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Document heading **doi: 10.21276/apjhs.2017.4.2.11** **Research article**

Our experience with CEA in the management of colorectal cancer – a prospective study

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ABSTRACT

Introduction : In India, colorectal cancer is the 6th most prevalent cancer and population based time trend studies show a rising trend in its incidence. CEA is expressed in significant amounts post-natally by the carcinomas arising from large intestine. Currently, the most useful application of CEA is in the detection of liver metastasis from colorectal cancers and serial determination of CEA is recommended for detecting cancer spread to the liver. **Aim**: To assess the role of CEA in the management of colorectal cancer, and detection of early recurrence. **Methods and Material**: 30 patients with colorectal cancer admitted in Vydehi Institute of Medical Sciences & Research Centre during the period of November 2012 to April 2014 were included in a prospective study. Statistical analysis used: Descriptive statistics were calculated for all variables. Analysis was performed using the SPSS 14.0 statistical package. **Results**: Total patients included in the study was 30. The mean age at presentation was 48.66yrs. The most common site of malignancy was rectum (46.66%), and most of the patients presented in stage I. Pre-operatively CEA was raised in 22 cases. On postoperative follow-up, CEA was found to be elevated in 7 cases. 6 out of these cases had proven recurrence. One case was found to have peritoneal deposit in spite of CEA levels being normal. The sensitivity and specificity of using CEA as an indicator for recurrence were 85.71% and 95.65% respectively. **Conclusions**: Since colorectal cancer is associated with considerable morbidity and mortality, early diagnosis and management provide a chance for better survival. The use of CEA as an early indicator for recurrence has been evaluated in this study and can be used for the same. However, a larger size and longer duration of study is needed to effectively prove the same.

Keywords: Carcinoembryonic antigen, colorectal cancer, tumour marker

Introduction

Colorectal cancer is the third most commonly diagnosed cancer in males and the second in females, with over 1.2 million new cancer cases and 608,700 deaths estimated to have occurred in 2008. The highest incidence rates are found in Australia and New Zealand, Europe, and North America, whereas the lowest rates are found in Africa and South-Central Asia [1]. Incidence rates have been decreasing for most of the past two decades owing to the use of colorectal cancer screening tests that allow the detection and removal of colorectal polyps before they progress to cancer. [2]. Human neoplasms may produce and release into circulation a variety of substances collectively called as tumour markers. The oncofetal antigens comprise one particular group of markers, of which the carcinoembryogenic antigen (CEA) has been most widely studied[3].CEA was first described more than three decades ago by Gold and Freedman when they identified an antigen that was present in both fetal colon and colon adenocarcinoma but appeared to be absent from healthy adults[4].This antigen is a glycoprotein of about 200,000 molecular size, absent from normal adult intestinal mucosa but present in primitive endoderm. It was, therefore, called carcinoembryonic antigen (CEA) [3, 5].In cancer localized to the mucosa and submucosa, the percentage of patients with an elevated test is between 30% and 40%. Therefore, the use of CEA as a screening

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technique for the asymptomatic population cannot be justified [5].Levels of CEA can be applied usefully in assessing the prognosis of individuals with colorectal cancer. If the tumor has been completely excised, any elevated level preoperatively should return to normal within a few days. A limited fall to an intermediate, albeit elevated, level is indicative of incomplete excision. Subsequent elevation after return to normal implies recurrence of tumor. This is true not only after resection of the primary cancer but also after resection for recurrent tumor. [5]

Specifically, by determining preoperative and postoperative CEA levels, one can identify patients in a poorer prognostic group who may benefit from early introduction of adjuvant therapy[5].The preoperative CEA level also has some prognostic significance. Patients with localized disease have a higher recurrence rate when preoperative CEA is high, than when the level is low. Such an elevation may be suggestive of unapparent spread of the tumor. This suggests undetected disseminated disease hence poorer prognosis[5].There is also a relationship between the preoperative CEA level and the depth of invasion according to Dukes' classification and tumor fixation.In contrast, Sener and colleagues showed, that the preoperative CEA level can be an indicator of survival that is independent of the stage of disease[5].

Factors affecting serum CEA concentrations in patients with Colorectal cancer.

Tumour stage –Both the concentration and proportion of patients with increased values tend to increase with increasing disease stage [6]

Tumour Grade – Well-differentiated colorectal cancers produce more CEA per gram of total protein than poorly differentiated specimens. A lack of differentiation or poor differentiation may explain why some patients with advanced colorectal cancer do not have increased serum CEA values [6]

Liver Status – The liver is the primary site for the metabolism of CEA. Impaired liver function affects the clearance of CEA, consequently increasing its serum levels [6]

Tumour site within the colon – Patients with tumours in the left side generally have a higher incidence of increased CEA concentrations than those with malignancies on right side of the colon [6]

CEA as a marker for Colorectal Cancer.

Screening – In screening for colorectal cancer, the aim should be to detect disease at an early stage. Using 2.5ng/dl as an upper limit, Fletcher calculated that CEA has a sensitivity of 36% and specificity of 87% in screening stage I and II cancers. These findings, combined with the low prevalence of this malignancy in unselected populations, render the positive predictive value of CEA unacceptably low and thus of little value in screening healthy subjects [6].

Diagnosis- Lack of sensitivity and specificity limit the application of CEA in diagnosing colorectal cancer, especially in early disease. Regarding specificity, it must be mentioned that CEA can be increased in most types of advanced adenocarcinomas as well as in multiple benign disorders. However, in patients with appropriate symptoms, highly increased concentration should be considered strongly suggestive for the presence of cancer in that particular patient [6].

Assessing Prognosis – Although less work has been carried out to investigate the prognostic value of postoperative CEA concentrations, the available evidence suggests that high concentrations at this time also predict adverse outcomes. Failure of an increased pre-operative value to decrease to normal concentrations within six weeks of surgery frequently is associated with early recurrent disease [6].

Surveillance – The aim of CEA monitoring after curative resection of colorectal cancer is to detect recurrent disease at an early and treatable stage. Longitudinal CEA measurements detect recurrent cancer with a sensitivity of 80% and specificity of 70%. The wide ranges of sensitivities and specificities are likely to be attributable to factors such as frequency of CEA assay and definition of a CEA increase [6]. Serial CEA determinations are most useful in detecting liver metastasis. In a prospective study of 305 patients, Arnould et al showed that increases CEA concentrations had a sensitivity of 94% and specificity of 96% in detecting liver metastasis. In another prospective evaluation CEA was reported to have 100% sensitivity in detecting liver metastasis [6].It appears to be the most cost effective test for the detection of potentially curable recurrent disease. [6]

Aim: To assess the role of CEA in the management of colorectal cancer in our institution.

Methodology: 30 patients with colorectal cancer admitted in Vydehi Institute of Medical Sciences and Research Centre, Bangalore during the period November 2012 to April 2013 were included in this study. Patients were followed up postoperatively for a period of 6 months for recurrence with evaluation of CEA.

Inclusion Criteria: Cases diagnosed as colorectal cancer, operated and diagnosis confirmed with histo-pathological examination.

Exclusion Criteria: Inoperable cases of colorectal cancer.

Data was recorded in a specifically designed proforma pertaining to patient particulars, history, clinical examinations, investigations (including serum CEA

levels), surgical procedures and follow- up. The decision of type of surgery was taken depending on the location of the tumour. Patients with malignancies in higher stage was subjected to adjuvant chemotherapy. All the patients were followed up at 3 months and then at 6 months. Patients were evaluated with serum CEA levels and various imaging studies. Those cases which were diagnosed to have recurrence and metastasis were further managed with curative resection, chemotherapy and radiation therapy.

Result

The maximum no. of cases was males having a percentage of 56.66% as compared to females with a percentage of 43.33%. The maximum no. of cases among males ranged in the age group 50-59 (35.29%). Maximum no. of cases among females were in the age group of 40-49 (38.46%).

Both sexes put together had majority of cases in the age group of 40-59 (60%).

The youngest patient was noted to be in the age group of 20-29. It was found that colorectal cancer is predominantly a disease of middle and old age group. Out of the 30 cases, 22 patients had elevated CEA levels pre-operatively, a percentage of 77.33%. Cut off value for elevation of CEA was taken as 5ng/dl.

Factors affecting CEA

I. Stage of tumour.

We found that there is an increase in proportion of patients having elevated levels of CEA with increase in the disease stage. Stage I had 56.23% of patients with elevated CEA level, stage II had 75% and Stage III had 100%.With respect to Duke's staging, none of the cases with Duke's Stage A had elevated CEA, 64.28% with Stage B1 had elevated CEA followed by 75% with B2 and 100% with C1 and C2 had elevated CEA.

II. Grade of tumour

Mean concentrations of CEA were found to be higher with better differentiation of the tumour. Well differentiated carcinomas had a mean concentration of 16.9ng/dl, moderately differentiated carcinoma had 10.63ng/dl and poorly differentiated carcinoma had 4.85ng/dl.

III. Side of tumour

Incidence of raised CEA levels were higher in colorectal cancer occurring on the left side(59.0%) in comparison to those on the right side (40.9%). Total number of patients with raised pre-operative CEA levels were 22 out of which 9 cases were that of right side and 13 were that of left side.

CEA LEVELS IN FOLLOW-UP PERIOD

We observed that that there was no rise in CEA levels during the first month follow up. During the 6th month follow-up, 8 out of 30 patients had increase in CEA levels (26.66%).

Pre-operative levels of CEA

Total no. of patients in the study - 30
Total no. of patients with raised CEA – 22
Percentage – 73.33%

Table 1: Statistical analysis of pre-operative CEA 1

TRUE POSITIVE (patients with increased levels of CEA and those who had colorectal cancer	**22**
TRUE NEGATIVE (patients without elevation of CEA and did not have colorectal cancer	0
FALSE POSITIVE (patients who had elevated levels of CEA but did not have colorectal cancer)	0
FALSE NEGATIVE (patients without elevation of CEA and had colorectal cancer)	8

Table 2: Statistical analysis of pre-operative CEA 2

Sensitivity	**73.33%**
Positive predictive value	100%

Post-operative levels of CEA (follow-up within 6 months)

Total no. of patients in the study -30
Total no. of patients with raised CEA levels on follow up – 7
Total no. of patients who were proven to have recurrences in the follow-up period by imaging studies – 7

Table 3: Statistical analysis of post-operative CEA 1

True positives (patients with raised levels of CEA with proven recurrence)	**6**
False positive (patients with elevated CEA without recurrence)	1
True negatives (patients without elevated CEA)	22
False negative (patients without elevation of CEA and with proven recurrence)	1

Table 4: Statistical analysis of post operative CEA 2

Sensitivity	**85.71 %**
Specificity	95.65%
Positive predictive value	85.71%
Negative predictive value	95.63%

Discussion

This was a prospective clinical study conducted on 30 cases of colorectal cancer and the role of the tumour marker Carcinoembryogenic Antigen in the management of the disease. The maximum no. of cases were males having a percentage of 56.66% as compared to females with a percentage of 43.33%. Both sexes put together had majority of cases in the age group of 40-59, having a percentage of 60%.Serum CEA was found to be elevated in 77.33% of cases at diagnosis. Serum CEA levels are found to depend on the site of tumour, the stage of the disease and the pathological grade of adenocarcinoma. Incidence of raised CEA levels were higher in left sided tumours (59%) when compared to right sided tumours (40.9%).CEA levels were found to be higher in patients with increased stage of the disease. 100% of cases in stage IIIA and stage IIIB of TNM staging system were found to have raised CEA levels, whereas 75% of stage IIA disease and only 56.25% of Stage I disease were found to have elevated CEA. 100% of cases in stage C1 & C2 of Duke's staging system were found to have elevated CEA, 75% of cases in stage B2 and 64.28% of cases in stage B1 had elevated levels of CEA. Serum concentrations of CEA were higher in cases with well differentiated adenocarcinoma (16.9%) followed by moderately differentiated (10.63%) and poorly differentiated (4.85%).The sensitivity of pre-operative CEA analysis was 73.33% and the positive predictive value was 100%.Post-operatively CEA was measured during follow-up after 3 months and 6months, to assess its efficacy in detecting early recurrence. None of the patients had elevated CEA within 3 months after surgery and none of them were found to have recurrence on evaluation with various imaging studies. 7 cases had elevated CEA on follow-up at 6 months. Out of these 7 cases 6 were proven to have recurrence, 1 local recurrence, 1 lung metastasis and 4 liver metastasis. 1case had peritoneal deposits on USG but CEA elevation was not found. Another case had elevated CEA but no recurrence was found on investigation. The cases with liver metastasis were subjected to hepatic segmentectomy. Patient with lung metastasis underwent chemotherapy and patient with local recurrence underwent radiation therapy. The sensitivity of serum CEA as an early indicator for recurrence was 85.71%, the specificity was 95.65%, positive predictive value was 85.71% and negative predictive value was 95.63%.

Following are the results with respect to various parameters included in the study and have been compared with various other published studies.

Comparison of pre-operative levels of CEA between studies

Table 5: Comparison of pre-operative levels of CEA between studies

	Takagawa R. et al %	Taratino et al	Present study %
Raised pre-op CEA	14.4	22.4	73.33

From table no. 5, we can see that in the present study pre-operative levels of CEA were elevated in 73.33% of cases. In studies by Takagawa et al [7] and Taratino et al [8] the pre-operative CEA levels were 14.4% and 22.4%.

Comparison of CEA levels with respect to Duke's staging

Table 6: Comparison of CEA levels with respect to Duke's staging

Duke's stage	Harold J. et al %	Present study %
A	4	0
B	26	66.66
C	44	100
D	65	-

From Table no.6, we can see that the findings of this study are consistent with the study conducted by Harold. J et al [9] that the proportions of patients with elevated CEA increases with increase in the stage of the disease. In this study, Duke's B stage had 66.66% patients with increase in CEA and 100% of cases in Duke's stage D had elevated levels of CEA pre-operatively.

Comparison of efficacy of CEA as a detector of early recurrence

Table 7: Comparison of efficacy of CEA as a detector of early recurrence

	Mc Call J.L et al	Present study
Sensitivity	58%	85.71%
Specificity	93%	95.65%
Positive predictive value	79%	85.71%
Negative predictive value	83%	95.63%

In the present study, the efficacy of CEA to assess early recurrence post-operatively is in correlation with the study performed by Mc Call J.L et al [10] where the sensitivity was 58%, specificity was 93%, the positive predictive value was 79% and negative predictive value was 83%.

Conclusion

In this study serum CEA was an indicator for recurrence in 85.7% cases within 6 months. Based on high sensitivity and specificity we can conclude that CEA can be used effectively to detect early post-operative recurrence in cases of colorectal cancer. Early detection followed by surgical or medical management of recurrence can improve the life expectancy and prognosis of cases of colorectal cancer. Limitations of this study is a small sample size and short period of study.

References

1. Global Cancer Statistics Ca Cancer J Clin .2011;61:69–90
2. Cancer facts and figures 2010, American Cancer Societ
3. Mitchell EP. Role of CEA in the management of advanced colorectal cancer, Semin Oncol, 1998 ;2(5suppl 11):12-20
4. Elevated pre-operative CEA is associated with worse survical in stage I-III rectal carcinoma patients. British Journal of Cancer.2012; 107: 266-274.
5. Corman textbook of colon and rectal surgery, 5 edition, Chapter 22 Carcinoma colon.
6. Michael J. Duffy. Carcinoembryogenic antigen as a marker for colorectal cancer: is it clinically useful? Clinical Chemistry, 2001;47(4): 624-630
7. Takagawa R et al, Preoperative serum carcinoembryogenic antigen level as a predictive factor of recurrence after curative resection of colorectal cancer. Ann Surgical Oncology, 2008; 15(12): 3433-9.
8. Taratino et al, Elevated pre-operative CEA levels is associated with worse survival in stage I-III rectal cancer patients. British Journal of Surgery, 2012;107: 266-274.
9. Harold.J et al, Use of CEA as an Indicator of Early Recurrence and as a guide to a selected second-look procedure in patients with Colorectal Cancer. Ann Surgery. 1978; 188(4): 481-492.
10. Mc Call JL et al, The value of serum carcinoembryogenic antigen in predicting recurrent disease following curative resection of colorectal cancer. Dis Colon Rectum. 1994; 37(9): 875-81.

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