Relationship of Dirty Necrosis with Histopathological Grading in Colorectal Adenocarcinoma

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Abstract

Background: Dirty necrosis (Intraacinar necrosis/garland necrosis) is defined as the presence of cell remnants in the lumen of the gland. Dirty necrosis consisting of an eosinophilic mass, which is a mass originating from the cytoplasm of dead cells mixed with the remnants of the cell nucleus. The remnants of the cell nucleus are blue and the eosinophilic mass is pink in the background. Dirty necrosis results from the breakdown of carcinoma cells, which usually accumulate in the lumen of intact tubular glands, and may be associated with spontaneous events involving insufficient tumor vascular supply. Assessment of the presence of a dirty necrosis is considered a characteristic of colorectal carcinoma.
Objective: This study was conducted to analyze the relationship between dirty necrosis and histopathological grading of colorectal adenocarcinoma.
Methods: The study used 55 paraffin block samples of colorectal adenocarcinoma cases that had been diagnosed at the Anatomical Pathology Laboratory, H. Adam Malik Hospital, Medan and at the Anatomical Pathology Laboratory, Faculty of Medicine, Universitas Sumatera Utara, since 2019-2020. Dirty necrosis was assessed using H&E staining with 400x magnification assessed over the entire lumen of the gland, if <10% was considered absent and if >10% was considered present.
Results: The results showed that there were 47 samples (85.4%) of dirty necrosis, while 8 samples (14.6%) did not. For the most histopathological grading, 42 samples (73.4%) were low grade, while the high grade was 13 samples (23.6%). Statistical tests between dirty necrosis and colorectal adenocarcinoma histopathological grading showed no significant relationship with p value = 0.376 (p >0.05).
Conclusion: There was no statistically significant relationship between dirty necrosis and histopathological grading in colorectal adenocarcinoma.
Keywords: Colorectal adenocarcinoma; dirty necrosis; histopathological grading

1. Introduction

Cancer is a disease characterized by uncontrolled abnormal cell division. When this process occurs in the large intestine or rectum, it is known as colorectal carcinoma. The large intestine and rectum (colorectum) to the anus are part of the gastrointestinal (GI) tract.[1]

Based on the 2020 Global Burden of Cancer (GLOBOCAN), worldwide at all ages and genders, colorectal carcinoma ranks third as the most common cancer after breast cancer and lung cancer. The estimated incidence of new cases is 1,931,590 (10%), and the death rate is 935,173 (9.4%). By gender, colorectal carcinoma ranks third in men after lung and prostate cancer with an estimated new case of 1,065,960 (10.6%) and an estimated mortality of 515,637 (9.3%) and is also the second most common cancer in women after breast with estimated new cases 865,630 (9.4%) and deaths 419,536 (9.5%).[2] Estimates of cancer in Indonesia in 2020, 396,914 new cases and 234,511 deaths from a total population of 273,523,621. Colorectal carcinoma ranks fourth most with the percentage of colorectal cancer itself that is equal to 8.6% after breast cancer (16.6%), cervical cancer (9.2%), and lung cancer (8.8%). Colorectal carcinoma is the third most common cause of death in men with a percentage of 10.2% after tracheal, bronchial, lung cancer (21.8%) and liver cancer (12.3%), while women are the fourth most common cause of death due to cancer. with a

percentage of 8.5%, after breast cancer (21.4 %), cervical cancer (10.3% %), and cancer of the trachea, bronchi, lungs (9.1 %).[3]

Colorectal carcinoma is defined as a malignant tumor of the large intestine originating from the epithelial component with the invasion of tumor cells between the stroma of the muscularis mucosal layer to the submucosa layer. Most colorectal malignancies are adenocarcinomas (90%). Colorectal carcinoma is one of the most common malignancies and is one of the leading causes of cancer-related deaths in the world.[4] The grading of colorectal adenocarcinoma is based on the gland formation, namely: (1). Low grade, ie colorectal adenocarcinoma well differentiated (well differentiated) to moderate (moderately differentiated). Colorectal adenocarcinoma was said to be well differentiated if 50% glandular formation was found and (2). High grade, namely colorectal adenocarcinoma poorly differentiated (poorly differentiated). Colorectal adenocarcinoma is said to be poorly differentiated if 50% glandular formation is present.[4] This grading indicates a colorectal carcinoma prognosis, where lesions with advanced stages or lesions with aggressive histopathological features (high grade) will worsen the prognosis of this disease. In addition, poor prognosis is also related to the degree of depth of tumor invasion, extent of tumor spread, lymph node involvement (KGB), lymphatic invasion, vascular invasion, and perineural invasion.[5] Cancer cell invasion is the process of moving cells from the primary tumor to deeper tissues. This situation allows cells to go towards the blood / lymph vessels and be transported to other parts of the body. The depth of invasion is one of the important factors influencing the prognosis of colorectal carcinoma and is a feature of a malignant neoplasm as a major cause of morbidity and mortality.[5]

Invasive colorectal carcinoma often represents a dirty necrosis. Dirty necrosis (Intraacinar necrosis/garland necrosis) is defined as the presence of cell remnants in the lumen of the gland.[6-11] Dirty necrosis consists of an eosinophilic mass, which is a mass originating from the cytoplasm of dead cells mixed with the remnants of the cell nucleus. . The remnants of the nucleus are blue and the eosinophilic mass is pink in the background.[7] Dirty necrosis results from the breakdown of carcinoma cells, which usually accumulate in the lumen of intact tubular glands, and are more likely to be associated with spontaneous events involving insufficient tumor vascular supply.[6] Assessment of the presence of dirty necrosis is considered a characteristic of colorectal carcinoma.[6,9,10,11] In the study of Toth et al., suggested that the appearance of lack of dirty necrosis is a feature of colorectal carcinoma which is useful diagnostically by examination of deoxyribonucleic acid (DNA) in microsatellite instability (MSI).[6,9] In the study of Greenson et al., it was stated that dirty necrosis was associated with grading of colorectal carcinoma, and some stated that dirty necrosis was not shown in high grade and mucinous.[6]

2. Materials and Methods

We studied 55 cases of histopathological slides of colonic adenocarcinoma at the Anatomical Pathology Laboratory, Faculty of Medicine, Universitas Sumatera Utara and the Anatomical Pathology Unit at H. Adam Malik Hospital using an analytical study design with a cross sectional approach to analyze the relationship between dirty necrosis and histopathological grading in colorectal adenocarcinoma.

Histopathological specimens stained with Haemotoxylin Eosin stain, were retrospectively reviewed by the authors. The histopathological slides were examined for the presence or absence of dirty necrosis in colorectal adenocarcinoma and whether there was a relationship between dirty necrosis and histopathological grading of colorectal adenocarcinoma.

3. Results

The research sample was histopathological slide which was diagnosed as colon adenocarcinoma at the Anatomical Pathology Laboratory, Faculty of Medicine, Universitas Sumatera Utara and the Anatomical Pathology Unit at H. Adam Malik Hospital. The total sample was 55 slides that met the inclusion criteria. The following are the results of the research obtained.

Table 1. Table of distribution of colorectal adenocarcinoma samples by age, sex and tumor location.

Variable	F	%
Gender		
• Male	31	56,4
• Female	24	43,6
Age	51,6 ± 12,7	
• ≤ 30 year	2	3,6
• 31-40 year	10	18,2
• 41-50 year	11	20,0
• 51-60 year	20	36,4
• 61-70 year	8	14,5
• 71-80 year	3	5,5
• > 80 year	1	1,8
Tumor location		
• Right colon	15	27,3
• Left colon	24	43,6
• Rectum	16	29,1

In this age category, the data obtained from medical records, the most colorectal adenocarcinoma sufferers were at the age of 51-60 years, as many as 20 samples (36.4%) and the youngest age was 22 years, namely 1 sample and the oldest age was 83 years, namely 1 sample. . The second most common age group was found in the 41-50 year age group, namely 11 samples (20.0%), the third group was 31-40 years old, with 10 samples (18.2%), then the 61-70 year age group , as many as 8 samples (14.5%), the age group 71-80 as many as 3 samples, the age group 30 years ranks second to last as many as 2 samples (3.6%) and the least is found in the age group > 80 years, that is as much as 1 sample (1.8%). The gender category was also obtained from medical records where data obtained were more male, namely 31 samples (56.4%) than female, namely 24 samples (43.6%). On the location of the tumor, the data obtained from medical records was also the most found in the left colon as many as 24 samples (43.6%), then the rectum 16 samples (29.1%), and the least was the right colon as many as 15 samples (27 ,3%). (Table 1)

Table 2. Frequency distribution of colorectal adenocarcinoma based on histopathological grading, histopathological subtype, vascular invasion, perineural invasion, and dirty necrosis.

Variabel	**f**	**%**
Grading		
• Low grade	42	73,4
• High grade	13	23,6
Subtype		
• Adenocarcinoma NOS	48	87,3
• Serrated adenocarcinoma	2	3,6
• Adenoma-like adenocarcinoma	0	0
• Micropapillary carcinoma	0	0
• Mucinous adenocarcinoma	5	9,1
• Poorly cohesive carcinoma	0	0
• Signet-ring cell carcinoma	0	0
• Medullary carcinoma	0	0
• Adenosquamous carcinoma	0	0
• Carcinoma, undifferentiated, NOS	0	0
• Carcinoma with sarcomatoid component	0	0
Vascular invasion		
• No invasion	25	45,5
• IMVI	9	16.36
• EMVI	21	38.19
Perineural invasion		
• No invasion	41	25,4
• Ada invasi	14	74,6
Dirty Necrosis		
• Negative	8	85,4
• Posititive	47	14,6

Based on the results of the evaluation, the highest histopathological grading was obtained as many as 42 samples (73.4%) low grade while high grade as many as 13 samples (23.6%). In the histopathological subtype of colorectal adenocarcinoma, only 3 subtypes were found, the most found were NOS adenocarcinoma with 48 samples (87.3%), followed by mucinous adenocarcinoma 5 samples (9.1%), and serrated adenocarcinoma 2 samples (3.6%), while the other subtypes were not found. In vascular invasion, the most obtained was the absence of vascular invasion as many as 25 samples (45.5%), and those with invasion were divided into two, namely: IMVI 9 samples (16.36%) and EMVI 21 samples (38.19%). The most common perineural invasion was no perineural invasion in 41 samples (74.6%) and there was perineural invasion in 14 samples (25.4%). The most dirty necrosis was dirty necrosis as many as 47 samples (85.4%), while there were 8 samples (14.6%). (Table 2)

Table 3. Relationship of dirty necrosis with histopathological grading of colorectal adenocarcinoma.

Dirty Necrosis	Grading				P-value*
	Low Grade		High Grade		
	n	%	n	%	
Negative	5	62,5	3	37,5	0,376
Positive	37	78,7	10	21,3	

*** Uji *Fisher's Exact***

This study examined the relationship between histopathological grading and dirty necrosis in patients with colorectal adenocarcinoma, the results were low grade and there was no dirty necrosis in 5 samples (62.5%), while there were 37 samples (78.7%). In the high grade, there were no dirty necrosis in 3 samples (37.5%), while there were 10 samples (21.3%). In this study, to assess the relationship of dirty necrosis with histopathological grading, the Fisher's Exact test was carried out and the p-value was 0.376 (> 0.05) so that there was an insignificant relationship. (Table 3)

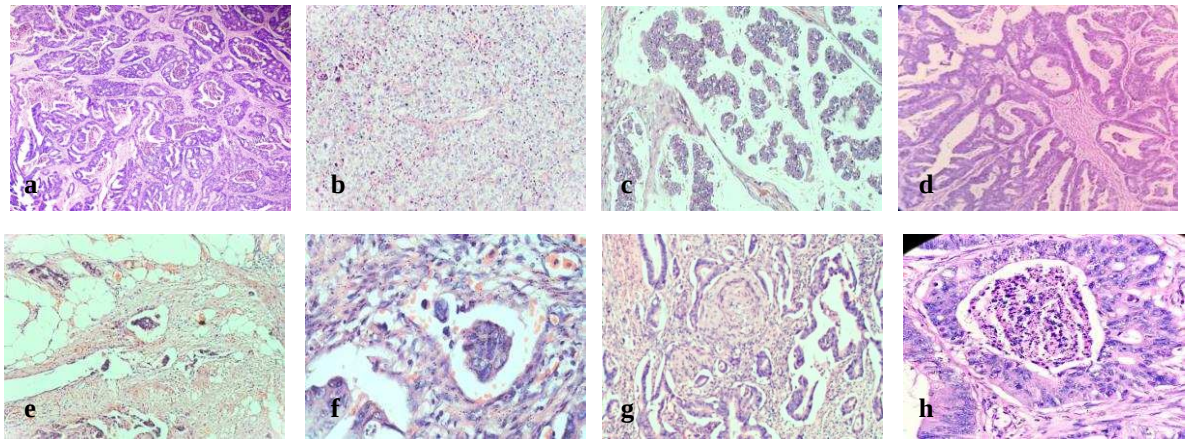

Fig. 1. (a) Low grade colorectal adenocarcinoma (HE, 100x); (b) High grade colorectal adenocarcinoma (HE, 100x); (c) Mucinous colorectal adenocarcinoma (HE, 100x); (d) Serrated colorectal adenocarcinoma(HE, 100x); (e) EMVI (HE, 100x); (f) IMVI (HE, 100x); (f) Perineural invasion (100x); (h) Dirty necrosis (HE, 400x).

In this study, 55 samples were found with an average age of patients with colorectal adenocarcinoma 51.6 years, with the youngest age being 22 years old and the oldest being 83 years old. The age group of most patients was 51-60 years with 20 samples (36.4%), the results of this study were not much different from previous studies. According to Asrul's research in 2018, the average age of patients with colorectal adenocarcinoma was 54.17 years.[12] Park et al., in 2014 also found that the highest age was 50 years with a mean age of 60.9 years,[13] while in the study of Young et al., it was found that the age of patients with colorectal adenocarcinoma was <40 years old.[14] It is also in accordance with the WHO book which states that patients with colorectal adenocarcinoma are more dominated by old age, in accordance with some literature which states that increasing age causes an increase in the incidence of colorectal adenocarcinoma.[4] With increasing age, the process of tissue's ability to repair/replace cells slowly begins to decrease and also decreases to maintain its normal function, so that it cannot survive infection and repair the damage that occurs, resulting in cumulative changes, which can reduce the body's resistance to stimuli. from inside and outside the body, so that the attack power against cancer cells decreases, which causes cancer cells to grow

freely.[15] Meanwhile, patients with colorectal adenocarcinoma under the age of 40 years generally have a family history such as a history of HNPCC, FAP, Crohn's disease intestinal infection and ulcerative colitis.[4,14]

In this study, 31 samples (56.7%) of colorectal carcinoma were suffered by men. The results of this study are not much different from previous studies. Nikijuluw et al. in 2019 reported that the most colorectal adenocarcinoma sufferers were in men, namely 17 of 35 samples (58.62%).[16] Kwon et al. in 2013 also reported that men were more often affected by colorectal carcinoma as many as 132 out of 256 samples (51.6%).[17] The mechanism by which sex differences affect the occurrence of colorectal carcinoma is partly due to differences in hormone levels between men and women. Estrogen hormone receptor ERβ is a protective factor against colorectal carcinoma. Experiments in mice showed that ERβ increased proliferation and reduced differentiation and apoptosis of colonic mucosal cells. Estrogen can also prevent the occurrence of colorectal carcinoma by reducing inflammation by inhibiting the inflammatory factor IL-6, namely in IBD which is one of the risk factors for colorectal carcinoma.[18] In another study, it was stated that the hormone pregesterone also has the potential to reduce the risk of colorectal carcinoma in women because of its activity in helping to synthesize endogenous sex hormones. Androgen deficiency in women is also said to increase the risk of colorectal carcinoma.[19] In addition, unhealthy lifestyle factors in men such as the habit of drinking alcoholic beverages are also a trigger for men's susceptibility to this malignancy. Excessive alcohol consumption changes the normal state of the digestive tract mucosa, this is caused by the oxidation of acetaldehyde from ethanol metabolism which will promote inflammation of the digestive tract mucosa and abnormal cell growth. In addition, acetaldehyde interferes with the DNA repair process by inhibiting the enzymes that play a role. Acetaldehyde is also able to bind to other molecules and cause DNA mutations that will trigger carcinogenesis.[20]

In this study, the most common location for colorectal adenocarcinoma was in the left colon with as many as 24 samples (43.6%), then located in the rectum with 16 samples (29.1%) and at least in the right colon with 15 samples (27, 3%). The results of this study are not much different from previous studies. Park et al. reported that the location of this colorectal carcinoma was mostly in the left colon, namely 451 of 579 cases (77.9%).[13] Wang et al also reported that the left colon as the most common location was 15,880 out of 26,908 cases (67.7%).[21] The location of the right colon is often asymptomatic in contrast to the left colon and rectum often causes symptoms of pain, constipation symptoms and bloody bowel movements, this can occur due to the diameter of the tumor and also the different growth patterns. In the colon on the right side growths at this location allow it to reach a larger size while still clinically asymptomatic.[4]

The grading of colorectal adenocarcinoma is determined based on the percentage of components of glandular differentiation, according to the WHO in 2019 the grading of colorectal carcinoma is divided into low grade and high grade. In this study, most were low grade as much as 73.4% compared to high grade as much as 23.6%. The results of this study are not much different from previous studies. Schwarz et al., in 2019 found that low grade colorectal adenocarcinoma cases were the most common cases, namely 576 of 180 cases (73.6%).[22] Zlobec et al., in 2020 found low grade colorectal adenocarcinoma cases in 81.9% of 771 cases.[23] This may be due to the fact that many of these samples are located on the left, so that there are complaints immediately for a health check with the use of colonoscopy or other imaging support tools that can accelerate the detection of this carcinoma.

This study only found 3 subtypes out of 11 subtypes according to the 2019 WHO division. The most common was the NOS adenocarcinoma subtype at 87.3%, then mucinous adenocarcinoma 9.1% and serrated adenocarcinoma 3.6%. This is in accordance with WHO's 2019 that most cases were diagnosed as NOS adenocarcinoma.[4]

Vascular invasion in this study was divided into intramural vascular invasion (IMVI) and extramural vascular invasion (EMVI). From the evaluation results, the histopathological picture of EMVI was found to be more common, namely 38.19% compared to IMVI which was only found to be 16.36%. This is not much different from the literature, in the 2019 WHO book which states that the incidence of EMVI is higher than

IMVI and previous studies. Bedge et al., found 16% IMVI and 62% EMVI in 87 cases of vascular invasion.[24] Gibson et al., who reported that EMVI features more (15.1%) than IMVI (3.3%).[25] It is known that the incidence of EMVI is higher than that of IMVI, but this figure is still considered underreported. EMVI is known to be an independent predictor of poor prognosis after resection of colorectal adenocarcinoma, whereas IMVI is not yet known. The negative prognostic impact of EMVI is higher than that of IMVI.[4,25]

In this study, 14 samples (25.4%) of perineural invasion (PNI) were found. This is not much different from the 2019 WHO book which states that the incidence of PNI is around 20% [4] and also not much different from previous studies. Knijn et al., 2016 reported that in their meta-analysis study found PNI 24.3% of 7653 cases.[26] PNI exhibits a significantly lower 5-year survival rate and indicates much more severe disease.[26] PNI status has been reported as a complementary factor for TNM staging in colorectal carcinoma. Zhou et al., found in their study that PNI status had a significant impact on life expectancy in patients with stage II and III colorectal carcinoma. Stage II patients are the most important population to benefit from the identification of a PNI, as they may be considered for adjuvant chemotherapy once their PNI status is known.[27]

This study assessed the presence of dirty necrosis in colorectal adenocarcinoma, and found 85.4% of the histopathological features of dirty necrosis in colorectal adenocarcinomas. This is in line with previous studies which state that dirty necrosis is a characteristic of colorectal adenocarcinoma. Milot et al., in their study found dirty necrosis in colorectal adenocarcinoma in 89% of 9 cases.[7] Greenson et al., reported that the histomorphology of dirty necrosis in colorectal adenocarcinoma in 356 of 465 cases (76.6%) were associated with MSS.11 Dirty necrosis is a constant histological feature and is important diagnostically for differentiating colorectal carcinoma types.[28] In particular, the absence of a feature of dirty necrosis is associated with MSI and has become an indispensable index factor as one of the pathological predictors of MSI in colorectal carcinoma.[8,29,30] Several studies have reported that MSI in colorectal carcinoma has a better prognosis. better than MSS tumors. Therefore, the identification of MSI in colorectal carcinoma is important, not only for the identification of the HNPCC syndrome but also for the success of therapy.[31,32] Studies show that lack of dirty necrosis is an indispensable factor in predicting MSI status and is also an important factor in MMR defects can cause MSI.[29,30] On the other hand, if only dirty necrosis can be detected, MSI can be excluded. So this dirty necrosis can help to differentiate MSI tumors from MSS tumors.[6]

The relationship between the variables used in this study was tested with the Fisher's Exact test where the test results obtained the significance value between dirty necrosis and histopathological grading in colorectal adenocarcinoma was p-value = 0.376 ($p > 0.05$) which indicated there was no significant relationship between dirty necrosis and histopathological grading in colorectal adenocarcinoma. This is not in accordance with the study of Greenson et al., which stated that dirty necrosis was associated with grading.[8] In this study, it was seen that at low grade and high grade both could be shown and both could not see the picture of a dirty necrosis. According to the authors, this difference was thought to be due to certain factors related to chromosomal instability.

5. Conclusion

Most patients with colorectal adenocarcinoma were aged 51-60 years, with a mean age of 51.6 years, where the youngest age was 22 years and the oldest age was 83 years. There are more males than females. The most common location is the left colon. Histopathological grading of low grade was more common than high grade, the most common subtype was adenocarcinoma NOS, no vascular invasion was more common than vascular invasion, no perineural invasion was more common, and dirty necrosis was more common than none. dirty necrosis in colorectal adenocarcinoma. There was no statistically significant relationship between dirty necrosis and histopathological grading in colorectal adenocarcinoma.

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