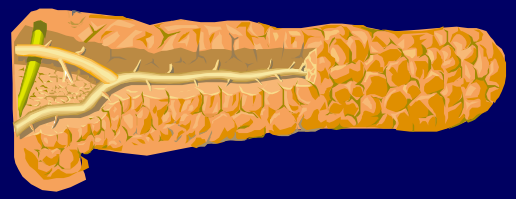
DIAGNOSI E TERAPIA DEI TUMORI ENDOCRINI DEL PANCREAS

www.fisiokinesiterapia.biz

Un po' di epidemiologia.....



INCIDENZA

REGISTRI SEER
1973 - 2000

♀ **1.8/1 000 000/anno**

♂ **2.6/1 000 000/anno**

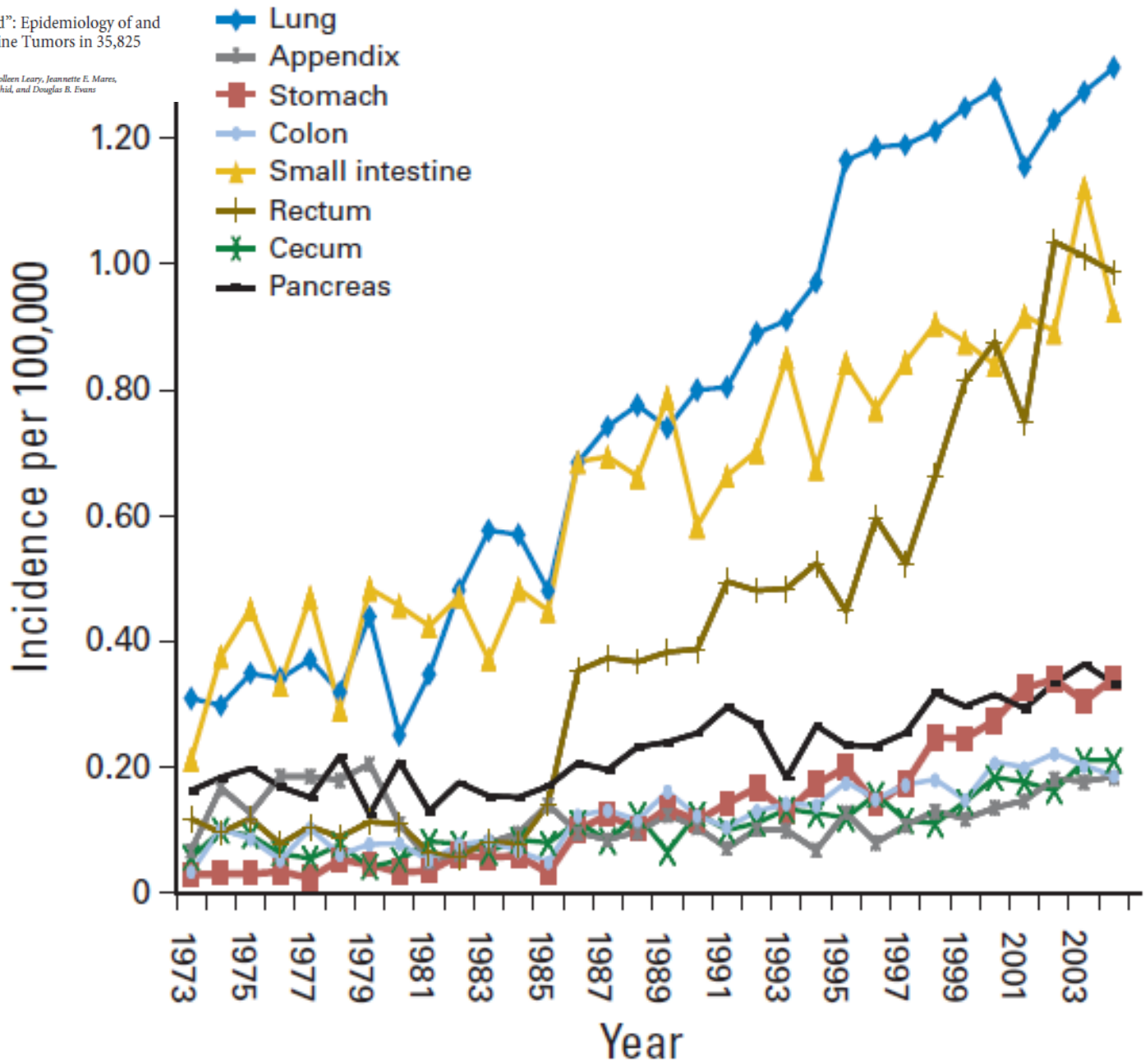
↑ **Dal 1973-1975**
Al 1996-2000

Halfdanarson TR., Annals of Oncology, 2008

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

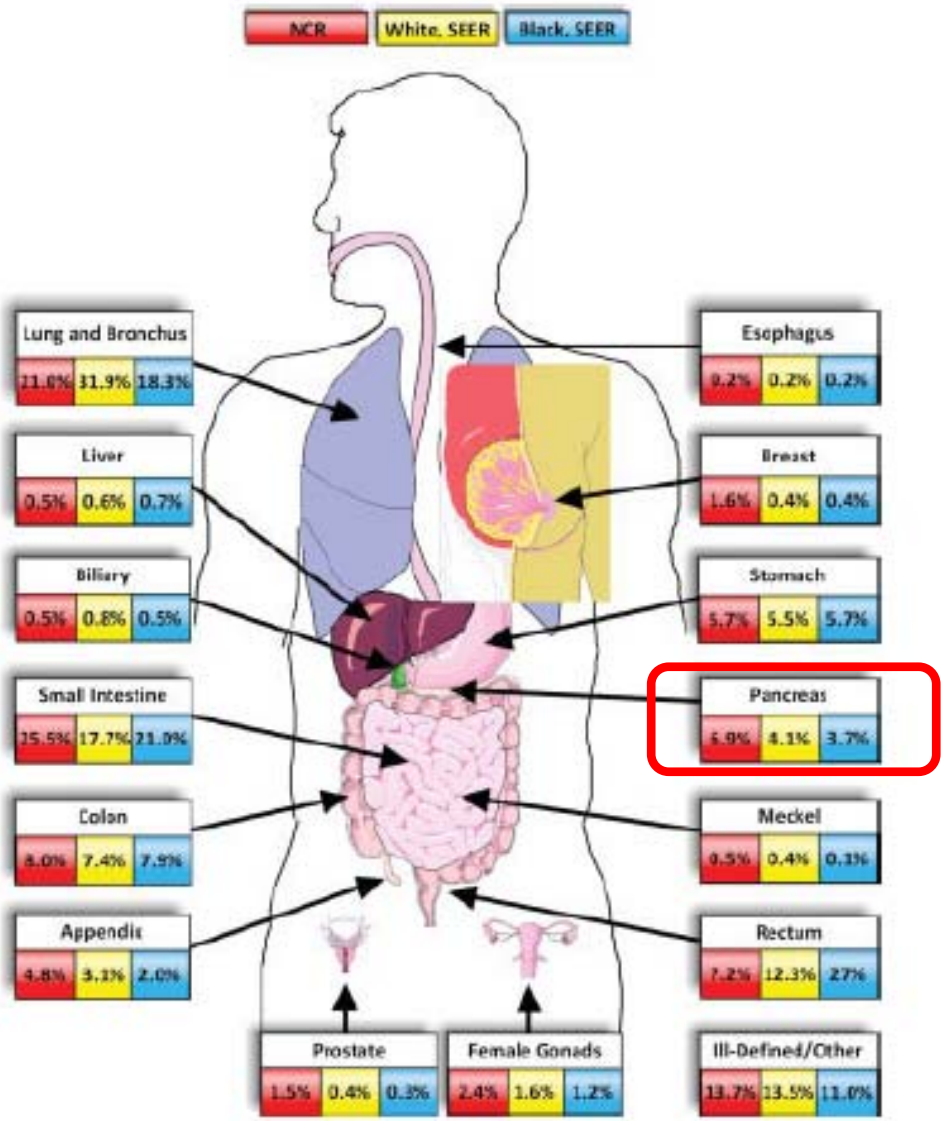
James C. Yao, Manal Hassan, Alexandria Phan, Cecile Dagohoy, Colleen Leary, Jeannette E. Mares, Eddie K. Abdalla, Jason B. Fleming, Jean-Nicolas Vauthey, Asif Rashid, and Douglas B. Evans



Neuroendocrine Tumor Epidemiology

Contrasting Norway and North America

Oyvind Hauso, MD[1,2]
Bjorn I. Gustafsson, MD, PhD[1,2]
Mark Kidd, PhD[1]
Helge L. Waldum, MD, PhD[2]
Ignat Drozdov, BS[1]
Anthony K. C. Chan, MD[3]
Irvin M. Modlin, MD, PhD, DSc[1]



CANCER November 15, 2008 / Volume 113 / Number 10

TABLE 4
Incidence Trends of Neuroendocrine Tumors: Norwegian Registry of Cancer and Surveillance, Epidemiology, and End Results Program (SEER), 1993 to 1997 and 2000 to 2004

	NR	NRC	Change	SEER White	Population	Change	SEER Black	Population	Change
NET site	93-97	00-04	%	93-97	00-04	%	93-97	00-04	%
All sites	2.35	4.06	72	4.22	5.79	37	5.48	7.67	40
Lung & bronchus	0.49	0.90	85	1.21	1.59	31	0.9	1.37	52
Small intestine	0.60	1.01	69	0.7	0.87	24	1.29	1.59	23
Rectum	0.22	0.25	15	0.39	0.68	74	1.36	1.89	39
Colon	0.19	0.33	73	0.27	0.39	44	0.46	0.64	39
Stomach	0.15	0.20	39	0.17	0.32	88	0.32	0.46	44
Pancreas	0.15	0.30	101	0.26	0.33	27	0.2	0.44	120
Appendix	0.10	0.23	125	0.1	0.17	70	0.06	0.14	133
Female gonads	0.05	0.12	130	0.07	0.07	0	0.07	0.07	0
Breast	0.03	0.05	75	0.01	0.02	100	0.02	0.04	100
Prostate	0.02	0.08	389	0.01	0.02	100	0.02	0.03	50
Biliary	0.01	0.03	165	0.03	0.04	33	0.03	0.05	67
Liver	0.02	0.01	−51	0.02	0.03	50	0.02	0.06	200
Meckel	0.02	0.01	−57	0.02	0.02	0	0	0.01	—
Esophagus	—	0.01	—	0.01	0.01	0	0.02	0.01	−50
Other	0.31	0.52	69	0.94	1.24	32	0.7	0.88	26

Rates are per 100,000 and age-adjusted to the 2000 US standard population (19 age groups, Census P25-1130).
NET indicates neuroendocrine tumor; NRC, Norwegian Registry of Cancer; SEER, Surveillance, Epidemiology, and End Results program.

REGISTRI SEER
1973 - 2000

→ **1483 PNETs**

♀ **44.8%**

♂ **55.2%**

Età media

Non funzionanti	58.8 anni
Funzionanti	55.2 anni

Stage

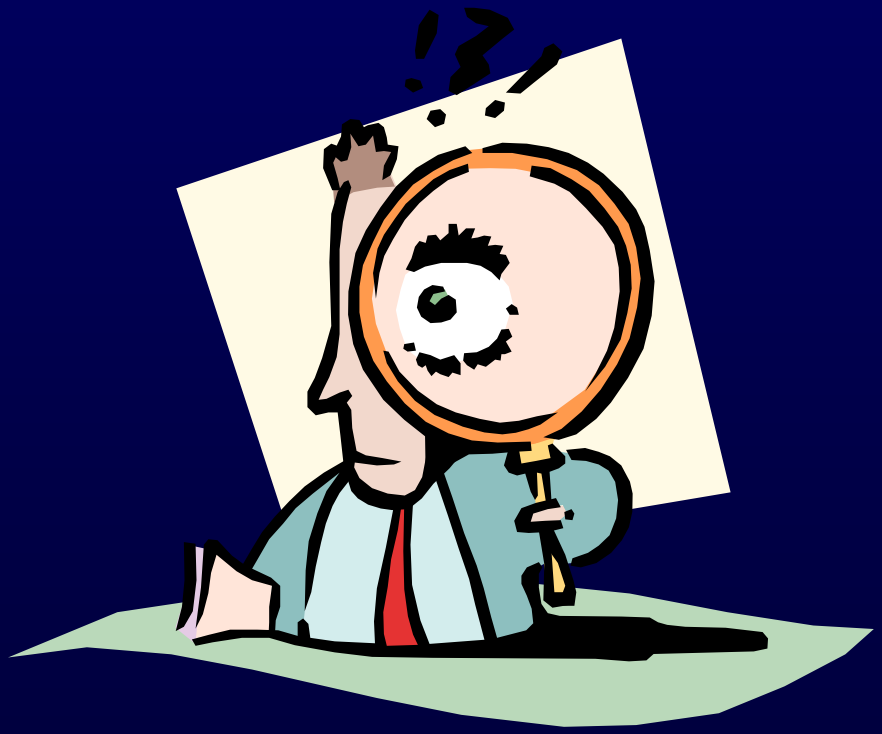
Localizzati	11.1%
Localmente avanzati	20.7%
Metastatici	60.2%
Non noto	8.0%

Presenza di sindrome

Non funzionanti	90.8%
Insulinomi maligni	2.5%
Gastrinomi maligni	4.2%
Glucagonomi maligni	1.6%
VIPomi maligni	0.9%

Halfdanarson TR., Annals of Oncology, 2008

CLINICA



TUMORI ENDOCRINI DEL PANCREAS

TUMORI NON ASSOCIATI A SINDROME

Fase precoce

CLINICAMENTE SILENTI

Malattia avanzata

DOLORE ADDOMINALE

ASTENIA

CALO PONDERALE

Bassi livelli di peptidi circolanti

Peptidi biologicamente inattivi

Concomitante secrezione di somatostatina

TUMORI ENDOCRINI DEL PANCREAS

TUMORI ASSOCIATI A SINDROME

- INSULINOMI
- GASTRINOMI
- VIPOMI
- GLUCAGONOMI
- SOMATOSTATINOMI
- GRF-OMI
- CARCINOIDI

→ **La sindrome clinica è correlata alla iperincrezione di peptidi**

GLUCAGONOMA

- Eritema necrolitico migrante
- Diabete
- Perdita di peso

VIPOMA

- Diarrea acquosa
- Ipokaliemia
- Ipoacloridria
- Ipercalcemia
- Flushing

SOMATOSTATINOMA

- Colelitiasi
- Diabete
- Diarrea/Steatorrea

INSULINOMA

Neuroglicopenia

- Cambiamento della personalità
- Confusione, diplopia
- Apatia, amnesia
- Coma

Eccesso di catecolamine

- Sudorazione
- Pallore
- Tachicardia

Altri sintomi

- Fame
- Astenia
- Nausea, vomito
- Neuropatia periferica

GASTRINOMA

SINDROME DI ZOLLINGER-ELLISON

SEGNI E SINTOMI

- ULCERA PEPTICA SINGOLA O MULTIPLA
- SINTOMI DA REFLUSSO
- DIARREA
- DOLORE ADDOMINALE

PPI

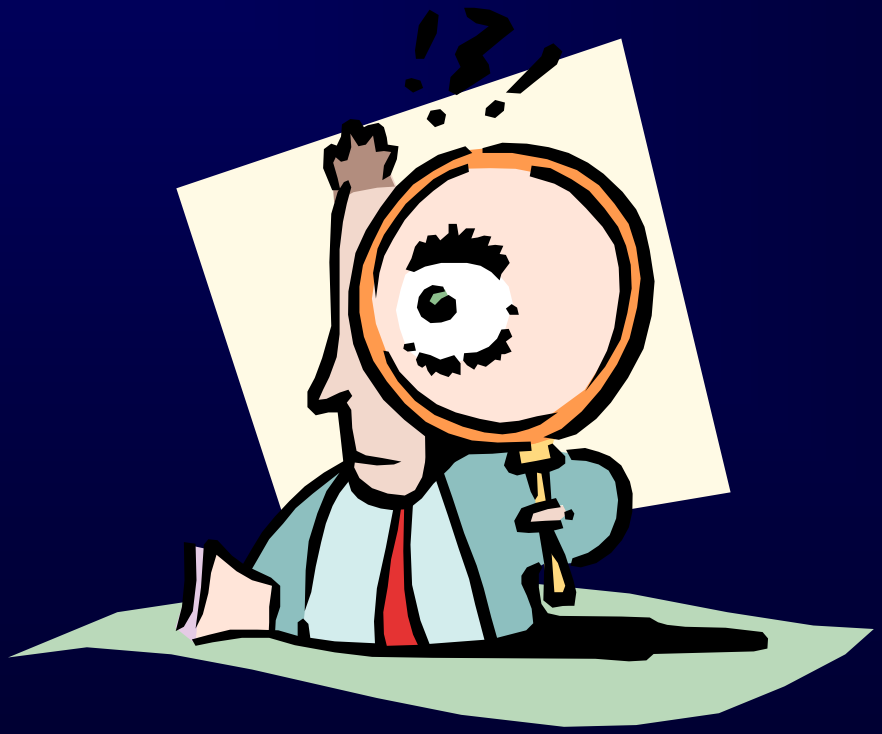
GASTRINOMA

SINDROME DI ZOLLINGER-ELLISON

Diagnosi in fase avanzata di malattia:

- ✓ **riscontro occasionale di metastasi epatiche**
- ✓ **comparsa di segni e sintomi da massa neoplastica**

DIAGNOSI



TUMORI NEUROENDOCRINI

I MARCATORI TUMORALI POSSONO ESSERE

ASPECIFICI

SPECIFICI

MARCATORI TUMORALI
SPECIFICI

	VALORI NORMALI	CUT-OFF
• **Insulina**	**< 15μmol/L**	**> 100**
• **Gastrina**	**< 40 pmol/L**	**> 200**
• **Glucagone**	**< 50 pmol/L**	**> 250**
• VIP	< 30 pmol/L	> 150
• **5-HIAA**	**2-8 mg/24h**	**> 20**

MARCATORI TUMORALI

TEST DI STIMOLO

INSULINOMA

↓

TEST AL DIGIUNO

GASTRINOMA

↓

TEST ALLA SECRETINA

Table 2 Protocol for 72-Hour Fast.

1. Date the onset of the fast as of the last ingestion of calories. Discontinue all nonessential medications.
2. Allow the patient to drink calorie-free and caffeine-free beverages.
3. Ensure that the patient is active during waking hours.
4. Measure the levels of plasma glucose, insulin, C peptide, and proinsulin in the same specimen; repeat measurements every six hours until the plasma glucose level is ≤60 mg per deciliter, when the interval should be reduced to every one to two hours.
5. End the fast when the plasma glucose level is ≤45 mg per deciliter (2.5 mmol per liter) and the patient has symptoms or signs of hypoglycemia.
6. At the end of the fast, measure the plasma levels of glucose, insulin, C peptide, proinsulin, β-hydroxybutyrate, and sulfonylurea in the same specimen; then inject 1 mg of glucagon intravenously and measure the plasma glucose level after 10, 20, and 30 minutes. Then feed the patient.
7. When a deficiency is suspected, measure plasma cortisol, growth hormone, or glucagon at the beginning and end of the fast.

Service F.J., N Engl J Med. 1995

CRITERI DIAGNOSTICI

GASTRINOMA

pH gastrico < 2

Gastrina > 1000 pg/ml

GASTRINOMA

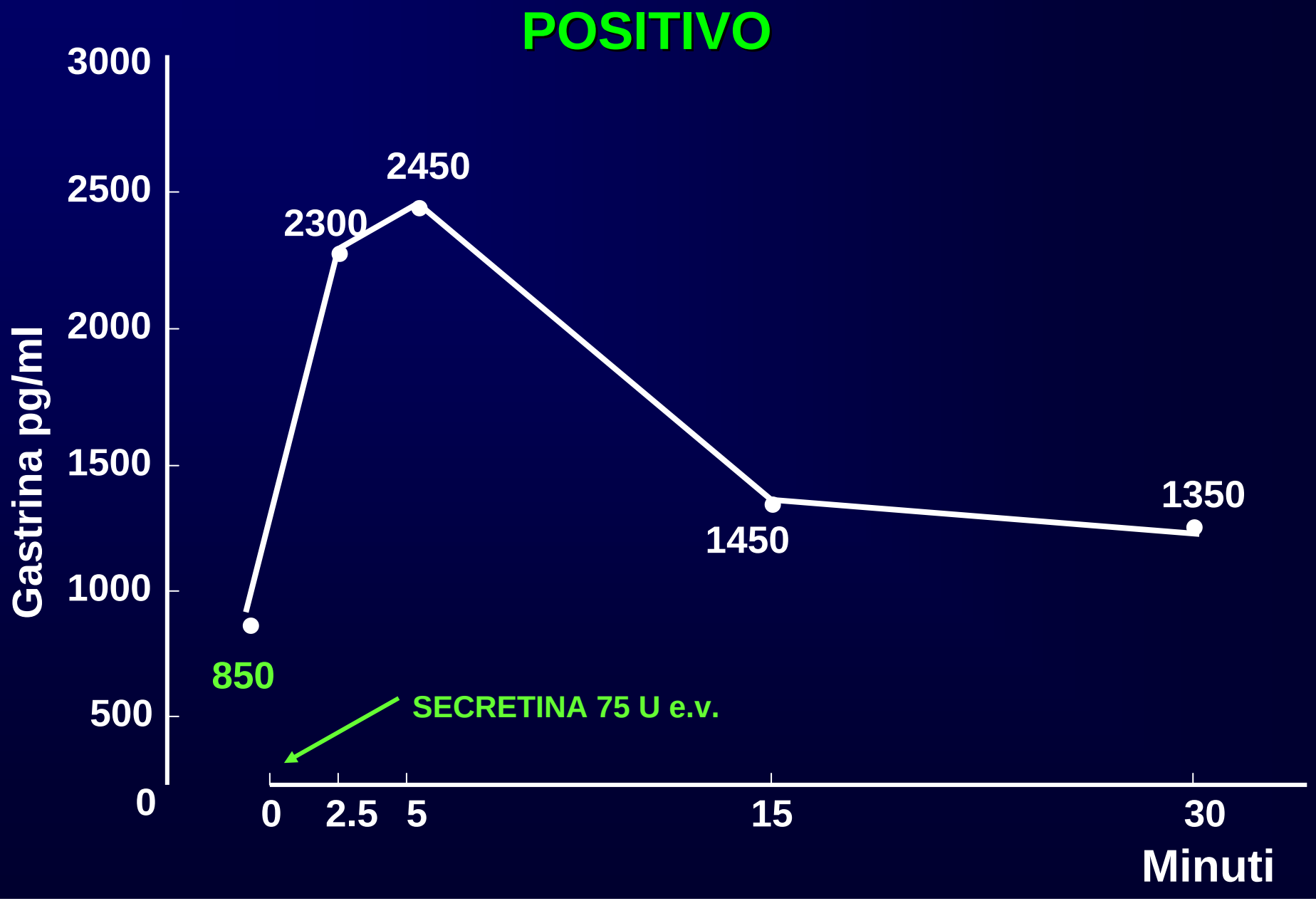
pH gastrico < 2

Gastrina = 100-1000 pg/ml

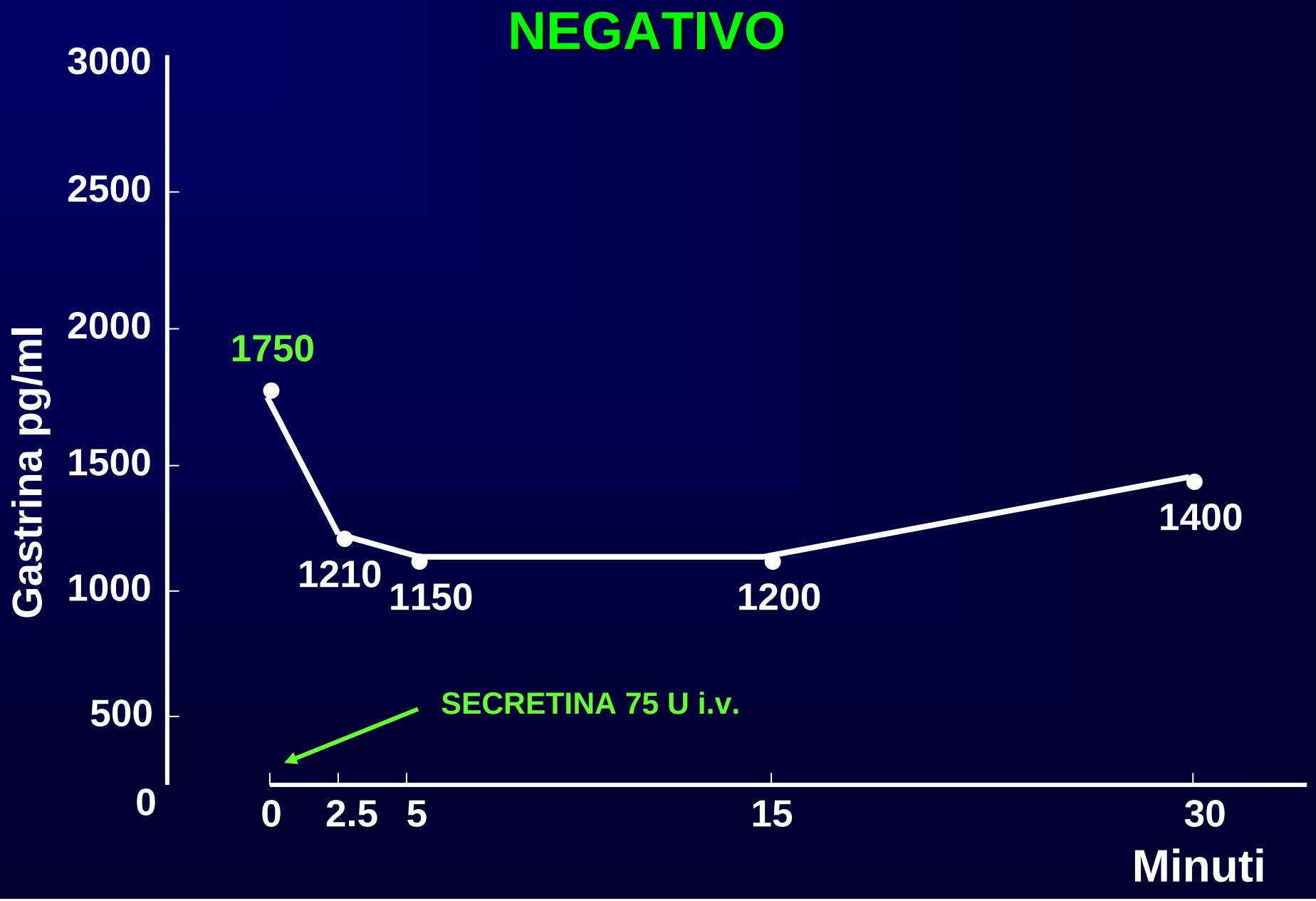
GASTRINOMA ?

TEST ALLA SECRETINA

TEST ALLA SECRETINA



TEST ALLA SECRETINA



CAUSES OF HYPERGASTRINEMIA

HYPERGASTRINEMIA WITH HYPERCHLORHYDRIA

- Zollinger-Ellison syndrome → sporadic
  → associated with MEN 1

- Antral G-cell hyperplasia
- Excluded gastric antrum syndrome
- Gastric outlet obstruction
- Small intestinal resection

CAUSES OF HYPERGASTRINEMIA

HYPERGASTRINEMIA WITH HYPOCHLORHYDRIA

- Chronic Atrophyc Gastritis type A
  1. Idiopathic
  2. Autoimmune → pernicious anemia
     → other autoimmune disorders

- Antisecretory agents
  H_2-antagonists
  $H^+ K^-$ ATPase inhibitors

TUMORI NEUROENDOCRINI

MARCATORI TUMORALI ASPECIFICI

MARCATORI TUMORALI
ASPECIFICI

ENOLASI NEURONO-SPECIFICA (NSE)

GONADOTROPINA CORIONICA UMANA (HCG) α, β

POLIPEPTIDE PANCREATICO (PP)

TUMOR M2-PIRUVATO KINASI (TM2-PK)

CROMOGRANINA A (CgA)

NSE SENSITIVITY AS CIRCULATION MARKERS FOR NET

NET	NSE SENSITIVITY %
CARCINOID	47, 38
PANCREAS ISLET CELL TUMOURS	43, 31
GASTRINOMA	44, 33
CARCINOID MIDGUT	50
SMALL CELL LUNG CARCINOMA	74, 61, 85, 62
LIMITED DISEASE	45, 77
EXTENSIVE DISEASE	68, 85

Seregni E, Q J Nucl Med 2000

CROMOGRANINA A

VOLUME 25 · NUMBER 15 · MAY 20 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Chromogranin A: Is It a Useful Marker of Neuroendocrine Tumors?

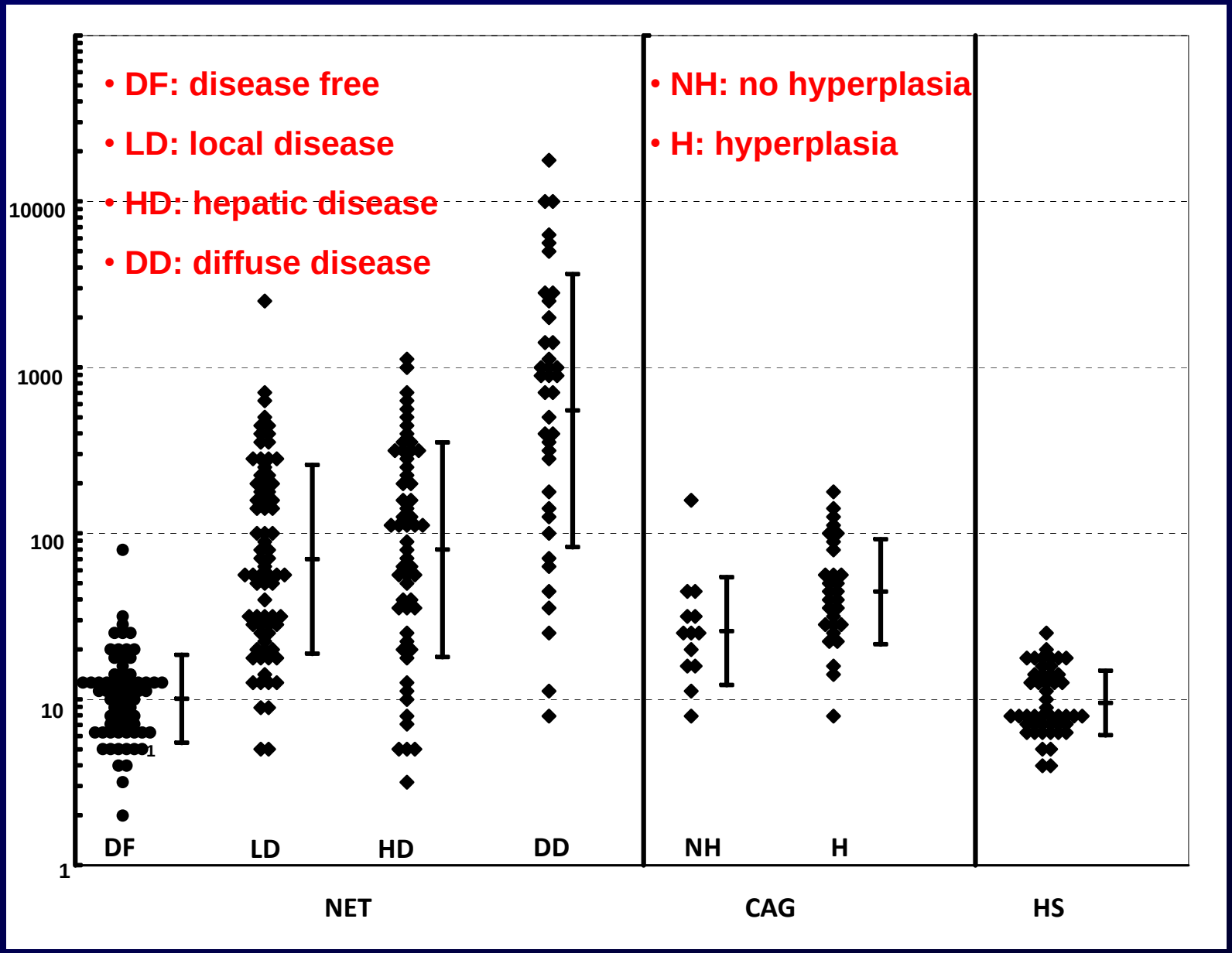
Davide Campana, Francesca Nori, Lidya Piscitelli, Antonio Maria Morselli-Labate, Raffaele Pezzilli, Roberto Corinaldesi, and Paola Tomassetti

Table 1. CgA Plasma Levels in the Three Groups of Participants

Group	No. of Participants	CgA Level (U/L)		P	Effect (%)	
		Mean	SD		Estimate	95% CI
NETs	238	428.1	1,584.3			
Compared with CAG patients				.114	153.5	90.1 to 261.6
Compared with healthy participants				< .001	606.7	367.3 to 1,000.0
CAG*	42	50.1	41.2	< .001	395.3	201.8 to 774.5
Healthy participants	48	10.5	4.7	—	—	—

NOTE. Comparisons among the groups were made using one-way analysis of variance. $P < .001$ among the three groups.
Abbreviations: CgA, chromogranin A; SD, standard deviation; NET, neuroendocrine tumor; CAG, chronic atrophic gastritis.
*P values and effect estimates compared with healthy participants.

Distribution of Chromogranin A in 238 endocrine tumor (NET) patients, in 42 chronic atrophic gastritis subjects (CAG) and in 48 healthy subjects (HS).



Campana D., JCO; 25(15) May 2007

Table 2. CgA Plasma Levels in the Subgroups of NET and CAG Patients

Group	No. of Patients	CgA Level (U/L)		P	Effect (%)	
		Mean	SD		Estimate	95% CI
NET						
Diffuse disease	38	2,055.5	3,539.4			
Compared with hepatic disease				< .001	687.3	398.5 to 1,185.4
Compared with local disease				< .001	786.2	468.2 to 1,320.2
Compared with disease free				< .001	5,452.6	3,218.5 to 9,237.4
Hepatic disease	57	187.2	237.4			
Compared with local disease				.563	114.4	72.4 to 180.7
Compared with disease free				< .001	793.3	497.1 to 1,266.1
Local disease*	75	163.5	312.5	< .001	693.5	448.5 to 1,072.4
Disease free	68	12.3	10.7	—	—	—
CAG						
Hyperplasia†	29	56.7	41.0	.032	172.7	105.2 to 283.6
No hyperplasia	13	35.3	39.2	—	—	—

NOTE. Comparisons among the subgroups were made using one-way analysis of variance.
Abbreviations: CgA, chromogranin A; NET, neuroendocrine tumor; CAG, chronic atrophic gastritis; SD, standard deviation.
*P values and effect estimates compared with disease free.
†P values and effect estimates compared with no hyperplasia

Table 3. CgA Plasma Levels in NET Patients According to the Site of Tumor

Tumor Site	No. of Patients	CgA Level (U/L)	
		Mean	SD
Lung	20	46.3	94.6
Stomach	14	78.0	69.2*
Pancreas	94	322.2	952.7*
Intestine	85	380.1	1,224.9*
ZES	25	1,490.5	3,819.3

NOTE. Comparisons among the subgroups were made using one-way analysis of variance. Overall $P < .001$ among the five localizations.
Abbreviations: CgA, chromogranin A; NET, neuroendocrine tumor; SD, standard deviation; ZES, Zollinger-Ellison syndrome.
*No significant differences ($P = .780$) were detected at the post hoc analysis among patients with stomach, pancreas, and intestinal tract neoplasia.

Campana D., JCO; 25(15) May 2007

CHROMOGRANIN A

FALSE POSITIVE

RENAL FAILURE

LIVER FAILURE

ATROPHIC GASTRITIS

INFLAMMATORY BOWEL DISEASE

NEOPLASMS

DRUGS (PPI)

STRESS

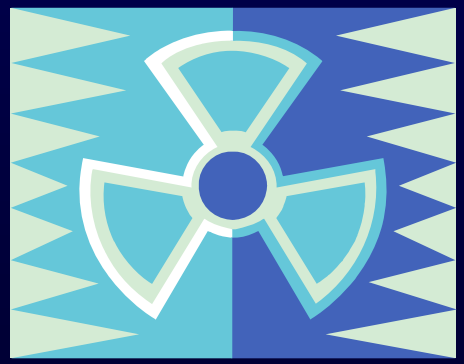
INTENSE PHYSICAL ACTIVITY

PREGNANCY

HYPERTENSION

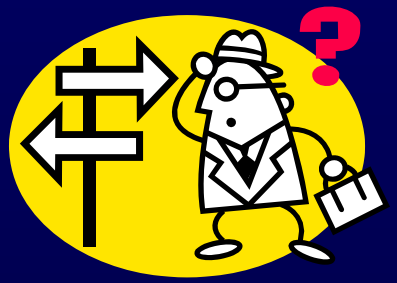
PARKINSON SYNDROME

TERAPIA

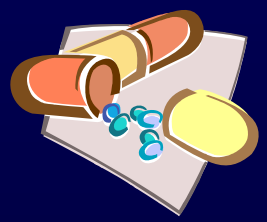


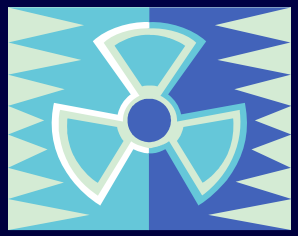
DECISIONI TERAPEUTICHE

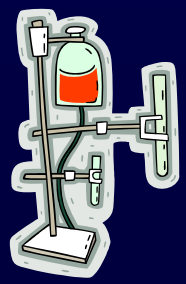
TERAPIA CHIRURGICA



TERAPIA MEDICA

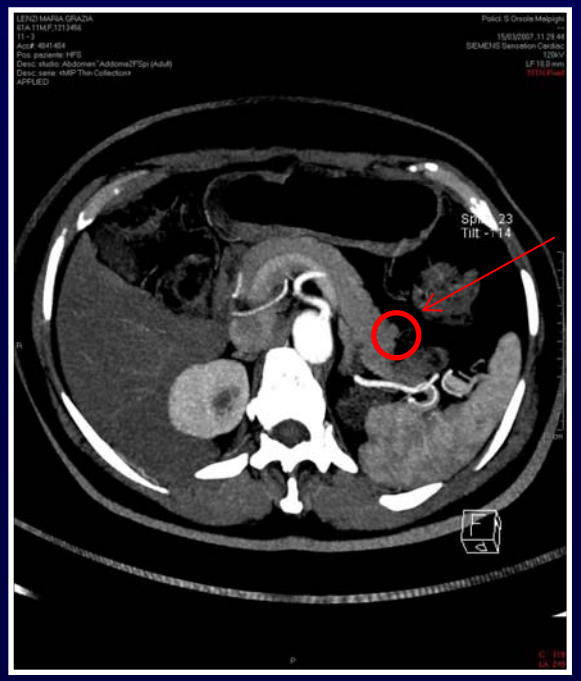


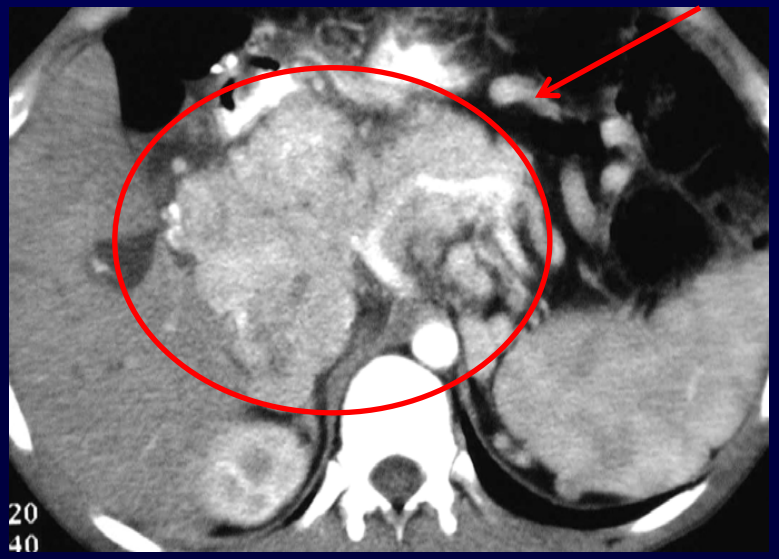




TERAPIA CHIRURGICA

QUANDO ← → **COME**





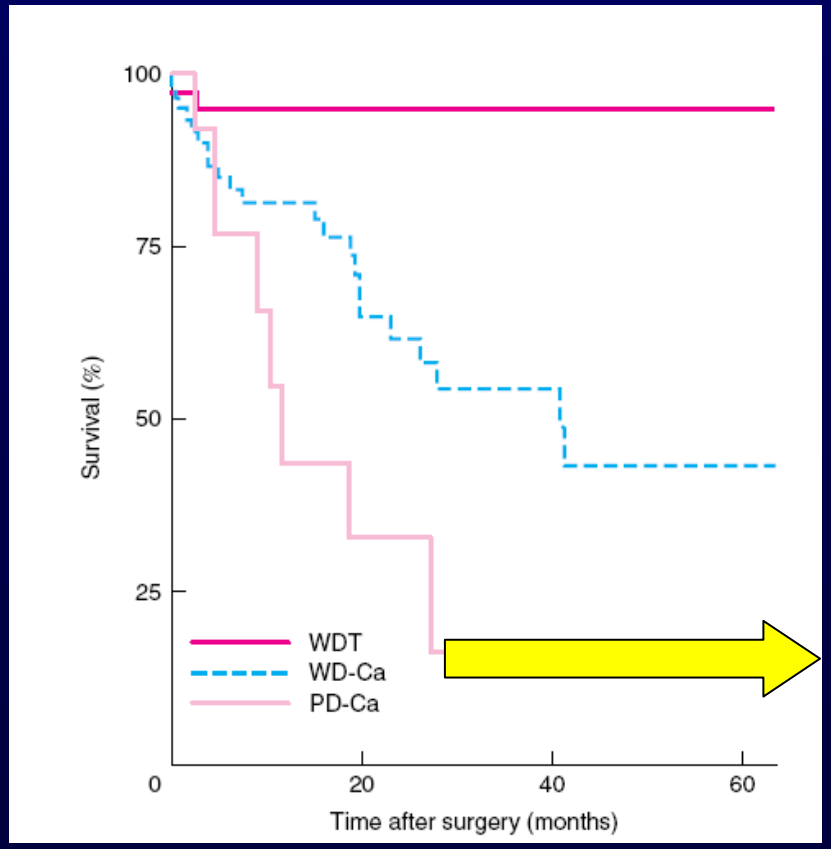
WHO

Clinical outcome and long-term survival in 118 consecutive patients with neuroendocrine tumours of the pancreas

L. Fischer[1], J. Kleeff[1], I. Esposito[2], U. Hinz[1], A. Zimmermann[3], H. Friess[1] and M. W. Büchler[1]

Departments of [1]Surgery and [2]Pathology, University Hospital Heidelberg, Heidelberg, Germany, and [3]Department of Pathology, Inselspital, University of Berne, Berne, Switzerland

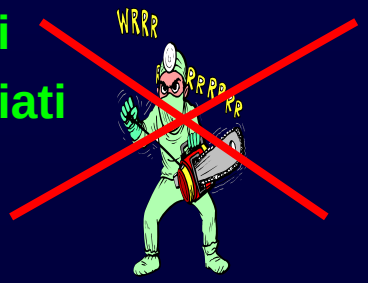
Correspondence to: Dr M. W. Büchler, Department of Surgery, University Hospital Heidelberg, Im Neuenheimer Feld 110, 69120 Heidelberg, Germany (e-mail: Markus.Buechler@med.uni-heidelberg.de)



Tumori endocrini ben differenziati

Carcinomi endocrini ben differenziati

Carcinomi endocrini scarsamente differenziati



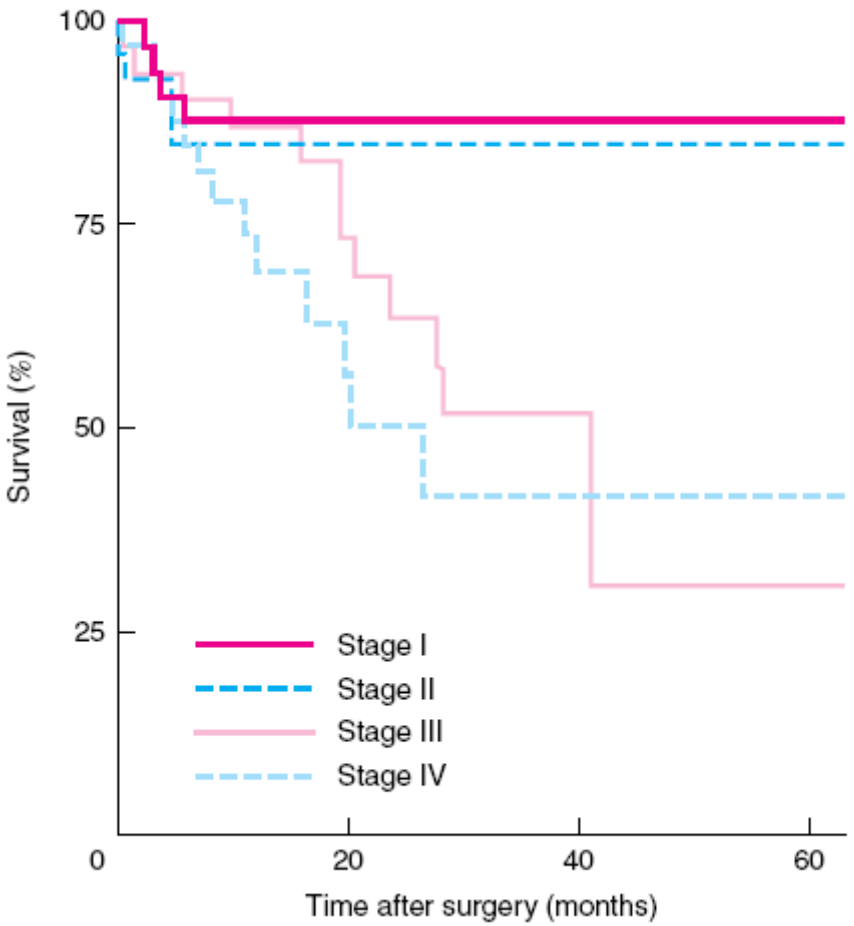
TNM

Clinical outcome and long-term survival in 118 consecutive patients with neuroendocrine tumours of the pancreas

L. Fischer[1], J. Kleeff[1], I. Esposito[2], U. Hinz[1], A. Zimmermann[3], H. Friess[1] and M. W. Büchler[1]

Departments of [1]Surgery and [2]Pathology, University Hospital Heidelberg, Heidelberg, Germany, and [3]Department of Pathology, Inselspital, University of Berne, Berne, Switzerland

Correspondence to: Dr M. W. Büchler, Department of Surgery, University Hospital Heidelberg, Im Neuenheimer Feld 110, 69120 Heidelberg, Germany (e-mail: Markus.Buechler@med.uni-heidelberg.de)



Malattia localmente avanzata / N1 / M1

CHIRURGIA

RADICALE / PALLIATIVA

original article

Annals of Oncology 19: 903–908, 2008
doi:10.1093/annonc/mdm552
Published online 21 January 2008

Prognostic factors at diagnosis and value of WHO classification in a mono-institutional series of 180 non-functioning pancreatic endocrine tumours

R. Bettini[1], L. Boninsegna[1], W. Mantovani[2], P. Capelli[3], C. Bassi[1], P. Pederzoli[1], G. F. Delle Fave[4], F. Panzuto[4], A. Scarpa[3] & M. Falconi[1]*

Departments of [1]Surgical and Gastroenterological Sciences; [2]Medicine and Public Health; [3]Pathology, University of Verona, Verona; [4]Department of Digestive and Liver Disease, II School of Medicine, University 'La Sapienza', Rome, Italy

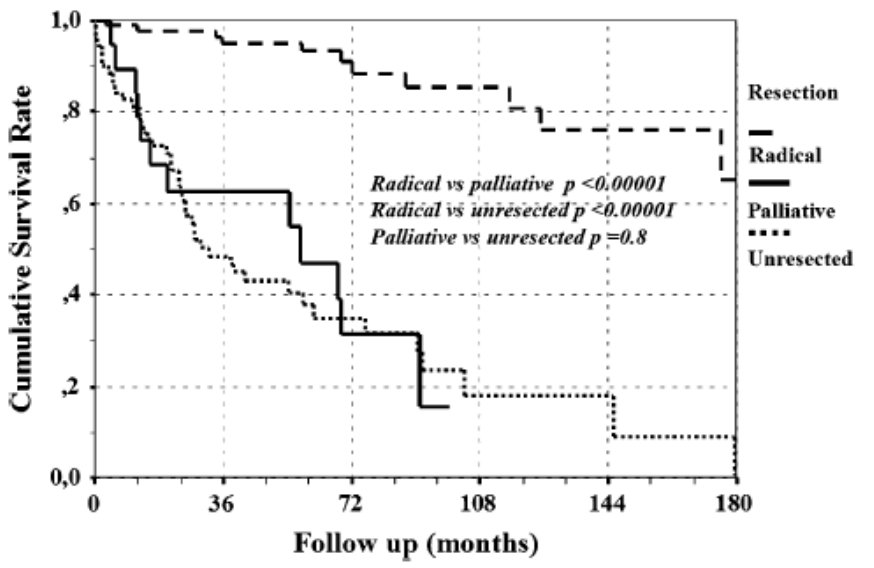
Original article

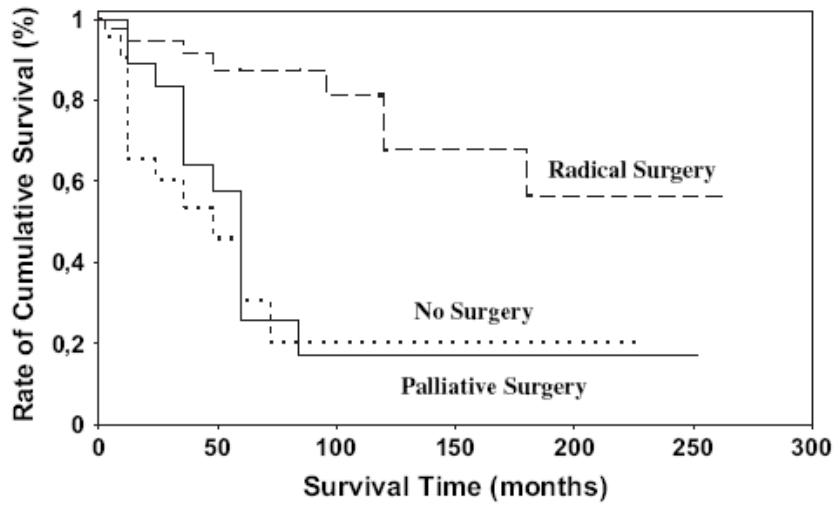
Annals of Oncology
doi:10.1093/annonc/mdi358

Endocrine pancreatic tumors: factors correlated with survival

P. Tomassetti[1]*, D. Campana[1], L. Piscitelli[1], R. Casadei[2], D. Santini[3], F. Nori[1], A. M. Morselli-Labate[1], R. Pezzilli[1] & R. Corinaldesi[1]

[1]Dipartimento di Medicina Interna e Gastroenterologia, [2]Dipartimento Clinico di Scienze Chirurgiche ed Anestesiologiche and [3]Dipartimento Clinico di Scienze Radiologiche ed Istopatologiche, Università di Bologna, Italy





Primary tumour resection in metastatic nonfunctioning pancreatic endocrine carcinomas

R. Bettini [a], W. Mantovani [b], L. Boninsegna [a], S. Crippa [a], P. Capelli [c], C. Bassi [a], A. Scarpa [c], P. Pederzoli [a], M. Falconi [a,*]

Gruppo 1 (19Pz)

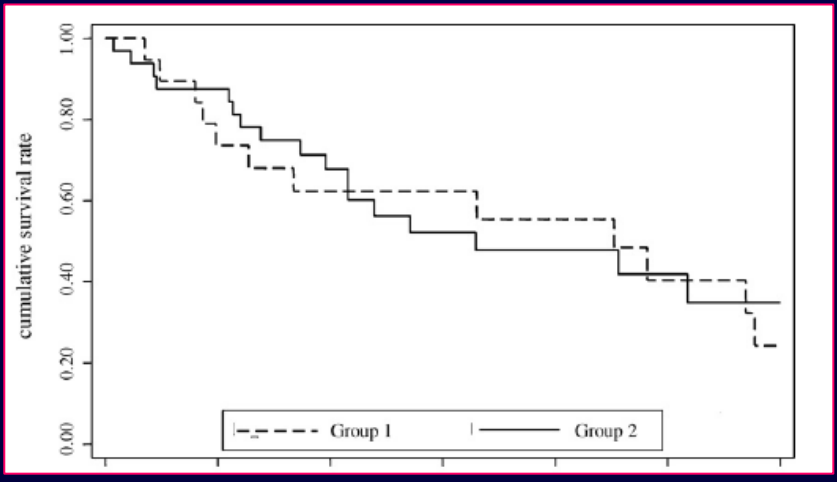
Pazienti con tumore primitivo resecabile

Resezione del tumore primitivo

Gruppo 2 (32Pz)

Pazienti con tumore primitivo non resecabile

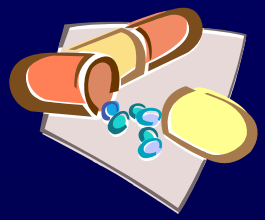
No chirurgia o chirurgia derivativa se necessario



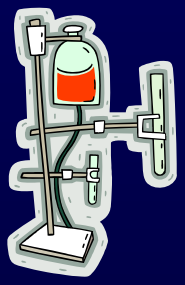
Bettini R. Dig Liver Dis. 2008 May 5

TERAPIA MEDICA

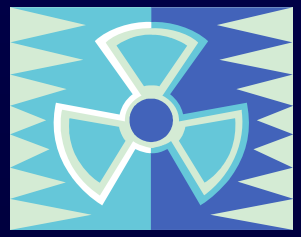
ANALOGHI DELLA SOMATOSTATINA



EVEROLIMUS (RAD001)

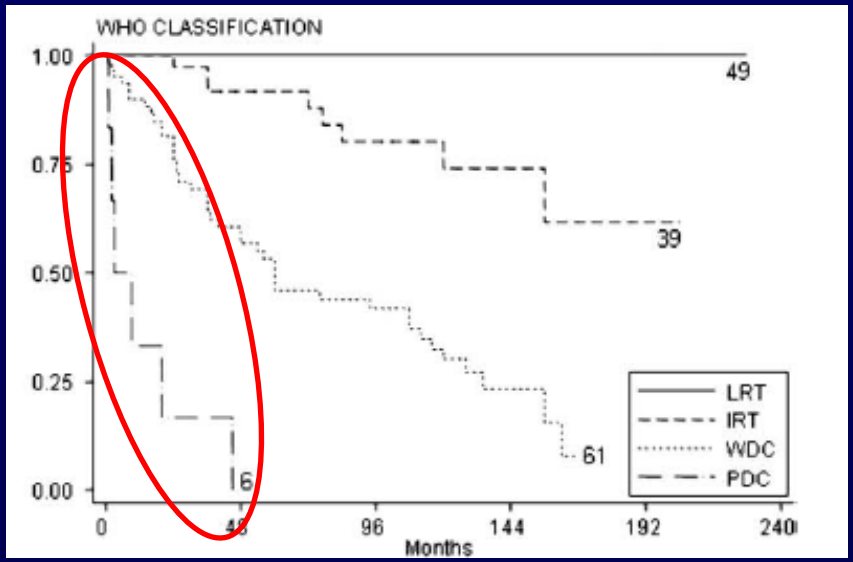


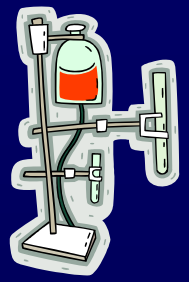
CHEMIOTERAPIA



RADIORECETTORIALE

WHO

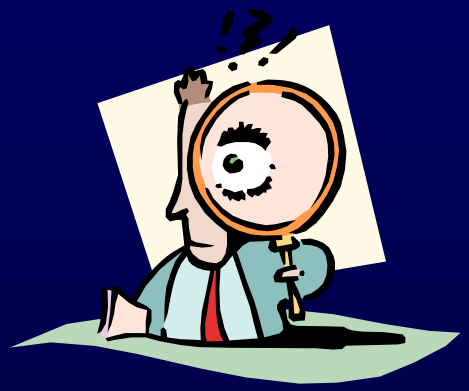




CHEMIOTERAPIA

Carcinomi endocrini
scarsamente differenziati

Tumori endocrini a comportamento incerto

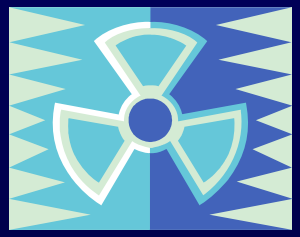


FOLLOW-UP

Carcinomi endocrini ben differenziati STADIO III

Chirurgia radicale

SST

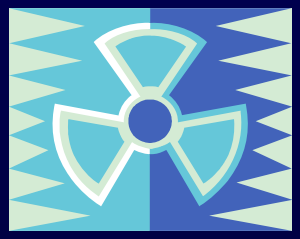


RADIORECETTORIALE

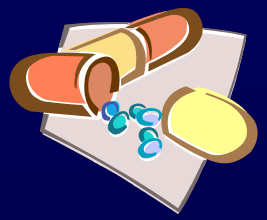
MANCANO EVIDENZE

Carcinomi endocrini ben differenziati
STADIO IV

SST



RADIORECETTORIALE



EVEROLIMUS

REVIEW

Somatostatin Analogues in the Treatment of Gastroenteropancreatic Neuroendocrine Tumors

THIERRY DELAUNOIT, MD; JOSEPH RUBIN, MD; FLORENCE NECZYPORENKO, MD; CHARLES ERLICHMAN, MD; AND TIMOTHY J. HOBDAY, MD

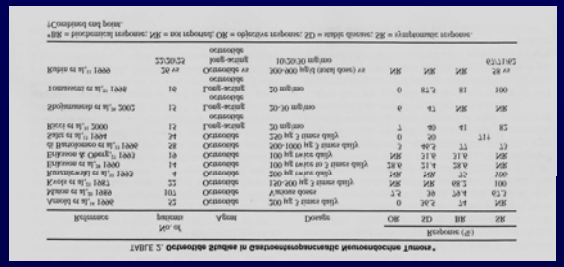


TABLE 3. Octreotide studies in gastroenteropancreatic neuroendocrine tumors.*

Reference	No. of patients	Affect	Dosage	Response (%)			
				OR	CD	MR	SR
Vinicki et al,[11] 1999	25	Carcinoids	300 μg 3 times daily	0	36.2	24	NR
Arnold et al,[12] 1999	101	Carcinoids	Various doses	2.2	16	59.4	12.9
Kanno et al,[13] 1997	35	Carcinoids	120-600 μg 3 times daily	NR	NR	5.88	100
Janssen et al,[14] 1999	14	Carcinoids	100 μg twice or 3 times daily	28.6	21.4	28.6	NR
Janssen et al,[15] 1999	4	Carcinoids	200 μg twice daily	NR	NR	25	100
Eriksson & Oberg,[16] 1997	19	Carcinoids	100 μg twice daily	NR	31.6	31.6	NR
Eriksson et al,[17] 1999	24	Carcinoids	250 μg 3 times daily	0	20	11†	15
di Bartolomeo et al,[18] 1999	28	Carcinoids	200-1000 μg 3 times daily	3	46.4	11	17
Eriksson & Oberg,[19] 1997	19	Carcinoids	100 μg twice daily	NR	31.6	31.6	NR
Rinke et al,[20] 2005	12	Foregut-derived carcinoids	30-60 mg/mo	0	41	NR	NR
Kozy et al,[21] 2000	12	Foregut-derived carcinoids	30 mg/mo	7	50	41	85
Toumbasis et al,[22] 1999	10	Foregut-derived carcinoids	30 mg/mo	0	37.5	10	100
Kulke et al,[23] 1999	36	Carcinoids or foregut-derived carcinoids	10-30-60-100 mg/mo	NR	NR	NR	61.11-85

*BR = biochemical response; NR = not reported; OR = objective response; CD = stable disease; SR = symptomatic response.
†Combined with bone.

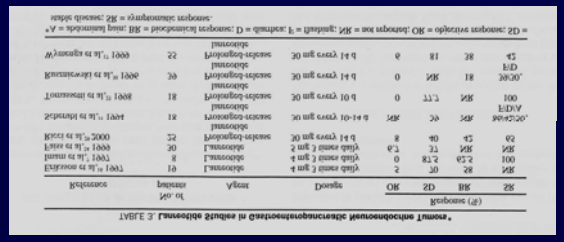


TABLE 3. Interferon studies in gastroenteropancreatic neuroendocrine tumors.*

Reference	No. of patients	Affect	Dosage	Response (%)			
				OR	CD	MR	SR
Eriksson et al,[24] 1997	19	Carcinoids	4 μg 3 times daily	2	50	28	NR
Lipari et al,[25] 1999	20	Carcinoids	2 μg 3 times daily	5.3	11	NR	NR
Janssen et al,[26] 1997	8	Carcinoids	4 μg 3 times daily	0	12.5	25.5	100
Kozy et al,[27] 2000	22	Foregonb-derived carcinoids	30 μg every 14 d	8	40	25	62
Strosberg et al,[28] 1999	18	Foregonb-derived carcinoids	30 μg every 4-10 d	NR	56	NR	NR
Toumbasis et al,[29] 1998	18	Foregonb-derived carcinoids	30 μg every 10 d	0	11.1	NR	100
Kanzawa et al,[30] 1999	26	Foregonb-derived carcinoids	30 μg every 14 d	0	NR	18	50/30*
Wymenga et al,[31] 1999	22	Foregonb-derived carcinoids	30 μg every 14 d	8	18	38	15

*A = alpha-interferon; BR = biochemical response; D = diminish; I = improve; NR = not reported; OR = objective response; CD = stable disease; SR = symptomatic response.

Risposta sintomatica → 67.3 – 100%

Risposta obiettiva → 0 - 7%

Malattia stabile→ 40 – 87.5%

Mayo Clin Proc. 2005;80(4):502-506

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 Blaker, Jan Harder, Christian Arnold, Thomas Gress, and Rudolf Arnold

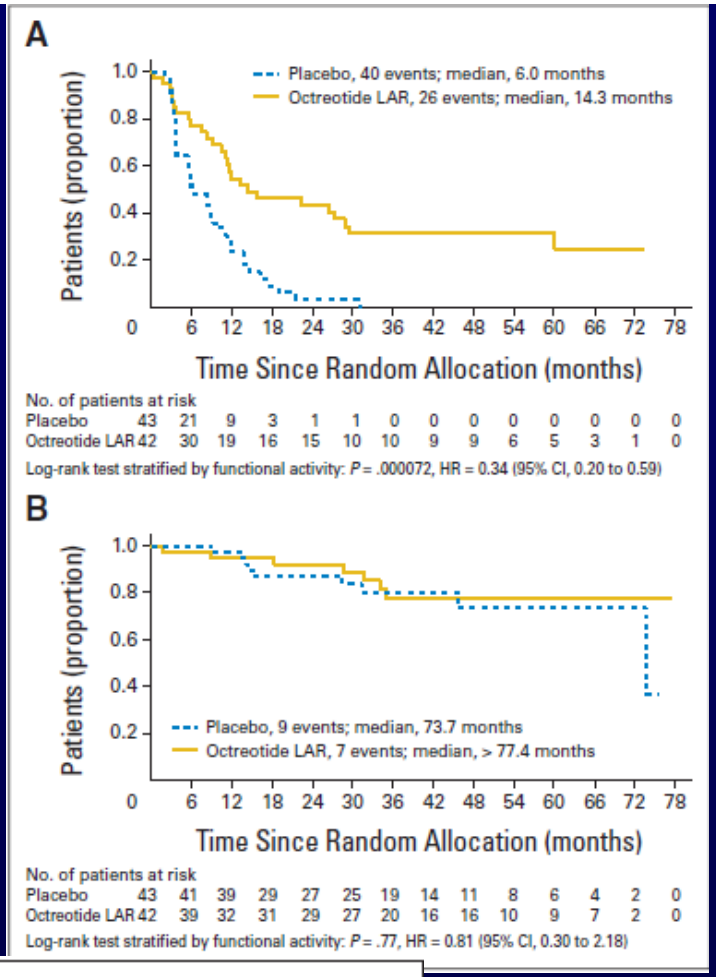


Table 3. Prognostic Factors for Time to Progression or Tumor-Related Death Adjusted for Treatment Based on the Per-Protocol Analysis

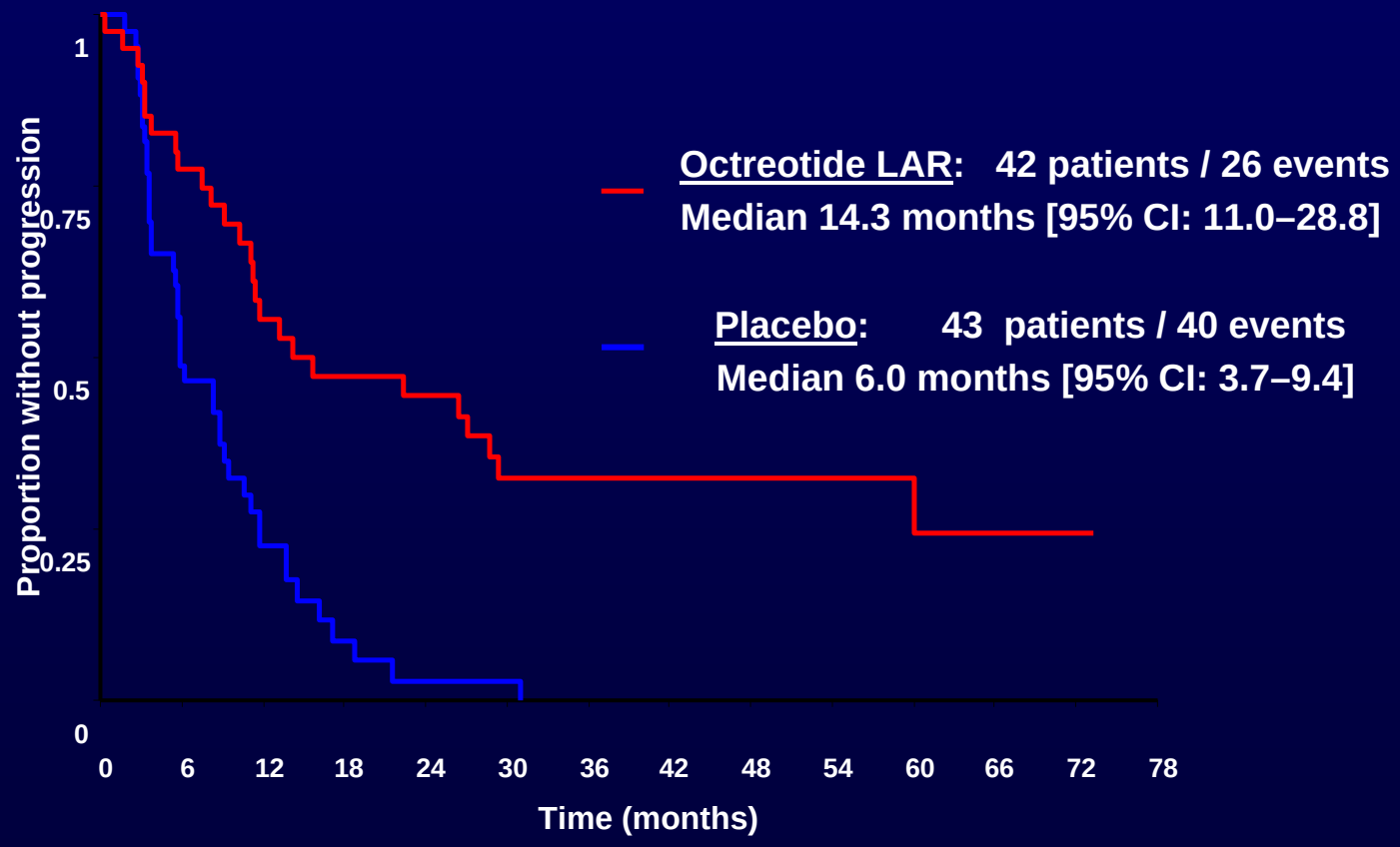
	Bivariate Analysis			Multivariate Analysis		
Factor	*P*	HR	95% CI	*P*	HR	95% CI
Octreotide LAR *v* placebo*				< .0001	0.27	0.14 to 0.49
Functional active tumor *v* inactive tumor	.2420	1.38	0.81 to 2.37			
Liver involvement > *v* ≤ 10%	.0009	2.81	1.53 to 5.18	.0023	2.63	1.41 to 4.90
Chromogranin A elevated *v* not elevated	.3098	1.36	0.75 to 2.48			
Karnofsky performance status ≤ *v* > 80%	.6518	1.21	0.54 to 2.71			
Age ≥ *v* < 63 years	.1709	1.47	0.85 to 2.56			
Primary tumor not resected *v* resected	.1040	1.60	0.91 to 2.80	.6784	1.45	0.60 to 2.20
Time since diagnosis ≥ *v* < 4.3 months	.0806	0.62	0.36 to 1.06	.2883	0.71	0.38 to 1.34

Abbreviation: HR, hazard ratio.
**P* value and effect size are only presented for multivariate analysis.

Octreotide LAR aumenta in modo significativo il tempo alla progressione

Octreotide LAR vs placebo *P*=0.000072

HR= 0.34 [95% CI: 0.20–0.59]



Based on the conservative ITT analysis

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

Dik J. Kwekkeboom, Wouter W. de Herder, Boen L. Kam, Casper H. van Eijck, Martijn van Essen, Peter P. Kooij, Richard A. Feelders, Maarten O. van Aken, and Eric P. Krenning

Table 2. Tumor Responses in Patients With GEPNETs, 3 Months After the Last Administration of ^{177}Lu-Octreotate (n = 310)

	Response										
	CR		PR		MR		SD		PD		
Tumor Type	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	Total No. of Patients
Carcinoid	1	1	41	22	31	17	78	42	37	20	188
Nonfunctioning pancreatic	4	6	26	36	13	18	19	26	10	14	72
Unknown origin			10	32	3	10	7	23	11	36	31
Gastrinoma			5	42	4	33	2	17	1	8	12
Insulinoma			3	60			1	20	1	20	5
VIPoma			1	50					1	50	2
Total	5	2	86	28	51	16	107	35	61	20	310

Abbreviations: GEPNETs, gastroenteropancreatic neuroendocrine tumors; CR, complete response; PR, partial response; MR, minimal response; SD, stable disease; PD, progressive disease; VIPoma, vasoactive intestinal peptide-secreting tumor.

VOLUME 26 · NUMBER 13 · MAY 1 2008

JOURNAL OF CLINICAL ONCOLOGY

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

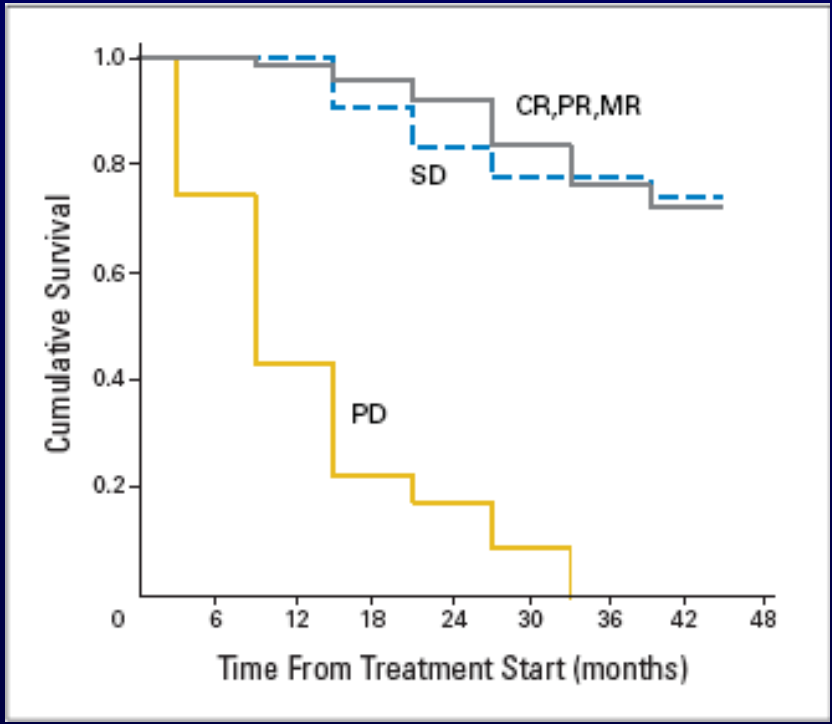
Dik J. Kwekkeboom, Wouter W. de Herder, Boen L. Kam, Casper H. van Eijck, Martijn van Essen, Peter P. Kooij, Richard A. Feelders, Maarten O. van Aken, and Eric P. Krenning

Table 3. Significant Factors Predicting Disease-Specific Survival in Patients (n = 310)

Factor	No. of Patients	Survival (months)	*P*
Treatment outcome			
PD	61	11	
SD	107	> 48	< .001
Remission	142	> 48	
Liver involvement			
Extensive	85	25	
Moderate	191	> 48	< .001
None	34	> 48	
KPS ≤ 70			
Yes	39	16	
No	271	> 48	.001
Baseline weight loss			
Yes	75	30	
No	235	> 48	.001
Presence of bone metastases			
Yes	68	37	
No	242	> 48	.004
Tumor type gastrinoma/insulinoma/VIPoma			
Yes	19	33	
No	291	> 48	.04

NOTE. Significance levels pertain to Cox regression with analysis of more factors than are listed in the Table, and which are listed in Table 1 and are marked with an asterisk.

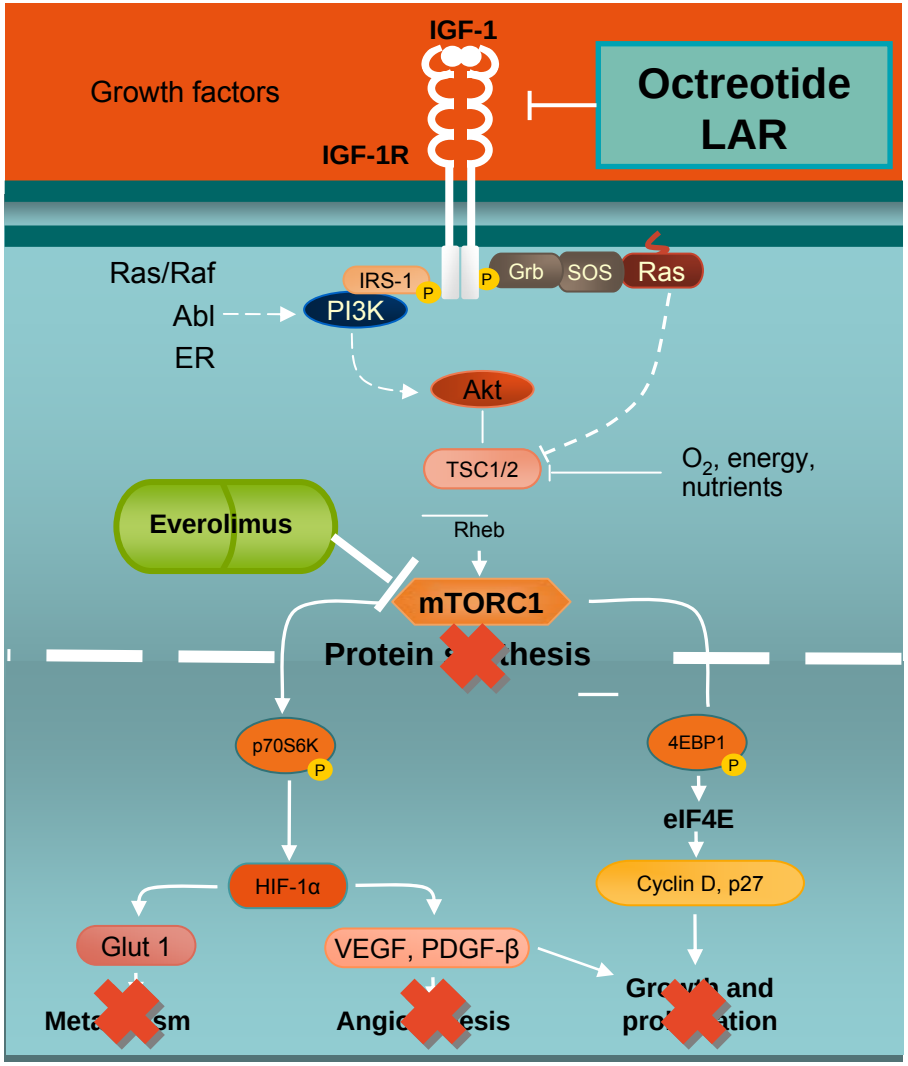
Abbreviations: PD, progressive disease; SD, stable disease; KPS, Karnofsky performance status; VIPoma, vasoactive intestinal peptide-secreting tumor.



VOLUME 26 · NUMBER 13 · MAY 1 2008

JOURNAL OF CLINICAL ONCOLOGY

Everolimus: an innovative molecular targeted therapy in NET



- Oral mTOR inhibitor
- Continuously inhibits mTOR through once-daily oral administration
- Immunosuppressive drug
- Potent anticancer activity
- Multifunctional inhibitor of:
  - cell growth and proliferation
  - cell metabolism (bioenergetics)
  - angiogenesis
- Synergistic action with octreotide

Tabernero J, et al. J Clin Oncol. 2008;26:1603-10.
O'Donnell A, et al. J Clin Oncol. 2008;23:1588-95.
Yao JC, et al. Ann Oncol. 2009;19: [abstract 508PD].
Zitzmann K, et al. Neuroendocrinology. 2007; 85:54-60.
O'Reilly KE, et al. Cancer Res. 2006;66:1500-08.
Huynh H, et al. J Cell Mol Med. 2009;13:1371-80.
Hörsch D, et al. J Clin Oncol. 2007;25:18S [abstract 1057].

Image courtesy Novartis.

VOLUME 26 · NUMBER 26 · SEPTEMBER 10 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Efficacy of RAD001 (Everolimus) and Octreotide LAR in Advanced Low- to Intermediate-Grade Neuroendocrine Tumors: Results of a Phase II Study

James C. Yao, Alexandria T. Phan, David Z. Chang, Robert A. Wolff, Kenneth Hess, Sanjay Gupta, Carmen Jacobs, Jeannette E. Mares, Andrea N. Landgraf, Asif Rashid, and Funda Meric-Bernstam

RAD001 5 mg/die (pts 1→30)

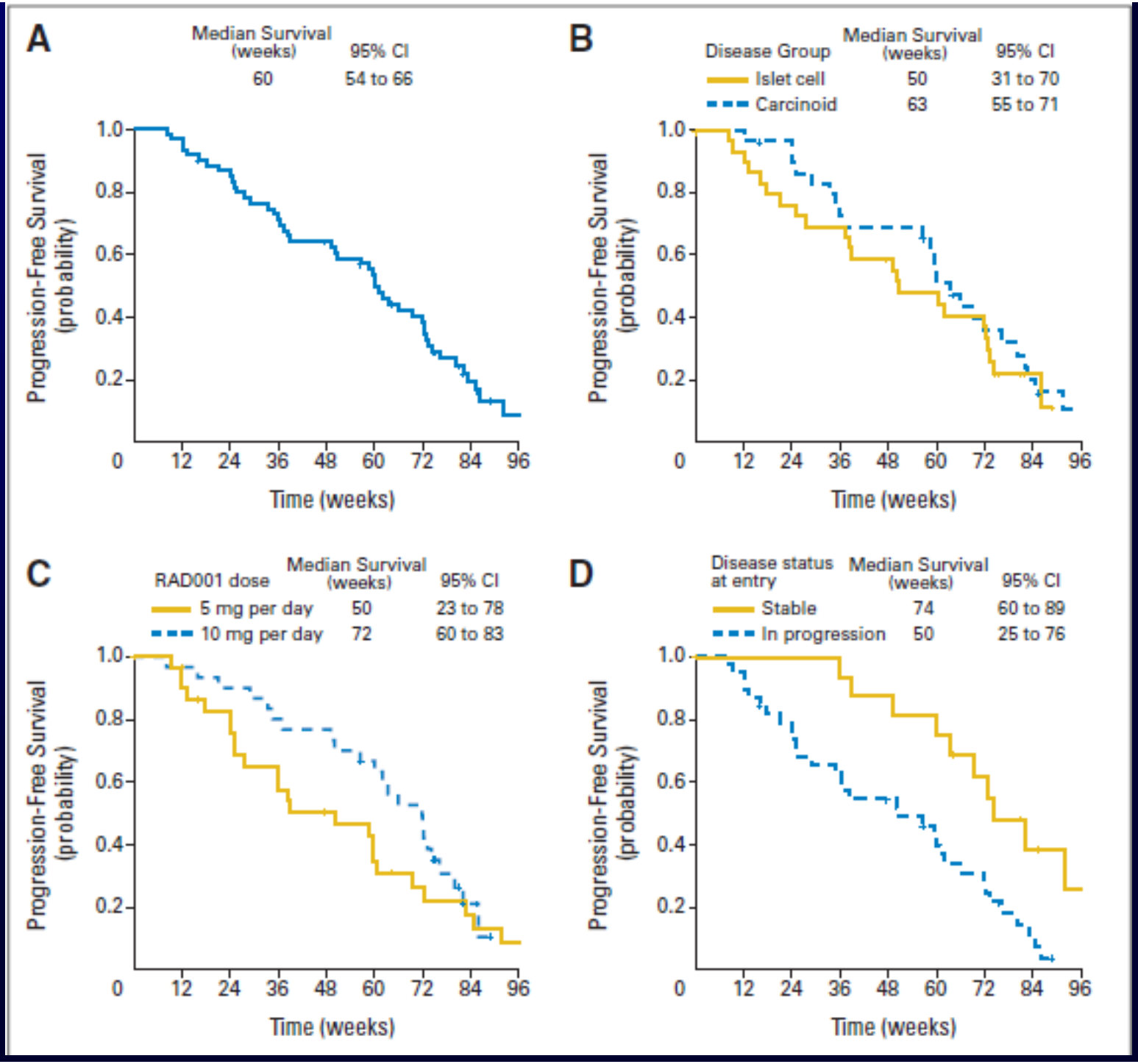
RAD001 10 mg/die (pts 31→60)

+

OCT LAR 30 mg q4w

Phase II study of RAD001 plus Octreotide LAR

	N	%
Disease at entry		
PD	39	65
SD	16	27
Unknown	5	8
Prior therapy		
Octreotide	38	63
Chemotherapy	25	42
Interferon	9	15
Bevacizumab	6	10
HAE	5	8
Primary site		
Foregut		
Gastric	1	2
Lung	4	7
Thymus	1	2
Pancreas	29	48
Midgut		
Small intestine	16	27
Hindgut		
Rectum	3	5
Other		
Renal	1	2
Unknown	5	8


A
Median Survival (weeks)
95% CI
60
54 to 66
Progression-Free Survival (probability)
1.0
0.8
0.6
0.4
0.2
0
12 24 36 48 60 72 84 96
Time (weeks)
B
Disease Group
Median Survival (weeks)
95% CI
Islet cell 50 31 to 70
Carcinoid 63 55 to 71
Progression-Free Survival (probability)
Time (weeks)
C
RAD001 dose
Median Survival (weeks)
95% CI
5 mg per day 50 23 to 78
10 mg per day 72 60 to 83
Progression-Free Survival (probability)
Time (weeks)
D
Disease status at entry
Median Survival (weeks)
95% CI
Stable 74 60 to 89
In progression 50 25 to 76
Progression-Free Survival (probability)
Time (weeks)

VOLUME 26 · NUMBER 26 · SEPTEMBER 10 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Efficacy of RAD001 (Everolimus) and Octreotide LAR in Advanced Low- to Intermediate-Grade Neuroendocrine Tumors: Results of a Phase II Study

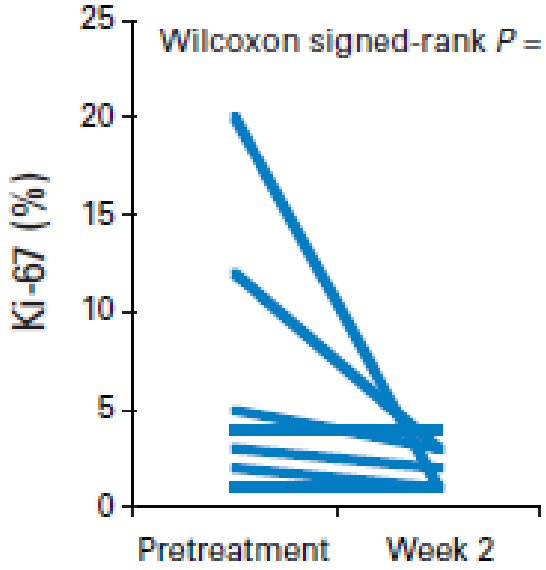
James C. Yao, Alexandria T. Phan, David Z. Chang, Robert A. Wolff, Kenneth Hess, Sanjay Gupta, Carmen Jacobs, Jeannette E. Mares, Andrea N. Landgraf, Asif Rashid, and Funda Meric-Bernstam

*Response and maximal tumor shrinkage may take **time to develop**, with some patients experiencing continued tumor shrinkage more than 12 months after initiation of therapy*

Patients with known progression at entry had inferior median survival (31 months) compared with those known to be stable (not reached; P.02).

Most common toxicity
aphtous ulcers

Main G3-4 toxicity
fatigue, diarrhea, hypophosphatemia



Primary site	Status at entry	Dose (mg)	Pre-Ki-67(%)	Post-Ki-67(%)	Protocol Response	PFS (weeks)
Thymus	PD	5	20	1	SD	16+
Pancreas	PD	5	2	1	SD	38
Rectum	PD	10	5	3	SD	56
Pancreas	PD	10	1	1	SD	74
Small bowel	PD	10	12	3	SD	63
Pancreas	PD	10	4	4	SD	8
Unknown	PD	10	3	2	SD	66

RAD001 In Advanced Neuroendocrine Tumors RADIANT

RADIANT-1: Phase 2 open label study of RAD001 in advanced pancreatic neuroendocrine tumors after failure of chemotherapy (2239) - CLOSED

RADIANT-2: Phase 3 double-blind placebo-controlled study of RAD001 in pts receiving Octreotide LAR for advanced carcinoid tumors (2325) - CLOSED

RADIANT-3: Phase 3 double-blind placebo-controlled study of RAD001 in advanced pancreatic tumors (2324)- CLOSED

RAMSETE: Phase II open label of RAD001 in advanced non-functioning NET in Europe - ONGOING

WHO + TNM

TERAPIA CHIRURGICA

- Radicale per guarire
- Per ridurre la massa
- Debulking

TERAPIA MEDICA

SST

Radiorecettoriale

RAD001

STABILIZZAZIONE DI MALATTIA