

Serum Tumor Markers can Predict Nonresectability in Gastric Cancer

Serum Tümör Belirteçleri Mide Kanserinde Nonrezektabiliteyi Öngörebilir

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ABSTRACT Background: Gastric cancer is one of the main causes of deaths on cancer worldwide. Serum tumor markers were investigated to work as effective and non-invasive diagnostic or prognostic tools. In this prospective study, we aimed to find that the serum levels of the tumor markers which have been used to predict the staging and prognosis may also be useful to predict the resectability. **Material and Methods:** From January 2005 to May 2007, 187 consecutive patients with histologically proven gastric cancer were enrolled in the study. The patients were divided into two groups; group 1 consisted of patients with R0 or R1 resection and group 2 patients with R2 resection. Age, sex, clinical and laboratory findings, type of gastrectomy, type of surgical procedure, and tumor markers, were analyzed for all patients. **Results:** There were 161 patients in group 1 and 26 patients in group 2. There were not any significant differences between groups regarding age, clinical and laboratory findings. The difference between groups with regard to gender was statistically significant, female had much more nonresectable gastric cancer ($p=0.001$). Among the evaluated serum tumor markers; only preoperative serum CA 72-4 levels were statistically significant to predict the nonresectability in gastric cancer patients ($p=0.05$). **Conclusion:** Identification of advanced disease by laparoscopy allows many patients to avoid an unnecessary laparotomy. Therefore, patients with elevated levels of CA 72-4 might be candidates for laparoscopic exploration to prevent an unnecessary laparotomy.

Key Words: Stomach neoplasms; general surgery; tumor markers, biological; laparoscopy

ÖZET Giriş: Mide kanseri kanserden ölümlerin en önemli sorumlularındandır. Serum tümör belirteçlerinin tanı ve tedavi takibinde etkinlikleri gösterilmiştir. Bu prospektif çalışmada mide kanserinin evresinin ve prognozunun tahmininde kullanılan tümör belirteçleri düzeylerinin rezektabiliteyi değerlendirmede de kullanılabilirliğini araştırmayı hedefledik. **Gereç ve Yöntemler:** Ocak 2005'ten Mayıs 2007'ye kadar mide kanseri olduğu histolojik olarak ispatlanmış ve ameliyat edilmiş olan 187 hasta iki gruba ayrılarak incelendi. Grup 1 R0 veya R1 rezeksiyon yapılan hastaları, grup 2 ise R2 rezeksiyon yapılan hastalar içeriyordu. Yaş, cinsiyet, klinik ve laboratuvar bulguları, gastrektomi ve rezeksiyon tipi ve tümör belirteçleri her hasta için kaydedildi. **Bulgular:** Grup 1 161, grup 2 ise 26 hastadan oluştu. Yaş, klinik ve laboratuvar bulguları açısından gruplar arasında fark yoktu. Cinsiyet açısından bakıldığında gruplar arasında anlamlı fark vardı; bayanlara daha fazla R2 rezeksiyon yapılmıştı ($p<0.01$). Serum tümör belirteçleri içinden sadece ameliyat öncesi CA 72-4 seviyesinin mide kanseri hastalarında R0 veya R1 rezeksiyonun yapılamayacağını önceden belirlemede faydalı olduğu görüldü ($p=0.05$). **Sonuç:** Mide kanserinde ilerlemiş hastalığın laparoskopiyile belirlenmesi pekçok hastanın gereksiz laparotomiye maruz kalmasını önlemektedir. Ameliyat öncesi yüksek serum CA 72-4 seviyesi olan hastaların rutin laparoskopik değerlendirilmesi gereksiz laparotomileri önleyebilir.

Anahtar Kelimeler: Mide kanseri ; cerrahi ; tümör markerları, laparoskopi

Gastric cancer is the second most lethal types of cancer.¹ Its etiology is not known but various predisposing factors are blamed. Although improvement of surgical treatment has increased the 5-year survival rate, survival of patients with gastric cancer still remains poor.² Besides gastroscopic surveillance, serum tumor markers were investigated to use as effective and non-invasive diagnostic or prognostic tools.³

Carbohydrate antigen 19-9 (CA 19-9) was found to be better than carcinoembryonic antigen as a prognostic factor in patients with gastric cancer.^{4,5} Elevated levels of CA 125 were reported in 30-55% of gastric cancer patients.⁶⁻⁹ In a recent study, CA 72-4 and CA 15-3 levels were reported above normal in 46.8% and 18.4% of gastric cancer patients respectively and serum CA 72-4 level was found to be correlated with staging and prognosis of the disease.⁶

It may not be possible to obtain R0 or even R1 resection in gastric cancer patients. Although the development of many radiological diagnostic modalities, laparoscopy becomes an essential component of pretreatment staging for gastric cancer to avoid unnecessary laparotomies in patients in whom surgical palliation is not indicated. Serum levels of the tumor markers used to predict the staging and prognosis may also be useful to predict the nonresectability. In this prospective study, we aimed to evaluate this opinion.

MATERIAL AND METHODS

From January 2005 to May 2007, 187 consecutive patients with histologically proven gastric cancer who underwent surgery at Erciyes University Medical School Department of General Surgery were enrolled in the study. The patients were divided into 2 groups; group 1 consisted of patients with R0 or R1 resection and group 2 patients with R2 resection (R0; no residual gross or microscopic disease, R1; microscopic residual disease only, R2; gross residual disease). Age, sex, clinical findings, laboratory findings, type of gastrectomy, type of resection, and tumor markers, were determined for all patients. The morbidity and mortality statistics were restricted to the hospital stay and postopera-

tive period (less than one month). Informed consent form was approved by the patients.

Serum was collected before operation from these patients for analysis of various tumor markers including AFP, CEA, CA 125, CA 15-3, CA 19-9, and CA 72-4. The results of analysis were compared between the two groups. Serum levels of markers were determined by immunoradiometric assays. The range of markers were as follows; AFP 0.6-6.65 ng/ml; CEA<2.5 ng/ml; CA 125, 0-21 U/ml; CA 15-3, 6.4-58 U/ml; CA 19-9, 0-33 U/ml; CA 72-4, 0-3,8 U/ml.

Data from the study were evaluated with the statistical SPSS package version 13.0 (Chicago, Illinois). Data were expressed as mean \pm standard deviation (SD) or median (range). Differences between categorical variables were compared with Chi-square test. The differences between the medians of the groups were compared with Mann-Whitney U test. A *p* value <0.05 was considered significant.

RESULTS

The levels of tumor markers of the patients with resectable or unresectable gastric cancer are summarized in table 1. There were 161 patients in group 1 and 26 patients in group 2. Total of 187 patients included in the study, 124 were male, 63 were female with an average age of $56 \pm 1,8$. There were not any significant differences between the groups regarding age, clinical and laboratory findings. Ten male (8.1%) and sixteen female (25.4%) patients were assessed to have nonresectable tumors. This difference between gender was statistically significant, female had much more nonresectable gastric cancer (*p*= 0.003).

Tube jejunostomy was performed in 10 patients, only exploratory laparotomy in 4 patients, gastrojejunostomy for the continuity of the passage in 5 patients and palliative gastrectomy in 7 patients in group 2 with laparotomy. Total gastrectomy was performed in 98 (60.9%) patients and subtotal gastrectomy in 63 (39.1%) patients in group 1.

The most frequent cause of morbidity was pleural effusion seen in 28 patients (15%). Wound infection in 15 patients (8%), and a fistula from

esophagojejunal anastomosis in 6 patients. Postoperative acute respiratory distress syndrome (ARDS) developed in 5 patients with one or more complications and 4 of them died with sepsis and multiorgan failure. Postoperative mortality rate was 4.3% representing 8 patients. As mentioned above, 4 patients died because of ARDS related multiorgan failure, 2 patients died from sepsis secondary to fistula from esophagojejunal anastomosis, one patient died secondary to myocardial infarction and one patient died with pulmoner embolus.

Among the evaluated markers; AFP, CEA, CA 125, CA 15-3, CA 19-9, and CA 72-4, only the serum levels of AFP were higher in group 1 compared to group 2. Similar results were obtained regarding to the age of the groups; group 1 was older than group 2 but this differences did not reach statistical significance (Table 1).

The difference of CA 125, CA 15-3 and CA 72-4 between two groups were notable. Their *p* values were 0,07, 0.05, and 0.02 respectively. Although preoperative CA 15-3 levels were of borderline significant, only preoperative serum CA 72-4 levels reached the statistically significant difference to predict the nonresectability in gastric cancer.

DISCUSSION

Despite the decline in its incidence, gastric cancer continues to be one of the main causes of deaths on cancer worldwide, 5-year survival is between 7-15%.⁷ Tumor markers are biological agents that have been investigated for a long time and nowadays they play an important role in diagnosis, evaluation to treatment response, monitoring and recurrences though to be from tumor cells.¹⁰

Shedding or secretion of tumor antigen depends on tumor volume, vascularity of tumor or immunogeneity of patients.³ There are numerous publications on the prognostic significance of tumor markers in gastric cancer. It is agreed that patients with advanced stage of disease have higher positive rate of serum markers. Our data correlated well with this opinion.

It is interesting that in our study, CA 125 and CA 15-3, the tumor markers commonly used in

TABLE 1: The comparison of the groups with regards to tumor markers, age and gender.

Variables	Resectable gastric cancer N= 161 mean ± SD median (min-max)	Nonresectable gastric cancer N= 26 mean ± SD median (min-max)	p
AFP	n= 122 28.8 ± 10.3 3.1 (0.0-819.0)	n= 16 6.2 ± 2.8 3.3 (0.0-45.3)	>0.05
CEA	n= 154 13.9 ± 5.3 1.8 (0.0-753.1)	n= 24 14.3 ± 5.0 2.8 (0.2-98.4)	>0.05
CA-125	n= 100 33.8 ± 9.0 12.9 (1.3-373.0)	n= 12 104.7 ± 33.2 2.8 (5.0-203.0)	>0.05
CA 15-3	n= 88 76.8 ± 39.4 19.2 (5.6-1714.3)	n= 16 270 ± 208.7 30.6 (15.2-1714.3)	0.05
CA 19-9	n= 137 44.6 ± 8.9 12.4 (0.0-655.1)	n= 19 108.4 ± 44.7 21.2 (0.0-655.1)	>0.05
Age	n= 161 58.0 ± 1.0 57 (23.0-85.0)	n= 26 53.2 ± 2.7 56 (27.0-81.0)	>0.05
CA 72-4	n= 130 45.3 ± 9.1 4.2 (0.0-446.2)	n= 26 82.2 ± 31.5 15.1 (0.8-440.0)	<0.05
Gender			<0.01
Male	114	10	
Female	47	16	

monitoring for ovarian and breast cancers, showed an important association with nonresectability in gastric cancer. Similar results have been reported.^{3,10} This findings may be related to aggressive biological nature of tumors. We found that CA 125 and CA 15-3 levels were elevated in 33.6% and 24.2% of gastric cancer patients respectively. Although this association did not reach a statistical significance, this issue deserves to be investigated; moreover, their combination may be significant.

In the literature, there are many studies reporting CEA, CA19-9 and CA 72-4 as prognostic factors in gastric cancer. Elevated CEA levels are reported between 15 to 57.6% and CA 19-9 levels are elevated in 14.4 to 44% of gastric cancer patients.¹¹⁻¹⁷ CEA and CA 19-9 act as intercellular adhesion molecules, and cells expressing these glycoproteins may have a greater invasive potenti-

al. Additionally, a correlation between CEA and proliferating cell nuclear antigen has been described, suggesting that cell expressing this antigen will exhibit an increased proliferating activity.¹⁸⁻²⁰ We found elevated CEA and CA 19-9 levels in 35.3% and 26.7% of the patients respectively. Although CEA and CA 19-9 have been demonstrated to have a prognostic value of survival,¹⁰ we did not find them as significant predictors for nonresectability.

CA 72-4 assay measures a human tumor-associated glycoprotein TAG-72 which has been investigated as a good marker for late stage gastric cancer.²¹ Elevated levels of TAG-72 were reported in the serum of 18.6% to 42.6% of the patients with gastric cancer and the specificity was reported to be very high, nearly 100%.^{22,23} The serum level of CA72-4 correlate well with the level of TAG 72. The serum level of TAG-72 represents the proliferative activity of cells in gastric cancer.²² There are numerous publications about the superiority of the CA 72-4 assay for prognostic significance in gastric cancer.²⁴⁻²⁶ Patients with high preoperative serum levels of CA 72-4 have been reported to have a greater risk of death due to gastric cancer. CA

72-4 assay was reported to be more sensitive, better reflect disease stage and activity, and better in predicting recurrence.^{6,24} Our results were harmonious with this reports and support them; CA 72-4 was the only significant marker in predicting nonresectability in gastric cancer.

The sensitivity of helical computed tomography performed with gastric-specific protocols for the detection of small metastases on the peritoneal surface is low. Identification of advanced disease afforded by laparoscopy allows many patients to be spared from nontherapeutic laparotomy. Therefore, patients with elevated serum levels of CA 72-4 might be candidates for laparoscopic exploration to prevent an unnecessary laparotomy. After laparoscopic examination, patients with nonresectable tumor may be candidates for chemoradiotherapy which can provide down staging to reach a resectable tumor.

In conclusion, elevated CA 72-4 levels correlates well with advanced stage of gastric cancer. Surgeons should asses CA 72-4 levels before the choice of therapy regimen due to risk of nonresectability of the tumor.

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