

# Hong Kong consensus recommendations on the management of pancreatic ductal adenocarcinoma

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Endorsed by the Hong Kong Society of Hepatobiliary and Pancreatic Surgery and the Hong Kong Cancer Therapy Society

## ABSTRACT

This project was undertaken to develop the first set of consensus statements regarding the management of pancreatic ductal adenocarcinoma (PDAC) in Hong Kong, with the goal of providing guidance to local clinicians. A multidisciplinary panel of experts discussed issues surrounding current PDAC management and reviewed evidence gathered in the local context to propose treatment recommendations. The experts used the Delphi approach to finalise management recommendations. Consensus was defined as  $\geq 80\%$  acceptance among all expert panel members. Thirty-nine consensus statements were established. These statements cover all aspects of PDAC management, including diagnosis, resectability criteria, treatment modalities according to resectability, personalised management based on molecular profiling, palliative care, and supportive care. This project fulfils the need for guidance regarding PDAC management in Hong Kong. To assist clinicians with treatment decisions based on varying levels of evidence and clinical experience, treatment options are listed in several consensus statements.

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## Introduction

Pancreatic ductal adenocarcinoma (PDAC), a malignant pancreatic epithelial tumour characterised by glandular and ductal differentiation, constitutes  $>90\%$  of all pancreatic cancers and is usually considered synonymous with the term 'pancreatic cancer' itself.<sup>1</sup> Although the exact aetiology of PDAC is unknown, many risk factors have been linked to its development, including smoking, obesity, alcohol intake, diabetes mellitus, chronic pancreatitis, and

familial cancer syndromes.<sup>2-4</sup> Pancreatic ductal adenocarcinoma is usually diagnosed in individuals aged  $>70$  years, with a male-to-female ratio of 1.4:1.0. Its incidence has been increasing worldwide, particularly among individuals aged  $>50$  years and among women.<sup>4</sup> In 2020, PDAC had the 14th highest incidence among cancers: approximately 495 773 people were diagnosed with PDAC, constituting 2.6% of new cancer cases.<sup>5</sup> Moreover, PDAC was the eighth most common cause of cancer death in

## 香港有關胰腺導管腺癌治療的共識聲明

陳林、蔣子樑、竺兆豪、李安誠、鄧承恩、林美瑩、李傑輝、戴燕萍、李慧敏、盧綽琳、陳永鴻、莫碧添（獲香港肝膽胰外科學會及香港腫瘤化療學會認可）

本項目旨在制定香港首套有關胰腺導管腺癌治療的共識聲明，目的是為本地臨床醫生提供指引。我們透過多學科專家小組討論了當前胰腺導管腺癌管理的問題，並審查了在本港收集的證據，以提出治療建議。專家小組使用德爾菲法確定最終的管理建議。共識的定義為所有專家小組成員接受率達80%或以上。我們建立了39項共識聲明。這些聲明涵蓋了胰腺導管腺癌管理的各個方面，包括診斷、手術切除標準、根據可切除性的治療方式、基於分子分析的個人化管理、舒緩治療和支持性護理。本項目為香港臨床醫生定立了本地胰腺導管腺癌管理指南。本指南根據不同程度的證據和臨床經驗，幫助臨床醫生替胰腺導管腺癌患者制定治療方案。

2020, with 466 003 deaths (4.7% of all cancer deaths worldwide).<sup>5</sup> In China, PDAC is one of the top 10 most common cancers in men and one of the top 10 most common causes of death among men and women.<sup>6</sup>

Pancreatic ductal adenocarcinoma, a highly aggressive malignancy with a poor prognosis, has one of the lowest 5-year survivals among cancers (11%).<sup>7</sup> Surgical resection of localised disease provides the best likelihood of a curative outcome, but approximately 80% to 85% of cases are diagnosed at an advanced, unresectable, or metastatic stage that requires palliative management.<sup>2</sup> Although resection of localised disease with adjuvant chemotherapy can improve 5-year survival to approximately 30%, this outcome depends upon complete removal of the primary tumour and regional lymph nodes, a complex procedure with a high rate of complications.<sup>8</sup>

In Hong Kong, the incidence of PDAC has been increasing since 2010; it had become the fifth leading cause of cancer-related death by 2019.<sup>9</sup> Considering the challenges of late diagnosis, poor clinical prognosis, and limited therapeutic options, PDAC has emerged as a key local health concern. Our group was established to develop the first set of consensus recommendations regarding the management of PDAC in Hong Kong. We initiated this project to provide practical guidance to Hong Kong healthcare practitioners based on the best available evidence and expert opinions.

## Methods

Based on a literature search in MEDLINE to identify articles published in the past 10 years, consensus development leads the first, second, and third authors brainstormed and drafted preliminary statements relevant to PDAC management that

addressed diagnosis, imaging, and surveillance; resectability criteria; stent management; stage-specific treatment; personalised medicine; and palliative care and supportive care. Subsequently, they invited nine Hong Kong experts to complete a 12-member consensus expert panel comprising clinical oncologists, surgeons, a gastroenterologist, and pathologists. All panel members were asked to review the draft statements in the context of current local practice and available evidence, then discuss these issues during the consensus meeting.

A virtual consensus meeting was held on 12 February 2022 to refine and vote on the statements. The consensus statements were developed through the Delphi process: after discussion, the members independently voted on each statement using a 5-point Likert scale (A: accept completely; B: accept with minor reservations; C: accept with major reservations; D: reject with reservations; E: reject completely). A consensus was reached if at least 80% of the panel members agreed with the statement (ie, selected either 'accept completely' or 'accept with minor reservations'). If acceptance was <80%, the panel members identified key concerns and proposed revisions before a second vote. When applicable, the level of evidence was evaluated using the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence.<sup>10</sup>

## Consensus statements

### Diagnosis

*Statement 1: Early symptoms of pancreatic cancer result from a mass effect.*

A: 70%; B: 30%; C: 0%; D: 0%; E: 0%

*Statement 2: In addition to progressive jaundice, patients may present with nonspecific symptoms including abdominal pain, weight loss, and new-onset/recently worsening diabetes. A differential diagnosis of PDAC should be considered in the presence of the above symptoms.*

A: 80%; B: 20%; C: 0%; D: 0%; E: 0%

*Statement 3: The involvement of a multidisciplinary team is recommended for diagnosis and disease management.*

A: 100%; B: 0%; C: 0%; D: 0%; E: 0%

The clinical presentation of PDAC varies according to whether the tumour is in the pancreatic head, neck, or tail, which would affect adjacent structures. For example, jaundice can be related to tumours in the head due to obstruction of the common bile duct, whereas pain can be related to effects on nearby vessels from tumours in the pancreas.<sup>11,12</sup> However, many patients present with nonspecific symptoms that may be attributed to other diseases and cause further diagnostic delays (Table 1).<sup>12-15</sup> These symptoms should alert general

TABLE 1. Signs and symptoms related to pancreatic cancer

|   |
|---|
| Abdominal mass                                  |
| Abdominal pain                                  |
| Back pain                                       |
| Post-prandial abdominal pain                    |
| Abnormal liver function tests                   |
| Jaundice  |
| New-onset diabetes                              |
| Dyspepsia                                       |
| Decreased appetite                              |
| Nausea or vomiting                              |
| Weight loss                                     |
| Fatigue   |
| Flatulence                                      |
| Change in bowel movements/loose bowel movements |
| Steatorrhea                                     |
| Fat malabsorption                               |
| Pancreatitis                                    |

practitioners and other healthcare professionals to consider PDAC as a differential diagnosis. Clinicians should attempt to distinguish stone-related obstruction from malignancy-related obstruction. In our clinical experience, stone-related obstruction usually causes intermittent jaundice, whereas malignancy-related obstruction causes progressive jaundice. Notably, Chinese patients typically have clay-coloured stool. They rarely present with the steatorrhea that is common among Western patients experiencing chronic pancreatitis from alcohol consumption.

Further workup and management require a multidisciplinary team encompassing a surgeon, clinical oncologist, medical oncologist, radiologist, and pathologist.<sup>11,16</sup> In Hong Kong, it is challenging to involve a multidisciplinary team; nevertheless, we recommend the multidisciplinary team approach to address the evolving definition of resectability, as well as the complexities of genetic profiling and planning for various treatment modalities.

*Statement 4: A thin-cut contrast-enhanced computed tomography scan of the entire abdomen should be performed for initial staging of the cancer. Positron emission tomography/computed tomography may be considered in selected cases. (Level 1)*

A: 40%; B: 60%; C: 0%; D: 0%; E: 0%

In many centres, a baseline ultrasound is used to initiate the investigation of gastrointestinal or biliary complaints, such as jaundice. Subsequently, a high-quality contrast-enhanced computed tomography (CT) scan of the abdomen can detect a pancreatic

mass and exclude other potential causes, such as cancers of the gallbladder or bile ducts. Computed tomography scanning is a well-validated method for PDAC staging.<sup>11,16-19</sup> A thin-cut, pancreas-specific CT scan can aid local staging by revealing adjacent vessel infiltration and lymph node involvement.<sup>17</sup>

Positron emission tomography (PET)/CT can facilitate accurate staging, particularly in cases with distant metastases. According to the National Institute for Health and Care Excellence of the United Kingdom, this approach may reduce unnecessary surgeries by 20%.<sup>16,20</sup> However, for initial staging, PET/CT generally does not offer information beyond the results of a high-quality CT scan of the abdomen.<sup>16,20,21</sup> Thus, a thin-cut contrast-enhanced CT scan of the entire abdomen is the imaging method of choice for initial staging. Positron emission tomography/CT can be used for preoperative staging in specific scenarios, such as lesions with borderline resectability or cases requiring lymph node staging.<sup>16</sup> The cost of PET/CT should be discussed with patients and their families.

In Hong Kong, magnetic resonance imaging may be utilised to investigate suspected lesions not clearly defined by CT scanning, such as peritoneal lesions. Although staging laparoscopy is rarely performed, the laparoscopic approach (eg, during the Whipple procedure) is common. Staging laparoscopy can be selectively used to rule out metastases and complement other imaging tools.<sup>11,16</sup>

*Statement 5: Tumour staging should follow the guidelines stipulated by the American Joint Committee on Cancer.*

A: 90%; B: 10%; C: 0%; D: 0%; E: 0%

*Statement 6: Pathology reports should contain all clinically significant essential parameters, including but not limited to tumour location, tumour size, histological type (according to the latest World Health Organization classification), histological grade, tumour extent, tumour response to neoadjuvant therapy (if any), lymphovascular invasion, perineural invasion, nodal status, and margin clearance status. Synoptic reports from the Royal College of Pathologists, Royal College of Pathologists of Australasia, and College of American Pathologists are recommended references.*

A: 100%; B: 0%; C: 0%; D: 0%; E: 0%

Pancreatic ductal adenocarcinoma is staged according to the most recent American Joint Committee on Cancer tumour, node, and metastasis classification,<sup>22</sup> a well-known and widely used standard in the Hong Kong oncology community. Clinicians can also categorise tumour resectability into four levels, namely, resectable, borderline resectable (BR), locally advanced (LA), and metastatic.<sup>2,3</sup>

Pathology data are necessary to fully assess the extent of PDAC. In Hong Kong, most institutions lack a standard pathology reporting protocol or minimal dataset for pancreatic specimens. Moreover, the Hong Kong College of Pathologists has not yet developed a standard report format. In the absence of such standards, we recommend that reports include all clinically significant pathology data, such as tumour location, tumour size, histological type (according to the 2019 World Health Organization classification), histological grade, tumour extent (organ-confined or local invasion to adjacent organs), tumour response to neoadjuvant therapy (if any), lymphovascular invasion, perineural invasion, nodal status, and margin clearance status (Table 2). The general structure of the report can incorporate elements from datasets provided by the Royal College of Pathologists, Royal College of Pathologists of Australasia, and College of American Pathologists.<sup>23-25</sup>

*Statement 7: For patients with suspected pancreatic head cancer without a definitive pancreatic mass observed on initial cross-sectional scan, endoscopic retrograde cholangiopancreatography and endoscopic ultrasound may be considered to detect small lesions in the pancreatic head or distal common bile duct. (Level 3)*  
 A: 70%; B: 30%; C: 0%; D: 0%; E: 0%

*Statement 8: For patients with intraductal papillary mucinous neoplasms and ‘worrisome features,’ as defined by the 2017 international consensus Fukuoka guidelines, endoscopic ultrasound may be considered for further workup.*  
 A: 40%; B: 60%; C: 0%; D: 0%; E: 0%

TABLE 2. Recommended items for inclusion in a pancreas pathology report

|   |
|---|
| Specimen type   |
| Macroscopic description   |
| <ul style="list-style-type: none"> <li>• Tumour location</li> <li>• Tumour size</li> <li>• Tumour extent</li> <li>• Macroscopic margin status</li> </ul>  |
| Microscopic description   |
| <ul style="list-style-type: none"> <li>• Histological type</li> <li>• Histological grade/differentiation</li> <li>• Tumour size</li> <li>• Tumour extent</li> <li>• Tumour response to neoadjuvant therapy (if any)</li> <li>• Lymphovascular invasion</li> <li>• Perineural invasion</li> <li>• Microscopic margin status</li> <li>• Regional lymph node status</li> <li>• Background pathology</li> </ul> |
| Pathological staging (AJCC TNM staging)   |

Abbreviations: AJCC = American Joint Committee on Cancer; TNM = tumour, node, and metastasis

*Statement 9: Endoscopic ultrasound with fine-needle tissue acquisition is recommended when (a) there is a clinical need to exclude benign pathology, (b) tissue diagnosis is needed to guide treatment for locally advanced or metastatic disease, or (c) neoadjuvant treatment is planned.*

A: 90%; B: 10%; C: 0%; D: 0%; E: 0%

Pancreatic head tumours usually present with obstructive jaundice caused by bile duct strictures. In these cases, endoscopic retrograde cholangiopancreatography (ERCP) can be diagnostic (through cytology from ERCP brushings and biopsies) and therapeutic (through stent insertion for biliary drainage). Endoscopic ultrasound (EUS) with fine-needle aspiration (FNA) can also retrieve tissue samples for the diagnosis of malignancy in cases of obstructive jaundice, with high sensitivity and specificity for detecting pancreatic masses and malignant strictures.<sup>26-28</sup>

Endoscopic ultrasound has a role in the investigation of intraductal papillary mucinous neoplasms (IPMNs). According to the Fukuoka guidelines, EUS can be used to assess ‘worrisome features’ and ‘high-risk stigmata,’ with the latter indicating a need for resection in surgically fit patients.<sup>29</sup> In Hong Kong, surgery is usually advised regardless of the EUS result because ‘worrisome features’ indicate pre-malignancy, but the Fukuoka guidelines suggest that EUS can facilitate further characterisation of ambiguous areas that cannot be resolved through cross-sectional CT scans, such as tumour nodule and main duct features, as well as cytological characteristics of the mass.<sup>29</sup>

In Hong Kong, EUS is not commonly used for routine staging. We concur with the National Comprehensive Cancer Network (NCCN) guidelines, which state that EUS with or without fine needle tissue acquisition provides information complementary to CT scans but is not recommended for routine staging.<sup>16,30-32</sup> Endoscopic ultrasound accuracy is largely operator-dependent and may be affected by anatomical variations of the hepatic arteries.<sup>16</sup> In the diagnosis of PDAC, EUS offers specificity and sensitivity comparable to CT; it may provide additional information for lesions with inconclusive results or lesions <2 cm on initial CT.<sup>18,21</sup> Contrast-enhanced EUS, an evolving technique, can distinguish characteristic traits of malignancy (eg, hypoenhancement versus hyperenhancement) in highly vascular neuroendocrine tumours.<sup>33</sup>

Endoscopic ultrasound–FNA is an important approach for obtaining tissue to establish a cytologic diagnosis. We have listed indications that require tissue diagnosis for treatment planning; in such instances, EUS-FNA may be strongly considered, especially for cases potentially requiring chemotherapy or radiation therapy.<sup>33-36</sup> However, the implementation of EUS-FNA may vary according to each centre’s protocols and relevant expertise.

## Surveillance

*Statement 10: Serum carbohydrate antigen 19-9 is recommended for diagnosis of PDAC and for treatment response monitoring, but not for routine screening of PDAC. (Level 1)*

A: 80%; B: 10%; C: 10%; D: 0%; E: 0%

For the diagnosis of PDAC in symptomatic patients, serum carbohydrate antigen 19-9 (CA19-9) exhibits a sensitivity of approximately 80% and a specificity of 80% to 90%.<sup>37,38</sup> There is also robust evidence suggesting that normal or decreased levels can predict resectability and improved survival. Carbohydrate antigen 19-9 levels <100 U/mL suggest resectability, whereas levels ≥100 U/mL suggest unresectability or metastatic disease. In the preoperative period, normal levels (<37 U/mL) may be prognostic of prolonged median survival (32-36 months) compared with elevated levels (≥37 U/mL; 12-15 months). Postoperative normalisation or decrease from baseline by 20% to 50% is associated with prolonged survival.<sup>38</sup> However, CA19-9 is not an effective screening tool for PDAC, considering its positive predictive value of <1% in symptomatic patients.<sup>16,38</sup>

*Statement 11: For patients with unresectable disease, a biopsy is recommended to obtain histological proof of PDAC.*

A: 20%; B: 60%; C: 20%; D: 0%; E: 0%

As discussed in the context of EUS-FNA, a biopsy is needed to confirm a histological diagnosis of PDAC before definitive therapy. This approach is warranted when advanced or inoperable disease is suspected and neoadjuvant or palliative therapy is considered.<sup>39</sup> Considering that some suspicious masses are not PDAC, histological proof is required to guide treatment planning. Common differential diagnoses include other malignant diseases, such as neuroendocrine tumour and teratoma, or benign conditions, such as autoimmune pancreatitis and chronic pancreatitis. Patients with tumours considered resectable based on imaging findings may be directly referred for surgical treatment without a routine biopsy.<sup>40</sup>

*Statement 12: There is no consensus on screening practices for PDAC.*

A: 70%; B: 20%; C: 10%; D: 0%; E: 0%

In Hong Kong, patients' families frequently enquire about their PDAC risk and need for screening. However, local clinicians lack a standardised screening protocol for PDAC. Evidence reviewed by the United States Preventive Services Task Force suggests that screening is unnecessary for asymptomatic individuals with a low risk of PDAC.<sup>41</sup> According to the International Cancer of the Pancreas Screening Consortium and the United States Preventive Services Task Force, screening

should be conducted in a research setting with a multidisciplinary team for high-risk individuals—specifically, individuals with a history of familial pancreatic cancer, individuals with inherited genetic disorders linked to pancreatic cancer (eg, Peutz–Jeghers syndrome and hereditary pancreatitis), and individuals with germline mutations such as *BRCA2* and *PALB*—by age 50 or 10 years earlier than the youngest relative was diagnosed with PDAC.<sup>41,42</sup> For these individuals, pancreatic imaging with CT, magnetic resonance imaging, magnetic retrograde cholangiopancreatography, and/or EUS is suggested for annual pancreatic surveillance.<sup>41,42</sup>

The American Gastroenterological Association states that the advantages of PDAC screening for high-risk individuals include the possibility of detecting IPMNs, which may be precursor lesions to PDAC.<sup>43</sup> There are no standard screening protocols for IPMNs. However, the Fukuoka guidelines suggest imaging for unresected, relatively indolent lesions at intervals of 3 to 6 months initially, then less frequently if the lesion size remains small. Long-term surveillance for lesions with 'worrisome features' or 'high-risk stigmata' may require more frequent monitoring, at intervals of 3 to 9 months, to detect the potential development of PDAC.<sup>29</sup>

Although these international practices can be considered, their applicability to the Hong Kong setting is uncertain.

## Management of localised disease

*Statement 13: Resectability depends on the involvement of the venous and arterial vasculature, mainly the superior mesenteric artery, superior mesenteric vein, celiac trunk, and hepatic artery.*

A: 20%; B: 60%; C: 20%; D: 0%; E: 0%

We established resectability criteria that are consistent with the most recent NCCN guidelines.<sup>16</sup> The assessment of resection potential involves determining the tumour's extent into the following critical structures: superior mesenteric vein (SMV), portal vein (and its tributaries), superior mesenteric artery (SMA), celiac trunk, hepatic artery, and gastroduodenal artery.<sup>44</sup> 'Resectable' PDAC lacks tumour contact with critical vessels and is characterised by the absence of metastasis. The SMV and portal vein remain patent. Borderline resectable PDAC is primarily characterised by tumour abutment with (contact with <180° of vessel wall circumference) the SMV, portal vein, SMA, and/or celiac trunk, as well as abutment with or limited enclosure of (contact with ≥180° of vessel wall circumference) the common hepatic artery. Locally advanced tumours are characterised by major occlusion of the portal vein or SMV, as well as enclosure of the SMA, celiac trunk, or proximal hepatic artery.<sup>44-46</sup>

*Statement 14: Stent placement may be considered for cholangitis or severe jaundice, or if the waiting time for surgery exceeds 4 weeks.*

A: 0%; B: 80%; C: 20%; D: 0%; E: 0%

Theoretically, preoperative biliary drainage should relieve symptoms of hyperbilirubinaemia, facilitate recovery from the metabolic derangements caused by obstructive jaundice, and improve surgical outcomes. However, as summarised by the NCCN, retrospective and prospective studies have either failed to show a decrease in postoperative mortality or have shown increases in wound complications and operating times among cases involving preoperative drainage.<sup>16</sup> Furthermore, a randomised controlled trial (RCT) showed a higher rate of complications in the group undergoing routine preoperative biliary drainage through ERCP with a plastic stent (74% in the biliary drainage group vs 39% in the early surgery group).<sup>47</sup> Considering the drainage preconditions in that trial and the trends we have observed in clinical practice, we recommend considering stent placement for patients with active cholangitis or severe jaundice, and in cases where the expected duration of preoperative drainage exceeds 4 weeks. In our experience, a bilirubin level of 250 µmol/L may be an acceptable threshold for stent placement, but this threshold should be evaluated in the context of the patient's overall clinical condition. The appropriate technique for preoperative biliary stenting (ie, percutaneous biliary drainage, endoscopic biliary drainage, or ERCP) remains a subject of debate, as does the need for preoperative stenting itself.

*Statement 15: The optimal procedure for resection of tumours in the pancreatic head is pancreaticoduodenectomy (Whipple procedure). The optimal procedure for resection of tumours in the pancreatic body and tail is distal pancreatectomy.*

A: 70%; B: 30%; C: 0%; D: 0%; E: 0%

Surgical resection of the tumour is the best option for patients with resectable PDAC. The procedure of choice depends on tumour location and its relationships with the bile duct and vessels. Patients with tumours in the head and uncinate process typically undergo pancreaticoduodenectomy (ie, the Whipple procedure). Distal pancreatectomy is usually performed as treatment for tumours of the body or tail, but a margin-negative (R0) resection should be targeted in such cases. If the tumour invades the portal vein, en bloc resection and reconstruction of the portal vein may achieve R0 resection.<sup>16</sup>

The NCCN has noted the emerging role of laparoscopic distal pancreatectomy, considering reported decreases in blood loss and length of hospital stay compared with open distal pancreatectomy.<sup>16</sup> Another important consideration regarding the Whipple procedure is that outcomes are best when

this surgical method is performed by surgeons who complete >20 such procedures annually, usually at high-volume centres.<sup>2,16</sup> Additionally, the best outcomes are achieved when a multidisciplinary team, with members whose experience ranges from the operating room to the recovery room, has extensive experience in perioperative care and complication management.

*Statement 16: Standard lymphadenectomy should involve the removal of ≥15 lymph nodes to allow adequate pathological staging of the disease.*

A: 70%; B: 30%; C: 0%; D: 0%; E: 0%

This recommendation is based on the 2015 guidelines from the European Society for Medical Oncology (ESMO).<sup>11</sup> The extent of lymphadenectomy remains a subject of debate because there is limited evidence of a benefit from extended lymphadenectomy.<sup>16</sup> The International Study Group of Pancreatic Surgery reviewed the available evidence and identified lymph node stations that should be included in a standard lymphadenectomy, despite their acknowledgement that expert opinions varied among group members.<sup>48</sup>

*Statement 17: Adjuvant therapy is recommended after surgical resection. Options include mFOLFIRINOX, gemcitabine plus capecitabine, gemcitabine monotherapy, or S-1. (Level 2)*

A: 100%; B: 0%; C: 0%; D: 0%; E: 0%

*Statement 18: After adjuvant treatment, patients are recommended to undergo monitoring every 3 to 6 months for 2 years and every 6 to 12 months thereafter.*

A: 30%; B: 70%; C: 0%; D: 0%; E: 0%

Good outcomes from postoperative adjuvant therapy have been demonstrated in RCTs. In the CONKO-001 trial (Charité Onkologie-001) [n=368], postoperative adjuvant chemotherapy with gemcitabine alone significantly prolonged overall survival (OS) compared with observation (22.8 vs 20.2 months; hazard ratio [HR]=0.76, 95% confidence interval [CI]=0.61-0.95; P=0.010).<sup>49</sup> The ESPAC-4 study (European Study Group for Pancreatic Cancer-4) [n=732] demonstrated that the combination of gemcitabine and capecitabine significantly prolonged postoperative OS compared with gemcitabine monotherapy (28.0 vs 25.5 months; HR=0.82, 95% CI=0.68-0.98; P=0.032).<sup>50</sup> A mFOLFIRINOX (modified 5-fluorouracil with leucovorin, irinotecan, and oxaliplatin) regimen yielded significantly longer OS compared with gemcitabine alone (54.4 vs 35.0 months; HR=0.64, 95% CI=0.48-0.86; P=0.003) in the PRODIGE 24-ACCORD 24/CCTG PA 6 study (n=493).<sup>51</sup> The JASPAC 01 study (Japan Adjuvant Study Group of Pancreatic Cancer) of 385 subjects in Japan

showed significantly better OS with S-1, an oral 5-fluorouracil prodrug containing tegafur, gimeracil, and oteracil potassium, compared with gemcitabine alone (46.6 vs 25.5 months; HR=0.57, 95% CI=0.44-0.72; P<0.0001).<sup>52</sup>

Although we do not recommend a standard regimen, we have listed the available options for Hong Kong clinicians who may need to plan individualised therapy with limited resources. Modified FOLFIRINOX may be considered for patients with an Eastern Cooperative Oncology Group performance status (PS) score of 0 to 1. Those with a poor PS can receive gemcitabine plus capecitabine or gemcitabine monotherapy.<sup>16</sup> S-1 may serve as an alternative to gemcitabine-based therapies.

Locally, some R2 resections (with macroscopic residual tumour) are followed by postoperative radiotherapy (RT), although the administration of RT in these cases is usually hindered by challenges regarding localisation of the tumour and administration of an adequate dose. In principle, adjuvant RT may address suspected residual disease or reduce local recurrence. However, the ESMO guidelines cite results from the EORTC (European Organisation for Research and Treatment of Cancer) and ESPAC-1 trials, which showed no benefit and suggested potential harm.<sup>11,53,54</sup> The ESMO panel does not recommend postoperative adjuvant RT except in clinical trials.<sup>11</sup>

In our clinical experience, we have found it challenging to ensure that patients continue follow-up after curative treatment. Currently, there are no evidence-based standards for the frequency and timing of follow-up visits, use of CT scans and other imaging methods, and assessment of tumour biomarkers. Based on extensive discussion within our group, we recommend follow-up monitoring every 3 to 6 months for the first 2 years and every 6 months thereafter. This follow-up approach will enable clinicians to diagnose recurrences, detect and monitor complications, assess PS and quality of life, and provide some education and counselling.

### Management of borderline resectable disease

*Statement 19: Neoadjuvant therapy is recommended for borderline resectable disease. (Level 1)*

A: 60%; B: 40%; C: 0%; D: 0%; E: 0%

*Statement 20: There is limited evidence to support the recommendation of specific neoadjuvant regimens. Generally, combination regimens are preferred. (Level 2/3)*

A: 70%; B: 30%; C: 0%; D: 0%; E: 0%

*Statement 21: Stereotactic body radiation therapy is not recommended outside of a clinical trial.*

A: 50%; B: 50%; C: 0%; D: 0%; E: 0%

Borderline resectable PDAC is characterised by blood vessel infiltration that increases the risk of R1 resection (with microscopic residual tumour) and decreases the feasibility of upfront surgery.<sup>11</sup> Neoadjuvant therapy may improve the likelihood of R0 resection, sterilise any potential metastasis, and assess the biological aggressiveness of the tumour to inform patient selection for surgery—if disease progression or intolerance to neoadjuvant treatment occurs, aggressive surgery may not be viable.<sup>16</sup>

The feasibility of neoadjuvant therapy in resectable and BR-PDAC was previously substantiated by a meta-analysis that evaluated various chemotherapy protocols, including gemcitabine-based and 5-fluorouracil-based combinations, with or without radiation.<sup>34</sup> Two subsequent meta-analyses, based on the intention-to-treat approach, demonstrated that OS and R0 resection rates favoured neoadjuvant therapy (primarily gemcitabine-based, with or without radiation) over upfront surgery.<sup>55,56</sup> Recently, several studies showed promising results for neoadjuvant therapy, specifically in BR-PDAC. First, a phase II, single-arm prospective trial (n=48) showed that neoadjuvant FOLFIRINOX followed by proton radiation (5 Gy in five fractions) with capecitabine resulted in a high degree of R0 resection among patients who underwent surgery (31/32).<sup>57</sup> Progression-free survival (PFS) and 2-year OS among all patients were 14.7 months and 56%, respectively; among patients who underwent surgery, the respective values were 48.6 months and 72%.<sup>57</sup> Subsequently, Korean researchers conducted the first multicentre phase II/III RCT of neoadjuvant therapy for BR-PDAC (n=58), where intention-to-treat analysis showed that among patients with BR-PDAC, gemcitabine-based neoadjuvant chemoradiation followed by surgery yielded a significantly higher 2-year survival than upfront surgery followed by chemoradiation (40.7% vs 26.1%, HR=1.495, 95% CI=0.66-3.36; P=0.028).<sup>58</sup> The R0 resection rate also was significantly higher with neoadjuvant treatment (P=0.004).<sup>58</sup> More recently, in the Dutch phase III PREOPANC trial (Perioperative or Adjuvant mFOLFIRINOX for Resectable Pancreatic Cancer) of patients with resectable and BR-PDAC (n=248), intention-to-treat analysis demonstrated improvements in distant metastasis-free interval (P=0.32), locoregional failure-free interval (P=0.0034), and R0 resection rate (P<0.001) among patients who received gemcitabine-based chemoradiation versus patients who underwent upfront surgery.<sup>59</sup> The neoadjuvant group received preoperative gemcitabine with radiation; both study groups received postoperative adjuvant gemcitabine. Final OS was significantly better with neoadjuvant chemoradiation (15.7 vs 14.3 months, HR=0.73, 95% CI=0.56-0.96; P=0.025). Five-year OS also favoured

neoadjuvant treatment (20.5% vs 6.5%).<sup>60</sup>

For tumours with a risk of incomplete resection, preoperative radiation may be administered after induction chemotherapy to increase the likelihood of R0 resection. Compared with fractionated RT, stereotactic body radiation therapy (SBRT) offers the potential advantage of delivering higher radiation doses while sparing adjacent tissues.<sup>16</sup> However, the benefit of SBRT after induction chemotherapy has not been established among patients with BR-PDAC. Participants in the Alliance for Clinical Oncology trial A021501 received, prior to surgery, either eight cycles of mFOLFIRINOX or seven cycles of mFOLFIRINOX followed by hypofractionated image-guided radiation or SBRT. Patients without disease progression after neoadjuvant treatment underwent surgery and received adjuvant FOLFOX (folinic acid, fluorouracil, and oxaliplatin).<sup>61</sup> The results showed that the mFOLFIRINOX plus SBRT group had worse median OS and worse 18-month OS compared with the group that received mFOLFIRINOX alone; notably, only 19 of 56 chemoradiation patients underwent resection.<sup>61</sup> Stereotactic body radiation therapy with chemotherapy requires further research before routine application in this setting.

Although the available literature does not provide strong support for a specific regimen, we recommend considering FOLFIRINOX or gemcitabine-based regimens. Stereotactic body radiation therapy with chemotherapy should be administered within a clinical trial; other RT techniques may be considered if neoadjuvant chemoradiation is planned.

*Statement 22: Surgical candidacy should be reassessed after neoadjuvant therapy, preferably through multidisciplinary team discussions.*

A: 100%; B: 0%; C: 0%; D: 0%; E: 0%

After preoperative treatment, restaging is recommended. The NCCN suggests repeating CT and performing a staging laparoscopy (if not previously conducted).<sup>16</sup> In our experience, tumour assessment after neoadjuvant treatment is challenging and requires the involvement of a multidisciplinary team that will also contribute to discussions of future treatment with the patient and their family. Conventional imaging may not reliably assess resectability. Regardless of radiographic stability, clinical improvement and a decrease in CA19-9 level, further evaluations are needed.<sup>16</sup> Before proceeding with resection, frozen section analyses of tumours responsive to neoadjuvant therapy should be performed to rule out metastasis and examine critical structures.

### Management of locally advanced disease

*Statement 23: For locally advanced disease, systemic*

*therapy is the primary treatment. Options include FOLFIRINOX, gemcitabine plus nab-paclitaxel, gemcitabine plus capecitabine, and gemcitabine monotherapy. (Level 1/2/3)*

A: 100%; B: 0%; C: 0%; D: 0%; E: 0%

The extensive infiltration of critical vessels in LA-PDAC precludes reconstruction and hinders tumour resection. The primary treatment is systemic chemotherapy. Similar to the statements regarding resectable disease, we have listed the various options for individualised management. Historically, gemcitabine has been used for LA-PDAC, providing a clinical benefit response of 23.8%, median OS of 5.65 months, and 1-year survival of 18% in one RCT focused on advanced PDAC.<sup>62</sup> A 6-month treatment duration has been endorsed by the ESMO guidelines.<sup>11</sup> Concerning 6-month OS, a meta-analysis showed that gemcitabine plus capecitabine reduced the mortality risk by 15% compared with gemcitabine monotherapy (relative risk=0.85, 95% CI=0.73-0.99; P=0.04).<sup>63</sup>

FOLFIRINOX and gemcitabine plus nab-paclitaxel regimens, initially established for metastatic PDAC (mPDAC), have been applied to LA-PDAC. A meta-analysis showed that the median OS with FOLFIRINOX for LA-PDAC was 24.2 months, which was approximately twofold longer than the OS of 6 to 13 months observed with gemcitabine.<sup>64</sup> In one case series (n=485), despite higher rates of RECIST (Response Evaluation Criteria in Solid Tumors) partial response and subsequent pancreatectomy among patients receiving FOLFIRINOX compared to those receiving gemcitabine plus nab-paclitaxel, both regimens (as first-line chemotherapy for LA-PDAC) provided similar OS (21 vs 20 months, HR=1.48, 95% CI=0.97-2.26; P=0.07).<sup>65</sup>

*Statement 24: Chemoradiation or stereotactic body radiation therapy can be considered for patients with no progression after chemotherapy.*

A: 60%; B: 40%; C: 0%; D: 0%; E: 0%

After tumour stabilisation via post-induction chemotherapy, concurrent chemoradiation is usually considered for LA-PDAC to optimise local control. Trials comparing chemoradiation with chemotherapy alone have shown conflicting results.<sup>66-68</sup> Notably, the contemporary phase III LAP-07 study, which randomly assigned patients with non-progressing LA-PDAC after 4 months of gemcitabine plus erlotinib (n=269) to either receive RT plus capecitabine or continue chemotherapy, did not show a survival benefit from the addition of RT (median OS from date of initial chemotherapy: 16.5 vs 15.2 months; P=0.83), despite a decrease in locoregional progression (32% vs 46%; P=0.04).<sup>69</sup> Therefore, no standard chemotherapy regimen, RT dose, or modality has been established. As



previously discussed, the advantages of delivering high RT doses while sparing critical tissues make SBRT a promising option for LA-PDAC. Pooled analyses of trials involving chemotherapy with SBRT for LA-PDAC revealed a median OS of 17 months, a 1-year locoregional control rate of 72.3%, and an overall severe adverse event incidence of  $\leq 10\%$ .<sup>70</sup> Another meta-analysis showed that SBRT improved 2-year OS compared with conventionally fractionated RT with concurrent chemotherapy (26.9% vs 13.7%;  $P=0.004$ ), although the rates of late grade 3/4 toxicity were similar (9.0% vs 10.1%;  $P=0.49$ ).<sup>71</sup> Despite the limited evidence favouring a specific protocol, the NCCN recommends systemic therapy or induction chemotherapy for 4 to 6 months, followed by chemoradiation or SBRT.<sup>16</sup>

### Management of metastatic disease

*Statement 25: The primary treatment for metastatic disease is palliative systemic therapy. (Level 2)*

A: 90%; B: 10%; C: 0%; D: 0%; E: 0%

*Statement 26: The treatment decision depends on performance status, bilirubin level, and the preferences of the clinician and patient. Combination therapy is generally recommended for patients with good performance status, bilirubin level <1.5 times the upper limit of normal, and intention to undergo aggressive treatment.*

A: 90%; B: 10%; C: 0%; D: 0%; E: 0%

*Statement 27: Combination treatment options include FOLFIRINOX, gemcitabine plus nab-paclitaxel, gemcitabine plus capecitabine, and gemcitabine plus S-1. (Level 2)*

A: 70%; B: 30%; C: 0%; D: 0%; E: 0%

*Statement 28: Monotherapy options include S-1 alone and gemcitabine alone. (Level 2)*

A: 60%; B: 40%; C: 0%; D: 0%; E: 0%

The benefit of systemic chemotherapy for mPDAC has been confirmed in phase III RCTs.<sup>62,72,73</sup> Surgery does not improve OS and should not be regarded as routine treatment.<sup>74,75</sup> With respect to treatment planning, we noted that patients enrolled in phase III RCTs for combination chemotherapy had an Eastern Cooperative Oncology Group PS score of 0 to 1 and a normal bilirubin level. The bilirubin threshold of <1.5 times the upper limit of normal was adapted from the American Society of Clinical Oncology and ESMO guidelines.<sup>11,76</sup> In practice, clinicians frequently accept a slightly higher level for specific chemotherapy regimens. The intended treatment strategy should be established based on the balance of benefits and harms—aggressive treatment with combination therapy may achieve good tumour control, whereas less aggressive options (eg, monotherapy) can maintain or improve

quality of life for patients with clinical statuses that preclude the use of combination therapy.<sup>77</sup>

The results of the PRODIGE 4/ACCORD 11 trial ( $n=342$ ) showed an improvement in median OS among patients receiving FOLFIRINOX compared with those receiving gemcitabine (11.1 vs 6.8 months,  $HR=0.57$ , 95%  $CI=0.45-0.73$ ;  $P<0.001$ ). Additionally, the median PFS and overall response rate were significantly better.<sup>72</sup> However, FOLFIRINOX had an inferior safety profile compared with gemcitabine.<sup>72</sup> The MPACT trial ( $n=861$ ) demonstrated that the combination of nab-paclitaxel and gemcitabine, compared with gemcitabine alone, significantly improved median OS (8.5 vs 6.7 months,  $HR=0.72$ , 95%  $CI=0.62-0.83$ ;  $P<0.001$ ), median PFS, and overall response rate.<sup>73</sup> Compared with gemcitabine, the combination regimen had higher rates of myelosuppression and peripheral neuropathy, although these effects appeared to be reversible.<sup>73</sup> Clinicians in Hong Kong may prefer gemcitabine plus capecitabine due to the convenience of the oral formulation. Individual trial results for this combination tended to indicate a survival benefit but did not demonstrate statistical significance; subsequent pooled analyses suggested a more robust benefit.<sup>78-81</sup> A possible survival benefit was also detected with gemcitabine plus S-1, which we have included in the list of recommended combination therapies (Table 3).

As previously stated, monotherapy options are necessary for patients with poor PS or elevated bilirubin levels that do not exhibit rapid normalisation. Some clinicians and patients may also prefer single-agent treatment. Gemcitabine monotherapy for mPDAC is already established—an early phase III trial ( $n=126$ ) revealed a clinical benefit response in 23.8% of gemcitabine-treated patients compared with 4.8% of 5-fluorouracil-treated patients ( $P=0.0022$ ).<sup>62</sup> Additionally, OS with gemcitabine in the MPACT and PRODIGE trials was approximately 6 months.<sup>72,73</sup> In all trials, gemcitabine was well-tolerated.<sup>62,72,73</sup> S-1 was evaluated in a phase III trial ( $n=834$ ); its use as monotherapy led to a median OS of 9.7 months with good tolerability.<sup>81</sup> S-1 also demonstrated non-inferiority to gemcitabine ( $HR=0.96$ , 97.5%  $CI=0.78-1.18$ ;  $P<0.001$  for non-inferiority).<sup>81</sup> In Hong Kong, capecitabine monotherapy is used for selected patients. The efficacy and tolerability of capecitabine are currently supported by phase II evidence.<sup>82</sup>

*Statement 29: The decision to undergo subsequent therapy after first-line treatment is highly individualised. Key factors to consider include the type and duration of first-line treatment, performance status, organ function, and treatment goals.*

A: 60%; B: 40%; C: 0%; D: 0%; E: 0%

We recognise that some patients will undergo

TABLE 3. Options for combination chemotherapy for metastatic pancreatic ductal adenocarcinoma

| Study                           | Regimen                                     | Phase | OS, mo             | P value   |
|---------------------------------|---|-------|--------------------|---|
| Conroy et al <sup>72</sup>      | FOLFIRINOX<br>Gemcitabine                   | III   | 11.1<br>6.8        | <0.001  |
| Von Hoff et al <sup>73</sup>    | Gemcitabine + nab-paclitaxel<br>Gemcitabine | III   | 8.5<br>6.7         | <0.001  |
| Scheithauer et al <sup>78</sup> | Gemcitabine + capecitabine<br>Gemcitabine   | II    | 9.5<br>8.2         | NS  |
| Herrmann et al <sup>79</sup>    | Gemcitabine + capecitabine<br>Gemcitabine   | II    | 8.4<br>7.2         | NS  |
| Cunningham et al <sup>80</sup>  | Gemcitabine + capecitabine<br>Gemcitabine   | III   | 7.1<br>6.2         | 0.08<br>(pooled meta-analyses: P=0.02)  |
| Ueno et al <sup>81</sup>        | Gemcitabine + TS-1<br>Gemcitabine<br>TS-1   | III   | 10.1<br>8.8<br>9.7 | Gemcitabine + TS-1 vs gemcitabine<br>(P=0.15 for superiority)<br>TS-1 vs gemcitabine (P<0.001 for<br>non-inferiority) |

Abbreviations: FOLFIRINOX = 5-fluorouracil, leucovorin, irinotecan, oxaliplatin; NS = not significant; OS = overall survival

several lines of treatment, but there is currently no consensus regarding the approach to next-line therapy for mPDAC. According to a multivariate analysis of patient variables from a cohort study of second-line treatment, prognostic factors for OS include liver metastases, PS, pain, jaundice, ascites, duration of first-line treatment, and type of second-line regimen.<sup>83</sup> These factors mirror our real-world experience in establishing individualised regimens for subsequent therapy. Evidence for next-line treatment is based on cohort studies, phase II trials, and phase III RCTs (Table 4).<sup>84-95</sup> Only the regimen of nanoliposomal irinotecan plus fluorouracil and folinic acid has been evaluated in a multicentre phase III trial demonstrating significant OS improvement; thus, it is the first regimen with high-level evidence supporting usage as second-line mPDAC treatment for patients who progressed on first-line gemcitabine treatment.<sup>89</sup>

**Personalised medicine**

*Statement 30: Germline testing of BRCA1/2 and somatic testing of microsatellite instability/mismatch repair can be considered for patients with unresectable disease, due to potential therapeutic implications.*

A: 40%; B: 60%; C: 0%; D: 0%; E: 0%

*Statement 31: Among patients who test positive for germline BRCA1 or BRCA2 mutations, olaparib may be considered for patients who have previously been treated with a platinum-based regimen and have not exhibited disease progression for at least 16 weeks. (Level 2)*

A: 50%; B: 50%; C: 0%; D: 0%; E: 0%

*Statement 32: For patients with tumours that harbour high microsatellite instability or genetic aberrations*

*in DNA mismatch repair genes, immune checkpoint inhibitors may be considered.*

A: 90%; B: 10%; C: 0%; D: 0%; E: 0%

Emerging evidence suggests that mPDAC treatment can be tailored according to underlying mutations, and we emphasise that individual tumour profiling can be considered for selecting patients who may benefit from such treatment. The notion that PDAC with germline *BRCA1/2* mutations responds well to platinum-based therapy is supported by retrospective analyses.<sup>96,97</sup> In contrast, the phase III POLO (Pancreas Cancer Olaparib Ongoing) RCT demonstrated that targeted therapy was effective for patients with a germline *BRCA* mutation who had prior platinum-based chemotherapy for mPDAC and whose disease had not progressed for 16 weeks; these patients experienced a clinical benefit with maintenance olaparib, a poly (adenosine diphosphate-ribose) polymerase inhibitor.<sup>98</sup> Among those 154 study subjects, median PFS was significantly longer in patients with maintenance olaparib than placebo group (7.4 vs 3.8 months, HR=0.53, 95% CI=0.35-0.82; P=0.0038).<sup>98</sup> The preliminary OS in both treatment groups was approximately 18 months.<sup>98</sup> Based on the inclusion criteria and results of the POLO study, we recommend olaparib for patients with *BRCA1/BRCA2*-positive mPDAC that has not progressed for 16 weeks.

Approximately 2% of pancreatic cancers have mismatch repair (MMR) deficiency.<sup>99</sup> Patients with advanced MMR-deficient cancers respond to programmed cell death protein 1 blockade. The efficacy of the anti-programmed cell death protein 1 antibody pembrolizumab was evaluated in patients with MMR-deficient tumour types. Among 86 patients, eight had pancreatic tumours. Overall, 53.5% (46/86) of the patients exhibited

TABLE 4. Options for second-line treatment for metastatic pancreatic ductal adenocarcinoma

| Study type  | Study                           | First-line regimen                              | Second-line regimen               | No. of patients | Median OS, mo | Median PFS, mo |
|---|---------------------------------|---|-----------------------------------|-----------------|---------------|----------------|
| Single-arm phase II trials: single-agent chemotherapy | Hosein et al <sup>84</sup>      | Gemcitabine-based therapy                       | Nab-paclitaxel                    | 19              | 7.3           | 1.7            |
|   | Boeck et al <sup>85</sup>       | Gemcitabine-based therapy                       | Capecitabine                      | 39              | 7.6           | 2.3            |
| Single-arm phase II trials: combination chemotherapy  | Soares et al <sup>86</sup>      | Gemcitabine-based therapy                       | Docetaxel + capecitabine          | 42              | 5.3           | 3.7            |
|   | Pelzer et al <sup>87</sup>      | Gemcitabine                                     | OFF*                              | 37              | 5.5           | 3              |
| Randomised controlled trials                          | Gill et al <sup>88</sup>        | Gemcitabine-based therapy                       | mFOLFOX6*<br>FU/LV*               | 54<br>54        | 9.9           | 2.9            |
|   | Wang-Gillam et al <sup>89</sup> | Gemcitabine-based therapy                       | Nanoliposomal irinotecan + FU/LV* | 117             | 6.1           | 3.1            |
|   |                                 |   | Nanoliposomal irinotecan<br>FF*   | 151<br>149      | 4.9<br>4.2    | 2.7<br>1.6     |
|   | Oettle et al <sup>90</sup>      | Gemcitabine                                     | OFF*                              | 76              | 5.9           | 2.9            |
| FF*   |                                 |   | 84                                | 3.3             | 2             |                |
| Yoo et al <sup>91</sup>                               | Gemcitabine                     | mFOLFIRI.3*                                     | 31                                | 4.2             | 2             |                |
|   |                                 | mFOLFOX*  | 30                                |                 |               |                |
| Dahan et al <sup>92</sup>                             | LV5FU2-CDDP<br>Gemcitabine      | Gemcitabine                                     | 102                               | 6.6             | 2.3           |                |
|   |                                 | LV5FU2-CDDP*                                    | 100                               | 8.0             | 2.6           |                |
| Pelzer et al <sup>93</sup>                            | Gemcitabine                     | OFF*  | 46                                | 4.82            | N/A           |                |
|   |                                 | Best supportive care                            |                                   | 2.3             |               |                |
| Cohort studies  | Portal et al <sup>94</sup>      | FOLFIRINOX                                      | Gemcitabine/nab-paclitaxel        | 57              | 8.8           | 5.1            |
|   | Zaanan et al <sup>95</sup>      | Gemcitabine alone or alternating with FOLFIR.3* | FOLFOX                            | 46              | 4.3           | 1.7            |

Abbreviations: N/A = not available; OS = overall survival; PFS = progression-free survival

\* For the dosage, please refer to the respective studies

objective radiographic responses, whereas 76.7% (66/86) demonstrated disease control.<sup>99</sup> These results indicate that immune checkpoint inhibition should be considered for high microsatellite instability mPDAC. The potential benefit of this approach has been acknowledged by international guidelines.<sup>16,76,100</sup>

Germline testing of *BRCA1/2* and somatic testing of microsatellite instability/MMR are conducted separately. In contrast to countries with extensive reimbursement, routine testing with comprehensive gene panels is not routinely feasible for all patients due to the limited resources in Hong Kong. Hong Kong clinicians, especially in private clinics, may utilise next-generation sequencing services to obtain a comprehensive genetic mutation profile. In next-generation sequencing, a broad mutational analysis panel can identify potentially actionable alterations, including *BRCA1/2* mutations. However, one study showed that only 1.3% of patients (3/225) received targeted therapy for PDAC based on next-generation sequencing results.<sup>101</sup> This observation is similar to our clinical experience, suggesting that next-generation sequencing has limited therapeutic utility for PDAC.

*Statement 33: Genetic counselling is recommended for patients who test positive for a germline mutation.*

A: 50%; B: 50%; C: 0%; D: 0%; E: 0%

Germline testing for *BRCA* mutations in PDAC is expected to increase in Hong Kong. We recommend genetic counselling for patients who plan to undergo tests for pathogenic variants. The NCCN also recommends germline testing and subsequent referral for genetic counselling at the time of PDAC diagnosis, especially for patients with suspected familial risk based on a family history of *BRCA*-linked tumours.<sup>16</sup> No detailed guidance regarding genetic counselling for PDAC is currently available. Nonetheless, guidelines regarding *BRCA*-associated tumours, particularly breast and ovarian tumours, recommend the provision of genetic counselling services for patients with germline pathogenic mutations.<sup>102-105</sup>

### Palliative and supportive care

*Statement 34: Assessments of physical and psychological symptoms should be performed for all patients with PDAC. Palliative management should be considered when clinically indicated.*

A: 70%; B: 30%; C: 0%; D: 0%; E: 0%

*Statement 35: Biliary drainage should be considered for patients with obstructive jaundice. Options include endoscopic or percutaneous drainage and surgical bypass.*

A: 70%; B: 20%; C: 10%; D: 0%; E: 0%

*Statement 36: Options for the management of gastric outlet obstruction include surgical bypass and endoscopic stenting.*

A: 100%; B: 0%; C: 0%; D: 0%; E: 0%

*Statement 37: Aggressive pain control is mandatory and frequently requires the involvement of a pain specialist.*

A: 60%; B: 40%; C: 0%; D: 0%; E: 0%

*Statement 38: In addition to pharmacological interventions, a coeliac axis block can be considered to optimise pain control.*

A: 60%; B: 40%; C: 0%; D: 0%; E: 0%

*Statement 39: Palliative radiation can be considered to relieve severe tumour-associated pain and/or bleeding from the primary tumour site.*

A: 40%; B: 60%; C: 0%; D: 0%; E: 0%

We acknowledge that palliative care and supportive care for PDAC are therapeutic aspects often overlooked by clinicians. Key guidelines have emphasised the need to coordinate palliative and supportive care with therapeutic care, thereby optimising quality of life and potentially improving survival. These guidelines have highlighted interventions to address symptoms such as pain, biliary obstruction, gastric outlet obstruction, and bleeding.<sup>11,16</sup>

Symptomatic biliary obstruction occurs in up to 75% of patients with pancreatic head tumours. Obstructive jaundice can lead to generalised wasting; untreated biliary obstruction can result in cholangitis and liver dysfunction, with the potential for early mortality.<sup>106</sup> Primary treatments consist of endoscopic or percutaneous drainage. Surgical bypass should only be utilised as a palliative option in cases where the planned Whipple procedure revealed an unresectable tumour.

Tumour invasion into the duodenum leads to gastric outlet obstruction. The choice of treatment depends on PS and predicted length of survival<sup>16</sup>—in an otherwise young and healthy patient with an unresectable tumour, surgical bypass is the best palliative option with respect to quality of life. Endoscopic enteral stenting may be preferred for frail patients.

Pain is experienced by almost all patients with advanced PDAC and requires aggressive management. Experts in pain management, such as pain specialists or oncologists with extensive experience in pain medicine, should often be

included in the care team. A coeliac axis block, which interrupts visceral pain innervation from the pancreas and nearby structures through injections of corticosteroids and anaesthetics, may be considered for severe pain refractory to analgesics or narcotics.<sup>16,107</sup> A coeliac axis block is usually performed under fluoroscopic or CT-based guidance, but EUS-based guidance provides better visualisation of the coeliac plexus.<sup>108</sup>

Palliative RT can be used to control pain caused by the tumour or sites of metastasis. Patients with non-mPDAC and poor PS or co-morbidities that preclude definitive therapy may be offered palliative RT. Additionally, RT is an option for the management of tumour-induced gastrointestinal bleeding.<sup>11,16</sup>

## Conclusion

Despite its relatively low incidence among cancers worldwide and in Hong Kong, PDAC represents a major health burden because of its aggressive nature and the complexities involved in its diagnosis and management. To familiarise Hong Kong clinicians with all aspects of PDAC care and provide practical guidance, our consensus group developed this initial set of recommendations for clinical management of PDAC. We discussed the current state of PDAC management, reviewed the best available evidence and international guidelines, and crafted statements that address real-world situations encountered by clinicians. We recognise that many aspects of PDAC treatment lack high-level evidence; moreover, clinical experiences, patient preferences, and resources availability vary across Hong Kong. Thus, several of our statements suggest options, rather than endorsing a specific technique or regimen, to facilitate individualised management based on available evidence and clinical judgement.

## Author contributions

Concept or design: SL Chan, CL Chiang, KSH Chok.

Acquisition of data: SL Chan, CL Chiang, KSH Chok.

Analysis or interpretation of data: All authors.

Drafting of the manuscript: All authors.

Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

## Conflicts of interest

SL Chan has served as an advisor for AstraZeneca, MSD, Eisai, and Ipsen, and has received research funding from Bayer, Eisai, Ipsen, Sirtex, and MSD. CL Chiang has served as an advisor for AstraZeneca, MSD, and Eisai, and has received research funding from Merck KGaA, AstraZeneca, and Taiho. Other authors have disclosed no conflicts of interest.

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