RESEARCH ARTICLE

pISSN: 0126-074X | eISSN: 2338-6223
MKB. 2020;52(4):233–37
https://doi.org/10.15395/mkb.v52n4.2028

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 that19 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

Hubungan Tingkat Diferensiasi Sel Tumor dengan Kadar Ekspresi CEA Pada Pasien Adenokarsinoma Rektum

Abstrak

Adenokarsinoma rektum merupakan kanker kolorektal paling tinggi di Indonesia. Kanker ini memiliki kekambuhan tertinggi setelah terapi bedah kuratif dengan atau tanpa terapi adjuvan. Dengan kemajuan histopatologi dan biologi molekuler modern, prognosis setelah terapi dapat diprediksi melalui surveilans menggunakan tingkat diferensiasi sel tumor dan carcinoembryonic antigen (CEA). Tujuan penelitian ini adalah menganalisis hubungan diferensiasi sel tumor dengan kadar CEA serum pada pasien adenokarsinoma rektum di RSUP Dr. Hasan Sadikin Bandung, Indonesia. Penelitian ini merupakan penelitian analitik observasional retrospektif yang dilaksanakan pada periode Januari 2018–Januari 2019. Terdapat 36 pasien yang dilibatkan dalam penelitian ini terdiri dari 3 pasien (8,3%) terdiagnosis Stadium II, 10 pasien (27,7%) Stadium IIIA, 20 pasien (55,5) %) dengan stadium IIIB, dan 3 pasien (8,3%) dengan stadium IIIC. Pada pemeriksaan histopatologi, terlihat bahwa 19 pasien (52,8%) berdiferensiasi baik, 15 pasien (41,7%) berdiferensiasi sedang, dan 2 pasien (5,6%) berdiferensiasi buruk. Rata-rata tingkat CEA (CI 95%) untuk pasien dengan diferensiasi baik sebelum operasi adalah 138,18 (15,99–260,38) ng/mL sedangkan tingkat yang sama untuk pasien dengan diferensiasi sedang adalah 64,34 (34,34–163,02) ng/mL. Rata-rata tingkat CEA untuk pasien dengan diferensiasi buruk adalah 1,55 (6,71–9,81) ng/mL. Hasil uji Kruskal Wallis menunjukkan nilai p 0,004. Ada korelasi kuat antara tingkat diferensiasi sel tumor dan tingkat CEA.

Kata kunci: Adenokarsinoma rektum, carcinoembryonic antigen (CEA), tingkat diferensiasi sel tumor

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Introduction

Colorectal cancer is one of the most common malignancies in the digestive tract[1]. Globocan in 2018 stated that colorectal cancer is the third most common malignant neoplasm worldwide and the second global cause of death due to cancer.[2] In Indonesia, colorectal cancer is the fourth most frequent malignancies (12/100.000) after breast cancer, cervical cancer, and lung cancer. Moreover, rectal cancer is the eighth most common cause of death in Indonesia. From all various cases of rectal cancer in Indonesia, adenocarcinoma is the most common type.[3]

Patients with adenocarcinoma of the rectum at Dr. Hasan Sadikin General Hospital are patients with advanced cases, i.e., locoregional and with distant metastasis. Patients with adenocarcinoma of the rectum have a higher recurrence than other colorectal cancer because of the nature of the rectum as 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.[4]

Tumor markers are required to assist the diagnosis, and the latest tumor markers currently in use have reached the molecular level. The recommendation of the American Society of Clinical Oncology (ASCO) stated that Carcinoembryonic Antigen (CEA) can be used as a molecular tumor marker to help the staging, planning, and monitoring of therapeutic response.[5] Tumor cell differentiation is one of the factors that influence the CEA level in patients with adenocarcinoma of the rectum, with other factors include the stage of the tumor, location of the tumor, impaired liver function, intestinal obstruction, and smoking history. Tumor size is also a factor that influences CEA.[6,7]

The level of tumor cell differentiation is divided into well-differentiated, moderately differentiated, poorly differentiated, and undifferentiated. Worse tumor cell differentiation reflects worse the prognosis.[5]

Hence, this study sought to assess the correlation between tumor cell differentiation and the level of the CEA expression in patients with adenocarcinoma of the rectum treated at Dr. Hasan Sadikin General Hospital Bandung. In terms of benefits, this study is expected to be able to assist in the assessment of the prognosis and its relevancy to the therapeutic plan in patients with adenocarcinoma of the rectum. Furthermore, considering most patients come with an advanced stage, meaning with a high frequency of recurrence, it is necessary to determine the best tumor markers in for assessing prognosis and postoperative surveillance or definitive management.

Methods

This was a cross-sectional retrospective analytic observational study on data collected from medical records of patients who treated at the Digestive Surgery clinic of Dr. Hasan Sadikin general Hospital with a diagnosis of adenocarcinoma of the rectum from January 2017–January 2018. This study has been approved by Dr. Hasan Sadikin General Hospital's Ethical Committee (LB.02.01/X.6.5/38/2020).

The inclusion criteria of this study were patients diagnosed with adenocarcinoma of the rectum based on the results of histopathological examination of the adenocarcinoma with well-differentiated, moderate differentiated, and poorly differentiated degrees with the same tumor size and tumor stage that had not involved metastasis. The medical record should also be complete and included data on gender, age, and CEA level, taken immediately after the diagnosis was established before surgery or other therapies.

The exclusion criteria of this study were other malignancies, metastases, presence of other chronic diseases (such as impaired liver function), synchronous tumors, intestinal obstruction, gastroenteritic inflammatory diseases as identified from abdominal CT scans with contrast, underwent definitive therapy (such as surgery and chemotherapy), presence of adenocarcinoma of the rectum with other histopathological results which did not include rectal adenocarcinoma, and smoking history.

Date were then processed and presented in the form of narratives, tables, and images based on the results of statistical analysis. The One Way ANOVA Statistical Test was used when data were normally distributed and Kruskal Wallis test was used as an alternatives if data were not normally distributed. The significance criterion used was the p-value with $p \leq 0.05$ considered to be statistically significant. A p-value of <0.05 demonstrated a significant correlation between the two variables tested while the p-value of > 0.05 demonstrated otherwise. Data were recorded in a dedicated form and then processed using the SPSS program version 25.0 for Windows.

Table 1 Subject Characteristics

Variable	(n=36)
Age	
Mean (CI95%)	53.53 (49.31–57.75)
Median	56.00
Range (min-max)	22.00–77.00
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

Results

From January 2017 to January 2018, 36 patients with adenocarcinoma of the rectum met the inclusion criteria and were recruited as study samples. Three patients were diagnosed with stage II adenocarcinoma, ten were diagnosed with stage IIIA, twenty were diagnosed with stage IIIB, and the remaining three were diagnosed with stage IIIC.

Data on the Preoperative CEA level was tested using the Kruskal Wallis test since the data were not distributed normally. The results showed that the preoperative CEA level was 0.004 (P-value <0.05), which means it was significant or statistically significant. Thus, there were statistically significant differences between the Preoperative CEA Level variables in the Tumor Cell Differentiation groups.

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 is a significant relationship between the CEA level and the incidence of metastases in colorectal cancer. In their study, it was demonstrated that there is a strong and significant relationship between the CEA levels and metastatic colorectal carcinoma. Of 55 patients with colorectal carcinoma, 36 patients have a CEA level above normal limit without metastases and 18 patients

Table 2 CEA Level Before and After Surgery by 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 (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
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

Table 3 Comparison between CEA levels before surgery by Tumor Cell Differentiation Group

Variable	Level of Tumor Cell Differentiation			P Value
	Well Differentiated	Moderately Differentiated	Poorly Differentiated	
	(n=19)	(n=15)	(n=2)	
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

have metastases in the liver, lungs, and bones.[3,4] Whereas, in a study conducted by Suwanagool et al. in Japan, patients with adenocarcinoma of the rectum with well-differentiated tumor level and the CEA level of ≥5ng/mL contribute 61.5% of the subjects, with the remaining 38.2% and 0.2% are moderately and poorly differentiated, respectively.[9]

In this study, the histopathological features are divided into 3: well-differentiated, moderately differentiated, and poorly differentiated. It was found that the most frequently observed histopathological features were well-differentiated (n=19), followed by moderately differentiated (n=15) and poorly differentiated (n=2). The p-value obtained from the Kruskal Wallis statistical analysis was 0.004. This shows a significant correlation with positive direction and moderate correlation (quite strong) between the tumor cell differentiation level and the CEA level before therapy. The correlation between the level of tumor cell differentiation and the CEA level before therapy in patients with rectal adenocarcinoma is found to be statistically significant (p=0.004). Therefore, it can be concluded that there is a relationship between the level of tumor cell differentiation and serum CEA level before therapy in patients with rectal adenocarcinoma at Dr. Hasan Sadikin General Hospital Bandung during the period of January 2017-January 2018. The CEA level before therapy in patients with good differentiation will be higher compared to those rectal adenocarcinoma patients with poor differentiation. Although not all rectal adenocarcinoma patients with poor differentiation havea low serum CEA level, in a study by Suwanagool et al., for instance, it was found that one rectal adenocarcinoma patient with poorly differentiation has a high serum CEA level, from a total of 55 patients.[9]

Therefore, for laboratory findings to be more efficient and effective, it is recommended that CEA examination should be done in patients with adenocarcinoma of the rectum after the examination of tumor cell differentiation, specifically in patients with rectal adenocarcinoma with good differentiation. Therefore, the laboratory examination costs will be more efficient without reducing the effectiveness.

This study's limitation is the small number of samples when compared to studies conducted by Suwaganool et al. Therefore, further research is needed regarding the correlation between tumor cell differentiation and serum CEA leves before therapy in patients with adenocarcinoma of the rectum using larger samples. The two most common factors that cause the small number of samples of this study include 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 patients preferred to receive traditional treatment rather than medical treatment, especially for cancer cases. Therefore, many patients came with advanced cases.

In conclusion, patients with good differentiation have a higher CEA level. For more efficiency and effectiveness, the researchers suggest that the CEA level in patients with adenocarcinoma of the rectum is examined after Tumor Cell Differentiation examination and that examination should also be done in patients with good differentiation.

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