Implication for Clinical Practice and Trial Design

Disclosure slide

- Advisory board and speaker:
  - Novartis
  - Ipsen
  - Pfizer

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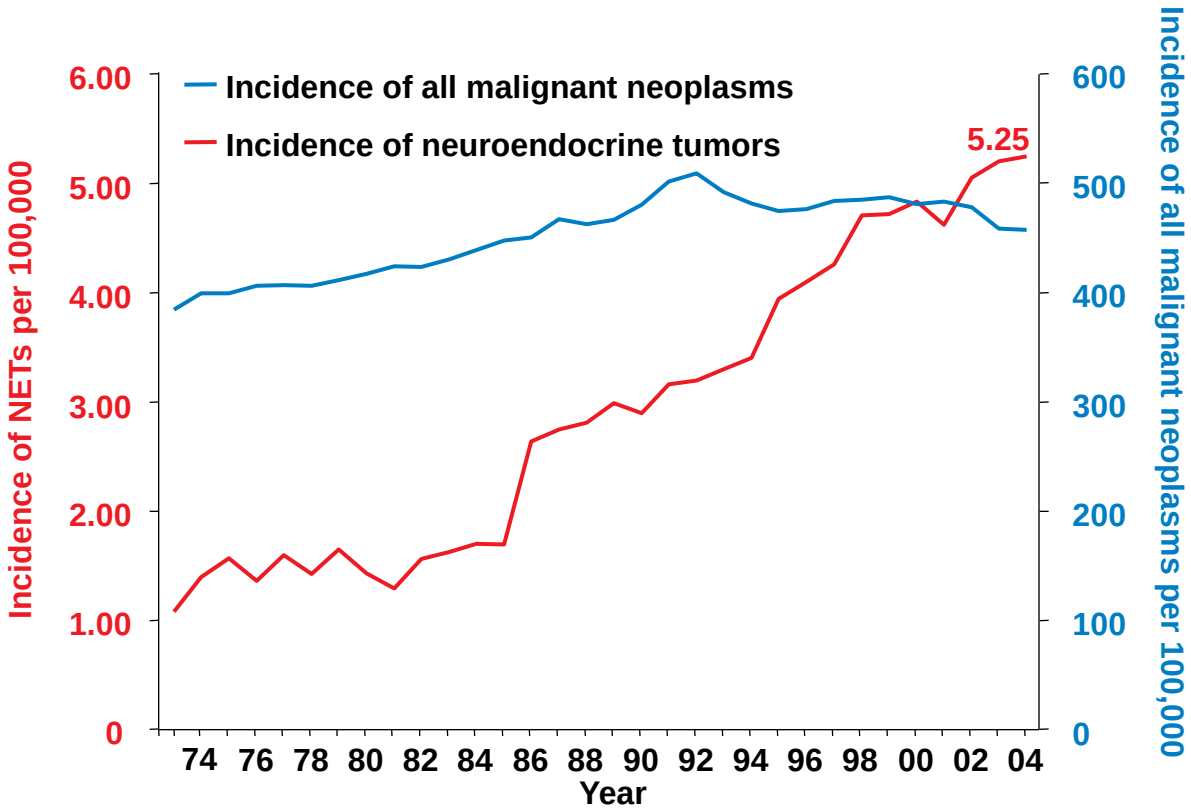
The Overall Incidence of NETs Is Increasing Rapidly Compared With All Malignant Neoplasms



- The incidence and prevalence of NETs has increased approximately 500% over the past 30 yr, which may be partially due to improved diagnosis

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Source: US SEER database.

Adapted with permission from Yao JC, et al. J Clin Oncol. 2008:26:3063-3072.

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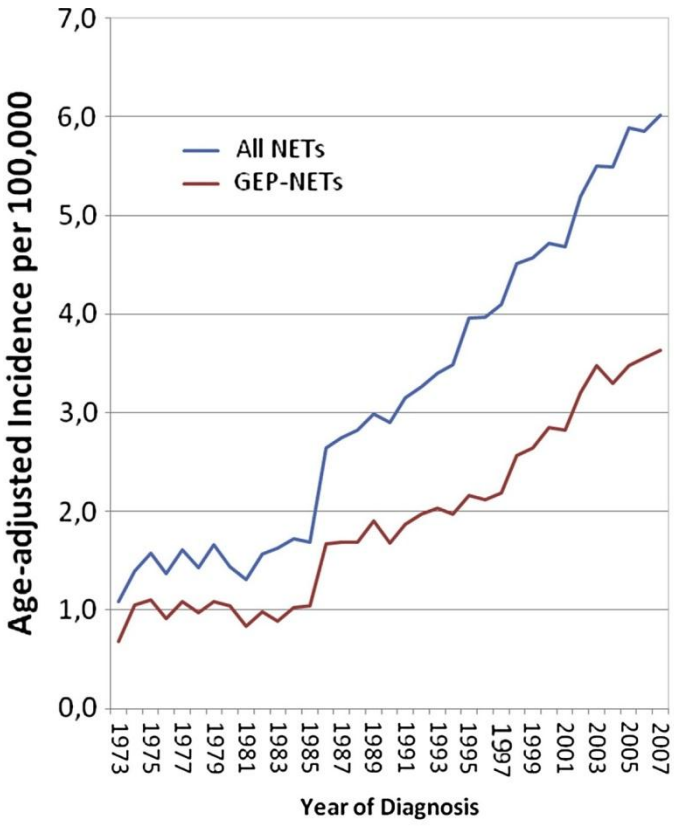
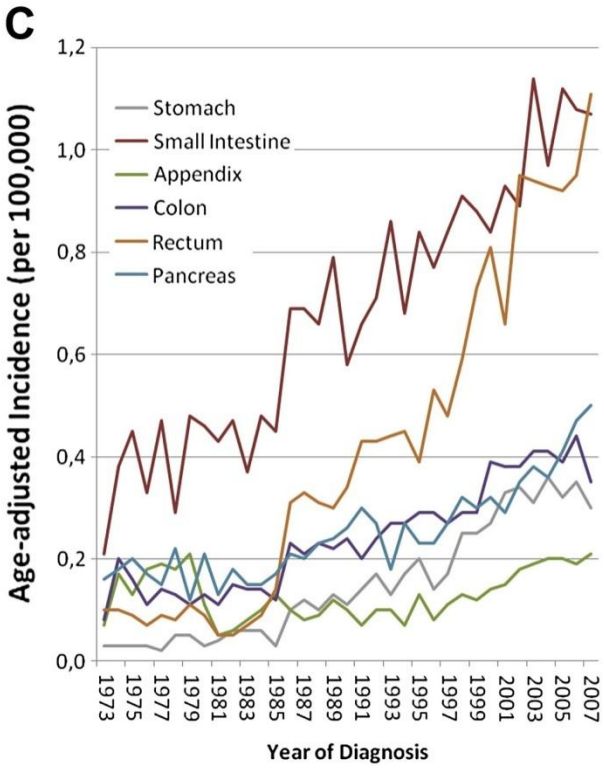
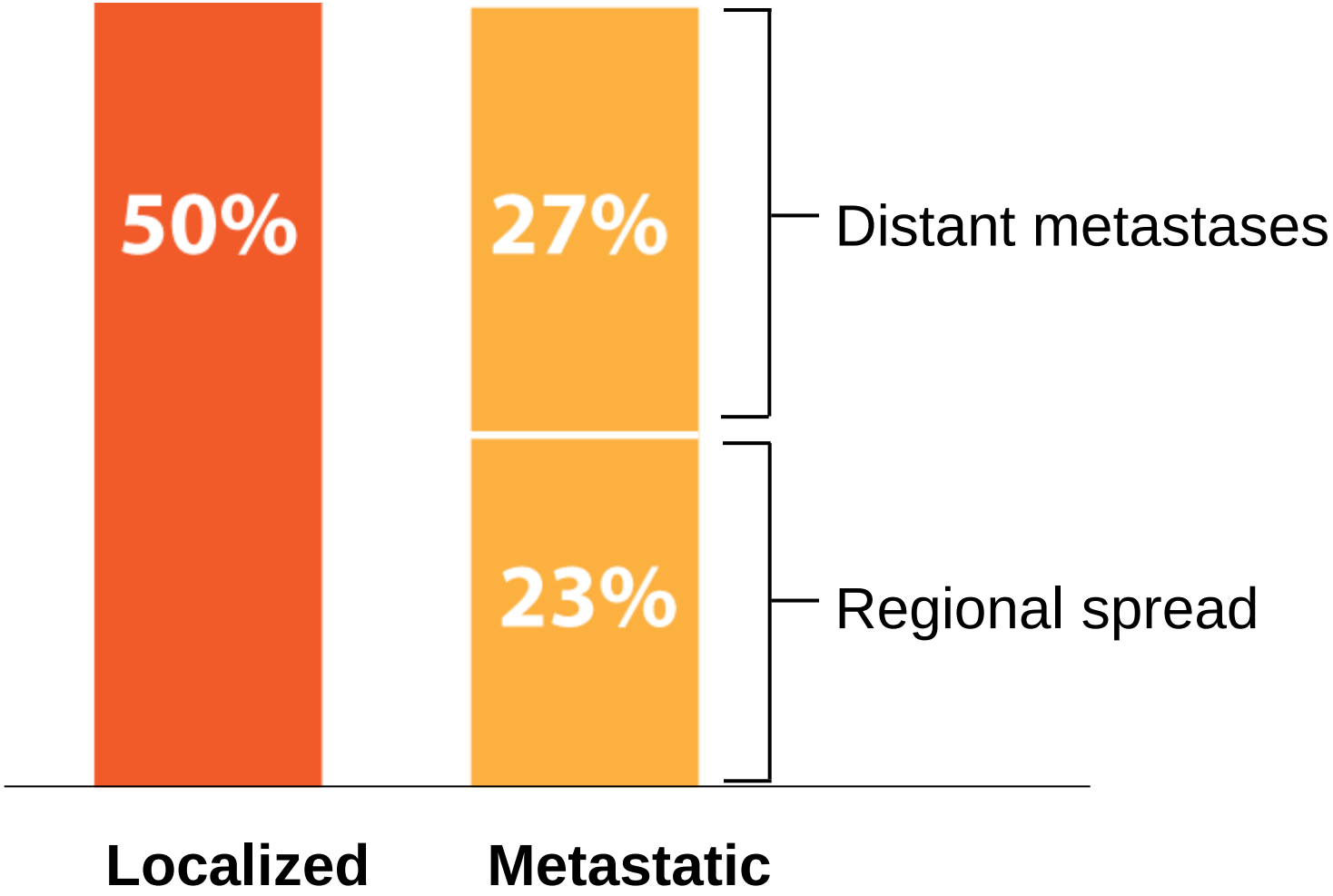


Lawrence B, et al. Endocrinol Metab Clin North Am. 2011 Mar;40(1):1-18, vii.



Lawrence B, et al. Endocrinol Metab Clin North Am. 2011 Mar;40(1):1-18, vii.

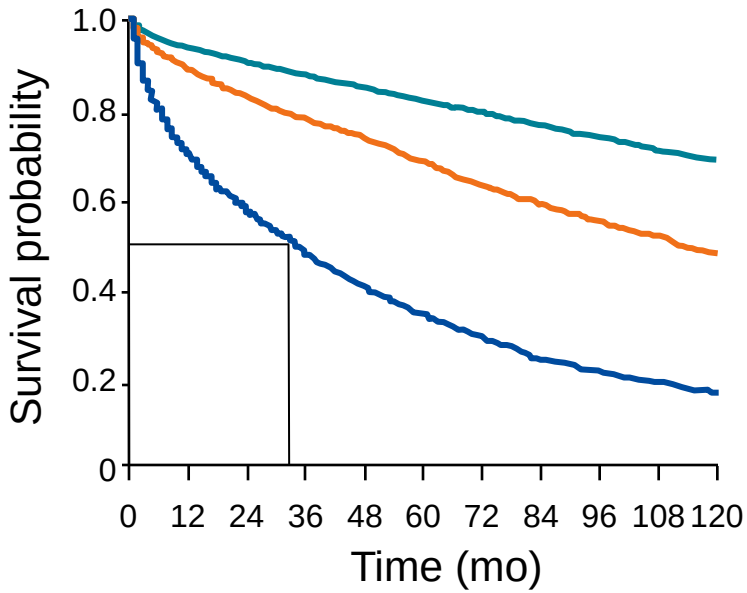
NETs Are Often Advanced at the Time of Diagnosis



Source: US SEER Database.
Yao JC, et al. J Clin Oncol. 2008;26:3063-3072.

33-mo Median Survival for Patients with Metastatic NETs

Tumors with well- and moderately differentiated histology[1]



Stage	Median survival	
	Month	95% CI
Localized	223	208–238
Regional	111	104–118
Distant	33	31–35

CI = confidence interval

- **5-yr survival rate in metastatic NETs is similar to that in other metastatic cancers**
  - Poorly differentiated NET—4%[1]
  - Well/moderately differentiated NET—35%[1]
  - Lung—4%[2]
  - Colorectal, breast, and prostate—11%, 23%, and 31%, respectively[2]

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1. Yao J, et al. J Clin Oncol. 2008;26:3063-3072; 2. Jemal A, et al. CA Cancer J Clin. 2010;60:277-300.

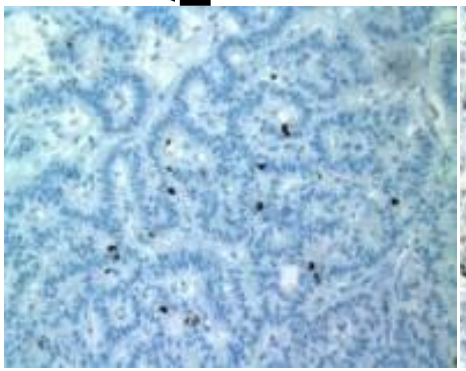
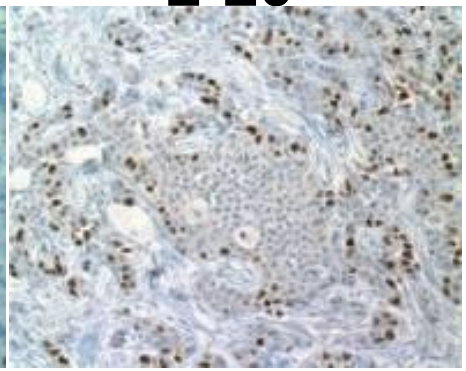
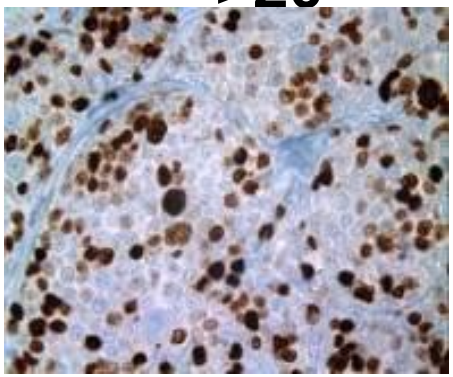
WHO Classifications of Neuroendocrine Neoplasms of the GEP System

WHO 1980	WHO 2000	WHO 2010
I. Carcinoid	Well-differentiated endocrine tumour (WDET) Well-differentiated endocrine carcinoma (WDEC) Poorly differentiated endocrine carinoma/small-cell carcinoma (PDEC)	Neuroendocrine tumours Grade 1 Grade 2 Neuroendocrine carcinoma Grade 3
II. Mucocarcinoid III. Mixed forms carcinoid-adenocarcinoma	Mixed exocrine-endocrine carcinoma (MEEC)	Mixed adenoneuroendocrine carcinoma (MANEC)
IV. Pseudotumour lesions	Tumour-like lesions (TLL)	Hyperplastic and preneoplastic lesions

Bosman FT, et al. *WHO Classification of Tumours of the Digestive System*. Lyon, France: IARC Press; 2010.

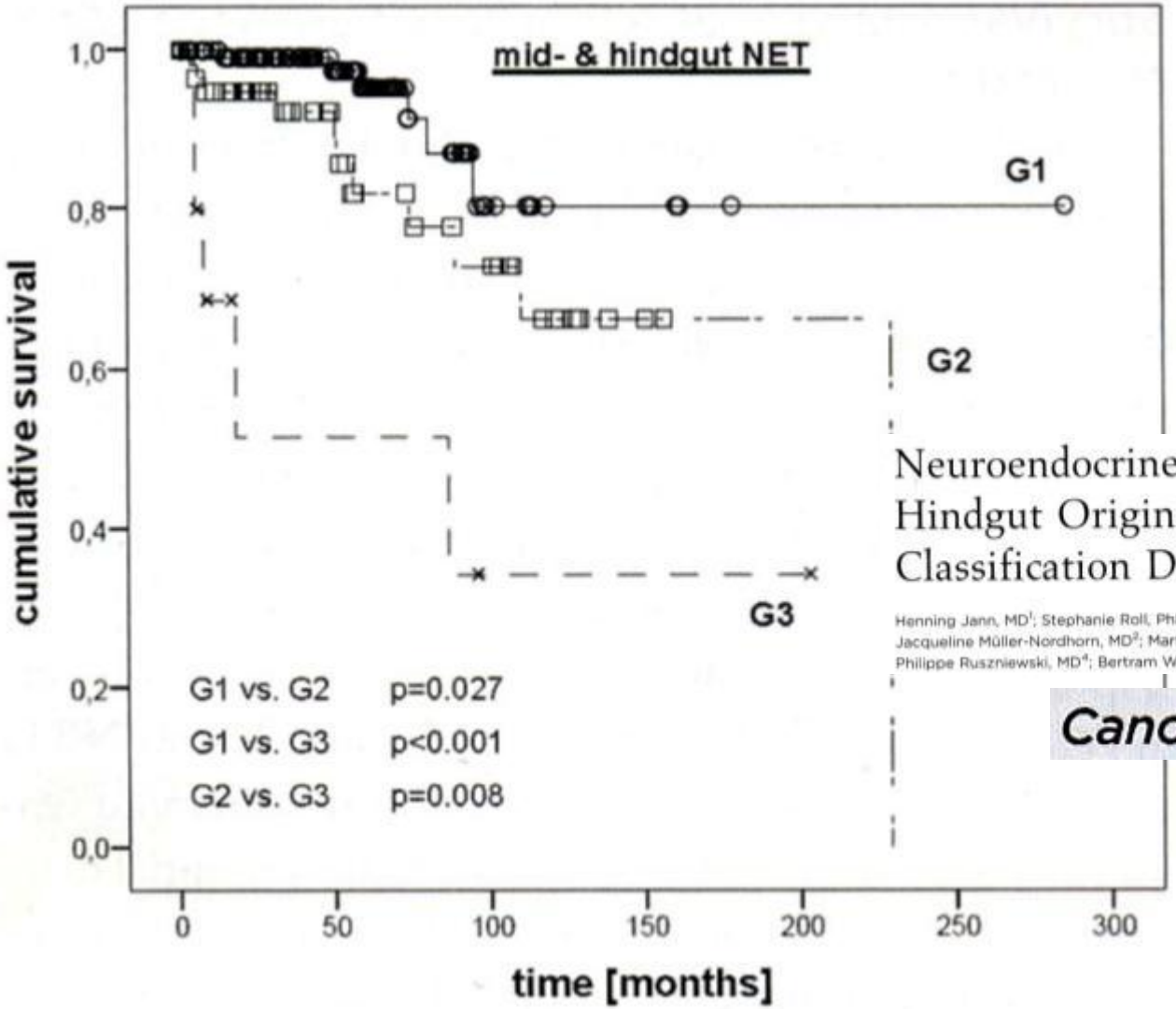
Grading of GEP-NENs According to ENETS/WHO/AJCC

Grade	G1	G2	G3
Ki67 index	≤2	3–20	>20
MI	<2	2-20	>20

1. Rindi G, et al. Virchows Archiv. 2006;449:395-401. 2. Rindi G, et al. Virchows Archiv. 2007;451:757-762.

Grading of GEP-NENs According to ENETS/WHO/AJCC



Neuroendocrine Tumors of Midgut and Hindgut Origin: Tumor-Node-Metastasis Classification Determines Clinical Outcome

Henning Jann, MD[1]; Stephanie Roll, PhD[2]; Anne Couvelard, MD[3]; Olivia Hentic, MD[4]; Marianne Pavel, MD[1]; Jacqueline Müller-Nordhorn, MD[2]; Martin Koch, MD[5]; Christoph Röcken, MD[5,6]; Guido Rindi, MD[7]; Philippe Ruszniewski, MD[4]; Bertram Wiedenmann, MD[1]; and Ulrich-Frank Pape, MD, MD[1]

Cancer 2011;117:3332–41.

Tumour Proliferative Activity With 5% Cut-off is a Strong Predictor of Progression in Pancreatic NET

- Multicentre, retrospective analysis of 202 patients with advanced **pancreatic NET**

Variable	Cut-off	Hazard Ratio	95% CI	*P*
Grade†				
2 *v* 1	2%	1.52	0.96 to 2.42	.074
3 *v* 1		3.43	1.89 to 6.23	< .001
3 *v* 2		2.11	1.38 to 3.22	<.001
Grade‡				
2 *v* 1	5%	1.70	1.16 to 2.50	.006
3 *v* 1		2.85	1.80 to 4.51	< .001
3 *v* 2		1.79	1.12 to 2.87	.015

- **Risk of progression increased by 2% for each increasing Ki-67 unit**

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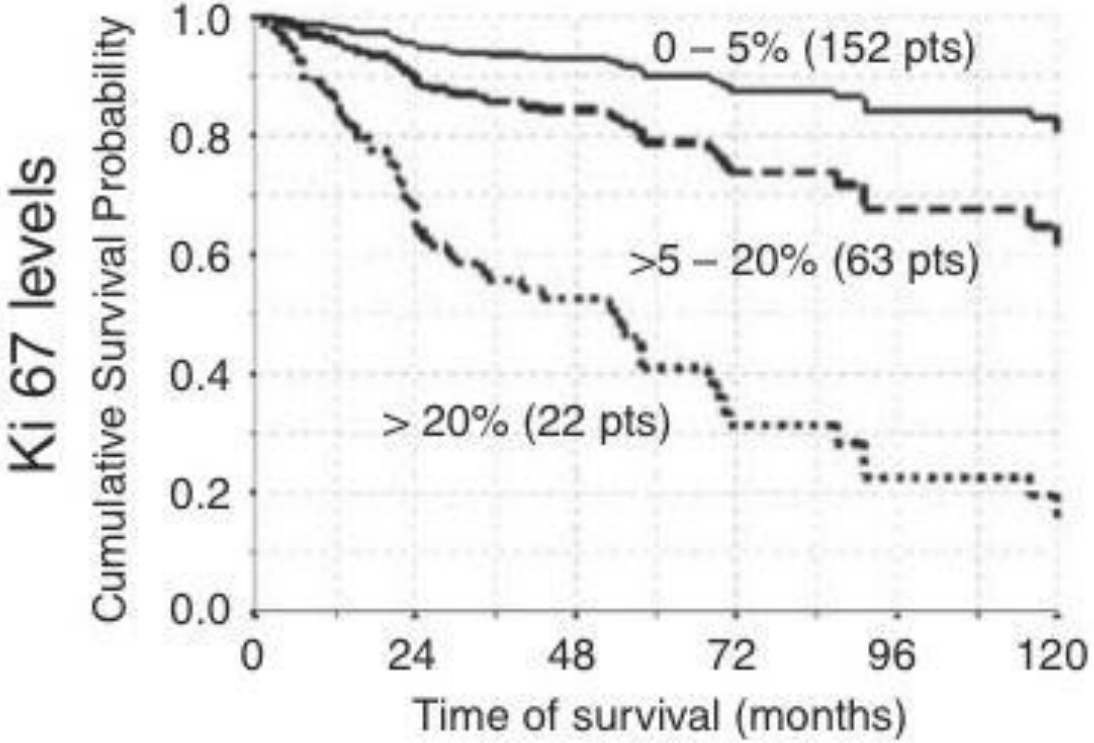
1. Scarpa A, et al. *Mod Pathol*. 2010;23:824-833
2. Panzuto F, *et al. J Clin Oncol* 2011;29:2372–7
3. Rindi et al. JNCI 2012, 104(10):764-77.

Pancreatic endocrine tumors: improved TNM staging and histopathological grading permit a clinically efficient prognostic stratification of patients

MODERN PATHOLOGY (2010) 23, 824–833

Aldo Scarpa[1,2], William Mantovani[3], Paola Capelli[1], Stefania Beghelli[1,2], Letizia Boninsegna[4] Rossella Bettini[4], Francesco Panzuto[5], Paolo Pederzoli[4], Gianfranco delle Fave[5] and Massimo Falconi[4]



Staging of NET According to Tumour-Node-Metastasis (TNM)

- The European Neuroendocrine Tumour Society (ENETS) and American Joint Committee on Cancer (AJCC) have developed TNM staging systems
- Staging systems are developed for the following tumour locations:
  - Gastric, duodenum/ampulla/proximal jejunum, pancreas[1]
  - Lower jejunum and ileum, appendix, and colon and rectum[2]

[1]Rindi G, et al. *Virchows Arch*. 2006;449:395-401; [2]Rindi G, et al. *Virchows Arch*. 2007;451:757-762.

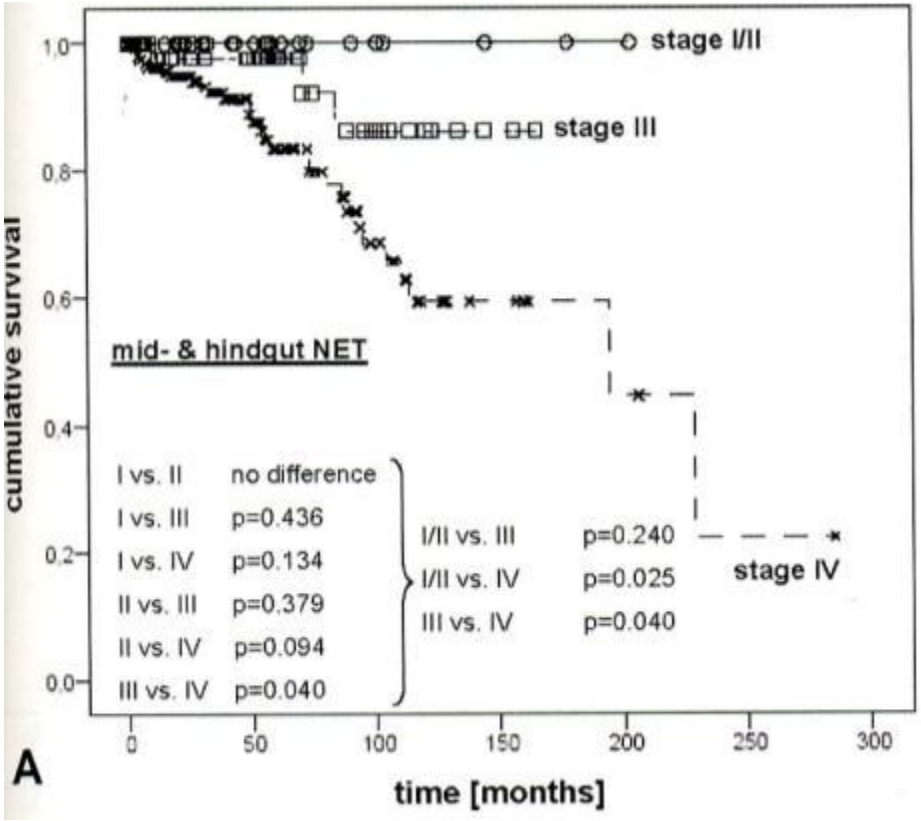
T – primary tumour	
x	primary tumour cannot be assessed
0	no evidence of primary tumour
1	tumour invades mucosa or submucosa and size ≤1 cm
2	tumour invades muscularis propria or size >1 cm
3	tumour invades subserosa
4	tumour invades peritoneum/other organs
	for any T add (m) for multiple tumours
N – regional lymph node metastasis	
x	regional lymph nodes cannot be assessed
0	no regional lymph node metastasis
1	regional lymph node metastasis
M – distant metastasis	
X	distant metastasis cannot be assessed
0	no distant metastases
1	distant metastasis

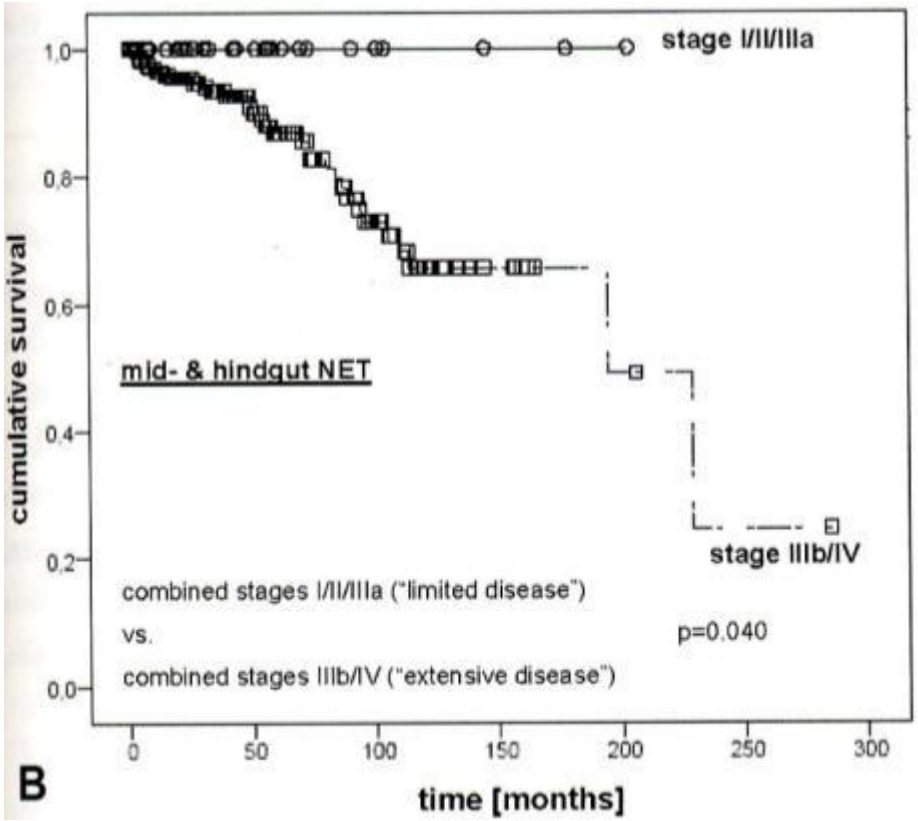
Stage:			
stage 0:	Tis	N0	M0 (stage 0: ENETS only)
stage I:	T1	N0	M0
stage IIa:	T2	N0	M0
stage IIb:	T3	N0	M0
stage IIIa:	T4	N0	M0
stage IIIb:	any T	N1	M0
stage IV:	any T	any N	M1

Grade	Ki67 index	Mitotic index (mitoses/10 HPF)
G1	≤2%	<2
G2	3–20%	2–20
G3	>20%	>20

Pape et al. Neuroendocrinology.2012;95(2):135-156

Staging of Digestive NENs According to ENETS/WHO/AJCC





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Cancer 2011;117:3332–41.

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ENETS TNM vs UICC-AJCC-WHO 2010
Multicentric cohort study of 1072 cases

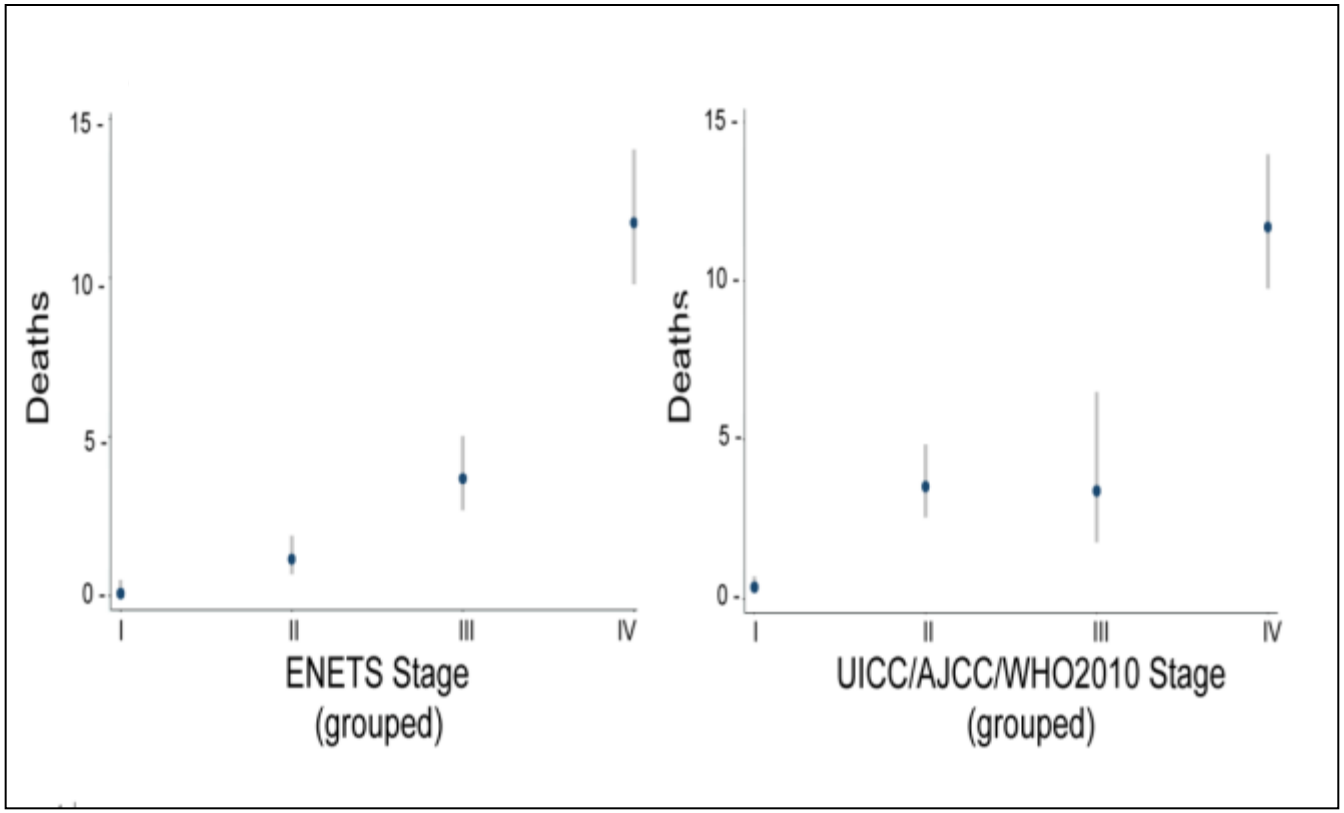
Death rates per 100 person per year according to TNM-Staging

Stage 1
N=1/248
0.4%
0.1

Stage 2
N=15/199
7.5%
1.1

Stage 3
N=39/194
20%
3.7

Stage 4
N=119/250
48%
12.0



Stage 1
N=9/399
2.2%
0.4

Stage 2
N=37/195
19%
3.5

Stage 3
N=9/47
19%
3.4

Stage 4
N=119/250
48%
10.2

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891 cases

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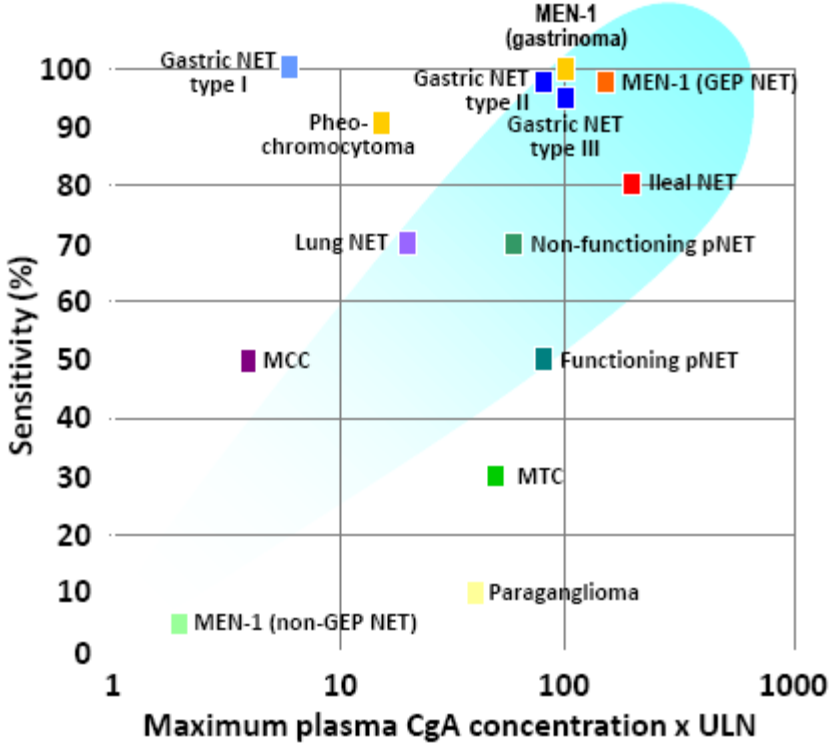
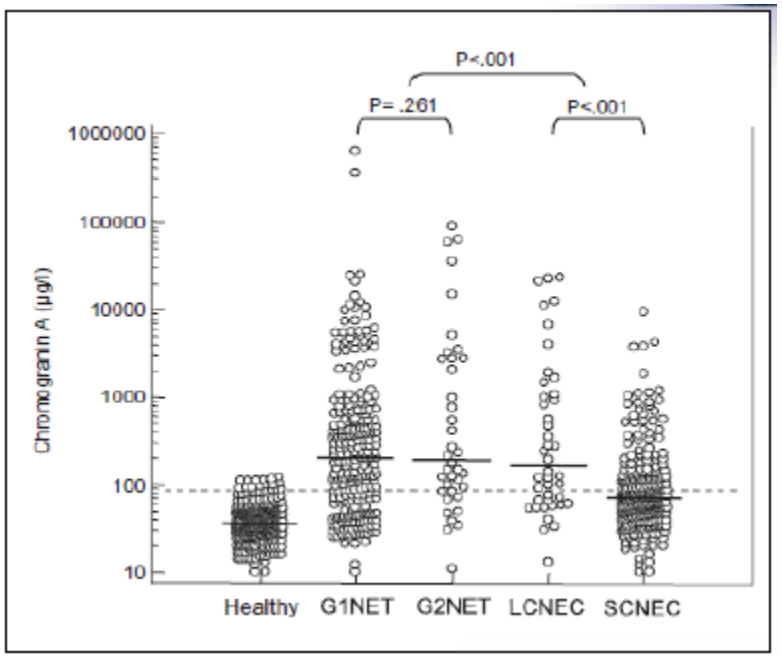
Rindi et al. JNCI 2012, 104(10):764-77.

Chromogranin A – Diagnostic Value



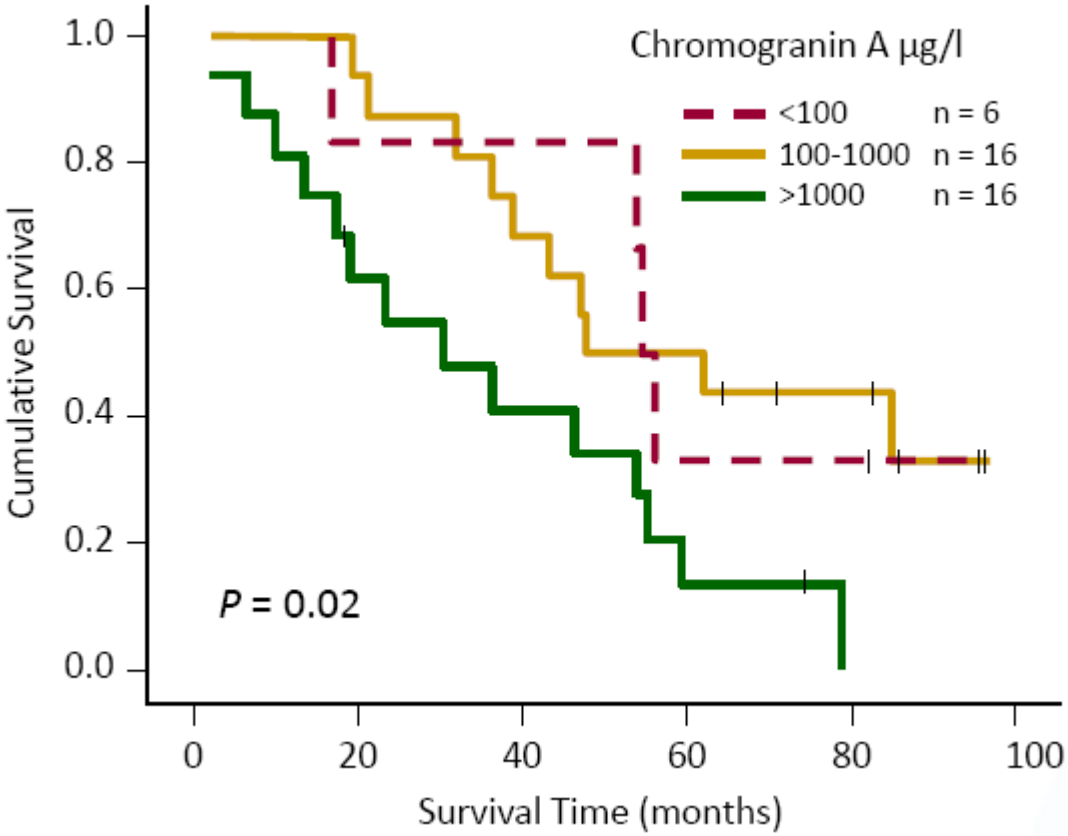


1. Modlin, IM. et al. *J Clin Gastroenterol* 2006; 40: 572-582
2. Modlin, IM. et al. *Lancet Oncol* 2008; 9: 61–72
3. Modlin, IM. et al., *Ann Surg Oncol* 2010; 17: 2427-2443
4. Korse, C.M. et al. Eur J Cancer. 2012; 48: 662-671

False positive results:

- PPI, CAG
- Renal insufficiency
- Heart insufficiency
- ……

Correlation of Baseline CgA Levels with Survival



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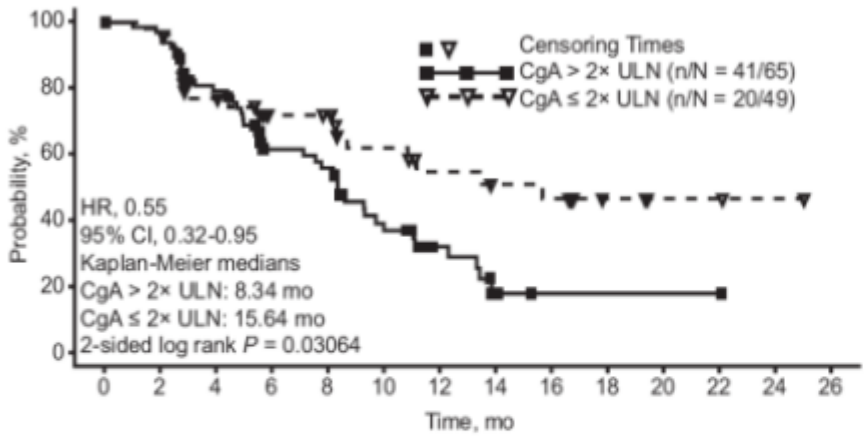
Korse C, Bonfrer J, Aaronson N, et al. Neuroendocrinology. 2009;89:296-301

CgA as Predictor of Disease Progression and Survival

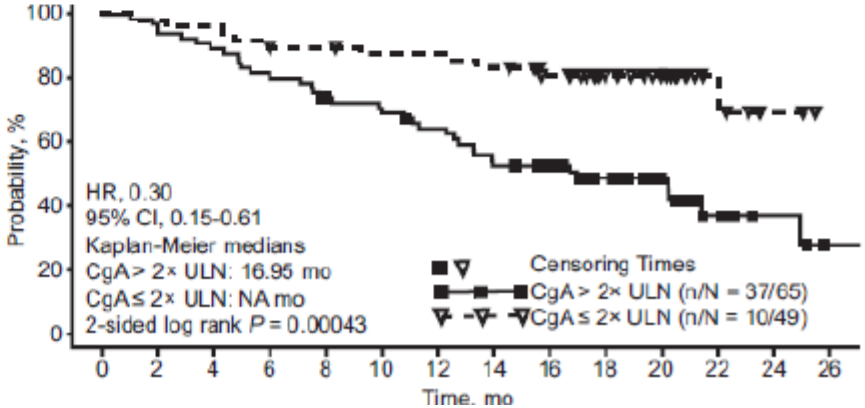
RADIANT-1 study, n=115
Everolimus in pancreatic NET patients

A



PFS by baseline CgA

Overall survival by baseline CgA



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Yao, JC. et al. J. Clin. Endocrinol. Metab. 2011;96:3741-3749

Molecular Imaging of NET

Specific Isotopes for NETs

- ^{11}C-5HTP (hydroxytryptophan)
- ^{11}C-Dopamine
- ^{18}F-Dopamine
- ^{68}Ga-DOTA-octreotide
- ^{99}Tc EDDA-HYNIC-octreotide
- [Lys40(Ahx-DTPA-^{111}In)NH2]-Exendin-4 (GLP-1)

^{68}Ga-DOTATOC

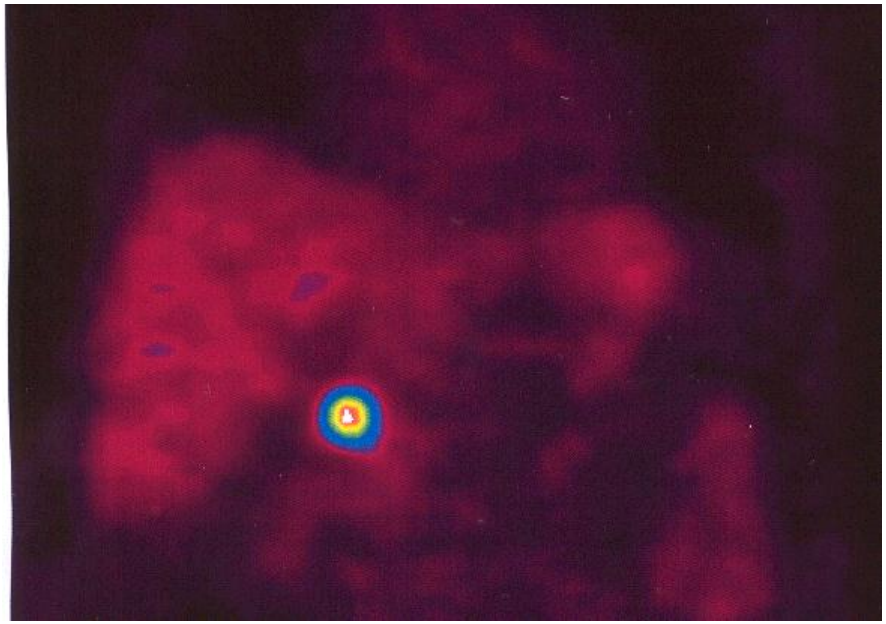
- ^{68}Ga positron emitter
- Half-life 68 min
- Generator production
- Better spatial resolution with PET than SPECT
- Examination 1 h after injection—logistical benefits

84 Patients with Various NETs

^{68}Ga-DOTATOC PET
SRS (^{99}Tc-HYNICTOC or ^{111}In-DOTATOC)

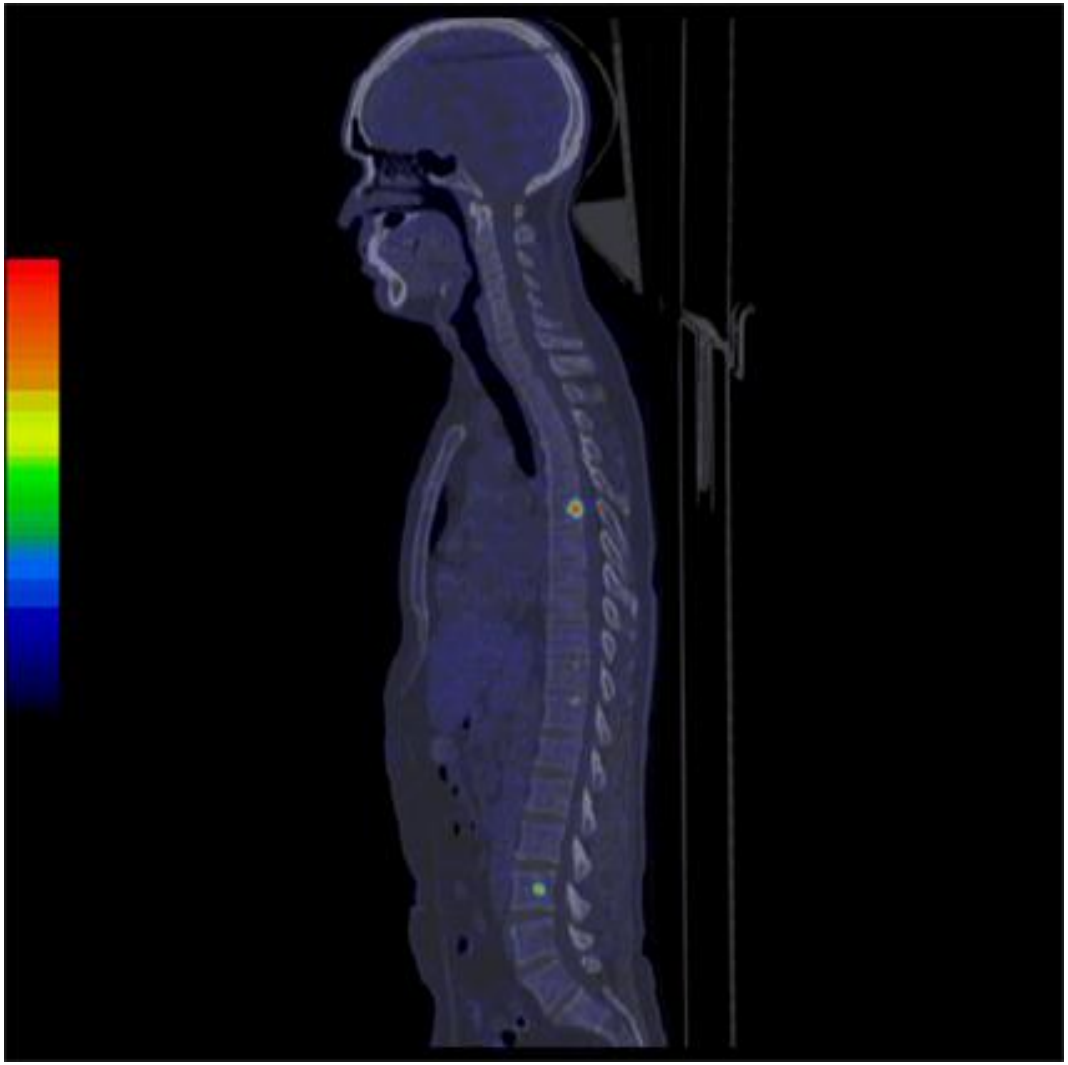
	PET	SPECT	CT
Sens	97%	52%	61%
Spec	92%	92%	71%

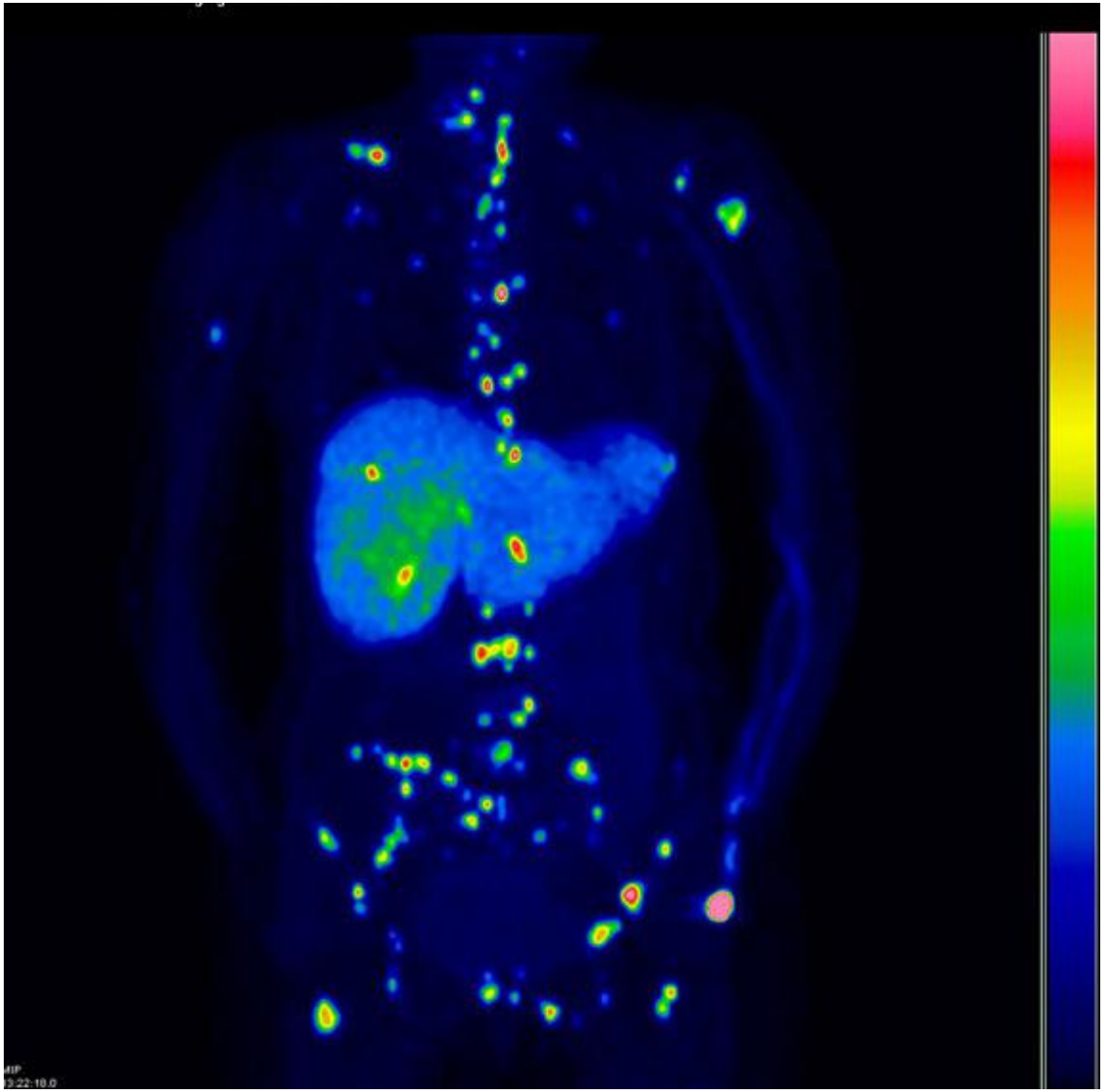
Gabriel M, et al. J Nucl Med. 2007;48:508-518.



^{11}C-5-HTP-PET of a patient with elevated gastrin levels showing a duodenal gastrinoma not detected by other methods

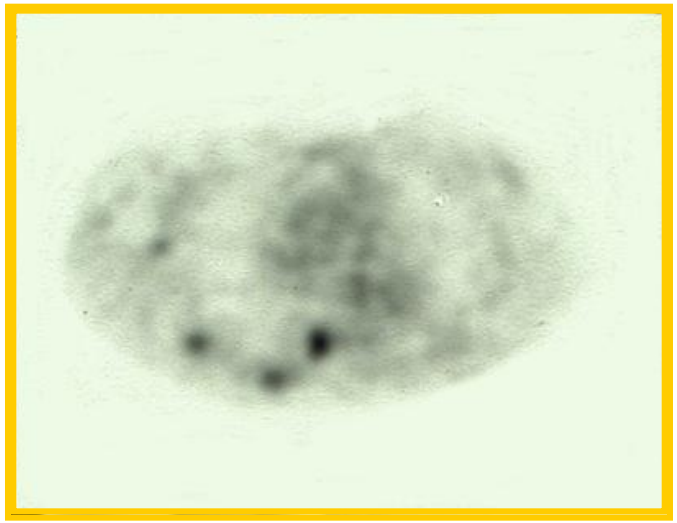
PET/CT with ^{11}C-5-HTP





Whole body FDG-PET

Frontal projection

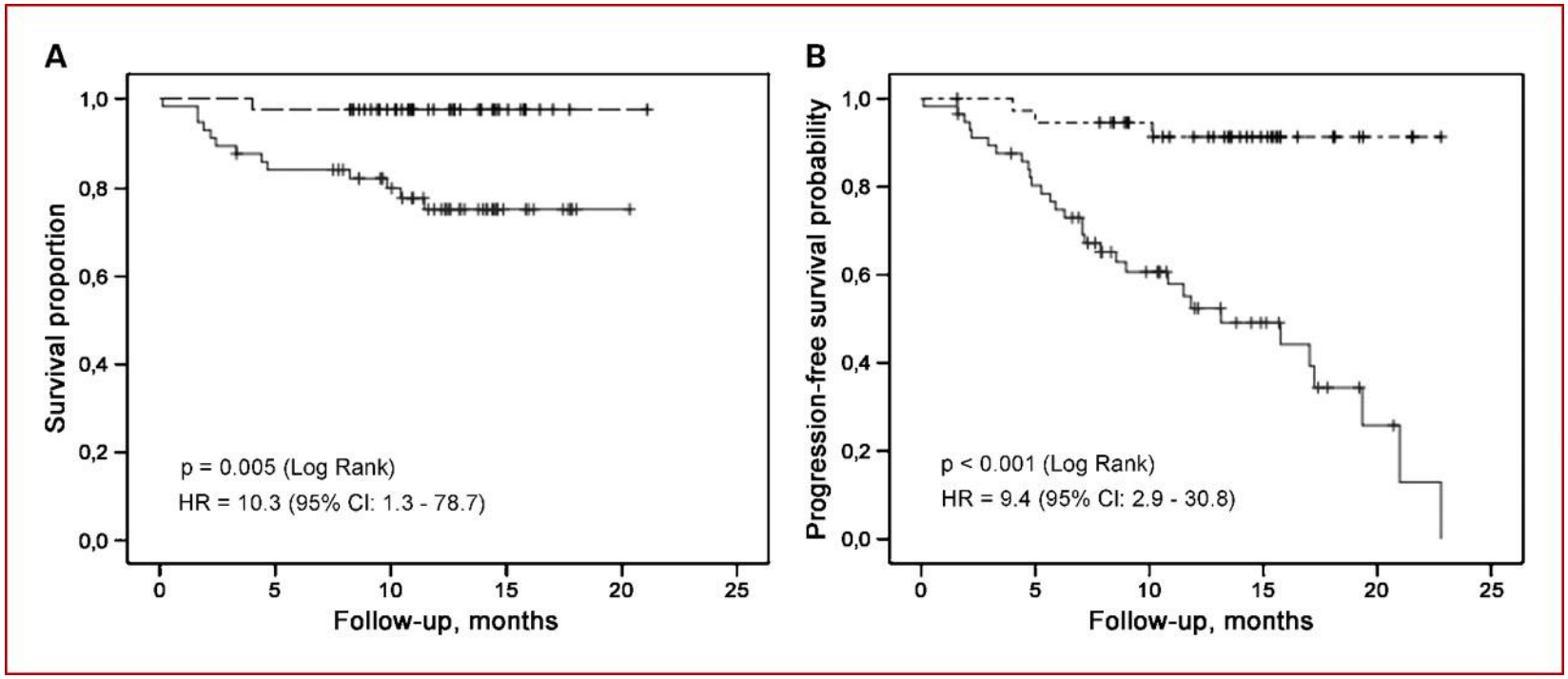


Transaxial

Sagittal

in a poorly differentiated neuroendocrine tumor

A, survival distribution among patients in the FDG-PET–negative (black, dashed) or FDG-PET–positive (black, solid) groups



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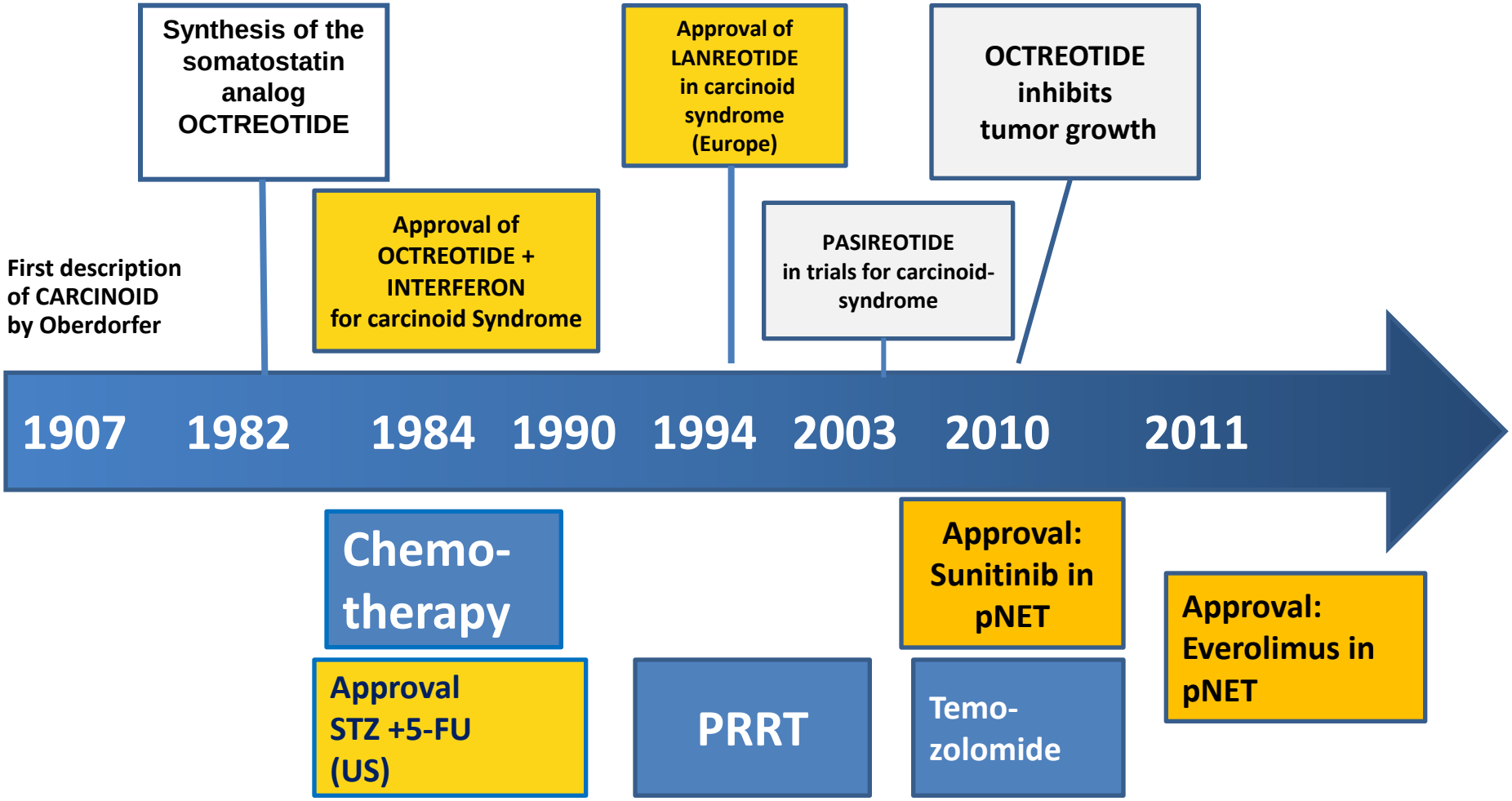
Binderup T et al. Clin Cancer Res 2010;16:978-985

Clinical Cancer Research

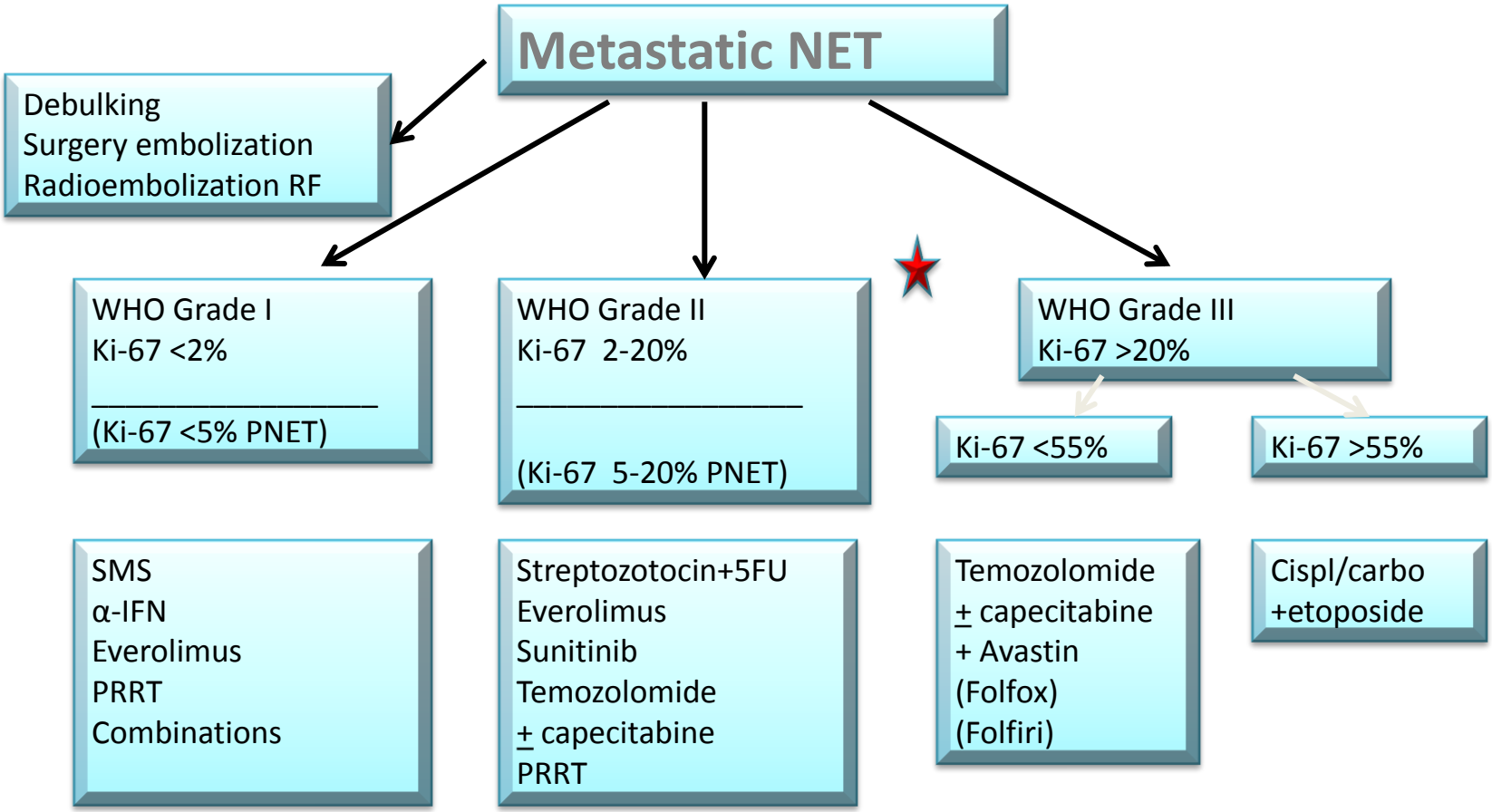
Evolution of Therapies in NET



Therapeutic Options NETs

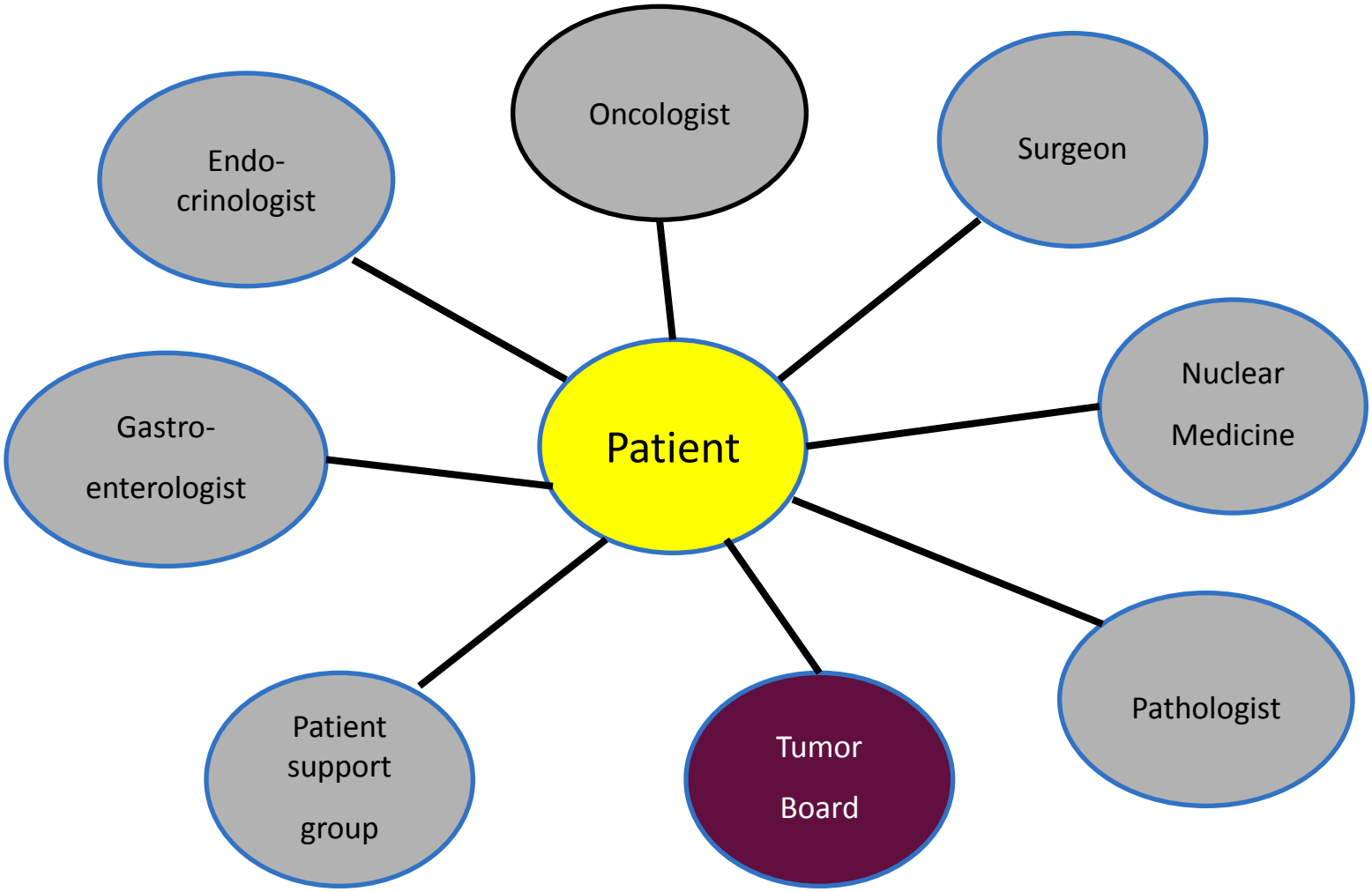
- **Surgery**
  - Curative (rarely), Ablative (very often)
- **Debulking**
  - Radiofrequency ablation (RFA)
  - Embolization/chemoembolization/radioembolization (Spherex®)
- **Medical therapy**
  - Chemotherapy
  - Biological treatment:
    - Somatostatin analogs
    - α-interferon
    - m-TOR inhibitors
    - VEGF R inhibitors
    - Other TKI's
- **Irradiation**
  - External (bone, brain-mets)
  - Tumor targeted, radioactive therapy (MIBG, Y^{90}-DOTATOC, Lu^{177} -DOTATATE)

Treatment Algorithm for NET
(modified by results from Nordic NET-study)



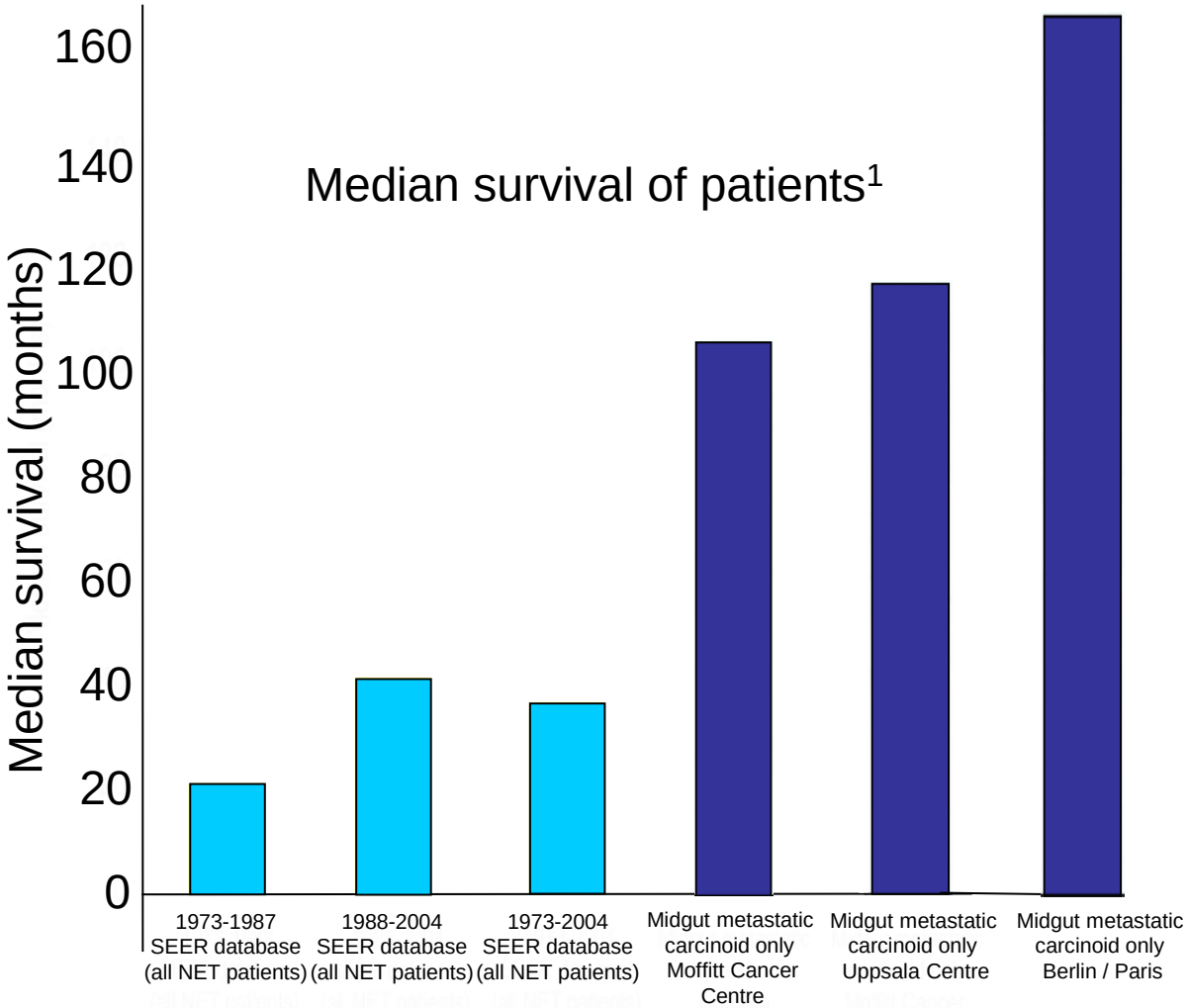
SMS with functioning tumors

NET Multidisciplinary Teams



Improving Access to Specialised Care Improves Patient Outcomes

- Multidisciplinary centres are associated with improved survival for patients with NETs
- Median survival of patients with metastatic NETs treated at "centres of excellence" is ≥3 times higher than median survival of patients with NETs in SEER database
- Data are consistent between "centres of excellence"



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1. Yao JC, et al. *J Clin Oncol* 2008;26:3063–3072 2. Öberg K. Oral presentations at ENETS, CCNETS, and NANETS, 2008;
3. Strosberg J. Poster presented at ASCO GI 2008; Jann et al Cancer, 2011.

Conclusions

Clinical practice and trial design

- The WHO/ENETS/AJCC classification, staging and grading system should be implicated in daily practice and clinical trials
- Biomarkers and molecular imaging are of value both for diagnosis and treatment evaluation
- “There are more treatment options than NET-patients” today – molecular genetics and tumor biology must be incorporated in the treatment decision. Personalized medicine
- Multi-disciplinary teams improve management and the outcome for NET-patients

Thank you!

Centre of Excellence Endocrine Tumors, Uppsala University
http://www.endocrinetumors.org/