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Original Research Article

Prognostic Role of Carcinoembryonic Antigen (CEA) in Colorectal Carcinoma

Muhammad Iftikhar[1], Abdul Basit[1], M. Bilal Uddin[1], Zia Ullah[1], Nayab Sarwar[1], Rashid Aslam[2*]

[1]Assistant Professor, Department of General Surgery Hayatabad Medical Complex Peshawar Pakistan
[2]Associate Professor & Chairman Department of General Surgery Hayatabad Medical Complex Peshawar Pakistan

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Abstract: ***Background:*** Preoperative carcinoembryonic antigen (CEA) level is considered as a factor predictive of survival in colorectal cancer patients. Patients with normal (<5 ng/ml) or lower pre-operative CEA levels were reported to have significantly longer survival. ***Objective:*** To evaluate the prognostic significance of preoperative CEA levels of patients with colorectal cancer in Taiwan. ***Methods:*** Between Jan 2016 and Dec 2017, 39 patients with histologically confirmed colorectal cancers were evaluated retrospectively at the General Surgery Department of Hayatabad Medical Complex Peshawar. All patients had undergone potentially curative surgery. Patients with metastatic diseases were not included. 5-Fluorouracil-based adjuvant chemotherapy was administered if the patients had Dukes' C disease. Reference to the Dukes' classification was according to the classical criteria described in 1932 for carcinoma of the rectum and adapted for use in colonic tumors. Data on gender, age, degree of tumor differentiation, location of the tumor, tumor size, lymph node metastasis, penetration of the bowel wall and preoperative CEA levels were analyzed to deter mine their association with survival. Blood samples for CEA measurement were taken a few days before operation and were analyzed using the radioimmunoassay method. ***Results:*** Total 39 patients were included in the study. Age ranged between 30-80 years with a mean age of 55 years. There were 26(66.7%) males and 13(33.3%) females, with male to female ratio of 2:1. Patients with preoperative CEA levels of <5 ng/ml had significantly longer survival than those with preoperative CEA levels of >5 ng/ml. The median 5 years survival rate for patients with preoperative CEA <5 ng/ml was 51.2 months, while 35.5 years for >5 ng/ml patients respectively ($p < 0.001$). The tumour was primary located at the colon in 23(59%) while the rest was found at the rectum 16(41%). Tumour size was <2cm in 25(64.1%) and >2cm in 14(35.9%) patients. ***Conclusions*:** The data from our study indicate that in addition to lymph node metastases and penetration of the bowel wall, the preoperative CEA levels are also an independent prognostic factor in non-metastatic colorectal cancer patients after curative surgery. This could serve as an appropriate modification to the initial Dukes' scheme in colorectal cancer.

Keywords: Preoperative CEA level, colorectal cancer.

INTRODUCTION

In Pakistan, one of the main causes of cancer-related morbidity and mortality is colorectal cancer. We are thus interested in looking into the prognostic factors for survival in colorectal patients [1]. The carcinoembryonic antigen (CEA), discovered by Gold and Freedman in 1965, has undergone substantial research to determine its therapeutic use in the treatment of colorectal cancer [2].

Carcinoembryonic antigen (CEA) is a glycoprotein, which is present in normal mucosal cells but increased amounts are associated with adenocarcinoma, especially colorectal cancer. CEA therefore has a role as a tumour marker [3]. Sensitivity and specificity are low, however, so it is of more use for monitoring than for screening or diagnosis. CEA levels are useful in assessing prognosis (with other factors), detecting recurrence (especially for disease that cannot be evaluated by other means) and monitoring treatment in people with colorectal cancer [4]. CEA is particularly recommended for postoperative follow-up of patients with colorectal cancer [3]. CEA may be elevated in colorectal cancer, which is where it is most clinically useful. However, it may also be elevated in a wide variety of other malignant and benign conditions [5, 6].

In general, the clinical value of CEA in the management of colorectal cancer can be divided into two parts: preoperative assessment of the extent and outcome of the tumor and postoperative monitoring of

***Corresponding Author:** Rashid Aslam
Associate Professor & Chairman Department of General Surgery Hayatabad Medical Complex Peshawar Pakistan

recurrence. The relationship between the preoperative CEA level and survival has been studied previously but without a definite conclusion [7]. It is justifiable to embark on this subject and investigate its possible existence in our population [8, 9].

The purpose of this study was to assess the role of preoperative CEA level as an independent prognostic factor in colorectal cancer.

PATIENTS AND METHODS

This retrospective prospective study of 39 patients was carried out at Department of General Surgery Hayatabad Medical Complex Peshawar from Jan 2016 to December 2017. All patients had surgically proven Dukes' A, B or C disease. Patients with metastatic (or Dukes' D) diseases were not enrolled. A 'B1' or 'C1' lesion refers to a tumor that had not penetrated the entire thickness of the bowel wall, whereas a 'B2' or 'C2' tumor manifested full thickness penetration of the bowel wall. 5-Fluorouracil-based adjuvant chemotherapy was administered for patients with Dukes' C disease (tumor located in the colon) and Dukes' B2 or Dukes' C disease (tumor located in the rectum). Data on gender, age, location of the tumor (colon or rectum), size of the tumor, degree of tumor differentiation, status of lymph node metastases, penetration of the bowel wall and preoperative CEA levels were analyzed to determine their association with survival. Blood samples for CEA measurements were taken a few days before operation. The blood samples were sent to the Department of Pathology / hematology and the CEA value was measured. A CEA value of >5 ng/ml was considered abnormal. All patients were followed up for 5 years and the duration from the CEA determination until 5 years was recorded.

Statistical analysis was done using SPSS 23.0. P value ≤0.05 was considered statistically significant.

RESULTS

Total 39 patients were included in the study. Age ranged between 30-80 years with a mean age of 55 years. There were 26(66.7%) males and 13(33.3%) females, with male to female ratio of 2:1. Patients with preoperative CEA levels of <5 ng/ml had significantly longer survival than those with preoperative CEA levels of >5 ng/ml. The median 5 years survival rate for patients with preoperative CEA <5 ng/ml was 51.2 months, while 35.5 years for >5 ng/ml patients respectively ($p < 0.001$). The tumour was primary located at the colon in 23(59%) while the rest was found at the rectum 16(41%). Tumour size was <2cm in 25(64.1%) and >2cm in 14(35.9%) patients, Table-1.

Of the 39 patients, 22(56.4%) had elevated CEA levels of >5 ng/ml and the remaining 17(43.6%) had CEA level of <5ng/ml. Bowel wall penetration was found in 18(46.1%) patients while the remaining 21(53.9%) didn't have bowel wall penetration. A higher incidence of abnormal CEA level was found in Dukes' C disease 21(53.8%), followed by Dukes' B 11(28.2%) and Dukes A diseases in 7(17.9%), Table-2.

Table-1: Outcome of the study

Outcome	Frequency	Percentage
Gender		
Male	26	66.7%
Female	13	33.3%
Mean age	55 years	
Ratio	2:1	
Tumour location		
Colon	23	59%
Rectum	16	41%
Tumour size		
<2cm	25	64.1%
>2cm	14	35.9%
Bowel wall penetration		
Yes	18	46.1%
No	21	53.9%
Preoperative CEA level		
>5ng/ml	22	56.4%
<5ng/ml	17	43.6%
Mean survival rate		
Survival in CEA <5 ng/ml	51.2 months	P value (0.001)
Survival in CEA >5 ng/ml	35.5 months	

Table-2: CEA values with Dukes stages

Stage	Value	Percentage
Stage C		
>5ng/ml	21	53.8%
<5ng/ml	18	46.1%
Stage B		
>5ng/ml	16	41%
<5ng/ml	23	59%
Stage A		
>5ng/ml	12	30.1%
<5ng/ml	27	69.2%

DISCUSSION

The most extensively studied tumour marker has been CEA ever since Gold and Freedman initially described it in 1965.[1] Preoperative assessment of the extent, outcome of the tumour and postoperative monitoring of recurrence are the two key elements of CEA's clinical relevance in the therapy of colorectal malignancies. Because it lacks sensitivity and specificity, measuring the CEA level is not a helpful diagnostic for detecting early and potentially curable colorectal cancer [10, 11].

Many workers have shown that preoperative serum CEA levels correlate with the extent of colorectal cancer [12]. In 1994, Wolmark *et al*., reported 318 patients with colorectal cancer staged from Dukes' A to D [13]. Of these, 133 (42%) had elevated preoperative CEA levels. They identified that the incidence of preoperative CEA levels of >5 ng/ml in Dukes stages A, B, C and D diseases are 0, 32, 48 and 79%, respectively. Similarly, in a report by Chu DZ *et al*., a total of 203 patients with colorectal cancer were enrolled and the authors identified that the incidence of preoperative CEA >5 ng/ml in Dukes' A, B, C and D diseases were 3, 25, 45 and 65%, respectively [14]. The current study confirmed this observation. In our study, the incidence of preoperative CEA >5 ng/ml in Dukes' A, B and C diseases were 30, 41 and 53%, respectively. The Dukes' stage is the most important predictor of survival in colorectal cancer and the incidence of abnormal preoperative CEA levels is higher in advanced colorectal cancer (Dukes' C) than in early-stage diseases (Dukes' A and B). Whether elevated preoperative CEA levels can serve as an 'independent' prognostic factor in colorectal cancer is of interest to us [15].

In 1978, Goslin *et al*., firstly reviewed 172 patients and reported the relationship between preoperative CEA and survival [16]. They found that the recurrence rate was higher in patients with Dukes' B and C diseases who had preoperative CEA levels >5 ng/ml. Scott NA et al analyzed 706 Dukes' B and C patients Breast and Bowel Project [17]. They found that the relative risk of treatment failure for patients with a preoperative CEA value >10 ng/ml compared with those with a CEA value <2.5 ng/ml was 3.24 (p = 0.003) in Dukes' B lesions and 1.76 (p = 0.05) in Dukes' C lesions.

Some investigators have reported that higher preoperative CEA levels are associated with poorer prognosis only in Dukes' C disease. Thirunavukarasu P *et al*., studied 113 patients who had undergone curative resection with follow-up for 36–72 months [18]. They did not find an adverse impact of abnormal CEA level on survival among 65 Dukes' B patients. However, the recurrence rate correlated significantly with preoperative CEA value (p < 0.005) among their Dukes'C group. Similarly, Agha RA *et al*., studied 217 Dukes' B and C colorectal cancer patients and found that there was no consistent correlation between survival and preoperative CEA values in patients with Dukes' B disease (p = 0.65) [19]. However, in the Dukes' C patients, a preoperative CEA value of >10 ng/ml was associated with a significantly decreased 5-year survival rate (p < 0.05). In contrast, after reviewing 563 colorectal cancer patients, Park JS et al reached a different conclusion [20]. They reported that the differences between survival curves based on preoperative CEA ranges of <5 and >5 ng/ml are significant for patients with TNM stage II tumors (p < 0.02) but not for patients with lymph node metastasis (p = 0.1).

There are several reasons that may account for such confusing and even contradictory results [21]. First, some reports with negative results did not have a large enough sample size after stratification. Second, the different statistical methods used may have resulted in different conclusions. Third, different definitions of abnormal CEA levels or different CEA kits were used. The current study of 39 patients treated at a single institution confirmed that an elevated preoperative CEA level of >5 ng/ml is associated with a poorer prognosis only in Dukes' C colorectal cancer [22].

In our study, besides preoperative CEA levels, the existence of penetration of the bowel wall was identified as another independent prognostic factor of colorectal cancer. The Dukes' classification scheme proposed in 1932 failed to subdivide patients with positive nodes on the basis of the depth of tumor penetration. At the time of formation of the Dukes' classifica tion, it was commonly believed that lymph node metastases occurred only when there was full thickness penetration of the bowel wall and once nodal metastases were in evidence, it was theorized that the depth of tumor penetration was of little prognostic significance.

CONCLUSION

Preoperative CEA level is an independent prognostic factor in colorectal cancer. The relationship is especially evident in Dukes' C disease. In our opinion, preoperative CEA levels could serve as appropriate modifications of the initial Dukes' scheme.

It is recommended that stratification for further clinical trials in colorectal cancer patients should be carried out according to preoperative CEA levels.

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