ng/ml がIPMN悪性例の診断に有用との報告もある．現時点では，IPMN症例にルーチンにERCPを行い膵液採取や擦過細胞診を行うことは推奨されず，研究として行うべきである．

本邦ではIPMNではなく，上皮内癌（PanIN 3）の診断を目的にERCP細胞診，あるいはENBD下細胞診を行い一定の成果が得られている[4]が，IPMNの細胞診の感度が必ずしも良好でないことから，本邦でも現段階では限られた施設で研究として行うべきと考えられる．

BD-IPMNと漿液性嚢胞腫瘍の鑑別（Distinction of BD-IPMN from serous cystic neoplasm (SCN)

前回はMCNとBD-IPMNの特徴比較の表が提示されていたが，今回はMCN，BD-IPMN，SCN，仮性嚢胞の臨床・画像診断上の特徴を掲載された．この項の記述を以下に記す．

漿液性嚢胞腫瘍はPolycystic（小嚢胞の集簇），Honeycomb（蜂巣状），Oligocystic（ここではmacrocystic SCNの意味：著者注）に分類される．BD-IPMNはpolycysticやhoneycomb状の漿液性嚢胞腫瘍とはCTまたはMRCPで鑑別できる．しかし，小さなoligocystic SCNはBD-IPMNとの鑑別は難しく，EUS-FNAで嚢胞液のCEAを測定することが鑑別に役立つかもしれない．

著者らの施設では前述のごとく膵嚢胞性病変でEUS-FNAを積極的に行う対象としてSCNがあり，理由も前述した通りである．しかし，EUS-FNAにより得られた検体でSCN自体を診断することは現時点では困難であり，不要な手術を避けるためにも免疫組織化学か遺伝子解析でSCN自体の確定診断の方法の確立が切に望まれる．

文　献

1) Tanaka M, Fernández-del Castillo C, Adsay V, et al; International Association of Pancreatology. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology 2012; 12: 183-97.
2) Tanaka M, Chari S, Adsay V, et al; International Association of Pancreatology. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology 2006; 6: 17-32.
3) Imaoka H, Yamao K, Salem AA, et al. Pancreatic endocrine neoplasm can mimic serous cystadenoma. Int J Gastrointest Cancer 2005; 35: 217-20.
4) Iiboshi T, Hanada K, Fukuda T, Yonehara S, Sasaki T, Chayama K. Value of cytodiagnosis using endoscopic nasopancreatic drainage for early diagnosis of pancreatic cancer: establishing a new method for the early detection of pancreatic carcinoma in situ. Pancreas 2012; 41: 523-9.

Explanation for IPMN Guideline 2012 and its problems to be solved

Kenji YAMAO, Nobumasa MIZUNO, Kazuo HARA,
Susumu HIJIOKA, Hiroshi IMAOKA[1], and Yasuhiro SHIMIZU[2]

Key words: IPMN, MCN, Guide line, EUS, EUS-FNA

The international consensus guidelines for management of IPMN and MCN of the pancreas established in 2006 have been revised in 2012. The new description about the diagnosis in the revised version included work-up for cystic lesions of the pancreas, distinction of BD-IPMN from MCN and other pancreatic cysts, roles of cyst fluid analysis and cytology obtained by EUS-FNA in the diagnosis of cystic lesions of the pancreas, and distinction of BD-IPMN from serous cystic neoplasm (SCN). In addition, the algorithm for the management of suspected BD-IPMN was changed according to the recent information and current understandings since 2006 and typical clinical and imaging features of common pancreatic cysts were also presented.

[1] Department of Gastroenterology, Aichi Cancer Center Hospital (Aichi)
[2] Department of Gastrointestinal Surgery, Aichi Cancer Center Hospital (Aichi)

J Epidemiol 2012;22(6):477-483
doi:10.2188/jea.JE20120010

Original Article

Selected Polymorphisms of Base Excision Repair Genes and Pancreatic Cancer Risk in Japanese

Makoto Nakao[1,2], Satoyo Hosono[1], Hidemi Ito[1], Miki Watanabe[1], Nobumasa Mizuno[3], Shigeki Sato[2], Yasushi Yatabe[4], Kenji Yamao[3], Ryuzo Ueda[2], Kazuo Tajima[1], Hideo Tanaka[1,5], and Keitaro Matsuo[1,5]

[1]Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan
[2]Department of Medical Oncology and Immunology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan
[3]Department of Gastroenterology, Aichi Cancer Center Central Hospital, Nagoya, Japan
[4]Department of Pathology and Molecular Diagnostics, Aichi Cancer Center Central Hospital, Nagoya, Japan
[5]Department of Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan

Received January 20, 2012; accepted April 10, 2012; released online July 28, 2012

ABSTRACT

Background: Although several reports have described a possible association between DNA repair genes and pancreatic cancer (PC) in smokers, this association has not been fully evaluated in an Asian population. We assessed the impact of genetic polymorphisms in the base excision repair (BER) pathway on PC risk among Japanese.

Methods: This case-control study compared the frequency of 5 single-nucleotide polymorphisms (SNPs) of BER genes, namely rs1052133 in *OGG1*, rs1799782 and rs25487 in *XRCC1*, rs1130409 in *APE1*, and rs1136410 in *PARP1*. SNPs were investigated using the TaqMan assay in 185 PC cases and 1465 controls. Associations of PC risk with genetic polymorphisms and gene–environment interaction were examined with an unconditional logistic regression model. Exposure to risk factors was assessed from the results of a self-administered questionnaire. We also performed haplotype-based analysis.

Results: We observed that the minor allele of rs25487 in *XRCC1* was significantly associated with PC risk in the per-allele model (odds ratio = 1.29, CI = 1.01–1.65; trend $P = 0.043$). Haplotype analysis of *XRCC1* also showed a statistically significant association with PC risk. No statistically significant interaction between *XRCC1* polymorphisms and smoking status was seen.

Conclusions: Our findings suggest that *XRCC1* polymorphisms affect PC risk in Japanese.

Key words: pancreatic cancer; SNPs; DNA repair gene; *XRCC1*

INTRODUCTION

The incidence of pancreatic cancer (PC) is increasing, and PC is now the fifth leading cause of cancer death in Japan.[1–5] Because early detection and curative treatment of PC are very difficult, the 5-year survival rate is only 5.5%.[6] This suggests that epidemiologic approaches to identifying PC high-risk groups have an important role in decreasing the number of PC deaths.

Possible risk factors for PC include advanced age, smoking, overweight, diabetes mellitus, and alcohol consumption.[2,7–10] A positive association between PC risk and a family history of PC has also been reported, suggesting the possible involvement of genetic factors in PC incidence.[5,10,11] Recently, several reports have observed an association between polymorphisms in DNA repair genes and PC risk, particularly among smokers.[12–20] Four major types of DNA repair system have been identified, namely base excision repair (BER), nucleotide excision repair, mismatch repair, and double-strand break repair.[14,21–23] With regard to the association between PC risk and DNA repair genes, genetic polymorphisms in the BER pathway are the most extensively investigated in molecular epidemiologic studies.[14] However, most studies of the association between PC risk and BER gene polymorphisms have been conducted in white populations.

We conducted a case-control study in a Japanese population to evaluate the impact of genetic polymorphisms in BER pathways on PC risk among Asians. The study focused on 4 key genes in this repair pathway: X-ray repair cross-complementing group 1 (*XRCC1*), apurinic/apyrimidinic endonuclease (*APE1*), 8-oxoguanine DNA glycosylase (*OGG1*), and poly(ADP-ribose) polymerase 1 (*PARP1*).

Address for correspondence. Keitaro Matsuo, Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan (e-mail: kmatsuo@aichi-cc.jp).

METHODS

Study subjects

The case subjects were 185 PC patients with no prior history of cancer who were diagnosed at Aichi Cancer Center Hospital (ACCH), Nagoya, Japan, between January 2001 and November 2005. The control subjects comprised 1465 randomly selected non-cancer ACCH outpatients, during the same period, who had no history of any cancer. All subjects were enrolled in the Hospital-based Epidemiological Research Program II at ACCH (HERPACC-II) at the time of their first visit to ACCH. The framework of HERPACC-II has been described elsewhere.[24,25] Briefly, all first-visit ACCH outpatients aged 20 to 79 years were asked to complete a self-administered questionnaire on their lifestyle before development of the presenting symptoms. Outpatients were also asked to provide a 7-mL blood sample. Approximately 95% of eligible subjects completed the questionnaire, and 50% provided blood samples. All data were loaded into the HERPACC database, which is periodically synchronized with the hospital cancer registry system. Approximately 35% of subjects were diagnosed with cancer within a year of the first visit. In the present study, we defined the case population as patients who received a diagnosis of PC within 1 year of the first visit, ie, we used the window period from first visit to final diagnosis of PC rather than prospectively identifying cases. A total of 75.7% of PC cases were histologically confirmed, among which 92.1% were diagnosed as having ductal adenocarcinoma. Our previous study showed that the lifestyle patterns of first-visit outpatients corresponded with those of individuals randomly selected from Nagoya's general population, which confirms the external validity of the study.[26] The present study was approved by the Ethics Committee of Aichi Cancer Center, and informed consent was obtained at first visit from all participants.

Genotyping

We examined 5 non-synonymous polymorphisms in BER pathway genes, namely rs1799782 (Arg194Trp) and rs25487 (Arg399Gln) in *XRCC1*, rs1130409 (Asp148Glu) in *APE1*, rs1052133 in *OGG1* (Ser326Cys), and rs1136410 (Val762Ala) in *PARP1*. In our study, these 5 single-nucleotide polymorphisms (SNPs) were selected on the basis of their association with cancer risk or their expected influence on BER systems.[13,14,17–22,27–29] DNA of each subject was extracted from the buffy coat fraction using a DNA Blood Mini Kit (Qiagen, Tokyo, Japan). All loci were examined by the TaqMan assay with probes and primers (Applied Biosystems, Foster City, CA, USA) and the Fluidigm EP1 SNP Genotyping 96.96 Dynamic Array (Fluidigm Corp., South San Francisco, CA, USA). Approximately 10% of subjects were examined in duplicate to confirm the consistency of genotyping.

Assessment of exposure

Exposure to potential PC risk factors was assessed from responses to the self-administered questionnaire, which was completed before diagnosis during the first visit to ACCH and reviewed by trained interviewers. Subjects were specifically questioned about their lifestyle before the onset of presenting symptoms. Daily alcohol consumption in grams was determined by summing the amount of pure alcohol in the average daily consumption of Japanese *sake* (rice wine), *shochu* (distilled spirit), beer, wine, and whiskey. Cumulative smoking exposure was measured in pack-years (PYs), ie, the product of the average number of packs per day and the number of years of smoking. Height and body weight at baseline and weight at age 20 years were self-reported. Current body mass index (BMI) and BMI at age 20 were calculated by dividing the weight in kilograms by the height in meters squared. Family history of PC was considered positive when at least 1 parent or sibling had a history of PC.

Statistical analysis

All statistical analyses were performed using Stata version 10 (Stata Corp., College Station, TX, USA). A *P*-value less than 0.05 was considered statistically significant. Differences in characteristics between cases and controls were assessed using the chi-square test. Odds ratios (ORs) and 95% CIs were estimated using an unconditional logistic regression model adjusted for potential confounders. Potential confounders considered in multivariate analysis were age, sex, PYs of smoking (<5, ≥5 but <20, ≥20 but <40, or ≥40), drinking habit (nondrinker, <23, ≥23 but <46, or ≥46 g/day), current BMI (<18.5, ≥18.5 but <22.5, ≥22.5 but <25, ≥25 but <27.5, or ≥27.5 kg/m^2), BMI at age 20 (<18.5, ≥18.5 but <22.5, ≥22.5 but <25, ≥25 but <27.5, or ≥27.5 kg/m^2), history of diabetes mellitus (yes or no), and family history of PC (yes or no). Interactions between environmental factors and genotypes were assessed by using likelihood ratio tests within logistic regression models, with and without interaction terms. In haplotype analysis, we used haplotype-effects logistic regression for case-control data.[30] This haplotype analysis uses phased and unphased SNP genotype data to estimate haplotype effects and haplotype–environment interactions in a case-control study.[30,31] It fits haplotype-effects logistic regression by using the retrospective likelihood method in a special case of a rare disease and a single candidate gene in the Hardy–Weinberg Equilibrium (HWE), under the assumption of gene–environment independence.[30,31] Accordance with the HWE was assessed by the chi-square test.

RESULTS

The background characteristics of the subjects are shown in Table 1. Men accounted for 68.7% of case subjects and 74.9% of controls. As compared with the control group, the case group had a significantly higher prevalence of heavy smokers

Table 1. Comparison of selected characteristics of pancreatic cancer (PC) patients and non-cancer controls

	Cases (%)	Controls (%)	*P*-values[a]
	n = 185	*n* = 1465	
Age			0.999
<40	10 (5.41)	75 (5.12)	
≥40 but <50	19 (10.27)	147 (10.03)	
≥50 but <60	60 (32.43)	479 (32.70)	
≥60 but <70	60 (32.43)	484 (33.04)	
≥70	36 (19.46)	280 (19.11)	
Sex			0.068
Male	127 (68.65)	1097 (74.88)	
Female	58 (31.35)	368 (25.12)	
Current BMI[b] (kg/m^2)			0.021
<18.5	15 (8.11)	61 (4.16)	
≥18.5 but <22.5	84 (45.11)	555 (37.88)	
≥22.5 but <25	47 (25.41)	478 (32.63)	
≥25 but <27.5	25 (13.51)	245 (16.72)	
≥27.5	14 (7.57)	111 (7.58)	
Unknown	0 (0.00)	15 (1.02)	
BMI[b] at age 20 (kg/m^2)			0.018
<18.5	14 (7.57)	168 (11.47)	
≥18.5 but <22.5	112 (60.54)	950 (64.85)	
≥22.5 but <25	36 (19.46)	226 (15.43)	
≥25 but <27.5	11 (5.95)	72 (4.91)	
≥27.5	6 (3.24)	14 (0.96)	
Unknown	6 (3.24)	35 (2.39)	
Cigarette pack-years			0.005
<5	69 (37.30)	638 (43.55)	
≥5 but <20	22 (11.89)	206 (14.06)	
≥20 but <40	34 (18.38)	308 (21.02)	
≥40	60 (32.43)	304 (20.75)	
Unknown	0 (0.00)	9 (0.61)	
Drinking, g ethanol/day			0.568
Non	56 (30.27)	488 (33.31)	
<23	53 (28.65)	425 (29.01)	
≥23 but <46	43 (23.24)	342 (23.34)	
≥46	31 (16.76)	193 (13.17)	
Unknown	2 (1.08)	17 (1.16)	
History of diabetes mellitus			<0.001
Yes	37 (20.00)	126 (8.60)	
No	148 (80.00)	1339 (91.40)	
Family history of PC			0.811
Yes	8 (4.32)	58 (3.96)	
No	177 (95.68)	1407 (96.04)	

[a]*P*-values calculated by chi-square test.
[b]BMI: body mass index.

($P = 0.005$), a higher prevalence of a history of diabetes mellitus ($P < 0.001$), a lower current BMI ($P = 0.021$), and a higher BMI at age 20 ($P = 0.018$).

Table 2 shows genotype distributions for the 5 SNPs (rs1052133, rs1799782, rs25487, rs1130409, and rs1136410). Three of the 5 SNPs (rs1799782, rs25487, and rs1130409) were in accordance with HWE. The remaining 2 loci (rs1052133 and rs1136410) were not and were thus excluded from further analysis. Rs25487 in *XRCC1* was significantly associated with PC risk in the per-allele model (OR = 1.29, CI = 1.01–1.65; trend $P = 0.043$) and in the dominant model (OR = 1.39, CI = 1.01–1.91; $P = 0.041$). No significant association with PC risk was observed for the remaining 2 loci.

We analyzed potential interactions of rs1799782 and rs25487 in *XRCC1* and rs1130409 in *APE1* with known risk factors for PC, such as smoking, alcohol consumption, overweight, diabetes mellitus, and family history of PC. Because of the low frequency of minor homozygous subjects, these subjects were combined with heterozygous subjects in this analysis. The exposure variables used were current and former BMI (BMI <25 or ≥25 kg/m^2), alcohol consumption (<23 or ≥23 g ethanol/day), smoking (<5 or ≥5 PYs), heavy smoking (<40 or ≥40 PYs), history of diabetes mellitus (yes or no), and family history of PC (yes or no). There were no statistically significant interactions (eTable 1). We also analyzed interactions of rs1799782 and rs25487 in *XRCC1* and rs1130409 in *APE1* with smoking duration and intensity and detected no statistically significant interactions (eTable 2).

Table 3 shows the results of haplotype analysis for *XRCC1*. The *R*-squared (R^2) value between rs1799782 and rs25487 was 0.15. Haplotype CA in *XRCC1* was associated with a statistically significant increase in PC risk (OR = 1.32, CI = 1.01–1.71; $P = 0.042$) as compared with the most common haplotype, CG, in *XRCC1*. As shown in Table 4, we defined haplotype CA in *XRCC1* as a risk haplotype and analyzed the potential interactions between risk haplotype and known PC risk factors (smoking, alcohol consumption, overweight, diabetes mellitus, and family history of PC). The results showed significant interactions between a family history of PC and the risk haplotype in *XRCC1* (interaction $P = 0.020$).

DISCUSSION

In this case-control study, we found that the genetic polymorphism rs25487 in *XRCC1* was associated with increased risk of PC in a Japanese population. However, we did not detect any statistically significant interactions with smoking.

The BER pathway has a primary role in the repair of oxidative base lesions such as 8-hydroxyguanine, formamidopyrimidines, and 5-hydroxyuracil.[21] Oxidative damage to DNA may lead to mutations that activate oncogenes or inactivate tumor suppressor genes and may eventually increase the probability of genetic alterations developing into neoplastic events.[21] Sequence variants in BER genes are thought to modulate DNA repair capacity and are consequently suspected of being associated with altered cancer risk.[20] With regard to the association between PC risk and DNA repair pathway, genetic polymorphisms in the BER pathway are the most widely studied in Western epidemiologic studies.[14] To our knowledge, however, this is the first study to detect an association between *XRCC1* polymorphisms and the development of PC in an Asian population.

Two common variants of *XRCC1* are rs1799782 (in which T substitutes for C) and rs25487 (in which A substitutes for

Table 2. Distribution of cases and controls, and odds ratios for pancreatic cancer associated with selected BER gene polymorphisms

Polymorphism	Genotype	No. of cases/controls (%)	Unadjusted ORs[a] (95% CI)	Adjusted ORs[b] (95% CI)
rs1799782 (XRCC1, Arg194Trp)	CC	88(47.57)/677(46.21)	1.00 (ref.)	1.00 (ref.)
	CT	80(43.24)/636(43.41)	0.97 (0.70–1.33)	0.96 (0.69–1.34)
	TT	17(9.19)/152(10.38)	0.86 (0.50–1.49)	0.81 (0.46–1.44)
	Per-allele model		0.94 (0.75–1.19)	0.96 (0.75–1.21)
	Dominant model		0.95 (0.70–1.29)	0.93 (0.68–1.28)
	(*P* trend)		0.622	0.709
	minor allele(T) frequency in control subjects = 0.321 (HWE[c]: *P* = NS)			
rs25487 (XRCC1, Arg399Gln)	GG	93(50.27)/842(57.47)	1.00 (ref.)	1.00 (ref.)
	GA	77(41.62)/538(36.72)	1.30 (0.94–1.79)	1.36 (0.98–1.90)
	AA	15(8.11)/85(5.80)	1.60 (0.89–2.88)	1.58 (0.85–2.93)
	Per-allele model		1.28 (1.00–1.63)	1.29 (1.01–1.65)
	Dominant model		1.34 (0.98–1.82)	1.39 (1.01–1.92)
	(*P* trend)		0.046	0.043
	minor allele(A) frequency in control subjects = 0.242 (*P* = NS)			
rs1130409 (APE1, Asp148Glu)	TT	77(41.62)/542(37.00)	1.00 (ref.)	1.00 (ref.)
	TG	75(41.62)/681(46.48)	0.78 (0.55–1.09)	0.77 (0.55–1.10)
	GG	33(17.84)/242(16.52)	0.96 (0.62–1.48)	1.02 (0.65–1.60)
	Per-allele model		0.94 (0.75–1.16)	0.96 (0.77–1.20)
	Dominant model		0.82 (0.60–1.12)	0.84 (0.61–1.15)
	(*P* trend)		0.548	0.745
	minor allele(T) frequency in control subjects = 0.398 (*P* = NS)			
rs1052133 (OGG1, Ser326Cys)	CC	55(29.73)/417(28.46)	—	—
	CG	87(47.03)/692(47.24)	—	—
	GG	43(23.24)/356(24.30)	—	—
	Per-allele model		—	—
	Dominant model		—	—
	(*P* trend)		—	—
	minor allele(G) frequency in control subjects = 0.479 (*P* = 0.040)			
rs1136410 (PARP1, Val762Ala)	TT	61(32.97)/550(37.54)	—	—
	TC	90(48.65)/657(44.85)	—	—
	CC	34(18.38)/258(17.61)	—	—
	Per-allele model		—	—
	Dominant model		—	—
	(*P* trend)		—	—
	minor allele(T) frequency in control subjects = 0.400 (*P* = 0.012)			

Abbreviation: OR, odds ratio.
[a]Unconditional logistic regression model (unadjusted).
[b]Unconditional logistic regression model adjusted for age, sex, current BMI, BMI at age 20, smoking status, drinking habit, history of diabetes mellitus, and family history of pancreatic cancer.
[c]HWE: Hardy–Weinberg Equilibrium.

Table 3. Haplotype frequencies of *XRCC1*, and odds ratios for pancreatic cancer associated with *XRCC1* haplotype

Haplotype	SNPs[a]		Haplotype frequency			Adjusted OR[b] (cases/controls 185/1465)	*P*-value
	1 (C>T)	2 (G>A)	Overall	Cases	Controls		
1	C	G	0.439	0.433	0.442	1.00 (ref.)	
2	C	A	0.240	0.274	0.239	1.32 (1.01–1.71)	0.042
3	T	G	0.319	0.292	0.318	1.05 (0.81–1.36)	0.691
4	T	A	0.002	<0.001	0.002	N.E.	N.E.

Abbreviation: OR, odds ratio.
[a]SNP 1 is rs1799782; SNP 2 is rs25487.
[b]Haplotype-effects logistic regression for case-control data was used. Multivariable adjustment by age, sex, current BMI, BMI at age 20, smoking status, drinking habit, diabetes mellitus, and family history of PC.

Table 4. Gene-environment interaction between *XRCC1* haplotypes and selected risk factors for pancreatic cancer

Haplotype	Exposure	Current BMI[a]	BMI[a] at age 20	Smoking[b]	Heavy Smoking[b]	Alcohol[c]	Diabetes mellitus[d]	Family history of PC[e]
non-CA[f]	(−)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
CA[g]	(−)	1.37 (1.05–1.79)	1.35 (1.05–1.73)	1.64 (1.13–2.38)	1.43 (1.08–1.90)	1.30 (0.95–1.77)	1.26 (0.97–1.65)	1.20 (0.93–1.54)
non-CA[f]	(+)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
CA[g]	(+)	1.01 (0.59–1.73)	1.12 (0.53–2.36)	1.09 (0.80–1.50)	1.02 (0.64–1.63)	1.24 (0.85–1.82)	1.42 (0.79–2.52)	4.68 (1.59–13.81)
interaction *P*		0.468	0.124	0.095	0.097	0.729	0.864	0.020

NOTE: All values expressed as odds ratio (95% CI). Haplotype-effects logistic regression for case-control data was used. Multivariable adjustment by age, sex, current BMI, BMI at age 20, smoking status, drinking habit, diabetes mellitus, and family history of PC. Interactions between environmental factors and genotypes were assessed by likelihood ratio tests between the logistic regression models, with and without interaction terms, between genes and environmental factors of interest.

[a]BMI <25 vs. ≥25.

[b]Smoking: pack-years <5 vs. ≥5; Heavy Smoking: pack-years <40 vs. ≥40.

[c]Alcohol: g ethanol/day <23 vs. ≥23.

[d]Diabetes mellitus: no vs. yes.

[e]Family history of pancreatic cancer: no vs. yes.

[f]Haplotype non-CA: other haplotypes (frequency > 0.01) except haplotype CA. Frequency in control subjects was 0.760.

[g]Haplotype CA: *XRCC1* SNPs at rs1799782 and rs25487. Frequency in control subjects was 0.239.

G), which lead to amino acid substitutions Arg194Trp and Arg399Gln, respectively.[32] In particular, the minor allele (A) for rs25487, namely the 399Gln allele, was found to be associated with a higher frequency of glycophorin mutant, elevated DNA adduct levels, higher baseline sister chromatid exchange frequency, and increased sensitivity to ionizing radiation, all of which might be due to reduced BER function.[18] In the present study, the minor allele of rs25487 in *XRCC1* was associated with elevated PC risk. Thus, our finding is consistent with the potential mechanisms described above.

It has been suggested that *XRCC1* gene polymorphisms are modulating factors for PC risk, particularly in smokers.[17–21] A synergistic effect between these gene polymorphisms and tobacco smoking in relation to PC risk has been suspected.[14] Oxidative DNA damage produced by smoking is expected to be repaired by the BER system, which includes the *XRCC1* gene.[33] In this study, we observed a significant main effect of rs25487 in *XRCC1* but found no statistically significant interaction between *XRCC1* loci and smoking. Although the reason for this difference is unclear, the results may have been affected by the heterogeneity of study populations, differences in ethnicity, the small sample size, and potential confounders. On the other hand, the minor allele of rs25487 in *XRCC1* was associated with increased risk of PC among light but not heavy smokers. These findings are consistent with past reports, and possible explanations for the limited effect among heavy smokers include enhanced apoptosis at the time of cell division from heavy smoking and induction of DNA repair capacity in response to DNA damage.[20,21]

In addition, we found that haplotype CG in *XRCC1* had a higher impact in those with a family history of PC than in those without such a history. To our knowledge, this phenomenon has not been reported previously and might be explained by family history acting as a surrogate for interaction with known/unknown genetic susceptibility factors. We did not observe any interaction with the *ABO* genotype, which has been reported to have a significant association with PC risk (data not shown).[34] Given our small study population, the finding of an interaction with family history may have been due to chance. Further study is required to duplicate our findings in a larger cohort.

Our study has several methodological issues that warrant discussion. First, the control population was selected from non-cancer patients at ACCH. It is reasonable to assume that this was the same population from which the case subjects were derived, which would bolster the internal validity of our study. Second, with regard to external validity, we previously showed that individuals selected randomly from our control population were similar to the general population of Nagoya City in terms of the exposure of interest.[26] However, only 50% of patients agreed to the collection of a blood sample, and the characteristics of these participants might differ from those of the general population. Third, case-control studies have an intrinsic information bias. However, the HERPACC system is less prone to this bias than are typical hospital-based studies, as the data for all patients were collected before diagnosis. In addition, the results from our self-administered questionnaire may be inaccurate. However, any such misclassification would be nondifferential and would likely underestimate the causal association.[35] Fourth, with regard to SNP analysis, because 2 SNPs (rs1052133 in *OGG1* and rs1136410 in *PARP1*) were not in accordance with HWE in our study, further studies that include these factors are required. Fifth, residual confounding by known and unknown risk factors might be present; given the small number of cases, our findings require replication in a larger study. Finally, our study was limited to a Japanese population, and the results cannot necessarily be extrapolated to other populations.

In summary, this case-control study showed a significant association between genetic polymorphisms in *XRCC1* and

PC risk in a Japanese population. Further investigation of our findings in larger populations are warranted, and the biological mechanisms responsible for the association should be fully elucidated.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the efforts and contributions of doctors, nurses, technical staff, and hospital administration staff at Aichi Cancer Center Hospital in the daily management of the HERPACC study. This study was supported by Grants-in-Aid for Scientific Research (B) from the Ministry of Education, Culture, Sports, Science and Technology of Japan; Grants-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan; Japan Society for the Promotion of Science A3 Foresight Program; and a grant from Daiwa Securities Health Foundation.

Conflicts of interest: None declared.

ONLINE ONLY MATERIALS

eTables and the Japanese-language abstract for articles can be accessed by clicking on the tab labeled Supplementary materials at the journal website http://dx.doi.org/10.2188/jea.JE20120010.

REFERENCES

1. Center for Cancer Control and Information Services. Japan: N.C.C. Center for Cancer Control and Information Services, National Cancer Center; 2007.
2. Kanda J, Matsuo K, Suzuki T, Kawase T, Hiraki A, Watanabe M, et al. Impact of alcohol consumption with polymorphisms in alcohol-metabolizing enzymes on pancreatic cancer risk in Japanese. Cancer Sci. 2009;100:296–302.
3. Matsuda T, Marugame T, Kamo K, Katanoda K, Ajiki W, Sobue T; Japan Cancer Surveillance Research Group. Cancer incidence and incidence rates in Japan in 2003: based on data from 13 population-based cancer registries in the Monitoring of Cancer Incidence in Japan (MCIJ) Project. Jpn J Clin Oncol. 2009; 39:850–8.
4. Tsugane S, Inoue M. Insulin resistance and cancer: epidemiological evidence. Cancer Sci. 2010;101:1073–9.
5. Low SK, Kuchiba A, Zembutsu H, Saito A, Takahashi A, Kubo M, et al. Genome-wide association study of pancreatic cancer in Japanese population. PLoS One. 2010;5:e11824.
6. Tsukuma H, Ajiki W, Ioka A, Oshima A; Research Group of Population-Based Cancer Registries of Japan. Survival of cancer patients diagnosed between 1993 and 1996: a collaborative study of population-based cancer registries in Japan. Jpn J Clin Oncol. 2006;36:602–7.
7. Lowenfels AB, Maisonneuve P. Epidemiology and risk factors for pancreatic cancer. Best Pract Res Clin Gastroenterol. 2006; 20:197–209.
8. Lin Y, Kikuchi S, Tamakoshi A, Yagyu K, Obata Y, Inaba Y, et al. Obesity, physical activity and the risk of pancreatic cancer in a large Japanese cohort. Int J Cancer. 2007;120:2665–71.
9. Larsson SC, Orsini N, Wolk A. Body mass index and pancreatic cancer risk: A meta-analysis of prospective studies. Int J Cancer. 2007;120:1993–8.
10. Inoue M, Tajima K, Takezaki T, Hamajima N, Hirose K, Ito H, et al. Epidemiology of pancreatic cancer in Japan: a nested case-control study from the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC). Int J Epidemiol. 2003;32:257–62.
11. Hruban RH, Canto MI, Goggins M, Schulick R, Klein AP. Update on familial pancreatic cancer. Adv Surg. 2010;44: 293–311.
12. Li D, Suzuki H, Liu B, Morris J, Liu J, Okazaki T, et al. DNA repair gene polymorphisms and risk of pancreatic cancer. Clin Cancer Res. 2009;15:740–6.
13. Duell EJ, Bracci PM, Moore JH, Burk RD, Kelsey KT, Holly EA. Detecting pathway-based gene-gene and gene-environment interactions in pancreatic cancer. Cancer Epidemiol Biomarkers Prev. 2008;17:1470–9.
14. Lin Y, Yagyu K, Egawa N, Ueno M, Mori M, Nakao H, et al. An overview of genetic polymorphisms and pancreatic cancer risk in molecular epidemiologic studies. J Epidemiol. 2011;21:2–12.
15. McWilliams RR, Bamlet WR, de Andrade M, Rider DN, Cunningham JM, Petersen GM. Nucleotide excision repair pathway polymorphisms and pancreatic cancer risk: evidence for role of MMS19L. Cancer Epidemiol Biomarkers Prev. 2009;18: 1295–302.
16. Jiao L, Hassan MM, Bondy ML, Abbruzzese JL, Evans DB, Li D. The XPD Asp312Asn and Lys751Gln polymorphisms, corresponding haplotype, and pancreatic cancer risk. Cancer Lett. 2007;245:61–8.
17. McWilliams RR, Bamlet WR, Cunningham JM, Goode EL, de Andrade M, Boardman LA, et al. Polymorphisms in DNA repair genes, smoking, and pancreatic adenocarcinoma risk. Cancer Res. 2008;68:4928–35.
18. Duell EJ, Holly EA, Bracci PM, Wiencke JK, Kelsey KT. A population-based study of the Arg399Gln polymorphism in X-ray repair cross-complementing group 1 (XRCC1) and risk of pancreatic adenocarcinoma. Cancer Res. 2002;62:4630–6.
19. Jiao L, Bondy ML, Hassan MM, Wolff RA, Evans DB, Abbruzzese JL, et al. Selected polymorphisms of DNA repair genes and risk of pancreatic cancer. Cancer Detect Prev. 2006;30:284–91.
20. Hung RJ, Hall J, Brennan P, Boffetta P. Genetic polymorphisms in the base excision repair pathway and cancer risk: a HuGE review. Am J Epidemiol. 2005;162:925–42.
21. Maynard S, Schurman SH, Harboe C, de Souza-Pinto NC, Bohr VA. Base excision repair of oxidative DNA damage and association with cancer and aging. Carcinogenesis. 2009;30:2–10.
22. Mandal RK, Mittal T, Kapoor R, Mittal RD. NER and BER repair gene polymorphisms in a healthy north Indian cohort and comparison with different ethnic groups worldwide. Asian Pac J Cancer Prev. 2010;11:1601–4.
23. Caldecott KW. Single-strand break repair and genetic disease. Nat Rev Genet. 2008;9:619–31.
24. Tajima K, Hirose K, Inoue M, Takezaki T, Hamajima N, Kuroishi T. A Model of Practical Cancer Prevention for Out-patients Visiting a Hospital: the Hospital-based Epidemiologic

Research Program at Aichi Cancer Center (HERPACC). Asian Pac J Cancer Prev. 2000;1:35–47.
25. Hamajima N, Matsuo K, Saito T, Hirose K, Inoue M, Takezaki T, et al. Gene-environment Interactions and Polymorphism Studies of Cancer Risk in the Hospital-based Epidemiologic Research Program at Aichi Cancer Center II (HERPACC-II). Asian Pac J Cancer Prev. 2001;2:99–107.
26. Inoue M, Tajima K, Hirose K, Hamajima N, Takezaki T, Kuroishi T, et al. Epidemiological features of first-visit outpatients in Japan: comparison with general population and variation by sex, age, and season. J Clin Epidemiol. 1997;50: 69–77.
27. Hill DA, Wang SS, Cerhan JR, Davis S, Cozen W, Severson RK, et al. Risk of non-Hodgkin lymphoma (NHL) in relation to germline variation in DNA repair and related genes. Blood. 2006;108:3161–7.
28. Huang M, Dinney CP, Lin X, Lin J, Grossman HB, Wu X. High-order interactions among genetic variants in DNA base excision repair pathway genes and smoking in bladder cancer susceptibility. Cancer Epidemiol Biomarkers Prev. 2007;16: 84–91.
29. Duell EJ, Wiencke JK, Cheng TJ, Varkonyi A, Zuo ZF, Ashok TD, et al. Polymorphisms in the DNA repair genes XRCC1 and ERCC2 and biomarkers of DNA damage in human blood mononuclear cells. Carcinogenesis. 2000;21:965–71.
30. Marchenko YV, Carroll RJ, Lin DY, Amos CI, Gutierrez RG. Semiparametric analysis of case-control genetic data in the presence of environmental factors. Stata J. 2008;8:305–33.
31. Epstein MP, Satten GA. Inference on haplotype effects in case-control studies using unphased genotype data. Am J Hum Genet. 2003;73:1316–29.
32. Shen MR, Jones IM, Mohrenweiser H. Nonconservative amino acid substitution variants exist at polymorphic frequency in DNA repair genes in healthy humans. Cancer Res. 1998;58: 604–8.
33. Sugimura T, Kumimoto H, Tohnai I, Fukui T, Matsuo K, Tsurusako S, et al. Gene-environment interaction involved in oral carcinogenesis: molecular epidemiological study for metabolic and DNA repair gene polymorphisms. J Oral Pathol Med. 2006;35:11–8.
34. Nakao M, Matsuo K, Hosono S, Ogata S, Ito H, Watanabe M, et al. ABO blood group alleles and the risk of pancreatic cancer in a Japanese population. Cancer Sci. 2011;102:1076–80.
35. Suzuki T, Matsuo K, Hasegawa Y, Hiraki A, Kawase T, Tanaka H, et al. Anthropometric factors at age 20 years and risk of thyroid cancer. Cancer Causes Control. 2008;19:1233–42.

Pancreatology 12 (2012) 183–197

Contents lists available at SciVerse ScienceDirect

Pancreatology

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

Review article

International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas

Masao Tanaka [a,*], Carlos Fernández-del Castillo [b], Volkan Adsay [c], Suresh Chari [d], Massimo Falconi [e], Jin-Young Jang [f], Wataru Kimura [g], Philippe Levy [h], Martha Bishop Pitman [i], C. Max Schmidt [j], Michio Shimizu [k], Christopher L. Wolfgang [l], Koji Yamaguchi [m], Kenji Yamao [n]

[a] Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan
[b] Pancreas and Biliary Surgery Program, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[c] Department of Anatomic Pathology, Emory University Hospital, Atlanta, GA, USA
[d] Pancreas Interest Group, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA
[e] U.O. Chirurgia B, Dipartimento di Chirurgia Policlinico "G.B. Rossi", Verona, Italy
[f] Division of Hepatobiliary-Pancreatic Surgery, Department of Surgery, Seoul National University College of Medicine, Seoul, South Korea
[g] First Department of Surgery, Yamagata University, Yamagata, Japan
[h] Pôle des Maladies de l'Appareil Digestif, Service de Gastroentérologie-Pancréatologie, Hopital Beaujon, Clichy Cedex, France
[i] Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[j] Department of Surgery, Indiana University, Indianapolis, IN, USA
[k] Department of Pathology, Saitama Medical University, International Medical Center, Saitama, Japan
[l] Cameron Division of Surgical Oncology and The Sol Goldman Pancreatic Cancer Research Center, Department of Surgery, Johns Hopkins University, Baltimore, MD, USA
[m] Department of Surgery I, University of Occupational and Environmental Health, Fukuoka, Japan
[n] Aichi Cancer Center Hospital, Aichi, Japan

ARTICLE INFO

Article history:
Received 7 December 2011
Received in revised form
6 April 2012
Accepted 8 April 2012

Keywords:
International guidelines
Intraductal papillary mucinous neoplasm
Mucinous cystic neoplasm

ABSTRACT

The international consensus guidelines for management of intraductal papillary mucinous neoplasm and mucinous cystic neoplasm of the pancreas established in 2006 have increased awareness and improved the management of these entities. During the subsequent 5 years, a considerable amount of information has been added to the literature. Based on a consensus symposium held during the 14th meeting of the International Association of Pancreatology in Fukuoka, Japan, in 2010, the working group has generated new guidelines. Since the levels of evidence for all items addressed in these guidelines are low, being 4 or 5, we still have to designate them "consensus", rather than "evidence-based", guidelines. To simplify the entire guidelines, we have adopted a statement format that differs from the 2006 guidelines, although the headings are similar to the previous guidelines, i.e., classification, investigation, indications for and methods of resection and other treatments, histological aspects, and methods of follow-up. The present guidelines include recent information and recommendations based on our current understanding, and highlight issues that remain controversial and areas where further research is required.

1. Introduction

Since the publication of the international consensus guidelines for management of intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN) of the pancreas in 2006 [1], these entities have been drawing increasing attention. As a consequence, a considerable amount of information has been added to the literature during the subsequent 5 years. In particular, new information has been obtained regarding endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) of the cyst contents, the indications for resection of branch duct IPMN (BD-IPMN) have changed from rather early resection to more deliberate observation, and some reports have documented the occurrence of concomitant pancreatic ductal adenocarcinoma (PDAC) in patients with BD-IPMN. All this new knowledge makes an update of the guidelines imperative. During the 14th meeting of the International Association of Pancreatology (IAP) held in Fukuoka, Japan, in 2010, we arranged a symposium where recent progress in preoperative diagnosis and management was presented. All the speakers in the symposium, including eight initial members and six

* Corresponding author. Tel.: +81 92 642 5437; fax: +81 92 642 5457.
E-mail address: masaotan@med.kyushu-u.ac.jp (M. Tanaka).

1424-3903/$ – see front matter
doi:10.1016/j.pan.2012.04.004

new members of the working group, have generated new guidelines based on an elaborate list of items to be addressed. Since the levels of evidence for all items addressed in these guidelines are low, being 4 or 5, we still have to designate them "consensus", rather than "evidence-based", guidelines. We have made a series of recommendations for all items in Table 1. However, since the grades of the recommendations are low, we have avoided repetition of grade C in almost all of the items.

All the authors contributed equally to the guidelines. M. Tanaka chaired and C. Fernandez-del Castillo co-chaired this working group of the IAP, and these two authors played a major role in the preparation of the manuscript. The remaining authors are listed in alphabetical order.

Table 1
Summary of recommendations.

1. Classification
   1a. The threshold of MPD dilation, segmental or diffuse, for characterization of MD-IPMN has been lowered to >5 mm without other causes of obstruction, thereby increasing the sensitivity for radiologic diagnosis without losing specificity. MPD dilation of 5–9 mm is considered a "*worrisome feature*", while an MPD diameter of ≥10 mm is one of the "*high-risk stigmata*".
   1b. The definition of "malignancy" of IPMNs and MCNs has been variable, hampering comparisons of data. We recommend abandoning the term carcinoma in situ in favor of high-grade dysplasia, reserving the descriptor of malignancy for invasive carcinoma, as outlined in the recent WHO classification.

2. Investigation
   2a. CT or MRI with MRCP is recommended for a cyst of ≥1 cm to check for "*high-risk stigmata*", including enhanced solid component and MPD size of ≥10 mm, or "*worrisome features*", including cyst of ≥3 cm, thickened enhanced cyst walls, non-enhanced mural nodules, MPD size of 5–9 mm, abrupt change in the MPD caliber with distal pancreatic atrophy, and lymphadenopathy. All cysts with "*worrisome features*" and cysts of >3 cm without "*worrisome features*" should undergo EUS, and all cysts with "*high-risk stigmata*" should be resected. If no "*worrisome features*" are present, no further initial work-up is recommended, although surveillance is still required.
   2b. MDCT and MRCP are most useful for distinguishing BD-IPMN from other cysts by showing multiplicity and a connection to the MPD.
   2c. Cyst fluid analysis is still investigational, but is recommended for evaluation of small BD-IPMNs without "*worrisome features*" in centers with expertise in EUS-FNA and cytological interpretation.
   2d. Routine ERCP for sampling of fluid or brushings in IPMN is not recommended, and should only be used in the context of research.
   2e. Distinction of BD-IPMN from a small oligocystic SCN is challenging and may require EUS-FNA with cyst fluid CEA determination.

3. Indications for Resection
   3a. Resection is recommended in all surgically fit patients with MD-IPMN. If the margin is positive for high-grade dysplasia, additional resection should be attempted to obtain at least moderate-grade dysplasia.
   3b. The indications for resection of BD-IPMN are more conservative. "*Worrisome features*" as well as "*high-risk stigmata*" are proposed. A BD-IPMN of >3 cm without "*high-risk stigmata*" can be observed without immediate resection.
   3c. Surgical resection is recommended for all surgically fit patients with MCN. For MCNs of <4 cm without mural nodules, laparoscopic resection as well as parenchyma-sparing resections and distal pancreatectomy with spleen preservation should be considered.

4. Methods of Resection and Other Treatments
   4a. Pancreatectomy with lymph node dissection remains the standard treatment for invasive and non-invasive MCNs and IPMNs. Focal non-anatomic resections or anatomic resections without lymphadenectomy or splenectomy may be considered for those without suspicion of malignancy, but carry a risk of possible leakage of mucin, and higher incidences of pancreatic fistulae and recurrence. Low-grade and possibly high-grade dysplasia of IPMN and MCN may be good candidates for laparoscopic surgery.
   4b. EUS-guided ethanol ablation cannot be recommended for patients with BD-IPMN or MCN outside of a closely monitored research protocol.
   4c. Multifocal BD-IPMNs carry a similar risk of malignancy to unifocal BD-IPMN. Segmental resection can be performed to remove the IPMNs at the highest oncological risk. The threshold for total pancreatectomy should perhaps be lowered in patients with a strong family history of PDAC and multifocal BD-IPMNs, but the data supporting this idea are incomplete.

Table 1 (*continued*)

5. Histological Aspects
   5a. The type of invasive carcinoma, colloid versus tubular, has major prognostic implications and should be part of the reporting of IPMNs, with colloid carcinomas being characterized by "intestinal" differentiation and a better prognosis than tubular carcinomas.
   5b. Instead of "minimally invasive carcinoma" derived from IPMN or MCN, it would be more appropriate to stage invasive carcinomas with the conventional staging protocols and further substage the T1 category into T1a (≤0.5 cm), T1b (>0.5 cm and ≤1 cm), and T1c (1–2 cm).
   5c. The histologic subtypes of IPMN have clinicopathologic significance. The gastric type is typically low grade, with only a small percentage developing into carcinoma. However, if a carcinoma does develop, it is usually of the tubular type and aggressive. Large intestinal-type IPMNs can have invasive carcinoma of the colloid type with indolent behavior.
   5d. If clear high-grade dysplasia or invasive carcinoma is present at the margin by frozen section analysis, further resection is warranted. All patients should be informed preoperatively about the possibility of total pancreatectomy. Moderate-grade or low-grade dysplasia may not require any further therapy.
   5e. Pathologists should make every attempt to classify the lesion as MD-IPMN or BD-IPMN, being careful to identify the MPD as precisely as possible when processing the specimen.
   5f. A distinction between PDAC derived from an IPMN and PDAC concomitant with an IPMN is proposed with regard to the topological relationship and histological transition, although the distinction sometimes remains undetermined.

6. Methods of follow-up
   6a. Patients without "*high-risk stigmata*" should undergo MRI/MRCP (or CT) after a short interval (3–6 months) to establish the stability, and then annual history/physical examination, MRI/MRCP (or CT) and serologic marker surveillance. Short interval surveillance (3–9 months) should be considered for patients whose IPMN progresses toward "*high-risk stigmata*" and patients with a family history of hereditary PDAC. Some investigators continue surveillance at short intervals owing to concern over the development of distinct PDAC.
   6b. Non-invasive MCNs require no surveillance after resection. IPMNs need surveillance based on the resection margin status. If there are no residual lesions, repeat examinations at 2 and 5 years may be reasonable. The aspect of whether a margin with moderate-grade dysplasia increases recurrence is unknown. For patients with low-grade or moderate-grade dysplasia at the margin, we suggest history/physical examination and MRCP surveillance at least twice a year. The follow-up strategy of invasive IPMN should be identical to that for PDAC.
   6c. In patients with two or more affected first-degree relatives, the risk rapidly escalates and merits aggressive surveillance by MRI/MRCP (or CT) and EUS. "*Worrisome features*" are of more concern. If present, patients should be considered for resection if they are surgically fit. If absent, patients should be followed by MRI/MRCP (or CT) at 3-month intervals and EUS annually for the first 2 years. Patients with a rapidly growing BD-IPMN and patients who develop "*worrisome features*" should be strongly considered for resection. The interval of surveillance after 2 years of no change can be lengthened to 6 months, but no longer in view of the relatively high incidence of PDAC reported for BD-IPMN.
   6d. There are no screening recommendations for detecting extrapancreatic malignancies in patients with IPMN on surveillance and after resection, but consideration of extrapancreatic neoplasms should be made based on the frequency of these malignancies in the general population of the country or region.

2. Classification

2.1. Criteria for distinction of BD-IPMN and main duct IPMN (MD-IPMN)

IPMNs can be classified into three types, i.e., MD-IPMN, BD-IPMN, and mixed type, based on imaging studies and/or the histology (Fig. 1) [1]. MD-IPMN is characterized by segmental or diffuse dilation of the main pancreatic duct (MPD) of >5 mm without other causes of obstruction. According to recent reports, a low threshold for MPD dilation (5 mm) can be adopted, which increases the sensitivity for radiologic diagnosis of MD-IPMN without losing specificity [2–10]. In the revised guidelines, MPD

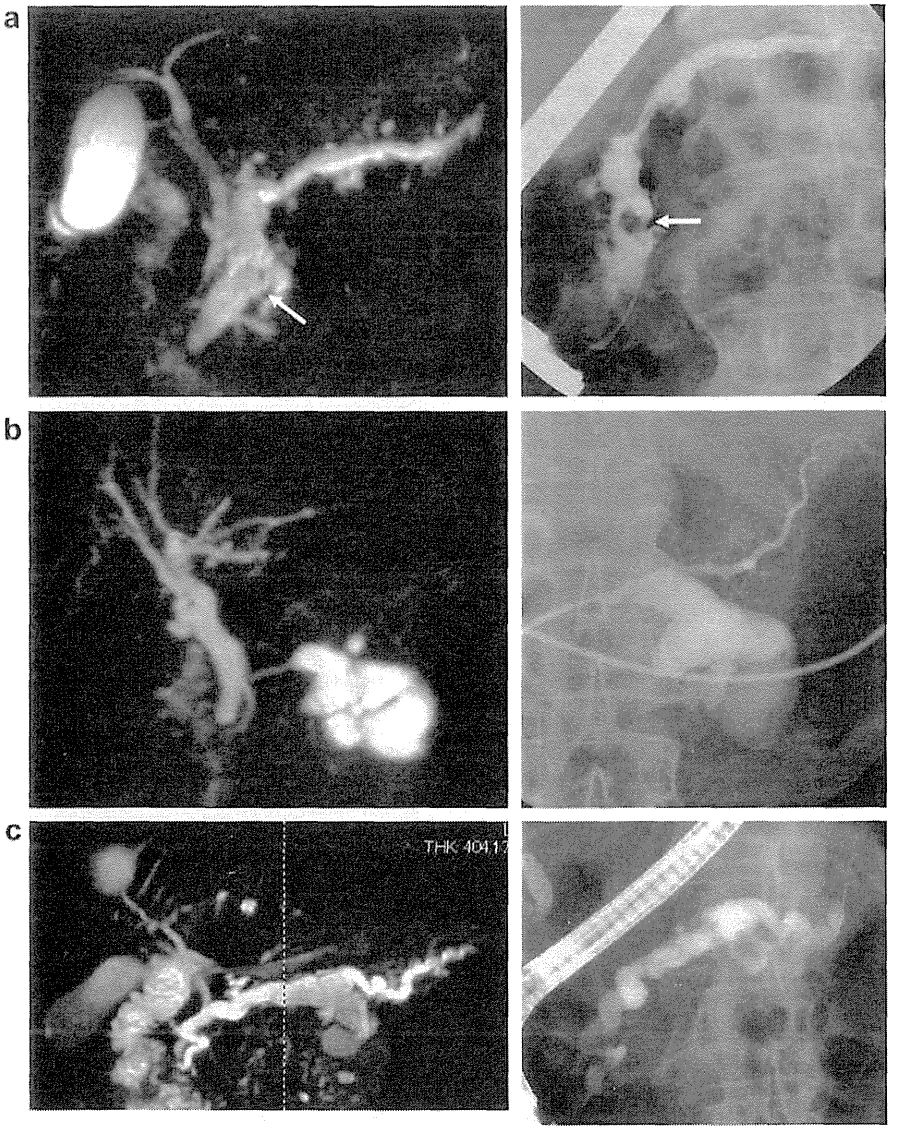


Fig. 1. MRCP (left panels) and ERCP (right panels) demonstrating the three morphological types of IPMN. a. Main duct type with a mural nodule (arrows). b. Branch duct type. c. Mixed type.

dilation of 5–9 mm is considered a "*worrisome feature*" and an MPD diameter of ≥10 mm is one of the "*high-risk stigmata*". Pancreatic cysts of >5 mm in diameter that communicate with the MPD should be considered as BD-IPMN, with pseudocyst being in the differential diagnosis for patients with a prior history of pancreatitis. Mixed type patients meet the criteria for both MD-IPMN and BD-IPMN.

There are considerable differences in the proportions of each type and the risks of malignancy (Table 2) [2–23]. The differences are partly caused by variation in the type definitions, since the correlation between the histologic and radiologic criteria is around 70% [8,24]. While the MPD can be dilated through ductal hypertension caused by mucin, protein plugs, and focal pancreatitis, neoplastic involvement without ductal dilation can be seen histologically [25]. Since the classification is important for clinicians to plan the management, it should be based on the preoperative radiologic images, and the pathological classification can be specified a posteriori.

2.2. Definition of malignant IPMN and MCN

IPMNs and MCNs exhibit a spectrum of neoplastic transformation, both within each category and often in a given case, ranging from innocuous lesions that used to be called "hyperplasia" or adenoma (currently classified as "low-grade dysplasia") to invasive carcinomas [26,27]. The definition of "malignancy" has been variable, with most authors including "carcinoma in situ" (CIS) in the malignant category, while others reserve this term for invasive neoplasms, and yet others define "malignancy" by aggressive clinical behavior [27]. This wide variation hampers comparisons of data, and hinders determination of the significance of lesions and placement of patients into clearly defined categories. For this reason, we recommend abandoning the term CIS in favor of high-grade dysplasia, reserving the descriptor of malignancy for invasive carcinoma, as outlined in the recent WHO classification [26].

Table 2
Frequencies of malignancy in IPMNs according to the morphological types.

Total IPMNs					Main duct type			Branch duct type			Mixed type		
First author	Year	Total number	Malignant *n* (%)	Invasive *n* (%)	Number *n* (%)	Malignant *n* (%)	Invasive *n* (%)	Number *n* (%)	Malignant *n* (%)	Invasive *n* (%)	Number *n* (%)	Malignant *n* (%)	Invasive *n* (%)
Sugiyama [11]	2003	62	34 (54.8%)	20 (32.3%)	30 (48.4%)	21 (70.0%)	17 (56.7%)	32 (51.6%)	13 (40.6%)	3 (9.4%)			
Sohn[a][12]	2004	136	>52 (38.2%)	52 (38.2%)	36 (26.5%)	>18 (50.0%)	18 (50.0%)	60 (44.1%)	>18 (30.0%)	18 (30.0%)	33 (24.3%)	>16 (48.5%)	16 (48.5%)
Salvia [13]	2004	140	83 (59.3%)	58 (41.4%)	140 (100%)	83 (59.3%)	58 (41.4%)						
Suzuki[a][14]	2004	1024	>446 (43.6%)	446 (43.6%)	201 (19.6%)	>120 (59.7%)	120 (59.7%)	509 (49.7%)	>150 (29.5%)	150 (29.5%)	228 (22.3%)	148 (64.9%)	148 (64.9%)
Lee [15]	2005	67	24 (35.8%)	9 (13.4%)	27 (40.3%)	12 (44.4%)	3 (11.1%)	35 (52.2%)	10 (28.6%)	4 (11.4%)	5 (7.5%)	2 (40.0%)	2 (40.0%)
Serikawa [2]	2006	103	41 (39.8%)	28 (27.2%)	47 (45.6%)	30 (63.8%)	21 (44.7%)	56 (54.4%)	11 (19.6%)	7 (12.5%)			
Schmidt [3]	2007	156	50 (32.1%)	29 (18.6%)	53 (34.0%)	30 (56.6%)	15 (28.3%)	103 (66.0%)	20 (19.4%)	14 (13.6%)			
Rodriguez [20]	2007	145	32 (22.1%)	16 (11.0%)				145 (100%)	32 (22.1%)	16 (11.0%)			
Schnelldorfer [16]	2008	208	82 (39.4%)	63 (30.3%)	76 (36.5%)	49 (64.5%)		84 (40.4%)	15 (17.9%)		48 (23.1%)	18 (37.5%)	
Kim [17]	2008	118	36 (30.5%)	28 (23.7%)	70 (59.3%)	25 (35.7%)	23 (32.9%)	48 (40.7%)	>3 (6.3%)	3 (6.3%)			
Nagai [4]	2008	72	44 (61.1%)	30 (41.7%)	15 (20.8%)	15 (100%)	10 (66.7%)	49 (68.1%)	25 (51.0%)	18 (36.7%)	8 (11.1%)	4 (50.0%)	2 (25.0%)
Jang [21]	2008	138	26 (18.8%)	17 (12.3%)				138 (100%)	26 (18.8%)	17 (12.3%)			
Ohno [18]	2009	87	45 (51.7%)	19 (21.8%)	14 (16.1%)	11 (78.6%)	4 (28.6%)	48 (55.2%)	20 (41.7%)	9 (18.8%)	25 (28.7%)	14 (56.0%)	6 (24.0%)
Nara [19]	2009	123	82 (66.7%)	61 (49.6%)	26 (21.1%)	26 (100%)	21 (80.8%)	59 (48.0%)	26 (44.1%)	14 (23.7%)	38 (30.9%)	30 (78.9%)	26 (68.4%)
Bournet [7]	2009	99	24 (24.2%)	14 (14.1%)				47 (47.5%)	6 (12.8%)	4 (8.5%)	52 (52.5%)	18 (34.6%)	10 (19.2%)
Hwang [5]	2010	187	58 (31.0%)	43 (23.0%)	28 (15.0%)	20 (71.4%)	17 (60.7%)	118 (63.1%)	19 (16.1%)	14 (11.9%)	41 (21.9%)	19 (46.3%)	12 (29.3%)
Mimura [6]	2010	82	54 (65.9%)	29 (35.4%)	39 (47.6%)	34 (87.2%)	19 (48.7%)	43 (52.4%)	20 (46.5%)	10 (23.3%)			
Sadakari [22]	2010	73	6 (8.2%)	1 (1.4%)				73 (100%)	6 (8.2%)	1 (1.4%)			
Kanno [23]	2010	159	40 (25.2%)	19 (11.9%)				159 (100%)	40 (25.2%)	19 (11.9%)			
Crippa [10]	2010	389	181 (46.5%)	118 (30.3%)	81 (20.8%)	55 (68%)	39 (48%)	159 (40.9%)	34 (22%)	17 (11%)	149 (38.3%)	92 (62%)	62 (42%)
Total		3568	>1440 (>40.4%)	1100 (30.8%)	883 (24.7%)	>549 (>62.2%)	385 (43.6%)	2027 (56.8%)	>494 (>24.4%)	337 (16.6%)	627 (17.6%)	>361 (>57.6%)	284 (45.3%)

Abbreviation: IPMN: intraductal papillary mucinous neoplasm.
[a] Since these reports only included invasive IPMNs, the frequency of malignant IPMNs is underestimated in this table owing to the absence of data for non-invasive IPMNs.

3. Investigation

3.1. Work-up for cystic lesions of the pancreas

Cystic lesions are increasingly being recognized by imaging studies, and the frequency of pancreatic cyst detection by MRI (19.9% [28]) is higher than by CT (1.2% [29] and 2.6% [30]). A cyst with invasive carcinoma is uncommon in patients with an asymptomatic pancreatic cyst, particularly one of <10 mm in size, and therefore no further work-up may be needed at that point, although follow-up is still recommended [31,32]. For cysts greater than 1 cm, pancreatic protocol CT or gadolinium-enhanced MRI with magnetic resonance cholangiopancreatography (MRCP) is recommended for better characterization of the lesion (Fig. 2) [33]. A recent consensus of radiologists suggested dedicated MRI as the procedure of choice for evaluating a pancreatic cyst, based on its superior contrast resolution that facilitates recognition of septae, nodules, and duct communications [33]. When patients are required to undergo frequent imaging for follow-up, MRI may be better for avoiding radiation exposure.

For amelioration of symptoms, and owing to the higher risk of malignancy, all symptomatic cysts should be further evaluated or resected as determined by the clinical circumstances.

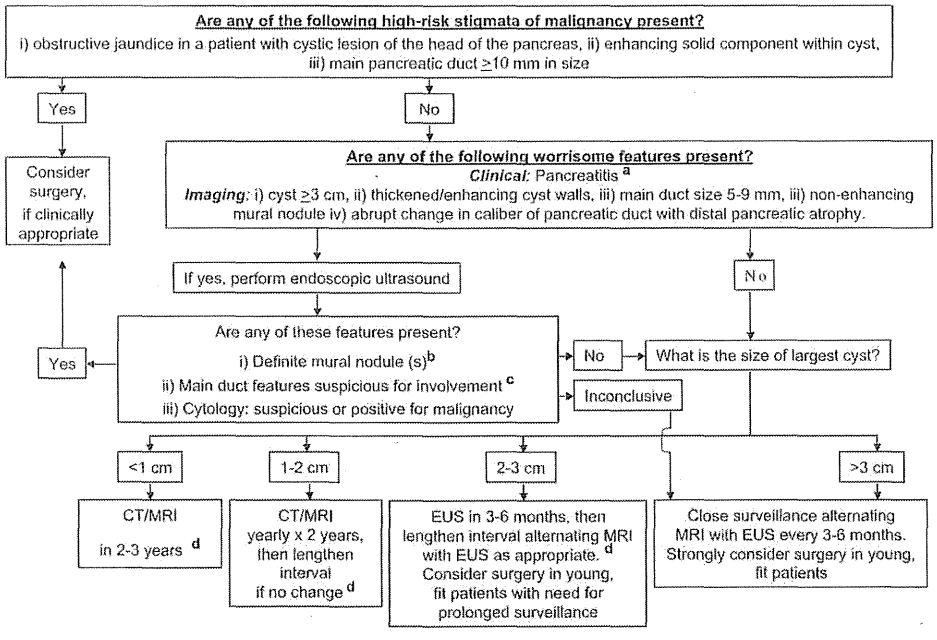
"*Worrisome features*" on imaging include cyst of ≥3 cm, thickened enhanced cyst walls, MPD size of 5–9 mm, non-enhanced mural nodules, abrupt change in the MPD caliber with distal pancreatic atrophy, and lymphadenopathy [34–38].

Cysts with obvious "*high-risk stigmata*" on CT or MRI (i.e., obstructive jaundice in a patient with a cystic lesion of the pancreatic head, enhanced solid component, MPD size of ≥10 mm) should undergo resection without further testing. All smaller cysts with "*worrisome features*" should be evaluated by EUS to further risk-stratify the lesion. Patients with cysts of >3 cm and no "*worrisome features*" can also be considered for EUS to verify the absence of thickened walls or mural nodules, particularly if the patient is elderly.

All patients with cysts of ≤3 cm in size without "*worrisome features*" should undergo surveillance according the size stratification (Fig. 2) [39].

3.2. Distinction of BD-IPMN from MCN and other pancreatic cysts

Using a combination of the clinical history, sex, imaging characteristics, cytology, and cyst fluid and chemical analyses of carcinoembryonic antigen (CEA) and amylase, pancreatic cysts can not only be characterized as mucinous or non-mucinous, but also accurately identified for their specific subtypes [40–56]. A combination of the clinical and imaging characteristics provides the best initial preoperative diagnosis of the cyst type (Table 2). For an imaging diagnosis of BD-IPMN, multidetector CT (MDCT) and MRCP are the most useful primary methods for defining the morphology, location, multiplicity, and communication with the MPD. [8,9,18,57,58]. Reliable distinguishing features of BD-IPMN include multiplicity and visualization of a connection to the MPD, although such a connection is not always observed. EUS can then be used for detecting mural nodules and invasion, and is most effective for delineating the malignant characteristics (Fig. 3) [18], although it has the limitation of operator dependency [13,58]. Chemical



a. Pancreatitis may be an indication for surgery for relief of symptoms.
b. Differential diagnosis includes mucin. Mucin can move with change in patient position, may be dislodged on cyst lavage and does not have Doppler flow. Features of true tumor nodule include lack of mobility, presence of Doppler flow and FNA of nodule showing tumor tissue
c. Presence of any one of thickened walls, intraductal mucin or mural nodules is suggestive of main duct involvement. In their absence main duct involvement is incolclusive.
d. Studies from Japan suggest that on follow-up of subjects with suspected BD-IPMN there is increased incidence of pancreatic ductal adenocarcinoma unrelated to malignant transformation of the BD-IPMN(s) being followed. However, it is unclear if imaging surveillance can detect early ductal adenocarcinoma, and, if so, at what interval surveillance imaging should be performed.

Fig. 2. Algorithm for the management of suspected BD-IPMN.

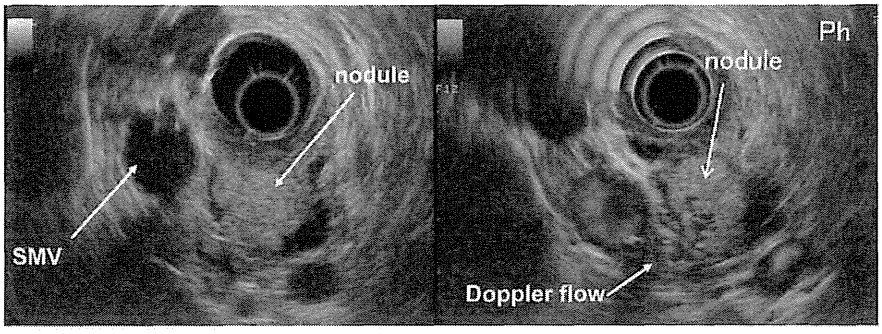


Fig. 3. EUS showing a mural nodule in the dilated MPD with Doppler flow indicating the presence of a blood supply.

analyses of the CEA and amylase levels as well as cytology of the cyst content obtained by EUS-FNA are often useful, but cannot distinguish MCN and IPMN [47,51,54–56]. A more recent study claimed that a molecular analysis for *GNAS* mutations can distinguish MCN from BD-IPMN [59].

3.3. Roles of cyst fluid analysis and cytology obtained by EUS-FNA in the diagnosis of cystic lesions of the pancreas

The use of EUS-FNA varies widely throughout the world. Elevated CEA is a marker that distinguishes mucinous from non-mucinous cysts, but not benign from malignant cysts [53–56,59–63]. A cut-off of ≥192–200 ng/ml is ~80% accurate for the diagnosis of a mucinous cyst [53–55]. An increase the cut-off value improves the specificity at the expense of the sensitivity [63]. A low CEA level does not exclude a mucinous cyst. Cyst fluid amylase is not uniformly elevated in IPMN, and MCN may also exhibit elevated amylase levels [53]. Serous cysts typically have low levels of both CEA and amylase. Cytology can be diagnostic, although the sensitivity is limited by the scant cellularity [50,51,63–71]. In summary, interpreting the results of biochemical markers in cyst fluid is a complex exercise in pattern recognition, and should be reserved for patients in whom additional information will have an impact on the surgical decision-making.

In centers with expertise in EUS-FNA and cytological interpretation, cytological analysis adds value, especially for evaluation of a small BD-IPMN without "*worrisome features*" [56]. "High-grade epithelial atypia" recognizes epithelial cells with cellular atypia that is qualitatively and quantitatively insufficient for a malignant interpretation, and may be a more sensitive predictor of malignancy than positive cytology [3,51,56,72,73]. Such cells in the cyst fluid predicted malignancy in a mucinous cyst with 72% sensitivity and positive predictive value (80% accuracy) in one study [51], and detected 30% more cancers in small IPMN than "*worrisome features*" in another study [56].

Molecular analyses of the cyst fluid for diagnosis are still evolving. Studies show that detection of *KRAS* mutations more accurately supports a mucinous rather than malignant cyst [45–47]. A recent study indicates that *GNAS* mutations may be helpful in distinguishing significant mucinous cysts from indolent cysts that can be conservatively managed [59].

It is important to highlight that Japanese investigators do not recommend cyst fluid analysis for the diagnosis of mucinous-like cystic lesions, and believe that a cyst of any size with "*worrisome features*" should not be aspirated, because it may cause leakage of the cyst content, possibly leading to peritoneal dissemination [74,75]. At present, EUS-FNA with cytological and molecular analyses is still considered investigational, but is recommended for evaluation of small BD-IPMNs without "*worrisome features*" only in centers with expertise in EUS-FNA and cytological interpretation.

3.4. Role of cytology and/or analysis of the pancreatic juice in the diagnosis of malignant BD-IPMN

Pancreatic juice can be obtained via endoscopic retrograde cholangiopancreatography (ERCP) by washing or brushing for cytology. Pancreatic juice can also be obtained from the MPD or a dilated branch duct affected by IPMN, although selective cannulation may be difficult. Only a few reports mention pancreatic juice cytology of BD-IPMN, with variable yields [70,76]. One large series showed a significant role of CEA levels of >30 ng/ml in diagnosing malignant BD-IPMN [77]. Routine ERCP for sampling of fluid or brushings in IPMN is not recommended, and should only be used in the context of research.

3.5. Distinction of BD-IPMN from serous cystic neoplasm (SCN)

Serous cystadenomas have three morphological patterns: polycystic, honeycomb, and oligocystic. BD-IPMN can be properly distinguished from SCN with a polycystic or honeycomb pattern by either CT or MRCP [55,74,78,79] (Table 3). The differentiation between a small oligocystic SCN and a BD-IPMN is challenging and may require EUS-FNA with cyst fluid CEA determination [80–82].

4. Indications for resection

4.1. Indications for resection of MD-IPMN

According to published series of ≥50 cases (Table 2), the mean frequency of malignancy in MD-IPMN is 61.6% (range, 36–100%) and the mean frequency of invasive IPMN is 43.1% (range, 11–81%) [2–6,11–19]. Considering these high incidences of malignant/invasive lesions and the low 5-year survival rates (31–54%) [3–5,12–14], surgical resection is strongly recommended for all surgically fit patients. However, MPD dilation of 5–9 mm should be considered as one of the "*worrisome features*", similar to the case for BD-IPMN (Fig. 2), with a recommendation of evaluation but no immediate resection. To date, there have been no consistent predictive factors for malignancy in MD-IPMN, including the degree of MPD dilation, presence of symptoms, or mural nodules [5,11,13].

The aim of resection is to achieve complete removal of a tumor with a negative margin. In the segmental ectatic type or diffuse type with focal lesions (mural nodules or combined branch lesions, etc.), it is relatively easy to determine the resection side (proximal or distal pancreatectomy) and transection line.

Table 3
Typical clinical and imaging features of common pancreatic cysts.

Characteristic	MCN	BD-IPMN	SCN	Pseudocyst
Sex (% female)	>95%	~55%	~70%	<25%
Age (decade)	4th, 5th	6th, 7th	6th, 7th	4th, 5th
Asymptomatic	~50%	Mostly when small	~50%	Nearly zero
Location (% body/tail)	95%	30%	50%	65%
Common capsule	Yes	No	Yes	N/A
Calcification	Rare, curvilinear in the cyst wall	No	30–40%, central	No
Gross appearance	Orange-like	Grape-like	Spongy or honeycomb-like	Variable
Multifocality	No	Yes	No	Rare
Internal structure	Cysts in cyst	Cyst by cyst	Microcystic and/or macrocystic	Unilocular
Main pancreatic duct communication	Infrequent	Yes (though not always demonstrable)	No	Common
Main pancreatic duct	Normal or deviated	Normal, or dilated to >5 mm, suggesting combined type	Normal or deviated	Normal or irregularly dilated, may contain stones

Abbreviations: MCN, mucinous cystic neoplasm; BD-IPMN, branch duct intraductal papillary mucinous neoplasm; SCN, serous cystic neoplasm; N/A, not applicable.

In the diffuse dilation type without focal lesions, more careful evaluation is warranted, including ERCP. Some of these patients may not even have IPMN, but rather chronic pancreatitis. A dilated papilla with mucin extrusion and/or a mural nodule visualized by ERCP definitely confirms the diagnosis of MD-IPMN. If indeed IPMN is diagnosed, right-sided pancreatectomy is preferred because it is technically easier to resect additional pancreatic tissue to achieve a negative margin.

Frozen biopsy sections are useful for deciding the resection line [83]. If the resection margin is positive for high-grade dysplasia, additional resection of the pancreas should be attempted to obtain a negative margin. If low-grade or moderate-grade dysplasia is found, further resection is controversial [84–87]. Total pancreatectomy should be applied selectively in younger patients who can handle the complexities of brittle diabetes and exocrine insufficiency [88,89]. Intraductal ultrasonography (Fig. 4), pancreatoscopy (Fig. 5), and cytology have been used to obtain additional information of the surgical margin in difficult cases [90,91]. However, all of these investigations should preferably be performed preoperatively to avoid leakage of mucin.

4.2. Indications for resection of BD-IPMN

The mean frequency of malignancy in resected BD-IPMN is 25.5% (range, 6.3–46.5%) and the mean frequency of invasive cancer is 17.7% (range, 1.4–36.7%) (Table 2) [2–7,11–23]. Although resection of BD-IPMN therefore warrants consideration, these lesions mostly occur in elderly patients, and the annual malignancy rate is only 2–3% [92,93]. These factors support conservative management with follow-up in patients who do not have risk factors predicting malignancy. The usefulness of the previous consensus criteria for resection [1] has been validated by many reports [5–8,22–24,94,95]. New high-risk factors proposed include a rapidly increasing cyst size [92,96] and high-grade atypia rather than "positive" cytology [51,56,65,67,72].

Although still controversial, younger patients (<65 years) with a cyst size of >2 cm may be candidates for resection owing to the cumulative risk of malignancy [21,97]. The decision needs to be individualized and to depend not only on the risk of malignancy but also on the patient's conditions and cyst location. Since a BD-IPMN size of >3 cm is a weaker indicator of malignancy than the presence

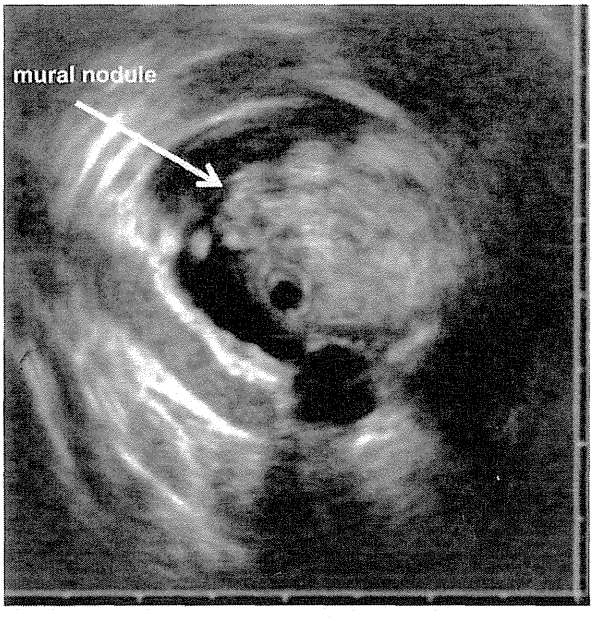


Fig. 4. Intraductal ultrasonogram demonstrating a 25-mm mural nodule in the MPD.

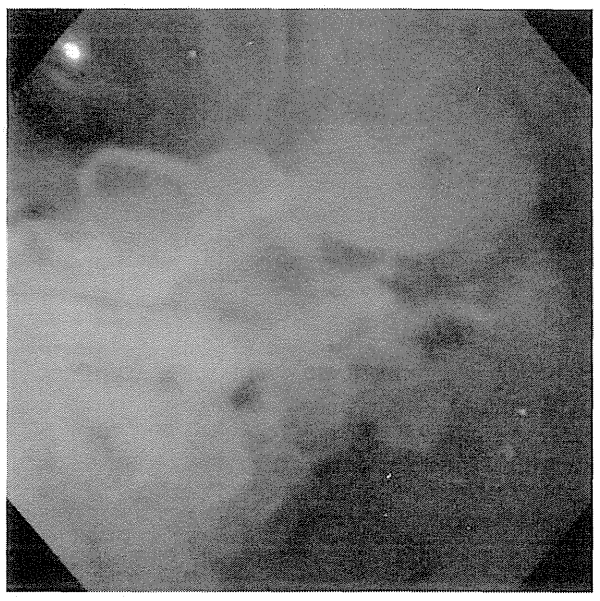


Fig. 5. Peroral pancreatoscopic photograph showing a fish egg-like mucosal lesion in the MPD.

of mural nodules and positive cytology, BD-IPMN of >3 cm without these signs can be observed without immediate resection, particularly in elderly patients.

4.3. Indications for resection of MCN

MCN defined by the presence of ovarian stroma has a low prevalence of invasive carcinoma (<15%) with no malignancy in MCNs of <4 cm without mural nodules [40,98]. Observation may be considered in elderly frail patients [40]. However, given the relatively young age of most patients, the risk of progression to invasive MCN, and their common locations in the pancreatic body and tail, surgical resection is recommended for all surgically fit patients, since the natural history of MCN is still unknown and nonoperative management would require years of follow-up based on high-resolution imaging associated with high costs [40,98–100]. Patients with invasive MCN are significantly older (by 11 years) than those with non-invasive MCN, [98–100], and frequently contain areas of low-grade dysplasia [40,98,99], suggesting that we are presently unable to securely identify invasive MCN. Resection is routinely curative in non-invasive MCN with no recurrence [40,98].

MCNs are usually located in the pancreatic body and tail, and thus require distal pancreatectomy that can be performed safely at high-volume centers [101,102]. In patients with MCNs of <4 cm without mural nodules, parenchyma-sparing resections (i.e. middle pancreatectomy) and distal pancreatectomy with spleen preservation as well as laparoscopic procedures should be considered [102,103].

5. Methods of resection and other treatments

5.1. Methods of pancreatectomy for invasive and non-invasive MCNs and IPMNs

Although preoperative and intraoperative assessment of the dysplasia grades of MCNs and IPMNs can be difficult, US, CT, MRI, and EUS will identify most tumors with a significant invasive component [104]. In such patients, pancreatoduodenectomy, left pancreatectomy, or total pancreatectomy according to the site and extent of the disease with lymph node dissection remains the standard treatment [105,106]. Limited resections or even focal non-anatomic resections (excision, enucleation, uncinatectomy) may be considered for MCN or BD-IPMN without clinical, radiologic, cytopathologic, or serologic suspicion of malignancy [107–124]. However, non-anatomic resections may be associated with rare, but possible, leakage of mucin followed by pseudomyxoma peritonei [125,126], and also have a higher incidence of pancreatic fistulae and risk of recurrence from potentially residual neoplasm. Low-grade and possibly high-grade dysplasia of IPMN and MCN may be good candidates for laparoscopic surgery [127–129]. Conversion to a standard resection with lymphadenectomy should occur if intraoperative findings raise concern for malignancy or frozen-section pathology reveals high-grade dysplasia or invasive disease. When the final pathology reveals invasion or positive margin for high-grade dysplasia undetected on frozen sections, a reoperation should be performed in surgically fit patients.

5.2. Role of mucosal ablation by ethanol injection under EUS guidance in the management of MCN or IPMN

Investigators have begun exploring the possibility of EUS-guided ablation of pancreatic cysts by ethanol or ethanol followed by paclitaxel [130–132]. Preferred candidates include (1) patients with cystic lesions of >2 cm, either unilocular or oligolocular, that show no communication with the MPD, and (2) cysts in patients who refuse surgery or are high-risk surgical candidates [133,134]. The reported short-term CT-defined cyst resolution rates were 33–79% [131–135], and variable histopathologic degrees of epithelial ablation were observed in the resected specimens [131,133,135]. DeWitt et al. [134] reported that follow-up by CT revealed no evidence of cyst recurrence for a median of 26 months after cyst resolution. Complications include acute pancreatitis (4.5–10%), abdominal pain (<20%), and splenic vein obliteration [131,133,135].

Although the procedure may be promising, there are some problems that remain to be addressed, including insufficient ethanol infiltration and impossible imaging surveillance after the cyst collapse [129]. Moreover, recent studies have shown that PDAC occurs quite frequently not only as malignant transformation of IPMN but also in other sites separate from IPMN [39,136–138]. More research needs to be carried out on the techniques, materials, long-term outcomes, and adequacy of this procedure. At present, EUS-guided ablation cannot be recommended for patients with BD-IPMN or MCN outside of a closely monitored research protocol.

5.3. Approach to multifocal BD-IPMN

IPMN probably represents a pancreatic "field defect", i.e., all pancreatic ductal epithelial cells are at risk of dysplastic change, and this can be apparent in patients with multifocal (two or more) BD-IPMNs (Fig. 6). Current series estimate that 25–41% of all BD-IPMNs are multifocal [3,8,20]. There is no convincing evidence that the risk of invasive IPMN multiplies according to the number of lesions. In fact, in one series, patients with symptomatic unifocal BD-IPMN carried a higher risk than those with symptomatic multifocal BD-IPMNs (18% versus 7%) [3].

The treatment approach to multifocal BD-IPMNs should mirror that of unifocal BD-IPMN. When resection is indicated, segmental anatomic pancreatectomy should be performed in cases where the multifocal disease is limited to a pancreatic region. In some cases, the disease may not be able to be eliminated without total pancreatectomy. Even then, it is reasonable to perform a segmental resection to remove the IPMNs at the highest oncological risk and perform surveillance of the remaining lesions. However, the threshold for total pancreatectomy should perhaps be lowered in patients with a strong family history of PDAC, because of the increased prevalence of higher-grade lesions [139].

Fig. 6. MRCP demonstrating multifocal BD-IPMNs.

6. Histological aspects

6.1. Types of invasive carcinoma of malignant IPMN

It is now well established that the type of invasive carcinoma, colloid versus tubular, has major prognostic implications and should therefore be part of the reporting of IPMNs [140–143]. Colloid carcinomas are characterized by "intestinal" differentiation, evidenced by diffuse and specific expression of CDX2 and MUC2, and have a better prognosis than tubular carcinomas [142]. It is conceivable that these histological differences may drive the use of distinct adjuvant chemotherapy protocols, although this has not yet been evaluated.

6.2. Pathologic definition of minimally invasive carcinoma derived from IPMN or MCN

6.2.1. Staging of invasive carcinomas (definition of "minimally invasive carcinoma")

Since the term "minimally invasive" has been variably defined by different authors [144–147], it is preferable to avoid such a non-specific term. Instead, it would be more appropriate to stage invasive carcinomas with conventional staging protocols including the AJCC/TNM [148], and then further substage the T1 category (those with invasive carcinomas of <2 cm) into T1a for those that are ≤0.5 cm, T1b for those that are >0.5 cm and ≤1 cm, and T1c for those that are 1–2 cm. This substaging of T1 conforms to the methods that are being employed for other organs and tumor types, allows the collection of more accurate and comparable data for future evaluation, and is in accordance with the recent proposal made by Furukawa et al. [149].

6.3. Distinction and clinical relevance of gastric, intestinal, pancreatobiliary, and oncocytic forms of IPMNs

The cell lineage of the "papillary component" of IPMNs has clinicopathologic significance (Fig. 7) [142,147,149–153]. The vast majority of BD-IPMNs are of the gastric type, which is MUC5AC-positive but MUC1-negative, with MUC2 highlighting only the scattered goblet cells. The gastric type is typically low grade, with only a small percentage developing into carcinoma, although if a carcinoma does develop in these patients, it is usually of the tubular type and behaves like a conventional PDAC [151,153]. A significant portion of MD-IPMNs are of the intestinal type, showing diffuse expression of CDX2 and MUC2. Large and complex intestinal-type IPMNs can have invasive carcinoma, typically of the colloid type (CDX2/MUC2-positive) and with relatively indolent behavior [142]. The oncocytic type is defined by complex arborizing papillae with delicate cores, oncocytic cells, and intraepithelial lumina formation, and common MUC6 expression [154,155]. This type tends to be large, with a more obscure intraductal nature and relatively uncommon and limited invasion, and most cases receive a clinical diagnosis of "cystadenocarcinoma" [156]. The pancreatobiliary type is the least well characterized and the least common, and is regarded by some as a high-grade version of the gastric type. Invasive carcinoma associated with this type is usually tubular and aggressive [150].

Based on the clinical associations described above, it is sometimes feasible to predict the subtypes preoperatively. In a preoperative biopsy, EUS-guided or otherwise, it may be possible to employ this subclassification, provided that the papillary component of the tumor is sampled. One study obtained consistent subclassifications in 15 of 19 patients (79%) by preoperative sampling of the pancreatic juice via endoscopy [157].

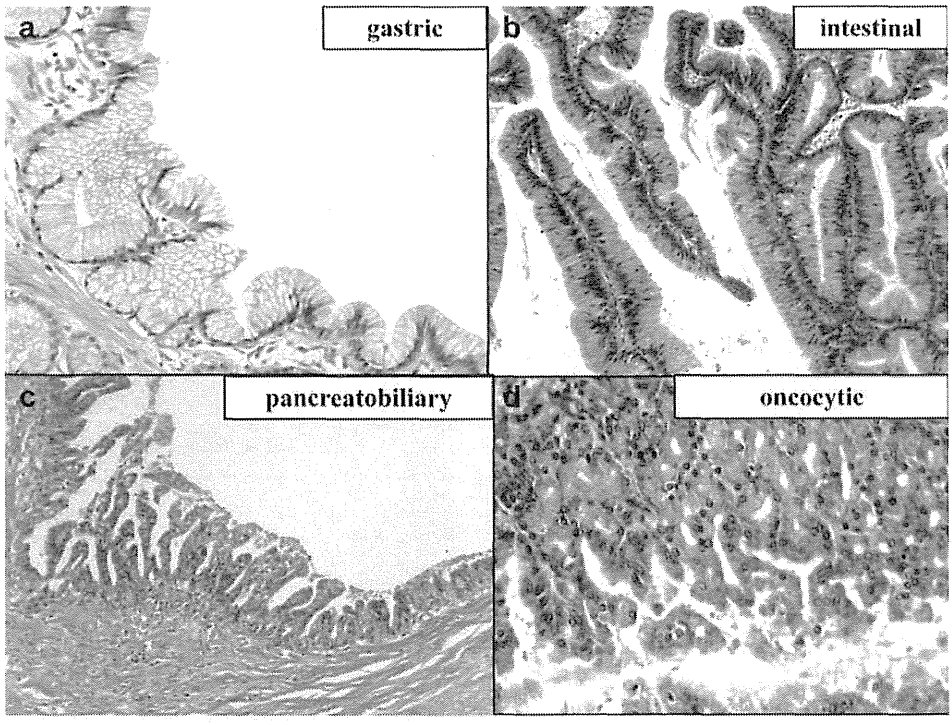


Fig. 7. Histological subclassification of IPMNs. a. The gastric type shows tall columnar cells with basally oriented nuclei and abundant pale mucinous cytoplasm. b. The intestinal type is composed of tall papillae lined by columnar cells with pseudostratified nuclei and basophilic cytoplasm with variable amounts of apical mucin. c. The pancreatobiliary type has thin branching papillae with high-grade dysplasia. The cells are cuboidal and have round hyperchromatic nuclei, prominent nucleoli, and moderately amphophilic cytoplasm with a less mucinous appearance. d. The oncocytic type usually exhibits complex arborizing papillae lined by two to five layers of cuboidal to columnar cells with large, round, fairly uniform nuclei containing single, prominent, eccentrically located nucleoli, and abundant eosinophilic granular cytoplasm sometimes in a cribriform or solid growth pattern.

6.4. Role of intraoperative frozen section evaluation in the surgical management of IPMNs

IPMNs can be ill-defined owing to the spread to branch ducts and smaller ductules. Therefore, the assessment of adequate margins may have to rely upon frozen section analysis [83,86,158,159]. However, frozen sections are a suboptimal method for analyzing tissue morphology, and should be used cautiously. If clear high-grade dysplasia or invasive carcinoma is present at the margin, further resection is warranted. Similarly, if exuberant papillary nodules are present at the margin, there may be abundant residual tumor in the pancreas [164]. All patients should be informed preoperatively that the resection may possibly be extended to total pancreatectomy. In contrast, the presence of lesser grades of dysplasia (moderate or low-grade) may not require any further therapy [141].

The common incidental occurrence of pancreatic intraepithelial neoplasia (PanIN)-1 and -2 in the general population may show up in frozen sections of the margin. Since low-grade PanINs can be indistinguishable from low-grade IPMNs [160], it may be preferable to report that "no in situ or invasive carcinoma is identified; intraductal/intraepithelial neoplasm of low/moderate grade, either PanIN or low-grade IPMN, is present". In addition, a section of the margin may show nothing but inflammation and denuded epithelium. The pathologist cannot render a diagnosis without an intact epithelium, and this should be reported as "denuded epithelium and inflammation", with such cases being carefully analyzed clinically because the denudation may prove to be the presence of an adjacent tumor [161].

6.5. Special instructions for specimen processing to differentiate BD-IPMN from MD-IPMN

Dilation of the MPD and neoplasia of the duct lining are not always correlated. Pathologists should make every attempt to classify the lesion as MD-IPMN or BD-IPMN according to the distribution of the neoplasm. There are no special instructions for specimen processing to differentiate BD-IPMN from MD-IPMN. The most important points are to identify the MPD as precisely as possible when processing the specimen, to sample the cystic lesion completely, and to examine the resected specimen thoroughly. There are different approaches to the dissection of these specimens [27,162].

6.6. Distinction of carcinoma derived from and concomitant with an IPMN

PDAC may develop independently in the pancreatic duct separately from an IPMN [39,163,164]. When PDAC originates in the vicinity of an IPMN, the distinction between PDAC derived from the IPMN and PDAC concomitant with the IPMN is sometimes difficult. Definitions of these conditions were proposed by the Japan Pancreas Society, mainly with regard to the topological relationship and histological transition between IPMN and PDAC [163]. Among 765 patients with resected IPMN, there were 183 patients with invasive carcinoma (24%). Of these, 122 (66%) were classified as PDAC derived from IPMN, 31 (17%) as PDAC concomitant with IPMN because the two lesions were discontinuous, and 30 (16%) as undetermined. It is also imperative to make every effort to distinguish between a retention cyst occurring from PDAC and IPMN accompanying PDAC. Retention cysts may be lined with epithelium with regenerative atypia or even by cancer cells extending from the PDAC, whereas IPMN is characterized by dilated pancreatic ducts lined with dysplastic mucinous epithelium showing micropapillary or macropapillary projections.

7. Methods of follow-up (Fig. 2)

7.1. Follow-up of non-resected IPMN

The decision to follow an IPMN is a matter of clinical judgment based on the patient age, family history, symptoms, comorbidities, perceived pancreatic cancer risk, and patient preference. There is little evidence in the literature to guide the frequency and type of surveillance for IPMNs.

At baseline, history/physical examination and MRI/MRCP (or pancreatic protocol CT) surveillance, and EUS when the presence of a mural nodule is suspected, are recommended. If the expertise is available, consideration may be given for EUS with cytopathology [3,51,71–73], CEA, [46,55,165], and molecular analyses [46,165–167].

For surveillance, patients without "*high-risk stigmata*" should undergo short interval (3–6 months) pancreatic MRI/MRCP (or CT) to establish the stability, if prior imaging is not available. Subsequently, surveillance should be performed according to the size stratification (Fig. 2). There are no good long-term data to indicate whether surveillance can be safely spaced to every 2 years or even discontinued after long-term stability. Concern over the development of PDAC in the pancreas harboring IPMN has prompted some investigators to continue surveillance at short intervals [39,136–138,163,164,168–173].

If surgically fit, patients with "*high-risk stigmata*" detected on surveillance should undergo resection. Shorter interval surveillance (3–9 months) should be considered in patients whose IPMN progresses toward these indicators or patients who already have "*high-risk stigmata*" and, for reasons of operative risk or personal preference, have chosen heightened surveillance over resection. The issue of whether a rapid growth rate is correlated with an increased risk of malignancy remains unclear, but shorter interval surveillance is recommended in such patients [92].

7.2. Follow-up of surgically resected IPMN and MCN

7.2.1. Recurrence of MCN following resection

MCNs are almost always solitary and complete resection of a non-invasive MCN is curative, thus necessitating no postoperative surveillance [74,98–100,174–176]. Although patients with invasive MCN have a poorer prognosis [98,100,174–176], the interval to follow-up imaging should match that of PDAC, despite a lack of proof that surveillance imaging improves the prognosis compared with a strategy based on symptom recurrence.

7.2.2. Follow-up and recurrence of IPMN following resection

Clinically relevant residual IPMN lesions may persist in patients postoperatively because (1) a known BD-IPMN was left unresected, (2) the surgical margins were found to have residual IPMN, and/or (3) new lesions developed in the remnant pancreas. Again, some investigators continue surveillance at short intervals owing to concern over the development of PDAC in the pancreas after resection of IPMN [39,136–138,163,164,168–173].

a) *Known IPMN in the remnant pancreas*: Patients with multifocal BD-IPMNs may have known IPMN in the remaining pancreas following IPMN resection. These patients should be followed as non-resected IPMNs (Item 7-1).

b) *Postoperative follow-up based on the resection margin status*: The resection margin may show (1) normal pancreatic tissue, (2) non-dysplastic changes (PanIN-1A or -1B), (3) low-grade dysplasia, (4) moderate-grade dysplasia, (5) high-grade dysplasia, or (6) invasive carcinoma [83].

1, 2) Normal columnar or mucinous metaplasia (PanIN-1A or -1B) should be considered as negative margins [86]. Such patients should undergo follow-up as per the guidelines for unresected

IPMN, if any, in the remnant pancreas (Item 4-2). If there are no residual lesions, repeat examinations at 2 and 5 years may be reasonable to check for new recurrence (see below).

3–5) It is unclear whether a margin that is microscopically positive for moderately dysplastic IPMN increases IPMN recurrence. For patients with low-grade or moderate-grade dysplasia at the margin, there is little evidence to guide the frequency and type of surveillance required to detect IPMN recurrence. We suggest that history/physical examination and MRCP surveillance are performed twice a year in cases of non-invasive IPMN following resection, and perhaps more often if symptoms, signs, radiographic findings, or cytopathology dictate a shorter interval of surveillance [173].

c) *New postoperative IPMN recurrence*: The rate of new recurrence of non-invasive IPMN following resection is difficult to determine from the literature, because MPD dilation in the distal pancreas following resection may be secondary to anastomotic stenosis or caused by true IPMN recurrence, and better imaging in the postoperative setting may reveal a previously undetected IPMN.

Despite these limitations, the recurrence rates in the first 5 years were reported to be 0–20% [4,85,86,177–181]. If there are no residual lesions and the margins are negative, repeat examinations at 2 and 5 years may be reasonable to check for new recurrence, although this guidance is not evidence-based. Several recent reports of distinct PDAC development in patients with BD-IPMN suggest that CT or MRCP at 6-month intervals is appropriate for surveillance, in view of the 0.7–0.9% yearly risk of PDAC development [39,136–138,163,164,168–173].

7.2.3. Recurrence of invasive IPMN following resection

The prognosis of invasive IPMN is globally better than that of conventional PDAC. However, in cases of stage II/III invasive IPMN, the prognosis is similar to that of PDAC [16,182,183]. The follow-up strategy should be identical to that for PDAC.

7.3. Possible occurrence of PDAC in patients with IPMN on follow-up and impact of family history of PDAC

Very little evidence exists to guide the management of patients with an IPMN and a family history of PDAC. Therefore, recommendations regarding the care of these individuals must draw upon what is known for familial PDAC. The risk of an individual developing PDAC based on family history alone has been well established [184,185]. An individual with one first-degree relative with PDAC has a 2.3-fold increased risk. The risk increases to 6.4-fold with two affected first-degree relatives and 32-fold with three affected first-degree relatives. A risk prediction calculator called PancPRO is available free online at http://astor.som.jhmi.edu/BayesMendel/pancpro.html [186]. In some individuals, the actual genetic defect is known and forms part of a described syndrome. The best characterized genetic defects include *BRCA2*/Fanconi anemia pathway defects (relative risk, 3.5–10-fold [187,188]), familial atypical mole malignant melanoma (FAMMM) syndrome (relative risk, 9–47-fold [189–191]), and Peutz–Jeghers syndrome (relative risk, 132-fold [192]).

The initial assessment of an IPMN should include a detailed family history and an estimate of the relative risk of developing PDAC based on the above sources. Patients with one affected first-degree relative can be followed closely using the same criteria for patients without a family history. For individuals with two or more affected first-degree relatives, the risk rapidly escalates and merits more aggressive surveillance, but does not necessarily require a recommendation for resection. In this risk category, patients with a newly diagnosed BD-IPMN should undergo high-quality MRI/MRCP or CT and EUS. In addition to "*malignant stigmata*", "*worrisome features*" are of more concern. If present, resection should be considered if the patient is surgically fit. If absent, the patient should be followed by MRI/MRCP or CT at 3-month intervals and EUS annually for the first 2 years to evaluate the development of "*worrisome features*". Patients with a cyst that shows rapid growth or develops "*worrisome features*" should be strongly considered for resection.

7.4. Possible occurrence of malignant neoplasms in other organs in patients with IPMN on follow-up

Synchronous and metachronous occurrence of malignant diseases in extrapancreatic organs in patients with IPMNs has an incidence of 20–30% [193]. Most reports describe the occurrence of malignant conditions as a part of the patient's past history [194]. However, extrapancreatic malignancies can occur even after resection of an IPMN. Therefore, attention should be paid to this phenomenon even after resection of an IPMN.

The frequency and location of extrapancreatic malignancies differ from country to country. Gastrointestinal cancer is common in Asia [195,196], while skin, breast, and prostatic cancers are frequent in the United States [197,198]. These facts may indicate that extrapancreatic malignancies occur depending on the incidences of cancer in the general populations in different regions [194].

The relationships between the types of IPMN and extrapancreatic malignancies are controversial. Some authors reported that extrapancreatic malignancies occur in all types of IPMN [194], while others reported that transcription of MUC2 may be related to the synchronous extrapancreatic gastrointestinal cancer development seen with IPMN [199].

At present, there are no screening recommendations for detecting extrapancreatic malignancies, but once the diagnosis is made, consideration of extrapancreatic neoplasms should be undertaken based on the frequency of malignancies in the general population of the country or region. Two reports have recommended screening of colorectal polyps and cancer in the United States [198,200].

8. Conclusions

Our understanding of IPMNs of the pancreas continues to evolve. Although many new publications are available since the first guidelines were published 6 years ago, the vast majority of the data are retrospective and uncontrolled, and long-term follow-up has been limited, meaning that our knowledge of the natural history of this disease is still incomplete. In this revision, the criterion for characterizing MD-IPMN has been lowered to MPD dilation of >5 mm, without losing specificity for radiologic diagnosis. "*High-risk stigmata*" and "*worrisome features*" have been defined to stratify the risk of malignancy in BD-IPMN and consider resection or increased frequency of surveillance. Resection is still recommended in all surgically fit patients with MD-IPMN or MCN. The indications for resection of BD-IPMN are more conservative. BD-IPMNs of >3 cm without "*high-risk stigmata*" can be observed without immediate resection. Methods and intervals of surveillance are proposed with an algorithm in view of "*high-risk stigmata*" and "*worrisome features*". The issue of whether the interval of surveillance can be lengthened after 2 years of no change is controversial. Some authors advocate continuation of surveillance every 6 months in view of the relatively high incidence of PDAC in patients with BD-IPMN. For MCNs of <4 cm without mural nodules, laparoscopic as well as limited resections should be considered. Pancreatectomy with lymph node dissection remains the standard treatment for invasive and non-invasive MCNs and IPMNs, while limited resections without lymphadenectomy or splenectomy are

reserved for those without suspicion of malignancy. The histologic types of invasive carcinoma, colloid versus tubular, and subtypes of IPMNs have prognostic implications. During resection, frozen section analysis of the surgical margin is required to ensure there is no high-grade dysplasia or invasive cancer. IPMNs need post-operative surveillance based on the resection margin status. For patients with low-grade or moderate-grade dysplasia at the margin, we suggest history/physical examination and MRCP surveillance at least twice yearly.

References

[1] Tanaka M, Chari S, Adsay V, Fernández-del Castillo C, Falconi M, Shimizu M, et al. International Association of Pancreatology. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology 2006;6:17–32.

[2] Serikawa M, Sasaki T, Fujimoto Y, Kuwahara K, Chayama K. Management of intraductal papillary-mucinous neoplasm of the pancreas: treatment strategy based on morphologic classification. J Clin Gastroenterol 2006;40:856–62.

[3] Schmidt CM, White PB, Waters JA, Yiannoutsos CT, Cummings OW, Baker M, et al. Intraductal papillary mucinous neoplasms: predictors of malignant and invasive pathology. Ann Surg 2007;246:644–51. discussion 651–654.

[4] Nagai K, Doi R, Kida A, Kami K, Kawaguchi Y, Ito T, et al. Intraductal papillary mucinous neoplasms of the pancreas: clinicopathologic characteristics and long-term follow-up after resection. World J Surg 2008;32:271–8. discussion 279–280.

[5] Hwang DW, Jang JY, Lee SE, Lim CS, Lee KU, Kim SW. Clinicopathologic analysis of surgically proven intraductal papillary mucinous neoplasms of the pancreas in SNUH: a 15-year experience at a single academic institution. Langenbecks Arch Surg 2012;397:93–102.

[6] Mimura T, Masuda A, Matsumoto I, Shiomi H, Yoshida S, Sugimoto M, et al. Predictors of malignant intraductal papillary mucinous neoplasm of the pancreas. J Clin Gastroenterol 2010;44:e224–229.

[7] Bournet B, Kirzin S, Carrere N, Portier G, Otal P, Selves J, et al. Clinical fate of branch duct and mixed forms of intraductal papillary mucinous neoplasia of the pancreas. J Gastroenterol Hepatol 2009;24:1211–7.

[8] Waters JA, Schmidt CM, Pinchot JW, White PB, Cummings OW, Pitt HA, et al. CT vs MRCP: optimal classification of IPMN type and extent. J Gastrointest Surg 2008;12:101–9.

[9] Kawamoto S, Lawler LP, Horton KM, Eng J, Hruban RH, Fishman EK. MDCT of intraductal papillary mucinous neoplasm of the pancreas: evaluation of features predictive of invasive carcinoma. Am J Roentgenol 2006;186:687–95.

[10] Crippa S, Fernández-del Castillo C, Salvia R, Finkelstein D, Bassi C, Domingues I, et al. Mucin-producing neoplasms of the pancreas: an analysis of distinguishing clinical and epidemiologic characteristics. Clin Gastroenterol Hepatol 2010;8:213–9.

[11] Sugiyama M, Izumisato Y, Abe N, Masaki T, Mori T, Atomi Y. Predictive factors for malignancy in intraductal papillary-mucinous tumours of the pancreas. Br J Surg 2003;90:1244–9.

[12] Sohn TA, Yeo CJ, Cameron JL, Hruban RH, Fukushima N, Campbell KA, et al. Intraductal papillary mucinous neoplasms of the pancreas: an updated experience. Ann Surg 2004;239:788–97. discussion 797–799.

[13] Salvia R, Fernández-del Castillo C, Bassi C, Thayer SP, Falconi M, Mantovani W, et al. Main-duct intraductal papillary mucinous neoplasms of the pancreas. Ann Surg 2004;239:678–87.

[14] Suzuki Y, Atomi Y, Sugiyama M, Isaji S, Inui K, Kimura W, et al. Cystic neoplasm of the pancreas: a Japanese multiinstitutional study of intraductal papillary mucinous tumor and mucinous cystic tumor. Pancreas 2004;28:241–6.

[15] Lee SY, Lee KT, Lee JK, Jeon YH, Choi D, Lim JH, et al. Long-term follow up results of intraductal papillary mucinous tumors of pancreas. J Gastroenterol Hepatol 2005;20:1379–84.

[16] Schnelldorfer T, Sarr MG, Nagorney DM, Zhang L, Smyrk TC, Qin R, et al. Experience with 208 resections for intraductal papillary mucinous neoplasm of the pancreas. Arch Surg 2008;143:639–46. discussion 646.

[17] Kim SC, Park KT, Lee YJ, Lee SS, Seo DW, Lee SK, et al. Intraductal papillary mucinous neoplasm of the pancreas: clinical characteristics and treatment outcomes of 118 consecutive patients from a single center. J Hepatobiliary Pancreat Surg 2008;15:183–8.

[18] Ohno E, Hirooka Y, Itoh A, Ishigami M, Katano Y, Ohmiya N, et al. Intraductal papillary mucinous neoplasms of the pancreas: differentiation of malignant and benign tumors by endoscopic ultrasonography findings of mural nodules. Ann Surg 2009;249:628–34.

[19] Nara S, Onaya H, Hiraoka N, Shimada K, Sano T, Sakamoto Y, et al. Preoperative evaluation of invasive and noninvasive intraductal papillary-mucinous neoplasms of the pancreas: clinical, radiological, and pathological analysis of 123 cases. Pancreas 2009;38:8–16.

[20] Rodriguez JR, Salvia R, Crippa S, Warshaw AL, Bassi C, Falconi M, et al. Branch-duct intraductal papillary mucinous neoplasms: observations in 145 patients who underwent resection. Gastroenterology 2007;133:72–9.

[21] Jang JY, Kim SW, Lee SE, Yang SH, Lee KU, Lee YJ, et al. Treatment guidelines for branch duct type intraductal papillary mucinous neoplasms of the pancreas: when can we operate or observe? Ann Surg Oncol 2008;15:199–205.

[22] Sadakari Y, Ienaga J, Kobayashi K, Miyasaka Y, Takahata S, Nakamura M, et al. Cyst size indicates malignant transformation in branch duct intraductal papillary mucinous neoplasm of the pancreas without mural nodules. Pancreas 2010;39:232–6.

[23] Kanno A, Satoh K, Hirota M, Hamada S, Umino J, Itoh H, et al. Prediction of invasive carcinoma in branch type intraductal papillary mucinous neoplasms of the pancreas. J Gastroenterol 2010;45:952–9.

[24] Baiocchi GL, Portolani N, Missale G, Baronchelli C, Gheza F, Cantù M, et al. Intraductal papillary mucinous neoplasm of the pancreas (IPMN): clinicopathological correlations and surgical indications. World J Surg Oncol 2010;8:25 [online].

[25] Fernández-del Castillo C. Intraductal papillary mucinous neoplasms of the pancreas: a plea for prospective differentiation between main-duct and side-branch tumors. Ann Surg Oncol 2005;12:98–9.

[26] Adsay NV, Fukushima N, Furukawa T, Hruban RH, Klimstra DS, Kloppel G, et al. Intraductal neoplasm of the pancreas. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO classification of tumors of digestive system. Lyon: WHO Press; 2010. p. 304–13.

[27] Hruban RH, Pitman MB, Klimstra DS. Tumors of the pancreas. In: Silverberg SG, editor. AFIP Atlas of tumor pathology series 4, vol. 6. Washington: ARP Press; 2007. p. 75–110.

[28] Zhang XM, Mitchell DG, Dohke M, Holland GA, Parker L. Pancreatic cysts: Depiction on single-shot fast spin-echo MR images. Radiology 2002;223:547–53.

[29] Spinelli KS, Fromwiller TE, Daniel RA, Kiely JM, Nakeeb A, Komorowski RA, et al. Cystic pancreatic neoplasms: observe or operate. Ann Surg 2004;239:651–9.

[30] Laffan TA, Horton KM, Klein AP, Berlanstein B, Siegelman SS, Kawamoto S, et al. Prevalence of unsuspected pancreatic cysts on MDCT. Am J Roentgenol 2008;191:802–7.

[31] Das A, Wells CD, Nguyen CC. Incidental cystic neoplasms of pancreas: what is the optimal interval of imaging surveillance? Am J Gastroenterol 2008;103:1657–62.

[32] Fernández-del Castillo C, Targarona J, Thayer SP, Rattner DW, Brugge WR, Warshaw AL. Incidental pancreatic cysts: clinicopathologic characteristics and comparison with symptomatic patients. Arch Surg 2003;138. 427–423; discussion 433–434.

[33] Berland LL, Silverman SG, Gore RM, Mayo-Smith WW, Megibow AJ, Yee J, et al. Managing incidental findings on abdominal CT: White paper of the ACR incidental findings committee. J Am Col Radiol 2010;7:754–73.

[34] Bassi C, Crippa S, Salvia R. Intraductal papillary mucinous neoplasms (IPMNs): is it time to (sometimes) spare the knife? Gut 2008;57:287–9.

[35] Brounts LR, Lehmann RK, Causey MW, Sebesta JA, Brown TA. Natural course and outcome of cystic lesions in the pancreas. Am J Surg 2009;197:619–23.

[36] Javle M, Shah P, Yu J, Bhagat V, Litwin A, Iyer R, et al. Cystic pancreatic tumors (CPT): predictors of malignant behavior. J Surg Oncol 2007;95:221–8.

[37] Lee SH, Shin CM, Park JK, Woo SM, Yoo JW, Ryu JK, et al. Outcomes of cystic lesions in the pancreas after extended follow-up. Dig Dis Sci 2007;52:2653–9.

[38] Salvia R, Crippa S, Falconi M, Bassi C, Guarise A, Scarpa A, et al. Branch-duct intraductal papillary mucinous neoplasms of the pancreas: to operate or not to operate? Gut 2007;56:1086–90.

[39] Tanaka M. Controversies in the management of pancreatic IPMN. Nat Rev Gastroenterol Hepatol 2011;8:56–60.

[40] Reddy RP, Smyrk TC, Zapiach M, Levy MJ, Pearson RK, Clain JE, et al. Pancreatic mucinous cystic neoplasm defined by ovarian stroma: demographics, clinical features, and prevalence of cancer. Clin Gastroenterol Hepatol 2004;2:1026–31.

[41] Fukushima N, Mukai K. Pancreatic neoplasms with abundant mucus production: emphasis on intraductal papillary-mucinous tumors and mucinous cystic tumors. Adv Anat Pathol 1999;6:65–77.

[42] Itai Y, Minami M. Intraductal papillary-mucinous tumor and mucinous cystic neoplasm: CT and MR findings. Int J Gastrointest Cancer 2001;30:47–63.

[43] Kimura W. IHPBA in Tokyo surgical treatment of IPMT vs MCT: a Japanese experience. J Hepatobiliary Pancreat Surg 2002;2003(10):156–62.

[44] Solcia E, Capella C, Klöppel G. Tumors of the pancreas. In: Rosai J, editor. Atlas of tumor pathology. 3rd ed., vol. 20. Washington, D.C: Armed Forces Institute of Pathology; 1997.

[45] Khalid A, McGrath KM, Zahid M, Wilson M, Brody D, Swalsky P, et al. The role of pancreatic cyst fluid molecular analysis in predicting cyst pathology. Clin Gastroenterol Hepatol 2005;3:967–73.

[46] Khalid A, Zahid M, Finkelstein SD, LeBlanc JK, Kaushik N, Ahmad N, et al. Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: a report of the PANDA study. Gastrointest Endosc 2009;69:1095–102.

[47] Shen J, Brugge WR, Dimaio CJ, Pitman MB. Molecular analysis of pancreatic cyst fluid: a comparative analysis with current practice of diagnosis. Cancer 2009;117:217–27.

[48] Sahani DV, Lin DJ, Venkatesan AM, Sainani N, Mino-Kenudson M, Brugge WR, et al. Multidisciplinary approach to diagnosis and management of intraductal papillary mucinous neoplasms of the pancreas. Clin Gastroenterol Hepatol 2009;7:259–69.