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Review

Endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB): past, present, and future

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Endoscopic ultrasound (EUS) is a combination of endoscopy and intraluminal ultrasonography. EUS also enables ultrasonographic images of high resolution to be obtained. However, whether a lesion is malignant or benign cannot be diagnosed solely from the findings of EUS. Endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB) was developed to enhance the diagnostic capabilities of EUS by providing additional pathological findings. Though more than 10 years have passed since EUS-FNAB was first used for pancreatic disease, EUS FNAB has not been widely accepted in Japan. This may be due to the technical difficulties, relatively low sensitivity for the detection of malignancies, and Japanese gastroenterologists' and surgeons' inherent conservative way of thinking. We describe here a short history of EUS-FNAB, with details of technical tips, current indications and contraindications, diagnostic accuracy, and complications. The clinical utility of EUS-FNAB has been gradually understood and EUS-FNAB procedures have been increasing in number in Japan. So in the near future, EUS followed by EUS-FNAB will be routinely performed in the same manner as gastrointestinal endoscopy, followed by biopsy under direct vision. Also, therapeutic EUS procedures, such as EUS-guided celiac plexus neurolysis, pancreatic tumor ablation, drainage of pancreatic pseudocysts, and the development of an anastomosis may become feasible as less invasive and safer techniques than those used at present.

Key words: EUS FNA, EUS-FNAB, Indication, Complication

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Introduction

Endoscopic ultrasound (EUS) is now a widely accepted modality for detecting pancreatobiliary diseases, and determining the depth of gastrointestinal malignancies, and often, for visualizing lesions more precisely than other imaging modalities. However, whether the lesion is malignant or benign cannot be diagnosed solely from the findings of EUS.[1] Endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB) was developed to enhance the diagnostic capabilities of EUS by providing additional pathological findings. More than 10 years have passed since EUS-FNAB was first used for pancreatic disease.[2] This technique is now popular worldwide.

We describe here the history of EUS-FNAB, with details of technical tips, current indications and contraindications, diagnostic accuracy, and complications, with special reference to the current status and special circumstances of EUS-FNAB in Japan.

History of EUS-FNAB

In order to review the history of EUS-FNAB, we searched MEDLINE to 2004 for English-language reports, and the Japanese Central Medical Library to 2004 was used to examine the Japanese literature.

DiMagno et al.[3] introduced the first electric linear array echoendoscope, and Strohm et al.[4] presented the first mechanical radial echoendoscope, in 1980. Rosch and Classen[1] stressed the advantages of EUS, and also predicted the limitations of EUS, the most important of which was the lack of specificity in the differentiation between benign and malignant changes. Under the prevailing conditions, Tio and Tytgat[5] in 1984, described the possibility of using the biopsy channel for cytological puncture, which would enhance the diagnostic value of EUS. Kouzu also proposed puncture through EUS at

Table 1. History of EUS-FNAB

1980	DiMagno et al.[3]	Linear array echoendoscope
	Strohm et al.[4]	Mechanical radial echoendoscope
1984	Tio and Tytgat[5]	Possibility of EUS-FNAB
1989	Kouzu[a]	Possibility of EUS-FNAB
1991	Harada et al.[6]	Experimental study of EUS-FNAB
	Calletti et al.[7]	EUS-assisted FNA for gastric submucosal tumor using guillotine needle biopsy
1992	Vilmann et al.[2]	EUS-FNAB using convex linear array echoendoscope for pancreatic cancer
1993	Vilmann et al.[8]	Development of a new needle (steel needle with Teflon sheath) and EUS-FNAB for upper gastrointestinal tract lesion
	Wiersema et al.[9]	EUS-FNAB for mediastinal lymph node
	Tio et al.[10]	EUS-FNAB using mechanical radial echoendoscope for pancreatic cancer
1994	Wegener et al.[11]	EUS-FNAB for mediastinal and left adrenal lesion
	Wiersema et al.[12,13] and Chang et al.[14]	EUS-FNAB for various lesions with on-site cytopathologist
1995	Chang et al.[15]	EUS-FNAB for ascites and pleural effusion
	Harada et al.[17]	Development of a new needle (histological biopsy needle)
1996	Vilmann and Hancke[18]	Development of a new needle (biopsy handle instrument)
1997	Binmoeller et al.[22]	Development of a new needle (automated biopsy device)
1999	Nguyen et al.[23]	EUS-FNAB for liver lesion
2000	Fritscher-Ravens et al.[24] and Fritscher-Ravens et al.[25] (2001)	EUS-FNAB for hilar lesion and metastatic pancreatic lesion
2001	Ribeiro et al.[26]	EUS-FNAB for lymphoma
	Brandwein et al.[27]	EUS-FNAB for pancreatic cystic and intraductal tumor
	Rader et al.[28] and Gu et al.[29]	EUS-FNAB for gastrointestinal stromal tumor
2002	Jhala et al.[30]	EUS-FNAB for pancreatic endocrine tumor
	Gress et al.[34]	EUS-FNT (tattooing)
	Wiersema et al.[35]	Development of a new needle (Trucut biopsy needle)
	Jacobson et al.[31]	EUS-FNAB for gallbladder
2003	Matsumoto et al.[32]	EUS-FNAB for autoimmune pancreatitis
	Fritscher-Ravens et al.[33]	EUS-FNAB for splenic lesion

[a]No reference given for this author (if details required, please contract present authors)

the Eleventh Japanese Gastroenterological Endoscopic Seminar in 1989. His concept was fulfilled by Harada et al.,[6] in a trial of EUS-guided puncture technique in a transesophageal puncture model and in two dogs. In 1991, Caletti et al.[7] reported that endoscopically guided guillotine needle biopsy after visualization by EUS (EUS-assisted FNA) had been performed in patients with submucosal tumor of the stomach. At the beginning of 1992, Vilmann et al.[2] reported the first case of direct EUS-guided FNA biopsy of a lesion in the pancreas head, using a curved linear array echoendoscope. Since then, many indications for EUS-FNAB have been reported world wide, as shown in Table 1. Tio et al.[10] reported endosonographically guided cytology for pancreatic cancer, using a mechanical radial echoendoscope. However, this technique only allowed the needle to be displayed as a small echogenic dot, making the procedure technically difficult and risky. In 1994, Wiersema et al.[12,13] and Chang et al.[14] stressed the importance of the presence of an on-site cytopathologist during the procedure to assess whether or not a specimen was adequate or whether further puncture attempts were necessary. Giovannini et al.[16] confirmed and extended these preliminary studies, and showed that EUS-FNAB was safe, with no significant complications. Harada et al.[17] reported the performance of EUS-FNAB for submucosal lesions, using a 21-gauge biopsy needle (endosonopsy). In 1996, Vilmann and Hancke[18] reported the development of a new biopsy handle instrument (type Hancke/Vilmann). Up to that time, there had been no articles on EUS-FNAB in Japan, except for a few case series. We performed EUS-FNAB for the first time in 1994. Then, in 1996, we reported our first experiences in 27 consecutive patients with various kinds of lesions,[19] followed by a report on the use of EUS-FNAB for submucosal tumors in the upper gastrointestinal tract[20] and for pancreatic mass lesions, in 1997.[21] In 1997, Binmoeller et al.[22] first reported an automated biopsy device for patients with pancreatic lesions that could not be penetrated with a conventional manually operated aspiration needle. Subsequently, numerous reports concerning extended indications for EUS-FNAB have been published, mainly in countries other than Japan.[23–33] As a new application technique of EUS-FNAB, Gress et al.[34] first described EUS-guided fine-needle tattooing for the preoperative localization of a neuroendocrine tumor of the pancreas, in 2002. Wiersema et al.[35] reported the initial experience with EUS-guided Trucut biopsies of perigastric organs in the same year.

Equipment

Three types of echoendoscope for EUS-FNAB are available to date. The linear array (Toshiba,. Tokyo, Japan) and curved linear array (Pentax, Tokyo, Japan and Olympus, Tokyo, Japan) scanning types, which scan in the same plane as the long axis of the endoscope, are equipped with color Doppler functioning.[36] The mechanical sector (Olympus) scanning type, which usually scans in a circle at 360° to the perpendicular axis of the endoscope, includes recently developed features such as a wide scanning plane (270°) parallel to the long axis of the endoscope, and is compatible with the mechanical radial scanning echoendoscopic console unit, which has been widely used in Japan as a standard instrument for diagnostic endosonography. Because the mechanical sector type of endoscope is not equipped with color Doppler functioning, this type of echoendoscope has not become popular for clinical use. At present, the most important function of the echoendoscope is as a large instrument channel, which allows histological biopsies to be taken as well as functioning for therapeutic use.

Several needles have been developed to date. The most recent models for EUS-FNAB consist of a steel needle that can be Luer-locked in a fixed position on the echoendoscope. Endoscopists can then advance the needle into the lesion by themselves, under ultrasonic guidance. Using the newly developed automated biopsy device, EUS-FNAB procedures are easier to perform and sufficient materials can more readily be obtained.[22] As to needle technology, the shapes of the tips and the diameter of the needle have been continuously developed and improved. Needles range from 19 to 22 gauge, with a depth of penetration of up to 10 cm.[36] A large-size 19-gauge Trucut needle is now commercially available (Fig. 1).[37,38] Specimens obtained with the Trucut needle can be easily processed for immunohistochemical analysis.

Technique

Detailed steps of EUS-FNAB procedures have been described in several articles.[12,39–41] The current technique uses a new needle system, in which the endoscopist is able to maintain the endoscope in the proper position and simultaneously advance the needle into the lesion, under endosonographic guidance. Using this newly developed echoendoscope and biopsy device, EUS-FNAB procedures are easier to perform, and sufficient materials can be obtained more readily. Papanicolaou and Giemsa stains have been adopted as conventional cytological stains for the aspirates obtained by EUS-FNAB. Sufficient tissue enables processing for

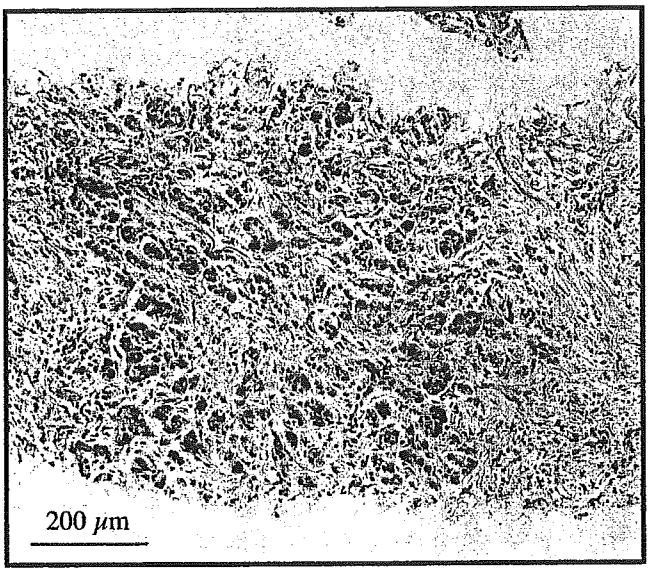

Fig. 1. Enough biopsy specimens could be obtained by endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB), using a 19-gauge Trucut needle, in a patient with autoimmune pancreatitis. Inflammatory cells can be observed. H&E

hematoxylin-and-eosin (H&E) staining, immunohistochemical staining, and flow cytometry,[26] as well as gene analysis.[42–44]

The main technical problems discussed in Japan include: (1) whether an on-site cytopathologist or cytotechnologist is absolutely necessary during the procedure; (2) which has the higher diagnostic accuracy rate, cytology or histopathology; and (3) the type of tumor for which reduced or non-negative pressure of the needle is useful during the procedure.

The most important of these problems may be the introduction of rapid staining performed by a cytopathologist or cytotechnician during the procedure. The aspirated materials mixed with blood are usually prepared on slides or placed directly into fixative for H&E staining. When a cytopathologist or cytotechnician is in attendance, the aspirated materials are spread onto a plate, picked up with tweezers, and sprayed onto glass slides.[45] One slide is air-dried for on-site interpretation and the other slide is fixed in ethanol for Papanicolaou staining. Any remaining material goes into a fixative or cell preservative for later cell block preparation for H&E staining or immunohistochemical staining. In Japan, there are insufficient numbers of cytopathologists or cytotechnologists to allow one to always attend a procedure on-site, and no special fee for rapid cytological diagnosis is charged to the patient. However, Erickson et al.[46] reported an increased number of passes, a reduction in definitive cytological diagnoses, extra procedure time, increased risk, and the use

Table 2. Chronological changes in sensitivity for the diagnosis of pancreatic cancer

Year	Pancreatic cancer
1997	9/15 (60.0%)
1998	12/20 (60.0%)
1999[a]	18/21 (86.0%)
2000[b]	18/20 (90.0%)
2001	37/39 (94.9%)
2002	31/33 (93.9%)
2003	30/31 (96.8%)

[a] Introduction of on-site evaluation
[b] Introduction of power-shot needle

of additional needles without a cytopathologist in attendance. Having said that, in our experience, the greatest advances in diagnostic accuracy (sensitivity) of EUS-FNAB in patients with pancreatic cancer have been achieved since the introduction of rapid staining techniques (Table 2). If a cytopathologist or a cytotechnician is not in attendance, three passes should be taken through lymph nodes and five to six passes through pancreatic masses to ensure adequate cellularity in more than 90% of patients.[46]

Most endoscopists believe that histopathology is a more sensitive technique than cytology to obtain histological evidence of gastrointestinal cancers (esophagus, stomach, and colon). Furthermore, and particularly in Japan, cytology is considered unnecessary when an endoscopic biopsy is available. However, cytology (or FNAB) has been reported to have equal or greater sensitivity than histopathology in the diagnosis of breast or thyroid cancer,[47] as cytology has been determined to be a SAFE (safe, accurate, fast, and economical) technique.[48] The present authors and our colleagues previously reported that cytology was more accurate than histopathology in EUS-FNAB for the differential diagnosis of pancreatic mass lesions.[43] On the other hand, the usefulness of histopathology combined with immunohistochemical analysis to determine specific etiology has been reported.[33] Thus, a system in which both cytology and histopathology are available needs to be developed.

For EUS-FNAB, the needle should be advanced into the target lesion under EUS guidance. When the needle has entered the lesion of interest, the stylet is removed and negative pressure is usually applied with a 10- to 20-ml syringe in most targets. However, reduced negative (1- to 2-ml syringe) or non-negative pressure may result in a less-bloody aspirate, particularly with vascular tumors or lymph nodes. In addition to the varying degrees of suction corresponding to the target, the number of back-and-forth motions of the needle through the lesion is very important to improve the chance of obtaining an adequate specimen. Some ten or more motions are commonly used.

With these refinements of instruments and technical skills described above, EUS followed by EUS-FNAB is expected to be performed on a routine basis at high-volume centers world wide, including Japan.

Indications and contraindications

A fundamental principle in establishing indications for EUS-FNAB is the determination as to whether or not the information obtained has the potential to affect patient management.[49] According to this principle, the current indications for EUS-FNAB include pancreatic mass, mediastinal lymph nodes (esophageal/lung cancer), celiac lymph node in association with a known upper gastrointestinal cancer or in a patient suspected of having cancer or lymphoma, intraabdominal lymph node in association with a known (or suspected) cancer, perirectal lymph node/mass, posterior mediastinal mass of unknown etiology, and intrapleural/intraabdominal fluid. In addition to the lesions indicative for EUS-FNAB mentioned above, the indications have been expanded to submucosal masses, small liver lesions, left adrenal mass, and suspected recurrent cancers in and adjacent to an anastomosis.

The current Japanese indications for EUS-FNAB[50] appear to be almost identical to those of other countries, and include differential diagnosis between benign and malignant lesions, cancer staging (ascites, lymph node), and histological evidence before chemotherapy and/or radiation therapy. Recently, EUS-FNAB has been used to make a diagnosis of a specific etiology, such as the histological type of pancreatic cancer, malignant lymphoma, autoimmune pancreatitis, gastrointestinal stromal tumor, and sarcoidosis. According to these indications, the present authors and colleagues have performed EUS-FNAB in over 700 patients. Table 3 showed a list of diseases in which a definitive diagnosis could be obtained only by EUS-FNAB, and not by conventional endoscopic biopsy or other imaging modalities in reported cases,[51] and in our experience.[52]

Contraindications to EUS-FNAB have included situations in which the FNAB result cannot affect management, there is an inability to visualize a lesion, a cancer or vessel is situated between the gut and the target, and pseudocyst aspiration.[49]

Pseudocyst aspiration was thought to be contraindicated due to the high complication rate. However, recent studies[53,54] have reported that pseudocyst aspiration followed by EUS-guided pseudocyst drainage is a very effective therapeutic modality. Thus, pseudocyst aspiration is now not a contraindication to EUS-FNAB. The indication or contraindication of EUS-FNAB for pancreatic cystic lesions suspected of being neoplastic pancreatic cystic tumors is a matter

Table 3. Gastrointestinal and perigastrointestinal lesions diagnosed by EUS-FNAB

• Esophagus	Carcinoma (type IV), myogenic tumor, schwannoma
• Stomach	Carcinoma (type IV), local recurrence, GIST, myogenic tumor, schwannoma, ectopic pancreas, glomus tumor, carcinoid tumor, metastatic tumor, duplication cyst
• Duodenum	GIST, cyst
• Rectum	Endometriosis, GIST, local recurrence, peritonitis carcinomatosa
• Mediastinum	Tuberculosis, malignant lymphoma, sarcoidosis, carcinoid, adenoid cystic carcinoma
• Pancreas	Ductal cell carcinoma, local recurrence, focal or diffuse pancreatitis (e.g., autoimmune), endocrine tumor, small-cell carcinoma, acinar cell carcinoma, solid-pseudopapillary tumor, IPMN, serous cystic tumor, pseudocyst, metastatic tumor
• Biliary duct/gallbladder	Adenocarcinoma, local recurrence, small-cell carcinoma, xanthogranulomatous cholecystitis
• Liver	Hepatocellular carcinoma, hemangioma, metastatic tumor
• Lymph node	Metastasis (gastrointestinal and pancreatobiliary cancer, lung, ovary, kidney, unknown)
Mediastinum/abdomen	Inflammatory (hepatitis C, sarcoidosis), malignant lymphoma
• Adrenal gland (left)	Metastasis (lung, esophagus)
• Spleen	Lymphoma, abscess
• Retroperitoneum	Paraganglioma
• Ascites/pleural effusion	Peritonitis/pleuritis carcinomatosa, pseudomyoma peritonei

of controversy. EUS-FNAB for these lesions has been actively performed in the United States, but not in Japan. This problem is discussed below.

EUS-FNAB for pancreatic mass lesions

Pancreatic mass lesions have been evaluated to be a good indication for EUS-FNAB, due to the high rate of diagnostic accuracy and low rate of complications. The presence of an on-site cytopathologist or cytotechnician during the examination can surely reduce the rate of inadequate specimens.[46] The sensitivity and specificity of EUS-FNAB for pancreatic neoplasms reported in different studies were 64%–85% and 90%–100%, respectively.[55] The complication rate in EUS-FNAB appears to be around 1%–2%.[56] However, cystic pancreatic lesions appear to have a greater risk of infectious complications 14%, compared to 0.5% for solid pancreatic masses.

Our current indications for EUS-FNAB for pancreatic mass lesions include: (1) histological evidence required for chemotherapy and/or radiation therapy, (2) differential diagnosis between localized pancreatitis and pancreatic cancer which shows an atypical imaging pattern and/or negative biopsy/cytology by the transpapillary approach, and (3) tumor staging in a patient with a small amount of ascites or lymph node swelling. On the other hand, Wallace et al.[57] described the indications for EUS-FNAB in pancreatic cancer as: (1) documented diagnosis of malignancy in a patient with an unresectable mass, as a prerequisite for adjuvant chemotherapy and/or radiation therapy; (2) exclusion of other tumors such as lymphoma, small-cell metastasis, or neuroendocrine cancer that may require a different management strategy; (3) reluctance of patients to undergo major surgery without a definitive diagnosis; and (4) documented absence of malignancy when the pretest probability of malignancy is low.

Pathological confirmation is accepted to be absolutely necessary in a patient with inoperable pancreatic cancer that is indicative for chemotherapy and/or radiation therapy. In Japan, some doctors claim that histological evidence need not be obtained when imaging modalities show typical findings of pancreatic cancer. In our personal experience from 1997, four patients with locally advanced pancreatic cancer who underwent chemotherapy and radiation therapy survived for more than 3 years. Taking this result into account, in the absence of pretreatment histological evidence of malignancy, how can the length of treatment be determined if the treatment is very effective and the patient survives for longer than was expected when the treatment began?

More controversial than its role in patients with inoperable pancreatic cancer is the role of EUS-FNAB in patients suspected of having pancreatic cancer that appears to be resectable on other imaging studies.[57] One view is that a tissue diagnosis will not alter management, and is therefore unnecessary. This is because, as with any FNAB technique, EUS-FNAB for pancreatic masses has a low negative predictive value for malignancy.[55] Thus, a negative FNAB for cancer will not exclude the diagnosis and the patient will be explored anyway. In addition, the risk of tumor seeding caused by EUS-FNAB is strongly stressed in the dissenting opinions against this indication, especially in Japan. Whether tumor seeding occurs with EUS-FNA has not been fully determined. There have been only three reports of seeding possibly caused by EUS-FNAB.[58–60] Bhutani[61] described the risk of seeding by EUS-FNAB as follows. Upon extrapolation of data from worldwide experience with percutaneous or computed tomography (CT)-guided FNA, seeding was found in 1 of 10766 patients.

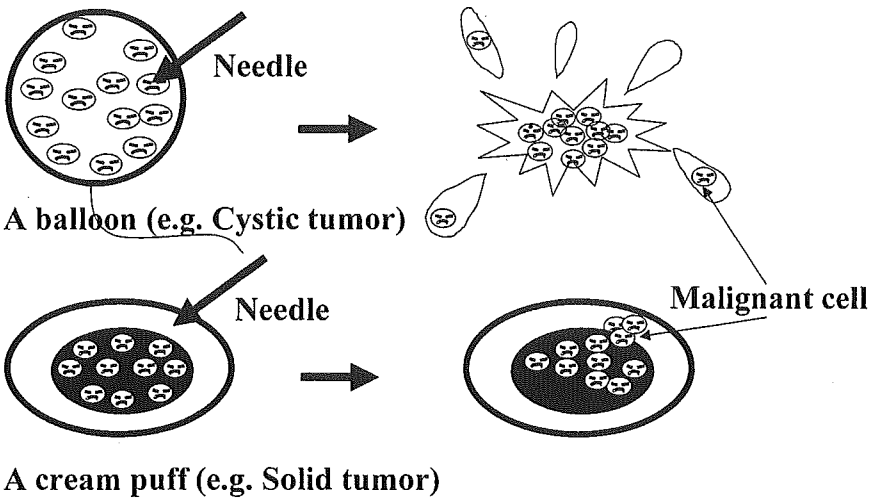

Fig. 2. Does EUS-FNAB cause tumor seeding? Theoretically, tumor seeding may occur more frequently in a cystic tumor (which resembles a balloon) than in a solid tumor (which is like a cream puff)

Table 4. Results of biopsies in patients with small pancreatic cancer (less than 2 cm [pTS1] in diameter) operated from 1997 to 2004 at Aichi Cancer Center Hospital

Patient age (years); sex	pTS (mm)	ERCP		FNAB
		Histopathology	Cytology	
1. 57/M	15	ND	Class II	ND
2. 54/F	19	Atypical cell	Class I	ND
3. 71/M	10	IM	Class II	ND
4. 64/M	12	Adenocarcinoma	IM	ND
5. 59/M	15	Adenocarcinoma	Class II	ND
6. 70/M	9	ND	Class V	ND
7. 42/F	10	ND	Class I	ND
8. 70/F	12	IM	Class II	ND
9. 75/M	8	IM	IM	ND
10. 68/F	20	IM	Class II	ND
11. 58/M	15	ND	Class IIIb	ND
12. 74/M	<20	ND	ND	Adenocarcinoma
13. 79/F	17	ND	ND	Adenocarcinoma
14. 75/F	12	Adenocarcinoma	IM	ND
Positive rate		50% (4/8)	16.7% (2/12)	100% (2/2)

pTS, Pathological tumor size; ND, not done; IM, insufficient material

The risk of malignant seeding in EUS-FNAB of the pancreas may be even lower, as the skin is not traversed in this procedure. Other advantages of EUS-FNAB may be the short needle track, with a reduced risk of spreading cancer cells, and the likely inclusion of the needle track in surgically resected neoplasms of the pancreatic head. However, this would not be true with pancreatic tail neoplasms, where a small possibility of seeding the gastric wall with malignant cells from a resectable pancreatic tumor may still exist, despite the short needle track in EUS-FNAB. In addition, tumor seeding may occur more frequently in cystic lesions than in solid lesions (Fig. 2). Though this idea[62] is only a speculation, it may be true, because there has been a case report of tumor dissemination in a patient with intraductal papillary-mucinous tumor, and there is a high rate of EUS-FNAB complications in cystic lesions.

Establishment of a histological diagnosis may alter the choice of treatment and the choice of operative procedure even when surgery is planned. Some patients (especially those at high risk for surgery), as well as surgeons, are eager to have histological evidence of malignancy when major surgery is scheduled. In our experience, in more than half (60%) of our patients with small pancreatic cancer, positive results for malignancy were revealed when transpapillary biopsy or cytology was used during endoscopic retrograde cholangiopancreatatography (ERCP; Table 4).[63] The results obtained in those with pancreatic cancers of less than 2 cm (pTS1) seem more accurate than the results obtained in pancreatic cancers more than 2 cm in diameter. In patient 6 in Table 4, ERCP showed localized stenosis of the main pancreatic duct (Fig. 3a) and brushing cytology (Fig. 3b) revealed a positive result for

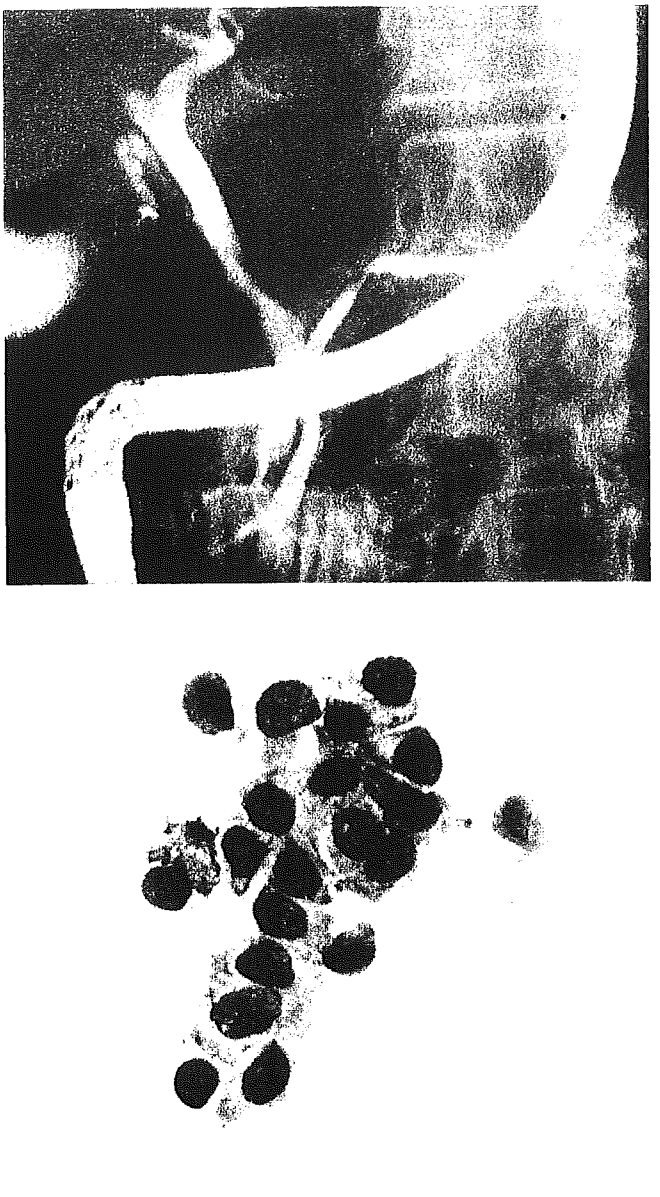

Fig. 3. **a** Endoscopic retrograde cholangio pancreatography (ERCP) revealed localized stenosis of the main pancreatic duct in patient 6 (see Table 4). **b** Brushing cytology during ERCP revealed positive cancer cells in this patient

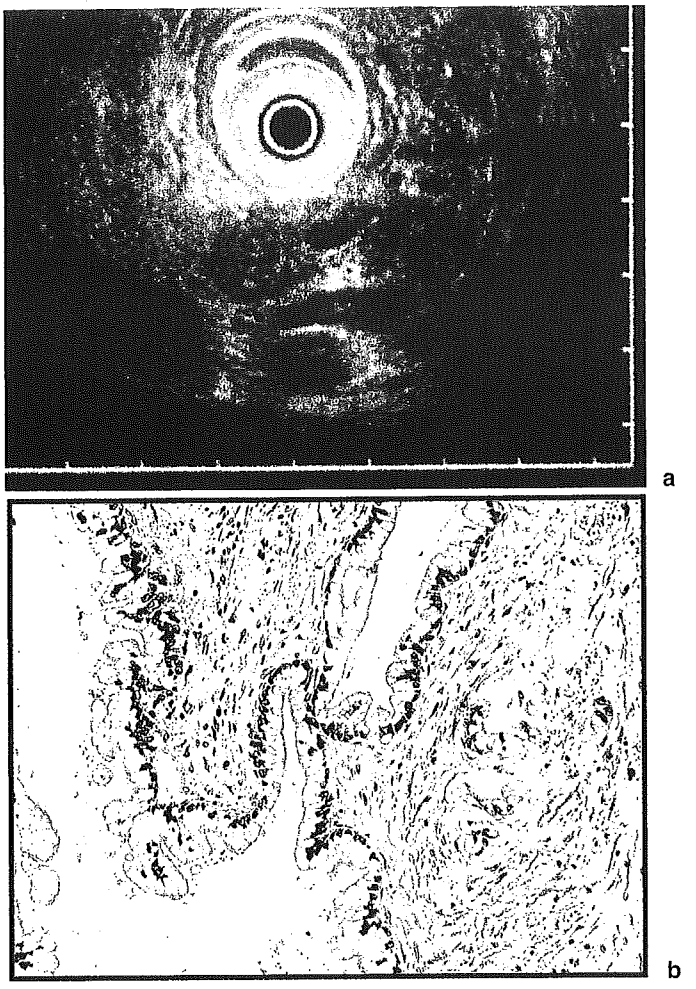

Fig. 4. **a** Endoscopic ultrasound (EUS) showed a low echoic mass less than 20 mm in diameter within the pancreas in patient 12 (see Table 4). **b** Biopsy specimens obtained by EUS-FNAB revealed well-differentiated adenocarcinoma in this patient. However, from the cytology, it was difficult to diagnose malignancy, because of the presence of well-differentiated cancer cells. H&E, ×120

malignancy. Patient 12 (Table 4) was eager to know whether the mass lesion detected by EUS (Fig. 4a) was malignant or not. Because biopsy specimens obtained by EUS-FNAB revealed malignancy (Fig. 4b), he finally decided to undergo pancreatoduodenectomy. He has been alive for more than 2 years without signs of recurrence. Further study is needed to determine the role of EUS-FNAB in patients suspected of having pancreatic cancer whose disease appears to be resectable on other imaging studies. Nonetheless, at the very least, EUS-FNAB should be performed with extra care, or it should not be performed by the transgastric approach for pancreatic body or tail lesions suspected of being mucin-producing cystic neoplasms (such as mucinous cystic neoplasms and intraductal papillary-mucinous neoplasms); this is the Japanese consensus at present.[64]

EUS-FNAB has several advantages compared to CT or conventional US-guided biopsy:[65] (1) the ability to sample lesions (including lymph nodes) too small to be identified by other methods; (2) the ability to biopsy the lesion through a segment of the intestinal wall, which typically becomes part of the resectied specimen, thereby minimizing the risk of needle-tract seeding; and (3) the provision of additional staging information through the EUS examination.

The efficacy of EUS-FNAB for other pancreatic mass lesions, such as endocrine cell tumor,[30,66,67] acinar cell carcinoma,[68] solid-pseudopapillary tumor,[69] metastatic

tumor,[25,70] and cystic pancreatic mass[71–74] has been reported. The differential diagnosis of pancreatic solid tumors may be helped by using immunohistochemical analysis.[69,70] Cystic fluid analysis has been reported to be useful for making a differential diagnosis of pancreatic cyst, especially for mucinous and nonmucinous neoplastic cysts, using analysis of the cancinoembryonicantign (CEA) level.[73,74] However, most mucinous cystic neoplasms, including mucinous cystic tumor (MCT) and intraductal papillary-mucinous tumor (IPMT), can be differentiated by their typical clinicopathological findings.[75] In addition, the occurrence of complications such as bleeding, pancreatitis, and infection is more frequent in cystic lesions than in solid lesions.[56] Furthermore, theoretically, tumor seeding may occur more frequently in mucinous cystic lesions, especially those located in the body or tail of the pancreas, than in solid lesions (Fig. 2). Thus, extra care needs to be taken when performing EUS-FNAB for pancreatic cystic lesions.

To document the absence of malignancy when the pretest probability of malignancy is low is very important in clinical practice. We make it a rule to perform EUS-FNAB at least once in the follow-up of patients suspected of having an inflammatory mass caused by autoimmune pancreatitis or alcohol intake, and in those with a benign pancreatic cystic neoplasm suspected to be a serous cystic neoplasm, as well as in those with benign cysts which show no positive high-risk stigmata for malignancy.[75] Our experience is that the "watch-and-wait" approach is very risky in patients with pancreatic mass lesions. The various kinds of pancreatic neoplasms diagnosed to date by EUS-FNAB by other researchers[51] and by the present authors[52] are shown in Table 3.

Submucosal gastrointestinal lesions

Although many attempts to obtain specimens from submucosal lesions via endoscopy may be performed, obtaining sufficient biopsy material from an artificial ulcer after ethanol injection is difficult. EUS-FNAB for these lesions is a useful technique for acquiring specimens from the wall of the digestive tract, with visualization by EUS images being sufficient for contributing to therapy decisions.[8,76,77] The rate of collection of adequate specimens and the diagnostic accuracy for submucosal lesions may be a little lower than those for pancreatic and lymph node specimens.[56,77] Once the specimens are procured, important data, usually unobtainable by other methods, become available. An endosonopsy needle[78] and a 19-gauge Trucut needle[37] have been developed to obtain larger specimens, allowing immunohistochemical analysis. Consequently, the EUS-FNAB procedure has had a revolutionary effect on the treatment of submucosal gastrointestinal lesions. EUS-FNAB has been useful not only in the upper gastrointestinal tract but also in the lower gastrointestinal tract.[79,80] No complications have been reported, apart from two cases of severe infection[81] and one case of aspiration pneumonia[82] after EUS-FNAB for these lesions.

Gastrointestinal stromal tumors (GISTs) are defined as tumors immunohistochemically positive for c-KIT and CD34 staining.[83] Performing EUS-FNAB and immunohistochemical staining for cases of suspected GISTs is important to obtain a definitive diagnosis of GISTs.[84] The precise diagnosis of high-grade malignant GISTs is essential, because two cases of recurrent GISTs appeared to be high-grade GISTs in one of our studies, and low-grade GISTs may not need treatment because of their slow growth.[85] In a series of surgically excised GISTs, Carrillo et al.[86] reported that the MIB-1 labelling index (LI) was an independent parameter in predicting clinical outcome. Ando et al.[84] and Okubo et al.[85] described the possibility of discrimination between malignant and benign, or and between high-grade malignant or low-grade malignant GISTs by EUS-FNAB with the addition of MIB-1 staining. Recently, mutational analysis of c-kit was performed on EUS-FNAB specimens,[87,88] and the relationship of c-kit mutation to the degree of malignancy was examined. Although the relationship between various grades of malignancies and the c-kit mutation point was unclear, GISTs with mutations at exon 11 showed a good response to imatinib.[89] Thus, the EUS-FNAB procedure may be a powerful technique with which to diagnose and treat submucosal gastrointestinal lesions.

Lymph node swelling

Although EUS is the most accurate modality for the local staging of primary gastrointestinal tumors (T-staging), N-staging accuracy has consistently ranged from 70% to 80% in most series.[1] On the other hand, a recent multicenter prospective evaluation of EUS-FNAB for determining lymph node metastasis found a sensitivity of 92%, a specificity of 93%, and an accuracy of 92%.[56] Thus, EUS-FNAB of lymph nodes provides an important adjunct for detecting malignant lymph node invasion. The locations of lymph nodes subjected to transesophageal or transgastric EUS-FNAB included subcarinal, aortopulmonary window, paraaortic, paratracheal, celiac axis, and peripancreatic sites.

Despite EUS-FNAB showing high diagnostic accuracy for lymph node metastasis, as mentioned above, regional lymph node swelling detected by EUS is not always seen as a good indication for EUS-FNAB, especially in Japan. This is because regional lymph node metastasis or the metastases of somewhat distant lymph

node are not contraindications for surgery. For example, some patients with gastrointestinal malignancies with regional lymph node metastasis, or even with distant lymph node metastasis, undergo tumor resection or palliative surgery. The EUS-FNAB result can change the management only in patients with esophageal cancer, lung cancer, or cancers of unknown origin (including lymphoma).

Complications

The overall complication rate of EUS-FNAB appears to be 1% to 2%.[55] The major complications reported with EUS-FNAB are infections in cystic lesions, bleeding, pancreatitis, and duodenal perforation.[82] In a large multicenter trial involving 554 consecutive mass or lymph node biopsies, only five complications (two perforations, two febrile episodes, one hemorrhage) were observed, all of which were nonfatal.[56] Cystic pancreatic lesions appear to have a greater risk of infectious complications than solid pancreatic masses. Two deaths have been reported with EUS-FNAB. One patient developed fulminating cholangitis associated with EUS-FNAB of a liver metastasis, and the other developed uncontrolled bleeding after EUS-FNAB of the pancreas.[51] The present authors have experienced EUS-FNAB-related complications in 0.79% (6/760) of patients; these complications were: two asymptomatic hemorrhages beneath the pancreatic capsule, one massive bleeding from a gastric GIST, one rupture of a pancreatic pseudoaneurysm followed by massive gastrointestinal bleeding, and one acute portal vein obstruction.[51] The last two complications might possibly have been caused by acute focal pancreatitis. The risk of acute pancreatitis after EUS-FNAB of pancreatic masses was estimated at 19 centers, and pancreatitis after EUS-FNAB was found to have a frequency of 0.29% in a retrospective analysis and 0.64% in a prospective study.[90] Thus, although EUS-FNAB for pancreatic lesions has been evaluated to be a good indicator for further treatments, largely due to the high technical reliability of pancreatic tissue sampling, the possibility of complications needs to be well considered.

In conclusion, together with a short history of EUS-FNAB, we have reviewed technical tips, current indications and contraindications, and details of diagnostic accuracy and complications. The clinical utility of EUS-FNAB has been gradually understood, and EUS-FNAB procedures have been increasing in number. So, in the near future, EUS followed by EUS-FNAB will be routinely performed in the same manner as gastrointestinal endoscopy followed by biopsy under direct vision. Also, therapeutic uses for EUS, such as EUS-guided celiac plexus neurolysis, pancreatic tumor ablation, drainage of pancreatic pseudocysts, and the development of an anastomosis may become feasible as less invasive and safer techniques than those used at present.

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Review

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International Consensus Guidelines for Management of Intraductal Papillary Mucinous Neoplasms and Mucinous Cystic Neoplasms of the Pancreas

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Key Words
Intraductal papillary mucinous neoplasm · Mucinous cystic neoplasm · Guidelines for management of IPMN/MCN · Pancreatic neoplasm · Pancreatectomy

Abstract
Non-inflammatory cystic lesions of the pancreas are increasingly recognized. Two distinct entities have been defined, i.e., intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN). Ovarian-type stroma has been proposed as a requisite to distinguish MCN from IPMN. Some other distinct features to characterize IPMN and MCN have been identified, but there remain ambiguities between the two diseases. In view of the increasing frequency with which these neoplasms are being diagnosed worldwide, it would be helpful for physicians managing patients with cystic neoplasms of the pancreas to have guidelines for the diagnosis and treatment of IPMN and MCN. The proposed guidelines represent a consensus of the working group of the International Association of Pancreatology.

Masao Tanaka chaired the working group and Suresh Chari served as a co-chair. They and the following six authors listed in alphabetical order equally contributed to preparation of the guidelines. Seiki Matsuno selected the members of the working group, planned and realized the consensus meeting and critically edited the manuscript.

Introduction

Non-inflammatory cystic lesions of the pancreas are more common than previously recognized. In an autopsy study [1], small cystic lesions were found in nearly half of the 300 patients studied, the prevalence increasing with age. While most cysts were non-neoplastic, 3.4% of the patients had cysts that showed epithelial atypia [1]. It is therefore not surprising that with the increasing use of high-resolution abdominal imaging techniques, cystic

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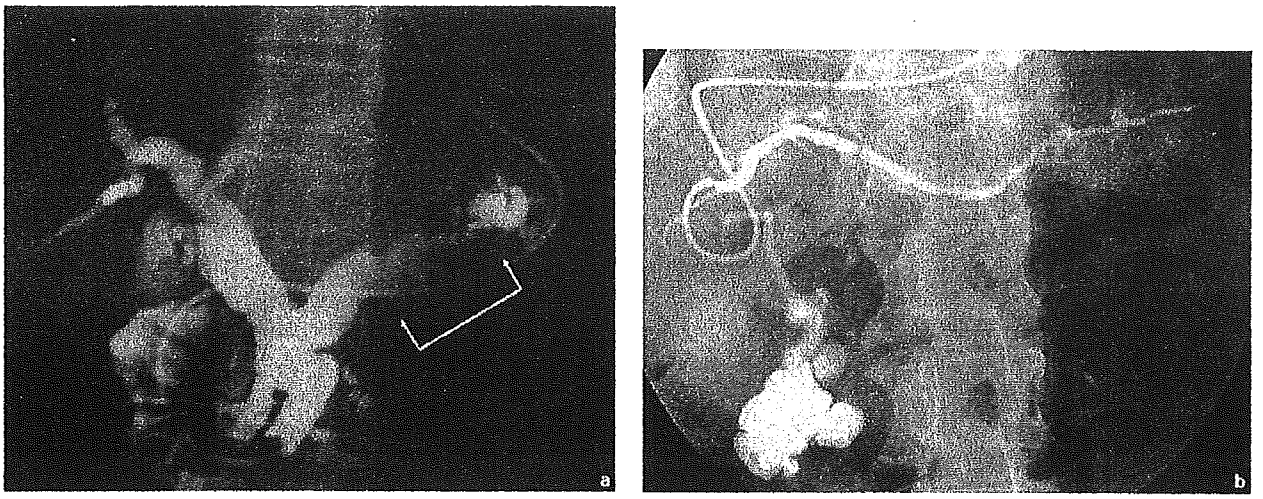

Fig. 1. Pancreatograms using a balloon catheter retained by ERCP showing a main duct IPMN (**a**) with mural nodules (arrow) and a branch duct IPMN in the head of the pancreas with clear communication with the pancreatic duct (**b**).

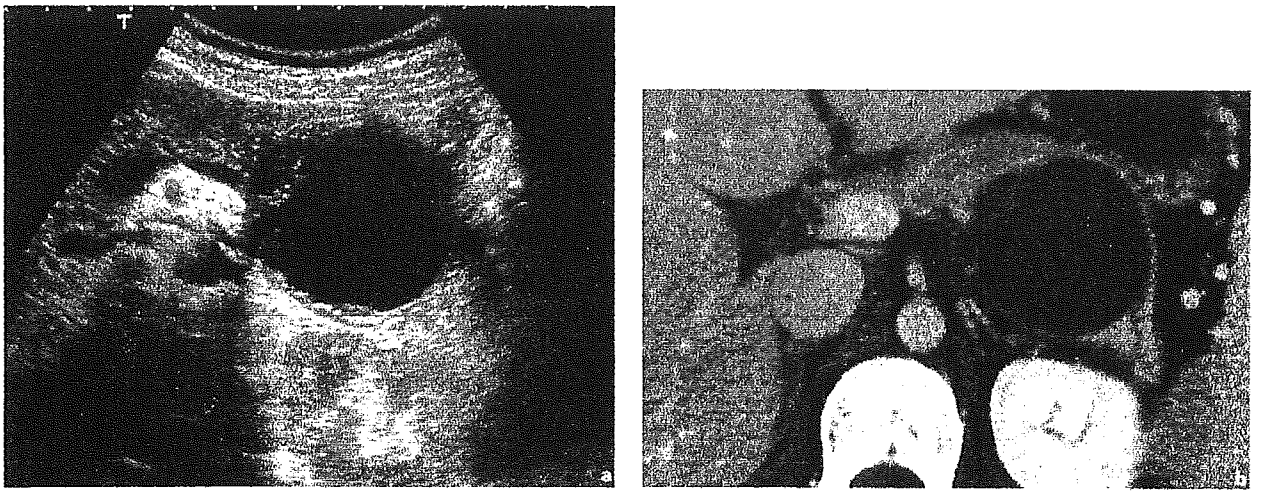

Fig. 2. Ultrasonogram (**a**) and computed tomogram (**b**) demonstrating an MCN.

neoplasms of the pancreas are being increasingly identified, often as incidental findings [2].

In 1996, the World Health Organization (WHO) classified cystic mucin-producing pancreatic neoplasms into two distinct entities [3], i.e., intraductal papillary mucinous tumor and mucinous cystic tumor. In the revised WHO classification in 2000 [4], the two neoplasms were renamed as intraductal papillary mucinous neoplasm (IPMN) (fig. 1) and mucinous cystic neoplasm (MCN) (fig. 2), respectively. Since then much has been learnt about the clinical, radiographic, and histological characteristics of these neoplasms. For example, the presence of ovarian-type stroma has been proposed as a characteristic feature of MCN that distinguishes it from IPMN. While there have been rapid advances in our understanding of the prevalence of cancer at diagnosis and the risk of recurrence following resection, there are still considerable gaps in our knowledge of the natural history of these neo-

Table 1. List of clinical questions

1. Definition and Classification
1a. It has been suggested that IPMNs arising in the branch ducts are less aggressive than those arising in the main duct. Can we preoperatively distinguish main duct IPMN from branch duct IPMN?
1b. In most IPMNs there are papillary growths in both the main duct and branch duct by histology. Do we still need the mixed category or should the mixed type IPMNs be considered as advanced branch duct IPMNs?
1c. Should ovarian-type stroma be a histological requirement for diagnosing MCN?
1d. If all mucinous neoplasms need resection, is distinction between MCN and IPMN merely an academic exercise?
2. Preoperative evaluation
2a. Can we reliably distinguish branch duct IPMN from MCN preoperatively? If so, which imaging modality is best to distinguish between branch duct IPMN and MCN? Is there a preferred order to the tests that should be performed?
2b. Is it possible to diagnose minimally invasive carcinoma derived from IPMN and MCN preoperatively?
3. Indication for resection
3a. Should all main duct IPMNs be resected? If not, what criteria should be employed to separate those that should be resected from those that can be watched (size, mural nodules, etc.)?
3b. Should all branch duct IPMNs be resected? If not, what criteria should be employed to separate those that should be resected from those that can be watched (size, mural nodules, etc.)?
3c. Should all MCNs be resected? If not, what criteria should be employed to separate those that should be resected from those that can be watched (size, mural nodules, etc.)?
4. Method of resection
4a. Pancreatectomy with lymph node dissection is necessary when an invasive carcinoma is suspected. What is an appropriate surgical procedure for non-invasive MCNs and IPMNs? Is pancreatectomy limited to some extent without lymph node dissection appropriate?
4b. Does limited resection (e.g., middle segmental pancreatectomy) have a role in surgical management of MCNs or IPMNs?
4c. What should be the approach to multifocal branch duct IPMNs? In an older patient, is it reasonable to resect the portion of the gland with the largest cyst(s) alone and follow clinically to avoid total pancreatectomy?
5. Histological questions
5a. What is the role of intraoperative frozen section consultation in the surgical management of patients with IPMNs and MCNs? In particular, should pancreatic parenchymal margins be frozen and what should be done if mucinous epithelium is identified in the larger or in the smaller pancreatic ducts?
5b. Are there special instructions for specimen processing in MCNs and IPMNs?
5c. Are there special instructions for specimen processing to differentiate branch duct IPMNs from main duct IPMNs?
6. Method of follow-up
6a. How should patients with non-resected IPMNs and MCNs be followed? How often should they be followed and which techniques should be employed as baseline investigations?
6b. How should patients with surgically resected IPMNs and MCNs be followed? How often should they be followed and which techniques should be employed as baseline investigations?
6c. Should care be taken to the possible occurrence of other malignant neoplasms in patients with IPMNs on follow-up?

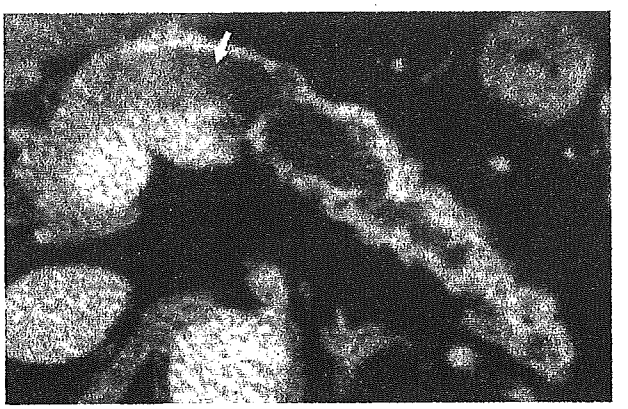

Fig. 3. Computed tomogram showing a markedly dilated main pancreatic duct in a patient with a main duct IPMN with a mural nodule in the body of the pancreas (arrow).

plasms. However, in view of the increasing frequency with which these neoplasms are being diagnosed worldwide, it would be helpful for physicians managing patients with cystic neoplasms of the pancreas to have guidelines for the diagnosis and treatment of IPMN and MCN. No doubt, as our understanding grows, these guidelines will need revision.

During the Eleventh Congress of the International Association of Pancreatology held in Sendai, Japan, from July 11 through 14, 2004, we had a consensus meeting on this topic. The working group set up 6 clinical questions with 18 subdivisions (table 1), and continued to work on the answers. The proposed guidelines represent a consensus of the working group of the International Association of Pancreatology at this moment.

1. Definition and Classification

1. It has been suggested that IPMN arising in the branch ducts are less aggressive than those arising in the main duct. Can we preoperatively distinguish main duct IPMN from branch duct IPMN?

IPMN can be classified as main duct IPMN or branch duct IPMN based on imaging studies or by histology [5]. On conventional imaging (i.e., computed tomography (CT) or magnetic resonance cholangiopancreatography (MRCP)), dilation of the main duct ≥ 1 cm strongly suggests main duct IPMN (fig. 3), whereas a presence of a pancreatic mucinous cyst communicating with the pancreatic duct without main duct dilation suggests branch

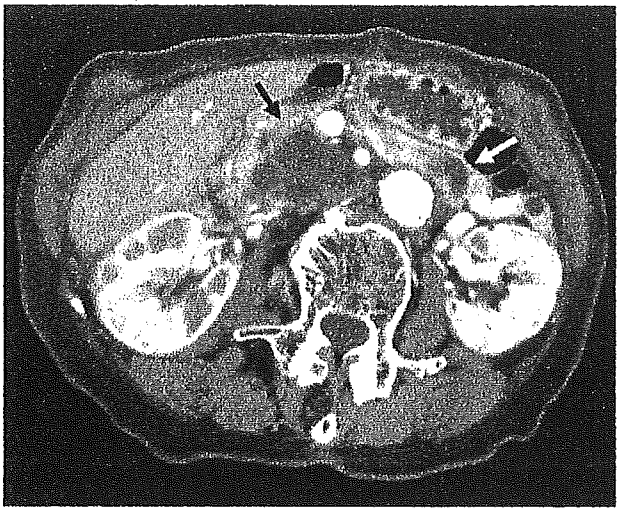

Fig. 4. Computed tomogram demonstrating a multilocular cystic lesion in the head of the pancreas (black arrow) and a unilocular cyst in the tail (white arrow), representing multiple branch duct IPMNs.

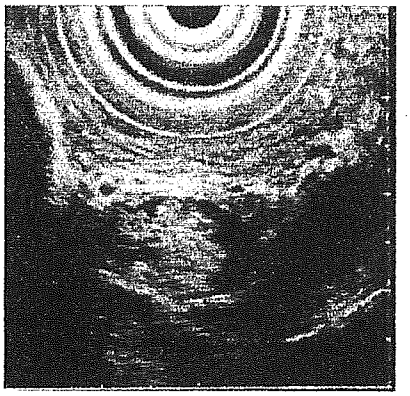

Fig. 5. Endosonogram demonstrating a mural nodule in a branch duct IPMN in the head of the pancreas.

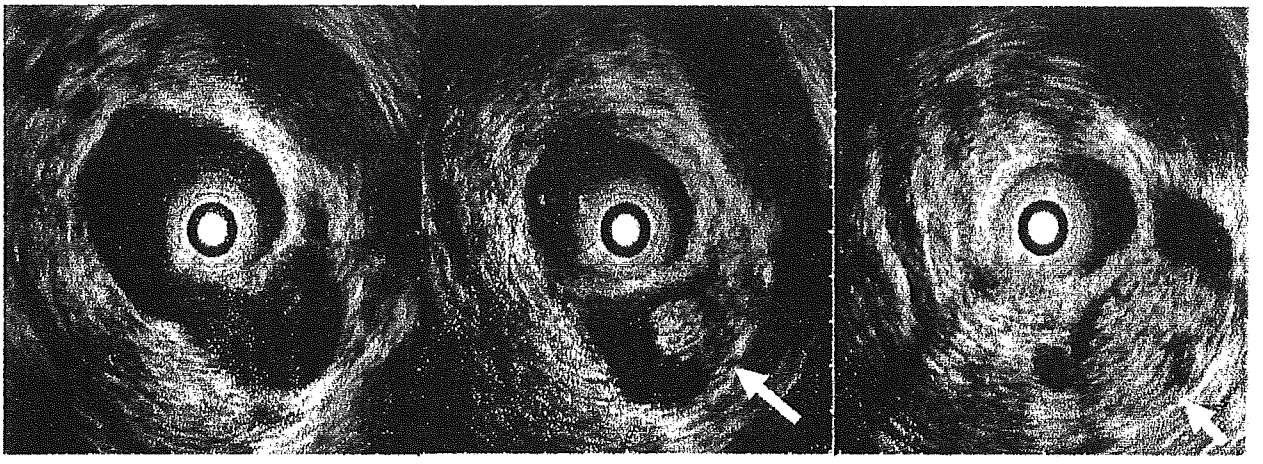

Fig. 6. Intraductal ultrasonogram visualizing a mural nodule in a branch duct IPMN in the head of the pancreas (arrows).

duct IPMN (fig. 4) [6–8]. The presence of the papillary growth in branch or main ducts can be ascertained with greater degree of certainty using more sophisticated and invasive imaging studies, such as endoscopic ultrasonography (EUS) (fig. 5) [9, 10], endoscopic retrograde cholangiopancreatography (ERCP) with or without the use of a balloon catheter (fig. 1a, b), intraductal ultrasonography (fig. 6) [11, 12] and peroral pancreatoscopy (fig. 7) [13, 14], or by a combination of intraductal ultrasonography and peroral pancreatoscopy [15]. However, these techniques are not widely available. The most definitive classification of IPMN into main or branch duct type is made by histology, provided the resected specimen is properly sectioned.

Table 2. Malignancy in main duct IPMNs (including the mixed type IPMN)

Reference (first author)	Year published	Patients	Malignant including CIS, %	Invasive malignancy, %
Kobari [16]	1999	13	92	23
Terris [17]	2000	30	57	37
Doi [18]	2002	12	83	Not stated
Matsumoto [19]	2003	27	63	Not stated
Choi [20]	2003	34	85	Not stated
Kitagawa [21]	2003	37	65	54
Sugiyama [22]	2003	30	70	57
Sohn [23]	2004	69	Not stated	45
Salvia [24]	2004	140	60	42
Mean of all series			70	43

Table 3. Malignancy in branch duct IPMNs

Reference (first author)	Year published	Patients	Malignant including CIS, %	Invasive malignancy, %
Kobari [16]	1999	17	31	6
Terris [17]	2000	13	15	0
Doi [18]	2002	26	46	Not stated
Matsumoto [19]	2003	16	6	Not stated
Choi [20]	2003	12	25	Not stated
Kitagawa [21]	2003	26	35	31
Sugiyama [22]	2003	32	40	9
Sohn [23]	2004	60	Not stated	30
Mean of all series			25	15

Main duct IPMN and branch duct IPMN have significant differences in prevalence of cancer ranging from 57 to 92% [16–24] and 6 to 46% [16–23], respectively (tables 2, 3) and therefore the classification has prognostic implications. In practice, patients classified as branch duct IPMN based on preoperative imaging studies sometimes show microscopic involvement of the main duct not detectable preoperatively. It is unclear if such subjects with 'predominantly' branch duct IPMN with microscopic main duct involvement have a higher prevalence of malignancy compared to those with dysplasia confined solely to the branch duct.

1b. In most IPMNS there are papillary growths in both the main duct and branch duct by histology. Do we still need the mixed category or should the mixed type IPMNS be considered as advanced branch duct IPMNS?

The categorization of IPMN according to the differential involvement of the branch vs. main duct is mostly based on imaging findings, and as such this classification scheme appears to have substantial value in preoperative management algorithms for IPMN. The role of this classification, however, may be overridden once the neoplasm is resected, re-evaluated pathologically, and graded as adenoma, borderline, CIS or invasive. On the other hand, there are significant pathologic correlates of this classification: IPMNs categorized as 'branch type' by radiographic methods are typically found to be smaller, less complex (less papillary), and non-malignant (more commonly adenomas with gastric/foveolar type epithelium), which explains why many branch duct IPMNs have been successfully managed by conservative therapy, even 'wait and watch'.

One pitfall in this classification scheme, however, is that many of the branch duct IPMNs prove, by microscopic examinations, to have some degree of involvement in the main duct as well. Therefore, predominantly main duct type and predominantly branch duct type may be a more accurate conceptualization of these categories, al-

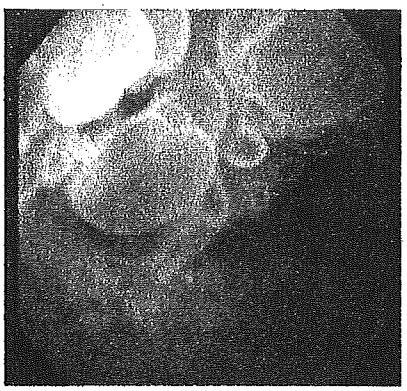

Fig. 7. Fish egg-like appearance of a main duct IPMN by peroral pancreatoscopy.

though the word predominantly is omitted for practical purposes. In fact, 'branch limited' vs. 'beyond the branch' may be even more accurate. On the other hand, there are more important and practical implications of this conceptual issue. First, it is difficult to determine how much of the main duct involvement is necessary to qualify the lesion as 'main duct IPMN'. In this regard, more clinical follow-up data need to accumulate before the criteria for this distinction can be established. In the meantime, however, the criteria advocated for the definition of IPMN in the recent international consensus manuscript [25] may be applicable for practical purposes. Even when these criteria are applied, however, many IPMNs would still fall into a mixed category. Therefore, it is necessary to retain this mixed category until future studies further clarify the criteria to distinguish these two groups.

Since clinicopathologic correlation is imperative in the management of IPMNs as well as in understanding the biologic behavior of the subsets of this type of neoplasm, it is recommended that surgical pathologists make every attempt to determine branch vs. main duct type, if nothing else, in order to provide verification to this clinical classification. For this purpose, the findings regarding the distribution of ductal involvement may be communicated in a note or comment following the main diagnosis in the surgical pathology report.

1c. Should ovarian-type stroma be a histological requirement for diagnosing MCN?

The most characteristic histological finding in MCN is the presence of a unique ovarian-type stroma (fig. 8) [26] not found in other pancreatic neoplasms. This ovarian-

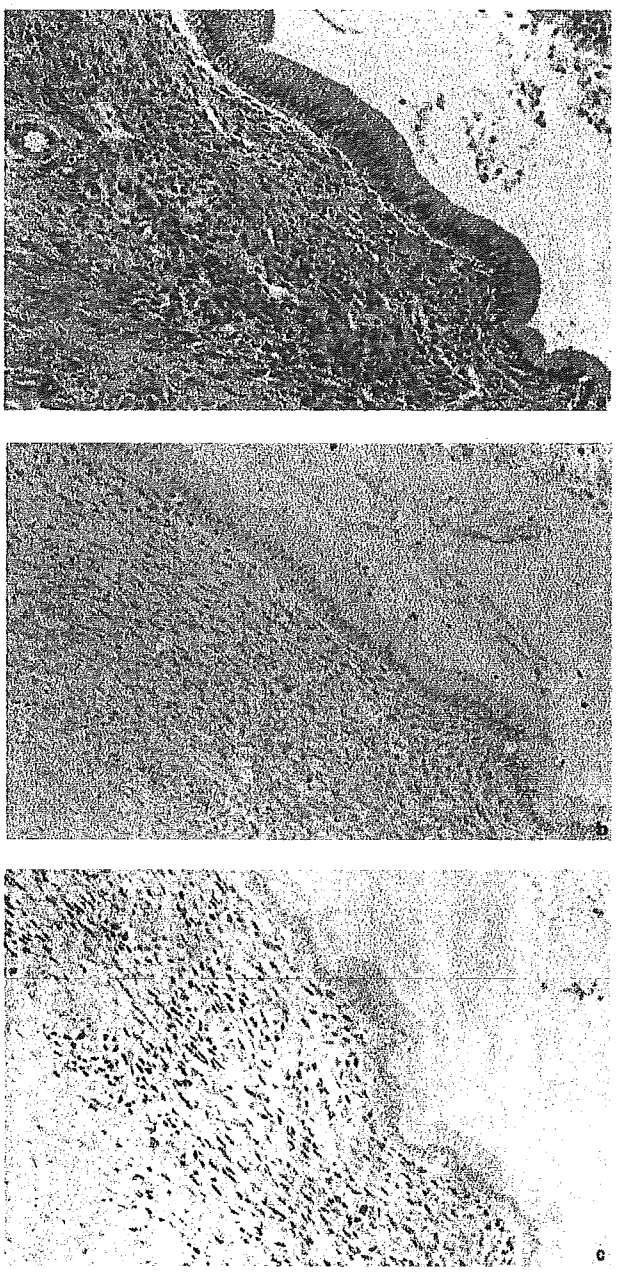

Fig. 8. Ovarian-type stroma in a mucinous cystic neoplasm. Hematoxylin and eosin staining (**a**) and immunohistochemical staining of estrogen receptor (**b**) and progesterone receptor (**c**). ×200.

type stroma forms a layer of variable thickness beneath the epithelial lining. The stromal cells have oval nuclei and spindled cytoplasm, and are arranged in long fascicles. The resemblance to ovarian stroma is further

strengthened by the presence of occasional 'lutenized' cells – epithelioid cells with abundant clear cytoplasm. A study of 34 pancreatic MCN and 10 ovarian MCN showed the ovarian stroma of MCN from the two organs shared the same immunohistochemical and histological characteristics [27].

Like its ovarian counterpart, the stroma of pancreatic MCN variably stains for estrogen and progesterone receptors (fig. 8b,c), with 61.8% of pancreatic MCN staining for human chorionic gonadotropin [27].

The most important question with regard to the accurate classification of MCN and its differentiation from branch duct form of IPMN is whether the presence of ovarian-type stroma is required to diagnose MCN. Three studies on MCN have used ovarian-type stroma as a requisite criterion for diagnosis of MCN [28–30]. When defined by the presence of ovarian-type stroma, MCN has a distinct demographic profile; it occurs almost exclusively in women and is almost always found in the pancreatic body/tail region [28, 29]. It has been argued that theoretically it may be possible that postmenopausal women and men with MCN may fail to demonstrate ovarian-type stroma. In a study of 56 MCN defined strictly by presence of ovarian stroma, 9 patients (16%) were >60 years of age [28]. Also, there are male patients with mucinous cystadenoma with ovarian-type stroma [28, 31].

In the absence of a definitive marker, other than ovarian-type stroma, to distinguish MCN from IPMN, it is currently impossible to say if neoplasms classified on the basis of any criterion other than presence of ovarian-type stroma (for example, non-communication with the duct) are indeed MCN. It has become clear over the past few years that making exceptions to the ovarian-type stroma rule frequently leads to misclassification of IPMN as MCN [28]. Therefore the term MCN should be restricted to neoplasms exhibiting ovarian-type stroma.

Clearly, typical MCN with ovarian-type stroma is rare in males and it is less common in postmenopausal women than in women of childbearing age. Occasionally, mucin-producing pancreatic cystic lesions are seen in men or postmenopausal women that neither have ovarian-type stroma nor have typical histological features seen in branch duct IPMNs such as a thin wall, grape-like appearance and a communication with the pancreatic duct. Rather than classify such lesions as MCNs, we propose the use of the term 'indeterminate mucin-producing cystic neoplasm of the pancreas'. In future, when specific markers of IPMN and MCN become available, these lesions may be more definitively classified.

1d. If all mucinous neoplasms need resection, is distinction between MCN and IPMN merely an academic exercise?

The general recommendation has been that all mucin-producing neoplasms undergo resection in view of their malignant potential, which questions the clinical utility of careful differentiation of MCN from IPMN [30, 32–34]. However, there are crucial differences between MCN and IPMN with regard to pathogenesis, multifocality, need for follow-up and prevalence of cancer that impact clinical management.

Due to its close histological and immunohistochemical resemblance to ovarian mucinous cystadenomas, MCN has been postulated to arise from ovarian rests in the pancreas [29]. IPMN appears to arise from the pancreatic duct.

MCN and IPMN also have important clinical differences. MCNs are generally solitary and do not recur after complete resection [35, 36]. On the other hand, branch duct IPMNs have been reported to be multifocal in distant regions of the pancreas in up to 30% of patients [37–39], and there is at least a 10% recurrent rate in those patients with non-invasive IPMN who undergo partial pancreatic resection with negative margins [40]. Thus, while no follow-up is needed after resection of non-invasive MCN, young patients with IPMN need follow-up, especially if they have unresected synchronous lesions.

The prevalence of invasive carcinoma reported in MCN has varied widely from 6 to 36% [28–30]. However, data on prevalence of invasive carcinoma in MCN are hard to interpret as few studies have used ovarian-type stroma as a necessary criterion for diagnosis of MCN. Even in studies restricted to neoplasms with ovarian-type stroma the prevalence of cancer has varied from 6 to 27% [28, 29]. In IPMN, prevalence of invasive carcinoma at diagnosis has been reported to be high in main duct IPMN (23–57%, table 2) and lower in branch duct IPMN (0–31%, table 3).

2. Preoperative Evaluation

2a. Can we reliably distinguish branch duct IPMN from MCN preoperatively? If so, which imaging modality is best to distinguish between branch duct IPMN and MCN? Is there a preferred order to the tests that should be performed?

There are some obvious differences in clinicopathological features between IPMN and MCN with ovarian-type stroma (table 4) [28–30, 41–47]. Understanding of

Table 4. Typical features of MCN and branch duct IPMN

Characteristic	MCN	Branch duct IPMN
Gender (% female)	>95%	~30%
Age (decade)	4th and 5th	6th and 7th
Location (% body/tail)	95%	~30%
Common capsule	Yes	No
Calcification	Rare, curvilinear, in the wall of cyst	No
Gross appearance	Orange-like	Grape-like
Internal structure	Cysts in cyst	Cyst by cyst
Pancreatic duct communication	Infrequent	Yes (though not always demonstrable)
Main pancreatic duct	Normal or deviated	Normal, or if dilated, suggests combined type

these distinctive features and characteristics of each imaging modality lead to differentiation of the two diseases in most patients. Cystic lesions in males and those in the head of the pancreas are unlikely to be MCN. Magnetic resonance imaging (MRI) with MRCP is the best to outline the gross appearance. Communication with the pancreatic duct demonstrated on imaging studies such as ERCP (most reliable), MRCP (helpful), and EUS (of some help) strongly suggests branch duct IPMN. However, even ERCP in branch duct IPMN may fail to fill the cystic side branch due to mucus plugging the communication. On the other hand, there has been a report of a histologically proven MCN showing communication with pancreatic ducts [47]. In some patients it may therefore be impossible to distinguish between the two entities with certainty preoperatively.

2b. Is it possible to diagnose minimally invasive carcinoma derived from IPMN and MCN preoperatively?

The Japan Pancreas Society (JPS) defined a non-invasive type of intraductal papillary mucinous carcinoma as limited to the pancreatic duct and a minimally invasive type as having invaded slightly beyond the ductal wall [48]. However, this definition is not so clear. If the minimally invasive intraductal papillary mucinous carcinoma is defined as microscopic cancer invasion to the pancreatic parenchyma, it is impossible to diagnose the minimal invasion preoperatively [49] at present as is the case in minimally invasive MCN.

3. Indication for Resection

3a. Should all main duct IPMNs be resected? If not, what criteria should be employed to separate those that should be resected from those that can be watched (size, mural nodules, etc.)?

The frequency of malignancy (in situ and invasive) in main duct IPMNs in 8 recent series from Japan, Europe, and the USA has ranged between 60 and 92%, with a mean of 70% [16–24], and approximately two-thirds of these malignant neoplasms have been invasive (table 2). In many studies there has been an attempt to identify radiologic or clinical characteristics that predict malignancy, although unfortunately many of these analyses have been made without separating main duct from branch duct variants. In a series reported by Sugiyama et al. [22], univariate analysis showed that presence of symptoms, a main pancreatic duct diameter >15 mm, and mural nodules were all significant predictors of malignancy in main duct or mixed type IPMNs, although there were patients without nodules or such marked pancreatic duct dilation that had in-situ or invasive carcinoma. The largest published series on main duct IPMNs combines the experiences of the Massachusetts General Hospital and the University of Verona [24]. This study comprised 140 patients, and found that patients with malignant neoplasms were significantly older (by 6.4 years), and had a higher likelihood of presenting with jaundice and/or worsening of diabetes; however, the study also showed that 29% of patients with malignant IPMNs involving the main duct were asymptomatic, and therefore reliance on symptoms could not exclude malignancy. Given the high prevalence of cancer and the data from the reviewed studies it is unlikely that any combination of clinical and radiological

parameters will accurately discriminate between malignant and non-malignant main duct IPMNs. Furthermore, evidence of 'clonal progression' in these neoplasms [50] and the age difference between patients with malignant and benign lesions (which was also shown in another large study) [30] are indicative that most if not all benign main duct IPMNs may progress into invasive cancer, and the long-term follow-up of resected patients shows excellent survival for benign and non-invasive neoplasms and 5-year survival between 36 and 60% for invasive carcinomas [21, 23, 24, 40]. Based on this, our current recommendation is to resect all main duct and mixed variant IPMNs as long as the patient is a good surgical candidate with a reasonable life expectancy. It is important that resections for IPMNs be carried out by surgeons familiar with this diagnosis and in centers where pancreatic surgery can be done safely.

3b. Should all branch duct IPMNs be resected?

Review of 7 recent series describing branch duct IPMNs shows a frequency of malignancy between 6 and 46%, with a mean of 25%, and a frequency of invasive cancer ranging between 0 and 31%, with a mean of 15% (table 3) [16–23]. It is of note that the two studies with the highest frequency of invasive cancer (30 and 31%, respectively) do not describe asymptomatic patients within their series [21, 23], whereas other series with low prevalence of invasive cancer show a significant proportion of incidentally discovered IPMNs [17, 19, 22]. In the series of Sugiyama et al. [22], 53% of branch duct IPMNs were asymptomatic, and none of those patients had invasive cancer. Two studies from Japan have looked at morphologic features of branch duct IPMNs and risk of malignancy. Matsumoto et al. [19] found no malignancy (in situ or invasive) in neoplasms measuring <30 mm and without mural nodules, and described non-operative management in 12 patients with branch duct IPMNs who either refused operation or were at high surgical risk. The majority of these patients were asymptomatic, and had no radiologic progression of their neoplasms during an average follow-up of 33 months. In the second study, Sugiyama et al. [22] found with multivariate analysis that the size >30 mm and presence of mural nodules were the strongest predictors of malignancy in branch duct IPMNs. Only 1/15 patients with a neoplasm <30 mm had in-situ carcinoma (none had invasive cancer), and only 5/22 patients without mural nodules had malignancy. Thus, the overall lower prevalence of malignancy in branch duct IPMNs and the reassurance from the above studies that the likelihood of invasive cancer is very low in small cysts raise the possibility of management with careful observation in asymptomatic patients. Patients with branch duct IPMNs who are symptomatic should be treated with resection not only to alleviate the symptoms, but also because of a higher likelihood of malignancy. It is important to emphasize that the decision to treat should be individualized and based on patient preferences and willingness or unwillingness to undergo follow-up studies, as well as on the availability of safe pancreatic resection. Moreover, more data based on pathological studies of branch duct IPMNs >30 mm and without main duct dilation or mural nodules are needed to determine if all branch duct IPMNs >30 mm in size should be resected immediately.

3c. Should all MCNs be resected? If not, what criteria should be employed to separate those that should be resected from those that can be watched (size, mural nodules, etc.)?

Unless there are contraindications for operation, all MCNs should be resected. Usually these neoplasms are localized in the body-tail of the gland and affect middle-aged women [29, 35, 36]. Current thinking is that all MCNs may progress to malignancy, and the life expectancy of most of these patients will allow development of mucinous cystadenocarcinoma, which has a very low resectability and a very poor prognosis [35, 36]. Furthermore, the operation, usually a left pancreatectomy, has a low morbidity and practically no mortality [51]. Predictors of malignancy such as large size, mural nodules, and eggshell calcification [32] mean only that spleen preserving techniques, either laparoscopically or open, must be avoided in order to obtain a correct oncological lymph node dissection [52–55].

4. Method of Resection

4a. Pancreatectomy with lymph node dissection is necessary when an invasive carcinoma is suspected. What is an appropriate surgical procedure for non-invasive MCNs and IPMNs? Is pancreatectomy limited to some extent without lymph node dissection appropriate?

It is not always easy to assess pre- and intraoperatively the grade of invasiveness [56]. Whenever any doubt exists, a typical resection (pancreatoduodenectomy, left pancreatectomy, total pancreatectomy according to the site and the extension of the disease) with lymph node dissection must be pursued [34, 57]. In very limited size lesions, without any laboratory, clinical or radiological