RESEARCH ARTICLE

Impact of Various Tumor Markers in Prognosis of Gastric Cancer. A Hospital Based Study from Tertiary Care Hospital of Kathmandu Valley

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Abstract

Background: To obtain the maximum additional information about the prognosis of gastric cancer, we compared CA-50 with other previously defined markers. Materials and Methods: This hospital based study was carried out in the Department of Biochemistry of Nepalese Army Institute of Health Sciences between 1st July 2012 and 31st December 2012. The variables collected were age, gender, AFP, CEA, CA19-9, and CA50, assayed with ELISA reader for all cases. The cut off values for serum AFP, CEA, CA19-9, and CA-50 were 10 µg/l, 10 µg/l, 37 U/ml, and 20 U/ml, respectively according to the manufacturer's instructions. Approval for the study was obtained from the institutional research ethical committee. Results: Of the 40 examined patients, 13 patients had tumors located in the upper third of the stomach, 6 patients had tumors in the middle third, 16 patients had tumors in the lower third, and 5 patients had tumors occupying two-thirds of the stomach or more. The distribution of lymph node staging of the patients was as follows: 7 patients belonged to N0, 9 patients to N1 stage, 10 patients to N2 stage, and 14 patients to N3 stage. The statistical method of Cox proportional hazards using multivariate analysis also illustrated that tumor markers including CEA (2.802), CA19-9 (2.690), CA50 (2.101), were independent prognostic factors, as tumor size (1.603), and lymph node stage (1.614). Conclusions: The tumour markers now available, like CEA, CA 19-9 and CA 50, chiefly perceive advanced gastric cancer. The preoperative rise in those tumour marker level have a prognostic significance and may be clinically helpful in choosing patients for adjuvant management.

Keywords: Tumor markers - gastric cancer - Kathmandu Valley

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Introduction

Gastric cancer was the fourth frequent cancer worldwide, and it was the subsequent most widespread basis of fatality from cancer. Gastric cancer is a multifactorial neoplastic pathology numbering among its causes both and genetic predisposing factors (Dikshit et al., 2011). Quite a lot of environmental factors are supposed to play a part in the development of gastric cancer such as diet rich in salted, smoked food exogenous chemicals and poor in fresh fruit and vegetables (Zagari et al., 2004). Highest morbidity percentages of gastric cancer are in South America and South-East Asia and it is comparatively barely diffused in Western countries and North America (Bertuccio et al., 2009).

Serum tumor markers including alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen CA 19-9, and CA-50, have found to be raised in clinical or pathological stages of gastric cancer (Ishigami et al., 2001). CEA is a multifarious glycoprotein produced by gastric cancer and have a say to the malignant distinctiveness of a tumor. It can be measured in serum quantitatively, and its level in plasma can be useful as a marker of disease. An elevated preoperative CEA is a poor predictive sign and associates with reduced overall survival after surgical resection of gastric carcinoma (Schauer et al., 2011). Because of its lack of sensitivity in the early stages of gastric carcinoma, CEA alone measurement is an unsuitable modality. Carbohydrate antigen 19-9 has recently been found to be raised in digestive tract malignancies, pancreatic and hepatobiliary malignancies (Kato et al., 2011). Even though no serological tumor marker has so far been amply sensitive and specific to be used in screening for colorectal, gastric, or pancreatic cancers, elevated pre-operative levels of carcinoembryonic antigen and carbohydrate antigen (CA) 19-9 correlate with advances stages of disease and a poorer clinical outcome. CA 50 is also not organ-specific and its elevated levels in serum can be observed in a variety of malignancies, especially gastrointestinal cancers

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(Kokociñska et al., 1996). Therefore, in our present study, in order to obtain the maximum additional information about the prognosis of gastric cancer, we compare CA-50 with other previously defined markers.

Materials and Methods

It was a hospital based study carried out in the Department of Biochemistry of Nepalese Army Institute of Health Sciences between 1st July 2012 and 31st December 2012. The variables collected were age, gender, AFP, CEA, CA19-9, and CA50. The approval for the study was obtained from the institutional research ethical committee. AFP, CEA, CA19-9, and CA50 were assayed with ELISA reader for all cases. The cut off value for serum AFP, CEA, CA19-9, and CA-50 were 10 µg/l, 10 µg/l, 37 U/ml, and 20 U/ml, respectively according to the manufacturer's instructions (Herberman et al., 1977).

The TNM staging classification for carcinoma of the stomach was done according to the American Joint Committee on Cancer (AJCC) (Sun et al., 2012).The association between tumor markers and clinicopathological factors was evaluated by Chi-square test. The 5-year survival rates were calculated by Kaplan-Meier method (Jager et al., 2008). The independent prognostic value of tumor markers and clinicopathological features was analyzed by Cox proportional hazards model Cox (1972). Differences were considered statistically significant when p Value was <0.05. The data was analyzed using Excel 2003, R 2.8.0 Statistical Package for the Social Sciences (SPSS) for Windows Version 16.0 (SPSS Inc; Chicago, IL, USA) and the EPI Info 3.5.1 Windows Version.

Results

Of the 40 examined patients, 13 patients had tumors located in the upper third of the stomach, 6 patients had tumors in the middle third, 16 patients had tumors in the lower third, and 5 patients had tumors occupying two-thirds of the stomach or more.

Table 1 showed that the distribution of lymph node staging of the patients was as follows: 7 patients belonged to N0, 9 patients to N1 stage, 10 patients to N2 stage, and 14 patients to N3 stage. Further , the factors such as gender , age, tumor site, tumor size, lymph node stage , showed the various percentage of patients having positive tumors markers (AFP, CEA, CA19-9, and CA50).

Table 2 illustrated that that there was a noteworthy disparity in 5-year overall survival in terms of tumor markers and distinct clinicopathologic factors, which incorporated AFP (0.001*), CEA (0.001*), CA19-9 (0.001*), and CA50 (0.001*) and gender (0.978), age (0.041*), tumor size (0.002*), tumor site (0.007*), lymph node stage (0.001*), according to univariate analysis. The 5-year survival was reduced in patients with elevated AFP (p=0.001*), CEA (p=0.001*), CA19-9 (p=0.001*), or CA50 (p=0.001*), compared with those patients with standard levels of tumor markers.

Table 3 depicted that subjects with high levels of CEA, CA19-9, and CA50 had a less survival rate and higher chances of mortality than patients with low levels of these markers. The statistical method of Cox proportional hazards using multivariate analysis also illustrated that tumor markers including CEA (2.802),CA19-9 (2.690),

Table 1. Percentage of Serum Tumor Markers According to Clinicopathologic Factors of Gastric Cancer Patients

Factors (n)	AFP(+) n (%)	CEA(+) n (%)	CA19-9(+) n (%)	CA50(+) n (%)
Sex (40)				
Male (27)	4(14.80)	5(18.50)	12(44.40)	10(37.00)
Female (13)	1 (7.60)	2(15.30)	4(30.70)	3(23.10)
Age				
≤40 (6)	1(16.60)	1(16.60)	3(50.00)	3(50.00)
>40 (34)	2 (5.80)	6(17.60)	13(38.20)	11(32.30)
Tumor site				
Upper (13)	2(15.30)	3(23.07)	4(30.70)	4(30.70)
Middle (6)	1(16.60)	2(33.30)	2(33.30)	3(50.00)
Lower (16)	3(18.75)	4(25.00)	5(31.25)	6(37.25)
≥2-3 (5)	3(60.00)	4(80.00)	4(80.00)	4(80.00)
Tumor size				
≤6 (30)	2 (6.60)	5(16.60)	8(26.60)	12(40.00)
>6 (10)	1(10.00)	2(20.00)	4(40.00)	4(40.00)
N stage				
N0 (7)	0 (0)	1(14.20)	1(14.20)	2(28.50)
N1 (9)	1(11.10)	2(22.20)	3(33.30)	3(33.30)
N2 (10)	1(10.00)	2(20.00)	3(30.00)	3(30.00)
N3 (14)	1 (7.10)	3(21.40)	6(42.80)	7(50.00)

Table 2. Univariate Analysis Envisage 5-year Survival for All Factors

Factors (n)		5-year survival (%)	p value
AFP	≥10 µg/l (5)	24.8	0.001*
	<10 µg/l (35)	39.2	
CEA	≥10 µg/l (8)	11.2	0.001*
	<10 µg/l (32)	42.8	
CA19-9	≥37 U/ml (14)	9.9	0.001*
	<37 U/ml (26)	52.2	
CA50	≥20 U/ml (17)	14.2	0.001*
	<20 U/ml (23)	47.9	
Sex (40)	Male (27)	37.9	0.978
	Female(13)	36.8	
Age	≤40(6)	22.8	0.041*
	>40(34)	40.2	
Tumor site	Upper (13)	33.9	0.007*
	Middle (6)	34.2	
	Lower (16)	43.1	
	≥Two-third(5)	13.8	
Tumor size	≤6(30)	43.1	0.002*
	>6(10)	28.3	
N stage	N0 7	66.8	0.001*
	N1 9	52.8	
	N2 10	43.8	
	N3 14	18.2	

Table 3. Autonomous Predictive Factors at Multivariate Analysis by Cox Model

Factors	Hazard ratio	95% CI	p Value
CEA	2.802	1.769-4.299	0.001*
CA19-9	2.690	1.589-4.665	0.001*
CA50	2.101	1.197-3.498	0.001*
Tumor size	1.603	1.137-2.209	0.001*
pN stage	1.614	1.378-1.899	0.001*

CA50 (2.101), were independent prognostic factors, as tumor size (1.603), and lymph node stage (1.614).

Discussion

There have been some studies on the prognostic impact of tumor markers in gastric cancer, but rarely have the previous studies evaluated the prognostic impact of tumor markers when specific depth of invasion was involved. We found that the serum levels of AFP, CEA, CA19-9, and CA50 were significantly correlated with survival rate in patients with gastric cancer. These correlations indicated that patients with positive values of tumor markers have worse prognosis. In our present of study, there was overrepresentation of males(27) and the underrepresentation of females (13) in cases of gastric cancer. The sex-bound differences in the tumour pathogenesis may be due to differences in the environment factors, in the dietary habits, metabolic differences and effects of sex hormones (Sipponen et al., 1988). There was significant difference in 5 year survival rate for AFP with levels ≥10 (24.8%) in comparison to levels <10 (39.2%). There was a higher frequency of lymph node metastasis, a deeper incursion of the gastric wall in the AFP(+) group than in the AFP(-) group. These results concurred with the findings of Kono (Kono et al., 2002). The expression levels of serum CEA and CA19-9 were closely related to tumor invasion, lymph node metastasis and TNM stage. The 5-year cumulative survival rates of patients with serum CEA-positive and CA19-9-positive were 11.2% and 9.9%, compared with 42.8% and 52.2% of the patients with serum CEA-negative and CA19-9-negative respectively (both p value <0.05). The high CEA levels interrelated well with gender, hepatic, peritoneal, and nodal metastases and the depths of tumors, but it was allied unconvincingly with a tumor's histological type. The elevated CA 19-9 levels have been significantly correlated with lymph node metastasis, vascular invasion and liver metastasis (Kodera et al., 1996). CA19-9 was a high molecular weight mucin that participates a role in the adhesion of cancer cells to endothelial cells. Similarly CA-50 , the 5-year cumulative survival rates of gastric cancer patients with serum CA-50 positive were 14.2% compared with 47.9% of the patients with serum CA-50 negative (Kuusela et al.,1987). Thus, the main findings of this study were that tumor markers such as CEA, CA19-9, and CA50 were independent prognostic factors for gastric cancer; and there were significant differences of overall 5-year survival rate when compared in between high and normal levels of tumor markers. Conclusion: The tumour markers accessible nowadays like CEA, CA 19-9 and CA 50, chiefly perceive advanced gastric cancer. The preoperative rise in those tumour marker level have a prognostic significance and may be clinically helpful in choosing patients for adjuvant management.

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