Non-operative Differentiation Between Pancreatic Cancer and Chronic Pancreatitis

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Eighty-five of 186 patients investigated for suspected pancreatic cancer had an unequivocal final diagnosis of either pancreatic cancer (58 patients) or chronic pancreatitis (27 patients). They had been studied prospectively using ultrasonography, computerized tomography, radionuclide scanning, endoscopic retrograde cholangiopancreatography (ERCP), selective celiac and superior mesenteric angiography, duodenal drainage studies, cytologic studies, serum carcinoembryonic antigen assay, and pancreatic oncofetal antigen assay. The results were compared to determine which test would most frequently and reliably differentiate between pancreatic cancer and pancreatitis in a patient believed to have one or other disease. Criteria for interpreting results, first for highest rate of correct diagnoses, and second for highest accuracy were derived. Applying these criteria, ultrasonography achieved the highest rate of correct diagnoses (97% of patients diagnosed with 84% accuracy). ERCP, duodenal drainage studies, and cytology were the most accurate tests (86% accuracy each test) but, with this accuracy, ERCP most frequently gave a diagnosis (diagnosis rate: ERCP—70%, duodenal drainage—32%, cytology—35%). The results suggest that ultrasonography is the best noninvasive test, and that a combination of ERCP, pancreatic juice assay and cytology in a single procedure may prove to be the best discriminating investigation.

THE SYMPTOMS AND SIGNS of pancreatic cancer are frequently indistinguishable from those of chronic pancreatitis. In fact, pancreatic cancer is often associated with secondary inflammatory changes. Not infrequently a physician is faced with the problem of a patient whose clinical picture and investigations indicate that one or other condition is present. The differentiation between the two diseases is clearly important; the cancer patient requires an early radical operation if there is to be any hope of cure. The pancreatitis patient may also require an operation, but if the diagnosis is certain, an initial period of conservative treatment may be beneficial, and may obviate the need for operation. At laparatomy, inspection and palpation of the pancreas may fail to disclose the correct primary disease, and the examination of biopsy material may fail to identify an underlying cancer. In such circumstances, a resectable cancer may be left behind, or a pancreatitis patient may be subjected to an extensive resection when a lesser procedure would have been adequate.

A major problem of most, if not all techniques of pancreatic investigation is the differentiation between these two diseases. The evaluation and comparison of tests in this respect is difficult, owing to uncertainty of the correct pathological diagnosis in all unresected cases. In recent years we have prospectively evaluated several methods of investigation in the diagnosis of pancreatic cancer. For the present study we have reexamined our data to determine which tests most frequently and reliably distinguish between pancreatic cancer and pancreatitis.

Patients Studied

Over a four year period, patients presenting to the University of Chicago Hospitals and Clinics with complaints compatible with a diagnosis of pancreatic cancer have been admitted to a prospective "diagnostic protocol," described in detail elsewhere.[18] At the time of writing, 186 patients have been investigated in this manner, and 39% have had a final diagnosis of pancreatic cancer, 17% having other cancers, and 44%, benign diseases including 15% with a final diagnosis of chronic pancreatitis.

For the present study, all patients falling into one of two groups have been considered. Patients with unequivocally confirmed adenocarcinoma of the pancreas form the first group of 58 patients (30 males, 28 females; mean age 60 years, range 31–89 years), all of whom underwent laparotomy. Twenty one patients (36%) had their cancers resected. These tumors ranged from 1.4 to 6.5 cm in diameter (mean 3.35 cm), and were located in

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Submitted for publication: August 29, 1978.

0003-4932/79/0400/0480 $00.90

the head (19 patients) or head and body of the gland (2 patients), and, according to the pathologist's reports, were associated with inflammatory changes elsewhere in the gland that were minimal (nine patients), mild (two patients), moderate (six patients), or severe (four patients). The remaining 37 patients (64%) had unresectable pancreatic cancers, all histologically confirmed by open biopsy. Of these tumors, 15 were located in the head of the pancreas, eight in the head and body, eight in the body, five in the body and tail, and one in the tail of the pancreas. Sixteen of these tumors were associated with hepatic metastases, and the size of pancreatic masses, as assessed at laparotomy, was reported for 12 patients and ranged from 2.5 to 10 cm in diameter (mean 7.2 cm), with seven others reported to be "large," and two "very large." The surgeon also noted inflammatory changes ranging from mild to severe in nine of these patients. Twenty-three of the 58 pancreatic cancer patients (40%) had obstructive jaundice at the time they underwent investigation.

The second group of patients examined in this report comprises those who were admitted to the "diagnostic protocol" having complaints similarly suggestive of pancreatic cancer, and in whom a confident final diagnosis of chronic pancreatitis was obtained. Of the 27 patients in this group (14 males, 13 females: mean age 49 years, range 10–73 years), 18 (67%) underwent laparotomy, all but one having open, usually multiple pancreatic biopsies. The remaining nine patients (33%) did not undergo laparotomy, a confident diagnosis of pancreatitis having been obtained on the basis of investigations and adequate follow-up. Of the 27 pancreatitis patients, six were finally judged to have mild, 11 moderate, and 10 severe disease. Nine patients were noted to have enlargment of the gland, and six had pseudocysts of varying size and location. Two patients (7%) had obstructive jaundice at the time of investigation. Only one pancreatitis patient, who had a total pancreatectomy, has been followed-up for less than six months. Four patients, three of whom underwent laparotomy and biopsy, have been followed up for six months to one year, and three patients, one of whom underwent laparotomy and biopsy and one, laparotomy and resection, have been followed-up for one to two years. All the remaining patients have been followed-up for more than two years without a change of diagnosis.

Investigations

The following investigations were carried out as part of the prospective "diagnostic protocol." Request forms indicated only that the patient was in our study group, and each test result was interpreted and reported on its own merits by expert investigators who were not directly involved in the clinical coordination and decision making.

Ultrasound examination of the pancreas was carried out using a commercially available gray scale unit, by obtaining a series of oblique transverse sections in the region of the pancreas after a preliminary survey of the upper abdomen. *Computerized tomography* (CT) of the pancreas using standard equipment became available to us more recently, and examinations have been obtained usually employing oral and/or intravenous contrast material. *"Conventional" radionuclide scanning* of the pancreas using an Anger camera and the intravenous administration of 250 uCi ^{75}Se-selenomethionine was carried out on all patients at the outset of the study. More recently, however, we have substituted a more promising technique[10] using *longitudinal multiplane emission tomography* (LMET). *Endoscopic retrograde cholangiopancreatography* (ERCP) was carried out using an Olympus JFB-2 duodenofiberscope and 50% Renograffin as contrast material. *Selective celiac and superior mesenteric angiographic studies* were obtained after percutaneous femoral artery puncture, and usually employed magnification techniques. Superselective catheterizations were made in approximately one third of studies, and pharmacologic agents were occasionally used. *Duodenal drainage studies* were undertaken using methods previously described.[4] Following placement of the tube and the intravenous administration of secretin (Boots) 1 unit/Kg body weight, the duodenal juice was collected in ten minute aliquots for thirty minutes. The volume was measured and expressed as mls/Kg/30 mins. (normal range: 0.50–3.22 mls/Kg/30 mins.), and the peak bicarbonate concentration was taken as the highest of the three estimations (normal range: 62.2–133.4 mEq/L). *Cytologic examination* was carried out as part of the duodenal drainage studies following centrifugation of the juice. More recently, material for cytology has been obtained at the time of ERCP by direct aspiration of the pancreatic duct following irrigation with normal saline.[3] *Serum carcinoembryonic antigen* (CEA) levels were determined by the Hansen Z-gel method,[15] a normal value being less than 2.5 ng/ml. Determinations were performed by the indirect method, and more recently those sera with a value greater than 20 ng/ml have been re-evaluated by the direct method. Serum was also assayed, by rocket immunoelectrophoresis, for a *pancreatic oncofetal antigen* (POA) that has been isolated and partially characterized in our laboratories,[8] a normal value being less than 14 standard units.

Analysis

The number of patients in the two groups who underwent each test varied for several reasons. First, for some patients the correct diagnosis became evident before all tests were done. Second, the frequency with which some of the tests have been requested, and their priority in the sequence of investigation changed as their relative usefulness and reliability was established over the period of study. Third, as newer techniques have become available, they have replaced or modified the role of former methods. A summary of the tests and patients studied is given in Table 1.

For each patient, reports on the pancreatic imaging tests were interpreted as indicating one of four results; first, that the pancreas appeared to be normal; second, that the pancreas appeared to be abnormal, but the causal pathology was indeterminate; third, that abnormalities favoring a diagnosis of pancreatitis were seen; or fourth, that abnormalities seen suggested a diagnosis of pancreatic cancer.

Cytologic examinations were positive (when malignant cells were seen), "atypical," or negative. Values obtained from duodenal drainage studies, and serum oncofetal antigen levels were plotted as scattergrams for one and two way discriminant analysis.

TABLE 1. *Summary of Tests and Patients Studied*

Test	Failure Rate	Number of Patients Studied (Successful)	
		Pancreatic Cancer	Pancreatitis
Ultrasound	12%	50	24
CT	16%	13	3
Conventional Scan	0%	19	17
LMET	0%	16	8
ERCP	16%	37	15
Angiography	0%	45	18
Cytology	13%	40	22
Duodenal Drainage Studies	24%	23	18
Oncofetal Antigens	0%	45	19
Total in study		58	27

Results

Several tests failed to examine some patients satisfactorily. The most common cause of a failed ultrasound examination was the presence of overlying bowel gas. CT failures were due to bowel gas shadows and the presence of surgical clips. ERCP failed occasionally due to faulty equipment, and more commonly when the duodenal papilla could not be cannulated. However, such studies were not deemed to have failed when diagnostic information was, nevertheless, obtained. Duodenal drainage studies and cytology failed when the tube could not be correctly placed. A zero yield of duodenal juice, indicating duct obstruction, was not regarded as a failed test. True failure rates appear in Table 1. Failed tests were excluded from further analysis.

The results of the pancreatic imaging tests, expressed as the percentage of cancer and pancreatitis patients who had each of the four possible results, are given as bar-grams in Figure 1. The results of cytologic examinations appear in Figure 2. Specimens were obtained by duodenal aspiration for 47 patients, and by direct ductal aspiration for 25 patients, 13 patients having both.

Two other patients had endoscopic duodenal brushings examined. In the cancer group, nine of 18 (50%) direct ductal samplings were positive, as were 16 of 28 (57%) duodenal aspiration samples. Two other duodenal samples showed atypia, one of these patients having a positive result on ductal aspiration. One patient with a positive ductal and negative duodenal sample had the only other conflicting report. In the pancreatitis group there were two false positives, one for each method of specimen collection.

The results of the duodenal drainage studies, plotted as scattergrams, appear in Figure 3. The volume for cancer patients (1.31 ± 0.15 ml/Kg/30 min.:mean $\pm$ SEM) was significantly lower than that for pancreatitis patients (1.71 ± 0.17 ml/Kg/30 min.) as assessed by the student's independent t-test ($p < 0.005$). No patient had a zero volume. The mean peak bicarbonate concentration for cancer patients (79 ± 5 mEq/L) was also lower than that for pancreatitis patients (88 ± 6 mEq/L), but the difference was not significant.

The results of the oncofetal antigen assays, plotted as scattergrams, are shown in Figure 4. The mean CEA level was significantly higher ($p < 0.02$) in pancreatic cancer (10.7 ± 1.2 ng/ml) than pancreatitis (5.8 ± 1.3 ng/ml). Since not all values above 20 ng/ml were determined, all such values were computed as 20 ng/ml. The mean value of POA for cancer patients (12.6 ± 1.1 units) was higher than that for pancreatitis patients (10.1 ± 1.7 units), but not significantly so.

Discussion

The data presented indicate with certain limitations discussed below, the comparative diagnostic performance of the various tests in patients with pancreatic cancer and pancreatitis. Given these data, the question arises—if we believe that a patient has either pancreatic cancer or pancreatitis, with an equal likelihood,

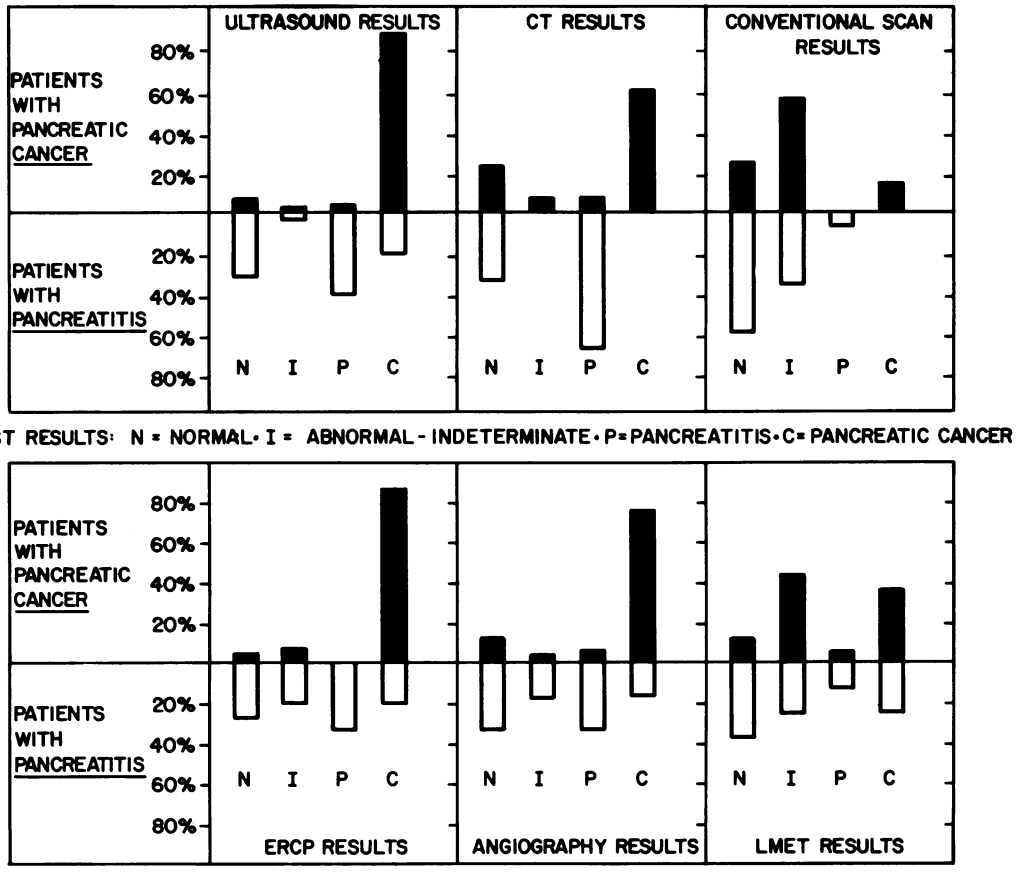

FIG. 1. Results of six pancreatic imaging tests showing the percentage of pancreatic cancer patients (solid bars) and chronic pancreatitis patients (open bars) obtaining each of the four possible test results.

which test will give a discriminant diagnosis, and how accurate will that diagnosis be?

A comparison of the tests may be made by considering the proportion of patients in each group, rather than the actual number, who obtained a particular result. In this way the test is evaluated as though the prior probabilities of cancer and pancreatitis for an individual patient are the same. If we assume that one or other of these two diagnoses will be correct, the accuracy of the test, that is the frequency with which its diagnosis of cancer or pancreatitis is correct, may be expressed as the sum of the correct diagnoses in both groups, divided by the sum of all diagnoses made.

In order to compare the ability of each test to differentiate between pancreatic cancer and pancreatitis, consideration should be given to the relative importance of the frequency with which the test can give the correct diagnosis, and the accuracy of the diagnoses given.

For most of the tests, given that the diagnosis must be either pancreatic cancer or pancreatitis, there are two distinct ways in which the results can be interpreted—first, to obtain a high degree of accuracy, and second, to obtain the maximum amount of discriminatory information, and thus a high rate of correct diagnoses. With cytology, for example, 86% of patients with a positive result (assuming equal numbers in the two groups) prove to have cancer, but only 30% of patients are thereby correctly diagnosed. If a negative result is taken to indicate pancreatitis, then 99% of all patients are diagnosed with 75% accuracy. Similarly with an imaging test, when studies reported to be normal occur more frequently in pancreatitis than cancer, as is usually the case (Fig. 1), we can say that a normal study favors a diagnosis of pancreatitis over cancer in that ratio. Interpreting normal studies as pancreatitis will increase the proportion of patients obtaining the correct differential diagnosis, but may reduce the accuracy with which all diagnoses are made. Table 2 summarizes the criteria for interpreting the tests to obtain a high rate of correct diagnoses. Table 3 summarizes the criteria that may be taken to maximize the diagnostic accuracy. Applying these two sets of criteria we have compared the various tests with respect to the rate and accuracy of information they provide on the differentiation between cancer and pancreatitis. These comparisons are given in Figures 5 and 6.

It can be seen that ultrasound and CT most frequently provided discriminatory information. Only three pancreatitis patients had CT examinations (Table

1), and so the high rate of correct diagnoses and the high accuracy of CT in this study must be regarded as unproven. Other workers[2,9] have compared these two imaging techniques in the diagnosis of pancreatic cancer, and have obtained conflicting results. A comparison of their values in pancreatitis[14] has shown little difference. Ultrasound should be preferred on the grounds of cost-effectiveness,[11] but a combination of the two might provide more information.

ERCP, duodenal drainage studies, and cytology each provided a similar amount of discriminatory information, but ERCP was the most accurate. Some workers[6] have found ERCP to be less accurate than ultrasound. The present study indicates that while ultrasound may suggest a diagnosis more frequently, its accuracy is no higher.

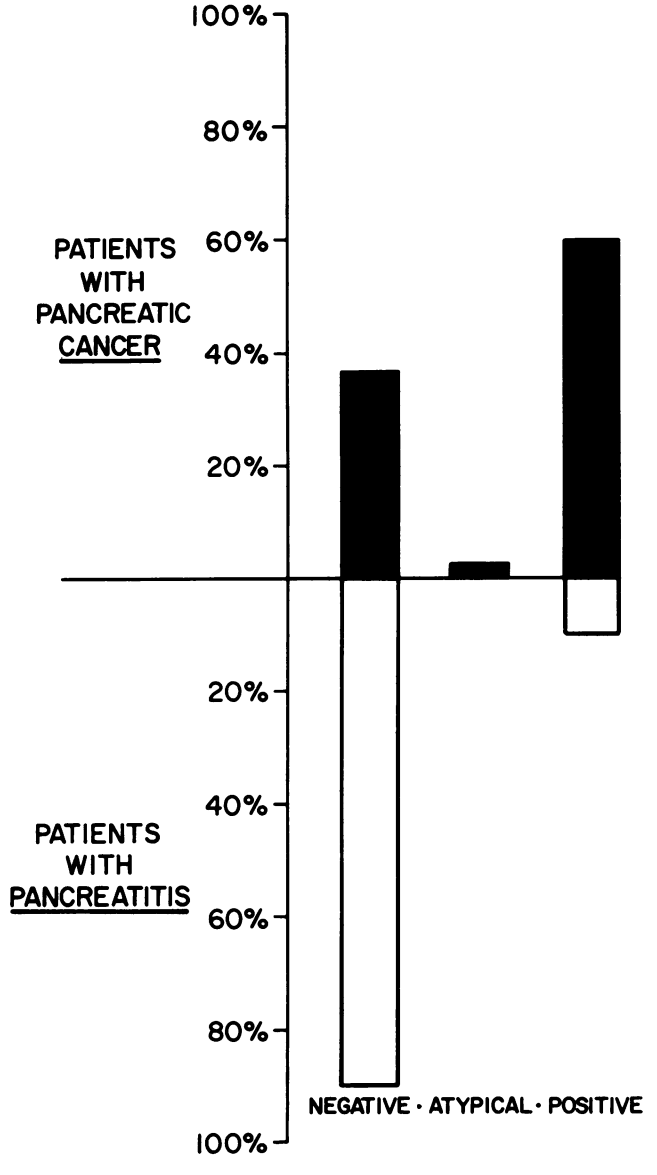

FIG. 2. Results of cytologic studies showing the percentage of pancreatic cancer patients (solid bars) and chronic pancreatitis patients (open bars) obtaining each of the three possible test results.

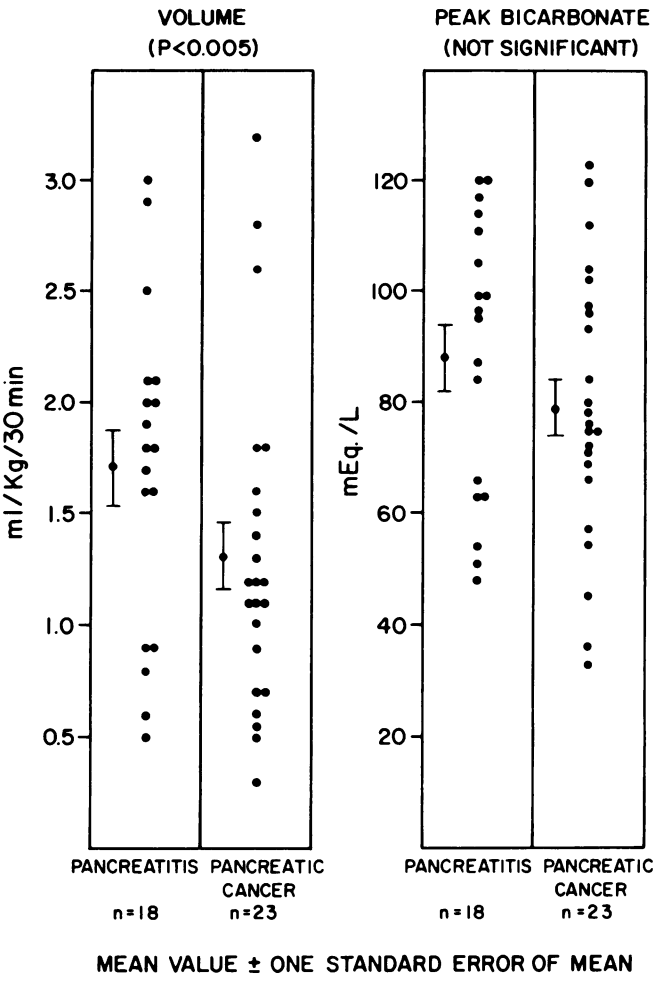

FIG. 3. Results of duodenal drainage studies plotted as scattergrams.

Our earlier experience with duodenal drainage studies[4] revealed this test's inability to clearly differentiate between pancreatic cancer and pancreatitis. However, while almost all values for volume and bicarbonate concentration in the present series were within normal range, the differences between the two groups, particularly in volume, were sufficiently great to give comparatively accurate discriminatory information. Other workers[1] agree that a low volume in this test should make one suspect a malignant cause.

Our overall positive cytology rate in pancreatic cancer (60%) is similar to that previously reported.[4] In this series, duodenal drainage cytology following secretin stimulation was slightly better than direct ductal aspiration following saline lavage, both yields being similar to that reported for pure pancreatic juice cytology following secretin stimulation.[16]

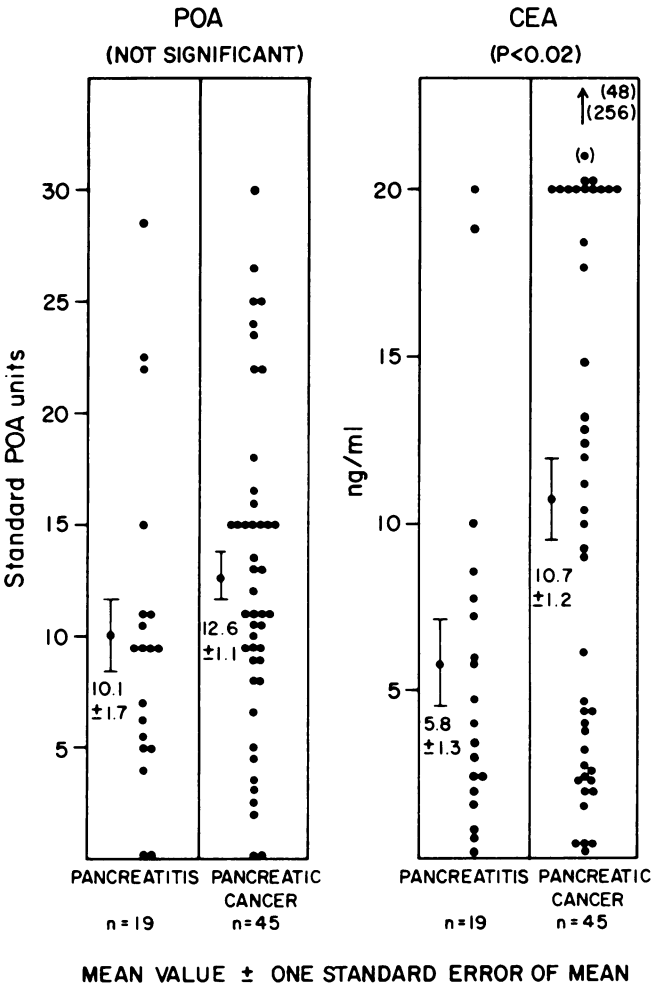

FIG. 4. Results of serum carcinoembryonic antigen (CEA) and pancreatic oncofetal antigen (POA) assays, plotted as scattergrams.

The combination of endoscopic retrograde pancreatography, pure pancreatic juice assays and cytology in a single investigative procedure is feasible, and has shown promise as a reliable method of distinguishing between neoplastic and inflammatory diseases.[12] These procedures are invasive and time consuming, and are attended by relatively high failure rates. Nevertheless, the performance of ERCP, duodenal drainage studies and cytology in the present series suggests that a combined procedure may prove to be the most informative and accurate investigation.

TABLE 2. *Criteria for High Rate of Correct Diagnoses*

Test	Result	Interpret as-
Ultrasound, CT, conventional scan, LMET, ERCP, Angiography	"pancreatic cancer"	pancreatic cancer
	"pancreatitis"	pancreatitis
	"normal"	pancreatitis
Cytology	"positive"	pancreatic cancer
	"negative"	pancreatitis
Duodenal drainage studies	volume ≤ 1.5 ml/Kg/30 min.	pancreatic cancer
	volume > 1.5 ml/Kg/30 min.	pancreatitis
Oncofetal antigens	CEA > 10 ng/ml	pancreatic cancer
	POA > 14 units	pancreatic cancer

TABLE 3. *Criteria for High Diagnostic Accuracy*

Test	Result	Interpret as-
Ultrasound, LMET	"pancreatic cancer"	pancreatic cancer
	"pancreatitis"	pancreatitis
	"normal"	pancreatitis
CT, conventional scan, ERCP, angiography	"pancreatic cancer"	pancreatic cancer
	"pancreatitis"	pancreatitis
Cytology	"positive"	pancreatic cancer
Duodenal drainage studies	volume > 1.5 ml/Kg/30 min. and bicarbonate > 80 mEq/L	pancreatitis
Oncofetal antigens	CEA > 5 ng/ml and POA > 14 units	pancreatic cancer

Angiography is invasive and time consuming, and other workers[7,13] have reported difficulty in differentiating between cancer and pancreatitis with this investigation. Our data confirm that it offers no additional diagnostic advantage over less invasive methods.

Conventional radionuclide scanning has proven to be of limited value in the detection of pancreatic abnormalities.[10,17] Our experience with LMET suggests that this is a more reliable technique, but the lack of specificity in defining abnormalities remains comparatively high. The high accuracy of conventional scans obtained when only results naming cancer or pancreatitis were considered (Fig. 6) remains unproven since there were only four patients in this group.

Serum oncofetal antigen levels have also shown a lack of specificity,[5,8] diminishing their value in the differentiation between cancer and pancreatitis. Although there is evidence that POA is more sensitive than CEA in the detection of pancreatic cancer in patients with suspected major intra-abdominal disease,[19] in the present series CEA proved to be considerably better at differentiating between pancreatic cancer and pancreatitis (Fig. 5). When the levels of both antigens were high, the likelihood of cancer was slightly higher than when CEA alone was elevated, providing good evidence for cancer rather than pancreatitis for a few patients. Both antigens were frequently found in normal levels in sera of pancreatic cancer patients, and therefore only high levels provided discriminatory information. An advantage of POA is that serum levels are not directly related to tumor bulk; elevations (>14 units) were noted for seven patients with resectable tumors (33%), with three having levels greater than 20 units. Other workers[12] have emphasized the value of determining the CEA content of pure pancreatic juice collected at

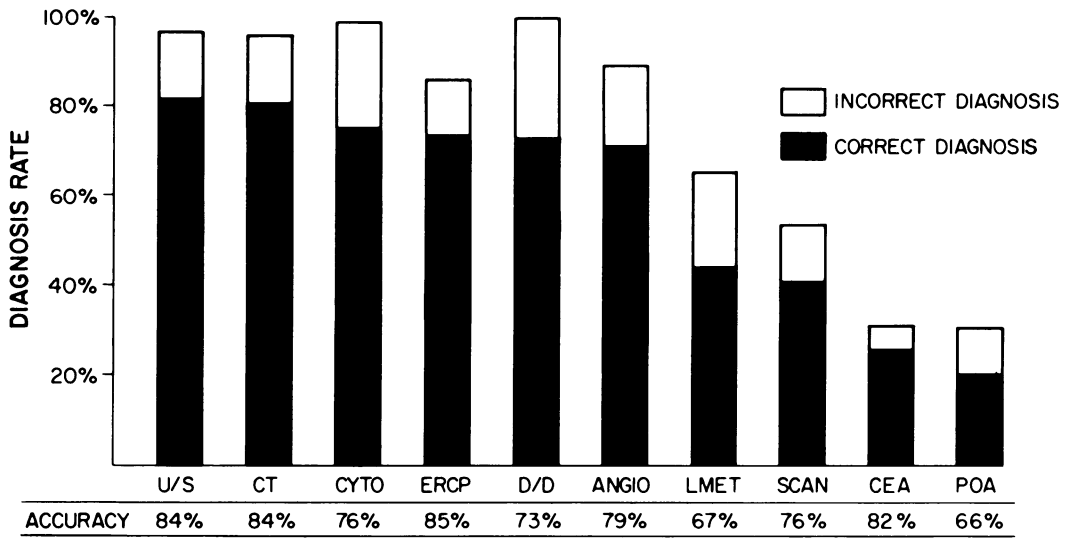

FIG. 5. Results obtained when all tests were interpreted by applying the criteria for a high rate of correct diagnoses (Table 2). Tests are shown in order (highest at left; lowest at right) of rates of correct diagnosis thus obtained, with corresponding accuracy given below bars. Abbreviations: U/S = ultrasonography, CT = computed tomography, cyto = cytologic studies, ERCP = Endoscopic retrograde cholangiopancreatography, D/D = duodenal drainage studies, angio = angiography, LMET = longitudinal multiplane emission tomography, Scan = conventional radionuclide pancreatic scan, CEA = serum carcinoembryonic antigen assay, POA = pancreatic oncofetal antigen assay.

the time of endoscopic cannulation. This may prove to be a useful adjunct, although our experience with CEA determination as part of duodenal drainage studies[4] has been disappointing.

Conclusions

Our results suggest that gray scale ultrasonography is the best noninvasive test for differentiating between pancreatic cancer and pancreatitis. CT scan may be as good as, or superior to ultrasound, but this remains unproven. Radionuclide scanning and angiography contribute little to this differentiation. ERCP provides valuable discriminatory information and appears to be the most accurate test. In combination with pancreatic juice studies and cytology, it may prove to be the best single discriminating procedure. Assay of serum oncofetal antigens can provide relatively reliable evidence for cancer in only a small number of patients.

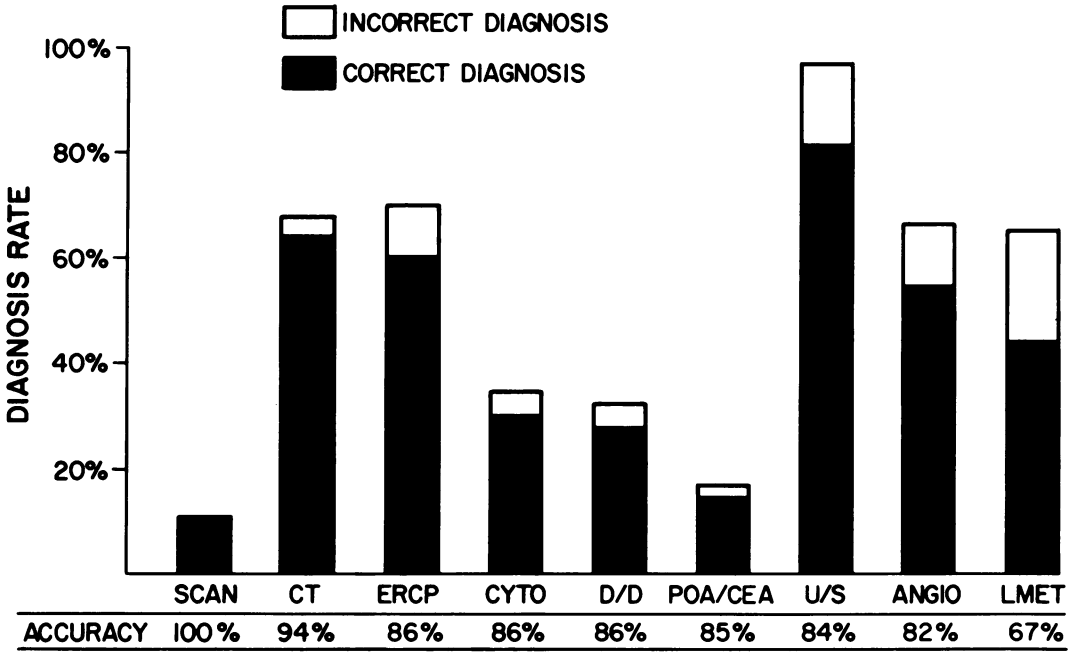

FIG. 6. Results obtained when all tests were interpreted by applying the criteria for high accuracy (Table 3). Tests are shown in order (highest at left; lowest at right) of accuracy thus obtained, with bar heights showing the corresponding rates of correct and incorrect diagnoses. Abbreviations: see key to Figure 5.

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