Prognostic Value of CEA and CA 19.9 in Gastric Cancer

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Abstract: *Introduction:* Gastric cancer (GC) is still a major health problem due to the majority of patients present with advanced disease. This considerably reduces the possibility of curative treatment. A critical decision in the treatment of GC is related to staging, which is mainly assessed by the use of the TNM classification. There are other factors that can influence in the prognosis during the preoperative period: pathological type, degree of differentiation or tumor markers level. The most commonly used tumor markers (TM) in GC are CEA and CA 19.9. The aim of the present study is to analyze the relationship between CEA and CA 19.9 markers with certain characteristics of the patients and tumors and to evaluate the utility of these TM determined at the time of diagnosis as prognostic factors.

Material and methods: A prospective collection of the data of all pacients operated by GC at our centre. A total of 501 cases were diagnosed. Mean age was 68.2 years. We analyzed age, sex, tumor location, clinical stage, tumor markers determined in the preoperative period, the use of perioperative chemotherapy and response to chemotherapy, the pathological characteristics and disease follow-up.

Results: At the time of diagnosis 23,3 % of the patients presented high values of CEA, 32,6 % presented high values of CA 19.9 and 14,1% presented with both elevated markers. Patients who were diagnosed at an advanced stage and presented high levels of CEA or CA 19.9 or both TM had worse survival compared to those with normal values.

Conclusion: the presence of an elevated serum level of tumor markers is related to advanced tumor stage and worse prognosis in terms of overall survival.

Keywords: Gastric cancer, CA 19.9, CEA, Tumor markers, Prognosis.

INTRODUCTION

Gastric cancer (GC) continues to be a serious health problem despite a decrease in its incidence in recent years. In the West, most cases occur in advanced stages, which reduces the possibility of curative treatment. This becomes the main reason for its poor prognosis.

Surgery remains the only curative treatment in early stages. In advanced stages, the treatment requires the use of perioperative chemotherapy. There are different chemotherapy regimens that have been proven to be effective and are being used in Japan, Europe and the United States [1-3]. The first requirement to plan an appropriate treatment of gastric cancer is to perform a correct staging [4]. For this it is essential to establish a stage according to the TNM classification basically by using imaging techniques (CT scan, ultrasound scan, endoscopic ultrasonography, MRI and/or PET). Each of these techniques has a different sensitivity for each of the factors of the TNM classification (T factor, N factor or M factor). There are characteristics, either the tumor or the patient, that could influence as prognostic factors according to some authors, and therefore could also influence in the choice of preoperative treatment [5, 6], such as age, sex, tumor location and size, tumor differentiation grade, Lauren classification type, vascular, neural or lymphatic invasion.

Liquid biopsy is a technique that has been recently introduced into the clinical practice. This analyzes a blood sample to determine the presence of tumor cells detached from the primary tumor and performs a genetic analysis of the same. It allows us to analyze the DNA of the tumor cells and to determine the presence of mutations in genes involved in the tumor growth such as k-RAS, PIK3CA and BRAF. This new technology can become an important tool at the time of diagnosis and can be decisive for deciding the treatment using effective agents against the cells that present the mutation [7, 8].

Tumor markers (TM) are circulating substances that are present in the blood or in other bodily fluids. They are usually produced by the cancer cells or by other tissues that are induced by the tumor. They can be used for screening purpose, for early diagnosis or for establishing a prognosis. Also variations in blood levels during follow-up may indicate a relapse. In addition variations after neoadjuvant chemotherapy allow us to

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evaluate the tumor response. In this way the persistence of elevated values after surgery may indicate the presence of residual tumor cells [9-12].

There is no specific TM for GC. The most commonly used are CEA and CA 19-9. It has been reported in the literature that elevated levels of CEA are correlated with depth of tumor invasion and the presence of distant metastases, whereas elevated levels of CA 19.9 are related to nodal involvement [13-15].

The objective of this study is to analyze the relationship between CEA and CA 19.9 levels with certain characteristics of the patient and the tumor, and to evaluate the usefulness of these determinations at the time of diagnosis as prognostic factors.

MATERIAL AND METHODS

Since 1994, the data of all patients operated by GC at the Hospital Clínico Universitario of Valencia have been collected prospectively. 501 cases were included (311 men and 190 women) with a mean age of 68.2 years. The diagnosis of gastric cancer was carried out by means of an endoscopic biopsy. Staging was performed using the CT scan. MRI or PET scan were only used in those cases where the CT did not provide enough information. Since 2007 an endoscopic ultrasonography was also performed for a better evaluation of the T and N factor. Levels of CEA and CA 19-9 were determined preoperatively. Patients were classified into two groups for each of the markers according to the value obtained (higher or not for the limit established by the manufacturer). Also patients who presented both markers elevated were divided into two groups according to the same criteria described above.

TNM classification (6^{th} ed.) was used to determine the clinical stage [16]. Those cases with T ≥ 3 and / or N+ stage were treated by the administration of chemotherapy (ChT) according to the Cunningham scheme/model (2). Patients received three preoperative chemotherapy cycles. A re-assessment of the stage was performed two weeks after the last preoperative chemotherapy cycle was administered by means of CT scan, and classified as follow: (1) complete regression; (2) partial regression; (3) stable disease/no response; and (4) progressive disease. Four to six weeks after the end of preoperative ChT the patients were operated. Depending on the patient's condition, three additional cycles of chemotherapy were administered postoperatively.

The follow-up was carried out by means of clinical evaluation, laboratory tests and CT scan every six months during the first two years, and every 12 months from the third year. In case of partial gastrectomy an annual endoscopy was performed for the first two years or if symptoms were present. Tumor growth in the anastomosis, or in locoregional lymph nodes or the appearance of carcinomatosis were defined as local recurrence, while distant relapse was defined as tumor growth in the liver or any other extraperitoneal organ.

Collected data were: age, sex, tumor location, clinical stage, tumor markers determined in the preoperative period, perioperative ChT, response to ChT treatment, pathological characteristics (vascular, neural or lymphatic invasion, presence of signet ring cells, differentiation grade, Lauren type classification, pathological stage) and disease follow-up (development of recurrence and overall survival). Statistical analysis was performed using the chi-square test for the qualitative variables and the Mann-Whitney U test for the quantitative ones. Survival analysis was performed using the Kaplan-Meier and the log-rank tests. The Cox regression test was performed for the identification of the variables that could influence on relapse and survival. A p-value of less than 0.05 was established as significant.

RESULTS

501 cases were finally included (311 men and 190 women) with a mean age of 68 years. Table **1** shows the characteristics of the patients, tumor location, clinical stage, administration of ChT, response to ChT and preoperative values of the tumor markers. There were 104 cases with elevated CEA (23.3%), 105 cases with elevated CA 19.9 (32.6%) and 45 cases with both markers elevated (14.1%).

Table **2** shows the pathological characteristics and the evolution of the patients (relapse and overall survival).

The presence of elevated levels of CEA was related to the male sex and tumor stage (higher CEA levels were found in both clinical and pathological advanced stages) (Table **3**).

The presence of elevated CA 19.9 was related to the presence of neural infiltration and clinical / pathological stage (Table **3**).

When the relapse analysis was performed, no differences were found between those cases with

elevated CEA and those with elevated CA 19.9. There were also no differences in the presence of relapses in the patients with both elevated TM.

Table 1: Patient's Age, Gender, Tumor Location, Clinical Stage and Tumor Markers

AGE	68.25 ±12 (22-95)
GENDER	
MALE	311 (62.1%)
FEMALE	190 (37.9%)
TUMOR LOCATION	
UPPER STOMACH	78 (15.6%)
MIDDLE STOMACH	148 (29.5%)
LOWER STOMACH	231 (46.1%)
WHOLE (stump, linitis)	44 (8.8%)
CLINICAL STAGE	
Ia	20 (4.8%)
Ib	55 (12.9%)
II	141 (33.2%)
IIIa	123 (28.9%)
IIIb	28 (6.6%)
IV	58 (13.6)
CEA ELEVATED	
YES	104 (23.3%)
NO	342 (76.7%)
Ca 19.9 ELEVATED	
YES	105 (32.6%)
NO	217 (67.4%)
CEA & CA 19.9 ELEVATED	
YES	45 (14.1%)
NO	274 (85.9%)
DIFFERENTIATION	
WELL	36 (11.9%)
MODERATE	150 (49.5%)
POOR	117 (38.6%)
LAUREN	
INTESTINAL TYPE	203 (50%)
DIFUSSE TYPE	164 (40.4%)
MIXED TYPE	39 (9.6%)
SIGNET RING CELLS	
POSITIVE	172 (40.7%)
NEGATIVE	251 (59.3%)
VASCULAR INVASION	
POSITIVE	133 (53.8%)
NEGATIVE	114 (46.2%)
LYMPHATIC INVASION	
POSITIVE	170 (63.9%)
NEGATIVE	96 (36.1%)
NEURAL INVASION	
POSITIVE	136 (53.8%)
NEGATIVE	117 (46.2%)
PATHOLOGICAL STAGE	
COMPLETE RESPONSE	*10 (2%)*
Ia	72 (14.2%)
Ib	46 (9.2%)
II	68 (13.6%)
IIIa	91 (18.2%)
IIIb	90 (18%)
IV	124 (24.8%)
RELAPSE	
YES	135 (26.9%)
NO	366 (73.1%)
SITE OF RELAPSE	
LOCAL OR LOCOREGIONAL	89 (65.9%)
DISTANT	37 (27.4%)
BOTH	9 (6.7%)
DEATH BY DISEASE	
YES	215 (42.9%)
NO	286 (57.1%)

However patients with elevation of CEA, CA 19.9 (Figure **1** and **2**) or both (Figure **3**) presented worse overall survival.

The multivariate analysis showed that among all factors that could influence on the overall survival, only the presence of both elevated TM (p = 0.012, HR 2.518 CI 95% 1.225-5.174) and the pathological stage (P = 0.004, HR 0.149, 95% CI 0.041-0.548) were significant.

DISCUSSION

Tumor markers have little value for the diagnosis of tumors because of their low sensitivity and the existence of non-tumoral diseases that can increase their value. Thus CEA level can be found increased in cases of inflammatory bowel disease, pancreatitis, cirrhosis, COPD or smoker patients; CA 19.9 level can be found elevated in pancreatitis or cholestasis syndrome [17]. Both markers have a lack of specificity for the diagnosis of gastric cancer. In this way, CEA can be found elevated in a wide range of tumors such as colorectal, gastric, pancreas, breast, lung or medullary thyroid cancer. Likewise, CA 19.9 may be elevated in pancreatic, colorectal, gastric and hepatic tumors [18]. TM may be useful to establish a prognosis at the time of diagnosis [17], to evaluate the outcome of preoperative chemotherapy and surgical treatment [19-21], and to suspect the occurrence of relapses during follow-up.

In our study, we found an elevation of CEA in 23% of cases and CA 19.9 in 32.6% which are quite similar to those described in the literature [9, 22, 23]. Both

Table 2: Pathological Characteristics and Disease Evolution

	CEA Elevated (p value)	CA 19-9 Elevated (p value)	Both Elevated (p value)
Gender (male)	0.001		
Clinical stage	0.004		
Clinical M stage	0.002		
Pathological M+ stage	0.000		
Pathological stage	0.002		
Clinical N stage		0.04	
Pathological T stage		0.004	
Pathological N stage		0.002	
Pathological M stage		0.027	
Pathological stage		0.004	
Clinical N stage			0.007
Pathological T stage			0.04
Pathological N stage			0.03
Pathological M stage			0.01

were found jointly elevated in the 14.1% of cases in our series. A relationship has been described between TM elevation and certain patient and tumor characteristics, although not all authors agree on which features are related. In our series CEA elevation is associated with males and with advanced tumor stages, especially in those cases with metastasis. This agrees with the found described by Zhang *et al.* [13] and Gaspar *et al.* [24]. Likewise we found that the increase of CA 19.9 is related to a more advanced stage and the presence of positive lymph nodes in the pathological study [14]. The presence of both elevated TMs is related to more advanced clinical and pathological stages as has also been described by Li *et al*. [25]. Perhaps this could be the reason why the presence of elevated TM is related to worse survival.

Table 3: Factors Related to Elevation of Tumor Markers

Global comparisons			
	Chi-cuadrado	gl	Sig.
Log Rank (Mantel-Cox)	7,337	1	0,007
Evidence of equality of survival distributions for different levels of CEA.			

The presence of elevated TM in the preoperative period may be important for the diagnosis of advanced stages that may be difficult to evaluate by imaging tests such as peritoneal dissemination. These findings may lead to the use of more aggressive diagnostic methods such as laparoscopy, suggest changes in the initial therapeutic approach, or even indicate preoperative treatment with chemotherapy [13, 15]. Although there are no prospective studies that determine the clinical utility of TM, there are authors who suggest that the joint elevation of both TM may be helpful in GC staging before surgery or chemotherapy [9, 25, 26].

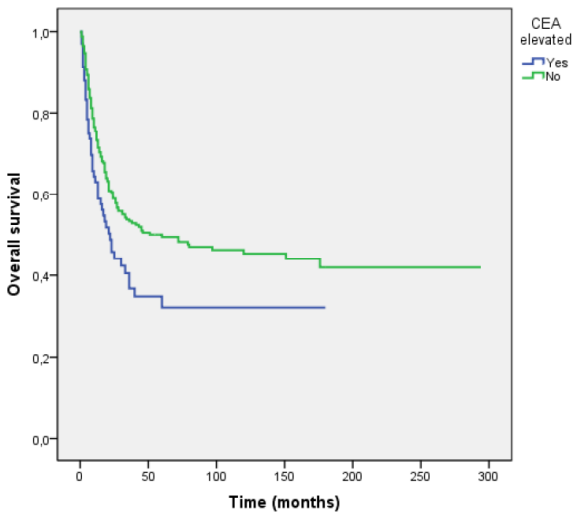

Figure 1:Comparison of overall survival between groups according to high CEA. Log-rank test 0.007.

It has been related the presence of elevated tumoral markers to a worse prognosis in different types of cancer [18, 27-30]. This has been widely studied in cases of patients with colon cancer. In our series, the presence of elevated CEA is associated with worse overall survival which has also been reported by several authors [31, 32], although it is not associated with worse disease-free interval as Marrelli *et al.* have reported [33]. The increase in CA 19.9 is also an

unfavorable prognostic factor in our series with worse overall survival. On the multivariate analysis, the jointly increase of both markers and the pathological stage are independent factors of poor prognosis.

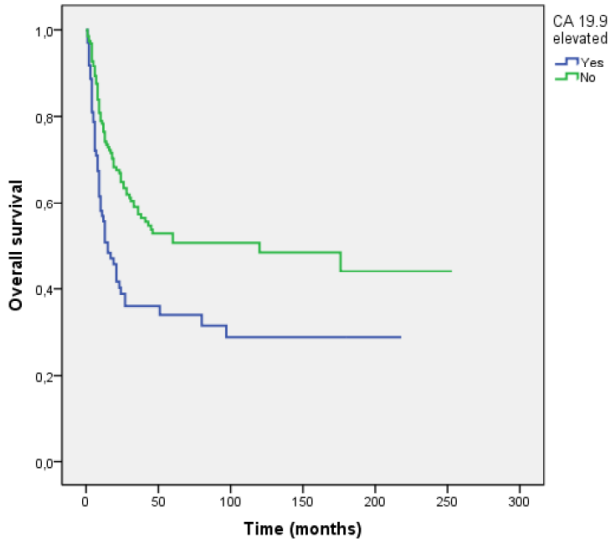

Figure 2: Comparison of overall survival in elevated CA 19.9 cases. Log rank: 0.001.

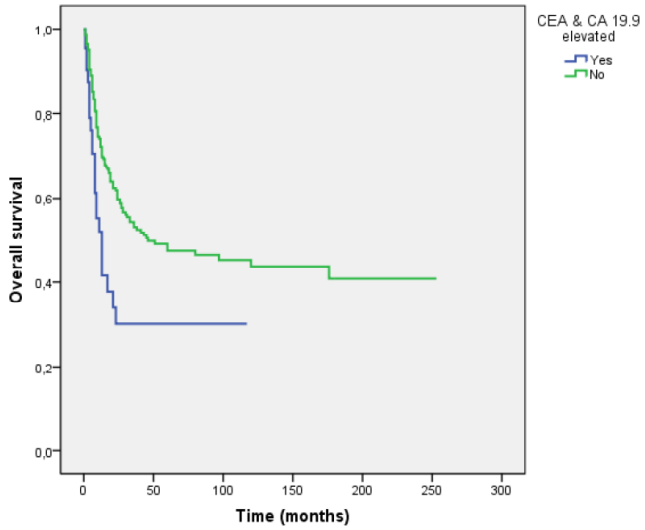

Figure 3: Comparison of overall survival in patients with both elevated and non-elevated TM markers. Log Rank, p = 0.004.

These data confirm those published by Wang *et al* that demonstrate that determination of CEA, CA 19.9 and CA 125 provides more information than the separate determination of each of them [34]. In our study, we found no differences in the analysis of the relapse-free interval and the presence of elevated TM, a fact that is consistent with the work of Huang and coworkers [29]. However, other authors find a relationship between elevated TM levels in the preoperative period and the relapse-free interval [35].

CONCLUSION

Therefore, we can conclude that the presence of elevation of CEA and CA 19.9 is related to the existence of advanced stages and with a worse prognosis in terms of overall survival. The determination of both elevated TM is an independent prognostic factor for overall survival and may provide important prognostic information in the preoperative period.

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