of applying EMR to all potentially endoscopically resectable lesions were size, location, and scarring from previous ulceration, so that only piecemeal removal was possible in such cases [9–11]. Unfortunately, piecemeal resection of EGC is associated with both difficulties in accurate histological assessment and a higher rate of local recurrence [12, 13]. Consequently, surgery was often chosen as the initial preferred method of treatment for lesions which were difficult to resect by EMR and those associated with difficulty in estimation of tumor depth.

A major breakthrough was achieved at the turn of the twenty-first century, with the advent of endoscopic submucosal dissection (ESD) [14–20]. ESD is a technique developed to enable the resection of large and ulcerative lesions, regardless of tumor location, that are unable to be removed using the conventional EMR procedure. The other major advantage of ESD is its ability to achieve a higher rate of en-bloc resection, thus providing more accurate histological assessment as compared to EMR [12, 21]. For the aforementioned reasons, ESD has translated into lower rates of local recurrence of gastric cancer as compared with EMR [22, 23]. The gastric cancer treatment guidelines of the Japanese Gastric Cancer Association for lesions that are considered curative by EMR are shown in Table 1 [24]. Based on the risk of lymph node metastasis determined from a large cohort of surgically treated cases of EGCs, ESD is now regarded as a curative procedure for lesions selected using the National Cancer Center expanded criteria (Table 2) [25].

Table 1 JGCA guideline criteria for endoscopic resection

Differentiated adenocarcinoma
Intramucosal cancer
≤20 mm in size without ulceration

JGCA Japanese Gastric Cancer Association

Table 2 NCC expanded histopathological criteria for curative endoscopic resection

Early gastric cancer with negligible risk of lymph node metastasis
Differentiated adenocarcinoma
No lymphatic or venous invasion
Intramucosal cancer regardless of tumor size without ulceration
Or intramucosal cancer ≤30 mm in size with ulceration
Or submucosal superficial cancer (sm1) ≤30 mm in size
Resection margin
Tumor-free horizontal margin
Tumor-free vertical margin

NCC National Cancer Center

An important advantage of ESD is that it can also be considered as improving diagnostic assessment due to the suboptimal accuracy of the endoscopic staging of EGC, which is sometimes difficult because EGC shows unclear margins due to gastritis, and depth diagnosis is not always accurate [26–28]. Thus, the use of ESD has enabled us to achieve enhanced diagnosis of lesions where it may have been difficult to estimate the tumor depth or where there was a technical difficulty in resection with EMR. The treatment strategy in which additional surgery is performed after confirmation of the histological assessment of the ER specimen has already been established as one of the therapies for EGC [29–31]. We hypothesized that ESD might reduce the rate of potentially avoidable surgery by its improvement of diagnostic and therapeutic capacity compared to that of EMR. We retrospectively investigated the relationship between the surgical and endoscopic treatment of EGC before and after the introduction of ESD, with particular attention to the rate of surgical resection and its potential consequences.

Patients and methods

We retrospectively reviewed the clinical records and endoscopic and histological reports of 2,785 consecutive patients with EGC treated by surgery with curative intent and 3,102 consecutive EGC lesions treated by ER at the National Cancer Center Hospital, Tokyo, between 1990 and 2005. Informed consent was obtained from all patients in accordance with the institutional protocol. Our primary aim in this study was to retrospectively compare the rate of potentially avoidable surgery before and after the introduction of ESD and to compare the rates of non-curative ER and rates of complications between the EMR and ESD groups. All patients and lesions were discussed and the treatment strategies were determined in weekly multidisciplinary conferences involving endoscopists, surgeons, radiologists, and pathologists. The study was divided into an EMR period (1990–1999), during which the main endoscopic modality of treatment for EGC was EMR, based on the guideline criteria of the Japanese Gastric Cancer Association (Table 1) [24] and an ESD period (2000–2005), during which ESD became the predominant method by which EGCs were endoscopically resected, based on the National Cancer Center expanded criteria (Table 2) [25].

For surgical patients, we defined cases of 'potentially avoidable surgery' as those cases with surgically resected histopathological specimens within the guideline criteria of the Japanese Gastric Cancer Association [24]. In other words, the patients with potentially avoidable surgery were those who underwent surgery for lesions curable by ER.

In the ER patients, 2,469 lesions, after exclusions, were treated by ER with curative intent; 417 lesions from the EMR group included only those lesions that were treated by EMR during the EMR period, while 2,052 lesions from the ESD group involved only those lesions that were treated by ESD during the ESD period. Another 248 lesions that were treated by ESD in the EMR period and 90 lesions that were treated by EMR in the ESD period, all with curative intent, were excluded from this study (Fig. 1). In addition, other EGCs were excluded from this study because ERs were performed for palliative purposes or because the ERs were performed for residual/recurrent lesions from previous endoscopic treatments. Palliative ERs were performed in patients who refused or were unfit for surgery because of comorbidities and for those lesions found during pre-therapeutic staging to have submucosal deep invasion (sm2) or deeper invasion, as well as those lesions with undifferentiated adenocarcinomas as revealed by biopsies. Palliative ERs included 191 lesions (150 by ESD and 41 by EMR) and residual/recurrent ERs included 104 lesions (100 by ESD and four by EMR) during each respective period (Fig. 1).

The curability of ER was divided into categories of curative and non-curative; the non-curative category included lesions that could not be precisely evaluated histologically based on the National Cancer Center expanded criteria and the tumor margins [25]. Non-curative ER was separated into two groups based on histological results: 'non-curative with positive or difficult to estimate horizontal margins only' and 'non-curative with a possible risk of lymph node metastasis irrespective of horizontal margin', based on submucosal deep invasion (sm2: ≥500 μm), positive lymphatic and/or venous invasion, intramucosal cancer more than 3 cm in size in the presence of ulceration, submucosal superficial invasion (sm1: <500 μm) in a lesion greater than 3 cm in size, predominantly undifferentiated type adenocarcinoma, and positive vertical margin (Table 3). Therefore, non-curative ERs with a possible risk of lymph node metastasis were cases of ER carried out in patients who went on to require additional surgery. In other words, these patients were those who underwent ER for lesions curable by surgery. Complications including perforation and delayed bleeding that required blood transfusion were also investigated in the EMR and ESD groups.

Clinical outcomes were analyzed using the χ^2 test and Fisher's exact test (Statview; Abacus Concepts, Berkeley, CA, USA), and $P < 0.05$ was considered statistically significant.

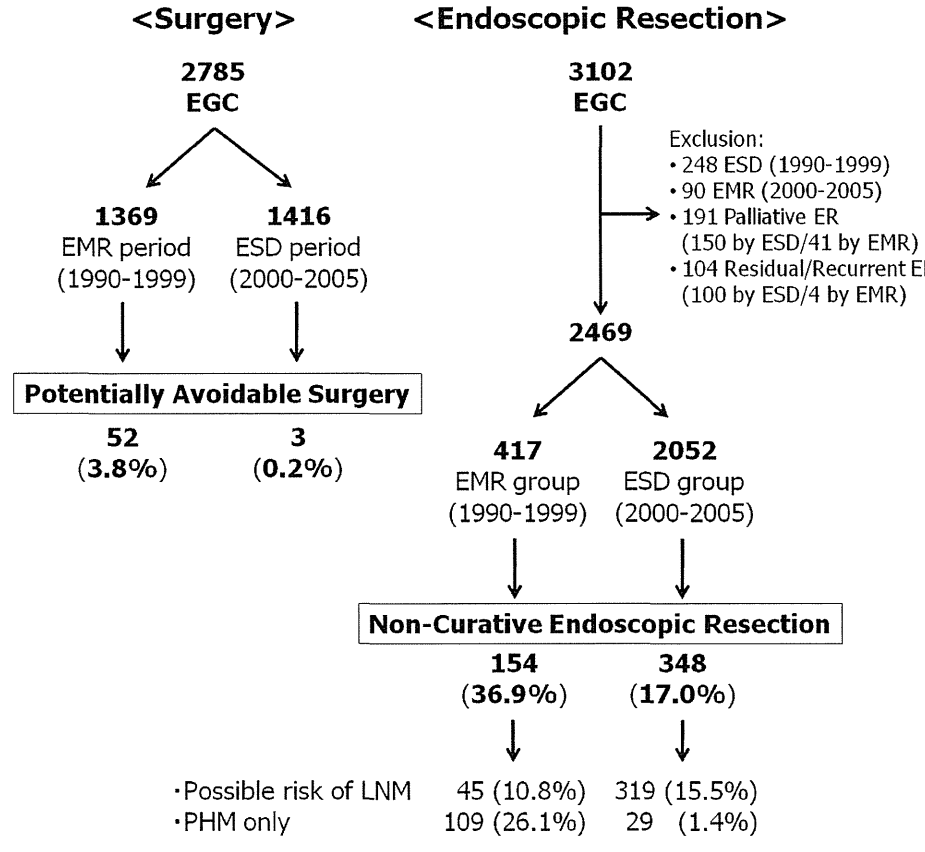

Fig. 1 Outline of the study, including rates of potentially avoidable surgery and non-curative endoscopic resection based on the histological results. *EGC* Early gastric cancer, *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *ER* endoscopic resection, *LNM* lymph node metastasis, *PHM* positive or difficult to estimate horizontal margin

Table 3 Non-curative endoscopic resection

Non-curative with possible risk of lymph node metastasis
Submucosal deep invasion (sm2)
Positive lymphatic and/or venous invasion
Intramucosal cancer >30 mm in size with ulceration
Submucosal superficial invasion (sm1) >30 mm in size
Predominantly undifferentiated type adenocarcinoma
Positive vertical margin
Non-curative with positive or difficult to estimate horizontal margins only

Table 4 Rates of potentially avoidable surgery

	EMR period (1990–1999)	ESD period (2000–2005)	*P*
Treated surgically	1,369	1,416	
Guideline lesion	52 (3.8%)	3 (0.2%)	<0.001
Technical difficulty	21	0	<0.001
Incorrect assessment	31	3	<0.001

EMR endoscopic mucosal resection, *ESD* endoscopic submucosal dissection

Results

Potentially avoidable surgery

The study results are outlined in Fig. 1. The rate of potentially avoidable surgery was 3.8% (52/1,369) in the EMR period and 0.2% (3/1,416) in the ESD period ($P < 0.001$) (Table 4). There were two possible contributory factors to potentially avoidable surgery: technical difficulty with ER and incorrect pre-therapeutic assessment of EGC. EMR was not possible in 21 patients where technical difficulty arose from there being a remnant stomach due to prior surgery; scarring from previous ulceration close to the lesion; and the location of the lesion, in particular those very close to the pylorus and the gastroesophageal junction. Thirty-one patients did not undergo EMR due to incorrect pre-therapeutic endoscopic findings suggesting submucosal invasion and unclear margins. In the ESD group, all attempted lesions were treated successfully with ESD, and, in the ESD period, there were three surgical patients with incorrect preoperative assessments with lesions thought to have submucosal invasion (Table 4).

Non-curative ER with possible risk of lymph node metastasis and positive or difficult to estimate horizontal margins only

The rate of overall non-curative ER was 36.9% (154/417) in the EMR group and 17.0% (348/2,052) in the ESD group ($P < 0.001$) (Fig. 1) (Table 5). Reasons for non-curative ER are summarized in Table 6. The rates of sm2 invasion and positive lymphatic and/or venous involvement did not differ between the two groups. However, rates of intramucosal cancer more than 3 cm in size with ulceration, sm1 lesions more than 3 cm in size, and predominantly undifferentiated type adenocarcinoma in the ESD group significantly increased compared to those in the EMR group. The rate of positive vertical margins significantly decreased in the ESD group. In Table 6, we have listed the causes of non-curative endoscopic resection. Lesions considered non-curative with possible risk of lymph node metastasis may have been considered as such for one or a combination of overlapping criteria. To put this another way, the rate of non-curative ER with possible risk of lymph node metastasis regardless of horizontal margin increased in the ESD group (15.5%; 319/2,052) compared to that in the EMR group (10.8%; 45/417) ($P < 0.01$) (Table 5). Conversely, the rate of non-curative ER with positive or difficult to estimate horizontal margins only dramatically decreased in the ESD group (1.4%; 29/2,052)

Table 5 Rates of non-curative endoscopic resection

	EMR group % ($n = 417$)	ESD group % ($n = 2,052$)	*P*
Non-curative with possible LNM	10.8 (45)	15.5 (319)	<0.01
Non-curative with PHM only	26.1 (109)	1.4 (29)	<0.001
Total	36.9 (154)	17.0 (348)	<0.001

EMR endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *LNM* lymph node metastasis, *PHM* positive or difficult to estimate horizontal margin

Table 6 Causes of non-curative endoscopic resection

	EMR group % ($n = 417$)	ESD group % ($n = 2,052$)	*P*
sm2 cancer	8.9 (37)	7.5 (153)	NS
Positive lymphatic and/or venous invasion	5.3 (22)	5.4 (110)	NS
Intramucosal cancer >30 mm in size with ulceration	0 (0)	1.7 (34)	<0.004
sm1 cancer >30 mm in size	0 (0)	2.3 (48)	<0.0003
Predominantly undifferentiated type	1.4 (6)	3.8 (79)	<0.01
Positive vertical margin	4.6 (19)	2.2 (46)	<0.007
Positive horizontal margin	31.4 (131)	3.0 (62)	<0.001

In some patients there was more than one cause

EMR endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *sm2* submucosal deep invasion, *sm1* submucosal superficial invasion, *NS* not significant

compared to that in the EMR group (26.1%; 109/417) ($P < 0.001$) (Table 5).

Complications

The rate of perforation in the EMR group (6.0%; 25/417) was significantly higher compared to that in the ESD group (3.0%; 62/2,052) ($P < 0.003$). All perforations were detected endoscopically during the procedure, except for one patient in the ESD group with a delayed perforation who had a gastric tube after esophagectomy. Seven patients in the EMR group and one patient in the ESD group underwent emergency surgery because the perforations were difficult to manage endoscopically using endoclips. Blood transfusion was required in one patient in each group.

Discussion

This retrospective study shows that the rate of potentially avoidable surgery decreased significantly and the overall non-curative ER rate also decreased with the development of ESD. In the ESD group, the rate of non-curative endoscopically resected specimens with positive or difficult to estimate horizontal margins only significantly decreased compared with that in the EMR group, but the rate of non-curative ERs with possible risk of lymph node metastasis increased significantly.

The rate of potentially avoidable surgery was 3.8% (52/1,369) during the EMR period and 0.2% (3/1,416) during the ESD period ($P < 0.001$) (Table 4). We believe this may be as a result of two factors, the technical progress of ER and improved diagnostic accuracy. The progress of ER with EMR, and now ESD, over the past two decades has involved major breakthroughs in endoscopy and has revolutionized the treatment of EGC. The advent of ESD has enabled us to achieve a higher rate of en-bloc resection in situations not possible before. These include remnant stomachs, scarring from previous gastric ulceration, and certain technically difficult locations. Despite the recent development of new technology such as narrow band and autofluorescence imaging [32, 33], there have been no significant changes in our ability to diagnose the depth of invasion of EGC [27, 28]. Other studies have reported that the endoscopic staging of EGC is not always accurate and is correct in only 80–90% of cases, even with endoscopic ultrasonography [26, 34–36]. In our study, we found that incorrect preoperative assessments such as endoscopic overstaging leading to potentially avoidable surgery dropped significantly with the use of ESD (Table 4), but we believe that the increased use of ESD for enhanced diagnosis, rather than improvements in other diagnostic modalities, resulted in this reduction.

For reference, the rate of surgery for lesions included within the National Cancer Center expanded criteria was 4.7% (67/1,416) during the ESD period (data not shown). These lesions consisted of 18 intramucosal cancers >20 mm without ulceration, 33 intramucosal cancers ≤30 mm in size with ulceration, and 16 sm1 cancers ≤30 mm in size. It is believed that surgery on some of these lesions was potentially avoidable, but a direct comparison using the guideline criteria of the Japanese Gastric Cancer Association and the National Cancer Center expanded criteria cannot be made because of differences between the two sets of criteria.

The rate of non-curative ER, secondary to positive or difficult to estimate horizontal margins only, in the ESD group (1.4%; 29/2,052) significantly decreased compared to that in the EMR group (26.1%; 109/417) ($P < 0.001$) (Table 5). This reflects the inability of EMR to resect large lesions en bloc, the lesion often being resected in multiple fragments, making it difficult to ensure complete resection [9–11]. The other main problem that arises with performing EMR, even for small lesions, is the uncertainty regarding inaccurate resection margins. Several previous articles have reported higher rates of local recurrence caused by piecemeal resection and positive tumor margins [12, 13, 22, 23, 37]. The development of ESD has addressed these problems, as it enables an en-bloc resection with tumor-free margins.

On the other hand, the rate of non-curative ERs with possible risk of lymph node metastasis (which should ideally be managed by gastrectomy with lymph node dissection) increased in the ESD group (15.5%:319/2,052) compared to that in the EMR group (10.8%:45/417) ($P < 0.01$) (Table 5). This five percent difference could have occurred due to several reasons, but the primary cause was most likely the increase in the number of patients who underwent diagnostic ESD for borderline lesions which were either difficult to resect technically by EMR or difficult to estimate tumor depth accurately. Specifically, the introduction of the National Cancer Center expanded criteria and the ability of ESD to resect larger lesions are two possible reasons for the increase in the number of intramucosal cancers more than 3 cm in size with ulceration and sm1 lesions more than 3 cm in size for which ER was undertaken. An increase in the number of lesions with predominantly undifferentiated adenocarcinoma also occurred, most likely because the heterogeneity of gastric carcinoma may increase in larger-size lesions. Thus, this five percent rise in the rate of non-curative ERs with possible risk of lymph node metastasis has to be weighed against the potential advantages in undertaking ESD and the significantly reduced rate of potentially avoidable surgery. Oda et al. [31] reported that the actual rate of lymph node metastases, as determined from surgically resected

specimens, in a group of cases of 'non-curative ESD with possible risk of lymph node metastasis', was 6.3%. This emphasizes the fact that this cohort of patients should receive additional surgery.

In the present study, the rate of perforation in the EMR group (6.0%) was significantly higher compared to that in the ESD group (3.0%) although it is widely recognized that the rate of perforation with ESD is higher than that with EMR [22]. There is no evident explanation for this result, but one possible reason may be that EMR procedures were performed more aggressively because of curative intent in the EMR group.

The surgically resected stomach never returns to its natural state. Currently, the pathway whereby we use ESD as the optimal therapeutic strategy for the treatment of EGC seems to reduce the rate of potentially avoidable surgery and allows us to more appropriately select those cases that would benefit from additional surgery, as it enables more accurate histological assessment, particularly in difficult EGC cases. As a result, this pathway has brought about major benefits for patients by reducing potentially avoidable surgery, because with this strategy the final diagnosis is obtained with higher reliability due to precise feedback from histological assessments. However, it would be prudent to advise caution in performing ESD for EGC unless the indications have been carefully reviewed in the individual to ensure that the EGC is within the established selection criteria. We would emphasize that recognition of resectability and curability are two very different matters. It is also important to recognize the role of ESD in providing enhanced diagnostic information, thus contributing to the optimal therapy being undertaken for the appropriate indication.

Limitations

This study was retrospective and there were differences in criteria for ER between the two groups. In addition, the transitional phase was at the turn of the twenty-first century, but it was not clearly delineated as both procedures were being used at that time. However, we believe that by analysis by procedure (EMR and ESD) we have minimized the impact of this last factor.

Conclusions

We believe that a pathway of undertaking ESD in lesions where it may be difficult to estimate the depth of invasion and in technically difficult cases results in a significant decrease in the rate of potentially avoidable surgery, this being due to the advantages associated with not only a potentially curative procedure, but also one which provides enhanced diagnostic information and consequently enables more appropriate therapy.

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Conflict of interest None.

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Should Elderly Patients Undergo Additional Surgery After Non-Curative Endoscopic Resection for Early Gastric Cancer? Long-Term Comparative Outcomes

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OBJECTIVES: Endoscopic resection (ER) including endoscopic submucosal dissection has been widely accepted for treatment of early gastric cancer (EGC) in Japan. Additional surgery is recommended when ER is non-curative histologically. Many elderly patients, however, do not undergo radical surgery due to comorbid disease or limited life expectancy. The aim of this study is to assess the survival outcomes of radical surgery compared with observation only in elderly patients after non-curative ER.

METHODS: We reviewed existing data of all elderly patients (older than 75 years) who had undergone ER for EGC at the National Cancer Center Hospital between January 1999 and December 2005. We compared the overall and disease-free survival rates between three patients groups: curative ER, non-curative ER with additional surgery, and non-curative ER without additional surgery.

RESULTS: In total, 428 patients underwent ER; 308 (72%) curative ER and 120 (28%) non-curative ER. Of the 120 non-curative ER patients, 38 patients (31.7%) underwent additional surgery and 82 patients (68.3%) were followed without surgery. There was no significant difference in American Society of Anesthesiologist score between three groups. Patients who did not undergo surgery tended to be older. Overall 5-year survival rates in the curative ER, non-curative ER with surgery, and non-curative ER without surgery were 85, 92, and 63%, respectively. There was no significant difference in overall and disease-free survival between patients in the curative ER and non-curative ER with surgery groups. On the contrary, a significant difference in overall and disease-free survival was evident between the curative ER and non-curative ER without surgery groups (hazard ratio (95% confidence interval): 1.89 (1.08–3.28), 2.30 (1.35–3.94)).

CONCLUSIONS: In our elderly patient cohort, additional surgery following non-curative ER improved overall and disease-free survival compared with non-surgical observation only. Thus, surgery should be considered following non-curative ER in EGC patients >75 years of age.

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INTRODUCTION

Life expectancy in elderly patients has increased dramatically worldwide (1,2). Although surgical techniques and preoperative management have improved minimally invasive curative treatment is preferable for the elderly, particularly for early stage cancer (EGC).

Endoscopic resection (ER) has been accepted as standard treatment for EGCs that meet guideline or expanded criteria (3,4), which have a low risk of lymph node metastasis. Following ER, meticulous pathological evaluation of the resected specimen is used to stratify patient management. Patients with lesions that meet the guideline or expanded criteria are followed closely, whereas those who have had a non-curative ER are considered for additional surgery.

Gastrectomy is associated with high surgical risk for the general population. Partial or total gastrectomy is also associated with short and long-term morbidity, and mortality (5,6). Furthermore, the majority of elderly patients who are 75 years or older

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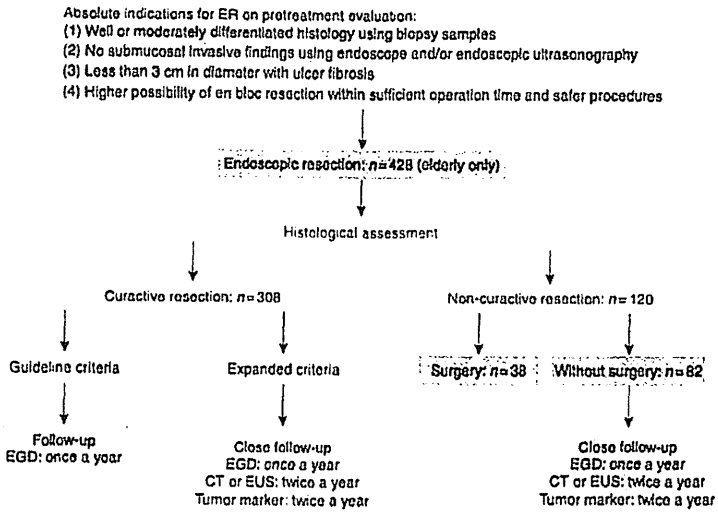

Figure 1. Flowchart of critical procedure. CT, computed tomography; EGD, endogastroduodenoscopy; ER, endoscopic resection; EUS, endoscopic ultrasonography.

have multiple diseases and functional disorders influencing daily life (7,8). In this study, we describe the long-term outcomes of ER for EGC in patients aged 75 years or older. We primarily aim to determine whether lesions beyond the guideline or expanded criteria in this elderly cohort can be treated adequately with ER alone.

METHODS

Study design

We reviewed existing data on all patients who had undergone ER for EGC at the National Cancer Center Hospital, Tokyo, between January 1999 and December 2005. Patients whose lesions did not meet criteria for ER following preoperative diagnosis were excluded. We defined elderly patients as 75 years or older (7). Elderly patients were divided into three groups: curative ER, non-curative ER with additional radical surgery, and non-curative ER without surgery. We used the American Society of Anesthesiologist (ASA) score and Charlson Index (9) as a measurement of patients overall health status, and surgical risk. All patients provided written informed consent.

Method

Starting in 1999, our institution has routinely followed a standard protocol for the ER of EGC.

Indication for ER

Indication criteria for ER—"differentiated histology," "macroscopic absence of submucosal invasive findings using endoscope and/or endoscopic ultrasonography," "lesion size- <3 cm in diameter with ulcer fibrosis," and "high probability of safe en bloc resection with short procedure duration." Patients deemed unfit for open surgery due to their general condition were also judged to be poor candidates for ER (**Figure 1**).

Historical assessment

Resection specimens were classified according to the Japanese Classification for Gastric Carcinoma (10). In this study, ER was declared curative when the specimen showed en bloc resection with margins free of cancer and if applicable, met the expanded criteria: (i) intramucosal cancer, differentiated type, no lymphatic or/and venous invasion, and no ulceration, irrespective of tumor size; (ii) intramucosal cancer, differentiated type, no angiolymphatic invasion, and tumor <3 cm in size, irrespective of ulceration findings; (iii) minimally invasive submucosal cancer (invasion depth ≤500 μm, sm1), differentiated type, no lymphatic or/and venous invasion, and tumor <3 cm in size.

Post ER management

All patients were followed according to our standard protocol (**Figure 1**). Surveillance upper endoscopy was performed annually. Curative cases with expanded criteria also underwent abdominal computed tomography or endoscopic ultrasonography and tumor-marker studies (carcinoembryonic antigen, CA19–9) every 6 months to exclude lymph node or distant metastasis. Patients who underwent non-curative ER and were deemed fit for surgery were referred and consented for radical resection and lymph node dissection. Patients with the non-curative ER without surgery due to physician judgment or strong patient refusal were followed up by the same protocol as patients with curative resection with expanded criteria.

Statistical analysis

Differences in patient characteristics between the three groups were examined by χ^2 test. Survival curves were calculated using the Kaplan–Meier method. To compare overall and disease-free survival among the treatment status, Cox proportional-hazards model was performed to estimate hazard ratio (HR) and 95% confidence interval (CI). The following covariates were included

in the multivariable analyses: age, sex, ASA score, past history of cancer (stratified by cancer stage), and comorbid illnesses. We also compare the overall and disease-free survival in the multivariable analyses included age, sex, and Charlson Index. All *P* values reported are two-sided, and significance level was set at $P<0.05$. All statistical analyses were performed with the SAS software version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

Patient characteristics

A total of 2,012 cases (2,399 lesions) of EGC were treated endoscopically at the National Cancer Center Hospital between January 1999 and December 2005. Of these, 1,947 cases (2,331 lesions) met the indication for ER following preoperative diagnosis. In all, 428 (519 lesions) of the 1,947 cases were elderly (75 years or older). Of these cases in elderly patients, 26 lesions were treated by endoscopic mucosal resection and 493 lesions were treated by endoscopic submucosal dissection. A total of 308 elderly patients (72%, 308/428) had a curative ER and 120 patients (28%, 120/428) had a non-curative ER. Of the 120 patients with non-curative ER, 38 patients (31.7%, 38/120) underwent radical surgery and 82 patients (68.3%, 82/120) were followed without surgery.

Patient characteristics are summarized in **Table 1**. ASA score of all patients except nine was 2. In all, 312 patients (72.9%, 312/428) were Charlson Index 2, 65 patients (15.2%, 106/428) were 3, 41 patients (9.6%, 41/428) were 4, and 10 patients were over 5 (2.3%, 10/428). There was no significant difference in ASA score and Charlson Index between three groups (ASA score, $P=0.17$; Charlson Index; $P=0.33$). There was a significant difference in age and the prevalence of cardiovascular disease. Patients who did not undergo surgery tended to be older.

Reasons for not undergoing surgery in the remaining 82 patients included patients' choice ($n=29$), physicians' judgment ($n=45$) (including 10 very elderly (mean age 84 years), one with chronic renal dysfunction, one with ventilatory impairment and one with aneurysm of the thoracic aorta, concomitant cancer in other organs ($n=7$)) and unknown ($n=8$).

Table 1. Patient characteristics

	Curative resection	Non-curative resection with surgery	Non-curative resection without surgery
Number of patients (%)	308 (72.0)	38 (8.9)	82 (19.2)
Age, mean (s.d.)	78.8 (3.3)	76.9 (2.3)	80.1 (3.9)
Gender ratio, men: women	228:80	32:6	67:15
Concomitant disease (%)			
Cancer	59 (19.2)	3 (7.9)	13 (15.9)
Cardiovascular diseases	48 (15.6)	16 (42.1)	11 (13.4)
Diabetes	29 (9.4)	6 (15.8)	7 (8.5)
Respiratory diseases	6 (1.9)	1 (2.6)	3 (3.7)
Other diseases	15 (4.9)	2 (5.3)	6 (7.3)
ASA score (%)			
2	304 (100)	37 (100)	78 (98.7)
3	0	0	1
Missing information	4	1	3
Charlson Index			
2	232 (75.3)	25 (65.8)	55 (67.1)
3	43 (14.0)	8 (21.1)	14 (17.1)
4	25 (8.1)	4 (10.5)	12 (14.6)
5+	8 (2.6)	1 (2.6)	1 (1.2)

ASA, American Society of Anesthesiologists.

Survival

The median follow-up period in the curative ER, non-curative ER with surgery, and non-curative ER without surgery was 40.6, 43.1, and 38.1 months, respectively. Overall 5-year survival in each group was 84, 95, and 63%, respectively (**Table 2**). Using ASA score, age, sex, clinical stage of cancer in past history, and past history of diseases, there was no significant difference in overall and disease-free survival between the patients with curative ER ($n=308$) and non-curative ER with surgery ($n=38$). On the contrary, a significant difference in overall and disease-free survival was evident between the patients with curative ER ($n=308$) and non-curative ER without surgery ($n=82$) (HR (95% CI): 1.89 (1.08–3.28), 2.30 (1.35–3.94); **Table 2, Figure 2**). The multivariable analysis using Charlson Index, age, and sex shows a statistical difference in overall and disease-free survival between the patients with curative ER and non-curative ER without surgery (HR (95% CI): overall survival, 2.35 (1.36–4.05); disease-free survival, 2.76 (1.64–4.67)).

In total, 59 patients (13.8%, 54/428) died during this study period. The majority (55.9%, $n=33/59$) of deaths occurred in the curative ER group followed by the non-curative ER without surgery group (40.7%, $n=24/59$). Only two (3.4%) deaths occurred in the group who had non-curative ER with surgery. Of the 428 patients, 1.2% ($n=5$) died as a result of gastric cancer and 12.6% ($n=59/432$) died from another causes (**Table 2**). Of the five patients who died of gastric cancer, one patient died from metachronous advanced gastric cancer following curative ER of the index lesion. Four patients in the non-curative ER without surgery died from lymph node metastasis or distant metastasis. There were no deaths from cancer recurrence in the non-curative ER with surgery.

Survival according to the risk of lymph node metastasis

We divided non-curative ER groups into two groups according to the risk of lymph node metastasis: A—high risk ("positive lymphatic or/and venous invasion" or "submucosal deep (sm2) invasion") and B—low risk (other reasons except high risk of lymph node metastasis such as intramucosal cancer >30 mm in size with ulcer findings and minute submucosal cancer

Table 2. Hazard ratio (HR) and 95% confidence intervals (CIs) of overall survival according to curability

	Number of deaths (death from gastric cancer)	Five-year survival rate (%)	Crude		Multivariable adjusted[a]	
			HR	95% CI	HR	95% CI
Curative ER	33 (1)	84	1.00		1.00	
Non-curative ER with surgery	7 (0)	95	0.52	0.13–2.17	0.70	0.16–2.98
Non-curative ER without surgery	24 (4)	63	2.62	1.54–4.46	1.89	1.08–3.28

ASA, American Society of Anesthesiologist; ER, endoscopic resection.
[a]Adjusted for age, sex, ASA score, clinical stage of cancer in past history, and past history of diseases (cardiovascular diseases, diabetes mellitus, respiratory diseases, and others).

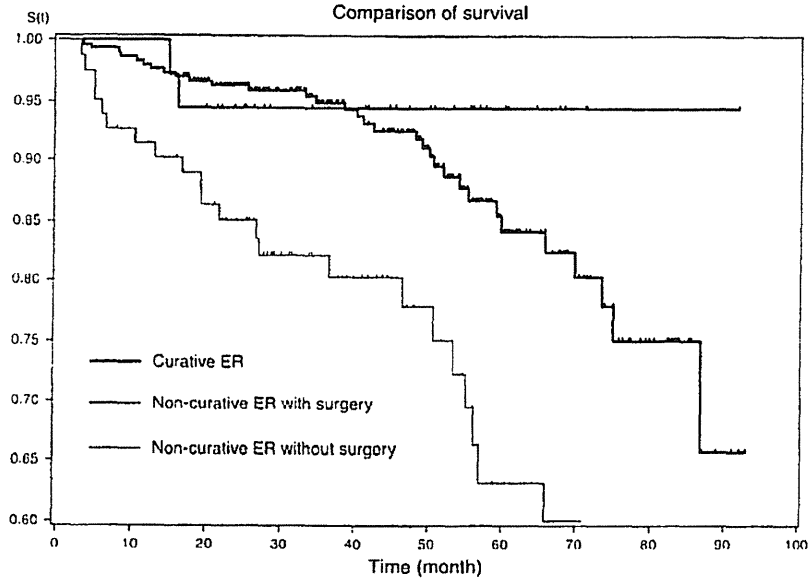

Figure 2. Survival for elderly patients (overall survival). ER, endoscopic resection.

(sm1) >30 mm in size). Among the non-curative ER patients, 29 of the 67 high-risk patients (43.3%) underwent additional surgery compared with only 9 patients of the 53 low-risk patients (17.0%). **Table 3** shows overall survival according to the risk of lymph node metastasis using ASA score, age, sex, clinical stage of cancer in past history, and past history of diseases. Overall 5-year survival rate in non-curative ER-A without surgery group was lowest (52%). There were significant difference in overall and disease-free survival between the patients with curative ER (n=308) and non-curative ER-A without surgery group (HR (95% CI): 3.31 (1.67–6.58), 4.26 (2.20–3.94); **Table 3**). In the multivariable analysis using Charlson Index, age, and sex, a statistical significance was evident in overall and disease-free survival between the patients with curative ER and non-curative ER-A without surgery (HR (95% CI): overall survival, 4.15 (2.18–7.89); disease-free survival, 5.30 (2.85–9.84)).

DISCUSSION

Surgery continues to be the mainstay of treatment for gastric cancer—with a reported high resection rate (96%) and a low surgical complication rate (8%) even in elderly patients (11). However, 5-year survival after surgery in elderly patients varies among institutions, and is reported to be 69–74% for EGC. This is compared with 5-year survival rates of >90% in young and middle-aged patients (12). Age-related disease, in fact, is the main etiology of the relatively low survival in elderly patients. Thus, less invasive surgical treatment is desirable in the elderly, and ER is attractive in this respect.

ER targets EGC lesions that have a negligible likelihood of lymph node metastasis, estimated at <1% for intramucosal cancer and <3% for submucosal invasive cancer (4). Several recent studies have reported that endoscopic submucosal dissection can be carried out on larger lesions resulting in a high rate of cancer-free

Table 3. Hazard ratio (HR) and 95% confidence intervals (CIs) of overall survival according to the risk of lymph node metastasis

	Number of subject	Number of deaths (death from gastric cancer)	Five-year survival rate (%)	Crude		Multivariable adjusted*	
				HR	95% CI	HR	95% CI
Curative ER	308	33	84	1.00		1.00	
Non-curative ER-A with surgery	29	1 (0)	96	0.36	0.05–2.66	0.54	0.07–4.07
Non-curative ER-B with surgery	9	1 (0)	89	0.96	0.13–7.01	1.09	0.15–8.14
Non-curative ER-A without surgery	38	14 (3)	52	4.72	2.52–8.85	3.31	1.67–6.58
Non-curative ER-B without surgery	44	10 (1)	71	1.55	0.75–3.22	1.17	0.56–2.47

ASA, American Society of Anesthesiologist; ER, endoscopic resection.
*Adjusted for age, sex, ASA score, clinical stage of cancer in past history, and past history of diseases (cardiovascular diseases, diabetes mellitus, respiratory diseases, and others).

margin (13,14). Long-term survival of EGC patients undergoing ER with expanded criteria has been equal to those undergoing ER with original guidelines (15). Expanded criteria for ER of larger tumors may benefit elderly patients with EGC (16).

As a general rule, additional surgery should be recommended for patients when curative ER is not achieved (17), as EGC surgical outcomes are known to be excellent (11). Our study provides long-term survival data of EGC in an elderly cohort. We demonstrate the efficacy of curative ER for EGC, showing a similar 5-year survival rate among elderly patients with curative ER and non-curative ER with surgery. We found that when curative ER was not achieved, elderly patients appeared to benefit from subsequent surgical gastrectomy. Furthermore, patients who had a non-curative ER without surgery and were established to have a high risk of lymph node metastasis had the lowest overall 5-year survival rate of 52%.

It was reported that lymphovascular involvement and massive submucosal penetration had a significant association with lymph node metastasis in EGC (18). From our data, there were significant difference in overall and disease-free survival between the patients with curative ER and non-curative ER-A without surgery group. Lymphovascular involvement or massive submucosal penetration was more frequent in surgical patients than in non-surgical patients. It is likely that the physician suggested additional surgery to these patients with high risk of lymph node metastasis. Considering the patient's age and the risk of lymph node metastasis in this recommendation.

Notably, the patients with the non-curative ER without surgery did not undergo additional surgery primarily due to subjective measures. Thus, although the treating physician routinely discussed and recommended radical surgery to all patients with non-curative ER, individual factors such as comorbid disease, reason for non-curative ER, age, and patient preference ultimately influenced treatment decisions. These conditions are subjective and cannot be expressed numerically, and are an inherent limitation of our retrospective study.

In conclusion, following non-curative ER for EGC, especially with lymphovascular involvement or massive submucosal penetration, additional surgery is recommended in elderly patients.

CONFLICT OF INTEREST

Guarantor of the article: Chika Kusano, MD, PhD.

Specific author contributions: Conceptualization, data analysis, and script preparation: Chika Kusano and Motoki Iwasaki; endoscopic diagnosis and treatment: Takuji Gotoda and Ichiro Oda; data collection: Chika Kusano, Ichiro Oda, and Takuji Gotoda; critical reviewer of the paper: Ichiro Oda, Takuji Gotoda, Tonya Kaltenbach, and Abby Conlin. All authors have read and approved the submitted version of the paper.

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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Endoscopic resection (ER) has been accepted as standard treatment for early gastric cancers, which have a low risk of lymph node metastasis.
- ✓ Additional surgery with lymph node dissection should be recommended for patients when curative ER is not achieved.
- ✓ Deciding whether or not to pursue gastric surgery or not is particularly complex in elderly patients who often have comorbidities and limited life expectancy.

WHAT IS NEW HERE

- ✓ A significant difference in overall and disease-free survival was evident between the patients with curative endoscopic resection (ER) and non-curative ER without surgery (hazard ratio (95% confidence interval): 1.89 (1.08–3.28), 2.30 (1.35–3.94)).
- ✓ Overall and disease-free survival of non-curative ER with "positive lymphatic or/and venous invasion" or "submucosal deep (sm2) invasion" are lowest.
- ✓ After non-curative ER for early gastric cancer, especially with lymphovascular involvement or massive submucosal penetration in historical findings, additional surgery is necessarily even in elderly patients.

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特集

Helicobacter pylori 感染とペプシノゲン

Helicobacter pylori 感染率減少時代における新しい対策型胃がん検診システム構築に向けての試み
—GALAPAGOSS Study—

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胃がん検診は，X線検査のみがいくつかの症例対照研究によって死亡率減少効果を示したことにより対策型検診として推奨されている．一方で近年，血清検査を用いた効率的な胃がん検診法が提唱されている．しかし，内視鏡検診も含めて有効性の評価がなされていないのが現状である．そこで，新しい胃がん検診システムの評価をおこなうことを目的として，「X線検査・精査内視鏡検査群」（バリウム検診群）と「抗 *H. pylori* 抗体＋ペプシノゲン測定・内視鏡検査群」（血清胃癌リスク検診群）の無作為化比較対照試験をスタートさせた．

KEY WORDS
対策型胃がん検診，症例対照研究，無作為化比較対照試験，血清胃癌リスク検診，バリウム検診

はじめに

胃癌の definite carcinogen である *Helicobacter pylori*（*H. pylori*）感染率が劇的に減少する時代において，効率的な対策型胃がん検診システムの構築は急務である．現在の X 線検査は *H. pylori* 感染がきわめて高く胃癌罹患が高率な時代には十分に機能してきた．さらに，胃癌の早期発見の重要性を広く国民に認識させたことでは世界に類をみないシステムであったことは事実であろう．しかし，胃癌発癌年齢においても *H. pylori* 感染率が 20%程度になる 2020 年後以降，将来にわたって持続可能で効率的な新たな胃がん検診システムの開発が望まれる．

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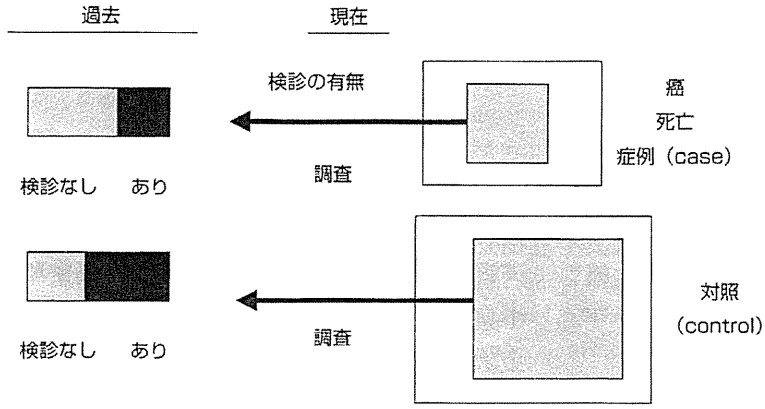
表❶　がん検診の種類

対策型検診 Organized Screening	任意型検診 Opportunistic Screening
集団の死亡率減少が目的	個人の死亡リスクの減少が目的
市町村がおこなう集団検診や個別検診が該当	総合検診や人間ドッグが該当
費用は公費補助	費用は自己負担
プログラム全体がモニタリングされている	プログラム全体のモニタリングはおこなわれていない



図❶　症例対照研究の概念
疫学の研究方法のひとつで，最初にすでに疾病にかかった人を「症例（case）」として抽出し，この「症例（case）」と性別や年齢などの要因が似た人を「対照（control）」として選び出し，「症例（case）」と「対照（control）」の双方に対して疾病の原因と考えられる要因（たとえば食生活，嗜好品など）を過去にさかのぼって調査し両者を比較する研究方法．

1．胃がん検診とエビデンスレベル

厚生労働省がん研究班（垣添忠生班長）による「有効性評価に基づく胃がん検診ガイドライン」にて[1]，胃X線検査による対策型胃がん検診（表❶）は死亡率減少効果を示す相応な証拠があるので，対策型および任意型検診として実施することを勧める，との結論が出された[2]．

がん検診の有効性を証明するための指標は，2004年度厚生労働省がん研究助成金（がん検診の適切な方法とその評価法の確立に関する研究班；主任研究者：祖父江友孝，有効性に基づくがん検診ガイドライン作成手順）にしたがえば，死亡率で死亡率減少効果についての証拠レベルを判定し推奨グレードが決定される[3]．胃X線検査の有効性の科学的根拠となる文献は症例対照研究（図❶）[4)~6)]とこれらの研究のメタ解析[7]によるもので，男女とも胃癌死亡率の減少効果が証明されている〔男性オッズ比（OR）：0.39，95%CI：0.29～0.52/女性OR：0.50，95%CI：0.34～0.72〕．症例数は阿部らの研究（日消誌，1995年）が最も多く，症例820人，対照2,413人である〔男性オッズ比（OR）：0.371（99% CI：0.242～0.568），女性OR：0.458（99% CI：0.263～0.797）〕．これらの研究のエビデンスレベルは2＋＋（死亡率減少効果について一致性を認める，質の高い症例対照研究/コホート研究が複数おこなわれている）で，推奨グレードはB（死亡率減少効果を示す相応な証拠があるので，実施することを勧める）となっている（表❷）．

ちなみに，エビデンスレベルは1＋＋（死亡率減少効果について一致性を認める，質の高い無作為化比較対照研

表❷ 対策型胃がん検診の有効性評価

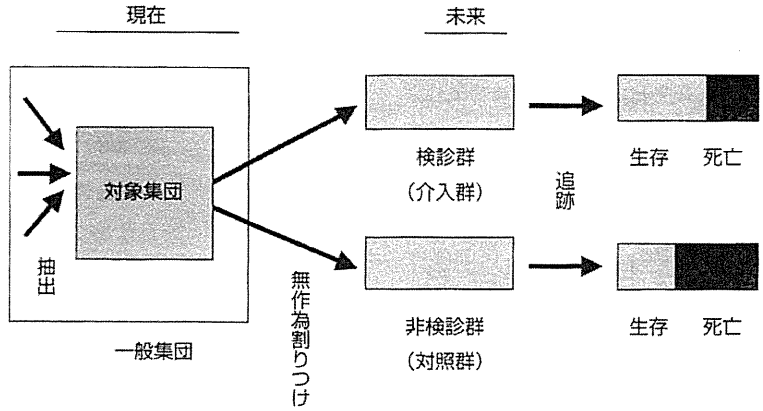
方法	推奨グレード	実施体制別の推奨	
		対策型	任意型
胃X線検査	B	○	○
胃内視鏡検査	I	×	△
ペプシノゲン法	I	×	△
H. pylori 抗体	I	×	△

推奨グレード

A：死亡率減少効果を示す十分な証拠があるので，実施することを強く勧める．

B：死亡率減少効果を示す相応な証拠があるので，実施することを勧める．

I：死亡率減少効果の有無を判断する証拠が不十分であるため，対策型検診として実施することは勧められない（任意型検診として実施する場合には，効果が不明であることと不利益について十分説明する必要がある）．

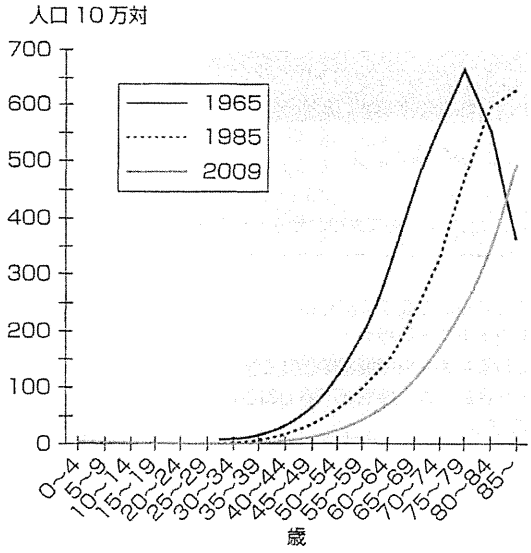


図❷ 無作為化比較対照研究

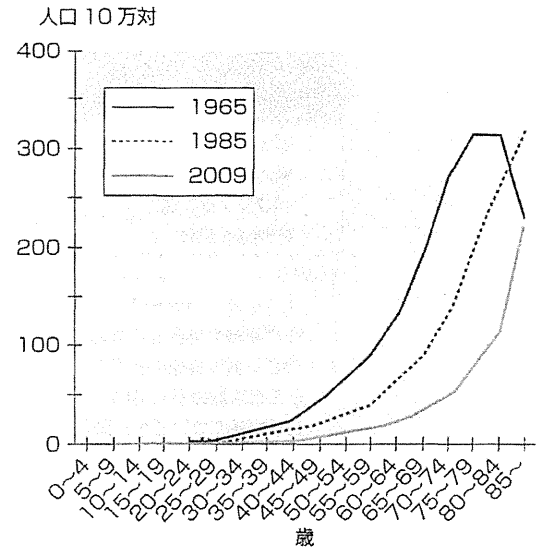
予防・治療の効果を科学的に評価するための介入研究で，対象者を無作為に介入群（検診など，決められた方法での予防・治療を実施）と対照群（従来どおりまたは何もしない）とに割り付け，その後の健康現象（罹患率・死亡率）を比較する研究方法．ランダム化割り付け比較試験ともよばれ，randomized controlled trial という英語を略した RCT という用語が使われることが多い．

究が複数おこなわれている）からレベル4（専門科の意見）まで八つに分類されている．そのうえでエビデンスレベル2++/2+（エビデンスレベルの高い方から4番目と5番目）は推奨グレードがBとなる．なお，死亡率減少効果について無作為化比較対照研究（図❷）がおこなわれても複数おこなわれていない場合はエビデンスレベル1−（エビデンスレベルの高い方から3番目）となり，祖父江らの「有効性に基づくがん検診ガイドライン作成手順」にしたがえば推奨グレードはI（死亡率減少効果の有無を判断する証拠が不十分であるため，対策型検診として実施することは勧められない）でエビデンスレベル3（横断研究や症例報告など）やレベル4と同等と評価されることになる．

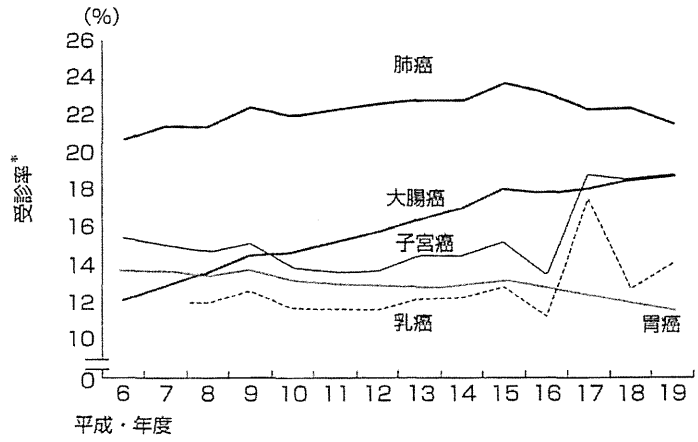
国際対がん連合（UICC）の勧告も，こうしたわが国での研究を評価し，X線検査による現行の検診実施を支持している[8]．しかし，UICCが日本国内での実施を容認しながらも，わが国以外の国での実施を推奨しているわけではないのは，胃癌の罹患の地域差に加え，無作為化比較対照試験がおこなわれたうえで評価されているわけではないことも影響していると考えられる．



図❸ 年齢階級別死亡率（男性）
（独立行政法人国立がん研究センターがん対策情報室[9]より引用）



図❹ 年齢階級別死亡率（女性）
（独立行政法人国立がん研究センターがん対策情報室[9]より引用）



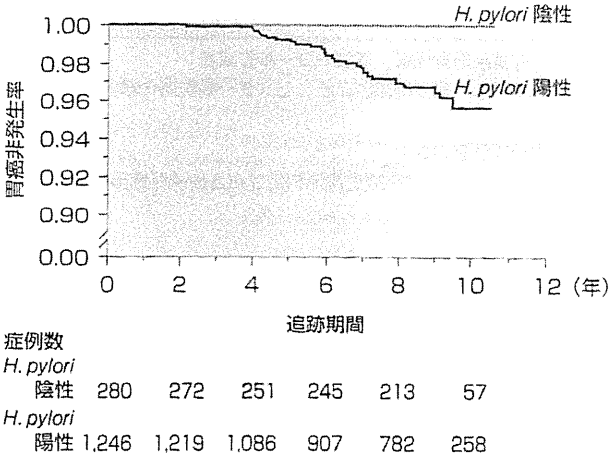
図❺ がん検診受診者数および受診率の年次推移
（厚生労働省，2008[12]より引用）

2．胃がん検診における問題点

胃癌の年齢階級別死亡率を図❸（男性）および図❹（女性）に示す[9]．男女ともに，1965年から減少傾向をつづけている．年齢調整死亡率でみても，1980年と2003年の比較でも男女ともにそれぞれ69.9から34.1（/100,000），34.5から13.2（/100,000）に漸減している[10]．

検診（スクリーニング）の基本的な考え方は，対象疾患が検診の対象となるに値するだけの条件を有しているかどうかが重要となる[11]．すなわち，①対象とする疾病は重篤で致死的な疾患であることがその社会で認知されていて，②症状発現前のより早期の状態である臨床前期状態が存在し，かつその有病率が高く，③疾患に対する適切な治療法が確立されていること，が必要となる．

1982年には老人保健法が制定され，全国の40歳以上の人を対象にX線検査による胃がん検診受診者数は増



図❻ *H. pylori* 感染と胃癌発生

(Uemura N *et al*, 2001[24] より引用)

加し 1994 年には 650 万人を超えた．しかし，がん検診の一般財源化が決定（実施は 1998 年）されて以降，胃がん検診受診者数は減少の一途をたどっている（図❺）[12][13]．対策型胃がん検診の受診者は年々減少してきており，2008 年度地域保健・健康増進事業報告によると 2008 年度は 10.2%でしかなかった[14]．しかし，はたしてこの減少が一般財源化のみの影響なのか，または近年の任意型検診も含めた内視鏡検診の普及によるものなのか，*H. pylori* 感染率の低下に伴う関心の薄れなのか，検証する必要がある．

内視鏡を用いた集検受診者は 2005 年度の全国集計では増えてはいるが[15]，X 線検査のそれと比較するときわめて少ないのが現状である．理由は，内視鏡検査は医師が施行しなければならないことや一人の医師の施行人数に限界があること，スコープの消毒と機器の整備，検査時における偶発症の問題，被験者の苦痛など多くの面で制約が大きいことである．よって，制約の多さから整った施設（総合検診センター，内視鏡センター）でのドック健診や任意型検診に限られてしまうのが現状である．

前述の「有効性評価に基づく胃がん検診ガイドライン」において，対策型・任意型を問わず有効性が確認されている胃がん検診は X 線検査だけであり，内視鏡検診については死亡率減少を証明する証拠がないので奨励できないとされている．一般論として，内視鏡集検の胃癌発見率は 0.30%（X 線検査では 0.091%）と高率であり，発見率においては有利であることは誰もが認めている[16]．しかし，集団が対象である対策型検診では胃癌死亡率減少の科学的証拠が検討されていないがために推奨する検診法ではないとされている．

3．最近の胃がん検診の試み

減少傾向があるとはいえ，胃癌の多いわが国では胃がん検診はいまだに重要なテーマであり効率的な胃がん検診のあり方についてさまざまな議論がなされている．

ペプシノゲン（PG）は胃粘膜細胞で産生され胃液中に分泌されるペプシンの前駆体であり約 1%が血液中に認められる．PG Ⅰは主として胃底腺の主細胞より，PG Ⅱは胃低腺，噴門腺，幽門腺に存在する．血液中の PG Ⅰ，PG Ⅱ，および両者の比である PG Ⅰ/Ⅱ比は胃粘膜の炎症，萎縮により変動する[17]．*H. pylori* 感染による胃粘膜の炎症で血中 PG Ⅰ，PG Ⅱとも上昇し，萎縮が進行すると PG Ⅰが低下する．それに伴い PG Ⅰ/Ⅱ比は次第に低下していく．したがって，PG Ⅰと PG Ⅰ/Ⅱ比が低値で胃粘膜萎縮が判定できる．つまり，PG Ⅰ値および PG Ⅰ/Ⅱ比が低下した状態が萎縮性胃炎であり，すなわち胃癌高危険群として精密検査をおこなうことで胃癌の効率的な発見に役立つ可能がある[18]～[22]．PG 法を用いた胃がん検診における死亡率減少効果を検討した症例対照研究がある[23]．胃癌死亡 41 例（男/女；25/16，平均年齢；70.3 歳）を対象とした結果，サンプルサイズの問題はあるが PG 法受診による胃癌死亡減少効果のオッズ比（95%信頼区間）は，1 年未満受診で 0.238（0.061～0.929），2 年未満で 0.375（0.156～0.905）と有意に減少を示した．

H. pylori 感染が胃癌発生の強力なリスク因子であることはさまざまな報告から議論の余地のないところである（図❻）[24]．そのうえで，三木[25]は *H. pylori* 抗体価・PG 法併用胃がん検診をおこない，10 年間の追跡調査を基礎にリスク別に検診間隔を決定することによって，効率的，経済的な検診ができることを提案している．すなわち抗 *H. pylori* 抗体価・PG 法にて血清学的に一次スクリーニングをおこない，二次スクリーニングは内視鏡を用いることを提唱している（ABC 検診）．危険度に応じて受診

者をA群（*H. pylori*－，PG－），B群（*H. pylori*＋，PG－），C群（*H. pylori*＋，PG＋），D群（*H. pylori*－，PG＋）に分ける血清胃癌リスク検診である．Watabeら[26]の9,293人を対象とした前向きコホート研究では，A群を基準とした胃癌罹患のハザード比は，B群は1.1，C群は6.0．D群は8.2となり，*H. pylori*の感染，胃粘膜の萎縮が胃癌発生の予測因子となる可能性が示されたと報告している．*H. pylori*関連胃炎の進展に伴い胃癌のリスクが段階的に上昇することを明確に示したものであり，*H. pylori*抗体価とPG法の二つの血清学的検査を駆使することで効率的に胃癌発生の高リスク群を抽出できる可能性が示唆された報告である．

さらに，*H. pylori*感染のないA群から胃癌が発症することはきわめてまれであることが明らかに示されたことも注目に値する．現在50歳以上の世代では感染者が半数以上を占めると考えられ，日本人に胃癌が多い要因になっている[27]．1947～1949年に生まれた団塊の世代は約800万人，この世代につづく3年間も出生数は年に200万人を超える．こうした世代の高齢化に引っ張られるかたちで著しい高齢化を迎える日本社会にあって胃癌の罹患数は今後しばらく大きく増えることが確実視される．しかしながら，*H. pylori*感染は40歳以下では非常に少ない．この世代が胃癌の好発年齢に達する時代，すなわち20～30年後には，胃癌の罹患率が急減すると推測される．つまり，この*H. pylori*低感染率世代，A群に相当する胃癌発生の低リスク集団を胃がん検診の対象者から除外することでスクリーニング効率を上げることが可能かもしれない．

4．*H. pylori*感染率減少時代における新しい対策型胃がん検診システム構築に向けての試み

ABC検診を胃がん検診のひとつとして取り入れる施設も増加しているが，**表❷**に示したように胃がん検診としては胃内視鏡検査，PG法および*H. pylori*抗体検査のいずれの方法もその有効性は証明されていない．血清胃癌リスク検診など新たな手法の有効性評価に関する研究をおこなう場合には，既存のX線検診との比較が必要である．

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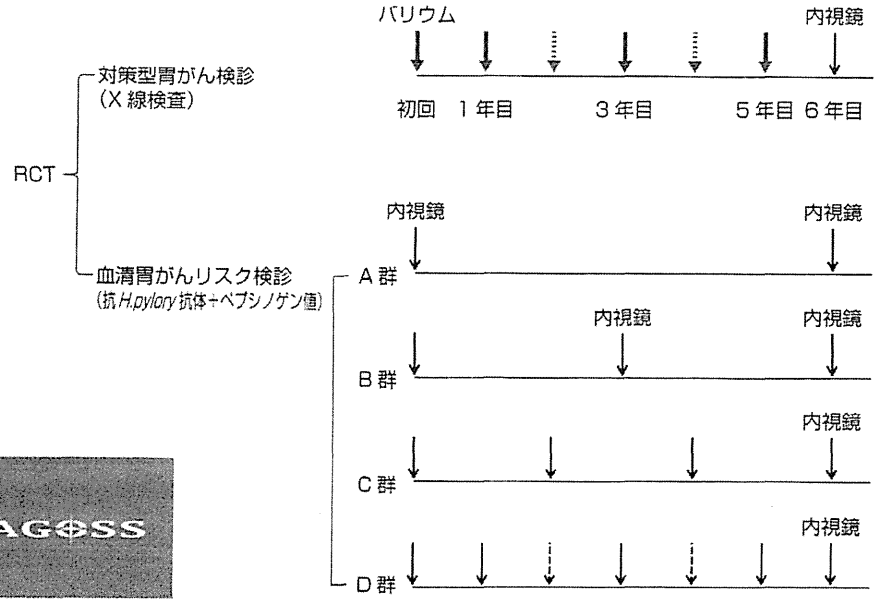
X線検査（バリウム検診）は，「40歳以上を対象に年に1回，X線検査」をおこない，胃癌の疑いがあると判断された場合（要精密検査）に，内視鏡などで詳しい検査（生検を含む）をおこなう対策型胃がん検診である．X線検査は，前述したように胃癌の死亡率減少に寄与したことが症例対照研究で証明されているが，科学的な証拠能力がより高い無作為化比較試験は実施されていない．つまり，X線検査による胃がん検診は，科学的な証拠能力が高い（エビデンスレベルⅡ以上）と国際的に評価されている大規模な無作為化比較試験は実施されていないままに導入され継続されている．

がん検診は，癌の早期発見・早期治療によって個々の患者の予後を改善することで，一定集団の死亡率を減らすことを目的に実施される．そのためには，科学的に有効性が証明された検診を正しくおこなわなければならない．しかし，死亡率減少効果の検証を目的とした大規模ながん検診法の前向き無作為化比較対照試験は非常に限

図❼ GALAPAGOSS Study ロゴ



図❽ GALAPAGOSS Study プロトコール

られている．とくに胃癌の検査法をめぐっては，有効性評価にもとづく胃がん検診ガイドライン以外にも，多くの医師や研究者から，内視鏡検査とX線検査の無作為化比較対照試験が必要だと指摘されながら，実施されてこなかった．

そこでわれわれは，厚生労働省第三次対がん総合戦略研究事業（表❸）として，2010年度より「ピロリ菌感染率減少時代における新しい対策型胃がん検診システム構築の検証に必要なプロトコール作成と実現可能性に関する研究（H22-3 次がん-一般-021）」（GAstric cancer screening LAbeled by serum examination in Place of Aged Gastric cancer Organized Screening System—GALAPAGOSS Study—）（図❼）を立ち上げた．GALAPAGOSS Study（図❽）は，「X線検査・精査内視鏡検査群」（バリウム検診群）と「*H. pylori* 抗体＋PG測定・内視鏡検査群」（胃癌リスク検診群）に無作為に振り分け比較することで，新しい胃がん検診システムの評価をおこなうことを目的としている．

対象は対策型胃がん検診受診者（30歳以上，74歳以下）で，通常の胃がん住民検診の申し込み者で申込み時に本研究について説明し，同意を得られた者としている．

主エンドポイントは，研究期間内の検査費用総額から検査1例あたりの平均値の比較を各群で比較すること．また，各群において胃癌1例を発見するのに要した費用も評価する．副エンドポイントとして，初回登録時における両群の胃がん検出率，観察期間内における両群の胃がん発見率とその進行度，検査終了時（6年目）の内視鏡検査における胃癌発見率とその進行度，両群におけるプロトコール以外の任意の胃検査の頻度と必要費用，両群間の死亡率減少効果の比較，各群における偶発症を評価する．

おわりに

科学技術の進展で新たな検査方法の開発があいついでいる．胃癌の検査方法をめぐっては，X線検査だけでなく，内視鏡検査が人間ドックなどに普及している現在，「有効性評価に基づく胃がん検診ガイドライン」にて「有効性評価に直結した研究が喫緊の課題である」と指摘されている．効率的で長期に持続可能な新たな対策型胃がん検診に向けて，「科学的評価に直結」した有効性の評価がなされなければならない．

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