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GUIDELINE

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Guidelines for holistic integrative management of pancreatic cancer

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Abstract

Background Pancreatic cancer ranks 10th in the incidence rate of malignant tumors in male, and 12th in female. Pancreatic cancer is the sixth leading cause of tumor-related deaths in China. It is a devastating malignancy with poor prognosis.

Methods Driven by the concept of "integrated medicine", the China Anti-Cancer Association Committee of Pancreatic Cancer organized relevant experts to complete this guideline.

Results This guideline aims to guide the integrated treatment and rehabilitation management of pancreatic cancer in an all-round way based on "Preventing, Screening, Diagnosing, Treating, and Rehabilitating".

Conclusions We hope that this guideline will provide effective references for clinicians, so as to achieve the best treatment effects for pancreatic cancer patients in China.

Keywords Pancreatic cancer, Guidelines, Holistic integrative management

1 Chapter I Epidemiology

At present, the incidence of pancreatic cancer (PC) is on the rise worldwide, with close death rate and incidence rate, and its mortality is high [1, 2]. According to the 2015 statistical data from the National Cancer Center of China, PC ranks 10th in the incidence of malignant tumors in males, 12th in females in China, and 6th in the mortality rate of all malignant tumors [3].

Early diagnosis of PC is difficult and the surgical resection rate is low. In addition, it has a highly malignant biological behavior and a very poor prognosis. In recent years, driven by the concept of "integrated medicine", the multidisciplinary integrated diagnosis and treatment model (MDT to HIM) has become popular, and the prognosis of PC has also tended to improve gradually. According to data released by the American Cancer Society, the 5-year survival rate of PC has increased from 5% ~ 6%, 10 years ago, to 9% ~ 10% at present, but it is still the lowest among all malignant tumors [4–6].

2 Chapter II Diagnosis

2.1 Section 1 Clinical manifestations

Most PCs have an insidious onset, atypical early symptoms and signs, and are easily confused with other digestive system diseases. According to its location and stage, tumor can present with epigastric fullness and discomfort, epigastric pain, lower back pain, nausea, loss of appetite, changes in stool characteristics, jaundice, new diabetes, occasional pancreatitis, weight decrease, and asthenia. Some patients do not present any clinical manifestations, and the tumor can be incidentally found by physical examination.

2.2 Section 2 Laboratory examination

2.2.1 Chemistry panel

There are no specific changes in blood biochemical parameters in the early stage; increased blood bilirubin may occur with enzymatic changes when bile ducts are compressed or obstructed; transient increases in blood

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amylase may occur when pancreatic duct is compressed or obstructed; and changes in blood glucose may be associated with the pathogenesis or progression of PC.

2.2.2 Test of serum tumor marker

(1) CA19-9, CEA, CA125 and CA242 are used for the diagnosis of PC in clinical practice, of which CA19-9 is the most commonly used and has the highest diagnostic value, with a diagnostic sensitivity and specificity of 78.2% and 82.8%, respectively [7, 8].
(2) CA19-9 is increased not only in PC, but also in other malignant tumors such as colorectal cancer, gastric cancer, lung cancer, breast cancer, liver cancer, pancreatic neuroendocrine tumors as well as bile duct obstruction, cholangitis, chronic pancreatitis, and cirrhosis, affecting its specificity in diagnosis.
(3) Five to ten percentage of PCs are Lewis antigen negative, CA19-9 is not secreted or rarely secreted, and such patients have undetectable elevated CA19-9 levels, which is called "false negative", requiring the combination with other tumor markers such as CEA and CA125 [9].
(4) The sensitivity and specificity of CEA in the diagnosis of PC are 43% and 82%, respectively, and those of CA125 are 59% and 78%, respectively, and the combined detection of the above multiple tumor markers helps to improve the sensitivity and specificity of PC diagnosis [10–12].

2.2.3 Liquid biopsy markers

In recent years, liquid biopsy technology has increasingly shown good application value and prospect in the diagnosis of PC, mainly including circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), exosomes, microRNAs, etc. The combination with CA19-9 can improve the accuracy of PC diagnosis, but its popularization and application in clinical practice still need to be verified by high-quality clinical studies [12–16].

2.3 Section 3 Imaging examination

Commonly used imaging examinations are B-mode ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), with different characteristics.

2.3.1 Ultrasound

It is a simple, non-invasive. radiation-free and polyaxial observation; its disadvantage is that it is easy to be interfered with by air in the gastrointestinal tract in front of the pancreas, and of note, the display of the pancreatic tail is not clear, and it is subjectively affected by the operator. It is generally used for the initial diagnosis and follow-up of PC.

2.3.2 CT

Thin-section contrast-enhanced CT with a cross-sectional thickness of 1 mm can clearly show the appearance, size and location of the tumor, pancreatic duct, bile duct, and the relationship between the tumor and the surrounding blood vessels and adjacent organs. At present, it is currently the most commonly used imaging examination for the diagnosis of PC.

2.3.3 MRI/MRCP

Contrast-enhanced MRI has multi-parameter, multi-axial imaging, and radiation-free characteristics, and can be used as an important supplement to contrast-enhanced CT when the differential diagnosis of PC is difficult, especially for those patients who cannot undergo contrast-enhanced CT due to renal impairment, allergy to iodinated contrast agents, and those with isodense masses on contrast-enhanced CT [17]. In addition, contrast-enhanced MRI is superior to contrast-enhanced CT in the diagnosis of liver micrometastases [18, 19]. Magnetic resonance cholangiopancreatography (MRCP) can clearly show the whole picture of pancreaticobiliary duct and help to determine the location of the lesion [20]. It features non-invasiveness compared with encoscopic retrograde cholangiopancreatography (ERCP) and has diagnostic value in combination with enhanced MRI.

2.3.4 PC Radiology report

Template is shown in Table 1 [21].

2.3.5 PET-CT/PET-MRI

It is a functional imaging examination that reflects the metabolic activity and metabolic load of the tumor through the uptake of imaging agents by the lesion. PET is a systemic examination that has certain advantages in finding the primary tumor, detecting extrapancreatic metastases, judging staging, assessing systemic tumor burden, efficacy assessment, and recurrence monitoring [22]. However, PET may also generate false positives and false negatives, and regional anatomy shows less clarity than contrast-enhanced CT and contrast-enhanced MRI [23]. In addition, it is expensive. Therefore, it only serves as a supplement to conventional imaging studies.

2.4 Section 4 Endoscopy

2.4.1 Endoscopic ultrasound (EUS)

(1) EUS is of diagnostic value for early small PC due to its probe being close to the pancreas and avoid-

Table 1 Template of PC radiology report

Morphological assessment			
Appearance (delayed phase of pancreatic parenchyma)	□ Low density	□ Isodense	□ High density
Size (maximum diameter)	□ Measurable: ___cm × cm ×_cm	□ Non-measurable (Isodense tumor)	
Location	□ Pancreatic head/□ Uncinate	□ Pancreatic body/□ Pancreatic tail	
Interruption of pancreatic duct stenosis with or without dilatation of the distal pancreatic duct	□ Yes	□ None	
Bile duct stenosis interruption with or without upstream bile duct dilatation	□ Yes	□ None	
Arterial assessment			
Superior mesenteric artery invasion	□ Yes	□ None	
Degree of superior mesenteric artery invasion	□ ≤ 180 °	□ > 180 °	
Local arterial stenosis or irregularity	□ Yes	□ None	
Celiac trunk invasion	□ Yes	□ None	
Degree of celiac trunk invasion	□ ≤ 180 °	□ > 180 °	
Local arterial stenosis or irregularity	□ Yes	□ None	
Common hepatic artery invasion	□ Yes	□ None	
Degree of common hepatic artery invasion	□ ≤ 180 °	□ > 180 °	
Local arterial stenosis or irregularity	□ Yes	□ None	
Arterial variation	□ Yes (□ Accessory right hepatic artery/□ Replaced right hepatic artery □ Replaced common hepatic artery/ □ Other_)	□ None	
Venous assessment			
Portal vein invasion	□ Yes	□ None	□ Complete occlusion
Degree of portal vein invasion	□ ≤ 180 °	□ > 180 °	
Local venous stenosis or irregularity	□ Yes	□ None	
Superior mesenteric vein invasion	□ Yes	□ None	□ Complete occlusion
Degree of invasion of superior mesenteric vein	□ ≤ 180 °	□ > 180 °	
Local venous stenosis or irregularity	□ (Yes	□ None	
Venous thrombosis	□ Yes (□ Portal vein/□ Superior mesenteric vein/□	□ None	
	Splenic vein)		
Venous collateral circulation	□ Yes (□ Head of pancreas/□ Hepatic portal/□ Root of mesentery/□ Left upper quadrant)	□ None	
Extrapancreatic assessments			
Hepatic lesions	□ Yes (□ High possibility of metastases/□ Indeterminate/□ High possibility of benignity)	□ None	
Peritoneal or omental nodules	□ Yes	□ None	
Ascites	□ Yes	□ None	
Suspected lymph nodes (hepatic portal/celiac trunk/splenic hilus/para-aortic/inter-aortic)	□ Yes; specifically: _____	□ None	
Other extrapancreatic invasion (inferior vena cava/abdominal aorta/adrenal glands/kidneys/spleen/stomach/colon/mesocolon/small intestine, etc.)	□ Yes; specifically: _____	□ None	

ance of gastrointestinal gas interference, especially in patients with high clinical suspicion of PC and abnormal pancreatic duct but no tumor being found by imaging examination.

(2) For patients whose pancreatic mass nature cannot be determined by contrast-enhanced CT or MRI, EUS also has auxiliary diagnostic value and can be used to assess the local and surrounding conditions of the tumor.

(3) The most important diagnostic value of EUS is that fine needle aspiration (FNA) can be done simultaneously for pathological examination and is also the method of choice for the patients prepared to receive neoadjuvant therapy or patients with advanced PC with the need of pathological examination on the primary lesion of the pancreas [24].

(4) There are also some new technologies and discoveries of EUS. For example, the test of tumor elastic strain rate can be used to guide the selection of chemotherapeutic drugs and improve the chemotherapy efficiency of pancreatic cancer [25].

(5) However, EUS is an invasive examination, and its accuracy is subjectively affected by the operator. It is not recommended for PCs with definite clinical diagnosis or no pathological needs.

2.4.2 ERCP

ERCP cannot directly show the tumor lesions and mainly relies on the morphology of the pancreatic duct and bile duct before making a diagnosis of PC, so it is of great value in the application to those with obstruction or abnormal changes in the lower end of the common bile duct and pancreatic duct [26]. In addition, ERCP can be cannulated into the pancreaticobiliary duct to collect bile and pancreatic juice, followed by pancreaticobiliary cell brushing and then exfoliative cytology related with pancreatic juice. Especially for inoperable obstructive jaundice, biliary drainage operation and pathological and cytological examination can be completed at one time, which should be the first choice of treatment for patients not surgically indicated for obstructive jaundice. However, the sensitivity and specificity of ERCP cytological brushing are suboptimal, and the results have yet to be improved [27].

2.5 Section 5 Laparoscopic exploration

(1) Laparoscopic exploration has potential diagnostic value for tumor staging and can detect peritoneal seeding metastases and liver micrometastases missed by imaging [28].

(2) Routine laparoscopic exploration is not recommended for all potentially resectable PC, but comprehensive and careful laparoscopic exploration is recommended for PC patients with combined factors (e.g., suspicious imaging studies or significantly elevated CA19-9) scheduled for radical resection to detect preoperatively undetected micrometastases.

(3) Laparoscopic biopsy: an alternative method to obtain histopathological diagnosis.

2.6 Section 6 Pathological diagnosis

2.6.1 Pathological classification of pancreatic malignancies

(1) According to WHO classification, pancreatic malignant tumors are divided into epithelial and non-epithelial sources according to tissue origin, the former mainly includes ductal adenocarcinoma, acinar cell carcinoma, neuroendocrine tumors and various mixed tumors from ductal epithelium, acinar cells and neuroendocrine cells.

(2) The Guidelines are mainly aimed at the diagnosis and treatment of patients with ductal adenocarcinoma (including adenosquamous carcinoma, colloid carcinoma, hepatoid adenocarcinoma, medullary carcinoma, signet ring cell carcinoma, undifferentiated carcinoma, undifferentiated carcinoma with osteoclast-like cells and other special subtypes) and acinar cell carcinoma, accounting for about 90% of the entire pancreatic malignant tumors.

2.6.2 Histopathological and/or cytological examination is the "gold standard" for the diagnosis of PC

Except for patients scheduled for surgical resection, attempts should be made to confirm the pathological diagnosis before formulating the treatment plan for the remaining patients. Histopathological or cytological specimens will be obtained as follows:

(1) Laparoscopic or open surgical biopsy: It is a reliable method to obtain histopathological diagnosis.

(2) Aspiration biopsy: If inoperable patients have no distant metastasis, endoscopic ultrasound-guided fine needle aspiration is recommended, or B ultrasound or CT-guided puncture can be performed; for metastatic PC, aspiration biopsy of metastases is recommended.

(3) Exfoliative cytology: pancreatic duct cell brushing, pancreatic juice collection and examination, ascites exfoliative cell examination and other methods can be used.

2.7 Section 7 Clinical diagnostic criteria

In view of the special anatomical location of the pancreas and the special biological behavior of PC, some patients

with high suspicion of PC who fail to receive cytological or histological diagnosis can carefully make clinical decisions and receive reasonable treatment after discussion with MDT to HIM. The following are recommended:

(1) complete clinical data, including comprehensive and multiple serological and various high-quality imaging examinations, especially CA19-9-based tumor marker examinations, and PET-CT/PET-MRI when necessary.
(2) Repeated aspiration biopsies can be performed by physicians specialized in interventional medicine or endoscopy, and centralized consultation can be performed by multiple experienced pathologists.
(3) The risks of treatment can be informed through multiple communications to the patients and their family, and informed consent forms need to be signed.
(4) The final decision is made jointly by the MDT to HIM experts and closely monitored during treatment.

3 Chapter III Prevention and screening

3.1 Section 1 Risk factors

The causes and exact mechanisms of PC are not fully understood, and epidemiological surveys have shown that PC incidence is associated with a variety of risk factors, which are specifically divided into individual factors, lifestyle, injury infection, benign diseases, and precancerous lesions [29].

3.1.1 Individual factors

(1) Age: Most malignancies are positively correlated with age, and PC is no exception. For patients over 40 years of age, especially for patients over the age of 50 years, the incidence of PC shows an increasing trend.
(2) Genetic susceptibility: 5% ~ 10% of PC have pathogenic germline gene mutations, mostly in DNA damage repair genes, which can increase the susceptibility of PC. Common genetic genes include ATM, BRCA2, CD KN2A, MSH2, MSH6, PALB2, TP53 and BRCA1 [30].
(3) The development of PC may also be associated with some genetic syndromes, and the common syndromes are as follows: [31, 32]

    1) Peutz-Jeghers syndrome: the associated gene is STK11/LKB1; the risk of PC is 132 times that of the general population
    2) Hereditary pancreatitis: The related genes are PRSS1, SPINK1 and CFTR; the risk of PC is 26 ~ 87 times that of the general population.
    3) FAMMM syndrome (familial atypical multiple mole melanoma): the related gene is CDKN2A; the risk of PC is 20 ~ 47 times that of the general population.
    4) Lynch syndrome: The related genes are MLH1, MSH2, MSH6, and PMS2; the risk of PC is 9 to 11 times that of the general population.
    5) Hereditary breast and ovarian cancer syndrome: the genes involved are BRCA2, BRCA1, PLAB2; the risk of PC is 2.4 to 6 times that of the general population.
    6) Familial adenomatous polyposis (FAP): the associated gene is APC; the risk of PC is 4.5 times that of the general population
    7) Ataxia telangiectasia syndrome: related gene is ATM; risk of PC is 2.7 times that of the general population

(4) Familial PC: Family history is a risk factor for PC, and PC patients are considered familial if two or more first-degree relatives have been diagnosed with PC at the time of diagnosis. If two first-degree relatives are diagnosed with PC, the risk of PC is 6.4 times higher than that of the general population; in case of three relatives, the risk of PC is 32 times higher than that of the general population [33, 34].

3.1.2 Lifestyle

(1) Smoking: Smoking is the strongest risk factor associated with the incidence of PC in lifestyle [35].
(2) Alcohol consumption: There is also a modest association between alcohol intake and PC onset. High alcohol intake, especially binge drinking, significantly increases PC risk; low alcohol intake and PC incidence risk were not greatly correlated [36, 37].
(3) Obesity: Obesity increases PC morbidity and mortality. Body mass index (BMI) > 30 increases the risk of PC, and the risk of PC increases by 10% for every 5-unit increase in BMI [38]. Pancreatic fatty infiltration is associated with the development of pancreatic intraepithelial neoplasia, and pancreatic intraepithelial neoplasia is a precancerous lesion of pancreatic ductal adenocarcinoma [39].

3.1.3 Injury and infection

(1) Occupational exposure: Practitioners exposed to chemicals and heavy metals, such as pesticides,

asbestos, benzene, and chlorinated hydrocarbons, are at increased risk of PC [40].

(2) Microorganisms: Decreased number of gastrointestinal streptococci and increased number of Porphyromonas gingivalis increase the risk of PC. In addition, hepatitis virus infection is also a risk factor for PC [41, 42].

3.1.4 Benign disease

(1) Diabetes and/or new onset of elevated fasting glucose: a long history of chronic diabetes increases the risk of PC. On average, PC patients will experience new episodes of elevated fasting glucose 30 to 36 months before diagnosis [43].

(2) Chronic pancreatitis: The risk of PC in chronic pancreatitis is 13 times higher than that in the normal population, and about 5% of them eventually develop PC [44].

3.1.5 Precancerous lesion

(1) Pancreatic intraepithelial neoplasia, and intraductal papillary mucinous neoplasm (IPMN), and mucinous cystadenoma have a certain probability of carcinogenesis [45].

Elevated CA19-9: The CA19-9 cut-off value is 37.0 U/mL, and this marker can start to increase as early as 2 years before the diagnosis of PC.The sensitivity of elevated CA19-9 in the first six months of PC diagnosis was 60%, which can be used as an early warning marker for PC [46].

3.2 Section 2 Prevention

PC prevention is to reduce the probability of PC occurrence by intervening with PC risk factors as much as possible [47]. Specific measures are as follows:

(1) Actively quit smoking and avoid secondhand smoke.

(2) Avoid alcohol abuse.

(3) Diet

1) High-sugar beverages and saturated fatty acid diets are associated with a younger trend in the incidence of obesity, diabetes, and PC, and such diets should be avoided as much as possible.
2) Consumption of red meat (especially when cooked at elevated temperatures), processed meat, fried foods, and other foods containing nitrosamines may increase the risk of PC, which is possibly related to carcinogens in meat and nitrites or N-nitroso compounds used to preserve processed meat, so the intake of red meat and processed meat should be minimized [48].
3) Folic acid intake can reduce the risk of PC and should increase the intake of vitamin-rich fresh fruits in the diet [49].
4) Consumption of cruciferous vegetables, such as broccoli, cabbage, radish and broccoli, is advocated [50, 51].
5) Other measures include diet control, balancing of intake of nutrition, and avoidance overeating and greasy diet.

(4) Strengthen exercise, reasonably release stress, and advocate outdoor aerobic activities [52].

(5) Lifestyle should be regular, and patients are advised to stay up less late, work and rest regularly and ensure adequate sleep every day [53].

(6) PC occurrence and obesity have a certain relationship. Once the body weight is out of specification, it is necessary to actively lose weight, eat less, move your legs, and control the body weight in a reasonable range as much as possible

(7) Enhance the protection of exposed personnel in the chemical industry, educate them to try not to contact pesticides and herbicides, and take protective measures when necessary.

(8) Active control measures should be adopted for diabetes.

(9) Prevent the deterioration of benign diseases, seek medical attention when there are pancreatic duct stones, IPMN, mucinous cystadenoma or other benign pancreatic diseases, and receive examinations regularly [54].

(10) Take regular physical examinations.

3.3 Section 3 Screening

In 2019, the U.S. Preventive Services Medicine Task Force proposed that the potential benefits of PC screening in asymptomatic adults did not outweigh the potential risks, that PC screening in asymptomatic adults was not recommended, and that targeted screening was generally recommended for individuals with high risk factors for the development of PC generally and with a lifetime risk of PC higher than 5% [55, 56].

3.3.1 Screened population

(1) All individuals carrying STK11/LKB1 pathogenic or possibly pathogenic germline mutations.

(2) All individuals carrying CDKN2A pathogenic or possibly pathogenic germline mutations.

(3) Presence of known mutations of PC susceptibility genes, such as BRCA2, BRCA1, PALB2, ATM, MLH1, MSH2, MSH6 and other pathogenic germ lines, and at least one first-degree relative diagnosed with PC.
(4) Individuals with PC in two or more first-degree relatives of the family (even if there are no known pathogenic/possibly pathogenic germline mutations).
(5) Individuals with PC in three or more first- and/or second-degree relatives of the family (even if there are no known pathogenic or possibly pathogenic germline mutations).

3.3.2 Starting age of screening

It depends on the genetic variation and family history.

(1) For individuals with pathogenic or possible pathogenic germline mutations in STK11/LKB1 or CDKN2A, the starting age for screening is 40 years; if there is a clear family history at the same time, the age of earliest diagnosis of PC in the family is advanced by 10 years, and a younger age is selected to start PC screening.
(2) For individuals carrying pathogenic or possible pathogenic germline variants of other PC susceptibility genes, the initial age of screening is 45 ~ 50 years; if there is a clear family history at the same time, the age of earliest diagnosis of PC in the family is advanced by 10 years, and a younger age is selected to start PC screening.
(3) For individuals with a family history of PC, the starting age for screening is 50 to 55 years even if there are no known pathogenic/possibly pathogenic germline mutations; if there is a clear family history at the same time, the age of earliest diagnosis of PC in the family is advanced by 10 years, and a younger age is selected to start PC screening [57, 58].

4 Chapter IV Treatment

4.1 Section 1 Staging and integration assessment

4.1.1 Staging

The 8th edition of AJCC-TNM staging for pancreatic cancer is currently the most widely used staging system in clinical practice (Table 2) [59]. It can be used guide

Table 2 AJCC-TNM staging of 8th edition for pancreatic cancer

Primary tumor (T)	Tx primary tumor not evaluable		
	T0: No evidence of primary tumor		
	Tis: Carcinoma in situ		
	T1: Maximum tumor diameter ≤ 2 cm		
	T1a: Maximum tumor diameter ≤ 0.5 cm		
	T1b: Maximum tumor diameter > 0.5 cm and < 1 cm		
	T1c: Maximum tumor diameter ≥ 1 cm and ≤ 2 cm		
	T2: Maximum tumor diameter > 2cm and ≤ 4 cm		
	T3: Maximum tumor diameter > 2 cm		
	T4: Tumors, regardless of size, involve the celiac trunk, superior mesenteric artery, and/or common hepatic artery		
Regional lymph nodes (N)	Nx: Regional lymph nodes not evaluable		
	N0: No regional lymph node metastasis		
	N1 1-3: Regional lymph node metastases		
	N2: Metastasis in 4 or more regional lymph nodes		
Distant metastasis (M)	M0: without distant metastasis		
	M1:with distant metastasis		
Stage			
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1-3	N1	M0
III	T1-3	N2	M0
	T4	Any N	M0
IV	Any T	Any N	M1

treatment and determine prognosis, with satisfactory accuracy and practicability. However, in terms of how to better balance the correlation between tumor size and lymph node metastasis, and how to optimize the tumor biological factors, the "Shanghai Fudan Edition" pancreatic cancer staging formed by improvement and optimization in combination with domestic and foreign patient data has drawn attention from the entire industry, which further improves the prediction and understanding of malignant behavior of pancreatic cancer [60–62].

4.1.2 Anatomic assessment of PC resectability

Radical (R0) resection is currently the most effective treatment for PC. PC should be discussed by MDT to HIM before treatment. According to the relationship between the tumor and its surrounding important blood vessels and distant metastasis, the anatomical resectability of the tumor is integrated and assessed, and it is divided into four categories: resectable, borderline resectable, locally advanced and PC with distant metastasis. This assessment classification is the cornerstone for the development of PC treatment strategy (Table 3). For patients suspected of distant metastasis who cannot be diagnosed by high-quality CT/MRI, PET should be performed and laparoscopic exploration should be performed when necessary.

The assessment of the resectability of the PC depends, on one hand, on the anatomical relationship between the tumor and the vessels, and on the subjective judgment, experience and skill level of the operator and the unit. Therefore, Therefore, different centers may vary in assessing resectability.In addition, clinicians are encouraged to make the judgement on the PC resectability in combination with tumor biological characteristics on the basis of imaging data assessment.

4.1.3 Performance status assessments

(1) PC performance status assessment is particularly important, can be used as an important reference for formulating treatment strategies and may affect prognosis [63, 64].
(2) Performance status is generally assessed by Eastern Cooperative Oncology Group (ECOG) score or Karnofsky Performance Status (KPS) score.

    1) PC Excellent performance status: ECOG score 0 to 1; or KPS score > 70.
    2) PC Good performance status: ECOG score 0 ~ 2 points; or KPS score ≥ 70 points.
    3) Poor performance status: ECOG score > 2; or KPS score < 70.

4.1.4 Resectability assessment after neoadjuvant/translational therapy

(1) Imaging evaluation: The traditional evaluation criteria based on imaging examination results, i.e., Response Evaluation Criteria in Solid Tumors (RECIST), are intuitive, standardized and operable to evaluate the efficacy according to the change of target lesion size shown by CT or MRI before and after treatment, but it is difficult to reflect the biological attributes such as tumor heterogeneity, cell activity, and immune cell infiltration. Because pancreatic cancer is rich in stroma, the tissue around the tumor will also produce inflammatory response and fibrosis after neoadjuvant therapy. Even if neoadjuvant therapy is effective, the tumor size and the extent of involvement of important blood vessels often do not change significantly. It is often difficult for RECIST to accurately assess the effect of neoadjuvant therapy for PC and tumor resectability [65, 66].
(2) CA19-9 is an independent predictor of patient prognosis after neoadjuvant therapy, and a > 50% decrease in CA19-9 levels after treatment has a good prognosis, and if it returns to normal levels, the postoperative survival benefit is more significant [67, 68].
(3) The assessment and decision of resectability after neoadjuvant therapy should be discussed by MDT to HIM.
(4) For patients with initially resectable or borderline resectable disease, if CA19-9 is stable or has decreased after neoadjuvant therapy and imaging studies do not show significant progression, surgical exploration should be performed. For patients with resectable borderline tumor, such as superior mesenteric vein/portal vein involvement or thrombosis, surgical exploration is feasible as long as vascular reconstruction can be performed. For borderline resectable tumor patients with mild increase in involved arteries and surrounding soft tissues, if other clinical manifestations improve (such as performance status, pain, nutritional status), it is considered as a contraindication for surgical exploration.
(5) For patients with locally advanced disease, surgical exploration should be considered if the level of CA19-9 decrease is greater than 50% and clinical symptoms improve, a sign suggesting that the treatment is effective.

Table 3 Anatomic assessment of PC resectability

Resectable state	Arterial	Venous
Resectable	The tumor does not touch the celiac trunk, superior mesenteric artery or common hepatic artery	Tumor does not touch the superior mesenteric vein and portal vein, or invades but with a degree of not exceeding 180 °, and the venous contour is regular
Borderline resectable	Pancreatic head and neck tumor: the tumor touches the common hepatic artery, but does not involve the celiac trunk or the origin of the left and right hepatic arteries, and can be completely resected and reconstructed; the tumor touches the superior mesenteric artery, but with a contact degree of not exceeding 180 °; if there are variant arterial anatomy (such as the accessory right hepatic artery, alternative right hepatic artery, alternative common hepatic artery, and the artery of origin of the alternative or accessory artery), it is necessary to determine whether there is tumor invasion and the degree of invasion, which may affect the surgical decision	Pancreatic head and neck tumor: the tumor touches the superior mesenteric vein or portal vein with a contact degree of more than 180 °, or veins are irregularly contoured although touch degree of no more than 180 °; or venous thrombosis, which can be safely reconstructed after resection; the tumor touches the superior mesenteric vein.
	Pancreatic body and tail tumor: the tumor touches the celiac trunk with a degree of not more than 180 °; the tumor touches the celiac trunk with a degree of more than 180 °, but does not touch the abdominal aorta, and the gastroduodenal artery is intact and not invaded	Pancreatic body and tail tumor: the tumor touches the portal vein confluence of splenic vein, or the left side of portal vein does not exceed 180 °, but there is venous contour irregularity; and there are appropriate vessels or distal vessels for safe and complete resection and venous reconstruction; the tumor touches the vein
Local progression	Pancreatic head and neck tumor: the tumor touches the superior mesenteric artery with a degree of more than 180 °; the tumor invades the celiac trunk with a degree of more than 180 °, and the tumor touches the first jejunal branch of the superior mesenteric artery	Pancreatic head and neck tumor: Tumor touches or unresectable reconstruction of the superior mesenteric vein or portal vein due to embolism (tumor thrombus or thrombus); tumor invading the proximal jejunal drainage branch of most of the superior mesenteric vein
	Pancreatic body and tail tumor: the tumor invades the superior mesenteric artery or celiac trunk with a degree of more than 180 °; the tumor invades the celiac trunk and abdominal aorta	Pancreatic tail tumor: tumor invasion or unresectable reconstruction of the superior mesenteric vein or portal vein due to embolism (which may be a tumor thrombus or thrombus)
Concurrent distant metastasis	Distant metastasis (including non-regional lymph node metastasis)	Distant metastasis (including non-regional lymph node metastasis)

4.1.5 Pathological evaluation of surgically resected specimens after neoadjuvant therapy

(1) The pathological results of resected specimens after neoadjuvant therapy for PC can be used to assess the efficacy and prognosis and guide subsequent treatment.
(2) Studies have shown that the prognosis of patients with complete or near complete response assessed by pathology is better than that of patients with extensive residual tumor.
(3) The International Panel of Pancreatic Pathologists concluded that the modified Ryan four-grade score of the College of American Pathologists (CAP) is by far the most reasonable scoring system, because it is based on the presence and number of residual cancer cells rather than on tumor regression alone, and the modified Ryan scoring scheme is shown in Table 4 [69].

4.2 Section 2 Surgical treatment

4.2.1 Principles of surgical treatment

(1) Surgical resection is the only effective method for PC to obtain a chance of cure and long-term survival, the extent of radical surgery includes primary tumor and regional lymph node dissection, and the location and size of the tumor and its relationship with surrounding important blood vessels determine the surgical approach. For pancreatic head and uncinate process cancer, pancreaticoduodenectomy (Whipple procedure) is required; for pancreatic body and tail cancer, combined pancreatectomy and splenectomy is required; for some pancreatic neck cancer or tumors with a large extent of involvement and multiple lesions in the pancreas, total pancreatectomy may be considered [70].
(2) There is no uniform standard for the optimal resection approach and procedure of tumors, and it is recommended to follow the principle of no tumor and No-touch operation as much as possible. Tamara et al. compared the effect of two open pancreaticoduodenectomy procedures (conventional surgery and No-touch surgery) on portal vein blood CTCs, and found that 83% of patients had increased portal vein CTCs after traditional surgical tumor resection, while no patients in the No-touch surgery group had increased CTCs [71].

4.2.2 Preoperative biliary drainage

(1) Need for biliary drainage before radical resection of PC

1) The necessity of preoperative biliary drainage therapy is currently debated, there is no clear preoperative biliary drainage index, and serum total bilirubin ≥ 250 μmol/L is mostly used as the boundary, but it needs to be comprehensively judged after discussion by MDT to HIM according to the actual situation in clinical practice.
2) As for the elderly or poor performance status, if obstructive jaundice time lasts long, combined with significantly abnormal liver function, or with fever and cholangitis and other manifestations of infection, preoperative biliary drainage treatment is recommended.
3) For patients with obstructive jaundice scheduled for neoadjuvant therapy before surgery, biliary drainage is recommended first.

(2) How to select a reasonable and effective way to reduce yellow

1) Patients scheduled for biliary drainage are recommended to undergo placement of a nasobiliary duct or stent under ERCP, or external drainage with percutaneous transhepatic cholangial drainage (PTCD). It is advocated to perform jaundice reduction by internal drainage as far as possible, which is helpful to improve the preoperative digestion and nutritional status of the disease.
2) Obstructive jaundice patients concurrently with upper gastrointestinal stenosis, obstruction and other obstructive jaundice which does not allow for stent implantation under ERCP, or patients

Table 4 Modified ryan scoring scheme

Description	Score
No residual cancer cells (complete response)	0
Residual single or small clusters of cancer cells (near complete response)	1
Residual cancer cells with evident tumor regression, but more than single or small clusters of cancer cells (partial response)	2
Extensive residual cancer cells without significant tumor regression (poor or no response)	3

with failed stent-based biliary drainage under ERCP and recurrent biliary tract infection are recommended to undergo the biliary drainage by PTCD, which has little effect on the operation area and has a definite drainage effect, but bile loss is not conducive to the improvement of preoperative digestive and nutritional status of patients.

4.2.3 Extent of lymph node dissection for radical resection of PC

(1) The extent of lymph node dissection in pancreaticoduodenectomy and combined distal pancreatectomy and splenectomy is divided into standard dissection and extended dissection, as shown in Table 5.

(2) Meta-analysis by Kotb A et al. included the clinical data of 724 patients with pancreatic head cancer who underwent pancreaticoduodenectomy in 5 previous randomized controlled clinical trials on the extent of lymph node dissection, and the results showed that the survival time of patients in the extended lymph node dissection group was not significantly prolonged compared with the standard lymph node dissection group [72]. The improvement of the prognosis of PC patients by extended lymph node dissection is still debated, and standard lymph node dissection is still recommended in addition to clinical studies.

(3) The correlation between the number of dissected lymph nodes, the ratio of positive lymph nodes to the number of total lymph nodes and prognosis is controversial, but a certain number of lymph nodes in the submitted samples is helpful for accurate N staging and guiding subsequent adjuvant therapy, and it is recommended to dissect more than 15 lymph nodes.

4.2.4 Radical antegrade modular pancreatosplenectomy (RAMPS) in pancreatic body and tail cancer

(1) RAMPS surgery is divided into anterior RAMPS and posterior RAMPS according to whether it is combined with left adrenalectomy or not.

(2) Meta-analysis by Zhou Q et al. included the previous data of 285 patients in 5 retrospective clinical trials comparing RAMPS with standard radical resection of pancreatic body and tail cancer. The results showed that there was no significant difference in postoperative complications between the two groups. RAMPS had advantages in terms of R0 resection rate, lymph node dissection and 1-year survival rate, but there was no significant difference in postoperative recurrence between the two groups [73].

(3) The effect of RAMPS surgery on the long-term survival of patients with pancreatic body and tail cancer remains to be confirmed by clinical studies, but it has become increasingly widely used in recent years because of its theoretical rationality, operational feasibility, and perioperative safety.

4.2.5 Combined vascular resection

(1) For PC with only superior mesenteric vein-portal vein involvement and resectable reconstruction, if R0 resection can be achieved, pancreaticoduodenectomy combined with superior mesenteric vein and/or portal vein resection is performed, the prognosis of patients was not significantly different from that of patients who underwent standard surgery without venous invasion and was significantly better than that of patients who underwent palliative surgery alone [74, 75].

(2) At present, the depth of venous invasion is not considered to affect the prognosis of patients undergoing venous resection and reconstruction, but further clinical study and demonstration are needed [76].

(3) Currently, there is no high-grade evidence to support combined arterial resection and reconstruction in radical resection of PC [77–80].

(4) If safe celiac trunk resection is feasible during radical resection of pancreatic body and tail cancer, and

Table 5 Extent of lymph node dissection in radical resection of PC

Surgical method	Dissection range	Lymph node dissection
Pancreaticoduodenectomy	Standard dissection	5, 6, 8a, 12b, 12c, 13a, 13b, 14a, 14b, 17a, 17b
	Extended dissection	Above range + 8p, 9, 12a, 12p, 14c, 14d, 16a2, 16b1
Combined distal pancreatectomy and splenectomy	Standard dissection	10, 11p, 11d, 18
	Extended dissection	Above range + 8a, 8p, 9, 14a, 14b, 14c, 14d, 16a2, 16b1

R0 resection is expected to be achieved, surgical resection is optional after discussion and evaluation by MDT to HIM.

(5) Because the surgical complications and mortality of PC with arterial resection are higher than those without arterial resection, and the radicality is limited, the choice of surgery should be more cautious than that with venous resection, and it is not recommended to combine superior mesenteric artery resection and reconstruction.

4.2.6 Laparoscopic and robotic surgery

(1) The safety of laparoscopic pancreaticoduodenectomy (LPD) continues to increase, but as a complex, high-risk procedure, a longer learning curve and professional training need to be emphasized. A prospective multicenter randomized controlled clinical study conducted by Chinese scholars evaluated the safety of LPD. The results showed that for the surgeons who completed the learning curve and had mature technology, the hospital stay in the LPD group was significantly longer than that in the open surgery group. There was no significant difference in the incidence rate of serious complications and the mortality within 90 days after operation between the two groups [81, 82].

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(2) The "minimally invasive" advantages of LPD compared with open surgery have been demonstrated, but the "oncological" beneficial effect still needs further validation. Clinical studies or experienced pancreatic surgeons performing these procedures at large specialized centers are recommended.

(3) Laparoscopic distal pancreatectomy (LDP) has obvious minimally invasive advantages and is widely used in China and abroad, but its "oncological" benefit still needs to be confirmed by high-level evidence.

(4) Compared with laparoscopic surgery, robotic surgery seems to have certain advantages in the conversion rate, without significant difference in other aspects [83].

(5) The implementation of laparoscopic and robotic surgery for PC with significant extrapancreatic invasion is controversial and needs further summary.

4.2.7 Standardized testing and margin status assessment of surgical specimens for PC

(1) Under the premise of ensuring the integrity of the specimen, it is advocated that the standardized detection of pancreaticoduodenectomy specimens should be completed by the cooperation of surgeons and pathologists, and each resection margin of the specimen should be marked and described, respectively, in order to objectively and accurately reflect the status of the resection margin. If resection of superior mesenteric vein and (or) portal vein is combined, the venous involvement should be reported separately, with details shown in Table 6.

Table 6 PC Surgical margin description and identification of depth of venous invasion

Margin description	Depth of infiltration
Anterior (ventral) pancreatic resection margin	Venous wall adventitial involvement
Posterior (dorsal) pancreatic resection margin	
Incisal margin of superior mesenteric vein groove of pancreas	
Incisal margin of superior mesenteric artery of pancreas	Involvement of the venous wall but not the intima
Broken end of pancreas	
Proximal incisal margin of stomach	
Distal jejunal incisal margin	
Incisal margin of bile duct	Involves the full thickness of the vein wall

(2) In the previous literature, the presence or absence of tumor cells on the resection margin surface was used as a criterion to determine R0 or R1 resection, and based on this criterion, there was no significant difference in the prognosis between patients with R0 and R1 resection [84].
(3) At present, the presence or absence of tumor invasion within 1 mm from the resection margin is mostly used as the standard for judging R0 or R1 resection, that is, R1 resection is performed if there is tumor cell invasion in the tissue 1 mm from the resection margin; R0 resection is performed if there is no tumor cell invasion. Using "1 mm" as the judgment principle, there is a significant difference in the prognosis between patients with R0 and R1 resection.
(4) The purpose of surgery is to achieve R0 resection, but due to the anatomical characteristics of the pancreas and the biological behavior of the tumor, it is difficult to avoid R1 resection as the surgical result, but it can still improve the prognosis of patients.
(5) Palliative resection, specifically R2 resection, has yet to be assessed for its role in improving prognosis. It has been reported in the literature that R2 resection does not improve prognosis and quality of life compared with palliative short-circuit surgery alone and should be avoided.

4.3 Section 3 Chemotherapy

4.3.1 Chemotherapy principle

(1) Chemotherapy is a systemic therapy that can be used for all stages of PC, including postoperative adjuvant chemotherapy, neoadjuvant chemotherapy for resectable and borderline resectable PC, first-line and subsequent chemotherapy for locally advanced, distant metastasis and recurrent PC [85, 86].
(2) MDT to HIM discussion should be performed before chemotherapy, including patient performance status, tumor staging, etc., to develop a reasonable treatment goal.
(3) Treatment goals should be discussed with the patient prior to initiation of chemotherapy and participation in the clinical trial should be encouraged.
(4) Patients receiving chemotherapy require close follow-up.

4.3.2 Commonly used chemotherapeutic drugs and chemotherapy regimens

Commonly used chemotherapeutic drugs for PC include: fluoropyrimidines (5-FU, capecitabine, tegafur), gemcitabine, platinum (urea, oxaliplatin), irinotecan (irinotecan, liposomal irinotecan), and albumin-bound paclitaxel, etc.

Commonly used chemotherapy regimens for PC are mainly divided into four major categories, as follows:

(1) Gemcitabine-based chemotherapy regimens:

① Gemcitabine
② Gemcitabine + albumin-bound paclitaxel
③ Gemcitabine + dexamethasone

(2) Fluoropyrimidine-based chemotherapy regimens:

① 5-FU + leucovorin
② Capecitabine
③ Tegafur
④ 5-FU + folinic acid + oxaliplatin (OFF)
⑤ FOLFOX
⑥ Capecitabine + oxaliplatin (CapeOx)
⑦ 5-FU + folinic acid + irinotecan (FOLFIRI)
⑧ 5-FU + leucovorin + liposomal irinotecan
⑨ FOLFIRINOX and modified FOLFIRINOX (mFOLFIRINOX)

(3) Gemcitabine plus fluoropyrimidine chemotherapy regimen:

① Gemcitabine + capecitabine
② Gemcitabine + tegafur

(4) Other chemotherapy regimens:

① PEXG (gemcitabine + capecitabine + cisplatin + epirubicin)
② Sequential chemotherapy

4.3.3 Application of chemotherapy

(1) Adjuvant chemotherapy: Adjuvant chemotherapy has a definite effect on PC after operation, and it can prevent or delay tumor recurrence and metastasis and improve postoperative survival rate. Postoperative adjuvant chemotherapy should be actively recommended. For patients who do not receive neoadjuvant chemotherapy and have good postoperative physical recovery, adjuvant chemotherapy should be performed as far as possible within 8 weeks. Recent studies have shown that appropriate delay of postoperative adjuvant chemotherapy to 12 weeks does not affect the prognosis. For those who have received neoadjuvant chemotherapy, adjuvant regimens should be selected based on their

response to neoadjuvant therapy and other clinical considerations.

(2) Neoadjuvant chemotherapy for resectable and borderline resectable PC: The understanding of the value of neoadjuvant therapy is gradually developing, and medical technology is developing towards expanding the extent of resection, but whether neoadjuvant therapy can improve the cure rate still needs to be confirmed by clinical study results. The purpose of neoadjuvant chemotherapy is to screen out those who can benefit from radical surgery and increase the R0 resection rate,reduce the rate of lymph node metastasis and ultimately improve patient survival and can sometimes be used in combination with radiotherapy.Chemotherapy regimens with high ORR are generally preferred based on performance status, such as FOLFIRINOX/mFOLFIRINOX (ECOG score 0 to 1) or gemcitabine plus albumin-bound paclitaxel (ECOG score 0 to 2).

(3) First-line and later-line chemotherapy for locally advanced, distant metastatic and recurrent PC: the main purpose is to prolong survival and improve quality of life. Some patients can also meet the criteria for surgical resection after systemic chemotherapy, with or without radiotherapy.

4.4 Section 4 Radiotherapy

4.4.1 Principles of radiotherapy

(1) PC has high radiation resistance to X-rays and cannot tolerate high-dose irradiation to its adjacent hollow organs; therefore, whether to perform radiotherapy for PC needs to be determined after MDT to HIM integration assessment.

(2) Radiation therapy is preferentially used in combination with chemotherapy:

1) Gemcitabine or fluoropyrimidines are commonly used as sensitizers during radiotherapy, also known as concurrent chemoradiotherapy [87].
2) Two to four courses of induction chemotherapy are strongly recommended before radiotherapy to inhibit potential metastases; it can serve as a means of screening patients, and patients with high malignancy and distant metastases have been excluded to avoid unnecessary radiotherapy [88, 89].

(3) Radiotherapy for PC is commonly used in six clinical situations:

1) Adjuvant radiotherapy
2) Neoadjuvant radiotherapy for resectable and borderline resectable PC
3) Local progression
4) Locally recurrent PC
5) Palliative radiotherapy
6) Intraoperative radiotherapy (IORT)

4.4.2 Common radiotherapy regimens

(1) Radiotherapy (RT)
(2) Chemoradiation (CRT)
(3) 3-D conformal radiation therapy
(4) Intensity-modulated radiation therapy (IMRT)
(5) Stereotactic body radiation therapy (SBRT) [90, 91]
(6) Proton heavy ion

4.4.3 Radiotherapy applications

(1) Adjuvant radiotherapy: The application of postoperative adjuvant radiotherapy is still controversial. Although there is no high-grade evidence to support it, the results of multiple retrospective large case-control studies have shown a survival benefit of postoperative radiotherapy in patients with high-risk factors such as R1 resection, lymph node positivity, or one of lymphovascular invasion. The 2019 STRAO guidelines recommend that: for some patients with PC after surgical resection (clinical features include positive lymph nodes and resection margins, regardless of tumor localization in the pancreas), conventional fractionated radiotherapy combined with chemotherapy is conditionally recommended. The American Radiation Therapy Oncology Group (RTOG) recommends that the extent of irradiation include the tumor bed, pancreaticojejunostomy stoma, and adjacent lymph node drainage areas (celiac trunk, superior mesenteric artery, portal vein, and around the abdominal aorta). However, in recent years, a number of studies based on the site of postoperative local recurrence suggest narrowing the irradiated target area, only irradiating the high-risk recurrent area around the celiac trunk and the initial segment of the superior mesenteric artery, and avoiding irradiating the choledochojejunostomy stoma and pancreaticojejunostomy stoma. The total dose of radiotherapy is 45 ~ 46 Gy, and the fractionated dose is 1.8 ~ 2.0 Gy/fraction, with the doses potentially increased at the high-risk recurrence sites. For PC patients who receive adjuvant therapy after resection, chemoradiotherapy is recommended after 4 to 6 months of systemic chemotherapy.

(2) Neoadjuvant chemoradiotherapy for resectable and borderline resectable PC: The aim is to increase the R0 resection rate and benefit survival, and neoadjuvant radiotherapy is recommended following induction chemotherapy. In the phase III PREOPANC study, 246 patients with resectable or borderline resectable PC were included, of whom 119 had received neoadjuvant chemoradiotherapy combined with gemcitabine preoperatively and 127 patients received surgery directly, and all patients were given adjuvant gemcitabine postoperatively. Compared with direct surgery, the R0 resection rate was significantly higher in patients treated with neoadjuvant chemoradiotherapy (71.0% vs 40.0%, P < 0.01); the results of resectability subgroup analysis showed that neoadjuvant chemoradiotherapy + surgery did not prolong the median OS compared with direct surgery (14.6 months vs 15.6 months, P = 0.830); however, neoadjuvant chemoradiotherapy prolonged the median OS of borderline resectable tumor subgroup (17.6 months vs 13.2 months, P = 0.029) [89]. There is no standard regimen for radiotherapy in neoadjuvant chemoradiation, and the usual total dose is 45 ~ 54 Gy, 1.8 ~ 2.0 Gy/fraction, irradiated five times a week. A total dose of 36 Gy, 2.4 Gy/fraction, 5 times a week irradiation can also be used.

(3) Simultaneous chemoradiotherapy for locally advanced PC: It is strongly recommended to be performed after 3-6 months of induction chemotherapy. Generally, it is recommended to irradiate only clinically visible tumors. When SBRT is used, non-uniform expansion can be performed according to the extent of visible tumors in the imaging to form the planning target area, which may obtain better local control effect. Radiation dose: conventional fractionated radiotherapy, total dose 45 ~ 54 Gy, 1.8 ~ 2.0 Gy/fraction, 5 fractions per week. If the tumor is far away from the digestive tract, the total dose of radiotherapy can be correspondingly increased under the premise of not exceeding the tolerated dose of the digestive tract. If the tumor does not invade the digestive tract, or is greater than 1 cm from the digestive tract, SBRT techniques can be used, and the recommended fractionation dose is 30 ~ 45 Gy/3 fractions, or 25 ~ 45 Gy/5 fractions.

(4) Chemoradiotherapy for local tumor and/or regional lymph node recurrence after surgery: For patients who have not received radiotherapy, concurrent chemoradiotherapy is recommended after chemotherapy. The radiation target area and dose are the same as "concurrent chemoradiotherapy for locally advanced PC".

(5) Palliative radiotherapy: For selective partial metastatic PC, palliative radiotherapy is recommended for primary or selected metastatic lesions to control symptoms. ① Lower back pain: Radiotherapy is performed on the primary lesion at a radiotherapy dose of 25 ~ 36 Gy and a fractionated dose of 2.4 ~ 5.0 Gy/fraction. ② Radiotherapy is performed for metastatic lesions (such as bone metastases) at a total dose of 30 Gy/10 fractions, or SBRT 8.0 Gy irradiation, or fractionated SBRT.

(6) Intraoperative radiotherapy: refined as a single high-dose irradiation given under direct vision during surgery to the tumor bed, lymphatic drainage area, or residual tumor, or unresectable tumor after resection of the tumor during surgery Because it is in the visual field under direct vision, it can protect the surrounding normal tissues while allowing the tumor to be irradiated with large doses, thereby improving the local control rate of the tumor. Intraoperative radiotherapy has not yet been confirmed by large-scale clinical studies to improve PC survival, and this aspect of the study should be clinically studied in conditional hospitals [92].

4.5 Section 5 Targeting and immunotherapy

4.5.1 Targeted therapy

(1) Erlotinib: It is an EGFR tyrosine kinase inhibitor. As early as 2007, erlotinib, as the first targeted therapy for PC, in combination with gemcitabine has been recommended as first-line treatment for locally advanced and PC with distant metastasis, and subsequent studies suggest that erlotinib may be more effective in KRAS wild-type patients [93]. However, due to the non-high overall efficacy of erlotinib and the negative results of subsequent adjuvant clinical studies, erlotinib is not widely used in the clinical application of PC [94, 95].

(2) Other subsequent targeted therapy studies: After erlotinib, there are many clinical studies of targeted therapy, such as anti-angiogenic therapy, but the results are negative [96].

(3) Olaparib: In the POLO study in 2019, the PARP inhibitor olaparib was utilized in the maintenance treatment of PC with BRCA1/2 gene mutation and distant metastasis after progression without first-line platinum-based chemotherapy, and the progression free survival (PFS) was prolonged from 3.8 months to 7.4 months, truly opening a new era of PC-targeted therapy [97].

(4) Studies in pan-tumor have confirmed that, for PC with locally advanced or distant metastasis with

NTRK gene fusion,larotrectinib or entrectinib can be selected for treatment.

(5) MD Anderson Cancer Center in the United States conducted a clinical study called "Know Your Tumor (KYT)" to see whether genetic variants that are more common in other tumors such as HER2 amplification, ROS1 fusion, and BRAF-V600E mutation respond to the treatment of PC. The results showed that among patients with treatable gene mutation, compared with those who did not receive matched therapy, the survival of patients who received matched therapy was significantly longer, and the risk of death decreased by 52%; compared with patients without pathogenic mutations, patients who received matched therapy also had a significantly longer survival time and a 66% reduction in the risk of death, which confirmed the prospect of targeted therapy for PC [98].

(6) There are also more clinical trials of targeted therapeutics to move the treatment of PARP inhibitors forward [99, 100].

4.5.2 Immunotherapy

(1) PD-1 monoclonal antibody immunotherapy is an option for locally advanced or PC with distant metastasis characterized by high microsatellite instability (MSI-H), mismatch repair deficiency (dMMR), or high mutational load (TMB) molecules.

(2) Currently, there is no evidence that the use of immune checkpoint inhibitors, CTLA-4/PD-1/PD-L1 antibodies, benefits PCs without the above molecular features.

(3) In general, PC is still an immune cold tumor, and the tumor microenvironment is in an immunosuppressive state. How to turn immune cold tumors into hot tumors is a hot topic in PC immunotherapy in recent years. Clinical studies to improve the efficacy of immunotherapy through treatments such as chemotherapy, radiotherapy, and nanotome are ongoing.

4.5.3 Gene detection

(1) PC has four major driver mutant genes, mainly Kras, followed by TP53, SMAD4 and CDKN2A, and unfortunately there is no clinically applicable targeted therapy for these four major mutant genes. In addition, there are some genetic variants with mutation frequency, but they are associated with PC occurrence and therapeutic efficacy. With the successful application of PARP inhibitors, homologous recombination defect-related gene mutations have drawn more and more clinical attention.

(2) For any diagnosed PC, it is recommended to use comprehensive genealogical germline mutation testing for hereditary tumors.

(3) For patients who test positive for pathogenic mutations or have a clear family history, in-depth genetic analysis assessment is recommended (such as detailed investigation of family history of the disease, etc.).

(4) For treated PC patients with locally advanced or distant metastasis, it is recommended to carry out somatic gene profiling based on tumor tissue samples; for patients with unavailable tissue samples, ctDNA detection in peripheral blood is feasible.

(5) Patients with locally advanced or distant metastatic PC should be tested for MSI/MMR/TMB.

(6) The International Agency for Research on Cancer/American College of Medical Genetics and Genomics and the Evidence-based Network for the Interpretation of Germline Mutation Alletes classify genetic variants into five grades according to the degree of risk: pathogenic (grade 5, likelihood of disease > 0.99); possible pathogenicity (grade 4, pathogenicity possibility 0.95 ~ 0.99); unknown significance (grade 3, pathogenicity possibility 0.05 ~ 0.949); possible benign (grade 2, pathogenicity possibility 0.001 ~ 0.049); benign (grade 1, pathogenicity possibility < 0.001).

4.6 Section 6 Other treatments

4.6.1 Nutritional support therapy

(1) PC can lead to malnutrition or even cachexia through a variety of different factors, including: ① tumor-related systemic factors, such as changes in adipose tissue physiology, systemic inflammation, etc.; ② related factors of pancreatic function changes, such as pancreatic exocrine insufficiency, pancreatic endocrine function changes, etc.; ③ related factors of close interaction between the pancreas and other digestive organs, such as gastrointestinal obstruction, bacterial disorders, etc. [101].

(2) Nutritional support should be used throughout PC treatment.

(3) Nutritional support is preferentially recommended for patients with poor performance status.

(4) Appropriate nutritional support should also be selected during PC system therapy [102, 103].

4.6.2 Pain therapy

(1) Pain is the main symptom at presentation in the vast majority of PC. The main causes of pain due to PC include direct infiltration of peripheral nerves by PC, inflammation of pancreatic peripheral nerves, increased capsular tension due to PC, and pancreatic duct due to pancreatic head tumors increased pressure [104].
(2) Pain treatment is based on analgesic drug therapy, which often requires multidisciplinary cooperation and multimodal combination such as surgery, intervention, nerve block, chemotherapy, radiotherapy, and psychotherapy. Choosing the best analgesic treatment first requires identifying the cause of pain [105].
(3) Analgesic drug management is particularly important in PC pain treatment and needs to be carried out according to the three-ladder method for cancer pain treatment after discussion from MDT to HIM.
(4) Opioids are the cornerstone of PC pain treatment, and plexotomy, EUS-guided or CT-guided plexus ablation, or absolute alcohol injection are recommended if opioids do not control pain or lead to intolerable adverse effects [106, 107].
(5) The goals that pain management should achieve: adequate analgesia, optimal survival, minimal adverse effects, and avoidance of abnormal medication.

4.6.3 Palliative treatment

(1) The aim of palliative treatment of PC is mainly to relieve bile duct and digestive tract obstruction, create opportunities for other treatments, improve quality of life, and prolong survival time

(1) The aim of palliative treatment of PC is mainly to relieve bile duct and digestive tract obstruction, create opportunities for other treatments, improve quality of life, and prolong survival time
(2) For unresectable PC complicated with obstructive jaundice, endoscopic biliary stenting is preferred. For failed stent retention or inability to perform endoscopic therapy for other reasons, PTCD is an option [108].
(3) Palliative choledochojejunostomy is only indicated for patients who cannot achieve biliary drainage via endoscopy or PTCD due to technical difficulties or contraindications.
(4) There is no consensus on the treatment of pancreatic head cancer complicated with gastrointestinal obstruction, and open or laparoscopic gastrojejunostomy and endoscopic gastrointestinal stent implantation are feasible options. For advanced PC complicated with gastrointestinal obstruction, gastrojejunostomy is recommended when the survival time of patients is expected to be long and the general condition is good; endoscopic stent implantation is feasible for patients with short survival time or poor general condition who cannot tolerate surgery.
(5) For PC patients without gastrointestinal obstruction who are found to have unresectable tumor during surgical exploration, there is no evidence that prophylactic gastrojejunostomy is beneficial to patients and may increase complications and delay systemic treatment, so prophylactic gastrojejunostomy is not recommended.
(6) Palliative choledochojejunostomy or double bypass surgery (choledochojejunostomy + gastrojejunostomy) is feasible for patients who are found to have tumors that cannot be radically resected during surgical exploration or who undergo gastrojejunostomy due to gastrointestinal obstruction if they also have biliary obstruction.

4.6.4 Nanotome

(1) Also known as irreversible electroporation, this technique was approved by the US FDA for clinical use in 2011, mainly for locally advanced PC [109, 110].
(2) Advantages of nanotome: short ablation time, preservation of important tissues such as nerves and blood vessels in the treatment area, no effect of heat island effect, thorough treatment, clear treatment boundary, and synergistic effect with immunotherapy.
(3) It was approved by China FDA for the treatment of PC and liver cancer in 2015, and the expert consensus on the use of nanotome for PC was also released in China in 2021 [111].

4.6.5 Traditional Chinese medicine (TCM) treatment

(1) Traditional Chinese medicine treatment is one of the components of PC integrated treatment; compared with Western medicine treatment, TCM does not focus on directly killing cancer cells, but on "strengthening the body resistance" for conditioning [112].
(2) TCM can be used in the consolidation stage after radical resection of early PC, which helps to promote the recovery of body function; it is used in the combination or consolidation or maintenance stage

after palliative surgery or chemoradiotherapy for intermediate and advanced stage PC, which helps to enhance the body's anti-cancer ability, reduce the toxicity of chemoradiotherapy or targeted drug therapy, improve symptoms, and improve the quality of life.

(3) In terms of treatment ideas, western medicine places more emphasis on precision treatment, and although it will achieve efficacy, the corresponding side effects cannot be ignored. TCM emphasizes more macroscopic and holistic concepts, attaches more importance to the whole of "people", and has a vague targeted ratio relative to Western medicine.

(4) TCM can find the causes of PC based on syndrome differentiation at each stage, examine the causes and treat them, and give the corresponding rational prescriptions, which vary from person to person. Integrating the treatment ideas of TCM and Western medicine can not only make up for the lack of microscopic understanding of PC in TCM, but also play its strengths and truly achieve the purpose of treating and saving lives.

(5) There is little evidence for the treatment of PC with traditional Chinese medicine, and clinical multicenter trial studies need to be actively carried out.

4.6.6 Interventional therapy

(1) Intra-arterial infusion chemoembolization: The effect of intra-arterial infusion chemotherapy in the treatment of PC is controversial. It is recommended in clinical operation that: ① If the tumor feeding artery is seen, perfusion chemotherapy should be performed after superselection. ② If the tumor feeding artery is not seen, it is recommended to perform perfusion and chemotherapy on pancreatic head and neck tumors through the gastroduodenal artery, and to perform perfusion and chemotherapy on pancreatic body and tail tumors through the celiac artery, superior mesenteric artery, or splenic artery according to the extent of the tumor and angiography. ③ For patients complicated with liver metastasis who receive proper perfusion and chemotherapy via proper hepatic artery, if angiography shows that intrahepatic metastasis has abundant blood supply, the procedure can be combined with embolization therapy.

(2) Other relevant interventions for advanced PC: refer to the "Guidelines for Clinical Operations of Interventional Therapy for Advanced PC"(Trial) (Fifth Edition).

4.6.7 Stromal ablation therapy

A great difference between PC and other malignancies is the abundance of stroma. Therefore, stromal ablation therapy has been a research focus for PC, including hyaluronidase inhibitors, hedgehog signaling blockers, matrix metalloproteinase inhibitors and tumor-associated fibroblast removal agents.

The phase III clinical study that has drawn the most attention in recent years is the study on polyethylene glycol hyaluronidase α, but unfortunately, even if hyaluronic acid is highly expressed, the efficacy of polyethylene glycol hyaluronidase α combined with gemcitabine + albumin-bound paclitaxel in PC with distant metastasis is not superior to chemotherapy alone [113].

At present, more studies suggest that the PC stroma is a complex and dynamic structure, there may be multiple subtypes, different subtypes may have different sensitivity to treatment and prognosis, tumor-associated fibroblasts play an important role in it, and a number of clinical studies for tumor-associated fibroblast therapy are on-going [114].

4.7 Section 7 Integration decision of PC treatment with distant metastasis

4.7.1 Treatment principle

(1) PC with distant metastasis is a systemic advanced tumor that is unresectable, and treatment is based on systemic therapy, such as chemotherapy.

(2) Performance status assessment is required before treatment: it is classified as excellent performance status (ECOG score 0 to 1), good performance status (ECOG score 0 to 2), and poor performance status (ECOG score > 2).

(3) Pathological diagnosis should be obtained before treatment: it is recommended to perform aspiration biopsy for metastatic lesions. If metastases are unavailable, endoscopic ultrasonography is recommended to perform puncture of the primary tumor.

(4) The overall efficacy of PC with distant metastasis is poor and active participation in clinical studies is recommended.

(5) For PC with distant metastasis, it is recommended to carry out genetic testing and MSI/MMR/TMB testing, which is helpful to guide the optimal drug treatment regimen and participate in relevant clinical studies.

4.7.2 Commonly used first-line regimens in patients with good performance status

First-line regimens are commonly used in patients with good performance status: combination regimens are mostly selected.

(1) FOLFIRINOX/mFOLFIRINOX (excellent performance status) [115].
(2) Gemcitabine + albumin-bound paclitaxel (excellent performance status) [116].
(3) For those with BRCA1/2 or PALB2 gene mutations, platinum-based chemotherapy regimens are recommended, e.g.FOLFIRINOX/mFOLFIRINOX or gemcitabine + cisplatin [117].
(4) Gemcitabine + tegafur [118].
(5) Gemcitabine + capecitabine [119].
(6) Gemcitabine + erlotinib.
(7) 5-FU + leucovorin + oxaliplatin (OFF) [120].
(8) Capecitabine + Oxaliplatin (CapeOx) [121].

4.7.3 First-line treatment options are commonly used in patients with poor performance status

First-line treatment is commonly used in patients with poor performance status: single agent regimens are used in most cases.

(1) Nutritional support therapy.
(2) Gemcitabine [122].
(3) Tegafur.
(4) Capecitabine.
(5) If NTRK fusion is detected by genetic testing, larotrectinib or entrectinib can be selected for treatment; if it has molecular characteristics of high microsatellite instability (MSI-H), mismatch repair deficiency (dMMR) or high mutation load (TMB), PD-1 monoclonal antibody immunotherapy can be selected.
(6) Palliative radiotherapy: Radiotherapy is generally not recommended for PC with distant metastasis, unless palliative radiotherapy is required for pain relief or the primary lesion is the only site of disease progression.

4.7.4 Maintenance treatment

(1) There is no progression after 4 to 6 months of first-line chemotherapy, and maintenance therapy may be considered if performance status is good.
(2) At present, the recommended maintenance treatment regimen is only for those with germline BRCA1/2 gene mutation, the tumor does not progress after ≥ 16 weeks of platinum-based chemotherapy, and maintenance treatment with olaparib is recommended.
(3) In addition, other maintenance regimens tried in clinical practice are: ① FOLFIRINOX regimen followed by FOLFIRI, FOLFOX or capecitabine maintenance therapy. ② After gemcitabine combined with albumin-bound paclitaxel, change the interval of original regimen or maintain treatment with gemcitabine alone. ③ Tegafur combined with albumin-bound paclitaxel followed by Tegafur maintenance therapy. ④ Time to maintenance therapy is defined as persistence until disease progression or intolerable adverse effects.

4.7.5 Second-line and multi-line treatment

(1) For patients who progress after first-line treatment, second-line treatment is selected based on first-line chemotherapy regimen, performance status, complications and adverse reactions [123].
(2) Generally, for first-line use of gemcitabine-based chemotherapy, fluoropyrimidine-based chemotherapy regimen is selected for second-line treatment; for first-line use of fluoropyrimidine-based chemotherapy, gemcitabine-based chemotherapy regimen is selected for second-line treatment [124, 125].
(3) If performance status is better, second-line chemotherapy is more effective than supportive care alone [126].
(4) After second-line treatment, whether to continue the later-line treatment is controversial. There is no clear protocol. It is recommended to participate in the clinical study.

4.7.6 Surgical treatment

(1) No cytoreductive surgery is recommended for PC with distant metastasis.
(2) For some PC with distant oligometastases (single organ metastasis, number of metastases ≤ 3), after a period of systemic chemotherapy, if the tumor shrinks significantly and the surgery is expected to achieve R0 resection, it is recommended to participate in the clinical study of surgical resection [127, 128].
(3) For distant metastatic PC with biliary or gastrointestinal obstruction, internal drainage stent placement is preferred to relieve obstruction. Palliative bypass surgery may be considered in cases of failed stent placement with fair performance status.

4.8 Section 8 Integrated decision making for treatment of locally advanced PC

4.8.1 Treatment principle

(1) Locally advanced PC belongs to locally advanced tumors, which are unresectable. Surgical resection is not recommended for initial treatment, while non-surgical treatment is used as the first-line treatment [129–131].
(2) Performance status assessment is required before treatment: it is classified as excellent performance status (ECOG score 0 to 1), good performance status (ECOG score 0 to 2), and poor performance status (ECOG score > 2).
(3) Pathological confirmation is required before treatment: endoscopic ultrasonography-guided aspiration biopsy is recommended.
(4) The overall efficacy of locally advanced PC is poor and active participation in clinical studies is recommended [132, 133].
(5) Genetic testing and MSI/MMR/TMB testing are recommended for locally advanced PC to help guide treatment regimens and participate in screening for clinical studies.

4.8.2 First-line treatment options are commonly used in patients with good performance status

First-line treatment is commonly used in patients with good performance status: it is basically the same as PC with distant metastasis.

4.8.3 First-line treatment options are commonly used in patients with poor performance status

First-line treatment is commonly used in patients with poor performance status: it is basically the same as PC with distant metastasis.

4.8.4 Second-line and multi-line treatment

(1) After 3 to 6 months of systemic chemotherapy, the disease is stable and radiotherapy can be considered.
(2) For patients who progress after first-line treatment, second-line treatment is selected based on first-line chemotherapy regimen, performance status, complications and adverse reactions.
(3) For first-line use of gemcitabine-based chemotherapy, fluoropyrimidine-based chemotherapy regimen is selected for second-line treatment; for first-line use of fluoropyrimidine-based chemotherapy, gemcitabine-based chemotherapy regimen is selected for second-line treatment.
(4) If performance status is better, second-line chemotherapy is more effective than supportive care alone.
(5) After second-line treatment, whether to continue the later-line treatment is controversial. There is no clear protocol. It is recommended to participate in the clinical study.

4.8.5 Surgical treatment

(1) In recent years, studies have found that more than 20% of patients with locally advanced PC can obtain the chance of surgical resection through transformation after first-line treatment, and the prognosis is obvious better than chemotherapy or chemoradiotherapy alone [134].
(2) Although there is a lack of randomized controlled studies on surgical resection of locally advanced PC, attempts at translational therapy are still recommended for locally advanced patients with better general condition.
(3) At present, there is no optimal translational therapy for locally advanced PC. FOLFIRI-NOX/mFOLFIRINOX or gemcitabine + albumin-bound paclitaxel regimen with higher objective response rate (ORR) is generally selected. Combination with radiotherapy may increase the R0 resection rate and pathological response rate, but the effect on survival is controversial, and radiotherapy may increase the difficulty of surgery [135].
(4) The following conditions might occur after translational therapy: ① CA19-9 level decreases by 50% [136]; ② clinical improvement (i.e., improvement in performance status, pain, weight/nutritional status); ③ partial response (PR) or stable disease (SD) by imaging assessment; ④ PET-CT metabolic value decreases by more than 30%, and surgical resection can be considered after MDT to HIM discussion, with laparoscopic exploration as the first choice.

4.9 Section 9 Integrated decision making for resectable PC treatment

4.9.1 Radical resection surgery

(1) Preoperative assessment: including high risk factors, performance status, nutritional assessment, jaundice, etc.
(2) Radical resection is recommended for patients without high risk factors and surgical contraindications.

4.9.2 Application of neoadjuvant therapy in resectable PC

(1) Neoadjuvant therapy can increase the R0 resection rate of resectable PC and decrease the lymph node positive rate, but there is no consensus on the effect of improving overall survival. In addition, the overall response rate of PC to neoadjuvant therapy is currently high, and some patients may miss the chance of radical resection due to failure of neoadjuvant therapy; moreover, puncture before neoadjuvant therapy to confirm the pathological diagnosis and perform biliary drainage is an invasive procedure, so caution should be exercised when deciding to routinely carry out neoadjuvant therapy for all resectable PC.
(2) Neoadjuvant therapy is recommended for resectable PC with the following high risk factors: ① very high serum CA19:9 level; ② large tumor; ③ large regional lymph nodes; ④ significantly reduced body weight; ⑤ extreme pain.
(3) However, there is still a lack of uniform quantitative criteria for the above high risk factors.
(4) The 2016 expert consensus of Chinese Study Group For Pancreatic Cancer (CSPAC) recommends neoadjuvant therapy for preoperative resectable PC with "CEA +, CA125 +, CA19 ≥ 1000 U/ml" [137, 138].
(5) Liquid biopsy markers and PET that can reflect the metabolic burden of tumors show potential clinical applications in assessing factors [139, 140].

4.9.3 Common regimens for neoadjuvant therapy

(1) FOLFIRINOX/mFOLFIRINOX (excellent performance status), or gemcitabine plus albumin-bound paclitaxel (good performance status) [141, 142].

(1) FOLFIRINOX/mFOLFIRINOX (excellent performance status), or gemcitabine plus albumin-bound paclitaxel (good performance status) [141, 142].
(2) For patients with BRCA1/2 or PALB2 mutations, platinum-based chemotherapy regimens are recommended, such as FOLFIRI,NOX/mFOLFIRINOX or gemcitabine + cisplatin.
(3) Gemcitabine + tegafur [143].
(4) PEXG.
(5) Gemcitabine [144].
(6) Neoadjuvant radiotherapy: There have been no high-quality clinical studies on the value of radiotherapy in the neoadjuvant treatment of resectable PC, and induction chemotherapy is usually recommended before radiotherapy if neoadjuvant radiotherapy is to be performed [145, 146].

4.9.4 Evaluation after neoadjuvant therapy

(1) Neoadjuvant therapy for resectable PC generally lasts 2 to 4 cycles, and surgical exploration is performed 4 to 8 times after the last neoadjuvant therapy [147, 148].
(2) Changes in serum tumor markers and imaging studies should be closely monitored during neoadjuvant therapy, and prompt surgical intervention may be considered in patients with poor response to neoadjuvant therapy. If disease progression is not amenable to surgical resection, treatment principles for unresectable PC should be followed.

4.9.5 Adjuvant therapy in resectable PC

(1) If there are no contraindications for PC after radical resection surgery, adjuvant therapy is recommended.
(2) However, it has also been reported in the literature that if the tumor is less than 1 cm, that is, patients with T1a and T1b, adjuvant therapy does not seem to bring a survival benefit.
(3) For patients with good postoperative recovery of performance status, the initial time of adjuvant therapy should be controlled at 8 weeks after operation as far as possible; for patients with poor recovery of performance status, the time of adjuvant therapy can be extended to 12 weeks after operation, but sufficient course of treatment (6 ~ 8 courses) should be completed as far as possible.

4.9.6 Common regimens for adjuvant therapy

(1) mFOLFIRINOX (excellent performance status) [149].
(2) Gemcitabine + capecitabine [150].
(3) Gemcitabine [151, 152].
(4) Tegafur [153].
(5) 5-FU + leucovorin [154].
(6) The results of APACT study (international multicenter phase III randomized controlled clinical trial) showed that gemcitabine + albumin-bound paclitaxel regimen could prolong the OS of patients after radical resection of PC. The subgroup analysis results showed that T3 stage with lymph node metastasis was more significant and could be used as an alternative to adjuvant chemotherapy [155].
(7) For resectable PC who receive sequential radical surgery after neoadjuvant chemotherapy and have no evidence of recurrence or metastasis after surgery, it is recommended to determine whether to continue adjuvant chemotherapy after evalua-

tion by MDT to HIM and develop a chemotherapy regimen with reference to the effect of neoadjuvant chemotherapy or the conclusion of clinical studies [156].

(8) Adjuvant radiotherapy: The application of postoperative adjuvant radiotherapy is still controversial. For postoperative residual tumor or patients with lymph node metastasis, postoperative adjuvant radiotherapy is recommended [157]. Although there is no high-grade evidence to support it, the results of multiple retrospective large case-control studies have shown that postoperative radiotherapy can achieve a survival benefit in patients with high risk factors such as R1 resection, lymph node positivity, or one of lymphovascular invasion.

4.10 Section 10 Integrated decision making for borderline resectable PC treatment

4.10.1 Surgical treatment

(1) Direct surgery in patients with borderline resectable PC may result in positive margins (R1/2) and affect prognosis. The study results confirmed that neoadjuvant therapy can improve the R0 resection rate of tumors, reduce the rate of lymph node metastasis, reduce neurological and vascular invasion, and prolong the disease-free survival time of patients; in addition, neoadjuvant therapy is helpful to assess the biological behavior of tumors, and if the disease progresses during neoadjuvant therapy, it indicates that the biological behavior of tumors is poor and it is difficult to benefit from surgery. Therefore, neoadjuvant therapy is recommended first for patients with borderline resectable PC with better performance status.

(2) For patients with sequential surgical resection after neoadjuvant therapy, if radical R0 eradication can be achieved with combined venous resection, the survival benefit of patients is comparable to that of resectable patients. The improvement of patient prognosis by combined arterial resection is debated, and prospective large-sample data evaluation is needed.

(3) Palliative R2 resection is not recommended for these patients, except in life-saving situations such as hemostasis.

(4) There is a lack of data from large clinical studies to support treatment strategies for borderline resectable PC, and patients are encouraged to participate in clinical studies.

4.10.2 Common regimens for neoadjuvant therapy

Commonly used regimens for neoadjuvant therapy: chemotherapy regimens are basically the same as resectable pancreatic cancer [158].

(1) FOLFIRINOX/mFOLFIRINOX (excellent performance status) [159, 160].

(2) Gemcitabine + albumin-bound paclitaxel (excellent performance status) [161].

(3) For patients with BRCA1/2 or PALB2 mutations, platinum-based chemotherapy regimens, such as FOL-FIRINOX/mFOLFIRINOX or gemcitabine + chemotherapy, are recommended.

(4) Gemcitabine + tegafur [162, 163].

(5) Neoadjuvant radiotherapy: There have been no high-quality clinical study to demonstrate value of radiotherapy in the neoadjuvant treatment of patients with borderline resectable pancreatic cancer, and induction chemotherapy is often recommended before radiotherapy if neoadjuvant radiotherapy is prepared [164].

4.10.3 Evaluation after neoadjuvant therapy

(1) At present, there is no clear standard for the cycle of neoadjuvant therapy, and 2 to 4 cycles of neoadjuvant therapy are generally recommended. The efficacy is assessed by MDT to HIM based on changes in tumor size, tumor markers, clinical manifestations, and performance status before and after treatment. In patients without disease progression after neoadjuvant therapy, surgical exploration should be performed even if no tumor downstaging is found on imaging studies. Laparoscopic exploration is preferred, and radical resection should be pursued after exclusion of distant metastasis.

(2) Patients with progressive disease after neoadjuvant therapy or whose tumor is still unresectable continue chemotherapy according to the principle of chemotherapy for unresectable PC.

4.10.4 Adjuvant therapy

(1) Borderline resectable PC should be treated preoperatively with neoadjuvant therapy, and the addition of adjuvant chemotherapy should be decided after postoperative evaluation by MDT to HIM [165].

(2) The adjuvant chemotherapy regimen should be established by referring to the effect of neoadjuvant chemotherapy or the conclusion of clinical study, and the commonly used neoadjuvant chemother-

apy regimen should be selected according to the patient's physical status.

5 Chapter V Rehabilitation

5.1 Section 1 Recovery after surgery

After radical resection of PC, attention needs to be paid in many aspects such as diet, rest, and activity in order to obtain a good postoperative rehabilitation effect. After PC surgery, especially after pancreaticoduodenectomy or total pancreatectomy, the diet needs to gradually transition from liquid and semi-liquid to soft food and normal diet, and trypsin capsules can be taken as supplementary treatment for a period of time according to digestion and absorption to help the digestion of foods, especially fatty foods; at the same time, attention should also be paid to closely monitor blood glucose and control the stability of blood glucose [166].

In daily life, PC patients should relax their mood, maintain a good mentality, develop regular routines, avoid staying up late and excessive fatigue, and at the same time carry out appropriate exercise to enhance their own resistance.

Good postoperative rehabilitation can help patients better tolerate postoperative adjuvant therapy, while improving immunity and reducing the chance of postoperative recurrence.

5.2 Section 2 Postoperative follow-up

Postoperative follow-up is to detect local recurrence or distant metastasis as early as possible by regular application of serum tumor markers and imaging examination, and timely treat it [167].

In the first year after operation, it is recommended to perform follow-up once every 3 months; in the second to third year, it is recommended to perform follow-up once every 3 to 6 months; and then perform follow-up once every 6 months for at least 5 years. The recurrence rate after radical resection of PC is close to 80%, and even patients with a survival time of more than 5 years experience recurrence [168].

In addition to medical history and signs, follow-up items include hematology, blood chemistry, serum tumor markers, chest CT, contrast-enhanced CT of the whole abdomen (including pelvis) and other examinations. In patients with suspected liver metastasis or bone metastasis, contrast-enhanced MRI and bone scan of the liver are additionally performed, and PET is performed for further examination if necessary [169]. In recent years, emphasis has been gradually placed upon the value of liquid biopsy markers in detecting recurrence and metastasis earlier in follow-up after radical resection [170, 171].

In addition to monitoring tumor recurrence during follow-up, special attention should be paid to other surgery-related long-term complications such as pancreatic endocrine and exocrine function and nutritional status to maximize the quality of life of patients.

5.3 Section 3 Treatment of postoperative recurrence

Nearly 80% of patients will experience recurrence after radical resection of PC, with most recurrences occurring within 2 years of surgery. Recurrences include: local recurrence and distant metastasis. Local recurrence is defined as recurrence of the remnant pancreas or surgical bed, such as recurrence along the celiac trunk, in the superior mesenteric artery, aorta, or soft tissue around the pancreaticojejunostomy site. Distant metastasis is divided into three types: simple liver metastasis, simple lung metastasis, and other types of metastasis [172].

Tanaka et al. performed a meta-analysis on 89 studies with 17,313 patients receiving radical resection of PC and found that initial recurrence was local recurrence in 20.8% of patients, with a mean OS of 19.8 months; initial recurrence was simple liver metastasis in 26.5% of patients, with a mean OS of 15.0 months; initial recurrence was simple lung metastasis in 11.4% of patients, with a mean OS of 30.4 months; and initial recurrence was peritoneal dissemination in 13.5% of patients, with a mean OS of 14.1 months [173].

Recurrence occurs after radical resection of PC and often has a poor prognosis, but a considerable number of patients still maintain a good performance status and can receive further treatment. Recurrence treatment should be discussed by MDT to HIM to develop individualized integrated treatment plan, and the "Expert Consensus on Early Diagnosis and Early Treatment of PC of Chinese Society of Oncology" can be referenced.

5.3.1 Local recurrence (without distant metastasis)

(1) As for the treatment, please refer to "locally advanced pancreatic cancer".
(2) Chemotherapy or chemotherapy combined with chemoradiation is recommended.
(3) Surgery may be considered in patients with isolated locally recurrent disease for whom R0 resection is technically expected to be feasible [174].
(4) It is necessary to identify new PC, and if the tumor is resectable and the physical condition can tolerate surgery, it can be treated as the initial surgery [175].

5.3.2 Distant metastasis (with or without local recurrence)

(1) As for treatment, please refer to the treatment modality for "PC with distant metastasis".

(1) As for treatment, please refer to the treatment modality for "PC with distant metastasis".

(2) Early postoperative metastasis (generally defined as within 2 years)

1) Systemic therapy, such as chemotherapy, should be the mainstay.
2) Systemic therapy regimen is based on patient performance status, disease progression and related symptoms, cumulative toxicity of previous chemotherapy, initial chemotherapy effect, and interval between previous chemotherapy.

(3) Late postoperative metastasis (generally defined as after 2 years)

1) Multiple metastases: systemic therapy should be the mainstay, such as chemotherapy. Adjuvant local therapy is considered after systemic treatment turns out good.
2) Isolated metastasis: If the patient's general condition permits, local treatment may be considered, such as surgery, radiotherapy, ablation therapy, etc., supplemented by systemic therapy before or after local treatment. For patients with no prior radiotherapy who can receive systemic chemotherapy, concurrent chemoradiation in the recurrent area may be considered. Usually the prognosis of simple lung metastasis of PC is better than that of metastasis at other sites [176]. For patients with solitary or localized lung oligometastasis, better response to chemotherapy, and tumor recurrence expected to obtain R0 resection, surgical resection or local treatment can be considered [177].

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