Effect of *Helicobacter Pylori* Infection on Malignancy of Undifferentiated-type Gastric Cancer

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Research article

Keywords: *Helicobacter pylori*, undifferentiated carcinoma, gastric cancer, malignancy

Posted Date: August 9th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-789828/v1>

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Version of Record: A version of this preprint was published at BMC Gastroenterology on January 6th, 2022. See the published version at <https://doi.org/10.1186/s12876-021-02034-7>.

Abstract

Background: Although almost all cases of gastric cancer are caused by *Helicobacter pylori* (HP) infection, there are some rare exceptions. Furthermore, the clinicopathological characteristics of gastric cancer may differ depending on HP infection status. This study aimed to determine the clinicopathological characteristics of undifferentiated-type gastric cancer (UD-GC) according to HP status.

Methods: The study involved 83 patients with UD-GC who were selected from 1559 patients with gastric cancer who underwent endoscopic resection at our hospital and whose HP infection status was confirmed. Clinicopathological characteristics were evaluated according to HP status (eradicated, n=28; infected, n=32; not infected, n=23).

Results: In patients without HP infection, UD-GCs were <20 mm and intramucosal with no vascular invasion. In patients with eradicated HP, there was no correlation between development of UD-GC and time since eradication. Furthermore, 75% of patients with a tumor detected ≥ 5 years after eradication had undergone yearly endoscopy. Submucosal or deeper invasion was observed in 50% of patients and vascular invasion in 75% of patients whose UD-GC was detected ≥ 10 years after eradication. The proportion of patients with UD-GC and submucosal or deeper invasion was zero in the group without HP infection, 14.3% in the group with eradicated HP, and 10.5% in the HP-infected group.

Conclusion: The clinicopathological characteristics of UD-GC were similar between HP-infected patients and HP-eradicated patients. Patients with eradicated HP whose UD-GC developed long after eradication had high rates of vascular and submucosal invasion. In contrast, UD-GC was curable by endoscopic resection in all patients without HP infection.

Introduction

Almost all cases of gastric cancer are caused by *Helicobacter pylori* (HP) infection (Correa 1995; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 1994; Parsonnet et al. 1991). Although rare, gastric cancer can also develop in the absence of HP infection (Kato et al. 2007; Matsuo et al. 2011; Ono et al. 2012), and the characteristics of gastric cancer without HP infection have become clearer with accumulation of cases (Sato et al. 2020; Yamada et al. 2018; Yamamoto et al. 2015; Yoon et al. 2011). The clinicopathological features of gastric cancer differ according to HP infection status. Differentiated-type gastric cancer (D-GC) undergoes morphological changes upon eradication of HP (Hori et al. 2016; Ito et al. 2005; Yamamoto et al. 2011), and changes on the mucosal surface of the tumor to a non-cancerous appearance after eradication hinder endoscopic diagnosis (Kobayashi et al. 2013). Meanwhile, the degree of malignancy of undifferentiated-type gastric cancer (UD-GC), including proliferative ability and progression rate, is reported to be higher in patients with HP infection (both post-eradication and current infection cases) than in those without HP infection (Horiuchi et al. 2016). However, details of UD-GC post-eradication remain unclear. The latest endoscopic mucosal resection/endoscopic submucosal dissection guidelines state that intramucosal lesions measuring ≤ 20

mm and ulcer-negative UD-GC are absolute indications for endoscopic resection (Ono et al. 2020). Therefore, it is important for endoscopists diagnosing and treating UD-GC to have a good knowledge of the clinicopathological features of this tumor according to HP infection status.

In this study, we classified patients with UD-GC according to HP status as a post-eradication (UD-E) group, a current infection (UD-I) group, and a non-infected (UD-U) group) with the aim of clarifying the clinicopathological features of each group.

Patients And Methods

The study involved patients with gastric cancer who underwent endoscopic resection at Toranomon Hospital between June 2011 and December 2019. A flow chart showing the patient selection process is provided in Fig. 1. After excluding 108 cases with residual gastric cancer and 446 with unknown HP infection status or unclear time of eradication, we reviewed 1559 cases (2032 lesions) with confirmed HP status. This study was approved by the ethics committee of Toranomon Hospital, approval number 1173.

The UD-E group was defined as follows: known time of eradication and HP-negative status confirmed by a stool antigen test (Meridian Inc., Cincinnati, OH) or a ^{13}C -urea breath test (Otsuka Pharmaceutical Co., Ltd., Tokushima, Japan). Current HP infection was defined as a positive urea breath test or stool antigen test, or a positive serum antibody test (E-plate test; Eiken Chemical Co., Ltd., Tokyo, Japan) plus endoscopic findings suggesting current HP infection (Haruma et al. 2017). Patients were deemed not to have HP infection if the following four criteria were satisfied: no history of HP eradication; a negative serum antibody test ($< 3 \text{ U/mL}$) and a negative stool antigen test or urea breath test; no atrophy of the background mucosa on pathological examination of the specimen obtained during endoscopic resection; and no atrophy according to the Kimura-Takemoto classification (Kimura and Takemoto 1969) with regular arrangement of the collecting venules in the lesser curvature of the gastric angle (Yagi et al. 2005).

HP status was confirmed in 66 cases (71 lesions) in the UD-E group, 503 cases (616 lesions) in the UD-I group, and 446 cases (622 lesions) in the UD-U group. UD-GC cases were then extracted for analysis; there were 28 cases (28 lesions) in the UD-E group, 32 cases (38 lesions) in the UD-I group, and 23 cases (24 lesions) in the UD-U group.

The following clinicopathological characteristics were evaluated: patient demographics (age and sex), endoscopic findings (degree of atrophy, macroscopic type, site, and color tone), and histopathological features (findings, tumor size, depth of invasion, and lymphovascular invasion). In the UD-E group, we also evaluated the time from eradication, tumor size, color tone, depth of invasion, and lymphovascular invasion. The Kimura-Takemoto classification (Kimura and Takemoto 1969) was used to evaluate the degree of atrophy (Close(C)-0, none; C-1 and C-2, mild; C-3 to Open(O)-3), moderate-severe). Color tone was classified as discolored or reddish; if mixed, the predominant tone was selected. Histopathological findings were classified into UD-GC or differentiated-type gastric cancer (D-GC); when both types were

present, the predominant type was used. UD-GC cases were further divided into pure signet ring cell carcinoma or other type (poorly differentiated adenocarcinoma or mixed poorly differentiated adenocarcinoma and signet ring cell carcinoma) (Japanese Gastric Cancer Association 2011).

The clinicopathological features were compared between the two groups using Fisher's exact test and the Mann-Whitney *U* test. All statistical analyses were performed using SPSS version 27 (IBM Corp., Armonk, NY). A *p*-value < 0.05 was considered statistically significant.

Results

There were 932 cases of D-GC (1,219 lesions) and 83 cases (90 lesions) of UD-GC. The ratio of UD-GC cases was 8.2%. The ratio of UD-GC to all tumors in each HP infection status group was significantly higher in the UD-U group (33.8%) than in the UD-E and UD-I groups (4.5% and 6.2%, respectively).

Patient characteristics

The characteristics of the patients in the UD-E, UD-I, and UD-U groups are shown in Table 1. The male-to-female ratio was 18:10 in the UD-E group, 14:8 in the UD-I group, and 20:3 in the UD-U group. There was a significantly higher proportion of women in the UD-I group than in the UD-U group ($p = 0.001$, UD-I vs UD-U; $p = 0.105$, UD-U vs UD-E). However, there was no significant difference in the sex distribution between the UD-E and UD-I groups or between the UD-E and UD-U groups. The mean age was 63.1 ± 14.3 , 64.0 ± 13.4 , and 56.3 ± 9.15 years, respectively, in the UD-E, UD-I, and UD-U groups; patients in the UD-U group were significantly younger than those in the UD-E and UD-I groups ($p = 0.017$ and $p = 0.019$, respectively). The background mucosa was significantly more atrophied in the UD-E and UD-I groups (both $p < 0.01$) than in the UD-U group (which had no cases of atrophy).

Table 1
Patient characteristics in the group with undifferentiated-type gastric cancer according to *Helicobacter pylori* infection status

	UD-E (A)	UD-I (B)	UD-U (C)	Significance
Patients (lesions) with undifferentiated AC, n	28 (28)	32 (38)	23 (24)	
Sex				$p = 0.001$ (B vs C)
Male	18 (64.3%)	14 (43.8%)	20 (87.0%)	NS (A vs B)
Female	10 (35.7%)	18 (56.2%)	3 (23.0%)	NS (C vs A)
Age, years (mean $\pm$ SD)	63.1 $\pm$ 14.3	64.0 $\pm$ 13.4	56.3 $\pm$ 9.15	$p = 0.017$ (A vs B) $p = 0.019$ (B vs C) NS (C vs A)
Atrophy				$p < 0.01$ (B vs C)
None (C-0)	0 (0%)	0 (0%)	13 (100%)	$p < 0.01$ (C vs A)
Mild (C-1, C-2)	7 (25.0%)	3 (9.4%)	0 (0%)	NS (A vs B)
Moderate to severe (C-3–O3)	21 (75.0%)	29 (90.6%)	0 (0%)	
AC, adenocarcinoma; NS, not statistically significant; SD, standard deviation; UD-E, post-eradication group; UD-I, current infection group; UD-U, noninfected group.				

Endoscopic findings

Endoscopic findings are shown in Table 2. The lesions were located in the upper third, middle third, and lower third of the stomach in 2/9/17 cases in the UD-E group, 2/22/14 cases in the UD-I group, and 1/5/18 cases in the UD-U group, indicating that the middle third of the stomach was a significantly more common site in the UD-I group than in the UD-U group ($p = 0.002$). There was no significant difference in macroscopic type of the lesions between the groups. The color tone was reddish in about half of the cases in the UD-E and UD-I groups (42.9% and 57.9%, respectively), whereas all cases in the UD-D group were discolored ($p < 0.001$, UD-I vs UD-U; $p < 0.001$, UD-U vs UD-E).

Table 2
Endoscopic findings in patients with undifferentiated-type gastric cancer according to *Helicobacter pylori* infection status

	UD-E (A)	UD-I (B)	UD-U (C)	Significance
Location				<i>p</i> = 0.002 (B vs C)
Upper third	2 (7.1%)	2 (5.3%)	1 (4.2%)	NS (A vs B, C vs A)
Middle third	9 (32.1%)	22 (57.9%)	5 (20.8%)	
Lower third	17 (60.8%)	14 (36.8%)	18 (75.0%)	
Macroscopic appearance				NS (A vs B, B vs C, C vs A)
Elevated	1 (3.6%)	2 (5.3%)	0 (0%)	
Flat or depressed	27 (96.4%)	36 (94.7%)	24 (100%)	
Color tone				
Discolored dominant	16 (57.1%)	16 (42.1%)	24 (100%)	NS (A vs B)
Reddish dominant	12 (42.9%)	22 (57.9%)	0 (0%)	
NS, not significant; UD-E, post-eradication group; UD-I, current infection group; UD-U, non-infected group.				

Histopathological features

Mean tumor diameter was significantly smaller in the UD-U group (10.1 ± 5.4 mm) than in the UD-E group (19.4 ± 11.7 mm; $p = 0.024$) and UD-I group (18.6 ± 10.2 mm; $p = 0.028$). In the UD-U group, the majority of lesions (87.5%, 21/24) were pure signet ring carcinoma; this type of gastric cancer was significantly less common in the UD-E and UD-I groups (50.0% and 28.9%, respectively; both $p < 0.01$; Table 3).

Table 3

Histopathological findings in the patients with undifferentiated gastric cancer according to *Helicobacter pylori* infection status

	UD-E (A)	UD-I (B)	UD-U (C)	Significance
Maximum lesion diameter, mean $\pm$ SD	19.3 $\pm$ 11.7	18.6 $\pm$ 10.2	10.1 $\pm$ 5.4	$p = 0.024$ (C vs A) $p = 0.028$ (B vs C) NS (A vs B)
Pathological type, % of pure signet ring cell CA	50.0% (14/28)	28.9% (11/38)	87.5% (21/24)	$p < 0.001$ (B vs C, C vs A) NS (A vs B)
Depth, % of SM invasive cancer	14.3% (4/28)	10.5% (4/38)	0% (0/24)	NS (A vs B, B vs C, C vs A)
Lymphovascular invasion, % of undifferentiated CA	10.7% (3/28)	0% (0/38)	0% (0/24)	NS (A vs B, B vs C, C vs A)
CA, carcinoma; NS, not statistically significant; SD, standard deviation; SM, submucosal; UD-E, post-eradication group; UD-I, current infection group; UD-U, non-infected group				

There was no significant between-group difference in the frequency of lesions with invasion into the submucosal layer or deeper (14.3%, 10.5%, and 0% in the UD-E, UD-I, and UD-U groups, respectively). All lesions in the UD-U group were intramucosal tumors. Lymphovascular invasion was seen only in the UD-E group (3 cases, 10.7%). Two of the 3 lesions with lymphovascular invasion had a tumor diameter of ≥ 30 mm (no significant difference compared with the UD-I and UD-I groups).

Relationship of time since eradication with tumor diameter, color tone, and depth of invasion in the UD-E group

Figure 2 shows the relationship of time since eradication with tumor diameter, color tone, and depth of invasion. The median interval between eradication and detection of gastric cancer was 56 (9–240) months in the UD-E group. UD-GC was detected ≥ 10 years after eradication in 4 patients, 3 (75%) of whom had undergone yearly endoscopy before gastric cancer was detected. Two of the 4 lesions (50%) invaded into the submucosal layer or deeper. Three of the 4 lesions showed lymphovascular invasion. Furthermore, 9 (75%) of 12 patients with UD-E detected ≥ 5 years after eradication and 3 (75%) of 4 with UD-E detected ≥ 10 years after eradication had undergone yearly endoscopy.

Discussion

The malignant potential of UD-GC is thought to be higher than that of D-GC (Hirasawa et al. 2009). Therefore, early detection of UD-GC is important. This study focused on clinically significant UD-GC and examined the relationship between UD-GC and HP status (post-eradication, current infection, and no

infection). We found that 33.8% of all lesions in the group without HP infection were UD-GC, whereas only 4.5% of those in the post-eradication group and 6.2% of those in the current infection group were UD-GC. However, all tumors in the UD-U group were intramucosal lesions and not highly malignant. These cases had the following features: (1) young age, (2) no atrophy in the background mucosa, (3) discolored tone, (4) relatively small tumor size, (5) predominantly pure signet ring cell carcinoma, (6) intramucosal lesions, and (7) no lymphovascular invasion. It has been reported that UD-GC without HP infection is less malignant than UD-GC with current HP infection (Yamamoto et al. 2015; Yoon et al. 2011). The clinicopathological features of UD-GC in patients with eradicated HP and those who were currently infected were similar in the present study.

Our study differs from previous reports in that we also examined the clinicopathological features of UD-GC that developed after eradication of HP. These features were similar between the UD-E group and the UD-I group and showed more malignant characteristics than the UD-U group, indicating that HP infection has a role in promoting gastric cancer.

Fukase et al. reported that eradication of HP reduced the incidence of cancer to about one third (Fukase et al. 2008), and there have also been studies in which eradication did not completely eliminate the risk of cancer even after a long period of time (Take et al. 2007, 2011, 2015, 2020).

A notable finding in this study was that UD-GC detected long after eradication was more malignant than UD-GC detected sooner. Alarming, 75% of patients in whom UD-E was detected ≥ 5 years after eradication had undergone yearly follow-up endoscopy. Although this finding alone does not provide sufficient evidence to conclude that yearly follow-up endoscopy after eradication is unnecessary, endoscopists should be aware that some patients who undergo regular endoscopy may still develop cancer that is not curable by endoscopic resection.

The limitations of this study include its single-center setting and lack of surgically treated cases. Furthermore, at less than 100, the number of cases was small. Given the low frequency of UD-GC, particularly UD-E, a multicenter study is needed to accumulate and examine more cases in the future.

Conclusion

The clinicopathological characteristics of UD-GC were similar between HP-infected patients and HP-eradicated patients. Patients with eradicated HP whose UD-GC developed long after eradication had high rates of vascular and submucosal invasion. In contrast, UD-GC was curable by endoscopic resection in all patients without HP infection.

Declarations

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors declare that they have no conflict of interest.

Availability of data and material

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability

Not applicable.

Authors' contributions

MT designed of the study, analyzed the data, and wrote the manuscript. SH conceived the study and revised the manuscript critically. DK, KN, YO, TO, JH, YS, YM, ND, HO, SY, and AM collected cases and data about *Helicobacter pylori* infection status.

Ethics approval

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Ethical approval was waived by the local ethics committee of our institution, Toranomon Hospital, approval number Number 1173, in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

Consent to participate

Informed consent was not required in view of the retrospective nature of the study.

Consent for publication

Not applicable.

Acknowledgements

Not applicable.

References

1. Correa P (1995) *Helicobacter pylori* and gastric carcinogenesis. Am J Surg Pathology 19:37-43

2. Fukase K, Kato M, Kikuchi S, Inoue K, Uemura N, Okamoto S, Terao S, Amagai K, Hayashi S, Asaka M; Japan Gast Study Group (2008) Effect of eradication of *Helicobacter pylori* on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. *Lancet* 372:392-397
3. Haruma K, Kato M, Inoue K, Murakami K, Kamada T (2017) Kyoto classification of gastritis. *Nihon Medical Center, Tokyo* (in Japanese)
4. Hirasawa T, Gotoda T, Miyata S, Kato Y, Shimoda T, Taniguchi H, Fujisaki J, Sano T, Yamaguchi T (2009) Incidence of lymph node metastasis and the feasibility of endoscopic resection for undifferentiated-type early gastric cancer. *Gastric Cancer* 12:148-152
5. Hori K, Watari J, Yamasaki T, Kondo T, Toyoshima F, Sakurai J, Ikehara H, Tomita T, Oshima T, Fukui H, Nakamura S, Miwa H (2016) Morphological characteristics of early gastric neoplasms detected after *Helicobacter pylori* eradication. *Dig Dis Sci* 61:1641-1651
6. Horiuchi Y, Fujisaki J, Yamamoto N, Shimizu T, Miyamoto Y, Tomida H, Taniguchi C, Morishige K, Omae M, Ishiyama A, Yoshio T, Hirasawa T, Yamamoto Y, Tsuchida T, Igarashi M, Nakajima T, Takahashi H (2016) Biological behavior of the intramucosal *Helicobacter pylori*-negative undifferentiated-type early gastric cancer: comparison with *Helicobacter pylori*-positive early gastric cancer. *Gastric Cancer* 19:160-165
7. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (1994) IARC monographs on the evaluation of carcinogenic risks to humans. Volume 61. Schistosomes, liver flukes and *Helicobacter pylori*. International Agency for Research on Cancer, Lyon, France, pp. 1-241
8. Ito M, Tanaka S, Takata S, Oka S, Imagawa S, Ueda H, Egi Y, Kitadai Y, Yasui W, Yoshihara M, Haruma K, Chayama K (2005) Morphological changes in human gastric tumours after eradication therapy of *Helicobacter pylori* in a short-term follow-up. *Aliment Pharmacol Ther* 21:559-566
9. Japanese Gastric Cancer Association (2011) Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 14:101-112
10. Kato S, Matsukura N, Tsukada K, Matsuda N, Mizoshita T, Tsukamoto T, Tatematsu M, Sugisaki Y, Naito Z, Tajiri T (2007) *Helicobacter pylori*-infection negative gastric cancer in Japanese hospital patients: incidence and pathological characteristics. *Cancer Sci* 98:790-794
11. Kimura K, Takemoto T (1969) An endoscopic recognition of the atrophic border and its significance in chronic gastritis. *Endoscopy* 1:87-97
12. Kobayashi M, Hashimoto S, Nishikura K, Mizuno K, Takeuchi M, Sato Y, Ajioka Y, Aoyagi Y (2013) Magnifying narrow-band imaging of surface maturation in early differentiated-type gastric cancers after *Helicobacter pylori* eradication. *J Gastroenterol* 48:1332-1342
13. Matsuo T, Ito M, Takata S, Tanaka S, Yoshihara M, Chayama K (2011) Low prevalence of *Helicobacter pylori*-negative gastric cancer among Japanese. *Helicobacter* 16:415-419
14. Ono H, Yao K, Fujishiro M, Oda I, Uedo F, Futamura S, et al. [[Please list all authors here.]] (2020) Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer. *Gastroenterol Endosc* 62:273-290 (in Japanese)

15. Ono S, Kato M, Suzuki M, Ishigaki S, Takahashi M, Haneda M, Mabe K, Shimizu Y (2012) Frequency of *Helicobacter pylori*-negative gastric cancer and gastric mucosal atrophy in a Japanese endoscopic submucosal dissection series including histological, endoscopic and serological atrophy. *Digestion* 86:59-65
16. Parsonnet J, Friedman G, Vandersteen D, Chang Y, Vogelman J, Orentreich N, Sibley RK (1991) *Helicobacter pylori* infection and the risk of gastric carcinoma. *N Engl J Med* 325:1127-1131
17. Sato C, Hirasawa K, Tateishi Y, Ozeki Y, Sawada A, Ikeda R, Fukuchi T, Nishio M, Kobayashi R, Makazu M, Kaneko H, Inayama Y, Maeda S (2020) Clinicopathological features of early gastric cancers arising in *Helicobacter pylori* uninfected patients. *World J Gastroenterol* 26:2618-2631
18. Take S, Mizuno M, Ishiki K, Nagahara K, Yoshida T, Yokota K, Oguma K (2007) Baseline gastric mucosal atrophy is a risk factor associated with the development of gastric cancer after *Helicobacter pylori* eradication therapy in patients with peptic ulcer diseases. *J Gastroenterol* 42(Suppl 17):21-27
19. Take S, Mizuno M, Ishiki K, Yoshida T, Ohara N, Yokota K, Oguma K, Okada H, Yamamoto K (2011) The long-term risk of gastric cancer after the successful eradication of *Helicobacter pylori*. *J Gastroenterol* 46:318-324
20. Take S, Mizuno M, Ishiki K, Hamada F, Yoshida T, Yokota K, Okada H, Yamamoto K (2015) Seventeen-year effects of eradicating *Helicobacter pylori* on the prevention of gastric cancer in patients with peptic ulcer; a prospective cohort study. *J Gastroenterol* 50:638-644
21. Take S, Mizuno M, Ishiki K, Kusumoto C, Imada T, Hamada F, Yoshida T, Yokota K, Mitsuhashi T, Okada H (2020) Risk of gastric cancer in the second decade of follow-up after *Helicobacter pylori* eradication. *J Gastroenterol* 55:281-288
22. Yagi K, Aruga Y, Nakamura A, Sekine A (2005) Regular arrangement of collecting venules (RAC): a characteristic endoscopic feature of *Helicobacter pylori*-negative normal stomach and its relationship with esophago-gastric adenocarcinoma. *J Gastroenterol* 40:443-452
23. Yamada A, Kaise M, Inoshita N, Toba T, Nomura K, Kuribayashi Y, Yamashita S, Furuhashi T, Kikuchi D, Matsui A, Mitani T, Ogawa O, Iizuka T, Hoteya S (2018) Characterization of *Helicobacter pylori*-naïve early gastric cancers. *Digestion* 98:127-134
24. Yamamoto K, Kato M, Takahashi M, Haneda M, Shinada K, Nishida U, Yoshida T, Sonoda N, Ono S, Nakagawa M, Mori Y, Nakagawa S, Mabe K, Shimizu Y, Moriya J, Kubota K, Matsuno Y, Shimoda T, Watanabe H, Asaka M (2011) Clinicopathological analysis of early-stage gastric cancers detected after successful eradication of *Helicobacter pylori*. *Helicobacter* 16:210-216
25. Yamamoto Y, Fujisaki J, Omae M, Hirasawa T, Igarashi M (2015) *Helicobacter pylori*-negative gastric cancer: characteristics and endoscopic findings. *Dig Endosc* 27:551-561
26. Yoon H, Kim N, Lee HS, Shin CM, Park YS, Lee DH, Jung HC, Song IS (2011) *Helicobacter pylori*-negative gastric cancer in South Korea: incidence and clinicopathologic characteristics. *Helicobacter* 16:382-388

Tables

Table 1 Patient characteristics in the group with undifferentiated-type gastric cancer according to *Helicobacter pylori* infection status

	UD-E (A)	UD-I (B)	UD-U (C)	Significance
Patients (lesions) with undifferentiated AC, n	28 (28)	32 (38)	23 (24)	
Sex				$p=0.001$ (B vs C)
Male	18 (64.3%)	14 (43.8%)	20 (87.0%)	NS (A vs B)
Female	10 (35.7%)	18 (56.2%)	3 (23.0%)	NS (C vs A)
Age, years (mean $\pm$ SD)	63.1 $\pm$ 14.3	64.0 $\pm$ 13.4	56.3 $\pm$ 9.15	$p=0.017$ (A vs B) $p=0.019$ (B vs C) NS (C vs A)
Atrophy				$p<0.01$ (B vs C)
None (C-0)	0 (0%)	0 (0%)	13 (100%)	$p<0.01$ (C vs A)
Mild (C-1, C-2)	7 (25.0%)	3 (9.4%)	0 (0%)	NS (A vs B)
Moderate to severe (C-3–O3)	21 (75.0%)	29 (90.6%)	0 (0%)	

AC, adenocarcinoma; NS, not statistically significant; SD, standard deviation; UD-E, post-eradication group; UD-I, current infection group; UD-U, noninfected group.

Table 2 Endoscopic findings in patients with undifferentiated-type gastric cancer according to *Helicobacter pylori* infection status

	UD-E (A)	UD-I (B)	UD-U (C)	Significance
Location				$p=0.002$ (B vs C)
Upper third	2 (7.1%)	2 (5.3%)	1 (4.2%)	NS (A vs B, C vs A)
Middle third	9 (32.1%)	22 (57.9%)	5 (20.8%)	
Lower third	17 (60.8%)	14 (36.8%)	18 (75.0%)	
Macroscopic appearance				NS (A vs B, B vs C, C vs A)
Elevated	1 (3.6%)	2 (5.3%)	0 (0%)	$p<0.001$ (B vs C, C vs A)
Flat or depressed	27 (96.4%)	36 (94.7%)	24 (100%)	
Color tone				
Discolored dominant	16 (57.1%)	16 (42.1%)	24 (100%)	NS (A vs B)
Reddish dominant	12 (42.9%)	22 (57.9%)	0 (0%)	

NS, not significant; UD-E, post-eradication group; UD-I, current infection group; UD-U, non-infected group.

Table 3 Histopathological findings in the patients with undifferentiated gastric cancer according to *Helicobacter pylori* infection status

	UD-E (A)	UD-I (B)	UD-U (C)	Significance
Maximum lesion diameter, mean $\pm$ SD	19.3 $\pm$ 11.7	18.6 $\pm$ 10.2	10.1 $\pm$ 5.4	$p=0.024$ (C vs A) $p=0.028$ (B vs C) NS (A vs B)
Pathological type, % of pure signet ring cell CA	50.0% (14/28)	28.9% (11/38)	87.5% (21/24)	$p<0.001$ (B vs C, C vs A) NS (A vs B)
Depth, % of SM invasive cancer	14.3% (4/28)	10.5% (4/38)	0% (0/24)	NS (A vs B, B vs C, C vs A)
Lymphovascular invasion, % of undifferentiated CA	10.7% (3/28)	0% (0/38)	0% (0/24)	NS (A vs B, B vs C, C vs A)

CA, carcinoma; NS, not statistically significant; SD, standard deviation; SM, submucosal; UD-E, post-eradication group; UD-I, current infection group; UD-U, non-infected group

Figures

Figure 1

Flow chart showing the patient selection process. Undifferentiated-type cases with confirmed HP infection status were extracted for analysis. GC, gastric cancer; ER, endoscopic resection; HP, Helicobacter pylori; UD-E, post-eradication group; UD-I, current infection group; UD-U, noninfected group

Figure 2

Relationship of time since eradication with tumor diameter, color tone, and depth of invasion in the post-eradication UD-GC cases. Por, poorly differentiated; sig, signet ring cell carcinoma; tub, tubular adenocarcinoma; UD-GC, undifferentiated-type gastric cancer