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Review

# Beyond precision surgery: Molecularly motivated precision care for gastric cancer

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**Abstract**

Gastric cancer is one of the leading causes of cancer-related deaths worldwide. Despite the high disease prevalence, gastric cancer research has not gained much attention. Recently, genome-scale technology has made it possible to explore the characteristics of gastric cancer at the molecular level. Accordingly, gastric cancer can be classified into molecular subtypes that convey more detailed information of tumor than histopathological characteristics, and these subtypes are associated with clinical outcomes. Furthermore, this molecular knowledge helps to identify new actionable targets and develop novel therapeutic strategies. To advance the concept of precision patient care in the clinic, patient-derived xenograft (PDX) models have recently been developed. PDX models not only represent histology and genomic features, but also predict responsiveness to investigational drugs in patient tumors. Molecularly curated PDX cohorts will be instrumental in hypothesis generation, biomarker discovery, and drug screening and testing in proof-of-concept preclinical trials for precision therapy. In the era of precision medicine, molecularly tailored therapeutic strategies should be individualized for cancer patients. To improve the overall clinical outcome, a multimodal approach is indispensable for advanced cancer patients. Careful, oncological principle-based surgery, combined with a molecularly guided multidisciplinary approach, will open new horizons in surgical oncology.


*Keywords:* Gastric cancer; Precision medicine; Patient-derived xenograft; Preclinical model; Biology; Classification

## Introduction

Gastric cancer has one of the highest global mortality rates of all cancers, accounting for 723 100 deaths annually.[1] In Korea and Japan, where mass screening system is available nationwide, the incidence of early gastric cancer (EGC) has increased.[2,3] The prognosis of EGC is excellent, with a 5-year survival rate of over 90%. The treatment of EGC widely involves less invasive surgery.[4] With the advent of sophisticated surgical devices and equipment, minimally invasive surgery, including laparoscopic and robotic surgery, and endoscopic resection (endoscopic mucosal resection and endoscopic submucosal dissection) have become the main treatment strategies for EGC.[4–10] This technical evolution has contributed to improvements in the quality of life of patients with early stage disease. However, advanced gastric cancer still accounts for a significant percentage of all global gastric cancer cases, and over 50% of patients with stage II–IV gastric cancer die from cancer recurrence, even after radical surgery with chemotherapy.[11–15] Therefore, understanding the tumor biology that underlies the clinical behavior of advanced gastric cancer is necessary to improve the prognosis of patients with advanced cancer.

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Cancer is a heterogeneous disease, which is the main reason for the various treatment outcome in clinical practice; thus, appropriate classification of disease and individualized treatment is essential. Two main classification systems have been used to classify gastric cancer based on its histo-morphologic features; these are the World Health Organization (WHO) classification (papillary, tubular, mucinous, and poorly cohesive),[16] and the Lauren classification (intestinal, diffuse, and mixed).[17] The modified WHO classification (differentiated and undifferentiated) is used to predict the risk of lymph node metastasis when deciding whether endoscopic resection is applicable.[6,7] However, the role of traditional morphology-based classification is ambiguous in advanced gastric cancer because it cannot guide clinical practice for determining prognosis or predicting treatment responsiveness.

Efforts to cure cancer have improved our knowledge of the disease, and now research is focused on understanding genomic alterations in cancer because cancer is a genetic disease. Recent new technological platforms have made it possible to explore the molecular landscape of gastric cancer, and some studies have suggested that gastric cancer can be classified into several subtypes according to its molecular characteristics.[18–20] Furthermore, new preclinical models which attempt to replicate *in situ* cancer, including 3 dimensional cell cultures and tumor organoid have replaced traditional cell line-based models; this could help identify true driver alterations in tumorigenesis and to determine the best treatment options. Consequently, such advances would enhance precision medicine in both cancer research and clinics.[21,22] This review will discuss the state-of-the-art research about the classification of gastric cancer based on its molecular characteristics. It will also describe a patient-derived xenograft (PDX) model, which is an emerging pre-clinical model in cancer research and drug development. We believe that this up-to-date information will provide insight into the direction of current and future clinical practice in the era of precision medicine for gastric cancer.

## Molecular classifications of gastric cancer

### *Intrinsic subtypes of gastric cancer*

Tan et al. identified two major intrinsic subgroups of gastric cancer in 37 gastric cancer cell lines based on a genomic expression signature; the result was validated in patients with gastric cancer.[20] Because the intrinsic subtypes were partially associated with Lauren's classification, they named the subtypes G-INT, which correlated with intestinal histology, and G-DIF, which was associated with diffuse histology. These subtypes had distinct gene expression patterns. G-INT cells had high expression of genes associated with carbohydrate and protein metabolism (*FUT2*) and cell adhesion (*LGALS4*, *CDH17*). G-DIF cells had elevated expression of genes related to high cell proliferation (*AURKB*) and fatty acid metabolism (*ELOVL5*). The most interesting outcomes of this study were that these intrinsic subtypes were related to the clinical outcomes. The intrinsic subtypes were prognostic factors; patients with a G-DIF tumor had poor prognosis compared with patients with G-INT gastric cancer, while Lauren's classification was not prognostic. Furthermore, the benefit from chemotherapy was distinctive between G-INT and G-DIF subtypes. In an *in vitro* study, G-INT cell lines were sensitive to 5-FU and oxaliplatin, while G-DIF cell lines were more sensitive to cisplatin than 5-FU and oxaliplatin. A similar trend was observed in a patient cohort study; adjuvant 5-FU chemotherapy was effective in G-INT tumors but not in G-DIF tumors. These results imply that genomic features can provide clinically actionable information, such as prognostic subgrouping and therapeutic regimen selection, for more precisely tailored patient care.

### *The Cancer Genome Atlas (TCGA)*

To understand how genomic alterations in cancer interact to drive tumorigenesis, the TCGA Research Network, a collaboration between the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI), analyzed the comprehensive molecular characteristics of 295 gastric cancer cases using 6 molecular platforms; whole exome sequencing, mRNA sequencing, miRNA sequencing, array-based somatic copy number analysis, array-based DNA methylation profiling and reverse phase protein array.[18] This integrative analysis identified 4 molecularly distinct subtypes of Epstein–Barr virus (EBV), microsatellite instability (MSI) type, chromosomal instability (CIN), and genomically stable (GS) type.

EBV-associated gastric cancer, which is characterized by the presence of the EBV genome (it indicates that this viral infection takes place during tumorigenesis) accounts for 9% of gastric adenocarcinoma cases. This type of gastric cancer exhibited a high prevalence of DNA hypermethylation (except *MLH1* hypermethylation, which is characteristic of MSI tumors), including in the CDKN2A ($p16^{INK4A}$) promoter region, and the result is silencing of the affected genes. *PIK3CA* mutations (non-silent type) in the phosphoinositide 3-kinase (PI3K)/Akt signaling pathway were frequently observed in EBV gastric cancer cases (80%) compared with other gastric cancer types (3–42%). It is therefore expected that PI3K inhibition could be an effective targeted therapy for EBV gastric cancer. Furthermore, 55% of EBV gastric cancer cases exhibited *ARID1A* mutations and 23% had *BCOR* mutations; however, *TP53* mutations were rarely observed. Interestingly, the amplification of *PD-L1/2* genes (15%), representative inhibitory immune checkpoints, and elevated expression of immune cell signaling pathways were distinctive characteristics of EBV gastric cancer. Therefore,

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