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Letter to Editor

Simplified molecular classification of gastric adenocarcinoma: Enhanced perspectives

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Dear Editor,

It is with great interest and appreciation that we read the recent article "Combined simplified molecular classification of gastric adenocarcinoma (GAC), enhanced by lymph Node status" by Daun et al[1] published in Cancers 2021, wherein they simplified the molecular classification of gastric adenocarcinoma with an integrative approach of lymph node status, IHC, ISH and NGS. The molecular classification of gastric adenocarcinoma by TCGS[2] and ACRG[3] is based on advanced molecular techniques, hence a simplified molecular classification based on the commercially available assays is perceptible. The authors emphasize the correlation of Lauren's and WHO classification to the new molecular classification with accentuation to the lymph node status yielding prognostic significance.

The authors have screened 115 GAC by IHC for p53, MutL Homolog 1 (MLH1) and E-cadherin, performed ISH for Epstein–Barr virus (EBV) and sequencing by NGS for TP53 and tumor associated genes. With this approach, they define five subtypes of GAC: (1) Microsatellite Instable (MSI), (2) EBV-associated, (3) Epithelial Mesenchymal Transition (EMT)-like, (4) p53 aberrant tumors surrogating for chromosomal instability and (5) p53 proficient tumors surrogating for genomics stable cancers. Furthermore, by considering lymph node metastasis in the p53 aberrant GAC, the authors segregated the GAC into poor (CIN ^{high}/p53-) and good-to-intermediate prognosis tumors (CIN ^{low}/p53-.

The authors observed a significantly better survival for the MSI subtype compared to both the EMT and the CIN^{high}/p53-subtypes. Finally, to receive a better discrimination with respect to prognosis, they grouped the EMT-like and CIN^{high}/p53- subtypes into a high risk, and the MSI, EBV and CIN^{low}/p53- into a low-risk prognostic subgroup with a median survival of 51.0 months and 167.8 months. Setia et al[4] and Pinto et al[5] proposed an even simpler classification based on immunohistochemistry and in-situ hybridization and subdivided GAC into 4 groups. Though NGS may yield a better picture on the mutational status, the feasibility of its use in regular practice in a developing country is debatable.

This study was done on resected primary gastric adenocarcinoma specimens. There is a significant population who are given neoadjuvant chemotherapy prior to the surgery and the expression of these markers on post-chemotherapy patients is to be further evaluated. Also, need to be considered is the study of these markers on endoscopic biopsies and metastatic sites, mainly in advanced gastric adenocarcinoma patients. In this study, 10.4% of patients have metastatic disease and the expression of these markers on metastatic sites may evoke a clinical significance.

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As we are progressing towards targeted therapy for more personalized and precise treatment, Her-2/neu, EGFR and PD-L1[5] expression in GAC are studied and targeted. Analysis of these markers and inclusion in the routine diagnostic testing would enhance the treatment perspectives.

However, the authors need to be congratulated for their exhaustive evaluation of the molecular markers in the most feasible method. NGS studies of these markers provide new insight into the various mutations expressed in GAC, notably p53 having missense, nonsense and frameshift mutation in variable proportion.

To conclude, the heterogeneity of immunophenotypic expression markers warrants further analysis as some markers are inconclusive. Further studies are required on the expression of these markers in post-chemotherapy patients and at metastatic sites with an emphasis on targeted therapy.

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