and blood loss as intermediate factors instead of outcome variables. Among patients undergoing D2 lymphadenectomy, being overweight increased the risk for surgical complications and blood loss, whereas overweight was associated with only blood loss and operation time among patients receiving D3 lymphadenectomy.

Conclusions: Overweight increased the risk of surgical complications in patients undergoing gastrectomy both directly and indirectly through operation time and blood loss. The impact of overweight on surgical complications was more evident in patients undergoing a D2 dissection.

Key Words: Overweight—BMI—Complication—Gastric cancer—RCT—JCOG.

The incidence of overweight and obesity has been increasing in the general population, but the impact of overweight on surgical outcomes is unclear. Cancer surgery in overweight patients often takes longer and is associated with greater blood loss than in lean individuals as a result of the presence of excessive fat tissue impairing surgical procedures and lymph node dissection. The influence of overweight on the outcomes, e.g., surgical complications, surgical quality, hospital stay, and prognosis, of gastrectomy with D2 lymph node dissection for patients with gastric cancer is controversial.[1–5] These data were derived retrospectively from a single institution, but the surgical procedures and disease stages varied.

A prospective study from multiple institutions that use a similar surgical procedure is the ideal means to assess the impact of overweight on surgical outcomes and overall prognosis. A randomized trial, Japan Clinical Oncology Group (JCOG) 9501, was launched in 1995 to explore the potential survival benefit of extended para-aortic D3 dissection over standard D2 dissection. This trial provided the opportunity to prospectively evaluate collected data regarding the effect of overweight on surgical outcome after D2 or D3 dissection. Because a patient's physical condition, including body mass index (BMI), could affect treatment indications for either D2 or D3, an observational study may not correctly compare potential differences between groups. Thus, we used the JCOG data to investigate the interaction of D2/D3 dissection and overweight on surgical complications in a randomized trial. In addition, we examined whether overweight directly influences the occurrence of complications or if the effects of overweight may be mediated by associated factors, such as operation time and blood loss.

PATIENTS AND METHODS

Between June 1995 and April 2001, a total of 523 patients registered in the JCOG9501 study were randomly allocated to either D2 (n = 263) or D3 dissection (n = 260) by balancing the groups according to institution, tumor growth pattern (expansive vs. infiltrative growth) and tumor (T) stage (cT2b vs. cT3/cT4). Patients aged < 76 years with histologically proven and resectable primary gastric carcinoma with an estimated depth of SS (invading subserosa: cT2b), SE (penetrating serosa: cT3), or SI (invading adjacent structures: cT4) were recruited after providing informed consent as described elsewhere.[6] Patients with free cancer cells by cytological examination of peritoneal washes and those with type 4 tumor (linitis plastica type) were excluded.

Patients underwent appropriate gastrectomy with systematic lymphadenectomy as allocated by the study protocol. Perigastric lymph nodes (nodal station nos. 1, 3, 4, 5, and 6 according to the Japanese Classification of Gastric Cancer) and nodes at the base of the left gastric artery (no. 7), along the common hepatic artery (no. 8) and at the base of the splenic artery (no. 11) were routinely resected. Lymph nodes along the hepatoduodenal ligament and behind the pancreatic head (nos. 12 and 13) were resected when the primary lesion was located in the lower third of the stomach. Lymph nodes along the left side of the cardia (no. 2), within the splenogastric ligament (no. 4sa) and at the splenic hilum (no. 10), were resected with the spleen when total or proximal gastrectomy was performed. In patients randomized to a D3 lymphadenectomy group, para-aortic lymph nodes from the level of the celiac trunk down to the root of the inferior mesenteric artery (nos. 16a2 and 16b1) were dissected. The mode of reconstruction after resection was not specified.

Information on complications (including major surgical complications) and patient backgrounds (including height and body weight) was extracted from the case report forms for the trial. In this study, anastomotic leakage, pancreatic fistula, and abdominal abscess are defined as surgical complications. Anastomotic leakage was defined as dehiscence confirmed by radiographic examination that used contrast medium. Pancreatic fistula was diagnosed if

there was prolonged purulent discharge that contained pancreatic juice from the drainage tube. In addition, pneumonia and other complications were evaluated as complications.

According to the World Health Organization classification, BMI ≥ 25 is considered as overweight and BMI < 25 as nonoverweight.[7] Factors that might affect the risk of overall and major surgical complications, such as sex, age, tumor location, pathological (p) T category (pT2 and pT3 vs. pT4), extent of lymphadenectomy, type of gastrectomy, splenectomy, and pancreatectomy were evaluated as potential confounding factors. The difference in the distribution of these factors between BMI < 25 and BMI ≥ 25 were examined by χ^2 test. The effect of overweight on the complications was evaluated by odds ratio. In addition, the effect of overweight on operating time, amount of blood loss, need for autologous blood transfusion, reoperation, and hospital death was also evaluated by odds ratio. Operating time, blood loss, and the number of retrieved lymph nodes were divided into tertiles as previously described[8] and used as binary variables by dichotomizing the highest tertiles and the remaining two tertiles because biologically meaningful cutoff points could not be defined. In addition to the univariate analysis, all the analyses were conducted adjusting all the potential confounding factors by logistic regression.

To evaluate the effect of overweight on complications, logistic regression on the complications were conducted with overweight as exposure and operating time and blood loss as intermediate factors in addition to the other potential confounding variables. This analysis reveals whether overweight affects complications directly, or indirectly through these intermediate factors.

To see the difference of the effect of overweight between D2 and D3 dissection, all the analyses were repeated separately for the D2 and D3 subgroups, and these interactions were also evaluated. All statistical analyses were performed SAS software version 8.12 (SAS Institute, Tokyo, Japan). *P* values less than .05 were considered statistically significant, and all tests were two-sided.

RESULTS

Seventy-seven patients were classified as overweight with BMI ≥ 25, and 38 and 39 of these patients underwent D2 or D3 lymphadenectomy, respectively. In 446 patients classified as nonoverweight with BMI < 25, 225 received D2 and 221 received D3 lymphadenectomy. Total gastrectomy was performed in 199 (38.0%) of 523 patients and proximal gastrectomy in 4; the remaining patients underwent distal gastrectomy. Splenectomy was performed in 191 patients (36.5%) and distal pancreatectomy in 22 (4.2%). The background characteristics of patients with different BMIs are listed in Table 1. There were no statistically significant differences in sex, age, tumor location, clinical T stage, lymph node dissection, type of gastrectomy, and incidence of combined resection between the two groups, and the two groups were well balanced.

TABLE 1. *Backgrounds of patients according to body mass index (BMI)*

Factor	BMI < 25 (n = 446)	BMI ≥ 25 (n = 77)	Total number	*P* value
Sex				
M	301	57	358	.26
F	145	20	165	
Age				
< 56	137	23	160	.93
56–65	176	31	207	
> 65	133	23	156	
Location				
A (lower third)	188	29	217	.59
M (middle third)	173	33	206	
C (upper third)	85	15	100	
Clinical tumor stage				
cT2b	161	31	192	.38
cT3	268	41	309	
cT4	17	5	22	
Lymph node dissection				
D2	225	38	263	.86
D3	221	39	260	
Type of gastrectomy				
Distal	272	48	320	.82
Total/proximal	174	29	203	
Splenectomy				
No	283	49	332	.98
Yes	163	28	191	
Pancreatectomy				
No	427	74	501	.88
Yes	19	3	22	

In the entire sample, any complications were identified in 128 patients (24.5%), and major surgical complications occurred in 49 patients (9.4%). Among overweight patients, however, the proportion developing either any or surgical complications was 35.1% and 19.5%, respectively. When assessed by univariate analysis, overweight statistically significantly increased the risk for pancreatic fistula, abdominal abscess, operation time, and blood loss (Table 2). Additionally, the number of retrieved lymph nodes was less in overweight patients. Multivariate analysis identified that overweight was significantly associated

TABLE 2. *Effect of overweight on postoperative complications and other outcome variables*[a]

Factors	BMI < 25	BMI ≥ 25	Univariate analysis: Odds ratio of BMI > 25 (95% CI)	Univariate analysis: *P* value	Multivariate analysis: Odds ratio of BMI > 25 (95% CI)	Multivariate analysis: *P* value
Operation time (min)						
>297	141	36	1.90 (1.16–3.10)	.01	2.24 (1.29–3.87)	.004
≤297	305	41	–		–	
Blood loss (mL)						
>710	131	44	3.21 (1.95–5.26)	<.001	3.74 (2.19–6.39)	<.001
≤710	315	33	–		–	
Blood transfusion						
Yes	98	17	1.01 (.56–1.80)	.98	1.10 (.59–2.03)	.77
No	348	60	–		–	
No. of retrieved lymph nodes						
≤54	137	33	1.69 (1.03–2.77)	.037	1.82 (1.06–3.14)	.031
>54	309	44	–		–	
Reoperation						
Yes	9	3	1.97 (.52–7.44)	.32	1.85 (.47–7.29)	.38
No	437	74	–		–	
Hospital death						
Yes	3	1	1.94 (.20–18.92)	.56	1.96 (.20–19.50)	.56
No	443	76	–		–	
Any complication						
Yes	101	27	1.84 (1.10–3.10)	.021	1.90 (1.11–3.24)	.019
No	345	50	–		–	
Surgical complication						
Yes	34	15	2.93 (1.51–5.69)	.002	3.35 (1.65–6.78)	<.001
No	412	62	–		–	
Anastomotic leak						
Yes	8	3	2.22 (.58–8.56)	.25	2.14 (.54–8.47)	.28
No	438	74	–		–	
Pancreatic fistula						
Yes	20	10	3.18 (1.43–7.09)	.005	4.18 (1.71–10.22)	.002
No	426	67	–		–	
Abdominal abscess						
Yes	19	10	3.35 (1.50–7.52)	.003	3.51 (1.52–8.12)	.003
No	427	67	–		–	
Pneumonia						
Yes	12	4	1.98 (.62–6.31)	.25	1.88 (.58–6.13)	.29
No	434	73	–		–	
Other complication						
Yes	65	11	0.98 (.49–1.95)	.95	0.97 (.48–1.95)	.93
No	381	66	–		–	

BMI, body mass index; 95% CI, 95% confidence interval.

[a] Multivariate covariables: BMI, sex, age, tumor location, clinical tumor stage, lymph node dissection, type of gastrectomy, splenectomy, pancreatectomy.

with pancreatic fistula, abdominal abscess, operation time, and blood loss, and the odds ratios (95% confidence intervals) were 4.18 (1.71–10.22), 3.51 (1.52–8.12), 2.24 (1.29–3.87), and 3.74 (2.19–6.39), respectively. The number of retrieved lymph nodes decreased in overweight patients with an odds ratio of 1.82 (1.06–3.14). When operation time and blood loss were treated as intermediate factors, the odds ratios for the development of pancreatic fistula and abdominal abscess decreased to 3.48 and 2.47, respectively, but were still statistically significant.

We next analyzed the D2 (n = 263) and D3 (n = 260) dissection subgroups (Table 3). In the D2 subgroup, overweight was significantly associated with pancreatic fistula, abdominal abscess, and blood loss with odds ratios (95% confidence intervals) of 4.74 (1.42–15.89), 4.72 (1.49–14.99), and 2.83 (1.33–6.04), respectively. In the D3 subgroup, only blood loss with an odds ratio of 5.05 (2.27–11.26) and operation time with an odds ratio of 2.27 were significantly associated with overweight, although the interaction *P* values between the D2 and D3 subgroups were not statistically significant for any of the factors examined.

DISCUSSION

We clearly showed that overweight patients are at increased risk for the development of organ/space

TABLE 3. *Effect of overweight on postoperative complications and other outcome variables stratified with lymph node dissection (D2 or D3)*[a]

Factor	D2 subgroup (n = 263)		D3 subgroup (n = 260)		
	Multivariate odds ratio of BMI ≥ 25 (95% CI)	*P* value	Multivariate odds ratio of BMI ≥ 25 (95% CI)	*P* value	Interaction *P* value
Operation time					
Operation time > 297 min	2.19 (.96–5.02)	.063	2.27 (1.09–4.73)	.028	.95
Blood loss > 710 mL	2.83 (1.33–6.04)	.007	5.05 (2.27–11.26)	< .001	.30
Blood transfusion	1.73 (.70–4.26)	.23	0.78 (.34–1.79)	.56	.20
No. of retrieved lymph nodes ≤54	2.73 (1.28–5.85)	.01	1.06 (.43–2.62)	.9	.12
Reoperation	4.21 (.64–27.61)	.13	0.82 (.09–7.39)	.86	.27
Hospital death	6.82 (.40–117.43)	.19	NE	.98	.94
Any complication	2.62 (1.23–5.61)	.013	1.39 (.65–2.98)	.4	.25
Surgical complications	4.20 (1.59–11.10)	.004	2.60 (.91–7.40)	.074	.51
Anastomotic leak	2.77 (.47–16.19)	.26	1.49 (.16–14.09)	.73	.67
Pancreatic fistula	4.74 (1.42–15.89)	.012	3.61 (.96–13.55)	.057	.77
Abdominal abscess	4.72 (1.49–14.99)	.009	2.55 (.73–8.85)	.14	.48
Pneumonia	2.81 (.79–10.04)	.11	NE	.97	.94
Other complications	1.08 (.34–3.37)	.9	0.91 (.37–2.23)	.83	.82

BMI, body mass index; NE, not able to estimate.
[a] Covariables: BMI, sex, age, tumor location, clinical tumor stage, type of gastrectomy, splenectomy, pancreatectomy.

surgical site infection (SSI) (abdominal abscess and pancreatic fistula) complications after gastrectomy with D2 or D3 dissection. Risk factors for the development of SSI in abdominal surgery have been intensively investigated. The presence of a preoperative cutaneous abscess or necrosis, sutures or anastomoses of the bowel, postoperative abdominal drainage, surgical treatment for cancer, and postoperative anticoagulant therapy were identified as risk factors for SSI in noncolorectal abdominal surgery.[9] However, others reported that operation time was the only statistically significant risk factor for SSI after gastrectomy,[10] and in colorectal surgery, diabetes and a 10% weight loss were associated with SSI.[11] Among all of these studies, overweight was not identified as a risk factor for SSI. BMI exhibited a direct relationship with operation time in cholecystectomy, colectomy, and unilateral mastectomy, but it was not associated with surgical complications.[12] Thus, BMI may not directly influence the occurrence of surgical complications or SSI in abdominal surgery, but increased operation time and blood loss secondary to BMI may be responsible for any identified negative outcomes. However, we analyzed operation time and blood loss as intermediate factors instead of outcome variables, and BMI was still associated with the development of pancreatic fistula and abdominal abscess, as seen previously.[8] This fact suggests that BMI has a direct effect on surgical complications besides indirect effects through operation time or blood loss.

Practically, the presence of a large amount of the viscera may disturb drainage of exudates and coagula, and excess fatty tissue may become necrotic more easily as a result of surgical manipulation. In addition, the demarcation between pancreas and fat tissues in overweight individuals is obscure because of greater fat deposition in the pancreas.[13,14] This could also be relevant in cases of gastrectomy requiring peripancreatic nodal dissection and mobilization of the pancreas. These factors may contribute to the increased occurrence of abdominal abscess and pancreatic fistula in overweight surgical patients.

Whites in general have a higher BMI than Japanese individuals, and the incidence of morbid obesity is marked and growing among patients in the United States and Europe. The proportions of patients with BMI ≥ 25 and BMI > 30 in the present study were only 14.7% and 1.0%, respectively, whereas one-third of the U.S. population is obese (BMI > 27).[15] These differences in patients' physique may partly explain observed differences in mortality and morbidity between the UK Medical Research Council (MRC) and Dutch trials and the present study.[16,17] The mortality of patients undergoing D2 dissection in the two Western studies was 13% and 10%, whereas morbidity was 46% and 43%. In contrast, we observed only 1.3% mortality and 35.1% morbidity in overweight patients undergoing D2 or D3 dissection. In addition to possible differences in patients' physique, experience and workload volume of surgeons are important factors that could contribute to different surgical outcomes.

In patients undergoing D2, but not D3, dissection, overweight was associated with surgical complications. Although these differences were not statistically

significant, this may be because of low statistical power to test the interactions. In contrast, only the odds ratios of long operation time and excessive blood loss increased were statistically significant in the D3 dissection group, as reported previously.[6] The increased risk of complications in nonoverweight patients in the D3 subgroup could explain these differences. Indeed, the cumulative incidence of all complications in normal patients was 17.8% in the D2 subgroup and 27.6% in the D3 subgroup. Thus, greater care should be taken in performing gastrectomy not only in all patients undergoing D3 dissection, but also in overweight patients undergoing D2 dissection.

The relationship between overweight and overall prognosis in patients with cancer is an important issue to resolve. The presence of excess fat impairs precise nodal dissection and decreases the yield of lymph nodes. In this study, the number of lymph nodes retrieved from overweight patients was far less compared with nonoverweight patients undergoing a D2, but not D3, dissection. In addition to the quality of lymph node dissection, comorbid conditions associated with overweight, such as cardiovascular diseases, pulmonary dysfunction, diabetes, and hypertension, may negatively affect the prognosis of postoperative patients.[18] The relationship between overweight and overall survival in patients with gastric cancer remains controversial.[1–4] A conclusive result cannot be obtained without a well-controlled prospective study, and the final results of the JCOG9501 trial should answer this important question. However, the present study provides some insight into this issue.

The proportion of overweight patients in this trial was low (14.7%). Therefore, the obtained results are not definitely conclusive, but they clearly suggest that caution is needed when performing gastrectomy for gastric cancer in overweight patients. In conclusion, overweight increased the risk of surgical complications in patients undergoing gastrectomy with lymphadenectomy.

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Tailoring treatments for curable gastric cancer

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Although its incidence is decreasing worldwide, gastric cancer is still a major cause of death. There is remarkable geographic variation, with 60 per cent of cases arising in Eastern Asia. In Japan and Korea, public access to endoscopy is assured and almost half of newly diagnosed patients are detected at an early stage. Surgeons in these countries have been able to develop new and exciting minimally invasive therapeutic options. In the West, on the other hand, most patients still present with advanced disease and the treatment options are limited. Furthermore, Western patients are often obese and unfit for surgery, making optimal gastrectomy difficult. Wherever they are in the world, however, surgeons must lead the treatment strategy for potentially curable gastric cancer because without resection there will be no cure.

Depth of tumour invasion (T) and lymph node metastasis are the most important prognostic factors, and they correlate closely with each other[1]. Clinical staging of lymph node status is unreliable, especially for early tumours, while the preoperative diagnosis of T1, and intraoperative distinction between T1/2 and T3/4, can be made quite accurately. So, unless extensive nodal metastasis is clinically evident, the T-stage serves as a key factor in therapeutic planning.

T1 tumours, or early gastric cancers, have a low risk of nodal metastasis and a gastrectomy with limited lymphadenectomy is sufficient for cure. Pylorus- and/or vagus-preserving gastrectomy, and laparoscopic surgery, are recent options in Japan and Korea. Some T1 tumours are even resected at endoscopy, without surgery[2]. The rationale for endoscopic mucosal resection derives from a meticulous analysis of the lymph node status of a large number of patients treated by gastrectomy; when an endoscopically resected tumour satisfies certain criteria, one can be confident that the patient is very unlikely to have nodal metastasis because hundreds of tumours in the same category have had no associated nodal metastasis. Surgeons should be aware of this option for early tumours, since the avoidance of gastrectomy has significant quality of life benefits for patients.

T2 gastric cancer might be regarded as localized disease, but it is associated with more frequent (over 50 per cent) and extensive nodal metastasis than T1, so sufficient lymphadenectomy should be planned. Systematic dissection of the nodes around the coeliac artery and its branches (D2) permits resection of the positive nodes associated with most T2 tumours. Hepatic metastases are rare. T1 and T2 gastric cancers are localized lesions that can be cured by surgery alone, and surgeons should take that responsibility.

Once the tumour penetrates the serosa (T3) or invades adjacent organs (T4), it begins to spread by routes other than the lymphatic system, notably through peritoneal dissemination and in the portal–hepatic blood. Furthermore, lymph node metastasis from T3/4 tumours sometimes overwhelms the regional network, with cancer cells entering the systemic circulation to cause bone and lung metastases. These are effectively beyond the surgeon's reach. In addition to these metastases, the primary lesion becomes larger and more infiltrative and the chance of obtaining an R0 resection diminishes. As a consequence, more than half the patients with T3/T4 tumours develop local or systemic recurrence of disease, which is almost always fatal.

Some surgeons are inclined to regard T3 and T4 gastric cancers as incurable, but the role of surgery should not be underestimated, even at these stages. Some local recurrence may be prevented by careful gastrectomy. Gastric and duodenal stump recurrence at least should be preventable by careful pre- and intraoperative histological examination of the resection margins. Other local recurrence can be attributed to residual lymph node metastasis around the coeliac artery. Complete clearance of the tumour-bearing nodes by D2 lymphadenectomy should diminish this problem and prolong survival. Japanese surgeons have believed this to be so for many years and two recent randomized controlled trials have now provided evidence to support the 'D2 concept' both directly and indirectly. One is the Taipei single-institution study comparing D1 and former D3 (current D2); this was completed without operative mortality and showed a significant survival benefit for D2[3]. The other is the American Intergroup study in which chemoradiation therapy to the gastric bed after limited lymphadenectomy (D0/D1) significantly decreased the local recurrence rate and increased long-term survival[4]. This can be

interpreted as showing that radiotherapy eliminated residual lymph node metastasis, which would have been removed by D2 resection.

The Intergroup study seems to have changed the standard care for gastric cancer in the USA, but its impact has been weak in Japan and Korea, where D2 lymphadenectomy is routinely and safely performed, and where local recurrence is not a major pattern of relapse. D2 lymphadenectomy is, however, technically demanding, with a pronounced learning curve. Patient fitness for surgery is another important factor for a safe operation, and patient obesity hampers the performance of even the most experienced surgeons[5]. When a safe D2 procedure cannot be expected due to any of these factors, adjuvant chemoradiotherapy might prove an adequate substitute. Surgeons now have alternatives for local tumour control and it is they who should assume responsibility for designing the best treatment for each patient.

Many randomized trials of adjuvant chemotherapy have failed to produce solid evidence of effect in patients with resectable cancers who are at high risk of systemic recurrence. However, the MAGIC trial in Europe has recently shown that a significant survival benefit accrues from peri-operative combination chemotherapy[6]. The role of lymphadenectomy is obscure in this trial because it was not standardized and simply left up to the choice of the individual surgeon. One must interpret the results as demonstrating that peri-operative chemotherapy has enough power to offset the influence of surgical diversity. Since the publication of this trial it has become more important than ever for surgeons to consider the treatment options for their patients before they operate.

In conclusion, the result of treatment for locally advanced gastric cancer is the sum of the effect of local tumour control by surgery, with or without radiotherapy and/or systemic chemotherapy. The role of each treatment modality varies according to the stage of disease, individual patient risk, surgical volume, available chemotherapy regimens and quality of radiotherapy. Evidence of the effect of different combinations of treatments should be established for each clinical circumstance and surgeons should play a key role here.

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Surgical Treatment of Advanced Gastric Cancer: Japanese Perspective

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Key Words
Esophagogastric junction · Gastric cancer, advanced · Surgical treatment

Abstract
The results of clinical trials regarding surgery of curable advanced gastric cancer and esophagogastric junction (EGJ) tumors are reviewed and summarized. Four clinical trials have evaluated D2 dissection for curable gastric cancer in the West. Two large trials in the UK and the Netherlands failed to prove the efficacy of D2 dissection. However, these trials had critical weak points. As they were carried out in a number of hospitals where there was no experience with this surgery, the quality of surgery and postoperative care were very poor making the hospital mortality unacceptably high. After these trials, an Italian group started a phase II study in 8 hospitals with a relatively high volume to confirm the safety of this procedure for Caucasians. They achieved 3% mortality, which was much smaller than that of even D1 in the former trials. These results first highlighted the importance of learning and hospital volume in D2 dissection. Survival results of the Dutch trial showed some difference between D1 and D2, but the difference was not statistically significant. This was attributed to the high hospital mortality and poor quality of surgery, especially low compliance of D2 and the high rate of extension of D1, making this comparison similar to that between D1.3 and D1.7. The results of the phase III study by the Italian group are awaited. Recently a Taiwanese trial proved the benefit of D2 dissection over D1 in a phase III trial. This was a single institutional trial with a sample size of 221 patients. The 5-year survival rate of D2 and D1 was 59.5 and 53.6%, respectively ($p = 0.04$). The Dutch trials for EGJ tumors showed a large difference in overall survival between the transthoracic and transhiatal approach for Siewert type 1 and 2 tumors, but this was not statistically significant, most likely due to the small sample size. In the subgroup analysis, they demonstrated that there was no survival difference in Siewert type 2 but a large difference in Siewert type 1. A Japanese study showed that there is no benefit to the thoraco-abdominal approach over the transhiatal approach for EGJ tumors whose invasion in the esophagus is 3 cm or less. These two trials clearly demonstrated that mediastinal dissection through a right thoracotomy is recommendable for Siewert type 1, while the transhiatal approach should be considered as standard for Siewert type 2.

Background

In the guidelines of the Japan Gastric Cancer Association, standard surgery for curable advanced gastric cancer is defined as a more than 2/3 gastrectomy with D2 dissection [1]. With the results of several important

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Table 1. Morbidity and mortality after D2 dissection and hospital volume

Trial	Type	n	Number of patients per hospital per year	Mortality %	Morbidity %	Reference
Hong Kong	RCT	30	7.5	3	57	Robertson et al. [7]
MRC	RCT	200	1.5	13	46	Cuschieri et al. [8]
Dutch	RCT	331	1.0	10	43	Bonenkamp et al. [2]
Taiwanese	RCT	211	18.5	0	17	Wu et al. [16]
IGCSG	Phase II	191	8.0	3	21	Degiuli et al. [4]
IGCSG	RCT	82	4.3	0	16	Degiuli et al. [6]
Italian study	Retro	451	21.5	2	17	Roviello et al. [9]

RCT = Randomized controlled trial; MRC = Medical Research Council; IGCSG = Italian Gastric Cancer Study Group.

clinical trials, not only in surgery but also multidisciplinary treatment, this policy of the Japanese guidelines might be challenged. In this article, the Japanese perspective of curative surgery for advanced gastric cancer is explained.

Results of European Trials

There have been four European clinical trials on D2 dissection for curable gastric cancer [2–5]. Three of them were phase III trials and the remainder was the only phase II trial in the world. The phase III trials were carried out by the Medical Research Council (MRC) [3], the Dutch Gastric Cancer Group (DGCG) [2] and the Italian Gastric Cancer Study Group (IGCSG) [5]. The first two trials have already shown negative results, while the long-term results of the last one are awaited. After the first two large phase III trials showed quite high hospital mortality after D2 dissection on Caucasians, the IGCSG started with a phase II study to confirm the safety of the D2 dissection in their population [4].

Morbidity and Mortality of D2 Dissection in These Trials

The Dutch and the MRC studies showed extremely high hospital mortality after D2 dissection, 10 and 13%, respectively. Such a high mortality is no longer accepted for any cancer surgery today. These results were heavily criticized and attributed to a very low hospital volume [6]. Table 1 shows the clear negative correlation between hospital volume and hospital mortality after D2 dissection in the literature. This high mortality was also attributed to splenectomy and pancreatectomy. Especially in the MRC trial, many surgeons thought that D2 distal gastrectomy included splenectomy, and splenectomy was carried out in many distal gastrectomy cases [10]. This was based on the misunderstanding of the definition of D2 gastrectomy by the Japanese Research Society for Gastric Cancer [11]. In Japan, splenectomy was included in D2 dissection only when a total gastrectomy was carried out. Together with thorough lymph node dissection of the lesser curvature, splenectomy causes serious ischemia of the remnant stomach, necrosis of the remnant stomach or anastomotic leakage. This was also the case in the DGCG trial [12]. In the multivariate analysis of hospital mortality, splenectomy was one of the factors most responsible for mortality. The lack of experience in treating major surgical complications after D2 dissection, namely, anastomotic leakage, pancreatic fistula (juice leak) or intra-abdominal abscess, led to a much higher mortality than a Japanese specialist center where a few hundred patients were treated yearly (table 2) [6]. With less than a few cases yearly, surgeons can never learn how to treat these major complications to avoid treatment-related death. This high mortality after D2 dissection in the Dutch trial might also be attributed to the greater fragility of the Dutch compared with the Japanese. However, the results of another Dutch trial comparing a transthoracic esophagogastrectomy via right thoracotomy with a transhiatal approach for esophagogastric junction (EGJ) tumors showed a much lower mortality in the both treatment arms, 4% for the former and 2% for the latter [13]. This trial was carried out exclusively in two major cancer hospitals which have a reasonably high hospital volume. This suggests that high mortality in the D1/D2 trial was not attributed to the fragility of the Dutch patients but to the very low hospital volume.

Table 2. Mortality after postoperative major surgical complications

Complication	Dutch trial (n = 711)			NCCH trial (1982–1987; n = 1,197)			p
	deceased patients	affected patients	%	deceased patients	affected patients	%	
Leakage	19	46	41.3	12	84	14.3	0.0005
Distal	9	22	40.1	2	23	8.7	0.012
Total	10	24	41.7	10	60	16.7	0.0047
Abscess or pancreatic fistula	19	91	20.9	2	75	2.7	0.0004

NCCH = National Cancer Center Hospital.

After these two trials with dismal short-term results, the IGCSG started a phase II trial to confirm the safety. Actually a 3% mortality was found in 8 hospitals with a total of 191 patients [4]. They avoided the routine use of distal pancreatectomy in cases of total gastrectomy; instead they adopted pancreas-preserving total gastrectomy, the so-called Maruyama technique [5]. Thus they avoided splenectomy in distal gastrectomy and distal pancreatectomy in total gastrectomy. The morbidity and mortality shown by the phase II study was confirmed by the results of the interim analysis of the IGCSG phase III trial. Hospital mortality was 1.3% after D1 but 0% after D2 gastrectomy in this study [6].

Survival Results after D2 Dissection

In the MRC trial, the survival curve of D2 was never better than that of D1 until the end of the trial. In the Dutch trial, the survival curve of D2 caught up with that of D1 after 4 years and remained superior, but the difference between D1 and D2 survival never reached statistical significance. Practically, in the MRC trial, there was no quality control of surgery and the quality seemed poor due to the mortality. In the Dutch trial, there were several efforts to control the quality of performance including direct tuition of the D2 dissection in the operation theater and quality evaluation by the number of dissected nodes. According to their results, there were many cases in the D1 group where more extended dissection than D1 was actually carried out and many patients in the D2 group underwent less than D2 dissection [14]. Eventually they compared D1.3 versus D1.7, for example, minimizing the difference between the arms. Low-quality surgery together with a much higher mortality immediately after surgery could explain why D2 dissection was not found to be beneficial. In fact, the Italian group showed much better survival results in their phase II trial than those of the Dutch trial [15]. The 5-year survival rates for stages IA, IB, II, IIIA and IIIB were 93, 88, 60, 40 and 20%, respectively, while those in the Dutch trial were 81, 61, 42, 28 and 13%, respectively. Survival results of the phase III study by the IGCSG are awaited.

Results of Taiwanese Trial

Recently a Taiwanese hospital published the results of a phase III study comparing D1 versus D2/3 surgery for curable gastric cancer in a single institution [16]. Their D3 includes lymph node stations in the hepatoduodenal ligament, on the superior mesenteric vein, behind the common hepatic artery and on the posterior pancreatic surface in addition to D2 dissection, according to the 1st English Edition of the Japanese Classification of Gastric Carcinoma [17]. They showed statistically significant improvement in survival by D2/3 surgery over D1. The 5-year overall survival of D2/3 and D1 was 59.5 and 53.6%, respectively ($p = 0.04$; fig. 1). This study included only three surgeons at a single institution, therefore the quality of surgery in this study seemed to be more identical than in multicenter trials. This is the first randomized controlled study which showed significantly better overall survival of D2/3 surgery than D1 in the world. There are several remarkable differences between this study and the Dutch study. Due to the much higher hospital volume and good quality control at a single institution, the hospital mortality after D2/3 was 0% in this study, while it was as high as 10% in the Dutch trial. More patients in the Taiwanese study had antral tumors and underwent distal subtotal gastrectomy than the Dutch trial. The proportion of those who underwent distal subtotal gastrectomy in this study and the Dutch study was 76 and 66%, respectively. Due to the rather small sample size and

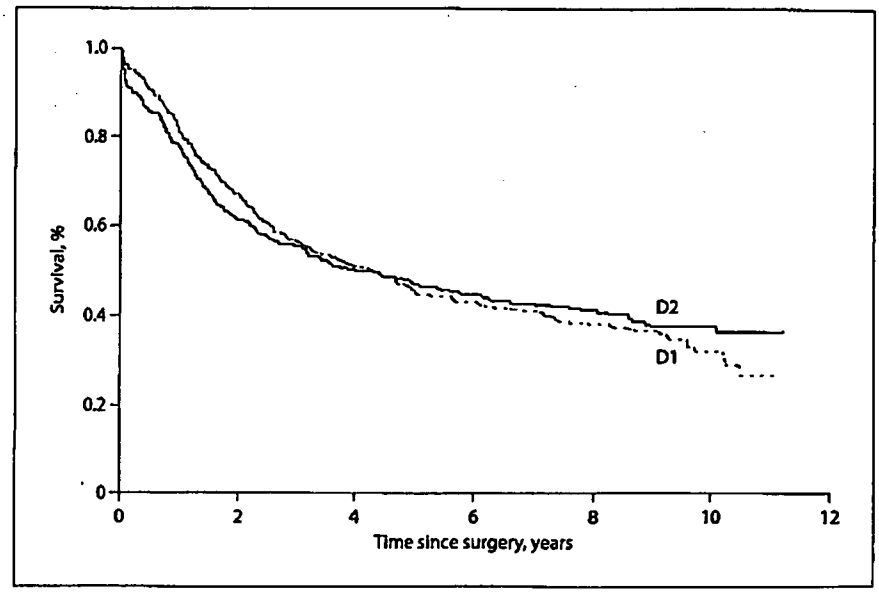

Fig. 1. Overall survival curves of the entire patient population by treatment groups in the Dutch trial.

modest survival benefit, this study cannot be considered as solid evidence for the superiority of D2 over D1 dissection.

Results of Adjuvant Chemoradiotherapy

A phase III study comparing surgery alone with postoperative adjuvant chemoradiotherapy (CRT), the INT0116/SWOG9008, showed a large survival benefit of CRT for curable gastric cancer; the median survival time of surgery alone was 27 months, compared with 36 months for CRT [18]. The hazard ratio for death was 1.35 (95% CI 1.09–1.66; p = 0.005). In this trial, the tested arm included curative surgery and radiation therapy of 45 Gy with combination chemotherapy using fluorouracil and leucovorin (5 courses of 5-day continuous infusion, including 2 courses of concomitant administration). However, detailed analysis of the type of surgery revealed that 54 and 36% of the patients underwent D0 and D1 surgery, respectively, while only 10% underwent D2 dissection. Although there was no statistically significant interaction between the subgroups divided by the degree of lymph node dissection and the effect of treatment, a benefit from treatment was observed only in the D0 or D1 group in the subset analysis [19]. In the retrospective detailed analysis, the researchers of this study found that surgical undertreatment clearly undermined the survival of patients [20]. Thus this study for the first time proved the efficacy of local control by radiation for gastric cancer and proved that limited surgery alone cannot be sufficient treatment for this cancer.

The patient population enrolled in the test arm of this study was by chance quite similar to the population enrolled in a Japanese clinical trial comparing surgery alone with surgery followed by adjuvant CTX (JCOG9206-2) [21]. Table 3 shows the tumor and patient characteristics of the 2 groups. Most of the prognostic factors, i.e., histological type, tumor location, age, tumor size, and, most important, tumor depth, were reasonably comparable between the groups. Although these 2 groups were the patients of two different trials with two different treatment methods, they are identical and therefore the treatment results are more or less comparable. The 5-year overall survival was 42 and 61% in the INT0116 and JCOG9206-2, respectively. This suggests strongly that D2 surgery alone might produce better survival than limited surgery followed by CRT and that the effect of adjuvant CTX might not be expected after D2 as suggested by the subgroup analysis.

Surgical Treatment for Esophagogastric Junction Tumors

Hulscher et al. [13] reported the results of a phase III trial for Siewert type 1 and 2 tumors, comparing two surgical approaches, a transthoracic esophagogastrectomy

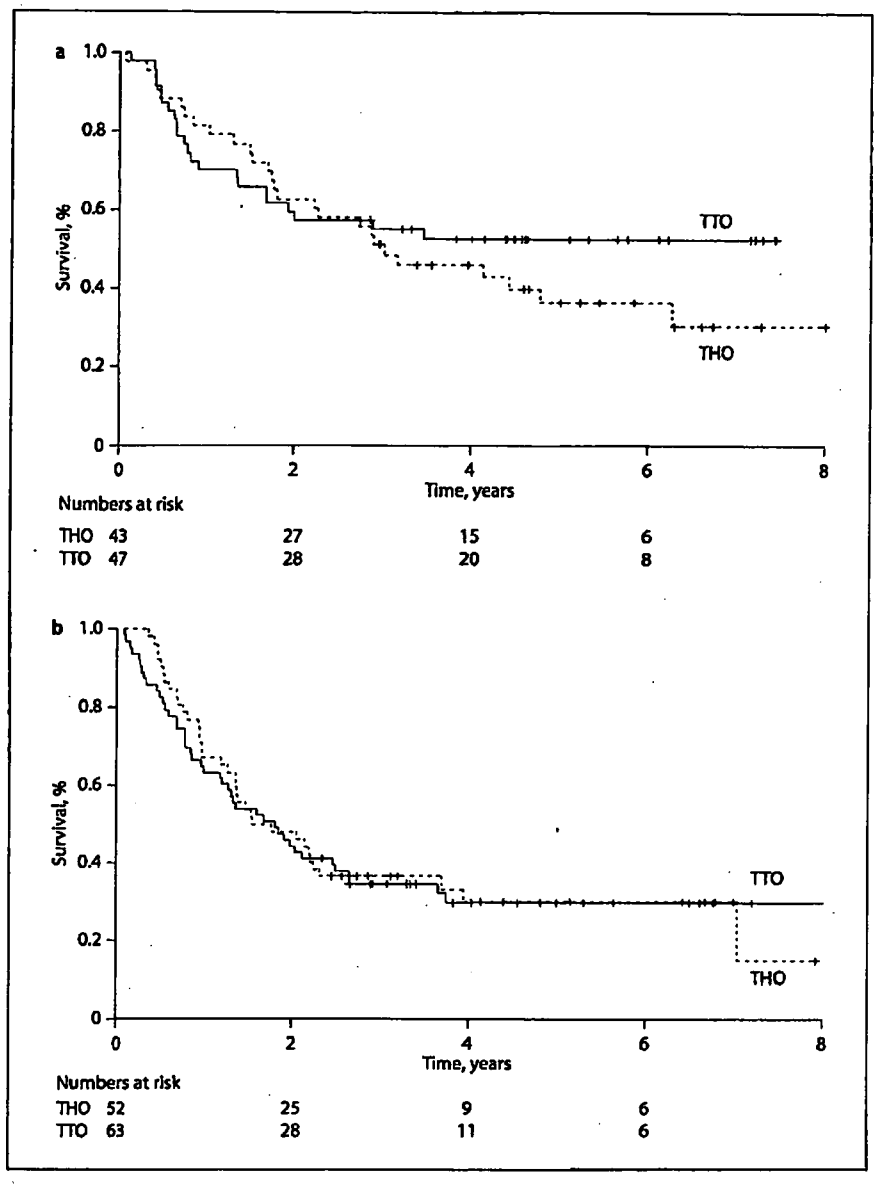

Fig. 2. Overall survival curves in patients with Siewert type 1 (**a**) and Siewert type 2 (**b**) tumors, by treatment groups. THO = Transthoracic esophagectomy; TTO = transhiatal esophagectomy.

via right thoracotomy with transhiatal one. The overall survival in the entire study population did not show statistically significant differences between the 2 groups. However, the actual difference in the survival curves was impressive and the overall 5-year survival rate was 29% for the transhiatal approach and 39% for the transthoracic one ($p = 0.38$; fig. 1). In the subgroup analysis according to the Siewert classification, the difference in overall 5-year survival was as large as 17% (95% CI −3 to 37%) for Siewert type 1 ($n = 90$), while it was only 1% for Siewert type 2 ($n = 115$; fig. 2) [22]. Due to the small sample size, this study was not able to show any statistically significant difference, but the results strongly suggest that thorough mediastinal dissection via right thoracotomy is needed for Siewert type 1 but not for type 2. With higher morbidity after transthoracic dissection, the transhiatal approach might be better treatment for Siewert type 2.

Sasako et al. [23] reported the results of a phase III trial for Siewert type 2 and 3 tumors, comparing a left thoraco-abdominal approach versus a transhiatal one. All these tumors were diagnosed to have esophageal in-

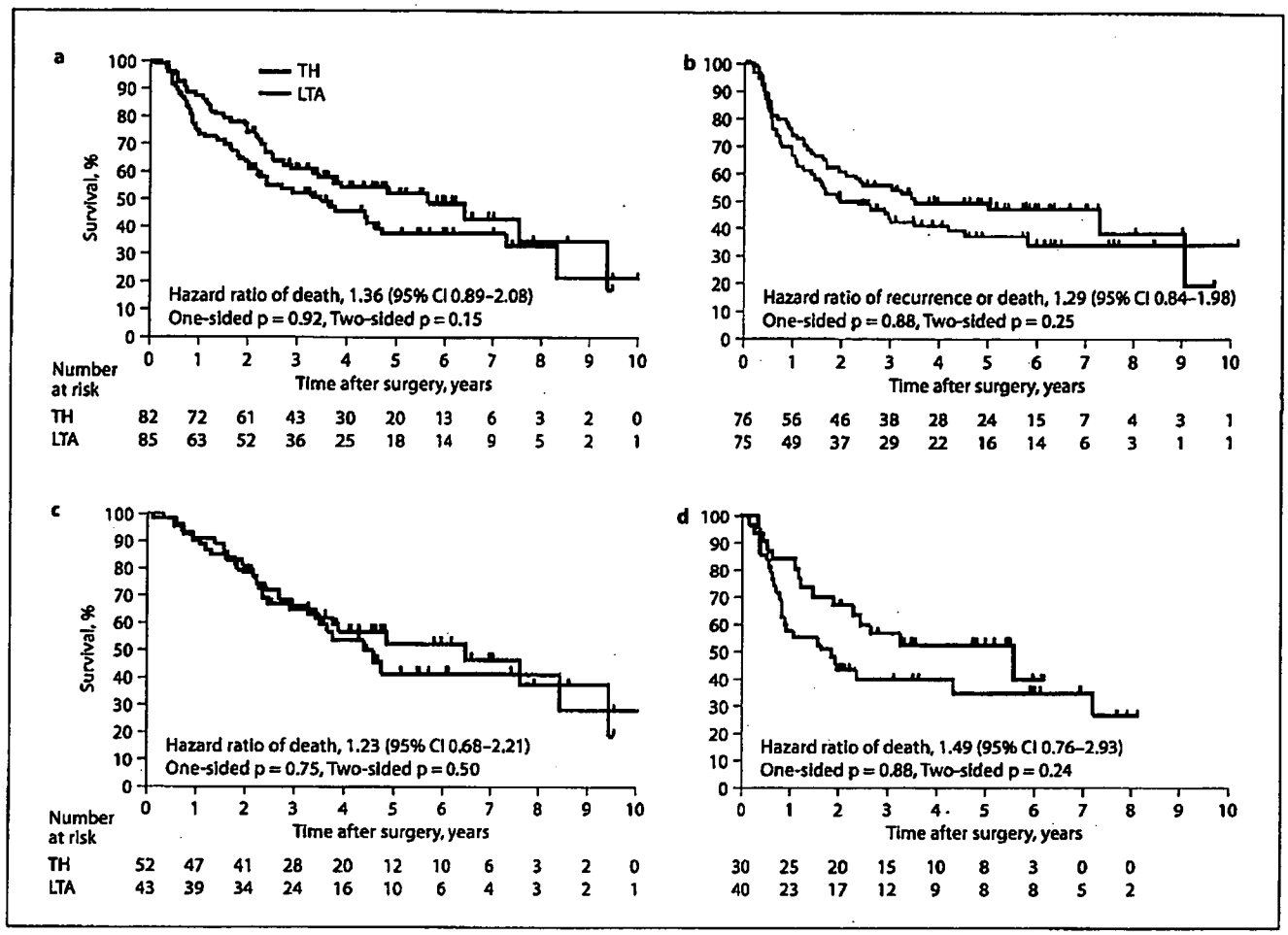

Fig. 3. Overall survival (**a**) and disease-free survival (**b**) of the entire patient population and overall survival in patients with Siewert type 2 (**c**) and type 3 (**d**) tumors by treatment groups. TH = Transhiatal; LTA = left thoraco-abdominal. Reprinted with permission from *The Lancet Oncology* [23].

Table 3. Comparison between the INT0116 study and JCOG9206-2 study

	IT0116/SWOG9008	JCOG9206-2
Surgery (D0/1/2), %	54/36/10	4/67/33
Adjuvant	Rad (45 Gy)+CX (5FU+LV)	CDDP+5FU+UFT (50%), none (50%)
Number of patients	281 (tested arm)	268 (control = 133, tested = 135)
Tumor location	A (53%), Corp (24%), cardia (21%), multifocal (2%)	L (31%), M (32%), U (28%), wide (9%)
pT (T1/T2/T3/T4)	14/74/175/18	5/87/165/11
Proportion of T3/4, %	69	66
Node positive, %	85	72
TRD	3 (1.1%)	4 (1.5%)
Overall survival (5 years), %	42	control 61, tested 62

Rad = Radiation; CX = chemotherapy; LV = leucovorin; 5FU = 5-fluorouracil; CDDP = cis-diamminedichloroplatinum; UFT = uracil-ftegafur; A = antrum; Corp = gastric body; L = distal one third; M = middle one third; U = upper one third; wide = wide spread; TRD = treatment-related death.

vasion of 3 cm or less. They clearly demonstrated that there was no survival benefit from the left thoraco-abdominal approach which was accompanied by a much higher morbidity and more remarkable deterioration of pulmonary function than the transhiatal approach. The subgroup analysis showed no survival benefit for both Siewert type 2 and 3. Especially for Siewert type 3, the transhiatal approach showed much better survival than the left thoracotomy approach (fig. 3).

From these two trials, the transhiatal approach is regarded as the standard treatment for Siewert type 2 and 3 tumors, while the transthoracic approach via right thoracotomy is recommended for Siewert type 1 tumors.

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Original Article

Two distinct pathways of tumorigenesis of adenocarcinomas of the esophagogastric junction, related or unrelated to intestinal metaplasia

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It is still uncertain whether intestinal metaplasia (IM) of the esophagogastric junction (EGJ) plays a role in the development of adenocarcinoma of the esophagogastric junction (AEGJ). The purpose of the present study was to clarify the relationship between AEGJ and IM in Japanese patients. Forty-eight AEGJ, <3 cm and centered within 1 cm of the EGJ, were investigated. The frequency of IM around AEGJ and the correlation between IM and clinicopathological features were examined. IM was present in the surrounding mucosa in 22 of 48 cases (46%), and was seen more frequently in older patients ($P = 0.008$). Lymph node metastasis was observed only in cases in which the tumors were not associated with IM ($P = 0.017$). The gastric phenotype was seen almost exclusively in the group without IM, while the intestinal phenotype was predominant in the group with IM ($P = 0.003$). The present study found a lower incidence of associated IM than Western studies, and there were significant differences in clinicopathological features between AEGJ with and without IM. It is suggested that AEGJ may develop via two distinct pathways in Japanese patients: IM-related and IM-unrelated.

Key words: adenocarcinoma, esophagogastric junction, gastric/intestinal phenotypic expression, intestinal metaplasia

In parallel with the rising incidence of adenocarcinoma of the esophagus, adenocarcinoma of the esophagogastric junction (AEGJ) has been observed with increasing frequency in Western countries.[1,2] Intestinal metaplasia (IM) is recognized as a precancerous lesion of Barrett's esophagus or the distal stomach,[3–5] but its role in the development of AEGJ is still unclear. Some Western studies have noted a variable frequency of IM in the background mucosa of AEGJ, ranging from 38% to 100%.[6–11] For instance, the frequency of accompanying IM was reportedly as high as 69–100% for tumors with a mean size of <2.3 cm,[8–10] whereas it was as low as 42% for tumors >3.5 cm[6,7] Cameron *et al.* have suggested that large-sized AEGJ probably overgrow and conceal the underlying specialized columnar epithelium (SCE) from which they arise, whereas small tumors preserve their background mucosa of origin.[6,10] They concluded that all AEGJ might arise from IM of the esophagogastric junction (EGJ). In contrast, in Japanese patients, Tsuji *et al.* found IM adjacent to the tumor in the resected specimen in 21 (38%) of 54 cases of AEGJ <4 cm[11] They reported that there were two different types of AEGJ in Japan: tumors straddling the EGJ and tumors occurring entirely below the EGJ, the former having less IM in the surrounding mucosa.

In the present study we reviewed 48 small AEGJ to clarify the relationship between AEGJ and IM in Japanese patients. AEGJ was defined as an adenocarcinoma with its center located within 1 cm of the EGJ, strictly excluding adenocarcinoma arising from gastric fundic gland mucosa. The present study involves the largest number of cases of AEGJ <3.0 cm reported to date.

MATERIALS AND METHODS

Cases

We reviewed files of consecutive cases of AEGJ resected surgically with lymph node dissection, or endoscopic

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Table 1 Antibodies and cell types recognized

Antigen (clone)	Clonality	Dilution	Source	Expression in normal tissue
MUC5AC (45M1)	Monoclonal	1:100	Novocastra, Newcastle upon Tyne, UK	Gastric foveolar epithelial cell
MUC6 (CLH5)	Monoclonal	1:100	Novocastra, Newcastle upon Tyne, UK	Mucous neck cell, pyloric gland cell
MUC2 (Ccp58)	Monoclonal	1:200	Novocastra, Newcastle upon Tyne, UK	Goblet cell in small intestine and colon
CD10 (56C6)	Monoclonal	1:200	Novocastra, Newcastle upon Tyne, UK	Brush border on luminal surface
Cdx2 (CDX2-88)	Monoclonal	1/200	BioGenex, San Roman, CA, USA	Intestinal epithelial cells
CK7 (OV-TL 12/30)	Monoclonal	1/500	Dako, Carpinteria, CA, USA	–
CK20 (Ks 20.8)	Monoclonal	1/50	Dako, Carpinteria, CA, USA	–

mucosal resection (EMR), between January 1989 and December 2003 at the National Cancer Center Central Hospital. In the present study AEGJ was defined as an adenocarcinoma with its center located within 1 cm of the EGJ, strictly excluding adenocarcinoma arising from gastric fundic gland mucosa. Patients who had tumors <3 cm in maximum diameter were selected. Those who had received neoadjuvant therapy were excluded. Finally, 48 patients with small AEGJ met the study criteria. Of these 48 cases, we obtained 32 specimens by surgical resection with lymph node dissection and 16 by EMR.

Clinicopathological review

Clinicopathological characteristics, including patient age and gender, macroscopic type of tumor, tumor size, depth of tumor invasion, lymph node metastasis, and histological type, were reviewed. Pathological stage of AEGJ was determined according to the TNM Classification of Malignant Tumors established by the International Union Against Cancer.[12] The tumors were classified macroscopically as elevated, depressed, combined (combination of elevated and depressed type), or ulcerated type.

Histological examination

The resected specimens were fixed in 10% buffered formalin, and cut into serial 5 mm-wide slices in the case of surgical specimens and into 2 mm-wide slices in the case of EMR specimens. The slices were embedded in paraffin, cut into 3 μm-thick sections, and stained with HE.

The tumors were divided into differentiated or undifferentiated type according to the histological classification of Nakamura *et al.*[13] Each tumor was primarily classified on the basis of its predominant histological features, and then the presence or absence of a focal undifferentiated component was recorded. Undifferentiated component was defined as the presence of even a little undifferentiated type tumor according to Nakamura's classification, despite its predominant histology. The surrounding mucosa adjacent to cancer tissue was checked, the presence of IM was examined. IM was defined as the presence of goblet cells detected by HE staining and by immunohistochemical staining for MUC2.

Immunohistochemistry was performed on representative tissue sections of each lesion, using monoclonal antibodies to examine the gastric and intestinal phenotypic expression, as shown in Table 1.

Except for Cdx2, immunohistochemistry was performed using the avidin–biotinyl–peroxidase complex (ABC) method, as described previously.[14] An avidin–biotin horseradish peroxidase complex kit (StreptABComplex/HRP, Dako, Glostrup, Denmark) was used for the ABC method, in accordance with the manufacturer's instructions. For Cdx2, we used the L-SAB method with a Super Sensitive Ready-to-Use kit (BioGenex, San Ramon, CA, USA), also in accordance with the instructions supplied. 3,3′-Diaminobenzidine tetrachloride was used as a chromogen. Nuclear counterstaining was carried out with Mayer's hematoxylin. Negative controls involved substitution of similar dilutions of control mouse IgG1. Sections containing gastric foveolar cells, deep gastric gland cells and small-intestinal epithelial cells were used as positive controls for MUC5AC, MUC6, MUC2, CD10 and Cdx2, respectively.

Staining for MUC5AC, MUC6, MUC2, CD10, and Cdx2 was judged positive when >25% of the tumor cells were stained. Staining for MUC5AC, MUC6, and MUC2 was judged positive when it occurred in the cytoplasm, that for CD10 when the luminal surface was stained, and that for Cdx2 when nuclei were stained. MUC5AC and MUC6 were used as gastric phenotype markers, and MUC2, CD10, and Cdx2 as intestinal phenotype markers. Based on the immunohistochemical results, tumors were classified as having the gastric phenotype when they were positive for MUC5AC and/or MUC6 and negative for MUC2, CD10 and Cdx2, and the intestinal phenotype when they were positive for at least one of MUC2, CD10, and Cdx2, and negative for MUC5AC and MUC6, and the mixed phenotype when both gastric and intestinal characteristics were present. If a tumor was negative for all five of these antigens, it was judged as unclassified. We also examined the correlation between the gastric or intestinal phenotype and the presence of undifferentiated components.

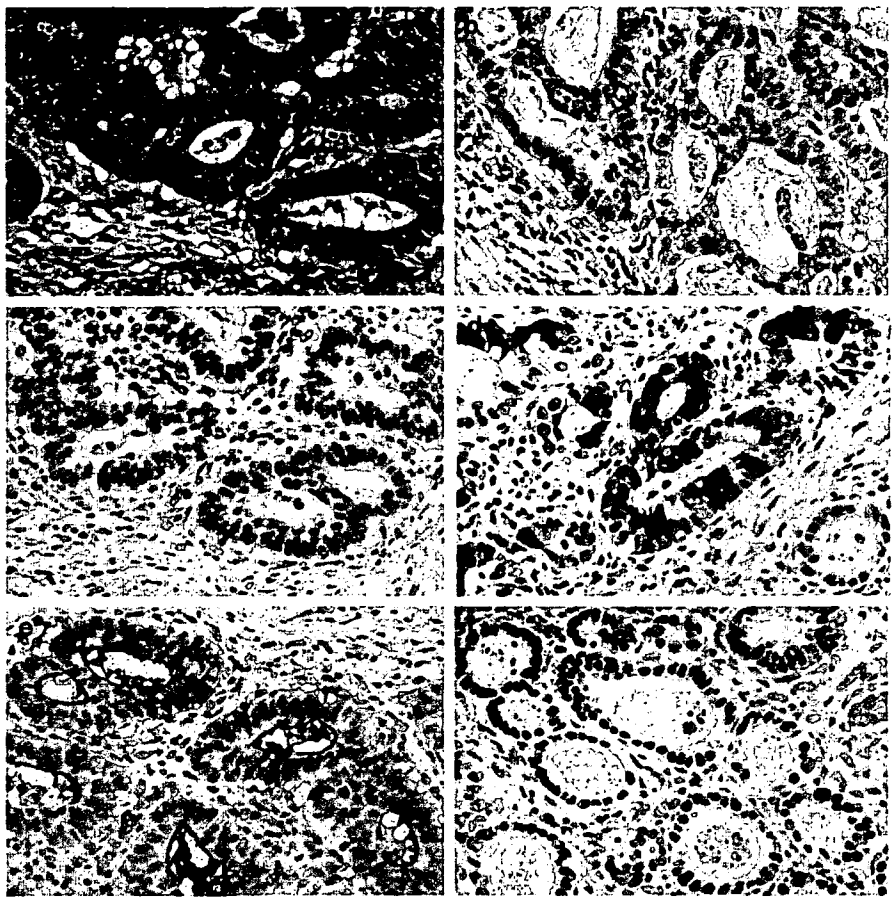

Figure 1 Adenocarcinoma of esophagogastric junction with intestinal phenotype. (**a**) Tumor cells have eosinophilic cytoplasm (HE). (**b**) MUC5AC and (**c**) MUC6 are not expressed in the cytoplasm of the tumor cells. Tumor cells are positive for (**d**) MUC2, (**e**) CD10, and (**f**) Cdx2.

The histological and immunohistochemical studies were reviewed by three pathologists (S. N., Y. N. and T. S.) without knowledge of the patients' clinical background.

Statistics

Statistical analysis was performed with the SPSS statistical software package (SPSS Japan, Tokyo, Japan). Comparisons between groups were made using χ^2 test or Mann–Whitney *U*-test as appropriate. Statistical significance was defined as $P < 0.050$.

RESULTS

Clinicopathological characteristics

The mean age of the patients was 65.0 years (range, 37–85 years). There was a strong predominance of men in the present series (male : female ratio, 43:5). The mean tumor width was 1.9 cm (range, 0.6–3.0 cm). On the basis of macroscopic appearance, the tumors were divided into four groups: 18 cases (38%) of the elevated type, 20 cases (42%) of the depressed type, nine cases (19%) of the combined type (combination of elevated and depressed), and one case (2%) of the ulcerated type. Histologically, most of the tumors were differentiated (45 cases; 94%) and there were only three cases (6%) of undifferentiated type. Undifferentiated components were found in 14 of the 48 patients (29%), and were frequently present at the invasive front in differentiated tumors. Carcinoma *in situ* or intramucosal cancer (Tis) was observed in 16 cases (33%), T1 in 26 (54%), T2 in four (8%), and T3 in two (4%) by the tumor nodes metastases (TNM) classification. Six (19%) of the 32 patients whose tumors were resected surgically had lymph node metastasis. Fifteen of the 48 patients had Barrett's epithelium.

The tumors were classified immunohistochemically into the gastric phenotype in 13 (27%) cases, the intestinal phenotype in 18 (38%), the mixed phenotype in 15 (31%), and

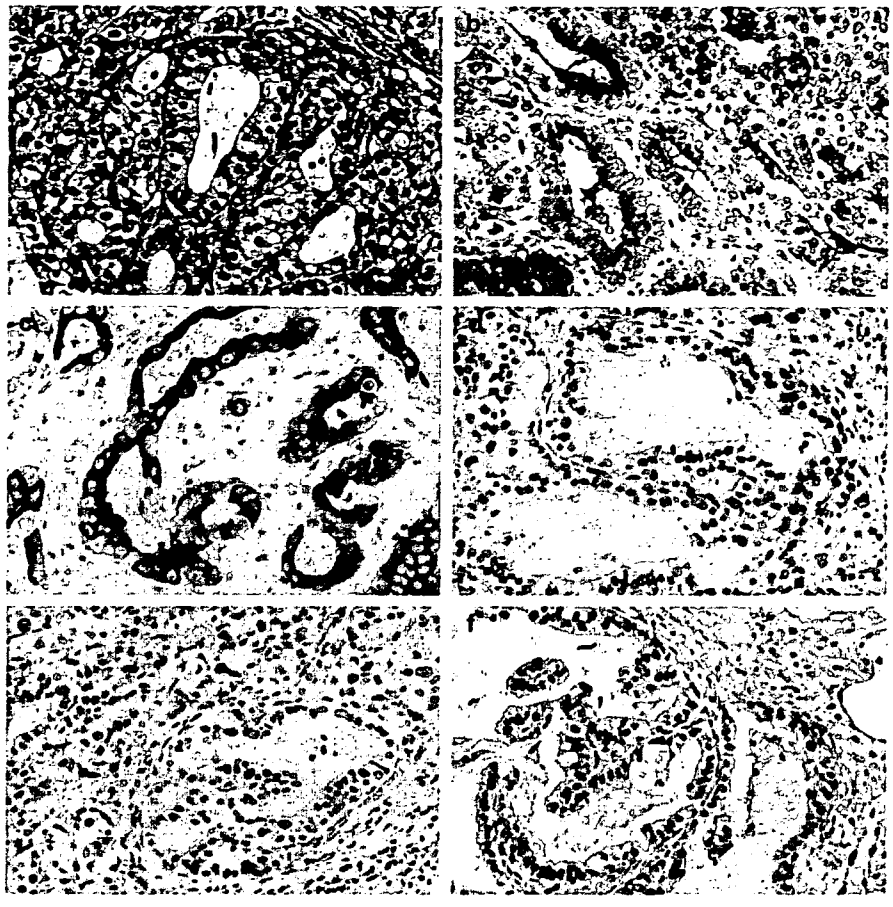

Figure 2 Adenocarcinoma of the esophagogastric junction with a gastric phenotype. (**a**) Tumor cells have clear cytoplasm (HE) and show cytoplasmic positivity for (**b**) MUC5AC and (**c**) MUC6. (**d**) MUC2, (**e**) CD10 and (**f**) Cdx2 are not expressed in the tumor cells.

Figure 3 Undifferentiated component of the tumor. Tumor cells permeate as single cells or as small nests.

unclassified in two (4%). The tumors with an intestinal phenotype tended to have eosinophilic cytoplasm, whereas those with a gastric phenotype tended to have clear cytoplasm in the sections stained with HE (Figs 1,2).

Correlation between clinicopathological features and the presence of IM in surrounding non-neoplastic mucosa

IM, also known as SCE, was found in the surrounding non-neoplastic mucosa in 22 of the 48 patients (46%), while the remaining 26 (54%) were not associated with IM. Tumors associated with IM were seen more frequently in older patients ($P = 0.008$), and lymph node metastasis was seen only in patients whose tumors were unassociated with IM ($P = 0.017$; Table 2). Other factors, such as gender, tumor size, gross appearance, and pT staging, had no significant difference between tumors associated and unassociated with IM.

The differentiated type was the predominant histological feature observed in both groups. However, tumors without IM had undifferentiated components more frequently than those with IM ($P = 0.030$, Fig. 3).

A gastric phenotype was seen almost exclusively in tumors without IM (12 of 13 cases, 92%), whereas an intestinal phenotype was predominant in those with IM (12 of 18 cases,

Table 2 Clinicopathological characteristics of small AEGJ

	With IM $n=22$	Without IM $n=26$	P
Gender (M/F)	18/4	25/1	0.126
Age (years)			
≥60	19	13	
<60	3	13	0.008
Mean (range)	68.7 (54–84)	61.9 (37–85)	
Mean tumor size (mm)	19.5	19.1	0.641‡
Gross appearance			
Elevated	7	11	
Depressed	10	10	
Combined†	5	4	
Ulcerated		1	0.642
pT			
Tis	7	5	
T1	13	17	
T2	2	2	
T3		2	0.466
pN (surgical cases)			
Negative	14	12	
Positive	0	6	0.017
Histological type			
Differentiated	21	24	
Undifferentiated	1	2	0.564
Undifferentiated component			
Present	3	11	
Absent	19	15	0.030
Gastric and intestinal phenotype (mucosa)§			
Gastric phenotype	1 (1)	12 (16)	0.003
Intestinal phenotype	12 (15)	6 (5)	(0.000)
Mixed phenotype	9 (6)	6 (3)	
Unclassified	0 (0)	2 (2)	

†Combination of elevated and depressed type.
‡Mann–Whitney U-test.
§Incidence of the intramucosal phenotype of the tumor.
AEGJ, adenocarcinoma of the esophagogastric junction; IM, intestinal metaplasia.

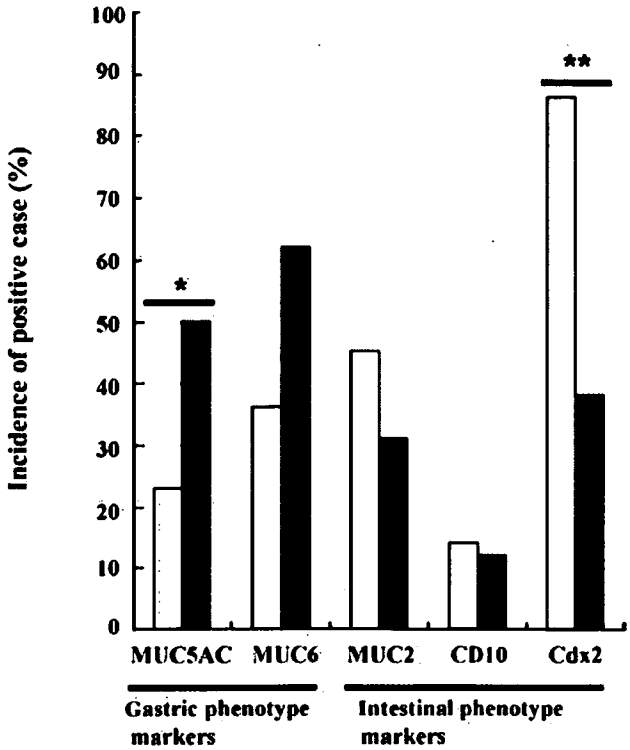

Figure 4 Expression of gastric and intestinal phenotype markers of adenocarcinoma of esophagogastric junction (AEGJ). The proportion of positive cases is shown on the vertical axis. There is a significant difference in MUC5AC and Cdx2 expression between AEGJ (□) with and (■) without intestinal metaplasia in the background mucosa. $^{*}P=0.049$; $^{**}P=0.001$.

Table 3 Correlation between presence of undifferentiated components and phenotype of AEGJ

	Undifferentiated component	
	Present	Absent
Gastric phenotype	9 (9)	4
Intestinal phenotype	1 (1)	17
Mixed phenotype	3 (2)	12
Unclassified	1 (1)	1

$P=0.001$.
(n), incidence of the phenotype in the undifferentiated components.
AEGJ, adenocarcinoma of esophagogastric junction.

67%; $P=0.003$). In the intramucosal phenotype, a gastric phenotype was also seen almost exclusively in tumors without IM (16 of 17 cases), whereas an intestinal phenotype was predominant in those with IM (15 of 20 cases; $P=0.000$). In some cases, gastric or intestinal phenotype were seen to be mixed type according to deeper invasion of the tumor. Expression of each of the gastric phenotype makers, MUC5AC and MUC6, was observed more frequently in tumors without IM than in those with IM, while expression of each of the intestinal phenotype markers, MUC2, CD10 and Cdx2, was observed more often in tumors with IM than in those without IM. There were significant differences in the incidence of positivity for MUC5AC and Cdx2 between AEGJ with IM and those without IM (Fig. 4, $P=0.049$ and 0.001, respectively).

Table 3 illustrates the correlation between phenotypic expression and the presence of undifferentiated components. The gastric phenotype was significantly related to the presence of undifferentiated components in the tumor ($P=$ 0.001). In cases of undifferentiated components, the phenotype in the undifferentiated components did follow the phenotype in almost all of the cases.

DISCUSSION

IM in Barrett's esophagus and the distal stomach is generally considered to be an important risk factor for the development of adenocarcinoma.[3–5] However, its contribution to