Clinical significance and prognostic value of CA72-4 compared with CEA and CA19-9 in patients with gastric cancer

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Carcinoembryonic antigen (CEA) and CA 19-9 are both widely used in the follow up of patients with gastrointestinal cancer. More recently another tumor marker, named CA 72-4 has been identified and characterized using two different monoclonal antibodies B72.3 and CC49. Several reports evaluated CA 72-4 as a serum tumor marker for gastric cancer and compared its clinical utility with that of CEA or CA 19-9; few reports concerned its prognostic value. In the present study, CA 72-4 is evaluated and compared with CEA and CA 19-9 in various populations of patients with gastric cancer and benign disease; for 52 patients with gastric adenocarcinoma and 57 patients without neoplastic disease CEA, CA 19-9 and CA 72-4 were evaluated before treatment. Sensitivity of the tumor markers CA 72-4, CA 19-9 and CEA at the recommended cut-off level in all 52 patients were 58%, 50% and 35% respectively. When all three markers were used, the sensitivity increased to 75%. Concerning the prognostic value of these markers, for non metastatic patients, multivariate analyses indicated that none of the markers were significant, when adjusted for gender and age (which were indicators of poor prognosis); patients with abnormal values of CA72-4 tended to have shorter survival than patients with normal values ($p < 0.07$). In the metastatic population, only high values of CA19-9 ($p < 0.02$) and gender (women) ($p < 0.03$) were indicators of poor prognosis in univariate analysis; multivariate analysis revealed that both CA72-4 ($p = 0.034$) and CA19-9 ($p = 0.009$), adjusted for gender were independent prognostic factors. However, CA72-4 lost significance ($p = 0.41$) when adjusted for CA19-9 and gender, indicating that CA19-9 provides more prognostic information than CA72-4.

When limited to the metastatic male population with normal values of CA 19-9 and CEA, CA 72-4 pretherapeutic positive levels were associated with a worse prognosis ($p < 0.005$).

In conclusion, this study suggests that the addition of CA 72-4 to CEA and/or CA 19-9 could improve sensitivity in gastric cancer. The prognostic role of this marker is not yet clearly demonstrated but its usefulness in the monitoring of gastric cancer should be taken into account.

Keywords: Serum marker, gastric carcinoma, prognosis

1. Introduction

Gastric cancer is the sixth most common cancer in both sexes in France [13] (the first in Japan and Portugal) [2] and the sixth most common cancer cause of death. Among the available tumor markers, carcinoembryonic antigen (CEA) and CA19-9 are both widely used in the follow-up of patients with gastrointestinal malignancies. Elevated serum levels of CEA and CA19-9 were respectively found between 15.4 and 72% [9,10,15,18] of the patients with gastric carcinomas. Some benign gastric diseases also showed positive serum levels for these tumor markers [25]. These data revealed some limitations for using those markers in monitoring gastric cancer and suggested the need to asses more-sensitive efficient markers for the improved management of this cancer.

Since 1986, a high molecular-weight, mucin-like protein, termed tumor-associated glycoprotein-72 (TAG-72), renamed CA72-4, which is the name of the RIA test used for its detection, has been identified and characterized, using two different monoclonal antibodies: B72.3 and CC49 [12,21,29]. Elevated serum CA72-4 levels are found in a large proportion of pa-

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tients with gastrointestinal malignancies [5,17,20,26], as well as ovarian, endometrium, lung and breast cancer [4,7,22,23,30]. Few reports evaluated CA72-4 as a serum tumor marker for gastric cancer, and compared its clinical utility with that of CEA or CA19-9. They indicated a very good specificity of this new marker (between 91 and 100%) but this specificity concerns benign diseases. Sensitivity varied between 18.6% [28] and 94% [1], and the presence of combined markers (CA72-4 and/or CEA and/or CA19-9) increased this sensitivity [8,14,27].

Some studies observed a good correlation between CA72-4 level and tumor stage or presence of lymph node involvement [1,6,8] in gastric carcinoma: measurement of serum level of CA72-4 therefore did not seem to be useful for assessing early staging but was predictive of the appearance of recurrence of cancer. Correlations between pre-operative CEA and CA19-9 concentration and prognosis have been studied [31,32]; however, there are few reports on the prognostic value of CA72-4 in gastric cancer [19,24,28].

The aims of this study were: (1) to evaluate and compare sensitivity of CA72-4 with that of CEA or CA19-9 in various populations of patients with gastric cancer or benign diseases.

(2) To assess the prognostic value of this marker according to the metastatic status at diagnosis.

2. Materials and methods

2.1. Patients

Serum samples for the determination of tumor marker concentration, collected at the Radioanalysis Department of Val d'Aurelle Regional Cancer Center in Montpellier, France from 1991 to 1995, were obtained for two groups of patients. The first group consisted of 57 patients (30 males, 27 females; mean age, 65.7 $\pm$ 19.7 years, ranging from 20 to 91) without neoplastic diseases, including 30 patients with cardiovascular diseases and several effusions such as: pneumonia, diabetes, brain disorders (15 patients), and traumatic and infectious diseases (13 patients). The second group consisted of 52 patients (40 males, 12 females; mean age, 62 $\pm$ 12.3 years, ranging from 29 to 87) with endoscopically and histologically diagnosed gastric adenocarcinoma.

Malignant gastric disease was pathologically staged according to TNM classification [11]. Metastatic lesions were identified by tomodensitometry. Hepatic parameters, bilirubin, SGOT, SGPT, and Alkaline Phosphatase, were also measured in all patients. Among the 52 patients with gastric cancer, we defined 2 populations according to the metastatic stage of the disease at the time of marker assessment: a first group of 15 cases without metastasis (M0) and a second group of 37 cases with metastasis (M1). Characteristics of each population are presented in Table 1.

Table 1
Baseline characteristics

		Patients without metastasis ($n = 15$)	Patients with metastasis ($n = 37$)
Gender	M	11 (73%)	29 (79%)
	F	4 (27%)	8 (21%)
Age	$\leqslant 60$	8 (53%)	15 (44%)
	> 60	7 (47%)	22 (56%)
T	T1	1 (7%)	0
	T2	2 (13%)	2 (5%)
	T3	6 (40%)	4 (11%)
	T4	3 (20%)	4 (11%)
	Tx	3 (20%)	27 (73%)
N	N0	3 (20%)	0
	N1	3 (20%)	4 (10%)
	N2	7 (47%)	11 (30%)
	N3	2 (13%)	3 (8%)
	Nx	0	19 (52%)

Serum samples were drawn prior to any treatment, as the patients entered into the study: prior to surgery (total, subtotal, or extended gastrectomy) for 13 of the 15 patients of the group M0 (two patients N3 were not operated on and underwent chemotherapy), prior to first line chemotherapy treatment including 5 Fluorouracil (5-FU) for these 2 patients and the 37 patients with metastasis (group M1), the most common regimens used being 5-FU Cisplatin followed by FAMTX (5-FU, Methotrexate, Adriamicin) and ELF (5FU Leucovorin Etoposide).

2.2. Markers

Venous blood samples for marker determination were separated by centrifugation and aliquots were stored at -20°C until assayed. Markers were measured by immunoradiometric procedures using ELSA 2-CEA kit for CEA assessment, ELSA-NSE and ELSA CA72-4 for CA19-9 and CA72-4 determination respectively (CIS bio international).

The cut-off values of 10 ng/ml, 60 U/ml and 6 U/ml were taken for CEA, CA19-9 and CA72-4 respectively.

2.3. Statistical methods

Marker sensitivities were compared using the predetermined cut-off values. The chi-squared test was

Table 2
Sensitivity of CEA, CA19-9 and CA72-4 levels in each of the two populations M0 and M1

	Patients without metastasis ($n = 15$)	Patient with metastasis ($n = 37$)	Total ($n = 52$)
CEA $\geqslant$ 10 ng/ml	3 (20%)	15 (41%)	18 (35%)
CA19-9 (60 U/ml	6 (40%)	20 (54%)	26 (50%)
CA72-4 (6 U/ml	8 (53%)	22 (60%)	30 (58%)
CA19-9+ and/or CEA+	8 (53%)	24 (65%)	32 (61%)
CA72-4+ and/or CEA+	8 (53%)	27 (73%)	35 (68%)
CA72-4+ and/or CA19-9+	10 (67%)	26 (70%)	36 (70%)
CA72-4+ and/or CA19-9 and/or CEA+	10 (60%)	29 (79%)	39 (75%)

+: $\geqslant$ Normal.

used to evaluate the positivity of CA72-4 according to normal or abnormal values of the other markers within each population.

Overall survival was calculated from the day of therapy until the day of death for patients who died or to the date last seen for patients still alive at last follow-up (all deceased patients, died of gastric cancer). Survival curves were performed according to the Kaplan-Meier method. The statistical significance of differences in survival rates were calculated using the log-rank test.

Multivariate analysis of survival was performed using the Cox proportional hazards model. The test results were regarded as significant if $p < 0.05$. Data management and statistical analysis used the EPI INFO and STATA software packages respectively.

3. Results

3.1. Marker distribution

Specificity, calculated among the 57 patients without malignancies, was estimated at 95%.

The distribution of markers levels, indicating the sensitivity of the tumor markers CA72-4, CA19-9 and CEA at the recommended cut-off levels in the two populations M0 and M1, are summarized in Table 2.

Percent positivity of CA72-4 when CA19-9 was positive (77%) was statistically significant ($p < 0.005$) when compared to patients with CA19-9 negative (38%). The same comparison between CA72-4 and CEA did not show a significant difference.

No correlation between CA72-4 and hepatic parameters (SGOT, SGPT and PAL) was found in this study. No patient had abnormal bilirubin levels.

3.2. Prognosis

The survival rates of the two populations M0 and M1 were respectively 60% and 30% at one year, with median survival of 24 months vs 8 months ($p < 0.0145$).

3.3. Univariate analyses

Median survival for potential prognostic variables are presented in Table 3.

In the M0 population, univariate analyses showed that none of these markers was a significant prognostic factor; however, gender (men) and older age were both indicators of poor prognosis.

In the M1 population, univariate analyses showed that only CA19-9 was a significant prognostic factor: patients with elevated CA19-9 marker values had a 10% one-year survival rate compared to patients with normal CA19-9 marker values who had a 51% one-year survival rate ($p = 0.022$). Moreover, gender seemed to be a poor prognostic factor but for the women this time.

3.4. Multivariate analysis (*Table 4*)

In the M0 population, multivariate analyses indicated that patients with abnormal values of CA 72-4, when adjusted for gender and age, tended to have shorter survival than patients with normal values (hazard ratio: 3.45 $p < 0.07$).

It was not possible to evaluate prognosis for CEA due to the small number of positive cases.

In the M1 population, both CA72-4 ($p = 0.034$) and CA19-9 ($p = 0.009$), adjusted for gender, were statistically significant. However, CA72-4 lost significance ($p = 0.41$) when adjusted for CA19-9 and gender, indicating that CA19-9 provides more prognostic information than CA72-4.

For the 9 male patients with both CA19-9 and CEA normal in the M1 population, elevated values of CA72-4 (5 patients) were significantly associated with lower survival rates (median 4 months versus 13 months, $p = 0.005$) (Fig. 1). In this group, all 5 patients died within the first year. Three of the 4 male patients who had all three markers normal, died between 12 and 24 months, while there was one long term survivor at 52 months.

Table 3
Univariate analysis: Potential prognostic variables for survival

Variables		Patients without metastasis ($n = 15$)			Patient with metastasis ($n = 37$)		
		No. of deaths/ patients	Median survival (months)	p^*	No. of deaths/ patients	Median survival (months)	p^*
Gender	M	10/11	17		26/29	10	
	F	2/4	38	0.038	8/8	5	0.028
Age	$\leqslant 60$	5/8	34		15/15	8	
	> 60	7/7	10	0.038	19/22	10	ns
CEA	< 10	10/12	24		21/22	8	
	$\geqslant 10$	2/3	10	ns	13/15	10	ns
CA19-9	< 60	6/9	26	ns	15/17	12	
	$\geqslant 60$	6/6	8	(0.07)	19/20	8	0.022
CA72-4	< 6	6/7	26		13/15	12	ns
	$\geqslant 6$	6/8	10	ns	21/22	7	(0.11)
SGOT (U/l)	< 40	8/10	17	ns	12/13	9	
	$\geqslant 40$	1/1	–	(0.051)	5/5	4	ns
SGPT (U/l)	< 35	9/11	17		13/14	9	
	$\geqslant 35$	0	–	n/a	4/4	4	ns
PAL (U/l)	< 258	9/11	17		14/15	9	
	$\geqslant 258$	0	–	n/a	3/3	9	ns

*Log-rank test; n/a, not applicable.

In our population, the five M1 female patients with both CA19-9 and CEA normal, also had normal values of CA72-4.

4. Discussion

The results of our study indicated that the measurement of serum CA72-4 may be useful in the monitoring of gastric carcinoma and confirmed its superiority to CEA in this role. At the cut-off of 6 UI/ml, the sensitivity of CA72-4 was 58% $\pm$ 13 when elevated values of CA72-4 have been reported in around 40% of patients with gastric carcinoma in most studies [5, 8,14,15,27]. However, sensitivity calculated only in the group of patients without metastasis, whose pretreatment population was similar to those of the studies quoted, was 53% i.e. not very different to the rates reported by OHUCHI [22] (48%) and KONISHI [16] (53%). Marker data on matched series confirmed the superiority of CA72-4 over CEA but showed a large enough concordance between the two markers to establish that they are not complementary. Nevertheless the presence of combined markers CA72-4, CEA and CA19-9, increasing by 14% the percentage of all the patients with gastric carcinoma (and among them, those with metastasis) identified by CA19-9 and/or CEA alone, seems useful for assessing the extent or the recurrence of the disease This improvement in sensitivity is similar to that reported by GUADAGNI [5] and TOCCHI [28]. The combination of CA72-4 with CEA in the group without metastasis did not change sensitivity, which is in agreement with HEPTNER [10] and SPILA [27] who did not consider CEA as a good marker particularly for identifying patients with gastric cancer.

Table 4
Multivariate analysis using cox proportional hazards model in each of the two populations M0 and M1

	Hazard ratio	95%IC	p
Population M0 ($n = 15$)			
CA72-4[a]	3.45	0.87–13.6	0.07
CEA[b]	1.62	0.33–8.03	ns
CA19-9[a]	2.77	0.62–12.39	ns
Population M1 ($n = 37$)			
CA72-4[c]	2.25	1.06–4.79	0.034
CEA[c]	0.85	0.41–1.77	ns
CA19-9[c]	2.73	1.28–5.86	0.009
CA72-4[d]	1.46	0.59–3.60	ns
CA19-9[e]	2.18	0.87–5.47	0.097

[a]Adjusted for gender and age; [b]Adjusted for age; [c]Adjusted for gender; [d]Adjusted for gender and CA19-9; [e]Adjusted for gender and CA72-4.

A high specificity of 95%, calculated in the control population, containing various medical pathologies except malignant diseases, was found in this study. This rate is in agreement with those reported by various authors [1,3,5,8,26].

Considering the prognostic data in this report, as expected, better survival was found in the group without metastasis compared with that of the metastatic

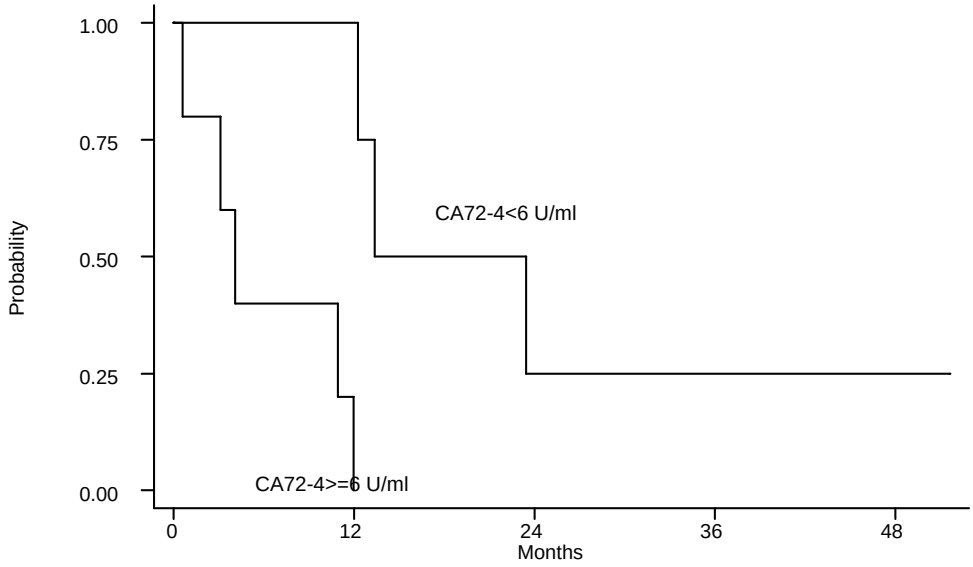

Fig. 1. Overall survival according to CA72-4 for metastatic male patients with normal Ca19-9 and CEA.

group [24].

The prognostic role of the three markers seems to be related to the metastatic status: in the population without metastasis, CA72-4 showed a tendency for a worsened survival in patients with elevated values (adjusted for gender and age) whereas CA19-9 and CEA were not significant. When metastasis were present, prognosis seemed independent of CEA serum level but related to CA19-9 level; CA72-4, in this case, did not have prognostic value independent of CA19-9 value, but it could be, alone, a predictive marker when both CEA and CA19-9 levels are low. The independent prognostic value of these last two markers has been reported already by several authors [19,24,28,31]. Additional prognostic information provided by CA72-4 in our study might be of some interest in the medical management of this disease.

Finally, these results suggest that the addition of CA72-4 to CEA and CA19-9, improving sensitivity, compared to one of these markers alone, could be useful in the monitoring of gastric cancer, either to detect recurrence after surgery, or to assess the efficacy of chemotherapy given for an advanced disease. Its prognostic value is not yet clearly demonstrated. Prospective studies are still needed to confirm this predictive role.

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