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TAG-72, CA 19.9 AND CEA AS TUMOR MARKERS IN GASTRIC CANCER

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Serum levels of CEA, CA 19.9 and TAG-72 were measured in 79 patients with active gastric cancer, 47 with treated gastric cancer and no clinical evidence of the disease and 33 with benign gastric disease. In the patients with active gastric cancer TAG-72 was increased in 47%, CA 19.9 in 46% and CEA in 33%. The sensitivity of these markers was related to the stage of the disease, although upon comparison of stages I–II and III–IV significant difference was observed only for TAG-72. The combined use of two of the markers increased the sensitivity compared with the use of only one. The results suggest that the combination of TAG-72 and CA 19.9 may be useful in the post surgical management of patients with gastric cancer.

Gastric cancer shows declining incidence in all European countries, although it still remains one of the most common cancers (1). Tumor markers may be useful for the management of patients with cancer (2–4) and several such markers are associated with gastric cancer, including carcinoembryonic antigen (CEA), carbohydrate antigen (CA 19.9) and tumor-associated glycoprotein-72 (TAG-72) (5–10). However, these antigens are not specific for gastric cancer since elevated levels may also be found in other neoplasms, particularly gastrointestinal (11–13). TAG-72 has most recently been introduced in clinical practices. It is an antigen recognized by the monoclonal antibody (mAb) B72.3 and was generated against a membrane-enriched fraction of human mammary carcinoma cells (14). High serum levels of TAG-72 have been found in patients with different malignancies, particularly gastrointestinal and ovarian cancer (15, 16).

The aim of the present study was to evaluate the specificity and sensitivity of serum CEA, CA 19.9 and TAG-72 in patients with gastric cancer. Likewise, the usefulness of combined application of these markers was studied.

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Material and Methods

Serum levels of CEA, CA 19.9 and TAG-72 were measured in 79 patients with active gastric cancer. This group included 66 newly diagnosed patients and 13 patients with recurrent cancer or metastasis. Untreated patients were staged according to the TNM classification: 6 patients being in stage IA, 2 in stage IB, 8 in stage II, 11 in stage IIIA, 11 in stage IIIB, and 28 in stage IV.

The serum levels of these markers were measured in 47 patients with no clinical evidence of disease following surgical resection of the primary tumor. None of these patients had clinical evidence of recurrence within a period of at least 6 months. The serum levels of CEA, CA 19.9 and TAG-72 were also measured in 33 patients with benign gastric diseases. Serum samples from these patients were drawn at the time of endoscopy.

Venous blood was drawn by venipuncture and the serum stored at −20°C until analyzed. CEA was measured by a commercially available immunoradiometric method (Abbott, Chicago, Il, USA), using a 5 ng/ml as cut-off level. CA 19.9 was measured by a commercially solid-phase immunoradiometric method (Sorin, Saluggia, Italy) and 37 U/ml was used as cut-off value. TAG-72 was measured by a commercially solid-phase immunoradiometric method (Sorin, Saluggia, Italy) using mAb B72.3. The

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standard curve covers the range 3–100 U/ml. The upper cut-off value for TAG-72 was defined as 6 U/ml. All cut-off values were obtained from a study of a normal population in our department. The interassay variance coefficient for CEA was 6.84% (4.75 ± 0.33), for CA 19.9 5.03% (81.5 ± 4.1) and for TAG-72 6.83% (12.18 ± 0.83). The Mann-Whitney U test was used for statistical analysis.

Results

None of the 33 patients with benign gastric disease presented elevated TAG-72 serum levels. CEA levels >5 ng/ml (median 2.2; range <2–9.3) were observed in 9% of these patients and in 15% the CA 19.9 levels were >37 U/ml (median 21.1; range <6–73).

Pretreatment serum levels of CEA, CA 19.9 and TAG-72 in patients with gastric cancer are shown in Table 1 and in Figs. 1–3. Elevated levels of these markers were observed in 33%, 39% and 44% of cases. The serum levels of CA 19.9 and TAG-72 were significantly higher in patients with gastric cancer than in those with benign gastric disease ($p < 0.001$ and $p = 0.06$ respectively). In contrast, no significant differences were observed with regard to the CEA between these groups of patients. The highest serum levels of the markers were generally found in patients with advanced disease. However, when patients in stages I–II and III–IV were compared, a significant difference was observed for TAG-72 only ($p = 0.006$) (Fig. 3).

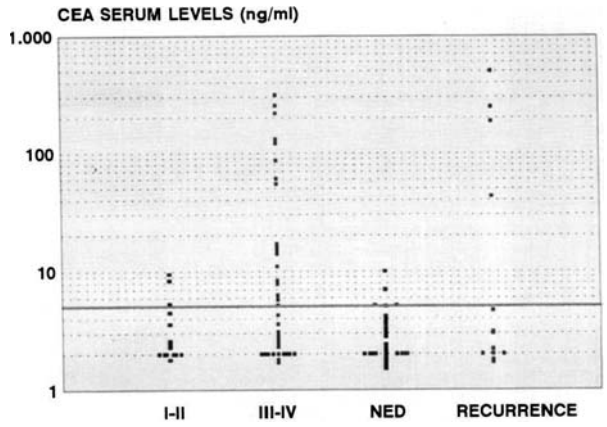

Fig. 1. CEA serum levels in patients with gastric cancer. The cut-off value for CEA (5 ng/ml) is indicated. NED = no evidence of disease.

Table 2 and Figs. 1–3 show the values of the three markers in operated gastric cancer patients without clinical evidence of disease. Only 4% of them had elevated CA 19.9 or TAG-72, whereas 13% had elevated CEA. CA 19.9 was >37 U/ml in 77% of the patients with local recurrence or metastases. The sensitivity of TAG-72 and CEA in this group of patients was 61% and 31% respectively (Table 2).

Table 3 compares the sensitivity of the three markers in patients with active gastric cancer. CA 19.9 and TAG-72 were the most sensitive markers (46% and 47% respectively). The simultaneous use of two markers increases the

Table 1

CEA, CA 19.9 and TAG-72 in patients with untreated gastric cancer

		CEA		CA 19.9		TAG-72	
	n	>5 ng/ml %	Median	>37 U/ml %	Median	>6 U/ml %	Median
Stage I	8	12.5	2	25	20	0	3
Stage II	8	25	2.5	12.5	17	25	3
Stage III	22	23	2.2	41	24	50	6
Stage IV	28	50	5.0	50	35	57	9.5
Total	66	33	2.6	39	24	44	4

Table 2

CEA, CA 19.9 and TAG-72 in patients without clinical evidence of disease (NED) after surgery for gastric cancer and in patients with relapse after surgery

		CEA		CA 19.9		TAG-72	
	n	>5 ng/ml %	Median	>37 U/ml %	Median	>6 U/ml %	Median
NED	47	13	<2	4	14	4	<3
Recurrence	13	31	3	77	113	61	27

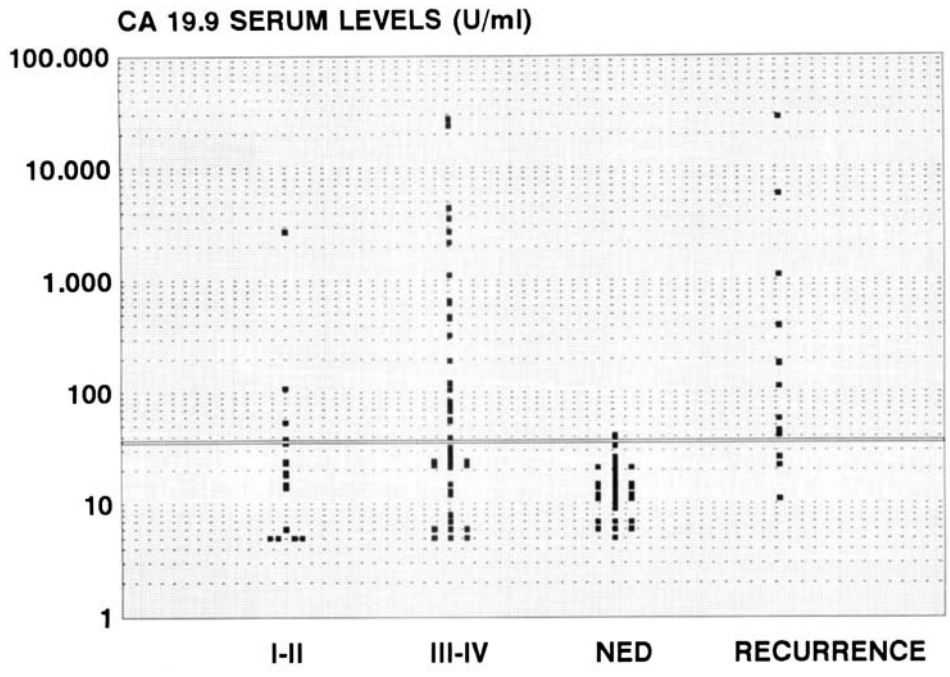

Fig. 2. CA 19.9 serum levels in patients with gastric cancer. The cut-off value for CA 19.9 (37 U/ml) is indicated. NED = no evidence of disease.

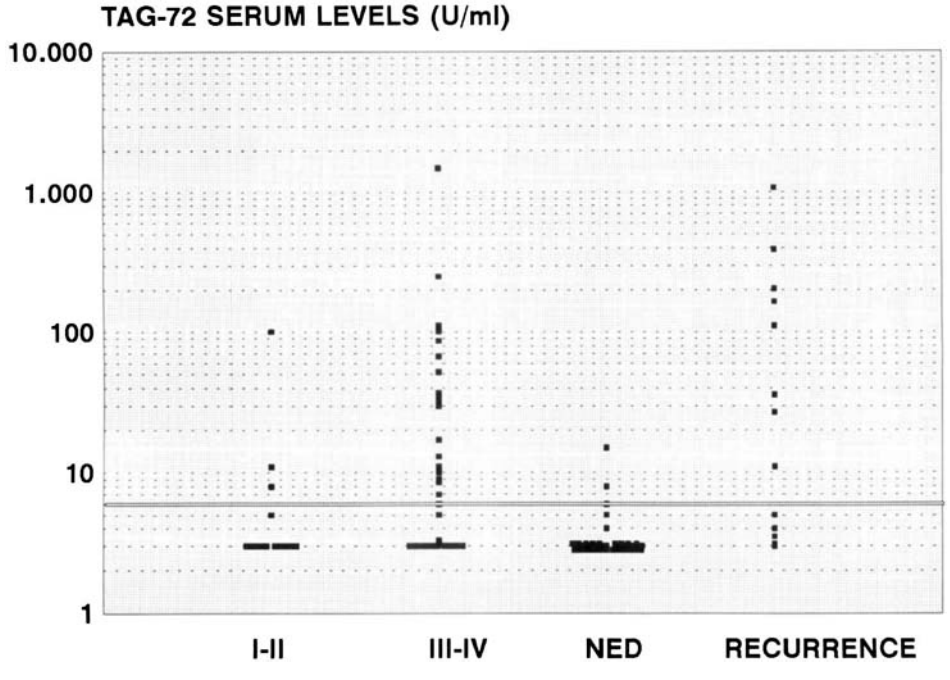

Fig. 3. TAG-72 serum levels in patients with gastric cancer. The cut-off value for TAG-72 (6 U/ml) is indicated. NED = no evidence of disease.

sensitivity. The greatest sensitivity was obtained when CA 19.9 and TAG-72 were combined (65%). Addition of CEA as a third marker only very slightly increased the sensitivity (72%). Table 3 shows the percentages of false positives obtained for each of these combinations in the group of patients without clinical evidence of disease. The percentage of false positives increased with the use of more than one marker.

Table 3

Comparison of CEA, CA 19.9 and TAG-72 values in patients with active gastric cancer (primary or recurrent) and in patients without evidence of disease after surgery

	Active cancer Percentage with elevated marker	No evidence of disease Percentage with elevated marker
CEA	33	13
CA 19.9	46	4
TAG-72	47	4
CEA and/or CA 19.9	58	17
CEA and/or TAG-72	61	15
CA 19.9 and/or TAG-72	65	8
All three markers	72	19

Discussion

Tumor markers may be useful parameters for early diagnosis of recurrence and evaluation of treatment response. They are as a rule not useful for the primary diagnosis of cancer as they may be elevated in different non-malignant diseases (17–19). According to some authors TAG-72 seems to be a marker with great specificity (20). The results of the present study indicate that the markers evaluated cannot be used for the diagnois of gastric cancer, since the values were sometimes elevated in the absence of active malignant disease. The authors have previously indicated the lack of specificity of TAG-72, emphasizing pulmonary and gynecologic diseases as the principal non-neoplastic causes of elevation of this glycoprotein. On the other hand, TAG-72 is seldom increased in other benign diseases including chronic renal failure, pancreatitis, diabetes mellitus and liver cirrhosis (16).

Serial determination of tumor markers in patients with gastric cancer may allow early diagnosis of relapse with greater percentage of resectability (21). However, markers with both high specificity and high sensitivity are required. Our results showed TAG-72 and CA 19.9 to be more sensitive than CEA (44, 39 and 33 respectively) and similar results have recently been shown by other authors (5, 7–9). These results differ from those presented by Byrne et al. (6), which indicated that TAG-72 had much higher sensitivity than CA 19.9 (94% versus 41%). The difference may, in part, be due to their use of a cut-off value of 4.4 U/ml for TAG-72, which is somewhat lower than the commonly used value of 6 U/ml.

In the present study a relationship was observed between CEA, CA 19.9 and TAG-72 and the stage of the disease. Both the sensitivity and the median serum levels of all three markers were higher in patients with advanced stage. Nonetheless, significant difference between stages I–II and stages III–IV was observed only for TAG-72, but not for CEA or CA 19.9. When studying the patients with local recurrence or metastasis, we observed greater sensitivity for CA 19.9 (77%) and TAG-72 (61%) than for CEA (31%). The combined determination of CA 19.9 and TAG-72 was found to provide the greatest sensitivity and 65% of the patients with active gastric cancer presented elevation of CA 19.9 and/or TAG-72. The addition of CEA showed a very slight increase of sensitivity up to 72%. The results indicate that a combination of CA 19.9 and TAG-72 may be useful in the management of patients with gastric cancer. Addition of CEA as a third marker, is probably of little use, especially as this also increases the percentage of false positives (Table 3). These results agree with those presented by Heptner et al. (5) and Guadagni et al. (7).

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