Expert Consensus

The Hong Kong consensus recommendations on the diagnosis and management of pancreatic cystic lesions

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Background: The finding of pancreatic cystic lesions (PCL) on incidental imaging is becoming increasingly common. International studies report a prevalence of 2.2–44.7% depending on the population, imaging modality and indication for imaging, and the prevalence increases with age. Patients with PCL are at risk of developing pancreatic cancer, a disease with a poor prognosis. This publication summarizes recommendations for the diagnosis and management of PCL and post-operative pancreatic exocrine insufficiency (PEI) from a group of local specialists.

Methods: Clinical evidence was consolidated from narrative reviews and consensus statements formulated during two online meetings in March 2022. The expert panel included gastroenterologists, hepatobiliary surgeons, oncologists, radiologists, and endocrinologists.

Results: Patients with PCL require careful investigation and follow-up due to the risk of malignant transformation of these lesions. They should undergo clinical investigation and pancreas-specific imaging to classify lesions and understand the risk profile of the patient. Where indicated, patients should undergo pancreatectomy to excise PCL. Following pancreatectomy, patients are at risk of PEI, leading to gastrointestinal dysfunction and malnutrition. Therefore, such patients should be monitored for symptoms of PEI, and promptly treated with pancreatic enzyme replacement therapy (PERT). Patients with poor response to PERT may require increases in dose, addition of a proton pump inhibitor, and/or further investigation, including tests for pancreatic function. Patients are also at risk of new-onset diabetes mellitus after pancreatectomy; they should be screened and treated with insulin if indicated.

Conclusions: These statements are an accurate summary of our approach to the diagnosis and management of patients with PCL and will be of assistance to clinicians treating these patients in a similar clinical landscape.

Keywords: Pancreatic cystic lesions; pancreatic endocrine insufficiency; pancreatic enzyme replacement therapy

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Introduction

Pancreatic cystic lesions (PCL) comprise a diverse group of neoplasms and are mostly diagnosed incidentally during radiographic scans for non-pancreatic indications (1). They may be benign, but can also progress to pancreatic cancer—a disease with limited treatment options and poor outcomes (2). Therefore, identifying and monitoring patients at risk of malignant disease is critical. Patients with PCL at low risk of malignant disease are managed with surveillance, but partial or total pancreatectomy is indicated for those with higher-risk PCL (3,4). Following pancreatectomy, patients are at risk of pancreatic exocrine insufficiency (PEI) and consequent gastrointestinal (GI) dysfunction and malnutrition (5), as well as new-onset diabetes mellitus (NODM) (6); these can be managed via pancreatic enzyme replacement therapy (PERT) (7,8) and insulin replacement, respectively (9).

Highlight box

Key findings

- Patients with pancreatic cystic lesions (PCL) should be monitored and undergo pancreas-specific imaging;
- Endoscopic ultrasound can be considered when worrisome features are identified;
- Medically fit patients at high risk of pancreatic cancer should undergo pancreatectomy;
- After pancreatectomy, patients should be monitored for the development of pancreatic exocrine insufficiency (PEI);
- Patients with PEI should be treated with pancreatic enzyme replacement therapy (PERT).

What is known and what is new?

- Previous guidelines focused on either PCL diagnosis and pre-surgical management or post-surgical management;
- Our recommendations offer comprehensive advice on both pre- and post-surgical management, adapted to the clinical landscape of East Asia.

What is the implication, and what should change now?

- These guidelines summarize the latest data on PCL management, focusing on current practice in Hong Kong;
- Future research topics include optimizing PCL monitoring, improving pancreatectomy outcomes, and optimizing PERT dosing in Asian patients.

The incidence of PCL in European and North American populations is increasing (10), and although formal data are not available, clinical experience suggests the incidence of PCL is also increasing in Hong Kong. Registry data from 2019 show that pancreatic cancer had the fifth highest mortality among cancer types in the territory (11). The challenges of correctly diagnosing PCL patients were illustrated in a recent retrospective study that compared preoperative versus final diagnosis and found that in 22% of patients, the pathology did not correlate between the two stages (12). Updated, evidence-based guidelines may reduce the risk of unnecessary surgeries, and although international guidelines for management of PCL and complications subsequent to pancreatectomy are available (13), there is a need for guidance that is tailored to the clinical landscape of Hong Kong. Furthermore, there is a need in East Asia for a broad guidance document that covers multiple aspects of the diagnosis and management of patients with PCL, PEI, and NODM. To meet these needs and assist physicians treating patients with PCL, a group of local experts formulated consensus statements to guide healthcare professionals in the diagnosis and management of PCL.

Literature review and consensus methodology

Two online meetings including gastroenterologists, surgeons, oncologists, radiologists, and endocrinologists were convened in March 2022. The selection of experts included physicians from both public hospitals and private practice and was representative of the specialists involved in the diagnosis and management of patients with PCL and subsequent PEI. Prior to the meeting, selected experts performed a narrative review of literature and formulated consensus statements on the diagnosis and management of PCL, PEI, and post-pancreatectomy diabetes mellitus (*Table 1*; Table S1). To integrate the diverse medical expertise of the authors into consensus statements in an adaptive, anonymized and unbiased manner, the Delphi methodology was used under the supervision of a medical writer (Figure S1). Draft consensus statements and their supporting data were presented to the committee and anonymously evaluated using a Likert scale (1, accept completely; 2, accept with some reservations; 3, accept

Table 1 Summary of narrative review search strategy

Item	Specification
Date of search	Up to March 2022
Databases and other sources searched	PubMed
Search terms used	See Table S1
Inclusion and exclusion criteria	Inclusion: English language
	Exclusion: Studies in model organisms, non-English language publications
Selection process	Relevance as assessed by reviewing author for each topic (listed in Table S1)

with major reservations; 4, reject with reservations; 5, reject completely). Voting was anonymous, and consensus was defined as ≥80% of participants voting to accept a statement 'completely' or 'with some reservations'. Where this threshold was not achieved, statements were revised and voting repeated until a consensus was met. Evidence supporting the statements was evaluated using the Oxford Centre for Evidence-Based Medicine's 2011 Levels of Evidence (14) and this manuscript was prepared in alignment with the CREDES reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-22-471/rc) (15).

Prevalence and classification of PCL

Statement 1: *Incidental pancreatic cystic lesions detected on cross-sectional imaging performed for non-pancreatic indications are common, and their prevalence increases with age (Level 2)*

Statement 2: *Pancreatic cystic lesions can be either neoplastic or non-neoplastic cysts. Neoplastic cysts can be broadly classified as serous or mucinous pancreatic cystic lesions, or cystic degeneration of solid tumors of the pancreas*

Statement 3: *Mucinous pancreatic cystic lesions such as intraductal papillary mucinous neoplasms (main duct type, branch duct type, or mixed type) and mucinous cystic neoplasms are considered pre-malignant lesions with variable malignant potential (Level 1)*

In epidemiological studies from the USA, Europe, and Korea, estimates of the prevalence of PCL range from 2.2% to 44.7% (*Table 2*), with many studies reporting increasing prevalence of PCL with increasing age (16-20). The authors' clinical experience suggests that the prevalence of PCL in Hong Kong is within this range, and that prevalence of PCL is increasing, consistent with the aging trend in the population of the territory (21). The wide range in prevalence rates reported is explained by differences in the methods of calculation, imaging indication, and imaging modality used; for example, studies that use magnetic resonance imaging (MRI) generally report higher incidences than studies using computed tomography (CT) scans (22). The very high prevalence seen in the study of Girometti and colleagues, 44.7%, is likely due to the use of magnetic resonance cholangiopancreatography (MRCP) (18), which is usually performed for patients with suspected bile duct or pancreatic pathology.

PCL can be classified as either neoplastic or non-neoplastic cysts, and neoplastic cysts can be further classified as serous PCL, mucinous PCL, or cystic degeneration of solid pancreatic tumors. Intraductal papillary mucinous neoplasm (IPMN), a common PCL subtype, is also classified according to its involvement with the main pancreatic duct (MD) or one of the branch ducts (BD) (10). Common mixed solid and cystic lesions may include cystic degeneration of neuroendocrine tumors, solid pseudopapillary tumors, adenocarcinoma, and mucinous cystic lesions with a solid component. The scheme from the European Study Group on Cystic Tumours of the Pancreas (ESGCTP), which broadly classifies cysts by epithelial/nonepithelial and neoplastic/non-neoplastic status based on the World Health Organization criteria (3), is a useful guide for cyst classification.

Accurate classification of PCL is important because the risk of malignant transformation varies among subtypes. For IPMN, in an extensive review performed by Tanaka and colleagues to inform a 2012 guideline publication (23), the chance of malignant transformation was >62.2% for MD IPMN, >24.4% for BD IPMN, and >57.6% for mixed-type IPMN (24-45). In a review of published surgical cases of resected MD IPMN, included in a 2017 guideline (4), invasive carcinoma and high-grade dysplasia were found in 61.6% of subjects (26,30-35,38-44). Risk of malignant transformation is generally lower in BD IPMN than MD

Table 2 Summary of prevalence data of PCL (16-20)

Study and location	Population, imaging modality, and indication	PCL prevalence	Comments
Laffan *et al.* USA (19)	Single-center study using contrast-enhanced multi-detector CT for non-pancreatic indications; n=2,832	2.6%	Increasing prevalence associated with older age and Asian ethnicity
de Jong *et al.* Germany (17)	Single-center study using MRI for a preventive medical examination; n=2,803	2.4%	Increasing prevalence associated with older age
Lee *et al.* USA (20)	Single-center retrospective review of all abdominal MRI scans performed; n=616	13.5%	Increasing prevalence associated with older age
Chang *et al.* Korea (16)	Single-center study reviewing CT scans from health screening examinations; n=21,745	2.2%	Increasing prevalence associated with older age
Girometti *et al.* Italy (18)	Single-center study reviewing MRCP scans of patients with unsuspected/unknown pancreatic disease; n=152	44.7%	Prevalence correlated with age ≥60 years and history of hepatobiliary autoimmune disease

PCL, pancreatic cystic lesion; CT, computed tomography; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography.

IPMN; in seven surgical series of resected BD IPMN, invasive carcinoma and high-grade dysplasia were found in 31.1% of subjects, and among natural history studies, this rate was even lower (1.4–6.9%) (4,46-52). Treating physicians must be aware that pancreatic cancer can develop from the IPMN itself or from parenchyma not involved in the cystic lesion—a phenomenon referred to as a 'field defect' (53).

Detection and diagnosis of PCL

Statement 4: *In patients with pancreatic cystic lesions, new-onset or worsening diabetes may be associated with underlying pancreatic adenocarcinoma*

Guidelines for the diagnosis of PCL are available from various international groups, most notably, the International Association of Pancreatology (IAP), the American Gastroenterological Association (AGA), the American College of Gastroenterology (ACG), the ESGCTP, and the American College of Radiology (ACR) (3,4,54-56). Mass screening for PCL is not recommended (22,57), because even a highly specific test would likely be subject to a high rate of false positives due to the low incidence in the overall population.

Genetic risk factors for pancreatic cancer include mutations in genes such as *BRCA1*, *BRCA2*, *MLH1* and others, but these mutations are present in fewer than 10% of pancreatic cancer cases, and the most commonly found mutations (e.g., *BRCA1* and *BRCA2*) increase the risk of pancreatic ductal adenocarcinoma (PDAC) moderately, by around two- to six-fold (58). Reports suggest 2–4% of patients who are finally diagnosed with PDAC present with symptoms that mimic acute pancreatitis (59), and a systematic review and meta-analysis found the lifetime risk of pancreatic cancer in patients with chronic pancreatitis was elevated 16-fold versus those without chronic pancreatitis (60). However, the majority of patients who present with PCL do not have a history of pancreatitis (61). Patients with NODM have a 6- to 8-fold increase in risk of underlying PDAC, and among patients with NODM, 3-year pancreatic cancer incidence is ~1% (62). The incidence of PCL in patients with NODM is unclear, and models using clinical characteristics to stratify NODM patients according to their risk of pancreatic cancer are limited by their low predictive value (63). Several studies have evaluated prospective screening for pancreatic cancer in subjects with NODM (64-66), but results suggest further selection methods (e.g., biomarkers) need to be identified to improve the diagnostic yield (67). Other reported risk factors associated with increased risk of pancreatic cancer include low dietary intake of whole grains (68), higher prevalence of smoking, alcohol consumption, physical inactivity and obesity (69), and the presence of metabolic syndrome (70).

Role of CT/MRI in the diagnosis and management of PCL

Statement 5: *Contrast-enhanced computed tomography and magnetic resonance imaging are the imaging modalities of choice for diagnostic workup and surveillance of pancreatic cystic lesions (Level 5)*

Statement 6: *When available, a specific pancreatic protocol fulfilling minimal technical and reporting standards for structural cross-sectional imaging should be used in the workup and surveillance of pancreatic cystic lesions (Level 5)*

The main radiographic modalities used to detect PCL are CT, MRI, and transabdominal ultrasound (71). The accuracy in identifying specific subtypes of PCL and differentiating malignant from benign lesions also varies with modality. MRI and CT have similar performance for distinguishing benign from malignant PCL and distinguishing between subtypes (72,73), but a comparison by Sainani and colleagues suggested MRI with MRCP may be more sensitive than CT for identifying a connection between PCL and the pancreatic duct as well as the presence of an enhancing mural nodule or internal septations, and for detecting multifocal disease (45,73). European guidelines recommend the use of CT for detection of parenchymal, mural or central calcification, and where assessment of vascular involvement is required (3). Transabdominal ultrasound imaging provides useful information on cyst site and size but expert opinion is that it is limited by operator-dependency and suboptimal visualization of the pancreas (74). Smaller PCL (<10 mm) can be difficult to characterize by cross-sectional imaging (75). Overall, MRI is the preferred choice, where available, because CT exposes patients to ionizing radiation, which is undesirable due to the associated risk of cancer (76), particularly in younger PCL patients who may need long-term surveillance requiring repeated imaging.

There is no universal standardized protocol for cross-sectional imaging of the pancreas. Single-phase non-contrast CT scans or MRI alone have limited diagnostic value. Pancreas-specific protocols for CT imaging specify the use of intravenous contrast, multi-phase acquisition and thin slices (77,78) and, for MRI, imaging with either 1.5T or 3T is acceptable (79,80). Guidelines from the ACR recommend the inclusion of five elements in a radiology report: MD size, the presence of 'worrisome features' and/or 'high-risk stigmata,' growth on the indexed lesion on serial imaging, and multiplicity of PCL (55).

The role of endoscopic ultrasound in diagnosis and management of PCL

Statement 7: *Endoscopic ultrasound with fine needle aspiration for cyst fluid analysis and tissue acquisition is useful to differentiate between neoplastic and non-neoplastic pancreatic cystic lesions*

Statement 8: *Endoscopic ultrasound should be considered in patients with suspected mucinous cystic neoplasms and intraductal papillary mucinous neoplasms on cross-sectional imaging with worrisome features*

Statement 9: *Endoscopic ultrasound-guided fine needle aspiration for fluid analysis or tissue acquisition should be considered if the result would change management*

The role of endoscopic ultrasound (EUS) is adjunctive to other imaging modalities used to make the initial diagnosis; it can detect features of concern, and EUS-guided fine needle aspiration (FNA) permits sampling of cystic fluid for biochemical and cyto-pathological evaluation (81). Furthermore, EUS can provide high-resolution images and information to guide subsequent management, such as lesion size, number and location, communication of lesion with MD, and presence of mural nodules. Detection of early signs of malignant transformation—e.g., nodules with vascular flow—is also possible with EUS techniques (81).

Although EUS is minimally invasive, guidelines from international expert groups limit the indication to higher-risk patients. In AGA guidance, EUS-FNA is indicated for patients with at least two of the following high-risk features: cyst size ≥3 cm, MD dilation, or the presence of a mural nodule/solid component (56). The IAP guidelines indicate EUS if imaging shows 'worrisome features' (4), and ESGCTP recommends EUS should be performed if the PCL has clinical or radiological features of concern in the initial imaging (3).

Biomarker analysis of EUS-FNA samples can differentiate mucinous versus non-mucinous lesions, but EUS alone cannot reliably differentiate malignant from benign lesions (82). In Hong Kong, typical analyses from EUS-FNA samples may include carcinoembryonic antigen (CEA), glucose, amylase and cytology; DNA analysis is not routinely performed. The diagnostic utility of these markers is supported by numerous studies. For example, in a meta-analysis of 10 studies, the sensitivity and specificity of EUS-FNA cytology for diagnosing mucinous versus non-mucinous PCN were 42% and 99%, respectively (83). A meta-analysis of eight studies concluded intracyst glucose could differentiate mucinous and non-mucinous PCN with 91% sensitivity and 86% specificity (84). Furthermore, analysis of cytologic samples from EUS-FNA may assist diagnosis and management in some patients and reduce unnecessary surgeries (12). A retrospective analysis of 585 patients undergoing pancreatic resection concluded EUS with cytologic sampling improved the accuracy of diagnosis of patients with PCL (12). 'Through-the-needle' EUS-guided biopsy in patients with PCL has also been shown to be feasible and clinically useful in a meta-analysis (85).

Although FNA can be performed with EUS, it should only be performed if the FNA or cyst fluid analysis will

Table 3 Worrisome features in patients with IPMN (3,4,54,56)

Clinical history
• NODM
• History of pancreatitis
Radiological
• Mural nodule <5 mm
• Cyst size ≥3 cm
• MD diameter 5–9 mm
• Rapidly increasing size of cyst (5 mm in 2 years)
Biochemical
• Elevated CA 19-9

IPMN, intraductal papillary mucinous neoplasm; NODM, new-onset diabetes mellitus; MD, main duct; CA 19-9, cancer antigen 19-9.

change clinical management (3). In patients with cross-sectional imaging or EUS showing obvious malignant transformation of the PCL indicative of surgical resection, EUS-FNA may not be necessary. Needle tract seeding—tumor cell implantation along the needle tract—has been reported as a very rare but serious complication of EUS-FNA (86). A meta-analysis of 10 studies (n=13,238) found a pooled rate of needle tract seeding of 0.3%, and the authors concluded that needle tract seeding is very unlikely to affect outcomes and should not be a reason to discourage EUS-FNA (86).

EUS-guided needle-based confocal laser endomicroscopy (EUS nCLE) is an emerging technique that enables real-time microscopic imaging during ultrasound-guided EUS-FNA (87). Several studies have demonstrated that EUS nCLE imaging is highly accurate and reliable for risk-stratification of pancreatic cysts (88-90), and EUS nCLE may have better specificity and sensitivity for diagnosing high-grade dysplasia than current guideline algorithms (Fukuoka and AGA) (89). A 2022 consensus statement concluded that EUS nCLE could improve the diagnosis of PCL and noted that it should be systematically considered when EUS-FNA is indicated (87). Currently EUS nCLE is not widely used in Hong Kong and local experience is limited.

Recommendations for surveillance

Statement 10: *A history of pancreatitis*, *new onset of diabetes mellitus*, *mural nodule sized <5 mm*, *cyst size ≥3 cm*, *main pancreatic duct diameter 5–9 mm*, *rapid increasing size of cyst (5 mm in 2 years) and elevated cancer antigen 19-9 level in patients with intraductal papillary mucinous neoplasms are worrisome features*

Statement 11: *Surveillance for neoplastic pancreatic cystic lesions should be lifelong, as long as the patient is fit for surgery*

Statement 12: *Patients with intraductal papillary mucinous neoplasms who are fit for surgery should receive regular follow-up with structural imaging to pick up malignant transformation changes*

Diverse guidelines make references to 'worrisome features'—i.e., features associated with a higher risk of malignancy—when guiding management of patients with PCL. The definition of worrisome features in patients with IPMN defined in this publication (*Table 3*) is largely informed by those of the IAP, ESGCTP, AGA, ACG (3,4,54,56). Similar to the ESGCTP guidelines, we denote NODM and elevated cancer antigen 19-9 (CA 19-9) as worrisome features; however, for cyst size, the threshold is aligned with that of other international organizations (≥3 *vs.* ≥4 cm for ESGCTP) (13). Cyst size ≥30 mm is associated with a higher risk of high-grade dysplasia or malignancy (3), and data from multiple studies of IPMN patients show MD dilatation ≥5 mm is associated with a higher rate of malignancy or high-grade dysplasia (91-93). Several studies have found elevated serum CA 19-9 (>37 U/mL) to be associated with increased risk of invasive carcinoma or high-grade dysplasia (94-96).

Patients with PCL should be regularly monitored due to their increased risk of pancreatic cancer compared with the general population (97). The risk of malignant transformation because of PCL going undetected must be carefully balanced against the cost, inconvenience, and invasiveness of surveillance. Recommendations for duration and interval of monitoring of IPMN vary among expert groups, but in general, patients with larger cysts and higher-risk features should receive more intensive follow-up. Guidance from the AGA specifies, in the absence of concerning EUS-FNA findings, MRI surveillance at 1 year then every 2 years, with surveillance discontinued at 5 years or if the patient is no longer eligible for surgery (56). The IAP recommends lifelong surveillance with CT/MRCP every 2 years, and initial short-term follow-up of PCL, increasing in frequency with larger cyst size, with patients who have cysts >3 cm receiving 3–6 monthly follow-up with MRI alternating with EUS (4). Guidelines from the ESGCTP recommend surveillance with MRI or EUS 6-monthly for 1 year then annual (lifelong) monitoring if no risk factors are present (3). Our recommendation is that patients with IPMN or mucinous cystic neoplasm (MCN) with no indications for surgery or worrisome features

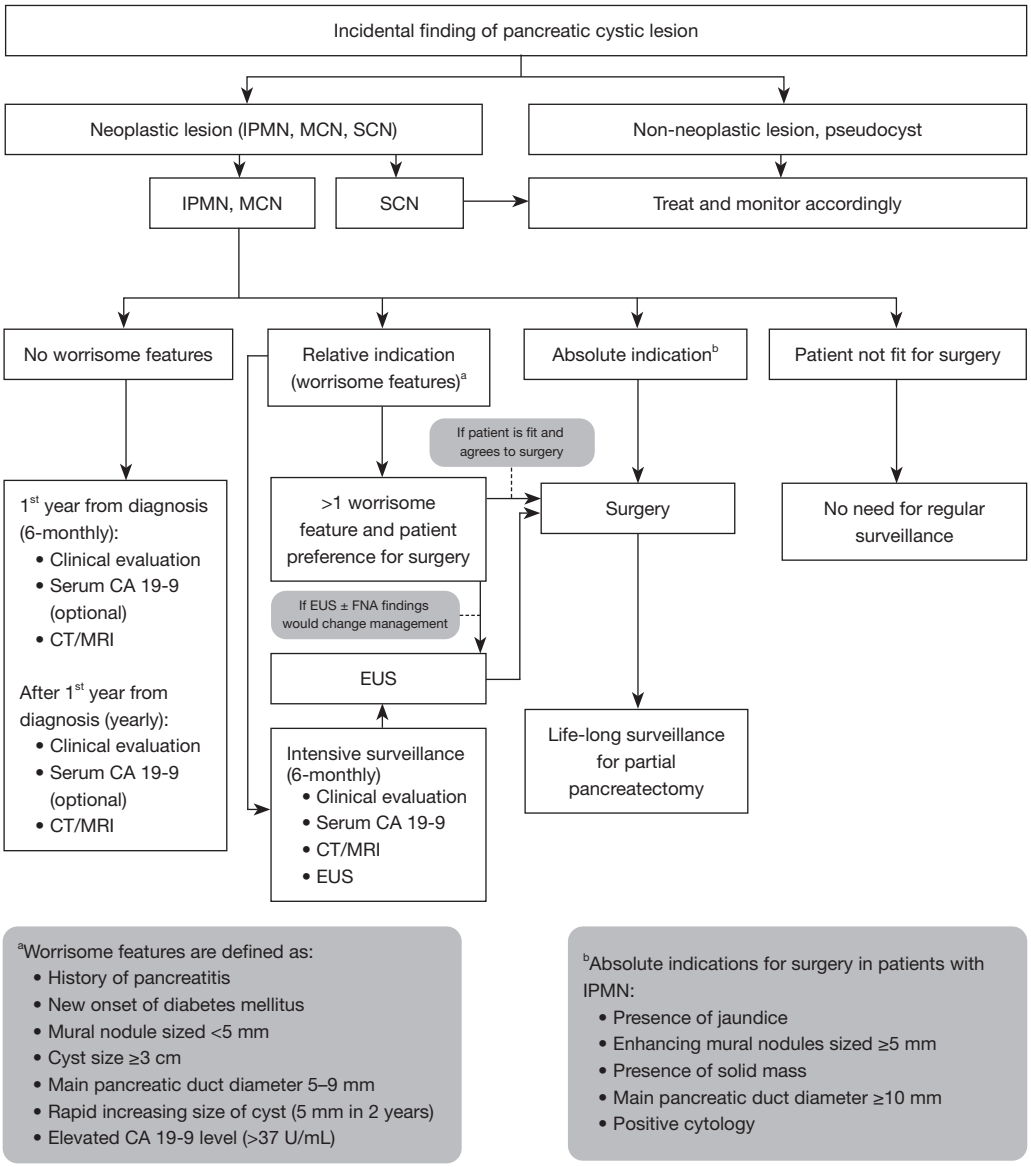

Figure 1 Algorithm for surveillance and management of patients with PCL. IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; SCN, serous cystic neoplasm; CA 19-9, cancer antigen 19-9; CT, computed tomography; MRI, magnetic resonance imaging; EUS, endoscopic ultrasound; FNA, fine needle aspiration; PCL, pancreatic cystic lesions.

receive monitoring (including clinical evaluation, MRI/CT imaging, and CA 19-9 tests) at 6–12 months, and 1-yearly intervals thereafter (*Figure 1*). Patients with worrisome features but no absolute indication for surgery should receive 6-monthly surveillance.

Management and prognosis of PCL

Statement 13: *Surgery may be offered to fit patients with symptomatic neoplastic pancreatic cystic lesions*

Statement 14: *Patients with main pancreatic duct type or mixed-type intraductal papillary mucinous neoplasms should be considered for surgery as there is a considerable risk of cancer formation*

Statement 15: *Presence of jaundice, enhancing mural nodules sized ≥5 mm, presence of solid mass, main pancreatic duct diameter ≥10 mm and positive cytology in patients with intraductal papillary mucinous neoplasms are absolute indications for surgery*

More than 90% of PCL may be classed as one of serous cystadenoma, IPMN (BD, MD or mixed type), or MCNs; all other types are rare, making up the remaining 10% (98-101). Serous cystic neoplasm has distinct morphological characteristics and, although considered benign, required resection in two-thirds of patients in a European study, even though the risk of transformation was <1% (102). Post-operative mortality among pancreatectomy patients has declined as techniques have matured. A US study found 30-day mortality rates halved from 6% in 1991 to 3% in 2005 (103). Another study of US patients who received pancreaticoduodenectomy (PDD) between 2014 and 2018 reported a mortality rate of 0.8% (104), and Hong Kong Hospital Authority data from 2018 to 2019 show a 30-day mortality rate of ~1% (105).

Indications for surgery vary among international guidelines; the absolute indications for surgery suggested here are aligned with ESGCTP guidelines: jaundice, enhancing mural nodules ≥5 mm, presence of solid mass, MD diameter ≥10 mm or positive cytology (3). Similar indications are endorsed by the 2017 IAP guideline (4). Patients with more than one worrisome feature may also be candidates for surgery, subject to EUS findings and patient preferences. Our recommendations for the surveillance and management of patients with PCL are summarized in *Figure 1*.

Enrollment in clinical trials is a potential option for patients unfit for surgery, and EUS-guided chemoablation or radiofrequency ablation are promising options in clinical development that may be suitable for selected patients unfit for pancreatectomy (106,107).

Systemic management and adjuvant treatment for cancer formation

Statement 16: *When a pancreatic cystic lesion manifests as malignant transformation*, *surgery is recommended for fit patients*

Statement 17: *Adjuvant chemotherapy is beneficial in the majority of patients with resectable pancreatic ductal cancer after malignant transformation of a pancreatic cystic lesion (Level 1)*

Pancreatic cancer is extremely difficult to manage, resulting in high mortality; US data (2012–2018) show only 12% of patients have localized disease at diagnosis; most have regional (30%) or metastatic (52%) disease (108). Survival at 5 years ranges from 44% for those diagnosed with localized disease to 3% for those diagnosed with metastatic disease (108).

Numerous studies have shown beneficial effects of chemotherapy in patients with PDAC who have resected or metastatic disease (*Table 4*) (109-117). FOLFIRINOX (oxaliplatin + irinotecan + leucovorin + fluorouracil) or modified FOLFIRINOX regimens are considered to be the current standard of care for these patients (118). Adjuvant chemotherapy is administered to a broader population of patients with pancreatic cancer, compared with other cancer types, possibly due to its poor prognosis. However, chemotherapy is not suitable for all patients; the decision should be guided by disease stage and the patient's clinical status following surgery. Ideally, chemotherapy should be initiated within a few weeks of surgery, but should patients need a longer time to recover, chemotherapy initiation can be delayed by up to 12 weeks from surgery without a negative effect on outcomes, according to an analysis of patients with PDAC (119). Chemotherapy is beneficial in many patients with PDAC, but a review of 361 published cases with gastroenteropancreatic neuroendocrine neoplasms by Lania and colleagues concluded that the current evidence does not support its use in patients with pancreatic neuroendocrine tumors (120)

Common adverse effects and management of patients following pancreatectomy

Statement 18: *New-onset diabetes mellitus occurs in up to one-quarter of patients after partial pancreatectomy (Level 2)*

Statement 19: *The incidence of pancreatic exocrine insufficiency following pancreaticoduodenectomy is higher than with distal pancreatectomy (Level 2)*

Statement 20: *After resection of intraductal papillary mucinous neoplasm*, *surveillance should be continued for as long as the patient remains fit for surgery (Level 5)*

Incidence of NODM has been reported in patients after various forms of pancreatectomy. A study of 25 patients who received distal pancreatectomy (DP) and islet auto-transplantation found six patients (24%) had NODM at a median of 185 days (121). Among 31 patients with spleen-preserving DP, a post-operative incidence of NODM of 16% (5/31) was reported (122), and in a retrospective matched-pairs study, 14 of 50 patients developed NODM after DP (123). Lee *et al.* investigated 188 consecutive patients undergoing DP, or spleen-preserving DP; in this study, 20 (11%) patients developed NODM (124). Comparable rates have been seen in larger studies. A US 2022 database study identified 311 nondiabetic patients who underwent pancreatectomy and

Table 4 Summary of overall survival in studies of chemotherapy in patients with PDAC (109-117)

Study	Setting	Comparators (n) and OS
ESPAC-4 (113)	Resected pancreatic cancer (adjuvant)	Gemcitabine (n=366): 25.5 months
		Gemcitabine + capecitabine (n=364): 28.0 months
		HR: 0.82 (95% CI: 0.68–0.98; P=0.032)
PRODIGE 24–ACCORD (111)	Resected pancreatic cancer (adjuvant)	mFOLFIRINOX (n=247): 54.4 months
		Gemcitabine (n=246): 35.0 months
		HR: 0.64 (95% CI: 0.48–0.86; P=0.003)
PRODIGE 4–ACCORD 11 (110)	Metastatic pancreatic cancer	FOLFIRINOX (n=171): 11.1 months
		Gemcitabine (n=171): 6.8 months
		HR: 0.57 (95% CI: 0.45–0.73; P<0.001)
APACT (109,115)	Resected pancreatic cancer (adjuvant)	nab-paclitaxel + gemcitabine (n=432): 40.5 months
		Gemcitabine (n=434): 36.2 months
		HR: 0.82 (95% CI: 0.680–0.996; P=0.045)
MPACT (117)	Metastatic pancreatic cancer	nab-paclitaxel + gemcitabine (n=431): 8.5 months
		Gemcitabine (n=430): 6.7 months
		HR: 0.72 (95% CI: 0.62–0.83; P<0.001)
PREOPANC (116)	Resectable/borderline resectable pancreatic cancer (perioperative)	Preoperative gemcitabine + RT + adjuvant gemcitabine (n=119): 16.0 months
		Adjuvant gemcitabine: 14.53 months
		HR: 0.78 (95% CI: 0.58–1.05; P=0.096)
Alliance A021501 (112)	Resectable/borderline resectable pancreatic cancer (neoadjuvant)	Neoadjuvant mFOLFIRINOX (n=70): 31.0 months
		Neoadjuvant mFOLFIRINOX + RT (n=56): 17.1 months
SWOG-s1505 (114)	Resectable pancreatic cancer (perioperative)	Perioperative mFOLFIRINOX (n=55): 23.2 months
		Perioperative gemcitabine + nab-paclitaxel (n=47): 23.6 months

PDAC, pancreatic ductal adenocarcinoma; OS, overall survival; HR, hazard ratio; CI, confidence interval; mFOLFIRINOX, modified FOLFIRINOX; nab-paclitaxel, albumin-bound paclitaxel; FOLFIRINOX, oxaliplatin + irinotecan + leucovorin + fluorouracil; RT, radiotherapy.

reported a NODM incidence of 20.2% at 24 months (125). Multivariable analysis revealed older age, obesity, hypertension and cardiovascular (CV) disease to be independent predictors of NODM (125). A meta-analysis of 476 patients who underwent DP for benign or potentially malignant lesions reported a ≥6 months incidence of NODM of 14% (126). Furthermore, a meta-analysis including 1,121 patients who underwent pancreatoduodenectomy reported a mean weighted overall proportion with NODM of 16% (127). Some studies have suggested a higher incidence of NODM in patients undergoing DP than with central pancreatectomy (CP) (128-130), but a matched-pairs analysis of 100 patients who underwent DP or CP did not find a significant difference in rates of NODM between groups (123).

The incidence of PEI reported following pancreatectomy varies considerably due to different definitions and study types, but data suggest a higher incidence of PEI after PDD compared with DP. These include a systematic review of nine studies (n=673) that reported pre-operative incidences of PEI in 44% of patients undergoing PDD and 20% prior to DP, and post-operative (6-month) rates of 74% (range, 36–100%) and 67–80%, respectively (131). Another review has reported a general trend of higher rates of PEI after PDD than after DP, reporting an incidence of 35–100% following PDD, 19–80% following DP, and 12% following CP (132). Risk factors for PEI include Caucasian race, lower body mass index (BMI), family history of diabetes

Table 5 Rates of postoperative recurrence in patients with IPMN (135-137)

Study	Patient population	Recurrence rates
He *et al.* (137)	N=130, non-invasive IPMN	Any new IPMN:
		1-year: 4%
		5-year: 25%
		10-year: 62%
		IPMN requiring surgery:
		1-year: 1.6%
		5-year: 14%
		10-year: 18%
		Invasive IPMN:
		1-year: 0%
		5-year: 7%
		10-year: 38%
Kang *et al.* (136)	N=298, non-invasive IPMN	Non-invasive IPMN: 2.0% (median follow-up 44.4 months)
		Invasive IPMN: 3.4% (median follow-up 44.4 months)
Marchegiani *et al.* (135)	N=299, non-invasive IPMN	Non-invasive IPMN: 9.3% (median follow-up 58 months)
		Invasive IPMN: 2% (median follow-up 58 months)

IPMN, intraductal papillary mucinous neoplasm.

mellitus, steatorrhea, elevated pre-operative bilirubin, duct-obstructive pancreatic pathology, and a history of acute pancreatitis (133,134).

Pancreatic cysts arise due to a 'field effect' in the remnant pancreas tissue that predisposes patients to recurrence of IPMN and new-onset PDAC (53); therefore, long-term postoperative surveillance is essential. Several large studies have provided data on postoperative recurrence rates of IPMN in large populations (*Table 5*) (135-137). A study of 195 patients who underwent pancreatectomy for IPMN reported cumulative 5- and 10-year incidence rates of PDAC of 4.5% and 5.9%, respectively (138). Predictors of recurrent IPMN and PDAC include high-grade dysplasia in resected specimens, margin-positive resection, family history of PDAC, and gastric and pancreatobiliary subtypes of IPMN (137,138).

Because the risk of progression of IPMN does not decrease over time after resection (137), surveillance should continue, providing the patient is fit for surgery. We suggest surveillance includes cross-sectional imaging every 6–12 months, with 6-monthly imaging recommended for high-risk groups (e.g., family history of PDAC, surgical margin positive for high-grade dysplasia and non-intestinal subtype of IPMN). Invasive IPMN should receive the same follow-up as PDAC.

Diagnosis of pancreatic exocrine insufficiency

Statement 21: *For patients with pancreatic cystic lesions, post-pancreatectomy pancreatic exocrine insufficiency diagnosis should be based on suggestive clinical and laboratory findings*

PEI occurs when secretion of pancreatic enzymes in the intestinal lumen is below the threshold level required for normal digestion, leading to impaired absorption of essential nutrients, including fat, liposoluble vitamins and antioxidants, and severe maldigestion (139,140). Symptoms of PEI vary with severity but may include diarrhea, abdominal pain or functional bowel disorders in undiagnosed patients, and steatorrhea, flatulence, weight loss and deficiencies in liposoluble vitamins such as vitamin D and other nutrients (139,140). These symptoms decrease patients' quality of life and may lead to CV events and malnutrition-related complications (141-143). A notable consequence of PEI is osteoporosis, with a meta-analysis

of 513 patients with acute pancreatitis (most of whom had PEI) reporting a pooled prevalence rate of osteoporosis and osteopenia of 65% (144).

Conditions with a high prevalence of PEI include chronic pancreatitis, pancreatic cancer and pancreatic surgery (145), and pathogenesis of PEI may involve insufficient stimulation secretion, reduced pancreatic function or enzyme production due to chronic pancreatitis or pancreatectomy, and obstruction of pancreatic ducts (139). Asynchrony of GI secretions after pancreatobiliary or GI surgery may also contribute to PEI (146).

Although the optimal method of PEI diagnosis is not defined, diagnosis is usually based on patient-reported changes in bowel function, weight loss, and other patient characteristics. Symptoms alone may lead to under- or over-diagnosis (139). Serum nutritional markers may be of assistance (140), but physicians need to investigate other causes of deficiencies. Imaging may identify structural causes (139), but PEI can occur in patients with a morphologically normal pancreas.

Direct functional tests of the pancreas involve the collection of stimulated pancreatic secretions, namely the secretin-cholecystokinin stimulation test, or an endoscopic pancreatic function test (139,146), but these tests are invasive and costly, limiting their clinical use. Indirect functional tests on blood, fecal or breath samples are cheaper and simpler but are less sensitive and specific (145). Coefficient of fat absorption measured by the 72-hour fecal fat test is considered to be the 'gold standard' test for fat malabsorption but requires the patient to follow a standardized diet for 5 days prior and a 3-day hospital stay (147,148). Compliance therefore tends to be poor. A more convenient alternative is the fecal elastase-1 (FE-1) test. FE-1 is an exocrine-specific pancreatic enzyme reflecting pancreatic exocrine function and is not degraded in the bowel lumen (7); FE-1 can be measured using an enzyme-linked immunosorbent assay (149). A system for staging PEI as 'mild', 'moderate', or 'severe' based on FE-1 levels, coefficient of fat absorption and other patient characteristics has been proposed (150), but these definitions are arbitrary. A meta-analysis found FE-1 tests had a sensitivity of 77% and a specificity of 88% versus direct pancreatic function tests (149). In Hong Kong, FE-1 testing is not widely available and therefore is rarely used. The ^{13}C-mixed triglyceride breath test (^{13}C-MTBT) measures pancreatic function and digestion using a triglyceride substrate that uses carbon dioxide as a metabolite (140). Sensitivity is high, but the test is not routinely available in Hong Kong. In Hong Kong, the usual clinical practice is to diagnose post-pancreatectomy PEI based on patient-reported symptoms and initiate PERT. Imaging and laboratory tests such as FE-1 may be used in the follow-up of patients who do not respond to initial treatment.

Management of PEI

Statement 22: *Pancreatic enzyme replacement therapy should be given in symptomatic patients with pancreatic exocrine insufficiency (Level 5)*

Statement 23: *In patients with suboptimal response after pancreatic enzyme replacement therapy, consider increasing the dose or adding a proton pump inhibitor (Level 5)*

Statement 24: *Monitoring of the nutritional status of the patients after pancreatic enzyme replacement therapy should be based on clinical parameters, with blood tests as an adjunct (Level 5)*

Patients diagnosed with suspected PEI are advised to avoid tobacco and alcohol use as these are risk factors for pancreatitis (151-153). The Pancreatic Exocrine Insufficiency Questionnaire (PEI-Q) is an 18-item patient questionnaire developed by European clinicians (with support from Abbott) to assist diagnosis and monitoring of patients with PEI (154,155). The PEI-Q calculates a score based on three domains: abdominal symptoms, bowel movements, and impact on patients' quality of life, and the reliability of this instrument has been demonstrated in a validation study of 162 European patients with PEI (155). The PEI-Q can provide useful insights to a clinician treating patients with PEI and may inform better decision making (155), and a certified Chinese translation of the PEI-Q is available.*

The mainstay of therapy in patients with PEI is PERT, formulated as pH-sensitive, enteric-coated mini-microspheres of lipase, protease, and amylase that protect enzymes from gastric acidity and allow them to disintegrate rapidly at pH 5.5 in the duodenum (146). The efficacy of PERT has been demonstrated in several randomized studies in patients with PEI from chronic pancreatitis and pancreatic surgery (156-159).

Patients need to be instructed on the correct use of PERT for it to be effective, most importantly taking

* The certified Chinese translation of the PEI-Q is available upon request from Abbott Laboratories Ltd., Hong Kong.

capsules with meals and snacks, and spacing multiple doses throughout a meal. European guidelines recommend a lipase dose of 40,000–50,000 Pharmacopeia units (PhU) per meal—which is approximately 10% of the physiologically secreted dose of post-meal lipase in the duodenum—and half this dose for snacks (151,160). A minimum of 30,000 PhU lipase is suggested per meal (~3 capsules per meal) (151). The UK consensus guidelines recommend a minimum starting dose of 50,000 PhU lipase for main meals and 25,000 for snacks (7). Australasian guidelines recommend 25,000–40,000 PhU lipase to be taken with food and this should be individualized based on bodyweight and titrated based on weight gain and bowel symptoms (8). Studies of PERT dosing specific to Asian populations are not available, but based on local clinical experience, the lower bodyweight of Asian patients, and lower dietary fat content versus Western populations, a smaller starting dose may be appropriate. The typical approach in Hong Kong is to start patients on low doses (e.g., 20,000–30,000 PhU per meal) and step up dosage until symptoms resolve.

Efficacy of PERT can be assessed by resolution of maldigestion symptoms and in non-responders, the use of pancreatic function tests may prove valuable (fat absorption, ^{13}C-MTBT). In patients with poor response, increases of PERT dose or the addition of proton pump inhibitors (PPIs) to reduce gastric acid and thereby decrease degradation of enzymes should be considered. It is important that nutritional deficiencies are resolved for treatment to be considered a success. Clinical evaluation for malnutrition, including screening patients for deficiencies of calcium, zinc, and liposoluble vitamins, should therefore be considered.

Our suggested approach to initiating PERT and dose adjustment is summarized in *Figure 2*. Briefly, PERT should be initiated at 20,000–30,000 PhU/meal in post-pancreatectomy patients with GI symptoms, although considerably higher doses may be needed depending on the severity of a patient's symptoms and composition of meals. The dose should be increased in one-capsule (10,000 PhU) increments until symptoms resolve. Assessment of symptoms with an instrument such as the PEI-Q is suggested at diagnosis, and during follow-up, to evaluate response to therapy. Patients should be clinically evaluated for nutritional deficiencies, with blood tests for nutritional deficiencies suggested for patients with poor response to therapy. Compliance should be checked, and addition of a PPI is suggested for patients with poor response. Maximum doses in post-pancreatectomy patients have not been defined, but in cystic fibrosis, a daily maximum dose of 10,000 lipase units per kg bodyweight is recommended (161).

Management of diabetes in post-pancreatectomy patients

Statement 25: *Clinicians should screen for diabetes following partial pancreatectomy, and subsequent management should follow standard of care (Level 5)*

Statement 26: *Multiple daily injection or continuous subcutaneous insulin infusion are the mainstays of insulin replacement therapy after total pancreatectomy (Level 2)*

The management of diabetes arising from pancreatic diseases, referred to as 'type 3c diabetes' in some literature, is mostly adapted from recommendations for type 1 diabetes, as there are few studies specific to this population to guide treatment (9). Following pancreatectomy, low levels of insulin, glucagon, and other pancreatic polypeptides contribute to rapid fluctuations in glucose levels, sometimes described as 'brittle diabetes' (162). However, studies suggest total daily insulin and basal insulin requirements (excluding prandial insulin) are significantly lower in patients who have undergone total pancreatectomy than in type 1 diabetes (162-164). Therefore, patients and their physicians should be aware that there may be an increased risk of hypoglycemia in this subtype of diabetes compared with other diabetes types (165).

Metabolic outcomes after total pancreatectomy were evaluated in a case series including 141 patients who received pancreatectomy between 1985 and 2006 (166). When surveyed in 2007, responses from 47 patients showed a mean glycosylated hemoglobin (HbA_{1c}) of 7.5%, with 89% of patients on a complex insulin regimen (≥3 insulin doses per day) (166). Hypoglycemia was experienced by 37 (79%) patients and severe hypoglycemia by 15 (41%) patients (166). A literature review of studies of perioperative management of endocrine insufficiency after total pancreatectomy found that ~80% of patients develop hypoglycemia episodes, and 40% develop severe hypoglycemia, leading to mortality in 0–8% of cases and morbidity in 25–45% of cases (162). These episodes can be reduced with patient education by nutritionists and endocrinologists before surgery, and re-evaluation to ensure the patient has the appropriate understanding, support, and resources.

Data on the prevalence of NODM following pancreatectomy are available from numerous studies. A retrospective cohort

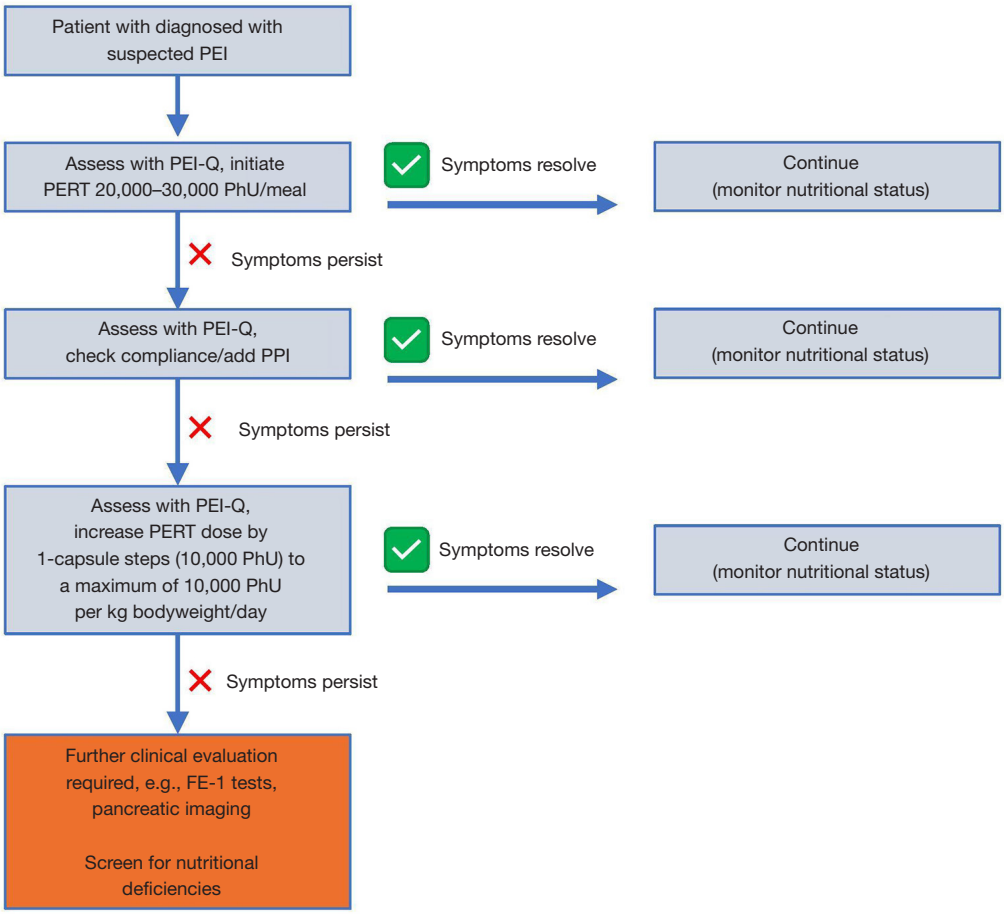

Figure 2 Dosing and monitoring of PERT in patients with PEI after pancreatectomy. PEI, pancreatic exocrine insufficiency; PEI-Q, Pancreatic Exocrine Insufficiency Questionnaire; PPI, proton pump inhibitor; PERT, pancreatic enzyme replacement therapy; PhU, pharmacopeia units; FE-1, fecal elastase 1.

study of 1,717 patients after pancreatectomy (median follow-up 18 months) found 20% had postoperative endocrine insufficiency, requiring introduction or escalation of pharmacologic intervention; NODM was reported in 217 (12.6%) patients—62.7% of whom needed insulin (134). Risk factors for diabetes in this population included male gender, increased BMI, tobacco use, family/personal history of diabetes, and PDD (134). Longer-term data are available from a study of 80 patients with median follow-up of 9.5 years (167). In this population, 12.5% had diabetes mellitus before surgery and 28.6% had NODM after surgery (21.9% after excluding patients with total pancreatectomy) (167). Of the 30 patients with diabetes mellitus, 22 (73.3%) needed insulin and 12 manifested microvascular complications (167). Predictors of post-pancreatectomy NODM have been evaluated in a retrospective cohort study of Japanese patients, 18.4% (125/681) of whom had NODM at 1–12 months (168). Predictors of NODM included BMI, HbA_{1c} prior to surgery, blood glucose level, and indication for surgery (168). A systematic review based on 36 articles assessed the literature for type 3c diabetes, including patients with PDD (n=5,636), DP (n=3,922), and CP (n=315) (6). Rates of NODM (median onset 3–15 months) were 9–24% after PDD, 3–40% after DP, and 0–14% after CP, and surgical site, higher preoperative HbA_{1c}, fasting plasma glucose and larger pancreatic resection volume had the strongest associations (6).

The optimal form of insulin replacement following pancreatectomy is not well defined, with data limited to small case series and observational studies (162,169,170). Consistent improvements in HbA_{1c} levels from continuous

subcutaneous insulin infusion (CSII) versus multiple daily injection (MDI) insulin have not been reported, although the former may be associated with lower rates of hypoglycemia. For example, a study that compared CSII with MDI insulin in 39 patients following total pancreatectomy reported no significant differences in median HbA_{1c} between groups (7.3% *vs.* 8.1%; P=0.16), but severe hypoglycemia rates were lower among patients receiving CSII compared with MDI (17% *vs.* 52%; P=0.02) (170). Despite the higher rate of severe hypoglycemia, no significant differences in quality of life were reported between groups (170).

In accordance with US guidance, we suggest that, following pancreatectomy for PCL, patients should be screened for diabetes using the criteria of fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L), ≥HbA_{1c} 6.5% (48 mmol/moL) or 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) following a 75 g oral glucose tolerance test (9), and insulin replacement should be initiated where indicated.

Conclusions

PCL are becoming increasingly common in Hong Kong, because of its aging population, and have the potential to give rise to pancreatic cancer, a disease with few treatment options and poor prognosis (3,19,57). We recommend patients with suspected PCL in incidental imaging receive careful follow-up, and those with PCL should undergo pancreas-specific imaging, including EUS if indicated. EUS combined with FNA has a central role in differentiating neoplastic and non-neoplastic PCL and detecting high-risk features. Patients with higher-risk features should be monitored more intensively than those without. Where indicated, patients with symptomatic neoplastic PCL who are fit for surgery should undergo pancreatectomy, and following pancreatectomy, patients should be monitored for symptoms of PEI. Treatment with PERT should be initiated for patients who report GI symptoms consistent with PEI, and patients should be monitored for resolution of symptoms. Increased doses of PERT and addition of PPIs should be considered for patients who do not respond to initial therapy, and pancreatic imaging and further clinical investigation may be needed to evaluate patients who continue to respond poorly. The nutritional status of patients on PERT should be monitored, and serum tests for nutritional deficiencies should be considered, especially in patients with prolonged poor response. Following pancreatectomy, patients should also be screened for post-operative diabetes, and insulin should be initiated if needed. Physicians should be aware that insulin-treated patients with type 3c diabetes tend to have lower insulin requirements and a higher risk of hypoglycemia than patients with type 1 diabetes mellitus. Topics that may be of interest for future research include PERT dose optimization in East Asian patients and optimizing the safety and efficacy of insulin therapy in patients with type 3c diabetes.

With these consensus statements, we have aimed to capture the contemporary approach to diagnosis and management of PCL and PEI in Hong Kong, and we hope this document serves as a useful guide to clinicians treating these diseases both in Hong Kong and abroad.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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