Ordine dei Medici Chirurghi e degli Odontoiatri della provincia di **Belluno**

FNOMCeO
Federazione Nazionale degli Ordini dei Medici Chirurghi e degli Odontoiatri

LA SORVEGLIANZA DELLE CONDIZIONI E DELLE LESIONI PRECANCEROSE IN GASTROENTEROLOGIA

La Pancreatite Cronica

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UNIVERSITÀ DEGLI STUDI DI VERONA

Pancreatite Cronica

Gestione Multidisciplinare di una patologia complessa

Inquadramento diagnostico
- Fattori di Rischio
- Clinica
- Radiologia

Trattamento del dolore
- Terapia Medica
- Terapia Endoscopica
- Terapia Chirurgica

Gestione dell'IPE / DM

Gestione Nutrizionale

Prognosi/ Gestione complicanze

Pancreatite Cronica

Approccio di un gastroenterologo

- ✓ Storia clinica (FR/eziologia)
- ✓ Valutazione dolore (ricorrenza, intensità, ecc)
- ✓ Altri sintomi associati: Ittero, calo ponderale, ecc
- ✓ Valutazione segni di malassorbimento / diabete
- ✓ Valutazione imaging (TC, RMN, EUS, ecc) – escludere k !
- ✓ Terapia specifica (medica/nutrizionale, endoscopica, chirurgica)
- ✓ Monitoraggio (rischio neoplastico, complicanze)

Chronic pancreatitis: An international draft consensus proposal for a new mechanistic definition

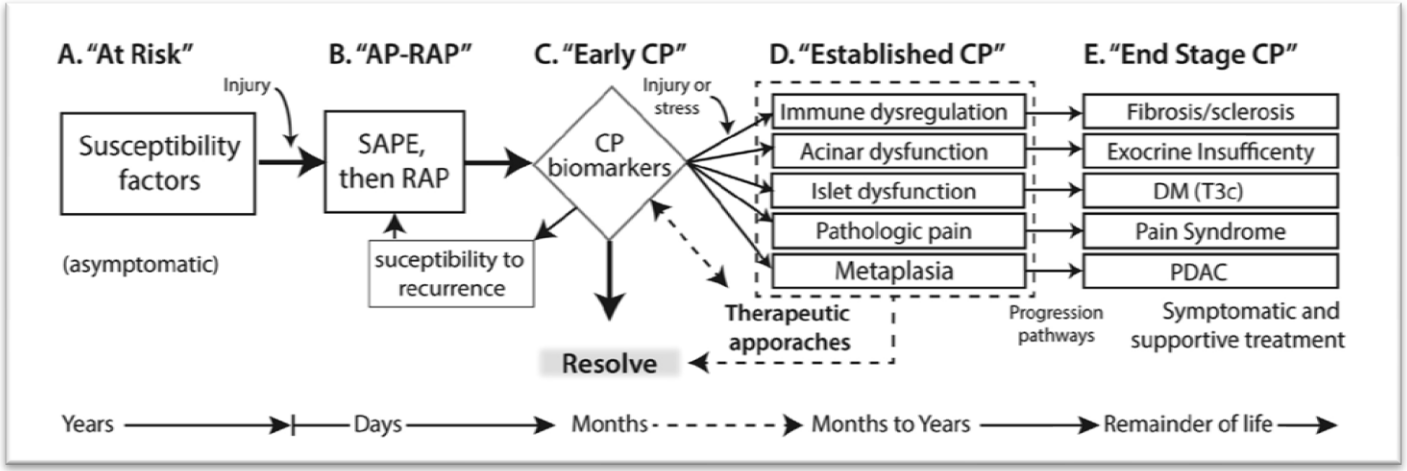
David C. Whitcomb [a, b, c, *], Luca Frulloni [d], Pramod Garg [e], Julia B. Greer [a], Alexander Schneider [f], Dhiraj Yadav [a], Tooru Shimosegawa [g]

"Chronic pancreatitis is a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress."

Annual ***incidence***: 5-8 cases/100.000 ***prevalence***: 42-73 cases/100.000 adults in the United States.

Yadav D et al. *AmJ Gastroenterol*. 2011;

Machicado JD et al. *Pancreatology*. 2019;
Yadav D et al. *Pancreatology*. 2011;



Pancreatology,2016 Mar-Apr; 16(2):218-24

Pancreatite Cronica

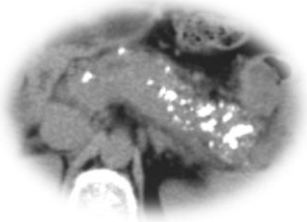
Evoluzione

- Se la causa persiste
- In presenza di fattori di rischio
(alcol, fumo, geni, necrosi)

Acuta

20-35%[1,2]

Ricorrente



20-25%[1]

Cronica

Riscontro Occasionale / Asintomatico

10 % ?

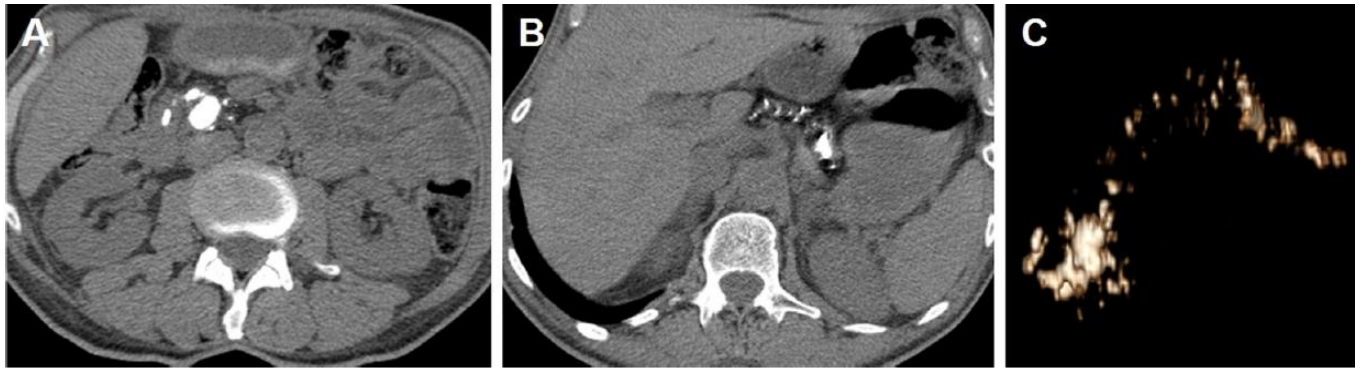
[1] *Am J Gastroenterol,* 2009; **104**: 2796-2805
[2] *Scand J Gastroenterol*, 2006; **41**: 234-238

Painless chronic pancreatitis

Antonio Amodio[a], Giulia De Marchi[a,*], Nicolò de Pretis[a], Stefano Francesco Crinò[a], Mirko D'Onofrio[b], Armando Gabbrielli[a], Rachele Ciccocioppo[a], Luca Frulloni[a]

Main characteristic of the study population.

N.	74
Sex, males, n (%)	50 (67.6)
Age at diagnosis, mean (range), y	60.8 (30-91)
Drinkers, g alcohol/day, n (%)	
0	48 (64)
1-40	17 (23)
41-80	4 (5)
81+	5 (7)
Smokers, cigarettes/day, n (%)	
0	29 (39)
1-10	19 (26)
11-20	22 (30)
21+	4 (5)
Body Mass Index, mean (range)	24.5 (19.2-32.8)
Familiarity for pancreatic diseases, n (%)	7 (10)
Previous cholecystectomy, n (%)	7 (10)



Symptoms reported by patients that led to diagnosis of painless CP.

Symptom	N (%)
New onset diabetes	15 (20)
Steatorrhea	14 (19)
Weight loss	12 (16)
Others*	7 (10)
More than 1	14 (19)
None	38 (51)

* jaundice, vomiting, nausea, asthenia, constipation, diarrhea.

Digestive and Liver Disease 52 (2020) 1333–1337

Pancreatitis: TIGAR-O Version 2 Risk/Etiology Checklist With Topic Reviews, Updates, and Use Primers

LIST 3. TIGAR-O VERSION 2.0—SHORT FORM (TIGAR-O_V2-SF)

Toxic-metabolic

- Alcohol-related (susceptibility and/or progression)
  - 3-4 drinks/d
  - 5 or more drinks/d
- Smoking (if yes, record pack-years)
  - Non-smoker (<100 cigarettes in lifetime)
  - Past smoker
  - Current smoker
  - Other, NOS
- Hypercalcemia (total calcium levels >12.0 mg/dL or 3 mmol/L)
- Hypertriglyceridemia
  - Hypertriglyceridemic risk (Fasting >300 mg/dL; non-fasting >500 mg/dL)
  - Hypertriglyceridemic acute pancreatitis, history of (>500 mg/dL in first 72 hours)
- Medications (name)
- Toxins, other
  - Chronic kidney disease (CKD)—(CKD Stage 5: end-stage renal disease, ESRD)
  - Other, NOS
- Metabolic, other
  - Diabetes Mellitus (with the date of diagnosis if available)
  - Other, NOS

Idiopathic

- Early onset (<35 years of age)
- Late onset (>35 years of age)

Genetic

- Suspected; No or limited genotyping available
- Autosomal dominant (Mendelian inheritance—single gene syndrome)
  - *PRSS1* mutations (Hereditary pancreatitis)
- Autosomal recessive (Mendelian inheritance—single gene syndrome)
  - *CFTR*, 2 severe variants in *trans* (cystic fibrosis)
  - *CFTR*, <2 severe variants in *trans* (CFTR-RD)
  - *SPINK1*, 2 pathogenic variants in *trans*. (SPINK1-associated familial pancreatitis)
- Complex genetics—(non-Mendelian, complex genotypes +/− environment)
- Modifier Genes (list pathogenic genetic variants)
  - *PRSS1*-PRSS1 locus
  - *CLDN2* locus
  - Others:
- Hypertriglyceridemia (list pathogenic genetic variants)
  - Other, NOS

Autoimmune pancreatitis (AIP)/Steroid responsive pancreatitis

- AIP Type 1—IgG4-related disease
- AIP Type 2

Recurrent acute pancreatitis (RAP) and severe acute pancreatitis (SAP)

- Acute pancreatitis (single episode, including date of event if available)
- AP Etiology—Extra-pancreatic (excluding alcoholic, HTG, hypercalcemia, genetic)
  - Biliary pancreatitis
  - Post-ERCP
  - Traumatic
  - Undetermined or NOS
- Recurrent acute pancreatitis (number of episodes, frequency, and dates of events if available)

Obstructive

- Pancreas divisum
- Ampullary stenosis
- Main duct pancreatic stones
- Widespread pancreatic calcifications
- Main pancreatic duct strictures
- Localized mass causing duct obstruction

TIGAR-O Version 2 risk/etiology classification–Short form—As additional information is received, the patient's list should be transitioned to the longer form.

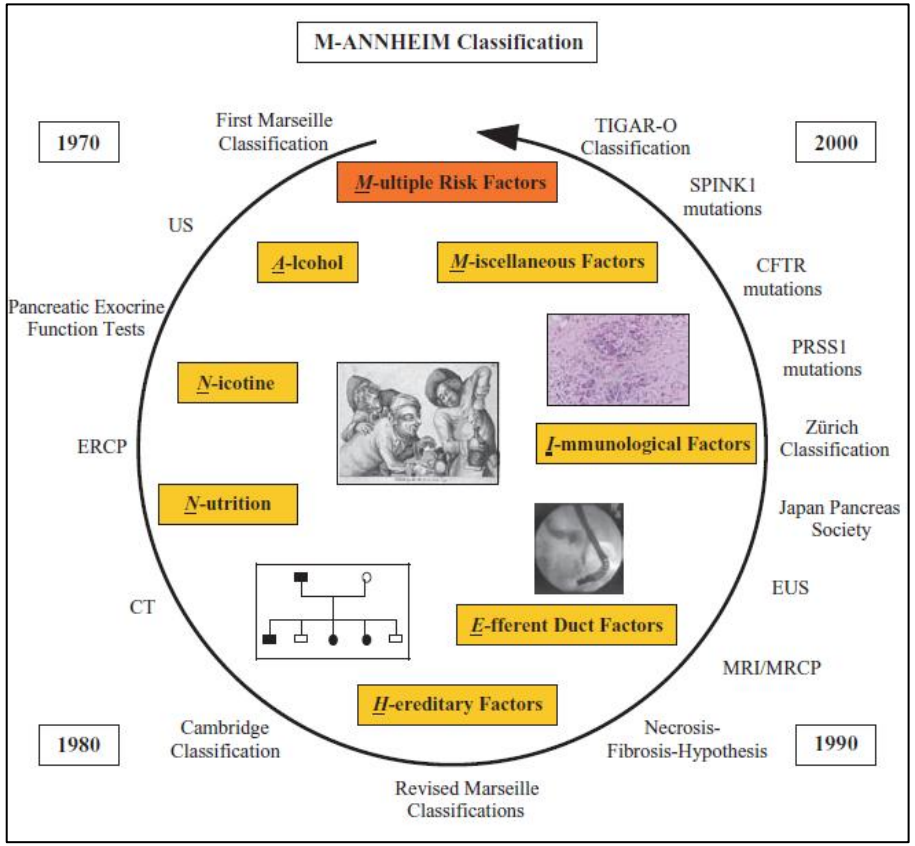
Whitcomb et al. Clinical and Translational Gastroenterology 2019;10:e-00027

The M-ANNHEIM classification of chronic pancreatitis: introduction of a unifying classification system based on a review of previous classifications of the disease

ALEXANDER SCHNEIDER, J. MATTHIAS LÖHR, and MANFRED V. SINGER

Table 2. The M-ANNHEIM multiple risk factor classification of chronic pancreatitis

	M Pancreatitis with Multiple risk factors
A	Alcohol consumption
	Excessive consumption (>80 g/day)
	Increased consumption (20–80 g/day)
	Moderate consumption (<20 g/day)
N	Nicotine consumption
	(In cigarette smokers: description of nicotine consumption by pack-years)
N	Nutritional factors
	Nutrition (e.g., high caloric proportion of fat and protein)
	Hyperlipidemia
H	Hereditary factors[a]
	Hereditary pancreatitis (defined according to Whitcomb[96])
	Familial pancreatitis (defined according to Whitcomb[96])
	Early-onset idiopathic pancreatitis
	Late-onset idiopathic pancreatitis
	Tropical pancreatitis
	(possible mutations in the *PRSS1*, *CFTR*, or *SPINK1* genes)
E	Efferent duct factors
	Pancreas divisum
	Annular pancreas and other congenital abnormalities of the pancreas
	Pancreatic duct obstruction (e.g., tumors)
	Posttraumatic pancreatic duct scars
	Sphincter of Oddi dysfunction
I	Immunological Factors
	Autoimmune pancreatitis
	Sjögren syndrome-associated chronic pancreatitis
	Inflammatory bowel disease-associated chronic pancreatitis
	Chronic pancreatitis with autoimmune diseases
	(e.g., primary sclerosing cholangitis, primary biliary cirrhosis)
M	Miscellaneous and rare metabolic factors
	Hypercalcemia and hyperparathyroidism
	Chronic renal failure
	Drugs
	Toxins



J Gastroenterol 2007; 42:101–119

Pancreatite Cronica

Vari Criteri diagnostici – Stratificazione

Table 5. Cambridge classification of pancreatic morphology in chronic pancreatitis[28–30]

Pancreatic morphology evaluated by ERCP

	Main duct	Abnormal side branches	Additional features
Normal	Normal	None	
Equivocal	Normal	<3	
Mild changes	Normal	≥3	
Moderate changes	Abnormal	>3	
Marked changes	Abnormal	>3	One or more of the following: large cavity, obstruction, filling defects, severe dilatation, or irregularity

Pancreatic morphology evaluated by computed tomography and ultrasound

Normal	Main pancreatic duct <2 mm, normal gland size and shape, homogenous parenchyma
Equivocal	One only of the following signs: Main pancreatic duct enlarged (between 2 and 4 mm), slight gland enlargement (up to 2 x normal), heterogeneous parenchyma, small cavities (<10 mm), irregular ducts, focal acute pancreatitis, increased echogenicity of the main pancreatic duct wall, irregular head / body contour
Mild changes	Two or more of the above listed criteria
Moderate changes	As with mild changes (not differentiated)
Marked changes	As above, with one or more of the following: large cavities (>10 mm), gross gland enlargement (>2× normal), intraductal filling defects or calculi, duct obstruction, structure or gross irregularity, contiguous organ invasion

The Cambridge classification established clear-cut criteria for the description of equivocal, mild, moderate, and severe changes of chronic pancreatitis using the imaging technique of ERCP.[28–30] The Cambridge classification also categorized chronic pancreatitis according to pancreatic imaging findings on CT and abdominal US, similar to the grading of ERCP changes.[28–30] However, the grading according to CT and US did not clearly differentiate between mild and moderate changes

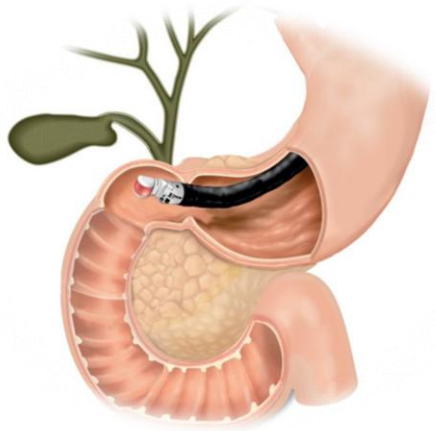


Table 6. Endoscopic ultrasound criteria of chronic pancreatitis[82,84,85,89]

Parenchymal features
- Gland size
- Cysts
- Echo-poor lesions (focal areas of reduced echogenicity)
- Echo-rich lesions (>3 mm in diameter)
- Accentuation of lobular pattern (e.g., echo-poor normal parenchyma surrounded by hyperechoic strands)

Ductal features
- Increased duct wall echogenicity
- Irregularity of the main pancreatic duct (e.g., with narrowing of the duct)
- Dilation of the main pancreatic duct
- Visible side branches (e.g., with dilation)
- Calcification

Table 4. M-ANNHEIM diagnostic criteria of chronic pancreatitis (modified from Ammann[32])

The diagnosis of chronic pancreatitis requires a typical clinical history of chronic pancreatitis (such as recurrent pancreatitis or abdominal pain, except for primary painless pancreatitis)
Based on these features, three forms of chronic pancreatitis

Definite chronic pancreatitis is established by one or more of the following additional criteria:
1. Pancreatic calcifications
2. Moderate or marked ductal lesions (according to the Cambridge classification)
3. Marked and persistent exocrine insufficiency defined as pancreatic steatorrhea markedly reduced by enzyme supplementation
4. Typical histology of an adequate histological specimen

Probable chronic pancreatitis is established by one or more of the following additional criteria:
1. Mild ductal alterations (according to the Cambridge classification)
2. Recurrent or persistent pseudocysts
3. Pathological test of pancreatic exocrine function (such as fecal elastase-1 test, secretin test, secretin–pancreozymin test)
4. Endocrine insufficiency (i.e., abnormal glucose tolerance test)

Borderline chronic pancreatitis is already established and is defined by a typical clinical history of the disease but without any of the additional criteria required for definite or probable chronic pancreatitis. This form is also established as a first episode of acute pancreatitis with or without (1) a family history of pancreatic disease (i.e., other family members with acute pancreatitis or pancreatic cancer) or (2) the presence of M-ANNHEIM risk factors

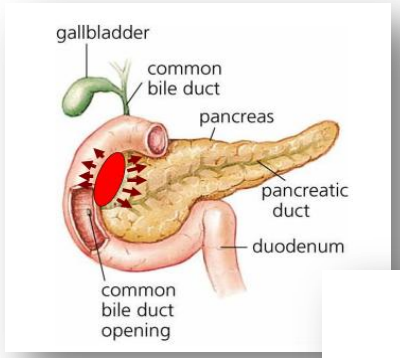
Pancreatite Cronica

CLINICA (Saper capire i sintomi)

TIPICA	ATIPICA	ASINTOMATICO
Dolore pancreatico + ↑ enzimi sierici pancreatici	Ittero Vomito Dolore lieve Diabete/Steatorrea Altro	Reperto occasionale
80 - 90 %		**10 %**

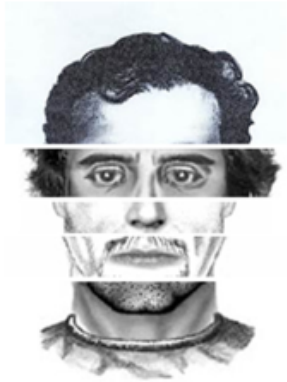
Per saper inquadrare setting specifici !

Pancreatite Paraduodenale

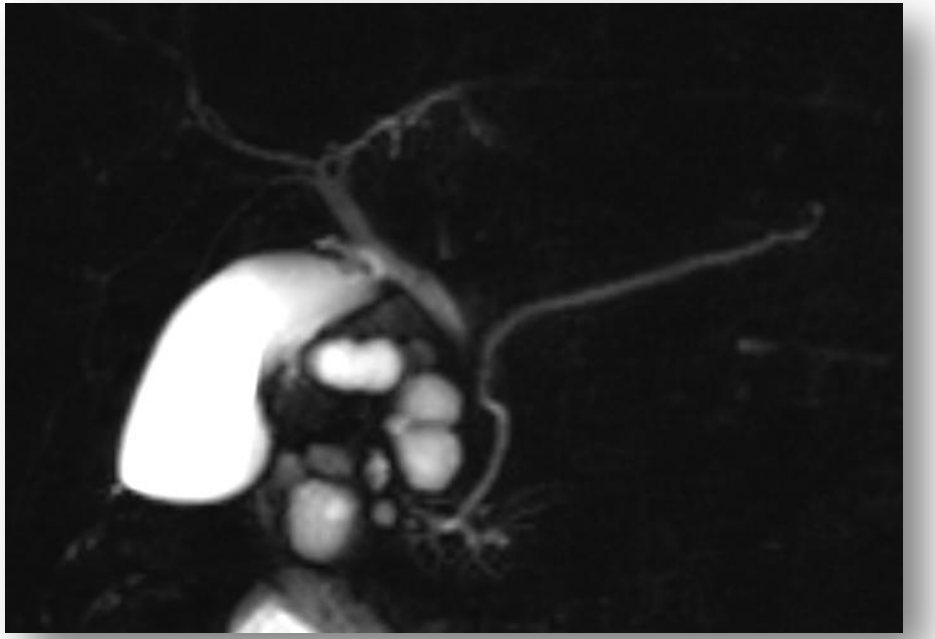


Pancreatite Paraduodenale

Caratteristiche Cliniche

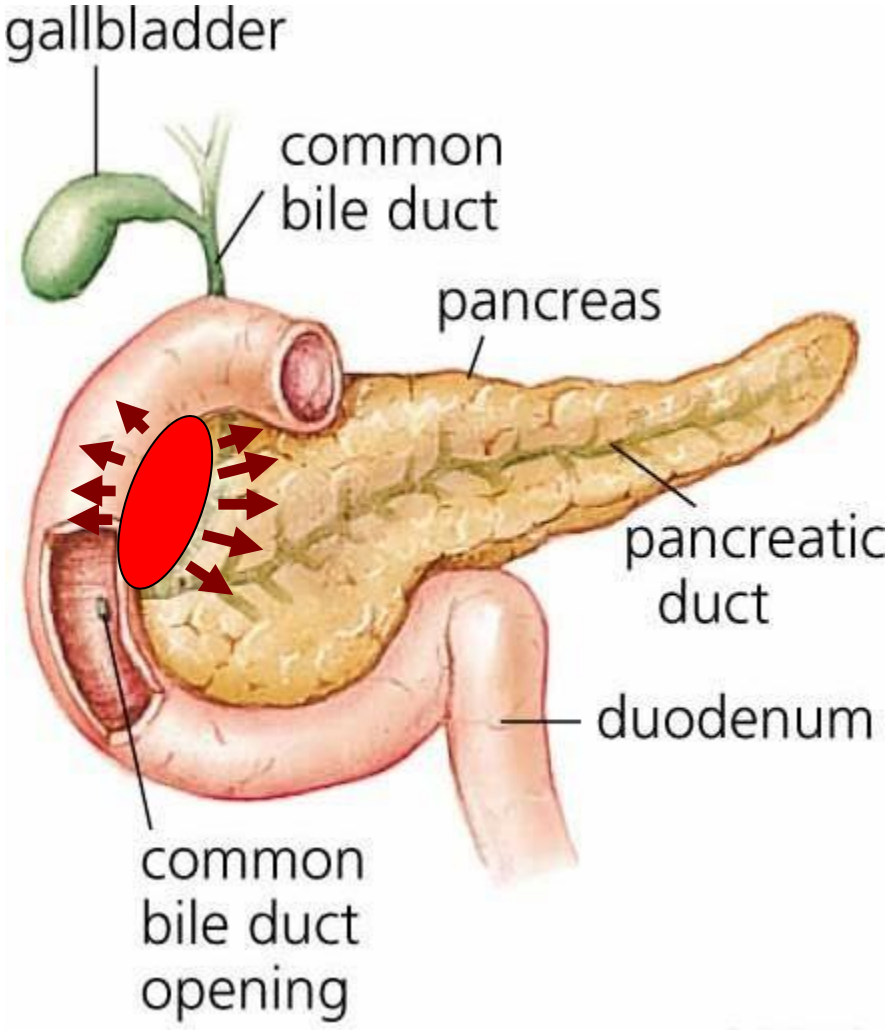


- Maschio
- Forte Bevitore
- Forte Fumatore
- Frequenti episodi dolorosi
- Vomito *(all'esordio)*
- Ittero *(all'esordio)*



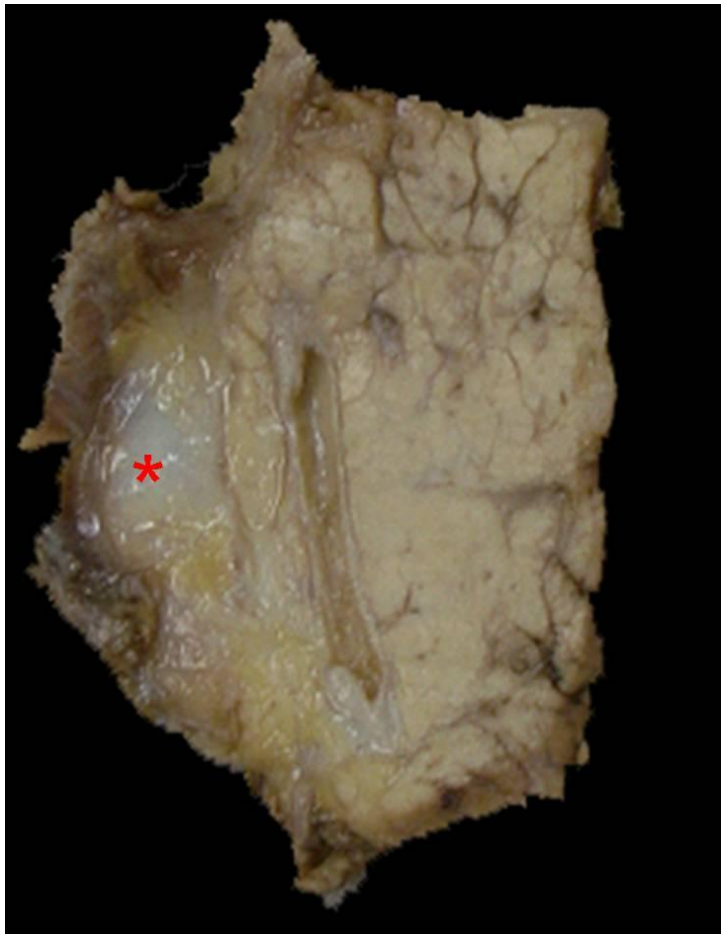
Pancreatite Paraduodenale

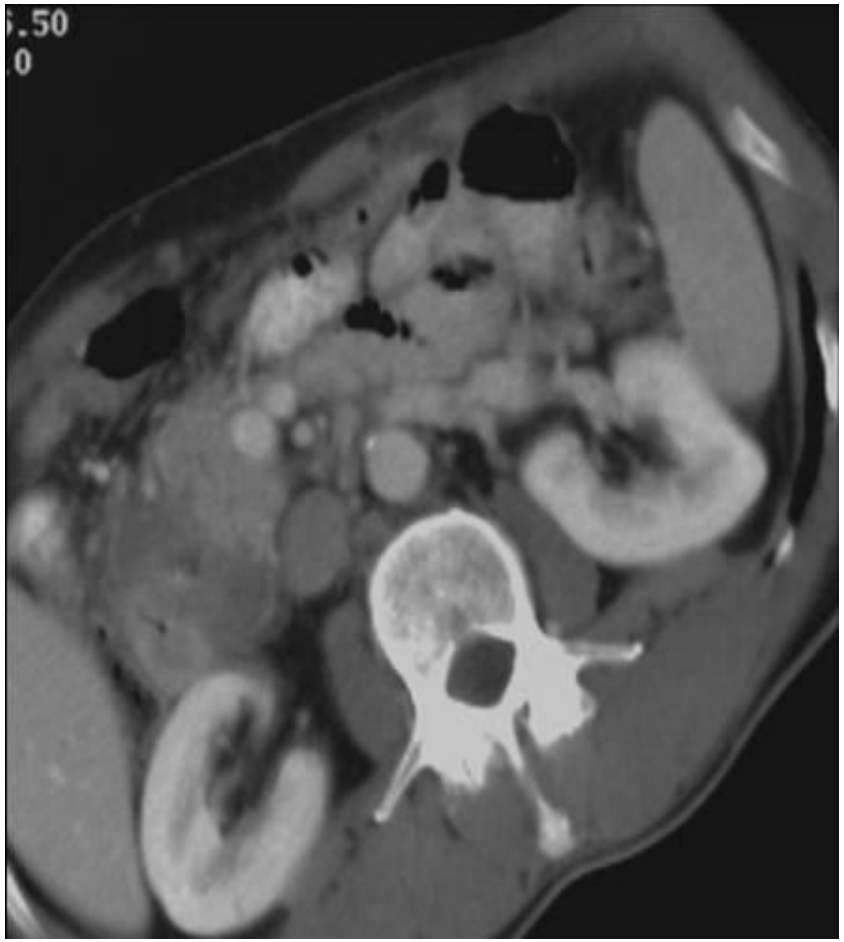
Groove Pancreatitis/ Distrofia Cistica della Parete Duodenale



Pancreatite Paraduodenale

Integrazione Patologia-Imaging





Radiologia, Anatomia Patologica, Verona

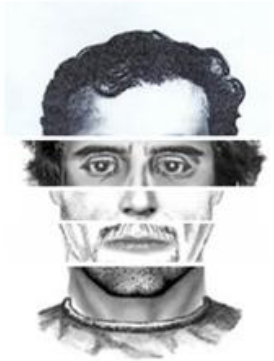
Pancreatite associate a Mutazioni Geniche

Pancreatite Associata a Mutazioni Geniche

- *Cationic Trypsinogen* – **PRSS1**[1]
- Cystic Fibrosis Gene – **CFTR**[2,3]
- *Pancreatic Secretory Trypsin Inhibitor (PSTI)* – **SPINK1**[4]

[1] Withcomb D et al, *Nature Gen*, 1996; **14**:141-145
[2] Sharer N et al, *N Engl J Med*, 1998: **339**; 645-652
[3] Cohn JA et al, *N Engl J Med*, 1998; **339**: 653-658
[4] Witt H et al, *Nature Gen*, 2000; **25**:213-216

Pancreatite Associata a Mutazioni Geniche
Caratteristiche Cliniche



- Familiarità
- Non bevitore
- Non fumatore
- Esordio giovanile *(<30 anni)*
- Numerosi episodi di PA lieve
- Progressione "lenta"
- Elevato rischio di K pancreas
  (> 30 anni di malattia)

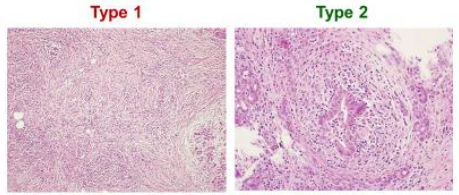
Pancreatite Autoimmune

Pancreatite Autoimmune
Sintomi all'esordio clinico

	Tutti
N. pazienti	207
Calo ponderale	65%
Ittero	47%
Pancreatite	32%
Diabete	13%
Steatorrea	8%

AIP Database of *Verona Pancreas Center*, 2015

Honolulu Consensus
Histological Classification on Surgical Specimens



Histology	Prevalent fibrosis *(storiform)*	Prevalent inflammation
ICH – IgG4	+	–
GEL	–	+
Association	IgG4-related diseases *(biliary, kidney, retroperitoneum, salivary)*	IBD *(ulcerative colitis)*
Relapse(s)	Frequent	Rare
Response to steroids	Yes	Yes

Chari ST et al, *Pancreas*, 2010; **39**: 549-554

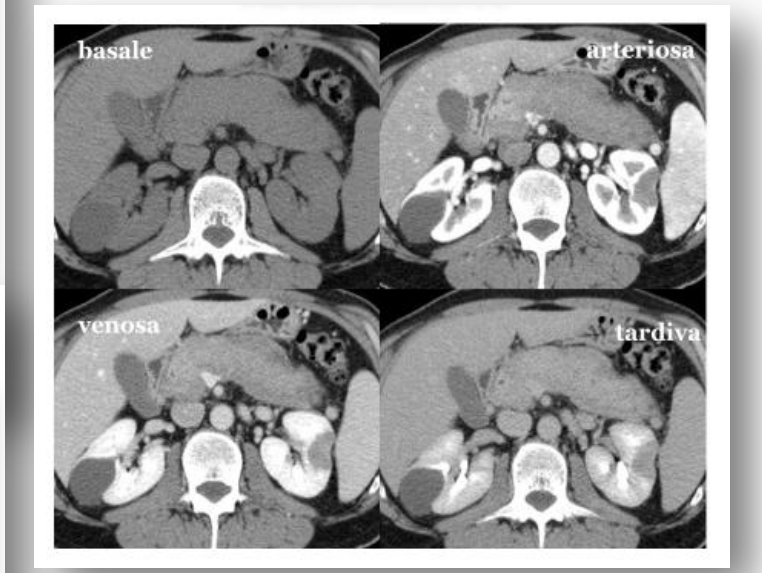
Autoimmune Pancreatitis Type 1
International Consensus Diagnostic Criteria (ICDC)

Criterion	Level 1	Level 2
P *parenchimal imaging*	Diffuse enlargement Delayed enhancement	Segmental/focal enlargement Delayed enhancement
D *ductal imaging*	Single long stenosis of MPD Multiple stenosis of MPD	Segmental/focal narrowing without upstream dilation
S *serology*	sIgG4 > 2x UNL	sIgG4 1-2x UNL
OOI *other organ involvement*	Intrahepatic bile duct stricture(s) Retroperitoneal fibrosis	Salivary/lacrymal glands Kidney
H *histology*	3 criteria	2 criteria
Rt *response to steroids*	Resolution/marked improvement of the pancreatic/extrapancreatic involvement	

Autoimmune Pancreatitis Type 2
International Consensus Diagnostic Criteria (ICDC)

Criterion	Level 1	Level 2
P *parenchimal imaging*	Diffuse enlargement Delayed enhancement	Segmental/focal enlargement Delayed enhancement
D *ductal imaging*	Single long stenosis of MPD Multiple stenosis of MPD	Segmental/focal narrowing without upstream dilation
S *serology*	sIgG4 > 2x UNL	sIgG4 1-2x UNL
OOI *other organ involvement*		Clinically diagnosed inflammatory bowel disease
H *histology*	(1) GEL of the wall duct ± granulocytic acinar inflammation (2) absent or scant IgG4+	(1) granulocytic acinar inflammation (2) absent or scant IgG4+ cells
Rt *response to steroids*	Resolution/marked improvement of the pancreatic/extrapancreatic involvement	

Shimosegawa T et al, *Pancreas*, 2011: **40**: 352-358



Pancreatite Cronica

Profili Clinici diversi

Paraduodenale	Autoimmune	Mutazioni Geniche
Maschi, età 40-50 anni	Maschi, età variabile	M=F, età giovanile
Forti Bevitori	Non bevitori	Non bevitori
Forti Fumatori	Non fumatori	Non fumatori
	Associazione con malattie autoimmuni	Familiarità
Dolore continuo	Ittero asintomatico	Numerosi episodi di PA
Vomito	Pancreatite “atipica”	Evoluzione lenta
Ittero	Risposta terapia steroidea	↑Neoplasie pancreatiche
IPE e DM frequenti	IPE e DM reversibili	IPE e DM molto tardivi

Pancreatite Cronica

Terapie specifiche per forme diverse **!**

Paraduodenale	Autoimmune	Mutazioni Geniche
Maschi, età 40-50 anni	Maschi, età variabile	M=F, età giovanile
Forti Bevitori	Non bevitori	Non bevitori
Forti Fumatori	Non fumatori	Non fumatori
	Associazione con malattie autoimmuni	Familiarità
Dolore continuo	Ittero asintomatico	Numerosi episodi di PA
Vomito	Pancreatite "atipica"	Evoluzione lenta
Ittero	Risposta terapia steroidea	↑Neoplasie pancreatiche
IPE e DM frequenti	IPE e DM reversibili	IPE e DM molto tardivi

TP

Tp Chirurgia: DCP, derivativa

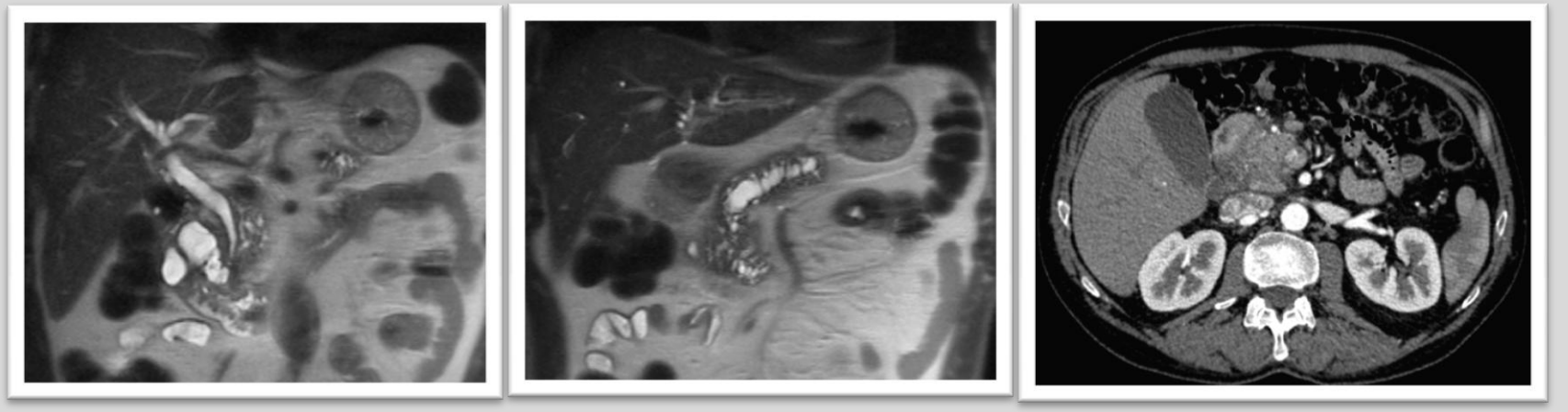
Tp medica: steroidi

Tp endoscopica x CFTR
(Tp medica: F potenziatori ?)

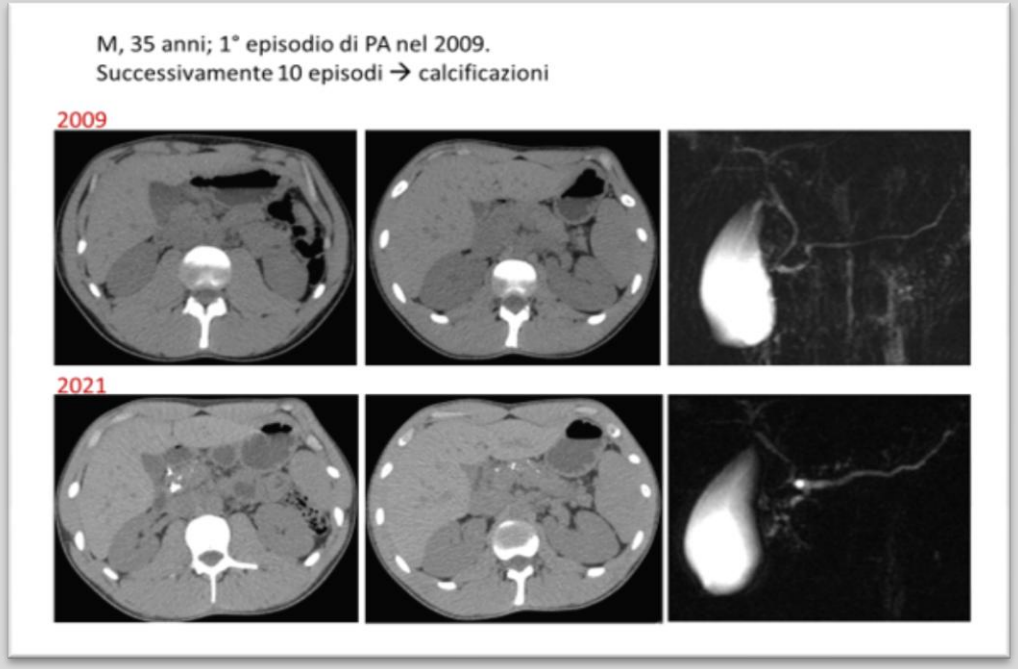
Pancreatite Cronica

Profili Clinici ma anche RADIOLOGICI diversi !

P. PARADUODENALE



P. GENETICA



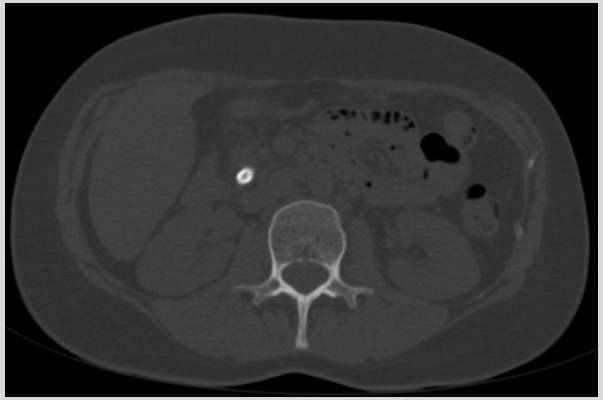
Radiol med (2012) 117:1275–1286
DOI 10.1007/s11547-012-0888-4

ABDOMINAL RADIOLOGY
RADIOLOGIA ADDOMINALE

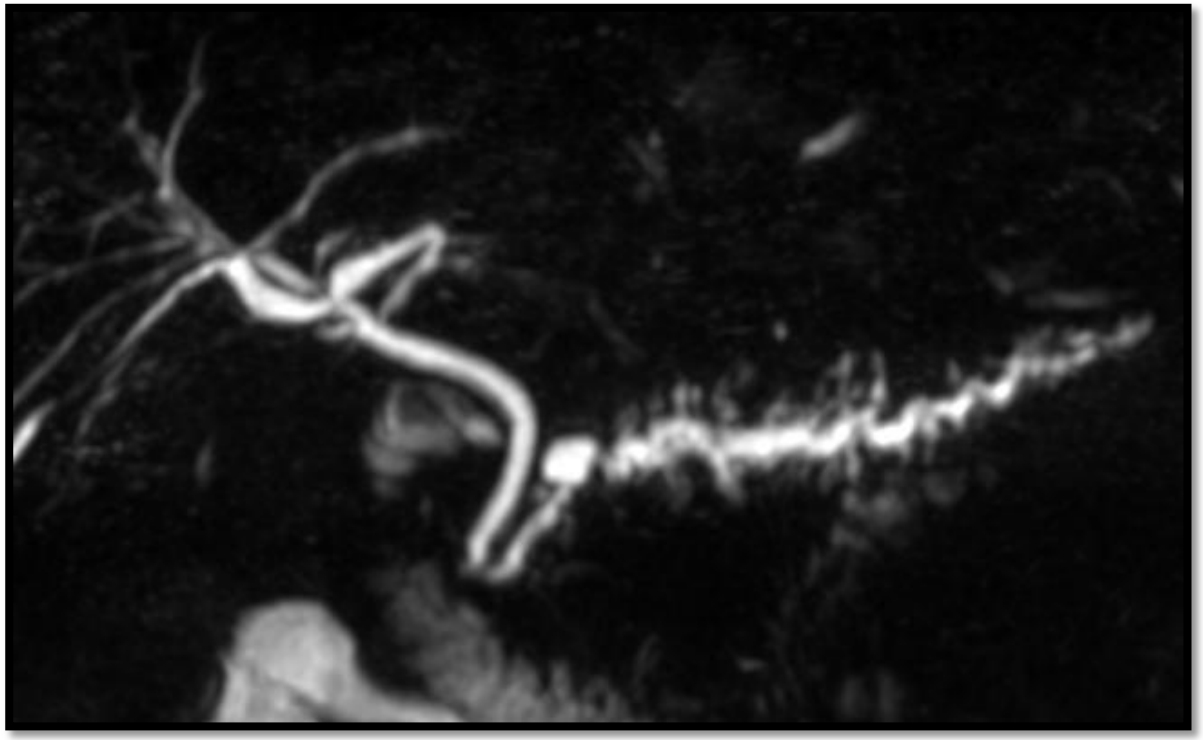
Bull's-eye pattern of pancreatic-duct stones on multidetector computed tomography and gene-mutation-associated pancreatitis (GMAP)

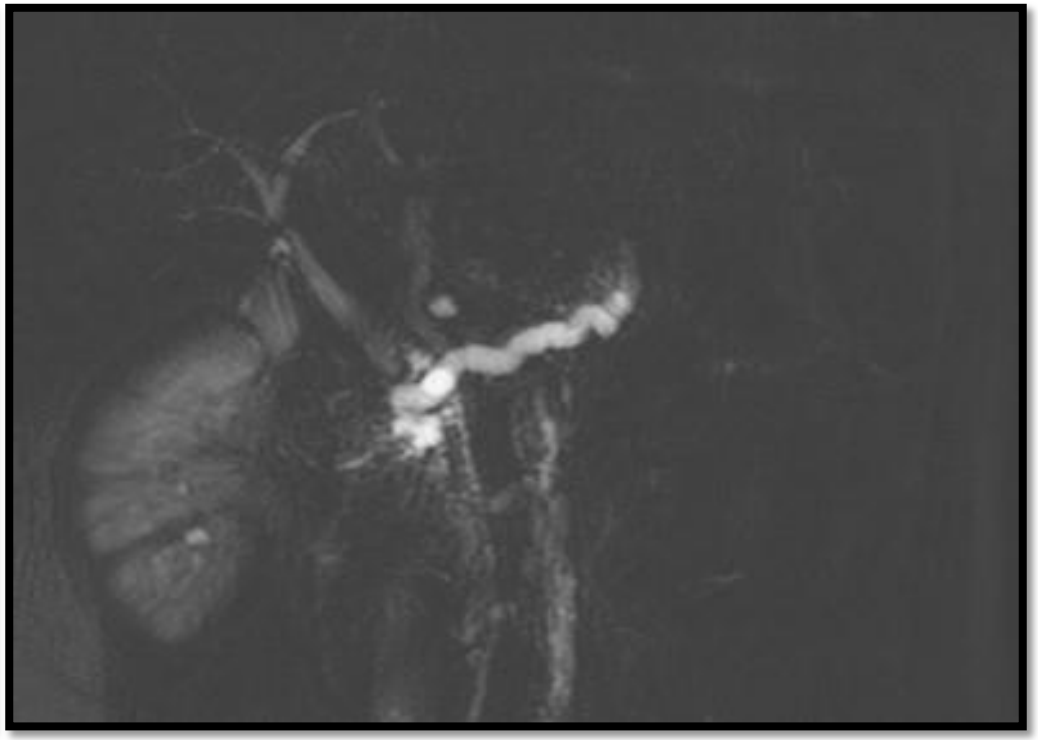
Il pattern TC multidetettore dei calcoli duttali pancreatici a "bull's eye" e pancreatite cronica associata a mutazione genetica (GMAP)

R. Graziani[1] · L. Frulloni[2] · C. Cicero[1] · R. Manfredi[1] · M.C. Ambrosetti[1] · S. Mautone[1]
R. Pozzi Mucelli[1]



Pancreatite Cronica

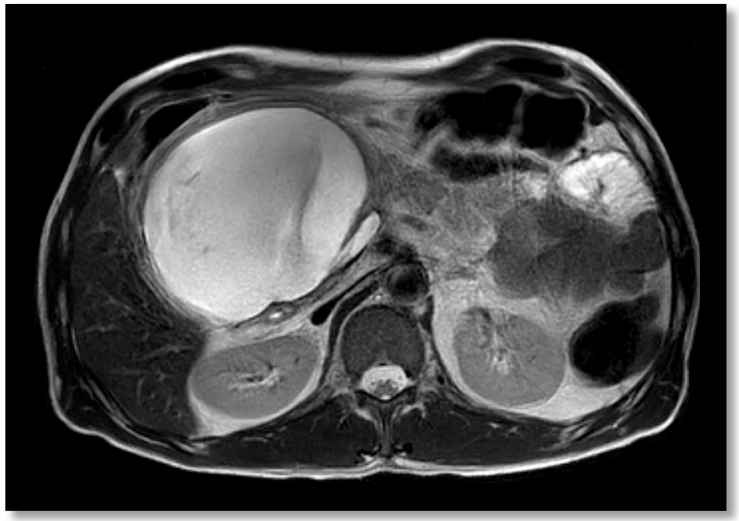


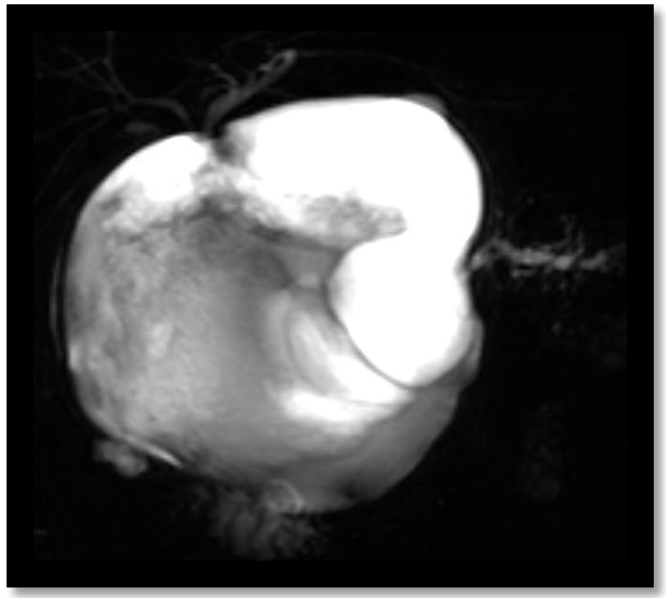


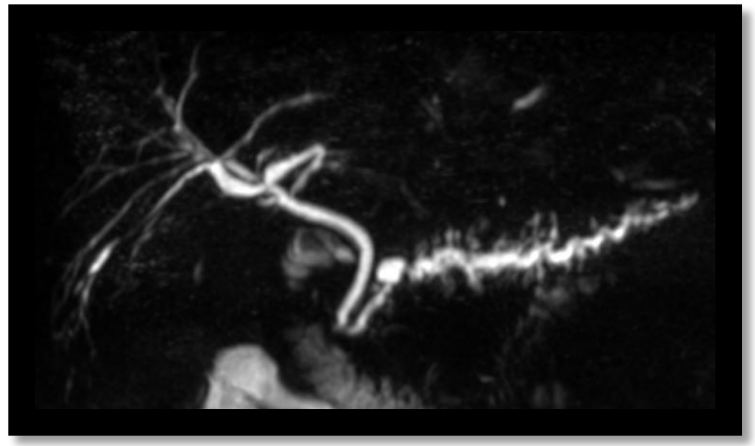
Pancreatite Cronica

Secondaria a Pancreatite Acuta Necrotizzante

M; 62 anni, PANE post-ERCP per coledocolitiasi con voluminosa pseudocisti sintomatica. Sottoposto a cistogastrostomia via EUS.







Pancreatite Cronica

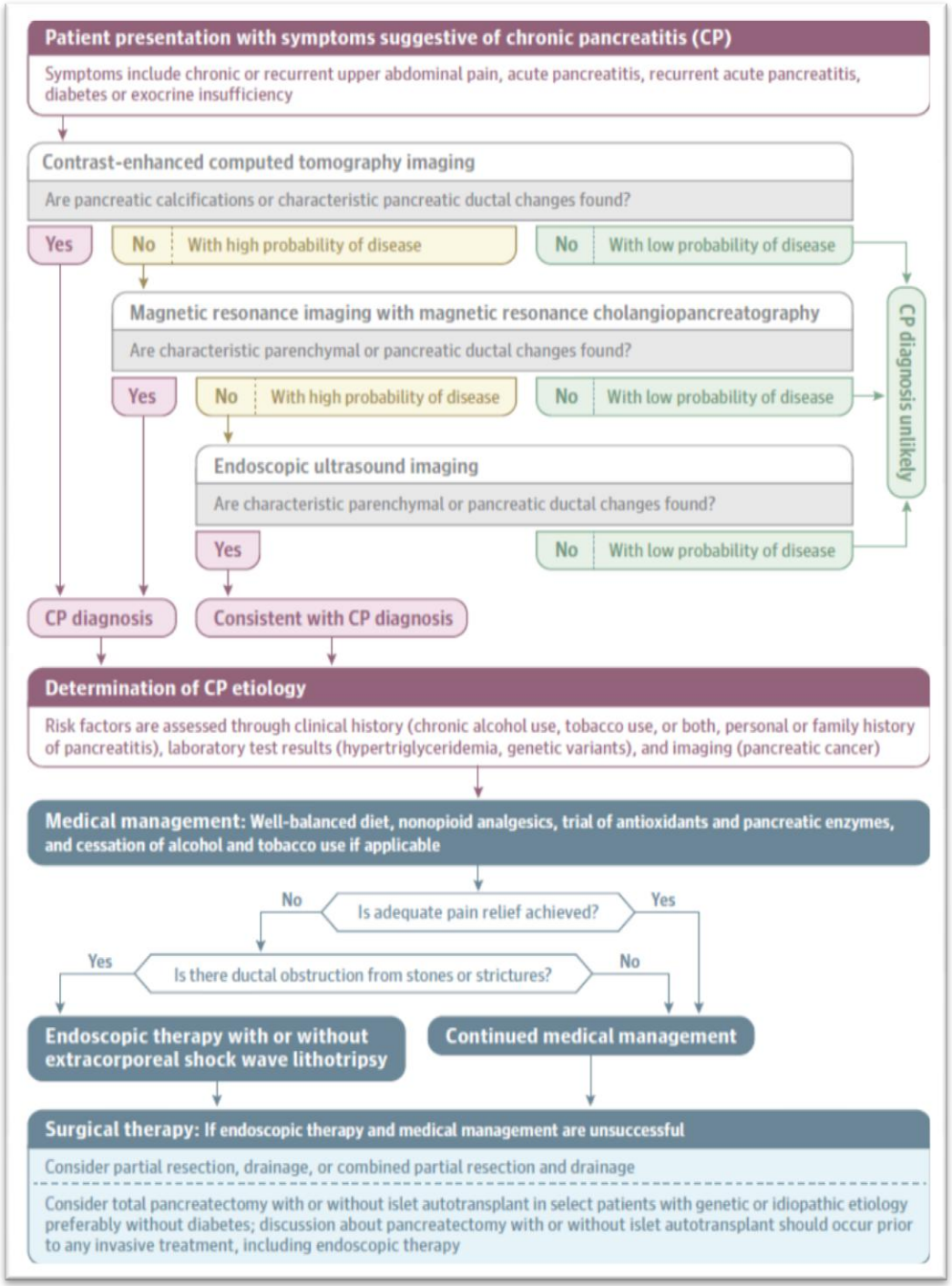
Imaging

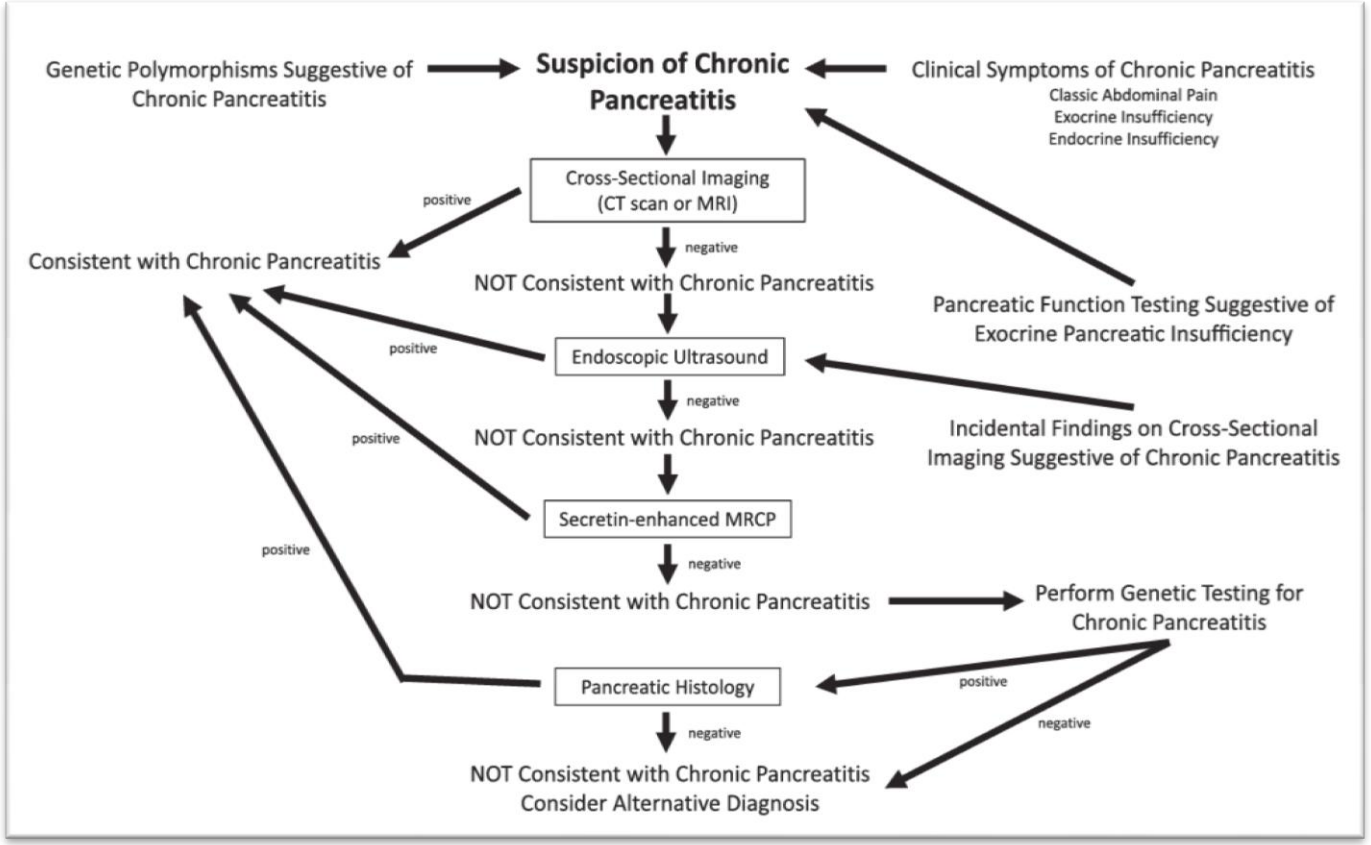
Diagnostic Study	Findings	% (95% CI)[a] Sensitivity	% (95% CI)[a] Specificity	Advantages	Disadvantages	Recommendation
CT	Calcifications, marked ductal dilation, atrophy,	75 (66-83)	91 (81-96)	High sensitivity for calcifications High sensitivity for diagnosing CP complications	Suboptimal visualization of pancreatic duct Low sensitivity and specificity for early CP	First-line diagnostic imaging study, best for calcification and marked dilation of the pancreatic duct
MRI with MRCP with or without secretin	Parenchymal changes (atrophy, T1 signal intensity) Ductal changes (main pancreatic duct dilation, stricture or irregularity as well presence of abnormal side branches) Secretin during MRCP stimulates pancreatic secretion, which causes duodenal filling that can be assessed quantitatively for exocrine function	78 (69-85)	96 (90-98)	Secretin-enhanced MRCP has higher sensitivity and specificity than CT for changes of the main pancreatic duct including dilation and strictures as well as changes in the side branches No ionizing radiation	Low sensitivity for small ductal calculi and parenchymal calcifications Lack of widespread availability	If CT shows normal results but suspicion of CP is high, MRI with MRCP should be obtained to evaluate for ductal changes
EUS	Four parenchymal criteria (lobularity, cyst, hyperechoic foci, and hyperechoic strands) Five ductal criteria (dilation, irregularity, calcifications or stones, echogenic duct wall margins, and side branch)	81 (70-89)	90 (82-95)	High sensitivity Less invasive than ERCP Allows for tissue sampling	Low specificity High interobserver variability Not all criteria carry similar importance	If CT and MRI are normal and the suspicion for CP is still high, especially in patients with RAP, EUS should be performed

JAMA. 2019;322(24):2422-2434.

Pancreatite Cronica

Algoritmo diagnostico





ACG Clinical Guideline: Chronic Pancreatitis

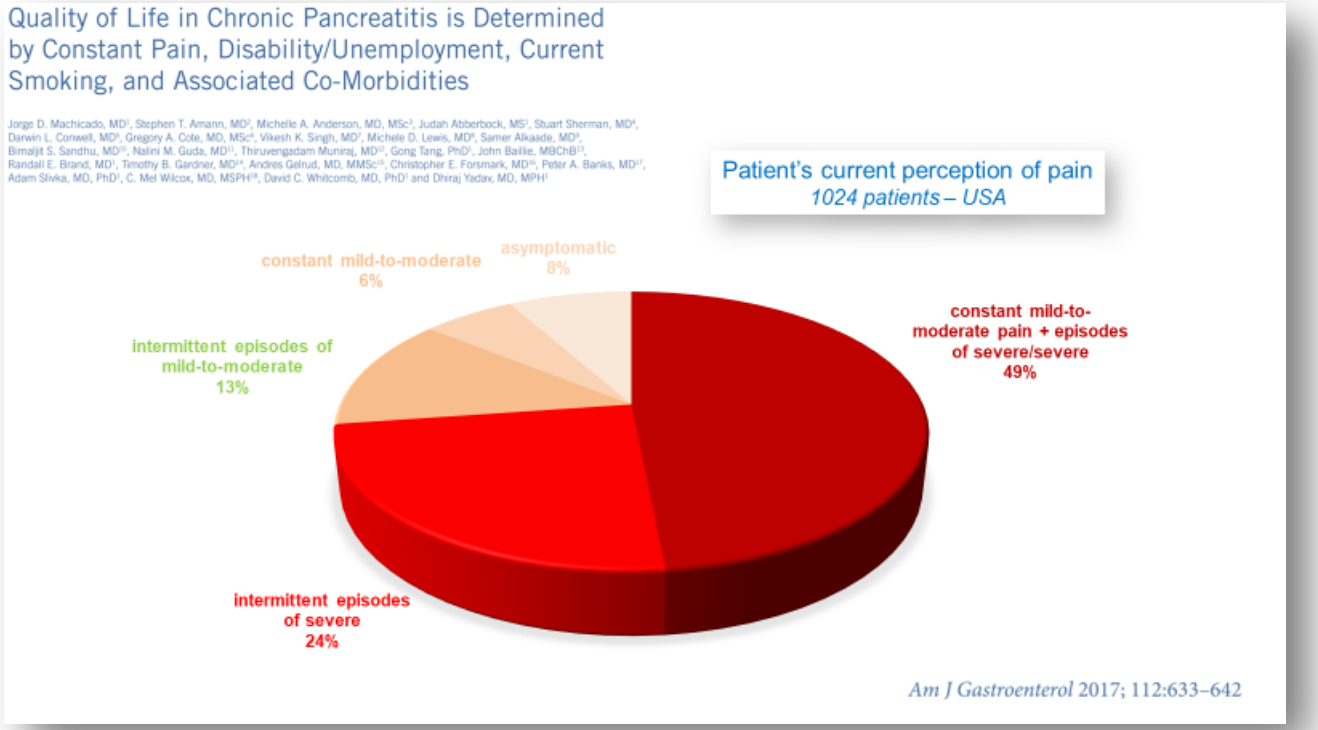
JAMA. 2019;322(24):2422-2434.

Pancreatite Cronica

Il dolore pancreatico

Quality of Life in Chronic Pancreatitis is Determined by Constant Pain, Disability/Unemployment, Current Smoking, and Associated Co-Morbidities

Jorge D. Machicado, MD[1], Stephen T. Amann, MD[2], Michelle A. Anderson, MD, MSc[3], Judah Abberbock, MS[3], Stuart Sherman, MD[4], Darwin L. Conwell, MD[5], Gregory A. Cote, MD, MSc[6], Vikesh K. Singh, MD[7], Michele D. Lewis, MD[8], Samer Alkaade, MD[9], Bimaljit S. Sandhu, MD[10], Nalini M. Guda, MD[11], Thiruvengadam Muniraj, MD[12], Gong Tang, PhD[2], John Baillie, MBChB[13], Randall E. Brand, MD[1], Timothy B. Gardner, MD[14], Andres Gelrud, MD, MMSc[15], Christopher E. Forsmark, MD[16], Peter A. Banks, MD[17], Adam Slivka, MD, PhD[1], C. Mel Wilcox, MD, MSPH[18], David C. Whitcomb, MD, PhD[1] and Dhiraj Yadav, MD, MPH[1]



Am J Gastroenterol 2017; 112:633–642

Symptoms	Prevalence in Chronic Pancreatitis, %
No pain[53-55]	6-24
Abdominal pain[53-57]	60-94
Pain pattern types	
A, Usually pain free, but episodes of mild to moderate pain[53,54]	9-13
B, Constant mild to moderate pain[53,54]	8-34
C, Usually free of abdominal pain, but episodes of severe pain[53,54]	19-51
D, Constant mild to moderate pain plus episodes of severe pain[53,54]	45
E, Constant severe pain[53,54]	6
Pain frequency	
Intermittent (types A and C)[58]	32
Constant (types B, D, and E)[58]	53
Pain severity	
Mild-moderate (types A and B)[58]	18
Severe (types C, D, and E)[58]	67

JAMA. 2019;322(24):2422-2434.

Pancreatite Cronica

Il dolore pancreatico

Almeno 3 componenti:

- **Infiammazione**

Pancreatite Cronica

Il dolore pancreatico

Almeno 3 componenti:

- **Infiammazione**
- **Ostruzione** del sistema duttale pancreatico

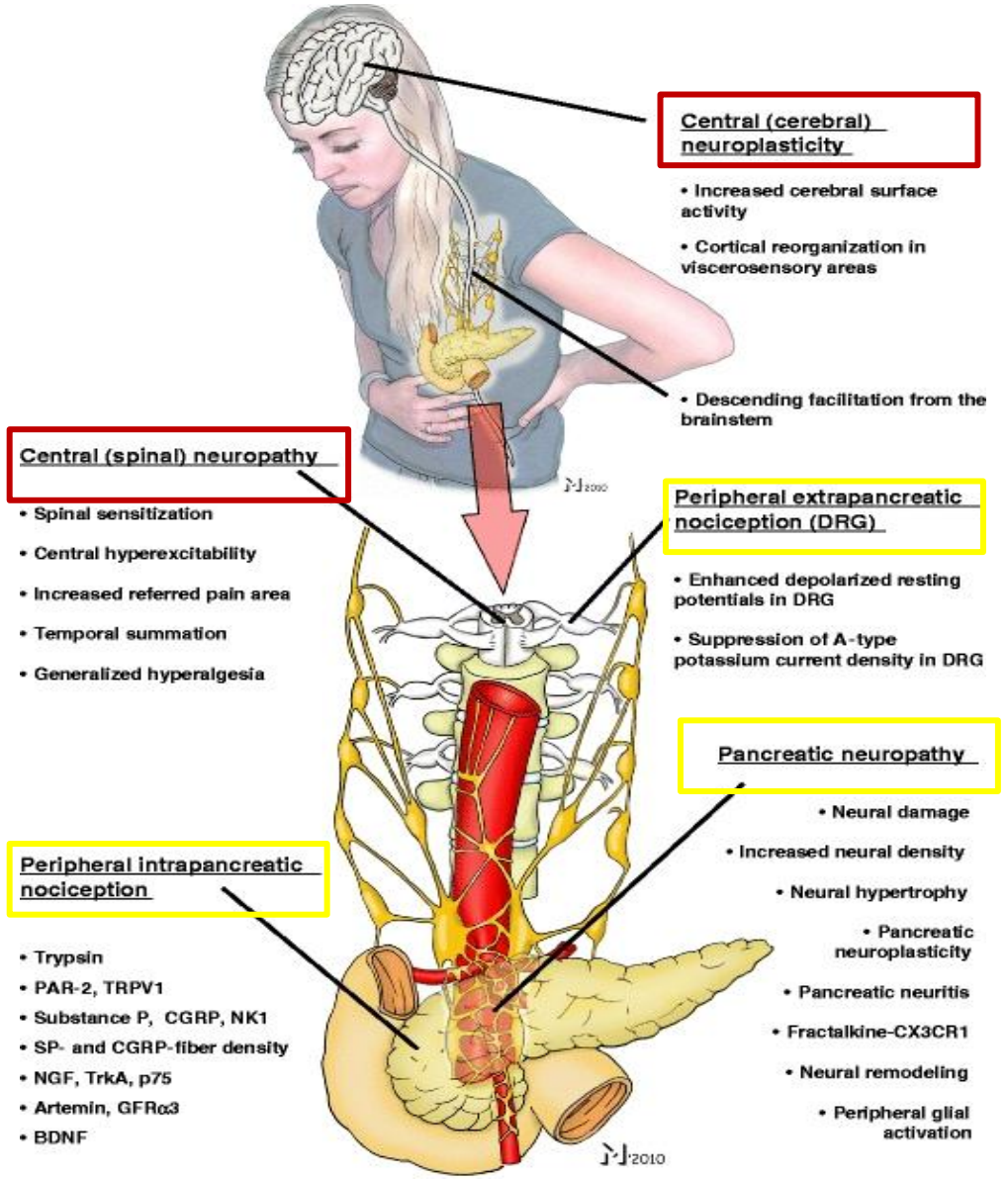
Pancreatite Cronica

Il dolore pancreatico

Almeno 3 componenti:

- **Infiammazione**
- **Ostruzione** del sistema duttale pancreatico
- Componente **Nervosa**: flogosi a livello perineurale → istamina, serotonina, IL, bradichinina, sostanza P, ecc.

→ «sensibilizzazione» al dolore del SNC che sviluppa un'eccessiva reazione agli stimoli dolorosi (iperalgesia) o percezione del dolore in assenza dello stesso (allodinia).



Pancreatite Cronica
Il dolore pancreatico

- Terapia del dolore pancreatico: STOP alcol e fumo !

ACG Clinical Guideline: Chronic Pancreatitis

Timothy B. Gardner, MD, MS, FACG[1], Douglas G. Adler, MD, FACG[2], Chris E. Forsmark, MD, FACG[3], Bryan G. Sauer, MD, MSc (Clin Res), FACG (GRADE Methodologist)[4], Jason R. Taylor, MD[5] and David C. Whitcomb, MD, PhD, FACG[6]

Table 3. Key concept statements on the management of CP

Diagnosis of CP
1. Pancreatic function testing is an important means of diagnosing exocrine pancreatic insufficiency; however, its role in establishing the diagnosis of CP is complementary.
Etiology of CP
2. In patients with clinical features of CP, a comprehensive review of all risk factors should be performed. This provides information on the underlying mechanisms, identifies both fixed and modifiable risk factors, identifies potential targets for therapies, and provides clinically relevant prognostic information.
Natural history and clinical symptoms of CP
3. Identification of the disorders(s) underlying pancreatic inflammation is important in predicting progression to CP.
4. The development of DM in CP is most likely related to duration of disease, although other etiologic factors such as BMI and smoking status may incur an increased risk.
5. There is a lack of evidence to suggest that performing screening examinations on patients with CP to detect pancreatic malignancy is beneficial.
Management of pain in CP
6. Performing elective interventional procedures on patients who are actively using alcohol should be considered cautiously. Patients requiring urgent or emergent procedures for complications of CP should be considered separately.
7. Opiates may be considered to treat painful CP only in patients in whom all other reasonable therapeutic options have been exhausted.
8. TPIAT should be reserved for highly selected patients with refractory chronic pain in which all other symptom control measures have failed.
9. Experimental treatment modalities should be limited to use in the context of a clinical research trial.
Management of exocrine pancreatic insufficiency in CP
10. Patients with CP should have periodic evaluation for malnutrition including tests for osteoporosis and fat-soluble vitamin deficiency.

Am J Gastroenterol 2020;115:322–339.

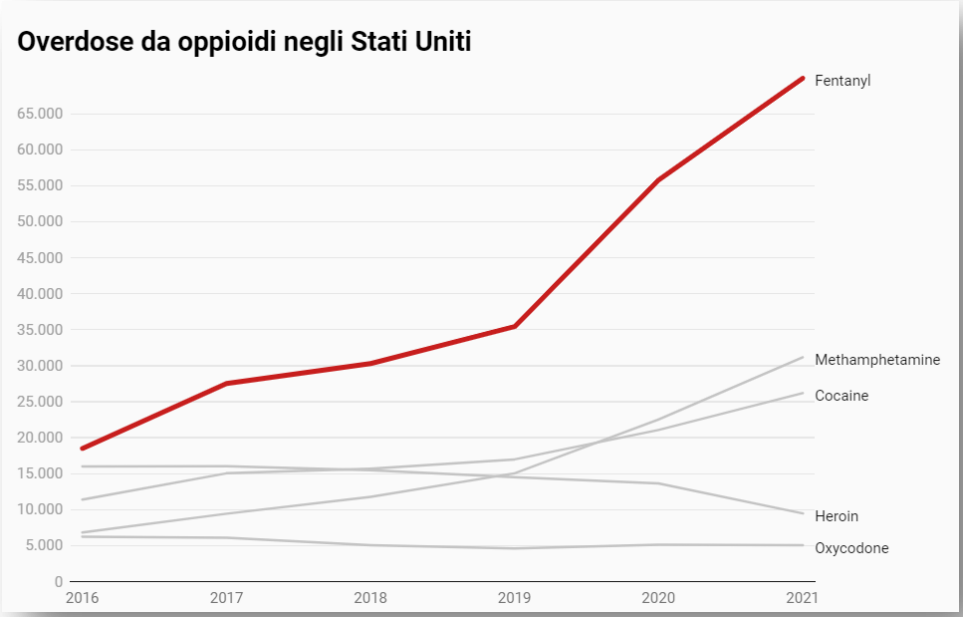
Pancreatite Cronica

Il dolore pancreatico

- Terapia del dolore pancreatico: STOP alcol e fumo !

- Paracetamolo e FANS (la prima scelta), oppioidi minori (es. tramadolo) e maggiori, ma anche agenti “neuromodulanti” (pregabalin) e farmaci antidepressivi.

Anderson MA, et al. Pancreatology 2016; 16: 83-94.



Pancreatite Cronica

Il dolore pancreatico

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- Paracetamolo e FANS (la prima scelta), oppioidi minori (es. tramadolo) e maggiori, ma anche agenti “neuromodulanti” (pregabalin) e farmaci antidepressivi.

  Anderson MA, et al. Pancreatology 2016; 16: 83-94.

- Meta-analisi con mix di antiossidanti (metionina, selenio, vitamina C, vitamina E e A) mostrava una certa efficacia ma studi «deboli».

  Talukdar R, Pancreatology 2015; 15: 136-44

ACG Clinical Guideline: Chronic Pancreatitis

Timothy B. Gardner, MD, MS, FACG[1], Douglas G. Adler, MD, FACG[2], Chris E. Forsmark, MD, FACG[3], Bryan G. Sauer, MD, MSc (Clin Res), FACG (GRADE Methodologist)[4], Jason R. Taylor, MD[5] and David C. Whitcomb, MD, PhD, FACG[6]

9. We do not suggest the use of pancreatic enzyme supplements to improve pain in CP (conditional recommendation, low quality of evidence).

Summary of evidence. Patients with CP often receive pancreatic enzyme supplementation, typically to treat symptomatic EPI. Although the beneficial effects of treating EPI with pancreatic enzyme supplementation are established, their role as a treatment for pain is less clear. Although it seems plausible that pain due to cramping, diarrhea, and other EPI symptoms could be treated by enzyme supplementation, it is unclear whether these agents treat primary pancreatic pain due to inflammation, ductal stones, etc. This question has been addressed by several studies.

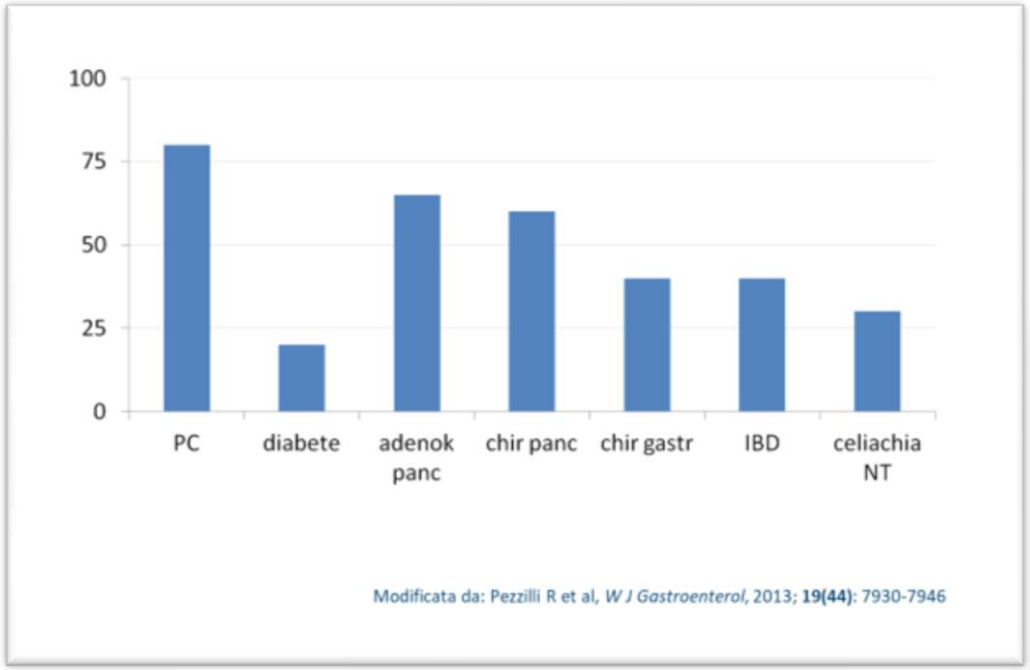
Practical clinical approach. Overall, pancreatic enzyme therapy should not be used as a form of pain control in patients with CP given their expense and general lack of clinical efficacy. However, patients with EPI usually derive some benefits in terms of relief from discomfort secondary to abdominal cramping, etc., from pancreatic enzyme replacement therapy (PERT). Nonetheless, if patients feel

La terapia con enzimi pancreatici non ha un effetto significativo sul dolore !

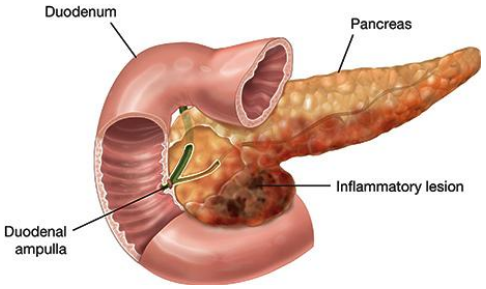
Am J Gastroenterol 2020;115:322–339.

Funzione Esocrina Pancreatica

Gestione dell'IPE



Modificata da: Pezzilli R et al, *W J Gastroenterol*, 2013; **19(44)**: 7930-7946



Prevalenza IPE

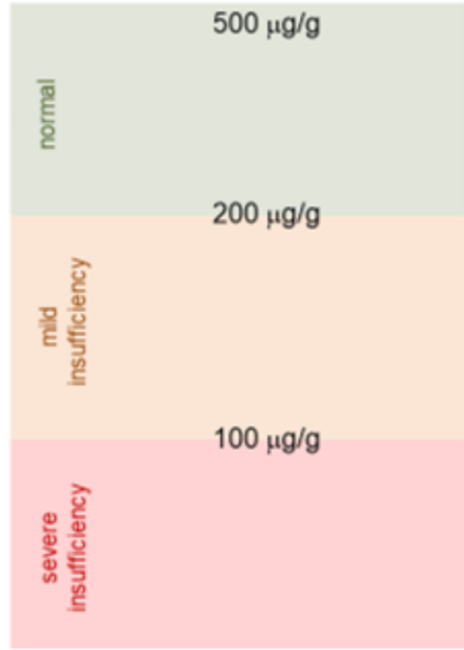
Pancreatite cronica	Medio-Alta
Pancreatite ricorrente	Bassa
Neoplasie pancreatiche	Media
Post-chirurgia pancreatica	Alta
Altro *(i.e. diabete, fibrosi cistica, dispepsia, diarrea, …)*	Bassa

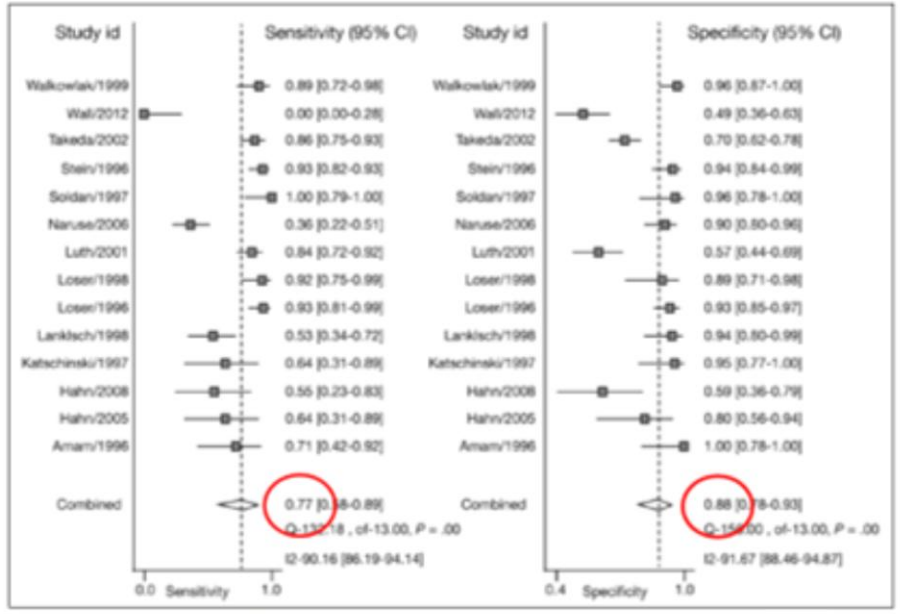
Funzione Esocrina Pancreatica

TEST Elastasi-1 Fecale

1. Non invasivo
2. Pancreas-specifico
3. Minime modificazioni durante il transito intestinale
4. Stabile *(non degradata)*
5. Rapidamente misurabile su campioni di feci
6. Non influenzata dalla terapia sostitutiva in atto
7. Economico

Classificazione: Pancreatic Exocrine Insufficiency *(PEI)*





Clinical Gastroenterology and Hepatology 2018;16:1220–1228

BMJ Open Gastroenterology

Consensus for the management of pancreatic exocrine insufficiency: UK practical guidelines

PEI is highly likely with high benefit from PERT: no further test required as significant benefit from treatments and the negative predictive value of FEL-1 is not strong enough to prevent starting treatment

- Head of pancreas cancer
- Pre-surgery and post-surgery for head of pancreas cancer with or without pylorus preserving operation
- Total pancreatectomy
- Steatorrhoea or malabsorption symptoms in patients with CP with dilated pancreatic duct or severe pancreatic calcification
- Severe necrotising pancreatitis

Patients that require initial investigation with FEL-1

- GI symptoms of maldigestion in secondary care with or without known associated conditions
- Maldigestion symptoms: steatorrhoea, weight loss, diarrhoea, abdominal pain or bloating
- Associated conditions: patients with coeliac disease, IBS-D, HIV, type 1 diabetes and acute severe pancreatitis after initial phase

Following a positive FEL-1 test

- A positive FEL-1 requires up-to-date cross-sectional imaging to exclude developing obstructive tumour or lesion as the cause
- If subsequent investigation cannot find a morphological pancreatic cause of PEI, FEL-1 should be repeated even if patient has already started PERT

The value of PERT

Statement 3.1: PERT is associated with improved survival in patients with CP (grade 1C) and PC (grade 2B). Additionally, PERT is associated with improved nutritional status in patients with CP (grade 1C) and PC (grade 1C) (95% agreement)

Statement 3.2: Treatment with PERT improves QoL in patients with PEI (grade 1C; 100% agreement)

Statement 4.5: There is no maximum dose of PERT in adults (GPP); however, where doses exceed 100,000 units lipase with meals, comorbidities should be excluded (GPP; 91% agreement)

Statement 4.6: Dietary fat restriction is not routinely recommended, but very high-fibre diets should be avoided (grade 1C; 96% agreement)

Adverse events

Statement 7.1: PERT is not associated with any significant complications (grade 1A; 100% agreement)

Phillips ME, *et al. BMJ Open Gastro* 2021

Medical therapy for exocrine pancreatic insufficiency (WP6)

UNITED EUROPEAN GASTROENTEROLOGY **ueg journal**

Q4-2.5: How should be the efficacy of PERT be evaluated?

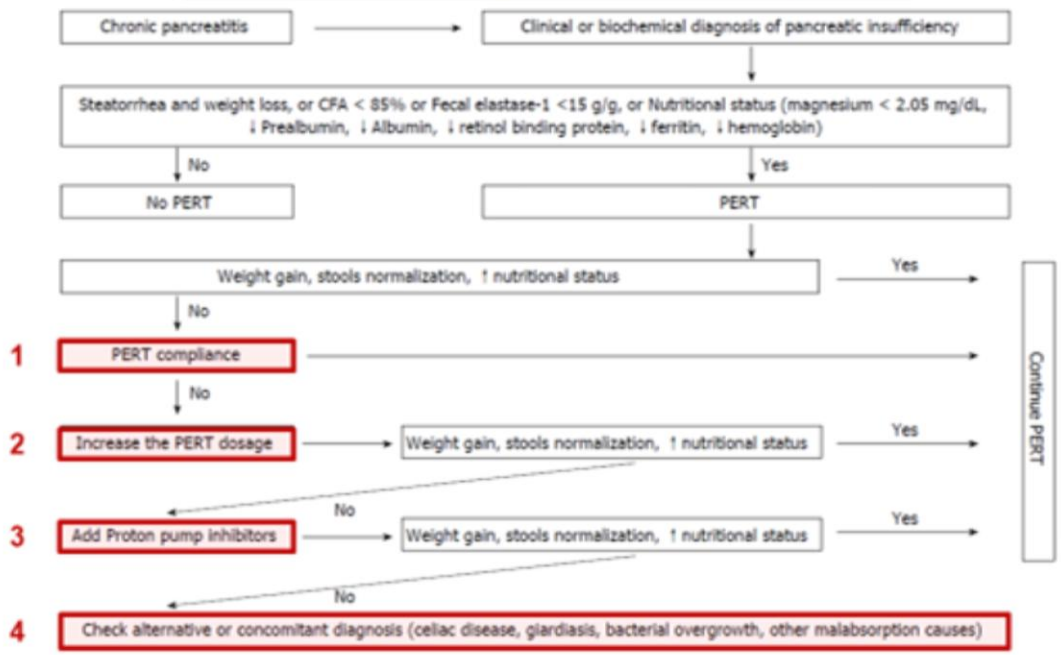
Statement 4-2.5. The efficacy of PERT can be evaluated adequately by the relief of maldigestion-related symptoms (e.g. steatorrhoea, weight loss, flatulence) and the normalisation of the nutritional status of the patients. In non-responder patients, the use of pancreatic function tests (CFA or ^{13}C-MTG-BT) with oral enzymes may be of help. **(GRADE 1B, strong agreement)**

Q4-2.6: What should be done in cases of unsatisfactory clinical response?

Statement 4-2.6. In cases of unsatisfactory clinical response, the enzyme dose should be increased (doubled or tripled) or a proton pump inhibitor (PPI) should be used. If these strategies fail, another cause for maldigestion should be sought. **(GRADE 2B, strong agreement)**

Exocrine pancreatic insufficiency in adults: A shared position statement of the Italian association for the study of the pancreas

Raffaele Pezzilli, Angelo Andriulli, Claudio Bassi, Gianpaolo Balzano, Maurizio Cantore, Gianfranco Delle Fave, Massimo Falconi, Luca Frulloni; the Exocrine Pancreatic Insufficiency collaborative (EPIc) Group



World J Gastroenterol 2013 November 28; 19(44): 7930-7946

Ottimizzazione della Terapia

Accorgimenti

Circa la metà dei pazienti non assume gli enzimi pancreatici in modo adeguato e limita fortemente l'intake lipidico !!

In caso di steatorrea e distensione addominale persistente:

- **Adeguata somministrazione di enzimi pancreatici (almeno 40-50.000 U pasto !)**
- **Verificare dosaggio, tempi e modalità di assunzione**
- **Frazionamento pasti (4-5 al giorno) → enzimi pancreatici**
- **Eventuale riduzione dell'assunzione di fibra alimentare**
- **Aggiungere PPI**
- **Uso di rifaximina per la SIBO**
- **Escludere altre cause concomitanti (celiachia, TSH, giardiasi, ecc)**
- **Eventuale riduzione dell'assunzione di grassi, garantendo l'apporto di acidi grassi essenziali e vitamine liposolubili.**

La frazione solubile può inferire con l'attività enzimatica, ostacolando e ritardando i tempi di digestione.

Berry AJ. Nutr Clin Pract 2013, Giannotti L. et al. Surgery 2018, Gilliland M. et al. Nutrients 2017

Pancreatite Cronica
Prognosi

RISCHIO E CAUSE DI MORTALITÀ

Rate di mortalità incrementato tra i pazienti affetti da PC, con aspettativa di vita di circa 8 anni inferiore.

Le cause di morte in paziente con PC possono essere legate a:

- ✓ Complicanze da riacutizzazione di malattia (trombosi/emorragie, raccolte, colangiti);
- ✓ Esposizione ai fattori di rischio (patologie alcol/fumo correlate);
- ✓ Conseguenze della patologia (per es., DM, deficit nutrizionali).

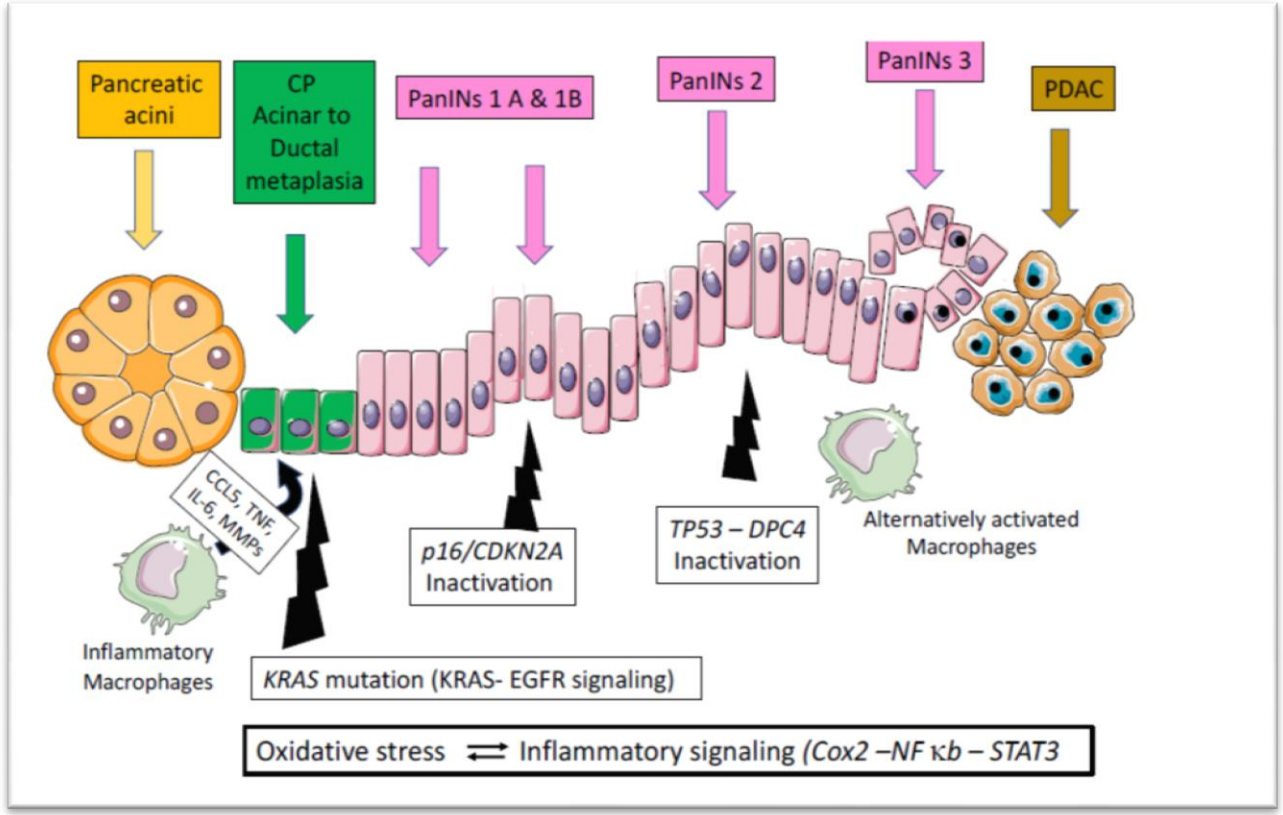
cancers

MDPI

Review

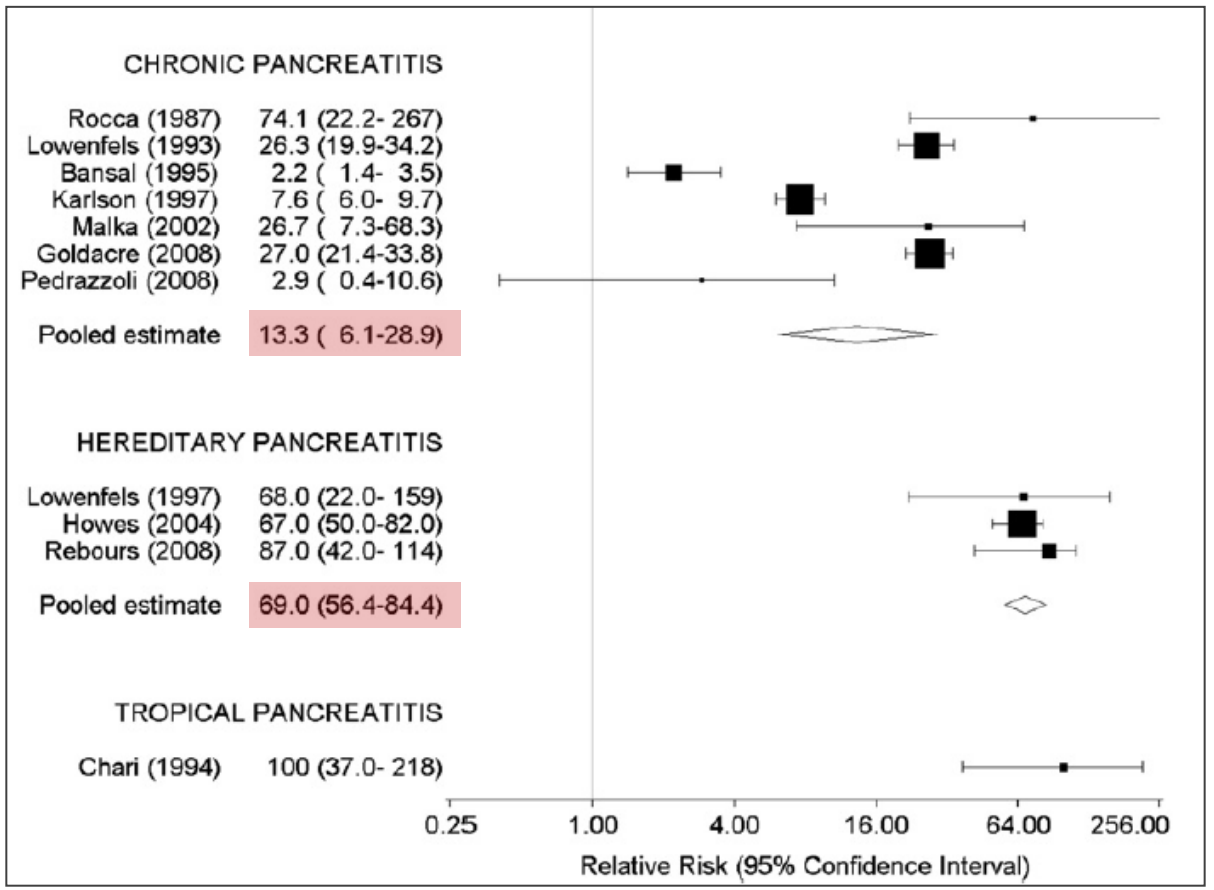
Pancreatic Cancer in Chronic Pancreatitis: Pathogenesis and Diagnostic Approach

Guillaume Le Cosquer [1,2], Charlotte Maulat [3,4], Barbara Bournet [1,4], Pierre Cordelier [4], Etienne Buscail [2,3] and Louis Buscail [1,4,5,*]



Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection☆

Sara Raimondi, Researcher[a], Albert B. Lowenfels, Professor of Surgery[b,*], Antonio M. Morselli-Labate, Research Fellow[c], Patrick Maisonneuve, Head of Department[a], Raffaele Pezzilli, Head of Pancreas Unit[c]



Best Practice & Research Clinical Gastroenterology 24 (2010) 349–358

cancers

MDPI

Review

Pancreatic Cancer in Chronic Pancreatitis: Pathogenesis and Diagnostic Approach

Guillaume Le Cosquer [1,2], Charlotte Maulat [3,4], Barbara Bournet [1,4], Pierre Cordelier [4], Etienne Buscail [2,3] and Louis Buscail [1,4,5,*]

Table 2. Pancreatic cancer risk according to the etiology of chronic pancreatitis.

Etiology	Pancreatic Cancer Estimated Risk
Alcoholic CP	Incidence of 2 and 4% after 5 and 20 years of evolution, respectively.
Hereditary pancreatitis (*PRSS1*)	Incidence of 10, 19, and 53.5% at 50, 60, and 75 years, respectively.
SPINK1 mutations	Incidence of 12, 28, and 52% at 60, 70, and 80 years.
CFTR mutations	Increased risk of PDAC of 1.41 compared to control patients.
CTRC, CASR, CLDN2, CPA1, TRPV6, CEL-HYB mutations	No available data due to very low incidence of these mutations.

CP: chronic pancreatitis; PDAC: pancreatic ductal adenocarcinoma.

Mortality, Cancer, and Comorbidities Associated With Chronic Pancreatitis: A Danish Nationwide Matched-Cohort Study

Ulrich Christian Bang,[1] Thomas Benfield,[2,3] Lars Hyldstrup,[1,3] Flemming Bendtsen,[3,4] and Jens–Erik Beck Jensen[1,3]

Table 2. Causes of Mortality Associated With CP Compared With Controls

	CP	Controls	HR[a]	95% CI
Number	11,972	119,720		
Person-years	71,814	917,436		
	% of total	% of total		
Death from all causes	46.4	13.0	5.0	4.8–5.2
Malignancies	10.2	3.3	1.4	1.3–1.5
Alimentary tract	10.6	0.4	26.1	23.1–29.4
Circulatory system	5.5	3.2	1.9	1.7–2.1
Respiratory system	2.8	1.0	3.3	2.8–3.8
Endocrine disorder	2.2	0.4	4.2	3.6–4.9
Psychiatric disorder	2.1	0.4	6.3	5.4–7.5
Infectious disease	0.6	0.1	4.4	3.2–6.0
Suicide	0.4	0.1	3.5	2.6–4.7
Accident	1.5	0.3	4.1	3.5–5.0
Missing diagnosis	7.8	2.7	N/A	N/A
Other diagnosis	2.1	1.1	1.3	1.1–1.4

Table 3. Risk of Malignancy During Follow-up Period for CP vs Non-CP and for Alcoholic CP vs Nonalcoholic CP

			CP vs controls[a]		Alcoholic vs nonalcoholic CP[a]	
Cancer site	CP cases	Controls	HR	95% CI	HR	95% CI
Person-years	68,245	888,573				
Any cancer, N	1622	9488				
Any cancer, %	13.6	7.9	1.2	1.1–1.3	0.9	0.8–1.0
Esophagus	0.46	0.21	1.4	1.0–1.9	1.4	0.8–2.5
Stomach	0.33	0.21	1.0	0.7–1.5	0.9	0.5–1.7
Small intestine	0.09	0.03	2.9	1.4–6.1	0.9	0.3–2.9
Colon	0.82	0.83	0.6	0.5–0.8	0.8	0.5–1.2
Liver	0.38	0.08	2.0	1.3–3.1	1.1	0.5–2.1
Pancreas	4.26	0.24	6.9	5.6–8.6	0.7	0.5–1.0
Lungs	1.00	0.44	1.5	1.2–1.8	0.7	0.5–1.0
Hematologic	1.00	0.79	0.9	0.7–1.1	0.5	0.3–0.7
Melanoma	0.23	0.35	0.6	0.4–0.9	0.4	0.2–0.9

Hazard Ratio for PDAC was **6.9-fold higher**: 14.6-fold within 2–4 years and 4.8-fold between 5 and 16 years after being registered as having chronic pancreatitis

Gastroenterology 2014;146:989–994

Adenocarcinoma Pancreatico in Pancreatite Cronica

ALERT

ALERT

cancers

MDPI

Review

Pancreatic Cancer in Chronic Pancreatitis: Pathogenesis and Diagnostic Approach

Guillaume Le Cosquer [1,2], Charlotte Maulat [3,4], Barbara Bournet [1,4], Pierre Cordelier [4], Etienne Buscail [2,3] and Louis Buscail [1,4,5,*]

Table 3. Predictive value of radiological signs.

	Signs Evocative of Benign Disease	Signs Evocative of Malignant Disease
Parenchymal signs	*Pseudotumorous CP and IPMN:* - Absence of enhancement of the mass - Hypointense T1; iso to hyperintense T2 - Moderate enhancement at portal phase after gadolinium *Paraduodenal pancreatitis:* - Parietal thickening of the second part of the duodenum on the pancreatic side - One or more cystic images inside the sulcus and in the duodenal wall - Absence of gland atrophy *AIP:* - Loss of lobulation ("sausage"-shaped pancreas) - Peripancreatic hypodense rim	- Late enhancement of the mass at portal phase (CT and gadolinium MRI) - Parenchyma atrophy associated with Wirsung dilation - Displaced parenchymal calcifications (mass pushing calcifications at periphery of the gland)
Duct signs	*Obstructive CP and IPMN:* - Duct-penetrating sign (mass penetrated by an unobstructed pancreatic duct) - Branch ducts dilation	- Complete obstruction of the Wirsung duct at the mass - Double duct sign (dilation of Wirsung and bile duct)
Vessels signs	*Pseudotumorous CP:* - Displaced vessels - Fat separating the mass and vessels	- Infiltration of the vessels (particularly arterial) and the celiac region
Other signs	*AIP:* - Other organs involved (kidneys, aorta, etc.)	- Peripancreatic tissue infiltration

Adenocarcinoma Pancreatico in pz di 47 anni con Pancreatite Cronica nota da circa 18 anni

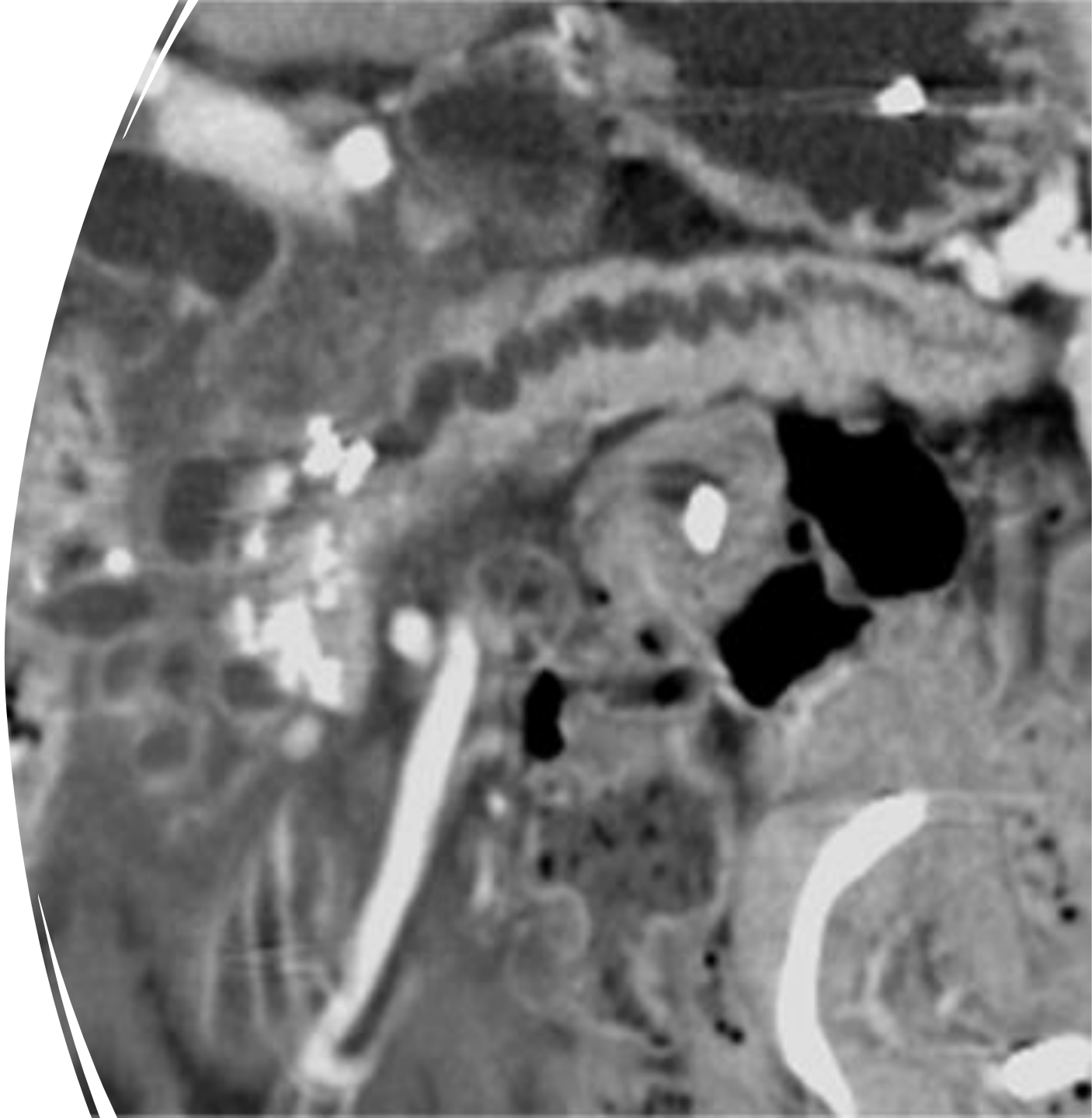
Ottobre 2012

Marzo 2013

Pancreatite Cronica

Approccio "gastroenterologico"

- **Malattia complessa, multifattoriale**
- **Setting clinico e imaging (alcuni suggestivi per eziologia)**
- **Escludere k alla diagnosi e nel FU**
- **Gestione del dolore: (medica / endoscopica / chirurgica), IPE - DM.**
- **Monitoraggio nel tempo per complicanze**



Istituto del Pancreas

Azienda Ospedaliera Universitaria Integrata Verona

Grazie!