

Length of negative resection margin does not affect local recurrence and survival in the patients with gastric cancer

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Abstract

AIM: To investigate the influence of the resection margin on local recurrence and survival in gastric cancer patients.

METHODS: We reviewed the medical records of 1788 patients who had undergone gastrectomy for gastric cancer at the Seoul National University Bundang Hospital, South Korea, between May 2003 and July 2009. The patients were divided into early and advanced gastric cancer groups. In each group, we analyzed the relationship between clinicopathologic factors and survival outcomes, and compared the hazard rates of event occurrence between patients with resection margins above and below the cut-off value, using a Cox

proportional hazard model.

RESULTS: The early and advanced gastric cancer groups included 1001 and 787 patients, respectively. The hazard rates of event occurrence did not significantly differ between the patients with resection margins above the cut-off value and those with resection margins below the cut-off value ($P > 0.05$, in all comparisons). Based on the multivariable analyses, the proximal and distal resection margins were not significantly associated with survival outcomes and local recurrence ($P > 0.05$, in all analyses).

CONCLUSION: The proximal or distal resection margins did not affect the prognosis of patients with gastric cancer if the margins were pathologically negative.

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Key words: Gastric cancer; Survival; Recurrence; Resection; Margin

Core tip: The correlation between the resection margin and survival outcomes was investigated in 1788 patients who had undergone curative surgery for gastric cancer. We found that the proximal or distal resection margins did not affect the prognosis of patients with gastric cancer if the margins were pathologically negative. Moreover, we believe that routine intraoperative frozen-section examination is important to confirm negative margins.

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INTRODUCTION

Surgical resection remains the only curative treatment option for gastric cancer^[1,2], and the resection range is determined on the basis of the location and size of the lesion and the lengths of the resection margins^[3-5]. However, optimization of resection margins remains controversial.

For many years, surgeons have studied the extent of surgical resection required to achieve tumor-free margins. As the ideal resection margin cannot be reliably determined by palpation or gross inspection, it is important to establish universal guidelines^[6]. In 1982, Bozzetti *et al.*^[6] proposed that an adequate proximal resection margin (PM) would exceed 6 cm, in agreement with other contemporary reports^[7,8]. However, these guidelines have not been well established, and new recommendations have emerged in recent decades. The 2010 Japanese gastric cancer treatment guidelines, for example, suggested minimum PMs of 2 cm for early gastric cancer (EGC) and 3 cm (expansive growth type) or 5 cm (infiltrative growth type) for advanced gastric cancer (AGC)^[9]. Concurrently, the National Comprehensive Cancer Network recommended a proximal resection margin of more than 4 cm as necessary to achieve a negative microscopic margin^[10]. However, the 2011 British guidelines differ in that they only recommend the achievement of clear margins, resulting in inconsistencies in the field^[11].

As described above, the recommendations for adequate resection margins have changed over time, and even contemporary guidelines are inconsistent. This global inconsistency has resulted in a lack of clinical confidence in the recommended guidelines. Furthermore, these guidelines have not been established through the analysis of survival outcomes, but rather by the analysis of the distances required to achieve negative margins as recorded in final pathologic reports. Additionally, many surgeons are concerned about the possibility of disease recurrence consequent to short resection margins, even in cases with negative margins^[12]. These concerns have been further highlighted by a growing interest in function-preserving procedures. In particular, there is no consensus regarding the treatment of gastric cancers located in the middle-third of the stomach, although several studies have reported no benefit of total gastrectomy with respect to adequate PMs^[13,14]. Additionally, despite the advantages proposed by several studies^[15-17], there is no consensus regarding resection margins in pylorus-preserving gastrectomy (PPG), which is an important concern for surgeons because the distal margin (DM) might be close to the tumor. In addition, the margin of limited resection in sentinel node navigation surgery (SNNS) should be clarified, although Fujimura *et al.*^[18] proposed a 2 cm margin for segmental resection combined with sentinel node mapping. Thus, more information about the correlation between resection margins and survival is required to establish universal guidelines in this era of function-preservation surgery. Accordingly, in this study, we investigated the correlation between resection margins and survival in patients with gastric cancer.

MATERIALS AND METHODS

Using a prospectively collected gastric cancer database, we retrospectively reviewed the clinicopathologic outcomes of 1788 patients who had undergone curative surgery for gastric adenocarcinoma at Seoul National University Bundang Hospital, South Korea, between May 2003 and July 2009. Patients who underwent a curative subtotal (DG) or a total gastrectomy (TG) with R0 resection and lymphadenectomy more than D1+ were enrolled in this study. Patients with positive resection margins, as recorded in the final pathologic reports, were excluded.

Clinicopathologic outcomes related to prognostic factors, including age, sex, tumor size, tumor type (according to Borrmann's classification), histologic type (according to Lauren's classification), number of harvested lymph nodes, positive lymph nodes, lymphatic invasion, vascular invasion, neural invasion, and stage (according to 7th edition AJCC^[19]), were investigated^[20,21]. The PM and DM were measured according to the guidelines in the Japanese Classification of Gastric Carcinoma: 3rd English edition^[22]. The actual 3-year overall survival (OS) and recurrence-free survival (RFS) were calculated using the Kaplan-Meier method.

The patients were divided into EGC and AGC groups. The EGC group included patients with T1 gastric cancer in the final pathologic reports, and the AGC group included patients with T2, T3 and T4 gastric cancer in the final pathologic reports. We used a Cox proportional hazard model to investigate the effects of the resection margin on survival. This model was applied to 2 distinct statistical analyses. First, we compared the hazard rates between the resection margin categories, using the following cut-off values: 0.5, 1, and 2 cm for each group. Second, univariable and multivariable analyses were performed to identify survival-related factors.

Additionally, we investigated whether the resection margins affected the incidence of local recurrence in each group by using a binary logistic regression model.

SPSS software, version 18.0 (SPSS, Inc., Chicago, IL, United States) and R software, version 2.15.2 (The R Project for Statistical Computing; available at <http://www.r-project.org/>) were used for statistical analyses. For all data analyses, $P < 0.05$ was considered statistically significant.

This study was approved for research on human subjects by the Institutional Review Board of Seoul National University Bundang Hospital (registration number: B-1305/202-104).

RESULTS

The EGC and AGC groups included 1001 and 787 patients, respectively (Table 1). In the EGC group, the number of cases where PM < 0.5 cm, 1 cm, 2 cm was 43, 109, 304, respectively, and the number of cases where DM < 0.5 cm, 1 cm, 2 cm was 27, 66, 160, respectively. In the AGC group, the number of cases where PM < 0.5 cm, 1 cm, 2 cm was 62, 155, 335, respectively, and the

Table 1 Demographics and clinicopathologic characteristics
n (%)

	EGC (<i>n</i> = 1001)	AGC (<i>n</i> = 787)
Sex (male:female)	668:333	520:267
Age (yr)	59.0 ± 11.5	59.4 ± 12.5
Tumor size (cm)	2.9 ± 1.8	5.8 ± 3.1
Borrmann type (%)	-	I : 3.3 II : 16.5 III : 64.7 IV : 10.2 V : 1.4
WHO classification (%)	Differentiated: 58.8 Undifferentiated: 40.2	Differentiated: 37.6 Undifferentiated: 62.0
Lauren classification (%)	Intestinal: 57.3 Diffuse: 34.9	Intestinal: 36.5 Diffuse: 55.3
Operation method (DG:TG)	915:86	539:248
Lymphatic invasion (%)	14.6	68
Vascular invasion (%)	1.2	20.5
Perineural invasion (%)	2.4	62.8
Harvested lymph nodes	40.2 ± 15.0	49.6 ± 19.5
Positive lymph nodes	0.4 ± 2.4	6.7 ± 9.6
Proximal resection margin (cm)	3.6 ± 2.4 (0.1-16.5)	3.3 ± 2.6 (0.1-13.5)
Distal resection margin (cm)	5.7 ± 3.8 (0.1-25.5)	5.6 ± 4.7 (0.1-26.2)
Stage (%)	I : 96.1 II : 3.9 III : 0.0 IV : 0.0	I : 14.1 II : 31.8 III : 48.5 IV : 5.6
Recurrence	19 (1.9)	233 (29.6)
Local recurrence	6 (0.6)	29 (3.7)

The cases involving local recurrence included 5 stump recurrences in EGC and 11 stump recurrences in AGC. EGC: The group including the patients undergoing gastrectomy for early gastric cancer; AGC: The group including the patients undergoing gastrectomy for advanced gastric cancer; DG: Distal gastrectomy; TG: Total gastrectomy.

number of cases where DM < 0.5 cm, 1 cm, 2 cm was 40, 95, 237, respectively.

EGC group

In the EGC group, the actual 3-year OS and RFS rates were 98.8% and 98.4%, respectively.

Regarding the PM, the hazard rates of OS and RFS were not significantly different for resection margin values above and below all cut-off values. Furthermore, regarding the DM, the hazard rates of OS and RFS did not differ significantly according to resection margin values (Table 2).

In multivariable analysis, age and stage were found to be significant risk factors for OS, whereas lymphatic invasion, vascular invasion, and positive lymph node status were significant risk factors for RFS (Table 3). In addition, neither the PM nor DM was associated with the incidence of local recurrence (Table 4).

AGC group

In the AGC group, the actual 3-year OS and RFS rates were 79.3% and 71.8%, respectively.

Regarding the PM, the hazard rates of OS and RFS

were not significantly different for resection margin values above and below all cut-off values. In addition, the hazard rates of OS and RFS for the DM did not differ significantly according to the resection margin values (Table 2).

In multivariable analysis, age, vascular invasion, positive lymph node, and stage were significant risk factors for OS, whereas tumor size, positive lymph node and stage were significant risk factors for RFS (Table 5). In addition, neither the PM nor DM was associated with the incidence of local recurrence (Table 4)

DISCUSSION

Concern regarding the potential for disease recurrence in cases with a short resection margin is a widely documented^[12]. Here, “short resection margin” indicates a resection margin, as determined by intraoperative palpation or gross inspection, that could be recorded as positive in the final pathologic report^[6]. A positive margin in the pathologic result has been reported to be associated with poor prognosis^[8,23-26]. However, even if a negative resection margin is achieved, many surgeons remain concerned about the fact that locoregional recurrence is the most commonly observed recurrence pattern in patients with negative margins^[27,28], and signet ring cell carcinomas intermittently exhibit skip spread^[29,30]. However, our data indicate that the length of resection margins did not affect OS and RFS. Moreover, no correlation was observed between the length of resection margins and the incidence of locoregional recurrence.

One concern regarding the PM, which has been debated in the literature, is the treatment of centrally located gastric cancers. To ensure an adequate PM, many surgeons insist upon a total gastrectomy, rather than a subtotal gastrectomy, for gastric cancers located in the middle-third of the stomach^[3,5]. In fact, if curative surgery is performed in compliance with the current guidelines for resection margins, total gastrectomy is generally the only option for tumors located in the middle-third of the stomach. However, these recommendations did not originate from finding a direct correlation between the PM and survival outcomes. Initially, studies concerning the PM were only undertaken to determine the range of resection required to avoid positive resection margins in the final pathologic report^[5,6,8,31-33]. In our study, we analyzed the correlation between the PM and survival and found no relationship between these variables. In other words, if a negative resection margin is pathologically confirmed, more resection is not necessary even in a PM less than 0.5 cm. Jang *et al.*^[13] and Lee *et al.*^[14] also did not find a relationship between the PM and survival for tumors located in the middle-third of the stomach.

However, these earlier studies did not evaluate the DM. Many surgeons recommend a DM of approximately 2-4 cm distal to the pylorus^[33-35], and these recommendations have been accepted without objection. Given this consensus, the current guidelines contain no mention of

Table 2 Overall appearance of adjusted hazard ratio

Tumor type	Cut-off value	HR (95%CI, <i>P</i> value) - OS	HR (95%CI, <i>P</i> value) - RFS
EGC	PM = 0.5 cm	0.300 (0.074-1.218, 0.092)	0.310 (0.050-1.927, 0.209)
EGC	PM = 1 cm	0.541 (0.158-1.850, 0.327)	0.494 (0.112-2.177, 0.351)
EGC	PM = 2 cm	1.208 (0.433-3.366, 0.718)	1.367 (0.379-4.928, 0.632)
EGC	DM = 1 cm	9.229 (0.479-177.727, 0.141)	12.979 (0.174-969.978, 0.244)
EGC	DM = 2 cm	2.350 (0.520-10.620, 0.267)	2.354 (0.444-12.476, 0.314)
AGC	PM = 0.5 cm	1.122 (0.658-1.915, 0.672)	0.870 (0.535-1.417, 0.577)
AGC	PM = 1 cm	0.922 (0.608-1.398, 0.703)	0.917 (0.623-1.351, 0.661)
AGC	PM = 2 cm	0.979 (0.674-1.422, 0.911)	1.050 (0.738-1.495, 0.786)
AGC	DM = 0.5 cm	0.615 (0.366-1.032, 0.066)	0.772 (0.458-1.302, 0.332)
AGC	DM = 1 cm	0.706 (0.466-1.070, 0.101)	0.852 (0.570-1.273, 0.434)
AGC	DM = 2 cm	1.109 (0.787-1.563, 0.554)	1.338 (0.952-1.882, 0.093)

In the EGC group, we excluded the comparison between the cases where DM < 0.5 and DM ≥ 0.5 because reliable estimates could not be obtained from such a small number of events. EGC: Early gastric cancer; AGC: Advanced gastric cancer; PM: Proximal resection margin; DM: Distal resection margin; OS: Actual 3-year overall survival; RFS: Actual 3-year recurrence-free survival.

Table 3 Survival-related factors in early gastric cancer

Clinicopathologic factors	Univariable analysis for OS (<i>P</i> value, HR)	Multivariable analysis for OS (<i>P</i> value, HR)	Univariable analysis for RFS (<i>P</i> value, HR)	Multivariable analysis for RFS (<i>P</i> value, HR)
Sex	0.094, 0.438		0.117, 0.373	
Age	< 0.001, 1.086	< 0.001, 1.081	0.848, 1.004	
Size of the tumor	0.003, 1.267	0.124, 1.158	0.018, 1.253	0.515, 1.079
Operation method	0.270, 1.185		0.618, 0.599	
Lymphatic invasion	< 0.001, 5.289	0.077, 2.437	< 0.001, 13.310	< 0.001, 7.689
Vascular invasion	0.219, 3.503		0.002, 10.119	0.046, 0.208
Perineural invasion	0.005, 5.642	0.173, 2.416	0.027, 5.229	0.492, 0.580
WHO classification	0.760, 0.886		0.441, 0.683	
Lauren classification	0.593, 0.783		0.601, 0.754	
Harvested lymph node	0.676, 0.994		0.658, 1.007	
Positive lymph node	< 0.001, 1.065	0.164, 1.038	< 0.001, 1.078	0.006, 1.068
PM	0.405, 0.930		0.592, 1.049	
DM	0.609, 1.025		0.235, 0.916	
Stage	< 0.001, 10.515	0.028, 3.836	< 0.001, 16.028	0.168, 2.416

Age, size of the tumor, harvested lymph node, positive lymph node, PM, DM were included as continuous values in this analysis. EGC: Early gastric cancer; OS: Actual 3-year overall survival; RFS: Actual 3-year recurrence-free survival; PM: The length of proximal resection margin; DM: The length of distal resection margin.

Table 4 Correlation between clinicopathologic factors and local recurrence

Clinicopathologic Factors	Univariable analysis for EGC (<i>P</i> value, HR)	Multivariable analysis for EGC (<i>P</i> value, HR)	Univariable analysis for AGC (<i>P</i> value, HR)	Multivariable analysis for AGC (<i>P</i> value, HR)
Sex	0.403, 0.399		0.650, 1.194	
Age	0.946, 0.998		0.267, 0.984	
Size of the tumor	0.032, 1.385	0.097, 1.318	< 0.001, 1.223	0.040, 1.146
Lymphatic invasion	0.031, 5.895	0.078, 4.409	0.023, 4.052	
Vascular invasion	0.999, 0.000		0.128, 1.879	
Perineural invasion	0.057, 8.357		0.013, 3.868	0.191, 2.327
Borrmann Type	-		0.007	0.167
WHO Classification	0.719, 0.731		0.059, 2.401	
Lauren Classification	0.602, 0.547		0.180, 1.825	
Harvested lymph node	0.696, 0.988		0.713, 1.003	
Positive lymph node	0.309, 1.055		0.012, 1.035	0.928, 1.002
PM	0.236, 0.745		0.579, 1.958	
DM	0.308, 0.862		0.769, 0.988	
Stage	0.998, 0.000		0.017	0.191

Age, size of the tumor, harvested lymph node, positive lymph node, PM, DM were included as continuous values in this analysis. EGC: Early gastric cancer; AGC: Advanced gastric cancer; PM: The length of proximal resection margin; DM: The length of distal resection margin.

Table 5 Survival related factors in advanced gastric cancer

Clinicopathologic factors	Univariable analysis for OS (<i>P</i> value, HR)	Multivariable analysis for OS (<i>P</i> value, HR)	Univariable analysis for RFS (<i>P</i> value, HR)	Multivariable analysis for RFS (<i>P</i> value, HR)
Sex	0.449, 1.113		0.306, 1.150	
Age	0.025, 1.013	0.001, 1.020	0.470, 0.996	
Size of the tumor	< 0.001, 1.139	0.127, 1.046	< 0.001, 1.177	0.012, 1.081
Operation method	0.029, 1.361	0.145, 0.727	0.004, 1.474	0.091, 0.697
Lymphatic invasion	< 0.001, 3.537	0.696, 1.094	< 0.001, 3.082	0.975, 0.993
Vascular invasion	< 0.001, 2.876	0.026, 1.428	< 0.001, 2.868	0.094, 1.313
Perineural invasion	< 0.001, 2.440	0.343, 1.189	< 0.001, 2.342	0.634, 1.092
Borrmann type	< 0.001	0.087	< 0.001	0.05
WHO Classification	0.025, 1.389	0.856, 1.030	0.003, 1.537	0.169, 1.745
Lauren Classification	0.099, 1.281		0.004, 1.530	0.165, 0.572
Harvested lymph node	0.191, 1.004		0.288, 1.003	
Positive lymph node	< 0.001, 1.048	0.001, 1.021	< 0.001, 1.047	< 0.001, 1.021
PM	0.278, 0.970		0.207, 0.966	
DM	0.047, 0.969	0.660, 1.009	0.035, 0.968	0.670, 1.009
Stage	< 0.001	< 0.001	< 0.001	< 0.001

Age, size of the tumor, harvested lymph node, positive lymph node, PM, DM were included as continuous values in this analysis. AGC: Advanced gastric cancer; OS: Actual 3-year overall survival; RFS: Actual 3-year recurrence-free survival; PM: The length of proximal resection margin; DM: The length of distal resection margin.

the DM^[9-11]. However, in function-preserving procedures such as PPG, segmental or wedge resection with SNNS, and proximal gastrectomy (PG), the DM might often be shorter than the length of resection margins recommended in the current guidelines. Therefore, the correlations of the DM with survival and recurrence should also be evaluated. To our knowledge, this is the first report to analyze the oncologic significance of the DM.

As described above, we evaluated the correlations between resection margins and survival outcomes in patients in whom R0 resection had been achieved. Overall, we observed no significant correlations. Accordingly, some guidelines could be obtained from the results of this study. One of the guidelines support the function-preserving concept in the treatment of gastric cancer. Although TG has been a representative surgical treatment for gastric cancer for several decades, surgeons have steadily challenged this paradigm. For example, in a multicenter randomized trial reported by Bozzetti *et al*^[36], which involved lesions in the middle and distal thirds of the stomach, the 5-year survival rates for both DG and TG were identical. That result agrees with our current results. To date, the concept of function preservation has been expanded to incorporate PPG, SNNS, and PG. These surgeries are not yet fully validated, and therefore it is necessary to clarify the correlations between resection margins and survival outcomes. Our present study serves to expand this field and provides additional evidence to advocate these surgeries by demonstrating a lack of a correlation between survival outcomes and the length of resection margins.

However, we never denied the importance of the resection margin itself. In terms of oncologic safety, it is more important to get negative resection margins than to achieve the function-preserving surgery. This point was even a precondition of this study, as only the cases with

negative resection margins were enrolled. Although survival was not affected by the length of resection margins, this conclusion is viable only as long as resection lines were free of tumor cells. Here, we suggest intraoperative frozen-section examination (IFSE) as the most significant recommendation that may be extracted from this study. To ensure tumor-free resection lines, negative margins should be confirmed during surgery. At our center, we routinely perform IFSE to determine the presence of tumor cells at the resection line. IFSE has some advantages. First, IFSE potentially minimizes local recurrences, as it has an approximate 98% accuracy^[37] (The accuracy for our data was 99.1%). Moreover, rapid cytokeratin immunohistochemistry staining might prevent false-negative results^[38]. Second, IFSE facilitates the attempt of limited and minimally invasive procedures for gastric cancer. Resections performed according to the guidelines but without IFSE might sometimes be unnecessarily extensive surgeries. However, by implementing IFSE, surgeons can achieve minimal resection without positive resection margins and thus provide a better quality of life for patients^[12].

Pathologically negative margins, whether PM or DM, did not affect the actual 3-year overall and recurrence-free survival rates and the incidence of local recurrence. Moreover, to confirm negative resection margins, routine IFSE should be established.

COMMENTS

Background

Surgical resection remains the only curative treatment option for gastric cancer, and the resection range is determined on the basis of the location and size of the lesion and the lengths of the resection margins. However, optimization of resection margins remains controversial.

Research frontiers

The current guidelines have not been established through the analysis of survival outcomes, but rather by the analysis of the distances required to achieve

negative margins as recorded in final pathologic reports.

Innovations and breakthroughs

The authors investigated the correlation between resection margins and survival in patients with gastric cancer. The distal margin (DM) as well as proximal resection margin (PM) were analyzed in this study. As a result, the length of resection margins did not affect the actual 3-year overall and recurrence-free survival rates and the incidence of local recurrence, if the margins were pathologically negative. To confirm negative resection margins, routine intraoperative frozen-section examination (IFSE) should be implemented.

Applications

By implementing IFSE, surgeons can achieve minimal resection without positive resection margins and thus provide a better quality of life for patients.

Terminology

Resection margin is the distance between the resection line and the tumor margin in the specimen. PM indicates the length of the proximal resection margin, and DM indicates the length of the distal resection margin. In this study, overall survival was the actual 3-year overall survival, and recurrence-free survival was the actual 3-year recurrence-free survival.

Peer review

Authors indicate the length of negative resection margin does not affect local recurrence and survival in the patients with gastric cancer. This manuscript is very interesting and well written.

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