



Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Resection of GIST in the duodenum and proximal jejunum: A retrospective analysis of outcomes



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ARTICLE INFO

Article history:

Received 20 November 2018

Received in revised form

29 April 2019

Accepted 2 May 2019

Available online 3 May 2019

Keywords:

GIST

Duodenum

Proximal jejunum

Limited resection

Resection with digestive reconstruction

ABSTRACT

Introduction: Gastrointestinal stromal tumors (GISTs), with a primary occurrence in the duodenum and proximal jejunum, are rare and treatment is poorly understood. This study aimed to evaluate the main factors influencing the prognosis of GIST resection in this complex anatomical structure.

Materials and methods: This retrospective study included 47 patients who underwent surgery for primary GIST of the duodenum (20) and proximal jejunum (27) between 2012 and 2017. Perioperative clinical data as well as relapse and survival information were collected.

Results: All patients underwent negative margin resection (R0) of duodenal and proximal jejunum GISTs. Complications occurred more frequently in treatment of duodenal GISTs than proximal jejunum GISTs ($p = 0.003$). GISTs in D3 (the 3rd portion of duodenum) were related to larger tumor size ($p = 0.001$), higher probability of severe complication rate ($p = 0.042$), longer hospital stays ($p = 0.023$) and fasting time ($p = 0.020$). More complications were found for patients with digestive reconstruction than limited resection ($p = 0.010$). Additionally, patients with a tumor mass larger than 5 cm or a mitotic index greater than 5 mitoses/50 HPFs showed poorer therapeutic outcomes. The 1- and 3-year overall survival was 97.9% and 86.1%, respectively and were not influenced by operation type ($p = 0.061$) or GIST position ($p = 0.447$).

Conclusion: With negative operational margins, limited resection is a safe and feasible procedure for duodenal and proximal jejunum GIST patients and unnecessary digestive reconstruction should be avoided. Considering the severe complication rate, resection for GISTs in D3 should be performed with care.

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Introduction

Gastrointestinal stromal tumors (GISTs), occurring in smooth muscle interstitial cells of Cajal, are the most common mesenchymal tumors of the digestive tract. GISTs occur in one per hundred thousand people, and can be found in any gastrointestinal location from the esophagus to the anus. Gastric stromal tumors account for 50%–70% of all GISTs, while duodenal and proximal jejunum GISTs are relatively rare with most published reports on

duodenal GIST being case reports or small case series.

In a long-term follow-up study of 1765 patients with gastric GISTs, Miettinen and colleagues reported that the metastatic rate was 86% for tumors >10 cm in diameter with a mitotic index of >5 mitoses/50 HPFs, whereas tumors of the same size with a mitotic index of <5 mitoses/50 HPFs had a relatively low metastatic rate of 11% [1]. In contrast, a subsequent report involving 906 patients with small intestinal GIST demonstrated that tumors >10 cm with a mitotic index of ≤5 mitoses/50 HPFs had a metastatic rate of 50%. Gastric GISTs have an indolent behavior; those that are ≤2 cm (irrespective of the mitotic index) are essentially benign, whereas small intestinal GISTs tend to be more aggressive [2]. The guidelines developed by Miettinen and colleagues for risk stratification of primary GIST include tumor site.

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Complete R0 surgical resection is the only curative treatment for GISTs; wedge local resection, segmental duodenectomy and pancreaticoduodenectomy are the three most common methods. Limited resection such as wedge local resection and segmental duodenectomy can be performed with small tumors that do not infiltrate the surrounding structures and the papilla of Vater can be preserved. In a large series, duodenal wedge resection was performed for small tumors (1–2 cm in diameter) which were located on the duodenal wall at least 2 cm from the papilla. It is therefore safe for resection and anastomosis to be carried out with minimal risk of stenosis.

In order to compare different primary lesion locations and surgical procedures, this study aimed to evaluate main influence factors on prognosis for GISTs in the duodenum and proximal jejunum, including short-term postoperative recovery, long-term recurrence rate and survival.

Materials and Methods

Study subjects

This study included 47 patients who underwent surgery for primary GISTs in the Second Affiliated Hospital of Zhejiang University School of Medicine between July 2012 and July 2017. There were 20 GIST patients with tumors located in the duodenum and 27 with tumors located in the jejunum within 25 cm of the treitz ligament. Basic characteristics, clinical symptoms and diagnosis, operation methods, pathological and morphological features, pathological risk classes (very low, low, intermediate and high) and therapeutic characteristics (complications, postoperative hospitalization duration, peak body temperature and fasting time) were collected from the EMRS system of the hospital. In the study, we followed strict criteria that all objects are followed up every 6 months over the phone or outpatient visit records.

Inclusion criteria for patient selection were as follows: (1) age between 18 and 80 years; (2) underwent radical surgery with negative margins of resection; (3) pathologically confirmed GIST located in the duodenum or jejunum within 25 cm of the treitz ligament; (4) drug naivety. And the exclusion criteria were: (1) multiple tumors or distant metastasis; (2) pregnant, or lactating; (3) having a history or presence of any severe unstable systemic disease.

The retrospective trial was approved by the human research ethics committee of the Second Affiliated Hospital of Zhejiang University School of Medicine.

Surgical complication grades

In this research, surgical complications were classified according to their Clavien–Dindo Classification. Grade I complications denote any deviation from the normal postoperative course without the need for pharmacological treatment or other surgical, endoscopic, and radiological interventions. Grade II complications are those requiring pharmacological treatment with drugs other than such allowed for grade I complications and grade III-a/III-b describes a situation where the patient needs intervention without/with general anesthesia. Finally, grade IV-a/IV-b denotes single or multiple organ dysfunction and grade V is used to note a complication resulting in death.

Statistical analyses

Data are expressed as means (range: minimum, maximum). Unpaired *t*-test and chi-square test were used to compare data results between two groups. In addition, one-way ANOVA with

post-hoc test of LSD was applied among three groups. Kaplan–Meier methodology and Log Rank test were used to analyze survival outcomes. In order to provide the most reliable results, all statistical tests were two-tailed and a *p*-value <0.05 was considered to be significant. All analyses were carried out using the Statistical Package for the Social Sciences (SPSS) version 18.0 for Windows (IBM, IL, USA).

Results

GISTs of duodenum and proximal jejunum

A total of 47 patients with duodenal and proximal jejunum GISTs underwent resection at the Second Affiliated Hospital of Zhejiang University School of Medicine, including 28 males (59.6%) and 19 females (40.4%). Basic clinical characteristics, operative methods, pathological types, pathological risk classes (very low, low, intermediate and high) and therapeutic characteristics (complications, post operation hospitalization duration, peak body temperature, fasting time, progression free survival and overall survival) were recorded.

In our study, the mean patient age at the time of operation was 56.1 years (range: 22–80). The most common symptoms were melena (21 patients, 44.7%) and abdominal discomfort (16 patients, 34.0%), while 10 patients (21.3%) were incidentally diagnosed with GISTs. Furthermore, the initial mean hemoglobin concentration was 103.7 g/L (range: 60–158 g/L) among all patients, but when restricted to melena patients, the mean value was reduced to 86.2 g/L (range: 60–137 g/L).

The total complication rate was 31.9% [(Clavien–Dindo class I (n = 5), II (n = 7), IIIb (n = 1), IVa (n = 1) and V (n = 1)] with a severe complication (Clavien–Dindo class ≥ III) rate of 6.4%. One proximal jejunum GIST patient died from severe lung infection two months after operation. The two other severe complications included renal insufficiency and anastomotic site bleeding requiring a second operation. Surgical complication occurred more frequently in duodenal GISTs than proximal jejunum GISTs (*p* = 0.003).

After the operation, 7 patients (14.9%) received ICU treatment. The mean postoperative peak body temperature, hospital stay and fasting time were 38.25 °C (range: 37.1–40.6 °C), 19.5 days (range: 5–99 days) and 12.8 days (range: 1–99 days) respectively and the mean tumor diameter was 5.85 cm (range: 1.5–15.0 cm). Based on the official standard for risk of progression, the number of patients in our study presented with very-low risk was 2 (4.3%), low risk was 23 (48.9%), intermediate risk was 12 (25.5%), and high risk was 10 (21.3%). The mean follow-up time was 27.29 months (range: 2.57–50.80 months) and 14 patients received adjuvant therapy with Gleevec.

During the follow-up period, there has been one tumor recurrence in the liver and three deaths that were not related to GIST relapse. Finally, there was no significant difference between all clinical characteristics for duodenal and proximal jejunum GIST patients including age, sex, symptoms, hemoglobin concentration, tumor size, risk classes, incidence of ICU treatment, severe complication rate, postoperative peak temperature, hospital stays, fasting time, relapse rate and mortality. Detail information is displayed in [Table 1](#).

Duodenal GISTs

Duodenal GISTs most frequently occurred in D2 (the 2nd portion of duodenum; 10 patients; 50% of total), followed in order by D3 (7; 35%), D1 (2; 10%) and D4 (1; 5%). As the results presented in [Table 2](#) show, GISTs in D3 had larger tumor sizes (*p* = 0.001), higher probability of severe complication rate (*p* = 0.042), longer hospital

Table 1
GISTs of duodenum and proximal jejunum.

Demographic Characteristics	Duodenum (n = 20)	Jejunum (n = 27)	P-value
Age (years)	55.50	56.56	0.786
Sex (males)	13/20	15/27	0.514
Symptoms	Melena	8	13
	Abdominal discomfort	5	11
	Incidental	7	3
Hemoglobin (g/L)	106.45	101.74	0.587
Tumor size (centimeters)	6.000	5.741	0.802
Risk Classes	Very low	1	1
	Low	11	12
	Intermediate	2	10
	High	6	4
ICU	4/20	3/27	0.397
Complication	11/20	4/27	0.003*
Severe Complication (≥ 3)	2/20	1/27	0.383
Hospital Stays (days)	24.05	16.04	0.172
Highest Body Temperature ($^{\circ}$ C)	38.325	38.196	0.541
Fasting Time (days)	17.35	9.48	0.157
Relapse	1	0	0.240
Mortality	2/20	1/27	0.383

Comparisons of basic clinical characteristics, pathological risk classes and therapeutic characteristics (ICU stays, complications, post operation hospitalization duration, peak body temperature, fasting time, progression free survival and overall survival) between duodenum and proximal jejunum GIST; *p < 0.05.

Table 2
Duodenal GISTs (D3 and others).

Portion (Duodenum)	D3 (n = 7)	Other Portions (n = 13)	P-value
Age (years)	56.14	55.15	0.894
Sex (males)	4/7	9/13	0.589
Symptoms	Melena	1	7
	Abdominal discomfort	2	3
	Incidental	4	3
Hemoglobin (g/L)	116.00	101.31	0.273
Tumor size (centimeters)	9.586	4.069	0.001*
Risk Classes	Very low	0	1
	Low	2	9
	Intermediate	1	1
	High	4	2
ICU	2/7	2/13	0.482
Complication	4/7	7/13	0.888
Severe Complication (≥ 3)	2/7	0/13	0.042*
Hospital Stays (days)	40.00	15.46	0.023*
Highest Body Temperature ($^{\circ}$ C)	38.200	38.392	0.551
Fasting Time (days)	34.57	8.08	0.020*
Relapse	1/7	0/13	0.162
Mortality	0/7	2/11	0.274

Comparisons of basic clinical characteristics, pathological risk classes and therapeutic characteristics (ICU stays, complications, post operation hospitalization duration, peak body temperature, fasting time, progression free survival and overall survival) between D3 and other portions of duodenal GIST; *p < 0.05.

stays ($p = 0.023$) and fasting time ($p = 0.020$) compared with GISTs of other portions in the duodenum. Four patients with post-operative ICU treatment were related to D2 and D3 duodenal GISTs, and all 11 surgical complications in this study also occurred in these areas. During the follow-up period, there was one tumor recurrence in D3 and two deaths due to D2 duodenal GISTs.

Proximal jejunum GISTs

Our study included 27 patients with proximal jejunum located within 25 cm of the treitz ligament. These patients were further subdivided into three groups according to distance where group 1, 2, and 3 had tumor less than 5, 5–15 and > 15 cm from the treitz ligament, respectively. Significant differences could be found among length of hospital stays between these three groups ($p = 0.044$). In post-hoc test of LSD, the hospital stays of group 1 proximal jejunum GIST patients was longer than group 2 ($p = 0.037$) and group 3 ($p = 0.024$). However, no other significant difference was observed among the three groups. Detailed information is displayed in Table 3.

Limited resection and resection with digestive reconstruction

Patients who underwent limited resection either received local excision ($n = 6$) or segmental resection with primary anastomosis ($n = 30$). Resection with digestive reconstruction included partial duodenal and gastric resection with digestive reconstruction ($n = 2$) as well as pancreatoduodenectomy ($n = 9$). More complications occurred in patients who underwent resection with digestive reconstruction rather than limited resection ($p = 0.010$). There was no difference in risk class, ICU treatment, severe complication rate, postoperative highest temperature, hospital stays, fasting time, relapse rate and mortality between two groups. Detailed information is displayed in Table 4.

Tumor size & mitotic index

The median tumor size was 4.8 cm in our research, and we chose 5 cm as the cut-off threshold. Patients with mass larger than 5 cm had a greater probability of ICU treatment ($p = 0.035$) and complications ($p = 0.022$), longer hospital stays ($p = 0.003$) and fasting

Table 3
Proximal jejunum GISTs.

Position (Jejunum)	≤5 cm (n = 9)	5–15 cm (n = 8)	15–25 cm (n = 10)	P-value	
Age (years)	53.89	53.25	61.60	0.214	
Sex (males)	5/9	4/8	6/10	0.914	
Symptoms	Melena	4	5	4	0.707
	Abdominal discomfort	4	3	4	
	Incidental	1	0	2	
Hemoglobin (g/L)	116.11	89.75	98.40	0.181	
Tumor size (centimeters)	6.967	4.688	5.480	0.306	
Risk Classes	Very low	0	0	1	0.603
	Low	3	5	4	
	Intermediate	4	3	3	
	High	2	0	2	
ICU	1/9	1/8	1/10	0.986	
Complication	2/9	1/8	1/10	0.738	
Severe Complication (≥3)	0/9	0/8	1/10	0.414	
Hospital Stays (days)	26.56	11.00	10.60	0.044*	
Highest Body Temperature (°C)	38.278	37.938	38.330	0.511	
Fasting Time (days)	14.89	6.50	7.00	0.237	
Relapse	0/9	0/8	0/10	–	
Mortality	0/9	0/8	1/10	0.414	

Comparisons of basic clinical characteristics, pathological risk classes and therapeutic characteristics (ICU stays, complications, post operation hospitalization duration, peak body temperature, fasting time, progression free survival and overall survival) between different groups of proximal jejunum GISTs according to distance where group 1, 2, and 3 had tumor less than 5, 5–15 and > 15 cm from the treitz ligament, respectively. *p < 0.05.

Table 4
Limited resection and resection with digestive reconstruction.

Operation Method	Limited Resection (n = 36)	Resection with Digestive Reconstruction (n = 11)	P-value
ICU	6/36	1/11	0.537
Complication	8/36	7/11	0.010*
Severe Complication (≥3)	3/36	1/11	0.937
Hospital Stays (days)	20.69	15.36	0.440
Highest Body Temperature (°C)	38.194	38.436	0.324
Fasting Time (days)	14.50	7.36	0.274
Relapse	1/36	0/11	0.576
Mortality	1/36	2/11	0.067

Comparisons of therapeutic characteristics (ICU stays, complications, post operation hospitalization duration, peak body temperature, fasting time, progression free survival and overall survival) between limited resection and resection with digestive reconstruction, *p < 0.05.

Table 5a
Tumor size.

Tumor size	<5 cm (n = 24)	≥5 cm (n = 23)	P-value
ICU	1/24	6/23	0.035*
Complication	4/24	11/23	0.022*
Severe Complication (≥3)	0/24	3/23	0.067
Hospital Stays (days)	11.21	28.04	0.003*
Highest Body Temperature (°C)	37.929	38.587	0.001*
Fasting Time (days)	5.83	20.13	0.007*
Relapse	0/24	1/23	0.302
Mortality	2/36	1/11	0.576

Comparisons of therapeutic characteristics (ICU stays, complications, post operation hospitalization duration, peak body temperature, fasting time, progression free survival and overall survival) between different tumor size (the cut-off threshold is 5 cm), *p < 0.05.

times (p = 0.007), and higher postoperative body temperature (p = 0.001). No significant difference was found in severe complications, relapse and mortality rate between two groups. Detailed information is displayed in Table 5a.

Patients with a mitotic index of ≥5 mitoses/50 HPFs had a greater probability of complications (p = 0.015), longer hospital stays (p = 0.010) and fasting time (p = 0.045), and higher postoperative body temperature (p = 0.001) than patients with a mitotic index of <5 mitoses/50 HPFs. Again, no significant difference was found in severe complications, relapse rate and mortality between the two groups. Detailed information is displayed in Table 5b.

Table 5b
Mitotic index.

Mitotic index (mitoses/50 HPFs)	<5 (n = 42)	≥5 (n = 5)	P-value
ICU	6/42	1/5	0.734
Complication	11/42	4/5	0.015*
Severe Complication (≥3)	2/42	1/5	0.188
Hospital Stays (days)	16.93	40.60	0.010*
Highest Body Temperature (°C)	38.143	39.160	0.001*
Fasting Time (days)	10.95	28.60	0.045*
Relapse	1/42	0/5	0.727
Mortality	3/42	0/5	0.537

Comparisons of therapeutic characteristics (ICU stays, complications, post operation hospitalization duration, peak body temperature, fasting time, progression free survival and overall survival) between different mitotic index (the cut-off threshold is 5 mitoses/50 HPFs), *p < 0.05.

Overall survival and progression free survival

In this study, the 1- and 3-year overall survival was 97.9% and 86.1% respectively, with no cases of recurrence within 3 years of treatment. Both overall survival and progression free survival were not influenced by the type of operation (p = 0.061; p = 0.154) or GIST positioning (p = 0.447; p = 0.265). Detailed information is displayed in Fig. 1.

Discussion

According to the latest NCCN GIST guidelines, gastric GISTs have

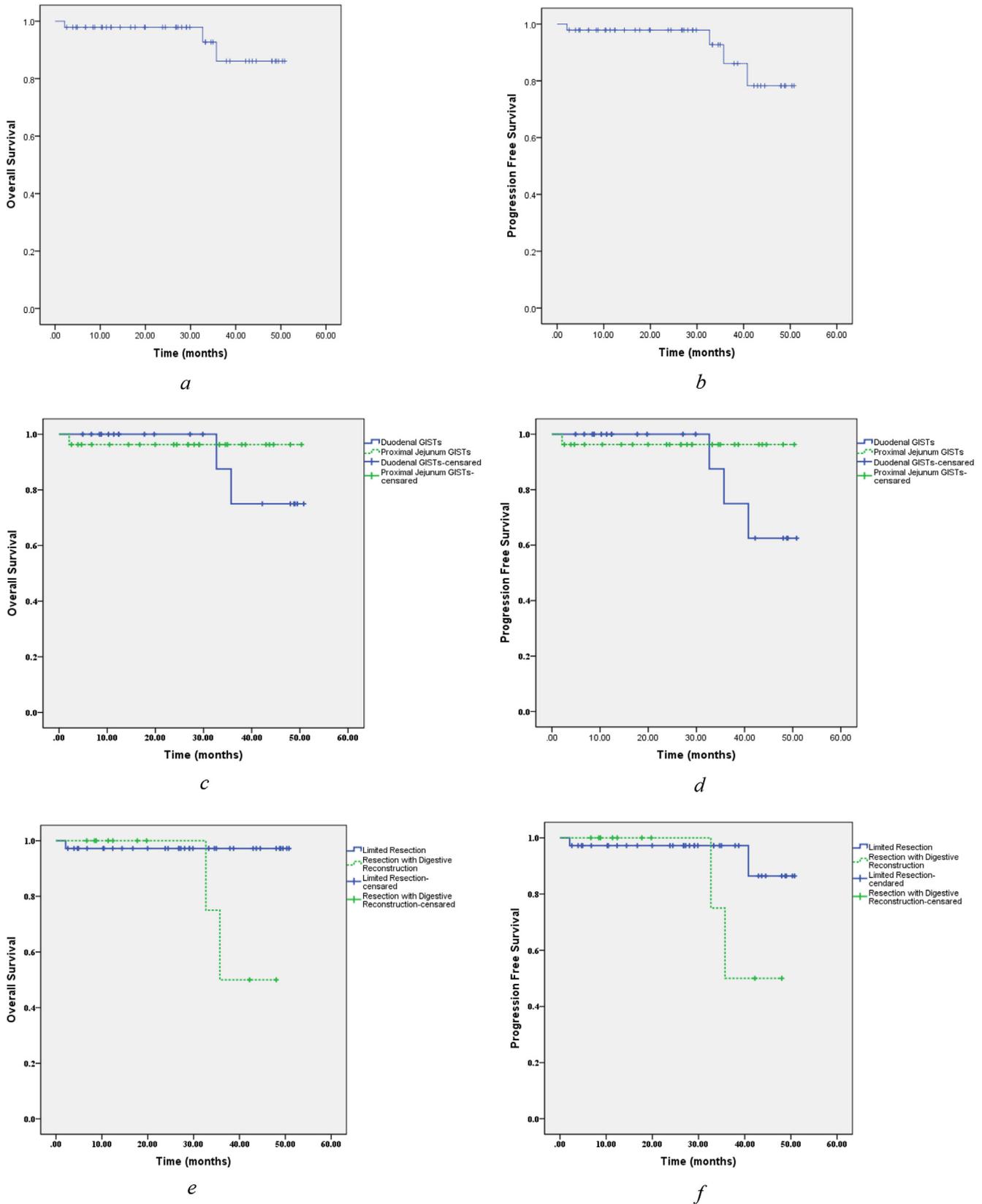


Fig. 1. Comparison of Overall and Progression Free Survival. Fig. 1a shows Overall Survival; Fig. 1b shows Progression Free Survival; Fig. 1c shows Overall Survival of Duodenal and Proximal Jejunum GISTs (Duodenum vs Proximal Jejunum GIST; $p = 0.447$); Fig. 1d shows Progression Free Survival of Duodenal and Proximal Jejunum GISTs: (Duodenum vs Proximal Jejunum GIST; $p = 0.265$); Fig. 1e shows Overall Survival of Limited Resection and Resection with Digestive Reconstruction: (Limited Resection vs Resection with Digestive Reconstruction; $p = 0.061$); Fig. 1f shows Progression Free Survival of Limited Resection and Resection with Digestive Reconstruction (Limited Resection vs Resection with Digestive Reconstruction; $p = 0.154$).

an overall indolent behavior and those that are ≤ 2 cm, irrespective of mitotic index, are essentially benign, whereas small intestinal GISTs tend to be more aggressive than gastric GISTs [1,2]. As the beginning section of the small intestine, the duodenum is a complex anatomical structure where the pancreatic duct and common bile duct enter through the major duodenal papilla. Our study focused on GISTs of the duodenum and proximal jejunum showed that the 3-year overall survival and progression free survival were both 86.1%. Our results were similar to a retrospective review report in the literature, which suggested that 4-year OS and EFS rate of localized duodenal GISTs were 89% and 58% respectively [3].

Regarding different positions of GISTs, results from the present study suggest that surgical complications occurred more frequently in duodenal GISTs than proximal jejunum GISTs (55.0% vs. 14.8%, $p = 0.003$). In addition, GISTs in D3 were related to larger tumor size, more severe complications, longer hospital stays and fasting time compared with other duodenum portions. GISTs located within 5 cm of the treitz ligament were associated with longer hospital stays. All involved differences are attributed to the complex adjacent anatomical structures. With longer hospital stays and fasting time, the empty delay syndrome after operation is common for primary GISTs located in these positions. To solve this problem, surgeons should put a nose-jejunum nutrient canal over the anastomotic stoma during operation, and pay more attention to postoperative management.

According to the latest guidelines, surgery is the primary treatment of choice for patients with localized or potentially resectable GIST lesions. Considering the low frequency of local recurrence, segmented or wedge resection to obtain negative margins is often most appropriate. Additionally, lymphadenectomy is usually not required given the low incidence of nodal metastases. As GIST tend to be very friable, every effort should be made not to violate the pseudocapsule of the tumor. Optimal surgical treatment for duodenal or proximal jejunum GISTs has not been well characterized because of the complex adjacent anatomical structures involved. In other words, local segmental or wedge resections are often difficult to perform, especially within D2 [4,5]. In D1, pancreatoduodenectomy is an optimal surgical method for large tumors located on the medial wall [4–7]. Wedge or segmented resection with Billroth I procedure or Roux-en-Y gastrojejunostomy are also feasible for small tumors located on the lateral wall [8–10]. For GIST in D2, large or even small tumors, located on the medial wall close the pancreatic head, should be treated by pancreatoduodenectomy [4,5,7]. Local wedge resection with primary closure of the duodenal wall or distal duodenectomy with reconstruction is also optional for small tumors located on the lateral wall [5,7,11]. For GIST in D3, resection of the third and fourth duodenal portions and primary end-to-end or side-to-end anastomosis with the jejunum should be first considered [12–14]. However, GIST in the D4 or proximal jejunum, small tumors could be treated with wedge resection [8,12], and large tumors could be removed with segmented resection [15]. In this study, more complications were identified in patients who underwent resection with digestive reconstruction rather than limited resection ($p = 0.010$). In one sense, limited resection with negative margins should be the first choice for GISTs of the duodenum and proximal jejunum.

The last but not least, tumor size and mitotic rate are the most widely used pathologic features in risk stratification of GISTs. Tumors of such different sizes and replication rates have very different biological behaviors. A previous study of over 1700 subjects on prognostication of GISTs by tumor size and mitotic rate showed that the progressive disease rate on duodenal GISTs during long-term follow-up were 8.3% (tumor diameter: 2–5 cm; mitotic index $\leq 5/50$ HPFs), 34% (tumor diameter: 5–10 cm; mitotic index

$\leq 5/50$ HPFs), 50% (tumor diameter: 2–5 cm; mitotic index $> 5/50$ HPFs) and 86% (tumor diameter: 5–10 cm; mitotic index $> 5/50$ HPFs), respectively. For small intestinal GISTs, the rate came to 4.3% (tumor diameter: 2–5 cm; mitotic index $\leq 5/50$ HPFs), 24% (tumor diameter: 5–10 cm; mitotic index $\leq 5/50$ HPFs), 73% (tumor diameter: 2–5 cm; mitotic index $> 5/50$ HPFs) and 85% (tumor diameter: 5–10 cm; mitotic index $> 5/50$ HPFs), respectively [16]. In our study, both tumor size and mitotic rate were found to have strong impacts on therapeutic outcomes during the perioperative period for resection of duodenum and proximal jejunum GISTs.

There are several limitations in this study. Firstly, retrospective studies may introduce bias due to its nature vis-a-vis prospective studies. Secondly, there is also an overly expanded age limit in the study. Patients with different ages have different bodies' capacities to recover from operations. Thirdly, tumors of different sizes and replication rates have very different biological behaviors that may influence our results. In order to solve those limitations above, our group plans to set up a randomized controlled trial that including age, tumor size and mitotic index stratifications with a large patient population and long-term follow-up to further confirm our findings.

Conclusion

In summary, we draw three clinical recommendations based on the results of this study. Firstly, based on negative operational margins, limited resection may be a safe and feasible surgical procedure for duodenal and proximal jejunum GIST patients, because no increased surgical complication or tumor recurrence risk was found. Additionally, unnecessary digestive reconstruction should be avoided after resection of duodenal and proximal jejunum GISTs. Secondly, considering the complex anatomical structures involved and the small excision range principle, surgeons should be careful when choosing the excision and reconstruction method for primary GISTs in D3 as it is close to the major duodenal papilla. Finally, we recommend that the nasal jejunal feeding tube is fairly useful to avoid postoperative delayed gastric emptying for primary GISTs located in duodenum and proximal jejunum, especially for horizontal part of duodenum.

Conflict of interest

We declare that we have no conflict of interest.

Competing interests

We declare that we have no competing interests.

Acknowledgements

Dr. Jian Chen was supported by National Natural Science Foundation of China (NO. 81372620), Zhejiang Provincial Key Project of Research and Development Grant (NO. 2019C03043, 2018C03G1360843), Natural Science Foundation of Zhejiang Province (NO. LY14H160034). And Dr. Muxing Kang was supported by National Natural Science Foundation of China (NO. 81301889).

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