Clinical Practice Guidelines for Pancreatic Cancer 2016 From the Japan Pancreas Society

A Synopsis

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Objectives: Clinical Practice Guidelines for Pancreatic Cancer based on Evidence-Based Medicine 2006 were first published by the Japan Pancreas Society, and they were revised to Clinical Practice Guidelines for Pancreatic Cancer 2009 in July 2009 and were further revised to Clinical Practice Guidelines for Pancreatic Cancer 2013 in October 2013. These guidelines were established according to evidence-based medicine. In October 2016, the Clinical Practice Guidelines for Pancreatic Cancer were newly revised in Japanese.

Methods: In the revised version, we introduced the concepts of GRADE grading recommendations assessment, development, and evaluation approach for better understanding of the current guidelines.

Results: The guidelines show algorithms for the diagnosis, treatment, and chemotherapy of pancreatic cancer and address 7 subjects: diagnosis, surgical therapy, adjuvant therapy, radiation therapy, chemotherapy, stent therapy, and palliative medicine. They include 51 clinical questions and 76 statements. There are statements corresponding to clinical questions, evidence levels, recommended strengths, and agreement rates.

Conclusions: These guidelines represent the most standard clinical and practical management at this time in Japan. This is the English synopsis of the Clinical Practice Guidelines for Pancreatic Cancer 2016 in Japanese, which aims to disseminate the Japanese guidelines worldwide for the introduction of Japanese clinical management of these diseases.

Key Words: pancreatic cancer, clinical guidelines, Japan Pancreas Society, GRADE system, diagnostic algorithm, treatment algorithm

Clinical Practice Guidelines for Pancreatic Cancer based on Evidence-Based Medicine 2006 were first published by the Japan Pancreas Society, and they were revised in Evidence-Based Medicine Clinical Practice Guidelines for Pancreatic Cancer 2009 in July 2009 and were further revised in Evidence-Based Medicine Clinical Practice Guidelines for Pancreatic Cancer 2013 in October 2013. These guidelines were established according to evidence-based medicine. Synopses of the Clinical Guidelines 2009 and 2013 were published in English. In October 2016, the Clinical Practice Guidelines for Pancreatic Cancer were newly revised. In the revised version, we introduced the concepts of grading recommendations assessment, development, and evaluation (GRADE) approach for better understanding. Additionally, the composition of the committee members changed for the revision, we included more specialists from various fields: doctors of palliative medicine (1) and psycho-oncology (1), a nurse of cancer therapy (1), a cancer pharmacist (1), a nutritionist (1), and a social medical worker (1) to avoid biases in the recommendations. These guidelines represent the most standard clinical and practical management at this time in Japan. This is the English synopsis of the Clinical Practice Guidelines for Pancreatic Cancer 2016 in Japanese, which aims to disseminate the Japanese guidelines worldwide for the introduction of Japanese clinical management of these diseases.

GENERAL OUTLINES OF THE REVISION PROCESS

The committee for Revision of Clinical Guidelines for Pancreatic Cancer in the Japan Pancreas Society consisted of K. Yamaguchi as the chairman; T. Okusaka as the vice chairman; K. Shimizu, J. Furuse, Y. Ito, and K. Hanada as chairs; and 34 reviewers.

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other specialists (doctors of internal medicine [6], surgery [11], oncology [3], radiology [4], endoscopy [3], psycho-oncology [1], palliative medicine [1], nurse of cancer therapy [1], cancer pharmacist [1], medical social worker [1], nutritionist [1], and a patient representative with pancreatic cancer [1]) as committee members for the revision of the guidelines. In addition, 30 other medical doctors helped the revision as assistants. The revision process with these committee members started in December 2013. The committee members proposed the guidelines consisting of algorithms that outline diagnosis, treatment, and chemotherapy and the following 51 clinical questions (CQs). Comprehensive literature searches of the latest references published after January 1990 (when the literature search was performed for the first version of the guidelines) were performed for each CQ by 4 librarians (Mr. N. Yamaguchi and Ms. Y. Miura, N. Suwa, and M. Hirawa). A total of 641 articles were collected from 10,899 reports concerning pancreatic cancer that were listed on PubMed and Igakuchuo Zasshi from January 2010 to August 2014 by the 4 librarians.

These new guidelines follow the GRADE system and are supported by Professor M. Yoshida and Mr. Y. Hatakeyama (Minds; Medical Information Network Distribution Service, Tokyo, Japan). These guidelines were selected as trial guidelines of the Guideline Innovation Development (GUIDE) system, an internet tool for making clinical guidelines provided by Minds. The guidelines show algorithm for the diagnosis (Fig. 1), treatment (Fig. 2), and chemotherapy (Fig. 3) of pancreatic cancer and address 7 subjects: diagnosis, surgical therapy, adjuvant therapy, radiation therapy, chemotherapy, stent therapy, and palliative medicine. They include 51 CQs and 76 statements. The corresponding CQ numbers are inserted in the algorithms. There are statements corresponding to CQ, evidence level, recommended strength, and agreement rate.

We used the GRADE system approach. The overall quality of the body of evidence across gross studies for each important outcome was assessed. Finally, the evidence level was decided from A (highest) to D (lowest). Each committee member who specialized in the field of each CQ prepared a draft of the statement, the evidence level, and the recommended strength. Committee members added some references from their own searches and performed meta-analysis independently if necessary. These were reviewed, modified, and finalized by all committee members. The recommended strength was decided considering 4 factors: evidence level, balance of benefits and harms/burdens, patients' preferences, and cost benefits. Finally, the recommended strength was divided into 2 categories (1 = strong, recommend to do or not to do; 2 = weak, propose to do or not to do) with the agreement degree by attending committee members in the available committee where 85% or more members attended. When the agreement rate was 75% or more, the state was judged to be accepted by the committee members. When the agreement rate was less than 75%, the state was judged to be unaccepted by the committee members. Acceptability was determined following Delphi method by voting using answer pad system by the committee member attended.

After the public hearings in the medical congresses and public comments on Internet, the guidelines were approved by the Assessments of the External Appraisal Committee (surgery: A. Nakao and K. Futami, internal medicine: A. Funakoshi and M. Sata, basic medicine: S. Kono and a patient representative with pancreatic cancer) independent from the revision committee members, and the guidelines were modified and finalized. These new Clinical Guidelines for Pancreatic Cancer 2016 follow the

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**Algorithm of the Pancreatic Cancer Diagnosis**

- **D1**
  - Clinical manifestations, pancreatic enzyme / tumor marker / risk factor, US

- **D2-1,2-2**
  - Dynamic CT and/or dynamic MRI (MRCP) and/or EUS†

- **D3-1,3-2**
  - ERCP and/or PET

- **D3-3,7**
  - Cytological and/or histological diagnosis ‡‡
    - (EUS or ERP or US or CT)

**Diagnosis**

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FIGURE 1. Dagger, Dynamic CT and/or dynamic MRI (MRCP) are more preferable to EUS. It is desirable to perform EUS in the institution where EUS technique is well mastered. Double dagger, It should be diagnosed pathologically as much as possible.

NOTES ON THE USE OF THE GUIDELINES

These guidelines represent the most standard clinical and practical care for pancreatic cancers at this time. However, they should not be inflexible for the practical management of individual patients. The Japan Pancreas Society is responsible for the statements in these guidelines. The Japan Pancreas Society and the committee members are not liable for any consequences arising from any treatment, for which individual physicians involved in the treatment should be responsible.

ALGORITHM

Algorithm presents the flow of diagnosis, treatment, and chemotherapy. For detailed explanation, each CQ refer to the indicated box (Figs. 1–3).

FIGURE 2. Cancer stage classification, the resectability classification according to the General Rules for the Study of Pancreatic Cancer, Seventh Edition, the Japan Pancreas Society. Dagger, Supportive care for pain, digestion and absorption disorder, pancreatic diabetes, and the anxiety are required in the patients with pancreatic cancer from the early period after the diagnosis of pancreatic cancer. Concerning the details, refer to details in the HP (http://www.jspm.ne.jp/guidelines/index.html). Double dagger, Stent therapy, bypass therapy, and radiotherapy may be indicated by a case (we explain the adaptation in detail in the text) of cancer stage IV.

FIGURE 3. Recommended strength/evidence level.
CLINICAL QUESTIONS AND STATEMENTS

Statement: Statement was noted concerning each CQ.
Recommended strength: Recommendation was graded to grade 1 (strong = recommend) and 2 (weak = propose) according to the concept of GRADE system.6
Grade 1: Recommend to do.
   Recommend not to do.
Grade 2: Propose to do.
   Propose not to do.
Evidence level: Evidence level was shown as A (highest), B, C, and D (lowest).
Agreement rate (%): agreement of members of revision committee voted using an answer pad system.

DISEASE CONCEPTS OR DC

DC1: What Is a Risk Factor for Pancreatic Cancer?

Statements:
1. The risk factors for pancreatic cancer are as follows:
   - Family history: Pancreatic cancer family history, familial pancreatic cancer (cf. DC2).
   - Complication: Diabetic, chronic pancreatitis, intraductal papillary mucinous neoplasm, pancreatic cyst, obesity.
   - Lifestyle choice: Smoking, heavy alcohol consumption.
   - Occupation: Chlorinated hydrocarbon practitioner.

Recommended strength: none; evidence level: pancreatic cancer family history (B), hereditary pancreatic cancer syndrome (B), hereditary pancreatitis (C), diabetes (B), obesity (B), chronic pancreatitis (B), smoking (B), alcohol use (C), occupation (B); agreement rate: 100%.

2. When we plurally include risk factors such as a family history, a complication, and a taste, we propose to examine these as the high-risk group for pancreatic cancer.

Recommended strength: 2; evidence level: pancreatic cancer family history (B), hereditary pancreatic cancer syndrome (B), hereditary pancreatitis (C), diabetes (B), obesity (B), chronic pancreatitis (B), smoking (B), alcohol use (C), occupation (B); agreement rate: 100%.

3. Concerning intraductal papillary mucinous neoplasm and pancreatic cyst, we propose to follow up these carefully as a precancerous lesion of the pancreatic cancer.

Recommended strength: 2; evidence level: C, agreement rate: 100%.

DC2: What Is Family-Related Pancreatic Cancer?

Statement:
Family-related pancreatic cancer is defined as “pancreatic cancer occurring in the families of patients with pancreatic cancer in more than 2 first-degree close relatives (parent, siblings, child) except for known hereditary pancreatic cancer syndrome.”

Recommended strength: none; evidence level: C, agreement rate: 100%.

DC3: What Is Borderline Resectable Pancreatic Cancer?

Statements:
1. The seventh edition of General Rules for the Study of Pancreatic Cancer7 was published by the Japan Pancreas Society, and the resectability was proposed by the degree of local invasion and the presence of the distant metastasis: resectable, borderline resectable, and unresectable. Borderline resectable pancreatic cancer is defined as mentioned hereafter and it is proposed that we use this classification.

Recommended strength: 2, evidence level: B, agreement rate: 100%.

Borderline resectable: BR.

BR pancreatic cancer is pancreatic cancer where a standard operation is performed; the operation is more likely to become R1 (with tumor histologically persistent at a resection stump) resection. We subdivide it by invasion of the portal system and the arterial system.

BR-PV (there is invasion to the portal vein/system alone): There is no invasion or contact with superior mesenteric artery, celiac artery, or common hepatic artery. There is contact of 180 degrees or more with superior mesenteric vein/portal vein or obstruction of superior mesenteric vein/portal vein but does not go over the duodenal inferior margin as a range of the invasion.

BR-A (there is invasion to the arterial system): There is contact of less than 180 degrees with superior mesenteric artery or celiac artery and no stenosis or distortion. There is invasion to common hepatic artery (CHA) but no invasion to proper hepatic artery or celiac artery.

2. For a diagnosis of BR pancreatic cancer, we recommend evaluation with dynamic multi-detector row computed tomography (MDCT).

Recommended strength: 1, evidence level: B, agreement rate: 97.4%.

3. Also we propose performing laparoscopic examination as needed and evaluate because a laparoscopic examination is useful in the detection of a micrometastasis of the liver and peritoneal dissemination.

Recommended strength: 2, evidence level: B, agreement rate: 100%.

DIAGNOSIS OR D

D1: How Is the Discovery of the Pancreatic Cancer Done?

Statements:
1. When symptoms such as stomachache, anorexia, early feeling of distention, jaundice, weight loss, new onset diabetes, or back pain are detected, we propose to examine these in consideration for the likelihood of the pancreatic cancer.

Recommended strength: 2, evidence level: C, agreement rate: 97.4%.

2. We propose to measure blood pancreatic enzymes and tumor markers, which have been reported to be of definite utility in the diagnosis of pancreatic cancer.

Recommended strength: 2, evidence level: C, agreement rate: 100%.

3. We propose to perform ultrasound for screening of pancreatic cancer.

Recommended strength: 2, evidence level: C, agreement rate: 100%.

4. When there are multiple risk factors (cf. CQ-DC-1) for pancreatic cancer, we propose to examine these in consideration of likelihood of the pancreatic cancer.

Recommended strength: 2, evidence level: C, agreement rate: 100%.
D2: Diagnostic Modalities When We Suspected Pancreatic Cancer

D2-1: When pancreatic cancer is suspected, are computed tomography (CT) and abdominal MRI useful for diagnosis?

Statement:
We recommend performing dynamic CT (MDCT is desirable) and/or MRI (MRCP) (dynamic and 3 T or more are desirable) so that pancreatic cancer is accurately diagnosed.
Recommended strength: 1, evidence level: B, agreement rate: 100%.

D2-2: When pancreatic cancer is suspected, is endoscopic ultrasonography (EUS) useful for diagnosis?

Statement:
EUS can diagnose pancreatic cancer with higher sensitivity compared to other imaging modalities; thus we propose performing EUS when we suspect the presence of pancreatic cancer.
Recommended strength: 2, evidence level: B, agreement rate: 100%.

D3: The Next Step to Diagnose Pancreatic Cancer

D3-1: Is ERCP useful as the next step to make a diagnosis of pancreatic cancer?

Statement:
When it is hard to make a diagnosis of pancreatic cancer by ultrasound, CT, MRI, or other imaging diagnostic methods including EUS, we propose performing an endoscopic retrograde cholangiopancreatography (ERCP).
Recommended strength: 2, evidence level: B, agreement rate: 100%.

D3-2: Is PET useful as the next step to make a diagnosis of pancreatic cancer?

Statement:
We propose performing positron emission tomography (PET) (PET/CT) for the differentiation of benign or malignant lesions in the diagnosis of pancreatic cancer. However, there is a limit in the diagnosis of small pancreatic cancer and small distant metastasis.
Recommended strength: 2, evidence level: C, agreement rate: 100%.

D3-3: Is cytological or histological diagnosis useful for the diagnosis of pancreatic cancer?

Statement:
Cytological and histological diagnosis are useful concerning the sensitivity and the specificity and are useful in the differentiation of pancreatic cancer and other pancreatic diseases, thus we propose performing cytological or histological diagnosis.
Recommended strength: 2, evidence level: C, agreement rate: 100%.

D4: How Is Staging Carried Out?

Statement:
1. We recommend determining staging (TNM classification) of the pancreatic cancer by dynamic MDCT and/or dynamic MRI (including the diffusion-weighted imaging).
Recommended strength: 1, evidence level: B, agreement rate: 100%.
2. We propose to perform EUS as needed.
Recommended strength: 2, evidence level: B, agreement rate: 92.1%.
3. We propose to perform laparoscopic staging for the assessment of liver metastasis or peritoneal dissemination as needed.
Recommended strength: 2, evidence level: B, agreement rate: 94.7%.

D5: How Is the Resectability of Pancreatic Cancer Determined?

Statement:
1. We recommend evaluating local infiltration by dynamic MDCT.
Recommended strength: 1, evidence level: B, agreement rate: 100%.
2. We propose to perform EUS as needed.
Recommended strength: 2, evidence level: B, agreement rate: 100%.
3. We recommend evaluating the presence or absence of distant metastasis by dynamic MDCT and/or dynamic MRI (including the diffusion-weighted image).
Recommended strength: 1, evidence level: B, agreement rate: 92.1%.
4. If distant metastasis is not found by dynamic MDCT and dynamic MRI (including the diffusion-weighted image), we propose performing PET (PET/CT) and/or laparoscopic staging as needed.
Recommended strength: 2, evidence level: B, agreement rate: 81.6%.

D6: Should We Perform a Laparoscopic Examination to Diagnose the Stages of Pancreatic Cancer?

Statement:
A laparoscopic examination is useful in the discovery of liver metastasis and peritoneal dissemination. We propose performing a laparoscopic examination in the case where the diagnosis of resectable pancreatic cancer or locally advanced pancreatic cancer was made but distant metastasis cannot be denied.
Recommended strength: 2, evidence level: C, agreement rate: 100%.

D7: What Should We do to Make a Diagnosis of Early Pancreatic Cancer where Long-Term Prognosis can be Expected?

Statement:
1. It is pancreatic cancer, 1 cm or less, where a long-term prognosis can be expected and the dilatation of the pancreatic duct and cystic lesion are important as indirect findings.
Recommended strength: none, evidence level: C, agreement rate: 97.4%.
2. When the direct depiction of a tumor is difficult by ultrasound and dynamic MDCT, we propose performing EUS or MRCP.
Recommended strength: 2, evidence level: C, agreement rates: 100%.
3. We propose performing EUS-fine needle aspiration cytology when mass lesion is detected by EUS.
Recommended strength: 2, evidence level: C, agreement rates: 97.4%.
4. When localized stenosis of the pancreatic duct, caliber change, and dilatation of the branch duct are found, we propose performing ERCP followed by multiple pancreatic juice cytology.
Recommended strength: 2, evidence level: C, agreement rates: 97.4%.
SURGICAL THERAPY FOR RESECTABLE PANCREATIC CANCER OR RS

RS1: Is Surgical Treatment Recommended for Resectable Pancreatic Cancer?
Statement:
Because resectable pancreatic cancer expects a favorable outcome, we recommend surgical treatment rather than a nonsurgical remedy. Treatment-related complications are not clearly different between the surgical treatment and nonsurgical remedy. Recommended strength: 1, evidence level: B, agreement rate: 100%.

RS2: Is Surgical Treatment for Pancreatic Cancer at a High Volume Center Recommended?
Statement:
We propose undergoing surgery at a high volume center because the reduction in overall mortality rate, reduction in hospitalization mortality, decrease of surgery-related complications, and shortening of postoperative hospitalization are expected. Recommended strength: 2, evidence level: B, agreement rates: 100%.

RS3: Is Surgical (Multidisciplinary) Treatment for Borderline Resectable Pancreatic Cancer Significant?
Statement:
The preoperative treatment for borderline resectable pancreatic cancer improves resection rate of the surgical resection and an R0 rate and may be connected to the improvement of the clinical outcome. We would conduct further large-scale prospective clinical trials to examine this. Recommended strength: none, evidence level: D, agreement rate: 100%.

RS4: Is Surgical Treatment for Peritoneal Lavage Cytology-Positive Pancreatic Cancer Significant?
Statement:
It is not clear whether we should treat peritoneal lavage cytology-positive pancreatic cancer surgically or not. Recommended strength: none, evidence level: D, agreement rate: 100%.

RS5: In Pancreatoduodenectomy for Cancer of the Head of Pancreas, Is It Significant to Preserve the Stomach?
Statement:
In pancreatoduodenectomy for cancer of the head of pancreas, we shorten the operative time and decrease perioperative blood loss by keeping the entire stomach or subcomponents of the stomach, whereas survival rate and post operative complications are not different. We propose preserving the entire stomach or subcomponents of the stomach in pancreatoduodenectomy for cancer of the head of pancreas. Recommended strength: 2, evidence level: B, agreement rate: 100%.

RS6: Does Combined Portal Vein Resection Improve the Clinical Outcome of Pancreatic Cancer?
Statement:
It is not clear whether combined portal vein resection improves the clinical outcome of pancreatic cancer or not. We may consider combined portal vein resection when R0 surgery is expected by it. Recommended strength: none, evidence level: C, agreement rate: 94.7%.

RS7: Is Extended Lymph Node and Nerve Plexus Dissection for Pancreatic Cancer Significant?
Statement:
Extended lymph node and nerve plexus dissection for pancreatic cancer does not contribute to the improvement of survival rate, and we do not recommend carrying it out uniformly. Recommended strength: 1, evidence level: B, agreement rate: 97.4%.

RS8: Is Prophylactic Bypass Recommended for Pancreatic Cancer Which was First Found Unresectable After Laparotomy?
Statement:
1. Biliary tract bypass: For cancer of the head of pancreas that was found to be unresectable after laparotomy for the purpose of curative surgical resection, we propose performing biliary bypass when bile duct invasion is present or suspected. Recommended strength: 2, evidence level: B, agreement rate: 89.5%.
2. Gastrointestinal bypass: For cancer of the head of pancreas that was found to be unresectable after laparotomy for the purpose of curative surgical resection, we propose performing gastrojejunostomy (bypass operation) when duodenal invasion is present or suspected. Recommended strength: 2, evidence level: B, agreement rate: 92.1%.

RS9: Is Laparoscopic Surgery for Pancreatic Cancer Significant?
Statement:
1. The utility of laparoscopic pancreatoduodenectomy for the treatment of pancreatic cancer is not confirmed by health insurance in Japan, and we do not recommend performing laparoscopic pancreactectomy other than in clinical trials. Recommended strength: 1, evidence level: D, agreement rate: 97.4%.
2. The utility of laparoscopic distal pancreactectomy for the treatment of pancreatic cancer has been approved by health insurance in Japan, but the significance and safety should be examined by further accumulation of cases. Prospective registration to the preoperative entry system managed by the 3 institutes (Japan Society of Endoscopic Surgery, Japanese Society of Hepato-Biliary-Pancreatic Surgery, and Japanese Society for Endoscopic Pancreatic Surgery) is strongly demanded. Recommended strength: none, evidence level: D, agreement rate: 94.9%.

RS10: How do you Perform Follow-Up of Patients After the Pancreatic Cancer Resection?
Statement:
We propose to follow up patients with pancreatic cancer after surgical resection with the measurement of the tumor markers...
and a dynamic CT scan every 3 to 6 months for 2 years postoperatively and every 6 to 12 months subsequently, at least for 5 years postoperatively. Recommended strength: 2, evidence level: C, agreement rate: 100%.

RS11: Is Nutritional Care Recommended for Patients After Pancreatic Cancer Resection?
Statement: Enteral feeding therapy has lower postoperative infection-related complication rates than intravenous hyperalimentation, and we propose providing enteral feeding therapy. Recommended strength: 2, evidence level: C, agreement rate: 100%.

ADJUVANT THERAPY FOR RESECTABLE PANCREATIC CANCER OR RA

RA1: Is Neoadjuvant Therapy (1. Chemoradiotherapy or 2. Chemotherapy) Recommended for Resectable Pancreatic Cancer?
Statement: Because perioperative effects and the effects to long-term prognosis are not proved definitely, neoadjuvant therapy (1. chemoradiotherapy for the resectable pancreatic cancer or 2. chemotherapy) should be performed in clinical trials. We propose to not include neoadjuvant therapy other than in clinical trials. Recommended strength: 2, evidence level: C, agreement rate: 97.4%.

RA2: Is Intraoperative Radiotherapy Recommended for Resectable Pancreatic Cancer?
Statement: We recommend not performing intraoperative radiotherapy for the resectable pancreatic cancer. Recommended strength: 1, evidence level: B, agreement rate: 100%.

RA3: Is Postoperative Adjuvant Chemoradiotherapy Recommended for Pancreatic Cancer?
Statement: We propose to not perform postoperative adjuvant chemoradiotherapy for the pancreatic cancer. Recommended strength: 2, evidence level: B, agreement rate: 97.4%.

RA4: Is Postoperative Adjuvant Chemotherapy Recommended for Resectable Pancreatic Cancer?
Statement: 1. Postoperative adjuvant chemotherapy for resectable pancreatic cancer extends the survival period significantly as compared with resection alone. Thus, we recommend performing postoperative adjuvant chemotherapy for the resectable pancreatic cancer. Recommended strength: 1, evidence level: A, agreement rate: 100%.

3. For patients with low tolerability for S-1, we recommend gemcitabine hydrochloride monotherapy as the postoperative adjuvant chemotherapy. Recommended strength: 1, evidence level: A, agreement rate: 100%.

LOCALLY ADVANCED UNRESECTABLE PANCREATIC CANCER OR LA

LA1: What Is the Primary Therapy Recommended for Locally Advanced Unresectable Pancreatic Cancer?
Statement: We recommend performing chemoradiotherapy or chemotherapy alone as the primary therapy for locally advanced unresectable pancreatic cancer. Recommended strength: 1, evidence level: B, agreement rate: 100%.

RADIOThERAPY FOR LOCALLY ADVANCED UNRESECTABLE PANCREATIC CANCER OR LAR

LAR1: What Is the Chemoradiotherapy Recommended for Locally Advanced Unresectable Pancreatic Cancer?
Statement: When radiotherapy is provided for locally advanced unresectable pancreatic cancer, 1. We propose to perform radiotherapy in combination with fluoropyrimidine or gemcitabine hydrochloride. Recommended strength: 2, evidence level: B, agreement rate: 100%.

2. Concerning the radiotherapy, we recommend conducting a 3-dimensional treatment plan and to plan an accurate radiation for the tumor and dosage reduction to normal organs. Recommended strength: 1, evidence level: B, agreement rate: 100%.

LAR2: What Kind of Clinical Target Volume Should We Set for External Radiation Treatment of Locally Advanced Unresectable Pancreatic Cancer?
Statement: For external radiation treatment of locally advanced unresectable pancreatic cancer, we propose to set a clinical target volume only including gross tumor volume and lymph nodes showing frequent metastasis. Recommended strength: 2, evidence level: C, agreement rate: 100%.

LAR3: For Locally Advanced Unresectable Pancreatic Cancer, Is Induction Chemotherapy Before the Chemoradiotherapy Significant?
Statement: For locally advanced unresectable pancreatic cancer, we propose induction chemotherapy before chemoradiotherapy as one of the treatments of choice. Recommended strength: 2, evidence level: C, agreement rate: 100%.

LAR4: Is Intraoperative Radiotherapy Effective for Locally Advanced Unresectable Pancreatic Cancer?
Statement:
There is a report in support of the utility of intraoperative radiotherapy for locally advanced unresectable pancreatic cancer, and we may consider performing it.

Recommended strength: none, evidence level: C, agreement rates: 84.6%.

**LAR5: Do Radiotherapy and Chemoradiotherapy Improve the Quality of Life of a Patient With Locally Advanced Unresectable Pancreatic Cancer?**

**Statement:**
For local symptoms such as pain with locally advanced pancreatic cancer, which cannot be treated surgically:
1. Chemoradiotherapy is expected to improve the quality of life.
   Recommended strength: none, evidence level: B, agreement rate: 89.7%.
2. Radiation alone is expected to improve the quality of life.
   Recommended strength: none, evidence level: C, agreement rate: 94.9%.

**CHEMOTHERAPY FOR LOCALLY ADVANCED UNRESECTABLE PANCREATIC CANCER OR LAC**

**LAC1: What Is the Primary Chemotherapy Recommended for Locally Advanced Unresectable Pancreatic Cancer?**

**Statement:**
1. We propose giving gemcitabine hydrochloride monotherapy, S-1 monotherapy, FOLFIRINOX therapy, or gemcitabine hydrochloride + Nab-paclitaxel combination therapy as primary chemotherapy for the locally advanced unresectable pancreatic cancer.
   Recommended strength: 2, evidence level: B (gemcitabine hydrochloride monotherapy), C (FOLFIRINOX therapy, gemcitabine hydrochloride + Nab-paclitaxel combination therapy), agreement rate: 94.1%.
2. In addition, you may consider providing gemcitabine hydrochloride + S-1 combination therapy.
   Recommended strength: none, evidence level: unavailable, no agreement (agreement rate: 74.4%).

**LAC2: Is a Second Chemotherapy Recommended for Locally Advanced Unresectable Pancreatic Cancer?**

**Statement:**
When we consider the prolongation of the survival period for unresectable pancreatic cancer refractory to the first-line chemotherapy, we propose giving second-line chemotherapy.
Recommended strength: 2, evidence level: B, agreement rate: 100%.

**LAC3: How Long Is Chemotherapy Recommended for Unresectable Pancreatic Cancer? (MC3)**

**Statement:**
We propose to continue chemotherapy until clinical condition progresses clearly unless adverse events appear which prevents continuing chemotherapy.
Recommended strength: 2, evidence level: C, agreement rates: 100%.

**LAC4: Is Immunotherapy Recommended for Unresectable Pancreatic Cancer? (MC4)**

**Statement:**
When we consider the prolongation of the survival period for unresectable pancreatic cancer, we propose not to provide immunotherapy as a general clinical situation.
Recommended strength: 2, evidence level: C, agreement rate: 94.9%.

**CHEMOTHERAPY FOR METASTATIC PANCREATIC CANCER OR MC**

**MC1: What Is the Appropriate Primary Therapy Recommended for Metastatic Pancreatic Cancer?**

**Statement:**
1. We recommend providing FOLFIRINOX therapy or gemcitabine hydrochloride + Nab-paclitaxel combination therapy as primary therapy for metastatic pancreatic cancer.
   Recommended strength: 1, evidence level: A, agreement rate: 100%.
2. However, we recommend performing gemcitabine hydrochloride monotherapy, gemcitabine hydrochloride + erlotinib hydrochloride combination therapy, or S-1 monotherapy based on a state, such as overall performance status, when the above 2 regimens are not suitable.
   Recommended strength: 1, evidence level: A, agreement rate: 100%.
3. In addition, performing gemcitabine hydrochloride + S-1 combination therapy may be considered for patients based on a state, such as overall performance status, when FOLFIRINOX therapy or gemcitabine hydrochloride + Nab-paclitaxel combination therapy is not suitable.
   Recommended strength: none, evidence level: none, agreement rate: 74.4% (no agreement).

**MC2: Is a Second Chemotherapy Recommended for Unresectable Pancreatic Cancer?**

**Statement:**
When we consider the prolongation of the survival period for unresectable pancreatic cancer refractory to the first-line chemotherapy, we propose giving second-line chemotherapy.
Recommended strength: 2, evidence level: B, agreement rate: 100%.


**Statement:**
We propose to continue chemotherapy until clinical condition progresses clearly unless adverse events appear which prevents continuing chemotherapy.
Recommended strength: 2, evidence level: C, agreement rate: 100%.

**MC4: Is Immunotherapy Recommended for Unresectable Pancreatic Cancer (LAC4)**

**Statement:**
When we consider the prolongation of the survival period for unresectable pancreatic cancer, we propose not to provide immunotherapy as a general clinical situation.
Recommended strength: 2, evidence level: C, agreement rate: 100%.
RADIOTHERAPY FOR METASTATIC PANCREATIC CANCER OR MR

MR1: Is Radiotherapy Useful for Bone Metastasis of Pancreatic Cancer?
Statement:
We recommend performing radiotherapy for pain relief due to bone metastasis.
Recommended strength: 1; evidence level: A, agreement rate: 100%.
Refer to PM2 for upper quadrant and back pain such as nerve invasion.

STENT THERAPY OR ST
ST1: Is Biliary Tract Drainage Recommended for an Unresectable Pancreatic Cancer With Obstructive Jaundice?
Statement:
1. We recommend performing biliary tract drainage for unresectable pancreatic cancer with obstructive jaundice.
   Recommended strength: 1, evidence level: C, agreement rate: 97.4%.
2. We propose performing endoscopic drainage rather than surgical drainage as biliary drainage for unresectable pancreatic cancer.
   Recommended strength: 2, evidence level: B, agreement rate: 100%.

ST2: Which Is the Appropriate Approach Route, Either Percutaneous or Endoscopy for Biliary Drainage of Unresectable Pancreatic Cancer?
Statement:
We propose performing biliary tract drainage endoscopically for unresectable pancreatic cancer.
Recommended strength: 2, evidence level: B, agreement rate: 100%.

ST3: Stent for Pancreatic Cancer With Obstructive Jaundice
ST3-1: What is the recommended stent type for pancreatic cancer with obstructive jaundice?
Statement:
The superiority and inferiority by the type of the stent is not clear and we can choose a stent depending on the situation of a case and the institution.
Recommended strength: none, evidence level: C, agreement rate: 100%.

ST3-2: What is the recommended stent type for an unresectable pancreatic cancer with obstructive jaundice?
Statement:
1. We propose using self-expandable metallic stents rather than plastic stents (PS), because they have a longer patency period.
   Recommended strength: 2, evidence level: C, agreement rate: 100%.
2. Concerning self-expandable metallic stents, we propose using the covered type from the viewpoint of probe patency period.
   Recommended strength: 2, evidence level: A, agreement rate: 100%.
However, we can choose uncovered type or PS depending on the technique familiar to an institution, a practice system, and the state of the patient.

ST4: Which Is Recommended, Either Surgical Gastrojejunostomy or Gastrointestinal Stent for Unresectable Pancreatic Cancer With Gastrointestinal Obstruction?
Statement:
The superiority or inferiority of surgical gastrojejunostomy and the gastrointestinal stent implantation is not clear at present.
Recommended strength: none, evidence level: C, agreement rate: 100%.

PALLIATIVE MEDICINE OR PM
PM1: What Is the Effective Way to Address Psychological Distress in Patients With Pancreatic Cancer and Their Families?
Statement:
1. We propose to provide care through the collaboration of a physician engaged in cancer therapy, psychiatrists, and many paramedical staff, including nurses.
   Recommended strength: 2, evidence level: C, agreement rate: 100%.
2. We propose providing pharmacotherapy while paying attention to side effects of moderate to severe degree.
   Recommended strength: 2, evidence level: C, agreement rate: 100%.

PM2: What are Effective Treatments for Upper Quadrant or the Back Pain?
Statement:
1. We recommend conducting an evaluation of the cause of the pain and the assessment of the pain.
   Recommended strength: 1, evidence level: D, agreement rate: 100%.
2. We recommend providing nonopioid analgesics and opioids.
   Recommended strength: 1, evidence level: B, agreement rate: 100%.
3. When analgesia is insufficient with either nonopioids or opioids, we propose using a sedative adjuvant.
   Recommended strength: 2, evidence level: B, agreement rate: 100%.
4. We propose to perform a nerve block.
   Recommended strength: 2, evidence level: A, agreement rate: 100%.
   MR1 is referred to for radiotherapy for bone metastasis aches regarding pain treatment with the radiotherapy (LAR5).

PM3: Is Elemental Diet Therapy Effective to Improve the Condition of Patients With Unresectable Pancreatic Cancer?
Statement:
We propose to perform an elemental diet therapy for patients with unresectable pancreatic cancer when there is a problem with meal intake and suspicious nutritional deterioration.
Recommended strength: 2, evidence level: C, agreement rate: 100%.

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