REVIEW ARTICLE

Intraductal Papillary Mucinous Neoplasia (IPMN) of the Pancreas

Its Diagnosis, Treatment, and Prognosis

Robert Grützmann, Stefan Post, Hans Detlev Saeger, Marco Niedergethmann

SUMMARY

Background: The many varieties of cystic pancreatic tumor, and especially intraductal papillary mucinous neoplasia (IPMN), have attracted increased attention recently. Their incidence may be rising, and their histopathological evaluation and classification have become more precise than before.

Methods: We discuss the current diagnostic evaluation of IPMN, along with treatment and prognostication, on the basis of the current international guideline as well as pertinent literature retrieved by a selective PubMed search.

Results: The preoperative diagnostic evaluation of IPMN is often problematic. In particular, it may not be possible to differentiate main-duct disease from branch-duct disease (MD-IPMN vs. BD-IPMN) before surgery—a distinction with implications for prognosis and treatment, as MD-IPMN is more often malignant. An IPMN adenoma can develop into invasive pancreatic cancer. Because firm diagnostic criteria are still lacking, it is recommended that all MD-IPMN lesions and all large BD-IPMN lesions should be resected. Partial pancreatectomy with clean margins is the treatment of choice.

Conclusion: As IPMN seems to be a slow-growing precursor of pancreatic cancer, it is possible that its early detection and surgical treatment can lead to a cure. No conclusion about the efficacy of surveillance and follow-up programs can be drawn from the available evidence. A better understanding of the natural course of IPMN and the biology of pancreatic cancer is needed to enable further improvements in diagnosis and treatment.

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Cystic pancreatic lesions are most often associated with post-inflammatory “pseudocysts”. Neoplastic cysts are, however, more common than was assumed in the past. Autopsy studies have shown cystic pancreatic lesions in up to 25% of cases; 5% of these were found to be neoplastic (1, 2). The increasing use of high-performance imaging modalities led to increasing numbers of such tumors are being identified (2, 3, e1). A computed tomography (CT) study in patients without pancreatic disorders found a prevalence of 2.6 cysts per 100 patients (e2). On the basis of larger series it has been concluded that two-thirds of patients with cystic pancreatic lesions have never had pancreatitis and that 30–50% of these lesions progress and become invasive (3–6).

The diagnosis and treatment of intraductal papillary mucinous neoplasias (IPMN) are of particular interest. In recent years it has become accepted that this combination of a diagnosable precursor of pancreatic cancers and its comparatively slow growth enable early diagnosis and curative surgical treatment (7). The entity IPMN was included in the WHO classification system in 1996 (5, 8). IPMN grow in the main duct or branch duct of the pancreas, produce mucin, and have differentiated papillary features. Since growths affecting the pancreatic main duct are associated with a higher malignant potential, IPMN are subcategorized clinically into main-duct (MD)–IPMN and branch-duct (BD)–IPMN (5). The 2010 WHO classification subcategorizes the IPMN according to their malignant transformation into IPMN with low or intermediate dysplasia, IPMN with high-grade dysplasia, and IPMN with invasive cancer. In addition to pancreatic intraepithelial neoplasia (PanIN), IPMN are the most important precursor lesions of ductal pancreatic cancer (8). We conducted a selective literature search in PubMed and international guidelines to extract publications, with the aim to set out what is currently known about the diagnostic evaluation, therapy, and prognosis of IPMN.

Diagnostic evaluation

Medical history and clinical features

Although there are no definite clinical signs for the presence of an IPMN, a patient's medical history and clinical examination are important. Some 20% of patients remain asymptomatic. Symptomatic patients

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TABLE

Frequency and type of symptoms in IPMN

Study	n	Asymp-tomatic	Symptoms					
			Pain	Jaundice	Weight loss	Nausea/vomiting	Pancrea-titis	Diabetes
Nagai [9]	72	43%	35 %	8%	22%	–	13%	29%
Niedergethmann [10]	97	–	43 %	30%	32%	–	–	38%
Schmidt [18]	150	7%	79 %	12%	32%	38%	43%	19%
Sohn [23]	136	–	52 %	17%	29%	14 %	13%	–
Wada [25]	100	8%	78 %	16%	30%	–	36%	16%
Wang [24]	57	22%	56 %	18%	32 %	16%	32%	39%

present with nausea, vomiting, abdominal pain or back-ache, and weight loss (9, 10, e1) (Table). Many patients have symptoms that resemble those of chronic recurrent pancreatitis. In 13–50% of cases, the medical history includes chronic pancreatitis (11). In most of those cases, the cause is the IPMN, whose mucin secretion obstructs the pancreatic duct. Patients with IPMN are mostly female and older than patients with chronic pancreatitis. A significant relation seems to exist between the occurrence of symptoms and the risk of malignant cystic neoplasia (11).

Differential diagnosis

The differential diagnosis (Figure 1) is of particular importance for detecting potentially malignant lesions. On the other hand, benign findings should be diagnosed as sensitively as possible in order to reduce the need for surgery.

Serous cystic neoplasias (SCN), formerly known as serous cystadenomas, are the most common of the cystic neoplasias, at 18–39% (11). They are equally distributed between the sexes and mostly asymptomatic. A characteristic feature is their honeycomb structure with a microcystic design, which can also be macrocystic (in 20%) (11). Since SCN are only very rarely malignant, only symptomatic and progressively growing lesions should be resected.

More than 90% of mucinous cystic neoplasias (MCN; 20%) affect women between the 4th and 6th decades of life; they are mostly localized in the tail of the pancreas. In terms of its differential diagnosis, this tumor differs from IPMN in terms of its lacking connection to the duct and the ovarian-type stromal component. Surgery is indicated in any case in a diagnosis of MCN as these tumors have the potential to turn malignant, in 6–36% of cases (e3).

Solid papillary neoplasias (SPN; 5%) are benign in more than 90% of cases and affect mainly young women. Strictly speaking, these are not “cystic” tumors but “pseudocystic” ones as they disintegrate necrotically at their center. Since they are not easily distinguishable from pancreatic cancer in terms of the

differential diagnosis, surgery is indicated. The prognosis of these tumors is excellent; 5-year survival after resection is 95% (11, e4).

Histopathology

Histologically, IPMN are characterized by intraductal proliferation of neoplastic duct epithelium, accompanied by mucin production. Most IPMN arise from the pancreatic main duct or its branch ducts. Most of these tumors are unifocal, 20–30% are multifocal, and 5–10% of the IPMN diffusely affect the entire duct system of the pancreas (9). IPMN may arise from the main duct, the branch ducts, or both. IPMN are subcategorized into main-duct-type IPMN, branch-duct-type IPMN, and mixed-type IPMN (Box 1) (6, 9–11). In branch-duct IPMN, a malignant tumor is found in 6–46%, and in main-duct IPMN in 57–92% (5). The main-duct type is therefore associated with a much poorer prognosis (6, 8, 9). When the main duct as well as branch ducts are affected, the main-duct lesion is the lesion on which clinical proceedings and prognosis should be based.

Histologically, different classifications can be applied to IPMN. According to the degree of dysplasia they can be categorized into non-invasive forms (low or intermediate dysplasia) or invasive cancers. The non-invasive tumors have a much better prognosis than the invasive cancers, with a 5-year survival rate after resection of 90% compared with 60% (10, e1). Immunohistochemical staining with mucin antibodies enables differentiation between four types of tumors with different prognoses (6): the gastric, intestinal, pancreaticobiliary, and oncocytic type. It is currently possible to distinguish between these subtypes only in resected surgical specimens. Molecular biological tests have identified a multitude of genetic modifications, similar to those in ductal pancreatic carcinoma (6).

Imaging diagnostics

Preoperative imaging should confirm the diagnosis, diagnose the type of IPMN, and predict the risk of malignant cystic neoplasia and resectability. The

FIGURE 1

Serous cystic neoplasia		Mucinous cystic neoplasia	
Age (Ø)	70 Years	Age (Ø)	47 years
Male:female	60:40	Male:female	5:95
Size (Ø)	6 cm	Size (Ø)	10 cm
Communication to duct	No	Communication to duct	No
Symptoms	Rarely	Symptoms	Common
Malignity	Rarely (< 5%)	Malignity	Common (> 70%)
Particular features	Microcystic SCN Macrocytic SCN	Particular features	Ovary-like stroma

Solid pseudopapillary neoplasia		Intraductal papillary mucinous neoplasia	
Age (Ø)	30 years	Age (Ø)	64 years
Male:female	13:87	Male:female	60:40
Size (Ø)	7 cm	Size (Ø)	5 cm
Communication to duct	No	Communication to duct	Always
Symptoms	Rarely	Symptom	Common (pancreatitis)
Malignity	Rarely (10%)	Malignity	Common
Particular features	"Young" women	Particular features	Main-duct type and branch-duct type

Differential diagnosis of relevant cystic tumors of the pancreas.

SCN; serous cystic neoplasia

following modalities are available:

Transabdominal sonography is the basic examination. It depends on the examiner, but in most cases it is possible to draw conclusions about the size and extent of the IPMN. Transabdominal contrast medium sonography may yield additional information for the differential diagnosis and for predicting malignity (12).

Endoscopic ultrasonography (EUS) is a useful diagnostic modality in patients with cystic pancreatic tumors. It enables high resolution and fine needle aspiration (FNA) of cystic fluid for cytology (tumor cells of atypical cells) and laboratory chemistry (amylase, carcino embryonic antigen [CEA]) analyses. The typical endosonographic sign for IPMN is papillary growth in the pancreatic ducts. A clearly distended main duct usually indicates MD-IPMN. A communication to the main pancreatic duct supports the differential diagnosis of IPMN to MCN. The precision of the EUS alone in differentiating benign and malignant IPMN varies in different studies from 40% to more than 90% (13).

Cytology was not discussed in the consensus report of the International Association of Pancreatology (IAP), but it was included in the algorithm for the management of BD-IPMN (5). The detection of atypical cells on cytology, combined with an analysis of the cystic fluid for CEA (>2500 ng/mL), seems more sensitive than a finding of malignant cells on cytology (14). The exact clinical importance of cytology and FNA will

BOX 1

Clinical definitions of main-duct and branch-duct type

- **Main-duct type:**
Cystic tumor, main pancreatic duct expanded to > 10 mm
- **Branch-duct type:**
Cystic tumor in the branches of the pancreatic duct with communication to branch duct, main duct < 6 mm

have to be investigated in prospective studies (15). Typical signs on computed tomography (CT) are a diffusely distended pancreatic duct with mucinous filling defects and grape-like, cystic, space-occupying lesions. The connection of the cystic lesion to the pancreatic duct system is often identified by thin layer CT. In this respect, however, CT is inferior to endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance cholangiopancreatography (MRCP) (16). A wide and gaping papilla with secretion of mucin and filling defects in the extended pancreatic duct is pathognomonic for ERCP (17). Magnetic resonance imaging (MRI) with MRCP can also expose the pancreatic duct system and the cystic, space-occupying lesions in detail. Compared with ERCP, MRI with MRCT is more sensitive in a scenario of mural nodules (*Figure 2b*) (e5). Furthermore, MRI also enables assessment of the entire pancreatic parenchyma and the intra-abdominal organs, and angiography (*Figure 2*). MRI seems superior to CT in terms of characterizing the lesion (16, e4). The sensitivity in diagnosing an IPMN is highest for MRI with MRCP (88%), followed by ERCP (68%) and CT (42%); MRI should therefore be the standard modality for diagnosing IPMN (16).

Predicting tumor malignity

Box 2 summarizes the diagnostic risk factors. Although the criteria for malignant IPMN defined in the IAP's consensus report include the presence of symptoms, a cyst size larger than 30 mm, and mural nodules (5), different studies have shown that these criteria are not absolute. Nagai et al showed in 2008, for example, that four of 57 patients with BD-IPMN <30 mm without nodular changes had a malignant tumor (9). Another study found that the size of the cystic lesion was not predictive for the presence of an invasive or malignant component in BD-IPMN (18). Furthermore, three invasive cancers were found among the 11 asymptomatic cases, including a BD-IPMN smaller than 10 mm. By comparison, a study of BD-IPMN showed that findings without mural nodules remained mostly unchanged.

Figure 2: a) MRCP and b) MRI of a multifocal MD-IPMN (arrows) with lesions in the entire pancreas in a 43-year old woman (exclusion of acute pancreatitis)

None of the resected patients without mural nodules had an invasive cancer, and in five patients with new mural nodules an adenoma was present in three cases and carcinoma in situ in one case (19). Depending on the clinical situation (age, expected quality of life post-operatively), a conservative strategy with close monitoring should be pursued only in asymptomatic BD-IPMN without mural nodules and a size of less than 20 mm (*Figure 3*).

Therapy

The therapeutic recommendations for IPMN are based on a consensus report from the IAP (5) and on case series from the past decade (3, 4, 7). No data with higher evidence levels are therefore available to support the therapeutic decision. Only one case-control study (evidence level 3) has thus far investigated the natural course in asymptomatic BD-IPMN (20). Prospective randomized studies are so far lacking. The therapeutic recommendations are therefore subject to limitations and reflect current expert opinion (7).

Watchful waiting in IPMN

Monitoring as the approach for IPMN that do not require resection is contingent on the distinction between MD-IPMN and BD-IPMN. MD-IPMN always constitute an indication for surgery, whereas the treatment of BD-IPMN depends on clinical, morphological, and imaging criteria. The probability for a malignant branch-duct IPMN ranges between 30% in the presence of symptoms and below 5% in the absence of symptoms (10). *Box 3* lists further criteria for potential malignancy (e6). According to the IAP's consensus recommendation, BD-IPMN >3 cm should be surgically resected because of their relevant malignant potential (5). A grey area is the size range between 2 cm and 3 cm. Whether a resection is generally to be recommended is the subject of discussion. An Asian resection study found invasive tumors of size 2–3 cm in 25% of cases (21). In theory, endosonography with aspiration cytology is a suitable investigative modality for

determining the malignant potential in the group of patients with BD-IPMN <3 cm. However, whether the sensitivity of this investigation is sufficient is not clear. A large case series showed that 67% of negative and 92% of non-diagnostic cytology tests were associated with a (pre-) malignant result after resection. The decision on whether surgery should be undertaken or not should therefore not be based on negative or non-diagnostic cytology alone (15).

In sum, asymptomatic BD-IPMN with a diameter <10 mm should be checked annually, and lesions of 10–20 mm every 6–12 months. In BD-IPMN >20 mm, the indication for surgery should be considered, depending on the clinical situation, and discussed individually with the patient. In the presence of symptoms, enlarged lymph nodes, a diameter >30 mm, or a distended main duct, surgery is indicated (5). If no changes have occurred after two years' monitoring, the interval may be extended (5) (*Box 3*).

Surgical treatment of IPMN

Because of the malignant potential of MD-IPMN, the indication for surgery is given, provided that the patient's clinical condition is acceptable. The same holds true for the so-called mixed types. For BD-IPMN, the indication for surgery needs to be defined according to the malignancy risk. In case of an unclear tumor dignity, the indication for resection should be defined liberally, since only surgical treatment offers an opportunity for cure. Because of the potential malignancy, which even today can be confirmed only in the final conclusive histopathological examination, oncological pancreatectomy with lymphadenectomy should be requested. Resections include the stomach-preserving resection of the head of the pancreas, distal pancreatectomy, and total pancreatectomy in multifocal lesions. In certified treatment centers in Germany the mortality associated with these interventions is below 5% (www.dgav.de). Possible risks—such as pancreatic fistula or bowel paralysis—have been reduced in recent years, thanks to improved surgical techniques and

BOX 2

Diagnostic risk factors for malignant IPMN

- Main-duct IPMN
- Male sex
- Elderly patient
- Symptoms present
- Tumor size > 2 cm (3 cm)
- Mural nodules
- Enlarged lymph nodes
- Distension of pancreatic main duct and biliary duct
- Positive cytology, CEA > 200 in the content of the cyst

appropriate management of complications, and have mostly been treated without the need for repeat surgery (e7). Intraoperative histological frozen sections determine the extent of the resection. Tumor-free resection margins are required for all IPMN. If higher-grade dysplasias are found in the resection margin then the resection should be continued until a negative margin has been achieved, even at the risk of total pancreatectomy, depending on the age and condition of the patients (Figure 4) (5, e1).

Follow-up and prognosis

Follow-up

Because evidence is lacking, no recommendations exist with regard to the exact modality for following up patients with resected lesions. In addition to several case series, the IAP's recommendations are available (3–5, 8, 10, 19, 20–25). Series from large centers allow the conclusion that non-invasive IPMN recur in up to 13% after resection or are diagnosed metachronously (4, 7, 8, 10, 23–25). For invasive IPMN, the recurrence rate is high, at 28–60%, and determines the prognosis (4, 7, 8, 10, 23–25). In the 10-year series from Dresden and Mannheim, the recurrence rate over 10 years was low for invasive IPMN, at 28%, but all patients ultimately died due to their disease (10). In sum, an annual follow-up interval is recommended for resected, non-invasive IPMN, and a six-monthly follow-up interval for invasive IPMN. CT or MRI are adequate diagnostic modalities for follow-up investigations. If a potentially resectable recurrence develops in a patient whose general condition is good then the resection should be repeated. No evidence exists for adjuvant therapy after resection of IPMN. If a cancer is present then the indication for adjuvant treatment should be weighed up in analogy to ductal pancreatic carcinoma.

Prognosis

With regard to the prognosis, significant differences exist between the main-duct type and the branch-duct type of tumor. This is because of the higher prevalence

FIGURE 3

Diagnostic algorithm in IPMN

EUS, endosonography; MRCP, magnetic resonance cholangiopancreatography; CEA, carcinoembryonic antigen; CA19–9, carbohydrate antigen 19–9; ERCP, endoscopic retrograde cholangiopancreatography; MRI, magnetic resonance imaging; CT, computed tomography; BC, blood count; BS, blood sugar; CRP, C-reactive protein; OGTT, oral glucose tolerance test

FIGURE 4

Therapeutic algorithm in IPMN

EUS, endosonography; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; CT, computed tomography

BOX 3

Indications and intervals for monitoring asymptomatic branch-duct IPMN

- Asymptomatic BD-IPMN
- Size < 20 (30) mm
- Pancreatic main duct < 6 mm
- No solid parts of the cyst
- < 10 mm (every 12 months)
- 10–20 mm (every 6–12 months)
- 20–30 mm (every 3–6 months), alternatively resection

of cancers among main-duct tumors (7, 8, 22). The prognosis for resected, non-invasive IPMN is notably better, with a 5-year survival rate of 80–100%, than that of patients with invasive IPMN (5-year survival 40–60%), and, in particular, it is better than for ductal pancreatic cancers (7, 22, e1). Particular attention should also be paid to synchronous ductal pancreatic cancers and extrapancreatic neoplasias.

Conclusion

IPMN are cystic tumors of the pancreas that are diagnosed increasingly often. The confirmation of the diagnosis and differential diagnosis is often difficult. IPMN is a combination of diagnosable precursors of pancreatic cancer, especially in symptomatic IPMN, and comparatively slow growth. This can enable early diagnosis and surgical therapy potentially resulting in cure. Monitoring can be recommended only for small, asymptomatic BD-IPMN. A better understanding of the natural history and tumor biology is needed in order to improve the current recommendations. Especially for patients with BD-IPMN this would be of great importance since individualized therapy might prevent surgery, in a scenario where potential precursor lesions of a pancreatic cancer should be resected in a targeted fashion.

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Conflict of interest statement

Professor Niedergethmann has received expenses from Ethicon and Covidien. The other authors declare that no conflict of interest exists.

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KEY MESSAGES

- Anatomically and prognostically, a distinction is made between main-duct IPMN and branch-duct IPMN.
- The criteria for a potentially malignant growth are main-duct IPMN, male sex, advanced age, tumor size >2 cm, mural nodes in the cyst, symptoms, distension of the pancreatic duct or bile duct, enlarged lymph nodes, positive cytology, CEA>200 in the cyst's contents.
- Surgical resection is the treatment of choice for all main-duct IPMN and larger (>2 cm) branch-duct IPMN.
- Asymptomatic branch-duct IPMN should be monitored every 6–12 months if they are <2 cm and have no solid cystic components.
- The prognosis for non-invasive IPMN is better, with a 5-year survival of 80–100%, than the prognosis for invasive IPMN (5-year survival 40–60%).

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