Correlation Between Tumor Cell Differentiation and CEA Levels in Patients with Adenocarcinoma of the Rectum

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Abstract

Adenocarcinoma of the rectum is the most common colorectal cancer in Indonesia. This cancer has the highest recurrence after curative surgical therapy with or without adjuvant therapy. With the advancing modern histopathology and molecular biology, the prognosis after therapy can be predicted through surveillance using tumor cell differentiation and carcinoembryonic antigen (CEA). The aim of this study was to analyze the correlation between tumor cell differentiation and serum CEA level in patients with adenocarcinoma of the rectum in Dr. Hasan Sadikin General Hospital Bandung, Indonesia. This was a retrospective observational analytic study conducted from January 2018–January 2019. There were 36 patients involved in this study consisting of 3 patients (8.3%) diagnosed with Stage II, 10 patients (27.7%) with Stage IIIA, 20 patients (55.5%) with stage IIIB, and 3 patients (8.3%) with stage IIIC. On histopathological examination, it was demonstrated that 19 patients (52.8%) were well-differentiated, 15 patients (41.7%) were moderately differentiated, and 2 patients (5.6%) were poorly differentiated. The mean CEA level (CI 95%) for well-differentiated patients before surgery was 138.18 (15.99–260.38) ng/mL while the same level for the moderately differentiated patients was 64.34 (34.34–163.02) ng/mL. The mean CEA level for poorly differentiated patients was 1.55 (6.71–9.81) ng/mL. The result of the Kruskal Wallis test showed a p-value of 0.004. There is a strong correlation between the level of tumor cell differentiation and CEA level.

Keywords: Adenocarcinoma of the rectum, carcinoembryonic antigen (CEA), tumor cell differentiation

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Introduction

Colorectal cancer is one of the most common malignancy in digestive tract. Data from Globocan 2018, colorectal cancer is the third most common malignant neoplasm worldwide and the second cause of cancer death worldwide. In Indonesia, incidence of colorectal cancer is the fourth malignancy (12/100,000) after breast cancer, cervical cancer, and lung cancer. And rectal cancer is the eight most common cause of death in Indonesia. From all the various cases of rectal cancer in Indonesia, adenocarcinoma is the most common type.

Patients with adenocarcinoma of the rectum at Dr. Hasan Sadikin General Hospital are the patients with advanced cases (locoregional and distant metastasis). Patients with adenocarcinoma of the rectum has the highest recurrence compared to other colorectal cancer, because it is in a narrow pelvic cavity. The therapeutic outcome of patients with adenocarcinoma of the rectum depends on the type, genetics, biology, and level of tumor cell differentiation.

To assist the diagnosis, tumor markers are needed and the latest tumor markers currently in use have reached the molecular level. Recommendation of the American Society of Clinical Oncology (ASCO) states that Carcinoembryonic Antigen (CEA) can be used as a molecular tumor marker to help staging, planning, and monitoring therapeutic response. The tumor cell differentiation is one of the factors that influence CEA levels in patients with adenocarcinoma of the rectum. Other factors are: stage of tumor, location of tumor, impaired liver function, intestinal obstruction, and smoking history. Furthermore, tumor size is also a factor that influences CEA. Level of tumor cells differentiation is divided into: well differentiated, moderately differentiated, poorly differentiated and undifferentiated. The worse the tumor cell differentiation, the worse the prognosis.

Because of that, this study need a research to assess the correlation between tumor cell differentiation with the levels of the CEA expression in patients with adenocarcinoma of the rectum at Dr. Hasan Sadikin General Hospital. The benefits of this study are expected to assist the assessment of the prognosis and its relevancy to the therapeutic plan in patients with adenocarcinoma of the rectum in Dr. Hasan Sadikin General Hospital. Furthermore, considering the majority of patients who come with an advanced stage have a high frequency and high recurrence, so it is necessary to determine the best tumor markers in the process of assessing prognosis and post-operative surveillance or definitive management.

Methods

This study was a retrospective analytic observational study with a cross-sectional design, then a correlation analysis was performed. Data was collected from medical records of patients who had been treated at the Digestive Surgery Polyclinic at Dr. Hasan Sadikin General Hospital with a diagnosis adenocarcinoma of the rectum from January 2017–January 2018. And this study has been approved by Dr. Hasan Sadikin General Hospital’s Ethical Committee (LB.02.01/X.6.5/38/2020).

Inclusion criteria of this study were: Patients diagnosed with adenocarcinoma of the rectum based on the results of histopathological examination of the adenocarcinoma with degrees of well differentiated, moderate differentiated and poorly differentiated with the same tumor size and tumor stage had not undergone metastasis, Having a complete medical record including gender, age, and CEA level (which is taken immediately after diagnosis is established before surgery or other therapies).

Exclusion criteria of this study were: There are other malignancies, metastases, have other chronic diseases (impaired liver function), have synchronous tumors, intestinal obstruction, gastroenteritic inflammatory diseases which are found from abdominal CT scans with contrast, have undergone definitive therapy, such as surgery and chemotherapy, patients with adenocarcinoma of the rectum with other histopathological results (which does not include rectal adenocarcinoma), history of smoking which is obtained from the patient’s history.

The data then processed and presented in the form of narratives, tables, and images based on the results of statistical analysis. Then the One Way ANOVA Statistical Test is used if the data is normally distributed and the alternative is Kruskal Wallis test if the data is not normally distributed. The significance criteria are the value of p, if p≤0.05 it means significant or statistically significant, and p>0.05 is not significant or not statistically significant. P value <0.05: there is a significant correlation between the two variables tested. P value >0.05; there is no significant correlation between the two variables tested.
The data was recorded in a special form and then processed through the SPSS program version 25.0 for Windows.19

### Results

During the period January 2017 to January 2018, 36 patients with adenocarcinoma of the rectum met the inclusion criteria and became the study sample, 3 from 36 patients were diagnosed with stage II adenocarcinoma, 10 from 36 patients were diagnosed with Stage IIIA, 20 patients were diagnosed with stage IIIB and the remaining 3 patients diagnosed with stage IIIC. The data of the Preoperative CEA level, was tested using the Kruskal Wallis Test because the data were not normally distributed. Statistical test results from this study group, the preoperative CEA level was 0.004 (P value <0.05), which means it was significant or statistically significant. Thus can be explained that there are statistically significant differences between the Preoperative CEA Level variables in Tumor Cell Differentiation group.

### Discussion

Carcinoembryonic Antigen (CEA) is widely used to assess postoperative recurrence and preoperative prognosis. In a study conducted by Fahrizal et al. it was stated that there was a

### Table 1 Characteristics of Study Samples

| Variable                              | (n=36)          |
|---------------------------------------|-----------------|
| Age                                   | 53.53 (49.31-57.75) |
| Mean (CI95%)                          | 56.00           |
| Median                                | 22.00-77.00     |
| Range (min-max)                       |                 |
| Sex                                   |                 |
| Male                                  | 19              |
| Female                                | 17              |
| Staging                               |                 |
| II                                    | 3               |
| IIIA                                  | 10              |
| IIIB                                  | 20              |
| IIIC                                  | 3               |
| Level of tumor cell differentiation   |                 |
| Well differentiated                   | 19              |
| Moderately differentiated             | 15              |
| Poorly differentiated                 | 2               |
| CEA level before surgery              |                 |
| Mean (CI 95%)                         | 99.83 (25.97-173.68) |
| Median                                | 14.35           |
| Range (min-max)                       | 0.20-1000.00    |

* CI: confident interval

### Table 2 Description of CEA Levels Before and After Surgery Based on the Tumor Cell Differentiation Level Group

| Variable                              | Level of Tumor Cell Differentiation |
|---------------------------------------|-------------------------------------|
|                                      | Well Differentiated | Moderately Differentiated | Poorly Differentiated |
|                                      | n=19                 | n=15                      | n=2                    |
| CEA Level Before Surgery              |                      |                          |                        |
| Mean (CI 95%)                         | 138.18 (15.99-260.38) | 64.34 (34.34-163.02)     | 1.55 (8.28-10.78)      |
| Median                                | 25.70                | 7.30                      | 1.55                   |
| Range (min-max)                       | 3.80-1000.00         | 0.20-693.20               | 0.50-2.00              |
| CEA Level After Surgery               |                      |                          |                        |
| Mean (CI 95%)                         | 89.80 (21.63-201.23) | 43.12 (20.93-107.17)     | 1.25 (8.28-10.78)      |
| Median                                | 19.70                | 5.40                      | 1.25                   |
| Range (min-max)                       | 3.60-1000.00         | 0.90-447.30               | 0.50-2.00              |

*CI: Confident Interval
significant relationship between CEA levels and the incidence of metastases in colorectal cancer. In that study it was said that there was a strong and significant relationship between CEA levels with the metastatic of the colorectal carcinoma. From 55 patients with colorectal carcinoma, 36 patients with CEA level above normal limit without metastases and 18 patients with metastases in the liver, lungs, and bones.3,4

Whereas in a study conducted by Suwanagool et al in Japan in 1990, patients with adenocarcinoma of the rectum with well differentiated tumor levels had CEA levels ≥ 5ng/mL were 61.5%, moderate differentiated were 38.2% and poorly differentiated 0.2%.9

In this study, the histopathological features is divided into 3, well differentiated, moderately differentiated, and poorly differentiated. It was found that the most histopathological features were well differentiated by 19 patients, followed by moderately differentiated 15 patients, then poorly differentiated by 2 patients. By using Kruskal Wallis statistical analysis, the p value=0.004; it shows that there is a significant correlation with positive direction and moderate correlation (quite strong) between the level of tumor cell differentiation with the CEA levels before therapy. The correlation between the level of tumor cell differentiation with the CEA levels before therapy in patients with well differentiation will be higher compared to rectal adenocarcinoma patients with poor differentiation. Although not all rectal adenocarcinoma patients with poorly differentiation have low serum CEA levels, for example in a study by Suwanagool et al., It was found that 1 rectal adenocarcinoma patient with poorly differentiation had high serum CEA levels (out of a total of 55 patients).9

Therefore, for laboratory findings to be more efficient and effective, the researchers recommend that CEA examination in patients with adenocarcinoma of the rectum in Dr. Hasan Sadikin General Hospital Bandung to be examined after the examination of the tumor cell differentiation, and specifically in patients with rectal adenocarcinoma with well differentiation. So that the costs for laboratory examinations will be more efficient without reducing the effectiveness.

The disadvantage of this study is the small sample size (when compared with studies conducted by Suwaganool et al), so further research is needed regarding the correlation between the tumor cell differentiation with serum CEA levels before therapy in patients with adenocarcinoma of the rectum using larger samples. The two most common factors that cause the small sample of this study; firstly the lack of compliance of medical personnel to complete the medical records and the lack of awareness of the surrounding communities to check their health to the doctor. Most of the patient were prefer to get traditional treatment rather than medical treatment, especially for cancer cases. So that many patients were come with advanced cases.

In conclusion, patients with adenocarcinoma of the rectum in Dr. Hasan Sadikin General Hospital Bandung shows that patient with well

| Variable                  | Well Differentiated | Moderately Differentiated | Poorly Differentiated | P Value |
|---------------------------|---------------------|---------------------------|----------------------|---------|
| CEA Level Before Surgery  |                     |                           |                      | 0.004** |
| Mean (CI 95%)             | 138.18 (15.99–260.38)| 64.34 (34.34–163.02)     | 1.55 (6.71–9.81)     |         |
| Median                    | 25.70               | 7.30                      | 1.55                 |         |
| Range (min-max)           | 3.80–1000.00        | 0.20–693.20               | 0.90–2.20            |         |

*CI : Confident Interval
differentiation has the higher CEA level. In order to be more efficient and effective, the researchers suggest that the examination of CEA levels in patients with adenocarcinoma of the rectum is examined after the examination of Tumor Cell Differentiation and examined in patients with well differentiation.

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