Digital peroral pancreatoscopy to determine surgery for patients who have intraductal papillary mucinous neoplasms of the pancreas with mural nodules

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Supplementary Material is available at https://doi.org/10.1055/a-2452-2919

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ABSTRACT

Background and study aims Because more than a few patients have intraductal papillary mucinous neoplasms of the pancreas (IPMNs) with mural nodules (MNs) that are benign, clinical plans should be determined by using histocytological specimens especially, for patients with high risk for surgery or with a small MN.

Patients and methods This study included 27 patients to evaluate the efficacy of peroral pancreatoscopy using a SpyGlass DS system (POPS-DS) for patients with MN-positive IPMN, mainly focusing on the ability of POPS-DS to detect malignancy.

Results Biopsy specimens obtained under POPS-DS guidance could be used for histological evaluation of all patients with MNs in the main pancreatic duct and 67% of the patients with MNs in the branch ducts, whereas fluid specimens collected during POPS-DS could be used for histocytological evaluation for all patients. For the 13 patients who underwent surgery just after POPS-DS, the sensitivity, specificity, and accuracy of POPS-DS to detect malignancy were 89%, 100%, and 92%, respectively. For the 12 patients who underwent surveillance without surgery, the cumulative 3-year progression rates for nine benign IPMNs and three malignant ones determined using POPS-DS were 0% and 100%, respectively. However, the sensitivity of POPS to detect IPMN epithelium in the resection margin was 20%. Only one patient developed procedure-related pancreatitis (mild).

Conclusions POPS-DS could be used to accurately detect malignancy in patients with MN-positive IPMN. Therefore, histocytological evaluation using POPS-DS can contribute to selection of patients for whom surgery would be appropriate.

Introduction

Mural nodule (MN) is widely known to be the most accurate indicators of malignant intraductal papillary mucinous neoplasms (IPMNs) of the pancreas [1, 2, 3, 4], and surgical resection is recommended for IPMNs with MNs ≥ 5 mm in the recent internal consensus guidelines (ICGs) [1, 2]. However, surgery should be determined cautiously even for those IPMNs because: 1) more than a few patients with MN-positive IPMNs are benign [5] and 2) the multice nter study in Japan concluded that urgent resection is unnecessary for IPMNs with MN <10 mm [6].

Peroral pancreatoscopy (POPS) has been shown to be useful for determining surgery for IPMNs by previous studies and a recent meta-analysis [7, 8, 9, 10, 11, 12]. A newly designed digital pancreatobiliary scope (SpyGlass DS [SpyDS] system: Boston scientific co., Natick, Massachusetts, United States) recently has become available and can be used to perform POPS for examining intraductal conditions of IPMNs, and this scope may be fit for evaluation of MNs under direct endoscopic vision due to its good manipulation. Regarding the significance of POPS for IPMNs, on the other hand, it may remain to be clarified whether the results of POPS for IPMNs truly contribute to patient selection for surgery or not because long-term clinical outcomes of IPMN patients who did not undergo surgery after POPS diagnosis have not been fully evaluated.
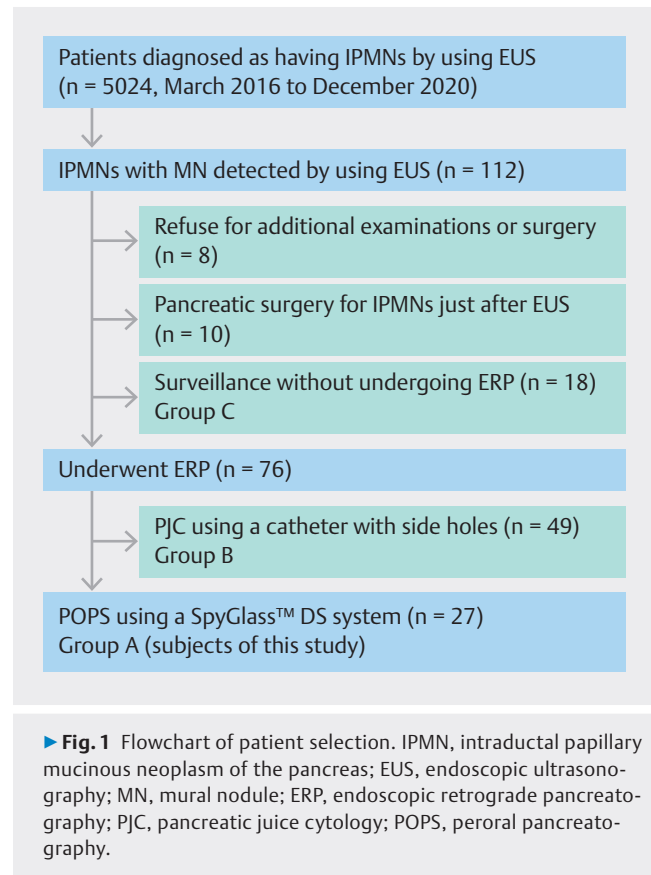
Thus, including the above-mentioned possibility of this scope and the unsolved issue related to POPS for IPMNs, we aimed to clarify the clinical significance of POPS using a SpyDS system for patients with MN-positive IPMNs, mainly focusing on patient selection for surgery.

Patients and methods

Study population

This study was approved by the Sendai City Medical Center institutional review boards (registration number: 2017–0015). A flowchart of this study is shown in ▶ Fig. 1. From our prospectively registered database of patients undergoing endoscopic ultrasound, data from 5024 consecutive patients with presumed/definitive IPMN determined by using EUS between April 2016 and December 2020 were obtained. Of those, 112 patients were found to have MN-positive IPMNs.

Of those 112 patients, 76 (68%) underwent endoscopic retrograde pancreatography (ERCP) to obtain histocytological specimens, and they included 27 patients who underwent POPS using a SpyDS scope (Group A, POPS-DS group) and 49 patients who underwent pancreatic juice cytology (PJC) using fluid specimens obtained through a catheter with side-holes (Group B, conventional PJC group). Of the remaining 36 patients with MN-positive IPMNs who did not undergo ERCP, 18 were monitored with regular imaging studies (Group C, non-intervention group), 10 underwent surgery just after EUS due to having large MNs (n = 4), invasive mass lesions adjacent to the IPMNs (n = 5), and malignant biliary stricture (n = 1), and the remaining eight refused to undergo additional examinations or surveillance. Thus, 27 patients classified into Group A were in-

▶ Fig. 1 Flowchart of patient selection. IPMN, intraductal papillary mucinous neoplasm of the pancreas; EUS, endoscopic ultrasonography; MN, mural nodule; ERP, endoscopic retrograde pancreatography; PJC, pancreatic juice cytology; POPS, peroral pancreatography.

cluded to evaluate the efficacy of POPS using a SpyDS scope for patients with MN-positive IPMNs and were compared with those classified into Groups B and C to analyze the clinical significance of POPS for IPMNs.

Indications for performing POPS-DS

Since April 2016, we have consecutively performed POPS using a SpyDS system (POPS-DS) for patients having MN-positive IPMNs who met the following criteria: 1) target MNs involving the main pancreatic duct (MPD); 2) target MNs in the branch duct near the connection with the MPD; 3) a minimum diameter of >4 mm of the pancreatic ducts along the route from the papilla to the target lesion was estimated by using magnetic resonance cholangiopancreatography (MRCP) or ERCP; and 4) there were no crooked parts of the MPD, which a SpyDS scope appears to be difficult to pass through.

For patients unfit to undergo POPS-DS, conventional PJC was used for histocytological evaluation (categorized into Group B), and fluid specimens obtained were processed by using a cell-block method [13, 14, 15]. In case of small MNs <5 mm in the branch duct, ERCP was not usually performed due to low risk of malignancy.

Outcome measurements

We retrospectively evaluated the following outcome measurements by using prospectively registered ERCP and pathological databases and the electronic medical records in our medical center. The primary outcome measurement was diagnostic ac-

curacy of POPS-DS to detect malignancy for patients undergoing surgery just after POPS-DS, and this accuracy was compared with that for Group B.

Secondary outcome measurements were: 1) clinical courses of patients undergoing surveillance without surgery just after POPS-DS and were compared with those of patients undergoing surveillance in Groups B and C; 2) detection rate for target MNs using POPS-DS; 3) successful rate of POPS-guided biopsy to obtain specimens with evaluable histology; 4) preoperative detection rate of IPMN epithelium in the resection margin by using POPS-DS; and 5) adverse events (AEs) associated with the procedures of POPS-DS.

Endoscopic procedures

All procedures related to POPS were performed by the team of pancreatobiliary endoscopists including those with more than 15 years endoscopy experience (S.K. and Y.K.). For obtaining specimens from IPMN lesions, ERCP was first carried out using a duodenoscope (TJF260V: Olympus, Tokyo, Japan) with a 4F cannula (PR-104Q-1 or PR-109Q-1: Olympus, Tokyo, Japan), and a 0.025-inch guidewire was carefully advanced deep into the MPD. After the cannula was removed from the guidewire, we usually performed intraductal ultrasound (IDUS, UM-DG20–31R: Olympus) along the guidewire placed in the MPD to detect the position of MNs in the MPD and/or the connecting part with the branch duct involving target MNs and to determine the estimated resection margin (the left margin of the portal vein).

After evaluations using IDUS, a SpyDS scope was advanced into the MPD along the guidewire. Endoscopic pancreatic sphincterotomy was performed only when the following criteria were met: 1) the diameter of the MPD near the papilla approximated that of the SpyDS scope (3.6 mm); and 2) the dilated orifice of the papilla with mucin extrusion was not observed. When performing POPS-DS, a dual operator (mother-daughter) endoscope technique was used for all patients. Clear visualization of the inside of the pancreatic ducts was obtained by alternating injection of saline and suction of fluid filling the pancreatic ducts through the two separate lumens of the SpyDS scope. All of the fluid obtained through the SpyDS scope was used for histocytological evaluation. When target MNs could be detected under POPS-DS guidance, we tried to perform multiple biopsy for MNs by using SpyBite biopsy forceps (Boston Scientific Co.).

Statistical analysis

All statistical analyses were performed using SPSS software version 11.0 (SPSS Inc., Chicago, Illinois, United States). A Pearson's χ2 test or a Fisher's exact test was used for categorical variables. A Mann-Whitney U-test was used for continuous data (distribution of variables is shown by using interquartile range [IQR] or range). Cumulative progression rate of the IPMNs and cumulative survival rate were calculated using the Kaplan-Meyer method.

Results

Baseline characteristics of 27 patients who underwent POPS-DS

Baseline characteristics of 27 patients are shown in ▶ Table 1 and Supplementary Table 1. All 27 patients could be classified into worrisome features (WF) or high-risk stigmata (HRS) listed in the ICGs. Locations of target MNs were the dilated branch duct in 12 patients (44%, median height: 11.0 mm [range: 3.5–20.0]) and the MPD in 21 patients (78%, median height: 5.0 mm

▶ Table 1 Baseline characteristics of 27 subjects.

Age (years), median (range)	74 (58–91)
Sex (Man/Woman)	24/3
Past history of pancreatic resection, n (%)	4 (15)
Laboratory data, median (range)	
▪ Serum AMY levels (IU/mL)	75 (37–354)
▪ Serum CA19–9 levels (IU/mL)	5.0 (2.0–890.0)
▪ HbA1c (%)	6.3 (5.4–11.4)
Imaging findings just before performing POPS-DS	
▪ Findings of MNs using EUS	
– MNs in the MPD	
• n (%)	21 (78)
• Height of MNs (mm), median (range)	5 (2.0–10.0)
– MNs in the branch ducts	
• n (%)	12 (44)
• Height of MNs (mm), median (range)	11 (3.5–20.0)
▪ MPD diameter (mm), median (range)	10 (4.5–26.0)
▪ Cyst size (mm), median (range), n = 23	35 (11–50)
Risk classification of the ICGs at the time of initial POPS-DS, n (%)	
▪ HRS	20 (74)
▪ WF	7 (26)
Patients who underwent surgery for IPMNs just after initial POPS-DS	
▪ n (%)	13 (48)
▪ PD/DP/TP/Partial	4/6/2/1
▪ Histological diagnosis using the resected specimens	
– Low-grade IPMN	4
– High-grade IPMN	6
– Invasive cancer/PDAC	3

AMY, amylase; CA-19, carbohydrate antigen 19–9; DP, distal pancreatectomy; EUS, endoscopic ultrasonography; HRS, high-risk stigmata; ICGs, international consensus guidelines; IPMN, intraductal papillary mucinous neoplasm; MN, mural nodule; MPD, main pancreatic duct; PD, pancreatoduodenectomy; PDAC, pancreatic ductal adenocarcinoma; POPS-DS, peroral pancreatoscopy using SpyGlass DS; TP, total pancreatectomy; WF, worrisome features.

[range: 2.0–10.0]). Thirteen patients (48%) underwent surgery for their IPMNs just after POPS-DS.

Success rates for detecting target MNs and obtaining biopsy/fluid specimens

All target MNs in the MPD of 21 patients were detected under POPS-DS guidance, and biopsy was performed for 19 of those lesions (POPS-DS biopsy was not performed for the remaining two patients at endoscopist discretion). In all 19 patients, biopsy specimens were evaluable for histology (median biopsy number: 4 [range: 1–9]).

Target MNs in the branch duct could be detected in 10 of 12 patients (83%) under POPS-DS guidance. In eight of 10 patients, biopsy specimens were evaluable for histology (median biopsy number: 2 [range: 2–4]). Therefore, the rate of obtaining specimens for which histocytological diagnoses could be made was 67% (8/12) in this population.

After POPS-guided biopsy, fluid specimen was collected through the SpyDS scope by using the intraductal saline lavage method in the location of the target MNs. For two patients in whom the SpyDS scope could not reach their MNs in the branch ducts (Patients 3 and 13 in Supplementary Table 1), lavage was performed in the location of the pancreatic duct where a SpyDS scope was advanced as near the target lesions as possible. Finally, histocytological evaluations using fluid specimens could be performed for all patients.

Diagnostic accuracy of POPS specimens for detecting malignancy

Of the 13 patients who underwent surgery for their IPMNs just after POPS-DS, nine (69%) had definitive pancreatic malignancy. Of the 13 patients, eight underwent surgery due to the diagnosis of malignancy by using POPS-DS and four due to having MNs >10 mm despite a benign diagnosis using POPS-DS, and the remaining patient preferred undergoing surgery despite a benign diagnosis using POPS-DS.

In this surgical population, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for detecting malignancy using biopsy specimens obtained under POPS-DS guidance (n = 12) were 63%, 100%, 100%, 57%, and 75%, respectively (▶ Fig. 2); whereas, those using POPS-DS-guided fluid sampling (n = 13) were 89%, 100%, 100%, 80%, and 92%, respectively. In addition, the concordance rate for histological subtype between POPS specimens and resected ones was 92% (12/13).

Regarding three patients in whom POPS-guided biopsy could not detect malignancy, a SpyDS scope could not reach the target lesion in one patient (Patient 3 in Supplementary Table 1). For another patient (Patient 1 in Supplementary Table 1), although the target MN in the MPD was diagnosed with low-grade IPMN (LG-IPMN) using POPS-DS-guided biopsy, malignant cells were detected by using POPS-DS-guided fluid sampling. By using the resected specimens, the target MN in the MPD was diagnosed with LG-IPMN, and latent concomitant pancreatic ductal adenocarcinoma (PDAC) also was found at a different location in the resected pancreas. For the remaining patient (Patient 10 in Supplementary Table 1), the majority of

the main IPMN lesion was found to be LG-IPMN by using the resected specimens, whereas a small high-grade IPMN (HG-IPMN) was detected in this IPMN.

Clinical courses of patients who underwent surveillance without surgery

Of the 14 patients who did not undergo surgery just after POPS-DS, nine underwent surveillance due to diagnosis of LG-IPMN using POPS-DS (gastric type, 8; not available, 1). Of the remaining five patients, three preferred undergoing surveillance without surgery despite diagnosis of malignancy using POPS-DS and two refused to undergo both surveillance and surgery.

In eight of nine patients with benign IPMN determined by using POPS-DS, their IPMNs did not progress during a median surveillance period of 1322 days (IQR: 599–1704) after POPS-DS (▶ Fig. 3). The remaining patient (Patient 17 in Supplementary Table 1) developed another 5-mm MN in the MPD 1348 days after the initial POPS-DS, and re-examination of POPS-DS detected malignancy. For this population, cumulative 3- and 5-year progression rates were calculated to be 0% and 20%, respectively (▶ Fig. 4).

On the other hand, IPMNs were progressive in all three patients who underwent surveillance without surgery after diagnosis of malignancy using POPS-DS. Metastatic lesions developed in two patients (Patients 14 and 18 in Supplementary Table 1) 570 and 229 days after POPS-DS, respectively, and a rapid increase in MPD diameter (from 12 to 18 mm) was observed after POPS-DS in the remaining patient (Patient 26 in Supplementary Table 1). The cumulative 3-year progression rate was calculated to be 100% for this population (▶ Fig. 4).

Comparison of clinicopathological factors between Groups A, B, and C

To analyze the efficacy of POPS-DS for IPMNs, clinicopathological factors in Group A were compared with those in Groups B and C (▶ Table 2). MPD diameter and percentage of MNs in the MPD were significantly larger in Group A than in Groups B and C (median MPD diameter: 10.0 mm, 3.5 mm, and 3.0 mm, respectively; rate of MNs in the MPD 78%, 6%, and 6%, respectively), indicating selection bias among three groups.

For diagnostic accuracy of preoperative histocytological examinations to detect malignant IPMN, sensitivity was excellent in Group A compared with Group B (89% vs. 67%, P = 0.341). In patients in Groups A, B, and C who underwent surveillance without surgery, the 3-year cumulative progression rates of IPMNs were 0%, 20%, and 19%, respectively (▶ Fig. 5), and the percentages of surgery during surveillance were 0%, 16% (6/38), and 19% (2/18), respectively (all 8 patients in Groups B and C who underwent surgery during surveillance were diagnosed with malignant IPMN or PDAC).

Detection of IPMN involvement in resection margin using IDUS and POPS-DS

Of the 13 patients undergoing surgery after POPS-DS, 11 undergoing pancreatoduodenectomy or distal pancreatectomy were included to evaluate the preoperative detection rate for
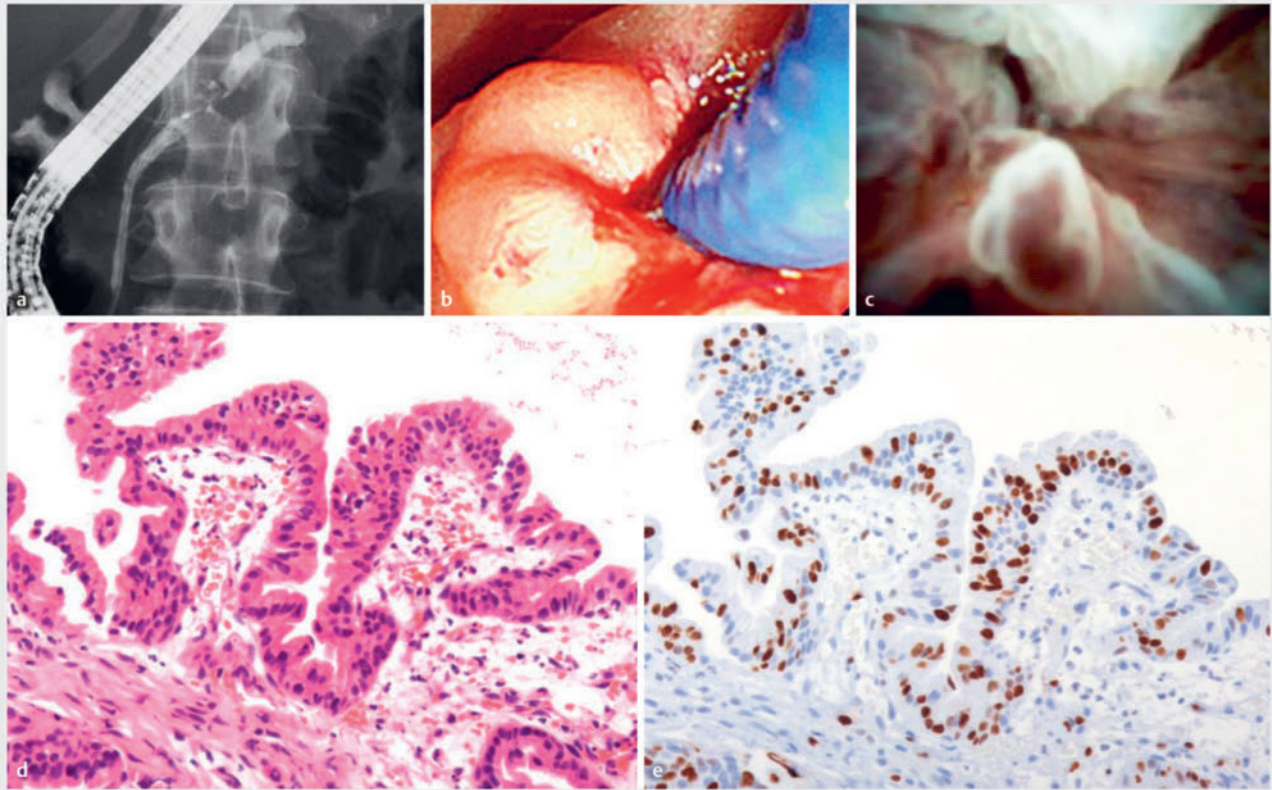
▶ **Fig. 2** Fifty-eighty-year-old woman (Patient 9 in Supplementary Table) who underwent pancreatic tail resection for IPMN 2 years ago. During surveillance after surgery, an intraductal neoplasm localized in the MPD of pancreatic body was detected using MRCP and EUS. She underwent POPS using a SpyGlass scope (**a**, pancreatography; **b**, insertion of SpyGlass scope to the major papilla after EPST). **c** Papillary protrusions indicative of MNs of IPMN were detected under POPS guidance, and biopsy using a SpyBite was performed. **d** HE staining for biopsy specimens showed atypical epithelium (x100), and **e** MUC1 was slightly positive, MUC2 was negative, and Ki67 labelling index was >30% (x100), which indicated malignant IPMN. She underwent partial resection for the remnant pancreatic body, and was diagnosed with HG-IPMN using the resected specimens. IPMN, intraductal papillary mucinous neoplasm of the pancreas; MPD, main pancreatic duct; MRCP, magnetic resonance cholangiopancreatography; EUS, endoscopic ultrasonography; POPS, peroral pancreatography; EPST, endoscopic pancreatic sphincterotomy; MN, mural nodule; HE, hematoxylin and eosin; HG, high-grade.

IPMN involvement in the resection margin by using POPS-DS (▶ Table 3), and two patients undergoing total pancreatectomy were excluded from this evaluation.

In one of 11 patients (9%), the IPMN epithelium was observed in the estimated resection margin under POPS-DS guidance, and histological diagnosis using POPS-guided biopsy for the estimated resection margin was LG-IPMN. In the resected specimens, LG-IPMN was detected in the actual resection margin of this patient. On the other hand, the actual resection margin was positive for five of 11 patients (LG-IPMN, 4; HG-IPMN, 1). Therefore, sensitivity, specificity, and accuracy to detect the IPMN involvement with the resection margin by using POPS-DS were 20% (1/5), 100% (6/6), and 64% (7/11), respectively.

### Adverse events associated with the POPS-DS procedures

Nonsteroidal anti-inflammatory drugs (diclofenac sodium suppository, 25 or 50 mg) were administered just before POPS-DS to all patients. Mild post-ERCP pancreatitis (PEP) developed in one patient. No other AEs associated with POPS-DS procedures developed.

Discussion

From the results of this study, biopsy/fluid specimens obtained through POPS-DS could be used to accurately detect malignancies in patients who had undergone surgery for their MN-positive IPMNs. In addition, there was a clear difference in the progression rate between malignant and benign IPMNs determined using POPS-DS for patients who underwent surveillance without surgery. Therefore, although MN-positive IPMNs were shown to be associated with a relatively high rate of malignancy [3,4], histocytological evaluations using POPS-DS can be used to select patients with MN-positive IPMNs for whom surgery is truly appropriate.

The efficacy of POPS-DS is mainly due to the ability to obtain histocytological specimens from the target MNs under direct visualization. For IPMNs with target MN in the MPD, the percentage of the close approach of the SpyDS scope to target MNs
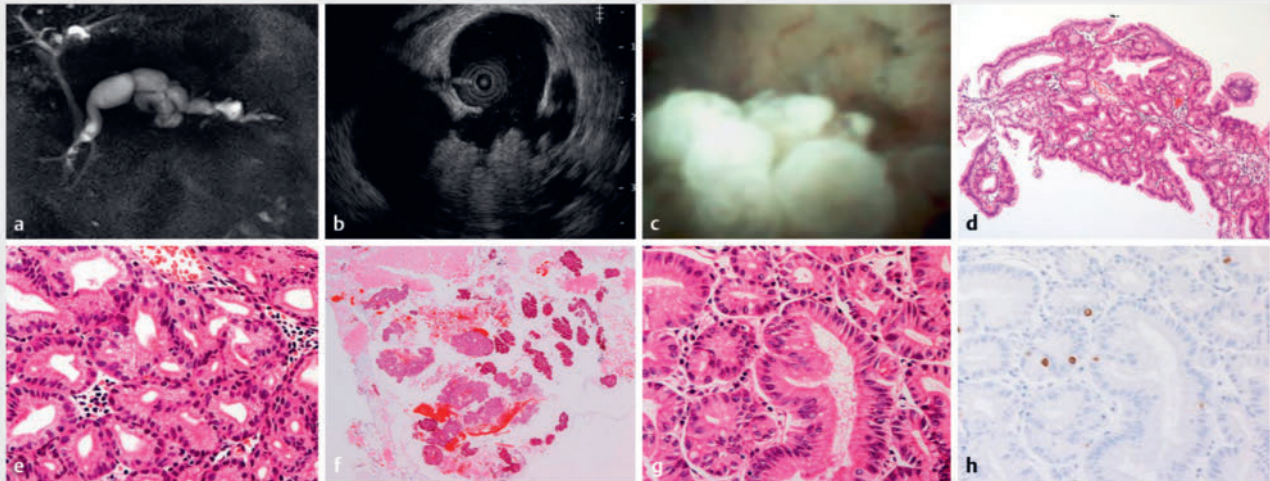
▶ **Fig. 3** **a** 85-year-old man (Patient 16 in Supplementary Table) diagnosed with IPMN using MRCP. Using EUS, an MN with the height of 12 mm was detected in the dilated branch duct. He underwent ERCP, and IDUS showed the connection part between the dilated MPD and **b** the cystic lesion in which an MN existed. **c** During POPS, a SpyGlass DS scope could be inserted into the cyst. HE staining for biopsy specimens showed atypical epithelium indicative of LG-IPMN (**d**, ×10; **e**, ×100). In addition, fluid specimens obtained via the SpyGlass scope during POPS were processed the cell-block method and used for cytology. HE staining for the specimens showed many of cell clusters indicating LG-IPMN (**f**, ×1.25; **g**, ×100). Ki67 labelling index was < 5% (**h**, ×100), and both MUC1 and MUC2 were negative. He was diagnosed with LG-IPMN, followed by semiannual surveillance using imaging studies without remarkable changes in the IPMN for more than 4 years after POPS evaluations. IPMN, intraductal papillary mucinous neoplasm of the pancreas; MRCP, magnetic resonance cholangiopancreatography; EUS, endoscopic ultrasonography; MN, mural nodule; ERCP, endoscopic retrograde cholangiopancreatography; IDUS, intraductal ultrasonography; MPD, main pancreatic duct; POPS, peroral pancreatography; HE, hematoxylin and eosin; LG, low-grade.
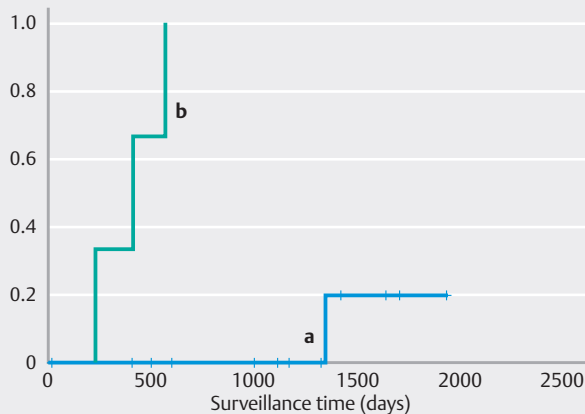
▶ **Fig. 4** Cumulative progression rates of 12 patients undergoing surveillance. a Cumulative 3- and 5-year progression rates in nine patients diagnosed with benign IPMN using POPS-DS were 0% and 20%, respectively, whereas b the cumulative 3-year progression rate in three patients diagnosed with malignant IPMN using POPS-DS was 100%. IPMN, intraductal papillary mucinous neoplasm of the pancreas; POPS-DS, peroral pancreatography using a SpyGlass DS scope.
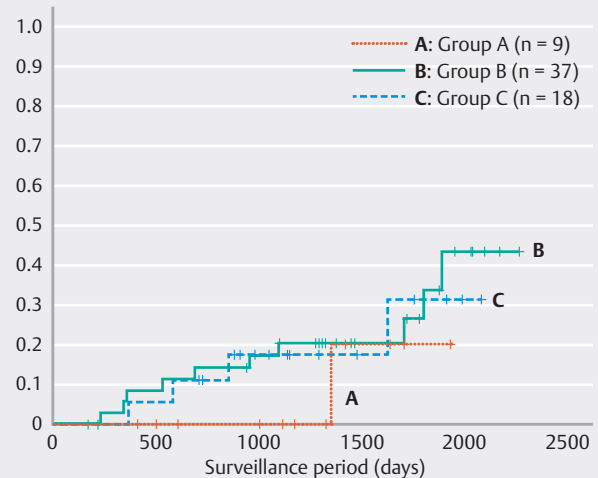
▶ **Fig. 5** Progression rates of IPMNs in patients who initially underwent surveillance without surgery in Groups A, B, and C. Cumulative 3- and 5-year progression rates in Group A were 0% and 20%, respectively, those in Group B were 20% and 34%, respectively, and those in Group C were 19% and 31%, respectively. IPMN, intraductal papillary mucinous neoplasm of the pancreas.

and that of obtaining histologically evaluable biopsy specimens were 100%. Because our previous report demonstrated benign main duct type IPMNs with MNs were not scarce (nearly 40% of the resected main duct type IPMNs with MNs) [6],this endo-scopic procedure is of great significance, especially for patients in whom surgery is likely to be avoided because they have some high-risk factors.

On the other hand, the percentages for the close approach of the SpyDS scope to the target MNs in the branch ducts and those for obtaining histologically evaluable biopsy specimens were limited (83% [10/12] and 67% [8/12], respectively). However, PJC using fluid specimens obtained via POPS-DS was histocytologically evaluable for all four patients with MN-positive BD-IPMN in whom histocytological evaluation using POPS-guided biopsy specimens failed. In addition, sensitivity of fluid specimen for detection of malignancy was higher than that for POPS-guided biopsy (89% vs. 63%), which may be due to the following: 1) the target MNs in the branch ducts sometimes cannot be detected under POPS-DS guidance and 2) the histology of biopsy specimens obtained from MNs does not necessarily reflect the highest tumor grade of IPMNs due to the diversity of tumor grades within IPMN lesions. On the other hand, fluid specimens collected near target MNs can overcome those problems because: 1) a large number of small specimens derived from several parts of the MN lesions can be collected by using the lavage method through the SpyDS scope, followed by processing using the cell-block method [13, 14, 15], which may be fit for the problem related to the diversity of the IPMN grade; and 2) this method can be performed as near the target MNs as possible even if a SpyDS scope cannot reach the target MNs in the branch ducts. Therefore, it is important to add PJC to POPS-guided biopsy when POPS-DS is performed for diagnosis of malignant IPMN.

Because almost all patients included in previous reports about the utility of POPS for IPMNs underwent surgery after POPS evaluations, long-term clinical outcomes of IPMN patients undergoing surveillance without surgery have not been fully studied. In this study, for the 12 patients undergoing surveillance without surgery, the cumulative 3-year progression rate for IPMNs was 0% for patients with benign IPMN determined by using POPS-DS, whereas it was 100% for those with malignant IPMN. Therefore, patients with MN-positive "benign" IPMN determined by using POPS-DS can be managed without immediate surgery, which may be best for elderly patients or patients with several comorbidities.

In this study, results of POPS-DS for IPMNs were compared with those for conventional PJC performed during the same study period (▶ Table 2). Although there was a selection bias between these methods, POPS-DS appears to be superior to conventional PJC in preoperative sensitivity for detection of malignancy and rate of progression of IPMNs during surveillance without surgery. Therefore, POPS-DS first should be used when POPS-DS scope is likely to reach the target MN on the basis of findings from ERP/MRCP, which is particularly indicated for patients who have IPMNs with MNs in or near the dilated MPD. In addition, conventional PJC, with a moderate sensitivity of 60%, should be performed when POPS-DS appears to be difficult for evaluation of malignancy for MN-positive IPMNs. On the other hand, because the progression rate of IPMNs was relatively low during surveillance in patients in Group C, a wait-and-see approach without further examination including POPS/PJC or urgent surgery may be appropriate for patients who have IPMNs with small MNs in the branch duct.

Furthermore, this study investigated the detection rate for IPMN epithelium extending to the resection margin by using POPS-DS. However, detection sensitivity was shown to be low (20%). On the other hand, because most of the IPMN epithelium extending to the resection margins was LG-IPMN (80%, 4/5), this result may not have affected patients' postoperative clinical courses [16]. However, local recurrence of HG-IPMN in the actual resection margin developed in the one remaining patient in whom no IPMN epithelium was preoperatively observed in the estimated resection margin by using POPS-DS. Therefore, this result may indicate the necessity of POPS-DS-guided biopsy for estimating the resection margin, even in patients in whom no IPMN epithelium extending to the estimated resection margin was observed under POPS guidance.

This study has several limitations. First, the number of subjects may be too small to evaluate clinical efficacy of POPS-DS for MN-positive IPMNs. Therefore, a large-scale, multicenter study is needed to clarify the clinical implications of POPS-DS in the future. Second, not all patients with MN-positive IPMNs can undergo endoscopic evaluation for their MNs by using POPS-DS because the SpyDS scope sometimes cannot reach the target MNs. In other words, POPS-DS possibly tended to be performed for patients with easy access. However, of the 25 consecutive patients who had IPMNs with MNs in the MPD, 24 (96%) could undergo POPS-DS/conventional PJC, and 21 (84%) could undergo POPS-DS (▶ Table 2). Therefore, because most patients who have IPMNs with MNs in the MPD can undergo POPS-DS, possibly due to MPD dilation, selection bias may be limited in them. On the other hand, of the 75 consecutive patients who had IPMNs with MNs in the branch duct during the same period, 58 (77%) could undergo POPS-DS/conventional PJC, and 12 (16%) could undergo POPS-DS, indicating that POPS-DS can be used for selected IPMNs with MNs in the branch duct, which may have easy access to target MNs in the branch duct. Nevertheless, because a certain number of patients are unfit for EUS-guided tissue acquisition (EUS-TA) [17] for some reason, POPS-DS should possibly be considered for those who have IPMNs with MNs in the branch duct. Furthermore, even when a SpyDS scope cannot reach target MNs, histocytological evaluation using fluid specimens may contribute to determination of the need for surgery. Third, for IPMNs with MNs in the branch ducts, EUS-TA [17] may be appropriate for evaluation of malignancy. Although it is unclear which of the two methods is better for obtaining tissue, POPS-DS may be an alternative for detecting malignancy, especially when MNs are in the MPD or when MNs in the branch ducts are involved with dilated MPD. In fact, EUS-guided tissue sampling for pancreatic cystic neoplasms has been avoided in Japan because EUS-guided interventions for those lesions may disseminate neoplastic cells more frequently than for pancreatic solid ones (As a side note, the rate of dissemination of neoplastic cells caused by EUS-guided fine. needle aspiration for pancreatic solid neoplasms including pancreatic cancers was estimated to be 0.3% on the basis of a nationwide survey in Japan [18]). In any case, selection of these two methods should be determined on a case-by-case basis in consideration of the strong and weak points of those methods. Fourth, because there was selection

▶ **Table 2** Baseline characteristics and clinical outcomes in Groups A, B, and C.

	Group A (n = 27)	Group B (n = 49)	P value (A vs. B)	Group C (n = 18)	P value (A vs. C)
Age (years), median (range)	74 (58–91)	73 (54–84)	0.187	75 (59–87)	0.676
Male, n (%)	24 (89)	29 (59)	**0.007**	13 (72)	0.151
Initial imaging findings					
▪ Cyst size (mm), median (IQR)	35 (25–39), n = 21	25 (20–33), n = 49	**0.018**	25 (19–33), n = 18	0.094
▪ MPD diameter (mm), median (IQR)	10.0 (6.0–15.0)	3.5 (3.0–6.0)	**<0.001**	3.0 (2.0–5.0)	**<0.001**
▪ MN in the branch duct					
– n (%)	12 (44)	46 (94)	**<0.001**	17 (94)	**0.001**
– Height (mm), median (IQR)	11.0 (6.0–15.0)	3.5 (2.0–5.0)	**<0.001**	3.0 (2.0–3.0)	**<0.001**
▪ MN in the MPD					
– n (%)	21 (78)	3 (6)	**<0.001**	1 (6)	**<0.001**
– Height (mm), median (IQR)	5.0 (2.5–7.5)	5.0 (3–15)	0.428	3	0.818
Classification described in the ICGs, n (%)					
▪ High-risk stigmata	20 (74)	18 (37)	**0.002**	1 (6)	**<0.001**
▪ Worrisome features	7 (26)	31 (63)		17 (94)	
Patients undergoing surgery just after initial examinations					
▪ n (%)	13 (48)	10 (20)	**0.012**	0	**<0.001**
▪ Percentage of definitive malignant IPMN in this population, %	69% (9/13)	60% (6/10)	0.49	–	–
▪ Accuracy of preoperative histocytological examination to detect malignancy (sensitivity/specificity/accuracy), %					
– Biopsy (POPS-DS guidance)	63/100/75	Not undergoing POPS	–	Not undergoing ERP	–
– PJC	89/100/92	67/100/80	0.341/1.000/0.398	Not undergoing ERP	–
Patients undergoing surveillance without surgery (except those diagnosed with malignancy using POPS-DS/PJC)					
▪ n (%)	9 (33)	38 (77)	**<0.001**	18 (100)	**<0.001**
▪ Surveillance period (days), median (IQR)	1322 (599–1704)	1504 (1018–1817)	0.646	1142 (900–1765)	0.471
▪ Cumulative 3-year progression rate, %	0%	20%	0.413	19%	0.447
▪ Surgery during surveillance, %	0%	16% (6/38) HG-IPMN, 4 IC/PDAC, 2	0.257	11% (2/18) HG-IPMN, 1 IC/PDAC, 1	0.436

ERP, endoscopic retrograde pancreatography; HG, high-grade; IC, invasive cancer derived from IPMN; ICGs, international consensus guidelines; IPMN, intraductal papillary mucinous neoplasm; IQR, interquartile range; MN, mural nodule; MPD, main pancreatic duct; PDAC, pancreatic ductal adenocarcinoma; PJC, pancreatic juice cytology; POPS-DS, peroral pancreatoscopy using a SpyGlass DS scope.

bias between Groups A, B, and C, it may remain unclear whether there were differences in the diagnostic accuracy for detection of malignancy for MN-positive IPMNs between POPS-DS and conventional PJC. However, because the progression rate of IPMNs during surveillance was significantly low in benign IPMNs determined by using POPS-DS compared with IPMNs in Groups B and C, POPS-DS first should be considered when the attending physicians are hesitant to perform surgery for pa-

▶ Table 3 Evaluations of involvement of IPMN lesions in estimated resection margin using IDUS/POPS-DS in patients undergoing surgery.

Patient no.	Age POPS-DS (years)	Sex	Past history of pancreatic surgery	Involvement of IPMN lesion in estimated resection margin using POPS-DS	POPS-DS-guided biopsy for epithelium in estimated resection margin	Surgical procedure	Histological diagnosis of resected specimens	Involvement of IPMN lesions in resection margin of resected specimens	Postoperative period or surveillance period (days)	Recurrence in resection margin after surgery
1	78	F	DP	Not performed (due to plan for TP)	–	TP	PDAC +LG-IPMN	–	722	–
2	71	M	None	Not involved	Not performed	PD	LG-IPMN	Involvement of IPMN (LG-IPMN)	1287	No recurrence
3	74	M	None	Not involved	Not performed	PD	LG-IPMN	Not involved	2156	No recurrence
4	78	M	None	Not involved	Not performed	PD	HG-IPMN	Involvement of IPMN (LG-IPMN)	2032	No recurrence
5	73	M	None	Not involved	Not performed	DP	LG-IPMN	Involvement of IPMN (LG-IPMN)	2121	No recurrence
6	74	M	None	Not involved	Not performed	DP	IC-D	Not involved	2031	No recurrence
7	83	M	None	Not involved	Not performed	DP	HG-IPMN	Not involved	198	No recurrence
8	77	M	None	Not involved	Not performed	DP	HG-IPMN	Not involved	1906	No recurrence
9	58	F	DP	Not involved	Not performed	Partial	HG-IPMN	Not involved	1816	No recurrence
10	68	M	None	Not performed (due to plan for TP)	–	TP	HG-IPMN <<LG-IPMN	–	1791	–
11	81	M	None	Not involved	Not performed	DP	HG-IPMN	Involvement of IPMN (HG-IPMN)	1498	Recurrence (565 days after surgery)
12	66	M	None	Not involved	Not performed	PD	IC-D	Not involved	1114	No recurrence
13	71	M	None	Suspected involvement of IPMN	Performed (LG-IPMN)	DP	LG-IPMN	Involvement of IPMN (LG-IPMN)	1426	No recurrence

DP, distal pancreatectomy; HG, high-grade; IC, invasive cancer derived from IPMN; IDUS, intraductal ultrasonography; IPMN, intraductal papillary mucinous neoplasm; LG, low-grade; PDAC, pancreatic ductal adenocarcinoma; POPS-DS, peroral pancreatoscopy using a SpyGlass DS scope; TP, total pancreatectomy.

tients with MN-positive IPMN due to lack of evidence for determination of malignancy. Fifth, for some of 13 patients who underwent POPS-DS followed by undergoing surgery, surgery was not determined based on the results of POPS-DS. Despite a benign diagnosis using POPS-DS, four of 13 patients underwent surgery due to MN size of >10 mm. However, because the accuracy of POPS-DS for detection of malignancy in this population was high (92%), patients diagnosed with benign MN-positive IPMNs using POPS-DS should probably undergo surveillance without immediate surgery from now on. Despite those limitations, this study indicates that POPS-DS is an accurate method for determining whether MN-positive IPMNs are malignant.

Conclusions

In conclusion, this study clarified the excellent sensitivity of POPS-DS for detection of malignancy for IPMNs with MNs. Although preoperative evaluation of involvement of IPMN lesions in the resection margin is needed for improvement, POPS-DS-guided histocytological evaluations can contribute to determination of whether patients with MN-positive IPMNs should undergo surgery.

Acknowledgement

Conflict of Interest

The authors declare that they have no conflict of interest.

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