning Pancreatic Neuroendocrine Tumors with [^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate

Pancreatic neuroendocrine tumors (NETs) are rare neoplasms for which surgery has almost the only potential for cure. When surgery is not possible because of tumor size and vascular involvement, neoadjuvant treatment with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu-octreotate) may be an option. **Methods:** We studied 29 Dutch patients with a pathology-proven nonfunctioning pancreatic NET treated with ^{177}Lu-octreotate. All patients had a borderline or unresectable pancreatic tumor (group 1) or oligometastatic disease (defined as ≤3 liver metastases) (group 2). Progression-free survival (PFS) was analyzed using the Kaplan–Meier method and Cox proportional hazards modeling. **Results:** After the treatment with ^{177}Lu-octreotate, successful surgery was performed in 9 of 29 patients (31%). Six patients had a Whipple procedure, 2 patients had a pylorus-preserving pancreaticoduodenectomy, and 1 patient had a distal pancreatectomy and splenectomy. The median PFS was 69 mo for patients with successful surgery and 49 mo for the other patients. For comparison, the median PFS in 90 other patients with a nonfunctioning pancreatic NET with more than 3 liver metastases or other metastases was 25 mo. **Conclusion:** Neoadjuvant treatment with ^{177}Lu-octreotate is a valuable option for patients with initially unresectable pancreatic NETs.

Key Words: pancreatic neuroendocrine tumor; PRRT; [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate; neoadjuvant treatment; surgery

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The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Medical Management of Midgut Neuroendocrine Tumors

(*Pancreas* 2017;46: 707–714)

When asked about appropriate choice of second-line treatment in patients with somatostatin receptor–positive midgut NETs, a significant majority of the expert panel selected ^{177}Lu-DOTATATE as the most appropriate option based on the results of the NETTER-1 study. It was noted that the evidence of everolimus efficacy appears stronger in nonmidgut NETs (which represented the majority of patients on the RADIANT-4 study) compared with midgut NETs (which represented the majority of patients on the RADIANT-2 study). Interferon-α was not selected as an option

Conclusion

- PRRT : Targeted Radionuclide therapy
- Safe in children and adults
- Low but definite side effects to be monitored
- Select patients appropriately SSR Expression
- Metastatic and Neoadjuvant settings
- **Effective in NET of origin from various organs**
- **Effective for Symptom control and Disease Control among a varied types of NET**
- Significant prolongation of survival
- Personalization of treatment
- Role of PRCRT and Alpha Therapy being explored.