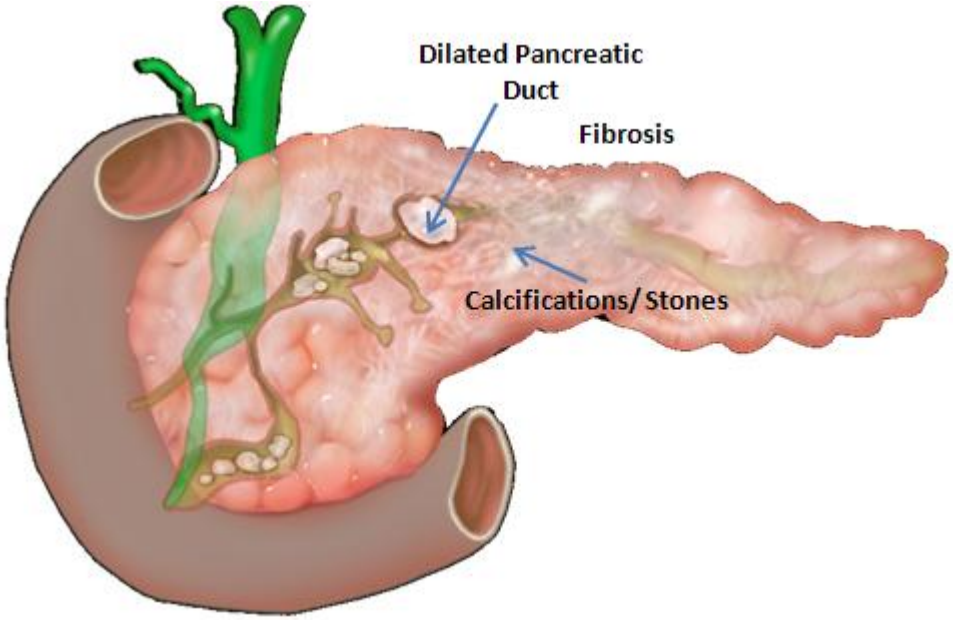
Bible Class
Chronic Pancreatitis



18.11.2020 Stefan Christen

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1. Definition
2. Etiology
3. Clinic / risk of carcinoma
4. Diagnosis
5. Therapy

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Definition

Statement 1 – 1 - 1 Definition

Chronic pancreatitis is a disease of the pancreas in which recurrent inflammatory episodes result in replacement of pancreatic parenchyma by fibrous connective tissue.

Morphological change

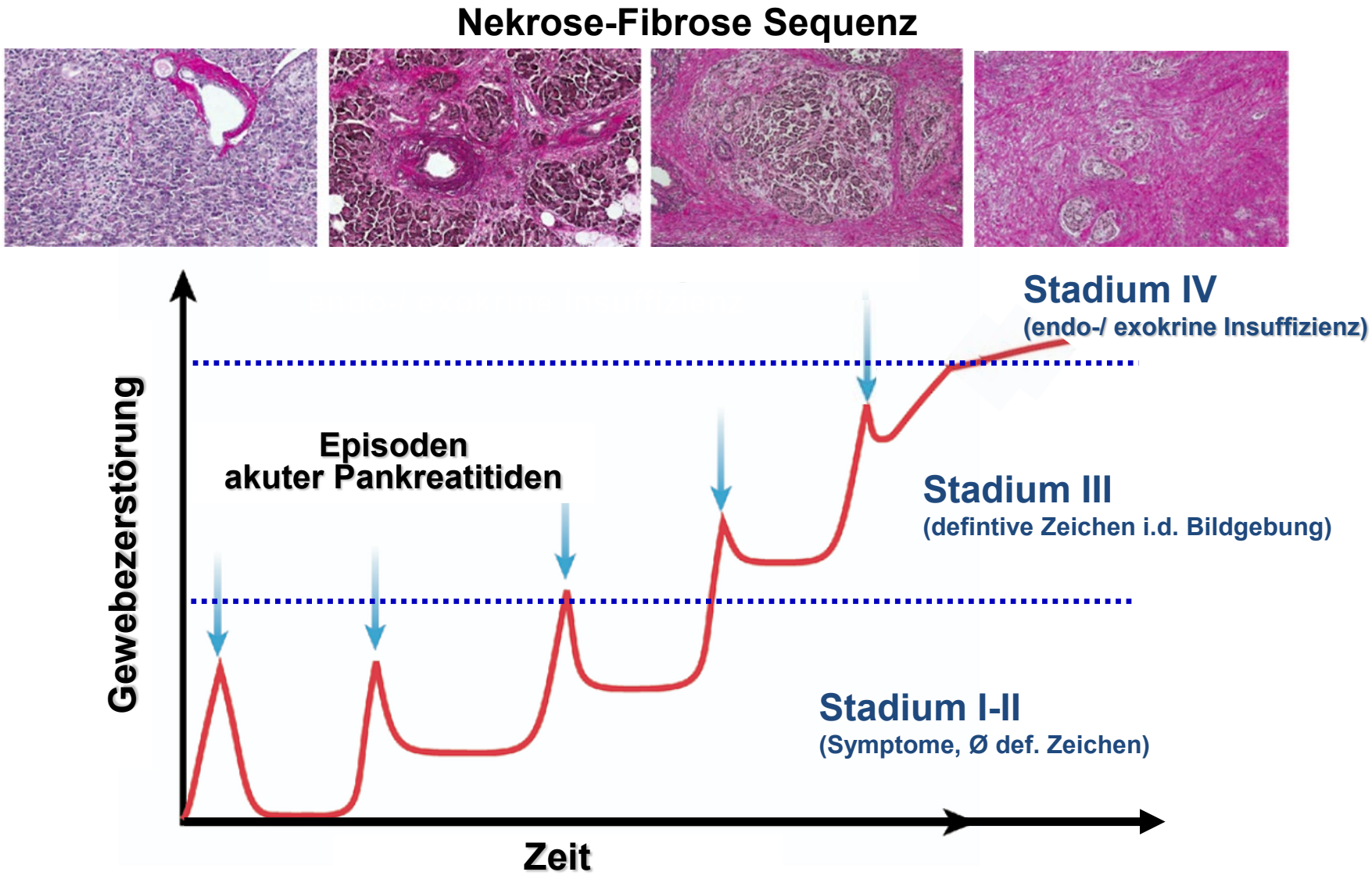
→ **Exo-, endocrine insufficiency**
Complications
Malnutrition
Pain
Risk for cancer

Functional consequences

→ **Reduced quality of life and life expectancy**

S3-Leitlinie Chronische Pankreatitis; Z Gastroenterol 2012

Natürlicher Krankheitsverlauf



Meier JJ & Schmidt WE Gastroenterology 2008

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Epidemiologie

- Inzidence: 1.6 - 23/100`000
- Prevalence: 50/100`000, man >> woman
- Rising numbers

- 10y survival 70 % (normal population 93%)
- 20y survival 45 % (normal population 65%)

- In western countries mostly due to alcohol and nicotine (>70%)

- up to 40% are forced to retire

Majumder S et al. Lancet. 2016 May 7;387(10031):1957-66
S3-Leitlinie Chronische Pankreatitis; Z Gastroenterol 2012; 50(11): 1176-1224
Yadav D et al. Gastroenterology 2013;144:1252–1261
Manser CN et al. Schweiz Med Forum 2014;14(31–32):570–577

Causes of chronic pancreatitis
Alcohol

- No threshold level ! Below which no risk

- Dose- Response: more = worse = higher risk

- 5% of «heavy drinkers» (> 80g/d für > 10 years) develop chronic pancreatitis

Getränk	typische Portion	Alkoholgehalt	Alkoholgehalt
Bier, groß	500 ml	4,8 Vol.-%	19 g
Bier, klein	330 ml	4,8 Vol.-%	13 g
Wein, Viertel	250 ml	11-13 Vol.-%	22-24 g
Wein, Achtel	125 ml	11-13 Vol.-%	11-12 g
Sekt, 1 Sektglas	100 ml	11 Vol.-%	9 g
Spirituosen, 1 Schnapsglas	20 ml	15-40 Vol.-%	2-6 g

nach Weiß C (2007). Alkohol. EU 54 (2)

Samokhvalov et al. Ebio Med 2015
Amann RW et al. Pancreas 1997

And smoking? +/- alcohol

- Smoking accellerates progression of CP-disease
- In hereditary pancreatitis: Ca 20y earlier!
- After two decades of smoking cessation risk of non-gallstone-related acute pancreatitis is reduced to a level comparable to that of never smokers

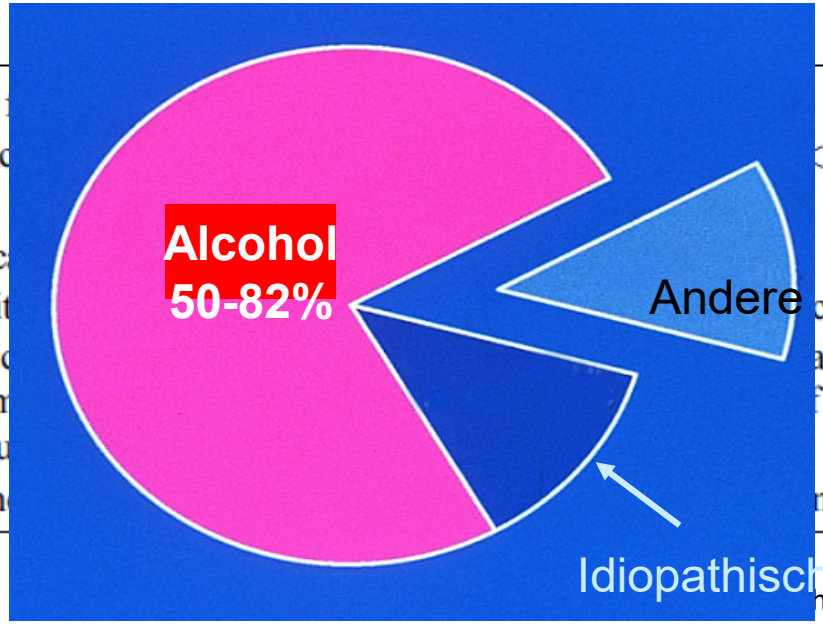
	Alcohol consumption (g/month)			
	<400		≥400	
	RR† (95% CI)	p Value	RR (95% CI)	p Value
Smoking status*				
Never	1 (Ref)		1 (Ref)	
Former	1.30 (0.88 to 1.90)	0.20	1.66 (1.09 to 2.53)	0.02
Current	1.63 (1.09 to 2.45)	0.02	2.10 (1.38 to 3.19)	<0.01
Pack-years of smoking*				
Never	1 (Ref)		1 (Ref)	
Former				
<20	1.33 (0.86 to 2.06)	0.20	1.97 (0.91 to 4.24)	0.08
≥20	1.44 (0.81 to 2.55)	0.21	3.96 (1.87 to 8.39)	<0.01
Current				
<20	1.69 (0.99 to 2.90)	0.06	2.13 (0.84 to 5.40)	0.11
≥20	1.94 (1.18 to 3.19)	<0.01	4.12 (1.98 to 8.60)	<0.01

Gut 2012 O-Sadr

Other causes

TIGAR-O
Toxic-metabolic: alcohol, tobacco smoking, hypercalcemia, hyperlipidemia, chronic renal failure, medications, toxins
Idiopathic: early onset, late onset, tropical
Genetic mutations: *PRSS1*, *CFTR*, *SPINK1*, others
Autoimmune: isolated, syndromic
Recurrent and severe AP-associated CP: postnecrotic (severe AP), vascular disease/ischemic, postirradiation
Obstructive: pancreas divisum, sphincter of Oddi, duct obstruction (eg, tumor), posttraumatic pancreatic duct scars

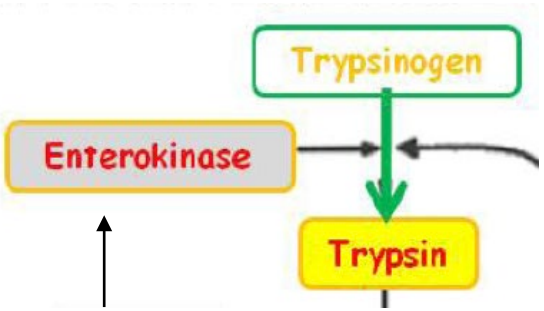
M indicates multiple risk
Alcohol consumption: exc ‹20 g/d)
Nicotine consumption
Nutritional factors: high c
Hereditary factors: heredit cal
Efferent duct factors: panc abnormalities of the pancreas, pancreatic duct obstruction (eg, tum f Oddi dysfunction
Immunological factors: au
Miscellaneous and rare m m, chronic renal failure, drugs, toxins



nneider A et al. J Gastroenterol. 2007;42:101–119
Yadav D et al. Gastroenterology 2013;144:1252–1261

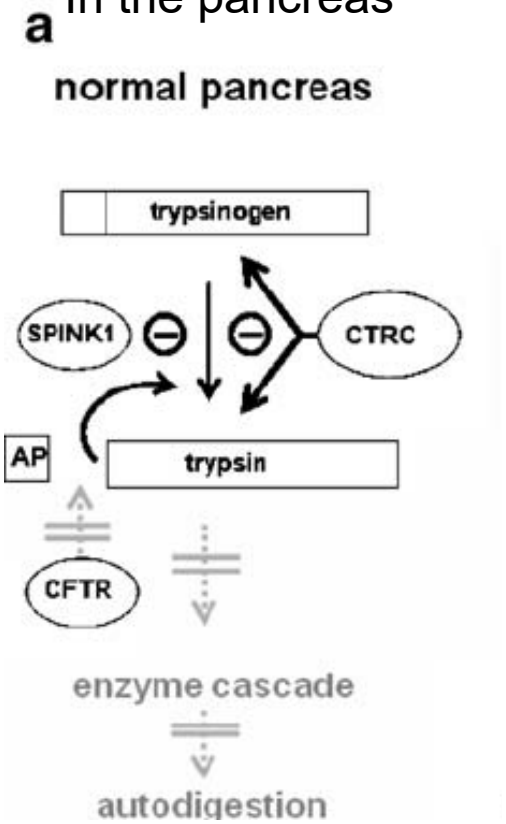
Hereditary pancreatitis

In the duodenum

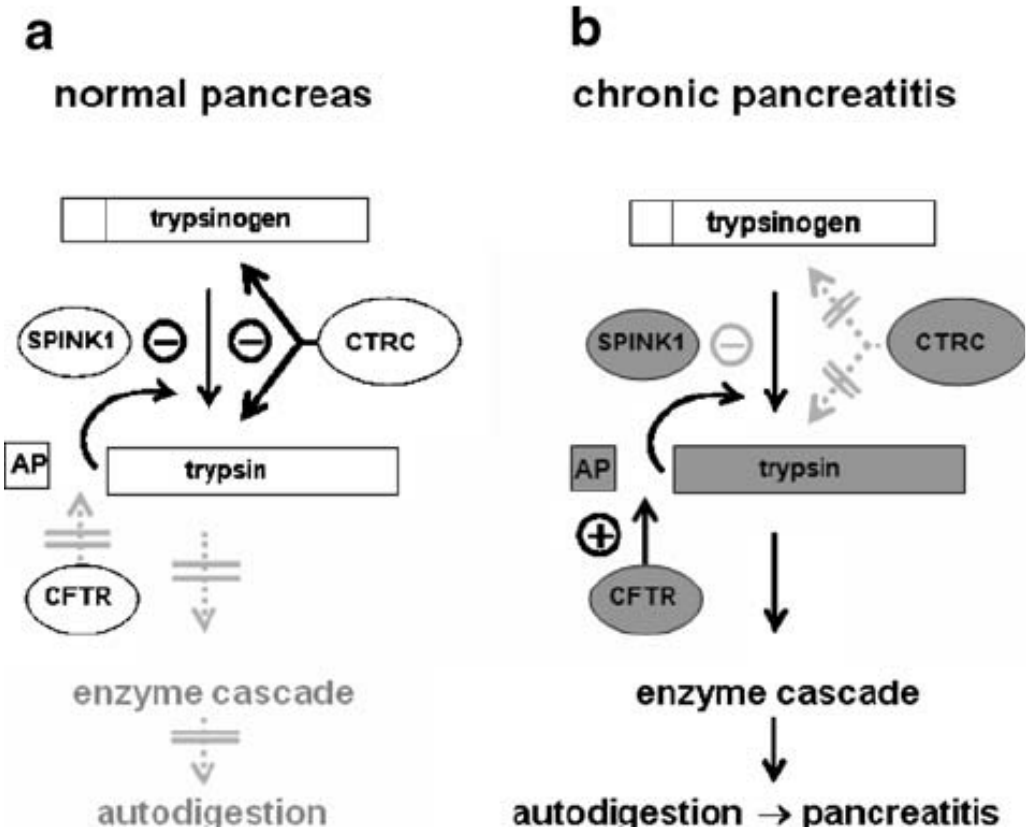


Produced in the duodenal mucosa

In the pancreas

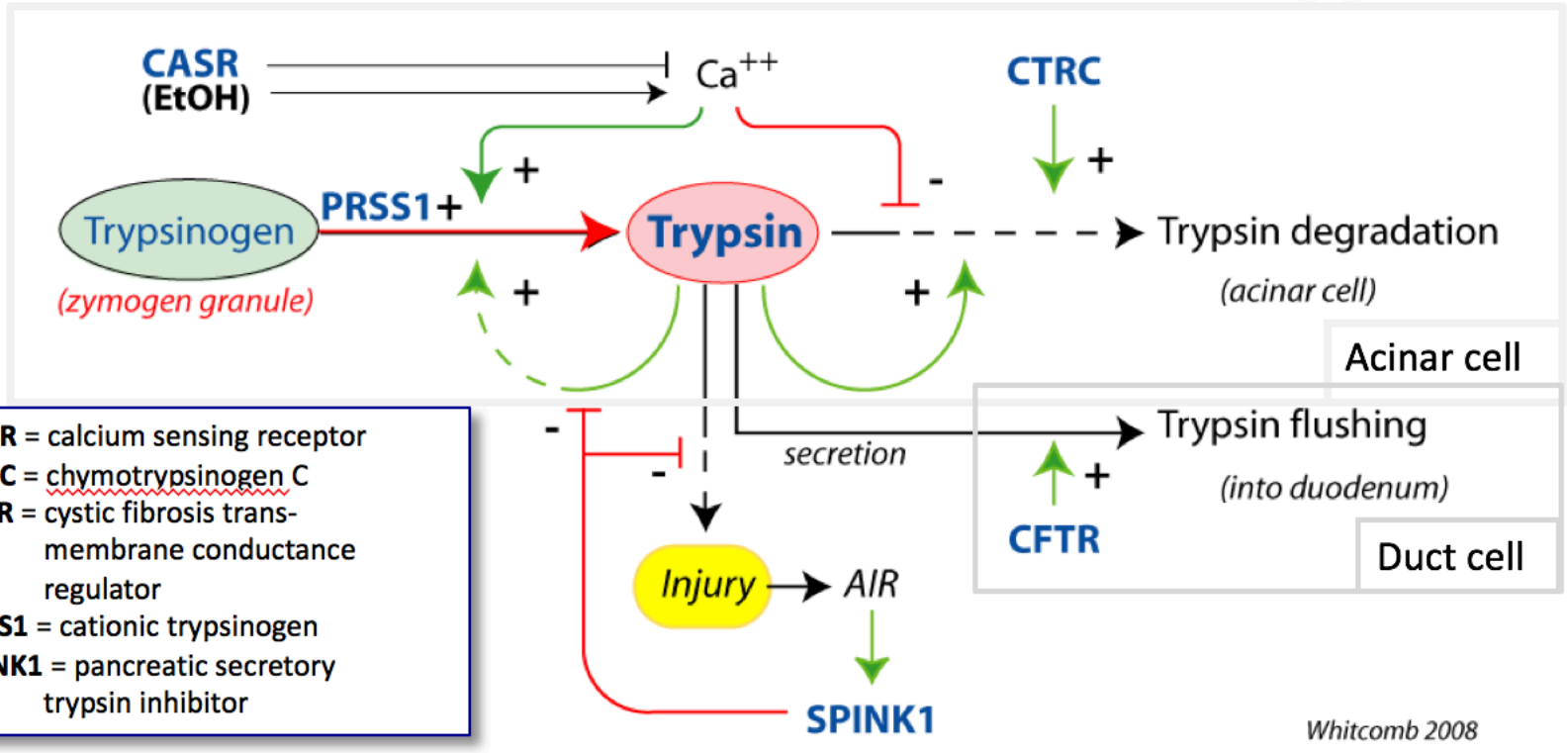


Hereditary pancreatitis



Model of chronic pancreatitis. a Condition in the normal pancreas: trypsin resulting from autoactivation of trypsinogen within the pancreatic parenchyma is inhibited by SPINK1 and degraded by chymotrypsin C (CTRC). This defence mechanism prevents the pancreas from activation of the pancreatic enzyme cascade and autodigestion. b Condition in chronic pancreatitis: mutations in PRSS1 , SPINK1 , or CTRC lead to an imbalance of proteases and their inhibitors within the pancreatic parenchyma resulting in an inappropriate conversion of pancreatic zymogens to active enzymes with autodigestion and inflammation. Mutations in CFTR may disturb this delicate balance by intrapancreatic acidification or by a defective apical trafficking of zymogen granules and thus facilitate the intrapancreatic activation of digestive enzymes. Dark boxes represent products of mutated genes. (AP, activation peptide)

Witt et al. Endocr Metab Disord 2008



AIR = Acute inflammatory response (acute phase protein expression)

- Genes linked to **CP susceptibility** all regulate intra-pancreatic **trypsin** activity.
- Both the acinar cells and duct cells are linked with pancreatitis-causing variations

Whitcomb DC. *Annu Rev Med*. 2010;61:413-24.

Hereditary pancreatitis

Mutation in the kationic Trypsinogen-Gen (PRSS1):

- Autosomal dominant, high penetrance (up to 80 %)
- Risk für pancreatic carcinoma: 49% in75 years
- usally symptoms before 20y

Mutationen im SPINK1-Gen:

- Autosomal recessive
- Common mutation (ca. 2%), only in 1% CP, «disease modifier»

CFTR-Mutation: (Cystic fibrosis transmembrane regulator gene)

- Autosomal recessive inheritance, Prevalence 1:2500,
- > 2000 mutations leding to alterations in secretion of Cl, Na and HCO3. Thick viscous mucus, low pancreatic fluid volume
- Increased acidic pancreatic juice-> precipitations -> duct obstruction
- Mild variants: e.g. R75Q or BD

Majumder S et al. Lancet. 2016 May 7;387(10031):1957-66
Kara L R et al, Clin and Experimental GE 2016:9 197-207
Rebours, Dig Liver Dis. 2012 Jan;44(1):8-15
S3-Leitlinie Chronische Pankreatitis; Z Gastroenterol 2012; 50(11): 1176-1224

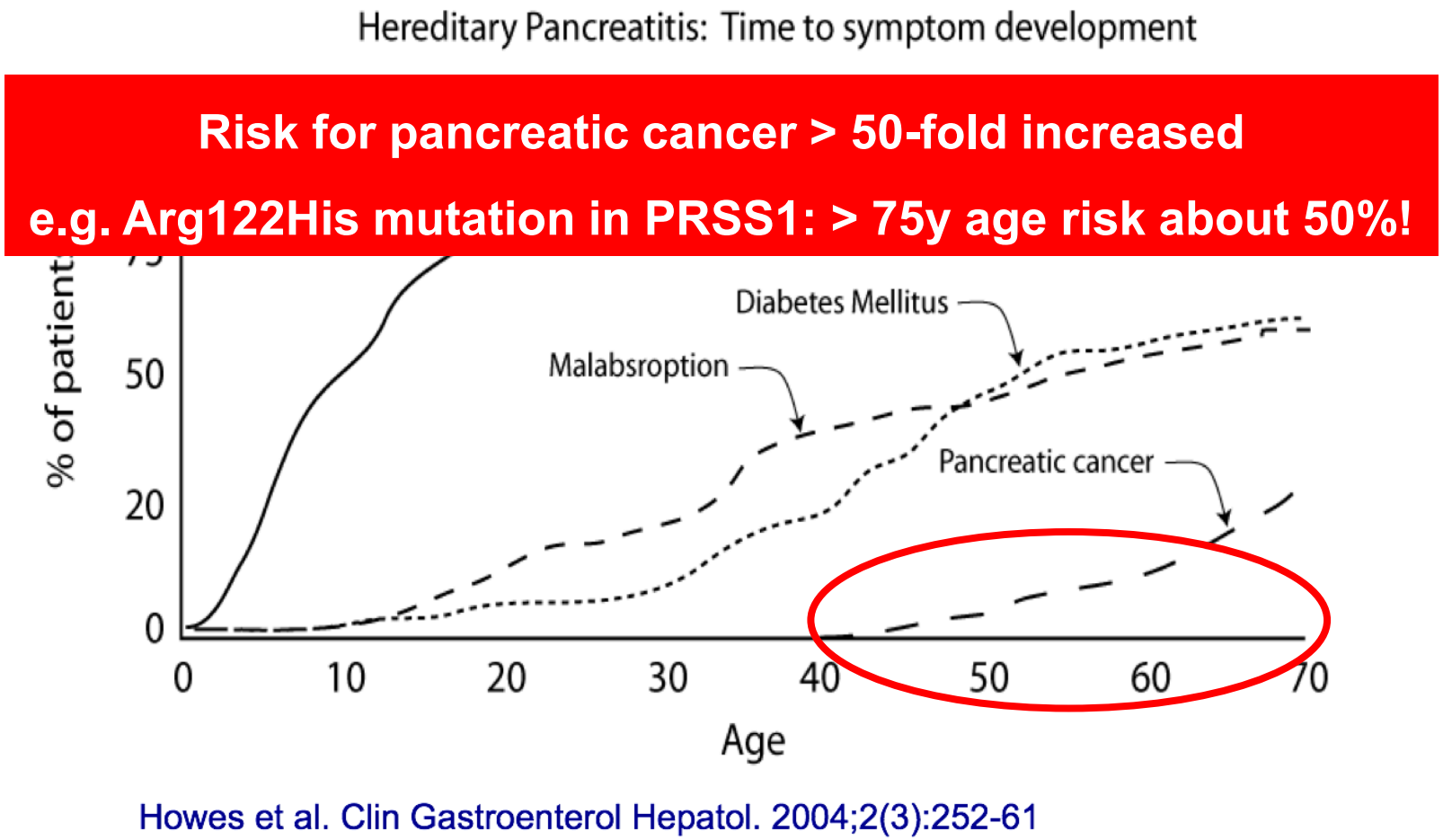
Who to test for HP?

- A family history of idiopathic chronic pancreatitis, recurrent acute pancreatitis or childhood pancreatitis
- Relatives with known mutations associated with HP
- Unexplained pancreatitis in a child
- Idiopathic chronic pancreatitis in patients <25 years
- Recurrent (≥ 2 episodes) acute pancreatitis of uncertain etiology

Pancréatite

- ❒ *CFTR*+5T (33 mutations) *450 CHF*
- ❒ mutation *SPINK* *215 CHF*
- ❒ gène *PRSS1* *!!* *530 CHF* → **Kostengutsprache einholen**

Surveillance of HP



Howes et al. Clin Gastroenterol Hepatol. 2004;2(3):252-61

Autoimmunpancreatitis

Subtypes of autoimmune pancreatitis.

Subtype of AIP	Type 1	Type 2
Other nomenclatures	AIP without GEL IgG4-related LPSP	AIP with GEL IgG4-unrelated IDCP
Prevalence	Asia > USA, EU	EU > USA > Asia
Age	High aged	Younger
Gender	Male ≫ female	Male = female (NS)
Symptoms		
Obstructive jaundice	Often	Often
Abdominal pain	Rare	Common
Pancreas swelling	Common	Common
Serology	High serum IgG, IgG4, autoAbs (+)	Normal IgG, normalIgG4, autoAbs (−)
Other organ involvement (OOI)	Sclerosing cholangitis Sclerosing sialadenitis Retroperitoneal fibrosis Others	Unrelated with OOI
Ulcerative colitis	Rare	Often
Steroid	Responsive	Responsive
Relapse	High rate	Rare

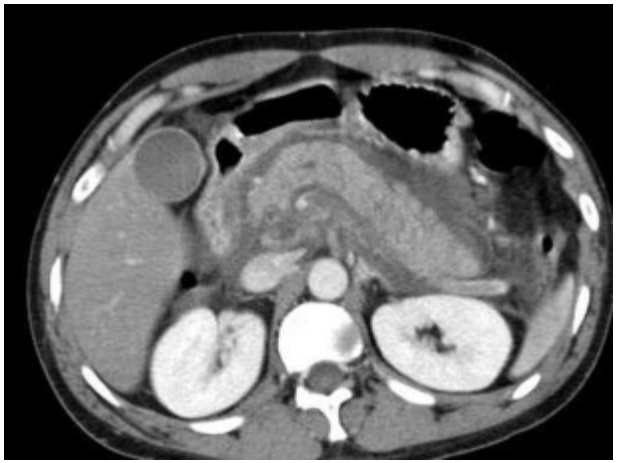
GEL=Granulocytic epithelial cells

K. Okazaki, Autoimmunity reviews 2014

AIP and international consensus diagnostic criteria (ICDC)

ICDC[1] 5 signs for AIP:

- Imaging of pancreatic parenchyma and duct
- Serology
- Other organ involvement
- Histology of pancreas
- Response to steroid therapy (optional)



70% of AIH 1do not need a biopsie for diagnosis. AIH 2 often needs biopsie

[1]Shimosegawa T et al. Pancreas 2011;40: 352Y358
[2]Manser CN et al. Digestion 2015;92:138–146

AIP – algorithm

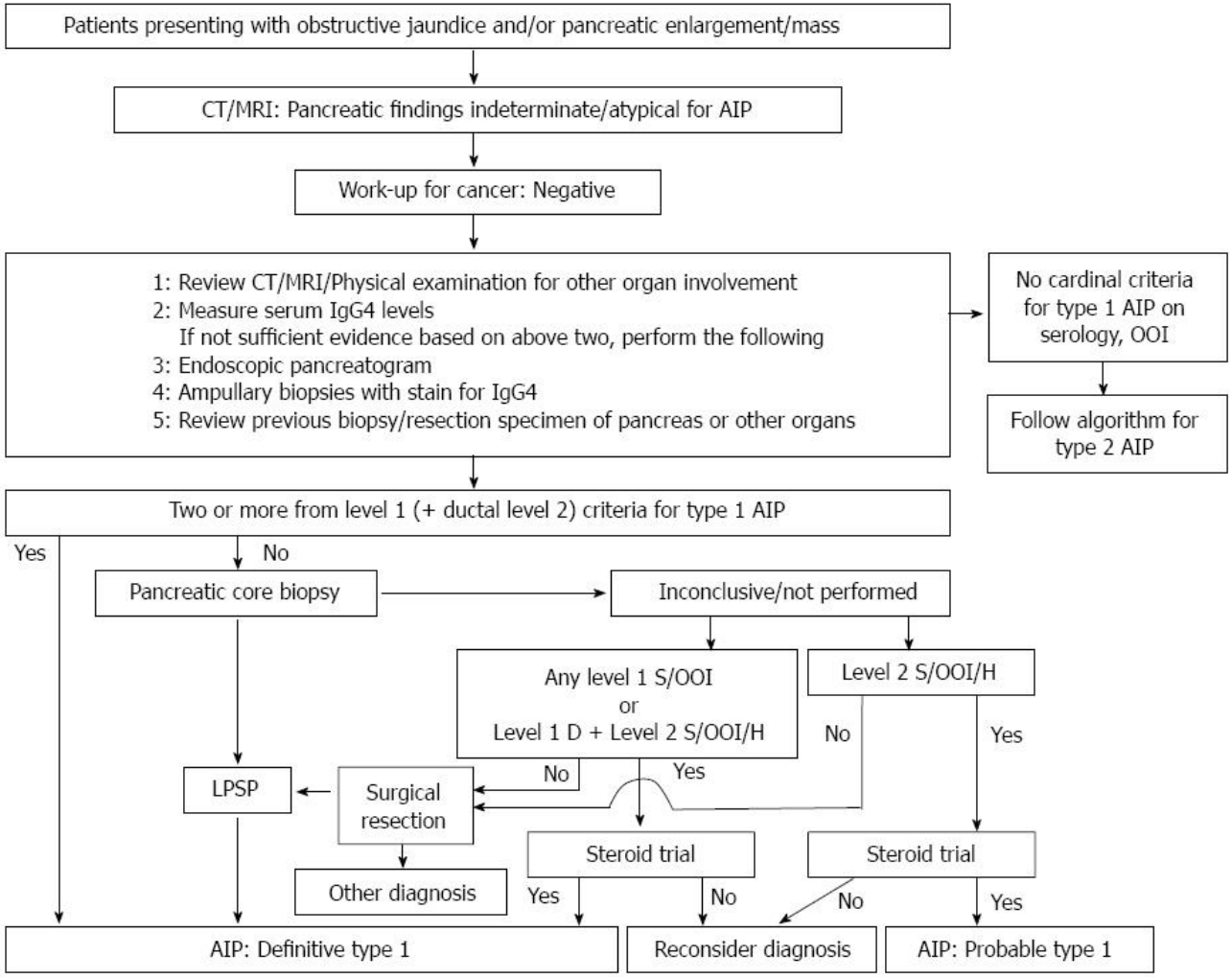
TABLE 2: Level 1 and Level 2 Criteria for Type 1 Autoimmune Pancreatitis (AIP) Using International Consensus Diagnostic Criteria [40]

Abbreviation	Criterion	Level 1	Level 2
P	Parenchymal imaging	Diffuse enlargement with delayed enhancement	Indeterminate and atypical findings such as segmental or focal enlargement with delayed enhancement
D	Ductal imaging (ERCP)	Long and multiple strictures without marked upstream dilatation	Segmental or focal narrowing without marked upstream dilatation (duct size < 5 mm)
S	Serology	IgG4 level > 2 times upper limit of normal value	IgG4 level 1–2 times upper limit of normal value
OOI	Other organ involvement	Either typical histology or radiology	a or b
		a. Histology of extrapancreatic organs	a. Histology of extrapancreatic organs including endoscopic biopsies of bile duct
		Any three of the following:	Both of the following:
		(1) Marked lymphoplasmacytic infiltration with fibrosis and without granulocytic infiltration	1) Marked lymphoplasmacytic infiltration without granulocytic infiltration
		(2) Storiform fibrosis	(2) Abundant (> 10 cells/HPF) IgG4-positive cells
		(3) Obliterative phlebitis	b. Physical or radiologic evidence
		(4) Abundant (> 10 cells/HPF) IgG4-positive cells	At least one of the following:
		b. Typical radiologic evidence	(1) Symmetrically enlarged salivary or lachrymal glands
		At least one of the following:	(2) Radiologic evidence of renal involvement described in association with AIP
		(1) Segmental or multiple proximal (hilar or intrahepatic) or proximal and distal bile duct stricture	
		(2) Retroperitoneal fibrosis	
H	Histology of the pancreas	LPSP (core biopsy or resection)	LPSP (core biopsy)
		At least 3 of the following:	Any 2 of the following:
		(1) Periductal lymphoplasmacytic infiltrate without granulocytic infiltration	(1) Periductal lymphoplasmacytic infiltrate without granulocytic infiltration
		(2) Obliterative phlebitis	(2) Obliterative phlebitis
		(3) Storiform fibrosis	(3) Storiform fibrosis
		(4) Abundant (> 10 cells/hpf) IgG4-positive cells	(4) Abundant (> 10 cells/hpf) IgG4-positive cells
Rt	Response to steroid	Diagnostic steroid trial; rapid (≤ 2 weeks) radiologically demonstrable resolution or marked improvement in pancreatic or extrapancreatic manifestations	

Note—hpf = high-power field, LPSP = lymphoplasmacytic sclerosing pancreatitis.

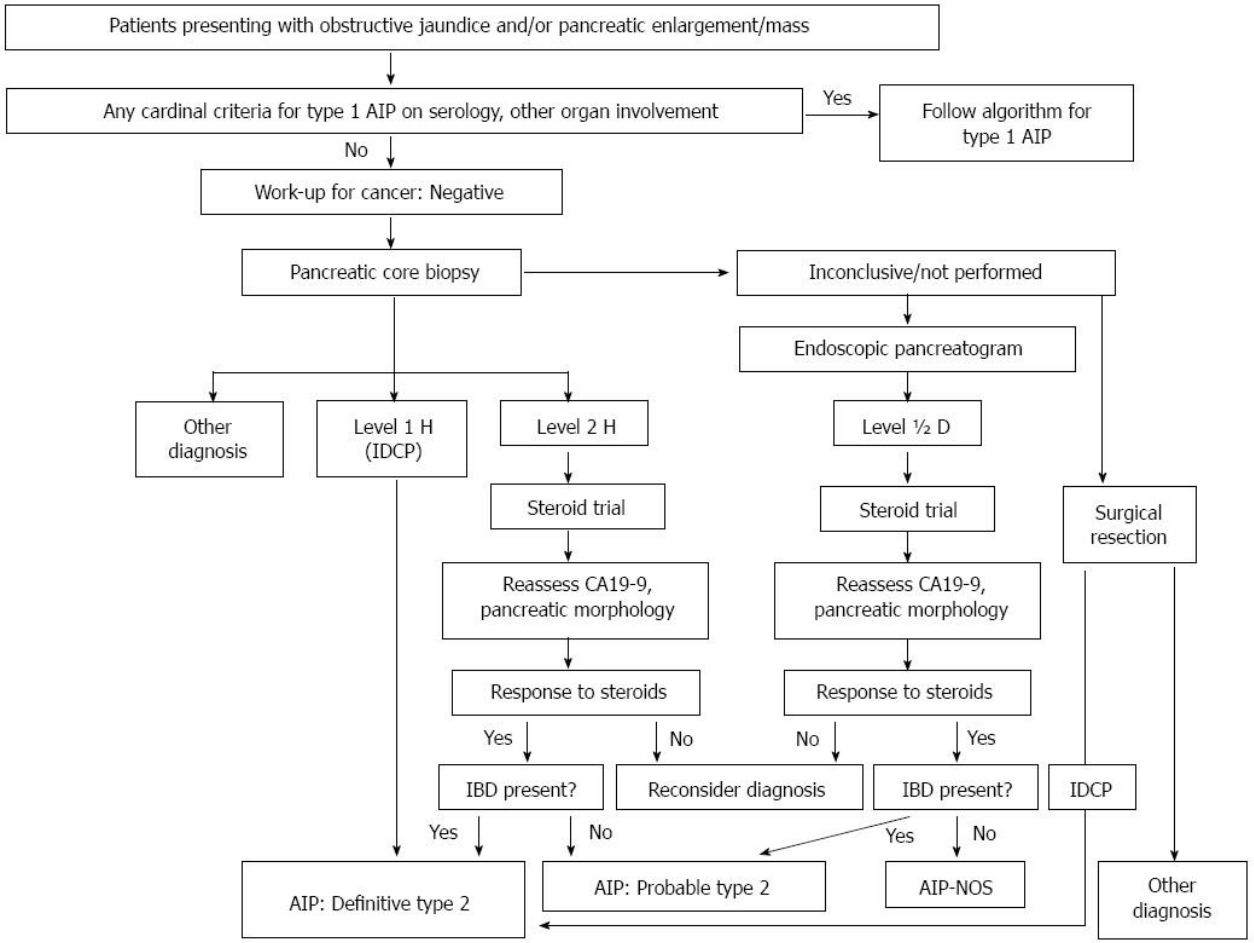
AJR:202, May 2014

AIP 1 – algorithm



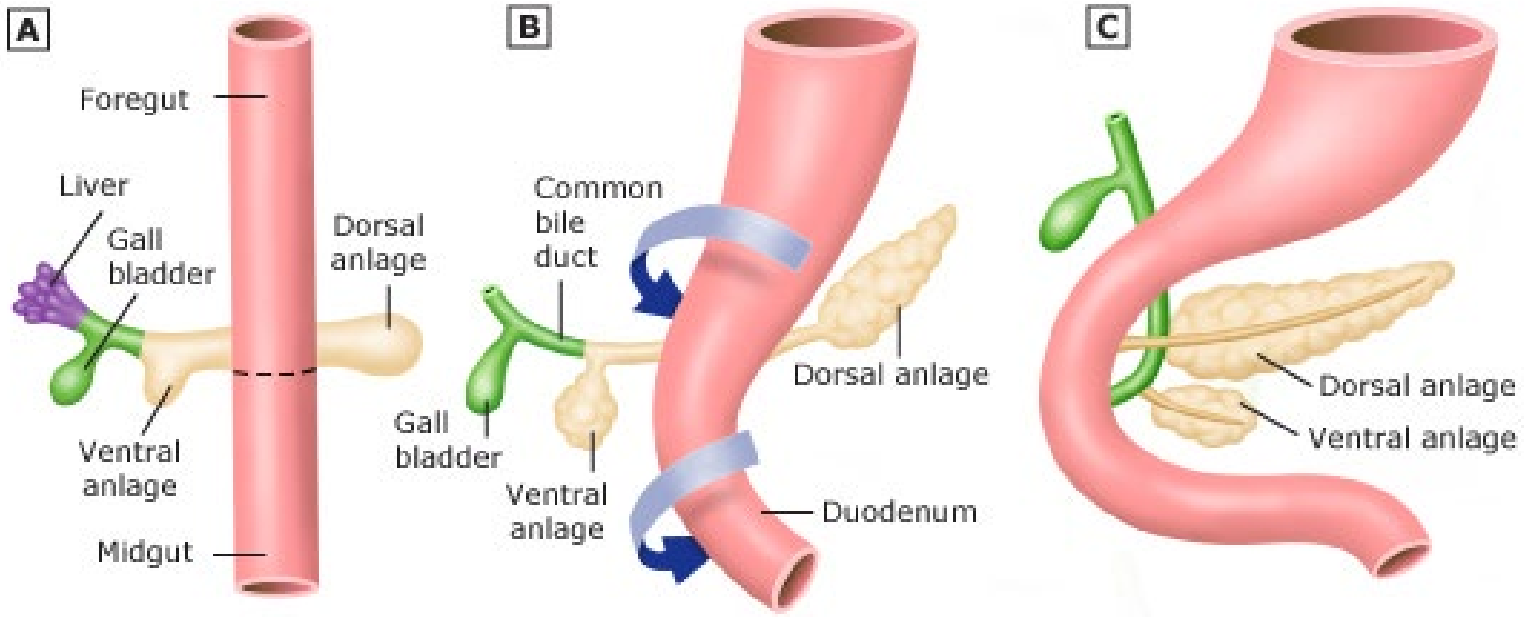
Hiroyuki Matsubayashi World J Gastroenterol 2014

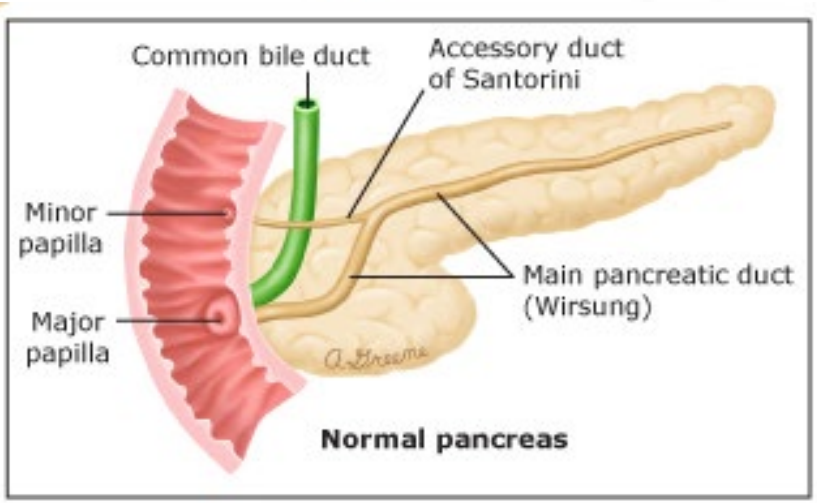
AIP 2 – algorithm



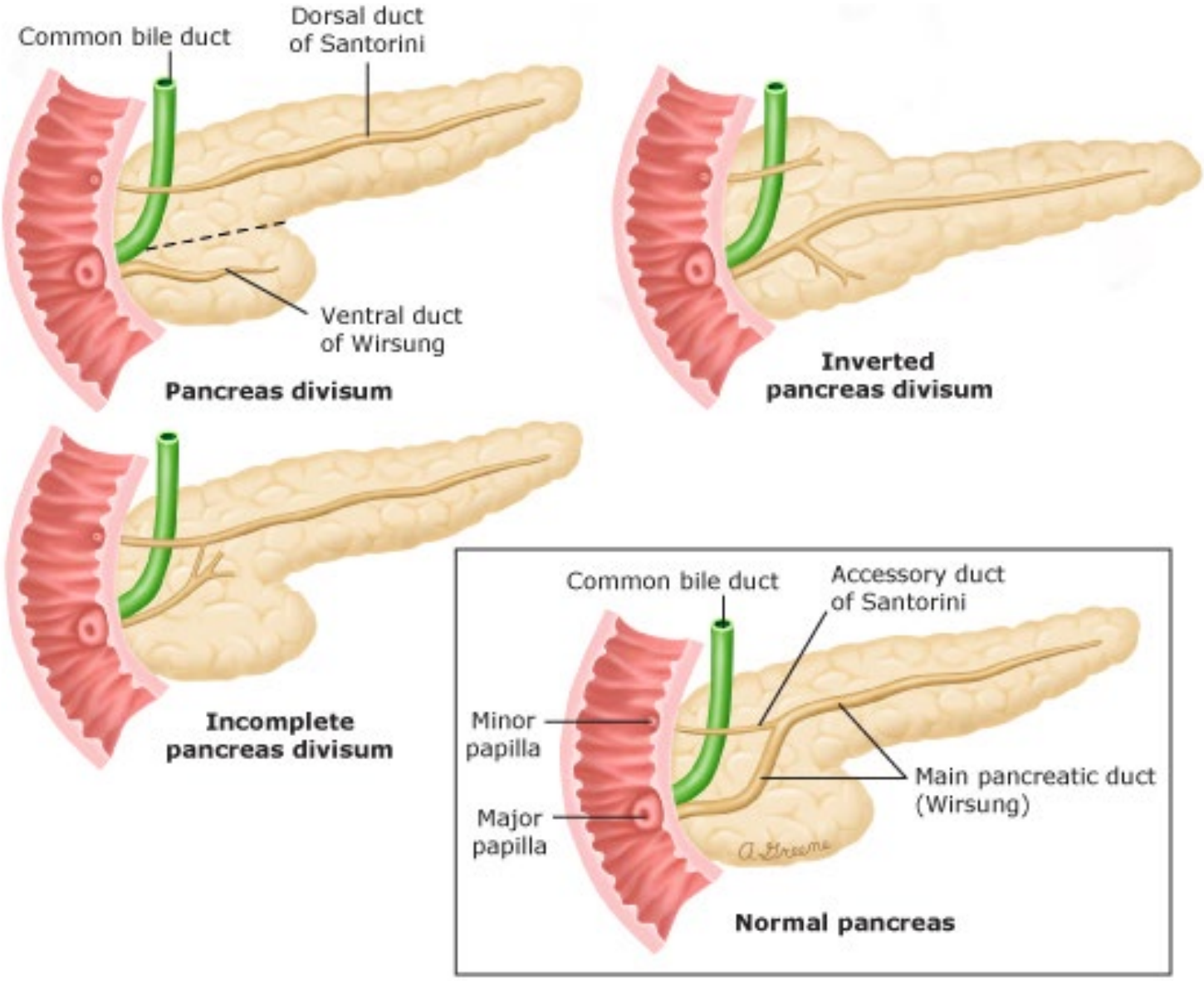
Hiroyuki Matsubayashi World J Gastroenterol 2014

Pancreas divisum





Pancreas divisum



Pancreas divisum

- Incomplete or lack of fusion D.santorini + D.wirsungianus with seperate drainage of ventral and dorsal pancreas in major and minor papilla
- Autopsies: 5-10% all individuals
- CP-cases: 6-26% of idiopathic CP-cases
- With other risk factors (genes, C2..): can cause CP
- Particularly in childhood pancreatitis search for it
- Endoscopic treatment can be/is appropiate individually

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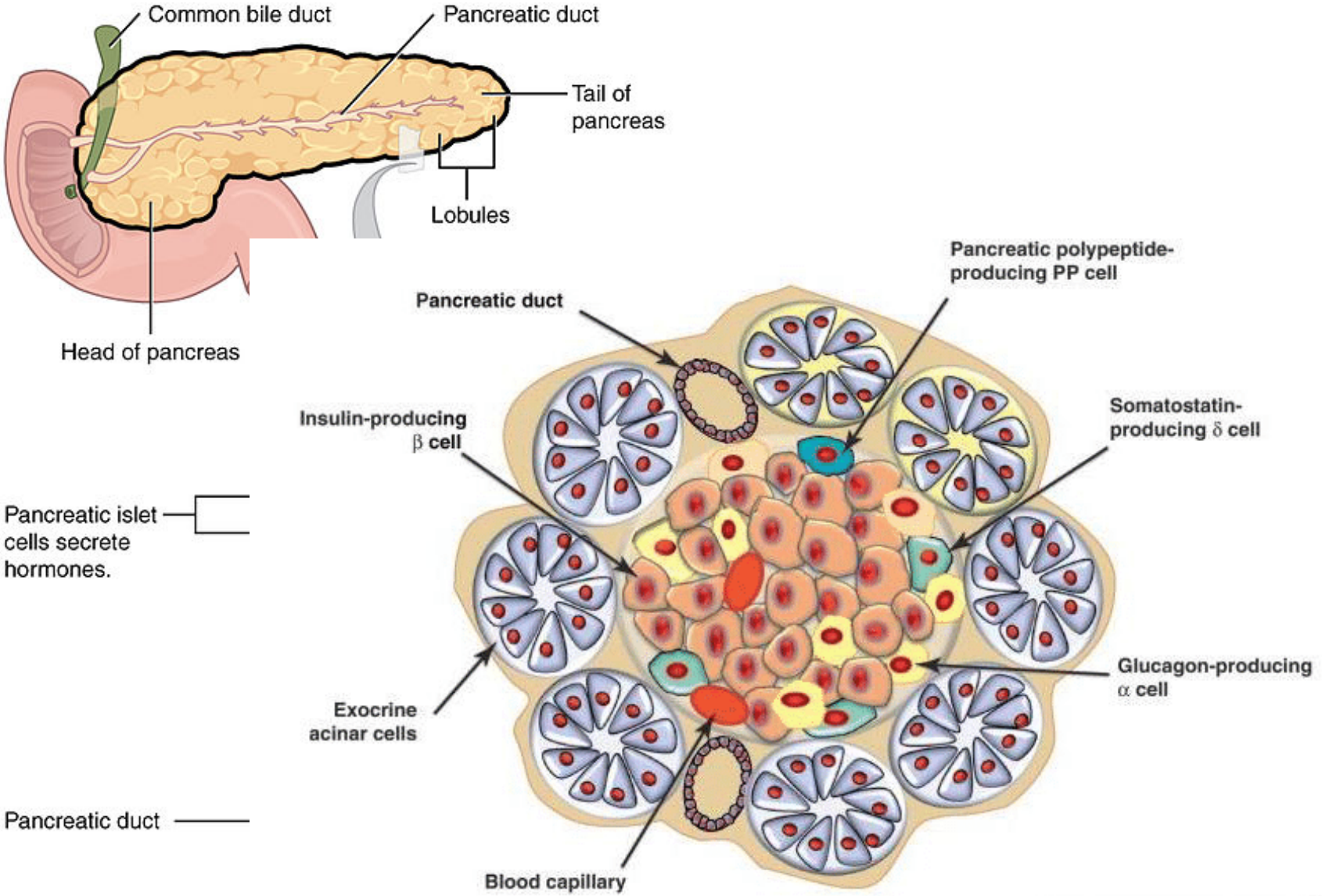
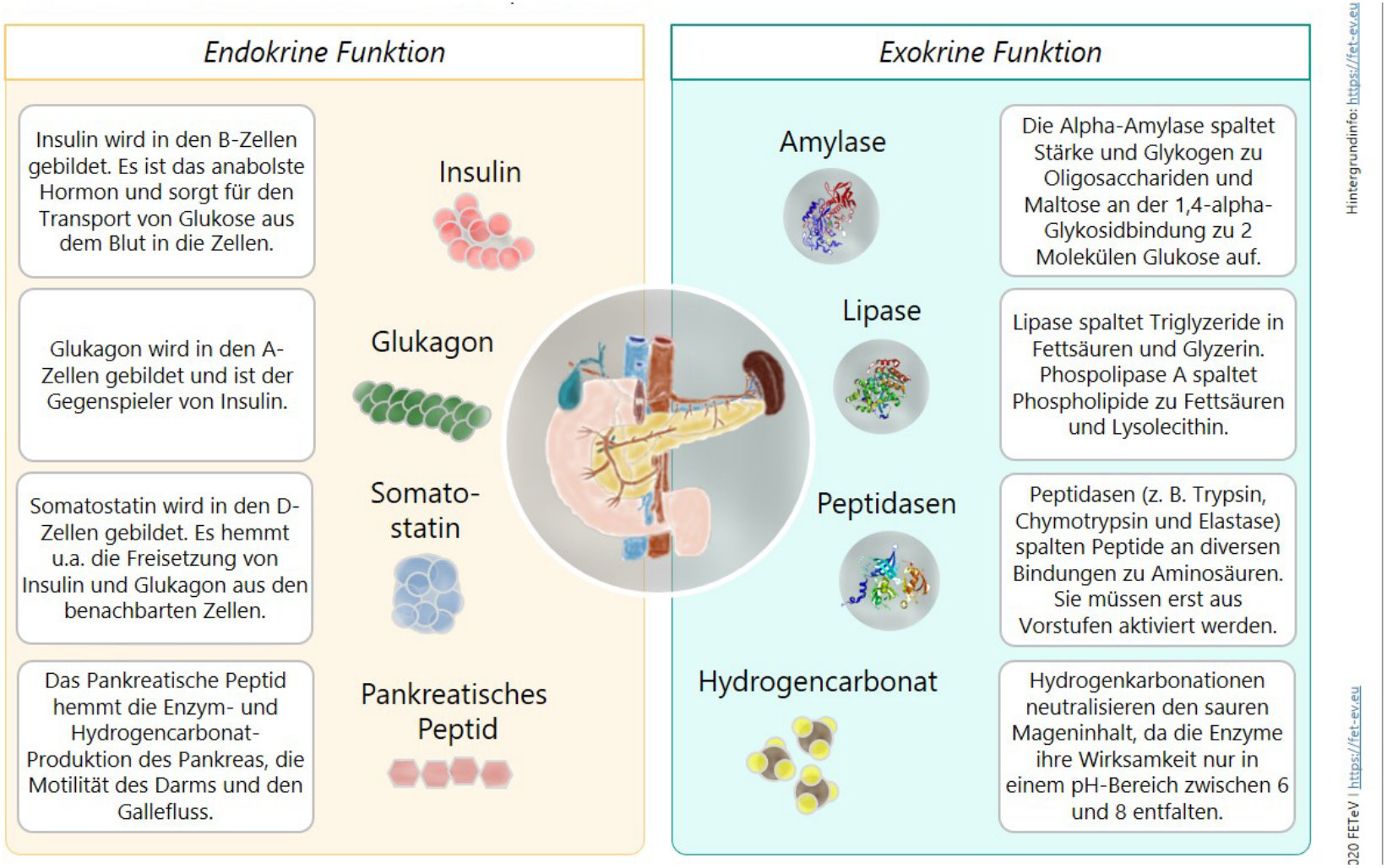
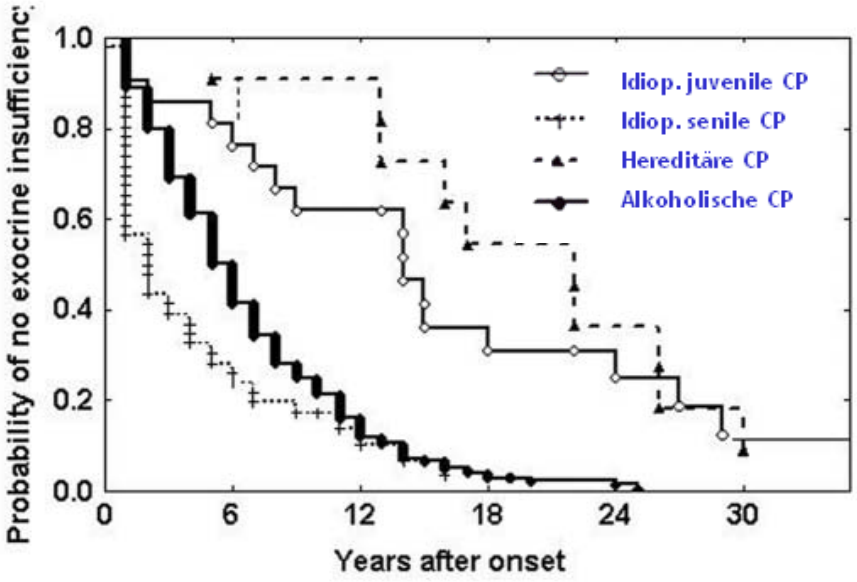
Endo- and exocrine function of Pancreas

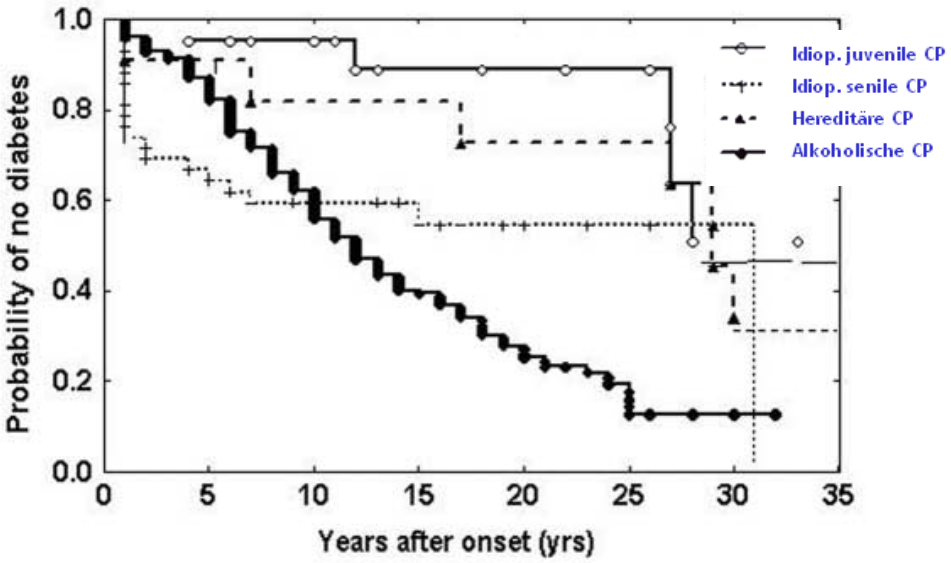


Endo- and exocrine function of Pancreas



Endo- and exocrine insufficiency



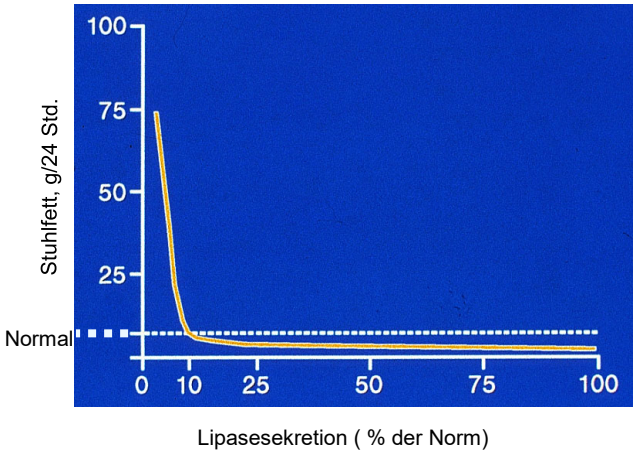


- Faster in smoker

Müllhaupt B et al; Z Gastroenterol 2005: 43: 1293-1301

Steatorrhea

- >7g fat/d at 100g fat ingestion/d
- Large volume, stinky stool, osmotic diarrhoe, undigested fibres
- No very good clinically detection (NPV < 30%) (neither negative nor positive predictive)
- > 90% reduction in lipase-secretion



ExPI Testing – How

Test	Leichte ePI	Mässige ePI	Höhergradige ePI	Spezifität
	Sensitivität	Sensitivität	Sensitivität	
Elastase-Stuhl	**54%**	75%	**95%**	**85%**
Qual. Stuhlfett	0%	0%	78%	70%
Chymotrypsinakt. Stuhl	<50%	Ca. 60%	80-90%	80-90%
C13 Atemtest (gem. Triglyceride)	**62-100%**	**-**	**90-100%**	**80-90%**

N = >200 ug/g, false low if diarrhea

C13-Atemtest-Triglyceride:
Better im mild ExPI
Only test to monitor therapy

ExPI and vitamin deficiency

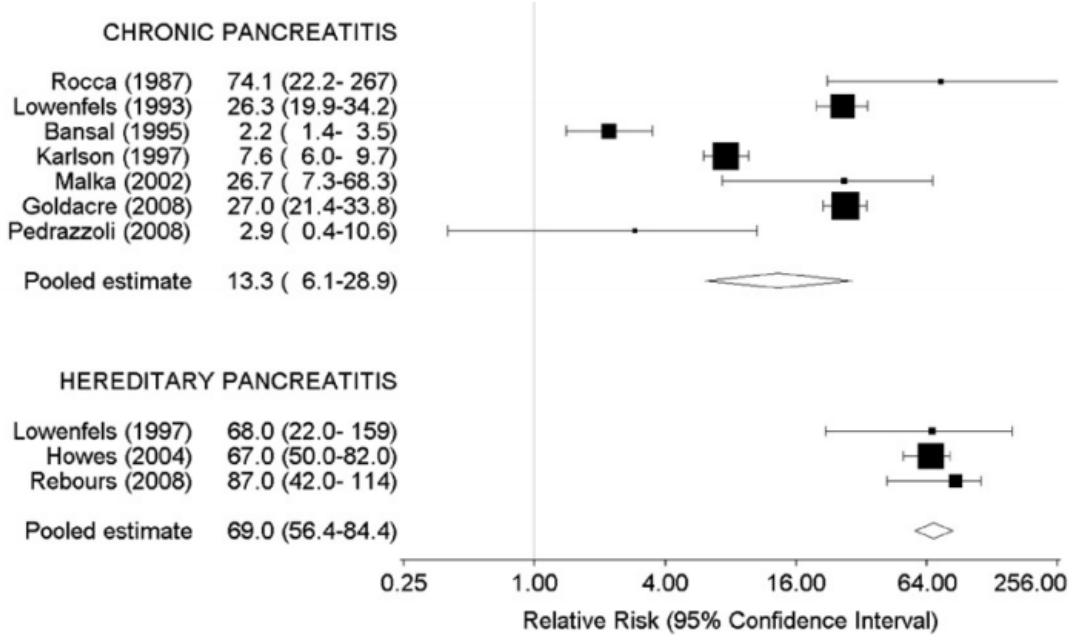
Vitamin	Laboratory Sign of Deficiency	Clinical Sign of Deficiency	Treatment/Prevention
Vitamin A	Retinol: retinol-binding protein <0.8 mol/mol	Xerophthalmia, keratomalacia	Vitamin A: 3,000–10,000 U/d
Vitamin D	25-Hydroxyvitamin D <14 ng/mL = deficiency; <30 ng/mL = insufficiency	Rickets, osteomalacia	Cholecalciferol: 800–5,000 IU/d; 1,25 OH_2 cholecalciferol: 0.05–0.2 μg/kg per d
Vitamin K	Prolonged prothrombin time, elevated protein in vitamin K absence	Coagulopathy	Phytonadione: 2.5–5 mg twice a week to every day
Vitamin E	Vitamin E: total serum lipid ratio <0.6 mg/g	Neurologic changes, hemolysis	TPGS: 15–25 U/kg per d; D-α tocopherol: up to 100 U/kg per d

TPGS=D-α-tocopheryl polyethylene glycol 1,000 succinate.

Risk of carcinoma

1

- 5y after diagnosis 8-time higher risk for pancreatic cancer[2]
- Highiest risk within the fist two years after diagnosis
- More extrapancreatic neoplasia[3]



[1]Raimondi S et al. Best Pract Res Clin Gastroenterol. 2010 Jun;24(3):349-58
[2]Kirkegard J, Am J GE 2017
[3]Talamini G et al. American Journal of Gastroenterology (1999) 94, 1253–1260

Screeing for carcinoma

- DGVS-Leitlinien 2012:
  - «Es kann sinnvoll sein, Hochrisikogruppen in regelmässigen Abständen auf das Auftreten eines Pankreaskarzinoms zu untersuchen» [Evidenzgrad 3b, Empfehlungsgrad D, starker Konsens]
  - Hochrisikogruppen: PRSS1-Mutation sowie Raucher
  - Abdomenultraschall alle 6-12 Monate, weitere Bilddiagnostik bei Verdacht
  - Keine Bestimmung von Tumormarkern
- AGA medical position statement pancreatic carcinoma 1999:
  - Hereditary pancreatitis: Screening after 35y
  - Familiary syndrome: 10 before symptomes of the first family member
  - Combination of CT, EUS und CA19-9; interval unclear
- Consensus Guidelines, Pancreatic Cancer in Hereditary Pancreatitis 2001:
  - **Offer** screening after 40 y
  - EUS, MRI, CT; interval unclear

AGA-Guidelines, Gastroenterology. 1999 Dec;117(6):1463-84
S3-Leitlinie Chronische Pankreatitis; Z Gastroenterol 2012; 50(11): 1176-1224
Ulrich CD et al. Pancreatology 2001;1:416–422

Riskfactors for cancer

Multicenter studiy (cross-sectional), 660 Pat with firs AP 2003-2007

Results:

RF for recurrent AP:

- Alcohol OR 2.29 (1.42-3.70)
- Smoking (active) OR 3.06 (1.98-4.74)
- Nekrot. AP OR 1.92 (1.2-3.08)

RF for CP:

- Alcohol OR 3.98 (1.64-9.65)
- Smoking (active) OR 2.90 (1.42-5.93)
- Nekrot. AP OR 6.65 (3.40-13.01)

- Cumulative risk of recurrent AP within 5y:
  - Smoking: 40% (non-smoker 13%)
  - Alcohol: 30%
- Cumulative risk of CP within 5y:
  - Smoking or alcohol 18% (each) (30% in combination)

Ahmed AU et al. Clinical Gastroenterology and Hepatology 2016;14:738–746
Di Leo M et al, Pancreas 2017 Feb; 46(2):225-229

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Diagnosis of CP

- **EUS**
- CT
- MRI, MRCP
- ERCP

EUS-diagnostic accuracy for chronic pancreatitis

25 Pts. with surgical wedge-resection; EUS and secrtin-test prior to operation

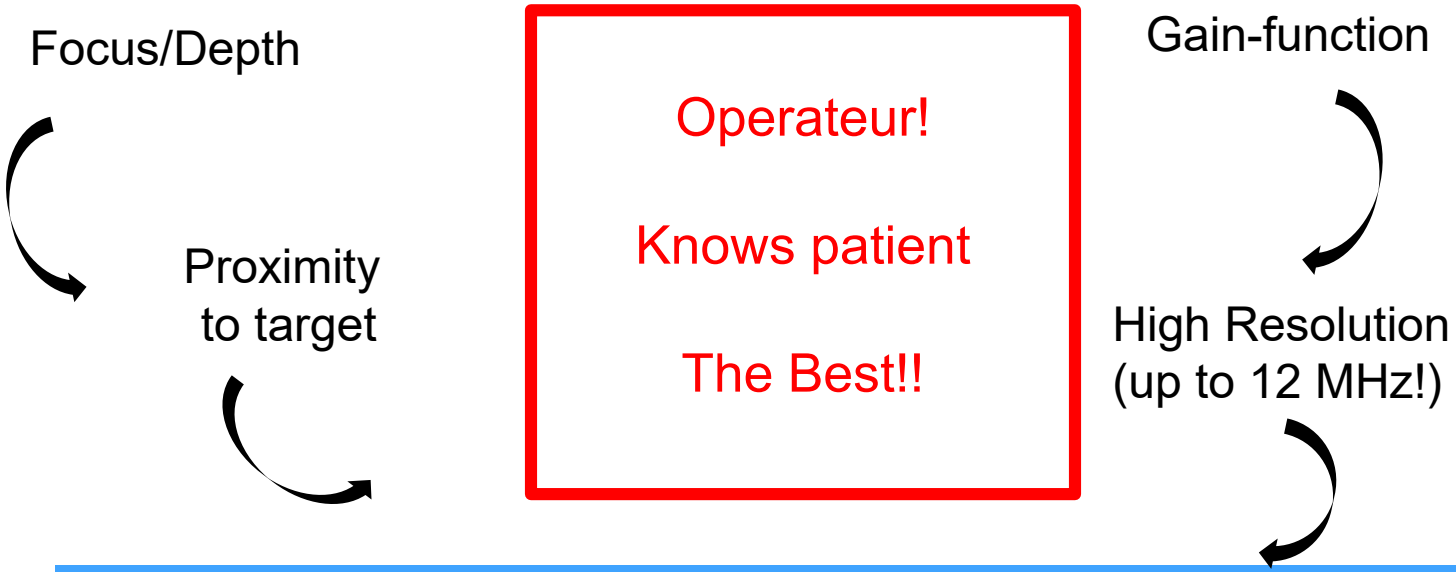
Goldstandard Fibrose-Histologie	Sensitivität	Spezifität
EUS	84%	100%
Secretin-Test	86%	67%

- EUS is the most sensitive imaging technique for the diagnosis of CP (mainly during the early stages of the disease)
- EUS best tool in differential diagnosis of CP, pancreatic masses or cystic lesions (fine needle biopsy)

Albashir S et al. AJG 2010
Dominguez et al Pancreatology 2018

Strength of diagnostic EUS

Real-time – dynamic – individual adaptation



Contrast-enhancment

Optimized examination of target

Fine-Needle-Aspiration/Bx

Rosemont Classification

Parenchymal:

- Major:
  - Hyperechoic foci + shadowing (Major A)
  - Lobularity (Major A)
    if honeycomb-typ (Major B)
- Minor:
  - Hyperechoic foci without shadowing
  - Cysts
  - Stranding

Ductal:

- Major:
  - MPD calculi (Major A)
- Minor:
  - Irregular MPD contour
  - Dilated side branches
  - MPD dilation
  - Hyperechoic MPD margin

Catalano et al. Gastrointest Endosc. 2009;69:1251–1261

Rosemont Classification

I. Consistent with CP

A. 1 major A feature (+) ≥3 minor features

B. 1 major A feature (+) major B feature

C. 2 major A features

II. Suggestive of CP†

A. 1 major A feature (+) <3 minor features

B. 1 major B feature (+) ≥3 minor features

C. ≥5 minor features (any)

III. Indeterminate for CP†

A. 3 to 4 minor features, no major features

B. major B feature alone or with <3 minor features

IV. Normal

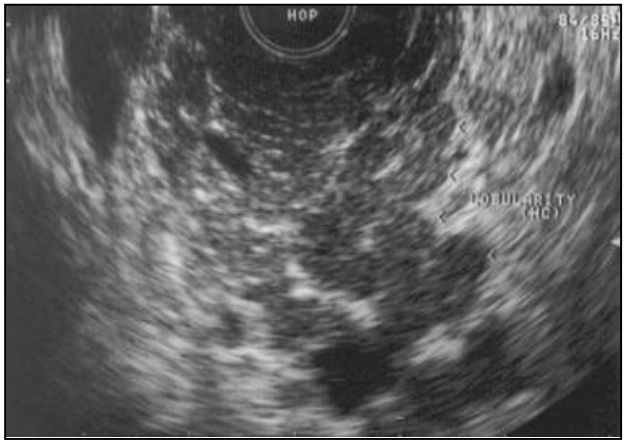
≤2 minor‡ features, no major features

*EUS diagnosis of CP should be made in the appropriate clinical setting.

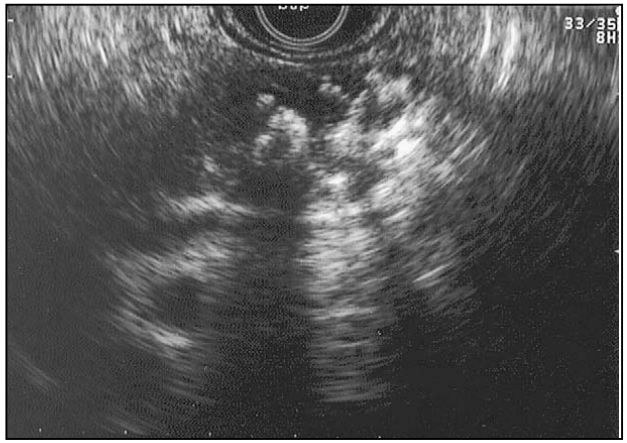
†Diagnosis requires confirmation by additional imaging study (ERCP, CT, MRI, or PFT).

Catalano et al. Gastrointest Endosc. 2009;69:1251–1261

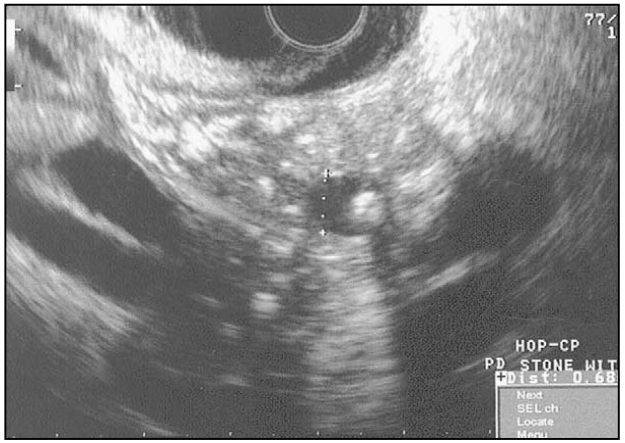
Picture in EUS



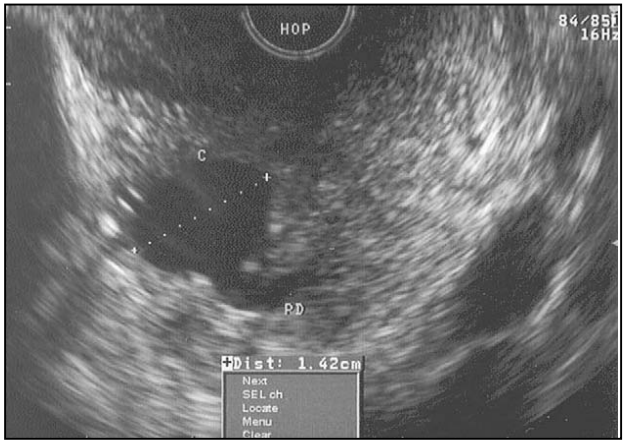
„Honeycombing“



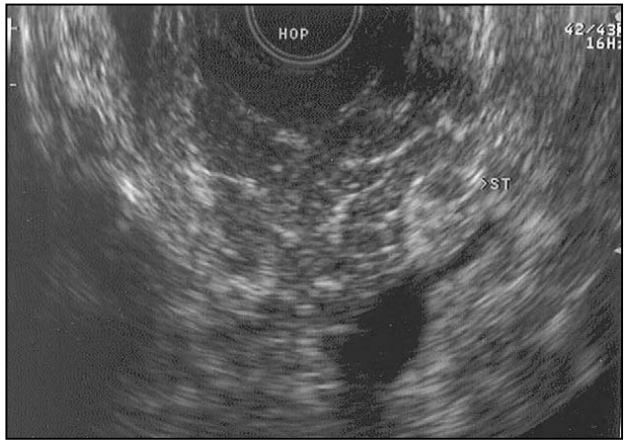
Hyperechogene Foci & Schatten



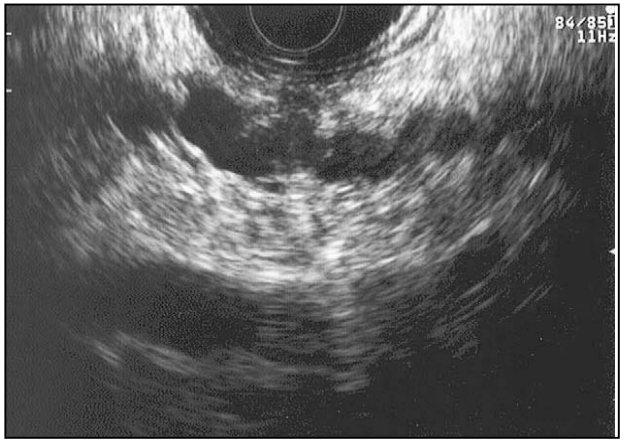
Intraduktale Steine



Zyste



„Stranding“



Dilatierter, unregelmässiger Gang

Catalano et al. Gastrointest Endosc. 2009;69:1251–1261

CH-EUS for pancreatic adenocarcinoma (AC) diagnosis

227 pts. with solid pancreatic lesion
After CT/MR/MRCP and conventional EUS
Diagnosis: surgery (n=92) or negative FNA + 12 months FU

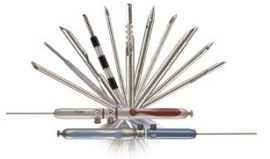
		Sensitivity	Specificity	AUC
All Lesions (n=277)	CH-EUS	95.1% (92.7-96.7%)	89.0% (83.0-93.1%)	0.91
	MDCT	91.7% (88.9-93.7%)	84.2% (76.9-89.7%)	0.88
Lesions < 2cm (n=67)	**CH-EUS**	**91.2%** (82.5%-95.1%)	**94.4%** (86.2-98.1%)	**0.93**
	MDCT	70.6% (60.3-76.1%)	91.9% (86.2%-98.4%)	0.81

p<0.03

Kitano et al. AJG 2012

MDCT= multidetector-row computed tomograph

Problems in Differentiation CP and carcinoma



	No pts./ With CP	Sensitivity Without CP %	Sensitivity With CP %	P-Value
Fritsch [illegible]	200/ 74	89.3%	**53.5%**	-
[illegible] 2005	300/75	91.3%	**73.9%**	0.02

Diagnostic accuracy < 75%

Significantly lower sensitivity of EUS-FNA in CP due to:

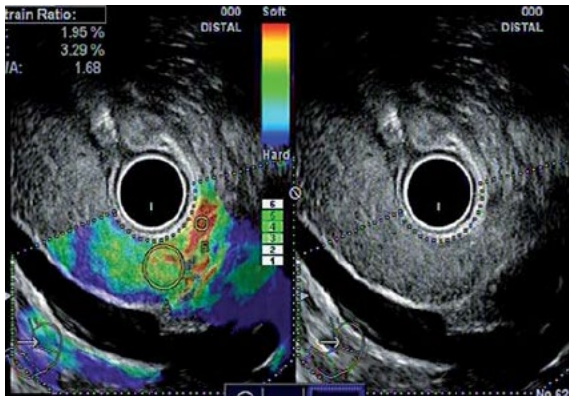
- ✓ Calcified stones can reduce the quality
- ✓ desmoplastic stroma traps cancer cells, yielding only a scant aspirate.
- ✓ Collaterals make FNA challenging: considering expert-recommendation of «funnel-technique» and > 7 passes/per puncture
- ✓ Occasional atypical cells can mimic malignancy
- ✓ *Well-differentiated Ca* overlooked: lack hyperchromasia; modest increase N/C-ratio

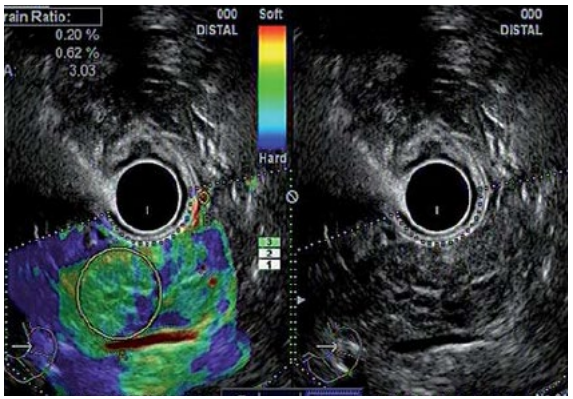
Diagnostik - Elastographie

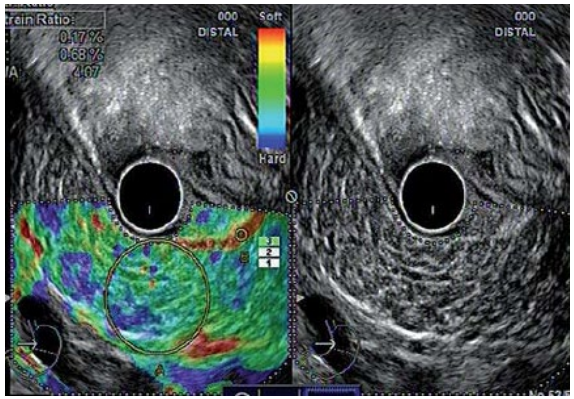
Normales Pankreas

Strands, irregulärer Hauptgang und dilatierte Seitenäste → suggestiv für CP

Hyperechogene Foci, honeycombing, dilatierter Hauptgang → vereinbar mit CP







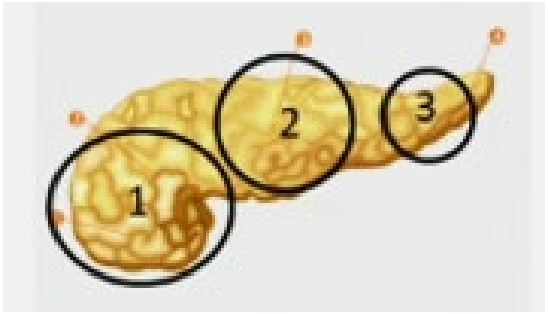


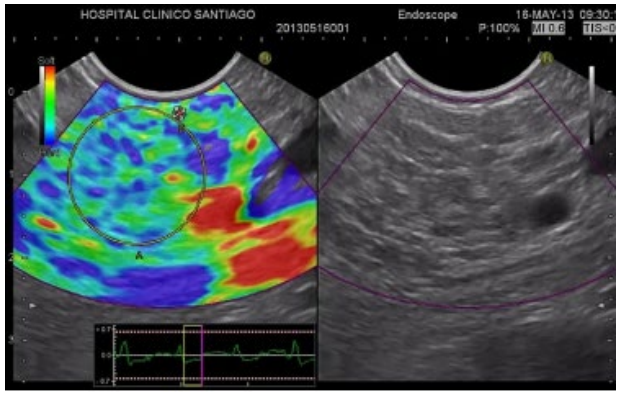
Table 3 Accuracy of quantitative elastography for the diagnosis of chronic pancreatitis. A strain ratio of 2.25 was used as the cut-off value.

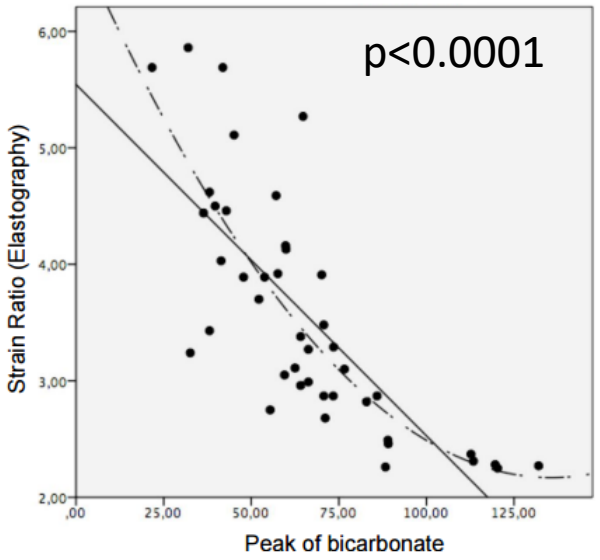
	Accuracy, % [95%CI]
Sensitivity	91.2 [84.8 – 97.6]
Specificity	91.0 [84.9 – 97.1]
Positive predictive value	90.2 [83.6 – 96.8]
Negative predictive value	91.9 [86.1 – 97.8]
Overall accuracy	91.1 [86.8 – 95.4]

Iglesias-Garcia J. et al. Endoscopy 2013; 45: 781-788

EUS - Elastography

- Prospective study with 43 Patienten, suspected CP with 3-4 EUS-Features
- EUS + Elastography an Sekretin-Stimulationtest
- Signifikant correlation of Pankreatic fibrosis (Elastography) and stimulated pankreatic bicarbonat secretion

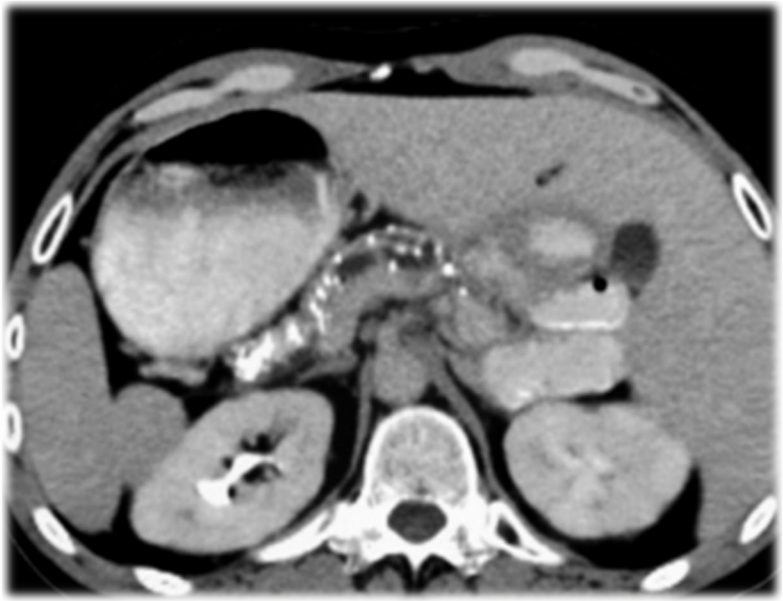


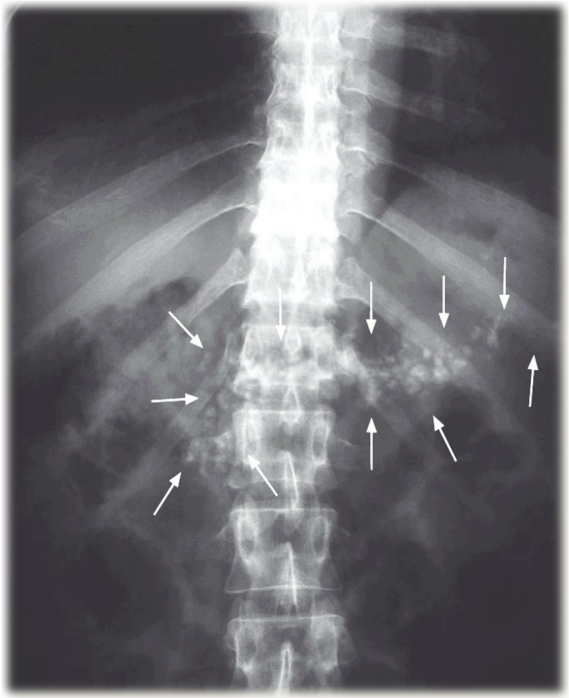


Iglesias-Garcia J. et al. UEGW 2016

CT

- Sensitivity 75-90%, specificity ca. 85%
- Other reason for pain, complications
- Not high sensitivity in early stages





Y. Issa Eur Radiol 2017; 27:3820-3844
Conwell et al, Pancreas, Vol 43, No 8, Nov. 2014
Manser CN et al. Schweiz Med Forum 2014;14(31–32):570–577
S3-Leitlinie Chronische Pankreatitis; Z Gastroenterol 2012; 50(11): 1176-1224

MRI/MRCP

- High sensitivity (78-88%) and specificity (96%), in eraly stages too
- Duct irregularity: dilatation, strictures, stones
- Parenchymal irregularity
  - Often before irregularity of the duct
  - Subtile reduces signal intensity, longer T1-relaxation time (fett-supprimierte T1-gewichtete Bilder)
  - Later and fewer absorption of Gadolinium
- No intervention

S3-Leitlinie Chronische Pankreatitis; Z Gastroenterol 2012; 50(11): 1176-1224
Conwell et al, Pancreas, Vol 43, No 8, Nov. 2014
Manser CN et al. Schweiz Med Forum 2014;14(31–32):570–577
Y. Issa Eur Radiol 2017; 27:3820-3844
Tirkes T et al, J Magn Reson Imaging. 2017 April; 45 (4): 1171-1176

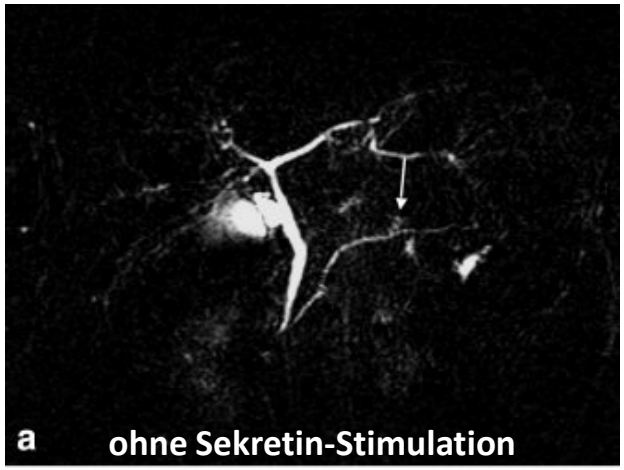
MRCP with Sekretin stimulation

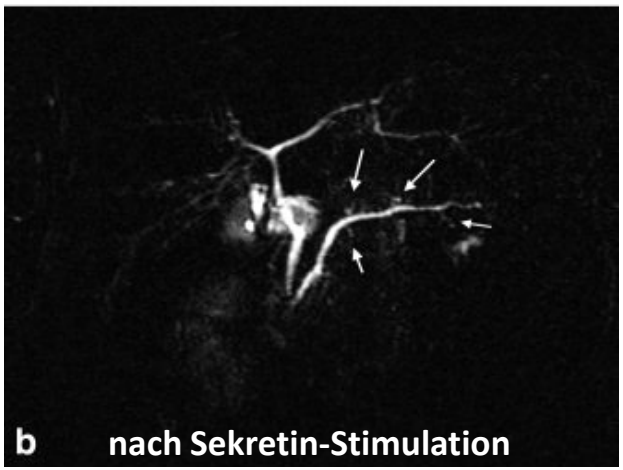
Sekretin leads to production of pancreatic Bicarbonat

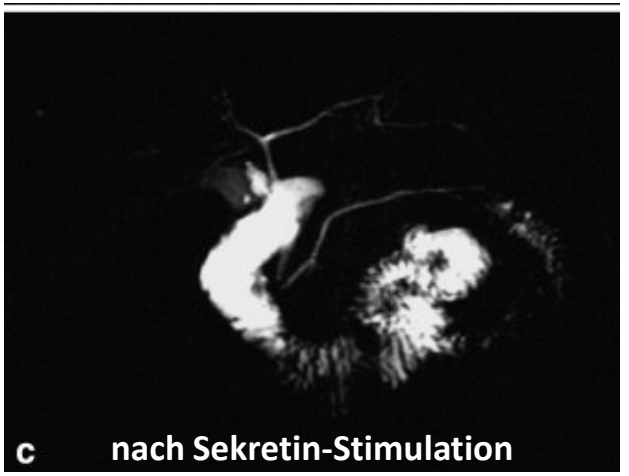
→ Better visualisation of the duct than MRCP (dilatation, strictures, communication with cyst)

→ Sensitivity 92% and specificity 75% even in erarly stage CP

→ Detection of exocrine insufficiency (Sensitivität 77%, Spezifität 83%)





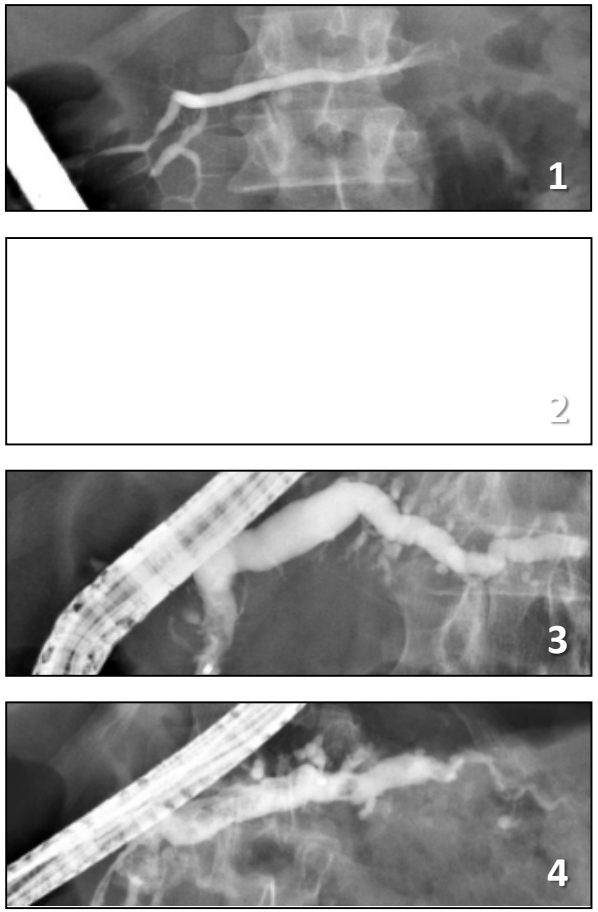


Sanyal; AJR Am J Roentgenol 2012;198:124– 132
Tirkes T et al. Abdom Radiol; 2017

MRCP vs. ERCP

	Sens.	Spez.	PPV	NPV
MRCP	88%	94%	93%	90%
ERCP	90%	91%	90%	91%

ERCP not for diagnostic reasons

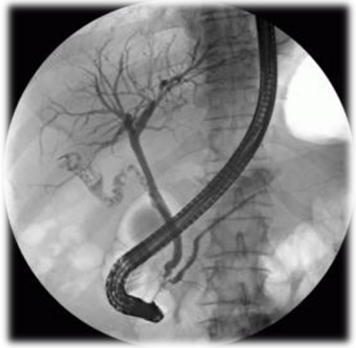


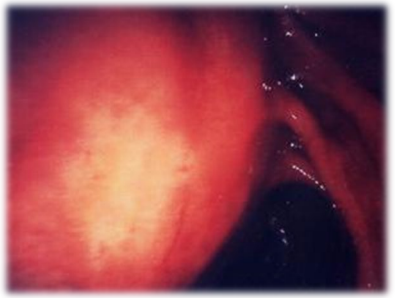
Conwell DL et al. Pancreas. 2014 Nov;43(8):1143-62
Adamek HE et al. Lancet 2000;356:190-193

Table of content

Therapy

- Encyme replacement
- Pain
- ESWL/ERCP
- Pseudocysts
- Coeliac infiltration





Encyme replacement

- Indication
  - Clinical (weightloss, high stoolfrequency, steatorrhea)
  - Malabsorption (Albumin, Zink, Ferritin, fettlösliche Vitamine)
  - Pain, not a good indication
- Treatment:
  - 25‘000 – 80‘000 to meal
  - 12‘500 – 40‘000 with snack
  - If no clinical response increase (not > 10`000 - 20`000 /kg KG); **add PPI**
- Control of therapy clinical:
  - Weight, vitamins, diarrhea
- In doubts
  - Measure fat in stool
  - 13C-Breath test

S3-Leitlinie Chronische Pankreatitis; Z Gastroenterol 2012; 50(11): 1176-1224
Manser CN et al. Schweiz Med Forum 2014;14(31–32):570–577

Pain

Pharmacological-conservative:
WHO-3-step-ladder:
Paracetamol/Novalgin/NSAR → low-> high potent long-acting opiate

tricyclic antidepressants or gabapentin

ERCP

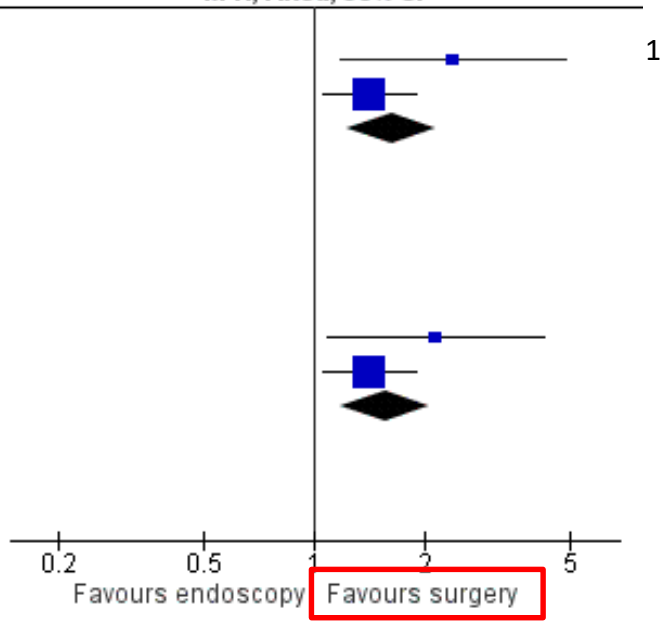
EUS guided panreaticogastrostomy

coeliac plexus blockade (passage effective)
ESWL, thorakoscop. Splanchiectomy.....

Dite P et al. Endoscopy 2003; Cahen DL et al. N Engl J Med 2007 + Gastroenterology 2011; Cochrane 2015

Pain
Endoscopy vs. Surgery

Study or Subgroup	Surgery Events	Surgery Total	Endoscopy Events	Endoscopy Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Middle/long-term follow-up (2 to 5 years)						
Cahen 2007	15	20	6	19	21.9%	2.38 [1.17, 4.82]
Díte 2003	31	36	22	36	78.1%	1.41 [1.05, 1.89]
Subtotal (95% CI)		**56**		**55**	**100.0%**	**1.62 [1.22, 2.15]**
Total events	46		28			
Heterogeneity: Chi² = 2.00, df = 1 (P = 0.16); I² = 50%						
Test for overall effect: Z = 3.34 (P = 0.0008)						
1.1.2 Long-term follow-up (≥ 5 years)						
Cahen 2007	12	15	6	16	20.9%	2.13 [1.08, 4.22]
Díte 2003	31	36	22	36	79.1%	1.41 [1.05, 1.89]
Subtotal (95% CI)		**51**		**52**	**100.0%**	**1.56 [1.18, 2.05]**
Total events	43		28			
Heterogeneity: Chi² = 1.28, df = 1 (P = 0.26); I² = 22%						
Test for overall effect: Z = 3.17 (P = 0.002)						
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.85), I² = 0%						



1

N=222

[1]Ahmed AU et al. Cochrane Database Syst Rev. 2015 Mar 19;(3):CD007884
[2]A.M. Drewes et al, Pancreatology 2017
[3]Dumonceau et al., ESGE Clin Guideline, Endoscopy. 2012 Aug;44(8):784-800

Pain
Endoscopy vs. Surgery

- No difference in morbidity and mortality (not enough power) [1]
- No difference in endocrine and exocrine insufficiency
- Surgery better in painful obstructive CP especially in[2]:
  - Early after first symptoms (2-3y)
  - after ≤ 5 endoscopic interventions
  - Without opiate
- ESGE: Endoscopy first-line therapy, if persistent pain after 6-8 week, discuss interdisciplinary[3]

[1]Ahmed AU et al. Cochrane Database Syst Rev. 2015 Mar 19;(3):CD007884
[2]A.M. Drewes et al, Pancreatology 2017
[3]Dumonceau et al., ESGE Clin Guideline, Endoscopy. 2012 Aug;44(8):784-800

Pain
Endoscopy vs. Surgery

Table 3 Selected series of treatment with plastic stents for main pancreatic duct (MPD) strictures in chronic pancreatitis.

First author, year	n	Stent sizes, Fr	Follow-up, months	Early pain relief, %	Sustained pain relief, %	Patients undergoing operation, %
Cremer, 1991 [58]	75	10	37	94	n.a.	15
Ponchon, 1995 [59]	23	10	14	74	52	15
Smits, 1995 [60]	49	10	34	82	82	6
Binmoeller, 1995 [68]	93	5–7–10	58	74	65	26
Morgan, 2003 [69]	25	5–7–8.5	n.a.	65	n.a.	n.a.
Vitale, 2004 [61]	89	5–7–10	43	83	68	12
Eleftheriadis, 2005 [62]	100	8.5–10	69	70	62	4
Ishiara, 2006 [63]	20	10	21	95	90	n.a.
Weber, 2007 [64]	17	7–8.5–10–11.5	24	89	83	n.a.

n.a., not available.

N=491

- After prolonged MPD stenting (>1 year), relapsing pain was observed in 36–48% of patients after “definitive” stent removal
- re-stenting was indicated in 22–30% of patients
- 4–26% of patients needed pancreatic surgery

ESGE Clin Guideline, Endoscopy. 2012 Aug;44(8):784-800

Strictures/Stones Endoscopy vs. Surgery

Pain is often caused by dilated main duct, caused by strictures (47%) or stones (18%) or both (32%)

Table 2 Long-term outcome after endoscopic treatment of chronic pancreatitis.

First author, year	n	Follow-up, months	Surgery	Ongoing endoscopic treatment	No further intervention
Binmoeller, 1995 [68]	93	58	26%	13%	61%
Rösch, 2002 [1]	1018	58	24%	16%	60%
Delhaye, 2004 [36]	56	173	21%	18%	61%
Tadenuma, 2005 [38]	70	75	1%	20%	79%
Inui, 2005 [45]	555	44	4%	–	–
Farnbacher, 2006 [37]	98	46	23%	18%	59%

- N= 1890 patients with chronic pancreatitis; only 17% did need pancreatic surgery
- Factors associated with long-term (≥2 years) pain relief after endoscopic therapy
  - obstructive calcifications in the head
  - short duration and low frequency of pain attacks before therapy
  - complete MPD stone clearance
- Maybe only sphincterotomy

ESGE-Guidelines Endoscopy 20112

Stones

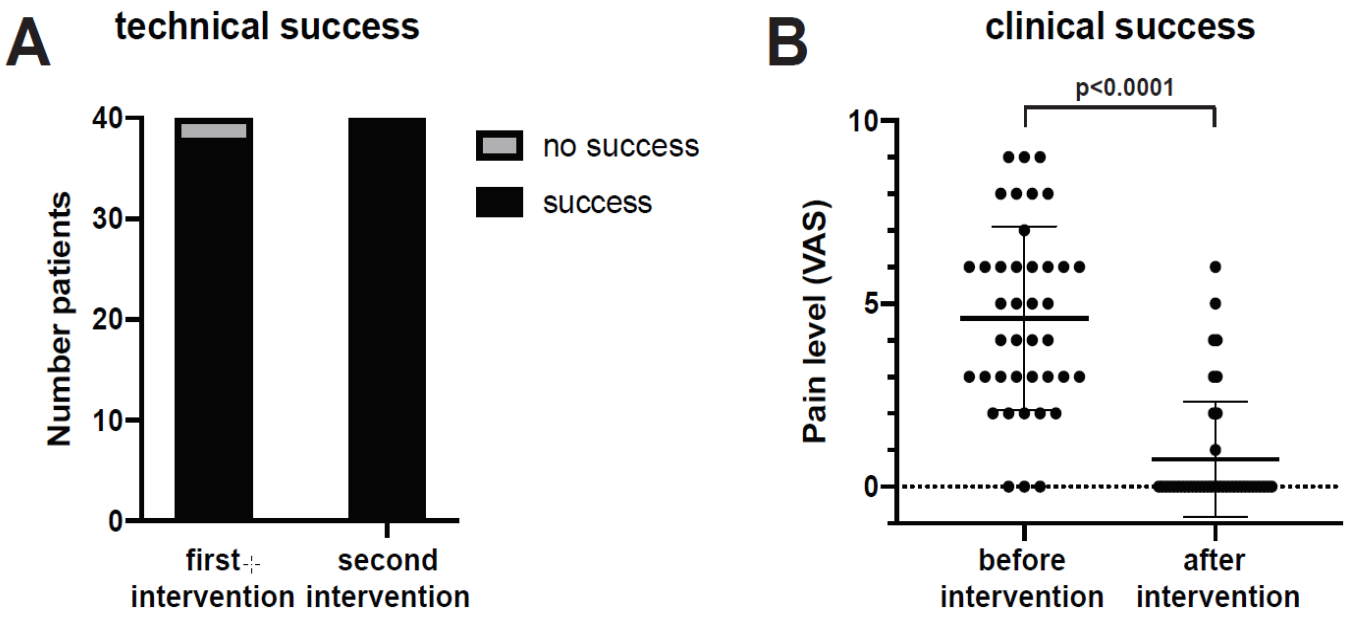
Stone main duct: (in 18% the reason of MPD obstruction, 32% + stricture)

- ESWL (specially stone≥5mm) [1,2]
  - Stone fragmented in 89-93%
  - Spontaneous elimination in 70-88%
  - Painfree in 50-80%, better Qol 88%[2], reduction of narcotica in 80%
  - No therapy of the stricture
- ERCP especially for smaller stones (<5mm)
  - Caput often difficult.
- Transcastric ERCP mit intraductal EHL

[1]A.M. Drewes et al, Pancreatology 2017
[2]Moole et al, Pancreas 2016
Dumonceau et al., ESGE Clin Guideline, Endoscopy. 2012 Aug;44(8):784-800

Transgastric ERCP

- Treatment strictures and stones, if transpapillary way is difficult

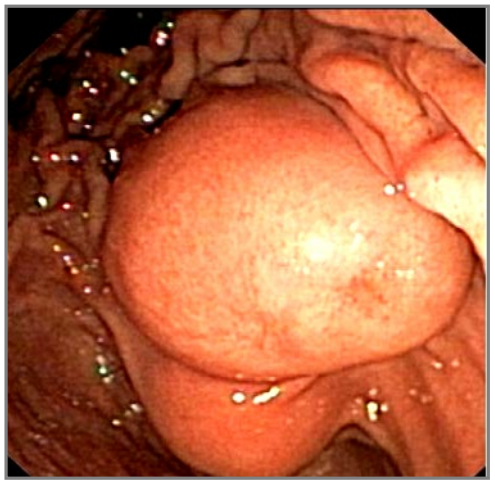


Transgastric ERCP

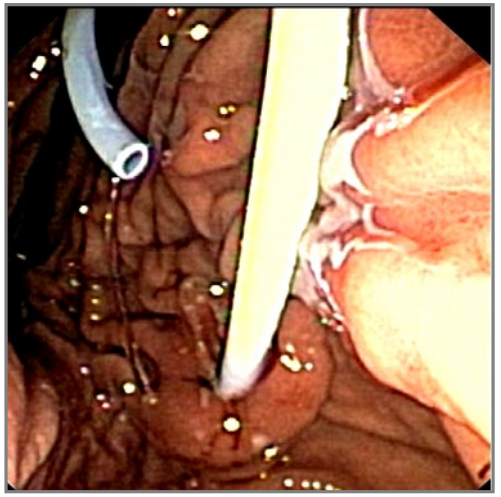
Table 5: Summary of clinical studies utilizing EUS-PD for treatment of chronic pancreatitis

Authors	Year of publication	Number patients	Technical success	Clinical success	Adverse events excluding pain and stent dislocation	Adverse events including pain	Stent dysfunction / dislocation
This study (results after first intervention)	2020	40	95.0%	76.3%	17.5%	30.0%	5.0%
Hayat et al. [19]	2020	8	88.0%	62.5%	12.0%	NA	12%
Dalal et al. [17] [1]	2020	18	77.8%	72.0%	33.0%	NA	NA
Honjo et al. [20]	2018	15	87.0%	NA	6.6%	21.0%	NA
Matsunami et al. [21]	2018	30	100.0%	100.0%	6.6%	23.0%	20.0%
Uchida et al. [25] [2]	2018	15	86.7%	80.0%	13.3%	NA	26.5%
Tyberg et al. [24]	2017	80	89.0%	81.0%	26.3%	31.3%	NA
Chen et al. [16] [3]	2017	40	92.5%	88.5%	7.5%	40.0%	NA
Oh et al [22] [4]	2016	25	100.0%	100.0%	4.0%	20.0%	0.0%
Will et al. [26] [5]	2014	74	59.0%	78.0%	20.0%	NA	NA
Fujii et al. [27]	2013	45	74.0%	83.0%	6.6%	35.5%	17.7%
Ergun et al. [18]	2011	20	90.0%	72.0%	10.0%	NA	50.0%
Tessier et al. [23][6]	2007	36	72.0%	69.0%	13.8%	NA	55.0%
Summary of previous literature [7]		432	81.3%	80.8%	15.0%	30.6%	27.2%

Therapy of pseudocysts



- Incidence
  - 20-40% of all patients with CP
- Clinic / Complications:
  - Pain, outflow obstruction
  - Biliary obstruction (10%)
  - Vasculary obsttruction, pleural-/pericardial fistula, abscess (10%)
  - Free perforation (< 3%)
  - Pseudoaneurysma (10%)
- Management:
  - 50% spontanous resolution over time (v.a. < 4 cm)
    - no treatment if asymptomatic
  - Ggf. EUS-guided drainage
    - Complications: Bleeding 4%, infection 4%, retroperitoneal leckage 4%, mortality 0.3%

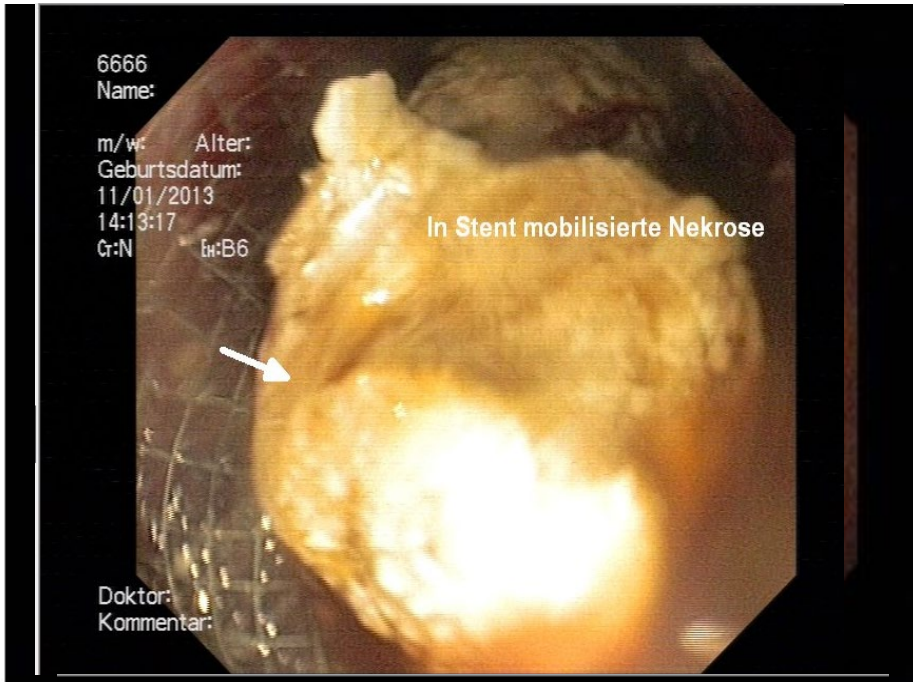


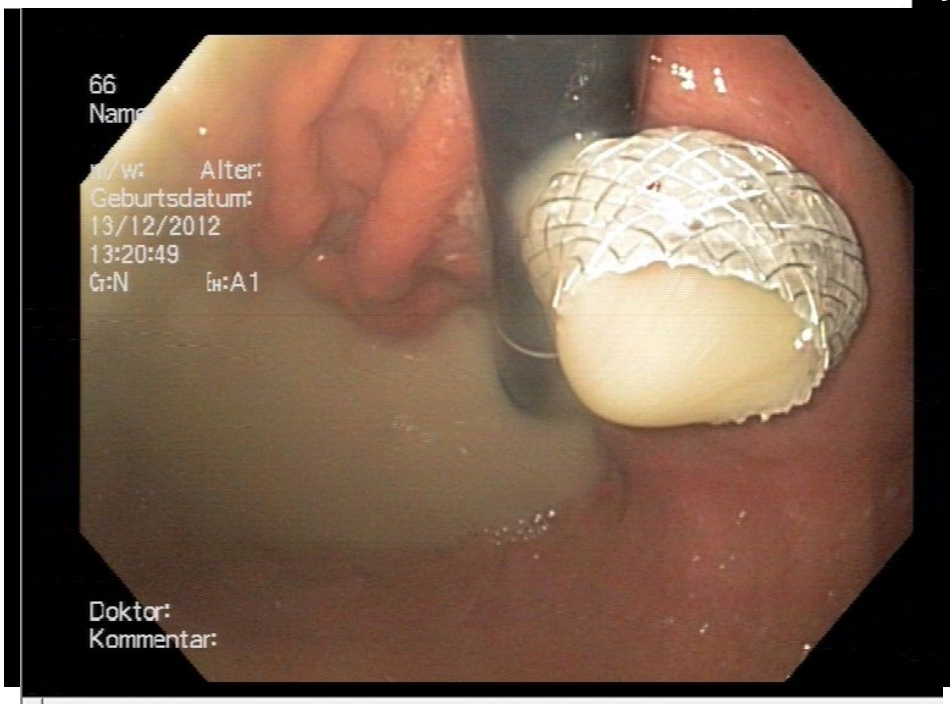
Dumonceau et al., ESGE Clin Guideline, Endoscopy. 2012 Aug;44(8):784-800
Lew et al, Dig dis Sci 2017 July 12

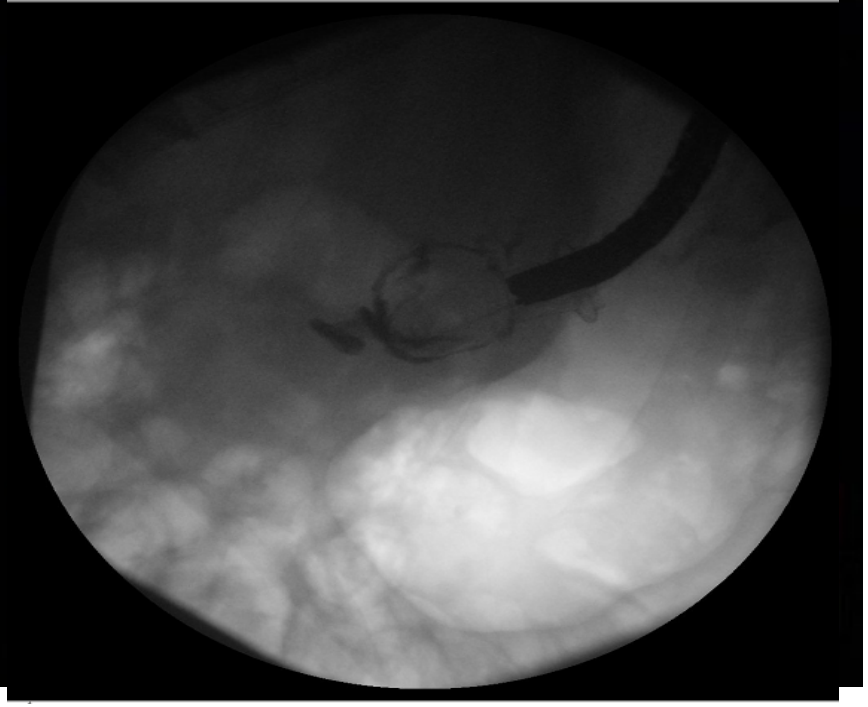
EUS method of choice

2 RCTs equal/superior vs. surgery

Bakker OJ et al. JAMA 2012
Varadarajulu et al. Gastroenterology 2013







Coeliac plexus block

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kawamata 1996	2.8	0.5	7	3.2	0.4	7	19.4%	-0.40 [-0.87, 0.07]
Lillemoe 1993	2.4	0.3	65	3.4	0.4	72	24.2%	-1.00 [-1.12, -0.88]
Mercadante 1993	3	0.2	4	3.66	0.17	3	22.6%	-0.66 [-0.93, -0.39]
Wong 2004	1.6	1.5	36	1.8	1.7	32	14.4%	-0.20 [-0.97, 0.57]
Zhang 2008	3.4	1	29	3.1	0.8	27	19.4%	0.30 [-0.17, 0.77]
Total (95% CI)			**141**			**141**	**100.0%**	**-0.44 [-0.89, 0.01]**

Heterogeneity: Tau² = 0.22; Chi² = 37.03, df = 4 (P < 0.00001); I² = 89%
Test for overall effect: Z = 1.90 (P = 0.06)

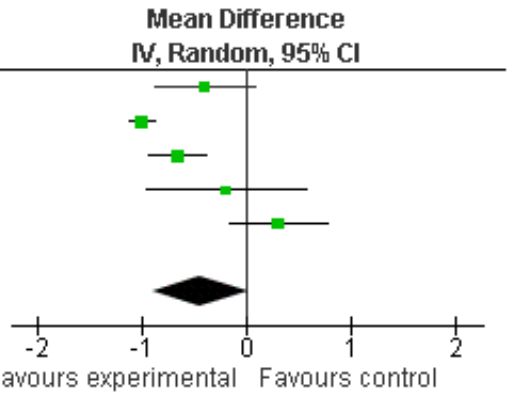


Figure 4. Forest plot of comparison: 1 CPB versus analgesic therapy, outcome: 1.2 Pain VAS at 8 weeks.

- EUS guided plexus block: low complication rate (cave: infections)
- Half of the patient have good effect but only for some weeks (usually <24W)
- ESGE: second-line Therapy

Arcidiacono PG et al. Cochrane Database Syst Rev. 2011 Mar 16;(3):CD007519
Kaufman Met al. J Clin Gastroenterol 2010;44:127-34
Dumonceau et al., ESGE Clin Guideline, Endoscopy. 2012 Aug;44(8):784-800


The End