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LETTER TO THE EDITOR

Discordance Rate of HER2 Status in Primary Gastric Cancer and Synchronous Lymph Node Metastases: Its Impact on Therapeutic Decision and Clinical Management

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Dear Editor,

We have read with great interest the article of Amato et al., "HER2 Status in Gastric Cancer: Comparison between Primary and Distant Metastatic Disease", which appeared in Pathol. Oncol. Res. [1]. In this paper, the Authors have evaluated the HER2 status, by IHC and/or FISH, 41 patients with primary gastric cancer (GC) and paired metastasis. HER2 positivity was encountered in 14.6% primary tumours and 24.4% corresponding metastasis with a concordance rate of 80.5%. Eight out forty-one cases appeared discordant: 6 patients with metastatic HER2 positive lesions were found HER2 negative in primary cancers, while two patients HER2 positive in primary lesions exhibited a negative conversion in metastasis [1]. In detail, in 1/8 metastatic metachronous lesion, a discordant HER2 status (negative conversion) was found; moreover, 7/33 synchronous metastasis showed a discordant HER2 status (6 positive and 1 negative conversion). The Authors suggested the higher rate of HER2 positive status found in metastatic lesions underlined the importance of HER2 assessment in all samples obtained from different sites of GC [1].

Intratumoral heterogeneity HER2 status in different areas of the primary neoplastic lesions has been considered a more common event in GC than in breast cancer (BC) [2]. Different concordance rates between biopsy and paired surgical resections have been reported ranging from 45.5% to 94% and questioning the reliability of HER2 status on biopsy (GC) specimens [3]. Moreover, Amato et al. [1] showed a high concordance rate between biopsy and surgical GC samples in term of HER2 status (85.7%), in line with previous data [3]. However, conflicting reports have suggested a different number of tissue fragments for adequate assessment in biopsies, such as four or five biopsy samples as the optimal number in GC [4, 5], even though the National Comprehensive Cancer Network guidelines recommended more than 6 samples to be taken [2]. We contend that additional investigations should be performed in order to clarify the optimal number of gastric biopsies to correctly assess HER2 status in advanced carcinomas, as elsewhere suggested [6].

It is well known that a considerable controversy concerns the issue of HER2 status between primary BC as well as GC and paired metastatic sites or recurrences from the same patient [7–11]. Amato et al. [1] demonstrated a higher rate of HER2 positive status in distant metastatic disease rather than in the related primary cancer due to a positive HER2 conversion. However, we have previously reported that HER2 status differed between primary GC and its nodal metastases in 9.26% of cases, in 10 out of the 108 analyzed GC [10]; in detail, a negative conversion was observed in 6 cases, which were HER2 amplified in the primitive carcinomas and negative in the metastases, while a positive conversion was found in 4 cases, which were HER2 negative in the GC and changed to positive in the lymph node metastases [10]. In our opinion, changes in HER2 status between primary GC and synchronous lymph node metastases may have relevant clinical impact. 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 - similarly to that reported by Amato et al. [1] - suggest that HER2 status should be re-assessed, not only in metachronous metastases, but also

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in synchronous nodal metastases before treatment decision. Consequently, testing HER2 expression only in primary GC may reduce the opportunity to be eligible for a targeted therapy in a percentage of patients with a negative primary tumour, but positive lymph node metastases. Hence, we agree with Amato et al., [1] regarding the need to define HER2 status in both primary and metastatic GC lesions in order to perform the best choice in the clinical management of advanced GC.

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