Original Article

Diagnostic sensitivity of serum carcinoembryonic antigen, carbohydrate antigen 19-9, alpha-fetoprotein, and beta-human chorionic gonadotropin in esophageal carcinoma (receiver operating characteristic curve analysis)

Bhawna Bagaria, Ashish Bagaria[1], Mamta Singh[2], Rameshwaram Sharma[3]

Department of Biochemistry, SDM Hospital, Departments of [1]Pathology and [3]Radiotherapy and Oncology, SMS Medical College and Hospital, [2]Department of Biochemistry, Mahatma Gandhi Medical College and Hospital, Jaipur, India

ABSTRACT

Background: Esophageal carcinomas are very lethal disease relatively unresponsive to therapy. The continued development of new and more effective chemotherapeutic agents and regimens offers hope that in the future, this carcinoma may be amenable to either more effective palliative treatment or possibly increased cure. We, therefore, aimed to evaluate the marker with best diagnostic sensitivity in esophageal carcinoma. **Materials and Methods:** Serum carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), alpha-fetoprotein (AFP), and beta-human chorionic gonadotropin (β-HCG) levels were assessed in healthy subjects ($n = 50$) and patients ($n = 50$) initially diagnosed of esophageal carcinoma by endoscopic examination and biopsy before receiving any therapy. The data were analyzed using SPSS software version 10.0 (SPSS Inc. USA) and MedCalc to estimate mean ± standard deviation, the significance of the observed differences (P value), for calculating sensitivity and for plotting receiver operating characteristic curves. **Results:** Sensitivity of CEA, CA19-9, AFP, and β-HCG detected in esophagus cancer was 38%, 18%, 10%, and 26% respectively. **Conclusion:** From the above studied markers, CEA has the highest sensitivity followed by β-HCG, CA19-9 and AFP. Although the sensitivity of tumor markers in esophagus cancer is low, they may be useful additional parameter in the prediction of neoplasms involved at the early stage of tumor growth.

Key words: Alpha-fetoprotein, beta-human chorionic gonadotropin, carbohydrate antigen 19-9, carcinoembryonic antigen, esophageal carcinoma

INTRODUCTION

Esophageal cancers are typically carcinomas which arise from the epithelium or surface lining, of the esophagus. Most esophageal cancers fall into one of the two classes: Squamous cell carcinoma (approximately 90–95% of all esophageal cancer worldwide) and adenocarcinoma (approximately 50–80% of all esophageal cancer in the United States). In Indian scenario, Esophageal Cancer is the second and fifth most common cancer in males and females, respectively.[1] Prevalence of squamous cell carcinoma is much higher (92.51%) than adenocarcinoma (7.35%).[2] As compared to USA high incidence of esophageal cancer were observed in Indian population. It was seen that incidence rates of 7.6 and 5.1 of esophageal cancer (in a population of 100,000 persons) of males and females were observed in India as compared to USA (4.9 and 1.4) for males and females, respectively. This can be attributed to the extensive use of tobacco by Indians in the form of Pan, Masala, Gutka, Zarda, etc.[3]

Squamous cell cancer arises from the cells that line the upper part of the esophagus they are similar to head

Access this article online

Quick Response Code:

Website: www.ccij-online.org

DOI: 10.4103/2278-0513.154279

Address for correspondence: Dr. Bhawna Bagaria, Department of Biochemistry, SDM Hospital, Mansarovar, Jaipur, India.
E-mail: bhawna_bagaria@yahoo.com

and neck cancer in their appearance and associated with tobacco and alcohol consumption. Adenocarcinoma arises from glandular cells that are present at the junction of the esophagus and stomach they are often associated with a history of gastroesophageal reflux disease and Barrett's esophagus.[4] Most of the people diagnosed with esophageal cancer have late-stage disease, because people usually do not have significant symptoms until half of the inside of the esophagus, called the lumen, is obstructed, by which point the tumor is fairly large. If the disease has spread elsewhere, this may lead to liver and lung metastasis. Advanced age, abnormal lung function, and poor performance status are reported to contribute to postoperative pulmonary complications.[5]

In general, the prognosis of esophageal cancer is quite poor because most patients are present with advanced disease. The underlying reasons for this disappointingly low survival rate are multifold: (a) Ineffective screening tools and guidelines (b) cancer detection at an advanced stage, with over 50% of patients with unresectable disease or distant metastasis at presentation (c) high risk for recurrent disease after esophagectomy or definitive chemoradiotherapy (d) unreliable noninvasive tools to measure complete response to chemoradiotherapy and (e) limited survival achieved with palliative chemotherapy alone for patients with metastatic or unresectable disease. Clearly, additional strategies are needed to detect esophageal cancer earlier and to improve our systemic treatment options.[6] In our study however, used as a research tool, it allowed us to evaluate the role of carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (β-HCG) values in the detection of esophagus cancer.

A clear correlation was seen between the degree of tumor differentiation and CEA expression for carcinomas of the esophagus, stomach and colon, the potential usefulness of CEA for monitoring the recurrence of gastric or esophageal tumors was established. CEA is primarily used to monitor cancer treatment, including response to therapy and recurrence, as an indicator of the amount of cancer or size of tumor present (tumor burden) and to assist in determining prognosis, it is used occasionally when cancer is suspected but not confirmed to aid in its detection.[7] The immunohistological distribution of CA19-9 in tissues is consistent with the quantitative determination of higher CA19-9 concentrations in cancer than in normal or inflamed tissues. Research studies demonstrate that serum CA19-9 values may have utility in monitoring subjects with gastrointestinal malignancies. The presence of CA19-9 in tumors was reported to be related to tumor cell adhesion and tumor cell-induced platelet aggregation.[8]

Alpha-fetoprotein is considered as one of the several tumor markers, elevated levels in adults of which can be indicative of metastatic cancers of the liver. HCG is a glycoprotein synthesized by normal placenta and released by the trophoblastic cells and different neoplastic cells. HCG is associated with esophagus squamous cell carcinoma as well as the esophagus adenocarcinoma and to preneoplastic lesions. The characteristics of this tumor marker permit the monitoring and evaluation of the treatments observed.[9] Tumor cells that expressed β-HCG often showed immunoreactivity for vascular endothelial growth factor (VEGF), and the two markers were often co-localized in the same tumors, a positive link between β-HCG and VEGF expression in Barrett's adenocarcinoma of esophagus, were observed.[10]

We therefore aimed to evaluate the diagnostic sensitivity of serum CEA, CA19-9, AFP, and β-HCG in patients suffering from esophageal cancer and to find out which marker has the best diagnostic sensitivity in the initial diagnosis.

MATERIALS AND METHODS

Study subjects

This study was conducted in the Department of Biochemistry, in association with the Department of Radiotherapy and Oncology, SMS Medical College and attached Hospitals, Jaipur, India from July 1, 2011 to June 30, 2012 after obtaining approval from the Institutional Research Committee and written informed consent from the patients. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation.

Totally, 50 clinically diagnosed patients with esophagus cancer participated in the study. 50 healthy accompanying subjects without a history of gastrointestinal disorders or endocrine illness, matched with the study group were used as controls. Patients and healthy subjects were screened with a specially designed screening proforma which encompassed the entire inclusion and exclusion criteria.

The diagnosis of cancer was done by the clinician viewing reports of biopsy, upper gastrointestinal radiography, fiber optic esophagoscopy, computed tomography, chest X-ray, and ultrasonography.

Selection criteria

Experimental group

Inclusion criteria

Patients of both genders with biopsy-proven esophagus cancer not received any therapy yet.

Exclusion criteria

Patients diagnosed long time back and previously treated with surgery, chemotherapy or radiotherapy, subjects

having history of any gastrointestinal, hepatic disorders, patients with significant physical illness, history of smoking, alcohol or any other substance abuse within the past 6 months, treatment with anti-inflammatory or immunosuppressive medication, pregnancy or lactating females.

Control group

Healthy subjects those willing to participate in the study and able to understand the nature of the study.

Collection and analysis of blood samples

In a calm and comforting environment, the subjects were explained about the various aspect of the study helping them to understand the purpose of the study and the nature of the forthcoming procedures. Blood was collected in plain vial. Serum was separated from the clotted specimen by centrifugation and subjected for following estimations:

Tumor markers

- CEA
- CA19-9
- AFP
- β-HCG

Statistics

Data analysis

The data were analyzed using SPSS software version 10.0 (SPSS Inc. USA) and MedCalc to estimate mean ± standard deviation (SD), the significance of the observed differences (*P* value), for calculating sensitivity and negative predictive value (NPV) at 100% specificity levels, and for plotting receiver operating characteristic (ROC) curves.

The diagnostic performance of a test or the accuracy of a test to discriminate diseased cases from normal cases was evaluated using ROC curve analysis. In ROC curve, the true positive rate (sensitivity) is plotted in function of the false positive rate (100-specificity) for different cut-off points. A test with perfect discrimination (no overlap in the two distributions) has a ROC curve that passes through the upper left corner (100% sensitivity, 100% specificity). Therefore the closer the ROC curve is to the upper left corner, the higher the overall accuracy of the test.[11] To demonstrate the accuracy, area under curve (AUC) were calculated. ROC analysis was done on 100% specificity level comparing the performance of single tumor markers in control subjects and patients of esophagus cancer. NPV was defined as a percentage of true-negative assays among all negative assays.

RESULTS

Table 1a: Gives comparison of age, sex of healthy control subjects and esophagus cancer patients. In our study, maximum patients of esophagus cancer were below 60 years. Males had higher prevalence than females.

Table 1b and c: Gives mean ± SD and *P* value of tumor markers in the control group and esophagus cancer group before therapy respectively. Mean serum value of CEA in esophagus cancer patients was significantly higher as compared to healthy control subjects. Mean serum value of CA19-9 and AFP was "not" significantly higher as compared to healthy control subjects. Mean serum value of β-HCG was significantly higher, as compared to healthy control subjects.

Table 2: Gives clinicopathologic characteristics (squamous cell carcinoma and adenocarcinoma) of Esophagus cancer patients.

Figures 1-4 gives sensitivity, AUC, standard error (SE), 95% confidence interval (CI), and significance level P of CEA, CA19-9, AFP, and β-HCG in esophagus cancer.

Table 1a: Comparison of age, sex of healthy control subjects and esophagus cancer patients

Variable	Control	Esophagus cancer	χ^2 (df)	*P*
Age				
<60	41	39	0.250 (1)	0.617
≥60	9	11		
Sex				
Male	25	28	0.361 (1)	0.548
Female	25	22		

Table 1b: Mean±SD value of tumor markers in the control group and esophagus cancer group

Group	CEA	CA19-9	AFP	β-HCG
Control group	2.23±0.82 (0.96-3.34)	17.18±8.49 (6.071-34.85)	2.12±1.02 (0.83-4.90)	2.35±1.48 (0.78-5.29)
Esophagus cancer	5.57±5.98 (1.11-28.70)	21.70±13.73 (7.17-71.27)	2.90±2.89 (1.23-16.85)	4.99±7.13 (1.01-31.57)

CEA: Carcinoembryonic antigen, CA19-9: Carbohydrate antigen 19-9, AFP: Alpha-fetoprotein, β-HCG: Beta-human chorionic gonadotropin, SD: Standard deviation

Table 1c: *P* value of tumor markers in control group versus esophagus cancer group

Group	CEA		CA19-9		AFP		β-HCG	
Cancer versus control	*t*	*P*	*t*	*P*	*t*	*P*	*t*	*P*
Esophagus cancer versus control	3.911	0.00	1.980	0.05	1.781	0.07	2.562	0.01

CEA: Carcinoembryonic antigen, CA19-9: Carbohydrate antigen 19-9, AFP: Alpha fetoprotein, β-HCG: Beta-Human chorionic gonadotropin

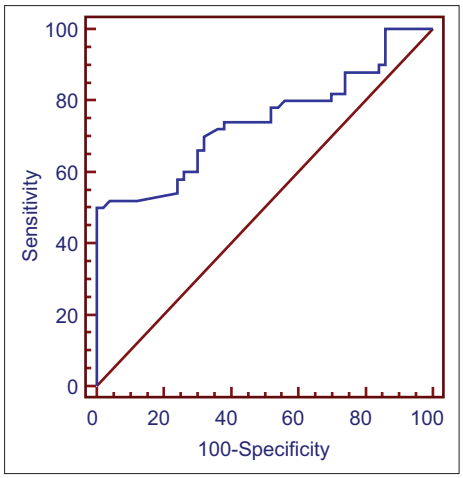

Figure 1: Carcinoembryonic antigen (CEA) in esophagus cancer. Sensitivity of CEA detected in esophagus cancer was 38%, negative predictive value = 61.72%, area under curve 0.742 (standard error = 0.05), 95% confidence interval (0.64–0.82), and significance level *P* < 0.0001

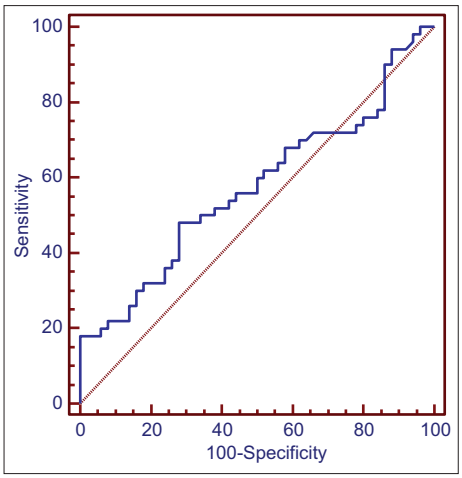

Figure 2: Carbohydrate antigen 19-9 (CA19-9) in esophagus cancer. Sensitivity of CA19-9 in esophagus cancer was 18%, negative predictive value = 54.94%, area under curve 0.573 (standard error = 0.05), 95% confidence interval (0.47–0.67), and significance level *P* = 0.2054

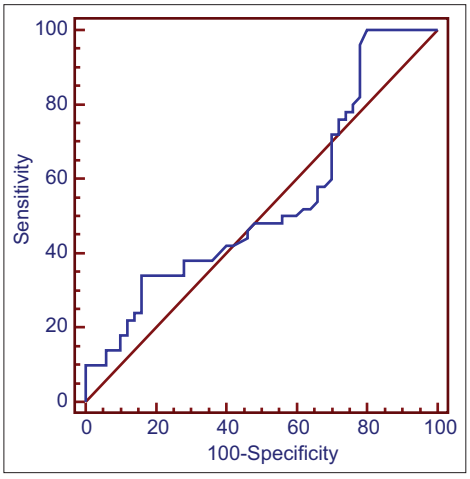

Figure 3: Alpha-fetoprotein (AFP) in esophagus cancer. Sensitivity of AFP detected in esophagus cancer was 10%, negative predictive value = 52.63%, area under curve 0.540 (standard error = 0.05), 95% confidence interval (0.43–0.64), and significance level *P* = 0.4925

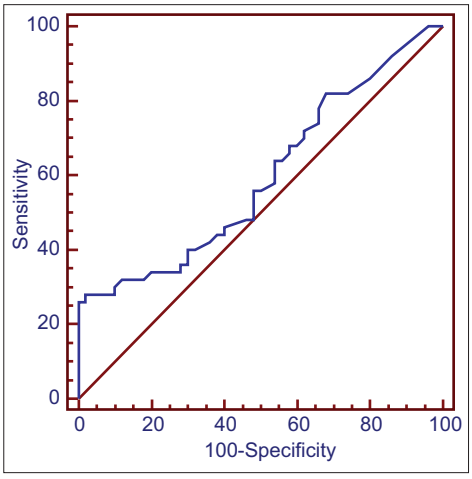

Figure 4: Beta-human chorionic gonadotropin (β-HCG) in esophagus cancer. Sensitivity of β-HCG in esophagus cancer was 26%, negative predictive value = 57.47%, area under curve 0.595 (standard error =0.05), 95% confidence interval (0.49–0.69), and significance level *P* = 0.0975

Table 2: Clinicopathologic characteristics of esophagus cancer patients

Clinicopathologic characteristics	Esophagus cancer
Histopathology squamous cell carcinoma	44
Well differentiated	9
Moderately differentiated	29
Poorly differentiated	6
Adenocarcinoma	6
Well differentiated	1
Moderately differentiated	4
Poorly differentiated	1

DISCUSSION

Sensitivity of CEA detected in esophagus cancer was 38%, NPV = 61.72%, AUC 0.742 (SE = 0.05), 95% CI (0.64–0.82) and significance level *P* < 0.0001 [Figure 1]. CEA sensitivity detected in esophagus cancer in our study was higher than previous studies done by Mao *et al.*, and Schneider *et al.*, they reported CEA sensitivity of 29.1% and 24%, respectively.[12,13] Our results were inconsistent with Choudhary *et al.*, they reported sensitivity of CEA 41.6% in esophagus cancer.[14] Kim *et al.*, evaluated an elevated serum CEA level enabled early detection of relapse in the absence of clinical symptoms in patients with adenocarcinoma of the esophagus or the stomach.[15] The level of CEA was useful in monitoring the response to chemotherapy in patients who had a high CEA level before treatment.

This oncofetal antigen is a glycoprotein with a molecular weight of 200,000 kDa located on the luminal surface of the tumor cell membrane of endodermal as well as nonendodermal origin. In well-differentiated cancer cells, CEA is expressed on the cell membrane, whereas in poorly differentiated cancer cells, CEA is distributed over the entire

cell surface and within the cytoplasm. CEA modulates intercellular adhesion and is involved in epithelial cell interactions with collagen. When free in circulation, CEA acts as an aggregant which facilitates entrapment of circulating tumor cells within the microvasculature of the liver. Tumors which produce CEA have a higher rate of metastatic implantation within the liver, as opposed to other sites. Due to its structural similarity to Igs CEA has been found to inhibit T-B cell cooperation, induce suppressor T-cell activity and inhibit natural killer cell cytolysis. For all these reasons, an elevated serum CEA level, while reflecting a poor prognosis on the basis of an increased tumor load may also be directly contributing to tumor metastatic potential.[16]

Sensitivity of CA19-9 in esophagus cancer was 18%, NPV = 54.94%, AUC 0.573 (SE = 0.05), 95% CI (0.47–0.67) and significance level $P = 0.2054$ [Figure 2]. CA19-9 sensitivity reported in our study was contradictory to results of Mealy *et al.*, they reported CA19-9 sensitivity of 34% in esophagus cancer patients. Our results were inconsistent with results obtained in cancer research, 2011.[17,18] CA19-9 is a ganglioside-containing sialylated lacto-N-fucopentaose II structurally related to Lewis-a blood group substance. It binds to endothelial cell surface receptors E-selectin and P-selectin activated by some cytokine which supports the idea that CA19-9 may actually play a role in adhesion of cancer cells to endothelial cells, resulting in hematogenous metastasis.[19] Very small amounts of CA19-9 may be found in healthy patients, making it useful as a tumor marker to follow the course of cancer.[20] Atila Turkyilmaz *et al.*, found a significant relationship between CA19-9 levels in esophagus cancer patients with liver metastasis and the pancreatic invasion. CA19-9 levels were significantly higher in patients with the pancreatic invasion compared to patients without the pancreatic invasion. There was a significant difference in CA19-9 levels between the group with liver metastasis and the group with the pancreatic invasion.[21]

Sensitivity of AFP detected in esophagus cancer was 10%, NPV = 52.63%, AUC 0.540 (SE = 0.05), 95% CI (0.43–0.64), and significance level $P = 0.4925$ [Figure 3]. AFP sensitivity detected in esophagus cancer in our study was very low which means having no utility in the initial diagnosis. Chiba *et al.*, evaluated increasing number of AFP producing carcinomas of the gastrointestinal tract in recent years. Most are gastric adenocarcinomas, whereas esophageal tumors are relatively few. Primary hepatoid adenocarcinomas are a subtype of AFP-producing adenocarcinoma, which can be seen in a pure form or association with ordinary adenocarcinoma in the upper gastrointestinal tract.[22,23] Shimakawa *et al.*, described a case of an AFP-producing esophageal adenocarcinoma with a number of metastatic liver deposits, suggesting the tumor is highly metastatic to the liver, interestingly two out of the four cases, reported by Inoue *et al.*, and Shimakawa *et al.*, were derived from Barrett's epithelium.[24,25]

Sensitivity of β-HCG in esophagus cancer was 26%, NPV = 57.47%, AUC 0.595 (SE = 0.05), 95% CI (0.49–0.69) and significance level $P = 0.0975$ [Figure 4]. β-HCG sensitivity detected in esophagus cancer was similar to results of Couvelard *et al.*, they studied that β-HCG was expressed in several nontrophoblastic tumors, and this was usually associated with aggressive behavior. A statistical link between β-HCG expression and infiltrative tumor type, perineural neoplastic invasion and VEGF protein expression was studied, β-HCG expression tended to be associated with a poor outcome. Both molecules play a co-ordinated role in the development of Barrett's adenocarcinomas of esophagus.[10]

William Regelson gave the concept that β-HCG gene expression was mediated by patterns of methylation. *In vitro*, HCG's presence can stimulate tumor cell growth. In addition, it was found that epidermal growth factor can stimulate cytotrophoblast invasion and HCG synthesis in choriocarcinoma cells. Placentation, differentiation, development, and malignant transformation apparently occurred under the same genetic and biochemical pathways, there was ample evidence that part of its role was the same as that of HCG in the trophoblast and fetoplacental unit, that is, to make a cell immunologically inert.[26] Louhimo *et al.*, observed elevated levels of β-HCG in gastrointestinal malignancies and found it may be a useful tumor marker for gastrointestinal cancers.[27]

Combined AFP and β-HCG testing is an essential adjunct in the evaluation and treatment of nonseminomatous germ cell tumors, and in monitoring the response to therapy. AFP and β-HCG may also be useful in evaluating potential origins of poorly differentiated metastatic cancer. Normalization of tumor marker values may indicate cure despite radiographic evidence of persistent disease. However, a consistent increase in tumor marker levels, coupled with the lack of clinical improvement, may indicate treatment failure and usually indicates persistent disease. Following tumor marker response is particularly useful when other evidence of disease is not readily accessible.[28]

CONCLUSION

Researches done previously indicated recurrent cancer may be detected earliest if both frequent clinical examination and serial tumor markers tests are utilized. In our study, CEA had the highest sensitivity followed by β-HCG, CA19-9, and AFP in detection of esophageal carcinoma.

These markers may be useful as a first-line surveillance investigation in patients using temporal trends in conjunction with clinical, radiological, and/or histological confirmation allowing more appropriate selection of initial treatment.

ACKNOWLEDGMENT

We express our sincere thanks to the Cancer Radiotherapy Department, SMS Medical College and Hospital, Jaipur, India for providing their help in above study.

REFERENCES

1. Nandkumar MA, Yamato M, Kushida A, Konno C, Hirose M, Kikuchi A, *et al.* Two-dimensional cell sheet manipulation of heterotypically co-cultured lung cells utilizing temperature-responsive culture dishes results in long-term maintenance of differentiated epithelial cell functions. Biomaterials 2002;23:1121-30.
2. Khan NA, Maqbool LM, Afroz F, Kharadi MY. Clinico-pathological profile of carcinoma esophagus and esophagogastric junction in Kashmir. JK Pract 2004;11:182-5.
3. Ali I, Wani WA, Saleem K. Cancer scenario in India with future perspectives. Cancer Ther 2011;8:56-70.
4. Halperin EC, Perez A, Brady LW. Perez and Brady's Principles and Practice of Radiation Oncology. Philadelphia: Lippincott Williams and Wilkins; 2008. p. 1137.
5. Law S, Wong KH, Kwok KF, Chu KM, Wong J. Predictive factors for postoperative pulmonary complications and mortality after esophagectomy for cancer. Ann Surg 2004;240:791-800.
6. Tew WP, Kelsen DP, Ilson DH. Targeted therapies for esophageal cancer. Oncologist 2005;10:590-601.
7. Common Cancers and the Tumor Markers Linked to them. American Cancer Society; 2012. Available from: http://www.cancer.org/acs/groups/cid/documents/web content/003189-pdf.pdf. [Last accessed on 2012 Oct]
8. Martini F, Guadagni F, Lenti L, D'Alessandro R, Aloe S, Roselli M, *et al.* CA 19-9 monosialoganglioside content of human colorectal tumor cells correlates with tumor cell-induced platelet aggregation. Anticancer Res 2000;20:1609-14.
9. Vegh I, Flores AI. Esophageal Cancer Cell and Molecular Biology, Biomarkers, Nutrition and Treatment. Biomarkers Stem Cells and Esophageal Cancer; 2012. Available from: http://www.intechopen.com/books/esophageal-cancer-cell-andmolecular-biology-biomarkers-nutrition-and-treatment/biomarkers-stem-cells-and-esophageal-cancer. [Last accessed on 2012 Mar 07]. DOI: 10.5772/27181. ISBN: 978-953-51-0223-6.
10. Couvelard A, Paraf F, Vidaud D, Dubois S, Vidaud M, Fléjou JF, *et al.* Human chorionic gonadotrophin beta expression in malignant Barrett's oesophagus. Virchows Arch 2004;445:279-84.
11. Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: A fundamental evaluation tool in clinical medicine. Clin Chem 1993;39:561-77.
12. Mao YS, Zhang DC, Zhao XH, Wang LJ, Qi J, Li XX. Significance of CEA, SCC and Cyfra21-1 serum test in esophageal cancer. Zhonghua Zhong Liu Za Zhi 2003;25:457-60.
13. Schneider J, Bitterlich N, Schulze G. Improved sensitivity in the diagnosis of gastro-intestinal tumors by fuzzy logic-based tumor marker profiles including the tumor M2-PK. Anticancer Res 2005;25:1507-15.
14. Choudhary AM, Ahmed MZ, Choudhary MS. Comparison of CEA and CA 19-9 with CA 72-4 in patients with upper gastrointestinal carcinomas in local population. Biomedica 2010;26:16-9.
15. Kim YH, Ajani JA, Ota DM, Lynch P, Roth JA. Value of serial carcinoembryonic antigen levels in patients with resectable adenocarcinoma of the esophagus and stomach. Cancer 1995;75:451-6.
16. Adams WJ, Morris DL. Carcinoembryonic antigen in the evaluation of therapy of primary and metastatic colorectal cancer. Aust N Z J Surg 2008;66:515-9.
17. Mealy K, Feely J, Reid I, McSweeney J, Walsh T, Hennessy TP. Tumour marker detection in oesophageal carcinoma. Eur J Surg Oncol 1996;22:505-7.
18. Clinical significance of monitoring preoperative CEA, CA125, CA 19-9 and β HCG serum level in Esophageal cancer. Cancer research >Esophagus cancer > 2011.08.25. Available online: http://www.cancerres.com/esophagus cancer/.
19. Dabelsteen E. Cell surface carbohydrates as prognostic markers in human carcinomas. J Pathol 1996;179:358-69.
20. CA 19-9 Immunoassays. Monobind Inc.; 2013. Available from: http://www.monobind.com/immunoassays-cancer-markers-ca-19-9.
21. Turkyilmaz A, Eroglu A, Aydin Y, Karaoglanoglu N. The relationship of serum CEA and CA 19-9 levels to liver metastasis and pancreatic invasion in esophageal cancer. Turk J Med Sci 2009;39:895-9.
22. Chiba N, Yoshioka T, Sakayori M, Mikami Y, Miyazaki S, Akiyama S, *et al.* AFP-producing hepatoid adenocarcinoma in association with Barrett's esophagus with multiple liver metastasis responding to paclitaxel/CDDP: A case report. Anticancer Res 2005;25:2965-8.
23. Plaza JA, Vitellas K, Frankel WL. Hepatoid adenocarcinoma of the stomach. Ann Diagn Pathol 2004;8:137-41.
24. Shimakawa T, Ogawa K, Naritaka Y, Wagatsuma Y, Katsube T, Hamaguchi K, *et al.* Alpha-fetoprotein producing Barrett's esophageal adenocarcinoma: A case report. Anticancer Res 1999;19:4369-73.
25. Inoue K, Unemura Y, Doi N. A case of Alpha-fetoprotein producing Barrett adenocarcinoma of the esophagus. J Jpn Surg Assoc 1996;57:1622-5.
26. Regelson W. Have we found the "definitive cancer biomarker"? The diagnostic and therapeutic implications of human chorionic gonadotropin-beta expression as a key to malignancy. Cancer 1995;76:1299-301.
27. Louhimo J, Carpelan-Holmström M, Alfthan H, Stenman UH, Järvinen HJ, Haglund C. Serum HCG beta, CA 72-4 and CEA are independent prognostic factors in colorectal cancer. Int J Cancer 2002;101:545-8.
28. Perkins GL, Slater ED, Sanders GK, Prichard JG. Serum tumor markers. Am Fam Physician 2003;68:1075-82.

Cite this article as: Bagaria B, Bagaria A, Singh M, Sharma R. Diagnostic sensitivity of serum carcinoembryonic antigen, carbohydrate antigen 19-9, alpha-fetoprotein, and beta-human chorionic gonadotropin in esophageal carcinoma (receiver operating characteristic curve analysis). Clin Cancer Investig J 2015;4:312-7.

Source of Support: Nil, **Conflict of Interest:** None declared.