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MODERN SURGERY FOR GASTRIC CANCER – JAPANESE PERSPECTIVE

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Key words: Gastric cancer; surgical treatment; lymph node dissection; function preserving surgery; radical surgery; tailored surgery

INTRODUCTION AND OVERVIEW

Although the role of surgery is changing for gastric cancer due to increased role of non-surgical treatment, surgery continues to be the most important curative treatment of this disease (1). Any patient with curable gastric cancer, from stage I to IV, inclusive, were treated by D2 dissection in Japan, in the 1970's and 80's, until a large data base of T1 tumors revealed that some subgroups of these tumors seldom have any metastases, allowing local excision as a curative treatment. With the development of endoscopic instruments, T1 gastric cancer or "dysplasia" of 5 cm or even larger can be treated by endoscopic submucosal dissection (ESD) (2, 3, 4).

For advanced gastric cancer, D2 dissection is the gold standard in the East Asian countries in spite of the negative results of the two European trials (5, 6). In Japan, there is a high incidence of gastric cancer which results in high hospital volume; surgical mortality is very low since patients are generally in better condition for this procedure (7). Survival after D2 surgery has never been surpassed by any other treatment, including multimodal ones with more limited surgery for advanced gastric cancer. More extensive surgery than D2 dissection was often carried out in Japan in the 1980's and early 1990's, without any solid evidence of benefit of this procedure over D2 dissection (8). This issue was solved by a large clinical trial, which showed no survival benefit for patients who underwent super-extended surgery (9). For locally advanced gastric cancer, which is often incurable, wide regional resection, such as left upper abdominal evisceration with or without Appleby's procedure, was sometimes attempted. However, many of these tumors were eventually incurable, and some curable tumors carried a very poor prognosis even after such surgery. Recently, neoadjuvant chemotherapy or chemoradiotherapy has been tried and seems to produce interesting results for these tumors. What kind of surgery should be performed after neoadjuvant treatment is not yet well studied.

STANDARD TREATMENT OF GASTRIC CANCER AND TAILORED SURGERY

Total or 2/3 to 4/5 distal gastrectomy with D2 dissection remains the gold standard for advanced gastric cancer in Japan (10). The Dutch and MRC trials comparing D1 versus D2 for gastric cancer failed to prove any survival benefit for D2 dissection (5, 6). However, these trials were heavily criticized for unacceptably high surgical mortality and poor quality of surgery (11). Table 1 shows the negative correlation between hospital volume and mortality (12). Due to low hospital volume, a much higher mortality rate was recorded after major surgical complications than in the Japanese data (Table 2) (12). With limited experience, it is impossible to learn how to manage major surgical complications in low volume hospitals. This high mortality is sometimes attributed to relative unfitness of Dutch patients. However, from the same country a much lower mortality rate was reported after esophageal resection or esophago-gastric resection in a RCT for esophago-gastric junctional tumors (13). The most remarkable difference between these two Dutch trials is that the gastric cancer trial was carried out in 80 hospitals including small community hospitals, while the junctional tumor trial was done in only two major university hospitals with a high hospital volume. Together with other surgical RCTs, it is now well known that high surgical mortality easily offsets long-term survival benefit of the treatment (4% and 10% hospital mortality in D1 and D2, respectively). A consistent finding was observed in female patients in the Dutch trial (14). Having similar hospital mortality rate for both arms in female patients (3.7% and 4.1% for D1

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TABLE 1

Morbidity and mortality after D2 dissection for gastric cancer.
From: M. Sasako: Principles of surgical treatment for curable gastric cancer (Table 5, with some corrections of wrong terms), J Clin Oncol 2003;21s:274–275, reprinted with permission from the American Society of Clinical Oncology.

Trial	Type	No. of patients per year	No. of patients per hospital	Mortality (%)	Morbidity (%)
Hong Kong	RCT	30	7.5	3	57
MRC	RCT	200	1.5	13	46
Dutch	RCT	331	1.0	10	43
Italian	Phase II	191	8.0	3	21
Sue-Ling	Retro	142	14.2	5	17
Pacelli	Retro	157	15.7	4	22

Abbreviations: RCT: randomized controlled trial; MRC: Medical Research Council; Retro: retrospective case series.

TABLE 2

Mortality after postoperative major complications.
From: M. Sasako: Principles of surgical treatment for curable gastric cancer (Table 4, slightly amended), J Clin Oncol 2003;21s:274-275, reprinted with permission from the American Society of Clinical Oncology.

Complication	Dutch Trial (N = 711)			NCCH Trial (1982–1987) (N = 1197)			
	No. of deceased patients	No. of affected patients	%	No. of deceased patients	No. of affected patients	%	P
Leakage	19	46	41.3	12	84	14.3	.0005
Distal	9	22	40.1	2	23	8.7	.012
Total	10	24	41.7	10	60	16.7	.0047
Abscess or pancreatic fistula	19	91	20.9	2	75	2.7	.0004

Abbreviation: NCCH, National Cancer Center Hospital.

and D2, respectively), the H.R. (hazard rate) over time was rather constant and survival curves did not cross in the follow-up period, thus showing a clear separation of the two curves (p = 0.04). Recently, much lower mortality rates have been reported from specialist centers in Europe. These papers emphasize the importance of a high hospital volume (15, 16).

The criticism against the Dutch trial included several technical aspects. First, in spite of putting much more effort into achieving good surgical quality than in the MRC trial, there was a high rate of protocol violations in terms of lymph node dissection (contamination and non-compliance) (17). Hundahl et al. reported the usefulness of the Maruyama index to predict the prognosis of the patients who undergo curative surgery for gastric cancer (18). Originally Maruyama's computer program was designed to recognize the important nodal stations in each patient based on the database of 5000 patients. Later, this was used to evaluate possible residual disease and prediction of prognosis. The method is explained in another paper in this same issue of the journal (pages 243–248, S. Hundahl). Theoretically, if perfect D2 dissection is carried out, the Maruyama index is always very low, while limited surgery like D1 usually yields a high Maruyama index. A retrospective analysis of the Maruyama index showed clearly that a high Maruyama index was an independent prognostic factor in the Dutch trial as well and thus pointed to disadvantages of limited surgery (19).

Second, in case of a total gastrectomy, splenectomy and distal pancreatectomy were mandatory for patients who were enrolled in the D2 arm. In the detailed analysis, it was shown that splenectomy and distal pancreatectomy were more important causes of morbidity and mortality than D2 dissection itself (20).

Recently, the results of a Taiwanese trial comparing D1 with D3 (D2 + α in the actual classification) was reported in Lancet Oncology (21). Although there are several weak points in this trial, it proved a modest benefit for D3 dissection over D1 with a statistical significance (Fig. 1. 5-year survival rate was 59.5% and 53.6% for D3 and D1, respectively).

The Intergroup study 0116 (INT0116) on adjuvant chemoradiotherapy (CRT) after curative surgery for gastric cancer showed a large benefit of adjuvant treatment over surgery alone : 3-year survival rates were 41% and 50% for surgery alone and surgery followed by CRT, respectively. H.R. for surgery alone = 1.35, p = 0.005) (22). For years, no adjuvant chemotherapy without radiotherapy had in a RCT been shown to be superior to surgery alone as the control arm. When radiotherapy was added for local control, adjuvant chemotherapy did work. In this trial, the lymph node dissection applied was D0 in 54% of patients, D1 in 36% and D2 in only 10%. The implication is that the INT-0116 proved the effect of CRT over limited surgery (D0/1) and insufficiency of D0/1 surgery. This type of surgery alone cannot be used as a

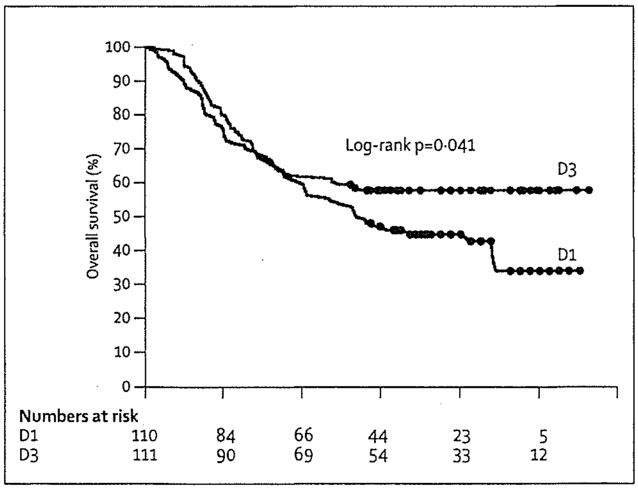

Fig. 1. Overall survival in intention-to-treat population (n=221). From: C.-W. Wu, C. A. Hsiung, S.-S. Lo, M.-C.Hsieh, J.-H. Chen, A. Fen-Yau Li, W.-Y. Li, J. Whang-Peng: Nodal dissection for patients with gastric cancer: a randomized controlled trial (Fig 2(A)) Published online March 15, 2006 DOI:10.1016/S1470-2045(06) 70623-4 and in: Lancet Oncol. 2006 Apr;7(4):309-15, with permission

treatment option for curable gastric cancer. If surgeons perform such surgery, postoperative CRT is mandatory.

EXTENDED SURGERY OR LIMITED SURGERY WITH RADIOTHERAPY

Macdonald reported the results of a subgroup analysis to examine the interaction of CRT for several prognostic factors. Although any interaction between the type of lymphadenectomy and CRT was not statistically significant, probably due to too small sample size of D2 population, in the D2 population the survival curves overlapped or surgery alone was even better. Thus there remain two questions (23): First, is D0/1 + CRT better than D2 surgery alone? Considering serious morbidity of CRT, especially for kidney, if D2 is better than D1 + CRT, D2 should be the standard treatment for these patients. Second, can postoperative CRT improve the results of D2 surgery? These questions remain open and should be solved by RCTs.

The results of the MAGIC trial were reported in July, 2006, in the New England Journal of Medicine (24). Although several questions arise regarding the quality of this trial, it is the first report demonstrating a clear benefit of neoadjuvant chemotherapy (with postoperative chemotherapy) over surgery alone. As the type of surgery applied in this study, i.e, type of lymph node dissection, is not reported, it is impossible to know the benefit of this neoadjuvant treatment in association with D2 surgery. Recently, it has been reported by a Japanese Pharmaceutical company, Taiho Pharmaceutical, that a pivotal study on the effect of postoperative adjuvant chemotherapy using S-1 was stopped prematurely due to positive results at the first interim analysis (25). Although the details are not available until they will be reported at the ASCO Gastrointestinal Symposium in January 2007, D2 + S-1 is already regarded as the standard method of care in Japan for stage II and III patients. Therefore the control arm of the above mentioned future RCTs on CRT should be D2+neoadjuvant or D2+S-1 as postoperative adjuvant.

MODIFICATION OF STANDARD TECHNIQUE FOR EARLY GASTRIC CANCER

Regarding T1 tumors, which are called "early gastric cancer" regardless of lymph node metastases, it is known that they have relatively low incidence of lymph node metastasis and rather limited spread of nodal metastasis. As the most postoperative sequelae after gastrectomy are caused by resection of the pyloric ring and the cardia, preservation of these two sphincters may provide better quality of life (26). For tiny tumors near the cardia, preservation of the distal half of the stomach would not increase recurrence due to low incidence of nodal metastasis surrounding the distal stomach. A proximal gastrectomy was once abandoned for high incidence of severe reflux esophagitis, but it has been recently applied for the treatment of proximal T1 tumors with or without jejunal interposition. For T1 tumors near the gastric angle or the lower gastric body, pylorus preserving gastrectomy is often used to avoid dumping syndrome after gastrectomy. For these tumors, metastasis to the suprapyloric nodes is rare (less than 1%) and preservation of the hepatic branch and the pyloric branch of the anterior vagal nerve does not provide oncological disadvantage. Although several papers report the advantage of this procedure, the number of the cases used for evaluation was not large enough. Theoretical advantage of these procedures should be further evaluated in comparison to conventional distal gastrectomy.

SURGICAL TRIALS FOR ADVANCED GASTRIC CANCER

Recently, the results of two surgical trials regarding extended surgery for advanced gastric cancer were reported. The first one is a RCT on the surgical treatment for esophago-gastric junctional (EGJ) tumors performed by Japan Clinical Oncology Group (JCOG). In this study two commonly used surgical approaches, the left thoraco-abdominal approach (LT) and transhiatal (abdominal only) approach (TH) for EGJ tumors were compared to test the superiority of LT as regards survival with acceptable increase of morbidity. This trial was terminated when the results of the first interim analysis after randomizing 163 patients indicated that the predictive probability of LT to be significantly superior to TH was as small as 3.65%. Thus, the test hypothesis was annulled and the standard procedure for Siewert type 2 or 3 EGJ tumors is now the abdominal and transhiatal approach (27). The other trial was a RCT comparing D2 versus D2 +

para-aortic lymph node dissection (PAND) by JCOG (9). The overall survival curves of the two procedures were almost overlapping. Although there was no difference in postoperative major complications or mortality, prophylactic PAND cannot be recommended for patients with curable advanced tumors. It should be emphasized, however, that about 20% of the patients with PAN metastases survived more than 5 years. Thus, some carefully selected, subgroups of patients may benefit from this procedure.

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Influence of Overweight on Surgical Complications for Gastric Cancer: Results From a Randomized Control Trial Comparing D2 and Extended Para-aortic D3 Lymphadenectomy (JCOG9501)

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Background: The impact of overweight on the outcome of gastrectomy with lymphadenectomy is controversial, and data from a well-controlled, randomized study are needed to identify a possible relationship.

Methods: We used data from 523 patients registered for a prospective randomized trial comparing D2 and extended para-aortic D3 lymphadenectomy to compare the effects of body mass index (BMI) and the extent of lymphadenectomy for the development of general or major surgical complications (anastomotic leakage, abdominal abscess, and pancreatic fistula).

Results: Seventy-seven patients were classified as overweight with BMI ≥ 25, and 38 and 39 of these patients underwent a D2 or D3 lymphadenectomy, respectively. Among the 446 patients classified as nonoverweight with BMI < 25, 225 received D2 and 221 received D3 lymphadenectomy. Surgical complications, operation time, and blood loss were statistically significantly associated with BMI, and logistic regression analysis revealed that overweight directly affected the occurrence of surgical complications even after considering operation time

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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]

			Univariate analysis		Multivariate analysis	
Factors	BMI < 25	BMI ≥ 25	Odds ratio of BMI > 25 (95% CI)	*P* value	Odds ratio of BMI > 25 (95% CI)	*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]*

	D2 subgroup (n = 263)		D3 subgroup (n = 260)		
Factor	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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Leading article

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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Predictive Factors of Lymph Node Metastasis in Patients With Undifferentiated Early Gastric Cancers

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Background: For intramucosal differentiated early gastric cancer that has little risk of lymph node metastasis, local treatment such as endoscopic mucosal resection has been generally accepted as an adequate treatment. We studied clinicopathological characteristics of undifferentiated early gastric cancer at our institution to identify the predictive factors for lymph node metastasis and qualify lesions that should be referred for gastrectomy and not endoscopic mucosal resection.

Methods: We retrospectively analyzed the clinicopathological features (patient age and gender, tumor size, location, macroscopic type and histological type, presence of ulceration, depth of tumor invasion, and lymphatic-vascular involvement) in 332 patients with undifferentiated early gastric cancer who underwent gastrectomy with regional lymph node dissection.

Results: Lymph node metastasis was observed in 45 patients (14%). Univariate analysis revealed that depth of tumor invasion (submucosa), tumor size (> 30 mm), and lymphatic-vascular involvement (positive) were associated with lymph node metastasis. Only lymphatic-vascular involvement (positive) was found to have a significant association (odds ratio, 7.4; 95% confidence interval, 2.9–19.0) by multivariate analysis.

Conclusions: Lymphatic-vascular involvement was the only independent predictive risk factor for lymph node metastasis. This pathologic factor was not useful for identifying patients at high risk of lymph node metastasis who should be offered gastrectomy rather than endoscopic mucosal resection.

Key Words: early gastric cancer, lymph node metastasis, undifferentiated carcinoma, predictive factor, endoscopic mucosal resection

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Early gastric cancer (EGC) is defined as cancer localized to the mucosa or submucosa, regardless of lymph node metastasis. Radical gastrectomy with regional lymphadenectomy is the "gold standard" treatment for patients with EGC.[1] The incidence of EGC has been increasing because of advances in diagnostic procedures.[2] However, because the incidence of lymph node metastasis in intramucosal EGC is approximately 3% and that in submucosal EGC is around 20%,[3] gastrectomy with regional lymphadenectomy may be overtreatment for many patients with EGC.

Several studies have identified risk factors that are predictive of lymph node metastasis in EGC.[2–7] It is known that histologically undifferentiated intramucosal EGC tends to have lymph node metastasis more often than differentiated intramucosal EGC.[5–7] The survival rate for those with lymph node metastasis is significantly lower than for those without lymph node metastasis.[3,6,8] Some groups report a better prognosis for early signet ring cell carcinoma than for other types of cancer,[9] but this is controversial.[10] For intramucosal EGC that has little risk of lymph node metastasis, local treatment such as endoscopic mucosal resection (EMR) has been generally accepted as an adequate treatment. EMR is employed when an intramucosal cancer is diagnosed as differentiated adenocarcinoma, is < 2 cm in diameter, and has no central ulceration.[4,5]

Recently, a new method of EMR, so-called endoscopic submucosal dissection (ESD), has been developed.[11] Compared with classic methods such as strip biopsy, ESD can remove a larger size of gastric mucosa as a single fragment with an adequate, safe negative margin.[12] Complete removal of the lesion in a single fragment is essential for an accurate histological diagnosis to determine whether EMR alone will be curative. Several institutions have suggested that use of EMR should be extended to larger, differentiated intramucosal EGCs because lesions < 30 mm in diameter without lymphatic-vascular invasion or ulceration have little risk of lymph node metastasis. However, there have been few reports about lymph node metastasis from undifferentiated EGC,[13] and the applicability of local treatment for it is unknown.

One of the critical factors that needs to be considered in choosing local treatment for EGC is the accurate prediction of whether lymph node metastasis is present. In this study, we retrospectively analyzed the clinicopathological characteristics of undifferentiated EGC by reviewing cases that had been treated previously at our institution in order to identify predictive factors of lymph node metastasis and qualify lesions that should be referred for gastrectomy and not EMR.

PATIENTS AND METHODS

Between January 1989 and April 2005, 1,004 patients with EGC underwent gastrectomy as an initial treatment at the National Hospital Organization Shikoku Cancer Center. Among these, 398 patients had undifferentiated EGC. Cases of multiple lesions and cases without regional lymph node dissection were excluded from this study, giving a final total of 332 patients whose clinicopathological features were retrospectively analyzed. They comprised 160 men and 172 women whose mean age was 58.0 years (range, 20 to 87 years), with a mean tumor size of 36.5 mm (range, 1 to 130 mm). Cancer description and histological evaluation of resected specimens were performed in accordance with the Japanese Classification of Gastric Carcinoma.[14]

A set of sections of the stomach parallel to the lesser curvature were made, and the histological classification was based on the predominant pattern of the tumor. Poorly differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous adenocarcinoma were regarded as undifferentiated. Lymph nodes were cut into two pieces, and the cut surfaces were examined to define the status of the nodes. Lymph node metastasis was identified with use of hematoxylin and eosin staining, and ulceration was defined histologically if fibrosis or deformity in the submucosal layer or deeper was observed.

Tumors were classified macroscopically into two groups: protruded (types 0 I and 0 IIa) or depressed (types 0 IIb, 0 IIc, and 0 III). Lesions showing a combination of these types were classified into a mixed group. The association between each of the nine clinicopathological factors and the presence or absence of lymph node metastasis was examined to identify risk factors predictive of lymph node metastasis.

Univariate analysis was performed with use of the chi-square test. Subsequently, significant factors identified by univariate analysis were included in the multivariate stepwise logistic regression analysis to evaluate the independent risk factors for lymph node metastasis. The odds ratio in the multivariate analysis was defined as the ratio of the probability that an event would occur to the probability that it would not occur. Statistical analyses were performed with use of the Statistical Package for Social Science (SPSS 11.5 for Windows, SPSS, Chicago, IL). Differences of $P < 0.05$ were considered significant.

RESULTS

Univariate Analysis of Risk Factors Predictive of Lymph Node Metastasis

Of the 332 patients with undifferentiated EGC, 45 (14%) had lymph node metastasis. Lymph node metastasis was observed in eight (5%) of the 177 patients with intramucosal cancers and in 37 (24%) of the 155 with submucosal cancers. Nine clinicopathological factors were examined: patient age and gender, tumor size, location, macroscopic type and histological type, presence of ulceration, depth of tumor invasion, and lymphatic-vascular involvement. Univariate analysis revealed that the depth of tumor invasion (submucosa), tumor size (> 30 mm), and lymphatic-vascular involvement (positive) were associated with lymph node metastasis (Table 1).

Multivariate Analysis of Risk Factors Predictive of Lymph Node Metastasis

Only lymphatic-vascular involvement (positive) was shown to have a significant association (odds ratio, 7.4; 95% confidence interval, 2.9–19.0) by multivariate analysis (Table 2).

Survival

Median period of follow-up was 50.5 months (range, 0 to 199 months). Survival curves for patients with and without lymph node metastasis are shown in

TABLE 1. Univariate Analysis of Risk Factors for Lymph Node Metastasis in Patients With Undifferentiated Early Gastric Cancer (EGC)

	Lymph Node Metastasis		
Factor	Positive (%) n = 45	Negative n = 287	*P* Value
Age, years			
< 59	19 (11%)	151	
≥ 59	26 (16%)	136	0.256
Gender			
Male	21 (13%)	139	
Female	24 (14%)	148	0.952
Location			
Upper third	6 (17%)	29	
Middle third	30 (13%)	195	
Lower third	9 (13%)	63	0.794
Macroscopic type			
Protruded	3 (33%)	6	
Depressed	40 (13%)	275	
Mixed	2 (25%)	6	0.129
Ulceration			
Negative	23 (15%)	131	
Positive	22 (12%)	156	0.601
Depth of invasion			
Mucosa	8 (5%)	169	
Submucosa	37 (24%)	118	< 0.001
Histological type			
Poorly differentiated adenocarcinoma	28 (17%)	137	
Signet ring cell carcinoma	15 (9%)	144	
Mucinous adenocarcinoma	2 (25%)	6	0.089
Size of tumor			
< 30 mm	12 (8%)	140	
≥ 30 mm	33 (18%)	147	0.009
Lymphatic-vascular involvement			
Negative	13 (5%)	236	
Positive	32 (39%)	51	< 0.001

Values are number of cases.

TABLE 2. Multivariate Analysis of Risk Factors for Lymph Node Metastasis in Patients With Undifferentiated EGC

Factor	Odds Ratio (95% CI)	P Value
Lymphatic-vascular involvement (positive)	7.42 (2.89–19.03)	< 0.001
Size of tumor (≥ 30 mm)	1.98 (0.92–4.22)	0.079
Depth of invasion (submucosa)	1.75 (0.60–5.13)	0.310

CI, confidence interval.

Figure 1. The 5-year survival rate was 96.7% for those without lymph node metastasis and 91.4% for those with lymph node metastasis. There was no statistical difference in overall survival rate between patients with or without lymph node metastasis. Of the patients with lymph node metastasis, three died of recurrence of gastric cancer (one with bone metastasis, one with bone and lymph node metastasis, and one with lymph node metastasis). Of the patients without lymph node metastasis, one died of liver metastasis.

DISCUSSION

EGC has been reported to have a favorable prognosis after gastrectomy.[15] Lymph node metastasis is one of the most important prognostic factors for patients with EGC; the survival rate for patients with lymph node metastasis is significantly lower than for those without it.[3,16] However, the incidence of lymph node metastasis in intramucosal EGC is approximately 3%, whereas that in submucosal EGC is 20%. Excessive gastrectomy and lymphadenectomy may affect perioperative morbidity and mortality.[17] Therefore, minimally invasive treatments such as EMR and laparoscopic wedge resection are considered to be appropriate options for EGC patients without lymph node metastasis.

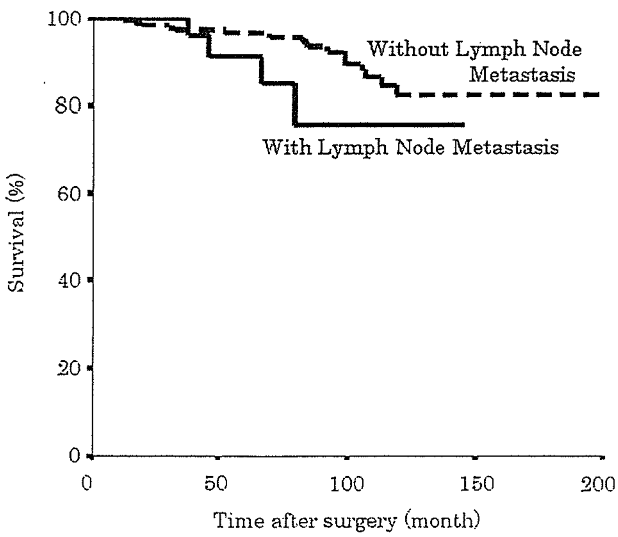

FIGURE 1. Survival curves for patients with and without lymph node metastasis. There was no statistical difference between them.

A new EMR technique that allows complete removal of a large lesion as a single fragment with an insulation-tipped diathermic knife[11] is promising for accurate histological examination of a specimen and subsequent determination of whether local treatment alone will be curative. Although undifferentiated EGC is reported to have more lymph node metastasis than differentiated EGC,[6,7] histological type has no association with survival.[18] Our survival data showed no statistical difference in overall survival rate between patients with or without lymph node metastasis. This may be due to the short follow-up period.

Current application of EMR is limited to differentiated EGC; thus, we sought to expand the use of EMR to undifferentiated EGC by retrospectively examining undifferentiated EGC to determine predictive factors of lymph node metastasis. Univariate analysis revealed three clinicopathological risk factors: depth of invasion, tumor size, and lymphatic-vascular involvement. These factors correlate with those reported previously for both differentiated and undifferentiated EGC by multivariate analysis.[3,4,6–8] Because lymphatic-vascular vessels are less likely to appear in the mucosal layer than in the submucosal layer, it would be reasonable to expect that submucosal tumors would have a more frequent association with lymph node metastasis than intramucosal tumors.

In the present study, multivariate analysis demonstrated that the presence of lymphatic-vascular involvement was the only independent predictive factor for lymph node metastasis, in agreement with previous studies of undifferentiated EGC.[13] Although lymphatic-vascular involvement seems to identify a high-risk population that perhaps should not be offered EMR, this can be determined only after a gastrectomy or EMR. Thus, this pathologic feature is not useful in EMR. There was no proper predictive factor to identify patients with undifferentiated EGC at high risk for lymph node metastasis who should be offered gastrectomy rather than EMR.

In our study, small, undifferentiated EGCs < 10 mm in size without lymphatic-vascular involvement had no lymph node metastasis, but with the narrow range of cases (seven in the mucosa and six in the submucosa), the statistical significance is too limited to make any conclusions. However, our trend is consistent with that described by Gotoda et al,[5] in which zero of 141 patients with undifferentiated intramucosal EGCs < 20 mm in size without ulceration had lymph node metastasis. In our study, one undifferentiated intramucosal EGC < 20 mm (13 mm) in size without ulceration and without lymphatic-vascular involvement had lymph node metastasis. Contrarily, Abe et al reported that lymph node metastasis was found in small, undifferentiated intramucosal EGC (10 mm and 12 mm) without ulceration.[13]

The prognosis for patients with differentiated EGC who undergo EMR is favorable.[19] Still, there is some concern about how micrometastasis affects the survival rate; Lee et al[20] reported that patients with micrometastasis had a lower 5-year survival rate than patients without micrometastasis, especially in Stage IA. It is suggested that micrometastasis is missed on conventional histological examination and that immunohistochemical examination is needed. Although there has been no report on the prognosis for patients with undifferentiated EGC treated by EMR, Ishida et al[21] reported that micrometastasis was more frequent in the undifferentiated type than in the differentiated type, and it is feared that cases of small, undifferentiated EGC treated with EMR could potentially recur with lymph node metastasis.

Currently the treatment procedure is decided on the basis of clinical findings, and despite recent improvements in diagnostic techniques, it is sometimes difficult to define the tumor margin and tumor depth by endoscopic examination.[22] The accuracy of determining tumor depth is reported to be significantly lower for undifferentiated tumors than for differentiated tumors and lower for a depressed tumor than for an elevated one.[23] Miyata et al[24] reported that the complete resection rate of EMR for EGC in poorly differentiated adenocarcinoma was lower than in differentiated types.

According to our results, lymphatic-vascular involvement was the only independent predictive risk factor for lymph node metastasis. However, this cannot be confirmed before surgery or EMR. This pathologic factor was not useful to identify patients at high risk for lymph node metastasis who should be offered gastrectomy rather than EMR. Clinical characteristics such as tumor size and depth were not so strong predictors for lymph node metastasis in our study. Therefore, it is prudent to choose EMR as a therapeutic procedure for patients with undifferentiated intramucosal EGCs.

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