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Practice Guidelines

Chinese Society of Clinical Oncology (CSCO): Clinical guidelines for the diagnosis and treatment of pancreatic cancer

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ABSTRACT

Pancreatic cancer is one of the leading causes of cancer-related mortality in both developed and developing countries. The incidence of pancreatic cancer in China accounts for about a quater of the global incidence, and the epidemiological characteristics and therapeutic strategies differ due to social, economic, cultural, environmental, and public health factors. Non-domestic guidelines do not reflect the clinicopathologic characteristics and treatment patterns of Chinese patients. Thus, in 2018, the Chinese Society of Clinical Oncology (CSCO) organized a panel of senior experts from all sub-specialties within the field of pancreatic oncology to compile the Chinese guidelines for the diagnosis and treatment of pancreatic cancer. The guidelines were made based on both the Western and Eastern clinical evidence and updated every one or two years. The experts made consensus judgments and classified evidence-based recommendations into various grades according to the regional differences, the accessibility of diagnostic and treatment resources, and health economic indexes in China. Here we present the latest version of the guidelines, which covers the diagnosis, treatment, and follow-up of pancreatic cancer. The guidelines might standardize the diagnosis and treatment of pancreatic cancer in China and will encourage oncologists to design and conduct more clinical trials about pancreatic cancer.

1. Background

Pancreatic cancer is one of the malignancies with the poorest prognosis (estimated 5-year survival rate less than 10%).[1,2] Pancreatic cancer is predicted to become the second leading cause of cancer mortality in the United States in the next 20-30 years.[3,4] The latest global data for 2020 released by International Agency for Research on Cancer (IARC) showed an estimated 495,000 new cases and 466,000 deaths worldwide.[5] In China, the estimated numbers of new cases and deaths were 125,000 and 122,000, respectively.[5] China accounted for more than about 1/4 of the global incidence and mortality of pancreatic cancer.[5–8] It is important to standardize the diagnosis and treatment of pancreatic cancer in China.

Two guidelines for pancreatic cancer are frequently used in clinical practice, including National Comprehensive Cancer Network (NCCN) Guidelines and the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines. NCCN Guidelines are more authoritative, but some regimens are not available in China, such as the liposomal irinotecan, which is the category 1 recommendation as the second-line therapy in NCCN for metastatic disease,[9–11] whereas ESMO guidelines are not frequently renewed, and the recommendations are relatively general.[12,13] Furthermore, some evidence-based medicine from Asia is adopted in neither guidelines. In the JASPAC-01 and GEST trials, which were phase III trials conducted in Asia, S-1 was recommended as adjuvant chemotherapy and first-line therapy. However, it was not recommended in the NCCN or ESMO Guidelines.[14,15] Furthermore, the dosages of some drugs used in China are usually lower than those used in Western countries. Thus, the clinical practice guidelines where the diagnosis and treatment of pancreatic cancer are tailored for Chinese are also needed in China.

The Chinese Society of Clinical Oncology (CSCO) organized senior pancreatic cancer experts to develop and update the national guidelines for diagnosing and treating pancreatic cancer via considering the clinical evidence, the accessibility to diagnosis and treatment in different regions, and the ethnic differences. The detailed search of pancreatic cancer literature and the categories of evidence and grades of recommendation of the CSCO clinical practice guidelines for common malignant tumors are summarized in Supplementary materials (Supplementary Tables 1 and 2). The guidelines were presented as different grades of recommendation based on expert consensus degrees. All the evidence cited is of category level 2A unless otherwise indicated and the best management of any patient with cancer is in a clinical trial. In 2018, the first edition of the Clinical Guidelines for the Diagnosis and Treatment of Pancreatic Cancer was published and it was updated in 2019 and 2020. In the latest edition, the guidelines included the importance of multidisciplinary treatment (MDT), diagnostic methods, treatment strategies, and follow-up visits for pancreatic cancer. The guidelines provide Chinese doctors and researchers with comprehensive and scientific guidelines for diagnosing and treating pancreatic cancer in China.

2. Multidisciplinary consultation of pancreatic cancer

Multidisciplinary consultation is extremely important to pancreatic cancer and is recommended to be carried out in highly qualified centers.[16] The main content of a multidisciplinary consultation model is shown in Table 1. Experts from multiple disciplines are recommended to comprehensively assess patients' performance status (PS), tumor stages, invasion, and prognosis based on their clinical symptoms, laboratory results, imaging, pathology, molecular detection, and other available data. Considering the domestic and international consensus, guidelines, or evidence base in combination with existing treatment measures, experts then should formulate a scientific and reasonable treatment plan for each patient by actively combining surgery, chemotherapy, radiotherapy, and other comprehensive treatment to achieve disease control, extend survival, and improve quality of life.

3. Diagnosis of pancreatic cancer

3.1. General guidelines for the diagnosis of pancreatic cancer

Most pancreatic cancer patients have an insidious onset, which may manifest as upper abdominal discomfort, dull pain, indigestion or diarrhea, sudden onset of type 2 diabetes, and other unspecific gastrointestinal symptoms. With the progress of the disease, positive signs may appear, including jaundice, weight loss, hepatomegaly, gallbladder enlargement, upper abdominal masses, ascites, and so on. If a patient presents clinical manifestations associated with pancreatic cancer or a pancreatic mass is discovered in the patient, the PS, physical examination, laboratory tests, imaging examination, pathological diagnosis, and multidisciplinary consultation should be considered (Fig. 1 and Table 2).

PS is particularly important to patients with pancreatic cancer, as it determines the overall treatment strategies. A comprehensive PS assessment is part of the diagnostic process and should contain four aspects. Good PS is defined as ECOG 0-2, good pain control shown by the Numerical Rating System for Pain (NRS) 0-3, good biliary drainage, and stable weight with adequate nutritional intake.

Table 1
Multidisciplinary consultation of pancreatic cancer.

Content	Grade I recommendation	Grade II recommendation	Grade III recommendation
Departments recommended to participate in multidisciplinary consultation	1. Surgery: pancreatic surgery (or hepatobiliary pancreatic surgery, or general surgery)[a] 2. Medical oncology 3. Radiation oncology[b] 4. Radiology 5. Pathology	1. Interventional therapy 2. Gastroenterology 3. Nutrition 4. Pain management 5. Endocrinology	1. Nuclear medicine 2. Ultrasonography 3. Molecular laboratory
Professional qualification reqired for panel experts	Senior Attending Doctor or above	Associate Chief Doctor or above	
Content of consultation	1. Borderline resectable disease 2. Locally advanced disease 3. Tumors in the pancreas head and neck with obstructive jaundice 4. Tumors with a contraindication to surgical resection	1. Neoadjuvant, adjuvant or conversion therapy 2. Synchronous resection of pancreatic cancer with oligometastasis 3. Multiple metastases, nutritional disorders, or pain 4. Postoperative elevated tumor markers	Other
Daily routines	Fixed discipline, experts, frequency (once every 1-2 weeks is recommended), place and equipment	Others	

[a] It is recommended that the surgery of pancreatic cancer should be performed in a high-volume pancreatic cancer clinical center (minimum of 20 pancreatic cancer surgeries annually).
[b] The radiotherapy of pancreatic cancer is complex, and a resonable increase in the radiation dose could improve the local control rate and survival.[11,12] It is recommended that radiotherapy for pancreatic cancer should be performed in a radiotherapy center with high-quality imaging diagnosis technology, along with image-guided intensity-modulated radiation therapy systems or systems to deliver stereotactic body radiotherapy.

3.1.1. Imaging examinations for pancreatic cancer

Imaging examinations are primarily used for the initial diagnosis, preoperative staging, and follow-up of pancreatic cancer. There are several medical imaging techniques and methods which can assist in the diagnosis of pancreatic cancer, including B-scan ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP), positron emission tomography (PET)-CT and endoscopic ultrasound (EUS) (Table 3). It has been reported that 70 to 85% of pancreatic cancer patients determined by CT imaging to have resectable tumors are able to undergo resection.[23] PET-CT is not recommended as a routine examination method for the diagnosis of pancreatic cancer, but is applicable for patients with suspected distant metastases that high-quality CT/MRI does not able to capture. In a retrospective study, the use of PET/CT following a standard CT protocol showed increased sensitivity for detection of metastatic disease when compared with the standard CT protocol

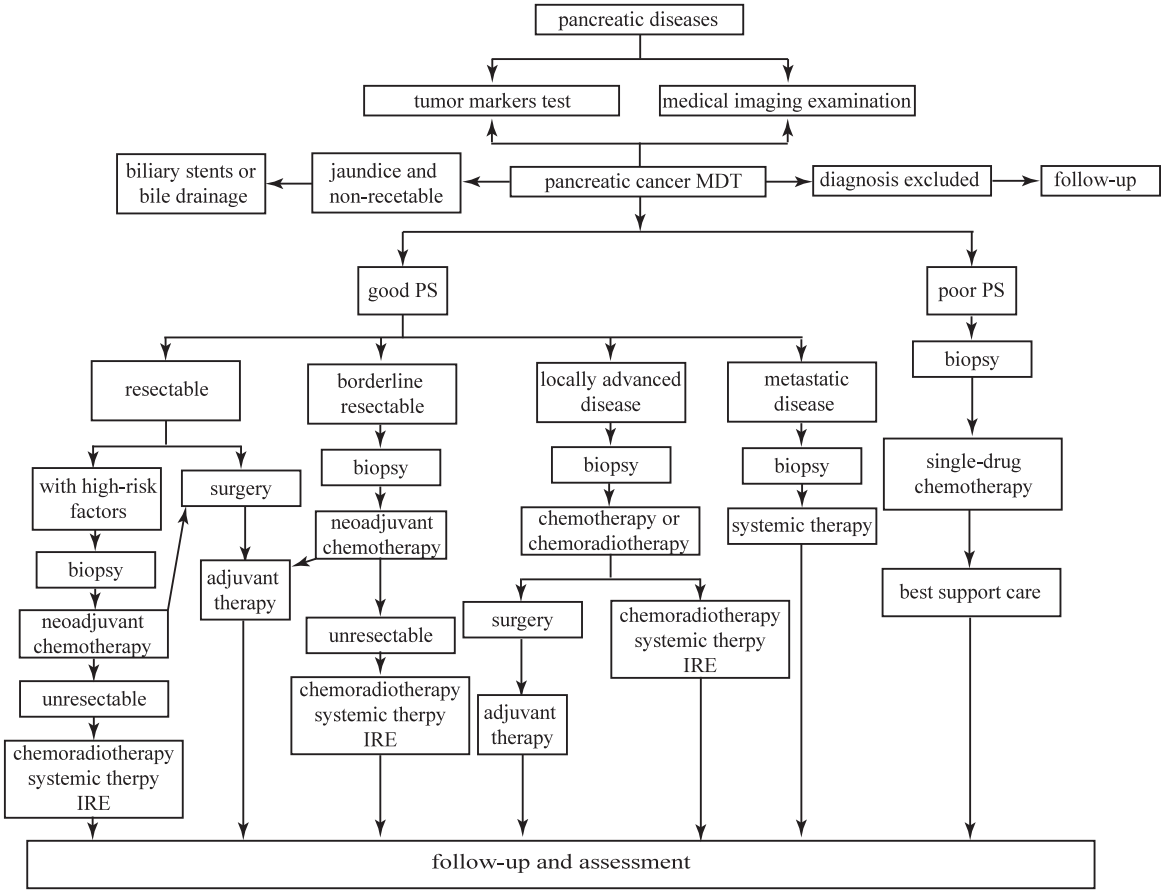

Fig. 1. Flow chart of the diagnosis and treatment of pancreatic cancer. IRE, rreversible electroporation; MDT, multidisciplinary treatment; PS, performance status.

Table 2
General guidelines for the diagnosis of pancreatic cancer.

Clinical issues	Grade I recommendations	Grade II recommendations	Grade III recommendations
Presence of clinical manifestations associated with pancreatic cancer or discovery of a pancreatic mass	1. Performance status 2. Physical examination 3. Laboratory tests[a] 4. Imaging examination 5. Pathological diagnosis 6. Multidisciplinary consultation	1. Family history[b]	None

[a] The tumor markers relevant to the diagnosis of pancreatic cancer include the glycan antigen carbohydrate antigen 19-9 (CA19-9),[17] the carcinoembryonic antigen (CEA)[18] and CA125,[19] CA50,[20] CA242,[21] and CA724.[22] Among them, CA19-9 is the most sensitive marker reported to date for pancreatic cancer,[17] but elevated CA19-9 does not necessarily indicate pancreatic cancer or disease progression. CA19-9 might be elevated when biliary tract is infected or obstructed and can be found in other benign or malignant tumors. Furthermore, changes in liver function should be evaluated, especially if the tumor is obstructing the bile ducts.
[b] A detailed family history should be collected for young patients diagnosed with pancreatic cancer. Germline testing is recommended for any confirmed pancreatic cancer patients.

Table 3
Imaging examinations for pancreatic cancer.

Clinical issues	Grade I recommendations	Grade II recommendations	Grade III recommendations
Initial diagnosis	Pancreatic contrast-enhanced CT or MRI scan	Abdominal B-scan ultrasound and ERCP	PET-CT and EUS
Clinical staging	Chest, abdominal, and pelvic contrast-enhanced CT or MRI scan	PET-CT	None
Follow-up evaluation	1. Chest, abdominal, and pelvic contrast-enhanced CT or MRI scan 2. Bone ECT scan for patients with bone-related symptoms 3. Cerebral contrast-enhanced MRI scan for patients with brain metastasis-related symptoms	None	PET-CT

Abbreviations: CT, computed tomography; ECT, emission computed tomography; EUS, endoscopic ultrasound; MRI, magnetic resonance imaging; PET-CT, positron emission tomography computed tomography.

or PET/CT alone.[24] EUS-guided fine-needle aspiration, laparoscopic exploration, or laparotomy may be considered for patients whose initial diagnosis or staging is not achieved by imaging and multidisciplinary discussions.

3.1.2. Pathological diagnosis of pancreatic cancer

Histopathological and cytological examinations are the gold standard for diagnosing pancreatic cancer. If histopathological or cytological evidence cannot be obtained, the initial clinical diagnosis can be performed by multidisciplinary consultation, according to medical history, clinical manifestations, and laboratory and imaging examinations. If multidisciplinary consultation cannot lead to a precise diagnosis, medical observation and surveillance are recommended. Methods of obtaining histopathological and/or cytological specimens include surgical resection, biopsy (Imaging-guided or EUS-guided puncture is recommended, and biopsy of the metastatic site is preferred), and cytology (cytopathological information is obtained by pancreatic ductal cell swabbing, pancreatic fluid collection, and abdominal cavity fluid analysis). This recommendation is only applicable to pancreatic cancer originating from the pancreatic ductal epithelium, according to the World Health Organization (WHO) histological classification of pancreatic cancer (Supplementary Table 3).

Clinicians should collaborate with pathologists to establish standard operating procedures to increase the positive rate. The recommended process is as follows: all specimens should be fixed promptly (preferably within 30 min after leaving the body) using fresh 3.7% neutral buffered formaldehyde fixative, the volume of which should be 10 times that of the tissue, for 8–48 h. The specimen should be submitted for analysis in its entirety, and the surgeon should segment the lymph nodes. For patients planning to undergo radical resection (R0), it is unnecessary to obtain a preoperative pathological confirmation if the diagnostic evidence (clinical, laboratory, and imaging data) is adequate. R0 is defined as tumors with a >1 mm resection margin according to European standards. Pathological TNM staging (pTNM) is based on the 8th edition of the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (Supplementary Tables 4 and 5). The prefixes c, p, m, r, and y before TNM stand for clinical, histopathological, multiple primary tumors, recurrent tumors, and post-therapy, respectively.

All patients are suggested to undergo germline genetic testing using a gene panel that detects hereditary tumor syndromes. When standard treatments fail, next-generation sequencing (NGS) testing is recommended to identify potential therapeutic targets and associated targeted drugs that may provide benefit to patients based on the "basket" approach. Targeted testing for treatment-associated somatic mutations includes, but is not limited to, gene fusions (*ALK, NRG1,*[25] *NTRK,*[26] and *ROS1*) and gene mutations (*BRAF, BRCA1/2,*[27] *HER2, KRAS,*[28] *PALB2*[29]). The tumor mutation burden (TMB) is suggested to be evaluated to assess the potential benefits of immunotherapy.[30] Immunohistochemistry (IHC), polymerase chain reaction (PCR), and NGS all could be used (Table 4).

4. Comprehensive treatment of pancreatic cancer

4.1. Treatment of resectable pancreatic cancer

The criteria for defining resectable pancreatic cancer include no distant metastasis, no arterial tumor contact (celiac axis, superior mesenteric artery or common hepatic artery), no tumor contact with the superior mesenteric and portal veins, and ≤180° contact without vein contour irregularity. For patients with good PS, R0 resection is the purpose of the surgery.[36] Detailed definitions of the surgical margins are in the Appendix (Supplementary Table 6). Multidisciplinary consultation is needed to fully evaluate the possibility of R0 resection, and clarify the presence of metastasis and comorbidities (baseline assessment).

Although most studies suggest that there may be a better chance of R0 resection with neoadjuvant therapy, phase III randomized trials are needed to address this issue, and neoadjuvant chemotherapy is not routinely recommended for patients with resectable disease.[37] It may be considered for patients with high-risk factors, including highly elevated CA19-9, large primary tumors, large regional lymph nodes, excessive weight loss, and extreme pain. Moreover, a definitive cytological or pathological diagnosis of the tumor is required before neoadjuvant ther-

Table 4
Pathological diagnosis of pancreatic cancer.

Sample type	Grade I recommendations	Grade II recommendations	Grade III recommendations
Surgical resection	1. Histological subtype 2. Pathological grade 3. Tumor size 4. Extent of tumor invasion 5. Vascular and lymphatic invasion 6. Neural invasion 7. Surgical marginal status 8. Condition and number of lymph nodes 9. *BRCA1/2, PALB2* and *NTRK* gene detection[a] 10. MMR and MSI detection[b]	1. Presence of pancreatitis 2. Presence of pancreatic intraepithelial neoplasia (PanIN) 3. Germline and treatment-related somatic mutant genetic test	1. Expression of PD-1 and PD-L1 2. NGS test to evaluate TMB and potentially beneficial therapeutic effect
Biopsy specimen	1. Identify the nature and histological type of the lesion: cancerous/non-cancerous,benign/malignant 2. Histological subtype 3. Tumor differentiation 4. Immunohistochemical markers 5. *BRCA1/2, PALB2* and *NTRK* gene detection[a] 6. MMR and MSI detection[b]	Germline and treatment related somatic mutant genetic test	1. Expression of PD-1 and PD-L1 2. NGS testing to evaluate TMB and potentially beneficial therapeutic effect
Cytology	1. Nature and histological type of the lesion: cancerous/non-cancerous; benign/malignant 2. Histological subtype 3. Immunohistochemical markers 4. *BRCA1/2, PALB2*, and *NTRK* gene detection[a] 5. MMR and MSI detection[b]	Germline and treatment-related somatic mutant genetic test	1. Expression of PD-1 and PD-L1 2. NGS testing to evaluate TMB and potentially beneficial therapeutic targets

[a] Platinum-based chemotherapy should be considered in the presence of *BRCA1/2* or *PALB2* mutations.[31,32] Patients with *NTRK* fusions may benefit from targeted NTRK therapy.[33,34] Patients with deficient mismatch repair (dMMR)/microsatellite instability-high (MSI-H) may benefit from PD-1 checkpoint inhibitors.[35]

[b] It is recommended that mismatch repair (MMR) should be tested by immunohistochemistry (IHC) to detect the expression of MLH1, MSH2, MSH6, and PMS2. DMMR is defined as loss of the expression of ≥ 1 MMR proteins, and mismatch repair-proficient (pMMR) is defined as intact MMR protein expression. For MSI, five microsatellite monitoring sites (BAT25, BAT26, D5S346, D2S123, and D17S250), recommended by the National Cancer Institute, should be tested. Microsatellite stable (MSS) was defined as all 5 sites stable. Low microsatellite instability (MSI-L) was defined as 1 site unstable; MSI-H was defined as ≥ 2 sites unstable. DMMR could cause MSI. Thus, dMMR and MSI-H are normally biologically identical.

Abbreviations: MMR, mismatch repair; MSI, microsatellite instability; NGS, next-generation sequencing; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; TMB, tumor mutation burden.

apy. Neoadjuvant chemoradiotherapy is only recommended in clinical trials.[38]

Results of a series of phase III randomized trials have shown that adjuvant therapy improves the outcomes of pancreatic cancer patients, yet this therapy is currently controversial.[39–44] It might improve the prognosis and reduce the local recurrence rate of patients with good PS with R1 resection.[43,44]

The poor PS is defined as patients who cannot tolerate or are not suitable for surgical resection due to medical reasons, their own wishes, or their advanced ages. For patients with poor PS, palliative chemotherapy could be considered after histopathological or cytological diagnosis. The regimens refer to the treatment of metastatic pancreatic cancer (Supplementary Table 9). Best supportive care, which includes nutritional support, biliary drainage, pain relief, treatment of tumor-associated thrombosis, and complications and side effects of surgery or radiotherapy, should be provided during the whole process of treatment. Radical radiotherapy is a grade III recommendation for poor PS patients. Radical radiotherapy is a therapeutic mode that uses precision radiotherapy technology to increase the dose and then implement radical treatment (Table 5). The intensity-modulated radiation therapy (IMRT) or stereotactic body radiation therapy (SBRT) techniques are recommended for irradiating the primary foci and metastatic lymph nodes at a dose pattern of 40-70 Gy divided into 5 to 20 times, without prophylactic irradiation in adjacent areas.[45]

4.1.1. Surgery for resectable pancreatic cancer

Surgical resection remains the only potentially curative therapy for pancreatic cancer. R0 resection confers longer disease-free survival (DFS) and overall survival.[46] The recommendations for surgical resection of different tumor locations are displayed in Table 6. Laparoscopic distal pancreatectomy for pancreatic cancer is technically safe and feasible, but the curative efficiency compared to laparotomy is still controversial. Both prospective and retrospective studies have shown that laparoscopic distal pancreatectomy has fewer complications and faster postoperative recovery than laparotomy. However, prospective randomized controlled trials (RCTs) are still required.[47,48] Expanded regional lymphadenectomy is not routinely recommended, as no sufficient evidence has proved its capability to improve patients' prognosis.[49,50]

4.1.2. Adjuvant chemotherapy for resectable pancreatic cancer

Adjuvant chemotherapy could prevent or delay recurrence and improve overall survival.[15,51–54] It is recommended that adjuvant

Table 5
Treatment of resectable pancreatic cancer.

PS	Grade I recommendations	Grade II recommendations	Grade III recommendations
Good PS	1. Radical resection 2. Adjuvant chemotherapy	1. Neoadjuvant chemotherapy 2. Adjuvant radiotherapy 3. Neoadjuvant chemoradiotherapy	None
Poor PS	1. Biopsy confirmation 2. Palliative chemotherapy 3. Best supportive care	Palliative radiotherapy	1. Radical radiotherapy 2. Interventional therapy

Abbreviation: PS, performance status.

Table 6
Surgery for resectable pancreatic cancer.

Tumor location	Grade I recommendations	Grade II recommendations	Grade III recommendations
Pancreatic head	Pancreatoduodenectomy (Whipple procedure)	None	Expanded regional lymphadenectomy
Pancreatic body or tail	Distal pancreatectomy and splenectomy	Laparoscopic distal pancreatectomy and splenectomy	Same as above
Whole pancreas or multiple foci in the pancreas	Total pancreatectomy	None	Same as above

Table 7
Adjuvant chemotherapy for resectable pancreatic cancer.

PS	Grade I recommendations	Grade II recommendations	Grade III recommendations
Good PS	1. Gemcitabine plus capecitabine (category 1A)[53] 2. mFOLFIRINOX (category 1A)[54] 3. Gemcitabine (category 1A)[51] 4. S-1 (category 1A)[15]	1. Gemcitabine-based chemotherapy 2. Clinical trials	None
Poor PS	1. Gemcitabine (category 1A)[51] 2. Fluorouracil-based chemotherapy (category 1A)[55]	1. Clinical trials 2. Observation	None

Abbreviation: PS, performance status.

Table 8
Adjuvant radiotherapy for resectable pancreatic cancer.

PS	Grade I recommendations	Grade II recommendations	Grade III recommendations
Good PS, R1	Clinical trials	1. Synchronous fluorouracil or gemcitabine chemoradiotherapy, followed by 5-fluorouracil or gemcitabine maintenance therapy (category 1B)[40,56] 2. Two cycles of gemcitabine chemotherapy, followed by synchronous gemcitabine-based chemoradiotherapy (category 2A)[42] 3. Synchronous gemcitabine chemoradiotherapy, followed by gemcitabine maintenance therapy (category 2B)[57]	None
Good PS, R0	Clinical trials	None	None

Abbreviation: PS, performance status.

chemotherapy should be initiated within 12 weeks after surgery. For patients with good PS, combination regimens should be considered. For patients with poor PS, single-agent chemotherapy and even observation are recommended (Table 7). The detailed chemotherapy regimens were provided in Appendix (Supplementary Table 7).

4.1.3. Adjuvant radiotherapy for resectable pancreatic cancer

Different results of adjuvant radiotherapy and adjuvant chemotherapy were found in Europe and the United States,[39–44] and no sufficient evidence has been found in China. RCTs are recommended. Adjuvant radiotherapy might improve the prognosis and reduce the local recurrence rate of patients with good PS with R1 resection.[43,44] If radiotherapy is considered due to a positive resection margin, chemotherapy should be administered before radiotherapy. The plan for adjuvant radiotherapy should be determined based on the results of a preoperative CT scan or the location of silver clips placed during surgery. The clinical target volume (CTV) should include the primary tumor and the high-risk lymphatic drainage regions. A dose increase is recommended for cases with positive resection margins. The detailed recommendations for radiotherapy are provided in Table 8.

4.2. Treatment of borderline resectable pancreatic cancer

The definition of borderline resectable pancreatic cancer (BRPC) is: tumor without distant metastasis; tumor invasion of the superior mesenteric venous-portal venous system with segmental stenosis, distortion, or occlusion, and allowing for safe and complete resection and reconstruction; gastroduodenal artery invasion up to the hepatic artery, without involvement of the celiac trunk; tumor abutment of the superior mesenteric artery not exceeding 180° of the circumference of the vessel wall. The treatment strategies of BRPC lack high-level evidence. Thus, clinical trials are preferred. Best supportive care should be provided throughout the treatment of pancreatic cancer and might be the best choice for patients with poor PS. Interventional therapy [placement of stents, percutaneous transhepatic cholangial drainage (PTCD), etc.] is recommended to relieve jaundice before neoadjuvant chemotherapy (Table 9).

Neoadjuvant chemotherapy and chemoradiotherapy for BRPC might increase the R0 resection rate and improve survival.[38,58,59] For patients with good PS, preoperative chemotherapy with combination regimens with a high objective response rate (ORR) is recommended (Supplementary Table 8).[38,60–63] Neoadjuvant chemotherapy is generally recommended as 2 to 4 cycles and can be adjusted based on short re-examination intervals. For neoadjuvant chemoradiotherapy, no standard regimens were recommended, and fluorouracil-based[64,65] or gemcitabine-based[38,66] regimens could be chosen.

If the tumor R0 resection can be achieved by combining with venous resection, the prognosis is comparable to that of patients without venous involvement. A meta-analysis which contained 26 studies showed that surgical resection combined with arterial resection might not improve the OS.[67] Patients who are still surgically unresectable or cannot tolerate surgery following neoadjuvant therapy could be treated with a first-line chemotherapy regimen for advanced pancreatic cancer. Following induction chemotherapy for 4 to 6 cycles, irreversible electroporation (IRE) is feasible for the patients who are unresectable.[68,69] Selective intra-arterial infusion could be considered for patients who cannot tolerate or are unwilling to receive systemic chemotherapy.

4.3. Treatment of locally advanced pancreatic cancer

The definition of locally advanced pancreatic cancer is: tumor without distant metastasis; tumor abutment of the superior mesenteric artery exceeding 180° of the circumference of the vessel wall; tumor abutment of the celiac trunk exceeding 180° of the circumference of the vessel wall; or tumor invading the jejunal branch of the superior mesenteric artery. Patients with locally advanced pancreatic cancer are recom-

Table 9
Treatment of borderline resectable pancreatic cancer.

PS	Grade I recommendations	Grade II recommendations	Grade III recommendations
Good PS, can tolerate surgery	1. Biopsy 2. Clinical trial 3. Best supportive care 4. Interventional therapy for jaundice 5. Neoadjuvant chemotherapy 6. Surgery	1. Palliative chemotherapy 2. Radical radiotherapy 3. Neoadjuvant chemoradiotherapy	1. Irreversible electroporation ablation following induction therapy 2. Radiotherapy 3. Interventional therapy
Poor PS, cannot tolerate surgery	1. Biopsy 2. Best supportive care 3. Interventional therapy for jaundice 4. Palliative chemotherapy	1. Palliative radiotherapy 2. Interventional therapy	Clinical trial

Abbreviation: PS, performance status.

Table 10
Treatment of locally advanced pancreatic cancer.

PS	Grade I recommendations	Grade II recommendations	Grade III recommendations
Good PS	1. Biopsy 2. Clinical trials 3. Palliative chemotherapy 4. Interventional therapy for jaundice	1. Conversion therapy 2. Synchronous chemoradiotherapy or subsequent chemoradiotherapy 3. Interventional therapy 4. Traditional Chinese medicine therapy	1. Surgical resection 2. Irreversible electroporation ablation[j] after induction therapy 3. Chemotherapy combined with tumor-treating fields therapy 4. Palliative radiotherapy
Poor PS	1. Biopsy 2. Interventional therapy for jaundice 3. Best supportive care	1. Clinical trials 2. Palliative chemotherapy 3. Palliative radiotherapy 4. Traditional Chinese medicine therapy	Interventional therapy

Abbreviation: PS, performance status.

Table 11
Treatment of metastatic pancreatic cancer.

PS	Grade I recommendations	Grade II recommendations	Grade III recommendations
Good PS	1. Biopsy 2. Interventional therapy for jaundice 3. First-line chemotherapy 4. Second-line chemotherapy	1. Clinical trials 2. Multi-line chemotherapy 3. Palliative radiotherapy 4. Maintenance therapy	1. Interventional therapy 2. Traditional Chinese medicine therapy 3. Chemotherapy combined with tumor-treating fields
Poor PS	1. Biopsy 2. Interventional therapy for jaundice 3. First-line chemotherapy 4. Best supportive care	1. Palliative radiotherapy 2. Traditional Chinese medicine therapy 3. Second-line chemotherapy	

Abbreviation: PS, performance status.

mended to participate in clinical trials. Palliative chemotherapy could be conducted according to therapies of the metastatic pancreatic cancer. Furthermore, traditional Chinese medicine could also be considered during the treatment.

For locally advanced pancreatic cancer patients who have undergone conversion therapy, surgical resection could be considered after MDT if the disease meets three criteria: the tumor curative effect evaluated as partial response (PR) or stable disease (reduced tumor size); > 50% decrease in the CA19-9 level and clinical improvement (i.e., improvement in PS, pain, weight/nutritional status); > 30% decrease in standard uptake value (SUV) on PET-CT. Recommendations of therapy regimens for locally advanced pancreatic cancer are summarized in Appendix (Supplementary Table 9). After 4-6 cycles of conversion chemotherapy, IRE can also be considered.[68,69]

For patients with good PS, concurrent chemoradiotherapy or subsequent chemoradiotherapy with a conventional radiation dosage can relieve symptoms and improve survival.[70–73] High-dose radiation can improve the local control rate and survival to a greater extent than conventional-dose radiation.[74] Hypofractionated IMRT or SBRT is only recommended to be used to irradiate the primary tumor and metastatic lymph nodes, excluding the high-risk lymphatic drainage regions (Table 10). Furthermore, in a phase II study, tumor treating fields plus gemcitabine and nab-paclitaxel prolonged the PFS and overall survival (OS, not reached) of locally advanced pancreatic cancer and metastatic pancreatic cancer. A randomized phase III study (PANOVA-3) is underway.[75]

For patients with poor PS, palliative radiation of the primary tumor or metastatic lesions could alleviate the obstruction and control pain to improve the quality of life; traditional Chinese medicine could also be considered.[76]

4.4. Treatment of metastatic pancreatic cancer

The principles and aim of the treatment of metastatic pancreatic cancer are as follows: firstly, chemotherapy-based comprehensive therapy is beneficial for alleviating symptoms, and improving survival and quality of life; and secondly, for patients with oligometastatic pancreatic cancer, chemotherapy-based systemic therapy combined with local treatment is more beneficial for reducing symptoms, enhancing local control and improving survival (Table 11).

First-line chemotherapy regimens (Table 12 and Supplementary Table 9) should be selected according to patients' PS. Combined regimens can be considered for patients with good PS. Patients with poor PS opt to receive single-agent chemotherapy or best supportive care (BSC). The overall therapeutic effect in metastatic pancreatic cancer is not satisfying. Thus patients are also recommended to participate in clinical trials. For patients with good PS, second-line chemotherapy is recommended (Table 13). No adequate evidence has shown that further lines treat-

Table 12
First-line therapy for metastatic pancreatic cancer.

PS	Grade I recommendations	Grade II recommendations	Grade III recommendations
Good PS	1. Gemcitabine plus albumin-bound paclitaxel (category 1A)[51] 2. FOLFIRINOX (category 1A)[79] 3. Gemcitabine (category 1A)[80] 4. S-1 (category 1A)[14] 5. Olaparib maintenance therapy should be considered for germline *BRCA1/2* mutations if no progression is observed after 16 weeks of previous platinum-based chemotherapy (category 1A)[27]	1. Gemcitabine plus S-1 (category 1B)[14] 2. Gemcitabine plus nimotuzumab (category 2A)[28] 3. Clinical trials	1. Gemcitabine plus erlotinib (category 1A)[81] 2. Gemcitabine plus capecitabine (category 1B)[82] 3. Others: Gemcitabine plus cisplatin; fixed-dose-rate gemcitabine, docetaxel, and capecitabine; fluorouracil plus oxaliplatin[83–85]
Poor PS	1. Gemcitabine (category 1A)[80] 2. S-1 single agent (category 1A)[14] 3. Best supportive care 4. Clinical trials		

Abbreviation: PS, performance status.

Table 13
Second-line therapy for metastatic pancreatic cancer.

PS	Grade I recommendations	Grade II recommendations	Grade III recommendations
Good PS	1. 5-fluorouracil /leucovorin plus liposomal irinotecan (category 1A)[11,86] 2. If first-line gemcitabine-based therapy is used, second-line therapy with 5-fluorouracil-based therapy should be considered 3. If first-line 5-fluorouracil-based therapy is used, second-line therapy with a gemcitabine-based regimen should be considered 4. For patients with recurrence disease, if the duration after adjuvant therapy to recurrence is more than 6 months, the regimens of adjuvant therapy can also be considered 5. Clinical trials	Previously not applied first-line therapy regimen used as second-line therapy	
Poor PS	1. Gemcitabine 2. Fluoropyrimidine-based therapy 3. Best supportive care		

Abbreviation: PS, performance status.

Table 14
Follow-up for pancreatic cancer.

Purpose	Grade I recommendations	Grade II recommendations	Grade III recommendations
Suspected pancreatic cancer patients (difficult to distinguish from chronic pancreatitis and pancreatic cysts, etc.)	1. Frequency: every 2 or 3 months until the reach of a clear diagnosis 2. Content: 1) Physical examination 2) Blood chemistry (including CA19-9, CEA, and CA125, etc.) 3) Contrast-enhanced CT or MRI scan	1. Frequency: more frequent than the Grade I recommendations 2. Content: chest and abdominal contrast-enhanced CT or MRI scan	Content: PET-CT[a]
Follow-up visits for patients with pancreatic cancer after surgery	1. Frequency: 1) Once every 3 months in the first year after surgery 2) Once every 3-6 months in the 2-3 years after surgery 3) Once every 6 months in the 3-5 years after surgery 2. Content: 1) Physical examination 2) Blood routine, blood chemistry, and coagulation tests 3) Blood tumor markers including CA19-9, CEA, CA125, etc. 4) Chest and abdominal contrast-enhanced CT or MRI scan 5) Bone ECT (every 6 months) 6) Head contrast-enhanced MRI scan (when patients have related symptoms)	1. Frequency: more frequent than the Grade I recommendations 2. Content: 1) Previously elevated tumor markers 2) Chest X-ray 3) Abdominal and pelvic ultrasound	Content: PET-CT[a]
Follow-up visits for patients with advanced pancreatic cancer	1. Frequency: once every 2-3 months 2. Content: 1) Physical examination 2) Blood routine, blood chemistry, and coagulation tests 3) Blood tumor markers including CA19-9, CEA, CA125, etc. 4) Chest and abdominal contrast-enhanced CT or MRI scan 5) Bone ECT (every 6 months) 6) Head contrast-enhanced MRI scan (when patients have related symptoms)	1. Frequency: more frequent than the Grade I recommendations 2. Content: 1) Elevated tumor markers 2) Chest X-ray 3) Abdominal and pelvic ultrasound	Content: PET-CT[a]

[a] PET-CT is recommended for patients with negative results from routine imaging but highly suspected recurrence, such as patients with continuously elevated CA19-9 levels. PET-CT is not recommended as a routine follow-up/surveillance method.
Abbreviations: CT, computed tomography; ECT, emission computed tomography; MRI, magnetic resonance imaging; PET-CT, positron emission tomography computed tomography.

ments after second-line chemotherapy improve survival, and no agents have been proven effective. However, previously unused first-line agents could be applied for the treatment of patients with good PS.

For patients with liver or lung metastasis, interventional therapy, including arterial chemoembolization and radiofrequency ablation, can be used for the metastatic and primary lesions when the tumor is well-controlled with systemic therapy. Palliative radiotherapy to relieve the obstruction, compression and pain, and enhance local control of the tumor can be carried out by irradiating the primary or metastatic sites.[77]

Many clinical trials have suggested that maintenance therapy after first-line chemotherapy can benefit patients. According to the POLO trial, for patients with germline mutations in *BRCA1/2*, maintenance therapy with olaparib after a first-line platinum regimen could significantly prolong the PFS (7.4 vs. 3.8 months; $P = 0.004$).[27] However, the maintenance therapy for patients without such mutation is still under phase II clinical trials and the regimens are mainly focused on S-1[63] or gemcitabine.[78] Phase III clinical trials majored in maintenance therapy are expected.

5. Follow-up for pancreatic cancer

The prognosis of pancreatic cancer is poor and there is no evidence that regular follow-up after initial therapy could improve the prognosis. The follow-up for pancreatic cancer is divided into three situations: suspected pancreatic cancer patients whose disease is difficult to be distinguished from chronic pancreatitis and pancreatic cysts; patients with pancreatic cancer after surgery; and patients with advanced pancreatic cancer. The detailed content of follow-up is shown in Table 14.

Declaration of competing interest

The authors declare that they have no conflict of interests.

Consent for publication

This paper was first published in Chinese by the Beijing: People's Medical Publishing House, entitled as the "Guidelines of Chinese Society of Clinical Oncology (CSCO): Pancreatic Cancer 2020" from the CSCO. Written informed consent has been obtained from CSCO for the authors to publish the translated version of the guideline in *Journal of the National Cancer Center*.

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Author contributions

W.W., H.Y., Q.K., F.L., L.J., L.J., X.Y., Z.T., Z.Y. and C.J. conducted the conception and design of the guidelines. C.J., J.F., L.Q., W.Z., D.H., Z.H., W.J., B.R., B.X., B.F., C.H., C.D., F.J., G.Y., G.J., H.H., H.Q., H.Y., L.C., L.F., L.D., L.J., L.X., L.W., P.M., S.L., S.W., T.M., W.F., W.H., X.P., Z.P., X.B., Z.Z., R.G., Z.T. and Z.J. wrote the manuscript. C.J., J.F., L.Q. and W.Z. assembled the data.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jncc.2022.08.006.

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