Chapter 9
Development of Pancreatic Carcinoma in IPMN Patients

Masao Tanaka

Abstract Patients with IPMN may synchronously or metachronously develop pancreatic ductal adenocarcinoma (PDAC) which is distinct from the IPMN. The idea of concomitant carcinoma emerged from an experience of a carcinoma in situ incidentally diagnosed by preoperative pancreatic juice cytology in a patient with a benign small branch duct (BD)-IPMN. Since then, many retrospective and prospective analyses reported the frequency of 1.9–9.2 % in various series of IPMN. The yearly incidence of concomitant PDAC has been reported to be 0.41–1.1 %. Patients at the age of >70 years and with a smaller size of BD-IPMNs and main pancreatic duct are more susceptible to the development of PDAC. The topological relationship and histological transition have been proposed for differentiation of distinct PDAC from invasive IPMN, but distinction is sometimes difficult. PDACs may frequently arise in patients with benign gastric-type IPMN in the absence of *GNAS* mutations, and so *GNAS* mutations might be useful in this context. Both of concomitant PDAC and invasive IPMN may be characterized by more favorable biological behaviors or be diagnosed earlier than ordinary PDAC. Worsening diabetes and elevation of CA 19-9 have been suggested to predict the presence of concomitant PDAC, but more sensitive markers are needed. The pancreas after resection of IPMN or concomitant PDAC is still at risk of metachronous development of PDAC. The presence of IPMN in the pancreas seems to pose the entire organ at increased risk for developing carcinoma, and then surveillance of the entire pancreas is needed to detect distinct PDAC.

Keywords Branch duct type • Concomitant pancreatic ductal adenocarcinoma • Intraductal papillary mucinous neoplasm • Malignant transformation • Pancreatic cancer

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9.1 History

Patients with IPMN develop pancreatic carcinoma in two ways. One is well-known malignant transformation of IPMN per se and the other is the development of distinct pancreatic ductal adenocarcinoma (PDAC) in the pancreas harboring IPMN. The former is addressed in Chaps. 2 and 3. This chapter describes the features of distinct PDAC which develops in the pancreas having IPMN.

Tanaka et al. (1997) reported a patient with a branch duct (BD)-IPMN who was diagnosed as having a carcinoma in situ (CIS) by preoperative ERCP pancreatic juice cytology. This was the first case report of concomitant PDAC in a patient with a BD-IPMN. They found a CIS in a branch of the pancreatic duct near but distinct from the small benign BD-IPMN in a specimen of distal pancreatectomy (Fig. 9.1). Localization of the origin of the positive cytology was performed by repeated cytological examinations after advancing a balloon catheter into the tail portion.

Yamaguchi et al. (1997) described the significance of IPMNs as a sentinel to detect a CIS of PDAC. Five years later, they further reported the association of concomitant PDAC in seven patients with BD-IPMNs (Yamaguchi et al. 2002). Of a total of 146 patients with pancreatectomy in their series, 69 patients had IPMN alone, 70 had PDAC alone, and the other seven had both of IPMN and PDAC. The seven patients (all male) with PDAC concomitant with IPMN corresponded to 9.2 % of 76 patients with IPMN and 9.1 % of 77 patients with PDAC. IPMNs are of branch duct type in all the seven patients with a mean diameter of 3.0 cm. They are all benign adenomas with mild dysplasia. PDAC occurred synchronously with IPMN in five patients, metachronously (4 years after IPMN) in one, and synchronously with IPMN and metachronously with IPMN and PDAC (7 years after IPMN) in the other. PDACs in two of these seven patients were CIS, one minimally invasive carcinoma and the remaining four invasive carcinoma. In four of these patients,

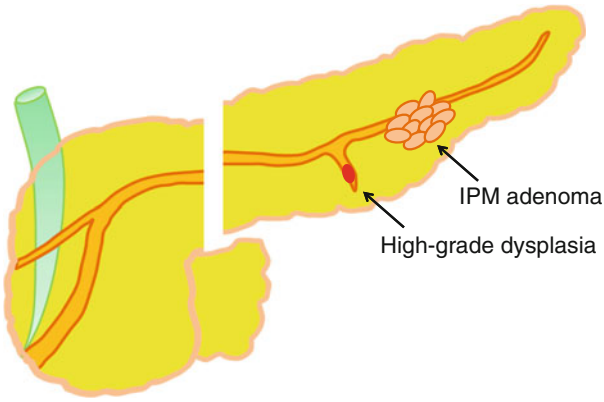

Fig. 9.1 Schematic presentation of a carcinoma in situ found by preoperative pancreatic juice cytology in a 59-year-old man with a BD-IPMN. There was a tiny area of high-grade dysplasia in a branch of the pancreatic duct near the IPMN, which proved to be low-grade dysplasia

Table 9.1 Frequency of pancreatic ductal adenocarcinoma (PDAC) in patients with branch duct IPMN

Authors (year)	Number of patients	Number of PDAC	Follow-up	Frequency (%)
Yamaguchi et al. (2002)	76	7	Retrospective analysis	9.2
Tada et al. (2006)	80	2	Retrospective analysis	2.5
Uehara et al. (2008)	60	5	Median, 87 months	8.0
Ingkakul et al. (2010)	236	22	Retrospective analysis	9.3
Tanno et al. (2010a)	168	9	Retrospective analysis	5.4
Tanno et al. (2010b)	89	4	Median, 64 months	4.5
Ikeuchi et al. (2010)	145	5	Retrospective analysis	3.5
Kanno et al. (2010)	159	7	Retrospective analysis	4.4
Sawai et al. (2010)	103	2	Retrospective analysis	1.9
Yamaguchi et al. (2011)	765	31	Retrospective analysis	4.1
Ohtsuka et al. (2012)	172	6	Retrospective analysis of patients after resection	3.5

the presence of IPMN led to the diagnosis of PDAC. Stage of the seven PDACs concomitant with IPMN was significantly earlier and the survival was better than that of the other 70 PDACs.

Since then, there have been many publications reporting the association of PDAC and IPMN (Table 9.1). The authors who first reported this phenomenon later investigated clinicopathological data of their consecutive series of 236 patients with IPMN treated by surgical resection or on follow-up to identify predictors of the presence of PDAC (Ingkakul et al. 2010). Concomitant PDAC was detected synchronously or metachronously in 22 patients (9.3 %) with BD-IPMNs (Fig. 9.2). Multivariate analysis revealed two significant factors predictive of the presence of PDAC, including worsening diabetes mellitus ($P \leq 0.001$) and an abnormal serum carbohydrate antigen (CA) 19-9 level ($P \leq 0.024$). Ikeuchi et al. (2010) reviewed the records of 145 patients with BD-IPMN observed for the mean period of 55.9 ± 45.3 months. The frequency of extrapancreatic cancers was 29.0 % (gastric, colon, breast, 25.5 %, 15.7 %, 13.7 %, respectively). The frequency of PDAC was 9.8 %. The cause of death was extrapancreatic carcinoma in 40 %, PDAC in 25 %, IPMN per se in 20 %, and benign disease in 15 %. In another retrospective study of 103 patients with BD-IPMN conservatively followed up for ≥2 years (median 59 months) by endoscopic ultrasonography (EUS) revealed that two patients (1.9 %) developed PDAC, while four IPMNs (3.8 %) progressed into IPMC (Sawai et al. 2010). The Japan Pancreas Society (JPS) conducted a large-scale retrospective study to define the clinicopathological features of IPMC and PDAC concomitant with IPMN (Yamaguchi et al. 2011). Of 765 patients with resected IPMN, 122 patients were diagnosed as having IPMC and 31 patients (4.1 %) PDAC concomitant with IPMN. By comparison of the clinicopathological data of these patients with that of 7,605 patients with PDAC registered in the JPS pancreatic cancer registry, IPMC and PDAC concomitant with IPMN were significantly smaller, less invasive, and less extensive than ordinary PDAC. The median survival of patients with the

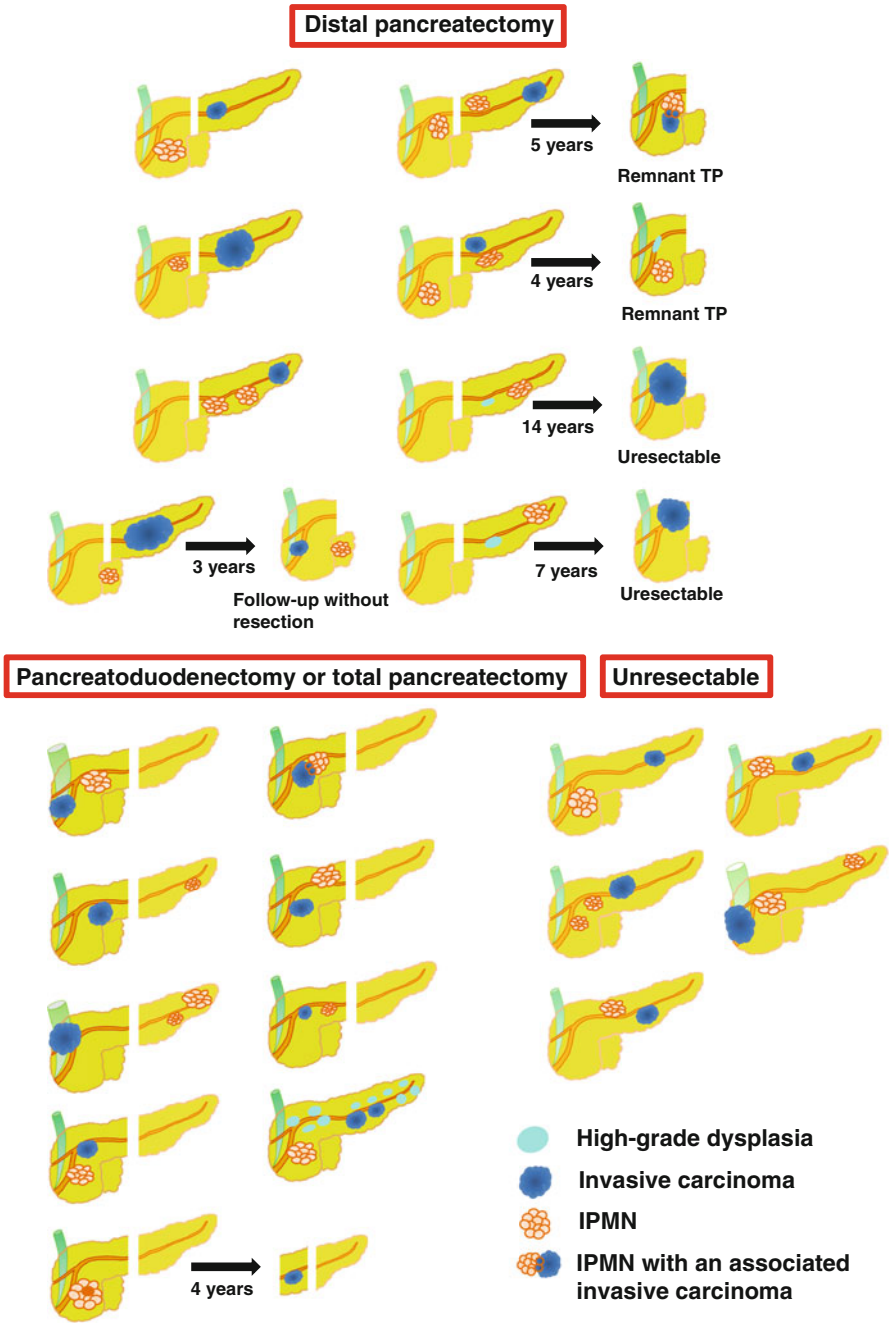

Fig. 9.2 Schematic presentation of 22 PDACs synchronously or metachronously occurring in the pancreas which harbors BD-IPMNs

former two conditions was significantly longer than for those with ordinary PDAC when compared overall or even when limited to TS2 (2.0 cm < tumor size ≤ 4.0 cm) or TS3 (4.0 cm < tumor size ≤ 6.0 cm) cases, suggesting that both of PDAC concomitant with IPMN and IPMC may have more favorable biological behaviors or be diagnosed earlier than ordinary PDAC.

Thus, in all probability, the presence of IPMN in the pancreas seems to pose the entire organ at increased risk for developing carcinoma, and surveillance of the entire pancreas is needed to detect an invasive carcinoma arising in a distinct area of the pancreas (Tada et al. 2006; Uehara et al. 2008; Ingkakul et al. 2010; Tanno et al. 2010a, b; Ikeuchi et al. 2010; Sawai et al. 2010; Yamaguchi et al. 2011; Ohtsuka et al. 2012).

9.2 The Incidence of Distinct PDAC in IPMN Patients

The incidence of PDAC development in patients with IPMNs has been estimated in a few prospective and several retrospective cohort studies. In one prospective study reported by Tada et al. (2006), 197 patients with cystic lesions including 80 IPMNs and 117 with "non-IPMN cysts" were surveyed twice a year for 3.8 years on average. Distinct PDAC developed in five patients (2.5 %, 0.68 % per year) while two IPMNs grew up to carcinoma (IPMC). Three of the five distinct PDACs developed in those with "non-IPMN cysts." Taken these PDACs and IPMCs altogether, a standardized incidence ratio (SIR) was 22.5 (95 % confidence interval, 11.0–45.3) as compared with the expected incidence calculated on the basis of age- and gender-matched mortality of pancreatic cancer in the general Japanese population. In another prospective study, 60 patients with BD-IPMN <10 mm on images and a negative cytology of the pancreatic juice were followed up mainly by ultrasonography (US) and additionally by EUS, computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP), or endoscopic retrograde cholangiopancreatography (ERCP) with cytological examination of the pancreatic juice for 87 months on average (Uehara et al. 2008). PDAC distinct from IPMN developed in five patients (8 %), thus the 5-year rate of development of PDAC 6.9 % (95 % confidence interval [CI] 0.4–13.4 %), incidence of PDAC 1.1 % (95 % CI 0.1–2.2 %) per year, and SIR of PDAC 26 (95 % CI 3–48). Patients at the age of >70 years were more susceptible to the development of PDAC than those under 69. Importantly, 4 out of the 5 PDACs found during the follow-up were resectable. On the other hand, IPMNs showed malignant transformation only in 2 of 60 (3 %) BD-IPMNs. Tanno et al. (2010a) surveyed 89 patients with BD-IPMN for more than 2 years (median 64 months; range 25–158 months). PDAC developed in four patients (7.2 per 1,000 patient-years), thus the SIR in comparison with the vital statistics compiled by the Ministry of Health, Labor, and Welfare of Japan 15.8 (95 % CI, 4.3–40.4 %; $P = 0.00014$). The incidence of PDAC was significantly greater in patients 70 years or older (SIR 16.7; 95 % CI, 3.4–48.7; $P = 0.0008$)

and in women (SIR 22.5; 95 % CI, 2.7–81.1; $P=0.0037$). The same group found PDAC in 9 (5.4 %) of 168 patients synchronously or metachronously with BD-IPMN under surveillance. The mean age of these patients was 73.1 years (range, 66–83). Patients developing PDAC were significantly older than patients not developing PDAC ($P=0.017$). The diameters of the BD-IPMNs and main pancreatic duct were significantly smaller in patients developing PDAC than those not developing PDAC ($P=0.013$ and $P<0.001$, respectively) (Tanno et al. 2010b). The JPS large-scale retrospective analysis (Maguchi et al. 2011) showed that 62 (17.8 %) of 349 patients with BD-IPMN observed or a median follow-up period of 3.7 years exhibited disease progression. PDAC and additional BD-IPMNs developed in seven (2.0 %) and 13 (3.7 %) patients, respectively, thus the yearly incidence of distinct PDAC 0.41 %.

9.3 Differentiation of Invasive IPMN and Distinct PDAC

WHO classification of IPMN pathology mentions invasive carcinoma derived from IPMNs as invasive carcinoma associated with IPMN (Adsay et al. 2010). However, the author would like to claim that the term "associated" should be defined more clearly. As we know by the aforementioned evidences, concomitant PDAC may occur in the pancreas harboring IPMNs, and this phenomenon can also be called "associated with IPMN." The author would like to propose more clear definition of carcinoma developing in the pancreas having IPMNs, i.e., invasive carcinoma derived from IPMN (identical to IPMC) and invasive carcinoma concomitant with IPMN just as we reported previously (Yamaguchi et al. 2011).

When far advanced, it is sometimes difficult to distinguish invasive IPMN (IPMC) and PDAC concomitant with IPMN. Yamaguchi et al. (2011) analyzed clinicopathological features of 765 resected IPMNs, 122 of which were diagnosed as having PDAC derived from IPMN and 31 with PDAC concomitant with IPMN. Additional 30 patients also had PDAC and IPMN, but the topological relationship and histological transition did not allow their pathologists performing central review of the histological slides to judge if the carcinoma was derived or separate from IPMN. Since there have been no other reports in regard with differentiation of PDAC derived from IPMN and distinct PDAC concomitant with IPMN, this is the current strategy and limitation of differentiation of these two types of pancreatic carcinoma. Some molecular and/or genetic analyses may be expected to contribute to more clear differentiation in the future.

9.4 Characteristics of Distinct PDAC Concomitant with IPMN

Regarding clinicopathological features of PDAC concomitant with IPMN, Yamaguchi et al. (2011) compared 122 invasive carcinomas derived from IPMN and 31 PDACs concomitant with IPMN with 7,605 patients with ordinary PDAC in the

aforementioned study by the JPS. They demonstrated that both of PDACs derived from IPMN and concomitant with IPMN were significantly smaller, less invasive, and less extensive than ordinary PDACs. The median survival of patients with these two conditions was significantly longer than of those with ordinary PDAC when compared overall or even when limited to TS2 (2.0 cm < tumor size ≤ 4.0 cm) or TS3 (4.0 cm < tumor size ≤ 6.0 cm). Thus, PDAC concomitant with IPMN and PDAC derived from IPMN may be characterized by more favorable biological behaviors or be diagnosed earlier than ordinary PDAC.

There is one report analyzing imaging characteristics of IPMNs of the pancreas which develops concomitant PDAC (Tanno et al. 2010b). BD-IPMNs in patients developing distinct PDAC were characterized by the significantly smaller size of the cyst and main pancreatic duct than in patients not developing PDAC. Whether the patients with PDACs concomitant with IPMN are more likely to have multicentric carcinogenesis or not has not been determined yet, although there have been anecdotal reports of multifocal PDACs and IPMNs (Yamaguchi et al. 2005; Mori et al. 2010).

Since the vast majority of PDACs concomitant with IPMN have been reported from Japan, one may argue that there may be racial predisposition to Japanese patients. However, the same phenomenon has begun to be noticed in Western countries as well. Jarry et al. (2010) reported a patient who was diagnosed as having a symptomatic IPMN in the uncinate process and a concurrent stenosis of the neck portion of the main pancreatic duct which resulted in distal dilation. During a Whipple procedure, a concomitant adenocarcinoma was diagnosed 2 cm from the primary IPMN, causing the stenosis. Just like us, they also suggested the possibility that IPMN may be a "red flag" enabling earlier diagnosis of a concurrent PDAC arising in another area of the pancreas. Although the viewpoint was reverse, Macari et al. (2010) pointed out that IPMN occurred with increased frequency in patients with PDAC as opposed to those without PDAC. They compared the frequency of IPMN on images of 68 patients who underwent pancreatectomy for PDAC and 183 different adult patients undergoing magnetic resonance imaging (MRI) for renal mass. Five of 68 (7.3 %) patients who underwent pancreatic resection for PDAC had IPMN at a site distant from the PDAC, whereas only two of the other 183 (1.1 %) patients undergoing MRI for renal cancer had imaging evidence of IPMN. The prevalence of IPMN was significantly different ($P = 0.017$) between patients with and without PDAC, and the odds ratio for IPMN as a predictor of PDAC was estimated as 7.18.

9.5 Detection of Concomitant PDAC in Patients with IPMN

Ingkakul et al. (2010) retrospectively reviewed the clinicopathological data of 236 patients with IPMN to determine the factors predicting the presence of concomitant PDAC. When clinicopathological variables were compared between 22 IPMN patients with concomitant PDAC (9.3 %) and those without concomitant PDAC,

all IPMNs concomitant with PDAC were of benign branch duct type and the histological grades of 12 resected IPMNs were low-grade ($n=8$) or intermediate-grade dysplasia ($n=4$). Multivariate analysis revealed that worsening diabetes mellitus ($P<0.001$) and an abnormal serum CA 19-9 level ($P=0.024$) were the significant predictive factors for the presence of PDAC in IPMN.

In a surveillance of BD-IPMN, how often and by what method we should examine our patients are the current issues remaining to be solved as soon as possible. A usual approach undertaken at present is blood tests for CA 19-9 and carcinoembryonic antigen (CEA) and imagings (CT, MRI/MRCP, with or without EUS) twice a year (Tada et al. 2006). However, whether this approach is appropriate and sufficient has not been determined yet. If not, what factors mandate closer intervals of surveillance must also be clarified. A family history of IPMN and/or PDAC, the growth rate of BD-IPMNs, and multiplicity of the IPMNs may be candidate factors, and there may be some other factors to be evaluated. With regard to family history of PDAC, one study reported that characteristics of surgically resected IPMNs were not different between 45 patients (13.9 %) with and 279 without a family history of PDAC (Nehra et al. 2012). Most importantly, the incidence of invasive IPMN was not different between the two groups. However, there have been very few studies to address the difference in the incidence of concomitant PDAC in patients with IPMN with and without the family history of PDAC. The growth rate of BD-IPMN has been suggested to predict the malignant change of IPMN per se (Rautou et al. 2008; Kang et al. 2011), but whether a rapidly enlarging IPMN is more likely to be associated with distinct PDAC remains unknown.

When resection is performed for an IPMN or a distinct PDAC in a patient with IPMNs, intraoperative pancreatic juice cytology should always be performed in order to confirm the absence of carcinoma in the pancreas to be left in place after planned resection. Eguchi et al. (2006) emphasized the importance of precise evaluation of intraductal cancer extension and skip lesions when resecting IPMN. Using intraoperative frozen section histology and pancreatic juice cytology, 18 out of 43 patients (42 %) required additional resection of the pancreas. Logistic regression analysis revealed that patients with a dilated main pancreatic duct, or those with cancerous lesions in the main tumors, were at high risk for positive histology and/or cytology. Mori et al. (2010) also reported a patient with multifocal PDACs concomitant with IPMN detected by intraoperative pancreatic juice cytology. Later, the same authors evaluated the technique of intraoperative irrigation cytology of the remnant pancreas to detect distinct PDAC during pancreatectomy in patients with IPMN (Mori et al. 2013). Of 48 patients who underwent irrigation cytology of the remnant pancreas during pancreatectomy, 13 patients had suspicious or positive results at the first attempt. Eight of these subsequently had negative results at the second or third attempt, while five patients (10 %) continued to show positive results, necessitating additional resection. All five patients had a distinct PDAC in the additionally resected specimen, none of which were detected by preoperative imaging studies. Noteworthy is the fact that four of these five PDACs were stage 0 or 1.

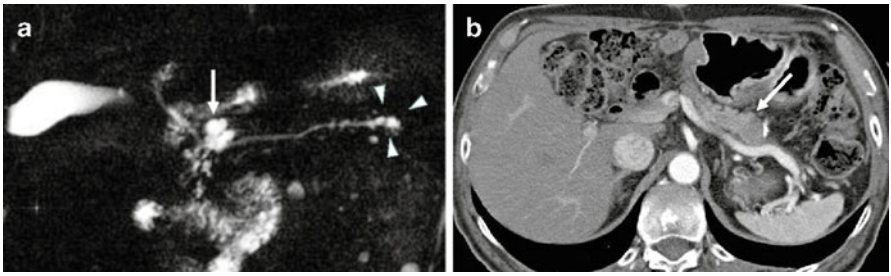

Fig. 9.3 Metachronous development of a PDAC in the remnant pancreas after resection of IPMNs in a 72-year-old man. Based on pancreatic juice cytology positive for Class IV, pylorus-preserving pancreatoduodenectomy was performed for a 15-mm BD-IPMN (**a**, *arrow*) of low-grade dysplasia as well as pancreatic tail resection for a 12-mm BD-IPMN (**a**, *arrowheads*) of high-grade dysplasia. During postoperative surveillance twice a year, a solid mass with delayed enhancement was detected near the margin of the tail of the pancreas 15 months later (**b**, *arrow*). Histological examination after remnant pancreatectomy revealed a well to moderately differentiated adenocarcinoma. The margin of the previous pancreatic tail resection was free from IPMN and the metachronous carcinoma did not reach the stump of the pancreatic tail

9.6 Development of PDAC after Resection of IPMN

The pancreas remaining after resection of IPMN with negative resection margins or after resection of PDAC concomitant with IPMN is still at risk of metachronous development of PDAC as well as IPMN. Miller et al. (2011) surveyed 153 patients who underwent resection for IPMN with negative margins. During a mean period of 73 months, 31 of the 153 (20 %) patients developed a new IPMN and three of them proved to be invasive cancer. Ohtsuka et al. (2012) reviewed 172 patients who underwent resection of IPMNs with a mean postoperative follow-up of 64 months. Ten metachronous IPMNs developed in the remnant pancreas after a mean time of 23 postoperative months, and two with main duct IPMNs (both were CIS) required remnant pancreatectomy. On the other hand, six distinct PDACs developed in the remnant pancreas of these 172 patients after a mean time of 84 postoperative months (range, 12–150 months). Four of them were found to have a tumor with a size <2 cm (Fig. 9.3), whereas the remaining two PDACs were found to be unresectable more than 10 years after resection of IPMNs. Intense long-term surveillance is necessary for early detection of metachronous occurrence of distinct PDACs as well as malignant IPMNs after resection of IPMNs.

9.7 Molecular Aspects of Development of PDAC in IPMN Patients

KRAS mutations are frequently detected in both PDACs and IPMNs (Tada et al. 1991; Mizuno et al. 2010). Several molecular studies showed heterogeneity within the pancreas with IPMN, demonstrating multiple subclones evidenced by the

presence of several different *KRAS* mutations (Wu et al. 2011a, b; Lubezky et al. 2011; Matthaei et al. 2012). However, few studies have investigated molecular alterations within IPMNs and synchronously or metachronously occurring distinct PDACs. *KRAS* mutations are present in 30–80 % of IPMNs, and *GNAS* mutations of codon 201, unique to IPMNs, have been detected in more than 60 % of IPMNs (Furukawa et al. 2011; Wu et al. 2011a, b). Wu et al. (2011a, b) carefully microdissected neoplastic cells of IPMN and invasive carcinoma derived from IPMN in eight patients and purified DNA. In seven of the eight patients (88 %), identical *GNAS* mutation was found in the neoplastic cells of the IPMN and invasive carcinoma derived from the IPMN. *KRAS* mutation of the PDAC was consistent with that of the associated IPMN in these patients. Although the *KRAS* mutations are found commonly in both PDACs derived from IPMN and PDACs not associated with IPMN, there was a marked difference between the prevalence of *GNAS* mutations in PDACs associated with IPMN (7 of 8) and that in PDACs unassociated with IPMN (0 of 116; $P<0.001$). In the eighth patient, however, the *KRAS* and *GNAS* mutations identified in the neoplastic cells of the IPMN were not found in the PDAC, suggesting that this invasive cancer arose from a separate precursor lesion. Lubezky et al. (2011) found concordant *KRAS* mutations in IPMNs and carcinoma derived from the IPMNs in 9 of 14 patients (64 %). Ideno et al. (2013) reviewed clinicopathological data of 179 resected IPMNs and 180 resected PDACs without IPMNs. Twenty-six synchronous or metachronous PDACs were identified in 20 patients (11.2 %) with IPMNs in their series. Occurrence of concomitant PDACs was more frequently observed in gastric-type IPMNs (18/110, 16.4 %) compared with intestinal (1/49, 2.0 %), pancreatobiliary (1/17, 5.9 %), or oncocytic type (0/3, 0 %) ($P=0.047$). The mucin-staining patterns were similar to those of invasive tubular adenocarcinoma arising from gastric-type IPMNs, being frequently positive for MUC1, MUC5AC, and MUC6 expression but negative for MUC2 and CDX2. Mutation of *GNAS* within codon 201 was not detected in PDACs and gastric-type IPMNs, while most of these exhibited *KRAS* mutations. However, the R201H *GNAS* mutation was detected in one intestinal-type IPMN with distinct PDAC. PDACs may frequently arise in the pancreas with benign gastric-type IPMN in the absence of *GNAS* mutations. All these data suggest that *GNAS* mutations might be useful to distinguish PDACs derived from IPMN (*KRAS* mutation+, *GNAS* mutation+) and PDACs concomitant with but distinct from IPMN (*KRAS* mutation+, *GNAS* mutation-) in most cases.

Matthaei et al. (2012) investigated the clonal relationships of 30 multifocal IPMNs arising in 13 patients. The majority of multifocal IPMNs were of branch duct type of gastric subtype with low or intermediate grades of dysplasia. *KRAS* mutation analysis and loss of heterozygosity (LOH) analysis on chromosomes 6*q* and 17*p* on these multiple IPMNs showed non-overlapping *KRAS* gene mutations in eight patients (62 %) and discordant LOH profiles in seven patients (54 %), thus depicting independent genetic alterations in 9 of the 13 patients (69 %).

9.8 Prevention of PDAC Concomitant with IPMN

A role for medical management of IPMNs such as chemoprevention remains an unanswered question. Although there have been clinical trials of chemoprevention conducted for a variety of malignancies, only one study examined the effect of sulindac in a series of 22 patients with BD-IPMNs (Hayashi et al. 2009). Ten of 22 patients who rejected surgical therapy despite their lesions meeting the Sendai criteria for surgical resection were assigned to the treatment group. Sulindac (150 mg twice daily) and omeprazole (20 mg once daily) were administered for 18 months, while the other 12 patients served as controls. The cyst size and height of mural nodules of BD-IPMNs monitored by MRCP or CT and EUS were significantly reduced in the treatment group, while those in the control group remained unchanged, suggesting the promise of chemoprevention of carcinoma derived from BD-IPMNs by sulindac. Immunohistochemical staining for cyclooxygenase-1 and cyclooxygenase-2 was negative in hyperplasia, adenoma, and carcinoma portions of resected specimens but was clearly positive for glutathione-S-transferase pi (GST-pi), suggesting that GST-pi is a putative target molecule for sulindac.

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