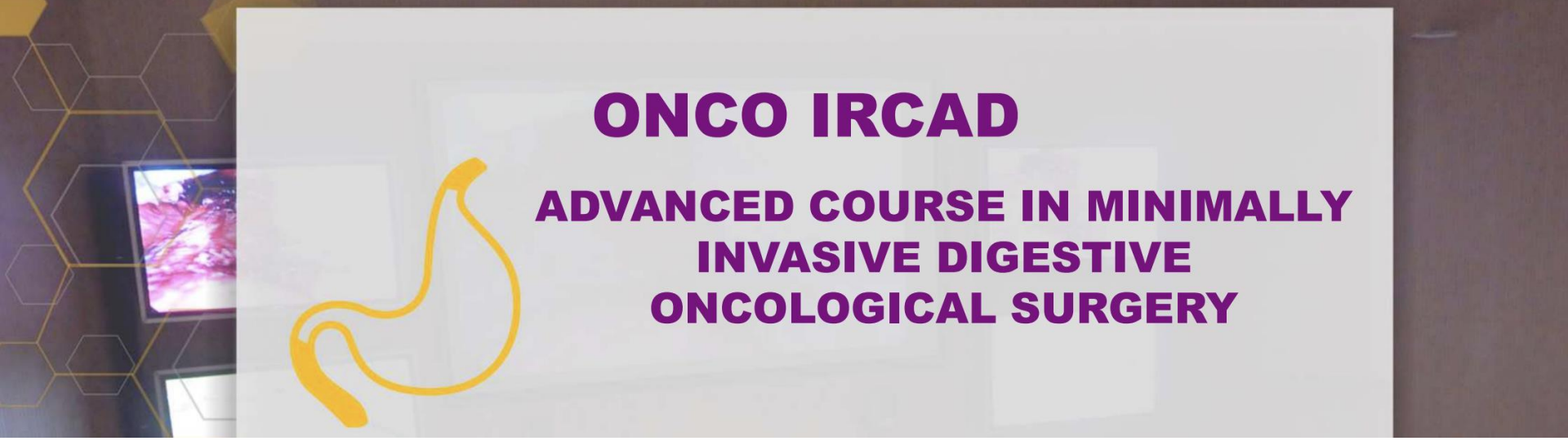

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas: diagnosis and surgical treatment

Orlando Jorge M. Torres
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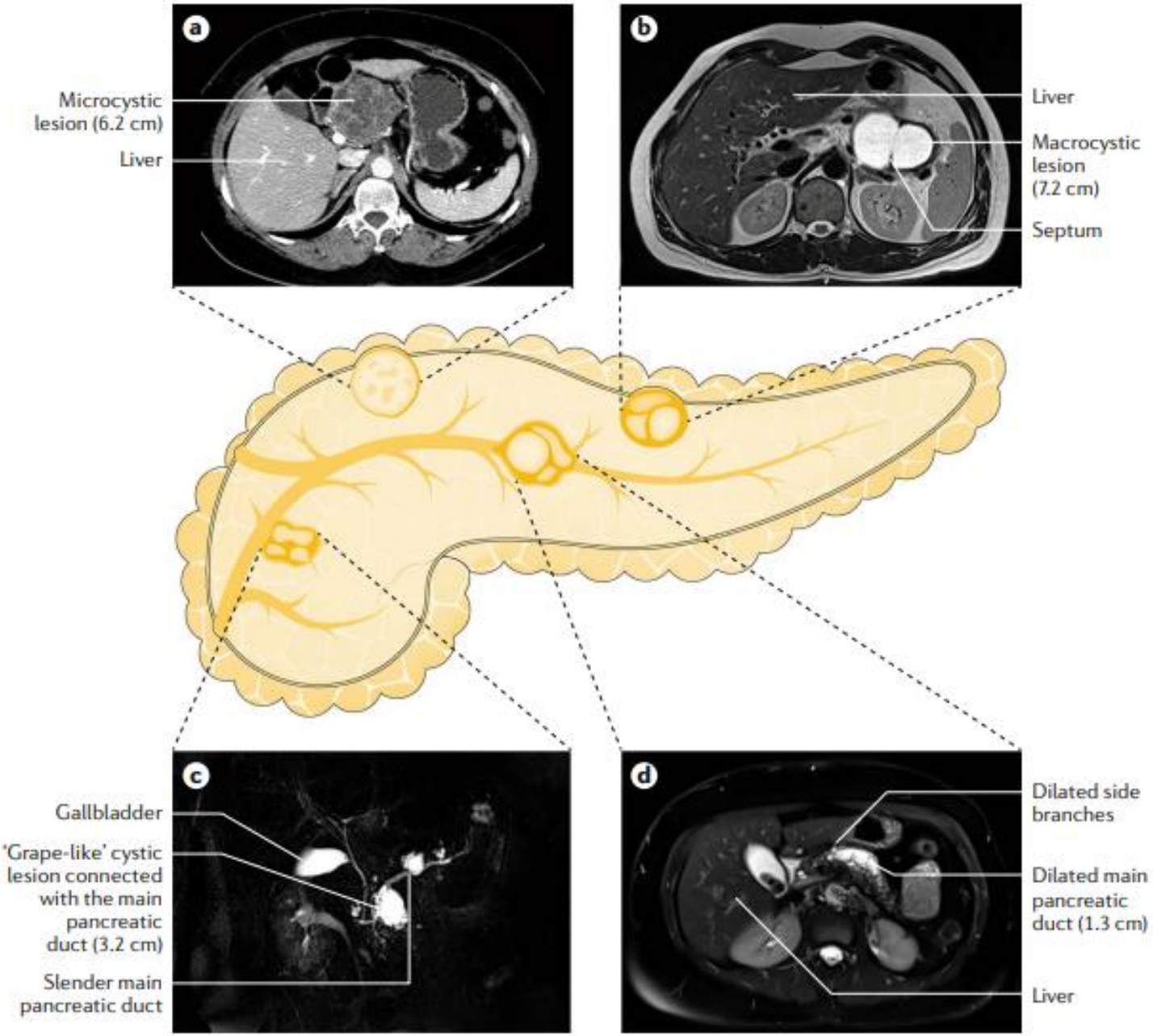
Cirurgia do Aparelho Digestivo
Unidade Hepatopancreatobiliar
Universidade Federal Maranhão - Brasil



van Huijgevoort NCM, et al. Nat Rev 2019

Table 1 | **Key demographic and clinical features of PCN**

Characteristics	SCN	MCN	MD/MT-IPMN	SB-IPMN	SPN	cNET
Age of presentation	Variable, usually 5th to 7th decade	Variable, usually 5th to 7th decade	Variable, usually 5th to 7th decade	Variable, usually 5th to 7th decade	2nd to 3rd decade	Variable, usually 5th to 6th decade
Gender distribution	70% female	90–95% female	Equal	Equal	90% female	Equal
Clinical presentation	Incidental finding, abdominal pain, mass effect	Incidental finding, abdominal pain or malignancy-related	Incidental finding, jaundice, pancreatitis, exocrine insufficiency, malignancy-related	Incidental finding, jaundice, pancreatitis, malignancy-related	Incidental finding, abdominal pain, mass effect	Incidental finding (usually nonfunctioning), abdominal pain, mass effect
Typical imaging characteristics	Microcystic (honeycomb appearance)	Unilocular, macrocystic	Dilated pancreatic duct or dilated pancreatic duct with dilated side branches	Dilated side branches	Solid and cystic mass	Solid and cystic mass, hypervascular
Connection or involvement with main pancreatic duct	No	No	Yes	Yes	No	No
Solitary or multifocal	Solitary	Solitary	Solitary/multifocal	Solitary/multifocal	Solitary	Solitary
Malignant potential[a]	Negligible	10–39%	36–100%	11–30%	10–15%	10%

cNET, cystic neuroendocrine tumour; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; MD, main duct; MT, mixed type; PCN, pancreatic cystic neoplasms; SB, side branch; SCN, serous cystic neoplasm; SPN, solid pseudopapillary neoplasm. [a] Percentage with advanced neoplasia in resected specimen[14–19,22–32,37–44].

van Huijgevoort NCM, et al. Nat Rev 2019

NEOPLASIAS DO PÂNCREAS

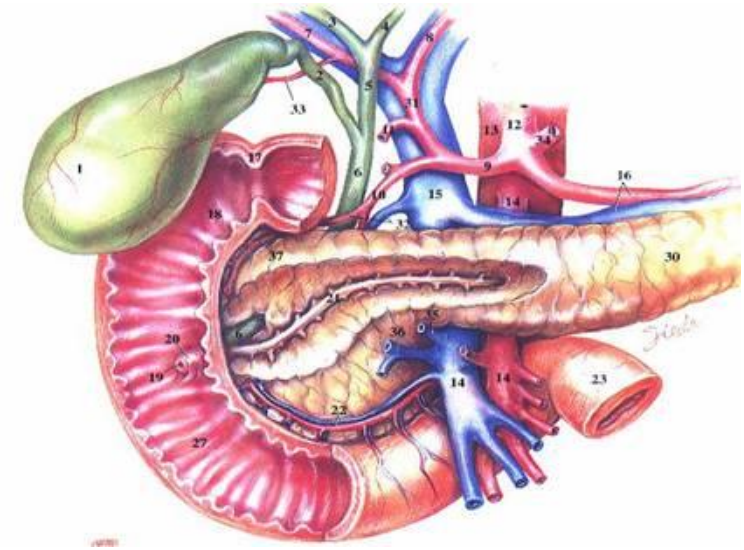
Table 3. Pathologic Examination of Lesions Resected Within 6 Months of Initial Visit (n = 422)

	1995–2010 (n = 422)	1995–2005 (n = 199)	2005–2010 (n = 223)
Noninvasive IPMN, n (%)	114 (27)	33 (17)	81 (36)
Serous cystadenoma, n (%)	98 (23)	68 (34)	30 (13)
Adenocarcinoma, n (%)	60 (14)	25 (13)	35 (16)
Mucinous cystadenoma, n (%)	45 (11)	25 (13)	20 (9)
Pancreatic endocrine tumor, n (%)	27 (7)	11 (5)	16 (8)
Pseudocyst, n (%)	18 (4)	16 (8)	2 (1)
Solid pseudopapillary tumor, n (%)	8 (2)	4 (2)	4 (2)
Simple cyst, n (%)	28 (7)	11 (5)	18 (8)
Other, n (%)	24 (6)	7 (3)	17 (7)
Lesion at risk of malignant progression, yes, n (%)†	169 (52)	66 (40)	103 (64)
Carcinoma including CIS, yes, n (%)	94 (23)	33 (17)	61 (28)

Brennan MF, J Am Coll Surg 2011

CISTO DE PÂNCREAS

Existe comunicação com o sistema ductal?



Sim

IPMN

Principal

Misto

Secundário

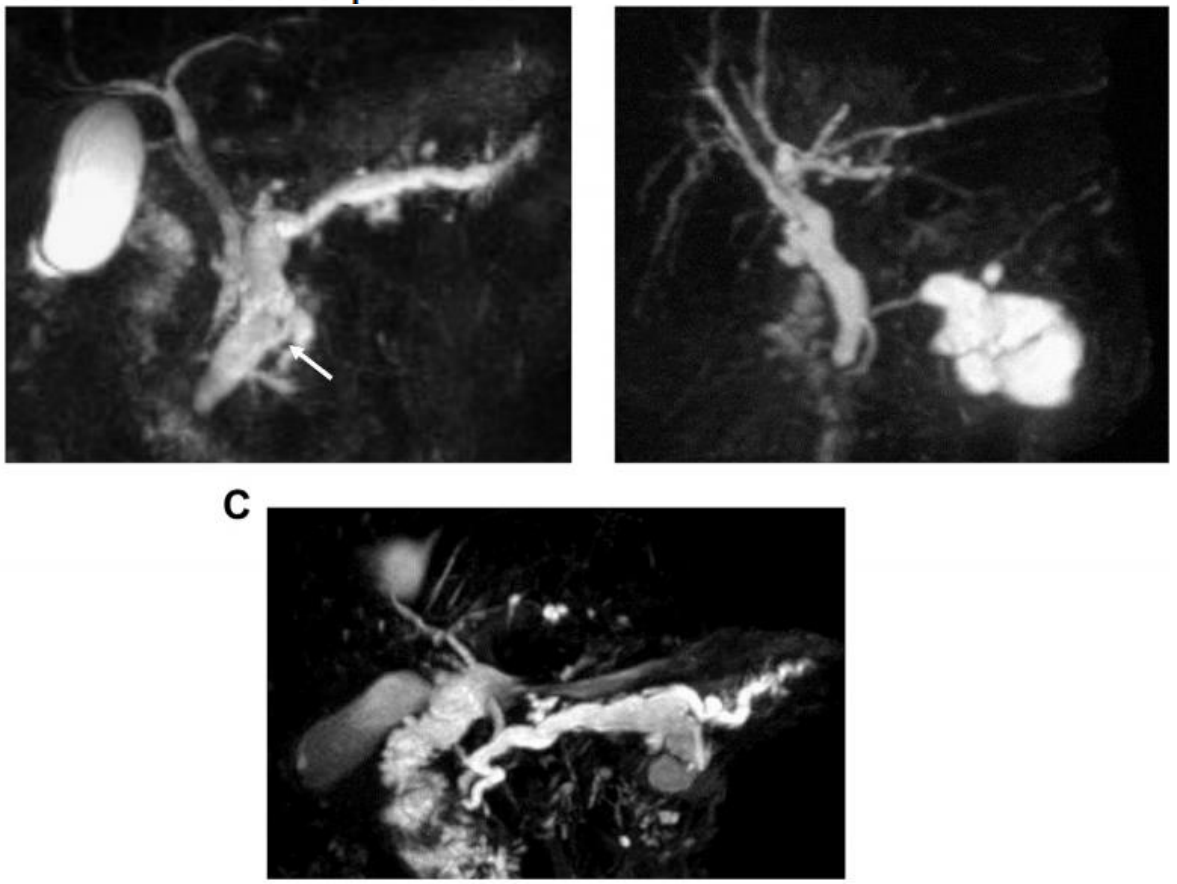
Cortesia: Dr. Paulo Amaral (BA)

Contents lists available at ScienceDirect

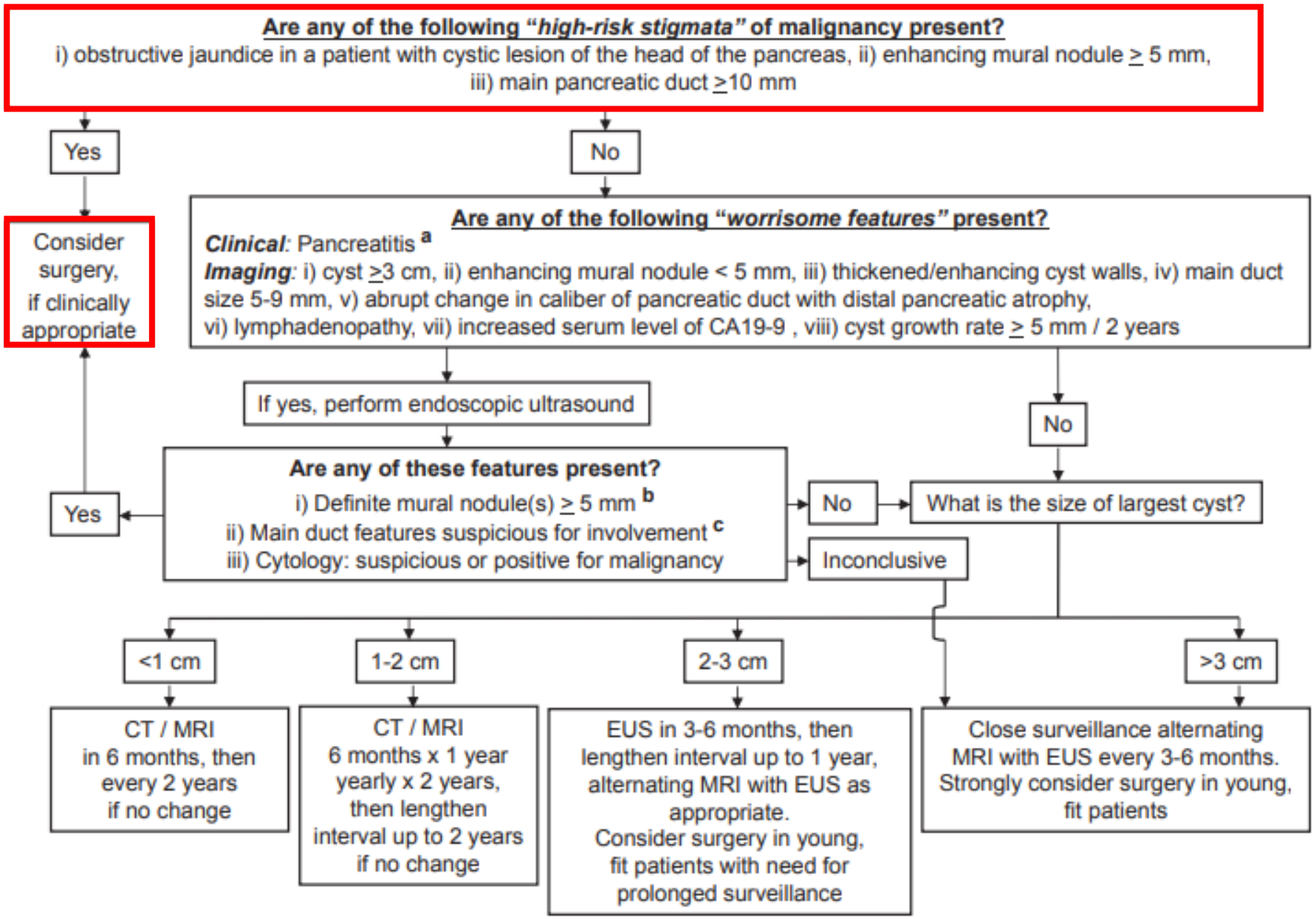
Pancreatology

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

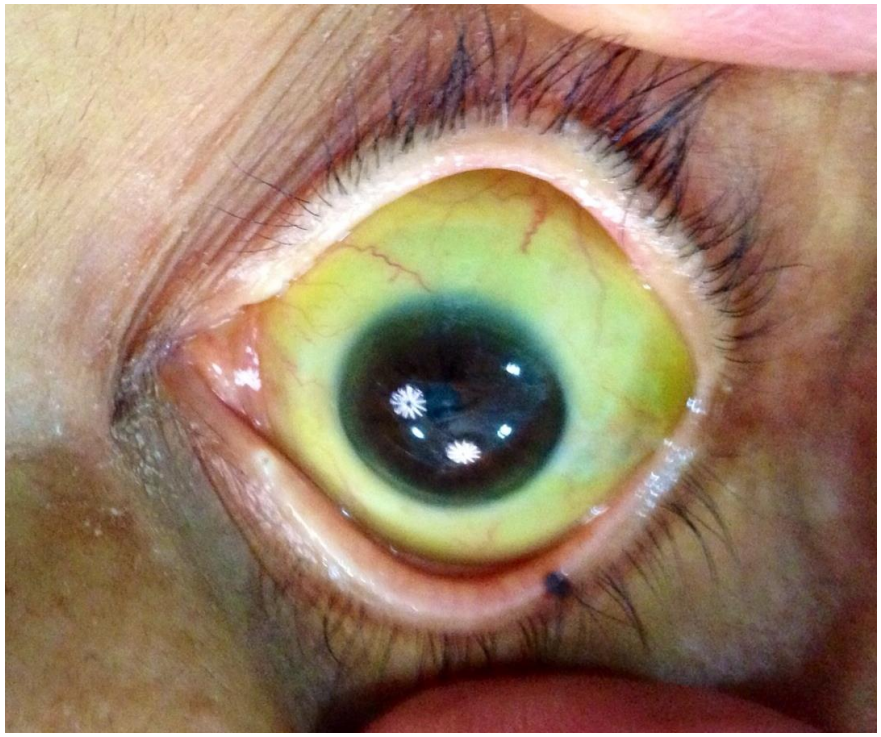
Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas

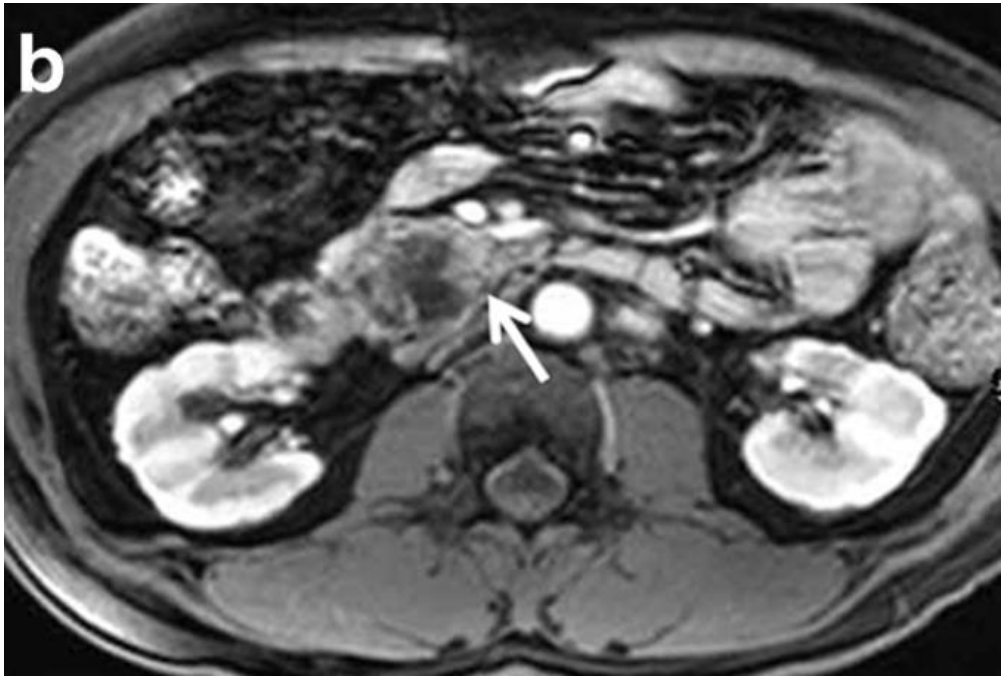


Tanaka M, et al. Pancreatology 2017;17:738-53



Tanaka M, et al. Pancreatology 2017;17:738-53





ICTERÍCIA + LESÃO CÍSTICA

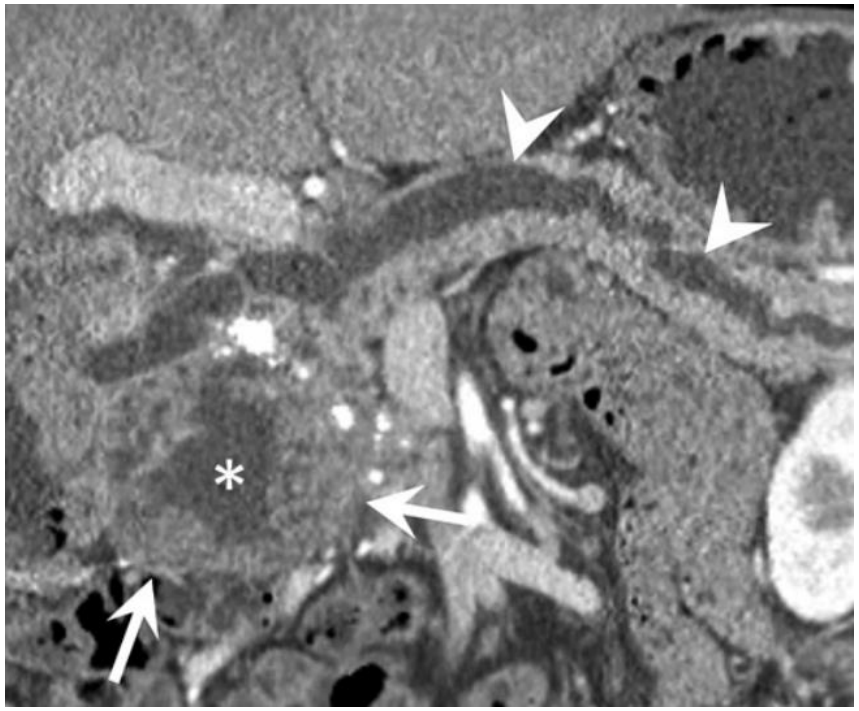
High-risk stigmata

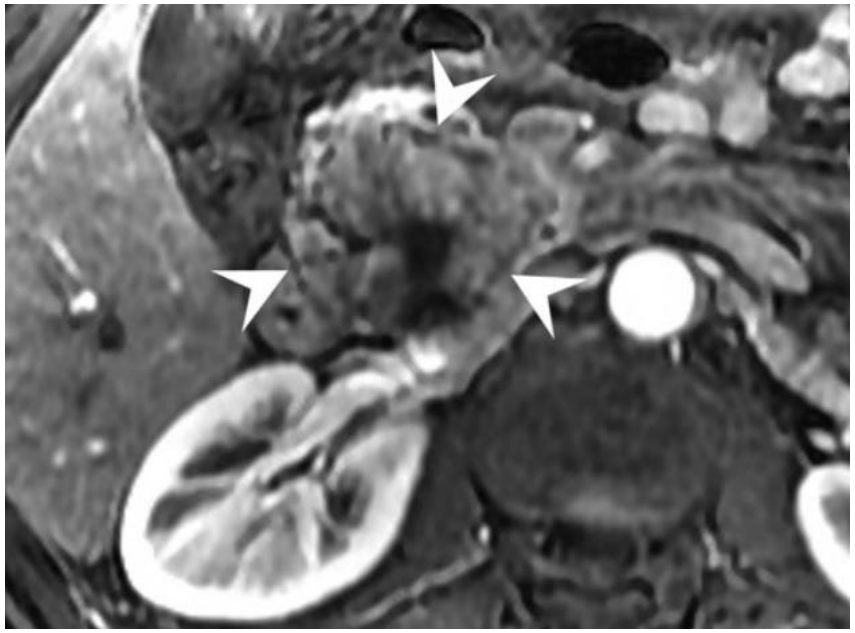
Obstructive jaundice in a patient with cystic lesion of the head of the pancreas

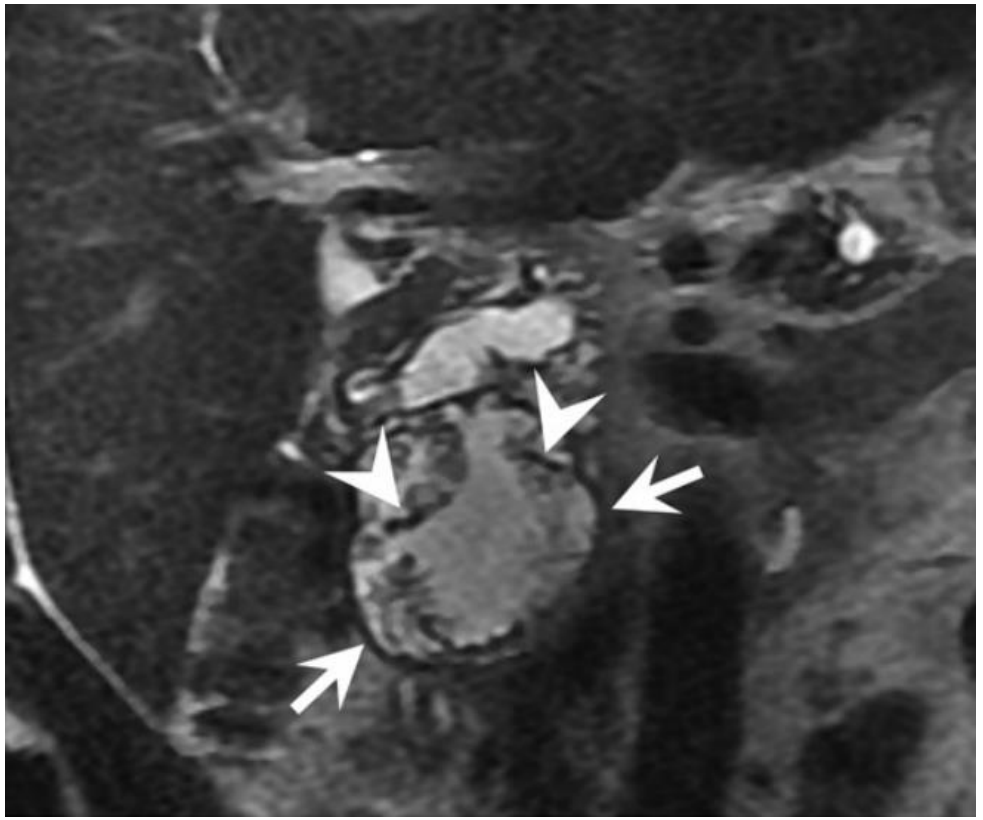
Enhancing mural nodule ≥ 5 mm

Main pancreatic duct ≥ 10 mm

Tanaka M, et al. Pancreatology 2017;17:738-53



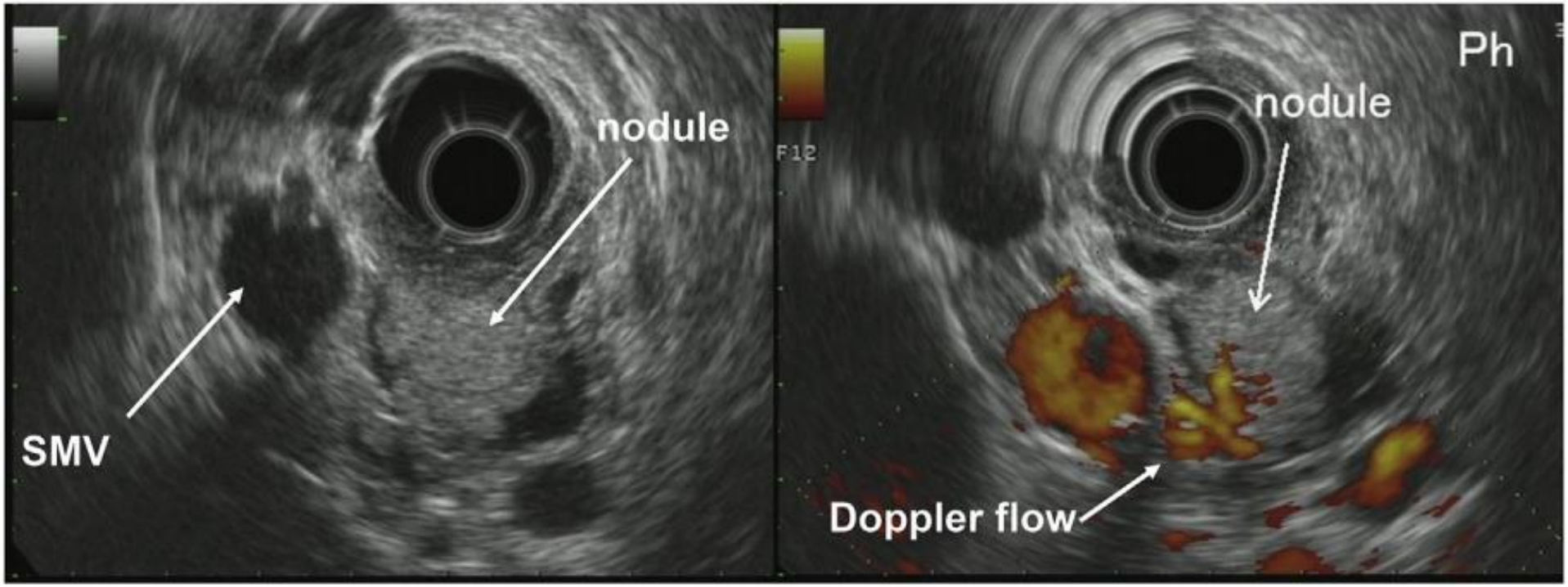




- Estigma de alto risco
  - Nódulo mural de 5 mm
  - Ducto principal de 13 mm
- Características preocupantes
  - Cisto de 4,4 cm (cabeça)
  - Cisto de parede espessada
  - Presença de septo

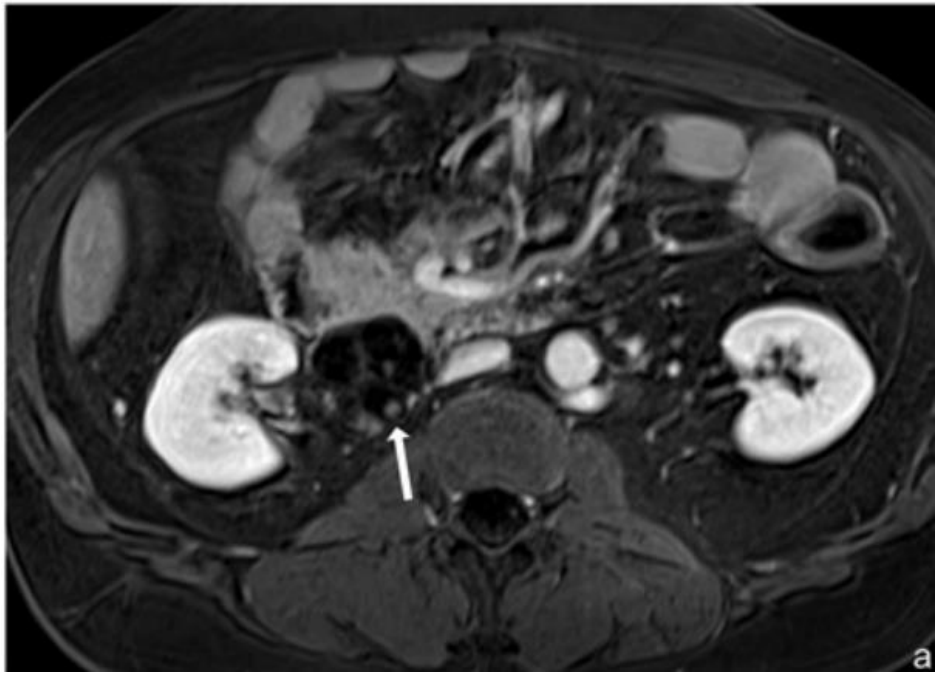
Lee JE et al. Radiology 2019

MURAL NODULE



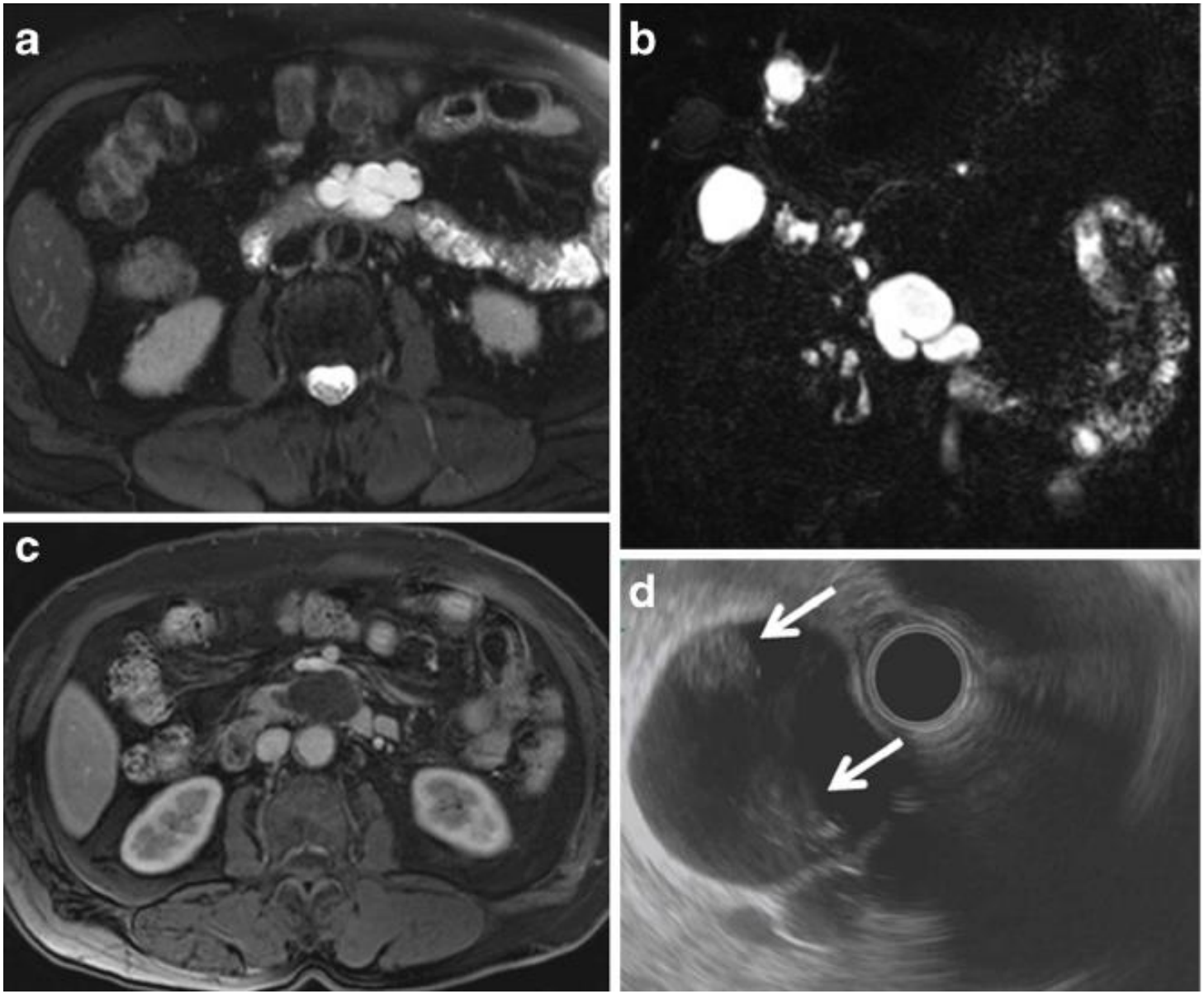
Tanaka M, et al. Pancreatology 2017;17:738-53

MURAL NODULE



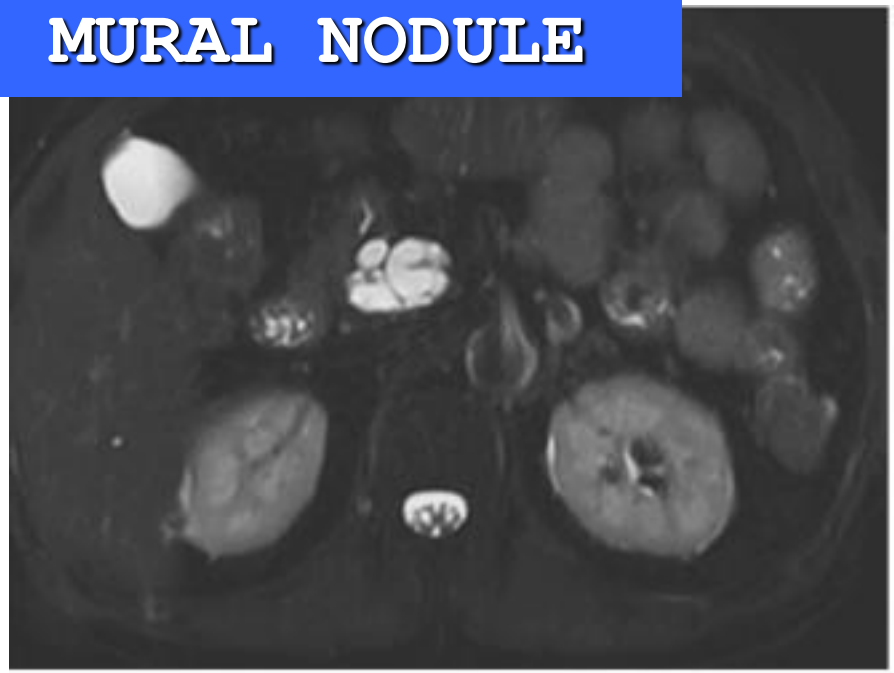
Strauss A, et al. Br J Radiol 2016

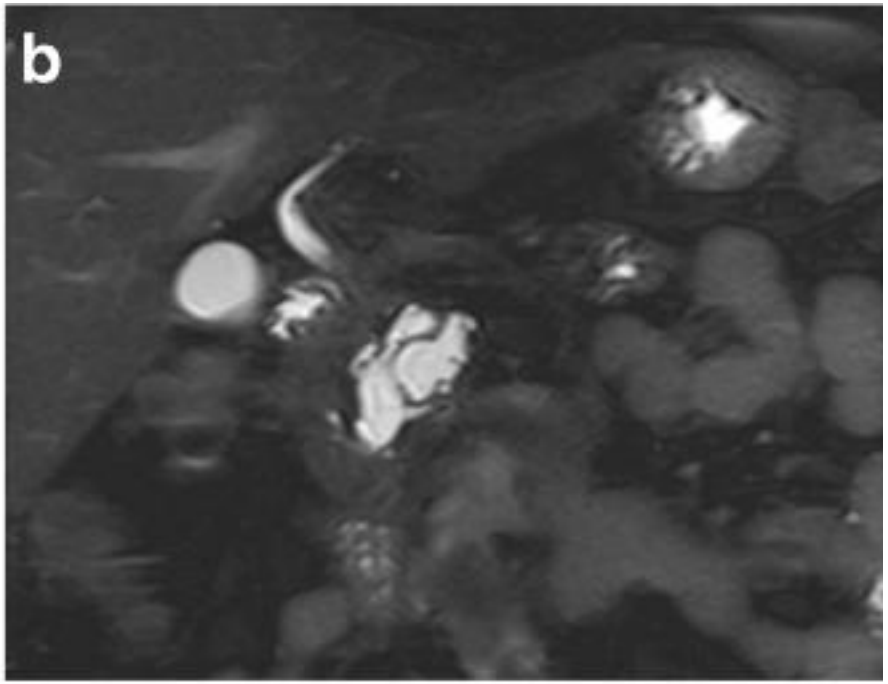
MURAL NODULE

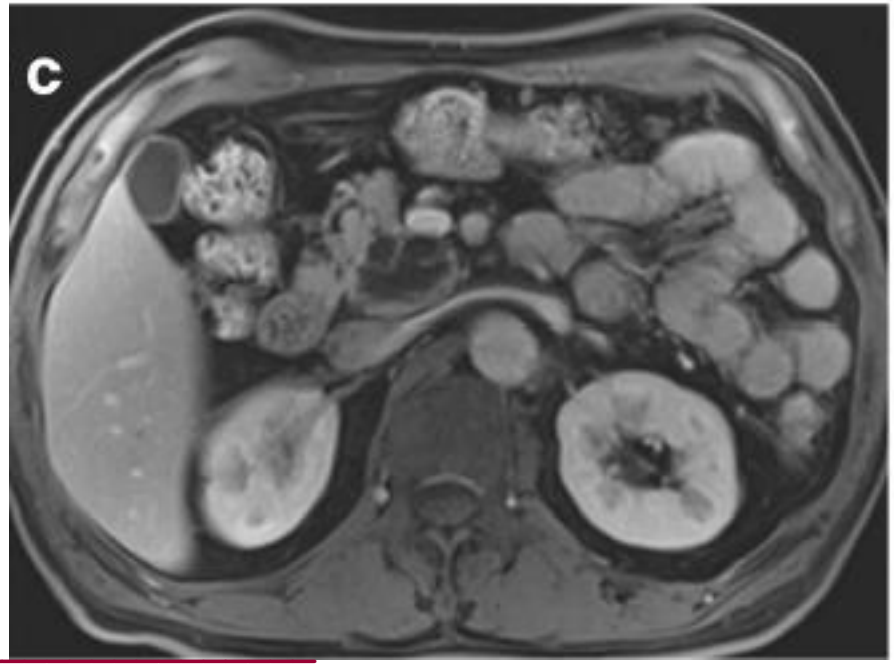


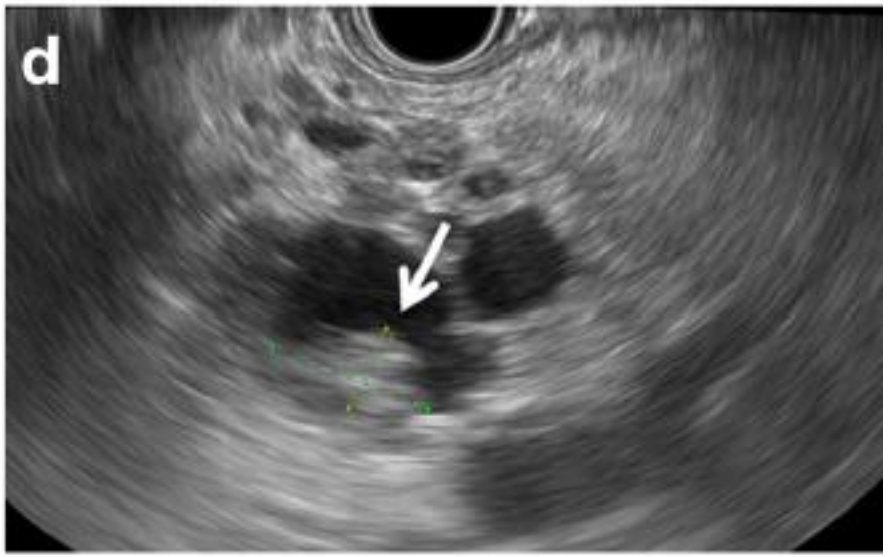
Hwang J, et al. Eur Radiol 2017

MURAL NODULE









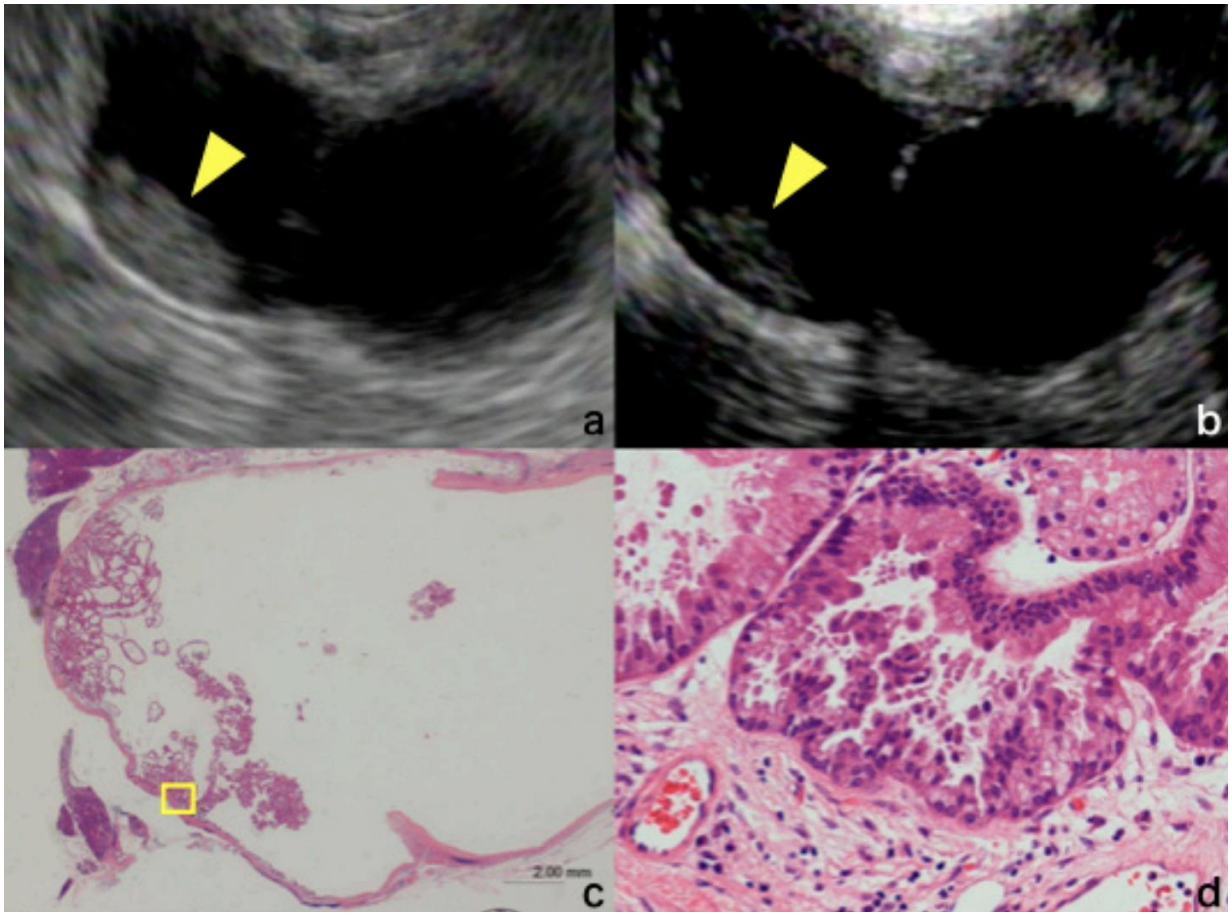
Hwang J, et al. Eur Radiol 2017

Journal of
Clinical Medicine

MDPI

Article

Should Contrast-Enhanced Harmonic Endoscopic Ultrasound Be Incorporated into the International Consensus Guidelines to Determine the Appropriate Treatment of Intraductal Papillary Mucinous Neoplasm?



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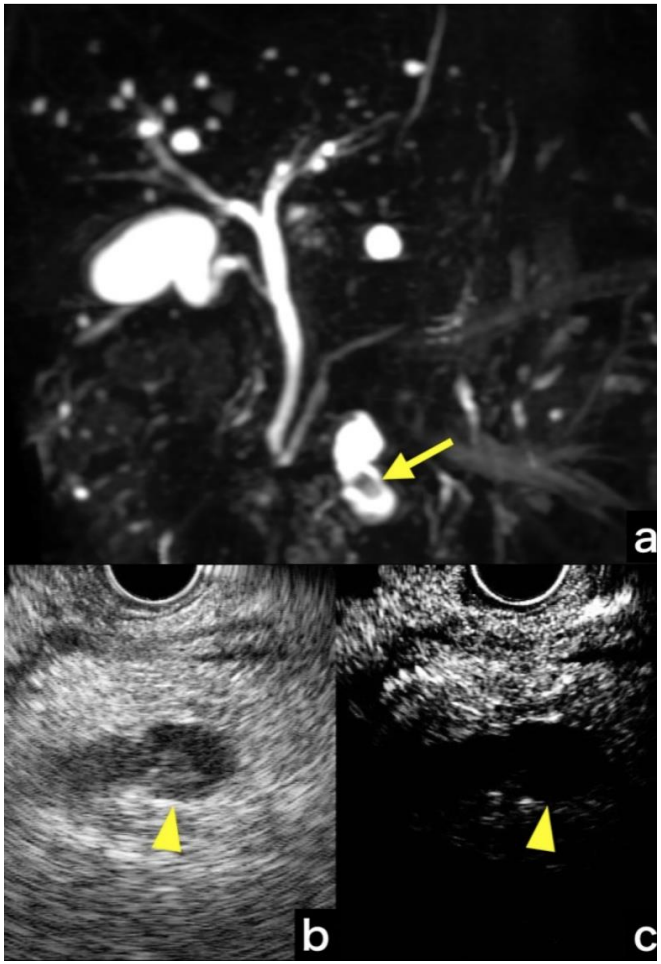


High-risk stigmata

Obstructive jaundice in a patient with cystic lesion of the head of the pancreas

Enhancing mural nodule ≥ 5 mm

Main pancreatic duct ≥ 10 mm

Tanaka M, et al. Pancreatology 2017;17:738-53

cancers

≥ 5mm

Systematic Review

Ductal Dilatation of ≥5 mm in Intraductal Papillary Mucinous Neoplasm Should Trigger the Consideration for Pancreatectomy: A Meta-Analysis and Systematic Review of Resected Cases

Table 1. Characteristics of included articles.

Author	Year	Country	Design	<5 mm (*n*)		5–9 mm (*n*)		≥10 mm (*n*)	
				M	NM	M	NM	M	NM
Takanami et al. [25]	2011	Japan	Retrospective	3	2	5	5	1	0
Barron et al. [26]	2014	U.S.A.	Retrospective	17	149	74	40	40	14
Roch et al. [27]	2014	U.S.A.	Retrospective	-	-	50	64	30	27
Hackert et al. [12]	2015	Germany	Retrospective	-	-	93	64	76	27
Kang et al. [28]	2015	S. Korea	Retrospective	44	206	39	38	34	14
Kim et al. [29]	2015	S. Korea	Retrospective	15	212	19	50	4	3
Kim et al. [30]	2015	S. Korea	Retrospective	43	195	38	39	36	16
Yamada et al. [31]	2015	Japan	Retrospective	10	42	29	39	22	24
Robles et al. [32]	2016	France	Retrospective	13	57	19	25	4	2
Seo et al. [33]	2016	S. Korea	Retrospective	11	62	27	29	14	15
Sugimoto et al. [14]	2016	U.S.A.	Retrospective	-	-	22	19	42	20
Choi et al. [34]	2017	S. Korea	Retrospective	1	20	29	16	9	1
Yu et al. [35]	2017	Japan	Retrospective	39	13	14	12	3	8
Marchegiani et al. [17]	2018	Italy	Retrospective	8	43	43	126	20	32
Tsukagoshi et al. [36]	2018	Japan	Retrospective	2	17	4	4	12	3
Del Chiaro et al. [15]	2019	U.S.A./Sweden	Retrospective	65	240	134	152	107	43
Jan et al. [37]	2019	Taiwan	Retrospective	17	65	11	11	23	31
Lee et al. [38]	2019	S. Korea	Retrospective	3	36	16	16	9	6
Masaki et al. [39]	2019	Japan	Retrospective	0	0	3	6	16	4
Hwang et al. [40]	2020	S. Korea	Retrospective	25	45	11	18	18	9
Total (% *)				316 (18.4%)	1404 (81.6%)	680 (46.8%)	773 (53.2%)	520 (63.5%)	289 (36.5%)

* Percentage of cases within MPD Dilatation category; Abbreviations: M = Malignancy; NM = Non-Malignancy.

cancers

MDPI

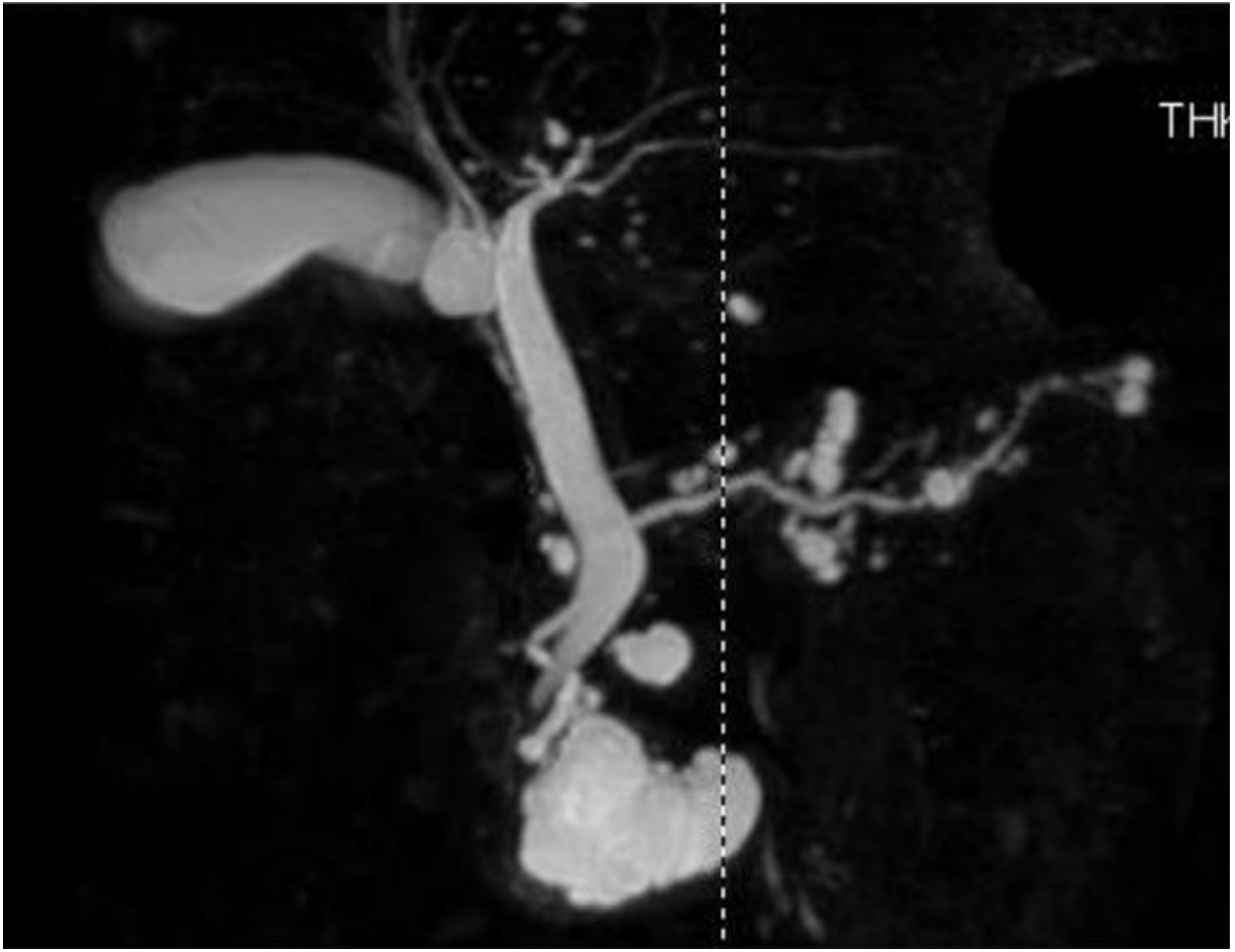
Systematic Review

Ductal Dilatation of ≥5 mm in Intraductal Papillary Mucinous Neoplasm Should Trigger the Consideration for Pancreatectomy: A Meta-Analysis and Systematic Review of Resected Cases

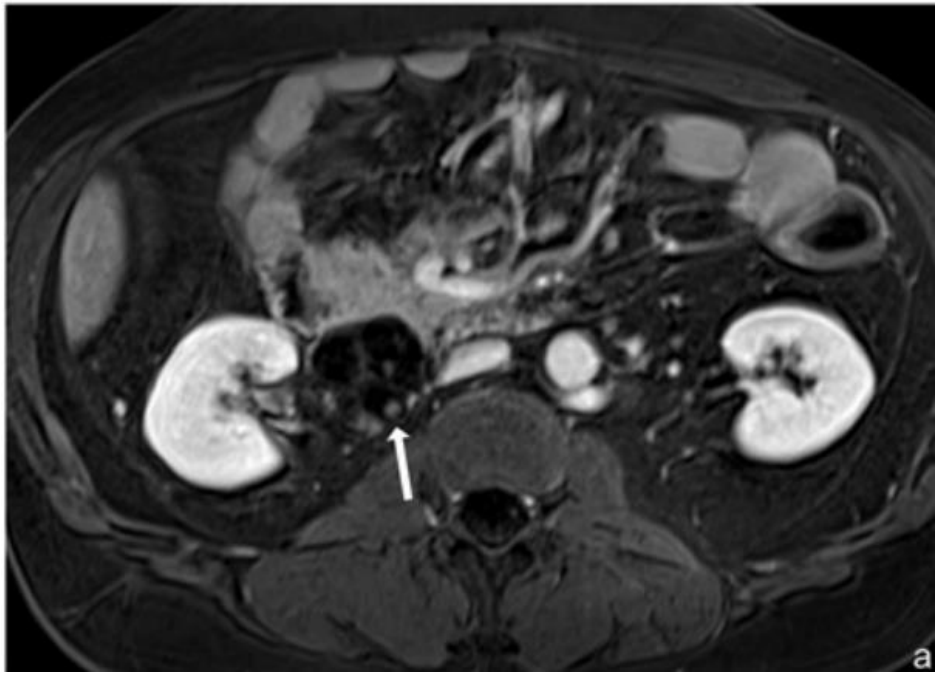
Table 2. Characteristics of included article with postoperative histology diagnosis of HGD and IC.

Author	Year	Design	<5 mm			5–9 mm			≥10 mm		
			HGD	IC	NM	HGD	IC	NM	HGD	IC	NM
Takanami et al. [25]	2011	Retrospective	3	0	2	5	0	5	0	1	0
Barron et al. [26]	2014	Retrospective	10	7	149	40	34	40	27	13	14
Roch et al. [27]	2014	Retrospective	-	-	-	19	31	64	15	15	27
Kang et al. [28]	2015	Retrospective	15	29	206	17	22	38	12	22	14
Kim et al. [29]	2015	Retrospective	6	9	212	7	12	50	0	4	3
Robles et al. [32]	2016	Retrospective	8	5	57	10	9	25	4	0	2
Sugimoto et al. [14]	2016	Retrospective	-	-	-	5	17	19	18	24	20
Tsukagoshi et al. [36]	2018	Retrospective	2	0	17	3	1	4	6	6	3
Del Chiaro et al. [15]	2019	Retrospective	45	20	240	78	56	152	53	54	43
Masaki et al. [39]	2019	Retrospective	0	0	0	3	0	6	10	6	4
Total (% *)			89 (8.5%)	70 (6.7%)	883 (84.7%)	187 (24.2%)	182 (23.6%)	403 (52.2%)	145 (34.5%)	145 (34.5%)	130 (31.0%)

* Percentage of cases within MPD Dilatation category; Abbreviations: HGD, High Grade Dysplasia; IC, Invasive Carcinoma; NM, Non-Malignancy.



Tanaka M, et al. Pancreatology 2017;17:738-53



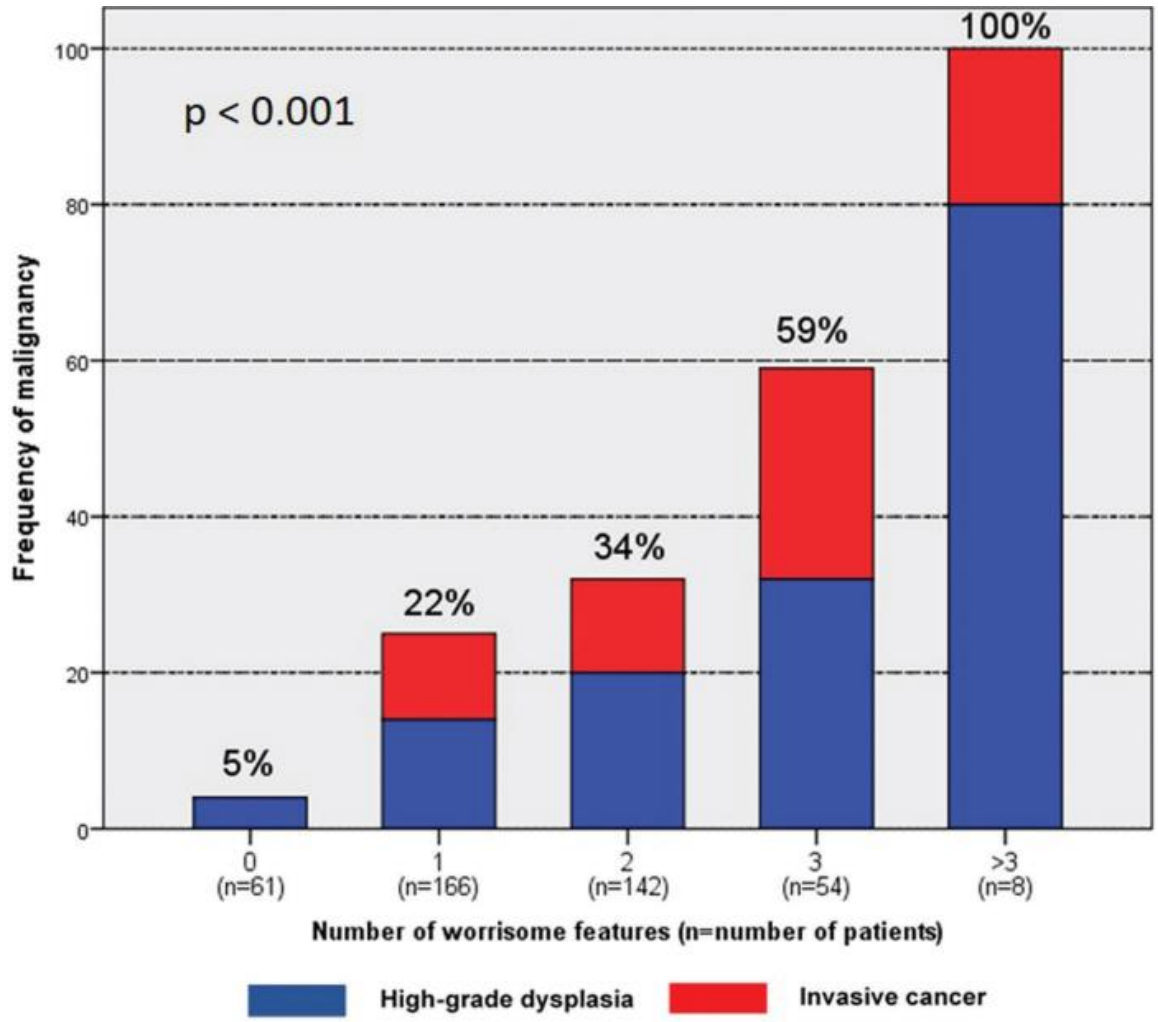
Strauss A, et al. Br J Radiol 2016

Worrisome features

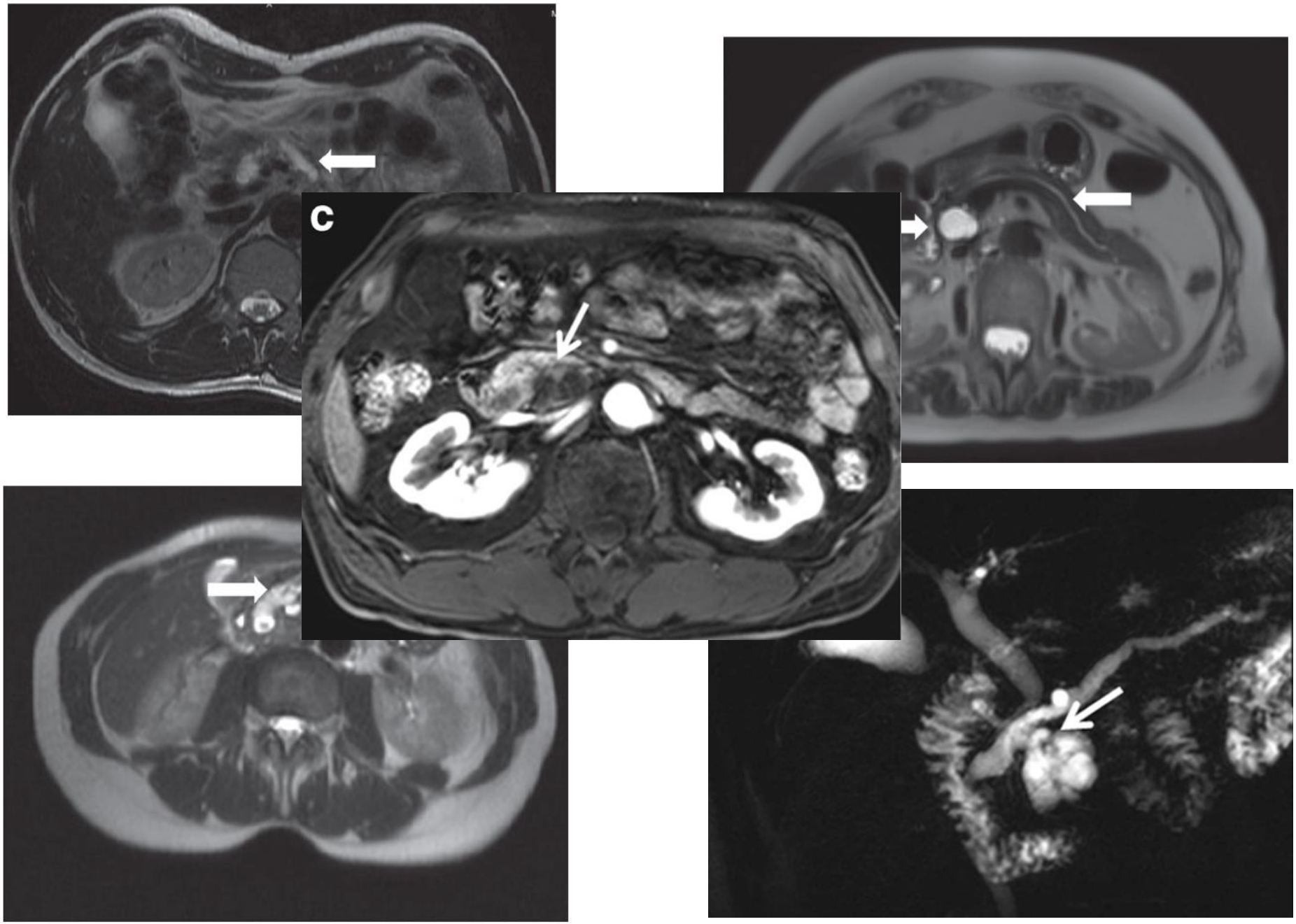
Pancreatitis
Cyst ≥ 30 mm
Thickened/enhancing cystic walls
Enhancing mural nodule < 5 mm
Main pancreatic duct 5–9 mm
Abrupt change in calibre of pancreatic duct with distal pancreatic atrophy
Lymphadenopathy
Increased serum level of carbohydrate antigen 19-9
Cyst growth rate ≥ 5 mm/2 years

Hipp J, et al. Br J Surg 2019

Number of Worrisome Features and Risk of Malignancy in Intraductal Papillary Mucinous Neoplasm

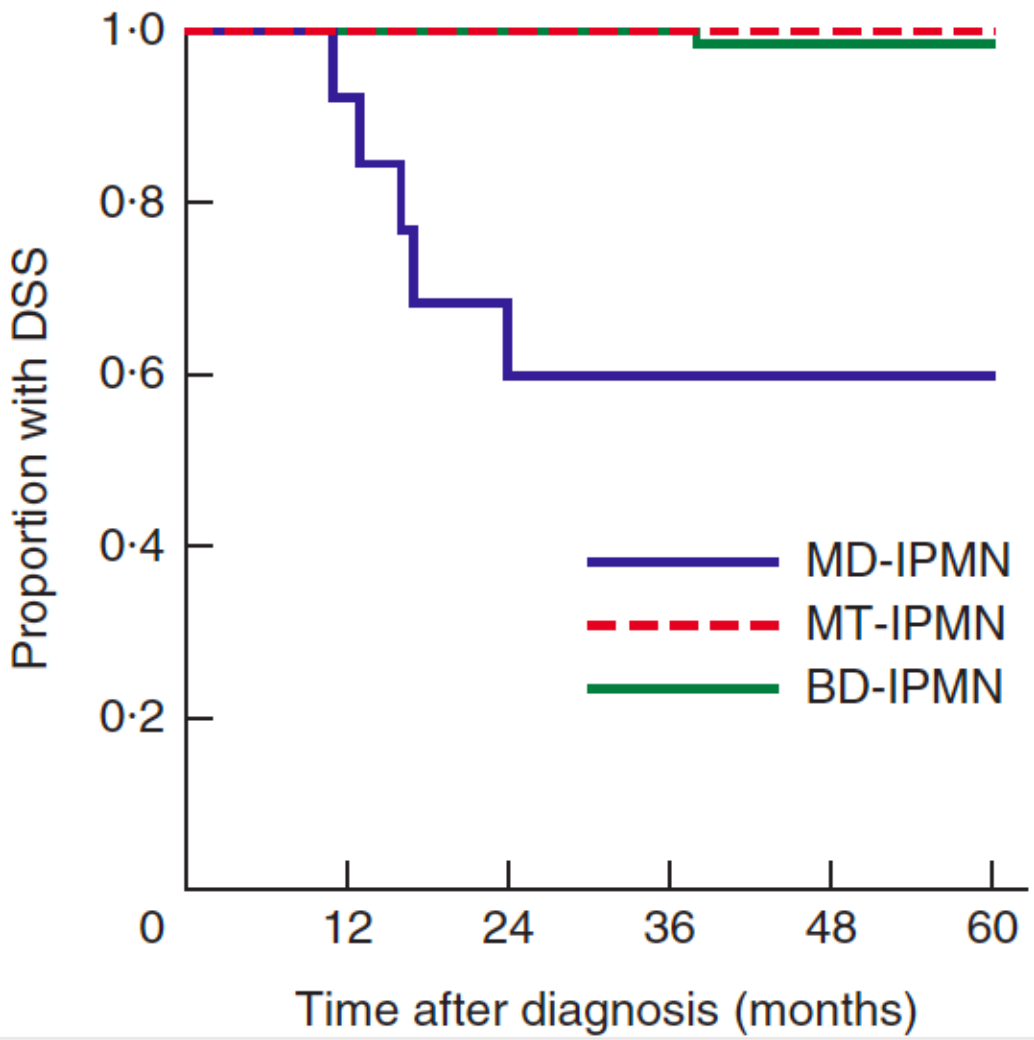


Zelga P, et al. J Am Coll Surg (2022)

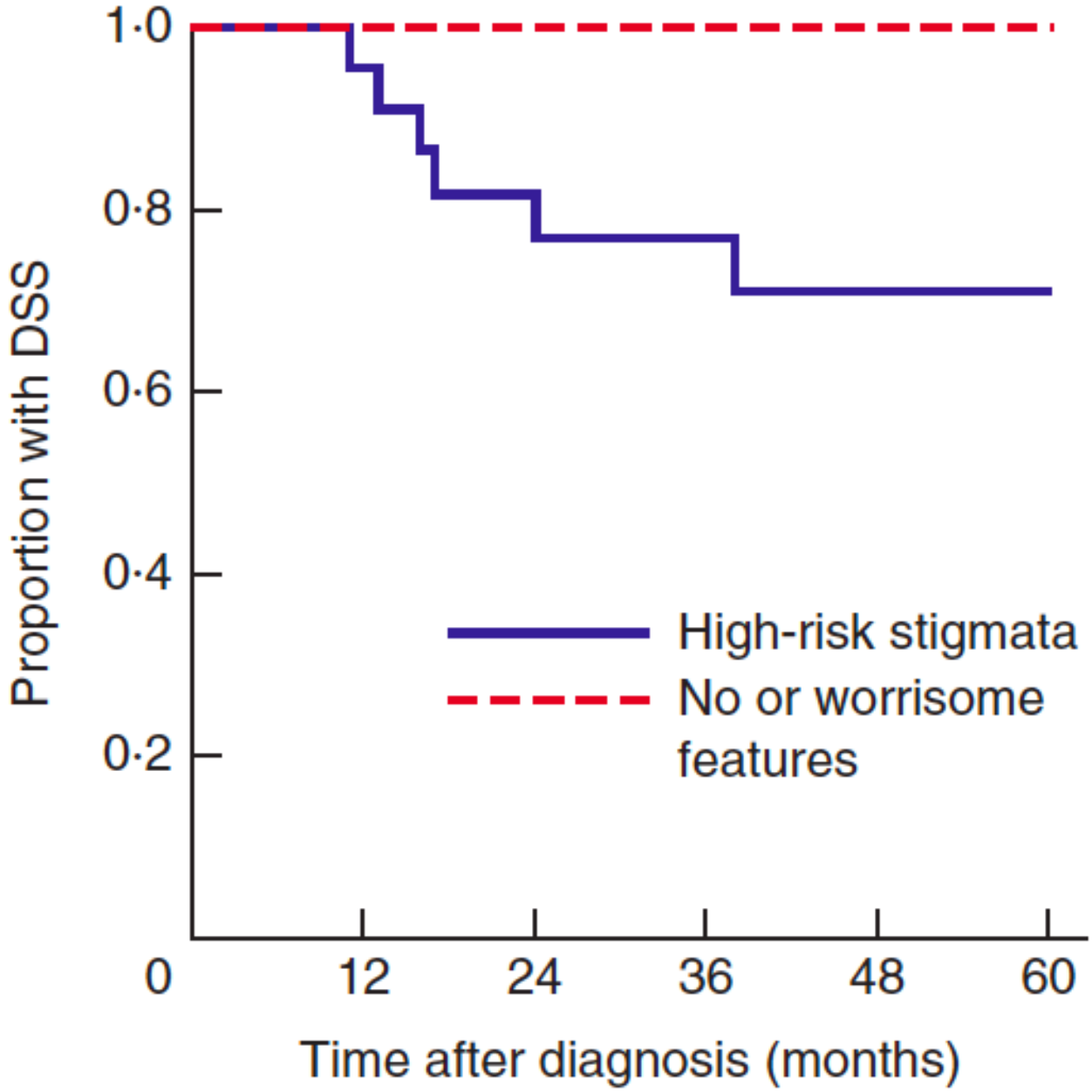


Hipp J, et al. Br J Surg 2019

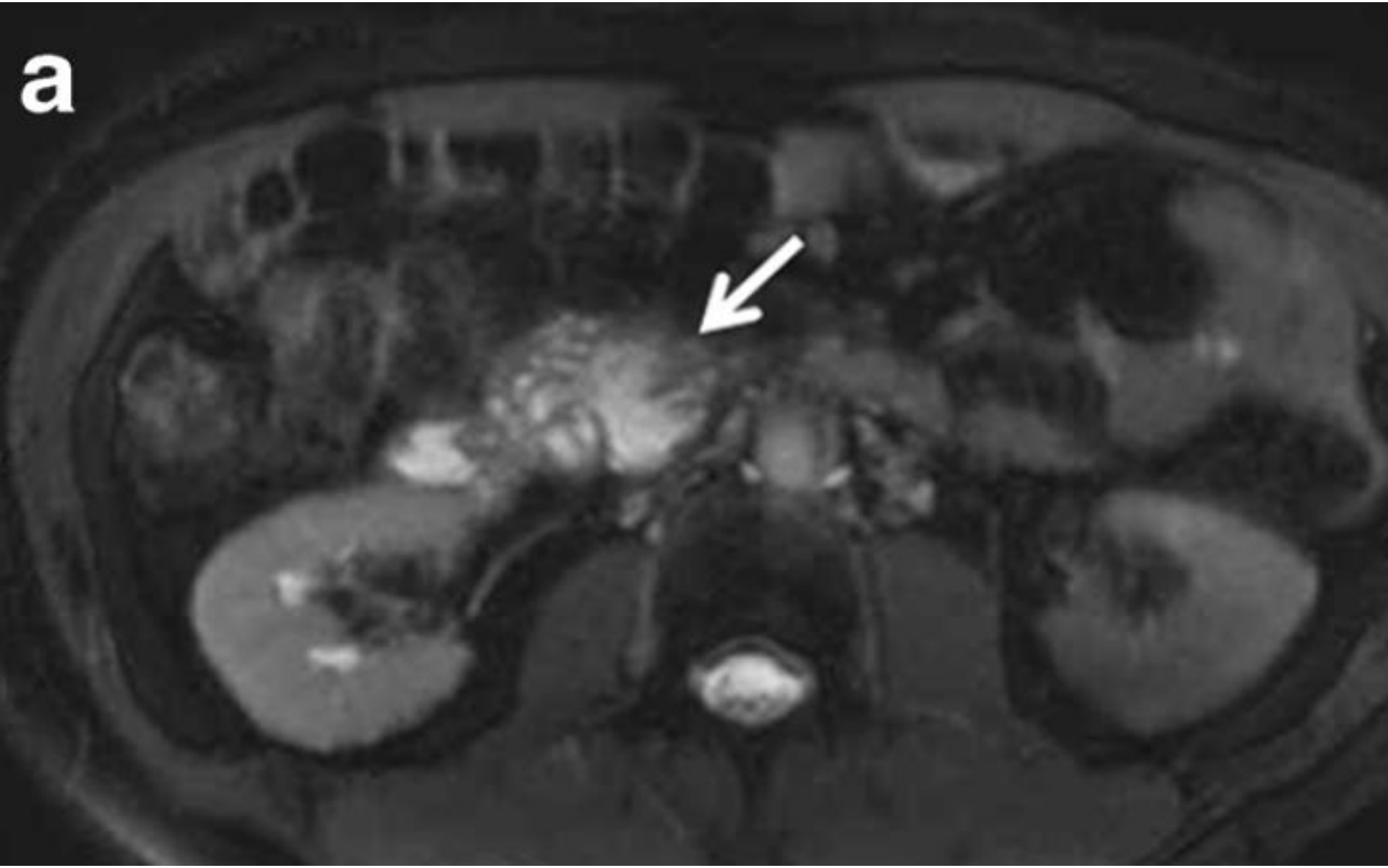
MD- *versus* MT- *versus* BD-IPMN



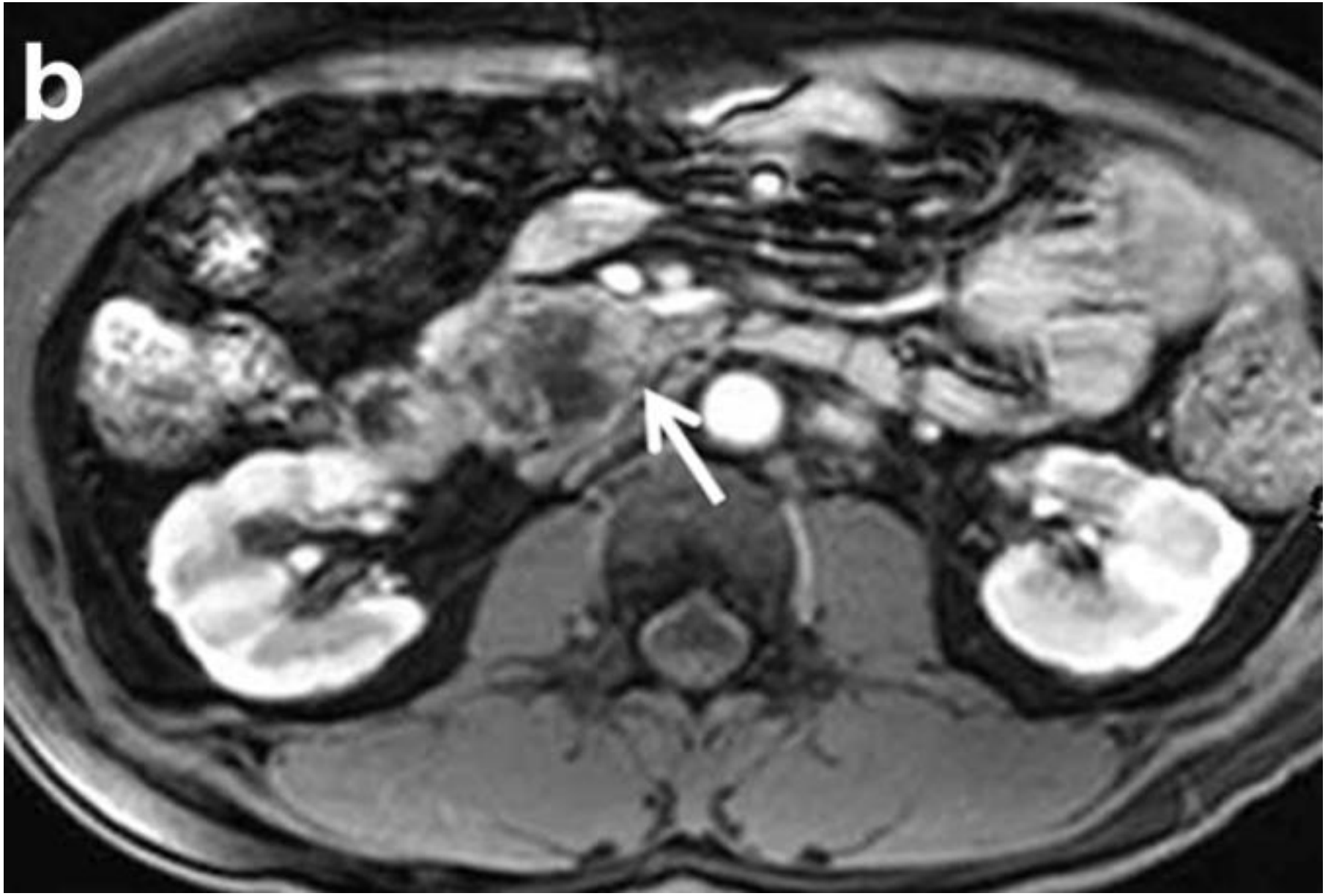
Hipp J, et al. Br J Surg 2019



Hipp J, et al. Br J Surg 2019



Hwang J, et al. Eur Radiol 2017



Hwang J, et al. Eur Radiol 2017

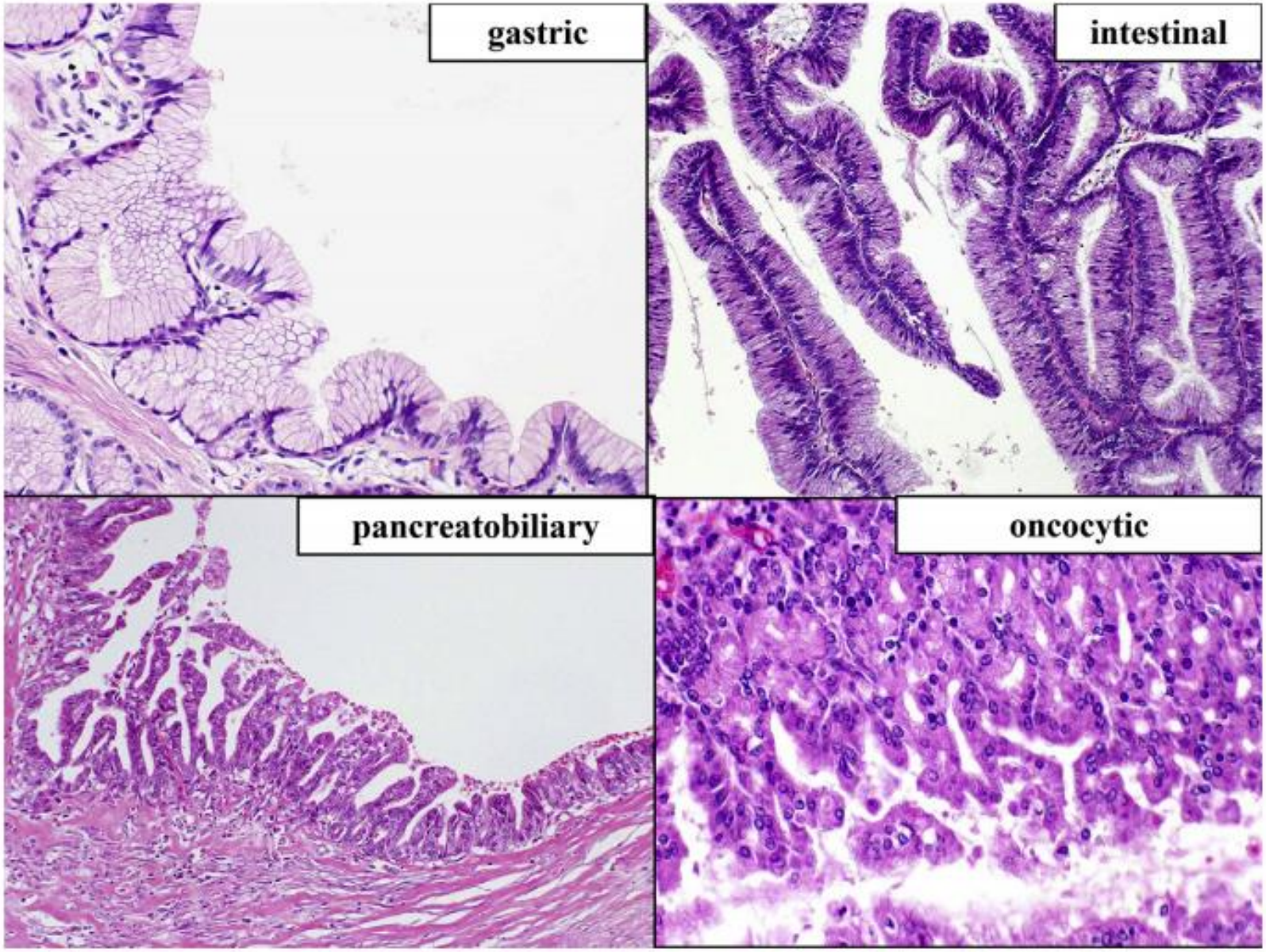
Table 1 Clinical parameters used to recommend resection of IPMN

	International Association of Pancreatology Guidelines, 2012 (revised 2017) [19, 25]	European Experts Consensus Statement, 2013 (revised, 2018) [20, 21]	American Gastroenterological Association Guidelines, 2015 [22]
Age	–	–	–
Obstructive jaundice	Presence	Presence	–
Abdominal pain/history of pancreatitis	Not definitive	Presence	–
Main duct size	> 10 mm	≥ 10 mm	Dilated[a]
Mural nodule	Enhancement	Enhancement, ≥ 5 mm	Presence[a]
Cyst size	Not definitive	Not definitive	≥ 3 cm[a]
Cytology	Suspicious or positive	Positive	Positive
Serum CA19-9	–	Not definitive	–

SUBTIPO HISTOPATOLÓGICO

	Histologic sub-type			
	Gastric	Intestinal	Pancreatobiliary	Oncocytic
Frequency (%)	60–70	30–40	< 10	< 5
Morphologic sub-type	BD > MD	MD > BD	MD or BD	MD or BD
Atypia	Low grade	High grade	High grade	High grade
Progression	Indolent	Indolent	Rapid	Rapid
Type of carcinoma	Tubular	Colloid	Tubular	Oncocytic
5, 10 years survival rate	0.937, 0.937	0.886, 0.685	0.520	0.839, 0.734
KRAS (%)	53-87	40-46	45-60	±
GNAS (%)	39-65	48-83	30	±
MUC1	−	−	+	±
MUC2	−	+	−	±
MUC5AC	+	+	+	+
MUC6	+	−	+	+

Lim J, Allen PJ. Updates Surg 2019; 71:209–16



Tanaka M, et al. Pancreatology 2017;17:738-53

Table 4 Surveillance in intraductal papillary mucinous neoplasm patients regarding indications for surgery according to the International, European and American Gastroenterological Association guidelines[5,8,13,20-22,41]

Guidelines	Indications	Investigations	Algorithm of follow-up
IAP (2006)	BD-IPMNs ≤ 30 mm; Without: Symptoms, mural nodules, positive cytology	MRI/MRCP or CT	Size ≤ 20 mm: every 6-12 mo; Size 20-30 mm: every 3-6 mo; The interval can be longer after 2 yr without changes
AGA (2015)	BD-IPMNs ≤ 30 mm; Without: Solid component, dilated MPD, HGD/cancer	MRI	Years 1, 2, 5 from initial diagnosis; It can be considered to discontinue; If there is no changes after years
IAP (2017)	No HRS/WF	MRI/MRCP, CT	Size < 10 mm: At 6 mo from diagnosis every 2 yr (if no change)
	No HRS/WF	MRI/MRCP, CT	Size 10-20 mm: At 6 mo from diagnosis yearly per 2 yr
	No HRS/WF	MRI/MRCP, EUS	Size 20-30 mm: EUS in 3-6 mo, yearly EUS or MRI
	No HRS, WF present and size < 30 mm	MRI/MRCPEUS	Every 3-6 mo EUS or MRI
European (2018)	No AI	MRI/MRCP or EUS, CA 19.9	Every 6 mo for the first year; Yearly after first year
	No AI, 1 RI in patient, with comorbidities	MRI/MRCP or EUS, CA 19.9	Every 6 mo

Jablonska B, et al. World J Gastrointest Oncol 2021;13:1880-95

Table 1. Worrisome features and high-risk stigmata for IPMN according to the 2017 Fukuoka Consensus Guidelines.

Worrisome Features	High-Risk Stigmata
1. Increased levels of CA 19.9 (>37 U/mL)	
2. Main pancreatic duct diameter 5–9.9 mm	
3. Cyst diameter >30 mm	
4. Enhancing mural nodules <5 mm	1. Jaundice
5. IPMN-induced acute pancreatitis	2. Enhancing mural nodule >5 mm
6. Thickened/enhancing cyst walls	3. Main pancreatic duct diameter >10 mm
7. Cyst grow-rate >5 mm/2 year	
8. Abrupt change in caliber of the pancreatic duct with distal pancreatic atrophy	
9. Lymphadenopathy	

CA 19.9 (Serum carbohydrate antigen 19-9), IPMN (Intraductal Papillary Mucinous Neoplasia).

Biomarkers	Description
Ca 19.9 (>37 U/mL)	89% sensitivity and 40% specificity in detecting degeneration.
CEA (>5 µg/L)	96.4% sensitivity and 6.1% specificity in detecting degeneration.
NLR (>2)	73.1% sensitivity and 58% specificity in detecting degeneration.
PLR	Not well-established cut-off. >200 associated in 83% to degeneration.
Cytological analysis	83–99% sensitivity and 25–88% specificity in detecting degeneration.
Cystic fluid mucins	Overexpression of MUC1, MUC2, and MUC4 and a down expression of MUC5A are associated with degeneration.
Cystic fluid DNA sequencing	The presence of KRAS, GNAS, and RNF43 is associated with degeneration.

Nista EC, et al. Int. J. Mol. Sci. 2021

International Journal of
Molecular Sciences

MDPI

Review

Intraductal Papillary Mucinous Carcinoma Versus Conventional Pancreatic Ductal Adenocarcinoma: A Comprehensive Review of Clinical-Pathological Features, Outcomes, and Molecular Insights

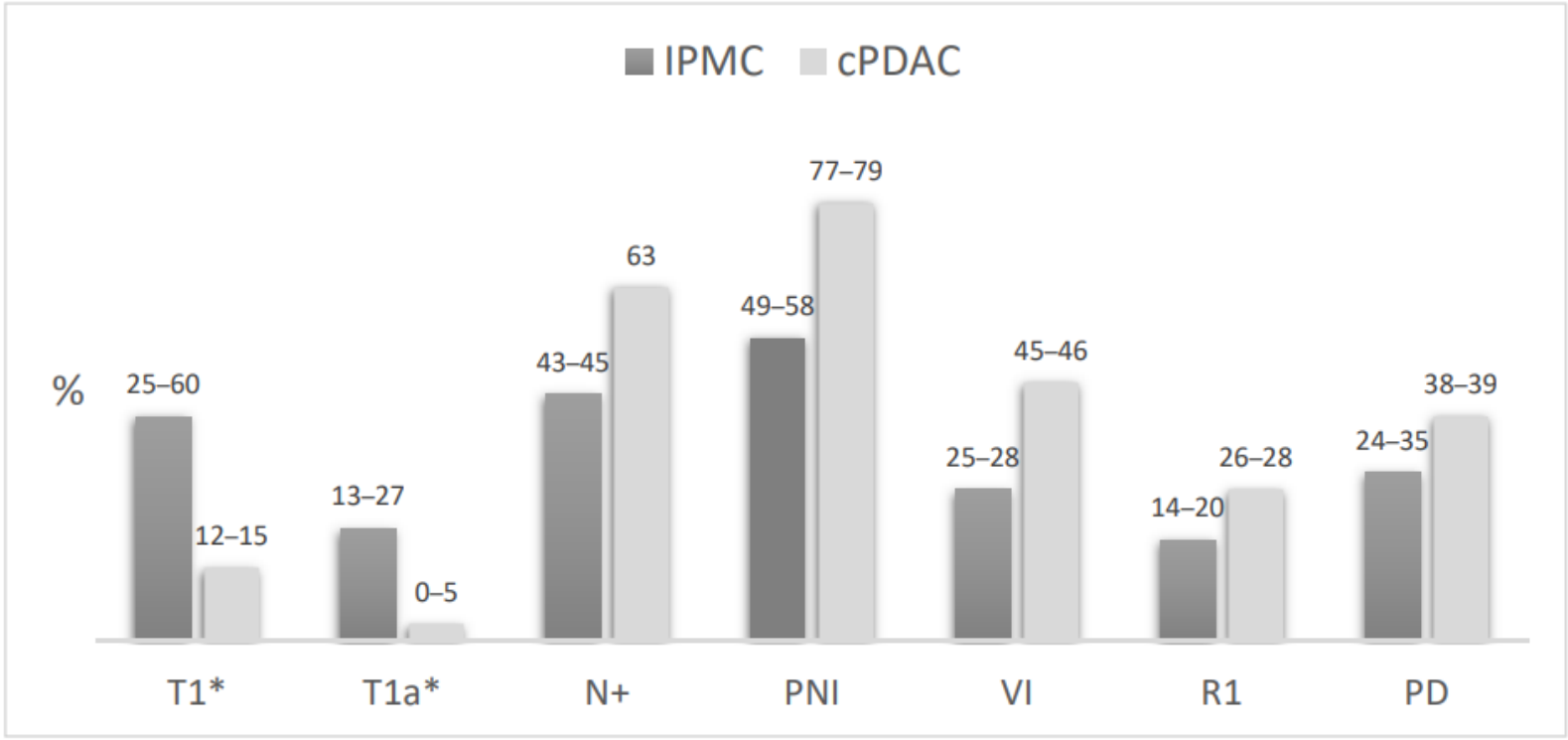


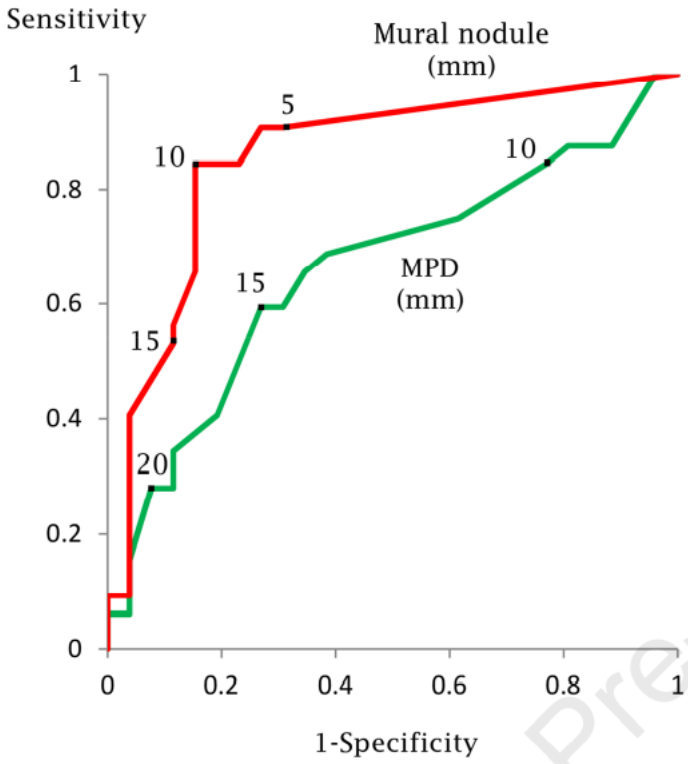
Figure 2. Comparison of pathological features of IPMC and cPDAC. Pooled data from Koh et al. [36] and Aronsson et al. [43]. * AJCC TNM 8th edition; PNI: perineural invasion; VI: vascular invasion; R1: resection margin positive for invasive carcinoma; PD: poor differentiation.

PREDITORES DE MALIGNIDADE

Table 3. Likelihood ratios of predictors of malignancy in MD-IPMNs

Predictors	PLR[2] (95% CI[3])	NLR[4] (95% CI)	
MN[1]≥10mm	5.5 (2.3-13.3)	0.18 (0.08-0.41)	
Positive cytology	20.3 (3.0-137)	0.23 (0.12-0.44)	
MN[1]≥10 mm or positive cytology		6.1 (2.5-14.9) (0.02-0.29)	0.07

[1]MN: Mural nodule. [2]PLR: positive likelihood ratio. [3]CI: confidence interval. [4]NLR: negative likelihood ratio.



Uehara H, et al. Gastrointest Endosc (2021)

Pancreatology 21 (2021) 1135–1145

Contents lists available at ScienceDirect

Pancreatology

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

Systematic review and meta-analysis of observational studies on BD-IPMNS progression to malignancy

Conclusion: Most presumed BD-IPMNs entering surveillance do not become malignant. Of those submitted to surgery, concomitant PDAC adds to the overall risk of detecting malignancy.

TRATAMENTO CIRÚRGICO

Table 1 Clinical parameters used to recommend resection of IPMN

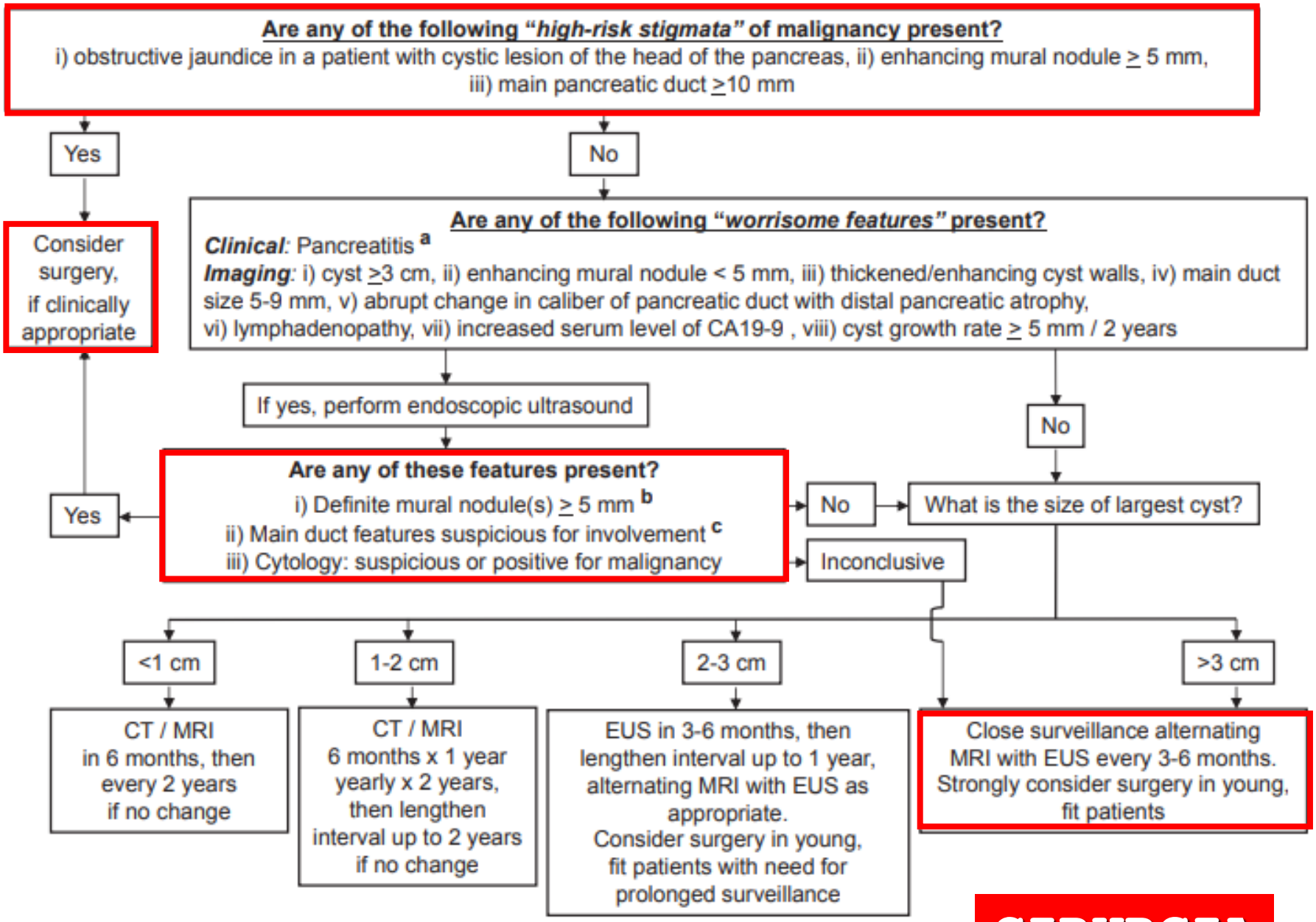
	International Association of Pancreatology Guidelines, 2012 (revised 2017) [19, 25]	European Experts Consensus Statement, 2013 (revised, 2018) [20, 21]	American Gastroenterological Association Guidelines, 2015 [22]
Age	–	–	–
Obstructive jaundice	Presence	Presence	–
Abdominal pain/history of pancreatitis	Not definitive	Presence	–
Main duct size	> 10 mm	≥ 10 mm	Dilated[a]
Mural nodule	Enhancement	Enhancement, ≥ 5 mm	Presence[a]
Cyst size	Not definitive	Not definitive	≥ 3 cm[a]
Cytology	Suspicious or positive	Positive	Positive
Serum CA19-9	–	Not definitive	–

Lim J, Allen PJ. Updates Surg 2019; 71:209–16

Table 2 Indications for surgery in intraductal papillary mucinous neoplasms according to the International, European and American Gastroenterological Association guidelines[5,8,13,20-22,41]

Guidelines	Indications for surgery
IAP (2006)	Symptoms; Cyst size ≥ 3 cm; Mural nodule; MPD ≥ 5 mm; Positive cytology
AGA (2015)	High risk features: Cyst size ≥ 3 cm; Presence of solid component; Dilated MPD
	HGD or cancer on cytology
IAP (2017)	High risk stigmata: Jaundice; Enhancing mural nodule ≥ 5 mm; MPD ≥ 10 mm
	HGD or cancer on cytology
	Worrisome features: Cyst size ≥ 3 cm; Acute pancreatitis (due to IPMN)
	Enhancing mural nodule ≥ 5 mm; Thickened and enhancing cyst wall
	MPD dilation 5-9 mm; Abrupt change of MPD caliber with distal pancreatic atrophy; Presence of lymphadenopathy; Elevated serum CA 19-9; Cyst growth rate > 5 mm/2 yr
European (2018)	Absolute indications: Jaundice; Enhancing mural nodule ≥ 5 mm; MPD ≥ 10 mm; HGD or cancer on cytology; Solid mass
	Relative indications: Cyst size ≥ 4 cm; Enhancing mural nodule ≥ 5 mm/years; Acute pancreatitis (due to IPMN); New onset of diabetes; Rapidly increasing cyst size; Elevated serum levels of CA19-9

IPMN: Intraductal papillary mucinous neoplasm; IAP: International Association of Pancreatology; AGA: American Gastroenterological Association; MPD: Main pancreatic duct; HGD: High grade dysplasia.



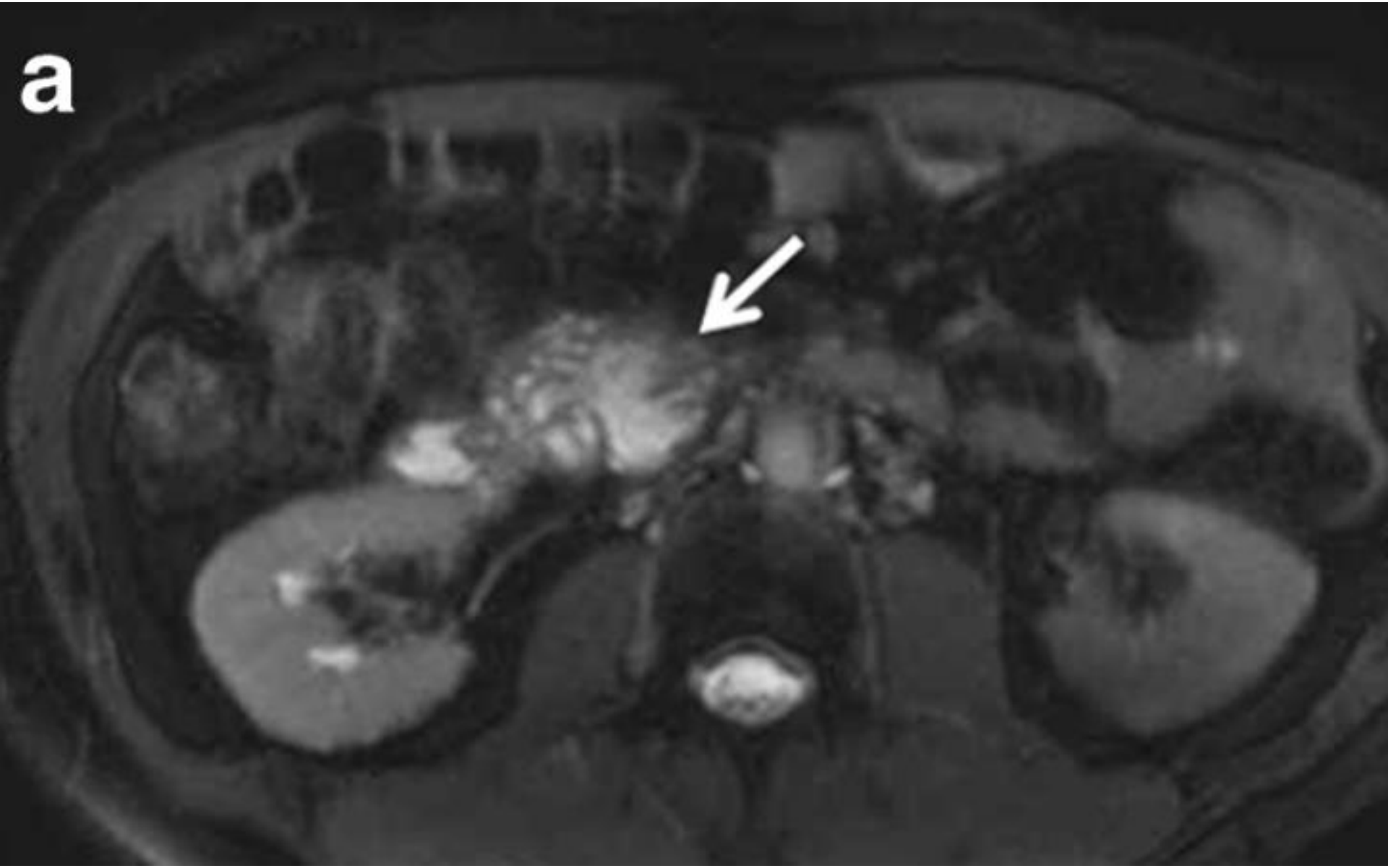
CIRURGIA

Tanaka M, et al. Pancreatology 2017;17:738-53

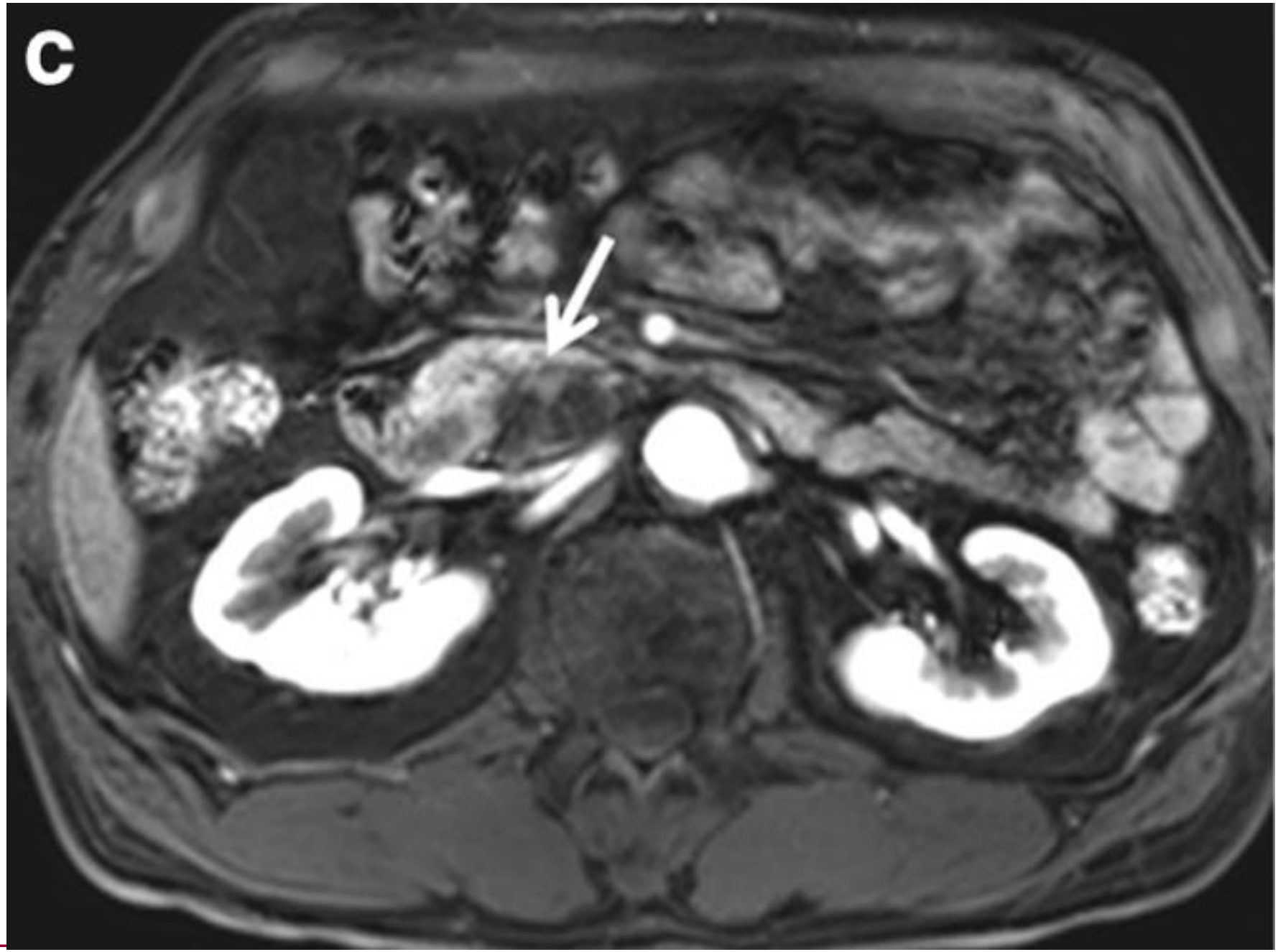
TRATAMENTO CIRÚRGICO

Variables	All resection types *N* = 124 *N (%)*
Procedures	
Pancreatoduodenectomy	56 *(45)*
Distal pancreatectomy	45 *(36)*
Enucleation	3 *(2.5)*
Total pancreatectomy	19 *(15)*
Central pancreatectomy	1 *(0.5)*

Buscail E et al. BMC Surgery 2019; 19:115



Hwang J, et al. Eur Radiol 2017



Hwang J, et al. Eur Radiol 2017

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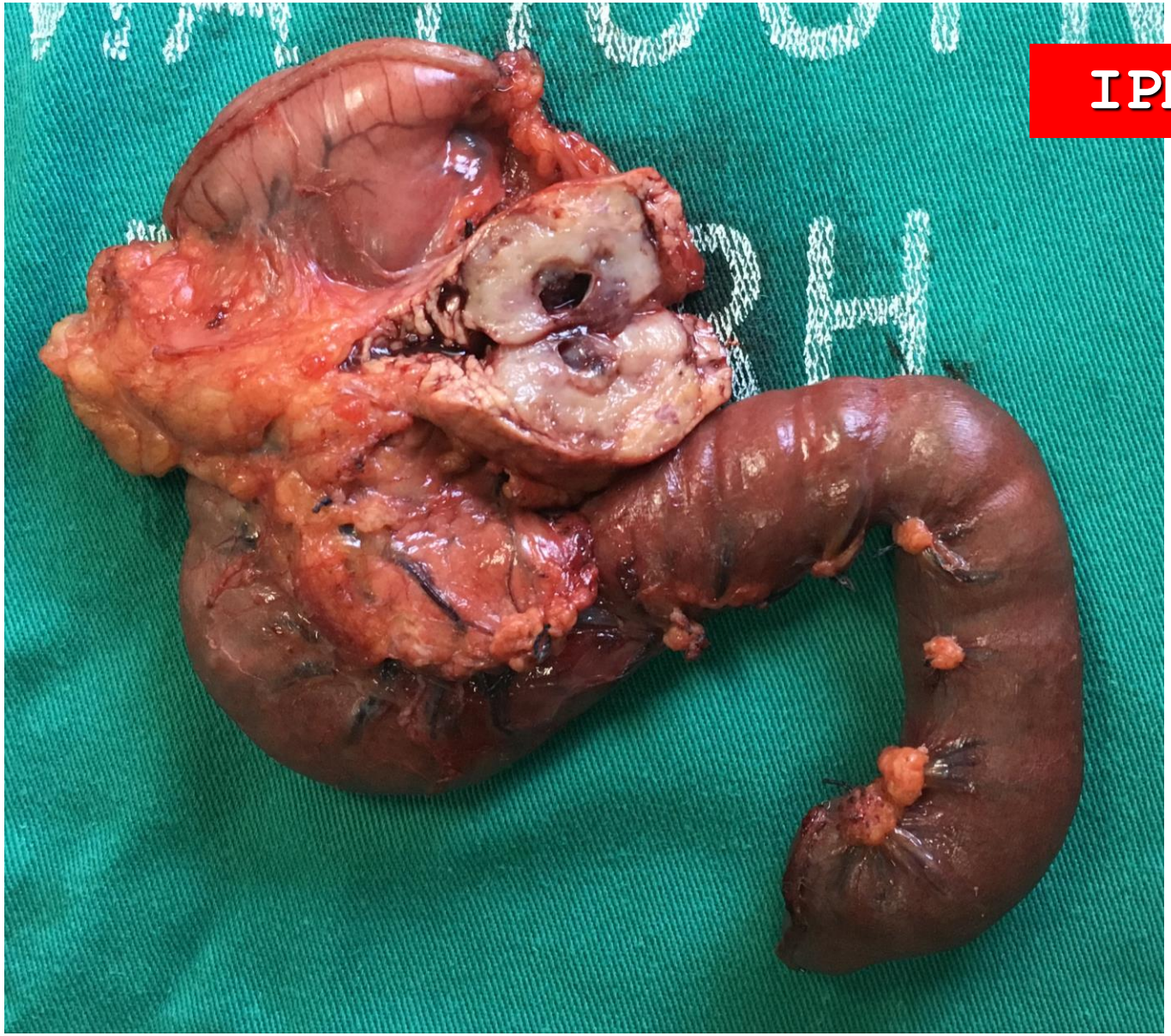
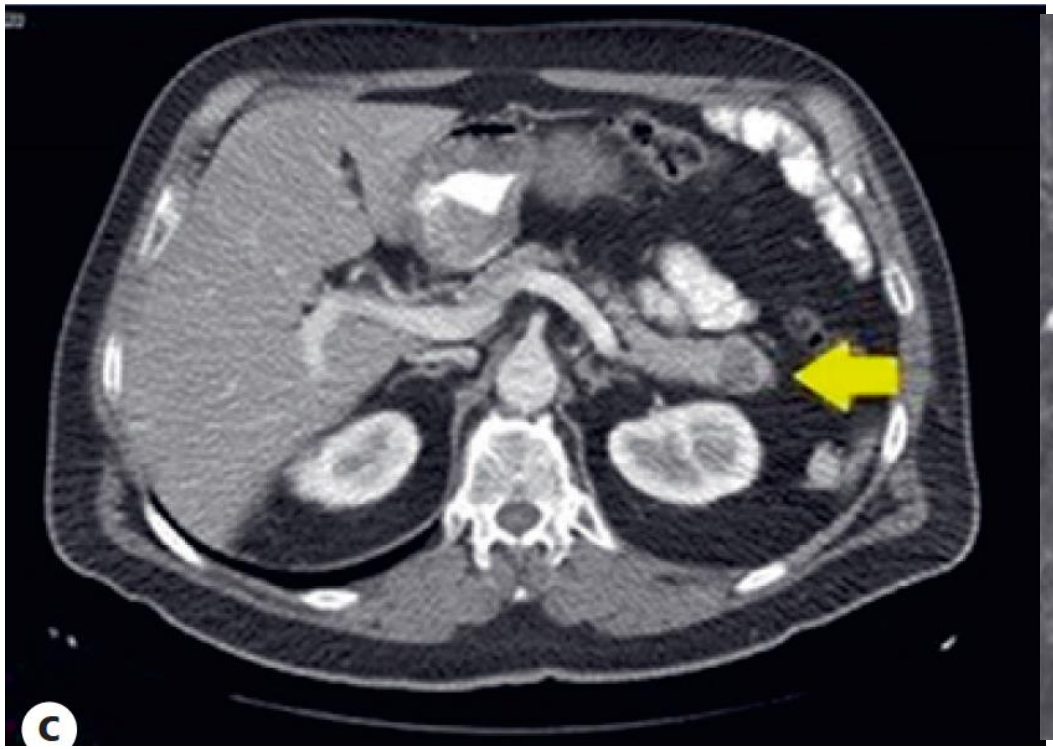
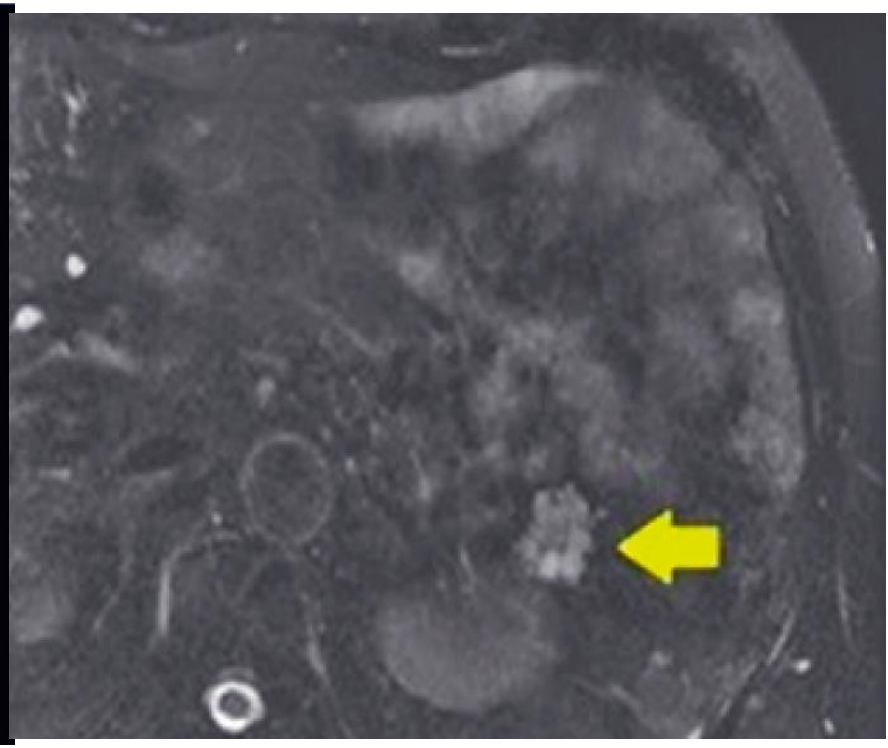


IPMN





Perri G, et al. Dig Surg 2019

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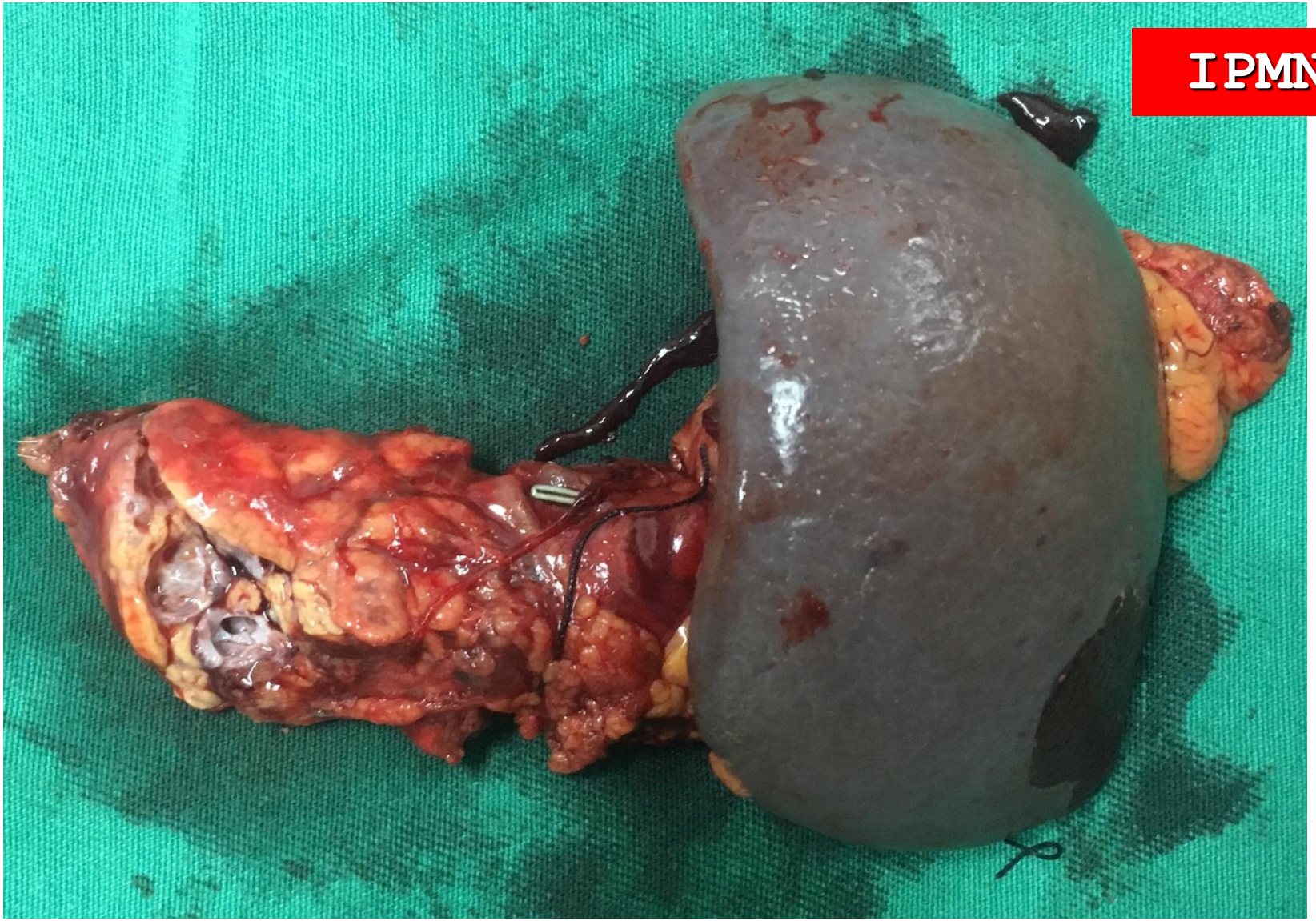


Review Article

Digestive Surgery

Dig Surg 2016;33:335–342
DOI: 10.1159/000445019

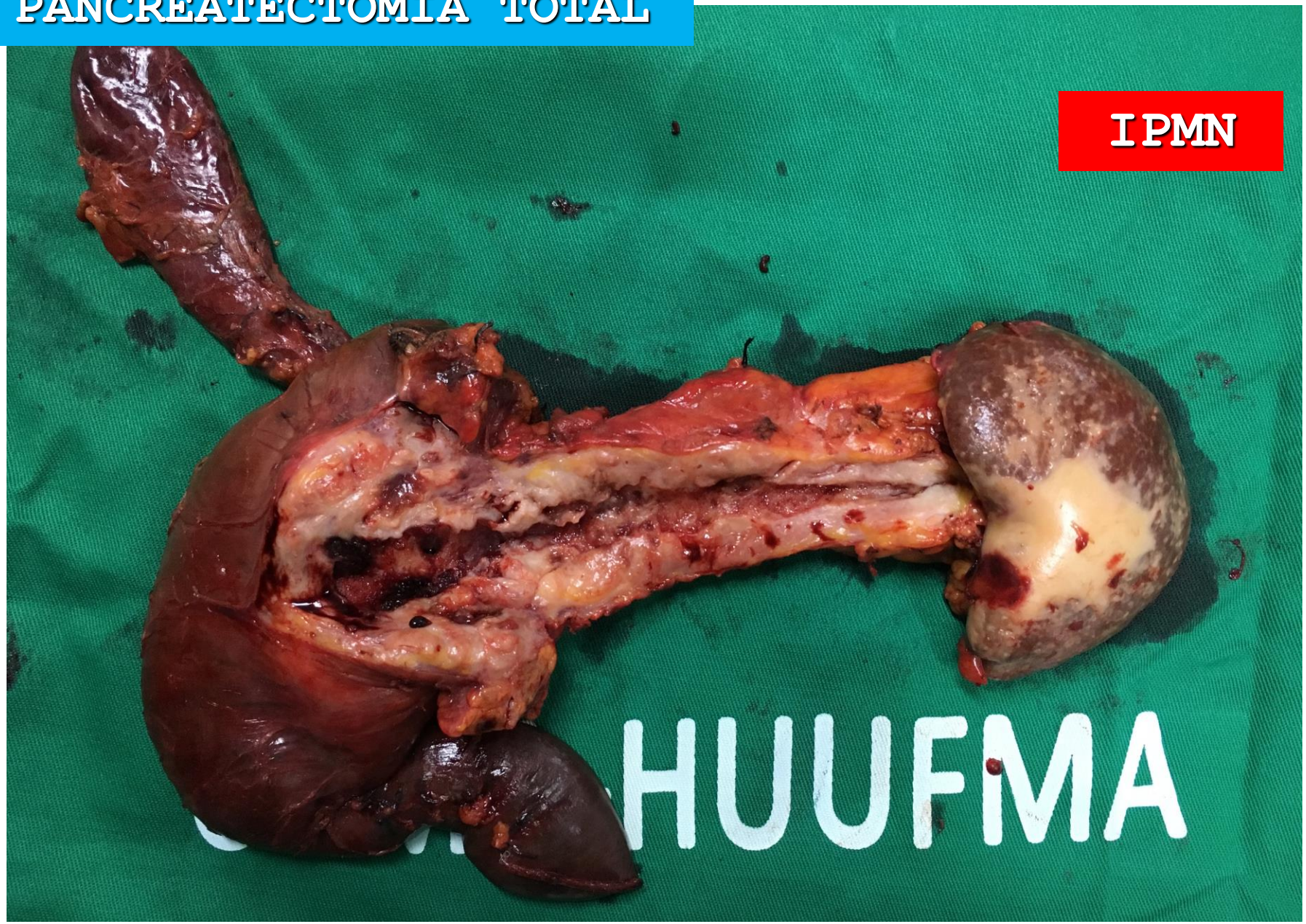
Published online: May 25, 2016

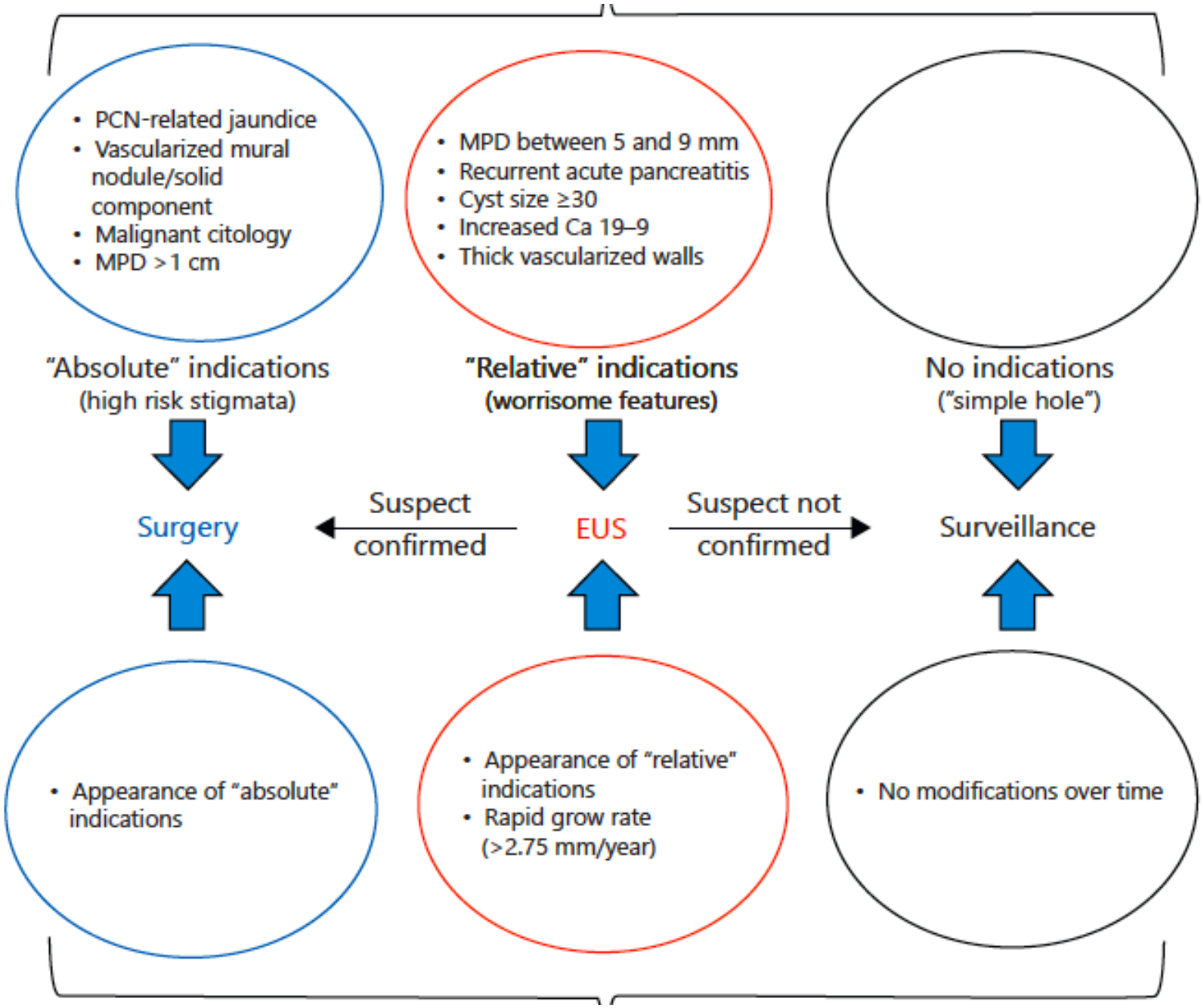
Is It Time to Expand the Role of Total Pancreatectomy for IPMN?

- Envolvimento difuso do ducto principal
- Doença multifocal em paciente de alto risco
- Persistente alto grau de displasia na margem de ressecção

Griffin JF, et al. Dig Surg 2016;33:335-42

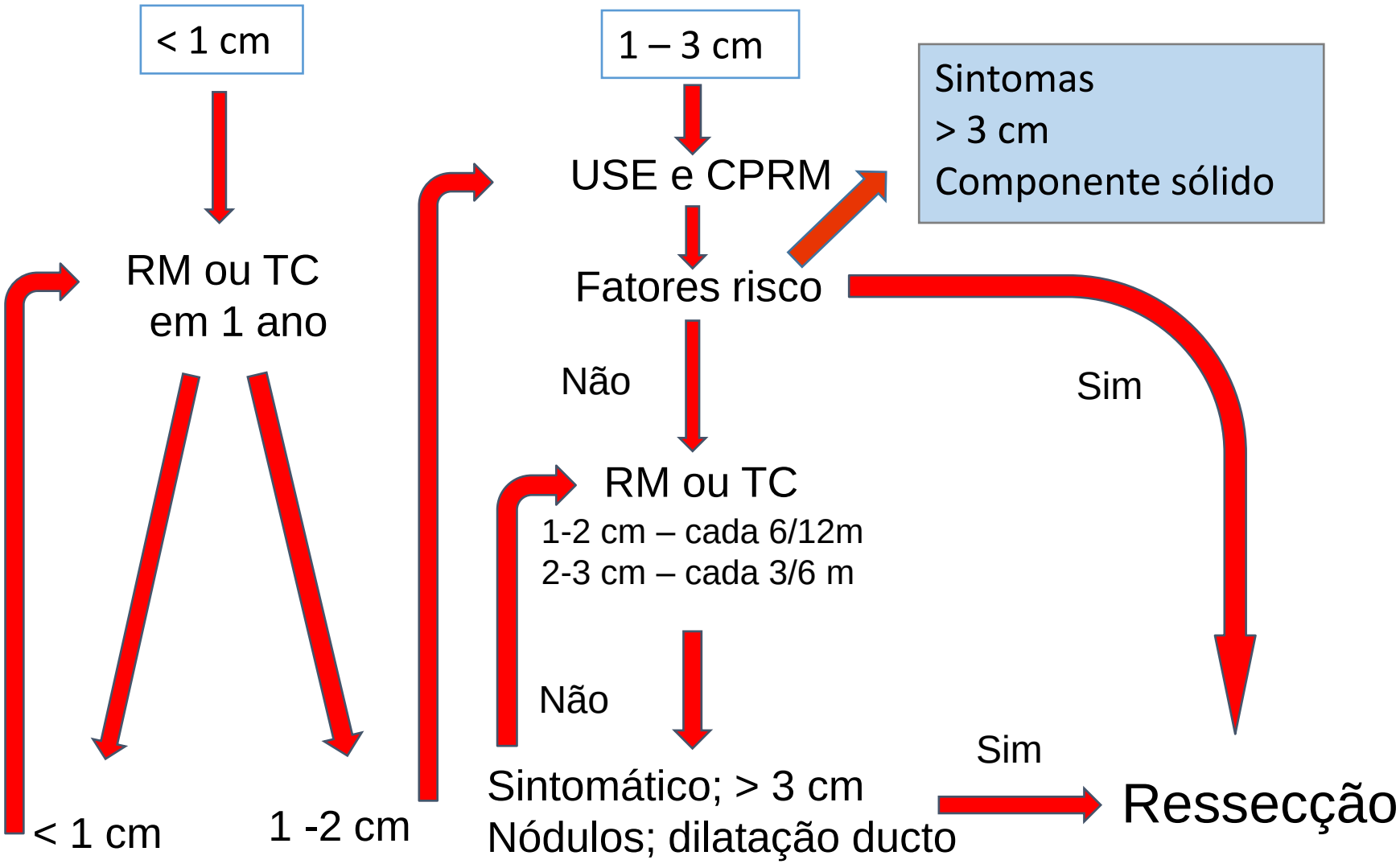
PANCREATECTOMIA TOTAL





Perri G, et al. Dig Surg 2019

IPMN INCIDENTAL



CONTROLE

Table 4 | **Surveillance interval of nonresected pancreatic cysts as stratified by different guidelines**

Guideline	Cyst type	Cyst size	Surveillance interval	Surveillance modalities
2015 AGA[48]	IPMN	<30 mm	Yearly for 1 year then every 2 years[a]	MRI with MRCP
2017 IAP[3]	IPMN	<10 mm	Within 6 months then every 2 years	CT or MRI with MRCP
		10–20 mm	Every 6 months for 1 year then yearly for 2 years, then every 2 years	CT or MRI with MRCP
		20–30 mm	3–6 months then yearly	EUS, alternating MRI with EUS
2018 European[4]	IPMN	<40 mm	Every 6 months for 1 year then yearly	CA19-9, EUS and/or MRI
	MCN	<40 mm	Every 6 months for 1 year then yearly	CA 19-9, EUS and/or MRI

AGA, American Gastroenterological Association; CA19-9, cancer antigen 19-9; European, European Study Group on Cystic Tumours of the Pancreas; EUS, endoscopic ultrasound; IAP, International Association of Pancreatology; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; MRCP, magnetic resonance cholangiopancreatography. [a] The 2015 AGA guideline suggests discontinuing the follow-up after 5 years if there is no change in size or characteristics of the cyst.

van Huijgevoort NCM, et al. Nat Rev 2019

Obrigado!

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