6th AME National Meeting
3rd Joint Meeting with AACE

NET: Treatment of Persistent Disease

Prognostic Criteria

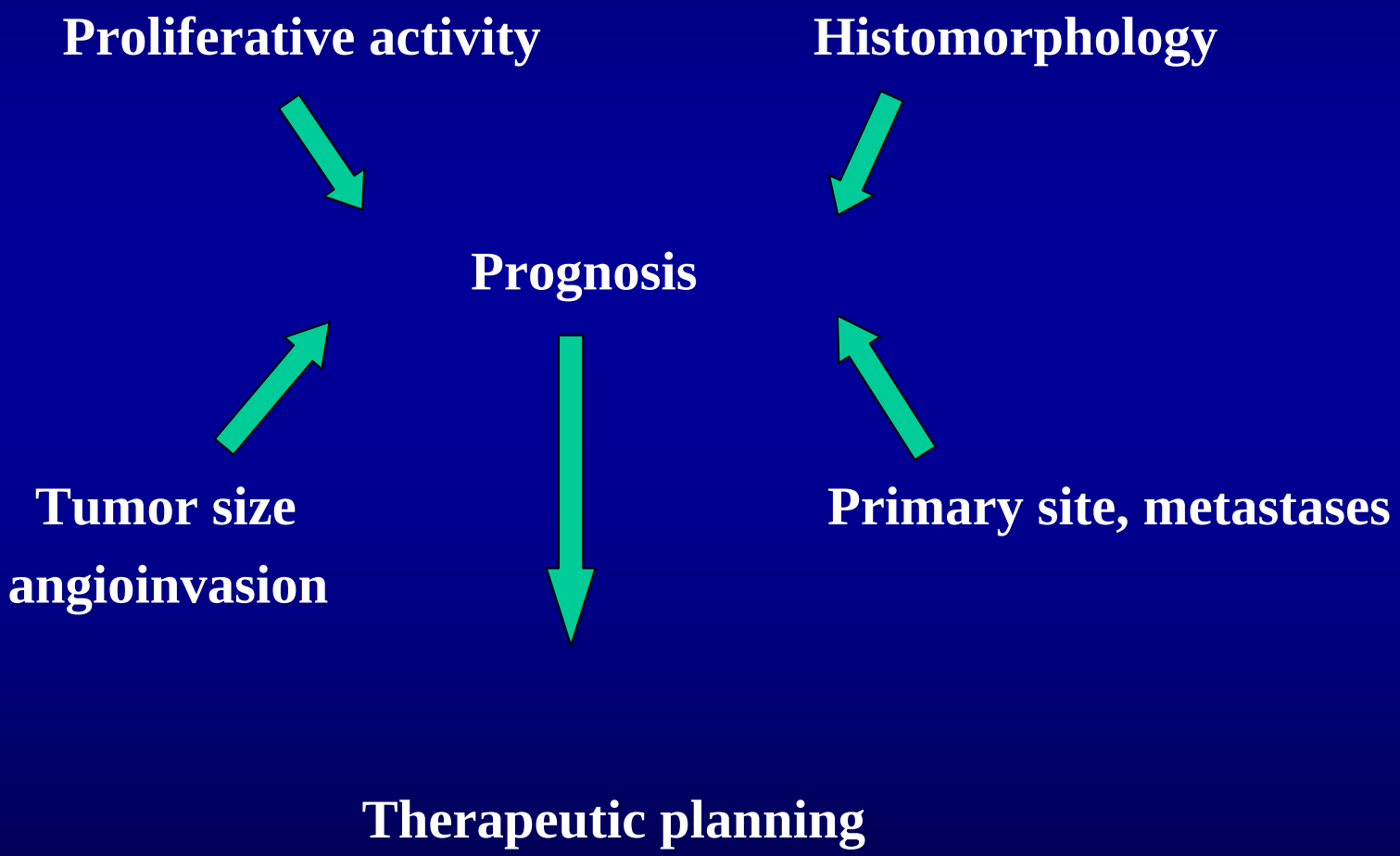
Giuseppe Francia

Introduction

Although histological pattern as prognostic factor of neuroendocrine tumors (NETs) has been recently revalued, several other variables are to be considered to predict biological behaviour of such tumors, mainly of differentiated neoplasms

It is common experience that, even in patients with metastatic NETs clinical course is highly variable

Main prognostic indicators

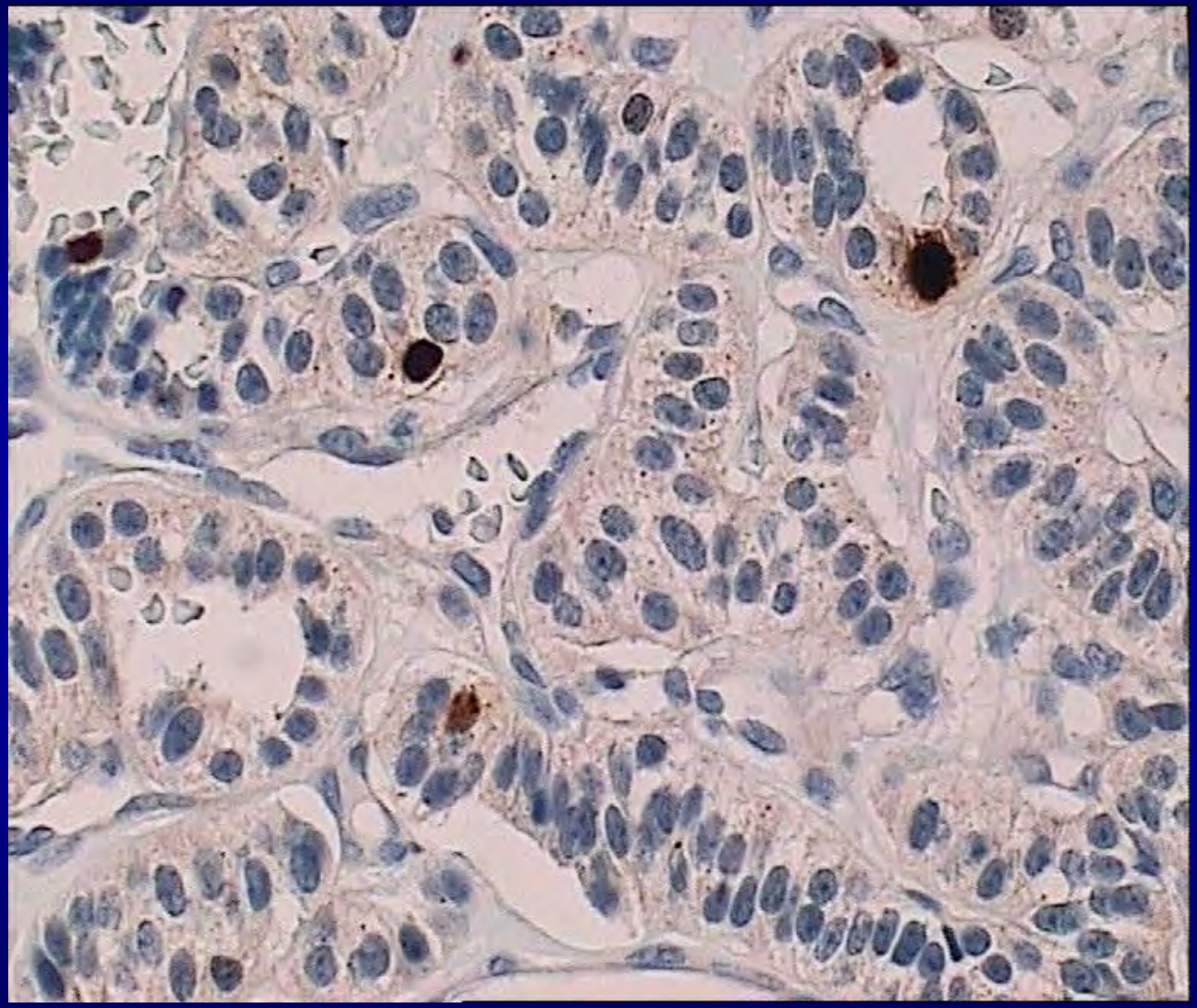


- Prognostic criteria
- Functional status and prognosis
- MEN 1 and prognosis
- Analysis of prognostic variables

Histologic features

- **Well differentiated NETs**
- Trabecular or glandular structure
- Cell monomorphism
- Absent cytological atypia
- Reactivity for chromogranin A, specific hormones, NSE, synaptophysin
- No overexpression of p 53

- **Poorly differentiated NET**
- Irregular solid areas, necrosis
- Cellular atypia
- Reactivity for cytosolic markers (NSE, synaptophysin)
- Scant or weak reactivity for chromogranin A or specific hormones
- Overexpression of p 53



Well differentiated NET

Primary site

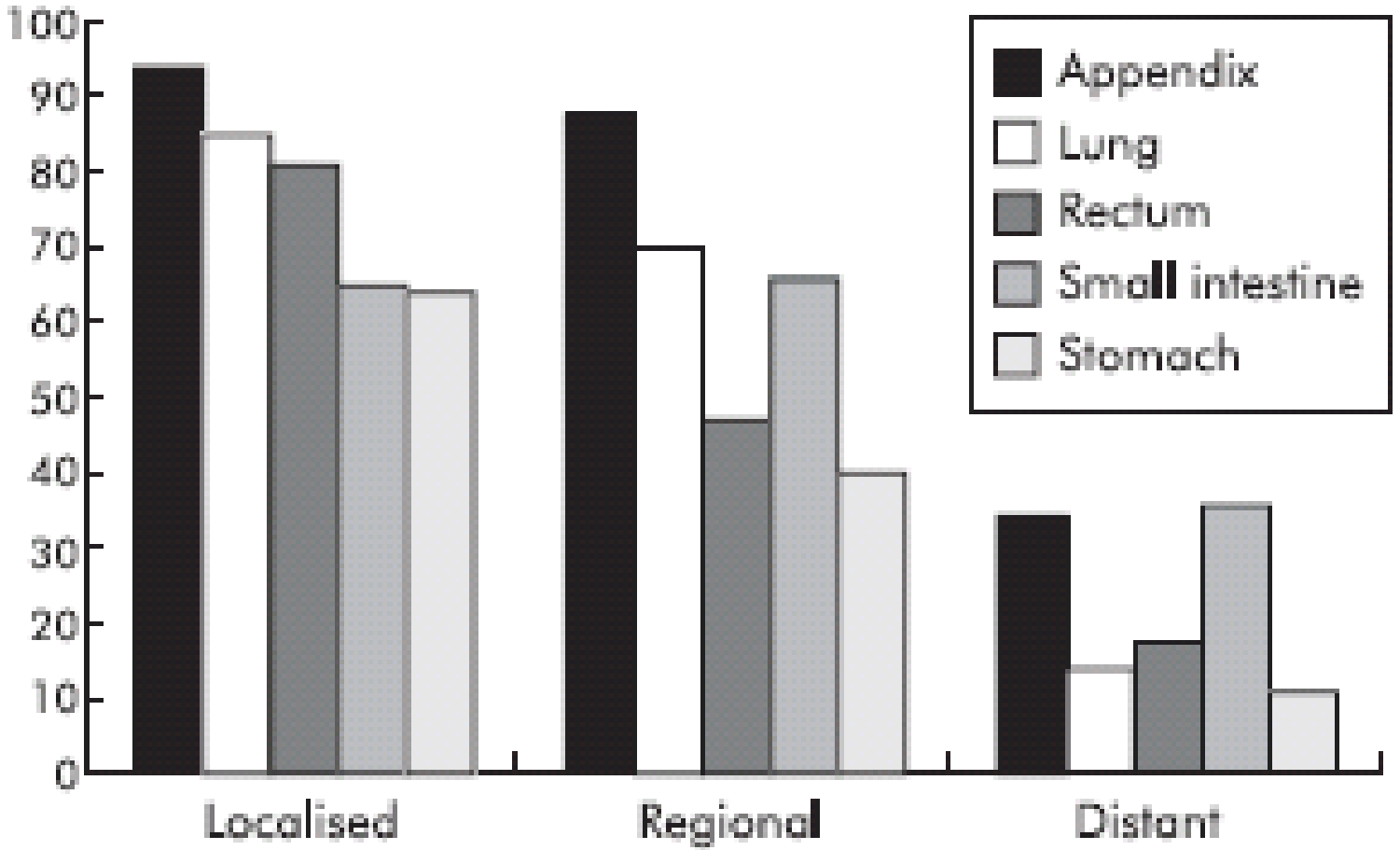


Figure 2 Five year survival of patients with carcinoid tumours related to the primary site and degree of spread.

Ramage et al, GUT, 2005

Major negative prognostic factors of gastro-enteropancreatic endocrine tumors

Pancreatic site

Tumor size > 3 cm

Distant extrahepatic metastases

Poor degree of cell differentiation

Panzuto et al

Endocr Relat Cancer 2005

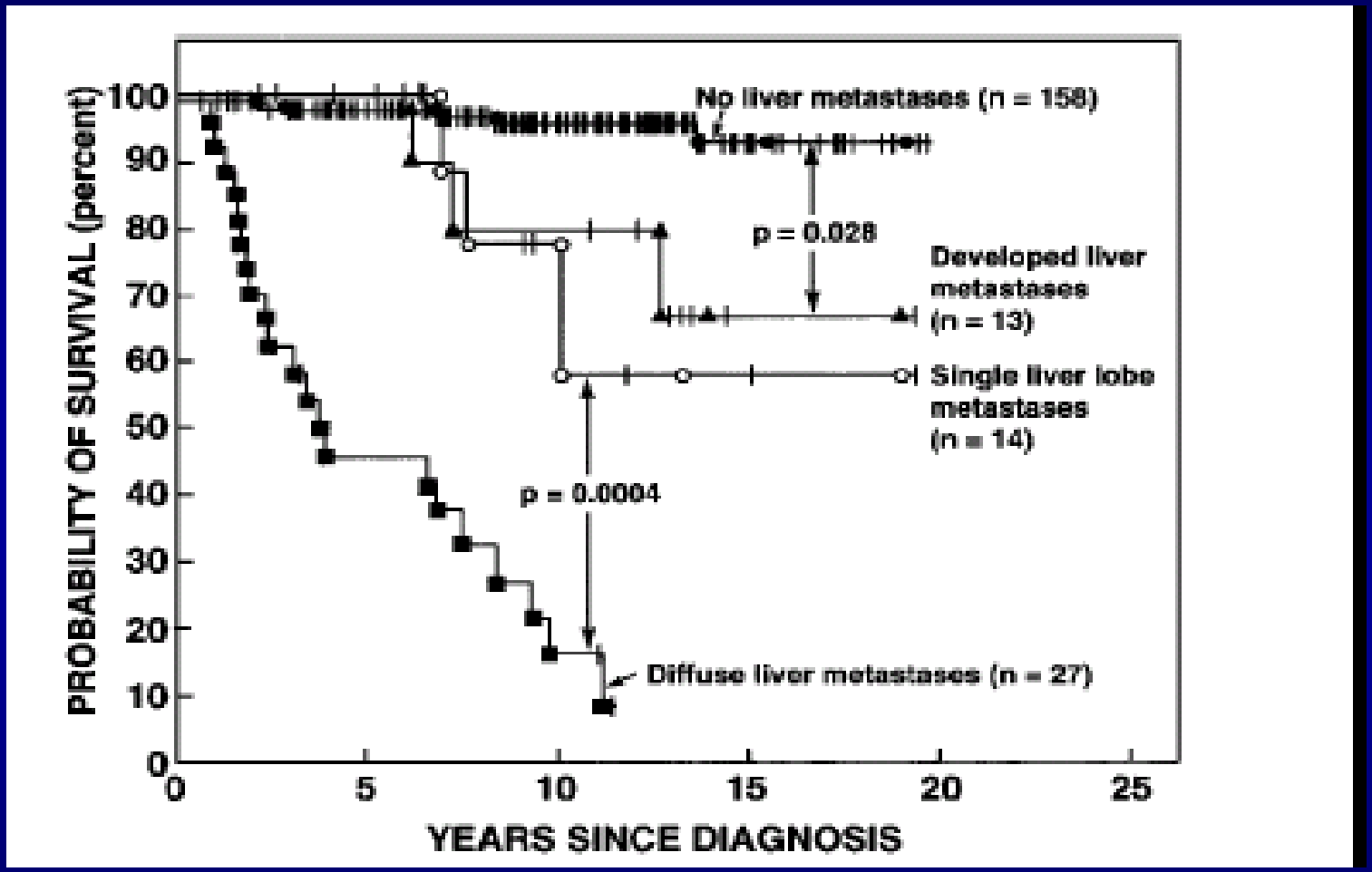
Metastases

Five year survival (%) of patients with carcinoid tumours related to primary site and presence of metastases (8305 cases)

Primary site	Localised	Nod. Met..	Dist. Met.
Stomach	64,3	39,9	10,0
Ileum	64,9	65,5	35,9
Colon	70,7	44,4	20,5
Appendix	94,0	44,4	33,7
Rectum	81,0	84,6	18,3
gallbladder	83,0	46,7	-
Lung	85	0	13,7
Ovary	95,0	70,1	13,3
All sites (media±SE)	79,7±4,3	50,6±9,9	21,8±3,0

Modlin, 1997

Gastrinoma



Patients without any liver metastases had a 95% 20-year survival from diagnosis, whereas patients with diffuse metastases had a 10-year survival of only 15%. Patients who had a single liver lobe metastasis or less than 5 discrete metastases in both liver lobes also had a decreased survival (60% at 15 years);

Norton and Jensen 2004

Tumor size

Tumor size in well differentiated GEP

Site	size (cm) Benign behaviour	uncertain behaviour + angionvasion
Pancreas	≤ 2	> 2
Stomach	≤ 1	> 1
Duodenum proximal/		
jejunum	≤ 1	> 1
ileum	≤ 1	> 1
Rectum colon	≤ 2	> 2
Appendix	≤ 2	> 2

from Bordi et al. 2003

NET pancreas: primary tumor size and liver metastases frequency

Tumor size	liver metastases
< 1 cm	4%
1-3 cm	28%
> 3 cm	61%

Norton J. A. 1997

These data suggest that surgery treatment of non functioning neuroendocrine pancreatic neoplasms < 2 cm should be carefully weighed against the mortality and the morbidity related to pancreatic resection

Proliferative activity

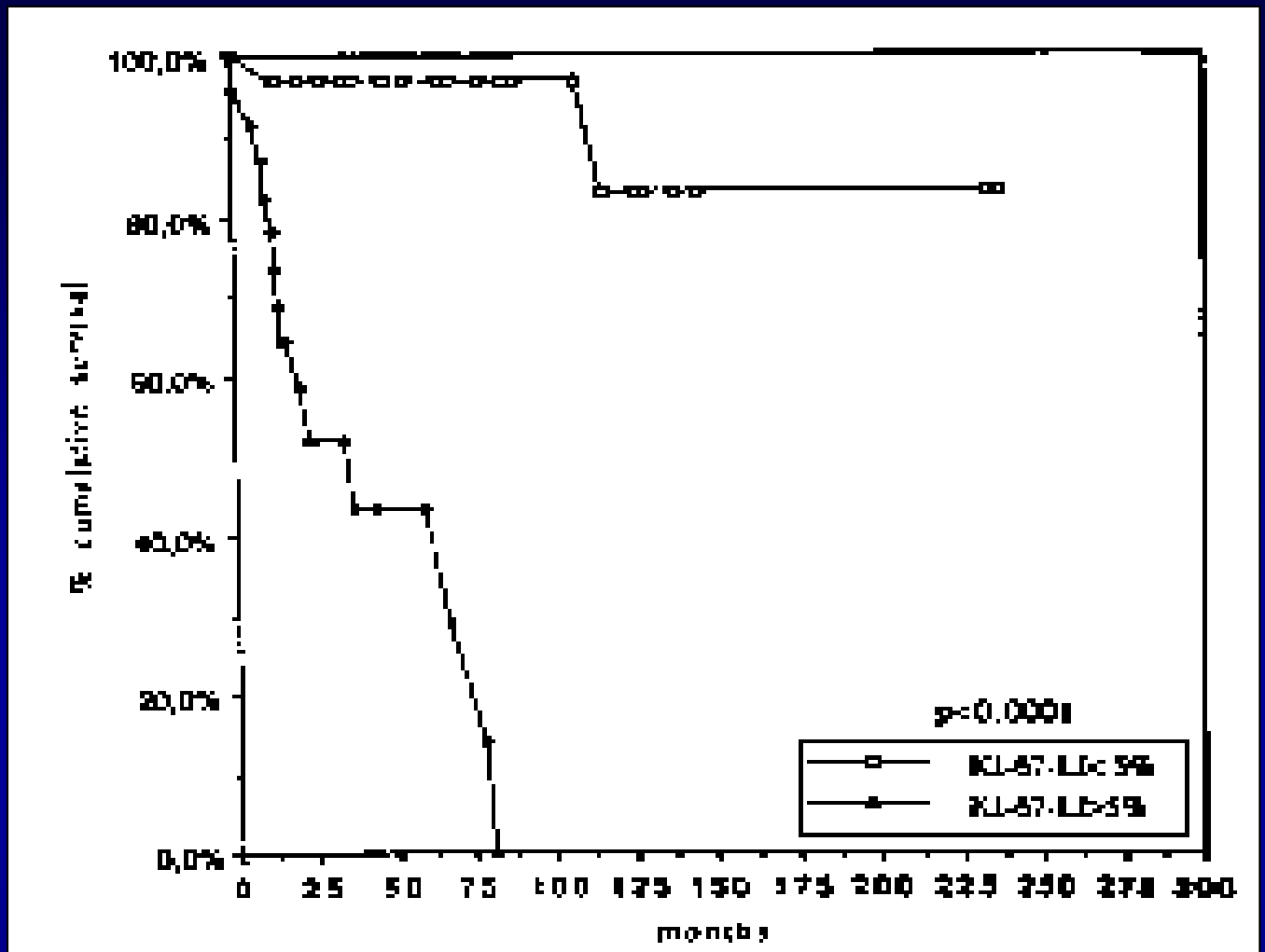


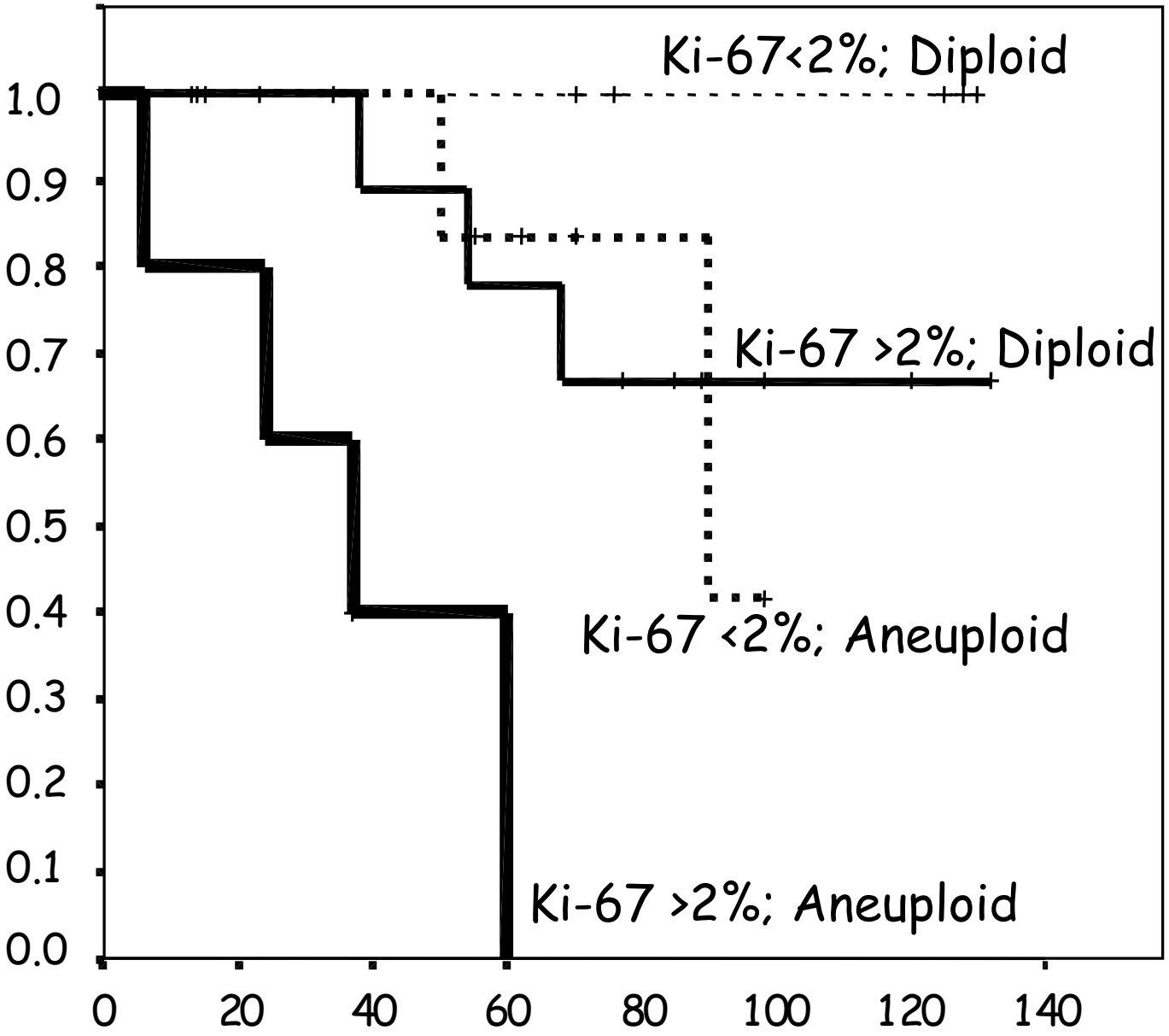
FIGURE 3. Actuarial survival of 54 PET according to Ki-67 index. Tumors showing Ki-67 index > 5% showed a decreased percentage of cumulative survival.

Ki 67 as Indipendenr Predictor for Malignancy Endocrine Tumors of the Pancreas:

Pelosi et al, 1996

	well differentiated NET	poorly differentiated NET
Mitotic counts (mitoses/mm^2 or 10 HPF)	< 2	≥ 10
Ki 67 index (% positive cells)	< 2%	> 15%

Ki-67 and PLOIDY



Ki-67 p = 0.007
Ploidy p = 0.003

Rigaud et al. Cancer Res 2001, 61:285

Does functional status of neuroendocrine pancreatic tumors affect the survival?

Data are conflicting: previous findings, showing longer survival of patients with functioning tumors, *(Broughan et al., 1986, Thompson et al. 1988)* were not confirmed *(White et al. 1994, Hochwald et al.2002)*

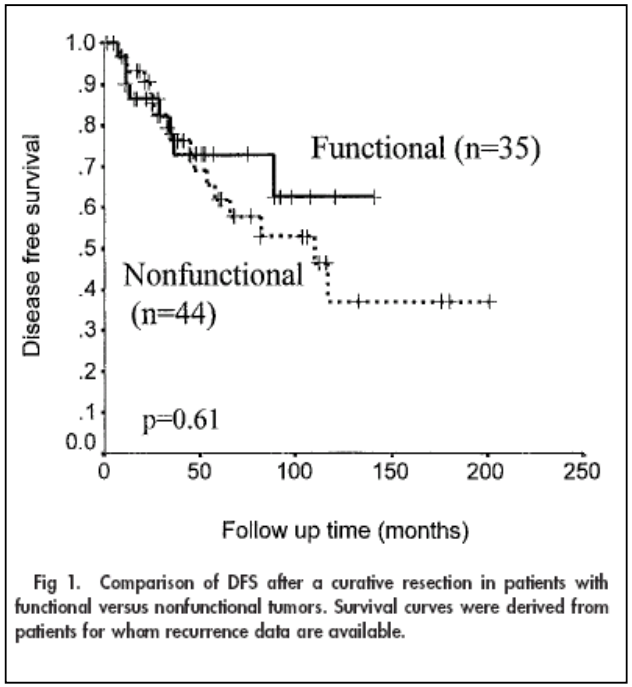


Fig 1. Comparison of DFS after a curative resection in patients with functional versus nonfunctional tumors. Survival curves were derived from patients for whom recurrence data are available.

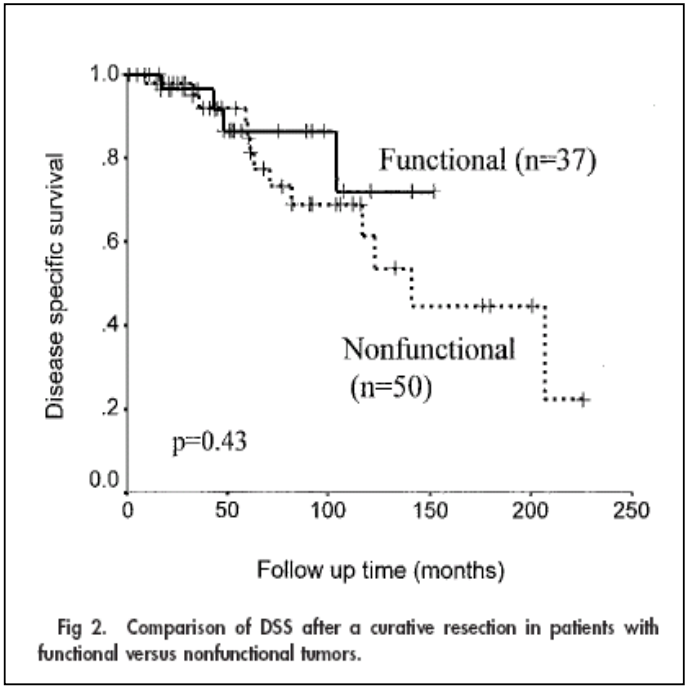


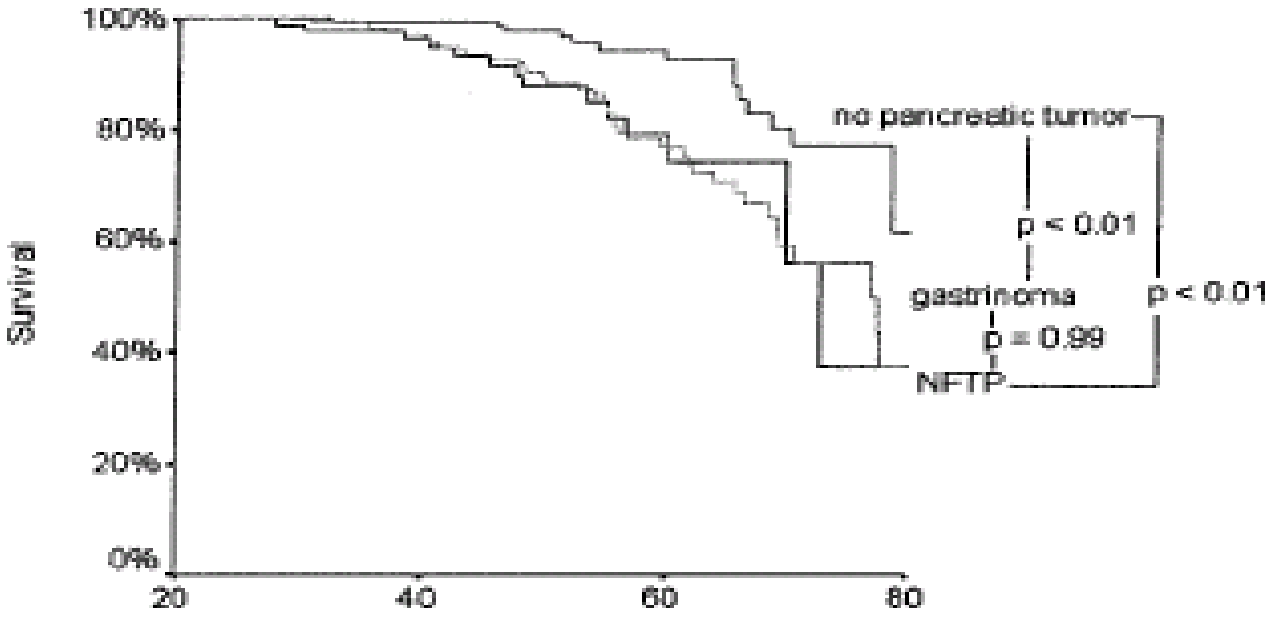
Fig 2. Comparison of DSS after a curative resection in patients with functional versus nonfunctional tumors.

Hochwald et al. 2002

MEN 1 and neuroendocrine tumors

Several studies show that pancreaticoduodenal neuroendocrine tumors in patients with MEN 1 have low growth rate with excellent survival *(Weber et al., 1995, Cadiot et al., 1999)*.

However in more recent studies such tumors proved to be a major cause of premature death in MEN 1

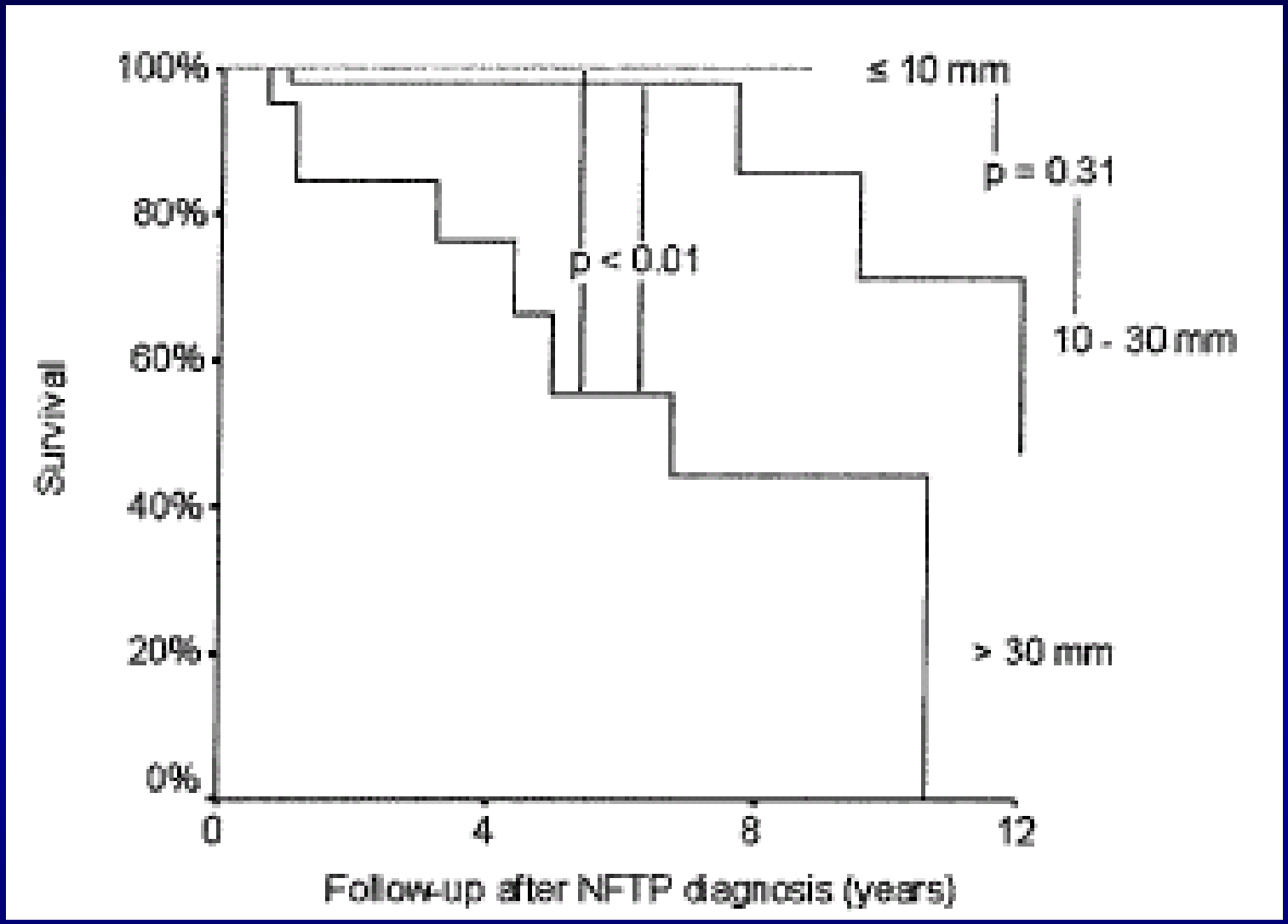


Number remaining:

No pan tu:	222	147	52	3
Gastrinoma:	169	148	53	6
NFTP:	109	68	17	0

FIGURE 3. Kaplan-Meier representation of life expectancy according to the type of pancreaticoduodenal tumor. Data are expressed as age at the end of follow-up. The number of patients at risk at each time point is shown below the graph.

Triponez et al 2006



Survival of non functioning tumors of the pancreas according to the size in108 patients affected by MEN 1

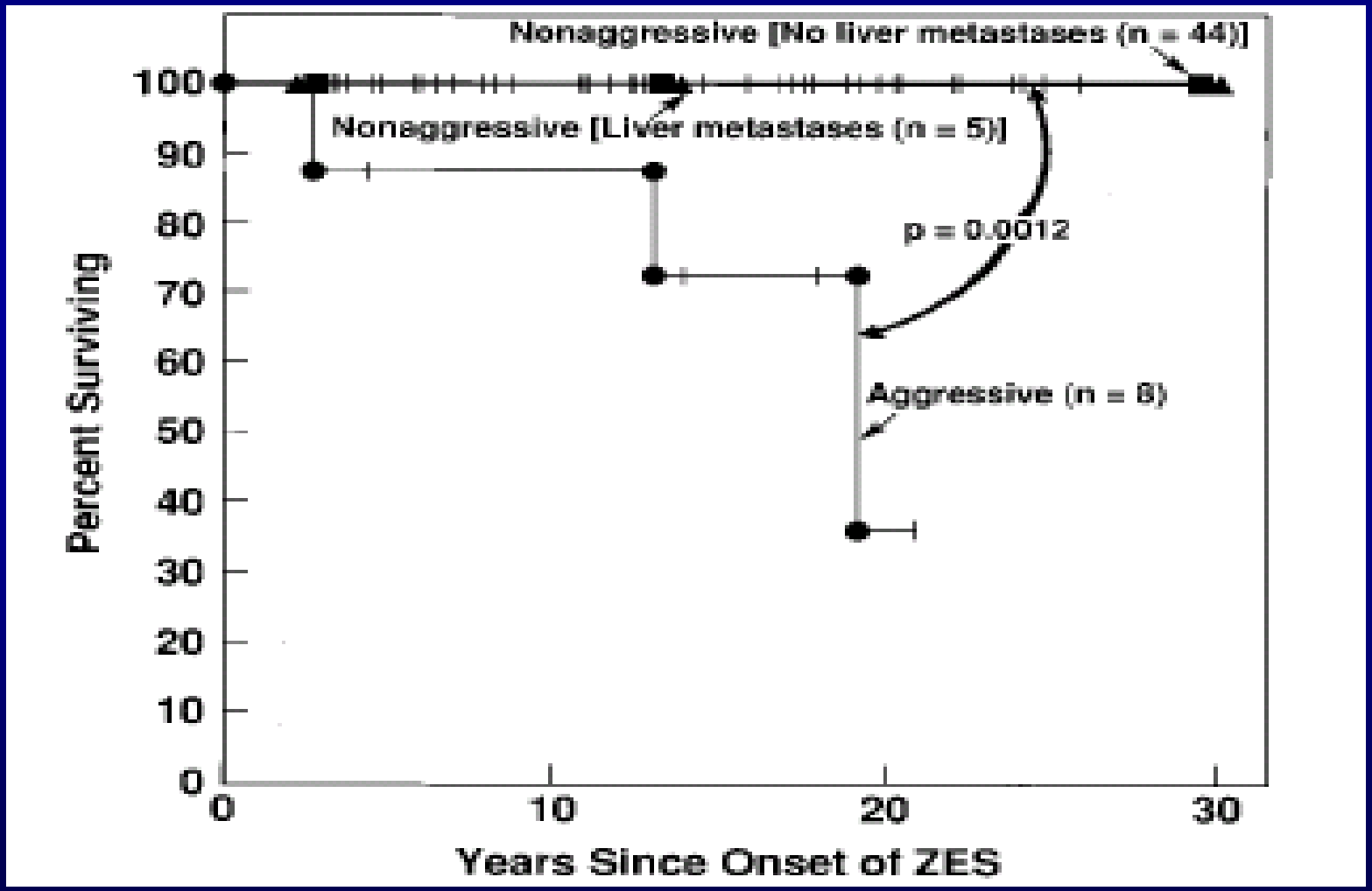
Triponez et al 2006

TABLE 4. Proportions of Patients Surviving 4 and 8 Years After NFTP Diagnosis

	4 Years (%)	8 Years (%)
No metastasis	98 (95–100)	98 (75–100)
Distant metastasis	73 (51–95)	34 (6–62)

Triponez et al 2006

Survival of patients with ZES and MEN 1 with or without aggressive disease

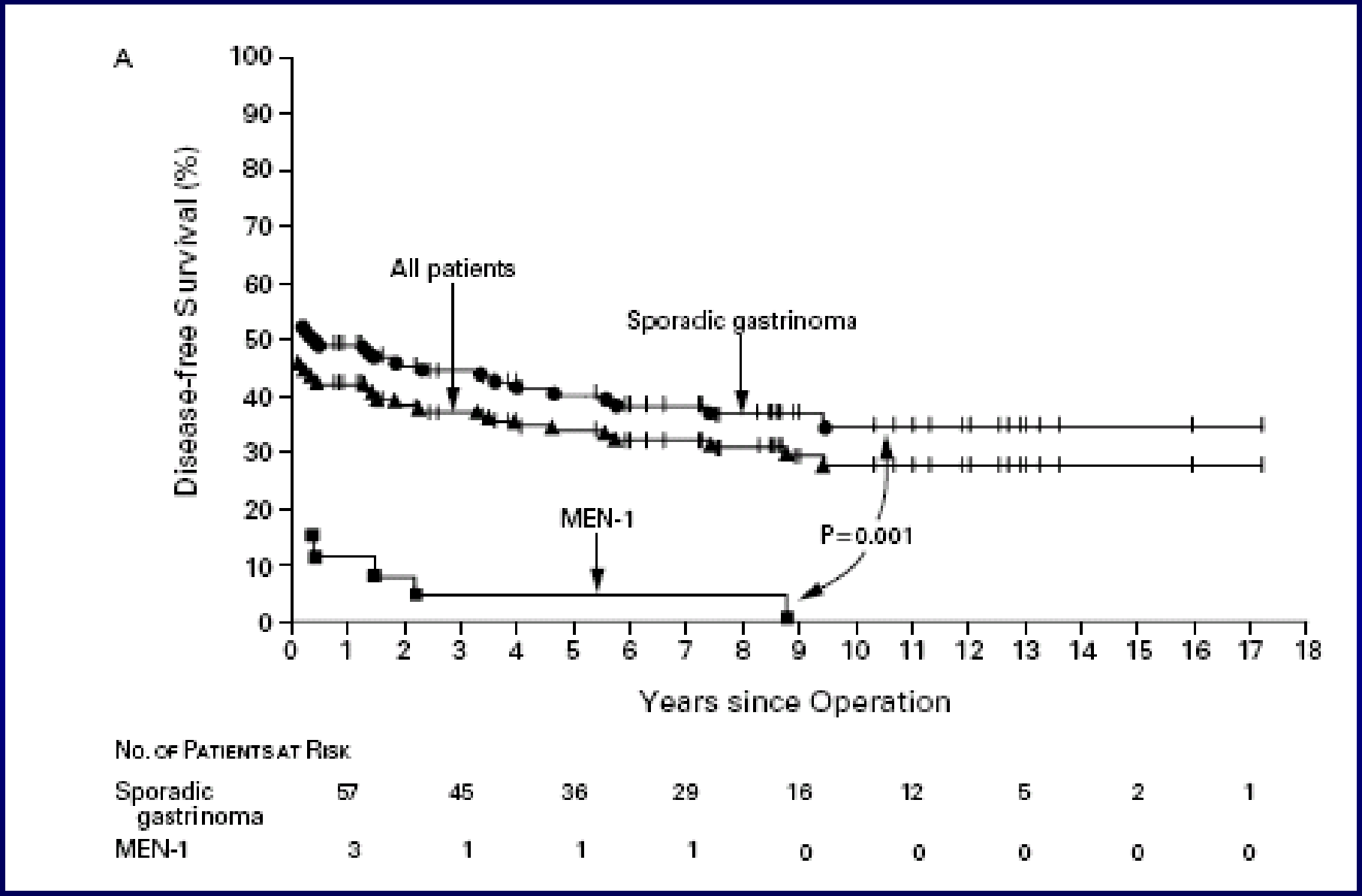


Gibril et al, 2001

The gastrinoma with "Talons"

	p
T ≥ 3 cm	p < 0.0001
Liver metastases	p < 0.0001
Gastrin levels>10.000 pg/ml	p < 0.0001
Bone metastases	p < 0.001
Gastric carcinoid ECLoma	P < 0.02
LOH 11q13	P = 0.0004

*SOLO IN MEN 1



Norton JA et al. 1999

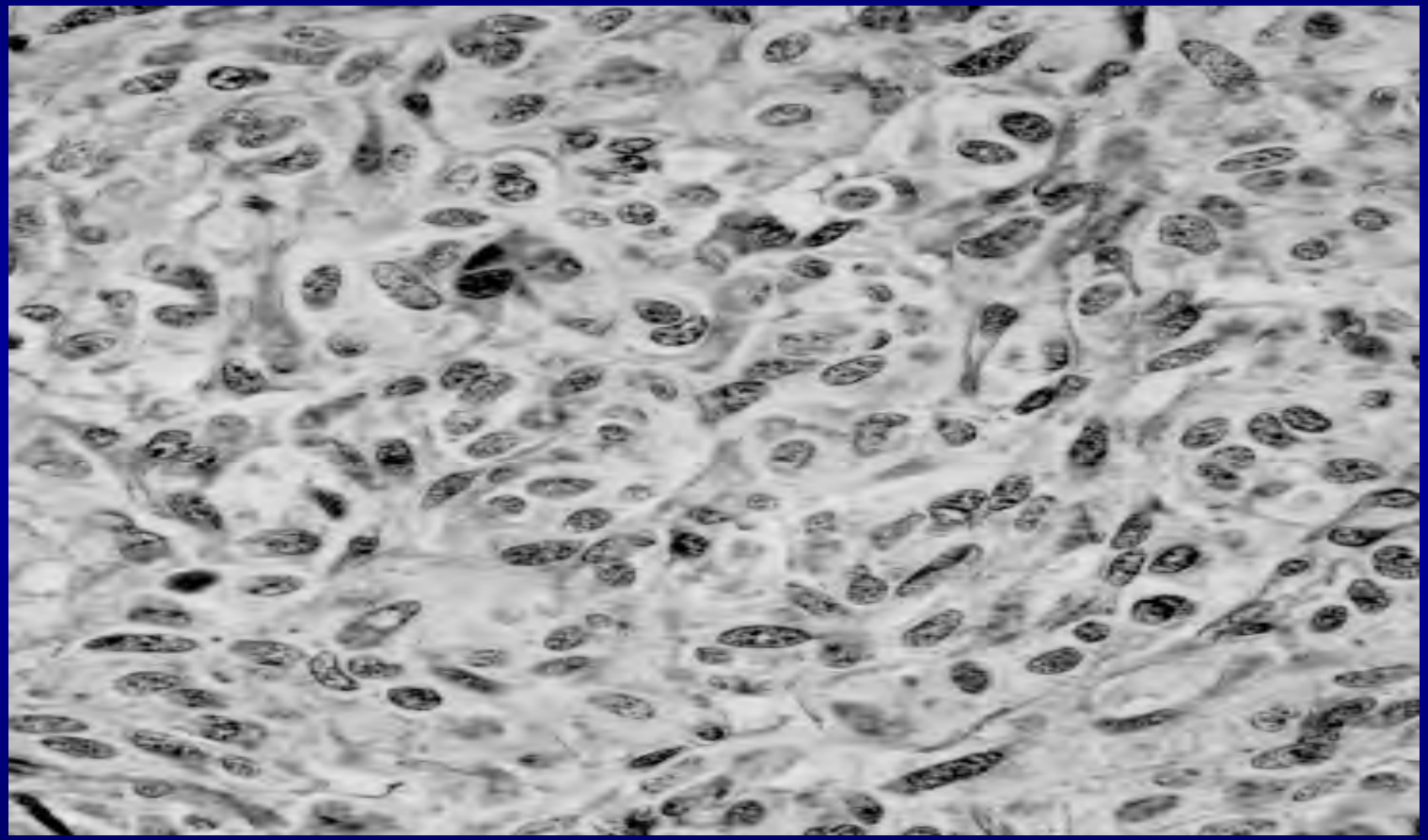
What prognostic factor has the major impact on the survival?

	All neuroendocrine tumors (p)	Carcinoids (p)
Univariate analysis		
Variable		
Stage	< 0.001	0.003
Mitoses	< 0.001	< 0.001
Necrosis	< 0.001	< 0.001
Vascular invasion	< 0.001	0.002
Nucleoli	0.021	0.003
Pleomorphism	NS	0.001
Multivariate analysis		
Variable		
Mitoses (average per 2 mm^2 [10 HPF])	0.05	< 0.001
Necrosis	0.002	NS
Vascular invasion	0.04	NS
Nucleoli	NS	NS
Variable		
Mitoses (2–10 per 2 mm^2 [10 HPF])*	< 0.001	NA
All other variables	NS	NA

HPF, high-power fields; NA, Not applicable; NS, Not significant.

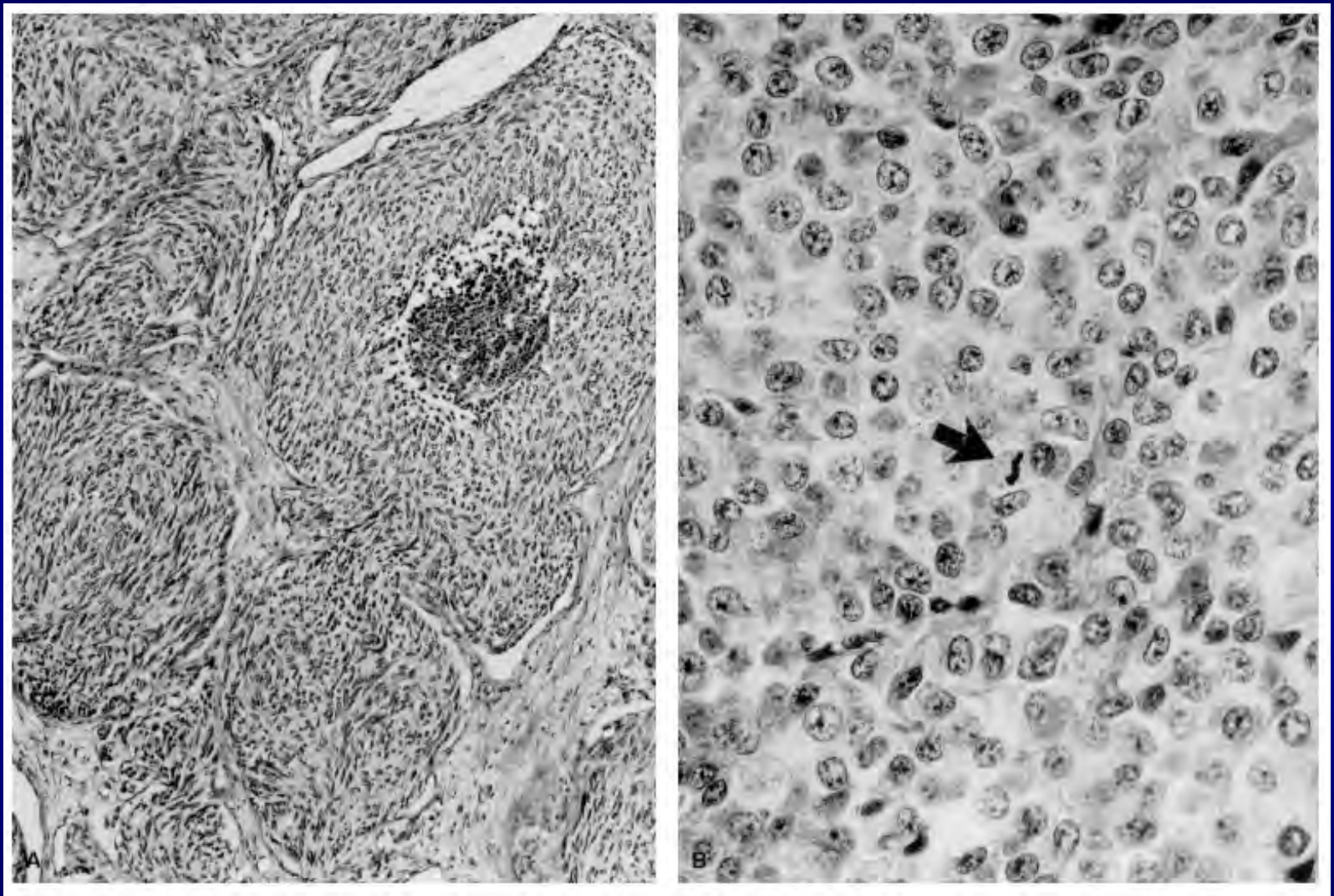
* Mitoses bracketed as 0 < 2, 2 < 10, and equal to or greater than 10 mitoses per 2 mm^2 (10 HPF).

Survival analysis of neuroendocrine lung tumors (200 cases) *Travis et al 1998*



Typical carcinoid tumor

Travis et al 1998



Atypical carcinoid tumor

Travis et al 1998

Table 8. Analysis of Factors Impacting DFS and DSS for 87 Patients (nonfunctional and functional) Undergoing a Curative Resection

	Univariate *P*		Multivariate *P*	
	DFS	DSS	DFS	DSS
Presence of tumor necrosis	.002	.16	.01	
Presence of lymph node or liver metastases	.0002	.07	.04	.22
Presence of soft-tissue invasion	.01	.36	.65	
Presence of vascular invasion	.02	.04	.56	.55
Nuclear grade 3 or 4 *v* 1 or 2	.04	.33	.98	
Tumor mitotic rate of > 2 *v* ≤ 2 per 50 HPFs	.001	.002	.16	.02
Size > 2 cm *v* ≤ 2 cm	.01	.05	.58	.80
MIB-1 value of > 50 *v* ≤ 50 per 10 HPFs	.001	.05	.67	.66
Progesterone receptor–positive *v* –negative	.79	.28		
013-positive *v* -negative	.51	.65		

Hochwald et al, 2002

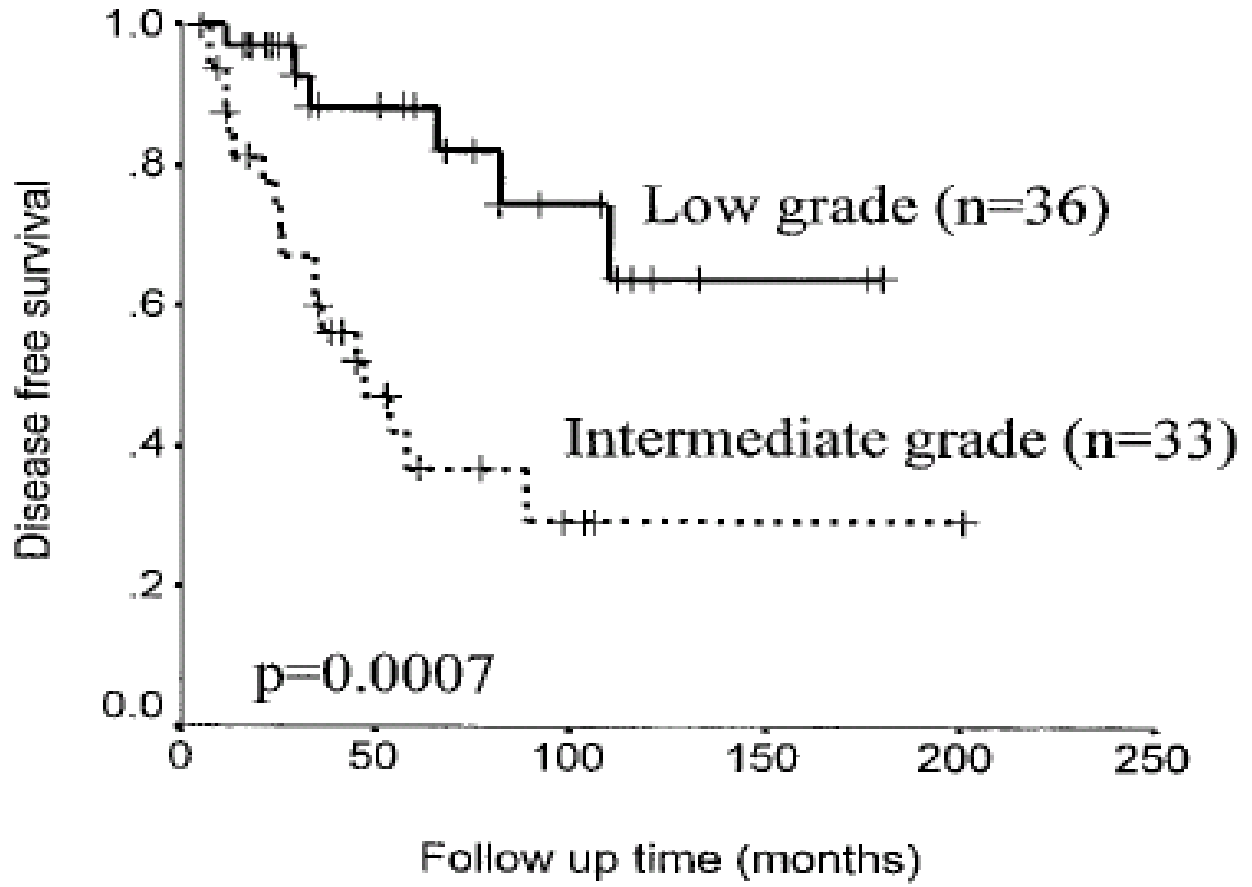


Fig 3. DFS in patients grouped according to new classification system (low grade: no necrosis and < 2 mitoses per 50 HPFs; intermediate grade: necrosis or ≥ 2 mitosis per 50 HPFs). Survival curves were based on cases for which recurrence and pathologic information was available.

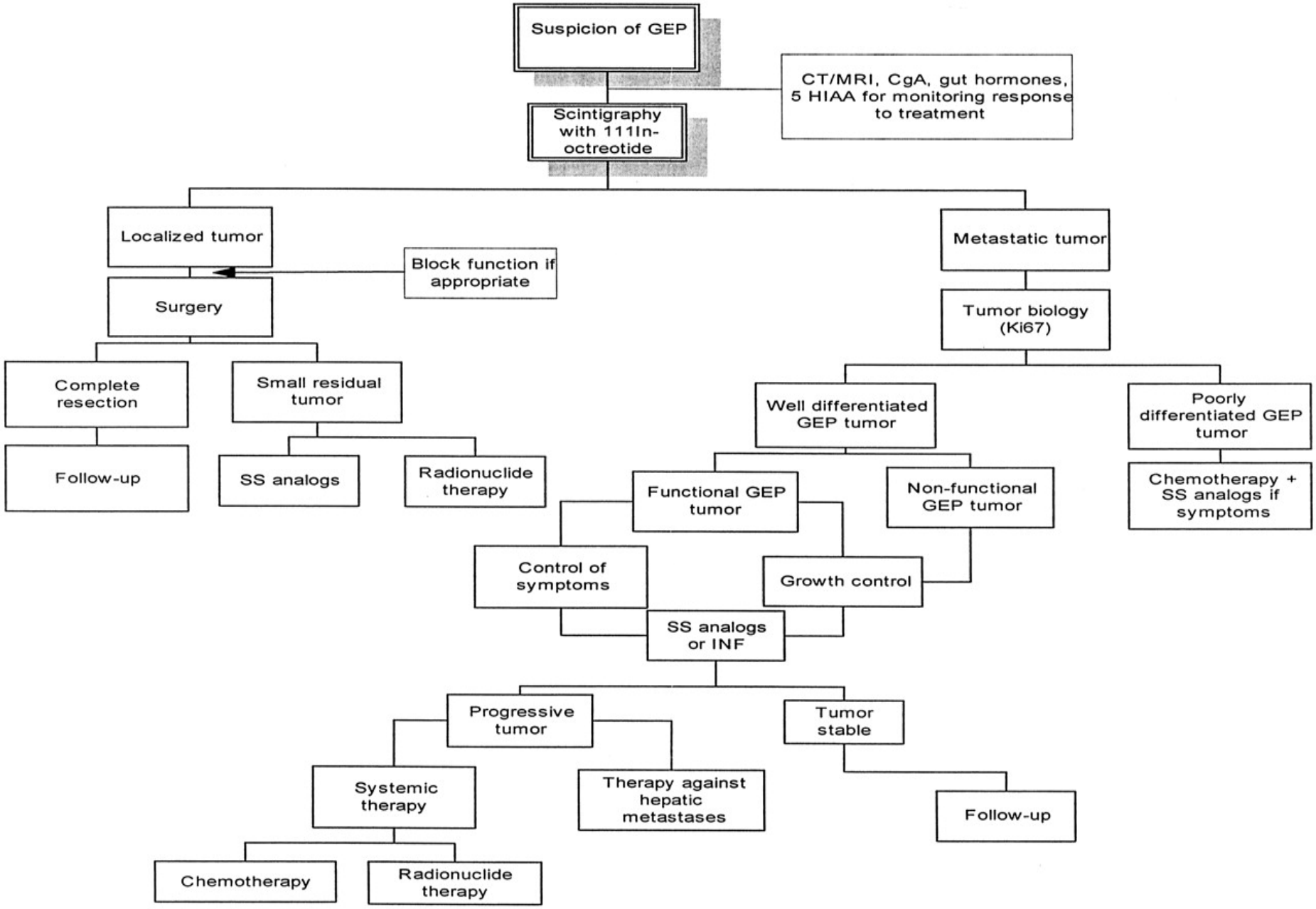
Hochwald et al, 2002

Multivariate analysis of prognostic factors in 180 sporadic non functioning neuroendocrine pancreatic tumors
Clinica Chirurgica, Università di Verona, 2006

	p
• Pain	0.167
• Weight loss	0.001
• Size	0.085
• Ki67	0.00001
• Stage	
• N0M0	
• N1MO	
• NanyM1	0.0001
• Histologic pattern	
- well-differentiated	
- poor-differentiated	0.0001

What are the major prognostic factors shared by the different types of neuroendocrine tumors ?

- Ki 67 or mitotic index
- Size and/or distant metastases
- Histologic findings (degree of differentiation, necrosis)



In the flow-pan of Kaltsas et al (2004) for the assessment of therapeutic strategy determination of Ki 67 plays a pivotal role

Virchows Arch (2006) 449:395–401
DOI 10.1007/s00428-006-0250-1

ORIGINAL ARTICLE

TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system

G. Rindi · G. Klöppel · H. Alhman · M. Caplin · A. Couvelard · W. W. de Herder · B. Erikssson · A. Falchetti · M. Falconi · P. Komminoth · M. Körner · J. M. Lopes · A-M. McNicol · O. Nilsson · A. Perren · A. Scarpa · J-Y. Scoazec · B. Wiedenmann · and all other Frascati Consensus Conference participants

Received: 11 April 2006 / Accepted: 6 June 2006 / Published online: 12 September 2006

Update in Clinical Endocrinology

NET: Treatment of Persistent Disease

Surgical therapy

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Verona, October 28, 2006

A series of question marks

- ✓ Does it exist?
- ✓ To which extent?
    1. Simple palliation
    2. Debulking resection
- ✓ Does it change according to the site of disease?
- ✓ Does it change according to other parameters?

A series of question marks

- ✓ Does it exist?

The surgeon and NETs

The surgeon and advanced NETs

A change of perspectives

- ✓ To reduce symptoms:

1. hormonal hypersecretion
2. obstructive

- ✓ To increase and/or make possible other therapies
- ✓ To prolong survival

To which extent? Simple palliation?

- ✓ To reduce symptoms:

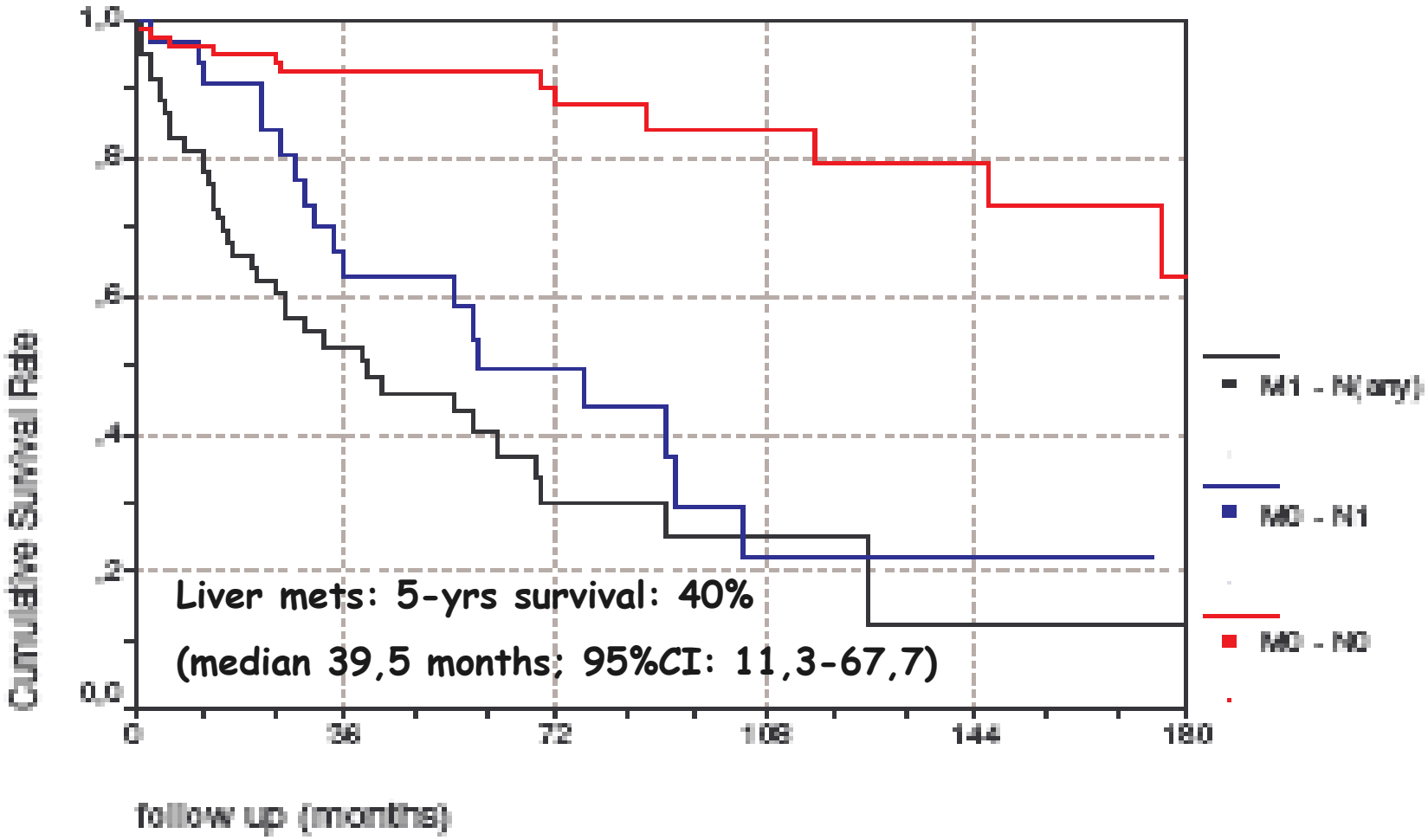
1. hormonal hypersecretion

   Nowadays medical therapy is better!

2. Obstructive

   Surgical by passes on G.I. and biliary tree still represent the best option due to the usually long life expectancy of NET patients

A truth even for advanced!



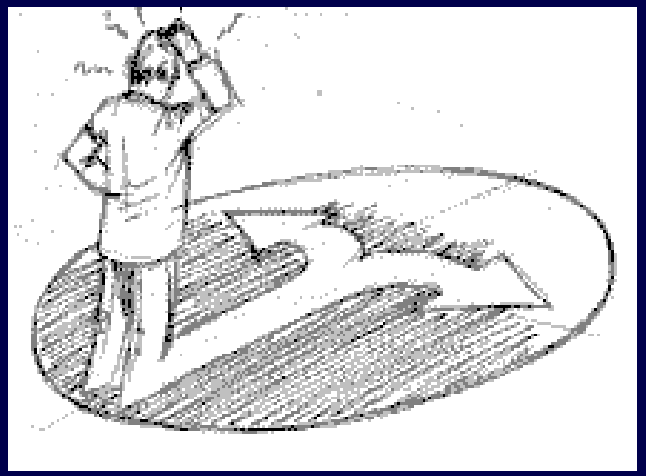
A surgical dream: to be a plummer!

To which extent? Debulking?

Primum non nocere!

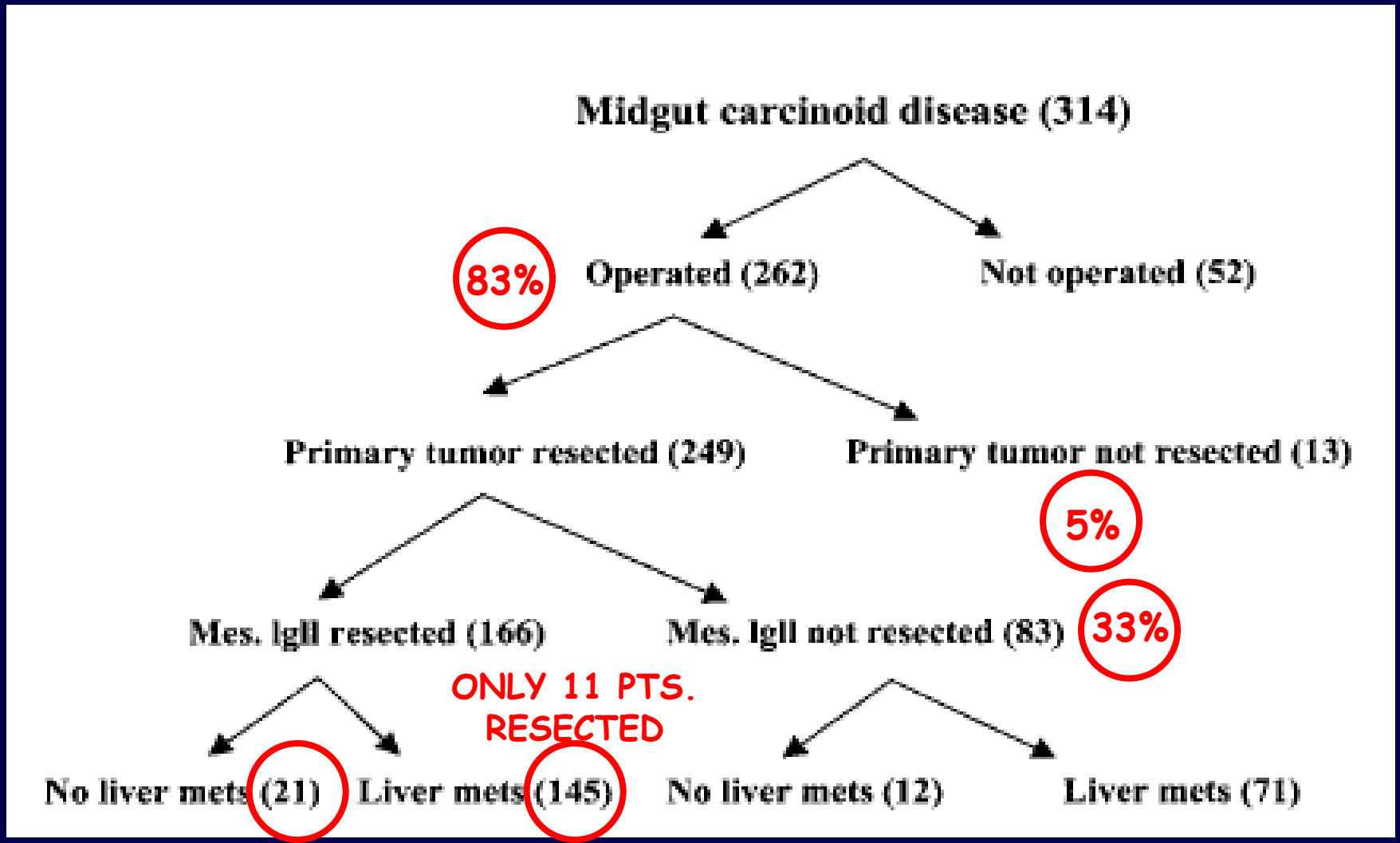
A scholastic division

Carcinoids of "midgut"



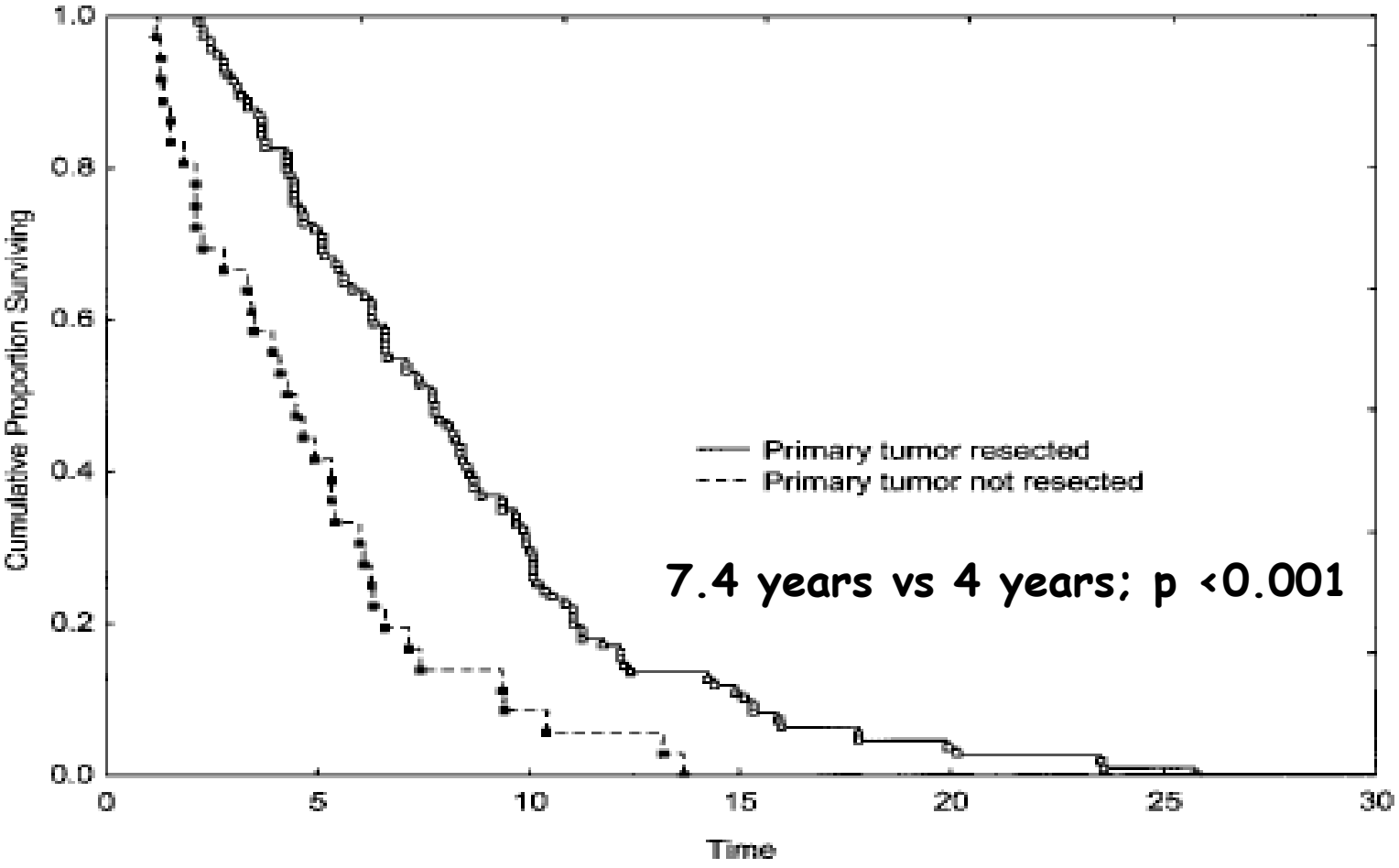
Pancreatic carcinomas

"Midgut real life"



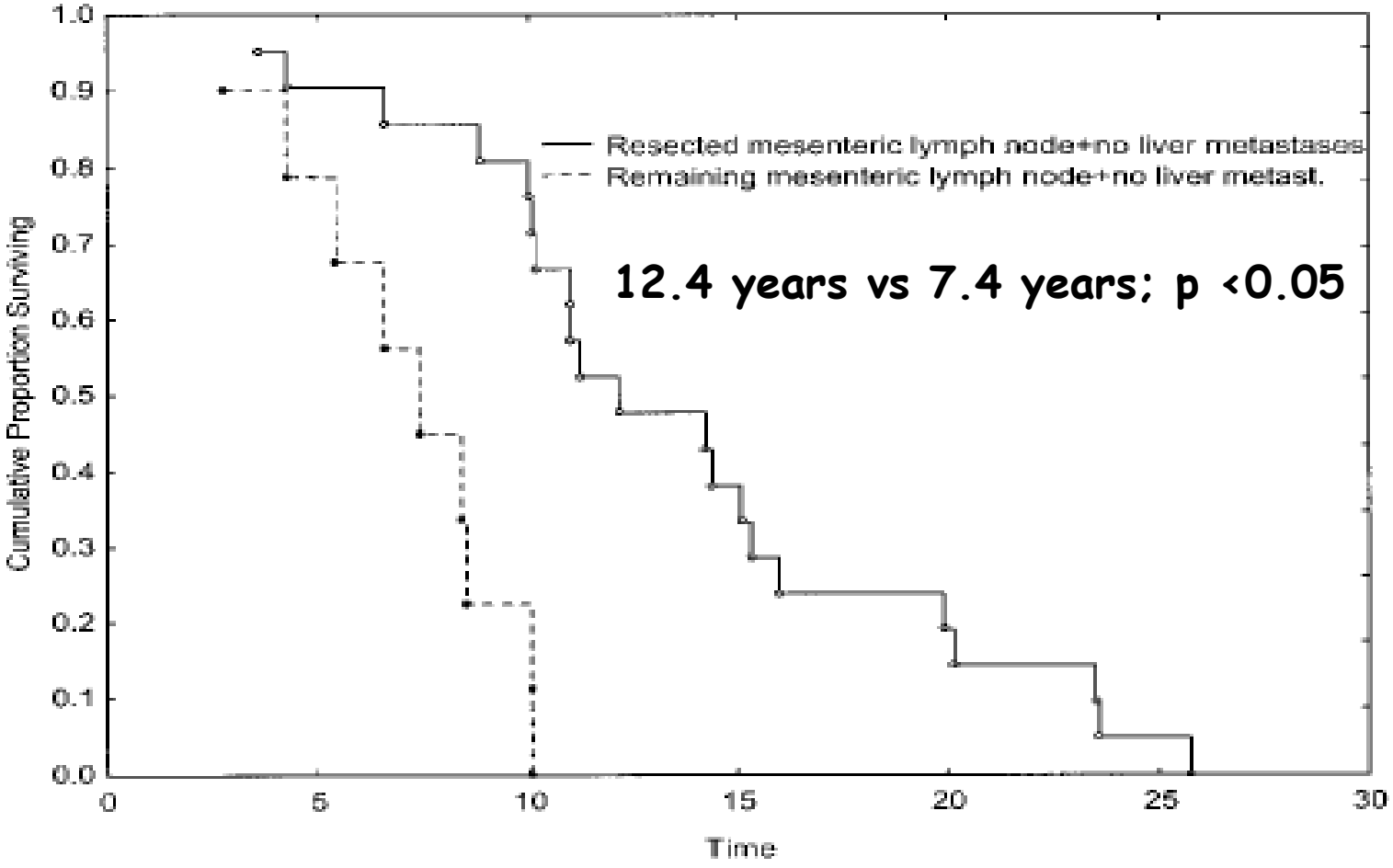
Helman, et al World J Surg 2002

Survival (I)
To resect the primary?



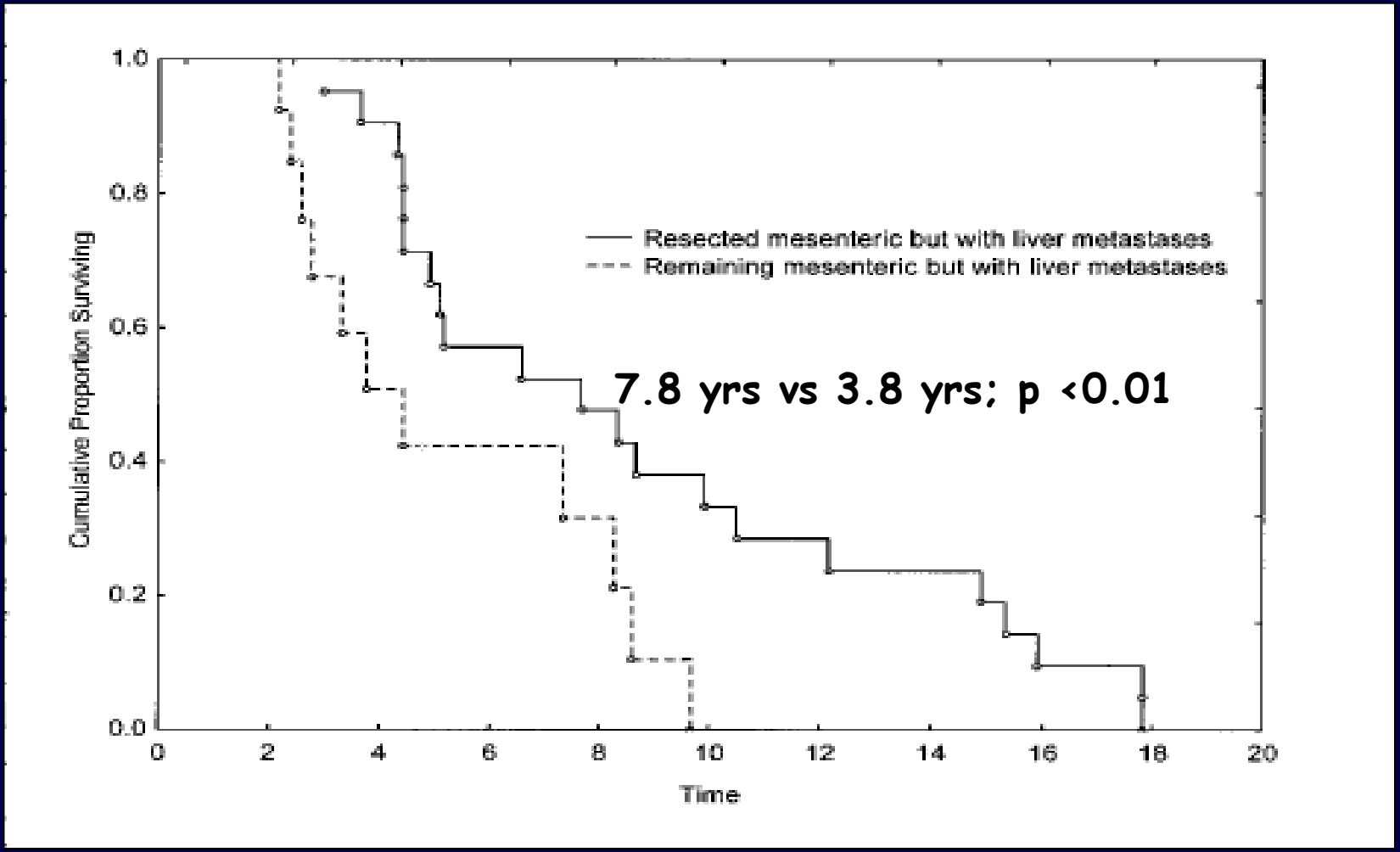
Helman, et al World J Surg 2002

Survival (II)
To resect also the nodes?



Helman, et al World J Surg 2002

Survival (III)
To resect the nodes in any case?



Helman, et al World J Surg 2002

Symptoms relief

- ✓ ↓ diarrhea episodes
- ✓ ↓ watery stools
- ✓ ↓ pain episodes
- ✓ = flush attacks

Whenever we do a good job on "the primary".....AFTER 1 yr: OLT

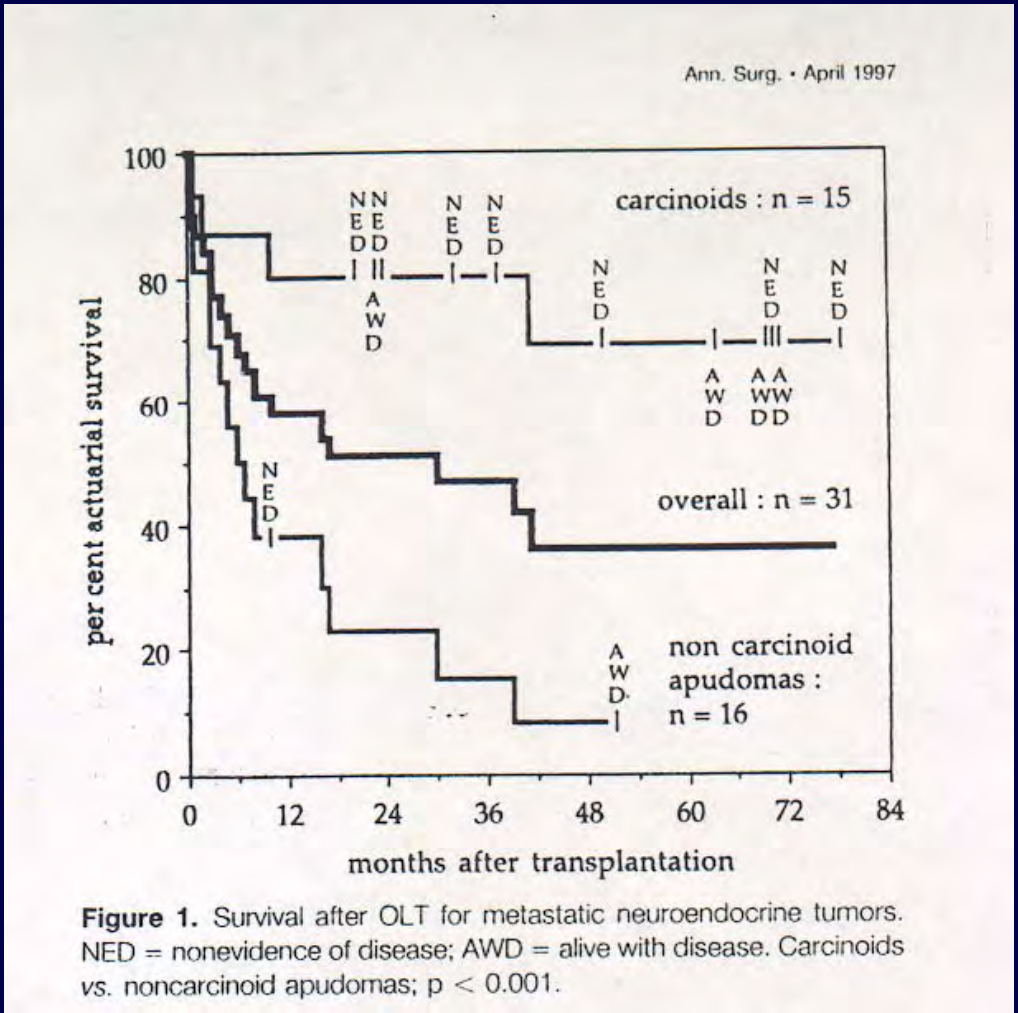


Figure 1. Survival after OLT for metastatic neuroendocrine tumors. NED = nonevidence of disease; AWD = alive with disease. Carcinoids *vs.* noncarcinoid apudomas; $p < 0.001$.

Palliative surgery on advanced carcinoids of midgut

- ✓ **We prolong** the survival
- ✓ **We reduce** symptoms:

1. Mechanical

- ✓ **We do not reduce** symptoms:

1. Hormonal hypersecretion

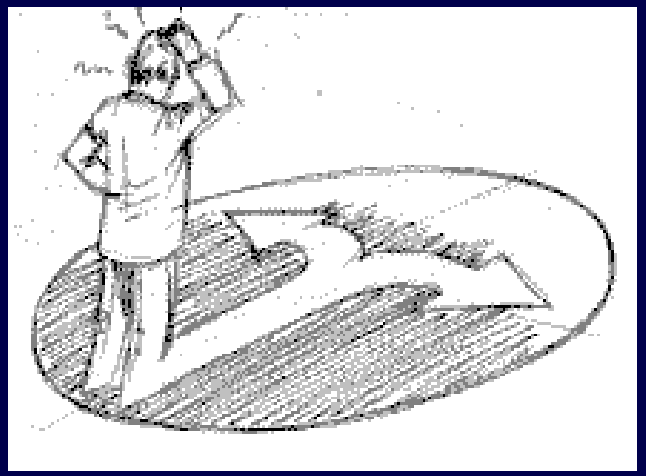
- ✓ **We make** possible other therapies

A series of question marks

✓ Does it change according to the site of disease?

A scholastic division

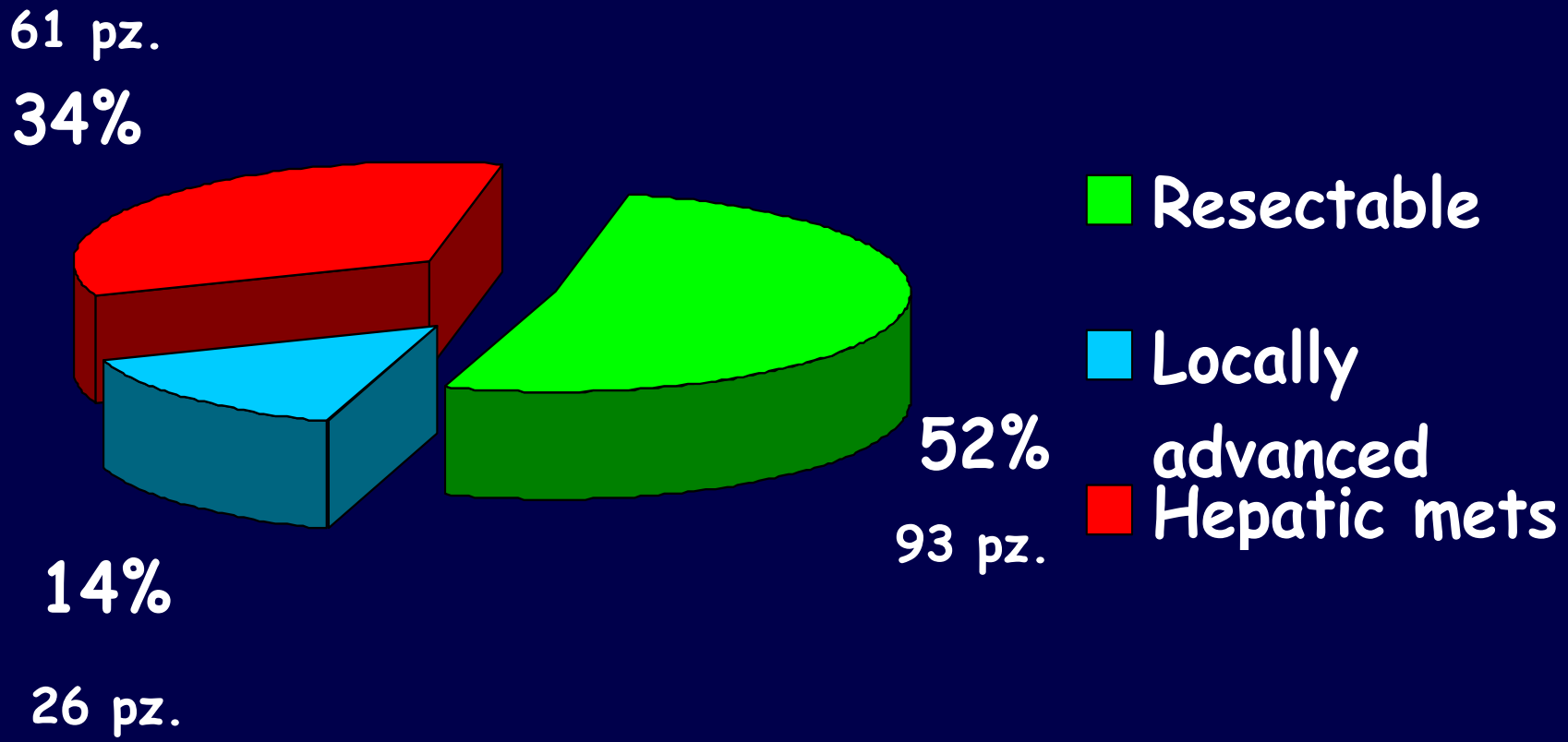
Carcinoids of "midgut"



Pancreatic carcinomas

Nonfunctioning pancreatic endocrine tumor

1985-2004 n= 180 pts.



Published data on survival according to surgical treatment

		Resected primary But no metastases			Radically resected primary and debulking on mets			Radically resected primary and all metastases		
Author	Type	n	5-yr (%)	Median (yr)	n	5-yr (%)	Median (yr)	n	5-yr (%)	Median (yr)
Evans 1993	ICT (NF)	12	41	4.5			*p ns*			
Chamberlain 2000	ICT (NF+F) + GI				19	63	5.5	15	85	nv
Solorzano 2001	ICT (NF)	16	49	3.0°				4	nv*	nv*
Touzios. 2005	ICT (NF+F) + GI	23	25	1.6	19 18	72 50	>8 4.1			
House 2006	ICT (NF+F)	5	20	1.4°		*p 0.06*		31	65	6.5°

Aim

To evaluate if complete resection of primary tumor gives any advantage in term of survival in patients suffering from NF-PECs with liver metastases.

Patients and methods

From 1990 to 2004 all patients suffering from unresectable hepatic metastases were divided in 2 group:

Group 1

Patients with resectable primary tumor

↓

Primary tumor resection

Group 2

Patients with unresectable primary tumor

↓

No surgery or palliative derivative if necessary

Results: population

	Total (n: 51)	Group 1 (n: 19)	Group 2 (n: 32)	p value
Age (y) median (IQR)	55 (47 - 66)	51 (41 – 65)	57 (50.3 - 66)	ns
Gender (M/F)	24/27	10/9	14/18	ns
Site of the primary				
Head (%)	19 (37.3)	5 (26.3)	14 (43.8)	ns
Body-Tail (%)	32 (62.7)	14 (73.7)	18 (56.3)	
Tumour size (mm) median (IQR)	45 (30 - 75)	35 (20 - 60)	54.5 (31.3 - 80)	ns (0.06)
Tumour differentiation				
CWD (%)	46(90.2)	16 (84.2)	30 (93.8)	ns
PDC (%)	5 (9.8)	3 (15.8)	2 (6.3)	
Liver involvement (%)				
<25 (%)	9 (17.6)	5 (26.3)	4 (12.5)	ns
25-50 (%)	34 (66.7)	13 (68.4)	21 (65.6)	
>50 (%)	8 (15.7)	1 (5.3)	7 (21.9)	

Results: procedures

Group 1 (n = 19)

14 Distal pancreatectomy
5 Pancreticoduodenectomy

Mortality	0%
Morbidity	47.1%

Group 2 (n = 32)

15 No surgery
9 Biliary and/or digestive derivative
8 Explorative laparotomy

Mortality	0%
Morbidity	0%

Antitumoral treatments

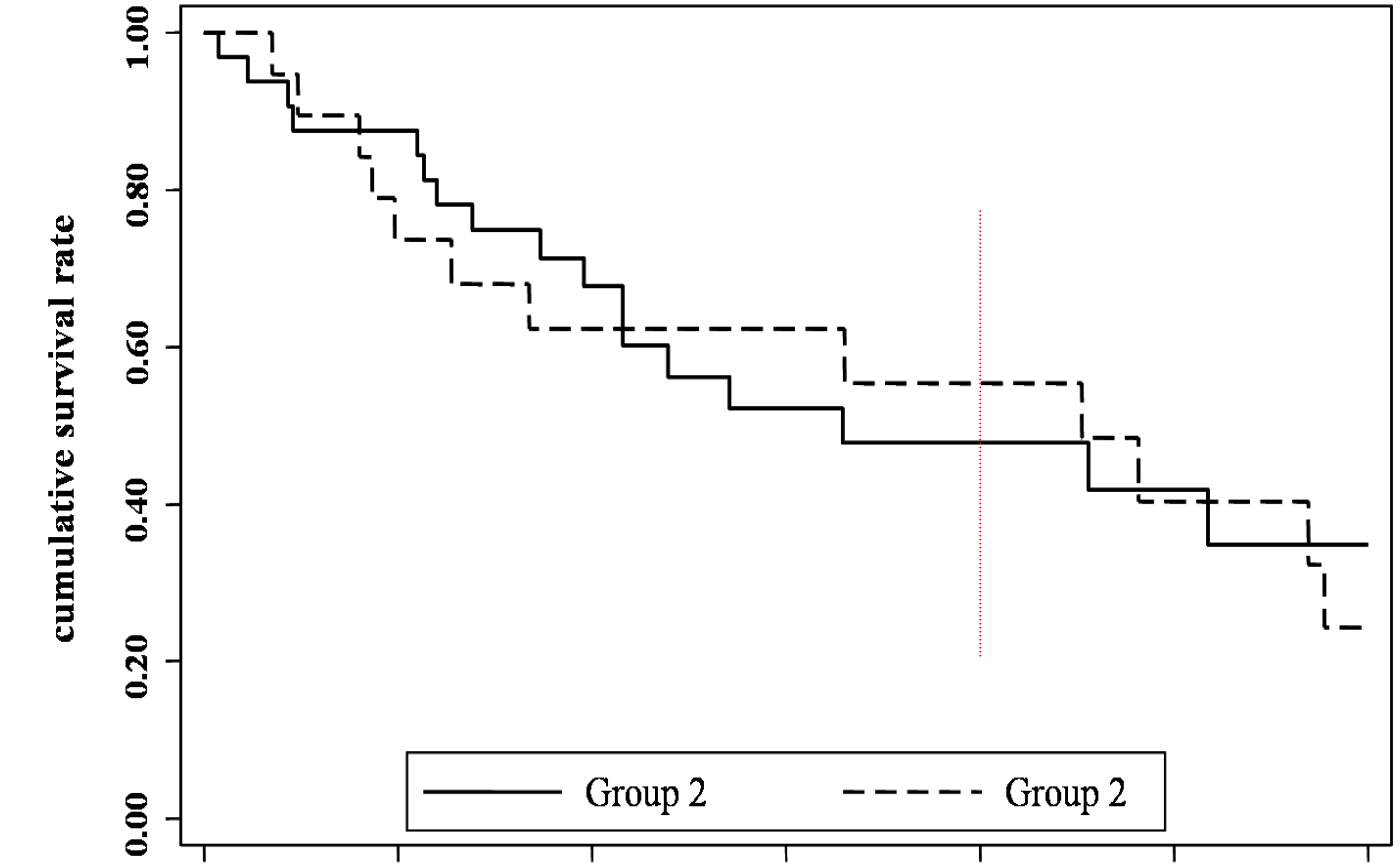
	Total (n: 51)	Group 1 (n: 19)	Group 2 (n: 32)	p value
First line (%)	**48 (94.1)**	**18 (94.7)**	**30 (93.8)**	
Somatostin analogues		6 (33.3)	25 (83.3)	
Somatostatin anologues+TACE		11 (61.1)	0 (0.0)	0.0001
Chemotherapy		2 (11.1)	5 (16.7)	
Second line (%)	**27 (52.9)**	**10 (52.6)**	**17 (53.1)**	
Chemotherapy		5 (50.0)	9 (52.9)	
Radiometabolic therapy		2 (20.0)	7 (41.2)	ns
TACE		3 (30.0)	1 (5.9)	
Third line (%)	**5 (9.8)**	**4 (21.1)**	**1 (3.1)**	
Chemotherapy		3 (75.0)	1 (100.0)	
Radiometabolic theraphy		1 (25.0)	0 (0.0)	ns

Follow up

	Group 1 (n=19)* n (%)	Group 2 (n=32) n (%)
Median survival (months)	54.3 (95% CI : 25-83.6)	39.5 (95%CI 5.4-73.6)
p 0.741		
Dead	13 (68.4%)	18 (56.2%)
p 0.389		

*No local recurrence

Survival curve



N° patients at risk

Group 1	19	14	10	9	8	5	3
Group 2	32	28	19	12	8	7	4
	0	**12**	**24**	**36**	**48**	**60**	**72**

time of survival (months)

Published data on survival according to surgical treatment

		Resected primary But no metastases				No resection both of primary and mets		
Author	Type	n	5-yr (%)	Median (yr)		n	5-yr (%)	Median (yr)
Evans 1993	ICT (NF)	12	41	4.5	*P n.s*	22	38	3.3
Solarzano 2001	ICT (NF)	16	49	3.0	*P 0.06*	80	16	1.8
Present series 2006	ICT (NF)	19	40.4	4.5	*P 0.07*	32	41.9	3.3

A series of question marks

✓ Does it change according to other parameters?

Significant predictors of survival

Variables in the equation		Hazard Ratio (95% CI)	p value
Tumour differentiation	CWD (%)	1	---
	PDC (%)	3.01 (1.08 - 8.4)	0.035
Ki67% at diagnosis	< 10%	1	---
	≥ 10%	4.4 (1.2 - 16.1)	0.023

Significant predictors of survival estimated with Cox's proportional hazards model in 51 patients suffering from non-functioning metastatic pancreatic endocrine carcinoma.

Flow-chart for advanced NET tumors

DIAGNOSIS OF ADVANCED NET TUMOR

DEGREE OF DIFFERENTIATION ?

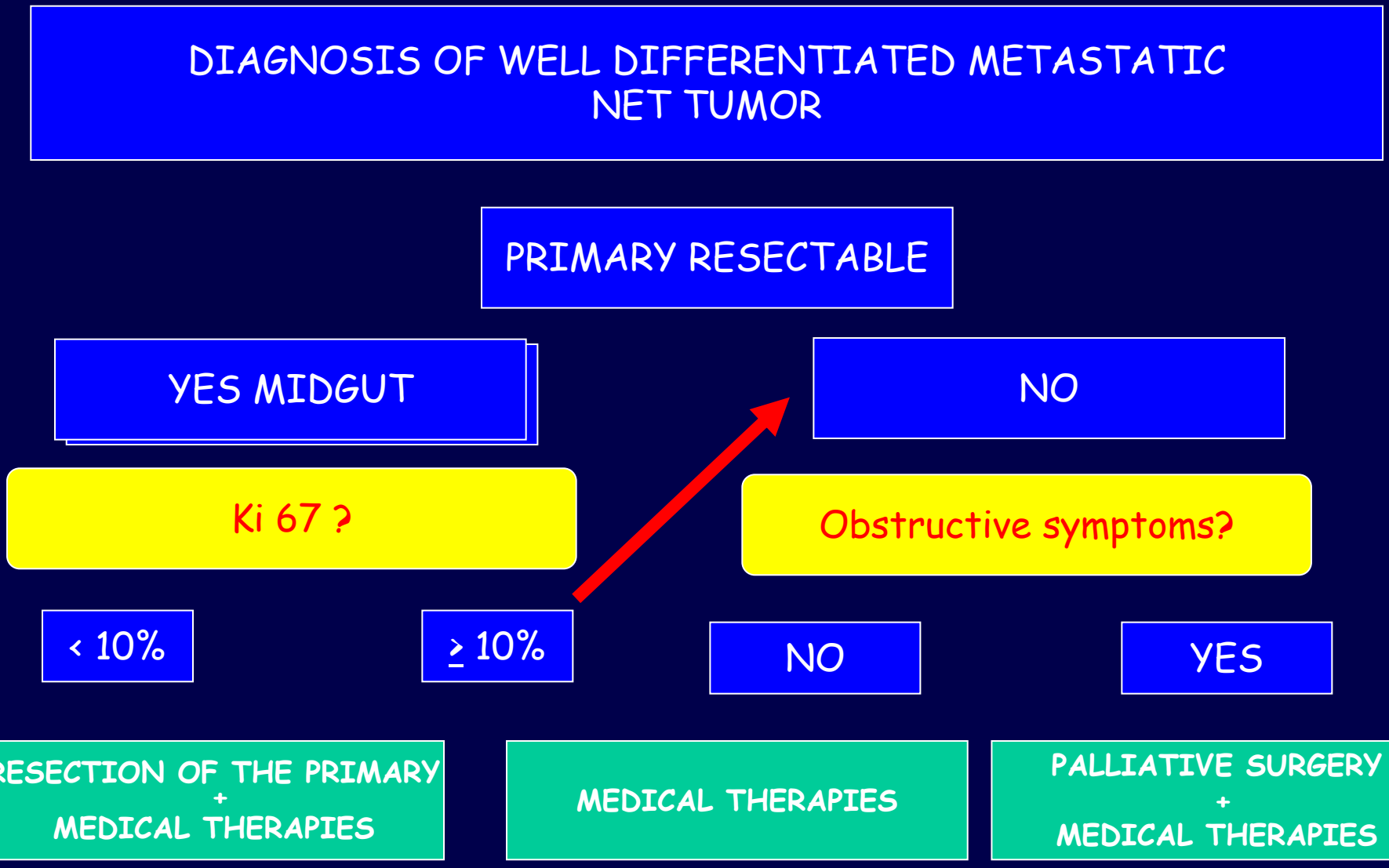
POOR DIFFERENTIATED

WELL DIFFERENTIATED

CHEMOTHERAPY (Cisplatin + etoposide)

PRIMARY RESECTABLE?

Flow-chart for advanced NET tumors



Thank you, very much, indeed!

Medical treatment of functioning tumors

Annnamaria Colao

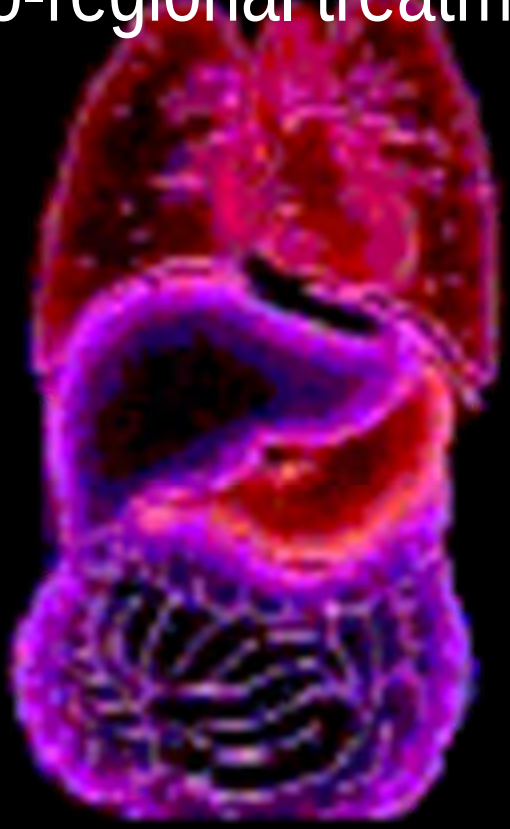
Department of Molecular and Clinical Endocrinology & Oncology,
”Federico II” University, Napoli

Treatment modalities in Neuroendocrine Tumors

Loco-regional treatments

Surgery

Somatostatin analogues

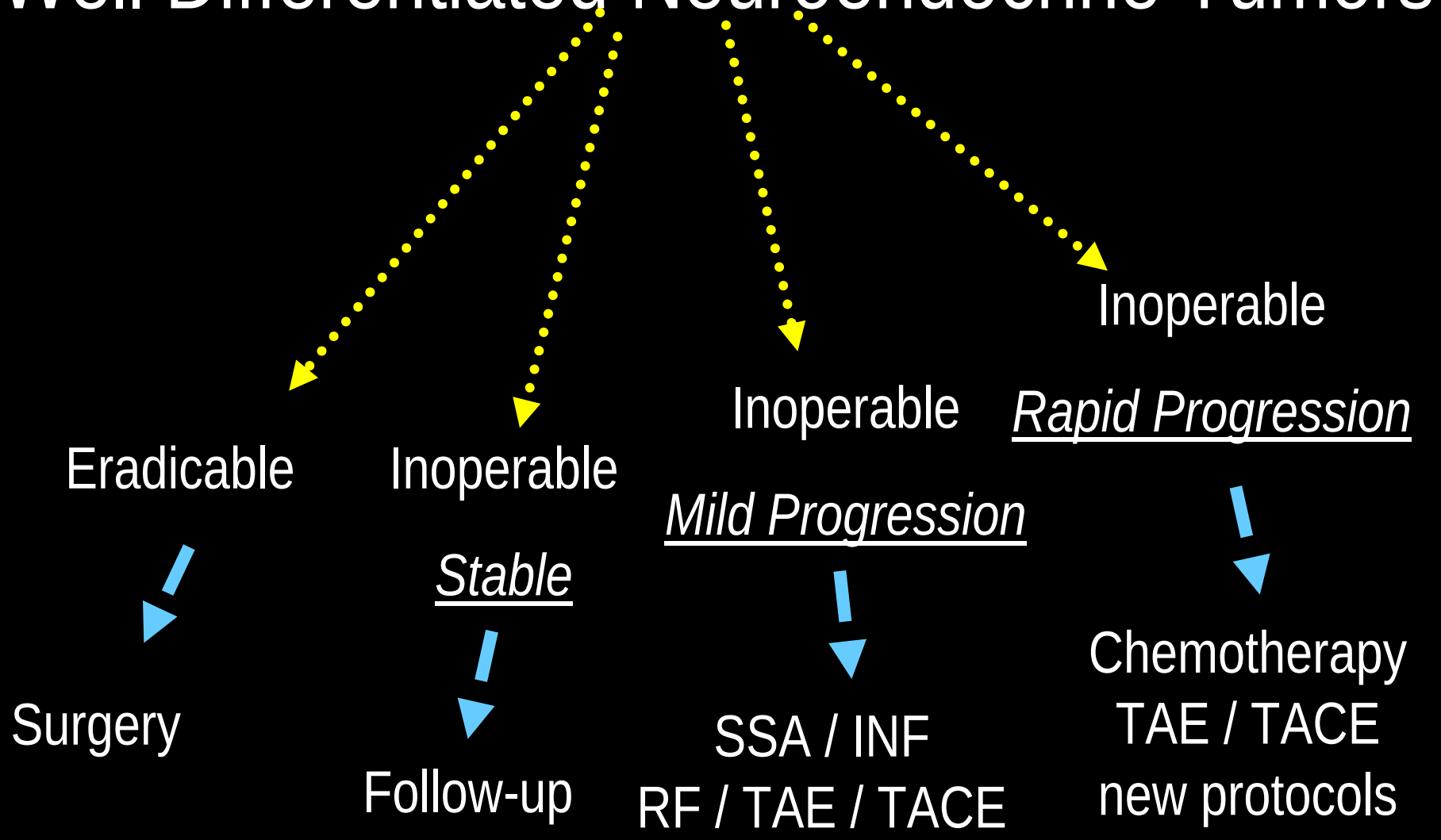


Chemotherapy

Interferon

Tumor-targeted radioactive treatments

Well Differentiated Neuroendocrine Tumors



Tumor-targeted radioactive treatments

Octreotide *sc vs.* Octreotide-LAR

Symptomatic response

OCT 0.3-0.9 mg	58.3%
OCT LAR 10 mg	66.7%
20 mg	71.4%
30 mg	61.9%

Rubin J, et al. J Clin Oncol 1999

Lanreotide Autogel

Symptomatic response

71 NET pts with carcinoid syndrome

LAN ATG:60-120 mg/m
duration: 24 weeks

	Baseline	Post-TTT
Diarrhoea	5.0	3.9
Flushing	3.0	1.7

Rubszniewski P, et al. Neuroendocrinology 2004

Potential mechanisms of tachyphylaxis and resistance to SSA therapy in patients with SST-positive Neuroendocrine Tumors

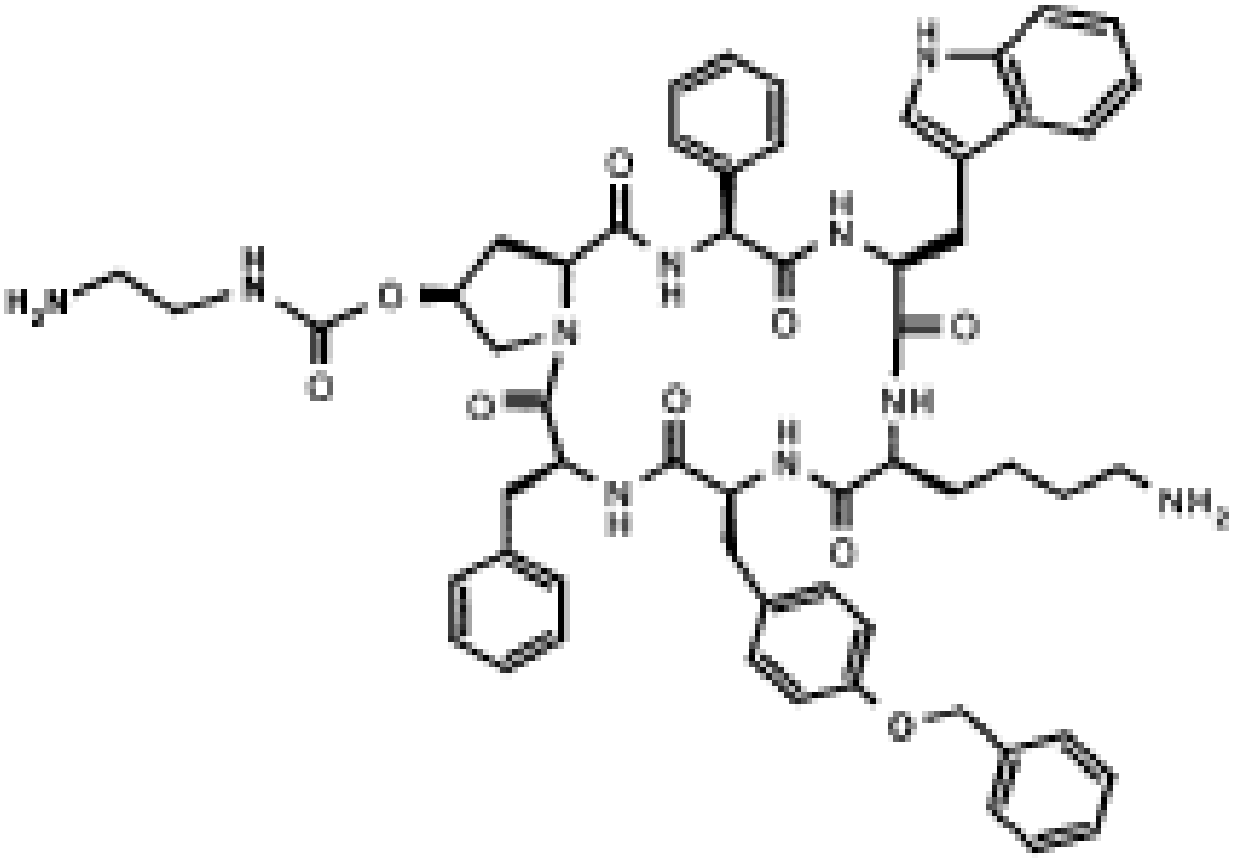
- Down-regulation of SS receptors
- Desensitization: receptor uncoupling from second messenger activation
- Nonhomogeneous expression of SST subtypes in tumors
- Absence of SST subtypes with high affinity for octapeptide SSAs
- Tachyphylaxis of the inhibitory effects of SSAs on indirect tumor growth-promoting mechanisms (i.e., GH or gastrin secretion)
- Mutations in sst genes leading to absence of functional receptor proteins

Hofland L et al, End Rev 2003

Schmid HA, Schoeffter P:

Functional Activity of the Multiligand Analog SOM230 at Human Recombinant Somatostatin Receptor Subtypes Supports Its Usefulness in Neuroendocrine Tumors.

Neuroendocrinology 2004;80(Suppl.1):47-50



IC50 nM

sst1	9.3±0.1
sst2	1.0±0.1
sst3	1.5±0.3
sst4	> 100
sst5	0.2±0.1

SOM230 (450-1200 mg bid) - 1st experience in NET (Phase II open-label multicenter study)

Early data on the efficacy and safety of the novel multi-ligand somatostatin analog, SOM230, in patients with metastatic carcinoid tumors refractory or resistant to octreotide LAR

Safety / Tolerability (evaluated in 35 pts)

➢ Gastro-intestinal disturbances	5-28%
➢ Weight loss	34%
➢ Fatigue	14%

Efficacy (evaluated in 28 pts)

➢ Partial Response	33%
➢ Complete Response	0

Kvols, ASCO 2005

Treatment with SSA high doses in Neuroendocrine Tumors

	n	Tumor	Agent	SR (%)	HR(%)	TR (%)
Saltz, 1993	34	20 CT, 13 IST	Octreotide		71	33	PR 0%, SD 50% (5 mesi)
Antony 1993	13		Octreotide 6 mg/d		-	-	PR 31%, SD 15%
Scherubl, 1994	12	-	Lanreotide 30 mg/14 d		40-90	-	SD 58%
Arnold, 1996	103	64 CT, 39 IST	Octreotide 200-500 μg 3x/d		85	33	PR 0%, SD 36.5% (18 mesi)
Di Bartolomeo 1996	43	31 CT, 12 IST	Octreotide 1500-3000 μg/d		73	77	PR 7%, SD 27 %
Ruszniewski, 1996	39	CT	Lanreotide 30 mg/14 d		55	42	PR 0%
Eriksson, 1997	19	13 CT, 6 IST	Lanreotide 12 mg/d		-	58	PR 5%, SD 70 %
Tommasetti, 1998	18	10 CT, 8 IST	Lanreotide 30 mg/10 d		90	33	SD 78 %
Faiss, 1999	30	20 CT, 10 UKW	Lanreotide 15 mg/d		70	43-52	CR 3.4 %, PR 3.4 %, SD 37%
Wymenga, 1999	55(PD)	48 CT, 7 IST	Lanreotide 30 mg/ 14 d		45	47	PR 6%, SD 81%
Ricci, 2000	25(PD)	12 CT, 13 IST	Lanreotide 30 mg/ 14 d		70	42	PR 8%, SD 40% (8.5 mesi)
O'Toole, 2000	33	CT	OCT 600 μg/d, LAN 30 mg/10 d		61	54	-
Ducreux, 2000	39 (PD)	CT	Lanreotide 30 mg/10-14 d		64	50	PR 5%, SD 49%
Aparicio, 2001	35 (PD)	22 CT, 12 IST	OCT 300 μg/d, LAN 30 mg/14 d		-	-	PR 3%, SD 57%

SR: Symptomatic Response
HR: Hormonal Response
TR: Tumor Response

Kaltsas et al., Endocr Rev, 2004

Octreotide Pamoate

160 mg i.m. / 14 days x 2 months and then 160 mg /28 days

12 pts with progressive metastatic ileal NET

Biochemical Response (CgA - 5HIAA)

- OR 4/12 - 2/12
- SD 7/12 - 9/12
- PD 1/12 - 1/12

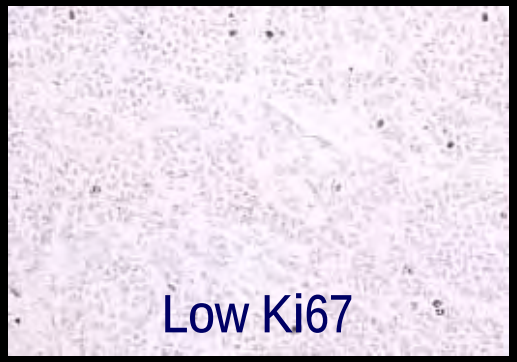
Tumour Response

- OR 0
- SD 9/12 (75%)
- PD 3/12 (25%)

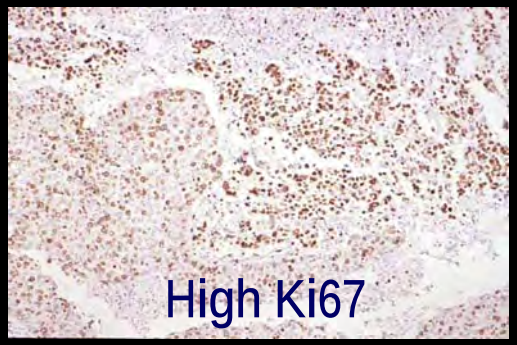
Welin SV et al. EJE, 2004

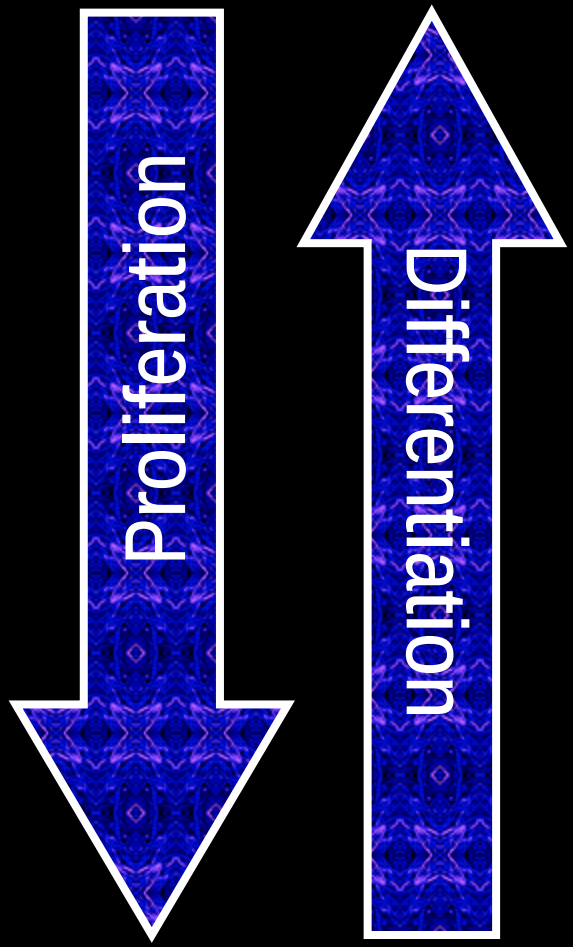
Well Differentiated Neuroendocrine Tumor
(benign or potentially malignant)

Well Differentiated Neuroendocrine Carcinoma



Poorly Differentiated Neuroendocrine Carcinoma





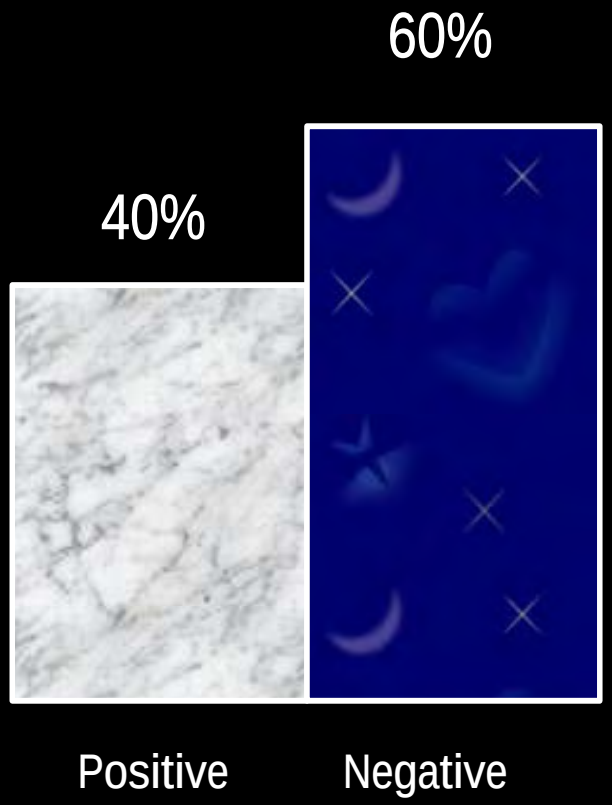
WHO Classification of Endocrine Tumors, 2000

Chemotherapy in Poorly Differentiated NET

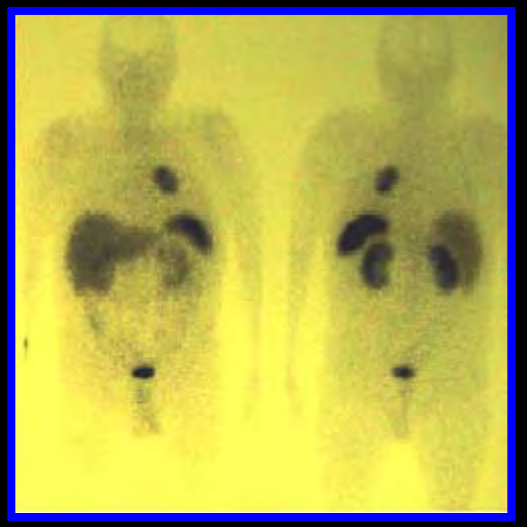
etoposide-cisplatin

Survival	n	OR %	Duration months	Mean Survival months	3 ys %
Moertel, '91	18	67%	8 (3-21)	19	35%
Hainsworth, '93	23	78%	-	-	-
Mitry, '99	41	41%	8 (2-24)	-	<20%

Octreoscan performance in 41 pts with large cell poorly differentiated neuroendocrine carcinomas



Octreoscan



Faggiano et al. In submission Eur J

SSA + Chemotherapy in the treatment of poorly differentiated NET

Retrospective study: 18 patients with large cell PD NET

Poorly differentiated small cell neuroendocrine carcinoma localized in three different endocrine glands: response to chemotherapy and octreotide LAR

Preoperative Octreoscan: 10/10 pts positive

Radical Surgery + lymphadenectomy: 18/18

Adjuvant Therapy:

- Radiotherapy if TNM > Ib : 13/18 pts
- Octreotide LAR 20 mg/28 days in pts with positive preoperative OS: 10/18 pts

Tauchmanova et al. JEI 2005

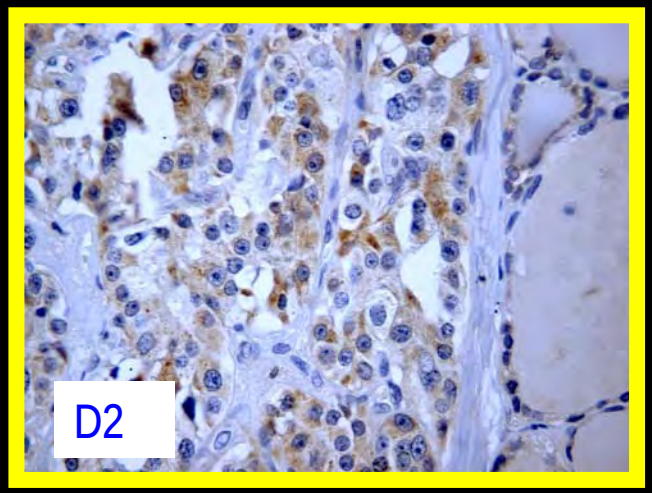
Tumor Relapse: 9/18 pts

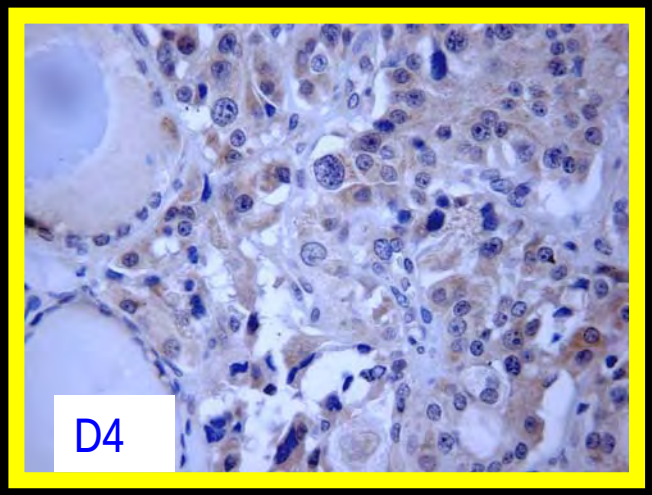
- with Octreotide : 1/10
- without Octreotide : 8/8

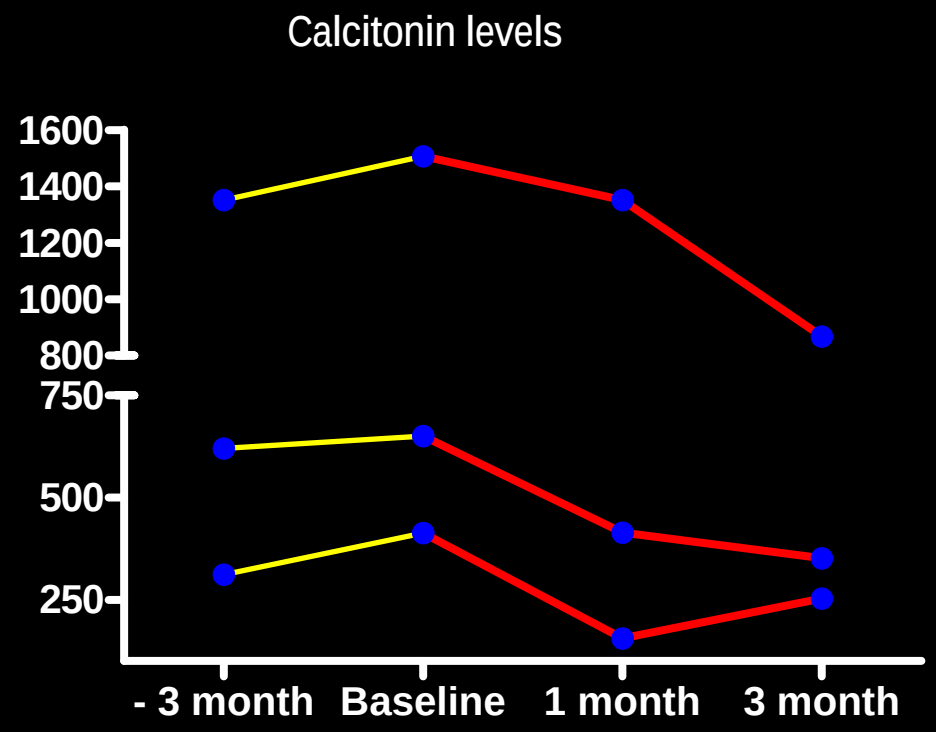
Filosso et al. General Thoracic Surgery 2005

Dopamine agonists

Perspectives







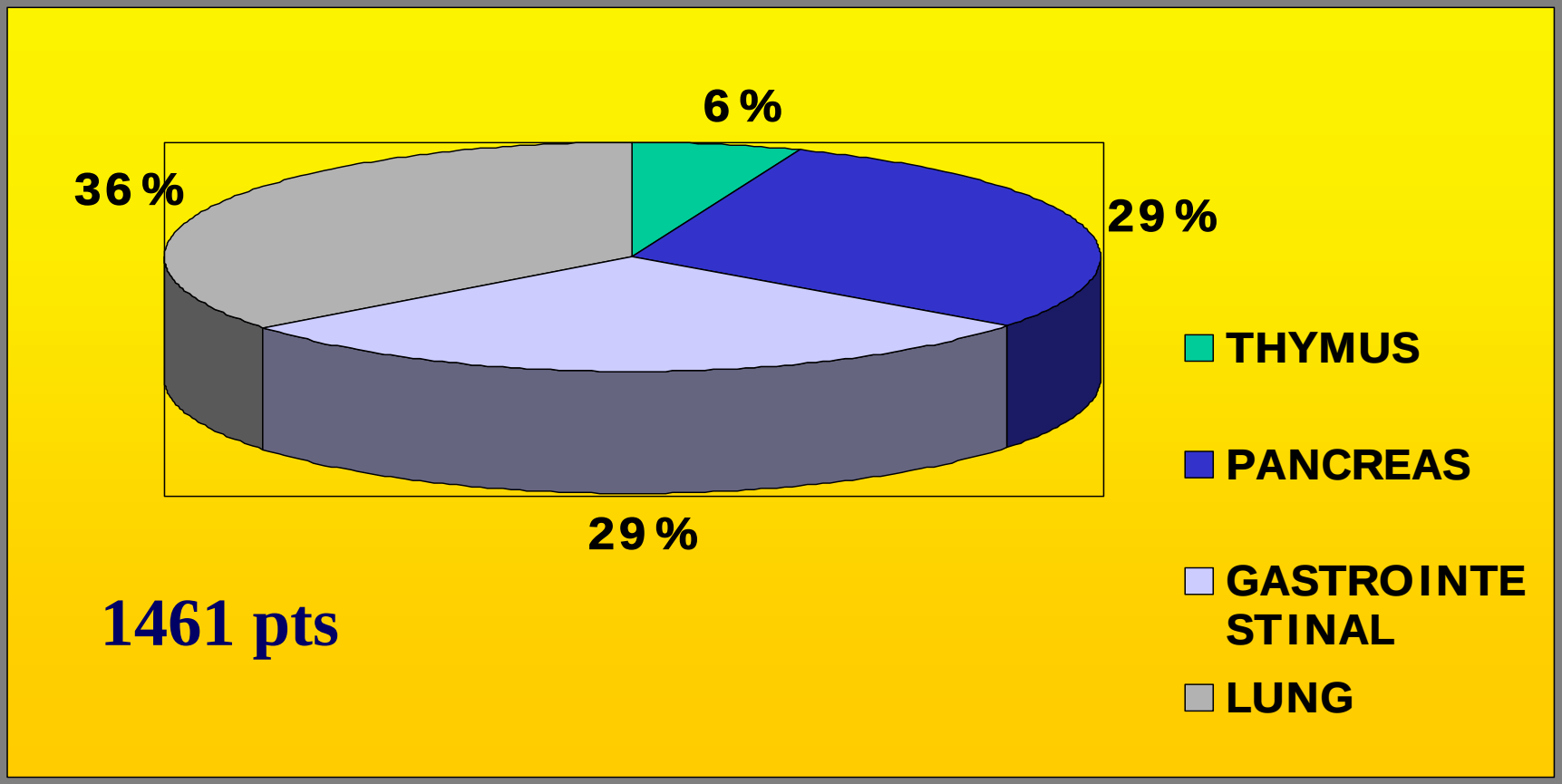
52 Centri riceived the specific software

16 contibuted to this preliminary data presentation

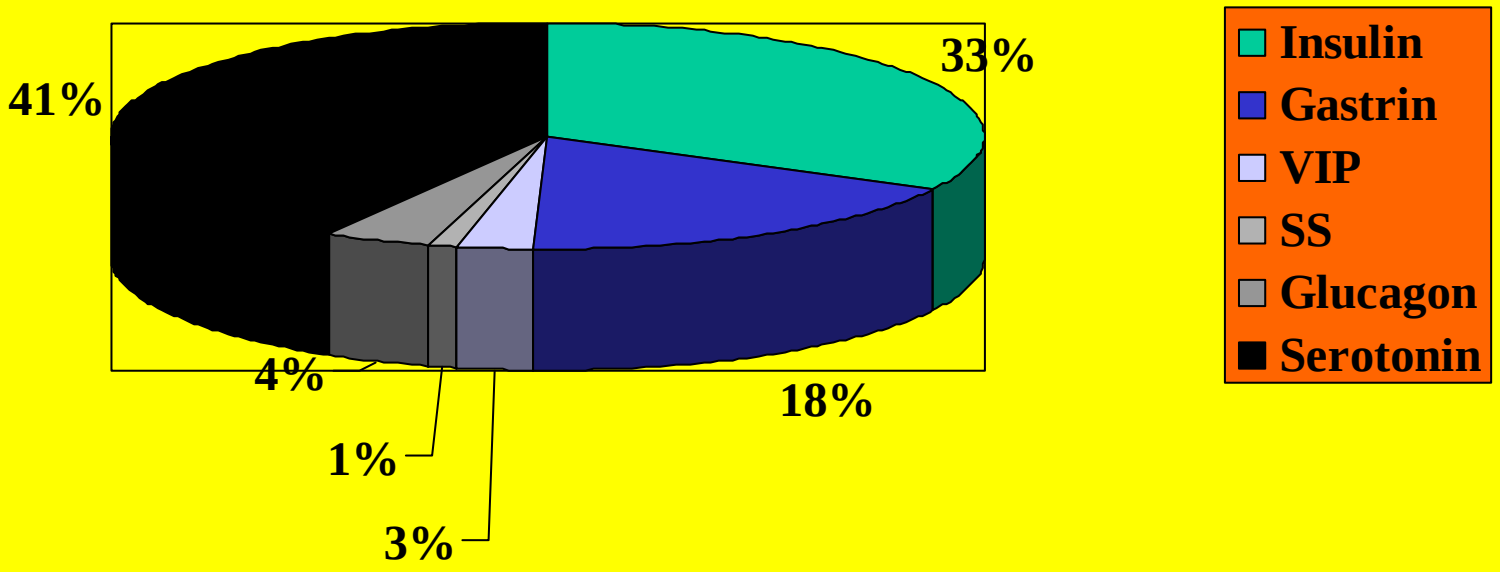
Patients & Methods:

- Data regarding of 1481 patients were collected.
- NET followed in 16 Italian referral centres from 1990 to 2006 were enrolled in the study.
- Data were collected utilising the *NET MANAGEMENT Software* (Ibis Informatica, Milan) developed specifically for the study

Distribution according to WHO classification



Associated Syndromes



•The data from this large series confirms that GEP-NET and T-NET are an heterogeneous group of tumors.

•CT and Octreoscan represents a indispensable tool for tumour staging and diagnosis.

• This procedure together with FDG-PET adds helpful information to establish prognosis and therapy and is usseful in follow-up.

•Endoschopic tecniques (and echo-endoschopy in selected cases) play a crucial role.

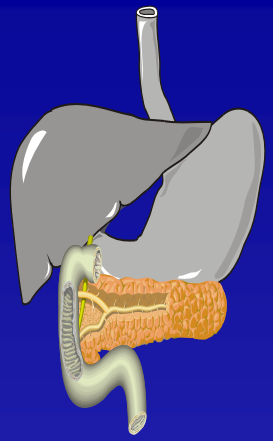
•*The prospective study, in course, will be essential to evaluate impact of diagnostic and therapeutic procedures.*

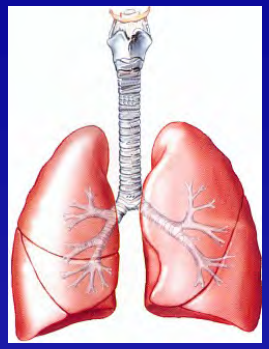
Net Management

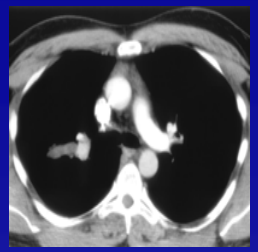
n.	CENTRO	SPERIMENTATORE
1	Centro 007 - Udine	Grimaldi
2	Centro 023 - Reggio Emilia	Valcavi
3	Centro 047 - Treviso	Roiter/De Menis
4	Centro 066 - Genova	Ferone/Minuto
5	Centro 069 - Napoli	Colao/Faggiano
6	Centro 115 - Viagrande	Giuffrida
7	Centro 131 - Napoli	Biondi/Pulcrano
8	Centro 133 - Verona:	Davì/Francia
9	Centro 139 - Sassari:	Fanciulli
10	Centro 140 - Torino	Ghigo/Grottoli
11	Centro 143 - Milano:	Manzoni/Franchi
12	Centro 149 - Perugia	Ferolla/Santeusanio
13	Centro 151 - Ancona:	Boscaro/Arnaldi
14	Centro 173 - Bologna	Tomassetti/Campana
15	Centro 174 - Pol. A. Gemelli - Roma	De Marinis/Bianchi
16	Centro 178 - Albano Laziale	Papini/Nasoni

Conclusion

- Somatostatin analogues are potentially effective in the majority of patients with Neuroendocrine Tumor; new formulations, new SSA with variable spectrum of binding to SSTs and the evaluation of SST subtype expressed in the tumor tissue may increase the proportion of NET pts responding to SSA therapy
- In the next years, new compounds acting on different molecular mechanisms involved in NET pathogenesis will be available to increase the anti-proliferative effects of SSA, INF or chemotherapy







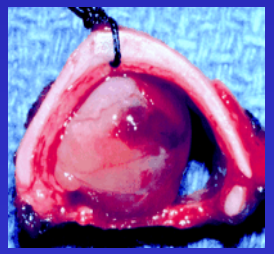
Stemma dell'Ospedale di S. Maria della Misericordia di Perugia

Azienda Ospedaliera di Perugia

Medical Treatment of

"NON FUNCTIONING"

WELL DIFFERENTIATED NET



Piero Ferolla

Dept. Internal Medicine and Endocrine Sciences

University of Perugia, Perugia, Italy

OBJECTIVES OF NET TREATMENT

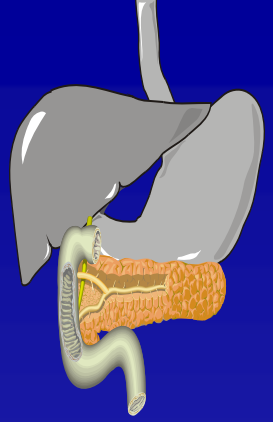
- HORMONE RELEASE INHIBITION
- IMPROVEMENT OF THE QUALITY OF LIFE
- TUMOR SIZE REDUCTION
- IMPROVED SURVIVAL

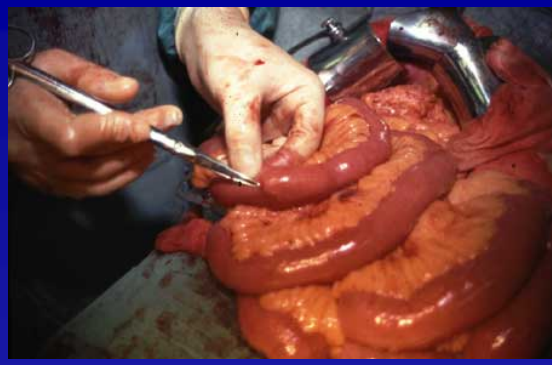
Surgery
Debulking Procedures
SST-Analogues
Interferon and others
Chemoembolization
Chemotherapy
Symptomatic Treatment
Octreother

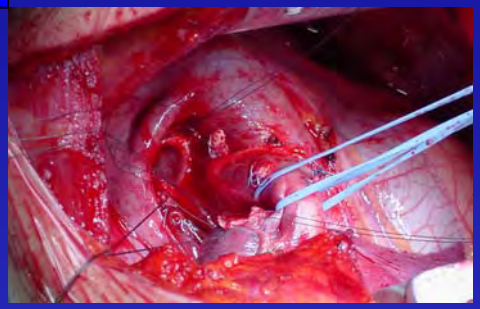
MULTIMODAL THERAPEUTIC APPROACH

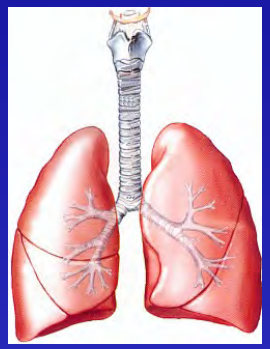
Well Differentiated NET

First: SURGERY !!









Curative Surgery

Palliative Surgery

Follow-up

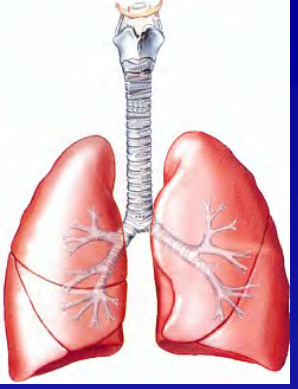
MEDICAL THERAPY

Nota C.U.F. 40

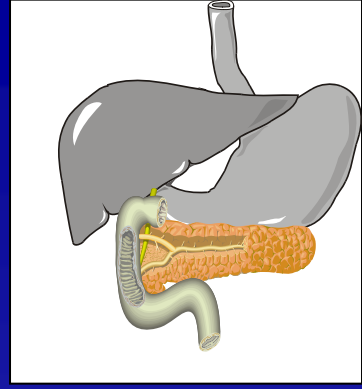
La prescrizione a carico del SSN, su diagnosi e piano terapeutico di centri specializzati, Universitari o delle Aziende Sanitarie, individuati dalle Regioni e dalle Province autonome di Trento e Bolzano, è limitata alle seguenti condizioni:

- L'indicazione al trattamento dei tumori "non funzionanti" è controversa e deve essere limitata a quei casi in cui è dimostrata la presenza di recettori per la somatostatina, in particolare con Octreoscan, che, pur con limiti di sensibilità, rappresenta l'unico test disponibile per rilevare la presenza "in vivo" di una sufficiente espressione di recettori per il farmaco in oggetto.

a.



NET: definition



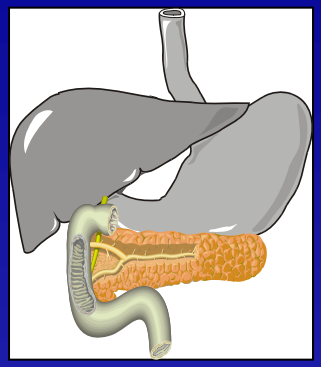
“FUNCTIONING”

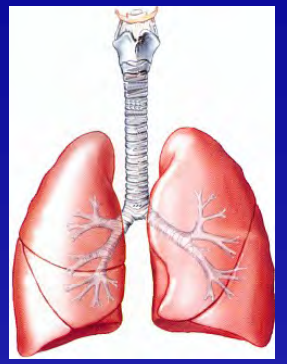
ASSOCIATED with a CLINICAL SYNDROME

“Non FUNCTIONING””

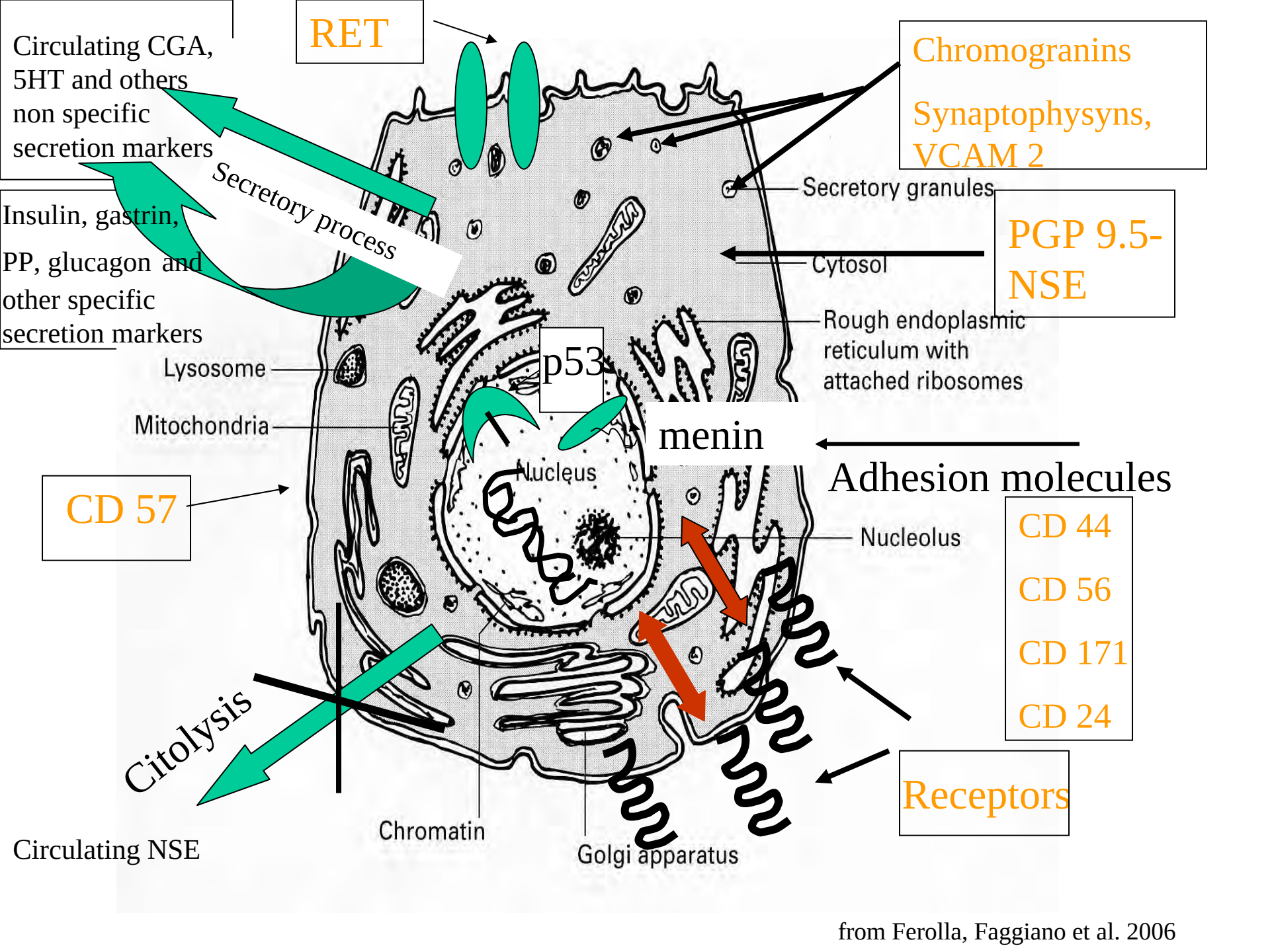
Not ASSOCIATED with a CLINICAL SYNDROME

NET *not* associated with clinical syndrome





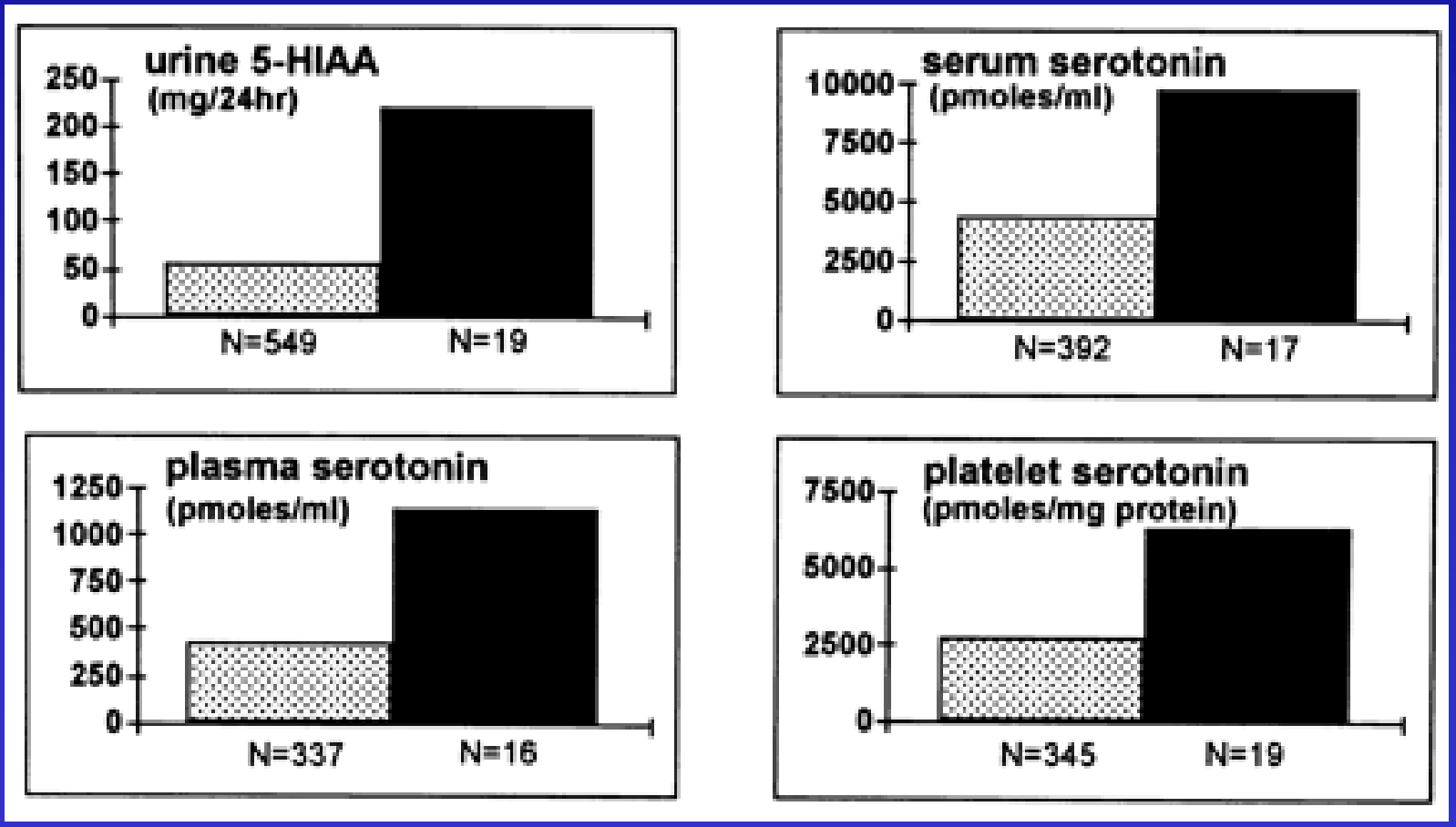
- PANCREATIC POLYPEPTIDE (PP)
- NEURO-SPECIFIC-ENOLASE (NSE)
- HUMAN CHORIONIC GONADOTROPIN (HCG) α AND β
- ISLET AMYLOID POLYPEPTIDE
- CHROMOGRANIN (Cg) A,B, AND C



from Ferolla, Faggiano et al. 2006

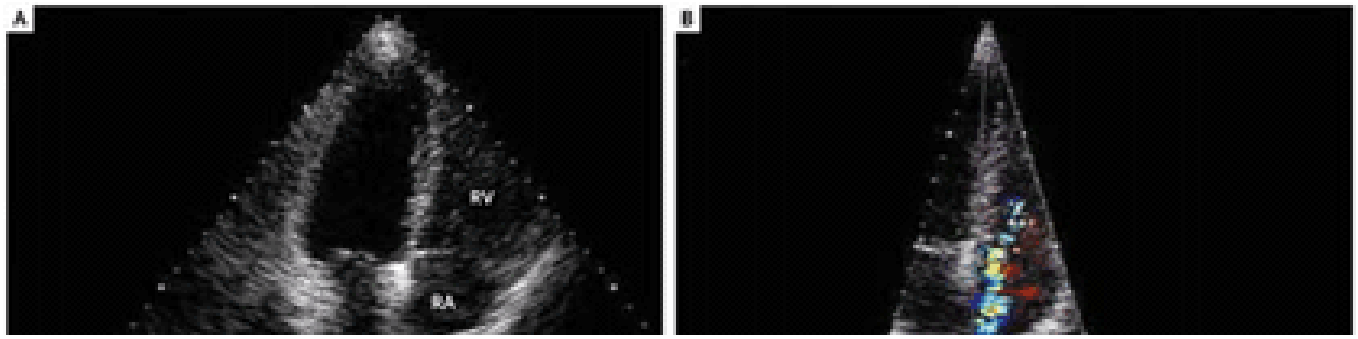
Carcinoid Heart Disease:

Correlation of High Serotonin Levels With Valvular Abnormalities Detected by Cardiac Catheterization and Echocardiography

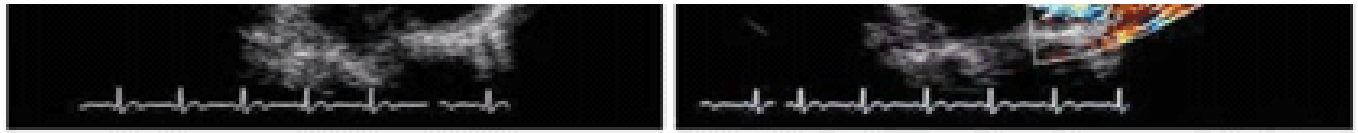


Circulation 1995

Carcinoid Heart Disease:
Factors Associated with Progression

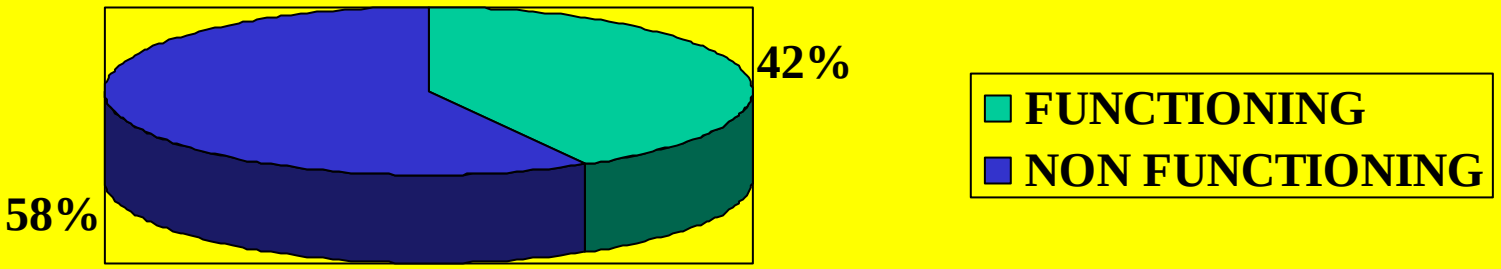


Conclusions Serotonin is related to the progression of carcinoid heart disease, and the risk of progressive heart disease is higher in patients who receive chemotherapy than in those who do not.



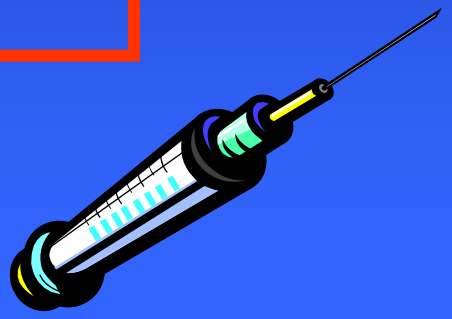
Møller et al NEJM 2003

NET GEP: Hypersecretion



Obiettivi della Terapia Medica nei NET

- *Controllo dei sintomi correlati all'ipersecrezione*
- *Miglioramento della qualità di vita*
- *Controllo della proliferazione tumorale*
- *Prolungamento della sopravvivenza*



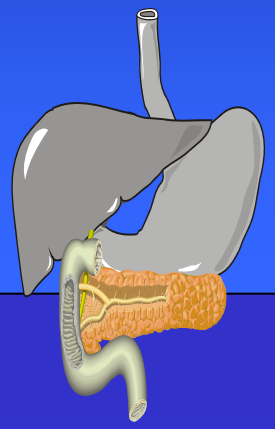
PROSPECTIVE STUDY OF ANTITUMOR EFFICACY OF LONG-TERM OCTREOTIDE TREATMENT IN PATIENTS WITH PROGRESSIVE METASTATIC GASTRINOMA

Pt treated only with PPI → 20-40% 5 y survival

- **53% of patients had a tumor growth response to octreotide**

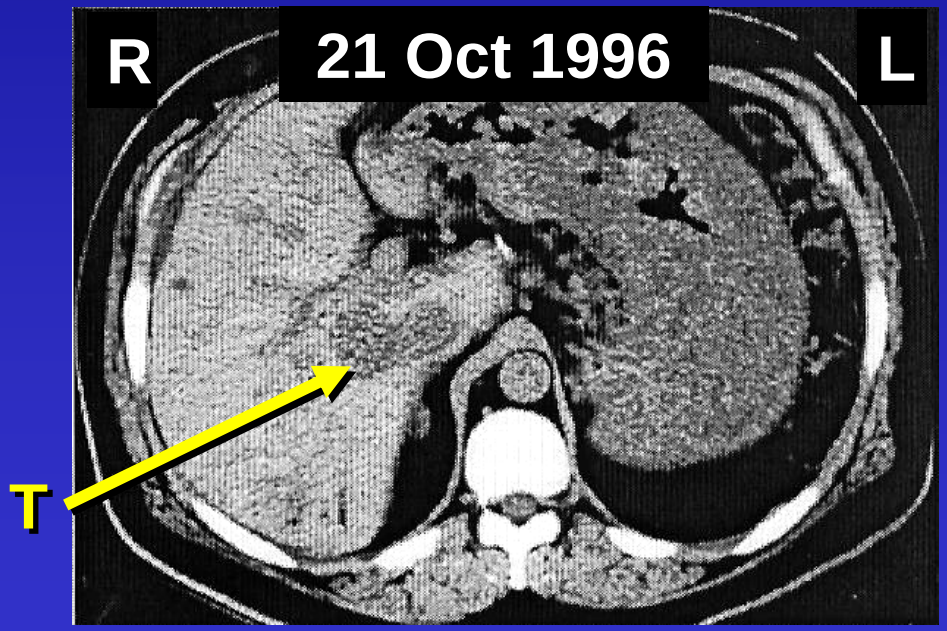
(47% tumor stabilization and 6% decrease in tumor size)

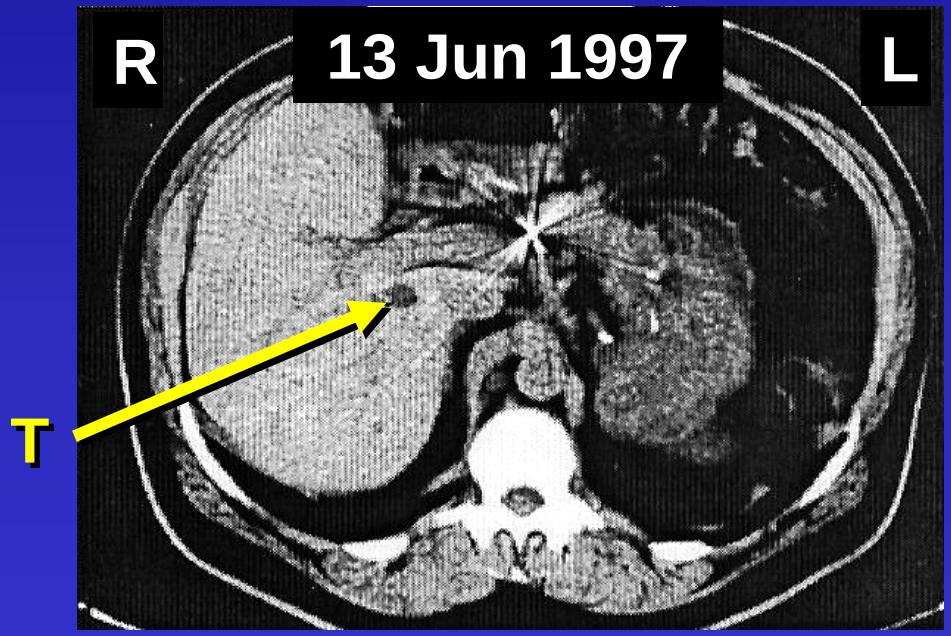
- **low incidence of serious side effects compared to other antitumor treatments commonly used**
- **the growth response is long-lasting**



Shojamanesh H et al. Cancer 2002

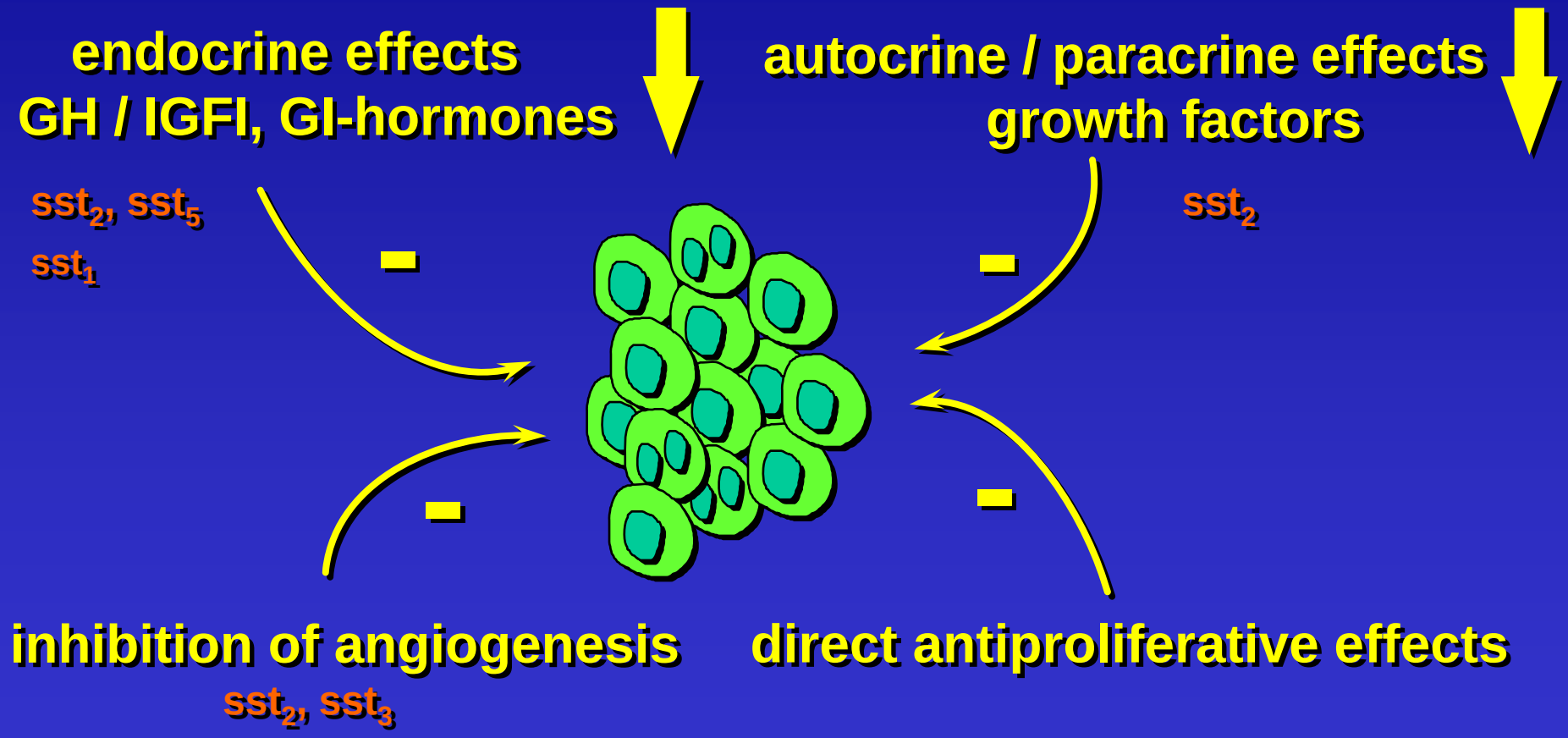
The Effect of Octreotide (2 x 200 µg/day) on Tumour Size in a Patient with Metastatic Gastrinoma

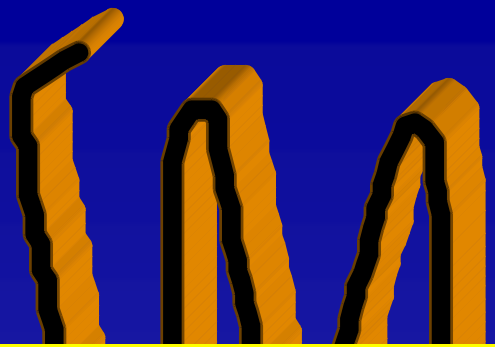




Shojamanesh, *et al*. 2002

Potential Mechanisms of Tumor Growth-Inhibitory Effects by Somatostatin Analogs

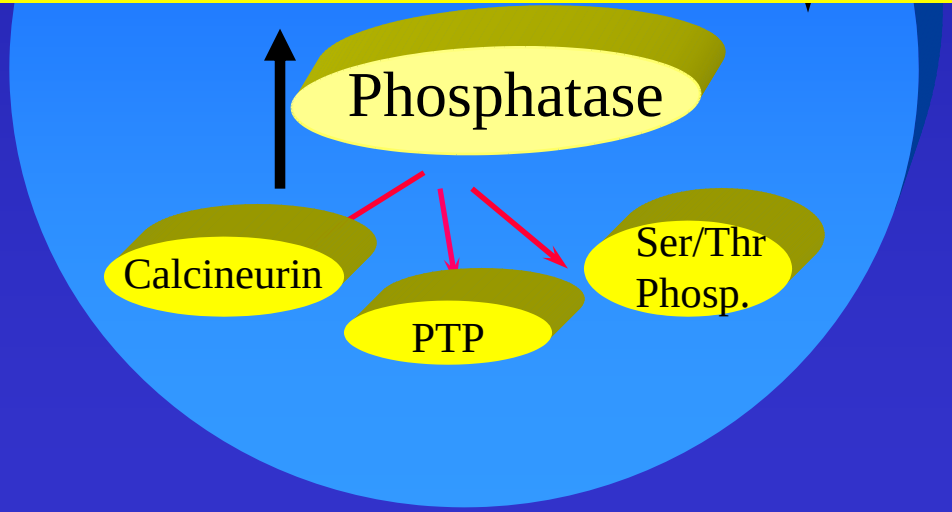




SSTR

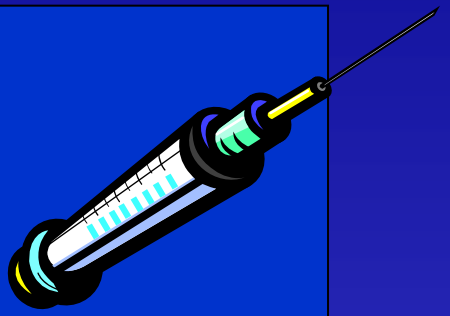
Guidelines for the management of neuroendocrine tumours including bronchopulmonary and thymic neoplasms

K. Oberg et al *A. Oncol 2004*



da Patel, J.En.Inv. (1997) modif.

Lack of controlled studies !!



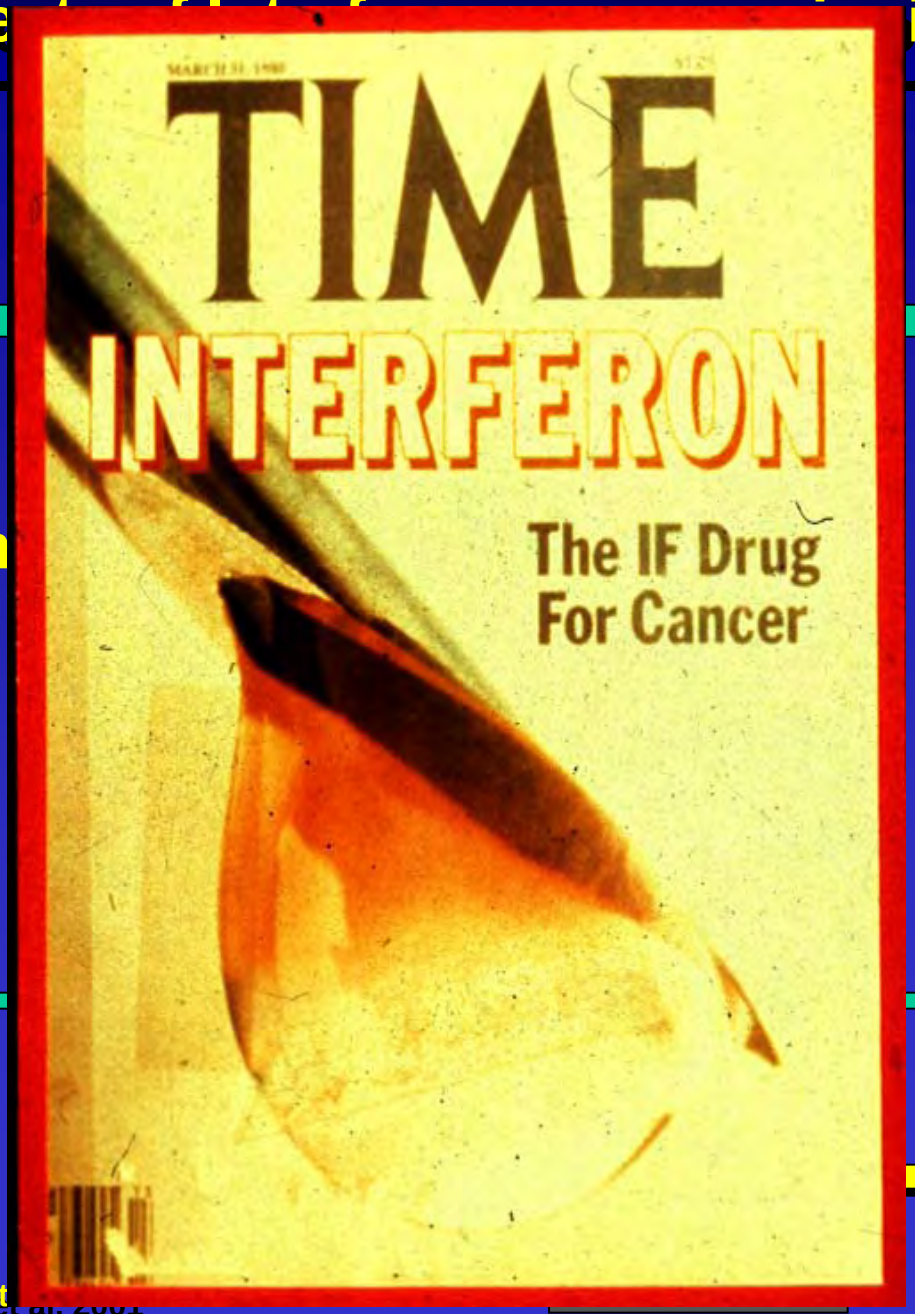
- small numbers
- unclear inclusion criteria
- different tumor subtypes
- indolent behavior, long follow-up
- spontaneous variation of growth
- stable disease vs. biochem. resp.
  vs. objective resp

Single agent chemotherapy in carcinoids : multiinstitutional phase II-III studies (except 5Fu and STZ), first/second line, W=WHO

Drug authors	n	CR/OR	duration m	G3/4
5Fu Moertel C 1983	19	0%/26%	3	UK
Doxorubicine Engstrom P 1984	81	1%/21%	6.5	> 25%
Cisplatine Moertel C 1983	15	0%/6%	3	UK
Etoposide Kelsen D 1987	20	0%/0%*	-	UK
Strepotozoticine Oberg K 1987	7	0%/14% ***	2.7	UK
Carbolatine Saltz L 1993	29	0%/0%*	-	UK
Dacarbazine Bukowski M 1993	56	0%/16%	2.7	29%
Paclitaxel Ansell M 2001	15	0%/8%	3.2	61%
Docetaxel Kulke M 2004 W	21	0%/0%	-	24%
Gemcitabine Kulke M 2004 W	9	0%/0%	-	22%
Campto** Ducreux M 2006 W	18	0%/5%	6	40%

* : 2 and 5OR reclassified as PDEC ; ** : + LV5Fu; ***: biological responses

Effe[illegible] id tumors



cell cycle
mRNA

cytoplasm

p21, p27
2-5-A-synthetase
P68 kinase

nucleus

GENE TRANSCRIPTION

Adapted from Jonash et al. 2001

PATIENTS = 80

PROSPECTIVE, RANDOMIZED, MULTICENTER TRIAL ON THE ANTIPROLIFERATIVE EFFECT OF LANREOTIDE, INTERFERON ALFA, AND THEIR COMBINATION FOR THERAPY OF METASTATIC NEUROENDOCRINE GASTROENTEROPANCREATIC TUMORS – THE INTERNATIONAL LANREOTIDE AND INTERFERON ALFA STUDY GROUP

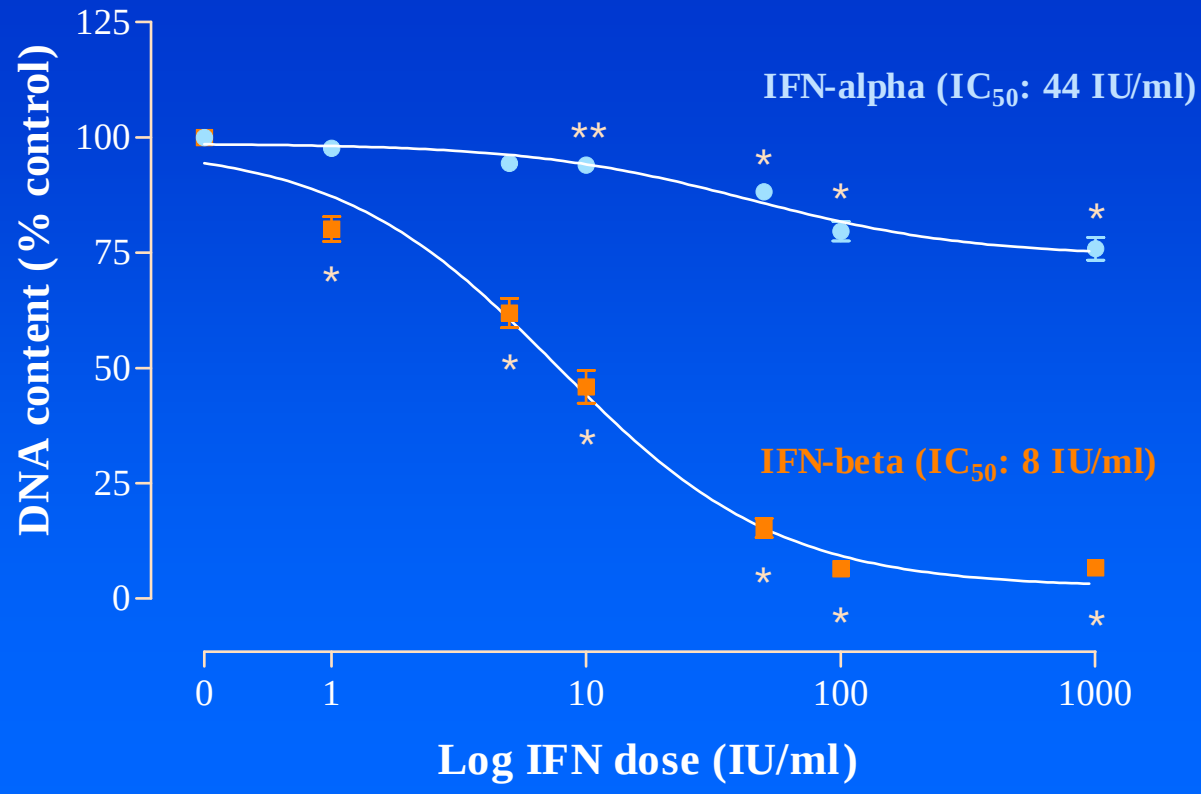
LOCALIZATION OF THE PRIMARY:	
FOREGUT	36 (45%)
MIDGUT	30 (37.5%)
HINDGUT	3 (3.8%)
UNKNOWN	11 (13.7%)

TERAPY:	
LANREOTIDE	25 (31.3%)
IFN-ALFA	27 (33.7%)
COMBINATION	28 (35%)

Faiss et al JCO 2003

Role of type I IFNs in the therapy of NETs

Effects on BON cell proliferation (6 days)

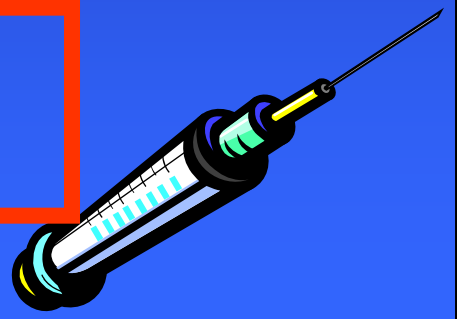


(*: p<0.001, **: p<0.05 vs control)

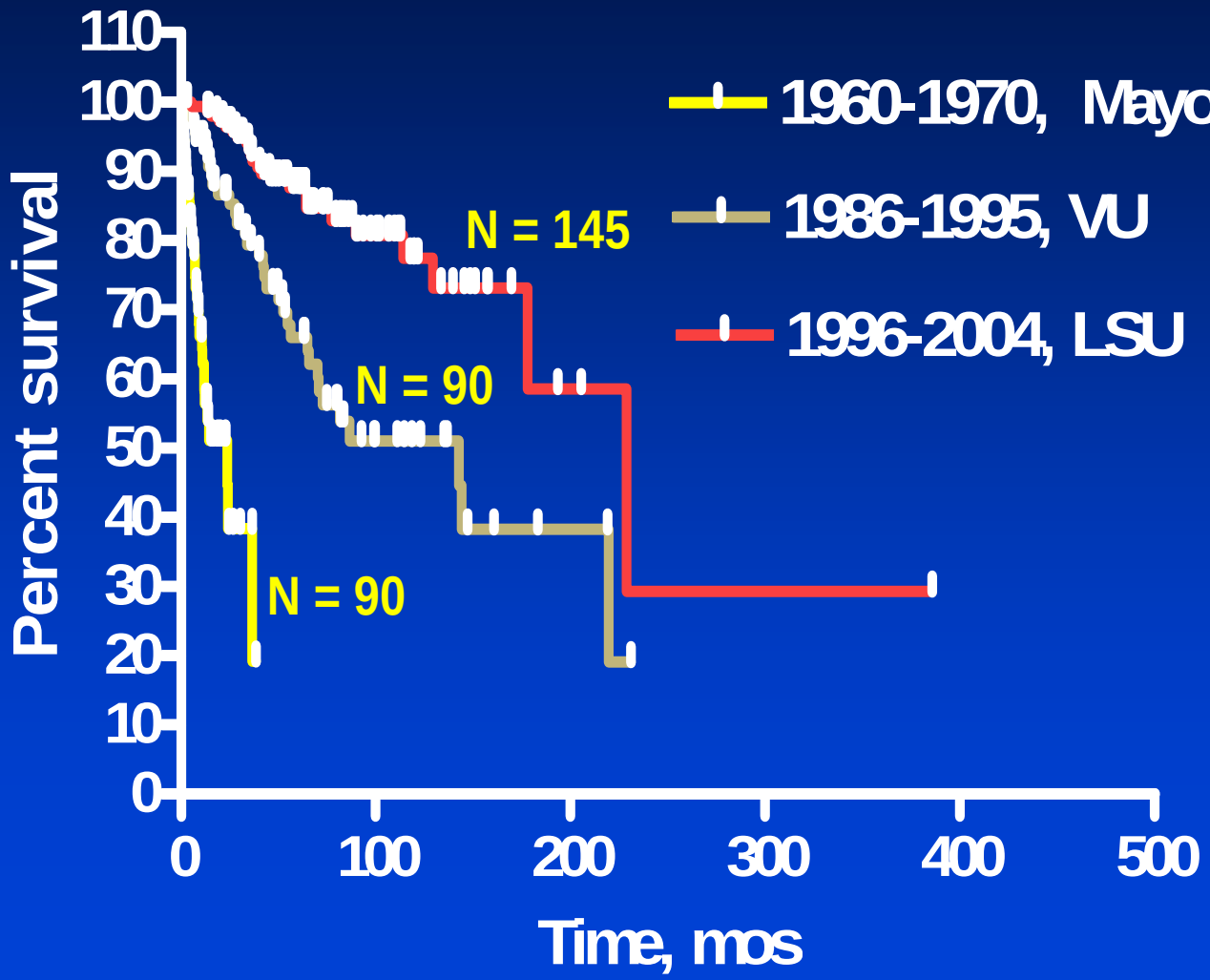
(Vitale G et al. Cancer Res 2006)

Obiettivi della Terapia Medica

- *Miglioramento della qualità di vita*
- *Controllo dei sintomi correlati all'ipersecrezione*
- *Controllo della proliferazione tumorale*
- *Prolungamento della sopravvivenza*



Survival in the Somatostatin Analog Era: Time from the Dx of Metastatic Carcinoid



LB Antony et al 2005

THE FUTURE

High dose treatment

• Faiss S et al	Digestion 1999
• Eriksson B et al	Digestion 1996
• Eriksson B-Oberg K	Ann Oncol 1999
• Filosso PL et al	EJCTS 2002
• Eikssonn et al	Digestion 1999

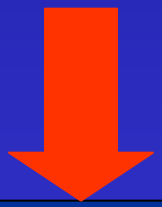
•Trial included only pt. with progressive NET tumors on stardard doses

•Few studies showed further additional antiproliferative effect in pt. failing on standard doses

•Increased number of apoptotic cells on serial tumor biopsies

Ultra High-dose treatment

- **Octreotide Pamoate 160 mg (Onco-LAR)**
  every 2 week for 2 months, then monthly
- ***12 advanced midgut carcinoid in progressive disease (median duration of disease more than 5 y)***



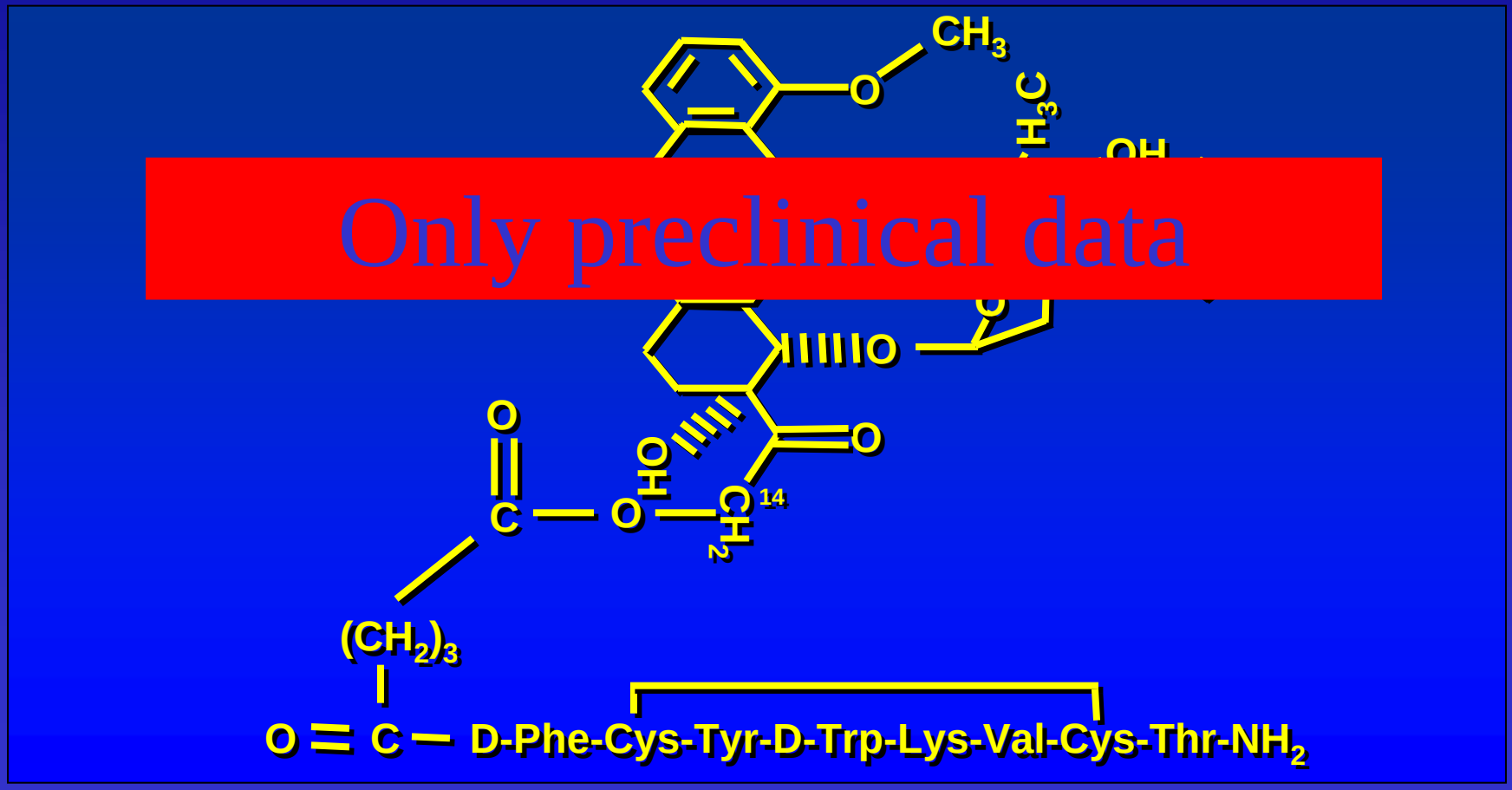
•TUMOR SIZE and BIOCHEMICAL MARKERS stabilization in 75% for a median of 12 months

•10/12 symptomatic improvement of flush and diarrhoea

EJE 2004 151 107-112

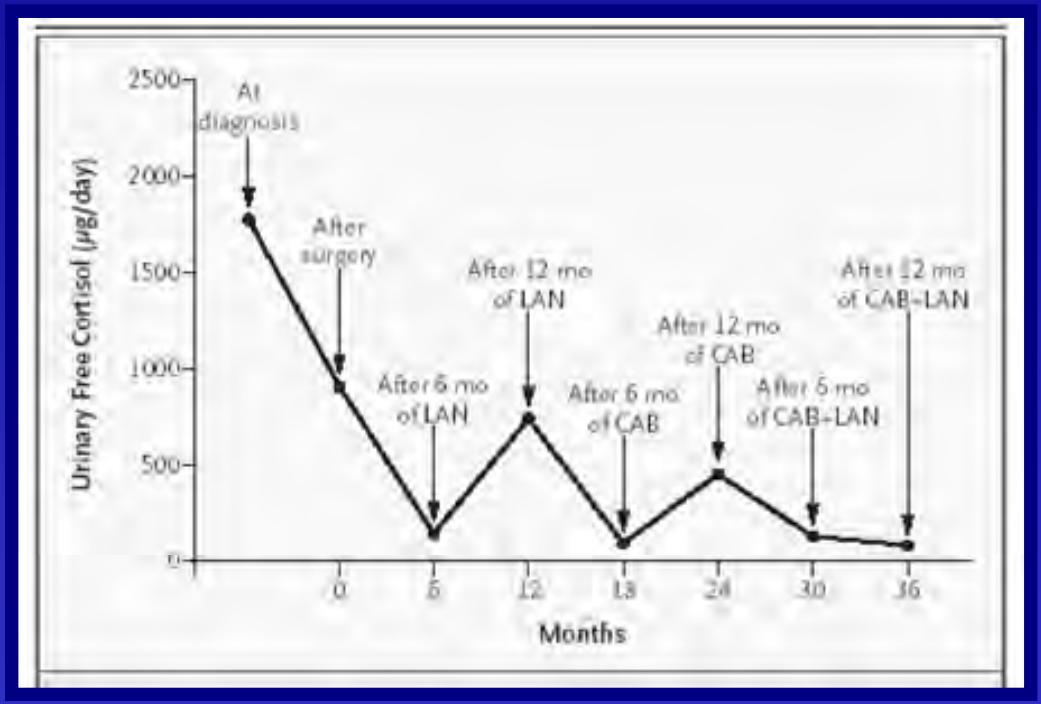
Cytotoxic SS Analogue

RC-121 with N-terminal by bound 2-pyrrolino-doxorubicin (AN-238)

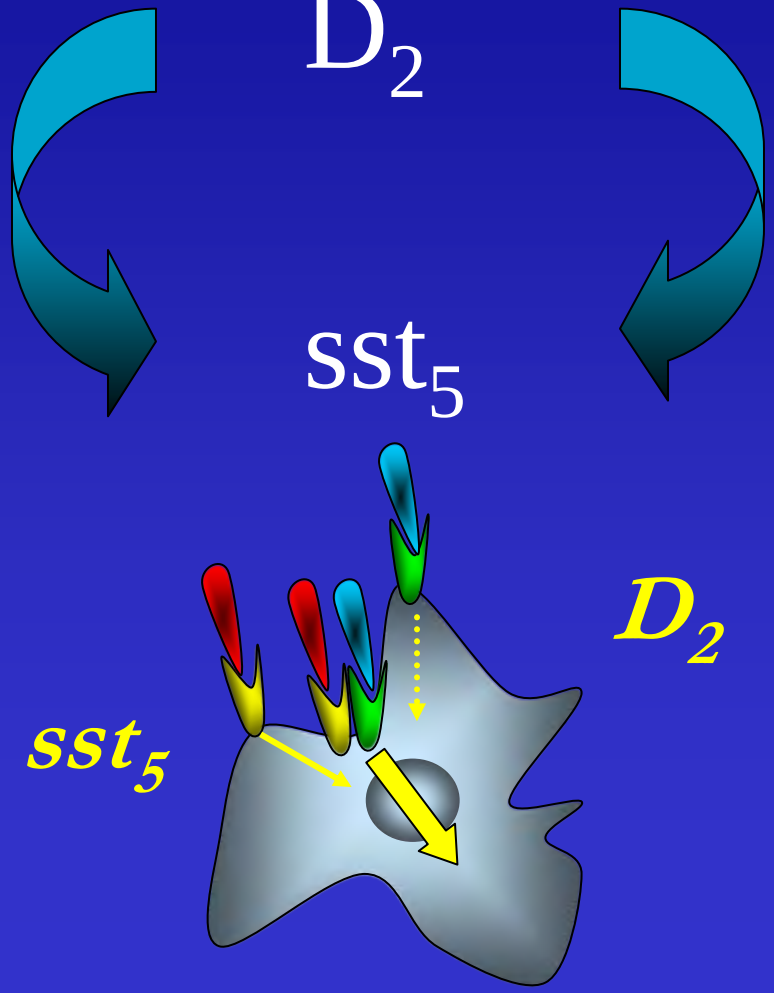


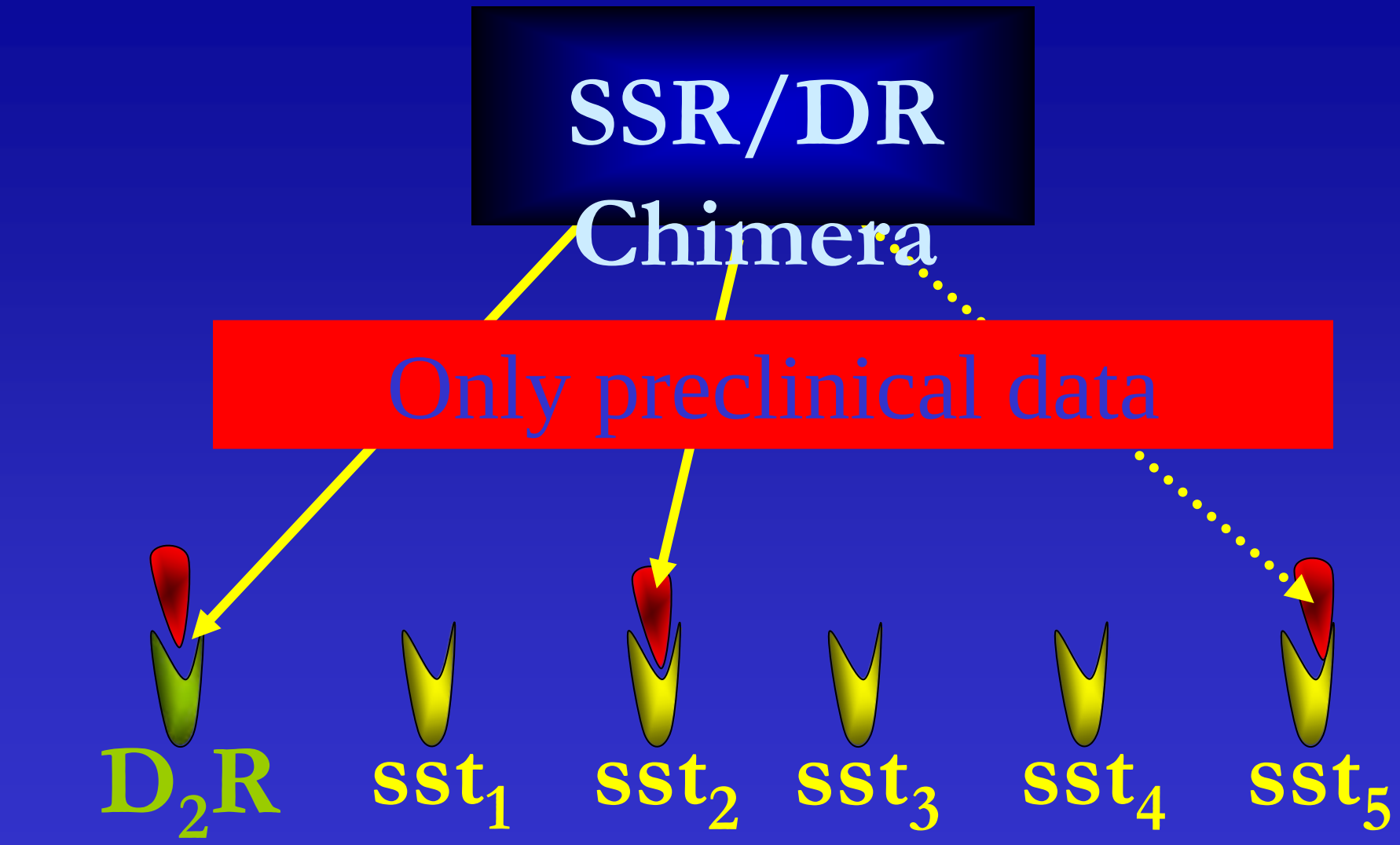
Cancer 2003

Lung "atypical carcinoid"



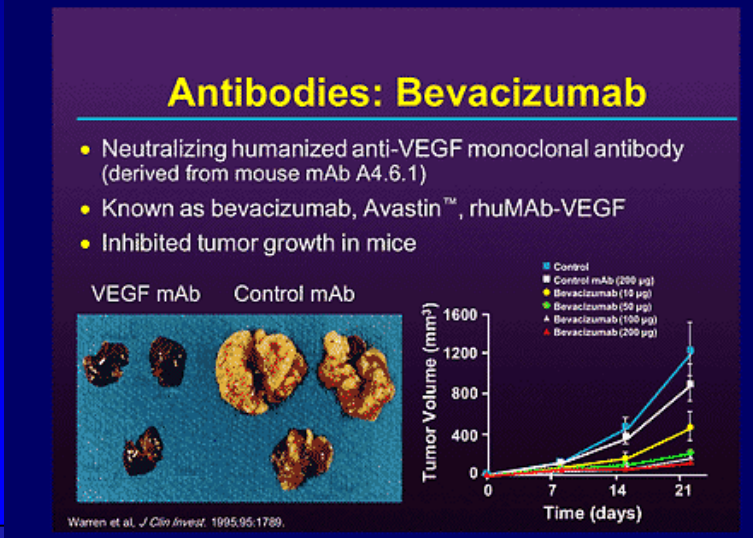
Pivonello et al., N.Engl. J. Med, 2005



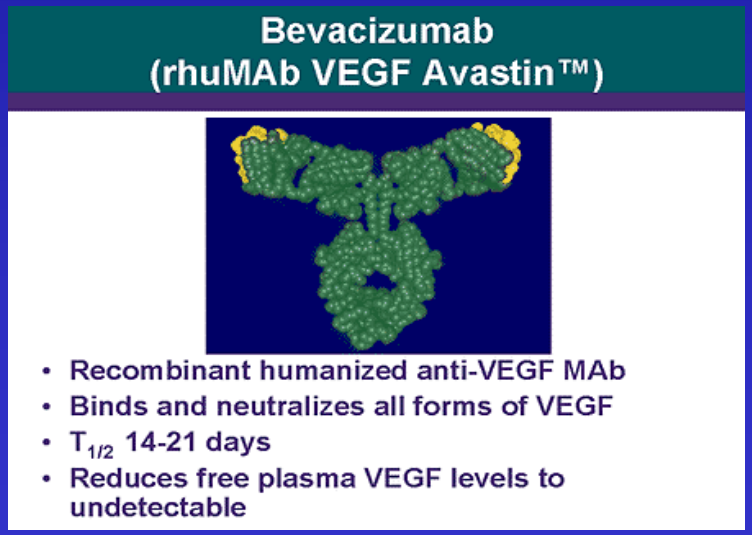

SSR/DR Chimera
Only preclinical data
D2R
sst1
sst2
sst3
sst4
sst5

Improved free survival and rapid sustained decrease in tumor perfusion among pt with advanced carcinoid treated with BEVACIZUMAB (Avastin)

Yao J et al ASCO 2005



Design: random BEVACIZUMAB or PEG IFN or both added to OCT LAR



	BEV (22)	PEG IFN (22)
PR	4	0
SD	17	16
PD	1	6

Conclusion: superior progression free survival and rapid and sustained reduction in tumor blood flow, blood volume and permeability by functional CT

Early data on the efficacy and safety of the novel multi-ligand somatostatin analog, SOM230, in patients with metastatic carcinoid tumors refractory or resistant to octreotide LAR

II open-label study

SOM230 450-1200 μg bid

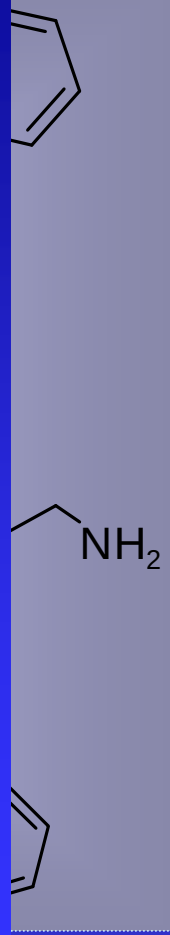
SAFETY : generally well tolerated

EFFICACY: effective in controlling diarrhea & flushing

7/21 patients (33%) had partial response; no CR

FIRST DATA PRESENTED THE 15 OF MAY AT THE ASCO CONFERENCE

sst
sst
sst
sst
sst

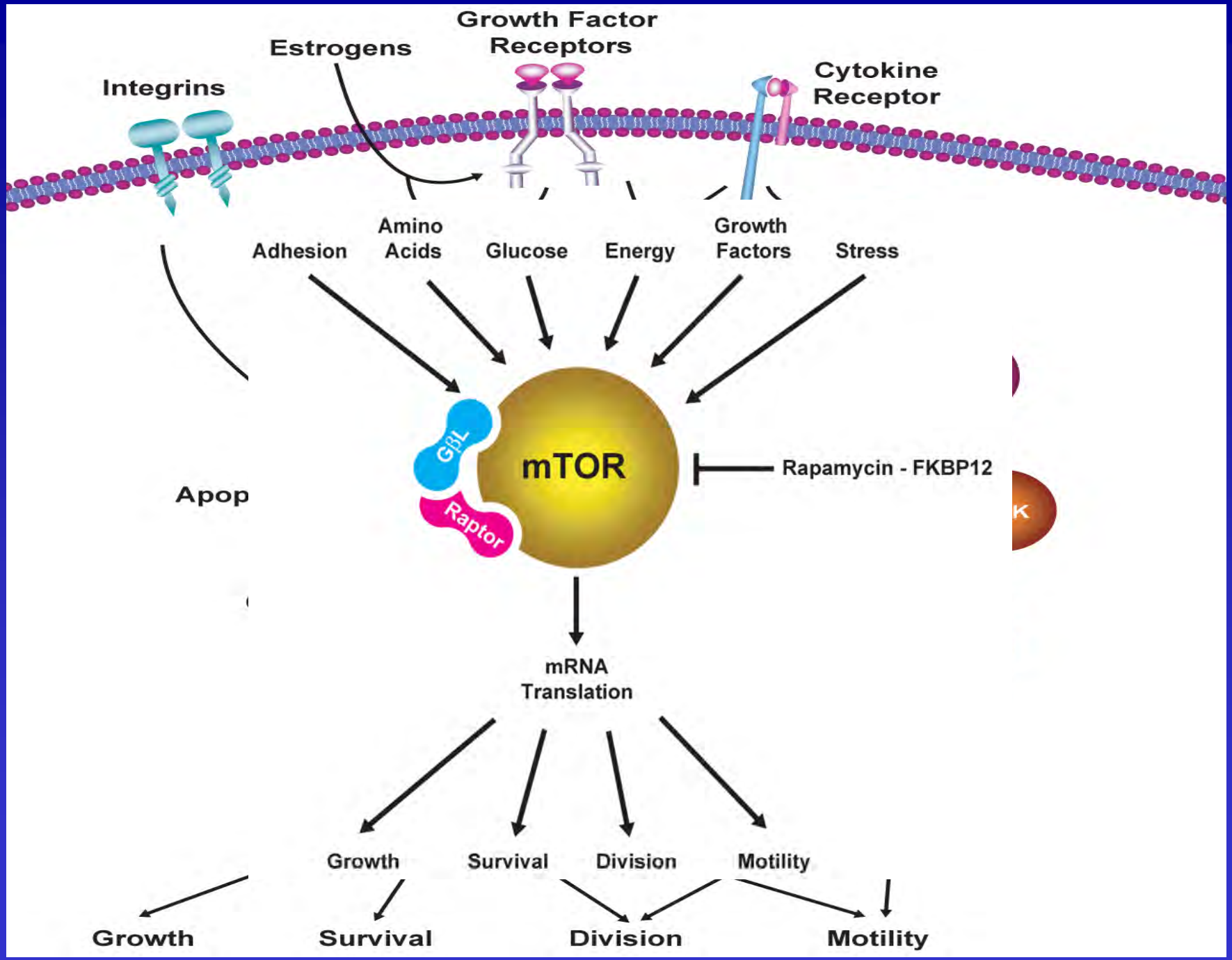


Results: Efficacy of SOM230

- In this interim analysis, 28 patients qualified for efficacy assessment
- 7 patients were partial responders to SOM230 therapy. 1 additional patient initially had a PR to therapy then subsequently achieved the criteria for CR
- 3 PR patients were receiving SOM230 600 µg bid, 2 were receiving SOM230 750 µg bid and 2 were receiving SOM230 900 µg bid. The patient with CR to SOM230 therapy was receiving 900 µg bid

Results: Safety and tolerability of SOM230

- Adverse events were evaluated in 35 patients
- Adverse events were primarily gastrointestinal, such as
  - Nausea (28.6%)
  - Abdominal pain (20.0%)
  - Diarrhea (5.7%)
  - Flatulence (5.7%)
- Weight loss (34.0%) and fatigue (14.3%) were also reported


Growth Factor Receptors
Estrogens
Integrins
Cytokine Receptor
Adhesion
Amino Acids
Glucose
Energy
Growth Factors
Stress
GβL
mTOR
Raptor
Rapamycin - FKBP12
mRNA Translation
Growth
Survival
Division
Motility
Growth
Survival
Division
Motility

Phase II study

OCTREOTIDE LAR

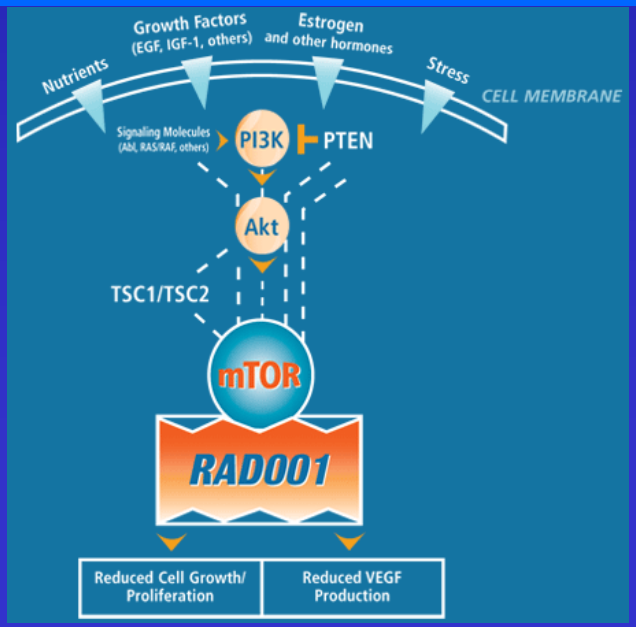
30 mg every 28 gg

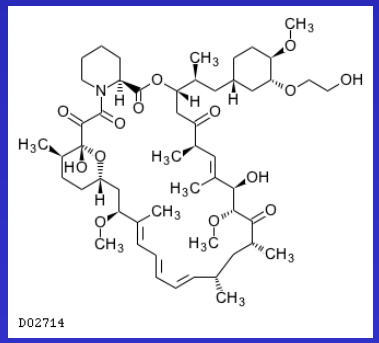
+

RAD001

5 mg p.o./d

advanced low grade neuroendocrine carcinoma





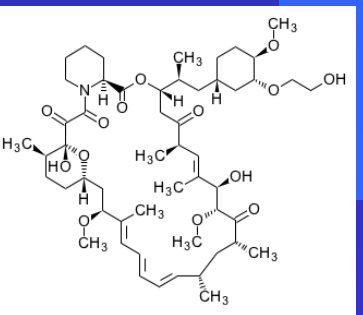
Yao JC et al ASCO 2006

Generally well tolerated:

CTC Grade 3/4 toxicity include:

anemia (1) thrombocytopenia (1)
aphthous ulcer (2)
diarrhea (2)
edema (1)
fatigue (1)
hypoglycemia (1)
nausea (1) pain (1) rash (1).

most common toxicity is mild aphthous ulceration.



Phase II study of RAD001 and Depot Octreotide in patients with advanced low-grade neuroendocrine carcinoma

[redacted]

Updated Abstract

[redacted]

Background

[redacted]

Objectives

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Treatment

- [redacted]
  - [redacted]
  - [redacted]
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  - [redacted]
  - [redacted]

Results

[redacted]

Sex	
[redacted]	[redacted]
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Disease evaluation	
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Efficacy

RECIST

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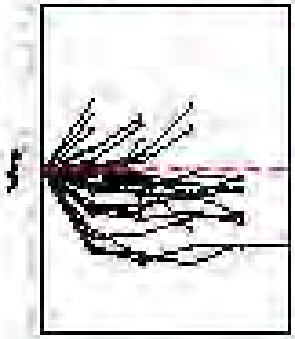
Tumor Angiogenesis Biomarkers



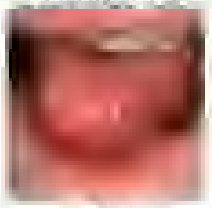
Safety/Tolerability

[redacted]

Response to Octreotide

Response to Everolimus

Mouth Ulceration



Rash

Conclusions

[redacted]

References

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P.Ferolla,
G. Scarpelli
G. Angeletti
F. Santeusanio

CHIR. TOR (PG)

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AM Colao

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(AP)

6th AME Italian Meeting
3th Joint Meeting with AACE
Verona, Italy October 27-29, 2006

NET: Treatment of Persistent Disease

Chemo-Embolization and Thermal Ablation of Metastatic Disease

Giancarlo Bizzarri, Dario Valle, Antonio Bianchini, Vincenzo Anelli, Stefano De Nuntis, S. Pacella and Claudio Maurizio Pacella

Radiological Interventional and Diagnostic Department
Regina Apostolorum Hospital
Albano Laziale

Introduction: epidemiology

- Rare tumors with variable clinical course
- Often indolent (“cancer in slow motion”)* but frequently with incurable metastatic disease

*Chamberlain RS J Am Coll Surg 2000;190:432-445

Introduction: natural history

- Presence of bone and liver metastases dramatically worsen the prognosis of patients
- Reported survival rate with metastatic liver disease is 0 to 40% versus 70-80% without liver metastases at 5 years
- In these patients survival rate is influenced by the presence of obstructive symptoms or symptoms related to the peptide secretion

Introduction: topic

- the role of image-guided oncologic liver directed therapies in the management of patients with NETs hepatic metastases
- how radiological intervention procedures interact with medical and surgical treatments in these difficult clinical scenarios

Introduction

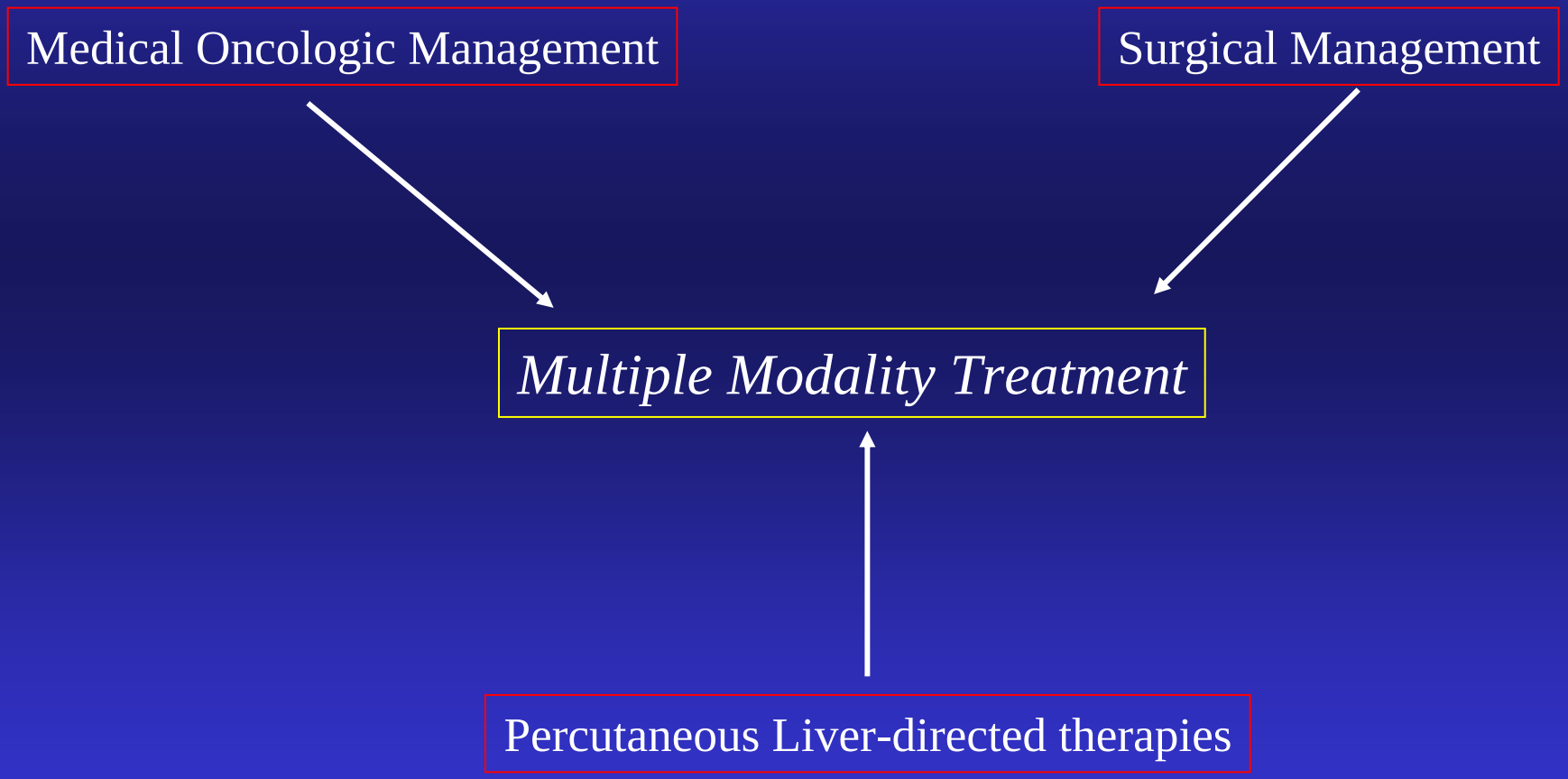
- Rationale for therapies of NETs has to take into account :

a) The quality of life (carcinoid syndrome, compressive and obstructive symptoms from bulky tumors and pain from bony mets)

b) The overall survival (carcinoid syndrome, hepatic failure from multiple liver metastases or obstructive jaundice)

Introduction

Therapeutic Approaches



Introduction

the role of radiologists

- Despite surgery and medical oncologic treatments carcinoid syndrome and tumor bulk may progress
- It is in this scenario that radiologists have an established primary role
- In this case the treatment has to be tailored to the goal (i.e.: reduction of tumor bulk, hormonal palliation, conversion to resectable status)

Introduction

Radiological Interventional Approach

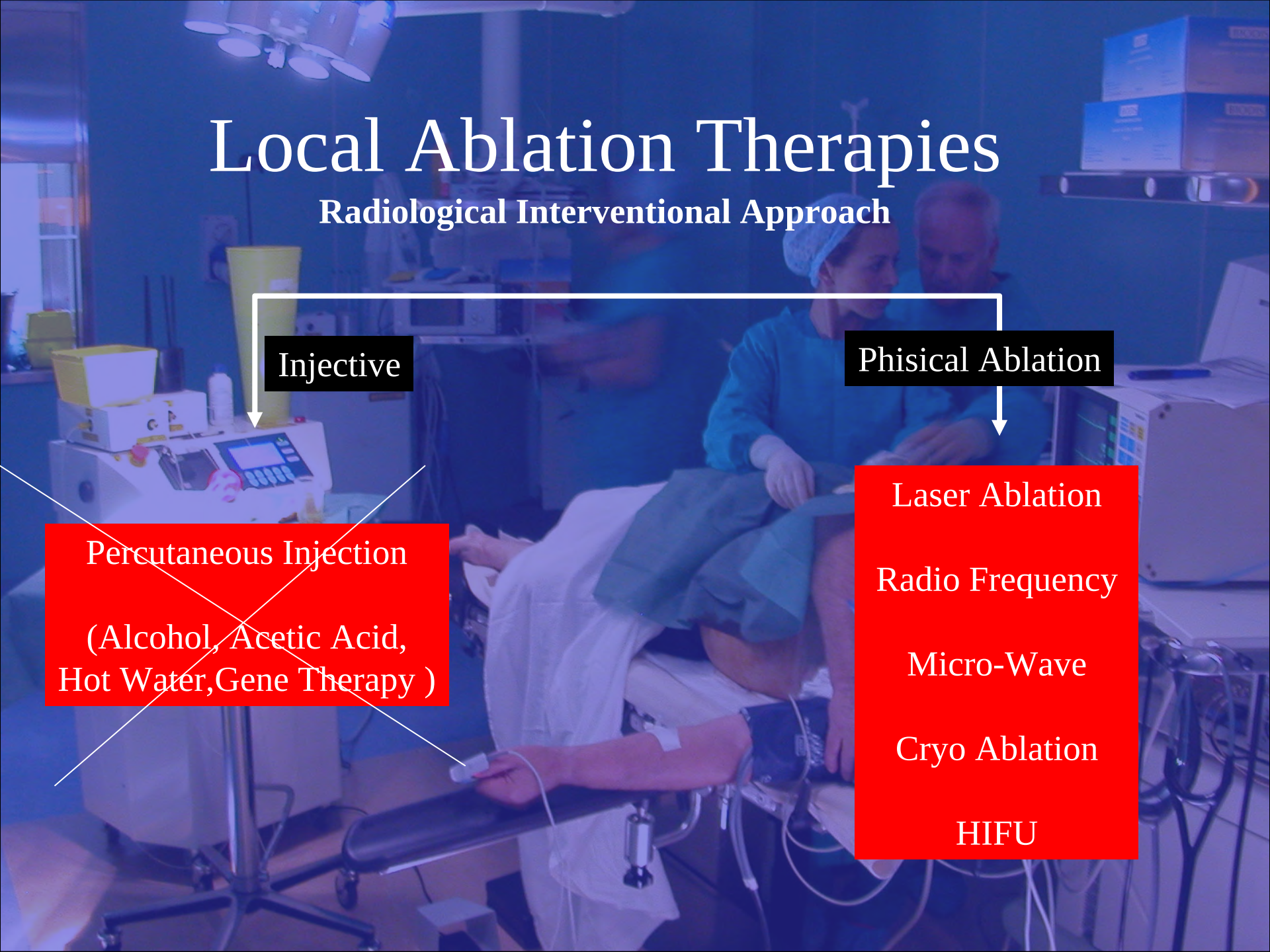
- From the radiological standpoint the minimally invasive liver directed therapies can be classified in two groups:

- a) Local ablation therapies

- b) Percutaneous trans-arterial-catheter treatments

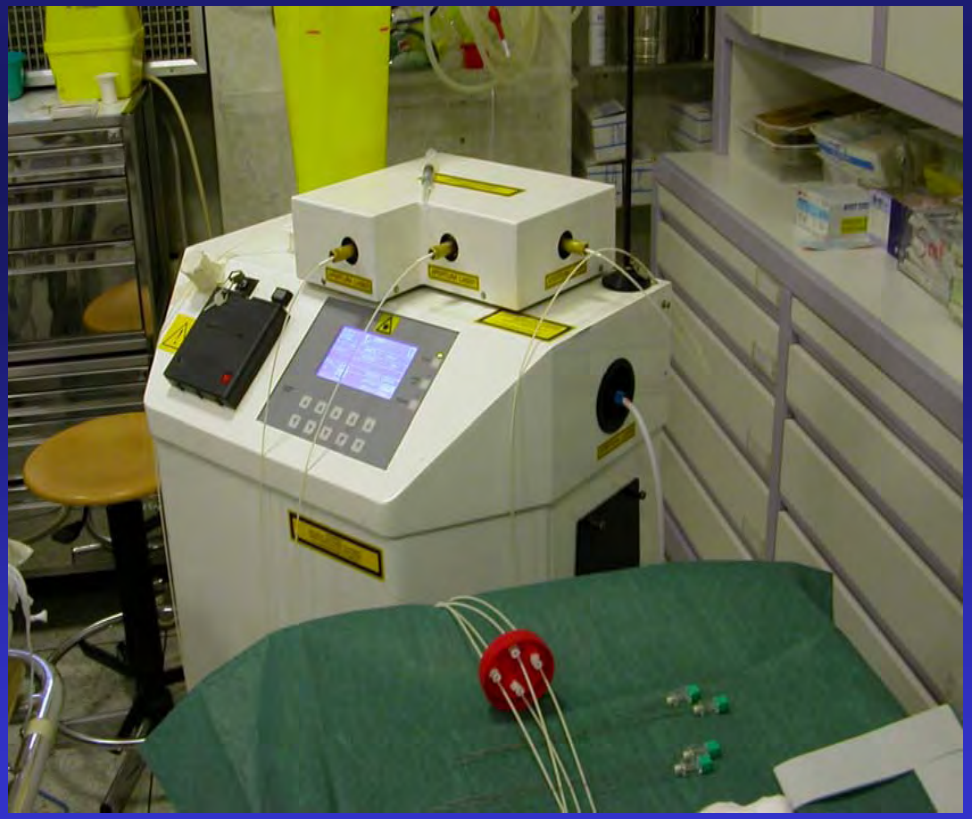
Local Ablation Therapies

Radiological Interventional Approach



Rationale for Local Ablation Therapies

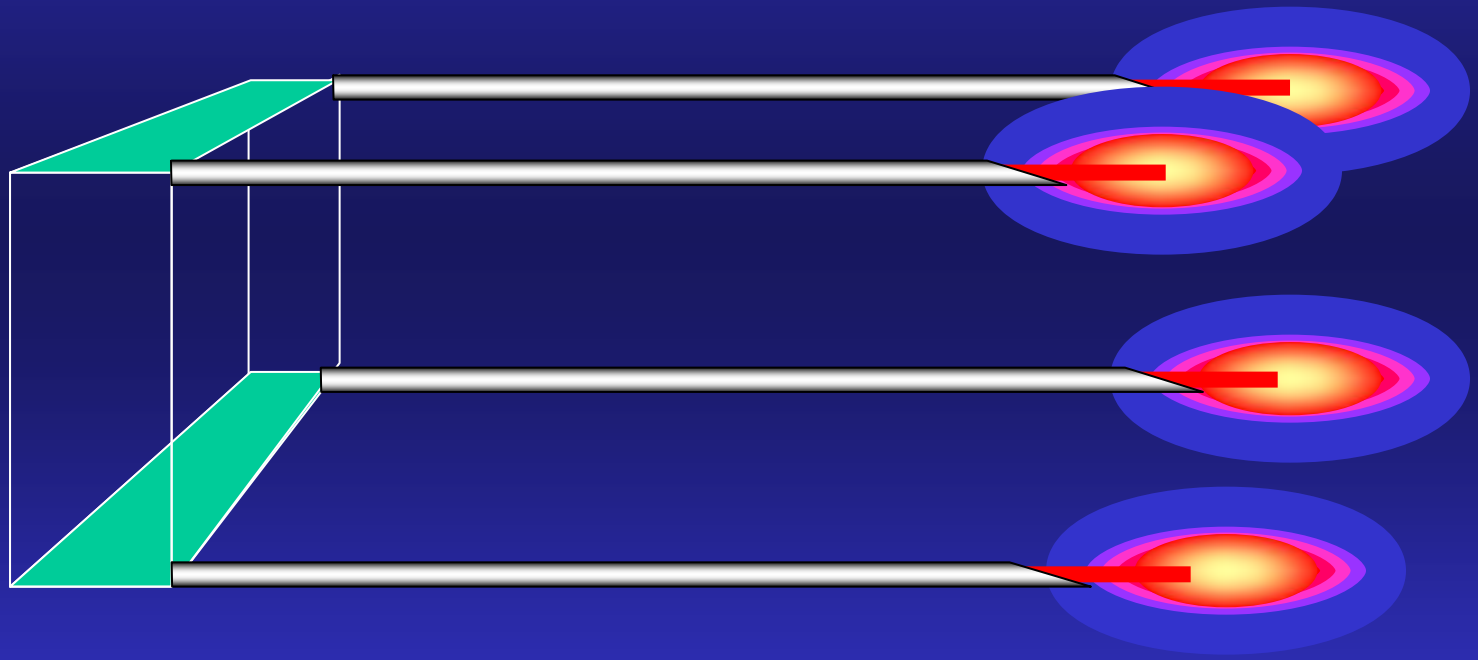
- Efficacious in tumor killing
- Rapid
- Safe
- Inexpensive
- Selective



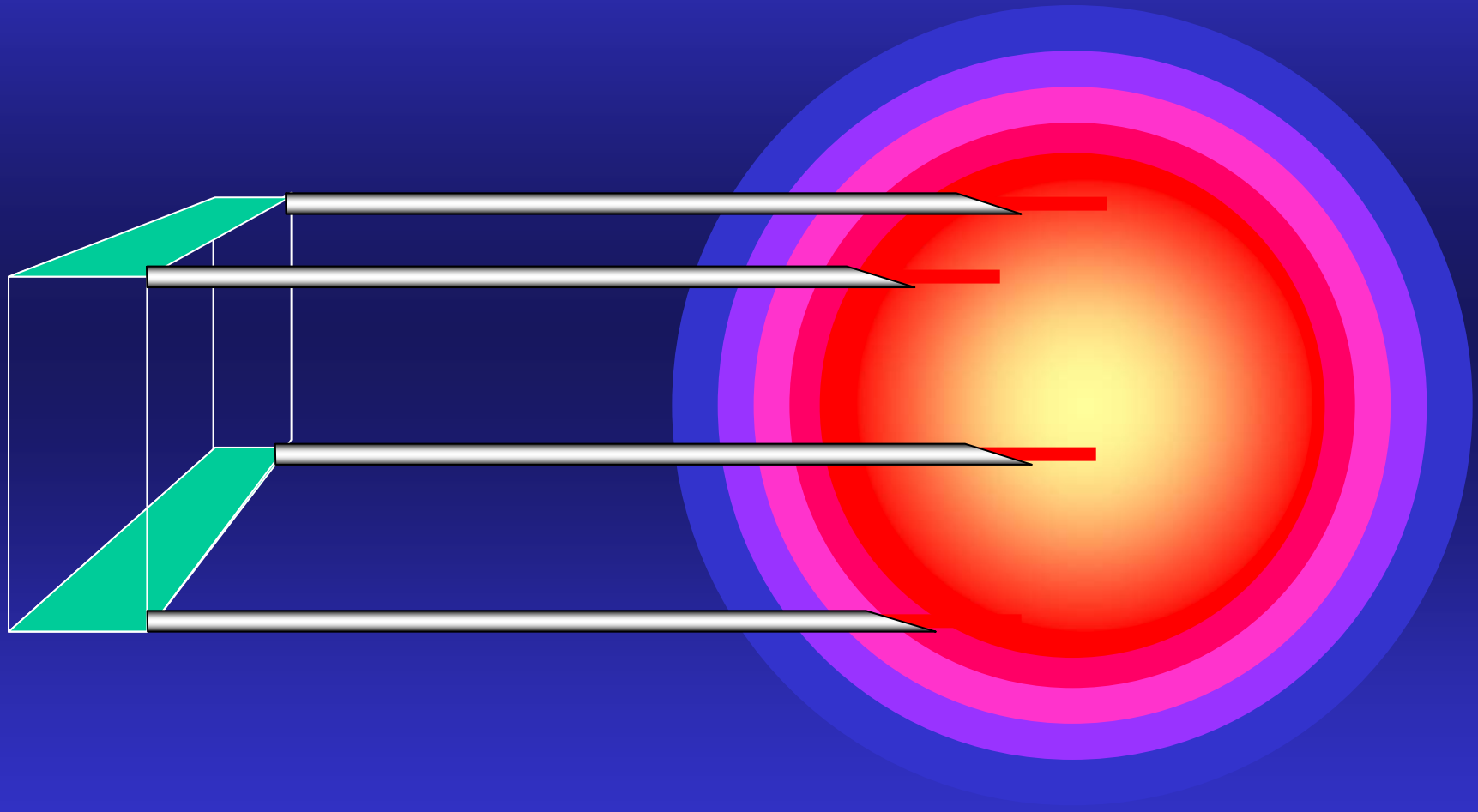
Local Ablation Therapies: drawbacks

- Local efficacy similar to surgical resection
- Lesions detectable on one imaging modality
- Not indicated for large and multiple lesions when curative ablation is required (Less than 5 lesions smaller than 4 cm.)

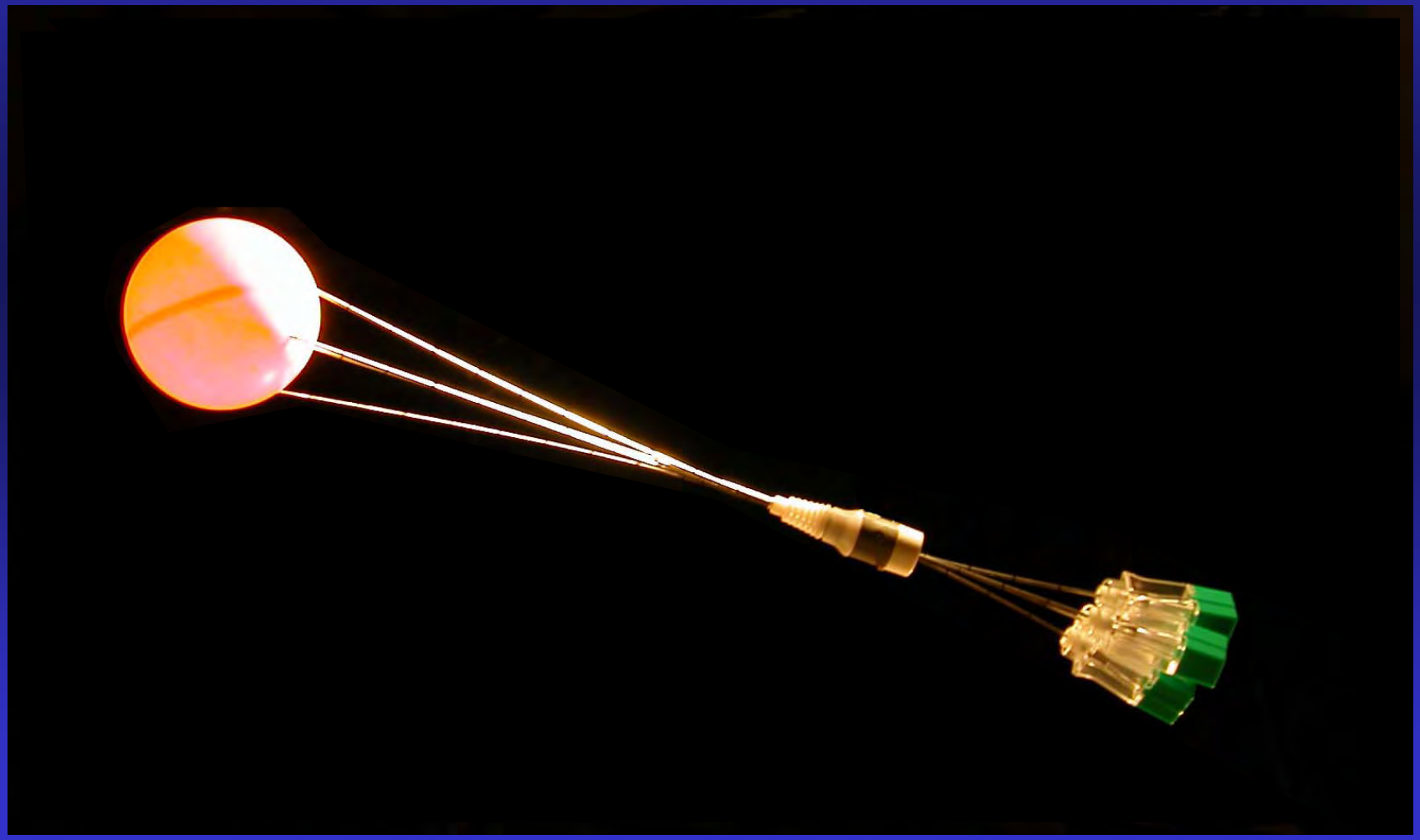
Laser Ablation (multifiber technique)



Laser Ablation (multifiber technique)

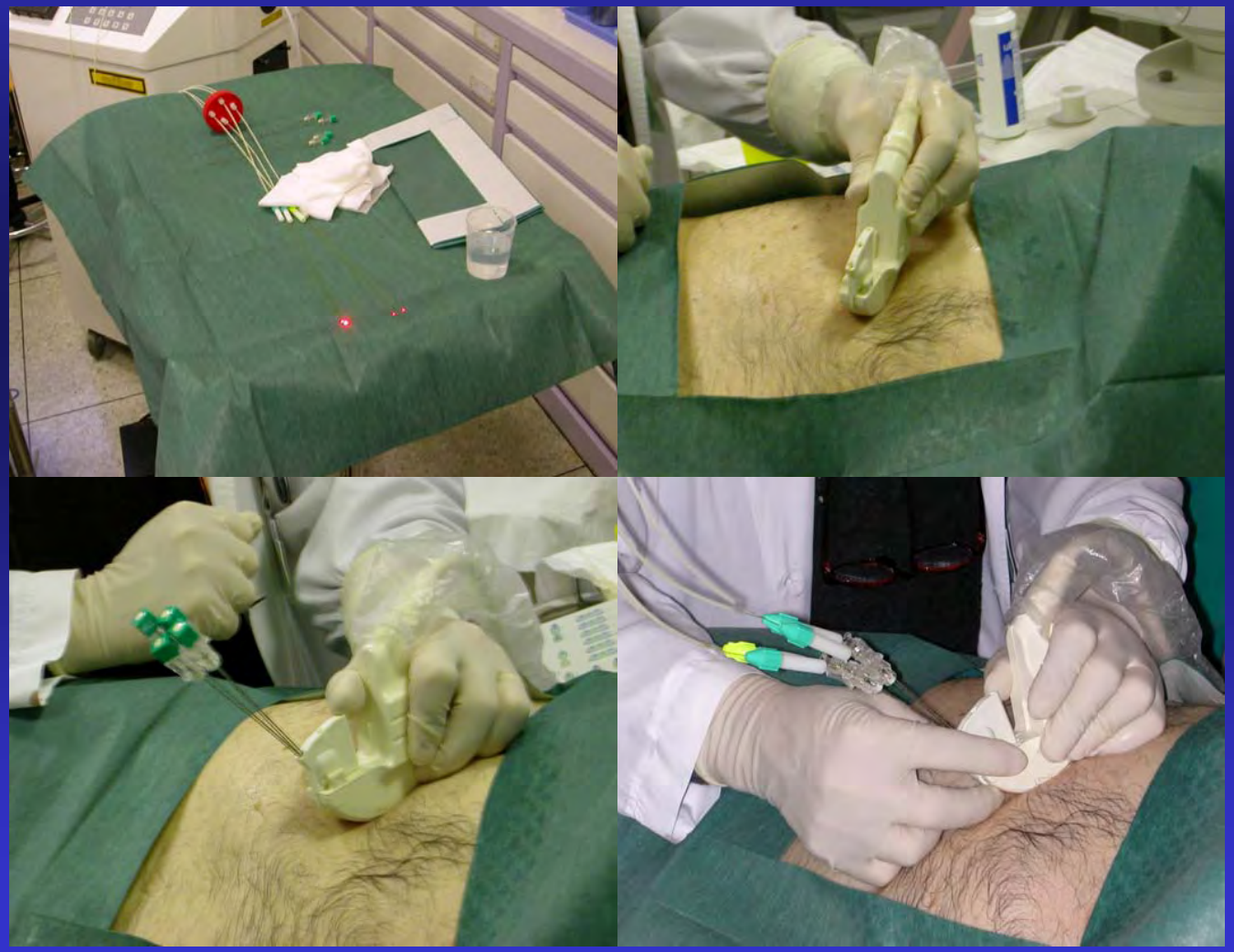


Laser Ablation (multifiber technique)



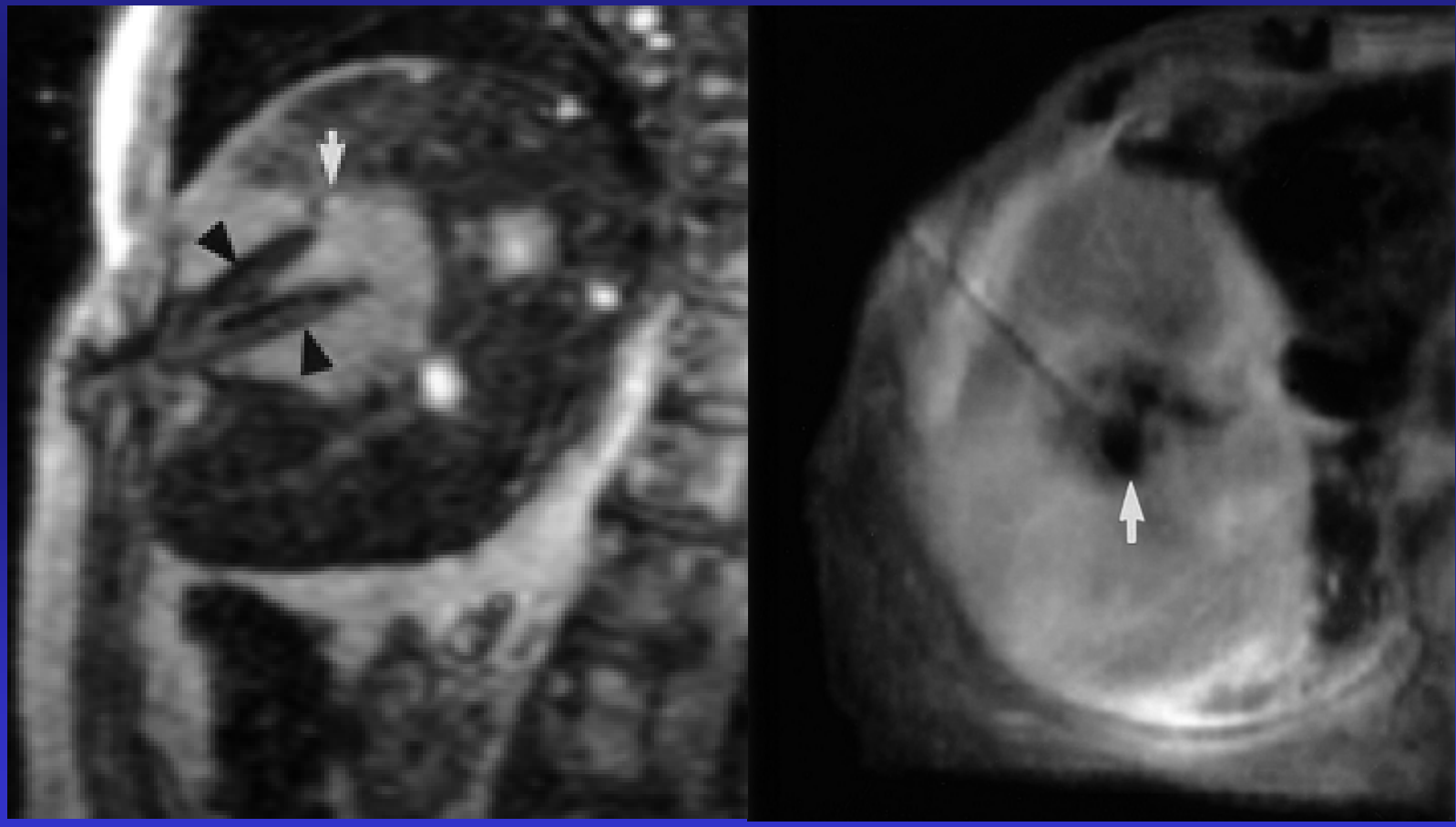
Laser Ablation (multifiber technique)

US guidance

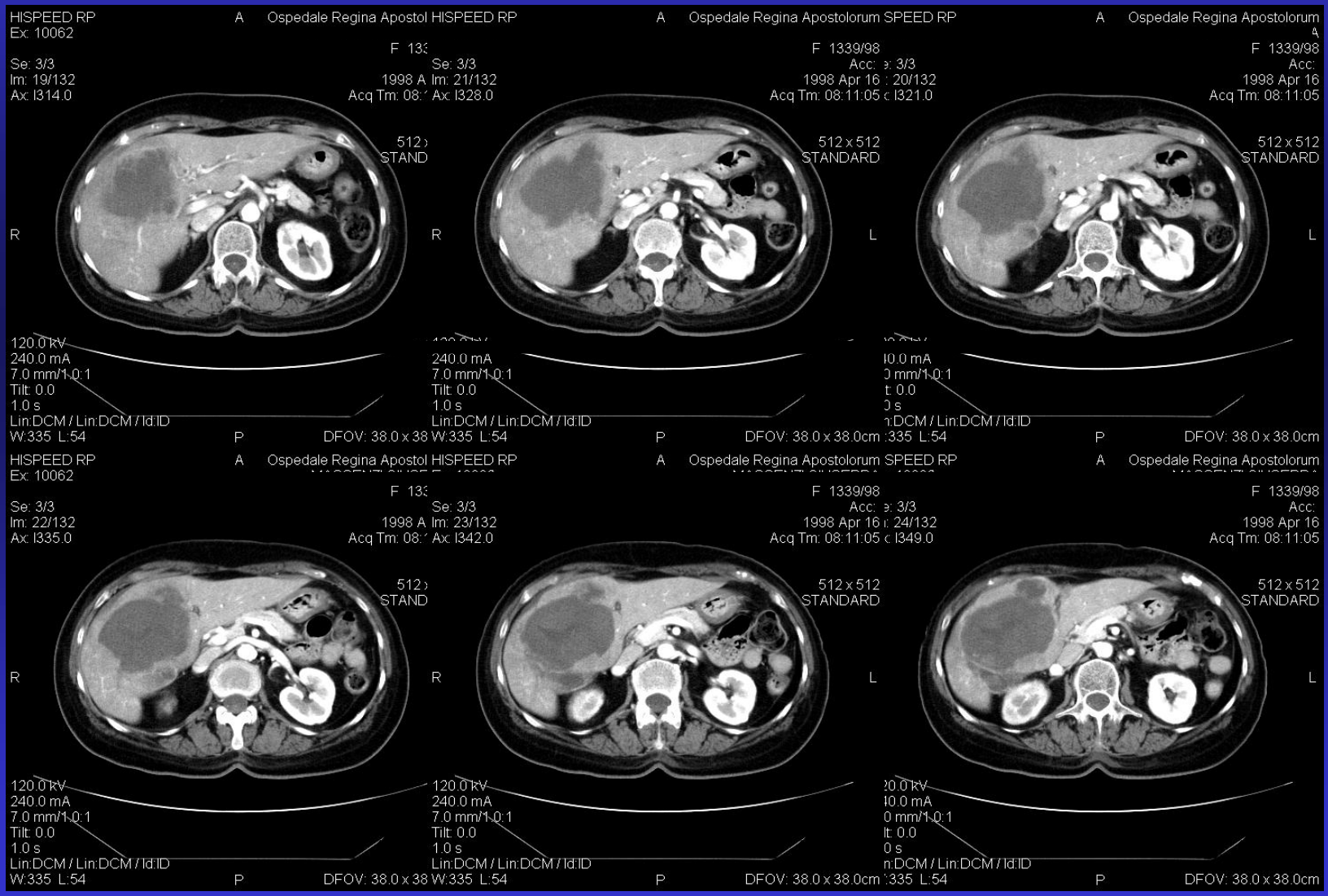


Laser Ablation (multifiber technique)

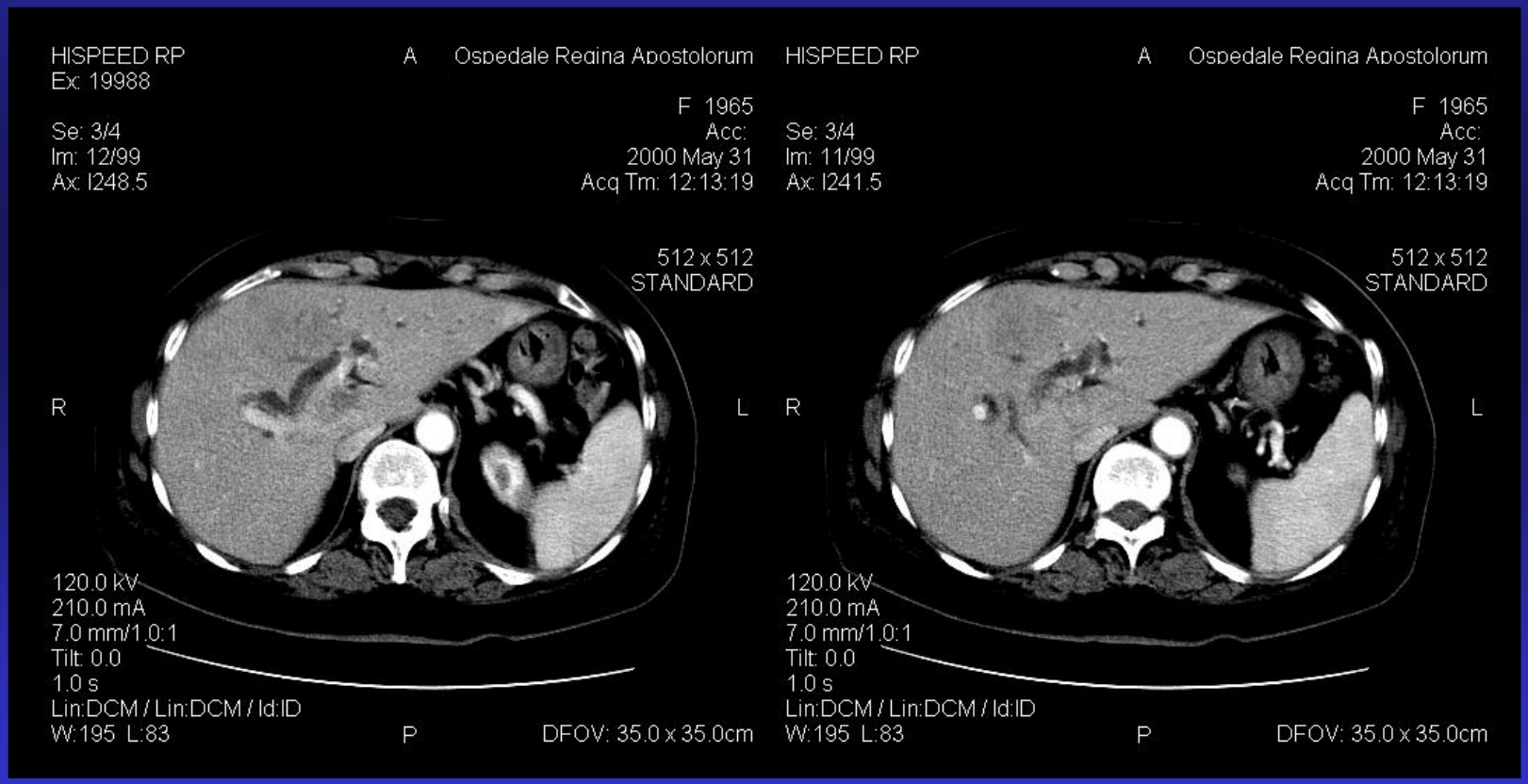
MRI guidance



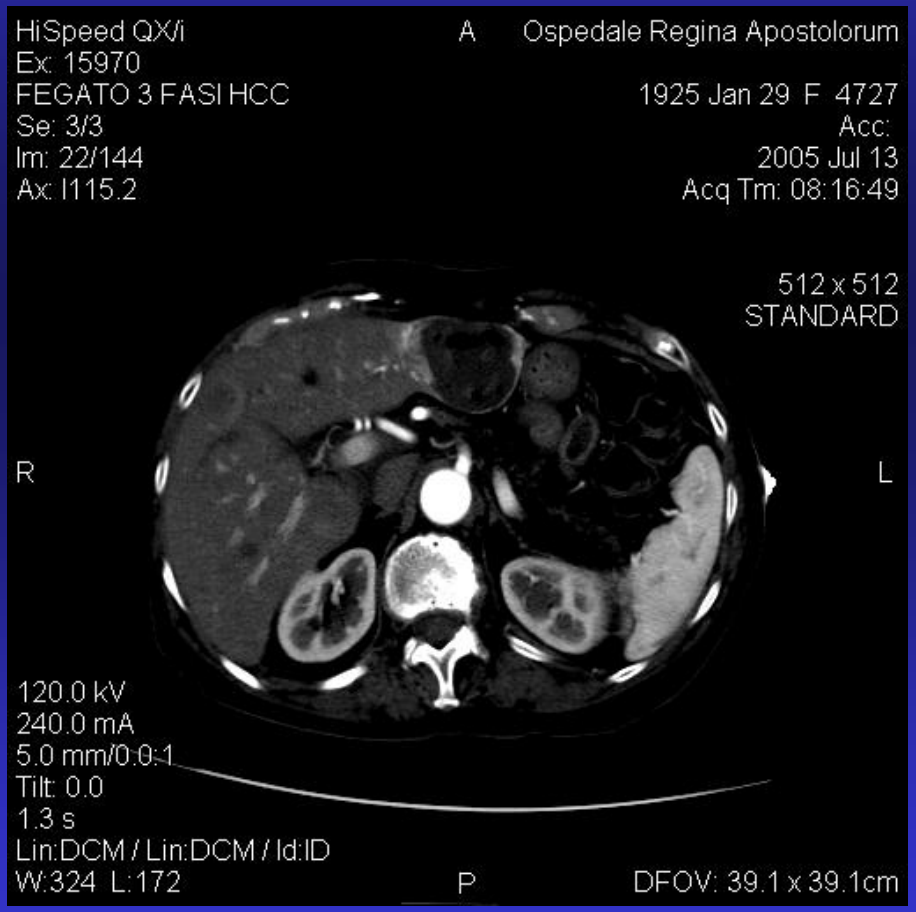
Laser Ablation (multifiber technique) cytoreduction

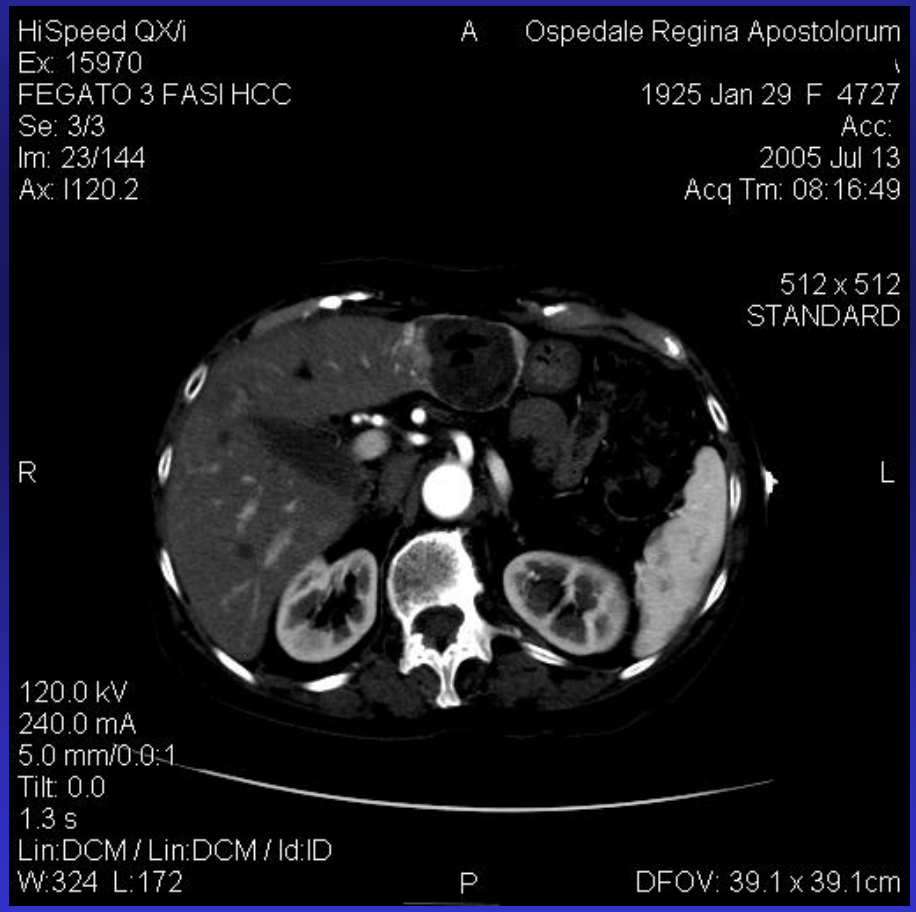


Laser Ablation (multifiber technique) cytoreduction

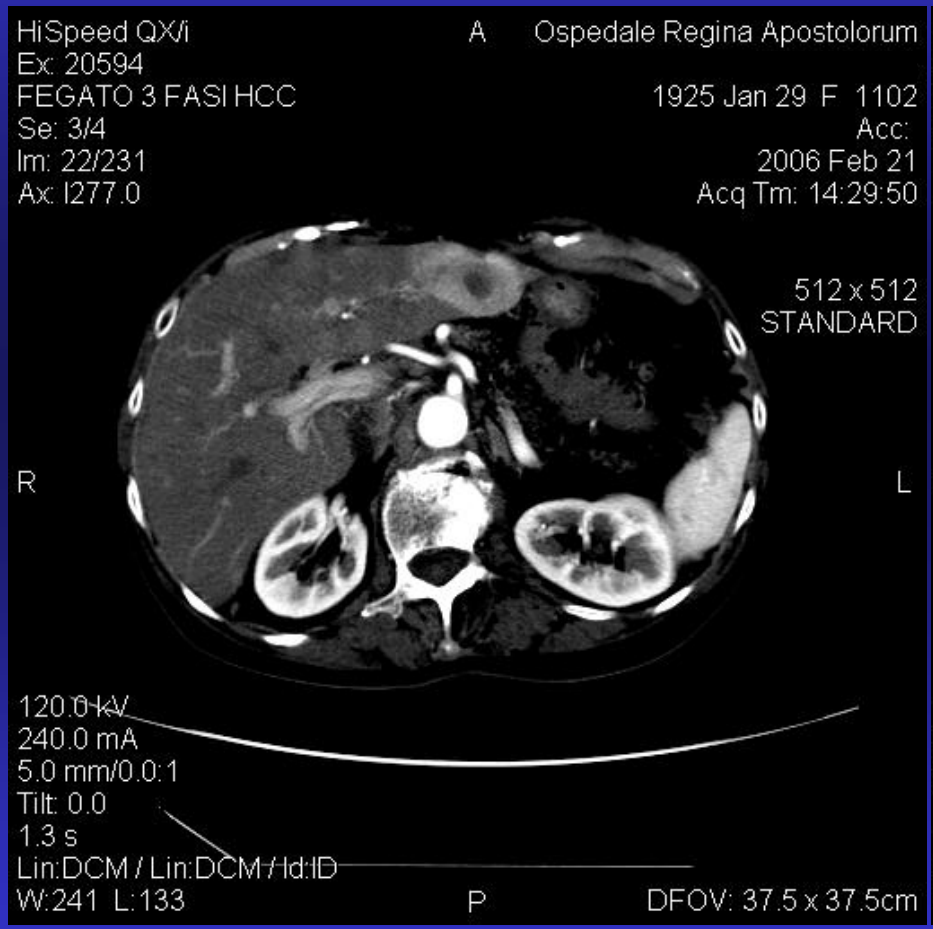


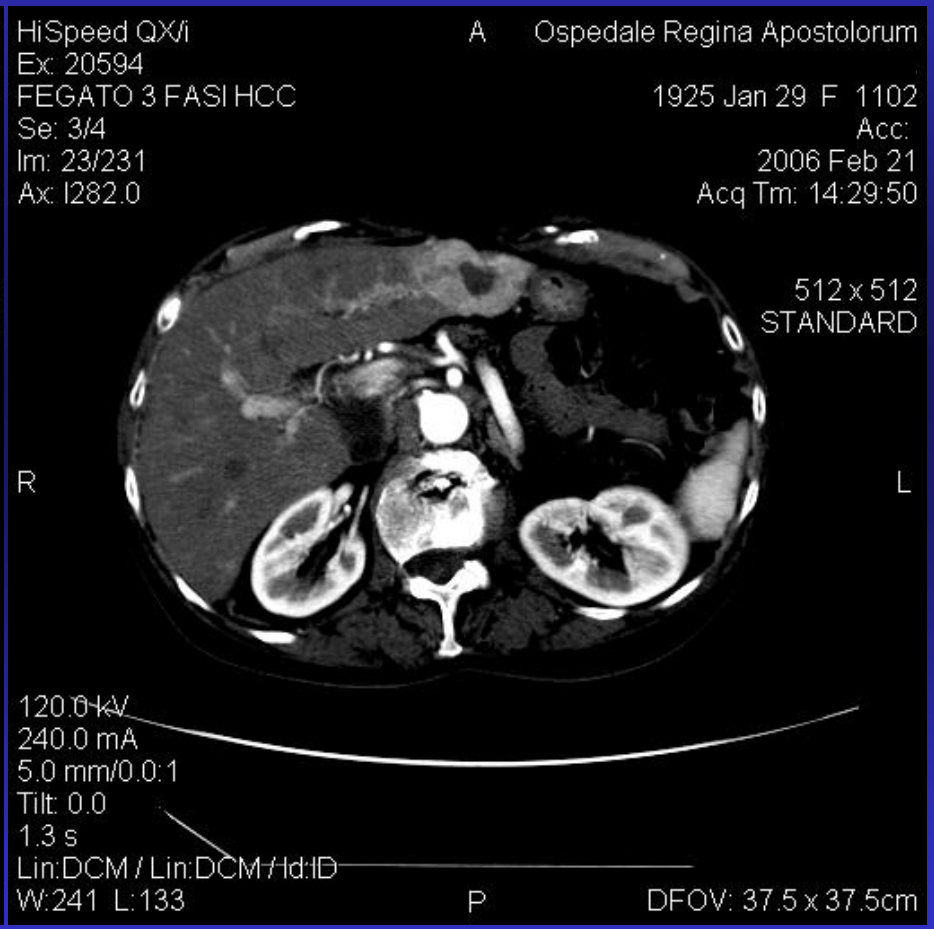
Laser Ablation (multifiber technique) cytoreduction



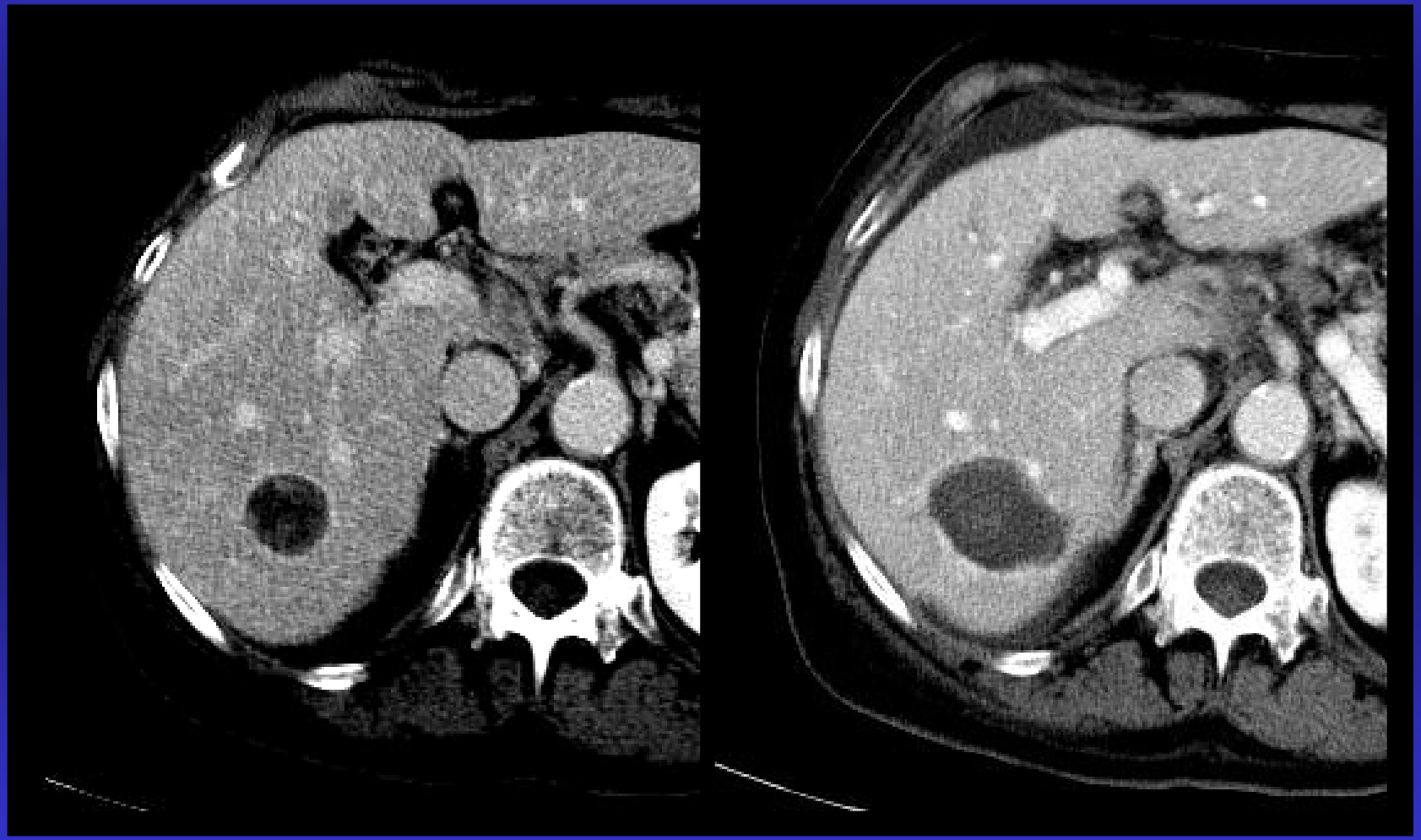


Laser Ablation (multifiber technique) cytoreduction

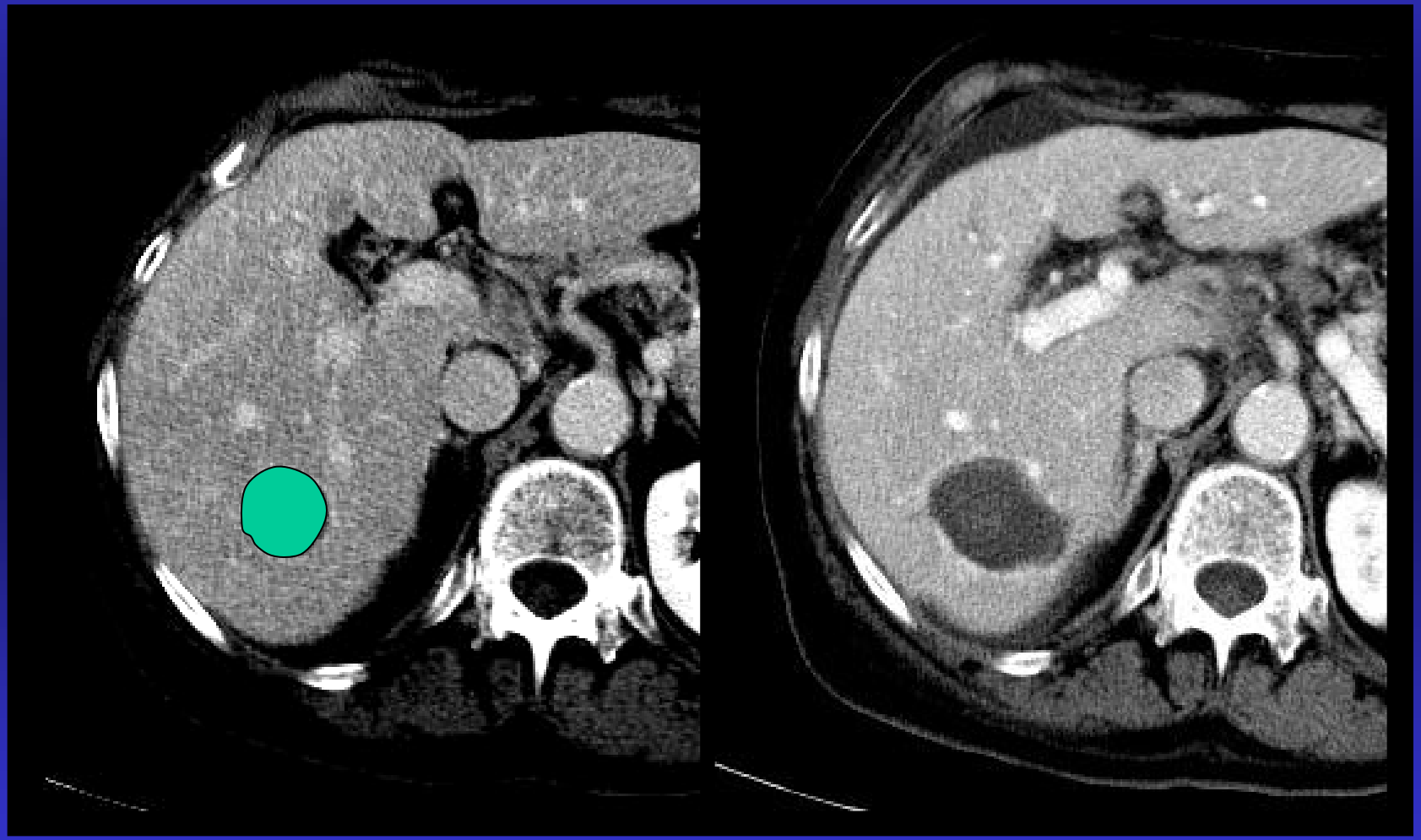




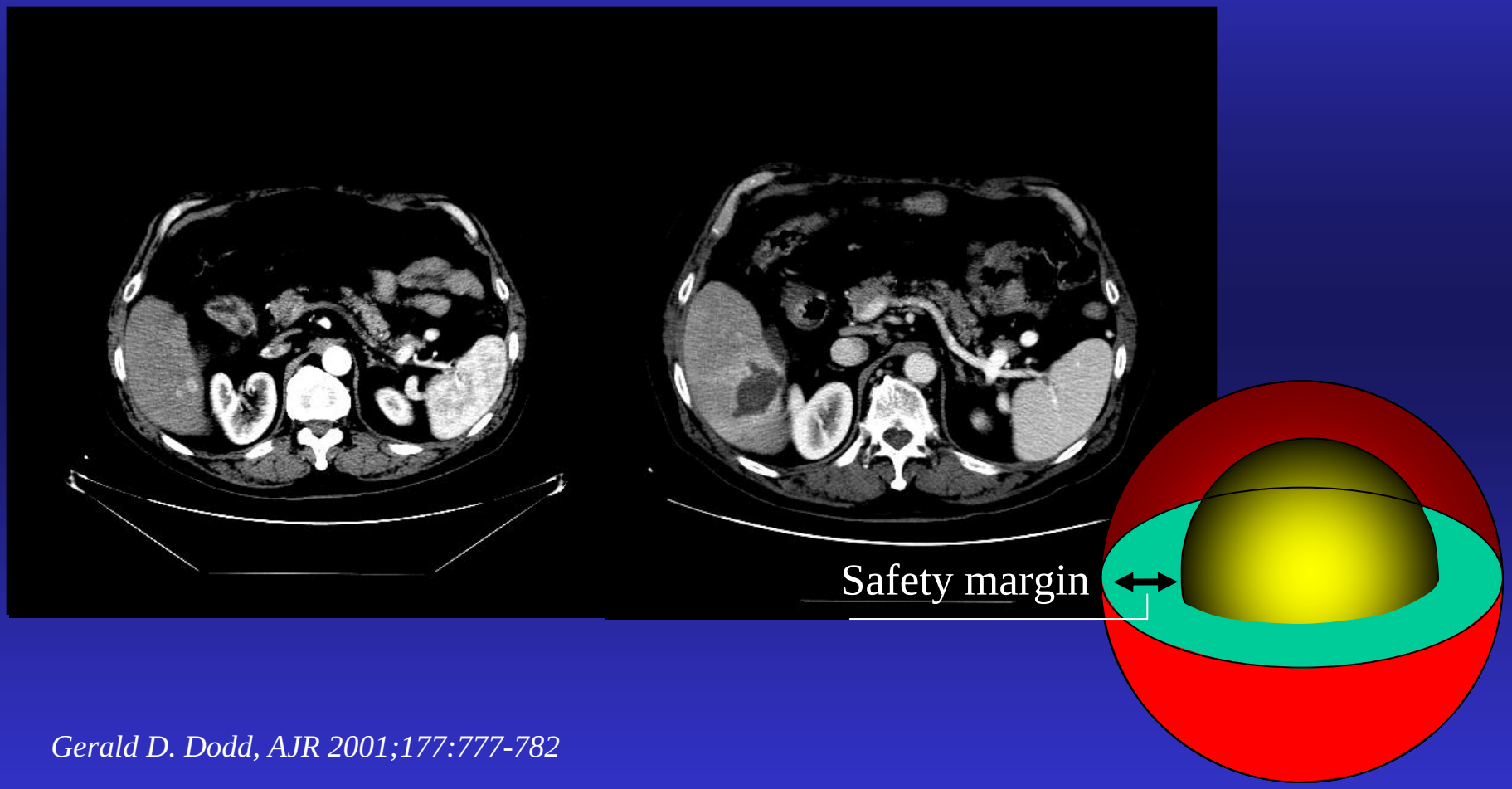
Laser Ablation (multifiber technique)
curative ablation



Laser Ablation (multifiber technique)
curative ablation



Laser Ablation (multifiber technique) curative ablation



Gerald D. Dodd, AJR 2001;177:777-782

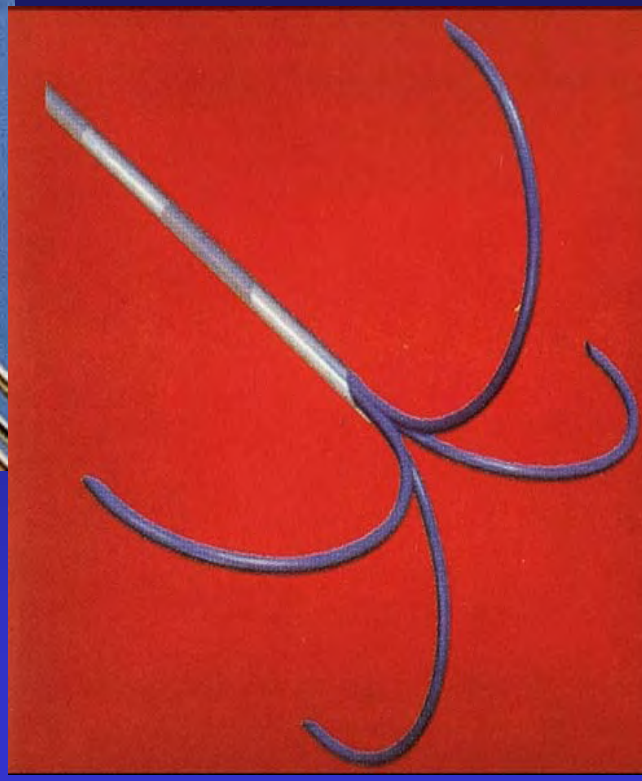
"It has been clearly documented that tumor-free resection margins of less than 1 cm are directly related to increased local hepatic tumor recurrence rate and decreased overall patient survival"

Drawback of Laser Ablation with multifiber technique ?

The apparent complexity of the procedure is paid off by:

- Small caliber of the needles
- The use of single skin entry port under US guidance
- Easy intercostal approch and control over all needles
- Possibility of changing the fibers array adapting it to lesion shape
- Finally, increased accuracy from a statistical perspective……..

Radio**F**requency Ablation



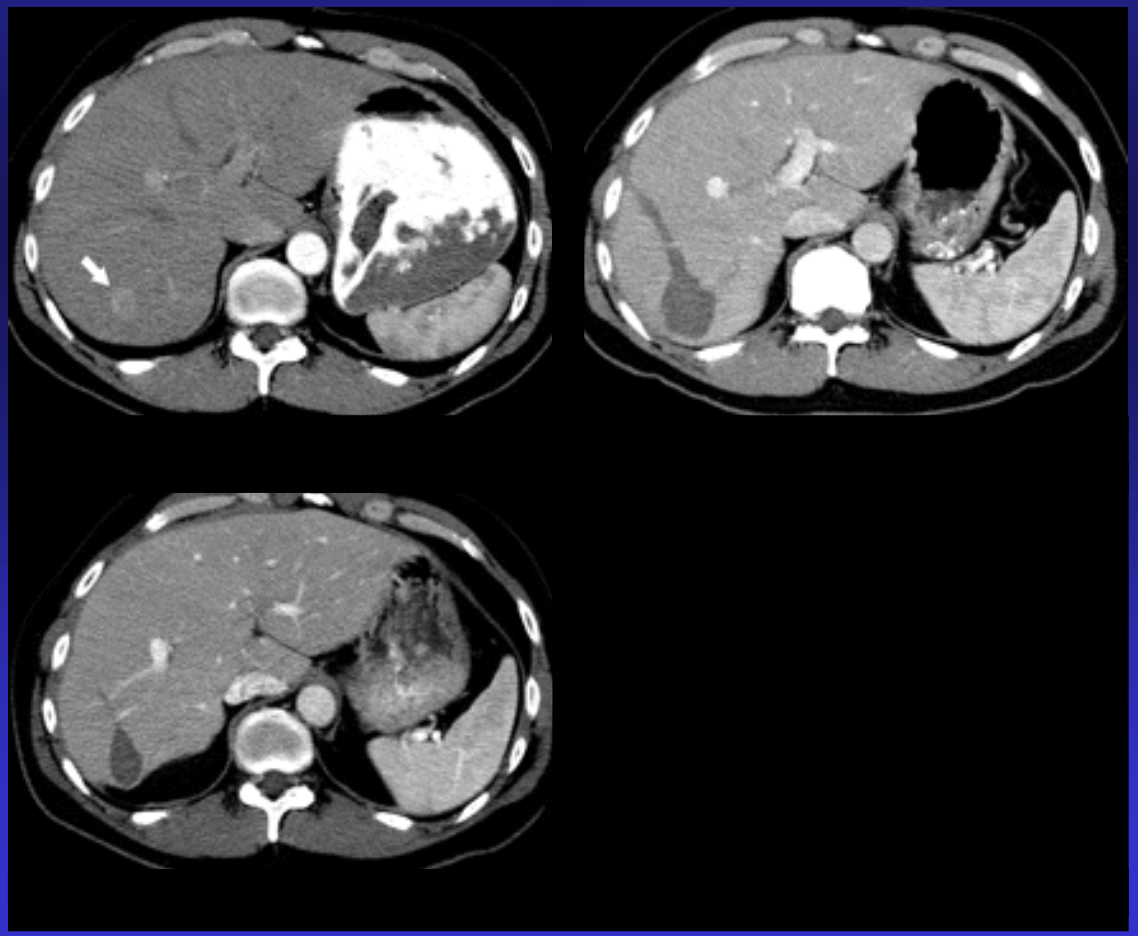
Radio**F**requency Ablation

- Despite the large use of this ablation technique for liver cancer and liver metastases there are limited reports about its use on hepatic metastases from NETs

Eren Berber -World J Surg 2002; 26:985-990
Gillams A -Abdom Imaging 2005; 30:435-441
Henn AR-AJR Am J Roentgenol 2003;181:1005-1010

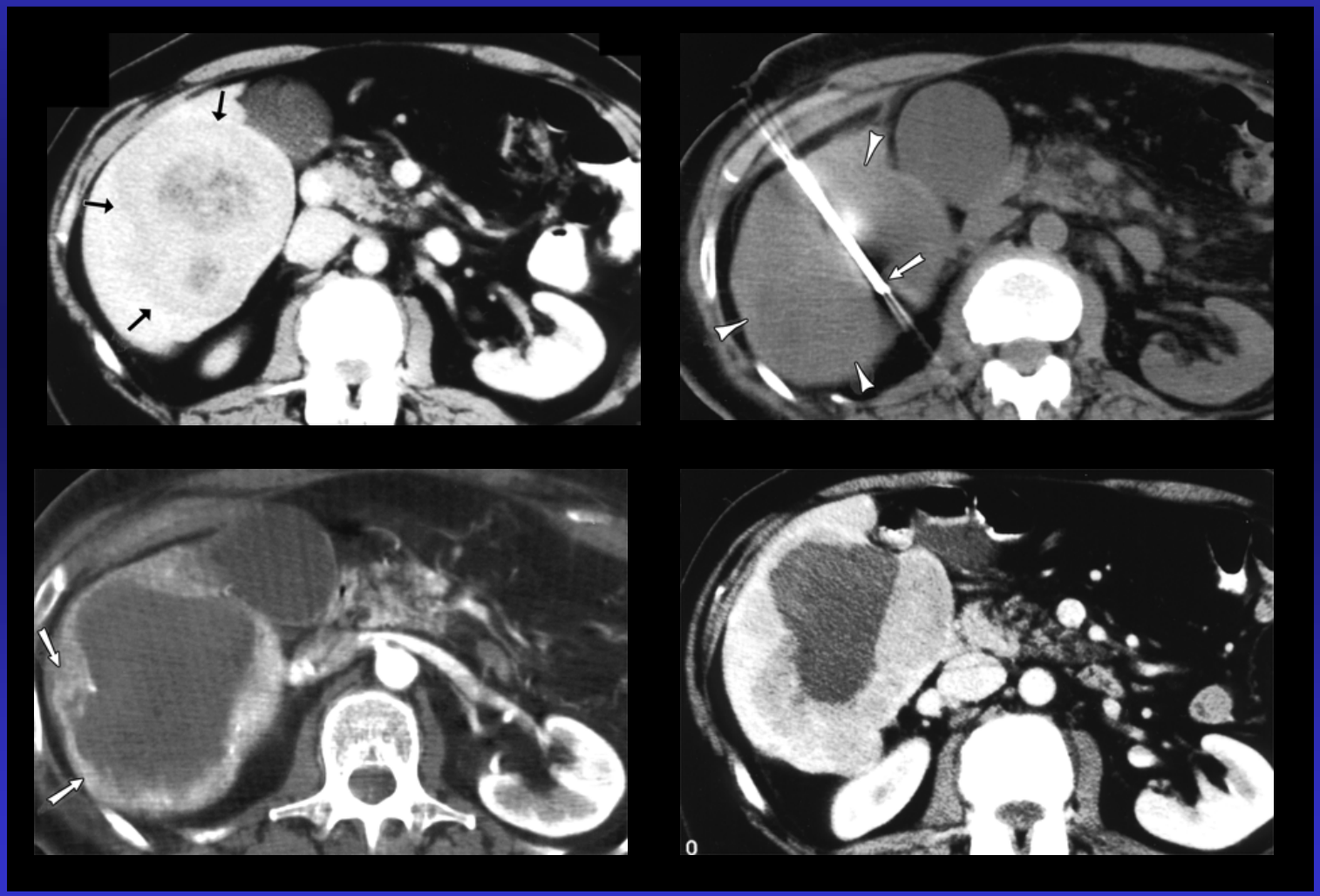
Radio**F**requency Ablation

(curative ablation)



Radio**F**requency Ablation

(palliative ablation)



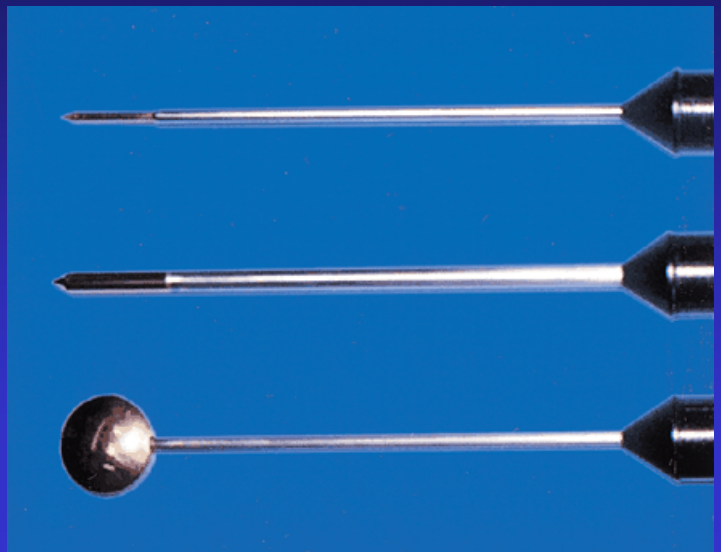
Radio**F**requency Ablation

- In a large majority the intent of the treatment was palliative
- Complete or significant symptom relief has been reported in 70-80% of patients
- No mortality is reported
- Complications were observed in less than 12% of cases

Cryoablation “the iceball”

- Large–diameter applicators frequently requiring intraoperative settings
- Higher rates of complications for large liver tumor especially hemorrhage

Shafir M Am J Surg 1996; 171:27-31
Cozzi PJ Cancer 1995;76:501-509
Sheen AJ Br J Surg 2002;89:1396-1401

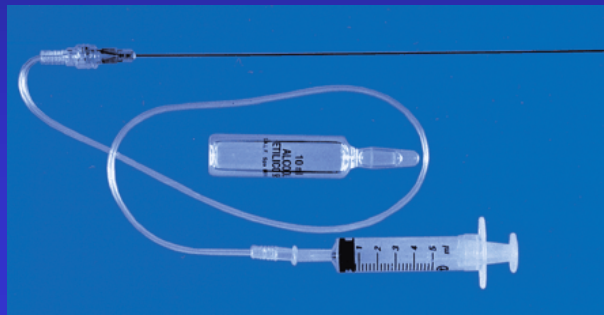


Cryoablation and “the iceball”

- More recently smaller caliber applicators has become available allowing safer percutaneous approach
- One advantage of cryoablation like Laser ablation is MRI compatibility that allows a real time monitoring of the ablated area

Percutaneous **E**thanol **A**blation

- Considered the reference treatment for HCCs, PEI has been essentially replaced by other ablation techniques
- In fact PEI demonstrated reduced efficacy on liver metastases
- Today its use is limited to particular conditions (lesion adjacent to vital structures, lesion in difficult location or close to the central bile ducts)



Livraghi T Radiology 1991;179:709-712
Atwell TD Cardiovasc Intervent Radiol 2005;28:409-421
Livraghi T Radiology 1999;210:655-661
Lencioni R Radiology 2003;228:235-240

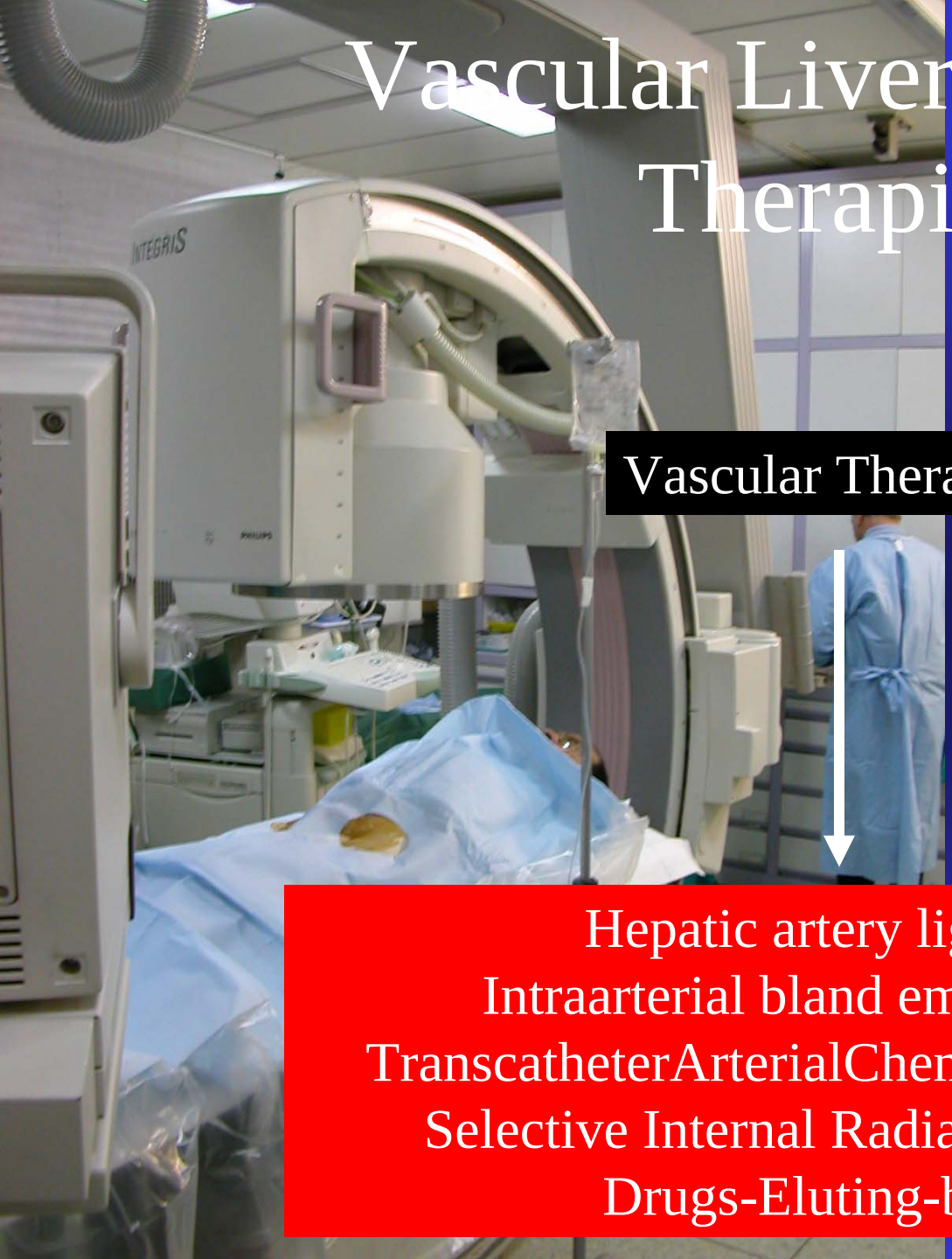
Ablation Therapies: results

- Local control for lesion smaller than 3.5 cm is reported in 96% of cases
- Are safe and efficient with only minor complications
- Are repeatable
- May be performed percutaneously and intraoperatively; this may expand the indications for liver resection.

Ablation Therapies: Take-home points

- In the case of small liver metastases Percutaneous Ablation Techniques (PATs) are expected to obtain results similar to curative liver resection probably with lower morbidity and mortality
- Percutaneous treatments can be preferred to surgery for cytoreduction with some exemption

Vascular Liver Directed Therapies

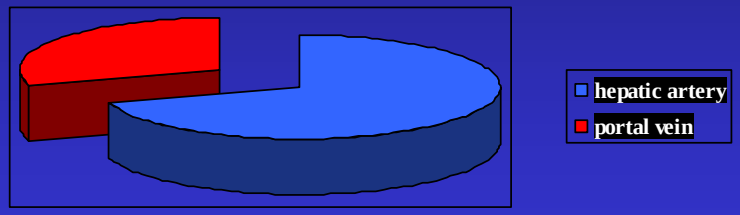


Vascular Therapies

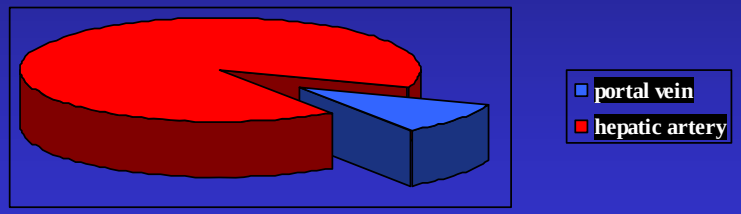
Hepatic artery ligation
Intraarterial bland embolization
TranscatheterArterialChemoEmbolization
Selective Internal Radiation Therapy
Drugs-Eluting-beads

Rational for vascular Therapies

- Liver vascular supply depends on portal vein (70%) and hepatic artery (30%)
- Carcinoid mets vascularity originates mainly from hepatic artery (90%)



Liver vascular supply



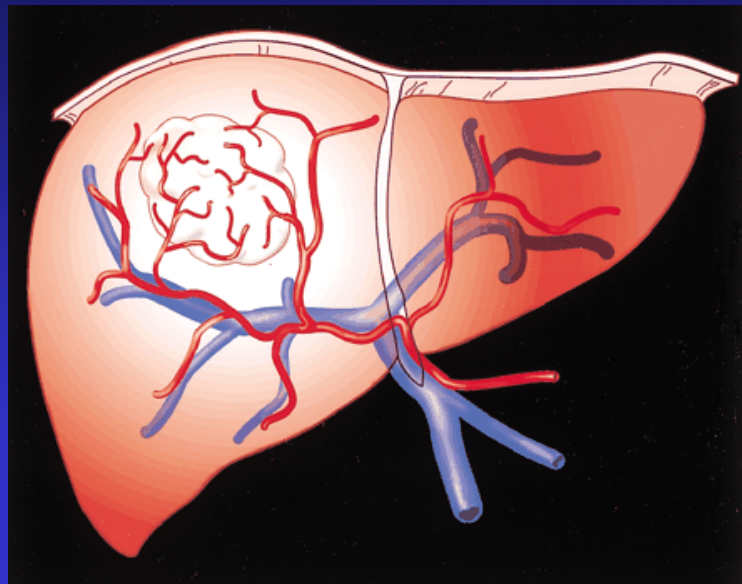
NETs metastases vascular supply

Rational for vascular Therapies

- Several reports have established that induction of tumor ischemia can reduce hormone levels, palliate symptoms and reduce tumor burden

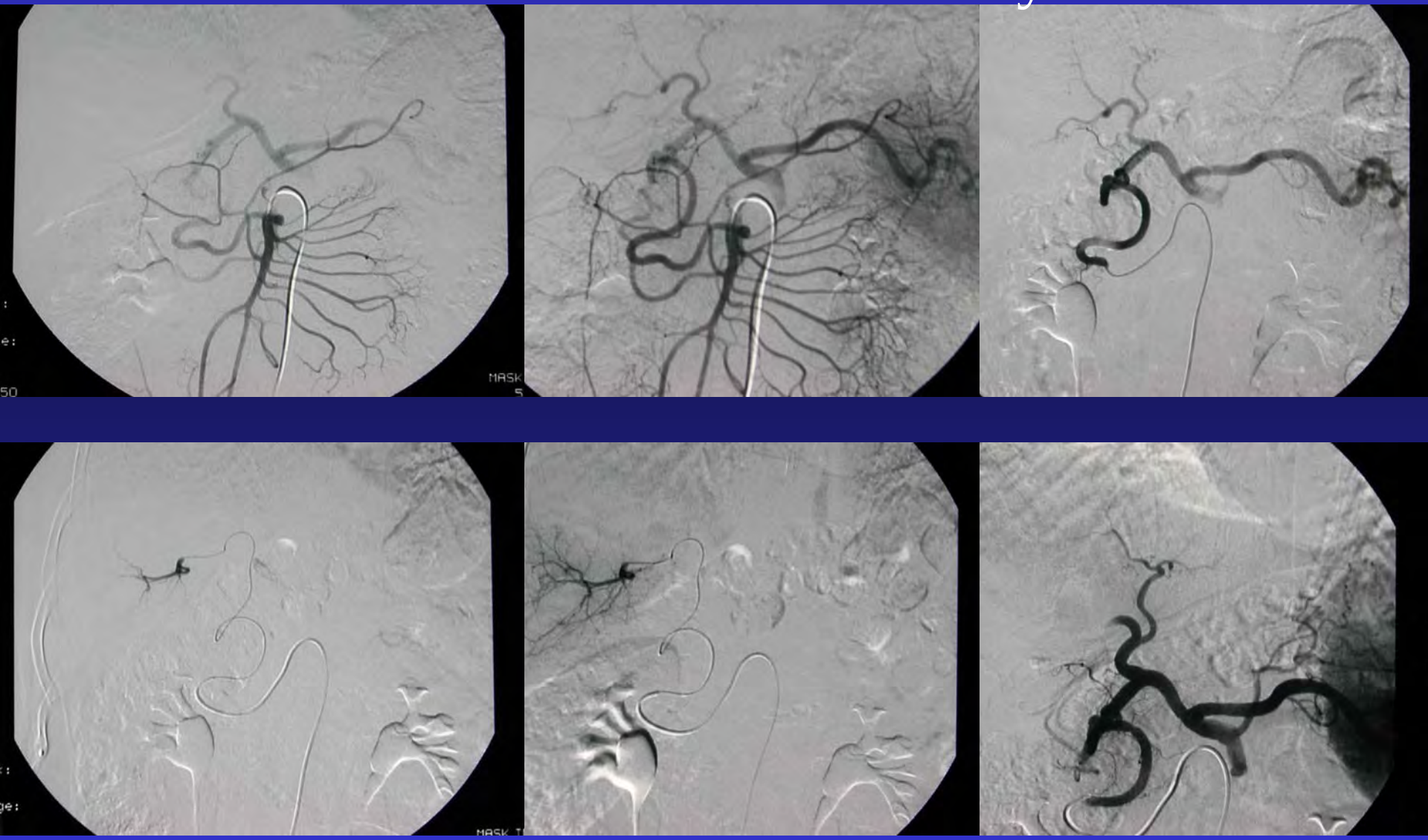
Vascular Therapies: drawbacks

- Collateralization of arterial supply
- Variable arterial anatomy
- Increase of tumor aggressiveness (upregulation of angioneogenesis factors ?)
- Vessel stricture or dissection preventing further treatments



Vascular Therapies: drawbacks

Variable arterial anatomy



Rational for TACE over TAE

- Increased efficacy of local delivered chemotherapy (increased concentration and exposure time)
- Enhanced biological effects of chemotherapy by hypoxia (doxorubicin, Mitomicin C, Streptozocin)

TACE over TAE: evidence based?

- It is unclear whether chemoembolization offers any therapeutic advantage over bland embolization
- No consensus on which chemotherapeutic agent or association have to be used
- There are some evidences that TACE obtains better results on mets from islet cell tumor

TACE and TAE: indications

- Symptoms related to hormonal excess
- Symptoms related to tumor bulk
- Rapid progression of liver disease

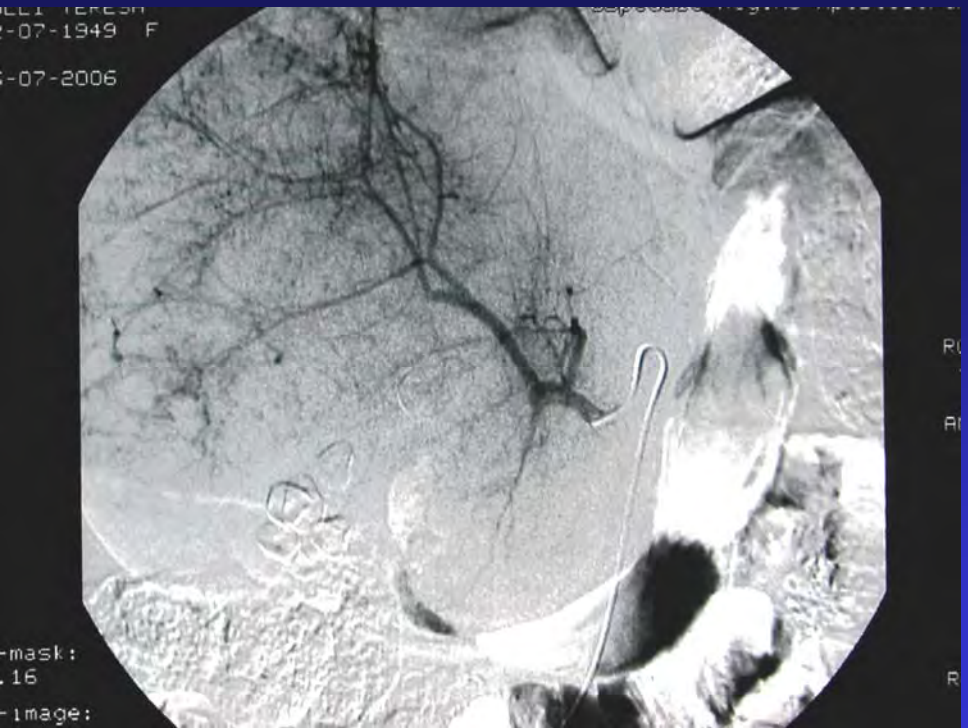
TACE and TAE: When to perform it?

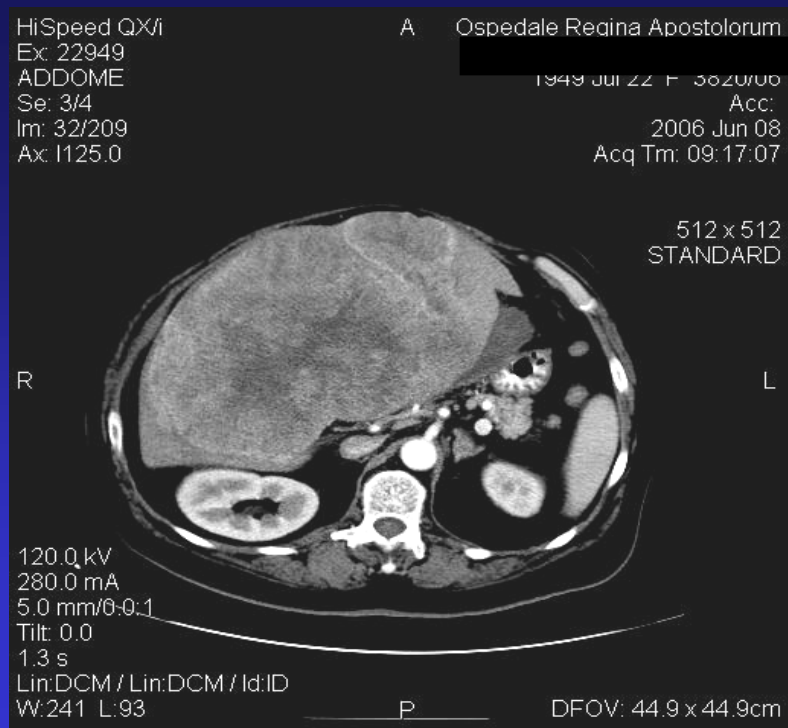
- Some authors advocate an early use of TACE
- TACE performed before systemic treatment (IFN) can enhance tumor response (RR 86% vs 42%)
- “Late” embolization is recognized to be effective

Hanssen LE Acta Oncol 1989;28:439-443
Eriksson BK Cancer 1998;83:2293-2301

TACE and TAE: What's the maximum liver involvement admitted ?

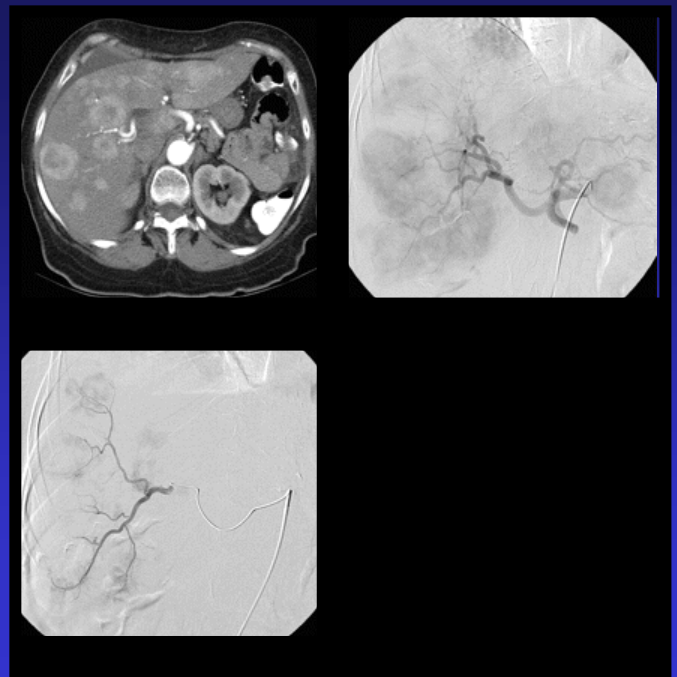
- A liver involvement > 50% has been used as exclusion criteria in many reports





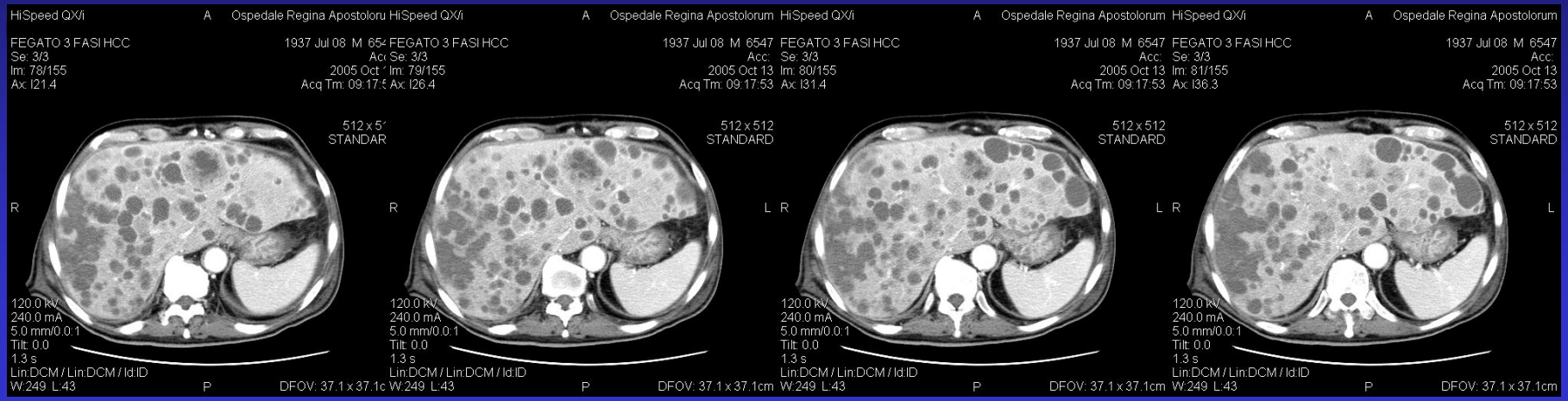
TACE and TAE: What's the maximum liver involvement admitted

- High mortality rate is reported for patients with >50% liver involvement
- Radiologic response rate is greater in patients with liver involvement <50%



TACE and TAE: how much of the liver should be embolized?

- Embolization of the whole liver in a single session should be avoided
- To avoid liver failure in patients with extensive disease (>75%) only a small portion of liver lobe should be embolized during each session



TACE and TAE: results

- Few studies with small number of patients are available from the last years literature
- Reported results are variable
- Reported OS 83% at 5 years to 58 % at 10 years
- Relief of symptoms for 4-18 months is reported

TACE and TAE: complications

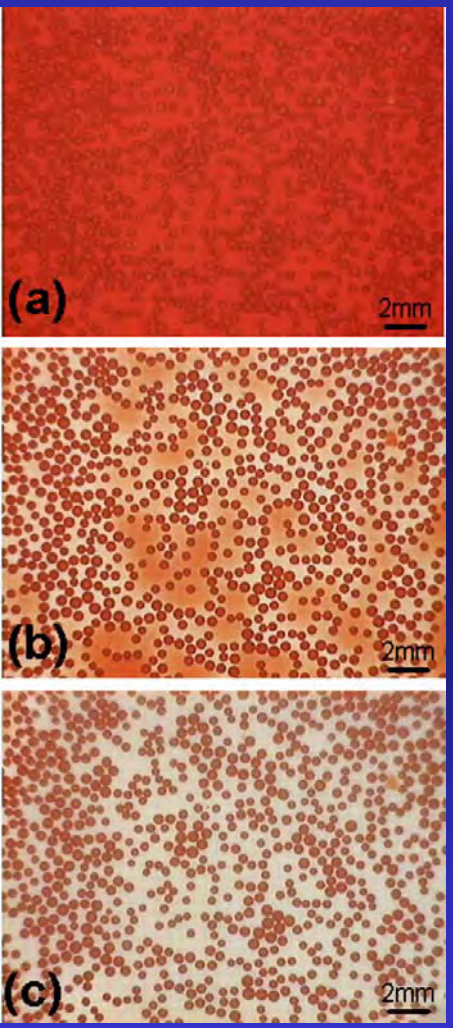
- Despite selective embolization there may occur:

  a) carcinoid crisis or other symptoms of acute hormone release (11-12%)

  b) liver failure (4% mortality)

  c) tumor lysis syndrome (postembolic syndrome) in 86% of cases

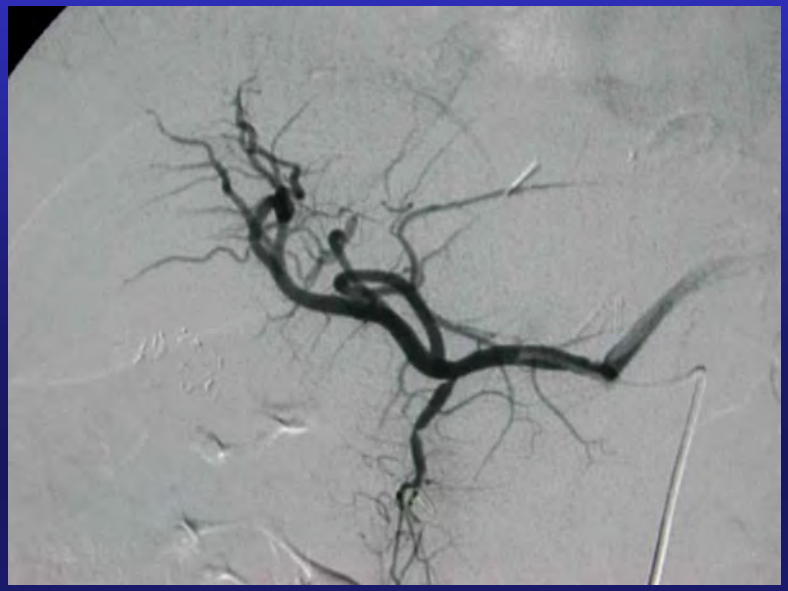
Transcatheter **A**rterial **C**hemo**E**mbolization (**TACE**) with Drug Eluting Beads (Precision TACE)

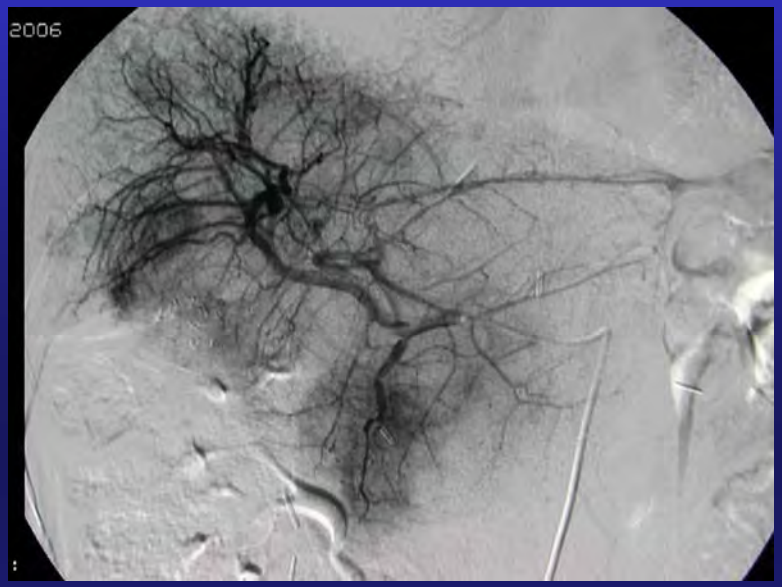


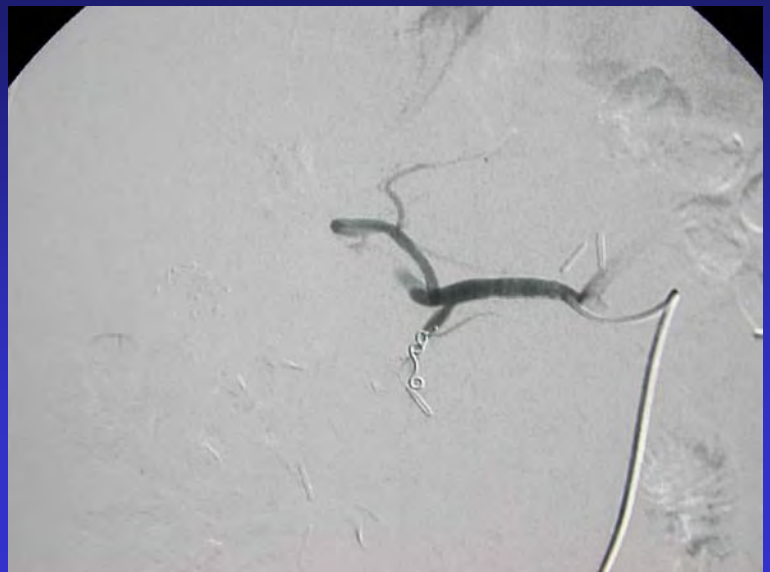
- It consists of injecting drug loaded beads in the hepatic vasculature
- It represents an evolution of standard TACE
- drug elution is controlled and sustained unlike the rapid separation of the drug from lipiodol

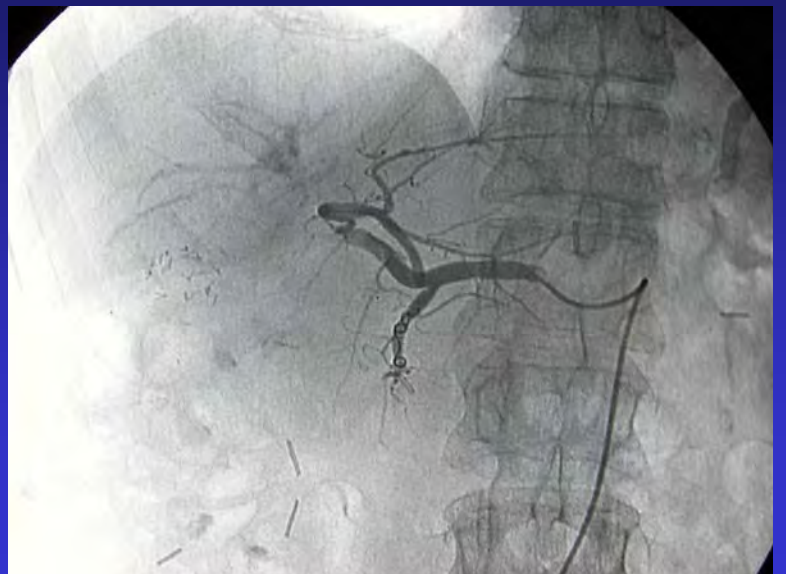
Loading of 300–500-µm beads with 25 mg/mL doxorubicin at 1 minute **(a)**, 10 minutes **(b)**, and 20 minutes **(c)**.

Transcatheter **A**rterial **C**hemo**E**mbolization (**TACE**) with Drug Eluting Beads (Precision TACE)



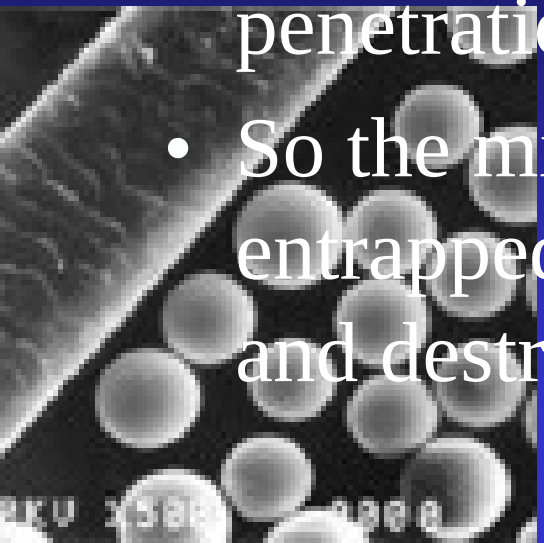






Selective Internal Radiation Therapy
SIRT

- Consists of injecting 90yttrium loaded glass or resin microsphere (20-40 mμ) in the hepatic vascular bed
- ^{90}Yttrium is a pure high energy β emitter (0.9367 MeV) with a mean tissue penetration of 2.5 mm.
- So the microspheres preferentially entrapped in hepatic metastases irradiate and destroy the surrounding cells



SIRT: possible advantages vs TACE

- The treatment produce minimal or bland embolization (↑ O^2 tension increase the efficacy !!!!!)
- Large portion or the entire liver can be treated in a single session with a superselective approaches
- Acute and subacute toxicity appear to be more tolerable than for other hepatic embolization procedures
- Less arterial endothelium toxicity

SIRT: possible disadvantages vs TACE

- The introduction of microsphere into the vasculature of organs other than liver can produce chronic pain, ulceration or bleeding
- Extrahepatic shunting needs to be identified through the injection of Tc-99m MAA into the hepatic artery
- Coiling of collaterals often required
- Hepatic fibrosis

Liver Directed Therapies as a bridge therapy to curative liver resection

- Tumor ablation and/or embolization can be used to improve performance status before resection
- Combined hepatic artery and portal vein embolization can increase number of patients amenable to extended liver resection
- Synchronous and asynchronous curative resection and curative ablation can be used in the same patient

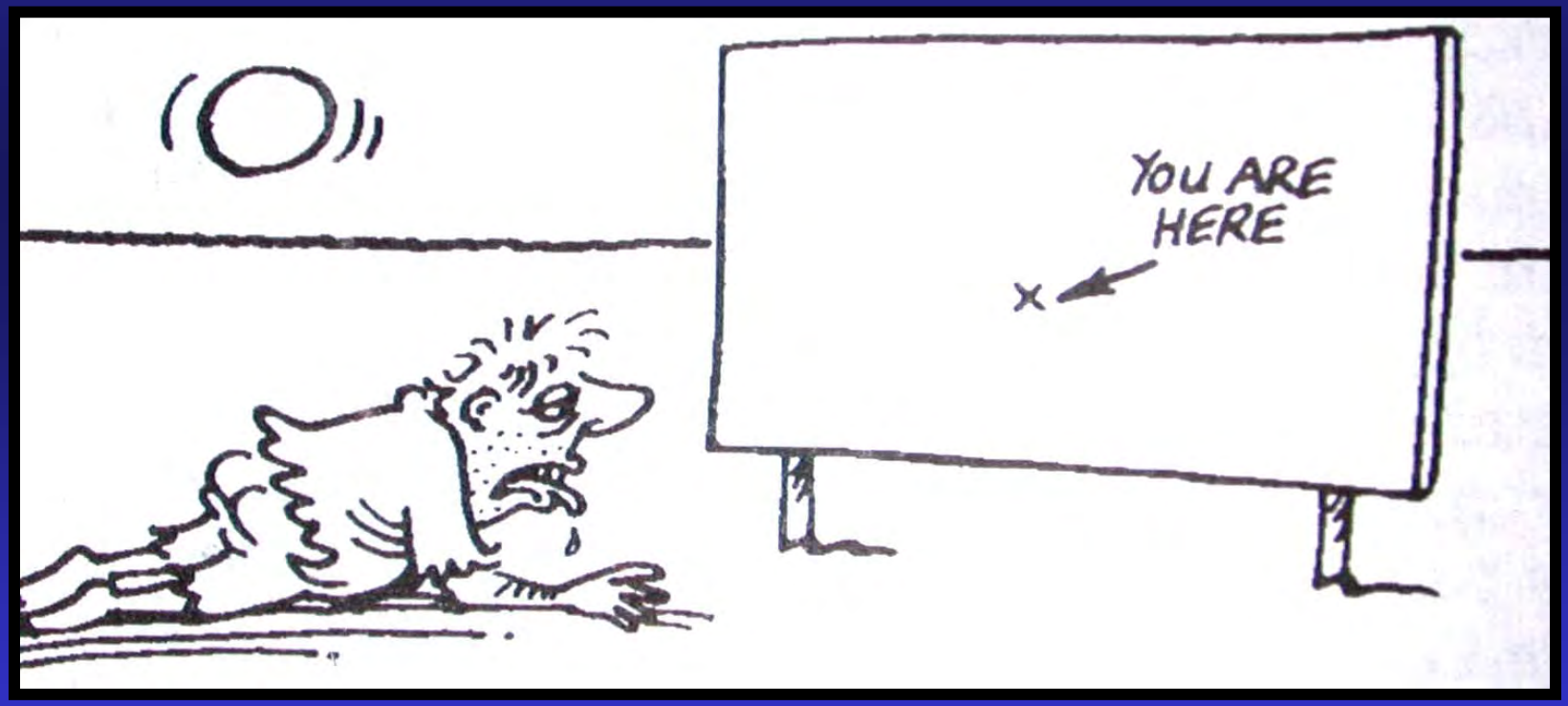
Minimally Invasive Therapies for NETs metastatic to the liver: take home points

- Data suggest that aggressive management of neuroendocrine hepatic metastases does improve Survival and life quality
- Minimally Invasive Treatments increase the patient population eligible for this strategy
- Patients with more than 50% liver involvement may not benefit from an aggressive approach.

Minimally Invasive Therapies for NETs metastatic to the liver: future directions

- Eluting beads with new drugs
- SIRT associated with radiosensitizing chemotherapy
- Laser Ablation with sensitizing nanoparticles
- Combination of novel molecular targeted therapies with liver directed therapies

The End



6th AME National Meeting
Italian Association of Clinical Endocrinologists

3rd Joint Meeting with AACE
American Association of Clinical Endocrinologist

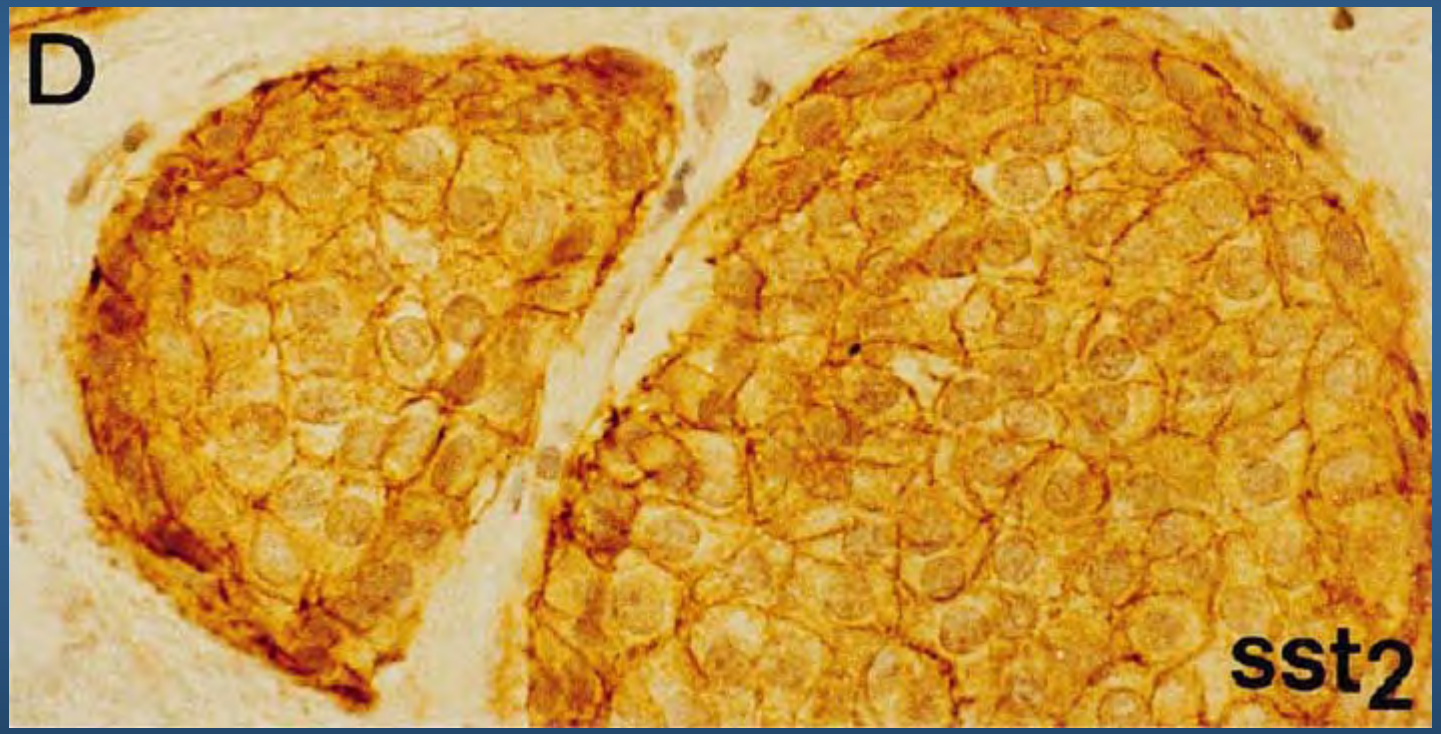
Update in Clinical Endocrinology
Verona, ITALY October 27-29, 2006

NET: treatment of persistent disease

Receptor radionuclide therapy

Lisa Bodei
European Institute of Oncology
Milano, Italy

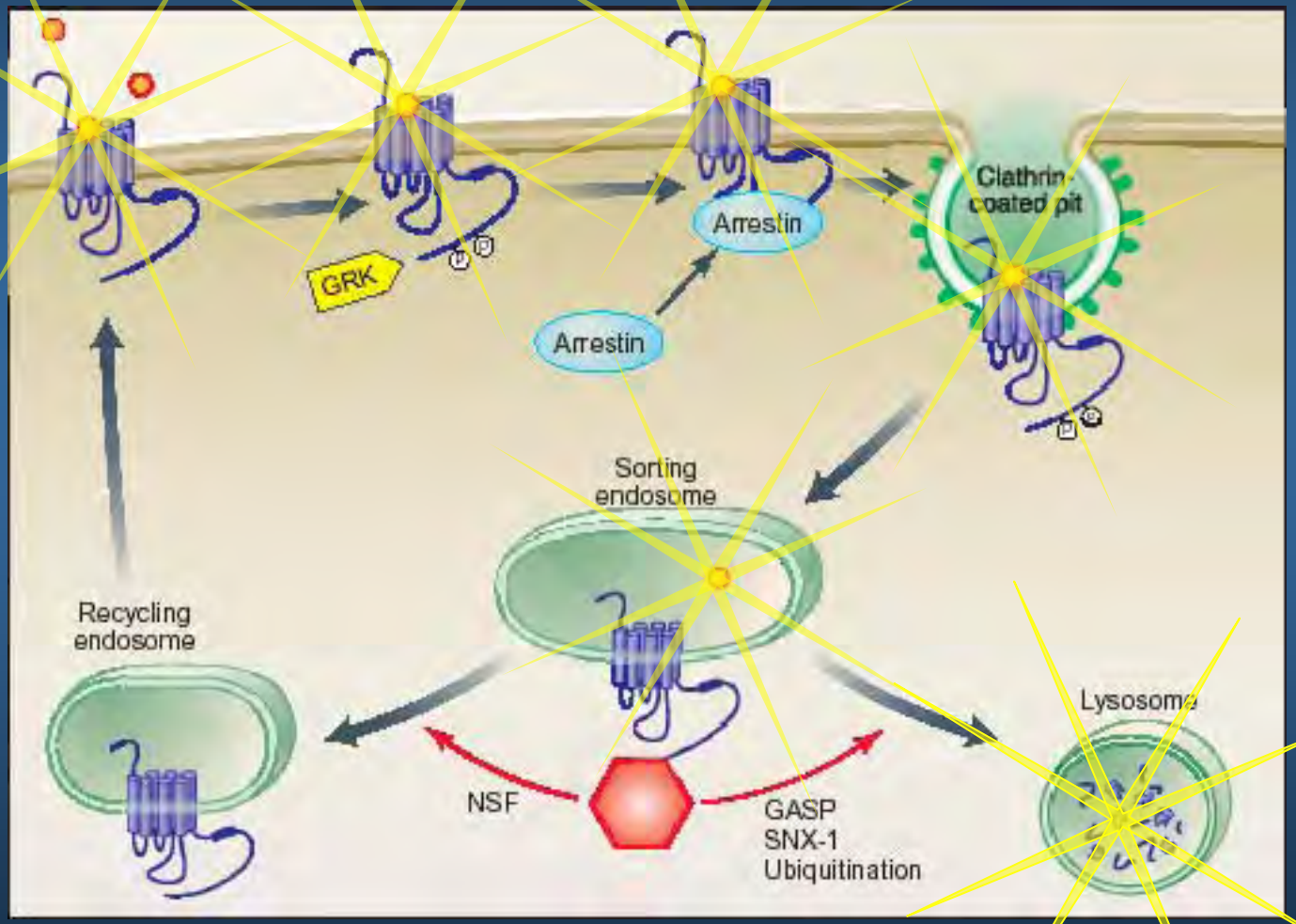
Peptide therapy: rationale basis
receptor over-expression



IHC for sst2 in human gastrinoma

Hofland LJ et al. JCE&M 1999

Peptide therapy: rationale basis
radioligand binding



Adapted from Gray JA and Roth BL, Science 2002

Current peptides

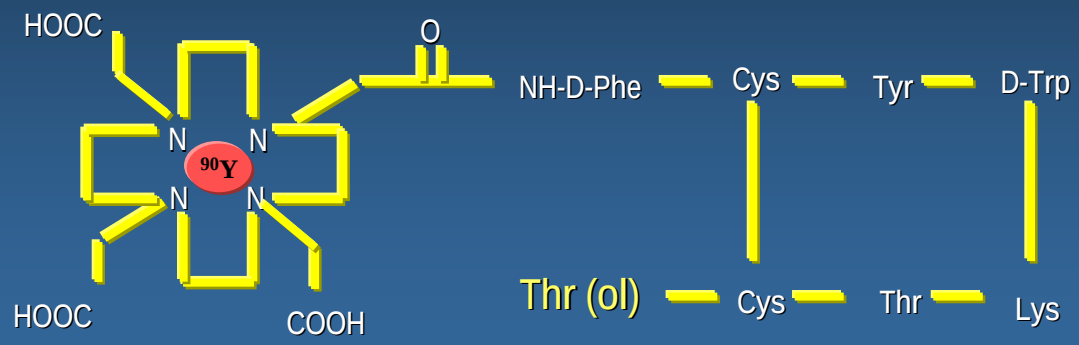
Peptide receptor	Radioligands used in humans for therapy	Radioligands in development
Somatostatin		Carbohydrated derivatives and other biodistribution modifiers
sst2	^{111}In-DTPAOC ^{90}Y-DOTATOC ^{177}Lu-DOTATATE	
sst2, sst5	^{90}Y-DOTA-lanreotide	
sst2, sst3, sst5		DOTANOC DOTABOC DOTANOCate DOTABOCate TETA-octreotide
Bombesin		
GRP-R	^{177}Lu-BNN8 analog	Bombesin analogs, including BBN8 analog, DOTA-[Lys^3]bombesin, and DOTA-PEG-BN(7–14)
Cholecystokinin		
CCK2		Minigastrin; CCK analog
Oxytocin		DOTALVT

Cremonesi M, JNM 2006

PRRT with SSA

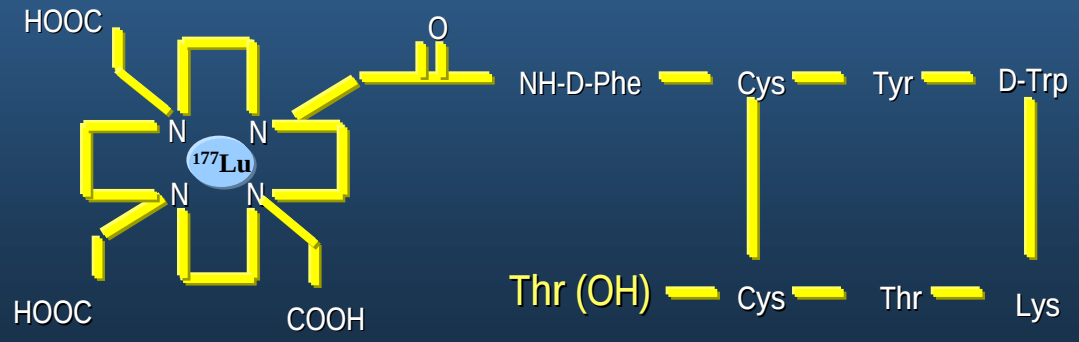
Radiopeptides

^{90}Y-DOTATOC



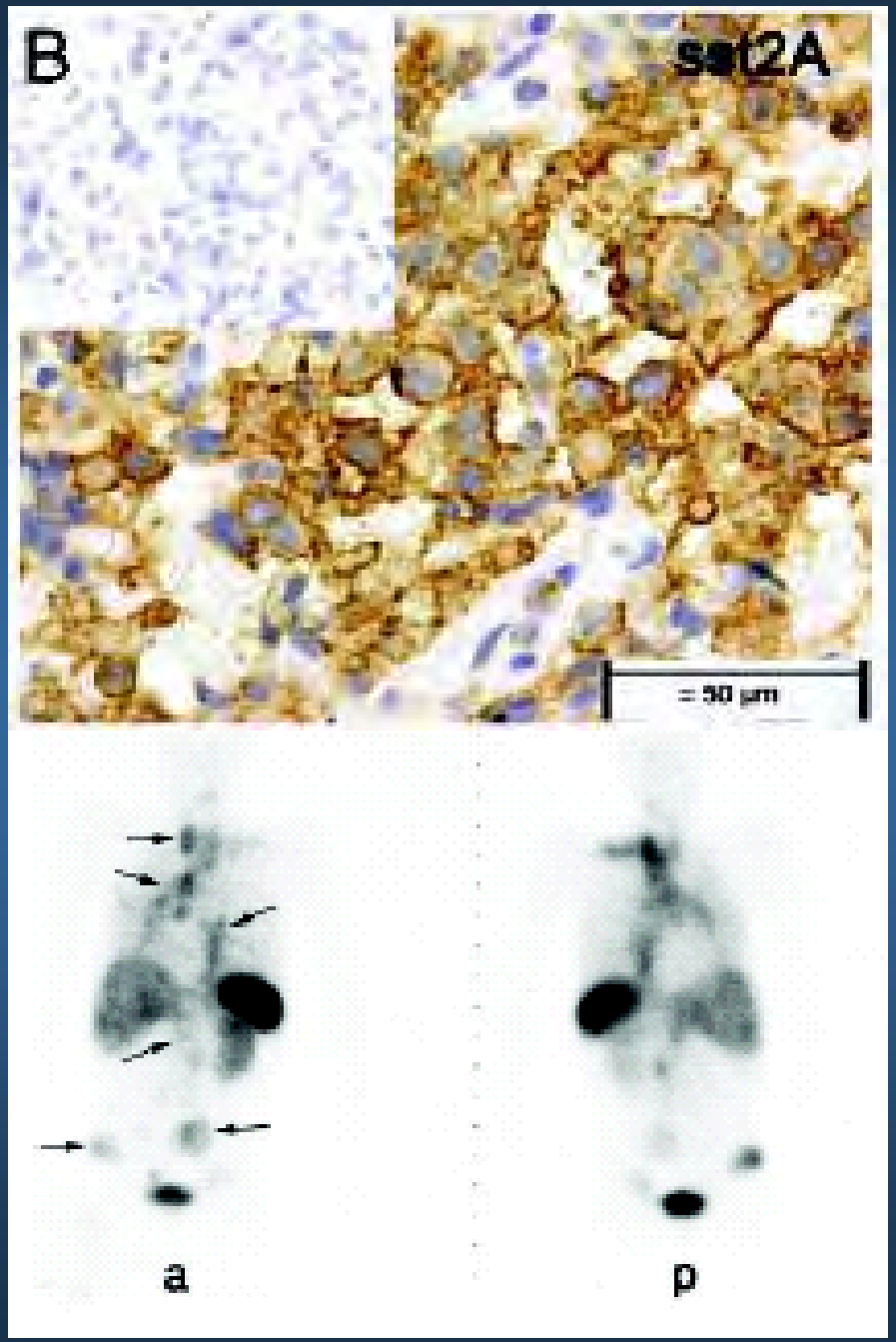
characteristics ^{90}Y	
beta- energy	2.3 MeV
range	R_{max} 11 mm
half-life	64 hrs

^{177}Lu-DOTATATE



characteristics ^{177}Lu	
beta- energy	0.5 MeV
range	R_{max} 2 mm
gamma 1 energy	113 KeV (6%)
gamma 2 energy	208 KeV (11%)
half-life	6.7 days

Which tumors to be treated

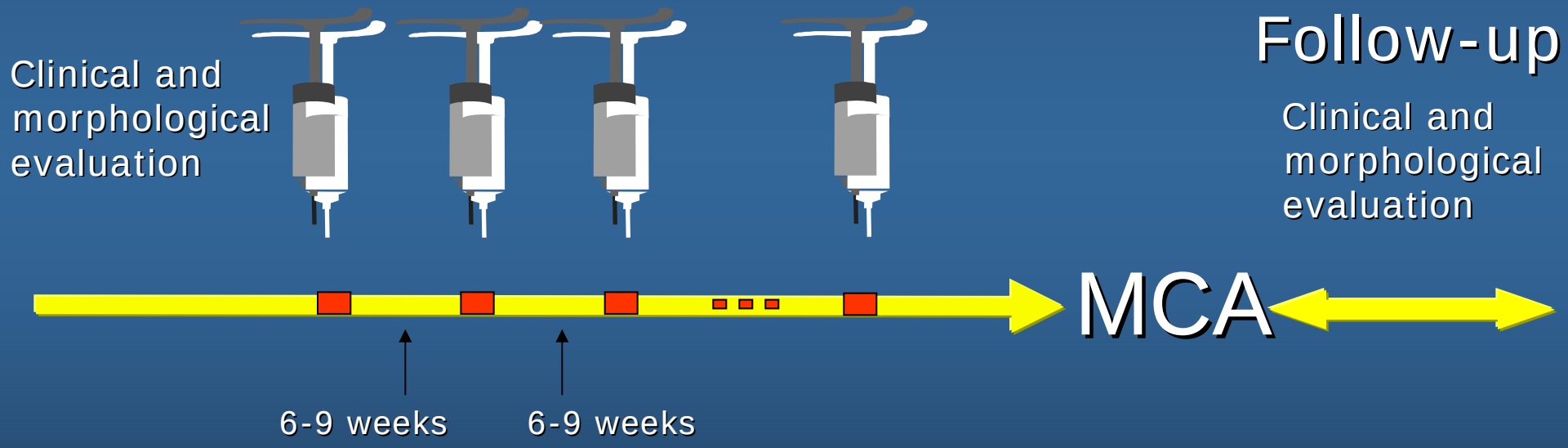


High receptor density

Mundschenk J et al. JCE&M 2003

How PRRT is performed

Systemic administration



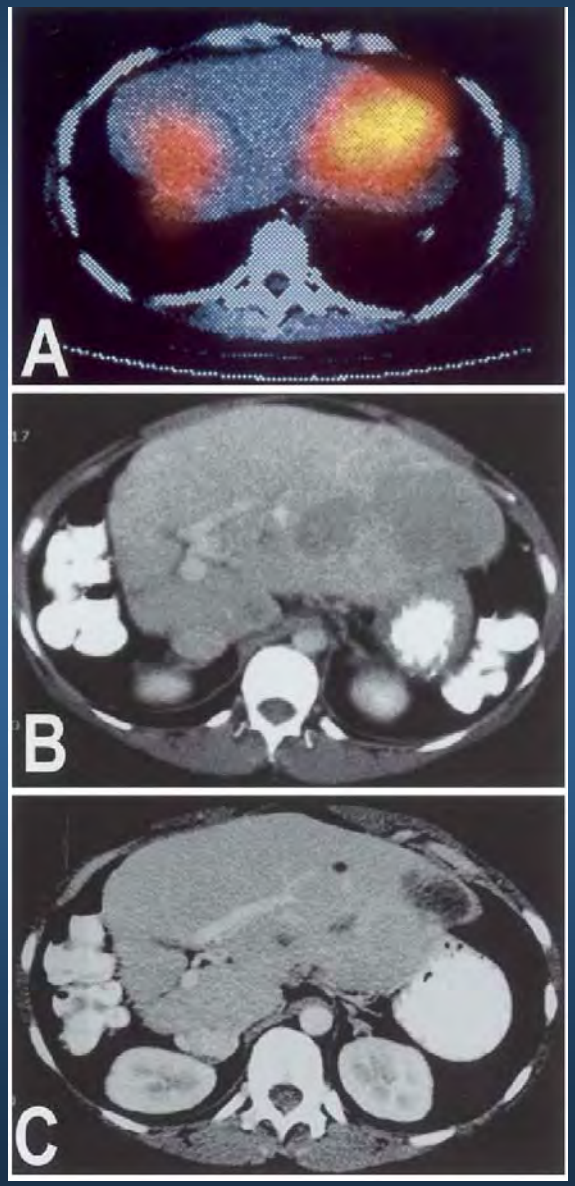
EFFICACY

General results in GEP tumors: [^{90}Y-DOTA^{0},Tyr^{3}]-octreotide

Center (reference)	Ligand	No. of patients	Tumor response					
			CR*	PR*	MR*	SD*	PD*	CR + PR†
Rotterdam (*2*)	[^{111}In-DTPA^{0}]octreotide	26	0	0	5 (19)	11 (42)	10 (38)	0
New Orleans (*3*)	[^{111}In-DTPA^{0}]octreotide	26	0	2 (8)	NA	21 (81)	3 (12)	8
Milan (*10*)	[^{90}Y-DOTA^{0}, Tyr^{3}]octreotide	21	0	6 (29)	NA	11 (52)	4 (19)	29
Basel (*5,6*)	[^{90}Y-DOTA^{0}, Tyr^{3}]octreotide	74	3 (4)	15 (20)	NA	48 (65)	8 (11)	24
Basel (*7*)	[^{90}Y-DOTA^{0}, Tyr^{3}]octreotide	33	2 (6)	9 (27)	NA	19 (57)	3 (9)	33
Rotterdam (*11*)	[^{90}Y-DOTA^{0}, Tyr^{3}]octreotide	54	0	4 (7)	7 (13)	33 (61)	10 (19)	7
Rotterdam (*18*)	[^{177}Lu-DOTA^{0}, Tyr^{3}]octreotate	76	1 (1)	22 (29)	9 (12)	30 (39)	14 (18)	30

Kwekkeboom DJ et al. J Nucl Med 2005

[^{90}Y-DOTA^{0},Tyr^{3}]-octreotide: response



Bodei L et al. Eur J Nucl Med 2003

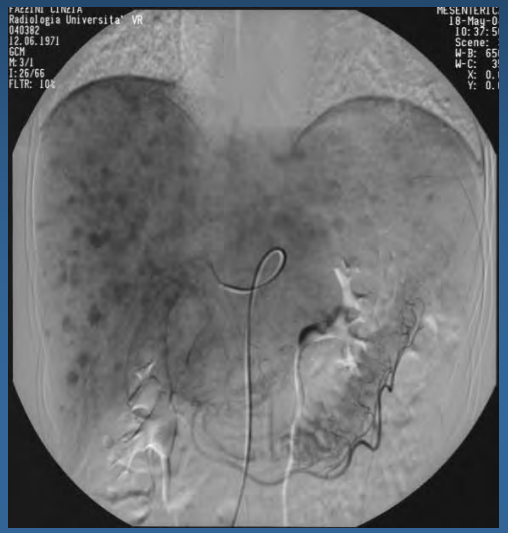
[^{177}Lu-DOTA^{0},Tyr^{3}]-octreotate: results in GEP tumors

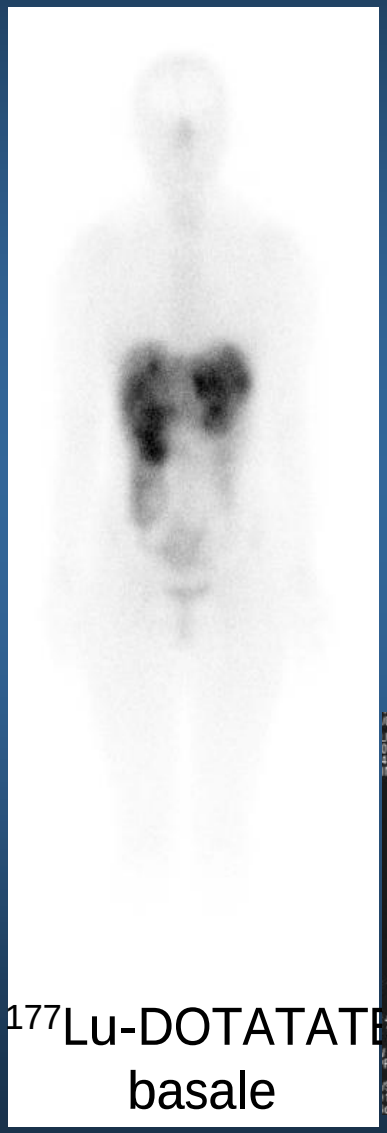
Tumor Type	CR %	PR %	MR %	SD %	PD %	Total Patients (No.)
Carcinoid	—	20	20	42	18	66
NE pancreas	9	22	22	34	13	32
NE unknown origin	—	35	12	24	29	17
Gastrinoma	—	63	25	12	—	8
Insulinoma	—	50	—	—	50	2
Total	2	26	19	35	18	125

Kwekkeboom DJ et al, J Clin Oncol 2005

[^{177}Lu-DOTA^{0},Tyr^{3}]-octreotate objective response

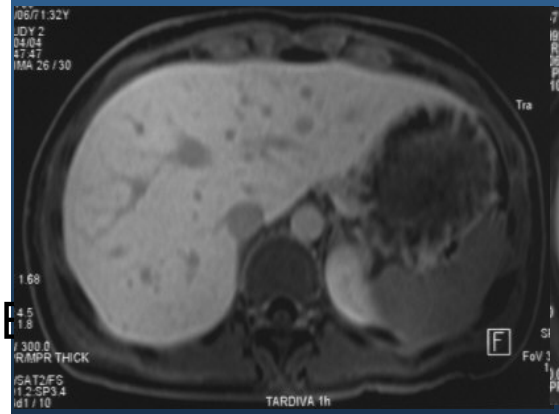
Arteriografia basale



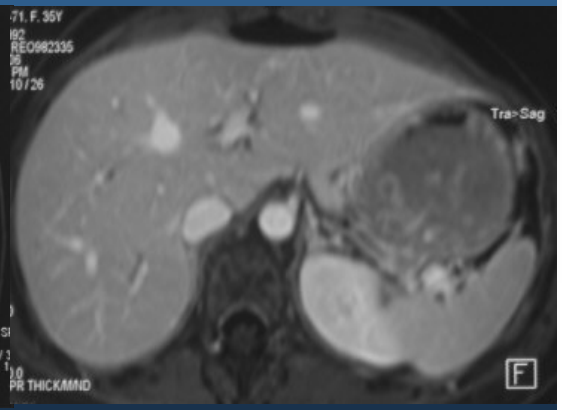


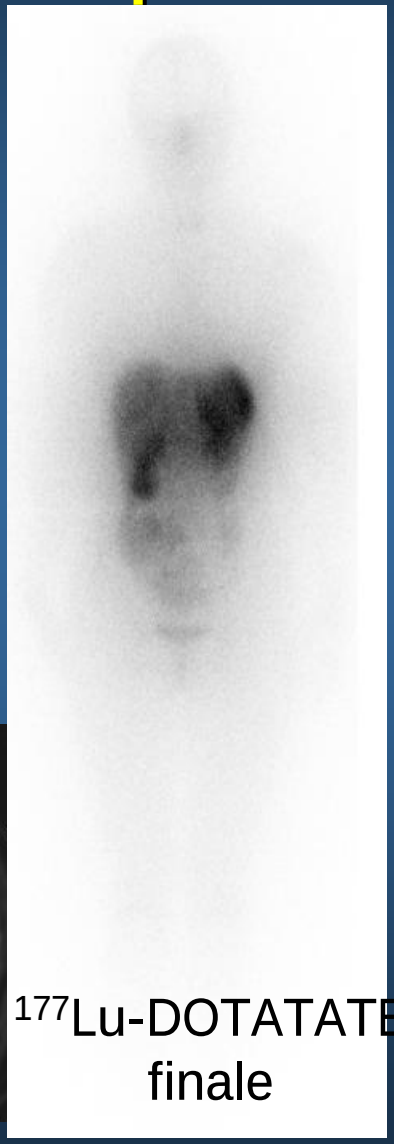
^{177}Lu-DOTATATE basale

RM basale



RM finale





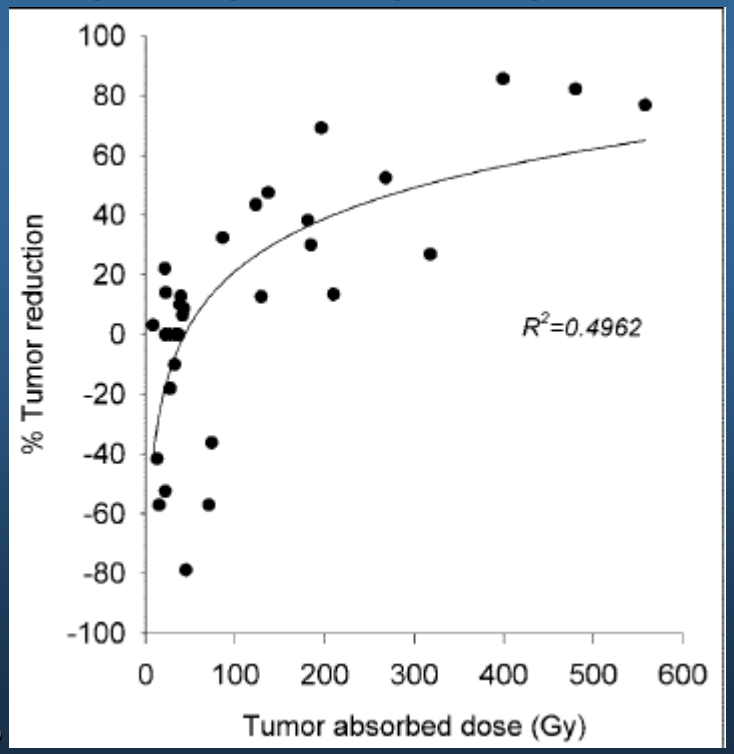
^{177}Lu-DOTATATE finale

EFFICACY: parameters involved

- Radiosensitivity:
  - growth pattern
  - DNA repair
- Radioactivity concentration on tumor

absorbed dose

- Dose-response relationship



Pauwels S et al. J Nucl Med 2005

Radioactivity amount in tumor: T/B ratio

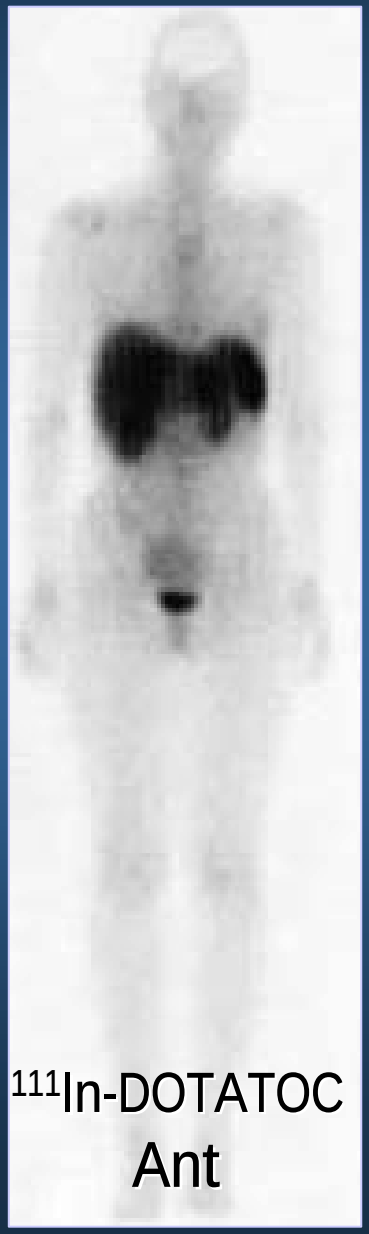
receptor affinity of radiopeptide

Peptides	hsst 1	hsst 2	hsst 3	hsst 4	hsst 5
SS-28	5.2±0.3 (19)	2.7±0.3 (19)	7.7±0.9 (15)	5.6±0.4 (19)	4.0±0.3 (19)
Octreotide	>10,000 (5)	2.0±0.7 (5)	187±55 (3)	>1,000 (4)	22±6 (5)
CH288	23±2 (3)	>10,000 (4)	>1,000 (3)	>10,000 (3)	>1,000 (4)
DTPA-octreotide	>10,000 (6)	12±2 (5)	376±84 (5)	>1,000 (5)	299±50 (6)
In-DTPA-octreotide	>10,000 (5)	22±3.6 (5)	182±13 (5)	>1,000 (5)	237±52 (5)
DOTA-TOC	>10,000 (7)	14±2.6 (6)	880±324 (4)	>1,000 (6)	393±84 (6)
Y-DOTA-TOC	>10,000 (4)	11±1.7 (6)	389±135 (5)	>10,000 (5)	114±29(5)
DOTA-LAN	>10,000 (7)	26±3.4 (6)	771±229 (6)	>10,000 (4)	73±12 (6)
Y-DOTA-LAN	>10,000 (3)	23±5 (4)	290±105 (4)	>10,000 (4)	16±3.4 (4)
DOTA-VAP	>10,000 (3)	29±7 (4)	419±104 (4)	743±190 (3)	80±19 (4)
Y-DOTA-VAP	>10,000 (4)	12±2 (5)	102±25 (5)	778±225 (5)	20±2.3 (5)
DOTA-OC	>10,000 (3)	14±3 (4)	27±9 (4)	>1,000 (4)	103±39 (3)
Y-DOTA-OC	>10,000 (5)	20±2 (5)	27±8 (5)	>10,000 (4)	57±22 (4)
Ga-DOTA-TOC	>10,000 (6)	2.5±0.5 (7)	613 ±140 (7)	>1,000 (6)	73±21 (6)
Ga-DOTA-OC	>10,000 (3)	7.3±1.9 (4)	120±45 (4)	>1,000 (3)	60±14 (4)
DTPA-[Tyr^3]-octreotate	>10,000 (4)	3.9±1 (4)	>10,000 (4)	>1,000 (4)	>1,000 (4)
In-DTPA-[Tyr^3]-octreotate	>10,000 (3)	1.3±0.2 (3)	>10,000 (3)	433±16 (3)	>1,000 (3)
DOTA-[Tyr^3]-octreotate	>10,000 (3)	1.5±0.4 (3)	>1,000 (3)	453±176 (3)	547±160 (3)
Y-DOTA-[Tyr^3]-octreotate	>10,000 (3)	1.6±0.4 (3)	>1,000 (3)	523±239 (3)	187±50 (3)
Ga-DOTA-[Tyr^3]-octreotate	>10,000 (3)	0.2±0.04 (3)	>1,000 (3)	300±140 (3)	377±18 (3)

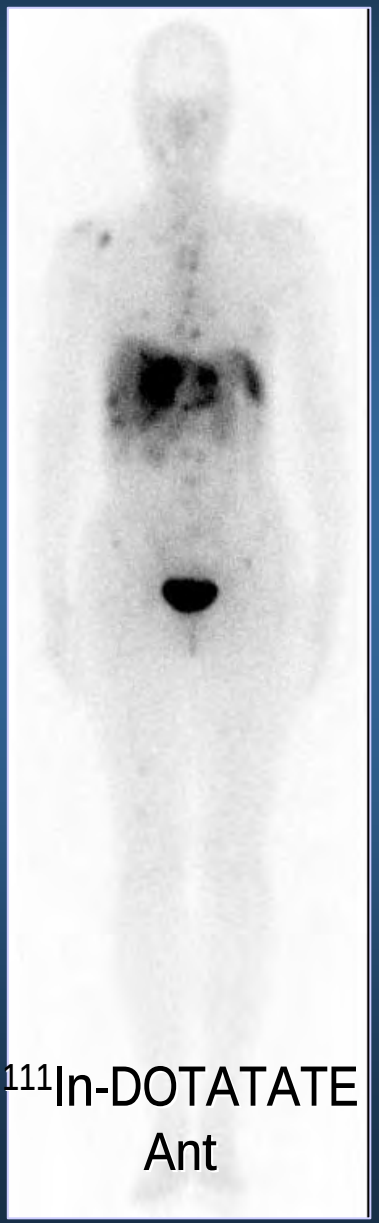
All values are IC_{50}±SEM in n*M*. The number of experiments is in parentheses

Reubi JC et al. Eur J Nucl Med 2000

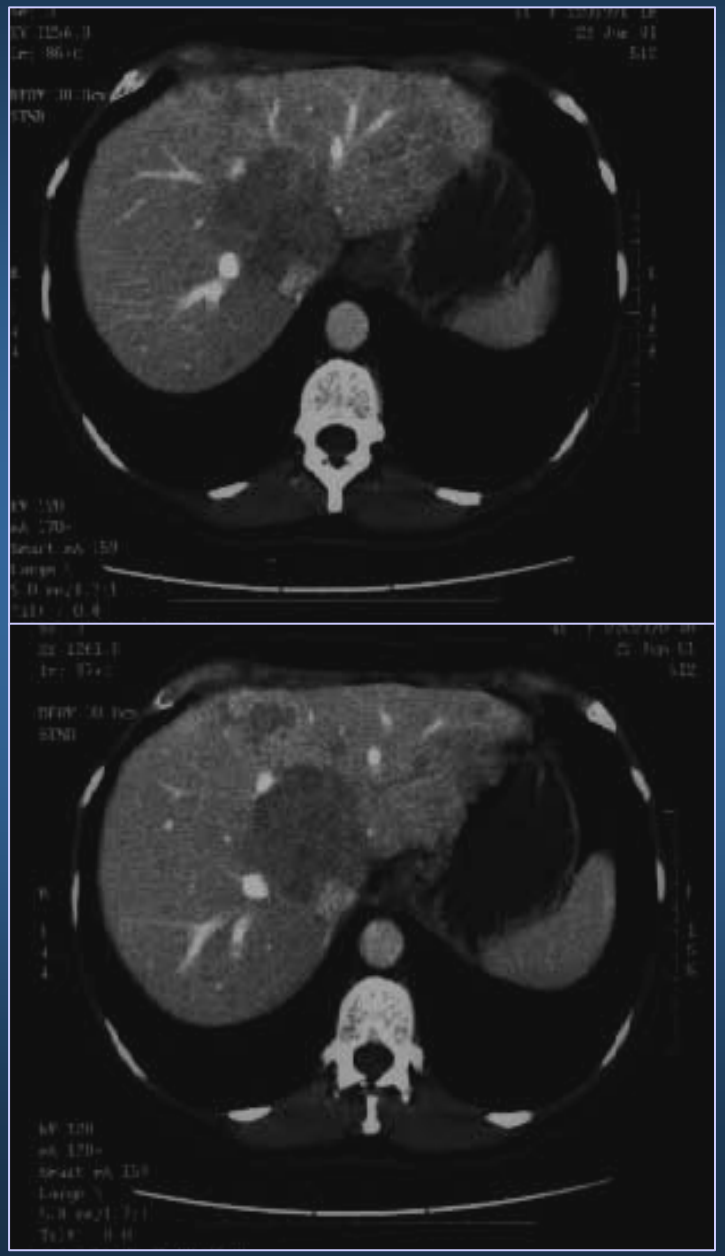
DOTATOC vs DOTATATE



^{111}In-DOTATOC
Ant

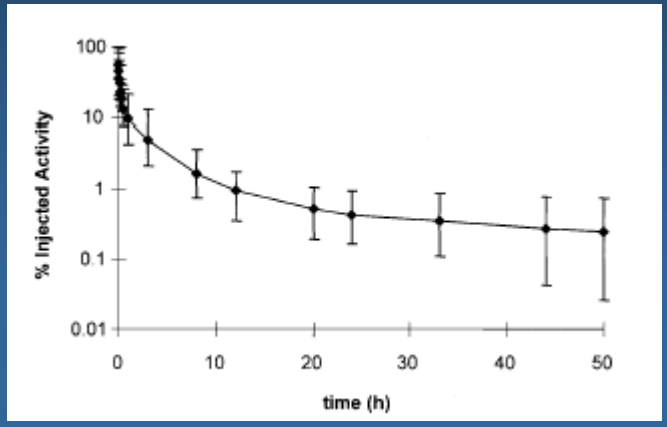


^{111}In-DOTATATE
Ant

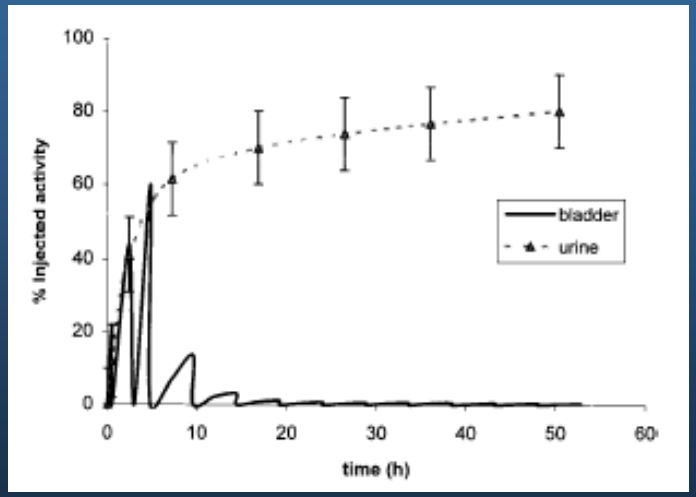


Radioactivity amount in tumour: T/B ratio

- Pharmacokinetics:
  - rapid plasma clearance:



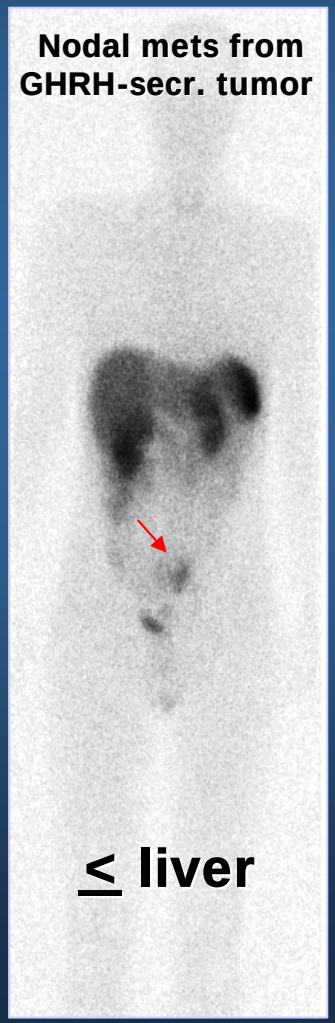
  - excretion/catabolism by the kidney:

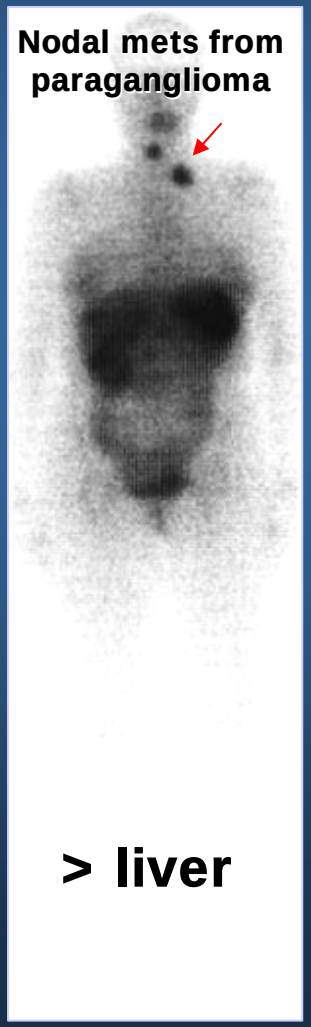


Cremonesi M et al. Eur J Nucl Med 1999

Radioactivity amount in tumour:
T/B ratio

receptor density on tumour and normal organs





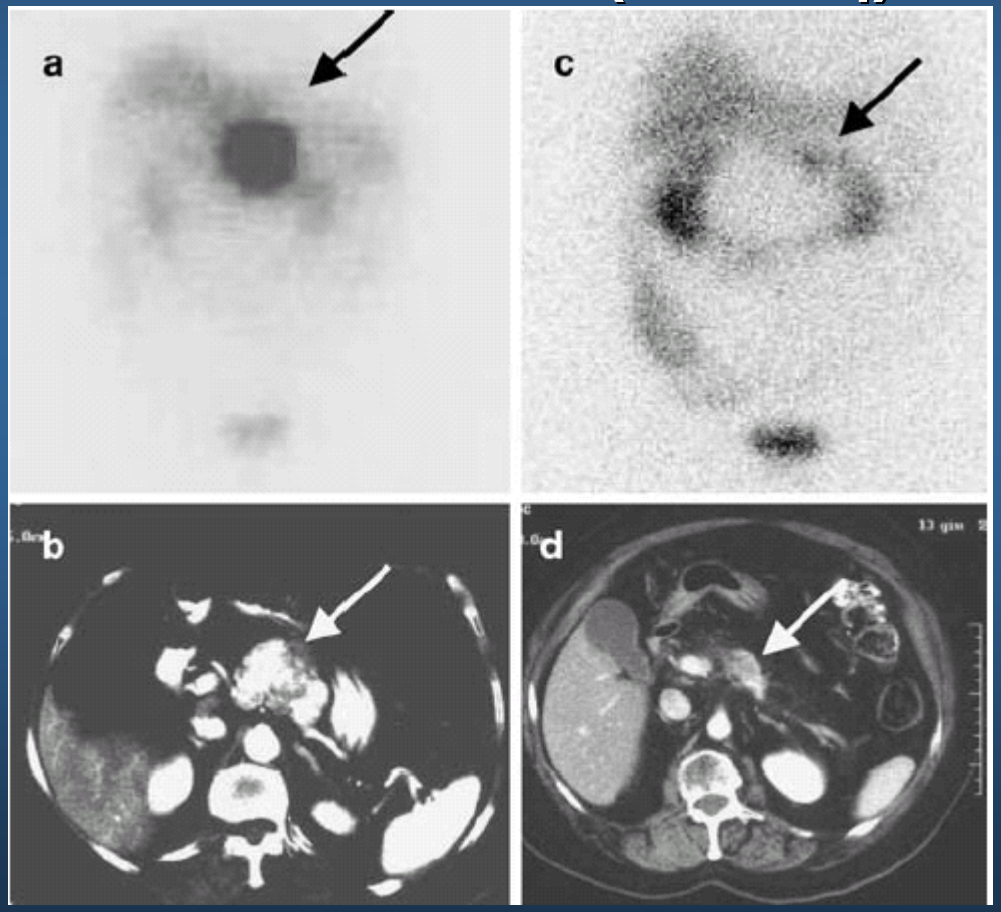
Absorbed dose to the tumor: tumor dosimetry

Radiopharmaceutical	Tumor mass (g)	Absorbed dose (mGy/MBq)	Reference
^{90}Y-DOTATOC	9 lesions (mass not specified)	Range = 2.4–41.7†	(*16*)
	23 lesions; range = 2–115 g	Range = 1.4–31.0†	(*15*)
	Mass not specified	Range = 2.1–29.5‡	(*23*)
^{177}Lu-DOTATATE	1 g*	37.9	(*30*)
	10 g*	3.9	(*30*)

Cremonesi M et al. J Nucl Med 2006

VIP-secreting pancreatic neuroendocrine carcinoma

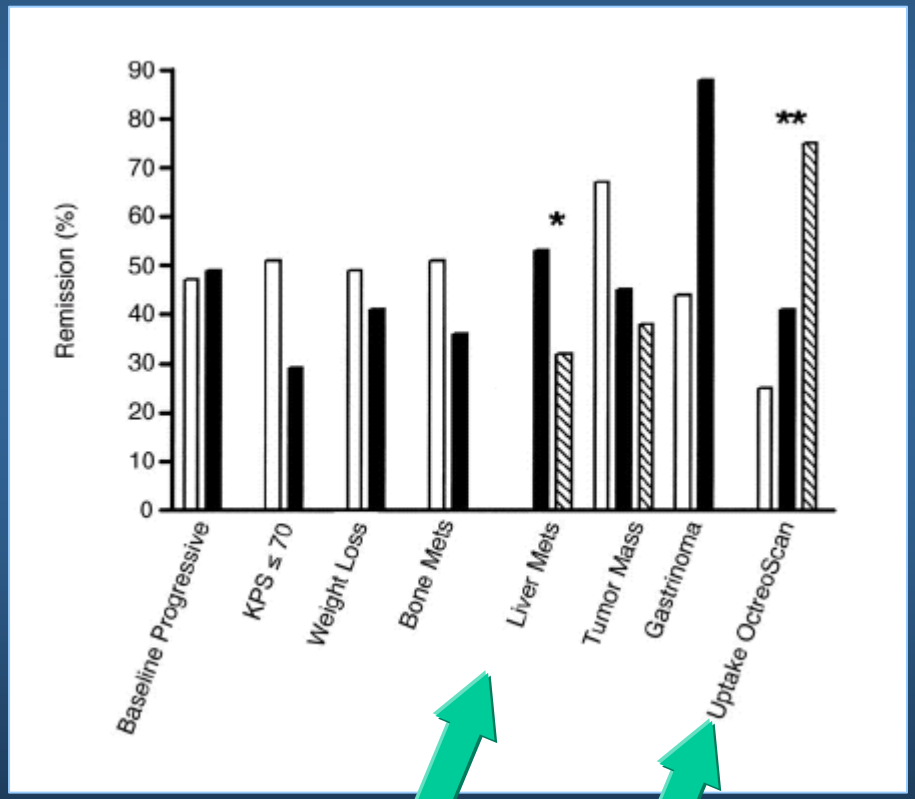
Basal **After ^{90}Y-DOTATOC (13.9 GBq)**



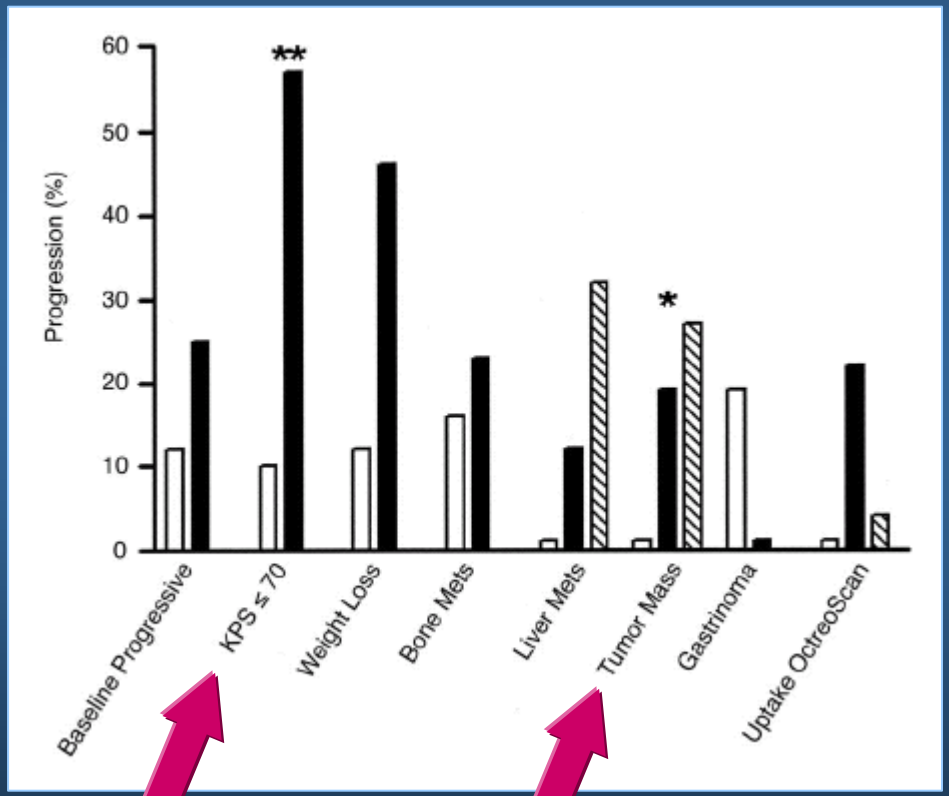
Bodei L, Eur J Nucl Med Mol Imaging 2004

PRRT: predictive factors

Response



Progression

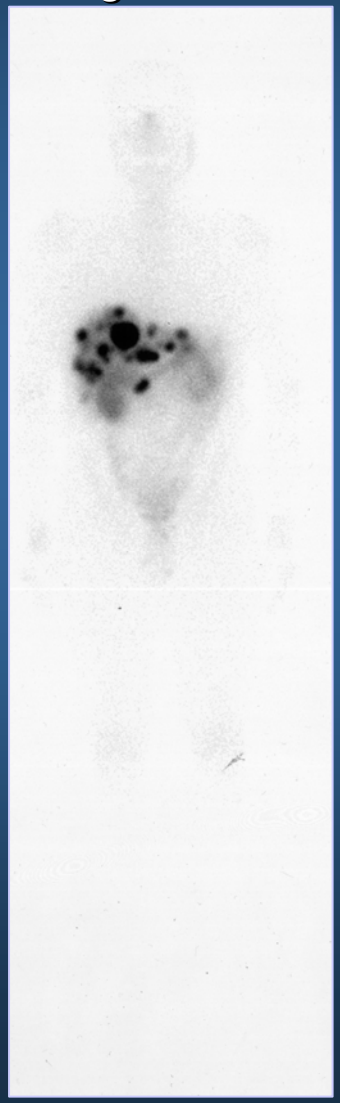


Kwekkeboom DJ et al, J Clin Oncol 2005

IEO S189/104: ^{177}Lu-DOTATATE

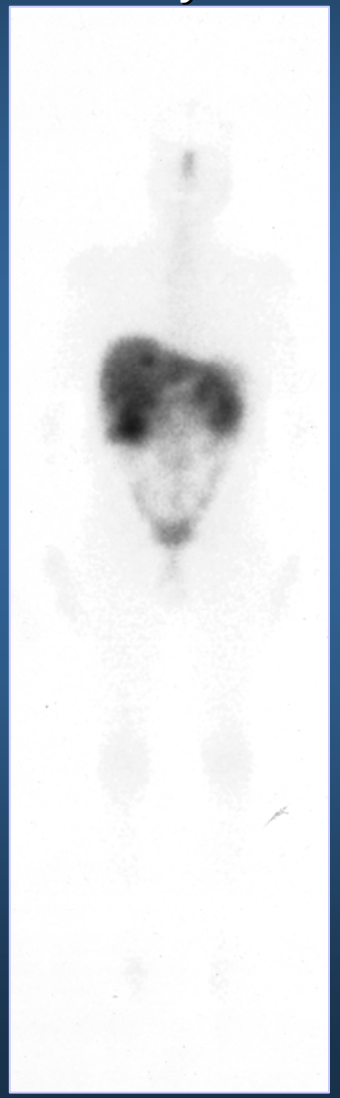
Favourable factors: limited # liver mets

August 2004

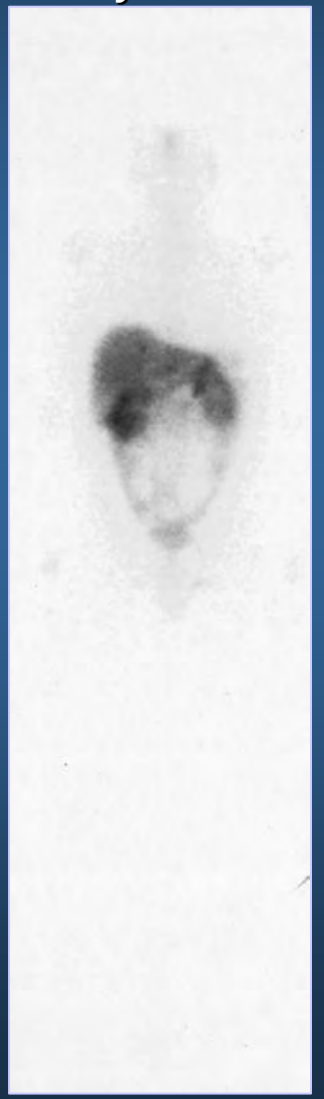


November 2004

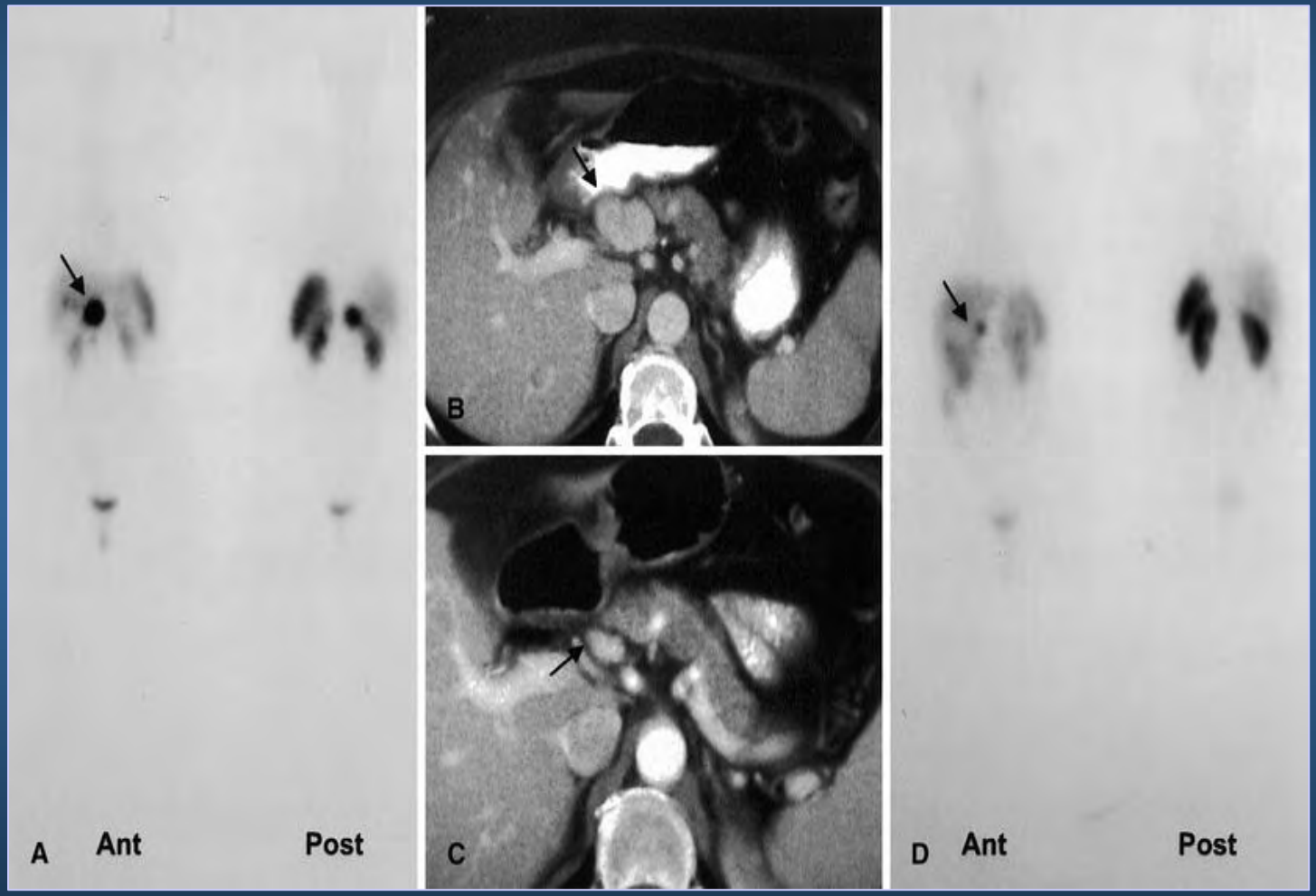
February 2005



May 2005



Favourable factors: OctreoScan uptake



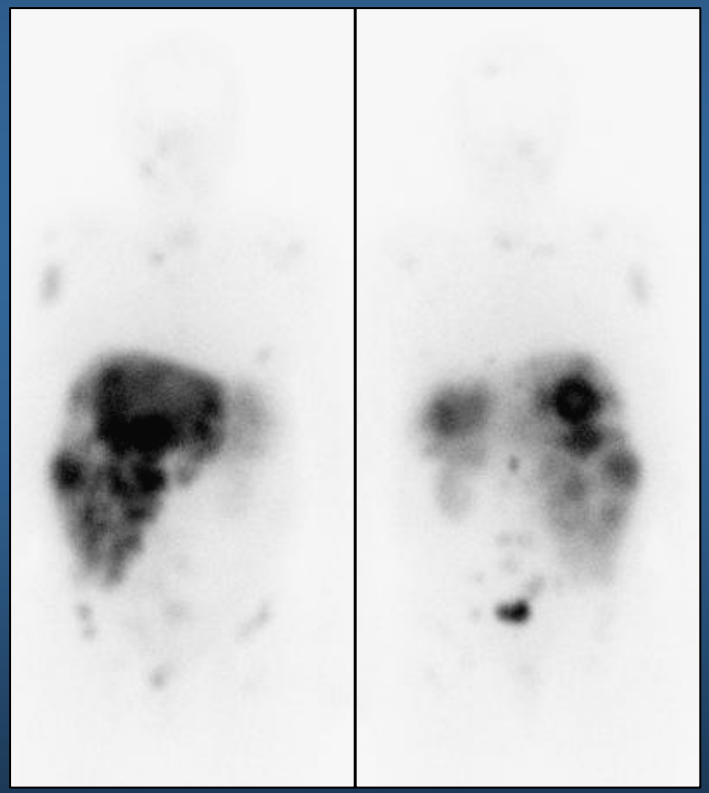
basal

after ^{90}Y-DOTATOC

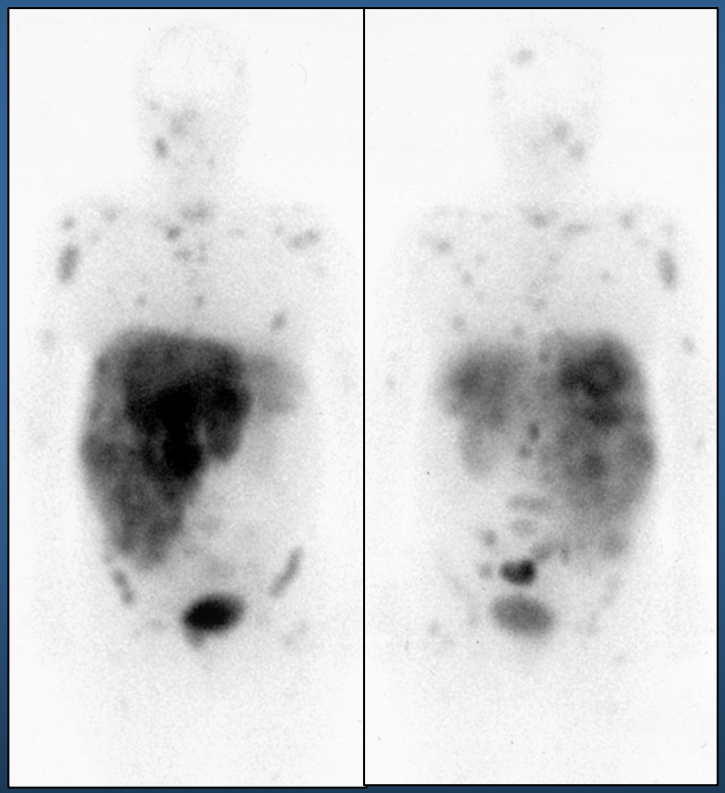
Paganelli G, Eur J Nucl Med 2001

Unfavourable factors: low PS and extensive disease

July 2004



October 2004

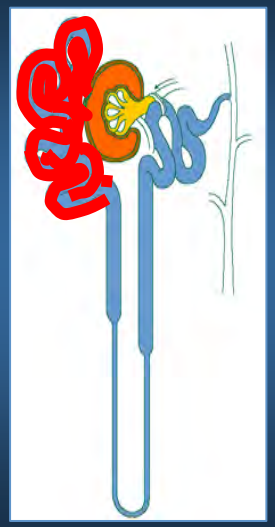


IEO S189/104: ^{177}Lu-DOTATATE

SAFETY:
KIDNEY TOXICITY

KIDNEY TOXICITY

Center (reference)	Ligand	No. of patients	Toxicity: Grade 3 or 4 hematologic* Platelets	Hb	WBC	Other†
Rotterdam (*2*)	[^{111}In-DTPA^0]octreotide	50	10	15	2	3 AML or MDS
New Orleans (*3*)	[^{111}In-DTPA^0]octreotide	27	7	11	7	3 liver, 1 renal
Milan (*10*)	[^{90}Y-DOTA^0, Tyr^3]octreotide	40	7	3	7	
Basel (*4*)	[^{90}Y-DOTA^0, Tyr^3]octreotide	29	3	7	0	4 renal‡
Basel (*6*)	[^{90}Y-DOTA^0, Tyr^3]octreotide	39	0	3	0	1 renal
Rotterdam (*11*)	[^{90}Y-DOTA^0, Tyr^3]octreotide	60	12	8	13	1 MDS, 1 liver, renal
Rotterdam (*18*)	[^{177}Lu-DOTA^0, Tyr^3]octreotate	200	3	1	2	1 MDS, 1 renal

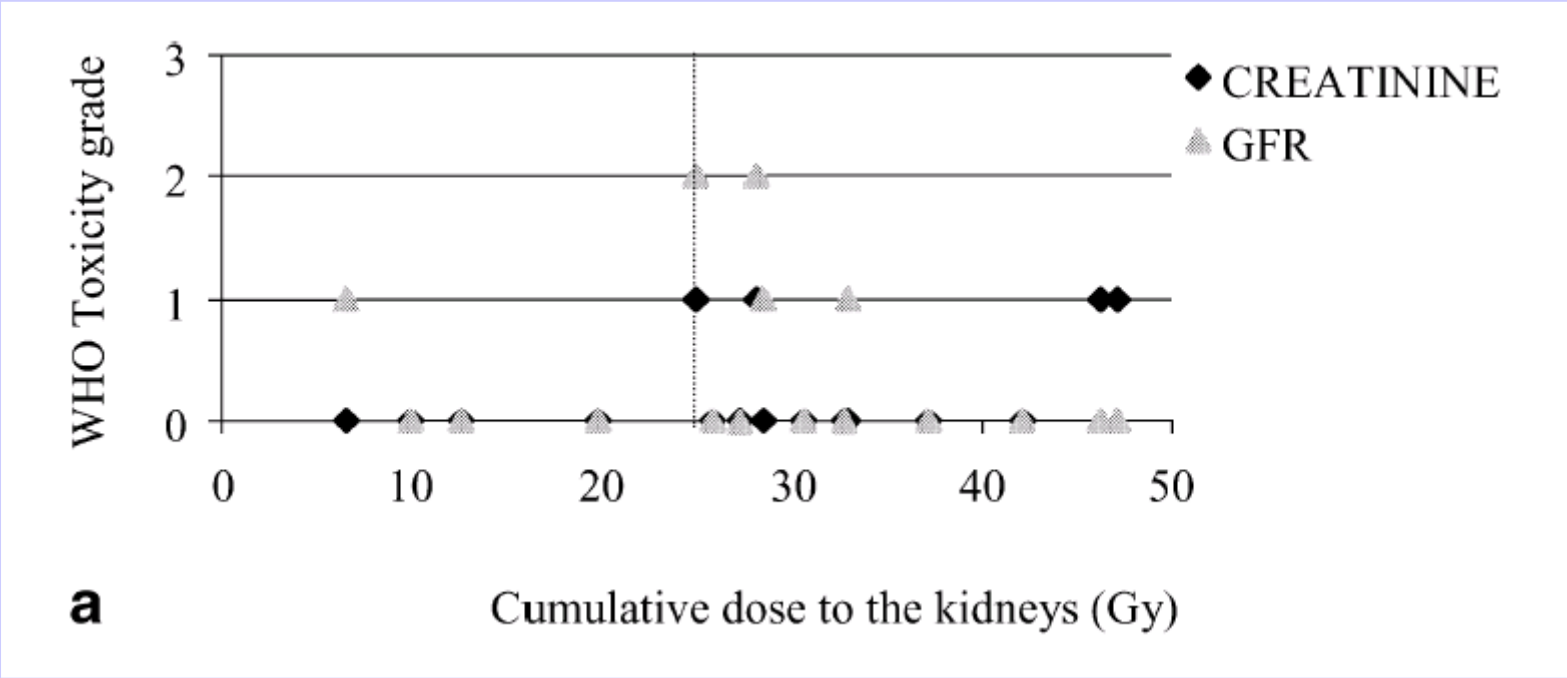


arginine **lysine**

dose reduction: 27-50%*

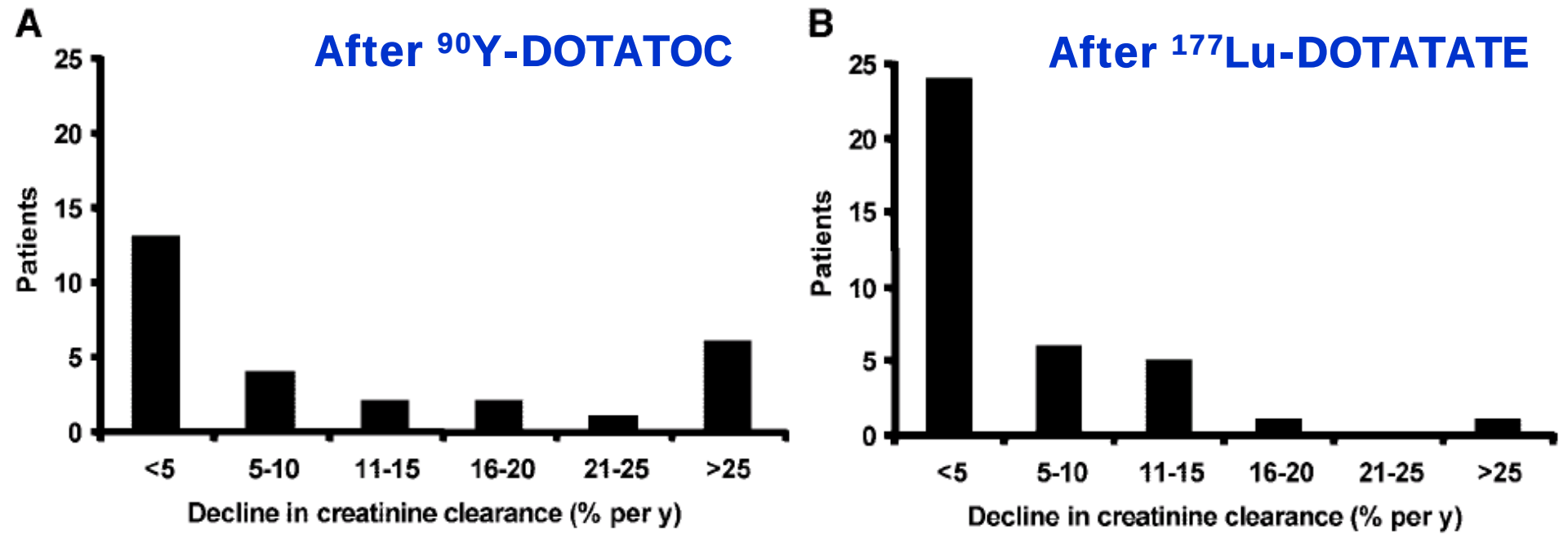
* de Jong J Nucl Med 2002

Renal toxicity and absorbed dose



Bodei L et al. Eur J Nucl Med 2004

Creatinine clearance decline after PRRT



Valkema R et al. J Nucl Med 2005

SAFETY:
BONE MARROW TOXICITY

BONE MARROW TOXICITY

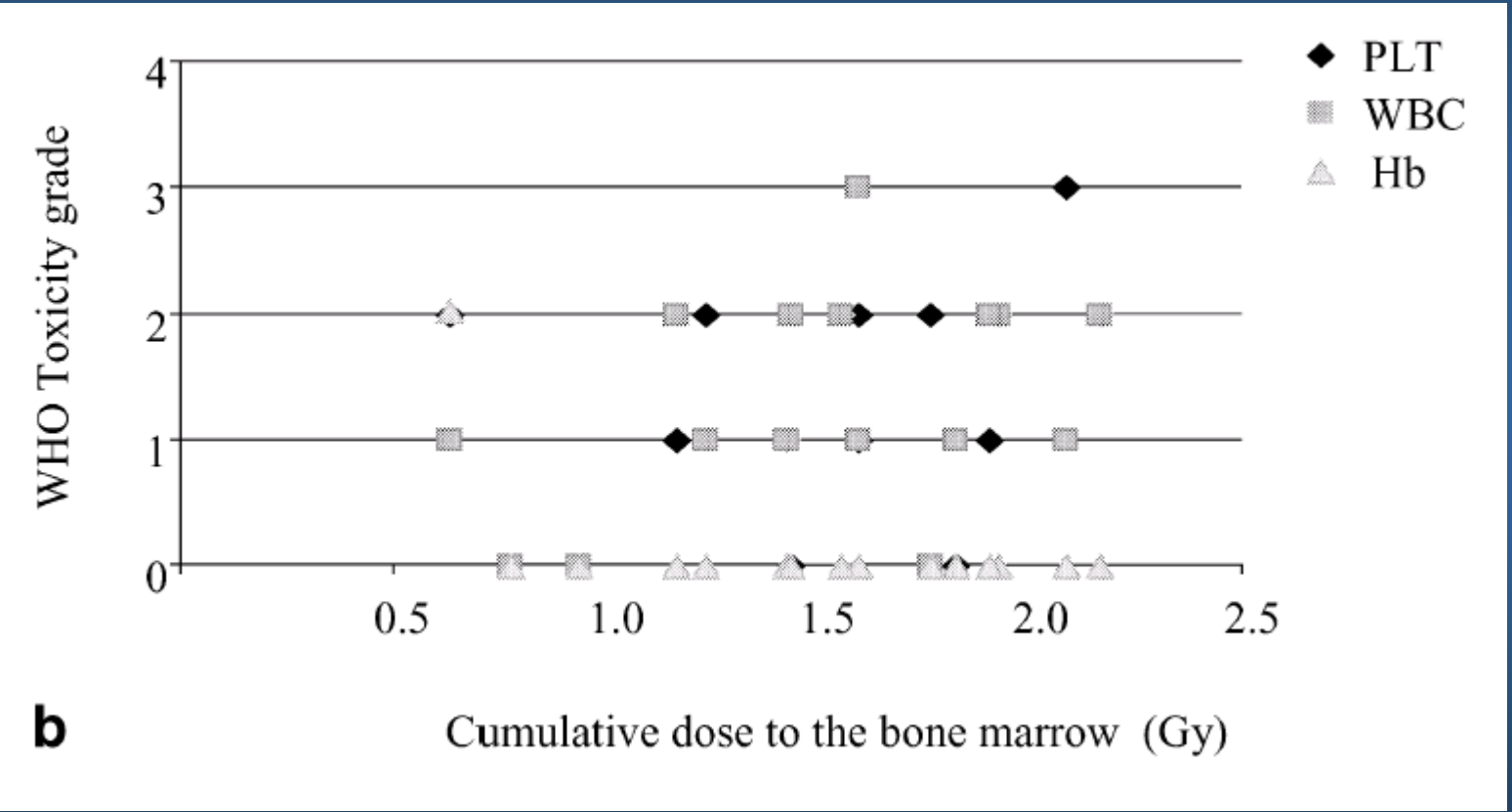
Center (reference)	Ligand	No. of patients	Toxicity: Grade 3 or 4 hematologic* Platelets	Hb	WBC	Other†
Rotterdam (*2*)	[^{111}In-DTPA^0]octreotide	50	10	15	2	3 AML or MDS
New Orleans (*3*)	[^{111}In-DTPA^0]octreotide	27	7	11	7	3 liver, 1 renal
Milan (*10*)	[^{90}Y-DOTA^0, Tyr^3]octreotide	40	7	3	7	
Basel (*4*)	[^{90}Y-DOTA^0, Tyr^3]octreotide	29	3	7	0	4 renal‡
Basel (*6*)	[^{90}Y-DOTA^0, Tyr^3]octreotide	39	0	3	0	1 renal
Rotterdam (*11*)	[^{90}Y-DOTA^0, Tyr^3]octreotide	60	12	8	13	1 MDS, 1 liver, 1 renal
Rotterdam (*18*)	[^{177}Lu-DOTA^0, Tyr^3]octreotate	200	3	1	2	1 MDS, 1 renal

*Reported as percentage of patients. Hb = hemoglobin; WBC = white blood cells.
†Reported as number of patients with indicated type of toxicity. AML = acute myeloid leukemia.
‡No amino acid infusion in half of patients.

Kwekkeboom DJ et al, J Nucl Med 2005

Bone marrow toxicity and absorbed dose

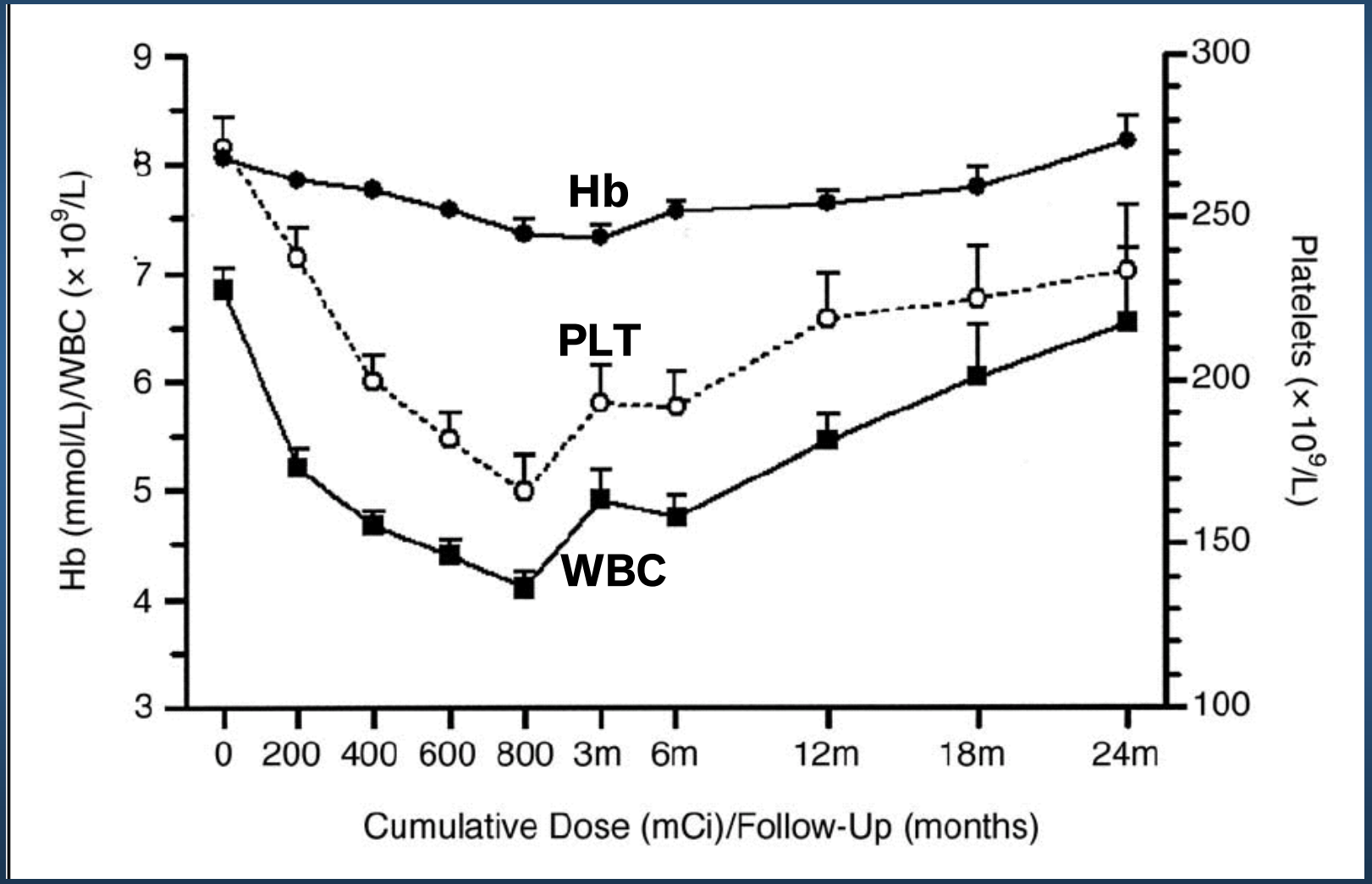
After ^{90}Y-DOTATOC



Bodei L et al, Eur J Nucl Med 2004

Bone marrow toxicity and absorbed dose

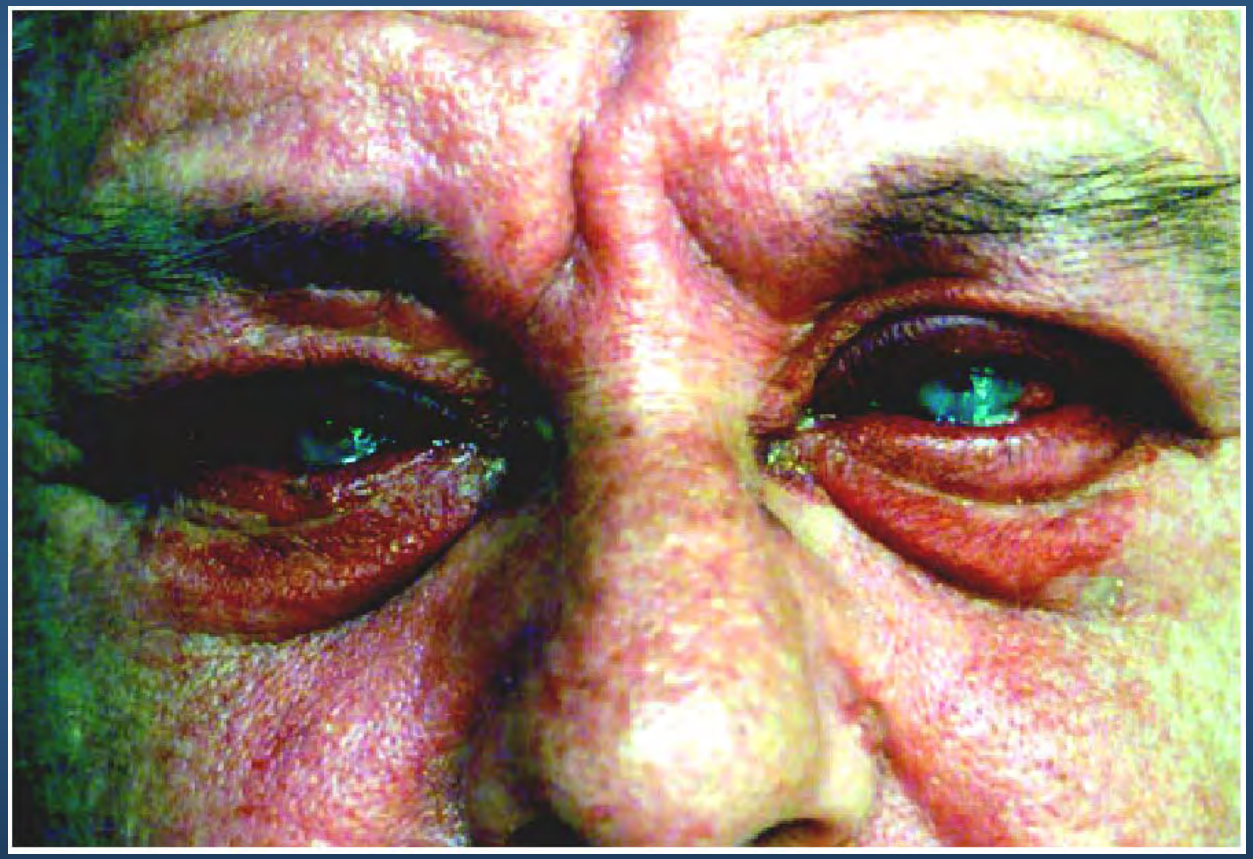
After ^{177}Lu-DOTATATE



Kwekkeboom DJ et al, J Clin Oncol 2005

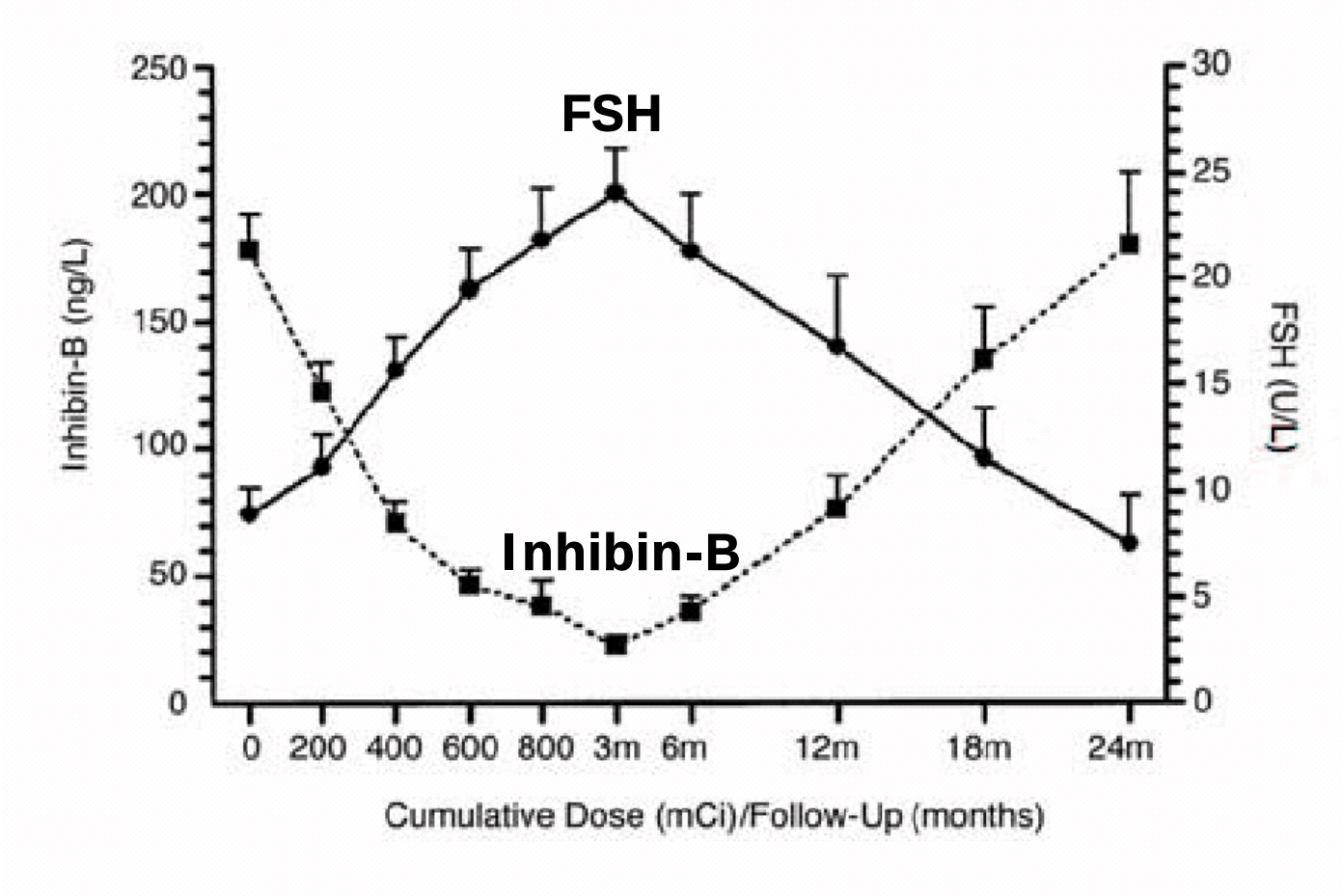
SAFETY:
OTHER EFFECTS

Exacerbation of syndromes in functioning tumors



Davì MV, Bodei L et al. J Endocrinol Invest 2006

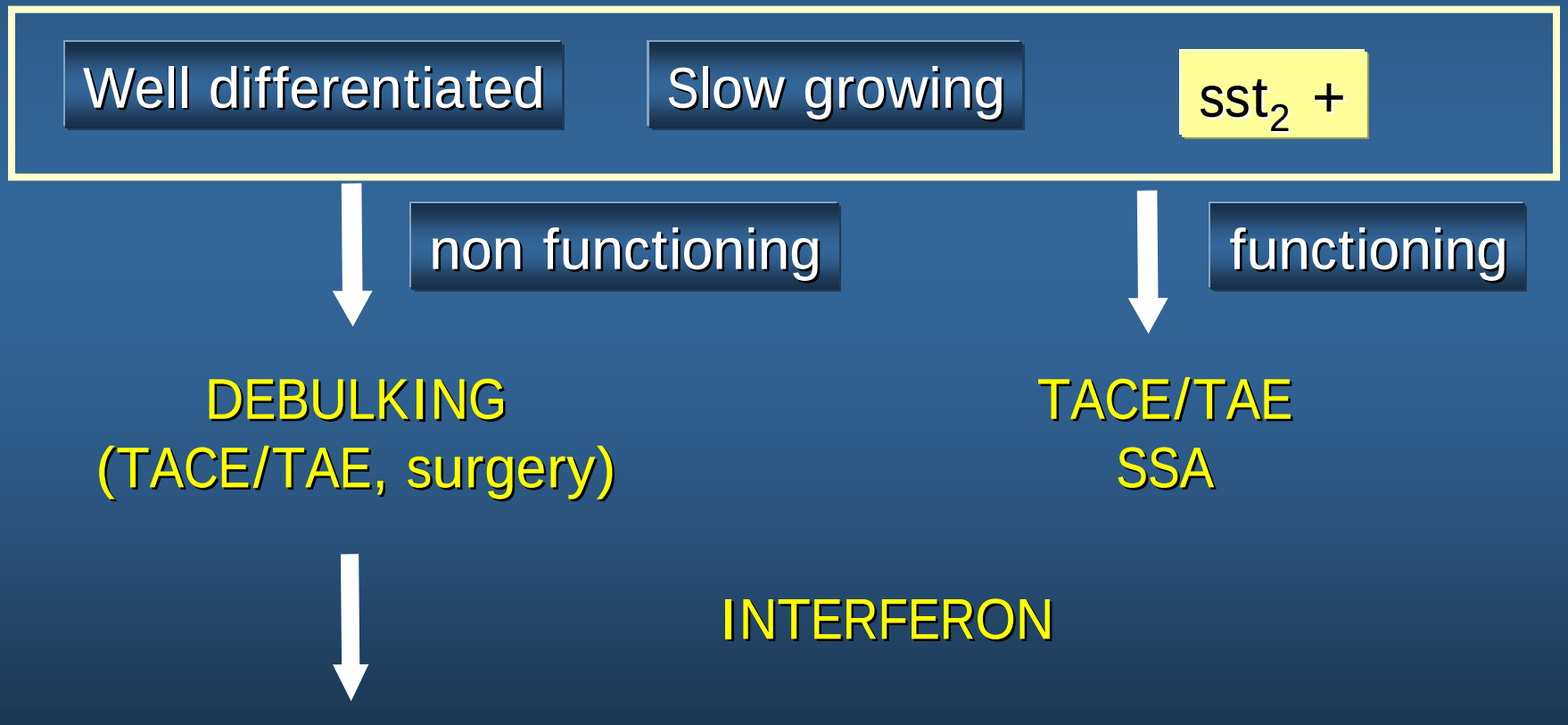
FERTILITY



Kwekkeboom DJ al. J Clin Oncol Invest 2005

PRRT vs other therapies

When should PRRT be proposed?



When should PRRT be proposed?

Poorly differentiated

Rapid growth

sst_2 +

↓

CHEMOTHERAPY
(Cis-/Carboplatin + Etoposide)

↓

^{90}Y-DOTATOC, ^{177}Lu-DOTATATE

WHAT IS LACKING

- UNIFORM STUDIES
  - phase II studies on single classes of diseases
  - comparison studies between ^{90}Y and ^{177}Lu

- GMP CENTRALIZED PRODUCTION AND DELIVERY OF RADIOPEPTIDES
  - to overcome the difficulties of legislation in various countries on experimental studies
  - to pass from experimental to standardized therapy

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- Endoscopy:

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