Eur J Cancer Clin Oncol, Vol. 21, No. 4, pp. 429-432, 1985.
Printed in Great Britain.

0277-5379/85$3.00+0.00

CA 19-9 in the Differential Diagnosis between Pancreatic Cancer and Chronic Pancreatitis*

ROBERTO FARINI,† CARLO FABRIS,† PIERO BONVICINI,‡ ANTONIO PICCOLI,† GIUSEPPE DEL FAVERO,† ROBERTA VENTURINI,‡ ALDO PANUCCI† and REMO NACCARATO†§

†*Istituto di Medicina Interna, Cattedra Malattie Apparato Digerente, Università Degli Studi di Padova, Padova, Italy and* ‡*Laboratorio Centrale di Analisi, Ospedale Civile di Padova, Padova, Italy*

Abstract—*CA* 19-9 *serum concentration was determined by a immunoradiometric technique in* 130 *subjects to evaluate its role in differentiating pancreatic cancer from chronic pancreatitis. Two threshold values were chosen,* 17 *and* 37 U/ml. *With the former, sensitivity, specificity and diagnostic accuracy were* 86.7, 62.3 *and* 49.0 *respectively, with the latter* 73.3, 87.0 *and* 60.3%. *The receiver-operating characteristic curves demonstrated a satisfactory discriminating capacity of CA* 19-9 *as regards pancreatic cancer and chronic pancreatitis; in contrast, the discrimination was poor for other gastrointestinal diseases, mainly of a malignant nature.*

INTRODUCTION

CA 19-9, a mucin-type glycoprotein [1], recently identified in colorectal carcinoma by means of a specific monoclonal antibody [2], has been studied in a variety of tumours and chronic inflammatory diseases, mostly of gastrointestinal origin [3-7]. With respect to pancreatic cancer, increased CA 19-9 serum levels have been reported in the majority of patients studied [4-6, 8]. Nevertheless, few data are present in the literature regarding the usefulness of such determination in differentiating malignant from non-malignant pancreatic diseases [4, 5, 8].

The aim of the present investigation was to ascertain the value of CA 19-9 in distinguishing pancreatic cancer from chronic pancreatitis and other gastrointestinal diseases.

MATERIALS AND METHODS

A total of 130 subjects was studied. Thirty-one were control subjects, healthy members of the medical staff (20 male, 11 female, aged 24-56 yr). Thirty were affected by pancreatic cancer of ductular cell origin [9], always histologically confirmed (18 male, 12 female, 35-79 yr). Twenty-nine were chronic pancreatitis patients, 16 calcifying, 13 non-calcified (26 male, 3 female, 25-59 yr); the diagnosis was assessed on the basis of the clinical picture and on the positive results of at least two of the following procedures: plain abdomen X-ray for pancreatic calcifications, pancreatic ultrasonography, computed axial tomography, ERCP and secretin-caerulein test. Forty presented non-pancreatic digestive diseases (21 male, 19 female, 21-81 yr), diagnosed on the basis of the clinical picture and on specific radiologic and/or histologic examinations (carcinoma of the papilla of Vater: 4 cases; carcinoma of the gall bladder or of the biliary tract: 7; carcinoma of the colon: 4; liver cirrhosis: 7; hepatic fibrosis: 3; acute viral hepatitis: 2; gallstones: 9; benign stenosis of the papilla of Vater: 1; gastroduodenitis: 1; irritable colon: 2). Informed consent was obtained in every case.

Serum CA 19-9 concentration was determined by means of an immunoradiometric method (GICAK Sorin Biomedica, Saluggia, Vercelli, Italy) previously described by Del Villano *et al.* [4]. The between-assay coefficients of variation (20 determinations), assessed on sample pools at different concentrations (from 16.3 to 120.3 U/ml), ranged from 8.1 to 11.1%.

In distinguishing normal from pathological results, two threshold limits were considered: one comprising 95% of our controls (≤17 U/ml), the other identical to that chosen in a previous study.

Accepted 6 September 1984.
*Supported in part by a grant from Ministero Pubblica Istruzione (1982).
§To whom requests for reprints should be addressed at: Istituto di Medicina Interna, Cattedra Malattie Apparato Digerente, Policlinico Universitario, 35100 Padova, Italia.

which considered the distribution of the values in a large control population (≤37 U/ml) [4].

The statistical evaluation of the results was carried out using the Kruskal-Wallis test (one-way analysis of variance) [10], chi-square test, Youden index [11] and ROC (receiver-operating characteristic) curves [12].

RESULTS

Figure 1 illustrates the individual values of serum CA 19-9 concentration in the studied material. The Kruskal-Wallis test showed a significant stochastic distribution difference among groups ($T = 60.76$, $P < 0.0000$).

A significantly increased frequency of pathological results was documented in pancreatic cancer patients with respect to the other groups considering both the cut-off values chosen (for 17 U/ml: $\chi^2 = 50.8$, $P < 0.0005$; for 37 U/ml: $\chi^2 = 57.3$, $P < 0.0005$).

The sensitivity of the test in distinguishing pancreatic cancer (Youden index) was 86.7 and 73.3% considering 17 U/ml and 37 U/ml as the threshold value respectively; the specificity was

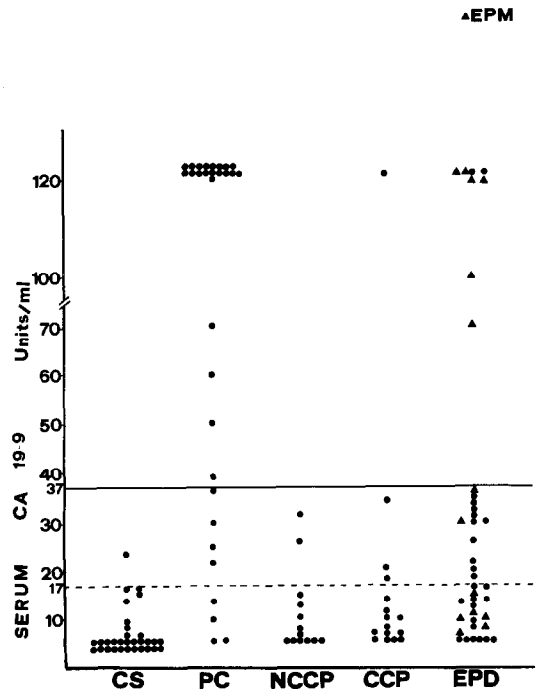

Fig. 1 Serum CA 19-9 values in 130 subjects. The continuous and the dotted lines represent the two threshold levels chosen. Abbreviations: CS, control subjects; PC, pancreatic cancer; NCCP, non-calcified chronic pancreatitis; CCP, calcifying chronic pancreatitis; EPD, extra pancreatic diseases; EPM, extra pancreatic malignancies.

62.3 and 87.0% and the diagnostic accuracy was 49.0 and 60.3% respectively.

Figure 2 shows the ROC curves assessed in the attempt to differentiate pancreatic cancer from

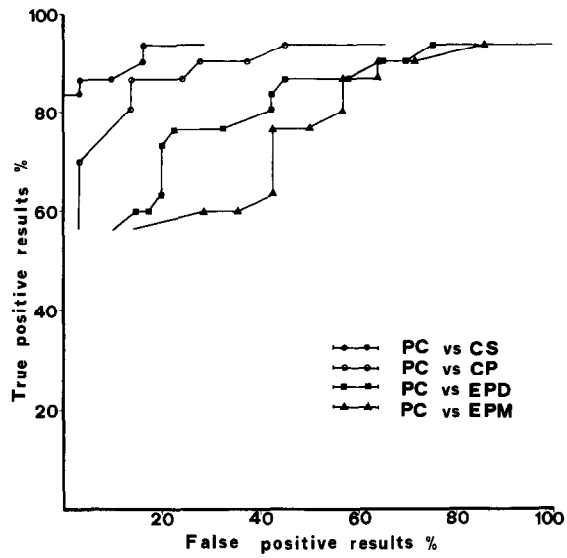

Fig. 2. Receiver-operating characteristic curves assessed in the studied material. Abbreviations: CS, control subjects; PC, pancreatic cancer; CP, chronic pancreatitis; EPD, extra pancreatic diseases; EPM, extra pancreatic malignancies.

control subjects, chronic pancreatitis and other gastrointestinal pathological conditions.

DISCUSSION

With the aim to support the diagnosis of pancreatic cancer by means of non-invasive techniques, different serum markers have been proposed, i.e. CEA, POA, ferritin, RNase, GT_{II} [13–18]. Nevertheless a number of false positive and negative results has always been described, thus limiting the diagnostic value and clinical usefulness of these tests.

In this study CA 19-9 concentration in serum was confirmed to be elevated in the vast majority of pancreatic cancer patients assuming the threshold value of 17 U/ml, which comprised 95% of our controls. In the chosen strategy, however, the specificity of the test, although superior to that reported for other proposed markers [13, 16], was not completely satisfactory.

In the attempt to improve such results, another cut-off point was adopted, according to Del Villano *et al.* [4] (37 U/ml). The slight decrease in sensitivity observed was largely compensated for by a decisive improvement in specificity (from 62.3 to 87.0%) and, consequently, in the diagnostic accuracy of the test.

Considering the receiver-operating characteristic curves, CA 19-9 was able to distinguish pancreatic cancer from control subjects in 87 and 93% of cases, pancreatic cancer from chronic pancreatitis in 77 and 87% and from non-pancreatic digestive diseases in 57 and 73% assuming 10 and 20% false positive results respectively.

These results stress that the discriminating capacity of CA 19-9 in distinguishing pancreatic cancer from chronic pancreatitis is at least as good as that reported for POA and GT_{II} [15, 17] and superior to that found for CEA, RNase and ferritin [13–18]. However, because of the presence of false-positive and -negative results, this marker may be considered an indicative but not a definitive test in differentiating benign from malignant pancreatic disease. Furthermore, the origin of the antigen, identified in colorectal carcinoma [19], accounts for the low specificity found when pancreatic was compared with extrapancreatic diseases of neoplastic nature.

The simultaneous evaluation of CA 19-9 with other proposed markers for pancreatic cancer may be attempted [8]. Nevertheless, our previous observations concerning the combined assessment of CEA and ferritin as well as of RNase and ferritin in diagnosing pancreatic cancer failed to improve the diagnostic accuracy [20, 21].

From these preliminary results, CA 19-9 determination may be considered a sensitive test for pancreatic cancer diagnosis, and one of the best markers currently available in differentiating chronic neoplastic from non-neoplastic pancreatic diseases. However, its specificity with respect to other gastrointestinal diseases mainly of neoplastic nature is, as expected, limited in extent.

REFERENCES

1. Magnani JL, Steplewski Z, Koprowski H, Ginsburg V. Identification of the gastrointestinal and pancreatic cancer-associated antigen detected by monoclonal antibody 19-9 in the sera of patients as a mucin. *Cancer Res* 1983, **43**, 5489–5492.
2. Chang TH, Steplewski Z, Sears HF, Koprowski H. Detection of monoclonal antibody-defined colorectal carcinoma antigen by solid-phase binding inhibition radioimmunoassay. *Hybridoma* 1981, **1**, 37–45.
3. Atkinson BF, Ernst CS, Herlyn M, Steplewski Z, Sears HF, Koprowski H. Gastrointestinal cancer-associated antigen in immunoperoxidase assay. *Cancer Res* 1982, **42**, 4820–4823.
4. Del Villano BC, Brennan S, Brock P *et al.* Radioimmunometric assay for a monoclonal antibody-defined tumor marker, CA 19-9. *Clin Chem* 1983, **29**, 549–552.
5. Herlyn M, Sears HF, Steplewski Z, Koprowski H. Monoclonal antibody detection of a circulating tumor-associated antigen. I. Presence of antigen in sera of patients with colorectal, gastric, and pancreatic carcinoma. *J Clin Immunol* 1982, **2**, 135–140.
6. Koprowski H, Herlyn M, Steplewski Z, Sears HF. Specific antigen in serum of patients with colon carcinoma. *Science* 1981, **212**, 53–55.
7. Sears HF, Herlyn M, Del Villano BC, Steplewski Z, Koprowski H. Monoclonal antibody detection of a circulating tumor-associated antigen. II. A longitudinal evaluation of patients with colorectal cancer. *J Clin Immunol* 1982, **2**, 141–149.
8. Andriulli A, Gindro T, Piantino P *et al.* Efficacy of CA 19-9, TPA and CEA assays in pancreatic cancer. *Digestion* 1983, **28**, 9.
9. Cubilla AL, Fitzgerald PJ. Pancreas cancer. 1—Duct adenocarcinoma. *Pathol Annu* 1978, **13**, 241–289.
10. Brown MB, Engelman L, Frane JW *et al. BMDP Statistical Software*. Berkeley, CA, University of California Press, 1981, 437.
11. Armitage P. *Statistical Methods in Medical Research*. Oxford, Blackwell Scientific Publications, 1971, 433–435.
12. Weinstein MC, Fineberg HV. *Clinical Decision Analysis*. Philadelphia, PA, Saunders, 1980, 114.
13. Fabris C, Farini R, Del Favero G, Piccoli A, Naccarato R. "Plasma"-type ribonuclease in pancreatic cancer diagnosis: a critical appraisal. *Hepato-gastroenterol* 1981, **28**, 316–318.
14. Kalser MH, Barkin JS, Redlhammer D, Heal A. Circulating carcinoembryonic antigen in pancreatic carcinoma. *Cancer* 1978, **42**, 1468–1471.
15. Mackie CR, Cooper MJ, Lewis MH, Moossa AR. Non-operative differentiation between pancreatic cancer and chronic pancreatitis. *Ann Surg* 1979, **189**, 480–487.
16. Nitti D, Fabris C, Del Favero G *et al.* Serum Ferritin in pancreatic disease. An accurate test of malignancy? *Digestion* 1982, **25**, 258–262.
17. Podolsky DK, McPhee MS, Alpert E, Warshaw AL, Isselbacher KJ. Galactosyltransferase isoenzyme II in the detection of pancreatic cancer: comparison with radiologic, endoscopic, and serologic tests. *N Engl J Med* 1981, **304**, 1313–1318.

18. Reddi KK, Holland JF. Elevated serum ribonuclease in patients with pancreatic cancer. *Proc Natl Acad Sci USA* 1976, **73**, 2308–2310.
19. Koprowski H, Steplewski Z, Mitchell K, Herlyn M, Herlyn D, Fuhrer P. Colorectal carcinoma antigens detected by hybridoma antibodies. *Somatic Cell Genet* 1979, **5**, 959–972.
20. Fabris C, Farini R, Piccoli A *et al.* CEA and Ferritin in chronic pancreatic disease. A comparative evaluation. Abstract of the 4th European Meeting, 'Plasma Proteins in Clinical Diagnosis', Milan, 1983, 58.
21. Farini R, Fabris C, Del Favero G *et al.* Combined evaluation of serum ribonuclease and ferritin in diagnosing pancreatic cancer. *Digestion* 1983, **28**, 25.