Node-negative gastric cancer: a good occasion for studying new prognostic factors

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Dr. Liu and Colleagues (1) present an interesting study that adds data to those already available in the literature from both Western (2-4) and Eastern series (5-7). The sense of all these papers, analyzing prognostic factors significantly related with survival in patients correctly staged as N0 (more than 15 lymph nodes removed at surgery), is that of trying to understand in depth if staging whether or grading is more important in determining the fate of patients with gastric cancer. In fact, analyzing the N0 patients may reveal that these patients have simply been treated at an earlier stage of their disease, and this would lead to stress once more the importance of screening practices, or on the contrary, the same analysis could reveal as other parameters that are actually kept in minor consideration (what might be called grading), significantly influence the biological behavior of the disease, which would lead to the need for better molecular characterization of a single tumor in a single patient.

The majority of studies investigating the clinicopathologic features and prognostic indicators of node-negative gastric carcinoma patients come from Eastern centers. Limits of many published studies are the presence of different surgical approaches, namely in terms of lymph node dissection, a follow-up too short for cancers whose recurrence if often late, the inclusion of cancers at very low risk of recurrence, such as T1 cancers, and finally the inclusion of patients that may be understaged as node-negative, as less than 15 nodes were retrieved and analyzed after surgery. The paper by Liu and Colleagues examined a remarkable series (4,426 patients in 12 years, i.e. almost 400 patients per year), in which, however, it appears unusual that the number of N0 cases is relatively low: in fact, the series focuses on only 234 patients (5.3%), a percentage much lower than reported in the literature, where N0 patients represent over 30% of all cases. This discrepancy is not clearly explained. All patients were correctly staged with more than 15 harvested lymph nodes, and the average number of examined nodes is 21.1, slightly lower than the limit considered optimal for a D2 lymphadenectomy, which is 25 lymph nodes. Another fact which deserves to be commented is a distribution of the degree of differentiation clearly biased in favor of medium and poor differentiation (G2+G3>95% of cases, while in most N0 studies it is around 50%). In addition, about 30% of cases of T1 cancers (Early Gastric Cancer), which should be excluded because at almost no risk of recurrence, are included. On the other hand, the pathological study appears accurate, and the oncological follow-up is intensive and long-term (51 months on average): we can therefore expect that this study provides reliable data for analysis.

Overall, 33 out of 234 N0 patients had a recurrence, representing a small treasure for pathologic analysis, looking for biological parameters that indicate a potential for an increased biological aggressiveness regardless of staging. However, in this paper a thorough analysis of biomolecular features is not performed: all the parameters taken into consideration belong to histology rather than to molecular biology, and they are easily detectable in the context of a basic pathologic assessment. This could be an advantage, as they provide useful elements for prognosis that are available in daily clinical practice.

The results seem to indicate that, between grading and staging, the latter is the most important factor: in fact,

out of 3 factors significantly related with prognosis in multivariate analysis, none is clearly correlated with the degree of cell differentiation or biological parameters, while all 3 show that patients who have relapsed would not have remained yet N0 for long term, since they had neoplastic emboli in peritumoral vessels and lymphatics, meaning that the process of metastasis had likely already started. It would be interesting to know the type of recurrence of these 33 patients having worse prognosis, but this data is not provided by the study.

Future lines of research should take into account both our ability to investigate the stage of the disease in greater depth (probably through research of micro-metastases in the lymph nodes apparently negative at hematoxylin-eosin staining (8-9), and the research for biological parameters able to explain a greater aggressiveness of tumors apparently low-stage (for example, a study is in progress under the Italian Research Group for Gastric Cancer auspices, evaluating HER 2 overexpression, chemochines receptor expression, TP53, KRAS, CTNNB1, APC and PI3CA).

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