EBM-based Clinical Guidelines for Pancreatic Cancer 2009 From the Japan Pancreas Society: A Synopsis

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Clinical Practice Guidelines for Pancreatic Cancer Based on Evidence-based Medicine, 2006, were published by the Japan Pancreas Society (Committee for Revision of Clinical Guidelines for Pancreatic Cancer) in March 2009 in Japanese1 and were revised to Clinical Practice Guidelines for Pancreatic Cancer Based on Evidence-based Medicine 2009 in July 2009 in Japanese.2 These guidelines were established according to Evidence-Based Medicine. A total of 443 papers were collected from 2544 reports concerning pancreatic cancer that were listed on PubMed and Igakuchuo Zasshi from July 2004 to April 2007. This new guidelines were written by members of the Committee for Revision of Clinical Practice Guidelines for Pancreatic Cancer in the Japan Pancreas Society. The guidelines show algorithm for the diagnosis (Fig. 1) and treatment (Fig. 2) of pancreatic cancer, address five subjects: diagnosis, chemotherapy, radiation therapy, surgical therapy and adjuvant therapy, and include 25 clinical questions (CQs) and 39 recommendations. The corresponding CQ numbers are inserted in the algorithms. There are five degrees of recommendation:

A Strongly recommended because there is strong scientific evidence.
B Recommended because there is scientific evidence.
C1 Recommended although there is no scientific evidence.
C2 Not recommended because there is no scientific evidence.
D Not recommended because there is evidence showing that it is ineffective or harmful.

This article presents a synopsis of the guidelines in English.

Diagnosis

CQ1-1 What are risk factors for pancreatic cancer?

The below-mentioned risk factors have been reported to have evidences supporting the relationship between the factors and pancreatic cancer:

(i) Family history: pancreatic cancer and hereditary pancreatic cancer syndrome.
(ii) Accompanying diseases: diabetes mellitus, obesity, chronic pancreatitis, hereditary pancreatitis, intraductal papillary mucinous neoplasm (IPMN).
(iii) Habits: tobacco.

RECOMMENDATION 1-1

(i) Patients with more than one risk factor are recommended to undergo further examination to detect pancreatic cancer (Grade B).
(ii) IPMN progresses to invasive cancer and accompanies pancreatic cancer. IPMN should be adequately assessed and carefully followed up (Grade B).

CQ1-2 What are the clinical symptoms of pancreatic cancer?

The below-mentioned clinical symptoms have been reported as those of pancreatic cancer:

(i) Abdominal pain is the most frequent symptom, followed by jaundice, back pain and body weight loss.
(ii) Clinically silent pancreatic cancer.
(iii) Fifty percent of pancreatic cancer patients show early-onset diabetes mellitus (glycogen metabolism disturbance) within 3 years.

RECOMMENDATION 1-2

(i) Patients with unexplainable abdominal pain, back pain, jaundice and/or body weight loss should undergo further examination for pancreatic cancer. However, the clinical outcome of symptomatic pancreatic cancer is poor (Grade B).
Early-onset diabetes mellitus (poor glycogen metabolism) and deterioration of diabetes mellitus suggest the presence of pancreatic cancer and necessitate further examination for pancreatic cancer (Grade B). Early-onset diabetes mellitus (within less than 3 years) may indicate pancreatic cancer.

CQ1-3 What is the first step when pancreatic cancer is suspected?

The below-mentioned examinations are the first-step diagnostic procedures of pancreatic cancer:

(i) Serum pancreatic enzyme
(ii) Tumor markers
(iii) Ultrasound (US)
(iv) Computed tomography (CT).

RECOMMENDATION 1-3

(i) The serum pancreatic enzyme level is important, but is not specific for pancreatic cancer (Grade C1).

(ii) Serum tumor makers including CA19-9 are recommended for the diagnosis of pancreatic cancer and follow-up of pancreatic cancer (Grade B), but they are not useful for the diagnosis of early pancreatic cancer.

(iii) US is recommended for the first screening for pancreatic cancer (Grade B) but has a low rate of detecting pancreatic cancer (Grade C1). Dilatation of the main pancreatic duct or a pancreatic cyst is an important indirect sign of pancreatic cancer (Grade B). Further examination, including CT, is therefore strongly recommended if such signs are evident (Grade A).

(iv) Patients the abnormal findings listed above should be periodically examined and careful follow-up is recommended if no diagnosis of pancreatic cancer obtained (Grade B).

CQ1-4 What is the second step when pancreatic cancer is suspected?

RECOMMENDATION 1-4

(i) Qualitative diagnosis is important and is strongly recommended to determine the treatment of pancreatic cancer (Grade A).

(ii) US and CT (enhancing) should be performed and additional examination by magnetic resonance cholangiopancreatography, endoscopic ultrasound (EUS), ERP or positron emission tomography is strongly recommended when necessary (Grade A).

CQ1–5 What is the significance and indications for cytology and biopsy of pancreatic cancer?

RECOMMENDATION 1-5

(i) Either a histological or cytological diagnosis is recommended before treatment started if no qualitative diagnosis of pancreatic mass obtained. Aspiration cytology or histology with US guidance, cytology or histology under endoscopic ultrasonography, pancreatic juice cytology under endoscopic retrograde cholangiopancreatography (ERCP) or histology under ERCP should be obtained to achieve a definite diagnosis, depending on the patients or institution (Grade B).

(ii) Aspiration cytology under endoscopic ultrasonography is useful when the lesion is not detected by ultrasonography or CT (Grade C1).

(iii) A genetic analysis is important to confirm the cytology or histology (Grade C1).

CQ1-6 How do you determine clinical staging of pancreatic cancer?

RECOMMENDATION 1-6

(i) Either a histological or cytological diagnosis is recommended before treatment started if no qualitative diagnosis of pancreatic mass obtained. Aspiration cytology or histology with US guidance, cytology or histology under endoscopic ultrasonography, pancreatic juice cytology under endoscopic retrograde cholangiopancreatography (ERCP) or histology under ERCP should be obtained to achieve a definite diagnosis, depending on the patients or institution (Grade B).

(ii) Aspiration cytology under endoscopic ultrasonography is useful when the lesion is not detected by ultrasonography or CT (Grade C1).

(iii) A genetic analysis is important to confirm the cytology or histology (Grade C1).

Chemotherapy

CQ2-1 Is chemotherapy alone recommended for locally advanced unresectable pancreatic cancer?
**RECOMMENDATION 2-1**

Chemotherapy alone is recommended as one of options for the treatment of locally advanced unresectable pancreatic cancer (Grade B).

**CQ2–2 What is the first-line chemotherapy for metastatic pancreatic cancer?**

**RECOMMENDATION 2-2**

Gemcitabine (GEM) is recommended as the first-line treatment for metastatic pancreatic cancer (Grade A).

**CQ2-3 How long is GEM continued for unresectable pancreatic cancer?**

**RECOMMENDATION 2-3**

GEM is continuously administered for unresectable pancreatic cancer until clear progression becomes evident if there are no adverse effects causing interruption of the administration of GEM (Grade B).

**CQ2-4 Is second-line chemotherapy recommended for unresectable pancreatic cancer?**

**RECOMMENDATION 2-4**

There is no scientific evidence of effective second-line chemotherapy within the insurance allowance in this country, but some reports suggest effectiveness. Some recent randomized clinical trials in other countries have reported effective second-line chemotherapy. Second-line chemotherapy can be considered in patients whose physical status is good and are fully informed after a detailed explanation (Grade C1).

**Radiotherapy**

**CQ3-1 Is chemoradiation effective for locally advanced unresectable pancreatic cancer?**

**RECOMMENDATION 3-1**

Chemoradiation is effective for locally advanced unresectable pancreatic cancer and is recommended as one of the options for treatment (Grade B).

**CQ3-2 What is the standard combined chemotherapy for chemoradiation for locally advanced unresectable pancreatic cancer?**

**RECOMMENDATION 3-2**

5-fluorouracil (5-FU) (Grade B) is the standard chemotherapy for chemoradiation for locally advanced pancreatic cancer.

Although there is no definite evidence supporting GEM-based chemoradiation, some report its usefulness. A safe regimen of GEM-based chemoradiation can be considered as one of the options for treatment after the procedure is fully explained and the patient provides informed consent (Grade C1).

**CQ3-3 Is the lymph node included in the clinical standard field of external radiation therapy for locally advanced unresectable pancreatic cancer?**

**RECOMMENDATION 3-3**

There have been no prospective randomized clinical trials concerning this CQ. Radiation including the tumor and the positive lymph nodes in the radiation field is recommended prophylactically, although there is no supportive scientific evidence (Grade C1).

**CQ3-4 Is intraoperative radiation effective for locally advanced pancreatic cancer?**

**RECOMMENDATION 3-4**

There are reports of the efficacy of intraoperative radiation for locally advanced unresectable pancreatic cancer. However, there is no scientific evidence that intraoperative radiation improves the clinical course of locally advanced unresectable pancreatic cancer (Grade C1).

**CQ3-5 Does chemoradiation improve the quality of life of patients with unresectable pancreatic cancer?**

**RECOMMENDATION 3-5**

Cancer radiation therapy (Grade C1) and chemotherapy (Grade B) are therefore recommended to improve the quality of patients with unresectable pancreatic cancer.

**Surgical therapy**

**CQ4–1 Is surgical resection useful for Stage IVa pancreatic cancer?**

**RECOMMENDATION 4-1**

Surgical resection with an intended curative resection is recommended for pancreatic cancer up to Stage IVa* (Grade B).

Stage IVa*: Stage IVa indicates (S2 or R2 or PV2) and (N0 or N1) by Japan Pancreas Society Classification of pancreatic cancer, 4th Edition.

**CQ4-2 Is preservation of the stomach useful in pancreato-duodenectomy for pancreatic head cancer?**

**RECOMMENDATION 4-2**

It is not clear whether preservation of the stomach improves the rate of post-operative complications, quality of life, post-operative pancreatic function and nutrition status of patients with pancreatic cancer or not (Grade C1).
Preservation of the stomach decreases the operation time and blood loss in pancreatoduodenectomy but does not decrease the survival rate after a surgical resection (Grade C1).

CQ4-3 Does combined portal vein resection improve the clinical outcome of patients with pancreatic head cancer?

RECOMMENDATION 4-3
The effect of prophylactic portal vein resection intended to increase the curability on the clinical course of patients with pancreatic cancer is unclear. A portal vein resection is indicated when surgical and dissection margins can be free from cancer cells by portal vein resection (Grade C1).

CQ4-4 Is a radical resection with extended lymph node dissection useful for pancreatic cancer?

RECOMMENDATION 4-4
The contribution of extended lymph node and nerve plexus dissection to the improvement of clinical course of patients with pancreatic cancer is unclear and there is no evidence to support the performance of such an extended radical resection (Grade C2).

CQ4-5 Is the incidence of complications after pancreas resection low in a high volume center?

RECOMMENDATION 4-5
The incidence of complications tends to be low in pancreatic surgery including pancreatoduodenectomy and the management of complications tends to be superior in institutions with a high volume of pancreatic surgery (Grade B).

CQ4-6 Is surgical bypass or biliary stent significant in unresectable pancreatic cancer?

RECOMMENDATION 4-6
Hepaticojejunostomy for the obstructive jaundice and prophylactic gastrojejunostomy is recommended in patients with unresectable obstructive jaundice after laparotomy (Grade B).

Adjuvant therapy

CQ5-1 Does pre-operative therapy improve the clinical outcome of patients with pancreatic cancer?

RECOMMENDATION 5-1
There is increasing evidence supporting the efficacy of pre-operative treatment [(i) chemoradiation and (ii) chemotherapy]. However, clinical trials or analyses of the long term are required to determine whether such therapy improves the clinical outcome (Grade C1).

CQ5-2 Is intraoperative radiation therapy recommended at the time of resection of pancreatic cancer?

RECOMMENDATION 5-2
There has been no definite evidence supporting the usefulness of intraoperative radiotherapy. However, clinical trials or analyses of the long term are required to determine whether such therapy improves the clinical outcome (Grade C1).

CQ5-3 Is post-operative chemoradiation recommended for pancreatic cancer?

RECOMMENDATION 5-3
Meta-analysis of 5-FU-based post-operative chemoradiation revealed no supportive evidence. However, clinical trials or analyses of the long term are required to determine whether GEM-based post-operative chemoradiation improves the clinical outcome (Grade C1).

CQ5-4 Is post-operative adjuvant therapy recommended for pancreatic cancer?

RECOMMENDATION 5-4
There is no definite international consensus on post-operative adjuvant therapy. Post-operative GEM is safe and effective and is recommended as post-operative chemotherapy (Grade B).

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Conflict of interest statement

None declared.

References
