Study of the Completion of Follow-up After *Helicobacter pylori* Eradication Therapy

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ABSTRACT

Background: *Because no therapeutic regimens have an eradication rate of 100%, post-treatment evaluation is necessary to ensure that adequate eradication therapy for Helicobacter pylori has been provided. The fact that not all patients are evaluated after eradication therapy is a serious concern for both the medical care system and medical economy.*

Method: *We performed a retrospective study of 411 patients who received first-line H. pylori eradication therapy at Fuyoukai Murakami Hospital from October 1, 2014 to March 31, 2016. We calculated the rate of post-treatment follow-up at 1 year after completing the eradication therapy. In addition, we excluded 76 patients who definitely received post-treatment evaluation because of follow-up appointments with gastroenterologists (n = 29) or return visits to other physicians (n = 47) and included 335 patients in the final study population. We used logistic regression models for identifying the relevant factors contributing to the completion of post-eradication follow-up.*

Results: *The rate of completion of post-eradication follow-up was 78.8% (324/411). Multivariate analysis revealed that the adjusted odds ratios for age (≥ 48 years), gender (female) and preventive measures for gastric cancer (esophagogastroduodenoscopy after radiographic screening for gastric cancer and a desire to be examined for H. pylori infection) were 1.85 [95% confidence interval (CI): 1.11–3.09; p < 0.05], 1.89 (95% CI: 1.07–3.34; p < 0.05) and 4.01 (95% CI: 1.61–10.0; p < 0.01), respectively.*

Conclusion: *Age ≥ 48 years, female gender and preventive measures for gastric cancer were independently related to a higher rate of completion of post-eradication follow-up.*

Keywords: *Helicobacter pylori, eradication, follow-up, completion*

ABSTRAK

Latar belakang: *Mengingat tidak ada regimen terapi yang memiliki tingkat eradikasi 100%, evaluasi pasca pengobatan diperlukan untuk memastikan bahwa terapi eradikasi Helicobacter pylori yang adekuat telah diberikan. Kenyataan bahwa tidak semua pasien dievaluasi pasca eradikasi merupakan persoalan serius yang menyangkut sistem layanan kesehatan dan ekonomi kesehatan.*

Metode: *Kami melakukan sebuah studi retrospektif terhadap 411 pasien yang mendapat terapi eradikasi H pylori lini pertama di Rumah Sakit Fuyoukai Murakami dari 1 Oktober 2014 hingga 31 Maret 2016. Kami menghitung angka pemantauan lanjutan pada satu tahun pasca pengobatan terapi eradikasi. Selain itu, kami mengeksklusi 76 pasien yang diketahui secara pasti menerima evaluasi pasca pengobatan karena diketahui melakukan pertemuan untuk pemantauan lanjutan dengan ahli gastroenterologi (n = 29) atau kunjungan ulang*

ke dokter lain (n = 47) dan mengikutsertakan 335 pasien dalam populasi studi akhir. Kami menggunakan model regresi logistik untuk mengidentifikasi berbagai faktor relevan yang berkontribusi pada penyelesaian pemantauan pasca terapi eradikasi.

Hasil: *Tingkat penyelesaian pemantauan pasca eradikasi adalah 78.8% (324/411). Analisis multivariat menunjukkan bahwa adjusted odds ratios untuk umur (≥ 48 years), jenis kelamin (perempuan), dan tindakan pencegahan kanker ic cancer (esofagogastroduodenoscopi setelah penapisan radiografis untuk kanker lambung dan permintaan untuk pemeriksaan infeksi H. pylori) adalah 1.85 (95% CI: 1.11–3.09; p < 0.05), 1.89 (95% CI: 1.07–3.34; p < 0.05) and 4.01 (95% CI: 1.61–10.0; p < 0.01), secara berturut-turut.*

Simpulan: *Pada usia ≥ 48 tahun, jenis kelamin perempuan dan tindakan pencegahan kanker lambung secara independen berhubungan dengan lebih tingginya angka penyelesaian pemantauan pasca eradikasi.*

Kata kunci: *Helicobacter pylori, eradikasi, follow-up, completion*

INTRODUCTION

Helicobacter pylori infection is associated with both peptic ulcers and gastric cancer, and the International Agency for Research on Cancer has recommended population-based screening and the eradication of *H. pylori* for controlling gastric cancer.[1,2] In Japan, the number of patients receiving *H. pylori* eradication therapy has been increasing rapidly since the introduction of gastric cancer screening (ABC method) and the recent use of *H. pylori* eradication therapy for chronic gastritis.[3]

Vonoprazan (VPZ), a novel oral potassium-competitive acid blocker, was approved for *H. pylori* eradication by the Japanese health insurance program in 2015, and recent studies have shown that VPZ-based triple therapy has greater efficacy for *H. pylori* eradication than does a proton pump inhibitor (PPI)-based triple therapy.[4,5] Because no therapeutic regimens have an eradication rate of 100%, post-treatment evaluation is necessary to ensure that sufficient eradication therapy for *H. pylori* has been provided.

However, not all patients are evaluated after receiving eradication therapy. Although patients without post-treatment evaluation should be contacted and invited for a post-eradication follow-up, the medical staffs might be inclined to reduce the load of patient contact. Therefore, we investigated the relevant factors contributing to the completion of post-eradication follow-up.

METHOD

We performed a retrospective study of 411 patients who received first-line *H. pylori* eradication therapy at Fuyoukai Murakami Hospital in Aomori city from October 1, 2014 to March 31, 2016. No patients had previously received *H. pylori* eradication therapy. We used esophagogastroduodenoscopy (EGD) to confirm the absence of malignancy and a rapid urease test to diagnose *H. pylori* infection. One of two gastroenterologists initiated *H. pylori* eradication therapy and used a ^{13}C-urea breath test (UBT) for the evaluation of *H. pylori* eradication. The subjects were instructed to visit Fuyoukai Murakami Hospital for a post-eradication test at > 2 months after completing the therapy and to avoid taking PPIs, VPZ, antibiotics, ecabet sodium and polaprezinc within 2 weeks of evaluating eradication due to the likelihood of false-negative results in the UBT.[6,7]

We calculated the rate of post-treatment follow-up at 1 year after completing the eradication therapy. In addition, we excluded 76 patients who definitely received post-treatment evaluation because of follow-up appointments with gastroenterologists (n = 29) or return visits to other physicians (n = 47) and included 335 patients in the final study population. We used logistic regression models for identifying the relevant factors that contributed to the completion of post-eradication follow-up and sequentially introduced six variables—age (≥ 48 years), gender (female), residential area (Aomori city), instructor (the first author), presence of dyspepsia and preventive measures for gastric cancer (EGD after radiographic screening for gastric cancer and a desire for the diagnosis of *H. pylori* infection)—into the model. The abovementioned cut-off value for age at the completion of post-eradication evaluation was obtained using the Youden index (sensitivity = 57.3%; specificity = 60.9%) in the receiver operating characteristic curve analysis [area under the curve = 0.598; 95% confidence interval (CI): 0.528–0.668].

The present study was approved by the institutional ethics committee, and informed consent was obtained from the patients. We conducted all statistical analyses using Easy R version 1.27 and considered a $p < 0.05$ to be statistically significant.[8]

RESULTS

The rate of completion of follow-up after *H. pylori* eradication therapy was 78.8% (324/411). The patients' backgrounds of the final study population are shown in Table 1. The median age was 48 years; the median ages of those in complete and incomplete groups were 50 years (range, 14–76 years) and 44 years (range, 21–79 years), respectively.

Multivariate analysis revealed that the adjusted odds ratios for age (≥ 48 years), gender (female) and preventive measures for gastric cancer were 1.85 (95% CI: 1.11–3.09; $p < 0.05$), 1.89 (95% CI: 1.07–3.34; $p < 0.05$) and 4.01 (95% CI: 1.61–10.0; $p < 0.01$), respectively (Table 2).

DISCUSSION

In the present study, the rate of patients who underwent a post-treatment examination to determine the efficacy of *H. pylori* eradication therapy was 33% higher than the value (45.7%; 48/105) reported in a Danish study; however, the patients' backgrounds differed between the two studies.[9] Furthermore, a Canadian study reported that patients who had a formal follow-up appointment were more likely to complete the therapy [96.3% (77/80) vs. 50.0% (11/22)].[10] In the present study, all 29 patients who were excluded from the final study population had follow-up appointments with gastroenterologists and definitely received post-eradication evaluation. Thus, it is very important to make a follow-up appointment for increasing the post-eradication evaluation rate. Additionally, UBT is the best option for confirming *H. pylori* eradication, and the monoclonal stool antigen test (SAT) is a suitable alternative.[11] Confirmatory tests for eradication should be performed at least 4-8 weeks after the completion of *H. pylori* eradication therapy.[11]

We performed a UBT at least 2 months after the completion of treatment to minimize the likelihood of false-negative results. However, it became more difficult to schedule a follow-up appointment after the initiation of *H. pylori* eradication therapy, and only

Table 1. Patients' backgrounds (n = 335)

	Overall (a)	Post-eradication follow-up		(b)/(a)×100 (%)
		Complete (b) (n = 248)	Incomplete (c) (n = 87)	
Age				
≥ 48 years	176	142	34	80.7
< 48 years	159	106	53	66.7
Gender				
Female	125	103	22	82.4
Male	210	145	65	69.0
Residential area				
Aomori city	291	219	72	75.3
Others	44	29	15	65.9
Instructor				
The first author	173	129	44	74.6
Another gastroenterologist	162	119	43	73.5
Purpose of EGD				
Asymptomatic on screening	173	115	58	66.5
Detailed examination	162	133	29	82.1
Presence of dyspepsia	101	78	23	77.2
Preventive measures for GC	61	55	6	90.2
After radiographic screening for GC	49	44	5	89.8
For the diagnosis of *H. pylori* infection	12	11	1	91.7

EGD: esophagogastroduodenoscopy; GC: gastric cancer

Table 2. Results of the multivariate analysis for identifying the relevant factors contributing to the completion of post-eradication follow-up

Variables	Crude OR (95% CI)	p	Adjusted OR (95% CI)	p
Age ≥ 48 years	2.09 (1.27–3.44)	0.004	1.85 (1.11–3.09)	0.019
Female	2.10 (1.22–3.62)	0.008	1.89 (1.07–3.34)	0.027
Residing in Aomori city	1.57 (0.80–3.10)	0.190	1.36 (0.67–2.75)	0.390
Instruction by the first author	1.06 (0.65–1.73)	0.817	1.01 (0.61–1.68)	0.971
Detailed examination				
Presence of dyspepsia	1.28 (0.74–2.21)	0.381	1.46 (0.82–2.62)	0.198
Preventive measures for GC	3.85 (1.59–9.29)	0.003	4.01 (1.61–10.0)	0.003

OR: odds ratio; CI: confidence interval; GC: gastric cancer

7.1% of the overall study population (29/411) received follow-up appointments in the present study. Although patients need to be cautious of the temperature for sample preservation and avoid the collection of a watery stool sample while performing the SAT, the provision of an SAT kit when introducing *H. pylori* eradication therapy might increase the motivation for a post-treatment evaluation. Another benefit of the SAT is that the patients are not required to fast on the morning of the appointed day. In Japan, an SAT comprising an immunochromatographic assay (Rapid Testmate Pylori Antigen®, Wakamoto Pharmaceutical, Tokyo, Japan) is manufactured as an 'in-the-office' test, and the results can be rapidly obtained on the day of examination.[12]

The fact that not all patients are evaluated after receiving eradication therapy is a serious concern for both the medical care system and medical economy. Undetected failure of eradication with the first-line therapy leads to wasted medical expenditures related to diagnosis and treatment [i.e. > 10000 Japanese yen (JPY) or 91 US dollars (USD) per patient are wasted; 1 USD = 110 JPY]. If *H. pylori*-associated diseases, including peptic ulcers and gastric cancer, occur in the failure group without follow-up, the amount of wasted medical expenditures is increased. Approximately 1.5 million people per year are estimated to receive *H. pylori* eradication therapy in Japan; therefore, a large amount of the money spent on health insurance could be wasted.[13] In addition, the annual reinfection rate after successful *H. pylori* eradication was reported to be 0.22–2.0% in Japan.[14,15] If *H. pylori* infection is diagnosed in a patient who has not undergone post-eradication tests for *H. pylori*, it is impossible to distinguish reinfection from first-line eradication failure. Because only first-line and second-line *H. pylori* eradication therapies are approved by the Japanese health insurance program, it becomes difficult to select the appropriate therapeutic regimen in such cases.

The present study clearly demonstrated that age ≥ 48 years, female gender and preventive measures for gastric cancer were independently related to a higher rate of completion of post-eradication follow-up. The concern regarding post-treatment evaluation is relatively stronger among patients with any relevant factors, and the application of preventive measures for gastric cancer has the greatest impact on the completion of post-eradication evaluation. Particularly, of the 12 patients who wished to be examined for *H. pylori* infection, 11 (91.7%) patients received post-treatment examinations (Table 1); this finding indicates that the desire to be assessed for *H. pylori* infection most highly motivated patients to evaluate the results of their eradication therapy. Contrary to expectation, presence of dyspepsia was not a relevant factor; this may be because resolution of the symptom due to the treatment might have decreased the motivation for post-treatment follow-up. The Japanese Society for Helicobacter Research has stated that any '*H. pylori* infection' is considered as the indication for eradication, irrespective of the background diseases.[1] In countries, such as Japan, with a high prevalence of *H. pylori* infection and gastric cancer, *H. pylori* eradication accompanied with active screening is recommended for young people. The importance of post-treatment evaluation, particularly among patients aged < 48 years and male patients, should be emphasized in a screening test.

The present study had several limitations. First, this was a single-center study. Second, the patients' lifestyle and personality could have influenced the completion of follow-up after *H. pylori* eradication therapy; however, these data were unavailable in the patients' electronic medical records. Furthermore, statistical analyses after adjustment for numerous confounding factors, including the patients' social and clinical characteristics, could not be conducted.

CONCLUSION

Age ≥ 48 years, female gender and preventive measures for gastric cancer were independently related to a higher rate of completion of post-eradication follow-up.

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