

## Original Research Article

# Routine baseline serum carcinoembryonic antigen as a negative predictor of peritoneal metastasis in colorectal malignancies: a cost-effective tool in South India

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### ABSTRACT

**Background:** Colorectal cancer, a formidable health problem worldwide has upto 8% synchronous peritoneal carcinomatosis. As only diagnostic laparoscopy can identify them, in countries with economic burden, selection of patients for laparoscopy is ideal. Our aim is to evaluate whether the baseline Carcinoembryonic antigen (CEA) is a good selection tool.

**Methods:** A retrospective study of 125 patients, who were diagnosed to have colorectal malignancy (any stage) and underwent elective surgery at our institution from 2012 till 2019 were included. The baseline serum CEA was compared with the intraoperative findings. The threshold levels of serum CEA compared were 6.5 and 100 ng/dl. The sensitivity, specificity, positive predictive value and negative predictive value for both thresholds were compared in 3 categories of patients, namely peritoneal metastasis (9 cases), metastasis to other organs (36 cases) and cases with no metastasis either in peritoneum or other organs (85 cases). The results were analysed using SPSS software.

**Results:** The mean age was 65, sex ratio (male:female) was 72:53. The sensitivity, specificity, positive predictive value, negative predictive value (NPV) for CEA threshold of 6.5 ng/dl was 44.44%, 60.34%, 8% and 93.33% for category 1. For CEA threshold of 100 ng/dl, it was 33.33%, 97.41%, 50% and 94.95% for category 1. NPV was 96.55% for category 3 (the highest value).

**Conclusions:** If the baseline CEA levels are less than 100 ng/dl, 96.55% of cases will not require a diagnostic laparoscopy. This hopefully will cut down the cost of unnecessary diagnostic laparoscopies, and reduce the morbidity of unnecessary laparotomies.

**Keywords:** Carcinoembryonic antigen, Peritoneal metastasis, Diagnostic laparoscopy, Colorectal malignancies, Cost, India

### INTRODUCTION

Colorectal cancer (CRC) is a formidable health problem worldwide. It is the third most common cancer in men (663000 cases, 10.0% of all cancer cases) and the second most common in women (571000 cases, 9.4% of all cancer cases).<sup>1</sup> Almost 60% of cases are encountered in developed countries. The number of CRC-related deaths is estimated to be approximately 608,000 worldwide, accounting for 8% of all cancer deaths and making CRC

the fourth most common cause of death due to cancer. In India, the annual incidence rates (AARs) of colon cancer and rectal cancer in men are 4.4 and 4.1 per 100000, respectively. The AAR for colon cancer in women is 3.9 per 100000. Colon cancer ranks 8th and rectal cancer ranks 9th among men. For women, rectal cancer does not figure in the top 10 cancers, whereas colon cancer ranks 9th.<sup>2</sup> Usually the patients have a favourable prognosis when diagnosed at an early stage: 70-80% are eligible for curative-intent surgery, with a 5 years survival of 72-93% for stages I-II.<sup>3</sup> Approximately 25% of the remaining

patients present metastases at the time of diagnosis.<sup>4</sup> Among these individuals, up to 8% have synchronous peritoneal carcinomatosis, and approximately 20% already have liver metastases.<sup>5</sup> Recurrent or systemic disease during the follow-up period after curative treatment of the primary tumor will develop in 20-30% of patients. Half of these recurrences will develop liver metastases.<sup>5</sup> Although it was believed that metachronous PM occur in less than 10% of cases of CRC, being the third most frequent site of recurrence after liver and lung, its prevalence is still not well known. As an example of the underestimation, due to the lack of reliability of traditional imaging and unspecific symptomatology, one study of autopsied patients that died from CRC reported an incidence of 40-80% unknown metachronous peritoneal carcinomatosis.<sup>6</sup>

Incisional hernia poses a great burden not only on the patient, but the healthcare as well. The overall costs for managing negative laparotomies pose even greater challenges. In one study involving 12,000 cases, the cumulative costs incurred for the management of hernia and related complications exceeded \$17.5 million overall.<sup>7</sup> As the need to reduce the negative laparotomies is clear, the methodology for identification of peritoneal metastasis as an end stage for colorectal malignancies is still difficult even with the current advances. The only proven method for identifying peritoneal metastasis is intraoperative visualisation of the peritoneum by a diagnostic laparoscopy. However, the cost for an additional diagnostic laparoscopy is less tolerated in developing countries where some centres are not even equipped with a sophisticated laparoscopic setting. In such cases, reducing the number of cases by a preliminary cheaper screening investigation is welcomed. This not only reduces the burden of screening every patient with a diagnostic laparoscopy, rather it also helps in the prognostication as well.

Carcinoembryonic antigen (CEA) describes a set of highly related glycoproteins involved in cell adhesion. CEA is normally produced in gastrointestinal tissue during fetal development, but the production stops before birth. Consequently, CEA is usually present at very low levels in the blood of healthy adults (about 2-4 ng/ml).<sup>8</sup> However, the serum levels are raised in some types of cancer, which means that it can be used as a tumor marker in clinical tests. Serum levels can also be elevated in heavy smokers.<sup>9</sup>

As CEA is a well-established tumour marker for follow-up of patients with colon cancer, it implies all patients with colon cancer will eventually have a baseline CEA done before the commencement of treatment. Our main aim is to know whether the routine CEA done, can predict peritoneal metastasis, or metastasis anywhere else which can make a case inoperable. Selecting these patients alone for a mandatory diagnostic laparoscopy instead of screening everyone, can not only reduce the burden of negative laparotomies, but also the unnecessary

diagnostic laparoscopies in operable cases where an open approach is often preferred in a low skill centre.

## METHODS

This is a retrospective study done in our institution in South India. 125 patients were selected as per convenient sampling due to the limited cases. All those who were diagnosed with colon cancer (all stages) in the age group of 20 years and above and underwent surgery from the year 2012 to 2019 were included. Those who needed an emergency laparotomy were excluded. The baseline serum CEA was compared with the intraoperative finding of the presence of peritoneal metastasis and metastasis in the other organs. The normal range of serum CEA in our institution lab was within 6.5 ng/dl. The threshold levels of serum CEA compared were 6.5 and 100 ng/dl. The sensitivity, specificity, positive predictive value and negative predictive value was compared in these 2 range values. 3 categories were selected, namely cases where peritoneal metastasis was present (with or without metastasis in other organs), cases where metastasis was present in other organs (with or without peritoneal metastasis), cases where there was no metastasis either peritoneum or other organs. Data was obtained from case records. The level of serum CEA was compared with the presence of metastasis. The results were tabulated and analysed by SPSS software.

## RESULTS

There was a total of 125 cases which met the inclusion and exclusion criteria. The age range was 42 to 85 years, the mean age was 65 years. There were 72 males and 53 females. All stages of colorectal cancer were operated. The distribution of colorectal malignancy was as follows as shown in (Figure 1). Seven cases were in the caecum (5.6%), 1 case in caecum and rectum (0.8%), 28 cases in ascending colon (22.4%), 9 cases in hepatic flexure (7.2%), 6 cases in transverse colon (4.8%) 2 cases in splenic flexure (1.6%), 7 cases in descending colon (5.6%), 23 cases in sigmoid colon (18.4%), 12 cases in recto-sigmoid junction (9.6%) and 30 cases in rectum (24%). Among the 125 cases operated, 11 underwent laparoscopic surgery, and 114 underwent open surgery. There were 9 cases with peritoneal metastasis. And none of them underwent laparoscopic surgery. 36 cases had metastasis in other organs. Among them, liver metastasis was the maximum with 9 cases (25%). Other regions involved were as follows. 2 were nodal metastasis (5.5%), 3 were in the lateral pelvic wall (8.3%), 1 was a combined urinary bladder and prostate involvement (2.8%), 2 cases involved the urinary bladder and the sacrum (5.5%), 4 cases were involving the urinary bladder alone (11.1%), 1 case involved the ureter (2.8%), 3 cases involved the small bowel (8.3%), 3 cases involved the duodenum (8.3%), 2 were uterine metastasis (5.5%), 1 was involving the spleen (2.8%), 1 was having a retroperitoneal involvement (2.8%) and 4 were involving the abdominal wall (11.1%). Among them, 3

cases of ascites were noted. (2 were combined with the liver metastasis and 1 was combined with duodenal metastasis). The distribution is shown in (Figure 2). 5 cases had metastasis in both the peritoneum and other organs (3 liver and 2 small bowel). 85 patients had no evidence of metastasis either in the peritoneum or any other organs.

Serum CEA levels with threshold of 6.5 ng/dl and 100 ng/dL were compared with 3 categories of patients, namely the one with peritoneal metastasis, one with metastasis in other organs and one with no metastasis in either the peritoneum or the other organs. The distribution of the cases among the 3 groups are shown in (Table 1). The sensitivity, specificity, positive predictive value, negative predictive value was calculated for the threshold of 6.5 and 100 ng/dl as shown in (Table 2 and Figure 3). The CEA with a threshold level of 6.5 ng/dl had a sensitivity of 44.4% in detecting peritoneal metastasis in category 1. The negative predictive value for predicting no evidence of metastasis in category 3 was 94.64%. The sensitivity for peritoneal metastasis in category 1 decreased when the CEA threshold was increased to 100 ng/dl to 33.33%. However, the negative

predictive value was increased to 96.55% in category 3. This was the highest value amongst all the other parameters.

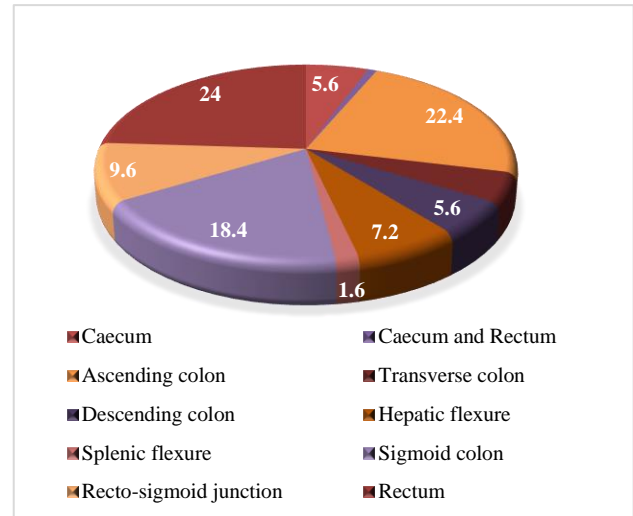


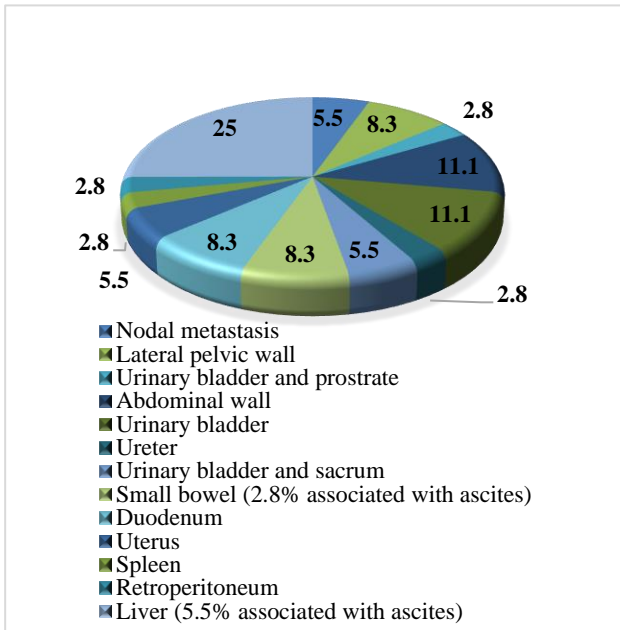
Figure 1: Distribution of colorectal malignancies in the colon.

Table 1: Distribution of cases among the two CEA cut-off groups.

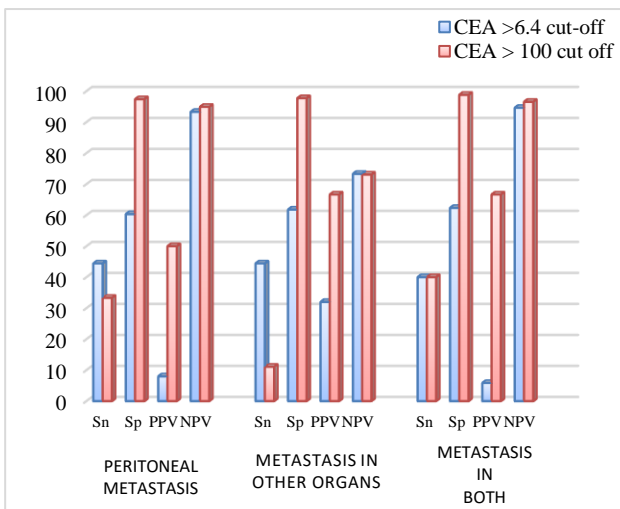
Variables		Peritoneal metastasis present (number of cases)	Peritoneal metastasis absent (number of cases)	Metastasis in other locations present (number of cases)	Metastasis in other locations absent (number of cases)	Metastasis in both peritoneum and other locations present (number of cases)	NO metastasis present - either in peritoneum or other organs (number of cases)
If CEA >6.4 ng/ml is considered as elevated	Elevated CEA	4	46	16	34	2	32
	Normal CEA	5	70	20	55	3	53
<b>Total</b>		<b>9</b>	<b>116</b>	<b>36</b>	<b>89</b>	<b>5</b>	<b>85</b>
If CEA >100 ng/ml is considered as elevated	Elevated CEA	3	3	4	2	2	1
	Normal CEA	6	113	32	87	3	84
<b>Total</b>		<b>9</b>	<b>116</b>	<b>36</b>	<b>89</b>	<b>5</b>	<b>85</b>

Table 2: Evaluation of the test results.

Variables		Peritoneal metastasis (%)	Metastasis in other locations (%)	Metastasis in both peritoneum and other locations (%)
If CEA >6.4 ng/ml is considered as elevated	Sensitivity	44.44	44.44	40
	Specificity	60.34	61.8	62.35
	Positive predictive value	8	32	5.88
	Negative predictive value	93.33	73.33	94.64
If CEA >100 ng/ml is considered as elevated	Sensitivity	33.33	11.11	40
	Specificity	97.41	97.75	98.82
	Positive predictive value	50	66.67	66.67
	Negative predictive value	94.95	73.1	96.55



**Figure 2: Distribution of metastasis other than peritoneum.**



**Figure 3: Effectiveness of CEA as a prediction tool.**

Sn - sensitivity, Sp - specificity, PPV - positive predictive value, NPV - negative predictive value.

**DISCUSSION**

The colorectal malignancies are known for their metastatic potentials. Wood et al reported, in a retrospective study, that 113 patients who presented with extended hepatic disease had a survival rate of 5.7%:27% for those with metastasis in one hepatic lobe, and 60% in those with isolated metastasis.<sup>10</sup> Peritoneal metastases are present in 20% of colorectal cancers and the former represents 40-70% of all recurrent disease. About 10-30% of recurrent disease is limited to peritoneum without distant metastasis.<sup>11</sup> In our study, there were only 9 cases with peritoneal metastasis (7.2%), 36 cases with organ metastasis (28.8%), 5 cases with metastasis in both

peritoneum and other organs (4%), and 85 cases were having no metastasis, neither in the peritoneum nor the other organs (68%).

With the advances in colorectal surgery, the fact that we are in the era where even the metastasis is operable is truly remarkable. When metastatic lesions are localized in the liver, which corresponds to 30% of patients, there are several options for localized treatment, such as hepatic partial resection, localized ablative therapy, administration of chemotherapy by infusion of the hepatic artery, systemic chemotherapy, and isolated hepatic fusion for patients with high doses of chemotherapy.<sup>12</sup> Similar treatments are available even for peritoneal metastasis, as mentioned from the first randomized trial comparing cytoreduction plus HIPEC followed by systemic chemotherapy vs systemic chemotherapy only.<sup>13</sup>

Even though advancements are there, the curative management of a peritoneal disease is still not standardised, and all patients are currently managed with a palliative intent. In our study, none of the 9 patients underwent a curative radical surgery. The screening of patients for peritoneal metastasis pre-operatively obviously avoids an unwanted elective negative laparotomy. In our study, there were 9 negative laparotomies (7.2%), and none of them were operated by laparoscopic method. A diagnostic laparoscopy with a lesser scar can attenuate the morbidities of a negative laparotomy, however, the cost of an additional diagnostic laparoscopy in a less expertise centre where the surgery is routinely done by open method is an issue especially in the economically challenged population. Thereby, this mandates a screening method to limit the number of diagnostic laparoscopies as well as negative laparotomies.

CEA was used as a prediction tool in various studies. In a study by Hasbahceci et al, high peritoneal CEA was shown to be significantly associated with peritoneal carcinomatosis (p=0.0321) in gastric adenocarcinoma patients.<sup>14</sup> CEA also predicted metastasis to other organs like the eye as per the study by Min et al, which concludes that CEA was a risk factor for ocular metastasis in colorectal cancer patients (p<0.001).<sup>15</sup> A study by Huang et al compared CA 125 and CEA and concluded that compared with CEA, CA 125 concentration had a lower sensitivity, higher specificity, and diagnostic accuracy, and significantly greater area under the curve.<sup>16</sup> In our study CA 125 was not compared because the main objective was a cost effective one. Hence only baseline serum CEA which was already done was compared. The study by Bagaria et al showed that sensitivity=74%, NPV=79.36%, and AUC=0.856 (SE=0.04), with a significance level of p<0.0001 and concluded that CEA exhibited the highest sensitivity for diagnosis of colon cancer, and CA19-9 exhibited the highest sensitivity for gastric cancer. Combined analysis indicated an increase in diagnostic sensitivity in esophageal and gastric cancer compared with that in

colon cancer.<sup>17</sup> Our study showed that CEA with a threshold level of 6.5 ng/dl had a sensitivity of 44.4% in detecting peritoneal metastasis in category 1. The negative predictive value for predicting no evidence of metastasis in category 3 was 94.64%. The sensitivity for peritoneal metastasis in category 1 decreased when the CEA threshold was increased to 100 ng/dl to 33.33%. However, the negative predictive value was increased to 96.55% in category 3. This was the highest value amongst all the other parameters. This implies that rather than predicting peritoneal metastasis, its better in ruling them out.

About 70% of all cancers of the large intestine occur below the midpoint of the descending colon (descending 10%, sigmoid 10% and rectum 50%). The remainder are in the right, middle and upper descending colon (29.5%).<sup>18</sup> In our study, the most common location was rectum (24%). The least common (0.8%) was a synchronous malignancy present in both the rectum and caecum needing a total proctocolectomy. Literature concludes that among all patients with metastatic cancer, the most common sites of metastasis were the liver (70% in colon cancer/70% in rectal cancer) and the thorax (32%/47%). In colon cancer, the third most common site was the peritoneum (21%) whereas in rectal cancer it was the bone (12%). Nervous system metastases were present in 5% of colon cancer, and in 8% of rectal cancer.<sup>19</sup> In our study, the most common metastasis was to the liver (25%).

### Limitation

Only a few cases of peritoneal metastasis was available for comparison with non-metastatic cases, leading to a disproportionate ratio.

### CONCLUSION

Thus, baseline serum CEA, which is done routinely for preoperative evaluation, is not only useful for prognostication, but also as a cost-effective tool to select patients who really need a diagnostic laparoscopy to rule out peritoneal metastasis. This study concludes that if the baseline CEA is less than 100 ng/dl, we can be 96.55% sure that we don't need a diagnostic laparoscopy. This hopefully will cut down the cost of unnecessary diagnostic laparoscopies, and at the same time, reduce the morbidity of negative laparotomies.

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