Semana Digestiva 2018
20 a 23 de junho
Alfândega do Porto

Pancreatic Cystic Lesions Guidelines: to adopt or to adapt?

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Pancreatic Cystic Lesions Guidelines: to adopt or to adapt?

To adapt!

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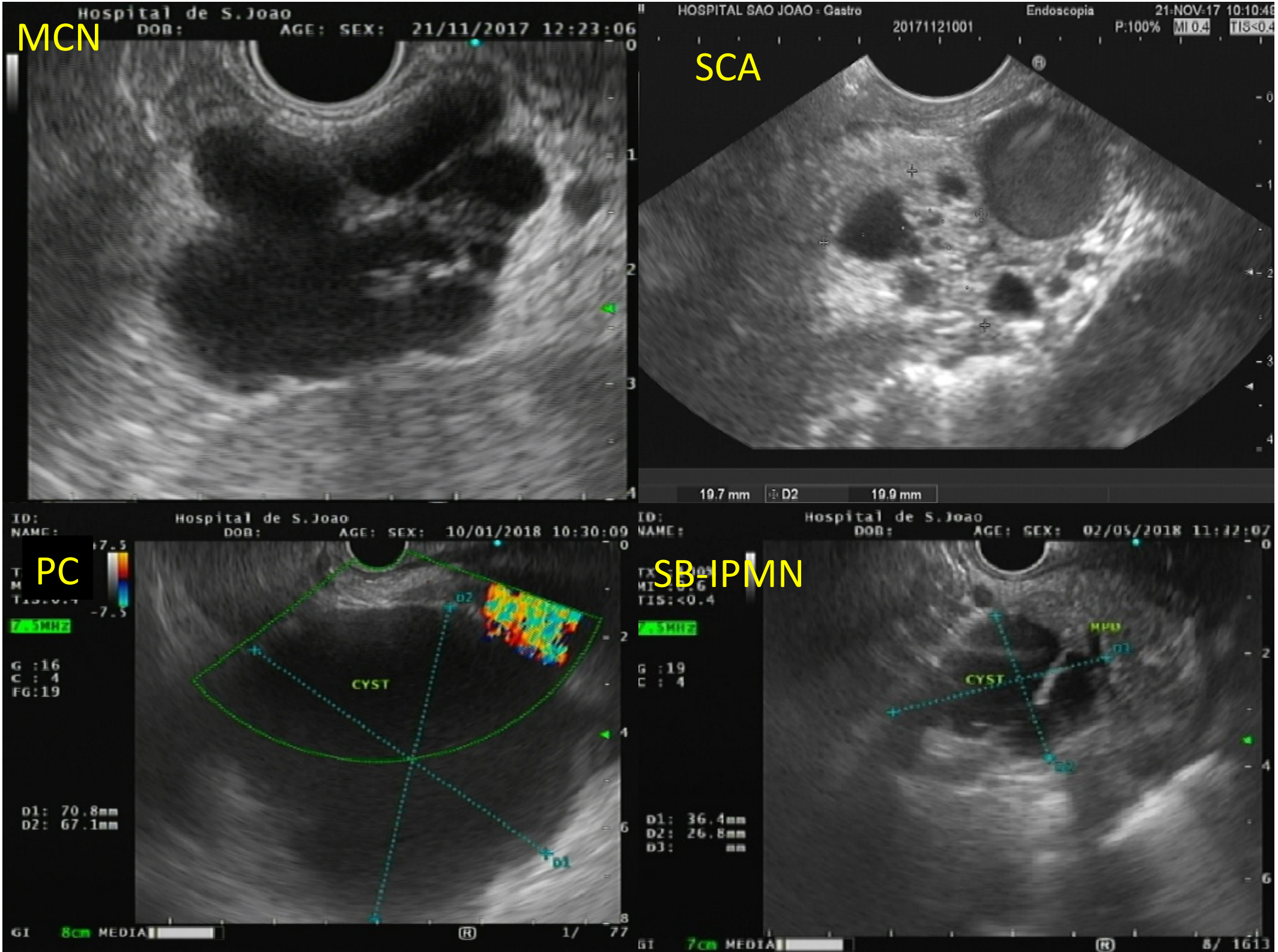
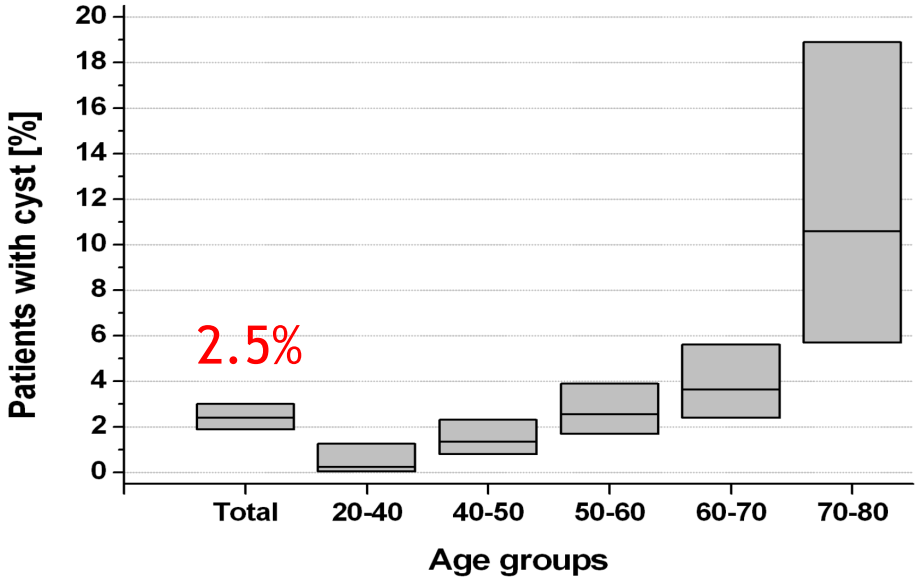
Agenda

- Importance of the problem
- Importance of trustworthy guidelines
- Current guidelines
- Main differences between guidelines:
  - Imaging modalities
  - Indications for EUS-FNA
  - Cyst fluid markers/new endoscopic modalities
  - Indications for surgery
  - Surveillance


MCN
Hospital de S.Joao
DOB:
AGE: SEX:
21/11/2017 12:23:06
SCA
HOSPITAL SAO JOAO - Gastro
Endoscopia
21-NOV-17 10:10:48
20171121001
P:100%
MI 0.4
TIS<0.4
19.7 mm
D2
19.9 mm
PC
Hospital de S.Joao
10/01/2018 10:30:09
CYST
D1: 70.8mm
D2: 67.1mm
SB-IPMN
Hospital de S.Joao
02/05/2018 11:42:07
TIS:<0.4
CYST
MPD
D1: 36.4mm
D2: 26.8mm
D3: mm

The problem of Pancreatic Cystic Lesions

Abdominal MRI Preventive medical care (Germany)
(n=2803; 1821 men; mean age 51 years)



Abdominal CT Health screen exam 2003-2013 (Seoul, Korea)
(n=21745; 60% men; mean age 58.7 years)

Crude prevalence of

Age, y	Total screened	Total Age-specific prevalence
10–19	9	0.000
20–29	191	0.010
30–39	2099	0.005
40–49	6740	0.009
50–59	8033	0.022
60–69	3827	0.037
70–79	772	0.067
80–	74	0.135
Total	21,745	0.021
P		0.007
R^2		0.730

2.1%

IPMN=intraductal papillary mu

De Jong et al. Clin Gastroenterol Hepatol 2010
Chang et al. Medicine 2016

Clinical Importance

ORIGINAL ARTICLE: Clinical Endoscopy

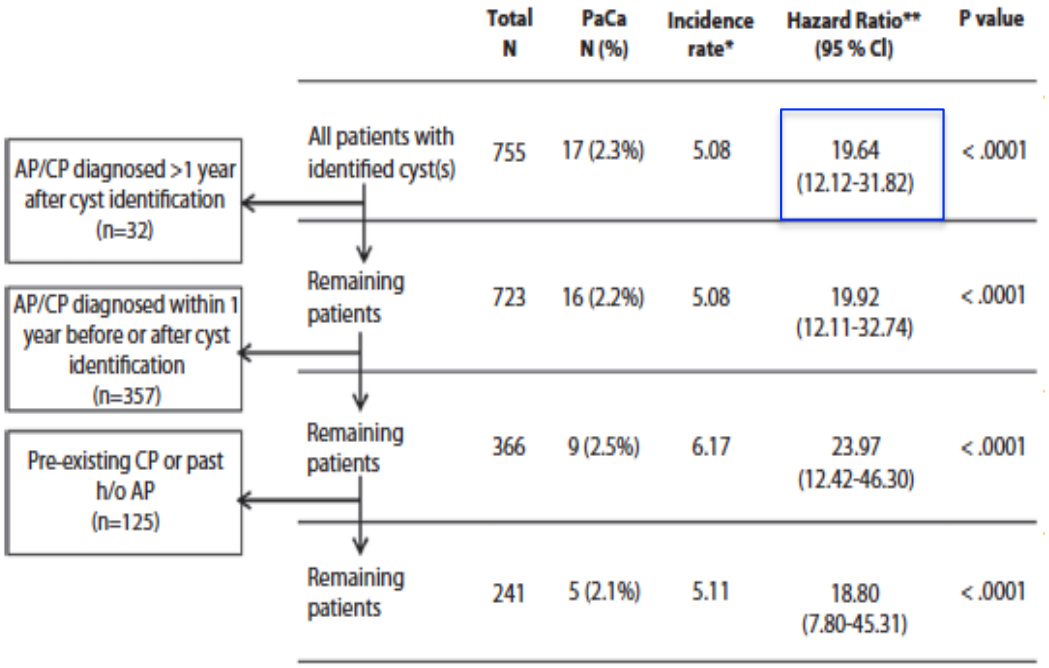
Risk of pancreatic cancer in patients with pancreatic cyst

Satish Munigala, MD, MPH,[1] Andres Gelrud, MD,[2] Banke Agarwal, MD[1]

St. Louis, Missouri; Chicago, Illinois, USA

Retrospective longitudinal cohort study
Panc Cysts CT/MRI **N=755 pts** Vs control without cysts **N=520215**
FU 1998-2007.

Incidence rate of PaCa was 5.08 and .32 per 1000 patient-years
HR PaCa in all patients with cysts was 19.64 (95% CI, 12.12-31.82; P < .0001)



Munigala S et al, Gastrointest Endosc. 2016

Clinical Importance

- Malignancy occurs virtually only in mucinous cysts;
- Most (~60%) incidental PCLs are BD-IPMNs

- IPMN can progress from lower to higher grades of dysplasia and, ultimately, PDAC;

- **IPMNs on surveillance:** 112 invasive cancers in 3980 pts (37 case series) over 14380 person-years FU
  - 2.8% overall, 0.72% per year

Shimizu Y et al. Pancreas. 2013
Scheiman JM et al. Gastroenterology. 2015

Guidelines

	"Eminence-based"	"Evidence-based"
Development	Single individual small group experts	Group process
Conflicts of interest	Strong risk	Disclosure of COI
Point(s) of view	Risk of domineering personalities	Collective process
Cost	Cheaper	Expensive
Methods	??	Delphi method Modified Delphi technique Nominal group NIH consensus conference

- Development of reliable guidelines:
  - Key priority for health care providers
  - Promote best care for patients

Nimish V et al. Am J Gastroenterol 2011

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Guidelines

Too many... Confusing… How to choose which to follow?

AGA 2015

Gastroenterology 2015;148:819–822

AGA SECTION

American Gastroenterological Association Institute Guideline on the Diagnosis and Management of Asymptomatic Neoplastic Pancreatic Cysts

ACG 2018

ACG Clinical Guideline: Diagnosis and Management of Pancreatic Cysts

Grace H. Elta, MD, FACG[1], Brintha K. Enestvedt, MD, MBA[2], Bryan G. Sauer, MD, MSc, FACG (GRADE Methodologist)[3] and Anne Marie Lennon, MD, PhD, FACG[4]

European 2018

Guidelines

ESS

European evidence-based guidelines on pancreatic cystic neoplasms

The European Study Group on Cystic Tumours of the Pancreas

Revised Fukuoka 2017

Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas

Masao Tanaka[a,*], Carlos Fernández-del Castillo[b], Terumi Kamisawa[c], Jin Young Jang[d], Philippe Levy[e], Takao Ohtsuka[f], Roberto Salvia[g], Yasuhiro Shimizu[h], Minoru Tada[i], Christopher L. Wolfgang[j]

Italian 2014

Progress Report

Italian consensus guidelines for the diagnostic work-up and follow-up of cystic pancreatic neoplasms

Italian Association of Hospital Gastroenterologists and Endoscopists, AIGO
Italian Association for the Study of the Pancreas, AISP

Cystic lesions Guidelines

Broadly concordant

- MD-IPMNs, mixed-IPMNs and SPNs…
  → SURGERY
- MCN: no malignancy if ø <4cm and no mural nodule
- Enhancing solid nodule/definite solid nodule≥5mm/+ cytology/ MPD≥10mm
- SCA: No need of resection or surveillance (except symptomatic)

Discordant in BD-IPMNs…

- EUS Indications
- Impact of cyst size
- Threshold for surgery
- Surveillance intervals and cessation

Reasons for the controversy…

- Dificult to develop guidelines without understanding the natural history of disease;
- Low quality of evidence;
- Key limitation of most of available guidelines:
  - Management based on knowledge of cyst histology
  - Focused on cyst characteristics rather than the patient and their ultimate prognosis
- Always **consider the authors and the methods**

Consider the authors…

American Gastroenterological Association Institute Guideline on the Diagnosis and Management of Asymptomatic Neoplastic Pancreatic Cysts

Santhi Swaroop Vege,[1] Barry Ziring,[2] Rajeev Jain,[3] Paul Moayyedi,[4] and the Clinical Guidelines Committee

[1]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota; [2]Division of Internal Medicine, Sidney Kimmel College of Medicine, Thomas Jefferson University, Philadelphia, Pennsylvania; [3]Texas Digestive Disease Consultants, Dallas, Texas; [4]Division of Gastroenterology, Hamilton Health Sciences, McMaster University, Hamilton, Ontario, Canada

4 Gastroenterologists
North America

Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas

Masao Tanaka [a,*], Carlos Fernández-del Castillo [b], Terumi Kamisawa [c], Jin Young Jang [d], Philippe Levy [e], Takao Ohtsuka [f], Roberto Salvia [g], Yasuhiro Shimizu [h], Minoru Tada [i], Christopher L. Wolfgang [j]

7 Surgeons
3 Pathologists
2 Oncologists
2 Gastroenterologists
America/Asia/Europe

Guidelines

ESS

European evidence-based guidelines on pancreatic cystic neoplasms

The European Study Group on Cystic Tumours of the Pancreas

Several Surgeons,
Gastroenterologists,
Radiologists,
Pathologists
Europe

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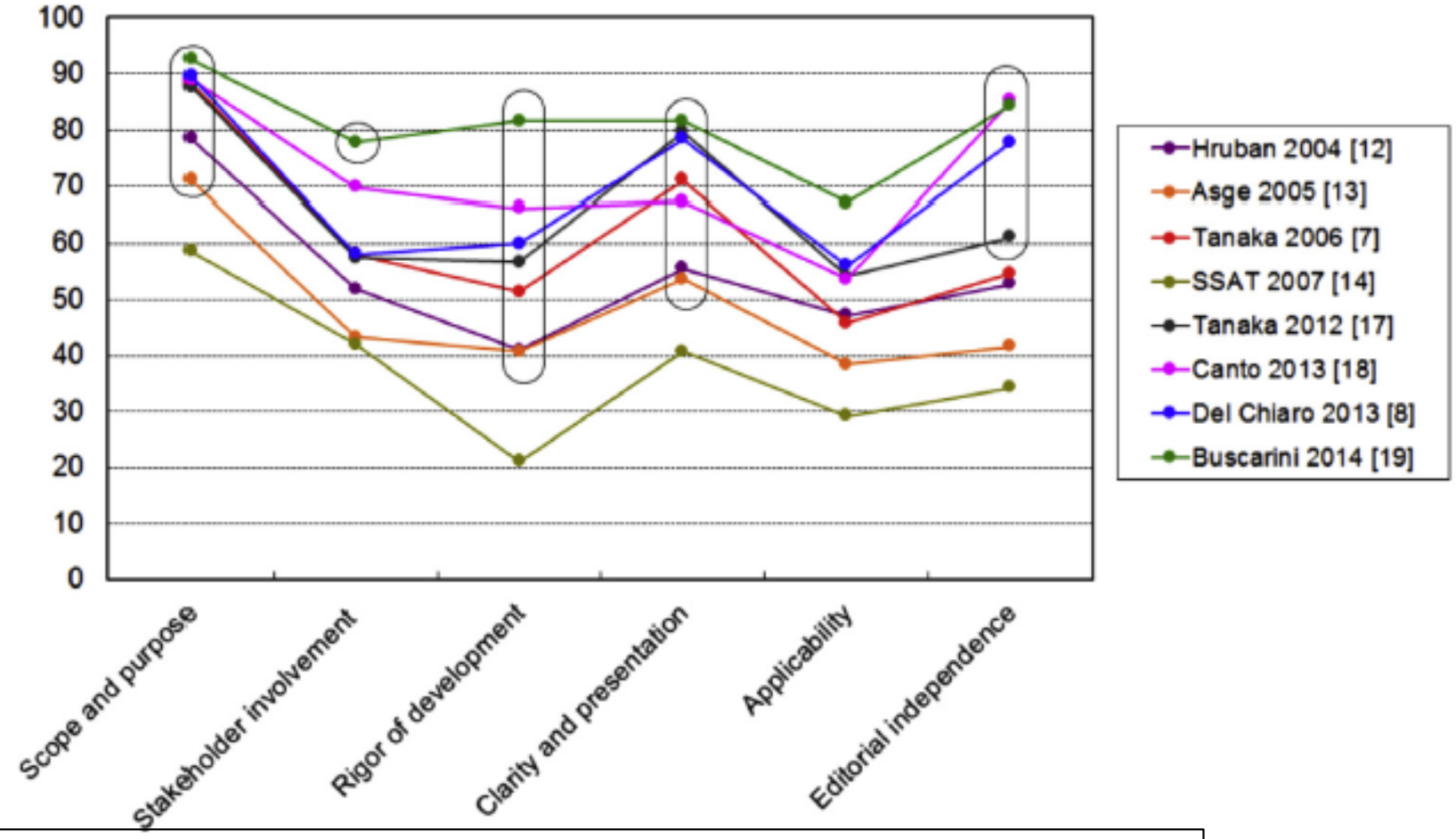
Consider the methods…

Appraisal of Guidelines, Research and Evaluation in Europe (AGREE) II instrument.



All guidelines: scores lower than the minimum AGREE standardized score regarding Rigor of Development

Falconi M et al. Pancreatology 2015

Consider the methods…

Guideline	Consensus process
ICG - Revised Fukuoka 2017	Consensus Symposium
AGA 2015	GRADE framework
European 2018	GRADE framework
ACG 2018	GRADE framework
Italian 2014	Delphi procedure ; Oxford criteria

GRADE: Grading of Recommendations Assessment, Development and Evaluation

http://www.gradeworkinggroup.org/

Main topics…

- Initial assessment: Imaging modalities
- Indications for EUS-FNA
- Cyst fluid markers/ New diagnostic modalities
- Indications for surgery
- Surveillance:
  - How?
  - Interval?
  - For how long?

Imaging modalities

Guideline	Imaging recomendation
ICG (Revised Fukuoka 2017)	Pancreatic protocol CT or MRCP for cysts **>5mm size**
AGA 2015	MRI
European 2018	MRI-MRCP and/or CT
ACG 2018	MRI or CT
Italian 2014	MRI-MRCP and/or CT

Indications for EUS-FNA

Guideline	EUS-FNA
ICG (Revised Fukuoka 2017)	*Worrisome features
AGA 2015	****≥2 high-risk features**
European 2018	Clinical or radiological features of concern; Hyperenhancement on CH-EUS
ACG 2018	Cysts in which the diagnosis is unclear, and where the results are likely to alter management
Italian 2014	"suspicious" morphological features or uncertain radiologic diagnosis

*Worrisome features: pancreatitis, cyst ≥3 cm, **enhancing mural nodule < 5 mm**, thickened/enhancing cyst walls, main duct size 5-9 mm, abrupt change in caliber of pancreatic duct with distal pancreatic atrophy, lymphadenopathy, **increased serum CA19-9** , **cyst growth rate > 5 mm / 2 years**

**AGA High-risk features: dilated MPD(≥5mm), ≥3 cm cyst or non-enhancing solid component

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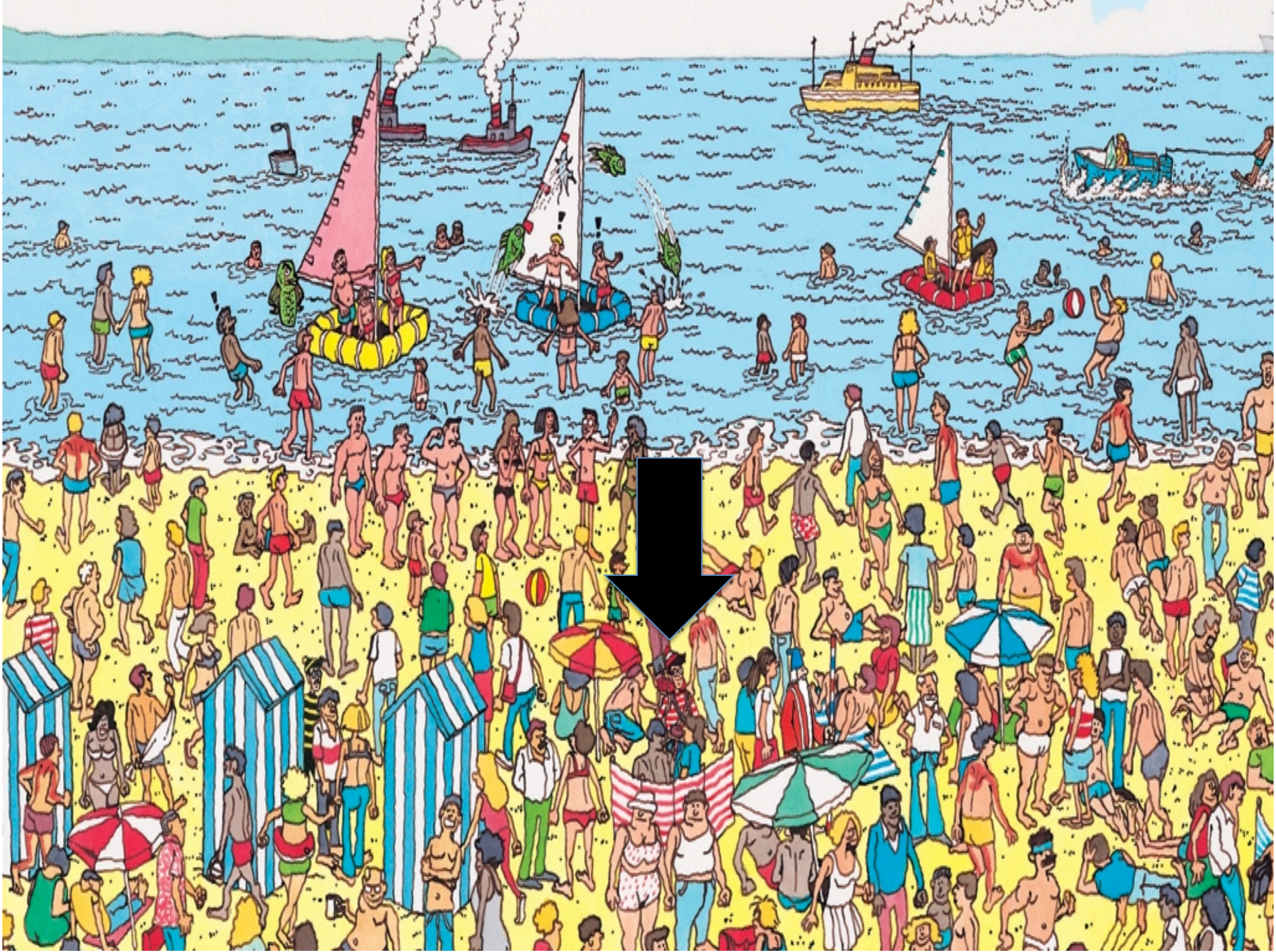


EUS-FNA

- Diagnose main duct involvement
- Confirm a solid component
- Diagnose high-grade dysplasia or cancer

- **Cysts that have clear indication for resection based on imaging/symptoms do not need EUS!**

EUS-FNA

Original Article

Requirement of a single high-risk feature as an indication for EUS for the diagnosis of asymptomatic pancreatic cysts

Divyanshoo R. Kohli*, Ashwani Kapoor, Doumit BouHaidar, Ravi Vachhani

Division of Gastroenterology, Virginia Commonwealth University, Richmond, VA, USA

Retrospective cohort study
210 pts with PCLs had EUS 2004-2015.

The requirement ≥2 HRF would have decreased the number of EUS procedures by 91%, but **reduced the sensitivity for pancreatic malignancy to 50%.**

Table 5
Statistical performance for diagnosis of pancreas cancer based on number of high-risk features.

Parameters	At-least 2 high risk features[a]	At-least 1 high risk feature
Sensitivity (%)	50	100
Specificity (%)	92	64

[a] Based on the AGA practice guideline 2015 [4].

Divyanshoo R et al. Surg Endosc. 2018

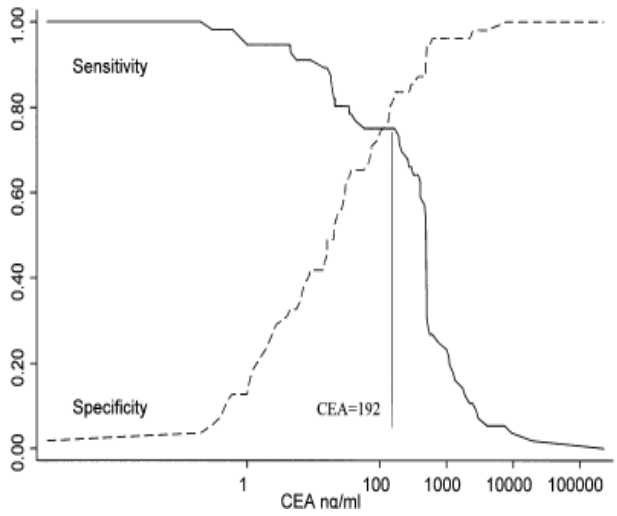
Cyst Fluid Analysis/New modalities

Guideline	CEA	Biochemistry	Cytology	Molecular analysis	Comments
ICG (Revised Fukuoka 2017)	M	amylase	investigational	KRAS/GNAS Investigational	EUS-FNA for citology and molecular is still considered **investigational**
AGA 2015	R		R	Investigational	
European 2018	R	Lipase	R	KRAS/GNAS (conditional)	**Brush citology and forceps biopsy not recommended**
ACG 2018	R	-	R	Not ready for clinical practice	Brush citology and forceps biopsy not recommended
Italian 2014	R	amylase	R	-	CA 19.9 when CEA indeterminate

R: recommended; M: mentioned; - not mentioned

Cyst Fluid Analysis

- **CEA:**
  - Level ≥192 ng/ mL distinguishes mucinous, from non-mucinous cysts (Sens 75%; Spec 84%)
  - Inaccurate to predict grade!



- **Cytology:**
  - Meta-analysis: 42% Sens; 99% Spec differentiating mucinous vs non-mucinous

- **KRAS/GNAS/other molecular markers**
  - Costly and may not add to standard analysis!

Gillis A et al. HPB (Oxford) 2015
Ngamruengphong S et al. Dig Liver Dis. 2013
Brugge WR et al. Gastroenterology 2004

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Pancreatic Cystic Lesions

New Endoscopic Trends in Diagnosis

Filipe Vilas-Boas, MD and Guilherme Macedo, PhD, FACG, FASGE, AGAF

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GINEP Porto Training Center WGO

Uso de micro-pinça Moray® no decurso de ecoendoscopia: um significativo avanço tecnológico para a caracterização de lesões císticas pancreáticas

Filipe Vilas-Boas, Joanne Lopes, Guilherme Macedo

Gastroenterology and Pathology Department, *Centro Hospitalar de São João, Porto*

- Through-the-needle forceps biopsy (Moray-US Endoscopy)
- Contrast Enhanced Endoscopic Ultrasound
- Cytology brush (Echobrush®)
- Needle with side fenestration (Procore – Cook)
- Cystoscopy and Pancreatoscopy (Spyglass®)
- Confocal LASER Endomicroscopy (nCLE)

Vilas-Boas F et al. J Clin Gastroenterol. 2018

Surgery

Guideline	Symptoms	MPD	Mural nodule	Positive citology	Size	Comments
ICG (Revised Fukuoka 2017)	+ jaundice	≥10mm	+ 5mm cut-off	+	**-***	HRS, **Consider life expectancy, comorbidities and location**
AGA 2015	NA	dilated	+	**+**	-	**and/or 2 features
European 2018	+ Jaundice, acute pancreatitis	≥10mm (5-9.9mm relative indication)	+ 5mm cut-off	+	≥4cm (relative indication)	**Growth rate** ≥5mm/year, new-onset DM **elevated CA19.9**
ACG 2018	+ Jaundice, acute pancreatitis	≥5mm	+	+	≥3cm	**Growth rate** ≥3mm/year, new-onset DM **elevated CA19.9**
Italian 2014	+	≥10mm	+	+		**Family history** (≥2 first degree reatives

*cyst size alone is not an appropriate parameter to indicate surgery BUT consider surgery >2cm, young fit pts
**positive citology and/or both solid component and MPD dilation

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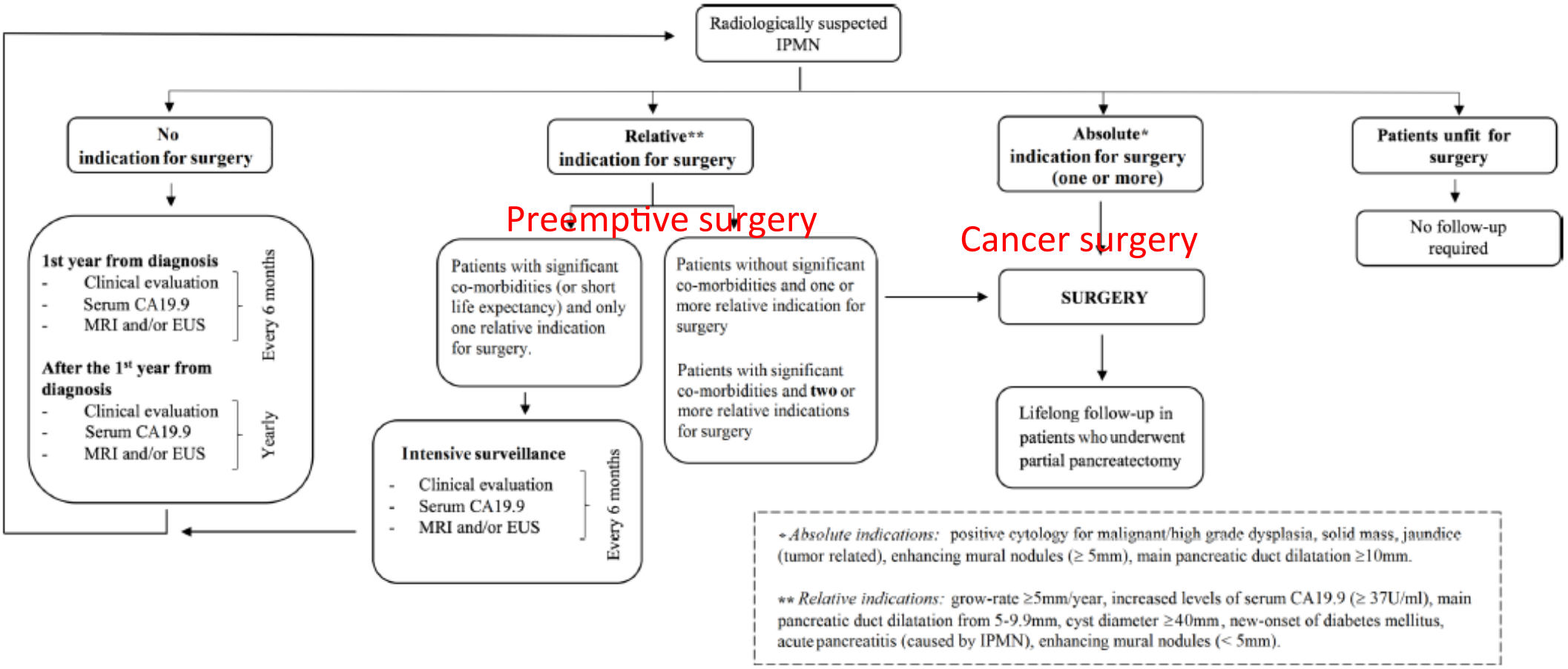
IPMNs: Individualized decision...

Consider the patient!!!



European Guidelines
Del-Chiaro M et al. Gut. 2018

Consider IPMN natural history…

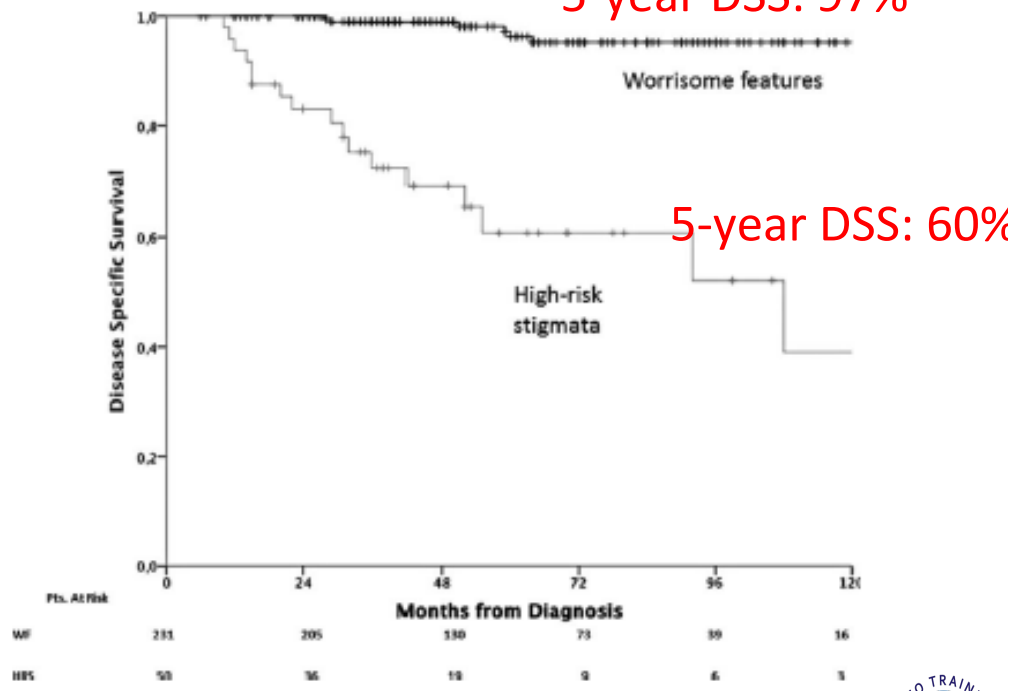
Low progression of intraductal papillary mucinous neoplasms with worrisome features and high-risk stigmata undergoing non-operative management: a mid-term follow-up analysis

Retrospective Multicentric study
N=281 eldery IPMN pts (BD 159; MD 122)
(231 WF; 50 HRS)
Median age: 70yrs
Median FU 51 months.

IPMNs WF: 5-year DSS is 96%→conservative management!

IPMNs HRS: 40% risk of IPMN-related death. reinforcing that surgical resection should be offered to fit patients

5-year DSS: 97%



5-year DSS: 60%

Figure 3 Patients with worrisome features had a significantly better 5-year disease-specific survival (DSS) compared with those with high-risk stigmata (5-year DSS: 96.2% vs 60.2%, p<0.0001).

Crippa S et al. Gut. 2017

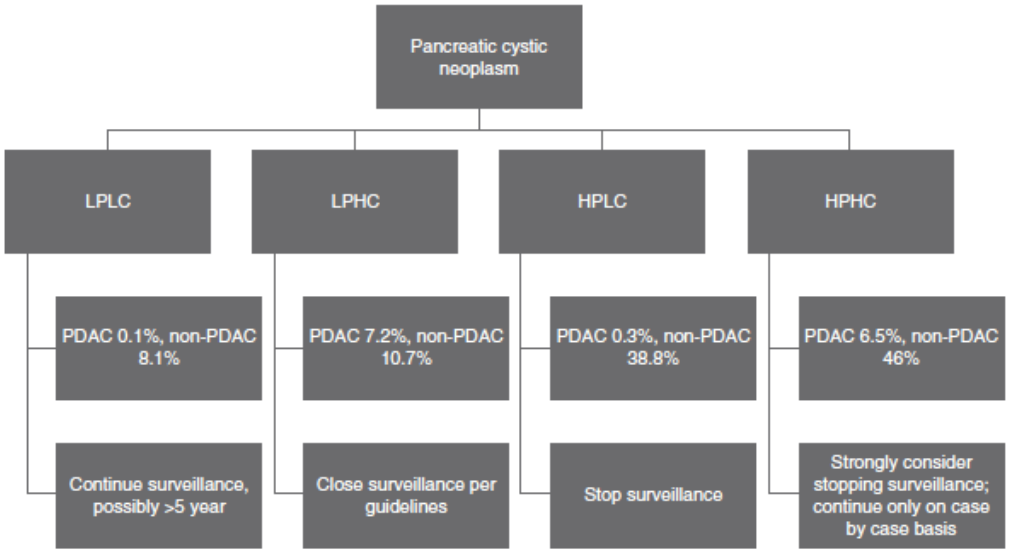
Patient-oriented PCN Management

Competing Risks for Mortality in Patients With Asymptomatic Pancreatic Cystic Neoplasms: Implications for Clinical Management

Karl Kwok, MD[1], Jonathan Chang, MD[2], Lewei Duan, MS[3], Brian Z. Huang, MPH[3] and Bechien U. Wu, MD, MPH[4]

Retrospective cohort (2005-2010)
N= 1800 pts with PCNs; Median FU=5.7yrs
Stratified based on **Charlson comorbidity** index and baseline cyst features

402 deaths – 22% (43 panc ca**; 359 non-pancreatic**)
Patient-related factors + cyst features→help guide PCN management



Kwok K et al. Am J Gastroenterol. 2017

IPMNs: importance of growth rate…

Rapid Growth Rates of Suspected Pancreatic Cyst Branch Duct Intraductal Papillary Mucinous Neoplasms Predict Malignancy

Wilson T. Kwong[1] · Robert D. Lawson[2] · Gordon Hunt[3] · Syed M. Fehmi[1] · James A. Proudfoot[4] · Ronghui Xu[5] · Andrew Giap[6] · Raymond S. Tang[7] · Ingrid Gonzalez[1] · Mary L. Krinsky[1] · Thomas J. Savides[1]

Retrospective Multicentric study
N=284 pts (BD-IPMN without WF or HRS)
FU median 56 months.

Growth rate ≥5mm/year-->HR 19.5 (95% CI 2.4-157.8)

Table 3 Diagnostic performance of BD-IPMN growth rates and total growth for predicting invasive carcinoma

	Sensitivity	Specificity	PPV	NPV	Accuracy
Growth rate					
2 mm/year	78	90	18	99	88
5 mm/year	56	97	36	99	95
Total growth					
10 mm	100	95	40	100	95
Percentage growth					
40 %	78	84	14	99	84

PPV positive predictive value, *NPV* negative predictive value

Kwong W et al. Dig Dis Sci 2015

Surveillance…mucinous cysts

Guideline	Follow-up indications	Stop surveillance
ICG (Revised Fukuoka 2017)	< 1cm – CT/MR in 2-3 years 1-2 cm – CT/MR yearly x 2 then lengthen as appropriate *2-3 cm – EUS in 3-6 months then lengthen as appropriate *>3 cm – **MRI/EUS** every 3-6 months up to 1year	Lifelong (until not fit for surgery)
AGA 2015	MRI after one year then MRI every 2 years	**Stable appearance after five years**
European 2018	**EUS/MRI** and CA 19-9 after six months then EUS/MRI and CA 19-9 yearly	Lifelong (until not fit for surgery) **Intensification after 5yrs?**
ACG 2018	Cyst size guides surveillance (similar to ICG)	When not fit for surgery, **assess utility in those >75years**
Italian 2014	Cyst size guides surveillance (similar to ICG)	Lifelong

*consider surgery in young fit patients with need for prolonged surveillance

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Stop surveillance? No!

Active Surveillance Beyond 5 Years Is Required for Presumed Branch-Duct Intraductal Papillary Mucinous Neoplasms Undergoing Non-Operative Management

Stefano Crippa, MD, PhD[1,2], Raffaele Pezzilli, MD[3], Massimiliano Bissolati, MD[4], Gabriele Capurso, MD, PhD[5], Luigi Romano, MD[6], Maria Paola Brunori, MD[7], Lucia Calculli, MD[8], Domenico Tamburrino, MD[1,2], Alessandra Piccioli, MD[2,9], Giacomo Ruffo, MD[1], Gianfranco Delle Fave, MD[5] and Massimo Falconi, MD[1,2]

Retrospective Multicentric study
N=144 pts (BD-IPMN without WF or HRS) with FU >5 years (yearly MRI/MRCP)
Median FU 84 months. Rate of malignancy 2%; 12 year DSS 98.6%

New-onset of WF/HRS in 26pts (18%) after median FU 71 and 77.5 months.
One out of six patients developed WF/HRS beyond 5 years of surveillance.

Persistent surveillance is required. Indeed, closer follow-up evaluations should be considered after 5 years from initial diagnosis.

Crippa S et al. Am J Gastroenterol. 2017

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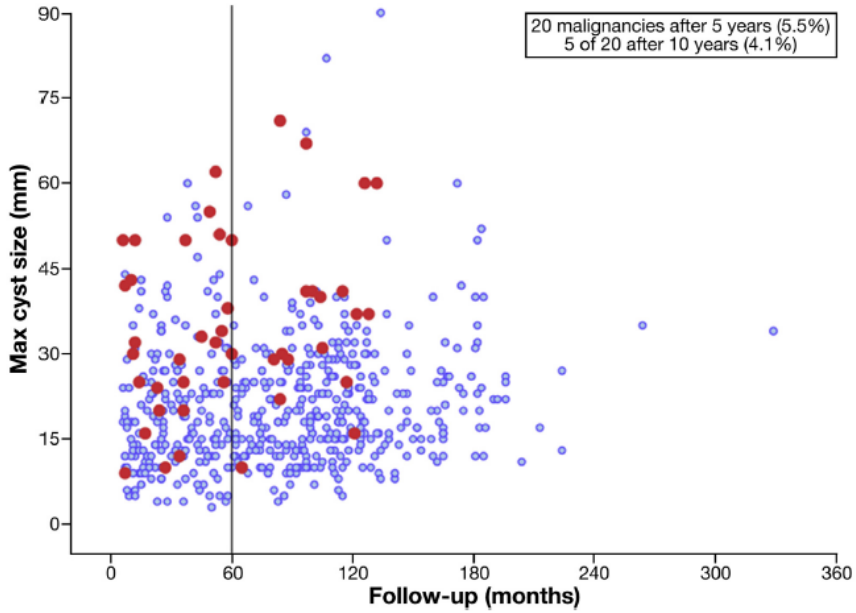
Stop surveillance? Maybe…

Long-term Risk of Pancreatic Malignancy in Patients With Branch Duct Intraductal Papillary Mucinous Neoplasm in a Referral Center

Ilaria Pergolini,[1,2] Klaus Sahora,[1] Cristina R. Ferrone,[1] Vicente Morales-Oyarvide,[1,3] Brian M. Wolpin,[3] Lorelei A. Mucci,[4] William R. Brugge,[5] Mari Mino-Kenudson,[6] Manuel Patino,[7] Dushyant V. Sahani,[7] Andrew L. Warshaw,[1] Keith D. Lillemoe,[1] and Carlos Fernández-del Castillo[1]

Retrospective unicentric study
N=577 pts BD-IPMN under surveillance
Median FU 82 months. **363 pts surveillance >5yrs**
Overall, 45 patients (7.8%) developed panc malignancy, **5 of them after 10yrs of FU**
Risk of malignancy, almost 8%, lasted for 10 years or more
Cysts that remain 1.5 cm for more than 5 years might be considered low-risk



Pergolini I et al. Gastroenterology 2017

Which guideline should we follow?

Revised Fukuoka	AGA	European
The most aggressive toward surgery	The most conservative	The most aggressive toward surveillance
Least likely to miss a malignancy	Higher possibility for missing a malignancy	Individualized decision
"Live with unnecessary surgery"	**"Live with uncertainty"**	**"Live with excessive cost"**

Adapted from Timothy B. Gardner, DDW Clinical Symposium 2017

Take-Home messages

- Full multidisciplinary discussion upfront!!
- Surgery at high-volume centers!
- Discuss the options with the patients
  - All the evidence related to the management of pancreatic cysts is graded as very low quality
  - High risk stigmata have the highest PPV for malignancy
- Treatment and surveillance decisions:
  - Decision to observe vs resect often remains individual
  - Consider life expectancy, comorbidities and location
  - Most patients will die with the cyst rather than from it…
- **Strict adherence to a particular guideline is probably not the best option→ ADAPT!!**

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