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THE VALUE OF MEASURING ALPHA-FETOPROTEIN IN PATIENTS WITH GASTRIC CANCER

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ABSTRACT

Gastric cancers are among the most frequently diagnosed cancer in the world. Advances in preclinical diagnostic methods have been resulted in dramatic changes in determining the survival of patients. Evaluation of serum level of tumor markers is one of these methods. Tumor markers are substances that can often be detected in higher than normal amounts in blood, urine, or body tissues of some patients with certain types of cancer. In this study the samples were collected from two groups; the first group consisted of 30 healthy volunteers (14 female and 16 male) aged between 20-60 years (45.47 ± 10.87), the second group consisted of 16 patients with gastric cancer, aged between 45-70 years (61.75 ± 9.32) were classified according to presence of metastasis (4 cases), regional lymph nodes involvement (4 cases), patients with distant metastasis (5 cases) and lastly patients with recurrence after previous operation (3 cases). Histologically they were classified into patients with well differentiated adenocarcinoma (10 cases), and those with poorly differentiated adenocarcinoma (6 cases). AFP measured for both healthy and patients' groups and give a significant difference at $p< 0.01$ for serum level of AFP as mean ± SD between control and patients with gastric cancer. The sensitivity of AFP in patients with gastric cancer in all studied subjects was 43.75% which increased to 58.3% in patients with metastasis only. The mean value of serum AFP level was shown to be higher in patients with metastasis than those without metastasis, this level is independent to the site of metastasis. The difference in AFP level showed a significant difference at $p<0.05$ between them, with a higher level of AFP being detected in patients with liver metastasis. In comparing the results of AFP in different histological types of gastric cancer, the results show that patients with undifferentiated carcinoma did not have significant lower level of AFP than those with more differentiated cancer.

KEYWORDS: Alpha-Fetoprotein, Gastric Carcinoma, Hepatocellular Carcinoma, Tumor Markers.

INTRODUCTION

A very broad definition of a tumor marker is a tool that enables the clinician to answer clinically the relevant question regarding a cancer disease.[1]

Alpha-Fetoprotein (AFP) is a major protein of fetal serum that falls to an undetectable level after birth. The primary malignancies associated with AFP are hepatocellular carcinomas and non seminomatous germ cell tumor. Other gastro-intestinal cancers occasionally cause elevation of AFP, but rarely to greater than 1000 ng/ml.[2]

The first clinical case of AFP associated with gastric cancer was reported by Boureille and his associates in 1970, some other disease can also be related with elevated levels of AFP, gastric cancer is the fourth common causes of cancer death worldwide.[3]

AFP is a 70 KDa glycoprotein homologous to albumin.[4] Its level is higher in two-thirds of patients with hepatocellular cancer. It is also elevated in acute and chronic hepatitis but seldom above 100 ng/ml.

Pregnancy also associated with elevated AFP levels, particularly if the pregnancy is complicated by spinal cord defect or other abnormalities.[2]

Identification of tumor markers is becoming increasingly popular in clinical oncology as a non-invasive method for cancer diagnosis and for monitoring response to treatment; their use is simple and easily accepted by patient,[5] and the main goals of clinical use of tumor

markers are to evaluate the adequacy of the treatment, monitor recurrence and follow up response to the applied treatment.[6]

Diagnosing and screening tests require high sensitivity to detect also have sufficient specificity to protect patients with false-positive results from unwarranted diagnostic evaluations.[7]

Specificity is defined as proportion of negatives that are correctly identified by the test.[8]

In order to raise the sensitivity of the test the cut-off value used for that test has to be lowered to separate normal from abnormal persons. While this may raise the sensitivity, more false positives are generated, and specificity goes down.

Although AFP is a useful biomarker for predicting survival and detecting and/or monitoring hepatocellular carcinoma, its correlation with gastric cancer remains to be clarified [9], because of their lack of sensitivity and specificity as intentioned above, and because serum marker levels are rarely elevated in patients with early malignancy, tumor markers are usually not used to diagnose cancer.[10]

Clinical application of tumor markers in gastric cancer.

AFP producing gastric cancer has been reported all over the world, but mostly in Asia. The reported incidence was 6.63% in China.[11] Some of the widely used tumor markers, in case of gastric cancers, were originally discovered through immunological approaches. Carcino-Embryonic Antigen (CEA) is the most frequent tumor marker examined in gastric cancer. Other discovered markers, such as CA125, CA19-9 and Alpha-fetoprotein, are also reported to be useful for prognosis in gastric cancer.[12]

Furthermore, many cases of AFP-producing gastric cancer (AFPGC) characterized by increased level of AFP and positivity of gastric cancer have been reported.[13]

AFP, producing gastric cancer have been associated with a poor prognosis because of its high proliferative activity, weak apoptosis and rich neo vascularization, compared to that of AFP negative gastric cancer.[14]

MATERIALS AND METHODS

The subjects participated in this study were divided into two groups.

1- Control group (healthy subjects)
This group consists of 30 apparently, healthy volunteers included 14 females and 16 males, aged 20-70 years, with a mean ± SD of 45.47± 10.87, without any evidence of malignancy or any disease or confounding factors which could cause non-specific elevation in tumor markers level.

2- Patients group
This group included 16 subjects, who were histologically proved to have gastric cancer, aged between 45-70 years with ± SD of 61.751±9.32.

They are classified as follows
a) Presence or absence of metastasis
This group is classified into 4 categories according to the presence or absence of lymph node involvement and distant metastasis.
1) 4 Patients had no metastasis.
2) 4 Patients had lymph node invasion.
3) 5 Patients had metastasis to the liver.
4) 3 Patients had local recurrence.

b) Type of histopathology:
Histopathologically, the subjects of this group were divided into:
1. Poorly differentiated adenocarcinoma which includes 6 patients.
2. Well differentiated adenocarcinoma which includes 10 patients.

Materials
The variable measured in this study included serum level of AFP for controls, and for patients with gastric cancer. Serum AFP level was measured by immune radiometric assay by using AFP IRMA DSL-840 kit.

RESULTS

The demographic characteristics of studies groups are presented in table (1).

Table (1): Demographic characteristics of the studied groups.

Groups	**Parameters**		**Mean** ± SD
Control (n=30)	Age (year)		45.47±10.87
	Gender	Male	16 (53.3%)
		Female	14 (46.7%)
Stomach Cancer (n=16)	Age (year)		61.75±9.32
	Gender	Male	7 (43.75%)
		Female	9 (56.25%)

AFP has measured for both control and patients' groups. The results of serum level of AFP for both groups are presented as mean ± SD in table (2).

Table (2): Comparison of alpha-fetoprotein (ng/ml) of diseased groups with control group.

Cancer type	Diseased groups AFP (ng/ml)		Control		p-value
	n	Mean ± SD	n	Mean ± SD	
Stomach	16	107.55±202.45	30	5.15±3.73	<0.001

When AFP level in control group and diseased group were compared, a highly significant difference (P<0.001) was noticed between control group and patients with gastric cancer.

Sensitivity and specificity of AFP in all studied subjects with gastric cancer:

Sixteen patients with gastric cancer shared in this study, the sensitivity and specificity of AFP were preoperatively established by using 2×2 contingency table. The results are shown in table (3).

Table (3): Sensitivity and specificity of AFP in stomach cancer (No Metastasis).

Type	Metastasis	AFP (ng/ml)			
		>3		≤3	
		No.	%	No.	%
Stomach cancer	+	7	43.75	9	56.25
	-	0	0.0	30	100.0
Sensitivity		43.75%			
Specificity		100.0%			
p-value		<0.001			

Sensitivity of AFP in metastatic gastric cancer

The distribution of patients with gastric cancer according to presence or absence of metastasis was as follow: 4 cases with no metastasis, 5 cases with liver metastasis 4 cases with lymph nodes metastasis, and 3 cases with recurrence after surgery. The sensitivity of AFP in patients with metastasis has shown in table (4).

Table (4): Sensitivity of AFP in the diagnosis of metastasis.

Type	Metastasis	AFP (ng/ml)			
		>20		≤10	
		No.	%	No.	%
Stomach	+	7	58.3	5	41.7
	-	0	0.0	30	100
	Sensitivity	58.3%			
	p-value	<0.001			

From the results shown it has clear that the sensitivity of AFP was higher in patients with metastasis compared with that obtained by using all subjects.

Relationship between AFP with respect to the site of metastasis in gastric cancer:

The results according to the site of metastasis presented in table (5).

Table (5): Relationship between site of metastasis and the measured parameters in gastric cancer.

Parameters / Metastasis	Mean ± AFP ng/ml
No Metastasis	4.54±7.4
Liver	313.69±273.8
Lymph Nodes	1.73±1.2
Recurrence	42.43±34.8
p-value	<0.05

On comparing the results above, there was a significant difference (P<0.05) present in AFP serum level among different groups with highest level in patients with metastasis to the liver.

Relationship between different histological types of gastric cancer and serum level of AFP.

Table (6): Relationship between histological type and the measured parameters in gastric cancer patients.

Histopathology / Parameters	Mean ± SD		p-value
	Poorly Differentiated Adenocarcinoma (n=6)	Well Differentiated Adenocarcinoma (n=10)	
AFP (ng/ml)	38.77±43.91	185.87±268.54	NS (Non-Significant)

The results shown that patients with an undifferentiated tumor did not have significant lower serum level of AFP than those with more differentiated tumors.

DISCUSSION

Carcinoma of stomach is one of the most prevalent cancer types in the world today, only a limited number of biomarkers are available for the detection and prognostic evaluation of gastric cancer.[12]

The serum level of AFP has been widely used for hepatocellular carcinoma screening in patients with chronic liver disease.[15] Metachronous liver metastasis is higher in AFP producing gastric cancer patients.[16]

Many years ago, many cases of AFP producing gastric cancer, characterized by increased serum AFP levels have been reported,[13]

Sensitivity and specificity of AFP in gastric cancer:
In the present study, the serum level of AFP as a mean ISD is significantly higher in patients with gastric cancer than in the control normal subjects with a sensitivity in all studied patients (with and without metastasis) was 43.75%.

However, the sensitivity increases when calculated for patients with metastasis to only to become 58.3%. this increase in sensitivity suggesting that the serum levels of AFP would be an indicator of metastasis or recurrence.

When the levels of AFP were presented according to the site of metastasis, the mean ±SD levels of AFP is higher in patients with metastasis than those with no metastasis. This difference between different sites of metastasis being higher in patients with liver metastasis which may suggest that an increase in AFP serum level is an indicator for liver metastasis.

AFP in relation with histological types of gastric cancer

Histological typing and histopathological grading allow the clinician to be more specific in characterizing gastric cancer and to predict a prognosis. The histological classification of gastric tumor developed by Lauren in 1965 has been used most often during the past several years. It distinguishes gastric carcinomas by dividing then into two types. The intestinal (or well-differentiated) type of tumor and the diffuse (or undifferentiated) type.[17]

In order to evaluate the correlation of serum tumor markers (CEA and AFP) with histological type in patients with gastric cancer,[18] established study in which they reported that patients with undifferentiated carcinoma did not have significant difference in serum CEA and AFP levels with those with well differentiated carcinoma.

Also reported that serum levels of tumor markers (CA19-9, CA72-4, CEA, and AFP) showed no correlation the histology of the tumor in gastric carcinoma.[19]

In the present study, the mean ISD of AFP shows no significant differences between the two histological types of tumor and these results were consistent to those stated by Wobbes et al., and Matter et al.[18,19]

CONCLUSION

1. The sensitivity for the detection of the early gastric cancer by tumor markers AFP is low. This sensitivity is higher in patients with an advanced disease and is related to the site of metastasis.
2. There is no correlation between histological type of gastric cancer and the level of AFP.
3. There is a strong correction between high serum level of AFP and liver metastasis in patients with gastric cancer.

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