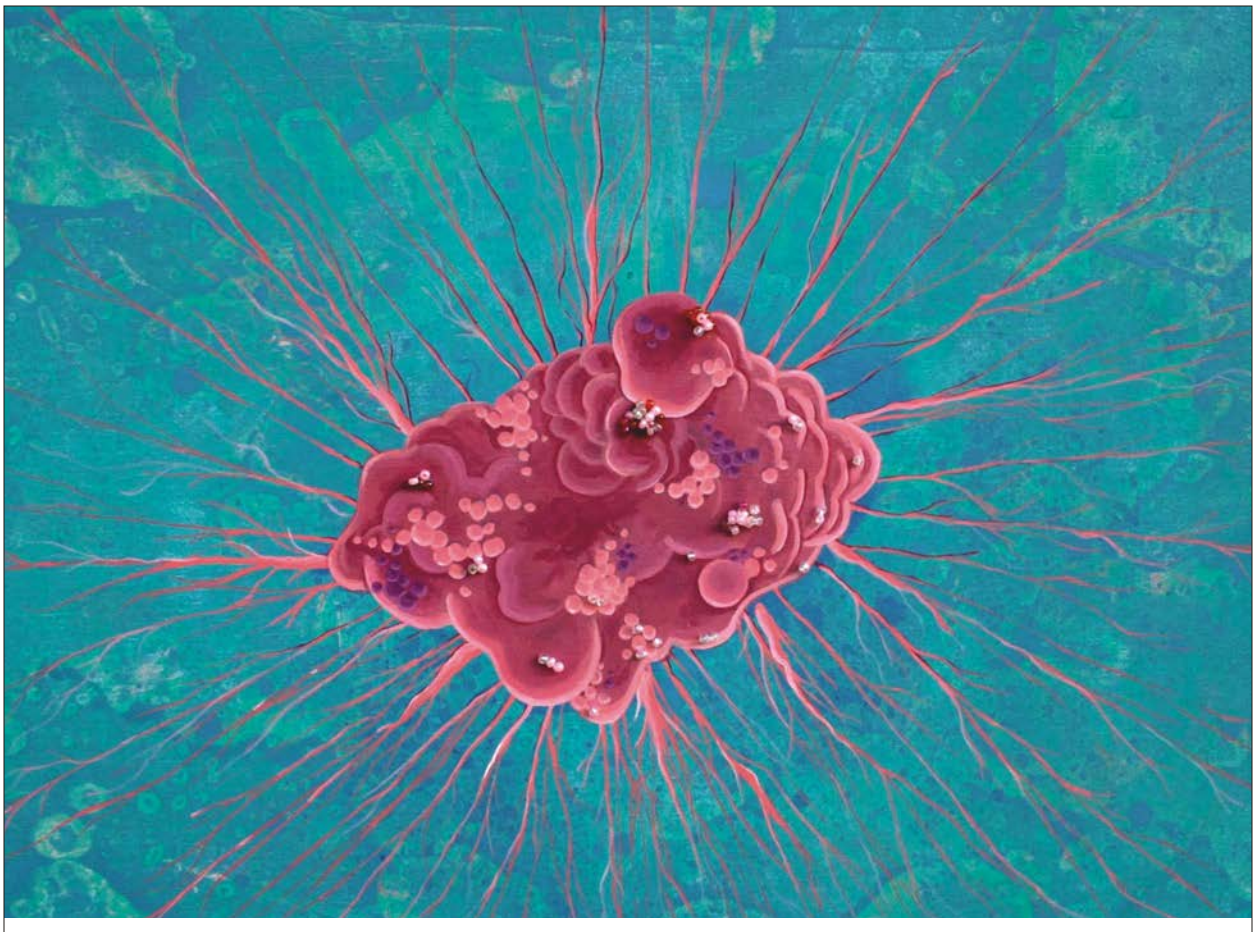

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Clinical Value of Serum CEA, CA 19-9, CA 242 and AFP in Diagnosis of Gastrointestinal Tract Cancers

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Abstract: Evaluation of single and combined testing of carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19-9), carbohydrate antigen (CA 242) and α-fetoprotein (AFP) in serum for diagnosis of gastrointestinal tumors were aimed in the present study. Sera of 28 healthy individuals and 181 patients with gastrointestinal tumors including colorectal cancer (n=50), pancreatic cancer (n=27), hepatocellular carcinoma (n=86), gastric cancer (n=18) were evaluated for different tumor markers. Complete liver functions were also determined. In colorectal cancer patients, single determination of CEA or CA 242 showed the highest sensitivity (48%) and combined determination improved the sensitivity to 72%. In pancreatic cancer patients, the combination of CA 19-9 with CA 242 did not increase the sensitivity above that (70.4%) of CA 19-9 alone. In HCC, AFP was the highly sensitive tumor marker. In addition, a significant positive correlation (r=0.816) was found between AFP and ALT in HCC patients. All evaluated tumor markers showed lower sensitivities (< 22%) for gastric cancer. Combined detection of CEA and CA 242 improved the sensitivity in colon cancer. CA 19-9 showed the best sensitivity for pancreatic cancer. AFP was the most sensitive tumour marker for HCC. None of the evaluated tumour markers had sufficient sensitivity to be taken as a marker for gastric carcinoma.

Key words: CEA, CA 242, AFP, gastrointestinal cancer

Introduction

Gastrointestinal tract (GIT) cancers are major causes for concern in the biomedical community due to their high mortality rates and the lagging ability for early diagnosis (Diaz-Rubio, 2004). The use of tumour markers has become a very attractive method for the detection and diagnosis of neoplastic diseases (Pectasides *et al*., 1997; Yamao *et al*., 1999). These soluble molecules in the blood are usually glycoproteins detected by monoclonal antibodies. Each tumour marker has a variable profile of usefulness for screening, determining diagnosis and prognosis, assessing response to therapy and monitoring for cancer recurrence. Thomson *et al*. (1969) successfully demonstrated circulating carcinoembryonic antigen (CEA) in the sera of patients with large bowel cancer. This finding led the way to a new field of interest in tumor-associated antigens that could be useful for the early

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detection of cancer. With the advent of monoclonal antibodies (Kohler and Milstein, 1995), other tumour markers with special application for GIT malignancies were described. For adenocarcinoma of the pancreas, CA 19-9 is more specific and sensitive than CEA, the most widely used tumour marker (Pezzilli *et al*., 1995; Nazli *et al*., 2000). For gastric cancer, CA 72-4 was the marker that showed the higher sensitivity (Kodama *et al*., 1995). However, their value in cancer detection has been controversial largely because no single tumour marker is sensitive and specific enough to meet strict diagnostic criteria. The present study aimed to investigate the clinical usefulness of four tumour makers, serum Carcinoembryonic Antigen (CEA), α-fetoprotein (AFP), carbohydrate antigen 19-9 (CA 19-9) and carbohydrate antigen 242 (CA 242) to evaluate the values of single and combined test in the diagnosis of GIT tumors.

Materials and Methods

Patients and Controls

The study population included 181 patients (64.3±10.9 years) with different gastrointestinal tumors include: colon cancer (n=50), hepatocellular carcinoma (HCC, n=86), pancreatic cancer (n=27) and gastric cancer (n=18). In addition, sera of 28 age-matched individuals without malignancy were used as a control group. They were 12 healthy individuals, 6 individuals with liver cirrhosis, 5 individuals with pancreatitis and 5 individuals with gastrites. They were recruited from Gastro-Enterology and Surgery Center, Mansoura University Hospitals, Mansoura, Egypt, which reviewed and approved the current study. Diagnosis was confirmed by histological examination of a post-operation or cytological intra-operative biopsy. Liver functions including alanine aminotransferase (ALT), Albumin, billirubin and alkaline phosphatase were routinely determined for all patients and controls. An informed consent was obtained from each individual participated in the present study and all were fully informed concerning nature of the disease and the diagnostic procedures involved.

Serum Tumor Markers

Serum levels of α-fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen 19.9 (CA 19.9) carbohydrate antigen 242 (CA 242) were measured using commercial kits (ABBOTT Laboratories, CA, USA). The cut-off levels of serum AFP, CEA, CA19.9 and CA 242 were 15, 5, 37 and 20 U mL^{-1}, respectively. A result was considered positive when the marker serum level was higher than the cut-off value.

Statistical Analyses

The results were computed on IBM PC microprocessor and analyzed by SPSS for Windows statistical software package (SPSS Inc., USA). Descriptive statistics include, Mean±SD, Wilcoxon rank–sum test were used for two nonparametric tests. A comparative study including student t-test for comparison between two independent groups, correlation study to investigate the relation between each two variables among each group using Ranked-Sperman correlation test (r) and diagnostic validity test to calculate sensitivity and specificity of tests. The corresponding p value was non-significant difference when $p>0.05$; mild significant difference when $p<0.05$; moderate significant difference when $p<0.01$ and highly significant difference when $p<0.001$.

Results

Determination of CEA, CA19.9, CA 242 and AFP in Different Gastrointestinal Tumors

In colon cancer, serum levels of CEA, CA 19.9 and CA 242) were significantly ($p<0.001$) higher than controls (Table 1), but levels of AFP showed no significant increase: In HCC, levels of AFP were significantly ($p<0.001$) higher than controls, but no significant differences were shown in serum levels of CEA, CA 19.9 or CA 242. In pancreatic cancer, serum levels of CA 19.9 and CA 242 showed significant higher ($p<0.001$) increase but no significant differences were shown in CEA and AFP levels. In gastric cancer, evaluated tumor markers showed no significant increase except CEA which showed mild significant increase ($p<0.05$).

Relationship Between Serum Levels of Tumor Markers and Liver Functions

In colorectal cancer, no difference was shown in liver functions of these patients compared with controls. ALT levels were significant higher ($p<0.001$) elevated in both pancreatic cancer and HCC. Alkaline phosphatase was significantly increased in pancreatic cancer ($p<0.001$), HCC ($p< 0.05$), colon cancer ($p<0.05$) and gastric cancer ($p<0.05$). Serum bilirubin was only increase significantly ($p<0.01$) in pancreatic carcinoma. Only in HCC, serum AFP levels showed a significant positive correlation with ALT levels ($r=0.816$). In other cancers, no significant correlation was shown between CEA, CA 19-9 or CA 242 and the ALT levels.

Diagnostic Potentials of Single and Combined Detection of Serum CEA, CA 19-9, CA 242 and AFP in Different Gastrointestinal Cancers

In colon cancer, CA 242 was the most sensitive (48%) and specific (100%) tumor markers. CEA showed similar degrees of sensitivity and specificity to CA 242. In HCC patients, AFP was the most sensitive and specific tumor marker (65 and 100%, respectively). In pancreatic cancer, the most sensitive and specific tumor marker was CA 19-9 with a sensitivity of 70.4% and specificity of 100%. None of the evaluated markers had a sufficient sensitivity to be taken as a marker for gastric cancer (Table 2).

Table 1: Serum levels (Mean±SD) of CEA, CA 19-9, CA 242 and AFP in different groups of cancer patients compared with the controls group

Groups	CEA (ng mL^{-1})	CA 19-9 (ng mL^{-1})	CA 242 (ng mL^{-1})	AFP (ng mL^{-1})
Controls	2.34±1.35	10.7±10.30	9.2±4.30	5.10±3.60
Colon cancer	10.0±9.50***	25.30±23.8***	34.5±25.20***	7.00±6.80*
HCC	2.50±.080*	12.90±8.05*	10.8±7.28*	36.90±30.85***
Pancreatic cancer	3.60±2.90*	193.67±189.16***	30.0±29.18***	6.00±3.80*
Gastric cancer	4.10±3.85**	13.22±8.30*	13.1±11.01*	6.70±4.97*

*No significant difference ($p>0.05$), ** Mild significant difference ($p<0.05$), *** highly significant difference ($p<0.001$) in comparison with controls

Table 2: Sensitivity evaluation of single tumor marker determination in the diagnosis of gastrointestinal tract cancers

	Sensitivity (%)			
Gastrointestinal tumor	CEA	CA 19.9	CA 242	AFP
Colon cancer	48.0	16.0	48.0	6.0
Hepatocellular carcinoma	0.0	7.7	7.7	56.0
Pancreatic cancer	14.8	70.4	29.6	3.7
Gastric cancer	11.1	5.6	11.1	5.6

CEA : Carcinoembryonic antigen; CA 19-9 : Carbohydrate antigen 19-9;
CA 242 : Carbohydrate antigen 242; AFP : α fetoprotein

Table 3: Different combinations of tumor markers for the diagnosis of different gastrointestinal tract cancers

		Sensitivity (%)			
Tumor	Marker	CEA	CA 19.9	CA 242	AFP
Colon cancer	CEA	48.0	54.0	72.0	48.0
	CA 19.9	54.0	16.0	50.0	18.0
	CA 242	72.0	50.0	48.0	48.0
	AFP	48.0	18.0	48.0	6.0
Hepatocellular	CEA	0.0	7.7	7.7	65.0
carcinoma	CA 19.9	7.7	7.7	7.7	69.0
	CA 242	7.7	7.7	7.7	69.0
	AFP	65.0	69.0	69.0	65.0
Pancreatic cancer	CEA	14.8	70.4	37.0	22.0
	CA 19.9	70.4	70.4	70.4	37.0
	CA 242	37.0	70.4	29.6	70.4
	AFP	22.0	37.0	70.4	3.7
Gastric cancer	CEA	11.1	5.6	22.0	11.1
	CA 19.9	5.6	5.6	22.0	11.1
	CA 242	22.0	22.0	11.1	22.0
	AFP	11.1	11.1	22.0	5.6

CEA : Carcinoembryonic antigen; CA 19-9 : Carbohydrate antigen 19-9; CA 242 : Carbohydrate antigen 242; AFP: α-fetoprotein

n colon cancer, the combined testing of CEA and CA 242 resulted in a significantly ($p<0.05$) higher degree of sensitivity (72%). In HCC patients, combined testing of AFP either with CA 19.9 or CA 242 improved the sensitivity of AFP to 69% ($p>0.05$). In pancreatic cancer, no remarkable improvement in sensitivity of CA 19.9. In gastric cancer, combined testing of CEA and CA 242 markers showed a non-significant increase in sensitivity (22%) (Table 3).

Discussion

The Gastrointestinal Tract (GIT) is the site of more cancers than any other organ system in the body. In terms of morbidity and mortality, the main GIT cancers are colorectal, gastric, pancreatic, oesophageal and hepatocellular carcinomas. Each type of GIT cancer has its own preferential marker or group of markers. The use of tumour markers has become a very attractive method for the detection and diagnosis of neoplastic diseases (Pecatasides *et al*., 1997 and Yamo *et al*., 1999). However, their value in cancer detection has been controversial largely because no single tumour marker is sensitive and specific enough to meet strict diagnostic criteria. In the present study, we investigated the clinical usefulness of four tumor makers (CEA, AFP, CA 19-9 and CA 242) to evaluate the values of single and combined test in the diagnosis of different gastrointestinal tumors. Serum concentrations of CEA and CA 242 were significantly higher ($p<0.001$) in patients with colorectal cancer than in control group. Carpelan-Holmstrom *et al.* (2002) found relatively 54% sensitivity of CEA in colorectal cancer patients. It is believed that the difference in the sensitivity of CEA in the present study and other studies is at least partially due to the use of different cut off values. The elevation of serum CEA and CA 242 may be due to, at least in part, their drainage by the lymph nodes. The equilibrium between their rate of synthesis and their hepatic clearance from peripheral circulation is another factor. The elevation of CA 242 level in serum may be attributed either to low synthesis of particular core protein carrying CA 242 epitope in benign conditions and high synthesis of CA 242 core protein in colorectal cancer, or to differences in glycosylation of the same protein core in benign and malignant tissues with preferential expression of CA 242 in cancerous tissue. This interpretation coincides to a great extent

with that given by Nilsson *et al.* (1992). The combination test of CEA and CA 242 in colon cancer changes the sensitivity to 72%. This is in agreement with that of Carpelan-Holmstrome *et al.* (1996a) who demonstrated that using CA 242 and CEA concomitantly increased the overall sensitivity in colorectal cancer patients compared with using either CEA or CA 242 alone. Also, we found positive significant correlation between CA 19-9 and CA 242 in patients with colorectal cancer. However, Carpelan-Holmstrom *et al.* (1996b) found significant ($r=0.59$, $p<0.001$) correlation between the logarithms of CA 242 and CEA in colorectal cancer patients. Recently, Yu *et al.* (2004) demonstrated that the combination of optimal serum tumor markers (CEA, CA199, CA 242, CA211, CA724) has a high sensitivity (83%) and specificity (95%) in diagnosis of colorectal carcinoma. In pancreatic cancer, although a variety of tumor markers are available for diagnosis, their sensitivity and specificity have not yet been ideal. Jiang *et al.* (2004b) demonstrated that serum CA 19-9, CA 242, CA-50 and CA72-4 are the preferred tumor markers to be used in the diagnosis and follow-up of operated cases of pancreatic cancer. Testing of a panel of multiple serum tumor markers may increase the sensitivity and specificity in the diagnosis of pancreatic cancer. In the present study, percentage of serum CA 19-9 above the cut off was 70.375% in pancreatic cancer. These findings agree with the results of Vanden-Bosch *et al.* (1996) who found that the percentage of pancreatic cancer patients having CA 19-9 levels above the cut off value was 77.5% and slightly lower than that the percentage reported by Ozkan *et al.* (2003) in 40 pancreatic cancer patients was 80% but slightly higher than the percentage (63.7%) as reported by Mc-Laughlin *et al.* (1999). Combination of CA 242 with CA 19-9 in pancreatic cancer did not increase the sensitivity. Thus CA 19-9 remains the marker of first choice for pancreatic cancer. Plebani *et al.* (1995) demonstrated that the two markers were remarkably similar in behavior due to cross reactivity between CA 242 antigen and CA 19-9 antibody and for this reason CA 242 can not be considered as a marker for pancreatic cancer. Jiang *et al.* (2004b) reported that the combined use of TSGF, CA 242 and CA 19-9 expressions can elevate the specificity for pancreatic cancer diagnosis In the present study, only there is positive significant correlation between CA 19-9 and CA 242 in pancreatic cancer patients. This result is in a good agreement with Ozkan *et al.* (2003). AFP levels was highly significant ($p<0.001$) elevated in patients with HCC than the corresponding control group or another evaluated cancer groups with sensitivity and specificity of 65% and 100%; respectively. So, measurement of serum AFP level in HCC is the most reliable tumour marker, as described in previous reports (Jiang *et al.*, 2004b and Tan *et al.*, 2003). On the other hand, Gupta *et al.* (2003) found a sensitivity of 41-65% and specificity of 80-94% using the cut off value of 20 ng mL^{-1} they and reported that AFP has limited utility for detecting HCC. In the present study, there was positive significant correlation between CA 19-9 and CA 242 in patients with HCC. Also, there was a positive significant correlation between ALT and AFP. So, these results suggested that AFP was most sensitive in addition to ALT in HCC patients. CEA level was significantly ($p<0.05$) elevated in gastric cancer patients than the corresponding control level. But the percentages of cases having value above the cut off value sensitivity have relatively low (11%). These data are partially agreeable with those of Carpelan-Holmstrom *et al.* (2002) who found a sensitivity of 25% in gastric cancer patients with over all accuracy of 66% using immunohistochemical technique. Levels of serum CA 19-9, CA 242 and AFP were slightly elevated than their corresponding control group indicating that these markers are of little importance in gastric cancer. These findings are disagreeable with those of Lundin *et al.* (1994) and Kodera *et al.* (1996) who reported elevated serum CA 19-9 in gastric cancer patients. Combination test of CEA and CA 242 changed the sensitivity to 22%, therefore, CA 242 may be used to increase the sensitivity of CEA in patients with gastric cancer. In conclusion, combined detection of CEA and CA 242 in colorectal cancer can improve the sensitivity. CA 19-9 showed the

best sensitivity for pancreatic cancer. In HCC, AFP was the most sensitive tumour marker. None of the tumor markers evaluated had the sufficient sensitivity to be taken as a marker for gastric cancer.

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