I NETs
A che punto siamo?

Differenziazione Neuroendocrina

Salvatore Artale
Divisione di Oncologia Medica
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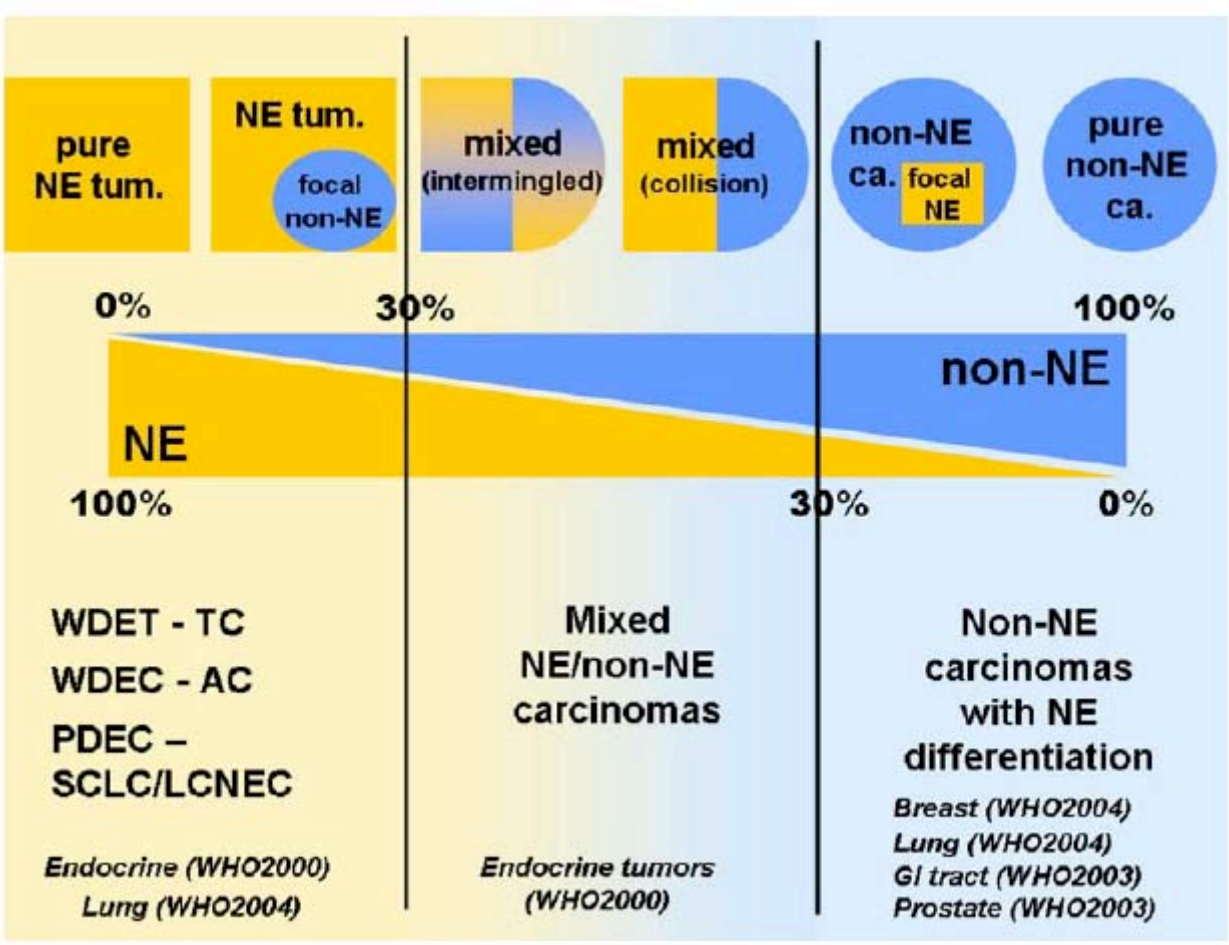
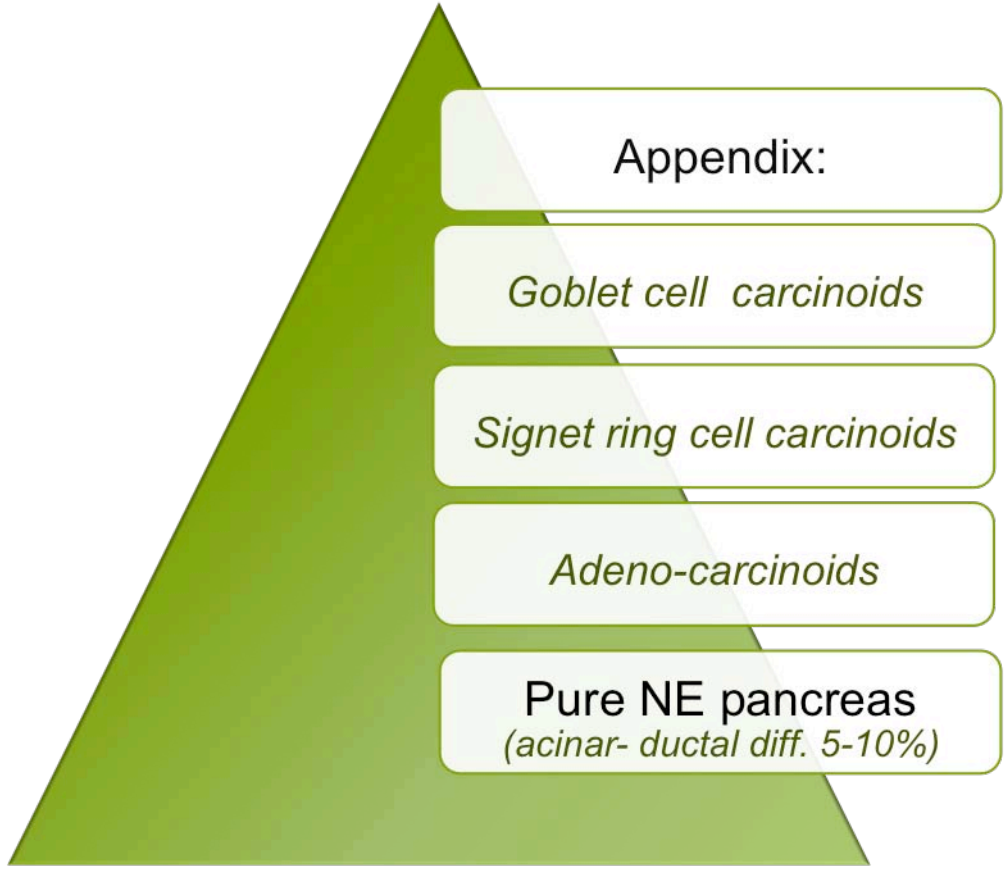
Neuroendocrine Differentiation



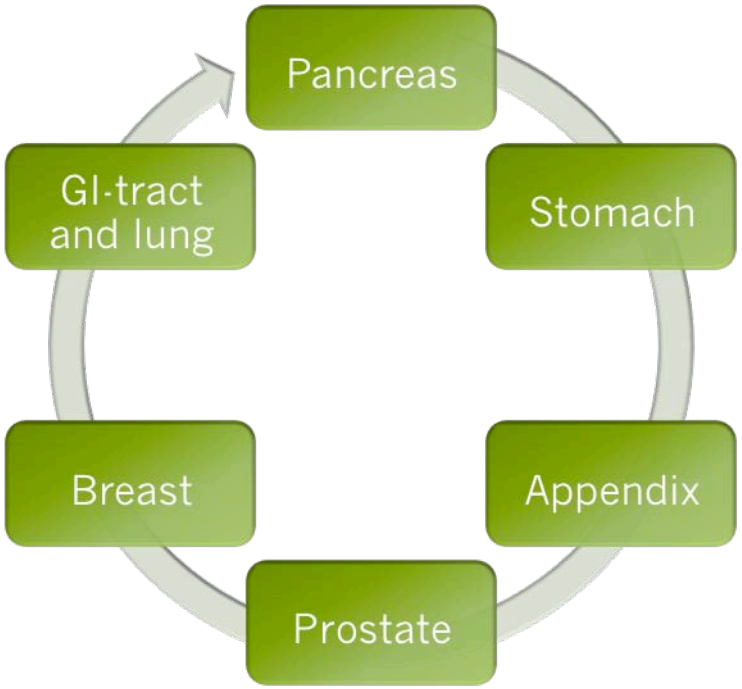
Volante et al . Virchows Arch 2006

NET with focal non-NE component
(< 30%)



Volante et al . Virchows Arch 2006
Solcia et al. WHO classification 2000

Mixed exocrine-endocrine carcinomas
(NE or non-NE cells >30%)



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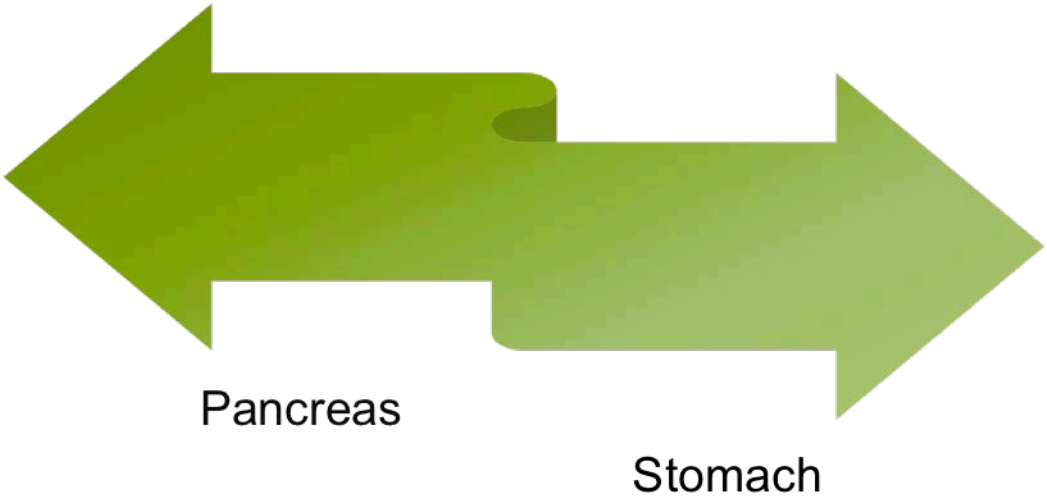
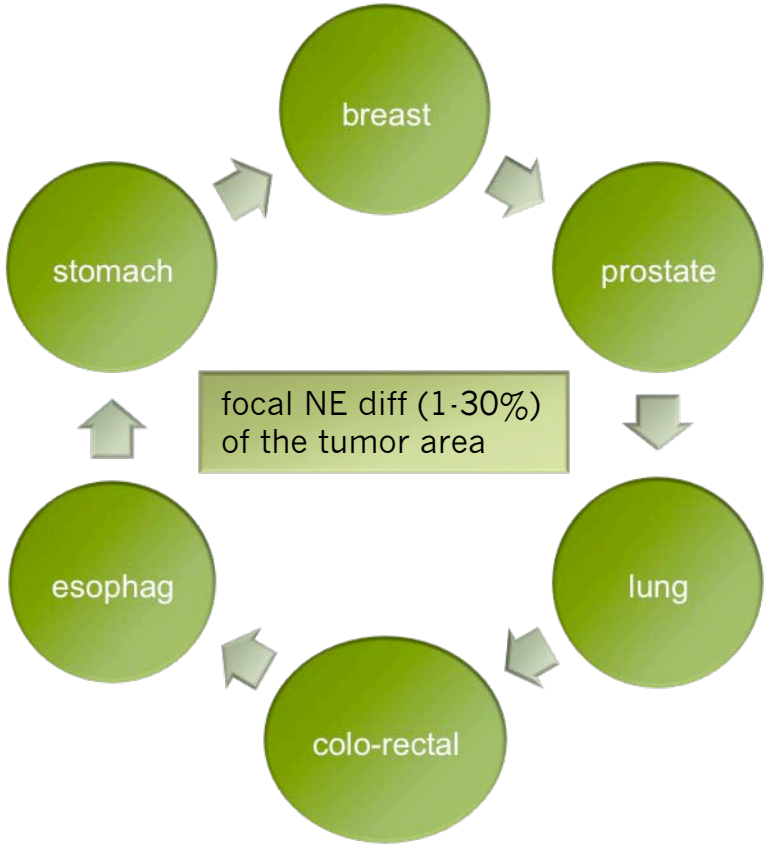


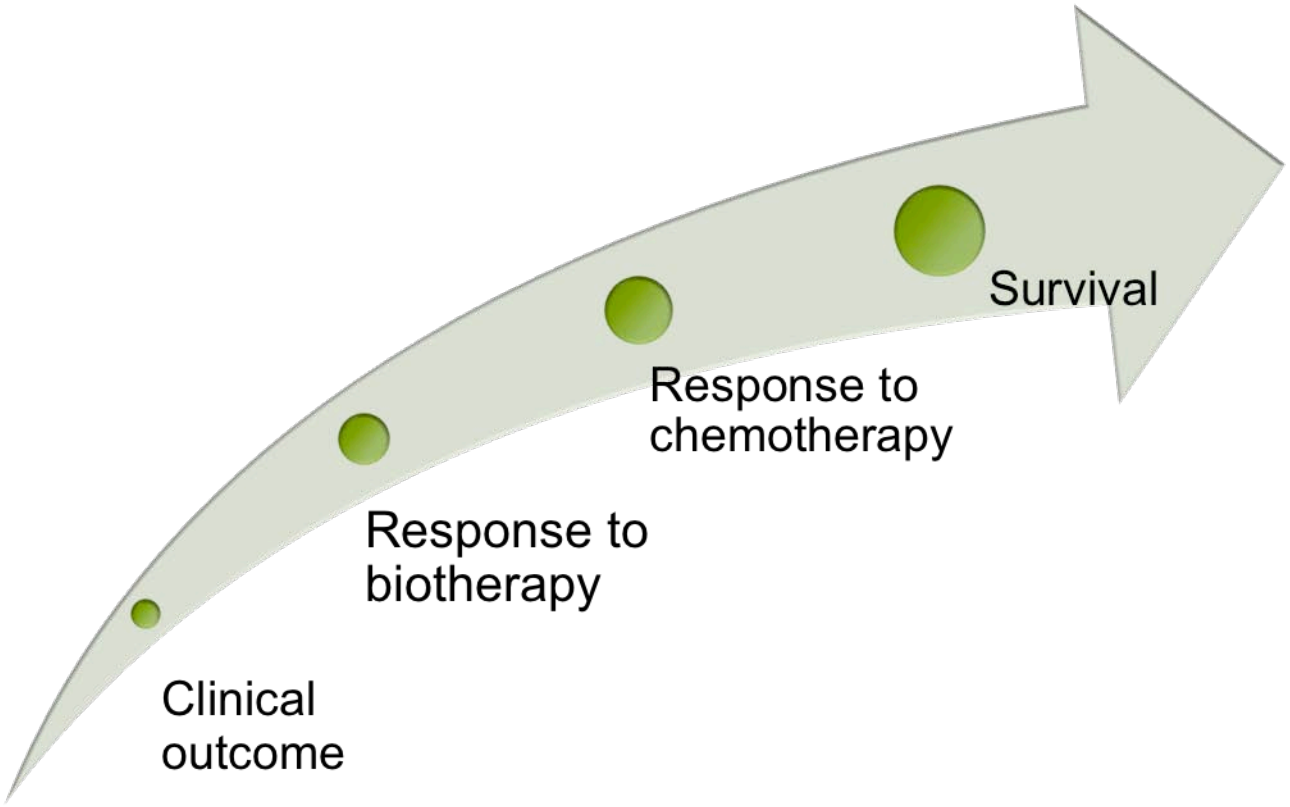
Volante et al . Virchows Arch 2006
Solcia et al. WHO classification 2000

epithelial malignant tumors with a predominant exocrine component +NE cell subpopolation
(at least 1/3 of the tumor area)

Adenocarcinomas with focal NE component (<30%)



Neuroendocrine Differentiation



GI carcinoma and NE differentiation

Prognostic significance of NE differentiation in GI carcinomas

Author/year	site	Prognosis (surv)
Lyoid et al./1998	CRC mod diff	not influence
Grabowski et al./2001	CRC stage III/IV	poor
Grabowski et al./2002	CRC undiff.	poor
Brenner et al./2004	GI tract-SCC	poor
Schwandner et al./2007	Rectal cancer	not influence
Eren et al./2004	Gastric-adenocarcinoma	not influence
Tezel et al./2000	pancreas	better

CRC= colorectal cancer

Primary Rectal Cancer and NE differentiation

94 rectal cancer

20% CgA+ and high Ki-67

- Correlated to ki-67 expression, 89,5% of CgA+ tumors showed a concurrent high ki-67 of more than 40% of cells

7% Syn+

3% NSE+

Schwandner et al.
Chir Gastroenterol 2007

Primary Rectal Cancer and NE differentiation

Variables	Categories	Incidence of distant recurrence (without local recurrence)	p value (chi square)
Tumor stage[a]	UICC I	0 (0%)	
	UICC II	2 (6.1%)	0.03
	UICC III	4 (12.9%)	
	UICC IV	2 (66.7%)	
Depth of invasion[a]	pT1+2	0 (0%)	
	pT3+4	8 (13.8%)	0.04
Preoperative CEA[b]	normal	4 (6.8%)	
	increased	4 (28.6%)	0.02
CgA	negative	4 (5.9%)	
	positive	4 (23.5%)	0.02

[a]Also statistically significant in multivariate Cox regression analysis.
[b]Patients without available CEA level not included.

Schwandner et al.
Chir Gastroenterol 2007

Conclusions:

NE markers did not show any relation with survival prognosis

The expression of the CgA seems to have a prognostic impact for the incidence of methachronous distant recurrence.

VOLUME 22 · NUMBER 13 · JULY 1 2004

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

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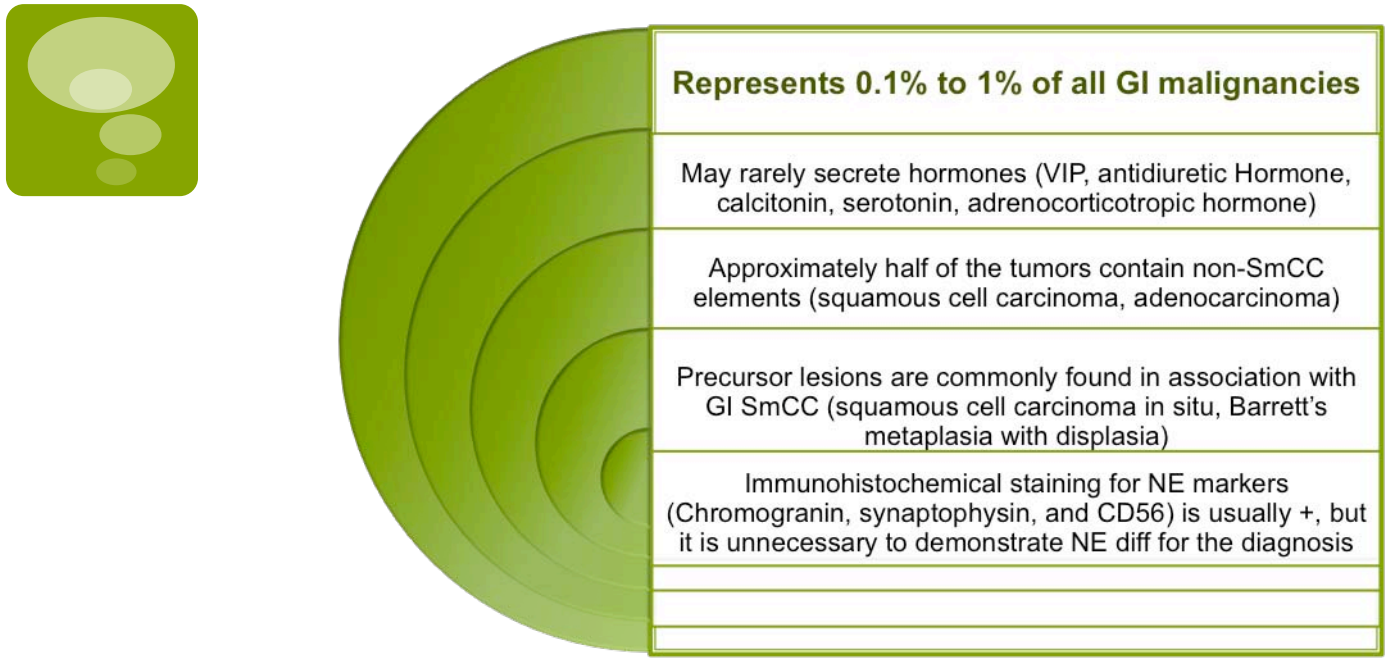
Baruch Brenner, Laura H. Tang, David S. Klimstra, and David P. Kelsen



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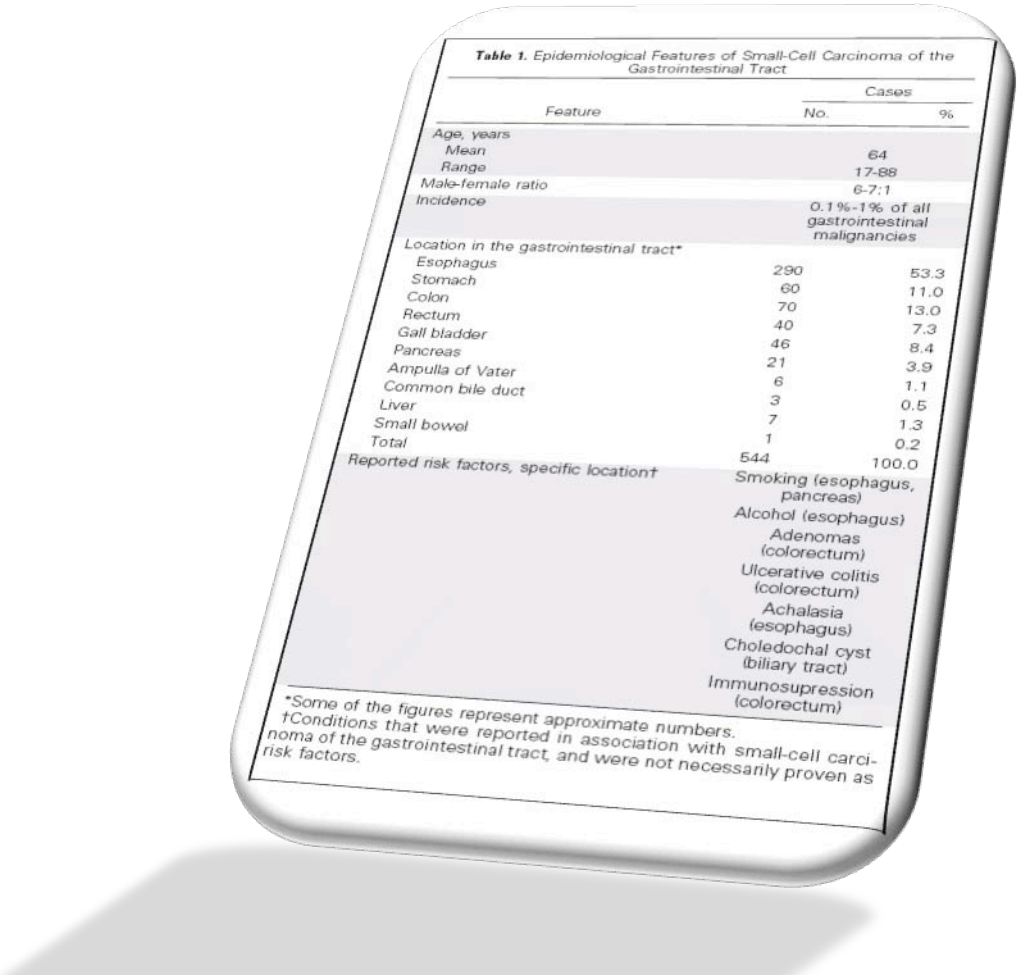

Table 1. *Epidemiological Features of Small-Cell Carcinoma of the Gastrointestinal Tract*

Feature	Cases	
	No.	%
Age, years		
Mean	64	
Range	17-88	
Male-female ratio	6-7:1	
Incidence	0.1%-1% of all gastrointestinal malignancies	
Location in the gastrointestinal tract*		
Esophagus	290	53.3
Stomach	60	11.0
Colon	70	13.0
Rectum	40	7.3
Gall bladder	46	8.4
Pancreas	21	3.9
Ampulla of Vater	6	1.1
Common bile duct	3	0.5
Liver	7	1.3
Small bowel	1	0.2
Total	544	100.0
Reported risk factors, specific location†	Smoking (esophagus, pancreas)	
	Alcohol (esophagus)	
	Adenomas (colorectum)	
	Ulcerative colitis (colorectum)	
	Achalasia (esophagus)	
	Choledochal cyst (biliary tract)	
	Immunosupression (colorectum)	

*Some of the figures represent approximate numbers.
†Conditions that were reported in association with small-cell carcinoma of the gastrointestinal tract, and were not necessarily proven as risk factors.

GI
Neuroendocrine differentiation and role of chemotherapy


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Table 3. Chemotherapy in SmCC of the Gastrointestinal Tract

Regimen	No. of Patients*	Response	RR (%)	References
CDDP single agent	3	2 CR/1 POD	66	54,58,60
VP16/CDDP†	11	9 CR/2 PR	100	4,6,17,51,61,63,64
CTX/VP16/CDDP	5	1 CR/2 PR/ 2 POD	60	4,12
CTX/DOX/VP16	2	2 CR	100	20,65
CTX/DOX/VCR	22	5 CR/11 PR/ 6 POD	73	3,5,17,26,62,66-70
CTX/VP16/VCR	2	2 PR	100	4,26
CTX/DOX/MTX/CCNU‡	2	1 CR/1 PD	50	4,51
CDDP/FU	4	1 CR/3 PR	100	4,53,55,71
FU/MMC	1	1 PD	0	59

Multimodality treatment for locally advanced disease

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Table 4. Radiotherapy in Gastrointestinal SmCC

Source	Sex	Age (years)	Site	Stage	Dose (Gy)	Response	Concomitant Treatment	Status	Duration (months)
MGH[4]	M	78	Esophagus	ED	40	PR	None	DOD	3
	M	69	Esophagus	LD	36	PR	None	DOD	5
	M	78	Esophagus	ED	50.4	PR	None	DOD	17
	F	73	Esophagus	LD	44	PR	None	DOD	4 w/o LP
	M	67	Esophagus	LD	66	CR	Chemo	DOD	6
	F	60	Esophagus	LD	57.6	CR	Chemo	ANED	≥ 24
MDA[5]	M	31	Esophagus	LD	61.6	CR	None	ANED	≥ 33
	F	79	Esophagus	LD	55.8	NA	None	DOD	5
	M	60	Esophagus	LD	45	Res Dis	Chemo>surg	ANED	≥ 10
	M	57	Esophagus	LD	59.4	Res Dis	Chemo>surg	DOD	16
	M	40	Esophagus	LD	30	Res Dis	Chemo>surg	ANED	≥ 57
Japan[16]	M	59	Stomach	LD	NA	Adjuvant	Surg>Chemo	DOD	18 w/o LP
	M	54	Stomach	LD	NA	Adjuvant	Surg>Chemo	DOD	18 w/o LP
	F	81	Stomach	LD	NA	Adjuvant	Surg>Chemo	DOD	22 w/o LP
Colum[75]	M	52	Pancreas	LD	NA	CR	Chemo	DOD	14 w/o LP
Japan[60]	M	67	CBD	LD	40	Adjuvant	Surg>Chemo	DOD	10 w/o LP
Japan[76]	F	29	Rectum	Recur	60	CR	Chemo	ANED	≥ 42

Conclusions

Immunohistochemical staining for NE markers is usually + but it is unnecessary To demontsrate NE diff for the diagnosis

- SmCC of the GI tract is rare and highly aggressive malignancy
- Without treatment surivival is measured in weeks
- Extensive disease (ED) and Locally advanced disease(LD) should be treated diffrently
- Chemotherapy represents the main therapeutic option wwith an impact on survival at least in esophageal SmCC(med. surv. of 8 and 3 months respectivelly
- Multimodaity treatment (chemoradiotherapy + surgery) results in occasional pCR as well as occasional long term survivors.

Endocrine differentiation induced by chemotherapy and Radiotherapy in GI cancer

Shia et al.The Am J of Surg Path 2002

- **53 cases of rectal adenocarcinomas treated with radiotherapy (33 with chemotherapy (20 cases without)**
- The proportion of Cg+ cells (>=20%) was significantly associated with the extent of treatment response (p=0.0005)
- Tumors treated with both chemoherapy and radiotherapy were more likely to have abundant Cg + cells compared with tumors treated with radiotherapy alone (p=0.0004)

Conclusions:

The extend of endocrine cells after neoadjuvant CT-RT appears proportional to the degree of treatment response, reflecting the relative resistance of low proliferating NE cells to conventional antiblastic therapy

Endocrine differentiation induced by chemotherapy and Radiotherapy in GI cancer

Retrospective study
Tsung-Teh Wu Cancer 2006

- 83 Pts with oesophageal or oesophagogastric junction adenocarcinoma
- **Overall Surv (p=0.045) and Disease–free surv(p=0.03)** in 73 Pts with residual tumour after preoperative CT-RT were significantly better for Pts who had residual tumor without NE diff

Conclusions:
NE diff in residual tumor was a prognostic factor of worse DFS independent of pStage and extent of residual tumor

Neuroendocrine differentiation in non GI carcinomas

NE diff. in Non-Small Cell Lung Cancer
prognostic significance

Prognostic significance of NE differentiation in Non-Small Cell Lung Cancer

Author/year	site	Prognosis
Linnoila et al /1994	NSCLCl	not influence
Sundaresan et al /1991	NSCLC	not influence
Berendsen et al/1989	NSCLC (>50%+ tumor cell)	Negative
*Howe et al./2005	NSCLC	Not influence
Hiroshima et al./2002	NSCLC (10 or >10 + cells)	Negative
Jungrithmayr et al./2006	NSCLC	Negative

NSCLC= Non small cell Lung cancer
*non association between NE markers and response to chemotherapy

World Journal of Surgical Oncology

BioMed Central

Research

Neuroendocrine differentiation and neuroendocrine morphology as two different patterns in large-cell bronchial carcinomas: outcome after complete resection

Wolfgang Jungraithmayr*[1], Gian Kayser[2], Bernward Passlick[1] and Stephan Eggeling[1]

Patient	M/F	Age	Stage	Resection	Follow-up (Months)	Postoperative Diagnosis	Status
1	M	41	II B	LL l	60	LCCNM	† intrapulmonary recurrence *
2	M	57	I B	LL r	96	LCCNM	Disease-free
3	M	76	I B	LL l	30	LCCNM	† intrapulmonary recurrence *
4	M	74	III A	UL r	11	LCCNM	† intrapulmonary recurrence *
5	M	61	I A	S 4/5 l	18	LCNEC	Disease-free
6	M	66	I B	Pneumonectomy l	26	LCNEC	† distant metastases
7	M	75	I A	UL l	24	LCNEC	Disease-free
8	M	67	I B	LL l	20	LCNEC	† brain metastases
9	M	70	II B	Pneumonectomy r	12	LCNEC	† bone metastases
10	F	58	IV	UL l	20	LCNEC	† bone metastases
11	M	80	I A	S 8 r	19	LCNEC	Disease-free
12	M	57	III B	Bifurcation	2	LCNEC	Disease-free

M = male; F = female; LL = lower lobe; UL = upper lobe; l = left; r = right; S = segment; † = deceased; * = intrapulmonary metastases.

Conclusions:

Large cell neuroendocrine carcinomas of the lung show aggressive behavior with a poor prognosis. **Expression of NE markers reduce tumor-free interval**
As well as survival and might influence the site of metastases

Neuroendocrine differentiation in pure type mammary mucinous carcinoma is associated with favorable histologic and immunohistochemical parameters

Gary MK Tse[1], Tony KF Ma[2], Winnie CW Chu[3], Wynnie WM Lam[3], Cycles SP Poon[4] and Wing-Cheong Chan[5]

Gary et al. M pathology 2004
Coady et al .Histopath 1989
Scopsi et al. Am J Surg Pathol 1994

- Incidence of NE diff 3% and 21%
- Good prognosis
- Older patient age
- Favorable histologic and immunohistochemical parameters:
- Lower tumor nuclear grade
- Lower incidence lymph node metastases
- Lower cerb2 oncoproetin expression

Review

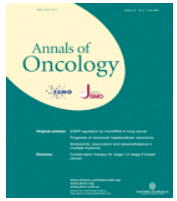
Annals of Oncology 13: 653–668, 2002
DOI: 10.1093/annonc/mdf142

The clinical role of somatostatin analogues as antineoplastic agents: much ado about nothing?

M. Hejna*, M. Schmidinger & M. Raderer

Department of Internal Medicine I, Division of Oncology, University Hospital of Vienna, Vienna, Austria

Received 20 June 2001; revised 17 November 2001; accepted 19 December 2001



- Expression of SSTR 1-2 in non NE solid tumors
- Gastric carcinomas
- Phaeochromocytomas
- Ependymomas
- breast cancer
- Renal cell carcinomas
- Medulloblastomas
- Small cell lun carcinomas
- Prostate cancer
- Sarcomas
- Hepatocellular carcinoma

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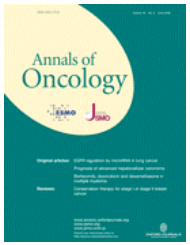

Thyroid cancer—predominant SSTR expression: not evaluated

Treatment	Dosage and application	Duration of treatment	Number of patients	Results	References*
Octreotide	100 µg tds, increasing to 500 µg tds s.c.	37 days in 11 patients, 60 days in 7 patients	18	Flushing improved in 4 of 5 patients, diarrhoea in 2 of 9 patients. Antisecretory effect of high dose octreotide on plasma calcitonin levels in some patients	Modigliani [104]
Octreotide	1.5–2 mg daily by pulsatile s.c. injection	Up to 14 months	3	In 1 patient, initial slight response then treatment ineffective. In 2 others, calcitonin levels decreased to −50% of pre-treatment levels. Diarrhoea improved	Mahler [105]
Octreotide	4 mg daily s.c.	12 months	6	No	
Octreotide plus IFN-α-2b	150 µg daily for 6 months and subsequently 300 µg daily for another 6 months s.c.	12 months	8	CEA levels decreased in all patients, no changes in size of metastasis were observed	Lupoli [107]

Colorectal carcinoma—predominant SSTR expression: SSTR1, SSTR2[a]

*By first author [ref. no.].

Small cell lung cancer—predominant SSTR expression: SSTR2[a]

Treatment	*Dosage and application*	*Duration of treatment*	*Number of patients*	*Results*	*References[b]*
Octreotide	*250 µg tds s.c.*	*1 week*	*20*	*No evidence of antitumour activity*	*Macauley [65]*
Lanreotide	*2.25–9 mg daily s.c.*	*Not stated*	*2*	*PR in 1 patient*	*Anthony [53]*
Lanreotide	*2–10.5 mg/day as a 24 h continous infusion*	*28 days*	*18*	*No evidence of antitumour activity*	*Cotto [66]*
Octreotide	*200 µg tds s.c.*	*1 week*	*13*	*Octreotide is effective in reducing neuroenolase levels*	*Soresi [117]*
Lanreotide	*2 mg tds s.c.*	*Until progression*	*18*	*No patient responded to treatment*	*Marschke [67]*

*According to Reubi et al. [12].
[b]By first author [ref. no.].

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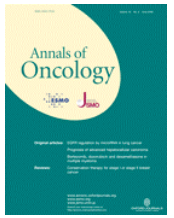

Pancreatic cancer—predominant SSTR expression: no clear pattern[a]

...ment	Dosage and application	Duration of treatment	Number of patients	Results	References[b]
Octreotide	Not stated	Not stated	4	No effect	Savage [118]
Octreotide	Continous s.c. Infusion at 3.5 μg/kg/h	2 weeks	1	Decrease in serum lipase, PR of skin lesions and pain relief after 2 weeks	Feliu [121]
Octreotide	100–200 μg tds s.c.	Until progression	14	Three patients had SD, the median survival was 2 months. Most patients experienced temporary subjective improvement with a decrease in pain	Klijn [119]
Octreotide	100–200 μg tds s.c.	Until progression	22		
Octreotide	0.1–2 mg/daily s.c.	Until progression	10	Low-dose octreotide is not effective	Friess [73]
Octreotide	Palliative surgery ± 1 mg/day s.c.	1 year	10	Median survival of 6 months and SD in 4 of 10 patients	Ebert [122]
Octreotide	200 μg tds s.c. or best supportive care	Not stated	32	The treatment with octreotide permitted a better quality of life and a prolonged median survival (15.3 versus 5.3 months)	Mittemperger [123]
Octreotide plus tamoxifen	100 μg tds s.c.	Until progression	12	Patients treated with octreotide had a significant advantage in duration of survival with a median time of 15 weeks versus 8 weeks in the control group. 7 patients showed stable disease versus only 2 in the control group	Cascinu [68]
Octreotide plus goserelin	50–500 μg tds s.c	7 months (range 1–27 months)	14	Apparently increased survival compared with historic cohort	Rosemberg [76]
Octreotide plus tamoxifen versus best supportive care	100 μg tds s.c.	Until progression	28	One patient with PR for 7 months, nine patients with SD up to 27 months	Fazeny [77]
Lanreotide	30 mg i.m. every 14 days	Until progression	14	Compared with the control group ($n = 14$) the median survival times for the octreotide–tamoxifen group were 7 and 3.5 months, respectively	Wenger [124]
				Four patients had SD. The median survival was 4 months (range 1.8–7 months)	Raderer [81]

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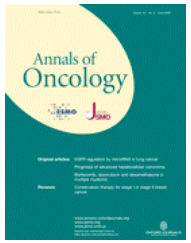

The data do not justify recommendation of SST analogues as antineoplastic agents outside of clinical trials

NE differentiation in prostate cancer and role of somatostatin analogues

General characteristics, functional roles, products and receptors of the neuroendocrine cell

General characteristics
Androgen-receptor negative
Non-proliferating
PSA-negative
Bcl-2-negative
Express intermediate & luminal cytokeratins
Functional roles
Regulation of cell growth and differentiation
Regulation of homeostasis
Regulation of prostatic secretion
Products
Calcitonin gene family
Chromogranin A
Chromogranin B
Cholecystokinin (CCK)
Gastrin-releasing peptide
Histamine
Neuron-specific enolase
Neuropeptide Y
Parathyroid hormone-related protein
Proadrenomedullin N-terminal peptide
Serotonin
Somatostatin
TSH-like peptide
Vascular endothelial growth factor
Receptors
Gastrin releasing peptide (GRPR)
Serotonin (5HTR1A, B)
Somatostatin (SSTR 1–5)
Calcitonin (hCTR-2)
Cholecystokinin
Neuropeptide Y
Vasoactive intestinal peptide
PTHrP receptor (highly expressed in bone metastases from prostate)

NE diff.is reported in 30-100%
NE diff associated with small cell

The aggressive malignant potential and hormonal indendence is partly due to the ability that most NE tumor cells escape apoptosis

The overexpression of Bcl-2 proto-oncogene involved in apoptosis is highly correlated with cancer progression and androgen independence

Correlation between CgA and NSE serum levels , androgen independence, progression of the disease and prognosis

Vashchenko et al. European Urology 2004

Cancer Therapy Vol 3, 159-166, 2005

Role of somatostatin analogues in the treatment of androgen ablation-refractory prostate adenocarcinoma

Review Article

Alessandro Sciarra*, Gianna Mariotti, Anna Maria Autran Gomez, Franco Di Silverio

Department of Urology, University La Sapienza, Rome, Italy

Table 1. Hormone-refractory prostate cancer: clinical experiences with somatostatin analogues

Treatment	Dosage	Number cases	Results	Reference
Octreotide	100μg tds s.c.	7	Pain reduction	Carteni et al, 1990
Octreotide	600-1350μg/day s.c.	10	Disease progression after 21 days	Dupont et al, 1990
Octreotide	400-1000μg/day s.c.	5	Temporary halt in PSA rising	Verhelst (28)
Octreotide	100mg qds s.c.	22	Stimulation of prostate tumor growth	Logothetis et al, 1994
Lanreotide	30mg once a week i.m.	30	20% partial response (PSA decrease) 40% improvement performance status	Maulard et al, 1995
Lanreotide	4-24 mg/day s.c.	25	No modifications	Figg et al, 1995
Octreotide	Not clarified	14	Symptom-free responses	Vainas et al, 1997
Lanreotide plus dexamethasone	30 mg/14 days i.m. + 4 mg/day os	11	90% objective (PSA decrease) and symptomatic response Progression-free survival =7 months	Koutsilieris et al, 2001
Lanreotide acetate plus ethinylestradiol	73.9 mg i.m. every 4 weeks + 1 mg/day os	10	90% objective (PSA decrease) and symptomatic response Progression-free survival = 18.5 months	Di Silverio and Sciarra, 2003

Conclusions

These data shows the need to improve our understanding of the biological nature of the NE phenotype to develop new therapeutic protocols and better therapeutic strategy