KEMENTERIAN PENDIDIKAN NASIONAL
UNIVERSITAS HASANUDDIN
FAKULTAS KEDOKTERAN
KOMISI ETIK PENELITIAN KESEHATAN

Sekretariat : Lantai 3 Gedung Laboratorium Terpadu
JL.PERINTIS KEMERDEKAAN KAMPUS TAMALANREA KM.10, Makassar. Telp. (0411)5780103, Fax (0411) 581431.
Contact person **dr. Agussalim Bukhari,PhD,SpGK** (HP. 081241850858), email: agussalimbukhari @ yahoo.com

REKOMENDASI PERSETUJUAN ETIK
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Komisi Etik Penelitian Kesehatan Fakultas Kedokteran Universitas Hasanuddin, setelah melalui pembahasan dan penilaian, pada rapat tertanggal **30 Nopember 2011**, telah memutuskan, protokol penelitian berjudul:

Hubungan Antara Gambaran Histopatologis Karsinoma Kolorektal dengan Metastasis

dengan Peneliti Utama: **dr. Rahmawati Minhajat, PhD**

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yang diterima pada tanggal: **14 Nopember 2011**

Perbaikan diterima tanggal: **16 Januari 2012**

dapat disetujui untuk dilaksanakan di **RS dr. Wahidin Sudirohusodo, RSI Faisal, RS Ibnu Sina, RS Akademis Jaury, dan RS Grestelina di Makassar.**
Persetujuan Etik ini berlaku sejak tanggal ditetapkan sampai dengan batas waktu pelaksanaan penelitian.

Pada akhir penelitian, **laporan pelaksanaan penelitian** harus diserahkan kepada KEPK Fakultas Kedokteran Unhas. Jika ada perubahan protokol dan /atau perpanjangan penelitian, harus mengajukan kembali permohonan kajian etik penelitian (amandemen protokol).

Makassar, 18 Januari 2012

Komisi Etik Penelitian Kesehatan Fak. Kedokteran Unhas

Ketua	Sekretaris
Prof.Dr.dr.Suryani As'ad,M.Sc,Sp.GK	**dr.Agussalim B, MMed,Ph.D,SpGK**
NIP 19600504 1986 01 2 002	**NIP 19700821 1999 03 1 001**

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The Relationship Between Histopathological Grading and Metastasis in Colorectal Carcinoma Patients

Rahmawati Minhajat[1], Andi Fachruddin Benyamin[2], Upik Andariana Miskad [3]

[1] Division of Hematology and Medical Oncology, Internal Medicine Department.
[#]Histology Department Medical Faculty of Hasanuddin University, Makassar Indonesia
[2] Division of Hematology and Medical Oncology, Internal Medicine Department, Medical Faculty of Hasanuddin University, Makassar Indonesia
[3] Pathology Anatomy Department, Medical Faculty of Hasanuddin University, Makassar Indonesia.

Corresponding Author:
Name: Rahmawati Minhajat
Email: : rahmawati.minhajat@gmail.com

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ABSTRACT

Introduction: *To Colorectal cancer (CRC) is a malignancy in the large intestine caused by uncontrolled cell growth. The cause of death due to metastasis and the prognosis is determined by the stage that can be assessed using Dukes classification or TNM (Tumor Nodes Metastasis) staging system. Determination of histopathological grading is important because of the differences in radiosensitivity, local behaviour and the metastasis tendency. The aim of this study is to determine the relationship between histopathological grading and metastasis in colorectal cancer patients.* ***Methods:*** *This study is a cross-sectional study using secondary data from the medical records of CRC patients at the RS. Dr. Wahidin Sudirohusodo and its networking hospital, that were obtained by consecutive sampling. Inclusion criteria are all patients who had surgery and have the results of histopathology, radiology and other datas that may be used as a reference for determining the staging based on the Dukes classification and TNM staging system* ***Results:*** *The number of CRC patients during January 2008 to April 2012 was 268 patients, 55,6% of them were males and*

mostly their age were around 51-60 years old (25,4%). Most of the CRC location was in the rectum (61,2%) and the highest number of metastasis location was in lymph nodes (40,4%). Out of 179 patients who had result of histopathological examination, adenocarcinoma type (100%) and moderately differentiated adenocarcinoma (45,3%) were the most frequently histopathological grading found. Most of the CRC stage based on the TNM staging system was stage IV (27,4%) and based on the Dukes classification was stage D (26,8%). There is a significant relationship (p<0,001) between histopathological grading and metastasis, and it showed that poorly differentiated adenocarcinoma was more frequent in advanced stage, based on both the Dukes classification and TNM staging system. ***Conclusions:*** *There is a significant relationship between histophological grading and metastasis. Poorly differentiated adenocarcinoma is more likely to be found in advanced stage of CRC.*

1. INTRODUCTION

Colorectal carcinoma (CRC) is a malignancy originated from colon caused by uncontrolled cell growth.[1,2] World Health Organization (WHO) reported that CRC incidence is quite high, and so is the mortality. In 2008, CRC incidence was 3rd highest among other types of cancer and 4th highest in the cause of death due to cancer in the world. In Indonesia, in 2008 mortality of CRC was estimated to be about 11,1 people per 100.000 inhabitant and also the most common malignancy in gastrointestinal.[2]

The main cause of death in CRC is metastasis. The most common sites for distant metastasis in CRC are liver, then followed by lung and peritoneum. It's reported that about 5-10% of CRC patients underwent surgery with lung metastasis and about 4% with bone metastasis. Based on the literatures, the prognosis of CRC patients are influenced by several parameters, including sex, age, resection of primary tumor, number of metastasis, and tumor differentiation degree.[3,4]

CRC patient's prognosis could be determined by staging CRC based on Dukes Classification and TNM (Tumor Nodes Metastasis) system. Both parameters are frequently used to determined CRC's stages, which assessed CRC's cell invasion to intestinal wall, lymph nodes metastasis, and distant metastasis to other organs. Those can be determined through clinical, radiologic, and histologic evaluation, where it's important to determine whether tumor spread locally or systemically.[5,6]

Histologically, 98% of CRC are adenocarcinoma with most subtype are non-mucinous adenocarcinoma, mucinous adenocarsinoma dan signet ring cell carsinoma. Based on the grading, adenocarcinoma are classified to well differentiation, moderate differentiation, and poor differentiation. Determination of histological type is important because the differences in histological features will also vary in terms of radio

sensitivity, local behavior, and a tendency for regional and systemic metastasis. CRC's degree of differentiation is an important indicator to assess the potential of local invasion and systemic metastasis.[7,8]

The aim of this study is to determine the relationship between histopathological grading and metastasis in CRC patients.

2. METHODS

This study is a cross sectional study using secondary data from CRC's patient medical record in Dr. Wahidin Sudirohusodo hospital and other affiliation hospital since January 2008 until April 2012, both outpatient and inpatient obtained by consecutive sampling. Sample of this study are population studies that met the inclusion criteria i.e. patients who have undergone surgery and have had the histopathological examination result originating from the resection (surgery), patients in it's medical record already provided data on TNM classification/Dukes, or patient medical records contained the results of a CT scan of the abdomen, chest X-ray, abdominal ultrasound, endoscopy, surgery reports and other data that can be used as a reference to determine the stage by the TNM classification and Dukes

Data analysis was performed using the statistical package for social science (SPSS) version 17. The descriptive statistical method used is the calculation of the frequency distribution. The statistical test used Chi Square test (Likelihood Ratio). The test results were considered significant if the p-value <0.05.

3. RESULTS

Data collection of CRC patient from Dr. Wahidin Sudirohusodo hospital, Labuang Baji hospital, Ibnu Sina hospital, Islam Faisal hospital dan Grestelina hospital di Makassar from January 2008 until April 2012 are 268 people, with male 149 people (55.6%) dan CRC most prevalent between age 51-60 years 68 people (25.4%). (Table 1)

Table 1. Patient's demographic characteristic

Characteristic	n	%
Total patient	268	100
Sex		
Male	149	55.6
Age (years)		
11-20	5	1.9
21-30	15	5.6
31-40	35	13.1
41-50	58	21.6
51-60	68	25.4
61-70	58	21.6
>70	29	10.8

From 268 CRC patient, only 179 people met the inclusion criteria. CRC with metastasis was found in 109 people, divided into; locoregional metastases were 60 (33.5%) and distant metastasis are 49 people (27.4%) and 70 (39.1%) with no metastasis. (Table 2)

Table 2. Metastasis distribution

Metastasis	n	%
Locoregional metastasis	60	33,5
Distant metastasis	49	27,4
No metastasis	70	39,1
Total	179	100

From histopatological pattern, all CRC patient has adenocarcinoma pattern (100%), which moderately differentiated is the most frequent histopatological pattern with 81 people (45.3%). (Table 3)

Table 3. Histopathologic grading distribution

Histopathologic pattern	**n**	**%**
Adenocarsinoma	**179**	**100**
Well differetiation	41	22.9
Moderately differetiation	81	45.3
Poor differentiation	50	27.9
Mucinosum type	3	1.7
Signet ring cell type	4	2.2

CRC's distribution based on Dukes classification (Astler Coller Modification), found Dukes D is the most prevalent staging with 48 people (26.8%), followed by Dukes C2 with 44 people (24.6%). In this study, there were 3 people (1.7%) which can not be staging with Dukes classification. (Table 4)

Table 4. CRC staging distribution based on DUKES classification (Astler Coller Modification)

Dukes	n	%
A	40	22,3
B1	13	7,3
B2	26	14,5
C1	5	2,8
C2	44	24,6
D	48	26,8
Unknown	3	1,7
Total	179	100

CRC's staging distribution based on TNM system, stage IV is the most the prevalent with 49 people (27.4%) dan the least is stage 0 with 5 people (2.8%). (Table 5)

Table 5. CRC staging distribution based on TNM system

Stadium	n	%
0	5	2,8
1A	27	15,1
1B	32	17,9
IIA	8	4,5
IIIA	37	20,7
IIIB	21	11,7

IV	49	27,4
Total	179	100

Correlation between CRC histopathological grading and staging based on Dukes Classification can not be tested, but the result is this study showed tendency of poorly differentiation CRC are more prevalent in advanced stage (C1, C2 and D) compared to early stage. While well differentiation CRC tend to be more common in early stage (A1, B1 and B2). (Table 6)

Table 6. Correlation between histopathological grading with CRC staging based on DUKES classification (Astler Coller Modification)

			Adenocarsinoma					
			Well Diff.	Moderately Diff.	Poorly Diff.	Mucinosum	Signet Ring Cell	Total
Dukes	A	n (%)	21 (52.5)	16 (40.0)	1 (2.5)	0 (0.0)	2 (5.0)	40 (100)
	B1	n (%)	5 (38.5)	8 (61.5)	0 (0.0)	0 (0.0)	0 (0.0)	13 (100)
	B2	n (%)	5 (19.2)	18 (69.2)	1 (3.8)	1 (3.8)	1 (3.8)	26 (100)
	C	n (%)	1 (33.3)	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100)
	C1	n (%)	0 (0.0)	2 (40.0)	3 (60.0)	0 (0.0)	0 (0.0)	5 (100)
	C2	n (%)	4 (9.1)	22 (50.0)	15 (34.1)	2 (4.5)	1 (2.3)	44 (100)
	D	n (%)	5 (10.4)	13 (27.1)	30 (62.5)	0 (0.0)	0 (0.0)	48 (100)
Total		n (%)	41 (22.9)	81 (45.3)	50 (27.9)	3 (1.7)	4 (2.2)	179 (100)

Correlation between CRC histopathological grading with staging based on TNM system also can not be tested, the this study showed tendency of poorly differentiation CRC are more prevalent in stage IIIA and above, while well differentiation are more common in stage IIA and below (Table 7)

Table 7. Correlation between histophatological grading with CRC staging based on TMN system

Stadium		Adenocarsinoma					
		Well Diff.	Moderately Diff.	Poorly Diff.	Mucinosum	Signet Ring Cell	Total
0	n (%)	4 (80.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (100)
IA	n (%)	12 (44.4)	13 (48.1)	0 (0.0)	1 (3.7)	1 (3.7)	27 (100)
IB	n (%)	12 (37.5)	19 (59.4)	0 (0.0)	0 (0.0)	1 (3.1)	32 (100)
IIA	n (%)	2 (25.0)	5 (62.5)	1 (12.5)	0 (0.0)	0 (0.0)	8 (100)
IIIA	n (%)	4 (10.8)	22 (59.5)	8 (21.6)	2 (5.4)	1 (2.7)	37 (100)
IIIB	n (%)	2 (9.5)	8 (38.1)	10 (47.6)	0 (0.0)	1 (4.8)	21 (100)
IV	n (%)	5 (10.2)	13 (26.5)	31 (63.3)	0 (0.0)	0 (0.0)	49 (100)
Total	n (%)	41 (22.9)	81 (45.3)	50 (27.9)	3 (1.7)	4 (2.2)	179 (100)

From the analysis of correlation between CRC histopathological grading with metastasis, there was a significant correlation between CRC differentiation with metastasis (p<0,001). Distant metastasis is the most prevalent in poorly differentiation CRC (62%), while no metastasis is the most prevalent in well differentiation CRC (73.2%). (Table 8)

Table 8. Correlation between histophatological grading with metastasis

Adenocarsinoma		Metastase			Total
		Locoregional	Distant	NM	
Well differentiation	n (%)	6 (14.6)	5 (12.2)	30 (73.2)	41 (100)
Moderately differentiation	n (%)	32 (39,5)	13 (16,0)	36 (44,4)	81 (100)
Poorly differentiation	n (%)	18 (36.0)	31 (62.0)	1 (2.0)	50 (100)
Mucinosum type	n (%)	2 (66,7)	0 (,0)	1 (33.3)	3 (100)
Signet Ring cell type	n (%)	2 (50.0)	0 (,0)	2 (50,0)	4 (100)

Total	n (%)	60 (33.5)	49 (27.4)	70 (39.1)	179 (100)

Likelihood Ratio test (p=0,000). NM; no metastasis

4. DISCUSSIONS

The prognosis of patient with CRC is influenced by several parameters, i.e. sex, age, resection of the primary tumor, number of metastasis lesions and the degree of differentiation.[3,4] The National Cancer Institute (2011), reported that the risk for TRC began to increase after the age of 40 years and increased sharply at the age of 50 to 55 years, the risk has doubled every next decade.[9] In our study, total of CRC, patients who were treated between 2008-2012, found male patients (56%) did not differ in number with female. Mainly found in the productive age range 20-60 years (60.1%) and CRC incidence increases with age and peaks at age 51-60 years (25.4%)

Metastasis in CRC can be grouped in to local and regional (*loco-regional*) metastasis and distant metastasis.[10] Based on metastasis, we found locoregional is 33,3% and distant metastasis 27,2%, while non metastasis CRC is 39.5%.

In this study, of 179 patients who had histopathologic examination, all of it is was adenocarcinoma (100%). Of the study evaluated 100 cases, reported that patients with poorly differentiation showed deeper invasion into the intestinal wall and lymph node metastasis compared to moderately and well differentiation.[11] The results were consistent with the study conducted by Chung et al.[12] These findings suggested that histological assessment is very significant for the evaluation of clinical and management of CRC patient. The results of our study, found the degree of differentiation of the vast majority were moderately differentiation adenocarcinoma (45.3%) followed by poorly differentiation (27.9%) and well differentiation (22.9%), while the adenocarcinoma type mucinous only found in 3 (1.7%) and signet ring on 4 patient (2.2%).

This study showed a significant correlation between the adenocarcinoma differentiation with metastasis ($p < 0.001$), in which distant metastases are found most prevalent in poorly differentiation adenocarcinoma (62%), while no metastasis is found mostly in well differentiation adenocarcinoma (73.2%). The results are consistent with the study conducted by Riboli RE (1983), which reported an association between adenocarcinoma differentiation with metastasis to lymph nodes in patients with moderately and poorly differentiation adenocarcinoma.[13] The correlation between of differentiation and metastasis in CRC is possible due to increased mitosis and hyper-proliferation of malignant cell in poorly differentiation adenocarcinoma compared to well or moderately differentiation adenocarcinoma. Thus, malignant cell invasion to surrounding tissue and cell penetration through hematogen and lyphogen to metastasis also greater.[14]

Nabi U (2010), reported a significant correlation between histology pattern in adenocarcinoma differentiation with CRC staging based on Dukes classification ($p < 0.000$), where poorly differentiation adenocarcinoma mostly found at an advanced stage (Dukes C), otherwise well differentiation adenocarcinoma only found at an early stage (Dukes A and B).[9] Similarly, Derwinger K (2010), also reported a significant correlation ($p < 0.001$) between histology pattern in adenocarcinoma differentiation with CRC staging based on TNM system, where poorly differentiation linked to the higher

number of metastasis to lymph nodes (stage III).[16] Although statistically the correlation between the CRC histopathology pattern with staging cannot be tested, but the results of this study showed a tendency of poorly differentiation adenocarcinoma are more prevalent in advanced stage (IIIA and above), while the well differentiation tend to be more prevalent in earlier stage (IIA or lower). Similarly, the correlation between the Dukes classification with CRC histopathology pattern, this study showed a tendency poorly differentiation adenocarcinoma more prevalent in advanced stage (C1, C2 and D), whereas well differentiation adenocarcinoma tend to be more prevalent in the early stages (A, B1, and B2). The tendency for poorly differentiated adenocarcinoma more prevalent in advanced stage CRC, either by Dukes classification and TNM system, also can be caused by the same reason that poorly differentiation adenocarcinoma, has greater ability to mitosis and proliferate, this increased malignant cell invasion and metastasis compared to moderately and well differentiation CRC.[15]

5. CONCLUSION

There is a correlation between histophological grading and metastasis. Poorly differentiation adenocarcinoma is more likely to be found in advanced stage of CRC, while well differentiation adenocarcinoma it more prevalent in non metastasis CRC. Poorly differentiation it more common in advance stage based on Dukes classification (C1, C2, and D) and advanced stadium based on TNM classification (IIIA and above).

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