What are the Appropriate Surgery and Postoperative Surveillance for Intraductal Papillary Mucinous Neoplasm?

Noboru Ideno, Kohei Nakata, Masafumi Nakamura

Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

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Corresponding author:

Masafumi Nakamura

E-mail: nakamura.masafumi.861@
m.kyushu-u.ac.jp

<https://orcid.org/0000-0002-6196-8643>

Although many guidelines for pancreatic cystic neoplasms focus on the management of intraductal papillary mucinous neoplasm of the pancreas (IPMN) at the highest oncological risk, there are many issues that surgeons need to consider at the time to plan the surgical procedures based on characteristics of IPMN subtypes, such as multiplicity of branch duct-IPMN (BD-IPMN) and intraductal spreading of main duct-IPMN (MD-IPMN). For multifocal BD-IPMN, partial pancreatectomy would be selected to remove BD-IPMN with predictors of malignancy, while the other lesions without risk factors can be left, although total pancreatectomy might be considered if the patients have a strong family history of pancreatic cancer. Partial pancreatectomy would be also adequate procedure for MD-IPMN if negative surgical margin for high-grade dysplasia or invasive carcinoma were achieved. It has become to be well-known that patients with BD-IPMN are at increased risk for developing not only IPMN-associated pancreatic ductal adenocarcinoma (PDAC) but also PDAC independent from the IPMN. Hence, the detection of a concomitant PDAC is also an important focus for strategies after resection of BD-IPMNs. Our recent analysis of patients after partial pancreatectomy for MD-IPMN with negative surgical margin identified an unexpected recurrence pattern, which we called “monoclonal skip” recurrence. MD-IPMN seems to be disseminated in the pancreatic ductal systems and MD-IPMN with identical genetic background was detected in the remnant pancreas even in a long time after index surgery. We proposed strategies of postoperative surveillance based on characteristics and natural history of each morphological subtype.

Key Words: Intraductal papillary mucinous neoplasms of the pancreas; Guideline; Recurrence

INTRODUCTION

Intraductal papillary mucinous neoplasm of the pancreas (IPMN) is a *bona fide* precursor lesion of pancreatic ductal adenocarcinoma. Similar to the well-defined adenoma-carcinoma sequence in colorectal cancer and pancreatic ductal adenocarcinoma, IPMNs seem to follow a pattern progressing from IPMN low-grade (LG), to IPMN high-grade (HG), and eventually IPMN with an associated invasive carcinoma (invasive IPMN). According to a pathological examination of resected IPMNs, the distinction of involved pancreatic duct seems to be important because main duct-IPMN (MD-IPMN), whether symptomatic or not, have a high rate of

malignancy, whereas branch duct-IPMN (BD-IPMN), which often are incidentally discovered, have a much lower rate.

These findings led to the publication of guidelines, like the Sendai guidelines, recommending resection for all MD-IPMN, but observation for asymptomatic BD-IPMNs that have a low risk of malignancy. Although strategies for IPMN at the highest risk of malignancy has been clearly described in guidelines, several issues need to be discussed, such as determination of transection lines in surgery for MD-IPMN and management of BD-IPMN left in the remnant pancreas. In addition, as an increased number of patients with IPMN were appropriately managed based on the guidelines,

the increased number of patients who were longitudinally surveyed with or without resection led to the publication of many studies demonstrating the development of high-risk lesions in the pancreas with IPMN with lower risk or remnant pancreas of patients who underwent partial pancreatectomy.

In this review, we provide an overview of current insights into studies focusing on the characteristic of IPMN which surgeons need to know for decision making in the management of multifocal BD-IPMNs and diffuse type MD-IPMN, and methods of post-operative surveillance considering patterns of recurrence according to the types of IPMN.

DEFINITION OF TERMINOLOGIES

Macroscopic Morphological Classification

IPMNs are divided into three morphological types including main duct type (MD-IPMN), branch duct type (BD-IPMN), and mixed type (Fig. 1). The classification should be determined by radiological findings obtained by imaging studies, most clearly by magnetic resonance cholangiopancreatography (MRCP). This review refers to the classification defined in the International Association of Pancreatology 2017 (IAP 2017) [1]. MD-IPMN is characterized by segmental or diffuse dilation of the main pancreatic duct of > 5 mm without other causes of obstruction. Pancreatic cysts of > 5 mm in diameter that communicate with the main pancreatic duct (MPD) should be considered as BD-IPMN. Mixed-type IPMN meets the criteria for both MD-

IPMN and BD-IPMN.

Histopathologic Grade of IPMN and Invasive Carcinoma Arising in the Pancreas with IPMNs

In this review, the histopathologic grade will be stated as proposed in the Baltimore consensus meeting for neoplastic precursor lesions in the pancreas [2]. Precursor lesions to invasive carcinoma are classified into Pancreatic intraepithelial neoplasia (PanIN)/IPMN LG and HG. PanIN LG and PanIN HG are equal to PanIN-1, 2, and PanIN-3, respectively. While IPMN LG and HG are equal to IPMN with low-grade/intermediate-grade dysplasia and high-grade dysplasia, respectively, which were defined in the 2010 World Health Organization (WHO) classification for tumors of the pancreas. When invasive carcinoma is identified in the pancreas with IPMN, the relationship between invasive carcinoma and IPMN will be carefully examined to clarify the precursor of invasive carcinoma. Invasive carcinoma which arises from an IPMN is “IPMN with an associated invasive carcinoma”, hereinafter called “invasive IPMN” (Fig. 2A, 2B). Invasive carcinoma can also arise independently in a pancreas containing IPMNs. This will be referred to as “invasive carcinoma concomitant with IPMN” (Fig. 2C–2F). As it is still controversial if PanIN/IPMN HG should be called “malignancy”, precursor lesions with high-grade dysplasia will be called “high-risk lesions” in this review, as we have previously described [3].

Fig. 1. Three morphological subtypes of intraductal papillary mucinous neoplasm of the pancreas (IPMN) demonstrated by magnetic resonance cholangiopancreatography. Main duct IPMN (A), branch duct-IPMN (B), mixed type-IPMN (C).

Fig. 2. Distinction of IPMN with an associated invasive carcinoma (invasive IPMN) and invasive carcinoma concomitant with IPMN. MD-IPMN with a tubular duct invading into pancreatic parenchyma (A, B). MRCP demonstrating BD-IPMN (white arrow) without MPD dilation (white arrowheads) (C). Development of pancreatic ductal carcinoma in the pancreatic body led to dilation of MPD (white arrowheads) not associated with BD-IPMN (white arrow) (D). Histopathologic assessment confirmed BD-IPMN-low grade (E) and invasive carcinoma concomitant with IPMN (F). IPMN, intraductal papillary mucinous neoplasm; MD-IPMN, main duct IPMN; BD-IPMN, branch duct-IPMN; MRCP, magnetic resonance cholangiography; MPD, main pancreatic duct.

SURGICAL MANAGEMENT FOR IPMN

Since IPMNs display various degrees of dysplasia following adenoma-carcinoma sequencing, dilated main pancreatic duct or pancreatic cyst suspected for IPMN will be initially investigated by physicians to predict the disease progression. Surgery will be recommended for all surgically fit patients who have IPMN with invasive features. Invasive IPMNs are classified into tubular adenocarcinoma and colloid carcinoma. Invasive IPMN with tubular subtypes essentially behave like conventional invasive ductal carcinoma, while those with colloid subtype have favorable prognosis [4,5]. Invasive IPMNs with either subtype should be removed by radical pancreatectomy with lymph node dissection as well

as conventional pancreatic ductal adenocarcinoma (PDAC), because 45 and 31% of invasive IPMN patients had T3/4 diseases and lymph node metastasis, respectively, according to a recent nationwide survey in Japan [6].

Patients with IPMN who underwent surgery before the IPMN became invasive carcinoma displayed significantly longer survival time [7,8], and therefore, management strategy is rather essential for patients who have IPMNs without invasive features to determine optimal timing for surgery.

The management of IPMN is based on morphological and clinical parameters because the risk of malignant transformation is not accurately predictable. Three major guidelines, including IAP 2017 [1], European evidence-based guidelines on pancreatic cystic neoplasms (EURO) [9], and American

Gastroenterological Association 2015 guidelines (AGA) [10] referred to diagnosis, treatment and surveillance of IPMN, as summarized in Table 1.

The IAP 2017 are most comprehensive and practical for decision making in the management of IPMN [1]. Surgical resection of MD-IPMN is strongly recommended for all surgically fit patients with MPD > 10 mm, jaundice, or mural nodules. Although the lower incidence of malignancy in BD-IPMN might lead the more conservative management of the patients with the disease, those with “high-risk stigmata”, including obstructive jaundice, enhancing mural nodule ≥ 5 mm, and main pancreatic duct ≥ 10 mm will be considered surgery if clinically appropriate. The final decision should be individualized and depends not only on the risk of malignancy but on the patient’s life expectancy, comorbidities and extent of MD dilation/cyst location in those with either subtype of IPMNs. Surveillance is necessary for early detection of malignant progression of IPMN and concomitant

pancreatic cancer both in patients on observation and after resection of IPMN.

There are some differences in the management of three subtypes of IPMN between IAP 2017 and EURO guidelines. Although IAP 2017 does not specifically describe management of mixed type IPMN, EURO guidelines advise resection of mixed type-IPMN as well as MD-IPMN with the same threshold of main duct size as that in IAP 2017. Indication for resection of IPMN in EURO guidelines also has 2 categories of indication for resection of IPMN including “absolute indications” and “relative indications”, which are similar to “high-risk stigmata” and “worrisome features”, respectively, in IAP 2017 as presented in Table 1. The AGA suggests that patients with both a solid component and a dilated pancreatic duct and/or concerning features on endoscopic ultrasound guided fine needle aspiration biopsy should undergo surgery to reduce the risk of mortality from carcinoma.

Table 1. Comparison of 3 Guidelines Stating Indications for Surgery and Surveillance of Resected IPMNs

Guidelines	International consensus guidelines 2017 (IAP)	European evidence-based guidelines on pancreatic cystic neoplasms (EURO)	American Gastroenterological Association Institution Guideline (AGA)
Types of guideline	Consensus guidelines	Evidence-based guidelines	Evidence-based guidelines
Type of tumor/ neoplasm	IPMN and MCN	Cystic tumors of the pancreas	Asymptomatic neoplastic pancreatic cyst
Indication for resection	High-risk stigmata: obstructive jaundice, enhancing mural nodule, MPD ≥ 10 mm) Worrisome features: pancreatitis, cyst ≥ 3 cm, enhancing mural nodule < 5 mm, thickened/ enhancing cyst walls, main duct size 5–9 mm, abrupt change in caliber of pancreatic duct, lymphadenopathy, increase serum level of CA19-9, cyst growth ≥ 5 mm/2 years EUS findings: definite nodule, MPD involvement, positive cytology	Absolute indications: positive cytology for malignant/high grade dysplasia, solid mass, jaundice, enhancing mural nodules (≥ 5 mm), main pancreatic dilation ≥ 10 mm. Relative indications: grow-rate ≥ 5 mm/year, increased levels of serum CA19-9 (≥ 37), main pancreatic duct dilation from 5–9.9 mm, cyst diameter ≥ 40 mm, new-onset diabetes mellites, acute pancreatitis (caused by IPMN), enhancing mural nodules (< 5 mm)	Two or more high-risk features + positive cytology in EUS-FNA
Surveillance of resected cases	Invasive IPMN: same surveillance as PDAC; noninvasive IPMN (without residual lesion): repeat examination at 2 and 5 years	Invasive IPMN: same surveillance as PDAC; IPMN with high-grade dysplasia or MD-IPMN: follow-up every 6 months for the first 2 years, followed by yearly surveillance. IPMN with low-grade dysplasia: same as non-resected IPMN	Cyst with invasive cancer or dysplasia: MRI every 2 years; cyst without high-grade dysplasia or malignancy: no routine surveillance

IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasms; MPD, main pancreatic duct; PDAC, pancreatic ductal adenocarcinoma; CA19-9, carbohydrate antigen 19-9; MRI, magnetic resonance imaging; EUS, endoscopic ultrasound; FNA, fine needle aspiration.

BD-IPMN

There are several biological characteristics of BD-IPMN that surgeons need to understand to determine types of procedure and surveillance methods. This section contains the frequency of malignancy of BD-IPMN, multiplicity of BD-IPMNs, and risk stratification of patients with BD-IPMN based on family history of PDAC.

Malignant Transformation of BD-IPMN

The frequency of invasive carcinoma and HG-IPMN in resected BD-IPMN varies ranging from 14.4 to 47.9%, and that of invasive cancer is 18.5% (6.1–37.7%) in recent series [1]. Although there is no prospective study that surveyed patients with BD-IPMN for a long time, a large case series including 1,404 patients with BD-IPMN demonstrated that the 5-year incidence rate of IPMN-derived carcinomas and pancreatic adenocarcinomas was 3.3%, reaching 12% at 15 years after IPMN diagnosis [11]. These findings indicated that a minor subset of BD-IPMNs has the potential to progress into high-risk lesions and the risk of malignancy increases according to the time course, supporting the recommendation of the lower threshold for surgery in younger IPMN patients in guidelines [1].

Multiplicity of BD-IPMN

The prevalence of multifocality in IPMNs varies, ranging from 25 to 45% [11–14]. Since partial pancreatectomy is recommended to remove BD-IPMN with the highest oncologi-

cal risk, BD-IPMNs will be left in the remnant pancreas of patients with multifocal BD-IPMNs. There is some evidence including ours which suggests acceptance of leaving BD-IPMNs without risk factors. Mori et al. [15] reported that residual lesions after partial resection for multifocal IPMN did not show significant progression and disease specific survival after partial resection was comparable between multifocal BD-IPMN and solitary BD-IPMN. In addition to the clinical data, molecular/pathological analyses also support this conservative management of multifocal BD-IPMN in the remnant pancreas. Matthaei et al. [16] assessed the histological subtypes and the clonal relationships among multifocal BD-IPMNs using *KRAS* mutational analyses and loss of heterozygosity (LOH) analyses. The majority of multifocal BD-IPMNs exhibited a gastric-subtype with low to intermediate dysplasia, and they identified nonoverlapping *KRAS* gene mutations and discordant LOH profiles among multifocal BD-IPMNs in the same pancreas. These findings indicated that the majority of multifocal IPMNs arise independently and possess a low risk of malignancy.

BD-IPMNs with Familial History of Pancreatic Cancer

There is some evidence suggesting the possible presence of high-risk lesions in the pancreas with benign IPMN in high-risk patients (Table 2). Shi et al. [17] examined resected pancreata from patients with a strong family history of pancreatic cancer. They found that noninvasive precursor lesions at higher grades were common in patients with a strong family history of pancreatic cancer than in those with sporadic disease. Multifocal small benign BD-IPMN might

Table 2. Studies Investigated IPMN Patients with Family History of Pancreatic Cancer and Germline Mutations in Patients with IPMN

Author	Journal	Year	Subject	No. of subject	Main findings
Shi et al. [17]	Clin Cancer Res.	2009	Patients with strong family history of pancreatic cancer	51	PanIN/IPMN were of a higher grade in patients with strong family history of pancreatic cancer
Bartsch et al. [18]	Fam Cancer	2013	Patients with family history of pancreatic cancer or <i>BRCA2</i> / <i>PALB2</i> germline mutations	125	Multifocal BD-IPMNs indicate presence of PanIN high-grade
Skaro et al. [19]	Gastroenterology	2019	Patients with IPMNs	315	23 patients had germline mutations associated with cancer risk.

IPMN, intraductal papillary mucinous neoplasm; BD-IPMN, branch duct-IPMN.

be a predictor of the presence of higher grade PanIN in patients with a family history of pancreatic cancer. Bartsch et al. [18] reported 4 cases of high-risk patients with a family history of pancreatic cancer who had benign multifocal BD-IPMNs and identified PanIN-HG lesions in the elsewhere of the pancreas of all 4 patients. Skaro et al. [19] sequenced 94 genes with variants associated with cancer risk in DNA obtained from nontumor tissue samples from 315 patients with histologically confirmed IPMN. They reported that 7.3% of IPMN patients had germline mutations associated with cancer risks, such as *ATM*, *BRCA2*, *MSH6*, and *PALB2* gene mutations. Patients with IPMNs and germline mutations associated with pancreatic cancer were more likely to have concurrent invasive carcinoma compared with those with IPMNs without these mutations. Based on these, IAP guideline suggested that the threshold for total pancreatectomy for IPMN should be lowered in patients with a strong family history of PDAC.

Summary of Surgery for BD-IPMN

For adequate management of multifocal BD-IPMN, partial pancreatectomy is indicated in lesions with the highest risks, while those without risks should be followed up. Prophylactic total pancreatectomy for multifocal BD-IPMN is not always recommended, except for patients with a family history of pancreatic cancer.

MD-IPMN

Resection of MD-IPMN aims to achieve complete removal of a tumor with a negative margin. Although it might be relatively easy to determine the resection side and transection line in MD-IPMN with segmental dilation of the main pancreatic duct or diffuse type with focal lesions, such as mural nodules or dilated branch lesions. On the other hand, a careful evaluation would be necessary for the diffuse dilation type without focal lesions. In this section, the frequency of malignancy of MD-IPMN and methods to determine the transection line pre-/intra-operatively would be demonstrated.

Malignant Transformation of MD-IPMN

The mean frequency of invasive carcinoma and high-grade dysplasia in MD-IPMN is 61.6%, range from 36 to 100%, and the mean frequency of invasive IPMN is 43.1%, range from 11 to 81% [1]. It is clear that MD-IPMN harbors a higher risk of malignancy compared to BD-IPMN. Although several studies have described clinical and radiologic features that are common in MD-IPMN carcinoma, malignancy predictors in MD-IPMN are shared with BD-IPMN in IAP 2017 [1].

Methods to Determine Transection Line in Surgery for MD-IPMN

Three studies demonstrated that there was no difference in recurrence between margin positive and margin negative mostly for LG [20-22]. Marchegiani et al. [23] reported that a significantly higher recurrence rate in MD-IPMN patients with margin positive for HG/invasive carcinoma. Tamura et al. [24] showed margin positive for LG or recurrence in the remnant pancreas did not worsen prognosis in MD-IPMN patients. Based on these studies, partial pancreatectomy can be planned in poor risk patients with diffuse type MD-IPMN, if it was possible to accurately differentiate HG from LG in an intraductal tumor.

Peroral pancreatoscopy (POPS) can detect superficial spread lesions in MPD and targeting biopsy using POPS might be helpful for the preoperative assessment to predict the extent of intraductal spreading of the tumor [25,26]. However, unfortunately, our recent case series demonstrated that the sensitivity of targeting biopsy during POPS to diagnose HG dysplasia was 0% [27].

Summary of Surgery for MD-IPMN

In summary, partial pancreatectomy for MD-IPMN with negative surgical margin for HG or invasive carcinoma is adequate. The presence of LG at the cut end seems not to be associated with clinically relevant recurrence. Although POPS might be useful for the determination of the transec-

tion line for the partial pancreatectomy for MD-IPMN, the significance of intraoperative pathological assessment has not been changed yet.

POSTOPERATIVE SURVEILLANCE

Postoperative Surveillance in Guideline

Methods of postoperative surveillance in three guidelines were summarized in Table 1. IAP 2017 and EURO guidelines recommend continuation of surveillance as long as the patient remains fit for surgery irrespective of histopathological grade or margin status of initially resected IPMN, because the patient may benefit from additional pancreatectomy for remnant pancreatic lesions.

Patterns of Recurrence or Development of New Lesions after Pancreatectomy for IPMN

The recommendations of surveillance after resection of IPMN by guidelines led to many studies reporting a recurrence of IPMN or development of new high-risk lesions in the remnant pancreas. Studies reported remnant pancreatic lesions after resection of IPMN are summarized in Table 3 [3,28-35]. Of note, rates of the patients who developed overall and malignant remnant pancreatic lesion were 5 to 22% and 1 to 7%, respectively, and some remnant pancreatic le-

sions developed in more than 10 years after initial resection of IPMN, indicating the importance of life-long surveillance.

Morphological classification and histopathologic grade of IPMN seem to be still important to predict patterns of recurrence or development of new lesions in the remnant pancreas after partial pancreatectomy for IPMN.

Tamura et al. [24] specifically analyzed the recurrence pattern after resection of MD-IPMN using pathological/genomic analyses. Recurrence after partial pancreatectomy for MD-IPMN was observed in 6 of 49 patients (12%), all of which were malignant IPMNs. Interestingly, examined 4 recurrent IPMNs had histological subtypes and *KRAS*/*GNAS* mutations identical to those of the initial lesions, despite the negative surgical margin at the initial operation. These findings suggested an unexpected recurrence pattern of MD-IPMN as we called “monoclonal skip progression”. Date et al. [36] confirmed the “monoclonal skip progression” of MD-IPMN using mRNA expression profiling.

Our previous studies [37-39], as well as others including a nationwide survey in Japan [40], which analyzed morphological/pathological subtypes of IPMN with concomitant PDAC, demonstrated the frequent occurrence of PDAC in the pancreas with BD-IPMN/gastric-type IPMN. Matsuda et al. [41] reported a significantly higher density of PanINs in the pancreas with IPMN and concomitant PDAC compared to PDAC without IPMN, which indicates the possible presence of undetectable precursor lesions in the remnant pan-

Table 3. Reports of Remnant Pancreatic Lesions after Resection of IPMN

Author	Journal	Year	No. of total patient	No. of patients with noninvasive IPMN	Follow-up period	Remnant pancreatic lesions		Maximum duration between 1st and 2nd lesions
						No. of total patients	No. of patients with malignant lesions	
Schnelldorfer et al. [28]	Arch Surg	2008	208	145	3.2 years	11	3	11 years
Miller et al. [19]	HPB	2011	243	243	73 months	31 (+38*)	4 (invasive IPMN)	145 months
Moriya et al. [30]	Arch Surg	2012	203	160	40 months	17 (+14*)	4	127 months
Frankel et al. [31]	HPB	2013	192	192	46 months	40	3	N/A
Pea et al. [32]	Ann Surg	2017	260	260	N/A	50	16	134 months
Hirono et al. [33]	Surgery	2016	257	172	53.5 months	14	12 (IPMN 7/PDAC 5)	71.6 months
Miyasaka et al. [3]	Ann Surg	2016	195	160	47 months	29	13 (IPMN 6/PDAC 7)	160 months
Rezaee et al. [34]	HPB	2016	616	433	28 months	62	28 (IPMN 5/PDAC 23)	N/A
Al Efshat et al. [35]	Ann Surg Oncol	2018	319	299	42 months	71	15 (IPMN 4/PDAC 11)	N/A

IPMN, intraductal papillary mucinous neoplasm; PDAC, pancreatic ductal adenocarcinoma; N/A, not assessed. *Residual lesions.

creas after pancreatectomy for BD-IPMN.

Miyasaka et al. [3] comprehensively investigated the natural history of remnant pancreas after partial pancreatectomy

for IPMN to identify factors associated with the metachronous development of high-grade dysplasia or invasive carcinoma of IPMN and concomitant PDAC, which we defined

Fig. 3. Recurrence patterns after resection of IPMN based on characteristics of each morphological subtype of IPMN. Gastric type IPMN, gastric. Pancreatobiliary type IPMN, PB. IPMN, intraductal papillary mucinous neoplasm; MD-IPMN, main duct IPMN; BD-IPMN, branch duct-IPMN; PDAC, pancreatic ductal adenocarcinoma; HGD, high-grade dysplasia; INV, invasive carcinoma; PB, pancreatobiliary type.

Fig. 4. A surveillance protocol after resection of BD-IPMN. IPMN, intra-ductal papillary mucinous neoplasm; BD-IPMN, branch duct-IPMN; MRCP, magnetic resonance cholangiography; CT, computed tomography; EUS, endoscopic ultrasound.

Fig. 5. A surveillance protocol after resection of MD-IPMN. IPMN, intra-ductal papillary mucinous neoplasm; MD-IPMN, main duct IPMN; CT, computed tomography; MRI, magnetic resonance imaging.

as high-risk lesions. Multiple regression analyses identified the independent predictive factors including IPMNs located in the distal pancreas, HG/invasive IPMNs at index surgery, pancreatobiliary type IPMNs and presence of PDAC concomitant with IPMN as summarized in Fig. 3. The 5- and 10-year cumulative incidences of metachronous high-risk lesions in the remnant pancreas were 7.8% and 11.8%, respectively.

Surveillance Strategy after Pancreatectomy for BD/MD-IPMN

Based on characteristics of each morphological subtype relevant to postoperative surveillance described above, we proposed surveillance protocols after resection of IPMN (Figs. 4, 5) [42,43]. Surveillance interval was classified according to the histopathologic grade of IPMN resected at initial operation. The problem will be any protocol have the potential to fail to identify resectable high-risk lesions, and therefore, as proposed in Fig. 4, identification of high-risk individuals who need shorter interval surveillance is essential.

CONCLUSIONS

A proposed simple progression model of IPMN and slow growing biology appear to ensure the time window to resect IPMN before it becomes invasive carcinoma, resulting in a favorable prognosis in comparison to conventional PDAC. Because of the longer life expectancy after removal of IPMN, organ preserving surgery, without spoiling curability, need to be considered to preserve patients' quality of life. Remnant pancreas after partial pancreatectomy for IPMN seems to be at risk of development of "high-risk lesions", of which early detection and additional resection may benefit the patients. To diagnosis "high-risk lesions" at an earlier stage, physicians need to have insight into the unique biology of various types of IPMN.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR'S CONTRIBUTIONS

Conceptualization: Masafumi Nakamura. Supervision: Kohei Nakata, Masafumi Nakamura. Writing—original draft: Noboru Ideno. Writing—review & editing: Kohei Nakata, Masafumi Nakamura.

ORCID

Noboru Ideno, <https://orcid.org/0000-0003-4745-8417>

Kohei Nakata, <https://orcid.org/0000-0002-5717-8569>

Masafumi Nakamura, <https://orcid.org/0000-0002-6196-8643>

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