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ORIGINAL ARTICLE

Clinicopathologic Characteristics and Optimal Surgical Treatment of Duodenal Gastrointestinal Stromal Tumor

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Abstract

Background The clinicopathologic characteristics of duodenal gastrointestinal stromal tumor (GIST) were unclear and the optimal surgical procedure for duodenal GIST remains poorly defined. We aimed to analyze clinicopathological characteristics, survival outcomes based on the surgical procedure, and recommend optimal surgical treatment for duodenal GIST.

Methods From July 2000 to April 2017, 118 patients with localized duodenal GIST underwent curative surgical resection at a single institution. We retrospectively reviewed the clinicopathological characteristics and survival outcomes.

Results The 5-year overall survival (OS) and disease-free survival (DFS) rates were 94.9 and 79.2%, respectively. On multivariate analysis, the mitotic count was a statistically significant prognostic factor for DFS. Limited resection (LR) was performed in 20 patients with GIST in the first or fourth portion of the duodenum. Both LR and pancreaticoduodenectomy (PD) were performed in 98 patients with GIST in second or third portion of the duodenum. The patients in the LR group had less late complications than in the PD group and no postoperative newly developed diabetes mellitus. The minimally invasive LR (MI-LR) group had a shorter duration of surgery and shorter length of postoperative hospital stay.

Conclusion LR is a feasible and effective surgical treatment for patients with small-sized and antimesenteric-sided duodenal GIST in terms of late complications and postoperative diabetic complications. MI-LR has better perioperative outcomes than open LR. Therefore, we should consider MI-LR as an optimal surgical treatment for selected patients with duodenal GIST.

Keywords Duodenum · Gastrointestinal stromal tumor · Limited resection · Pancreaticoduodenectomy · Minimally invasive surgery

Introduction

Gastrointestinal stromal tumors (GISTs) represent the most common tumor of mesenchymal origin arising in the gastrointestinal tract (GI tract).[1,2] They are most commonly found in the stomach (50–60%), small intestine (20–30%), and colorectal region (10%). Duodenal GISTs represent a rare subset of GISTs, with a frequency of 3–5%.[3] The clinical manifestation of duodenal GISTs is nonspecific and varies widely based on size, location, and growth pattern. The most common presenting symptoms are related to gastrointestinal bleeding including melena, hematemesis, hematochezia, or symptomatic anemia.[4,5]

Due to its low incidence, the prognosis and recurrence pattern of duodenal GIST have not been well clarified. Recently, only few reports have proposed the prognostic factors of duodenal GIST,[6–8] and no studies have investigated the recurrence pattern of duodenal GIST alone.

Complete surgical resection with negative margins remains the main curative treatment modality for primary GISTs.[8–11] However, the optimal surgical procedure for duodenal GISTs remains poorly defined because of their low incidence and unclear clinicopathologic characteristics.[12] The choice of surgical procedure depends not only on the tumor size but also on its location in the duodenal wall proximity to the pancreatic head, common bile duct, ampulla, and mesenteric root.[13] Various surgical procedures have been reported, such as

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pancreaticoduodenectomy (PD) and limited resection (LR), which preserve the pancreatic head, including wedge and segmental resection of the duodenum.[9,14–18] Whether lymph node dissection should be performed is still controversial. Multi-institutional analyses reported that they found metastasis in 2% or less of patients after lymphadenectomy was performed.[7] Furthermore, laparoscopic surgery in patients with gastric GIST has been recently included within formal therapeutic strategies.[19] However, minimally invasive surgery (MI) defined as laparoscopic or robotic surgery for duodenal GIST has not been clearly established, and studies on similar cases are limited.[20,21]

We retrospectively reviewed the clinicopathological characteristics of duodenal GIST. We aimed to evaluate prognostic factors and recurrence patterns of duodenal GIST, and also analyze the perioperative and long-term clinical outcomes, including late complications and survival outcomes based on the type of surgical procedure and recommend optimal surgical treatment for duodenal GIST.

Materials and Methods

Patients and Definition of Data

From July 2000 to April 2017, 126 patients underwent LR or PD for duodenal GIST at the Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, University of Ulsan College of Medicine and Asan Medical Center, Seoul, Republic of Korea. We analyzed 118 patients who underwent curative surgical resection for localized duodenal GIST. We excluded eight patients with metastasis at diagnosis. The diagnosis of GIST was based on standard postoperative histopathologic examination and immunohistochemistry and was reviewed retrospectively.

The following characteristics were analyzed for each patient: age at surgery, sex, preoperative symptom, type of surgical procedure, surgical complication, tumor location, tumor size, mitotic count, resection margin status, lymph node status, neoadjuvant and adjuvant therapy with imatinib, modified National Institutes of Health (NIH) risk assessment, etc. The preoperative symptoms were classified as hemorrhage (including symptomatic anemia), abdominal pain, jaundice, and asymptomatic. The patients were grouped according to the type of surgery: LR, defined as pancreatic head-preserving surgery; segmental or wedge resection of the duodenum or trans-duodenal ampullectomy (TDA) versus PD. Moreover, they were also grouped into MI surgery, defined as laparoscopic or robotic surgery, versus open surgery. Mitosis was counted in 50 high power fields (HPFs). Tumor size (in cm) was defined as the greatest dimension of the tumor in the surgical specimen reported by the original pathologists. Tumor site (portion of duodenum) and location in the duodenal wall (mesenteric or antimesenteric) were defined based on preoperative CT and operative findings. The risk categories were classified according to the NIH classification.[1] Surgical complications were classified according to the Clavien–Dindo classification,[22,23] and late complication was defined as that occurring 30 days postoperatively. Disease relapse was defined as local recurrence or distant metastases detected on postoperative follow-up CT scan.

Indication of Neoadjuvant Imatinib

The neoadjuvant imatinib was recommended if a tumor was borderline resectable, locally advanced and unresectable but nonmetastatic, or potentially resectable and if a reduction in tumor size would significantly decrease the morbidity and extent of surgical resection. The optimal duration of neoadjuvant imatinib has not been established. In most cases, patients were treated until there was a maximal response, usually not exceeding 12 months.

Indication of Adjuvant Imatinib

Since 2010, the adjuvant imatinib (400 mg daily) has been primarily recommended to patients with high risk according to NIH GIST Consensus Criteria. The duration of the adjuvant therapy was 12–36 months.

Statistical Analysis

Results were expressed as median (range) and percentage for continuous and categorical variables, respectively. We retrospectively analyzed the associations between patient data and surgical procedures using χ^2 tests. Disease-free survival (DFS) was defined as the time from surgery to either the first recurrence or death. Overall survival (OS) was defined as the time from surgery to death. DFS and OS rates were estimated using the Kaplan–Meier method and compared with the log rank test. Cox proportional hazard regression analysis was used for univariate and multivariate analyses for DFS. All statistical tests were two-sided, and the threshold for statistical significance was $p = 0.05$. Statistical analyses were performed using SPSS software (version 24.0 IBM Corp., Armonk, NY, USA).

Results

Patient's Demographic and Disease Characteristics

All patient's demographic and disease characteristics are listed in Table 1. Of the 118 patients in our study, most patients were male (56.8%), with a median age of 54 years at surgery. The most common symptom at presentation was hemorrhage,

Table 1 Patient's demographics and disease characteristics

All patients ($n = 118$)	Number (%)
Sex	
Male	67 (56.8%)
Female	51 (43.2%)
Median age (IQR)	54 (45–64)
Preoperative symptom	
Hemorrhage (including symptomatic anemia)	44 (37.3%)
Abdominal pain	32 (27.1%)
Jaundice	3 (2.5%)
Asymptomatic	39 (33.1%)
Tumor site in duodenal portion	
D1 (First portion of the duodenum)	10 (8.5%)
D2 (Second portion of the duodenum)	61 (51.7%)
D3 (Third portion of the duodenum)	37 (31.4%)
D4 (Fourth portion of the duodenum)	10 (8.5%)
Tumor location in duodenal wall	
Antimesenteric side	63 (53.4%)
Mesenteric side	55 (46.6%)
Median tumor size (cm, IRQ)	3.9 (3.0-5.4)
Number of mitosis	
< 5/50HPF	89 (75.4%)
≥ 5/50HPF	29 (24.6%)
NIH GIST Consensus Criteria for risk	
Very low	13 (11.0%)
Low	63 (53.4%)
Intermediate	19 (16.1%)
High	23 (19.5%)
Lymph node (LN) status	
LN cannot be assessed (NX)	67 (56.8%)
LN metastasis negative	51 (43.2%)
LN metastasis positive	0
Resection margin (RM) status	
RM negative	114 (96.6%)
RM positive	4 (3.4%)
Imatinib	
Neoadjuvant therapy	12 (10.2%)
Adjuvant therapy	28 (23.7%)

including symptomatic anemia (37.3%), and 39 patients were asymptomatic (33.1%). The most common tumor site was the second or third portion of the duodenum in 98 patients (83.1%). The incidence of tumor located at the antimesenteric side (53.4%) in the duodenal wall was similar to that of tumors located at the mesenteric side (46.6%). The median tumor size was 3.9 cm. The mitotic count of < 5/50 HPF was more common (75.4%). According to the NIH classification, the low-risk group (53.4%) was the most predominant. Lymph node dissection was performed in 51 patients (43.2%), and no lymph node metastasis was found. Most patients had tumor-free resection margin (96.6%).

Surgical Procedures and Complication

All surgical procedures performed were categorized based on tumor location, surgical scope, and surgical method (Fig. 1). LR was performed in 20 patients with GIST in the first or fourth portion of the duodenum, regardless of their tumor size. Both LR and PD were performed in 98 patients with GIST in second or third portion of the duodenum. Detailed surgical procedures are shown in Table 2. Twenty-three patients with postoperative in-hospital complications (19.5%), and 11 (9.3%) had a major complication (≥ grade 3). Late complications occurring 30 days postoperatively were found in nine patients (7.6%). Detailed postoperative complications are shown in Table 3.

OS and DFS in All Patients

At the time of the analysis, the median follow-up was 46 months (range, 3.9–167.9 months), and 111 patients (94.1%) were alive. The 5- and 10-year OS rate were 94.9 and 89.8%, respectively.

Nineteen patients (16.1%) had recurrence, with a median of 26.1 months postoperatively (range, 6.0–105.6 months). Approximately one half of the recurrences occurred within 2 years postoperatively (47.3%). Of 19 patients, 4 (21.1%) showed primary recurrence more than 5 years after resection. The most common recurrence site was liver (63.2%), and the recurrence site was not located in extra-abdominally. DFS rate for all patients were 79.2 and 38.3% at 5 and 10 years.

Of those patients who had relapse, nine patients underwent reoperation, followed by treatment with imatinib and five and four of these nine patients underwent hepatic resection and recurrent mass excision. Of nine patients who underwent re-operation, two patients underwent surgery for the third time because of repeated recurrence in the liver. Of those patients without reoperation, six were administered with imatinib only, two were administered with imatinib with target agents (sunitinib, regorafenib), one was administered with imatinib with radiofrequency ablation of the liver, and one patient did not receive any treatment.

OS and DFS in Patients with Neoadjuvant or Adjuvant Imatinib Therapy

Neoadjuvant imatinib was administered in 12 patients (10.2%). The 5-year OS and DFS in patients with neoadjuvant imatinib were 100 and 45.5%, respectively. Adjuvant imatinib was administered in 28 patients (23.7%). The 5-year OS and DFS in patients with adjuvant therapy were 100 and 42.9%, respectively. Of the 23

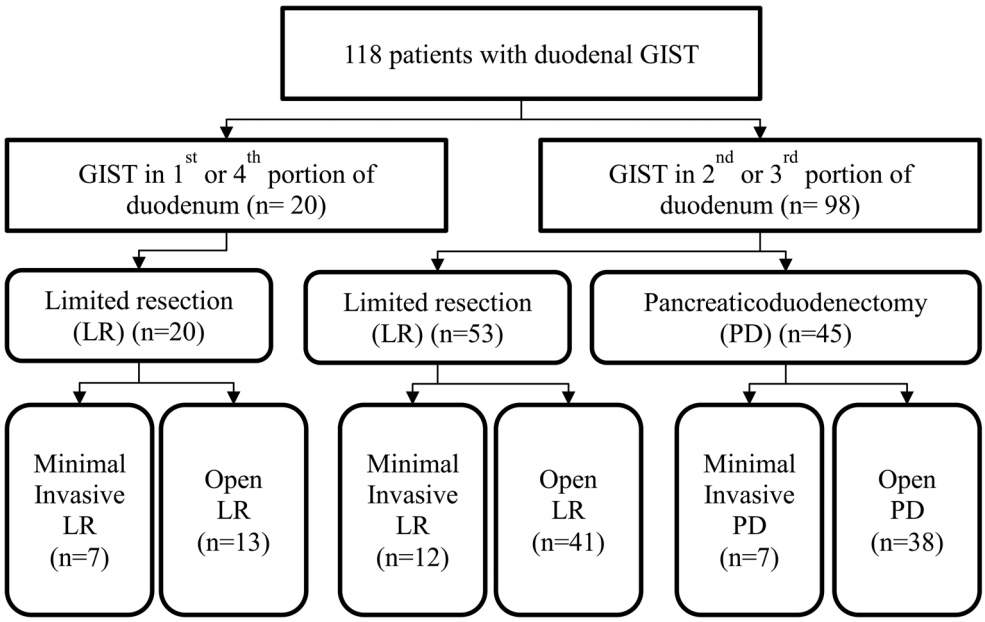

Fig. 1 Flow diagram on surgical procedure by tumor location and surgical method

patients in high-risk group, 13 patients received adjuvant imatinib and 7 patients did not. Three patients in the high-risk group received neoadjuvant imatinib. The five-year OS and DFS were higher in patients with adjuvant imatinib than in patients without adjuvant imatinib; however, the difference was not statistically significant (OS: 100 vs. 83.3%, $p = 0.221$; DFS: 92.3 vs. 42.9%, $p = 0.155$).

Table 2 Surgical procedure for patients with duodenal GIST

Type of surgery	Number (%)
Open surgery group	92 (78.0%)
Minimal invasive (MI) surgery group	26 (22.0%)
Limited resection (LR) group	73 (61.9%)
Open wedge resection of duodenum	29 (24.6%)
Open segmental resection of duodenum	22 (18.6%)
Laparoscopic wedge resection	13 (11.0%)
Laparoscopic segmental resection	3 (2.5%)
Robot wedge resection	2 (1.7%)
Trans-duodenal ampullectomy	2 (1.7%)
Robot segmental resection	1 (0.8%)
Distal gastrectomy	1 (0.8%)
Pancreaticoduodenectomy (PD) group	45 (38.1%)
Open pylorus preserving pancreaticoduodenectomy	27 (22.9%)
Open subtotal stomach preserving pancreaticoduodenectomy	8 (6.8%)
Laparoscopic pylorus preserving pancreaticoduodenectomy	6 (5.1%)
Open pancreaticoduodenectomy	3 (2.5%)
Robot pylorus preserving pancreaticoduodenectomy	1 (0.8%)

Prognostic Analysis

The results of univariate and multivariate analyses are presented in Table 4. Univariate analyses revealed that tumor size, mitosis, and preoperative symptom were the statistically significant prognostic factors for DFS. On multivariate analyses, mitosis was the only predictor for disease recurrence.

Comparison Between LR and PD in Patients with GIST at D2/D3

We compared the LR and PD groups (Table 5). The patients in the LR group had a smaller tumor size (median, 4.0 vs. 5.3 cm, $p = 0.026$) and had less mitotic count ≥ 5/50 HPF (15.1 vs. 37.8%, $p = 0.010$). Based on the NIH criteria, patients in the LR group had less intermediate- and high-risk assessment than those in the PD group (20.8 vs. 53.3%, $p = 0.002$). Patients in the LR group had more tumors located in the antimesenteric side (77.4 vs. 15.6%, $p < 0.001$) and had less tumors involving the ampulla (3.8 vs. 55.6%, $p < 0.001$) than those in the PD group. Resection margin involvement was only detected in the LR group. However, it was not statistically significant (5.7 vs. 0%, $p = 0.105$). The postoperative hospital stays were also not statistically significant between the two groups. In-hospital complications were observed in 13 (24.5%) and 11 (24.4%) patients in the LR and PD groups, respectively ($p = 0.992$). The occurrence of major in-hospital complications (≥ grade 3) was also similar between the two groups (11.3 vs. 15.6%, $p = 0.538$). However, the occurrence of late complications were more common in the PD group (1.9 vs. 15.6%, $p = 0.014$).

Table 3 Classification of postoperative surgical complication

Postoperative surgical complications	Number (%)	
	LR group	PD group
In-hospital complication		
Major complication (grade ≥ 3)	5 (6.8%)	6 (13.3%)
Duodenal stricture with balloon dilatation	3	0
Ampulla edema with ERPD insertion	1	0
Intra-abdominal fluid collection with pig-tail insertion	1	3
CJ stricture with stent insertion	0	1
SMV stenosis with stent insertion	0	1
PJ leakage with PJ revision	0	1
Minor complication (grade < 3)	8 (10.9%)	4 (8.9%)
Passage disturbance with conservative management	4	0
Passage disturbance with TPN	4	0
POPF (grade A) without other complications	0	1
POPF (grade B) without other complications	0	1
Fluid collection with antibiotic therapy	0	1
Chyle leakage with conservative management	0	1
Late complication		
Major complication (grade ≥ 3)	0 (0.0%)	2 (4.5%)
CJ stricture with stent insertion	0	1
GDA pseudoaneurysm with coil embolization (ICU care)	0	1
Minor complication (grade < 3)	2 (2.7%)	5 (11.1%)
Cholangitis with antibiotic therapy	1	1
Bile leakage with antibiotic therapy (after T-tube removal)	1	0
Paralytic ileus with conservative management	0	1
Fluid collection with antibiotic therapy	0	1
Pancreatitis with conservative management	0	1
Delayed gastric emptying	0	1

Furthermore, postoperative newly developed diabetes mellitus (DM) was only checked in the PD group (0 vs. 8.9%, $p = 0.027$).

The 5-year OS and DFS rates were not statistically significant between the LR and PD groups. (OS: 91.9 vs. 96.2%, $p = 0.616$/DFS: 84.0 vs. 72.6%, $p = 0.071$).

Comparison Between MI and Open Surgery in Patients with GIST at D2/D3 Who Underwent LR

The 53 patients in the LR group were further divided into minimal invasive LR (MI-LR) and open LR. We compared these two groups (Table 6). The patients in the MI-LR group had a shorter duration of surgery (155.0 vs. 218.8 min, $p = 0.013$) and shorter length of postoperative hospital stay (12.0 vs. 19.4 days, $p = 0.036$) than those in open-LR group. The 5-year OS and DFS rates were also not statistically significant between the MI-LR and open-LR groups. (OS: 100 vs. 90.8%, $p = 0.490$/DFS: 100 vs. 81.7%, $p = 0.310$).

Discussion

GISTs can arise anywhere the GI tract, but most are commonly found in the stomach.[24,25] Because they are uncommon, duodenal GISTs are not well understood, and only a limited number of studies have reported on its clinicopathologic characteristics, survival, and long-term prognosis.[5,26,27] In our study, we retrospectively evaluated the clinicopathologic characteristics, prognostic factors, and recurrence patterns of 118 patients with duodenal GIST from a single institution. In addition, we analyzed the perioperative and long-term clinical outcomes, including late complications and survival outcomes based on the type of surgical procedure.

The clinical manifestation of duodenal GIST can be variable in size, location, and presence of mucosal ulceration.[7,28] Similar to previous studies, the most common symptom at presentation in patients with duodenal GIST in the present study was hemorrhage and abdominal pain.[5,26,29] The majority of duodenal GIST are reported to occur in the second portion of duodenum,[7,8] which consistent with this study.

Table 4 Association of clinicopathological factors with disease-free survival

variable	Univariate		Multivariate	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Tumor size (≥ 5 vs. < 5 cm)	2.535 (1.062–6.050)	0.036	1.340 (0.497–3.616)	0.563
No. of mitosis/50 HPF (≥ 5 vs. < 5)	4.146 (1.730–9.932)	0.001	3.133 (1.090–8.999)	0.034
Type of surgery (LR vs. PD)	2.494 (0.992–6.267)	0.052	1.256 (0.384–4.106)	0.706
Imatinib treatment (Yes vs. no)	2.131 (0.900–5.048)	0.086	0.978 (0.354–2.704)	0.996
Tumor site (D2, 3 vs. D1, 4)	0.953 (0.316–2.877)	0.932	1.494 (0.345–6.472)	0.592
Preoperative symptom (Yes vs. no)	8.609 (1.153–64.263)	0.036	6.791 (0.885–52.144)	0.065
Comorbidity (Yes vs. no)	0.476 (0.159–1.422)	0.184	0.675 (0.213–2.136)	0.503

In the present study, the 5-year OS and DFS rates were 94.9 and 81.0%, respectively, which were similar to the results of recent reports.[8,26,30,31] The OS rate was relatively high compared with the recurrence rate, which explains why duodenal GISTs have a non-aggressive behavior. Unlike carcinoma, duodenal GISTs are rarely associated with submucosal spread and lymphatic metastasis.[2,3,9,11] Another reason is that we have various treatment options despite recurrence of the disease. In our cases, most first recurrences were presented by hepatic metastasis (63.2%), intraperitoneal mass (15.8%), and surgical bed mass (15.8%), which means local recurrence. Reoperation was possible in few cases of hepatic recurrence, peritoneal masses, or isolated local recurrence. The nine patients who underwent reoperation were all alive, and five of them had no recurrence, with a mean of 34.6 months postoperatively. Even if reoperation was impossible, we could attempt to treat the patient with imatinib or other target agents. One patient who manifested with multiple peritoneal seeding was sequentially administered imatinib, sutene, and regorafenib, and he survived for 38 months after the recurrence. Relatively good survival outcomes

Table 5 Comparisons between limited resection group vs pancreaticoduodenectomy group in patients with GIST at 2nd or 3rd portion of duodenum (D2, D3)

D2 or D3 (*n* = 98)	LR (*n* = 53)	PD (*n* = 45)	*P* value
Male:female	23:30	31:14	0.011
Median age	54 (47-61.5)	54 (44-64)	0.999
Mesenteric side	12 (22.6%)	38 (84.4%)	< 0.001
Antimesenteric side	41 (77.4%)	7 (15.6%)	
Median tumor size (cm, IQR)	3.5 (2.6-4.5)	4.7 (3.2-6.6)	0.030
Ampulla of Vater involvement			< 0.001
Yes	2 (3.8%)	25 (55.6%)	
No	51 (96.2%)	20 (44.4%)	
Mitotic count ≥ 5/50 HPF	8 (15.1%)	17 (37.8%)	0.010
NIH GIST Consensus Criteria for risk			0.001
Intermediate/high	11 (20.8%)	24 (53.3%)	
Resection margin positive	3 (5.7%)	0 (0.0%)	0.105
Operation time (min)	204.3 ± 83.3	310.1 ± 96.2	< 0.001
Postoperative hospital stay (day)	17.7 ± 14.4	16.4 ± 10.6	0.600
In-hospital overall complication	12 (22.6%)	10 (22.2%)	0.960
In-hospital major complication (≥ grade 3)	5 (9.4%)	6 (13.3%)	0.542
Late complication	1 (1.9%)	7 (15.6%)	0.014
Postoperative diabetes mellitus	0 (0.0%)	4 (8.9%)	0.027

Table 6 Comparisons between minimal invasive group vs open group in patients treated limited resection with GIST at second or third portion of duodenum

LR ($n = 53$)	MI-LR ($n = 12$)	Open LR ($n = 41$)	P value
Male:female	5:7	18:23	0.891
Median age	53 (43-67)	54 (47-60)	0.717
Mesenteric side	1 (8.3%)	11 (26.8%)	0.178
Antimesenteric side	11 (91.7%)	30 (73.2%)	
Median tumor size (cm)	3.5 (2.4-4.2)	3.5 (2.6-4.7)	0.474
Ampulla of Vater involvement			0.435
Yes	0 (0.0%)	2 (4.9%)	
No	12 (100.0%)	39 (95.1%)	
Mitotic count ≥ 5/50 HPF	2 (16.7%)	6 (14.6%)	0.863
NIH GIST Consensus Criteria for risk			0.691
Intermediate/high	2 (16.7%)	9 (22.0%)	
Resection margin positive	0 (0.0%)	3 (7.3%)	0.335
Operation time (min)	155.0 ± 68.1	218.8 ± 82.5	0.013
Postoperative hospital stay (day)	12.0 ± 8.3	19.4 ± 15.5	0.036
In-hospital overall complication	2 (16.7%)	10 (24.4%)	0.574
In-hospital major complication (≥ grade 3)	1 (8.3%)	4 (9.8%)	0.882
Late complication	0 (0.0%)	1 (2.4%)	0.585
No. of pain killer injection	3.9 ± 2.3	5.5 ± 4.6	0.109

can be expected because of these multidisciplinary therapies. Local recurrence was not associated with microscopic resection margin-positive patients, and no statistical difference was found in the local recurrence rate based on the type of surgical procedure (2.8 vs. 2.3%, $p = 0.862$).

As seen in our study and other studies,[7,8,30] the recurrence rate of duodenal GIST was relatively high. Therefore, appropriate follow-up strategies are required. Some studies showed that the proportion of GIST recurrence more than 5 years after complete resection was about 10–30%.[32,33] Similarly, the proportion of GIST recurrence more than 5 years postoperatively was 21.1% in the present study. These findings suggest that the duration of follow-up after complete surgical resection require more than 5 years in patients with duodenal GIST.

The outcomes of patients with GIST are usually estimated with some risk classification systems. Of these, the Armed Forces Institute of Pathology risk stratification, and the modified NIH scheme may be the most frequently used methods.[34,35] Joensuu et al.[33,36] reported that low-risk patients have generally favorable outcomes and might not be candidates for adjuvant therapy and recommend no follow-up or an annual follow-up for approximately 5 years. However, in the present study, more than 10% of recurrence was observed in the low-risk group, and one patient showed primary recurrence more than 5 years after resection. Therefore, further research regarding the risk assessment for duodenal GIST and role of adjuvant therapy in the low-risk group may be needed.

The following recognized prognostic factors were analyzed in present study: tumor size (≥ 5 cm, < 5 cm), mitoses (≥ 5/50HPF, < 5/50HPF), type of surgical procedure (LR vs. PD), imatinib administration (yes/no), tumor location (second and third portion of the duodenum vs. first and fourth portion of the duodenum), preoperative symptom (yes/no), and comorbidity (yes/no). Among them, mitosis is clinically the most significant factor associated with DFS in univariate analysis and the only factor in multivariate analysis. In addition, the type of surgical procedure and tumor location were not associated with DFS.

Complete surgical resection with clear surgical margins remains the main curative treatment for duodenal GIST.[8–11] However, the extent to which lymphadenectomy should be performed is unclear for duodenal GIST. Of 118 patients, 51 (43.2%) patients underwent lymph node dissection, and lymph node metastasis was not seen. If we expand to eight exclusion cases, only one case, a 7-cm sized GIST in the second portion of the duodenum invading the portal vein, with liver metastasis, was positive for metastatic lymph node. The very low incidence of lymph node metastases in our large sample in a single institution study and that shown by other studies[5,7,29] confirms that radical lymphadenectomy is not routinely warranted.

The choice of surgical procedure for duodenal GIST generally is customized mainly to the size, location, and extent of the disease. LR is mostly preferred over radical surgical procedures, such as PD, because usually PD is known to have a higher risk of complications compared with LR.[8] However, PD may be sometimes indicated for complete tumor resection

if the tumor is located in the second or third portion of the duodenum or has invaded the ampulla or pancreas.[37] In our study, duodenal GIST in first or fourth portion in 20 patients could be completely resected by LR, regardless of the tumor size. In this study, LR or PD was performed in 98 patients with GISTs in the second or third portion of the duodenum. We had no surgery-related mortality, and only one patient underwent reoperation (0.8%) due to pancreaticojejunostomy site disruption. Most complications could be managed conservatively or with radiological interventions. In the LR group, passage disturbance was considered as a complication, and three patients were treated by balloon dilatation. The most common in-hospital major complication in the PD group was intra-abdominal fluid collection, which was treated by pig-tail insertion. The overall and major in-hospital complication was not statistically significant between the two groups, respectively (22.6 vs. 22.2%, $p = 0.960$/9.4 vs. 13.3%, $p = 0.543$). The survival outcomes were also not statistically significant between the two groups. With regard to the occurrence of the late and postoperative diabetic complications, the patients in the LR group had a better result than those in the PD group. Only one patient in LR group had late complication but seven patients in the PD group had late complication, including two patients with major complication (grade III, gastroduodenal artery pseudoaneurysm, choledochojejunostomy site stricture). As expected, postoperative DM occurred in four patients in the PD group only. As previously mentioned in the results, the patients in the LR group had a smaller median tumor size, more commonly antimesenteric sided, and less commonly involving the ampulla than those in the PD group. Therefore, LR could be first considered in the cases of small-sized and antimesenteric-sided duodenal GIST in the second or third portion.

A few studies showed using laparoscopic technique with limited resection of duodenal GIST.[21,38,39] In this study, 12 of 53 patients with duodenal GIST in second or third portion treated LR, underwent MI-LR. The duration of the surgery and length of postoperative hospital stay in patients who underwent LR were significantly shorter in those who underwent MI-LR compared with open LR. Patients in the MI-LR group had lesser number of analgesic injections (3.9 vs. 5.5, $p = 0.109$) than those in the open-LR group, but this was not statistically significant. With regard to cosmetic aspect, patients' satisfaction was relatively high in the MI-LR group. The advantages of conventional minimal invasive surgery (MIS), such as early recovery, less pain, and cosmetic effects, were applicable to MIS for patients with duodenal GIST. Furthermore, the survival outcomes were not statistically significant between the MI-LR and open-LR groups. Therefore, MI-LR can be possibly performed in selected patients with GIST in second or third portion of the duodenum.

The present study has several limitations. Imatinib plays a key role in management of GISTs both as neoadjuvant and adjuvant therapy, and in patients with recurrent and metastatic disease.[12] Dematteo et al.[40] reported that adjuvant imatinib therapy seems to improve the recurrence-free survival compared with placebo after the resection of primary GIST. In the current study, the 5-year OS and DFS rates were higher in high-risk patients who receive adjuvant imatinib than those in patients who did not receive adjuvant imatinib, but the difference is not statistically significant (OS: 100 vs. 83.3%, $p = 0.221$; DFS: 92.3 vs. 42.9%, $p = 0.155$). In Korea, the use of imatinib is influenced by the national insurance system. Before 2010, adjuvant imatinib was not covered by insurance for all patients with duodenal GIST. Since 2010, patients classified as high risk by the NIH GIST Consensus Criteria are covered by insurance. Adjuvant imatinib was covered by insurance for 1 year from 2010 to 2013 and for 3 years thereafter. Because of the change in the insurance system, there are different indications and length of adjuvant imatinib according to the timeframe of surgery. Because the optimal duration and indication of adjuvant imatinib has not been established, it is difficult to determine the efficacy of adjuvant imatinib.

Another limitation of our study is that molecular characteristics, such as gene mutation, are not identified in some patients. Ki-67, p53, and p16 expressions were reported to be correlated with the prognosis of GITSs.[41–44] Yang WL et al.[45] reported that duodenal GISTs had a better prognosis compared with GISTs of other sites, and this may be explained by the lower prevalence of p16 loss and lower Ki-67, which are both indicated as a negative prognostic factor. However, we were unable to analyze these tumor suppression proteins as a prognostic factor because p16 was not measured in our institution and another factor, such as Ki-67, and p53, was checked since 2008. Despite these limitations, the results of the current study are significant because large-scale data are used to define the clinicopathologic characteristics, recurrence pattern, prognostic factors, and surgical indication of duodenal GIST. In addition, perioperative and oncologic outcomes were compared based on the type of surgical procedure. To our knowledge, this is the first study to compare MI-LR and open LR in patients with duodenal GIST.

Conclusion

Patients with duodenal GIST who underwent complete surgical resection have favorable survival outcomes. The predictor of disease recurrence on multivariate analysis was only the mitotic count. LR is a feasible and effective surgical treatment for patients with small-sized and antimesenteric-sided duodenal GIST in terms of late complications and postoperative diabetic complications, and MI-LR has better perioperative outcomes (shorter duration of surgery and length of postoperative hospital stay) than open LR. Therefore, we should

consider MI-LR as an optimal surgical treatment for selected patients with duodenal GIST.

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