Evaluation of Routine Sonography for Early Detection of Pancreatic Cancer

Sachiko Tanaka[1], Tsugio Kitamra[1], Kiyomi Yamamoto[1], Sachiko Fujikawa,[1] Tomoko Imaoka[1], Shigeri Nishikawa[1], Akihiko Nakaizumi[2], Hiroyuki Uehara[2], Osamu Ishikawa[3] and Hiroaki Ohigashi[3]

[1]Laboratory of Ultrasonography, Departments of [2]Gastrointestinal Oncology and [3]Surgery, The Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka

The diagnostic accuracy of routine abdominal sonography for the detection of pancreatic cancer was examined. During the one-year period of 1994, sonographic examination of the upper abdominal region was performed 12,761 times on a total of 9410 patients for the screening of abdominal disorders. In 655 cases (7%) part of the pancreas could not be observed. Based on the "Diagnostic criteria for pancreatic cancer" published by the Japanese Society of Ultrasound in Medicine, sonographic finding was evaluated to be positive for pancreatic tumor in a total of 411 cases. At the end of 1995, 51 patients were proven to have pancreatic cancer, and 45 of these cases were ductal adenocarcinoma. In 26 cases the tumor was surgically resected. Fifty cases were true sonographic positives and one was a false negative. The sensitivity, specificity, overall accuracy, and positive and negative predictive values of sonography for pancreatic cancer were 98.0%, 95.9%, 95.9%, 12.2% and 100.0%, respectively. Among the 50 true positive cases, the tumor diameter was less than 1 cm in four (8%). In conclusion, the diagnostic accuracy of sonography for the detection of pancreatic cancer is sufficiently high. Therefore, a detailed study aimed at mass screening for pancreatic cancer using sonography as the main modality seems warranted as a countermeasure for the rapid increase of pancreatic cancer in Japan.

(Jpn J Clin Oncol 26: 422–427, 1996)

Key words: Pancreatic cancer—Ultrasonography—Diagnostic accuracy

Introduction

The prognosis of pancreatic cancer has been reported to be very poor.[1–3] However, recent reports have described a better prognosis if the cancers are small and detected early. Crist *et al.*[1] reported that the 5-year actuarial survival rate after surgical treatment for pancreatic cancer without lymph node metastasis was quite high, 48%. Ishikawa *et al.*[4] summarized 32 reported cases of small pancreatic cancer measuring 1 cm or less, and described a good 5-year survival of 67% after surgery. Moreover Nakaizumi *et al.*[5] reported that cytologically-diagnosed *in situ* pancreatic cancer or cancer with minimal invasion could be expected to have a good long-term prognosis. Hence, early detection of pancreatic cancer with a highly sensitive modality is required to improve the prognosis of this disease.

Following the introduction of real-time sonography, the diagnostic accuracy of ultrasonographic examination (US) for hepatocellular carcinoma has improved markedly,[6, 7] and a mass survey with US was reported to be effective for early diagnosis of hepatocellular carcinoma.[8] Although the pancreas has been considered difficult to visualize by US,[9] introduction of the convex-type probe has brought an obvious improvement in the visualization of this organ.

Furthermore, many reports[2–4] have described that US has been the major aid for initial detection of resectable pancreatic cancer.

In the present study, the diagnostic accuracy of routine abdominal US for pancreatic cancer was examined retrospectively, and the possibility of mass

Received: February 29, 1996
Accepted: June 3, 1996
For reprints and all correspondence: Sachiko Tanaka, Laboratory of Ultrasonography, The Osaka Medical Center for Cancer and Cardiovascular Diseases, 3-3, Nakamichi 1-chome, Higashinari, Osaka 537

Downloaded from https://academic.oup.com/jjco/article/26/6/422/1785637 by guest on 24 April 2024

Table I. Diagnostic Criteria for Pancreatic Cancer

Existence of pancreatic tumor[10]
A. Definite
1: Markedly abnormal echoic area* (echo level, pattern, boundary)
2: Abnormal echoic area with dilatation of the distal pancreatic duct
3: Abnormal echoic area with stenosis or obstruction of the common bile duct in the pancreas and the pancreatic area
4: Abnormal echoic area with localized swelling of the pancreas
B. Suspected mass
1: Abnormal echoic area in the pancreas
2: Abnormal echoic area in the vicinity of the pancreas
3: Localized swelling of the pancreas including the pancreatic margin
C. Further examination recommended
1: Dilatation of the pancreatic duct
2: Dilatation of the common bile duct and/or swelling of the gallbladder

Remarks: *, an abnormal echoic area is defined as one which is either lighter or darker, more or less dense, and with a different arrangement of echoic elements than the surrounding tissues. In addition, there is a clearly discernible border and a change from the normal echoic patterns.

Table II. Results of US Findings According to the Criteria for Pancreatic Cancer

US findings	No. of positive cases	Pancreatic cancer (< 1 cm)
Definite		
A-1 (solid)	62	15
(cystic)	118	2 (1)
A-2*	40	19 (2)
A-3	10	7
A-4	7	3
Suspected		
B-1	5	0
B-2	2	2
B-3	8	0
Further exam. recommended		
C-1*	122	1 (1)
C-2	37	1
Total	411	50 (4)

*A-2, C-1: 3 mm or more is regarded as dilatation of the pancreatic duct.

screening for pancreatic cancer was assessed.

Patients and Methods

During the one-year period from January 1 to December 31, 1994, US of the upper abdominal region was performed 12,761 times on a total of 9410 patients (5309 males and 4101 females; age range: 14–96 years; mean: 59 years) at the hospital of the Osaka Medical Center for Cancer and Cardiovascular Diseases. US was performed routinely by several well trained sonographers and doctors specializing in gastroenterology. The US took about 15 min. for each patient in a supine position and sometimes in a sitting position. Requests for US were received from various departments of our hospital and sometimes from other hospitals, for the screening of abdominal disorders.

The instruments used were a EUB-565, EUB-450 and EUB-40 with 3.5- and 5-MHz convex probes (Hitachi, Tokyo), and a UM9-HDI with 3- and 4 to 7-MHz convex probes (ATL, Seattle, WA).

Based on the "Diagnostic criteria for pancreatic cancer" (Table I), published by the Japanese Society of Ultrasound in Medicine,[10] the existence of pancreatic tumors was evaluated using three ranks: definite (A), suspected (B) and further examination recommended (C). For the final diagnosis of pancreatic cancer, all subjects were checked against the Cancer Registry in our hospital at the end of 1995. For patients who ceased attending, their recent physical condition was confirmed by telephoning the patients or their families.

Results

US Findings

Of the 9410 cases, the pancreas was successfully observed and evaluated by US in 8755 (93.0%). In the remaining 655 cases, part of the pancreas could not be visualized clearly, although no abnormal US findings were detected. The results of US are shown in Table II: 237 cases were ranked as A, 15 as B and 159 as C.

For the total of 411 patients with positive US findings, CT, ERCP, pancreatic juice cytology, repeated US and/or other examinations were performed.

Pancreatic Cancer Cases

Of the 9410 patients, 51 (0.54%) (31 males and 20 females) were proven to have pancreatic cancer by the end of 1995. Of these cases, 36 (71%) were histologically proven to be pancreatic cancer, and the remaining cases were cytologically proven. The cancers included 45 ductal adenocarcinomas, two cystadenocarcinomas, one adenosquamous cell carcinoma and three islet cell carcinomas. The patients ranged in age from 30 to 54 years (mean: 42 years) for islet cell carcinoma and 41 to 81 years (mean:

Downloaded from https://academic.oup.com/jjco/article/26/6/422/1785637 by guest on 24 April 2024

Table III. Final Diagnoses of Cases with Positive US Findings

Pancreatic cancer	50	
Other pancreatic diseases	171	
benign pancreatic tumor		5
metastatic pancreatic cancer		3
tumor-forming pancreatitis		4
benign pancreatic cyst		125
chronic pancreatitis		29
pancreatic swelling		5
Cancer of neighboring organs	6	
Idiopathic cholangio dilatation	3	
Choledochal stone	2	
Lymph node swelling	8	
Normal intestine	8	
No focal lesion	150	
Others	13	
Total	411	

61 years) for the other carcinomas. The tumor was located in the pancreatic head in 27 cases, the body in ten, the tail in five, the head to body in four and the body to tail in five. Eight lesions (16%) were smaller than 2 cm in diameter, and four (8%) were smaller than 1 cm. In 26 cases (51%), surgical resection of the tumor was performed, and in 11 other cases (22%) infusion chemotherapy and/or anastomosis was performed. In the remaining 14 cases, conservative treatment with mild chemotherapy was performed.

Diagnostic Accuracy

Of the 51 pancreatic cancer cases, 46 were diagnosed as rank A, two as rank B and two as rank C by US. The remaining case was a false-negative. Of the 8755 cases in which the pancreas could be observed and evaluated by US, 237 (2.7%) were ranked as A, of which 46 (19.4%) were finally diagnosed as pancreatic cancer. A total of 411 cases (4.7%) were ranked as A, B or C. The final diagnoses of these cases are shown in Table III. Fifty patients (12.2%) were proven to have pancreatic cancer, and 171 (41.6%) had other pancreatic diseases. One hundred fifty patients were proven by other modalities not to have focal lesions, and 13 showed no symptoms and were followed up for one to two years after the US examination.

Thus, when only rank A was regarded as positive, the sensitivity, specificity, overall accuracy, and positive and negative predictive values of US for the detection of pancreatic cancer were 90.2%, 97.8%, 97.9%, 19.4% and 100.0%, respectively. When the total of ranks A, B and C were regarded as positive, the figures were 98.0%, 95.9%, 96.2%, 12.2% and 100.0%, respectively.

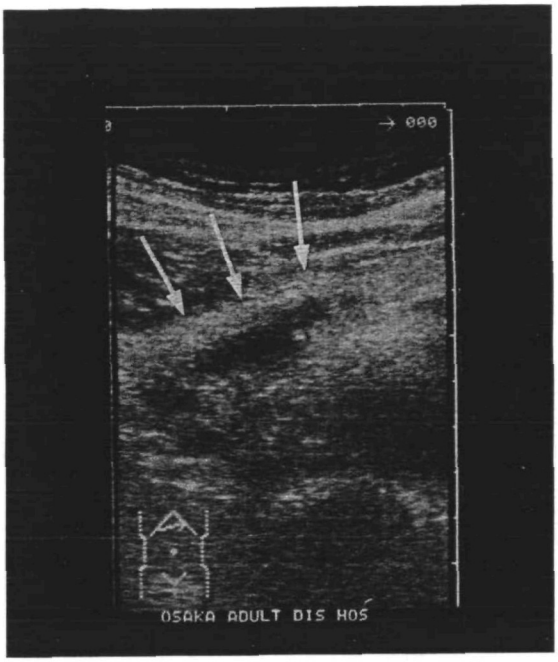


Fig. 1. Longitudinal pancreatic sonogram of a true positive case. A dilated (5 mm) pancreatic duct (arrow heads) is shown running through the middle of the hyperechoic pancreas (arrows). Though no focal lesion was detected by any imaging modalities, a cytologic examination of the pure pancreatic juice showed positivity for cancer. Following the intraoperative cytodiagnosis, ductal adenocarcinoma located in the head was resected.[18]

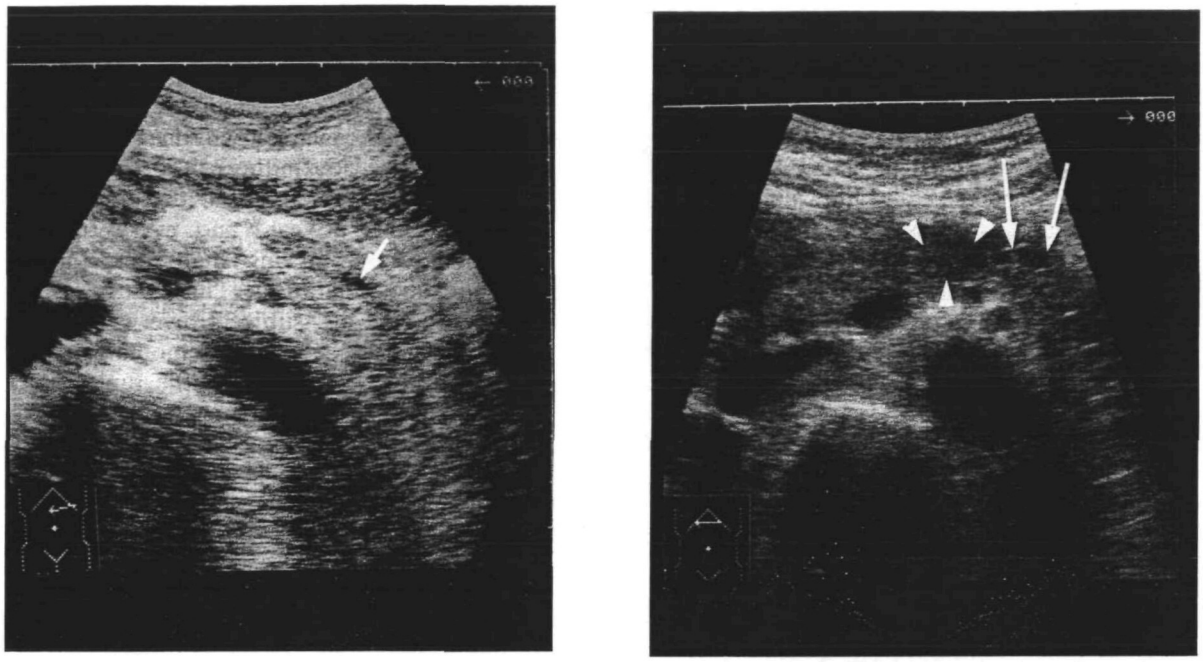
Small Cancers

There were four cases where the tumor was less than 1 cm in diameter. These included two ductal adenocarcinomas, a cystoadenocarcinoma and an islet cell carcinoma. In each of these four cases, US findings were positive and radical curative surgical resection was performed. The US findings in these four cases were pancreatic duct dilatation (Fig. 1) in one case, small cystic lesion in one case, and a hypoechoic lesion with distal pancreatic duct dilatation in two cases.

False-negative Case

In one case, no abnormal findings were detected by US, but pancreatic cancer was confirmed later. A retrospective review of the sonogram in this case revealed slight dilatation (about 2 mm or less) of the main pancreatic duct in the body to tail portion (Fig. 2a). Thirteen months later, US was performed again for screening when the patient was asymptomatic. A 15-mm faint hypoechoic lesion was detected in the body, with 4-mm dilatation of the distal pancreatic duct (Fig. 2b). After further examination, a 15-mm ductal adenocarcinoma was resected

Downloaded from https://academic.oup.com/jjco/article/26/6/422/1785637 by guest on 24 April 2024



(a) (b)

Fig. 2. Longitudinal pancreatic sonograms of a false negative case. (a) Only slight dilatation (<2 mm) of the main pancreatic duct (arrow) is shown in the body. (b) (13 months later): A faint hypoechoic lesion 15 mm in diameter (arrow heads) with distal dilatation of the pancreatic duct (arrows) is visualized.

by radical curative surgery.

Discussion

There have been various reports[11–16] concerning the diagnostic accuracy of various imaging modalities for pancreatic cancer, but most of them have dealt with only selected cases where pancreatic cancer was suspected or patients with pancreatitis. DelMaschio *et al.*[11] examined the accuracy of CA19-9, US, CT and fine-needle biopsy for differential diagnosis of pancreatic cancer from pancreatitis, and concluded that US should be performed first for screening because of its high negative predictive value.

In the present study, the accuracy of routine US for detection of pancreatic cancer was examined. The results showed a high negative predictive value of 100.0% and a sensitivity of 98%. The positive predictive value was not high at 12.2%, since only pancreatic cancer cases were considered to represent a positive result. Among patients with a false positive result, 47% (171/361) had some disorder of the pancreas. However, in general, a high sensitivity or high negative predictive value is much more important than a positive predictive value for screening. In our series, part of the pancreas could not be observed in 7% of the subjects. Therefore, spiral CT or other modalities will be necessary for cases in which pancreatic disorder is suspected and the pancreas cannot be observed in its entirety by US.

According to the cancer mortality and morbidity statistics for Japan,[17] the age-adjusted death rate per 100,000 population due to pancreatic cancer in Japan was less than two for both sexes until 1952. However, it increased rapidly thereafter, surpassing the rate among white Americans and for some European countries during the period 1983–1987. The rate in Japan reached 12.2 for males and 7.2 for females in 1990,[17] and a further increase is predicted in the near future. Therefore, countermeasures to combat this increase in pancreatic cancer are now required.

Meanwhile, three conditions must be satisfied to warrant the introduction of mass screening for cancers: non-invasive and accurate diagnostic modality, existence of an established curative therapy, and cost effectiveness.

As to the first condition, it has been clearly demonstrated in the present study that US, a non-invasive imaging modality, has a high diagnostic accuracy of more than 95% in terms of both sensitivity and specificity for the detection of pancreatic cancer.

Downloaded from https://academic.oup.com/jjco/article/26/6/422/1785637 by guest on 24 April 2024

As to the second condition, recent reports[5, 18] have described that pancreatic cancer is curable if it is diagnosed in an early stage.

Cost efficiency, the third condition, means that the cost of examination to detect one curable cancer must be reasonable. This is related to the examination cost per person and the incidence of cancer cases in the study population. Although, the incidence of pancreatic cancer has become higher, it is still low in comparison with that of hepatocellular carcinoma or gastric cancer.

Based on the age- and sex-specific pancreatic cancer mortality rates in Japan (1990), we propose that only males aged 45 to 74 years and females aged 50 to 74 years should be included, since these represent the group in which the pancreatic cancer mortality rate is more than five per 100,000 population and who can also tolerate radical surgery. As a result, the expected incidence of pancreatic cancer would become 0.021% (0.024% for men and 0.017% for women). This value is considered to be rather low for cost-effective mass screening.

With regard to periodic check-ups for hepatocellular carcinoma by US,[8] started in 1987 and continued successfully, the subjects were previously limited to those at high risk of the disease. Thus the incidence of cancer cases among the subjects was rather high at more than 3% in one year. It is desirable to establish proper criteria for deciding "high-risk" for pancreatic cancer. Many retrospective or prospective studies have attempted to do this using the presence of symptoms, elevation of the serum amylase level,[2, 3, 19] or elevation of the serum CA 19-9 and elastase-1 levels.[19–22] However, these trials resulted in detection of only advanced cases, and the establishment of "high-risk" criteria was reported to be very difficult.

On the other hand, Inamoto *et al.*[19] reported the results of an abdominal mass survey using US, based on a questionnaire distributed to 14 institutions. According to their report, the incidence of pancreatic cancer among the subjects was low at 0.011%, but small (<2 cm) cancers were included at a higher rate of 30% compared with the rate based on the data from the national registration of pancreatic cancer.[3]

However, the use of US as a first choice for the screening of pancreatic cancer may be considered expensive. According to Mihara *et al.*,[23] more than ten times the number of malignant cases other than pancreatic cancer are also detectable by mass screening with US. Considering the present situation, therefore, the criteria used for defining patients at high risk for pancreatic cancer must be settled by US.

In our series, there was one false-negative case in which the tumor was detected at the next US examination performed 13 months after the first, when the cancer was still curable. Here, slight dilatation of the main pancreatic duct was evident upon retrospective review of the first sonogram. Also, all of four cancers less than 1 cm in diameter showed positive US findings.

Thus, it seems reasonable to perform periodic examinations once a year, and every three or six months for cases showing slight (less than 3 mm) pancreatic duct dilatation. This contrasts with the examination of all subjects every three or six months for hepatocellular carcinoma.

In conclusion, to counteract the rapid increase in the mortality rate due to pancreatic cancer, and for improving the diagnostic accuracy and prognosis after treatment, a detailed study aimed at mass screening for pancreatic cancer is warranted.

References

1) Crist DW, Sitzmann JV, Cameron JL: Improved hospital morbidity, mortality and survival after the Whipple procedure. *Ann Surg* 206: 358–365, 1987
2) Miyazaki N, Saitoh Y: Clinical features of the pancreatic carcinoma smaller than 2 cm in diameter. *Fukubu Gazoushindan* 12: 8–12, 1992 (in Japanese)
3) Pancreatic Cancer Registration Committee of Japan Pancreas Society: Annual report of national registration of pancreatic cancer patients in 1994. *Suizo* 10: 535–564, 1995 (in Japanese)
4) Ishikawa O, Ohigashi H, Nakamori S, Imaoka S, Sasaki Y, Furukawa H, Iwanaga T, Nakaizumi A, Uehara H, Kitamura T: Diagnosis and long-term result of minute and occult carcinoma of the pancreas. *Shokaki Gan* 3: 87–91, 1993 (in Japanese)
5) Nakaizumi A, Tatsuta M, Uehara H, Takenaka A, Iishi H, Kitamra T, Ohigashi H, Ishikawa O, Okuda S, Wada A: Effectiveness of the cytologic examination of pure pancreatic juice in the diagnosis of early neoplasia of the pancreas. *Cancer* 76: 750–757, 1995
6) Tanaka S, Kitamura T, Ohshima A, Umeda K, Okuda S, Ohtani T, Tatsuta M, Yamamoto K: Diagnostic accuracy of ultrasonography for hepatocellular carcinoma. *Cancer* 58: 344–347, 1986
7) Tanaka S, Kitamura T, Nakanishi K, Okuda S, Kojima J, Fujimoto I: Recent advances in ultrasonographic diagnosis of hepatocellular carcinoma. *Cancer* 63: 1313–1317, 1989
8) Tanaka S, Kitamura T, Nakanishi K, Okuda S, Yamazaki H, Hiyama T, Fujimoto I: Effectiveness of periodic checkup by ultrasonography for the early diagnosis of hepatocellular carcinoma. *Cancer* 66: 2210–2214, 1990
9) Kamin PD, Bernardino ME, Wallace S, Jing BC: Comparison of ultrasound and computed tomography in the detection of pancreatic malignancy. *Cancer* 46: 2410–2412, 1980
10) The Committee for the Diagnostic Criteria in the Japanese Society of Ultrasound in Medicine: Diagnostic criteria for pancreatic cancer. *Chouonpa Igaku* 19:

Downloaded from https://academic.oup.com/jjco/article/26/6/422/1785637 by guest on 24 April 2024

553–557, 1992 (in Japanese)
11) DelMaschio A, Vanzulli A, Sironi S, Castrucci M, Mellone R, Staudacher C, Carlucci M, Zerbi A, Parolini D, Faravelli A, Cantaboni A, Garancini P, Carlo VD: Pancreatic cancer versus chronic pancreatitis: diagnosis with CA19-9 assessment, US, CT and CT-guided fine-needle biopsy. *Radiology* 178: 95–99, 1991
12) Vellet AD, Romano W, Bach DB, Passi RB, Taves DH, Munk PL: Adenocarcinoma of the pancreatic ducts: comparative evaluation with CT and MR imaging at 1.5 T. *Radiology* 183: 87–95, 1992
13) Muller MF, Meyenberger C, Bertschinger P, Schaer R, Marincek B: Pancreatic tumors: evaluation with endoscopic US, CT and MR imaging. *Radiology* 190: 745–751, 1994
14) Bluemke DA, Cameron JL, Hruban RH, Pitt HA, Siegelman SS, Soyer P, Fishman EK: Potentially resectable pancreatic adenocarcinoma: spiral CT assessment with surgical and pathologic correlation. *Radiology* 197: 381–385, 1995
15) Stollfuss JC, Glatting G, Friess H, Kocher F, Beger HG, Reske SN: 2-(Fluorine-18) fluoro-2-deoxy-D-glucose PET in detection of pancreatic cancer: value of quantitative image interpretation. *Radiology* 195: 339–344, 1995
16) Megibow AJ, Zhou XH, Rotterdam H, Francis IR, Zerhouni EA, Balfe DM, Weinreb JC, Aisen A, Kuhlman J, Heiken JP, Gatsonis C, McNeil B: Pancreatic adenocarcinoma: CT versus MR imaging in the evaluation of resectability: report of the Radiology Diagnostic Oncology Group. *Radiology* 195: 327–332, 1995
17) Tominaga S, Aoki K, Hanai A, Kurihara N: Cancer Mortality and Morbidity Statistics-1993. Shinohara Shuppann, Tokyo. 1993 (in Japanese)
18) Ishikawa O, Imaoka S, Ohigashi H, Nakaizumi A, Uehara H, Wada A, Nagumo S, Yamamoto R, Sasaki Y, Iwanaga T: A new method of intraoperative cytodiagnosis for more precisely locating the occult neoplasms of the pancreas. *Surgery* 111: 294–300, 1991
19) Inamoto Y, Kawamura S, Takemoto T: The actual condition and feature of pancreatic carcinomas detected by mass examination using ultrasonography. *Fukubu Gazoushindan* 13: 471–478, 1993 (in Japanese)
20) Hayashi S, Takebe T, Ohyama K, Odake Y, Takiyama Y, Koike D, Miyakawa H, Moriai T, Yamadera K, Myoen R, Yokotama Y, Satoh M, Terasawa K, Ishii K, Nohda K, Miyashita F: A trial of the mass examination of pancreatic cancer using measurement of serum CA 19-9 and elastase-1 and ultrasonography. *Nippon Shokakibyo Gakkai Zasshi* 83: 1360–1366, 1986 (in Japanese)
21) Frebourg T, Bercoff E, Manchon N, Senant J, Basuyau JP, Breton P, Janvresse A, Brunelle P, Bourreille J: The evaluation of CA19-9 antigen level in the early detection of pancreatic cancer: a prospective study of 866 patients. *Cancer* 62: 2287–2290, 1988
22) Nakaizumi A, Tatsuta M, Uehara H, Iishi H, Yamamura H, Okuda S, Kitamra T: A prospective trial of early detection of pancreatic cancer by ultrasonographic examination combined with measurement of serum elastase1. *Cancer* 69: 936–940, 1992
23) Mihara S, Yoshioka R, Sawatari M, Koba H, Narimatu R, Nagano K, Fujita S, Nishiono A, Hirao S, Tanaka S, Migita K, Miyata T, Machihara M, Okazaki T, Yamabe H, Ueno K, Suminaga Y, Fujimoto Y, Goto Y, Hondou K, Morimoto E, Tanaka K, Ishihara E, Koyama W: Actual status of malignant neoplasm cases detected by ultrasonic mass survey. *Shokaki Shudan Kenshin* 33: 69–79, 1995 (in Japanese)

Downloaded from https://academic.oup.com/jjco/article/26/6/422/1785637 by guest on 24 April 2024