

Ethnicity-related differences in tumor immunity: a new possible explanation for gastric cancer prognostic variability?

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Gastric cancer (GC) is a very heterogeneous disease. Despite the decreasing incidence with time, it represents the second most common cause of cancer-related death after lung cancer; however, it is well known that incidence rates are very different throughout the world, with some geographic areas showing much higher rates than other regions (1,2). Subtypes of GC present different and sometimes opposite epidemiological trends, with reference to proximal *vs.* distal tumor locations, or intestinal *vs.* diffuse Lauren histological types (3).

Along with wide variations in epidemiological characteristics, survival probabilities of GC patients are also different between Countries or risk areas in the same country (4). In a report from the EURO CARE Working Group, the improvement in 5-year relative survival of GC during a decade was negligible (4.1% in males and 1.4% in females) (5). Notably, GC exhibited the largest variability in survival rates among European countries, much more than other neoplasms, as breast or colorectal cancer. A recent study from our group also demonstrated strong differences in long-term outcome in GC patients coming from high or low risk areas of Italy, and treated at the same center with a similar surgical approach (6).

The exact reasons of such prognostic variability are still unknown, because differences in tumor (location, histotype) and individual characteristics (age, gender) are not able to completely explain these disparities (7). In general, it seems that a correlation exists between incidence and survival rates. Indeed, the highest is the incidence, the highest seems to be the survival probability (7,8).

We could speculate, as possible explanation of this phenomenon, that different biological form of GC may be

linked to its epidemiology; more aggressive forms may have a uniform incidence throughout the world, whereas less aggressive forms may be more prevalent in high-risk areas. This could lead to better survival probability when the survivals of overall GC cases are analyzed in such areas (8).

Microsatellite instability (MSI) has been reported, in several studies, as an important favourable prognostic factor for GC; we recently confirmed its prognostic value in a large series (9). Furthermore, in our experience we observed a different proportion of MSI cases in patients coming from high-risk or low-risk areas of Italy, being MSI more common in regions with higher GC incidence (manuscript to be submitted). An alarming feature linked to this aspect is that the decreasing incidence of GC, above all in high-risk areas, may be due to the decreasing number of less aggressive forms. As a result, in the future we could observe less GC case, but with more aggressive tumor biology (3).

Two recent important studies which analyzed molecular biological characteristics of GC, the The Cancer Genome Atlas (TCGA) in America and Asian Cancer Research Group (ACRG) in Asian countries, may be helpful to provide possible explanations for these clinical heterogeneities (10,11).

The TCGA proposed molecular division of GC into four subgroups, based on genomic clustering combined to the molecular data: Epstein-Barr virus (EBV)-positive, microsatellite unstable tumors (MSI), genomically stable (GS) and chromosomally unstable (CIN) GC. The ACRG proposed a division into MSI, and three microsatellite stable subtypes: epithelial—to mesenchymal transition (MSS/EMT), p53 positive (MSS/TP53+), and p53 negative

(MSS/TP53-). In our opinion, the most important clinical characteristics of these molecular classifications, revealed to date, are the much better survival of MSI group, and the higher rate of peritoneal metastases in patients with MSS/EMT tumors.

If these molecular classifications may be able to explain heterogeneity in epidemiological features and prognosis of GC in different risk areas should be verified in future clinical studies, many of which are still ongoing.

Another feature linked to GC prognostic variability is patient's ethnicity. It is well known the survival difference between Eastern and Western patients (12-14). Several studies also reported better outcome in Asian Americans when compared with other ethnicities in the US (15,16). Even when adjusting for several tumor and patients' related factors, evaluated by means of validated prognostic scores, survival difference between Eastern and Western series still persisted (17); this may lead to suspect that other biological factors are responsible for these disparities (18).

Recent studies also reported that Asian-American patients have a worse prognosis if born in the USA, whereas those born in Asia exhibited better survival (19), thus suggesting that factors acquired in the youth may have affected the biological characteristics of GC (8).

Other reports from international phase III randomized trials, where the study populations and treatments are standardized across multiple countries, confirmed these differences. In the AVAGAST trial, subgroup analysis revealed a survival benefit in non-Asians but not in Asians. Conversely, in the LOGiC trial, benefit from lapatinib was observed in Asians but not in non-Asians.

In the paper by Lin *et al.*, entitled "Signatures of tumour immunity distinguish Asian and non-Asian gastric adenocarcinomas", considered in the present commentary, gene expression differences between Asian and non-Asian GC, and their potential impact on clinical outcome, were analyzed (20).

The methods adopted in this study are particularly relevant and innovative. First, nine independent GC microarray cohorts comprising 1,016 tumour gene expression profiles—six from Asian localities, and three from non-Asian localities, were assembled. The comparative analysis of patients' characteristics showed no significant differences in most clinical-pathological variables, with the exception of the higher rate of upper third tumors in non-Asian patients, which corresponds to reported data in literature. Importantly, it was confirmed that Asian patients exhibited a better prognosis with respect to non-Asian patients.

A very interesting methodological tool was the adoption of a novel algorithm, RUV-4, to reduce study-specific effects in gene expression data. This method reduced the impact of unwanted variation between and within cohorts, but preserving locality-specific variation, thus allowing the comparison between the characteristics of different cohorts.

The main result of the present study is the observation that tumor immunity signatures differ significantly between Asian and non-Asian GC. Non-Asian GC were associated with multiple signaling pathways related to T-cell biology. To validate the immune-related gene expression differences between Asian and non-Asian GC, an immunohistochemistry analysis on two independent tissue microarray cohorts was also performed. Results confirmed that the two patients' categories have distinct immune-related components, especially a higher abundance of T-cell infiltration in non-Asian GC. Further statistical adjustments suggested that these tumor immunity differences may contribute to the geographical differences in clinical outcome observed in study cohorts. Although *H. pylori* status information was unavailable for the entire series, precluding a correlative analysis between the immune differences and *H. pylori* exposure, these results are absolutely innovative in GC translational research.

The role of immunological system in GC is still far to be completely explored, and this important paper may provide a crucial step in this field. We are also convinced that immunological status is able to affect the prognosis of GC patients, and when related to patient's ethnicity this could lead to clarify still unexplained clinical features.

We have to also to note that overall survival was the end-point considered in this study. Cancer-related survival may be also interesting to be evaluated, in consideration of the potential impact of postoperative complications and comorbidities on the prognosis of GC patients. Indeed, in this study the divergence in survival curve between Asians and non-Asians cohorts was particularly evident in the first year after surgery, and afterwards the two survival curves appear to run in a parallel way. Potential differences in the pattern of relapse may be also interesting, in order to analyze the impact of immune-related features on hematogenous, local or peritoneal recurrence, in light of possible future therapeutic applications. The observations that chemotherapy outcomes and immune effects may be interdependent, and the emerging role of immunotherapy in GC, are particularly relevant from a therapeutic point of view.

In conclusion, the results of the present study by Lin *et al.* may have important clinical and scientific implications,

in a flourishing scientific context of biological and molecular characterization of GC, which is expected to shed more lights on this still enigmatic disease.

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Footnote

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