別紙４

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Katai H, Sasako M, Fukuda H, et al. JCOG Gastric Cancer Surgical Study Group.	Safety and feasibility of laparoscopy-assisted distal gastrectomy with suprapancreatic nodal dissection for clinical stage I gastric cancer: a multicenter phase II trial (JCOG 0703).	Gastric Cancer	13 (4)	238-244	2010
Tanaka N, Katai H, et al.	Trends in characteristics of surgically treated early gastric cancer patients after the introduction of gastric cancer treatment guidelines in Japan.	Gastric Cancer	13 (2)	74-77	2010
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小嶋一幸、山田博之、井ノ口幹人 杉原健一、他	今日の胃癌治療を知る－腹腔鏡下胃切除はどこが有利か？	外科治療	102(1)	23-28	2010
宮崎光史、小嶋一幸、杉原健一. 他」	自律神経温存腹腔鏡下胃癌リンパ節郭清—腹腔鏡下幽門側切除術における神経温存手術の工夫—	手術	64 (13)	1939-1944	2010
X. Jiang, Hiki N, Sano T, Yamaguchi T., et al.	Long-term outcome and survival with laparoscopy- assisted pylorus-preserving gastrectomy for early gastric cancer.	Surg. Endosc.	25	1182-1186	2011
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青山　徹、吉川貴己、長晴彦、林勉、尾形高士、円谷彰	腹腔鏡補助下幽門側胃切除後の合併症評価—Clavien-Dindo 分類と Common Terminology Criteria for Adverse Events v3.0 の比較・検討—	外科	73 (4)	400-405	2011
寺島雅典	がん治療のエビデンスと臨床試験 —胃癌—	外科治療	103 (2)	115-123	2010

Ⅳ.　研究成果の刊行物・別刷

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Original article

Safety and feasibility of laparoscopy-assisted distal gastrectomy with suprapancreatic nodal dissection for clinical stage I gastric cancer: a multicenter phase II trial (JCOG 0703)

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Abstract

Background. **Although the number of patients undergoing laparoscopy-assisted distal gastrectomy (LADG) has been increasing, a prospective study with a sample size sufficient to investigate the benefit of LADG has never been reported. We conducted a multi-institutional phase II trial to evaluate the safety of LADG with nodal dissection for clinical stage I gastric cancer patients.**

Methods. **The subjects comprised patients with clinical stage I gastric cancer who were able to undergo a distal gastrectomy. LADG with D1 plus suprapancreatic node dissection was performed. The primary endpoint was the proportion of patients who developed either anastomotic leakage or a pancreatic fistula. The secondary endpoints included surgical morbidity and short-term clinical outcome.**

Results. **Between November 2007 and September 2008, 176 eligible patients were enrolled. The proportion of patients who developed anastomotic leakage or a pancreatic fistula was 1.7%. The overall proportion of in-hospital grade 3 or 4 adverse events was 5.1%. The short-term clinical outcomes were as follows: 43.2% of the patients requested an analgesic on postoperative days 5–10; the median time from surgery until the first episode of flatus was 2 days; and 88 patients (50.0%) had a body temperature of 38 °C or higher during their hospital stay.**

Conclusions. **This trial confirmed the safety of LADG performed by credentialed surgeons in terms of the incidence of anastomotic leakage or pancreatic fistula formation. A phase III trial (JCOG 0912) to confirm the noninferiority of LADG to an open gastrectomy in terms of overall survival is ongoing.**

Key words Gastric cancer · Laparoscopy-assisted distal gastrectomy · Morbidity

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Introduction

The proportion of patients with early gastric cancer among all gastric cancer patients has increased to more than 50% at major institutions in Japan [1]. The Japanese guidelines allow laparoscopy-assisted gastrectomy as an investigational treatment for early gastric cancer, with consideration of the patient's performance status [2]. Since Kitano et al. [3] reported the first laparoscopy-assisted gastrectomy in 1994, this technique has attracted the attention of surgeons. A nationwide survey of laparoscopic surgery for gastric cancer has shown that the total number of patients who were treated using a laparoscopic technique has increased and that this increase was most remarkable among patients with cT1N0 (stage IA), cT1N1 (stage IB), and cT2N0 (stage IB) tumors [4].

D1 + suprapancreatic node dissection for stage I tumors could indeed be considered as excessive surgery in western countries because of their low incidence of suprapancreatic node metastasis. However, a Japanese database showed that N2 node metastasis was found in 5.8% of patients with T1 tumors (submucosal [SM]) and in 17% with T2 tumors (muscularis propriae [MP]) [5]. Surgeons should aim at a cure rate of 100% as a general concept. Therefore, Japanese guidelines demand D1 + suprapancreatic node dissection for this population (i.e., those with clinical stage I gastric cancer).

Recent advances in operative techniques and endoscopic instrumentation have led to the standardization of laparoscopy-assisted distal gastrectomy (LADG) with suprapancreatic node dissection among experienced laparoscopic surgeons. Although whether this modality is appropriate for cancer treatment remains a concern, the technical difficulties of LADG have been

gradually solved. Several studies have reported that LADG allows a better quality-of-life outcome than an open distal gastrectomy (ODG) [6–11]. Although several studies have reported that LADG is a safe procedure with regard to morbidity and mortality [12, 13], other studies have reported that LADG has a higher risk of surgical morbidities such as anastomotic leakage, stenosis, and pancreatic fistula formation than ODG [14, 15]. Therefore, the safety of LADG should first be confirmed as an initial step.

On the other hand, several retrospective and small prospective studies have reported that the long-term results of LADG are similar to those of ODG [15, 16]. However, a prospective study with a sample size sufficient to investigate the long-term survival of LADG has not yet been reported. Thus, once the safety of LADG has been confirmed, the long-term survival after LADG should be evaluated as a next step.

The present report describes a multi-institutional phase II trial conducted by the Gastric Cancer Surgical Study Group of the Japan Clinical Oncology Group (JCOG 0703) to evaluate the safety of LADG with nodal dissection for clinical stage I gastric cancer patients. If the safety of LADG was verified, a subsequent phase III trial was to be designed to evaluate the noninferiority of LADG to ODG in terms of long-term survival.

Patients and Methods

Our study was designed as a multicenter, prospective phase II trial. The study protocol was approved by the JCOG Protocol Review Committee and the institutional review boards (IRBs) of each of the 17 participating Japanese hospitals before the activation of the study. The inclusion criteria were as follows: histologically confirmed adenocarcinoma of the stomach, a c-stage IA (T1N0) or IB (T1N1/T2N0) tumor according to the *Japanese classification of gastric carcinoma, 2nd English edition* [17], no indications for endoscopic mucosal resection (EMR) according to the Japanese endoscopic treatment guidelines [2] ("no indications for EMR" corresponds to a clinical node-positive or clinical node-negative status with any of the following criteria: a tumor size 2 cm or larger, invasion to the submucosa or deeper, a histologically undifferentiated type, the presence of an ulcer or ulcerative scar [in the case of depressed type], or the impossibility of an en-bloc resection), a distal gastrectomy-treatable tumor located in the middle or lower third of the stomach, no involvement of the duodenum, a patient age of 20–80 years, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, a body mass index (BMI) of less than 30 kg/m^2, the absence of a recurrent tumor after EMR, no prior upper abdominal surgery or intestinal resection other than an appendectomy, no prior chemotherapy or radiotherapy for any malignancy, adequate organ function, and written informed consent. The exclusion criteria were as follows: a synchronous or metachronous (within 5 years) malignancy other than carcinoma in situ or mucosal cancer, pregnancy or lactation, severe mental disease, the systemic administration of corticosteroids, unstable angina or myocardial infarction within 6 months before registration, uncontrolled hypertension, diabetes mellitus (both uncontrolled and controlled with insulin), and severe respiratory disease requiring continuous oxygen therapy.

After the inclusion/exclusion criteria were confirmed by telephoning or faxing the JCOG Data Center, the patients were registered in this JCOG 0703 trial.

Surgery

An LADG with D1 plus suprapancreatic node dissection was performed. The extent of the suprapancreatic node dissection was decided according to the surgical T and N stage of the tumor, based on the second version of the *Gastric cancer treatment guidelines in Japan* [2]. If the intraoperative findings revealed a tumor stage of II or greater, the LADG was converted to an ODG. Patients requiring a pylorus-preserving distal gastrectomy, but not a total gastrectomy, were included in this series. The size of the minilaparotomy incision was 6 cm or less, in principle. The reconstruction approach and the surgical method following resection were not specified. Postoperative analgesia, such as the use of epidural anesthesia, also was not specified. Requests for analgesia on postoperative days 5–10 were recorded. Adjuvant chemotherapy with S-1 for 1 year was recommended for patients with a curative resection and a pathological stage II, IIIA, or IIIB tumor.

Follow-up

All the enrolled patients were followed up at least every 6 months for the first 2 years and then every year for another 3 years until 5 years after the close of registration. Blood tests, an upper gastrointestinal endoscopy, and an abdominal computed tomography examination were performed every year.

Quality control of surgery

Before the start of this trial, all participating surgeons agreed to the technical details for LADG. Significant experience in gastric cancer surgery, especially in LADG

and ODG, was a prerequisite for a surgeon's participation in the trial. Only surgeons who had performed 30 or more LADG procedures and 30 or more ODG procedures were selected. Furthermore, we performed a central review of the surgical procedure by photographing all the surgeries and by videotaping arbitrarily selected surgeries. To assess compliance with the lymphadenectomy, the number of dissected nodes at all stations was recorded on the case report forms and the results were monitored.

Endpoints

The primary study endpoint was the proportion of patients who developed either anastomotic leakage or a pancreatic fistula, defined as the proportion of patients with either a grade 1 or greater anastomotic leakage or a grade 2 or greater pancreatic fistula among all the operated patients. The secondary endpoints were overall survival (OS), relapse-free survival (RFS), the proportion of LADG completions, the proportion of conversions from LADG to ODG, surgical morbidity, and the short-term clinical outcomes. The OS and RFS are not reported in this article because the current follow-up time was not long enough.

In this trial, adverse events were classified based on the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v 3.0). Anastomotic leakage and pancreatic fistula formation were also categorized based on the CTCAE v 3.0, with the following supplementary explanation of the *JCOG surgical morbidity criteria* [18]: a grade 1 or more anastomotic leakage was diagnosed radiologically and was recorded regardless of its clinical significance; a grade 2 or greater pancreatic fistula was diagnosed when fluid with a high amylase concentration drained from the peripancreatic area and led to an infection. The completion of LADG was defined as the proportion of patients without conversion from LADG to ODG among all the operated patients. The proportion of conversions from LADG to ODG was defined as the proportion of patients with a conversion among the patients who were diagnosed before gastrectomy as having clinical stage IA or IB. As for both the completion of LADG and the proportion of conversions, all LADG cases that required a skin incision of more than 6 cm were regarded as conversions to an ODG. The expected values for LADG completions and the proportion of conversions were stated as 70% and 5% in the protocol.

The short-term clinical outcomes were: (i) the proportion of patients requesting an analgesic on postoperative days 5–10, (ii) the time from the end of surgery until the first episode of flatus, (iii) the highest body temperatures during the first 3 days after surgery, and (iv) the highest body temperatures during hospitalization. The expected values for these four endpoints were 20% or less, within 3 days, 38 °C or less, and 38 °C or less, respectively. The data regarding analgesic use were collected on postoperative days 5–10 because epidural anesthesia was administered on the first 3 or 4 postoperative days in most patients.

Study design and statistical methods

This trial evaluated the safety of LADG in terms of the incidence of either anastomotic leakage or pancreatic fistula formation. If the incidence of these two postoperative complications was as low as expected, a subsequent phase III trial was designed to evaluate the noninferiority of LADG to ODG in terms of overall survival. In this phase II trial, the sample size was 170 cases, providing a 90% power under the hypothesis of a primary endpoint with an expected value of 3% and a threshold value of 8%, using one-sided testing at a 10% significance level. The expected value was decided according to the postoperative outcome of 1493 patients who had undergone an ODG at institutions belonging to the Gastric Cancer Surgical Study Group in 2004; among these patients, the proportion of those who developed anastomotic leakage was 1.3% and the proportion of those who developed pancreatic fistula formation was 0.5%. All the statistical analyses were performed using SAS software version 9.1 (SAS Institute, Cary, NC, USA).

This study was registered with UMIN-CTR [www.umin.ac.jp/ctr/], identification number UMIN000000874.

Results

Patient characteristics

Between November 2007 and September 2008, 177 patients from 14 out of the 17 hospitals with IRB approval were registered in the trial. One patient was deemed ineligible after enrollment because of a lack of written informed consent, which originated from a miscommunication among the patient's physicians.

The patients' characteristics are summarized in Table 1. The clinical and histological stages in the text are described based on the *Japanese classification of gastric carcinoma, 2nd English edition* [17], while the results shown in Table 2 are based on both the *Japanese classification of gastric carcinoma* (hereafter "Japanese classification") and the International Union Against Cancer (UICC) TNM classification, 6th edition. The median age of the patients was 59 years. The male-to-female ratio was nearly 1:1. More than 90% of the patients had clinical

Table 1. Baseline characteristics

Age (years)	
Median	59
Range	24–80
Sex, no. (%)	
Male	91 (51.7%)
Female	85 (48.3%)
Body-mass index (BMI), no. (%)	
<20	42 (23.9%)
20–24.9	107 (60.8%)
≥25.0	27 (15.3%)
Tumor location, no. (%)	
Upper third of stomach	0
Middle third of stomach	114 (64.8%)
Lower third of stomach	62 (35.2%)
Clinical T stage, no. (%)[a]	
T1	163 (92.6%)
T2	13 (7.4%)
Clinical node status, no. (%)[a]	
N0	175 (99.4%)
N1	1 (0.6%)
Clinical stage, no. (%)[a]	
IA	162 (92.0%)
IB	14 (8.0%)

[a] The distributions of c-stage were the same in the *Japanese classification of gastric carcinoma, 2nd English edition* [17] and in the International Union Against Cancer (UICC) TNM classification, 6th edition

Table 2. Histological findings

Histological type, no. (%)	
Differentiated	69 (39.2%)
Undifferentiated	107 (60.8%)
Tumor size (cm)	
Median	2.5
Range	0.5–10.0
Histological T stage, no. (%) (same in the Japanese and UICC classifications)	
T1	156 (88.6%)
T2	19 (10.8%)
T3	1 (0.6%)
Histological node status (Japanese), no. (%)	
N0	149 (84.7%)
N1	22 (12.5%)
N2	5 (2.8%)
Histological stage (Japanese), no. (%)	
IA	140 (79.5%)
IB	23 (13.1%)
II	9 (5.1%)
IIIA	4 (2.3%)
Histological node status (UICC), no. (%)	
N0	149 (84.7%)
N1	25 (14.2%)
N2	2 (1.1%)
Histological stage (UICC), no. (%)	
IA	140 (79.5%)
IB	22 (12.5%)
II	14 (8.0%)

Japanese, *Japanese classification of gastric carcinoma, 2nd English edition* [17]; UICC, UICC TNM classification, 6th edition

stage IA (cT1N0) disease. The median body mass index was 21.8. About two-thirds of the tumors were located in the middle third of the stomach.

The histological findings are shown in Table 2. Early gastric cancer (T1) was confirmed pathologically in about 90% of the patients. The proportion of patients with nodal involvement was 15.3% overall (27 out of 176 patients). About 20% of the node-positive patients had suprapancreatic node metastasis. The accuracy of the preoperative diagnosis of stage I (Japanese classification) disease was 92.6%. Adjuvant chemotherapy with S-1 was performed in 14 patients (8.0%).

Operative procedures (Table 3)

All the operations were performed with curative intent. The median duration of the operations was 250 min. A distal gastrectomy or a pylorus-preserving distal gastrectomy was performed in 174 patients. A total gastrectomy was performed in 2 patients after the identification of a positive left gastroepiploic node and a positive proximal margin, respectively. The proportion of Billroth I operations was about 50%, and this procedure was the most commonly used method.

All the patients underwent a D1 plus some extent of suprapancreatic dissection. Thirty of the 176 patients underwent a D2 lymphadenectomy.

The median length of the skin incision was 5 cm. The length of the skin incision was more than 6 cm in 5 patients. The LADG was successfully completed in 170 (96.6%; 95% confidence interval [CI], 92.7–98.7) of the 176 patients, which was far better than the expected value (70%). One patient was diagnosed as having stage II disease prior to gastrectomy, and the procedure was converted to an ODG.

The surgical procedure was converted from an LADG to an ODG in 5 patients with a preoperative diagnosis of clinical stage IA or IB; consequently, the proportion of conversions was 2.9% (95% CI, 0.9%-6.5%), which was lower than expected. The reasons for conversion were a positive proximal resected margin ($n = 1$), difficulty with the anastomosis ($n = 1$), a skin incision longer than 6 cm ($n = 1$), and bleeding ($n = 2$).

The median blood loss was 43.5 ml, and blood transfusions were required in 3 patients. The median postoperative hospital stay was 12 days (range, 7–58 days).

Operative complications and deaths

Minor injuries (grade 1, CTCAE v 3.0) were observed in two patients during the operations (transverse colon, right gastroepiploic vein).

Grade 1 or greater anastomotic leakage was observed in two patients. Grade 2 or greater pancreatic fistula formation was observed in two patients. One patient

Table 3. Details of surgical procedures

Operation time (min)	
Median	250
Range	130–495
Type of gastrectomy	
Proximal gastrectomy	0
Pylorus-preserving distal gastrectomy	43 (24.4%)
Distal gastrectomy	131 (74.4%)
Total gastrectomy	2 (1.1%)
Reconstruction method	
Roux-en-Y	48 (27.3%)
Billroth I	85 (48.3%)
Gastro-gastrostomy	43 (24.4%)
Extent of lymph node dissection, no. (%)	
D1+α[a]	4 (2.3%)
D1+β[b]	142 (80.7%)
D2	30 (17.0%)
Length of skin incision (cm)	
Median	5
Range	3–20
Length of skin incision, no. (%)	
≤6 cm	171 (97.2%)
>6 cm	5 (2.8%)
Number of ports	
Median	5
Range	4–7
Completion of LADG[c]	
Yes	170 (96.6%)
No	6 (3.4%)
Conversion to open procedure (n = 175)[d]	
Yes	5 (2.9%)
No	170 (97.1%)
Blood loss (ml)	
Median	43.5
Range	0–490
Perioperative blood transfusion	
Yes	3 (1.7%)
No	173 (98.3%)

[a] D1+α, D1 dissection + dissection of the nodes along the left gastric and common hepatic arteries
[b] D1+β, D1+α dissection + dissection of the nodes along the celiac artery
[c] Completion of LADG was counted for all operated patients (n = 176)
[d] Conversion to open procedure was counted for all patients diagnosed before gastrectomy as having clinical stage IA or IB

suffered from both an anastomotic leakage and a pancreatic fistula. The proportion of patients with either anastomotic leakage or pancreatic fistula, the primary endpoint, was 1.7% (3/176; 80% CI, 0.6–3.8; one-sided $P = 0.0003$, binomial test of the null hypothesis that the proportion is equal or greater than 8%).

The overall proportion of in-hospital adverse events (grade 3 or 4 according to the CTCAE v 3.0) was 5.1% (9/176) and the proportion of grade 1 or greater events (excluding fever) was 9.1% (16/176). Grade 3 or greater postoperative bleeding, anastomotic stricture, and intestinal obstruction were observed in two patients, one patient, and one patient, respectively.

Re-operations were performed in three patients. The reasons for the re-operations were anastomotic stricture, pancreatic fistula, and obstruction. The patient with the obstruction had developed grade 3 disseminated intravascular coagulopathy (DIC) and required a blood transfusion. The postoperative mortality rate was zero.

Short-term clinical outcomes

Flatus was recognized in all the patients during the period of hospitalization. The median time from the end of surgery until the first episode of flatus was 2 days (range, 1–5 days).

Seventy-six of the 176 patients (43.2%; 95% CI, 35.8–50.9) requested an analgesic on postoperative days 5–10, although we expected this value to be 20% or lower.

The highest body temperature during the first 3 days after surgery was recorded. The median body temperature during this period was 37.9 °C (range, 36.6 °C–39.1 °C). A body temperature of 38 °C or greater was observed in 67 patients (38.1%) on postoperative day 1, in 38 patients (21.6%) on postoperative day 2, and in 11 patients (6.3%) on postoperative day 3.

The highest body temperature during hospitalization was recorded: 88 patients had a body temperature of 38 °C or higher during their hospital stay.

Discussion

The proportion of patients who developed anastomotic leakage or pancreatic fistula formation, the primary endpoint of this study, was 1.7%. The proportion of these two postoperative complications was as low as expected in this study design and was also lower than that reported in previous publications [14, 15].

In retrospective reports about LADG, the proportions of patients who developed anastomotic leakage were quite different (1.7%–14%) [8, 9, 12], while that of patients who developed pancreatic fistula formation was 1.0% [9]. The primary endpoint in the present prospective study demonstrated that the proportion of patients who developed these two postoperative complications was lower than expected, compared with the proportions in these retrospective reports. In addition, the proportion of patients who developed these complications was considered to be equivalent to that of those who developed complications after ODG, where the proportion of patients who developed anastomotic leakage has been reported as 0.6%–2.7% and that of patients who developed pancreatic fistula as 0.6% in Japan [12, 19, 20]. The overall proportion of in-hospital adverse events itself was 5.1%, which was also relatively

low [12, 15]. These results demonstrated that LADG can be performed very safely by credentialed surgeons.

One possible reason for the low proportion of in-hospital complications in the present study might be the strict criteria that were used to select the attending surgeons. We only selected surgeons who had performed more than 30 LADG procedures and more than 30 ODG procedures prior to this trial, because we were aware that LADG requires more experience to obtain sufficient skill than its conventional open counterpart. This low complication rate also showed that the experience of performing 30 LADG procedures with suprapancreatic node dissection was sufficient to achieve proficiency. The strict selection of the attending surgeons might also have contributed to the favorable results regarding the high proportion of successful LADG procedures and the low proportion of conversions to ODG. These rates were low enough to justify a subsequent phase III trial (LADG vs ODG) [7, 21].

A second possible reason for the low proportion of in-hospital complications in the present study might be the measures used to ensure the quality control of the actual surgeries. In addition to our strict criteria for selecting surgeons, we obtained a consensus regarding the details of the surgical procedure prior to the start of the clinical trial, and the procedures were reviewed using photographs and videotapes during the enrollment period.

A third possible reason for the low proportion of in-hospital complications in the present study was the low body mass index (BMI) of the registered patients. Patients with a BMI of more than 30 were excluded from this study; as a result, the median BMI was 21.8. In western countries, the median BMI was reported as 26–29, and higher morbidities (10%–26% as grade 1–4 adverse events) than that in this study (9.1%) were demonstrated [22, 23]. Thus, BMI should be taken into consideration to interpret the morbidity results. Of note, at the National Cancer Center Hospital, Tokyo, the proportion of patients with a BMI of 25 or more was 24.0%, which is higher than the proportion in this study (15.3%). This implies that the surgeons might have preferred nonobese patients for the present trial [24].

The accuracy of preoperative staging is a key factor in the implementation of a subsequent phase III trial. Some surgeons consider that LADG should not be applied for stage II or more advanced disease. From the viewpoint of these surgeons, the accuracy of the preoperative diagnosis needs to be confirmed in this phase II study. The accuracy of the preoperative diagnosis for stage I disease (Japanese classification) was 92.6%, which was sufficient to convince these surgeons of the feasibility of a subsequent phase III study.

The major advantage of LADG over ODG is that it is less invasive. Therefore, we evaluated the short-term clinical outcomes (proportion of patients who requested an analgesic on postoperative days 5–10, time from end of surgery until first episode of flatus, and body temperature) as secondary endpoints. A visual analog scale is the most common way of evaluating pain [6]. This scale is, however, a subjective indicator and is not appropriate for comparison with historical data in a single-arm setting. Instead, we adopted the proportion of patients who requested an analgesic as a measure of pain. The proportion of patients who requested an analgesic was more than 40%, which was higher than expected and higher than that described in previous reports [6, 7, 25]. This result was paradoxical. Because this study was a phase II study, this endpoint will need to be evaluated further in a subsequent phase III trial (LADG vs ODG).

The time from the end of surgery until the first episode of flatus was a good indicator of bowel function recovery. The time until flatus was as we expected and was similar to the results of a previous report [6].

Measures of inflammation are important for evaluating the invasiveness of surgery. Body temperature is one parameter of inflammation. A body temperature greater than 38°C is one of the clinical manifestations of systemic inflammatory response syndrome (SIRS) [26], and patients can suffer greatly from this complication. The change in body temperature was as we expected and was similar to the results of previous reports [27, 28].

Although the safety of LADG was confirmed in the present study, this result may not fit in western countries. LADG will remain an investigational treatment even in Japan until its effectiveness is fully evaluated in a phase III trial. We are now conducting a JCOG phase III trial (JCOG 0912) with a recruitment of about 1000 patients to confirm the noninferiority of LADG to ODG in terms of overall survival.

Conclusion

The present trial confirmed the safety of LADG performed by credentialed surgeons in terms of the incidence of anastomotic leakage or pancreatic fistula formation. A phase III trial to confirm the noninferiority of LADG to ODG in terms of overall survival is now ongoing.

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Appendix

Study participants

The following institutions and investigators participated in the trial: Hakodate Goryoukaku Hospital (A. Takagane), Yamagata Prefectural Central Hospital (N. Fukushima), National Cancer Center Hospital (H. Katai, M. Saka), Tokyo Medical and Dental University (K. Kojima, M. Inokuchi, H. Yamada), Cancer Institute Hospital (N. Hiki, T. Fukunaga, H. Yoshiba, M. Tokunaga), Kanagawa Cancer Center (T. Yoshikawa, H. Cho), Aichi Cancer Center Hospital (Y. Mochizuki, K. Misawa), Fujita Health University (I. Uyama, S. Kanaya, K. Taniguchi), Kinki University Hospital (H. Imamoto), Osaka Medical Center for Cancer and Cardiovascular Diseases (I. Miyashiro), Department of General and Gastroenterological Surgery, Osaka Medical College (N. Tanigawa), Wakayama Medical University (M. Iwahashi, K. Takifuji), Hiroshima City Hospital (M. Nishizaki), and Oita University (S. Kitano, N. Shiraishi, T. Eto).

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Review article

Adenocarcinoma of the esophagogastric junction: incidence, characteristics, and treatment strategies

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Abstract
The incidence of adenocarcinoma of the esophagogastric junction (AEG) is dramatically increasing in Western countries, while it is not increasing in Eastern countries. Siewert type I tumors are observed less frequently in Eastern countries in comparison to Western countries. On the other hand, other clinicopathological features of AEG, including age, male-to-female ratio, pathological grade, tumor progression, and prognosis, are similar in Western and Eastern countries. Two surgical phase III trials have indicated that AEG type I should be treated surgically as esophageal cancer, while types II and III should be regarded as true gastric cancer. No phase III trials have demonstrated a significant interaction comparing hazard ratios for death between AEG and true gastric cancer in the subset analyses with regard to chemotherapy.

Key words Gastric cancer · Cardia · Esophageal neoplasms · Esophagogastric junction · Incidence · Surgery · Chemotherapy

Introduction

The incidence of adenocarcinoma of the esophagus and esophagogastric junction (AEG) is dramatically increasing in Western countries [1–3]. Moreover, in many Western countries, the incidence of AEG is increasing more rapidly than that of any other type of neoplasm [4]. Siewert proposed a classification of AEG, based on the anatomical location, in 1996, and it has been accepted worldwide. This classification divides AEG into three subtypes (Fig. 1). A retrospective analysis showed that more than 80% of AEGs in Western countries were in an advanced stage, and the prognosis was quite poor, with a 5-year survival rate of less than 30% [5]. Therefore, it is necessary to establish an optimal treatment strategy for AEG in Western countries. On the other hand, several reports from Eastern countries indicate that the incidence of AEG is strikingly different from that in Western countries. This article reviews the clinicopathological features of AEG in terms of the differences between Western and Eastern countries. In addition, this report also evaluates the treatment strategies for AEG based on the results of major clinical trials.

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Siewert classification (Fig. 1)

An appropriate and commonly used classification is essential for the analysis of the characteristics of a disease and the establishment of the optimal treatment strategy. Siewert and Stein [6] proposed a new classification of AEG in 1996, which was based on topographic anatomical criteria. AEG was divided into three types, each of which had different characteristics, thereby influencing the selection of the surgical strategy. Type I is defined as tumors in which the center is located 1 to 5 cm above the esophagogastric junction (EGJ), regardless of invasion to the EGJ; type II is defined as tumors invading the EGJ, in which the center is located between 1 cm above and 2 cm below the EGJ; and type III is defined as tumors invading the EGJ, in which the center is located 2 to 5 cm below the EGJ (Fig. 1). This classification was approved at the consensus conference of the International Gastric Cancer Association (IGCA) and the International Society for Diseases of the Esophagus (ISDE) [7], and has been accepted and is now used worldwide. The Siewert subtype should be determined prospectively, based on the findings of endoscopy, contrast radiography, and computed tomography. A definition of anatomical cardia is determined by the findings of endoscopy [8].

Origin of AEG tumors

Theoretically, type I tumors arise from the esophageal glandular epithelium or specialized intestinal epithelial

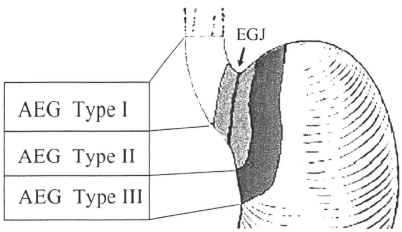

Fig. 1. Siewert classification. *AEG*, Adenocarcinoma of the esophagogastric junction; *EGJ*, esophagogastric junction

metaplasia (so-called Barrett's esophagus); the latter is considered to be deeply associated with the development of AEG [9, 10]. The prevalence of Barrett's esophagus in patients with type I tumors is higher than that in patients with type II/III tumors, in both Western and Eastern countries [11, 12].

Type II tumors are true AEG arising from the junctional epithelium; however, some type II tumors can arise from the same origin as type I tumors, and some can arise from the same origin as type III tumors. Many previous studies have demonstrated that the characteristics of type II tumors are more like those of type III tumors than those of type I tumors, thus indicating that the origin of type II tumors is similar to that of type III tumors [5, 7, 10].

Type III tumors arise from the gastric mucosa, and this origin might be associated with *Helicobacter pylori* and atrophic gastritis [10, 13]. Tumors whose center is located 2 to 5 cm below the EGJ are classified as non-AEG or true gastric cancers when the tumors do not invade the EGJ. The tumor classification changes to AEG type III when they invade the EGJ by horizontal progression. Therefore, subcardial gastric cancers are classified as type III tumors when they are enlarged. Type III tumors should be treated as gastric cancers invading the EGJ, considering the origin of the tumors.

In summary, AEG may contain two distinct etiologies [13]. It is often difficult to determine the tumor origin, especially in advanced cases. The examination of biomarkers may thus provide the key to accurately determine the tumor origin [14, 15].

Incidence and characteristics

Incidence of AEG in Western countries

Carrie described, in his review, that the first case of adenocarcinoma of the esophagus was reported by White in 1898 [16]. In several case series in the 1950s, the incidence of adenocarcinoma of the esophagus was reported to be 8% in the United Kingdom [17] and 10% in the United States[18]. These types of tumors were believed to arise from ectopic patches of gastric mucosa in the esophagus. Barrett [19] first described the columnar epithelium lining the lower part of the esophagus at that time.

Table 1. The proportion of AEG among upper gastrointestinal carcinomas at Kanagawa Cancer Center, Japan

Period	Gastric (%)	Esophageal (%)	AEG (%)
1986–1990	75.8	20.7	3.5
1991–1995	76.3	19.3	4.5
1996–2000	76.2	19.6	4.2
2001–2005	74.8	21.6	3.6

AEG, adenocarcinoma of the esophagogastric junction

Once a rare tumor [20], the incidence of AEG is currently increasing faster than that of any other type of tumor; especially, the incidence of AEG types I and II is increasing in the United States [2]. The rate of increase has outpaced that of the next most commonly increasing tumor, melanoma, by approximately three times [2, 21, 22]. Similar trends are also reported in the United Kingdom, Scotland, Norway, Sweden, Denmark, France, Switzerland, Australia, and New Zealand [3, 23–30]. This increase began in the 1970s, and it seems to be most prominent in white men [1, 2].

Incidence of AEG in Eastern countries

In contrast to reports in Western countries, there are only a few reports of the incidence of AEG in Eastern countries. Shibata et al. [31] reported on trends in the incidence of adenocarcinoma of the esophagus in Japan, and indicated that no increase in the incidence of these tumors was observed. The proportion of AEG among upper gastrointestinal (GI) tract cancers at Kanagawa Cancer Center was analyzed and the incidence had not changed in 20 years (Table 1). Chung et al. reported similar results in Korea [32]. Conversely, Kusano et al. [33] reported a slight increasing trend of AEG in Japan in a retrospective analysis of lesions resected as gastric cancer, although they did not include cases which were treated as esophageal cancer. There is no obvious evidence that indicates a rapid increase of AEG in Eastern countries.

Clinicopathological characteristics: similarities and differences between Western and Eastern countries (Table 2)

The frequency of the three types of AEG is strikingly different between Western and Eastern countries. Type I tumors occur less frequently in Eastern countries than

Table 2. Differences in the incidence and clinicopathological features of AEG between Western and Eastern countries

Author	Siewert	de Manzoni group	Bai	Chung	Hasegawa	Fang
Reference number	[11]	[34, 35]	[12]	[32]	[36]	[37]
Country	Germany	Italy	China	Korea	Japan	Taiwan
Siewert subtype	I/II/III	I/II/III	I/II/III	I/II/III	I/II/III	I/II/III
Number of patients (I/II/III)	NA	21/32/38	29/80/94	23/47/540	5/82/60	0/51/180
Incidence (%; I/II/III)	38.8/30.3/31.0	23.1/35.2/41.8	14.3/40.0/45.5	3.7/7.7/88.5	3.4/55.8/40.8	–/22.1/77.9
Age ≥60 years (%; I/II/III)	61/62/64	66/67/69	59.7/60.1/61.3	64.7/62.8/57.7	54/63/67	–/84.3/79.4
	NS	NA	NS	$P = 0.01$	NS	$P = 0.199$
Male-to-female ratio	10.7/4.9/2.1	9/5.8/5.8	3.5/3.1/2.9	6.7/10.1/2.8	1.5/3.3/2.2	–/9.2/4.5
(I/II/III)	$P < 0.01$	NA	NS	$P = 0.01$	NS	$P = 0.199$
Histology						
G3/4 (%; I/II/III)	54.4/60.2/73.4	20/22.6/37.7	19.5/42.8/65.9	26.1/38.3/53.9	60/30.5/56.7	NA
	$P < 0.01$	NA	$P < 0.01$	$P < 0.01$	$P = 0.002$	
Intestinal metaplasia	79.5/5.6/0.8	NA	39.1/6.6/1.6	NA	NA	NA
(%; I/II/III)	$P < 0.01$		$P < 0.01$			
Tumor progression						
T1 (%; I/II/III)	34.3/16.2/8.3	28.6/20.6/2.4	NA	NA	60.0/20.7/3.3	–/29.4/24.4
Stage 3–4 (%; I/II/III)	NA	NA	27.6/41.3/67.0	87.0/57.4/53.9	0/50/80	–/41.2/46.7
				$P = 0.07$	$P < 0.001$	NS
5-Year survival (%; I/II/III)	40–50/40–50/20–30	NA	34.0/27.5/24.5	4.8/47.9/47.4	–/44.2/31.0	–/59.6/63.5
				$P < 0.01$ vs type 1	$P = 0.013$	NS

G3/4, grade 3/4 undifferentiated histology; NA, not available; NS no significant difference

in Western countries. Table 2 summarizes the differences in the incidence and clinicopathological features of AEG between Western and Eastern countries, including patients' ages, male-to-female ratios, pathological grades, intestinal metaplasia, and tumor progression [11, 12, 32, 34–37]. The average age of the patients was around 60 years, and was similar in the three AEG types. All types of tumors showed a male predominance. Siewert and Stein reported that the male-to-female ratio was 10.7 in type I, 4.9 in type II, and 2.2 in type III, with significant differences [11]. Types II and III demonstrated a similar trend in Eastern countries; although the difference did not reach statistical significance except in Korea [12, 32, 36, 37]. Differentiated tumors (intestinal type) were frequently observed in type I AEG, and poorly/undifferentiated tumors (diffuse type) were found in type III. Type II tumors had characteristics rather intermediate between those of types I and III. These characteristics seem to be common between Western and Eastern countries. The presence of specialized intestinal metaplasia in the distal esophagus (Barrett's esophagus) was observed more frequently in type I than in types II and III. Siewert and Stein reported that the proportions of patients with Barrett's esophagus were 79.5% in type I, 5.6% in type II, and 0.8% in type III [11], findings that were similar to the results in China [12]. Type III disease seems to be more progressive than types I and II, and this trend is similar in Western and Eastern countries. This finding of type III disease being more progressive than types I and II is not surprising, because type III represents the progression of a subcardial gastric cancer which originates from the gastric mucosa 2 to 5 cm below the EGJ, and the size of the tumor tends to be larger than that of type II [36].

The clinicopathological features of AEG are quite similar in Western and Eastern countries, except for the prevalence of type I tumors, most of which arise from Barrett's esophagus. The established risk factors for adenocarcinoma of the esophagus are Barrett's esophagus, gastroesophageal reflux, and obesity; conversely, *Helicobacter pylori* infection might reduce the risk [38]. The difference in the prevalence of type I tumors in Western and the Eastern countries may be explained by differences in the proportions of obese patients and differences in the prevalence of *H. pylori* infection.

The incidence of gastric cancer in the United States (noncardial cancer) has decreased gradually since the 1930s, whereas that of AEG has increased rapidly since the 1970s. The decrease in the incidence of gastric cancer is associated with the decrease in the *H. pylori* infection rate; thus, the increase of AEG might have followed the decrease of gastric cancer, after several decades. Therefore, there may be a dramatic increase of AEG in the near future in Eastern countries where there is currently a decrease in the rate of gastric cancer, although there is no evidence that indicates an increase of AEG, as described previously.

Treatment strategies for resectable disease

Surgical strategy

A multivariate analysis demonstrated an R0 resection to be an independent predictive factor associated with

Table 3. Multivariate analysis of 142 patients with type II/III tumors who underwent surgical resection at Kanagawa Cancer Center, Japan

Variables	Factors	*P* value	Hazard ratio
Siewert type	Type II/III	0.090	0.666
Length of esophageal invasion (cm)	<3.0/≥3.1	0.212	1.466
R category	R0/R1–2	<0.001	3.433
T	T1/2/3/4	<0.001	1.919
N	N1/2/3	<0.001	1.647
M	M0/1	0.021	1.994

survival, as well as T, N, and M factors (Table 3). Siewert et al. also reported that an R0 resection was a strong prognostic factor in patients with AEG [39]. Therefore, the primary goal of a surgical resection of AEG is the complete removal of the primary tumor and lymph nodes. The reported occurrence of mediastinal lymph node metastasis of AEG is 7.1%–40.8% [40–44]. The necessity of a prophylactic mediastinal nodal dissection remains controversial [42–44]. Two major trials were conducted, in the Netherlands and in Japan, to clarify the optimal surgical approach and sufficient extent of mediastinal lymph node dissection.

Phase III trial in the Netherlands (Dutch trial) [45]. The first of the major trials mentioned above was a phase III trial performed in the Netherlands in 1994–2000. This study was designed to elucidate the optimal surgical approach and the extent of lymph node dissection for patients with lower esophageal adenocarcinoma (type I) and adenocarcinoma of the gastric cardia (type II). The study evaluated the superiority of a transthoracic esophagectomy with an extended en-bloc lymphadenectomy via the right thoracic approach (RTA) to a transhiatal esophagectomy (TH). The study was performed at two high-volume centers in Amsterdam and Rotterdam. In the TH group, the esophagectomy was performed under direct vision through the enlarged hiatus of the diaphragm to the inferior pulmonary vein, and the esophagus was bluntly resected. A gastric tube was constructed, and an esophagogastrostomy was performed in the neck. The lymph nodes adjacent to the tumor were dissected en bloc, and the left gastric artery was resected for the removal of the lymph nodes. No cervical or upper-middle mediastinal lymphadenectomy was performed. The celiac lymph nodes were not dissected unless there was clinical evidence of metastasis. In the patients in the RTA group, a mediastinal lymphadenectomy was performed, as well as an abdominal lymphadenectomy including the paracardial, lesser-curvature, left gastric artery, celiac trunk, common hepatic artery, and splenic artery nodes. The hypothesis was that an RTA would yield a 15% better 2-year survival rate than TH, with an alpha error of 0.05 and beta error of 0.1. The required sample size was calculated to be 220. The main results were published in 2002 [45]. The 5-year overall survival rate was better in the RTA group than in the TH group (39% vs 29%), although the difference did not reach statistical significance. On the other hand, pulmonary complications and chylous leakage were observed more frequently in the RTA group in comparison to the TH group (57% vs 27%; $P < 0.001$ and 10% vs 2%; $P = 0.002$). The durations of intensive care unit (ICU) stay and hospital stay were longer in the RTA group than in the TH group (6 vs 2 days; $P < 0.001$ and 19 vs 15 days; $P < 0.001$). In-hospital mortality did not differ between the groups (4% vs 2%; $P = 0.45$). An additional analysis of the updated survival data was published in 2007 [46]. The 5-year survival rates did not differ between the groups (36% in the RTA group and 34% in the TH group; $P = 0.71$); however, a survival benefit of 14% was seen in the RTA group in the patients with a type-I tumor (51% vs 37%; $P = 0.33$). The P value did not reach statistical significance, and this may have been due to a type-II error. On the other hand, the 5-year locoregional disease-free survival was significantly better in the RTA group, when stratified to the patients having a type I tumor and one to eight positive nodal metastases (64% vs 23%; $P = 0.02$).

In conclusion, an extended transthoracic resection was found to be more hazardous surgery in regard to morbidity than a transhiatal esophagectomy, although mortality did not differ between these two groups. Extended surgery could therefore be recommended only for patients with type I tumors; however, it could not be recommended for patients with type II tumors.

Phase III trial in Japan (JCOG 9502) [47]. The above Japan Clinical Oncology Group (JCOG) phase III trial was conducted to clarify the significance of the left thoracoabdominal approach (LTA) for patients with type II/III AEG, in comparison to the transhiatal approach (TH). Patients were eligible if they had AEG through the submucosa, which invaded less than 3 cm into the esophagus. The patients in the TH group received a total gastrectomy with D2 lymphadenectomy (including splenectomy) plus paraaortic nodal dissection (lateral to the aorta and above the left renal vein). The patients in the LTA group received a thorough mediastinal nodal dissection below the left inferior pulmonary vein, as well as the same procedure in the abdominal cavity. The first interim analysis was done when the 165 patients were enrolled. The 5-year survival rate was estimated to be 53.4% (95% confidence interval [CI],38.1–68.6) in the TH group, and 38.9% (95% CI, 22.4–55.4) in the LTA group ($P = 0.93$). The probability of LTA being significantly better than TH at the final analysis was considered to be quite low (3.65%); consequently, the accrual

was closed at that point. The survival data were updated afterwards; the 5-year survival rate was 52.3% (95% CI, 40.4–64.1) in the TH group, whereas it was 37.9% (95% CI, 26.1–49.6) in the LTA group. The adjusted hazard ratio of death for an LTA in comparison to a TH was 1.36 (95% CI, 0.89–2.18). Complications were observed more frequently in the LTA group than in the TH group (49% vs.34%; $P = 0.06$). In-hospital mortality was also higher in the LTA group (4% vs 0%; $P = 0.25$). This result suggested that an LTA for type II/III tumors did not provide a survival benefit; on the contrary, it might increase the surgical morbidity and mortality. In conclusion, LTA is therefore not recommended for type II/III tumors.

Optimal surgical strategy for AEG

The results of these two trials are summarized in Table 4. These two phase III studies and the retrospective analyses examining the pattern of the lymph node metastases suggest the optimal surgical approaches and the extent of the nodal dissection for a resectable AEG. The results of the Dutch trial [45] indicated that RTA with a mediastinal lymph node dissection may be recommended for type I tumors, if the patients can tolerate the surgery. Patients with type I tumors in the RTA group underwent a D2 abdominal lymphadenectomy. It is unclear whether or not the D2 abdominal dissection affected the results.

A thoracoabdominal approach with a radical mediastinal nodal dissection could not improve the survival for patients with type II tumors in both phase III trials; however, it did increase the surgical risk. Therefore, the transhiatal approach is recommended for type II tumors. The JCOG 9502 trial showed that there were no differences in the survival rates or hazard ratios between type II and type III tumors. The principle of the surgical strategy did not differ. A transhiatal extended gastrectomy is the preferable approach for type II and type III tumors. A D2 plus partial paraaortic nodal dissection (PAND) was performed in both groups in the JCOG 9502 trial, while D1 was performed in the control arm and D2 in the test arm of the Dutch trial. Which abdominal nodal dissection should therefore be recommended for types II and III? Strictly speaking, there is no evidence to indicate the appropriate abdominal nodal dissection for AEG types II and III. However, many previous reports have indicated that abdominal nodal metastases are frequently observed in type II/III tumors [11, 36]. One analysis showed that 32.9% of type II tumors had involvement of the lymph nodes along the major branched arteries (the left gastric artery, common hepatic artery, splenic artery, and celiac axis), and the rate was 50% in type III tumors [36]. Siewert and Stein also reported similar results; 25% nodal involvement in type II tumors and 39% in type III tumors [11]. These reports clearly indicate that abdominal nodal metastases are frequently observed in AEG type II/III tumors, as in true gastric cancer. Moreover, the major recurrence patterns are nodal, peritoneal, and liver metastases after curative surgery in AEG types II and III, from the results of the JCOG 9502 trial, with these patterns being the same as those of true gastric cancer [47]. Therefore, the extent of a nodal dissection for AEG type II/III should be same as that applied for gastric cancer. A Japanese phase III trial comparing D2 and D2+PAND (JCOG 9501) demonstrated that D2+PAND could not improve the survival of patients with gastric

Table 4. Phase III surgical trials of AEG in the Netherlands (Dutch trial) and Japan (JCOG 9502)

	Dutch trial [45, 46]	JCOG 9502 [47]
Surgery (test/control)	RTA/TH	LTA/TH
Number of patients	220	167
Type I	90	0
Type II	115	95
Type III	—	70
Other	15	2
Primary endpoint	2-Year survival rate	Overall survival
5-Year survival rate (%)		
Test/control	36/34	38.9/53.4
Survival benefit of test arm		
Type I	+14%	NA
Type II	−4%	−10.7%
Type III	NA	−17.5%
Surgical morbidity (test/control)		49%/34% (any, $P = 0.06$)
Pulmonary complications	57%/27% ($P < 0.001$)	13%/4% ($P = 0.05$)
Anastomotic leakage	16%/14% ($P = 0.85$)	8%/6% ($P = 0.77$)
Surgical mortality (test/control)	4%/2% ($P = 0.45$)	4%/0% ($P = 0.25$)

RTA, right thoracic approach; LTA, left thoracoabdominal approach; TH, transhiatal approach; NA, not available

cancer [48]. Therefore, D2 became the standard surgery for gastric cancer in Japan. On the other hand, a Taiwanese phase III trial comparing D1 and D3 (which is a D2 dissection according to the present definition) clearly showed that D2 could improve survival [49]. Although two phase III trials performed in Europe comparing D1 and D2 did not confirm the survival superiority of D2 [50, 51], there was a lot of criticism of the quality of the D2 surgery; it seemed that this surgery led to the results showing an extremely high mortality. Therefore, an abdominal D2 lymphadenectomy is recommended for patients with type II/III tumors, unless D2 increases the surgical risk. In summary, AEG type I should be treated as esophageal cancer, while types II and III should be treated as true gastric cancer.

Multimodal treatment

Although surgery is the primary modality that can cure AEG cancer, the long-term outcome is not satisfactory, even after an R0 resection. The results of surgical resection, not including perioperative chemotherapy, were obtained from the two randomized controlled trials. The 5-year survival rate in the Dutch trial [46] was 34% in the TH group and 36% in the RTA group, and the rate in the JCOG trial [47] was 52.3% in the TH group (95% CI, 0.4–64.1) and 37.9% in the LTA group (95% CI, 26.1–49.6). Approximately 70% of AEG patients develop recurrence in distant organs (peritoneum, liver, pleura, other) [47], which may suggest the limitations of surgery. Therefore, perioperative chemotherapy may be required to improve the prognosis of AEG.

Perioperative chemotherapy (Table 5)

A phase III trial of adjuvant chemotherapy for gastric cancer was performed in Japan (ACTS-GC) to clarify the effect of S-1 in stage II/III patients who underwent a curative D2 surgery, and its survival benefit [52]. The 3-year overall survival rate was 80.1% in the S-1 group and 70.1% in the surgery-only group, and this difference was significant ($P = 0.003$). The result of this phase III trial has affected the strategy for the treatment of gastric cancer in Japan, and the Japanese guidelines for gastric cancer have been revised. The relevance of this result for patients with AEG is unknown, because the ratio of AEG among the patients enrolled was not shown in this trial. However, the results of the ACTS-GC trial could be applicable to AEG type II and type III tumors, as these tumors have characteristics similar to those of true gastric cancer in terms of lymph node metastasis and recurrence patterns [47]. Postoperative S-1 chemotherapy could be a standard for AEG type II and type III tumors in the countries in which abdominal D2 surgery is the standard, although ethnic differences must be considered in the effects of S-1.

Neoadjuvant chemotherapy for esophageal cancer is associated with an improvement in the prognosis [53]. The Medical Research Council (MRC) Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial compared perioperative cisplatin-based chemotherapy plus surgery to surgery alone, and found a significant survival improvement of 13% at 5 years with multimodal treatment (36% vs 23%) [54]. The initial design of this trial included patients with gastric carcinomas, and the eligibility criteria were extended to include adenocarcinomas of the lower third of the esophagus, on the basis of

Table 5. Phase III trials of perioperative chemotherapy

Author, year	Sakuramoto, 2007 [52] (ACTS-GC)	Cunningham, 2006 [54] (MAGIC trial)	Boige, 2007 [55] (ACCORDO07-FFCD9703)
Country	Japan	UK	France
Mode	Adjuvant	Perioperative	Perioperative
Subjects (stage)	Gastric (II/III)	Gastroesophageal (II–)	Gastroesophageal (II–)
Treatment: Test arm	S1, 1 Year	ECF × 3 (pre-), × 3 (post-)	FP × 2–3 (pre), × 3–4 (post-)
Control arm	Surgery alone	Surgery alone	Surgery alone
Number of patients (test/control)	529/530	250/253	113/111
Tumor location (gastric/AEG)	NA	74/26	25/75
3-Year survival rate (test/control)	80.1/70.1	40–45/30–35	48/35
Hazard ratio for death (95% CI)	0.68 (0.52–0.87, $P = 0.003$)	0.75 (0.60–0.93, $P = 0.009$)	0.69 (0.50–0.95, $P = 0.02$)
Interaction comparing hazard ratios for death between gastric cancer and AEG in the subset analyses	NA	None	None

ECF, epirubicin/cisplatin/fluorouracil; FP, fluorouracil/cisplatin; CI, confidence interval; NA, not available; ACTS-GC, Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer; MAGIC, The Medical Research Council Adjuvant Gastric Infusional Chemotherapy

the increased incidence of AEG. Seventy-three of the 503 patients enrolled (14.5%) had tumors of the lower esophagus, and 58 (11.5%) patients had tumors of the esophagogastric junction. Although the number of patients was relatively small, no difference in the treatment effect was observed according to the site of the primary tumor (P for interaction = 0.25). Recently, the efficacy of perioperative chemotherapy was confirmed by a French Intergroup trial, in which approximately 75% of the patients enrolled had tumors located in the esophagogastric junction [55]. These trials suggested that perioperative chemotherapy, when combined with limited nodal dissection, improved the prognosis of patients with AEG tumors. However, the extent of abdominal nodal dissection was usually less than D2 in these trials, which is quite different from the Japanese standard D2 dissection. A difference in the extent of local control influences the overall effect of the treatment. Therefore, the results shown in these trials would not be applicable to countries in which the standard surgery is D2.

Perioperative chemoradiotherapy (Table 6)

The role of radiotherapy, specifically concurrent chemoradiotherapy, remains controversial. Macdonald et al. reported the significance of chemoradiotherapy after curative surgery in 2001 [56]. The median duration of survival was 36 months in the chemoradiotherapy group and 27 months in the surgery-only group, with a median follow-up period of 5 years, and the difference was significant (P = 0.005). This study was a valuable trial, for this is the first report which demonstrated the effect of adjuvant therapy in gastric cancer. However, the most common location of the primary tumor was the distal portion of the stomach (53% in the chemoradiotherapy group, 56% in the surgery-only group), and the ratio of cardia tumors was relatively small (21% in the chemoradiotherapy group, 18% in the surgery-only group). The association between AEG and true gastric cancer was not shown in this trial. Moreover, the extent of abdominal nodal dissection was mostly D0 or D1, which was quite different from Japanese D2 surgery.

A meta-analysis showed that preoperative chemoradiotherapy improved survival in resectable esophageal cancer in comparison to surgery alone, although the extent of nodal dissection was limited and the surgery-related mortality was significantly higher in preoperative chemoradiotherapy followed by surgery than surgery alone [57, 58]. There is little data comparing preoperative chemoradiotherapy to chemotherapy. Recently, a randomized controlled trial was reported from Germany, which compared preoperative chemoradiotherapy with preoperative chemotherapy in patients with locally advanced AEG [59]. An abdominal D2 dissection was performed in type II and type III tumors, whereas a transthoracic esophagectomy or transhiatal esophagectomy was used in type I tumors. The patients who received preoperative chemoradiotherapy showed a higher 3-year survival rate in comparison to the patients who received preoperative chemotherapy (47.4% vs 27.7%), although the difference did not reach statistical significance (P = 0.07). In summary, perioperative chemoradiotherapy contributes to survival when combined with a limited nodal dissection. It is still unclear whether chemoradiotherapy could improve the prognosis when combined with an extended nodal dissection.

Treatment strategies for advanced disease (Table 7)

Patients with systemic metastatic disease are recommended to receive systemic chemotherapy. The regimen of fluorouracil plus cisplatin (FP) is considered to be the standard, based on earlier trials in patients with squamous cell carcinoma [60, 61]. Phase III trials performed in Japan show that the response to FP therapy does not differ between the histological types, with a response rateof 33.3% in squamous cell carcinoma (JCOG 9407

Table 6. Phase III trials of perioperative chemoradiotherapy

Author, year	Macdonald, 2001 [56]	Stahl, 2009 [59]
Country	USA	Germany
Mode	Adjuvant	Neoadjuvant
Subjects	Gastroesophageal	Gastroesophageal
Stage	IB–IV, M0	T3–4NXM0
Treatment: Test arm	FL + FL/RT (45 Gy)	FLP × 2 + PE/RT (30 Gy)
Control arm	Surgery alone	Surgery alone
Number of patients (test/control)	281/275	60/59
Tumor location (gastric/AEG)	80/20	0/100
3-Year survival rate (test/control)	50/41	47.4/27.7
Hazard ratio for death (95% CI)	0.74 (0.60–0.92, P = 0.005)	0.67 (0.41–1.07, P = 0.07)
Interaction comparing hazard ratios for death between gastric cancer and AEG in the subset analyses	None	NA

FL, fluorouracil/leucovorin; FLP, fluorouracil/leucovorin/cisplatin; PE, cisplatin/etoposide; RT, radiation therapy; CI, confidence interval

Table 7. Phase III trials of systemic chemotherapy for advanced disease

Author, year	Webb, 1997	Ross, 2002	Van Cutsem, 2006	Koizumi, 2008	Cunningham, 2008	Van Cutsem, 2009
Reference number	[63]	[64]	[66]	[67]	[68]	[69]
Country	UK	UK	Global	Japan	UK	Global
Subjects	Gastroesophageal	Gastroesophageal	Gastric/AEG	Gastric	Gastroesophageal	Gastroesophageal, HER-2-positive
Treatment: Test arm	ECF	ECF	DCF	S1+cisplatin	F→Cape., C→O	5FU or cape. + cisplatin + trastuzumab
Control arm	FAMTX	MCF	CF	S1	ECF	5FU or cape. + cisplatin
Study design	Superiority	Superiority	Superiority	Superiority	Noninferiority	Superiority
Number of patients (test/control)	126/130	289/285	221/224	148/150	239/235/241/249	294/290
Tumor location (gastric/AEG; %)	57/43	43/55[a]	78/22	NA	40/60[b]	82/18
MST (test/control, months)	8.9/5.7	9.4/8.7	9.2/8.6	13.0/11.0	11.2/9.3/9.9/9.9	13.8/11.1
Hazard ratio for death (95% CI)	0.61 (0.45–0.81)	0.88 (0.73–1.07)	0.78 (0.6–1.0)	0.77 (0.61–0.98)	0.86 (0.80–0.99)[c] 0.92 (0.80–1.10)[d]	0.74 (0.60–0.91)
Statistics for primary endpoint	$P = 0.009$	$P = 0.315$	$P = 0.02$	$P = 0.04$	$P < 0.05$ for both	$P = 0.0046$
Interaction comparing hazard ratios for death between gastric cancer and AEG in the subset analyses	NA	None	NA (RR: gastric < AEG)	NA	None	None

ECF, epirubicin/cisplatin/fluorouracil; FAMTX, doxorubicin/methotrexate/fluorouracil; MCF, mitomycin/cisplatin/fluorouracil; DCF, docetaxel/cisplatin/fluorouracil; F, fluorouracil; Cape., capecitabine; C, cisplatin; O, oxaliplatin; 5FU, 5-fluorouracil; MST, median survival time; CI, confidence interval; NA, not available; RR, response rate

[a] Including the patients with squamous cell carcinoma (7%)

[b] Including the patients with squamous cell carcinoma (10%)

[c] Hazard ratio in the capecitabine group, as compared with the fluorouracil group

[d] Hazard ratio in the oxaliplatin group, as compared with the cisplatin group

[62] and a response rate of 34% in adenocarcinoma (JCOG 9205). An FP-based regimen is regarded as the standard therapy for gastric cancer in both Western and Eastern countries. Randomized trials in Western countries have demonstrated higher response rates and survival benefits with a regimen of epirubicin, cisplatin, and infused fluorouracil (ECF) [63, 64], and the efficacy of this regimen has also been confirmed by a meta-analysis [65]. Of these trials, one trial demonstrated a higher response rate in the patients with AEG than in those with gastric cancer (48.0% in AEG vs 37.0% in gastric cancer; $P = 0.041$) [64]. The REAL-2 trial demonstrated that cisplatin and fluorouracil in the ECF regimen could be replaced by oxaliplatin and capecitabine, respectively [68]. On the other hand, Van Cutsem et al. [66] demonstrated a survival benefit of a regimen of docetaxel, cisplatin, and fluorouracil (DCF) in 2006. In this trial, 22.1% (98/444) of the patients had primary tumors located in the esophagogastric junction, although the report did not show differences in treatment effects between the primary tumor sites. A phase III trial performed in Japan with a regimen of S-1 plus cisplatin demonstrated a significant survival benefit in comparison to S-1 alone [67], although the proportion of patients with AEG was not shown. In the light of these findings, such fluoropyrimidine and platinum-based regimens may be recommended for AEG patients with metastatic disease. The ToGA trial was performed for patients with human epithelial growth factor receptor (HER)-2-positive gastric carcinoma and AEG as a global trial and demonstrated that 5-fluorouracil (5-FU) or capecitabine/cisplatin with trastuzumab could improve the prognosis, in comparison to the regimens without trastuzumab [69]. This trial included 16.6%–19.7% of patients with AEG and there was no interaction between gastric cancer and AEG. Therefore, fluoropyrimidine/cisplatin with trastuzumab could be a standard chemotherapy for HER-2-positive AEG tumors.

Conclusions

The incidence of AEG is increasing dramatically in Western countries but not in Eastern countries. The incidence of Siewert type I tumors is less frequent in Eastern countries than in Western countries. On the other hand, other clinicopathological features, including patient's age, the male-to-female ratio, the pathological grade, tumor progression, and prognosis are similar in Western and Eastern countries. Surgically, AEG type I should be treated as esophageal cancer, while types II and III should be regarded as true gastric cancers. No phase III trials have yet identified a significant interaction comparing hazard ratios for death between AEG and true gastric cancers in the subset analyses.

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