Correlation between differentiation grade and lymphovascular invasion in colorectal adenocarcinoma

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ABSTRACT

Colorectal carcinoma is the third most common malignant tumor worldwide. It is a heterogeneous disease with diverse clinicopathological and prognostic characteristics. The TNM (tumor, node, metastasis) staging system is currently used as a prognostic predictor. However, its predictive value is limited, as approximately 30% of patients with lymph node-negative disease die due to metastasis progression. It is suspected that other prognostic factors other than TNM staging system, may play a significant role. Differentiation grade and lymphovascular invasion have been proposed as essential prognostic factors for lymph node-negative colorectal carcinoma. This study aimed to evaluate the correlation between differentiation grade and lymphovascular invasion in colorectal carcinoma. It was an observational study with a cross-sectional design. Samples were collected from 4 Anatomical Pathology laboratories in West Sumatera in 2018. A total of 97 paraffin blocks of colorectal adenocarcinoma met the inclusion criteria. Differentiation grade and lymphovascular invasion were evaluated according to the 2019 World Health Organization (WHO) classification. The correlation between differentiation grade and lymphovascular invasion was analyzed using Fisher's Exact test. A p value <0.05 considered statistically significant. The most prevalent age group for cases of colorectal adenocarcinoma was 51–60 yr (36.1%). Low-grade differentiation was the most common grade of differentiation (72.2%). Lymphovascular invasion in small vessels was commonly encountered (73.3%). High-grade differentiation adenocarcinomas had 100% lymphovascular invasion. A significant correlation between differentiation grade and lymphovascular invasion was observed (p = 0.031). This study confirms that lymphovascular invasion is a valuable predictor of colorectal carcinoma progressiveness.

ABSTRAK

Karsinoma kolorektal merupakan keganasan ketiga terbanyak di dunia. Karsinoma kolorektal adalah tumor heterogen dengan gambaran klinikopatologik dan nilai prognostik berbeda. Sistem stadium tumor, node and metastasis (TNM) merupakan prediktor prognostik yang digunakan saat ini. Namun stadium TNM masih memberikan nilai prognostik yang terbatas, sekitar 30% pasien dengan kelenjr getah bening (KGB) negatif meninggal karena penyakit metastasis. Diduga terdapat faktor prognostik lain yang mempengaruhi prognosis selain stadium TNM. Derajat diferensiasi tinggi dan invasi limfovaskular termasuk faktor prognostik buruk yang telah ditetapkan untuk karsinoma kolorektal KGB negatif. Tujuan penelitian ini untuk mengkaji korelasi antara derajat diferensiasi dengan invasi limfovaskular pada adenokarsinoma kolorektal. Penelitian ini merupakan penelitian observasional dengan desain potong lintang. Sampel blok parafin sebanyak 97 adenokarsinoma kolorektal berasal dari 4 Laboratorium Patologi Anatomik di Sumatera Barat tahun 2018. Derajat diferensiasi dan invasi limfovaskular dievaluasi berdasarkan klasifikasi *World Health Organization* (WHO) tahun 2019. Korelasi antara tingkat diferensiasi dan invasi limfovaskular dianalisis dengan uji Fisher's Exact. Nilai p <0,05 dianggap signifikan. Kelompok usia terbanyak kasus adenokarsinoma kolorektal adalah usia 51-60 tahun (36,1%). Derajat diferensiasi adenokarsinoma kolorektal terbanyak adalah derajat diferensiasi low grade (72,2%). Sebagian besar kasus ditemukan adanya invasi limfovaskular yaitu di pembuluh kecil sebanyak 73,3%. Adenokarsinoma diferensiasi tingkat tinggi mempunyai invasi limfovaskular sebanyak 100%. Analisis statistik menunjukkan hubungan bermakna antara derajat diferensiasi dengan invasi limfovaskular (p=0,031). Hasil penelitian ini menunjukkan bahwa invasi limfovaskular merupakan prediktor yang signifikan untuk progresivitas perkembangan karsinoma kolorektal.

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INTRODUCTION

Colorectal carcinoma is the third-most common malignancy and the second-most cause of cancer-related death worldwide. Global Cancer International Agency for Research on Cancer (GLOBOCAN IARC) data shows that there were 1.8 million cases of colorectal carcinoma in 2018. In Indonesia, colorectal carcinoma is the fourth most common malignancy after breast, cervix, and lungs cancer with an incidence of 30.017 cases.[1,2]

The clinicopathological characteristics and prognostic values of colorectal cancer are varied. The most accurate prognostic predictor at the moment is the tumour, node, and metastasis (TNM) staging system. Nonetheless, approximately 30% of patients with lymph node-negative illness pass away from metastatic disease, and stage estimates based on lymph node examination only offer limited predictive values. For instance, extra predictive variables are essential to the evaluation of metastatic spread.[3]

High-grade differentiation and lymphovascular invasion are recognised as a poor prognostic markers for colorectal cancer without lymph nodes involvement. A study on early stages colorectal carcinoma shows, lymphovascular invasion is required to forecast prognosis and recurrence.[3] A meta-analysis reported, lymphovascular invasion is not a good indicator for individuals with stage I or stage II colorectal cancer. Adjuvant therapy should be considered for stage II patients who have a positive lymphovascular invasion, whereas strict follow-up is necessary for stage I patients who have a positive lymphatic invasion.[4]

The differentiation grade is a significant biological and prognostic determinant for tumours. It is still controversial that differentiation grade act as an independent predictive value. Many studies have shown that differentiation grade, which is determined using a two degree system with high-and low-grade distinctions became an independent prognostic predictive. It is additionally associated with the possibility of local and venous vein spread.[5]

The study aimed to analyse the correlation between the differentiation grade and lymphovascular invasion in patients with colorectal cancer.

MATERIAL AND METHODS

Design and cases

It was an observational study with a cross-sectional design. All colorectal adenocarcinoma cases diagnosed in 2018 in four West Sumatra anatomical pathology laboratories i.e. the Diagnostic Pathology Anatomy Centre of the Medical Faculty of Andalas University, M. Djamil Padang Hospital, Ibnu Sina Padang Hospital, and Ahmad Mochtar Bukittinggi Hospital were included in the research population. The samples included at least three tumour blocks and were from a patient of colorectal adenocarcinoma that underwent colectomy. A total of 97 cases of colorectal adenocarcinoma were collected.

Procedure

Evaluation of the differentiation grade was classified into low-grade and high-grade based on the proportion of glandular structures, WHO 2019 classification. It is included as low-grade criteria, when the gland structure is more than 50%, while high-grade gland structure is less than 50%.[6] Lymphovascular invasion is the presence of tumor cells within the endothelial-coated space or damage to the lymphovascular vessels' walls by tumor cells. The results of the evaluation of lymphovascular invasion are positive

and negative. The histopathological assessment of differentiation degree and lymphovascular invasion was conducted by three pathologists. The kappa test results for inter-observer agreement yielded a score of 0.68.

Data analysis

Univariate analysis was conducted to describe the characteristics of colorectal adenocarcinoma patients, including age, gender, differentiation grade, and lymphovascular invasion. The association between differentiation grade and lymphovascular invasion in colorectal adenocarcinoma was assessed using Fisher's Exact test. A p value <0.05 was considered statistically significant.

RESULTS

Our study included 97 patients, 51 females (52.6%) and 46 males (47.4%) with the majority age range of 51-60 yr with average age was 54.78 yr Seventy cases (72.2%) of colorectal adenocarcinoma showed low-grade differentiation as the most common differentiation grade. The majority of lymph-vascular invasions (88.7%) were positive. The characteristics of the sample are show in TABLE 1.

Lymphovascular invasions with a positive outlook were classified into four distinct categories, i.e. small vessel invasion, intramural venous invasion, extramural venous invasion, and combined invasion. Small vessel invasion refers to a tumor's engagement with the delicate walls lined by endothelium. Intramural venous invasion involves the infiltration of tumor cells into blood vessels situated in the submucosa and/or the muscularis propria layer. Extramural venous invasion entails the intrusion of tumor cells into blood vessels located beneath the muscularis propria layer.[8] The predominant form of lymphovascular invasion observed was small vessel invasion, accounting for 73.2% of cases. Details of lymphovascular invasion findings are in TABLE 2.

TABLE 1. Clinical characteristics of patients with colorectal adenocarcinoma

Characteristics	[n (%)]
Age (yr)[7]	
• 21-30	6 (6.2)
• 31-40	10 (10.3)
• 41-50	14 (14.4)
• 51-60	35 (36.1)
• 61-70	25 (25.8)
• 71-80	5 (5.10
• 81-90	2 (2.10
Sex	
• Female	51 (52.6)
• Male	46 (47.4)
Differentiation grade	
• Low	70 (72.2)
• High	24 (27.8)
Lymphovascular invasion	
• Negative	11 (11.3)
• Positive	86 (88.7)

TABLE 3 shows that lymphovascular invasion was present in all cases of high-grade differentiation (100%). A significant relationship was observed between the differentiation grade and lymphovascular invasion (p=0.031). The picture of differentiation grade and lymphovascular invasion can be seen in FIGURE 1 and 2.

TABLE 2. Distribution of lymphovascular invasion finding

Lymphovascular invasion	[n (%)]
Positive	
• Small vessel invasion	71 (73.2)
• Intramural venous invasion	0 (0.0)
• Extramural venous invasion	3 (3.1)
• Combined invasion	12 (12.4)
Negative	11 (11.3)

TABLE 3. Differentiation grade relationship with lymphovascular invasion in colorectal adenocarcinoma

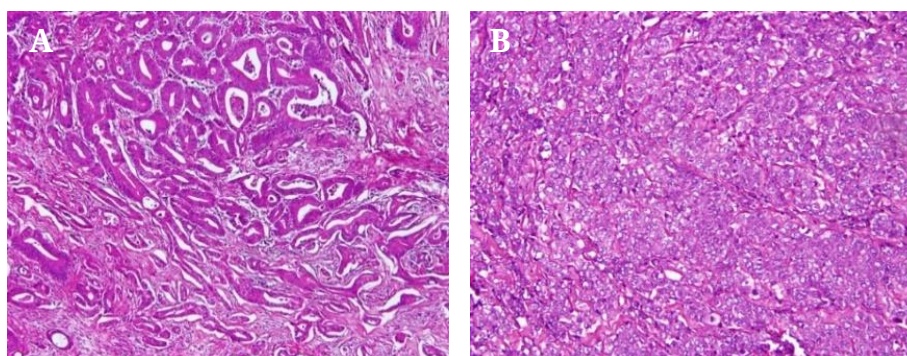| Differentiation grade	Lymphovascular invasion [n (%)]			p
	Negative	Positive	Total	
Low	11 (15.7)	59 (84.3)	70 (100.0)	0.031
High	0 (0.0)	27 (100.0)	27 (100.0)	

FIGURE 1. Differentiation grade. A) Low grade. B) High grade (HE magnification x200)
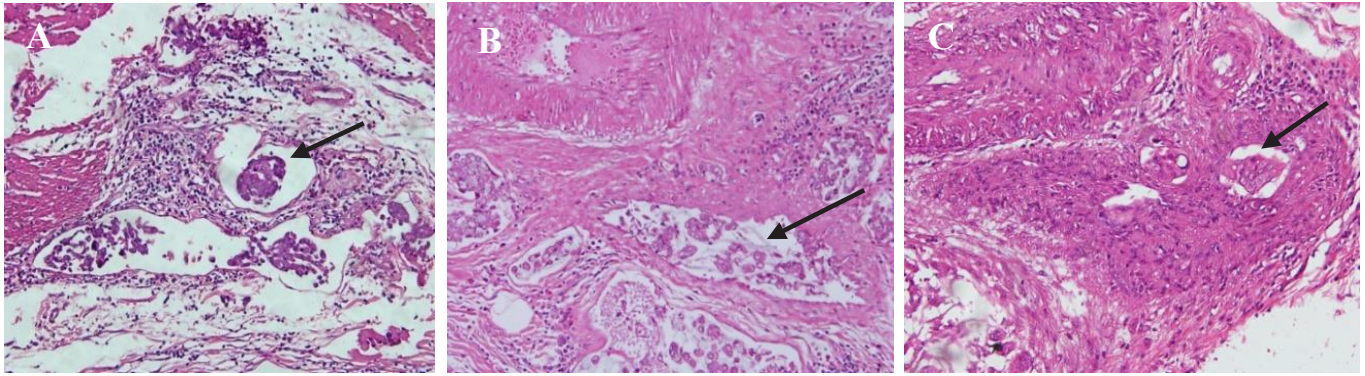
FIGURE 2. Lymphovascular invasion. A) Invasion of small vessel. B) Intramural venous invasion. C) Extramural venous invasion (HE magnification x100)

DISCUSSION

The most prevalent age group for colorectal adenocarcinoma was 51-60 y.o. (36.1%). The lowest age group was 81-90 with 2.1%. The total age rate of the sample in this study was 54.78. Similar findings were found in the study published by Syukri *et al.*[9] in the Laboratory of Anatomic Pathology of Western Sumatra from July 2016 to June 2017, which revealed a 27.71% rise in cases at the 51–60 y.o. group. The same findings were found in a study performed at Sanglah General Hospital Denpasar by Gunasekaran *et al.*[10] The most cases were found in the age range of 50-60 yr (39.7%) and the age group >70 yr, and the group with the lowest number of cases was 14.9%.

According to GLOBOCAN data, the incidence of colorectal cancer rises sharply beyond 50, and almost 59% of the 1.8 million cases worldwide are thought to occur between 50 and 74 y.o.[1] Age-related increases in the incidence of colorectal adenocarcinoma are probably caused by multifactorial cancer pathogenesis, which is mostly affected by environmental and lifestyle factors that initiate carcinogenesis. It takes an extended period for this exposure to occur continuously.[11,12] It usually takes ten years for a small adenoma to transform into an infiltrative adenocarcinoma.[12]

In this study, colorectal adenocarcinoma was slightly more prevalent in women, which was 52.58%. Similar finding was found by Syukri *et al.*[9] The study reported that the prevalence in female are 57.83% and male are 42.17%. However, unlike other studies, Gunasekaran *et al.*,[10] earned more male, which is 59.5%.

The incidence of these malignancies is probably going to vary depending on how people are exposed to different risk factors, like diet and physical activities. Increased gallic acid in the faeces is due to a high meat and fat diet that may lead to oxidation damage of DNA. Lack of physical activity will increase insulin and insulin growth factor-1 (IGF-1). Insulin growth factor 1 is a procarcinogenic factor that induce cell growth and reduce cell death. Low-fiber diets increase transit time in the colon, thus increasing the contact of irritant substances with the rectal colon mucosa.[13]

Chacko *et al.*[14] found that the interaction between estrogen exposure and body fat distribution are contributed to this gender-related factor, i.e., the proportion of proximal colon carcinoma in female was higher than in male.[11,14] In another study, postmenopausal female with a high body mass index (BMI) were at increased risk of developing colorectal adenocarcinoma. The female sex hormones protect against the occurrence

of colorectal carcinoma by modifying the metabolism of cholesterol in the liver and reducing bile acid.[15] Increased levels of bile acid are seen in postmenopausal female due to decreased progesterone and estrogen levels. Molecular genetic studies suggest that gallic acid can promote oxidative stress and KRAS gene mutations.[16]

The most commonly encountered differentiation grade was low-grade differentiated adenocarcinoma (72.2%). This finding similar to Gunasekaran *et al.*[10] who found low grade differentiation more often than high grade one, which is 90.9%. Other studies by Devianti *et al.*[20] in Bukittinggi, Jayadi *et al.*[19] in Yogjakarta, Anggunan in Lampung, and Ratnasari in Semarang were also have similar findings.[17-20]

The percentage of tumor cells found in the glands structure determined the differentiation grade. The differentiation grade was classified by a system of two levels, i.e. low-grade (glandular structure > 50%) and high-grade (grade structure < 50%). This degree of differentiation is applied to the subtypes of adenocarcinoma NOS, micropapillary adenocarcinoma, and serrated adenocarcinoma because other histopathological subtypes show their prognosis.[6]

Differentiation grade has a significant role in prognosis and has a major impact on survival. Patients with low-grade differentiation have a better 5-yr survival rate than those with high grades. The role of the differentiation grade as an independent prognostic factor remains controversial. Many studies have shown that the degree of tumor differentiation becomes an independent prognostic factor, especially when using a 2-degree differentiating system.[5] High-grade differentiations are associated with lymphatic metastases in more than 50% of cases. In contrast, lower degrees of differentiation have fewer lymphatic metastases. Additionally, the degree of differentiation correlates to the possibility of local and venous vein spread.[21]

Lymphovascular invasion in this study obtained a positive outcome in 86 cases (88.7%), with details of small-vascular invasion in 71 cases (73.2%) and extramural vein invasion in three cases. In addition, thecombined lymphovascular invasions were also found, including 1 case of small vein invasion and intramural venous invasion, as well as 11 cases of small vessel invasion and extramural vena invasion. In this study, it was concluded that invasion of small vessels were more frequent than venous invasions, while based on the invasion of the veins, there were more extramural locations than intramural ones.

The study of Betge *et al.*[22] also found that small vein invasions were more common than venous invasions, with a percentage of 33 and 23%, respectively, as well as extramural vein invasions being more common than intramural vena invasions. Based on the history, the incidence of lymphovascular invasion ranged from 10 to 89.5%.[23]

The possibility of lymphovascular invasion is strongly related to the number of tumor blocks investigated. According to Bedge *et al.* when only two tumor blocks were examined, 42% of malignancies with vein vascular invasion would be unnoticed, but an average evaluation of five tumor blocks would miss only 4% of tumors with venous invasion. The information is gained from multimodal analysis, however an experimental evidence has not been found.[22] Other investigations which assesed lymphovascular invasion in five tumor block preparations that are most likely showed insufficient. The College of American Pathologists suggests a minimum number of assessed block is three block preparations and the ideal number is five block tumors to determine lymphovascular invasion.[23]

Lymphovascular invasion is one of the predictive factors for colorectal adenocarcinoma. Lymphovascular invasions are associated with a higher progression of the disease and a worse prognosis.[24] Invasion of the extramural veins is an independent risk factor for metastasis to hepar. The Gastrointestinal Pathology Study Group (GIP) of the Korean Society of Pathologists recommends reporting extramural vein invasions separately from intramural.[25]

In this study, adenocarcinomas with high-grade differentiation had a lymphovascular invasion rate of 100%, while 84.3% of low-grade differentiation had lymphovascular invasion. Statistically, there was a significant correlation between differentiation grade and lymphovascular invasion (p< 0.05).

The same result was described by Betge *et al.*[22] which discovered that a 16.2% vein invasion and a 26.3% small-scratch invasion in his study belongs to low-grade differentiation. Lymphovascular invasion at a higher degree of differentiation were observed, with a small-vascular invasion of 47.2% and a vein invasion of 37.4%. The presence of lymphovascular invasion is significantly associated with the degree of differentiation (p=0.001).[22]

Lymphovascular invasion is an independent prognostic factor in both early and advanced lesions.[22,26,27] Lymphovascular invasion increases lymph node metastases and distant metastases. Furthermore, lymphovascular invasion, which is independent of disease stage, is a significant indicator of adjuvant treatment.[27] Patients with negative lymph node metastases, especially stage II, are the most important group that get benefit identification of lymphovascular invasion. Normally, adjuvant chemotherapy is not given to patients with stage II; however, because of the patient's high-risk category according to lymphovascular invasion, the patient does get adjuvant chemotherapy. This is in accordance with the clinical practice guidelines of the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) which list lymphovascular invasion as a factor to be considered for adjuvant chemotherapy therapy in stage II.[28]

Betge *et al.*[22] reported venous invasion proved to be a strong independent factor. Patients with venous invasion have about twice higher risk in having disease progression or death from cancer than patients without venous invasion. The prognosis for extramural venous invasion is better than that of intramural venous invasion. Extramural venous invasion is poor prognostic factor and increases the risk of hepatic metastases. The Schneider NI and Langner C study conducted on 381 cases of colorectal carcinoma found 5-yr cancer-specific survival in patients with 30% venous invasion and 75% without venous invasion. Based on the site of venous invasion, 46% of patients with intramural venous invasion and 77% of patients with extramural venous invasion died due to disease progression (p<0.001).[26]

Betge *et al.*[22] also reported that small vessel invasion is an independent prognostic factor but to a lesser extent. Small vessel invasion affects only disease progression but not cancer-specific survival. Similar with venous invasion, extramural small vessel invasion proved to be a significantly stronger prognostic variable than intramural small vessel invasion. Few studies reporting a prognostic effect of small vessel invasion on univariable analysis alone or fail to identify a prognostic effect.

High-grade differentiated adenocarcinoma was more commonly observed in advanced stages of colorectal adenocarcinoma, while low-grade differentiated adenocarcinoma

was more prevalent in non-metastatic cases. Histopathological grading and metastasis showed a significant correlation, with high-grade differentiated adenocarcinomas having a greater likelihood of being associated with metastasis. This association is attributed to the higher mitotic activity and proliferative capacity of high-grade differentiated adenocarcinoma, which facilitates malignant cell invasion and metastasis more effectively than low-grade differentiated colorectal adenocarcinoma.[29]

CONCLUSION

A significant correlation is observed between the degree of differentiation and lymphovascular invasion in colorectal adenocarcinoma. The prevalence of lymphovascular invasion increases as the degree of differentiation worsens. This study further confirms that lymphovascular invasion serves as an important predictor of colorectal carcinoma progression.

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