PROFILE OF CEA LEVELS IN COLORECTAL CARCINOMA PATIENTS: A DESCRIPTIVE ANALYTIC WITH CROSS-SECTIONAL DESIGN

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PROFILE OF CEA LEVELS IN COLORECTAL CARCINOMA PATIENTS: A DESCRIPTIVE ANALYTIC WITH CROSS-SECTIONAL DESIGN

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ABSTRACT Background: Colorectal cancer is the third most common malignancy worldwide and the second most lethal cancer in the world.[1],[2],[3] In general, the development of CRC is an interaction between environmental factors and genetic factors.[1] Carcinoembryonic Antigen (CEA) is a tumour marker that has been widely used throughout the world.[4] In addition to assessing recurrence and prognosis of CRC, CEA can also be used to assess the presence of metastasis.[5] **Objective:** To determine the profile of CEA levels in patients with CRC. **Methods:** This study was descriptive analytic research with a cross-sectional design. The study was conducted at Wahidin Sudirohusodo Hospital from Jun 2012 until Dec 2017. **Results:** Subjects who met the study criteria were 326 patients. CRC patients were more commonly found in male 179 (54,9%), the age range of 41-60 years 168 (51,5%), the most cell types was adenocarcinoma cells 288 (88.3%), moderate degree of differentiation 189 (58,0%) and the most location in the rectum 213 (65,3%). The majority of patients had no metastases 256 (78,5%). Degree of differentiation (p=0,0014) and metastasis (0,004) had significant correlation with CEA levels. Multivariate analysis showed that degree of differentiation (OR=3,0), metastasis (OR=2,2) and age ≤40 years old (OR= 1,7) were significantly associated with CEA levels (all p<0,05). **Conclusions:** The degrees of differentiation, metastases and age were associated with elevated CEA levels.

KEYWORDS Colorectal cancer, Carcinoembryonic antigen.

Introduction

Colorectal cancer is a malignancy that originates in the large intestinal tissue consist of the colon and rectum.[1],[6],[7],[8],[9] In general, the development of CRC is an interaction between environmental factors and genetic factors.[1] Most patients with colorectal cancer succumb to the effect of distant metastatic lesions, especially liver metastasis rather than the primary colorectal cancer itself.

Carcinoembryonic Antigen (CEA) is a tumour marker that has been widely used throughout the world.[4] In general, the clinical value of CEA in the management of colorectal cancer can be divided into two: 1) Assessment of tumour preoperational and its consequence; 2) Post operation monitoring of recurrence. The diagnostic capabilities of CEA in addition to assessing the prognosis of colorectal cancer is still very lack. Due to the limitation of CEA use for screening for colorectal cancer, assessment of metastasis is needed which is then associated with the CEA level.[5]

DOI:10.5455/IJMRCR.carcinoembryonic-antigen-colorectal-cancer
First Received: December 03, 2018
Accepted: December 27, 2018
Manuscript Associate Editor: Ivon Ribarova (BG)

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Several prior studies have also evaluated the correlation of CEA with metastasis in colorectal cancer. Similar to our study, Maradjabessy et al. concluded that there was a significant relationship between CEA levels and metastasis in colorectal cancer.[5] Lalosevic et al. reported that CEA serum levels were significantly higher in patients with metastases (p<0,05).[10] Chapman et al. showed that histological patients with poorly differentiated have a higher elevated of CEA levels in preoperative than well-moderately differentiated.[11]

Materials and Methods

This study was a descriptive, analytical study with cross-sectional design conducted at Wahidin Sudirohusodo Hospital in Makassar from Jun 2012 until Dec 2017. It has been approved by the ethical committee of Faculty of Medicine with reference number: 395/ H4.8.4.5.31 / PP 36-KOMETIK/ 2018.

A. Population

The population of this study were all inpatients and outpatients whose underwent serum CEA levels, colonoscopy, histopathology, ultrasound and or abdominal CT scan examination at Wahidin Sudirohusodo Hospital in Makassar. The inclusion criteria were CRC patients, the age ≥ 18 years old, complete medical record data, while exclusion criteria are incomplete medical record data.

B. Methods and data collection

Data collected from medical record patient were entered into the Wahidin Sudirohusodo hospital. Data for each patient were extracted from the database, to include age, gender, colorectal cancer diagnosis, CEA levels, histopathology examination, ultrasound and or abdominal CT scan.

C. Statistical analysis

Data were analyzed using the Statistical Package for Social Science (SPSS) program version 22. The statistical analysis performed was the calculation of frequency distribution and Chi-Square statistical test. Statistical test results were significant if the value of p <0.05.

Results

During the 5-years of the study period, we found 326 patients colorectal cancer with age range from 20-88 years old. (Table 1) shows the characteristic patients. (Table 1) shows CRC patients are more commonly found in male 179 (54,9%), the age range of 41-60 years 168 (51,5%) with the most cell types is adenocarcinoma cells 288 (88,3%), moderate degree of differentiation 189 (58,0%) with the most location in the rectum 213 (65,3%). The majority of patients had no metastases 256 (78,5%). Based on CEA levels, there was no difference in distribution between patients with CEA levels <5 ng/mL (50,9%) and CEA levels ≥ 5 ng/mL (49,1%). Table 2, shows that there is a significant difference in age distribution according to CEA levels (p <0.05). The proportion of subjects with CEA ≥5 ng/mL was highest at the age of 41-60 years (56,5%) and the lowest at the age of ≤40 years (38.5%).

(Table 3) shows the analysis relation between the degree of differentiation with CEA levels of patients. There is a significant correlation between the degree of differentiation with CEA

Table 1 Characteristics of CRC Patients (n=326)

Variables		n	%
Gender	Male	179	54,9
	Female	147	45,1
Age (Years)	≤40	52	16,0
	41-60	168	51,5
	>60	106	32,5
Types of Tumour Cell	Adenocarcinoma	288	88,3
	Mucinosum	38	11,7
Degree of Differentiation	Well	97	29,8
	Moderate	189	58,0
	Poor	40	12,3
Tumor Location	RCC	83	25,5
	LCC	30	9,2
	Rectum	213	65,3
Metastases	Yes	70	21,5
	No	256	78,5
Level of CEA (ng/ml)	<5	166	50,9
	≥5	160	49,1

Table 2 Gender Distribution According to CEA Levels in CRC patients

		CEA Levels (ng/ml)		
Age (years)		<5	≥5	Total
≤40	N	32	20	52
	%	61,5%	38,5%	100,0%
41-60	N	73	95	168
	%	43,5%	56,5%	100,0%
>60	N	61	45	106
	%	57,5%	42,5%	100,0%
Total	N	166	160	326
	%	50,9%	49,1%	100,0%
Chi-Square test (p=0,019)				

Table 3 Relation Between Degree of differentiation and CEA Levels in CRC patients (n=326)

		CEA Levels (ng/ml)		
Degree of differentiation		<5	≥5	Total
Well	N	58	39	97
	%	59,8%	40,2%	100,0%
Moderate	N	95	94	189
	%	50,3%	49,7%	100,0%
Poor	N	13	27	40
	%	32,5%	67,5%	100,0%
Total	N	166	160	326
	%	50,9%	49,1%	100,0%
Chi-Square test (p=0,014)				

Table 4 The relation between Metastases and CEA Levels in CRC Patients (n=326)

		CEA Levels (ng/ml)		
Metastases		<5	≥5	Total
Yes	N	25	45	70
	%	35,7%	64,3%	100,0%
No	N	141	115	256
	%	55,1%	44,9%	100,0%
Total	N	166	160	326
	%	32,5%	67,5%	100,0%
Chi-Square test (p=0,004)				

levels (p<0,05). The highest found in patients with poorly differentiated (67,5%) and the lowest found in well-differentiated (40,2%).

(Table 4) shows the analysis relation between metastases with CEA levels. There is a significant correlation between metastasis with CEA levels (p<0,01), with the proportion subject with CEA levels ≥5 ng/mL highest found with metastases (64,3%) than without metastases (44,9%).

(Table 5) shows multivariate analysis with significant variables associated with CEA levels. Multivariate analysis was performed using multiple logistic regression, to assess significant variables related to CEA by controlling other variables. The variables analyzed were age, tumour cell type, the degree of differentiation, tumour location and metastasis. Based on the odds ratio (OR), the most significant sequence of variables related to CEA is poor differentiation (OR = 3.0) having a risk 3.0 times greater than those with good differentiation to have elevated CEA levels. Metastases (OR = 2.2) has a risk 2.2 times greater than non-metastases to have elevated CEA levels. Moderate differentiation (OR = 2.2) has a risk of 2.2 times greater than those with well differentiated to have elevated CEA levels. At age 41-60 years (OR=0,6), which shows protective factors compared to age ≤40 years. In the other sentences that the age of ≤40 years has a risk of 10/6 (1,7) times greater than the age of 41-60 years to have elevated CEA levels. In conclusion, the results of multivariate analysis show that variables with the most significant related to CEA were degrees of differentiation, metastases and age.

Discussion

The diagnostic capabilities of CEA in addition to assessing the prognosis of colorectal cancer is still very lack. Due to the limitation of CEA use for screening for colorectal cancer, assessment of metastasis is needed which is then associated with the CEA level. (Table 1) describes the sample distribution by gender with males 54.9% were higher than females 45.1%. The range of age 41-60 years had the highest number of subjects 51,5% and the lowest number of subjects was found in the age range ≤ 40 years 16,0%. This result was similar the research by Permana et al. reported that the highest CRC subjects were found in the age range of 41-60 years.[12] In (table 2) shows that there was a significant difference in age distribution according to CEA levels (p<0,05). The proportion of subjects with CEA >5 ng/mL was found to be highest at the age of 41-60 years 56,5% and the lowest at age ≤40 years 38,5%. This was also supported by research conducted by Qin et al. shows that CRC patients in the age ≤60 years were more in male than female. The study by Lin et al. reported that the incidence of colorectal cancer in male was related to estradiol level. Normal amounts of estradiol function in spermatogenesis and fertility. However, the excessive amounts of estradiol inhibit the secretion of gonadotropin proteins such as LH which further reduces testosterone secretion. High amounts of testosterone have been shown to have a relationship with reduced risk of colorectal cancer.[14]

Based on the histopathological results shows that the type of tumour cells was higher in adenocarcinoma with 88.3% than mucus adenocarcinoma with 11.7% (see table 1). The degree of differentiation showed that the most subjects with CRC has a moderate differentiated of 58.0% while the poorly differentiated is at least 12.3%. These results were similar to Qin et al. research which reported that the type of histopathology of CRC patients was more adenocarcinoma than non-adenocarcinoma. In those study that was also found the degree of well and moderate differentiation was higher than poor differentiated.[14] Some of the causes CRC are tumour suppressors gene mutations such as APC, TP53, and activation of mutations in K-RAS oncogenes.[15] Histopathological features of the CRC are most often adenocarcinomas because most of the rectal mucous layer consists of poorly differentiated goblet cells due to prolonged exposure to carcinogens so that these cells can become malignant (adenocarcinoma).[15]

In our study found that the location of the tumour was mostly found in the rectum 65.3% and at least in the right colon 9.2%. The results of this study were similar with the researched by Permana F et al. reported that the higher CRC subjects were found at 77.8% rectum location than in the right colon and left colon.[12] However, those result was different from the study conducted by Chapman et al. which reported that the CRC subjects with right-sided location higher than the rectum and right sided.[11] The molecular pathogenesis of microsatellite in the left colon is different from the right colon. Right colon cancer generally has histological types of mucin adenocarcinoma and

Table 5 Multivariate Analysis with Significant variables associated with CEA levels in CRC patients (n=326)

Step	Variable	B	Wald	p	OR
Step1	Age:				
	≤40 years*		7.08	0,029	
	41-60years	-0,46	3,05	0,081	0,6
	>60years	0,38	1,04	0,307	1,5
	Type of Cell	-0,44	1,33	0,248	0,6
	The degree of Differentiation :				
	Well*		5,33	0,070	
	Moderate	0,70	3,27	0,071	2,0
	Poor	0,97	5,33	0,021	2,6
	Tumour Location:				
	RCC*		1,50	0,472	
	LCC	0,29	0,47	0,493	1,3
	Rectum	-0,24	0,75	0,387	0,8
	Metastases	0,84	8,22	0,004	2,3
Step2	Age:				
	≤40 years*		8,80	0,012	
	41-60 years	-0,50	3,60	0,058	0,6
	>60years	0,42	1,34	0,248	1,5
	Type of cell	-0,49	1,68	0,195	0,6
	Degree of Differentiation:				
	Well*		6,41	0,041	
	Moderate	0,76	3,98	0,046	2,1
	Poor	1,05	6,41	0,011	2,9
	Metastases	0,83	8,07	0,004	2,3
Step3	Age:				
	≤40 years*		8,77	0,012	
	41-60years	-0,54	4,36	0,037	0,6
	>60years	0,34	0,90	0,343	1,4
	The degree of Differentiation :				
	Well*		7,12	0,029	
	Moderate	0,79	4,24	0,040	2,2
	Poor	1,10	7,11	0,008	3,0
	Metastases	0,77	7,14	0.008	2,2

carcinogenesis involved mostly through microsatellite instability (MSI), and methylation CpG island methylator phenotype (CIMP) pathways. Whereas LCCs often show different histological types, carcinogenesis through chromosomal instability (CIN) pathways.[16],[17]

Based on the metastasis, the most subjects was without metastases 78.5%. This result was similar to the study conducted by Lalosevic et al., which reported that CRC subjects with no metastases 81,0% higher than subjects without metastases 19,0%.[10] In our study shows that CEA levels <5 ng/mL had higher subjects 50,9% than CEA levels ≥5 ng/mL 49,1%. This result was different from the study conducted by Permana F et.al which reported that the CRC subjects with CEA levels <5 ng/mL was higher than CEA levels ≥5 ng/mL.[12] In our study it was showed that there were no significant differences in the distribution of men and women based on CEA (p>0.05). Also, there was a significant difference in age distribution according to CEA levels (p<0,05). The proportion of subjects with CEA level ≥5 ng/mL was found to be highest at the age of 41-60 years 56,5% and the lowest at age ≤40 years 38,5%. Elevated serum CEA levels are varieties in CRC patients. Serum CEA levels are produced from several factors, include the average production of CEA from tumour cells, tumour location, stage, vascularization and elimination.[18]

In (table 3) Shows that there was a significant relationship between the degree of differentiation with CEA levels (p <0.05). This result was similar to the research conducted by Chapman et al. reported that patients with poorly differentiated have elevated CEA levels compared to well/moderate differentiated (chi-square test, P<0.005).[11] Poorly differentiated tumours are containing 5-50% glandular components adenocarcinoma mucinosum. While in well-differentiated tumours containing> 95% glandular structure and moderately differentiated tumours containing 50-95% glandular components.[6] In (table 4) shows that there was a significant relationship between metastasis with CEA levels (p<0,05), where the most proportion of subjects was with CEA levels ≥ 5 ng/mL 64,3%. This result was similar with the study of Lalosevic et al. who compared the examination of CEA levels with Ca 19-9 indicating the proportion of serum CEA and Ca 19-9 levels were significantly elevated in subjects with metastasis, with p-value <0.001. Overexpression of CEA is associated with liver metastasis.[10] Carcinoembryonic antigens block Pro-Glu-Leu-Pro-Lys (PELPK) located at 108-12 between N and A1 areas of the CEA domain hinges. The Penta amino acid sequence PELPK peptide is the motive for binding of CEA to Kupffer cells, which is associated with the initiation of metastatic and mesenchymal-epithelial transition (MET) liver metastases from circulating CRC cells.[3]

Multivariate analysis in this study was conducted using multiple logistic regression. Based on the odds ratio (OR), the most significant sequence of variables related to CEA is poorly differentiated (OR = 3.0), metastases (OR = 2.2) moderate differentiated (OR = 2.2) and age of ≤ 40 years (OR=1,7) (see table 5). In a multivariate analysis study conducted by Sun Z et al., reported that there was a correlation between CEA levels and several variables, including family history, smoking, tumour size, metastasis and tumour stage with a value of p <0.05. The hazard ratio (HR) in tumours with metastasis was 3 times compared to without metastasis. In the study, it was also reported that the serum preoperative CEA levels were highest in poor or undifferentiated differentiation. However, there was no relationship between CEA level and tumour cell type, the degree of differentiation, and tumour location where P> 0.05.[19] The high and low CEA

values apart from being determined by tumour stage were also determined by other factors such as the degree of differentiation, size of primary and metastatic tumours. The more cells that produce CEA, the more CEA in the blood circulation. Moreover, if metastasis occurs, then the CEA value will rise higher in the blood circulation.[12]

Conclusion

The degrees of differentiation, metastases and age were associated with elevated CEA levels.

Conflict of Interest

The authors declare that there is no conflict of interest in this study

Fund

All funds in this study were covered by personal fund of the authors.

Ethics Committee

It has been approved by the ethical committee of Faculty of Medicine with reference number: 395/ H4.8.4.5.31/ PP 36-KOMETIK/ 2018.

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