top ten
in gastroenterologia
14^ EDIZIONE
24-25 NOVEMBRE 2023
BERGAMO

Le lesioni cistiche del pancreas e il rischio di cancro

Gabriele Capurso, MD, PhD

Deputy Director

Pancreas Translational & Clinical Research Center

IRCCS S. Raffaele, Milano

capurso.gabriele@hsr.it

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Un problema di Epidemiologia

…Epidemiologia

(επι= riguardo, δημος= la gente e λογος= lo studio)

La disciplina biomedica che studia la **distribuzione**, la **frequenza** e la **rilevanza per la salute** di una malattia nella popolazione…

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E di Storia Naturale

«La storia naturale di qualsiasi malattia in senso generale è la descrizione dell'esordio, della **progressione e del risultato** della malattia o della condizione clinica dal punto di vista **osservazionale**, che non implica l'indagine o trattamento»

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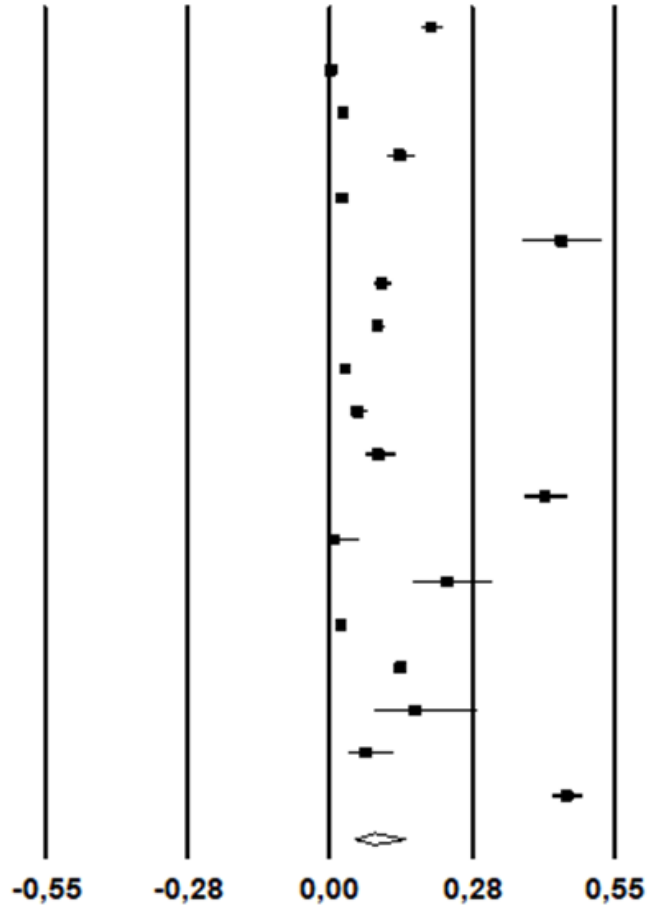
Diagnosi incidentali molto comuni

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
Zhang	0,196	0,18	0,22	-21,29	0,00
Kim YS	0,002	0,00	0,00	-12,63	0,00
Laffan	0,026	0,02	0,03	-30,63	0,00
Lee	0,135	0,11	0,16	-15,76	0,00
De Jong	0,024	0,02	0,03	-29,90	0,00
Girometti	0,447	0,37	0,53	-1,30	0,20
Matsubara	0,100	0,08	0,12	-23,08	0,00
De Oliveira	0,093	0,08	0,10	-33,62	0,00
Ippolito	0,030	0,03	0,03	-47,41	0,00
Zanini	0,054	0,04	0,07	-16,49	0,00
Sey	0,094	0,07	0,13	-12,21	0,00
Moris	0,416	0,37	0,46	-3,74	0,00
Ulus	0,008	0,00	0,06	-4,74	0,00
Kim JA	0,227	0,16	0,31	-5,38	0,00
Chang	0,021	0,02	0,02	-81,25	0,00
Mizuno	0,137	0,13	0,15	-46,07	0,00
Zerboni MR	0,164	0,09	0,29	-4,48	0,00
Zerboni TC	0,069	0,04	0,12	-7,92	0,00
Kromery	0,459	0,43	0,49	-2,71	0,01
	0,084	0,05	0,14	-7,79	0,00

Statistics for each study

Event rate and 95% CI



I^2 99.5%; publication bias: p=0.48

Zerboni et al. Pancreatology 2019

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in soggetti asintomatici

		Statistics for each study			Event rate and 95% CI
		Event rate	Lower limit	Upper limit	
Imaging performed	CT scan	0,027	0,02	0,04	
	CPRM	0,248	0,10	0,48	
					0,00 0,28 0,55

La maggior parte sono (Branch-Duct) IPMNs

Kromery	0,459	0,43	0,49	-2,71	0,01
	0,084	0,05	0,14	-7,79	0,00

8.4%

-0,55 -0,28 0,00 0,28 0,55

I^2 99.5%; publication bias: p=0.48

Zerboni et al. Pancreatology 2019

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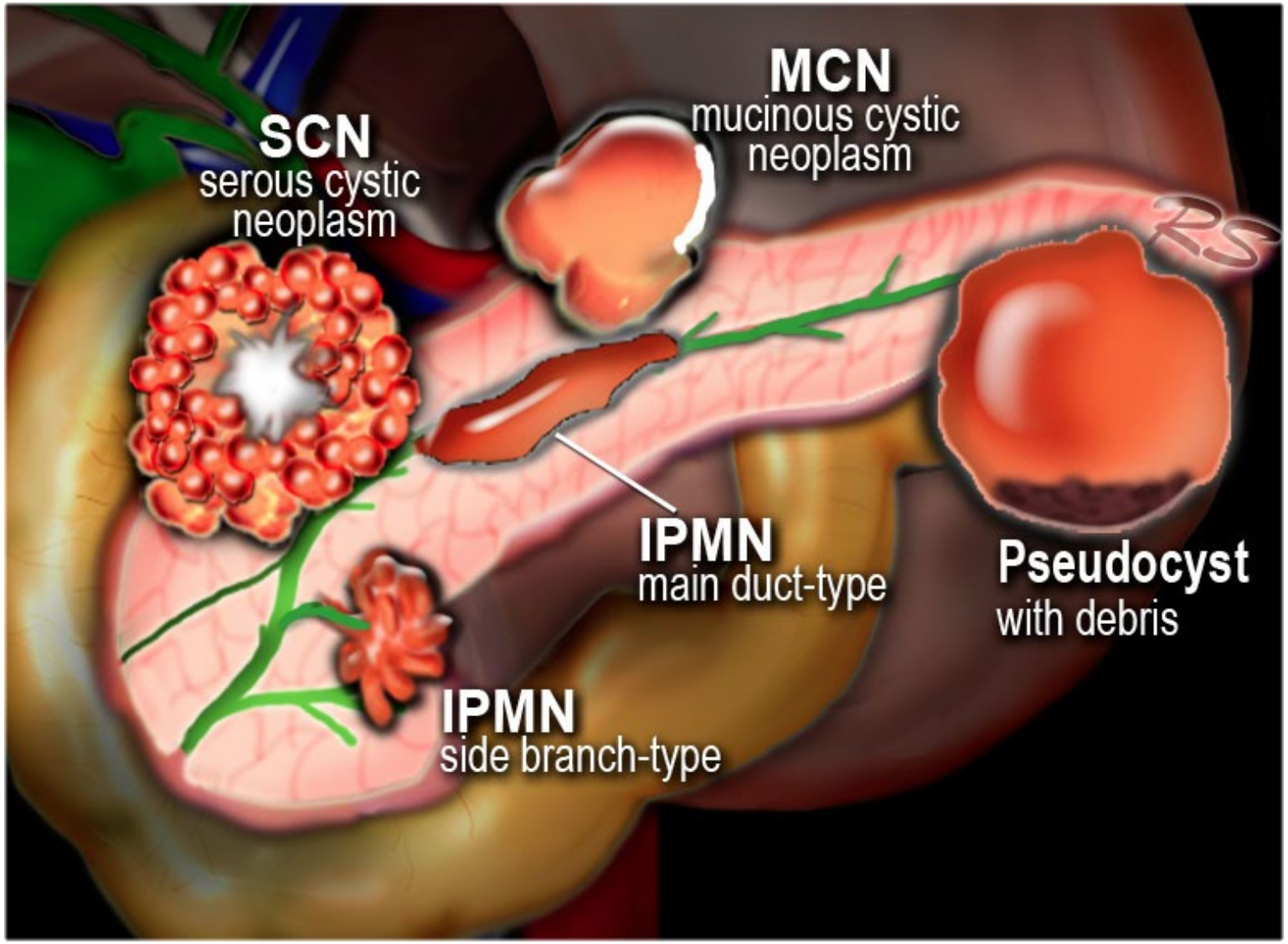
Lesioni diverse con comportamenti diversi



Lesioni diverse con comportamenti diversi

Pseudocisti

Cisti sierosa

Asintomatica

Sintomatica

Nessun Monitoraggio

Drenaggio (PP) O Chirurgia

Cistoadenoma Mucinoso o IPMN

Potenziale Maligno

Follow-up o Chirurgia

Adenocarcinoma con componente cistica
O
Tumore Endocrino Cistico
O
Solido Pseudopapillare

Maligno

Chirurgia

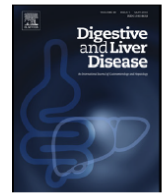
Caratteristica	Pseudocisti	Cistoadenoma Sieroso	Tumore Endocrino Cistico	Solido Pseudopapillare	Cistoadenoma Mucinoso	IPMN
Sesso	M>F	F>M	F=M	F>>>M	F>>>M	F=M
Età	>40	>60	40-60	10-30	40-50	>60
Relazione con Pancreatite	++++	-	-	-	-	+
Calcificazioni	-	+ (centrali)	-	-	+ (periferiche)	-
Sede	Qualsiasi	Coda	Qualsiasi	Qualsiasi	Coda	Testa/qualsiasi
Multifocale	+/-	-	-	-	-	+++
Connessione con Dotti	+/-	-	-	-	-	++++
Conformazione	uniloculare	Nido d'ape + Scar centrale	Solido-cistico ipervascolarizzato	Solido-cistico	Uniloculare/macrocisti	Multiloc. a grappolo
Amilasi intracistica	+++	-	?	?	-	++
CEA intracistico	-	-	?	?	++	++
Muco	-	-	?	?	++	++
Glucosio intracistico	+/-	>50	?	?	<50	<10
Kras mutato	-	-	?	?	-	+
Gnas mutato	-	-	?	?	-	++
VHL mutato	-	++	?	?	-	-

La quota di lesioni cistiche che va a chirurgia è molto piccola

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld



Liver, Pancreas and Biliary Tract

Epidemiology, clinical features and diagnostic work-up of cystic neoplasms of the pancreas: Interim analysis of the prospective PANCY survey

<u>1385 patients:</u>

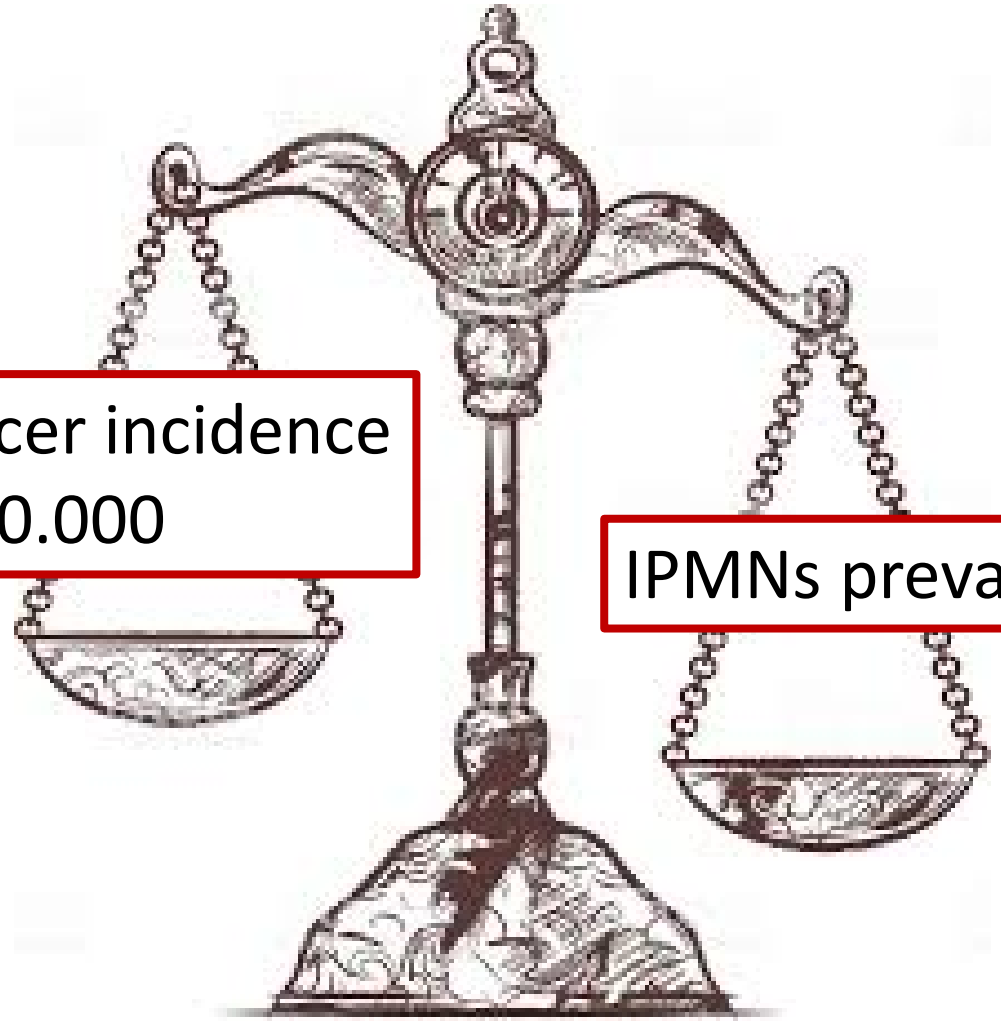
76% asymptomatic

90% IPMN

5.7% operated upon after the initial work-up

Pezzilli et al. DLD 2020

Confronto incidenza cancro del pancreas e prevalenza IPMNs



Pancreatic cancer incidence
13 / 100.000

IPMNs prevalence almost 10%

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Le Cisti Pancreatiche ed in particolare gli IPMNs: scenario clinico

Grosso **problema epidemiologico**

Molto comuni **dai 60 anni in su**

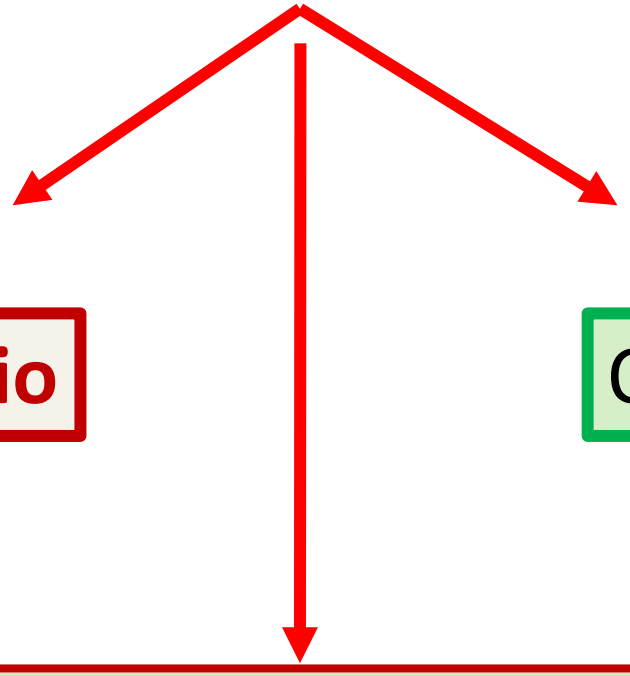
Ma grosso **gap tra la loro incidenza e quella di tumore** del pancreas!

La **maggior parte viene osservata (storia naturale)**

Neoplasia cistica del pancreas

Benigna or maligna ?

Linee Guida…



Sorveglio

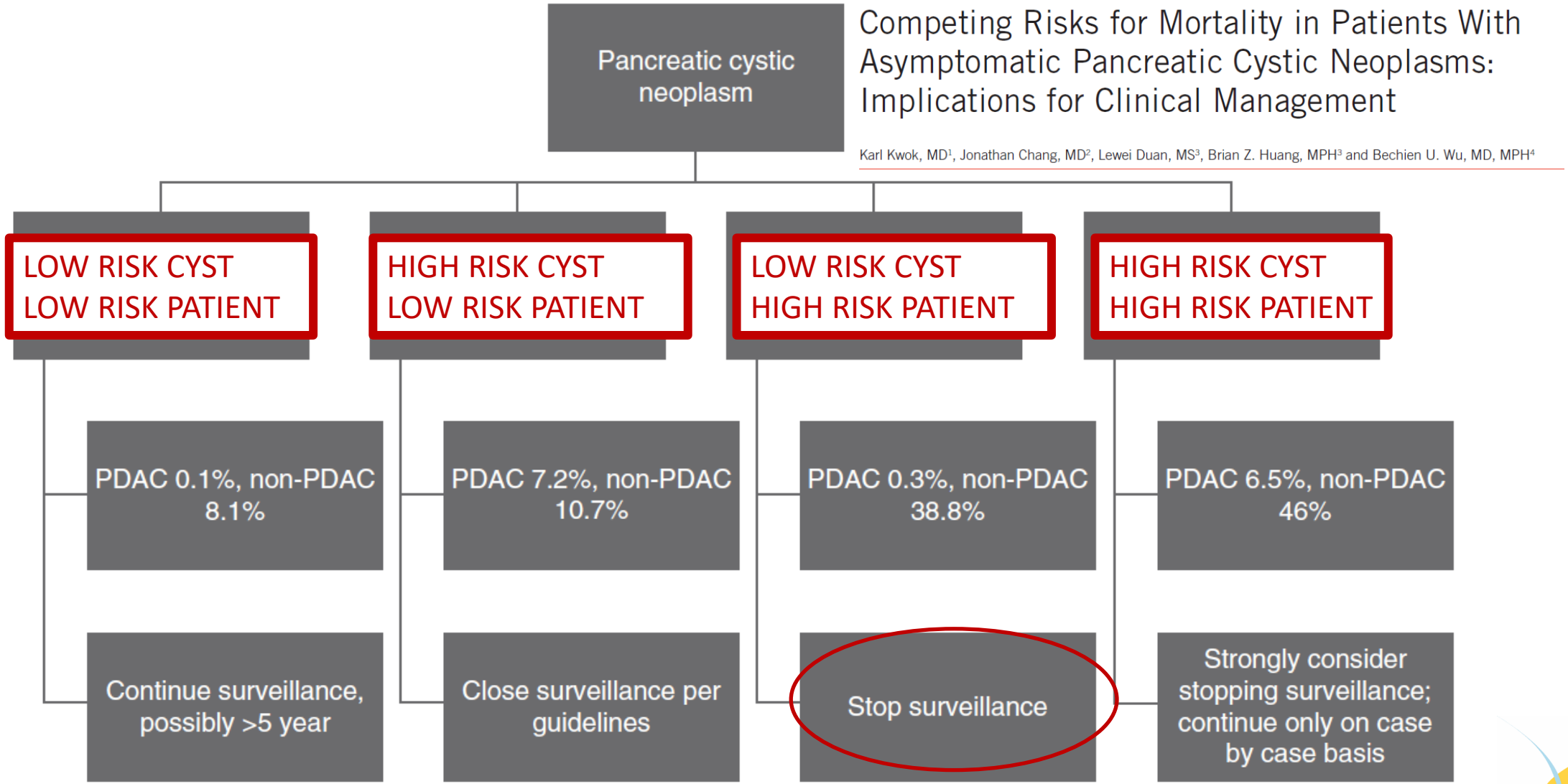
Opero

Paziente che non potrà mai essere operato per comorbidità/età/scelta… non fare nulla

IPMNs: linee guida: dimensioni, noduli, diametro wirsung, sintomi

EUROPEAN	**Relative indication for surgery:** - MPD 5–9.9 mm - Cyst >40 mm - New onset of DM - Growth >5 mm/y - Ca 19.9 >37 U/mL - Acute pancreatitis (caused by IPMN) - Enhancing mural nodules < 5 mm	**Absolute indication for surgery:** - Positive cytology for malignancy or HGD - Enhancing mural nodules (≥ 5 mm) - Jaundice (mass related) - Solid mass - MPD ≥ 10 mm
IAP	**EUS-FNA if any worrisome features:** - Abrupt change in MDP caliber and distal pancreatic atrophy - Cyst >30 mm - Growth >5 mm/2y - Ca 19.9 >37 U/mL - Acute pancreatitis - Thickened/enhancing walls - Lymphadenopathy	**Consider surgery if any high-risk stigmata:** - Enhancing mural nodules (≥5mm) - Jaundice (mass related) - Solid mass - MPD ≥10 mm
AGA	**EUS-FNA** if > 2 high risk features: - Abrupt change in MDP caliber and distal pancreatic atrophy - Cyst >3cm - Solid mass	**Multidisciplinary discussion:** - Positive cytology for malignancy or HGD - MPD suspicious for involvement - Mural nodules >5 mm

..alcuni pazienti non devono neppure fare Follow-up

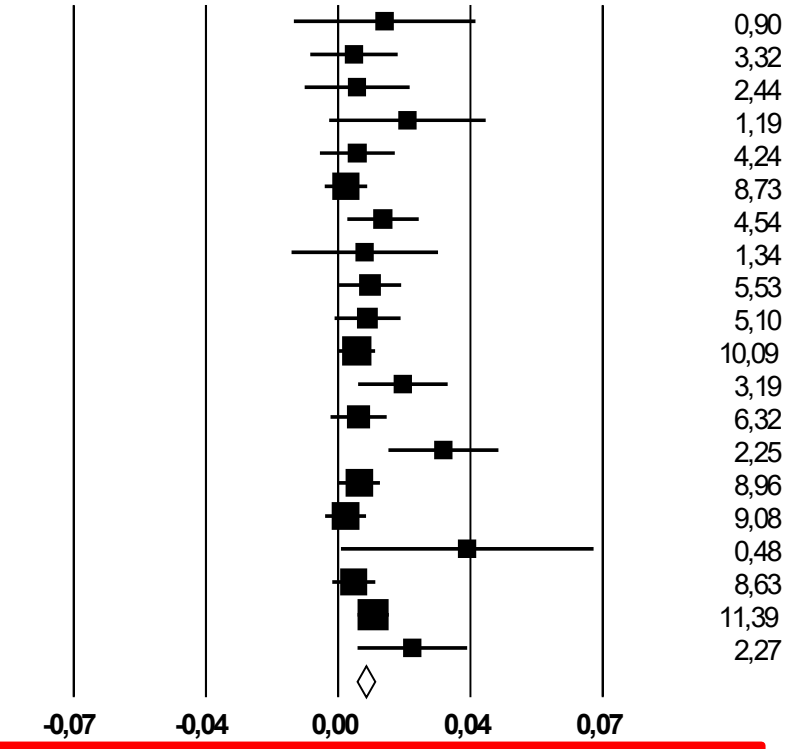


Kwok et al. AJG 2017

Il rischio di evoluzione verso la malignità dei BD-IPMNs è limitato ma non zero

Development of overall pancreatic malignancy

Study name	Rate	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Wakabayashi	0,012	0,012	0,000	-0,012	0,036	1,000	0,317	0,90
Sai	0,004	0,006	0,000	-0,007	0,016	0,707	0,480	3,32
Irie	0,005	0,007	0,000	-0,009	0,019	0,707	0,480	2,44
Kobayashi	0,018	0,011	0,000	-0,002	0,039	1,732	0,083	1,19
Pelaez-Lula	0,005	0,005	0,000	-0,005	0,015	1,000	0,317	4,24
Salvia	0,002	0,003	0,000	-0,004	0,008	0,707	0,480	8,73
Sawai	0,012	0,005	0,000	0,002	0,021	2,449	0,014	4,54
Shin	0,007	0,010	0,000	-0,012	0,026	0,707	0,480	1,34
Tanno	0,008	0,004	0,000	0,000	0,017	2,000	0,046	5,53
Bae	0,008	0,004	0,000	-0,001	0,016	1,732	0,083	5,10
Uehara	0,005	0,002	0,000	0,000	0,010	2,000	0,046	10,09
Kang	0,017	0,006	0,000	0,005	0,029	2,828	0,005	3,19
Khanoussi	0,005	0,004	0,000	-0,002	0,013	1,414	0,157	6,32
Ohno	0,028	0,007	0,000	0,013	0,042	3,742	0,000	2,25
Cauley	0,006	0,003	0,000	0,000	0,011	2,000	0,046	8,96
Arlix	0,002	0,003	0,000	-0,003	0,007	0,707	0,480	9,08
Othman	0,034	0,017	0,000	0,001	0,068	2,000	0,046	0,48
Mori	0,004	0,003	0,000	-0,002	0,010	1,414	0,157	8,63
Sahora	0,009	0,002	0,000	0,005	0,013	4,359	0,000	11,39
Kamata	0,020	0,007	0,000	0,005	0,034	2,646	0,008	2,27
	0,007	0,001	0,000	0,005	0,010	6,018	0,000	



7/1000 pyrs; 0.7% per year

Crippa, Capurso et al. DLD 2016

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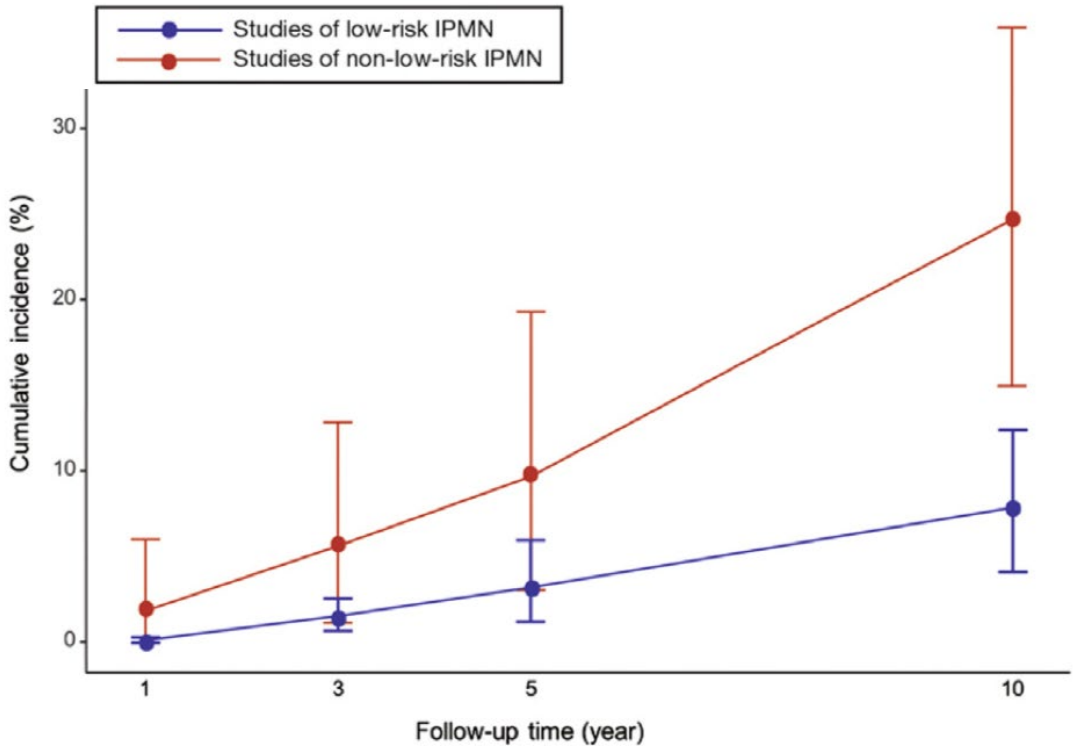
Natural history BD-IPMN: Risk of malignancy?

10 year cancer risk	**(95% CI)**
Non low risk IPMN	25% (15 - 36)
Low risk IPMN	**7.8% (4.1 - 12.4)**



Choi et al. Clinical Gastroenterology and Hepatology 2017

IPMN Summary:
…. Verifica diagnosi
identificare quelli unfit da non controllare

Poi identificare quelli a maggior rischio

1. **Caratteristiche della cisti**

2. **La dinamica** (il film e non la fotografia)

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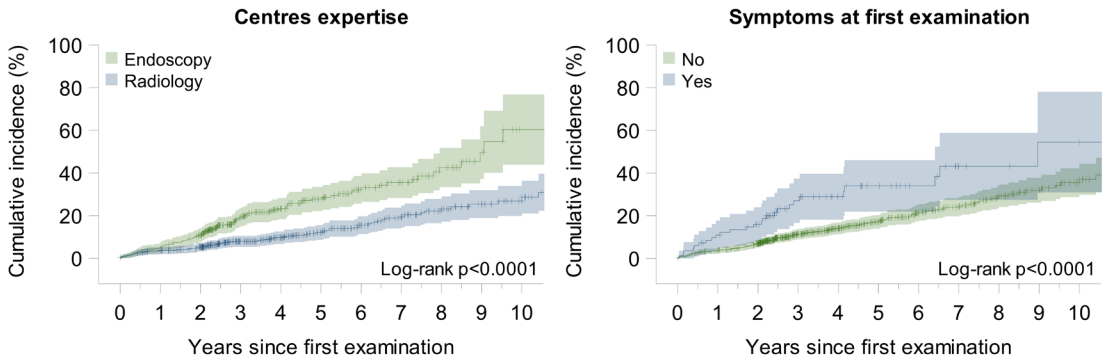
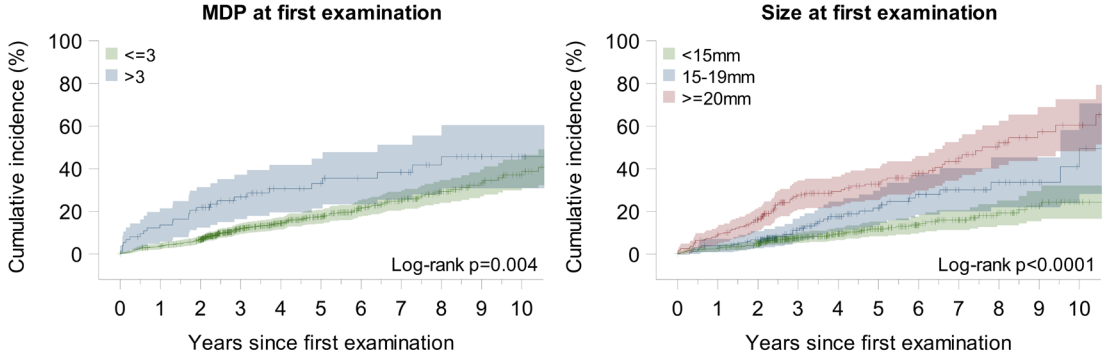
Visione tradizionale: Importanza delle caratteristiche della cisti (WFs, HRS)



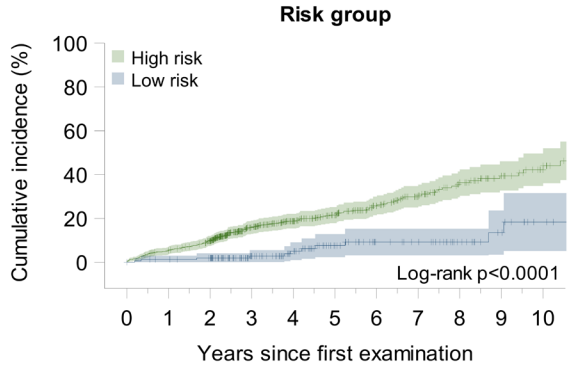
Patients at risk						
Endoscopy	372	325	129	65	27	3
Radiology	465	407	247	154	82	41

Patients at risk						
No	753	668	347	204	103	41
Yes	83	64	29	15	6	3



Patients at risk						
≤3mm	721	648	338	195	93	38
>3mm (<5)	74	56	32	23	15	5

Patients at risk						
<15mm	495	450	223	122	64	26
15-19mm	151	132	68	43	19	7
≥20mm	190	149	84	54	26	11



Patients at risk						
Low risk	159	150	83	43	27	11
High risk	635	553	286	175	81	32

	All patients	Low-risk	High risk
Eligible patients	837	159	635
WF or HRS during surveillance	168	12	152
1-year cumulative incidence	4.3%	1.3%	5.4%
5-year cumulative incidence	18.7%	7.6%	21.5%
10-year cumulative incidence	37.3%	18.3%	42.2%
Indication to surgery	45	2	41
Surgery	40	2	36
% of those with WF/HRS	24%	17%	24%
Final histology			
Benign/Low-grade	22	1	20
High-grade	9	0	9
Invasive	9	1	7

837 pazienti
FU mediano 4,8 anni

Low Risk:
< 15 mm
MPD< 3 mm
No symptoms

Tamburrino et al. BJS 2022

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Gli errori che possiamo commettere seguendo IPMN

1. Under treatment

Non riconoscere una lesione già maligna

2. Overtreatment

Offrire una chirurgia **PESANTE** ad un soggetto con lesione benigna

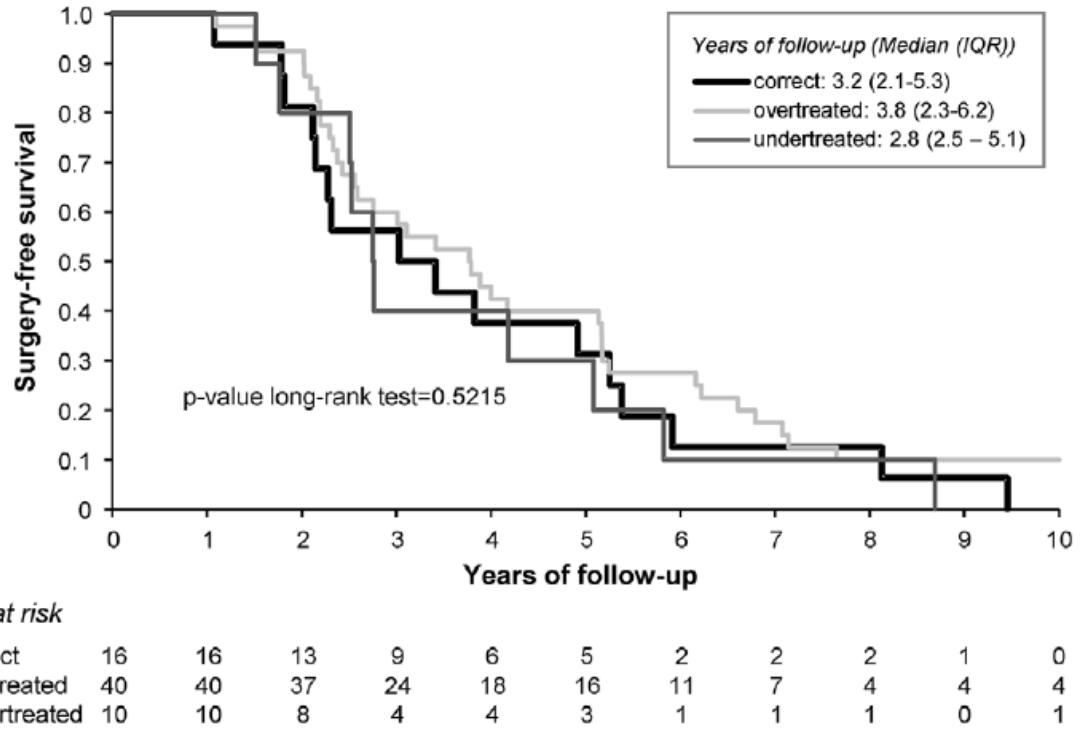
3. Seguire inutilmente chi non ha rischi

IPMN-BD in follow-up in centri di riferimento

Real-world costs and dynamics of surveillance in patients who underwent surgery for low-risk branch duct intraductal papillary mucinous neoplasms

Domenico Tamburrino [a, 1], Paolo Cortesi [b, 1], Rita Facchetti [b], Nicolò de Pretis [c], Enrique Pérez-Cuadrado-Robles [d, e], Laura Uribarri-Gonzalez [f, g], Zeeshan Ateeb [h], Giulio Belfiori [a], Paolo Giorgio Arcidiacono [i], Lorenzo Giovanni Mantovani [b], Marco Del Chiaro [j], Johanna Laukkarinen [k], Massimo Falconi [a], Stefano Crippa [a, *], Gabriele Capurso [i, 2]

EJSO 2023



837 pazienti

FU mediano 4,8 anni

66 operati (7.8%)

16 HGD - CORRECT (1.9%)

40 LGD - OVER (4.7%)

10 K - UNDER (1.2%)

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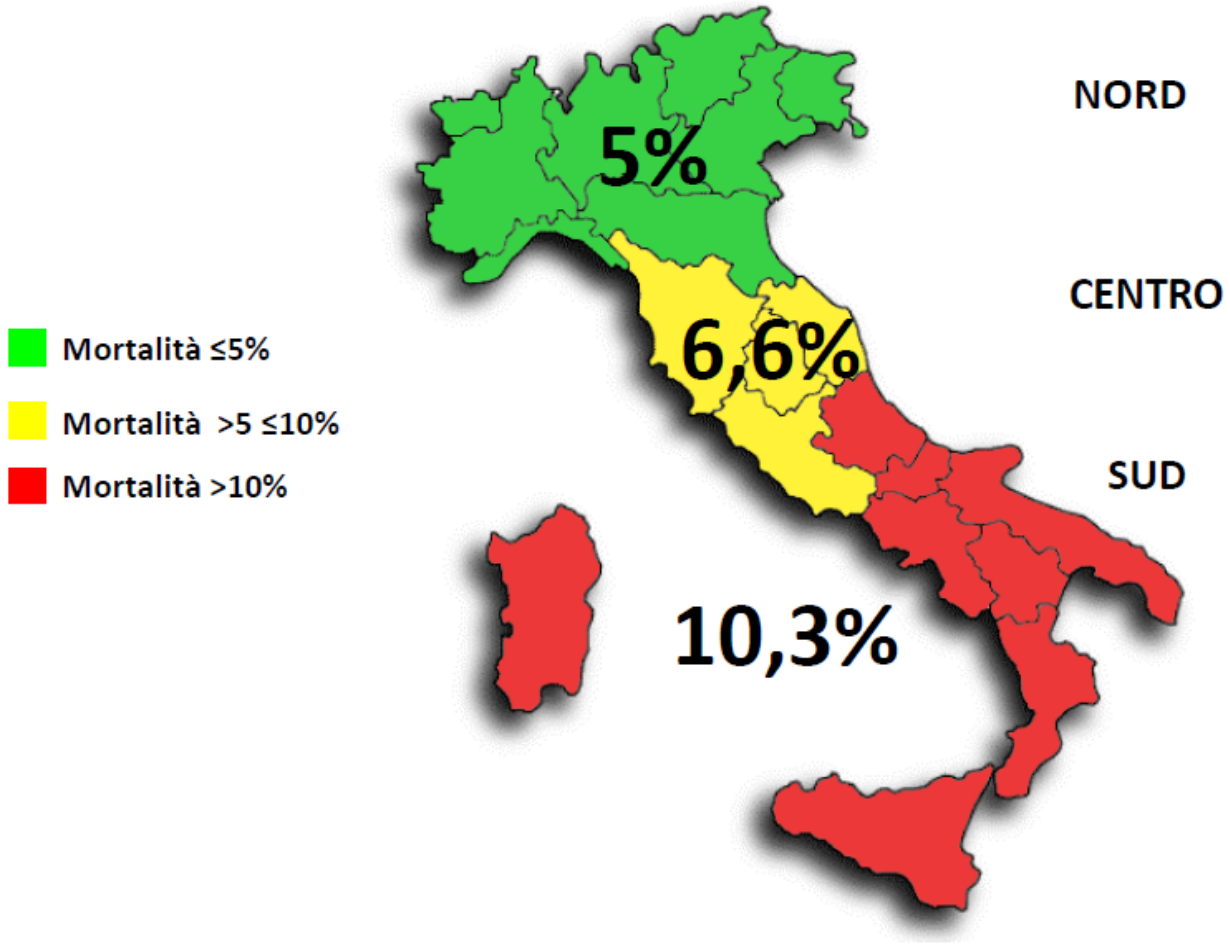
Cosa succede mandando a chirurgia pancreatica una malattia benigna in Italia?



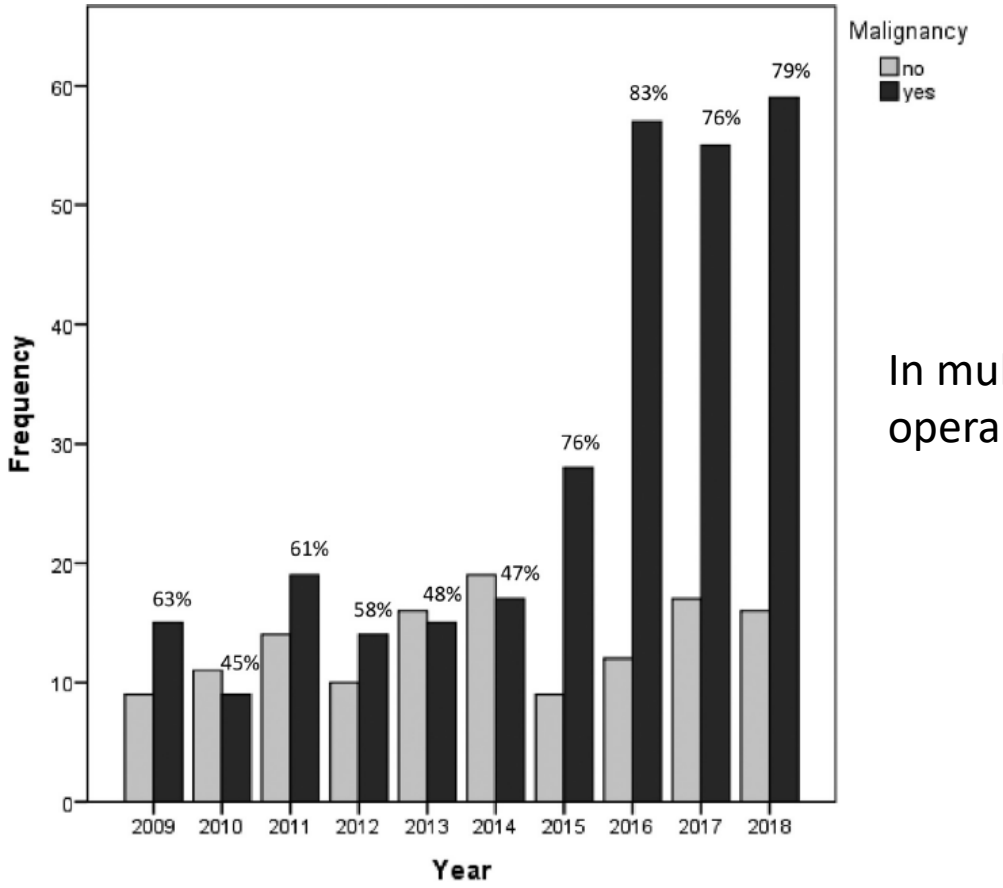
Balzano et al. Cancers 2023

Pancreatic resections for benign intraductal papillary mucinous neoplasms: Collateral damages from friendly fire

Francesca Aleotti, MD[a], Stefano Crippa, MD, PhD[a,*], Giulio Belfiori, MD[a], Domenico Tamburrino, MD, PhD[a], Stefano Partelli, MD, PhD[a], Enrico Longo, MD[a], Diego Palumbo, MD[b], Nicolò Pecorelli, MD[a], Marco Schiavo Lena, MD[c], Gabriele Capurso, MD, PhD[d], Paolo Giorgio Arcidiacono, MD[d], Massimo Falconi, MD[a]

Surgery 2022

Malignant = HGD/cancer



In multivariata, l'EUS diminuisce rischio di operare benigno

Malignancy	Year										Total
	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	
No	9	11	14	10	16	19	9	12	17	16	133
Yes	15	9	20	14	15	17	28	57	55	59	289
Total	24	20	33	24	31	36	37	69	72	75	422

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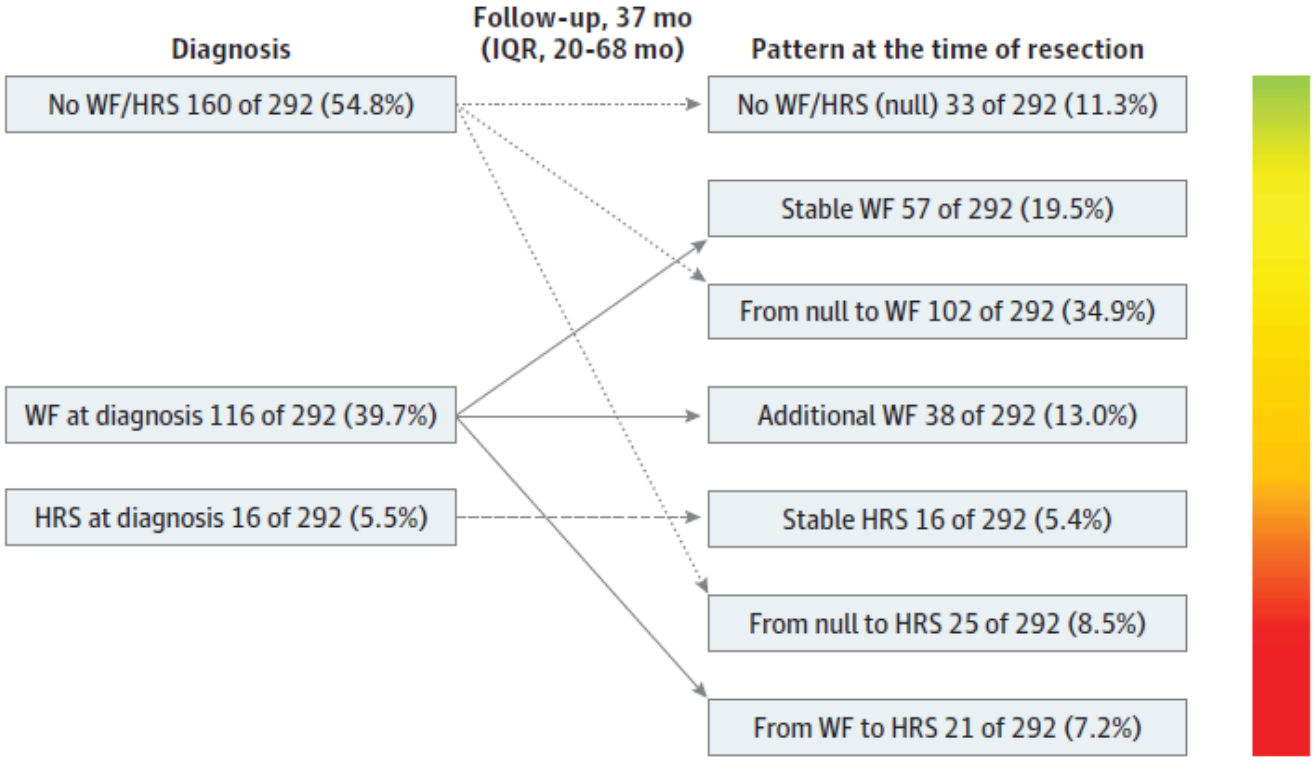
Pensa al film, non alla fotografia!

A Evolutive patterns

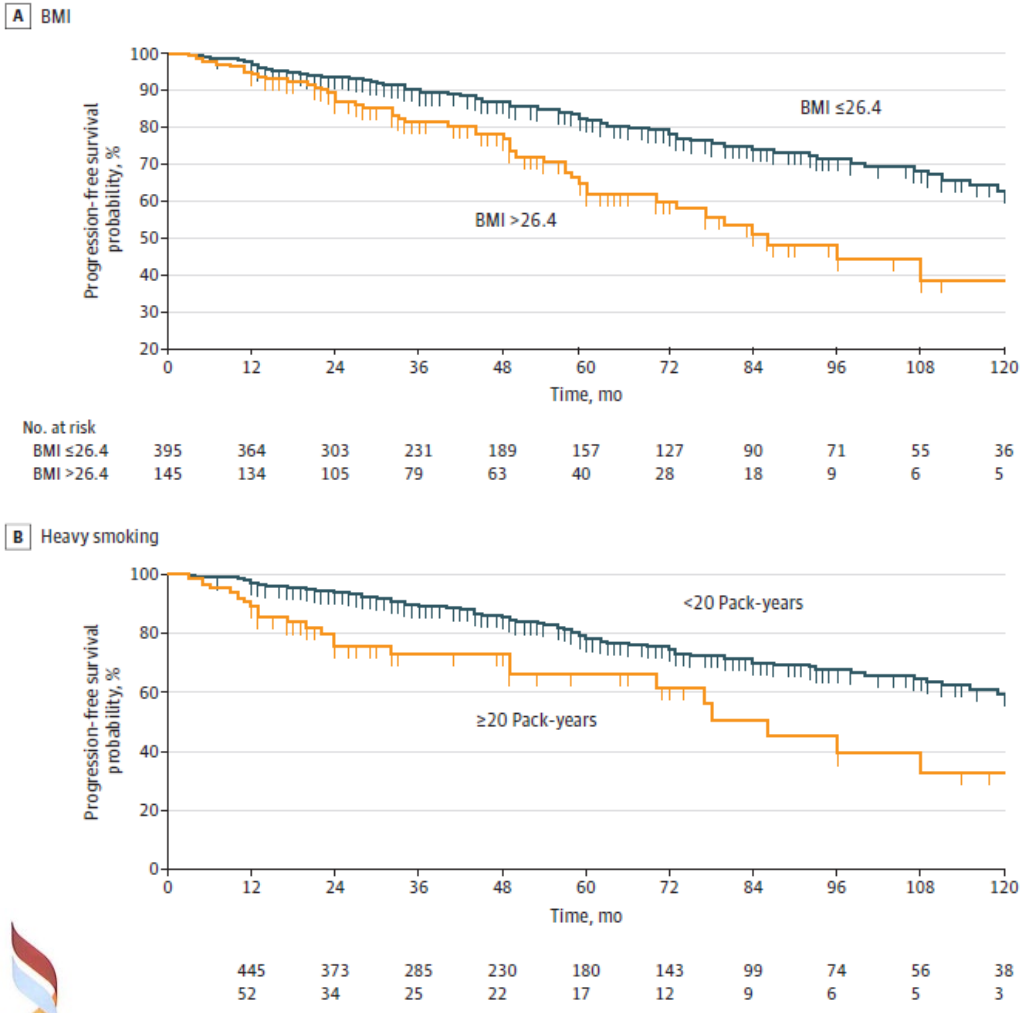


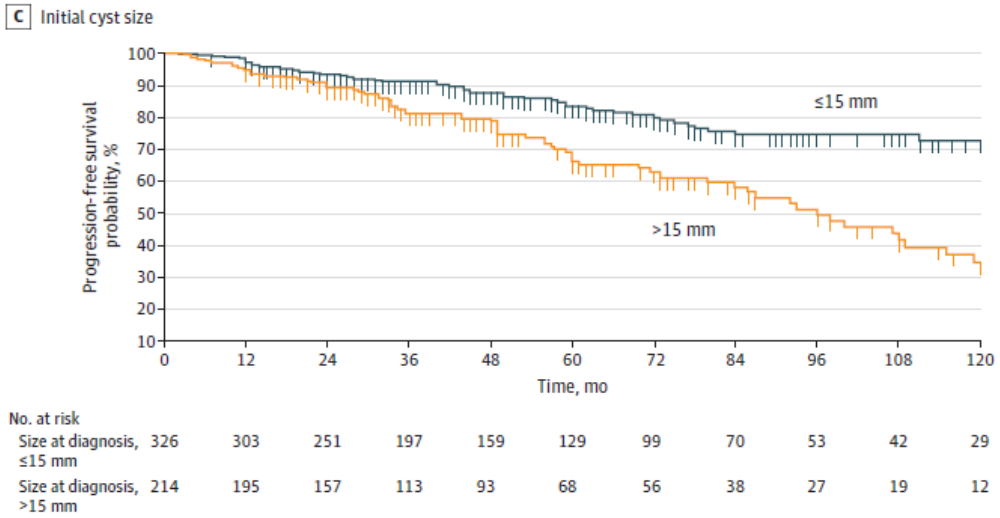
B Rate of HGD and invasive cancer

Pattern	HGD	Invasive cancer	HGD/ invasive
No WF/HRS [reference]	*X*	*X*	*X*
Stable WF	2.5*X*	0.19*X*	0.96*X*
From null to WF	1.61*X*	0.80*X*	1.07*X*
Additional WF	3.75*X*	0.72*X*	1.73*X*
Stable HRS	4.12*X*	0.68*X*	1.83*X*
From null to HRS	2.19*X*	1.97*X*	2.05*X*
From WF to HRS	4.18*X*	1.30*X*	2.26*X*

Marchegiani et al. Jama Surg 2021

Fattori associati al rischio di progressione non sono solo quelli della cisti!





Capurso et al JAMA Open Netw 2020

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IPMN dei soggetti ad alto rischio

	High-Risk Cohort				
	All (N = 81)	FPC Kindreds (n = 54)	PV Carriers (n = 27)	Control Cohort (n = 442)	*P* Value: High-Risk vs Control
Patient characteristics					
Age at IPMN detection, y	59 ± 8 (37–74)	60 ± 8 (37–74)	57 ± 8 (41–72)	65 ± 11 (20–88)	<.001
Body mass index, kg/m^2	26 (6)	26 (6)	26 (7)	25 (5)	.013
Diabetes mellitus	7 (9)	4 (7)	3 (11)	60 (14)	.279
History of acute pancreatitis	4 (5)	4 (7)	0 (0)	3 (1)	.013
History of nonpancreatic malignancy	23 (28)	8 (15)	15 (56)	110 (25)	.491
Largest size at first detection, mm	6 (7)	6 (7)	5 (3)	15 (10)	<.001
Growth rate					
>2.5 mm/y at any moment	25 (31)	12 (22)	13 (48)	32 (7)	<.001
≥5 mm/y at any moment	14 (17)	4 (7)	10 (37)	6 (1)	<.001
≥10 mm/y at any moment	7 (9)	2 (4)	5 (19)	1 (0)	<.001
Development of WFs or HRS[a]					
Excluding growth rate	7 (9)	5 (9)	2 (7)	69 (16)	.123
Including growth rate	26 (32)	13 (24)	13 (48)	82 (19)	.010
Development of multiple WFs or HRS[a]					
Excluding growth rate	2 (3)	1 (2)	1 (4)	15 (3)	1.000
Including growth rate	6 (7)	4 (7)	2 (7)	31 (7)	.817
Development of PC	3 (4)	0 (0)	3 (11)	6 (1)	.150
Surgical resection	3 (4)	1 (2)	2 (7)	10 (2)	.435
Low-grade dysplasia	2 (2)	1 (2)	1 (4)	5 (1)	—
High-grade dysplasia	0 (0)	0 (0)	0 (0)	0 (0)	—
PC	1 (1)	0 (0)	1 (4)	5 (1)	—
All-cause mortality	5 (6)	0 (0)	5 (19)	14 (3)	.194
PC disease-specific mortality	3 (4)	0 (0)	3 (11)	3 (1)	.050
Treatment-specific mortality	0 (0)	0 (0)	0 (0)	0 (0)	—
Nonpancreatic mortality	2 (2)	0 (0)	2 (7)	11 (2)	1.000

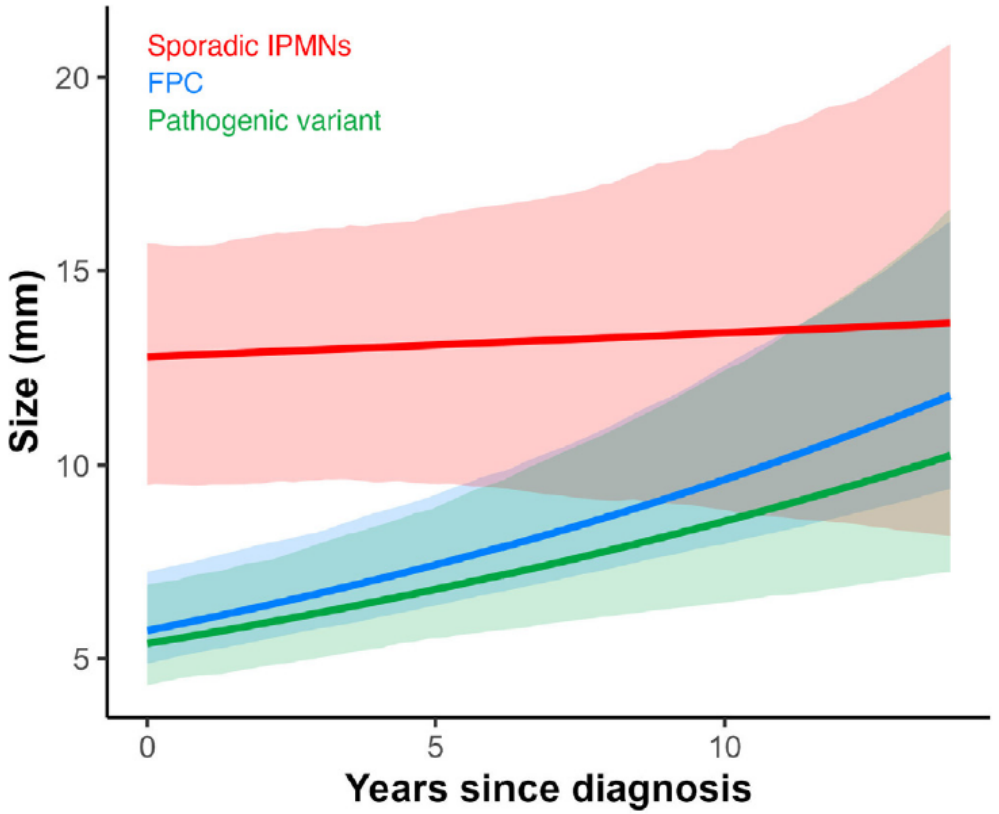

Figure 3. Estimated IPMN size and growth in HRIs and the control cohort.

Overbeek et al. CGH 2023

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Come definire un gruppo in cui Follow-up può essere interrotto?

Table 2. Univariable and multivariable analysis of predictors for PC development

	Univariable			Multivariable		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Sex			0.409			
Male	1					
Female	1.910	0.411–8.869				
Age ≥65 yrs			0.752			
Yes	1					
No	1.211	0.367–3.996				
Growth rate			<0.001			<0.001
<2.5 mm/yr	1			1		
≥2.5 mm/yr	19.827	5.726–68.645		17.882	4.979–64.224	
Development of WF during follow-up			0.047			0.008
No	1			1		
Yes	4.734	1.019–21.984		8.224	1.738–38.903	

BD-IPMNs <15 mm not developing WF or HRS for at least 5 years from the baseline observation were defined as trivial BD-IPMNs.

Marchegiani et al. AJG 2019

OVERALL POPULATION

N= 3844

Female 2313 (60.2%)

SURVEILLANCE 53 (29-82) months

WF during surveillance 775 (20.2%)

HRS during surveillance 68 (1.8%)

Marchegiani et al. Gastroenterology 2023

The Trivial BD-IPMN Study

TRIVIAL POPULATION

NO WF or HRS for the first 5 years of surveillance

N= 1617

Female 925 (57.2%)

SURVEILLANCE 85 (71-108) months

WF after 5 years 235 (14.5%)

HRS after 5 years 30 (1.9%)

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Standardized Incidence Ratio of **PANCREATIC CANCER**

BD-IPMN subgroup	Patients (N)	Person-years	Observed (N)	Crude rate (per 100.000)	Expected (N)	SIR (95% CI)
All patients	3844	33251.76	40	120.29	8.61	4.65 (3.32-6.33)
Non-trivial	2227	10626.36	27	254.08	2.93	9.23 (6.08-13.42)
Trivial	1617	22625.40	13	57.45	5.68	2.29 (1.22-3.91)
Trivial <15 mm	678	8765.40	2	22.81	2.15	0.93 (0.10-3.36)
Trivial 15-29 mm	791	11277.80	4	35.46	2.81	1.42 (0.38-3.64)
Trivial > 30 mm	148	2441.14	7	286.75	0.68	10.29 (4.12-21.21)
Trivial < 65 anni	523	7775.86	5	64.30	0.71	7.02 (2.26-16.38)
Trivial 65-74 y/o	619	8826.22	5	56.64	2.30	2.17 (0.70-5.07)
Trivial 75 + y/o	475	6023.32	3	49.80	2.67	1.12 (0.23-3.39)
Trivial 65 + y/o and lesions < 15 mm	486	6265.9	2	31.91	2.11	0.95 (0.

Marchegiani et al. Gastroenterology 2023

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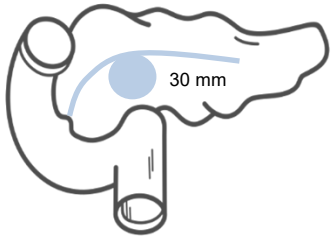
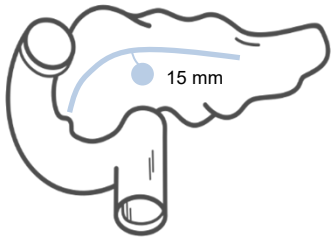
	SIZE AFTER 5 YEARS		AGE
Trivial cyst		NO WF or HRS for the first 5 years of surveillance	75 y/o or older
Trivial cyst < 15 mm			65 y/o or older

CONSIDER SURVEILLANCE DISCONTINUATION

Marchegiani et al. Gastroenterology 2023

Summary

- Le cisti pancreatiche sono molto frequenti, una diagnosi differenziale corretta per **evitare misdiagnosi tra sierosi e mucinosi** (IPMN) ad inizio

è fondamentale

Una volta **definite la diagnosi di IPMN i sintomi,la morfologia e la DINAMICA di crescita sono predittori del rischio di**

Evoluzione verso la Malignità

Summary

- Alcuni **fattori, sia "cisti-relati" che "paziente-relati"** sembrano modificare il rischio di progressione

- **Stop sorveglianza in bassa aspettativa di vita**

(e piccole cisti "Trivial"?)

L'integrazione tra genoma, radioma e esposoma sarà la chiave per un approccio personalizzato

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Conclusion

6th Meeting

PANCREAS

Quality & Innovation in Personalised Pancreatic Care

Where Evidence Based meets Precision Medicine

2023 6th EDITION

28 novembre 2023 Ospedale San Raffaele - Milano

SESSIONE I

Organization Models and Process for an Optimal Pancreatic Neoplasms Care

Chairs: *Gabriele Capurso (OSR Milano, ITA), Massimo Falconi (OSR Milano, ITA)*

09.30 **Pancreatic Disorders Care in Europe: organization models, unmet needs and the way to go**
Matthias Lohr (Stockholm, SWE)

09.45 **Models for Pancreatic Disorders Care in Italy**
Gianpaolo Balzano (OSR Milano, ITA)

10.00 **Relevance of Centers' organization and experience in determining patients' experience and engagement**
Guendalina Graffigna (Catholic University Milano, ITA)

10.15 **Wrap up with Patients' Advocacy Organizations**

SESSIONE II

Early diagnosis of Pancreatic Cancer: opportunities and pitfalls

Chairs: *Stefano Crippa (OSR Milano, ITA), Silvia Carrara (Humanitas Milano, ITA)*

10.30 **Surveillance of high-risk individuals: personalization and biomarkers, where is the holy grail?**
Kasper Overbeek (Erasmus, Rotterdam, NED)

10.45 **IPMNs: too much for nothing?**
Giovanni Marchegiani (Padova, ITA)

11.00 **Wrap up**

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