A Social Program for the Early Detection of Pancreatic Cancer: The Kishiwada Katsuragi Project

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Keywords

Pancreatic cancer · Early pancreatic cancer · Intraductal papillary mucinous neoplasm · Endoscopic ultrasound · Kishiwada Katsuragi project

Abstract

Objectives: The early-stage pancreatic cancer (e-PC; stage I/II) detection rate is quite low at approximately 25%. The aim of this study was to evaluate the feasibility of a social program (the Kishiwada Katsuragi project) wherein our hospital, which specializes in PC, and primary care medical offices (PMOs) used clinical findings to detect e-PC. **Methods:** Patients with a score of ≥ 2 points on clinical findings were enrolled: symptoms of abdominal pain/back pain (1 point), new-onset diabetes (1 point), high amylase (AMY) and/or pancreatic AMY (P-AMY) (1 point), high carbohydrate antigen 19-9 (1 point), and ultrasonography (US) findings including direct (e.g., a solid pancreatic tumor) and/or indirect findings (e.g., dilatation of a pancreatic diameter of ≥ 2.5 mm

and/or cystic lesions) (2 points) were evaluated using the protocol for social programs. **Results:** Between November 2014 and December 2016, 244 patients were enrolled by 41 PMOs as cooperative facilities, and 15 e-PC cases (53.6%) of the 28 PC patients were detected. The mean clinical finding score of the e-PC group (3.13 ± 1.9) was significantly higher than that of the overall non-PC group (2.1 ± 0.4) ($p < 0.05$). “High AMY/P-AMY” and “symptoms” were significantly more frequent in the e-PC group than in the non-PC group ($p < 0.05$). Although the sensitivity of direct findings by US was 40.0%, that of indirect-findings was 93.3% in the e-PC group. Nine and 6 of the 15 patients with e-PC were enrolled via general internal medicine offices (GIMs) and other PMOs without GIMs (general surgery, $n = 3$; urology, $n = 2$; otolaryngology, $n = 1$). **Conclusion:** This social program with collaborations between medical centers that specialize in PC and PMOs used clinical findings, suggesting that not only GIMs but also other PMOs and indirect findings by US may play an important role in improving the e-PC detection rate.

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Introduction

Pancreatic cancer (PC) is generally associated with a poor prognosis and is difficult to diagnose early enough for surgical resection, the only potentially curative treatment for PC, to be performed. Indeed, only 25% of PC patients have early-stage PC (e-PC) at the time of detection [1, 2].

A screening program is needed to improve the detection rate of e-PC. Previous studies have identified various risk groups and factors (a family history of PC and pancreatitis, smoking, alcohol consumption, diabetes (DM), obesity, and cystic lesions, including intraductal papillary mucinous neoplasm and main pancreatic duct [MPD] dilatation), but few standard programs are available for screening high-risk patients. Evidence-based clinical guidelines for PC were published by the Japan Pancreas Society (JPS) in 2006, with the third edition released in 2013 [3]. The guidelines include a protocol for diagnosing and treating PC. The sections of Clinical questions 1 and 2 suggest several risk factors that may be involved in the development of PC [4–11].

The guidelines include a protocol for a social program to diagnose e-PC by consulting clinical findings (the

Kishiwada Katsuragi project). The aim of the present study was to evaluate the feasibility of such a social program via collaboration between our medical center, which specializes in PC, and primary-care medical offices (PMOs).

Patients and Methods

Forty-one PMOs, including 27 general internal medicine offices (GIMs) and 14 other PMOs (otolaryngology, $n = 4$; general surgery, $n = 3$; orthopedic surgery, $n = 2$; gynecology, $n = 2$; urology, $n = 2$, and psychiatry, $n = 1$), were enrolled. If a patient presented with ≥ 2 points for 5 clinical findings, they were examined in accordance with the protocol for social programs for diagnosing e-PC (Fig. 1). If a patient did not receive ultrasonography (US) and/or did not undergo a carbohydrate antigen 19-9 (CA19-9) examination by the PMO at entry into this study, then they received these evaluations before undergoing magnetic resonance cholangiopancreatography (MRCP) including magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS) at our institution.

Between November 2014 and October 2016, 244 patients in whom PC was suspected based on the clinical findings (at the co-operating facilities) were evaluated. Twenty-eight (11.5%) of these 244 patients were ultimately diagnosed with PC. This study received approval from the ethics committee of Katsuragi Hospital.

Fig. 1. The protocol for the social program for diagnosing early-stage pancreatic cancer. ENPD, endoscopic nasopancreatic drainage; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; FNA, fine-needle aspiration; MPD, main pancreatic duct; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; US, ultrasonography; CA19-9, carbohydrate antigen 19-9; P-AMY, pancreatic amylase.

Clinical Findings

Patients with 2 points for the following clinical findings were diagnosed with suspected PC: (1) symptoms (abdominal pain or fatigue, or back pain) (1 point) [3], (2) new-onset DM (1 point) [12–14], (3) a high amylase (AMY) level (≥ 116 U/L) and/or pancreatic amylase (P-AMY) level (≥ 51 U/L) (1 point) [3], (4) a high CA19-9 level (≥ 37 U/mL) (1 point) [15–17], and (5) US findings (2 points) [18, 19]. The US findings included direct (e.g., a solid pancreatic tumor) and indirect findings (e.g., dilatation of the MPD to a diameter of ≥ 2.5 mm or a pancreatic cyst). DM was defined as a fasting blood sugar level of ≥ 126 mg/dL, a casual blood glucose level of ≥ 200 mg/dL, or HbA1c (NGSP) $\geq 6.5\%$.

Protocol for Social Programs for Diagnosing e-PC (Fig. 1)

The JPS guidelines include a protocol for diagnosing and treating PC [3]. The protocol in the present study (the Kishiwada project) referenced the protocol for the diagnosis of PC.

Patients who were enrolled based on their clinical findings underwent diffusion-weighted imaging (DWI) MRI and MRCP, and EUS (GF-UC240P-AL5; Olympus, Tokyo, Japan) was performed. If EUS revealed a solid mass in the pancreas, then EUS-fine needle aspiration (EUS-FNA) was performed [20, 21]. If the findings revealed irregular stenosis in the MPD or dilatation of the MPD, then endoscopic retrograde cholangiopancreatography was performed, and a cytological examination of pancreatic juice samples obtained by multiple endoscopic nasopancreatic drainage (ENPD) samplings was performed (Fig. 1).

Fig. 2. Clinical characteristics of patients. a-PC, advanced pancreatic cancer; e-PC, early-stage pancreatic cancer; EK, neuroendocrine; LN, lymph node; AIP, autoimmune pancreatitis; TFP, tumor-forming pancreatitis; GIMT, gastrointestinal mesenchymal tumor; SCN, serous cyst adenoma; IPMN, intraductal papillary mucinous neoplasm; ND, no disease. For all other abbreviations, see Figure 1.

Fig. 3. A 66-year-old woman positive at entry for 3 points (“symptoms [abdominal pain]” and “US findings”) of 5 clinical findings from a primary-care medical office. **a** Ultrasonography did not detect a tumor without dilatation of the main pancreatic duct. **b** Magnetic resonance cholangiopancreatography shows stenosis and dilatation of the main pancreatic duct (arrow). **c** Endoscopic ultrasonography shows a low-echoic lesion measuring 18 mm in diameter (arrow) adjacent to the bile duct. The histological diag-

nosis was adenocarcinoma by endoscopic ultrasonography-fine needle aspiration. **d** She received subtotal stomach-preserving pancreaticoduodenectomy. The resected specimen showed a white solid tumor, measuring 20 × 18 mm (arrowheads). A pathologic examination of the resected specimen showed invasive ductal carcinoma, moderately differentiated. The final pathological diagnosis was stage IIA pancreatic cancer. PV, portal vein; CBD, common bile duct.

DWI-MRI and MRCP Techniques

MRI examinations were carried out with a 2.0-Tesla unit (Vantage Titan, Toshiba, Japan) with a 12-channel body and spine matrix coil combination. DWI was performed as a part of the routine abdomen MRI protocol for the evaluation of hepato-pancreato-biliary ducts in our institution. The protocol included axial fat-sat T1-weighted images, axial T2-weighted images, axial T2-weighted half-Fourier acquisition single-shot turbo spin echo images, coronal 2D MRCP, coronal 3D MRCP, and DWI images.

Apparent diffusion coefficient maps were automatically reconstructed for all DWI.

Diagnosis and Classification of PC

The final diagnoses were made according to the histology of the resected tumor. For patients who did not undergo surgical resection, the final diagnoses were made according to the histology or cytology of samples obtained by EUS-FNA or ENPD. In cases where pancreatic malignancy was excluded by EUS-FNA or

ENPD, the final diagnosis was confirmed by following the patient for at least 6 months.

Tumor classification was performed accordance with the Union for International Cancer Control (UICC) guidelines for PC. In this study, e-PC was defined as stage 0-IIb and advanced PC (a-PC) was defined as stage III-IV accordance with the UICC guidelines.

Statistical Analyses

The mean total scores of the e-PC, a-PC, and non-PC groups were compared using Wilcoxon's signed-rank test. The χ^2 test was used to compare the frequencies of each clinical findings category between the e-PC, a-PC, and non-PC groups. Sensitivities for detecting pancreatic findings (direct and indirect) by MRCP were calculated and compared between the e-PC and a-PC groups. A p value <0.05 was considered to be statistically significant.

Results

Among the 244 cases diagnosed with PC based on the clinical findings, pancreatic disease was detected in 155 cases (63.5%), while diseases other than pancreatic disease were detected in 64 (26.2%), and 25 cases (10.3%) were found to have no disease at all (Fig. 2).

Three of these 155 patients received a cytodiagnosis using pancreatic juice obtained by ENPD, as EUS revealed a tumor in the MPD; they were therefore diagnosed with adenocarcinoma by cytology of the ENPD sample. One of these 3 patients underwent distal pancreatectomy, and the other 2 received best supportive care because they were elderly. Forty-one cases in whom EUS revealed a tumor in the pancreas parenchyma underwent EUS-FNA. The final UICC tumor classification of pancreatic adenocarcinoma revealed that 15 of the 28 PC (53.6%) cases were e-PC (stage IA, $n = 4$; IB, $n = 1$; IIA, $n = 4$; IIB, $n = 6$); 11 and 4 patients in the e-PC group received surgery and best supportive care because 4 patients were elderly, respectively (Fig. 3). Thirteen of the 28 PC (46.4%) cases were a-PC (stage III, $n = 4$; IV, $n = 9$); 9 and 4 patients in the a-PC group received chemotherapy and best supportive care, respectively. In 105 cases, EUS revealed a cystic lesion or pancreatic swelling but did not reveal a solid tumor in the pancreas; therefore, these patients are being followed up without EUS-FNA or ENPD (Fig. 2).

Comparison of the Mean Total Scores at Entry among the e-PC, a-PC, and Non-PC Groups (Fig. 4)

The average total scores were 3.1 ± 1.9 , 3.9 ± 0.9 , and 2.1 ± 0.4 in the e-PC, a-PC, and non-PC groups, respectively. The average total score of the e-PC and a-PC group

Fig. 4. A comparison of the mean total scores at entry among the early-stage pancreatic cancer (e-PC), advanced pancreatic cancer (a-PC), and non-pancreatic cancer (non-PC) groups. ns, not significant.

was significantly higher than that of the non-PC group ($p < 0.05$). There were no significant differences in the average total score between the e-PC and a-PC groups (Fig. 4).

Comparison of Each Score Item among the e-PC, a-PC, and Non-PC Groups (Fig. 5)

“High AMY/P-AMY” was found in 8 of 15 (53.3%), 2 of 13 (15.4%), and 36 of 216 (16.7%) patients in the e-PC, a-PC, and non-PC groups, respectively; the frequency in the e-PC group was significantly higher than in the other groups ($p < 0.05$). “Symptoms” was found in 8 of 15 (53.3%), 10 of 13 (77%), and 42 of 216 (19.4%) patients in the e-PC, a-PC, and non-PC groups, respectively; the frequency in the e-PC and a-PC groups was significantly higher than in the non-PC group ($p < 0.05$). “US findings” was found in 11 of 15 (73.3%), 10 of 13 (66%), and 160 of 216 (74.5%) patients in the e-PC, a-PC, and non-PC groups, respectively, which was not significantly different. “New-onset DM” was found in 1 of 15 (6.7%), 5 of 13 (38.5%), and 17 of 216 (7.9%) patients in the e-PC, a-PC, and non-PC groups, respectively; the frequency in the e-PC group was significantly higher than in the other groups ($p < 0.05$). “High CA19-9 levels” was found in 8 of 15 (53.3%), 13 of 13 (100%), and 17 of 216 (7.9%) patients in the e-PC, a-PC, and non-PC groups, respectively; the frequency in the e-PC group was significantly higher than in the non-PC group ($p < 0.05$).

Fig. 5. A comparison of each score item among the early-stage pancreatic cancer (e-PC), advanced pancreatic cancer (a-PC), and non-pancreatic cancer (non-PC) groups. P-AMY, pancreatic amylase; US, ultrasonography; DM, diabetes mellitus; CA19-9, carbohydrate antigen 19-9; ns, not significant.

Clinical Findings of the PC Patients at Entry

Nine of the 15 (60.0%) patients in the e-PC group, were enrolled via GIMs, while the remaining 6 (40.0%) were enrolled via PMOs (general surgery, $n = 3$; urology, $n = 2$; otolaryngology, $n = 1$). Six patients with abdominal pain in the e-PC group had acute pancreatitis; the abdominal pain coincided with a high AMY level. Abnormal US findings were detected at entry in 11 of the 15 (73.3%) patients in the e-PC group, and the remaining 4 (26.7%) were enrolled via facilities in which US was not conducted. After having being introduced to our hospital, all of these patients underwent US. The total sensitivity of direct detection by US (both US findings at entry and at our institution) was 40.0% (6 of 15) in the e-PC group. The total sensitivity for detecting MPD dilatation by US was 66.7% (10 of 15) in the e-PC group. The sensitivity for detecting a cystic lesion by US was 20.0% (3 of 15) in the e-PC group. The overall sensitivity of indirect US findings (MPD dilatation and/or cystic lesion) by US was 93.3%.

Comparison of the Sensitivities of Detecting Pancreatic Findings by MRCP between the e-PC and a-PC Groups (Table 1)

The sensitivities for detecting pancreatic carcinoma by diffusion MRI were 33.3% (5 of 15) and 92.3% (12 of 13) in the e-PC and a-PC groups, respectively, which was significantly different ($p < 0.05$). The sensitivities for detecting MPD dilatation by MRCP were 93.3% (14 of 15) and 84.6% (11 of 13) in the e-PC and a-PC groups, respectively. The sensitivities for detecting MPD cystic lesion by MRCP were 26.7% (4 of 15) and 38.5% (5 of 13) in the e-PC and a-PC groups, respectively. There were no significant differences in the indirect findings for MPD dilatation and MPD cystic lesions between the e-PC and a-PC groups.

Discussion

PC is one of most lethal malignant cancers, ranking fifth in mortality related to cancer worldwide. The overall 5-year survival rate of PC has been reported to be

Table 1. Total sensitivities for detecting pancreatic findings by diffusion magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) between the early-stage pancreatic cancer (e-PC) and advanced pancreatic cancer (a-PC) groups

	Direct finding on diffusion MRI, <i>n</i> (%)	Indirect findings on MRCP, <i>n</i> (%)		
	solid tumor	MPD dilatation	cystic lesion	MPD dilatation and/ or cystic lesions
e-PC group (<i>n</i> = 15)	5 (33.3)	14 (92.3)	4 (26.7)	8 (100)
a-PC group (<i>n</i> = 13)	12 (92.3) } <i>p</i> < 0.05	11 (84.6) } ns	5 (38.5) } ns	6 (100) } ns

MPD, main pancreatic duct; ns, not significant.

around 1–4% [22]. Egawa et al. [23] analyzed 32,619 cumulative records from 1981 to 2007. The survival curve in their report was divided into that for patients who underwent pancreatectomy and that for those who had unresectable disease. There was a significant increase in the survival rate in the patients who underwent resection. Chiang et al. [24] compared the clinicopathological characteristics and prognosis of large PC (tumor size >2 cm) and small PC (tumor size ≤2 cm) patients undergoing resection. Small-PC and large-PC patients had a similar prognosis after resection [23]. A high albumin level (>3.5 g/dL) and early-stage disease (stage I, II) were favorable prognosis factors for small-PC patients. The detection of PC at an early stage and the performance of curative surgery can be expected to improve the long-term patient outcomes.

Hanada et al. [4, 22] reported that a social program for the early diagnosis of PC, with collaborations between Onomichi Hospital, specialists in PC from medical centers, and general practitioners (Onomichi project), was useful for the early detection of PC. Developing an effective screening strategy for PC will require the establishment of a network wherein facilities specializing in PC cooperate with medical offices of various channels. Screening for cases of PC is simple and easy for various doctors, and a sensitive screening method that is safe with low invasiveness eagerly waited.

The pathogenesis of neoplasm remains unclear, but some risk factors have been noted for identifying candidates for screening, such as DM, obesity, cigarette smoking, a family history of PC, chronic pancreatitis, and intraductal papillary mucinous neoplasm. Evidence-based clinical guidelines for PC were published by the Japan Pancreas Society (JPS) in 2013 [3]. The sections of Clinical questions 1 and 2 suggest some risk factors that may

be involved in the development of PC [4–11]. With reference to this information, this social program (Kishidawa Katsuragi project) adopted clinical findings.

We compared each item in the scores among the e-PC, a-PC, and non-PC groups. “US findings” showed no significant difference among the three groups. Three of the five clinical findings (“symptoms,” “new onset DM,” and “high CA19-9”) were more frequent in the a-PC group than in the other groups. In contrast, “high AMY/P-AMY” was significantly more frequent in the e-PC group than in the other groups. Six patients with abdominal pain in the e-PC group had acute pancreatitis; abdominal pain coincided with a high AMY/P-AMY level. Thus, regarding the clinical findings, abdominal pain in patients with a high AMY/P-AMY level was important for the detection of e-PC. Homma et al. [25] reported that, in a study of 10,162 asymptomatic individuals, abnormal CA19-9 levels were only noted in 18 (0.2%) subjects. Although their study used a variety of screening tests, only 4 cases of PC (0.04%) were detected [25]. The measurement of CA19-9 levels alone was therefore ineffective as a screening test for PC, especially in asymptomatic individuals. In our study, when the finding of a high CA19-9 level was combined with at least one other clinical finding, the rate of CA19-9 elevation in the e-PC group at entry was 53.3%. As such, the combined finding of a high CA19-9 level and another clinical finding may be useful for detecting e-PC.

In this study, the total (both US findings at entry and our institution) sensitivity for detecting a direct finding by US was 40.0% in the e-PC group. However, the sensitivities for indirect findings, such as MPD dilatation or cystic lesions, by US were high and were therefore deemed very important for the detection of e-PC. Although the diagnostic ability of US depends on the operator’s experi-

ence and the patient's condition (in terms of obesity and bowel gas content), US remains useful noninvasive, convenient technique, and it is associated with lower costs than multiple detector computed tomography (MDCT), MRCP/diffusion MRI, and EUS, which are necessary primary imaging modalities for diagnosing e-PC.

Although there were no significant differences in the average total score between the e-PC and a-PC groups, the average total scores of the e-PC and a-PC groups were significantly higher than those of the overall non-PC groups at entry. Therefore, our findings suggested that if the average score for clinical findings was ≥ 3 , we should strongly doubt pancreatic cancer and perform a more detailed inspection with MRCP/diffusion MRI, EUS and MDCT.

In the Kishiwada Katsuragi project, patients who were enrolled according to clinical findings initially underwent MRCP/diffusion MRI. MDCT involves radiation exposure and carries an unpredictable risk of an allergic response to the iodine contrast medium; however, MRCP/diffusion MRI carries no such risk or exposure requirements. In addition, MRCP is a noninvasive and increasingly common procedure in cases of biliary and pancreatic diseases and is as sensitive as endoscopic retrograde cholangiopancreatography in detecting pancreatic carcinomas [26–28]. Furthermore, diffusion MRI measures the Brownian motion (random thermal diffusion) of molecules in tissues and depicts locoregional characteristics of water diffusion. Thus, diffusion MRI can be used to distinguish neoplastic lesions from the surrounding normal tissues without the need for an imaging contrast agent. Diffusion MRI can be used for the diagnosis of PC. In our study, patients who were enrolled based on their clinical findings initially underwent diffusion MRI/MRCP. In our study, the sensitivities of detecting direct finding by diffusion MRI were 33.3 and 92.3% in the e-PC and a-PC groups, respectively. Although diffusion MRI was useful for detecting a-PC, it was not sufficient to detect e-PC. However, in the e-PC group, the sensitivities for overall indirect findings, including dilatation of the

MPD and/or cysts, was 100%, suggesting that these findings were very important for detecting e-PC.

In the Kishiwada Katsuragi project, we hoped that the clinical findings would allow e-PC to be readily detected by any PMO. Therefore, 41 PMOs (27 GIMs and 14 other PMOs) were enrolled as cooperative facilities, including 27 GIMs and 14 other types of PMO (general surgery, urology, and orthopedics departments) to determine which clinical findings were most closely associated with the detection of PC. Six (6/15) of all patients with e-PC were detected by other PMOs, suggesting that the participation of other PMOs, as well as GIMs, plays an important role in improving the e-PC detection rate. Regarding the clinical findings at entry, the rates of patients with symptoms, high AMY/P-AMY, high CA19-9, and new-onset DM were lower than those with US findings in the e-PC groups; however, these findings were important for the detection of PC because 4 of the 15 (26.7%) patients were from facilities in which US was not conducted.

The present study is associated with several limitations, including the small study population. Further examinations are therefore necessary. The accumulation of a greater number of cases and the modification of the clinical finding score will be necessary to improve the efficiency of PC detection.

In conclusion, social programs with collaborations between medical centers that specialize in PC and PMOs used clinical findings, suggesting that not only GIMs but also other PMOs may be important for the early detection of PC. Findings from US and MRCP/diffusion MRI, especially indirect findings such as dilatation of the MPD and cystic lesions, were useful for the detection of e-PC. Further studies with the accumulation of a greater number of cases are necessary to confirm our findings.

Disclosure Statement

There are no companies in a relation of conflict of interest requiring disclosure in relation to this paper.

References

- 1 Egawa S, Toma H, Ohigashi H, Okusaka T, Nakao A, Hatori T, Maguchi H, Yanagisawa A, Tanaka M: Japan Pancreatic Cancer Registry; 30th year anniversary: Japan Pancreas Society. *Pancreas* 2012;41:985–992.
- 2 D'Haese JG, Werner J: Resectability of pancreatic cancer: new criteria. *Radiologe* 2016; 56:318–324.
- 3 Yamaguchi K, Okusaka T, Shimizu K, Furuse J, Ito Y, Hanada K, Shimosegawa T: Committee for revision of clinical guidelines for pancreatic cancer of Japan Pancreas Society. EBM-based clinical guidelines for pancreatic cancer (2013) issued by the Japan Pancreatic Society: a synopsis. *Jpn J Clin Oncol* 2014;44: 883–888.

- 4 Hanada K, Okazaki A, Hirano N, Izumi Y, Te-
raoka Y, Ikemoto J, Kanemitsu K, Hino F, Fu-
kuda T, Yonehara S: Diagnostic strategies for
early pancreatic cancer. *J Gastroenterol* 2015;
50:147–154.
- 5 Okano K, Suzuki Y: Strategies for early detec-
tion of resectable pancreatic cancer. *World J*
Gastroenterol 2014;20:11230–11240.
- 6 Raimondi S, Lowenfels AB, Morselli-Labate
AM, Maisonneuve P, Pezzilli R: Pancreatic
cancer in chronic pancreatitis; aetiology, inci-
dence and early detection. *Best Pract Res Clin*
Gastroenterol 2010;24:349–358.
- 7 McKay CJ, Glen P, McMillan DC: Chronic in-
flammation and pancreatic cancer. *Best Pract*
Res Clin Gastroenterol 2008;22:65–73.
- 8 Rebours V, Boutron-Ruault MC, Schnee M,
Férec C, Maire F, Hammel P, Ruszniewski P,
Lévy P: Risk of pancreatic adenocarcinoma in
patients with hereditary pancreatitis: a na-
tional exhaustive series. *Am J Gastroenterol*
2008;103:111–119.
- 9 Klein AP, Brune KA, Petersen GM, Goggins
M, Tersmette AC, Offerhaus GJ, Griffin C,
Cameron JL, Yeo CJ, Kern S, Hruban RH:
Prospective risk of pancreatic cancer in fami-
lial pancreatic cancer kindreds. *Cancer Res*
2004;64:2634–2638.
- 10 Canto MI, Harinck F, Hruban RH, Offerhaus
GJ, Poley JW, Kamel I, Nio Y, Schulick RS,
Bassi C, Kluijdt I, Levy MJ, Chak A, Fockens P,
Goggins M, Bruno M: International Cancer of
Pancreas Screening (CAPS) Consortium. In-
ternational Cancer of the Pancreas Screening
(CAPS) consortium summit on the manage-
ment of patients with increased risk for fami-
lial pancreatic cancer. *Gut* 2013;62:339–347.
- 11 Brune KA, Lau B, Palmisano E, Canto M,
Goggins MG, Hruban RH, Klein AP: Import-
ance of age of onset in pancreatic cancer kin-
dreds. *J Nat Cancer Inst* 2010;102:119–126.
- 12 Pannala R, Basu A, Petersen GM, Chari ST:
New-onset diabetes: a potential clue to the
early diagnosis of pancreatic cancer. *Lancet*
Oncol 2009;10:88–95.
- 13 Ogawa Y, Tanaka M, Inoue K, Yamaguchi
K, Chijiwa K, Mizumoto K, Tsutsu N, Naka-
mura YA: A prospective pancreatographic
study of the prevalence of pancreatic carcino-
ma in patients with diabetes mellitus. *Cancer*
2002;94:2344–2349.
- 14 Mizuno S, Nakai Y, Isayama H, Yanai A,
Tahagara N, Miyabayashi K, Yamamoto K,
Kawakubo K, Mohri D, Kogure H, Sakaki T,
Yamamoto N, Sahahira N, Hirano K, Tsujino
T, Ljichi H, Takeishi K, Akanuma M, Taka M,
Koike K: Risk factors and early signs of pan-
creatic cancer in diabetes: screening strategy
based on diabetes onset age. *J Gastroenterol*
2013;48:238–246.
- 15 Pleskow DK, Berger HJ, Gyves J, Allen E,
McLean A, Podolsky DK: Evaluation of a se-
rologic marker, CA19-9, in the diagnosis of
pancreatic cancer. *Ann Intern Med* 1989;110:
704–709.
- 16 Marrelli D, Caruso S, Pedrazzani C, Neri A,
Fernandes E, Marini M, Pinto E, Roviello F:
CA19-9 serum levels in obstructive jaundice:
clinical value in benign and malignant condi-
tions. *Am J Surg* 2009;198:333–339.
- 17 Glenn J, Steinberg WM, Kurtzman SH, Stein-
berg SM, Sindelar WF: Evaluation of the util-
ity of a radioimmunoassay for serum CA19-9
levels in patients before and after treatment of
carcinoma of the pancreas. *J Clin Oncol* 1988;
6:462–468.
- 18 Nakaizumi A, Tatsuta M, Uehara H, Iishi H,
Yamamura H, Okuda S, Kitamura T: A pro-
spective trial of early detection of pancreatic
cancer by ultrasonographic examination
combined with measurement of serum elas-
tase 1. *Cancer* 1992;69:936–940.
- 19 Tanaka S, Nakao M, Ioka T, Takakura R,
Takano Y, Tsukuma H, Uehara H, Suzuki R,
Fukuda J: Slight dilatation of the main pan-
creatic duct and presence of pancreatic cysts as
predictive signs of pancreatic cancer: a pro-
spective study. *Radiology* 2010;254:965–972.
- 20 Sakamoto H, Kitano M, Komaki T, Noda K,
Chikugo T, Kudo M: Small cell carcinoma of
the pancreas: role of EUS-FNA and subse-
quent effective chemotherapy using carbopla-
tin and etoposide. *J Gastroenterol* 2009;44:
432–438.
- 21 Sakamoto H, Kitano M, Komaki T, Noda K,
Chikugo T, Dote K, Takeyama Y, Das K, Ya-
mao K, Kudo M: Prospective comparative
study of the EUS guided 25-gauge FNA needle
with the 19-gauge Trucut needle and 22-gauge
FNA needle in patients with solid pancreatic
masses. *J Gastroenterol Hepatol* 2008;55:
1785–1788.
- 22 Hanada K, Okazaki A, Hirano N, Izumi Y,
Minami T, Ikemoto J, Kanemitsu K, Hino F:
Effective screening for early diagnosis of pan-
creatic cancer. *Best Pract Res Clin Gastroen-
terol* 2015;29:929–939.
- 23 Egawa S, Toma H, Ohigashi H, Okusaka T,
Nakao A, Hatori T, Maguchi H, Yanagisawa
A, Tanakan M: Japan Pancreatic Cancer Reg-
istry; 30th year anniversary: Japan Pancreas
Society. *Pancreas* 2012;41:985–992.
- 24 Chiang KC, Yeh CN, Lee WC, Jan YY, Hwang
TL: Prognostic analysis of patients with pan-
creatic head adenocarcinoma less than 2 cm
undergoing resection. *World J Gastroenterol*
2009;15:4305–4310.
- 25 Homma T, Tsuchiya R: The study of the mass
screening of persons without symptoms and
of the screening of outpatients with gastroin-
testinal complains or icterus for pancreatic
cancer in Japan, using CA19-9 and elastase-1
or ultrasonography. *Int J Pancreatol* 1991;9:
119–124.
- 26 Lopež Hänninen E, Amthauer H, Hosten N,
Ricke J, Böhmig M, Langrehr J, Hintze R,
Neuhaus P, Wiedenmann B, Rosewicz S, Felix
R: Prospective evaluation of pancreatic tu-
mors: accuracy of MR imaging with MR chol-
angiopancreatography and MR angiography.
Radiology 2002;224:34–41.
- 27 Adamek HE, Albert J, Breer H, Weitz M,
Schilling D, Riemann JF: Pancreatic cancer
detection with magnetic resonance cholangi-
opancreatography and endoscopic retrograde
cholangiopancreatography: a prospective
controlled study. *Lancet* 2000;356:190–193.
- 28 Holzapfel K, Reiser-Erkan C, Fingerle AA, Er-
kan M, Eiber MJ, Rummeny EJ, Friess H,
Kleeff J, Gaa J: Comparison of diffusion-
weighted MR imaging and multidetector-row
CT in the detection of liver metastases in pa-
tients operated for pancreatic cancer. *Abdom*
Imaging 2011;36:179–184.