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ANALYSIS OF PIK3CA EXPRESSION TO CLINICOPATHOLOGY FEATURES OF COLORECTAL CANCER IN MAKASSAR, INDONESIA

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ABSTRACT Introduction: Phosphatidylinositol 3-Kinase (PI3KCA) were signal pathways that play essential roles in cell proliferation, resistance to apoptosis, angiogenesis, and metastasis in CRC. The effect of PI3K in the growth and development of tumor was mediated by Akt (Kinase serine-threonine) and was correlated with cell proliferation, apoptosis inhibition, and clinicopathological parameter difference. There is currently no data on PI3KCA to Colorectal Cancer clinicopathology in Makassar. **Methods:** This is an observational study with a cross-sectional design. As many as 55 samples fulfilled inclusion criteria and were subjected to immunohistochemistry examination using PIK3CA Monoclonal Antibody with semiquantitative analysis. Data were analyzed with the Chi-Square test and Fisher's exact test. **Results:** Analyzed between PI3KCA expression and Clinicopathology features was not one negative PI3KCA expression was found in the right colon. Meanwhile, 30.8% positive PI3KCA expression was found in right colon ($p = 0.009$). Similar results were found in the histopathological type. Not one negative PI3KCA expression was found in mucinous histopathological type, while 28.2% positive PI3KCA expression was found ($p = 0.014$). **Conclusion:** Frequency of PI3KCA mutation was 70.9% out of total samples of CRC patients in Makassar. PI3KCA expression was found to be significantly related to tumor location and histopathological type but insignificantly related to the clinical stage.

KEYWORDS PI3KCA, PI3K, Phosphatidylinositol, Clinicopathology, Colorectal Cancer

Background

Colorectal cancer (CRC) is one of the causes of mortality and morbidity in the world. This disease is the third most frequent malignancy in the world and the fourth cancer-related cause of death in the world with reported 1,400,000 new cases and 700,000 deaths in the world.[1]

Viewed from molecular biology aspect, CRC is unique cancer, i.e. it transforms an effect of accumulation of changes, both genetic and epigenetically where normal epithelial sequence

changes into adenocarcinoma. The progression of the stage occurs for years and can even reach decades. This progression can also be accompanied by several changes in characteristics or genetic type. [2]

PIK3CA mutation has been reported in several tumor types. Genetic mutation frequency in gastrointestinal carcinoma, however, is still controversial. Besides, there is little known regarding the frequency of PIK3CA mutation in the context of colorectal carcinoma with mismatch repair deficiency. It is known that 15% of sporadic gastrointestinal carcinoma have mismatch repair deficiency which causes hundred thousand of mutation in microsatellite level in all of the genomes (MSI phenotype), especially due to hMLH1 silencing through methylation promoter. [3]

Phosphatidylinositol 3-kinase/ Akt/ mammalian target of rapamycin (PI3K/Akt/mTOR) is a signal pathway that plays an important role in cellular proliferation, resistance to apoptosis, angiogenesis, and metastasis in colorectal cancer. Activation

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that deviates from the path of PI3K-Akt-mTOR produces tumor cell proliferation and survivability in various cancer in human. PIK3CA mutation has been reported as many as 10-20% in colorectal cancer. The variation in this frequency was observed in a large population-based study compared with a clinical study.[4]

The effect of PI3K in tumor growth and development is mediated by Akt (Kinase serine-threonine) which is a downstream effect of PI3K. It has been reported that Akt phosphorylation in colorectal cancer is correlated with cell proliferation and apoptosis inhibition, and clinicopathological parameter differences such as tumor invasion, vascular infiltration, lymph nodes metastasis and stages in CRC.[5]

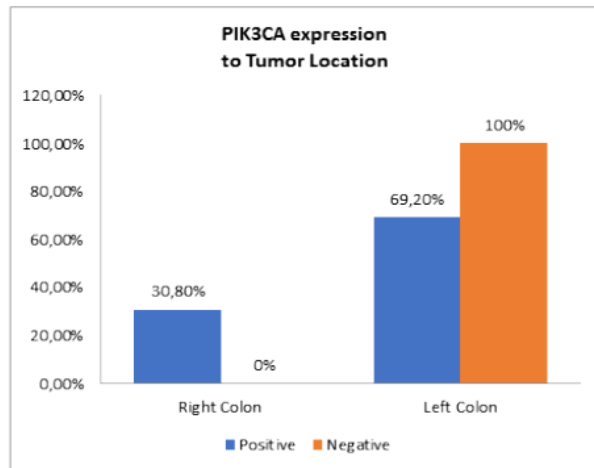
Interestingly, detailed analysis showed a gradual decrease of PIK3CA mutation anatomically from the proximal colon (caecum/ascending colon) to the distal colon (sigmoid and rectum). The difference in the microbiome, clinical characteristics, chromosome, and molecular characteristics has been the base of difference between right colorectal cancer and left colorectal cancer in the colorectal organ. As an example, the finding found that activation of PIK3CA and PTEN (Phosphatase and TENsin homolog) showed a low count in the rectum compared to the tumor on the right and left colon. [6] Even though there is an increase in knowledge regarding this disease, the choice of therapy for colorectal cancer patients in an advanced stage which had undergone metastasis is still limited with poor prognosis. Production of new therapy target, i.e. antibody formation to epidermal growth factor receptor (EGFR) has increased a new hope in curing advanced stage colorectal carcinoma. However, only one subgroup of a patient, especially those with KRAS wild type tumor, gained benefit from anti-EGFR therapy. Unfortunately, KRAS wild type is not enough to predict clinical response and mutation of other effectors from KRAS or pathways related to KRAS, which has been anticipated to be predictive for an anti-EGFR response. The candidate for that prediction is PIK3CA which not only predictive for target therapy by anti-EGFR antibody, but also might be a positive biomarker for the use of aspirin as neoadjuvant [4]. There is currently no data on PIK3CA frequency and clinicopathology on CRC in Makassar. This has motivated the author to conduct PIK3CA research in Makassar City.

Material and Method

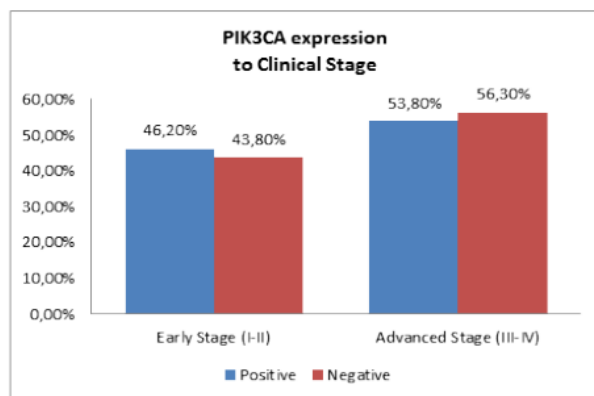
This is an observational study with a cross-sectional design. This study was conducted in Digestive Surgery Division of Dr. Wahidin Sudirohusodo General Hospital, Makassar. The study was conducted from June 2018 to October 2018. The research population consisted of CRC patients who were admitted to Dr. Wahidin Sudirohusodo Hospital, Makassar.

Samples were all accessible population who fulfilled study criteria. Samples were taken from tumor tissue of CRC patients that had been diagnosed as colorectal cancer (according to clinical and histopathological findings). Subjects that had fulfilled inclusion criteria underwent surgery, then histopathological and immunohistochemistry examination was performed on PI3KCA.

PIK3CA expression was assessed with immunohistochemistry examination using PIK3CA Monoclonal Antibody (H.843.0) (Thermo Fisher Scientific, Waltham, MA 02451. USA). Objective criteria in PIK3CA expression interpretation according to intensity were categorized into: Negative Expression (Negative: Not brown and Positive 1+ Smooth Brownish), Positive Expression (Positive 2++ Light Brown and Positive 3+++ Dark Brown). Data were analyzed using SPSS ver. 22 with statistical tests used were



Graph 1: PIK3CA expression to Tumor Location.



Graph 2: PIK3CA expression to Clinical Stage.

Spearman's correlation test. Results were significant if $p < 0.05$.

Results

Out of 55 samples, clinicopathological distribution was obtained as follows, age group below 60 years was almost comparable to those above 60 years (52.7% vs 47.3%), men were higher than women (63.65 vs 36.4%), left colon was higher than right colon (78.2% vs 21.8%), advanced stage was higher than early-stage (54.5% vs 45.5%), and mucinous type was higher than adenocarcinoma (20.0% vs 80.0%). Meanwhile, positive PIK3CA expression was higher than negative PIK3CA expression (70.9% vs 29.1%). (Table 1) After statistical analysis using Chi-Square in this distribution, the only gender showed a significant correlation ($p = 0.05$) to PIK3CA expression. There were more positive PIK3CA found in women than men (95.0% vs 57.1%). (Table 2)

Statistical analysis of PIK3CA was performed on tumor location, clinical stage, and histopathological type. Not one negative PIK3CA was found in the right colon, while positive PIK3CA in the right colon was 30.8% ($p = 0.009$). Similar results were found in histopathological type, not one negative PIK3CA expression was found in mucinous histopathological type, while positive PIK3CA expression was found 28.2% ($p = 0.014$). PIK3CA expression was significantly related to tumor location and histopathological type ($p < 0.05$), but it did not significantly relate to the

Table 1 Distribution of clinicopathology.

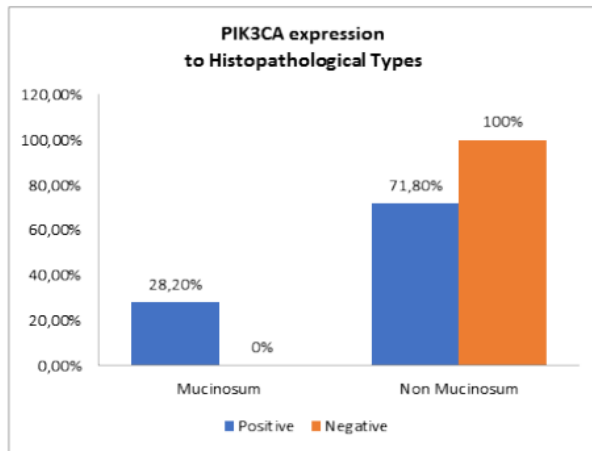
Variable	Frequency distribution		
	Category	n	%
Age (year)	20 – 60	29	52,7%
	>60	26	47,3%
Gender	Male	35	63,6%
	Female	20	36,4%
Differentiation degree	High	10	18,2%
	Moderate	39	70,9%
	Low	6	10,9%
Location of tumor	Right colon	12	21,8%
	Left colon/ Rectum	43	78,2%
Stadium	Early (I-II)	25	45,5%
	End (III-IV)	30	54,5%
Histopathology result	Mucinous	11	20,0%
	Non- mucinous	44	80,0%
PIK3CA expression	Negative	16	29,1%
	Positive	39	70,9%

Table 2 Analysis of PIK3CA Expression to Age and Gender.

Variable		PIK3CA Expression		P
		Negative n (%)	Positive n (%)	
Age (year)	<60	6 (20,7%)	23 (79,3%)	0,250*
	>60	10 (38,5%)	16 (61,5%)	
Gender	Male	15 (42,9%)	20 (57,1%)	0,008*
	Female	1 (5,0%)	19 (95,0%)	

Table 3 PIK3CA Expression To Tumour Location, Clinical Stage, And Histopathological Type

Variable		PIK3CA Expression		P
		Negative n (%)	Positive n (%)	
Location of tumor	Right Colon	0 (0,0%)	12 (30,8%)	0,009**
	Left Colon/ Rectum	16 (100,0%)	27 (69,2%)	
Clinical Stage	Early Stage (I-II)	7 (43,8%)	18(46,2%)	1,000*
	Advanced stage (III-IV)	9(56,3%)	21 (53,8%)	
Histopatologic types	Mucinous	0 (0,0%)	11 (28,2%)	0,014**
	Non-Mucinous	16 (100,0%)	28 (71,8%)	



Graph 3: PIK3CA expression to Histopathological Types.

clinical stage ($p > 0.05$). Graph 1 shows no negative PIK3CA expression in the right colon (0%) and positive PIK3CA expression as many as 12 people (30.8%). Whereas in the left colon negative PIK3CA expression was 16 people (100%), and the expression of PIK3CA was positive, 27 patients (69.2%). Graph 2 shows as many as seven patients (43.8%) in the early stage with negative PIK3CA expression, and as many as 18 patients (46.2%) with positive PIK3CA expression. Whereas in the advanced stage there were nine patients negative PIK3CA expression (56.3%) and 21 patients PIK3CA positive expression (53.8%). Graph 3 those with negative PIK3CA expression (0.0%) mucinous, and those with positive PIK3CA expression 28 patients (71.8%) including mucinous.

Discussion

Out of 55 samples, clinicopathological distribution was obtained as follows, age group below 60 years was almost comparable to those above 60 years (52.7% vs 47.3%), men were higher than women (63.65 vs 36.4%), left colon was higher than right colon (78.2% vs 21.8%), advanced stage was higher than early-stage (54.5% vs 45.5%), and mucinous type was higher than adenocarcinoma (20.0% vs 80.0%). Meanwhile, positive PIK3CA expression was higher than negative PIK3CA expression (70.9% vs 29.1%). In a study by Nosho et al., there was no correlation between PIK3CA mutation and age, gender and tumor location in CRC. Meanwhile, a study conducted on 174 CRC patients in Benvenuti stated that PIK3CA increased in women. This study analyzed deeper according to an exon. Therefore PIK3CA mutation was found to be correlated with exon 9, young age (0.03), and proximal tumor location (0.03).[7]

Interestingly, PIK3CA distribution in this CRC showed that out of 55 samples of CRC patients, 39 samples (70.9%) of positive PIK3CA expression and 16 samples (29.1%) of negative PIK3CA were found. This was not in agreement with previous studies regarding the frequency of PIK3CA in CRC. PIK3CA mutation frequency occurred in 10%-32% of colorectal cancer and correlated with poor clinical outcome in its patients.[7] Meanwhile, another study stated that PIK3CA mutation in colorectal cancer was found to be 10%-20%. Variation of this frequency was found in a large population study compared to clinical study [4].

Meanwhile, a study in Japan found PIK3CA mutation in 10-15% metastatic CRC patients (Akihito Kawazoe). Most of

the previously stated studies used PCR (Polymerase Chain Reaction) technique for their samples, while in this study we used immunohistochemistry technique. A study conducted by Samowitz WS titled PCR versus immunohistochemistry for microsatellite instability (2008) found that PCR examination was not superior compared to IHC in assessing mismatch repair samples in HNPCC.[8]

PIK3CA Expression was found to be significantly related to tumor location and histopathological type ($p < 0.05$); however, it was insignificantly related to the clinical stage ($p > 0.05$). This was following a study conducted by Rosty C who assessed PIK3CA activation in 757 colorectal cancer patients with PIK3CA characteristics of CRC as follows, PIK3CA was found in 105 tumors (14%), there were no differences in PIK3CA mutation between men and women ($p = 0.56$). There were no significant differences in age group in PIK3CA mutation and wild type. Tumors were mostly distributed in proximal colon (54% vs 34%, $p = 0.001$) and correlated with mucinous cancer (54% vs 32%, $p = 0.001$).[9]

Currently, many clinical studies strongly proved that the prognostic effect of metastatic colorectal cancer was correlated with the differences in the anatomical location of a tumor in colorectal. Detailed analysis showed a gradual decrease of PIK3CA mutation to the anatomical location from proximal (caecum/ascending colon) to distal (sigmoid and rectum). The correlation between primary tumor location to medication response effect is currently being investigated in many large clinical studies. Differences in the microbiome, clinical characteristics, chromosome, and molecular characteristics have been the basis of differences between right colorectal cancer and left colorectal cancer in the colorectal organ. As an example, activation of PIK3CA and PTEN showed a lower count in rectum compared to a tumor in the right and left colon.[6] This was by the results of our study.

Several studies had reported the differences between chromosome and molecules between right and left CRCs. Chromosome instability (CIN) was detected 75% in left CRC and 30% in the right CRC. Hypermethylation was more often found in the right CRC compared to left CRC. Right CRC had shown correlation with increased mutation of RAS gene and mutation in PIK3CA pathway. Meanwhile, left CRC most often showed a mutation in APC, KRAS, SMAD4 and TP53 genes.[6]

Meanwhile, the clinical stage of colorectal cancer correlation analysis in this study showed an insignificant correlation with PIK3CA expression. This was per the study conducted by Rafal Stecin Medical University of Bialystok in Poland in 2015 who wrote that frequency of PIK3CA gene mutation was more often found in advanced stage III and IV of CRC. However, there was a statistically insignificant correlation between these two variables.[10]

Conclusion

This study concludes that 70.9% of positive PIK3CA expression was found out of total samples of CRC patients. PIK3CA expression was found to be significantly related to tumor location and histopathological type ($p < 0.05$), but insignificantly related to the clinical stage ($p > 0.05$).

Conflict of Interest

There are no conflicts of interest to declare by any of the authors of this study.

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There were no financial support from any organization.

Ethics committee approval

I hereby declare that this article has full compliance with consent committee. The approval was taken before submission of the manuscript.

Patient informed consent

Not applicable.

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