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Original Research Article

Study of carcinoma embryonic antigen and carbohydrate antigen 19-9 levels in patients of esophageal cancer

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ABSTRACT

Background: The aim of the study was to analyze the role of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) as diagnostic and prognostic markers in patients of esophageal cancer. Various tumor markers are being investigated as non-invasive diagnostic and prognostic tools in patients of esophageal cancer.
Methods: This was a prospective observational study in which we analyzed the levels of CEA and CA 19-9 in blood samples of 35 patients of esophageal cancer. All patients underwent esophagoscopy and computed tomographic (CT) scan to assess site and extent of tumor. Histological diagnosis was confirmed in all cases by endoscopy guided biopsy.
Results: The sensitivity of CEA and CA 19-9 in detecting disease was found to be 34.3% and 28.6% respectively. The difference in CEA levels between squamous cell carcinoma and adenocarcinoma of esophagus was not found to be significant (p value=0.69). However, the difference in levels of CA 19-9 was found to be statistically significant (p value=0.02) between the two groups. The sensitivity and specificity of CEA to predict severity of disease was 66.7% and 70% respectively with positive and negative predictive value of 62.5% and 73.4 % respectively. In case of CA 19-9, sensitivity, specificity, positive and negative predictive values were 26.7%, 55%, 30.8% and 50% respectively.
Conclusions: CEA was found to be a more sensitive diagnostic marker than CA 19-9 and better at predicting prognosis. However sensitivity and specificity of both were relatively low. CA 19-9 levels were seen to be higher in esophageal squamous cell carcinoma versus adenocarcinoma.

Keywords: Esophageal cancer, Esophagus, CA-19-9, CEA, Tumour markers

INTRODUCTION

Esophageal cancer is the eight most common cancers worldwide and the sixth most common cause of cancer related deaths.[1] Approximately 480,000 cases occur worldwide annually.[2] Endoscopy followed by biopsy is currently used to confirm the diagnosis of esophageal cancer and also for screening in high incidence areas. However tumour markers can be used as a non-invasive and less painful method of screening, diagnosis as well as assessing response to treatment and predicting prognosis. The tumour markers that have been used in esophageal cancer are cytokeratin 19 fragment antigen 21-1 (Cyfra 21-1), carbohydrate antigen 19-9 (CA 19-9), carbohydrate antigen 72-4 (CA 72-4), carcinoembryonic antigen (CEA) and squamous cell carcinoma antigen (SCC-Ag). The most commonly used markers for early detection of esophageal cancer are CEA, CA 19-9 and SCC-Ag.[7] This study aims at studying the role of CEA and CA19-9 in detection and predicting prognosis in cases of esophageal cancer.

METHODS

This is an observational prospective study which was conducted at the Gandhi Medical College and associated

Hamidia Hospital, Bhopal, Madhya Pradesh, India after taking the necessary ethical approval from the ethical committee of the hospital (letter no 3612729/MC/IEC/2018). The duration of the study was a period of 2 years starting from December 2018 to December 2020. The sample size of the study was 35 patients. The sample size was calculated using an online same size calculator. The confidence level was taken to be 75%, population size 1000 and margin of error was 10%. The inclusion criteria were all biopsy proven patients of esophageal cancer that were admitted in the department of surgery and those admitted in the department of radiotherapy for chemo-radiation during the period of study. The patients that were unwilling to continue any form of surgical or palliative treatment were excluded from the study.

Data from all the patients of cancer esophagus was collected and filled in preformed proformas. Blood samples were sent of all the patients at the time of admission to determine levels of CEA and CA 19-9. Esophagoscopy was performed in all patients to assess the site, luminal patency and to extract a biopsy to confirm histological diagnosis. Contrast enhanced computed tomographic (CT) scan of the chest and abdomen was done in all cases to see the size and extent of the growth and assess nodal status and local invasion status. All the information collected was used to determine the stage and operability. Patients found to be operable were taken for curative surgery mostly by Ivor Lewis esophagectomy and then referred for post-operative radiotherapy once stable. The patients that has advanced inoperable disease or distant metastases underwent palliative procedures such as esophageal stent placement or feeding jejunostomy and were then referred for palliative chemo-radiation. The final outcome was noted at the time of discharge.

Statistical analysis

The collected data were transformed into variables, coded and entered in Microsoft excel. Data were analyzed and statistically evaluated using statistical package for the social sciences (SPSS) -PC-21 version.

Quantitative data was expressed in mean±standard deviation or median with interquartile range and depends on normality distribution difference between two comparable groups were tested by Mann Whitney 'U' test. Qualitative data were expressed in percentage. Statistical differences between the proportions were tested by chi square test or Fisher's exact test. The cut off values for CEA and CA 19-9 were taken to be 2.5 ng/ml and 35 U/ml as determined by various previous studies for detection of disease. Receiver operating characteristic (ROC) curve was prepared using CEA and CA 19-9 level to predict severity of disease and based on ROC curve cut off value was calculated and sensitivity, specificity, positive predictive value and negative predictive value was calculated. 'P' value less than 0.05 was considered statistically significant.

RESULTS

Among the total sample of 35 patients that were included in the study it was observed that only 6 were below 50 years of age and 7 were above 65 years of age (Table 1). Majority of the patients were in the age group of 51-65 years of age constituting 62.9 % of the sample size. In our study the disease was seen to occur more commonly among males accounting for 65.7% (23) of the sample size (Table 2).

Table 1: Age wise distribution of esophageal cancer study subjects (n=35).

Age group (years)	No.	%
Up to 50	6	17.1
51-65	22	62.9
>65	7	20.0

Table 2: Gender wise distribution of esophageal cancer study subjects (n=35).

Gender	No.	%
Male	23	65.7
Female	12	34.3

The youngest case diagnosed in our study was a 35 year old male with more males (4) diagnosed less than 50 years of age than females. The most commonly involved part of the esophagus was the lower third and gastro-esophageal junction (GEJ) in 23 patients comprising more than half of the sample size (Table 3).

Table 3: Site of esophageal cancer in study subjects (n=35).

Site of oesophagus	No.	%
Lower third	8	22.9
Middle third	8	22.9
Upper third	3	8.6
Lower and GEJ	6	17.1
Middle and lower third	4	11.4
Upper and middle third	1	2.9
GEJ	2	5.7
GEJ, cardia and fundus of stomach	1	2.9
Lower, GEJ and cardia of stomach	2	5.7

Isolated involvement of the upper third of the esophagus was seen in 3 patients while that of the middle third was seen in 8 patients. Most of the patients in our study at the time of presentation had advanced inoperable disease.

77% of the patients were inoperable at presentation while only 23% (8) had resectable growth without distant metastases. The 8 operable patients underwent curative Ivor Lewis esophagectomy while the rest 27 underwent palliative chemo-radiation with or without some form of palliative intervention. Feeding jejunostomy was the most commonly employed method of palliative intervention in this study (Table 4).

Table 4: Type of treatment modality in esophageal cancer study subjects (n=35).

Type of treatment modality	No.	%
Feeding jejunostomy followed by chemo-radiation	15	42.9
Chemo-radiation	11	31.4
Ivor-Lewis surgery	8	22.86
Oesophageal stenting f/b chemo-radiation	1	2.9

In this study, it was observed that there was a clear predominance of squamous cell esophageal cancer. Almost three quarters (74.3%) of the patients had squamous cell cancer while only 9 (25.7%) patients had adenocarcinoma. Of the 9 patients with adenocarcinoma, 6 had involvement of the lower esophagus and GEJ.

The cut off values for disease detection were taken to be 2.5 ng/ml for CEA and 35 U/ml for CA 19-9. 12 patients had CEA values above the cutoff indicating a positivity rate of 34.3% while 10 patients had CA19-9 values above the cutoff with a positivity of 28.6% (Table 5).

Table 5: CEA and CA 19-9 level distribution in esophageal cancer study subjects (n=35).

CEA and CA 19-9 level	No.	%
CEA level (ng/ml)		
<2.5	23	65.7
>2.5	12	34.3
CA19-9 level (U/ml)		
<35	25	71.4
>35	10	28.6

Table 6: Sensitivity of serum biomarker in esophageal cancer study subjects (n=35).

Serum biomarker	Sensitivity (%)
CEA	34.3
CA 19-9	28.6

Hence the sensitivity of CEA and CA19-9 in detecting disease was observed to be 34.3% and 28.6% respectively (Table 6). While comparing the level of biomarkers in both the histological groups it was observed that the mean value of CEA in adenocarcinoma cases was 3.05 and squamous cell carcinoma was 2.54. The difference between both the groups for CEA was not statistically significant with a p value of 0.69. On the other hand, comparing the levels of CA19-9 between the two groups it was seen that the mean value of CA 19-9 in adenocarcinoma cases was 10.90 and for squamous cell cancer was 409.80 with medians of 11.6 and 18.13 respectively. This showed a statistically significant difference between the two groups with a p value of 0.02 (Table 7).

Table 7: Comparison of levels of serum biomarkers in squamous cell carcinoma and adenocarcinoma of esophagus.

Serum biomarkers	Adeno CA (n=9)	Squamous cell Ca (n=26)	P value
CEA level (ng/ml)	3.05±3.23	2.54±2.02	0.69
Median (IQR)	2.1 (1.6-2.75)	2.05 (1.17-3.63)	
CA 19-9 level (U/ml)	10.90±5.08	409.80±1956.12	0.02
Median (IQR)	11.6 (6.1-13.45)	18.13 (11.45-47.70)	

In order to determine the prognostic power and predict severity of disease, ROC curves of both the serum markers were plotted (Figure 1). In the case of CEA the area under the curve was observed to be 0.67 with the 95% confidence interval of 0.49-0.86. The cutoff value of CEA using ROC curve was determined to be 2.15. Depending on this cutoff value the sensitivity and specificity of CEA to predict the severity of disease was 66.7% and 70% respectively with a positive and negative predictive value of 62.5% and 73.4% respectively. The role of CEA to predict the severity of disease in esophageal cancer patients was found to be almost statistically significant with a p value of 0.07. In the case of CA 19-9, the area under the curve was observed to be 0.39 with a confidence interval of 0.21-0.59.

Table 8: CEA level and CA 19-9 level to predict severity of disease using ROC curve.

Variables	CEA level (ng/ml)	CA19-9 level (U/ml)
AUC	0.67	0.39
95% CI	0.49-0.86	0.21-0.59
P value	0.07	0.30
Cut off value	2.15	20.17
Sensitivity (%)	66.7	26.7
Specificity (%)	70.0	55.0
Positive predictive value (%)	62.5	30.8
Negative predictive value (%)	73.7	50.0

The cutoff value using ROC curve was determined to be 20.17. The sensitivity and specificity of CA 19-9 was

determined to be 26.7% and 55% respectively. The positive and negative predictive value of CA 19-9 was seen to be 30.8% and 50% respectively. The p value of CA 19-9 to predict the severity of disease was observed to be 0.30 which indicated that its role as a prognostic test was not statistically significant (Table 8).

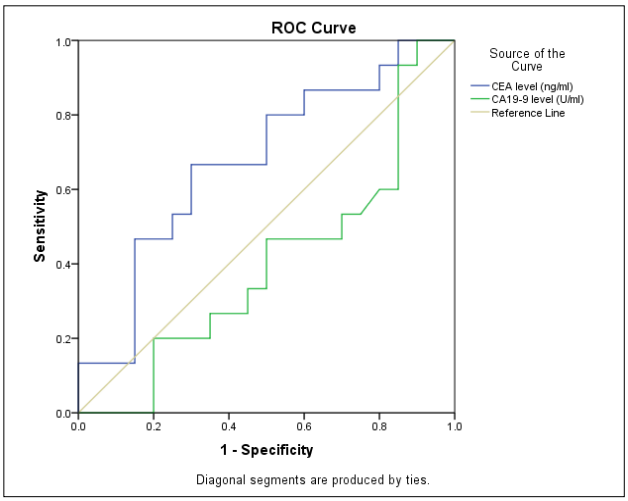

Figure 1: ROC curve using CEA level and CA 19-9 level to predict severity of disease.

DISCUSSION

Multiple studies have been done and are ongoing to assess the role of various markers in different malignancies including esophageal cancer. In the case of esophageal cancer a number of biomarkers have been evaluated but the best marker has not yet been determined. The clinical application of these biomarkers such as CEA, CA 19-9, SCC-Ag and Cyfra 21 is still limited due to their low sensitivity and specificity.[3] Few studies have shown Cyfra 21-1 to be better than CEA as a predictor of overall survival and prognosis.[4, 5] Another study showed that SCC-Ag was a better prognostic serum biomarker than CEA.[6] Kosugi reported that SCC-Ag was superior to CEA and CA 19–9 as a predictor for overall survival in esophageal cancer patients.[7] Squamous cell cancer of the esophagus is more common in the developing world while the incidence adenocarcinoma of the esophagus is rising in the western world and is seen to involve the GEJ more commonly. As this study was conducted in a South East Asian institute squamous cell cancer was seen 3 times more commonly than adenocarcinoma in our study. Most of the patients of esophageal cancer present when dysphagia occurs by the time of which the disease is locally advanced. Hence most of the cases are diagnosed at an advanced stage. This was confirmed in our study in which 74% cases were stage 4 indicating inoperability due to nodal and/or distant metastases. Yang et al observed that 63.9% patients had advanced disease of clinical stage 3 and above in their study.[8] As most of the patients presented at an advanced stage and were inoperable, they were managed by chemotherapy and radiotherapy.

Assessment of the effect of chemotherapy on serum CEA and CA 19-9 levels was not done in our study due to poor follow up and patient loss. Comparison of the level of serum biomarkers in both histological groups revealed that there was no statistically significant difference (p=0.69) in the levels of CEA between patients of adenocarcinoma and squamous cell cancer. However the study found that CA 19-9 levels were higher in cases of squamous cell cancer than in adenocarcinoma with a statistically significant difference (p=0.02). Hence the efficacy of CA 19-9 was inferred to be superior to CEA for detection of esophageal squamous cell cancer. This correlated with the findings of Das et al who stated that CA 19-9 has the highest diagnostic accuracy for esophageal squamous cell cancer.[9] Bagaria et al on the other hand concluded that in esophageal squamous cell cancer, a combination of both the markers had higher efficacy.[10] Tokunaga et al studies the role of CA 19-9 as a prognostic marker in GEJ adenocarcinoma. His study concluded that CA 19-9 was a more useful prognostic marker than CEA for GEJ adenocarcinoma and its levels were significantly correlated with depth of tumour invasion.[11] Therefore there is still a lot of controversy as to which is the better marker for each histological type.

In our study CEA levels were above the cutoff value of 2.5 ng/ml in 34.3% of cases while CA 19-9 levels were above the cutoff of 35 U/ml in 28.6 % of cases. This showed that the sensitivity of CEA for detection of esophageal cancer was higher than that of CA 19-9. The sensitivity of CA 19-9 and CEA in the study conducted by Zhai et al was 17.2% and 27.6%.[3] Das et al reported a higher sensitivity of 48% for CEA and 76% for CA 19-9.[9] In contrast Tokunaga et al and Scarpa et al both reported similar CA 19-9 positivity of 12.9% and 12.3% respectively.[11] Therefore studies have shown a low sensitivity of both markers in detection of esophageal cancer. Similar to studies conducted by Bagaria et al and Das et al, a ROC curve was plotted to calculate the cut off value of both the markers for determining the prognostic value of the biomarkers. The sensitivity and specificity of CEA was found to be higher than that of CA 19-9 with higher positive and negative predictive values. This indicated CEA to have a higher prognostic value in esophageal cancer patients when compared to CA 19-9. In the study conducted by Bagaria et al, the sensitivity of CEA was 38%, while Mao et al and Schneider et al had lower sensitivity of 29.1% and 24% respectively.[10] A low CA 19-9 sensitivity of 18% was also reported by Bagaria et al. Bagaria et al hence concluded that the tumour marker sensitivity was too low for esophageal cancer screening and had poor prognostic significance.[10] Closer values for CEA were reported by Das et al with sensitivity of 50% and cutoff value of 2.92 ng/ml.[9] Tuncer et al also reported similar CEA findings.[12] CA 19-9 sensitivity was 84% in contrast to our study. Yang et al indicated that patients with low CA 19-9 and CEA levels were more likely to benefit from post-operative chemotherapy.[8] Most of the above mentioned studies were conducted in patients of esophageal

squamous cell carcinoma while this study included both. We were able to give a comparison of both the histological groups which has not been seen in previous studies.

This study however was limited by its short duration and small sample size being a single centre study. Our study also did not compare the levels of these markers before and after surgical intervention or chemotherapy as was done by Yang et al. Therefore the effect of resection of tumour or chemotherapy on the level of these markers could not be assessed.

CONCLUSION

Our study found CEA to be a more sensitive marker than CA 19-9 for detection of esophageal cancer. CEA also has a superior prognostic value in esophageal cancer patients. Although the study shows the prognostic and diagnostic value of these markers, the sensitivity and specificity of these markers is not high enough to use these markers alone in order to diagnose or predict the severity of the disease. This study was limited by a smaller sample size due to patient loss and poor follow up as well as the shorter duration of the study. The role of serum biomarkers as a screening and prognostic tool in esophageal cancer and other GI malignancies is constantly being evaluated and many new markers have been introduced recently. This is a vast field that requires further research.

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REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55(2):74-108.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65:5-29.
3. Zhai XH, Yu JK, Lin C, Wang LD, Zheng S. Combining proteomics, serum biomarkers and bioinformatics to discriminate between esophageal squamous cell carcinoma and pre-cancerous lesion. J Zhejiang Univ Sci B. 2012;13(12):964-71.
4. Zhang HQ, Wang RB, Yan HJ, Zhao W, Zhu KL, Jiang SM, Hu XG, Yu JM. Prognostic significance of CYFRA21-1, CEA and hemoglobin in patients with esophageal squamous cancer undergoing concurrent chemoradiotherapy. Asian Pac J Cancer Prev. 2012;13(1):199-203
5. Yan HJ, Wang RB, Zhu KL, Jiang SM, Zhao W, Xu XQ, Feng R. Cytokeratin 19 fragment antigen 21-1 as an independent predictor for definitive chemoradiotherapy sensitivity in esophageal squamous cell carcinoma. Chin Med J. 2012;125(8):1410-5.
6. Shimada H, Nabeya Y, Okazumi S, Matsubara H, Shiratori T, Gunji Y, Kobayashi S, Hayashi H, Ochiai T. Prediction of survival with squamous cell carcinoma antigen in patients with resectable esophageal squamous cell carcinoma. Surgery. 2003;133(5):486-94.
7. Kosugi S, Nishimaki T, Kanda T, Nakagawa S, Ohashi M, Hatakeyama K. Clinical significance of serum carcinoembryonic antigen, carbohydrate antigen 19-9, and squamous cell carcinoma antigen levels in esophageal cancer patients. World J Surg. 2004;28(7):680-5.
8. Yang Y, Huang X, Zhou L, Deng T, Ning T, Liu R, et al. Clinical use of tumor biomarkers in prediction for prognosis and chemotherapeutic effect in esophageal squamous cell carcinoma. BMC Cancer. 2019;19(1):526.
9. Das S, Mudra KL, Ahmed S, Sarma A, Kataki A. Study of Serum CEA and Ca 19.9 in Esophageal Squamous Carcinoma and ROC Curve Analysis. APJCB. 2020;5(4):141-5.
10. Bagaria B, Sood S, Sharma R, Lalwani S. Comparative study of CEA and CA19-9 in esophageal, gastric and colon cancers individually and in combination (ROC curve analysis). Cancer Biol Med. 2013;10(3):148-57.
11. Tokunaga R, Imamura Y, Nakamura K, Uchihara T, Ishimoto T, Nakagawa S, et al. Carbohydrate antigen 19-9 is a useful prognostic marker in esophagogastric junction adenocarcinoma. Cancer Med. 2015;4(11):1659-66.
12. Tuncer I, Dülger A, Uygan I, Öztürk M, Kotan C, Şekeroğlu R. Comparison of serum cytokeratin-18, CEA and CA 19-9 levels in esophageal and gastric cancers. Eastern J Med. 2004;9:72-8.

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