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LETTER TO THE EDITOR

# Letter to the editor: reply to Antonio Ieni "Intratumoral HER2 heterogeneity in early gastric carcinomas: potential bias in therapeutical management"

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Dear Editor,

We read the letter by Ieni et al. commenting on our study published in Virchows Archiv, as well as the articles by Ieni et al. [1, 2] and Yan et al. [5].

The objective of our study was to evaluate the HER2 amplification status/onset in primary early gastric cancer (EGC), but not particularly with lymph node metastasis. In our previous studies, HER2 status was consistent between primary tumor and lymph node metastases in gastric cancer (GC) [4]. Because the frequencies of HER2 heterogeneity in categories 5.1 and 5.2 were higher than those of HER2 homogeneity, we speculate that HER2 heterogeneity is formed by subpopulations with HER2 gene amplification appearing at an early stage in GC and may progress while still maintaining HER2 heterogeneity [3]. According to an analysis of a nationwide GC registry, 12,647 EGC patients were treated with endoscopic mucosal dissection or resection (ESD), and the 5-year disease specific survival (DSS) rates were 99.9%, 99.7%, and 98.7% in patients with absolute indication of curative resection (CR), patients with expanded indications of CR, and non-CR patients, respectively [7]. In another study, the 5-year DSS of CR in 1537 EGC patients who underwent ESD was 99.9% [8]. More importantly, the 5-year relative survival rate of the same group in their study was nearly 100%, demonstrating that treatment is comparable to the risk in the general population [8].

In Ieni et al.'s letter, they stated, "HER2 immunoexpression appears to be significantly associated with development of micrometastases in pN0 EGC, as elsewhere reported," while citing Yan et al. [5]. It is true that Yan et al. discussed micrometastases in pN0 EGC, but the referenced study [6] in Yan's paper has nothing to do with HER2 immunoexpression. Yan et al. apparently made an inaccurate citation and presented incorrect information. Moreover, Yan et al.'s paper contains a serious flaw in their results. They observed that poorly differentiated adenocarcinoma expresses HER2 more than moderate/well-differentiated adenocarcinoma does and that the same was true for Lauren's histological types. Their data is inconsistent with the consensus observation over the years: over-expressed HER2 was detected predominantly in intestinal type adenocarcinoma. This casts considerable doubt on the methodology and results found in the Yan et al. study. Because their poorly differentiated adenocarcinoma was HER2 positive, they found that the 5-year survival was lower than that for HER2-negative cases.

The clinical impact of lymph node micrometastasis (LNM) on GC prognosis remains controversial. A meta-analysis focusing on GC patients revealed that, regardless of LNM status, no significant difference was found in the number of patients who died in 5 years in EGC cohort studies [9].

Anti-HER2 drug administration is not the first-line therapy in GC treatment guidelines in Japan [10]. We suggest that Ieni et al. either reconsider their scientific strategy toward GC therapy or present evidence of a randomized controlled trial investigating the effects of anti-HER2 therapies on EGC with HER2-positive lymph node GC metastasis cells. Without such evidence, changing the standard therapy would be inappropriate.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflicts of interest.

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