# 2° Convegno interregionale AME

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**ASSOCIAZIONE MEDICI ENDOCRINOLOGI**
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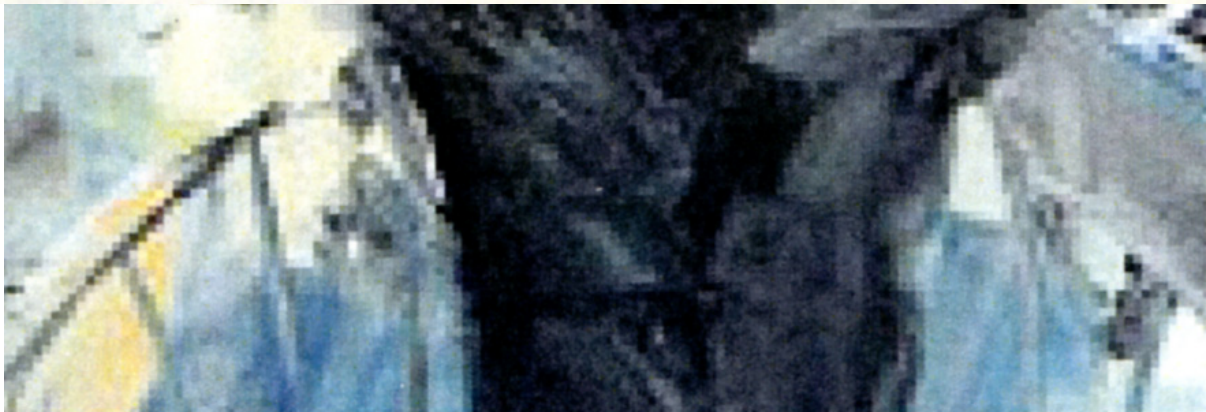
## SESSIONE I

## TUMORI NEUROENDOCRINI DEL TRATTO GASTRO-ENTERO-PANCREATICO

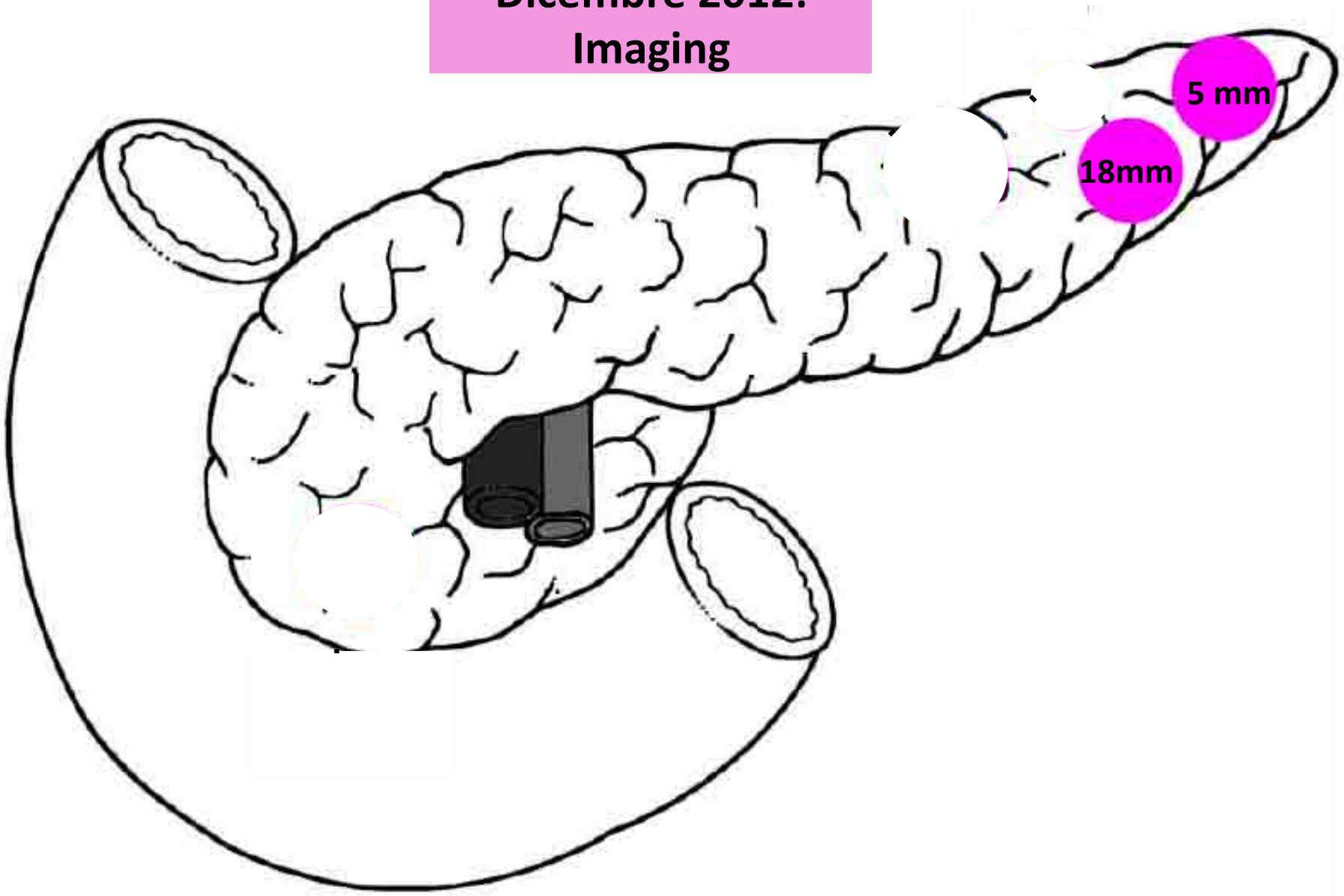
- Il ruolo dell'anatomo-patologo *S. Pizzolitto*

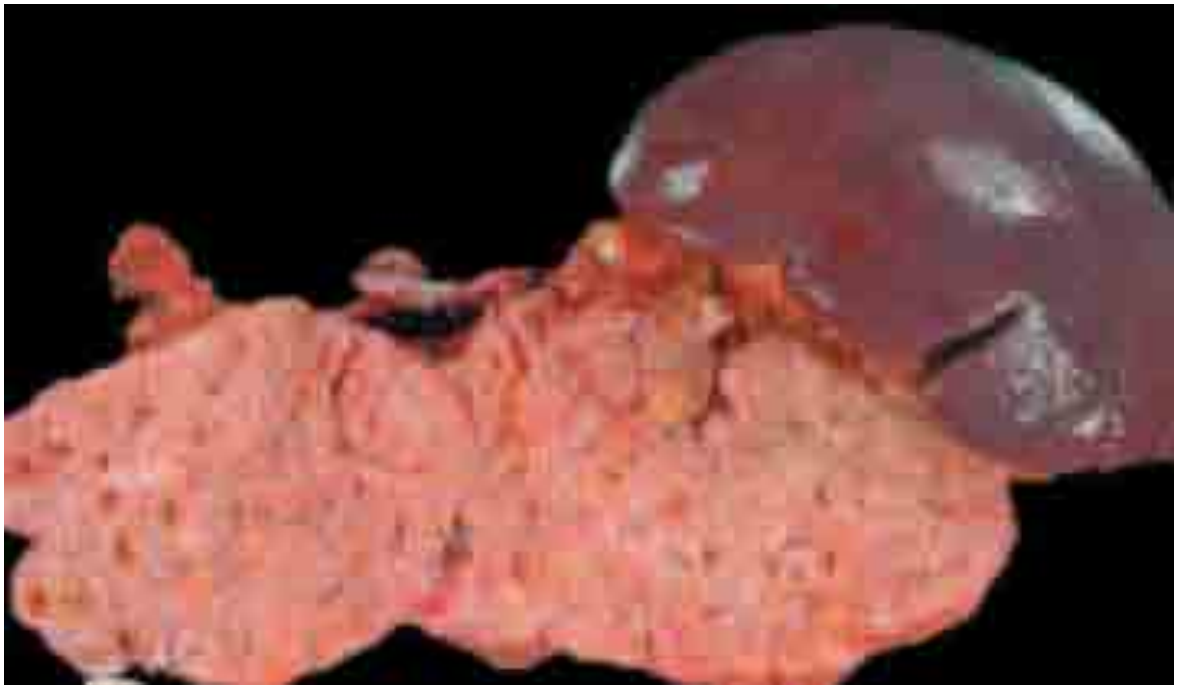


# *Cosa chiedere al Patologo?*

***"LA DIAGNOSI"***

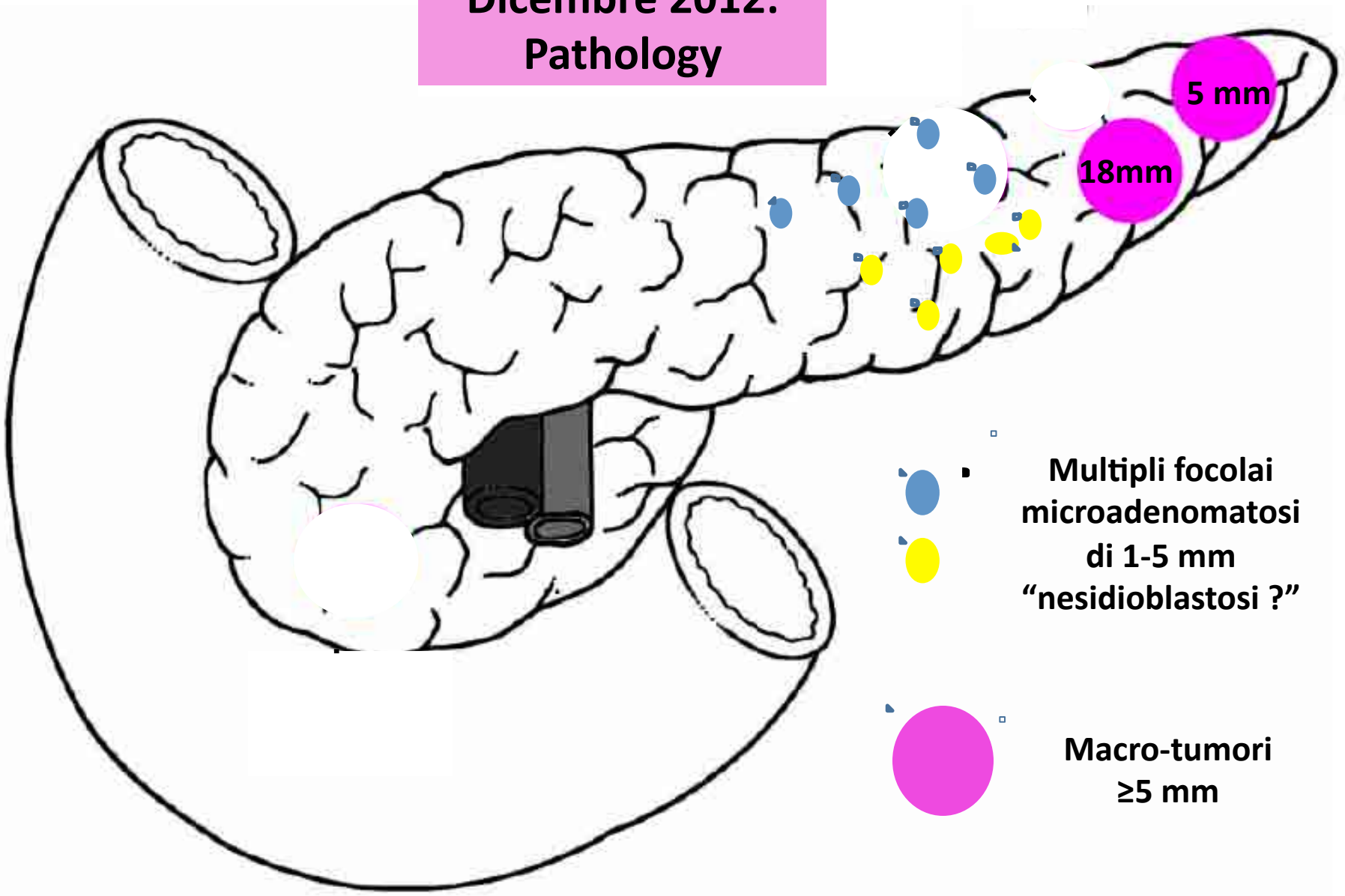
# Dicembre 2012: Imaging

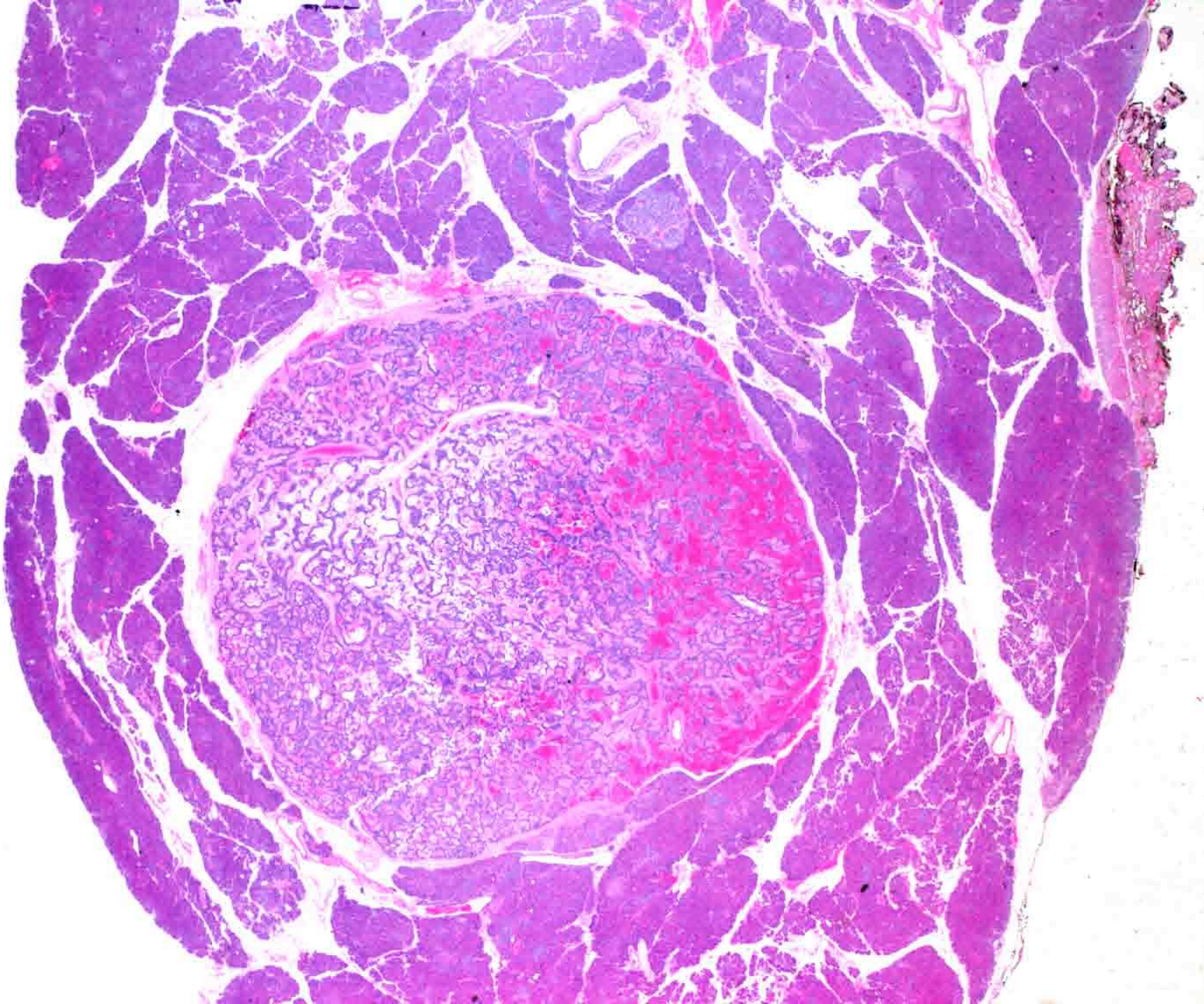


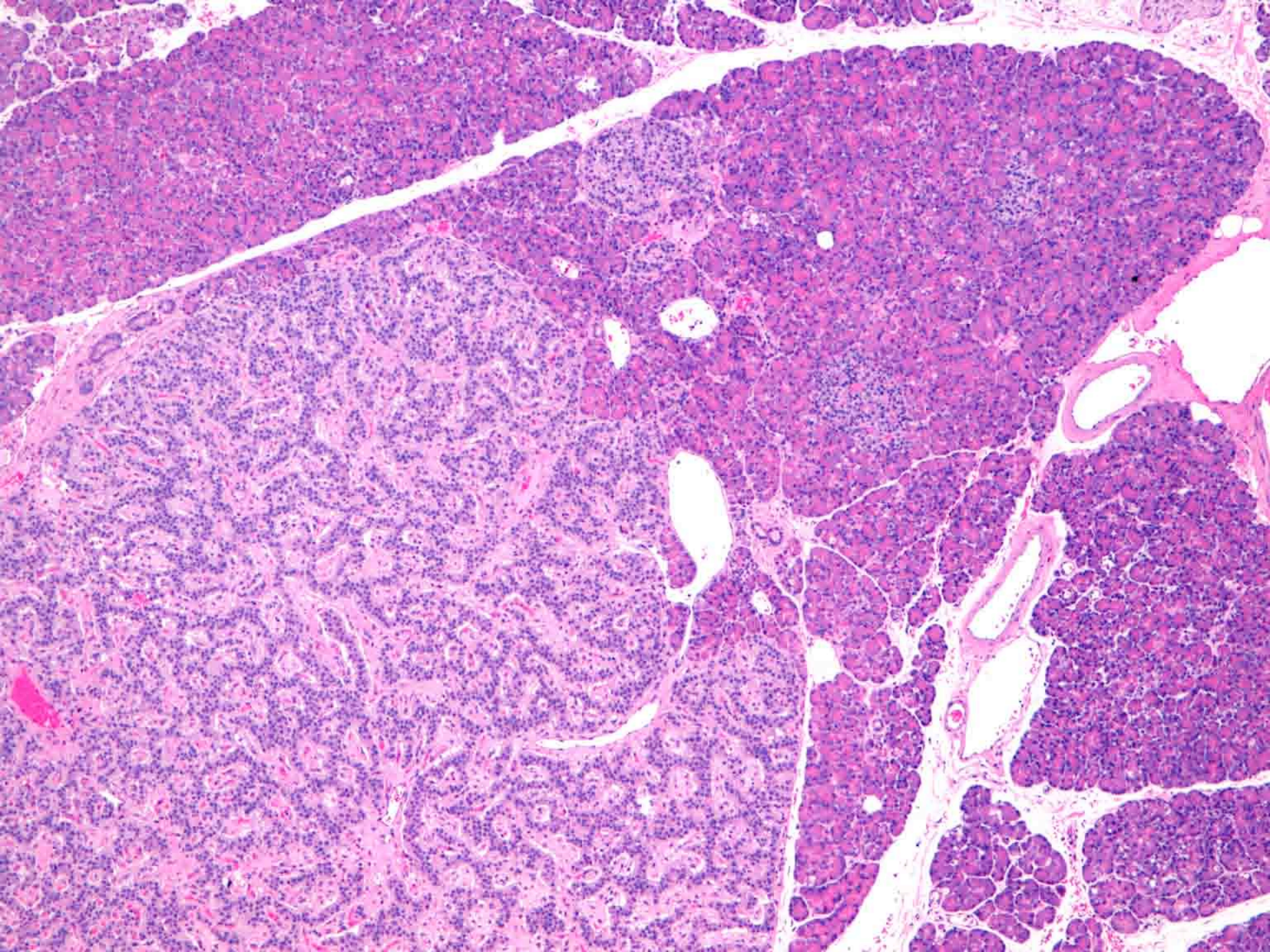


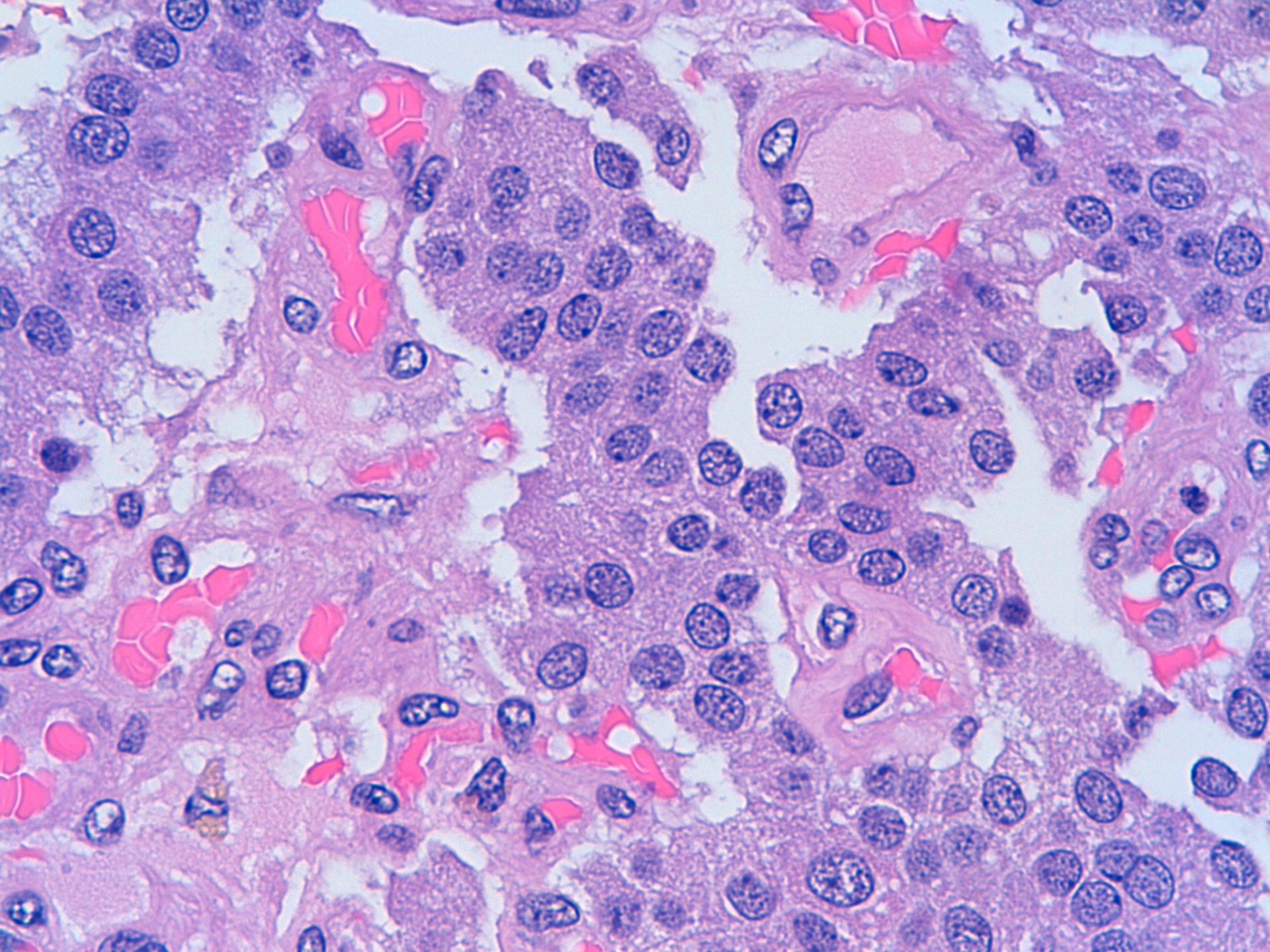
Spleno-pancreasectomia distale

# Dicembre 2012: Pathology

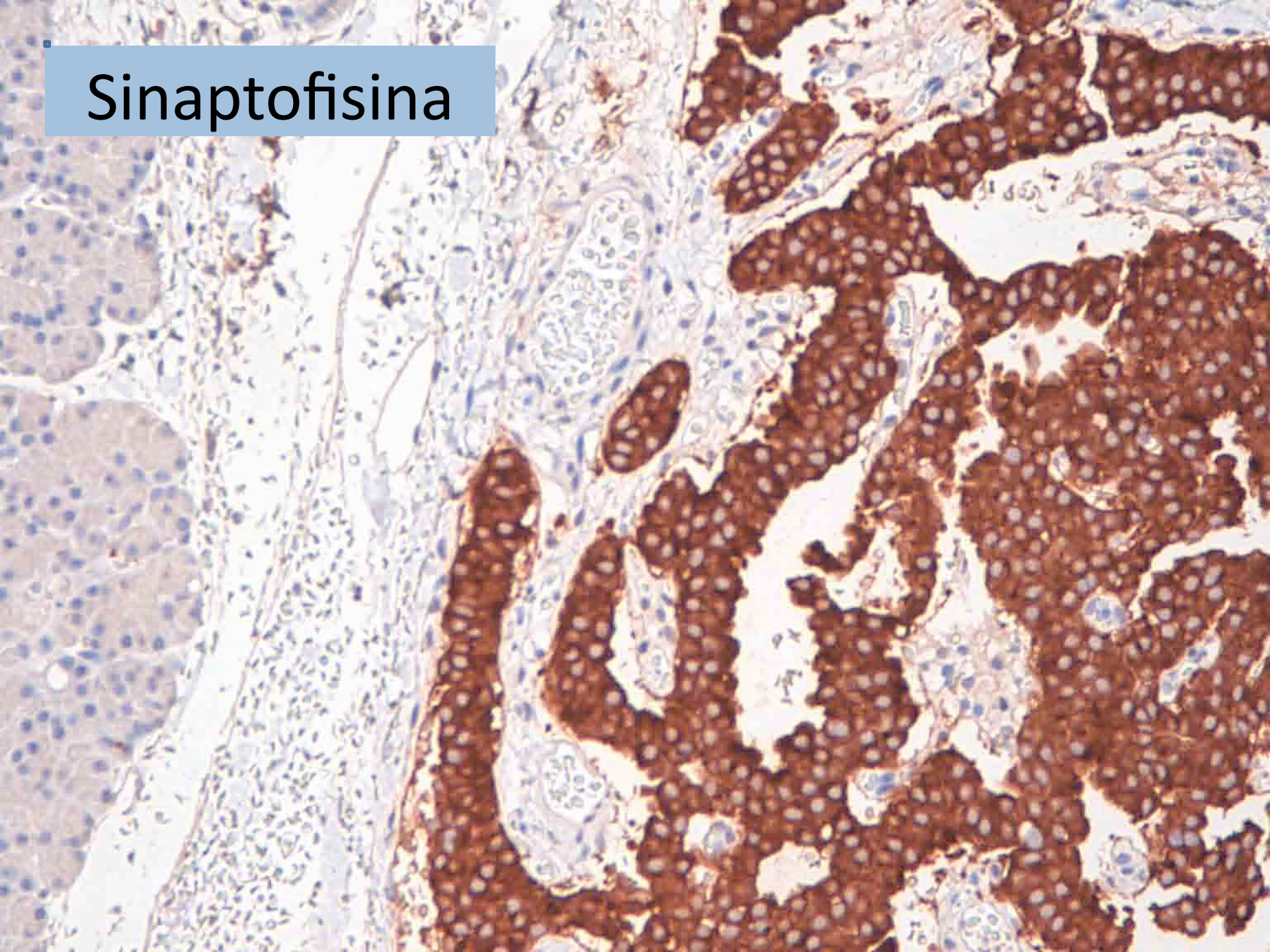


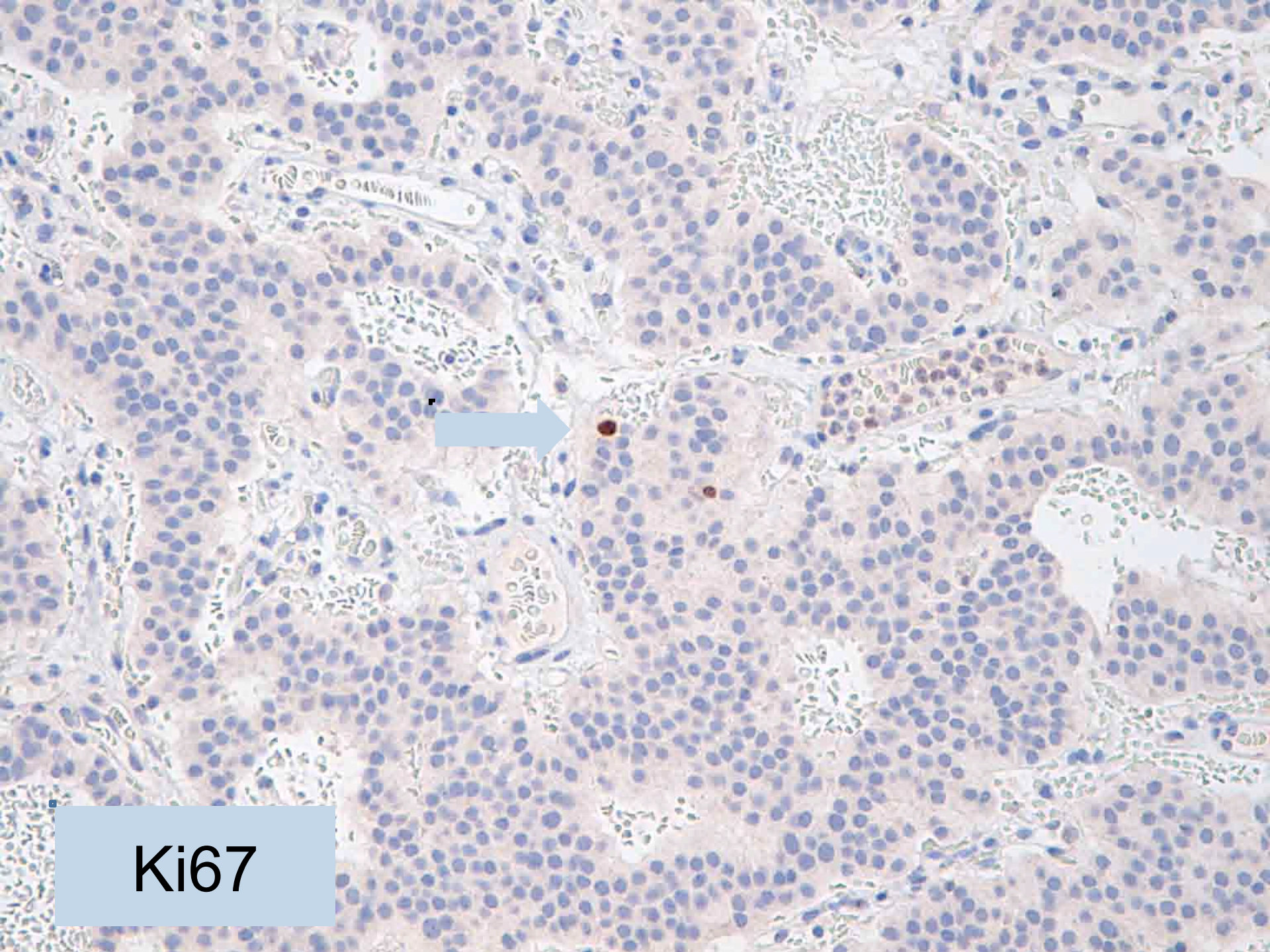


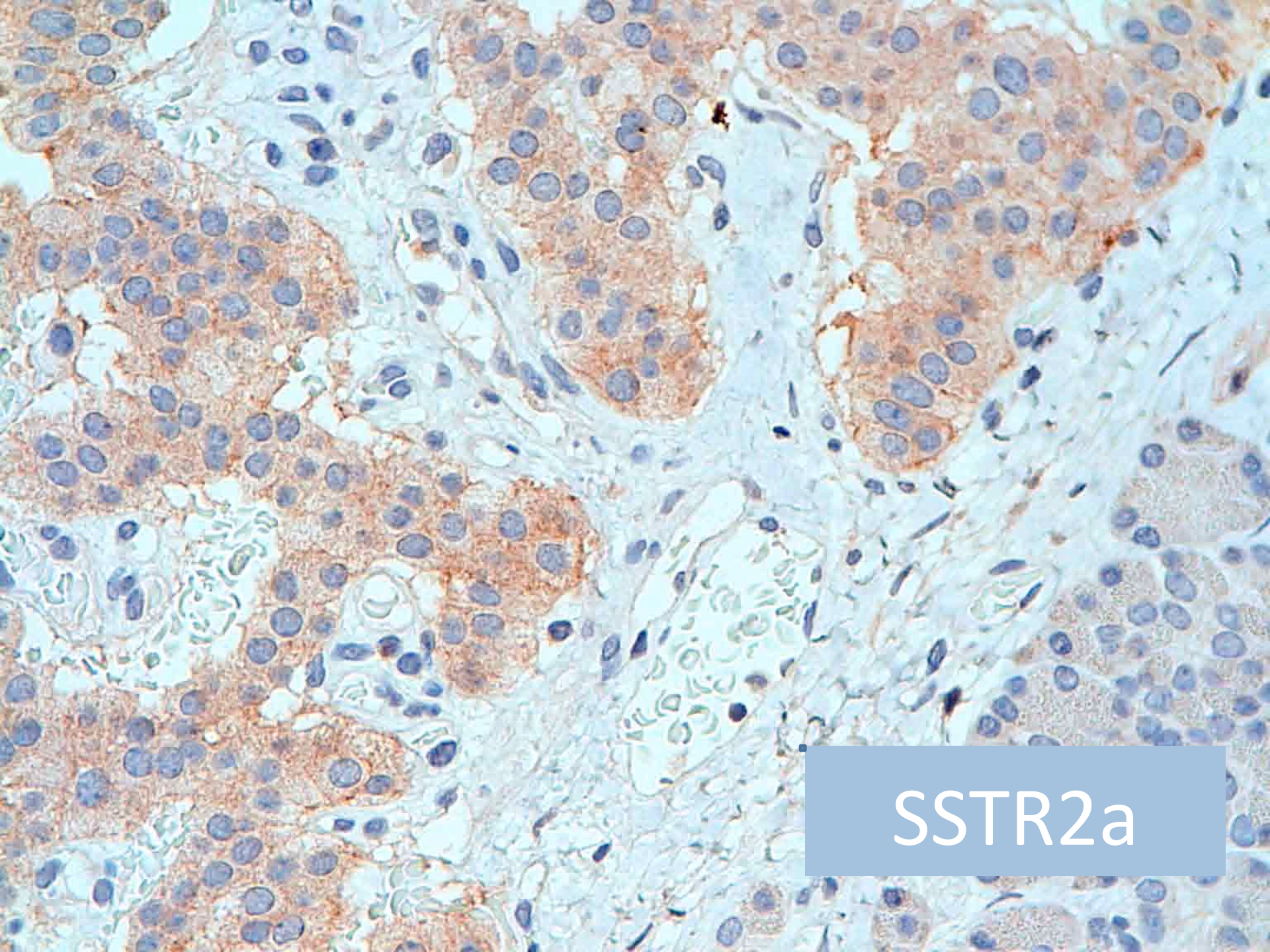


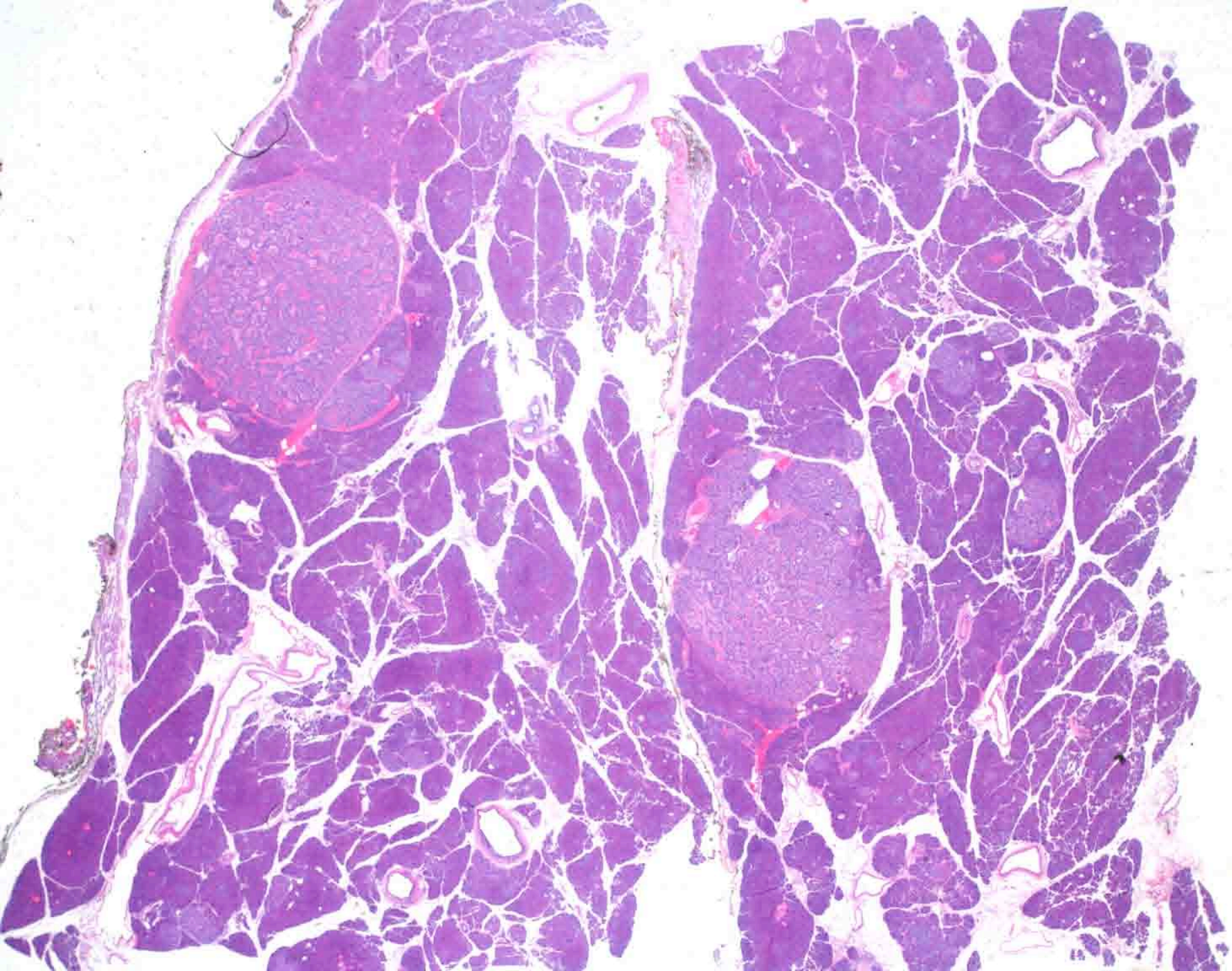


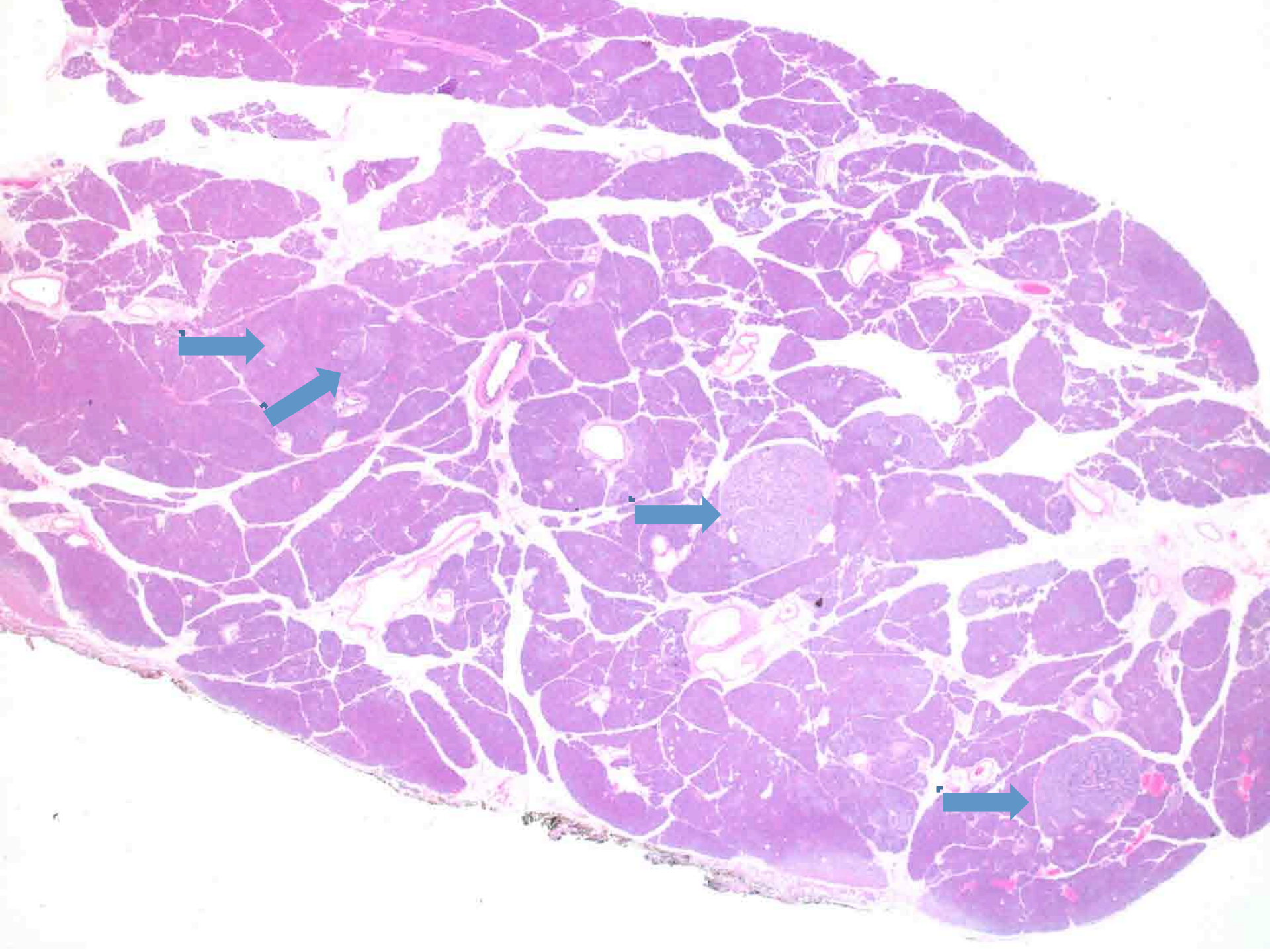
# Sinaptofisina

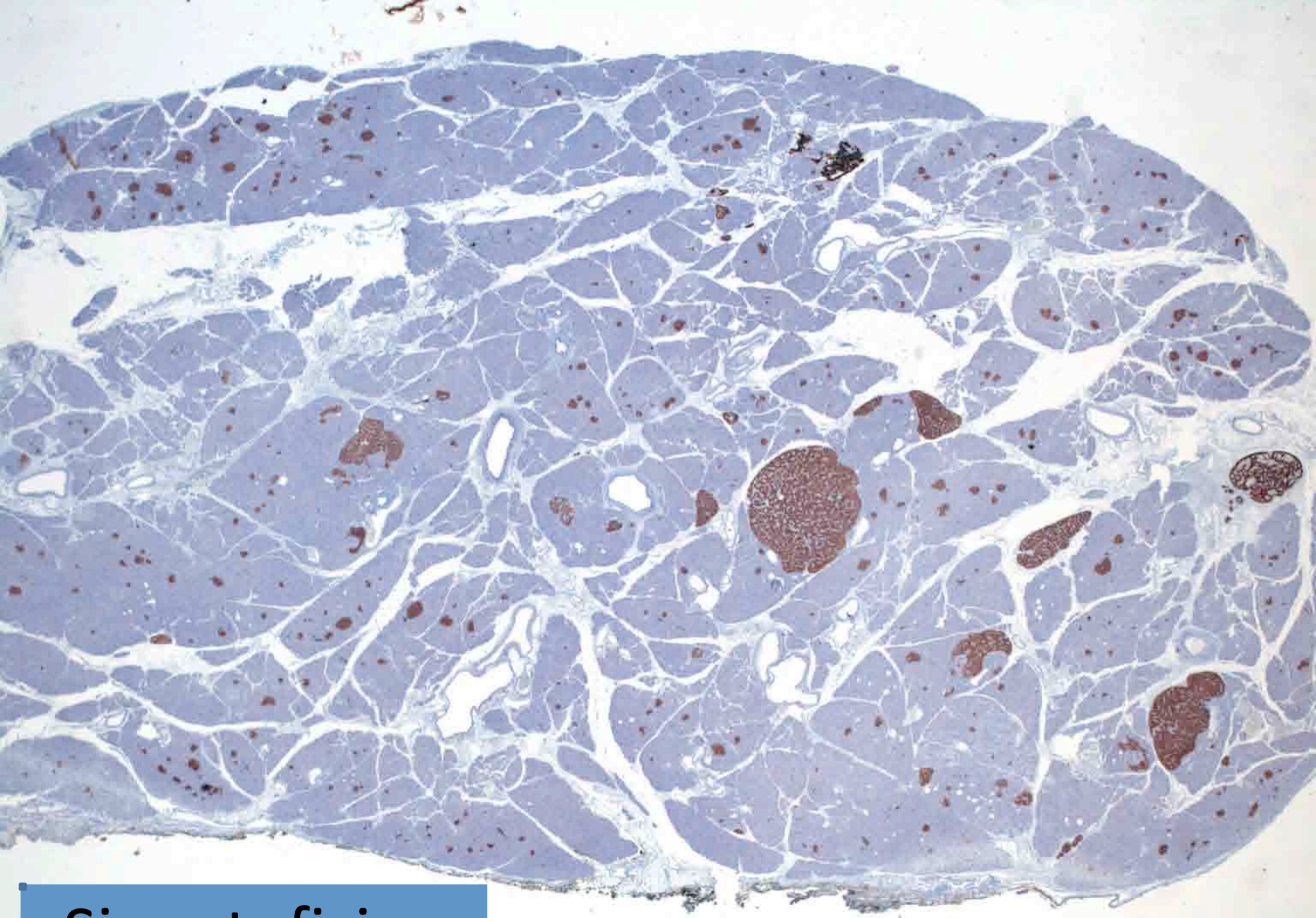



Ki67


SSTR2a

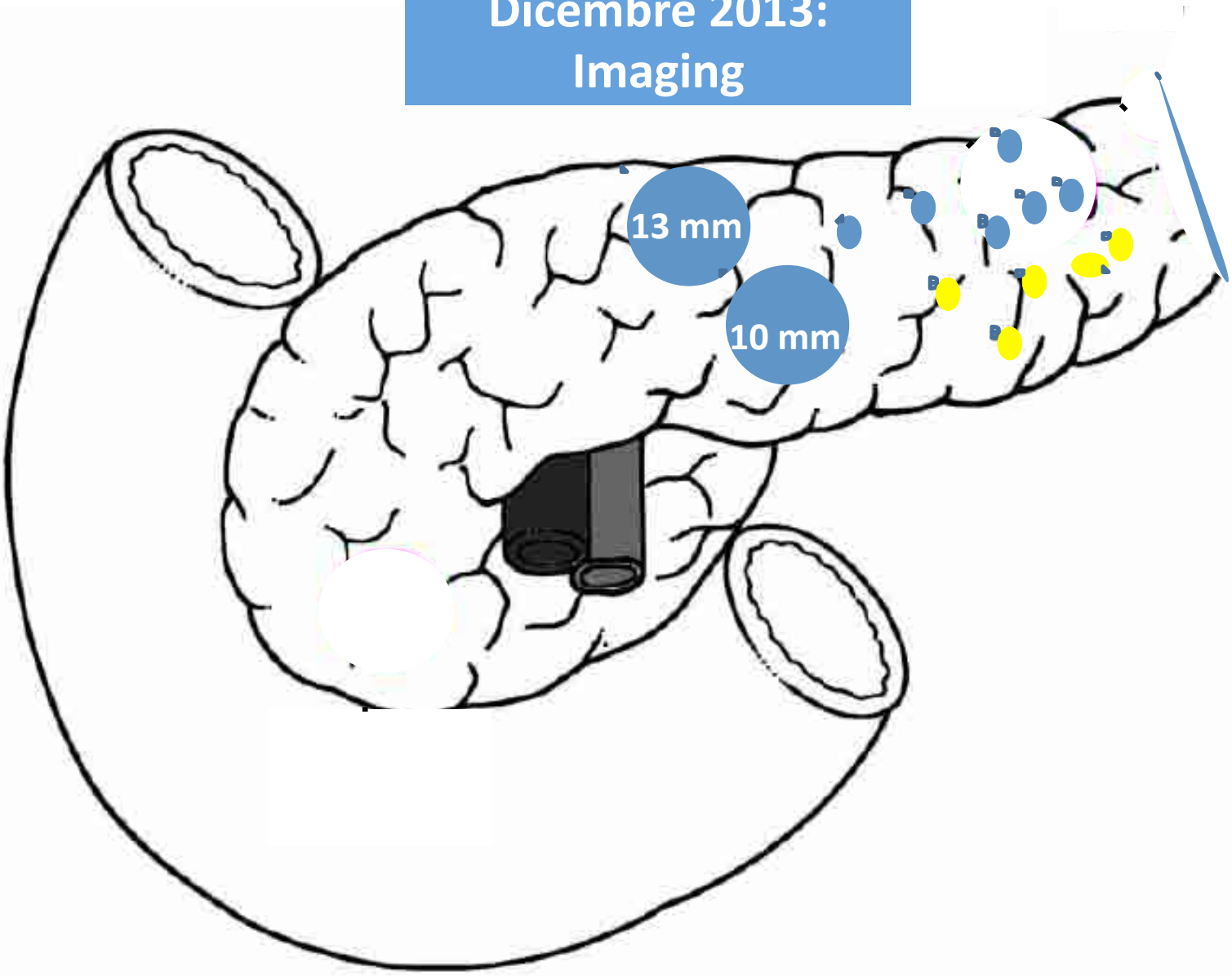






Sinaptofisina

# Dicembre 2013: Imaging



# What is your diagnosis?

1. β-cell and islet hyperplasia
2. Multicentric insulinoma
3. Metastasized insulinoma
4. MEN-1 with yhe development of multiple insulinomas
5. Adult nesidioblastosis
6. Insulinomatosis

Neuroendocrinology 2012;95:98–119
DOI: 10.1159/000335591
Published online: February 15, 2012
Neuro-endocrinology

# ENETS Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Neoplasms: Functional Pancreatic Endocrine Tumor Syndromes

Robert T. Jensen[a] Guillaume Cadiot[b] Maria L. Brandi[c] Wouter W. de Herder[d]
Gregory Kaltsas[e] Paul Komminoth[f] Jean-Yves Scoazec[g] Ramon Salazar[h]
Alain Sauvanet[i] Reza Kianmanesh[j]

The immunohistochemical determination of insulin expression by tumor cells is not absolutely necessary for diagnosis.

but it provides verification of hormonal production, it may identify specific cell types

In patients without MEN1 but with multiple insulinomas or multiple recurrences, insulinomatosis should be suspected [140].

# Insulinomatosis

## *A Multicentric Insulinoma Disease that Frequently Causes Early Recurrent Hyperinsulinemic Hypoglycemia*

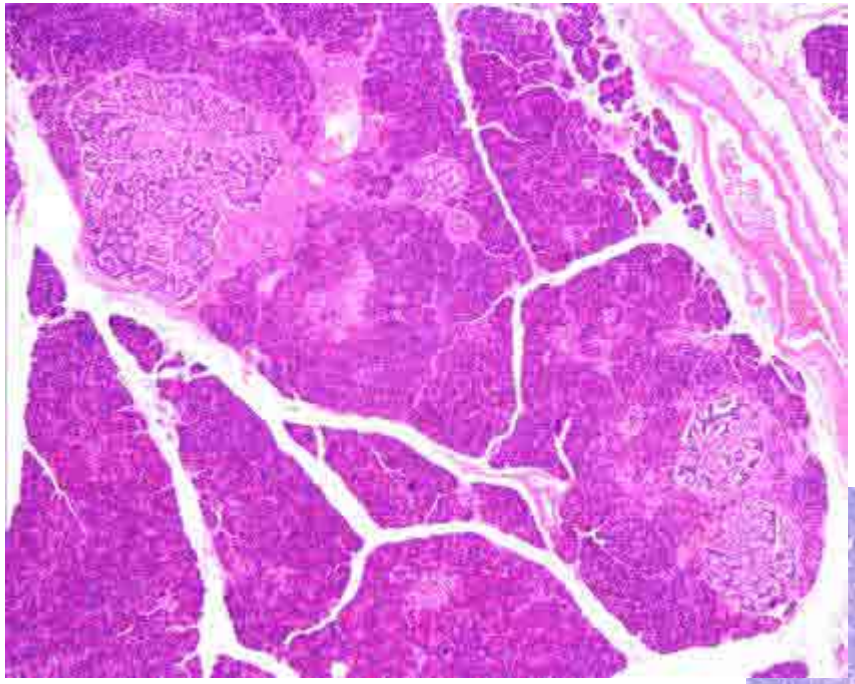
*Martin Anlauf, MD,*† Juliane Bauersfeld, MD,* Andreas Raffel, MD,‡ Christian A. Koch, MD,§ Tobias Henopp, MD,* Ibrahim Alkatout, MD,*‖ Anja Schmitt, MD,¶ Achim Weber, MD,¶ Marie L. Kruse, MD,# Stefan Braunstein, MD,** Klaus Kaserer, MD,†† Michael Brauckhoff, MD,‡‡ Henning Dralle, MD,‡‡ Holger Moch, MD,¶ Philipp U. Heitz, MD,¶ Paul Komminoth, MD,§§ Wolfram T. Knoefel, MD,‡ Aurel Perren, MD,‖‖ and Günter Klöppel, MD**

(*Am J Surg Pathol* 2009;33:339–346)

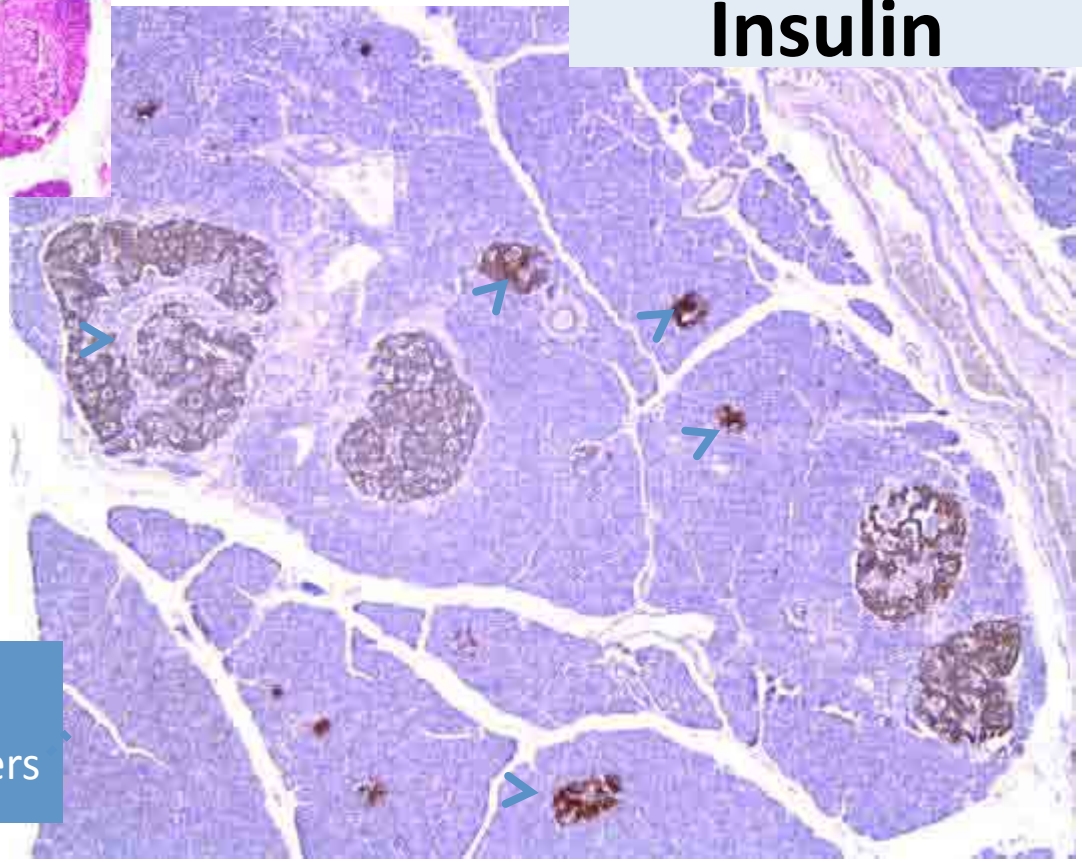
| Insulinoma | Patients | No. Insulinomas (Total/Mean per Patient) | |
|---|---|---|---|
| | | ≥ 5 mm | < 5 mm |
| Solitary/sporadic | 253 (90%) | 253/1 | 0/0 |
| MEN1 associated | 13 (4.6%) | 20/1.5 | 21/1.6 |
| NF1 associated | 1 (0.4%) | 1/1 | 0/0 |
| Insulinomatosis | 14 (5%) | 53/3.8 | 285/20.4 |

**Incidence of patients (281) with solitary and multiple insulinomas**

# Insulinomatosis no MEN-1

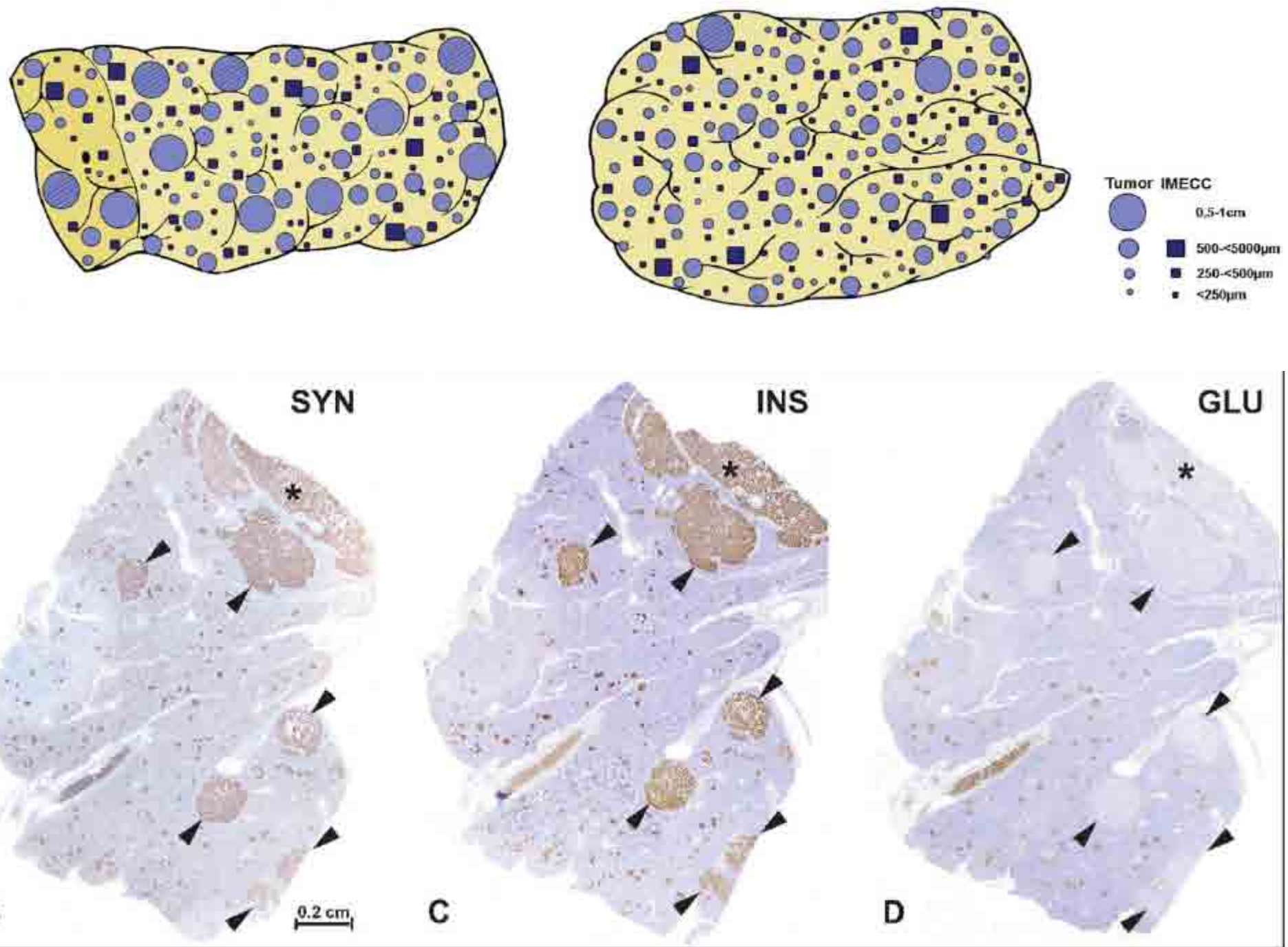


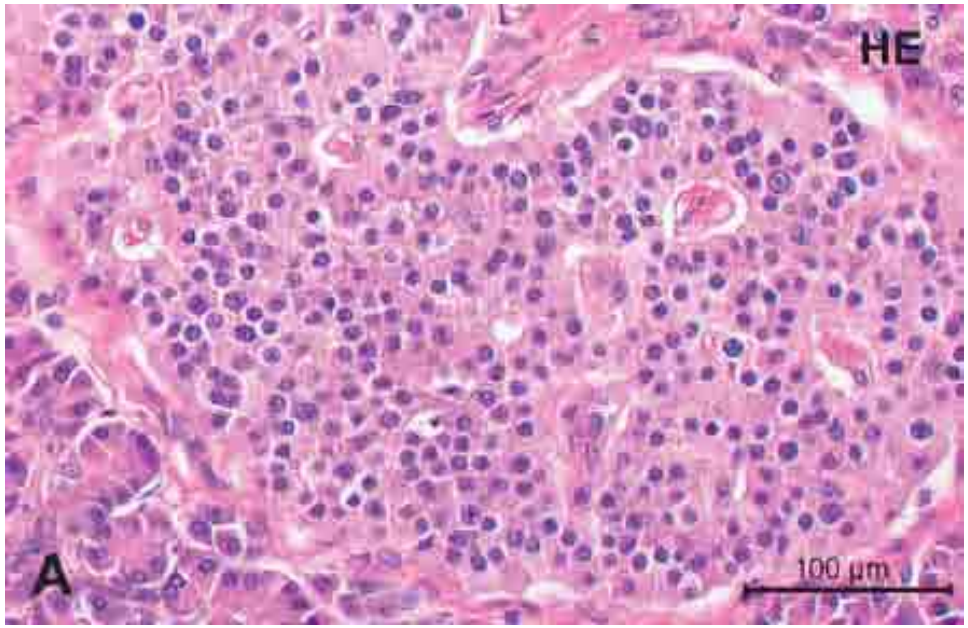
Insulin



Insulin-microadenomatosis

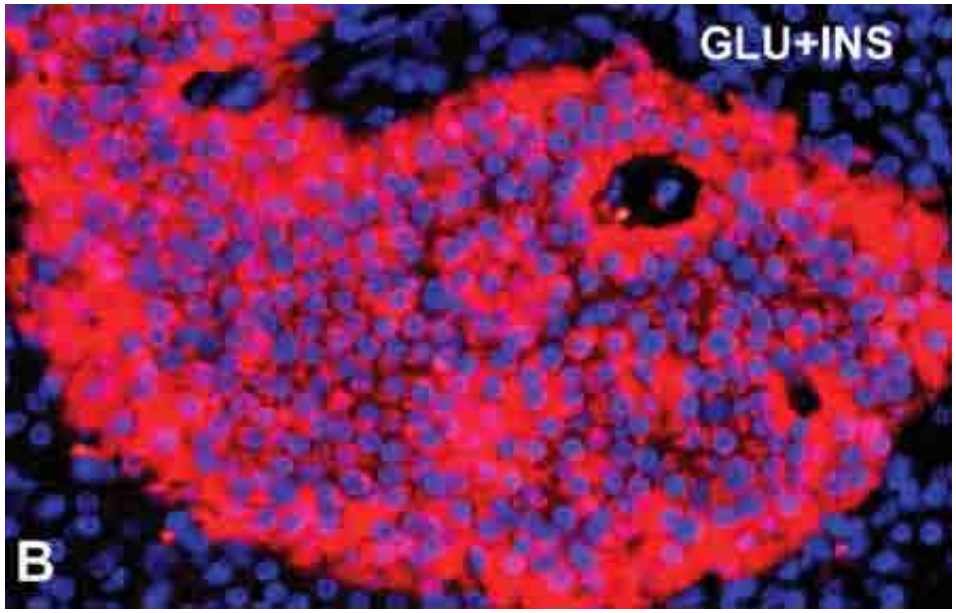
IMECCs: insulin-expressing monohormonal endocrine cell clusters

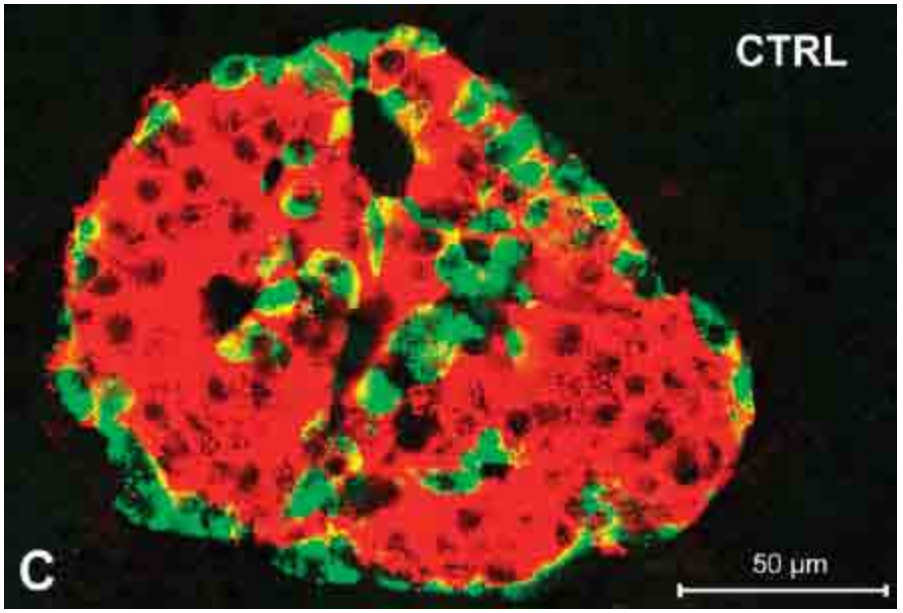

Tumor IMECC
0,5-1cm
500-<5000µm
250-<500µm
<250µm
SYN
INS
GLU
*
B
0.2 cm
C
D




# *Insulinomatosis*

**is a monohormonal disease that affects the entire β-cell population**



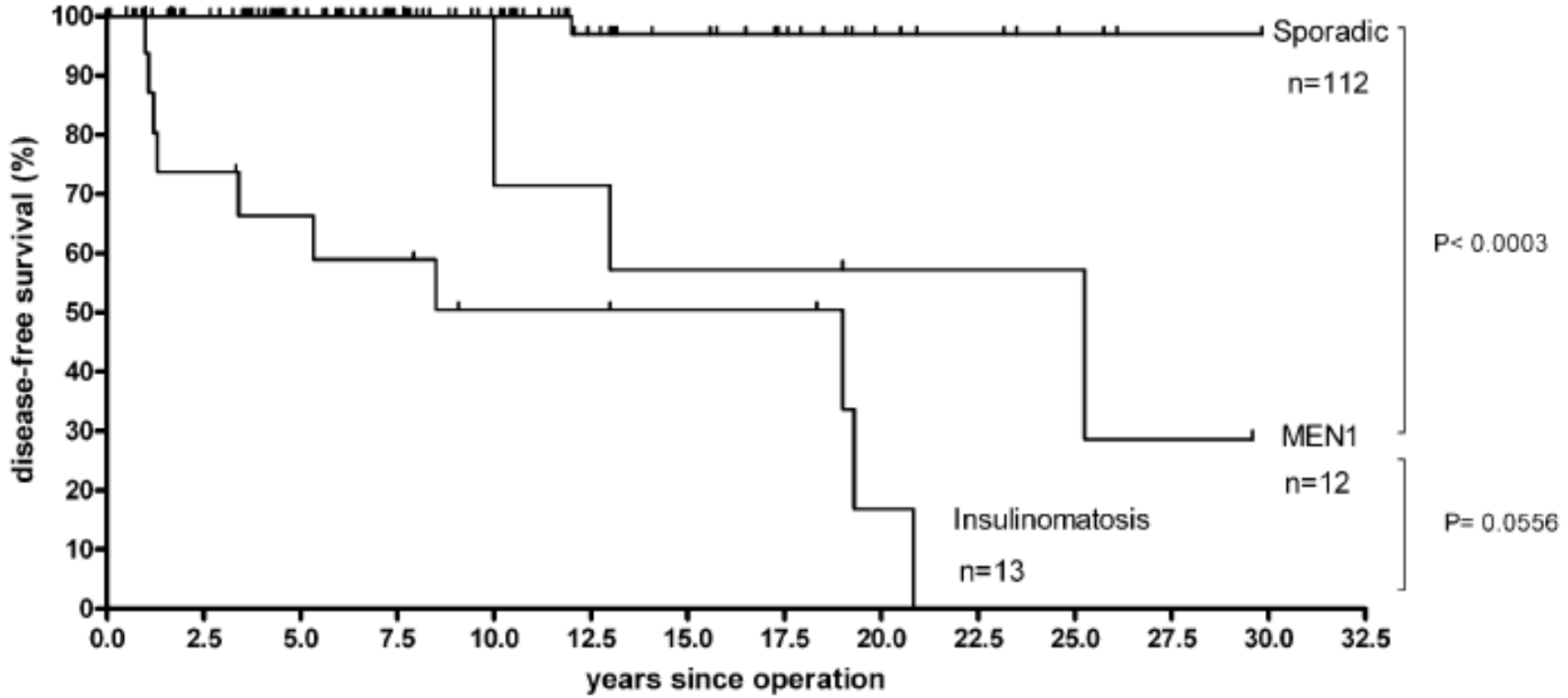
# Insulinomatose

(disease that affects the entire β-cell population)

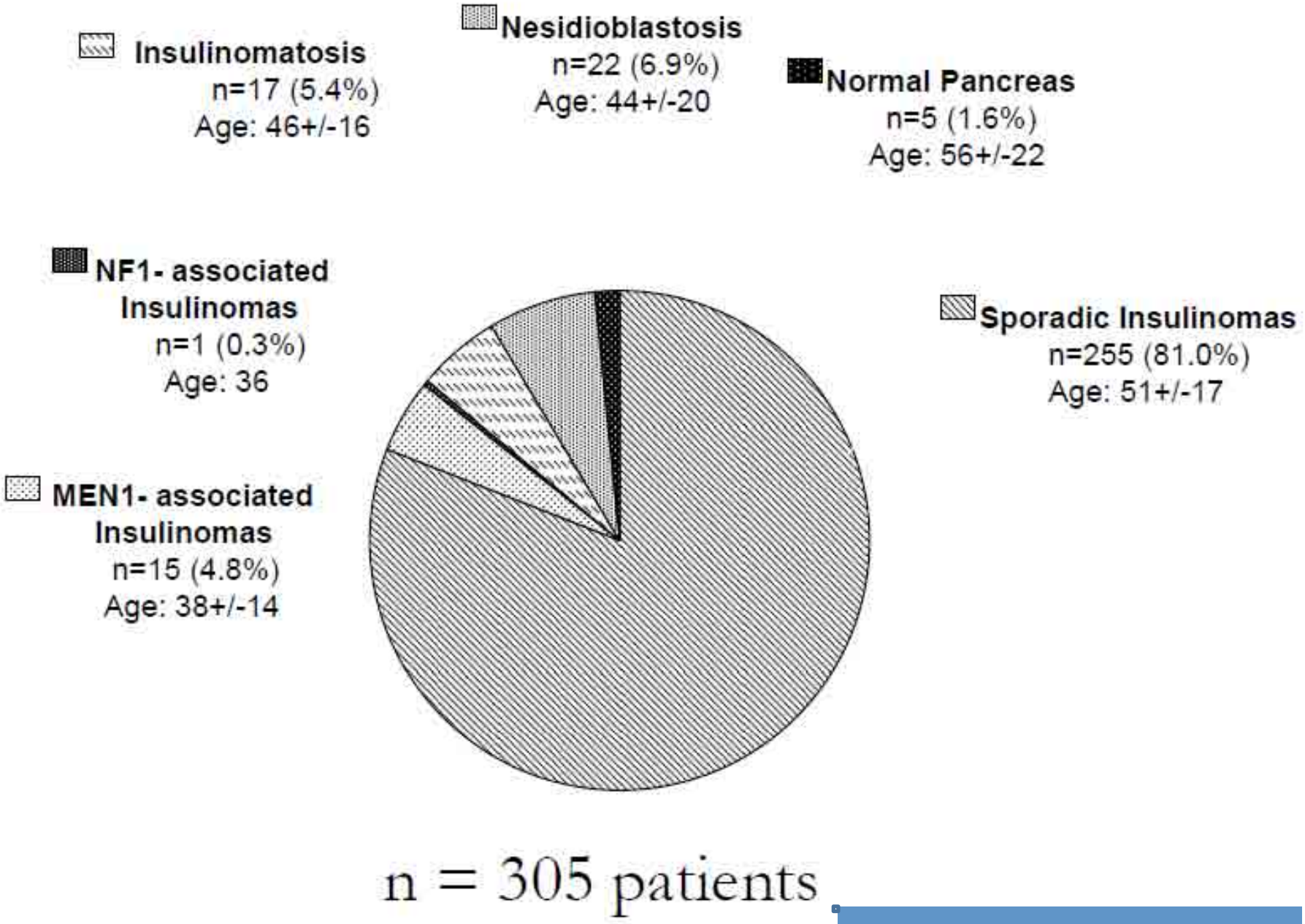
- Multifocal multicentric beta-cell disease
- Hyperplasia-neoplasia sequence (precursor lesions)
- IMEECs: insulin-expressing monohormonal endocrine cell clusters < 1 mm in size
- Insulin microadenomas (< 0.5 cm)
- Metachronous development of insulin
- macrotumors (> 0.5 cm)
- No hereditary background
- Female/Male ratio 10/4 and younger patients
- Recurrent hypoglycemia

Anlauf M, Bauersfeld J, et al. AJSP 2009

# Kaplan-Maier analysis of disease recurrences




*Am J Surg Pathol* • Volume 33, Number 3, March 2009

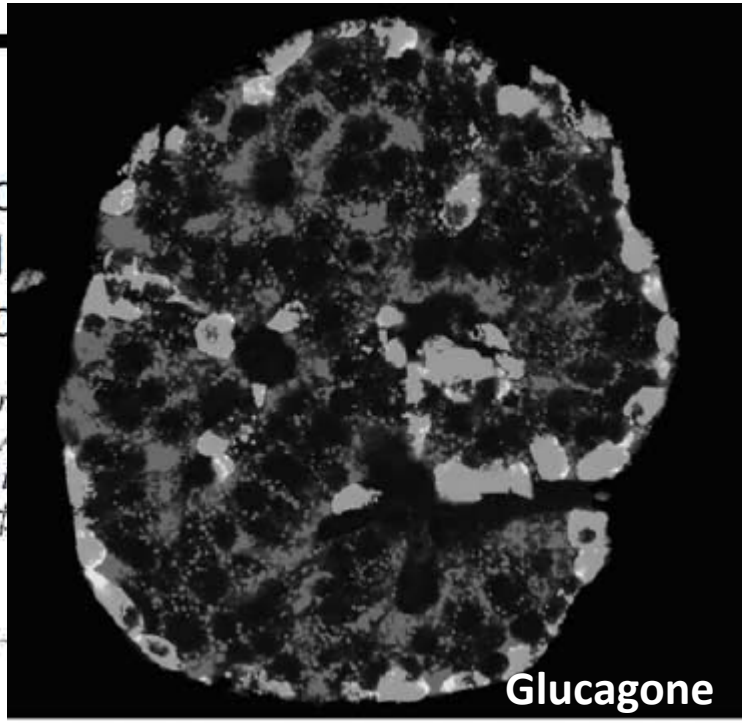



Courtesy of Gunter Kloppel

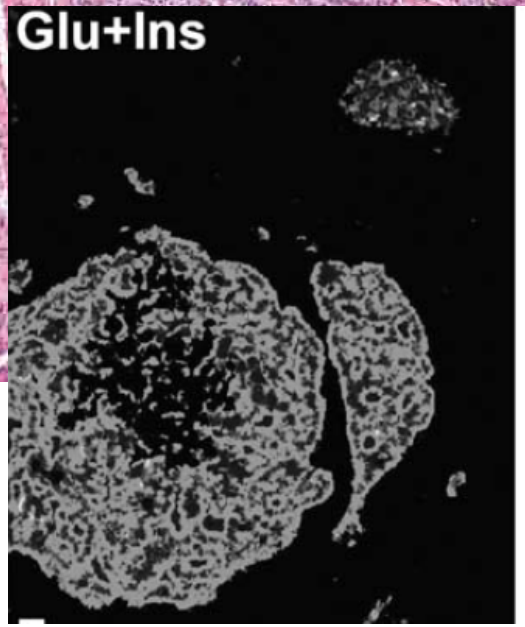
# Microadenomatosis of the Endoc
# Patients With and Without the M
# Neoplasia Type 1 Sync

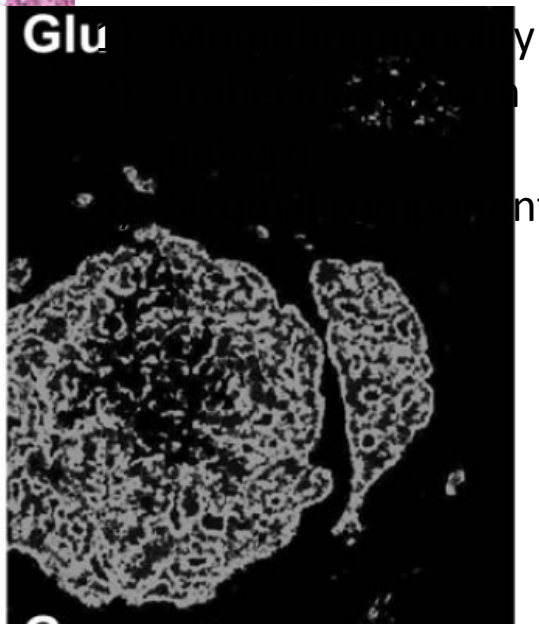
*Martin Anlauf, MD,* Regina Schlenger, MD,*† Aurel Perr*
*Christian A. Koch, MD,§ Henning Dralle, MD,⊥ A*
*Wolfram T. Knoefel, MD,¶ Eberhard Weihe, MD,# Phi*
*and Anne Couvelard, MD,†† Paul Komminoth, MD,‡‡*
*and Günter Klöppel, MD**

(*Am J Surg Pathol* 2006;30:560-




≤ 5 mm

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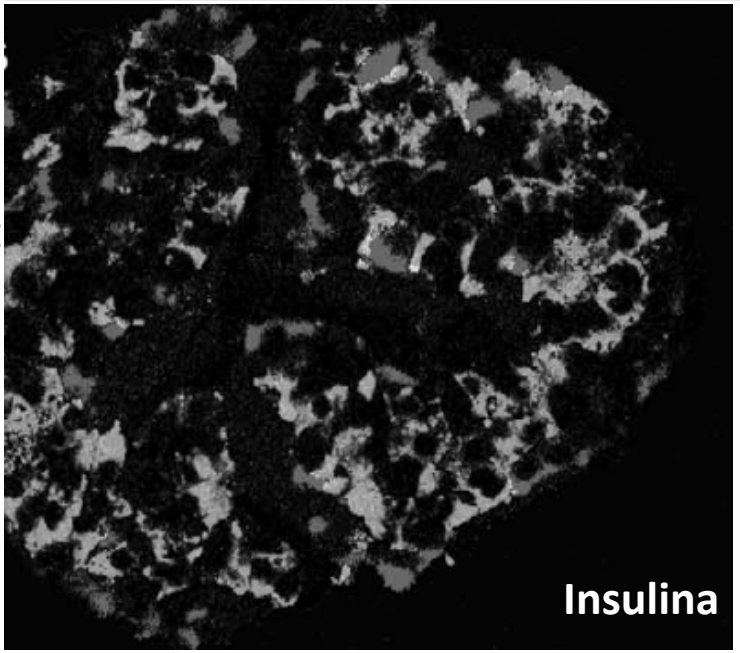


Endocr Pathol. 2014 Apr 10. [Epub ahead of print]

**Hyperplasia to Neoplasia Sequence of Duodenal and Pancreatic Neuroendocrine Diseases and Pseudohyperplasia of the PP-cells in the Pancreas.**

Klöppel G[1], Anlauf M, Perren A, Sipos B.

**Author information**

[1]Department of Pathology, Technical University, Ismaningerstr. 22, 81675, München, Germany, guenter.kloeppel@alumni.uni-kiel.de.

**Abstract**

**Hyperplastic changes of the neuroendocrine cell system may have the potential to evolve into neoplastic diseases.** This is particularly the case in the setting of genetically determined and hereditary neuroendocrine tumor syndromes such as MEN1. The review discusses the MEN1-associated hyperplasia-neoplasia sequence in the development of gastrinomas in the duodenum and glucagon-producing tumors in the pancreas. **It also presents other newly described diseases (e.g., glucagon cell adenomatosis and insulinomatosis) in which the tumors are (or most likely) also preceded by islet cell hyperplasia.** Finally, the pseudohyperplasia of PP-rich islets in the pancreatic head is defined as a physiologic condition clearly differing from other hyperplastic-neoplastic neuroendocrine diseases.

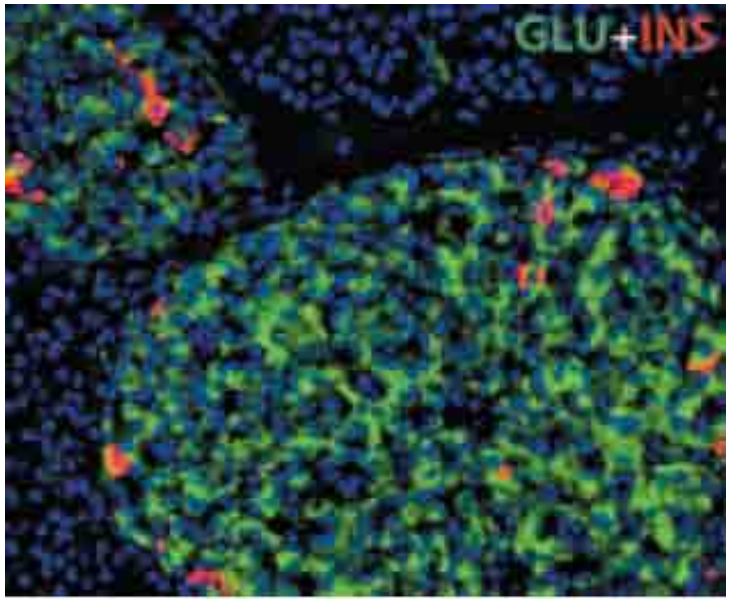
ORIGINAL ARTICLE

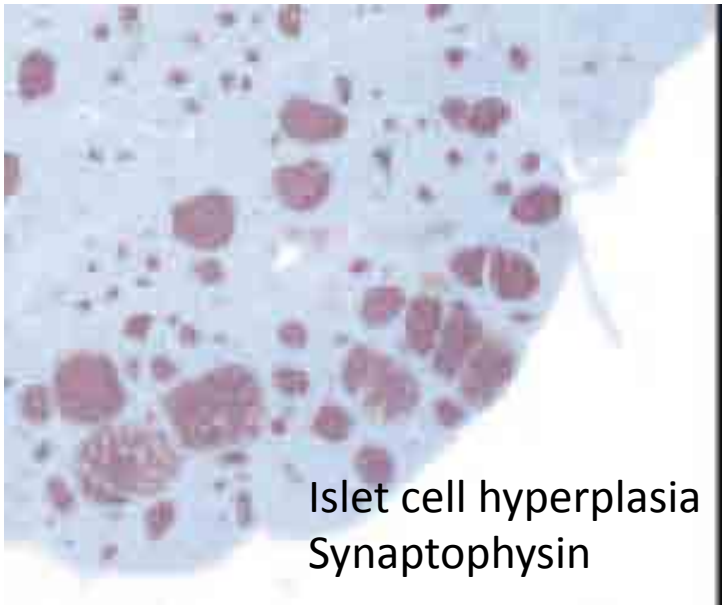
Endocrine Care—Brief Report

# Glucagon Cell Adenomatosis: A Newly Recognized Disease of the Endocrine Pancreas

Tobias Henopp,* Martin Anlauf,* Anja Schmitt, Regina Schlenger, Attila Zalatnai, Anne Couvelard, Philippe Ruszniewski, Klaus-Peter Schaps, Yvonne M. H. Jonkers, Ernst-Jan M. Speel, Natalia S. Pellegata, Philipp U. Heitz, Paul Komminoth, Aurel Perren,† and Günter Klöppel†

J Clin Endocrinol Metab, January 2009, 94(1):213–217



Islet cell hyperplasia
Synaptophysin

# Nesidioblastosis in adults

ORIGINAL ARTICLE

## Persistent Hyperinsulinemic Hypoglycemia in 15 Adults With Diffuse Nesidioblastosis

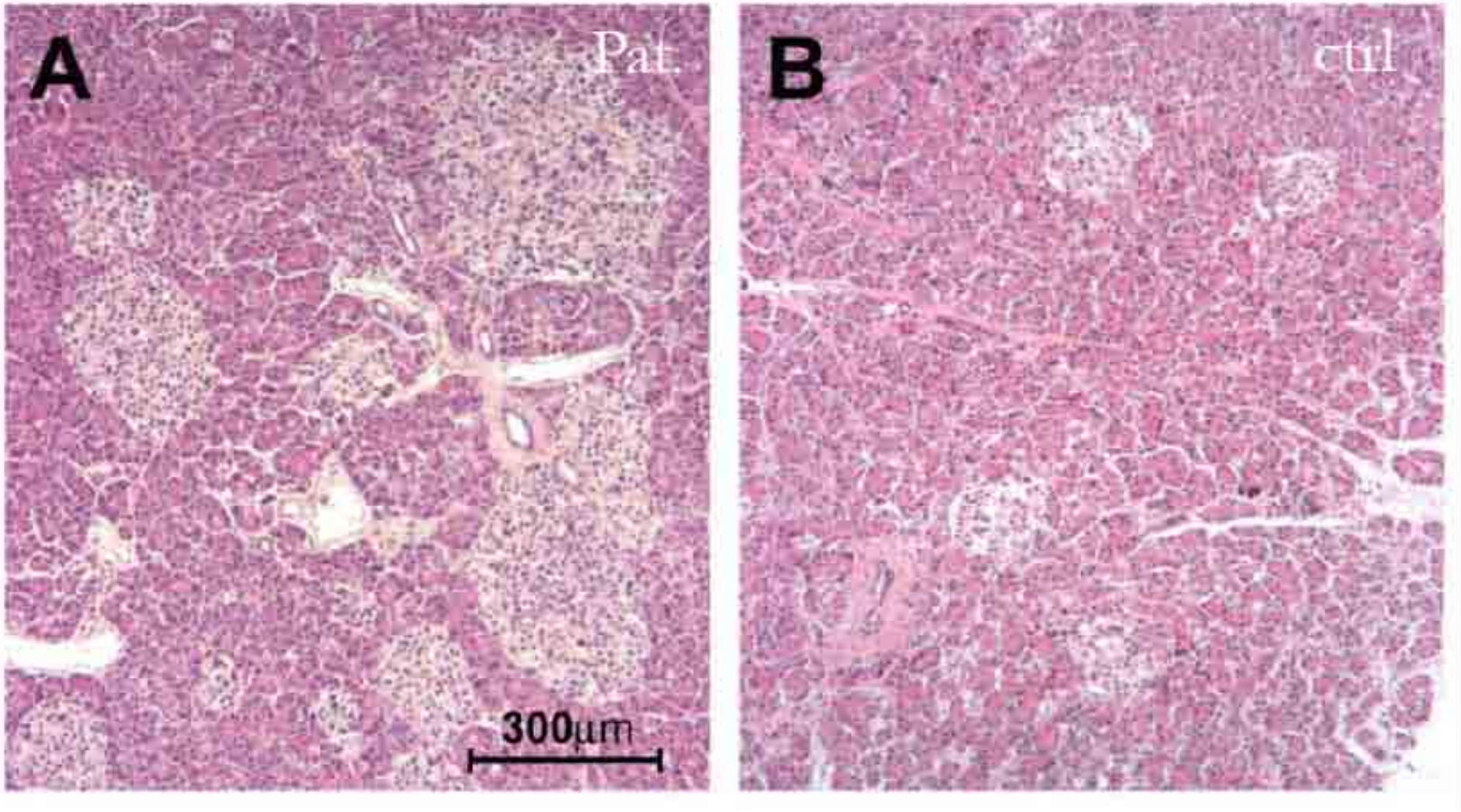
*Diagnostic Criteria, Incidence, and Characterization of β-Cell Changes*

*Martin Anlauf, MD,* Daniel Wieben,* Aurel Perren, MD,† Bence Sipos, MD,* Paul Komminoth, MD,† Andreas Raffel, MD,‡ Marie L. Kruse, MD,§ Christian Fottner, MD,‖ Wolfram T. Knoefel, MD,‡ Heiner Mönig, MD,§ Philipp U. Heitz, MD,† and Günter Klöppel, MD**

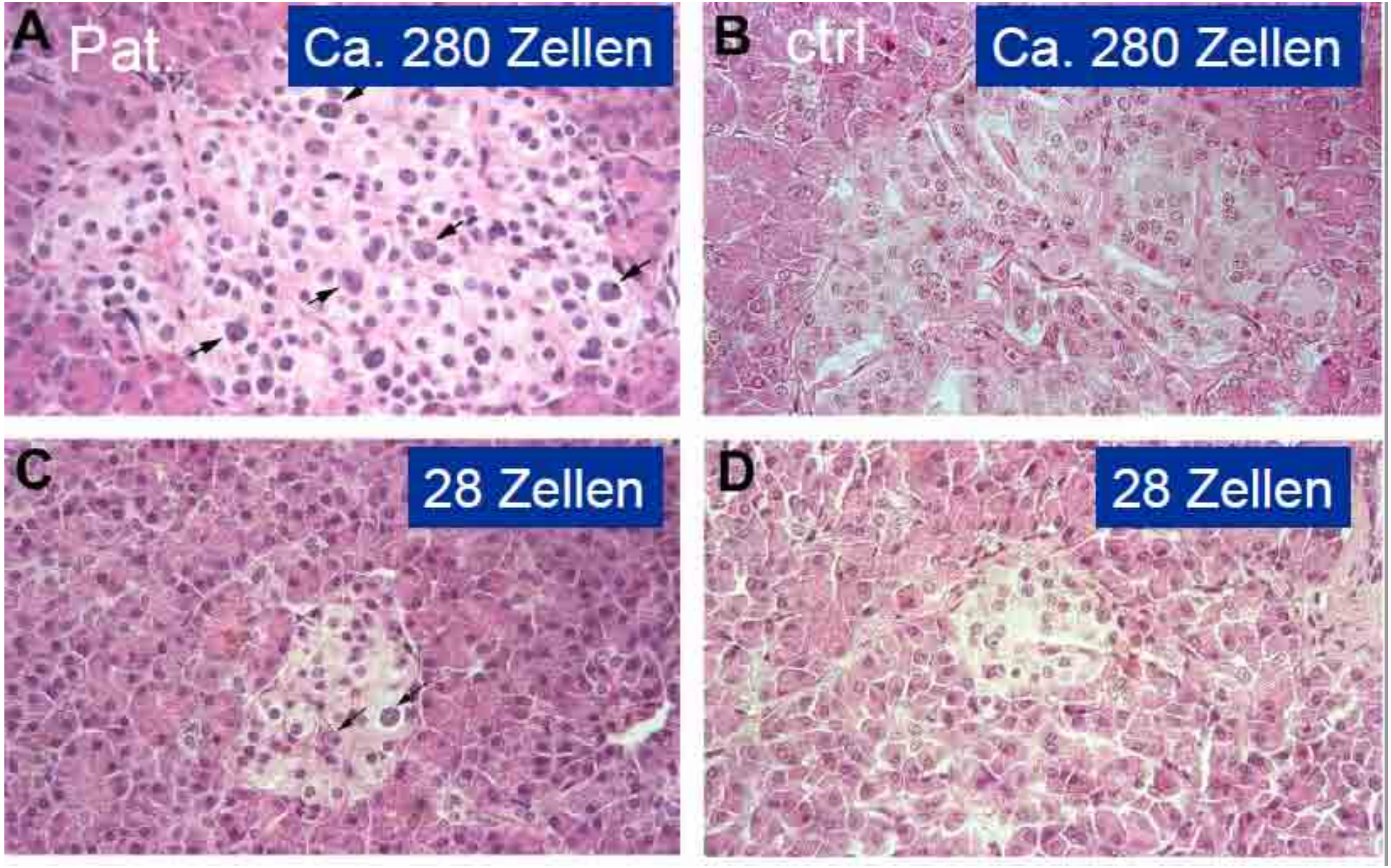
(*Am J Surg Pathol* 2005;29:524–533)

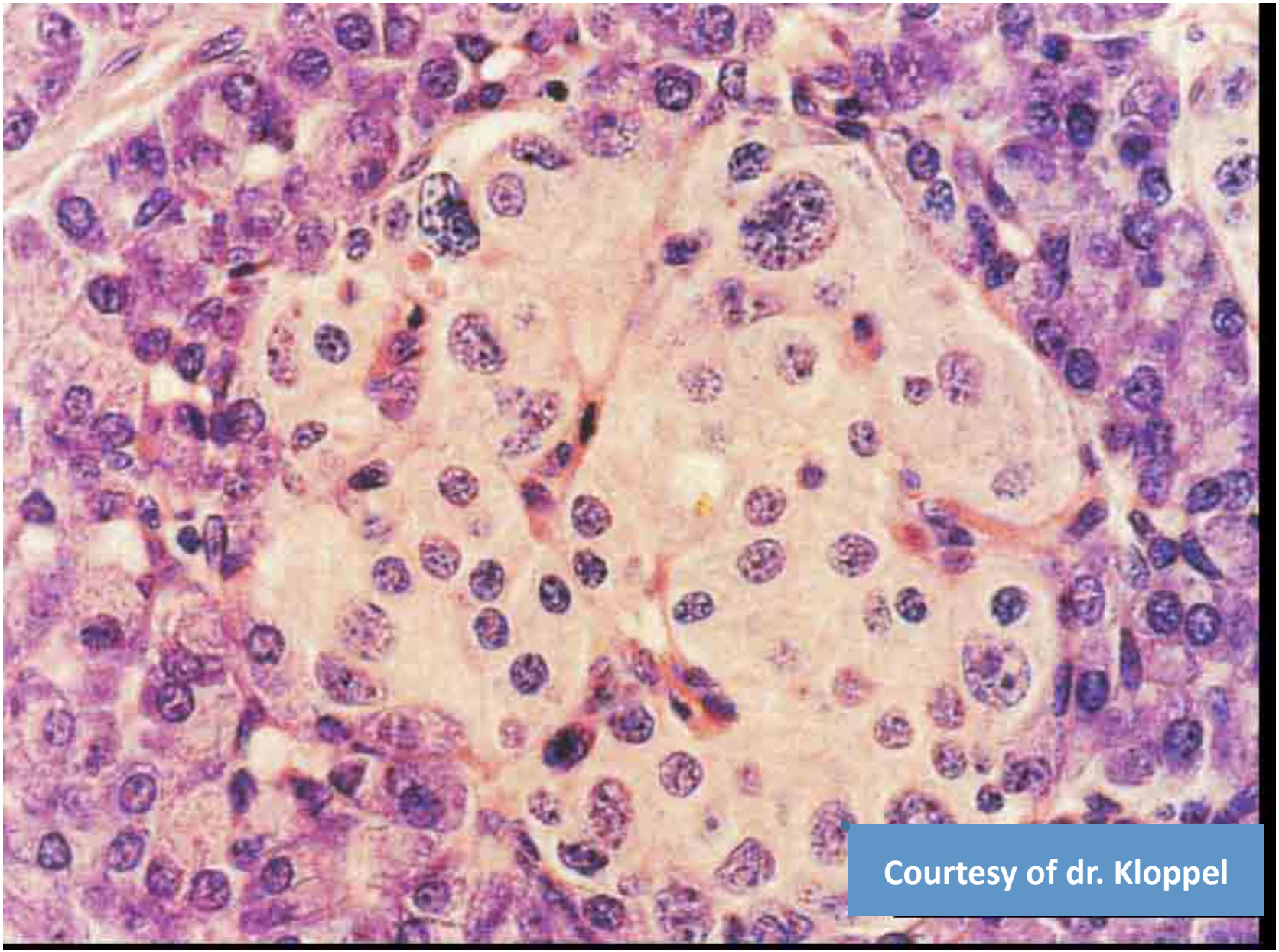
Anlauf M, Wieben D, et al. **AJSP 2005**

# More islets as well  as enlarged islets (above 300 µm)



- Lobular arrangement of islets cells
- ß-cells with enlarged nuclei and clear cytoplasm

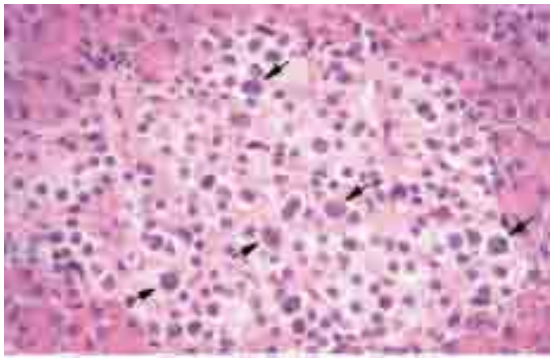


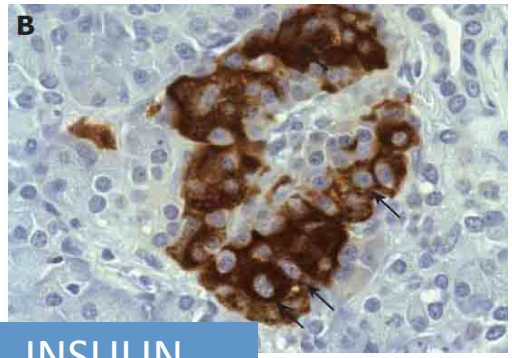

Courtesy of dr. Kloppel

# NESIDIOBLASTOSIS

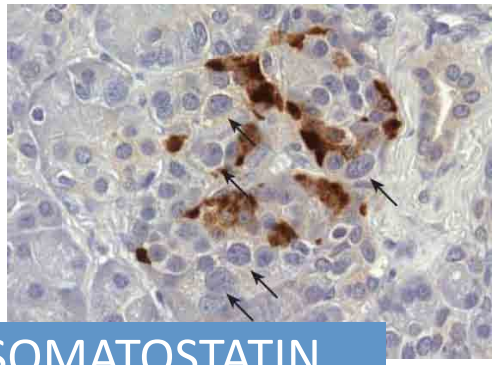
**ß-cells hypertrophy, hyperplasia and hyperphunction**

| Major criteria |
| --- |
| • Macroscopic, microscopic, and immunohistochemical exclusion of an insulinoma<br>• Multiple β-cells with enlarged and hyperchromatic nucleus and abundant clear cytoplasm in the majority of the islets<br>• Islets with normal spatial distribution and regular hormone expresion patterns of the various cell types<br>• No proliferative activity of the Ki-67 antigen (Mib-1) of endocrine cells |






INSULIN



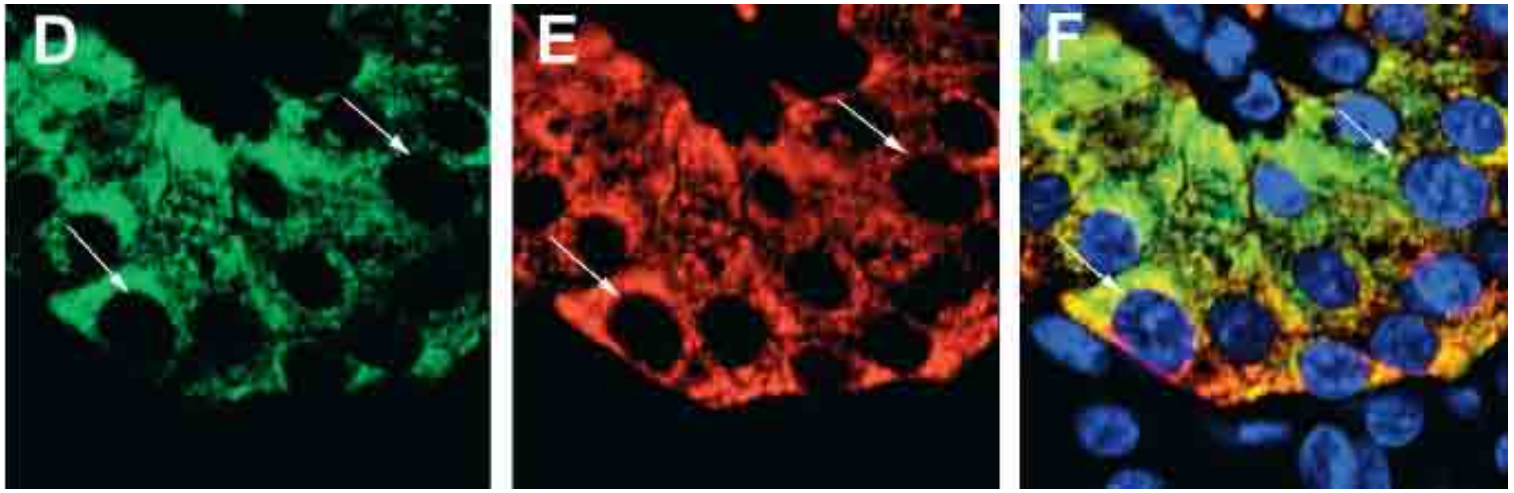
SOMATOSTATIN

# Original communication

## Diffuse nesidioblastosis as a cause of hyperinsulinemic hypoglycemia in adults: A diagnostic and therapeutic challenge

Andreas Raffel, MD,[a] Markus Krausch M,[a] Martin Anlauf, MD,[b] Daniel Wieben,[b] Stefan Braunstein, MD,[c] Günter Klöppel, MD,[b] Hans-Dietrich Röher, MD,[d] *and* Wolfram Trudo Knoefel, MD,[a] *Düsseldorf, Germany*

*(Surgery 2007;141:179-84.)*



JOP. Journal of the Pancreas

*JOP. J Pancreas (Online) 2013 May 10; 14(3):286-288.*

# Adult Onset Nesidioblastosis Treated by Subtotal Pancreatectomy

**Rahul Amreesh Gupta[1], Roma Prahladbhai Patel[2], Sanjay Nagral[1]**

Departments of [1]Surgical Gastroenterology and [2]Histopathology, Jaslok Hospital and Research Centre. Mumbai, Maharashtra, India

**The extent of pancreatic resection is controversial**. Some studies have shown that selective arterial calcium stimulation test may be useful to guide the extent of resection [14] but a study by Witteles *et al*. has shown that resection of 60-89% of pancreas (i.e., **distal or subtotal pancreatectomy**) is possibly the most appropriate surgery for nesidioblastosis because the risk of diabetes mellitus is below 10% with 70% success rate in achieving normoglycemia [2].

JOURNAL OF MEDICAL CASE REPORTS

CASE REPORT Open Access

# Diffuse nesidioblastosis with hypoglycemia mimicking an insulinoma: a case report

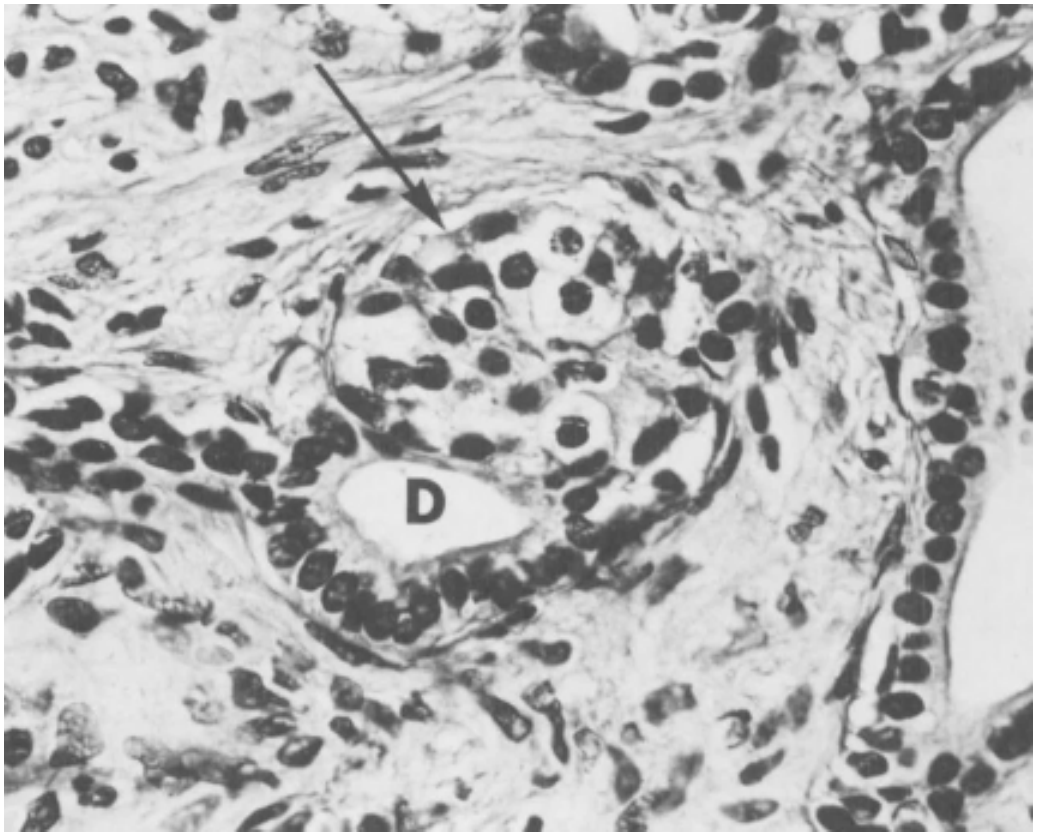
Chiara Ferrario[1*], Delphine Stoll[1], Ariane Boubaker[2], Maurice Matter[3], Pu Yan[4] and Jardena J Puder[1]

[13]. Conservative therapy is sometimes suggested. Diazoxide, octreotide and verapamil could be effective and safe alternative conservative therapies when surgery has failed or is considered to be too risky [8,10]. Patients' information should include the necessity for multiple diagnostic procedures and the postoperative risks for pancreatic exocrine insufficiency and diabetes. In the

# Pancreatic Nesidioblastosis in Adults

Tse-Ling Fong, MD
Nancy E. Warner, MD
Dinesh Kumar, MD

*Diabetes Care* 12:108–14, 1989



# Nesidioblastosis Arising from Heterotopic Pancreas and Presenting with Hypertension A Clinical, Immunohistochemical and Ultrastructural Study

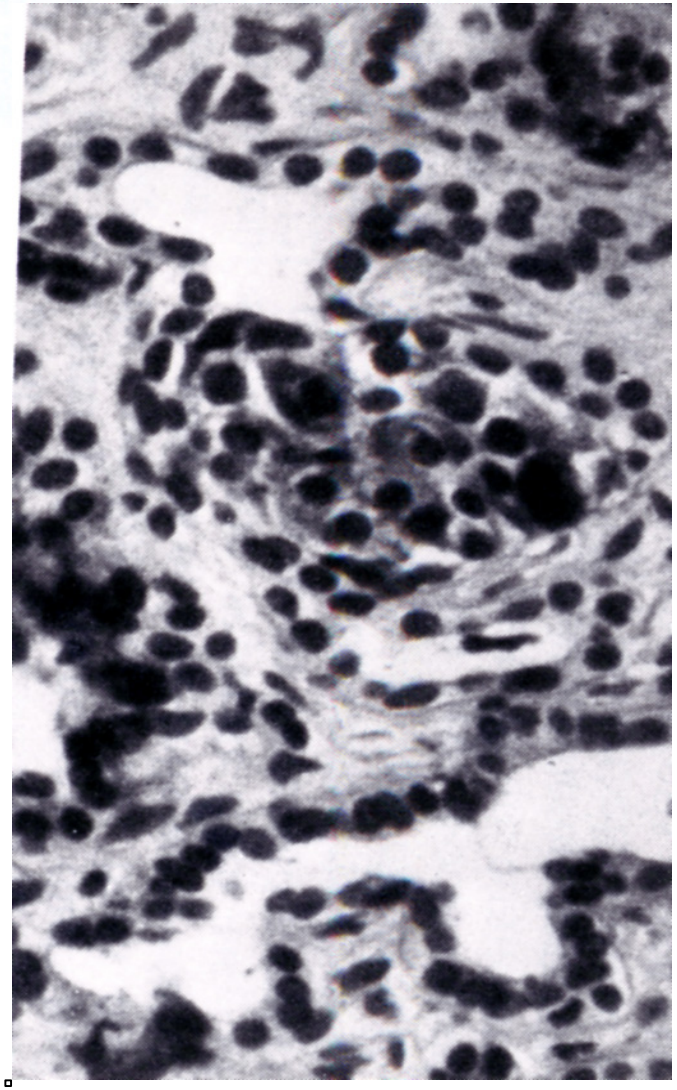
A. RISALITI[1], S. PIZZOLITTO[2]

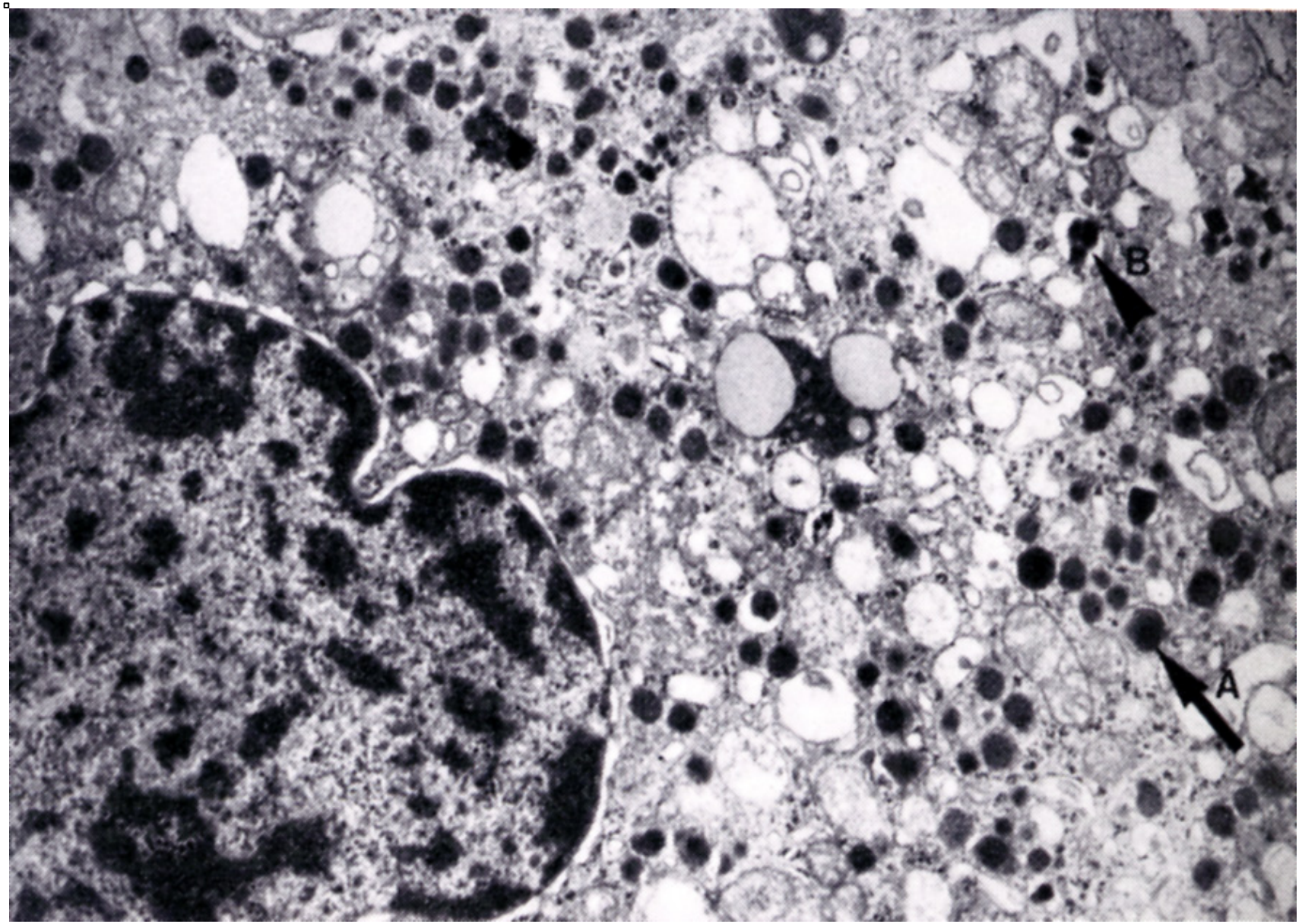
RISALITI A., PIZZOLITTO S. — Nesidioblastosis arising from heterotopic pancreas and presenting with hypertension. A clinical immunohistochemical and ultrastructural study.

**Ann Chir,** 1989, **43,** n° 6, 459-464.

SUMMARY : A rare case of nesidioblastosis in an adult arising from heterotopic pancreas and presenting with hypertension is reported. To our knowledge it is the first case to be described in literature. The pathogenic mechanisms to explain hypertension are not clear. The stimulating action of glucagon on the adrenal gland or on peripheral beta receptors could be considered as hypothetical factors.

KEY-WORDS : Nesidioblastosis. — Heterotopic pancreas. — Hypertension. — Adult.




B
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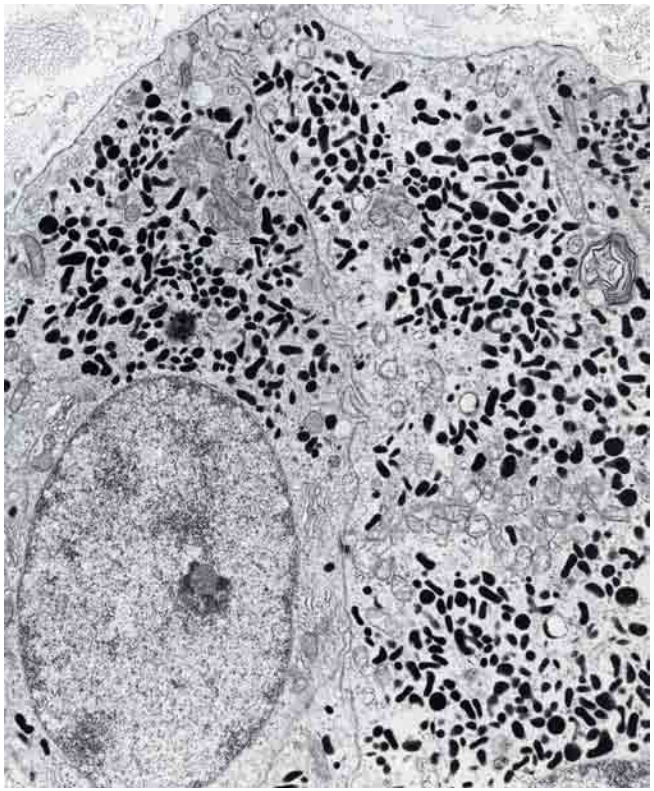
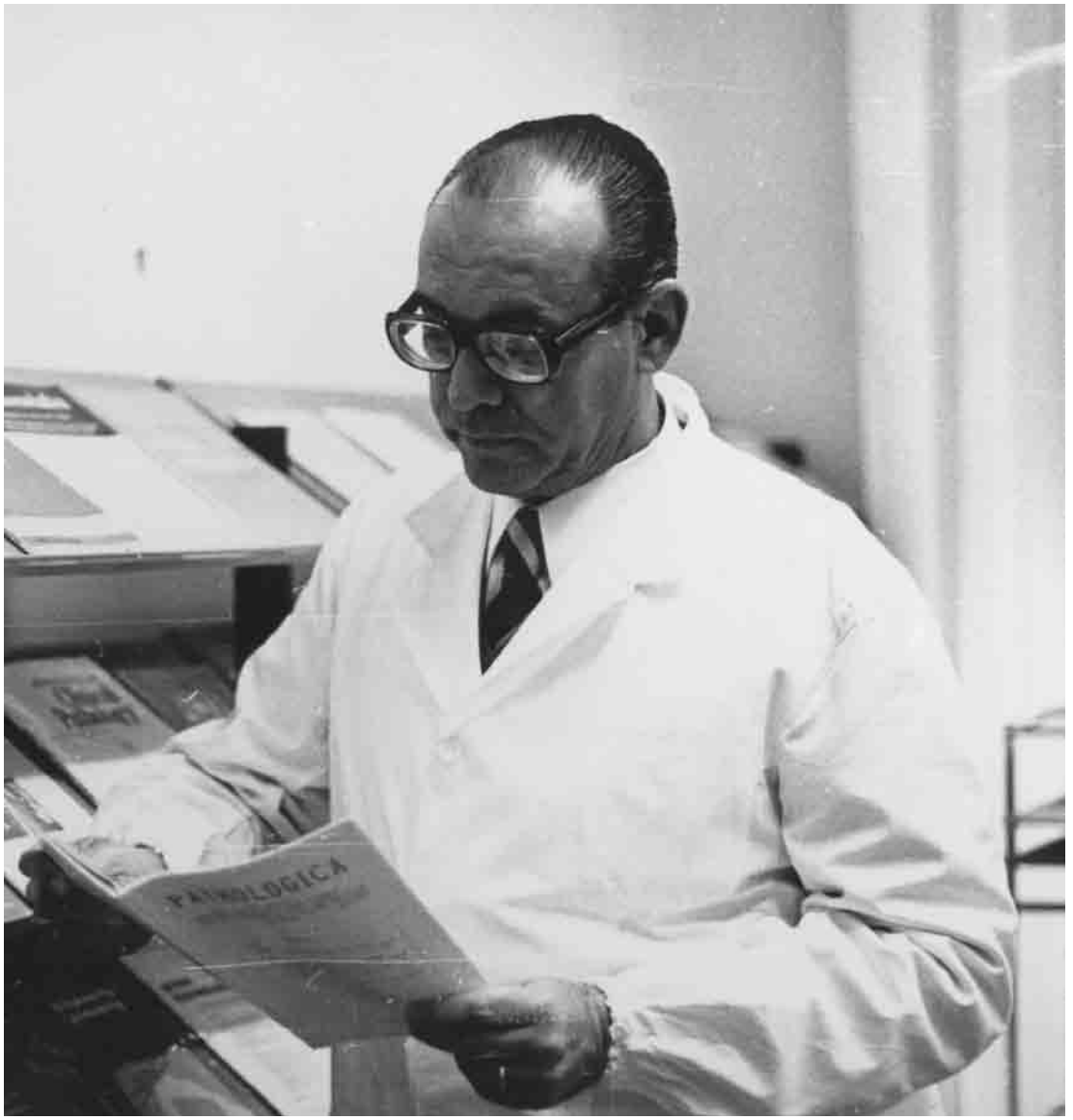
# APUDOMAS TODAY-'70s






***TRIBUTE***

***TO BENIAMINO ANTOCI***

# IN CONCLUSIONE:
## MA LA DIAGNOSI NELLO SPECIFICO CASO?

1. La diagnosi più “attraente” potrebbe essere quella di insulinomatosi non MEN-1
2. Tuttavia dovrebbe essere ricercata la mono-ormonalità per insulina con anticorpi specifici nelle IMEECs (Insulin-expressing Monohormonal Endocrine Cell Clusters)
3. Tenuto conto dell’ancora breve follow up della PHH il razionale della terapia conservativa adottato sembra prudente e giustificato.

# Multidisciplinary care

**C'era un tempo in cui i dottori curavano tutti con i salassi.**
**Poi e' venuto un periodo intermedio, con numerose strade, ma obbligate.**
**Adesso le strade sono infinite: solo i Medici molto bravi sanno scegliere quella buona, in collaborazione fra di loro.**

*(Piero Ottone, 2000)*