Virchows Archiv (2019) 474:401–402
https://doi.org/10.1007/s00428-018-2502-2

LETTER TO THE EDITOR

Intratumoral HER2 heterogeneity in early gastric carcinomas: potential bias in therapeutic management

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Received: 14 November 2018 / Accepted: 28 November 2018 / Published online: 30 November 2018

Dear Editor,

We read with great interest the paper "Association of HER2 gene amplification and tumor progression in early gastric cancer" by Kanayama et al., which was published in your journal [1]. The authors evaluated HER2 status in 149 lesions from patients with early gastric cancer (EGC); the gene amplification was detected in 23.5% of cases, and 2/3 of these showed intratumoral heterogeneity [1]. We fully agree with suggestions present in the paper concerning the similar HER2 expression in EGC and advanced gastric carcinomas (AGC). However, no significant association between HER2 amplification and muscularis mucosae or submucosal invasion has been found. In addition, a correlation with tumor size ($P = 0.0533$) and Lauren's classification ($P = 0.0821$) has been reported [1]. Nevertheless, no information about involvement of lymph nodes was available due to endoscopic resections performed without surgical procedures.

It has been reported that the HER2 gene is significantly correlated with disease recurrence and poor prognosis in patients affected by EGC [2]. Moreover, patients with HER2-negative pN0 EGC have significantly higher 5-year overall survival (91.1%) compared to patients with HER2-positive pN0 EGC (81.8%) [2]. In addition, HER2 immunoexpression appears to be significantly associated with development of micrometastases in pN0 EGC, as elsewhere reported [2].

Although most studies have documented a highly homogenous HER2 amplification in gastric cancer, the occurrence of tumor heterogeneity ranged from 5 to 69% [3]. Furthermore, HER2 heterogeneity decreased in AGC, while HER2 homogeneity in early gastric cancer has been related to the risk of tumor progression [1]. Interestingly, the rate of tumor heterogeneity (74.3%) revealed by Kanayama et al. represents one of the highest values reported in EGC [1].

Until now, the mechanisms leading to HER2 expression heterogeneity have been largely unknown in EGC. A possibility includes neoplastic clonal selection with HER2 amplification in an otherwise HER2 negative tumor or, alternatively, the appearance of HER2 silenced tumor areas in EGC cases with homogeneous HER2 amplification.

Intratumoral HER2 heterogeneity in different areas of the primary neoplastic lesion has been considered a more common event in GC than in breast cancer (BC) [4]; specifically, gastric cancer heterogeneity in HER2 status has been described in discordance between primary and metastatic sites, either with positive or negative conversion [5]. In our opinion, changes in HER2 status between primary EGC and possible synchronous lymph node metastases may have relevant clinical impact. In the light of these considerations, a critical bias in the study of Kanayama et al. is represented by the unavailability of data concerning regional lymph node involvement and HER2 status. In fact, testing HER2 expression only in primary EGC may reduce the opportunity to be eligible for a targeted therapy in a percentage of patients with a negative primary tumor, but positive lymph node metastases; however, this loss of possibility is greatly increased by the high rate of heterogeneity reported in EGC. Therefore, additional larger casuistries comprehending HER2 node status, as well as outcomes of patients, are needed in order to identify subpopulations of EGC with different risks of cancer progression.

Authors' contributions A.I. and G.T.: designed the study and edited the manuscript.
R.C. and M.L.: reviewed the manuscript.
All authors gave final approval for publication.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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