The Relationship Between Carcinoembryonic Antigen (CEA) and The Severity Risk of Colorectal Adenocarcinoma Grading

Gusti Ayu Laksmi Dewi Saputri[a], Ketut Sudartana[a], I Made Mulyawan[a]

e-mail: gstayulaksmi.dewisaputri@gmail.com

[a]Department of Surgery, Prof. dr. I.G.N.G. Ngoerah Hospital, Faculty of Medicine, Universitas Udayana, Bali, Indonesia

Abstract

Colorectal carcinoma is the third most common malignancy among all carcinoma patients. Carcinoembryonic antigen (CEA) is used as a tumor marker for colorectal carcinoma patients as it is inexpensive, easily measured through serum tests, and can be repeated multiple times with minimal impact, however its use in the risk of colorectal adenocarcinoma is unclear. We aimed to investigate the relationship between CEA levels and the severity risk of grading in colorectal adenocarcinoma patients. There is a significant relationship between grading and CEA, namely, the higher the CEA, the worse the grading becomes. No significant difference was found between the CEA values in different grades, but the average value increases as the grading of colorectal carcinoma worsens. A CEA value of 8.45 serves as the cut-off point for worse differentiation, with a sensitivity of 61.8% and a specificity of 65.2%.
Keywords: colorectal carcinoma, colorectal adenocarcinoma, carcinoembryonic antigen, CEA

1. Main text

1.1. Introduction

Colorectal carcinoma is the third most common malignancy among all carcinoma patients and the fourth leading cause of death among all carcinoma-related deaths worldwide. In 2014, 136,830 patients were diagnosed with colorectal carcinoma, and 50,130 of them died from the disease (Kuipers et al., 2015). In Indonesia, colorectal carcinoma is also the third most common type. In 2008, Indonesia ranked fourth among ASEAN countries, with an incidence rate of colorectal carcinoma at 17.2 per 100,000 adults, with a mortality rate of 8.4% of all carcinoma cases; this number is predicted to continue rising annually (Sayuti et al., 2019). Nearly 98% of colorectal cancers are adenocarcinomas.

Colorectal carcinoma originates from precancerous lesions. Early detection at the initial stage of the lesion can reduce the morbidity and mortality of this malignancy. Additionally, non-invasive markers are needed to assist in the early diagnosis of colorectal carcinoma (Swiderska et al., 2014). Currently, biochemical tests are very helpful in managing carcinoma patients, including colorectal carcinoma. Several carcinomas are associated with abnormalities in enzyme, protein, and certain hormone production that can be measured in plasma or serum, known as tumor markers. Tumor markers are also a relatively commonly used screening test in the community and are easy to perform. Their primary clinical use is as a laboratory test to support diagnoses (Effendi R et al., 2015). Tumor cells produce a unique substance or compound that indicates the presence of a tumor. Tumor markers are also useful for identifying the type of tumor. Colorectal carcinoma has a tumor marker called Carcinoembryonic Antigen (CEA) (Yunasti et al., 2018).

Levels of CEA can be associated with tissue inflammatory responses. Carcinoma begins with long-term or chronic inflammation. CEA is a heavy glycoprotein molecule with carboxyl groups containing a hydrophobic area where glycosyl phosphatidylinositol groups from cell membranes attach. CEA is obtained from biopsy results of tissues and from serum (Duffy et al., 2001).

Several studies have been conducted to support CEA as a tumor marker for colorectal carcinoma. These include research on the relationship between CEA levels and the stages of colorectal carcinoma at Sanglah hospital in 2016, and the relationship between CEA and the degree of differentiation and location of colorectal tumors at Haji Adam Malik Hospital in Medan. The findings have been diverse, thus creating some controversy about CEA as a tumor marker for colorectal carcinoma. There are still questions about the applicability of CEA as a tumor marker for

determining the management of colorectal carcinoma. Some studies show that higher CEA levels correlate with higher or more severe stages, and that CEA levels increase in well-differentiated compared to poorly differentiated rectal carcinomas, which makes surveillance using CEA level tests less reliable (Buchari et al., 2018; Hall et al., 2019). However, other studies found opposite results, or that CEA is independent of histopathological features (Buchari et al., 2018). According to the guidelines for managing colorectal carcinoma, the Ministry of Health states that CEA levels are significant for ongoing monitoring after surgical intervention, with a sensitivity of 44% and specificity of 90% for detecting recurrence. Regular CEA level tests are needed after surgical intervention for surveillance and prognosis determination. There is no evidence stating that CEA should be used as a screening test, as its sensitivity and specificity are low, limiting its use in determining prognosis at early stages (Liang et al., 2014). CEA is used as a tumor marker for colorectal carcinoma patients as it is inexpensive, easily measured through serum tests, and can be repeated multiple times with minimal impact (Liang et al., 2014).

This study aimed to investigate the relationship between CEA levels and the severity risk of grading in colorectal adenocarcinoma patients. It is expected to serve as baseline data to support existing research or to address some of the ongoing controversies.

1.2. Materials and Methods

This study is an analytical-observational research with a cross-sectional design that aims to examine CEA levels in patients diagnosed with colorectal adenocarcinoma. It was conducted by analyzing data from the Medical Records Installation of RSUP Prof. dr. I.G.N.G Ngoerah in Denpasar, Bali. Patients with colorectal adenocarcinoma at RSUP Prof. dr. I.G.N.G Ngoerah Denpasar who meet the inclusion and exclusion criteria were included. The inclusion criteria wre patients with colorectal carcinoma who were treated at RSUP Prof. dr. I.G.N.G Ngoerah in the years 2020-2021 and are recorded in the medical records. The exclusion criteria are patients with other carcinomas and those with incomplete medical records. Sample collection is done using quota sampling. Samples are selected by including all samples that meet the inclusion criteria until the required number of samples is fulfilled. The evaluated parameters included age, colorectal adenocarcinoma grade, and CEA. Grading of colorectal carcinoma is the result of supplementary histopathological examination, which contains information about the degree of differentiation of colorectal carcinoma. It consists of an evaluation of how much the tumor or neoplasm has developed (differentiated), the number of mitoses within the tumor, and the degree of difference between cancer cells and normal cells. G1 (Well-differentiated) involves atypical glands, disorganization with epithelium, pleomorphic nuclei, hyperchromatic, coarse chromatin, and eosinophilic cytoplasm. G2 (Moderately differentiated) involves proliferative glands, disorganization with isolated epithelium, pleomorphic nuclei, hyperchromatic, irregular nuclear membrane, and eosinophilic cytoplasm. G3 (Poorly differentiated) involves dysplastic epithelial cells, enlarged pleomorphic nuclei, coarse chromatin, eosinophilic cytoplasm, and partially glandular structures still appearing. CEA is a glycoprotein found on the surface of cells that enters the bloodstream and is used as a serological marker to monitor the status of colorectal carcinoma. The CEA value before the first therapy is examined and recorded in the medical records. It is assessed based on the results of blood laboratory tests (Normal: ≤5 ng/mL, increased: >5 ng/mL). Before conducting data analysis, a verification of data accuracy and completeness is performed. Data is tabulated, coded, and entered into analysis. The data analysis method used is an observational analytical method using computer data processing software. The hypothesis test used is the Spearman correlation test. The description of the data obtained includes the patient's age, gender, CEA levels, and carcinoma stage, and is presented in the form of frequency tables and graphs.

1.3. Results

The average age of the sample obtained is 53.49 years (SD 1.30). The number of female samples in this study is greater, with 31 females and 26 males. The treatment modalities for the sample (patients with colorectal carcinoma) include surgery, chemotherapy, and undergoing both surgery and chemotherapy. The highest total number of patients underwent both surgery and chemotherapy, with 33 samples. The grading of colorectal carcinoma in the sample showed that the data was divided into three gradings, with the largest number of samples, 31, falling under G2. Of the 57 samples for which CEA levels were known, the average CEA level was 34.10 (SD 8.61). Table 1 shows the data characteristics of the sample and research variables.

Table 1. Samples' Characteristics

Characteristics	(n=57)
Age (Years) (average ± SD)	53.49 ± 1.30
Sex (n, %)	
Male	26 (45.6%)
Female	31 (54.4%)
Treatment modalities (n,%)	
Operation	22 (38.6%)
Chemotherapy	2 (3.5%)
Operation + chemotherapy	33 (57.9%)
Grade (n, %)	
G1	23 (40.4%)
G2	31 (54.4%)
G3	3 (5.3%)
CEA (ng/mL) (average ± SD)	34.10 ± 8.61

Table 2, using Spearman's correlation test, shows a significant positive correlation (p=0.048) between grading and CEA levels, indicating that higher CEA levels are associated with worse grading. The P-value for this relationship is 0.048.

Table 2. CEA and Colorectal carcinoma grade

Grade Variable	CEA
r-value	0.203
p-value	0.048*
n	57

*significant (p<0.05)

Table 3 indicates that no statistically significant difference (p = 0.988) was found between the CEA levels in grades G1, G2, and G3. However, the average value of CEA tends to increase with the severity of the colorectal carcinoma grading.

Table 3. CEA Average value difference between grade groups

Grade	CEA (ng/mL) (rerata ± SD)	F	p
G1	32.62 ± 82.16	0.12	0.988
G2	34.87 ± 53.27		
G3	37.38 ± 38.63		

A CEA value greater than 8.5 carries a threefold greater risk of being classified as grading G2-G3 compared to those with a CEA value less than 8.5, as shown in table 4.

Table 4. Risk Analysis of CEA value on colorectal carcinoma grade

Variables	Grade		OR	IK 95%	p
	G2-G3	G0-G1			
CEA ≥8.5	21 (72.4%)	8 (27.6%)	3.02	1.06-9.11	0.044*
CEA <8.5	13 (46.4%)	15 (53.6%)			

The ROC (Receiver Operating Characteristic) graph in figure. 1 below indicates that a CEA value of 8.45 serves as the cut-off point for predicting worse degrees of differentiation. This comes with a sensitivity of 61.8% and a

specificity of 65.2%. The Confidence Interval (CI) range is from 0.47 to 0.77, suggesting that this cut-off point is clinically meaningful. A CEA (Carcinoembryonic Antigen) value greater than 8.5 carries a risk of progressing to grading G2-G3 that is three times higher than for individuals with a CEA value of less than 8.5. This indicates a significant correlation between elevated CEA levels and a more advanced or aggressive grade of colorectal adenocarcinoma. Therefore, this finding could be important for clinicians in terms of risk stratification and planning appropriate treatment for patients.

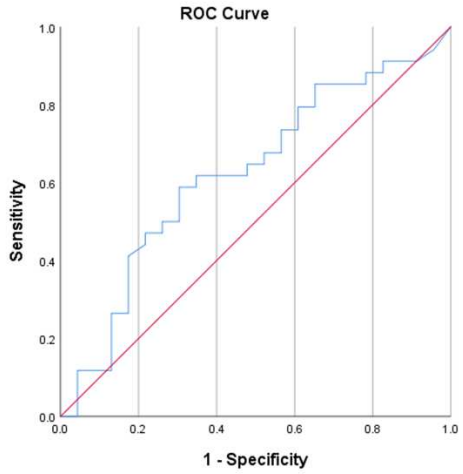

Figure 1. Receiver operating characteristics (ROC) curve of CEA and Colocrectal carcinoma grade

1.4. Discussion

The sample characteristics in this study include age, gender, treatment modality, histopathologic grading based on anatomical pathology results, and CEA levels. In the data analysis, the average age of the sample was found to be around 53 years (SD 1.30). According to previous research, more than 30% of cases were found in patients aged 40 or younger, while in developed countries, patients younger than 50 make up only 2-8% (Sayuti et al., 2019). In 2017 at Sanglah General Hospital, 44 cases were found with the youngest patient being 23 and the oldest 80 years old (Batara et al., 2018). Other research also mentioned that the most frequent age group was 50-59 years, making up 18 people (32.7%), followed by the age group of 60-69 with 13 people (23.6%), and 70-79 years old with 10 people (18.2%). The sample in this study has more females (31 individuals) compared to males (26 individuals). This aligns with some literature stating that colorectal carcinoma is the second most common carcinoma among women. Other studies state that it occurs more frequently in men (23.6%) than women (16.3%) per 100,000.

Treatment of colorectal cancer varies and is assessed considering the tumor size, stage at diagnosis, tumor location, risk of relapse, and the patient's physical health (Nakayama et al., 2016). Generally, the treatment options are surgery, chemotherapy, or both. The largest proportion of the sample, 33 individuals, underwent both surgery and chemotherapy. Histopathologic grades are determined by a pathologist and describe the degree of differentiation of tumor cells. Normal cells are well-differentiated, whereas cancer cells are less well-differentiated; the less differentiated a cell is, the faster it grows and the more likely it is to metastasize. Histopathologically, cancer can be divided into well-differentiated (G1), moderately differentiated (G2), poorly differentiated (G3), and undifferentiated (G4). In the sample, grading of colorectal carcinoma was found to be divided into 3 grades, with the largest number of samples, 31, being in the G2 category.

Previous research has shown that normal CEA levels in healthy tissue are <3 ng/ml, but in malignant conditions, they can reach levels up to 60 times higher than the normal limit. Among the 57 samples with known CEA levels, the average CEA level was 34.10 (SD 8.61).

there is a significant positive correlation between CEA levels and the grading of colorectal carcinoma (P-value: 0.048). This suggests that higher CEA levels in the blood correspond to worse histopathological grading of the cancer. This grading is usually measured on a scale from G1 to G3 or G4, where G1 represents the best-differentiated tumors, and G3 or G4 represents the worst-differentiated ones.

Although there is no significant difference in CEA levels between G1, G2, and G3 based on your Table 5.3, the average CEA levels appear to increase as the grading worsens. This indicates that while it may not be sufficient to distinguish between grades with certainty, CEA levels can serve as an additional indicator of how far the cancer has progressed.

Moreover, the ROC graph shows that a CEA level of 8.45 can be considered as a cut-off point for predicting worse differentiation, with a sensitivity of 61.8% and a specificity of 65.2%. This suggests that patients with CEA levels above 8.5 are three times more likely to have worse grading (G2-G3) compared to those with CEA levels below 8.5.

Overall, this data reaffirms that CEA is a useful biomarker not only for early detection but also for monitoring the progression of colorectal carcinoma, particularly in the context of the degree of differentiation. Adenocarcinoma accounts for 98% of colorectal carcinoma. Carcinoembryonic Antigen (CEA) is a serum marker for the presence of colon and rectal carcinoma. CEA is a glycoprotein found on cell surfaces that enters the bloodstream and is used as a serological marker to monitor the status of colorectal cancer and to detect early recurrence and metastasis to the liver. CEA is too insensitive and nonspecific to be used for colorectal cancer screening. However, elevated serum CEA levels are associated with several parameters. High CEA values are related to tumor grades 1 and 2, advanced stages of the disease, and the presence of metastasis to internal organs. Although serum CEA concentration is an independent prognostic factor, its value can only be considered significant in ongoing monitoring after surgery (Nazha et al., 2015).

In the research results, there is a significant positive correlation between grading and CEA, meaning that higher CEA levels will result in worse grading, with a P-value of 0.048. This is in line with previous research; some studies have shown that rectal cancer with well-differentiated histopathology produces higher CEA compared to poorly differentiated ones. However, in theory, it is stated that in colon cancer, the absence of a basal lamina occurs and there is an increase in the amount of tissue. Additionally, tumor cells lose their polarity, and CEA is distributed around the cell surface. This is known to cause components of the plasma membrane to be continuously "exfoliated" from the surface as derivatives of blood vessel plasma membranes, allowing CEA to freely access blood vessels or lymph through intercellular tissue. According to tumor size, CEA will increase and accumulate in the blood.

In the test comparing average differences in CEA values with the grading of colorectal carcinoma, no significant difference was found between the CEA values in G1, G2, and G3. However, the average value increased as the grading of colorectal carcinoma worsened. The research findings can be considered in screening and in determining the grading and subsequent management of patients with colorectal carcinoma at RSUP Prof Dr. I G.N.G. Ngoerah.

The limitation of this study is that it only focuses on three gradings and does not consider the duration of the disease in each sample studied. Therefore, further research is needed to understand the relationship between CEA values and more varied sample characteristics and histopathology with higher grading.

1.5. Conclusion

There is a significant relationship between grading and CEA, namely, the higher the CEA, the worse the grading becomes. No significant difference was found between the CEA values in different grades, but the average value increases as the grading of colorectal carcinoma worsens.

2. Acknowledgements

None

3. References

1. Buchari UB.2018. Perbedaan Kadar CEA Menurut Derajat HIstopatologi adenokarsinoma Rektum DI RSUP Haji Adam Malik Medan. Thesis. Universitas Sumatera Utara.

2. Chen CC, Yang SH et al. 2005. Is it reasonable to add preoperative serum level of CEA and CA19-9 to staging for colorectal cancer?. Journal of Surgical Research,124(2):169-174

3. Duffy MJ.2001. Cracinoembryonic Antigen as a Marker for Colorectal Cancer: Is it Clinically Useful? Clinical Chemistry,47(4):623-30.

4. Effendi R, Rey I.2015. Molecular Diagnostics in Colorectal Cancer. Molecular Diagnostics in Colorectal Cancer,16(1):26-32.

5. Fisher SR, Daniels IR.2007. The clinical presentation of colorectal cancer. Cambridge University Press,pp.10.

6. Granados-Romero JJ, alderrama-Treviño AI, Contreras-Flores EH et al.2017. Colorectal cancer: a review. Int J Res Med Sci,5(11):4668-70

7. Gold P, Freedman S.1965. Specific Carcinoembryonic Antigens Of The Human Digestive System. Journal of Experimental Medicine (JEM),122(3):467–481.

8. Hall C, Clarke L, Pal A et al. 2019.A Review of the Role of Carsinoembryonic Antigen in Clinical Practice. Ann Coloproctol,35(6):294-302.

9. Hammarstrom, S. 1999. The carcinoembryonic antigen (CEA) family: structures, suggested functions and expression in normal and malignant tissues. Seminar in Cancer Biology, 9(2), 67-81.

10. Horig, H.2000. Strategies for Cancer Theraphy Using Carcinoembryonic antigen vaccines.ISNN Cambridge University Press 1462-3994 (1-24)

11. Kuipers EJ, Grady WM, Lieberman D et al.2015. Colorectal cancer. Nature Reviews Disease Primers;1:1-8.

12. Liang Y, Tang W, et al.2014. Genetic Variations Affecting Serum Carcinoembryonic Antigen Levels and Status of Regional Lymph Nodes in Patients with Sporadic Colorectal Cancer from Southern China. Plos One. Juni,9(6):1-16

13. Marmol I, Sánchez-de-Diego C, Dieste AP et al.2017.Colorectal Carcinoma: A General Overview and Future Perspectives in Colorectal Cancer. Int. J. Mol. Sci,8(197):3-5.

14. Saur NM.2020.Colorectal Cancer: Symptoms, Risk Factors, Diagnosis and Treatment. Colorec Cancer,6(2):1.

15. Sayuti M, Nouva 2019. Karsinoma kolorektal. Jurnal Averrous,5(2):76-87.

16. Siegel RL, Miller KD, Jemal A.2016. Cancer statistics, 66: 7–30.)

17. Swiderska M, Choromanska B, Dabrowska E et al. 2014. The diagnostics of colorectal cancer. Contemp Oncol (Pozn),18(1):1-6.

18. Tomasevic Z, Jelic S et al. 2003. Negative CEA values in metastatic colorectal carcinoma and the likelihood of complete chemotherapy response. Int J Biol Markers,18(1):28-32

19. Yunasti Batara IGNPN, Sueta MAD, Adnyana MS.2018.Hubungan Antara Kadar Carcinoembryonic Antigen (CEA)Dan Stadium Karsinoma Kolorektal Di Rsup Sanglah Tahun 2016-2017. E-Journal Medika,7(12):1-4.