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K-RAS mutation profile in colorectal carcinoma patients in Sanglah Hospital Denpasar, Bali-Indonesia

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ABSTRACT

Background: Today is an era of personalized medicine where treatment is tailored and personalized according to patient status. Assessment of K-ras mutation is one of the routine molecular examination in colorectal carcinoma, and the result will determine the treatment decision particularly, avoidance of using anti-EGFR in such patients. This study was a preliminary research to determine the profile of *K-RAS* mutation in colorectal carcinoma in Bali.

Methods: Formalin-fixed paraffin embedded tissue of 23 colorectal carcinoma patients in Sanglah Hospital which admitted in 2016 were collected from Anatomical Pathology Department and sent to Laboratory of Molecular Pathology of Dr. Cipto Mangunkusumo Hospital and Kalgen for *K-RAS* mutation examination. All of H-E slides were examined, and the specimen with well-preserved tumor cells were selected. The PCR was performed to determine K-RAS mutational status.

Result: From 23 samples, 70% was male, and 30% was female with a mean age 48.3 years. Fourteen cases (60.9%) had K-ras mutation (9 cases with codon 12 mutation, 4 cases with codon 13 mutation, 1 case with codon 59 mutation and 1 case with codon 117 mutation).

Conclusion: It is found that *K-RAS* mutation was quite common in colorectal carcinoma in Bali with two most common mutations observed in codon 12 and 13.

Keywords: K-RAS, mutation, colorectal cancer, Bali

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INTRODUCTION

Molecular research has been become an integral part of cancer research since decades ago including those conducted in the field of colorectal cancer. The translational research is of particular importance because it could alter the trend of cancer patient management. Both of them have been culminating in personalized patient treatment in which the management was tailored according to patient condition.[1]

Colorectal carcinoma (CRC) is the third most common cancer in Indonesia, after breast and cervical cancer.[1] This disease is an emerging public health problem because of its grave prognosis and the tendency of the patients to come at an advanced stage. Recent development in the treatment of colorectal cancer had changed the modalities choice for advanced colorectal cancer with the additional targeted therapy. It is usually is given in conjunction with surgery or chemotherapy.

However, several groups of cancer cell could be resistant or even gain a growth advantage when treated with targeted therapy. One of the most significant molecular determinants in colorectal cancer is K-RAS. *K-RAS* mutation is one of important molecular examination in colorectal carcinoma, and the result will direct the treatment decision to the patient as it will act as contraindication marker for anti-EGFR.[2,3,4] Thus, it is important to elucidate the prevalence of such mutation in the population with colorectal carcinoma since there is no epidemiological data of K-RAS mutation among colorectal cancer patients, especially in Bali.

METHOD

Formalin-fixed paraffin embedded tissue from 23 colorectal carcinoma patients in Sanglah General Hospital that was admitted in 2016 was collected from Anatomical Pathology Department and sent to Laboratory of Molecular Pathology Dr. Cipto Mangunkusumo Hospital and Kalgen for *K-RAS* mutation assessment. All of H-E slides were examined, and the specimens with well-preserved tumor cells were selected. The paraffin-fixed embedded tissues were sent to Kalgen for K-ras mutation testing. The DNA was isolated using Qiagen QIAamp^{R} DNA FFPE-kit, and the mutational status was determined using HRM PCR, Fragment Analysis, and Direct sequencing. The test has 100% specificity; mutant allele could be detected in at least 25% of tumor cells.

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Table 1 **The clinicopathological characteristics of patients and *K-RAS* mutation status (n=23)**

Patient Characteristics	*K-RAS* mutation positive n=14	*K-RAS* mutation negative n= 9
Age		
≤50 year	9 (64%)	7 (78%)
>50 year)	5 (36%)	2 (22%)
Sex		
Male	9 (64%)	7 (78%)
Female	5 (36%)	2 (22%)
Tumor location		
Colon ascendens	1 (7%)	1 (11%)
Colon transversum	1 (7%)	0 (0)
Colon descendens	2 (14%)	2 (22%)
Rectosigmoid	10 (72%)	6 (67%)
Histology type		
Adenocarcinoma, *NOS*	14 (100%)	8 (89%)
Others	0 (0)	1 (11%)
Histology grade		
Grade 1	5 (36%)	5 (56%)
Grade 2	8 (57%)	4 (44%)
Grade 3	1 (7%)	0 (0)

RESULT

A total 23 samples were selected for this study of which 70% was male, and 30% was female with a mean age 48.3 years (ranged from 31 to 70 year). Fourteen patients (60.9%) had *K-RAS* mutation with 9 cases with codon 12 mutation, 4 cases with codon 13 mutation, 1 case with codon 59 mutation and 1 case with codon 117 mutation. The clinicopathological features of the patients according to their *K-RAS* mutation status are shown in Table 1.

Most of the tumors were located in the rectosigmoid colon with the others located in descending, transverse and ascending colon. According to histological grades, 95.6% of samples were classified as Adenocarcinoma or NOS and just 1 sample classified as another type. From histological grade, most of the samples were classified as grade 1 and grade 2 with just one grade 3 tumor which was positive for K-RAS mutation.

DISCUSSION

Colorectal carcinoma is a heterogeneous disease. The concept of multistep process in carcinogenesis of CRC is necessary to improve our understanding of the biology of this tumor. It may arise through at least three main pathways namely sporadic CRC (classical pathway), Hereditary non-polyposis colorectal cancer (HNPCC) and colitis-associated cancer. Most of CRCs result from the sporadic path of CRC with chromosomal instability involving mutation of *APC*, *K-RAS*, and *P53* genes.[5] *K-RAS* is of particular importance both for prognosis and treatment of CRC, and it was found in about 35-45% of CRC cases.[2]

K-RAS gene is a proto-oncogene located on chromosome 12. This gene encodes Ras protein found in the inner portion of the cell membrane. Ras protein is a guanine-nucleotide-binding protein and acts as binary molecular switches that control intracellular signals. Ras protein is involved in the downstream signaling pathway of epidermal growth factor receptor (EGFR).[6] Development of monoclonal antibody against EGFR (cetuximab and panitumumab) and its application in the treatment of advanced CRC has significantly improved overall survival of patients with metastatic CRC. However, these drugs are only effective in patients with wild-type *K-RAS*.[2,3,4]

In our study, only 23 cases of CRC were sent for *K-RAS* mutation testing. From 23 cases, 70% was male, and 30% was female, with a mean age of 48.3 years old. Based on pathology data, the prevalence of CRC is more common in male patients. The most common location of the tumor was rectosigmoid. These findings are consistent with CRC data in Singapore.[7] Furthermore, the most common histological type was *adenocarcinoma, NOS,* and mostly low-grade tumors (grade1 and 2).

Fourteen cases (60.9%) had *K-RAS* mutation with 9 cases with codon 12 mutation, 4 cases with codon 13 mutation, 1 case with codon 59 mutation and 1 case with codon 117 mutation. A study from CRC patient in Jakarta showed the different result with only 16.3% *K-RAS* mutation found.[5] Another study by Phua *et al.* revealed that 33.3% of Singaporean CRC patients had K-RAS mutation.[7] Different results might be caused by different sampling procedure or data sources. In both studies as well as in our study, codon12 and 13 were the most common location of the mutation.[2]

K-RAS mutational testing is not a routine testing in advance CRC patient in Bali. Although there is a national health system in Indonesia that covered targeted therapy in advanced CRC patient, the importance of targeted therapy is still not fully understand by the clinicians nowadays. Another factor that contributes to such problem is limited facilities which inhibit the general performance of this testing in Indonesia. With increasing popularity and importance of personalized therapy in CRC patients, targeting therapy will gain a greater role in the near future. With it, mutational assessment of *K-RAS* will gain an even more important role as treatment determinant for CRC patient. Thus, according to aforementioned facts and our study, *K-RAS* mutation testing should be carried out in all metastatic CRC patient in order to give them the

best treatment. Furthermore, Indonesian national health system should accommodate this testing and its targeting therapy.

CONCLUSION

In conclusion, it was found that *K-RAS* mutational rate was quite common in CRC patients in Bali with most mutations located in codon 12 and 13.

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