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Relationship Between Age and Depth of Invasion and Histopathological Features in Colorectal Cancer Patients in the Anatomical Pathology Department of Cut Meutia General Hospital (RSUCM) 2018 - 2021

Mulyati Sri Rahayu[1], Khairunnisa Z.[2], Nabil Ibnu Sina[3*]
Universitas Malikussaleh, Lhokseumawe
Corresponding Author: Nabil Ibnu Sina nabilibnusina@gmail.com

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ABSTRACT

Colorectal cancer has become one of the most common and most diagnosed cancers in the world, with as many as 1.4 million new cases being discovered each year. This cancer affects many elderly patients, but not a few young patients also experience it. Depth of invasion and type of histopathological appearance are the determining factors in determining the prognosis of colorectal cancer. The purpose of this study was to determine the relationship between age and depth of invasion and histopathological features in patients with colorectal carcinoma in the anatomical pathology section of RSU Cut Meutia, North Aceh for the 2018-2021 period. This research is a retrospective analytic study using the approach *cross sectional study* and use data taken from the results of laboratory examinations. Anatomical Pathology during the 2018-2021 period. The results of the study found that cancer that had invaded the subserosa to the peri-colorectal tissue (T3) and invaded other organs and/or perforated visceral peritoneum (T4) had a higher percentage in the age group.≤54 years, but statistically no significant relationship was found. Description *adenocarcinoma* is the most common histopathological appearance and has a higher percentage in the age group≤54 years, but statistically no significant relationship was found. So it can be concluded that there is no significant relationship between age and depth of invasion and the histopathological appearance of colorectal cancer patients

INTRODUCTION

Colorectal cancer (CRC) is a malignancy originating from the colon, namely the colon and/or rectum (Ministry of Health, 2018). Colorectal cancer is one of the most common and most diagnosed cancers in the world. Colorectal cancer is also the third most common malignancy in the world, with 1.4 million new cases diagnosed each year (Arnold*et al.*, 2017).

It is known from epidemiological data on colorectal cancer that a person's risk of developing this cancer is 1 in 20 people with a higher risk found in males than females. In 2020, it is estimated that there will be 1.93 million cases of colorectal cancer worldwide with 935,173 deaths. This number of cases makes KKR the third largest contributor in terms of cancer cases after cases of breast cancer and lung cancer and the second most deaths in cancer patients after deaths from lung cancer (WHO, 2020).

On the Asian continent, Southeast Asia is ranked second after East Asia with a total of 106,995 cases with a ratio of 60,505 cases in men and 46,490 cases in women. Data*World Health Organization* (WHO) in 2018 the incidence of colorectal cancer (CRC) in Indonesia was 12.1% of the adult population, with a mortality rate of 6.9% of all cancer cases. The comparison of the incidence of colorectal cancer in men is 7.7% and in women it is 4.4% (WHO, 2020).

Based on medical record data from the Department of Medical Surgery, Faculty of Medicine, University of Indonesia (FK UI) at the National Central General Hospital (RSUPN) dr. Cipto Mangunkusumo is known to have had 142 patients with CRC and 55.6% were dominated by males (Subrata, 2020). Meanwhile at the General Hospital dr. Zainoel Abidin (RSUZA), Banda Aceh reported that 46.36% of 140 patients who underwent colonoscopy had CRC patients (Abubakar, 2012).

The peak incidence of CRC patients is generally found at the age of 60 to 70 years, less than 20% of cases occur at the age of <50 years. If cases are found at a younger age, then it is necessary to suspect a connection with other diseases such as vulcerative colitis or Familial Adenomatous Polyposis (FAP) (Robbins, Ramzi S. and Kumar, 2018).

Clinical epidemiological studies of CRC in Indonesia show that there are more young CRC patients in Indonesia than patients of the same age in developed countries. In Indonesia, >30% of cases of CRC were found in patients aged 40 years or younger, while patients aged <50 years in developed countries only accounted for 2-8% (Abdullah*et al.*, 2012).

In a study that took place at the Dharmais Cancer Hospital in 2020, it showed that the age factor had a significant relationship with the incidence of colorectal cancer (Majid and Ariyanti, 2020). The age-to-age pathomechanism can cause colorectal carcinoma is thought to occur because with age it increases the accumulation of DNA mutations of cells making up the walls of the colonic organs and is also caused by increased intake of carcinogenic agents and decreased immune function with age (Kurahmawati, 2012).

In determining the stage of CRC and the depth of cancer invasion in the patient, it is used*TNM staging*, which is a colorectal cancer staging system based on international standards. T represents the primary tumor, N represents lymph node involvement, and M represents metastasis (Ministry of Health, 2018).

Internationally, the histopathological classification for colorectal cancer uses the WHO classification. WHO classifies the histopathological type of colorectal cancer into:*adenocarcinoma*, *mucinous adenocarcinoma*, *signet ring carcinoma*, *adenous carcinoma*, and several other types. In general, the most common histopathological appearance is*adenocarsinoma* (Feldman, M., Friedman, L. and Brandt, 2015).

Based on the background that has been described and the many incidents of CRC incidents in Indonesia, researchers are interested in conducting a scientific research entitled "Age Relationship with Depth of Invasion and Histopathological Features in Colorectal Cancer Patients in the Anatomical Pathology Department." RSU Cut Meutia North Aceh for the 2018-2021 period.

METHODS

This study is a retrospective analytic study based on the results of patient medical record data. The approach used is*cross sectional study*. This research will be carried out from February to April 2022 at Cut Meutia Hospital (RSUCM), to be precise, in the Anatomical Pathology section. Sampling technique using *purposive sample* with a total sample of 33 patients.

RESULTS

Age description, depth of invasion, and histopathological picture of the samples based on the year of examination

In this study, the age group was obtained ≤54 years old was the age group with the highest number, namely 22 samples (66.7%) while the lowest number was in the age group >54 years, amounting to 11 people (33.3%). In this study, colorectal cancer (KKR) patients at Cut Meutia General Hospital (RSUCM) had an average age of 54 years. In terms of sample distribution for CRC patients at Cut Meutia General Hospital (RSUCM) based on the year of examination, the most colorectal cancer patients were examined, namely in 2019 as many as 12 examinations (36.4%), while the least examination was in 2020 as many as 5 examinations (30.3%). An overview of the sample can be seen in the graph below.

Based on data on the depth of invasion of colorectal cancer using the T classification of *TNM Staging* it is known that the highest depth of invasion is T3 as many as 14 people (42.4%) and the least depth of invasion is T2 as many as 7 people (21.2%). Meanwhile, for the distribution of samples in CRC patients at Cut Meutia General Hospital (RSUCM) based on the depth of invasion and year of examination, the most depth of invasion was found for colorectal cancer patients, namely T3 in 2019 as many as 7 and no depth of invasion for colorectal cancer patients T3 in 2020 and T2 in 2021.

In this study it was found that the most common histopathological picture of colorectal cancer found in this study was the image *adenocarcinoma* namely as many as 29 people (87.9%) while the histopathological picture at least is an image*signet ring cell carcinoma, mucinous adenocarcinoma, mucinous carcinoma dan spheroidal carcinoma* amounted to 1 person each (3.0%). Distribution of samples in CRC patients at Cut Meutia General Hospital (RSUCM) based on histopathological features and year of examination, the histopathological features of colorectal cancer patients were mostly *adenocarcinoma* in 2019 there were 11 fruits and no other type of histopathological picture was found *adenocarcinoma* in 2018 and 2021. For more complete data, see table 1.

Table 1. Description of Age, Depth of Invasion, and Histopathological Features of the Sample Based on the Year of Examination

Age	Year				Total	Percentage (%)
	2018	2019	2020	2021		
≤54 years	4	9	2	7	22	66,7
>54 years	2	3	3	3	11	33,3
Depth of Invasion						
T2	1	3	3	0	7	21,2
T3	3	7	0	4	14	42,4
T4	2	2	2	6	12	36,4
Histopathological Picture						
Adenocarcinoma	6	11	2	10	29	87,9
Signet Ring Cell Carcinoma	0	1	0	0	1	3,0
Mucinous Adenocarcinoma	0	0	1	0	1	3,0

Mucinous Carcinoma	0	0	1	0	1	3,0
Spheroidal Carcinoma	0	0	1	0	1	3,0
Total	6	12	5	10	33	100

Correlation between the age of colorectal cancer patients and the depth of invasion

The results of the Kolmogorov Smirnov test analysis showed that there was no relationship between age and depth of invasion with a p value > 0.05 (p value 0.646).

Table 2. Relationship Between Sample Age and Invasion Depth

Age	T2		T3		T4		Total		*p* value
	n	%	n	%	n	%	n	%	
≤54 Years	4	18,2	8	36,4	10	45,4	22	66,7	0.646
>54 Years	3	27,3	6	54,5	2	18,2	11	33,3	
Total	7	21,2	14	42,4	12	36,4	33	100	

Correlation between age of colorectal cancer patients and histopathological features

The results of the Kolmogorov Smirnov test analysis showed that there was no relationship between age and the histopathological appearance of colorectal cancer patients with a p value > 0.05 (p value 0.969).

Table 3. Relationship Between Sample Age and Histopathological Features

Age	Adeno carcinoma	Signet Ring Cell Carcinoma	Mucinous Adeno carcinoma	Mucinous Carcinoma	Spheroidal Carcinoma	Total		*P* value
	n	n	n	n	n	n	%	
≤54 tahun	20	1	1	0	0	22	66,7	0.969
>54 tahun	9	0	0	1	1	11	33,3	
Total	29	1	1	1	1	33	100	

DISCUSSION

Age frequency distribution of the sample

Based on the results of research conducted at the Anatomical Pathology Laboratory of North Aceh Cut Meutia General Hospital (RSUCM) during the 2018-2021 period, 97 colorectal cancer patients were recorded as having examined at RSUCM, but only 33 samples met the inclusion criteria. The results showed that the youngest age of KKR patients at RSUCM was 17 years and the oldest was 72 years. The mean age of the patients was 54 years and found to be more in the age group≤54 years. This result is in line with the results of previous studies which stated that the most age category in colorectal cancer is the age category with ages 50 to 60 years (Gunasekaran, Ekawati and Sumadi, 2019). The incidence of colorectal cancer over the age of 50 years can occur because as you get older, there will be an accumulation of somatic mutations caused by the development of neoplasms and also factors that decrease immunity with age (Robbins, Ramzi S. and Kumar, 2018).

Colorectal cancer (CRC) begins in the form of polyps which are non-neoplastic growths and will develop in the mucous lining of the colon and rectum. Polyps usually occur and are detected in someone who has an average age of 50 years or more with a higher prevalence at an older age (Robbins, Ramzi S. and Kumar, 2018). The appearance of polyps can be associated with an increase in aberrant gene hypermethylation in someone aged > 50 years, especially in CRC. Global genome hypermethylation causes the death of tumor suppressor genes which are indicated as CpG Island Methylator Phenotype (CIMP) so that colorectal cancer can form sporadically (Mojarad, Ehsan N., Kuppen, Peter JK., Aghdaei, Hamid A., & Zali, 2013). An individual also has a sharply increased risk of developing tumor growth after the age of 40 years with the general population and 90% occurs over the age of 50 years (Feldman, M., Friedman, L. and Brandt, 2015).

In this study, it was also found that cases occurred at a younger age, namely two patients aged 17 years. According to the literature, carcinoma detected <40 years, usually occurs followed by a number of other risk factors, especially familial adenomatous polyposis (FAP) (Brunicadi*et al.*, 2017). Data from the American Cancer Society (2020) also shows that there is a shift in the age category for the incidence of CRC to be younger due to the interaction of hereditary factors and changes in lifestyle which can be in the form of dietary patterns as a consequence of the shift towards eating patterns that follow western country diets. About Colorectal Cancer; What Is Colorectal Cancer ?', 2021).

In this study, the frequency of CRC patients based on the year of examination showed that for the distribution of samples in colorectal cancer patients at Cut Meutia General Hospital (RSUCM), according to the examination, the highest number of CRC patients were examined, namely in 2019 there were 12 examinations (36.4%), while the least inspections, namely in 2020 as many as 5 examinations (30.3%). It is estimated that the least number of examinations in 2020 is one of the impacts of the Covid 19 pandemic. Several studies have stated that cancer patients who undergo examinations or undergo chemotherapy during the Covid-19 pandemic feel an increase in anxiety with varying levels ranging from mild to severe anxiety related to factors. Factors that influence it include fear of being infected with Covid-19, type of cancer experienced, age and gender, information overload on social media, uncertainty over the end of Covid-19, lack of understanding and information possessed by patients, delays or changes in care and treatment plans, presence of restrictions applied in hospitals and feelings of loneliness while undergoing isolation during the Covid-19 pandemic (Lihawa and Zainuddin, 2022).

Depth of invasion in the sample

Based on the depth of invasion, it was found that most of the tumor cases had invaded the subserosa to the peri colorectal tissue (T3) as much as 42.4%. These cases were slightly more than cases of carcinoma which invaded other organs and/or perforated visceral peritoneum (T4) as much as 36.4%. While the fewest cases were tumors that invaded the muscularis propria (T2) as much as 21.2%. This is in accordance with the results of a

study at the Hasan Sadikin Hospital, Bandung which found that the most cases were in the form of a carcinoma that had reached the serous layer (T3) as much as 20.2%. These cases were higher than cases of carcinoma which had only reached the muscularis layer by 19% and carcinoma which had only reached the submucosa layer by 0.8%. (Sander, 2012).

The results of this study are also in accordance with the results obtained from research conducted at the Anatomical Pathology Lab at RSUP dr. M. Djamil, Padang who got more than half of the tumors (58.2%) had invaded up to T3 (Farhan Hasan, 2022). However, these results are slightly different from the results of research at RSUP dr. Kariadi, Semarang, which got the most depth of invasion results at T4 as much as 36.7% (Pratama and Adrianto, 2019). This is because the early stages of colorectal carcinoma usually do not show typical symptoms and signs compared to other diseases. Most new patients come for treatment when symptoms have occurred which generally arise due to complications, for example being unable to defecate or bleeding in the stool when defecating (Desen and Japaries, 2013). So it is necessary to carry out screening tests routinely in patients who have a high risk of developing CRC.

Histopathological picture of the sample

The most common histopathological features in this study were *adenocarsinoma* as much as 87.9%. Previous research conducted in the anatomical pathology section of FK Unand also found the same thing, namely the most histopathological features were found, namely images *adenocarsinoma* as many as 168 cases (81.95%) (Kurniawan, Zahari and Asri, 2017). This relates to early lesions in the colon which tend to transform into *adenocarsinoma*, one of them *Chron's disease*. Number of occurrences of*adenocarsinoma* which appeared on*Chron's disease* is about 20% (Brunicadi *et al.*, 2017).

This study also showed mucinous adenocarcinoma which is a histological subtype of adenocarcinoma with extracellular mucin collections comprising >50% of tumor volume which occurs in 6-21% of all cases of CRC. Mucinous adenocarcinoma has different characteristics compared to adenocarcinoma. Mucinous adenocarcinoma is more frequently located in the right colon, and prognostic factors, including histological differentiation and TNM stage, are poorer than those of adenocarcinoma. From most of the studies, the prognosis of mucinous adenocarcinoma has been reported to have a poorer prognosis than adenocarcinoma (Bong*et al.*, 2022).

Relationship between age and depth of invasion in the sample

In the bivariate analysis of age with depth of invasion statistically, no significant relationship was found between age and depth of invasion (p=0.646). However, this study found a trend in the age category≤Age 54 years has a higher percentage of carcinomas that have invaded the subserosa to the peri-colorectal tissue (T3) and invasion of other organs and/or perforation of the visceral peritoneum (T4) (54.5%) compared to old age (> 54 years)) (24.2%). This was also explained in previous research conducted in the anatomical pathology section of FK Unand. In this study it was explained that although there were differences in the percentage depth of invasion in the young and old age categories, this was not significantly related (p=0.640) (Kurniawan, Zahari and Asri, 2017).

The results of this study are also in line with the results of a previous study conducted by Sutrisna (2018) which stated that the most common stages found in patients with CRC were stages III and IV (advanced stages) or at deeper depths of invasion (T3-T4) (Sutrisna, I.W.W. , Sudartana, I.K., Widiana, 2018). The rate of improvement and survival depend on the stage of the CRC in the patient. Other factors that need to be considered in further diagnosis are knowledge, age, black race, social and economic status, while factors related to survival other than stage and age at diagnosis are the presence of other diseases (comorbidities) or tumors in other organs. Most of the patients who come at an advanced stage show that there is still a lack of knowledge and attention from the community about CRC, especially at an early stage where there are not many symptoms ('About Colorectal Cancer; What Is Colorectal Cancer ?', 2021).

Another factor that can influence the incidence of CRC at a young age is related to the stage, namely the presence of regional lymph node involvement. The incidence of CRC involving the lymph nodes was higher in young patients compared to the elderly for all categories of depth of invasion. Previous studies have also shown that stage II CRC with depth of invasion T1/T2 is more common in elderly patients, and stage III with depth of invasion T3 and later is more common in young patients. Other studies have stated that patients aged <50 years tend to have colorectal carcinoma at stages III and IV, which means that the cancer has involved regional lymph nodes and metastases have also occurred (Ahmad Yusra, 2012).

Relationship between age and histopathological picture in the sample

In the bivariate analysis of age with histopathological appearance statistically, no significant association was found between age and histopathological appearance (p=0.969). These results are different from the results of research in the anatomical pathology section of FK Unand which explains that there is a relationship between age and histopathological features, (p=0.001) (Kurniawan, Zahari and Asri, 2017). However, in this study it was found that the description *adenocarcinoma* has a higher percentage in the age category≤54 years (60.6%) compared to the age category >54 years (27.3%). This percentage difference may affect the prognosis of carcinoma at a younger age because of the features *adenocarcinoma* has a relationship with a worse prognosis and according to the degree of differentiation is also defined in the degree of differentiation III (Sudoyo*et al.*, 2010).

In this study, colorectal cancer patients were also found with histopathological features *Signet ring cell carcinoma* in age group ≤54 Years. This is in accordance with a previous study in Brazil in 2020 which showed that the histopathological picture *Signet ring cell carcinoma* has a significant relationship with young age (p=0.001) (Pear tree*et al.*, 2020). Percentage *Signet ring cell carcinoma* which is higher in the younger age category can occur due to differences in pathogenesis. *Signet ring cell carcinoma* usually a carcinoma with a path of microsatellite instability, this pathway in several previous studies was more frequently found in young patients who are usually associated with heredity (Sudoyo*et al.*, 2010).

CONCLUSION

From a total of 33 samples of colorectal cancer patients, the average age of the patients was 54 years. The highest depth of invasion was found, namely at the T3 stage, while the histopathological picture that was found the most was the picture *Adenocarcinoma.* There is no significant relationship between age and depth of invasion in colorectal cancer patients at Cut Meutia General Hospital (RSUCM) in 2018-2021. There is no significant relationship between age and histopathological features in colorectal cancer patients at Cut Meutia General Hospital (RSUCM) in 2018-2021.

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