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.

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ABSTRACT

Background

Although the relationship between *H.pylori* infection and gastric cancer has been proved in epidemiological studies and animal experiments, prophylactic effect of *H. pylori* eradication is controversial in human studies.

Methods

We conducted a large-scale, multi-center, randomized controlled open-labeled study to determine whether eradication of *H. pylori* had inhibitory effects on the development of metachronous gastric carcinomas after endoscopic resection. The study included 542 subjects including patients diagnosed with early gastric cancer, either newly diagnosed and planning to have endoscopic treatment; or in the post-resection follow-up phase after endoscopic treatment. They were randomly allocated to eradication and control arms and examined endoscopically at 6, 12, 24, and 36 months after allocation. Diagnosis of new carcinoma at another site of stomach was defined as primary endpoint. Metachronous cancers were confirmed through histological examination.

Results

Between eradication and control groups, there were no significant differences in baseline characteristics. Overall successful eradication rate was 79.6%. During follow-up of three years, metachronous gastric cancer developed in 33 cases, including 9 in the eradication group and 24 in the control group. The incidence of metachronous gastric cancer in eradication group was significantly lower than in control group both in the analysis ignoring observation period (Odds

ratio: 0.353, 95% CI: 0.161-0.775, p=0.009) and in the analysis considering it (Hazard ratio: 0.34, 95% CI: 0.16-0.70, p=0.003). Kaplan–Meier analysis revealed that the cumulative incidence of gastric cancer was different between the two groups.

Conclusions

This study showed that the eradication of *H. pylori* is indicated to prevent development of metachronous gastric cancers after endoscopic resection.

INTRODUCTION

H. pylori plays an important role in gastric carcinogenesis as almost all non-cardiac gastric cancers develop from a background of *H. pylori*-infected mucosa.[1] The World Health Organization categorized *H. pylori* as a group 1 carcinogen for gastric cancer based on results of epidemiological studies.[2-10] From animal experiments using Mongolian gerbil, it is clear that causality has almost been established.[11-14] In experimental studies, *H. pylori* eradication has been proven to have a prophylactic effect on gastric cancer.[15-17] In human studies, however, prophylactic effect of *H. pylori* eradication remains controversial. Recent non-randomized intervention studies, in which eradicated and non-eradicated subjects underwent endoscopic follow-up to assess development of gastric cancer, have suggested an inhibitory effect of *H. pylori* eradication on gastric cancer incidence.[18] However, a large-scale double-blind randomized study in China showed that gastric cancer still occurred after successful eradication of *H. pylori* and that *H. pylori* eradication did not lead to significant decrease in the incidence of gastric cancer.[19] Meta-analysis of four randomized intervention studies with gastric cancer incidence as the secondary outcome measure showed an overall Odds ratio of 0.67 but the 95% confidence interval exceeded 1.[20-24] Of interest, despite the fact that the intention-to-treat analysis in the Zhou study did not demonstrate a significant effect of *H. pylori* eradication on gastric cancer development, a significant difference between *H. pylori* positive and negative patients was found based on consequent diagnosis after *H. pylori* eradication treatment.[25] No randomized studies so far have shown a significant preventive effect of *H. pylori* eradication on gastric cancer development in the analyses planned beforehand.

In Japan, mucosal gastric cancer without concomitant lymph node metastasis is usually treated with endoscopic resection. This approach was confirmed by the gastric cancer treatment guidelines which stated that intestinal type mucosal cancer less than 20mm in diameter with no evidence of ulcer or ulcer scar was indication for endoscopic resection.[26] Endoscopic resection removes the tumor bearing and surrounding mucosa such that metachronous gastric cancer may develop at sites other than that of endoscopic resection of primary gastric cancer.[27,28] A non-randomized Japanese study involving 132 early gastric cancer patients and a multi-center historical cohort study reported that eradication of *H. pylori* after endoscopic resection reduced the development of metachronous gastric cancer.[29, 30] These studies suggested that even after the development of a primary gastric cancer, *H. pylori* eradication may have benefit. These studies, however, may have contained several biases because of their non-randomized and/or retrospective study designs. There exists a discrepancy in results between the randomized studies using subjects without history of gastric cancer and the non-randomized studies evaluating the effect of eradication after endoscopic resection of early gastric cancer. Thus it is still unclear whether *H. pylori* eradication after endoscopic resection has significant benefit. In this study, we targeted development of metachronous gastric cancers after endoscopic treatment of early stage gastric cancer. The subjects of this study had a higher risk of gastric cancer compared with those without history of gastric cancer in previous randomized population based studies. The presence of more gastric cancer events would be predicted to increase the power of this study compared to the previous population based studies.

This large-scale, multi-center, randomized controlled open-labeled trial was conducted to determine the effect of eradication of *H. pylori* on the subsequent development of metachronous gastric carcinomas after endoscopic resection.

SUBJECTS and METHODS

The details of the study design have been published elsewhere.[31] Fifty-one hospitals affiliated with the Japan Gast Study Group (JGSG) participated. Patients eligible for enrollment included those age 20 to 79 years diagnosed with early gastric cancer, either newly diagnosed and planning to have endoscopic treatment (newly diagnosed stratum); or those in whom early gastric cancer had been resected and were in follow-up phase after endoscopic treatment (post-resection stratum). Exclusion criteria were absence of an active *H. pylori* infection; development of another gastric cancer after endoscopic treatment prior to entry; and a history of gastric surgery. All subjects gave written informed consent. The study was approved by the ethics committee in each hospital.

Absence of gastric carcinoma at baseline was determined through endoscopic examination. Newly diagnosed patients underwent examination 1 to 3 months after endoscopic resection. Post-resection patients underwent endoscopy prior to random allocation. Before randomization, the presence of *H. pylori* infection was confirmed using biopsy samples. Biopsy samples were taken from two sites in the greater curvature of the antrum, two sites in the greater curvature of the upper body, and a site in the lesser curvature of the lower body. Both rapid urease test and histopathological examination were performed; positive result on at least one test was considered evidence of *H. pylori* infection. Biopsy samples were fixed in formalin, and slides were prepared with Giemsa stains for *H. pylori* diagnosis. Information regarding the status of the background gastric mucosa, the presence and severity of atrophy and existence of intestinal metaplasia were recorded for both corpus and antrum. Atrophy was endoscopically evaluated according to the

Sydney system and intestinal metaplasia was evaluated histologically.[32]

Patients satisfying entry criteria were registered through the study website by the doctors in hospitals participating in the study. Information was encoded so that initials and age were used instead of full name or date of birth. Patient data were entered into a website where software identified the strata to which participants belonged (newly-diagnosed or post-resection), and then randomly allocated them to one of two treatment arms: the eradication group in which *H. pylori* eradication therapy was given and a control group in which no eradication treatment was given. Random allocation was carried out within each stratum, Patients in the eradication group received lansoprazole 30 mg bid, amoxicillin 750 mg bid and clarithromycin 200 mg bid for one week; patients in control group received standard care but no antibiotics to eradicate *H. pylori*. Thus, the study design was a randomized open-labeled clinical trial.

Clinic visits were held 0.5, 1, 2, and 3 years after randomization during which patients were examined endoscopically for metachronous gastric cancer (new carcinoma occurring at a previously uninvolved site in the stomach) or recurrent tumors (carcinoma at the resection site). *H. pylori* status was checked using the same procedure as that for confirmation of infection at baseline. Diagnosis of new tumors was defined as primary endpoint. Recurrent tumors were considered progression of residual tumor and patients were censored upon the diagnosis of such tumor. If a subject dropped out during the follow-up period, associated data was also censored at the time of final endoscopic examination. Metachronous and residual cancers were confirmed through histological examination of samples obtained through biopsy or additional endoscopic resection.

The histological criteria of gastric cancer were defined as categories 4 and 5 using Vienna classification.[33] The study was continued until last entry patient had 3 years of follow up.

Data analyses

Final analyses were performed when the observation period for all enrolled patients reached 3 years. Exact observation period of each patient and whether she/he reached the primary end point was decided by two nonclinical investigators who remained blinded to the patient's allocation and stratum. Clinic visits and procedures occurring less than 3.5 years after randomization were considered as valid observation procedures. The first analysis did not consider observation period of each patient, or the effect of allocation (the eradication or the control groups) on incidence of metachronous carcinoma among all allocated patients (intention-to-treat analysis). Calculation was performed using unconditional logistic regression adjusted for stratification factor (newly diagnosed or post-resection). In the analyses, patients were considered to belong to their initially assigned group, irrespective of the result eradication therapy. Then, analyses taking into account observation period were performed. Using a proportional hazard model, the effect of allocation on risk of metachronous carcinoma (primary endpoint) was evaluated, adjusted for stratification factor. To exclude the effect of possible confounders, distributions of gender, age, site and size of initial lesions and interval between endoscopic resection and randomization (for post-resection patients only) were compared between the eradication and control groups with statistical significance determined using Chi-square test for gender and site, and Wilcoxon's rank sum test for age, size and

interval depending on distribution of variables. If p-values for factors were less than 0.10, the model adjusted for the factors was also calculated. Significance level of final analyses was defined as p = 0.045.

Required sample size and interim analysis

Based on a historical cohort study showing an incidence rate of 8.5 persons per 1000 person-years among those who underwent eradication and 29 among those without eradication after endoscopic resection, the required sample size was 700 person-years for each group. The significance level was defined as 5% and power as 80%.[31] For a mean observation period of 3 years, 234 patients per group (468 in total) would be required. Thus, target enrollment was set at 500 patients observed for 3 years (1500 person-years total).

Interim analysis was planned for when half of the planned total person-years was reached, namely 750 person-years. For the interim analysis the significance level was defined as p= 0.01. If the eradication group had showed significantly lower incidence of metachronous gastric cancer, the managing committee would have halted the study immediately and advised the control group to undergo eradication therapy. If the opposite significant result had been obtained, the committee would also have halted the study.

Role of funding source

The steering committee was responsible for the study design, data collection, data analysis, data

interpretation, and content of the manuscript. All authors had full access to all the data in the medical report. The steering committee had full access to the study and had final responsibility for the decision to submit for publication.

RESULTS

Enrollment

From April 2001 to July 2003, 749 patients were invited to the study, of which 201 of them did not give consent to the random allocation. Four of 548 were erroneous; a double registration of one patient, and three registrations of patients not satisfying the inclusion criteria including one *H. pylori*-negative case. Ultimately, 544 patients were enrolled and randomly allocated. Data of the 544 patients were used in analyses without considering observation period.

One patient in the eradication group and one in the control group were dissatisfied with the allocation and voluntarily withdrew from the study. Consequently, 542 patients entered the study. Thirty-seven patients left the study: one suffered harmful side effect of the eradication therapy, two died of extra-gastric diseases, and 34 failed to visit the hospital for endoscopy. Data of 505 patients were used in analysis taking into account observation period, (Fig. 1).

Baseline demographic data

Among the 505 patients followed up, there were 110 patients in the control group with newly diagnosed cancers and 140 patients in post-resection stratum. In the eradicated group there were 114 patients with newly diagnosed cancers and 141 in the post-resection strata. Time intervals between endoscopic resection and random allocation in the post-resection cases ranged from 0.0 to 15.3 years. The baseline characteristics of both groups are shown in Table 1. Between the two groups, there were no significant differences in distribution of gender, age, characteristics of the

endoscopically resected lesions or that of the background gastric mucosa. Because of the endoscopic treatment criteria for gastric cancer, 96% of study subjects overall had intestinal type mucosal cancer, with a mean size of about 10 mm. Eighty percent of subjects had moderate or severe atrophy in corpus, and more than half had intestinal metaplasia in corpus.

Interim analysis

Interim analysis was performed when total observed person-years exceeded 750. As stopping condition had not been reached, (p=0.07) the study was continued until observation period of all subjects exceeded 3 years.

Development of metachronous gastric cancer

The successful eradication rate was 79.6% (203/255) overall, 77.2% (88/114) in newly diagnosed stratum, and 81.6% (115/141) in the post-resection stratum. In the control group, the disappearance rate of *H. pylori* infection was 4.8% (12/251) over the follow-up. The observation periods were between 34 and 1277 days. Overall, 52.2% (133 cases) of eradication group and 44.8% (122 cases) received endoscopic examinations according to the protocol, 65.5% (167 cases) of the eradication group and 62.8% (157 cases) of the control group received endoscopic examination three years after study enrollment. The distribution of endoscopic procedures between the two groups is shown in Table 2. There was no significant difference between groups, and mean number of endoscopic procedures was 3.1 per case overall. The observed person-years in eradication group and control

group were 639 and 593, respectively.

During follow-up of three years after endoscopic treatment of primary gastric cancer, metachronous gastric cancer developed in 33 participants, including 9 in eradication group and 24 in control group. When adjusted for the stratification factor, eradication group showed a significantly lower frequency of metachronous cancer by the analysis ignoring observation period (Odds ratio: 0.353, 95% CI: 0.161-0.775, p=0.009). In the analysis considering observation period, metachronous gastric cancer developed in 33 of 505 participants, including 9 (3.5%) in eradication group and 24 (9.6%) in control group (Table 2). The incidence was 14.1 and 40.5 per 1000 person-years, respectively and the incidence of metachronous gastric cancer in the eradication group was significantly smaller than that in the control group (Hazard ratio: 0.34, 95% CI: 0.16-0.70, p=0.003). The effect of eradication did not differ depending on strata (newly diagnosed case or post resection), and no interaction between the strata and the allocation was observed, which was also true in the analyses done without considering the observation period. As p-value for time period between endoscopic resection and random allocation in post-resection stratum was near 0.10, a proportional hazard model that included this variable was also calculated. However, this adjustment had no effect and there was no association between this variable and incidence of metachronous carcinomas (data not shown). On the other hand, recurrence of residual cancer because of incomplete resection developed in 18 participants, including 8 in eradication group and 10 in control group. There was no significant difference in the incidence between groups.

Kaplan–Meier analysis revealed that cumulative incidence of gastric cancer differed between the

eradication and control groups (Figure 2). The risk ratio between the two groups appeared to be independent of the time from baseline. All but one of the metachronous cancers were histologically intestinal type. There were no differences between the two groups with regard to gender, age, location, histological type, depth of invasion, or diameter of metachronous cancers.

DISCUSSION

This large-scale, multi-center, randomized controlled trial evaluated the effect of *H. pylori* eradication on the development of metachronous gastric carcinomas after endoscopic resection. Those with unsuccessful eradication were included in the eradication group in analyses to evaluate the effect of *H. pylori* eradication as a clinical indication. During the three-year follow-up, metachronous gastric cancer developed in 9 subjects in the eradication group and 24 subjects in the control group (the p-value was 0.009 when the observation period was ignored and 0.003 when it was taken into account). Overall results show that *H. pylori* eradication reduces risk of developing new gastric cancer even in the highest risk group (ie, a history of a previous gastric cancer).

The consistent results increased the reliability of this result. It revealed that incidence of metachronous cancer and dropping-out was mutually independent. The results were stable even if the effect of missing and censored cases were considered. To examine the robustness of the results, we calculated the metachronous cancer cases expected if all 544 subjects were observed for 3 years without any dropping-out. From the incidence rate of metachronous cancer cases, 11 more cases (total 44 cases) would be expected. In the worst case scenario, 6 (about half of the 11) additional metachronous cancer cases would be observed in eradication group and 5 in the control group. If this occurred there would be 15 (9+6) cases in in eradication and 29 (24+5) in control group (Fisher's exact probability = 0.04). Thus, the significant difference in the primary outcome would be maintained even in the worse case scenario.

There were two primary reasons why we conducted an open-labeled study rather than a placebo controlled one. The most important was to increase the feasibility of the study as Japanese feel strong anxiety when they do not know whether th are given blinded drugs and thus often refuse to join placebo controlled trials. The other reason was that the use of placebo eradication therapy actually made little sense in that Japanese endoscopists can predict whether a patient has undergone eradication therapy or not based on the severity of redness in gastric mucosa and mucous status changes after eradication of *H. pylori*.[34,35]

Although random allocation was designed to reduce potential bias at baseline, one subject from each group voluntarily left the study at allocation, and 21 patients in control group and 16 subjects in eradication group left the study during the observation period. However, baseline characteristics were not different between the two groups except for time period between endoscopic resection and random allocation in post-resection stratum. Therefore, no bias was expected at baseline in subjects that were included in final analyses. As this is an open study, there can be observation bias toward finding metachronous cancers, the primary endpoint. Nevertheless, there was no significant difference in size or depth of invasion of metachronous cancers between the two groups. The effect of observation bias seems negligible, and we conclude that eradication of *H. pylori* is indicated after endoscopic resection of early gastric cancer. For ethical reasons, the managing committee therefore advised eradication therapy for the control group patients as well as eradication group patients with unsuccessful eradication, just after the results of final analyses were evaluated.

A Japanese prospective randomized trial of *H. pylori* eradication was originally designed with incidence of gastric cancer as primary endpoint. However, due to the low final number of participants, the endpoint was changed in order to examine the reversibility of precancerous gastritis. It revealed the difficulty in conducting properly designed intervention study for gastric cancer: It would require enrollment of thousands subjects and last for decades.[36,37] A theoretical model estimated that in high-risk countries, a sample size of 17,625 middle-aged subjects per group and follow-up period of 10 years would be required to demonstrate 50% reduction in expected increase of gastric cancer incidence after *H. pylori* eradication.[38] Gastric cancer prevention studies

designed to evaluate the long-term effect of *H. pylori* eradication have had the problem that after receiving informed consent, few participants are prepared to enter the placebo arm.[39,40] In this study, we targeted metachronous gastric cancers after endoscopic treatment of early stage gastric cancer. The subjects were those with high risk of metachronous gastric cancer, which reduced the required number of participants and shortened follow-up period. Furthermore, as they knew that they had high risk of metachronous cancer, they were not reluctant to visit clinics for endoscopic examinations frequently. These may be the reasons why this study succeeded in getting participants and follow-up period for analyses with enough statistical power.

In Japan, mucosal gastric cancer is usually resected by endoscopic treatment. As only a small part of the gastric mucosa is resected, metachronous gastric cancer after endoscopic treatment often develops at another site of the stomach. During median follow-up period of 57 months after endoscopic treatment, 14% of metachronous cancer and 11% of synchronous cancer were reported.[28] Another study reported that carcinomas existed at other sites than the main lesion in 4.8% of surgically resected stomachs.[41] Similar results were shown in other Japanese studies.[42,43] The incidence of new gastric cancer after endoscopic treatment seems consistent with the frequency of undiagnosed gastric cancers in resected stomach. The high incidence of metachronous gastric cancer may be the result of occult gastric cancers that were not detectable at the time of endoscopic treatment, but had grown enough to be diagnosed during the follow-up.

Gastric cancer risk is directly related to the degree of atrophy. In the study from China, a benefit was seen only among those with low baseline risks (without atrophy).[22] This study showed

that *H. pylori* eradication was also prophylactic in the highest risk group, (ie, those with moderate or severe atrophy and a history of prior early gastric cancer). In the current study the risk of subsequent cancer was reduced from approximately 4,000 per 100,000 per year to 1,400 per 100,000 per year and this high baseline risk and the marked reduction accounts for difference in ability to determine differences within the time frame of the study and the sample sizes used.

To our knowledge, this is the first randomized intervention study to achieve significant reduction of gastric cancer incidence according to analysis determined beforehand. As subjects of this study have history of gastric cancer, it is expected that they have specific genotypes and environmental factors. While there might be limitations in generalization of study results, the results add new proof to previous studies confirm the causal relationship between *H. pylori* infection and gastric cancer, and also support the concept of *H. pylori* eradication to prevent development of gastric cancer.[44]

CONCLUSION

This large-scale, multi-hospital, randomized controlled trial showed that the eradication of *H. pylori* is indicated to prevent development of metachronous gastric cancers after endoscopic resection.

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Contributors

KF, MK, KI, NU, SO, ST, and KA conceived and designed this study with the Japan Gast Study Group. MK was the coordinating principal investigator for the study. SK and SH analyzed and interpreted the results. MK and SK drafted the report. MA was responsible for the overall planning and conduct of the study. All authors were members of the steering committee. All authors have seen and approved the final version of the manuscript.

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Figure legend

Figure 1. Flow of study participants.

Figure 2. Kaplan-Meier analysis of cumulative incidence rate of new carcinoma.

During follow-up, metachronous gastric cancer developed 9 (3.5%) in eradication group and 24 (9.6%) in control group. The two cumulative incidence rate lines of eradication group and control group seemed to diverge gradually over time ($P<0.005$).

Table 1. Characteristics of patients who were included in the final analysis

Characteristics			Control	Eradication	p-value
Total			250	255	
Newly diagnosed			110	114	0.929*
Post-resection			140	141	
Years between endoscopic resection and randomization among post-resection patients			1.6 (1.0-3.7) †	1.2 (0.9-2.9)	0.104‡
Gender	Male		191 (76.4%)	195 (76.5%)	1.000*
	Female		59 (23.6%)	60 (23.5%)	
Age (years)			69 (64, 73)	68 (62, 73)	0.244‡
Resected lesion					
Location	Upper		33 (13.2%)	29 (11.4%)	0.471¶
	Middle		103 (41.2%)	96 (37.6%)	
	Lower		114 (45.6%)	130 (51.0%)	
Histology	Intestinal type		247 (98.8%)	253 (99.2%)	0.683*
	Diffuse type		3 (1.2%)	2 (0.8%)	
Depth of invasion		Mucosa	241 (96.4%)	245 (96.1%)	1.000*
		Submucosa	9 (3.6%)	10 (3.9%)	
Diameter (mm)			11 (8, 15)†	10 (8, 15)	0.68‡
Atrophy					
Degree in corpus					
No			1 (0.4%)	1 (0.4%)	0.817¶
Mild			35 (14.0%)	45 (17.6%)	
Moderate			109 (43.6%)	101 (39.6%)	
Severe			84 (33.6%)	86 (33.7%)	
Unknown			21 (8.4%)	22 (8.6%)	
Intestinal metaplasia					
Antrum	Negative		49 (19.6%)	48 (18.8%)	0.935¶
	Positive		172 (68.8%)	175 (68.7%)	
	Unknown		29 (11.6%)	32 (12.5%)	
Corpus	Negative		96 (38.4%)	91 (35.7%)	0.745¶
	Positive		118 (47.2%)	129 (50.6%)	
	Unknown		36 (14.4%)	35 (13.7%)	

* Fisher's exact probability
† Median (25 %ile, 75 %ile)

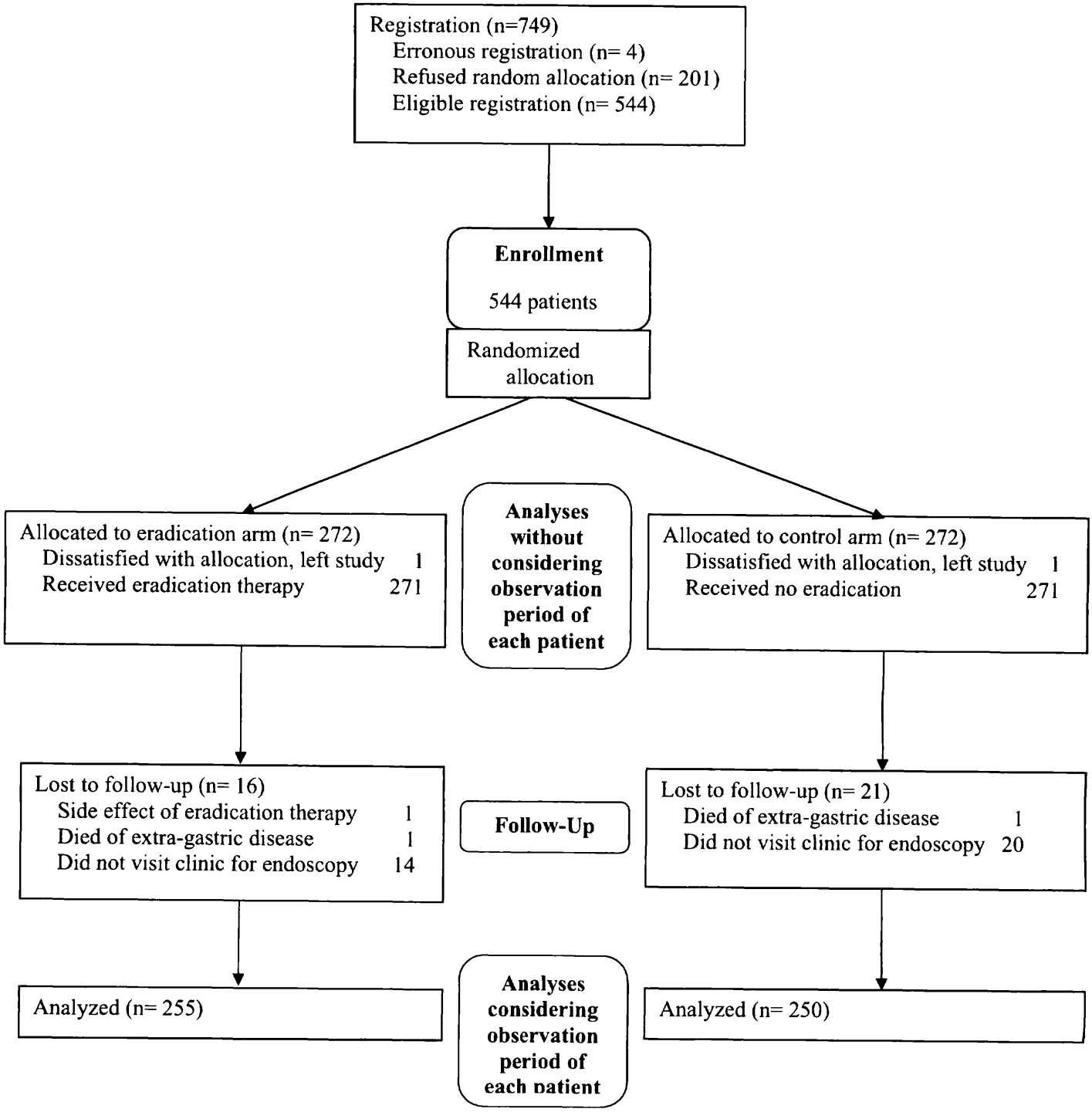
‡ by Wilcoxon rank sum test
¶ by goodness for fit test

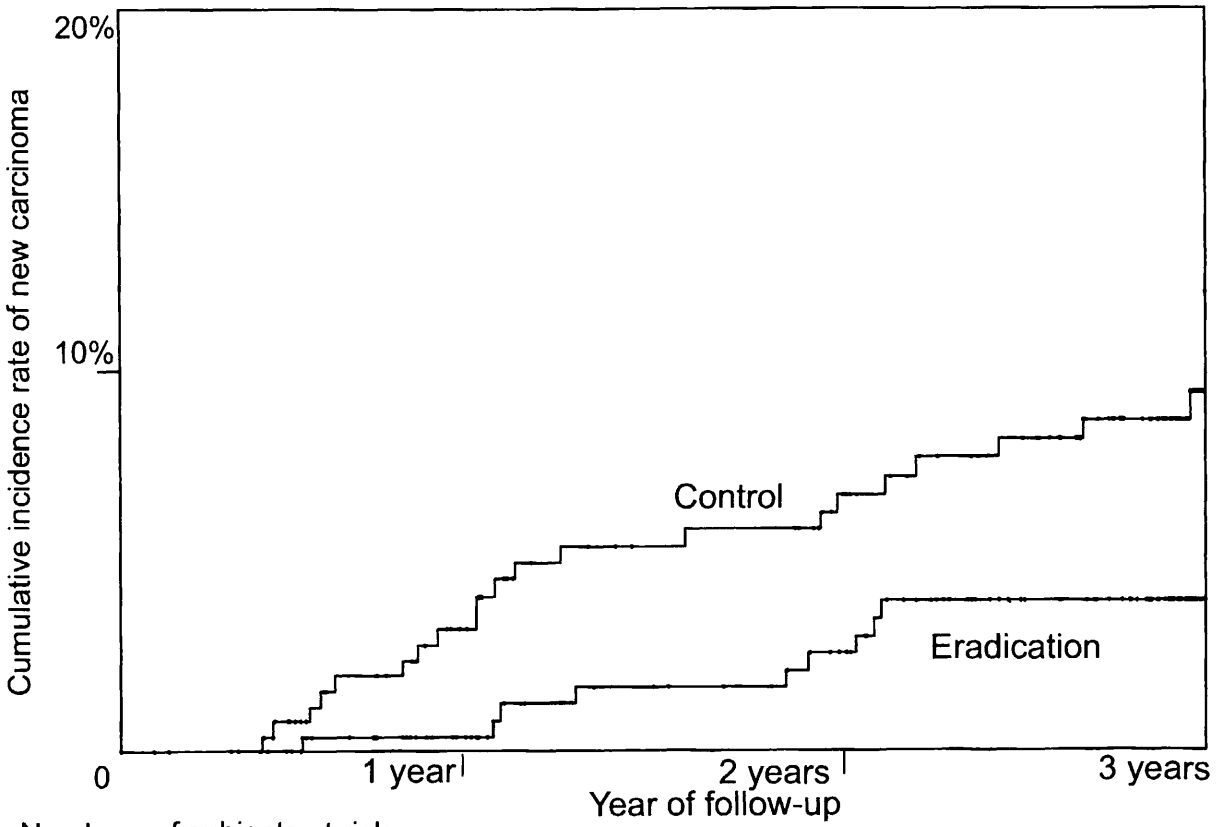
Table 2. Performed observation and incidence of new carcinoma at a site of stomach previously uninvolved

Item			Control	Eradication	p-value
Observation					
Procedure	1		37 (13.6%)	34 (13.3%)	0.890*
	2		31 (11.4%)	31 (12.2%)	
	3		60 (22.1%)	57 (22.4%)	
	4		122 (44.8%)	133 (52.2%)	
Person-years			593	639	
New carcinoma					
Incidence			24	9	
Incidence rate (per 1000 person-years)			40.5	14.1	
Hazard ratio (95% CI†)			1.0	0.339 (0.157, 0.729)‡	0.003
Gender¶	Male		21 (87.5%)	7 (77.8%)	0.597
	Female		3 (12.5%)	2 (22.2%)	
Age (years) ¶			71 (65, 74)	70 (71, 73)	0.584
Location¶	Upper		3 (12.5%)	1 (11.1%)	0.160
	Middle		8 (33.3%)	6 (66.7%)	
	Lower		13 (54.2%)	2 (22.2%)	
Histology¶	Intestinal type		23 (95.8%)	9 (100%)	1.000
	Diffuse type		1 (4.2%)	0 (0.0%)	
Depth of invasion¶		Mucosa	23 (95.8%)	8 (88.9%)	1.000
		Submucosa	1 (4.2%)	1 (11.1%)	
Diameter of carcinoma¶			7 (5, 10)	8 (7, 15)	0.383

* by goodness for fit test
† 95 % confidence interval,
‡ adjusted for whether newly-diagnosed or post-resection using a proportional hazard model.
¶ tested and expressed as in Table 1

Figure 1.


Registration (n=749)
Erronous registration (n= 4)
Refused random allocation (n= 201)
Eligible registration (n= 544)
Enrollment
544 patients
Randomized allocation
Allocated to eradication arm (n= 272)
Dissatisfied with allocation, left study 1
Received eradication therapy 271
Analyses without considering observation period of each patient
Allocated to control arm (n= 272)
Dissatisfied with allocation, left study 1
Received no eradication 271
Lost to follow-up (n= 16)
Side effect of eradication therapy 1
Died of extra-gastric disease 1
Did not visit clinic for endoscopy 14
Follow-Up
Lost to follow-up (n= 21)
Died of extra-gastric disease 1
Did not visit clinic for endoscopy 20
Analyzed (n= 255)
Analyses considering observation period of each patient
Analyzed (n= 250)



Numbers of subjects at risk				
Control	255	237	196	157
Eradication	250	250	213	167

Figure 2.