How long should patients be surveyed for gastric cancer risk after *Helicobacter pylori* eradication therapy? 10 years is no longer enough

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Helicobacter pylori infection is a major risk factor for the development of gastric cancer, particularly in East Asian populations, including Japan. Gastric cancer is caused by a multifactorial and multistep process mainly related to long-term infection with *H. pylori* in the gastric mucosa. Nevertheless, eradication treatment for *H. pylori* infection has also been shown to reduce the risk of gastric cancer in patients with atrophic gastritis, and recent meta-analyses confirmed the same effect in patients after endoscopic and operative resection for gastric cancer [1–3]. The Maastricht V/Florence Consensus Report issued by the European *Helicobacter* Study Group in 2017 recommended the eradication of *H. pylori* as first-line treatment in patients with peptic ulcer disease, autoimmune thrombocytopenia, chronic urticaria, iron deficiency anemia, gastric mucosa associated-lymphoid tissue lymphoma, and functional dyspepsia as a means of preventing gastric cancer [4]. For the first time anywhere, the Japanese health insurance system initiated coverage of *H. pylori* eradication treatment in all patients with endoscopically confirmed *H. pylori*-associated gastritis in 2012. Against annual gastric cancer death rates of around 50,000 extending back more than 40 years, this expansion of coverage led to a significant

decrease in deaths, from 48,427 in 2013 to 45,509 in 2016 [5]. National gastric cancer screening programs with upper endoscopy may have contributed to this decrease by decreasing the risk of diagnosis at an advanced stage, and by *H. pylori* eradication therapy after endoscopic diagnosis of *H. pylori* infection [6]. To date, however, most studies investigating the incidence of gastric cancer after eradication therapy have done so over the relatively short period of about 10 years, and it has remained unclear whether the chemopreventive effect of eradication therapy extends beyond 10 years, in consideration of pathological differentiation and the severity of gastric mucosal atrophy.

In this issue of *Journal of Gastroenterology* [7], Take et al. report a single-center retrospective cohort study of 2737 patients who received endoscopic follow-up survey after *H. pylori* eradication therapy for as long as 21.4 years (mean 7.1 years). Gastric cancer developed in 68 patients (0.35% per year). Incidence was associated with the severity of gastric mucosal atrophy at baseline, developing in 0.15% per year with mild atrophy (Kimura–Takemoto classification: C-1 and C-2), 0.29% per year with moderate atrophy (C-3 and O-1) and 0.67% per year in patients with severe atrophy (O-2 and O-3) [8]. In their follow-up survey over > 20 years after eradication therapy, the authors surprisingly showed that the risk of developing diffuse-type gastric cancer was greater in the second decade of follow-up than in the first, and that the risk of diffuse-type gastric cancer increased in patients with mild-to-moderate gastric mucosal atrophy at baseline. This observation suggests that the efficacy of *H. pylori* eradication therapy differs by both the severity of gastric mucosal atrophy at baseline and duration after eradication therapy.

More than 90% of *H. pylori* isolated in Japan carry the *cagA* factor, which is associated with increased

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proliferation and pro-inflammatory gene expression, and the *vacA* s1m1 type, which is associated with enhanced production of toxin with higher vacuolating activity [9–12]. For this reason, Japanese infected with *H. pylori* are at a higher risk for gastric atrophy, intestinal metaplasia and gastric cancer than *H. pylori*-positive European and US populations. The data tell the story: the age-standardized incidence rate (ASR) per 100,000 persons in 2018 was 39.6 in both sexes (57.8 in men and 23.5 in women) in Korea, 27.5 (40.7 and 16.0) in Japan and 20.7 (29.5 and 12.3) in China. These stand versus a world rate in 2012 of 12.1 (17.4 and 7.5, respectively) (<https://www.wcrf.org/dietandcancer/cancer-trends/stomach-cancer-statistics>). Thus, evaluating the association of *H. pylori* infection with gastric cancer risk in Japanese is an important step in formulating strategies to reduce the risk of gastric cancer.

In general, gastric cancer risk differs between patients with atrophic gastritis and patients after resection for gastric cancer. Metachronous cancer incidence in *H. pylori*-positive patients after resection of gastric cancer is > 2000 per 100,000 person-years, which is greater than that in patients with gastritis alone (100–500 per 100,000 person-years). Recent meta-analyses showed that eradication therapy for *H. pylori* infection had a significant protective effect against the development of gastric cancer (Yoon (OR 0.42, 95% CI 0.32–0.56) [2]; Xiao (RR 0.50, 95% CI 0.41–0.61) [3]; and Sugano (OR 0.46, 95% CI 0.39–0.55) [1]). Accordingly, *H. pylori* eradication therapy should be required in all patients with *H. pylori* infection to prevent the development of gastric cancer. As Take et al. show in this issue [7], endoscopic surveillance should be continued beyond 10 years after eradication therapy for *H. pylori* irrespective of the severity of gastric atrophy.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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