REVIEW AND PERSPECTIVE

Pancreatic intraductal papillary-mucinous neoplasms: a new and evolving entity

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Abstract For a long time, intraductal tumors of the pancreas were neglected because they were misdiagnosed as mucinous cystadenocarcinoma, ordinary ductal adenocarcinoma, or chronic pancreatitis. Only in recent years have they been recognized as clinical and pathological entities. Most common are the intraductal papillary-mucinous neoplasms. Although they show an adenoma-carcinoma sequence, they have proved to have a more favorable prognosis than ductal adenocarcinoma, when resected in a preinvasive state. Recently, it has become clear that they constitute a heterogeneous group with at least four subtypes. Their stratification reveals that the various intraductal papillary-mucinous neoplasm subtypes have different biological properties with different prognostic implications.

Keywords Intraductal papillary mucinous neoplasm · Pancreas · Outcome

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Historical notes and a rising incidence

The pancreatic tumors that are characterized by an intraductal origin and growth pattern include intraductal papillary-mucinous neoplasms [3, 24, 41], intraductal tubular carcinomas [22, 45], intraductal tubular adenomas of the pyloric type [6], and intraductal acinar cell carcinomas [15]. Most common are the intraductal papillary-mucinous neoplasms (IPMNs). They are mucin-producing epithelial tumors that usually show a papillary architecture and are associated with dilatation of the ducts. Before 1990, these tumors were thought to be rare. They first started to be recognized approximately 20 years ago [31, 36, 39], when the many different names given to the tumor in the 1980s were replaced by the term IPMN [41]. This name was also introduced in the classification of exocrine pancreatic tumors propagated by the World Health Organization (WHO) [24] and the fascicles of the Armed Forces Institute of Pathology [44]. Since then, IPMNs have been reported with increasing frequency (Table 1) and currently account for about 7% of clinically diagnosed pancreatic neoplasms and up to 16% of surgically resected pancreatic neoplasms and for almost 50% of pancreatic cysts found incidentally [8, 17]. When only the cystic tumors of the pancreas are considered, IPMNs take first place, with a frequency of 24% [26].

The new incidence data on IPMNs raise the question whether their increase in number is real or not. Of course, it is difficult to accept that IPMNs might have been overlooked in the past, not only clinically but also morphologically. There are good reasons, however, to believe that IPMNs did always exist and did not really increase in frequency. One reason is related to the rapid improvements in modern imaging techniques, which enable more precise recognition of cystic lesions, even if they are small and

Table 1 Incidence data on intraductal papillary-mucinous neoplasms

Author	Period 1	Number of incidence	Period 2	Number of incidence
Sohn et al. [43]	1987–2001	58	2001–2003	78
Wada et al. [47]	1988–2000	63	2001–2003	37
Our series	1981–2000	55	2001–2007	50

asymptomatic. Another is connected with the decreasing risk of pancreatic surgery. The most important fact, however, may be that until 1999, the distinction between IPMNs and mucinous cystic neoplasms (MCNs) was unclear, so that many IPMNs were classified as MCNs [50] or regarded as ductal adenocarcinomas or chronic pancreatitis.

Adenoma-carcinoma sequence

In IPMNs, the normal ductal epithelium is replaced by mucin-producing columnar cells showing papillary proliferations and variable degrees of cellular atypia, even within an individual neoplasm. They are graded according to the most atypical area as IPMN with low grade dysplasia (adenoma), IPMN with moderate dysplasia (borderline), and IPMN with high grade dysplasia (carcinoma in situ). An invasive component may be found in 38–50% of the cases [7, 26, 40, 43]. Progression from adenoma to carcinoma is estimated to occur at about 5 years [43]. IPMNs therefore provide a model of neoplastic progression from a benign intraductal neoplasm through increasing grades of dysplasia to invasive carcinoma.

Prognosis after resection

Between 80 and 90% of IPMNs are surgically resectable. For these IPMNs, a 5-year survival rate of 77–100% was reported, provided the tumors did not have an invasive component (Table 2). By contrast, IPMNs with an invasive component had a 3- to 5-year survival rate of only 36–46% [12, 16, 43] (Table 2). Interestingly, the survival rate did not

appear to be dependent on the grade of dysplasia in the IPMN if there was no invasive component [12, 16, 43, 47]. These data imply that the overall outcome of IPMNs therefore largely depends on the presence of an invasive component. If the tumor is already invasive, criteria for a poor outcome are lymph node involvement, vascular invasion, and bilirubin elevation [13]. A comparison of the prognosis of all patients with invasive IPMNs with that of patients with ductal adenocarcinoma reveals that patients with IPMNs survive longer than those with ductal adeno-carcinomas [29, 40, 43].

Several studies have reported recurrences after resection of noninvasive IPMNs, some of which revealed only moderate dysplasia [12, 43, 47, 48]. The recurrences were either local or metastatic (Table 2). To explain the recurrences, particularly the local ones, it has to be assumed that either tumor tissue was overlooked at the pancreatic resection margin, or an invasive component remained undetected in the resected specimen, or there was multifocal disease. The last possibility has to be considered if the surgical margins were negative and the recurrence occurred in the pancreatic remnant. This has been observed only in a few cases [40]. When metastatic recurrences occur, it is most likely that they resulted from inadequate sampling that failed to detect an invasive component. Regarding the impact of a positive resection margin on IPMN recurrence, it is interesting to note that it has been reported that even IPMNs with positive margins did not recur during a median follow-up period varying from 19–40 months [13, 48]. The reason for this phenomenon might be that the growth of the remaining intraductal tumor tissue is so slow that clinical symptoms

Table 2 Five year survival rate and recurrence in 349[a] intraductal papillary-mucinous neoplasms

	Noninvasive 77–100%	Invasive 36–46%
No recurrence	93–98.7%	52–70%
Recurrence	1.3–7%	30–48%
Local	up to 6%	8–48%
Distant (metastases)	1%	12%
Both	0%	10–48%

[a] [12, 43, 47]

Table 3 Histopathological data on 105 intraductal papillary-mucinous neoplasms collected during a period of 26 years

IPMN	Gastric (n=27) (26%)	Intestinal (n=57) (54%)	Pancreatobiliary (n=7) (7%)	Oncocytic (n=14) (13%)
Noninvasive (65%)	n=20 (74%)	n=35 (62%)	n=3 (43%)	n=10 (72%)
Adenoma	9	12	1	5
Borderline	7	18	2	1
Carcinoma in situ	4	5	0	4
Invasive (35%)	n=7 (26%)	n=22 (38%)	n=4 (57%)	n=4 (28%)

Fig. 1 Histological subtypes of intraductal papillary-mucinous neoplasms of the pancreas and their usual mucin pattern. **a**, **b** IPMN of the intestinal type positive for MUC2; **c**, **d** IPMN of the pancreatobiliary type positive for MUC1; **e**, **f** IPMN of the oncocytic type showing scattered positivity for MUC2; **g**, **h** IPMN of the gastric type, positive for MUC5
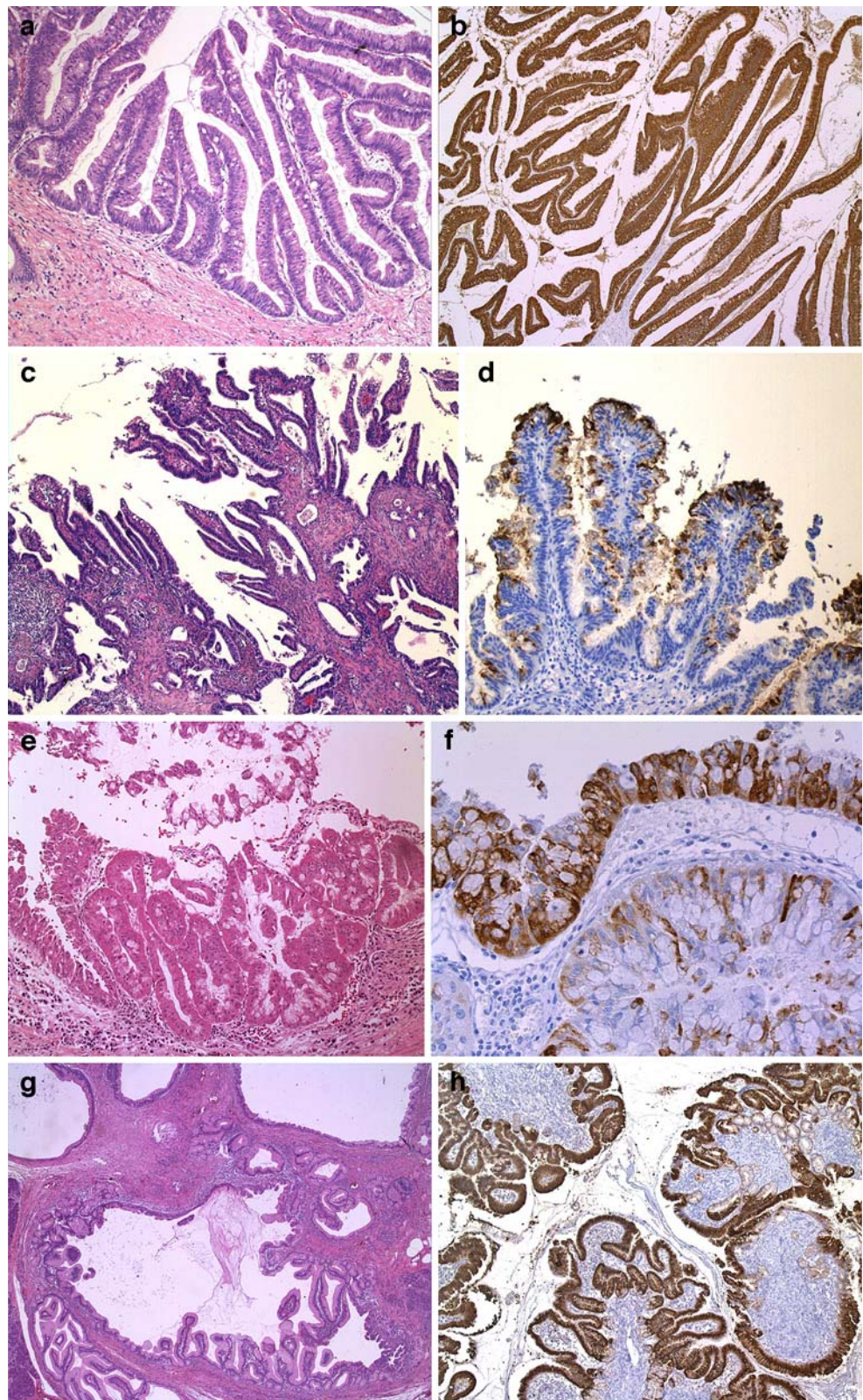

only appear after a follow-up period of 2 to 3 years. However, even if intraductal recurrences may take a long time to become clinically apparent, a positive margin in any IPMN case should lead to further tissue resection.

Histological type and prognosis

In 1991, it was reported that the invasive component of IPMNs corresponded either to an ordinary ductal adeno-

Fig. 2 IPMN of the gastric type showing severe cellular atypia and MUC5 positivity
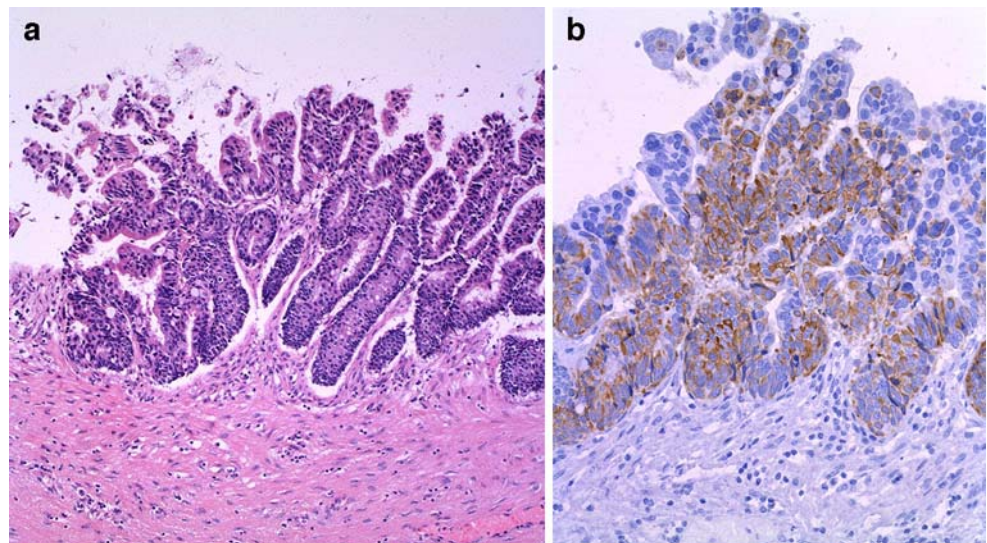
carcinoma or, more frequently, to that of a mucinous (colloid) carcinoma [49]. This observation suggested that IPMNs form a group of heterogeneous neoplasms. A further argument for the heterogeneity of IPMNs was the detection of IPMNs in branch ducts rather than in the main duct, where most of the IPMNs are found. Finally, it was recognized that IPMNs differ in their histological and cytological features and in their mucin profile [3, 4, 18, 28, 32, 33]. Currently, four subtypes of IPMN can be distinguished: an intestinal type, a pancreatobiliary type, an oncocytic type, and a gastric type [18].

The most common type of IPMN is the intestinal type (Table 3). It usually occurs in the main duct of the pancreatic head [9] and shows a villous growth pattern similar to that of villous adenoma in the colon. It also expresses MUC2 and CDX2 but not MUC1 (Fig. 1a,b). When this IPMN type becomes invasive, the invasive component resembles mucinous (colloid) carcinoma [5,

28], a tumor of which at least 80% is composed of pools of extracellular mucin containing single cells or strands of neoplastic glandular epithelium or even a small component of signet ring cells. Patients with colloid carcinoma have a 55% 5-year survival rate after resection [5]. These tumors therefore seem to be much less aggressive than ordinary ductal adenocarcinomas.

The pancreatobiliary type of IPMN is much rarer than the intestinal type IPMN (Table 3). It shows complex arborizing papillae and expresses MUC1 only (Fig. 1c,d). Its invasive component usually corresponds to a conventional ductal adenocarcinoma. The prognosis of this type of IPMN, if invasive, seems to be similar to that of ductal adenocarcinoma and therefore poorer than that of the intestinal type of IPMN [4].
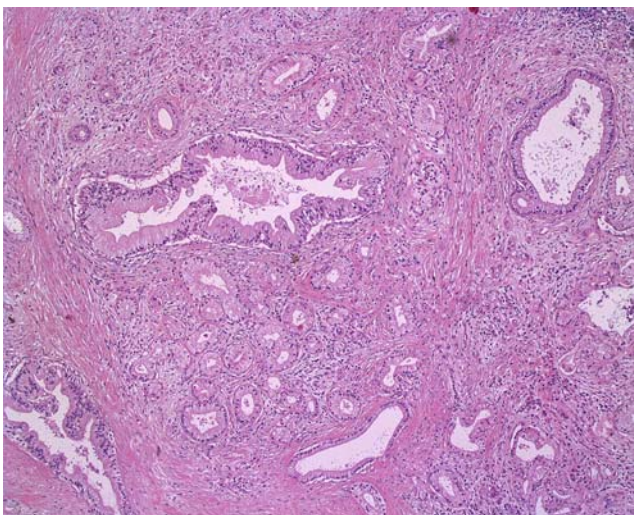

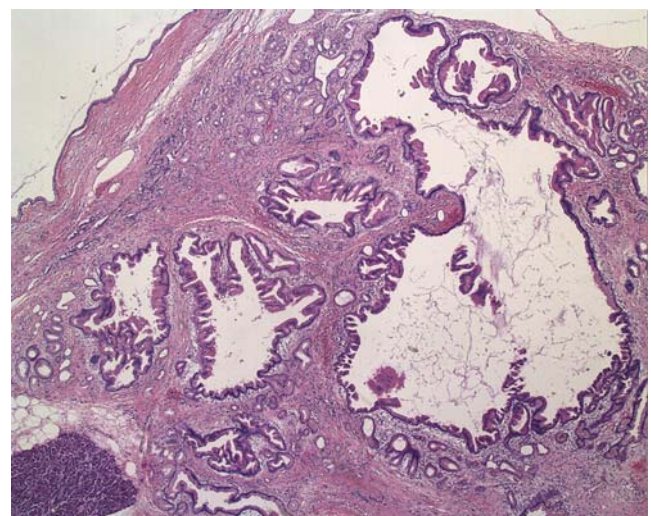Fig. 3 PanIN-1 lesion associated with lobular fibrosis

Fig. 4 Small multicystic duct-associated lesion in the periphery of pancreatic tissue suggestive of an IPMN of the gastric type but difficult to distinguish from a large PanIN-1 lesion

The oncocytic type of IPMN (also called intraductal oncocytic papillary neoplasm [2]) shows the same complex papillae as the pancreatobiliary type, but the lining cells reveal strongly eosinophilic cytoplasm. In addition, there are often numerous goblet cells. The tumor cells express MUC1 and MUC2 inconsistently (Fig. 1e,f). With fewer than 20 cases reported in the literature to date [2, 20, 34, 35, 37, 38, 42], the clinical and pathological behavior of this type is still unclear. Most of the cases (94%) were diagnosed as carcinoma, some of them with an invasive component or even distant metastases [37]. As the follow-up in this patient group is very short, no relevant data are available yet on survival and outcome.

The gastric type of IPMN exhibits papillary projections lined by epithelial cells resembling gastric foveolar cells and shows pyloric gland-like structures at the base of the papillae. These cells express MUC5 (Fig. 1g,h), while MUC1, MUC2, or CDX2 positivity is only occasionally observed. The gastric type of IPMN corresponds to the branch duct type, which occurs in the periphery of the pancreatic parenchyma, most often in the uncinate process, where it usually presents as a multicystic lesion with cysts no larger than 3 cm [9]. The gastric type seems to be less aggressive, i.e., less invasive, than the other IPMN subtypes [10, 25, 33, 46] but may show severe cellular atypia in a few cases (up to 25%) [46] (Table 3, Fig. 2) The size of the lesion was unrelated to the grade of cellular atypia [46].

Interestingly, pancreatic intraepithelial neoplasia (PanIN)-like complexes are frequently observed next to gastric type IPMNs. This raises the question whether IPMNs of the gastric type are a focal accentuation of a diffuse disease rather than a localized lesion. They might therefore also be related to the small peripheral cystic changes described by Kimura et al. [21] in non-neoplastic pancreata or the patchy lobular fibrosis associated with PanIN-1B lesions described by Detlefsen et al. [14] (Fig. 3). If this were the case, IPMNs of the gastric type would actually be large PanIN-1 lesions. An argument for this assumption is that both IPMNs of the gastric type and PanIN-1 lesions stain for MUC5 in the absence of MUC1 and MUC2 positivity. This assumption would also explain why it is difficult to distinguish PanIN lesions from some IPMNs [27] (Fig. 4), despite a consensus definition of both lesions [19].

Although the malignant potential of IPMNs of the gastric type seems to be rather low, it has to be pointed out that the fibrocystic changes that have been described in pancreata removed from patients with a strong family history of pancreatic cancer [11, 30] are similar, if not identical, to IPMNs of the gastric type and their associated PanIN lesions. This implies that IPMNs of the gastric type/ PanIN-1 lesions are not innocuous lesions but have a malignant potential.

Summary and perspectives

The significance of IPMNs among the pancreatic tumors has increased greatly in recent years because of their improved recognition, both clinically and histopathologically and their much better prognosis than ordinary ductal adenocarcinomas. Moreover, they appear to fall into four subtypes that have special biological properties with prognostic implications. Of particular interest in relation to the development of ductal adenocarcinomas is the fact that the so-called gastric type IPMNs seems to occur in pancreata from patients with a strong family history of pancreatic cancer. Furthermore, it is of interest that the pancreatic IPMNs have their counterparts in IPMNs of the biliary duct system, where the same subtypes may occur [1, 23, 51, 52]. The treatment of choice is resection, but future trials may reveal that the extent of resection could depend on the IPMN subtype.

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