

The distance of proximal resection margin dose not significantly influence on the prognosis of gastric cancer patients after curative resection

Min Gyu Kim, Ju-Hee Lee, Tae Kyung Ha, Sung Joon Kwon

Department of Surgery, Hanyang University College of Medicine, Seoul, Korea

Purpose: It is well known that the curative resection with an adequate proximal margin length is the most effective treatment in gastric cancer. However, despite surgeon's effort to achieve a sufficient proximal margin length, it is often difficult to obtain a recommended proximal margin length in some cases. Therefore, this study was planned to investigate the impact of the length of proximal margin on prognosis of overall survival.

Methods: Between June 1992 and December 2010, 1,888 gastric cancer patients who underwent gastrectomy with curative intent were reviewed. According to tumor's location (total vs. subtotal gastrectomy), pathologic T staging, and differentiation, univariate and multivariate analyses were performed to evaluate the impact of the discrepancies of proximal margin length on overall survival. Also, the impact of the discrepancies of proximal margin length on local recurrence was assessed.

Results: The 5-year survival rate of positive proximal margin group was 5.9%. In negative proximal margin groups, multivariate analysis showed that the discrepancies of proximal margin length have no impact on overall survival. Kaplan-Meier analyses showed that there is no association between discrepancy of proximal margin length and local recurrence.

Conclusion: It takes effort to secure a negative proximal margin in the surgical treatment of gastric cancer because of the poor prognosis of positive proximal margin. In negative proximal margin patients, there's no need to achieve an additional proximal margin length for long-term survival benefit because there was no impact of proximal margin length on overall survival and local recurrence.

[Ann Surg Treat Res 2014;87(5):223-231]

Key Words: Gastric cancer, Proximal margin length, Overall survival, Local recurrence

INTRODUCTION

Despite the continued medical and surgical advancement in the treatment of gastric cancer, gastric cancer is still the main cause of death in Korea and other countries [1-6]. In the surgical treatment, the complete surgical resection with an adequate resection margin length is well known for the most effective treatment of gastric cancer [7-9]. Especially, the negative resection margin is considered critical as the most important

treatment based on the philosophy that minimal residual cancer cells have the possibility of recurrence.

Under the conventional rule, most surgeons try very hard to achieve a sufficient proximal resection margin length more than 2–3 cm in early gastric cancer, and 5–6 cm in advanced gastric cancer. In practice however, we are experiencing that the intraoperative measurement of proximal margin length may quite different from the pathologic measurement for a variety of reasons. In rare cases, the involvement of proximal margin

Received January 16, 2014, Revised March 11, 2014,
 Accepted March 14, 2014

Corresponding Author: Sung Joon Kwon

Department of Surgery, Hanyang University College of Medicine, 222 Wangsimni-ro, Seongdong-gu, Seoul 133-791, Korea

Tel: +82-2-2990-8453, Fax: +82-2-2281-0224

E-mail: sjkwon@hanyang.ac.kr

Copyright © 2014, the Korean Surgical Society

© Annals of Surgical Treatment and Research is an Open Access Journal. All articles are distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

was determined by pathology report.

In these cases, many surgeons are wondering what to perform a reoperation to achieve a negative resection margin or sufficient proximal resection margin length. Therefore, this study was designed to investigate the impact of the involvement of proximal resection margin and the discrepancy of proximal margin length on the prognosis of overall survival and the recurrence pattern.

METHODS

Study population

From June 1992 to December 2010, 2,047 patients underwent gastrectomy for gastric cancer at Hanyang University Hospital. Of these patients, 1,888 gastric cancer patients who underwent gastrectomy with curative intent were enrolled in this study. Patients who underwent noncurative gastrectomy for stage IV gastric cancer were excluded in this study. Seventeen patients with involvement of distal resection margin were excluded. The curative intent surgery is defined as R0 resection with an adequate resection margin length on intraoperative findings. The involvement of resection margin was defined as the presence of tumor cells at the resection line on final histologic examination in spite of a negative result on the intraoperative frozen-section examination. Preoperative assessment included medical and surgical history, gastrofiberscopy, tumor markers, CT of the abdomen and pelvis, and PET CT or chest CT with bone scan. Detailed information on patient and operative findings, postoperative clinical courses, pathologic reports, adjuvant therapy, and follow-up data were prospectively entered into the database. Data pertaining to the distances of proximal resection margin were confirmed by examination of pathologic reports.

Definition of variables

Data pertaining to the status of proximal margin were collected from pathology reports. In this study, the involvement of proximal resection margin was defined as the presence of tumor cells at the resection line on final histologic examination in spite of a negative result on the intraoperative frozen-section examination. Because the frozen-section test has the possibility of false negative [10-12], the results of intraoperative frozen-section test were excluded from the study. The lengths of proximal margin were measured after fixation of 10% formalin solution over 12 hours. When a stapler device was used in reconstruction, the tissue in the stapler doughnut and the stapled tissue were not included in the measurement of proximal margin length.

The location of tumor, depth of tumor invasion, histologic type, and lymph node metastasis are already well known as prognostic factors on overall survival. Of these factors, the

location, depth, and histologic type could be assessed prior to surgery by preoperative studies such as CT scan, endoscopic ultrasonography, and endoscopic biopsy. Therefore, the analyses for the impact of proximal margin length on overall survival were performed depending on these variables.

In this study, the type of surgery for total or subtotal gastrectomy is used to represent the location of tumor. The policy at our institution is to obtain a proximal margin length more than 2 cm in early gastric cancer, and more than 5 cm in advanced gastric cancer. The extent of gastric resection was decided by the intraoperative measurement of proximal margin length. Therefore, a total gastrectomy was performed in patients with insufficient proximal resection margin length.

Histological types were classified as differentiated carcinoma (papillary carcinoma, well differentiated tubular adenocarcinoma, and moderate tubular adenocarcinoma) and undifferentiated adenocarcinoma (poorly differentiated tubular adenocarcinoma, signet ring cell carcinoma, and mucinous adenocarcinoma), based on the 14th Japanese Classification of Gastric Carcinomas [13].

Based on pathologic T staging (American Joint Committee on Cancer/International Union for Cancer Control staging 6th edition), all patients were divided into four groups (T1, T2, T3, and T4 group).

Statistical analysis

Statistical analysis was performed using PASW Statistics ver. 18.0 (SPSS Inc., Chicago, IL, USA). All values are expressed as mean \pm standard deviation or medians and interquartile ranges for continuous factors and frequencies for categorical factors. Univariate analysis was performed using chi-square and Fisher exact probability tests for categorical variables. Student t-test was used for continuous factors. Patients with a proximal margin of ≤ 1 cm were compared with those with a proximal margin >1 cm for extent of gastrectomy, and tumor characteristics. The impacts of a proximal margin ≤ 2 cm vs. >2 cm, ≤ 3 cm vs. >3 cm, ≤ 2 cm vs. >5 cm, and ≤ 5 cm vs. >5 cm were also assessed in the same method. The 5-year survival rate and overall survival were compared between groups using Kaplan-Meier analysis and log-rank tests. In univariate analysis for overall survival, variables with the significance statistically were reanalyzed to adjust for confounding factors. Multivariate analysis was performed to identify risk factors associated with overall survival. The Cox proportional hazards model was employed for multivariate regression analysis. Hazard ratios with 95% confidence intervals were estimated for each variable in the multivariate analysis. A P-value less than 0.05 was considered statistically significant.

Table 1. Clinical characteristics and overall survival rate according to the distance of proximal margin

Variable	All patients				Patients with negative proximal resection margin				P-value		
	Positive (n = 17)	Negative (n = 1,871)	P-value		≤1 cm (n = 34)	>1 cm (n = 1,837)	P-value	≤2 cm (n = 230)		>2 cm (n = 1,641)	≤3 cm (n = 493)
Age, mean ±SD	55.7 ± 13.2	56.8 ± 11.8	0.705	55.1 ± 11.4	56.8 ± 11.8	0.412	55.6 ± 12.1	56.9 ± 11.8	0.114	55.3 ± 12.2	57.3 ± 11.6
Sex			0.033			0.887			0.716		
Male	7 (41.2)	1,232 (65.8)		22 (64.8)	627 (34.1)		149 (64.8)	81 (35.2)		324 (65.7)	169 (34.3)
Female	10 (58.8)	639 (34.2)		12 (35.3)	1,210 (65.9)		1,083 (66.0)	558 (34.0)		908 (65.9)	470 (34.1)
Operation name			<0.001			<0.001			<0.001		<0.001
Total gastrectomy	14 (82.4)	429 (22.9)		21 (61.8)	408 (22.2)		126 (54.8)	303 (18.5)		217 (44.0)	212 (15.4)
Subtotal gastrectomy	3 (17.6)	1,442 (77.1)		13 (38.2)	1,429 (77.8)		104 (45.2)	1,338 (81.5)		276 (56.0)	1,166 (84.6)
Lymph node dissections			0.032			1.000			0.780		
Over D2	15 (88.2)	1,841 (98.4)		34 (100)	1,807 (98.4)		226 (98.3)	1,615 (98.4)		486 (98.6)	1,355 (98.3)
Below D2	2 (11.8)	30 (1.6)		0	30 (1.6)		4 (1.7)	26 (1.6)		7 (1.4)	23 (1.7)
Pathologic T staging			<0.001			0.262			0.029		
T1 gastric cancer	0 (0)	841 (44.9)		12 (35.3)	829 (45.1)		89 (38.7)	752 (45.8)		207 (42.0)	634 (46.0)
T2 gastric cancer	1 (5.9)	427 (25.2)		8 (23.5)	464 (25.3)		53 (23.0)	419 (25.5)		126 (25.6)	346 (25.1)
T3 gastric cancer	10 (58.8)	512 (27.4)		12 (35.3)	500 (27.2)		81 (35.2)	431 (26.3)		150 (30.1)	362 (26.3)
T4 gastric cancer	6 (35.3)	46 (2.5)		2 (5.9)	44 (2.4)		7 (3.0)	39 (2.4)		10 (2.0)	36 (2.6)
Pathologic N staging			<0.001			0.069			0.005		
N0 gastric cancer	0 (0)	968 (51.7)		14 (41.2)	954 (51.9)		100 (43.5)	868 (52.9)		241 (48.9)	727 (52.8)
N1 gastric cancer	1 (5.9)	472 (25.2)		6 (17.6)	466 (25.4)		56 (24.3)	416 (25.4)		116 (23.5)	356 (25.8)
N2 gastric cancer	7 (41.2)	237 (12.7)		9 (26.5)	228 (12.4)		41 (17.8)	196 (11.9)		72 (14.6)	165 (12.0)
N3 gastric cancer	9 (52.9)	194 (10.4)		5 (14.7)	189 (10.3)		33 (14.3)	161 (9.8)		64 (13.0)	130 (9.4)
Differentiation			0.028			0.275			<0.001		<0.001
WD (MD, PAP)	3 (17.6)	833 (44.5)		12 (35.3)	821 (44.7)		77 (33.5)	756 (46.1)		182 (36.9)	651 (47.2)
UD (PD, SRC, MUC)	14 (82.4)	1,038 (55.5)		22 (64.7)	1,016 (55.3)		153 (66.5)	885 (53.9)		311 (63.1)	721 (52.8)
5-Year survival rate (%)	5.9	75.0	<0.001	72.4	75.0	0.327	68.3	75.9	0.002	73.8	75.4
Overall survival (mo), median (range)	10.3 (4.7–15.8)			127.3 (78.3–76.2)			147.1 (96.6–197.5)				
Follow-up (mo), median (range)	10.3 (2–116)	72.5 (0.3–235)	<0.001	80.0 (10–231)	72.3 (0.3–235)	0.912	60.5 (1–235)	75.9 (0.3–235)	<0.001	61.4 (0.3–235)	78.5 (1–235)

Values are presented as number (%) unless otherwise indicated. SD, standard deviation; WD, well differentiated adenocarcinoma; MD, moderately differentiated adenocarcinoma; PAP, papillary adenocarcinoma; UD, undifferentiated adenocarcinoma; PD, poorly differentiated adenocarcinoma; SRC, signet ring cell adenocarcinoma; MUC, mucinous adenocarcinoma.

Table 2. Clinical characteristics, 5-year survival rate and overall survival between TG and STG groups

Variable	Proximal resection margin								
	≤1 cm (n = 34)	>1 cm (n = 1837)	P-value	≤2 cm (n = 230)	>2 cm (n = 1641)	P-value	≤3 cm (n = 493)	>3 cm (n = 1378)	P-value
Total gastrectomy	21	408		126	303		217	212	
T staging			0.558			0.198			0.366
T1 gastric cancer	2 (9.5)	80 (19.6)		20 (15.9)	62 (20.5)		40 (18.4)	42 (19.8)	
T2 gastric cancer	6 (28.6)	107 (26.2)		29 (23.0)	84 (27.7)		60 (27.6)	53 (25.0)	
T3 gastric cancer	11 (52.4)	197 (48.3)		71 (56.3)	137 (45.2)		108 (49.8)	100 (47.2)	
T4 gastric cancer	2 (9.5)	24 (5.9)		6 (4.8)	20 (6.6)		9 (4.1)	17 (8.0)	
Differentiation			0.911			0.578			0.882
WD	6 (28.6)	112 (27.5)		37 (29.4)	81 (26.7)		59 (27.2)	59 (27.8)	
PD	15 (71.4)	296 (72.5)		89 (70.6)	222 (73.3)		158 (72.8)	153 (72.2)	
5-Year survival rate (%)	64.6	58.1	0.662	55.0	59.7	0.454	58.4	58.3	0.655
Overall survival (mo), median (range)	96.8 (62.2–131.3)	98.0 (60.9–135.0)		84.9 (47.2–122.5)	106.2 (58.2–154.1)		98.0 (60.7–135.2)	95.7 (47.6–143.7)	
Subtotal gastrectomy	13	1,430		104	1,339		276	1,166	
T staging			0.399			0.006			0.006
T1 gastric cancer	10 (76.9)	749 (52.4)		69 (66.3)	690 (51.5)		167 (60.5)	592 (50.8)	
T2 gastric cancer	2 (15.4)	357 (25.0)		24 (23.1)	335 (25.0)		66 (23.9)	293 (25.1)	
T3 gastric cancer	1 (7.7)	303 (21.2)		10 (9.6)	294 (22.0)		42 (15.2)	262 (22.5)	
T4 gastric cancer	-	21 (1.5)		1 (1.0)	20 (1.5)		1 (0.4)	19 (1.6)	
Differentiation			0.806			0.019			0.064
WD (MD, PAP)	6 (46.2)	709 (49.6)		40 (38.5)	675 (50.4)		123 (44.6)	592 (50.8)	
UD (PD, SRC, MUC)	7 (53.8)	721 (50.4)		64 (61.5)	664 (49.6)		153 (55.4)	574 (49.2)	
5-Year survival rate (%)	84.6	79.8	0.941	84.7	79.5	0.323	86.3	78.5	0.011

Values are presented as number (%) unless otherwise indicated.

TG, total gastrectomy; STG, subtotal gastrectomy; WD, well differentiated adenocarcinoma; PD, poorly differentiated adenocarcinoma; MD, moderately differentiated adenocarcinoma; PAP, papillary adenocarcinoma; UD, undifferentiated adenocarcinoma; SRC, signet ring cell adenocarcinoma; MUC, mucinous adenocarcinoma.

RESULTS

Eighteen hundred eighty-eight patients were included in this study. Seventeen patients had the involvement of proximal margin after surgery by pathologic report. Their 5-year survival rate was 5.9%. Although there were significant differences in the extent of lymph node dissection, distribution of pathologic T and N staging, and histologic type between patients with positive margin and negative margin, their survival rate was very low compared to the result of patients with negative proximal margin. In patient with negative proximal margin, twelve hundred thirty-two patients (65.8%) were male. A mean age was 56.8 ± 11.8 years at surgery. Four hundred twenty-nine patients (22.9%) underwent total gastrectomy and most patients (98.4%) underwent D2 or more lymph node dissections. According to variables, there were some significant differences between each group (proximal margin length ≤ 1 cm vs. >1 cm, ≤ 2 cm vs. >2 cm, and ≤ 3 cm vs. >3 cm) (Table 1).

According to the type of surgery, there was significant difference of 5-year survival rate between proximal margin length ≤ 3 cm group and >3 cm group in patients who underwent subtotal gastrectomy (≤ 3 cm group vs. >3 cm

group; 86.3% vs. 78.5%; $P = 0.011$). In subtotal gastrectomy patients, there was also significant difference in distribution of pathologic T staging (≤ 2 cm group vs. >2 cm group, $P = 0.006$) (Table 2).

According to the pathologic T staging, our statistical analyses did not reveal a significant difference in 5-year survival rate. According to the histologic type, there was significant difference between proximal margin length ≤ 2 cm and >2 cm in patients with undifferentiated adenocarcinoma (≤ 2 cm group vs. >2 cm group; 66.5% vs. 72.9%; $P = 0.022$). (Tables 3, 4)

In patients who having poor prognostic factors, multivariate Cox proportional hazard analysis for pathologic T and N staging and these prognostic factors was performed. As a result, the 5-year survival rate was not affected by the discrepancy of proximal margin length (with 2 cm in undifferentiated adenocarcinoma, and 3 cm in subtotal gastrectomy) (Table 5).

In subsets of patients who having same pathologic T staging, there was no significant difference of 5-year survival rate in proximal margin length ≤ 2 cm and >5 cm, and ≤ 5 cm and >5 cm (Table 6).

After 88.0 months' median follow-up (1–235), local recurrence occurred in 16 patients (0.9%). Local recurrence analysis by

Table 3. Clinical characteristics, 5-year survival rate and overall survival among T1, T2, T3, and T4 groups

Variable	Proximal resection margin								
	≤1 cm (n = 34)	>1 cm (n = 1,837)	P-value	≤2 cm (n = 230)	>2 cm (n = 1,641)	P-value	≤3 cm (n = 493)	>3 cm (n = 1,378)	P-value
T1 gastric cancer	14	829		89	752		207	634	
OP name			0.416			<0.001			<0.001
TG	2 (16.7)	80 (9.7)		20 (22.5)	62 (8.2)		40 (19.3)	42 (6.6)	
STG	10 (83.3)	749 (90.3)		69 (77.5)	690 (91.8)		167 (80.7)	592 (93.4)	
Differentiation			0.636			0.018			0.005
WD	6 (50.0)	471 (56.8)		40 (44.9)	437 (58.1)		100 (48.3)	377 (59.4)	
PD	6 (50.0)	358 (43.2)		49 (55.1)	315 (41.9)		107 (51.7)	257 (40.6)	
5-Year survival rate (%)	83.3	92.7	0.280	89.5	92.8	0.171	93.9	92.1	0.964
T2 gastric cancer	8	464		53	419		126	346	
OP name			0.002			<0.001			<0.001
TG	6 (75.0)	107 (23.1)		29 (54.7)	84 (20.0)		60 (47.6)	53 (15.3)	
STG	2 (25.0)	357 (76.9)		24 (45.3)	335 (80.0)		66 (52.4)	293 (84.7)	
Differentiation			0.872			0.692			0.430
WD	3 (37.5)	187 (40.3)		20 (37.7)	170 (40.6)		47 (37.3)	143 (41.3)	
PD	5 (62.5)	277 (59.7)		33 (62.3)	249 (59.4)		79 (62.7)	203 (58.7)	
5-Year survival rate (%)	75.0	81.0	0.758	81.3	80.9	0.857	84.1	79.7	0.436
T3 gastric cancer	12	500		81	431		150	362	
OP name			<0.001			<0.001			<0.001
TG	11 (91.7)	197 (39.4)		71 (87.7)	137 (31.8)		108 (72.0)	100 (27.6)	
STG	1 (8.3)	303 (60.6)		10 (12.3)	294 (68.2)		42 (28.0)	262 (72.4)	
Differentiation			0.715			0.016			0.014
WD	3 (25.0)	149 (29.8)		15 (18.5)	137 (31.8)		33 (22.0)	119 (32.9)	
PD	9 (75.0)	351 (70.2)		66 (81.5)	294 (68.2)		117 (78.8)	243 (67.1)	
5-Year survival rate (%)	62.9	46.0	0.927	42.0	47.1	0.344	42.6	47.9	0.362
Overall survival (mo), median (range)	63.3 (20.4–106.1)	48.4 (36.9–59.8)		41.6 (28.6–54.5)	51.6 (37.2–65.9)		38.6 (28.4–48.7)	54.7 (39.4–69.9)	
T4 gastric cancer	2	44		7	39		10	36	
OP name						0.073			0.010
TG	-	-		6 (85.7)	20 (51.3)		9 (90.0)	17 (47.2)	
STG	-	-		1 (14.3)	19 (48.7)		1 (10.0)	19 (52.8)	
Differentiation						0.907			0.404
WD	-	-		2 (28.6)	12 (30.8)		2 (20.0)	12 (33.3)	
PD	-	-		5 (71.4)	27 (69.2)		8 (80.0)	24 (66.7)	
5-Year survival rate (%)	-	-		28.6	29.0	0.307	30.0	29.4	0.186
Overall survival (mo), median (range)	-	-		13.1 (5.1–21.0)	25.1 (15.1–35.0)		10.0 (5.0–14.9)	25.1 (15.5–34.6)	

Values are presented as number (%) unless otherwise indicated.

OP, operation; TG, total gastrectomy; STG, subtotal gastrectomy; WD, well differentiated adenocarcinoma; PD, poorly differentiated adenocarcinoma.

Kaplan-Meier test didn't show the significant difference in patients with different proximal margin length (Table 7).

DISCUSSION

The TNM staging system is most important prognostic factor for predicting overall survival in gastric cancer patients. With this system, the degree of differentiation of tumor cells, tumor size, tumor location, and presence of lymphovascular invasion are known as independent prognostic factors [14-21].

Recently, many studies have been carried out to explore the impact of prognostic factors on overall survival. Especially in patients with the involvement of proximal margin, many reports suggested different philosophies, consequences, and needs for reoperation [22-25]. Also, in the cardiac or middle-third gastric cancer patients, there is a great chasm between the need for total gastrectomy and for subtotal gastrectomy [26,27]. Some surgeons recommended that total gastrectomy is standard treatment to decrease local recurrence rate in the cardiac cancer or middle-third of the stomach cancer because of

Table 4. Clinical characteristics, 5-year survival rate and overall survival between WD and PD groups

Variable	Proximal resection margin								
	≤1 cm (n = 34)	>1 cm (n = 1,837)	P-value	≤2 cm (n = 230)	>2 cm (n = 1,641)	P-value	≤3 cm (n = 493)	>3 cm (n = 1,378)	P-value
WD (MD, PAP)	12	828		77	763		182	651	
Pathologic T staging			0.797			0.777			0.699
T1 gastric cancer	6 (50.0)	471 (56.9)		40 (51.9)	437 (57.3)		100 (54.9)	377 (57.9)	
T2 gastric cancer	3 (25.0)	187 (22.6)		20 (26.0)	170 (22.3)		47 (25.8)	143 (22.0)	
T3 gastric cancer	3 (25.0)	149 (18.0)		15 (19.5)	137 (18.0)		33 (18.1)	119 (18.3)	
T4 gastric cancer	-	21 (2.5)		2 (2.3)	19 (2.5)		2 (1.1)	12 (1.8)	
Operation name			0.004			<0.001			<0.001
Total gastrectomy	6 (50.0)	116 (14.0)		37 (48.1)	85 (11.1)		59 (32.4)	59 (9.1)	
Subtotal gastrectomy	6 (50.0)	712 (86.0)		40 (51.9)	678 (88.9)		123 (67.6)	592 (90.9)	
5-Year survival rate (%)	72.7	78.3	0.741	71.6	78.9	0.128	78.6	78.7	0.462
Overall survival (mo), median (range)		217.6 (203.6–31.5)		139.9 (77.4–202.3)	217.6 (204.1–31.0)			217.6 (204.1–31.0)	
PD (SRC)	22	1017		153	885		311	727	
Pathologic T staging			0.279			0.100			0.584
T1 gastric cancer	6 (27.3)	359 (35.2)		49 (32.0)	315 (35.6)		107 (34.4)	257 (35.4)	
T2 gastric cancer	5 (22.7)	277 (27.3)		33 (21.6)	249 (28.1)		79 (25.4)	203 (27.9)	
T3 gastric cancer	9 (40.9)	351 (34.5)		66 (43.1)	294 (33.2)		117 (37.6)	243 (33.4)	
T4 gastric cancer	2 (9.1)	30 (3.0)		5 (3.3)	27 (3.1)		8 (2.6)	24 (3.3)	
Operation name			<0.001			<0.001			<0.001
Total gastrectomy	15 (68.2)	296 (29.1)		89 (58.2)	222 (25.1)		158 (50.8)	153 (21.0)	
Subtotal gastrectomy	7 (31.8)	720 (70.9)		64 (41.8)	663 (74.9)		153 (49.2)	574 (79.0)	
5-Year survival rate (%)	72.2	71.9	0.405	66.5	72.9	0.022	70.9	72.4	0.518
Overall survival (mo), median (range)	127.3 (84.1–170.4)			180.0 (124.2–35.7)					

Values are presented as number (%) unless otherwise indicated.

WD, well differentiated adenocarcinoma; MD, moderately differentiated adenocarcinoma; PAP, papillary adenocarcinoma; PD, poorly differentiated adenocarcinoma; SRC, signet ring cell adenocarcinoma.

Table 5. Multivariate analysis of factors associated with overall survival

Variable	Patients who underwent subtotal gastrectomy			Patients with PD		
	Relative risk	95% Confidence interval	P-value	Relative risk	95% Confidence interval	P-value
Pathologic T staging						
T2/T1 gastric cancer	1.61	1.157–2.240	0.005	2.40	1.499–3.881	<0.001
T3/T1 gastric cancer	3.28	2.341–4.596	<0.001	5.06	3.154–8.063	<0.001
T4/T1 gastric cancer	6.69	3.642–12.294	<0.001	11.10	6.153–20.141	<0.001
Pathologic N staging						
N1/N0	1.62	1.196–2.195	0.002	1.79	1.230–2.623	<0.001
N2/N0	2.04	1.428–2.941	<0.001	2.21	1.466–3.310	<0.001
N3/N0	3.78	2.582–5.538	<0.001	4.69	3.134–6.953	<0.001
Distance of proximal margin						
Over 2 cm vs. below 2 cm	-	-		1.10	0.836–1.454	NS
Over 3 cm vs. below 3 cm	0.79	0.585–1.084	0.148	-	-	

PD, poorly differentiated adenocarcinoma; NS, not significant.

the short proximal resection margin length.

Before we begin our study, we could not find satisfactory evidences regarding safe proximal margin length from Web search and PubMed. Conventionally, a 2- to 3-cm proximal

resection margin is regarded as the safety proximal margin length for early gastric cancer and a 5- to 6-cm is safe for advanced gastric cancer. Several investigators reported various lengths of safety proximal margin [28,29]. According to the

Table 6. Clinical characteristics, 5-year survival rate and overall survival according to the distance of proximal margin

Variable	Proximal resection margin					
	≤2cm (n = 230)	>5 cm (n = 851)	P-value	≤5 cm (n = 1,020)	>5 cm (n = 851)	P-value
T1 gastric cancer						
OP name			<0.001			<0.001
TG	20 (22.5)	19 (4.5)		63 (15.0)	19 (4.5)	
STG	69 (77.5)	401 (95.5)		358 (85.0)	401 (95.5)	
Differentiation			0.005			0.009
WD	40 (44.9)	257 (61.2)		220 (52.3)	257 (61.2)	
PD	49 (55.1)	163 (38.8)		201 (47.7)	163 (38.8)	
5-Year survival rate (%)	89.5	91.8	0.395	93.2	91.8	0.264
T2 gastric cancer						
OP name			<0.001			<0.001
TG	29 (54.7)	22 (11.1)		91 (33.3)	22 (11.1)	
STG	24 (45.3)	177 (88.9)		182 (66.7)	177 (88.9)	
Differentiation			0.269			0.024
WD	20 (37.7)	92 (46.2)		98 (38.5)	92 (46.2)	
UD	33 (62.3)	107 (53.8)		175 (64.1)	107 (53.8)	
5-Year survival rate (%)	81.3	78.4	0.734	82.7	78.4	0.070
T3 gastric cancer						
OP name			<0.001			<0.001
TG	71 (87.7)	49 (23.4)		159 (52.5)	49 (23.4)	
STG	10 (12.3)	160 (76.6)		144 (47.5)	160 (76.6)	
Differentiation			0.005			0.019
WD	15 (18.5)	74 (35.4)		78 (25.7)	74 (35.4)	
UD	66 (81.5)	135 (64.6)		225 (74.3)	135 (64.6)	
5-Year survival rate (%)	42.0	47.8	0.373	45.3	47.8	0.675
Overall survival (mo), median (range)	41.6 (28.6–54.5)	51.5 (33.4–69.5)		44.2 (29.4–58.9)	51.5 (33.4–69.5)	
T4 gastric cancer						
OP name			0.040			0.074
TG	6 (85.7)	10 (43.5)		16 (69.6)	10 (43.5)	
STG	1 (14.3)	13 (56.5)		7 (30.4)	13 (56.5)	
Differentiation			0.925			1.000
WD	2 (28.6)	7 (30.4)		7 (30.4)	7 (30.4)	
UD	5 (71.4)	16 (69.6)		16 (69.6)	16 (69.6)	
5-Year survival rate (%)	28.6	30.4		28.5	30.4	0.470
Overall survival (mo), median (range)	13.1 (5.1–21.0)	28.2 (14.3–42.8)		20.3 (5.1–35.4)	28.6 (14.3–42.8)	

Values are presented as number (%) unless otherwise indicated.

OP, operation; TG, total gastrectomy; STG, subtotal gastrectomy; WD, well differentiated adenocarcinoma; PD, poorly differentiated adenocarcinoma; UD, undifferentiated adenocarcinoma.

Japanese gastric cancer guidelines 2010, a gross resection margin of 2 cm should be done in T1 gastric cancer. More than 3 cm of proximal margin length is recommended in advanced gastric cancer with expansive growth pattern, and more than 5 cm is recommended in infiltrative advanced gastric cancer [30].

In practical, all surgeons try very hard to achieve the recommended proximal margin length from tumor due to intramural infiltration spreading in the proximal direction. However, it is often very difficult to secure a recommended proximal margin length depending on the situation such as patient's general

condition, and the advancement of cancer stage. Also, there are times when we have no way to demarcate the tumor boundary on intraoperative findings through the use of palpation and inspection techniques. Besides, the distinction in proximal margin length between intraoperative findings and pathologic findings can occur depending on the tumor characteristics and the process of formalin fixation. Even, the prevalence rates of positive margin were reported from 0.8% to 2.0% in patients who underwent gastrectomy with curative intent [4,22-25].

Therefore, our study was planned to explore the impact of the

Table 7. Kaplan-Meier estimates of local recurrence by proximal margin length in the same staging group

Variable	Proximal resection margin											
	≤1 cm	>1 cm	P-value*	≤2 cm	>2 cm	P-value*	≤3 cm	>3 cm	P-value*	≤5 cm	>5 cm	P-value*
Stage IA	0 (0)	1 (0.1)	0.897	0 (0)	1 (0.2)	0.756	0 (0)	1 (0.2)	0.588	0 (0)	1 (0.3)	0.300
Stage IB	0 (0)	3 (1.1)	0.866	0 (0)	3 (1.2)	0.530	0 (0)	3 (1.4)	0.361	2 (1.4)	1 (0.8)	0.490
Stage II	0 (0)	2 (0.7)	0.905	0 (0)	2 (0.8)	0.664	0 (0)	2 (1.0)	0.434	1 (0.7)	1 (0.8)	0.989
Stage IIIA	0 (0)	3 (1.3)	0.765	1 (3.7)	2 (1.0)	0.292	1 (1.8)	2 (1.1)	0.745	1 (0.7)	2 (2.2)	0.388
Stage IIIB	0 (0)	3 (2.1)	0.803	1 (3.3)	2 (1.7)	0.564	1 (2.0)	2 (2.0)	0.879	3 (3.4)	0 (0)	0.106
Stage IV		4 (1.9)	0.724	1 (2.6)	3 (1.6)	0.708	2 (2.9)	2 (1.3)	0.432	2 (1.6)	2 (2.2)	0.712

Values are presented as number of events (%).

*Log-rank test.

involvement and length of proximal margin on overall survival. Although there were significant differences in the ratio of total gastrectomy, distribution of tumor depth, nodal staging, and tumor cell differentiation between proximal margin positive group and negative group, the 5-year survival rate (5.9%) of positive proximal margin group was very low compared to the rate (75.0%) of negative proximal margin group (Table 1). This result supports curative resection margin should be done. But in practice, we often have trouble securing proximal resection margin in total gastrectomy case. In our study, we can identify that there were more patients with positive resection margin in total gastrectomy. In our institution, we have a policy to perform a reoperation in patients with positive resection margin. Although positive proximal margin was confirmed by pathologic report, we did not additional reoperation in patients who refuse reoperation because of their general condition and far advanced stage.

In patients with negative proximal margin, univariate analysis showed a significant difference of overall survival rate in subtotal gastrectomy group (proximal margin length ≤3 cm vs. >3 cm; 86.3% vs. 78.5%; $P = 0.011$). And, there was significant difference in patients with undifferentiated adenocarcinoma group (proximal margin length ≤2 cm vs. >2 cm; 66.5% vs. 72.9%; $P = 0.022$) (Tables 2, 4). However, a multivariate analysis of these prognostic factors and others (depth of tumor invasion, and nodal staging) didn't show statistical significance (Table 5). Therefore, the discrepancies of proximal margin length have little to predict overall survival compared to those of depth of tumor invasion, and lymph node metastasis. Also, Table 6 showed that an extension of proximal margin length doesn't help the improvement of overall survival. Based on these results, reoperation to achieve an additional proximal margin

length offers nothing to improve overall survival.

And, it is considered that the proximal margin length is related to local recurrence in gastric cancer patients. Our study showed that the discrepancies of proximal margin length do not affect the local recurrence rate in gastric cancer patients with negative proximal margin (Table 7). We speculate that the discrepancies of proximal margin length have little effect on local recurrence rate in patients with gastric cancer. In other words, the impact of proximal margin length on oncologic outcomes is relatively lower than other factors such as depth of tumor invasion and lymph node metastasis.

In this study, we are not arguing that clear resection margin is enough for surgical treatment of gastric cancer, regardless of the proximal margin length. Also, we feel the need to explore the safety of proximal margin length 1 cm in T4 gastric cancer, and the impact of subcentimeter on prognosis, because of a small number of patients. We also expect that future studies through large volume can lead to the resolution of these problems.

In conclusion, surgeons should try to secure the negative proximal margin in the surgical treatment because of a poor prognosis of positive proximal margin and a philosophy of the possibility of residual cancer cells. Based on our analyses for the impact of the proximal margin length on overall survival and local recurrence, it is clear that reoperation to achieve an additional proximal margin length does nothing to improve oncologic outcomes.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Cunningham SC, Kamangar F, Kim MP, Hammoud S, Haque R, Maitra A, et al. Survival after gastric adenocarcinoma resection: eighteen-year experience at a single institution. *J Gastrointest Surg* 2005;9:718-25.
2. Roukos DH. Current status and future perspectives in gastric cancer management. *Cancer Treat Rev* 2000;26:243-55.
3. Crew KD, Neugut AI. Epidemiology of gastric cancer. *World J Gastroenterol* 2006;12:354-62.
4. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011;61:69-90.
5. Goggins WB, Wong GK. Poor survival for US Pacific Islander cancer patients: evidence from the Surveillance, Epidemiology, and End Results database: 1991 to 2004. *J Clin Oncol* 2007;25:5738-41.
6. Maehara Y, Kakeji Y, Oda S, Takahashi I, Akazawa K, Sugimachi K. Time trends of surgical treatment and the prognosis for Japanese patients with gastric cancer. *Br J Cancer* 2000;83:986-91.
7. Sun Z, Li DM, Wang ZN, Huang BJ, Xu Y, Li K, et al. Prognostic significance of microscopic positive margins for gastric cancer patients with potentially curative resection. *Ann Surg Oncol* 2009;16:3028-37.
8. Munson JL, O'Mahony R. Radical gastrectomy for cancer of the stomach. *Surg Clin North Am* 2005;85:1021-32.
9. McCulloch P. The role of surgery in patients with advanced gastric cancer. *Best Pract Res Clin Gastroenterol* 2006;20:767-87.
10. Kasakura Y, Fujii M, Mochizuki F, Imai S, Kanamori N, Suzuki T. Clinicopathological features of the superficial spreading type of early gastric cancer. *Gastric Cancer* 1999;2:129-35.
11. Schrock TR, Way LW. Total gastrectomy. *Am J Surg* 1978;135:348-55.
12. Papachristou DN, Agnanti N, D'Agostino H, Fortner JG. Histologically positive esophageal margin in the surgical treatment of gastric cancer. *Am J Surg* 1980;139:711-3.
13. Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma - 2nd English Edition -. *Gastric Cancer* 1998;1:10-24.
14. Esaki Y, Hirayama R, Hirokawa K. A comparison of patterns of metastasis in gastric cancer by histologic type and age. *Cancer* 1990;65:2086-90.
15. Ishigami S, Natsugoe S, Miyazono F, Hata Y, Uenosono Y, Sumikura S, et al. Clinical merit of subdividing gastric cancer according to invasion of the muscularis propria. *Hepatogastroenterology* 2004;51:869-71.
16. Borch K, Jonsson B, Tarpila E, Franzen T, Berglund J, Kullman E, et al. Changing pattern of histological type, location, stage and outcome of surgical treatment of gastric carcinoma. *Br J Surg* 2000;87:618-26.
17. Msika S, Benhamiche AM, Jouve JL, Rat P, Faivre J. Prognostic factors after curative resection for gastric cancer. A population-based study. *Eur J Cancer* 2000;36:390-6.
18. Maehara Y, Kakeji Y, Koga T, Emi Y, Baba H, Akazawa K, et al. Therapeutic value of lymph node dissection and the clinical outcome for patients with gastric cancer. *Surgery* 2002;131(1 Suppl):S85-91.
19. Yokota T, Kunii Y, Teshima S, Yamada Y, Saito T, Takahashi M, et al. Significant prognostic factors in patients with early gastric cancer. *Int Surg* 2000;85:286-90.
20. Adachi Y, Shiraishi N, Suematsu T, Shimizu A, Yamaguchi K, Kitano S. Most important lymph node information in gastric cancer: multivariate prognostic study. *Ann Surg Oncol* 2000;7:503-7.
21. Pinto-De-Sousa J, David L, Seixas M, Pimenta A. Clinicopathologic profiles and prognosis of gastric carcinomas from the cardia, fundus/body and antrum. *Dig Surg* 2001;18:102-10.
22. Songun I, Bonenkamp JJ, Hermans J, van Krieken JH, van de Velde CJ. Prognostic value of resection-line involvement in patients undergoing curative resections for gastric cancer. *Eur J Cancer* 1996;32A:433-7.
23. Kim SH, Karpeh MS, Klimstra DS, Leung D, Brennan MF. Effect of microscopic resection line disease on gastric cancer survival. *J Gastrointest Surg* 1999;3:24-33.
24. Hallissey MT, Jewkes AJ, Dunn JA, Ward L, Fielding JW. Resection-line involvement in gastric cancer: a continuing problem. *Br J Surg* 1993;80:1418-20.
25. Yokota T, Sawai K, Yamaguchi T, Taniguchi H, Shimada S, Yoneyama C, et al. Resection margin in patients with gastric cancer associated with esophageal invasion: clinicopathological study. *J Surg Oncol* 1993;53:60-3.
26. Jang YJ, Park MS, Kim JH, Park SS, Park SH, Kim SJ, et al. Advanced gastric cancer in the middle one-third of the stomach: Should surgeons perform total gastrectomy? *J Surg Oncol* 2010;101:451-6.
27. Stein HJ, Sendler A, Siewert JR. Site-dependent resection techniques for gastric cancer. *Surg Oncol Clin N Am* 2002;11:405-14.
28. Hermann RE. Newer concepts in the treatment of cancer of the stomach. *Surgery* 1993;113:361-4.
29. Kim JP, Kwon OJ, Oh ST, Yang HK. Results of surgery on 6589 gastric cancer patients and immunochemosurgery as the best treatment of advanced gastric cancer. *Ann Surg* 1992;216:269-78.
30. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer* 2011;14:113-23.