6thAME Italian Meeting
Verona, 27-29 October 2006

Clinical significance and treatment of neuroendocrine pulmonary tumors

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Background

- NE tumors of the lung have been viewed as a spectrum extending from low grade Typical carcinoid, to intermediate grade Atypical carcinoid, to high grade NE tumors, including Large cell neuroendocrine (LCNEC) and Small cell (SCLC) carcinomas.
- Because of differences in clinical behavior, therapeutic implications and epidemiological context, these tumors have been presented separately in the WHO revised classification.

1994

Digestion 1994;55(suppl 3):11–23

Revised Classification of Neuroendocrine Tumors of the Lung, Pancreas and Gut

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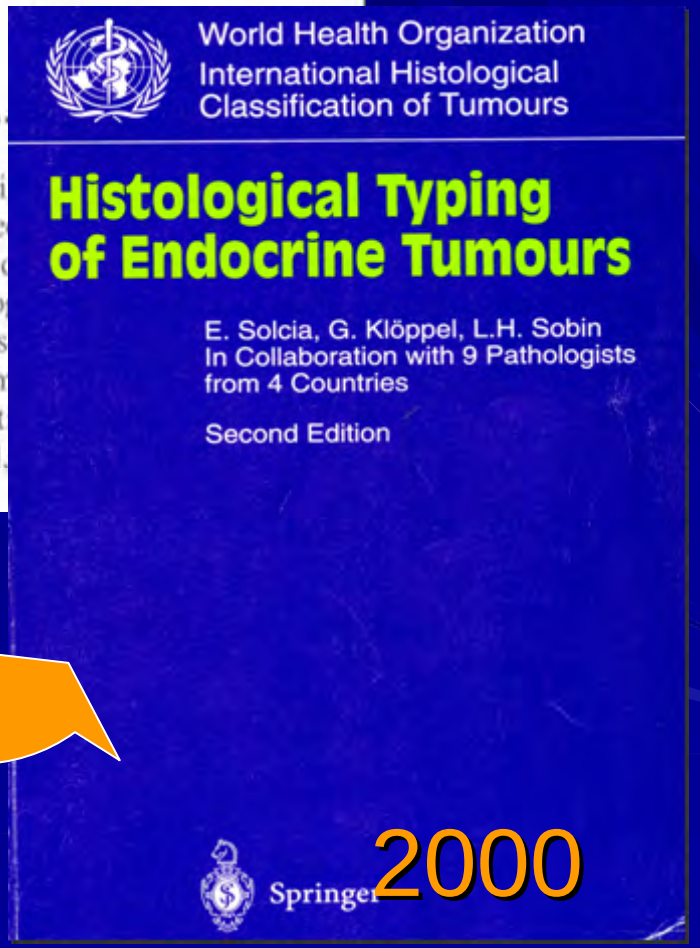
Key Words
Neuroendocrine tumors
Lung
Pancreas
Gut
Classification

Abstract
The general use of the term carcinoid for the classi
tumors has become increasingly difficult during re
tion and prognosis varies from site to site. Second
does not cover the whole morphological and biolo
docrine tumors known today. We therefore propos
neuroendocrine tumors of the lung, pancreas, ston
ileum, appendix and colorectum. These classificat
work and attempt to con[illegible]r the morphological
features of these tumors.



Neuroendocrine lung tumors

- **Well differentiated neuroendocrine tumor (Typical Carcinoid)**
- **Well differentiated neuroendocrine carcinoma (Atypical Carcinoid)**
- **Large cell neuroendocrine carcinoma *(LCNEC)***
- **Small cell neuroendocrine carcinoma *(SCLC)***

  - *E. Solcia et al. Histological typing of Endocrine Tumours WHO, 2000*

Classification of NET of the lung: criteria

Table 2
Pathologic Differential Findings in NE Lung Tumors

	Typical carcinoid	*Atypical carcinoid*	*Large cell NE carcinoma*	*Small cell carcinoma*
Organoid pattern	Characteristic	Characteristic	Present, less extensive	Absent
Cell size	Large	Large	Large	Small (less than the diameter of three lymphocytes
Cytoplasm	Abundant	Abundant	Abundant	Scant
Nuclear pleomorphism	Usually absent	Often present	Present	Present
Nucleoli	Small or absent	Small or absent	Present, often prominent	Absent
Mitosis	<2 × 10 HPF	2–10 × 10 HPF	≥11 × 10 HPF (mean 70)	Mean 70 × 10 HPF
Necrosis	Absent	Present, focal, or punctate	Present, large zones	Present, large zones
Disease-free survival at 5 yr	100%	69%	27%	9%

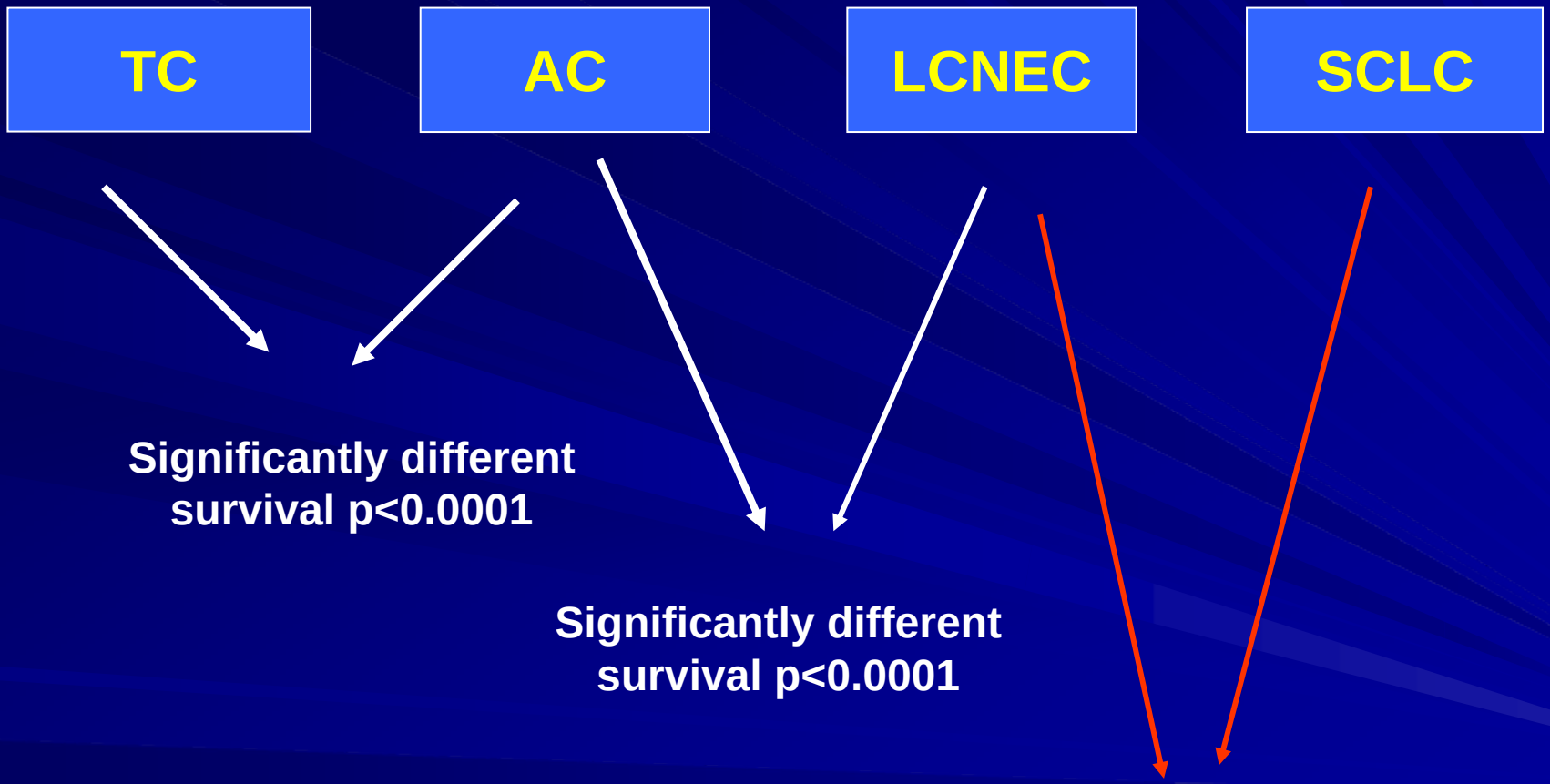
Synonym .... **Well differentiated neuroendocrine tumor**

Well differentiated neuroendocrine carcinoma

Large cell neuroendocrine carcinoma

Small cell neuroendocrine carcinoma

Spectrum of NE tumors of the lung



Travis et al Am J Surg Pathol 1998

Diagnosis of lung Net

- No major diagnostic problems for the two entities at the extremes of the spectrum:

TC - SCNC

- Difficulties in identifying the intermediate entities:

AC - LCNEC

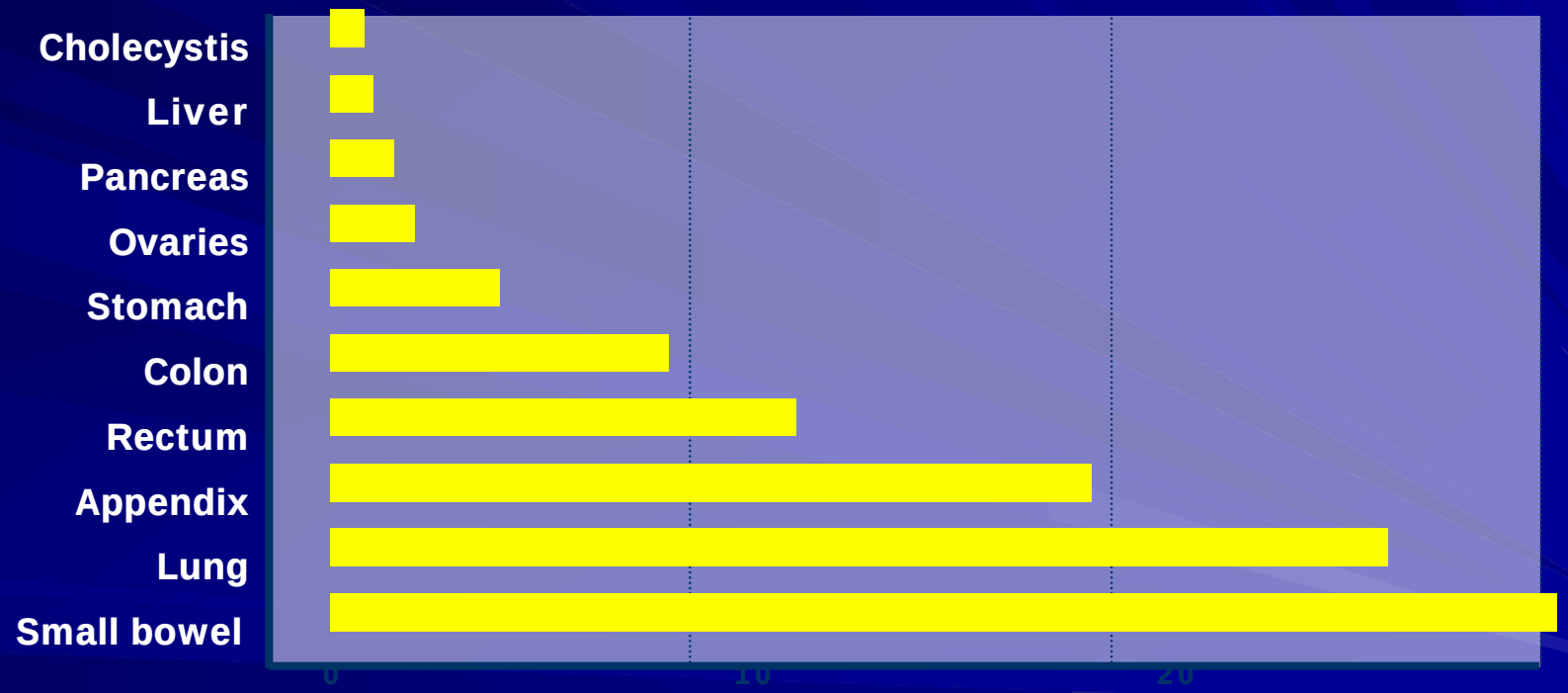
The spectrum of neuroendocrine proliferations

- **Carcinoid tumorlets**
  - Dissemination of neuroendocrine particle in the interstitium. Differential Diagnosis with carcinoid: size < cm 0.5
- **Neuroendocrine cell hyperplasia**
  - NE cell hyperplasia with fibrosis and/or inflammation
  - NE cell hyperplasia adjacent to carcinoid tumours
  - Diffuse idiopathic NE cell hyperplasia with or without airway fibrosis

Travis et al WHO Classification of Tumours, 2004

Analysis of 8305 carcinoid tumors

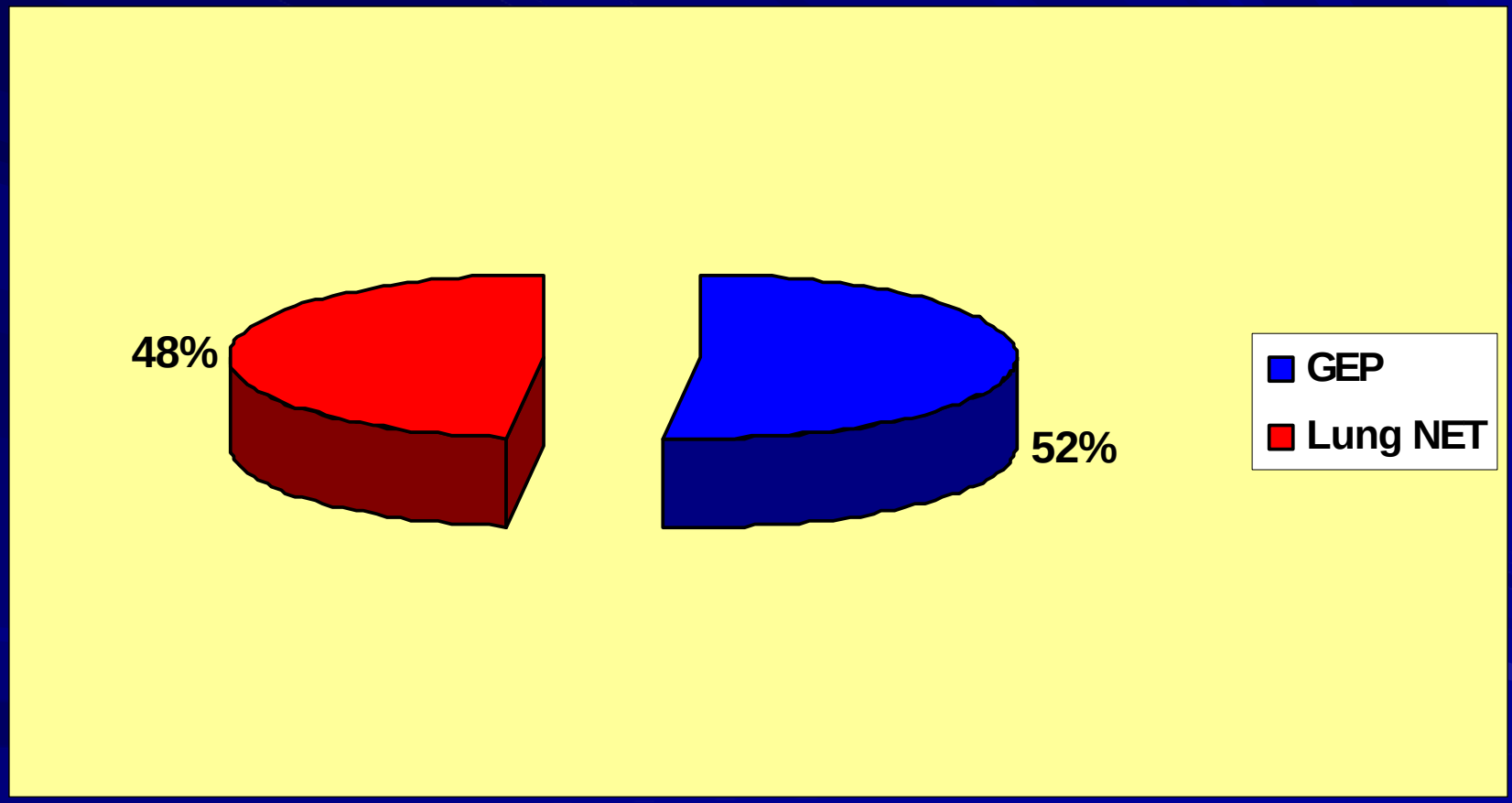
Location



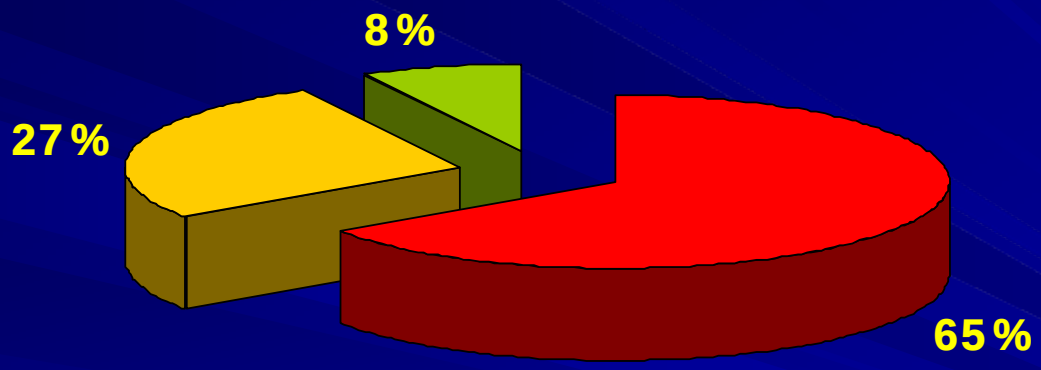
Modlin et al 1997

Neuroendocrine Tumors

Udine: Jan. 1991 – Sept 2006
patients n. 162



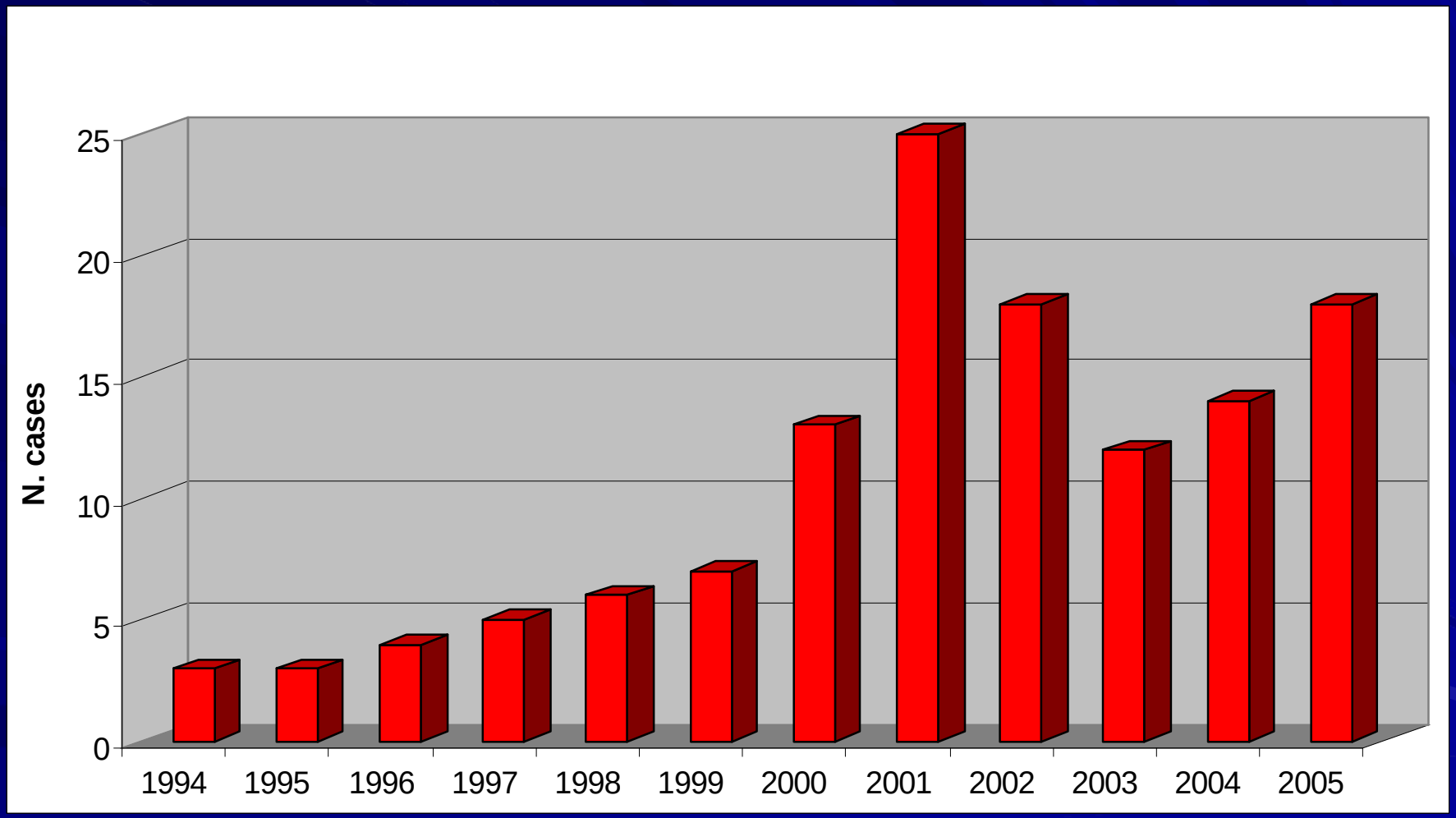
Lung NET
Udine: pts n. 78



TC = Typical Carcinoid
AC = Atypical Carcinoid
LCNC = Large Cell Neuroendocrine Carcinoma

Annual incidence Lung NET

Udine: 1994 - 2005



Clinical features

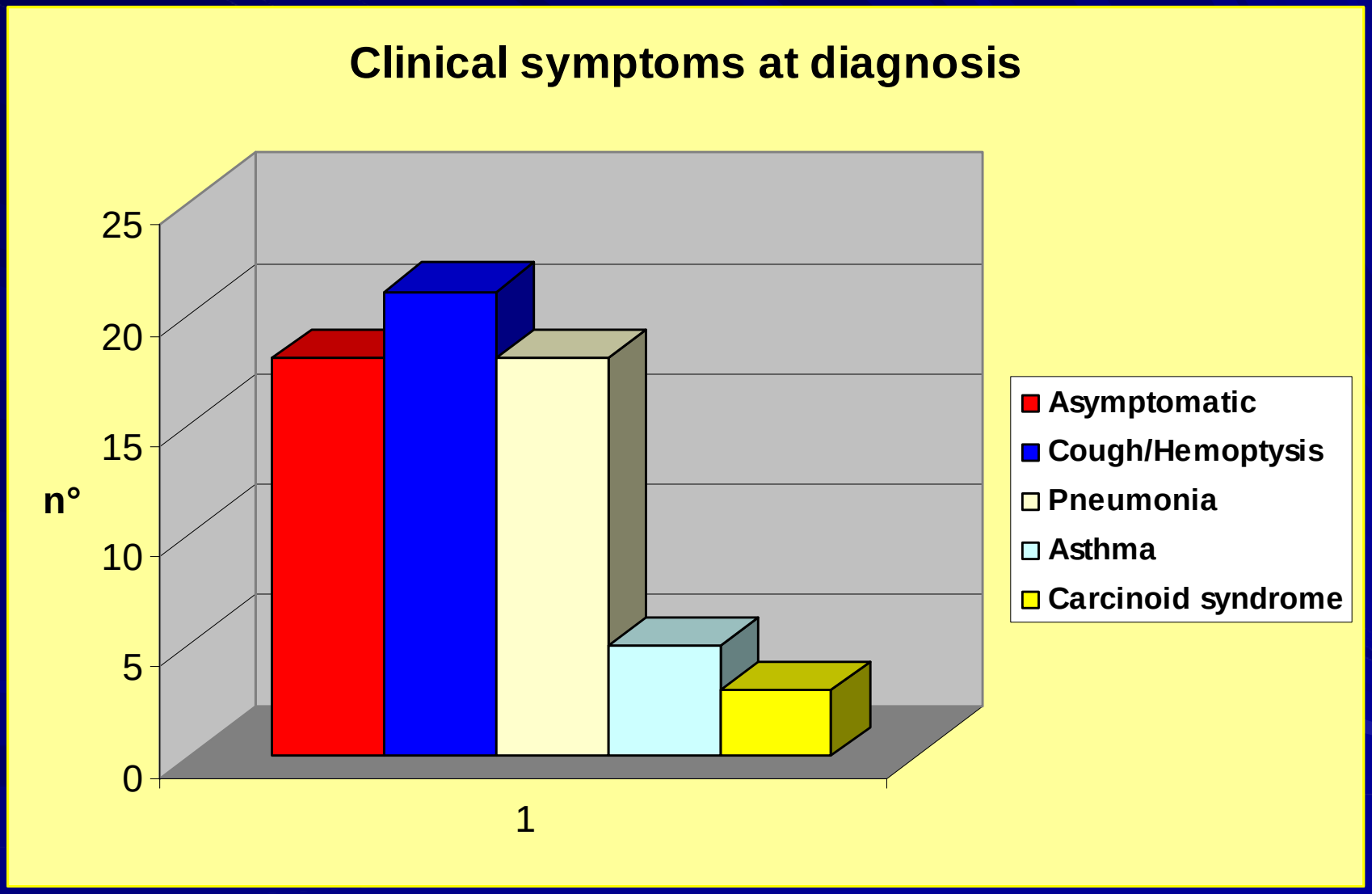
Symptoms:

- Asymptomatic 23%
- Recurrent infections* 42%
- Cough / Hemoptysis* 21%
- Chest pain 7%
- Dyspnea / Wheezing*
- Endocrine symptoms: 12%

  Carcinoid syndrome, Atypical carcinoid syndrome, Cushing, Acromegaly

*All had central tumors demonstrable by bronchoscopy

Lung NET - Udine



Diagnosis

- Imaging: Radiology, Nuclear Medicine
- Bronchoscopic diagnosis
- Neuroendocrine tissue markers
- Biochemical investigation:
  - Neuroendocrine tumors markers
  - Exclude the presence of MEN and of ectopic secretion

Radiology

- More than 60% are detectable on **Chest X-ray**
- **CT and MRI** most sensitive, especially for detection of local metastases
- 75% of central tumors detectable by **bronchoscopy**
- **Somatostatin receptors scintigraphy:** 80% primary bronchial carcinoids, and 64% of cases with proven liver metastases

Bronchoscopic diagnosis

- **Bronchoscopy is often positive: 70% of carcinoid are proximal**
- **Major issues:**
  - **Biopsies may induce major bleeding**
  - **Difficulty to do a precise diagnosis with bronchial biopsies: typical or atypical**
  - **Useful for definitive diagnosis by surgical resection and pathological reviewing**

Scintigraphy with ^{111}In-octreotide

- Positive scintiscan is predictive of a good therapeutic response to chronic SS-analogs administration in patients with NET.
- Is helpful in staging and identification of the primary lesion.
- Has an 83% diagnostic accuracy and a positive predictive value of 100%, and can also identify lesions that are not seen by other imaging modalities.

Role of Positron Emission Tomography (PET

- PET with F-18 fluorodeoxyglucose, the most common tracer in Italy, has demostrated very little utility in the diagnosis of NET at least in the well differentiated tumor
- Useful in diagnosing poorly, differentiated more aggressive Lung NET

Neuroendocrine tissue markers

- CgA, Synaptophysin are useful NE markers recommended for diagnosis
- Other NE markers like CD56 (n-CAM), NSE, PGP 9.5 may be considered
- Subtypes of somatostatin identification is potentially useful for diagnostic/therapeutic purposes
- **Useful non NE markers** may included Ki67/MIBI1, cytokeratin pool

Immunohistochemical markers

- To confirm diagnosis
- For prognostic value
- For therapy

Neuroendocrine tumors markers

- **General markers:**
  - **Chromogranin A (CgA)**
  - **Neuro-specific-enolase (NSE)**
- **Specific markers:**
  - **5-HIAA**

CgA in patients with NET

Disease characteristics	CgA sensitivity (%)
Loco-regional	37
Metastatic	
Liver	78
Lung	80
Skeletal	67
Multiple	65
Syndromic	68
Non syndromic	53

Seregni E, Q J Nucl Med 2000

Chromogranin A: false positive

- Chronic renal insufficiency
- Drugs (pump inibitori, calcium antagonist es. verapamil)
- Hepatic insufficiency
- Chronic atrophic gastritis
- Small bowel inflammatory diseases
- Essential hypertension
- Extreme physical activity
- Stress
- Pregnancy
- Parkinson’s disease

NSE in patients with NET

Endocrine tumors	NSE sensitivity (%)
Carcinoid	47, 38
Pancreas islet cell tumors	43, 31
Gastrinoma	44, 33
Carcinoid midgut	50
Small cell lung carcinoma	74, 61, 85, 62
Limited disease	45, 77
Extensive disease	68, 85

Seregni E, Q J Nucl Med 2000

5-HIAA

False positive

- **Celiac disease**
- **Intestinal bacterial contamination**
- **Food:** bananas, avocados, pineapple, hazelnuts, chocolate
- **Drugs:** paracetamol, diazepam, atenolol, indometacin, fenothizine

False negative

- **L-Dopa**
- **Salicilates**

Exclude the presence of MEN and of ectopic secretion (ACTH-Cortisol, GH)

- Sachithanandal N et al. Bronchopulmonary Carcinoid in Multiple Endocrine Neoplasia Type 1, *Cancer* 2005 **"Conclusions: the findings suggested that bronchopulmonary carcinoid is more prevalent in patients with MEN 1 than was recognized previously"**
- Scanagatta P, Francia G. Cushing's syndrome induced by bronchopulmonary carcinoid tumours: **a review of 98 cases** and our experience of two cases. Chir Ital. 2004

Biochemical investigation of Lung tumors

- **Cushing:**
  - Low-dose dexamethasone
  - Midnight cortisol, plasma ACTH [overnight Dex 1 mg, UFC]
- **Acromegaly:**
  - IGF1, OGTT
  - plasma GH-RH
- **For MEN-1:** Ca^{++}, gut peptides, prolactin

Surgical treatment of bronchopulmonary carcinoids

All NE tumors require major surgical procedures with radical node dissection to obtain oncological favorable outcomes

Endobronchial laser treatment

- Endobronchial laser treatment is justified only as palliation and pre-op treatment
- It's impossible to exclude the presence of lymph node micrometases and extension to the bronchial wall

Endobronchial laser treatment

Author	year	cases	Eradication	Follow up
Sauvaget J.	1980	1 *	Complete	n.r.
Guerin J.C.	1986	1 *	Complete	n.r.
Berendsen H.H.	1986	2 *	Complete	n.r.
Harpole D.H.Jr.	1992	6 *	Complete	n.r.
Sutedja T.G.	1995	11 *	Complete	47 months
Mazzetti M.	1995	1 *	Complete	n.r.
Venu K.	1997	1 *	Complete	Relapse 24 mo.
Van Boxen T.J.	1998	19 *	Complete 14 Incomplete 5 (surg)	29 months
Hansen G.	2000	6 *	Complete 4 Incomplete 2	60 months
Fink G.	2001	1 *	n.r.	n.r.
Hansen G.	2003	5 *	Complete	10 months
Orino K.	2004	1 **	Complete	n.r.

n.r = non reported - *Laser Nd YAG - **Argon plasma

Role of Pathology:
Immunohistochemistry

- Chromogranin A
- NSE
- Synaptophysin
- Ki67/MBI1
- PGP 9.5
- CD 56
- S-100
- Cytokeratin
- P53
- Nm23
- Bcl-2
- CD44

Prognosis in typical bronchial carcinoids

D. Granberg et al, JCEM 2000

- Typical bronchial carcinoids are considered relatively benign but a subgroup shows a more aggressive course
- Overall 5-years survival is excellent
- But 10 % die early:
  - How to recognize those at risk ?
  - Should these patients be treated differently ?

Size and metastases

- **Metastases at diagnosis**: Typical 5-20 %

  Atypical ≤ 70 %
- **Size and location** does not correlate to nodal invasion
- **Size > 3.5 cm** correlates to poor survival
- **Site of metastases**: lymph nodes, liver, bones, brain, skin, mammary gland

Interdisciplinary approach

Endocrinology

Pathology

Oncology

Radiology

Surgery

— Siamo tutti specialisti: perché non ci consultiamo con un medico generico?

Medical treatment: with persistent disease

Background

- Lack of controlled studies
- Small numbers
- Unclear inclusion criteria
- Different tumor subtypes
- Spontaneous variation of growth
- Outcomes: biochemical response
  objective response

OBJECTIVES OF TREATMENT IN NEUROENDOCRINE TUMORS

FUNCTIONING TUMORS

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

NONFUNCTIONING TUMORS

- IMPROVEMENT OF THE QUALITY OF LIFE
- TUMOR SIZE REDUCTION
- IMPROVED SURVIVAL

Tomasetti

Medical treatment

- Somatostatin analogs
- α-Interferon (INF-α)
- Combination therapy:
  - SS analogs plus (INF-α)
- Chemotherapy
- Chemoembolization

What is the Evidence

- **Evidence appraised:**
  - **Practice guidelines**
    - **National Guideline Clearinghouse**
    - **CMA Infobase**
    - **Scottish Intercollegiate Guidelines Network SIGN**
    - ***eGuidelines***
  - **Randomized controlled → studies (RCT)**
  - **Systematic reviews → Other Meta-analyses**

Cochrane

- Systematic Reviews: none
- Reviews: 7 as of August 2006

Somatostatin analogs formulation

- **Octreotide** 50-500 μg/day (s.c., 1-3 times daily)
- **Octreotide LAR** 20-30 mg (i.m., monthly)
- **Lanreotide** 30 mg (i.m., 2 weeks) or 60 mg (i.m., monthly)
- **Lanreotide Autogel** 60-90-120 mg (s.c., monthly)

SS-A: inhibition of tumor growth in patients with “non functioning” tumors

Effects

- **Direct:** mediated by specific somatostatin receptors present on tumor membrane
- **Indirect:** acting on different target cell types where they exert:
  - Inhibition of several growth factors secretion (IGF1, EGF)
  - Modulation of the immune system
  - Induction of apoptosis
  - Inhibition of angiogenesis

Which patients should be treated?

- Medical treatment should always be considered as an adjuvant to surgery
- **Functional NET:** yes
- **Non functioning NET**: may be controversial
  - Selection of patients is based on: positive Scintigraphy with ^{111}In-octreotide

Adapted from Oberg et al., 2004

How should a patient on SS-analogs therapy be followed ?

- A complete history and physical examination should be performed every 6 months.
- The patient should be examined using conventional imaging studies (CT/MRI or ultrasonography) and markers every 6 months.

Adapted from Oberg et al., 2004

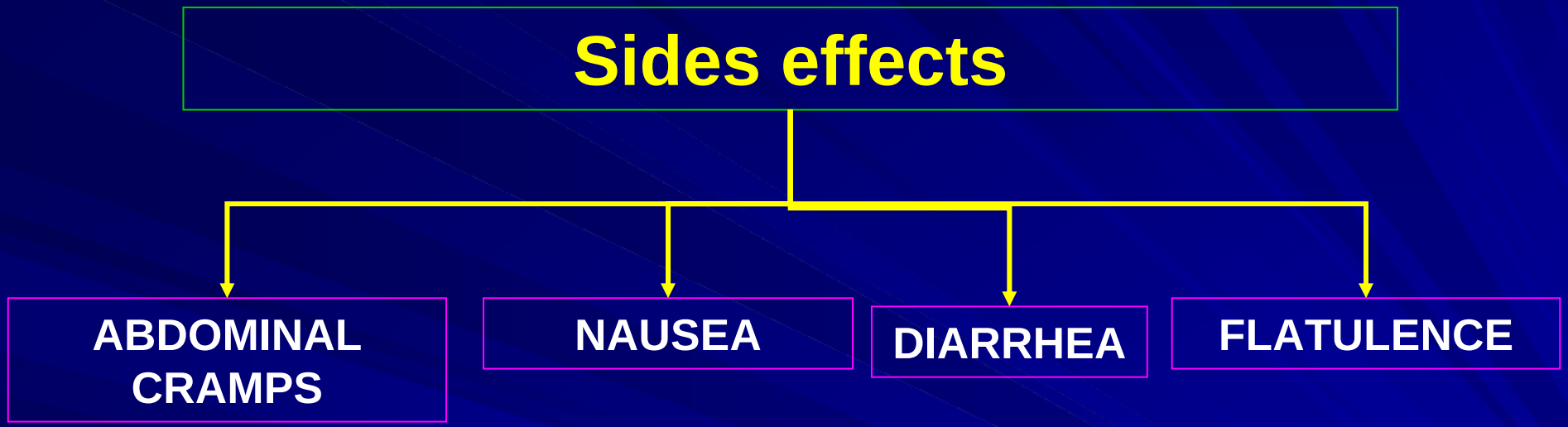
Octreotide

Data from 62 studies
(Total patients 621)

- **Improves symptoms (diarrhea and flushing)**
- **Improves the biochemical response (reduces 5-HIAA)**

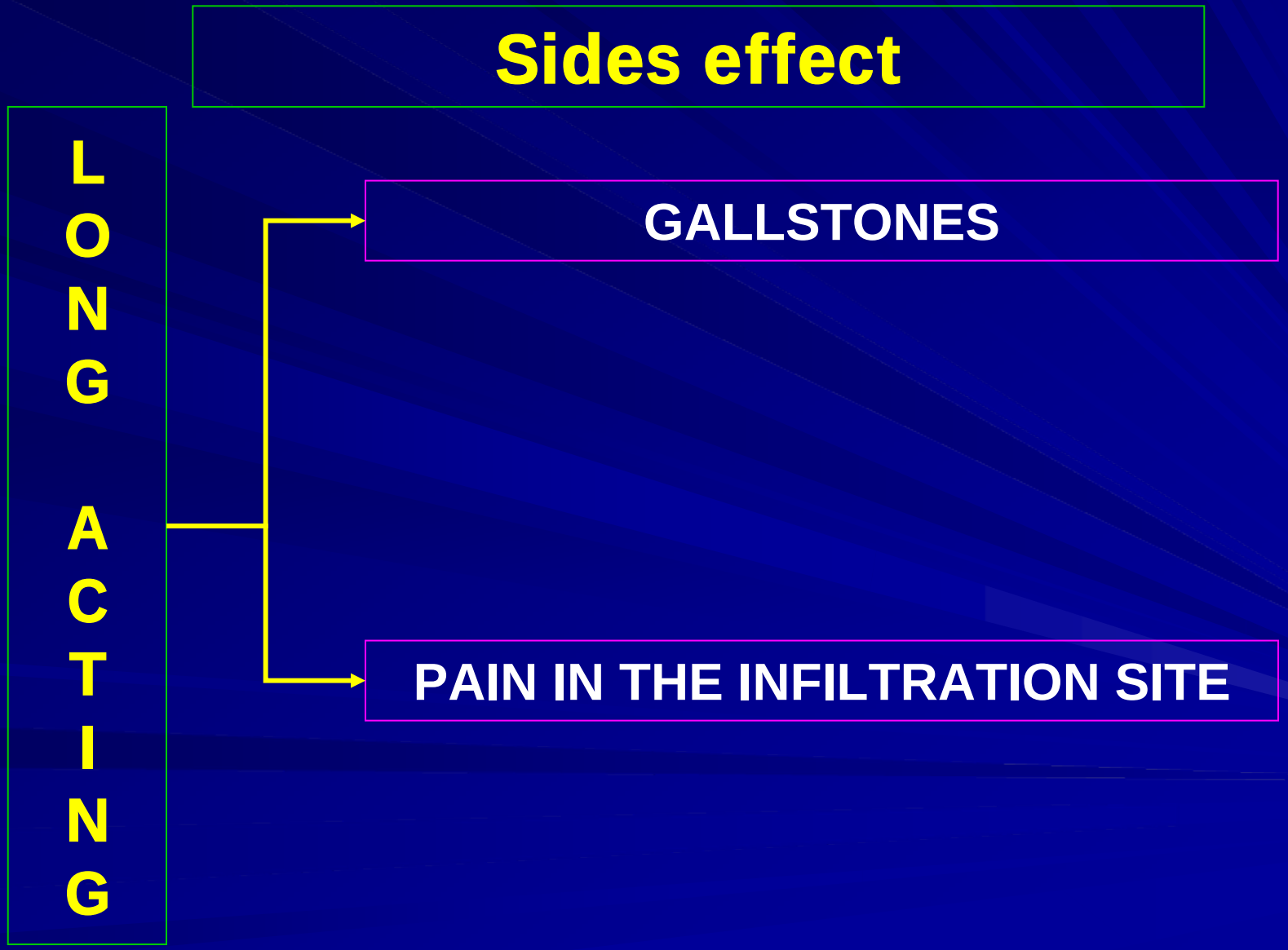
Tomasetti, J End Invest 2003

Somatostatin analogs



BETWEEN 1 AND 7 DAY AFTER FIRST INJECTION, RESOLVE SPONTANEOUSLY IN THE MAJORITY PATIENTS

Somatostatin analogs



α-Interferon

- Effects on tumor growth were reported to be relatively minor and limited to intestinal carcinoid tumors.
- Dose of IFN-α has been 3-9 MU 3-7 times per week subcutaneously.

Response

- Biochemical response: in 40-50％
- Symptomatic improvement in 40-70％
- Significant tumors shrinkage in 10-15％

Combined use of SS Analogs plus INF-α

- Few studies published on the combined use of SS-A plus INF α with **biochemical response** being reported in 60-80% of patients.

  (Janson et al., Eur J Cancer 1992; Frank et al., Am Gastroenterol 1999; Fjallskog et al., Med Oncol 2002).

- The **objective responses** are conflicting:
  - Frank observed response in 69%
  - Fjallskog and Janson observed in only 1-19%

Does interferon-α add to any tumoristatic effect of SS-Analogs ?

- 68 pts with metastatic midgut carcinoids
- Treatment:
  - Octreotide alone: n. 35
  - Octreotide + Interferon-α: n. 33

Results:

- Overall 5-year survival 47 %
- Octreotide alone 37 %
- Octreotide + Interferon-α 57 %

Conclusion:

- may retard tumor growth in pts with midgut carcinoid tumours.

Kolby et. al, 2003

Does interferon add to any tumoristatic effect of SS-Analogs ?

- 80 with progressive NETs

Stabilization

- Lanreotide sc : n. 25 44%
- Interferon-α: n. 27 44%
- Lanreotide + Interferon-α: n. 28 50%

Conclusion

- The addition of alfa Interferon offers no clear benefit over and above SS-Analogs alone.

Faiss et al., 2003

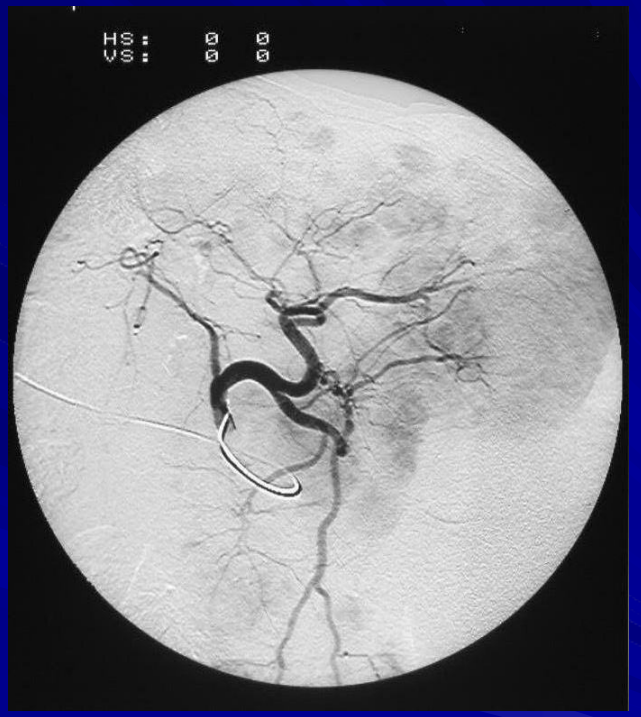
Interferon-Related Thyroid Disease

Carella, JCEM 2004

Thyroid disorders	Diagnosis	Treatment	Antiviral treatment
Hypothyroidism	TSH ↑	L-T4	Continue IFN
Destructive thyrotoxicosis: ▪Symptomatic ▪Asymptomatic	TSH ↓ FT4 ↑ FT3 ↑ RAIU ↓	▪No therapy ▪Beta-blocking drugs	Continue IFN
Graves' Hyperthyroidism	TSH ↓ FT4 ↑ FT3 ↑ RAIU ↑ TrAb +		
Mild Graves		Antithyroid drugs	Continue IFN
Severe Graves		Radioiodine	Withdraw IFN until thyroid function normalizes

Hepatic metastases: Chemoembolization (TACE)

- **Embolization of the hepatic arteries causing a temporary but complete ischemia combined with liver-targeted intraarterial administration of chemotherapy**
- **Contraindications:**
  - **complete portal vein obstruction**
  - **hepatic insufficiency**



TACE: results

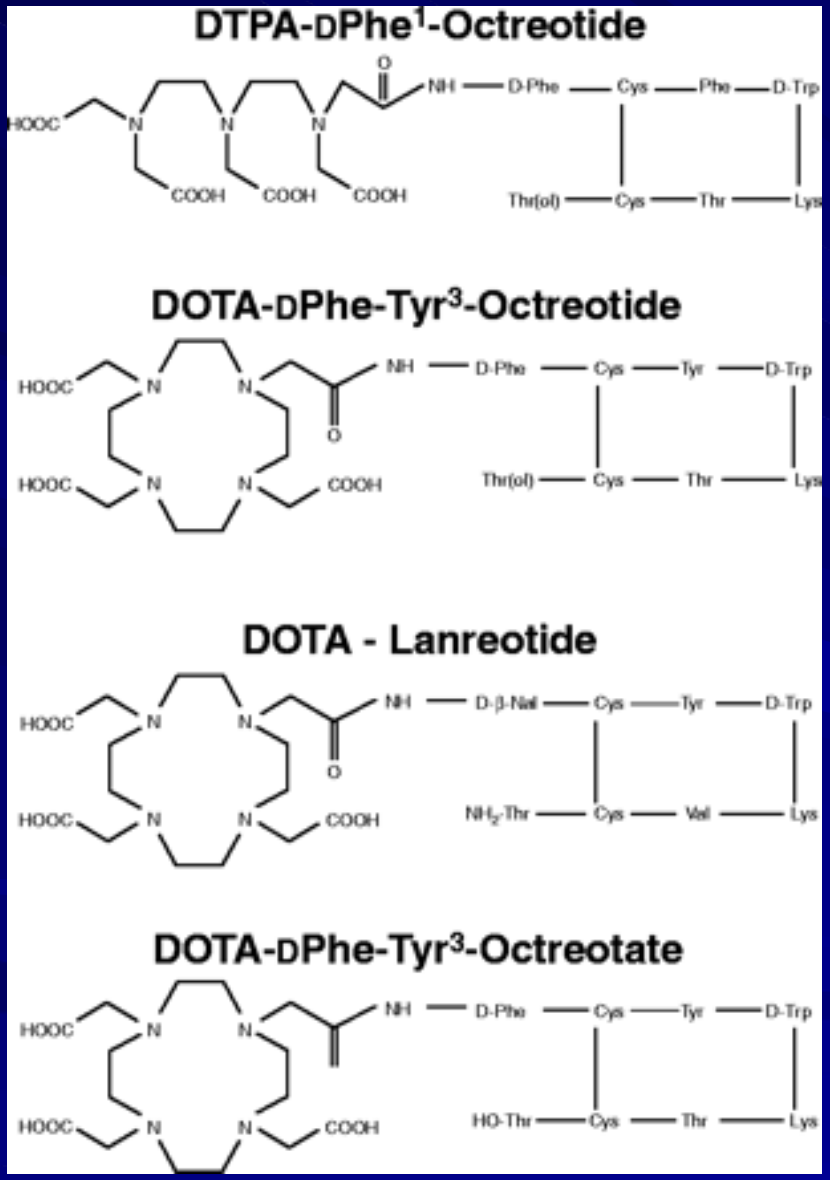
	Pts	Symptoms improvement	Decrease >50 % 5-HIAA	% < Size	Survival Months
Therasse ‘93	23	100	91	35	-
Ruszniewski ‘93	23	73	57	33	21
Clouse ‘94	14	90	69	78	6-8.5
Diaco ’95	10	100	-	60	42.5
Ruszniewski & Malka ’00	15	67	50	53	10.5
Roche ‘03	14	70	75	86	-

Chemotherapy: indication

- High Ki67/MIBI-1 （>10%）
- Treatment failure of surgery and biotherapy
- Poor symptom control

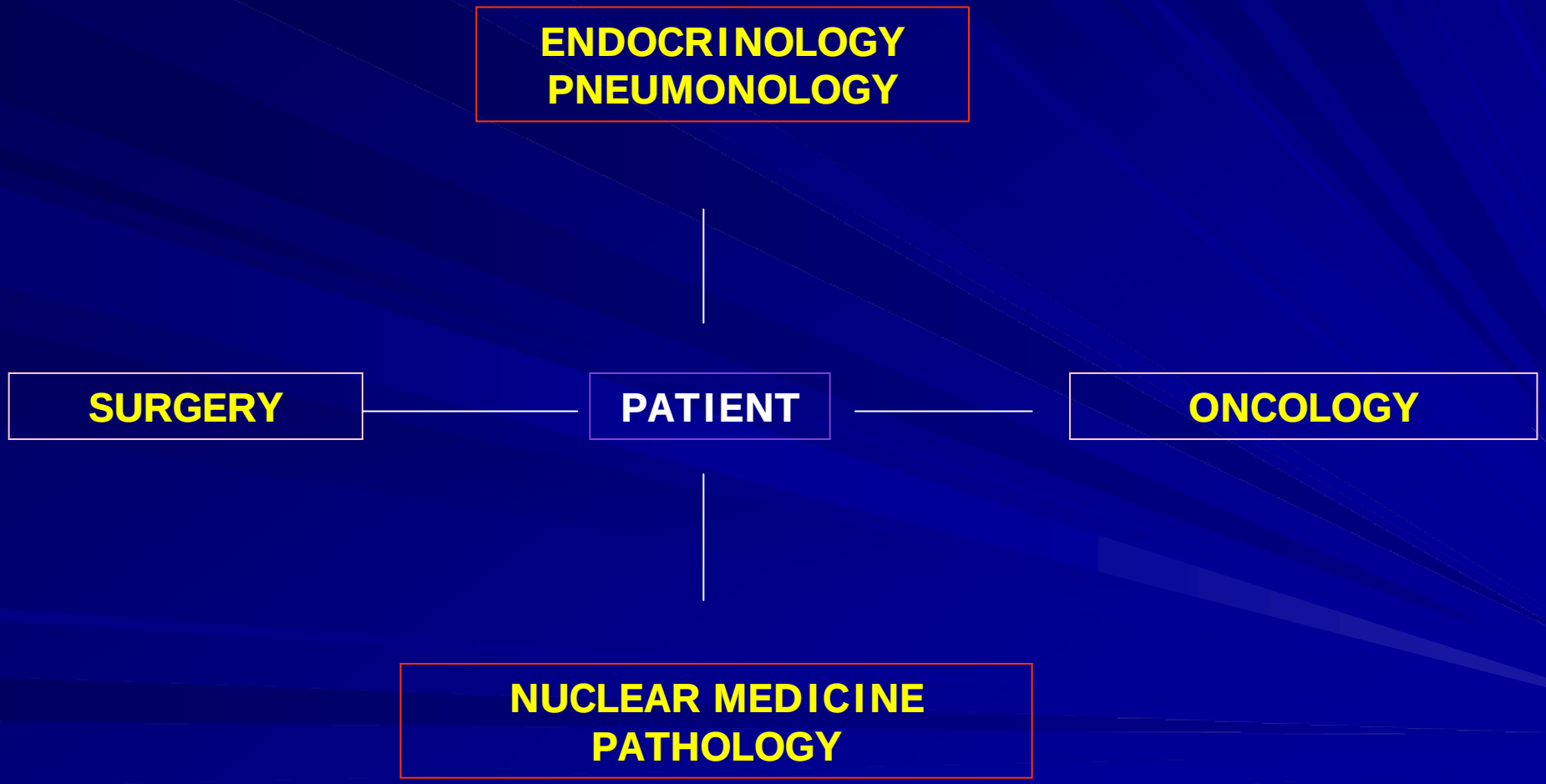
Chemotherapy poorly differentiated Lung NET

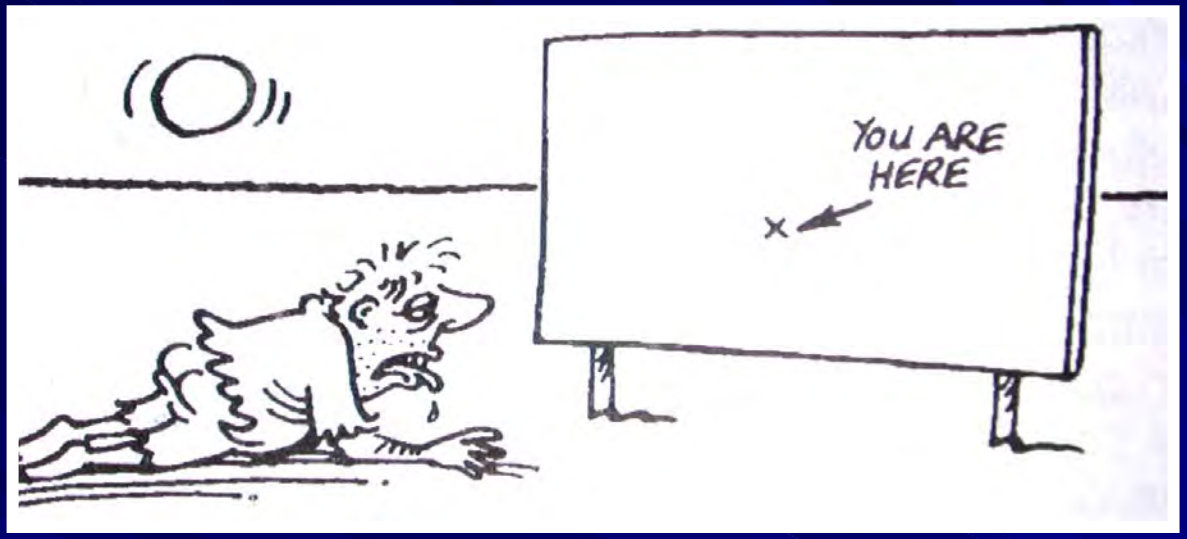
- Surgery early stages, followed by adjuvant chemotherapy
- Combined with radiotherapy in limited disease (Takada M. J. Clin. Oncol. 2002; Fried D.B. Lung Cancer 2003)
- **Polychemotherapy:**
  - 5 fluorouracil + Dacarbazine
  - Cisplatin + Etoposide



RADIONUCLIDE TARGETING AGENTS

Interdisciplinary approach





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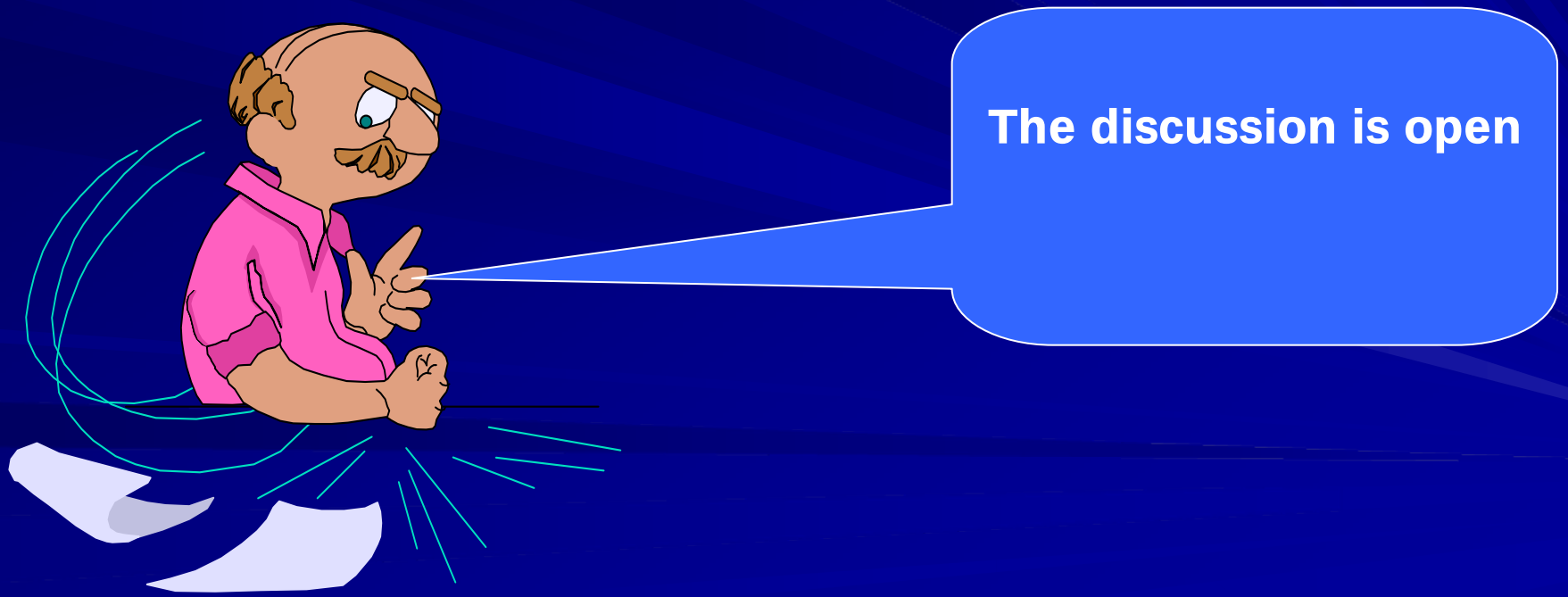


3rd Joint AME/AACE Italian Meeting
October 27th-29th, Verona 2006

Neuroendocrine differentiation in Prostate Cancer: an overview

Filiberto Zattoni

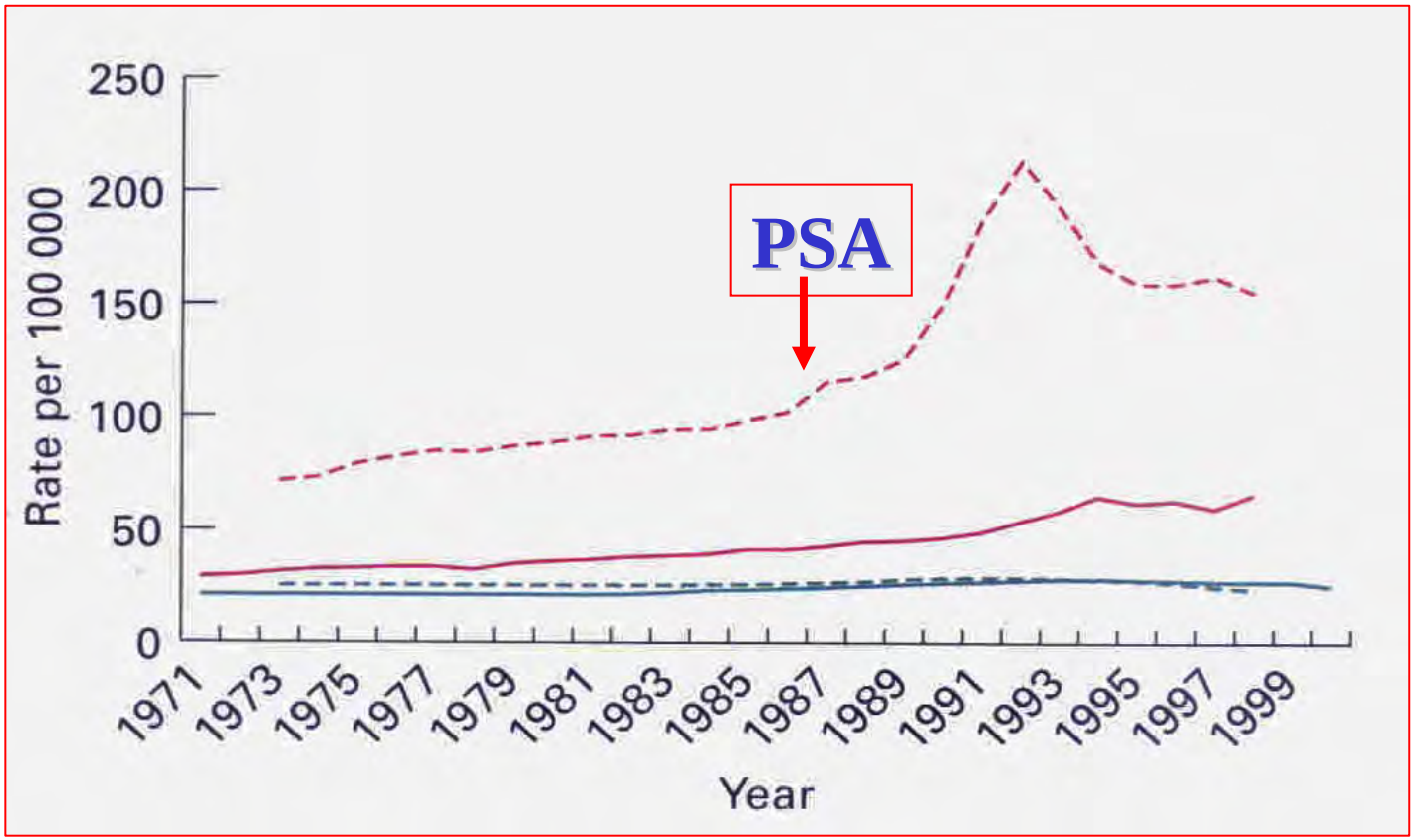
Chair of Urology - University of Verona, Italy

Prostate Cancer

- Prostate cancer (CaP) is the most commonly diagnosed cancer in men in the Western world
- CaP is the second leading cause of male cancer deaths
- CaP accounts for about 33% of incident cases in men

- PSA-based screening and case finding together with an increasing awareness of CaP in the population has led to identification of early stage CaPs

CaP incidence, mortality and PSA



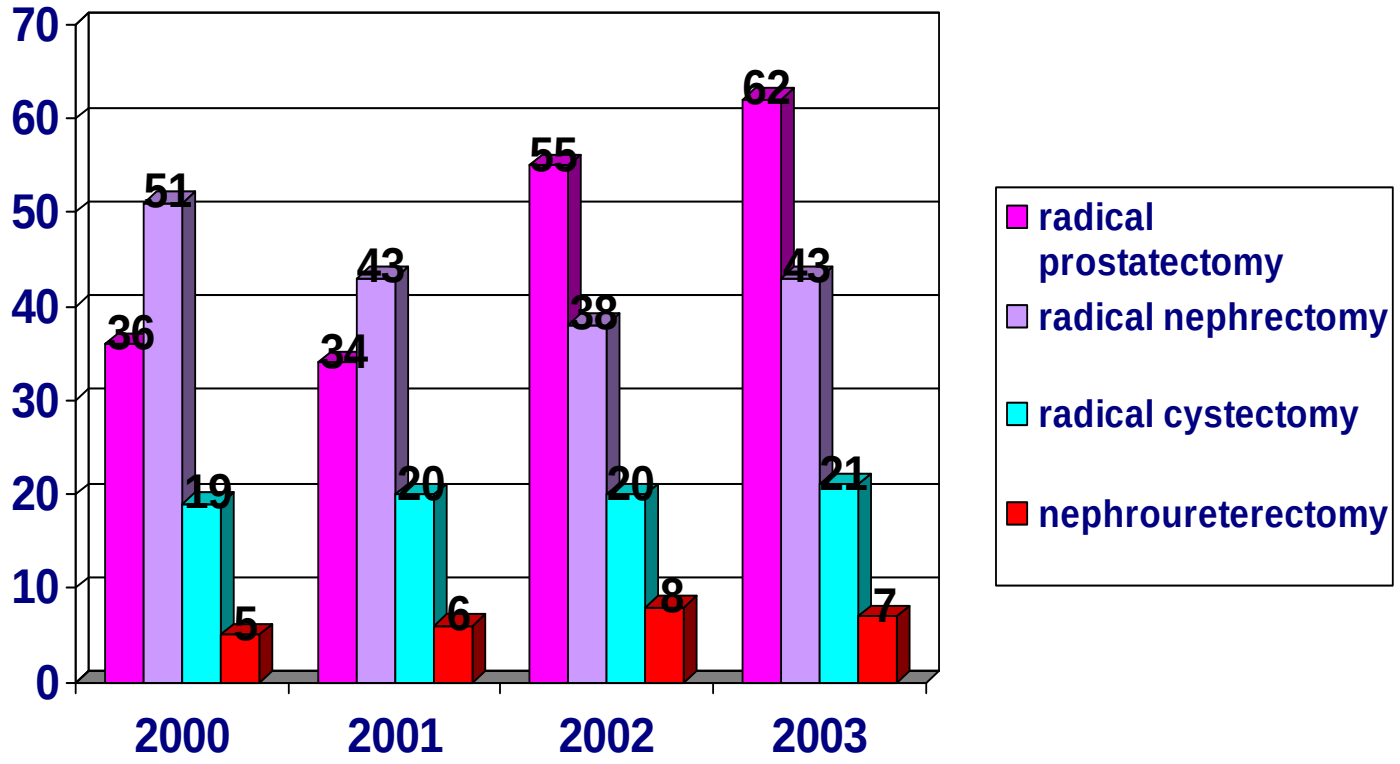
Incidence (red) – Mortality (green)
UK (unbroken lines) – USA (broken lines)

Quinn 2002

Localised Prostate Cancer

Major Oncological Procedures

Personal Experience [January ’00-December’03]



CaP radical surgery

Reasonably a direct relationship exists between cancer situation at the time of the intervention and distance outcomes

The question is: how early should the treatment be?

Using an analysis "number-need-to-treat" 15 patients with clinically localised prostate cancer have to be treated in order to save only one of them

[Talcott JA, 2006 AUAs Highlights]

A balance has to be found between early diagnosis and need to treat!

CaP natural history

- **The natural history of CaP is variable and difficult to be predicted**
- **There is a wide discrepancy between incidence and mortality rates highlighting the variable biological behavior of the disease**

Thus …

…characterizing the clinical and biological significance of early stage CaP in an individual would provide valuable information in planning therapy and predicting prognosis

Prognostic factors in CaP

Category I: **factors proved to be of prognostic importance and useful in clinical patient management**
(preoperative PSA levels, TNM stage, Gleason score, surgical margin status)

Category II: **factors that have been extensively studied biologically and clinically but whose importance remains to be validated in statistically robust studies**
(tumor volume, histologic type and DNA ploidy)

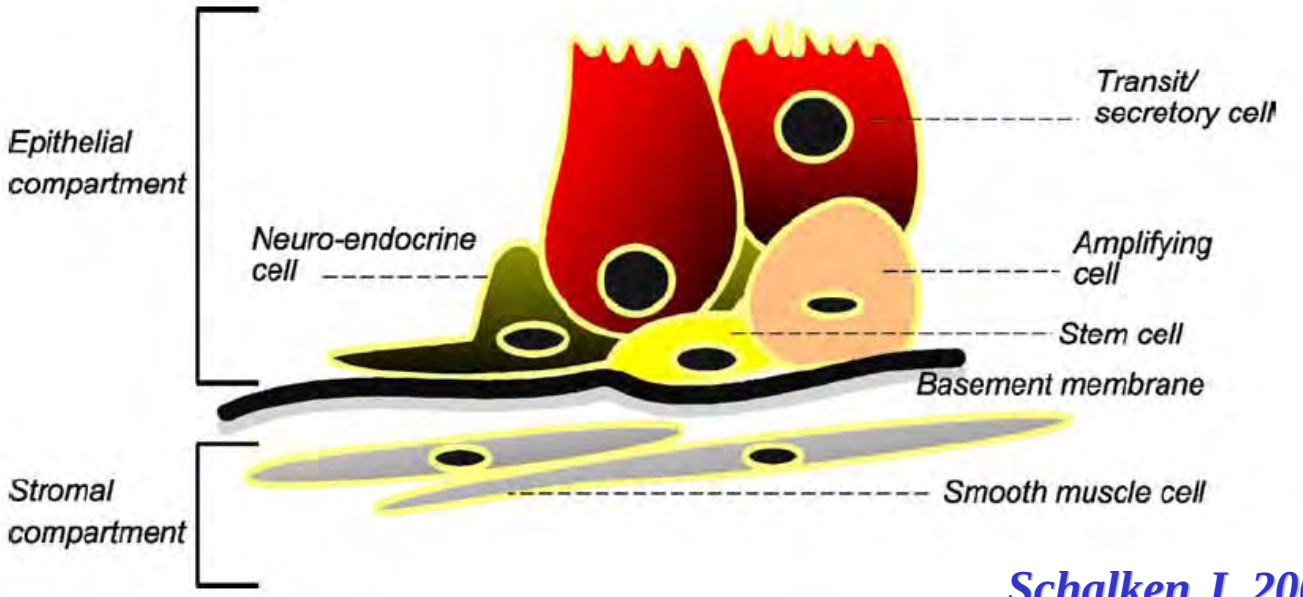
Category III: **all other factors not sufficiently studied to demonstrate their prognostic value**
(perineural invasion, NE differentiation, microvessels density, nulear roundness, chromatine texture, proliferation markers, PSA derivatives and other factors)

The College of American Pathologists Consensus Statement, 1999

Prostate biology

Normal prostate-

- **The basal layer is populated by epithelial stem cells and transiently proliferating/amplifying (TP/A) cells intermediate to the stem cells and fully differentiated cells**
- **The luminal layer is composed of fully differentiated prostate epithelial cells**
- **Neuroendocrine cells (NEC) are scattered throughout the gland**

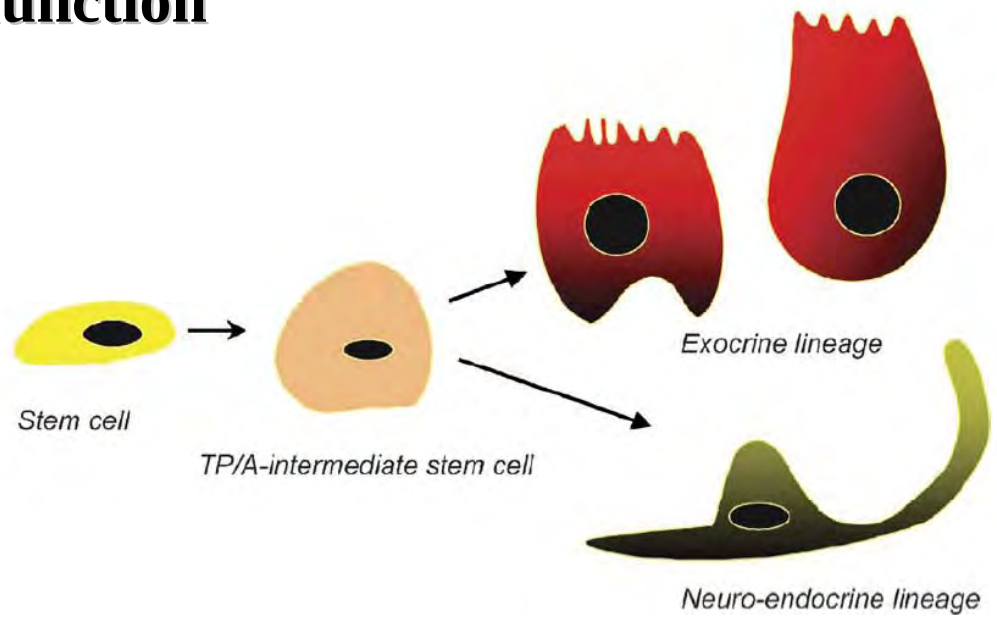


Schalken J, 2003&2005

Prostate biology

❖ **According to epithelial cellular hierarchy TP/A cells originate from stem cells**

❖ **From TP/A cells originate cellular lines with esocrine and neuroendocrine (NE) function**



Schalken J, 2005

Prostate biology:
NE cells characteristics

NE cells may be involved in regulating

- growth and differentiation of the developing prostate
- secretory processes in the mature gland

NE cells produce

- serotonin, chromogranin A and B , secretogranin (Cg C), neuron-specific enolase (NSE) and other substances in smaller quantities

Abrahamsson PA, J Androl 1993

Prostate biology

- **NE peptides may have a growth factor activity through lumecrine, endocrine, paracrine and autocrine mechanisms**

- **NE cells do not show proliferative activity; they are postmitotic and terminally differentiated cell population in human prostate**

- **NE cells do not show nuclear androgen receptor (AR) being androgen insensitive: they may function independently of hormonal regulation**

- **NE cells, incidentally, may expand to replace the androgen-sensitive tumor cell population during androgen ablation therapy**

Bonkhoff H, 1991; Krijnen J, 1993

NE differentiation in CaP

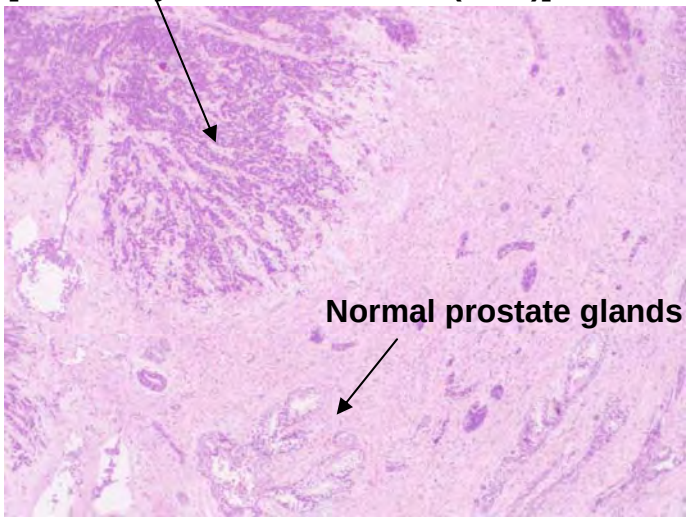
NE differentiation is more frequently observed in CaP than in any other GU malignancy and occurs in three different forms:

- **small cell carcinoma**
- **carcinoid and carcinoid-like tumors**
- **focal NED in conventional CaP**

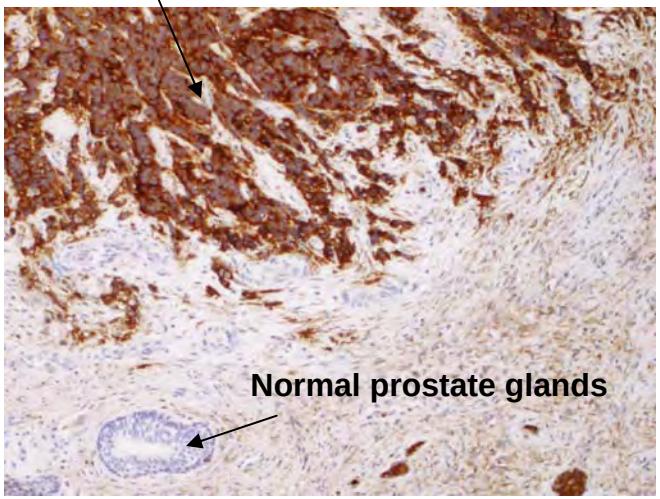
Di Sant'Agnese PA, 1992

Prostate small cell carcinoma

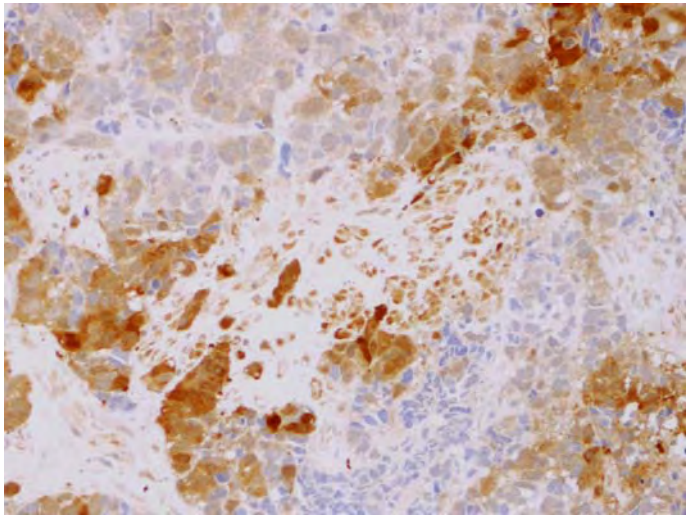
Small cell carcinoma with nuclear “molding” [Hematoxylin and eosin stain(H&H)]



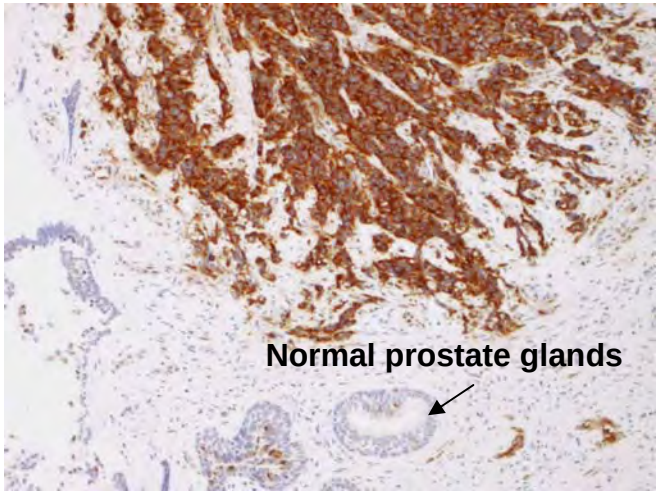
Small cell carcinoma with CD56 positivity



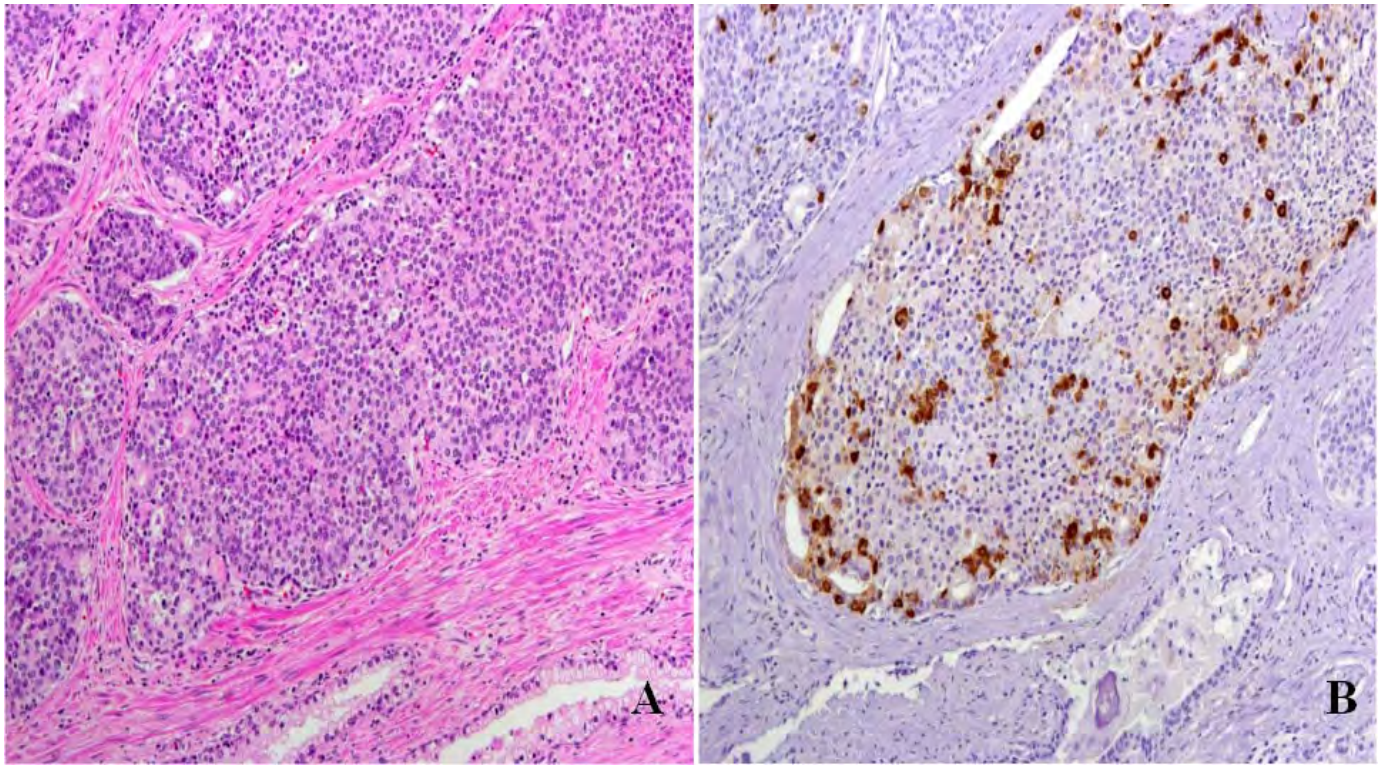
Small cell carcinoma with NSE positivity



Small cell carcinoma with synaptophysin positivity



Focal NED in conventional CaP



Prostate adenocarcinoma: A) Hematoxylin and eosin stain(H&H, 10X); B) Chromogranin A immunohistochemical stain (envision immunoperoxydase, 10X)

NE differentiation in CaP

Focal NED is present in virtually all cases of CaP

The number of cells may widely vary (24-92%) even according to:

- **tissue fixative**
- **antibody and method used**
- **number of examined tissue sections**

Abrahamsson PA, 1987 and 1989; Bostwick DG, 1994; Taplin ME, 2005

NE differentiation and prognosis

Prognostic significance of neuroendocrine differentiation

Investigator	Cases (n)	Technique	Significant Prognostic Value	Multivariate Analysis	Independent Prognostic Value
Taplin *et al.*[7]	390	Quantitative sandwich immunoassay	Yes	Yes	Yes
Berruti *et al.*[23]	108	Quantitative sandwich immunoassay	Yes	Yes	Yes
McWilliam *et al.*[11]	92	IHC (CgA, NSE)	Yes	No	No
Hvamstad *et al.*[51]	138	Serum CgA, NSE	Yes	Yes	Yes
Weinstein *et al.*[24]	104	IHC (CgA)	Yes	No	Yes
Ahlegren *et al.*[9]	111	IHC (CgA)	No	Yes	No
Cohen *et al.*[8]	110	IHC (CgA, NSE)	Yes	No	No
Theodorescu *et al.*[6]	71	IHC (CgA)	Yes	Yes	Yes

KEY: *IHC = immunohistochemistry; CgA = chromogranin A; NSE = neuron-specific enolase.*

- **NED in CaP received attention because of its prognostic and therapeutic implications**
- **The prognostic importance of focal NED is controversial; it may have an influence on prognosis related to hormone-resistant tumors or a role in the conversion to a hormone-resistant phenotype**

Shariff AH, 2006

NE differentiation and prognosis

NED variable prognostic significance in different studies could be explained by differences in:

- **determining NE differentiation**
- **interpreting immunohistochemical results whose methods lack in standardization**
- **cohorts of patients**
- **serious sampling error when limited tissue samples are available (NE cells have unequal distribution in most tumors)**

Shariff AH, 2006

NE differentiation and apoptosis

- **The vast majority of CaP cells with NE features escape programmed cell death**
- **Resistance to apoptosis can enhance the malignant potential of tumor cells in different ways, including resistance to drug and hormonal therapies**
- **Malignant cells in close proximity to NE cells express the anti-apoptotic protein *bcl-2***
- **Normal NE cells and NE differentiated epithelial cells express *survivin*, another apoptosis inhibitor**

Shariff AH, 2006; Hanahan D, 2000; Ambrosini G, 1997

NE differentiation and angiogenesis

- **NE cells through their secretory products are directly involved in angiogenesis**
- **Significantly greater neovascularization was found in high-grade CaP with many tumor NE cells compared to those with few ones**
- **NE cells are a significant source of vascular endothelial growth factor in CaP**

Grobholz R, 2000

NE differentiation in HR-CaP

- **Mutations in AR gene and in the complex downstream signaling pathways are found in up to one half of all HR-CaP**

- **An alternative pathway by which CaP cells may escape hormonal control refers their ability to acquire NE features**

- **NED is greatly increased in pts with HRCaP after long-term androgen deprivation therapy *but* it is not clear if this is attributable to hormone refractoriness or to long-term hormonal therapy**

Hirano D, 2004

CgA and NE differentiation

- **CgA is a valuable marker for NE tumors and may be considered the preferred marker of NED**
- **It has been found to be more frequently elevated in pts with CaP than with PIN and BPH**
- **CgA levels were found greater in pts with metastatic disease than in those with organ-confined or locally advanced disease**
- **CgA better reflects NE status than NS Enolase**
- **CgA in combination with PSA may predict for prognosis in pts with advanced CaP**

Deftos LJ, 1991; Berruti A, 2000; Cussenot O, 1996

CgA and localized CaP: personal experience

Aim of the study

- … whether preoperative levels of serum NE markers (CgA and NSE) and the CgA immunohistochemical expression may add further information for a better staging in pts with localized CaP and candidates to RP
- … possible relationships between preop. serum concentration of NE markers and the commonly recognized prognostic variables (PSA, pT, definitive GS), seeking for any further correlation between CgA levels and pathological findings (CgA immunohistochemical expression)

Grimaldi F … Zattoni F, IJBM 2007 [in press]

CgA and localized CaP: personal experience

Patient population

- From November 2003 and April 2004
- 41 consecutive newly diagnosed CaP patients satisfied the following inclusion criteria:

- cT1-2
- no prior adjuvant therapy
- no prior prostatic surgery
- histological demonstration of CaP at biopsy confirmed at the definitive surgical specimen

- All patients underwent RRP

Grimaldi F … Zattoni F, IJBM 2007 [in press]

CgA and localized CaP: personal experience

TABLE I. Patients' Characteristics.

No.		41
Age (years)		65.44 ± 6.41 (48-75)[a]
Pathological stage	pT2	22 (53.5%)
	pT3	17 (41.6%)
	pT4	2 (4.9%)
	pN1	2 (4.9%)
Pathological Gleason score	< 7	26 (63.4%)
	≥ 7	15 (36.6%)
Preoperative serum PSA (ng/mL)		8.75 ± 6.98 ng/mL (2.33-34.50)[a] **6.1 ng/ml (4.8-9.3)[b]**
Preoperative serum CgA (ng/mL)		78.84 ± 114.63 ng/mL (23.4-754)[a] **49.7 ng/mL (41.9-77.1)[b]**
Preoperative serum NSE (ng/mL)		6.58 ± 3.11 ng/mL (2.40-17.36)[a] **5.8 ng/mL (5.1-7)[b]**

[a] Mean ± SD (range)

[b] Median and interquartile range

Grimaldi F … Zattoni F, IJBM 2007 [in press]

CgA and localized CaP: personal experience

Results

TABLE II. Association among the different parameters evaluated in 41 patients.

Association	*P*-value
Preop. serum PSA - Preop. serum NSE	0.975
Preop. Serum CgA - Preop. serum PSA	0.374
Preop. serum CgA - Preop. serum NSE	0.541
Pathological stage - Pathological Gleason score	0.001
Preop. serum CgA – Patients' Age	0.177
Immunohist. CgA - Preop. serum CgA	0.979
Immunohist. CgA - Preop. serum NSE	0.893
Immunohist. CgA - Preop. serum PSA	0.979
Immunohist. CgA - Pathological Gleason score	0.014
Immunohist. CgA - Pathological stage	1.000

Grimaldi F … Zattoni F, IJBM 2007 [in press]

CONCLUSIONS: … tumor grade is associated with a change in the biomolecular profile, even in pts with similar serum PSA levels. As the prognosis of HG CaP is poor, these tumours should be analysed by immunohistochemical staining to identify specific tumour features for appropriate selection of adjuvant therapy

Augustin H et al, J Cancer Res Clin Oncol. 2003 Nov;129(11):662-8

CgA and localized CaP: personal experience

Results

TABLE III. Serum PSA, plasma NSE and serum CgA according to pathological staging.

Path. staging	II (pT2)	> II (pT3-4/N1)	*P* value
No.	22	19	
Preop. PSA (ng/mL)	**6.2 (4.4-12.4)** [a]	**5.8 (4.9-8.0)** [a]	0.875
Preop. NSE (ng/mL)	**5.7 (5.0-6.9)** [a]	**5.9 (5.4-6.8)** [a]	0.745
Preop. CgA (ng/mL)	**49.3 (35.2-65.6)** [a]	**49.7 (45.6-88.3)** [a]	0.049

[a] PSA, NSE and CgA values are presented as **median and interquartile range.**

Grimaldi F … Zattoni F, IJBM 2007 [in press]

CgA and localized CaP: personal experience

Results

TABLE IV. Serum PSA, plasma NSE and serum CgA according to pathological Gleason score.

Path. Gleason score	< 7	≥ 7	*P* value
No.	26	15	
Preop. PSA (ng/mL)	**6.2 (4.9-13.1)**[a]	**5.9 (4.7-6.8)**[a]	0.449
Preop. NSE (ng/mL)	**5.9 (5.0-6.9)**[a]	**5.7 (5.3-6.8)**[a]	0.955
Preop. Cg-A (ng/mL)	**46.8 (32.7-70.3)**[a]	**57.3 (48.4-101.5)**[a]	0.038

[a] PSA, NSE and CgA values are presented as **median and interquartile range**.

Grimaldi F … Zattoni F, IJBM 2007 [in press]

CgA and localized CaP: personal experience

Conclusions

These data are just preliminary and they require to be confirmed in a larger study population

These results support the idea that preoperative circulating CgA may be useful as diagnostic as well as prognostic marker in the newly diagnosed localized CaP, potentially offering additional information with respect to serum PSA. Serum CgA in association with the other commonly utilized prognostic factors might induce the decision forwards possible early adjuvant therapy in patients with localized disease undergone definitive treatments in view of potential clinical progression.

NED and new treatment strategies

- **Growth factor inhibitors are being developed against the products of NE cells**
- **Suramin can bind several growth factors as well as block receptor binding**
- **Combination therapy with lanreotide acetate (a somatostatin analogue) and ethinylestradiol was found to produce a significant decrease in serum CgA as well as to reintroduce objective clinical responses in pts with HRCaP**
- **CgA antibodies may suppress CgA apoptosis-inhibiting activity leading to programmed cell death through the apoptotic pathways**

Di Silverio F, 2003; Yu DS, 2003

NED and new treatment strategies

- **In animal models bombesin/ gastrin-related peptide antagonist, RC-3095, seem to enhance the inhibitory effects of LHRH analogs** (no clinical trials have been performed as yet)

- **Serotonin antagonist pindobind was shown to have a marked antiproliferative effects both in vitro and in vivo in athymic nude mice**

- **Pindobind inhibited proliferation of androgen-independent tumor cell lines in a dose-dependent manner**

Pinski J, 1993;Abdul M, 1994; Hvamstad T, 2003

Conclusions

- Much remains to be understood about NE cells in both normal and neoplastic prostate
- NED effects on CaP prognosis is still controversial
- CgA represents an established marker for NED in the prostate and in combination with PSA may predict survival in patients with HRCaP
- New approaches towards HRCaP treatment targeting NED are in trial and in development

Verona 27 ottobre 2006

Somatostatin Analogs in Hepatocellular Carcinoma

Vito D. Corleto

Malattie Dell'Apparato Digerente e del Fegato

II Facolta di Medicina e Chirurgia

Universita' "La Sapienza" Roma

Somatostatin Analogs and Hepatocellular Carcinoma (HCC)

Some issues to be addressed:

Does HCC possess functional SS receptors (SSTR)

Are SSTR quantitatively differet from normal liver

Which SSTR subtypes are expressed by HCC

Why SS treatment should work in HCC

Results from “in vitro” and “in vivo” studies

Treatment options of hepatocellular carcinoma

Localized or resectable HCC: 10%

Surgery and liver transplantation may offer long-term survival

5 yrs survival rate 30%

Non-resectable HCC: 90%

Transcatheter arterial Chemoembolization TACE

Percutaneus ethanol injection (PEI)

Laser intestinal thermotherapy (LITT)

Chemotherapy or Hormone therapy: SS analogs

5 yrs survival rate 1%

Treatment options of hepatocellular carcinoma

Non-resectable HCC:

Pre-existing chronic liver disease limits treatment options in HCC

Response rate <20% with single agent systemic chemotherapy

Multiagent chemotherapy may offer better response rate but patients are unable to tolerate its toxicity

SS analogs have been proposed in HCC patients with advanced disease and poor liver function

SSTR expression and SS analogs on HCC cell lines

SSTR 2, 3, 4 in HepG2 (NB); Lanreotide (dose-dependent) inhibition of cell proliferation and apoptosis induction in HepG2

Int J Oncol 2000;16:1197-201

Octreotide (0,2 μg) stimulate apoptosis in BEL-7402 (SSTR not investigated)

Chin Med J 2001;114:1167-70

SSTR expression and SS analogs on HCC cell lines

SSTR 2-5 in HepG2, 7721 and L-02 Cells (RT-PCR); Octreotide (dose-dependent) stimulate apoptosis and reduce alpha feto production

Acta Pharmacol Sin 2004;25:1380-6

SSTR 2, 3, 5 in HepG2 (WB); Octreotide (dose-dependent) inhibit PCNA expression and stimulate apoptosis in HepG2

HBV gene transfection decrease SSTR expression and grow inhibitory effects of Octreotide

Ai Zheng. 2005 Aug;24(8):965-9. Chinese.

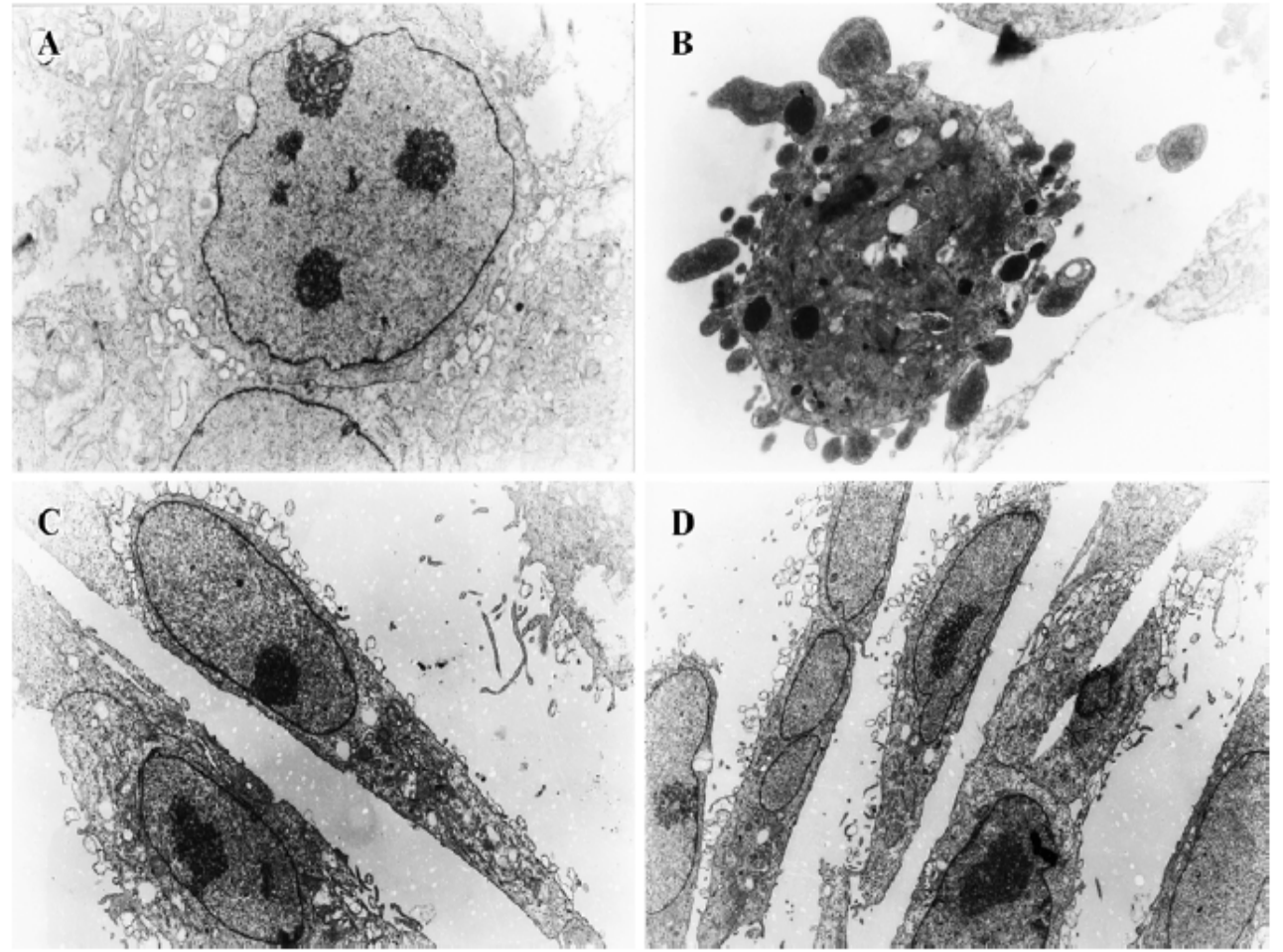
HCC cells apoptosis: electron microscopy view

Control

Octreotide

HepG2

L-02

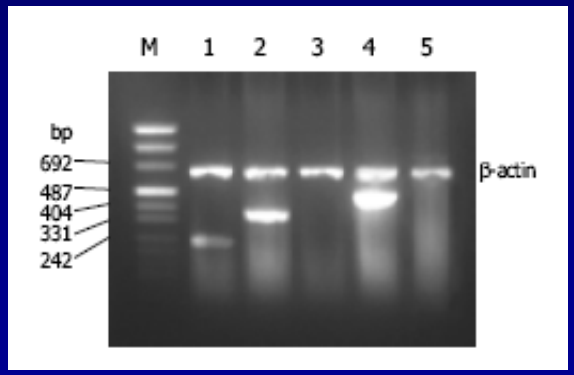


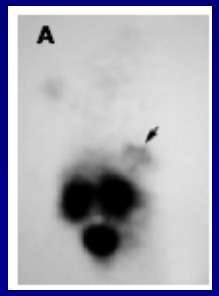
Acta Pharmacol Sin 2004;25:1380-86

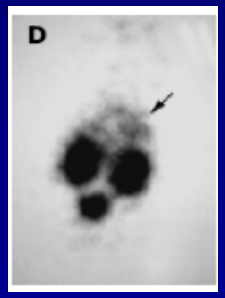
SSTR expression and SS analogs on HCC cell lines

SSTR 1, 2, 4 in HepG2 (RT-PCR); HCC-bearing nude mice were positive after 2 and 4,5 hs injection of radiolabelled SS

World J gastroenterol 2005;11:3953-3957





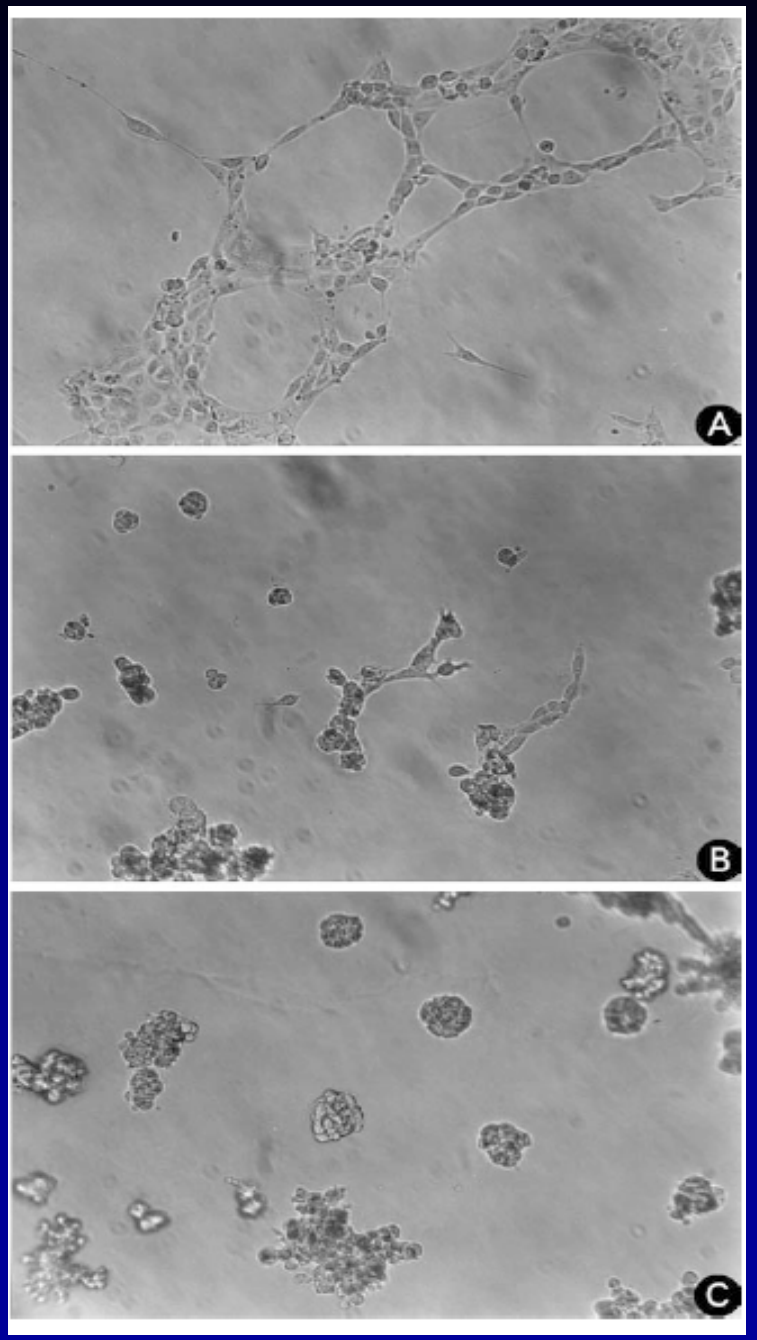


Octreotide suppressive effect on blood vessels supply in nude mice bearing HCC xenografts

VEGF →

OCTR 10^{-8} M →

OCTR 10^{-6} M →



J Cancer Res Clin Oncol 2003;129:327-334

Data from HCC cell lines and experimental animals bearing HCC xenografts show promising results on the “antiproliferative” effects of SS analogs

SS analogs efficacy in human studies

58 HCC: OCTR 250 μg twice vs no treatment

median survival: 13m vs 4m, (p=0,002);

cumulative survival rate a 12m: 37% vs 13%

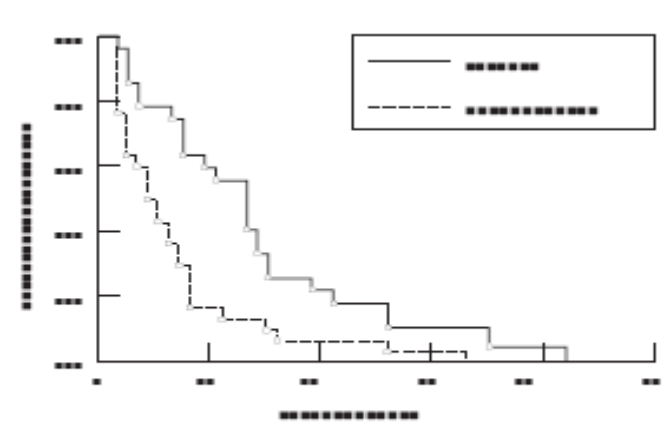


Figure 2 Survival curves for treated and non-treated patients with HCC.

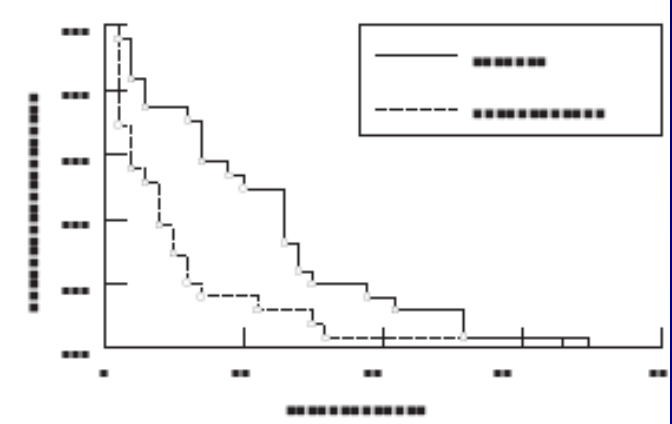


Figure 3 Survival curves for treated and non-treated cirrhotics with HCC.

(GUT 1998;42:442-447)

SS analogs efficacy in human studies

21 SRS-neg HCC: 30 mg LAR/14gg

median survival: 4,2m;

median time to progression: 2,5m

(Int J Oncol 2000;16:1197-1201)

SS analogs efficacy in human studies

70 HCC: OCTR 250 μg twice for 2 weeks followed by LAR 30 mg/4 weeks vs placebo

median survival: 1,93m vs 1,97m

no difference in survival, alfa feto decrease or QoL vs control

(Hepatology 2002;36:687-691)

SS analogs efficacy in human studies

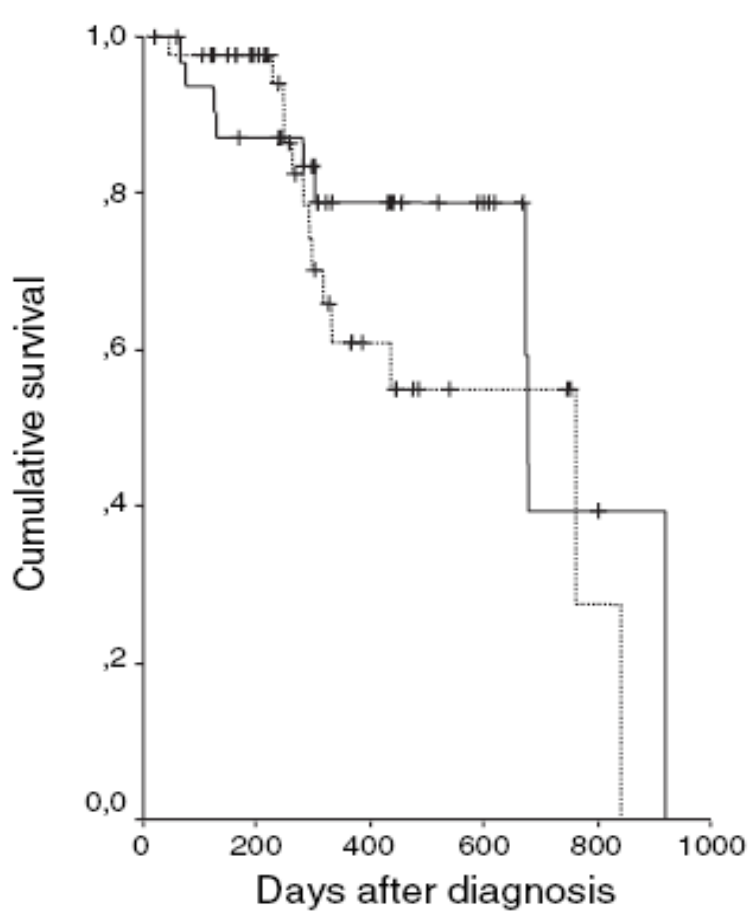


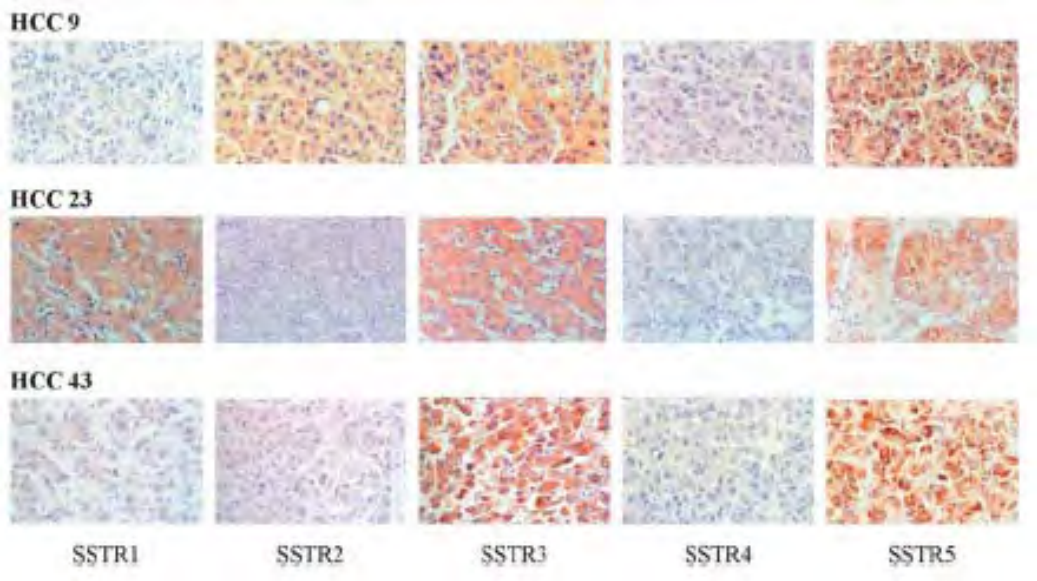
Figure 3 Survival curves of patients treated with (---) octreotide and (—) transarterial chemoembolization (TACE).

41 advanced HCC randomly assigned to Octreotite or Transcatheter arterial Chemoembolization (TACE)

Similar survival

(J Gastroenterol Hepatol 2005;20:1422-1428)

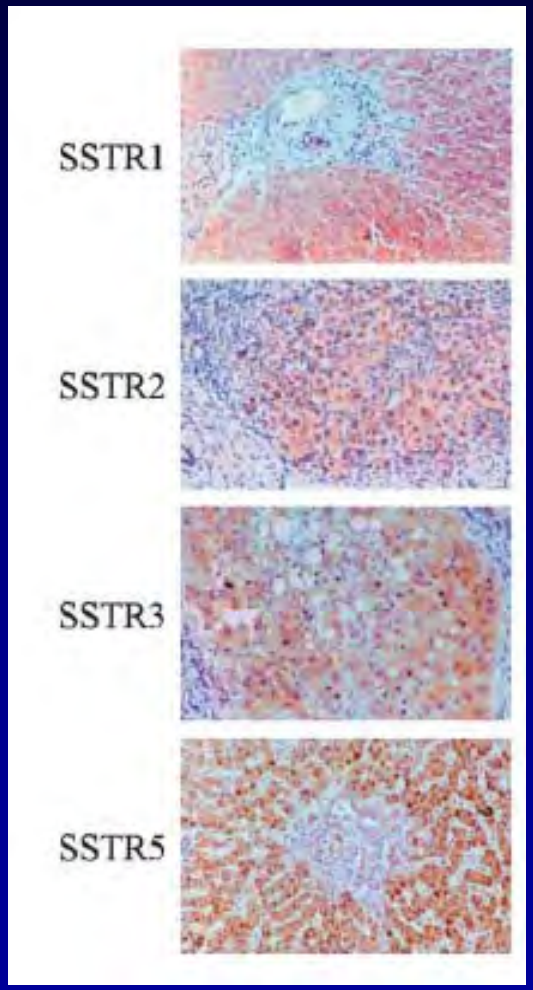
Differential expression of somatostatin receptor subtypes in hepatocellular carcinomas

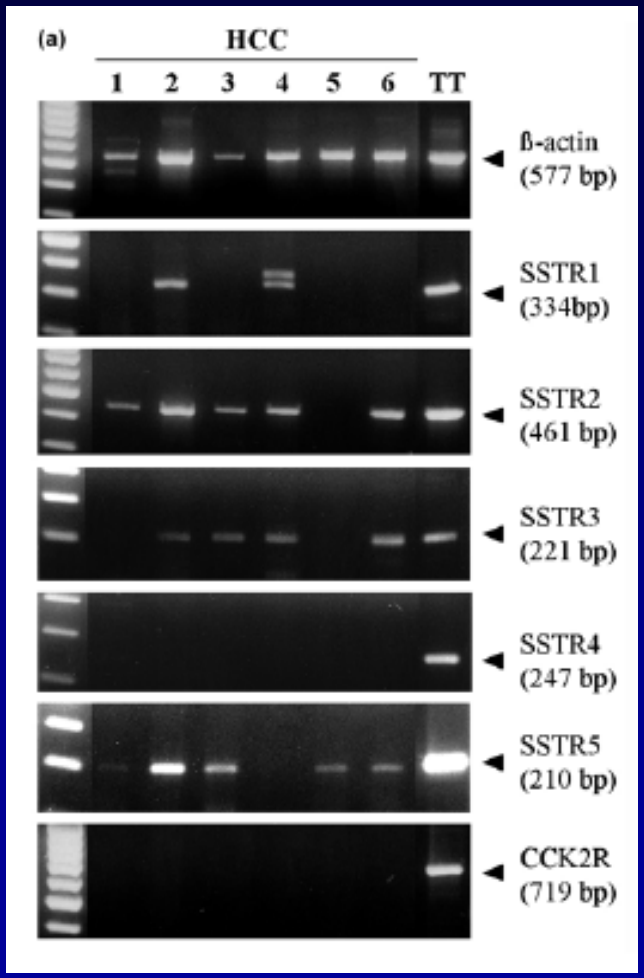


Journal of Hepatology 2004;41:112-118

SSTR subtype expression in HCC

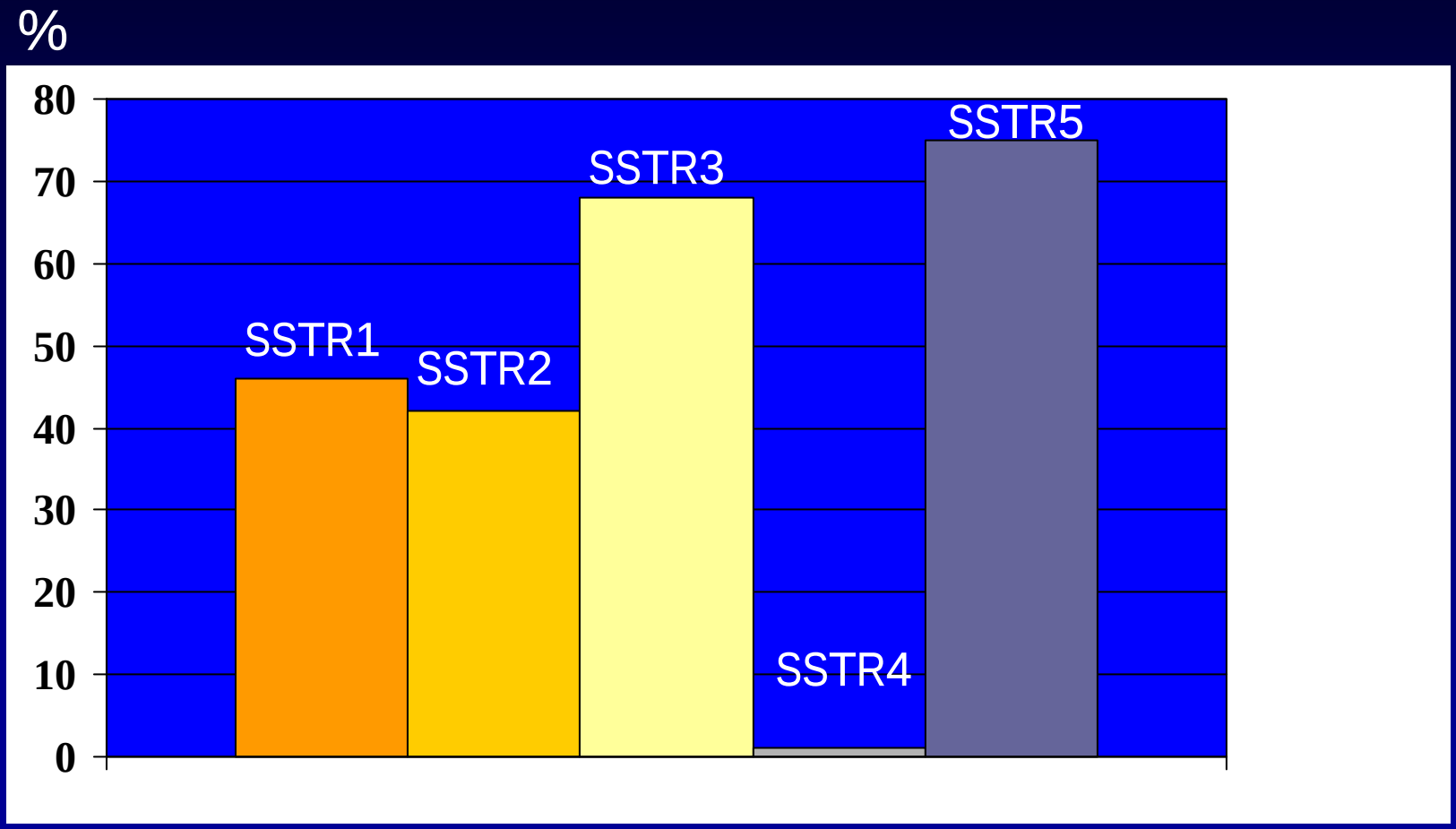
Himmunohistochemistry vs RT-PCR (98 % corr.)





Journal of Hepatology 2004;41:112-118

SSTR subtype expression in 56 HCC



Journal of Hepatology 2004;41:112-118

Which HCC characteristic correlate with SSTR expression

SSTR expression is independent from

- Tumor stage
- Differentiation
- Histological type
- Underlying liver disease

None of these parameters is predictive of SSTR subtype expression and then of the response to SS analogue therapy

Journal of Hepatology 2004;41:112-118

SS analogs efficacy in human studies

108 HCC: OCT-LAR 30 mg/monthly vs Placebo;
end-point: death of any cause;

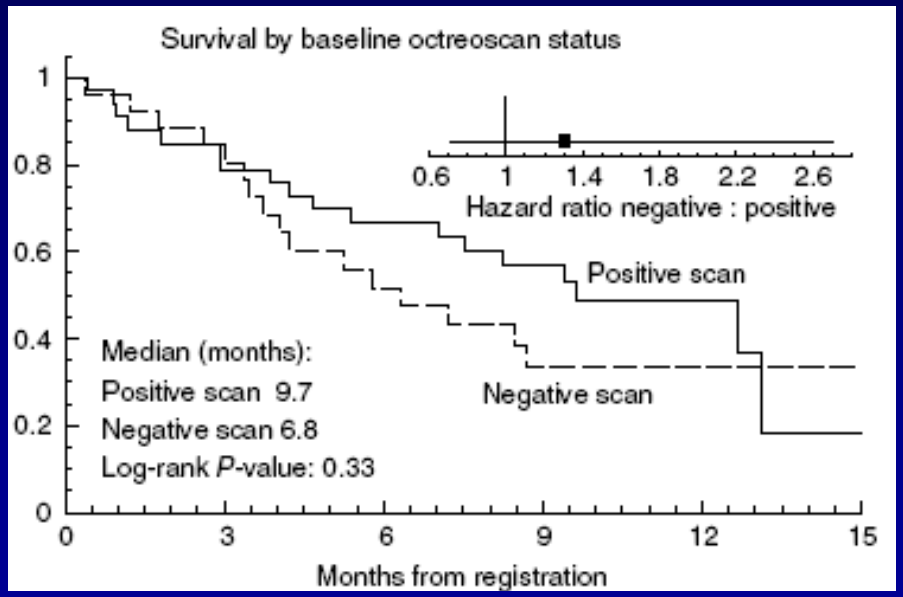
Results: no statistical differences

(Hepatology 2003;38:706A)

SS analogs efficacy in human studies

63 HCC: 20 mg OCT-LAR /mountly

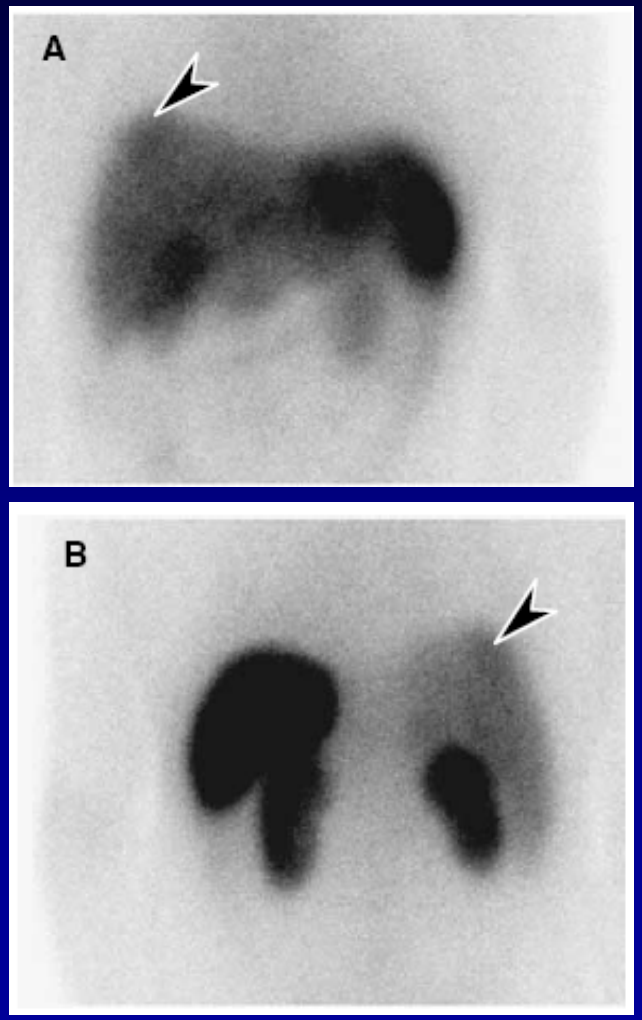
median survival: 8m; 61 % were SRS positive;



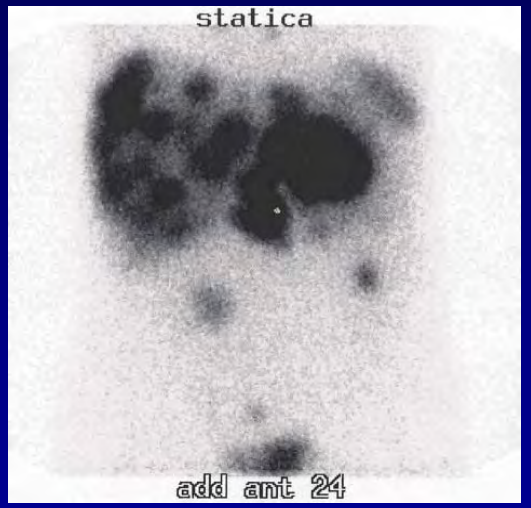
(British J of Cancer 2006)

Octreotide scintigraphy in HCC

HCC positive scan



NET liver metastases



SS analogs and HCC: Where we are

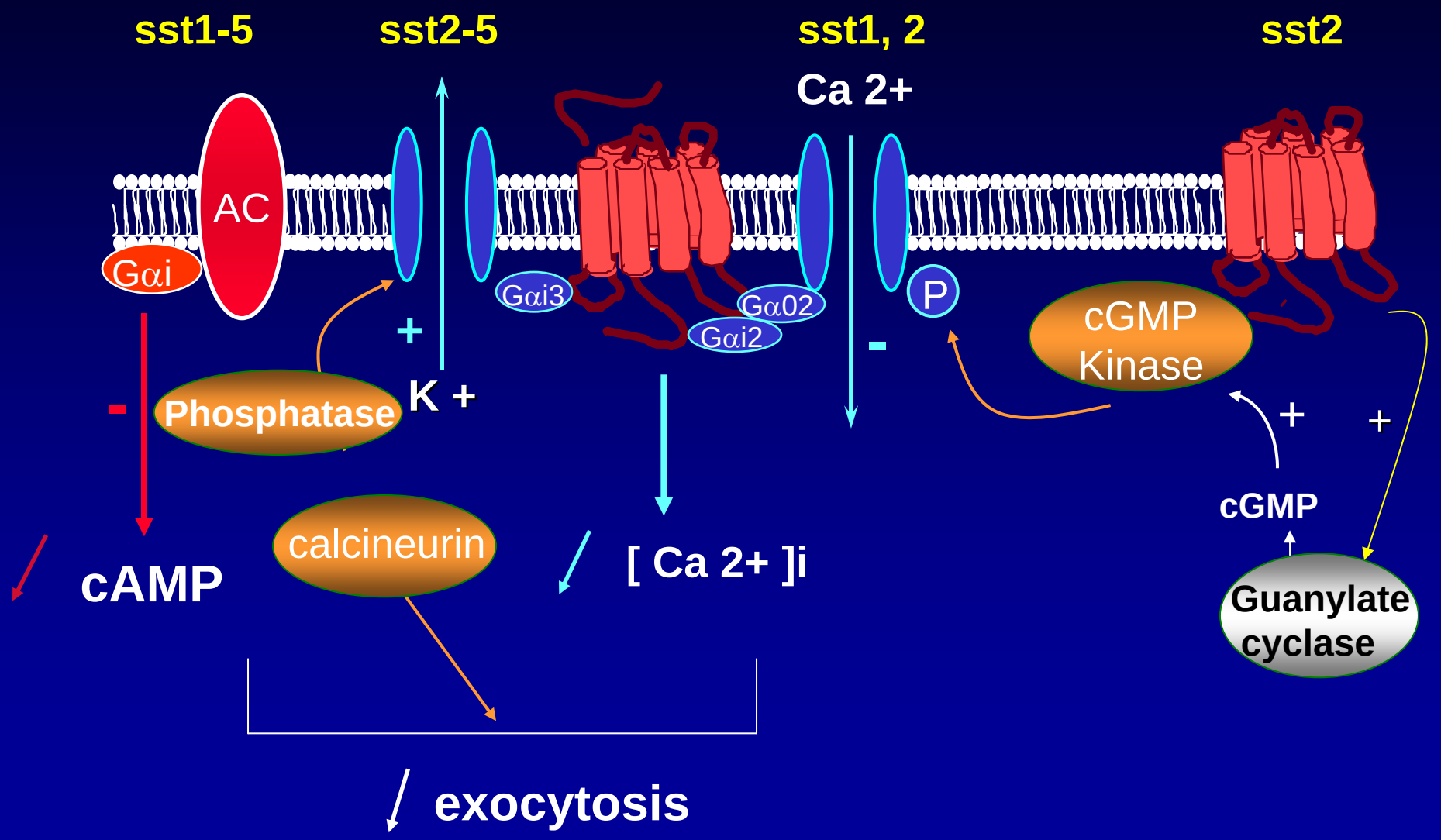
Over all results from “in vivo” studies are limited or poor

Although, well tolerated, SS analogs did not show a clear antitumor activity

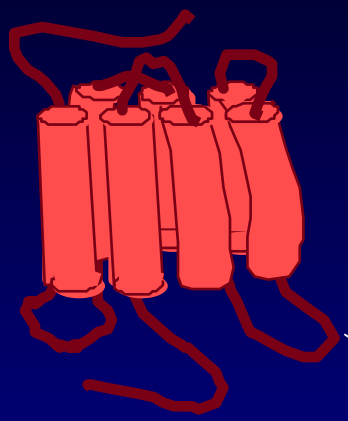
Positive Octreascan does not predict SS analogs efficacy

Better selection of patients and doses may improve the efficacy in a subgroup of HCC patients

Somatostatin receptors mechanisms



SSTR: growth inhibition



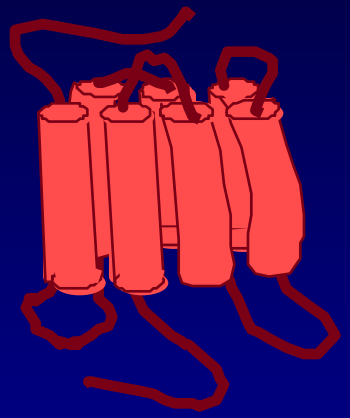
induction of cell death

inhibition of autocrine growth factor/hormone secretion

inhibition of cell cycle progression

SSTR: growth inhibition

Indirect effects



Inhibition of angiogenesis

myofibroblasts migration

Immunomodulatory effects

Inhibition of secretion
of growth factors/hormones

Thank you for your attention

Chemotherapy and Biotherapy in the treatment of Neuroendocrine Tumors

Salvatore Artale
Oncologia Medica Falck
Ospedale NIguarda Ca' Granda
Milano

Verona 27.10.2006

WHO Classification 2000

- Well differentiated endocrine tumors
  (benign or low grade malignancy)
- Well differentiated endocrine carcinomas
- Poorly differentiated endocrine carcinomas
  (small cell carcinomas)
- Mixed exocrine and endocrine carcinomas
- Tumor-like lesions

WHO Classification 2000

THE DIFFERENTIATION IS BASED ON :

HISTOMORPHOLOGY

PRESENCE/ABSENCE OF LOC.INVASION/METASTASIS

PROLIFERATION INDEX (Ki67):

< 2% Well Diff.Tumors

> 2% / <15% Well.Diff.Carcinomas

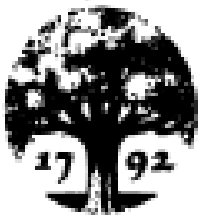
> 15 % Poorly Diff.Carcinomas

The Distribution of GI Carcinoid Lesions and Overall 5-Year Survival rates

Gastrointestinal distribution		Overall 5-year survival (%)
Stomach	Type I/I	81
	Type III/IV	33
Duodenum		60
Jejunum		60
Ileum		60
Appendix	Benign	98
	Malignant	27
Colon		62
Rectum		87

Modlin et al . Gastroenterology 2005

August 1987
Volume 206, Number 2



Annals of Surgery

Malignant Carcinoid Tumors

An Analysis of 103 Patients with Regard to Tumor Localization, Hormone Production, and Survival

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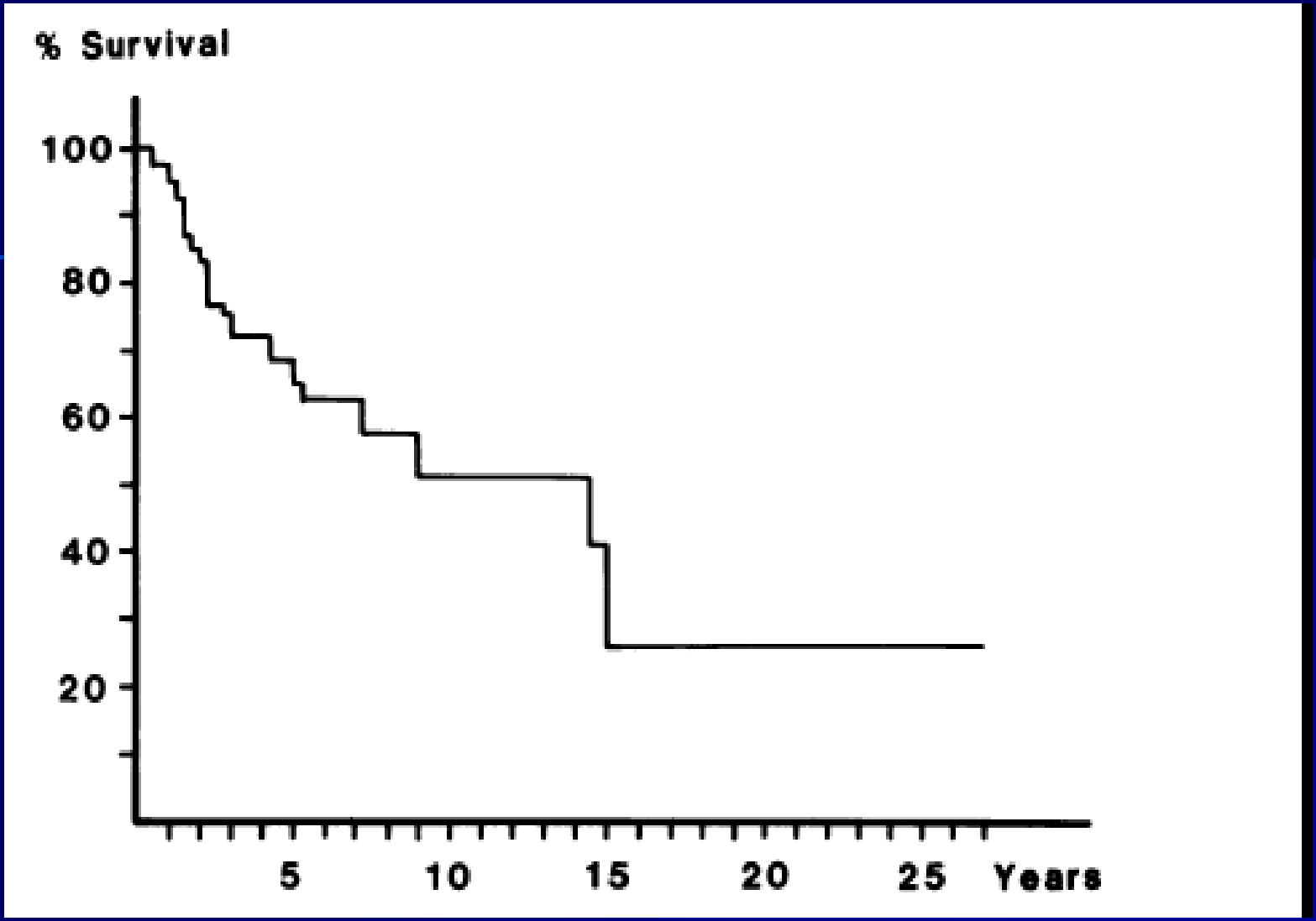
ANNALS OF SURGERY

1987



Survival from the time of histologic diagnosis in patients with carcinoid tumors.The estimated 5-year survival rate was 65%

WHO Classification 2000

- Well differentiated endocrine tumors
  (benign or low grade malignancy)
- Well differentiated endocrine carcinomas
- Poorly differentiated endocrine carcinomas
  (small cell carcinomas)
- Mixed exocrine and endocrine carcinomas
- Tumor-like lesions

WHO Classification 2000

Well differentiated endocrine tumors

(benign or low grade malignancy)

↓

The treatment of choice

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SURGERY

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WHO Classification 2000

- Well differentiated endocrine carcinomas

Which is the best treatment ?

Medical treatment

- Biotherapy ?
- Chemotherapy ?

Medical treatment

- Biotherapy

Objectives of Medical Treatment

- Efficacy
  - Symptom control
  - Biochemical control
  - Control of tumor burden

Well Differentiated carcinoma and biotherapy

- Rationales:
  - NETs carry receptor(s) for growth factor responsable in cellular proliferation, angiogenesis,hormone secretion and clinical symptoms:
  - Insulin like growth factor-1
  - PDGF-alpha
  - TGF-alpha
  - TGF-beta
  - VEGF expression
  - The identification of high-affinity somatostatin receptors in 80-90% of neuroendocrine tumors

Somatostatin Analogues

- Octreotide
- Lanreotide
- Somatoline-BIM 230146
- SOM 230
- Octastatin- RC-160

Somatostatin analogue therapy

Response	Standard dose (100–1500 μg/day) (%)	High dose (>3000 μg/day) (%)	Slow release (20–30 mg/day every 2–4 weeks) (%)
Symptomatic	64 (146/228)	42 (11/26)	63 (76/119)
Biochemical			
Complete response	11 (6/54)	3 (1/33)	3 (3/119)
Partial response	55 (116/211)	72 (24/83)	64 (76/119)
Stable disease	34 (72/211)	21 (7/33)	18 (21/119)
Progressive disease	11 (23/211)	3 (1/33)	15 (19/119)
Tumour			
Complete response	–	2 (1/53)	–
Partial response	5 (7/131)	11 (6/53)	3 (4/119)
Stable disease	38 (50/131)	47 (25/53)	79 (94/119)
Progressive disease	56 (74/131)	39 (21/51)	18 (21/119)

Oberg K. Annals of Oncology 2004

What about interferon ?

Interferon-α

Response	Regular dose 3–9 MU 3–7 times a week
Subjective	40–70%
Biochemical	40–50%
Tumor	10–15%

Interferon-α/somatostatin analogues in combination: Non randomized trials

Author	N. pts	Subjective response n. pts (%)	Biochemical response n. pts (%)	Radiological response n. pts (%)
Janson *et al.* (1992)	24	NR	17/22 (77)	4(SD)
Frank *et al.* (1999)	21	NR	9/13 (69)	14 (67) Responders MS 68 vs 23 months
Fjällskog *et al.* (2002)	16	NR	10/16 (63)	11 SD 3 PR

Interferon-α/somatostatin analogues in combination: randomized trials

Responses

Pts treated with IFN had reduced risk of tumour progression P=0.008						
						P= 0,132
Faiss 2003	80	IFN, LAN IFN+LAN	Better P=0,037	NO DIFF	PR 4/SD 8 PR 4/SD 26 PR 7/SD 18	1-y PFS NO DIFF

INTERFERON AND BEVACIZUMAB

Improved progression free survival (PFS), and rapid, sustained decrease in tumor perfusion among patients with advanced carcinoid treated with bevacizumab

ASCO 2005

Methods: Patients on a stable dose of octreotide were randomly assigned to therapy with BVZ or PEGI for 18 weeks. After 18 weeks, the patients receive both drugs.

Results: Planned accrual of 44 patients is complete. By RECIST criteria, 3 PR (3 BVZ, 0 PEGI), 31 SD (16 BVZ, 15 PEGI), 6 PD (1 BVZ, 5 PEGI) have been observed. An additional patient achieved PR on BVZ + PEGI following PD on PEGI alone. Twenty-two patients remain on study. PFS duration was superior in the BVZ arm (P=.01). PFS rates after 18 weeks of monotherapy were 95% in BVZ versus 67% in PEGI arm.

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Conclusions: BVZ therapy is associated with suppression of tumor blood flow and prolongation of PFS duration in carcinoid tumors. Addition of PEGI may help to control hormonal output in patients refractory to octreotide.

J.C. Yao et al.

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WHO Classification 2000

- Poorly differentiated endocrine carcinomas

Which is the best treatment ?

Medical treatment

- Chemotherapy

Cytotoxic therapy for carcinoid tumors

Drug	Regimen	Number of patients	Overall response (%)	Median duration (months)
Single agents				
Doxorubicin	60 mg/m^2 every 3–4 weeks	81	21	6
5-Fluorouracil	500 mg/m^2/day ×5 every 5 weeks	30	17–26	3
Streptozotocin	500–1500 mg/m^2/day ×5 every 3–5 weeks	14	0–17	2
Dacarbazine	250 mg/m^2/day ×5 every 4–5 weeks	15	13	4.5
Cisplatin	45–90 mg/m^2 every 3–4 weeks	16	6	4.5
Combinations				
Streptozotocin	500 mg/m^2/day ×5 every 3–6 weeks	175	7–33	3–7
+5-Fluorouracil	400 mg/m^2/day ×5 every 3–6 weeks			
Streptozotocin	1000 mg/m^2/week ×4	10	40	5
+Doxorubicin	25 mg/m^2/week then every 2 weeks			
Streptozotocin	500 mg/m^2/day every 6 weeks	24	39	6.5
+Cyclophosphamide	100 mg/m^2 once every 3 weeks			
Etoposide	130 mg/m^2/day ×3	13	0	–
+Cisplatin	45 mg/m^2/day on day 2 and 3, repeat cycle every 4 weeks			

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Chemotherapy of endocrine pancreatic tumors

	No. of patients	Objective response (%)	Duration (months)
Streptozotocin + 5-fluorouracil	170	45–63	18–36
Streptozotocin + doxorubicin	50	40–69	12–24
Cisplatinum + etoposide	14	50	9
Dacarbazine	11	9	6
Paclitaxel	15	7	5

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Pancreatic endocrine tumors: Is Streptozotocin and Doxorubicin the gold standard?

- True
- False

SURPRISE!!!

Failure to Confirm Major Objective Antitumor Activity for Streptozotocin And Doxorubicin in the treatment of Patients with Advanced Islet Cell Carcinoma

MSKCC. 2/92-2/98

16 patients with ICC treated with STZ + Doxo

Results:
1/16 (6%) with imaging PR
9/16 (56%) with stable disease
6/16 (38%) progressed during treament

Cheng et al Cancer 1999

Lack of Efficacy of Streptozocin and Doxorubicin in Patients With Advanced Pancreatic Endocrine Tumors.

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Methods: We retrospectively reviewed the records of 16 consecutive patients who received streptozocin and doxorubicin for advanced PETs at Dana Farber/Partners Cancer Care institutions. Baseline patient characteristics, radiographic response to therapy, treatment-related toxicity, progression-free and overall survival were analyzed.

Results: One patient demonstrated an objective partial response to therapy (objective response rate [ORR], 6%; 95% confidence interval [CI], 0-18%). Six patients achieved stable disease (38%; 95% CI, 14-62%) and 9 patients demonstrated disease progression on initial restaging (56%; 95% CI, 33-77%). The median progression-free survival and overall survival were 3.9 months (95% CI, 2.8-8.8) and 20.2 months (95% CI, 9.7-37.4), respectively.

Conclusions: In this retrospective cohort, the combination of streptozocin and doxorubicin failed to demonstrate substantial antitumor activity in patients with advanced PET.
Our findings underscore the need for new therapeutic options in this patient population.

American Journal of Clinical Oncol 2004

Cisplatin Based Therapy

CHEMOTHERAPY IN POORLY DIFFERENTIATED NETs

Chemotherapy regimen	Patient no.	Response rate	Survival months	Reference
CDDP-VP16	18	% 67	19	Moertel, Cancer 1991
CDDP-VP16	11	% 50	-	Fjallskog Cancer 2001
CDDP-VP16	41	% 42	15	Mitry, Br J Cancer 1999

RESPONSE TO CISPLATIN AND ETOPOSIDE COMBINATION ACCORDING TO CELLULAR DIFFERENTION

	Well differentiated (n:11, %)	Poorly differentiated (n:41, %)	P Value
Tumor response			
CR	0	4 (9.8 %)	0.09
PR	1 (9.1 %)	13 (31.7 %)	
Stable	4 (36.4 %)	14 (34.1 %)	
Progressive	6 (54.5 %)	10 (24.4 %)	
Response duration	8.5 month	9.24 (4.5 – 23.5) month	0.36
TTP	2.3 (0.9-12.1) month	8.9 (6.7-13.4) month	0.3
Survival	17.6 (8.6-72+) month	15 (11.7-25) month	0.18

Mitry et al, Br J Cancer 1999

RESPONSE TO CISPLATIN AND ETOPOSIDE COMBINATION ACCORDING TO CELLULAR DIFFERENTION

	Well differentiated	Poorly differentiated
Patient no.	4	11
Overall response	% 45	% 67
Biochemical	% 45	% 0
Radiological	% 27	% 50
Stable	% 36	% 25
Progressive	% 18	% 0

Fjallskog Cancer 2001

Treatment of Metastatic Neuroendocrine Carcinomas Based on WHO Classification

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Table I. *Clinical characteristics of patients with NECs.*

	Grade of differentiation (WHO classification)		
	All patients	Well-differentiated	Poorly-differentiated
Males/Females	19 10/9	11 6/5	8 4/4
Median age (range)	63 (29-83)	68 (29-83)	54 (40-77)
ECOG status			
0	11	8	3
1	8	3	5
2	-	-	-
3	-	-	-
Site of primary tumour			
Pancreas	5	-	5
Stomach	2	2	-
Bowel	7	7	-
Unknown	5	2	3
Median (range) tumour proliferation index as % of Ki-67 positive cells		Well 1 (1–5)	Poorly 30 (7–90)
Carcinoid syndrome		5	4 1
- Flushing		2	-
- Diarrhoea		3	1
Elevated levels of:			
serum CgA	17	9	8
serum NSE	8	2	6
urinary 5-HIAA	nd	2	nd
Positive whole body somatostatin scintigraphy/patients evaluated	15/18	10/10	5/8

Abbreviations: CgA, chromogranin A; NSE, neurone specific enolase; 5-HIAA, 5-hydroxy indolacetic acid; nd, not determined.

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Table II. *Therapeutic responses in patients with NECs.*

Response to octreotide plus IFN-α-2b in WD-NECs*

Site of primary tumour		Objective treatment responses: Partial response		Stable disease	Clinical benefit	Progressive disease
Stomach	2	0		2	1	0
Bowel	7	4	36%	3	4	0
Unknown	2	0		2	2	0
Total	11	4		7	7	0

*Median follow-up 20 months (range 4-40)

Response to cisplatin and L-leucovorin/fluorouracil in PD-NECs*

Site of primary tumour		Objective treatment responses: Partial response		Stable disease	Clinical benefit	Progressive disease
Pancreas	5	2		1	1	2
Unknown	3	1	37%	1	1	1
Total	8	3		2	2	3

*Median follow-up 10.5 (range 3-30) months

Table III. *Adverse effects related to biotherapy or chemotherapy.*

Octreotide plus IFN-α-2b in WD-NECs

Adverse effect	Grade 1-2	Grade 3-4
Nausea/vomiting	18%	0
Neutropenia	18%	0
Thrombocytopenia	9%	9%
Myalgia	27%	0
Fever	27%	0
Pruritus	9%	0
Headache	9%	0
sGOT/sGPT elevation	9%	0
Cholelitiasis	9%	0

Cisplatin and L-leucovorin/fluorouracil regimen in poorly-differentiated NECs

Adverse effect	Grade 1-2	Grade 3-4
Nausea/vomiting	37.5%	0
Diarrhoea	12.5%	0
Neutropenia	25%	12.5%
Thrombocytopenia	0	0
Peripheral neuropathy	37.5%	0
Nephrotoxicity (creatinine levels)	12.5%	0
Alopecia	0	25%

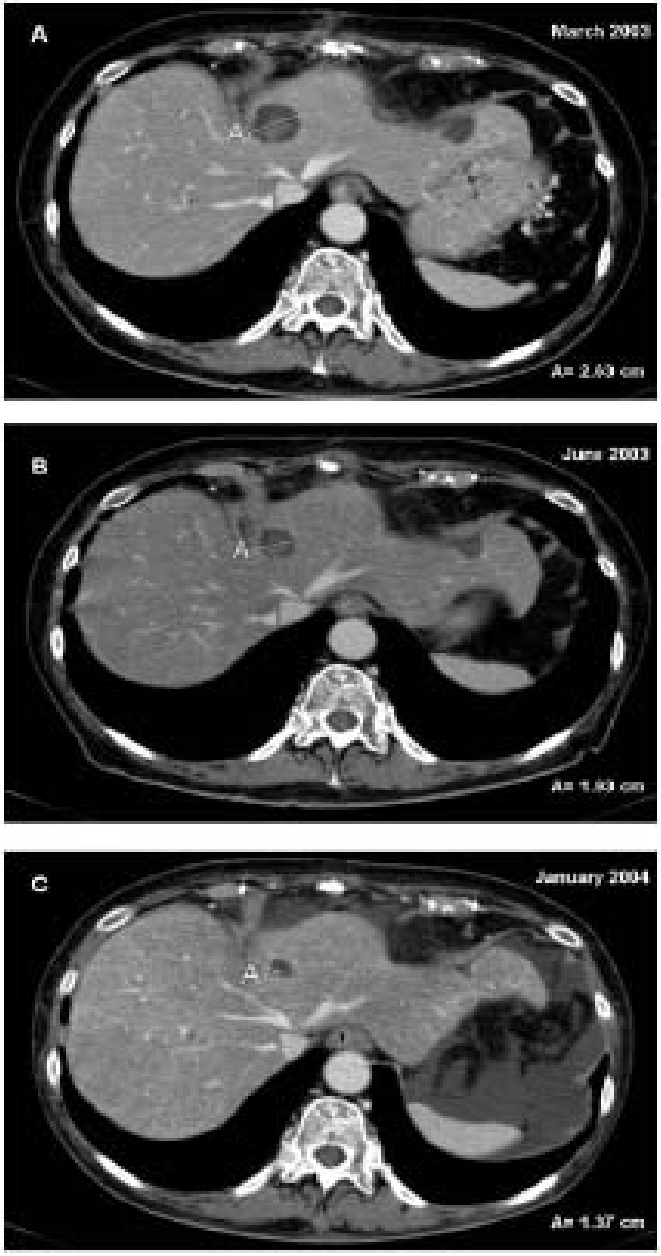

Figure 1. *CT scans of a representative patient with WD-NECs undergoing octreotide LAR plus IFN-α-2b therapy. Panel A shows pre-treatment assessment; panels B and C show tumour regression at 3 and 12 months, respectively.*

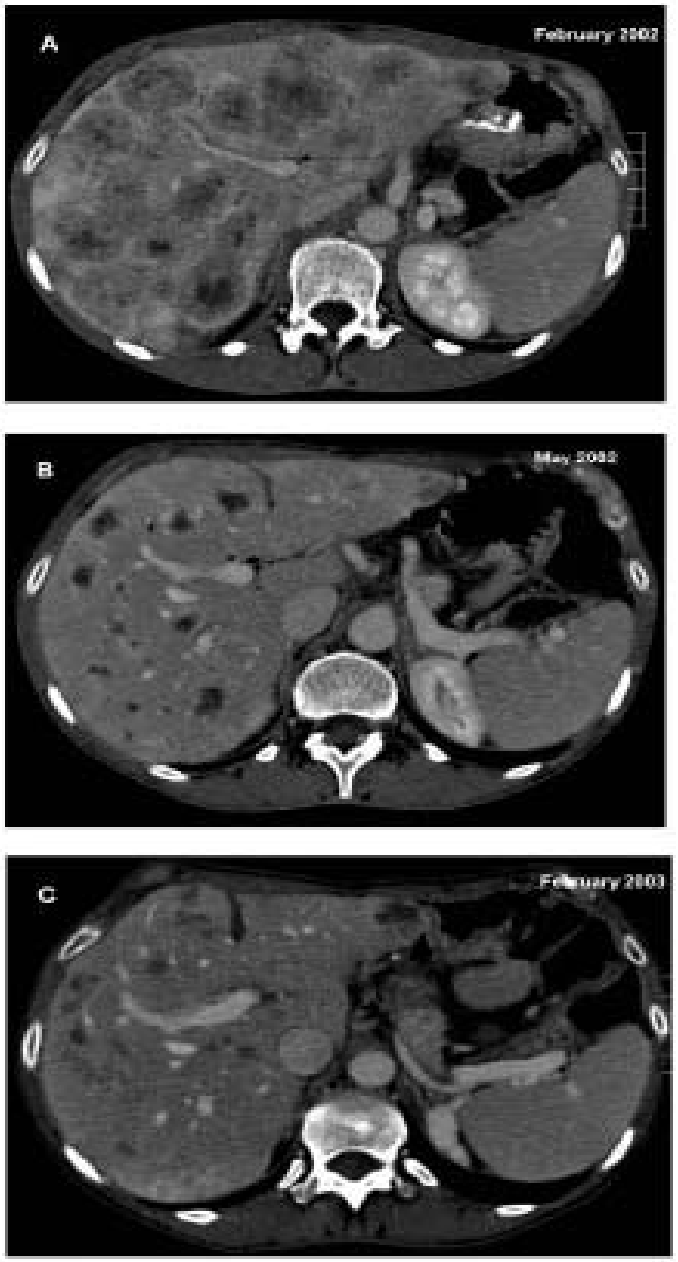

Figure 2. *CT scans of representative patient with PD-NECs undergoing cisplatin and L-leucovorin/fluorouracil combination chemotherapy. Panel A shows pre-treatment assessment; panels B and C show objective response of multiple liver metastases at 3 and 12 months, respectively.*

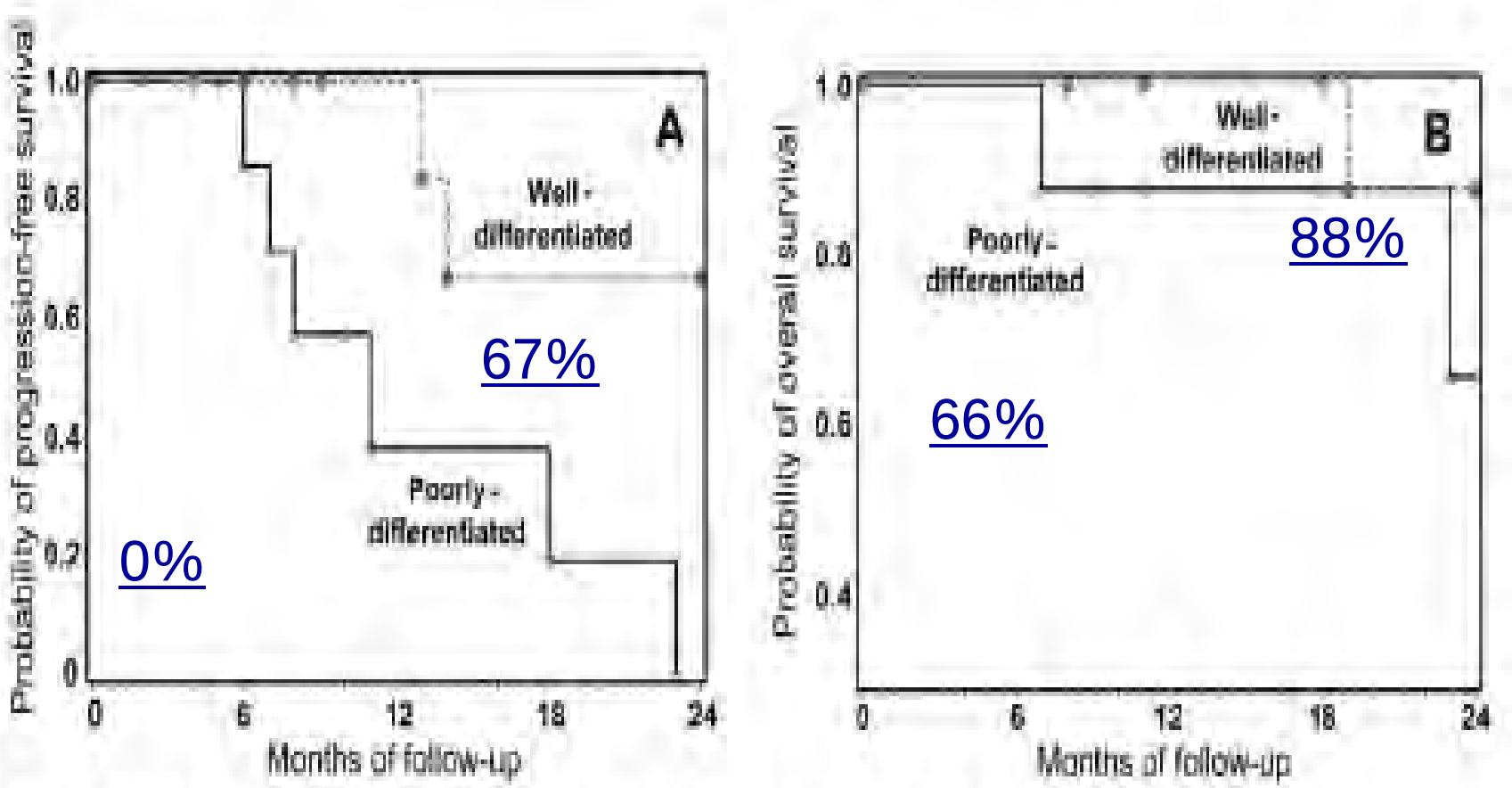

Figure 3. Two-year probability of progression-free (A) and overall (B) survival of WD- and PD-NECs.

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Conclusions

- Management with either biotherapy and chemotherapy can be guided by WHO classification in patients with malignant carcinoid.
- Ki-67 proliferation index might be considered as an additional parameter for choosing between chemotherapy or biotherapy
- Combination chemotherapy with Cisplatin, lederfolin, fluororuracil represents a valid therapeutic option in malignant carcinoid, having a good therapeutic index and favourable toxicity profile

Open Questions

- A standard chemotherapy is still not in existence because a small number of patient cases and consequently a small number of randomized trials
- What is the best treatment for Endocrine Pancreatic Tumors?
- How can we select the best method of treatment for patients in the grey area (Ki-67 2-15%) ?