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Role of Endoscopy in Clinical Management of Intraductal Papillary Mucinous Neoplasms

Tsuyoshi Hamada[1,2] | Hiroki Oyama[1] | Naminatsu Takahara[1] | Yousuke Nakai[1,3] | Mitsuhiro Fujishiro[1]

[1]Graduate School of Medicine, Department of Gastroenterology, The University of Tokyo, Tokyo, Japan | [2]The Cancer Institute Hospital, Department of Hepato-Biliary-Pancreatic Medicine, Japanese Foundation for Cancer Research, Tokyo, Japan | [3]Institute of Gastroenterology, Department of Internal Medicine, Tokyo Women's Medical University, Tokyo, Japan

Correspondence: Tsuyoshi Hamada (hamada-tky@umin.ac.jp)

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ABSTRACT

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a well-recognized precursor of pancreatic carcinoma. Along with cross-sectional abdominal imaging tests, endoscopic examinations remain the cornerstone in the diagnosis of pancreatic cysts, early detection of IPMN-derived carcinomas, and risk stratification of patients with IPMNs for subsequent surveillance strategies. In particular, endoscopic ultrasound (EUS) facilitates the optimal patient management by providing high-resolution morphological information, and the contrast-enhanced harmonic mode may further enhance diagnostic accuracy. EUS-guided fine-needle aspiration for solid mass and/or cyst fluid is considered for pathological and molecular examinations for the diagnosis of pancreatic cysts and malignancy. Emerging evidence suggests the usefulness of through-the-needle biopsy and confocal laser microendoscopy in this setting. In addition to the undoubtful diagnostic utility, recent studies have demonstrated the potential effect of endoscopic interventions (i.e., ablation) on the control of IPMNs. Despite the increasing role of endoscopy in the clinical management of IPMNs, there remains a gap in our understanding of how to utilize endoscopy in the personalized care for patients with IPMNs (e.g., the optimal interval of EUS) and the prevention of deaths due to pancreatic carcinomas developing concomitantly with IPMNs.

This review summarizes the current evidence on the role of endoscopy in both the diagnostic and therapeutic landscapes of clinical management of IPMNs and identifies key clinical unmet needs that should be addressed in future research. Combined with emerging technologies (e.g., artificial intelligence and high-throughput molecular profiling), endoscopy would offer more effective and tailored management strategies for patients with IPMNs.

Abbreviations: AI, artificial intelligence; CEA, carcinoembryonic antigen; CH-EUS, contrast-enhanced harmonic endoscopic ultrasound; CI, confidence interval; EUS, endoscopic ultrasound; EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration; IPFD, intrapancreatic fat deposition; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; MPD, main pancreatic duct; nCLE, needle-based confocal laser endomicroscopy; PDAC, pancreatic ductal adenocarcinoma; TTNB, through-the-needle biopsy.

Tsuyoshi Hamada and Hiroki Oyama contributed equally as co-first authors.

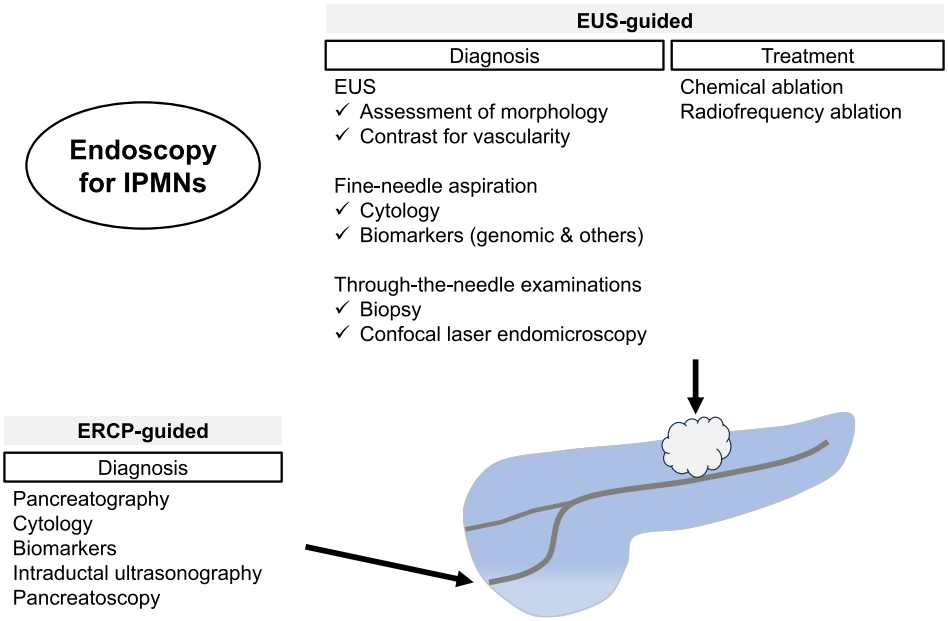

FIGURE 1 | Endoscopic procedures as diagnostic and therapeutic modalities for the clinical management of patients with IPMNs. Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; IPMN, intraductal papillary mucinous neoplasm.

1 | Introduction

Intraductal papillary mucinous neoplasm (IPMN) is the most common type among pancreatic cystic lesions that are identified incidentally on imaging studies for unrelated indications [1, 2]. In the latest version of the international consensus guidelines, IPMNs are classified into branch-duct, main-duct, and mixed-type IPMNs based on the involvement of the main pancreatic duct (MPD) [3]. While IPMNs carry a potential for malignant transformation, branch-duct IPMNs (representing >90% of all IPMNs) exhibit largely indolent biological behavior [4–6]. Consequently, the overwhelming majority of patients diagnosed with IPMNs are subjected to long-term surveillance programs rather than upfront surgery.

Endoscopy plays a critical role in the clinical management of IPMNs. Endoscopic ultrasound (EUS) provides high accuracy in differentiating mucinous from non-mucinous cysts and detecting solid components and wall thickening as morphological findings suggestive of malignant transformation. Contrast-enhanced harmonic mode may increase diagnostic accuracy by providing information on vascularity. Beyond those diagnostic applications, recent advancements in invasive endoscopic techniques have expanded the role of endoscopy in managing IPMNs. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) allows for cytological evaluation and cyst fluid analysis, and EUS-guided through-the-needle biopsy (TTNB) provides tissue specimens for histological examinations. In addition, EUS-guided needle-based confocal laser endomicroscopy (nCLE) enables real-time, in vivo assessment of the intracystic cellular lining. Despite the predominant use of endoscopy as a diagnostic tool, endoscopic ablation of pancreatic cysts is being explored as a potential therapeutic approach in select cases.

In this review, we summarize the current evidence on the established and emerging roles of endoscopy in both the short- and long-term management of patients with IPMNs (Figure 1). In addition, we discuss unresolved clinical and research questions, particularly in the context of long-term surveillance, which warrant further investigation for better consequences for patients diagnosed with IPMNs.

2 | Endoscopic Ultrasound (EUS) for a Differential Diagnosis of Pancreatic Cystic Lesions

EUS plays a crucial role in the non-invasive differential diagnosis of pancreatic cystic lesions by providing high-resolution, real-time images for cyst morphology. This diagnostic modality permits the detailed visualization of the wall, septations, and vascularity of cysts (based on the fundamental B-mode). Among the wide repertoire of pancreatic cystic lesions, IPMN has been the most common type with others including mucinous cystic neoplasm (MCN), serous cystadenoma, solid pseudopapillary neoplasm, cystic neuroendocrine tumor, and pseudocyst [1, 2]. A high-degree consensus has been reached on the typical endosonographic findings of the respective cyst types: e.g., uni- or multi-locular cyst(s) communicating with the MPD for IPMNs, uni- or oligo-locular cyst with a cyst-in-cyst structure at the pancreatic tail in women for MCN, and intracystic honeycomb structure and/or central scar for serous cystadenoma (Figure 2A–E) [1–3]. From the perspective of clinical management, it is important to differentiate mucinous cysts (IPMNs and MCNs) harboring the inherent potential of malignant transformation from the other types. In this setting, EUS along with magnetic resonance cholangiopancreatography provides intermediate to high-level accuracy for the differentiation [7]. It also provides a high sensitivity for the communication of a cyst with the MPD, which is a typical feature of branch-duct (or mixed-type) IPMNs.

Despite the reasonable diagnostic accuracy of EUS for pancreatic cystic lesions, interobserver disagreement has been an issue

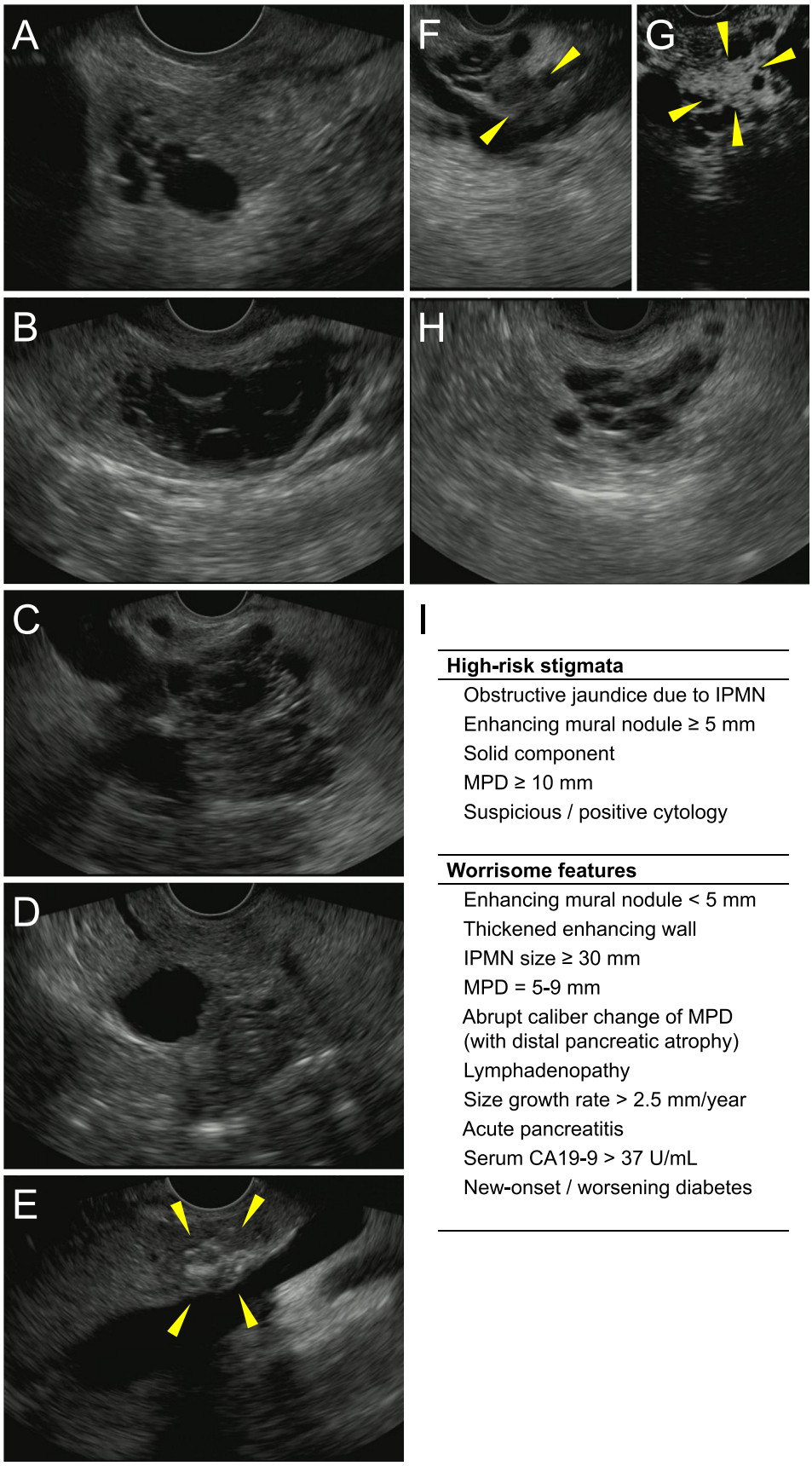

FIGURE 2 | Legend on next page.

FIGURE 2 | Endoscopic ultrasound for neoplastic cystic lesions of the pancreas and risk signatures of IPMNs. (A) Branch-duct IPMN. (B) Mucinous cystic neoplasm. (C) Serous cystadenoma. (D) Cystic neuroendocrine tumor. (E) Solid pseudopapillary neoplasm. (F) Mural nodule developing within a mixed-type IPMN. (G) Mural nodule with vascularity demonstrated on the contrast-enhanced harmonic mode. (H) Thickened wall of a branch-duct IPMN. (I) High-risk stigmata and worrisome features of IPMNs, proposed by the international consensus guidelines. Abbreviations: CA19-9, carbohydrate antigen 19-9; IPMN, intraductal papillary mucinous neoplasm; MPD, main pancreatic duct.

[7]. Educational programs focusing on EUS-based diagnosis of pancreatic cystic lesions should be designed and implemented for quality control. To fill this gap, a reliable quality indicator should be developed for effective education (e.g., cyst detection rate proposed by Nakai, et al. [8]). Artificial intelligence (AI)-driven computer-aided diagnosis system may facilitate an objective endosonographic assessment [9, 10].

3 | Endoscopy for a Diagnosis of Intraductal Papillary Mucinous Neoplasms (IPMNs) and Associated Malignancy

When individuals are diagnosed with IPMNs, it is most important to rule out the possibility of malignancy. In cases without an indication for upfront surgery, the positivity of risk signatures should be evaluated to stratify the future risk of pancreatic carcinoma development and personalize the surveillance intensity. Therefore, a variety of endoscopy-based diagnostic modalities have been investigated. Given the invasiveness of some highly reliable diagnostic modalities, the risk–benefit balance should be considered on a case-by-case basis.

3.1 | Endoscopic Ultrasound (EUS) and a Contrast-Enhanced Harmonic Mode

The latest version of the international consensus guidelines has updated "high-risk stigmata" as strong surgical indications and "worrisome features" as relative surgical indications (Figure 2F–I) [3]. A validation study based on 3336 patients demonstrated the high predictive ability of those clinical variables for the prevalence and future risk (long-term incidence) of pancreatic carcinomas [11]. At the time of IPMN diagnosis, pancreatic carcinomas exist in nearly half of IPMNs with high-risk stigmata but rarely in IPMNs with worrisome features only and no risk factors (0.4%). In long-term analyses of patients without high-risk stigmata, the MPD diameter of 5–9.9 mm, acute pancreatitis, and IPMN growth rate of 2.5 mm/year were associated with the long-term incidence of pancreatic carcinoma. Of note, the number of worrisome features had an incremental effect on the prevalence and long-term incidence of pancreatic carcinoma. Therefore, it is important to evaluate the positivity of each risk factor prudently, and EUS has been the most reliable modality for the assessment of morphological risk factors, including a mural nodule and wall thickening. In the above study, EUS had a sensitivity of >95% for a mural nodule of ≥5 mm in size and wall thickening (Figure 2F,H) [11]. Recently, AI-based technology has revolutionized the endosonographic detection and differentiation of pancreatic mass lesions [9, 10]. Future research should examine the effectiveness of AI-driven endosonographic evaluation in diagnosing cyst types and detecting malignancy in patients with IPMNs. In a study of 43 patients with histologically proven IPMNs, a convolutional neural network platform based on EUS images provided extremely high accuracy for the differentiation of low-grade IPMNs vs. high-grade dysplasia/invasive carcinoma (99.6%; 95% confidence interval [CI], 99.5%–99.9%) [12], which outweighed the clinical guidelines [13–16]. A larger-scale validation study is warranted to facilitate the introduction of the deep-learning model into clinical practice.

According to the invention of contrast agents and the corresponding EUS system, contrast-enhanced harmonic endoscopic ultrasound (CH-EUS) has become the front-line modality of contrast-enhanced EUS, which helps differentiate malignant and benign IPMNs [17, 18]. This modality enhances traditional EUS examinations by providing high-resolution images and real-time vascularity information. In the setting of the diagnostic workup for IPMNs with suspected malignancy, CH-EUS is particularly useful for differentiating a mucinous nodule from mucus clots (Figure 2G) [16, 17]. In a surgical series of 70 cases with IPMNs, CH-EUS was superior to fundamental B-mode EUS (non-enhanced) in terms of the detection of a mural nodule with a sensitivity of 97%, a specificity of 75%, and an accuracy of 84% [19]. In another surgical series of 30 cases, the time-intensity curve via CH-EUS (graphical presentation of serial changes in echogenicity in a region of interest) was highly predictive for the presence of high-grade dysplasia/invasive carcinoma [20]. Change, reduction rate, and nodule-pancreatic parenchyma ratio of echogenicity were associated with the diagnostic accuracies of 80% (95% CI, 63–89%), 87% (95% CI, 70–95%), and 93% (95% CI, 79–98%), respectively. High-resolution images via CH-EUS allow us to evaluate the detailed morphology of mural nodules beyond their presence. Ohno and colleagues classified mural nodules into four types: type I, low papillary type; type II, polypoid type; type III, papillary type; and type IV, invasive nodule [21]. In a validation study, the types III and IV were associated with a higher prevalence of malignancy compared to the types I and II [21]. In addition, CH-EUS may reliably detect the involvement of the MPD [22], which has been associated with the short- and long-term risks of pancreatic carcinoma [23]. When the MPD involvement based on EUS findings was pathologically examined in 166 patients with resected IPMNs, CH-EUS provided high performance metrics: i.e., sensitivity, 84%; specificity, 87%; and accuracy, 85% [22]. This high diagnostic accuracy may guide decisions about surveillance versus surgery, ensuring more targeted treatment for patients at a high risk of malignancy. Nonetheless, the additional benefit of routine use of contrast has not been fully validated, and contrast agents are unavailable for EUS in some countries.

Despite the undeniable usefulness of EUS (with or without contrast enhancement) in diagnosing pancreatic cyst types and detecting associated malignancy, the indication for diagnostic EUS should be carefully considered on a case-by-case basis. Ultimately, EUS is reserved as an additional work-up for cases where high-risk features are suspected or the pancreatic cyst type remains inconclusive on cross-sectional imaging modalities (i.e., computed tomography and magnetic resonance imaging).

This recommendation is supported by cost considerations and the risk of procedure-related adverse events. Determining cyst types in small pancreatic cystic lesions is not always necessary and may remain challenging, even with EUS examination. In most large pancreatic cystic lesions, cross-sectional imaging modalities can provide sufficient diagnostic information. In addition, diagnostic accuracy of EUS depends on the expertise of endosonographers and each patient's anatomy [7]. However, it should be noted that EUS by expert endosonographers has higher sensitivity for detecting mural nodules and wall thickening in patients with IPMNs, compared to the cross-sectional abdominal imaging [11]. In our prospective cohort of patients with branch-duct IPMNs, the absence of worrisome features, including large cyst size and the high annual growth rate over the initial two years of follow-up, was associated with a low risk of incident pancreatic carcinoma during the subsequent surveillance [11, 24]. Therefore, EUS is not always required during the surveillance of patients with such low-risk IPMNs.

3.2 | Endoscopic Retrograde Pancreatography, Intraductal Ultrasonography, and Pancreatoscopy

Endoscopic retrograde pancreatography and adjunctive diagnostic procedures are performed at some centers for patients with suspected malignancy (Figure 3). The potential of this diagnostic modality has been investigated in preoperative examinations of IPMNs, which help plan the extent of resection [18]. Intraductal ultrasonography may enhance diagnostic accuracy in assessing the lateral spread of IPMNs within the MPD [25, 26].

In patients with MPD dilatation, peroral pancreatoscopy enables direct visualization of IPMN lesions involved in the MPD. It helps differentiate benign from malignant IPMNs through visual assessment and targeted biopsies. Morphological features suggestive of malignancy include a coarse mucosa, friability, and tumorous angiogenesis [27]. In addition, pancreatoscopy can be used to detect skip lesions and thereby reduce the risk of undersurgery. In a pooled analysis, the overall diagnostic accuracy in three studies was high, ranging from 88% to 100% [27]. The results of pancreatoscopy helped define the appropriate resection line by providing the information on IPMN extension and/or identifying skip lesions in 13%–62% of patients in five studies [27]; the varying proportions might be attributable to the variations in procedural indications and patient populations. The recently developed dedicated digital scope has reduced the hurdle due to the cumbersome manipulation of a mother-baby system [28, 29]. At some centers, surgeons prefer to conduct intraoperative pancreatoscopy after the initial transection with the same intent, which may help identify residual skip lesions [30]. The risk of procedure-related adverse events should be considered. In

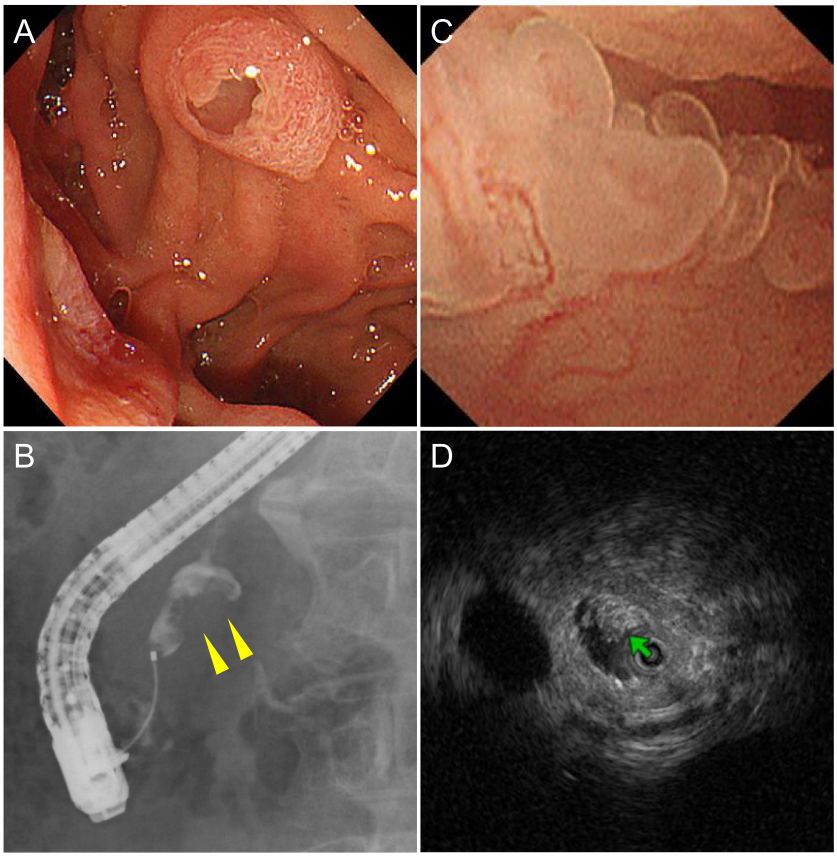

FIGURE 3 | Endoscopic retrograde pancreatography-based procedures for mixed-type intraductal papillary mucinous neoplasms with suspected malignancy. (A) Endoscopic view demonstrating an enlarged ampulla with a "fish-eye" sign due to an enhanced mucin secretion. (B)–(D) Pancreatography, digital pancreatoscopy, and intraductal ultrasonography, respectively, delineating a large papillary lesion within the main pancreatic duct at the pancreatic head. No skip lesion was identified during the procedure, and a diagnosis of carcinoma was pathologically confirmed. Subsequently, pancreatoduodenectomy was carried out with an R0 resection margin.

a meta-analysis, the pooled rates of the total adverse events and pancreatitis were 12% (95% CI, 9%–17%) and 10% (95% CI, 7%–15%) [27]. Given the indolent biological behavior of IPMNs and the risk of procedure-related adverse events, there has been a paucity of long-term outcome data associated with this additional examination. Therefore, the major international guidelines have no positive recommendations for endoscopic pancreatography for this indication [3, 14–16].

3.3 | Endoscopic Ultrasound-Guided Fine-Needle Aspiration (EUS-FNA)

EUS-FNA and adjunctive assays are currently the most promising diagnostic tests for differentiating mucinous from non-mucinous cysts and diagnosing malignancy, to which enormous research efforts have been directed. The diagnostic accuracy of EUS-FNA for solid pancreatic masses has been established, and studies attest to the effectiveness of EUS-FNA for cyst fluid sampling. The major international guidelines currently recommend EUS-FNA for high-risk IPMNs at diagnosis and during long-term surveillance [3, 14–16]. Nonetheless, given the risk of tumor seeding due to the procedure, the indications for EUS-FNA should be considered prudently.

Cytology of cyst fluid has served as a straightforward pathological examination for malignancy but is associated with lower sensitivity due to low cellularity compared to other EUS-guided modalities [31]. In addition to cytology, EUS-FNA has provided opportunities for the analysis of biomarkers in cyst fluid (Table 1 [31–34]). Overall, molecular biomarkers in cyst fluid have been associated with very high specificity but low sensitivity. CEACAM5 (carcinoembryonic antigen [CEA]) is one of the most widely used biomarkers in distinguishing mucinous from non-mucinous cysts with elevated levels suggesting mucinous types. In a meta-analysis of 10 studies, the pooled sensitivity and specificity for the diagnosis of mucinous cysts were 58% (95% CI, 45%–71%) and 87% (95% CI, 82%–92%), respectively [32]. Glucose has emerged as a complementary biomarker with low glucose levels in the cyst fluid being indicative of mucinous cysts. In a study of 93 cases with histologically confirmed pancreatic cysts, the intracystic glucose concentration of ≤ 25 mg/dL had a sensitivity of 88% and a specificity of 91% [35]. Glucose has the notable advantage of being cost-effective and easy to implement. Given that differentiating between malignant and non-malignant cysts is clinically important, numerous studies have investigated the usefulness of genetic biomarkers for diagnosing malignancy. *KRAS* mutations are the most fundamental mutational driver of pancreatic cancer overall [36], and *GNAS* mutations are known to be highly specific to IPMNs and associated carcinomas [37]. However, these genes are often mutated in the precursor lesions, and therefore, their specificity for the diagnosis of malignancy has been low. In parallel with the advancement of sequencing technologies characterized by decreasing costs and shortened turnover time, multi-gene mutational analysis has been examined extensively in the diagnosis of mucinous cysts and malignancy. In a large prospective study with a 22-gene next-generation sequencing panel for cyst fluid, the mutations in MAPK (mitogen-activated protein kinase)-associated genes (*KRAS*, *BRAF*, and *NRAS*) and *GNAS* gene had a sensitivity of 90% and a specificity of 100% for mucinous cysts [33]. The combination of MAPK/*GNAS* and *TP53*/*SMAD4*/*CTNNB1*/MTOR (mechanistic target of rapamycin kinase)-associated genes (*PIK3CA*, *PTEN*, and *AKT1*) had a sensitivity of 89% and a specificity of 98% for high-grade dysplasia/invasive carcinoma [33]. The high specificity for the diagnosis of malignancy was reported for the mutations in *CDKN2A*, *TP53*, *SMAD4*, and *PIK3CA* [32]. The combination of these biomarkers, along with cytology and imaging features, enhances the diagnostic accuracy for malignancy and helps stratify the future risk of malignancy, guiding appropriate management strategies for pancreatic cystic lesions. However, the biomarker assays require additional costs due to the procedures and assays, and therefore, an analysis is warranted to identify the diagnostic strategy that maximizes the cost-utility balance.

3.4 | Endoscopic Ultrasound-Guided Through-The-Needle Examinations (Through-The-Needle Biopsy [TTNB] and Needle-Based Confocal Laser Endomicroscopy [nCLE])

EUS-guided through-the-needle examinations refer to the diagnostic procedures that can be carried out by inserting miniature devices through a prepositioned EUS-FNA needle [38].

EUS-guided TTNB is a valuable technique for obtaining tissue samples from the intracystic wall or septum of IPMNs [39]. TTNB is achieved by inserting microforceps through a prepositioned 19-gauge EUS-FNA needle in a cyst and obtaining a tissue sample from the target lesion under the endosonographic guidance. A major strength of this procedure is the availability of tissue for histological examinations, which provides a more accurate pathological diagnosis than cytology. Therefore, cases with indeterminate cyst types after other examinations and cases with suspected malignancy may be good candidates for this diagnostic procedure. Nonetheless, TTNB should be performed only when the results are assumed to change the management strategy. In a meta-analysis of 11 studies, TTNB provided higher rates of sample adequacy and diagnostic accuracy with pooled ratios of 85% (95% CI, 78%–93%) and 79% (95% CI, 73–84%), respectively, which outperformed EUS-FNA alone [40]. For the mutational analysis, cyst wall specimens obtained via TTNB potentially provide a larger amount of DNA compared to aspirated cyst fluid [41]. There may be technical challenges in performing EUS-guided TTNB for IPMNs. The microforceps can only access the part of the intracystic wall located at the opposite side of a puncture site and may be difficult to advance through a deflected needle [42]. Therefore, it is important to select a puncture site considering the subsequent advancement of the microforceps. As procedure-related adverse events, mild bleeding and pancreatitis were observed in 4% and 2% of the patients, respectively [40].

nCLE has emerged as an imaging modality that provides real-time cellular visualization of epithelial morphology [43, 44] with a remarkably high resolution ($<4\,\mu$m) [45]. nCLE has replaced EUS-guided cystoscopy for which a fiberoptic probe became unavailable [46]. This imaging technique can be carried out by inserting a confocal probe into a cyst cavity through a prepositioned 19-gauge EUS-FNA needle and has shown promise in

TABLE 1 | Selected studies reporting cyst fluid biomarkers for a diagnosis of pancreatic mucinous cysts and malignancy.

Study (year)	Biomarker(s)	N	Design	Diagnostic performance	
				Sensitivity	Specificity
Diagnosis of mucinous cysts					
Pflüger et al. (2023) [32]	CEACAM5 (CEA)	10 studies	Meta-analysis	58%	87%
Pflüger et al. (2023) [32]	Glucose	3 studies	Meta-analysis	93%	76%
Pflüger et al. (2023) [32]	*KRAS*	6 studies	Meta-analysis	61%	99%
Pflüger et al. (2023) [32]	*GNAS*	4 studies	Meta-analysis	44%	100%
Pflüger et al. (2023) [32]	*KRAS* or *GNAS*	4 studies	Meta-analysis	79%	98%
Paniccia et al. (2023) [33]	MAPK or *GNAS*[a]	246 patients	Multicenter, prospective USA	90%	100%
Diagnosis of malignancy					
Li et al. (2022) [31]	CEACAM5 (CEA)	27 studies	Meta-analysis	69%	52%
Springer et al. (2017) [34]	*CDKN2A*	600 patients	Multicenter international, retrospective	11%	97%
Pflüger et al. (2023) [32]	*PIK3CA*	2 studies	Meta-analysis	10%	97%
Springer et al. (2017) [34]	*SMAD4*	600 patients	Multicenter international, retrospective	9%	98%
Pflüger et al. (2023) [32]	*TP53*	2 studies	Meta-analysis	42%	95%
Paniccia et al. (2023) [33]	MAPK/*GNAS* or *TP53*/*SMAD4*/*CTNNB1*/ MTOR alterations[a]	246 patients	Multicenter, prospective USA	89%	98%

Abbreviation: CEA, carcinoembryonic antigen.
[a]MAPK (mitogen-activated protein kinase)-associated genes include *KRAS*, *BRAF*, and *NRAS*; and MTOR (mechanistic target of rapamycin kinase)-associated genes include *PIK3CA*, *PTEN*, and *AKT1*.

evaluating the intracystic cellular morphology of pancreatic cystic lesions. In the context of the clinical management of IPMNs, nCLE may help differentiate mucinous and non-mucinous cysts. In a study of 144 patients receiving EUS-FNA for pancreatic cysts ≥ 20 mm, EUS with nCLE provided a high accuracy of 97% for the differentiation of mucinous vs. non-mucinous cysts, compared to 71% associated with CEACAM5 (CEA) and cytology [47]. Another possible potential of nCLE is the risk stratification of IPMNs based on the morphological patterns of the papillary size and density. A large papillary morphology with thick and dark epithelium, nuclear stratification, and a prominent vascular core on nCLE suggests the malignant transformation of IPMNs [43]. Despite those promising advantages, there have been hurdles to the clinical use of nCLE in the management of patients with IPMNs. High costs associated with the nCLE system and dedicated devices have been a major disadvantage, considerably limiting the availability of this imaging technique. In addition, there may be technical challenges in accessing the target intracystic lesion as in EUS-guided TTNB [46]. Even though a high agreement between expert endosonographers has been reported in the differential diagnosis of mucinous vs. non-mucinous cysts or specific cyst types [48, 49], the interpretation of nCLE findings requires expertise. Given that nCLE observations generate a dynamic cellular and subcellular video image, resulting in a large number of two-dimensional spacially-resolved images, research is desired to evaluate the usefulness of deep-learning technology in the objective assessment of nCLE findings [43]. Using the video frames from 35 patients with IPMNs, researchers developed a convolutional neural network-based algorithm, which yielded high accuracy for the identification of high-grade dysplasia or invasive carcinoma compared to the clinical guidelines [12, 13] (> 82% vs. < 75%, respectively) [50]. It should be noted that time-consuming video editing by an expert is a prerequisite for the application of the deep learning model. A

validation study including a larger number of patients is warranted before the deep learning-based diagnostic system is introduced to clinical practice.

4 | Endoscopic Ultrasound-Guided Ablation for IPMNs

While endoscopy has been used predominantly as a diagnostic modality in the context of clinical management of IPMNs, recent studies have demonstrated the potential of EUS-guided ablation in achieving the resolution of pancreatic cystic lesions, offering a less invasive alternative to surgical resection. These ablation techniques have been expected to induce necrotic changes in the epithelial cells lining the intracystic wall, potentially causing cyst regression. Various techniques and ablation agents (e.g., ethanol and chemotherapeutic agents) have been investigated (Table 2 [51–59]). However, long-term efficacy and safety remain areas of ongoing research, with concerns about adverse events and recurrence of the targeted lesion. Long-term adverse events, such as MPD strictures and recurrent pancreatitis [53, 59], can significantly impair patient quality of life. In addition to the short-term safety profile reported in the previous literature, recent studies have reported the long-term outcomes of EUS-guided ablation compared to surgery [52, 53]. In a large study involving 620 patients, EUS-guided ablation via ethanol (with paclitaxel for lesions harboring high-risk morphological signatures) resulted in a lower level of long-term morbidities compared to surgery [53]. Further randomized controlled trials are needed to establish standardized protocols and to evaluate long-term outcomes in larger patient cohorts. Given that IPMNs inherently communicate with the MPD and ablation agents may cause an injury in the MPD, the safety profile should be validated with a long post-procedural follow-up. Radiofrequency ablation via the EUS-guided transmural or endoscopic transpapillary approach is also under investigation with the same goal [60, 61]. The transmural radiofrequency ablation may be performed safely for lesions located apart (> 1 mm) from the MPD [59]. However, EUS-guided ablation alone is unlikely to completely eliminate the epithelial cells lining the intracystic wall. Given that the prevention of pancreatic cancer-specific deaths is the primary goal of this intervention, long-term follow-up data are required to evaluate the risk–benefit balance of EUS-guided ablation and define its therapeutic indications [62].

5 | Endoscopic Ultrasound (EUS) Targeting the Development of Concomitant Pancreatic Carcinomas During Long-Term Surveillance Programs

Accumulating evidence supports that individuals with IPMNs are at a higher risk of developing pancreatic carcinoma independent of pre-existing IPMNs compared to the general population (Figure 4) [4–6]. This carcinoma type represents similar molecular signatures to non-IPMN-associated PDACs and similarly worse survival outcomes [63]. Therefore, we should pay attention to early signs of concomitant PDACs when following up patients with IPMNs. In a previous study of 46 concomitant carcinomas identified during long-term surveillance of IPMNs [64], IPMN surveillance appeared to reduce the risk of deaths due to concomitant PDACs by approximately 40%. However, it is noteworthy that a substantial proportion of concomitant PDACs were identified at an advanced and thus incurable stage. This is at least in part because concomitant PDACs less frequently exhibit considerable morphological and serological alterations (other than carbohydrate antigen 19–9 elevation that occurs only at a very late stage of prediagnostic clinical course) before the clinical manifestation [65]. Therefore, there are numerous opportunities for new diagnostic modalities, including liquid-based biomarkers and imaging analysis, which supplement the current surveillance strategy for patients with IPMNs.

Another reason for the delayed identification of concomitant PDACs has been our poor understanding of risk factors for concomitant PDACs. Previous studies have only demonstrated nonspecific demographic factors (e.g., high age and male sex [5, 66]) correlated with subsequent risk of concomitant PDACs. It is considered that EUS may help stratify the future risk of developing concomitant PDACs by providing detailed information on the background pancreatic parenchyma. Emerging evidence suggests that intrapancreatic fat deposition (IPFD, also known as fatty pancreas) is implicated in a wide variety of pancreatic diseases including pancreatic cancer [67]. IPFD-induced lipotoxicity may provoke a chronic inflammatory reaction and oxidative stress in various cell types in the pancreas, potentially exerting cancer-promoting effects [67]. EUS can provide metrics that may be correlated with the degree of IPFD. On a non-enhanced observation, the echogenicity of the pancreatic parenchyma relative to that of the reference organ (e.g., the spleen or kidney) may be a surrogate for IPFD [68], but this semi-quantification approach has drawbacks such as operator dependency and overestimation due to parenchymal fibrosis. Given these limitations, Dixon-based magnetic resonance imaging has been the gold standard modality for the assessment of IPFD. Research efforts should be directed to new EUS-based technologies (e.g., elastography) for the information on the pancreatic parenchyma correlated with the risk of concomitant PDACs.

6 | Unmet Needs in the Use of Endoscopy in the Clinical Management of Intraductal Papillary Mucinous Neoplasms (IPMNs)

With its high-level spatial resolution, EUS has played an important role in classifying pancreatic cystic lesions and evaluating the possibility of malignancy. In line with this, the major international guidelines recommend the inclusion of EUS in surveillance programs for high-risk patients [15, 16]. Given the recent remarkable advances in diagnostic and interventional endoscopic procedures, the role of endoscopy will be likely to increase in the clinical management of patients with IPMNs. Nonetheless, future research should investigate the current unresolved questions to maximize the utility of endoscopy in this setting (Figure 5). First, the optimal surveillance strategies combined with EUS and associated procedures should be established. No robust data have been available on the optimal interval of EUS-based examinations according to the risk profile. In addition, there has been an ongoing debate over the optimal timing of discontinuing long-term surveillance [69, 70], and it is unclear how endoscopy is useful in this decision-making. Second, the indications of various endoscopic examinations and

TABLE 2 | Selected studies reporting endoscopic ultrasound-guided ablative techniques for pancreatic cystic lesions.

Study (year)	Lesions, N	Design	Cyst resolution		AEs, N	Other findings
			Complete	Partial		
Chemical ablation						
Ethanol						
Choi et al. (2019) [51]	SCA, 69 IPMN, 63 MCN, 57	Single center, retrospective South Korea	25%	44%	Total, 71 Abdominal pain, 49 Pancreatitis, 21 Duodenal stricture, 2 Bleeding, 1	
Moyer et al. (2024) [52]	IPMN, 36 MCN, 9 Indeterminate, 7 Multilocular, 13	Multicenter, RCTs (long-term) USA	69%	21%	Not available	EUS-guided ablation was associated with lower long-term medical costs compared to no treatment or guideline-compliant surveillance.
Ethanol+paclitaxel[a]						
Cho et al. (2024) [53]	MCN, 117 IPMN, 96 SCA, 40 Indeterminate, 57	Single center, retrospective (long-term) South Korea	76%	12%	Major AE, 4	Compared to surgery, EUS-guided ablation was associated with lower rates of morbidities (1.6% vs. 34% at 10 years), early major AEs (1.0% vs. 8.7%), late major AEs (0.3% vs. 5.5%), and readmission (1.0% vs. 15%).
Paclitaxel+gemcitabine						
Moyer et al. (2017) [54]	IPMN, 27 MCN, 9 Indeterminate, 3	Single center, RCT USA				
With ethanol			61%	22%	Abdominal pain, 4 Pancreatitis, 1	
Without ethanol			67%	14%	None	
Large-surface microparticle paclitaxel						
Othman et al. (2022) [55]	IPMN, 17 MCN, 2	Multicenter, prospective USA	≥ 30% reduction, 35%	1–29% reduction, 35%	Gastric outlet obstruction, 1 Abdominal pain, unknown rate	

(Continues)

TABLE 2 | (Continued)

Study (year)	Lesions, N	Design	Cyst resolution		AEs, N	Other findings
			Complete	Partial		
Krishna et al. (2024) [56]	IPMN, 6	Multicenter, prospective USA	50%	33%	Pancreatitis, 1	Intracystic fibrosis or calcification, 83% Loss of IPMN-related mutations in cyst fluid, 83%
Radiofrequency ablation						
Barthet et al. (2019) [57]	Total, 31 IPMN, 16 MCN, 1	Multicenter, prospective France	65%	6%	Pancreatitis, 1	At one year of follow-up, all lesions harbored no mural nodule.
Younis et al. (2022) [58]	Cystic NET, 7 IPMN, 4 MCN, 1	Single center, prospective Israel	64%	9%	Total, 3 Abdominal pain, 2 Pancreatitis, 1	
Napoléon et al. (2023) [59]	Total, 104 IPMN, 10	Multicenter, retrospective France	63%	37%	Total, 22 (21%)[b] Pancreatitis, 11 Abdominal pain, 7 Leak, 3	Proximity (< 1 mm) to the main pancreatic duct is a risk factor for AEs (OR, 4.10; 95% CI, 1.02–15.2).

Abbreviations: AE, adverse event; CI, confidence interval; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; NET, neuroendocrine tumor; OR, odds ratio; RCT, randomized controlled trial; SCA, serous cystadenoma.

[a]In the early study period (2004–2009), all lesions were ablated with ethanol lavage and paclitaxel injection, and only lesions with thickened walls or multiple septations were additionally ablated with paclitaxel following ethanol lavage thereafter (2010–2019).

[b]The data on the total study population are shown because data were not reported specifically for pancreatic cystic lesions.

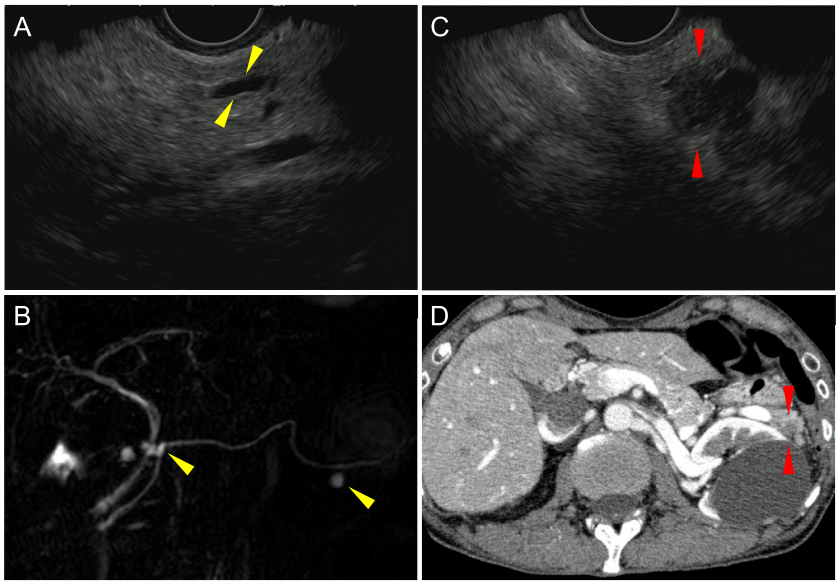

FIGURE 4 | Pancreatic carcinoma developing independently from pre-existing IPMNs. (A) and (B) Endoscopic ultrasound and magnetic resonance cholangiopancreatography, respectively, at a diagnosis of branch-duct IPMNs communicating with the main pancreatic duct. (C) and (D) Endoscopic ultrasound and contrast-enhanced computed tomography, respectively, delineating pancreatic carcinoma developing concomitantly with IPMNs during long-term IPMN surveillance. Abbreviation: IPMN, intraductal papillary mucinous neoplasm.

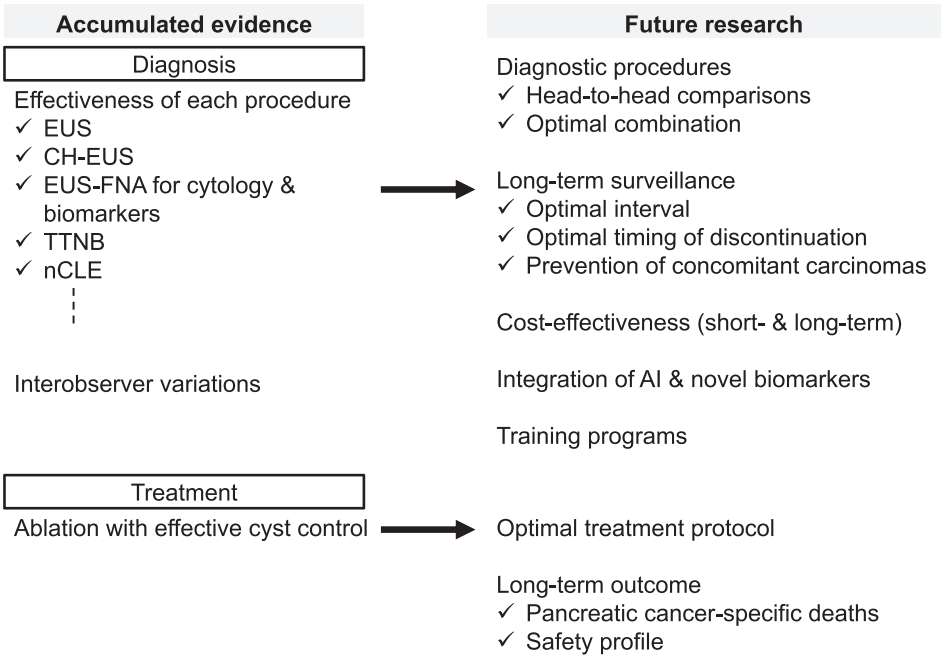

FIGURE 5 | Unmet needs in endoscopy for the clinical management of patients with IPMNs. Abbreviations: AI, artificial intelligence; CH-EUS, contrast-enhanced harmonic endoscopic ultrasound; EUS, endoscopic ultrasound; EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration; nCLE, needle-based confocal laser endomicroscopy; TTNB, through-the-needle biopsy.

their combination have not reached a consensus. Independent studies have reported the clinical utility of each endoscopic procedure in diagnosing pancreatic cysts and detecting malignancy. However, there has been a lack of data on head-to-head comparisons and the effectiveness of the combination of advanced EUS-based diagnostic procedures. Given that it is unrealistic to perform all endoscopic procedures for patients with high-risk IPMNs and/or suspected malignancy, we should determine the optimal combination of endoscopic procedures, considering the risk–benefit balance. Third, the cost-effectiveness has not been fully discussed in the context of endoscopy use in the clinical management of patients with IPMNs. Given their higher costs and burden on patients compared to cross-sectional imaging modalities, the usefulness of endoscopy-based diagnostic modalities should be examined taking into account the benefits, costs, and quality of life. Fourth, the usefulness of emerging anti-tumor interventions for IPMNs (i.e., ablation) should be evaluated in long-term investigations with pancreatic cancer-specific survival as

the primary endpoint. Fifth, endoscopy combined with emerging technologies potentially increases the diagnostic accuracy for malignancy. The molecular analytic platform has enabled the highly sensitive detection of molecules in body fluid and blood (so-called liquid biopsy). It is unclear how endoscopic examinations can be combined with blood-based biomarkers to facilitate the early identification of pancreatic carcinoma [71]. Given the recent epoch-making advances in AI-based technologies for image analysis, there are ample opportunities for the application of AI to diagnostic endoscopy for IPMNs. Last but not least, given the substantial interobserver variability in endosonographic findings with and without contrast enhancement, it is important to design and implement effective training programs focusing on pancreatic cystic lesions using validated performance indicators [72]. Additionally, computer-aided diagnostic systems can assist by providing real-time objective information on the possible diagnosis of pancreatic cystic lesions and malignancy. Compared to other fields of GI endoscopy, research on AI in endoscopy for pancreatic cystic lesions has lagged.

7 | Conclusions

Recent advances in endoscopy and adjunctive modalities have increased our ability to diagnose pancreatic cystic lesions and identify malignant lesions at an early stage. Despite the undeniable role of endoscopy in the care of patients with IPMNs, longstanding gaps persist between preclinical data on its usefulness and its clinical application. High-quality prospective data are warranted to address these unmet clinical needs and promote precision management of patients with IPMNs for better clinical outcomes. Further research is required to evaluate survival benefits from emerging therapeutic options via EUS for IPMNs. If the appropriate combination and timing of endoscopic procedures according to the risk profile is identified, we endoscopists will further expand the role of endoscopy in the management of patients with IPMNs and improve clinical outcomes during their lifetime.

Ethics Statement

The use of clinical images was approved by the ethics committee of The University of Tokyo (Tokyo, Japan; #1804, 2058, and G0500). Informed consent was obtained from the participants on an opt-out basis given the non-invasive nature of the work.

Conflicts of Interest

The authors declare no conflicts of interest.

Use of Standardized Official Symbols

We use HUGO (Human Genome Organisation)-approved official symbols for genes and gene products; all of which are described at www.genenames.org. Gene names are italicized, and gene product names are non-italicized.

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