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Clinical Impact of Neoplastic Heterogeneity in Gastric Cancer

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Introduction

The intratumoral heterogeneity in HER2 expression has been already reported in breast cancer (BC) [1,2]. However, also the HER2 staining in gastric cancer (GC) is greatly influenced by the neoplastic heterogeneity, requiring a concordance between endoscopic gastric biopsies and full tissue sections to correctly assess HER2 status before neoadjuvant treatment in GC [3,4]. In particular, a crucial point to verify HER2 status heterogeneity is if endoscopic biopsies may be considered adequate for HER2 assessment [5]. Up to date, no codified official guidelines are available on the number of biopsies to be tested for HER2 testing, although not concordant data are obtained from a different number of tissue bioptic fragments. In detail, four or five biopsy samples of cancer have been regarded as the gold standard number [6,7], although the National Comprehensive Cancer Network recommended more than 6 samples to be taken [8]. On this way, variable concordance rates between biopsy and paired surgical resections have been reported ranging from 45.5% to 94% and inquiring the reliability of HER2 status on biopsy specimens [5]. Furthermore, a high risk of false negative HER2 status in biopsies or tissue microarray assays (TMA) has been strongly stressed [5-7]. Therefore, we and others suggested that additional investigations on this topic should be realized in order to determine the best possible number of gastric biopsies to correctly assess HER2 status in advanced carcinomas [9,10].

Another intriguing point regarding the clinical impact in GC is represented by the potential discrepancy in the HER2 status between gastric primitive cancer and its corresponding metastases or among different kinds of metastasis either distant lymphatic or distant by the same tumour; in fact, all these aspects may have a clinical importance in order to modify the patient's eligibility to targeted therapies [4,11,12]. In this field, our personal experience confirmed the presence of a high level of concordance in HER2 status between the primary GC and their corresponding lymph node metastases, while only the 9.68% GC cases documented a HER2 discordant status between the primary and secondary tumors [11]. Generally, four cases had HER2 amplifications in the primary GC but there were no HER2 amplifications in the metastatic tumors. By contrast, two of the gastric discordant cases exhibited no HER2 amplifications in the primitive tumor but lymph node metastases were amplified. Therefore, together with other some investigators we have suggested that detection of HER2 status should be re-evaluated either in the metastatic tissues to establish whether the therapy is really suitable [11,12].

Finally, in order to establish if changes in HER2 status may be referred to technical reproducibility or to other pre-analytical variables, such as not standardized inadequate fixation or to biological modifications in tumors, we have already performed a study on HER2 status on paired GC samples as well as synchronous metastatic lymph nodes, collected at the same surgery procedure, submitting them to the same pre-analytical conditions [11]. Indeed, at present patients with advanced GC are candidates for therapy with Trastuzumab on the basis of HER2 positivity in the GC only, while our findings recommend that HER2 status should be assessed, not only in metachronous neoplastic lesions, but mainly in synchronous metastatic lymph nodes before treatment decision. As a matter of fact, testing HER2 treatment a percentage of patients with a negative primary tumour but positive lymph node metastases. Hence, we may hypothesize that HER2 discordance may be attributed to the biological tendency of the tumour leading to the selection of a new neoplastic cellular sub-clone in metastatic synchronous lymph nodes as a result of disease progression (HER2 positive conversion).

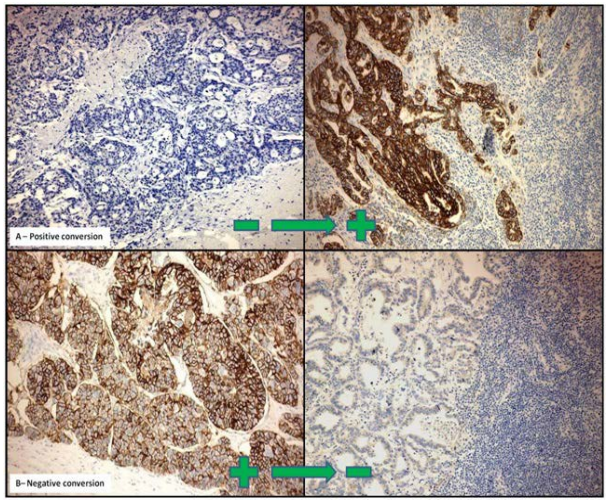

Figure 1: HER2 immunohistochemical negative staining in primary GC (a, ×200), demonstrated a positive reactivity in the metastatic synchronous lymph node (positive conversion) (a, ×200) (IHC, Mayer's hematoxylin counterstain). A score of 3+ HER2 expression was encountered in neoplastic elements in a primary GC (b, ×200) but vanished in the corresponding metastatic lymph node (negative conversion) (b, ×200) (IHC, Mayer's hematoxylin counterstain).
HER2: Human epidermal growth factor receptor 2; GC: Gastric carcinomas; IHC: Immunohistochemistry

Competing Interests

The authors declare that they have no competing interests.

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