

Rare tumors of the (distal) pancreas-surgical view

Case-report

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WHO 5th ed. (2019)

Benign epithelial tumors and precursors

Serous cystadenoma, NOS

Serous cystadenocarcinoma

[Glandular intraepithelial neoplasia, low grade](#)[Glandular intraepithelial neoplasia, high grade](#)[Intraductal papillary mucinous neoplasm with low grade intraepithelial neoplasia](#)[Intraductal papillary mucinous neoplasm with high grade intraepithelial neoplasia](#)[Intraductal papillary mucinous neoplasm with associated invasive carcinoma](#)[Intraductal oncocytic papillary neoplasm](#)[Intraductal oncocytic papillary neoplasm with associated invasive carcinoma](#)[Intraductal tubulopapillary neoplasm](#)[Intraductal tubulopapillary neoplasm with associated invasive carcinoma](#)[Mucinous cystic neoplasm with low grade intraepithelial neoplasia](#)[Mucinous cystic neoplasm with high grade intraepithelial neoplasia](#)[Mucinous cystic neoplasm with associated invasive carcinoma](#)

Malignant epithelial tumors

[Duct adenocarcinoma](#)[Acinar cell carcinoma](#)[Pancreatoblastoma](#)[Solid pseudopapillary neoplasm of the pancreas](#)[Pancreatic neuroendocrine neoplasms](#)

Pancreatic neuroendocrine microadenoma

[Neuroendocrine tumor, NOS](#)

Neuroendocrine tumor, grade 1

Neuroendocrine tumor, grade 2

Neuroendocrine tumor, grade 3

[Pancreatic neuroendocrine tumor, nonfunctioning](#)[Functioning pancreatic neuroendocrine tumors](#)[Neuroendocrine carcinoma, NOS](#)

Mixed neuroendocrine - nonneuroendocrine neoplasm (MiNEN)

NORDIC NEC study
platinum-based chemotherapy among high-grade NETs
tumors with a Ki-67 ↓ **55%** better prognosis
tumors with Ki-67 ↑ 55%.

Sorbye H, Welin S, Langer SW, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. *Ann Oncol.* 2013;24:152–160

Well-Differentiated NEN	Ki-67 Index (%)	Mitotic Index (HPF ² /10 HPF)
NET G1 (low-grade)	<3	<2/10
NET G2 (intermediate-grade)	3–20	2–20/10
NET G3 (high-grade)	>20	>20/10
Poorly differentiated NEN		
NEC Small-cell type, Large-cell type	>20	>20/10
Mixed neuroendocrine–nonneuroendocrine neoplasm (MiNEN)		

Neuroendocrine tumors

Express neuroendocrine markers (synaptophysin or chromogranin A)

M = F

Peak incidence: 30 - 60 years

Comprise ~2 - 5% of all pancreatic neoplasms (PanNET)

Nonfunctional tumors represent 60 - 90% of all PanNETs

Asymptomatic pancreatic neuroendocrine tumors are increasingly common

Somatostatin receptors (SSTRs) NETs (G1/G2);
G3 NETs (87%-92%),
mostly negative in NECs.

Raj N, Valentino E, Capanu M, et al. Treatment response and outcomes of grade 3 pancreatic neuroendocrine neoplasms based on morphology: well differentiated versus poorly differentiated. *Pancreas*. 2017;46:296-301

IHC of SSTRs differential diagnosis of G3 NET and NEC.
Prognosis: NETs patients with strong positivity of SSTR2 have longer OS.

Nielsen K, Binderup T, Langer SW, et al. P53, Somatostatin receptor 2a and Chromogranin A immunostaining as prognostic markers in high grade gastroenteropancreatic neuroendocrine neoplasms. *BMC Cancer*. 2020;20:27

Ki-67 index of G3 NETs 21% and 55%,

Ki-67 index of NECs ↑ 55%

Shi H, Chen L, Zhang Q, et al. Concordance between the Ki-67 index cutoff value of 55% and differentiation in neuroendocrine tumor and neuroendocrine carcinoma in grade 3 pancreatic neuroendocrine neoplasms. *Pancreas*. 2020;49:1378-1382

The 2021 NCCN guidelines classified G3 NETs into 2 categories:

G3 NETs with **favorable biological behavior**

Ki-67 <55%, slow growth rate, and positive SSTR expression

G3 NETs with **unfavorable biological behavior**

Ki-67 ≥55%, fast-growing, and negative SSTR expression

Shah MH, Goldner WS, Benson AB, et al. Neuroendocrine and adrenal tumors, version 2.2021, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2021;19:839-868.

TREATMENT OPTIONS

Anti-hormone treatment

Anti-tumor treatment

- Somatostatine analogues therapy (octreotide, lanreotide)
- Targeted therapy (everolimus, sunitinib, surufatinib)
- Immunotherapy
- Chemotherapy (CAPTEM, EP)
- PRRT-peptide receptor radionuclide therapy
- Radiofrequency ablation and microwave ablation
- Hepatic artery embolisation (liver metastasis)
- Surgery

SURGERY

radical surgery, debulking surgery and surgery for treatment of liver metastatic lesions

Radical surgery for locoregional resectable G3 NETs without distant metastasis

Kulke MH, Anthony LB, Bushnell DL, et al. NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. *Pancreas*. 2010;39:735-752.

O'Toole D, Kianmanesh R, Caplin M. ENETS 2016 Consensus Guidelines for the management of patients with digestive neuroendocrine tumors: an update. *Neuroendocrinology*. 2016;103:117-118.

Garcia-Carbonero R, Sorbye H, Baudin E, et al. ENETS Consensus Guidelines for high-grade gastroenteropancreatic neuroendocrine tumors and neuroendocrine carcinomas. *Neuroendocrinology*. 2016;103:186-194.

Surgery is often indicated in G1-2 NETs but contraindicated for NECs

Worth PJ, Leal J, Ding Q, et al. Pancreatic grade 3 neuroendocrine tumors behave similarly to neuroendocrine carcinomas following resection: a multi-center, international appraisal of the WHO 2010 and WHO 2017 staging schema for pancreatic neuroendocrine lesions. *HPB (Oxford)*. 2020;22:1359–1367.

The role of surgery for localised Pan-NEC G3 is still controversial

Yoshida T, Hijioka S, Hosoda W, et al. Surgery for pancreatic neuroendocrine tumor G3 and carcinoma G3 should be considered separately. *Ann Surg Oncol*. 2019;26:1385e1393.

Summary

CAPTEM, SSA and local therapies

M.Boutin, A.Mathews, J.Badesha, A.Paul, M.Safro, S.Gill, H.Stuart, D.Schaeffer, D.Farnell, J.M.Loree. Well-Differentiated Grade 3 Neuroendocrine Tumors Characteristics, Treatments, and Outcomes From a Population-Based Study. *Pancreas* 51(7):p 756-762, August 2022.

G3 NETs with unfavorable biological behavior, platinum-based EP/EC/IP and posterior-line options FOLFOX/CAPEOX/Captem chemotherapy regimens can be considered

J.Chien, W.Wu, Ch Bai, Y.Chi, L.Jiang, Y. Ji, et all. Consensus on the clinical diagnosis and treatment of grade 3 pancreatic neuroendocrine tumors. *J Pancreatology*, Vol. 7, issue 02, 2024. 97-105

the diagnostic and treatment principles for G3 grade pNETs with favorable biological behavior tend to lean towards G2 grade NETs, while those with unfavorable biological behavior lean more toward NEC

J.Chien, W.Wu, Ch Bai, Y.Chi, L.Jiang, Y. Ji, et all. Consensus on the clinical diagnosis and treatment of grade 3 pancreatic neuroendocrine tumors. *J Pancreatology*, Vol. 7, issue 02, 2024. 97-105

Patient: female, 68 years-old

Comorbidities: hypothyroidism, arterial hypertension, hyperglycemia

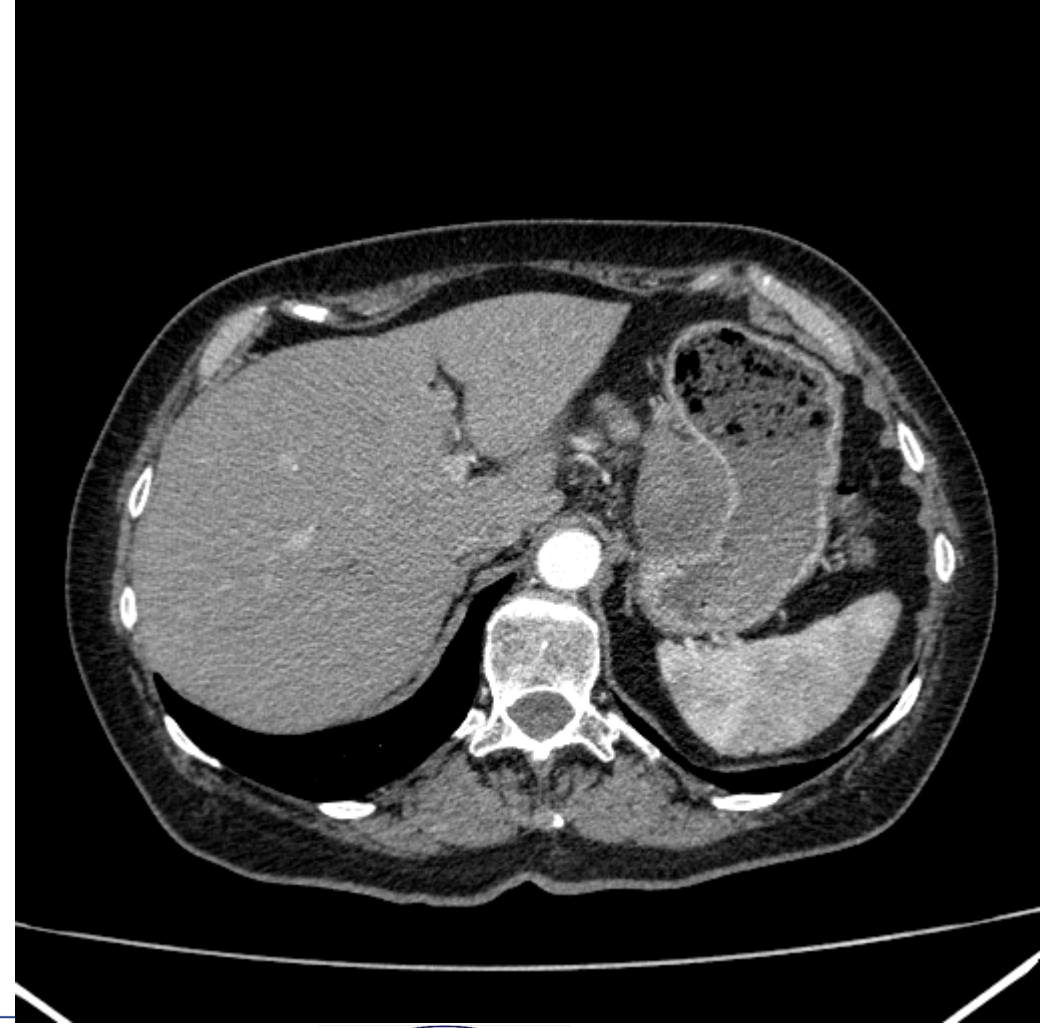
Family history: leukemia (mother)

Complaints: pain in left knee, mild instability

Neurologist (04.02.26.)

Abdominal US

CT scan (05.03.26)



Oncologist:

CEA: 1.61 (0.00-5.00 ng/ml)

CA 19-9: < 0.8 (0.00-37.0 U/ml)

CT scan: thorax, pelvis (20.03.26.)

Abdominal MRI+MRCP (13.03.26.)

Oncologist+Surgeon: biopsy vs. Radical resection (08.04.26)

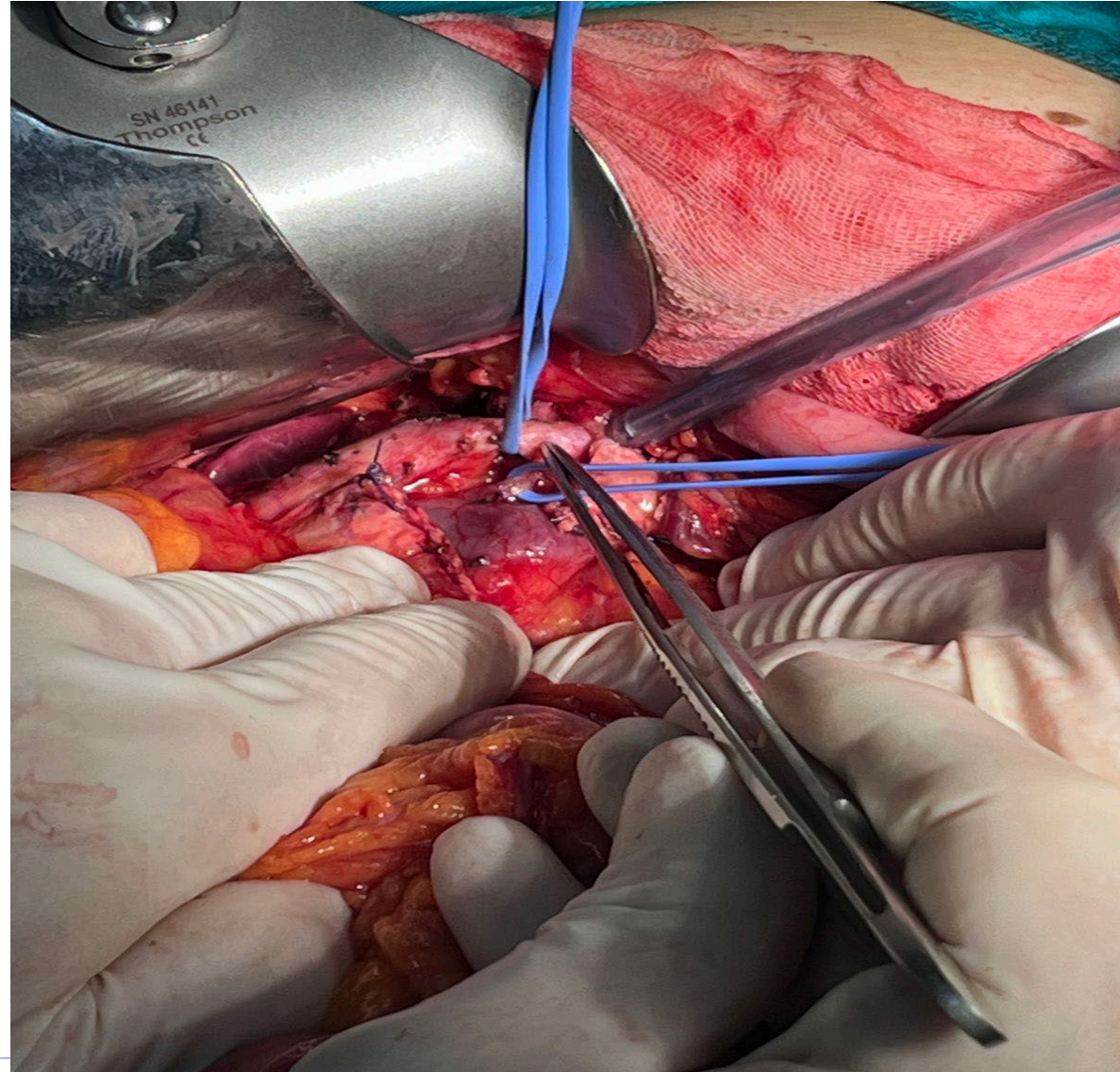
Preoperative vaccination (Haemophilus influenzae, meningococcus, pneumococcus)

Interreg



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Morphologically, differential diagnosis: **high grade neuroendocrine carcinoma, acinar cell carcinoma, but it could also be a solid pseudopapillary neoplasm with aggressive behavior...**

Prognostic parameters:

- surgical procedure: partial pancreatectomy with splenectomy
- location of the tumor: the tail of the pancreas
- histological type: **immunohistochemical analysis is necessary**
- tumor size: 5.5 x 4.5 x 4.5 cm-tumor extension: tumor limited to pancreatic tissue
- **lymphovascular invasion: present**
- neoadjuvant therapy: no
- pancreatic resection margin: without tumor tissue
- number of examined lymph nodes: 25
- number of lymph nodes affected by the tumor: 6
- pTNM: **pT3N2Mx**

Pathologist

Lymph nodes 8a (anterosuperior along CHA): 2 of 3 positive

Lymph nodes 8p (posterior along CHA): 1 negative

Lymph nodes 9 (celiac artery): 3 of 3 positive

IHH:

Intense cytoplasmic chromogranin A and synapthophysin positivity is multifocally evident

Ki-67 index 40%

Positive markers: AE1/AE3, CD10, beta-catenin (membrane), E-cadherin, cyclin D1

Negative markers: CK7, CK20, vimentin, AR, CD117, CD56, SOX11

27.04.26

PH: Carcinoma basocellulare invasivum cutis

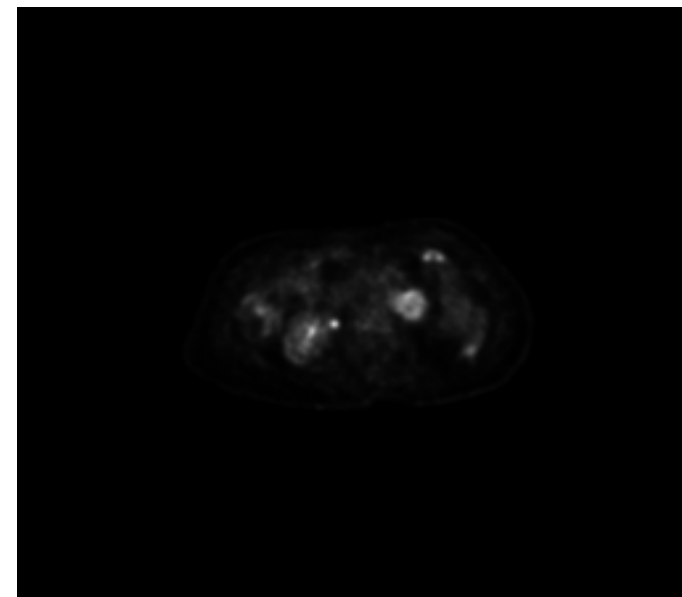
Somatuline Autogel[®] (LANREOTID) amp. a 120mg, 1x120mg s.c./28th day

Octreo-scan

PET/CT scan: **local recurrence**

III cycles EP protocol (etoposide-cisplatin)

I cycle: febrile neutropenia



THANK YOU FOR YOUR ATTENTION