ORIGINAL ARTICLE

A well-known marker for predicting peritoneal metastasis in gastric cancer: carbohydrate antigen 125

Un marcador bien conocido para predecir la metástasis peritoneal en el cáncer gástrico: antígeno carbohidrato 125

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Abstract

Objectives: *Detection of peritoneal metastasis in gastric cancer is still not successful enough despite all the tests performed. In this study, the success of five well-known and commonly used tumor markers in detecting peritoneal metastasis was investigated.* **Method:** *A total of 361 patients with 61 peritoneal metastases and 25 distant organ metastasis were included in the study. The relationship between tumor markers and peritoneal metastases was investigated.* **Results:** *There was a statistically significant correlation between carbohydrate antigen (CA) 125 and the presence of peritoneal metastasis in gastric cancer ($p < 0.001$). CA 125 values > 22.75 U/mL were significantly associated with peritoneal metastasis (Area under the curve: 0.771, Sensitivity: 73.5%, Specificity: 77.7%, 95% confidence interval: 0.667-0.875). No correlation was found between the presence of peritoneal metastasis and carcinoembryonic antigen, CA 19-9, CA 15-3, and α-fetoprotein levels ($p = 0.197$, $p = 0.087$, $p = 0.497$, $p = 0.128$, respectively).* **Conclusion:** *CA 125 is an effective, non-invasive, easily accessible marker for predicting peritoneal metastasis. At levels > 22.75 U/mL, the risk of peritoneal metastasis in gastric cancer can be predicted.*

Keywords: *Gastric cancer. Peritoneal metastasis. Tumor markers. Carbohydrate antigen 125. CA125.*

Resumen

Objetivo: *Investigar el éxito de cinco marcadores tumorales bien conocidos y de uso común en la detección de metástasis peritoneales.* **Método:** *Se incluyeron en el estudio 361 pacientes con 61 metástasis peritoneales y 25 metástasis en órganos distantes. Se investigó la relación entre los marcadores tumorales y las metástasis peritoneales.* **Resultados:** *Hubo una correlación estadísticamente significativa entre el CA 125 y la presencia de metástasis peritoneales en el cáncer gástrico ($p < 0.001$). Los valores de CA 125 > 22.75 U/mL se asociaron significativamente con metástasis peritoneales (AUC: 0.771; sensibilidad: 73.5%; especificidad: 77,7%; IC 95%: 0,667-0,875). No se encontró correlación entre la presencia de metástasis peritoneal y los niveles de CEA, CA 19-9, CA 15-3 y AFP ($p = 0.197$, $p = 0.087$, $p = 0.497$ y $p = 0.128$, respectivamente).* **Conclusiones:** *El CA 125 es un marcador eficaz, no invasivo y de fácil acceso para predecir metástasis peritoneales. Con valores > 22.75 U/mL se puede predecir el riesgo de metástasis peritoneal en el cáncer gástrico.*

Palabras clave: *Cáncer gástrico. Metástasis peritoneal. Marcadores tumorales. Antígeno carbohidrato 125. CA 125.*

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Introduction

Gastric cancer is the fourth leading cause of cancer-related deaths worldwide, is usually diagnosed in advanced stages, and has a poor prognosis[1]. In gastric cancer, 60% of patients are not eligible for curative treatment due to late presentation and comorbidities. The diagnosis is made by endoscopic biopsy, and peritoneal metastasis cannot be detected confidently despite imaging modalities such as computed tomography and endoscopic ultrasonography[2]. Patients with peritoneal metastasis should receive chemotherapy before a surgical procedure, and the most effective method for detecting peritoneal metastasis is still diagnostic laparoscopy with cytologic investigation, which is still an invasive procedure[3]. Non-invasive, effective, easily applicable, and inexpensive tests are needed to detect peritoneal metastasis in gastric cancer.

Carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9, CA 15-3, CA 125, and α-fetoprotein (AFP), known as serum tumor markers, are survival-related tests that have been shown to increase in advanced stages of gastric cancer and in the presence of metastasis and recurrence[4-6].

The aim of this study is to evaluate the effectiveness of CEA, CA 19-9, CA 15-3, CA 125, and AFP tumor markers in detecting the presence of peritoneal metastasis in patients diagnosed with gastric adenocarcinoma.

Method

This study was performed in line with the principles of the Declaration of Helsinki. Local ethics board approval was obtained for this study; through registration number E1-23-4046 (Date: September 20, 2023).

The study included a total of 361 patients with 61 peritoneal metastases and 25 distant organ metastasis, who were followed and treated for gastric adenocarcinoma in the Institution General Surgery Clinic between January 2011 and December 2021. Patient data were obtained from patient follow-up files and hospital electronic medical record system.

Men and women over 18 years of age who were examined and treated in general surgery clinics for gastric adenocarcinoma were included in the study. Peritoneal metastasis was detected by pre-operative imaging methods and peritoneal cytology, or detected during surgery, and peritoneal cytology was performed. Patients with distant organ metastasis and patients undergoing emergency surgery were not included in the study. In stage 4 disease, only patients with peritoneal metastasis were included in the study. Patient age, gender, TNM stage, tumor markers (CEA, CA 19-9, CA 15-3, CA125, and AFP) laboratory values were analyzed.

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) (SPSS Version 21.0, Chicago, IL). Normality test was performed by the Kolmogorov–Smirnov test. Normally distributed numeric data were expressed as mean ± standard deviation, non-parametrically distributed numeric data as median (minimum-maximum), and categorical data as frequency (percentage). X^2 test was performed for categorical data, t-test for parametric data, and Kruskal-Wallis test for non-parametric data. Receiver operating characteristic (ROC) curve was used to determine the cut-off value for the marker that was successful in detecting metastasis. $p < 0.05$ was considered statistically significant.

Results

The pathologic diagnosis of all patients was gastric adenocarcinoma. A total of 333 patients were primarily evaluated, 61 with peritoneal metastases and 275 with non-metastatic disease. There were 103 (30.7%) female and 233 (69.3%) male patients. The mean age of the patients was 63.65 ± 12.56 years. Of the patients, 35 (10.4%) were diagnosed with Stage 1, 80 (23.8%) with Stage 2, 160 (47.6%) with Stage 3, and 61 (18.2%) with Stage 4 cancer (peritoneal metastasis only). Of the patients with Stage 4, 50 (82%) were diagnosed with pre-operative imaging methods, but 11 (18%) patients had peritoneal metastasis during surgery despite being non-metastatic. Not all tumor markers were studied in all patients at the time of diagnosis. The number of patients with available tumor marker results is given in table 1. Demographic, clinical, laboratory, and pathologic characteristics of the patients are shown in table 2.

CA125 value was found to be significantly higher in patients with peritoneal metastasis ($p < 0.001$) (Table 2). There was no association between CEA, CA 19-9, CA 15-3, or AFP levels and the presence of peritoneal metastasis ($p = 0.197$, $p = 0.087$, $p = 0.497$, and $p = 0.128$, respectively).

Of the 61 metastatic patients, 11 were diagnosed with metastatic disease at the time of surgery, and when these patients were compared with those with peritoneal metastases in the pre-operative period,

Table 1. Number of patients with available tumor marker results

Stage	CEA (%)	CA 19-9 (%)	CA 15-3 (%)	CA 125 (%)	AFP (%)	Total (%)
Non-metastasis	271 (81.6)	275 (81.8)	93 (78.2)	94 (73.4)	223 (85.4)	275
Stage 1	34 (10.2)	35 (10.4)	13 (10.9)	14 (10.9)	29 (11.1)	
Stage 2	80 (24.1)	80 (23.8)	28 (23.5)	31 (24.2)	63 (24.1)	
Stage 3	157 (47.3)	160 (47.6)	52 (43.7)	49 (38.3)	121 (50.2)	
Peritoneal metastasis	61 (18.4)	61 (18.2)	26 (21.8)	34 (26.6)	38 (14.6)	61
Total	332 (98.8)	336 (100)	119 (35.4)	128 (38.1)	261 (77.7)	336

CEA: carcinoembryonic antigen; CA: carbohydrate antigen; AFP: α-fetoprotein.

Table 2. Demographic, clinical, laboratory, and pathologic characteristics of the patients

Variables	Non-metastasis	Peritoneal metastasis	p
Age (years)	62.57 ± 11.7	57.54 ± 15.34	0.018
Gender			
Female	88 (85.4%)	15 (14.6%)	0.286
Male	187 (80.3%)	46 (19.7%)	
CEA, (U/mL), Median (Min-Max)	1.96 (0.01-1083)	2.6 (0.50-1000)	0.197
CA19-9, (U/mL), Median (Min-Max)	11.78 (0.01-4351)	18.09 (0.01-5668.82)	0.087
CA 15-3, (U/mL), Median (Min-Max)	11.4 (3.20-128.4)	12.85 (0.50-791.30)	0.497
CA 125, (U/mL), Median (Min-Max)	13.65 (2.00-562.20)	56.85 (4.10-5173.80)	< 0.001
AFP (U/mL), Median (Min-Max)	2.43 (0.01-1367.87)	3.17 (1.05-562.83)	0.128

CEA: carcinoembryonic antigen; CA: carbohydrate antigen; AFP: α-fetoprotein.

CEA levels were significantly higher, while CA 19-9 levels were not significantly different (p = 0.019, p = 0.431, respectively). For CA 15-3, 26 patients were known to have peritoneal metastases, 9 (34.6%) of these patients were diagnosed intraoperatively, and there was no statistically significant difference between those diagnosed preoperatively or intraoperatively (p = 0.426). Of the 35 metastatic patients with known CA 125 values, 9 (25.7%) had undergone surgery, and there was no significant difference between the two groups (p = 0.335). For AFP, 38 patients were in the known value group, and 9 (23.6%) of these patients underwent surgery, and the AFP value was significantly higher in the operated group (p < 0.001).

In addition to the 336 patients we evaluated in the study, there were 25 patients who were found to have liver, lung, or adrenal metastases other than peritoneal metastases at the time of diagnosis and were referred to as distant organ metastases. The mean age of the patients was 63.32 ± 11.41 years, and there was no significant difference between distant organ metastasis and non-metastatic disease (p = 0.758). Eighteen (71%) of these patients were male, and there was no significant difference between the other groups in terms of gender (p = 0.533). 24 patients had a CEA value, and the median value was 3.28 U/mL (min.1.02 U/mL -max.289.9 U/mL). CA 19-9 value was known in all patients, and the median value was 20.94 U/mL (min 0.60 U/mL, max 1487.80 U/mL). CA 15-3 was present in 16 patients, and the median value was 14.92 U/mL (min.3.60 U/mL, max.52.07 U/mL). CA 125 was present in 16 patients, and the median value was 33.68 U/mL (min 4.50 U/mL, max 94.75 U/mL). The median value for AFP was 2.46 U/mL (min. 0.75 U/mL, max. 245.90 U/mL) and was present in 24 patients. CEA and CA 125 values were significantly higher in patients with distant organ metastases (p = 0.017, p = 0.029, respectively), but there were no

other statistically significant differences in tumor markers between distant organ metastases and non-metastatic disease or peritoneal disease. When a total of 86 patients with 25 distant organ metastases and 61 peritoneal metastases were evaluated together, CEA, CA 19-9, and CA 125 were the tumor markers with statistically higher levels of metastasis (p = 0.016, p = 0.010, and p < 0.001, respectively).

The distribution of CA 125 value according to stages is given in table 3. Pairwise comparison was made for CA 125 according to stages, and it was found to be statistically significant in differentiating Stage 2 and Stage 3 disease from Stage 4 disease (p < 0.001, p = 0.002) (Fig. 1). ROC curve was performed to find the cut-off value for CA 125, and 22. 75 U/mL. (Fig. 2). Patients were divided into two groups, which were CA 125-high (CA > 22.75 U/mL) and CA 125-low (CA 125 < 22.75 U/mL) groups, and the CA 125-high group was found to have metastatic (Stage 4) disease, which was statistically significant (p < 0.001) (Table 4).

Discussion

Tumor markers are biochemical substances secreted from tumor tissue or secreted by normal tissue against tumor tissue and should ideally have high sensitivity, specificity, low false negatives and positives, distinguish between healthy and tumor patients, correlate with tumor size, detect tumors in early stages, detect recurrence, provide information about prognosis, and be universally accepted[7]. There is still no effective tumor marker for the diagnosis, follow-up, and prognosis of gastric cancer. CEA and AFP, which belong to the oncofetal protein group, and CA 19-9, CA 15-3, and CA 125, which contain carbohydrate episodes, are the most well-known tumor markers[8]. CEA, CA 19-9, CA 15-3, and CA 12-5 are used in the follow-up of treatment and prognosis rather than early diagnosis and screening in gastric cancer[9].

CEA is one of the most studied tumor markers, and elevated CEA in gastric cancer patients is associated with TNM staging, especially the detection of liver metastasis, tumor size, serosal, lymphatic, and vascular invasion[4]. There are a few studies showing that CEA is also associated with peritoneal metastasis[6]. In our study, CEA was found to be associated with distant organ metastasis and metastatic disease, but not with peritoneal disease (p = 0.017, p = 0.016, p = 0.197, respectively).

Table 3. CA 125 distribution according to stages

Stage	Patients count	CA 125, (U/mL), Median (Min-Max)	p*
Stage 1	14	15.04 (8.0-25.36)	< 0.001
Stage 2	31	9.80 (3.90-58.0)	
Stage 3	49	14.40 (2.0-562.20)	
Stage 4**	34	56.85 (4.10-5173.80)	
Total	128		

*Kruskal-Wallis test results.
**Only peritoneal metastasis.
CA: carbohydrate antigen.

Table 4. Comparison of CA 125-low and CA 125-high groups by stage

Stage	CA 125 group		p
	CA 125 < 22.75 U/mL (%)	CA 125 > 22.75 U/mL (%)	
Stage 1	12 (85.7)[a]	2 (14.3)[a]	< 0.001
Stage 2	27 (87.1)[a]	4 (12.9)[a]	
Stage 3	34 (69.4)[a]	15 (30.6)[a]	
Stage 4*	9 (26.5)[b]	25 (73.5)[b]	

*Only peritoneal metastasis.
[a,b]There is no statistical difference between the groups with the same letters.
CA: carbohydrate antigen.

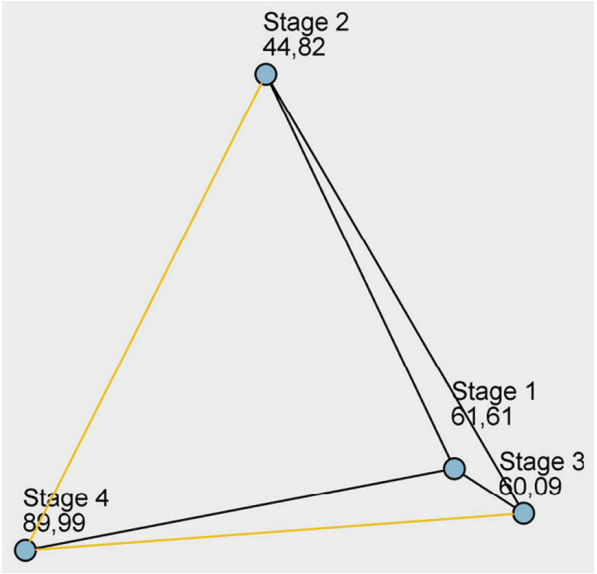

Figure 1. *Comparative analysis of carbohydrate antigen 125 value according to stages. Stage 1-Stage 2: p = 0.960, Stage 1-Stage 3: p = 1.000, Stage 1-Stage 4: p = 0.096. Stage 2-Stage 3: p = 0.437, Stage 2-Stage 4: p < 0.001*. Stage 3-Stage 4: p < 0.01*. *: There is a statistically significant difference between Stage 2 and 3 disease and Stage 4 disease.*

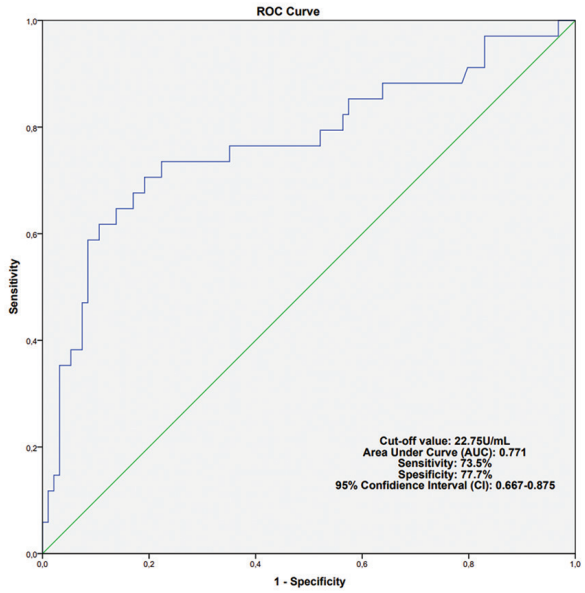

Figure 2. *Receiver operating characteristic curve analysis for carbohydrate antigen 125.*

CA 19-9 is one of the most studied tumor markers, and there are studies showing that its elevation is associated with tumor depth, nodal involvement, peritoneal and liver metastasis in gastric cancer[6]. However, in this study, although there was a statistically significant association between CA 19-9 elevation and metastatic disease, there was no statistically significant association with peritoneal disease ($p = 0.010$, $p = 0.087$, respectively).

CA 15-3, a marker used in the diagnosis of breast cancer with low sensitivity, is also known to be increased in pancreatic, ovarian, colorectal, lung, and gastric cancer metastases[7]. In the study, no association was found between CA 15-3 level and peritoneal metastasis ($p = 0.497$).

AFP is a tumor marker used for hepatocellular carcinoma and yolk sac tumor, and is increased in many solid tumors, most commonly gastric cancer, although AFP-producing gastric cancer with liver metastases was described by Bourreille in 1970 (10!!). AFP-producing gastric cancer is a rare type of gastric cancer with serosal invasion, lymph node metastasis, and liver metastasis, and a poor prognosis[10,11]. In previous studies, liver metastasis was more common in AFP-producing gastric cancers, while peritoneal metastasis was more common in non-AFP-producing gastric cancer groups[12]. In this study, no correlation was found between AFP elevation and peritoneal metastasis ($p = 0.128$).

CA 125 is a high molecular weight glycoprotein secreted from tissues of cholomic and Müllerian epithelial origin, such as the endometrium, pleura, pericardium, peritoneum, intestines, and lungs, and is used in the clinic primarily for the diagnosis and monitoring protocols of ovarian cancer[13]. The fact that CA 125 is secreted from different organs, especially from mesothelial cells in the peritoneum, explains why it is increased in different organ cancers and peritoneal metastasis[14]. Nakata et al. showed that a CA 125 level > 35 U/mL is effective in indicating peritoneal metastasis, and an increase in CA 125 level after the first 2 months postoperatively indicates peritoneal metastasis[15]. In the study by Emoto et al., it showed that a CA 125 value > 30 U/mL had a correlation with the presence of peritoneal metastasis in gastric cancer and related to the disease's severity[14]. CA 125 was found to increase the probability of peritoneal metastasis when > 17.3 U/mL in the study by Huang et al.[4].

In this study, the relationship between these tumor markers and peritoneal metastasis was evaluated. There was a statistically significant association between CA 125 and metastatic disease and distant organ metastasis ($p < 0.001$, $p = 0.029$, respectively). When peritoneal metastasis was analyzed specifically, it was shown that only elevated CA 125 was associated with peritoneal metastasis ($p < 0.001$). CA 125 > 22.75 U/mL was found to be effective in detecting peritoneal metastasis with 77.7% specificity and 73.5% sensitivity.

Conclusions

Pre-operative examinations have significance in the treatment of gastric adenocarcinoma to successfully complete the process in a way that combines surgery and oncological treatment and to make the optimal decision. Imaging techniques are used to stage the disease, but even if the malignancy is determined to be non-metastatic in imaging, metastasis remains detectable during surgery. It has been shown in this study that CA 125, one of the tumor markers, is useful for detecting metastatic disease; however, despite the fact that it is not detectable during examinations of patients with CA 125 > 22.75 U/mL, care should be used to rule out the possibility of peritoneal metastasis. The limitation of our study is the limited patient population, particularly the relatively small patient population in the Stage 1 group.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the World Medical Association and the Declaration of Helsinki. The procedures were authorized by the Institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely collected and anonymized clinical data; therefore, individual informed consent was not required. Relevant ethical recommendations have been followed.

Ethics Committee of Ankara City Hospital E1-23-4046 (Date: 20.09.2023).

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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