






ORIGINAL ARTICLE

# Clinicopathological characteristics of advanced gastric cancer after *Helicobacter pylori* eradication

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## Key words

advanced gastric cancer, endoscopic surveillance, eradication, *Helicobacter pylori*.

Accepted for publication 26 September 2022.

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**Declaration of conflict of interest:** None.

**Financial support:** The authors have no funding sources.

## Abstract

**Background and Aim:** *Helicobacter pylori* (*H. pylori*) eradication has become popular as it prevents the development of gastric cancer. There have been no comprehensive studies on advanced gastric cancer (AGC) after eradication; thus, the clinical characteristics remain unclear. This study aimed to compare the characteristics of AGC after eradication and with current *H. pylori* infection and evaluate the esophagogastroduodenoscopy (EGD) follow-up after eradication.

**Methods:** This single-center, retrospective study included 261 consecutive patients diagnosed with AGC through EGD. The patients were grouped based on their *H. pylori* status: eradication ( $n = 48$ ) and infection ( $n = 213$ ) groups. Univariate analysis was conducted to compare clinicopathological characteristics between groups. The clinical course of the eradication group was analyzed by dividing the patients into three groups according to the interval from the last EGD until AGC detection: short-interval (<1 year), intermediate-interval (2–3 years), and long-interval (4–5 years) groups.

**Results:** The radical resection (R0) rate was higher in the eradication group. In surgical cases, the median tumor diameter was shorter in the eradication group. Analysis of EGD surveillance after eradication in 36 available cases showed that 24 (66.7%) were detected within 5 years after eradication, and 3 (8.3%) were diagnosed as AGC > 20 years after eradication. The R0 rates in the short-, intermediate-, and long-interval groups were 83.3%, 71.4%, and 60%, respectively.

**Conclusions:** AGC after eradication was more often detected at the phase in which R0 resection was possible. EGD follow-up with tight intervals of at least 5 years after eradication is advisable.

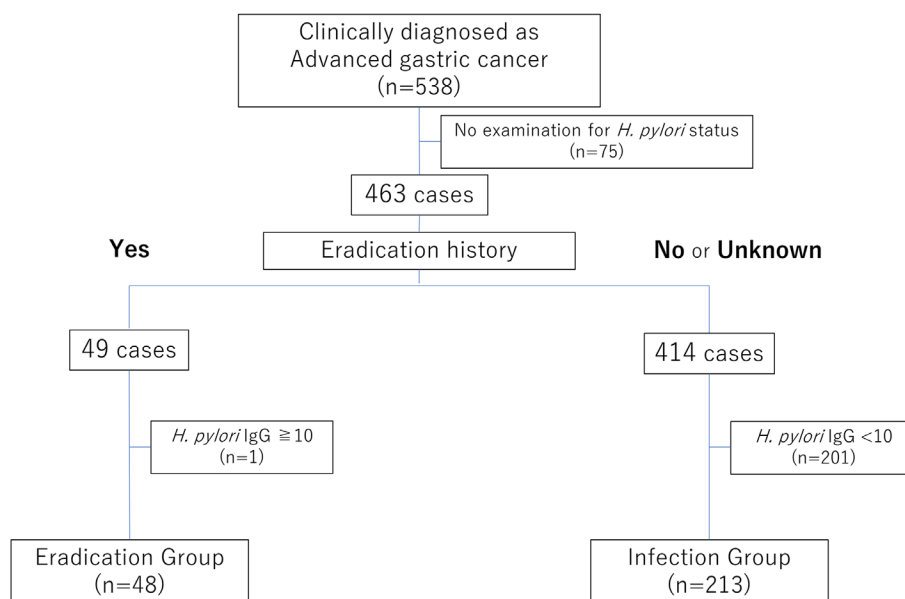
## Introduction

*Helicobacter pylori* (*H. pylori*) infection is a risk factor for gastric cancer (GC).<sup>1–3</sup> Fukase et al.<sup>4</sup> showed that *H. pylori* eradication reduces the risk of GC development in patients who underwent endoscopic submucosal dissection for managing early GC (EGC). Based on these results, *H. pylori* eradication treatment has become common. Accordingly, several studies have reported on the clinicopathological characteristics of GC after *H. pylori* eradication,<sup>5–7</sup> most of which focus on EGC. In Japan, the 2018 statistics showed that GC is the third leading cause of death among all cancerous lesions, due to advanced GC (AGC). In routine esophagogastroduodenoscopy (EGD), we occasionally encounter AGC that has progressed despite *H. pylori* eradication. There have been no comprehensive studies on the characteristics of AGC after *H. pylori* eradication, and its characteristics remain unclear.

Therefore, this study aimed to clarify the clinicopathological characteristics of AGC after *H. pylori* eradication in comparison with AGC with current *H. pylori* infection. Furthermore, to explore the optimal strategy for EGD follow-up after eradication, we analyzed the number of years after eradication and the intervals of EGD surveillance in cases with eradication.

## Methods

**Patients.** This retrospective, single-center study included 538 consecutive patients who were clinically diagnosed with AGC through EGD between January 2018 and December 2019. Among the 538 patients, 463 were selected after excluding those who had not been examined for *H. pylori* status ( $n = 75$ ). The 463 patients, according to the criteria outlined below, were grouped into the eradication group and infection group (Fig. 1).



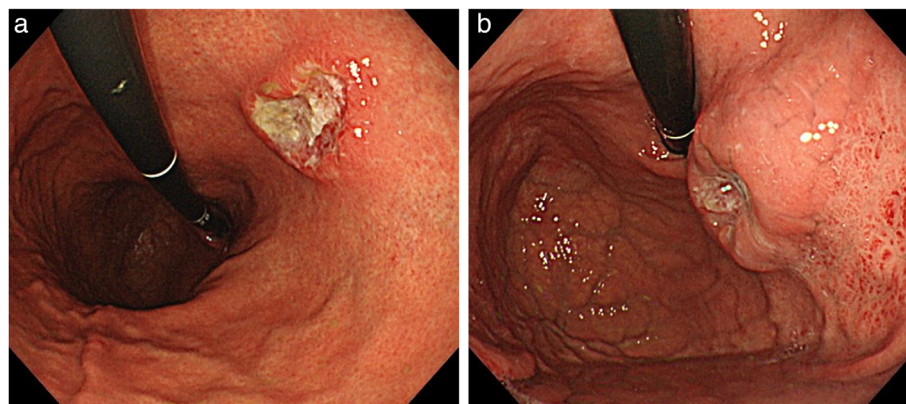
**Figure 1** Flowchart of patient enrollment

The eradication group included patients (1) with a history of *H. pylori* eradication and (2) negative for *H. pylori* on laboratory examinations (i.e., *H. pylori* immunoglobulin G [IgG] antibody [*H. pylori* antibody II, EIKEN Co. Ltd.] level < 10 U/mL or negative urea breath test result). Patients with no eradication history or unknown eradication history were excluded from the eradication group. A representative endoscopic image of the eradication group is shown in Fig. 2a.

The infection group included patients (1) with no history of *H. pylori* eradication and (2) positive for *H. pylori* on laboratory examinations (i.e., *H. pylori* IgG antibody level ≥ 10 U/mL or positive urea breath test result). Patients with a history of eradication were excluded from the infection group. A representative endoscopic image of the infection group is shown in Fig. 2b.

This study was approved by the Institutional Review Board of the Cancer Institute Hospital (Institutional Review Board no. 2020–1179).

**Clinicopathological assessment.** According to the Japanese Classification of Gastric Carcinoma,<sup>8</sup> AGC comprises pT2, pT3, or pT4 tumors irrespective of lymph node metastasis. The location and macroscopic type of GC were classified according to the Japanese Classification of Gastric Carcinoma. The histological type was classified into differentiated and undifferentiated types according to the definition by Nakamura et al.<sup>9</sup> According to the Japanese Classification of Gastric Carcinoma, the differentiated type consists of tumors corresponding to papillary adenocarcinoma (pap), well-differentiated tubular



**Figure 2** Endoscopic images of advanced gastric cancer. (a) Advanced gastric cancer (AGC) after *Helicobacter pylori* (*H. pylori*) eradication. Type 2 lesion located at the lesser curvature of the middle body. The background mucosa shows atrophic gastritis, consistent with after *H. pylori* eradication. (b) AGC with current *H. pylori* infection. Type 2 lesion located at the anterior wall of the upper body. Diffuse redness is exhibited, suggesting *H. pylori* current infection.

adenocarcinoma (tub1), or moderately differentiated tubular adenocarcinoma (tub2), and the undifferentiated type consists of tumors corresponding to poorly differentiated tubular adenocarcinoma (por) or signet-ring cell carcinoma (sig). In this study, differentiated-type predominant adenocarcinoma and undifferentiated-type predominant adenocarcinoma were considered as differentiated type and undifferentiated type, respectively. Other histological types, such as neuroendocrine carcinoma, squamous cell carcinoma, and hepatoid adenocarcinoma, were defined as special types.

In the present analysis, we considered the family history of GC in first-degree relatives only, that is, parents, siblings, and children. The Brinkman index (BI) is the product of the number of cigarettes smoked per day multiplied by the duration of use (days). BI was calculated based on the data recorded during patient interviews.

**Comparative analysis of the eradication group and infection group.** Patients' characteristics were summarized by subgroups of the eradication group and infection group, and all cases in both groups were compared using univariate analysis to clarify the clinical characteristics of the eradication

group. The clinical characteristics included age, sex, family history of GC, comorbidities requiring medication (hypertension, dyslipidemia, and type 2 diabetes mellitus), smoking history (BI), tumor location, morphological type, radical resection (RO) rate, and clinical stage.

**Comparative analysis confined to surgical cases.**

Furthermore, cases in which surgery was performed as initial treatment in both groups were compared using univariate analysis to clarify the pathological characteristics of the eradication group. Pathological characteristics included tumor diameter, histological type, invasive depth, lymphovascular invasion, and pathological stage. Cases in which chemotherapy was administered before surgery were excluded from surgical cases.

**Clinical course after *H. pylori* eradication.** We analyzed the clinical course after *H. pylori* eradication relative to the number of years after eradication and the interval of EGD surveillance. Patients in the eradication group were classified into three groups according to the interval from the last EGD until AGC was detected, short-interval group (within 1 year), intermediate-interval group (within 2–3 years), and long-interval

**Table 1** Comparison of characteristics between the eradication and infection groups

	Eradication group ( <i>n</i> = 48)	Infection group ( <i>n</i> = 213)	<i>P</i> value
Age, years	66 ± 13.3	66 ± 12.5	ns
Sex, male, <i>n</i> (%)	34 (70.8)	136 (63.8)	ns
Family history of gastric cancer, <i>n</i> (%)	12 (25.0)	53 (24.9)	ns
Hypertension, <i>n</i> (%)	16 (33.3)	67 (31.5)	ns
Dyslipidemia, <i>n</i> (%)	12 (25.0)	29 (13.6)	ns
Type 2 diabetes mellitus, <i>n</i> (%)	8 (16.7)	32 (15.0)	ns
Smoking history, <i>n</i> (%)	35 (72.9)	109 (51.2)	<0.05
Brinkman index	280 (0–492.5) [0–1520]	70 (0–640) [0–3300]	ns
Location, <i>n</i> (%)			ns
Upper region	15 (31.3)	52 (24.4)	
Middle region	22 (45.8)	91 (42.7)	
Lower region	11 (22.9)	69 (32.4)	
Macroscopic type, <i>n</i> (%)			ns
Type 0	4 (8.3)	22 (10.3)	
Type 1	2 (4.2)	7 (3.3)	
Type 2	11 (22.9)	42 (19.7)	
Type 3	15 (31.3)	99 (46.5)	
Type 4	16 (33.3)	38 (17.8)	
Type 5	1 (2.1)	5 (2.3)	
Treatment method, <i>n</i> (%)			ns
Surgery	28 (58.3)	96 (45.1)	
Conversion surgery	6 (12.5)	31 (14.5)	
Chemotherapy	14 (29.2)	77 (36.2)	
Radical resection, <i>n</i> (%)	35 (72.9)	117 (54.9)	<0.05
Clinical stage, <i>n</i> (%)			ns
IB	6 (12.5)	15 (7.0)	
II	11 (22.9)	41 (19.2)	
III	16 (33.3)	56 (26.3)	
IV	15 (31.2)	101 (47.4)	

Age is expressed as mean ± SD. Brinkman index is expressed as median (interquartile range). Eradication group: advanced gastric cancer after *Helicobacter pylori* (*H. pylori*) eradication; infection group: advanced gastric cancer with current *H. pylori* infection; ns, not significant.

group (within 4–5 years). Patients who were uncertain about when they had their last EGD were excluded.

**Statistical analysis.** All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, version 3.4.1).<sup>10</sup> Categorical parameters were compared using the  $\chi^2$ -test and continuous parameters using the Mann–Whitney U test. In all analyses, a *P* value <0.05 indicated statistical significance.

## Results

Forty-eight patients in the eradication group and 213 patients in the infection group (28 patients in the eradication group and 96 patients in the infection group underwent surgical treatment as initial treatment) were selected.

**Comparison of clinicopathological characteristics between the eradication and infection groups in all cases in this study.** A comparison of characteristics between the eradication and infection groups is shown in Table 1. The ratio of smoking history was significantly higher (*P* < 0.05) in the eradication group (*n* = 35, 72.9%) than in the infection group (*n* = 109, 51.2%), while the BI showed no difference between the two groups (*P* = 0.18). The R0 rate was significantly higher in the eradication group (*n* = 35, 72.9%) than in the infection group (*n* = 117, 54.9%) (*P* < 0.05). There were no significant differences in age, sex, family history of GC,

hypertension, dyslipidemia, type 2 diabetes mellitus, tumor location, macroscopic types, treatment methods, and clinical stage.

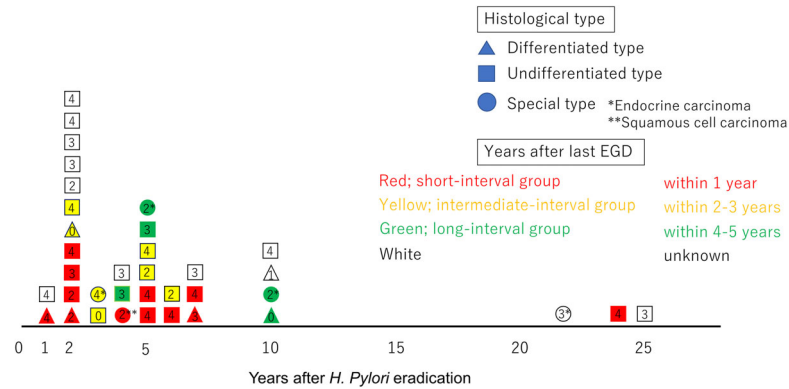
**Comparison of clinicopathological characteristics between the eradication and infection groups in surgical cases in this study.** A comparison of the characteristics of surgical cases with initial treatment between the eradication and infection groups is shown in Table 2. The median tumor diameter of the eradication group tended to be smaller than that of infection group (37.5 ± 56.4 mm vs. 50.0 ± 36.6 mm, *P* = 0.056). No significant differences were found between groups in age, sex, and histological type, invasion depth, lymphovascular invasion, and pathological stage. In both groups, the histological type of more than half of the patients was undifferentiated-type adenocarcinoma, and there was no significant difference between the two groups.

**Analysis of the clinical course in the eradication group.** Of the 48 cases in the eradication group, 36 (75%) had information on the period between the time of their eradication therapy and the time when AGCs were detected. Their distribution is shown in Figure 3. The median interval period was 4.5 years; 24 cases (66.7%) were detected in <5 years after eradication and 3 cases were detected >20 years after eradication. Twenty-four patients (50%) were able to identify the interval from the last EGD until AGC was detected. There were 12, 7, and 5 patients in the short-, intermediate-, and long-interval groups, respectively. The R0 rates for the short-, intermediate-, and long-interval groups

**Table 2** Comparison of characteristics in surgical cases between the eradication and infection groups

	Eradication group ( <i>n</i> = 28)	Infection group ( <i>n</i> = 96)	<i>P</i> value
Age, years	65 ± 13.0	64 ± 13.1	ns
Sex, male, <i>n</i> (%)	19 (67.9)	57 (59.4)	ns
Tumor diameter, mm	37.5 ± 56.4 [15–200]	50 ± 36.6 [18–203]	0.056
Histological type, <i>n</i> (%)			ns
Differentiated type	9 (32.1)	29 (30.2)	
Undifferentiated type	17 (60.7)	66 (68.8)	
Special type	2 (7.1)	1 (1.0)	
Invasion depth, <i>n</i> (%)			ns
pT2	8 (28.6)	24 (25.0)	
pT3	11 (39.2)	26 (27.1)	
pT4a	7 (25.0)	44 (45.8)	
pT4b	2 (7.1)	2 (2.1)	
Lymphovascular invasion, <i>n</i> (%)			ns
Ly0 and V0	4 (14.3)	10 (10.4)	
Ly1 or V1	7 (25.0)	41 (42.7)	
Ly1 and V1	17 (60.7)	45 (46.9)	
Pathological stage, <i>n</i> (%)			ns
IB	6 (21.4)	16 (16.7)	
II	8 (28.6)	37 (38.5)	
III	14 (50.0)	34 (35.4)	
IV	0	9 (9.3)	

Age is expressed as mean ± SD. Tumor diameter is expressed as median ± SD [range]. Eradication group: advanced gastric cancer after *Helicobacter pylori* (*H. pylori*) eradication; infection group: advanced gastric cancer with current *HH. pylori* infection; ns, not significant; Ly0 and Ly1, negative and positive for lymphatic invasion, respectively; V0 and V1, negative and positive for venous invasion, respectively.



**Figure 3** Distribution of years elapsed after *Helicobacter pylori* (*H. pylori*) eradication. Thirty-six cases (75%) had information on the period between the time of their eradication therapy and the time when advanced gastric cancers were detected. Histological types are indicated by the different shapes, and groups based on years after the last esophagogastroduodenoscopy are indicated by the different colors. The numbers in the diagrams indicate the morphological type.

were 83.3% (10/12), 71.4% (5/7), and 60% (3/5), respectively ( $P = 0.53$ ).

## Discussion

We evaluated the clinicopathological characteristics of AGC after *H. pylori* eradication by comparison with currently *H. pylori*-infected AGC as the control group. The results of this study showed that AGC after eradication was significantly more often detected at the phase in which R0 resection was possible. The analysis of the clinical course and the interval between EGDs after eradication suggest the optimal strategy for EGD follow-up after eradication. To our knowledge, no comprehensive study on the characteristics of AGC after eradication has been conducted because eradication therapy has not been widely used for a long time. Therefore, the present study is considered valuable because a relatively large number of patients with AGC were examined based on the *H. pylori* infection status.

In recent years, there have been several reports<sup>5–7</sup> on the characteristics of EGC after *H. pylori* eradication. EGC after *H. pylori* eradication is a smaller size than EGC with current *H. pylori* infection. Regarding AGC in the present study, in the eradication group, the tumor diameter of AGC in the eradication group tended to be smaller than that in the infection group. In a pathological study by Yamamoto et al.,<sup>5</sup> GC detected after *H. pylori* eradication was smaller and had a lower Ki-67 labeling index than *H. pylori*-positive GCs, speculating that GC cell proliferation was suppressed by *H. pylori* eradication. Yamamoto et al.'s study was confined to EGC; furthermore, most GCs after eradication were differentiated-type adenocarcinoma (17/18). Therefore, the result of the previous study cannot be generally applied to our study, because more than half of the AGCs after eradication we examined were undifferentiated-type adenocarcinoma. However, in the present study, the R0 rate was significantly higher, and the tumor size tended to be smaller in the eradication group. Therefore, *H. pylori* eradication may have some inhibitory effects on cell proliferation in AGC as well as EGC, but these need to be investigated in the future. It is not clear whether AGC after *H. pylori* eradication has the same

suppressed tumor proliferative ability as EGC, or our result might be because AGC in the eradication group was detected at a relatively earlier stage than that in the infection group, simply due to the tight interval between EGD surveillance.

Reportedly, most EGCs after *H. pylori* eradication are detected within a short period.<sup>6</sup> In the present study, 66.7% (24/36) of the cases were detected within 5 years after *H. pylori* eradication. In addition, 91.7% (11/12) in the short-interval group were detected within 7 years after eradication. Therefore, EGD follow-up with tight intervals of at least 5 years after eradication is advisable. In cases where AGC was detected 10 years after eradication, at least half of the patients did not undergo endoscopic follow-up 4 or 5 years prior, resulting in GC being diagnosed in the advanced stage. Furthermore, there were three cases of AGC detected 20 years after *H. pylori* eradication, and two of them were undifferentiated-type adenocarcinomas, which are known to have a poorer prognosis than the differentiated type.<sup>11–13</sup> The possibility of GC development should be considered even after long periods after *H. pylori* eradication. By contrast, the present study included two cases of AGC that developed within 1 year after eradication therapy. They were both type 4 AGC, which is known to progress rapidly and show poor prognosis.<sup>14,15</sup>

In the present study, the proportion of patients with smoking history was significantly higher in the eradication group than in the infection group (72.9% vs. 51.2%,  $P < 0.05$ ), while the BI showed no difference between the two groups ( $P = 0.18$ ). Two previous meta-analyses have reported on smoking and GC and concluded that smoking is associated with GC<sup>16,17</sup>; however, no association has been proven for the amount or duration of smoking. Horiuchi et al. compared patient characteristics, such as medical history and alcohol and tobacco use, between patients with *H. pylori*-uninfected undifferentiated-type EGC and patients with *H. pylori*-positive undifferentiated-type EGC. The investigation of clinical factors identified smoking history as possibly contributing to the pathogenesis of *H. pylori*-uninfected undifferentiated-type EGC.<sup>18</sup> In the eradication group, the effects of chronic inflammation due to *H. pylori* infection may be weak, if any, especially in patients who have been eradicated for a long



time.<sup>19</sup> In fact, in this study, the smoking rate was as high as 85.7% (6 of 7) among the patients who had been eradicated for more than 10 years. Therefore, the results of the present study may indicate a correlation between smoking and carcinogenesis after *H. pylori* eradication.

In the short-interval group, the RO rate was 83.3% (10 of 12), while in the long-interval group, the RO rate was 60% (3 of 5). A previous report<sup>20</sup> regarding the interval of endoscopic screening for GC showed that the survival rates were significantly higher in patients with an endoscopic screening history 1 and 2 years before diagnosis than in patients with endoscopic screening history 3 years before diagnosis. The present study indicates that an extended interval of endoscopic screening may be a potential risk factor for non-curative GC, even in patients who had *H. pylori* eradication.

The present study has some limitations. First, this was a retrospective, single-center study. Second, the present study did not accumulate enough AGC cases after *H. pylori* eradication for analysis. Third, the interval of EGD surveillance may differ between groups; this might have affected the characteristics of AGC after *H. pylori* eradication. Last, because our institution is a cancer-specialized hospital, there might have been a selection bias when our study's prevalence rate is compared with the general prevalence rate, considering the frequency of patient referrals. However, this study included all patients with AGC who underwent EGD, and the bias is likely to be minimal in this single-center study.

In conclusion, the RO rate in the eradication group was significantly higher than that in infection group, and the tumor diameter in the eradication group tended to be smaller. The clinical characteristics of the eradication group might indicate a correlation between smoking and carcinogenesis after *H. pylori* eradication. Analysis of EGD surveillance methods in the eradication group suggested that EGD surveillance should be uninterrupted, and the interval between EGDs should not be extended.

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