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Correlation between Carcinoembryonic Antigen (CEA) Levels and Colorectal Carcinoma Stage Using Computed Tomography (CT) scan : a Study at Dr. Hasan Sadikin Central General Hospital Bandung 2019

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ABSTRACT

Background : Colorectal carcinoma (CRC) ranks as the third most common cancer and the fourth most lethal cancer among other malignancy around the world. Carcinoembryonic antigen (CEA) is one of the most common tumor marker used in CRC for predicting prognosis and therapeutic response. Several studies reported correlation between CEA level and the clinical stage of CRC. The determination of clinical stage has an important role in management planning of CRC. Determination of the CRC clinical stage using Computed Tomography (CT) scan demonstrates good sensitivity and specivicity rates.

Objective : To review the correlation between CEA level and the stage of CRC using CT scan.

Methods : This study was of retrospective observational analytic study with cross sectional design. Simple random sampling was used to collect data from available medical records and the data were analyzed statisticaly using Spearman test.

Results: There were 40 subjects, 24 were men (60%) and 16 women (40%). The average age of the patients was 55,02±10,84 and ranged from 28 to 79 year old. The highest average CEA level was found in stage IV with a value of 351.26 + 833.65 ng/ml and the lowest average CEA level was in stage I with a value of 1.53 + 2.04 ng/ml. The results of the statistical test with Spearman gave a p value of 0.0001 ($p < 0.05$) and a correlation coefficient (R) of 0.588 showed a significant correlation between CEA level with clinical stage with a positive correlation direction and moderate correlation strength.

Conclusions : There is a significant correlation between CEA level with clinical stage of colorectal carcinoma using CT scan examination in Dr. Hasan Sadikin General Hospital.

Key words: Carcinoembryonic antigen (CEA)–clinical stadium–colorectal carcinoma–Computed Tomography (CT) scan.

1 INTRODUCTION

Colorectal carcinoma (CRC) is a malignancy arising from the colonic and rectal epithelium. The World Health Organization (WHO) classifies colorectal carcinoma as an entity, although colon cancer and rectal cancer have differences in diagnosis, surgery approach, recurrence rates and manage-

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ment, where rectal cancer receives neoadjuvant and radiotherapy that is not given to colon cancer [1].

Colorectal carcinoma has a high mortality and morbidity rate, which ranks as the third most common cancer and the fourth most lethal cancer among other malignancy around the world, after lung, gastric and hepatic cancer [2, 3]. Frequency in industrial countries tend to be higher with varying incidence in various countries in the world. Carcinoma of the sigmoid and rectal colon is one of the most common gastrointestinal malignancies that occupy 20% of all gastrointestinal malignancies [4, 5]. Incidence in males is higher with a ratio of 1.4 and tends to increase associated with sedentary lifestyle such as lack of physical activity, obesity, alcohol consumption, low-fiber diet, high intake of red meat and smoking habits [3]. Globocan data in 2012 revealed that the incidence of CRC in Indonesia was 12.8 per 100,000 adult population, with a 9.5% mortality rate from all cancer cases [6].

The most common type of CRC based on histopathology is adenocarcinoma (90%) derived from colorectal mucosal epithelial cells, followed by other types of carcinomas, such as neuroendocrine, squamous cell, adenosquamous, spindle cells and undifferentiated carcinoma [7, 8].

The determination of the CRC management depends on the clinical stage. CRC clinical stage determination can use the Modified Duke Classification System or based on TNM from the American Joint Committee on Cancer (AJCC). This TNM system is a classification of tumors based on tumor infiltration (T) characteristics, metastases to regional lymph nodes (N) and the presence of distant metastases to other organs (M). Colorectal malignancies are initially located in the intraepithelial mucosa, then invade submucosa, muscularis propria, pericolorectal tissue and finally invade the visceral peritoneum, and the surrounding structures and organs [8–10].

Carcinoembryonic antigen (CEA) is the most commonly used tumor marker for CRC. The Colorectal Working Group of the American Joint Committee on Cancer (AJCC) recommends the use of CEA and its prognostic value at various tumor stages, where elevated levels of CEA (defined as > 5 ng/ml) must be differentiated from normal CEA levels (<5 ng/ml) [2, 11].

CEA is a glycoprotein produced during intrauterine fetal development, in which excess CEA production after birth is considered abnormal and indicates a malignant process, especially CRC. "Carcinoembryonic" or "oncofetal" antigens reflect that CEA is produced by fetuses and some types of cancer. CEA values can also increase in several other conditions such as gastrointestinal tract infections, peptic ulcer, inflammatory bowel disease, pancreatitis, hypothyroidism, cirrhosis, biliary obstruction and also other malignancies such as lung cancer, gastric, thyroid, head-neck, cervix, liver, lymphoma and melanoma. Research conducted by Younesi et al shows that CEA can also increase in elderly people and smokers even though they do not suffer from CRC. According to study by Shinkins et al and Tarantino et al, elevated CEA level can also indicate CRC reccurence so that it could be used for periodic evaluation after treatment [12–14].

A study conducted by Vukobrat-Bijedic et al in 2013 showed that the highest CEA levels was found in CRC patients with liver metastases, followed by pulmonary metastases, lymph nodes and adipose tissue, so an increase in CEA levels was a tumor marker at an advanced stage [2]. Lee et al in 2017 stated that overexpression and elevated serum CEA levels in CRC patients are important factors in determining the stage of cancer and are associated with liver metastases through complex mechanisms [15]. In contrast to Vukobrat and Lee, Nan et al in 2016 stated that preoperative serum CEA levels in CRC patients is an indicator of prognosis but is independent of the stage of the cancer at the time of initial diagnosis [16].

Modality of choice to determine the stage of rectal cancer is Magnetic Resonance Imaging (MRI) or Endorectal Ultrasound (ERUS), while staging of colon cancer using Computed Tomography (CT) scan. High-risk rectal tumors based on MRI are defined as tumors with mesorectal fascia involvement, and are treated with chemoradiotherapy. There are no official guidelines for the administration of chemotherapy nor chemo radiotherapy in colon cancer, so the stage of colon cancer is carried out primarily to determine operability based on tumor growth into the surrounding structure and the presence of distant metastases [1].

Singla et al's study in India shows that multiplanar CT scan is a good radiodiagnostic modality for colon and rectal lesions because it can accurately depict the extent and involvement of primary and secondary lesions. CT scan on T1 and T2 lesions showed a sensitivity of 83.3%, specificity 92%, positive predictive value (NPP) 71.4% and negative predictive value (NPN) 95.8%. T3 lesions showed a sensitivity of 88.2%, specificity of 93.8%, NPP of 93.8% and NPN 86.7%, while T4 lesions showed sensitivity of 100%, specificity of 100%, NPP of 100% and NPN 100%.[4] MRI examination to determine the stage of CRC showed varying sensitivity and specivicity. The Dam et al study in 2017 showed MRI sensitivity for colon cancer is 89%, specificity 88% -96%, NPP 89% and NPN 88% -96% [17]. While Horvat et al's research in 2017 showed an MRI examination for rectal carcinoma had a sensitivity of 87% and specificity of 75% [18].

The diagnosis of a CRC is a collaboration of clinical, imaging, laboratory and gold standard from histopathological examination [8].

2 RESEARCH DESIGN AND METHODOLOGY

This study is an observational analytic study with cross sectional design. The simple random sampling method was applied to obtain 40 sample size by selecting retrospective data from colorectal carcinoma patient's medical record that fulfilled inclusion criteria who came for treatment at Dr. Hasan Sadikin Central General Hospital Bandung from January 2018 to July 2019. The subjects that were included in this study is those who had : 1). CEA examination from clinical pathology laboratory RSUP Dr. Hasan

Sadikin Bandung before any treatment 2). Had undergone abdominal-pelvic CT examination at Radiology Departement RSUP Dr. Hasan Sadikin Bandung 3). Confirmed as colorectal carcinoma patient from histopatological examination 4). Examined for chest x-ray or chest CT. Exclusion criteria for this study were: 1). Patients who had treatment before study (surgery, chemotherapy, radiotherapy) 2). Paients who had other malignancy in any other organs 3). Patients with any other diseases that could elevate the CEA level.

The CRC staging was determined by two radiologists who specialized in gastrointestinal and oncology imaging, using 8^{th} Edition TNM staging system from the American Joint Committee on Cancer (AJCC). Normality test uses Saphiro Wilk test and statistical analysis uses Spearman.

3 RESULTS

This study included 40 subjects with characteristics based on age and sex is shown in Table 1. In this study, out of a total of 40 subjects, most of the colorectal carcinoma patients in Dr. Hasan Sadikin Central General Hospital Bandung were men, 24 patients (60%), while women were 16 patients (40%). The average age was 55.02 + 10.84 year old, and the median was 57.5 year old. The youngest age being 28 year old and the oldest age being 79 year old.

Table 1. Characteristics of research subjects based on age and sex of patients with colorectal carcinomaat Dr. Hasan Sadikin Central General Hospital

Variable	n	%
Age (years)		
Mean (SD) : 55,02+10,84		
Median : 56,5		
Minimum : 28		
Maximum : 79		
Sex		
Male	24	60%
Female	16	40%
Total	40	100%

Table 2 demonstrates the characteristics of research subjects based on CEA level and CRC stage. The mean CEA level is 135,48 ± 460,56 ng/ml with minimum level is 0,09 ng/ml and maximum level 2834,65 ng/ml. Stage III was found in most patient as many as 22 person (55,0%), followed by stage IV, stage II and stage I is the least as many as 2 patients (5,05%). Description of CEA level based on CRC stage is summarized in Table 3.

4 DISCUSSION

Characteristic of the subjects in this study showed that CRC is more frequent in men (24 people or 60%) than women. This is consistent with some literature, such as the research conducted by Vukobrat Bijedic et al. which reveales that the prevalence of CRC in men is higher than women by a ratio of 63.7%: 36.3% or 1.75: 1 and research conducted by Labianca et al which stated that the prevalence of CRC in men compared to women was 1.4: 1 [2, 3].

Table 2. Characteristics of research subjects based on CEA level and CRC stage of patients with colorectal carcinoma at Dr. Hasan Sadikin Central General Hospital

Variabel	N=40
CEA level (ng/ml)	
Mean ± Std	135,48 ± 460,56
Median	11,12
Range (min-max)	0,09-2834,65
CRC stage	
I	2 (5,0%)
II	5 (12,5%)
III	22 (55,0%)
IV	11 (27,5%)

Table 3. Descriptionof CEA level based on CRC stage of patients with colorectal carcinoma at Dr.Hasan Sadikin Central General Hospital

	Carcinoembryonic Antigen (CEA) level				
CRC Stage	Mean	SD	Median	Min	Max
I	1,54	2,04	1,54	0,09	2,98
II	4,38	4,91	1,08	0,65	11,41
III	69,56	168,04	9,65	1,46	779,34
IV	351,27	833,65	100,0	1,80	2834,65

Table 4. Correlation between CEA level and CRC stage of patients with colorectal carcinoma at Dr. Hasan Sadikin Central General Hospital

Variable	Correlation	r	p
CEA level with CRC stage	Spearman	0,588	0,0001

The characteristics of the subjects of this study based on age, shows that the mean age of CRC patients in RSUP Dr. Hasan Sadikin Bandung is 55.02 + 10.84 years and the median is 57.5 years. This is not much different from some studies which stated the average age of diagnosed CRC was 60 years, such as study by Granados-Romero et al, Vukobrat Bijedic et al, Labianca et al and McCance et al [2, 3, 19, 20].

The characteristic of the clinical stage in this research showed that the most common clinical stage was stadium III with 22 people (55%), followed by stage IV, stage II and the least was stadium I with 2 people (5%). This is due to the progression of the tumor which can be initialy asymptomatic, so that it is not detected earlier. Most CRC originate from adenomatous polyp epithelial tissue. The progression from polyps to colon cancer (adenocarcinoma) takes a long time and involves a series of gradual processes of genetic mutations [20].

Initial symptoms that develop are usually pain with a palpable mass in the lower right quadrant for right colon tumors. Other symptoms include anemia, fatigue and feces mixed with dark red mahogany blood, causing persistent blood loss and anemia. Symptoms of obstruction are rarely encountered because usually the growth does not circum-

ferent the colon. Tumors in the left colon (descending) are usually small, prominent, grow circumferentially, surround the entire intestinal wall and eventually tumors penetrate vascular and cause ulceration in the central. Symptoms of obstruction are often found in this type, appear slowly and the stools change into small shapes. Other manifestations include abdominal distension, abdominal pain, vomiting, constipation, abdominal cramps and fresh red blood in the stool. Intestinal obstruction is found in 8% to 29% of cases as the main symptom at the time of diagnosis. Other symptoms that arise are related to distant organ metastases [20].

The highest average CEA level was found in stage IV with a value of 351.26 ± 833.65 ng / ml, followed by stage III, II and the lowest average CEA level was found in the stage I group of patients with a value of 1.53 ± 2.043 ng / ml. This is consistent with the research conducted by Vukobrat-Bijedic et al and Lee et al who stated that elevated levels of CEA are associated with advanced stages [2, 15, 21].

The mechanism of CEA in increasing the incidence of advanced stages in CRC is still not fully understood yet, but according to Lee et al, CEA can activate Kupfer cells in the liver to change the liver microenvironment so that it can accept the existence of CRC cells in the liver [15].

The Spearman test result is shown in table 4. With p value 0,0001 ($p<0,05$), this study indicates that there is a correlation between CEA level and CRC stage using CT scan examination at Dr. Hasan Sadikin Central General Hospital. The correlation strength using Guilford criteria in this study is moderate ($r = 0,588$), probably due to the interval time between CEA level examination and CRC staging using CT scan was variable.

5 CONCLUSIONS

There is a significant correlation between CEA level with colorectal carcinoma stage using CT scan examination with p value 0,0001 ($p<0,05$).

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