**Name of journal:** **World Journal of Gastroenterology**

**ESPS Manuscript No: 9425**

**Columns: Retrospective Study**

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

Lee CM *et al*. Resection margin and recurrence in GC

Chang Min Lee, Ye Seob Jee, Ju-Hee Lee, Sang-Yong Son, Do-Hyun Jeong, Sang-Hoon Ahn, Do Joong Park, Hyung-Ho Kim

**Chang Min Lee, Sang-Yong Son, Do-Hyun Jeong, Sang-Hoon Ahn, Do Joong Park, Hyung-Ho Kim,** Department of Surgery, Seoul National University Bundang Hospital, Seongnam 463-707, South Korea

**Do Joong Park**, **Hyung-Ho Kim,** Colledge of Medicine, Seoul National University, Seoul 110-799, South Korea

**Ye Seob Jee**, Department of Surgery, Dankook University Hospital, Cheonan 330-715, South Korea

**Ye Seob Jee**, Colledge of Medicine, Dankook University, Cheonan 330-715, South Korea

**Ju-Hee Lee**, Department of Surgery, Hanyang University Medical Center, Seoul 133-792, South Korea

**Author contributions:** Lee CM and Kim HH designed the research; Son SY, Jeong DH and Ahn SH performed the research; Jee YS, Lee JH and Park DJ contributed new analytic tools; Lee CM analyzed data; and Lee CM wrote the paper.

**Correspondence to**: **Hyung-Ho Kim, MD, PhD**, Department of Surgery, Seoul National University Bundang Hospital, 82, Gumi-ro 173 beon gil, Bundang-gu, Seongnam 463-707, South Korea. lapakh2@gmail.com

**Telephone:** +82-31-7877095  **Fax:** +82-31-7874078

**Received:** February 11, 2014 **Revised:** April 1, 2014

**Accepted:** May 23, 2014

**Published online:**

**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.

© 2014 Baishideng Publishing Group Inc. All rights reserved.

**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.

Lee cm, Jee ys, Lee JH, Son SY, Jeong DH, Ahn SH, Park DJ, Kim HH. Length of negative resection margin does not affect local recurrence and survival in the patients with gastric cancer. *World J Gastroenterol* 2014; In press

**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 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 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***

We 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, OS was the actual 3-year overall survival, and RFS was the actual 3-year recurrence-free survival.

***Peer review***

Authors indicate the length of negative resection margin dose not affect local recurrence and survival in the patients with gastric cancer.

This manuscript is very interesting and well written.

**References**

1 **Songun I**, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol* 2010; **11**: 439-449 [PMID: 20409751 DOI: 10.1016/S1470-2045(10)70070-X]

2 **Russell MC**, Mansfield PF. Surgical approaches to gastric cancer. *J Surg Oncol* 2013; **107**: 250-258 [PMID: 22674546 DOI: 10.1002/jso.23180]

3 **Stein HJ**, Sendler A, Siewert JR. Site-dependent resection techniques for gastric cancer. *Surg Oncol Clin N Am* 2002; **11**: 405-414 [PMID: 12424859]

4 **Dicken BJ**, Bigam DL, Cass C, Mackey JR, Joy AA, Hamilton SM. Gastric adenocarcinoma: review and considerations for future directions. *Ann Surg* 2005; **241**: 27-39 [PMID: 15621988]

5 **Clark CJ**, Thirlby RC, Picozzi V, Schembre DB, Cummings FP, Lin E. Current problems in surgery: gastric cancer. *Curr Probl Surg* 2006; **43**: 566-670 [PMID: 17000267 DOI: 10.1067/j.cpsurg.2006.06.003]

6 **Bozzetti F**, Bonfanti G, Bufalino R, Menotti V, Persano S, Andreola S, Doci R, Gennari L. Adequacy of margins of resection in gastrectomy for cancer. *Ann Surg* 1982; **196**: 685-690 [PMID: 7149820]

7 **Eker R**. Carcinomas of the stomach; investigation of the lymphatic spread from gastric carcinomas after total and partial gastrectomy. *Acta Chir Scand* 1951; **101**: 112-126 [PMID: 14818627]

8 **Papachristou DN**, Fortner JG. Local recurrence of gastric adenocarcinomas after gastrectomy. *J Surg Oncol* 1981; **18**: 47-53 [PMID: 7289619]

9 **Daimon Y**, Takahashi M, Yabuno T, Watanabe J, Mochizuki Y, Kito F, Yoshida S. [A case report of bi-weekly docetaxel and S-1 combination chemotherapy for gastric cancer with carcinomatous lymphangitis of the lung]. *Nihon Shokakibyo Gakkai Zasshi* 2011; **108**: 605-610 [PMID: 21467767]

10 **Ajani JA**, Barthel JS, Bekaii-Saab T, Bentrem DJ, D'Amico TA, Das P, Denlinger C, Fuchs CS, Gerdes H, Hayman JA, Hazard L, Hofstetter WL, Ilson DH, Keswani RN, Kleinberg LR, Korn M, Meredith K, Mulcahy MF, Orringer MB, Osarogiagbon RU, Posey JA, Sasson AR, Scott WJ, Shibata S, Strong VE, Washington MK, Willett C, Wood DE, Wright CD, Yang G. Gastric cancer. *J Natl Compr Canc Netw* 2010; **8**: 378-409 [PMID: 20410333]

11 **Allum WH**, Blazeby JM, Griffin SM, Cunningham D, Jankowski JA, Wong R. Guidelines for the management of oesophageal and gastric cancer. *Gut* 2011; **60**: 1449-1472 [PMID: 21705456 DOI: 10.1136/gut.2010.228254]

12 **Shin D**, Park SS. Clinical importance and surgical decision-making regarding proximal resection margin for gastric cancer. *World J Gastrointest Oncol* 2013; **5**: 4-11 [PMID: 23738049 DOI: 10.4251/wjgo.v5.i1.4]

13 **Jang YJ**, Park MS, Kim JH, Park SS, Park SH, Kim SJ, Kim CS, Mok YJ. Advanced gastric cancer in the middle one-third of the stomach: Should surgeons perform total gastrectomy? *J Surg Oncol* 2010; **101**: 451-456 [PMID: 19924722 DOI: 10.1002/jso.21431]

14 **Lee JH**, Kim YI. Which Is the Optimal Extent of Resection in Middle Third Gastric Cancer between Total Gastrectomy and Subtotal Gastrectomy? *J Gastric Cancer* 2010; **10**: 226-233 [PMID: 22076190 DOI: 10.5230/jgc.2010.10.4.226]

15 **Park do J**, Lee HJ, Jung HC, Kim WH, Lee KU, Yang HK. Clinical outcome of pylorus-preserving gastrectomy in gastric cancer in comparison with conventional distal gastrectomy with Billroth I anastomosis. *World J Surg* 2008; **32**: 1029-1036 [PMID: 18256877 DOI: 10.1007/s00268-007-9441-4]

16 **Kong SH**, Kim JW, Lee HJ, Kim WH, Lee KU, Yang HK. The safety of the dissection of lymph node stations 5 and 6 in pylorus-preserving gastrectomy. *Ann Surg Oncol* 2009; **16**: 3252-3258 [PMID: 19639365 DOI: 10.1245/s10434-009-0646-7]

17 **Suh YS**, Han DS, Kong SH, Kwon S, Shin CI, Kim WH, Kim HH, Lee HJ, Yang HK. Laparoscopy-assisted pylorus-preserving gastrectomy is better than laparoscopy-assisted distal gastrectomy for middle-third early gastric cancer. *Ann Surg* 2014; **259**: 485-493 [PMID: 23652333 DOI: 10.1097/SLA.0b013e318294d142]

18 **Fujimura T**, Fushida S, Kayahara M, Ohta T, Kinami S, Miwa K. Transectional gastrectomy: an old but renewed concept for early gastric cancer. *Surg Today* 2010; **40**: 398-403 [PMID: 20425540 DOI: 10.1007/s00595-009-4151-1]

19 **Washington K**. 7th edition of the AJCC cancer staging manual: stomach. *Ann Surg Oncol* 2010; **17**: 3077-3079 [PMID: 20882416 DOI: 10.1245/s10434-010-1362-z]

20 **Kattan MW**, Karpeh MS, Mazumdar M, Brennan MF. Postoperative nomogram for disease-specific survival after an R0 resection for gastric carcinoma. *J Clin Oncol* 2003; **21**: 3647-3650 [PMID: 14512396 DOI: 10.1200/JCO.2003.01.240]

21 **Peeters KC**, Kattan MW, Hartgrink HH, Kranenbarg EK, Karpeh MS, Brennan MF, van de Velde CJ. Validation of a nomogram for predicting disease-specific survival after an R0 resection for gastric carcinoma. *Cancer* 2005; **103**: 702-707 [PMID: 15641033 DOI: 10.1002/cncr.20783]

22 **Japanese Gastric Cancer Association**. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011; **14**: 101-112 [PMID: 21573743 DOI: 10.1007/s10120-011-0041-5]

23 **Sun Z**, Li DM, Wang ZN, Huang BJ, Xu Y, Li K, Xu HM. Prognostic significance of microscopic positive margins for gastric cancer patients with potentially curative resection. *Ann Surg Oncol* 2009; **16**: 3028-3037 [PMID: 19626373 DOI: 10.1245/s10434-009-0624-0]

24 **Nagata T**, Ichikawa D, Komatsu S, Inoue K, Shiozaki A, Fujiwara H, Okamoto K, Sakakura C, Otsuji E. Prognostic impact of microscopic positive margin in gastric cancer patients. *J Surg Oncol* 2011; **104**: 592-597 [PMID: 21744353 DOI: 10.1002/jso.22022]

25 **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 [PMID: 10457320]

26 **Wang SY**, Yeh CN, Lee HL, Liu YY, Chao TC, Hwang TL, Jan YY, Chen MF. Clinical impact of positive surgical margin status on gastric cancer patients undergoing gastrectomy. *Ann Surg Oncol* 2009; **16**: 2738-2743 [PMID: 19636636 DOI: 10.1245/s10434-009-0616-0]

27 **Roviello F**, Marrelli D, de Manzoni G, Morgagni P, Di Leo A, Saragoni L, De Stefano A. Prospective study of peritoneal recurrence after curative surgery for gastric cancer. *Br J Surg* 2003; **90**: 1113-1119 [PMID: 12945079 DOI: 10.1002/bjs.4164]

28 **D'Angelica M**, Gonen M, Brennan MF, Turnbull AD, Bains M, Karpeh MS. Patterns of initial recurrence in completely resected gastric adenocarcinoma. *Ann Surg* 2004; **240**: 808-816 [PMID: 15492562]

29 **Maehara Y**, Sakaguchi Y, Moriguchi S, Orita H, Korenaga D, Kohnoe S, Sugimachi K. Signet ring cell carcinoma of the stomach. *Cancer* 1992; **69**: 1645-1650 [PMID: 1312889]

30 **Seo JH**, Park JC, Kim YJ, Shin SK, Lee YC, Lee SK. Undifferentiated histology after endoscopic resection may predict synchronous and metachronous occurrence of early gastric cancer. *Digestion* 2010; **81**: 35-42 [PMID: 20029207 DOI: 10.1159/000235921]

31 **Ito H**, Clancy TE, Osteen RT, Swanson RS, Bueno R, Sugarbaker DJ, Ashley SW, Zinner MJ, Whang EE. Adenocarcinoma of the gastric cardia: what is the optimal surgical approach? *J Am Coll Surg* 2004; **199**: 880-886 [PMID: 15555971 DOI: 10.1016/j.jamcollsurg.2004.08.015]

32 **Kim JH**, Park SS, Kim J, Boo YJ, Kim SJ, Mok YJ, Kim CS. Surgical outcomes for gastric cancer in the upper third of the stomach. *World J Surg* 2006; **30**: 1870-186; discussion 1870-186; [PMID: 16957826 DOI: 10.1007/s00268-005-0703-8]

33 **Morgagni P**, Garcea D, Marrelli D, de Manzoni G, Natalini G, Kurihara H, Marchet A, Vittimberga G, Saragoni L, Roviello F, Di Leo A, De Santis F, Panizza V, Nitti D. Does resection line involvement affect prognosis in early gastric cancer patients? An Italian multicentric study. *World J Surg* 2006; **30**: 585-589 [PMID: 16547613 DOI: 10.1007/s00268-005-7975-x]

34 **Kakeji Y**, Tsujitani S, Baba H, Moriguchi S, Mori M, Maehara Y, Kamegawa T, Sugimachi K. Clinicopathologic features and prognostic significance of duodenal invasion in patients with distal gastric carcinoma. *Cancer* 1991; **68**: 380-384 [PMID: 2070336]

35 **Kakeji Y**, Korenaga D, Baba H, Watanabe A, Tsujitani S, Maehara Y, Sugimachi K. Surgical treatment of patients with gastric carcinoma and duodenal invasion. *J Surg Oncol* 1995; **59**: 215-219 [PMID: 7630166]

36 **Bozzetti F**, Marubini E, Bonfanti G, Miceli R, Piano C, Gennari L. Subtotal versus total gastrectomy for gastric cancer: five-year survival rates in a multicenter randomized Italian trial. Italian Gastrointestinal Tumor Study Group. *Ann Surg* 1999; **230**: 170-178 [PMID: 10450730]

37 **Ferreiro JA**, Myers JL, Bostwick DG. Accuracy of frozen section diagnosis in surgical pathology: review of a 1-year experience with 24,880 cases at Mayo Clinic Rochester. *Mayo Clin Proc* 1995; **70**: 1137-1141 [PMID: 7490913 DOI: 10.1016/S0025-6196(11)63438-1]

38 **Matsusaka S**, Nagareda T, Yamasaki H, Kitayama Y, Okada T, Maeda S. Immunohistochemical evaluation for intraoperative rapid pathological assessment of the gastric margin. *World J Surg* 2003; **27**: 715-718 [PMID: 12732996 DOI: 10.1007/s00268-003-6792-3]

**P-Reviewers:** Nakajima T, Nakayama Y, Sasson AR **S-Editor:** Ma YJ **L-Editor:** **E-Editor:**

**Table 1 Demographics and clinicopathologic characteristics**

|  |  |  |
| --- | --- | --- |
|  | **EGC**  **(*n* = 1001)** | **AGC**  **(*n* = 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 | 68.0 |
| **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%) |

1The 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.

**Table 2 overall appearance of adjusted hazard ratio**

|  |  |  |  |
| --- | --- | --- | --- |
| **Tumor type** | **Cut-off value** | **Hr (95%CI, *p-*value) - OS** | **Hr ( 95% CI, *p-*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 = 1cm** | 0.922 (0.608-1.398, 0.703) | 0.917 (0.623-1.351, 0.661) |
| **AGC** | **PM = 2cm** | 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) |

1In 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**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Clnicopathologic Factors** | **Univariable analysis for OS ( *p-*value, HR)** | **Multivariable analysis for OS (*p-*value, HR)** | **Univariable analysis for RFS ( *p-*value, HR)** | **Multivariable analysis for RFS ( *p-*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 |

1Age, 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; HR: hazard ratio; PM: The length of proximal resection margin; DM: The length of distal resection margin.

**Table 4 Correlation between clinicopathologic factors and local recurrence**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Clnicopathologic Factors** | **Univariable analysis for EGC (*p-*value, HR)** | **Multivariable analysis for EGC (*p-*value, HR)** | **Univariable analysis for AGC (*p-*value, HR)** | **Multivariable analysis for AGC (*p-*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 |

1Age, 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; HR: Hazard ratio; PM: The length of proximal resection margin; DM: The length of distal resection margin.

**Table 5 Survival related factors in advanced gastric cancer**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Clnicopathologic Factors** | Univariable analysis for OS (***p-*value**, HR) | Multivariable analysis for OS (***p-*value**, HR) | Univariable analysis for RFS (***p-*value**, HR) | Multivariable analysis for RFS (***p-*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** | 0.050 |
| **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** |

1Age, 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; HR: Hazard ratio; PM: The length of proximal resection margin; DM: The length of distal resection margin.