Risk Factors for Development of High-Risk Stigmata in Branch-Duct Intraductal Papillary Mucinous Neoplasms

Tatasuhiro Yamazaki (✉ ty1114db@gmail.com)
Okayama University Hospital  https://orcid.org/0000-0001-7728-074X

Takeshi Tomoda
Okayama University Hospital

Hironari Kato
Okayama University Hospital

Kazuyuki Miyamoto
Okayama University Hospital

Akihiro Matsumi
Okayama University Hospital

Eijiro Ueta
Okayama University Hospital

Yuki Fujii
Okayama University Hospital

Yosuke Saragai
Okayama University Hospital

Daisuke Uchida
Okayama University Hospital

Kazuyuki Matsumoto
Okayama University Hospital

Shigeru Horiguchi
Okayama University Hospital

Koichiro Tsutsumi
Okayama University Hospital

Hiroyuki Okada
Okayama University Hospital

Research article

Keywords: Surveillance, Prognosis factor, Intraductal papillary mucinous neoplasm, Pancreatic Cancer
Abstract

Background: Strict follow-up is recommended for branch-duct intraductal papillary mucinous neoplasms (BD-IPMN) to avoid missing the development of high-risk stigmata (HRS) at a premalignant stage. This study aimed to identify the risk factors associated with the development of HRS during follow-up.

Methods: We performed a retrospective analysis of 283 patients with BD-IPMN, treated at the Okayama University Hospital in Japan between January 2009 and December 2016. Only patients with imaging studies indicative of classical features of BD-IPMN without HRS and followed for >1 year were included in the study. We performed radiological follow-up every 6 months and collected patients’ demographic data, cyst characteristics, and clinical outcomes. Cyst size was recorded at the initial and final imaging studies and growth rate was calculated. The primary outcome was to evaluate the risk factors for development of HRS in patients with BD-IPMN without HRS at the initial diagnosis.

Results: Patients with BD-IPMN had a median follow-up of 53.3 months. Based on image analyses, a mean cysts size were initially 18.0 mm and their final size was 20.4 mm, and the mean annual cyst growth was 0.57 mm. Among them, 10 patients (3.5%) developed HRS after a median surveillance period of 55.8 months. Main pancreatic duct (MPD) size (5-9 mm) and cyst growth rate (>2.5 mm/year) were, both, independent risk factors for the development of HRS (odds ratio, 14.2; 95% CI, 3.1-65.2, P = .0006, and odds ratio, 6.1; 95% CI 1.5-25.5, P = .014). Considering the number of worrisome features (WFs), the rate of HRS development was not a WF: 2.0% (4/199), a single WF: 1.6% (1/62), multiple WFs: 22.7% (5/22), and significantly higher in multiple WFs (95% CI: 4.0–57.1; p=.0003).

Conclusions: MPD dilation, rapid cyst growth, and multiple WFs were significant risk factors for the development of HRS. In the presence of such features, it is necessary to closely follow the development of HRS and avoid missing the best opportunity for surgical intervention.

Introduction

The detection of intraductal papillary mucinous neoplasms (IPMN) of the pancreas has increased due to the use of cross-sectional imaging, such as computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), and endoscopic ultrasound (EUS).[1, 2] However, depending on the type of case, it is determined if resection is required and how to follow up.

The 2017 International Association of Pancreatology guideline (Fukuoka guideline) classifies clinical and radiological findings predicting malignancy into “high-risk stigmata (HRS)” and “worrisome features (WFs”).[3] HRS include i) obstructive jaundice, ii) enhancing mural nodule ≥ 5 mm, and iii) main pancreatic duct (MPD) ≥ 10 mm, with surgical resection is recommended for patients with any findings due to the high prevalence of cancer. WFs include i) history of pancreatitis, ii) cyst ≥ 3 cm, iii) enhancing mural nodule < 5 mm, iv) thickened/enhancing cyst walls, v) main pancreatic duct size 5–9 mm, vi) abrupt change in caliber of the pancreatic duct with distal pancreatic atrophy, vii) lymphadenopathy, viii) increased serum level of CA19-9, and ix) cyst growth rate ≥ 5 mm/2 years. The latter two features were recently
added as a new WF in the IPMN International Guidelines for 2017 (Fukuoka Guideline). When following branch-duct IPMN (BD-IPMN), it is also necessary to be aware of the tumor markers and the rate cyst growth.

Strict follow up is recommended for cases without HRS, and it seems important to not miss the development of HRS at a premalignant stage.[4] However, it is unclear which factors are associated with the development of HRS during follow-up. The aim of this study was to evaluate which WF of BD-IPMN is a risk factor for the development of HRS during follow up.

Materials And Methods

Study design

This single-center retrospective study examined the predictive factors for the development of HRS from BD-IPMN during follow-up. Informed consent was obtained from all participants. The study protocol was approved by the ethical guidelines of the World Medical Association Declaration of Helsinki and was approved by the Okayama University Ethics Committee.

Patients and diagnosis of BD-IPMN

Patients were identified from our EUS database and consecutive patients with a clinical diagnosis of BD-IPMN at the Okayama University Hospital with a minimum of 12 months follow up between January 2009 and December 2016 were included in this study. Patients had at least one cross-sectional imaging study (CT, MRI/MRCP, and EUS) performed 3 months or longer after the initial diagnosis. If there were no contraindications, EUS, contrast-enhanced CT (CE-CT), and MRCP were performed in all cases at the initial diagnosis. BD-IPMN was defined as the presence of unilocular or multicystic lesions of $\geq 5$ mm communicating with the MPD, as clearly demonstrated by CT, MRCP, or EUS. When EUS reveals a suspected nodule in the cystic lesions, contrast-enhanced EUS (CE-EUS) using an ultrasound contrast agent (Sonazoid™, Daiichi-Sankyo, Tokyo, Japan) was performed. If there was an absence of blood flow signals in the intracystic structures, we diagnosed it as a protein plaque.

All patients with HRS at the initial diagnosis or with cysts suspicious for another diagnosis rather than BD-IPMN (e.g., serous cystadenoma, mucinous cystic neoplasm, cystic neuroendocrine tumor, solid pseudopapillary tumor, or pseudocyst) were excluded from the study.

Follow-up and data collection

Patients diagnosed with BD-IPMN underwent radiological follow up by CE-CT or MRCP alternately every 6 months, and cyst characteristics including location, maximum cyst size, a solid component with or without enhancement, thickened cyst walls, MPD size, lymphadenopathy, and abrupt change in MPD caliber with distal pancreatic atrophy were examined. CA19-9 serum levels were routinely measured. The diameter of the cyst size and MPD size were defined as the maximum diameter measured by MRCP imaging, as recommended by the Fukuoka guidelines for evaluating pancreatic cysts.[3, 5, 6] In
multifocal cases, the largest cyst was used. Thickened cyst walls were defined if cyst walls were thicker than 2 mm. Increased serum levels of CA19-9 were defined as > 40 U/ml. If findings such as increased cyst diameter or appearance of nodules were suspected on CE-CT or MRCP imaging, EUS examination was performed. The follow-up period was recorded as the time between the initial cyst diagnosis (the first cross-sectional imaging on which the cyst was detected) and one of the following endpoints: date of last visit or death for patients without development of HRS; date of HRS development; and date of first discovery of malignancy on imaging for patients with an unresectable tumor.

We recommended surgical resection for cases in which HRS developed during follow up. For other patients with a solid mass suspected of pancreatic cancer or rapid growth in the cyst size, we considered surgical resection. Some patients who met the criteria for resection did not undergo surgery due to severe comorbidities or patient preference.

Assessment

The primary outcome was to evaluate the risk factors for development of HRS in patients with BD-IPMN without HRS at the initial diagnosis. The evaluated risk factors were following: history of pancreatitis, cyst ≥ 3 cm, enhancing mural nodule < 5 mm, thickened/enhancing cyst walls, MPD size 5–9 mm, abrupt change in caliber of the pancreatic duct with distal pancreatic atrophy, lymphadenopathy, increased serum level of CA19-9 (≥ 40 U/mL), and cyst growth rate ≥ 5 mm/2 years, which is defined as a WF by the Fukuoka guidelines. Cyst growth rate was calculated as follows: cyst size at last follow-up, cyst size at initial diagnosis / follow-up period, and increase of 2.5 mm/year or more was defined as a WF. Moreover, the comparison between initial cyst size and cyst growth rate was examined and placed into 4 different groups according to cyst size.

Statistical analysis

Continuous variables were presented as the mean with standard deviation (SD) or the median with range when appropriate, and categorical variables were expressed as frequencies with percentages. The Wilcoxon rank sum test was performed to compare the continuous variables, and a Fisher's exact test was performed to evaluate the categorical variables. A P-value < 0.05 was considered statistically significant. Univariate analysis was performed to predict the odds ratio (OR) of developing HRS. A multivariate model was not feasible because of the small sample size of the HRS group. All statistical analyses were performed using JMP® version 14 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

A total of six patients who underwent EUS for suspicious IPMN on CT/MRCP images were identified during the study period. Among these patients, 48 were excluded for the following reasons: not communicated with MPD (n = 8), cyst size < 5 mm (n = 6), possibility of another pancreatic cyst disease (n = 11), and main duct IPMN (n = 23). A total of 428 patients were diagnosed with BD-IPMN. However,
those who underwent surgical resection within 6 months or diagnosed with advanced pancreatic ductal adenocarcinoma (PDAC) or HRS at the initial diagnosis (n = 76) and with follow-up periods of less than one year (n = 69) were excluded from the study. Finally, 283 patients were included in this analysis (Fig. 1).

The baseline characteristics are summarized in Table 1. In this study, 139 men and 144 women with a mean age of 66.3 years were included. The median follow-up duration was 53.3 months (13.7-121.6). The WF excluding cyst growth rate > 2.5 mm which could not be identified at the initial diagnosis were detected in 89 of 76 patients at the initial diagnosis.

**Table 1.** Clinical characteristics of patients with branch-duct intraductal mucinous papillary neoplasms
| Gender      | n (%)         |
|-------------|---------------|
| Male        | 139 (49.1)    |
| Female      | 144 (50.9)    |
| Age (mean ± SD), year | 66.3 ± 10.5 |
| Cyst location |              |
| Head        | 140 (49.5)    |
| Body        | 86 (30.4)     |
| Tail        | 57 (20.0)     |
| Cyst morphology |          |
| Unilocal    | 36 (12.7)     |
| Multilocular| 247 (87.3)    |
| Multifocal disease | 162 (57.2) |
| Initial cyst size (mean ± SD), mm | 18.0 ± 9.9 |
| MPD (mean ± SD), mm | 2.5 ± 1.1 |
| CA19-9 (mean ± SD), U/ml | 20.3 ± 44.9 |
| Follow-up periods, median (range), month | 53.3 (13.7-121.6) |

Patients with WFs | 76 (26.9)
Counts of WFs at the initial diagnosis | 89
  - Pancreatitis | 5
  - Thickened cyst walls | 4
  - Cyst size >3 cm | 38
  - Mural nodule <5 mm | 4
  - MPD 5-9 mm | 11
  - Abrupt change in caliber of PD with distal atrophy | 1
  - Lymphoadenopathy | 2
  - CA19-9 >40 U/ml | 24

SD, standard deviation; MPD, main pancreatic duct; CA19-9, carbohydrate antigen 19-9; WF, worrisome feature; PD, pancreatic duct
Morphological data at initial diagnosis and during follow-up

Mean initial cyst size was 18.0 mm and MPD was 2.5 mm. At the final follow-up examination, the mean cyst size was 20.4 mm and MPD was 2.8 mm. The mean annual rate of cyst growth was 0.57 mm and 21 cases (7.4%) increasing by more than 2.5 mm/year, which is one of the WFs (Table 2). Among them, 8 patients had no WFs at the initial diagnosis. Finally, 110 WFs in 84 patients were detected at the initial diagnosis, including a cyst growth rate > 2.5 mm/year.

Table 2
Morphological changes in cysts (n = 283)

|                          | Initial     | Final       |
|--------------------------|-------------|-------------|
| Cyst size (mean ± SD), mm| 18.0 ± 9.9  | 20.4 ± 12.4 |
| Cyst growth rate (mean ± SD), mm/y | 0.57 ± 1.14 |             |
| Cyst growth rate ≥ 2.5 mm/y, n (%) | 21 (7.4)    |             |
| MPD (mean ± SD), mm      | 2.5 ± 1.1   | 2.8 ± 1.6   |
| CA19-9 (mean ± SD), U/mL | 20.3 ± 44.9 | 20.3 ± 41.1 |

SD, standard deviation; MPD, main pancreatic duct; CA19-9, carbohydrate antigen 19–9

Development of high-risk stigmata and risk factors

Of the 283 patients, 10 patients (3.5%) developed HRS after a median surveillance period of 55.8 months (30.4-112.3) before HRS development, enhancing solid component with cyst ≥ 5 mm (n = 7), MPD size ≥ 10 mm (n = 2), and enhancing solid component ≥ 5 mm with MPD size ≥ 10 mm (n = 1). No patients developed obstructive jaundice. Among them, 5 patients developed HRS after a 5-year surveillance period.

We evaluated which WF was the potential risk factor for development of HRS in this study (Table 3). MPD size (5–9 mm) and cyst growth rate (> 2.5 mm/year) were both independent risk factors for the development of HRS (OR 14.2, 95% CI 3.1–65.2, P = .0006 and OR 6.1, 95% CI 1.5–25.5, P = .014). CA19-9 level (> 40 U/mL) was not a feature of HRS development (P = .20).
Table 3
Risk factors for the development of HRS

|                | Development of HRS | Not HRS | Odds ratio (95% CI) | P-value |
|----------------|--------------------|---------|---------------------|---------|
|                | n = 10             | n = 273 |                     |         |
| Pancreatitis   | 0 (0)              | 5 (1.8) | 0                   | 0.99    |
| Thickened/enhanced cyst walls | 1 (10.0)          | 3 (1.1) | 10.0 (0.9-105.8)    | 0.06    |
| Cyst size > 3 cm | 3 (30.0)           | 35 (12.8) | 2.9 (0.7-11.8)    | 0.14    |
| Mural nodule < 5 mm | 1 (10.0)         | 3 (1.1) | 10.0 (0.9-105.8)    | 0.06    |
| MPD 5–9 mm     | 3 (30.0)           | 8 (2.9) | 14.2 (3.1–65.2)    | 0.0006  |
| Abrupt change in caliber of PD with distal atrophy | 0 (0)              | 1 (0.4) | 0                   | 0.99    |
| Lymphadenopathy| 0 (0)              | 2 (0.7) | 0                   | 0.99    |
| CA19-9 > 40 U/mL| 2 (20.0)          | 22 (8.1) | 2.9 (0.6–14.3)    | 0.20    |
| Cyst growth rate > 2.5 mm/y | 3 (30.0)          | 18 (6.6) | 6.1 (1.5–25.5)    | 0.014   |

HRS, high-risk stigmata; CI, confidence interval; MPD, main pancreatic duct; PD, pancreatic duct; CA19-9, carbohydrate antigen 19–9

Subsequently, we examined whether the simultaneous presence of WF at initial diagnosis could be used as a predictive marker of HRS development during follow-up. For each patient, the number of WFs was counted and the rate of HRS development was compared (Fig. 2). When the patients were classified into groups with no WF, single WF, and multiple WF group, HRS development was seen in 4 of 199 (2.0%) patients with no WF, 1 of 62 (1.6%) patients with a single WF, and 5 of 63 (22.7%) patients in the multiple WF group. Multiple WF group was significantly higher incidence rate of HRS and OR of the group with multiple WF compared to the other groups was 15.1 (95% CI: 4.0–57.1; P = .0003).

Morphological changes in cysts in terms of initial size

The participants were categorized into 4 groups according to their initial cyst sizes: group 1, < 10 mm (n = 51); group 2, 10 mm to < 20 mm (n = 125); group 3, 20 mm to < 30 mm (n = 69); and group 4, ≥ 30 mm (n = 38). Their respective median annual growth rates were 0 mm, 0.20 mm, 0.40 mm, and 0.98 mm (Fig. 3). The annual growth rates were significantly different among the 4 groups (P < .001). However, the incidence of newly developed HRS was not related to the initial cyst size (0% (0/51), 2.4% (3/125), 5.8% (4/69), and 7.9% (3/38) in groups 1, 2, 3, and 4, respectively; P = .11).

Surgery and progress
Out of the 10 patients who developed HRS, 3 patients underwent surgery (diagnosed with IPMN-derived invasive carcinoma in 2 and IPMN with low-grade dysplasia in 1) and 1 was found to have pancreatic cancer with bone metastases. The other 6 patients continued to follow up because of severe comorbidities or patient preference. In addition, to the patients who developed HRS, 5 patients (1.8%) underwent surgery, 2 for suspected concomitant PDAC, and 3 for patient’s wish for cyst size enlargement after a mean surveillance period of 62.4 months. The former were pathologically diagnosed PDAC, and the latter were IPMN with low-grade dysplasia.

Discussion

Previous reports showed that the presence of HRS is associated with a 40% risk of IPMN-related death, reinforcing that surgical resection should be offered to fit patients.[7] In IPMN with HRS, 3-year pancreatic carcinoma risk of obstructive jaundice, enhancing solid component, and main pancreatic duct > 10 mm were 79.8%, 37.3%, and 39.4%, respectively.[4] Thus, in the follow-up of BD-IPMN, HRS is considered to be the most important factor for predicting the appearance of IPMN-derived carcinoma. In this study, we evaluated the risk factors associated with the development of HRS during follow-up.

Reports have evaluated the risk factors of malignancy associated with individual cyst features of BD-IPMN, and cyst size > 3 cm, presence of mural nodule, and MPD dilatation > 5 mm proved to be the strongest predictors of pancreatic malignancy.[8, 9]

In our study, in addition to the dilation of MPD, rapid cyst growth and multiple WFs were significant factors in the development of HRS. Kang et al. reported that cysts growing faster than 2 mm/year presented a significantly higher risk of malignancy in all 201 subjects with an initial cyst size of < 30 mm without MPD dilation and no mural nodule.[10] Kolb JM et al. studied a group of 188 patients with low-risk IPMN and 12 patients developed WF. Among them, the rate of BD-IPMN growth was greater in patients who developed WF than in those who did not (2.84 mm/year vs 0.23 mm/year, P < .001).[11] In a recent study, rapid cyst growth rate (≥ 2.5 mm/year) is the main predictor of malignancy development in presumed BD-IPMN without WF or HRS.[12] In our study, of the 21 patients with a cyst growth rate ≥ 2.5 mm/year, 3 patients (14.3%) developed HRS. Although most BD-IPMNs are indolent and dormant, some cysts rapidly grow with the development of HRS. During surveillance of BD-IPMN, a particular focus should be placed on the cyst growth rate.

In a recently published multi-institutional study by Wilson et al., high-grade dysplasia and invasive carcinoma was found in 57.4% of patients with multiple WFs, 31.1% with single WF, and 24.6% with non-WF, in surgical cases of IPMN. This study indicated that the number of WFs was associated with malignancy of BD-IPMN.[13] Other studies scored the morphology of IPMN and created a risk model for malignancy, arguing that the larger the nodule diameter, cyst size, and main pancreatic duct diameter, the higher the risk of malignancy.[14] Consistent with these studies, the group with multiple WF developed HRS more frequently compared to the other groups in this study. However, another study found that WF counts were not related to the risk of malignant-IPMN. In surgical cases, the mean WF counts were 1.52,
2.11, 2.14, and 2.20 for low-grade, intermediate-grade, high-grade dysplasia, and invasive carcinoma, respectively.[15] Therefore, additional confirmatory studies are necessary to support our results.

Cyst size > 3 cm was not a significant factor in the development of HRS, but larger cysts had a greater cyst growth rate in this study. Han et al. reported that larger cysts, particularly those larger than 2 cm, showed significantly faster annual growth rates, and patients with initially larger cysts developed more WF during surveillance.[16] Thus, the initial cyst size is an important factor for the follow-up of BD-IPMN because it is related to the rate of cyst growth. Although a mural nodule, which has been reported to be associated with cancer in many reports, was not extracted as a risk factor, our study was underpowered to detect the difference for the small cases with mural nodule at the initial diagnosis.[16, 17]

The American Gastroenterological Association guidelines recommend discontinuing surveillance of non-progressive IPMNs within 5 years.[18] Conversely, accumulating evidence suggests that patients with BD-IPMN may remain at high risk of developing pancreatic carcinoma after 5-year surveillance.[19–21] In a Japanese study involving 804 patients with BD-IPMNs followed for > 5 years, the overall cumulative incidence of pancreatic cancer was 3.5% at 10 years from initial diagnosis.[21] In a study at a US referral center, high-grade dysplasia and invasive carcinoma were observed in 20 (5.5%) and 16 (4.4%) patients, respectively, of 363 patients included at the time of 5 years of follow-up.[22] Consistent with these studies, 5 out of the 10 patients who developed HRS appeared HRS after 5 years in our study, providing evidence supporting prolonged surveillance of patients with BD-IPMN. Further investigation is warranted to create surveillance programs based on these results.

This study has some limitations. First, it was a retrospective single-center study with a small sample size. Therefore, the possibility of unintentional selection bias in the selection of patients could not be fully excluded. Second, there were only 10 patients out of 285 who met the primary outcome (development of HRS). Due to the small outcome number, multivariate analysis was not performed. A further study in a large patient cohort with a long follow-up period is required to validate our results.

In conclusion, this study shows that BD-IPMN without HRS at the initial diagnosis developed HRS in 3.5% during surveillance, and the dilation of MPD, rapid cyst growth, and multiple WF were significant risk factors for the development of HRS. In the presence of such features, it is necessary to closely follow the development of HRS and be careful not to miss the timing of surgery.

**List Of Abbreviations**

BD-IPMN: Branch-duct intraductal papillary mucinous neoplasms

HRS: High-risk stigmata

MPD: Main pancreatic duct

WFs: Worrisome features
Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki, and approved by the Okayama University Hospital review board. Informed consent was omitted and information of this study was disclosed in the form of opt-out on our hospital website. Information regarding the conduct of the research including the objectives was disclosed and the research subjects were provided an opportunity to refuse inclusion in the research.

Consent for publication

Not applicable.

Competing interests

The authors declared no conflicts of interest.

Funding

This study was not funded.

Authors' contributions

Tatsuhiro Yamazaki and Takeshi Tomoda contributed to the study design, draft, and manuscript writing. Kazuya Miyamoto, Akihiro Matsumi, Eijiro Ueta, Yuki Fujii, Yosuke Saragai, Daisuke Uchida, Kazuyuki
Matsumoto, Shigeru Horiguchi and Koichiro Tsutsumi contributed to collection and assembly of data. Hironari Kato and Hiroyuki Okada participated in the final approval of the article.

Acknowledgements

Not applicable.

References

1. Klibansky DA, Reid-Lombardo KM, Gordon SR, Gardner TB. The clinical relevance of the increasing incidence of intraductal papillary mucinous neoplasm. Clin Gastroenterol Hepatol. 2012;10:555–8.
2. Bassi C, Sarr MG, Lillemoe KD, Reber HA. Natural history of intraductal papillary mucinous neoplasms (IPMN): current evidence and implications for management. J Gastrointest Surg. 2008;12:645–50.
3. Tanaka M, Fernandez-Del Castillo C, Kamisawa T et al.. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas Pancreatology. 2017;17:738–753.
4. Mukewar S, de Pretis N, Aryal-Khanal A et al.. Fukuoka criteria accurately predict risk for adverse outcomes during follow-up of pancreatic cysts presumed to be intraductal papillary mucinous neoplasms Gut. 2017;66:1811–1817.
5. Zhang XM, Mitchell DG, Dohke M, Holland GA, Parker L. Pancreatic cysts: depiction on single-shot fast spin-echo MR images Radiology. 2002;223:547–553.
6. Berland LL, Silverman SG, Gore RM et al.. Managing incidental findings on abdominal CT: white paper of the ACR incidental findings committee J Am Coll Radiol. 2010;7:754–773.
7. Crippa S, Bassi C, Salvia R et al.. Low progression of intraductal papillary mucinous neoplasms with worrisome features and high-risk stigmata undergoing non-operative management: a mid-term follow-up analysis Gut. 2017;66:495–506.
8. Anand N, Sampath K, Wu BU. Cyst features and risk of malignancy in intraductal papillary mucinous neoplasms of the pancreas: a meta-analysis. Clin Gastroenterol Hepatol. 2013;11:913–21. quiz e959-960.
9. Petrone MC, Magnoni P, Pergolini I et al.. Long-term follow-up of low-risk branch-duct IPMNs of the pancreas: is main pancreatic duct dilatation the most worrisome feature? Clin Transl Gastroenterol. 2018;9:158.
10. Kang MJ, Jang JY, Kim SJ et al.. Cyst growth rate predicts malignancy in patients with branch duct intraductal papillary mucinous neoplasms Clin Gastroenterol Hepatol. 2011;9:87–93.
11. Kolb JM, Argiriadi P, Lee K. al.. Higher Growth Rate of Branch Duct Intraductal Papillary Mucinous Neoplasms Associates With Worrisome Features Clin Gastroenterol Hepatol. 2018;16:1481–1487.
12. Marchegiani G, Andrianello S, Pollini T et al.. "Trivial" Cysts Redefine the Risk of Cancer in Presumed Branch-Duct Intraductal Papillary Mucinous Neoplasms of the Pancreas: A Potential Target for Follow-Up Discontinuation? Am J Gastroenterol. 2019;114:1678–84.
13. Wilson GC, Maithel SK. Bentrem Det al.. Are the Current Guidelines for the Surgical Management of Intraductal Papillary Mucinous Neoplasms of the Pancreas Adequate? A Multi-Institutional Study. J Am Coll Surg. 2017;224:461–9.

14. Shimizu Y, Hijioka S. Hirono Set al.. New Model for Predicting Malignancy in Patients With Intraductal Papillary Mucinous Neoplasm Ann Surg. 2018. https://doi.org/10.1097/SLA.0000000000003108.

15. Aso T, Ohtsuka T, Matsunaga Tet al.. "High-risk stigmata" of the 2012 international consensus guidelines correlate with the malignant grade of branch duct intraductal papillary mucinous neoplasms of the pancreas Panreas. 2014;43:1239–1243.

16. Han Y, Lee H, Kang, JSet. al.. Progression of Pancreatic Branch Duct Intraductal Papillary Mucinous Neoplasm Associates With Cyst Size Gastroenterology. 2018;154:576–584.

17. Seo N, Byun JH, Kim JHet al.. Validation of the 2012 International Consensus Guidelines Using Computed Tomography and Magnetic Resonance Imaging: Branch Duct and Main Duct Intraductal Papillary Mucinous Neoplasms of the Pancreas Ann Surg. 2016;263:557–564.

18. Vege SS, Ziring B, Jain R, Moayyedi P, Clinical Guidelines C, American Gastroenterology A. American gastroenterological association institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts Gastroenterology. 2015;148:819–822; quize812-813.

19. Imbe K, Nagata N, Hisada Yet al.. Validation of the American Gastroenterological Association guidelines on management of intraductal papillary mucinous neoplasms: more than 5 years of follow-up Eur Radiol. 2018;28:170–178.

20. Oyama H, Tada M, Takagi Ket al.. Long-term Risk of Malignancy in Branch-Duct Intraductal Papillary Mucinous Neoplasms Gastroenterology. 2020;158:226–237 e225.

21. Khannoussi W, Vullierme MP, Rebours Vet al.. The long term risk of malignancy in patients with branch duct intraductal papillary mucinous neoplasms of the pancreas Panreatology. 2012;12:198–202.

22. Pergolini I, Sahora K, Ferrone CRet al.. Long-term Risk of Pancreatic Malignancy in Patients With Branch Duct Intraductal Papillary Mucinous Neoplasm in a Referral Center Gastroenterology. 2017;153:1284–1294 e1281.