GASTROİNTESTİNAL VE MEME MALİGN NEOPLASMLI PREOPERATİF HASTALARDA, CEA, CA 19-9, CA 15-3, CA 125 VE AFP TÜMÖR BİYOBELİRTEÇLERİNİN PROGNOSTİK DEĞERİ

PROGNOSTIC VALUE OF CEA, CA 19-9, CA 15-3, CA 125 AND AFP TUMOR MARKERS IN GASTROINTESTINAL AND BREAST MALIGNANT NEOPLASM PREOPERATIVE PATIENTS

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ÖZET

Biyobelirteçler, günümüzde gastrointestinal ve meme malign karsinomlu hastaların saptanmasında ve tedavisinde önemli bir rol oynamaktadır. Bu amaçla preoperatif hastalarda başlıca tümör belirteçleri olan CEA, CA 19-9, CA 15-3, CA 125 ve AFP düzeylerini, bu belirteçlerin prognostik önemini ve aralarındaki ilişkileri araştırdık.

Ekim 2019 ile Aralık 2019 tarihleri arasında laboratuvarımıza başvurmuş preoperatif gastrointestinal malign neoplasm (Kolon, kolorectal, rectum, secum, ileum, mide ve pankreas) ve meme malign neoplasm tanısı almış olan 72'si erkek, 96'sı kadın olan toplam 168 hastanın CEA, CA 19-9, CA 15-3, CA 125 ve AFP test sonuçları retrospektif olarak incelendi.

Çalışmaya alınan gastrointestinal malign neoplasmı olan preoperatif 102 hastanın 72'si erkek (%61), 30'u kadındı(%29).Bu hasta grubunda, 20 mide, 45 kolon, 12 rectum, 6 sekum, 8 pankreas, 5 karaciğer, 6 duodenum malign neoplasmlı hasta bulunuyordu(Tablo 2).Erkek hastaların yaş ortalaması 63.1 ± 9.3, kadın hastaların yaş ortalaması da 66,3 ± 9,8 olarak bulundu.

Gastrointestinal malign neoplasmı olan hastalarda, CEA tümör biyobelirtecinin , CA 19-9 ve AFP testlerinden bağımsız bir prognostik faktör olduğu, meme malign neoplasmlı preoperatif hastalarda ise CEA düzeylerinin, CA 15-3, CA 125 tümör biyobelirteçleri ile uyumlu bir şekilde korelasyon gösterdiği sonucuna vardık.

Anahtar Kelimeler: EGTM; tümör markerleri; kolorektal kanser; gastrointestinal kanser; meme kanseri.

ABSTRACT

Biomarkers now play an important role in the detection and treatment of patients with gastrointestinal and breast malignant carcinoma. For this purpose, we investigated the main tumor markers CEA, CA 19-9, CA 15-3, CA 125 and AFP levels in preoperative patients, their prognostic significance and their relationships.

CEA of 168 patients, 72 male and 96 female, diagnosed with preoperative gastrointestinal malignant neoplasm (colon, colorectal, rectum, secum, ileum, stomach and pancreas) and breast malignant neoplasm between October 2019 and December 2019, CA 19-9, CA 15-3, CA 125 and AFP test results were analyzed retrospectively.

Of 102 preoperative patients with gastrointestinal malign neoplasm included in the study, 72 were male (61%) and 30 were female (29%). In this patient group, 20 stomach, 45 colon, 12 rectum, 6 secum, 8 pancreas, 5 liver, 6 There were patients with malignant neoplasm of the duodenum (Table 2). The mean age of male patients was 63.1 ± 9.3, and the mean age of female patients was 66.3 ± 9.8.

We concluded that in patients with gastrointestinal malignant neoplasm, the CEA tumor biomarker is an independent prognostic factor independent of CA 19-9 and AFP tests, while in preoperative patients with breast malignant neoplasm, CEA levels correlate consistent with the tumor biomarkers CA 15-3, CA 125.

Keywords: EGTM; tumormarkers; colorectal cancer; gastrointestinal cancer; breast cancer.

1. INTRODUCTION

Tumor markers have a fundamental importance in the diagnosis, treatment and follow-up of the disease in cancer patients. For example, carcinoembryonic antigen (CEA), which is a tumor marker, has a prognostic importance in colorectal cancer (CRC), one of the most common gastrointestinal cancers (1). CEA is a glycoprotein produced by colonic cancer cells with a half-life of 3-11 days as well as columnar and goblet cells in normal colon cells (2). CEA is recommended to be detected when a case of gastrointestinal system cancer is suspected (3). High CEA levels appear to be associated with poor outcome in preoperative patients (4).

In addition, CEA has diagnostic power in postoperative follow-up and early diagnosis of recurrent disease. However, CEA cannot be used for screening purposes due to its low sensitivity in the early stages of cancer (5). Colorectal carcinoma (CRC) is one of the most common and fatal cancers in men and women worldwide [6]. Although CEA is an important tumor marker in colorectal cancer, serum levels may also increase in benign diseases (7). In liver cancer, alpha-fetoprotein (AFP) can be used as a screening marker for preoperative prognostic evaluation, for postoperative monitoring, and also as a tumor marker to monitor advanced disease in patients at high risk of developing hepatocellular carcinoma. AFP can increased not only in hepatocellular carcinoma, but also in other benign diseases and malignancies. In gastric cancer, no tumor marker is recommended for screening or diagnosis. (8). CA 19-9 is normally synthesized by human pancreatic and bile duct cells and stomach, colon, endometrial and salivary epithelium. It is also a high molecular weight glycoprotein that can be detected in human blood. CA 19-9 is used to diagnose pancreatic, stomach, and colorectal cancer. CA19-9 is a well-known tumor marker in pancreatic cancer (9, 10) and continues to be the gold standard tumor marker in postoperative follow-up.CA19-9 may be elevated, usually in advanced gastrointestinal malignancies as well as in benign gastrointestinal diseases (11). Synthesis of CA19-9 in individuals with Lewis (ab-) phenotype Since it is not, it may cause false negative results in these patients. In recent years, a large number of biomarkers for pancreatic cancer have been proposed, but most of these have no significant validity. Moreover, none of these can been no shown to have the necessary sensitivity / specificity to be applied in clinical use. Therefore, CA 19-9 continues to be the only pancreatic cancer marker in clinical use (12).

Breast cancer is one of the most common malignant tumors in women (13). The number of patients is increasing rapidly (14). Thanks to early diagnosis methods and new treatment methods, the mortality rate of breast cancer has decreased in recent years (15). However, patients' quality of life and survival are significantly affected if treatment fails. Therefore, it is essential to identify reliable prognostic factors to guide decision making during breast cancer treatment to improve survival rates. Traditional prognostic factors, including tumor size, axillary lymph node status, hormone receptor status, and human epidermal growth factor receptor 2 (HER2) expression are widely used in clinical practice (16). However, these features do not fully reflect the prognosis of breast cancer.

Table.1 Major tumor markers used in clinical practice.

Organ and tissue	Specific Tumor Marker	Organ and tissue	Specific Tumor Marker
Bladder	Cyfra 21-1 CEA TPA	**Breast**	CEA Ca 15-3 MCA
Colon, rectum	CEA CA. 19-9 CA. 50	**Stomach**	CEA CA 72-4 CA 50
Prostate	PSA PAP	**Pancreas**	CA 19-9 Elastase
Testis	ß -hcg AFP SP-1	**Thyroid**	CEA Calcitonin Thyroglobulin
Liver	AFP	**Nervous System**	5-HIAA
Head, neck	SCC		
Lungs	CEA SCC/NSE Cyfra 21-1	**Ovary**	CEA CA 125 AFP ß -hcg
Blood	ß2-Microglobulin	**Cervix**	SCC

Circulating tumor markers such as carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA15-3) have been studied as prognostic tests in breast cancer for over 30 years. Plasma CEA and CA15-3 are the most common tumor markers used in breast cancer (17, 18, 19, 20, 21, 22). CEA is the first tumor antigen used (11). CEA is a type of cell adhesion molecule, and CEA levels in blood generally increase when cancer metastasizes (12). CA15-3, a member of the mucin-1 (MUC-1) glycoprotein family, is overexpressed in cancers, and the altered glycosylation of CA15-3 makes it a useful tumor marker (23).

2. MATERIALS AND METHODS

Between October 2019 and December 2019, CEA, CA 19-9, CA 15-3, CA 125 and AFP test results of patients who were diagnosed with gastrointestinal malignant neoplasm (Colon, duodenum, stomach, ileum, pancreas, secum, liver and rectum) and breast malignant neoplasm from our hospital's general surgery, medical oncology and internal medicine clinics, It was reviewed retrospectively. In our study, there were a total of 168 preoperative patients, 96 women and 72 men.

CEA, CA 19-9, CA 15-3, CA 125 and AFP tests of the patients were studied by chemiluminescence method on UniCel DxI 800 (Beckman Coulter Diagnostics, USA) immunoassay device. These tests were studied in UniCelDxI 800 (BeckmanCoulterDiagnostics, USA) immunoassay device by chemiluminescence method using 3 different level control serum (low, normal, high). Statistical analyzes were performed in IBM SPPP 25 statistical program. Since our data did not show normal distribution, it was decided to use nonparametric tests. The Nonparametric Mann-Whitney U test was used to compare two independent groups that did not show normal distribution, and the Nonparametric Spearman correlation test was used to calculate the correlations between the two variables.

3. RESULTS

Of 102 preoperative patients with gastrointestinal malignant neoplasm included in the study, 72 were male (61%) and 30 were female (29%). In this patient group, there were patients with malignant

neoplasm of 20 stomach, 45 colon, 12 rectum, 6 secum, 8 pancreas, 5 liver, 6 duodenum (Table 2). The mean age of male patients was 63.1 ± 9.3, and the mean age of female patients was 66.3 ± 9.8.The average age of 66 preoperative women with breast malignant neoplasm is 58.1 ± 12.6 and other demographic data are given in Table 2.

Table 2. Demographic data and distribution of parameters of patients with gastrointestinal and breast malignant neoplasms

Gastrointestinal malign neoplasm	
Male	**72(%61)**
Female	**30(%29)**
Kolon malign neoplazm	**45(%44)**
Mide malign neoplazm	**20(%20)**
Rectum malign neoplazm	**12(%11)**
Pankreas malign neoplazm	**8 (%8)**
Duodenum malign neoplazm	**6 (%6)**
Sekum malign neoplazm	**6 (%6)**
Karaciğer malign neoplazm	**5 (%5)**
Age, Years (Male)	
Mean	**63.1 ± 9.3**
Median	**65(42-79)**
Age, Years (Female)	
Mean	**66,3 ± 9,8**
Median	**65.5(36-83)**
Meme malign neoplasm	
Female	**66 (%100)**
Age, Years (Female)	
Mean	**58,1 ± 12,6**
Median	**59(22-89)**

Values are given as n (%), mean ± SD or median (min-max).

Our reference range is 0-3 ng / ml for CEA, 0-35 U / ml for CA 19-9, 0-31.3 U / ml for CA 15-3, 0-35 U / ml for CA 125, while for AFP It was determined as 0-9 ng / ml. CEA values were found to be 103.5 ± 229.3 ng / ml in patients with gastrointestinal malignant neoplasm and 31.9 ± 55.3 ng / ml in patients with breast malignant neoplasm (Table 3). CEA levels were lower in patients with breast malignant neoplasm than in the other group. Mean CA 19-9 values were 217.5 ± 485.4 U / L in patients with gastrointestinal malignant neoplasm, and 72.4 ± 242.1 U / L in patients with breast malignant neoplasm, three times higher than in patients with breast malignant neoplasm (Table 3). While the mean of CA 15-3 test in patients with breast malignant neoplasm is 130.2 ± 297.2 U / ml, it is 31.2 ± 40.2 U / ml in the patient group with gastrointestinal malignant neoplasm. There is approximately 4-5 fold difference between the two groups. When we looked at the CA 125 test, it was seen that it was higher in patients with breast malignant neoplasm compared to the other group (Table 3). The mean AFP test was higher in the group of patients with gastrointestinal malignant neoplasm compared to the breast carcinoma patient group (Table 3).

Table 3. Demographic data and test parameters in patients with gastrointestinal and breast malignant neoplasms.

Variables	Gastrointestinal malign neoplasm group		Meme malign neoplasm group	
Age(Years) **Female** **Male**	66,3 ± 9,8 63.1 ± 9.3	65.5(36-83) 65(42-79)	58,1 ± 12,6	59(22-89)
CEA (ng/ml)	103.5 ± 229.3	15.8(1.35 -1245)	31.9 ± 55.3	10.9(1.9-251.4)
CA 19-9 (U/ml)	217.5 ± 485.4	39.9(0.6 -2061)	72.4 ± 242.1	20.3(0.6-1154)
CA 15-3 (U/ml)	31.2 ± 40.2	16.4(6.8- 132.5)	130.2 ± 297.2	21.5(5.4 -1260)
CA 125 (U/ml)	34.2 ± 85.8	12.4(2.3 – 1057)	45.7 ± 325.4	12.5(3.8 -365.6)
AFP(ng/ml)	7.2 ± 17.1	2.54(1.26 - 69.1)	5.1 ± 3.2	3.3 (3.2 – 8.7)
Values are given as n (%), mean ± SD or median (min-max).				

Nonparametric Spearman correlation test was used to calculate the correlations between tumor markers known to be specific for both patient groups.

Table 4. Correlations and significance levels in the patient group with gastrointestinal malignant neoplasm.

CEA	**r** [a]	**P**
Yaş	0,13	0,17 (>0,05)
CA 19-9	0,10	0,30 (>0,05)
Correlations is significant (p<0,05)×, [a] Spearman rho correlation coefficient.		

No significant correlation was found between CEA (carcinoembryonic antigen), which is considered to be specific tumor markers in gastrointestinal malignant neoplasms, and CA 19-9 and patient age(P> 0.05) Table 4). Statistically very significant correlations were found between CA 15-3, which is accepted as a specific tumor marker in the diagnosis of patients with breast malignant neoplasm, and CEA, CEA and CA 125 (respectively, r = 0.56; P <0.001, r = 0.44; p < 0.005) (Table.5). It was observed that CA 15-3 and CA 125 biomarkers also showed a statistically significant correlation (r = 0.56; P <0.001).

Table 5. Correlations and significance levels in the patient group with breast malignant neoplasm.

CEA	**r** [a]	**P**
Yaş	0,07	0,55 (>0,05)
CA 15-3	0,56	0,000 (<0,001)×
CA 125	0,44	0,001 (<0,005)×
Correlations is significant (p<0,05)×, [a] Spearman rho correlation coefficient.		

Both patient groups with gastrointestinal and breast malignant neoplasms were compared in terms of CEA test using the Nonparametric Mann-Whitney U test. A statistically significant difference was found between the two groups according to the test results ($p = 0.03$; $p < 0.05$).

4. DISCUSSION

In recent years, biomarkers have started to play an increasingly important role in the detection and treatment of patients with gastrointestinal malignancies. This is particularly true for colorectal cancer (CRC), gastrointestinal stromal tumors (GISTs), gastric and gastroesophageal associated (GOJ) cancers. In 2003 and 2007, the European Tumor Markers Group (EGTM) published guidelines on the use of biomarkers in CRC (Colorectal cancer). (24, 25). Numerous studies over the past 30 years have addressed the prognostic impact of CEA levels at first admission in preoperative patients with colorectal cancer (26, 27). Many studies have shown that CEA is an independent prognostic factor and, more importantly, predicts outcome in patients with Stage II disease (28,29).

In our study, it was consistent with the study of the European Tumor Markers Group (EGTM) and found that the average CEA level was approximately 4.5 times higher in patients with gastrointestinal malignancies compared to the patient group with breast malignant neoplasms (Table 3). According to the Speerman correlation test analysis, there is no significant correlation between CEA and CA 19-9 ($P > 0.05$). CEA appears to be an independent biomarker in patients with gastrointestinal malignancies.

In many studies, the prognostic value of biomarkers such as CEA and CA15-3 has attracted great attention in preoperative patients with breast malignant neoplasm.

It has been shown, in particular, that preoperative plasma CEA levels, together with CA15-3 levels, can provide useful information for the diagnosis and treatment of breast cancer (30). Some studies have suggested that preoperative serum CEA and CA15-3 levels in breast cancer patients are associated with prognostic factors such as tumor size, axillary lymph node status, and hormone receptor status (5, 6, 7, 8, 9, 10). Accordingly, the European Tumor Markers Group(EGTM) recommended the use of CEA and CA15-3 levels in determining the prognosis in patients with breast cancer, and in the treatment and follow-up of the disease (14). In contrast, Maric et al.(31) did not support this result, suggesting that there is evidence that these markers are not sensitive or specific enough for early detection of breast cancer. The American Society of Clinical Oncology (ASCO) also does not recommend the use of CEA and CA15-3 for breast cancer screening, diagnosis, staging, and treatment monitoring [32]. Our study, on the other hand, complies with the guidelines of the European Tumor Markers Group and showed that there is a statistically very significant correlation between CA 15-3 and CEA in patients with malignant neoplasm ($r = 0.56$; $P < 0.001$) (Table 5). There was also a very significant correlation between CEA and CA 125 ($r = 0.44$; $P < 0.005$) (Table 5). In addition, it was observed that CA 15-3 and CA 125 biomarkers also showed a statistically very significant correlation ($r = 0.56$; $P < 0.001$).

5. CONCLUSION

We retrospectively examined tumor biomarkers such as CEA, CA 19-9, CA 15-3, CA 125 and AFP in preoperative patients with gastrointestinal and breast malignant neoplasmsWe concluded that the CEA tumor biomarker has a prognostic value independent of CA 19-9 and AFP tests in patients with gastrointestinal malignant neoplasia, but that CEA is significantly correlated with the CA 15-3 and CA 125 tests in preoperative patients with breast malignant neoplasia.

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