Comment on: “Long-term persistence of gastric dysbiosis after eradication of *Helicobacter pylori* in patients who underwent endoscopic submucosal dissection for early gastric cancer. Gastric Cancer, 2020 Nov 17” by Watanabe et al.

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Received: 20 December 2020 / Accepted: 21 December 2020 / Published online: 7 January 2021
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Dear Editor,

A recent Japanese study analyzed the alterations of gastric microbiota before and after *Helicobacter pylori* (*H. pylori*) eradication in patients with early gastric cancer (GC) who underwent endoscopic submucosal dissection (ESD) [1]. Watanabe et al. found that *H. pylori* eradication partially restored microbial composition but not to the extent of normal status, which indicates the persistent dysbiosis long after the eradication of *H. pylori*. However, several questions need to be addressed.

First, this study enrolled *H. pylori*-infected patients with GC who underwent ESD. However, the authors did not illustrate the sampling details, including the timing of sampling such as before or after ESD, and the sampling site such as tumor or adjacent normal tissues, which may influence the results of gastric microbial analysis. A previous study showed that the structure of gastric microbiota was significantly changed after subtotal gastrectomy in patients with GC, probably due to the alterations of the gastric environment such as reduced secretion of gastric acid and bile reflux after surgery [2]. Besides, the micro-ecological systems of tumoral and peritumoral tissues have been reported to differ in composition and function [3, 4]. Thus, we think that the comparisons between different groups will be much credible if the samples collected at baseline were consistent.

Mounting studies demonstrated that the infection of *H. pylori* shifted the overall structure of gastric microbiota with higher *H. pylori* abundance and lower microbial diversity

[5]. Additionally, the composition of gastric microbiota is affected by disease stage. Differences in microbial profiles were identified among superficial gastritis, atrophic gastritis, intestinal metaplasia and GC [6]. The authors investigated the effects of *H. pylori* infection on gastric microbiota by comparing *H. pylori*-positive patients with negative patients. Notably, the pre-eradication patients were all diagnosed with GC while the negative group had none or mild gastric pathology. Based on the discrepant disease stage between *H. pylori*-positive and negative groups, it might be difficult to distinguish whether the microbial disturbance in pre-eradication group was attributed to *H. pylori* infection or gastric pathology. Thus, the comparison of gastric microbiota between *H. pylori*-positive and negative patients within the same histological stage would be much representative for evaluating the role of *H. pylori*.

This study innovatively explored the eradication of *H. pylori* on gastric microbiota in patients underwent ESD for GC. Unexpectedly, the authors reported that the gastric dysbiosis persists long after *H. pylori* eradication, which seems to weaken the beneficial effect of *H. pylori* eradication in GC patients to some extent. Conversely, a study in high-risk area of GC showed that successful *H. pylori* eradication restores gastric microbiota to a similar status as found in uninfected individuals [7]. We speculate that microbial dysbiosis observed in this study might due to the progressive gastric pathology, which could not be reversed soon after *H. pylori* eradication.

In conclusion, this study firstly unveiled the alterations of gastric microbiota in *H. pylori*-infected patients with GC after ESD. Further larger, prospective cohort studies would help to identify the role of gastric dysbiosis in the development of metachronous GC after *H. pylori* eradication.

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