

ORIGINAL ARTICLES

PREOPERATIVE SERUM LEVELS OF CA 72-4, CEA, CA 19-9, AND ALPHA-FETOPROTEIN IN PATIENTS WITH GASTRIC CANCER

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INTRODUCTION: The clinical importance of preoperative serum levels of CA 72-4, carcinoembryonic antigen (CEA), CA 19-9, and alpha-fetoprotein (AFP) was prospectively evaluated in 44 patients with gastric cancer.

METHOD: The serum tumor marker levels were determined by commercial radioimmunoassay kits. Positivity for CA 72-4 (>4 U/mL), CEA (>5 ng/mL), CA 19-9 (>37 U/mL), and AFP (>10 ng/mL) were correlated according to the stage, histology, and lymph node metastasis.

RESULTS AND DISCUSSION: CA 72-4 showed a higher positivity rate for gastric cancer (47.7%) than CEA (25%), CA 19-9 (25%), and AFP (0%). The combination of CA 72-4 with CEA and CA 19-9 increased the sensitivity to 61.4%. The positivity rates of CA 72-4 in patients at stages I and II (initial disease) and in patients at stages III and IV (advanced disease) were 9% and 60.6%, respectively ($P < 0.005$). No correlation was found between CEA and CA 19-9 levels and the stage of gastric cancer. There was a tendency of positivity for CA 72-4 to suggest lymph node involvement, but it was not significant ($P = 0.075$). Serum levels of tumor markers did not show a correlation with the histological types of gastric cancer.

CONCLUSION: Preoperative serum levels of CA 72-4 provided a predictive value in indicating advanced gastric cancer.

DESCRIPTORS: Gastric cancer. CEA. CA 72-4. CA 19-9. Alpha-fetoprotein.

The high mortality rate from gastric cancer arises from its late detection and surgical resection at advanced stages of the disease¹. However, particularly in Japan, mass screening for gastric cancer performed by endoscopy and double-contrast barium X-ray has contributed to early diagnosis and reduction of mortality from gastric cancer².

In 1969, Thomson et al.³ 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 detection of cancer.

With the advent of monoclonal antibodies⁴, other tumor markers with special application for gastrointestinal tract malignancies were described. For adenocarcinoma of the pancreas, CA 19-9 is more specific and sensitive than CEA, the most widely used tumor marker^{5,6}. For gastric cancer, CA 72-4 was the marker that showed the higher sensitivity⁷. Nonetheless, due to their low sensitivity and specificity in detecting early primary tumor, tumor markers have shown little benefit as a method

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for screening in the general population.

Tumor markers can be used clinically for the monitoring of tumor recurrence and used as prognostic factors because higher levels have been observed in advanced disease⁸⁻¹⁰. The combined assay of preoperative serum levels of CEA, CA 19-9, and CA 72-4 has provided additional prognostic information for patients resected for gastric cancer; patients with preoperative positivity for one of these possible tumor markers have a high risk of recurrence, even in the early stages of gastric cancer¹⁰.

The serum level of AFP (alpha-fetoprotein) has been widely used for

hepatocellular carcinoma screening in patients with chronic liver disease¹¹⁻¹³. In recent years, many cases of AFP-producing gastric cancer, characterized by increased AFP serum levels and AFP positivity of the gastric cancer tissues, have been reported¹⁴. Alphafetoprotein-producing gastric cancer has been associated with a poor prognosis because of its high proliferative activity, weak apoptosis, and rich neovascularization, compared to that of AFP-negative gastric cancers. These biological characteristics of AFP-producing gastric cancer reflect the aggressive behavior of the tumor and the poor prognosis of patients with this type of cancer¹⁵.

The purpose of our study was to determine which marker or combination of markers among CA 72-4, CEA, CA 19-9, and AFP would be the most useful for detecting gastric cancer.

MATERIAL AND METHODS

Patients

Forty-four patients with gastric cancer were selected for the study. The average age of patients (27 men, 17 women) was 64.3 ± 10.9 years. The tumors were classified as intestinal and diffuse types, according to Láuren¹⁶; 18 patients had the diffuse type and 26 patients had the intestinal type. The TNM staging was performed according to the criteria of the Japanese Classification of Gastric Cancer¹⁷; 4 patients had stage Ia cancer, 3 patients had stage Ib, 4 patients stage II, 5 patients stage IIIa, 13 patients stage IIIb, 8 patients stage IVa, and 7 patients stage IV.

Serum Markers

Quantitative determinations of CA 72-4, CEA, CA 19-9, and AFP were performed using commercial radioimmunoassay kits (CIS Bio International, France). The cut-off values were 5 ng/mL for CEA, 37 U/mL for CA 19-9, 4 U/mL for CA 72-4, and 10 ng/mL for AFP.

A result was considered positive when the marker serum level was higher than the cut-off value.

Statistics

The serum level of these tumor markers was investigated with respect to stage (initial or advanced disease), regional lymph node metastasis, and histology (intestinal or diffuse types) using the chi-square or Fisher exact test. Gender and age of the patients were correlated with the stage of the disease, regional lymph node metastasis, and histology using the chi-square or Fisher exact test.

RESULTS

Preoperative serum levels of CA 72-4, CA 19-9, CEA, and AFP were assayed in 44 patients with gastric cancer. Since none of the patients were positive for AFP, the analysis of AFP was excluded. CA 72-4 was positive in 21 (47.7%) patients, CEA in 11 (25%) patients, and CA 19-9 in 11 (25%) patients. The sensitivity of the combination of CA 72-4 and/or CA 19-9 was 56.8%; of CA 72-4 and/or CEA was 54.5%, and of CEA and/or CA 19-9 was 43.2%. The three markers together showed a sensitivity of 61.4%.

CA 72-4 was positive in 9% of patients at stages I and II (initial disease) and in 60.6% of patients at stages III and IV (advanced disease), as shown in table 1. This difference was signifi-

cant ($P < 0.005$) when assessed by the chi-square test. CEA was positive in 9% of patients with initial disease and in 30% of patients with advanced disease ($P > 0.05$). CA 19-9 was positive in 18.2% of patients with initial disease and in 27.3% of patients with advanced disease ($P > 0.05$).

Regarding the lymph node status of the patients, 12 had no lymphatic invasion and 22 had regional lymph node metastasis (Table 1). Ten patients who had advanced disease did not undergo surgery; thus, they were excluded from this analysis. CA 72-4 was positive in 11 (50%) patients with lymph node metastasis and in 2 (16.7%) patients negative for lymphatic invasion ($P = 0.075$). CEA was positive in 5 (22.7%) patients with lymph node metastasis and in 2 (16.7%) patients negative for lymphatic invasion ($P > 0.05$). CA 19-9 was positive in 3 (13.7%) patients with lymph node metastasis and in 2 (16.7%) patients negative for lymphatic invasion ($P > 0.05$).

There was no correlation of the positivity rate of CEA, CA 72-4, and CA 19-9 with the histological types (Table 1). There was also no correlation of sex and age to histology, early and advanced disease, and lymph node invasion (data not shown).

DISCUSSION

The use of tumor markers has become a very attractive method for the detection and diagnosis of neoplastic

Table 1- Positive rate of CA 72-4, carcinoembryonic antigen (CEA) and CA19-9 in gastric cancer patients grouped according to initial and advanced disease, lymphatic invasion and histology.

Gastric cancer	CA 72-4	Carcinoembryonic antigen (CEA)	CA 19-9
Initial (stages I/II) n=11	1 (9%)	1(9%)	2 (18.2%)
Advanced (stages III/IV) n=33	20 (60.6%) *	10 (30.3%)	9 (27.3%)
Lymph node invasion (-) n=12	2 (16.7%)	2 (16.7%)	2 (16.7%)
Lymph node invasion (+) n=22	11 (50%)	5 (22.7%)	3 (13.6%)
Diffuse type n= 18	10 (55.6%)	5 (27.8%)	4 (22.2%)
Intestinal type n= 26	11 (42.3%)	6 (23.1%)	7 (26.9%)

* $p < 0.005$ for CA 72-4

diseases, as well as for the monitoring of their course after radical surgery or during chemotherapy^{18,19}. One of the challenging problems in the diagnosis and postoperative follow-up of patients with gastric cancer is the low sensitivity of the tumor markers that are currently being used⁸.

Since the role of tumor markers in gastric cancer is still controversial, we prospectively studied the serum levels of CA 72-4, CEA, CA 19-9, and AFP in patients with gastric cancer who were being evaluated for surgery. Previous studies of serum levels of CEA, CA 19-9, and CA 72-4 in gastric cancer have demonstrated that the positivity of these markers has a wide range of variation, from 14% to 42% for CEA^{1-8,10,20-22}, from 16% to 38.4% for CA 19-9^{7,8,10,21,22}, and from 24.2% to 45.3% for CA 72-4^{7,9,10,22}.

According to our results, CA 72-4 alone presented an even higher positivity rate (47.7%) than the combination of CEA and CA 19-9 (43.2%). The best combination of tumor markers was CA 72-4 and CA 19-9 (56.8%), which was similar to that of a previous report²³. None of the patients were positive for AFP; the positivity of AFP in gastric cancer has been reported to be low (15%)²⁴, and usually, AFP has been a marker of aggressive behavior tumor and poor prognosis¹⁵.

When the patients with gastric cancer were divided into 2 groups, initial

(stage I/II) and advanced disease (stage III/IV), CA 72-4 was the best marker (60.6%) for advanced disease ($P < 0.005$). Serum levels of CEA and CA 19-9 exhibited no significant differences between cases of initial and advanced disease. The superiority of CA 72-4 for gastric cancer over CEA and CA 19-9 has been previously demonstrated by other authors^{7,22,23}. However, CA 72-4 seems to be a marker of advanced disease, rather than a marker for mass survey screening for the detection of early disease. After curative surgery, CA 72-4 could be used to monitor recurrence or metastasis in those cases that had elevated serum levels prior to surgery.

There was a tendency for CA 72-4 to also be a marker for lymph node involvement; nonetheless, it was not significant ($P = 0.075$). The discrimination of the lymph node status of the patients could have clinical applications for staging. CEA, CA 72-4, and CA 19-9 were considered markers of lymph node involvement in other reports^{8,10,20}. Ikeguchi et al⁹ found that CEA was a good indicator of lymph node metastasis, while CA 72-4 was a good predictor of peritoneal metastasis. In our study however, CEA and CA 19-9 were neither indicators of lymph node involvement nor of advanced disease.

Serum levels of tumor markers showed no correlation to the histology

of the tumor. Some authors have tried to explain the low sensitivity of tumor markers in their studies in terms of the histology of the tumor, with the diffuse type of gastric cancer presenting the lowest positivity rate of the markers²¹. However, this correlation is still controversial, since in other reports, the positivity rate of CEA, CA 72-4, and CA 19-9 was higher in the diffuse type⁷. Nonetheless, other authors have also shown no correlation between tumor marker levels and the histology of gastric cancer¹⁰.

The ease of blood sampling makes serologic tumor marker tests very attractive for the detection of neoplastic diseases. The search for more sensitive methods, along with more specific and sensitive tumor markers for gastric cancer, is still under way. A novel sensitive method, which has been termed immuno-polymerase chain reaction (immuno-PCR), was developed for the detection of gastric carcinoma-associated antigen MG7-Ag. The comparison of immuno-PCR and commercial assays for tumor markers demonstrated that the sensitivity of immuno-PCR was 81.4%²².

In conclusion, the results of the current study showed that CA 72-4 was the best marker for advanced gastric cancer; nevertheless, in the future, more sensitive techniques using other tumor-associated antigens should be developed.

RESUMO

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MATTAR R e col.- Níveis séricos pré-operatórios de CA 72-4, CEA, CA 19-9 e Alfa-fetoproteína em pacientes com câncer gástrico. *Rev. Hosp. Clín. Fac. Med. S. Paulo* 57(3): 2002.

INTRODUÇÃO: A importância clínica dos níveis séricos pré-operatórios de CA 72-4, antígeno carcinoembrionário (CEA), CA 19-9 e alfa-fetoproteína (AFP)

foi avaliada prospectivamente em 44 pacientes com câncer gástrico.

MÉTODOS: Os marcadores tumorais foram quantificados com o emprego de kits comerciais de radioimunoensaio. A positividade dos marcadores, CA 72-4 (>4 U/ml), CEA (>5 ng/ml), CA 19-9 (>37 U/ml) e AFP (>10 ng/ml), foi correlacionada com o estágio da doença, a histologia do tumor e comprometimento de linfonodo.

RESULTADOS E DISCUSSÃO: O marcador CA 72-4 apresentou maior positividade para o câncer gástrico (47,7%) que CEA (25%), CA 19-9 (25%) e AFP (0%). A associação de CA 72-4, CEA e CA 19-9 aumentou a sensibilidade para 61,4%. A positividade do CA 72-4 nos pacientes com estágios I e II (Doença Inicial) e nos pacientes com estágios III e IV

(Doença Avançada) foi de 9 e 60,6%, respectivamente ($p < 0,005$). Não foi observada correlação entre os níveis séricos de CEA e CA 19-9 com o estágio do câncer gástrico. O CA 72-4 apresentou tendência de sugerir

comprometimento de linfonodo, mas não foi significativo ($p = 0,075$). Não houve correlação entre os níveis séricos dos marcadores tumorais com os tipos histológicos de câncer gástrico.

CONCLUSÃO: A positividade do CA 72-4 teria o valor de indicar os casos de câncer gástrico avançado no pré-operatório.

DESCRIPTORES: Câncer gástrico. CA 72-4. CEA. CA 19-9. Alfa-fetoproteína.

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