Surgical management and outcomes of duodenal gastrointestinal stromal tumors

L. Gu[1], P. A. Khadaroo[2], M. Chen[3], H. Qian[1], H. Zhu[1], X. Li[1], J. Pan[1], Xinzhong[1], X. Wang[1]

(1) Department of General Surgery, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China ; (2) Zhejiang University School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China ; (3) The Fourth Clinical College, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China.

Abstract

***Background and study aims* : This retrospective study purports to examine these characteristics and compare the surgical procedures available and appropriate for the treatment of patients affected by duodenal GISTs.**

***Patients and methods* : A retrospective examination of reports and studies carried out between May 2012 and March 2017, and covering patients with primary GISTs of the duodenum was performed using modules from the SPSS package. Comparisons of treatment effects resulting from the administration of two differential methods of surgical treatment namely pancreaticoduodenectomy (PD), and limited resection (LR), were effected on the reports of the GIST patients thus selected.**

***Results* : Out of these 62 patients who had undergone resection of duodenal GISTs, 47 (76%) had limited resection (LR) and 15 (24%) underwent pancreaticoduodenectomy (PD). In Multivariate analyses, tumor size was an independent predictive factor for recurrence (p=0.008). ASA, tumor size, and PD were independent and significant prognostic factors on OS (p=0.021, p=0.024, and p=0.030, respectively). In the very low and low risk group, and high-risk group, there were no significant differences in the RFS (recurrence-free survival) and OS (overall survival) between the LR and PD groups.**

***Conclusions* : When technically feasible, LR should be given due consideration as a reliable and curative option for duodenal GISTs achieving satisfactory RFS and OS.** (Acta gastroenterol. belg., **2019**, 82, **11-18**).

Keywords : gastrointestinal stromal tumors (GISTs), limited resection (LR), pancreaticoduodenectomy (PD), duodenal tumors, prognosis.

Introduction

According to Joensuu *et al.* (1) and Corless *et al.* (2), amongst all the mesenchymal tumors, gastrointestinal stromal tumors (GISTs) are the most commonly encountered with an incidence rate worldwide, of 11 to 19.6 per million population. There is a probability that they originate from the interstitial cells of Cajal (3, 4). GISTs can occur throughout the entire gastrointestinal tract but they are most commonly found in the stomach (50-60%) and the small intestine (30-35%) and less in the colon and rectum (5%) and the esophagus (<1%) (5-7).

Duodenal GISTs (D-GISTs) represent about 30% of primary small bowel tumors despite being a rare occurrence among all gastrointestinal tumors (3-5%) (8). Complete surgical excision with negative margins without dissection of clinically negative lymph nodes is the benchmark for treatment of localized GISTs except in pediatric GISTs (9, 10). Despite being technically feasible, performing a limited resection (LR) may be more difficult because of the need for other important considerations such as the proximity of other anatomical structures including the duodenal papilla, the pancreas and the biliary and pancreatic ducts (11-13). Therefore pancreaticoduodenectomy (PD) may be an option for a subset of patients. Yet, owing to the complexity of the anatomy around the pancreatoduodenal region and the high morbidity rate, many surgeons remain cautious about performing a PD even though mortality rates associated with it are showing downward trends (14).

Segmental duodenectomy and local resection are amongst the different LR surgical options adopted in recent years for the management of duodenal GISTs (15-18). The characteristics, prognosis and optimal surgical management have not yet been well established because of the rarity of duodenal GISTs (19). Recently, several studies have attempted to more closely scrutinize and clarify the outcomes of the patients who underwent LR compared to those who had PD. The results of these studies, however, remain limited by their small sample size (20-22). The use of adjuvant targeted therapy improves the recurrence-free survival (RFS) and overall survival (OS) (23, 24). This study purports to analyze and compare the oncological outcomes of the types of surgical procedures of LR against PD on primary non-metastatic duodenal GISTs and the effect of adjuvant imatinib.

Patients and methods

Eligibility of patient's reports for this retrospective study was based on the histological proof of their localized duodenal GISTs. From May 2002 until March 2017, there were 62 eligible patients who underwent surgical resection for duodenal GISTs at Sir Run Run Shaw Hospital. Patients with recurrent or metastatic disease at diagnosis were excluded. None of the patients had undergone pre-surgery radiotherapy, chemotherapy, imatinib therapy or any pre-surgery medical interventions.

Methods for data collection

A standard data file was created to retrieve information on patients characteristics (e.g. gender, age at diagnosis,

Correspondence to : Xianfa Wang, Department of General Surgery, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, No.3, East Qingchun Road, Hangzhou 310016, Zhejiang, China.
Email : 3195011@zju.edu.cn

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first symptom), pathologic data (e.g. tumor location, size, margins, mitoses per 50 high-power fields [HPF]), treatment approaches including surgical procedures (LR vs. PD) and imatinib therapy postoperatively, operation condition including operation time and intraoperative blood loss, short-term outcome (the length of hospitalization, complications) and long-term outcome (local recurrence, metastasis), and treatment expense. Follow-up information was obtained through outpatient visits record and by individually contacting patients.

Tumor variable

Tumor size was defined by the largest dimension of the tumor in the surgical specimen reported by the original pathologist. Histological subtypes, mutational analysis and site of tumor origin were classified according to CD117 (KIT), CD34, S-100, SMA, Desmin and DOG1 immunostaining (25). Tumors were classified using NIH risk classification (26), based on tumor size, and HPF of the microscope. The location of the tumor (first, second, third and fourth duodenum portion) was recorded accordingly.

Treatment variables

Surgery was classified as PD or LR, which included duodenal wedge or segmental resection. The choice of treatment was made according to the size and location of tumor relative to the pancreas and bile duct. Post-surgical complications were graded according to Dindo scale (27). The choice of post-operative imatinib therapy treatment was made by the internal medicine physicians according to the NIH risk classification (28-31). Follow-up was carried out through routine visits for clinical assessment at outpatient clinic every 3 months during the first two years after surgery and roughly every 6 months thereafter. Yearly chest X-rays and abdominal computed tomography (CT), upper gastrointestinal endoscopy were routinely performed in all patients and additional imaging was requested would there have been clinical suspicion of GISTs recurrence.

Statistical analysis

Treatment effects were expressed in terms of means for continuous variables as percentages for categorical variables. The following putative prognostic factors were retrospectively analyzed: gender, age at diagnosis, American Society of Anesthesiologist (ASA) classification, BMI, tumor size, mitotic count, CD117, CD34, S-100, SMA, Desmin and DOG1 positivity (yes/no), anatomical location, type of resection (PD vs. LR), margins status (R0 vs. R1), tumor rupture (yes/no), NIH risk of classification (High Risk vs. Low Risk), imatinib therapy (yes/no). Wilcoxon test and *t* test were used to rank the data. Pearson Chi-square test and Fisher's exact test were used to compare percentages. The short-term outcome included surgical outcomes such as operative time, length of postoperative hospital stay, complication rates as well as treatment cost. The study endpoints (namely the long-term outcome) were RFS and OS, computed from the date of diagnosis (done by surgery) to the date the event was recorded (local and/or regional and/or metastatic relapse) for RFS and patient's death for OS or censored at the date of the last follow-up in recurrence-free patients.

Survival curves were plotted using the Kaplan-Meier method and compared with the Log-Rank test. Median follow-up was calculated using the reverse Kaplan-Meier method. Cox proportional hazards regression analysis was used for Multivariate analysis for RFS and OS. All statistical tests were 2-sided and the threshold for statistical significance was P= 0.05. Analyses were performed using SPSS software (version 20.0, SPSS Inc. IL, USA).

Results

Patients and characteristics

This cohort comprises a total of 62 patients, of which 47 patients (76%) underwent LR and 15 patients (24%) underwent PD, as listed in Table 1. The most common primary symptom at presentation was bleeding (48%). Tumors were more commonly located in the second portion of the duodenum. This was the case for 93% of the patients who underwent PD. The immunohistochemical staining for CD117, CD34, S-100, SMA, Desmin and DOG1 was reported in Table 2. 34 patients were classified as low and very low risk, and 28 patients as high risk and no patient found to be classified as intermediate risk.

Surgical techniques and complications

Amongst the patients who underwent LR, 30 patients (63.83%) received segmental duodenectomy, and 17 patients (36.17%) received wedge resection. All patients who underwent PD and segmental duodenectomy had an R0 resection compared to 94% of patients who underwent wedge resection. From the 17 patients who underwent wedge resection only one patient achieved R1 resections: a 56 years old female patient, classified as NIH low risk, who did not have any local recurrence or distant metastases identified as of 12 years now, and did not received imatinib therapy. No patient had any tumor rupture during the operation. Compared with LR, patients who received PD had significantly longer operation time, greater intraoperative bleeding loss, longer post-operative hospital stay, and more expensive treatment costs. ($p<0.001$, $p=0.003$, $p=0.016$, $p=0.001$, respectively; Table_1).

Grade III or worse complications were more common in PD as compared to LR (46.7% vs. 8.5%, $p=0.002$). Post-operative complications developed in

Table 1 — **Comparison of clinicopathologic features, treatment and outcome between patients treated with LR and PD**

	Total (N=62)	LR (N=47)	PD (N=15)	p value
Male/Female	31/31	22/25	9/6	0.554
Age	56.65±10.04	56.94±9.65	55.73±11.47	0.690
ASA (1+2) / (3+4)	53/9	41/6	12/3	0.674
BMI (kg/m^2)	22.84±2.84	22.98±2.79	22.38±3.03	0.480
First Symptom				
abdominal discomfort	14	12	2	
GI bleeding	30	23	7	
asymptomatic	18	12	6	
Primary tumor site				<0.001
First	9	9	0	
Second	32	18	14	
Third	11	10	1	
Fourth	10	10	0	
Tumor size				0.790
≤2cm	12	9	3	
2.1-5.0cm	28	21	7	
5.1-10.0cm	17	14	3	
>10.0cm	5	3	2	
Mitotic index (MI)				0.414
≤5/HPF	52	41	11	
6-10/HPF	6	4	2	
>10/HPF	4	2	2	
NIH risk classification				0.557
Very low and low risk	34	27	7	
High risk	28	20	8	
Margins				
Resection R0	61	46	15	
Resection R1	1	1	0	
Tumor rupture	0	0	0	
Operative time(minute)		177±81	347±79	<0.001
Intraoperative blood loss(cm^3)		169±290	443±347	0.003
Postoperative hospital stay(day)		17±11	29±23	0.016
Cost (RMB)		46706±21800	157633±262720	0.001
Postoperative complication	11	4	7	0.002
Grade III	8	4	4	
Grade IV	1	0	1	
Grade V	2	0	2	
Imatinib therapy (400mg/d)				
Very low and low risk	0/34	0	0	
High risk	12/28	10	2	

11 patients (grade III-V), of which 4 post LR surgery and 7 post PD; Amongst post PD patients, there were 2 perioperative death from pancreatic anastomosis leakage and intra-abdominal hemorrhage (grade V); one acute haemorrhagic shock (grade IV); 4 pancreatic anastomosis leakages requiring percutaneous drainage (grade IIIa). Comparatively, amongst post LR surgery patients, there was one duodenal stenosis requiring reoperation by a bypass of the gastrointestinal tract anastomosis (grade IIIb); two duodenal stenosis requiring placement of an enteral feeding tube; one bile leakage requiring percutaneous drainage (grade IIIa) (Table 1).

Imatinib therapy and clinical outcome

No patient received preoperative imatinib prior to surgical resection. 34 patients with low and very low risk did not receive imatinib therapy post-operatively. 3 patients had recurrences, including one patient who developed distant metastasis at 15 months and died after 26 months, and 2 had locoregional recurrence at 9 months and 22 months respectively and are still alive. There were 2 perioperative deaths (see above). 29 patients were alive at the last follow-up date without evidence of disease. The median follow-up was 40 months (range, 2-180).

12 of 28 patients with high risk were treated with imatinib post-operatively at 400 mg daily, with a median duration of 33 months (range, 12-82), 10 patients were alive at the last follow-up date without evidence of disease and 2 patients developed distant metastasis at 22 months and 32 months respectively. Amongst the 12 patients none has died of their disease, 16 patients with high risk did not receive imatinib therapy after surgical

Table 3 — **Univariate and multivariate analysis on RFS**

	Univariate analysis on RFS			Multivariate analysis on RFS		
	HR	95%CI	P-value	HR	95%CI	P-value
Age >60	1.113	(0.346-3.577)	0.857			
Male	0.717	(0.249-2.070)	0.539			
ASA(3+4)	2.508	(0.695-9.049)	0.160			
BMI<19 or >24	0.394	(0.110-1.413)	0.153			
Tumor Size >5cm	4.823	(1.510-15.403)	0.008	4.823	(1.510-15.403)	0.008
MI >5/50 HPF	2.735	(0.916-8.164)	0.071			
PD	1.726	(0.577-5.159)	0.329			
High Risk	4.352	(1.213-15.615)	0.024			
Imatinib	0.558	(0.125-2.494)	0.445			

Table 4 —**Univariate and multivariate analysis on OS**

	Univariate analysis on OS			Multivariate analysis on OS		
	HR	95%CI	P-value	HR	95%CI	P-value
Age >60	1.846	(0.438-7.779)	0.404			
Male	0.594	(0.142-2.489)	0.476			
ASA(3+4)	4.863	(1.158-20.416)	0.031	6.610	(1.331-32.834)	0.021
BMI<19 or >24	0.511	(0.103-2.533)	0.411			
Tumor Size >5cm	5.286	(1.066-26.216)	0.042	7.334	(1.307-41.150)	0.024
MI >5/50 HPF	2.656	(0.634-11.127)	0.181			
PD	2.997	(0.749-11.993)	0.121	5.940	(1.186-29.746)	0.030
High Risk	7.581	(0.932-61.649)	0.058			
Imatinib	0.033	(0.000-36.860)	0.341			

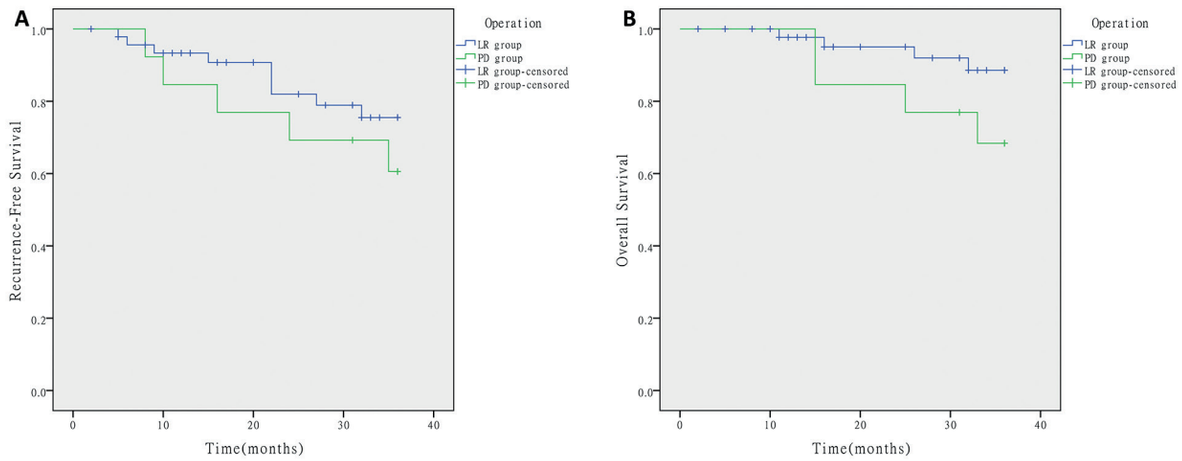

Fig. 1 — RFS and OS in all patients

resection among which 7 patients were alive at the last follow-up date without evidence of disease, 7 patients with recurrent disease have died of their disease and 2 developed distant metastasis at 27 months and 32 months respectively and were still alive. The median follow-up was 79 months (range, 10-175).

Prognostic analysis

The 3-year RFS for the entire cohort, the very low and low risk cohort and the high-risk cohort were 76.7%, 90.6%, and 60.7%, respectively. Statistical analyses were performed on the data about the patients with

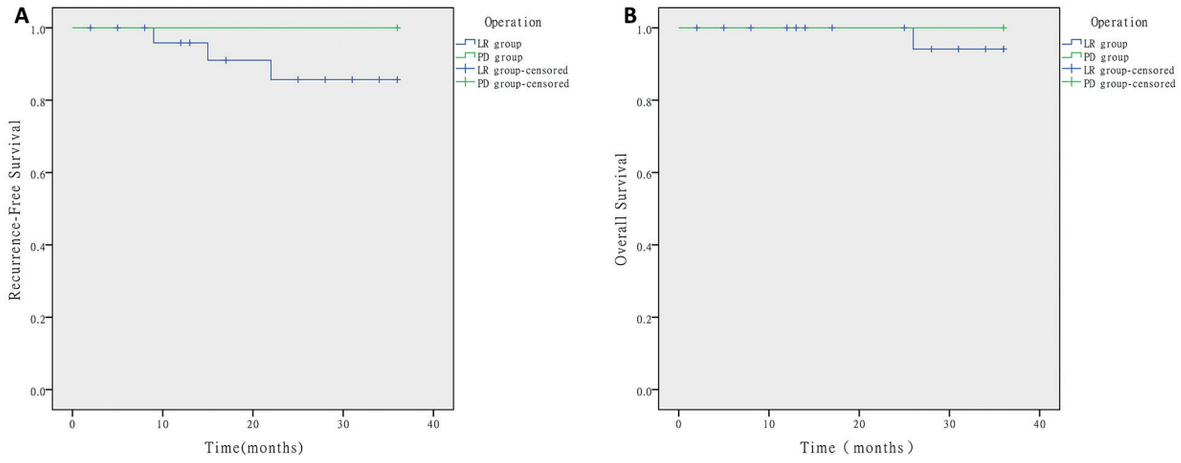

Fig. 2 — RFS and OS in very low and low risk group

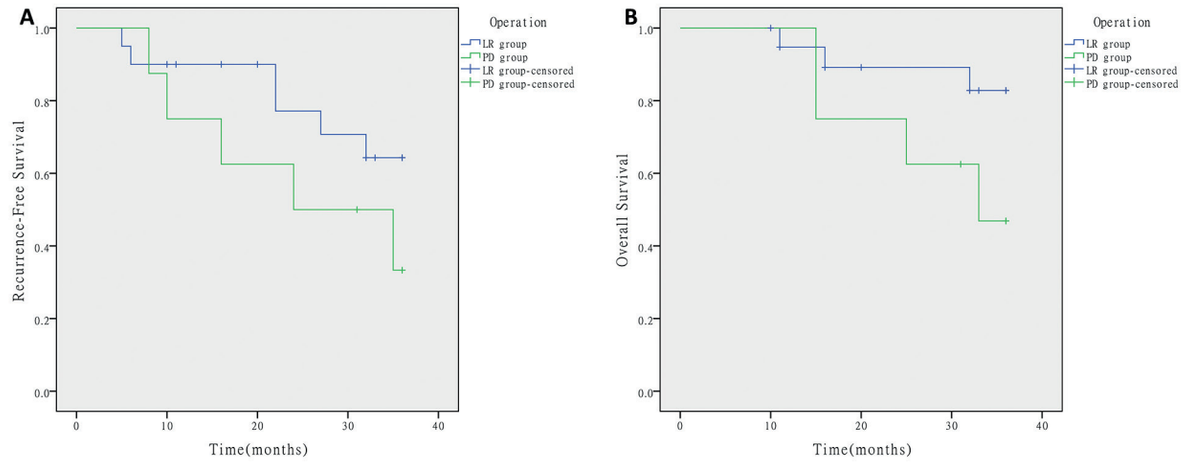

Fig. 3 — RFS and OS in high-risk group

resected duodenal GISTs. The results of the Univariate and Multivariate analyses were presented in Table 3. In Multivariate analyses, tumor size was independent predictive factors for recurrence (p=0.008).

The 3-year OS for the entire cohort, the very low and low risk cohort and the high-risk cohort were 86.7%, 96.9%, and 75.0%, respectively. The results of the Univariate and Multivariate analyses were presented in Table 4. In Multivariate analyses, ASA, tumor size, and PD were independent and significant prognostic factors on OS (p=0.021, p=0.024, and p=0.030, respectively).

Amongst all 62 patients, there were no significant differences in the RFS (p=0.320) and the OS (p=0.102) between the LR and PD groups (Fig 1). In the very low and low risk group, there were no significant differences in the RFS (p=0.386) and OS (p=0.588) between the LR and PD groups (Fig 2). Similarly in the high-risk group, no significant differences were found in the RFS (p=0.180) and OS (p=0.088) between the LR and PD groups (Fig 3).

Discussion

The clinical presentations of duodenal GISTs vary. Similar to previous reports (19, 20, 22), in this paper, patients with duodenal GISTs most commonly presented with gastrointestinal bleeding (48.4%). GISTs often express c-kit protein and react with CD117 antibody (32). They can arise anywhere in the gastrointestinal tract, but the duodenum represents a very rare location (33). These tumors are a real challenge in diagnosis and surgical management because of the complexity in the anatomy of the duodeno-pancreatic region. Treatment by radical resection may also be an alternative choice but it requires extensive procedures such as PD (34). Tumor size, specific site, and involvement of the head of the pancreas and bile duct and mesenteric vessels are the defining factors to the choice of the type of surgical procedure (20). The main curative treatment modality for GISTs is the total surgical resection with clear margins and adjacent organs as mentioned by Blay et al (35). In

this study, GISTs have been observed to most frequently involve the second portion of the duodenum(51.6%), followed by the third portion (17.7%), fourth portion (16.1%), and first portion (14.6%) (Table 1). Patients whose tumors were located in the second segment of the duodenum, 43.8% underwent PD. One should always be prepared for a PD as it is likely to be the prime choice when the tumor is found in this location (36).

PD, as compared to LR, is known involve higher risks of complications supported by this study. Postoperative complications have been shown to be higher in PD group than in the LR group. Notably, there were 2 perioperative deaths because of pancreatic leakage and intra-abdominal hemorrhage after PD. One cannot be too careful in choosing the PD for duodenal GISTs, especially in elderly patients and very low and low risk patients (18, 20). Additionally, 54.8% patients were classified as very low and low risk according to NIH risk classification in the present study. A few recent articles reported that duodenal GISTs might have better prognosis than other small bowel GISTs (37).

As reported by some previous articles, LR can be performed for small tumors not infiltrating their surrounding structures and for cases where the papilla of *Vater* can be preserved (8, 21). Recent literatures reported that duodenal wedge resection can be performed for small tumors which were located on the duodenal wall at least 2cm from the papilla (38), segmental duodenectomy, with end-to-end or side-to-end duodeno-jejunal anastomosis which can be performed for larger tumors located below the papilla of Vater in the third or fourth duodenal portions (11). Partial duodenectomy with a Roux-en-Y duodeno-jejunal anastomosis has been proposed for lager tumors which involved the antimesenteric border of the second and third portions of the duodenum (13). In this review, no significant difference was found between the PD group and the LR group for tumor size; MI and NIH risk classification (p=0.790, p=0.414, and p=0.557, respectively; Table 1). Some articles have observed that the LR group had lower R0 resection rate (20, 21), compared with the PD group. In this paper, however, all patients in the PD group and segmental duodenectomy group were found to have had an R0 resection as compared to 94% in the wedge resection group. Even though PD resection can provide a wider tumor clearance, it is associated with a longer operation time, a greater intraoperative bleeding loss, a longer postoperative hospital stay, a more expensive treatment costs and a higher rate of postoperative complications than LR resection. As per some reports, LR proffers a better quality of life, preserving the continuity and functions of the pancreas and gastrointestinal tract despite an increased risk of local recurrence and the surgical margin involvement risks (18).

However, in this study, no significant differences were noted in the RFS and OS between the LR and PD groups. In recent years, there has been a tendency to perform PD for large tumors which have a higher risk of malignancy and recurrence, and LR for small tumors which have a benign behavior (39). In the very low and low risk group, there were no significant differences in the RFS and OS between the LR and PD groups. In the high risk group, there were no significant differences in the RFS and OS between the LR and PD groups yet. The conclusions of this article suggest that LR should be a procedure of choice for duodenal GISTs whenever technically feasible, because it is associated with favorable oncologic outcomes as compared with PD.

Imatinib, a small molecule tyrosine kinase inhibitor (TKI) with activity against KIT and PDGFR, have played a prime role in the management of GISTs (40, 41). The history of metastatic and recurrent GISTs has been changed by the use of imatinib as neoadjuvant, adjuvant therapy and in tumor recurrence (42-45). The administration of imatinib impacts strongly on the outcome of high risk group (46-49). In this study, in the very low and low risk group, 85% patients were alive at the date of last follow-up without evidence of disease. 3 patients had recurrences, including one patient who developed distant metastasis and died, and 2 had locoregional recurrence and are alive. In the high risk group, 12 patients were treated with imatinib post-operatively at 400 mg daily, with a median duration of 33 months (range, 12-82), 10 patients were alive at the date of last follow-up without evidence of disease and 2 patients developed distant metastasis. No patient has died of their disease. 16 patients did not receive imatinib therapy after surgical resection. 7 patients were alive at the date of last follow-up without evidence of disease. 7 patients with recurrent disease have died of their disease. 2 developed distant metastasis at 27 months and 32 months respectively and were alive. On univariate analysis, imatinib's association with DFS and OS, was not statistically significant (p=0.445, p=0.341, respectively). The reasons for the results might however be that the sample sizes were very small and the follow-up time too short. TKI as a neoadjuvant therapy has been recommended as a method to downstage tumors especially tumors located in the second portion of the duodenum (50). This, however, requires a precise preoperative diagnosis of GISTs, which is not always easy to obtain.

Conclusions

Our data do not indicate any differences in RFS and OS among patients with duodenal GSITs having undergone PD versus LR. But PD was associated with higher risks of postoperative complications. Thus PD should be preferred for patients where LR is not technically feasible because of the involvement of the papilla of Vater. It should however be noted that patients with high risk are not a necessary condition for PD. Treatment with imatinib should be recommended for patients with high risk of recurrence. Its administration

in the neoadjuvant setting should always be considered, especially in patients candidate to PD.

Author contribution

LG and PK manuscript writing, performing procedures and data analysis; MC and HQ data analysis; HZ, XL, JP and XZ contribution to writing the manuscript; XW contribution to drafting conception and design. All authors read and approved the final manuscript.

Compliance with ethical standards

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Conflicts of interest

The authors declare that they have no conflict of interest.

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