Differences in Carcinoembryonic Antigen (CEA) Levels Based on the Degree of Histopathological Differentiation of Colorectal Cancer: Single Center Observational Study at Dr. M. Djamil General Hospital, Padang, Indonesia

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A B S T R A C T

Background: Colorectal cancer is the third malignancy and second leading cause of death in the world. CEA levels before surgery can be used as a cancer marker to help staging, planning, monitoring therapy and disease recurrence. One factor that influences CEA levels is the degree of differentiation of cancer cells. This study aims to determine differences in CEA levels based on the degree of histopathological differentiation in colorectal cancer patients at Dr. M. Djamil General Hospital Padang. **Methods:** This study was a cross-sectional analytical observational study using medical record data from colorectal cancer patients from January 2021 – August 2023. The sample was 65 patients who met the inclusion and exclusion criteria. CEA examination uses the ELFA method. The Mann Whitney test was used to see differences in CEA levels based on the degree of differentiation, statistically significant if p < 0.05. **Results:** A total of 65 patients with an average age of 56.89 years, 58.5% men, 41.5% women. A total of 10 patients were stage I, 29 stage II, and 26 stage III. Based on histopathology, 50 patients were classified as low grade and 15 as high grade. Low-grade CEA levels were 67.72 (3.14-200) ng/mL, while high grade were 3.2 (0.57-11.42) ng/mL. There was a significant difference in CEA levels based on histopathological differentiation (p < 0.001). **Conclusion:** CEA levels are higher in low-grade than high-grade colorectal cancer.

1. Introduction

Colorectal cancer, which includes cancer of the colon and rectum, has become a frightening threat to human health throughout the world. In 2020, this cancer was ranked third in terms of new cases and the second leading cause of death, with an estimated 10 million new cases and 5 million deaths. In Indonesia, the shadow of colorectal cancer is no less gloomy. Data for 2020 shows that this cancer is in third place with 34,733 new cases and 15,333 deaths. These figures are a loud alarm that reminds us of the importance of prevention efforts, early diagnosis, and appropriate treatment to combat this disease. Colorectal cancer is

characterized not only by uncontrolled cell growth but also by complexity in terms of cell differentiation. Cell differentiation refers to the process by which cancer cells develop from stem cells into more specialized cells. The level of cancer cell differentiation can be categorized into two, namely low grade and high grade. Low-grade cancer cells are more similar to normal cells and have slower growth, while high-grade cancer cells are more different from normal cells and have faster and more aggressive growth.[1-3]

These differences in levels of cell differentiation have important implications for the development and prognosis of colorectal cancer. Low-grade cancer cells

generally have a better prognosis compared to high-grade cancer cells. This is because low-grade cancer cells are generally more responsive to therapy and have a lower risk of metastasis. Carcinoembryonic antigen (CEA) is a protein produced by several types of cells, including colorectal cancer cells. CEA levels in the blood can be used as a cancer marker to help with diagnosis, staging, monitoring therapy, and detecting disease recurrence. High CEA levels in colorectal cancer patients are generally associated with more aggressive cancer growth and a worse prognosis. Although much research has been conducted on colorectal cancer, there is still a gap in knowledge regarding the relationship between cell differentiation and CEA levels in colorectal cancer patients in Indonesia. This study aims to fill this gap in knowledge by examining differences in CEA levels based on the degree of histopathological differentiation in colorectal cancer patients at Dr. M. Djamil General Hospital Padang. High CEA levels in patients with low-grade cell differentiation can be an indicator of a worse prognosis, so doctors can provide more intensive attention and therapy. A decrease in CEA levels after therapy can be an indicator of a good response to therapy, while an increase in CEA levels can signal disease recurrence. Information about cell differentiation and CEA levels can help doctors choose the therapy that best suits the characteristics of the patient and the cancer.[4-6] This study aims to determine differences in CEA levels based on the degree of histopathological differentiation in colorectal cancer patients at Dr. M. Djamil General Hospital, Padang, Indonesia.

2. Methods

This study used a cross-sectional analytical observational approach to examine the relationship between CEA levels and the degree of differentiation of colorectal cancer cells. This research design allows researchers to observe research variables at one specific point in time and then analyze the relationships between these variables. This approach was chosen because this research did not aim to manipulate research variables, but rather to understand the natural relationships that occur in colorectal cancer patients. The population of this study were all colorectal cancer patients who were diagnosed and underwent surgery at Dr. M. Djamil General Hospital Padang from January 2021 to August 2023. The research sample was selected using a non-probability purposive sampling method. Inclusion and exclusion criteria were applied to ensure a representative sample and appropriate to the research objectives. The inclusion criteria are patients with a histopathological diagnosis of colorectal cancer, patients who have undergone colorectal cancer resection surgery, and patients with CEA-level data available in the medical record. Meanwhile, the exclusion criteria are patients with pre-operative therapy (for example, chemotherapy or radiation), patients with significant postoperative complications, and patients with incomplete medical record data. A total of 65 patients who met the inclusion and exclusion criteria were included in this study.

Research data was obtained from two main sources: 1. Medical Records: Patient data such as age, gender, cancer stage, and histopathological examination results were collected from medical records. 2. CEA Level Examination: CEA level examination is carried out using the Enzyme Linked Fluorescent Immunoassay (ELFA) method on patient blood samples. The ELFA method was chosen because it has high sensitivity and specificity for measuring CEA levels in blood. Data analysis was carried out using SPSS 26.0. The Mann-Whitney test was used to see differences in CEA levels based on the degree of cancer cell differentiation. This test was chosen because the CEA-level data is non-parametric. A p-value < 0.05 was considered statistically significant.

3. Results

This study involved 65 patients with colorectal cancer who underwent surgery at Dr. M. Djamil General Hospital Padang between January 2021 and August 2023. The average age of patients is 56.89 years with an age range of 34-82 years. A total of

58.5% of patients were male and 41.5% female. A total of 15.4% of patients were at stage I, 44.6% at stage II, and 40% at stage III. The distribution of cancer stages showed that the majority of patients (85%) were in stages II and III, which indicates disease that has progressed locally or regionally. Based on histopathological examination, 76.9% of patients had low-grade cancer cell differentiation, while 23.1% had high-grade cancer cell differentiation. The proportion of patients with low-grade cancer cell differentiation was higher than those with high-grade cancer cell differentiation. This suggests that most patients have cancer cells that grow more slowly and have a better prognosis. Table 1 shows that this study included patients with colorectal cancer who were diverse in terms of age, gender, cancer stage, and cancer cell differentiation.

Table 1. Characteristics of respondents.

Characteristics	Frequency (%)	Average (SD)
Age (years)	-	56,89 (11,08)
Gender		
Male	38 (58,5%)	-
Female	27 (41,5%)	-
Cancer stages		
Stage I	10 (15,4%)	-
Stage II	29 (44,6%)	-
Stage III	26 (40%)	-
Cancer cell differentiation		
Low grade	50 (76,9%)	-
High grade	15 (23,1%)	-

Table 2 shows significant differences in CEA levels in colorectal cancer patients with low-grade and high-grade cancer cell differentiation. The average CEA level in the low-grade differentiation group was 67.72 ng/mL with a standard deviation of 54.42 ng/mL. The median CEA level in the low-grade differentiation group was 63.90 ng/mL. The range of CEA levels in the low-grade differentiation group was 3.14-200 ng/mL. The average CEA level in the high-grade differentiation group was 3.2 ng/mL with a standard deviation of 2.84 ng/mL. The median CEA level in the high-grade differentiation group was 3.2 ng/mL. The range of CEA levels in the high-grade differentiation group was 0.57-11.42 ng/mL. The Mann-Whitney test showed a significant difference in CEA levels between the low-grade and high-grade differentiation groups with a p-value <0.001. This means that CEA levels in patients with low-grade differentiation are significantly higher than in patients with high-grade differentiation.

Table 2. CEA levels based on cancer cell differentiation.

Cancer cell differentiation	Frequency	Average (SD)	Median (Range)	p-value
Low grade	50	67,72 (54,42)	63,90 (3,14-200)	0,001
High grade	15	3,2 (2,84)	3,2 (0,57-11,42)	

4. Discussion

This study found significant differences in CEA levels in colorectal cancer patients with low-grade and high-grade differentiation. This indicates that CEA levels can be used as a marker to help differentiate the degree of cancer cell differentiation in these patients. These findings support the research hypothesis and are in line with previous research showing similar trends. Several previous studies have examined the relationship between CEA levels and cancer cell differentiation in colorectal cancer patients. One study found that CEA levels were significantly higher in patients with low grade differentiation compared to those with high grade differentiation. This is associated with the ability of low-grade cancer cells to produce more CEA and higher tumor vascular permeability. Other studies also show similar results. This study found that CEA levels can be used as an independent marker to predict the prognosis of colorectal cancer patients. Patients with higher CEA levels have a higher risk of death compared with patients with lower CEA levels. The findings of this study have important clinical implications in the diagnosis and treatment of colorectal cancer. High CEA levels in patients with colorectal cancer may be an indicator of low-grade cell differentiation, which generally has a better prognosis. This can help doctors make a more accurate diagnosis and determine the appropriate treatment strategy. CEA levels can be used to monitor a patient's response to colorectal cancer therapy. A decrease in CEA levels after therapy may indicate a good response, while an increase in CEA levels may indicate disease recurrence. Information about cancer cell differentiation and CEA levels can help doctors choose the therapy that best suits the characteristics of the patient and the cancer. Patients with low grade cell differentiation and high CEA levels may require more aggressive therapy compared with patients with high grade cell differentiation and low CEA levels.[7-10]

Carcinoembryonic antigen (CEA) is a protein produced by several types of cells, including cancer cells. CEA levels in the blood can be used as a cancer marker to help with diagnosis, staging, monitoring therapy, and detecting disease recurrence. Research shows that CEA levels are higher in colorectal cancer patients with low-grade cancer cell differentiation compared to those with high-grade differentiation. This phenomenon is interesting to study in more depth, considering its implications in cancer diagnosis and prognosis. CEA secretion in cancer cells involves several complex processes, which can vary depending on the type of cancer and the level of cell differentiation. Low-differentiated cancer cells have a structure and function that is more similar to normal cells compared to highly differentiated cancer cells. Certain normal cells, such as intestinal epithelial cells, naturally produce small amounts of CEA. Low-differentiated cancer cells, due to their similarity to normal cells, have the ability to retain this function and produce CEA in greater quantities. Mutations in the gene that controls CEA expression can increase the production of this protein. Low-differentiated cancer cells are more susceptible to genetic mutations compared to highly differentiated cancer cells. This mutation can cause activation of the CEA gene, thereby increasing CEA secretion. Low-differentiated cancer cells often experience hypoxic conditions (lack of oxygen) and use anaerobic glycolysis (glucose metabolism without oxygen) to produce energy. This condition can trigger activation of the CEA gene and increase protein secretion. Chronic inflammation, which often occurs around tumors, can induce CEA secretion by low-differentiated cancer cells. Inflammatory cytokines, such as IL-6 and IL-8, which are produced during chronic inflammation, can activate the CEA gene and increase protein secretion. The tumor microenvironment, consisting of cancer cells, stromal cells, and signaling molecules, can influence CEA secretion. Stromal cells, such as fibroblasts and inflammatory cells, can produce factors that stimulate CEA secretion by low-differentiated cancer cells. Knowledge of the mechanisms of higher CEA secretion in low-differentiated cancer cells has several important clinical implications. High CEA levels can help

diagnose and staging colorectal cancer, especially in patients with low grade cancer cell differentiation. A decrease in CEA levels after therapy can be an indicator of a good response to therapy, while an increase in CEA levels can signal disease recurrence. High CEA levels in colorectal cancer patients with low grade cancer cell differentiation are generally associated with a worse prognosis. This is because low-differentiated cancer cells are generally more aggressive and have a higher risk of metastasis. Higher CEA secretion in low-differentiated cancer cells is a complex phenomenon involving multiple mechanisms. Understanding this mechanism can help doctors in the diagnosis, staging, therapy monitoring, and prognosis of colorectal cancer, especially in patients with low grade cancer cell differentiation. Further research is needed to identify new therapeutic targets that can inhibit CEA secretion and improve treatment outcomes in colorectal cancer patients.[11-14]

Previous studies have shown that CEA levels in colorectal cancer patients with low-grade cell differentiation are significantly higher than those with high-grade differentiation. One factor thought to contribute to this difference is higher vascular permeability in tumors with low-grade differentiation. Vascular permeability refers to the ability of blood vessels to pass molecules and fluids. As vascular permeability increases, larger molecules, such as CEA, can more easily exit the blood vessels and enter the surrounding tissue. Several mechanisms underlie the higher vascular permeability in low-grade tumors. Low-grade tumors generally have newly formed blood vessel tissue (angiogenesis) that is more fragile and leaky compared to normal blood vessels. This is caused by overexpression of angiogenic growth factors, such as VEGF, which promote the formation of new blood vessels. Blood vessels in low-grade tumors often have abnormal structures, such as uneven diameters, thin wall structures, and an increased number of gaps between endothelial cells. These structural changes make blood vessels leak more easily. Low-grade cancer cells can release inflammatory mediators, such as prostaglandins and leukotrienes, which can increase

vascular permeability by triggering vasodilation and the release of protein fenestrations in endothelial cells. High vascular permeability in low-grade tumors has several important consequences. CEA produced by low grade cancer cells can more easily leave the tumor and enter the bloodstream through leaky blood vessels. This causes an increase in CEA levels in the patient's blood, which can be used as a marker for cancer. High vascular permeability can facilitate cancer metastasis by allowing cancer cells to more easily exit the tumor and enter the bloodstream. Cancer cells circulating in the blood can then embed in other organs and form metastases. High vascular permeability can cause tumor edema, which is a buildup of fluid in the tumor. Tumor edema can interfere with blood flow and delivery of oxygen and nutrients to cancer cells, which can negatively impact cancer cell growth and survival. The finding of higher vascular permeability in low-grade tumors has several important clinical implications. CEA levels can be used as a cancer marker to assist in diagnosis, staging, and monitoring therapy in low-grade colorectal cancer patients. Tumor vascular permeability may be a novel therapeutic target for colorectal cancer. Anti-angiogenic agents, which can inhibit the formation of new blood vessels and reduce tumor vascular permeability, are being studied as potential therapies for low-grade colorectal cancer. Tumor vascular permeability may be a prognostic factor in colorectal cancer patients. Patients with low-grade tumors who have high vascular permeability may have a worse prognosis compared with patients who have low vascular permeability. Further research is needed to understand in more depth the mechanisms underlying higher vascular permeability in low-grade tumors and to develop more effective therapeutic strategies to target tumor vascular permeability and improve treatment outcomes in colorectal cancer patients.

Higher vascular permeability in low-grade tumors is one factor that contributes to higher CEA levels in colorectal cancer patients with low-grade cell differentiation. Understanding the mechanisms and consequences of high tumor vascular permeability

may aid in the development of new cancer markers, therapeutic targets, and prognostic strategies for colorectal cancer.[15-17]

Colorectal cancer, which includes cancer of the colon and rectum, is one of the most common and deadly types of cancer in the world. One of the important factors that determines the prognosis and treatment strategy in colorectal cancer patients is tumor size. Larger tumors generally have a poorer prognosis and require more aggressive therapy. Besides tumor size, cancer cell differentiation is also an important factor influencing patient prognosis and treatment. Cancer cell differentiation refers to the degree of similarity of cancer cells to normal cells. Cancer cells with low differentiation (low grade) are more similar to normal cells and have slower growth, while cancer cells with high differentiation (high grade) are more different from normal cells and have faster and more aggressive growth. Research has shown that there is a relationship between tumor size and cancer cell differentiation in colorectal cancer patients. Cancers with low differentiation generally have larger tumor sizes than those with high differentiation. Cancer cells with low differentiation have a slower cell proliferation rate compared to cancer cells with high differentiation. This means that cancer cells with low differentiation take longer to grow and divide. As a result, low-differentiated tumors generally grow more slowly and are smaller in the early stages of diagnosis. Apoptosis is the process of programmed cell death. Cancer cells with low differentiation generally have higher levels of apoptosis compared to cancer cells with high differentiation. This means that cancer cells with low differentiation die more easily and cannot develop into large tumors. Cancer cells with low differentiation generally have lower invasion and metastasis abilities compared to cancer cells with high differentiation. This means that cancer cells with low differentiation do not easily spread to other tissues and organs in the body. As a result, low-differentiated tumors generally have a lower risk of metastasis and their size does not. Low-differentiated cancers are generally more responsive to therapy compared with highly differentiated cancers. This means that low-differentiated tumors are generally easier to control with treatments such as chemotherapy and radiation. As a result, the growth of tumors with low differentiation can be inhibited more effectively, so their size is not. The relationship between tumor size and cancer cell differentiation in colorectal cancer patients has several important clinical implications. Tumor size and cancer cell differentiation can be used as factors determining cancer stage. Cancer stage is an important indicator for determining a patient's prognosis and treatment strategy. Cancer with low differentiation and small tumor size generally has a better prognosis compared to cancer with high differentiation and large tumor size. Tumor size and cancer cell differentiation can be used as a guide to choosing the right therapy for the patient. Patients with large, highly differentiated tumors generally require more aggressive therapy, such as chemotherapy and high doses of radiation.[18-20]

5. Conclusion

This study found that there was a significant difference in CEA levels in colorectal cancer patients with low-grade and high-grade differentiation. Higher CEA levels in low-differentiated colorectal cancer can be used as a marker to help differentiate the degree of cancer cell differentiation and determine appropriate treatment strategies.

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