Pre-operative Serum CEA and CA19-9 Levels in Patients with Gastric Cancer: A Single-Center Experience

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ABSTRACT

Introduction: To evaluate the preoperative CEA and CA19-9 levels and their association with clinicopathologic features and mortality. **Methods:** This retrospective study was conducted on patients who underwent gastric surgery due to gastric adenocarcinoma from 2008 to 2015. Preoperative serum CEA and CA19-9 levels were compared according to the TNM classification and survival data were compared. **Results:** A total of 335 patients were included in the study with the mean age of 66.1±11.0 years. CEA and CA19-0 positivity were 29.1% and 28.1%, respectively. According to the CEA groups, T stages of the cases were statistically significant (p = 0.013). The rates of T stage 1 in group 1 (CEA positive) were significantly higher than the group 2 (CEA negative) (p=0.007). According to the CA19-9 positivity; rate of stage 2 was significantly higher in the group 1 (CA19-9 positive) (p=0.001); however, rates of stage 2 and 3 were significantly higher in the group 2 (CA19-9 negative) (p=0.004 and p=0.007, respectively). Mortality information could be accessed for 309 cases and 108 deaths (36%) were observed. The mean survival time was 45.21±2.42 months. No significant difference was observed between the groups (p>0.05). **Conclusion:** Patients with higher levels of CEA and CA19-9 seem to have higher grades of gastric cancer. However, CEA and CA19-9 level does not seem to be in association in our study population.

Key words: Gastric adenocarcinoma, tumor marker, carcinoembryonic antigen, carbohydrate antigen 19-9.

Tumor markers (TMs) are the substances that are produced in response to the cancer and they are found in blood, urine or body tissues. Since the TMs may be measured quantitatively and have a causative association with the malignancies, they are usually used for the early detection or follow-up for various malignancies [1,2]. Although there is no precise TM for the gastric cancer, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) are widely used in the clinical practice. Until now, there are several studies considering the CEA and CA19-9 measurements in gastric cancer have been conducted in the literature [1-11]. However, sensitivity and specificity of these two TMs and their correlations with clinic or pathological features yielded conflicting results. Therefore, the objective of this study was to evaluate the preoperative CEA and CA19-9 levels and their association with clinicopathologic features.

MATERIALS & METHODS

This study was conducted retrospectively and patients who underwent gastric surgery, in the general surgery department of our hospital with the pathologic diagnosis of gastric adenocarcinoma between the years 2008 and 2015, were included. Patients, who underwent surgery for the tumor recurrence, had an unresectable tumor, and were diagnosed with other pathologic diagnosis, were excluded from the study. Demographical features such as age and gender, laboratory parameters, pathologic reports were collected from the hospital records retrospectively. Correlation between the preoperative CA19-9 and CEA

levels and clinicopathologic factors (age, gender, tumor level, lymph node metastasis occurrence, serousal invasion) were explored. Since the study was retrospective, ethics committee approval was not received.

Preoperative serum CEA and CA19-9 levels were measured with the electrochemiluminescence immunoanalyzer technique, as suggested in the literature (1). Blood specimens were obtained pre-operatively within the one-week. According to the instructions of the manufacturer, the cut-off levels of CEA and CA19-9 were accepted as 5 ng/mL and 37 U/mL, respectively. The patients were classified and graded according to the 7th edition of American Joint Committee on Cancer tumor, node, and metastasis (TNM) classification and staging system for gastric cancer.

Number Cruncher Statistical System (NCSS) program version 2007 (Kaysville, Utah, USA) was used for statistical analysis. The Pearson Chi-Square test and the Yates 'Continuity Correction test (Chi-square test with Yates' correction) were used to compare qualitative data as well as descriptive statistical methods (mean, standard deviation, median, minimum, maximum). Kaplan Meier Survival analysis and Log Rank test were used to assess survival. Significance was assessed at p <0.01 and p <0.05 levels.

RESULTS

A total of 335 patients were included in the study; out of them, 226 were male and 109 were female and their mean age was 66.1±11.0 years. Clinical features and laboratory parameters of the patients are summarized in table 1. The patients were allocated into two groups according to the CEA positivity. Comparison of the patients according to the CEA positivity is summarized in table 2.

According to the CEA groups, T stages of the cases were statistically significant (p = 0.013). According to binary comparisons; the rates of T stage 1 in group 1 were significantly higher than the group 2 (p=0.007) whereas rates of T stage 4 were significantly higher in the group 2 (p=0.029). While rate of stage 2 was significantly higher in the group 1 (p=0.006), rate of stage 3 was significantly higher in the group 2 (p=0.001). CEA and CA19-0 positivity were 29.1% and 28.1%, respectively.

Table-1: Clinical features and laboratory parameters of patients

Parameters		Min – Max	Mean ± SD
Follow-up Period (M)		1 – 96	20.24±20.33
Positive Lymph Node		1 – 52	8.72±8.12
		n	**%**
CEA	Negative	238	71.0
	Positive	97	29.0
CA19-9	Negative	239	71.3
	Positive	96	28.6
T Stage	Stage 1	20	6.0
	Stage 2	21	6.3
	Stage 3	111	33.1
	Stage4	183	54.6
TNM Stage	Stage1	25	7.5
	Stage2	68	20.3
	Stage 3	232	69.3
	Stage4	10	3.0
Histologic Grade	Grade 1	20	6.0
	Grade 2	126	37.6
	Grade 3	189	56.4
Mortality	No	201	65.0
	Yes	108	35.0
Surgery	Gastrectomy, Total	203	60.6
	Gastrectomy, Subtotal	132	39.4
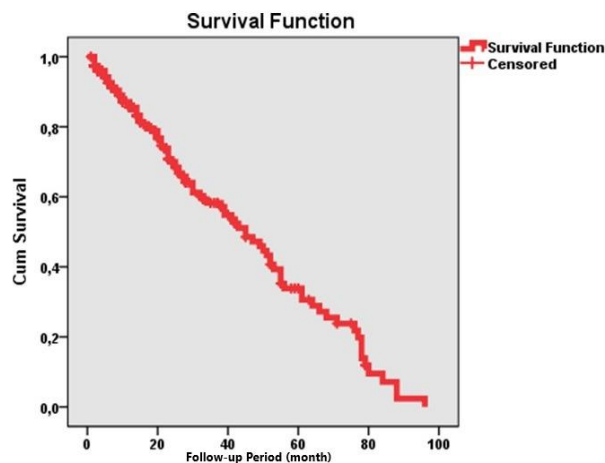
Figure 1: Survival of the gastric cancer patients

The patients were allocated into two groups according to the CA19-9 positivity. Comparison of the patients according to the CA19-9 positivity is summarized in table 3. Rate of stage 2 was significantly higher in the group 1 (p=0.001); however, rates of stage 2 and 3 were

significantly higher in the group 2 (p=0.004 and p=0.007, respectively).

Table-2: Comparison of the patients according to the CEA levels

		CEA		P value
		Group 1, <5 (n=238)	Group 2, ≥5 (n=97)	
T Stage	Stage 1	**20 (8.4)**	0 (0)	[a]0.013
	Stage 2	15 (6.3)	6 (6.2)	
	Stage 3	82 (34.5)	29 (29.9)	
	Stage 4	121 (50.8)	**62 (63.9)**	
Stage	Stage 1	22 (9.2)	3 (3.1)	[a]0.003
	Stage 2	**58 (24.4)**	10 (10.3)	
	Stage 3	151 (63.4)	**81 (83.5)**	
	Stage 4	7 (2.9)	3 (3.1)	
Grade	Grade1	16 (6.7)	4 (4.1)	[a]0.565
	Grade2	91 (38.2)	35 (36.1)	
	Grade3	131 (55)	58 (59.8)	
Positive Lymph Node	No	**56 (23.5)**	6 (6.2)	[b]0.001
	Yes	182 (76.5)	**91 (93.8)**	

[a]Pearson Chi-Square Test [b]Yates' Continuity Correction Test. P value <0.05 was considered as significant.

The mortality information could be accessed for 309 cases and 108 deaths (36%) were observed with the mean survival time of 45.21±2.42 months. The latest death was seen at the 96th month. Survival analyses according to CEA and CA19-9 measurements are shown in table 4 and 5. No significant difference was observed between the groups (all p>0.05). The survival rates, according to the groups, were evaluated by Log Rank test and there was no statistically significant difference between 8-year survival rates (p: 0.649) (Figure 2 and 3).
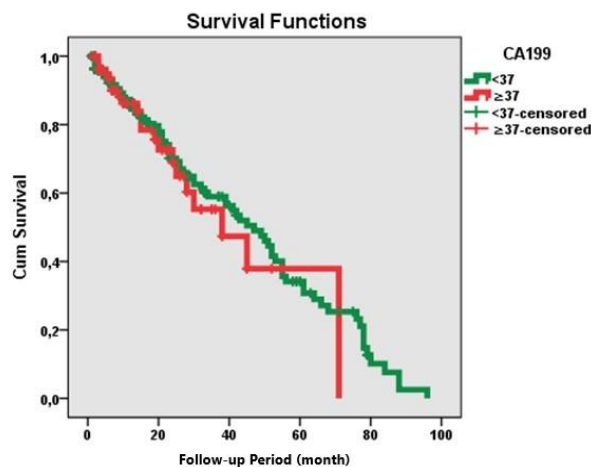
Table-3: Comparison of the patients according to the CA19-9 levels

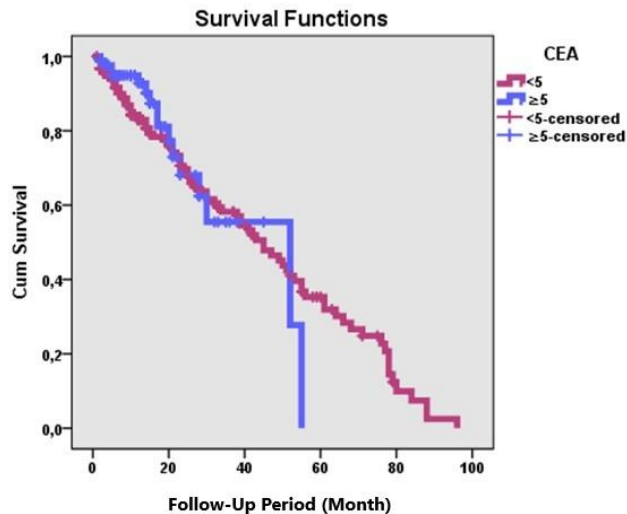**Table 4: Survey Analysis According to the CEA and CA19-9 Levels**

		CA19-9		P value
		Group 1 <37 (n=239)	Group 2 ≥37 (n=96)	
T Stage	Stage 1	18 (7.5)	2 (2.1)	[a]0.093
	Stage 2	18 (7.5)	3 (3.1)	
	Stage 3	78 (32.6)	33 (34.4)	
	Stage 4	125 (52.3)	58 (60.4)	
Stage	Stage 1	22 (9.2)	3 (3.1)	[a]0.001
	Stage 2	**60 (25.1)**	8 (8.3)	
	Stage 3	154 (64.4)	**78 (81.3)**	
	Stage 4	3 (1.3)	**7 (7.3)**	
Grade	Grade1	17 (7.1)	3 (3.1)	[a]0.324
	Grade2	91 (38.1)	35 (36.5)	
	Grade3	131 (54.8)	58 (60.4)	
Positive Lymph Node	No	56 (23.4)	6 (6.3)	[b]0.001
	Yes	183 (76.6)	90 (93.8)	

[a]Pearson Chi-Square Test [b]Yates' Continuity Correction Test. P value <0.05 was considered as significant.

Figure 2: Survival of the gastric cancer patients according to the CEA levels

	N	Expired	Living	Survival Rate	Mean Survival Time	95% CI
CEA<5	219	92	127	58.0	45.13±2.65	39.93-50.33
CEA≥5	90	16	74	82.2	38.44±3.51	31.57-4532
CA199<37	222	87	135	60.8	45.76±2.69	40.49-51.04
CA199≥37	87	21	66	75.9	42.00±4.97	32.26-51.73

Figure 3: Survival of the gastric cancer patients according to the CA19-9 levels

DISCUSSION

In this retrospective study, we intended to explore the role of preoperative CEA and CA19-9 levels and their association with clinicopathologic features. According to our results, we have two main findings. First, the patients with higher levels of CEA and CA19-9 levels had higher grades of gastric cancer. Second, CEA and CA19-9 level were not associated with the mean survival. The clinical significance of CEA and CA19-9 in gastric cancer has been studied previously also.

Shimada et al [12] evaluated the clinical significance of serum tumor markers (CEA, CA19-9, and CA72-4) in gastric cancer patients in their review. They have conducted a systematic literature search and included a total of 187 publications. According to their results, positivity rates of the CEA and CA19-9 were 21.1% and 27.8%, respectively. On the contrary to this study, some studies have also reported different rates of positivity of CEA and CA19-9 [1,8]. Moreover, they highlighted that TMs were associated with the stage of the tumor and survival. Since the positivity rates were small, the use of these TMs for the screening tool was not suggested. By contrast, monitoring of the TMs is convenient –the TMs become positive approximately two months before the radiologic occurrence and for the post-operative follow-up.

According to our results, the positivity rates of CEA and CA19-9 were 29.1% and 28.1%, respectively. While we found a significant relation with the stages and level of the TMs, we did not find a relation with the survival and level of TMs. This fact could be related to the sample size, study populations, and particularly the normal distribution of the cases included in the study. For instance, the incidence of the gastric cancer in Japan is significantly higher than that of United States and western countries. Differences in Helicobacter pylori infection, food storage, dietary habits, environmental factors, genetic predisposition, lifestyles, and smoking may be the underlying factors. By the way, detection of the tumor in an early stage might affect the survival [13]. Yu et al. [8] suggested that the combination of the TMs would be more sensitive. In our study, we did not study relation of the combination of the CEA and CA19-9, which is a limitation of this study.

As for the association with the stages of gastric cancer and CEA or CA19-9 in the literature, Sisik et al. [14] included 49 patients with gastric cancer in their study and concluded that CEA and CA19-9 positivity could be indicative for an advanced stage. Komada et al. [15] compared the CA72-4 levels with CA19-9 and CEA in 100 patients whereby, CA 72-4 gave the highest positivity rate for the advanced cancers. Additionally, CEA and CA19-9 levels were higher in the advanced stages of cancer. Similarly, in our study CEA and CA19-9 levels were significantly higher in the higher stages of the cancer. However, differently from the previous studies, we have included only the patients with resectable tumor. Patients with distant organ metastasis and unresectable tumor were excluded. This condition might have affected our results. In addition, lack of CA72-4 evaluation is a limitation of our study. Since we did not measure the levels of CA72-4, we could not compare the data with respect to the CA72-4 levels. Lymph node positivity and levels of CEA and CA19-9 were found to be associated in the previous studies [8]. Similarly, we found higher levels of TMs in patients with positive lymph nodes.

CONCLUSION

Our results showed that patients with higher levels of CEA and CA19-9 had higher grades of gastric cancer. However, CEA and CA19-9 levels were not associated with the survival in our study population. Further studies considering association of the TMs, maybe the

combination of the TMs, with the survey analysis in cohort designs are awaited.

REFERENCES

1. Zhou YC, Zhao HJ, Shen LZ. Preoperative serum CEA and CA19-9 in gastric cancer--a single tertiary hospital study of 1,075 cases. Asian Pac J Cancer Prev. 2015; 16(7):2685-91.

2. Choi SR, Jang JS, Lee JH, Roh MH, Kim MC, Lee WS et al. Role of serum tumor markers in monitoring for recurrence of gastric cancer following radical gastrectomy. Dig Dis Sci. 2006; 51(11):2081-6.

3. Chen C, Chen Q, Zhao Q, Liu M, Guo J. Value of Combined Detection of Serum CEA, CA72-4, CA19-9, CA15-3 and CA12-5 in the Diagnosis of Gastric Cancer. Ann Clin Lab Sci. 2017; 47(3):260-3.

4. Yu J, Zheng W. An Alternative Method for Screening Gastric Cancer Based on Serum Levels of CEA, CA19-9, and CA72-4. J Gastrointest Cancer. 2018; 49(1):57-62

5. Feng F, Sun L, Liu Z, Liu S, Zheng G, Xu G, et al. Prognostic values of normal preoperative serum cancer markers for gastric cancer. Oncotarget. 2016; 7(36):58459-69.

6. Liang Y, Wang W, Fang C, Raj SS, Hu WM, Li QW, et al. Clinical significance and diagnostic value of serum CEA, CA19-9 and CA72-4 in patients with gastric cancer. Oncotarget. 2016; 7(31):49565-73.

7. Liu X, Qiu H, Liu J, Chen S, Xu D, Li W et al. Combined preoperative concentrations of CEA, CA 19-9, and 72-4 for predicting outcomes in patients with gastric cancer after curative resection. Oncotarget. 2016; 7(23):35446-53.

8. Yu J, Zhang S, Zhao B. Differences and correlation of serum CEA, CA19-9 and CA72-4 in gastric cancer. Mol Clin Oncol. 2016; 4(3):441-9.

9. Cǎinap C, Nagy V, Gherman A, Cetean S, Laszlo I, Constantin AM et al. Classic tumor markers in gastric cancer. Current standards and limitations. Clujul Med. 2015; 88(2):111-5.

10. Yin LK, Sun XQ, Mou DZ. Value of Combined Detection of Serum CEA, CA72-4, CA19-9 and TSGF in the Diagnosis of Gastric Cancer. Asian Pac J Cancer Prev. 2015; 16(9):3867-70.

11. Sun Z, Zhang N. Clinical evaluation of CEA, CA19-9, CA72-4 and CA125 in gastric cancer patients with neoadjuvant chemotherapy. World J Surg Oncol. 2014; 29(12):397.

12. Shimada H, Noie T, Ohashi M, Oba K, Takahashi Y. Clinical significance of serum tumor markers for gastric cancer: a systematic review of literature by the Task Force of the Japanese Gastric Cancer Association. Gastric Cancer. 2014; 17(1):26-33.

13. Inoue M, Tsugane S. Epidemiology of gastric cancer in Japan. Postgrad Med J. 2005; 81(957):419-24.

14. Sisik A, Kaya M, Bas G, Basak F, Alimoglu O. CEA and CA 19-9 are still valuable markers for the prognosis of colorectal and gastric cancer patients. Asian Pac J Cancer Prev. 2013; 14(7):4289-94.

15. Kodama I, Koufuji K, Kawabata S, Tetsu S, Tsuji Y, Takeda J, et al. The clinical efficacy of CA 72-4 as serum marker for gastric cancer in comparison with CA19-9 and CEA. Int Surg. 1995; 80(1):45-8.