CA 72-4 Measurement of Tumor-associated Glycoprotein 72 (TAG-72) as a Serum Marker in the Management of Gastric Carcinoma

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ABSTRACT

The present study evaluates the preoperative serum levels of TAG-72, CEA, and CA 19-9, alone or in combination, in patients diagnosed with primary gastric carcinoma or benign gastric disease. The findings suggest the potential utility of using the CA 72-4 assay to detect serum TAG-72, either alone or in combination with CA 19-9, for the diagnosis of gastric carcinoma. In addition, a longitudinal follow-up of gastric carcinoma patients also revealed the potential utility of the CA 72-4 assay alone, or in combination with CA 19-9, as part of serum markers specifically associated with a high percentage of patients diagnosed with gastric carcinoma. Among the serum markers currently available for the diagnosis of gastric carcinoma are CEA3 and CA 19-9 (8-13). CEA, a M, 180,000 glycoprotein, and CA 19-9, a sialylated Lewisx antigen, are distinct tumor markers expressed by human gastric carcinomas (9, 14). An analysis of the data shows that of all patients diagnosed with gastric carcinoma, 20.6% had positive serum CEA levels. Of those patients with advanced stage (stage IV) gastric carcinoma, measurable serum CEA was found in 37% (13). CA 19-9 has also been evaluated as a possible serum marker for gastric cancer. Elevated serum levels of this tumor antigen were found in 26% (15) to 72% (11) of the patients with gastric carcinoma, while 7% of the patients diagnosed with benign gastric disease had positive serum CA 19-9 levels (11).

The studies revealed some potential utility as well as limitations for monitoring CEA and/or CA 19-9 serum levels in patients diagnosed with gastric carcinoma. The data also suggest the need to evaluate other serum tumor markers for their potential role in the management of gastric cancer.

INTRODUCTION

Although the incidence and death rate from gastric cancer in the United States have declined in past decades, it remains a common cause of cancer-related death (1, 2). The highest incidence rates of gastric carcinoma are found in certain Mediterranean countries, in Eastern Europe, and in the Pacific Rim, with Japan having the highest incidence worldwide (3-5). In Italy, the incidence of gastric carcinoma is 25.1/100,000 for males and 16.1/100,000 for females, representing the second most common cause of cancer-related deaths (14,500/year, in the past 5 years) (3).

The early stage of gastric carcinoma is often complicated and extremely difficult to diagnose due to presentation with vague, nonspecific symptoms which are sometimes associated with nonmalignant diseases (6, 7). The development of additional methods for this diagnosis includes the desire for efficient, noninvasive diagnostic procedures such as the identification of

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2 To whom requests for reprints should be addressed, at Laboratory of Tumor Immunology and Biology, Building 10, Room 8B07, National Cancer Institute, NIH, Bethesda, MD 20892.

3 The abbreviations used are: CEA, carcinoembryonic antigen; TAG-72, tumor-associated glycoprotein 72; MAb, monoclonal antibody.
the clinical management of postsurgical gastric carcinoma patients.

MATERIALS AND METHODS

Patient Information. One hundred ninety-four patients, 94 with histologically diagnosed primary gastric adenocarcinoma (50 males, 44 females; mean age, 58 ± 1.3 (SE) years, ranging from 30 to 89 years old), and 100 patients with histologically confirmed benign [gastritis, ulcer, adenomas, polyps] gastric disease (54 males, 46 females; mean age, 53 ± 1.9 years) were evaluated. All patients with malignant disease underwent surgery for their primary tumor at the Department of Surgery, while patients diagnosed with benign gastric disease underwent endoscopic examination at the Department of Digestive Endoscopy of the Regina Elena National Cancer Institute, Rome, Italy. Malignant gastric disease was pathologically staged according to the tumor-nodes-metastasis classification (Union International Contre le Cancer tumor-nodes-metastasis classification of malignant tumors, 1983): Stage I (n = 14); Stage II (n = 16); Stage III (n = 36); and Stage IV (n = 28). Serum samples were drawn within 1 week prior to surgery, 3, 7, and 14 days postoperatively; and every 3 months during clinical follow-up. Serum samples from patients with benign disease were drawn at the time of endoscopy. All samples were aliquoted, coded, and stored at −20°C until assays were performed.

CA 72-4, CEA, and CA 19-9 Radioimmunoassays. Serum TAG-72 antigen levels were determined by a double-determinant immunoaradiometric assay kit, CA 72-4, supplied by Centocor (Malvern, PA), as described previously (25). Samples and TAG-72 standards were assayed in duplicate. Briefly, 100 μL of specimen in the presence of 100 μL of phosphate buffer were incubated at 37°C for 4 h with beads coated with MAb CC49. The beads were washed 3 times with distilled water and incubated with 125I-B72.3 for 18 to 20 h at 4°C. After 3 washes with distilled water, bound radioactivity was measured in a gamma counter. TAG-72 levels, expressed as units/ml, were determined by converting cpm to concentration values using a concurrently obtained standard curve. The cutoff limit for this assay was set at 6 units/ml as suggested (25). CEA serum levels were determined using a CEA RIA MAb kit (Abbott Laboratories, Inc., Chicago, IL). Several different cutoff limits, ranging from 2.5 to 10.0 ng/ml, have been used for the analysis of CEA serum levels (31–33). In the present study, we used a cutoff limit of 5.0 ng/ml for better specificity. CA 19-9 serum levels were determined as previously described using the suggested cutoff limit of 37 units/ml (12). Measurement of serum TAG-72, CEA, and CA 19-9 was done without any prior knowledge of the clinical diagnosis. A significant increase of the serum marker levels was considered, either when negative serum levels became positive or when there was an increase of >50% over the mean of previous positive levels.

Statistical Analysis. A Student t test (STATVIEW softwear package) was used to evaluate statistical differences among the serum tumor markers.

RESULTS

Sera from 94 patients with primary gastric carcinoma and 100 patients with benign gastric disease were evaluated for the presence of TAG-72 using the CA 72-4 assay, for 19-9 using the CA 19-9 assay, and for CEA using the CEA-radioimmunoassay-monoclonal antibody assay. As shown in Table 1, 42.6% of the sera from patients diagnosed with primary gastric carcinoma had elevated TAG-72 levels (>6.0 units/ml). In contrast, only 1% of the sera from patients with benign gastric disease had positive TAG-72 levels. CA 19-9 serum levels were elevated (>37.0 units/ml) in 31.9 and 7% in patients with malignant and benign disease, respectively. Serum CEA was elevated (>5.0 ng/ml) in 20.2% of sera from patients with gastric carcinoma and 9% of sera from patients with benign disease.

The relationships between serum TAG-72, CA 19-9, and CEA levels and the clinical staging of the patients with gastric carcinoma were also evaluated (Table 2). In particular, positive serum TAG-72 levels were found in patients diagnosed with advanced stage gastric carcinoma. Of the 40 patients which had positive serum TAG-72 levels, 37 were diagnosed with either stage III or stage IV gastric carcinoma. Likewise, elevated serum CA 19-9 and CEA were also found predominantly in sera samples from patients with advanced stage gastric carcinoma (Table 2). Fig. 1 summarizes the statistical analysis of the mean CA 72-4, CEA, and CA 19-9 presurgery serum levels for gastric carcinoma patients classified as early (stages I and II) and advanced (stages III and IV) disease. The mean serum TAG-72 levels from patients with stage I and II gastric carcinoma was 3.3 ± 0.6, while the mean value from patients with stage III and IV disease was 24.1 ± 7.8 (Fig. 1A) (P < 0.002). A statistically significant difference between serum CA 19-9 levels in patients diagnosed with early and advanced gastric carcinoma was also observed. As shown, the mean serum CA 19-9 level from patients with stage III or IV gastric carcinoma was 92.3 ± 25.2 compared with 23.2 ± 4.0 from patients diagnosed with stage I or II disease (P < 0.05) (Fig. 1B). No statistical difference was observed for differences in serum CEA levels between those patients diagnosed with early and advanced disease. Thus, these results indicate that measurement of TAG-72 may be useful in differentiating early versus advanced gastric carcinoma.

Studies were then conducted to determine if there was any advantage in the use of combinations of the CA 72-4, CA 19-9, and CEA assays. Fig. 2 illustrates the presence of TAG-72 and/or CA 19-9 in the sera of the 94 patients diagnosed with

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of patients</th>
<th>Range</th>
<th>Mean</th>
<th>No. of patients &gt;6 units/ml</th>
<th>Range</th>
<th>Mean</th>
<th>No. of patients &gt;37 units/ml</th>
<th>Range</th>
<th>Mean</th>
<th>No. of patients &gt;5 ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma</td>
<td>94</td>
<td>1-478.0</td>
<td>17.7 ± 4.2</td>
<td>40 (42.6)</td>
<td>1.5-1040</td>
<td>68.9 ± 16.7</td>
<td>30 (31.9)</td>
<td>1-184.2</td>
<td>10.4 ± 1.9</td>
<td>19 (20.2)</td>
</tr>
<tr>
<td>Benign</td>
<td>100</td>
<td>1-6.1</td>
<td>1.9 ± 0.2</td>
<td>1 (1)</td>
<td>1.5-122.9</td>
<td>15.1 ± 3.2</td>
<td>7 (7)</td>
<td>1-23.7</td>
<td>3.4 ± 0.3</td>
<td>9 (9)</td>
</tr>
</tbody>
</table>

* Mean ± SE.

Numbers in parentheses, percentage of patients' serum samples with detectable levels of the respective tumor antigen.

Table 1 Summary of TAG-72, CA 19-9, and CEA serum levels in sera of patients diagnosed with malignant or benign gastric diseases

Table 2 Correlation of presurgical TAG-72, CA 19-9 and CEA serum levels and clinical stage in gastric cancer patients

<table>
<thead>
<tr>
<th>Stage</th>
<th>No. of patients</th>
<th>TAG-72 &gt;6 units/ml</th>
<th>CA 19-9 &gt;37 units/ml</th>
<th>CEA &gt;5 ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>14</td>
<td>1 (7.1)</td>
<td>4 (28.6)</td>
<td>1 (7.1)</td>
</tr>
<tr>
<td>II</td>
<td>16</td>
<td>2 (12.5)</td>
<td>2 (12.5)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>36</td>
<td>11 (30.6)</td>
<td>7 (19.5)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>28</td>
<td>13 (46.4)</td>
<td>9 (32.2)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>94</td>
<td>40 (42.6)</td>
<td>30 (31.9)</td>
<td>19 (20.2)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, percentage of patients within each stage of malignant gastric cancer in which their serum samples contain positive titers of the indicated tumor antigen.
gastric carcinoma. As shown in Table 1, serum samples from 30 of the 94 patients has positive CA 19-9 levels. Of those 30, 17 serum samples also had positive TAG-72 levels. Of the remaining 64 samples which were negative for CA 19-9, 23 (35.9%) had positive titers of TAG-72. Therefore, combining the measurement of TAG-72 with CA 19-9, 53 of the 94 (56.4%) serum samples were positive for either tumor marker. Similar analyses were done with TAG-72 versus CEA (Fig. 3) and CEA versus CA 19-9 (Fig. 4). As shown in Fig. 3, of 94 patients serum samples 8 (8.5%) were CEA positive, and 11 (11.7%) were positive for both CEA and TAG-72. Of the

Fig. 1. Comparison of the presence of TAG-72 (A), CA 19-9 (B) and CEA (C) in the serum of patients diagnosed with early (stage I and II) or advanced (stage III and IV) gastric carcinoma. , serum cutoff values for TAG-72 (6 units/ml) and CA 19-9 (37 units/ml), n, number of patients in each quadrant (i.e., 23 patients were TAG 72 positive and CA 19-9 negative).

Fig. 2. Serum TAG-72 and CA 19-9 levels in patients diagnosed with gastric carcinoma. See Fig. 1 for explanation of symbols.

Fig. 3. Serum TAG-72 and CEA levels in patients diagnosed with gastric carcinoma. See Fig. 2 for explanation of symbols.

Fig. 4. Serum CA 19-9 and CEA levels in patients diagnosed with gastric carcinoma. See Fig. 2 for explanation of symbols.
remaining 75 patients whose serum samples were CEA negative, 38.7% were TAG-72 positive. When combining the measurement of serum CEA with TAG-72, serum samples from 48 of the 94 (51.1%) patients were positive. The relationship between serum CEA and CA 19-9 in the serum samples from these patients was also investigated (Fig. 4). Serum from 9 of the 94 patients was positive for CEA, and serum samples from 10 patients contained positive levels of both CEA and CA 19-9. Of the 75 patients whose serum CEA levels were negative, 26.7% had positive CA 19-9 serum levels. Combining the measurement of both tumor markers revealed that 41.5% of serum samples were positive for either CEA or CA 19-9.

Table 3 summarizes the percentage of patients diagnosed with gastric carcinoma (n = 94) or with benign gastric disease (n = 100) whose serum samples contained either TAG-72, CA 19-9, and/or CEA. Serum TAG-72 (42.6%) alone was found in a higher percentage of patients with gastric carcinoma than either CEA (20.2%) or CA 19-9 (31.9%) alone. Furthermore, combining serum TAG-72 measurement with either CA 19-9 or CEA increased the percentage of serum positive to 56.4 and 51.1%, respectively. It should be noted that a concomitant elevation of tumor antigens other than TAG-72 was detected in 7 of the 10 clinical recurrences, whereas serum CA 19-9 and CEA levels were positive in 5 and 2 cases, respectively. In all cases, detectable serum levels of TAG-72 either occurred prior to or concomitant with the clinical diagnosis of recurrent disease. As an example, Fig. 5 illustrates the changes in serum TAG-72 (panel A), CA 19-9 (panel B), and CEA (panel C) in patient DSA who was diagnosed with stage II gastric carcinoma and was followed for approximately 2 years after surgical resection of the primary tumor. Prior to surgery, serum samples from patient DSA were positive for CEA and negative for TAG-72 and CA 19-9. During the postsurgical follow-up, positive TAG-72 serum was detected, whereas serum CA 19-9 and CEA remained negative. Elevation of serum TAG-72 was detected at 297 days prior to clinical recurrence.

Table 4 Summary of longitudinal evaluation of TAG-72 serum levels in gastric patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Stage</th>
<th>TAG-72</th>
<th>CEA</th>
<th>CA 19-9</th>
<th>Follow-up (days)</th>
<th>First detectable elevation of tumor antigens*</th>
<th>Time of clinical evidence (days)</th>
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<tbody>
<tr>
<td>FG</td>
<td>I</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>860</td>
<td>ND*</td>
<td>NED</td>
</tr>
<tr>
<td>BL</td>
<td>II</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>427</td>
<td>ND</td>
<td>NED</td>
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<tr>
<td>DSA</td>
<td>II</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>665*</td>
<td>ND</td>
<td>NED</td>
</tr>
<tr>
<td>MD</td>
<td>II</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>372</td>
<td>ND</td>
<td>NED</td>
</tr>
<tr>
<td>PA</td>
<td>II</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>207</td>
<td>ND</td>
<td>NED</td>
</tr>
<tr>
<td>PF</td>
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<td>-</td>
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<td>241</td>
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<td>NED</td>
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<tr>
<td>PU</td>
<td>II</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>384</td>
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<td>NED</td>
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<tr>
<td>RA</td>
<td>II</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>550*</td>
<td>ND</td>
<td>NED</td>
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<tr>
<td>SF</td>
<td>II</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>989</td>
<td>ND*</td>
<td>NED</td>
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<tr>
<td>FEG</td>
<td>III</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>160*</td>
<td>ND</td>
<td>NED</td>
</tr>
<tr>
<td>FI</td>
<td>III</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>434</td>
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<td>NED</td>
</tr>
<tr>
<td>FL</td>
<td>III</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>60*</td>
<td>16</td>
<td>45</td>
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<td>III</td>
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<td>+</td>
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<td>VU</td>
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<td>+</td>
<td>504</td>
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<td>NED</td>
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<tr>
<td>AD</td>
<td>III</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>757</td>
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<td>NED</td>
</tr>
<tr>
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<td>III</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>145</td>
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<td>NED</td>
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<tr>
<td>AP</td>
<td>IV</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>130</td>
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<td>NED</td>
</tr>
<tr>
<td>CM</td>
<td>IV</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>180*</td>
<td>54</td>
<td>97</td>
</tr>
<tr>
<td>FA</td>
<td>IV</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>200*</td>
<td>ND</td>
<td>NED</td>
</tr>
<tr>
<td>PA</td>
<td>IV</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>80*</td>
<td>ND</td>
<td>NED</td>
</tr>
</tbody>
</table>

* Days postsurgery.
* ND, not detectable; NED, no evidence of disease.
* Patients in which detectable serum TAG-72, CEA, and/or CA 19-9 preceded the time of diagnosis of clinical recurrent disease.
Arrow, time of surgery; , serum cutoff values for each of the tumor antigens. Observations suggest that the presence in the serum of TAG-72 (A) and CEA (C) in patients diagnosed with stage II gastric adenocarcinoma. The present data clearly indicate that serum TAG-72, CA 19-9, and CEA appear in 42.6, 31.9, and 20.2%, respectively, among various serum tumor markers which may be exploited in the diagnosis of gastrointestinal carcinoma (30). Ideally, one would envision that the complementarity might increase the sensitivity with respect to clinical diagnosis with little change in the specificity (i.e., little increase in false positives). For example, the present data indicate that combining the measurement of serum TAG-72 with CA 19-9 increased the percentage of patients diagnosed with gastric carcinoma who also had measurable serum titers of either tumor antigen. At the same time, there was no change in the number of false positive serum samples (i.e., patients with benign gastric disease), suggesting that the simultaneous measurement of TAG-72 and CA 19-9 may selectively identify a higher percentage of patients with gastric cancer. Additional studies with higher numbers of samples are needed to further investigate whether the analysis of multiple serum tumor markers may be advantageous in the diagnosis of gastric carcinoma.

One of the important applications of any serum marker is the ability to use the measurement of the serum tumor antigen in predicting the clinical course of the malignant disease, particularly, the diagnosis of disease recurrence. In the present study, 21 patients diagnosed with primary gastric cancer were followed postsurgery for up to 3 years or to time of disease recurrence. As seen in Table 4, none of the 12 patients with no clinical evidence of disease had positive TAG-72 levels. Six of 9 patients [1 patient (RA) had 2 recurrences], however, with clinically confirmed disease recurrence had elevated serum TAG-72 levels. In 5 of the 6 patients with recurrent disease, positive serum TAG-72 levels were detected prior to the clinical diagnosis (Table 4) and, in some patients, positive serum TAG-72 levels preceded clinical evidence of disease by 100 to 300 days. Monitoring both serum CA 19-9 as well as CEA did not correlate as well as TAG-72 with the onset of recurrent disease. While additional studies with larger population groups and different population bases are needed, these findings indicate that the measurement of serum TAG-72 levels may be useful in the clinical diagnosis of primary and recurrent gastric cancer.

It is generally agreed that the sensitivity as well as the specificity of a single serum tumor marker for the diagnosis of primary and recurrent carcinoma is limited. No one serum tumor marker will unfailingly predict the presence of malignant disease or differentiate between benign versus malignant disease. The present data clearly indicate that serum TAG-72, CA 19-9, and CEA appear in 42.6, 31.9, and 20.2%, respectively, of serum of patients diagnosed with gastric carcinoma (Table 1). Therefore, a majority of patients (i.e., >50%) with malignant gastric disease do not contain measurable serum levels of any of these three tumor markers if analyzed separately. Recent findings have suggested a complementarity among various serum tumor markers which may be exploited in the diagnosis of gastrointestinal carcinoma (30). Ideally, one would envision that the complementarity might increase the sensitivity with respect to clinical diagnosis with little change in the specificity (i.e., little increase in false positives). For example, the present data indicate that combining the measurement of serum TAG-72 with CA 19-9 increased the percentage of patients diagnosed with gastric carcinoma who also had measurable serum titers of either tumor antigen. At the same time, there was no change in the number of false positive serum samples (i.e., patients with benign gastric disease), suggesting that the simultaneous measurement of TAG-72 and CA 19-9 may selectively identify a higher percentage of patients with gastric cancer. Additional studies with higher numbers of samples are needed to further investigate whether the analysis of multiple serum tumor markers may be advantageous in the diagnosis of gastric carcinoma.

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