

Nonfunctioning Pancreatic neuroendocrine tumors

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Epidemiology

- Age-adjusted incidence 0.52/100.000 (2004-2012)
 - Pancreatic adenocarcinoma: 7.34/100.000
- Median age at diagnosis: 60 years
- Slight majority of males, females slightly more often operated
- Increasing prevalence:
 - Increased awareness among clinicians
 - Well defined histological and immunohistochemical criteria
 - Increased use and availability of imaging

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Incidence in the Netherlands per 100.000



Time trend of pNET surgery 1990-2015

High volume institution: 587 consecutive cases



Pancreatic NETs

- Functioning
 - Insulinoma: 1-32 per 1.000.000
 - Gastrinoma/ Zollinger Ellison Syndrome: 1-22 per 1.000.000
 - Rare functioning pNETs: > 100 cases
 - VIPoma, Glucagonoma, Ssoma, GRHoma, ACTHoma, PTHrPoma
 - Very rare functioning pNETs (1-5 cases)
 - pNETs secreting: renin, erythropoietin, IGF-2, CCK, GLP-1
- Non-Functioning pNETs (NF-pNETs)
 - Tumors without clinical symptoms of hormonal hypersecretion
 - Most common pNETs



pNETs associated with hereditary syndromes

- **Multiple endocrine neoplasia type 1 (MEN1)**
 - 80-100%
 - Penetrance 80% by age of 80 years
 - Non-functioning pNETs > functioning pNETs
- **Von Hippel Lindau (VHL)**
 - 10-17%
 - 98% non-functioning pNETs
- **Neurofibromatosis 1 (NF-1)**
 - 0-10%
- **Tuberous sclerosis (TSC)**
 - Uncommon

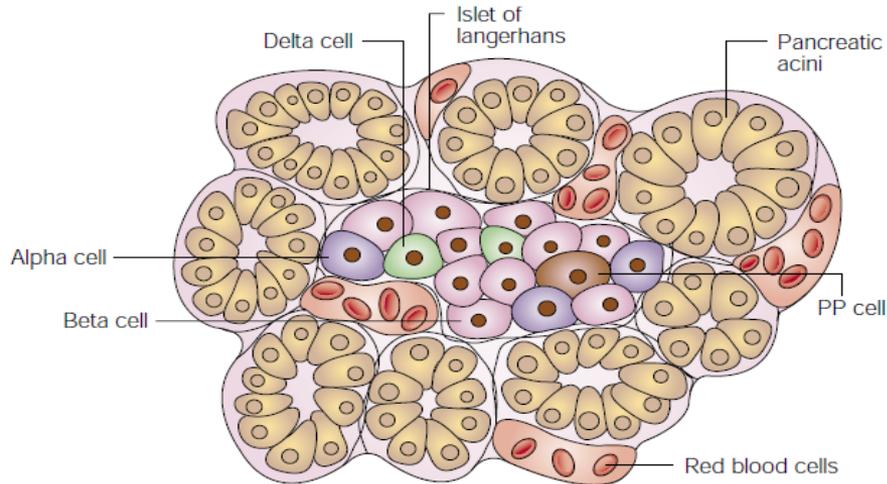
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Triponez, F. *et al.* Epidemiology Data on 108 MEN 1 Patients From the GTE With Isolated Nonfunctioning Tumors of the Pancreas. *Ann. Surg.* **243**, 265–272 (2006).

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The endocrine pancreas - differentiation



Non-functioning pNETs (NF-pNETs)

- Mainly asymptomatic
 - Therefore screening in patients with hereditary syndromes
- Clinically apparent:
 - Compression
 - Invasion of adjacent organs
 - Metastasis
- Symptoms:
 - Abdominal pain (35-78%)
 - Weight loss (20-35%)
 - Anorexia and nausea (45%)
- 32% metastases at diagnosis
- Stage I (5%), stage II (15%), stage III (22%) and stage IV (55%)





Work-up sporadic NF-pNETs



Screening for NF-pNETs in MEN1

Current guidelines and recent insights

Thakker 2012:

- Annual plasma biochemical evaluation
- Annual pancreatic visualization with MRI, CT or EUS.

Systematic review 2018:

- Biomarkers should no longer play a role
- EUS highest sensitivity
 - Combined strategy of EUS and MRI most useful
- Ga68-labelled PET/CT could be added to identify metastases



Preoperative localization and staging

- PET/CT + 68 Ga-labeled somatostatin analogues
 - Highest sensitivity: 86-100%
 - High specificity: 79-100%
- 68 Ga-labeled somatostatin analogues:
 - Change of management (surgical, medical, staging) in 20–55% of all patients
- FDG PET might be considered for risk stratification
 - Further evidence is demanded



Surgical indications NF-pNETs

- NF-pNETs ≥ 2 cm (< 2 cm low risk lesions)
- Presence of (lymph node) metastases
- Symptomatic NF-pNETs
- Yearly increase in size of > 0.5 cm



Surgical considerations

- Patients: relatively young with an acceptable prognosis
- Location of pNET:
 - Head: pancreaticoduodenectomy
 - Body/tail: distal pancreatectomy (\pm splenectomy)
- Typical vs atypical resections:
 - Typical: high risk of complications and pancreatic insufficiency
 - Atypical: high risk of pancreatic fistulas, decreased risk of insufficiency
 - Middle pancreatectomy: small tumors of pancreatic body
 - Enucleation: safe distance to main pancreatic duct
- Radicality of resection
- Lymph node resection
 - A routine dissection and harvesting of lymph nodes should be performed
 - Usually not performed in case of atypical resections
 - Atypical resections recommended for demarcated and small NF-pNET (low-risk pNETs)



Routine lymph node dissection?

- Depending on nodal-status, enucleation alone may not be oncologically appropriate.
- Lymph node metastases in 38% (mean 2.9 ± 2.5 +Inn) and 24% (1-11)

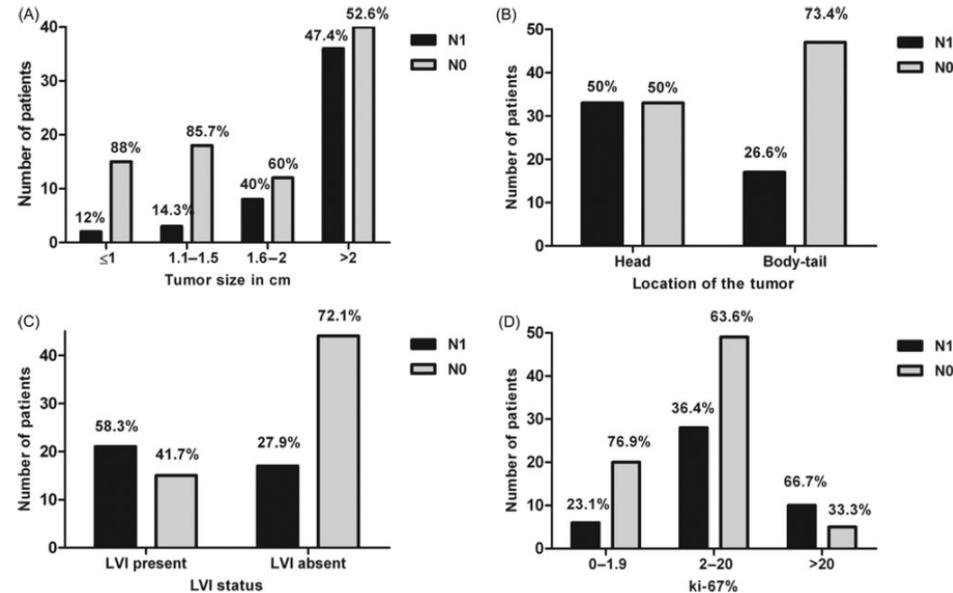


Preoperative predictors of lymph node metastases

Postlewait et al (2016)

- Male gender (OR 3.2 (1.2 – 8.5))
- Head tumor (OR 5.4 (2.1 – 14.0))
- Tumor size ≥ 2 cm (OR 6.5 (1.8 – 24.3))

Hashim et al. (2014)



What do we know of MEN1 patients?

Early and Late Complications After Surgery For MEN1-related Nonfunctioning Pancreatic Neuroendocrine Tumors

Sjoerd Nell, MD, Inne H. M. Borel Rinkes, MD, PhD,† Helena M. Verkooijen, MD, PhD,‡
Bert A. Bonsing, MD, PhD,§ Casper H. van Eijck, MD, PhD,¶ Harry van Goor, MD, PhD,||
Ruben H. J. de Kleine, MD,** Geert Kazemier, MD, PhD,†† Elisabeth J. Nieveen van Dijkun, MD, PhD,‡‡
Cornelis H. C. Dejong, MD, PhD,§§ Gerlof D. Valk, MD, PhD,¶¶, On behalf of the DMSG, and
Menno R. Vriens, MD, PhD|||*

Dutch MEN Study Group:

- 61 NF-pNET resections:
 - Mainly enucleations (20%) and distal pancreatectomies (56%)
 - Major resections: Whipple/PPPD (6%) and total pancreatectomy (8%)
 - Combination: 10%
- 33% major early Clavien Dindo grade III/IV complications
 - Majority ISGPS grade B/C pancreatic fistula
- 23% endocrine or exocrine insufficiency



Surgical advances

- Minimally invasive techniques
 - Laparoscopic
 - Robot-assisted
- Safe modality for treatment of pNETs
- Lower complication rate compared to open technique
- Malignant pNETs: not associated with compromise in oncologic resection
- Decreased postoperative pain, better cosmetic results, shorter hospital stay and shorter postoperative period
- Future RCT's should compare minimally invasive and open



Postoperative complications

- Pancreatic surgery related complications
 - Pancreatic Fistulas
 - Delayed Gastric Emptying
 - Post-pancreatectomy hemorrhage
 - Chyle leak
- General complications
 - Pneumonia



Complications rates – Systematic Review (2016)

- 2000-2013; 62 studies included -> 26 complication data
- Data scored according to International Study Group of Pancreatic Surgery (ISGPS) (if possible)

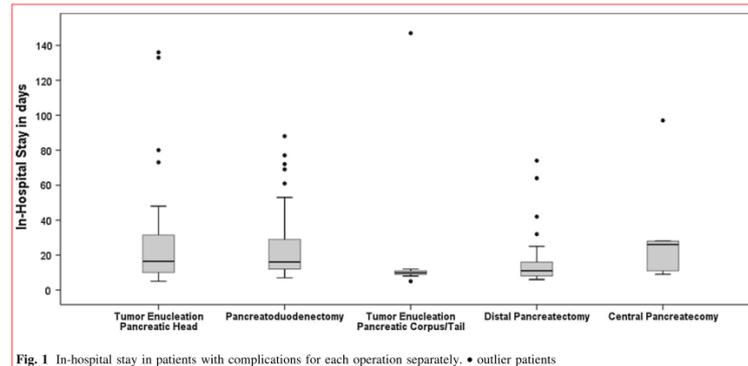
	Enucleation	Distal pancreatectomy	Whipple	Central pancreatectomy
Pancreatic fistula	45%	14%	14%	58%
Delayed gastric emptying	5%	5%	18%	16%
Postoperative hemorrhage	6%	1%	7%	4%
In-hospital mortality	3%	4%	6%	4%

- Complications in literature not systematically addressed



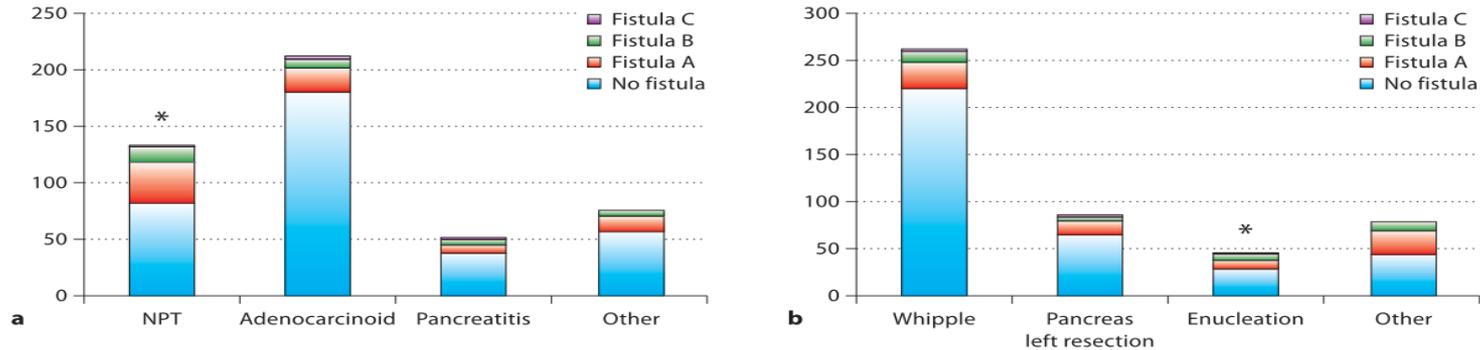
Comparison of different resections for pNETs

- 2 tertiary centers the Netherlands 1992-2013
- Enucleation (29%), Whipple/PPPD (31%), distal pancreatectomy (35%), central pancreatectomy (4%)
- Complication rates, need for re-interventions and readmissions were comparable for all resections



Pancreatic fistula: pNET vs other diseases

- Marburg, Germany : N=473 (133 pNET)

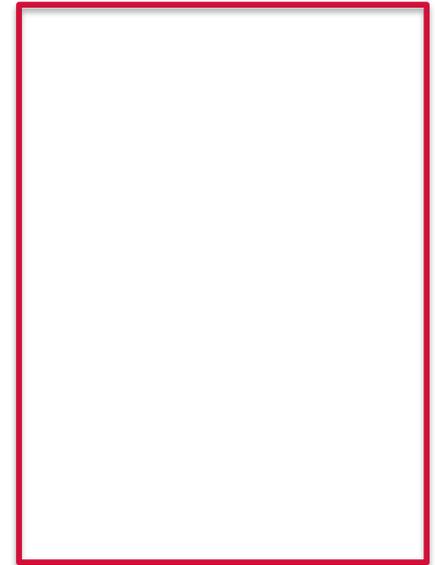


- Amsterdam UMC, the Netherlands: N=832 (88 pNET)
 - High rates of POPF were found in patients operated for PNET.
 - Atypical resections were performed more frequently in these patients.
 - Multivariable analysis: pNET not associated with POPF.



Postoperative pancreatic fistula

- pNETs high risk population for severe fistulas (grade B/C)
- 10-point Fistula Risk Score

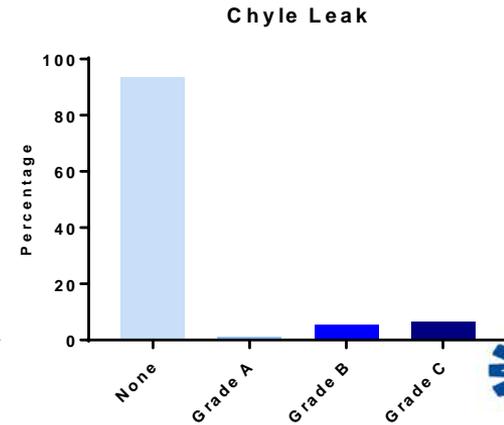
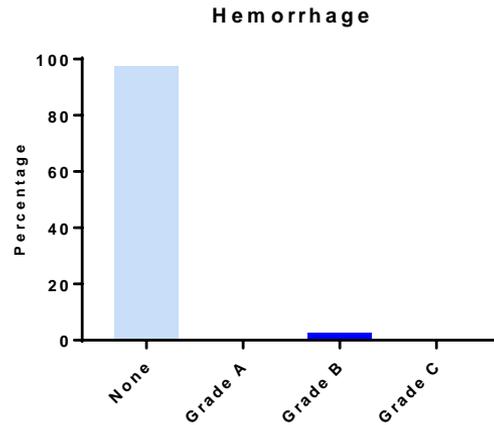
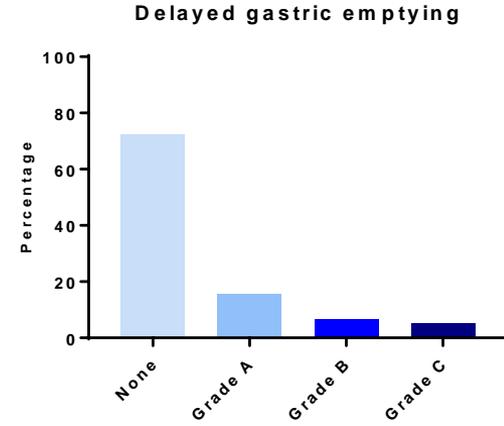
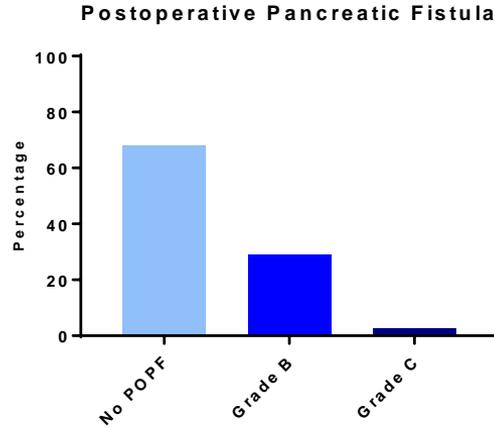
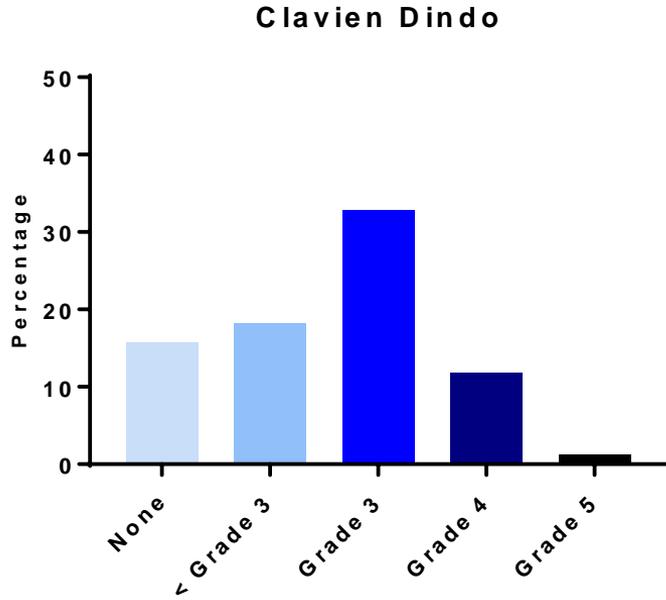


Utrecht pNET experience 2008-2019

- 76 pNET resections
- Mean age: 54 years (\pm 14)
- Male vs female: 49 vs 51%
- ASA 2: 57%
- Approach:
 - Open: 54 (71%)
 - Robot-assisted: 19 (25%)
 - Conversion: 3 (4%)
- Procedures:
 - Whipple/PPPD: 29 (38%)
 - Distal pancreatectomy: 31 (41%)
 - Enucleation: 5 (7%)
 - Total pancreatectomy: 4 (5%)
 - Combination: 7 (9%)



Utrecht experience 2008-2019



Histopathological examination

- AJCC, WHO 2010 and ENETS TNM classification/grading systems independent predictors of survival
 - ENETS TNM superior to the AJCC/WHO 2010 classification
- pNETs should be classified and graded using the WHO 2010 classification and grading system
- Presence of somatostatin receptor type 2 (SSTR2)
 - Future therapy



TNM Staging



WHO grade 2017 definition

Definition	Grade	Mitotic count (10 HPF) ^a		Ki-67 index, % ^b	
		2010	2017	2010	2017
NET	G1	<2	<2	≤2	< 3
NET	G2	2–20	2–20	3–20	3–20
NET	G3	n.a.	>20	n.a.	>20
NEC	G3	>20	>20	>20	>20

Differences are highlighted in bold. NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; n.a., not available. ^a 10 HPF: high power field = 2 mm², at least 50 fields (at ×40 magnification) evaluated in areas of highest mitotic density; ^b MIB1 antibody; % of 500–2,000 tumor cells in areas of highest nuclear labeling.

Poorly differentiated NEC:

- Solid or organoid structure
- Extensive necrosis
- Severe cytological atypia
- Small size cell with thin rim of cytoplasm (small cell type)
- Abundant eosinophilic cytoplasm (large cell type)
- Large nuclei with salt + pepper chromatin
- Inconspicuous nucleoli (small cell type)
- Conspicuous nucleoli (large cell type)



NET G3:

- Organoid and trabecular architecture
- Regular intratumoral vascular pattern
- Abundant granular cytoplasm
- Stippled nuclei

NEC G3 (small cell):

- Stromal desmoplasia
- Tumor necrosis
- Fusiform nuclei lacking nucleoli

NEC G3 (large cell):

- Tumor necrosis
- Expansile and irregular nests
- Rosettes/tubular structures in large nests



Validation of staging systems

- 2102 patients from 18 expert centers
- Resection of pNET with at least 2 years of follow-up
- Staging according to WHO 2010 and 2017
- Outcome: (time to) tumor-related death or recurrence

OS ->

<- Event-free



WHO 2010 versus 2017

2010:

OS ->

<- Event-free

2017:



WHO 2010 versus 2017

- NET G3 were not statistically different from NEC in both OS and EFS in univariable analysis
 - Low statistical power
- Both grading systems equally effective after adjusting for confounders
- In multivariable analysis, overall survival significantly worse for NEC compared to NET G3
 - In line, NET G3 more aggressive than G2
- Clinically difficult to direct to NET G3 or NEC classes

Rindi, G. *et al.* Competitive testing of the WHO 2010 versus the WHO 2017 grading of pancreatic neuroendocrine neoplasms: Data from a large international cohort study. *Neuroendocrinology* **107**, 375–386 (2019).

Tang, L. H., Basturk, O., Sue, J. J., & Klimstra, D. S. (2016). A Practical Approach to the Classification of WHO Grade 3 (G3) Well-differentiated Neuroendocrine Tumor (WD-NET) and Poorly Differentiated Neuroendocrine Carcinoma (PD-NEC) of the Pancreas. *The American journal of surgical pathology*, *40*(9), 1192-202.



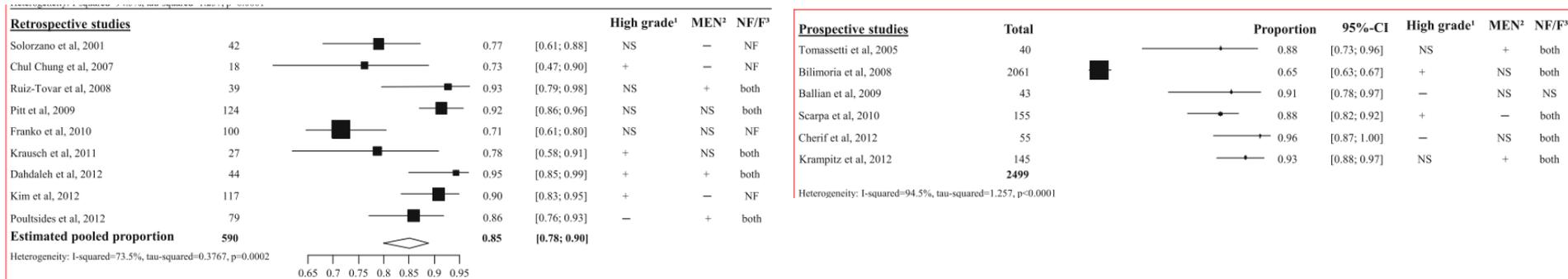
Postoperative follow-up regimen

- CgA and CT/MRI: every 3-9 months in WHO grade 1 & 2
 - Stable disease: increase interval
- Positive CT/MRI: somatostatin receptor imaging (Ga68)
 - Repeat every 2 years
 - Repeat earlier in case of suspected progression



Overall survival in patients without liver metastases

- 5-year overall survival and disease-specific survival after surgery: 85 (78-90%) and 93% (88-96%).
 - Retrospective studies
 - Prospective studies too heterogeneous to be pooled



Predictors of progression free survival

TABLE 2. Univariate and Multivariate Analysis for Predictors of PFS in the Overall Study Population

	Univariable Cox Regression			Multivariable Cox Regression		
	HR	95% CI	P	HR	95% CI	P
Male sex	1.887	1.238–2.876	0.003			
Functioning tumor	0.124	0.045–0.337	<0.001	0.272	0.098–0.750	0.012
Tumor Grade	4.112	3.036–5.568	<0.001	1.949	1.337–2.842	0.001
N status (0/1)	4.691	2.996–7.344	<0.001	2.161	1.306–3.575	0.003
Microscopic vascular invasion	7.728	4.825–12.380	<0.001	2.862	1.679–4.880	<0.001
R status	2.089	1.652–2.641	<0.001			
Tumor size ≥ 20 mm	3.673	2.192–6.155	<0.001			

- G1: 94.7% likelihood of being progression-free at 5 years
- G2: 65% likelihood of being progression-free at 5 years
- Functioning G1 N0 without vascular invasion: 5yr PFS 100%



Recurrence in grade 1 and 2 NF-pNETs

Landoni et al. (2017)

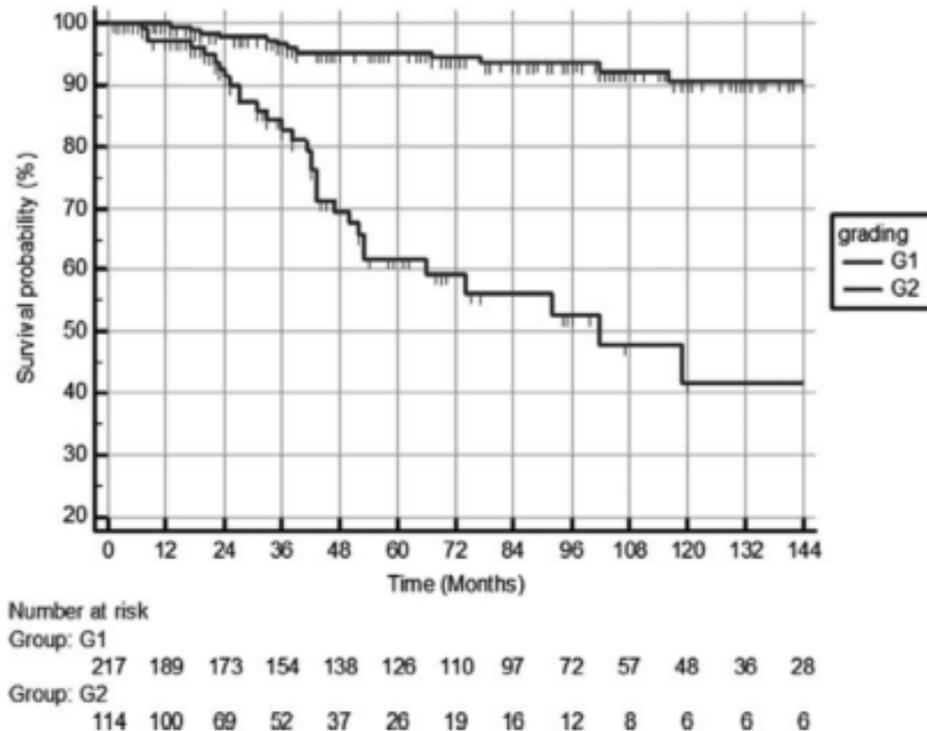
- Tumor grade (2): HR 7.3 (3.8 – 14.4)
- Perineural invasion: HR 3,9 (2.1 – 7.1)
- Sex, vascular invasion, N-status, tumor size >2cm not significant in multivariable analysis

Ceng et al. (2018)

- Tumor grade (2): HR 4.1 (1.9 – 8.8)
- Positive lymph nodes: HR 2.4 (1.2 – 5.1)
- Perineural invasion: HR 2.4 (1.1 – 5.1)
- Age, size, radicality, vascular invasion not significant in multivariable analysis



Progression free survival in grade 1 and 2 NF-pNETs

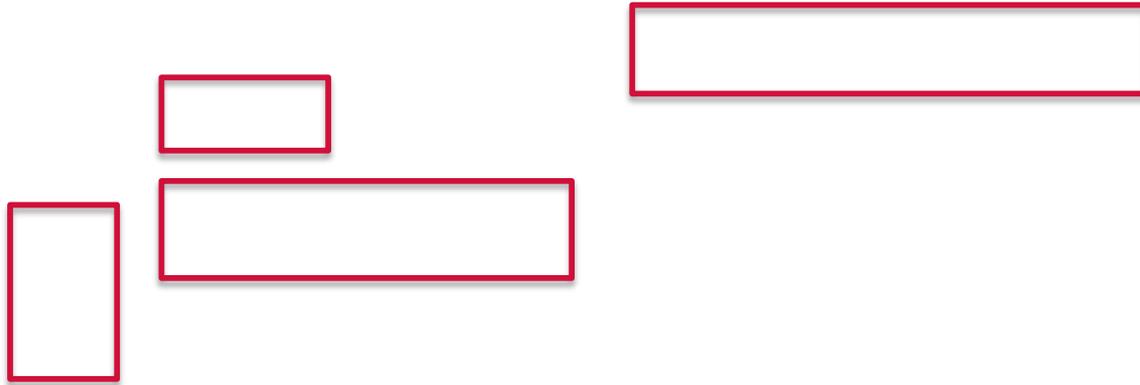


Advanced/metastatic disease

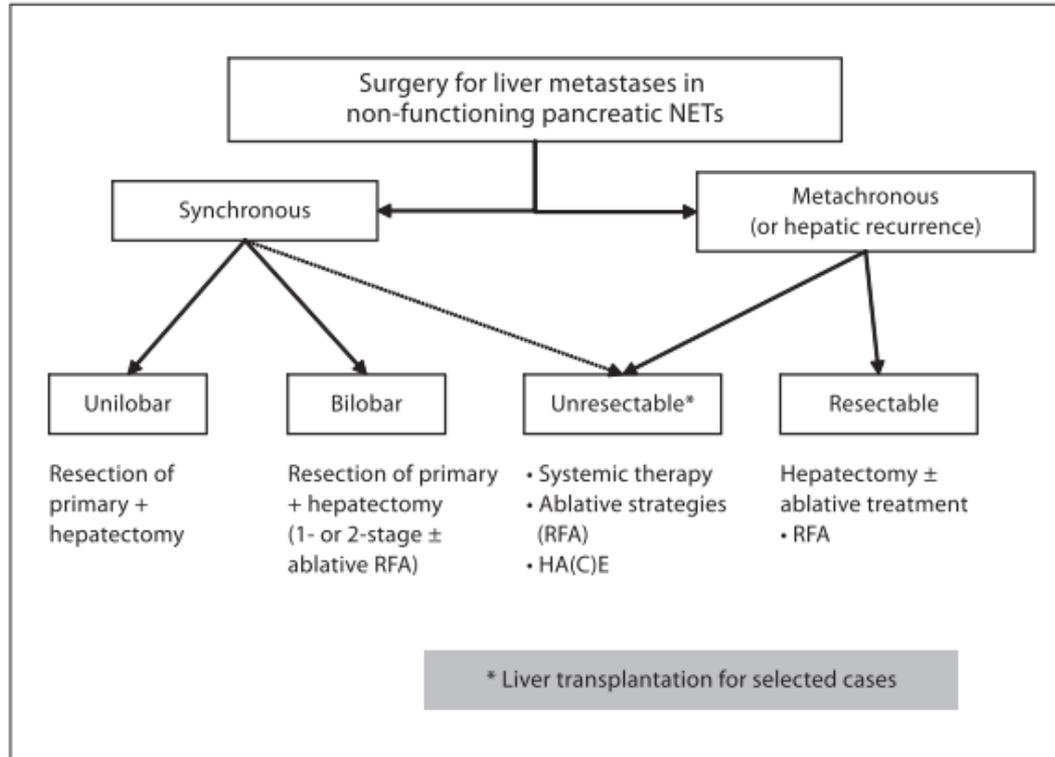
- Surgery:
 - Locoregional control
 - Liver metastases:
 - Resection of single metastases
- Ablative therapies
 - Hepatic arterial (chemo)embolization
 - RFA
- Medical:
 - Somatostatin analogues
 - Chemotherapy
- PRRT



ENETS treatment algorithm advanced disease: surgery



Surgical opportunities for liver metastases



Surgical opportunities for liver metastases



Conclusion

- pNETs are increasingly diagnosed
- Surgery is the cornerstone for treatment of functioning pNETs and NF-pNETs $\geq 2\text{cm}$
 - NF-pNETs $< 2\text{cm}$ should be carefully followed
 - Screening intervals have to be established
- Nevertheless, surgery is associated with a substantial risk of complications
- Tailoring of surgical indications could be guided by WHO grade
- Substantial advances in the field of minimal invasive surgery which seems safe and feasible for pNETs



Questions?



Future research perspectives

- DAXX/ATRX
- Individual risk stratification

