

# Role of post-operative carcinoembryonic antigen as predictor of outcome: Evaluation of patients with colorectal malignancy at a tertiary care center



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## ABSTRACT

**Background:** Colorectal cancer is the third most common cancer worldwide. The colorectal cancer has varied presentation and often patients present in late stages of disease. Pre-operative carcinoembryonic antigen (CEA) levels are indicative of tumor stage and thus are predictive of prognosis. However, the importance of post-operative CEA value is seldom discussed and utility of this clinically relevant parameter needs to be established to predict survival of subjects after surgical resection of tumor. **Aims and Objectives:** This study aims to understand the colorectal malignancy in a group of population and evaluate its complexity, clinical presentations, modalities of treatment, and its complications. Furthermore, we aimed to access predictive utility of post-operative CEA levels for forecasting the long-term outcome in the patient. **Materials and Methods:** All subjects with diagnosed cases of colorectal malignancy were included in the study. The subjects presenting complaints were clinically examined and the observations were noted. Colonoscopy and histopathological investigations were scheduled, and based on CT findings, further management was planned. Carcinoembryonic antigen levels were assessed in pre-operative and post-operative serum sample. Follow-up was done at regular intervals. CEA levels in subjects with different outcome were compared retrospectively. **Results:** The most common age group of subjects with colorectal malignancies was 51–60 years. Bleeding per rectum was the most common symptom and the most common sign was per rectal palpable mass. Laparoscopic surgery had less hospital stay, less blood loss, and lower rate of wound site infection. The pre-operative CEA levels were found to be matched; however, post-operative CEA levels were found to be significantly elevated in non-survivor subjects compared to those who survived. **Conclusion:** Patients with high post-operative CEA values should be closely followed up for relapse and dealt with more caution to reduce the mortality.

**Key words:** Colorectal malignancy; Laparoscopy; Colonoscopy; Surgery; Cancer

## INTRODUCTION

Cancer of colon and rectum, also known as colorectal cancer, is the third most common cancer worldwide and it ranks second accounting for the most common causes of death in terms of cancer-related mortality in 2020.<sup>1</sup> It

is characterized by non-specific presenting symptoms and there is a close relationship between the stage of disease at diagnosis and survival.<sup>2</sup> Although reduced incidence and mortality have been observed due to advances in screening and medical treatments, around 20% of patients are believed to present with metastases at the time of diagnosis, and

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approximately 35% of patients will subsequently develop a metastatic disease.<sup>3</sup> The susceptibility of this progressive cancer varies for different individuals. Familial cancer comprises 25% of all the colon cancers and another 15% involves strong family history with a first- or second-degree relative.<sup>4</sup> Epidemiological studies suggest that 1–5% of all colorectal cancer are caused by single-gene syndromes resulting in hereditary non-polyposis colorectal cancer, also known as familial adenomatous polyposis (FAP) or Lynch syndrome which progresses in families with excess incidence of adenocarcinoma of the endometrium and also cancers of the stomach and ovary.<sup>5</sup> Apart from age and familial background, other non-modifiable risk factors include personal history of adenomatous polyps or of inflammatory bowel disease. Environmental risk factors involved in the development of the disease if identified readily, a large proportion of cases could be prevented theoretically. These factors include nutritional practices, especially with diets low in fat, lack of physical activity and obesity, cigarette smoking, and heavy alcohol consumption.<sup>6</sup>

Pre-operative carcinoembryonic antigen (CEA) levels are indicative of tumor stage and thus are predictive of prognosis.<sup>7</sup> However, the importance of post-operative CEA value is seldom discussed and utility of this clinically relevant parameter needs to be established to predict survival of subjects after surgical resection of tumour.<sup>8</sup> Management of the disease can be done through surgery, adjuvant chemotherapy, and radiotherapy in case of rectal cancers. However, prolonged survival is likely if tumor is removed completely.<sup>9</sup> Even with all the progress made in the field of diagnosis and management of colorectal malignancy, the incidence rates are rising in the developing countries like India.<sup>10</sup>

### Aims and objectives

Thus, our aim was to study colorectal malignancy in a group of population and evaluate its complexity, clinical presentations, modalities of treatment, and its complications and to assess predictive utility of post-operative CEA levels for forecasting the long-term outcome in the patient.

## MATERIALS AND METHODS

This observational hospital-based study was conducted in the Government Medical College and Hospital (GMCH), Nagpur, Maharashtra, during the period of July 2015–November 2017. All subjects with diagnosed cases of colorectal malignancy admitted in GMCH, Nagpur, were included in the study. While, those diagnosed and treated outside the institute and visited for further management, subjects with carcinoma of anal canal and appendix and subjects who refused to give consent were excluded from the study. Ethical approval was obtained from the ethical

committee of the institute (IEC 860 EC/Pharmac/GMC/NGP dated February 2, 2016). Written and informed consents were obtained from the subjects.

All subjects with the complaints of rectal bleeding, altered bowel habits, discharge, weight loss, and history of chronic constipation were examined. Patient history, physical examination, systemic examination, and exploratory laparotomy results were noted. Subjects with palpable mass per rectum were evaluated through colonoscopy and on histopathology evaluation. Based on CT findings, further management was planned. Follow-up was done in every 3 months interval for the 1<sup>st</sup> year, every 6 months for the next year yearly thereafter. The subjects were analyzed as per age, gender, site of malignancy, clinical presentation, histopathological staging, and management protocol. Carcinoembryonic antigen levels were evaluated preoperatively and postoperatively 1 week after surgery on Siemens ADVIA<sup>®</sup> Centaur XP electrochemiluminescence analyzer (Siemens Healthcare GmbH Henkestr, Erlangen, Germany) as per manufacturer protocol.

Data were expressed as percentage and mean $\pm$ S.D. Kolmogorov–Smirnov analysis was performed for checking linearity of the data. Fisher's exact test or Chi-square test was used to assess the significance of difference between frequency distribution of the data.  $P < 0.05$  was considered as statistically significant. SPSS<sup>®</sup> for Windows<sup>™</sup> version 21, Armonk, NY: IBM Corp. 2013 and Microsoft Excel<sup>™</sup> 2007, Microsoft<sup>®</sup> Inc., USA, were used to perform the statistical analysis.

## RESULTS

Table 1 shows the baseline characteristics in the study subjects. Subjects of all age groups were included in the study. Maximum subjects with colorectal malignancy were observed in the age group of 51–60 years of age. Youngest subject was 17 years age and oldest subject was 78 years of age. No patients were found below 10 years and above 80 years of age. Male preponderance of about 2:1 was noted. The most common presenting feature was found to be bleeding per rectum (62%) and altered bowel habits. The most common site of malignancy was rectum in 43 (43%) subjects followed by rectosigmoid junction in 27 (27%) and ascending colon in 11 (11%) subjects.

Table 2 denotes investigation findings in study subjects. Out of 100 subjects in total, 89 (89%) subjects were found to have normal X-ray. Pre-operative USG revealed circumferential bowel wall thickening in 77% of subjects. About 4% of subjects were noted to be having concomitant liver metastasis also. Contrast-enhanced computed tomography

**Table 1: Baseline characteristics in the study subjects**

Characteristics	Frequency (%)
Age (years) (mean±SD)	49.94±15.45
Gender	
Female	33 (33%)
Male	67 (67%)
Signs and symptoms	
Bleeding per rectum	62 (62%)
Altered bowel habits	55 (55%)
Pain in abdomen	36 (36%)
Constipation	31 (31%)
Loss of weight and anorexia	26 (26%)
Malena	20 (20%)
Lump in abdomen	10 (10%)
Vomiting, distension of abdomen	07 (7%)
Per vaginal feces	01 (1%)
Growth palpable on DRE/proctoscopy	35 (35%)
Palpable lump per abdomen	22 (22%)
Fistula in ANO	02 (02%)
Site of malignancy	
Cecum	05 (15%)
Ascending colon	11 (11%)
Hepatic flexure	03 (3%)
Transverse colon	02 (2%)
Splenic flexure	01 (1%)
Descending colon	07 (7%)
Rectosigmoid junction	27 (27%)
Rectum	43 (43%)
Familia adenosis polyposis coli	01 (1%)
Operability	
Surgeries performed	92 (92%)
Not operated	08 (8%)

(CECT) exposure was done on 98 (98%) subjects since the other two subjects were presented in the emergency. Pre-operative CECT showed growth in colon and rectum in 98 (98%) subjects, metastasis in locoregional lymph node was observed in 45 (45%), and local advancement of tumor was observed in 6 (6%) subjects. On follow-up, post-operative metastasis was visible in 8 (8%) and post-operative local recurrence was observed in 6 (6%) subjects. Pre-operative colonoscopy was done on 65 (65%) subjects which revealed absence of synchronous malignancies in them while; one of the subjects was detected with polyps surrounding the colon. In 35 (35%) patients with palpable growth on per rectal examination, colonoscopy was not done. Among all the 100 subjects, barium enema was done in only one of these cases showing multiple polyps present in entire large colon (from cecum to rectum). Histopathology staging was performed according to Duke's staging criteria and metastasis was noted.

Table 3 shows the various methods of radical and palliative surgeries performed in the study subjects. Out of total 92 surgeries performed, 79 were radical surgeries. While, 13 were palliative surgeries out of which 10 were elective and three were performed as emergency. All subjects undergoing surgery survived. Intestinal obstruction was observed in 7 (7%) subjects presented in emergency who

**Table 2: Radiological investigations in the study subjects**

Characteristics	Frequency (%)
X-ray chest and abdomen	
Multiple air fluid obstruction	07 (7%)
Abdominal bony metastasis	02 (2%)
Spinal metastasis	01 (1%)
Metastasis in ribs	01 (1%)
Normal X-ray	89 (89%)
USG abdomen and pelvis	
Circumferential bowel wall thickening	77 (77%)
Bowel wall thickening with Liver metastasis	04 (4%)
Normal	23 (23%)
Pre-operative CECT	
Growth in colon and rectum	98 (98%)
Local regional lymph node	45 (45%)
Local advanced tumor	06 (06%)
Follow-up CECT	
Metastasis	08 (08%)
Local recurrence	06 (06%)
Colonoscopy	
Pre-operative colonoscopy	65 (65%)
Synchronous malignancies	00 (00%)
Polyps in colon	01 (01%)
Barium enema	01 (01%)
Histopathology (Duke's staging)	
Stage A	13 (13%)
Stage B	21 (21%)
Stage C	45 (45%)
Stage D	21 (21%)
Type of neoplasm	
Adenocarcinoma	81 (81%)
Mucinous adenocarcinoma	15 (15%)
Signet ring cell carcinoma	04 (4%)
Metastasis	
Distant	21 (21%)
Locally advanced with distant	06 (6%)

underwent urgent exploratory and treatments accordingly. Wound site infection was 26% of subjects, 5 (5%) patients of laparoscopic APR were found to have perianal sutured site infection, stoma prolapsed was observed in 2 (2%) and post-operative intestinal obstruction due to adhesion was noted in 3 (3%) subjects.

Groups with different outcomes were compared regarding various parameters. The groups were found to be matched regarding age also pre-operative CEA was found to be comparable between groups with different outcomes. However, follow-up CEA was found to be significantly elevated in subjects who died compared to those who survived ( $P<0.0001$ ). Furthermore, change in CEA (follow-up CEA-pre-operative CEA) was found to be significantly higher in subjects who died compared to survivors ( $P<0.0001$ ) (Table 4 and Figure 1).

## DISCUSSION

In the present study, the incidence of colorectal cancer was found to be raised with the increase in age and was

highest in the age group of 51-60 years. This finding was comparable to the study done by Fleshner et al., who found the most common age group to be 65-75 years.<sup>11</sup> Although the incidence is increasing with age and compared to earlier decades, a number of patients of colorectal malignancy are now higher in younger adult groups. This can be explained on the basis on dietary habits, environmental factors, genetic changes, and various screening modalities assisting in early detection of malignancy. It was seen that 47% of the patients were <50 years of age. Male predominance was noted for the disease which is similar to those observed by McGillivray et al., and Kanda et al.<sup>12,13</sup> In our study, we found rectum to be the most common site of malignancy followed by rectosigmoid junction and ascending colon. Studies done by Limaïem et al., and Silva et al., also found similar observations with rectum being the most common site of malignancy.<sup>14,15</sup> On comparing

general occurrence of symptoms, we found that bleeding per rectum was the most common complaint according to the present study which was also reported by Walton et al.<sup>16</sup> However, Steinberg et al., found altered bowel habits as the most common complaint in the studied subjects.<sup>17</sup>

All the study participants were subjected to proctoscopic biopsy or colonoscopic biopsy or CT-guided fine-needle aspiration cytology depending on site of malignancy and the diagnosis of malignancy was confirmed by histopathological examination. Histopathological intervention revealed that 45 (45%) subjects had advanced Duke's Stage C. While, each of the Duke's Stages B and D comprised 21 (21%) subjects. Only 13 (13%) subjects were found under Stage A category. The most common histopathology type was adenocarcinoma as observed in 81% of the total subjects. The reason behind maximum subjects under Stage C can be interpreted by the fact that there is limited treatment success rate and diagnosis of metastatic cancer; also, in this study, distant metastasis was observed in 21 (21%) subjects and 6 (6%) subjects were diagnosed with locally advanced with distant metastasis.

Out of all the subjects in the study, we found that 79 (79%) subjects exhibited operable tumors and 21 (21%) subjects were diagnosed with inoperable tumors. For all the patients with advanced stage, that is, those possessing inoperable tumors, palliative surgeries were performed. Similar operability percentage was observed in the previous studies as well. Shimoyama et al., studied colorectal cancer in patients <40 years of age and found 71.4% operability.<sup>18</sup> Zorluoglu et al., who conducted study on colorectal cancer under 45 years age found 86.7% operability.<sup>19</sup> On comparing the discharged and dead patients with different outcomes regarding various parameters, age and pre-operative CEA were found to be matched. Follow-up CEA was found to be significantly elevated in subjects who died compared to those who survived. Furthermore, change in CEA (follow-up CEA-pre-operative CEA) was found to be significantly higher in subjects who died compared to survivors. The patients with persistent elevation of CEA levels post-surgery might suggest an increased amount of CEA secretion. This could also imply that an increased

**Table 3: Type of surgeries and post-operative complications**

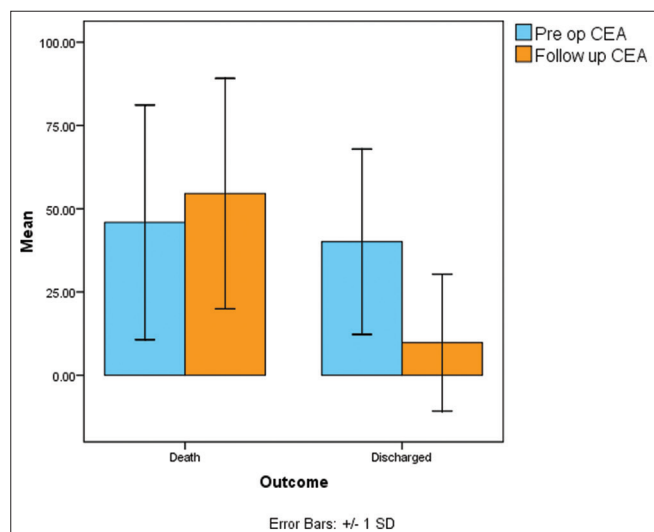
Surgeries performed	Frequency (%)
Abdominoperineal resection	
Laparoscopic	22 (22%)
Lap converted to open	01 (1%)
Open exploratory laparotomy	04 (4%)
Anterior resection	
Laparoscopic	18 (18%)
Lap converted to open	03 (3%)
Open exploratory laparotomy	01 (1%)
Left hemicolectomy	
Laparoscopic	04 (4%)
Lap converted to open	02 (2%)
Open exploratory laparotomy	05 (5%)
Right hemicolectomy	
Laparoscopic	04 (4%)
Open exploratory laparotomy	14 (14%)
Total proctocolectomy	
Laparoscopic	01 (1%)
Palliative sigmoid colostomy	10 (10%)
Palliative transverse colostomy	02 (2%)
Ileostomy	01 (1%)
Post-operative complication	
Intraoperative mortality	00 (0%)
Intestinal obstruction	07 (7%)
Wound infection	26 (26%)
Perianal sutured site infection	05 (5%)
Stoma prolapse	02 (2%)
Obstruction due to adhesion	03 (3%)

**Table 4: Comparison of age and CEA levels in the outcome of study subjects**

Characteristics	Outcome	Mean	SD	t-test	P value
Age (years)	Death	47.5600	16.43695	-0.677	0.502
	Discharged	50.1579	14.96041		
Pre-operative CEA	Death	45.8889	35.22681	0.510	0.615
	Discharged	41.1717	27.73872		
Post-operative CEA	Death	54.5889	34.59558	6.324	<0.0001
	Discharged	9.7795	20.53502		
Change in CEA	Death	8.7000	31.02934	4.225	<0.0001
	Discharged	-30.3318	37.44808		

CEA: Carcinoembryonic antigen





**Figure 1:** Comparison of carcinoembryonic antigen levels and the outcome in study subjects

amount of CEA secretion associated with greater tumor load. Early post-operative CEA concentration is an independent prognostic factor for CRC. Patients with high post-operative CEA values should receive aggressive follow-up examinations for early relapse of CRC.<sup>20</sup> However, the reason for elevated post-operative CEA levels is not always clear. Although, it is convenient to assume that it is due to inadequate resections or overlooked metastasis, other factors such as nicotine abuse or other associated hepatic, pulmonary, or renal conditions may also lead to high post-operative CEA levels.<sup>21,22</sup> However, despite thorough history, examination and investigations, and intraoperative findings, no such obvious factors could be detected in subjects with high post-operative CEA levels. Use of high-end techniques such as positron emission tomography might help to find the cause in such cases.

#### Limitations of the study

Although this was a single-center study, the findings are quite strong and thus can be expected to be replicated in multicenter study also.

## CONCLUSION

Based on our study, we conclude that patients with persistent elevation of CEA levels post-surgery indicate greater tumor load and thus worse prognosis in long term. Thus, we recommend that patients with high post-operative CEA values should be closely followed up for relapse and dealt with more caution to reduce the mortality.

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**Authors Contribution:**

**SD-** Concept and design of study, finalized manuscript; **SP-** Concept, literature review, and coordination; **SJ-** Concept, coordination, and procedure contribution; **NM-** Concept, coordination, revision of manuscript, and procedure contribution; and **DA-** Statistical analysis, interpreted the result, preparation of manuscript, and revision of manuscript.

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