

Long-Term Surgical Outcome of 1057 Gastric GISTs According to 7th UICC/AJCC TNM System

Multicenter Observational Study From Korea and Japan

Min-Chan Kim, MD, PhD, Jeong-Hwan Yook, MD, PhD, Han-Kwang Yang, MD, PhD, Hyuk-Joon Lee, MD, PhD, Tae-Sung Sohn, MD, PhD, Woo-Jin Hyung, MD, PhD, Seung-Wan Ryu, MD, PhD, Yukinori Kurokawa, MD, PhD, Young-Woo Kim, MD, PhD, Sang-Uk Han, MD, PhD, Hyung-Ho Kim, MD, PhD, Do-Joong Park, MD, PhD, Wook Kim, MD, PhD, Sang-Il Lee, MD, PhD, Haruhiko Cho, MD, PhD, Gyu-Seok Cho, MD, PhD, Jin-Jo Kim, MD, PhD, Ki-Han Kim, MD, PhD, and Moon-Won Yoo, MD, PhD

Abstract: The aim of this study was to evaluate the treatment and prognosis of gastric gastrointestinal stromal tumors (GISTs) according to the 7th UICC/AJCC tumor-node-metastasis (TNM) system and the modified National Institutes of Health (NIH) risk classification. The study cohort consisted of 1057 patients with gastric GIST who underwent surgery between January 2000 and December 2007 from 13 institutions in Korea and 2 in Japan. Clinicopathologic characteristics, surgical outcomes, recurrence, and 5-year recurrence-free survival were evaluated.

The mean age of the patients was 58.6 years. Thirty patients (2.8%) had distant metastasis preoperatively. Median tumor size was 4.0 cm.

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Received: May 3, 2015; revised: July 28, 2015; accepted: August 13, 2015. From the Department of Surgery, Dong-A University College of Medicine, Seoul, Korea (M-CK, K-HK); Department of Surgery, University of Ulsan College of Medicine, Seoul, Korea (J-HY, M-WY); Department of Surgery and Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea (H-KY, H-JL); Department of Surgery, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Korea (T-SS); Department of Surgery, Yonsei University Health System, Yonsei University College of Medicine, Seoul, Korea (W-JH); Department of Surgery, Keimyung University School of Medicine, Seoul, Korea (S-WR); Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University, Seoul, Korea (YK); Center for Gastric Cancer, National Cancer Center, Seoul, Korea (Y-WK); Department of Surgery, School of Medicine, Ajou University, Seoul, Korea (S-UH); Department of Surgery, Seoul National University Bundang Hospital, Seoul, Korea (H-HK, D-JP); Department of Surgery, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea (WK); Department of Surgery, Chungnam National University Hospital, Seoul, Korea (S-IL); Department of Gastrointestinal Surgery, Kanagawa Cancer center, Seoul, Korea (HC); Department of Surgery, Soonchunhyang University College of Medicine, Seoul, Korea (G-SC); and Division of Gastrointestinal Surgery, Department of Surgery, Incheon St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea (J-JK).

Correspondence: Jeong-Hwan Yook, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, 138-736 Seoul, Korea (e-mail: jhyook@amc.seoul.kr).

Author contributions—Conception and design: all authors; provision of study materials or patients: Jeong-Hwan Yook and Min-Chan Kim; collection and assembly of data: Min-Chan Kim and Ki-Han Kim; data analysis and interpretation: Min-Chan Kim and Ki-Han Kim; manuscript writing: Min-Chan Kim; and final approval of manuscript: all authors.

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Complete resection (R0 resection) was achieved in 1018 patients (96.3%). Eighty-six patients (8.1%) had postoperative complications, and 2 patients (0.2%) died within 30 days after surgery. According to the 7th UICC/AJCC TNM system, 5-year recurrence-free survival rates were 95% to 99% in stage I, 94.1% in stage II, 74.1% in stage IIIA, 48.6% in stage IIIB, and 50.0% in stage IV patients. On survival analysis of high-risk patients according to the TNM system, the 5-year recurrence-free survival rates were 91.6% in stage II, 74.1% in stage IIIA, and 48.6% in stage IIIB patients. Independent factors of recurrence following surgery for gastric GIST were gender, tumor size, mitotic count, and radicality on multivariate analysis.

The treatment outcome and prognosis of gastric GIST in Korea and Japan seem more favorable compared to those in Western countries. Compared to the modified NIH risk classification, the 7th UICC/AJCC TNM system is more reflective of the 5-year recurrence-free survival of patients with gastric GIST.

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Abbreviations: AJCC = American Joint Committee on Cancer, CRF = case report form, GIST = gastrointestinal stromal tumor, HPF = high power field, NIH = National Institutes of Health, TNM = tumor-node-metastasis, UICC = Union for International Cancer Control.

INTRODUCTION

Gastrointestinal stromal tumors (GIST) originate from the interstitial cells of Cajal, intestinal pacemaker cells in the gastrointestinal tract.^{1,2} GISTs metastasize mainly to the liver via hematogenous spread and disseminate throughout the peritoneal cavity.³ They are primarily located in the stomach (60–70%) and are also found in the small intestine (20–30%), esophagus (5%), and colon and rectum (5%).⁴ Surgery is a potentially curative treatment for patients with resectable GIST. The purpose of surgery for resectable GIST is complete resection with tumor-free margins, avoiding tumor rupture,⁵ because tumor rupture, either spontaneously or at surgery, is associated with a high risk of recurrence. Whether rupture is an independent risk factor remains controversial.⁶ However, the prognosis of patients with primary GIST is influenced by tumor size and its mitotic count.^{3,4,6} Imatinib mesylate (Glivec[®], Novartis, Basel, Switzerland) was established as the treatment of choice for patients with inoperable or metastatic disease. A recent prospective multicenter phase III trial has shown that 3 years of imatinib therapy improves overall survival compared to 1 year

of therapy.⁷ Imatinib is also being investigated in the neoadjuvant setting to downstage unresectable tumors to resectable stage.⁸

In 2005, Miettinen et al⁹ reported on a large retrospective study of 1765 patients with gastric GISTs who were followed over the long term. Their study provides extensive information on gastric GIST, including clinicopathologic, immunohistochemical, and molecular genetic characteristics and corresponding prognosis. According to the new 7th Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) tumor-node-metastasis (TNM) system, progression rates of gastric GIST were 0% to 3.6% in stage I, 12% to 31.6% in stage II, 55% in stage IIIA, and 86% in stage IIIB.¹⁰ Gastric GIST had a more favorable prognosis than other GISTs.¹¹

There have been a number of studies on clinical outcome, risk of recurrence, prognosis, and imatinib therapy for all GISTs including gastric GIST. However, there has been no multicenter study on gastric GIST patients with long-term follow-up that has sufficient information regarding follow-up and surgery. The aim of this study was to evaluate the treatment and prognosis of gastric GISTs according to the 7th UICC/AJCC TNM system and the modified National Institutes of Health (NIH) risk classification.

MATERIALS AND METHODS

Study Cohort and Data Collection

The study cohort consisted of 1057 patients with gastric GIST who were treated with surgery between January 2000 and December 2007 at 1 of 13 institutions in Korea: Ulsan University, Seoul National University, Sungkyunkwan University, Yonsei University, Keimyung University, Dong-A University, National Cancer Center, Ajou University, Seoul National University Bundang Hospital, the Catholic University Yeouido St. Mary's Hospital, Chungnam University, Soonchunhyang University, and the Catholic University Incheon St. Mary's Hospital and 2 institutions in Japan: Osaka University and Kanagawa Cancer Center Hospital. The diagnosis of GIST was confirmed at each institution by positive staining for KIT (CD117) protein and/or CD34 as assessed by immunohistochemical staining, regardless of myogenic and neurogenic markers.

Data were collected by reviewing the medical records and prospectively designed gastric GIST database from each institution. The Institutional Review Board of each participating institution approved this study. All data were collected in the same case report form (CRF) from each institution, and data were collected without revealing any personal information.

Personal Characteristics and Follow-Up

Clinicopathologic characteristics included age, gender, weight (kg), height (m), preoperative metastatic status, preoperative symptoms, tumor location, tumor size (cm), mitotic count (/50 high power field [HPF]), National Institutes of Health (NIH) classification, and whether the patient received pre- or postoperative imatinib mesylate treatment. Surgical outcomes included operation date, operation method, radicality, type of surgery, intraoperative tumor rupture, combined surgery, operation time (minute), postoperative hospital stay (day), complications, and death within 30 days after operation. Fifty-one patients who could not be classified via NIH classification, 10 patients lost to follow-up, and 30 preoperative M1 patients were excluded in the analysis of recurrence and long-term survival.

The follow-up schedule for patients after curative resection in most institutions was as follows: physical examination,

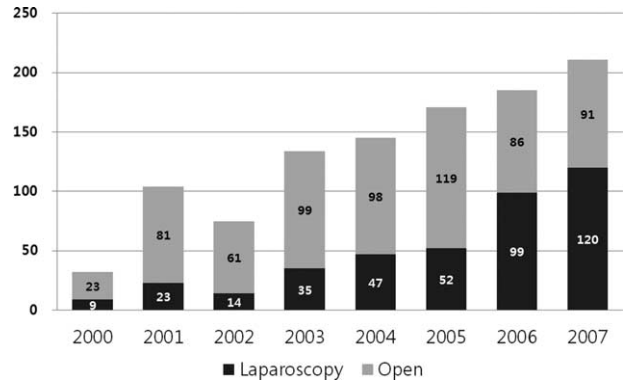


FIGURE 1. Annual number of patients. The number of patients with gastric GIST increased annually. Laparoscopic surgery was performed in more than half of the patients since 2006.

endoscopy, and abdominal pelvic computed tomography (CT) scan performed annually for very low-risk or low-risk patients and every 6 months for intermediate or high-risk patients. Recurrence was diagnosed from clinical, radiologic, or endoscopic findings of disease.

Statistics

For statistical analysis, qualitative data are presented as number (%). Continuous variables are expressed as mean with standard deviation (SD). Actuarial recurrence free survival was calculated using the Kaplan–Meier method. Factors associated with recurrence were tested by univariate log-rank analysis. Variables that were significant in univariate analysis were entered into multivariate analysis. Multivariate analysis was performed with the Cox proportional hazard regression model. Odds ratio (OR) for comparison of the 2 groups was summarized with its 95% confidence interval (CI) and *P*-value using logistic regression. ORs were also adjusted for factors affecting the response variable. All statistical analyses were carried out using PASW ver. 18.0 (IBM Co., Armonk, NY); the level of significance was set at $P < 0.05$.

RESULTS

Annual Patient Number

The number of patients with gastric GIST increased annually. Laparoscopic surgery was performed in more than half of the patients at 2006 (Figure 1).

Clinicopathologic Characteristics of 1057 Gastric GISTs

The mean age of the patients was 58.6 years, and there were approximately the same number of male and female patients. Thirty patients (2.8%) had distant metastasis preoperatively. There were 11 cases of metastasis to the liver, 19 to the peritoneum, 2 to the pancreas, 1 to the spleen, and 1 to the lungs and bone. Almost half of the patients had symptoms such as abdominal pain (36.4%), dyspepsia (30.2%), melena (18.5%), and a palpable mass (4.4%). Other symptoms were fatigue, diarrhea, dizziness, dyspnea, shoulder pain, and chest pain. The most common site was the upper body (41.7%) of the stomach. The most common category of tumor size was >2.1 cm and ≤ 5 cm (51.8%). The median tumor size was 4.0 cm. Only 9

TABLE 1. Clinicopathologic Characteristics of 1057 Gastric GISTs

	n = 1057 (%)
Age (years)	58.6 ± 11.8
Gender	
Male	531 (50.2)
Female	526 (49.8)
BMI (kg/m ²)	24.0 ± 3.1
Preoperative metastasis	
No	1027 (97.2)
Yes	30 (2.8)
Symptom	
Asymptomatic	502 (47.5)
Symptomatic*	555 (52.5)
Abdominal pain	222 (36.4)
Dyspepsia	184 (30.2)
Melena	113 (18.5)
Palpable mass	27 (4.4)
Weight loss	20 (3.3)
Others	44 (7.2)
Tumor location	
Cardia	145 (13.7)
Upper 1/3	441 (41.7)
Middle 1/3	192 (18.2)
Lower 1/3	239 (22.6)
Mixed	18 (1.7)
Undefined	22 (2.1)
Tumor size (cm)	
≤2	131 (12.4)
>2.1 to ≤5	548 (51.8)
>5.1 to ≤10	239 (22.6)
>10.1	139 (13.2)
Median tumor size (cm, range)	4.0 (0.2–33)
Imatinib mesylate treatment	
Preoperative	9 (0.9)
Postoperative	94 (8.9)
Both	5 (0.5)

BMI = body mass index
* Combined number.

TABLE 2. Surgical Outcomes of 1057 Gastric GIST

	n = 1057 (%)
Operative method	
Laparoscopic surgery	399 (37.7)
Open surgery	638 (60.4)
Conversion to open surgery	19 (1.8)
No resection	1 (0.1)
Radicality	
R0	1018 (96.3)
R1	18 (1.7)
R2	20 (1.9)
No resection	1 (0.1)
Type of surgery	
Wedge resection	793 (75.0)
Partial gastrectomy	134 (12.7)
Total gastrectomy	105 (9.9)
Enucleation	19 (1.8)
Others	6 (0.6)
Intraoperative tumor rupture	
Yes	17 (1.6)
No	1040 (98.4)
Combined surgery (other organ)	
No	868 (82.1)
Yes	189 (17.9)
Operation time (minute)	126.4 ± 78.5
Postoperative hospital stay (days)	9.1 ± 7.3
Postoperative complication*	
No	971 (91.9)
Yes	86 (8.1)
Wound infection	22
Ileus	12
Bleeding, intraabdominal	11
Bleeding, intraluminal	6
Narrowing	5
Leakage	5
Others	34
Postoperative mortality	2 (0.2)

* Combined number.

patients (0.9%) were treated by imatinib preoperatively and 94 (8.9%) postoperatively (Table 1).

Surgical Outcomes of 1057 Gastric GISTs

Complete resection (R0 resection) was achieved in 1018 patients (96.3%). Laparoscopic surgery was performed in 399 patients (37.7%), even though more than half the patients underwent open surgery. Various types of surgery were performed and included wedge resection for 793 patients (75.0%), partial gastrectomy for 134 patients (12.7%), total gastrectomy for 105 patients (9.9%), and enucleation for 19 patients (1.8%). Intraoperative tumor rupture occurred in only 17 patients (1.6%). Postoperative complications occurred in 86 (8.1%) patients. Wound infection was found in 22 patients, ileus in 12 patients, intraabdominal bleeding in 11 patients, and intraluminal bleeding in 6 patients. Two patients (0.2%) died within 30 days after surgery (Table 2).

Modified NIH Risk Classification According to Tumor Size

The most common NIH risk was low-risk (38.4%), even though there were 138 (13.7%) patients with tumor >10 cm. In clinical practice, the decision to perform surgery for gastric GIST depends on preoperative tumor size. The percentage of patients who were classified as high-risk gastric GIST stratified by tumor size were 1.8% in ≤2 cm, 12.2% in >2.1 cm and ≤5 cm, 39.0% in >5.1 cm and ≤10 cm, and 100% in >10.1 cm (Table 3).

Five-Year Recurrence-Free Survival Rates by Modified NIH Risk Classification and 7th UICC/AJCC TNM System

According to the NIH classification, the 5-year recurrence-free survival rates were 9% to 99% in very low- or low-risk patients, 96.3% in intermediate-risk, and 74.9% in high-risk patients. Moreover, according to the 7th UICC/AJCC TNM

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TABLE 3. Modified NIH Risk Classification According to Tumor Size (n = 1006)

	Very Low	Low	Intermediate	High
≤2 cm	96	0	16	2
>2.1 cm to ≤5 cm	4	385	70	64
>5.1 cm to ≤10 cm	0	1	140	90
>10.1 cm	0	0	0	138
	100	386	226	294

system, the 5-year recurrence-free survival rates were 95% to 99% in stage I, 94.1% in stage II, 74.1% in stage IIIA, 48.6% in stage IIIB, and 50.0% in stage IV patients (Figure 2).

On survival analysis of high-risk patients according to TNM system, the 5-year recurrence-free survival rates were 91.6% in stage II, 74.1% in stage IIIA, and 48.6% in stage IIIB patients (Figure 3).

Recurrence

Among 1057 patients, 51 patients who could not be classified using the NIH classification, 10 patients lost to follow-up, and 30 preoperative M1 patients were excluded. The median follow-up duration of 967 patients was 95.2 (0.1–167.9) months. The overall recurrence rate was 8.9%. One hundred three episodes of recurrence occurred in 86 patients: 45 in the liver, 28 in the peritoneum, 3 in the bone, 1 in the axilla, and 4 in undefined sites. In addition, there were 23 incidences of local recurrence; 18 occurred in previous operation sites, 3 in other sites of the stomach, and 1 in the distal esophagus. Most recurrences occurred in patients who were intermediate- or high risk (Table 4).

Factors Associated With Recurrence Following Surgical Treatment for Gastric GIST

On univariate analysis, gender, age, preoperative symptom, tumor location, tumor size, tumor rupture during surgery,

mitotic count, operation method, postoperative complication, and radicality were associated with recurrence. In contrast, independent factors associated with recurrence following surgical treatment on multivariate analysis for gastric GIST were gender (odds ratio [OR] 0.48, 0.27 < 95% confidence interval [CI] < 0.85, P = 0.012), tumor size (OR 3.85, 1.77 < 95% CI < 3.66, P < 0.001), mitotic count (OR 13.93, 4.73 < 95% CI < 16.80, P < 0.001), and radicality (OR 5.55, 1.17 < 95% CI < 13.46, P = 0.027) (Table 5).

DISCUSSION

This large-scale multicenter and retrospective study can be useful for evaluating clinical outcomes of gastric GIST, which is a rare disease. Previous studies using a national registry database had some limitations,^{9,12} such as a lack of sufficient information regarding surgery and follow-up visits. This information can affect the surgical outcome of patients with gastric GIST, because the gold standard for localized primary gastric GIST is surgical resection. Moreover, although the risk of recurrence of all GISTs after surgery has been analyzed and published,⁶ the risk of recurrence of gastric GIST should be investigated separately, because gastric GIST has a more favorable prognosis than other GISTs. This study was conducted on patients who had gastric GIST and long-term follow-up using a prospectively designed database in 15 representative institutes in Korea and Japan.

Compared to results in Western countries,^{9,11} patients in this study were younger and their gastric GIST was detected earlier, likely due to improved nationwide surveillance for gastric cancer in Korea and Japan. Therefore, the patients in this study have distinctive characteristics, such as smaller tumor size, fewer symptoms, earlier stage of tumor, more frequent treatment with laparoscopic surgery, higher rate of R0 resection and local resection (wedge resection or enucleation), and lower postoperative mortality rate. These differences can explain the difference in prognosis of gastric GIST between patients from western and eastern countries. In this study, only 9 and 94 patients were treated with imatinib mesylate preoperatively and postoperatively, respectively. At that time, the use of imatinib mesylate was limited due to national insurance in Korea.

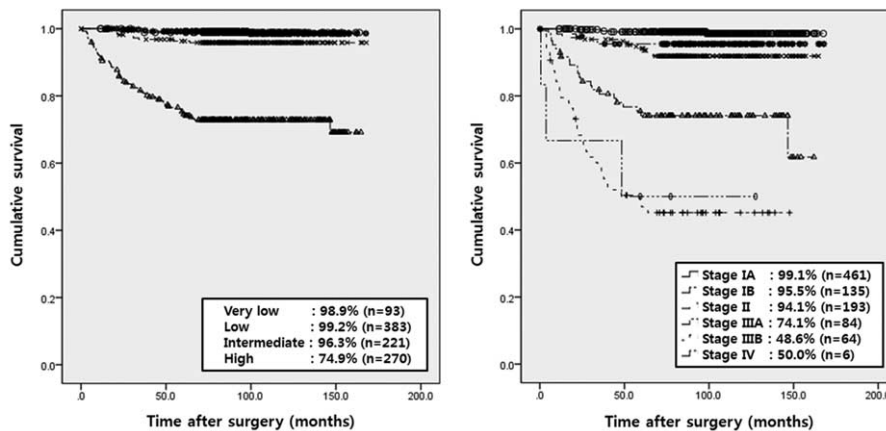


FIGURE 2. Five-year recurrence-free survival rate by modified NIH risk classification and 7th UICC/AJCC TNM system. According to the NIH classification, the 5-year recurrence-free survival rates were 98% to 99% in very low- or low-risk patients, 96.3% in intermediate-risk, and 74.9% in high-risk patients. Moreover, according to the 7th UICC/AJCC TNM system, the 5-year recurrence-free survival rates were 95% to 99% in stage I patients, 94.1% in stage II, 74.1% in stage IIIA, and 48.6% in stage IIIB patients.

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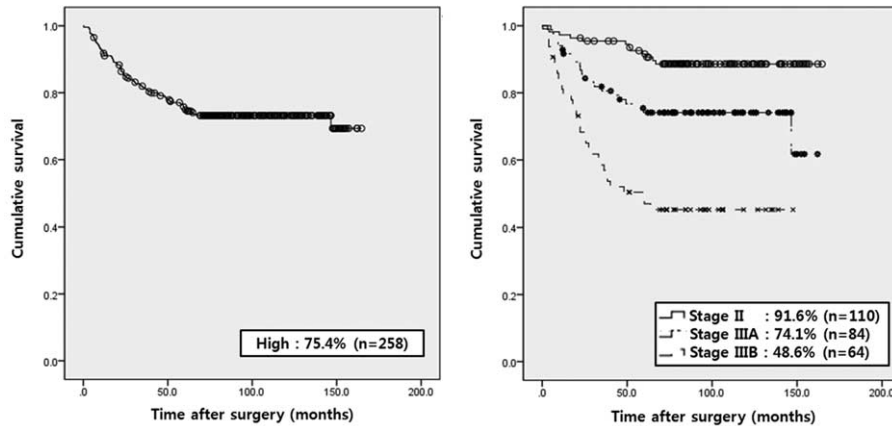


FIGURE 3. Five-year recurrence-free survival rate of high-risk patients according to NIH classification and TNM systems. The 5-year recurrence-free survival rates were 91.6% in stage II, 74.1% in stage IIIA, and 48.6% in stage IIIB patients.

It is well known that gastric GIST usually presents in clinical practice as gastric submucosal tumor (SMT). Almost half of gastric SMT is found to be gastric GIST after surgery.¹³ As demonstrated in Table 3, preoperative tumor size can predict the incidence of the level of risk of gastric GIST after surgery if the tumor is GIST and thus determine the follow-up plan. Roughly one-third of patients with gastric GIST >5.1 cm to ≤10 cm can be high risk.

One hundred three recurrences in 86 patients occurred, and the most common recurrence site was the liver (43.7%). The 5-year recurrence-free survival rate of very low-, low-, and intermediate-risk patients was above 96%, and the 5-year recurrence-free survival rate of stage I and II patients using

the 7th UICC/AJCC TNM system was above 94%. Otherwise, patients who were high risk or stage III had high recurrence rates. High-risk patients can be divided into stage II or IIIA or IIIB according to the TNM staging system. The 5-year recurrence-free survival rate of those stages of high-risk patients was similar to the TNM stages in all risk patients. The 7th UICC/AJCC TNM system is more reflective of the 5-year recurrence-free survival of patients with gastric GIST rather than the modified NIH risk classification. Therefore, adjuvant treatment with imatinib after surgery may be reasonable for over stage IIIA patients rather than all high-risk patients.

Tumor rupture is thought to be associated with a substantially higher risk. Hohenberger et al¹⁴ stated that patients with a preoperative spontaneous or intraoperative rupture of GIST into the peritoneal cavity have a risk of recurrence of nearly 100%. However, whether or not rupture is an independent risk factor for recurrence is controversial,⁶ because there has been no study on intraoperative tumor rupture and long-term prognosis. Tumor rupture during surgery in this study occurred in 17 patients. After surgery, 5 patients had recurrence.

In other studies on all GISTs,^{5,6} independence adverse prognostic factors were larger tumor, high mitotic count, non-gastric location, presence of rupture, and male sex. The mitotic count was a predictor of outcome following surgical resection of 112 gastric GISTs.¹⁵ On multivariate analysis of this study, male, larger tumor, high mitotic count, and R1 or R2 resection were associated with recurrence after curative resection of gastric GIST. Operation method (laparoscopy vs. open) was not a factor associated with recurrence. Further comparison study of laparoscopy versus open surgery for gastric GIST according to tumor size is being prepared using our data.

This study has 2 limitations. First, there is lack of central review of pathology results from multicenter data. Pathologic diagnosis for GIST has been well established at each institution in Korea since 2000. Therefore, we enrolled the patients diagnosed with gastric GIST at each institution since 2000. Second, no molecular genetic study was performed. The method and response of imatinib treatment has been shown to be related to these findings. Recently, many studies of imatinib mesylate given in accordance with IHC and molecular genetic results have been published.¹⁶⁻¹⁸ However, we focused on only long-term surgical outcomes of gastric GIST regardless of molecular genetic results.

TABLE 4. Recurrence in 967 Patients

	n = 967 (%)
Median FU duration (month, range)	95.2 (0.1–167.9)
Recurrences	
No	881 (91.1)
Yes	86 (8.9)
NIH classification	
Very low	1 (1.2)
Low	4 (4.7)
Intermediate	9 (10.5)
High	72 (83.7)
Pattern (n = 86)*	
Liver	45
Peritoneum	28
Bone	3
Axilla	1
Local recurrence	23
Stomach	
Operation site	18
New lesion	3
Distal esophagus	1
Others	4

NIH = National Institutes of Health.
* Combined number.

TABLE 5. Factors Associated With Recurrence Following Surgical Treatment for Gastric GIST (n = 967)

Variable	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	P-Value	OR	95% CI	P-Value
Gender						
Male/female	0.48	0.30–0.76	0.002	0.48	0.27–0.85	0.011
Age (years)						
<60/≥60	1.72	1.08–2.74	0.023	1.32	0.76–2.32	0.327
Symptom						
No/yes	3.34	2.01–5.55	<0.001	1.42	0.77–2.61	0.264
Tumor location						
Cardia/upper/middle/lower/undefined	0.78	0.63–0.97	0.023	0.90	0.70–1.17	0.446
Tumor size						
<2 cm/2.1 cm to 5 cm/>5.1 cm	3.85	2.89–5.13	<0.001	2.54	1.77–3.66	<0.001
Tumor rupture during surgery						
No/yes	6.74	2.15–21.07	0.001	2.23	0.42–11.79	0.346
Mitotic count						
≤5/>5	13.93	7.70–25.20	<0.001	8.91	4.73–16.80	<0.001
Operation method						
Laparoscopy/open	4.57	2.45–8.53	<0.001	1.44	0.68–3.05	0.341
Complication						
No/yes	3.43	1.90–6.21	<0.001	1.63	0.74–3.57	0.227
Radicality						
R0/R1 or R2	5.55	2.30–13.37	<0.001	3.97	1.17–13.46	0.027

CI = confidence interval, OR = odds ratio.

CONCLUSIONS

The treatment outcome and prognosis of gastric GIST in Korea and Japan seem more favorable compared to those in Western countries, likely due to the greater proportion of patients in Korea and Japan who are younger and diagnosed at an early stage as well as the high rate of complete resection. Compared to the modified NIH risk classification, the 7th UICC/AJCC TNM system is more reflective of the 5-year recurrence-free survival of patients with gastric GIST.

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