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# LETTER TO THE EDITOR
# MOLECULAR CLASSIFICATION OF GASTRIC CANCER

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***Dear Editor,***

Gastric cancer (GC) is the third cause of cancer-related death worldwide, with a different distribution, higher among Asians. GC is a multifactorial disease and 90% of cases are sporadic[1]. *Helicobacter pylori* is the most common etiological factor, shared with MALT Gastric Lymphoma[1,2]. Even if its incidence is declining, many efforts are focused on new target therapies[3]. In fact, the prognosis is often poor because GC is almost asymptomatic in the early stages, and the curability is related to the surgical treatment. The Cancer Genome Atlas (TCGA) has proposed a new classification in four subtypes, based on molecular categorization: EBV-positive, Microsatellite-instable (MSI), genomically stable, and chromosomally unstable[4–6].

EBV is estimated to be present in 9% of GCs, mainly located in fundus and corpus. Molecular alterations include the hypermetilation of the promoter CDKN2A, codifying for two proteins: p16 and p14, both of them are tumour suppressor[7]. Another mutation is alpha catalytic subunit of enzyme PIK3CA, present in 5-10% of the cases. PIK3 is involved in numerous cellular functions, including growth, proliferation, motility and differentiation[8]. Overexpression of JAK2 is observed in this subtype. This is a tyrosine kinase implied in signalling of numerous cytokine receptors. Through these receptors, STAT genes are activated and regulate genic transcription. Moreover, PD-1/2 and their ligands PD-L1/2 are often overexpressed in this molecular variant. These molecules are involved in an escape process of the cancer from the immune system, protecting the neoplastic cells from T-lymphocytes[9].

MSI are DNA repetitive sequences that can undergo to errors during the replication process. DNA errors are frequent in normal condition but are repaired by a group of proteins, mismatch repair proteins (MMRPs), responsible of recognize and correct DNA errors. This variant tends to accumulate many errors in the tumour genome. Four of these proteins, MLH1, PMS2, MSH2 and MSH6, are tested in case of Lynch syndrome suspect, but TCGA observed that MSI was present in about 21% of GCs[10]. The patients with this subtype have specific clinicopathological characteristics, like advanced age, female prevalence, intestinal subtype sec. Lauren, less incidence of lymph node metastasis, and a better prognosis[11].

Genomically stable GCs represent 19% of all GCs, according to TGCA. They have more often mutation of RHO-family GTPase activating proteins, like RAS, and the deregulation of adhesion and motility processes, like E-cadherin. They are histologically a diffuse-type aspect, and the prognosis is unfavourable[12].

Chromosomal instability GC subtype is the more conspicuous group, accounting about 45% of GCs[13]. There are many different chromosomal aberration, amplification of receptor of tyrosine kinase genes, MET, EGFR, HER2 and FGFR2, and have predominantly intestinal-type histology. Actually, genic amplifications are the principal target of new drug development. Among them, HER2 is the most studied. It is a tyrosine kinase receptor, encoded by the protooncogene ErbB2, located on chromosome 17q21, and is involved in cell growth and survivor[14]. Overexpression of HER2 receptor was identify prior in breast cancers, then also in GCs[15]. HER2 expression status is the only estab-

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lished predictive marker and is used to predict therapy response. It is tested by immunohistochemistry, and just in some cases, by FISH, but his prognostic role is still discussed, being associated to worst prognosis according to some authors[16].

The use of easier methods on tissues, such as immunohistochemistry and in situ hybridization for EBV and other clinical genes, could be used to apply molecular classification of gastric cancer for its significant prognostic stratification.

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