Original article

Prognostic characteristics of duodenal gastrointestinal stromal tumours

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Background: **This study evaluated the clinical characteristics, surgical procedures and prognosis of duodenal gastrointestinal stromal tumours (GISTs).**

Methods: **Patients with a diagnosis of primary duodenal GIST treated between January 2000 and December 2012 were analysed. Patients with gastric and small intestinal GISTs were chosen as control groups according to the following parameters: age, tumour size, mitotic index and adjuvant imatinib therapy. Operative procedures for patients with duodenal GIST included pancreaticoduodenectomy or limited resection. Disease-free survival (DFS) was calculated using Kaplan–Meier analysis.**

Results: **Some 71 patients with duodenal, 71 with gastric and 70 with small intestinal GISTs were included in the study. DFS of patients with duodenal GIST was shorter than that of patients with gastric GIST (3-year DFS 84 *versus* 94 per cent; hazard ratio (HR) 3.67, 95 per cent c.i. 1.21 to 11.16; $P = 0.014$), but was similar to that of patients with small intestinal GIST (3-year DFS 84 *versus* 81 per cent; HR 0.75, 0.37 to 1.51; $P = 0.491$). Patients who underwent pancreaticoduodenectomy were older, and had larger tumours and a higher mitotic index than patients who had limited resection. The 3-year DFS was 93 per cent among patients who had limited resection compared with 64 per cent for those who underwent PD (HR 0.18, 0.06 to 0.59; $P = 0.001$).**

Conclusion: **The prognosis of duodenal GISTs is similar to that of small intestinal GISTs.**

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Introduction

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the gastrointestinal tract[1]. Surgical resection with negative margins remains the standard treatment for patients with GIST. The anatomical location of the tumour is a well documented prognostic factor for GIST after radical surgery[2,3]. Patients with small intestinal GISTs have a poorer prognosis than those with gastric GISTs[4], but a more favourable prognosis than those with colorectal GISTs[5,6]. Extragastrointestinal GISTs are associated with the poorest outcomes[4].

The duodenum develops early in the fourth week of embryonic development from the distal part of the foregut and the proximal part of the midgut; the junction of the two parts is just distal to the origin of the bile duct[7]. The prognostic characteristics of duodenal GISTs remain uncertain owing to small numbers in reported cohorts[8–10]. In addition, the surgical management of duodenal tumours is challenging. Few studies have investigated whether the prognosis of duodenal GISTs is different from that of lesions in other anatomical locations[11]. The purpose of this study was to evaluate the clinical characteristics and prognostic features of duodenal GISTs and to suggest a reasonable surgical strategy for these tumours.

Methods

Patients with a histopathological diagnosis of primary GIST who underwent radical operation at the Department of Gastrointestinal Surgery, First Affiliated Hospital, College of Medicine, Zhejiang University, between January 2000 and December 2012, were included in the study. The diagnosis of GIST was based on a combination of histopathological evaluation and immunohistochemistry for CD117. Sex, age, chief symptom, type of surgical procedure, surgical complications, tumour size, mitotic index and adjuvant imatinib treatment were also analysed.

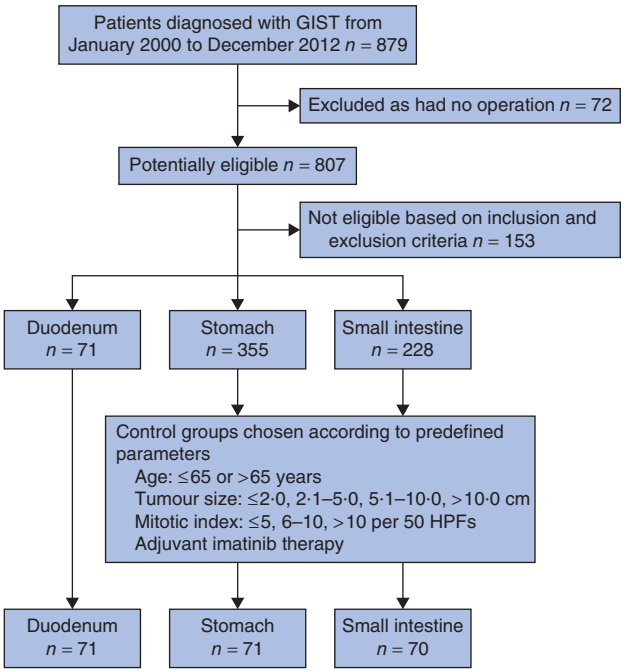


Fig. 1 Flow chart of patients diagnosed with gastrointestinal stromal tumour (GIST). HPF, high-power field

Tumour size was defined as the largest diameter of the tumour in any dimension after formalin fixation. Mitotic index was measured in the area with highest proliferation of the tumour, and the number of mitoses in 50 high-power fields (HPFs) was calculated. The major inclusion criteria were: aged 18 years or older, complete tumour resection with negative margins, Eastern Cooperative Oncology Group performance status score 2 or less, and survival more than 1 month after surgery. Patients who underwent preoperative chemotherapy or radiotherapy were excluded from analysis. Patients with metastatic disease or other malignant tumours were also excluded.

Patients with gastric and small intestinal GISTs were chosen as control groups based on the following parameters: aged 65 years or less, or older than 65 years; tumour size 2.0 cm or smaller, 2.1–5.0 cm, 5.1–10.0 cm, or larger than 10.0 cm; mitotic index 5 or less, 6–10, or more than 10 per 50 HPFs; and adjuvant imatinib therapy (yes, no). None of the patients with duodenal GIST had a rupture of the tumour or neoadjuvant imatinib therapy, and so patients with tumour rupture or neoadjuvant imatinib therapy were excluded from the groups with gastric and small intestinal GISTs.

Tumour locations in the duodenum were defined as follows: location A, tumour located proximal to the duodenal papilla; location B, tumour located within 2 cm of the duodenal papilla; and location C, tumour located distal to the duodenal papilla. The operative procedures for patients with duodenal GIST included pancreaticoduodenectomy (PD) or limited resection with local wedge and segmental resections.

Table 1 Comparison of predefined variables among patients with duodenal, gastric and small intestinal gastrointestinal stromal tumours

	Duodenum (*n* = 71)	Stomach (*n* = 71)	Small intestine (*n* = 70)	*P*†
Age (years)*	51 (27–84)	53 (24–84)	53 (19–86)	0.593‡
Sex ratio (M : F)	39 : 32	35 : 36	36 : 34	0.794
Tumour size (cm)				1.000
0–2.0	3	3	3	
2.1–5.0	48	48	47	
5.1–10.0	16	16	16	
>10.0	4	4	4	
Mitotic index (per 50 HPFs)				0.998
0–5	59	59	59	
6–10	7	7	7	
>10	5	5	4	
Adjuvant imatinib	15	15	15	0.999

*Values are median (range). HPF, high-power field. †χ^2 test, except ‡Kruskal–Wallis test.

Table 2 Clinical characteristics of 71 patients with duodenal gastrointestinal stromal tumours compared by anatomical location

	Location A (*n* = 16)	Location B (*n* = 30)	Location C (*n* = 25)	*P*†
Age (years)*	47 (36–77)	52 (31–84)	52 (27–76)	0.252‡
Sex ratio (M : F)	9 : 7	16 : 14	14 : 11	0.974
Main presentation				0.576
Bleeding	9	15	18	
Abdominal pain	3	4	3	
Other	1	6	2	
No symptoms	3	5	2	
Tumour size (cm)				0.220
0–2.0	1	2	0	
2.1–5.0	14	16	18	
5.1–10.0	1	10	5	
>10.0	0	2	2	
Mitotic index (per 50 HPFs)				0.430
0–5	14	22	23	
6–10	1	5	1	
>10	1	3	1	
Surgical procedures				<0.001
Limited resection	14	11	22	
Pancreaticoduodenectomy	2	19	3	
Adjuvant imatinib	5	4	6	0.333

*Values are median (range). Location A, tumour located proximal to duodenal papilla; location B, tumour located within 2 cm of duodenal papilla; location C, tumour located distal to duodenal papilla. HPF, high-power field. †χ^2 test, except ‡Kruskal–Wallis test.

Table 3 Comparison of patients with duodenal gastrointestinal stromal tumours treated with limited resection or pancreaticoduodenectomy

	Limited resection ($n = 47$)	Pancreaticoduodenectomy ($n = 24$)	P†
Age (years)*	48 (27–77)	59 (36–84)	0.009‡
Sex ratio (M : F)	25 : 22	14 : 10	0.170
Main presentation			0.218
Bleeding	30	12	
Abdominal pain	8	2	
Other	4	5	
No symptoms	5	5	
Duration of surgery (min)*	177 (72–320)	320 (192–505)	<0.001‡
Estimated intraoperative blood loss (ml)*	200 (50–1000)	500 (100–1500)	<0.001‡
Postoperative stay (days)*	13 (7–66)	18 (12–94)	<0.001‡
Complications	5	3	0.814
Anastomotic leakage	1	1	
Wound infection	2	1	
Pulmonary infection	0	1	
Gastroplegia	2	0	
Tumour size (cm)			0.012
0–2.0	3	0	
2.1–5.0	35	13	
5.1–10.0	9	7	
>10.0	0	4	
Mitotic index (per 50 HPFs)			0.028
0–5	43	16	
6–10	2	5	
>10	2	3	
Tumour site			0.001
Location A	14	2	
Location B	11	19	
Location C	22	3	
Adjuvant imatinib	12	3	0.203

*Values are median (range). Location A, tumour located proximal to duodenal papilla; location B, tumour located within 2 cm of duodenal papilla; location C, tumour located distal to duodenal papilla. HPF, high-power field. †χ^2 test, except ‡Mann–Whitney U test.

Follow-up

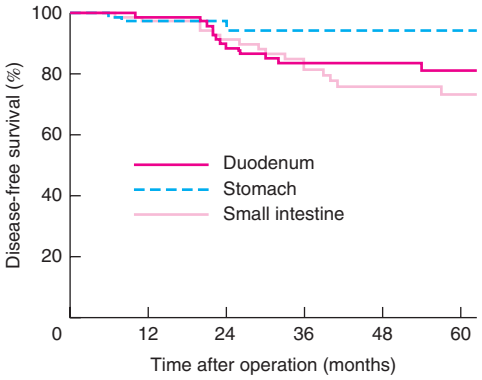
All patients were followed up every 3–6 months for 1–2 years, every 6–12 months for 3–5 years and then annually after 5 years. The follow-up included blood count, imaging (CT or MRI) and biopsy if necessary.

Statistical analysis

Categorical variables were analysed using χ^2 test. Median values were used to describe continuous data, which were analysed by means of Mann–Whitney U test or Kruskal–Wallis test. Disease-free survival (DFS) was defined as the time from operation to GIST recurrence. Patients who were alive and free from recurrence on 1 August 2014, or who had died without GIST recurrence were censored for the analysis of DFS. DFS was estimated by Kaplan–Meier analysis and values were compared using the log rank test. The hazard ratio (HR) and 95 per cent c.i. for DFS between groups was estimated by a Cox proportional hazards regression model, which was stratified by tumour location (stomach, duodenum, small intestine) or surgical procedure (limited resection, PD). Statistical analysis was performed using SPSS® version 19.0 for Windows® (IBM, Armonk, New York, USA) and two-tailed $P < 0.050$ was considered to indicate statistical significance.

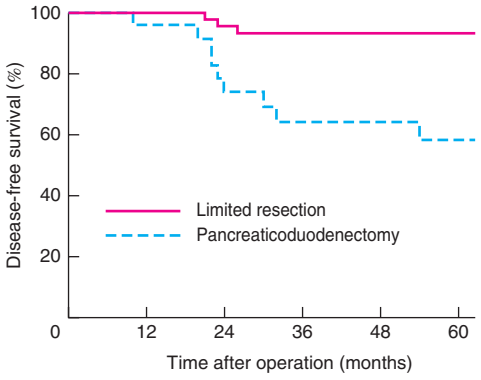
Results

During the study interval, 879 patients were diagnosed with GIST. Of these, 72 did not undergo surgery. Some 71 patients with duodenal GIST were included in the analysis, of median age 51 (range 27–84) years. There were 39 men and 32 women. Seventy-one patients with gastric and 70 with small intestinal GIST comprised the control groups, selected according to the predefined parameters (age, tumour size, mitotic index and adjuvant imatinib treatment) (*Fig 1*, *Table 1*). There were no intergroup differences in median age, sex, tumour size, mitotic index and use of adjuvant imatinib therapy.



No. at risk						
Duodenum	71	70	59	44	35	25
Stomach	71	69	61	54	46	38
Small intestine	70	68	59	46	31	25

Fig. 2 Comparison of disease-free survival for patients with gastric, duodenal and small intestinal gastrointestinal stromal tumours. $P = 0.013$ (log rank test)



No. at risk						
Limited resection	47	47	42	31	24	18
Pancreaticoduodenectomy	24	23	17	13	11	7

Fig. 3 Comparison of disease-free survival for patients with duodenal gastrointestinal stromal tumours according to surgical procedure. $P = 0.001$ (log rank test)

Of the 71 patients with duodenal GIST, tumours were located proximal to the duodenal papilla (location A) in 16 patients (23 per cent), within 2 cm of the duodenal papilla (location B) in 30 (42 per cent), and distal to the duodenal papilla (location C) in 25 patients (35 per cent). The most common symptom at presentation was gastrointestinal bleeding, followed by abdominal pain. There were ten asymptomatic patients. The median size of the duodenal GISTs was 4.0 (range 2.0–15.0) cm. The clinicopathological characteristics of patients with duodenal GISTs based on the anatomical location of the tumour are shown in *Table 2*.

Some 47 patients (66 per cent) with duodenal GIST underwent limited resection and 24 (34 per cent) had PD. Patients who underwent PD were older, had larger tumours and a higher mitotic index than those who had limited resection (*Table 3*). Patients who underwent PD more often had tumours located within 2 cm of the duodenal papilla, a longer duration of surgery, greater estimated blood loss, and longer hospital stay. However, there was no difference in postoperative complications between PD and limited resection (*Table 3*).

Survival analysis

No patient was lost to follow-up. The median follow-up time of patients with duodenal, gastric and small intestinal GISTs was 51 (range 10–156), 61 (6–173) and 46 (7–133) months respectively ($P = 0.109$). At the end of the study, 53 patients with duodenal GIST were alive without disease, ten were alive with tumour recurrence, four patients had died from recurrent disease, and four from other causes. Of patients with small intestinal GIST, 52 were alive without disease, 14 were alive with tumour recurrence and four had died from recurrent disease. Among patients with gastric GIST, 65 patients were alive without disease, two were alive with tumour recurrence, two patients had died from recurrent disease and two from other causes. The liver was the most frequent site of distant metastasis (20 patients).

Patients with duodenal GIST had a shorter DFS than those with gastric GIST (3-year DFS 84 *versus* 94 per cent; HR 3.67, 95 per cent c.i. 1.21 to 11.16; $P = 0.014$) and a similar DFS to patients with small intestinal GIST (3-year DFS 84 *versus* 81 per cent; HR 0.75, 0.37 to 1.51; $P = 0.491$) (*Fig. 2*).

Three-year DFS rates for patients with duodenal GISTs at the three locations were 87, 82 and 79 per cent for those with tumour located proximal to the duodenal papilla, within 2 cm of the duodenal papilla, and distal to the duodenal papilla respectively ($P = 0.566$).

Median follow-up of patients with duodenal GIST who underwent limited resection and PD was 53 (18–144) and 47 (10–156) months respectively ($P = 0.868$). Three-year DFS rates were 93 and 64 per cent respectively (HR 0.18, 0.06 to 0.59; $P = 0.001$) (*Fig. 3*).

Discussion

The present cohort study analysed 71 patients who underwent radical surgery for localized duodenal GIST, and compared DFS with that in patients with gastric and small intestinal GISTs. DFS for those with duodenal GIST was

worse than that of patients with gastric GIST, but similar to that among patients with small intestinal GIST.

The curative treatment for GIST comprises surgical resection with sufficient surgical margins and without intraoperative tumour rupture[12]. For gastric and small intestinal GISTs, segmental or wedge resection is sufficient to obtain negative margins[13–15]. Owing to the anatomy of the duodenum, the optimal surgical procedures for duodenal GISTs are unknown. One multi-institutional study[8] suggested that PD was associated with a longer hospital stay, higher risk of perioperative complications and a similar recurrence-free survival compared with limited resection. Some other studies[10,16–18] also showed that disease recurrence was not correlated with the surgical procedure and that the postoperative mortality rate was very low. In the present study, PD was associated with a longer duration of operation, increased operative blood loss and longer postoperative hospital stay. However, the postoperative complication rate was similar to that for limited resection of duodenal GISTs. Patients with duodenal GIST who underwent PD had a worse 3-year DFS than those who had a limited resection, but the PD group had larger tumours and a higher mitotic index. In agreement, a meta-analysis[19] showed that the outcome in patients with duodenal GIST was more likely to be dependent on tumour biology than the type of surgical procedure.

Tumour location is one of the key risk factors for recurrent disease after radical surgery for GISTs[20,21]. However, the modified National Institutes of Health risk classification system distinguishes only gastric from non-gastric tumours, and the prognostic characteristics of duodenal GISTs are not discussed[2]. Although the European Society of Medical Oncology clinical practice guidelines[22] mention duodenal GISTs as an entity, the prognostic features are not described in detail. Most studies reporting on duodenal GISTs have been focused on the optimal surgical procedure[8,10,11,16,23], and only one[11] suggested that the DFS of patients with duodenal GISTs was poorer than that of patients with non-duodenal tumours. However, only seven patients with duodenal GIST were included, possibly biasing the results.

The gain-of-function mutations of *KIT* and platelet-derived growth factor receptor α (*PDGFRA*) are considered important factors in the pathogenesis of GISTs. Approximately 85–90 per cent of GISTs have a mutation in *KIT* or *PDGFRA*[1]. Although the gene mutation is associated with the response to target therapy in patients with advanced GISTs, the mutational status does not correlate strongly with the biological potential of these tumours[24]. However, it is acknowledged that one of the limitations of the present study was that the gene mutation was not analysed and so the mutational characteristics of the duodenal GISTs were not known. Based on the results of the present investigation, it may be concluded that the prognosis of duodenal GISTs is similar to that of small intestinal GISTs, but worse than that of gastric GISTs. The choice of surgical procedure should be determined by tumour size and involvement of the duodenal papilla.

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