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ORIGINAL RESEARCH

Clinical Evaluation of Serum Tumor Markers in the Diagnosis of Gastric Adenocarcinoma Staging and Grading

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Abstract
Detection and quantitative measurements of diffused tumor markers in blood samples of patients with cancer is a facile and convenient method to determine prognosis and the appropriateness of the treatment. This study was done to evaluate the level of CA125, CEA, AFP, Beta HCG, and CA19-9 tumor markers and their relation to the stage and grade of the disease in patients with gastric adenocarcinoma.
Materials and Methods In a descriptive cross-sectional study, of 81 patients referred to the oncology department of Tohid Hospital, Sanandaj, Iran, in 1 year, with recently detected gastric adenocarcinoma, serum level of CEA, CA19-9, CA125, AFP, and Beta HCG tumor markers was measured by ELISA method before chemotherapy and surgery. Patients were divided into four groups based on stage of disease (I, II, III, IV), and in terms of tumor differentiation, degrees were classified in to three groups: low, high, and intermediate. To determine the correlation of tumor markers level with the stage and grade of the disease, the Kruskal-Wallis and Mann-Whitney *U* tests were used.
Results By progression, the stages of the disease, the serum level of CA19-9, CA125, and AFP tumor markers demonstrated a significant increase. But this difference between level of HCG and CEA was not significant with the staging. There was no significant difference between the serum level of tumor markers and the grading of disease in the patients.
Conclusion Preoperative CA19-9, CA125, and AFP tumor markers measurements could be beneficial in detecting the progressed stages of the disease.

Keywords Gastric adenocarcinoma · CEA · AFP · Beta HCG · CA125 · CA19-9 · Grading · Staging

Introduction

Although by improving lifestyle in recent decades, the prevalence of the gastric cancer has decreased, nevertheless gastric cancer is the fourth most common cancer and the second leading cause of cancer deaths worldwide. According to global reviews, 930,000 new cases annually and at least 700,000 deaths from the disease are reported [1]. For the time being, the primary therapeutic treatment for gastric cancer is surgery, but in most of the patients, after the operation, a recurrence of the disease is seen which leads to death in most cases. Latent metastasis at the time of surgery is one of the major causes of recurrence [2]. The first priority after decisive recognition and awareness in dealing with a patient is disease spread determination. In an optimal mode, tumor is diagnosed before symptoms appear or as a result of screening tests. Detection and quantitative measurements of diffused tumor markers in blood samples of patients with cancer is a facile and convenient method to determine prognosis and the appropriateness of the treatment. Estimating the predictive value of a number of tumor markers could provide better treatments in patients with advanced gastrointestinal cancers include the following: gastric and colorectal cancers. Studies have shown that tumor markers of the biochip C12 system have substantial diagnostic value in detecting gastric cancer. It should be noted that CEA, CA125, CA19-9, and CA242 are four fundamental tumor markers in tumor detection [3]. Furthermore, studies have proved that high serum level of Beta HCG have seen more frequently in the advanced stages of gastric tumors and undifferentiated carcinoma [4]. Moreover, blood level of Beta HCG

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is closely related to the amount of this hormone in the cancerous tissue [5]. According to previous studies which corroborated the important diagnostic value of tumor markers, if there are remarkable discrepancies in different grades and stages of the disease, checking the serum level could be helpful in diagnosis of grading and staging and can have a great role in progression of the diagnosis and treatment process of the patients. The aim of this study was to determine the value of serum tumor markers CEA, CA 19-9, CA125, Beta HCG, and AFP with regard to staging and grading of disease in patients with gastric adenocarcinoma.

Material and Methods

Study Design and Patients

In a descriptive cross-sectional study, 81 patients (gastric cancer was diagnosed by endoscopic biopsy and were hospitalized in Tohid Hospital, Sanandaj, Iran, during 2014–2015) were selected for the study. Patients with history of any malignancies in the past or bearing other malignancies except gastric cancer were exempted from the study. The protocol of the study was approved by the Ethics Committee of Sanandaj University of Medical Sciences (No.1392.183). During the study, all of the researchers adhered to the principles of the Helsinki Declaration. Written consent was obtained from the patients.

Evaluation of Staging and Grading and Tumor Marker Assay

For all the patients, abdomen ultrasonography, *chest* x-ray, abdomen, and pelvic and thorax CT scan were requested for stage determination of the disease. Staging of the disease was done by TNM method which is determined by the tumor tissue involvement (T), regional lymph node involvement (N), and distant metastasis (M), and patients are classified into four groups [6].

One week prior to surgery, blood samples were collected from the patients for determination of CEA, CA125, CA19-9, AFP, and Beta HCG tumor markers and were transmitted to the respective laboratory. Level of tumor markers was measured by ELISA method. According to pathologic findings, in terms of tumor differentiation degree, the patients were classified into three grades which include: high, intermediate, and low [7].

Statistical Analysis

The relevance between staging, grading, age, and sex with the defined tumor markers was analyzed. Data were analyzed by SPSS (version 20). To determine the correlation between tumor markers level and tumor grading and staging of the disease, the Kruskal-Wallis and Mann-Whitney *U* tests were utilized. To verify the correlation between age and biomarkers level the Spearman's rank correlation coefficient and for evaluation of sex relation with the level of tumor markers the Mann-Whitney *U* test were done. Furthermore, the sex relevance with tumor grading and disease staging was evaluated by Chi-squared test. Significance level in this study is less than 0.05.

Results

Of the 81 patients include in this study, 62 patients (76.5%) were male and 19 (23.5%) were female. Age mean of the patients was 64.60 (± 10.98) year olds (min age, 31 and max age, 89).

Of disease stage, 29 patients (35.8%) were in the second stage, 13 (16%) in the third stage, and 39 (48.1%) were in the fourth stage of the disease.

Tumor grading in 34 individuals were high (42%), 27 were intermediate (33.3%), and 20 individuals were low (24.7%). In Table 1, the frequency of patients with gastric cancer by sex dissociation according to the staging and grading of the disease were shown.

In this study, there was no significant relation between sex and tumor grading at the time of cancer detection ($p = 0.16$), but there was a remarkable relevance between sex and staging of the disease ($p = 0.001$). According to these considering facts, men were at higher stages of the disease than women at the time of diagnosis. The average level of tumor markers according to the staging (Table 2) and grading (Table 3) of the disease were shown. At serum level of tumor markers according to the grading, there was no significant difference in different groups ($p > 0.05$). According to the stage of the disease in different groups, there were not any remarkable differences at serum level of Beta HCG and CEA tumor markers ($p > 0.05$). In patients who were at stage 4 of the disease, serum level of CA19-9 tumor marker was extremely increased

Table 1 Frequency of patients by gender based on staging and grading of gastric cancer

	Male *N* (%)	Female *N* (%)	*P* value
Stage			
2	16 (25.8%)	13% (68.4%)	0.115
3	11 (17.7%)	2 (10.5%)	
4	35 (56.5%)	4 (21.1%)	
Grade			
1	12 (19.4%)	8 (42.1%)	0.003
2	23 (37.1%)	4 (21.1%)	
3	27 (43.5%)	7 (36.8%)	

Table 2 Median values (P25–P75) of CA125 (U/mL), beta HCG (mIU/ml), AFP (IU/ml), CEA (ng/mL), and CA19-9 (U/mL) in different stages of cancer patients

Tumor markers	Stage 2 ($n = 29$)	Stage 3 ($n = 13$)	Stage 4 ($n = 39$)	p value
CEA	4 (1.5–9)	1.7 (1–5.5)	3.2 (2–40.5)	0.06
CA125	11 (3–19.95)	16 (3–19.2)	18.8 (8.5–110)	0.03
CA19-9	14.4 (5–56)	17.7 (5.5–42)	42 (10.65–376.5)	0.01
AFP	2 (1.5–3)	3.7 (3–233)	3.2 (1.95–23)	0.003
Beta HCG	1 (1–2)	1 (1–1)	1 (1–2)	0.62

than those who were at the stage 2 ($p = 0.009$) and stage 3 ($p = 0.031$) of the disease. Moreover, increased serum level of CA125 tumor marker in patients at stage 4 of the disease versus the patients who were at the stage 2 had remarkable relevance ($p = 0.013$). AFP tumor marker in patients who were at stage 3 ($p = 0.002$) and stage 4 ($p = 0.006$) in comparison with the patients at the stage 2 was highly enhanced. In evaluating the relation of some variables like age and sex with serum level of each tumor marker, no significant relation was found ($p > 0.05$).

Discussion

In the present study, results showed that of the five defined tumor markers, increased serum level of CA19-9, CA125, and AFP had notable relevance with progression of disease stage which was not considerable with grading as respect. AFP is a well-known tumor marker for screening and monitoring of hepatocellular carcinomas and yolk sac. However, some studies have pointed to its production in some other carcinomas including gastric carcinoma [8]. Production of this tumor marker in gastric cancer will attenuate the long-term survival rate due to high prevalence of liver metastasis and vascular-lymphatic invasion; however, the cellular-molecular mechanisms which are responsible for feeble prognosis are poorly understood [9].

Studies which evaluated the relation of defined tumor marker with gastric cancer prognosis up to now demonstrated that in the case of AFP production, hepatocyte growth factor (HGF), and c-met expression in patients with gastric cancer is higher than the tumor marker is not produced. HGF could enhance proliferation, mobility, morphogenesis, and angiogenesis in a variety of cells including tumor cells which AFP consequently could accelerate tumor growth via HGF and c-met pathways [10]. In one study, serum level of AFP in patients with gastric cancer and liver metastasis significantly increased in comparison with the patients with no sign of metastasis. Furthermore, there was a remarkable correlation between increased serum level of the defined tumor marker and lymph nodes involvement [8]. In the present study, the AFP serum level in advanced disease stages (stage 3 and 4) versus early stages (1 and 2) was extremely increased. Nevertheless, this tumor marker is not produced in all the patients with gastric cancer, and consequently low level of it in patient's serum could not be a result of low stages of the disease. However, high serum level of AFP indicates the invasive behavior and poor prognosis of the disease in patients with this cancer, so it should be noted that this tumor marker is a suitable criterion for disease prognosis determination.

CA19-9 is a prevalent tumor marker which is expressed in human tissues and could diagnose the tumor existence and progression specifically in pancreatic cancer. The high level of this tumor marker in patients whom the cancer is detected recently indicates the progression of the disease [11, 12]. The results of a meta-analysis study shows that the increased serum concentration of CA125 is concomitant of poorer overall survival in patients with gastric cancer and have a great role in determining the prognosis of the disease. Therefore, CA19-9 tumor marker could indicate the invasiveness of gastric cancer and could be a reliable criterion in the involved patients [13]. In one study, high concentration of CA19-9 tumor marker (0–37 U/ml) was found in 42% of the patients with gastric cancer. High level of this tumor marker existed mostly in the patients with metastatic cancer (85%), and only three individuals (15%) had no sign of metastasis [14]. In this study, serum level of CA19-9 at fourth stage of the disease was significantly higher than the second and third stages.

CA125 tumor marker is widely used in ovarian cancer detection. The increased level of this tumor marker is found

Table 3 Median values (P25–P75) of CA125 (U/mL), beta HCG (mIU/ml), AFP (IU/ml), CEA (ng/mL), and CA19-9 (U/mL) in different grades of cancer patients

Tumor markers	Low ($n = 20$)	Intermediate ($n = 27$)	High ($n = 34$)	p value
CEA	6 (1.6–10)	2.9 (0.95–8)	3.4 (1.7–17)	0.59
CA125	7 (3–19.97)	12 (4–24.5)	17.6 (10–130)	0.06
CA19-9	15.4 (3.95–42)	24 (8.3–71.7)	41.1 (9–265)	0.20
AFP	2.85 (1.5–3.7)	3 (1.8–6.3)	3.6 (1.7–60)	0.46
Beta HCG	1 (1–2)	1 (1–1.5)	1 (1–2)	0.58

in malignant tumors of pancreas, liver, yolk sac, stomach, colon, and lung [15]. It has been reported that serum level of CA125 tumor marker increases in advanced gastric cancers [16]. In the present study, a significant increase in plasma level of CA125 was found during the stage of metastasis (stage 4) compared with the early stages (stage 1 and 2). There is a remarkable relevance between CA125 and gastric cancer with peritoneal diffusion. Polat et al. showed that there is no significant correlation between serum levels of this tumor marker based on N, T, and M stages. However, in the presence of peritoneal carcinomatosis, the level of this tumor marker was extremely increased [17]. In another study, measuring the serum level of CA125 together with other tumor markers include CA19-9 had a high sensitivity in detection of gastric cancer peritoneal diffusion [18]. In another study, Hwang et al. showed that the average serum level of this tumor marker providing peritoneal metastasis is remarkably increased in patients with gastric cancer. Although this tumor marker is not suitable for diagnosis of gastric cancer due to its non-specificity but evaluating the serum level in suspected patients of peritoneal metastasis is highly effective before surgery and chemotherapy [19]. By evaluating the result of this study, it could be concluded that CA125 has a diagnostic value in determining the late stages of the disease and could be beneficial in selecting the utilization of other diagnostic methods including diagnostic laparoscopy and intra-peritoneal chemotherapy.

CEA is a prevalent tumor marker in gastrointestinal malignancies. It should be noted that there is a strong association between the overexpression of this tumor marker with cancer progression in patients [20]. Measuring the preoperative serum CEA level is so profitable in determining the gastric tumor prognosis [21, 22]. In the presence of distant metastases, CEA levels increase significantly [17]. Kochi et al. showed that the CEA serum level in the fourth stage is considerably higher than the other three stages. (Positive tumor markers in stage 4 was 53.9%, but in three other stages was 30%.) The results of this study indicated that liver, peritoneal, lymphatic, and distant metastasis in patients with gastric cancer and positive serum level of CEA tumor marker than other patients with negative serum level of this tumor marker is extremely increased [22]. In Ucar study, there was no relation between the positive serum level of this tumor marker and the stages of disease. Howsoever, in patients with liver metastases, CEA levels were intensively increased [23]. In the present study, there was no remarkable increase in CEA level with disease progression based on staging and grading.

HCG is expressed in a variety of gastrointestinal malignancies [24, 25]. Furthermore, older studies showed that the increased level of HCG is related to poor prognosis in advanced gastric cancer [26] and could be beneficial as an independent factor in determining the prognosis of the disease [27]. In this study, there was no substantial difference between the serum level of this tumor marker with disease staging and tumor grading. However, in another study, there was a significant correlation between tumor staging and increased positive level of this tumor marker (hCG > 2 pmol/L) [27].

One limitation of this study is the small sample size, and it is suggested that in the future, a larger sample size should be considered in order to confirm the results of this study.

Conclusion

According to our findings, CA19-9 and CA125 tumor markers in the patients involved in this study were remarkably higher than other tumor markers. There was no considerable difference between the serum level of tumor markers and tumor grading. Nevertheless, statistically substantial differences between AFP, CA125, and CA19-9 level with the staging of the disease were observed.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Abbreviations CEA, carcinoembryonic antigen; CA-125, cancer antigen 125; HCG, human chorionic gonadotropin; AFP, alpha-fetoprotein; CA 19-9, cancer antigen 19-9

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