（書式１８）課程博士

学　位　論　文　要　約

博士論文題目　CpG island methylator phenotype is associated with EGFR related gene mutation and the efficacy of irinotecan- and oxaliplatin-based chemotherapy in Japanese patients with metastatic colorectal cancer.

（日本人進行大腸癌におけるＣｐＧアイランドメチル化表現型とＥＧＦＲ 関連遺伝子変異およびイリノテカン、オキサリプラチンを含む化学療法の効果との相関性）

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Background: Colorectal cancer (CRC) is one of the most common malignancies leading to significant morbidity and mortality worldwide. Colorectal cancer (CRC) is the third leading cause of cancer-related death, and accounts for more than 14,000 deaths each year in Japan. Colorectal tumorigenesis involves the accumulation of sequential genetic and epigenetic alterations. Epigenetics broadly dues to heritable alterations in gene expression that are not accompanied by changes in the DNA sequence. It is increasingly reported that epigenetic alterations including aberrant DNA methylation. In recent decades, the most extensively studied epigenetic alteration in colorectal cancer is aberrant DNA methylation, in the form of hypermethylation in promoter-associated CpG islands, which leads to transcriptional silencing or inactivation of DNA repair and tumor suppressor genes. The CpG island methylator phenotype (CIMP) with multiple promoter methylated loci has been widely observed in human colorectal cancer (CRC). CIMP status tightly associated with special clinicopathological and molecular characteristics has been referred to a potential epigenetic predictive marker or biomarker. However, the effect of standard chemotherapy and anti-epidermal growth factor receptor (EGFR) antibody therapy based on CIMP status is not fully known. **Methods**: In 125 metastatic colorectal cancer (mCRC) patients, I analyzed the relationship between clinical outcome of mCRC therapy, CIMP status detected by methylation-specific PCR (MSP), and genetic status in 5 EGFR related genes (*KRAS, BRAF, PIK3CA, NRAS,* and *AKT1*) detected by direct sequencing. **Results:** CIMP-positive status was significantly associated with proximal tumor location, lung and peritoneum metastasis (all P values < 0.05). The progression free survival of the sequential first- and

second-line therapy with irinotecan-based regimen followed by FOLFOX (median = 15.2 months) was superior to the reverse sequence (median = 6.6 months) in CIMP-positive tumors (*P* = 0.043). Furthermore, CIMP-positive tumors showed higher frequency of mutation in any of 5 EGFR related genes (74.0%) than CIMP-negative tumors (48.0%). Among *KRAS* wild-type tumors, CIMP-positive tumors showed worse clinical outcomes of mCRC patients in the anti-EGFR antibody therapy than CIMP-negative tumors. **Conclusion:** Sequential irinotecan-based regimen followed by FOLFOX was superior to reverse sequential treatment in CIMP-positive tumors. High frequency of mutations in EGFR related genes in CIMP-positive tumors cause the lower response for anti-EGFR antibody therapy in *KRAS* wild-type and CIMP-positive tumors.