The role of pancreatoscopy in the diagnostic work-up of intraductal papillary mucinous neoplasms: a systematic review and meta-analysis

INFOGRAPHIC

What is the role of pancreatoscopy for IPMN?

- Limited accuracy of diagnostic imaging (CT, MRI, EUS, ERCP)
- Risk of over- or undertreatment

Methods: Meta-analysis: 25 articles

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</table>

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Submitted 6.12.2021
Accepted after revision 23.5.2022
Published online 3.6.2022

Bibliography
Endoscopy
DOI 10.1055/a-1869-0180
ISSN 0013-726X
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tients undergo unnecessary pancreatic surgery for IPMN with
progression to malignancy and is considered an indication for sur-
IPMN, including the impact of pre- and intraoperative POP
on the management of IPMN.
Methods The EMBASE, Medline Ovid, Web of Science, Cochran CENTRAL, and Google Scholar databases were

Introduction
Intraductal papillary mucinous neoplasm (IPMN) is a common
precancerous lesion of the pancreas, characterized by intraduc-
tal papillary proliferation of mucin-producing cells, resulting in
cystic dilatation of the pancreatic duct (PD) [1, 2]. IPMN may
progress from adenomatous lesions to high grade dysplasia
(HGD) and finally to invasive carcinoma. Branch-duct IPMN
(BD-IPMN) is the most prevalent subtype. Main-duct IPMN
(MD-IPMN) is however associated with the highest risk of pro-
gression to malignancy and is considered an indication for sur-
gery if the main PD (MPD) diameter is > 10 mm, or if there is evi-
dence of jaundice or mural nodules [3, 4]. Early identification of
MD-IPMN is important to allow surgery to be performed before
the development of cancer.

Currently, imaging modalities used for the diagnosis of IPMN
include computed tomography (CT), magnetic resonance ima-
ging (MRI), and endoscopic ultrasonography (EUS). Even with
the addition of endoscopic retrograde cholangiopancreatogra-
phy (ERCP) and ERCP-guided brushing, the diagnosis of MD-
IPMN and BD-IPMN can be challenging, as is determining the
presence of HGD or invasive carcinoma. As a result, some pa-
tients undergo unnecessary pancreatic surgery for IPMN with
low grade dysplasia (LGD) or benign cystic lesions [5]. In addi-
tion, when surgery is indicated, preoperative determination of
the extent of MD-IPMN using these techniques can be difficult.
This could result in either unnecessary loss of pancreatic tissue
in the case of an overly extensive resection, or progression of
disease in the case of an incomplete resection. Although intra-
operative frozen section analysis of the resection margin is rou-
systematically searched for articles. Eligible articles investig-
gated cohorts of patients who underwent POP for (suspect-
ed) IPMN.

Results 25 articles were identified and included in this re-
view; with 22 of these reporting on the diagnostic yield of
POP in IPMN and 11 reporting on the effect of pre- or intra-
operative POP on clinical decision-making. Cannulation and
observation rates, and overall diagnostic accuracy were high
across all studies. Frequently reported visual charac-
teristics of IPMN were intraductal fish-egg-like lesions, hy-
pervascularity, and granular mucosa. Overall, the adverse
event rate was 12 %, primarily consisting of post-endo-
scopic retrograde cholangiopancreatography pancreatitis,
with a pooled rate of 10 %, mostly of mild severity. Regard-
ing the impact of POP on clinical decision-making, POP
findings altered the surgical approach in 13 %–62 % of pa-
tients.

Conclusion POP is technically successful in the vast major-
ity of patients with (suspected) IPMN, has a consistently
high diagnostic accuracy, but an adverse event rate of 12 %. Data
on intraoperative pancreatoscopy are scarce, but small studies suggest its use can alter surgical manage-
ment. Future studies are needed to better define the role
of POP in the diagnostic work-up of IPMN.

Methods
Eligibility criteria
Studies eligible for inclusion were randomized controlled trials,
prospective and retrospective cohort studies, and case series.
Case reports, reviews, poster abstracts, and studies in a lan-
guage other than English were excluded. Studies examining
adults with a (suspected) diagnosis of IPMN, undergoing POP,
either performed during diagnostic work-up for IPMN or perio-
operatively, were deemed eligible.

Search strategy and study selection
On 11 February 2022, according to the PRISMA guidelines (Ta-
ble 1, see online-only Supplementary material), a systematic
literature search was performed in EMBASE, Medline Ovid,
Web of Science, Cochrane CENTRAL, and Google Scholar. Pre-defined keywords used in this search were “pancreatoscopy” and “IPMN” to identify relevant articles. The full search strategy is presented in Table 2.

After duplicates of the retrieved articles had been removed, the titles and abstracts were independently screened for eligibility by two authors (D.d.J. and P.S.). The full text of potentially relevant articles was retrieved and independently assessed. Disagreement was resolved by consensus after discussion with a third author (P.J.d.J.). The references listed within the selected articles were screened to identify additional studies relevant for inclusion in this literature review.

Data extraction

Data were systematically extracted from all included studies using a predefined standardized form. Data extracted included study design, patient characteristics, and intervention-related characteristics (e.g. successful cannulation and the ability to visualize the target area). In addition, any pancreatoscopic visual characteristics of IPMN that were reported in the articles, the use and diagnostic value of adjunctive modalities such as NBI, and the effect of POP findings on clinical management were noted.

The evaluated outcomes were: (i) technical success, defined as the ability to advance the pancreatoscope to the target area/lesion within the MPD, and safety, including adverse events (AEs) such as post-ERCP pancreatitis (PEP), perforation, and bleeding; (ii) diagnostic pancreatoscopic features and accuracy, defined as the rate of agreement between these features and pathological examination of the surgical or autopsy specimens, for both POP visualization alone and for POP-guided biopsy or cytology; and (iii) the effect on clinical decision-making, defined as the surgical approach being altered on the basis of the pre- or intraoperative pancreatoscopic findings.

Statistical analysis

Statistical analyses were mostly limited to descriptive statistics using frequencies and percentages. For the pooled AE rate, meta-analysis was performed using R version 4.0.1 with the “meta” package. Random-effects meta-analysis was used, regardless of the results of heterogeneity testing. The effect size can vary per study because of differences in cohorts and the included patients, therefore random-effect meta-analysis is more suitable than fixed-effects meta-analysis. Data are presented as means with 95% CIs. Sensitivity analysis was performed for studies that reported the AEs on patients with IPMN only and for POP-guided biopsy or cytology; and the effect on clinical decision-making, defined as the surgical approach being altered on the basis of the pre- or intraoperative pancreatoscopic findings.

Results

A total of 25 articles met the inclusion criteria [8–32]. The process of article selection and reasons for exclusion are summarized in Fig. 1. The data extracted from the included studies are summarized in Table 1 and Table 2. There were 22 studies that primarily reported on the diagnostic yield of POP for all IPMN types [8–19, 21, 22, 24–30, 32] and 11 articles that reported on the effect of the POP findings, in the preoperative and/or intraoperative setting, on clinical decision-making (i.e. choice to proceed to surgery and extent of surgery) [10, 13, 14, 19, 21–24, 28, 29, 31].

Technical success and adverse events

In all studies, technical success rates were reported, defined as the ability to advance the pancreatoscope into the MPD. This cannulation rate ranged from 86% to 100% [8–32]. Pancreatoscopy was performed for diagnosis of a suspected MD-IPMN, BD-IPMN, or mixed-type IPMN (MT-IPMN). A dilated MPD was not required. Predictive factors reported for successful cannulation were a dilated MPD or a wide papillary orifice. It was not often reported how many patients underwent papillotomy prior to or during the POP procedure; however, where reported, it ranged from 0% to 92.7%. One study reported that POP was successfully performed via the minor papilla in four patients [20].

After successful cannulation, the rate of adequate visualization of the PD and region of interest ranged from 60% to 100%, but the specific location of the lesion in the PD was often not described. Of the 25 included studies, only six reported an observation rate lower than 100% [11, 12, 19, 22, 25, 26], resulting in a combined observation rate of 95.6%. Reasons for the inability to visualize the target area were: inadequate clearance of mucus; a nondilated MPD; and concomitant anatomical features, such as a ductal stricture. Abundant mucus impaired vis-
Table 1  Studies investigating the role of peroral pancreatoscopy in the diagnosis and treatment of intraductal papillary mucinous neoplasm (IPMN).

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Design</th>
<th>Cannulations/target area observed, %</th>
<th>Pancreatoscopy type</th>
<th>Key findings</th>
<th>Adjunct modalities</th>
<th>AE, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fujita et al. (1990) [8]</td>
<td>Retro (8)</td>
<td>86/100</td>
<td>Mother–baby: PF24, XCPF 3.3, BF-3C10, CHF-P10</td>
<td>IOP is useful for determination of lesion extent</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Özkan et al. (1995) [9]</td>
<td>Retro (9)</td>
<td>89/100</td>
<td>Mother–baby: CFS-B20SL</td>
<td>IPMN is characterized by villous-like mucosal growths and clear jelly-like mucin substances</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Kaneko et al. (1998) [10]</td>
<td>Prosp (24)</td>
<td>100/100</td>
<td>Ultrathin pancreatoscope</td>
<td>IOP is able to detect lesions not detected by preoperative ERCP or EUS</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mukai et al. (1998) [11]</td>
<td>Retro (25)</td>
<td>100/60</td>
<td>Mother–baby: CHF-B20, CHF-BP30, XCHF-B27</td>
<td>Papillary lesions &gt;3 mm have a higher chance of malignancy</td>
<td>Biopsy: sensitivity 57 %, specificity 100 %, accuracy 75 %</td>
<td>4</td>
</tr>
<tr>
<td>Yamaguchi et al. (2000) [12]</td>
<td>Retro (41)</td>
<td>100/73</td>
<td>Mother–baby: XCHF-B27, CHF-B20, CHF-BP30</td>
<td>Severe atypical adenoma and carcinoma are associated with multiple morphologic features (i.e. frequently villous or vegetative elevations and red colored markings)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Atia et al. (2002) [13]</td>
<td>Retro (5)</td>
<td>100/100</td>
<td>FCP-9P</td>
<td>100 % correct diagnosis of IPMN by POP</td>
<td>NA</td>
<td>20</td>
</tr>
<tr>
<td>Hara et al. (2002) [14]</td>
<td>Retro (60)</td>
<td>100/100</td>
<td>Mother–baby: CHF-BP30, OP-TISCOPE</td>
<td>Combination of IDUS and POP improve differentiation between malignant and benign IPMN</td>
<td>Pancreatic juice cytology: sensitivity 13 %, specificity 100 %, accuracy 44 %</td>
<td>6.7</td>
</tr>
<tr>
<td>Yamao et al. (2003) [15]</td>
<td>Retro (60)</td>
<td>95/100</td>
<td>Mother–baby: CPF-PAB, PF8</td>
<td>Friability and protruding lesions more frequently seen in malignancy</td>
<td>NA</td>
<td>12^1</td>
</tr>
<tr>
<td>Yamaguchi et al. (2005) [32]</td>
<td>Retro (103)</td>
<td>100/100</td>
<td>Mother–baby: CHF-BP30</td>
<td>Cytology has better diagnostic accuracy when collected by POP than when catheter-assisted</td>
<td>Pancreatic juice cytology: sensitivity 68 %, specificity 100 %</td>
<td>NA</td>
</tr>
<tr>
<td>Yasuda et al. (2005) [16]</td>
<td>Retro (26)</td>
<td>100/100</td>
<td>Mother–baby: NA</td>
<td>Detection of polypoid tumor &gt;3 mm by POP 67 % No adenocarcinoma in protrusions &lt;3 mm</td>
<td>Biopsy: sensitivity 50 %, specificity 100 % Pancreatic juice cytology: sensitivity 50 %, specificity 100 %</td>
<td>0</td>
</tr>
<tr>
<td>Itoh et al. (2007) [17]</td>
<td>Prosp (5)</td>
<td>100/100</td>
<td>Mother–baby: CHF-BP260</td>
<td>NBI improves visualization of small vessels and superficial architecture</td>
<td>NBI</td>
<td>NA</td>
</tr>
<tr>
<td>Itoi et al. (2007) [18]</td>
<td>Retro (3)</td>
<td>100/100</td>
<td>Mother–baby: CHF-BP260</td>
<td>NBI is able to identify skip lesions otherwise not seen and shows capillary vessels more clearly</td>
<td>NBI</td>
<td>0</td>
</tr>
<tr>
<td>Miura et al. (2010) [19]</td>
<td>Prosp (21)</td>
<td>100/91</td>
<td>Mother–baby: CHF-BP260, CHF-B260</td>
<td>POP combined with NBI shows vascular patterns and protrusions more clearly and is useful for differentiation</td>
<td>NBI: correct excision line based on POP + NBI in 100 % patients</td>
<td>0</td>
</tr>
<tr>
<td>Author (year)</td>
<td>Design (n)</td>
<td>Cannulations/target area observed, %</td>
<td>Pancreatoscopy type</td>
<td>Key findings</td>
<td>Adjunct modalities</td>
<td>AE, %</td>
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<tr>
<td>Brauer et al. (2013) [20]</td>
<td>Retro (4)</td>
<td>100/100</td>
<td>Mother–baby: CHF-BP30 or SpyGlass DVS</td>
<td>POP via dorsal duct is technically feasible</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Aranelo et al. (2014) [21]</td>
<td>Prosp (41)</td>
<td>93/100</td>
<td>SpyGlass DVS</td>
<td>Overall: sensitivity 84%, specificity 75% Accuracy: for MD-IPMN 76%, for BD-IPMN 78%</td>
<td>Biopsy in 17/41: benign 9, HGD 4, inadequate 4 Irrigation fluid cytology in 22/41: malignancy 5%</td>
<td>17</td>
</tr>
<tr>
<td>Nagayoshi et al. (2014) [22]</td>
<td>Retro (17)</td>
<td>77/100</td>
<td>SpyGlass DVS or ERCP catheter pancreatoscopy</td>
<td>100% sensitivity of irrigation fluid cytology for detecting malignancy</td>
<td>Biopsy: sensitivity 25%, specificity 100% Irrigation fluid cytology: sensitivity 100%, specificity 100%</td>
<td>35</td>
</tr>
<tr>
<td>Pucci et al. (2014) [23]</td>
<td>Retro (18)</td>
<td>100/100</td>
<td>Flexible choledochoscope</td>
<td>IOP is a valuable tool to determine the surgical resection margin</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Navez et al. (2014) [24]</td>
<td>Retro (21)</td>
<td>100/100</td>
<td>NA</td>
<td>IOP is able to detect occult lesions and in combination with biopsies it could change the initial surgical plan</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kurihara et al. (2016) [25]</td>
<td>Prosp (17)</td>
<td>88/100</td>
<td>SpyGlass DVS</td>
<td>Visual diagnostic accuracy of POP in MD-IPMN was 87.5% (i.e. papillary stricture, fish-egg-like lesion)</td>
<td>Biopsy: 91% adequate samples</td>
<td>0</td>
</tr>
<tr>
<td>El Hajj et al. (2017) [26]</td>
<td>Retro (78)</td>
<td>100/97</td>
<td>Mother–baby: CHF-BP30, CHF-BP160, CHF-Y002 or SpyGlass DVS</td>
<td>POP-directed biopsies increased diagnostic accuracy of visual impression</td>
<td>Biopsy: sensitivity 87%, specificity 100%, PPV 100%, NPV 84%, accuracy 92% (in differentiating between neoplasia and non-neoplasia)</td>
<td>12²</td>
</tr>
<tr>
<td>Parbhui et al. (2017) [27]</td>
<td>Retro (16)</td>
<td>100/100</td>
<td>SpyGlass DVS and DS</td>
<td>Accuracy of biopsy alone (64%) increased to 100% in combination with visualization to correctly diagnose IPMN</td>
<td>Biopsy: sensitivity 64%, specificity 100% (in diagnosing IPMN)</td>
<td>6</td>
</tr>
<tr>
<td>Ohtsuka et al. (2018) [28]</td>
<td>Retro (7)</td>
<td>100/100</td>
<td>SpyGlass DS</td>
<td>Good visualization of the target area in all patients, with low diagnostic accuracy of targeted biopsies for detecting HGD</td>
<td>Biopsy: sensitivity 0% Irrigation fluid cytology: sensitivity 33%</td>
<td>14</td>
</tr>
<tr>
<td>Trindade et al. (2018) [29]</td>
<td>Retro (31)</td>
<td>100/100</td>
<td>SpyGlass DS</td>
<td>POP is of added value in patients with MD-IPMN and a diffusely dilated MPD, without focal lesions on cross-sectional imaging or EUS</td>
<td>Biopsy in 28/31: LGD 79%, HGD 18%, adenocarcinoma 4%</td>
<td>29</td>
</tr>
<tr>
<td>Han et al. (2019) [30]</td>
<td>Retro (13)</td>
<td>100/100</td>
<td>Mother–baby: CHF-BP30 or SpyGlass DS</td>
<td>In patients with presumed idiopathic chronic pancreatitis, POP is able to identify MD-IPMN</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Tyberg et al. (2019) [31]</td>
<td>Retro (13)</td>
<td>100/100</td>
<td>SpyGlass DS</td>
<td>POP can be effectively used as mapping tool preoperatively</td>
<td>NA</td>
<td>0</td>
</tr>
</tbody>
</table>

**AE, adverse events; BD, branch duct; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; HGD, high grade dysplasia; IDUS, intraductal ultrasonography; IOP, intraoperative pancreatoscopy; MD, main duct; MPD, main pancreatic duct; NBI, narrow-band imaging; NPV, negative predictive value; NA, not applicable; POP, peroral pancreatoscopy; PPV, positive predictive value; Prosp, prospective; Retro, retrospective.**

¹ Calculated over the total group of patients and not in patients with IPMN only.

² Calculated per pancreatoscopy procedure, not per patient.
ual characterization of the IPMN or wall of the MPD, despite flushing [12,25]. Visualization of BD-IPMN was more difficult as compared with MD-IPMN, mainly owing to more difficult angulation of the pancreatoscope in reaching the area of interest and the smaller diameter of the MPD [11, 12, 22].

The occurrence of AEs was reported in 17 out of 25 studies [9, 11, 13–16, 18–22, 25–29, 31]. The overall pooled AE rate of these 17 studies was 12% (95%CI 9%–17%) (▶ Fig. 2). PEP was the most common AE, with a pooled incidence rate of 10% (95%CI 7%–15%) [11, 13–15, 20–22, 26–29] (Fig. 1). The severity of PEP was mild in 24 patients (70.6%), moderate in seven (20.6%), severe in two (5.9%), and unknown in one (2.9%). One patient with severe PEP died [21].

In reporting AE rates, three studies did not make a difference between patients with and without (suspected) IPMN and therefore the reported overall AE rate and PEP rate might differ for patients with IPMN, albeit sensitivity analysis showed no significant difference between these [15, 20, 26]. Most studies did not elaborate on the MPD diameter in relation to PEP. Trindade et al. reported that PEP occurred more frequently in patients with a focally dilated MPD (n= 7/18; 39%) compared with patients with a diffusely dilated MPD (n = 1/13; 8%; P = 0.05) [29]. In addition, Arnelo et al. reported that 6/7 patients diagnosed with PEP had a normal or only slightly dilated MPD [21]. Other AEs included post-sphincterotomy bleeding (1.3%) [26], a mild sedation-related event (3.2%) [29], and cholangitis (8.3%) [22].

### Table 2: Studies investigating the effect of preoperative or intraoperative pancreatoscopy on clinical management of intraductal papillary mucinous neoplasm (IPMN).

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Design (n)</th>
<th>Timing</th>
<th>Gold standard</th>
<th>Adjunctive modality</th>
<th>Excision line based on pancreatoscopic findings</th>
<th>Altered surgical approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaneko et al. (1998) [10]</td>
<td>Prosp (24)</td>
<td>IOP</td>
<td>Surgical specimen</td>
<td>NA</td>
<td>NA</td>
<td>13%: 10/24 extra lesions detected; 5/10 multifocal lesions; 3/5 more extensive resection</td>
</tr>
<tr>
<td>Atia et al. (2002) [13]</td>
<td>Retro (5)</td>
<td>Preop</td>
<td>Surgical specimen</td>
<td>NA</td>
<td>In 4/4 of patients with IPMN (100%); pancreatic cyst identified in fifth patient</td>
<td>NA</td>
</tr>
<tr>
<td>Hara et al. (2002) [14]</td>
<td>Retro (40)</td>
<td>Preop</td>
<td>Surgical specimen</td>
<td>IDUS</td>
<td>Continuous lesion in 35/40 (87.5%). Positive resection margin in one patient (2.5%)</td>
<td>NA</td>
</tr>
<tr>
<td>Miura et al. (2010) [19]</td>
<td>Retro (21)</td>
<td>Preop</td>
<td>Surgical specimen</td>
<td>NBI</td>
<td>In 7/7 patients, negative resection margins</td>
<td>NA</td>
</tr>
<tr>
<td>Arnelo et al. (2014) [21]</td>
<td>Prosp (44)</td>
<td>Preop</td>
<td>Surgical specimen, follow-up</td>
<td>NA</td>
<td>NA</td>
<td>95% additional information, in 76% affected clinical decision-making</td>
</tr>
<tr>
<td>Nagayoshi et al. (2014) [22]</td>
<td>Retro (17)</td>
<td>Preop</td>
<td>Radiology, surgical specimen</td>
<td>NA</td>
<td>In three patients (17.6%), excision line determined</td>
<td>NA</td>
</tr>
<tr>
<td>Pucci et al. (2014) [23]</td>
<td>Retro (18)</td>
<td>IOP</td>
<td>Surgical specimen</td>
<td>NA</td>
<td>NA</td>
<td>95%: 29% extended margins; 6% spared margins</td>
</tr>
<tr>
<td>Navez et al. (2015) [24]</td>
<td>Retro (21)</td>
<td>IOP</td>
<td>Radiology, surgical specimen</td>
<td>NA</td>
<td>NA</td>
<td>Additional lesions detected in 38%; 29% extended margins, 6% spared margins</td>
</tr>
<tr>
<td>Ohtsuka et al. (2018) [28]</td>
<td>Retro (7)</td>
<td>Preop</td>
<td>Surgical specimen</td>
<td>NA</td>
<td>NA</td>
<td>14% extended margins</td>
</tr>
<tr>
<td>Trindade et al. (2018) [29]</td>
<td>Retro (31)</td>
<td>Preop</td>
<td>Surgical specimen</td>
<td>NA</td>
<td>Surgery dictated by POP on basis of additional findings in 42%; significantly more often in patients with a diffusely dilated MPD (77% vs. 17%, P = 0.001)</td>
<td>NA</td>
</tr>
<tr>
<td>Tyberg et al. (2019) [31]</td>
<td>Retro (13)</td>
<td>Preop</td>
<td>Surgical specimen</td>
<td>NA</td>
<td>NA</td>
<td>62%: 31% extended margins, 31% spared margins</td>
</tr>
</tbody>
</table>

IDUS, intraductal ultrasonography; IOP, intraoperative pancreatoscopy; NA, not applicable; NBI, narrow-band imaging; Prosp, prospective; MPD, main pancreatic duct; Preop, preoperative; Retro, retrospective.
The included articles did not clarify whether surgery was deferred or postponed because of these AEs.

**Visual diagnosis of IPMN and detection of high risk features by POP**

Pancreatoscopic characteristic features of IPMN were intraductal papillary or villous projections, and the presence of mucus [33]. Other features included: intraductal fish-egg-like lesions, that were sometimes seen on a protruding lesion, and granular mucosa [8, 9, 11–16, 18, 19, 22, 24–26, 28–30]. However, not all classical features are consistently seen. For example, in patients with a radiological diagnosis of MD-IPMN, the classical features of IPMN, such as a fish-eye papilla and oozing of mucus from the papilla, were detected in only 35% of patients in whom MD-IPMN was confirmed by histology [21]. Examples of some of the visual characteristics of IPMN seen on POP can be found in ▶ Fig. 3 and ▶ Video 1 and ▶ Video 2.

Seven studies reported on the sensitivity, specificity, and overall diagnostic accuracy rates of POP in the visual diagnosis of IPMN [10, 13, 16, 21, 25, 27, 30]. In these studies, the results

<table>
<thead>
<tr>
<th>Study</th>
<th>Events</th>
<th>Total</th>
<th>Proportion</th>
<th>95% CI</th>
<th>Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atia, 2002</td>
<td>1</td>
<td>5</td>
<td>0.20</td>
<td>[0.01 – 0.72]</td>
<td>2.8 %</td>
</tr>
<tr>
<td>Yamao, 2003</td>
<td>4</td>
<td>33</td>
<td>0.12</td>
<td>[0.03 – 0.28]</td>
<td>9.7 %</td>
</tr>
<tr>
<td>El Hajj, 2017</td>
<td>12</td>
<td>102</td>
<td>0.12</td>
<td>[0.06 – 0.20]</td>
<td>18.7 %</td>
</tr>
<tr>
<td>Ozkan, 1995</td>
<td>0</td>
<td>9</td>
<td>0.00</td>
<td>[0.00 – 0.34]</td>
<td>1.7 %</td>
</tr>
<tr>
<td>Yasuda, 2005</td>
<td>0</td>
<td>26</td>
<td>0.00</td>
<td>[0.00 – 0.13]</td>
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</tr>
<tr>
<td>Itoi, 2007</td>
<td>0</td>
<td>3</td>
<td>0.00</td>
<td>[0.00 – 0.71]</td>
<td>1.6 %</td>
</tr>
<tr>
<td>Miura, 2010</td>
<td>0</td>
<td>21</td>
<td>0.00</td>
<td>[0.00 – 0.16]</td>
<td>1.8 %</td>
</tr>
<tr>
<td>Brauer, 2013</td>
<td>0</td>
<td>4</td>
<td>0.00</td>
<td>[0.00 – 0.60]</td>
<td>1.7 %</td>
</tr>
<tr>
<td>Kurilhara, 2016</td>
<td>0</td>
<td>17</td>
<td>0.00</td>
<td>[0.00 – 0.20]</td>
<td>1.8 %</td>
</tr>
<tr>
<td>Tyberg, 2019</td>
<td>0</td>
<td>13</td>
<td>0.00</td>
<td>[0.00 – 0.25]</td>
<td>1.8 %</td>
</tr>
<tr>
<td>Mukai, 1998</td>
<td>0</td>
<td>25</td>
<td>0.04</td>
<td>[0.00 – 0.20]</td>
<td>3.4 %</td>
</tr>
<tr>
<td>Hara, 2002</td>
<td>4</td>
<td>60</td>
<td>0.07</td>
<td>[0.02 – 0.16]</td>
<td>10.2 %</td>
</tr>
<tr>
<td>Arnelo, 2014</td>
<td>7</td>
<td>41</td>
<td>0.17</td>
<td>[0.07 – 0.32]</td>
<td>13.6 %</td>
</tr>
<tr>
<td>Nagayoshi, 2014</td>
<td>4</td>
<td>17</td>
<td>0.24</td>
<td>[0.07 – 0.50]</td>
<td>8.8 %</td>
</tr>
<tr>
<td>Parbhu, 2017</td>
<td>1</td>
<td>16</td>
<td>0.06</td>
<td>[0.00 – 0.30]</td>
<td>3.3 %</td>
</tr>
<tr>
<td>Ohtsuka, 2018</td>
<td>1</td>
<td>7</td>
<td>0.14</td>
<td>[0.00 – 0.58]</td>
<td>3.0 %</td>
</tr>
<tr>
<td>Trindade, 2018</td>
<td>9</td>
<td>31</td>
<td>0.29</td>
<td>[0.14 – 0.48]</td>
<td>14.4 %</td>
</tr>
</tbody>
</table>

Random effects model

<table>
<thead>
<tr>
<th>Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>430</td>
</tr>
</tbody>
</table>

Heterogeneity: \( I^2 = 19 \% \), \( \tau^2 = 0.1129 \), \( P = 0.23 \)

The included articles did not clarify whether surgery was deferred or postponed because of these AEs.

▶ Fig. 2 Pooled AE rate for all studies that reported adverse events.

▶ Fig. 3 Example images during peroral pancreatoscopy (POP) in four patients with intraductal papillary mucinous neoplasm (IPMN) showing: a a clear proximal margin of a main-duct IPMN (MD-IPMN) that was suspicious for malignancy, but was found to be a mixed-type IPMN without any malignancy on pancreatoduodenectomy (see also ▶ Video 1); b a clear image of a visible polypoid lesion in the setting of MD-IPMN, with biopsy revealing focal malignant transformation; c the clear fish-egg-like lesions in an MD-IPMN; d a very wide side branch in the body of the pancreas, with a nodular mass seen at the opening of the side branch, which showed mild dysplasia on POP-guided biopsy and later pancreatoduodenectomy.

The included articles did not clarify whether surgery was deferred or postponed because of these AEs.

**Visual diagnosis of IPMN and detection of high risk features by POP**

Pancreatoscopic characteristic features of IPMN were intraductal papillary or villous projections, and the presence of mucus [33]. Other features included: intraductal fish-egg-like lesions, that were sometimes seen on a protruding lesion, and granular mucosa [8, 9, 11–16, 18, 19, 22, 24–26, 28–30]. However, not all classical features are consistently seen. For example, in patients with a radiological diagnosis of MD-IPMN, the classical features of IPMN, such as a fish-eye papilla and oozing of mucus from the papilla, were detected in only 35% of patients in whom MD-IPMN was confirmed by histology [21]. Examples of some of the visual characteristics of IPMN seen on POP can be found in ▶ Fig. 3 and ▶ Video 1 and ▶ Video 2.

Seven studies reported on the sensitivity, specificity, and overall diagnostic accuracy rates of POP in the visual diagnosis of IPMN [10, 13, 16, 21, 25, 27, 30]. In these studies, the results
of POP were compared to pathology results after resection or from biopsies, or the absence of progression during long-term follow-up. Reported sensitivity rates ranged between 64% and 100% [10,13,16,21,27,30], specificity rates between 75% and 100% [13,21,27,30], and overall diagnostic accuracy between 87.5% and 100% [10,13,25].

The ability to differentiate noninvasive and malignant MD-IPMN with POP has been investigated in eight studies [8,10–12,14–16,26]. The visual classification system proposed by Hara et al. allowed for discrimination of malignant IPMN from noninvasive IPMN with an accuracy of 88% for MD-IPMN and 67% for BD-IPMN [14]. Pancreatoscopic findings that were more frequently observed in patients diagnosed with malignancy were a coarse mucosa, friability, and tumor vessels [12,15,16]. Another important finding by Trindade et al. was that 13 patients (42%) had additional high risk features on POP that were not seen on imaging or EUS, for example papillary projections, nodules, and in one patient a frank mass [29].

Additional imaging modalities, such as narrow-band imaging (NBI) using the Olympus CHF-BP260, have been evaluated in three studies [17–19] and are described in Appendix 1s. The diagnostic value of targeted biopsies, cytology, and pancreatic juice collection are presented in Table 1 and Appendix 2s.

Effect on clinical decision-making

Eleven articles reported on the pre- or intraoperative assessment of the intraductal extent of IPMN by pancreatoscopy and the effect of its findings on clinical management [10,13,14,19,21–24,28,29,31]. In four studies, the resection line was based on preoperative POP findings [13,14,19,29]. Atia et al. reported that POP correctly identified and located IPMN in 4/4 patients with a final diagnosis of IPMN (100%) and correctly identified a pancreatic cyst in a further patient [13]. In another study, the resection margin was based on preoperative POP and intraductal sonography, and comparison with postoperative surgical specimens revealed only one positive resection margin (2.5%) [14]. Miura et al. used POP with NBI to determine the extent and resection line in seven patients, with postoperative examination showing no tumor in the excision stumps [19]. In a study by Trindade et al., POP dictated the surgical plan determined prior to POP in 42% of patients with MD-IPMN (13/31) [29]. This was more common in those with a diffusely dilated MPD >10mm (10/31; 77%: P=0.001).

Five studies investigated whether pre- or intraoperative pancreatoscopy findings altered the intended surgical approach, which was based on cross-sectional imaging, ERCP, and/or EUS [10,23,24,28,31]. After initial transection, IOP was performed to check the remaining PD for lesions. For POP, it was not clearly reported how the additional margin was determined. Overall, determination of the extent of the lesion or identification of skip lesions by visualization or biopsy resulted in an altered surgical approach in 13%–62% of patients: in 13%–31% of patients, it resulted in a more extensive surgical resection [10,23,24,28,31]; in 6%–31% of patients, it resulted in a less extensive surgical resection [23,24,31]. Two studies reported that preoperative POP findings affected clinical decision-making or determination of the excision line, without reporting the initial surgical plan [21,22]. The specifics of these studies can be found in Table 2 and Appendix 3s. Complications related to IOP were not reported.
**Discussion**

The risk of malignancy in IPMN is highly variable as BD-IPMNs contain malignancy in a minority of patients, while MD-IPMNs have a higher reported incidence of malignancy [3, 4]. Although the general recommendation of the International Association of Pancreatology and others is that mucin-producing neoplasms with high risk features or MD-IPMN >10mm should undergo surgical resection, obtaining a definite diagnosis and assessing the possible intraductal extent can often be difficult. As such, the primary utility of POP in IPMN is considered threefold: (i) to confirm the diagnosis in equivocal cases based on imaging and history, especially when there is a question of chronic pancreatitis versus IPMN; (ii) to assess the presence of malignancy or high grade dysplasia; and (iii) to map the IPMN in order to guide resection margins. In current clinical practice, the exact role of POP remains to be determined. Its use remains limited to large volume referral centers, and available data regarding its efficacy and safety are limited and heterogeneous. In this meta-analysis, we summarize the available data on the use of POP in patients with (suspected) IPMN. Following a strict predefined search strategy, we identified 25 articles eligible for inclusion.

Overall, cannulation of the MPD with the pancreatoscope was successful in the vast majority of patients in whom standard MPD access had already been achieved (86%–100%), and adequate visualization of the target area could be achieved in 60%–100% of patients, with the vast majority of studies reporting success rates of 100%. Predictive factors reported for failure to reach the target area were: impaired visibility due to an abundance of mucus; anatomical features such as strictures; or a nondilated MPD [11, 12, 22, 25].

Despite these high technical success rates, AEs occurred in 12% of patients [11, 13–15, 20–22, 26–29]. Because the indication for pancreatoscopy is only diagnostic, the risk of complications may more readily outweigh the benefit of the procedure in comparison with therapeutic procedures. An acknowledgement of the high risk of pancreatitis is of clinical relevance because it may lead to postponement or even deferral of surgery. However, in the majority of the patients, PEP was treated conservatively and its severity was mild to moderate. The most important risk factor for PEP in the evaluated studies was the presence of a focally or mild-to-nondilated MPD, as compared with patients with a diffusely widened MPD, in whom the incidence of PEP was lower [21, 29]. All this should be interpreted in light of the observation that preoperative pancreatoscopy influenced the type/extent of surgery in the vast majority of patients with a diffusely dilated MPD, but only in less than 20% of those with a focally dilated MPD [29].

Several studies have investigated the different pancreatoscopic features that are consistent with benign and malignant IPMN [8, 10–12, 14–16, 26]. Features that were more frequently identified in patients diagnosed with malignant IPMN were intraductal fish-egg lesions, prominent vascular changes, villous projections, and vegetative projections. Also, friability and a coarse mucosa were described as being related to malignancy. In addition, three studies investigated the additional value of NBI in the assessment of intraductal lesions and showed promising results, with improved visualization of the vasculature and flat lesions, along with identification of skip lesions that were otherwise not detected [17–19]. Subsequently, identification of these areas could improve the yield of intraductal (targeted) biopsies.

Unfortunately, there are no studies available that have investigated the interobserver agreement of the different pancreatoscopic features and therefore their exact clinical value remains unclear. Sethi et al. previously showed that interobserver agreement of visual assessment of indeterminate biliary strictures is very low, even among experienced endoscopists [34]. It is likely that this would be the case for IPMN as well.

Considering the moderate sensitivity and specificity rates reported in this review for a visual diagnosis of IPMN (64%–100%, and 75%–100%, respectively), histological confirmation remains important. The yield of POP-guided targeted biopsies and/or cytology was reported in eleven studies with widely varying results, with sensitivity rates ranging from 13% to 100% and specificity rates ranging from 53% to 100% [11, 14, 16, 21, 22, 25–29, 32]. This variation can be explained by the small biopsies obtained via POP, owing to difficult maneuvering of the biopsy forceps, which make pathological diagnosis difficult. With regard to cytology examination, different sampling methods were used and different rates were reported for irrigation fluid compared with pancreatic juice obtained via POP. Interestingly, two studies showed that samples obtained by POP showed higher diagnostic accuracy rates than samples obtained by a catheter [22, 32].

To improve the diagnostic yield of POP-guided targeted biopsies and cytology, future studies are needed to investigate the best collection method of fluid for cytology examinations and biopsy samples. To further optimize the yield of POP, there are some studies that have indicated that probe-based confocal laser endomicroscopy might be helpful in determining the nature of pancreatic lesions, such as IPMN, and its clinical management [35, 36].

The most important question in the setting of pancreatoscopy as a complementary diagnostic tool in the work-up of IPMN is its actual impact on clinical (therapeutic) management and patient outcomes. Results varied greatly between the studies, from only 13% of patients having their surgical approach altered to almost all patients being impacted [10, 13, 14, 19, 21–24, 28, 29, 31]. In some studies, POP detected multifocal lesions that were otherwise not detected or could have been mistaken for chronic pancreatitis [10, 20–37]. The nature of the included studies makes it difficult however to determine the exact role of POP in the preoperative diagnostic work-up. Ideally, the primary utility of POP in IPMN would be to confirm the diagnosis of IPMN in persistent equivocal cases, or to map the extent of the IPMN where there is uncertainty regarding the extent of surgery. However, it should preferably only be performed after a diagnostic work-up including imaging (CT and/or MRI) and EUS with tissue acquisition, and following a multidisciplinary meeting. The Fukuoka guidelines advise performing EUS if there are worrisome features present on cross-sectional imaging [4]. However, the yield is relatively low with a pooled sen-
sitivity of 54 % (95 %CI 49 %–59 %) and specificity of 93 % (95 %CI 90 %–95 %) for EUS-guided fine-needle aspiration [38].

When determining the exact position of POP in the diagnostic work-up of IPMN, the risks and benefits should be weighed. As mentioned before, POP carries a considerable risk of PEP, although this is mainly mild. In addition, POP might be more costly compared with other diagnostic tools, such as CT or MRI. On the other hand, performing unnecessary or overly extensive surgery carries a risk of surgery-related AEs and is also costly. Currently, new studies on POP and IOP are underway that are also taking into account cost-effectiveness (NCT03062124 and NCT03729453), and results are eagerly awaited.

Some limitations need to be discussed. First, most studies were of a retrospective nature, did not involve a consecutive case series, and reported only descriptive data. Second, many different types of pancreatoscopes were used and, maybe more importantly, only five studies used the Spyglass DS, a digital pancreatoscope with an improved image quality compared with previous through-the-scope pancreatoscopes. In today’s clinical practice the Spyglass DS and the Spyglass DS II are the most commonly used pancreatoscopes [39]. These scopes have a wider range of view, with an enhanced image quality, which may increase the diagnostic yield of pancreatoscopy in the setting of the diagnostic work-up of IPMN. Third, as discussed in the previous paragraph, the included studies used different diagnostic work-up protocols and different outcome measurements, making it difficult to directly compare their outcomes in order to define the role of POP in the current diagnostic work-up. For all these reasons, a systematic quantitative data analysis was not possible for most outcome parameters, which prohibits the drawing of a definite conclusion regarding the role of POP in current clinical practice.

In conclusion, this is the first literature review to summarize the current knowledge on the role of POP in the diagnostic algorithm of IPMN. POP has a high technical success rate and seems to provide adequate visualization of the target area, in particular in patients with a dilated MPD. POP may be useful in the preoperative work-up for assessment of the extent and exact location of the lesion, as well as to identify the existence of skip lesions. However, despite the reasonably high diagnostic accuracy rates that have been reported, the exact role of POP in the diagnostic work-up still remains unclear, mostly because of methodological shortcomings and heterogeneity between studies. Large multicenter consecutive prospective studies performed according to a predefined protocol, including well-described procedural aspects, imaging documentation (preferably by video), and the application of intraductal pancreatoscopy-guided biopsies, are needed to better define the role of POP in the diagnostic algorithm of IPMN.

Acknowledgments

We thank W. M. Bramer, Erasmus MC, for his support in performing the systematic search.

Competing interests

M.J. Bruno received research funding from Boston Scientific, Cook Medical, Pentax Medical, InterScope, and Mylan; he is a consultant to Boston Scientific, Cook Medical, and Pentax Medical. M. Ellrichmann received research funding from Boston Scientific and is a consultant to Boston Scientific. L. Kylänpää is a speaker and consultant for Boston Scientific, Cook Medical, and Olympus. A. Anderloni is a consultant for Boston Scientific. George Webster is a consultant and invited speaker for Boston Scientific, Cook Endoscopy, and Pentax Medical. The remaining authors declare that they have no conflict of interest.

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