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Expression of p53 Mutants in Determining the Degree of Differentiation and Prognosis of Colorectal Adenocarcinoma in the Laboratory of Anatomical Pathology of Haji Adam Malik Hospital Medan

Yessi Devita Azraini Dewi
Universitas Imelda Medan

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ABSTRACT

Cancer is important problem in public health worldwide especially in developed countries. About 10 millions new cases was diagnosed every year. Colorectal carcinoma is more common in man than woman. Despite significant advances in both surgical methodology and adjuvant therapy regimes, long-term survival for CRC patients remains in the range of 50-60%. Based on WHO, 90 % colorectal carcinoma was adenocarcinoma. Colorectal carcinoma is caused by a collection of various genetic changes and the most common cause is a loss of function of the p53 tumor suppressor gene. P53 tumor suppressor gene plays an important role in cell cycle and apoptosis. This gene encodes for a 53 kDa phosphoprotein and is frequently targeted for inactivation in a wide range of tumours. It is the target of point mutations and small deletions and insertions that lead to total or partial abolition of protein function. Inactivation is believed to abolish the ability of p53 to maintain genomic integrity through regulation of various activities, including the control of cell cycle arrest, DNA repair and apoptosis. Accumulation of p53 in tumor cells can be detected with a specific p53 antibody. Mutation on p53 gen and overekspression of p53 is common incolorectal carcinoma tissue then p53 mutant and p53 wild type can be targeted by p53 specific antibody. P53 overexpression associated with colorectal carcinoma histologycal grade and tend more common in colorectal carcinoma with high proliferation activity. To assess p53 mutan expression in determining differentiation grade and prognose adenocarcinoma colorectal and the prognose of adenocarcinoma colorectal at Anatomic Pathology laboratory of RSUP Haji Adam Malik Medan. The study design was observational design with cross sectional approach. All variables were immunohistochemically stained with p53 mutant. The variables were measured only once and at one moment. The samples used in this study were the sample preparation of paraffin blocks from 59 colorectal carcinoma tissues which diagnosed patologically according inclusion criteria. All variables were immunohistochemically stained with p53 mutant. Distribution of patients by age group mostly aged over 60 years which is 24 cases (40.68%). Distribution of patients by sex mostly male which is 36 cases (61.02%). 36 cases (61,02%) were located on colon. The majority, 27 cases (45,76%) were diagnosed as well differentiated adenocarcinoma. Colorectal carcinoma samples based on p53 mutant expression were score +1 (weak) were 35 cases (59,32%). Calculation of chi-square with 2x2 crosstab table, p value = 0.427 (p value> 0.05). No difference between p53 mutant expression with histopathological grade in colorectal adenocarcinoma.

Email :
essi.devita@gmail.com

INTRODUCTION

In developed countries with a western lifestyle, about half of all deaths are caused by vascular diseases and a quarter are caused by cancer. Cancer is an important problem for public health around the world. The type of cancer that is ranked fourth in the world is colorectal carcinoma. The incidence of colorectal carcinoma is more in men than in women.

According to the World Health Organization (WHO), ninety percent of colorectal carcinoma cases are colorectal adenocarcinoma types. Generally, gland-forming of colorectal adenocarcinoma has

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various sizes and patterns of glandular structure.

Colorectal cancer cells are caused by a combination of several genetic changes. The most frequent cause is the loss of function of tumor suppressors of the p53 gene. In colorectal cancer, p53 expression is found in 50% to 70% of tumor cells. Because mutations in the p53 gene and p53 overexpression are associated with normal tumor tissue, mutant p53 and wild-type p53 can be antibody-specific p53 targets.

The p53 gene suppressor tumor is a 53 kDa phosphoprotein and is usually found in most tumors. The presence of mutations, small lacerations and insertions can cause total or partial damage to protein function. This damage causes p53's ability to maintain genome integrity through the regulation of various activities such as controlling cell cycle stopping, DNA repair and apoptosis because it is difficult to recognize p53 by the sequence method, immunohistochemistry techniques are usually used to detect mutant p53 on the assumption that overexpression of p53 is usually caused by mutations while weak expression of p53 is usually caused by wild type p53. In several immunohistochemical studies of p53 on colorectal carcinoma by Yamac Erhan et al, Khudier H et al, and Houbiers JGA et al, it was stated that p53 overexpression was not related to histolopathological grading of colorectal carcinoma. In the study, Erhan et al. from Turkey stated that there was a relationship between p53 expression and the metastasis of carcinoma to other organs. In the study, Tien et al. from Taiwan stated that there was a relationship between mutant p53 and poor prognosis.

METHOD

In this study, slides from colorectal tissue that had been diagnosed as colorectal carcinoma were collected in the Anatomical Pathology Laboratory of RSUP HAM Medan. Then a slide review of colorectal adenocarcinoma was carried out by 2 pathologists together with the researcher, after which the paraffin block of colorectal tissue used for immunohistochemistry p53 was re-cut.

RESULTS AND DISCUSSION

The distribution of patients based on age is grouped into 4 groups, namely the age group <= 40 years, the age group of 41 years – 50 years, the age group of 51 years – 60 years and the age group > 60 years.

Table 1. Distribution of Colorectal Adenocarcinoma Patients by Age

Age	Frequency	%
<= 40	10	16.95
41-50	12	20.34
51-60	13	22.03
> 60	24	40.68
Total	59	100.00

Based on Table 1. Above, the highest number was found in colorectal adenocarcinoma patients in the group > 60 years as many as 24 cases (40.68%) and the least was found in the age group <= 40 years as many as 10 cases (16.95%).

The distribution of patients based on gender is divided into two groups, namely men and women.

Table 2. Distribution of Colorectal Adenocarcinoma Patients Based on Gender

Gender	Frequency	%
Man	36	61.02
Woman	23	38.98
Total	59	100.00

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Based on Table 2. Above, the distribution of colorectal adenocarcinoma patients was 36 cases (61.02%) male and 23 cases (38.98%) were female.

In the distribution of colorectal adenocarcinoma patients based on tissue location, it is divided into four groups, namely caecum, colon, rectum and sigmoid.

Table 3. Distribution of Colorectal Adenocarcinoma Patients Based on Network Location

Network Location	Frequency	%
Colon	36	61.02
Rectum	15	25.42
Sigmoid	6	10.17
Caecum	2	3.39
Total	59	100.00

Based on Table 3. Above, the distribution of colorectal adenocarcinoma patients based on tissue location was most often found in colon tissue as many as 36 cases (61.02%) and least found in caecum tissue as many as 2 cases (3.39%).

In the distribution of colorectal adenocarcinoma patients based on histopathological grading, it is divided into well differentiated adenocarcinoma, moderately differentiated adenocarcinoma, poorly differentiate adenocarcinoma.

Table 4. Distribution of Colorectal Adenocarcinoma Patients Based on Histopathological Grading

Grading	Frequency	%
Well Differentiated Adenocarcinoma	27	45.76
Moderately Differentiated Adenocarcinoma	26	44.07
Poorly Differentiated Adenocarcinoma	6	10.17
Total	59	100.00

Based on Table 4. Above, the distribution of colorectal adenocarcinoma patients based on histopathological grading, which was found in 27 cases (45.76%), moderately differentiated adenocarcinoma in 26 cases (44.07%) and least in poorly differentiated adenocarcinoma in 6 cases (10.17%).

Table 5. Distribution of Colorectal Adenocarcinoma Patients Based on Mutant p53 Expression

Expression p53 Mutant	Frequency	%
-	29	49.20
+	30	50.80
Total	59	100.00

Based on Table 5. Above, the distribution of colorectal adenocarcinoma patients based on mutant P53 expression in positive and negative colorectal adenocarcinoma was not much different, namely 30 cases (50.80%) were positive and 29 cases (40.20%) were negative. The p53 score for the statistical test is grouped based on a score of 0 and a score of +1 which is categorized as a negative (-) p53 expression, a score of +2 and a score of +3 is categorized as a positive (+).9

To analyze the difference in the immunohistochemical appearance of mutant p53 between histopathological grading of colorectal adenocarcinoma and crosstabulation analysis using SPSS 18. In the fisher exact test with a 2x2 crosstabulation table, it was determined that H0 is the absence of a difference in mutant p53 expression with histopathological grading.

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Table 6. Crosstabulation 2x3 Expression p53 Mutant with Histopathology Grading Colorectal Adenocarcinoma

Variable		Grading			
		Well Diff	Moderate Diff	Poorly Diff	Total
Expression of		n (%)	n (%)	n (%)	n (%)
mutant p53	-	16 (55.2)	10 (34.5)	3 (10.3)	29 (100)
	+	11 (36.7)	16 (53.3)	3 (10.0)	30 (100)
Total		27 (45.8)	26 (44.1)	6 (10.2)	59 (100)

Based on Table 6. The 2x3 crosstabulation above, states that there is an observed value of 0 and there are 2 cells (33.3%) that have an expected count of less than 5, so the test is not feasible to be carried out with chi square analysis, so it is simplified to 2x2 crosstabulation is carried out.

In this test, a combination of well differentiated adenocarcinoma and moderately differentiated adenocarcinoma into low grade and poorly differentiated adenocarcinoma into high grade was carried out, this combination was based on the literature in WHO.

Table 7. Crosstabulation 2x2 Expression p53 Mutant with Histopathology Grading Colorectal Adenocarcinoma

Variable		Grading n (%)			
		Low grade	High grade	Total	p value
Expression of mutant	-	26 (89.7)	3 (10.3)	29 (100)	0.648
p53	+	27 (90.0)	3 (10.0)	30 (100)	
Total		53 (89.8)	6 (10.2)	59 (100)	

In table 7 of the 2x2 crosstabulation there is no observed value of 0 and there are still 2 cells (50%) that have an expected count of less than 5, this 2x2 table is not suitable to be tested with chi square analysis and this test is followed by the Fisher exact test. From the results of the statistical analysis of the Fisher exact test, it was concluded that the p value = 0.648 (p value> 0.05).

Discussion

Based on research that has been carried out by taking data from medical records at H. Adam Malik Hospital Medan with a sample of 59 cases. The study data was used to determine the difference in mutant p53 expression with histopathological grading of colorectal adenocarcinoma. The p53 gene is mutated in about 80% of colon cancers, suggesting that the p53 mutation also occurs in the advanced stages of tumor development.

In this study, it was found that the most patients with colorectal adenocarcinoma were over 60 years old with 24 cases (40.68%), in the age group between 51 years to 60 years as many as 13 cases (22.03%), in the age group between 41 years and 50 years as many as 12 cases (20.34%), in the age group less than 40 years as many as 10 cases (16.95%), So that the results of the analysis of age characteristics show that the incidence of colorectal adenocarcinoma is increasing in frequency in line with age. In the gender group, according to research data, there are many cases of male sex as many as 36 cases (61.02%), followed by female sex sufferers as many as 23 cases (38.98%). This research is in accordance with the literature. This is because men more often consume foods that contain less fiber.

Meanwhile, colorectal adenocarcinoma patients based on tissue location mostly occurred in the location of colon tissue as many as 36 cases (61.02%), rectal tissue location as many as 15 cases (25.42%), sigmoid tissue location as many as 6 cases (10.17%) and caecum tissue location as many as 2 cases (3.39%). This study is in accordance with the WHO literature which states that the most locations are in colons because of its location in the proximal area with exophytic tumor growth.

This study is in accordance with previous research by Watson et al. based on histopathology

grading, the most are well differentiated adenocarcinoma as many as 27 cases (45.76), followed by moderately differentiated adenocarcinoma as many as 26 cases (44.07%) and poorly differentiated adenocarcinoma as many as 6 cases (10.17%).

Based on the expression of mutant p53, the most were expressed in p53 positive (+) expression as many as 30 cases (50.80%) and p53 negative (-) expression was in 29 cases (49.20%). This is in accordance with previous research by Georgescu et al. In the calculation of the fisher exact test, the 2x2 crosstabulation table produced a value of p value=0.648 > 0.05, so Ho failed to be rejected, namely there was no difference in appearance between the mutant p53 and the degree of differentiation of colorectal carcinoma. This data is in accordance with previous research conducted by Houbiers JGA et al, Yamac Erhan et al and H Khudier.

CONCLUSION

There was no difference between the expression of mutant p53 among the degrees of differentiation of colorectal adenocarcinoma. Colorectal adenocarcinoma is most commonly found in the age group over 61 years old. Most people with colorectal adenocarcinoma are men. Network location often occurs in colons. The most common types of histopathological grading are found in well differentiated adenocarcinoma, moderately differentiated adenocarcinoma and poorly differentiated adenocarcinoma. The most mutant p53 expression was found at a score of 1+ (weak), a score of 2+ (moderate), a score of 3+ (strong) and a score of 0 (negative).

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