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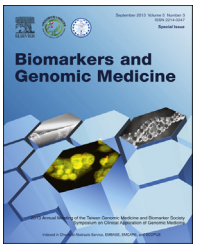

ABSTRACT

LINE-1 methylation correlates to early relapse in stage III CRC patients following radical resection and FOLFOX chemotherapy

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Background: Methylation levels of long interspersed nucleotide elements (LINE-1) are representative of genome-wide methylation status and play a crucial role in maintaining genomic stability and gene expression. Its prognostic impact on colorectal cancer (CRC) patients has not been well established. We aim to evaluate the association between LINE-1 methylation status and postoperative oncological outcome in stage III colorectal cancer patients.
Materials and Methods: Between Jan, 2008 and July, 2012, a total of 129 stage III CRC patients following radical resection and FOLFOX chemotherapy were enrolled for the present study. Global methylation was estimated by analyzing tumor LINE-1 methylation status using bisulfite-polymerase chain reaction (PCR) and pyrosequencing. Clinical information including demographics, clinicopathological data, and postoperative outcomes were recorded by trained abstractors. Outcome measurement included postoperative recurrence and cancer-specific mortality. Univariate and multivariate analysis were conducted for recognizing prognostic factors of oncological outcome.
Results: The tumor LINE-1 methylation level of 129 cases distributed normally and ranged from 37.4 to 77.9 of 0-100 scale (mean 63.3; median 63.7, standard deviation 7.1). In the univariate analysis, LINE-1 hypomethylation was more common in those who aged above and of 65 years and the patients with postoperative recurrence (both $p<0.05$). Prognostic impact of LINE-1 hypomethylation on cancer-specific survival was not observed ($p=0.164$). In the multivariate analysis, lower LINE-1

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methylation level demonstrated to be the independent risk factors of postoperative recurrence. With introducing a cutoff value of 70.15%, Kaplan-Meier analysis depicted the low methylation group had more recurrences with shorter disease free survival (Log rank test, $p=0.010$), and those with lower LINE-1 methylation level had a higher adjusted risk of postoperative recurrence (adjusted OR = 8.118, 95% CI =1.190-55.369).

Conclusion: Stage III CRC patients following radical resection and FOLFOX chemotherapy with LINE-1 hypomethylation status showed a significantly increased risk for more postoperative recurrence and shorter disease-free survival.