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12° Congresso Nazionale AME

Associazione Medici Endocrinologi

6th Joint Meeting with AACE

American Association of Clinical Endocrinologists

Update in Endocrinologia Clinica

NET della mammella: realtà o fantasia

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European Society of Endocrinology
the European hormone society

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ISTITUTO NAZIONALE TUMORI
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AULA 4

Lunch Symposium 2

I NET "rari"

Moderatori: L. De Marinis, F. Grimaldi

NET della mammella
R. Baldelli

NET della prostata
A. Isidori

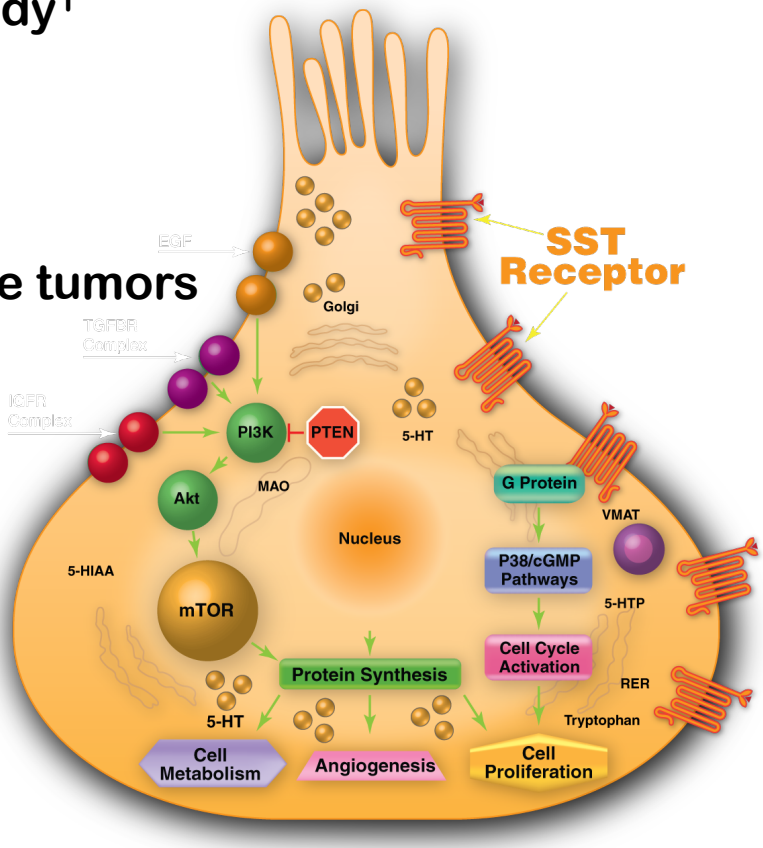
NET del tratto uro-genitale
A. *Bianchi*

Take home messages
F. Grimaldi

Con il contributo non condizionante di Italfarmaco

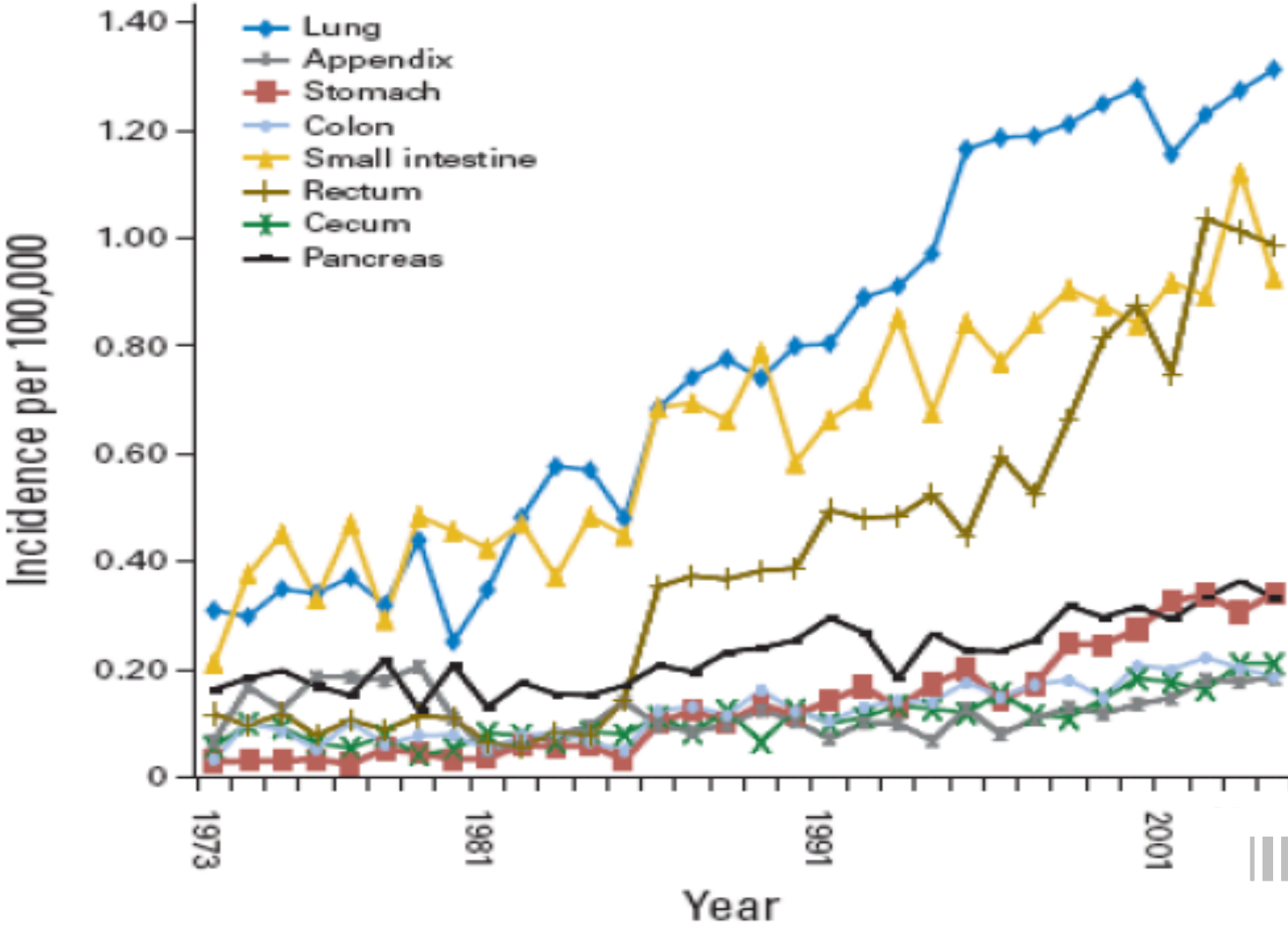
Neuroendocrine cell

- Tumors arising from enterochromaffin cells located in neuroendocrine tissue throughout the body[1]
- NETs can be functional or nonfunctional and include a heterogeneous group of neoplasms[2,3]
  - Gastroenteropancreatic neuroendocrine tumors (GEP-NETs)[3]
  - Islet cell tumors[2]
  - Pheochromocytoma/paraganglioma[2,3]
  - Poorly differentiated/small cell/atypical lung carcinoid[2]
  - Small cell carcinoma of the lung[2,3]
  - Merkel cell carcinoma[2,3]



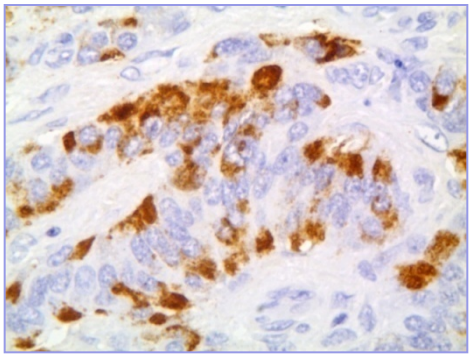
References: 1. Caplin ME, Buscombe JR, Hilson AJ, Jones AL, Watkinson AF, Burroughs AK. *Lancet*. 1998;352(9130): 799-805. **2.** National Comprehensive Cancer Network. Neuroendocrine tumors. In: *NCCN Practice Guidelines in Oncology: Neuroendocrine Tumors*. V.1. 2008. **3.** Modlin IM, Kidd M, Latich I, Zikusoka MN, Shapiro MD. *Gastroenterology*. 2005;128(6):1717-1751.

NET incidence

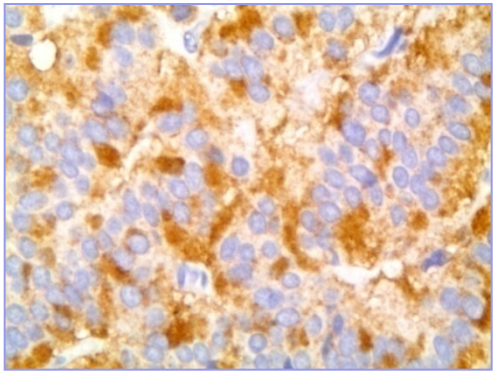


Yao et al., 35.825 cases from SEER, JCO Jun 2008

Rare cases of NET



Cromogranin A



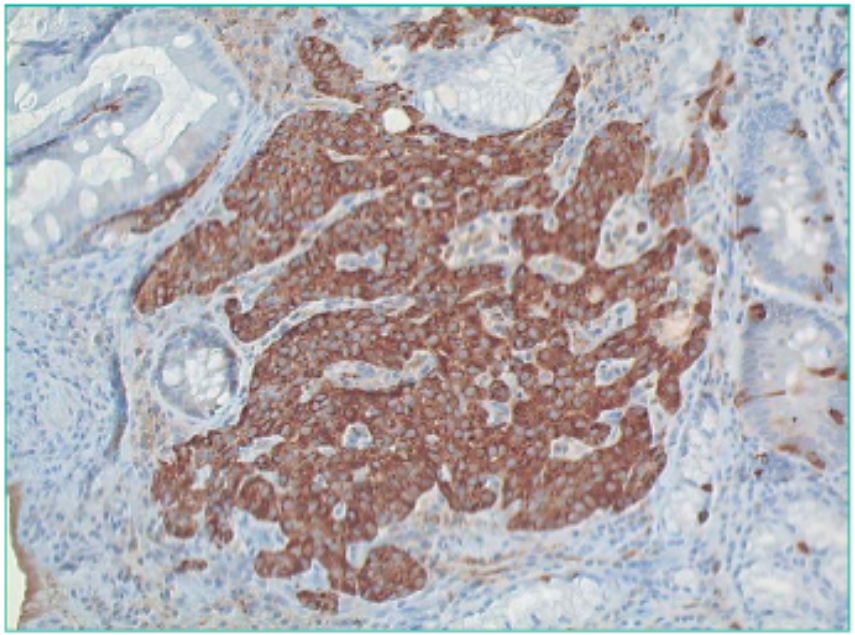
Synaptophysin

Classification

Do we share the same definition of a neuroendocrine tumor (NET) ?

Classification

NET : Various terminologies but a simple definition



Endocrine morphology

Positive Chromogranine A / Synaptophysine / CD 56 … staining

Endocrine Tumors

Neuroendocrine tumors

Apudoma

Neural crest tumors

Neuroectodermal tumors

Carcinoid tumors

Karzinoide

Others : gastrinomas, insulinomas …..

Sigfrid Oberndorfer in 1907

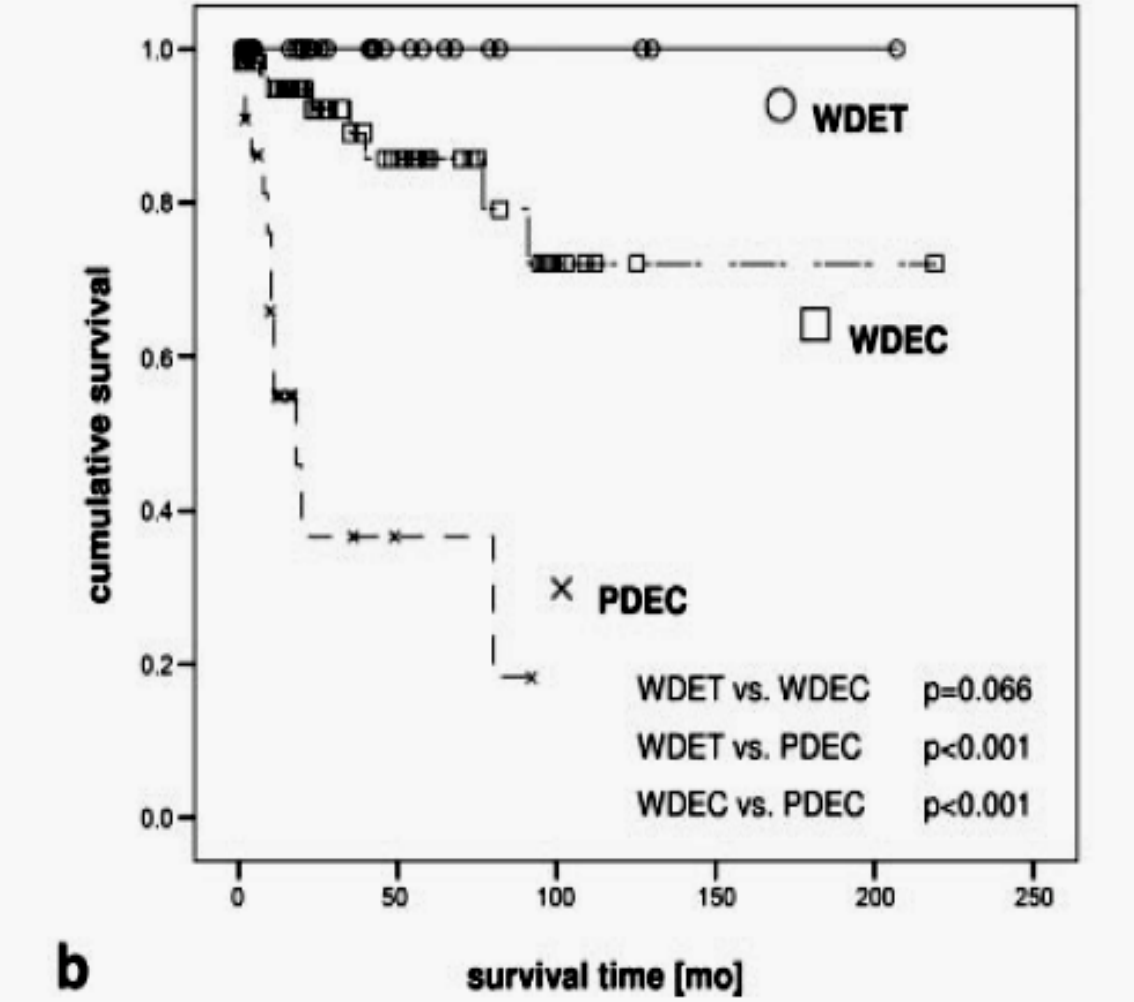
("des Karzinoide des Dundarms" in "Virchow Archive")

Classification

Table A1 WHO classification of gastroenteropancreatic endocrine tumours[1 2]

Site	Well differentiated endocrine tumour (Benign behaviour)	Well differentiated endocrine tumour (Uncertain behaviour)	Well differentiated endocrine carcinoma (Low grade malignant)	Poorly differentiated endocrine carcinoma (High grade malignant)
Pancreas	Confined to pancreas <2 cm	Confined to pancreas ≥2 cm	Well to moderately differentiated Gross local invasion and/or metastases	Small cell carcinoma Necrosis common
	<2 mitoses per 10 HPF	>2 mitoses per 10 HPF	Mitotic rate often higher (2–10 per 10 HPF)	>10 mitoses per 10 HPF
	<2% Ki-67 positive cells No vascular invasion	>2% Ki-67positive cells or vascular invasion	Ki-67 index >5%	>15% Ki-67 positive cells Prominent vascular and/ or perineural invasion
Stomach	Confined to mucosa-submucosa, ⩽1 cm. No vascular invasion	Confined to mucosa-submucosa, >1 cm or vascular invasion	Well to moderately differentiated Invasion to muscularis propria or beyond or metastases	Small cell carcinoma
Duodenum, upper jejunum	Confined to mucosa-submucosa, ⩽1 cm. No vascular invasion	Confined to mucosa-submucosa, >1 cm or vascular invasion	Well to moderately differentiated Invasion to muscularis propria or beyond or metastases	Small cell carcinoma
Ileum, colon, rectum	Confined to mucosa-submucosa, ⩽1 cm (small intestine)	Confined to mucosa-submucosa, >1 cm (small intestine)	Well to moderately differentiated Invasion to muscularis propria or beyond or metastases	Small cell carcinoma
	⩽2 cm (large intestine). No vascular invasion	>2 cm (large intestine) or vascular invasion		
Appendix	Non-functioning Confined to appendiceal wall	Enteroglucagon-producing Confined to subserosa	Well to moderately differentiated Invasion to mesoappendix or beyond or metastases	Small cell carcinoma
	⩽2 cm. No vascular invasion	>2 cm or vascular invasion		

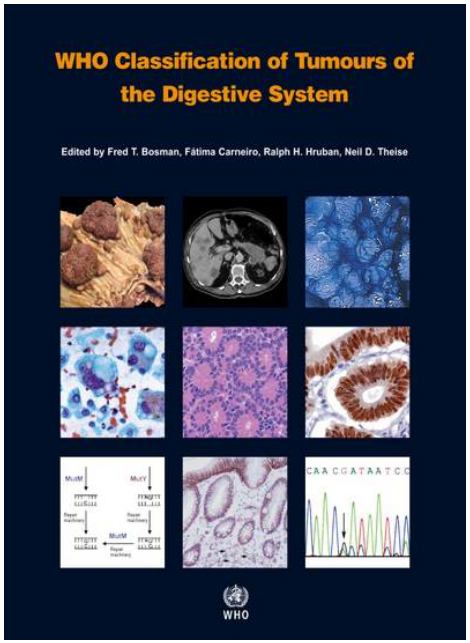
Classification



UF Pape et al. Cancer 2008

Classification

Bosman et al, IARC , 2010



Well differentiated

Neuroendocrine tumor – grade 1

Neuroendocrine tumor – grade 2

Poorly Differentiated

Neuroendocrine Carcinoma – Grade 3 – small cells

Neuroendocrine Carcinoma – Grade 3 – large cells

Classification

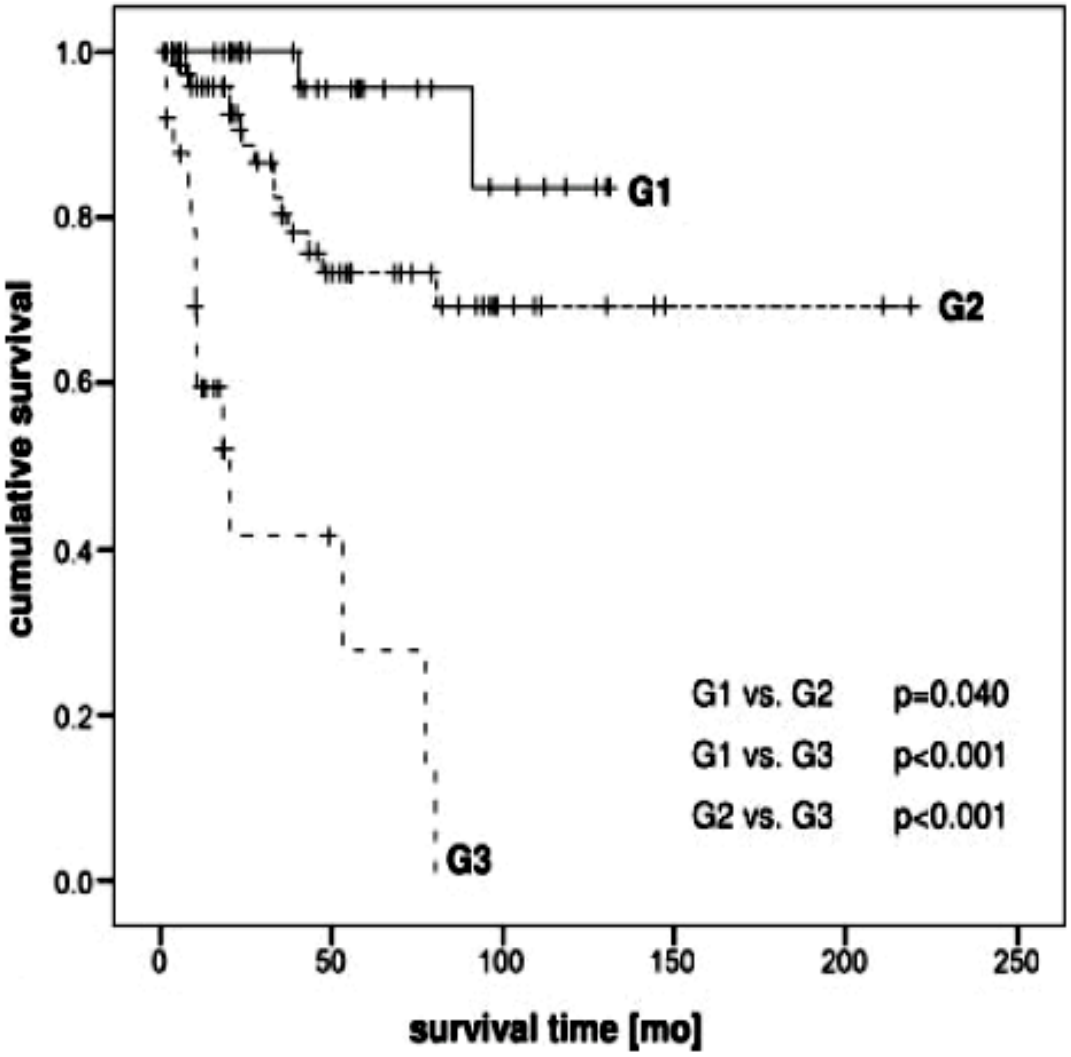
Grading proposal for foregut (neuro)endocrine tumors

Grade	Mitotic count (10 HPF)[a]	Ki-67 index (%)[b]
G1	<2	≤2
G2	2–20	3–20
G3	>20	>20

[a]10 HPF: high power field=2 mm^2, at least 40 fields (at 40× magnification) evaluated in areas of highest mitotic density
[b]MIB1 antibody; % of 2,000 tumor cells in areas of highest nuclear labeling

Rindi et al. Virchows Arch, 2006

Classification



Pape et al. Cancer 2008

Classification

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
IIA	T2	N0	M0
IIB	T3	N0	M0
IIIA	T4	N0	M0
IIIB	Any T	N1	M0
IV	Any T	Any N	M1

T indicates tumor classification; N, lymph node status; M, metastatic status.

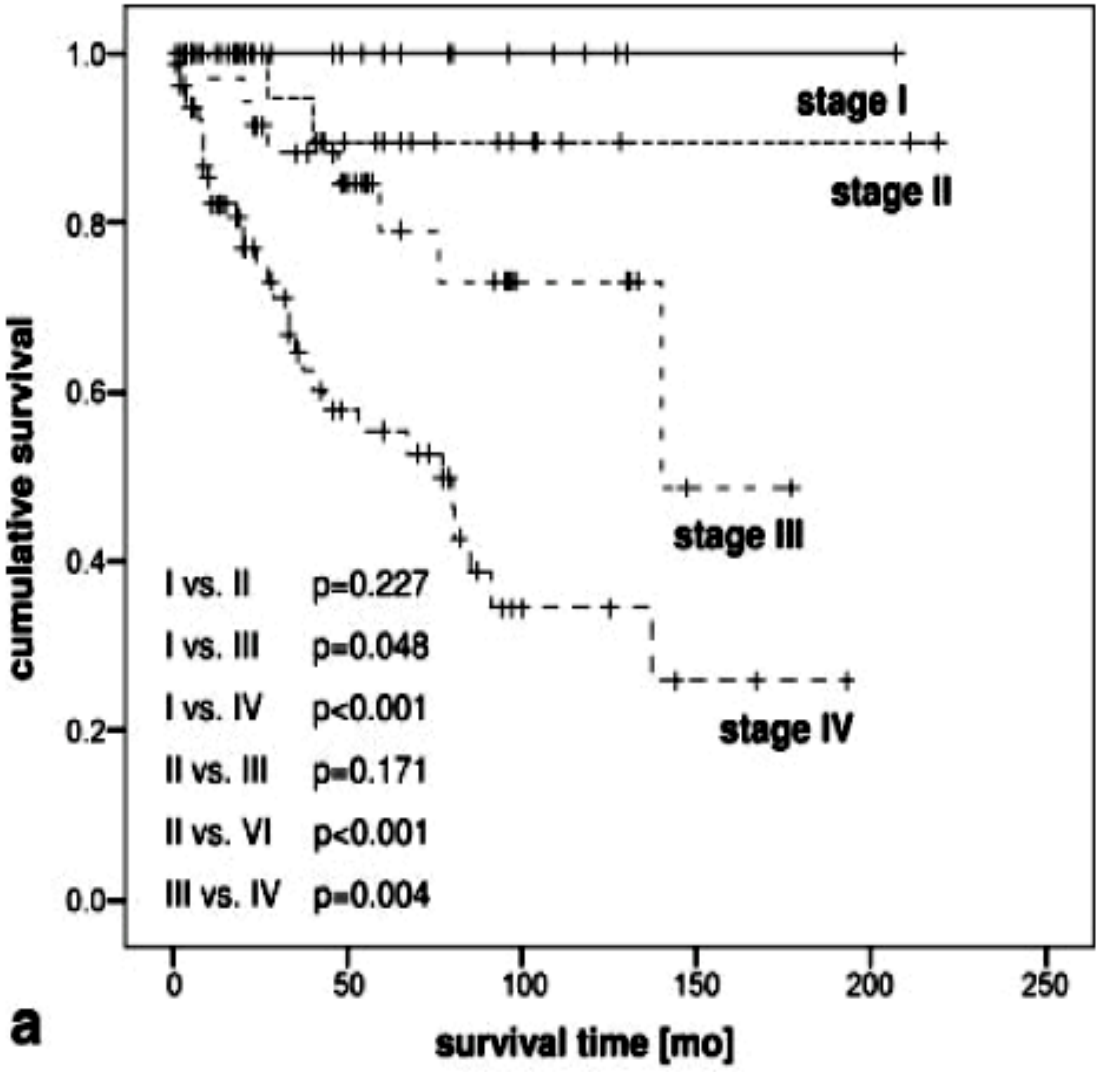
T0 indicates no evidence of primary tumor; **Tis**, tumor in situ/dysplasia (size <5 mm); **T1**, gastric or duodenal tumor invading the lamina propria or submucosa and size <10 mm or pancreatic tumor limited to the pancreas and size <20 mm; **T2**, gastric or duodenal tumor invading the muscularis propria or subserosa, or size >10 mm, or pancreatic tumor limited to pancreas and size between 20 mm and 40 mm; **T3**, gastric or duodenal tumor penetrating the serosa, or duodenal tumor infiltrating the pancreas, or pancreatic tumor limited to pancreas and size >40 mm, or pancreatic tumor invading the duodenum or the common bile duct; **T4**, gastric, duodenal, or pancreatic tumor invading adjacent structures.

N0 indicates absence of regional lymph node metastasis; N1, invasion of regional lymph nodes.

M0 indicates absence of dista
presence of distant metastasi

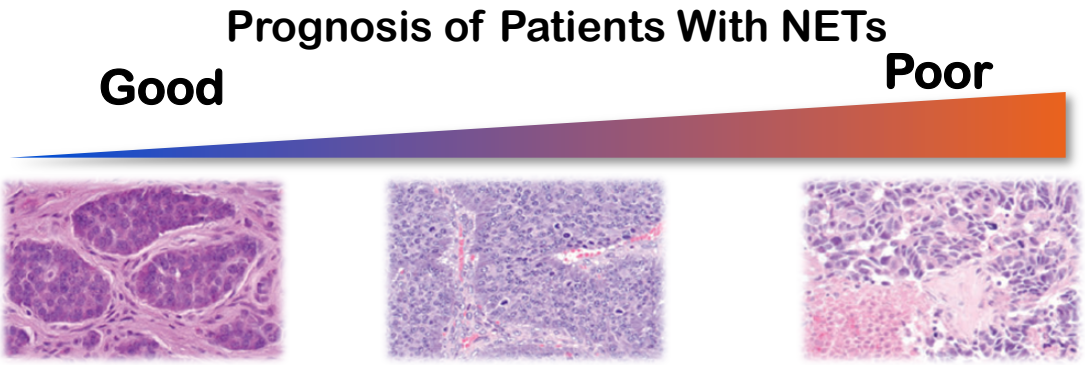
Rindi et al. Virchows Arch, 2006

Classification



Pape et al. Cancer 2008

Prognosis



WHO classification	Well-differentiated neuroendocrine tumor	Well-differentiated neuroendocrine carcinoma	Poorly differentiated neuroendocrine carcinoma
Biological behavior	Benign or uncertain malignancy	Low malignancy	High malignancy
Metastases	–	+	+
Ki-67 index (%)	<2	>2	>10
Infiltration, angioinvasion	–	+	+
Tumor size	≤2 cm >2 cm[a]	>2 cm >3 cm[a]	Any size

Epidemiology

Neuroendocrine tumors of the breast are rare, accounting for:

1. Represente about 2-5 % of all breast cancer
2. less than 1% of all neuroendocrine tumors
3. Most patients are in the 6th or 7th decades of life
4. Neuroendocrine differentiation also occurs in male breast carcinoma

Focal neuroendocrine differentiation can be found in different histological types of breast carcinoma including *in situ* and invasive ductal, lobular, colloid or papillary breast cancer.

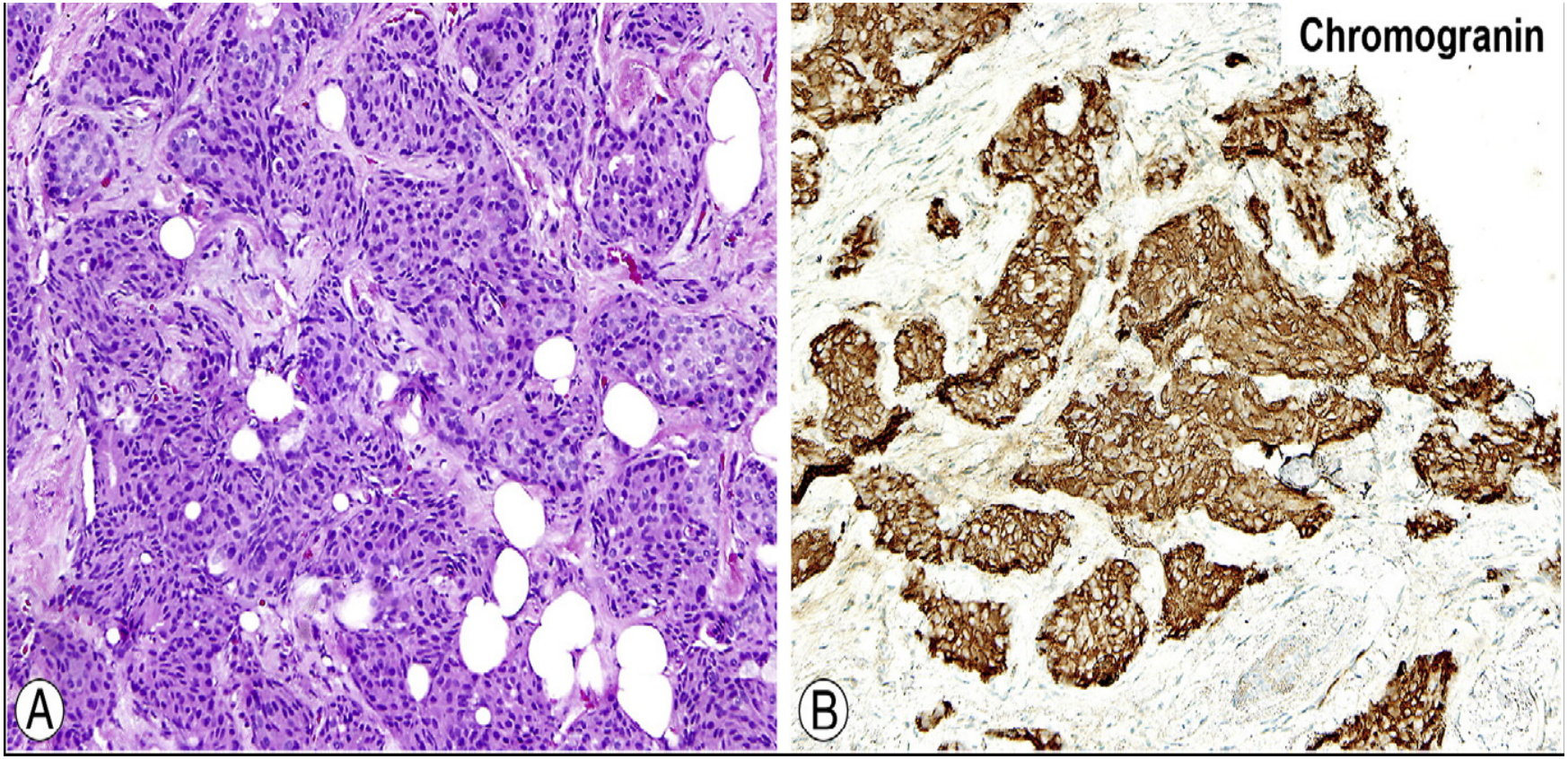
Definition

The WHO (2003) defines neuroendocrine tumours (NETs) of the breast as primary neuroendocrine carcinomas (NECs) exhibiting morphological features similar to NETs of both the gastrointestinal tract and the lung, and in which greater than 50% of the cell population expresses NE markers (chromogranin A and synaptophysin).

Definition

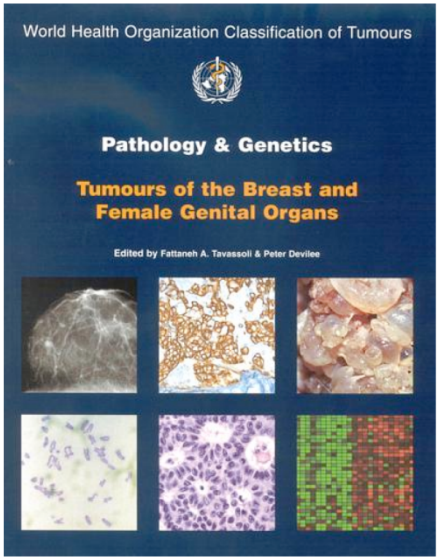
A) Hematoxylin and eosin section shows nested growth pattern.

B) Immunohistochemical staining of chromogranin confirms the NE differentiation of the tumor.



Classification

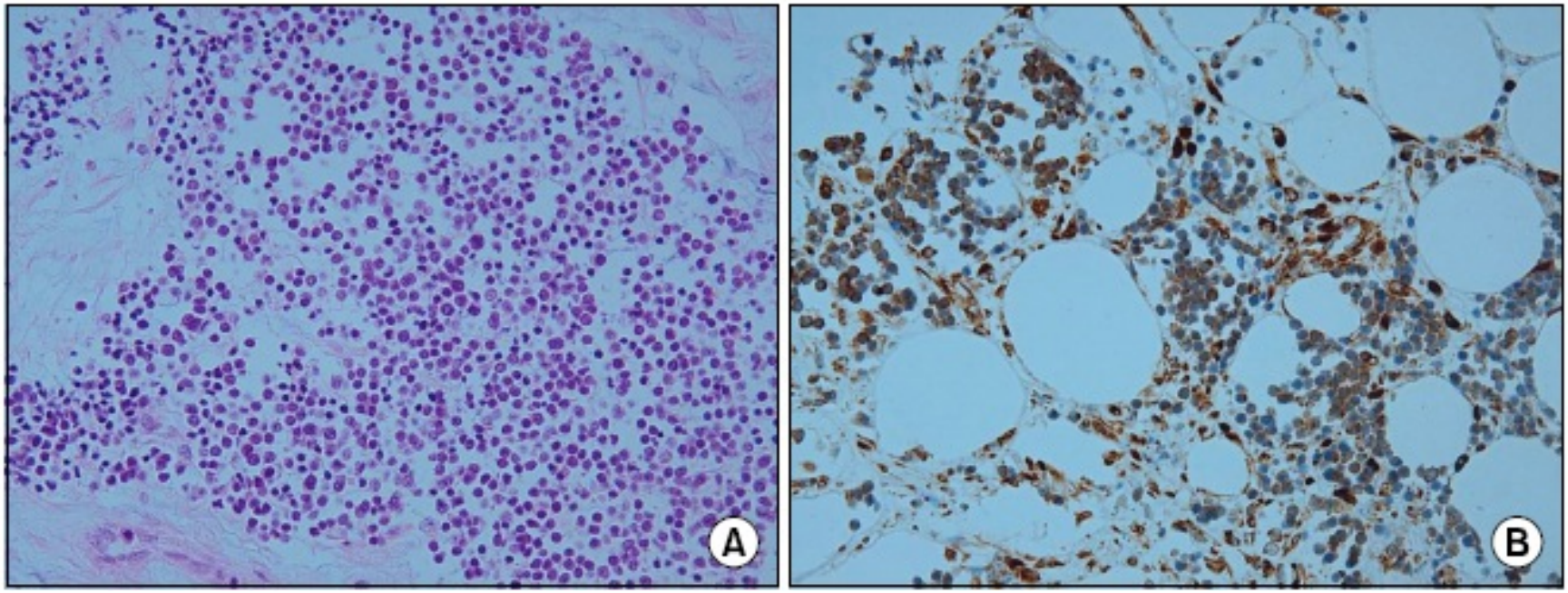
The histogenesis of B-NET is thought to arise from endocrine differentiation of a breast carcinoma rather than endocrine cells of the mammary tissue.



B-NET include:

1. solid neuroendocrine carcinoma
2. large-cell neuroendocrine carcinoma
3. small-cell carcinoma.

Classification



(A) Microscopic finding showed infiltrating nests of **small cells** in fibrotic stroma. Tumor cells had small hyperchromatic nuclei and scanty cytoplasms (H&E, ×200).

(B) Immunohistochemical stain showed strong positivity of tumor cells for **neuron-specific enolase** (×400)

Classification

Microinvasivo

Invasivo

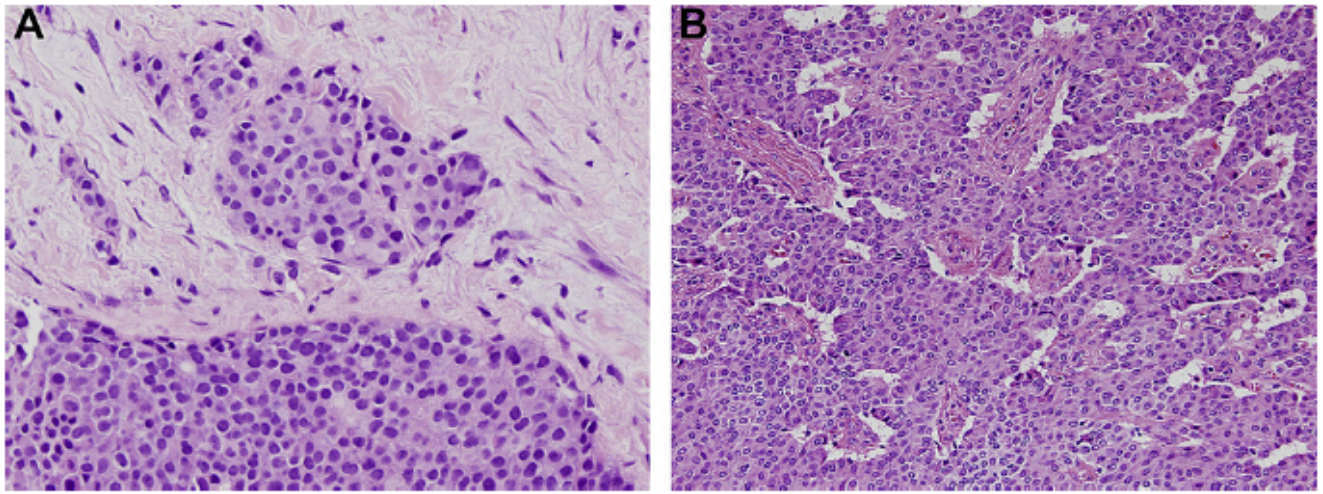


Fig. 2. Histological findings of microinvasive (A) and invasive (B) neuroendocrine tumors (cases 12 and 23). (A) Microinvasive focus (upper side) and intraductal component (lower side). (B) Infiltrating cancer cells showing solid growth accompanied by a highly vascular, fibrovascular stroma.

Clinical characteristics

High prevalence of neuroendocrine carcinoma in breast lesions detected by the clinical symptom of bloody nipple discharge

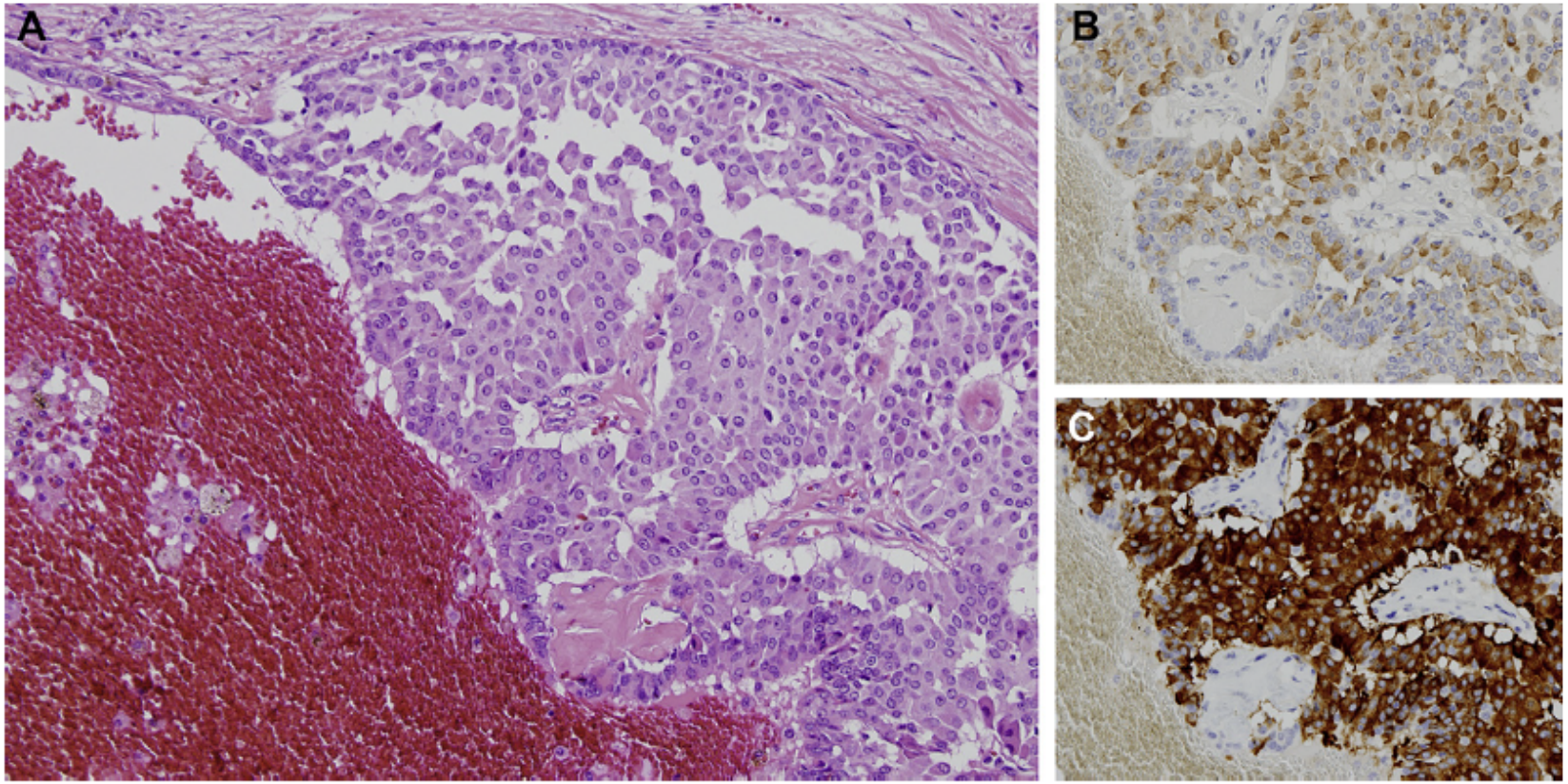


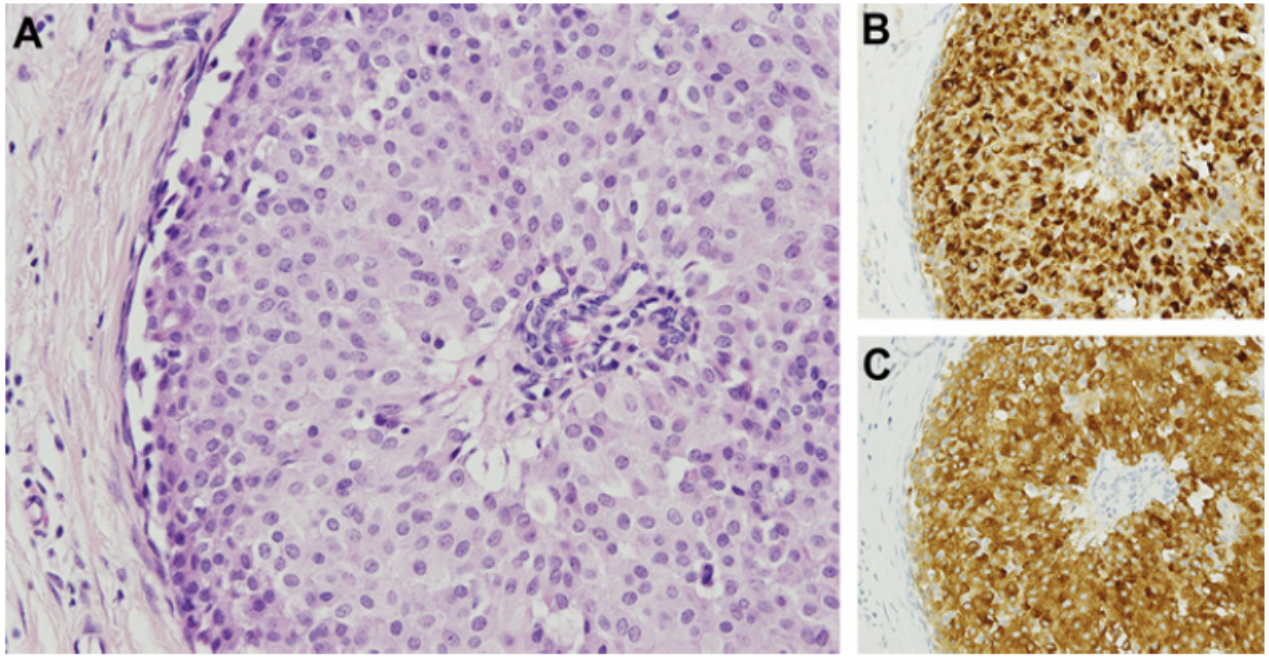
Fig. 1. Histopathological findings of the intraductal component in a neuroendocrine tumor (case 18). (A) Cancer cells show a solid arrangement with well-developed fibrovascular cores (right side) and intraductal hemorrhage (left side). Polygonal cancer cells have abundant, relatively eosinophilic cytoplasm and round to ovoid nuclei lacking pleomorphism. (B and C) Immunohistochemistry: chromogranin A (B) and synaptophysin (C) are diffusely demonstrated in the cytoplasm of cancer cells.

Clinical characteristics

Table 1 Summary of three patients having breast neuroendocrine carcinomas (B-NECs) with NE cells in the background tissue

Case	Sex/age	Site	Clinical presentation	Treatment	B-NECs
1	F/38	R	Bloody nipple discharge	Total mastectomy	Two foci of NE-DCIS
		L	Bloody nipple discharge	Total mastectomy	Multiple foci of NE-DCIS with microinvasion
2	F/28	R	Bloody nipple discharge	Total mastectomy	Two foci of NE-DCIS
3	F/31	R	Bloody nipple discharge	Total mastectomy	Two foci of NE-DCIS with invasion (solid NEC)

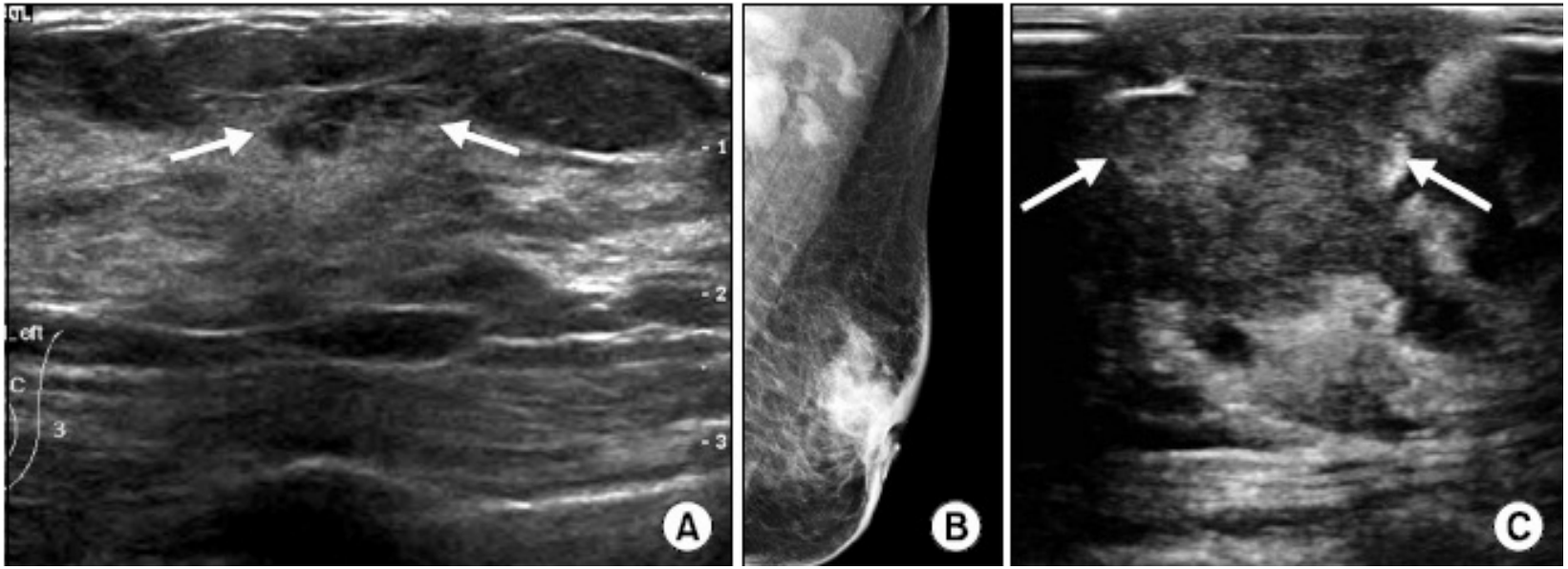
DCIS, ductal carcinoma in situ; F, female; L, left breast; R, right breast.



Breast cancer in case 1 showing a neuroendocrine ductal carcinoma in situ. (A) Intraductal solid proliferation of cancer cells with capillary stroma (H&E, magnification ×200). (B,C) Immunohistochemically, cancer cells were diffusely positive for chromogranin A (B) and synaptophysin (C) (magnification ×200).

Primary Neuroendocrine Tumor of the Breast: Imaging Features

Radiological Findings

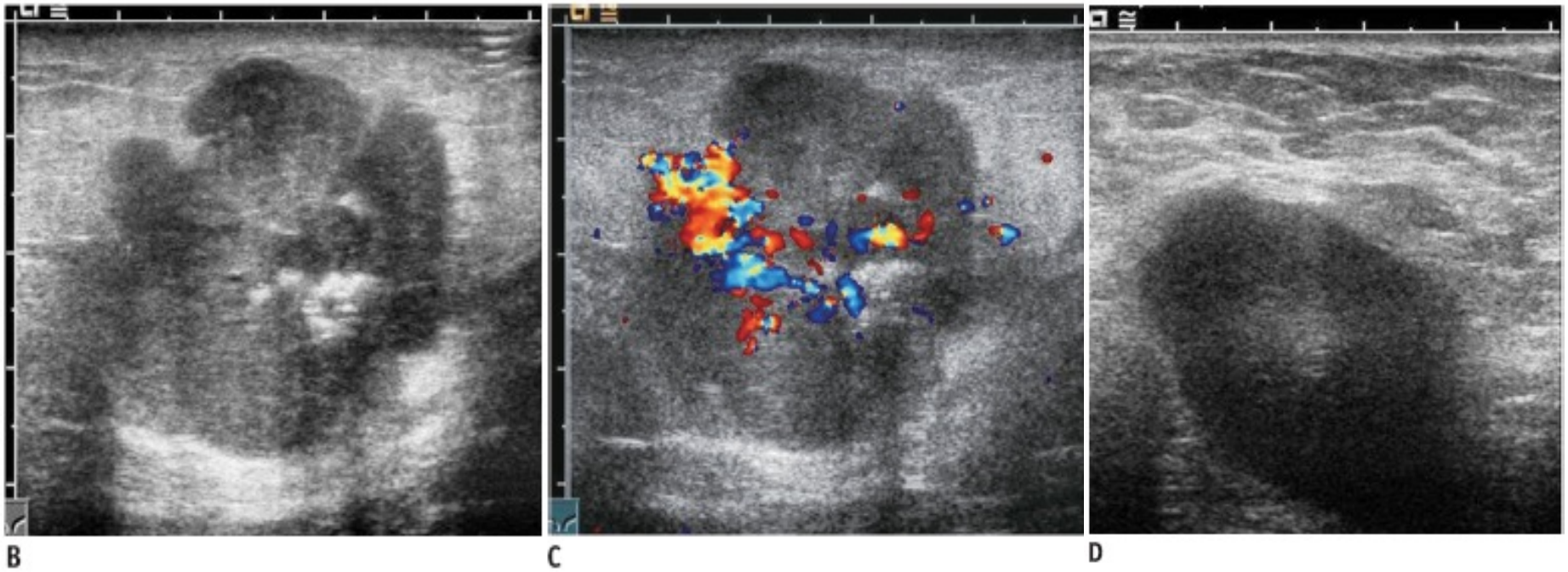


(A) Sonography showed small irregular hypoechoic lesion with angular margin and spiculations (arrows).

(B) Mammography showed ill-defined hyperdense mass in left subareolar area which was adherent to areola. Nipple retraction, diffuse skin thickening, and multiple enlarged lymph nodes in left axilla were noted with shrinkage of volume of left breast.

(C) Sonography showed irregular hypoechoic mass with invasion to nipple (arrows).

Radiological Findings

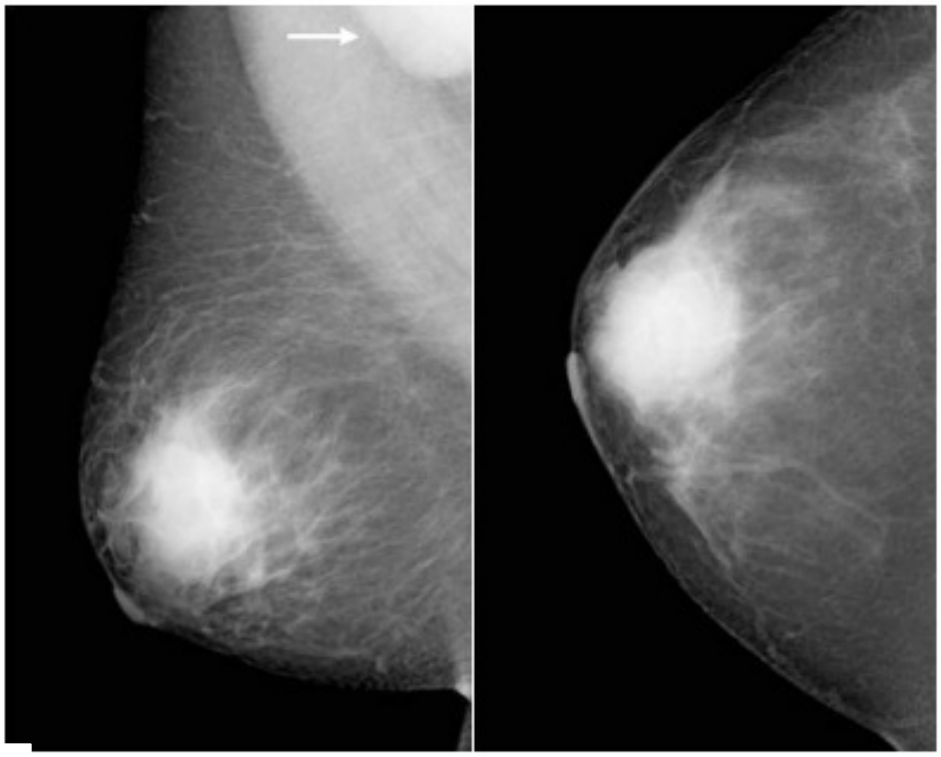


B.Sonography reveals irregularly shaped, microlobulated marginated, heterogeneously echo-textured mass with posterior enhancement.

C.Increased vascular flow is noted on color Doppler scan.

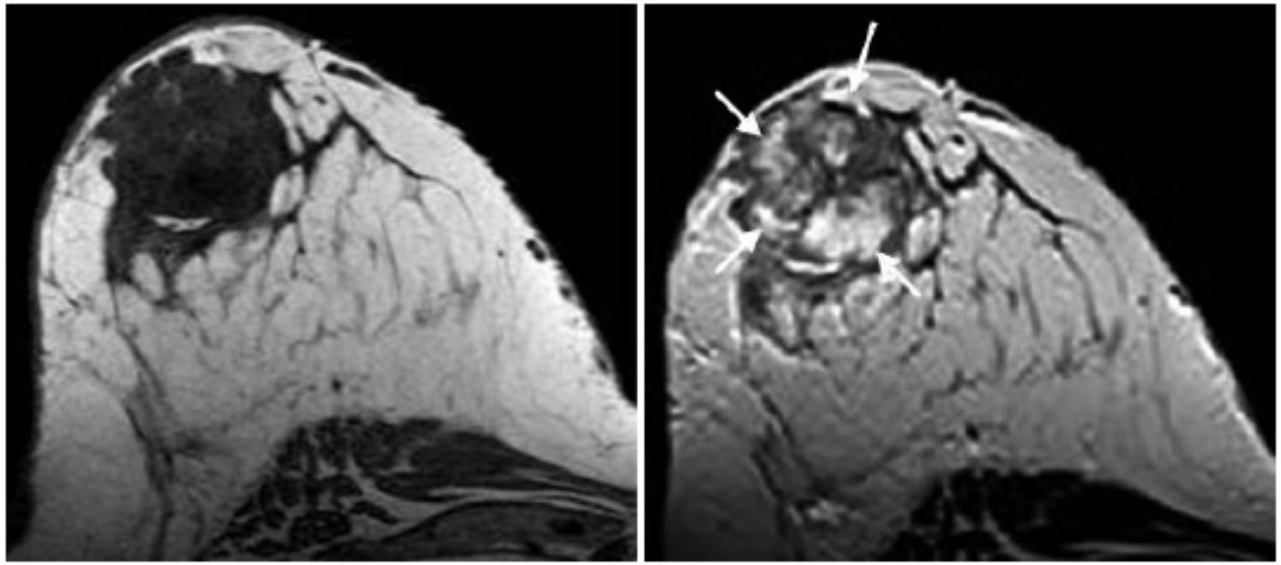
D.There is enlarged lymph node with cortical thickening and loss of fatty hilum in right axilla.

Radiological Findings



Mammography shows high-density mass with ill defined margin in subareolar area of right breast. Enlarged axillary lymph node is noted in right mediolateral oblique view (arrow).

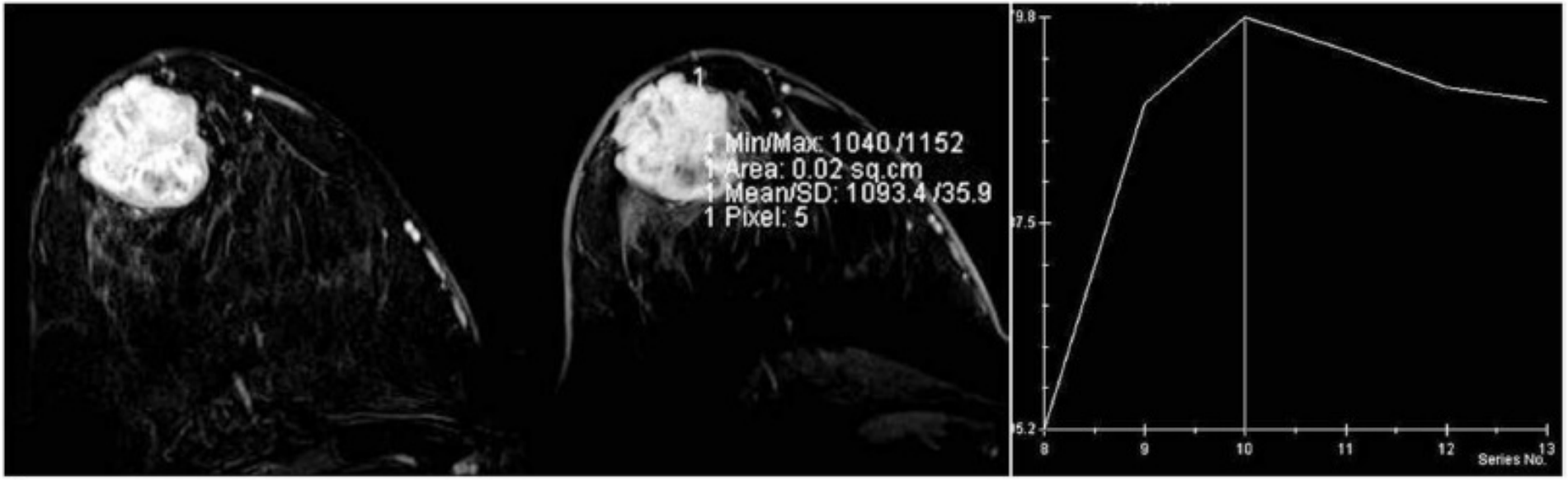
Radiological Findings



E. On non-fat-saturated T1 weighted sequences, mass shows heterogeneously low signal intensity.

F. On non-fat-saturated T2 sequences, central portion of mass shows intermediate to high signal intensity (arrows).

Radiological Findings



G

G. On post-contrast, subtraction image obtained two minutes after administration of gadolinium contrast (left) and kinetic curve (right) derived from signal intensity measurements in selected region within lesion (middle), there is rapid initial enhancement of peripheral portion as well as washout in delayed phase.

Radiological Findings

However, the radiologic findings are hard to differentiate from those of much more commonly seen invasive ductal carcinoma. Reports of new cases will be necessary in order to determine the radiologic presentation of primary neuroendocrine tumor of the breast.

Primary Neuroendocrine Tumor of the Breast: Imaging Features

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Departments of [1]Clinical Pathology, [2]Radiology and [3]Surgery, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Uijeongbu 480-717, Korea

Functional study in vivo

Radiolabelled somatostatin analogs for diagnosis and radio-guided surgery of neuroendocrine breast cancer undetectable with conventional imaging procedures

S. Panareo[a,*], P. Carcoforo[b], S. Lanzara[b], S. Corcione[c], E. Bagatin[a], M. Casali[a], A. Costanzo[a], E. Basaglia[b], L.M. Feggi[a]

[a]*Nuclear Medicine Unit, Imaging Diagnostic and Laboratory Medicine Department, University Hospital "S. Anna", Corso Giovecca 203, 44100 Ferrara, Italy*
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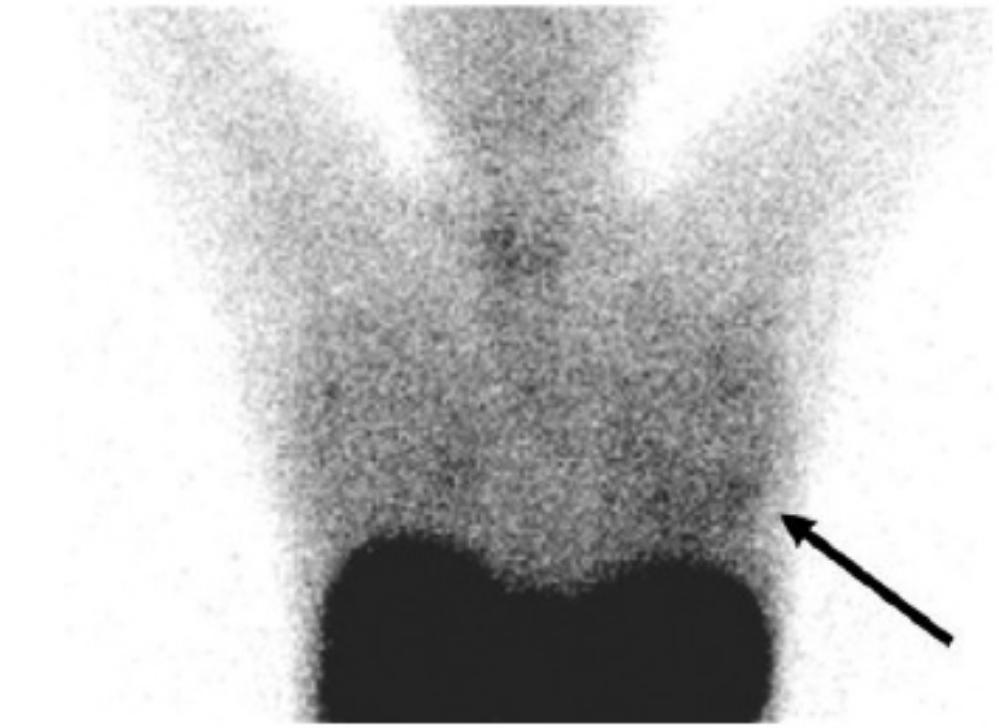
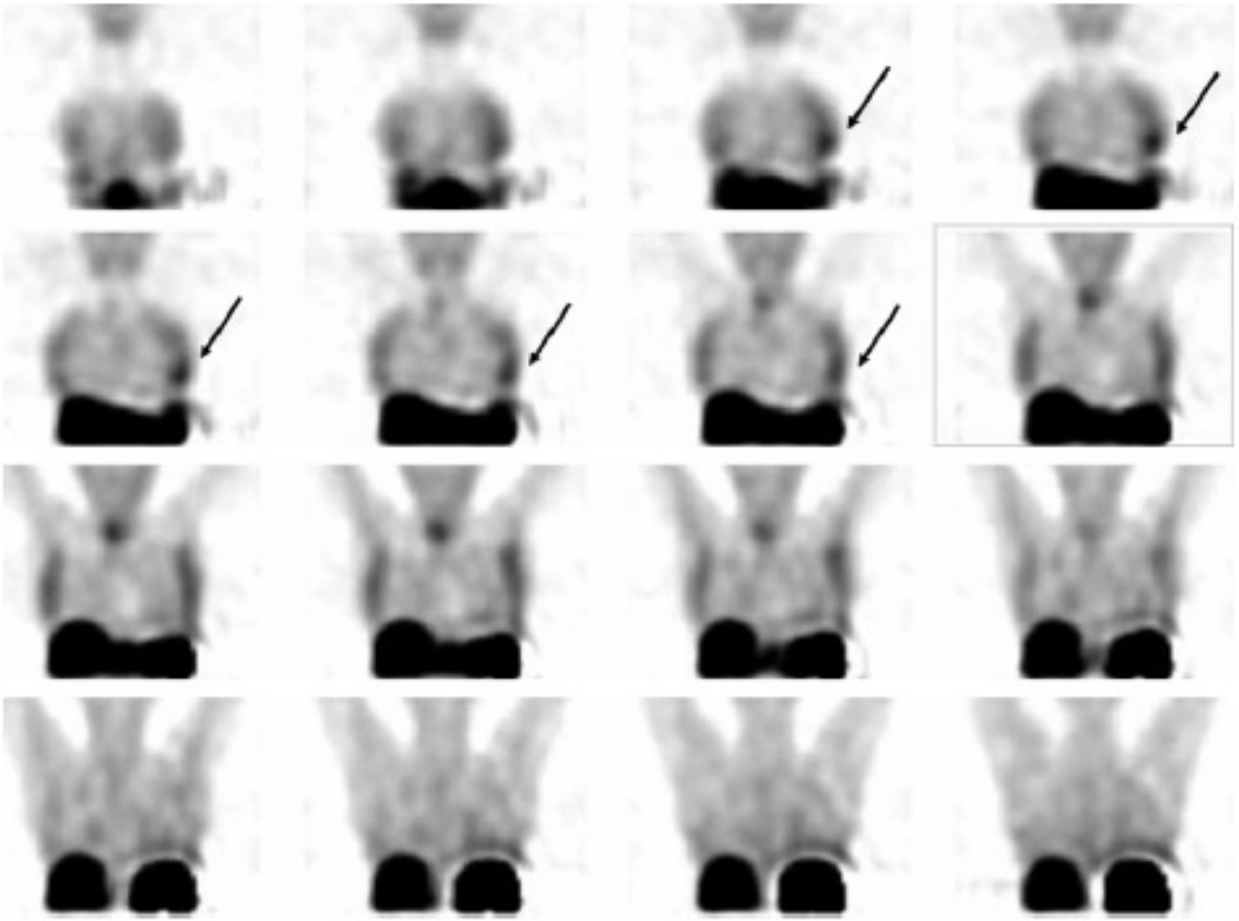
Functional study in vivo

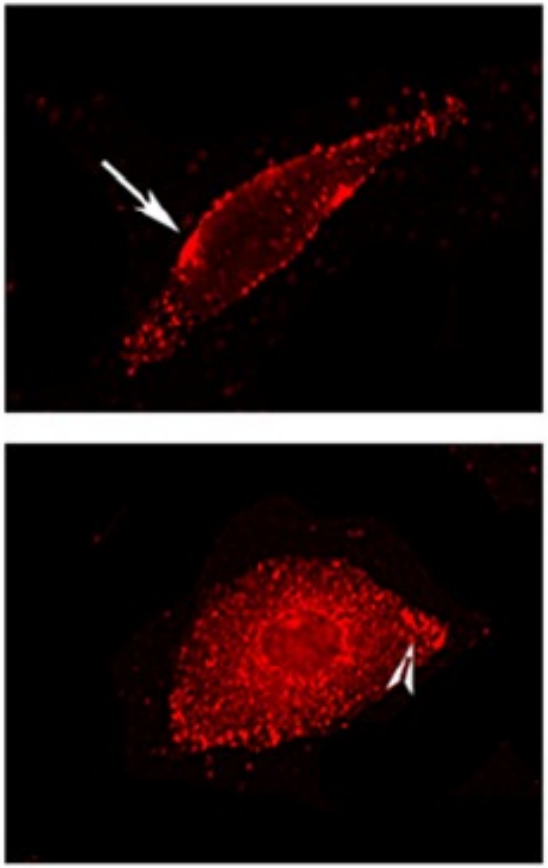


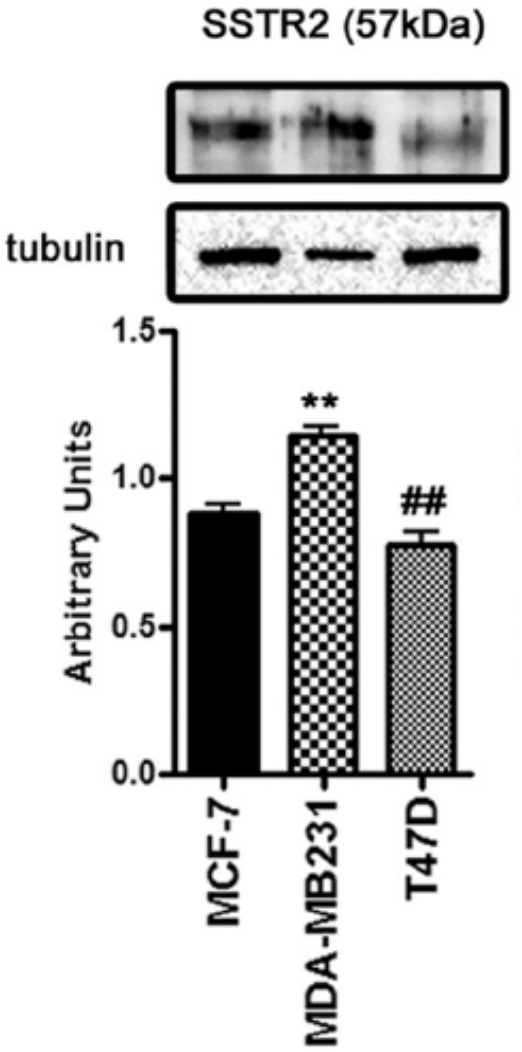
In-111 pentetreotide scan in planar projection of a thorax with increased uptake in the left mammary gland (arrow).

Functional study in vivo

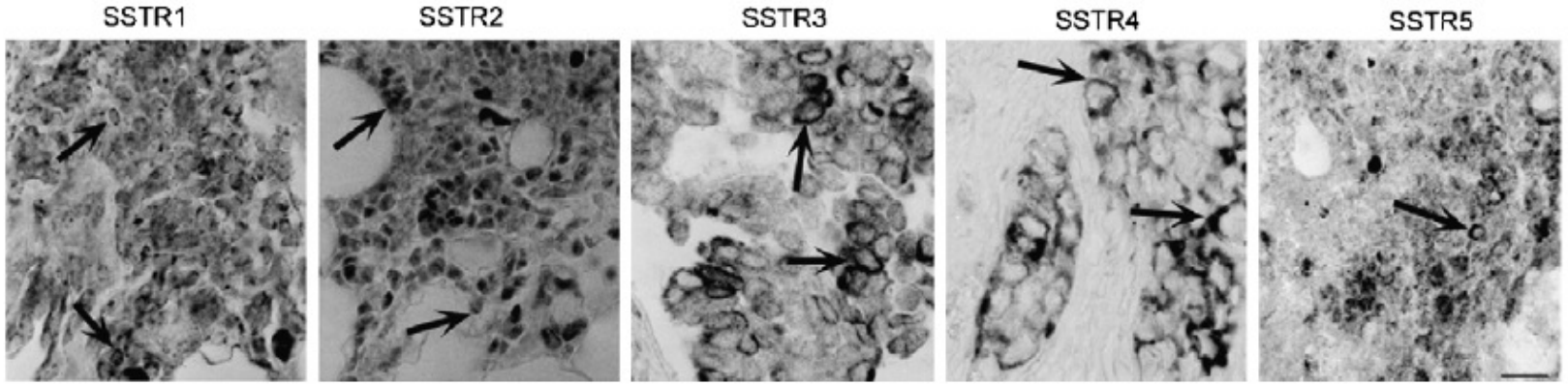


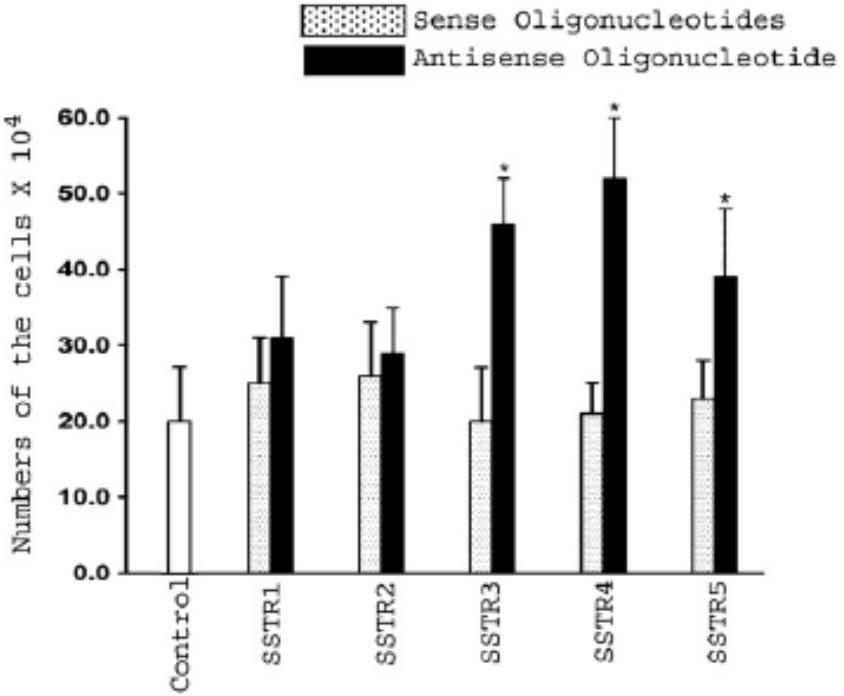
Basic research on cell cultures



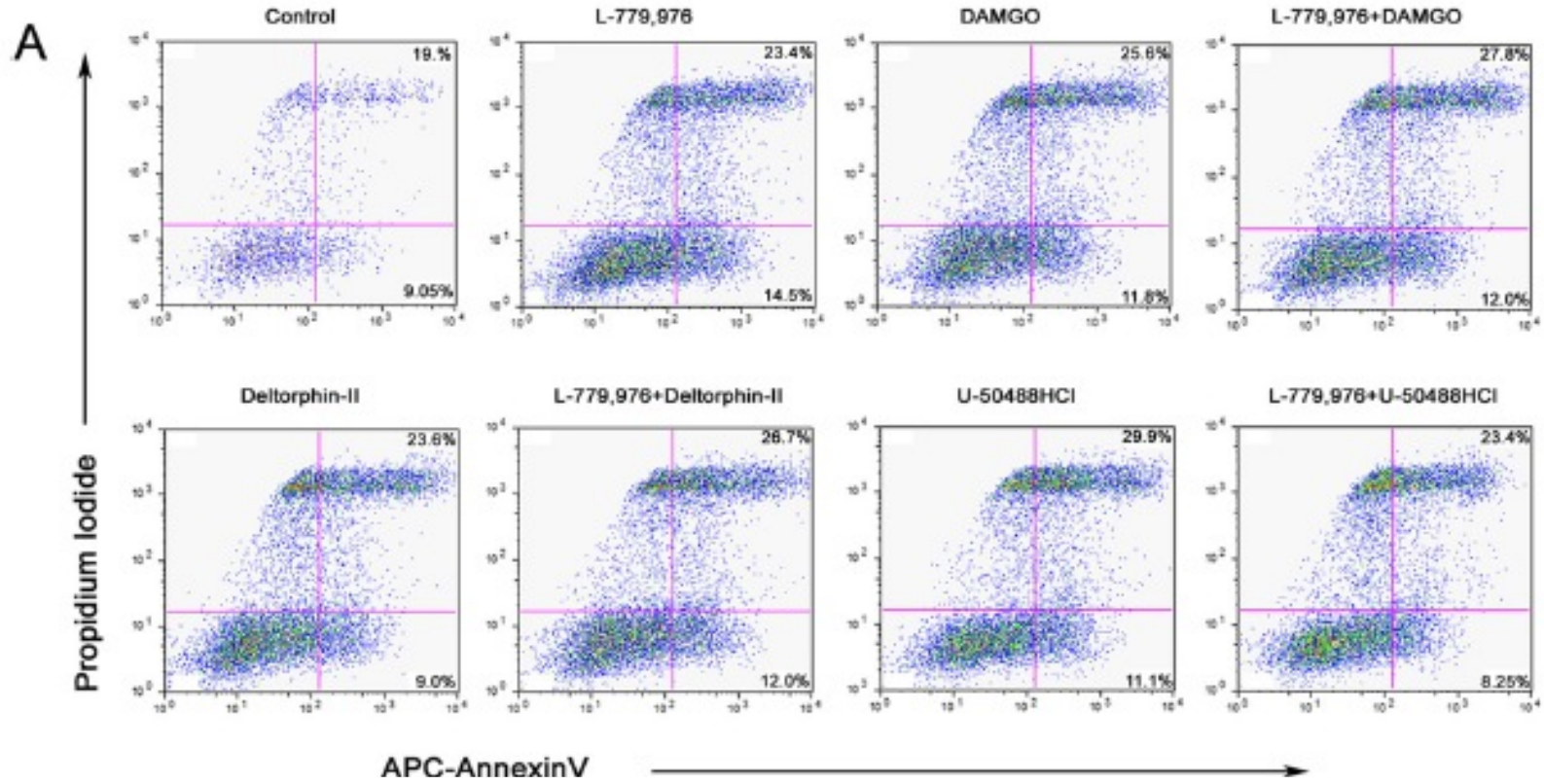


Basic research on cell cultures





Basic research on cell cultures



Representative flow cytometry analysis displaying apoptosis and necrosis after exposure to SSTR2 agonist in breast cancer cells. Cells were harvested and treated with SSTR2 agonist.

The percentage of apoptosis (lower right quadrant) and necrosis (upper right quadrant) was evaluated in MCF-7.

Prognostic Factors

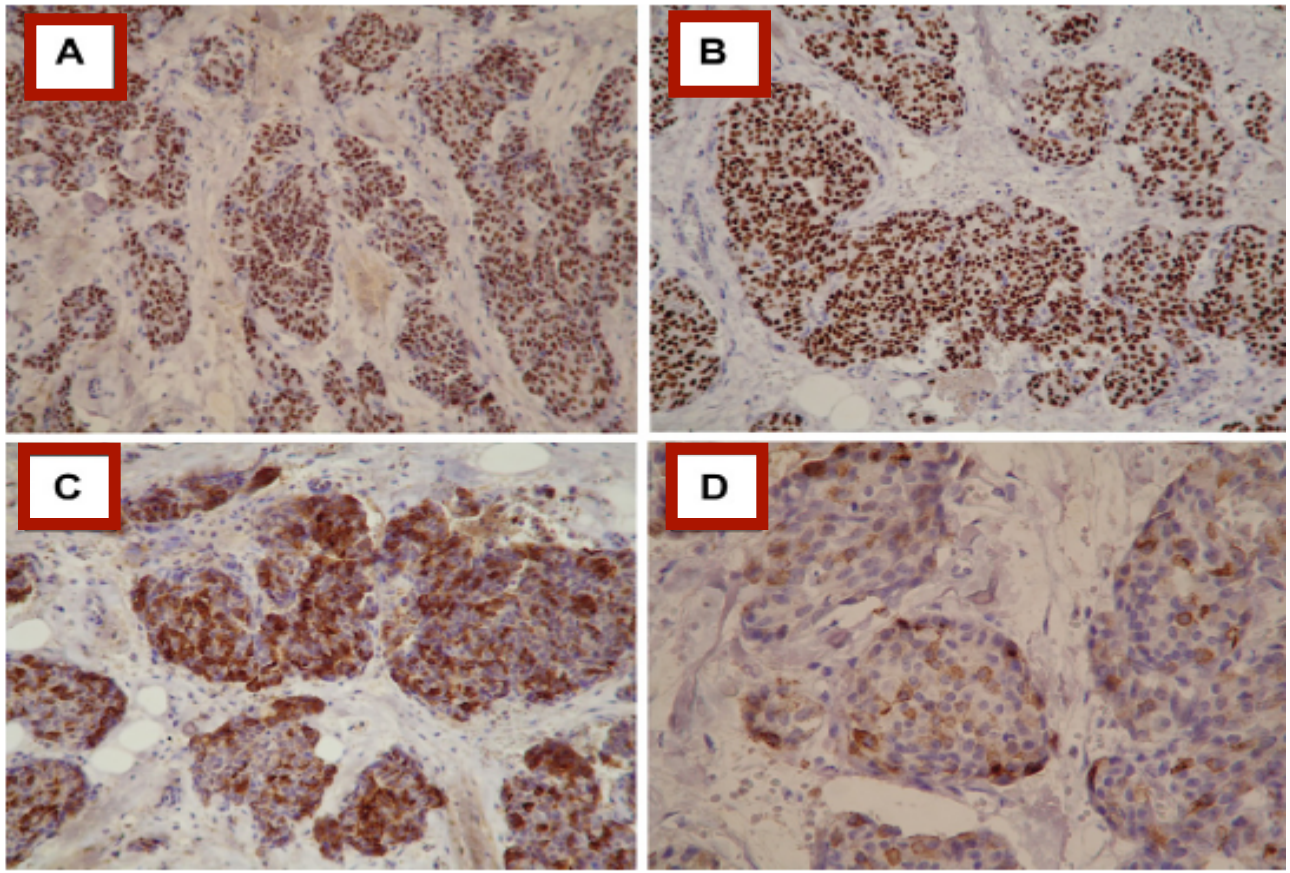
There is no consensus if B-NET have better or worse prognosis than the other breast tumors.

1. Solid neuroendocrine carcinoma is considered to be a well-differentiated neoplasia. Some authors have proposed that patients with a solid carcinoma have a better prognosis.

2. Small-cell and large-cell carcinomas are poorly differentiated lesions.

3. Mucinous differentiation and positivity for estrogen and progesterone receptors are also favorable prognostic factors.

Prognostic Factors



The breast tumor cells were reactive to: (A) estrogen receptor; (B) progesterone receptor. Tumor cells (80%) were reactive to Synaptophysin (C) and 60% were reactive to Chromogranin A (D).

Prognostic Factors

Compared with invasive ductal carcinoma, B-NET is more aggressive with a higher tendency for local and distant recurrence and poorer overall survival.

Prognostic Factors

Prognostic significance of tumor grading and staging in mammary carcinomas with neuroendocrine differentiation☆,☆☆

Zhen Tian MD, PhD[a], Bing Wei MD[b], Feng Tang MD, PhD[c], Wei Wei MS[d], Michael Z. Gilcrease MD, PhD[e], Lei Huo MD, PhD[e], Constance T. Albarracin MD, PhD[e], Erika Resetkova MD, PhD[e], Lavinia Middleton MD[e], Aysegul Sahin MD[e], Yan Xing MD, MPH[f], Kelly K. Hunt MD[f], Jieqing Chen MD[e], Hong Bu MD, PhD[b], Asif Rashid MD, PhD[e], Susan C. Abraham MD[e], Yun Wu MD, PhD[e,*]

Human Pathology (2011) **42**, 1169–1177

The study of Tian et al with 74 cases of B-NET, gave prognostic significance to the tumor size, regional lymph node status, lymphovascular invasion, and Ki-67 proliferation index for overall survival and distant recurrence-free survival.

Prognostic Factors

Multivariate Cox model for OS

Variables	*P*	Hazard ratio	95% Hazard ratio confidence limits
Age (>60 y *vs* ≤60 y)	NS	0.87	0.15-5.09
N1, N2, N3 *vs* N0	.007	5.09	1.98-69.07
Ki-67 (≥30% *vs* <30%)	.006	8.25	1.82-37.48
ER (positive *vs* negative)	NS	0.25	0.02-3.05

NS indicates not significant.

Multivariate Cox model for OS

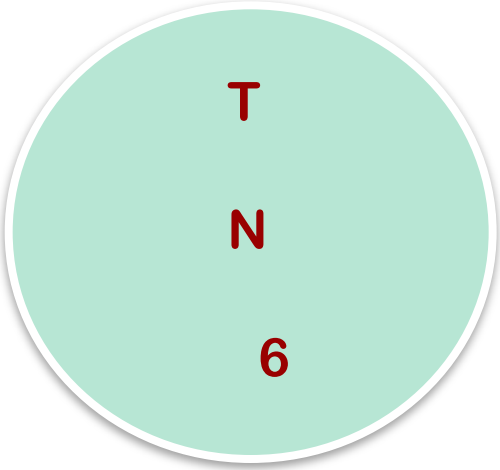
Variables	*P*	Hazard ratio	95% Hazard ratio confidence limits
Age (>60 y *vs* ≤60 y)	NS	2.94	0.33-26.23
T2, T3, T4 *vs* T1	.011	40.82	2.38-698.80
Nuclear grade 3 *vs* grades 1 and 2	NS	1.44	0.26-7.93
Ki-67 (≥30% *vs* <30%)	.011	11.68	1.74-78.42

NS indicates not significant.

Prognostic Factors

Studies of prognostic factors in mammary NECs confirm the importance in predicting survival outcomes in these patients (indipendent prognostic factors):

1. tumor size
2. regional lymph node status
3. Ki67 proliferation



Prognostic Factors

The data further suggest that some prognostic features for mammary carcinomas may not carry the same importance in mammary NECs due to natural differences in the architecture of these unusual tumors.

Finally, Ki-67 proliferation index could be identify as an important prognostic marker for OS in mammary NECs; its routine evaluation in these tumors may provide more valuable information.

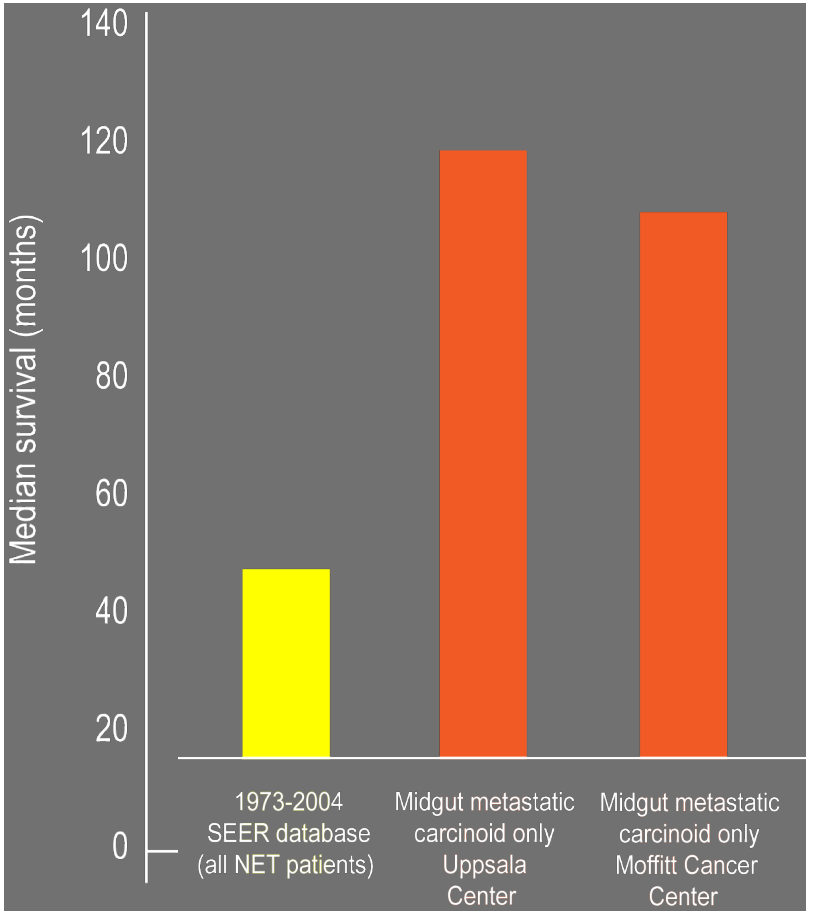
THERAPY

NECs were treated similarly to non neuroendocrine breast cancer, but **they failed to respond as well to conventional therapies** for breast cancer including hormonal manipulation, chemotherapy, and radiation.

Multidisciplinary approach

Median survival of patients with metastatic carcinoids treated at "centers of excellence" is more than 3 times higher than median survival of patients with NETs in SEER database

Median survival of patients



Clinical Practice Points

- Neuroendocrine breast carcinoma is as a subtype of invasive mammary carcinoma in which >50% of the tumor cells express neuroendocrine markers; immunohistochemical staining include chromogranin, synaptophysin, and neurospecific enolase. the reported incidence is 2%-5%, accounting for <0.1% of all breast cancers and <1% of all neuroendocrine tumors.

- The lack of specific clinical or imaging features of neuroendocrine breast carcinoma (NEBC), involves that the diagnosis of nebc often depends upon the recognition of its histologic growth pattern, the immunohistochemical staining for neuroendocrine markers being necessary for its confirmation.

- Several studies are needed to give the recommendations for the correct handling, treatment, and surveillance of this subtype of carcinoma, and also the prognostic factors for the clinical outcome.

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