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# THE ROLE OF CARCINOEMBRYONIC ANTIGEN IN ASSESSING THE SUCCESS OF SURGICAL TREATMENT IN COLORECTAL CANCER BASED ON STAGING

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## ABSTRACT

Colorectal cancer is the third most common cancer in Indonesia. Determination of staging is needed to determine the treatment of colorectal cancer which has four stages. Carcinoembryonic Antigen (CEA) is a serological marker for monitoring colorectal cancer status, prognostic determination, monitoring of treatment success, detecting early recurrence and spreading. The purpose of this study was to determine the evaluation of successful surgical therapy in colorectal cancer by CEA examination at each stage. Descriptive observational studies were conducted using secondary data of pre and post-surgical colorectal cancer patients examined for CEA and treated at the Dr. Soetomo Hospital from January 2015 to December 2016. The samples obtained from this study were 48 patients, with the most of them at the age of 41-60 years as much as 70.83%. Females were more than males (66.67% vs. 37.33%). The most staging stage, stage 4 was as much as 43,75% followed by stage 3 as much 41.67%, the rest were stage 1 as much as 10.42%, and stage 2 as much as 4,17%. The highest decrease in CEA levels was found in stage 4 by 85%, followed by stage 2 of 53.5%, stage 1 of 43.4% and stage 3 of 33.1% but statistically only the decrease in stage 3 was significant. In stage 1, there was a difference in pre-operative CEA with a mean of 3.09 ng/mL (0.17-5.83 ng/mL) vs. post-operative with a mean of 1.75 ng/mL (0.84-3.14 ng/mL), stage 2 levels of pre-operative CEA with a mean of 3.82 ng/mL (0.15-7.48 ng/mL) vs. post-operative with a mean 1.77 ng/mL (1.46-2.08 ng/mL), stage 3 levels of pre-surgical CEA with a median of 13.85 ng/mL (1.09-71.21 ng/mL) vs. post-operative with a median 9.26 ng/mL (<0.5-68.23 ng/mL), stage 4 pre-surgical CEA levels with a median 183.77 ng/mL (0.54-2861 ng/mL) vs. post-operative with a median 27.28 ng/mL (0.51-155.10 ng/mL). There was a decrease in CEA levels from the total number of patients by 67%, whose CEA levels remained at 12% and as much as 21% of their CEA levels increased. Successful evaluation of surgical therapy in the colon and rectal cancer by CEA examination was still varied at each stage where CEA levels decreased significantly in stage 3.

**Key words:** Colorectal cancer, CEA, pre-surgery, post-surgery, staging

## INTRODUCTIONS

Evaluation of success in colorectal cancer therapy consists of several ways, among others, clinical, ultrasonography, colonoscopy, CT Scan, PET Scan, and CEA. Other examinations require periodic, and costly inspections, while Carcinoembryonic antigen (CEA) alone is a reasonably practical, inexpensive, and accurate examination. CEA levels are not always consistent with stages and degrees of differentiation, but CEA is still used to see the success of colorectal cancer therapy, whether there is a difference in each stage of colorectal cancer based on the assessment of postoperative CEA reduction.

Ultrasonography only is able the solid material in the liver and the abdominal aorta but, can not assess the local residue. Moreover, the accuracy of the diagnosis is only 85.2%.<sup>1</sup> Colonoscopy can only see the intraluminal residues, it is not able see the residues that are in the extraluminal. CT Scan can only detect local tumors or residues as well as metastases if the residue diameter is more than two centimeters and, also can only detect if the contrast is inserted

intravenously, whereas contrasting materials can damage the kidneys. The PET Scans only look at cancer spread/metastasis in general, can not detect its own tumor, moreover, the cost of PET Scan examination is also expensive.

CEA is the marker of choice in monitoring colorectal carcinoma cancer. CEA levels greater than 15 ng/mL in the blood indicate that patients who are examined are at high risk and require chemotherapy with either adjuvant or neoadjuvant. The prognosis of successful surgery in the first stage is better than the advanced stage. The success of treatment assessed the comparison based on CEA levels before surgery with CEA levels after surgery. Decreasing levels of CEA in each stage of surgical therapy will provide a different success; it is expected CEA has a role in assessing the success of surgical therapy each stage.

On the basis of these thoughts, the researchers collected medical records in the Medical Record Center Dr. Soetomo Hospital from 2015 to 2016 by assessing levels of CEA before and after surgery of colon and rectal

**METHODS**

This research was a retrospective observational study with a descriptive design based on secondary data in the form of CEA levels taken from the patient medical record. Analysis of CEA levels was performed in the medical records of a colon and rectal cancer patients. The study was conducted for 12 months starting from June 2016 until May 2017 at the Dr. Soetomo Hospital Surabaya with data retrieval from the Medical Record Center of Dr. Soetomo Hospital in a colon and rectal cancer patients pre and post-surgery CEA levels. The population in this study consisted of colon and rectal cancer patients who had been diagnosed by a digestive surgeon and treated at the Surgery Department of Dr. Soetomo Hospital Surabaya. The study samples were a colon and rectal cancer patients who underwent pre-surgical and post surgical CEA examination from January 2015 to December 2016 treated at the Surgery Room of the Dr. Soetomo Hospital, Surabaya. The amount of sample used in this study was by taking all data from the Medical Records that include the diagnosis of colon cancer and rectal cancer with pre-surgical and post-surgical CEA levels from January 2015 to December 2016. Inclusion were patients with colon cancer and rectal cancer as diagnosed by a digestive surgeon and examined for pre-surgical CEA and post-surgery, age ≥ 18 years.

The patients who already had surgery in the past. Exclusion for this research was a colon and rectal cancer patients with incomplete medical record data. Research variables were patients with colon cancer, rectal cancer, colon, and rectal cancer therapy, serum CEA levels (CEA pre and post-surgery).

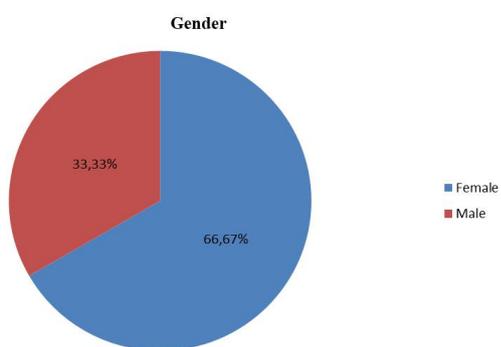


Figure 1. Distribution of sex

**RESULTS AND DISCUSSION**

This research was descriptive a observational study by taking data of medical records of colorectal cancer (colon and rectal cancer) patients pre and post-surgery examined for CEA, and were treated at the Dr. Soetomo Hospital from January 2015 until December 2016.

Based on data from the medical records obtained in 2016 there were as many as 1,186 patients with the diagnosis of colorectal cancer, while in 2015 as many as

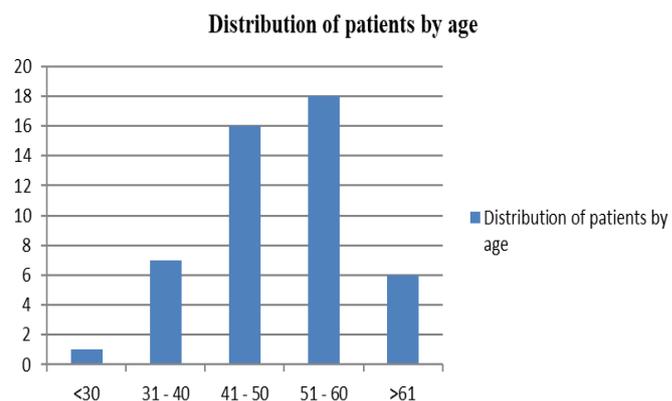
1,126 patients with the same diagnosis but who met the inclusion criteria were only 48 (2.08%) patients from 2,312 patients with complete CEA data pre and post surgery. The rest were incomplete such as only preoperative CEA levels, or postoperative CEA levels alone, the therapy did not include surgery but only chemotherapy while some were not mentioned the stage of the disease.

In this study, the female sex with more colorectal cancer were 32 patients (66.67%) out of 48 compared to male patients, 16 patients (37.33%). This can be seen in Figure 1.

Table 1. Distribution by sex and age

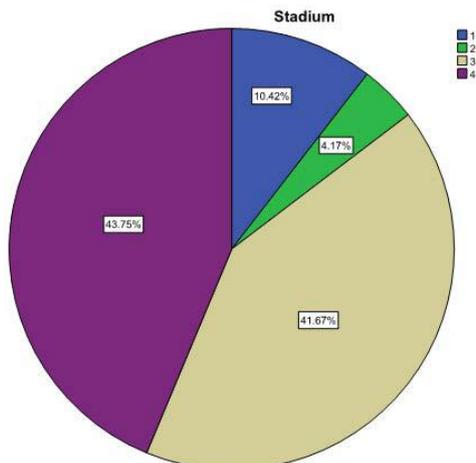
Age distribution	Male	Female	Total	Percentage (%)
<30	0	1	1	2.08%
31 – 40	1	6	7	14.58%
41 – 50	6	10	16	33.33%
51 – 60	6	12	18	37.50%
> 61	3	3	6	12.50%
Total	16	32	48	100%

Colorectal cancer most commonly affects people with age ranged between 51 years to 60 years (37.5%), while the next is the age group ranged from 41 years old up to 50 years (33.3%).



Figures 2. Distribution of the patients by age

The highest distribution of colorectal cancer patients was stage IV of 43.75% (21/48), followed by stage III 41.67% (20/48), stage I was 10.42% (5/48) and stage II as much as 4.17% (2/48). At the Dr. Soetomo Hospital, most colorectal cancer patients were patients who had reached stage 4. The second was colorectal cancer patients who had stadium 3. This was because the Dr. Soetomo Hospital is a referral hospital so that more common patients who come were at the time already in a late stages.



**Figure 3.** Distribution of patients based on the stage of colorectal cancer

The highest decrease in CEA was in stage 4 85% followed by stage 2 of 53.5%, then stage 1 was 43.4% and last stage 3 was 33.1%. So it turned out that colorectal cancer stage 4 showed the most decreased levels of CEA post-surgery.

Data obtained from the study were analyzed using SPSS 19.00. Each stage in the normality test with Kolmogorov-Smirnov, in colorectal cancer stage 1 and 2 normal data distribution ( $\alpha > 0.5$ ), then paired T-test was done to see whether the decrease was meaningful or not. The decrease of CEA was not significant at stage 1 ( $p = 0.199$ ) and stage 2 ( $p = 0.652$ ). Distribution of data at stage 3 and 4 is not normal ( $\alpha < 0.5$ ), then tested the Wilcoxon Rank test. There was a significant decrease in postoperative CEA levels ( $p = 0.009$ ) only in patients with stage 3 samples.

From these 48 samples, ten samples were actually higher in CEA after surgery than before surgery. There were 20.83% (10/48) samples whose CEA levels increased that from total samples. There were also samples with CEA levels that did not undergo change (persistent) from before surgery until after surgery. The sample rate was 6 samples (12.5% of samples).

**Table 3.** Average and range of CEA detection in colorectal cancer

Stadium	CEA levels operation	CEA levels post-operation
1	3.09 (0.17 – 5.83)	1.75 (0.84 – 3.14)
2	3.82 (0.15 – 7.48)	1.77 (1.46 – 2.08)
3	13.85 (1.09 – 71.21)	9.26 (<0.5 – 68.23)
4	183.77 (0.54 – 286.1)	27.28(0.51 – 155.10)

This study was a descriptive observational of colorectal cancer by observing changes in serum CEA levels in pre-operative and post-operative sera. Data obtained by researchers found more female patients than males as much as 32 people (66.67%) compared to male patients

as many as 16 people (37.33%). This data was in contrast to most other colorectal cancer studies in which there were more males than females. A possible cause is that the data taken were complete data CEA levels before and after surgery therapy, so do not reflect the overall colorectal cancer patients, colorectal cancer data obtained in 2015-2016 were as many as 2312 patients who are likely to be males.

The age of the most patients in colorectal cancer was in range of 41-60 years that was as much as 70.83%, the age range between 51 years to 60 years was as many as 37.5%, followed by the age range 41 years up to 50 years of 33.3%. The age above is most in accordance with age with high risk factors malignancy. The result was also in accordance with a research held at the Dr. Kariadi Hospital Semarang in 2009 and 2010 showing that the most affected colorectal cancer was at age 51 - 60.<sup>2</sup>

**Table 4.** Percentage decrease in pre and post CEA levels

Stage	Pre CEA levels	Post CEA levels	Difference between pre and post-CEA	% decrease
1	3,0920	1,7540	1.34	43.4%
2	3,8150	1,7700	2.04	53.5%
3	13,8510	9,2585	4.59	33.1%
4	183,7748	27,2800	156,49	85%

Colorectal cancer is a type of malignancy in the area of the colon and rectum are often dumped in the gastrointestinal tract. In developing countries, it is the second highest cause of death among all types of malignancy. Four stages determine the severity of colorectal cancer:<sup>3</sup> Stage 1. At this stage cancer has begun to grow in the colon (large intestine) but has not spread because the intestinal wall still blocked it; Stage 2. At this stage cancer has spread throughout the walls of the colon, even through the walls of the colon; Stage 3. At this stage the lymph nodes located adjacent to the colon have also been attacked by cancer cells; Stage 4. This stage is the most severe stage of colon cancer spread, where cancer has spread to distant organs such as the lungs and liver. Determination of this stage is critical to do in the process of diagnosis to determine the treatment of therapy for doctors treating colon cancer patients.

The distribution of stage of colorectal cancer patients in this study was the highest as stage IV of 43.75% (21/48), followed by stage III 41.67% (20/48), stage I was 10.42% (5/48), and stage II as much as 4.17% (2/48). At the Dr. Soetomo Hospital, most of the colorectal cancer patients are patients who have reached stage 4 which is the most severe stage that has undergone metastasis to lung or liver organs. The second largest is colorectal cancer patients who are at stadium 3. Thus, 85.42% of patients at the Dr. Soetomo Hospital come in a state that is already

late has reached the stage 3 and stage 4. The finding is common because Dr. Soetomo Hospital is a referral hospital so it encountered more patients who come at the time already in the final stadium.

Carcinoembryonic antigen is a glycoprotein present in the cell surface that enters the bloodstream, and is used as a serological marker to monitor the status of colorectal cancer, detect early relapse and spread to the liver. Pre-operative CEA levels are important for the identification of early metastases because metastatic tumor cells often result in elevated CEA levels. The American Society of Clinical Oncology (ASCO), 2006, stated that CEA examined before surgery can help in determining stages or action plans, while also monitoring the response during active treatment. Several factors that affect the CEA levels of colorectal cancer patients are tumor stage, degree, liver function, and its location.<sup>4</sup>

Carcinoembryonic antigen levels based on their stages

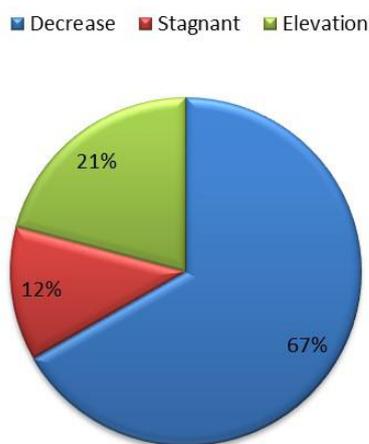


Figure 4. Differences between pre and post-operative CEA levels

can be seen in Table 3 showing mean CEA levels increased pre-operative. By the level of CEA in stage 1 was still at the mean level of 3.09 ng/mL, stage 2 at a mean level of 3.82 ng/mL, stage 3 was seen elevated at a mean level of 13.85 ng/mL and the highest CEA levels achieved in stage 4 of 183.77 ng/mL. This was similar to another researches<sup>5,6</sup> which stated that the higher the stage of colorectal cancer, the higher the levels of CEA produced.<sup>5,6</sup>

The highest decrease in CEA was in stage 4, 85% followed by stage 2 of 53.5%, then stage 1 43.4% and the last stage 3 at 33.1%. So it turned out in the colorectal cancer stage of the four most experienced decreased levels of CEA post-surgery. This is because the possibility of a person's immune system that has experienced advanced cancer has declined.

The carcinoembryonic antigen has a sensitivity and specificity of 70-80% in detecting recurrence. Carcinoembryonic antigen will decrease to normal within 4-8 weeks after resection of treatment. In the research that held at 2010 which using 16 colorectal cancer patients at the Dr

Kariadi Hospital Semarang from 2007-2009 showed that there was no decrease in CEA levels after therapy but did not mention what kind of therapy was used.<sup>7</sup> This is different from this study in which there was a decrease after surgery of 66.67% of patients. Significant decrease was found in stage 3 (p = 0.009), but for stage 1, 2, and 4 the decrease was not significant. Stage 1, 2, and 4 decrease is not significant, this is indicated by the result of the p-value of each stage more than 0.05. This is probably because stage 1 and 2 show the state of cancer has grown in the colon (stage 1), even has penetrated the colon wall (stage 2) where the number of patients is very low is 7 people (14.6%) so it does not reflect the state of content real CEA. In stage 4 the number of sufferers is quite a lot of 43, 75%, the level of CEA is not significant probably caused by having metastases to distant organs that vary from one patient to another patient. Only in the third stage had a significant decrease where the number of patients was 41.67%.

Based on one of the research on the topic of evaluating serum CEA levels before and after the surgery in Turkey, said that high CEA levels remained postoperative 59.3% for unclear reasons.<sup>8</sup> The levels of CEA before abnormal surgery were significantly correlated with the depth of tumor invasion, metastasis to lymph nodes, TNM staging, and recurrence. For postoperative abnormal CEA levels significantly associated with depth of tumor invasion, TNM staging and postoperative relapse. TNM is a classification system introduced by the American Joint Committee on Cancer and International Union Against Cancer in 1987 that is extension or extension of tumor (T), gland involvement (N) and distant metastases (M).<sup>8</sup>

Interestingly in this study, initially suspected after surgery would have been a decrease in CEA levels in accordance with the hypothesis of this study. However, 10 people (20.83%) experienced an increase in postoperative CEA levels, while 6 (12.5%) had stable levels before or after surgery. The causes of elevated CEA after surgery are still estimates, such as the possibility of metastases outside the colon and rectum.

**CONCLUSION AND SUGGESTION**

There was a difference of pre-surgical CEA level in stage 1 with the mean of 3.09 ng/mL with a range from 0.17 to 5.83 ng/mL and post-stage surgery with an average of 1.75 ng/mL with a range of 0.84-3.14 ng/mL. There was a difference of pre-surgical CEA level in stage 2 with mean of 3.82 ng/mL with range of 0.15-7.48 ng/mL and post-surgery with an average of 1.77 ng/mL with a range of 1.46-2.08 ng/mL. There was difference of pre-surgical CEA level in stage 3 with a median of 13.85 ng/mL with a range of 1.09-71.21 ng/mL and post-stage stem surgery with median 9.26 ng/mL with range <0.5-68.23 ng/mL.

There was a difference of pre-surgical CEA level in stage 4 with median 183.77 ng/mL with a range of 0.54-2861 ng/mL, and post-stage stem 4 with median

27.28 ng/mL with range 0.51-155.10 ng/mL. There was a decrease in CEA levels in stage 1, 2, and 4, but not significantly, whereas in stage 3 showed decreased mean CEA levels. There was a decrease in CEA levels from the total number of patients with 67%, which as its CEA levels remain at 12% and as much as 21% of its CEA levels increase. Research should be continued by looking at the degree of histopathology, TNM staging and the type of surgery as well as the therapy to determine and see the benefits of postoperative CEA reduction in 6 to 8 weeks after surgery.

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