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Management and Survival Analysis of Patients with Duodenal Gastrointestinal Stromal Tumors

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Abstract

Among human gastrointestinal tumors, duodenal Gastrointestinal Stromal Tumors (GISTs) occur infrequently with a lack of lymphatic and submucosal dissemination and a location adjacent to the bile duct and pancreas, leaving the optimal surgical approach underexplored. Options aiming at a R0 resection include Limited Resection (LR) and Pancreaticoduodenectomy (PD). Fifteen patients with duodenal GIST were retrospectively reviewed who underwent surgical resection in our department from January 2008 to December 2012 and were separated into two groups (pancreaticoduodenectomy, PD, n=5 versus limited resection, LR, n=10). A total of 15 patients (seven males/eight females) with a median age of 57 years (range: 33 years to 76 years) were treated. Ten of the patients underwent limited resection: four went for wedge resections with primary closures and six went for segmental resections with end-to-end anastomosis. Patients undergoing PD were more likely to present with a larger tumor (median size: PD, 7.8 cm *vs.* LR, 5.1 cm; p=0.021) and longer operation time (median time: PD, 274 mins *vs.* LR, 196 mins; p=0.000). Duodenal GISTs treated by PD had more Mitotic number (median No.: PD, 9.2 *vs.* LR 4.3; p=0.006) and higher risk compared to LR group. In survival analysis of these patients, OS and DFS rates for the 10 duodenal GIST patients undergoing limited resection were 100% and 93.7% at 1 year and 75% and 67.8 % at 3 years respectively. Additionally, compared with patients undergoing LR, those treated with PD also tended to have a worse OS (p=0.04). And a worse disease-free survival and overall survival was also found associated with tumor size >5 cm and NIH high-risk classification, both with P<0.05. As a result, we recommended LR be performed whenever technically feasible.

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Introduction

Gastrointestinal Stromal Tumors (GISTs) are the most common mesenchymal tumors in the gastrointestinal tract, the main mechanism involved in the pathogenesis process is the mutation in one of two receptor tyrosine kinase genes (KIT and PDGF) [1-4]. While GISTs can arise anywhere along the gastrointestinal tract and most commonly originate from the stomach (60% to 70%), followed by small bowel (20% to 25%), of which, 3% to 5% are from the duodenum [5-7].

GISTs can arise in any part of the duodenum but most commonly arise from the second portion, which accounts for 30% of primary duodenal neoplasms [8]. There are so few studies centering on medical and surgical management of duodenal GISTs, and reports are limited by small sample size.

Most of the patients with duodenum GISTs present with abdominal pain caused by obstruction, anemia, or gastrointestinal bleeding from a central ulceration [9]. Nevertheless, obstructive jaundice is rarely found even the tumor is located at the periampullary. Additionally, the special anatomic features of GISTs in the duodenum pose particular challenges for diagnosis and management. Tumor size, mitotic activity and anatomic site are currently used to predict malignant courses according to the modified Miettinen classification [10]. Furthermore, the results of mutation analysis of the KIT and PDGFRA gene and Comparative Genomic Hybridization (CGH) are employed as additional prognostic factors with impact on diagnosis and therapy [11,12].

A complete surgical resection remains the only curative treatment for localized GISTs despite of progression in systemic therapy in question [2,5,7,13,14]. But, unlike carcinomas, GISTs rarely develop lymph node infiltration although they can also develop liver and peritoneal metastases [15]. An extensive lymphadenectomy is unnecessary if no evidence showing lymph node metastases. Generally, local wedge resection, segmental duodenectomy and Pancreaticoduodenectomy (PD) are the most commonly used surgical procedures for duodenal GISTs [2,16-18]. The optimal surgical technique for duodenum GISTs, however, remains to be determined due to the anatomic and biological characteristics. The purpose of this study was to compare the efficacy of different surgical

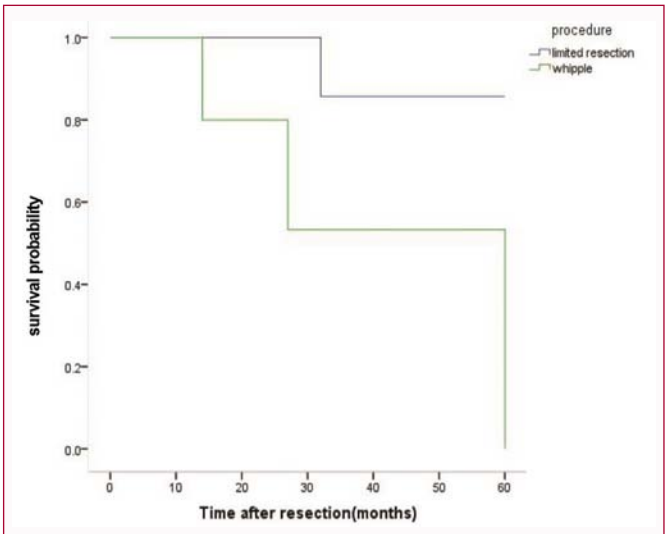

Figure 1: Disease-free survival rate of patients who went through limited resection was 93.3% at the first year and 67.8% at the third year.

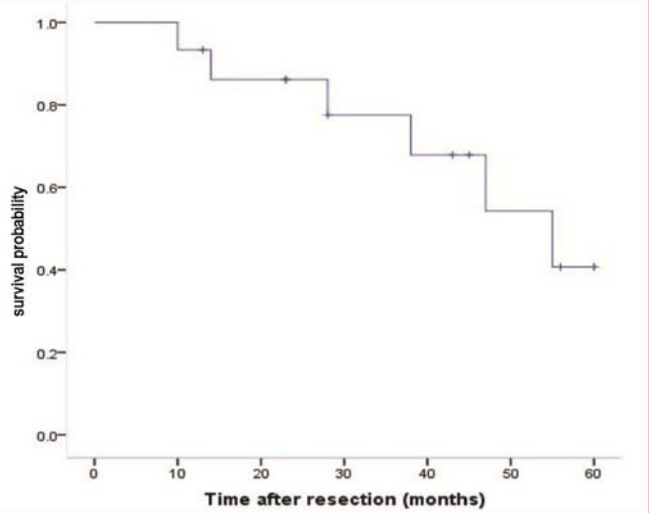

Figure 2: Overall survival of 15 patients after resection of duodenal GIST: stratified by surgical procedure, PD (green line): 26.2 months *vs*. LR (purple line): 40.7 months (P=0.04).

procedures in primary non-metastatic duodenal GISTs with regard to recurrence and survival at our institution.

Material and Methods

Fifteen patients with histology-assured diagnosis of duodenal GIST undergoing surgical resection from January 2008 to December 2012 in our department were retrospectively reviewed and were divided into two groups (pancreaticoduodenectomy, PD, n=5 versus limited resection, LR, n=10). Pathological diagnosis of GIST was achieved postoperatively by the biopsy and was confirmed by immunohistochemical staining for CD117. Data concerning age, gender, presentation, location of tumor, tumor size, surgical procedure and disease status were obtained from the patients information, including operation notes, pathology reports, and follow-up data. Tumor size and mitotic index were used for risk classification according to the NIH score [2,16,17]. Surgical procedures other than Pancreaticoduodenectomy (PD) were defined as Limited Resection (LR) which includes local, wedge and segmental resection of the duodenum [4,15,19]. The duodenal defect was primarily closed using absorbable suture after wedge resection. End-to-end anastomosis was performed after segmental duodenectomy. Whether a patient should be subject to a LR or PD procedure was determined by size and location of tumor. Nasogastric tube was put into the proximal end of the jejunum for better drainage of duodenal content during wedge or segmental resection. Surgical complications were classified as follows: abdominal bleeding, abdominal infection, pancreatic fistula, biliary leak and delayed gastric empting and so on. Octreotide was routinely used after surgery and was withdrawn when amylase of abdominal drainage was normal.

Follow-up was carried out through routine visits for clinical assessment at outpatient clinic every 6 months during the first 2 years after surgery and 1 year thereafter. Yearly chest and abdominal Computed Tomography (CT) upper gastrointestinal endoscopy were performed in all patients. Disease relapse was defined as local recurrence or distant metastases.

Statistical Analysis

The study endpoints were Overall Survival (OS) and Disease Free Survival (DFS). OS was calculated from the date of operation to last follow-up or death. DFS was determined as the time from operation to either biopsy-proven or radiologically-evidenced disease recurrence, or to death. All of the data was analyzed by SPSS software, version 19 (StatSoft, Hamburg, Germany). Comparisons of clinical characteristics between surgical groups were assessed using the t-test (continuous variables) and chi-square test (dichotomous variables).

Table 1: Comparison between LR and PD for duodenal GIST.

Variables	LR(n=10)	PD (n=5)	P value
Female	4(40%)	3(60%)	0.427
Median age(years)	59.5(33-76)	55.6(43-70)	0.59
Tumor size(cm)	5.1(3-8)	7.8(6-10)	0.021
Mitotic No (mitosis/50 HPF)			
<5 mitosis/50 HPF	6(60%)	2(40%)	
6-10 mitosis/50 HPF	3(30%)	2(40%)	0.006
>10 mitosis/50 HPF	1(10%)	1(20%)	
Tumor site			
D1	1(10%)		
D2	5(50%)	3(60%)	
D3	3(30%)	2(40%)	
D4	1(10%)		
NIH risk			
Low	5(50%)		
Intermediate	3(30%)	1(20%)	0.047
High	2(20%)	4(80%)	
Operation time(min)	196	274	0
CD177(+)	10(100%)	5(100%)	1
CD34(+)	3(30%)	2(40%)	0.4
S100(+)	1(10%)	1(20%)	0.44
Complications	1(10%)	1(20%)	0.571
Recurrence rate	1(10%)	4(80%)	0.017

Note: Values were presented with an actual count and proportion. *P* value of the comparison of patients receiving a PD procedure and a limited resection. HPF, high power field.

Table 2: Characteristics and clinicopathologic factors and their effects on disease-free survival and overall survival by Kaplan-Mierer analysis.

Variables	No.	DFS			OS		
		Mean (95% CI)	Overall	p	Mean (95% CI)	Overall	p
Age >50	11	29.9(20.1-39.7)	33.7(24.9-42.5)	0.16	32.8(24.2-41.4)	35.9(28.0-43.7)	0.22
<or = 50	4	44.2(27.5-61.0)			44.3(27.5-61.0)		
Gender							
Male	8	37.9(26.2-49.6)		0.34	45.0(28.0-49.7)		0.44
Female	7	29.0(15.7-42.3)			32.4(20.7-44.1)		
Tumor size							
>5 cm	9	21.7(15.9-27.5)		0	25.2(19.9-30.5)		0
<or = 5 cm	6	51.8(45.6-58.0)			51.8(45.6-58.0)		
Mitosis							
>5/50HPF	7	30.1(17.2-43.1)		0.47	34.7(24.5-44.9)		0.79
<or = 5/50 HPF	8	36.9(24.6-49.2)			36.9(24.6-49.1)		
NIH risk							
High	6	21.8(13.7-29.9)			27.2(20.6-33.7)		
Inter	4	34.8(15.0-54.5)		0.03	34.8(15.0-54.5)		0.09
Low	5	47.2(35.5-58.9)			47.2(35.5-59.0)		
Procedure							
PD	5	20.6(11.0-30.1)		0.03	26.2(18.5-33.9)		0.04
LR	10	40.3(30.0-50.5)			40.7(30.7-50.7)		

Abbreviations: DFS: Disease Free Survival; OS: Overall Survival; HR, CI: Confidence Interval

OS and DFS curves were estimated by the Kaplan-Meier method compared by log-rank test. The estimates of the influence of different risk factors on OS and DFS were obtained by a univariate Cox's proportional hazards regression model. All statistical tests were two-sided, and P<0.05 was considered statistically significant.

Results

15 patients with primary nonmetastatic duodenal GIST who underwent surgical resection from January 2008 to December 2012 in our department were enrolled in this retrospective study. The clinicopathological characteristics of 15 patients with duodenal GISTs were analyzed (Table 1). There were 7 (47%) men and 8 (53%) women with a median age of 57 years (range: 33 years to 76 years). Of the 15 patients, 6 (40%) patients were detected incidentally by routine health checkup. The most common clinical presentation was epigastric pain (n=4, 26.7%), followed by swell (n=3, 20%), anemia (n=1, 7%) and acute upper gastrointestinal bleeding (n=1, 7%). However, no patient had jaundice and ileus history. Two patients without clinical presentation were mistaken as pancreatic head tumor before surgery. The lesion was located in the second (n=8, 63%), third (n=5, 33%), first (n=1, 7%) and forth (n=1, 7%) portion of duodenum. The tumor size ranged from 3 cm to 12 cm (mean 5.9 cm).

These patients were divided into 2 groups (PD *vs.* LR) by different surgical procedure to analyze the difference in clinicopathological characteristics and survival rate (Table 1). LR was performed for 10 patients and PD for 5 patients. One patient underwent emergent PD procedure owing to acute upper gastrointestinal bleeding and his recovery was uneventful.

No patients received neoadjuvant therapy with imatinib mesylate before surgical procedures. The surgical margins for all studied patients were clear. There were no significant differences between the two groups in patient age, gender, and clinical presentation, length of hospitalization and occurrence of complications. However, patients undergoing PD were more likely to present with a larger tumor (median size: PD, 7.8 cm *vs.* LR, 5.1 cm; p=0.021) and longer operation time (median time: PD, 274 mins *vs.* LR, 196 mins; p=0.000). Comparison of pathological data between the 2 groups revealed no significant differences in immunohistochemical staining for CD117, CD34 and S-100. Anyway, duodenal GISTs treated by PD had more Mitotic number (median No.: PD, 9.2 *vs.* LR 4.3; p=0.006) and higher risk compared to LR group. A Fisher exact test indicated that the mitoses more than 5/50 HPF and the NIH high-risk classification were associated with recurrence (P=0.026 and 0.015 respectively).

Survival data could be obtained for all patients. The median follow-up was 43 (range 14-60) months. During the follow-up period, 5 patients developed recurrence: 1 after LR (27 months) and 4 (10 months, 14 months, 28 and 37 months) after PD. The pattern of recurrence was liver metastasis in 5 patients. In survival analysis of these patients, the 1-year and 3-year OS of the entire cohort were 100% and 75%, respectively, and the 1-year and 3-year DFS of the entire cohort were 93.3% and 67.8%, respectively. Two patients had tumor rupture upon surgery; they both had recurrence after 10 months and 28 months respectively. Several factors were associated with a worse OS, such as tumor size >5 cm (p=0.037) and high risk (p=0.006). Additionally, compared with patients undergoing LR, those treated with PD also tended to have a worse OS (p=0.045). Furthermore, univariate Kaplan-Meiere analysis indicated that a worse disease-free survival and overall survival was found associated with surgical option PD, tumor size >5 cm and National Institute of Health high-risk classification, all with P<0.05, which were characterized in detail in Table 2. And the estimates of the hazardous effects of such factors as tumor size, NIH risk, and procedure on the DFS and OS were obtained through an unvaraite Cox's proportional hazards regression

Table 3: Univariate Cox model analysis of DFS and OS.

Variables	DFS		OS	
	HR(95% CI)	P	HR(95% CI)	P
Tumor size (>5 cm)	117.4 (0.48-28,863)	0.09	129.1(1.02-15.17)	0.087
NIH risk (high *vs.* low)	7.57 (1.31-19.65)	0.016	3.94 (1.02-15.17)	0.029
Procedure (PD *vs.* LR)	5.07 (1.31-19.65)	0.019	3.94 (1.02-15.17)	0.046

model which was characterized in Table 3.

Discussion

GISTs, a kind of low-grade malignant tumors, are the most common mesenchymal tumors originating from the gastrointestinal tract and account for only 1% to 3% of all gastrointestinal tumors [3,5,14]. Duodenal GISTs are rare tumor entities and account for about 4% of GISTs, but still represent approximately 30% of primary duodenal tumors.

The clinical manifestations of duodenal GISTs are variable depending on tumor's size, the growth pattern and the existence of mucosal ulceration. Some patients with duodenal GISTs have no clinical symptoms and are therefore usually detected incidentally by routine health checkup. Thus, it is difficult to get an early diagnosis owing to the lack of special clinical presentation. In our study, 6 patients without clinical symptoms are detected by health checkup. For those patients with clinical symptoms, epigastric pain is the most common clinical presentation, followed by swell, anemia and acute upper gastrointestinal bleeding. There is no patient with ileus and jaundice because most GISTs are soft and extraluminal growth. Sometimes extraluminal growth-type duodenal stromal tumors are difficult to distinguish from other organ tumors, such as pancreatic tumor.

Surgical resection is the optimal treatment for those patients with primary GISTs without distant metastasis. However, duodenal GISTs represent a unique dilemma with varied surgical-procedure options owing to its peculiar distribution of anatomic location and specific biological features. To date, the optimal surgical procedure for duodenal GISTs has not been well defined. First, GIST spreads specifically hematogenously and is rarely, if ever, associated with lymphatic invasion, as in other sarcomas. Secondly, GISTs are well-encapsulated tumors that rarely have a tendency to locally invade. Thus, radical lymphadenectomy or extended resection of adjacent organs may not confer a survival advantage to patients with non-metastatic duodenal GIST. As only 30% of duodenal GISTs show a malignant appearance [3,4,16], patients might in part be over-treated by pancreaticoduodenectomy, especially as this procedure leads to a significant morbidity and mortality.

In our study, limited resection with clear margins was carried out as a treatment for 10 patients with duodenal GIST. The mitotic count in 53% (13% in PD, 40% in LR) of the studied patients is less than or equal to 5 mitoses/50 HPF which is not finely consistent with the findings reported by others. Miettenen, et al. reported a 72% of duodenal GISTs whose mitotic count is less than or equal to five mitoses/50 HPF [3]. Similarly, Winfield and colleagues reported that 75% of duodenal GISTs had a mitotic count less than five mitoses/50 HPF [7]. It is also noteworthy that the median tumor size in our study is relative larger than most of the current reports, which may suggest that duodenal GISTs formerly considered unsuitable for limited resection could also benefit in an unexpected and safe way from a wedge or segmental resection of the duodenum.

Survival analysis results were later obtained for all the 15 patients in our study. OS and DFS rates for the 10 duodenal GIST patients undergoing limited resection were 100% and 93.7% at 1 year and 75% and 67.8% at 3 years respectively (Figure 1). These results are much consistent with the sporadically few studies previously reported in the literatures in which the sample sizes varied from 9 to 114 [20,17-26].

As expected, mitotic count, in a great measure, determined the outcome of patients in the studied two groups. Patients in LR group had a smaller median tumor size, obtained far better survival outcome and were testified to have larger percent of mitotic count <5/HPF than those in PD group (Table 1). And the NIH high-risk classification and more mitoses (>5/50 HPF) were potentially responsible for tumor recurrence (P=0.015 and 0.026 respectively).

The type of procedure correlated less with OS (Figure 2) than risks (NIH risk classification), owing to the distribution of the two major risk factors (mitotic count and size) among patients in the two groups (Table 1). Moreover, in univariate analysis, only NIH high-risk classification and the PD procedure were statically evidenced to have an impact on the OS and DFS conditions of the patients enrolled (Table 2).

In addition to their biological features, duodenal GISTs are characterized by an extra complicacy relating to the anatomic location. Therefore the choice of procedure is usually depended on tumor size, location, and involvement of circumambient tissues and organs. PD is traditionally thought to bear a higher risk of complications than LR, which was not confirmed in our series (10% *vs.* 20% rate of complications in LR and PD respectively, p>0.05) but is explainable in that the sample size in our study is limited. A statistical analysis for a limited size of patients included in our retrospective study may lead to conclusions with confined credibility. But we considered it still worthwhile in offering such a comparison of a limited resection and a traditional PD procedure and further in explaining the efficacy and survival advantage of a limited resection for patients with duodenal GISTs. Of note, these two procedures eventually both proved to be safe for the management of duodenal GIST, because we did not identify any surgically related death. Most of the complications could be managed conservatively or with radiological interventions; As was mentioned above, patients who underwent PD had larger tumors (median size 7.8 cm in the PD *vs.* 5.1 cm in the LR) with higher mitotic count (60% had a mitotic count 6-10 or >10/50 HPF compared with 40% in the LR group) (Table 1).

It was reported in a study that the origin site of a duodenal GIST also correlated to the adoption of types of procedure and a Whipple procedure may be more likely to be performed for duodenal GISTs arising from the second portion of duodenum [1], however, we observed different results that the second portion of the duodenum usually indicated a larger size of tumor (median size: 6.13 cm) and a limited resection procedure (PD 25% *vs.* LR 75%) for patients with duodenal GISTs. Unlike the recently published retrospective studies, we additionally performed a univariate cox proportional hazards regression model which helped confirm that the NIH high-risk classification and the PD procedure were independent hazardous risks potentially yielding worse OS and DFS status, in which, however, tumor size (>5 cm) wasn't as expected to have been statistically significant in imposing a higher risk on patients, and the tremendously high HR (117.4 for DFS and 129.1 for OS) with P>0.05 (Table 3). But that may be explained in part by the limitations of our study. Our study was designed in a retrospective manner and the

sample size was small, observations from a larger number of duodenal GIST patients might offer more comprehensive understandings about the complications and clinical course, which, though, is difficult but helpful in accurately assessing the advantages of the limited resection over the PD procedure.

In conclusion, surgical resection with negative margin is the only modality non-metastatic GIST patients could resort to for a curative treatment. Since limited resection yield better survival status comparing with pancreaticoduodenectomy in our findings which are consistent with other studies demonstrating that LR achieves similar oncologic results while offering a more favorable morbidity profile, we propose that LR is a reasonable option for resection of GISTs of the duodenum and should be considered whenever technically feasible. Additionally, our findings support the use of neoadjuvant imatinib to facilitate downsize of GISTs that may otherwise require PD and allow them to receive LR instead. And the type of procedure should be chosen also according to the specific duodenal site of origin, tumor size and NIH risk classification.

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