Commentary

A new molecular classification of gastric cancer proposed by Asian Cancer Research Group (ACRG)

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The data released from World Health Organization (WHO) show that 989,600 new cases of gastric cancer per year occurred globally and more than half of the patients happened in East Asia. Among them, more than 400,000 cases per year of gastric cancer occurred in China, occupying about 40% of new cases in the world. Apparently, gastric cancer has become a big killer for Asian people. At present, a specific targeted therapy for gastric carcinoma is lack. Many patients still get homogeneous (one-size-fits-all) treatment, that is, surgical resection followed by conventional chemotherapy. In clinical practice, we usually encountered that the patients underwent same regimen, but their clinical outcomes are significantly different at same clinical TNM staging (tumor, node, metastasis). Some tumors are sensitive to regimen, but others do not have responses. The reason is related to tumor heterogeneity. Heterogeneity of gastric cancer can be reflected to their origin, such as cardia, body and antrum of the stomach. The heterogeneity of gastric cancer is also related to histological variances of stomach tumor, such as histological phenotypes of papillary carcinomas, tubular adenocarcinoma, signet-ring cell carcinoma, mucinous carcinomas, and so on.

Actually, early in 1965, a Nordic pathologist proposed a histological classification system (famous Lauren classification), which was based on observation of over 1,400 cases of gastric cancer. This classification divides gastric cancer into intestinal type, diffuse type and undetermined type. Lauren also noticed that intestinal type gastric cancer shown a better prognosis than other types of gastric cancer (1). Since the classification system appeared in half century ago, it is not detailed enough and lack of scientific basis of molecular biology. Therefore, the guidance value of classic classification for clinical practice is limited in precision medicine era.

On May, 2015, the Asian Cancer Research Group (ACRG) published a molecular classification of gastric cancer, which is based on a large sample size (300 cases) and integrated molecular data from gene expressing profile (251 cases), gene chip for copy number variation (251 cases), targeted gene sequencing (251 cases), as well as whole genome sequencing (49 cases) analysis. By the integration of the data analysis, ACRG proposed a molecular classification of four molecular subtypes for gastric cancer (2). In their report, all patients were collected from the Samsung Medical Center of Korea. The biospecimens were obtained after surgery resection. The tumor purity exceeded 60% for each case. All patients were followed up for a long-term (median 86.4 months). By principal component analysis (PCA) on gene expression data, they found that PC1 subtype was related to epithelial-to-mesenchymal transition (EMT) phenotype, and negatively related to cell proliferation signature. PC2 mainly reflected stomach tissue signature. PC3 related to phenotype of microsatellite instability (MSI), cytokine signaling, cell proliferation and methylation signals. Regarding to the remaining of non-EMT and non-MSI patients, they further divided them into microsatellite stability (MSS)/p53– and MSS/p53+ molecular subtypes. This step is based on detection of CDKN1A and MDM2, both of them are considered as representatives of p53 activation. If the detection of CDKN1A and MDM2 got a high score, the case is defined as intact p53-activity. If the detection of CDKN1A and MDM2 got a low score, the case is defined as functional loss of *p53* gene. More importantly, the new molecular subtypes was also validated by other separated cohorts from The Cancer Genome Atlas (TCGA) data set as well as Singapore

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data set (GSE15459), both of them were published before (3,4). The four molecular subtypes of MSS/EMT, MSI, MSS/p53+ and MSS/p53– were outlined on both TCGA and Singapore groups, with slight difference in proportion of four molecular subtypes. This reproducible result means that the newly proposed molecular classification has well creditability.

The new molecular classification of gastric cancer demonstrated a close clinical correlation. For example, the subtype of MSS/EMT showed younger onset. Among MSS/EMT subtype, over 80% cases were in clinical stage III/IV with diffuse type histology by Lauren classification. The subtype of MSI occurs mainly in antrum of the stomach. Over 60% of patients were intestinal type in Lauren classification. Many of patients were diagnosed at clinical I/II stage. In addition, MSS/p53+ molecular subtype was closely linked to Epstein-Barr virus (EBV) infection. By survival analysis, MSI subtype disclosed best prognosis. In this subtype, the recurrence rate was lower, and the recurrence often occurred in liver. Subsequently, the better prognosis was observed in subtype of MSS/p53+, followed by subtype of MSS/p53–. The subtype of MSS/EMT revealed the worst prognosis with a high recurrence rate. Importantly, the recurrence location of MSS/EMT subtype was mainly in peritoneal cavity. The correlation between molecular classification and prognosis was not only in Korea cohort, but also in dataset previously published by Singapore group and TCGA group.

Although the paper did not explore the relationship of new classification with the targeted therapy, they tell us some valuable hints. By targeted gene sequencing and copy number profiles, the MSI subtype revealed hypermutation with gene mutations of *KRAS*, *PI3K-PTEN-mTOR*, *ALK* and *ARID1A*. The MSS/EMT subtype had lower number of mutation events. The subtype of MSS/p53– showed higher *p53* mutation rate, as well as focal amplification of *ERBB2*, *EGFR*, *CCNE1*, *CCND1*, etc. The MSS/p53+ subtype showed a higher mutation rate of *APC*, *ARID1A*, *KRAS*, *PIK3CA* and *SMAD4*. These findings implied that the subtype of MSS/p53– maybe suitable for approved targeted therapy (trastuzumab, HER2-targeting agent) (5).

Regarding to the clinical operability, the authors proposed some simple methodologies such as immunohistochemistry or RNA-*in situ* hybridization as alternative. For instance, *MLH1* immunohistochemistry will help to define the MSI subtype. The immunohistochemistry of *VIM*, *ZEB1* or *CDH1* will help to define MSS/EMT subtype. The immunohistochemistry of *MDM2* and *CDKN1A* will help to define subtypes of MSS/p53+ and MSS/p53–. Anyway, this paper presents a novel molecular classification of gastric cancer, which is composed of four different subgroups. The new molecular classification is produced based on a large sample set, and shows a good repeatability. It provides us a good paradigm, especially for Chinese researchers to establish new molecular classification of gastric cancer in Chinese cohort. However, we noticed some regrets in this publication. At first, the molecular classification system is mainly based on gene expression profiles, and the data from whole genome sequencing or whole transcriptomic sequencing is not enough. Secondly, regarding to the recurrence of gastric cancer, the end-point of recurrence is not strict enough, because the biological significance of recurrence time is different (1-year recurrence, 2-year recurrence or 5-year recurrence post-operation) (6). Finally, the clinicians are expected to get more guidance of treatment for different molecular subtypes, but not only telling us subtype itself.

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Footnote

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