Intraductal Papillary Mucinous Neoplasms

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Isabella Frigerio, Giuseppe Zamboni, Riccardo Manfredi, Antonio Pea, Silvia Pennacchio, Eugene Lim and Roberto Salvia

5.1 Introduction

After 30 years during which intraductal papillary mucinous neoplasms (IPMNs) were considered to be rare neoplasms of the pancreas, we now know that they represent a specific entity that is seen in daily clinical practice. This awareness has highlighted the need for an improved understanding of pancreatic diseases. In fact, nowadays, IPMNs are the most frequent cystic neoplasm of the pancreas; this is the case ev en in asymptomatic patients, in whom they are detected as an incidental finding [1]. In our experience, IPMNs are one of the most common indications for pancreatic resection.

Since the first report by Ohashi, in 1982 [2], knowledge of this emerging disease has significantly improved, to the extent that it has been included in the classification of exocrine pancreatic neoplasms proposed by the World Health Organization (WHO), beginning in 1996 [3]. The WHO defines IPMNs as intraductal papillary mucinous neoplasms with tall, columnar, mucin-containing epithelium, with or without papillary projections, involving the main pancreatic duct and/or its branch ducts. In the two decades since this description, updates of the WHO classification have been published, first in 2000 [4] and again in 2010 [5]. Consequently, some authors now distinguish two different entities among intraductal neoplasms according to the site of origin: main duct-IPMN (MD-IPMN) and the less-aggressive branch duct-IPMN (BD-IPMN) [6, 7].

The first guidelines on the management of mucinous tumors of the pancreas were developed during a consensus conference held in Sendai, Japan, in 2005.

I. Frigerio (✉)
Surgery Unit, Casa di cura "Dr. P. Pederzoli",
Peschiera del Garda (VR), Italy
e-mail: isifrigerio@yahoo.com

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5.2 Epidemiology

The diagnosis of IPMN has significantly improved in the last 15 years but the true incidence of these neoplasms is unknown. It is clear that IPMNs occurred before 1982, but they were misclassified as mucinous cystic neoplasms or mucinous ductal cancers and probably also misdiagnosed as chronic pancreatitis. The increased incidental diagnosis of these cystic lesions, their unification under the common name of IPMN, and the acceptance by clinicians of this new terminology has enabled an estimation of its incidence in patients undergoing resection, for whom the reported value is around 0.8/10 [8]. A slightly higher incidence in men is widely accepted, while patients undergoing resection are typically in the 6th decade of life, in both men and women [9].

Recently some authors have reported a higher incidence of extrapancreatic neoplasms among patients with IPMNs than in either patients with other pancreatic disorders or in the general population [10, 11]. If we consider patients with pancreatic adenocarcinoma (PADC) and those with IPMN, the risk for colonic adenomatous polyps, Barret's metaplasia, and urinary tract malignancies is significantly higher in the IPMN group. There is no difference regarding malignant tumors that have a high incidence in the general population (skin, breast, colorectal, and lung cancers). A group from the Mayo Clinic was the first to show a higher incidence of malignant and benign neoplasms, the latter being possible precursors of future malignancies. To explain this higher incidence, two hypotheses have been formulated: the increased medical surveillance of patients with IPMN (often incidentally diagnosed), and common genetic or extragenomic risk factors for both IPMN and extrapancreatic neoplasms. Another interesting finding is that the majority of extrapancreatic neoplasms are detected before or coincidently with IPMN. However, before a screening program aimed at the early detection of colonic, esophageal, or urinary malignant diseases in IPMN patients can be established, further data are needed.

5.3 Pathology

As noted above, the new 2010 WHO classification recognizes two different entities: MD-IPMN and BD-IPMN. The former are characterized by involvement of the main pancreatic duct, with or without associated involvement of the branch ducts (combined or mixed IPMNs). MD-IPMN usually presents as a dilated (≥ 1 cm) main pancreatic duct filled with mucus that may extrude through a bulging ampulla. In some cases, this appearance may mimic that of a cyst along the main pancreatic duct. MD-IPMNs are usually located in the proximal portion of the gland (75%) but they can spread to the rest of the main pancreatic duct; BD-IPMNs more commonly involve the uncinate process, even if they have been described in the whole gland, as well as in the head, neck, and distal pancreas. In BD-IPMNs, the side branches of the pancreatic

ductal system are involved. These neoplasms appear as a cystic lesion communicating with a non-dilated main pancreatic duct. The communication might be macroscopically demonstrable or not; this is usually related to the amount of mucus produced.

Multifocal involvement of the gland by two or more BD-IPMNs is not an uncommon finding. In recent years the diagnosis of multifocal IPMNs at our institution has dramatically increased, whereas metachronous IPMN may reflect either multifocality or a "field defect," predisposing the entire ductal epithelium to the development of this neoplasm.

Non-invasive IPMNs are classified into three categories based on the highest degree of cytoarchitectural atypia: low-grade dysplasia, moderate dysplasia, and high-grade dysplasia/carcinoma in-situ. Invasive neoplasms are classified as IPMN with associated invasive carcinoma. At least four cell-types have been described, according to their histology and mucin immunophenotype:

1 MUC2+, CDX2+: intestinal type (Fig. 5.1 a, b)
2 MUC2-/CDX2-/MUC1+: pancreatobiliary (Fig. 5.2 a, b)

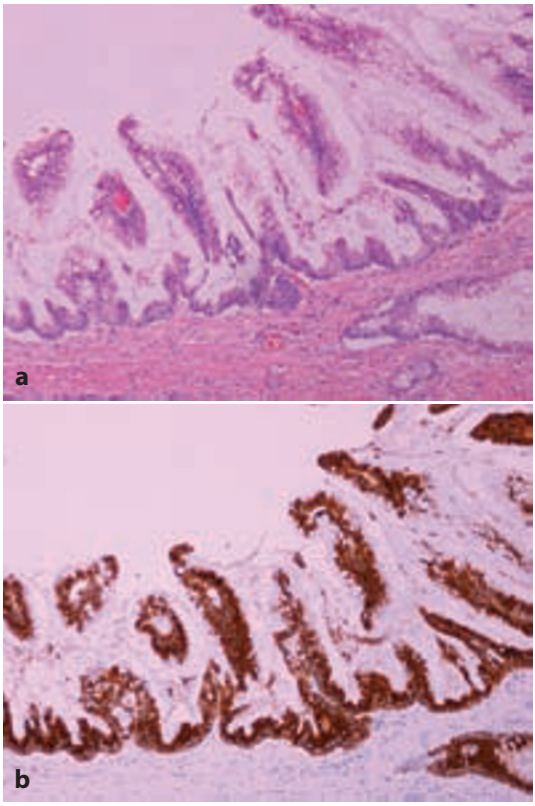

Fig. 5.1 Intraductal papillary mucinous neoplasm (IPMN), intestinal type papillae, with moderate dysplasia (**a**) and MUC2-positivity (**b**)

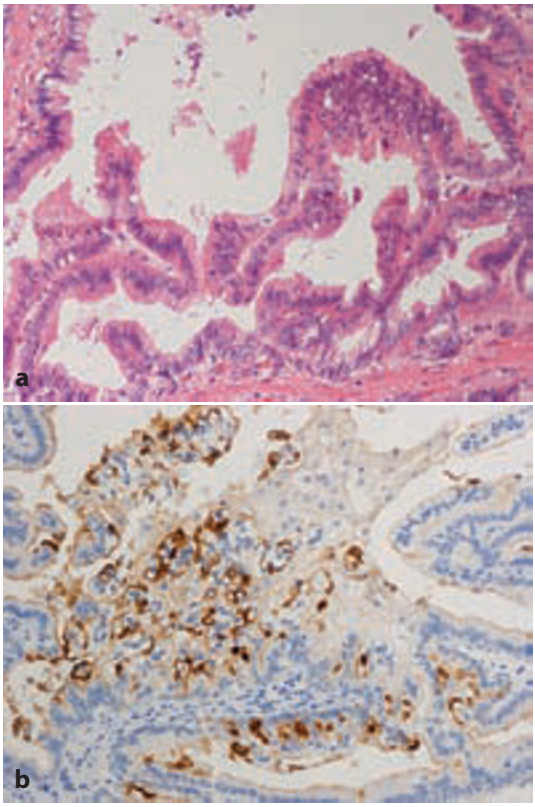

Fig. 5.2 IPMN, pancreatobiliary type papillae, with severe dysplasia (**a**) and MUC1-positivity (**b**)

3 MUC5AC+/ MUC6+ and MUC1-/MUC2-/CDX2-: gastric foveolar type (Fig. 5.3a, b)
4 MUC1+/MUC2+/CDX2-: oncocytic types (Fig. 5.4)

Patients with the first type have a good prognosis while those with the second type have a poorer prognosis. In the third type there is frequent involvement of branch ducts; the fourth type is not yet clinically well characterized.

The invasive component, present in approximately one-third of patients, is either a tubular or a mucinous invasive component. The former resembles the conventional ductal carcinoma (Fig. 5.5), while the latter shows features of colloid (mucinous non-cystic) carcinoma (Fig. 5.6). Although MUC2+ intestinal IPMNs can be considered as precursors of MUC2+ mucinous non-cystic carcinoma, characterized by good prognosis, MUC2-/MUC1+ pancreatobiliary IPMNs appear to be closely associated with an aggressive tubular carcinoma [12, 13]. The progression from benign IPMN to malignancy can be radiologically detected, considering either the increase in the diameter of the main duct or the cyst, or the emergence of a mural nodule [14].

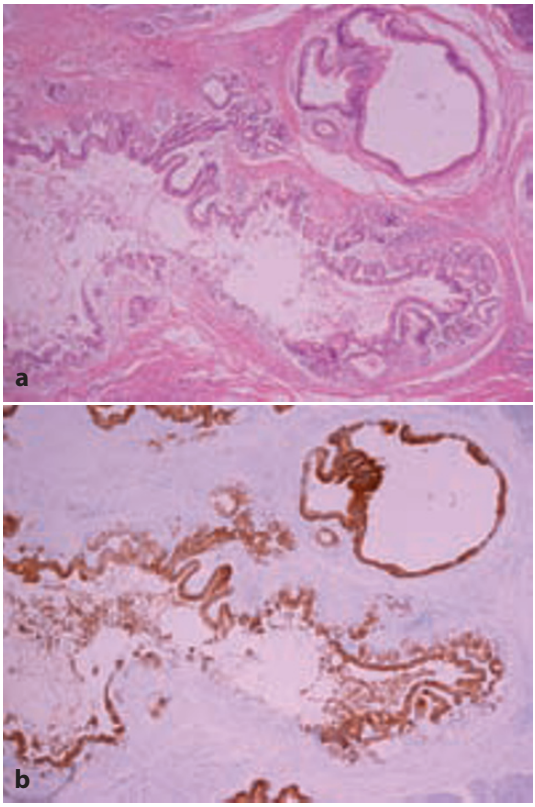

Fig. 5.3 IPMN-branch-duct, gastric type, of the uncinate process, with low-grade dysplasia (**a**) and MUC5AC-positivity (**b**)

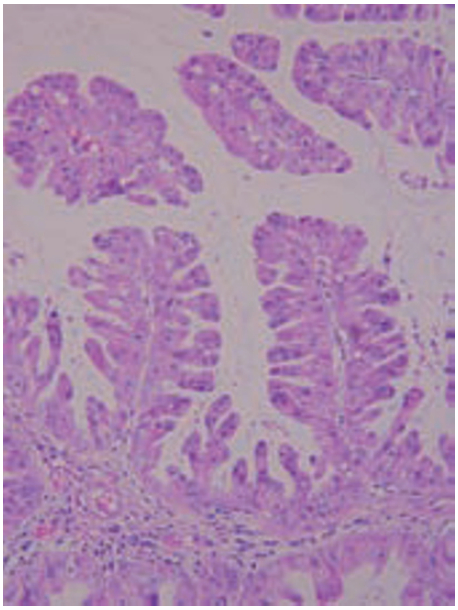

Fig. 5.4 IPMN-oncocytic type. The papillary proliferations are lined by cells with a finely granular cytoplasm and containing nuclei with prominent nucleoli

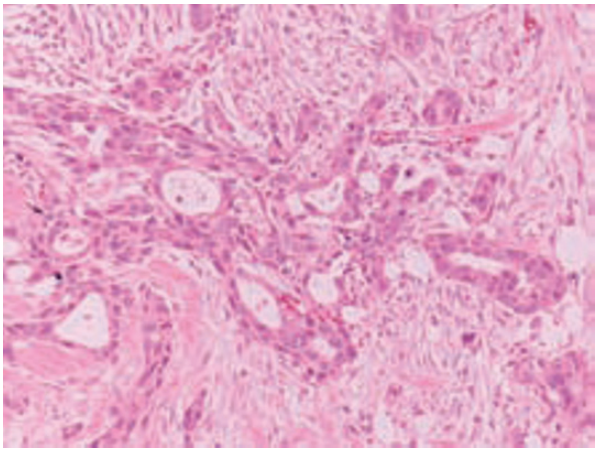

Fig. 5.5 IPMN with tubular-type carcinoma, characterized by infiltrating, irregular tubular structures, similar to those of ordinary ductal carcinoma

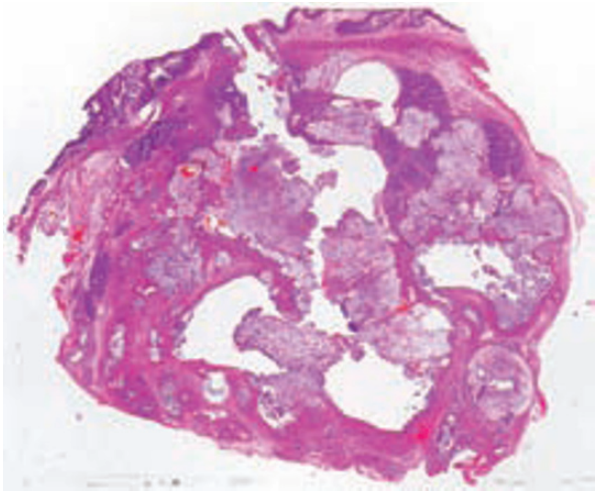

Fig. 5.6 IPMN with "muconodular" carcinomatous transformation. Whole-mount macrosection from a duodenopancreatectomy shows multiple areas of nodular gelatinous carcinomatous tissue

Interestingly, IPMNs can be associated with familial syndromes. For example, they have been detected in asymptomatic family members of patients with familial pancreatic cancer [15], in patients with Peutz-Jeghers syndrome (PJS), with inactivation of the *STK11/LKB1* gene [16], and in association with familial adenomatous polyposis (FAP) [17]. These findings highlight that in patients with IPMN screening for curable pancreatic neoplasia may be possible.

In our experience in collaboration with the Massachusetts General Hospital, among 140 patients with MD-IPMNs who were treated by resection, 12% had adenoma, 28% borderline disease, 12% carcinoma in situ, and 42% invasive carcinoma. Similar data have been reported by other authors [18, 19].

Tanaka et al. found that MD- and BD-IPMNs were associated with malignancy in 70% and 25% of the cases, respectively, while the rate of invasive carcinoma was 43% for MD-IPMN and 15% for the BD type. Thus, these two neoplasms seem to have a significantly different biological behavior, which may influence clinical decision-making with regard to the appropriate management of these two entities.

Moreover, it is not uncommon to recognize different degrees of dysplasia within the same surgical specimen. In our experience, the average age of patients with malignant MD-IPMN is 6.4 years older than that of patients with adenoma or borderline tumor; these observations support the theory of a clonal progression to malignancy in this variant [20].

5.4 Genetics

Regarding the molecular pathogenesis of IPMNs, *KRAS* activating mutations have been identified as an early event that increases in occurrence according to the histological severity of the neoplasm. Mutations in the *KRAS*, *p16*, and *p53* genes are present but are less common in IPMN than in ductal carcinoma, and *DPC4* loss is usually not detected. In a study of 23 cases of resected IPMNs, Wada et al. showed that 65% had a *KRAS* mutation. A loss of heterozygosity (LOH) in 9p21 (p16) increased from 12.5% in adenomas to 75% for carcinomas while LOH in 17p13 (p53) was present only in invasive carcinomas [20]. These results suggest LOH in 9p21 (p16) as an "early" event and LOH in 17p13 (p53) as a later event, providing additional support for a clonal progression process.

A recent report showed that DNA damage checkpoint activation due to *CHK2* inactivation occurs in the early stage of IPMN and seems to prevent its progression whereas p53 accumulation was mostly detected in malignant IPMNs. It was suggested that the DNA damage checkpoint exerts selective pressure on the p53 mutation and that a disturbance of CHK2 inactivation or p53 mutation contributes to the carcinogenesis of IPMNs.

Several other genetic alterations have also been reported in IPMNs. *AKT*/*PKB* and *HER2*/*EGFR* activation has been demonstrated in a large portion of these neoplasms, while *CDKN2A*/*P16* expression is frequently lost, suggesting a correlation with the hypermethylation of the promoter region of P16, more frequently detected in high-grade neoplasms. Some IPMNs show abrogation of *TP53*, especially those with high-grade atypia [21-26]. Despite frequent hemizygous or homozygous deletions of chromosome 18q, *SMAD4* is completely retained in IPMNs [27, 28].

Mutation of *STK11*/*LKB1*, a PJS gene, and the abrogated expression of *DUSP6*/*MKP-3*, a gene identified in the deleted region 12q21-q22, suggest a role for these molecules in the development of a subset of IPMNs [29, 30]. Aberrant hypermethylation of at least one CpG island is detected in about 80% of IPMNs, with the overall number of methylated loci significantly higher in

high-grade tumors. Genes encoding cyclin D2, TFPI-2 and SOCS-1 have been reported as aberrantly methylated in IPMNs [31].

Global gene expression analysis performed for IPMNs revealed that many of the overexpressed genes are also highly expressed in pancreatic ductal adenocarcinomas. In addition, gene expression profiles evidenced the up-regulation of the genes encoding members of the trefoil factor family (TFF1 and TFF3), CLD4, CXCR4, S100A4, and mesothelin. Some of the encoded proteins have been suggested to play a role in the progression to the invasive form of IPMNs [32-34]; among the underexpressed genes in IPMNs, *CDKN1C/P57KIP2* has been shown to be epigenetically down-regulated.

Recent investigations suggest the involvement of the sonic hedgehog (SHH) pathway in the tumorigenesis of IPMN and that SHH measurement of pancreatic juice may provide some advantages in the treatment or follow-up of a subset of patients with these tumors. The study by Ohuchida et al. [35] provides an outstanding survey of the SHH pathway involvement of IPMN, with its possible clinical implications. The involvement of this pathway was further supported by the report of Jang et al. [36] in their study of the immunohistochemical expression of SHH in IPMNs.

Fascin expression was found to be significantly higher in borderline neoplasms and carcinomas than in adenomas, suggesting that overexpression is involved in the progression of IPMNs. Thus, fascin could become a new therapeutic target for the inhibition of IPMN progression or, at least in the short term, a prognostic marker of IPMN [37].

PIK3CA mutations have been reported in 11% of IPMNs, providing evidence that the oncogenic properties of this gene contribute to these neoplasms [38].

Recent results suggest that HTERT expression in epithelial cells is an indicator of malignant transformation in IPMN. Immunohistochemical detection of HTERT in cells derived from pancreatic juice may therefore ´provide a powerful diagnostic tool and, in this case, a marker of the malignant progression of IPMN [39].

MUC4 and MUC5AC were recently evaluated as potential markers in distinguishing more aggressive IPMNs from less malignant ones, in a study by Kanno et al. [40].

5.5 Clinical Presentation

There are no signs or symptoms suggestive of IPMNs. Patients with MD-IPMN are more often symptomatic, complaining of abdominal pain, pancreatitis, steatorrhea, jaundice, diabetes, or weight loss [41]. Even though some patients with BD-IPMN may present with the above-described symptoms, most are asymptomatic and the neoplasms are incidentally detected during a radiological work-up performed for unrelated problems [42, 43].

It is remarkable that, unlike in pancreatic adenocarcinoma, jaundice is an

uncommon presentation of IPMN and occurs only in 15–20% of patients. Jaundice and steatorrhea at presentation are a cause for concern as together they are associated with a much higher incidence of malignant IPMN (8- and 5- fold, respectively). A recent onset or worsening of diabetes is more common in patients with IPMNs with invasive carcinoma (3-fold). In our experience, patients with benign IPMNs had a higher frequency of abdominal pain and a longer duration of symptoms.

5.6 Diagnostic Work-up

Previously, Ohhashi's triad, consisting of a bulging ampulla of Vater, mucin secretion, and dilated main pancreatic duct, was an indicator of IPMN. Today, the great majority of IPMNs are characterized on cross-sectional imaging study, such as computed tomography (CT) or magnetic resonance cholangiopancreatography (MRCP). The radiological and endoscopic features of IPMNs vary according to the morphologic type of the neoplasm. The typical feature of MD-IPMNs is dilatation of the main pancreatic duct > 1cm (Fig. 5.7), eventually extending into the secondary branches, which may appear as cysts (Fig. 5.8). The dilatation can involve the duct of the distal pancreas or, if it is located in the head or in the uncinate process, may be present throughout because of an obstructive effect. BD-IPMN appears as cysts or a cluster of cysts without dilatation of the main duct and is more commonly located in the head-uncinate process. Between 39% and 64% of BD-IPMNs are multifocal (Fig. 5.9a, b).

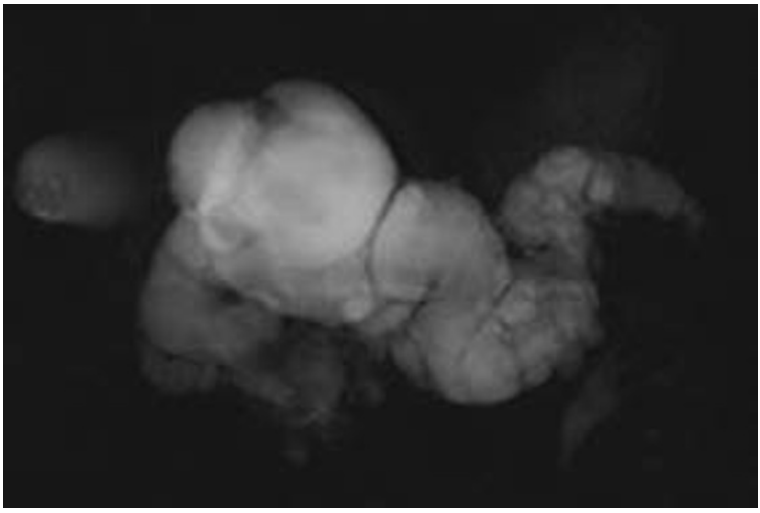

Fig. 5.7 Main pancreatic duct IPMN (MD-IPMN). Coronal magnetic resonance cholangio-pancreatography (MRCP) shows diffuse dilatation of the main pancreatic duct due to the involvement of the entire pancreatic ductal system

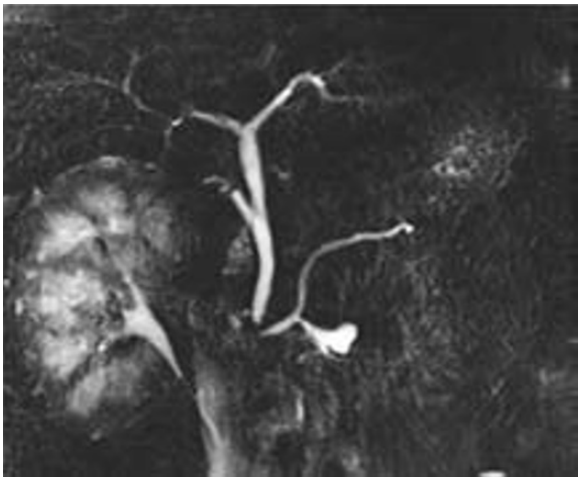

Fig. 5.8 Side-branch IPMN (SB-IPMN). Coronal MRCP shows a cystic dilatation of a side branch in the head of the pancreas, connected with the Wirsung duct

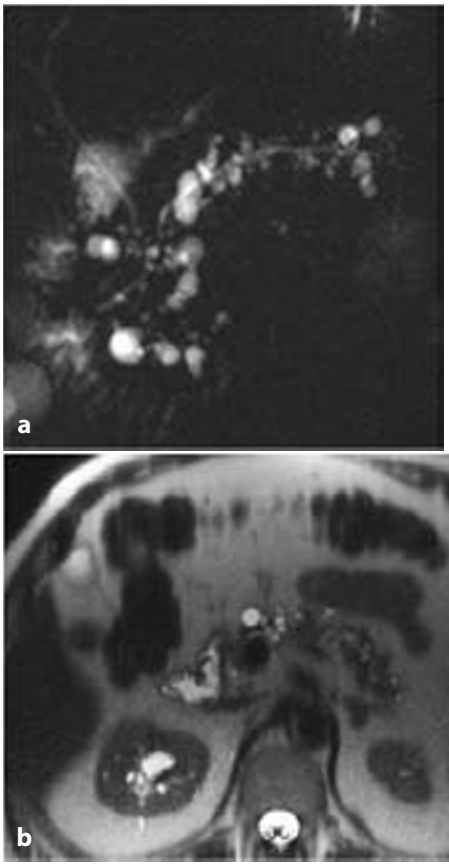

Fig. 5.9 Multifocal SB-IPMN. Coronal MRCP shows a cystic dilatation of multiple side branches located along the whole pancreas (**a**). Axial T2-weighted image shows the connection between the cystically dilated side branches and the main pancreatic duct (**b**)

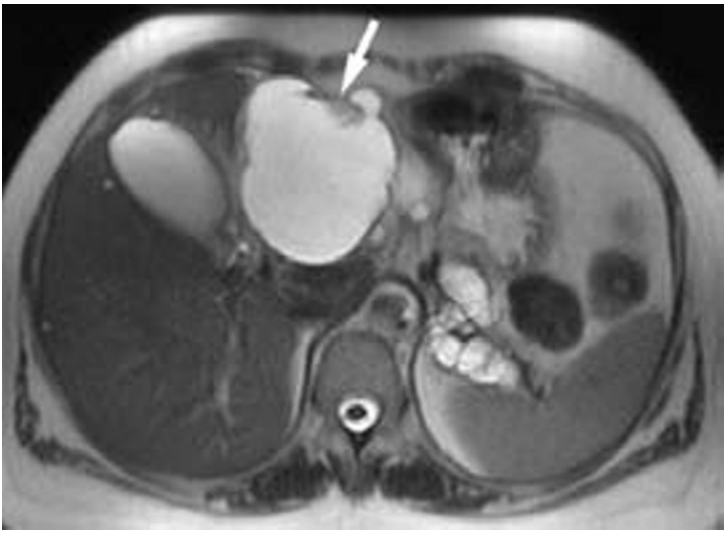

Fig. 5.10 MD-IPMN: mural nodule. Axial T2-weighted image shows dilatation of the main pancreatic duct, with a mural nodule on the non-dependent wall of the duct (*arrow*), indicative of malignant IPMN, which was surgically confirmed

Calcifications are detected in 11% of cases. Nodules and papillary projections, which are significantly associated with the presence of a malignant neoplasm, usually appear as filling defects within the cystic lesions (Fig. 5.10). The pancreatic gland may be enlarged, with signs of pancreatitis, or it may be atrophic. CT and MRCP can localize the tumor and assess its relationship with nearby vessels and other organs. MRCP is particularly useful in the characterization of single or multifocal BD-IPMNs, given the ability of this imaging technique to demonstrate a communication between the main duct and the cyst.

At our institution, in the initial assessment of patients with suspected IPMN we additionally use contrast-enhanced ultrasound (US), which is able to identify and characterize the "cysts" in detail [44].

In those cases in which the diagnosis is uncertain, endoscopic ultrasound (EUS) may be helpful, as it can well identify the dilated main pancreatic duct. In addition, EUS demonstrates the morphological details of any solid component, nodules, or small projections, in the main duct and/or in the cyst communicating with it. EUS is also a safe method for fluid sampling and targeted biopsies by fine-needle aspiration or core biopsy. Examination of fluid sampled from an IPMN provides diagnostic information about the tumor, revealing its viscous aspect, the presence of mucin or mucinous cells, and carcinoembryonic antigen levels [45]. However, it is important to keep in mind that the puncture is done through the gastric or duodenal wall, potentially allowing the needle to carry tumor cells.

Cytologic examination of the pancreatic juice and the subsequent detection of a *KRAS* mutation can also be helpful and, to a limited extent, may predict the likelihood of malignancy, even though this procedure has a low sensitivity (< 20%). More recent work has shown that high-grade atypia on cytology has a sensitivity of 72% for malignancy for all mucinous cysts (mostly IPMN) [46]. We consider EUS as a second-level procedure that should be performed only in selected cases.

In recent years, intraductal endoscopy and/or peroral pancreatoscopy have been introduced but experience is limited and further studies are needed.

Blood tests that include tumor markers are mandatory, with measurements of CEA, Ca19-9, and Ca125.

Clinical history, radiology, and endoscopy should contribute to obtaining a correct diagnosis of IPMN and to differentiate it from other cystic neoplasms, such as serous cystadenoma or mucinous cystic neoplasms, and from other cystic lesions of the pancreas (pseudocyst, true pancreatic cyst). Once IPMN is identified, the following step is the differential diagnosis between MD- and BD-IPMN and the determination of those parameters associated with a high risk of malignancy. Jaundice, steatorrhea and new or worsening diabetes should raise suspicion for degeneration. A lesion > 30 mm in diameter, a dilated main pancreatic duct (> 10 mm), and the presence of nodules, thick walls, or papillary projections are morphological aspects that should always alert clinicians [47].

5.7 Management

During the consensus conference held in Sendai in 2005, a group of surgeons, gastroenterologists and pathologists edited the first guidelines pertaining to the management of IPMNs. Before 2005, all patients with a diagnosis of IPMN were considered to be at risk of developing malignancy, and therefore surgery was always proposed. Since the Sendai meeting, two different approaches have been defined when considering MD-IPMN (including the mixed form) and BD-IPMN.

5.7.1 Main Duct-IPMNs

Patients with MD-IPMN or the mixed form, when surgically fit, should always be candidates for resection because of the high prevalence of in situ and invasive carcinoma found in resected specimens (70%). Of note is the observation that in patients with MD-IPMNs there may be malignancy regardless of the presence or absence of symptoms. Accordingly, the radiological aspect of these lesions can determine the indication for surgery.

The surgical management of MD-IPMNs is challenging. While in other pancreatic tumors preoperative imaging can accurately locate the tumor and

thereby allow the planning of a pancreatic resection, this is not always the case in MD-IPMNs. Segmental dilatation of the main duct, as seen on preoperative studies, may occur both proximal and distal to the tumor, because of mucus overproduction. In such case, localization of the neoplasm is more difficult.

A typical resection (pancreaticoduodenectomy, left pancreatectomy, total pancreatectomy, according to the site and extension of the disease) with lymph node dissection is mandatory. Limited resections, such as middle pancreatectomy, have been proposed for MD-IPMN, but in our experience with MD-IPMN patients this results in a high rate of positive resection margins and recurrences, with similar results reported by other authors [48]. Consequently, in this setting we recommend standard resections. Since IPMN extends along the pancreatic duct and may do so without macroscopic tumor, it is important to exclude residual tumor on frozen section [49].

Three different aspects of the ductal mucosa can be detected by analyzing the surgical margin: (1) normal ductal epithelium in the main duct means that radical resection has been achieved; (2) de-epithelialized or a denuded epithelium should not be considered as a negative margin since local recurrence is also possible; (3) adenoma, borderline, or carcinoma requires an extension of the surgical resection up to total pancreatectomy.

In cases of de-epithelialization, adenoma, or borderline tumor at the surgical margin, the optimal surgical strategy is controversial: we usually extend the resection by a few centimeters to obtain a new margin, aiming to achieve a negative resection margin. In our experience involving 140 patients with MD-IPMN who underwent surgical resection, the rate of negative margins in the surgical specimen was 58.5%, and the results of the intraoperative frozen section analysis modified the surgical plan, leading to an extension of the resection or to total pancreatectomy in 29 patients (20.7%) [50].

Recurrence in the pancreatic remnant may develop even if the transection margin is negative and even in patients with noninvasive disease. The presence of a positive resection margin, multicentric IPMNs with synchronous skip lesions along the main duct that are still present (but not detectable) at the time of surgery, and metachronous lesions (given that IPMN may be a marker of a "field defect" associated with a propensity for tumor development) may explain recurrence in the pancreatic remnant after the resection of a MD-IPMN.

For all these reasons, the role of total pancreatectomy in IPMN must be carefully evaluated and tailored to each single patient. Some authors have reported that for malignant IPMNs the frequency of recurrence (local recurrence or distant metastases) is similar whether or not total pancreatectomy is performed [51, 52]; Chari et al. reported a recurrence rate of 62% after total pancreatectomy and of 67% after partial pancreatectomy [19]. The risks and long-term complications of total pancreatectomy must be considered and discussed with patients. Finally, in patients with MD-IPMN undergoing pylorus-preserving pancreaticoduodenectomy, pancreaticogastrostomy may be preferred instead of pancreaticojejunostomy because it allows direct endoscopic

access to the pancreatic stump during follow-up, leaving open the possibility of pancreatic juice sampling for cytological examination [53].

5.7.2 Branch-Duct IPMNs

The prevalence of malignancy is much lower (25%) in BD-IPMNs than in MD-IPMNs and it is predictable on the basis of symptoms, tumor size, and morphological criteria. Thus, a strict follow-up is advocated for patients with BD-IPMN < 3 cm, with no nodules or duct dilatation (which would imply a combined IPMN). Follow-up consists of MRCP repeated 6 months after the first diagnosis and then yearly, together with measurement of Ca19-9 levels, unless there is an increase in size, the development of nodules, or the onset of symptoms. It should be emphasized that this non-operative approach should be carried out in experienced centers and that data from large series are still needed for its validation (Fig. 5.11a, b).

In our earlier experience of 109 patients with BD-IPMN [54], 20 patients (18.3%) underwent immediate surgery because of the presence of symptoms

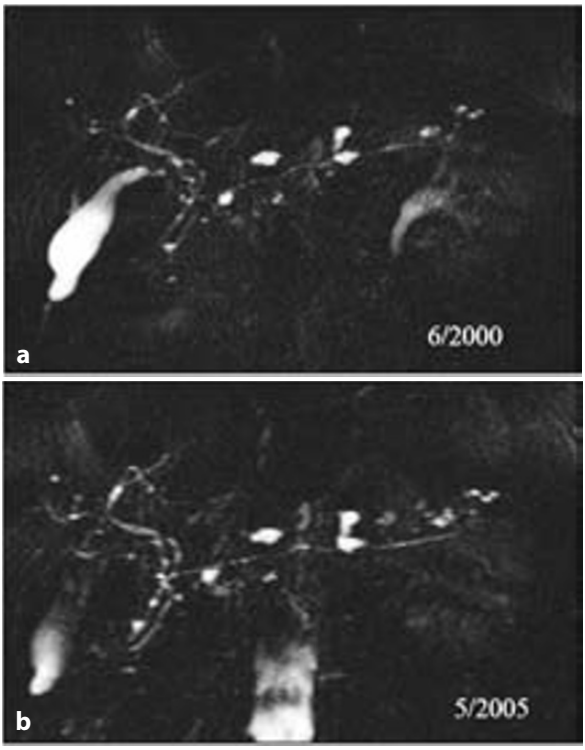

Fig. 5.11 SB-IPMN evolution. Coronal MRCP obtained in June 2000 shows multifocal side-branch IPMNs. The number and size of the dilated side branches were unchanged in May 2005

and/or parameters associated with malignancy. A pathological diagnosis of BD-IPMN was always confirmed; an invasive carcinoma was diagnosed in two patients (10%) and a carcinoma in situ in one (5%). Eighty-nine patients (81.7%) were followed for a median of 32 months. After a mean follow-up of 18.2 months, in five patients (5.6%) an increase in size of the lesion was determined and surgery was performed. The pathological diagnosis was branch-duct adenoma in three patients and borderline in two. None of the patients had malignant changes on follow-up. This study suggests that in very selected cases a non-operative approach is safe and feasible. It also provides further evidence that the biological behavior of BD-IPMN is different than that of the main-duct type.

Other authors have described similar experiences in the conservative management of BD-IPMN. Cauley et al. [55] followed 244 patients with BD-IPMN (described as low risk IPMN); in this group, 32 patients (12%) developed a new indication for resection and two (1%) developed invasive cancer during a mean surveillance of 35 months. No patient with an increasing size of the cyst developed malignancy. In a follow-up of 103 patients, Sawai et al. [56] reported that progression to invasive cancer occurred in 3.9%.

With more data emerging in the literature, it appears that cyst size does not correlate well with the risk of malignancy [57, 58]. The threshold of 3 cm for observing BD-IPMN is currently under scrutiny. According to Markov-based normograms in guiding the indication for surgery, a cyst size > 2 cm favours overall survival regardless of quality of life (QOL), but with a QOL-adjusted survival a 3-cm threshold is more appropriate [59]. This has prompted calls for a review of the Sendai criteria for observing BD-IPMNs. The Heidelberg unit has suggested that only BD-IPMN cysts < 1–1.5 cm should be observed for surgically fit patients [60]. Clearly, controversies remain regarding the best treatment strategies for patients with BD-IPMNs [61]

In terms of the surgical approach, a typical resection should be performed for BD-IPMNs. For asymptomatic patients with a small single lesion (< 3 cm) at the neck of the pancreas, without any suspicion for malignancy, a middle pancreatectomy is an option. In the case of multifocal disease, a total pancreatectomy or an extended standard resection ensures radical treatment; however, a more selective approach can be considered, with segmental resection of the largest lesion (or of the lesion "suspected" of malignancy) and non-operative management with strict follow-up of the remnant BD-IPMN.

Indications for surgery in multifocal BD-IPMN follow the same rules as established for uni-focal BD-IPMN: symptomatic patients and suspicion of malignancy.

5.7.3 Combined IPMNs

The origin of the mixed form of IPMNs is unknown; that is, whether they originate from MD-IPMN or arise as a combined form. Regardless of their patho-

genesis, their biological behavior is known to be similar to that of MD-IPMNs and their treatment follows the same rules: high risk of malignant change and, for all surgically fit patients, an indication for surgery [62].

5.8 Post-operative Follow-up

After resection, strict follow-up is necessary. Patients with malignant IPMN have an obviously higher risk of recurrence, but neoplastic recurrence can arise even in the presence of a benign tumor with negative resection margins, particularly for MD-IPMNs. It is important to detect a recurrence or the development of a new disease in the remnant since this is an indication for a second resection. In our experience with 140 patients with MD-IPMN who underwent resection, eight (7%) developed a recurrence in the remnant. Of these, seven had invasive carcinoma at initial histology and one had an adenoma with negative resection margins; this patient underwent a completion pancreatectomy for carcinoma in situ.

In our opinion, clinical examination, biochemical assessment, and US, CT, or MRCP—performed every 6 months in patients with malignant tumors and yearly for those with benign IPMNs—offers a safe follow-up approach. In patients with multifocal BD-IPMN treated by partial pancreatectomy, strict follow-up should be performed to evaluate the remnant gland or lesions in the remaining pancreas and the eventual development of new lesions. MRCP is particularly useful in this setting [63].

5.9 Prognosis

The survival of patients with IPMN, even when malignant and invasive, is always better than that of patients with pancreatic ductal adenocarcinoma. In our experience, based on a follow-up of 137 patients treated by resection, 5- and 10-year disease specific survival (DSS) for 80 patients with adenoma, borderline, and in situ carcinoma was 100%, while for 57 patients with invasive carcinoma the DSS was 60% and 50%, respectively. In another large series, the 5-year DSS for patients with IPMN with invasive carcinoma ranged from 36% to 43% [64].

In a recent study [65] based on a multivariate analysis, we identified three independent factors associated with poor prognosis in invasive IPMN carcinoma: Ca19-9 value > 37 U/ml (adjusted for jaundice), a family history of pancreatic cancer, and a lymph node ratio (LNR) > 0.2. These three factors are associated with a 5-year survivals of 44.2%, 16.7%, and 11%, respectively. However, it is still difficult to define the impact on clinical practice of these prognostic factors. Only a family history and Ca19-9 levels can be determined preoperatively and are therefore able to influence decision-making, for example, in those patients with BD-IPMN in whom surgery may not be the first

option. Our current strategy is to recommend early surgery for patients with high-risk lesions; the early detection of signs of malignancy or recurrence may be prognostically beneficial for these patients.

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