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ORIGINAL ARTICLE

Gastrointestinal stromal tumors of the duodenum: Surgical management and survival results

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Abstract

AIM: To provide long-term survival results of operable duodenal gastrointestinal stromal tumors (DGISTs) in a tertiary center in China.

METHODS: In this retrospective study, the pathological data of 28 patients with DGISTs who had been treated surgically at the Second Department of General Surgery, Sir Run Run Shaw Hospital (SRRSH) from June 1998 to December 2006 were reviewed. All pathological slides were examined by a single pathologist to confirm the diagnosis. In patients whose diagnosis was not confirmed by immunohistochemistry at the time of resection, representative paraffin blocks were reassembled, and sections were studied using antibodies against CD117 (c-kit), CD34, smooth muscle actin (SMA), vimentin, S-100, actin (HHF35), and desmin. Operative procedures were classified as wedge resection (WR, local resection with pure closure, without duodenal transection or anastomosis), segmental resection [SR, duodenal transection with Roux-Y or Billroth Ⅱ gastrojejunostomy (G-J), end-to-end duodenoduodenostomy (D-D), end-to-end or end-to-side duodenojejunostomy (D-J)], and pancreaticoduodenectomy (PD, Whipple operation with pancreatojejunostomy). R0 resection was pursued in all cases, and at least R1 resection was achieved. Regional lymphadenectomy was not performed. Clinical manifestations, surgery, medical treatment and follow-up data were retrospectively analyzed. Related studies in the literature were reviewed.

RESULTS: There were 12 males and 16 females patients, with a median age of 53 years (20-76 years). Their major complaints were "gastrointestinal bleeding" (57.2%) and "nonspecific discomfort" (32.1%). About 14.3%, 60.7%, 17.9%, and 7.1% of the tumors originated in the first to fourth portion, respectively, with a median size of 5.8 cm (1.6-20 cm). Treatment was by WR in 5 cases (17.9%), SR in 13 cases (46.4%), and by PD in 10 cases (35.7%). The morbidity and mortality rates were 35.7% and 3.6%, respectively. The median post-operative stay was 14.5 d (5-47 d). During a follow-up of 61 (23-164) mo, the 2-year and 5-year relapse-free survival was 83.3% and 50%, respectively. Eighty-four related articles were reviewed.

CONCLUSION: Surgeons can choose to perform limited resection or PD for operable DGISTs if clear surgical margins are achieved. Comprehensive treatment is necessary.

Key words: Gastrointestinal stromal tumors; Duodenum; Limited resection; Pancreaticoduodenectomy; Survival

Core tip: Duodenal gastrointestinal stromal tumors (DGISTs) represent a subset of small bowel gastrointestinal stromal tumors that require special consideration given their clinical manifestations, particularly difficult surgical

decisions and poor prognosis. Surgeons can choose to perform limited resection or pancreaticoduodenectomy for operable DGISTs according to the tumor size, location, proximity to the duodenal papilla, and their technical feasibility, and both these two approaches lead to a similar oncological prognosis if clear surgical margins are achieved. The prognosis of a DGIST is poor, thus comprehensive treatment is necessary.

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract, although the annual incidence rates reported worldwide are less than 20 per million, and only about 5000 new cases are diagnosed annually in the United States[1-3]. GIST is a primary gastrointestinal disease that can arise anywhere along the digestive tract in adults. The stomach (60%) and jejunoileum (30%) are the most common primary sites, and only a small number of cases have been reported in the colorectum (< 5%), esophagus and appendix (< 1%)[4,5]. In addition, duodenal lesions represent approximately 5% of GISTs.

All GISTs harbor some malignant potential, although only 10%-30% are clinically malignant. In the past decade following Fletcher's report[6], primary GISTs are not classified as "benign" or "malignant", but are stratified by the probability of recurrence after complete resection into very low, low, intermediate, and high risk on the basis of their size and mitotic rate. Subsequently, Miettinen *et al*[7] suggested that the anatomical origin may be another independent factor for risk stratification, indicating that DGISTs share maximal risks with rectal GISTs compared with those of the stomach and jejunoileum.

Although DGISTs are relatively rare, they account for nearly 30% of all primary tumors of the duodenum, and the vast majority of patients present with gastrointestinal bleeding[4]. With regard to treatment, DGISTs often pose difficult surgical problems, due to the complex anatomical relationship around the duodenum, *i.e.*, unlike the stomach or other intestinal segments where complete excision with wide margins are relatively straightforward procedures, wide resection of DGISTs will almost always entail a pancreaticoduodenectomy (PD), which is massively invasive and technically challenging[8,9].

In recent years, a limited resection (LR) of DGISTs demonstrated a comparable effect to PD in selected cases[10]. However, the optimal surgical approach (LR or PD) for DGISTs is largely unknown, as all the available evidence has been derived from small retrospective series[11]. In addition, scholars have gradually recognized the complexities of DGISTs, and these tumors have been classified separately from other small intestine GISTs into an independent category[12]. Also, a number of papers on DGISTs have been released[8-10,13-16]. Nevertheless, more experience with long-term oncological observations is required, especially for surgeons. This article aims to provide a single center experience of operable DGIST cases in China, and an update on the clinical management of DGISTs.

MATERIALS AND METHODS

Data collection

In this retrospective study, the pathological data of 28 patients with DGISTs who had been treated surgically at the Second Department of General Surgery, Sir Run Run Shaw Hospital (SRRSH) from June 1998 to December 2006 were reviewed. All data were collected once a definite diagnosis had been made. The author (Xiu-Jun Cai) managed his first case of DGIST as an independent attending and maintained his interests. During this review period, the patients of five attending surgeons in our department were included, and the priority of these data was approved by the patients while in hospital and by the surgeons. In addition, the patients were confirmed as cases by an inverse retrieve from the inpatient system of our hospital. This study was approved by the Institutional Review Board of SRRS.

All pathological slides were reviewed by a single pathologist to confirm the diagnosis. In patients whose diagnosis was not confirmed by immunohistochemistry at the time of resection, representative paraffin blocks were reassembled, and sections were studied using antibodies against CD117 (c-kit), CD34, smooth muscle actin (SMA), vimentin, S-100, actin (HHF35), and desmin. Tumors were classified as GISTs only if tumor cells were characterized by the typical morphology with positive staining for CD117 and/or CD34. Patient age, gender, presentation, medical history, laboratory and radiology examinations, surgery, medical treatment and follow-up data were obtained from patient records, including operative notes, pathology reports, and outpatient data. None of the patients were lost to follow-up due to good communication between the authors, patients and their primary care providers.

Operative procedures were classified as wedge resection (WR, local resection with pure closure, without duodenal transection or anastomosis), segmental resection [SR, duodenal transection with Roux-Y or Billroth Ⅱ gastrojejunostomy (G-J), end-to-end duodenoduodenostomy (D-D), end-to-end or end-to-side duodenojejunostomy (D-J)], and pancreaticoduodenectomy (PD, Whipple operation with pancreatojejunostomy). R0 resection was pursued in all cases, and at least R1 resection was achieved. Regional lymphadenectomy was not performed.

Statistical analysis

The overall survival (OS), disease-related survival (DRS), and relapse-free survival (RFS) were conventionally de-

Table 1 Summary of patient preoperative information

No.	Age (yr)	Sex	Chief complaint	Comorbidity	Past history	Hb	US	CT	MRI	GI	ES	EUS	DSA	Biopsy	Preoperative diagnosis
1	28	F	Melena	Cholecystolithiasis		46	0	1	N	1	1	N	N	1/ES	Duodenal GIST(Biopsy)
2	48	F	Incidentally found		Sub gastrectomy	79	0	1	N	1	N	N	N	N	Duodenal tumor
3	60	M	Melena			104	1	1	N	1	0	N	N	0/CT	Duodenal GIST (CT)
4	70	M	Pain			128	0	1	1	1	1	1	N	1/EUS	Duodenal GIST(Biopsy)
5	71	M	Incidentally found			130	0	0	N	N	0	N	N	N	Abdominal tumor
6	76	F	Melena	Cholecystolithiasis	Appendectomy, stripping of right great saphenous vein	65	0	1	N	N	1	1	N	0/EUS	Duodenal GIST (EUS)
7	42	F	Melena			50	0	1	N	N	N	N	N	N	Duodenal tumor
8	74	M	Melena			81	1	1	N	N	1	N	N	0/ES	Duodenal tumor
9	53	F	Melena			75	1	1	N	N	1	N	N	1/ES	Duodenal GIST(Biopsy)
10	47	F	Melena		Schistosomiasis	99	0	1	N	1	0	N	N	N	Duodenal tumor
11	55	F	Melena			61	1	1	N	1	0	N	N	N	Duodenal tumor
12	51	M	Melena			66	1	1	N	1	1	N	N	1/ES	Duodenal GIST (Biopsy)
13	50	M	Hematemesis	Polyp of gallbladder (1.9 cm)	Essential hypertension	52	0	0	N	N	1	N	N	0/ES	Duodenal tumor
14	69	F	Pain			87	0	0	N	N	N	N	N	N	Retroperitoneal tumor
15	65	M	Melena			65	1	1	N	N	1	1	N	0/EUS	Duodenal GIST (EUS)
16	63	M	Acute abdomen			148	1	N	N	N	N	N	N	N	Acute abdomen
17	44	F	Hematemesis			56	0	1	N	1	1	N	N	0/ES	Duodenal tumor
18	57	F	Discomfort		Cholecystectomy, left nephrectomy	126	1	1	N	N	N	N	N	N	Duodenal GIST (CT)
19	20	F	Melena			61	0	1	N	N	1	N	N	0/ES	Duodenal tumor
20	52	M	Pain			118	0	0	N	N	N	N	N	N	Abdominal tumor
21	53	F	Pain			118	0	0	N	1	N	N	N	N	Abdominal tumor
22	71	F	Early satiety			131	0	1	1	1	0	1	N	0/EUS	Retroperitoneal tumor
23	53	M	Early satiety		Resection of gluteal hemangioma	156	0	1	1	N	1	1	N	0/EUS	Duodenal GIST (EUS)
24	50	F	Melena	Cholecystolithiasis	Right radical mastectomy, hysteromyomectomy	91	0	1	N	N	1	N	N	0/ES	Duodenal tumor
25	46	F	Pain			93	0	0	N	N	N	N	N	N	Abdominal tumor
26	55	M	Melena		Appendectomy	69	0	0	N	N	1	N	N	0/ES	Tumor of pancreas head
27	51	M	Incidentally Found			155	0	1	1	0	0	N	N	N	Duodenal tumor
28	46	F	Melena		Radical cystectomy	87	0	1	N	N	N	N	1	N	Duodenal GIST (CT)

0: Negative; 1: Positive; N: Not evaluated; Hb: The initial hemoglobin (g/L) before liquid resuscitation; M: Male; F: Female; CT: Computed tomography; US: Ultrasonography; GIST: Gastrointestinal stromal tumor; MRI: Magnetic resonance imaging; GI: Gastrointestinal; ES: Gastroduodenoscopy; EUS: Endoscopic ultrasonography; DSA: Digital subtraction angiography.

fined. Survival was determined using the Kaplan-Meier method, and Cox regression was employed for multivariate analysis. A Pearson's, Spearman Rank, or Kendall's tau-b correlation was evaluated between variables if appropriate, and differences were analyzed using the Mann-Whitney *U* or unpaired Student's *t* test. All tests were two-sided and *P* values less than 0.05 were considered statistically significant. Software including Prism v5.04 (GraphPad Software Inc., La Jolla, CA, United States), SAS 9.2 for Windows (SAS Institute Inc., Cary, NC, United States), and the Thomson Data Analyzer (Thomson Reuters Corp., New York, NY, United States) were used for statistics and literature reviews.

RESULTS

Patients

There were 12 males and 16 females patients, aged 54.3 ± 2.4 years (mean ± SEM if Gaussian distributed, median: 53, range: 20-76 years), and male patients (50.3 ± 3.6 years) were younger than female patients (59.6 ± 2.5 years, $P = 0.0595$). The chief complaint (lead symptom) was summarized as "gastrointestinal bleeding" (57.2%), "nonspecific discomfort" (32.1%), and "incidentally

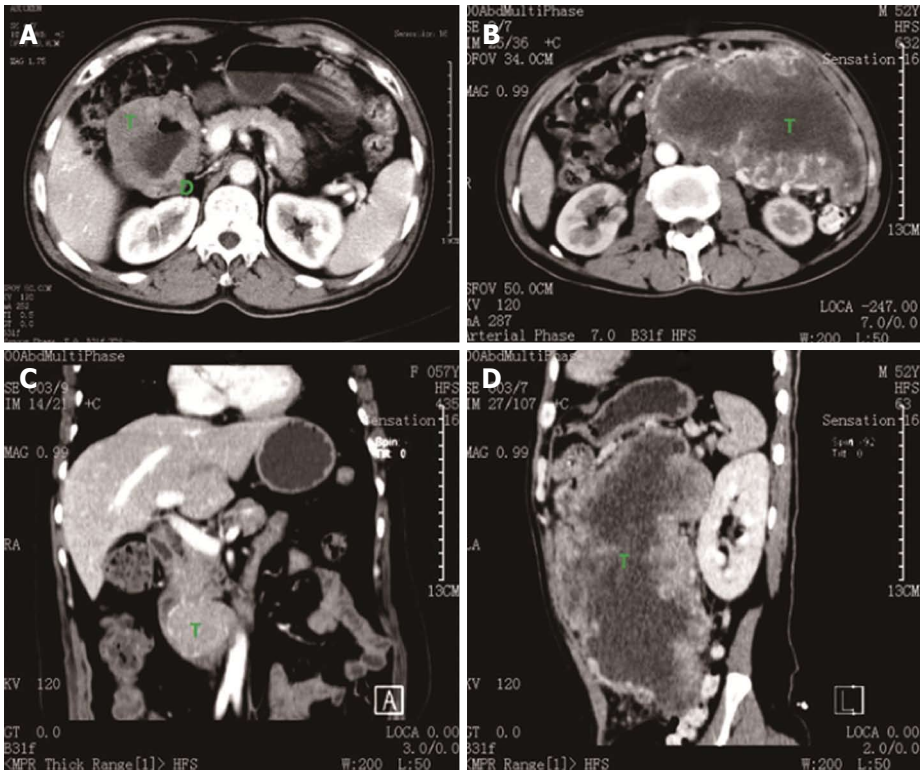

Figure 1 Respective computed tomography images. A: For case 28; B, D: For case 20; C: For case 18. (T: Tumor; D: Duodenum).

found" (10.7%); the symptoms were not correlated with tumor size or site ($P > 0.05$). Four patients (14.3%) had comorbid gallbladder diseases. Seven patients (25.0%) had undergone one or two previous operations, two of which were for malignancy, and another two patients had essential hypertension or schistosomiasis. None of the patients had diabetes or neurofibromatosis (Table 1).

The hemoglobin in all patients was 92.8 ± 6.3 g/L, which was highly correlated with the symptoms: the hemoglobin in patients with "gastrointestinal bleeding" was 70.5 ± 4.4 g/L, whereas that of "non-gastrointestinal bleeding" patients ($n = 12$) was 122.4 ± 7.3 g/L ($P < 0.0001$).

Each patient underwent abdominal ultrasonography (US), with 100% clinical availability, and only eight patients had positive results for DGISTs or duodenal tumors (vague reports of abdominal tumors were defined as negative), giving a sensitivity of 28.6% (8/28). The clinical availability of computed tomography (CT), magnetic resonance imaging (MRI), upper gastrointestinal barium examination (GI), gastroduodenoscopy (ES), endoscopic ultrasonography (EUS), digital subtraction angiography (DSA), and preoperative biopsy guided by CT, ES or EUS were 96.4%, 14.3%, 39.3%, 67.9%, 17.9%, 3.6%, and 53.6%, respectively. The sensitivities in sequence were 74.1%, 100%, 90.9%, 68.4%, 100%, 100%, and 26.7%. Collectively, twenty patients (71.4%) were diagnosed with duodenal tumors preoperatively, including ten (35.7%) with DGISTs; four patients (14.3%) were diagnosed with abdominal tumors of uncertain origin; minor diagnoses were retroperitoneal tumors (7.1%), tumors of the pancreas head (3.6%) and acute abdomen (3.6%). Representative images are shown in Figures 1-3.

Surgery

All surgical techniques were performed under general anesthesia. Intraoperatively, all tumors were single, solid, encapsulated but fragile, part of which had an irregular thick-walled necrotic core or multiple necrotic loculi. Four tumors originated in the bulb (D1, 14.3%), seventeen in the descending section (D2, 60.7%), five in the horizontal section (D3, 17.9%), and two in the ascending section (D4, 7.1%). The tumor size varied from 1.6 cm to 20 cm with a median of 5.8 cm (95%CI: 5.3-8.6), and was independent of the tumor site ($P > 0.05$) (Table 2).

Five patients (17.9%) underwent a WR, 13 (46.4%) a SR, and 10 (35.7%) a PD. When SR patients were subdivided, four G-J (30.8%), four D-D (30.8%), and five D-J (38.4%) reconstructions were carried out. In addition, six concomitant operations were performed, *i.e.*, four cholecystectomies for gallbladder comorbidities and two intestinal resections for iatrogenic vessel injuries in the mesocolon transversum or the root of the small bowel mesentery.

Perioperative blood transfusions were common (78.6%) in this cohort, and eleven patients (39.3%) required intensive care as a postoperative transition, staying for 1-5 d (median: 2 d; 95%CI: 1.2-3.4 d). Eight (28.6%) major early complications occurred, including leakage of the choledochoenterostomy/duodenojejunostomy (7.1%) and delayed gastric emptying (DGE, 21.4%). Consequently, due to the intraoperative and early postop-

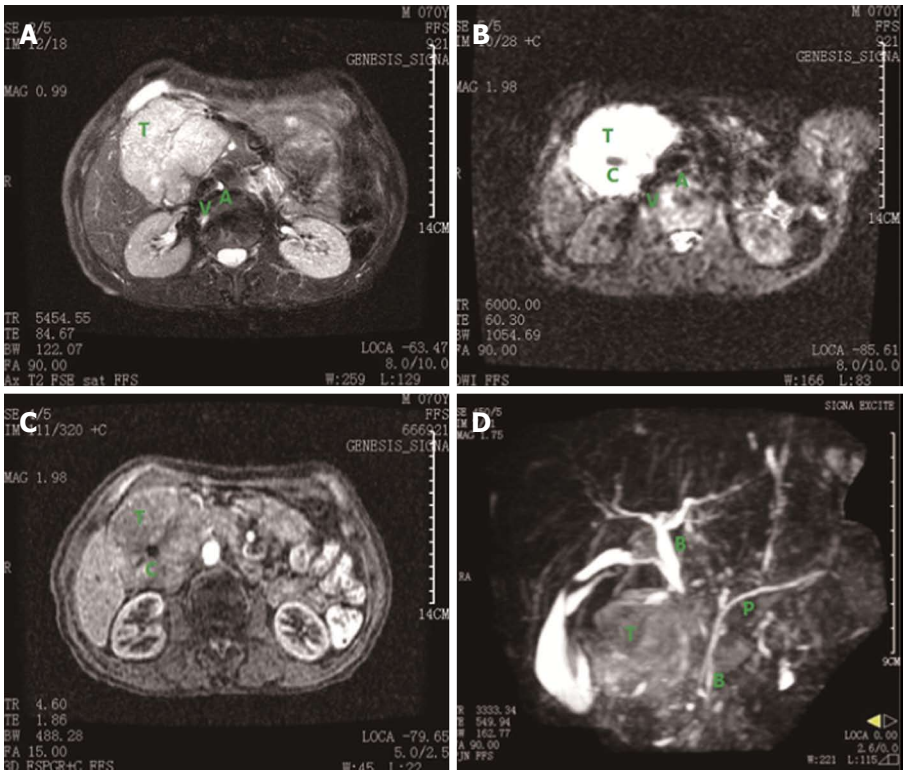

Figure 2 Respective magnetic resonance imaging images. A-C: For case 4; D: For case 22. T: Tumor; C: Necrotic core; A: Abdominal aorta; V: Inferior vena cava; B: Common bile duct; P: Main pancreatic duct.

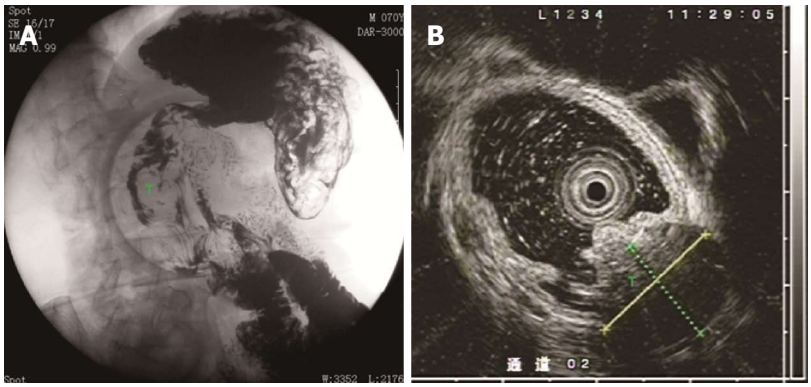

Figure 3 Respective gastrointestinal and endoscopic ultrasonography images. A: Gastrointestinal for case 4; B: Endoscopic ultrasonography for case 23. T: Tumor.

erative morbidities, the following three reoperations were performed: a total enterectomy for the mesenteric root injury; an abdominal irrigation and drainage for the choledochoenterostomy failure; and a gastrojejunostomy for DGE.

The overall post-operative stay was 5-47 d (median: 14.5 d; 95%CI: 14.2-24.1 d), and was closely correlated with the surgical approaches; the intervals from the WR, PD, and SR to discharge were 10.6 ± 1.3, 14.6 ± 2.5 (P > 0.05 for WR), and 25.9 ± 4.1 d (P = 0.0412 for PD, P = 0.0393 for WR), respectively.

Pathology and risk classifications

The positive rates of the four principal immunohistochemistry markers, CD117, CD34, SMA, and S-100 were 96.4%, 64.3%, 60.7%, and 42.9%, respectively. Moreover, another three markers were introduced in certain patients: vimentin (13/13, total/positive), actin (18/8), and desmin (9/0). According to Fletcher's criterion 6, there were two patients (7.1%) with very low risk, nine patients (32.1%) with low risk, six patients (21.4%) with intermediate risk, and 11 patients (39.3%) with high risk, however, by applying Miettinen's criterion 7, 11 patients (39.3%) showed low risk and the other 17 (60.7%) possessed high risk (Table 3).

Survival analysis

The median OS was 64.5 mo, including three elderly pa-

Table 2 Summary of surgery and perioperative information

No.	Surgery	Site	Size (L)	Size (W)	Size (H)	Combined operation	Transfusion[1]	ICU stay	Major complications	Reoperation (post-operative time)	POS
1	SR (G-J)	D2	4	3.5	3	Cholecystectomy	Y	0		Hepatectomy for liver metastasis (103 mo)	22
2	WR	D2	4	3	3		Y	2			12
3	PD	D2	10	9	7.5		Y	0			17
4	PD	D2	11	9	7.5		Y	1	Leakage of choledochoenterostomy	Abdominal irrigation and drainage (8 d)	14
5	SR (D-D)	D3	9	6	6	Partial colectomy	N	1	vessel injury in the mesocolon transversum		11
6	SR (D-J)	D2	4	4	4	Cholecystectomy	Y	5	Anastomotic leakage		36
7	PD	D2	6	5.5	5		Y	0			6
8	WR	D1	3.5	2.5	2.5		Y	1			8
9	SR (D-D)	D1	2.5	1.5	1.5		Y	0			5
10	PD	D2	4	3	2.5		Y	0			11
11	SR (G-J)	D4	8	5.5	3		Y	0			10
12	PD	D2	12	10	8.5		Y	0			10
13	WR	D2	3.5	3.2	3	Cholecystectomy	Y	0			15
14	PD	D3	13	11	11	Major enterectomy	Y	5	Injury of superior mesenteric vessels	Total enterectomy (1 d)	5
15	SR (D-J)	D3	5	4	3.5		Y	0	DGE	Gastrojejunostomy (21 d)	32
16	PD	D2	6.5	5	4		N	4			24
17	PD	D2	9.5	8.5	8		Y	1		Gastroscopic injection of sclerosing agents (21 mo)	28
18	SR (D-J)	D3	5.5	5	4		N	0	DGE		46
19	SR (D-D)	D2	2	2	2		Y	0	DGE		47
20	SR (D-J)	D4	20	18	8.5		Y	2	DGE		26
21	WR	D2	15	12	6.5		Y	0			10
22	SR (G-J)	D2	5.5	5	2.5		Y	2			42
23	WR	D1	1.6	1.3	1.2		N	0			8
24	SR (G-J)	D1	4.5	3	2	Cholecystectomy	N	0	DGE		17
25	SR (D-D)	D2	7.6	5	4.6		Y	0			8
26	PD	D2	6	4	4		Y	0		Adhesiolysis for ileus (43 mo)	9
27	SR (D-J)	D3	5.5	4.5	3.5		N	1	DGE		35
28	PD	D2	6	5	4		Y	0			22

[1]Perioperative transfusion, including the transfusion before surgery; Size (L/W/H): tumor size (length, width and height in centimeters) measured after fixation by 10% neutral buffered formalin; DGE: Delayed gastric empty; POS: Post-operative stay till discharge; ICU: Intensive care unit; PD: Pancreaticoduodenectomy; WR: Wedge resection; SR: Segmental resection.

tients who died of lung cancer, pneumonia, and stroke, respectively. The median RFS and DRS in the whole patient group and subgroups are listed in Table 4, and the results of multivariate analysis are shown in Table 5. Moreover, a nomogram developed by Gold *et al*[17] to predict the probability of 2- and 5-year RFS was used, and the predicted values were compared to the actual values (Table 4 and Figure 4).

DISCUSSION

GISTs are a family of tumors thought to arise from the interstitial cells of Cajal in the gastrointestinal tract. Recently, the putative stem and progenitor cells for GISTs have been identified[1]. Most GISTs have oncogenic mutations in either KIT or platelet-derived growth factor receptor-α (PDGFRA), and there is substantial evidence that these mutations are pathogenetic for the initiation of GISTs. Histopathologically, GISTs are usually well circumscribed and surrounded by a pseudocapsule, ranging in size from millimeters to 40 cm, with a median size between 5 cm and 8 cm, while large GISTs often show cystic degeneration or central necrosis[18]. Microscopically, GISTs are defined as morphologically spindle cell, epithelioid, or occasionally pleomorphic, mesenchymal tumors, usually (approximately 95%) express the KIT protein and often (up to 90%) harbor mutations of a gene that encodes for a type Ⅲ receptor tyrosine kinase (either KIT or PDGFRA)[19].

Surgery is the mainstay of treatment for localized, resectable GISTs. The tumor should be removed *en-bloc* with its pseudocapsule to yield an adequate resection margin. The optimal width of the tumor-free margin has not been defined, and it is unclear if re-resection is beneficial for positive microscopic surgical margins (R1), especially as the free radial margin is the one that is positive in most instances and there is no additional tissue to be removed[20]. Lymphadenectomy is not warranted unless there is gross nodal involvement. In cases of unresectable or marginally resectable disease, adjuvant tyrosine kinase inhibitor (TKI) therapy should be considered. Following surgical resection, GISTs often recur locally, spread diffusely throughout the serosal surfaces of the abdomen and/or metastasize to the liver. Advanced disease is associated with

Table 3 Summary of pathological data and risk classifications

No.	CD117	CD34	SMA	S100	Vimentin	Actin	Desmin	Mitotic rate/50HPF	Fletcher's risk	Miettinen's risk	UICC TNM	Gold's point	RFS	DRS	Status of death	Glivec
1	1	0	1	0	N	0	0	0-1	L	L	UICC Ⅰ	64	103	164	0	0
2	1	1	1	0	1	0	N	0-1	L	L	UICC Ⅰ	64	RF	146	0	0
3	1	0	1	0	1	0	N	5-8	H	H	UICC ⅢB	173	54	61	1	0
4	1	1	1	1	1	0	N	> 10	H	H	UICC ⅢB	175	26	35	1	0
5	1	1	1	0	1	N	N	1-2	I	H	UICC Ⅱ	89	RF	23	1 (lung cancer)	0
6	1	1	0	1	1	1	0	2-3	L	L	UICC Ⅰ	64	RF	25	1 (pneumonia)	0
7	1	0	1	1	1	N	0	6-8	H	H	UICC ⅢB	155	64	73	1	0
8	0	1	0	0	1	1	N	0-1	L	L	UICC Ⅰ	61	RF	61	1 (stroke)	0
9	1	1	1	1	N	0	N	3-4	L	L	UICC Ⅰ	55	RF	116	0	0
10	1	0	1	1	N	0	N	0-1	L	L	UICC Ⅰ	64	101	111	1	0
11	1	1	0	1	N	0	N	5-6	H	H	UICC ⅢB	164	29	55	1	0
12	1	1	0	1	1	N	N	> 10	H	H	UICC ⅢB	178	15	23	1	0
13	1	1	1	0	1	0	N	0-1	L	L	UICC Ⅰ	61	RF	102	0	0
14	1	1	1	0	1	1	N	> 10	H	H	UICC ⅢB	180	NN	NN	1	0
15	1	1	1	0	N	0	N	1-4	L	L	UICC Ⅰ	70	62	68	1	0
16	1	1	0	1	1	0	N	5-8	H	H	UICC ⅢB	156	37	49	1	0
17	1	1	0	1	N	0	N	> 10	H	H	UICC ⅢB	172	21	33	1	0
18	1	1	0	0	N	0	N	2-3	I	H	UICC Ⅱ	71	53	57	1	0
19	1	0	1	0	N	N	0	0-1	VL	L	UICC Ⅰ	51	RF	86	0	0
20	1	1	0	0	N	N	0	> 10	H	H	UICC ⅢB	190	22	33	1	0
21	1	0	1	0	N	0	N	5-8	H	H	UICC ⅢB	184	29	40	1	0
22	1	1	0	0	N	0	0	1-2	I	H	UICC Ⅱ	71	47	59	1	0
23	1	0	1	1	N	N	0	0-1	VL	L	UICC Ⅰ	50	RF	75	0	0
24	1	0	1	0	N	N	0	3-5	L	L	UICC Ⅰ	67	69	73	0	0
25	1	0	1	0	N	0	N	0-1	I	H	UICC Ⅱ	81	51	71	0	1 (20 mo/PR)
26	1	0	0	1	1	N	N	5-7	H	H	UICC ⅢB	155	59	70	0	0
27	1	1	0	0	N	N	0	0-1	I	H	UICC Ⅱ	71	RF	63	0	1 (24 mo)
28	1	1	1	1	1	N	N	0-1	I	H	UICC Ⅱ	73	RF	61	0	0

0: Negative; 1: Positive; N: Not evaluated; HPF: High-power fields; VL: Very low; L: Low; I: Intermediate; H: High; RF: Relapse free; NN: Not necessary; PR: Partial remission; UICC: Union for International Cancer Control; TNM: Tumor, nodes, metastasis; RFS: Relapse-free survival; DRS: Disease-related survival; SMA: Smooth muscle actin.

Table 4 Results of survival analysis

	n	Median RFS (mo)	95%CI of HR	Median DRS (mo)	95%CI of HR	Median Gold's point (range)	Predicted 2-year RFS probability	Actual 2-year RFS rate	Predicted 5-year RFS probability	Actual 5-year RFS rate
Total	25	60.5	-	73	-	73 (50-190)	83%	83.30%	70%	50%
Fletcher's risk										
Very low/low	9	103[c,e]	1.564-158.6	Undefined	0.6931-149.1	64 (50-70)[d,f]	86%	100%	75%	100%
Intermediate	5	53	0.7675-7.845	Undefined	0.9385-10.78	71 (71-81)[b,f]	84%	100%	70%	40%
High	11	29[b,d]	4.812-68.51	40[b,d]	3.449-44.94	173 (155-190)[b,d]	< 10%	70%	< 10%	< 10%
Miettinen's risk										
Low	9	103[f]	2.882-26.67	Undefined	2.224-21.94	64 (50-70)[f]	86%	100%	75%	100%
High	16	47[b]	-	56	-	160 (71-190)[b]	< 10%	80%	< 10%	20%

[a]$P < 0.05$, [b]$P < 0.01$ *vs* Very low/Low; [c]$P < 0.05$, [d]$P < 0.01$ *vs* Intermediate; [e]$P < 0.05$, [f]$P < 0.01$ *vs* High; DRS: Disease-related survival; RFS: Relapse-free survival.

metastases to distant sites, including the lung and bone. Prior to the advent of TKI therapeutics, the prognosis for advanced GISTs was poor owing to their inherent resistance to both chemotherapy and radiation therapy[1].

DGISTs share the above-mentioned factors, but have individuality. DGISTS are unique entities, not only due to their anatomical location, but also their clinical manifestations, particularly difficult surgical decisions and poor prognosis. This is why DGISTs have attracted the authors' interests as well as the attention of the French Sarcoma Group (GSF-GETO). In the 47th Annual Meeting of the American Society of Clinical Oncology held in Chicago in June 2011, Duffaud *et al*[12] at GSF-GETO12 retrospectively analyzed 66 resectable DGIST patients with a median tumor size of 6 cm (1.5-31 cm), 29 of whom underwent WR, 23 SR, and 14 PD. During a median follow-up of 36 (1-168) mo, their 4-year OS and RFS rates were 89% and 58%, respectively. Duffaud's report is the largest cohort study in the surgical rather than pathological field, thus has current significance.

The clinical presentations of DGISTs are highly variable according to their size and the existence of mucosal

Table 5 Results of Cox multivariate analysis

Variable	RFS *P* value	DRS *P* value
Mitotic rate/50HPF	0.0000	0.0000
Gold's point	0.0000	0.0000
Fletcher's risk	0.0000	0.0000
Miettinen's risk	0.0001	0.0009
Size > 5 cm	0.0001	0.0009
Preoperative diagnoses as duodenal tumors or DGISTs	0.0048	> 0.05
Age > 60 yr	0.0428	0.0059
LR or PD	> 0.05	0.0346
ICU stay	> 0.05	0.0054

HPF: High-power fields; DRS: Disease-related survival; RFS: Relapse-free survival; ICU: Intensive care unit; LR: Limited resection; PD: Pancreaticod uodenectomy.

ulceration, but not tumor site[8,9]. The most common clinical presentation is reported to be gastrointestinal bleeding or abdominal pain. Interestingly in this series, the authors found that large tumors (> 5 cm) caused less gastrointestinal bleeding ($P < 0.05$); this can be rationalized by the different phenotype of DGISTs, "submucoscal/ulcerous type" or "serosal/massive type", most small tumors were the former type and the majority of large tumors were the latter type[21]. More than 60% of DGISTs are located in the descending section, however, the reason for this is unclear.

Preoperatively, a variety of alternative examinations can be adopted, among which CT and MRI seem to be the best imaging modalities for assessment of the primary lesion and detection of metastases, whereas EUS is the optimum non-invasive tool for the clinical diagnosis[22,23]. Furthermore, EUS-guided biopsy has been established for the pathological diagnosis, although the sensitivity of DGIST samples obtained by EUS-guided biopsy is unsatisfactory compared with stomach GISTs (37.5% *vs* 84.4%)[24]. Recently, CT- or US-guided biopsy has been abandoned for resectable GISTs, due to the risk of pseudocapsule rupture and tumor spillage in the peritoneal cavity[4]. By integrating all the diagnostics, 71.4% of patients were accurately or probably diagnosed as having a DGIST. Moreover, the sensibility of preoperative diagnosis was correlated to Fletcher's or Miettinen's risk ($P < 0.01$) and initial hemoglobin levels ($P < 0.05$); that is, the tumor with malignant behavior has a tendency to be diagnosed as an abdominal/retroperitoneal tumor or a pancreatic cancer rather than a DGIST, whereas decreased hemoglobin potentially raises suspicion of gastrointestinal diseases, and possibly DGISTs.

The optimal surgical approach (LR or PD) for DGISTs is controversial. Goh *et al*[10] suggested that LR is associated with a shorter operation time, a similar complication rate, and a comparable disease-specific survival; Duffaud *et al*[12] concluded that LR rather than PD should be pursued to preserve optimal pancreas function for a better quality of life. According to the relatively few patients with long-term follow-up in this report, the findings support the views above. Although the DRS following PD seemed poor ($P < 0.05$), after adjusting the covariates, PD tended to be performed in patients with high risk ($P < 0.05$), and the results proved that LR and PD had a similar impact on RFS and DRS ($P > 0.05$), thus, both surgical approach lead to a similar oncological prognosis if clear surgical margins are achieved[4,14]. Patients undergoing LR and PD showed similar overall morbidities (44.4% *vs* 20.0%; $P > 0.05$) with the excep-

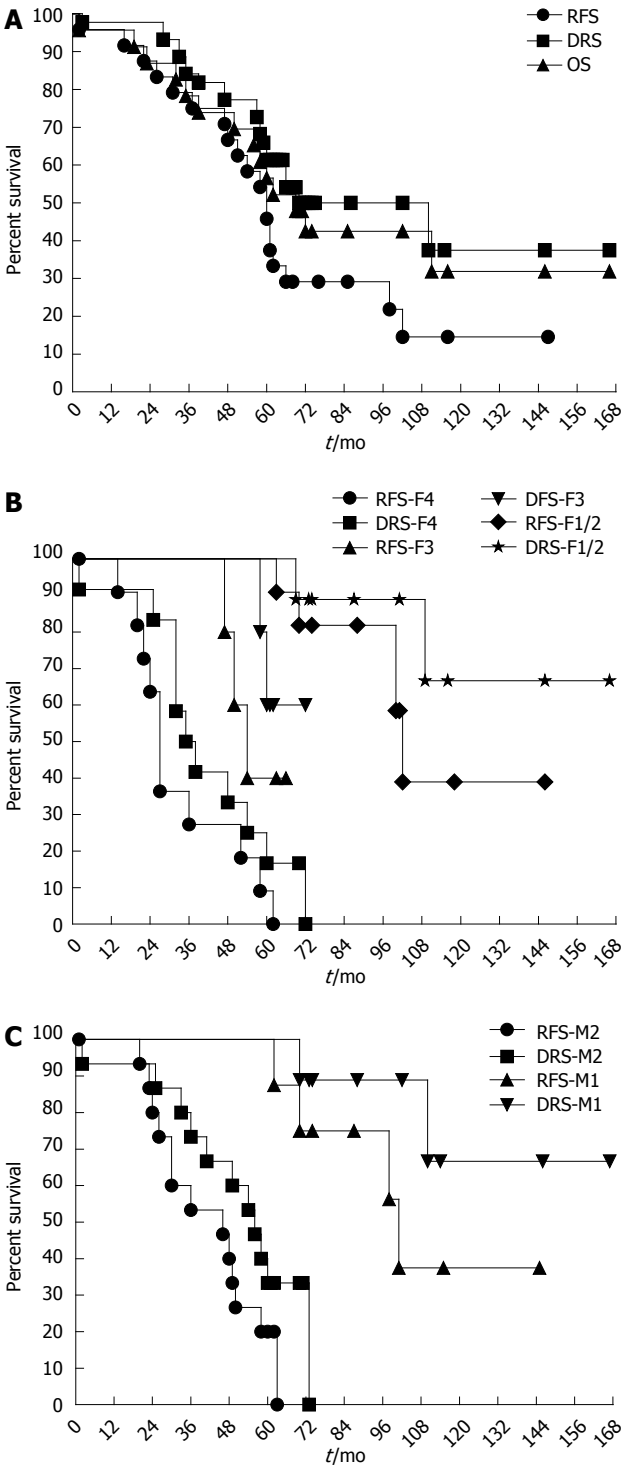

Figure 4 Survival curves. DRS: Disease-related survival; RFS: Relapse-free survival; OR: Overall survival; DFS: Disease free survival.

tion of DGE which was more frequent in the SR group (46.2%), and prolonged postoperative stay ($P > 0.05$).

Regardless of the pros and cons outlined above, essential factors which influence whether LR or PD is chosen are tumor size, location, proximity to the duodenal papilla, and technical feasibility[25-28]. In general, WR with primary closure can be performed for small lesions if the resulting lumen is adequate and the Vater ampulla can be preserved, even by laparoscopy or combined laparo-endoscopic surgery[29,30]. Occasionally, the antimesenteric defect after WR can be closed by Roux-en-Y duodenojejunostomy, whereas the mesenteric defect inside the "C" loop of the pancreas head can by repaired by translocation of the distal common bile duct as a patch[31,32]. SR with gastrojejunostomy or end-to-side/-end duodenojejunostomy may be performed for larger tumors located in the D1, D3 and D4. The side[D]-to-end[J] duodenojejunostomy is not recommended due to possible duodenal leakage and stump stasis (stump syndrome)[33]. Some scholars advocate resection and anastomosis even for lesions close to the papilla by performing the anastomosis just below the ampulla, which has been achieved by performing a lateromedial anastomosis opposite the papilla or by performing papilloplasty with a temporary stent catheter inserted into the papilla to avoid possible postoperative stenosis[34,35]. PD is only indicated when the tumor is located in the D2 and involves the papilla, pancreas, or if the tumor is large with high malignant potential and has involved the adjoining organs[8]. PD combined with major hepatectomy for a DGIST with localized liver metastases has also been reported[36]. PD can provide a wider tumor clearance, but reconstruction is difficult and there is an increased risk of long-term anastomotic stenosis, as both the pancreatic and common bile ducts are likely to be smaller in diameter[37]. In this context, the author introduced the binding pancreaticojejunostomy, which resolved these problems, improved the anastomotic operability, and decreased postoperative complications[38,39]. In addition, for ES-accessible mini tumors (less than 1.2 cm) in the D1, D2, and proximal D3, EUS-assisted band ligation is also feasible, although the necessity is debated[40].

Beside complete resection, pharmacological treatments are necessary[41]. Glivec® (imatinib), a TKI, is now widely prescribed in the United States and Western countries for high-risk local GIST patients as adjuvant therapy after surgery and in metastatic GIST patients as first-line treatment[2,20,42]. However, in China, only 8.1% of urban patients (Table 3, 7.1% of present cases) take imatinib, although the Glivec® International Patient Assistance Program (GIPAP) was officially started in September 2003 by the China Charity Foundation, the Tumor Drug Department of Novartis, and the Max Foundation, with the objective of providing free medicines to patients who needed treatment. GIPAP has relatively strict eligibility criteria, and the annual Glivec® cost is far beyond the economic realities in China, therefore only a few urban patients benefit from this donation program, let alone rural populations. Accordingly, neoadjuvant imatinib therapy is impractical in China, despite the fact that it is believed to allow LR in patients with locally advanced DGISTs[12].

In terms of the survival analyses, Duffaud *et al*[12] indicated that only mitotic rate predicted RFS; whereas the present study showed that not only mitotic rate, but also tumor size and various combinations of these two parameters in addition to Gold's point, Fletcher's risk and Miettinen's risk predict RFS with similar statistical powers ($P < 0.001$). Moreover, preoperative diagnosis of a duodenal tumor is also a positive factor for better patient survival, however, it is not an independent parameter. Gold *et al*[17] of the Memorial Sloan-Kettering Cancer Center have developed a nomogram to predict the probability of 2- and 5-year RFS for resected GISTs patients, and tested it in patients from the Spanish Group for Research on Sarcomas and the Mayo Clinic. With regard to the present cohort, Table 4 shows that the actual 2-year RFS rate was similar to the predicted value (83.3% *vs* 83%), but the actual 5-year RFS rate was lower than the predicted value (50% *vs* 70%), this may be due to the more malignant behavior of DGISTs compared with other small intestinal GISTs.

The limitations of this study include its retrospective design, small sample size, single center experience, and lack of adjuvant therapy. As analyses with small numbers of patients sometimes give misleading results, readers should be careful in evaluating these findings. However, based on a comprehensive literature review, it is necessary to strengthen these results. Future prospective studies enrolling larger numbers of patients and/or multiple medical centers are required.

COMMENTS

Background

Duodenal gastrointestinal stromal tumors (DGISTs) are a rare entity of gastrointestinal stromal tumors (GISTs), with characteristic clinical manifestations. Few cohorts with the exception of case studies have been reported. The purpose of this report is to provide long-term survival results of operable DGISTs in a tertiary center in China.

Research frontiers

Although DGISTs are relatively rare, they account for nearly 30% of all primary tumors of the duodenum, and the vast majority present with gastrointestinal bleeding. With regard to treatment, DGISTs often pose difficult surgical problems, due to their complex anatomical relationship around the duodenum, *i.e.*, unlike the stomach or other intestinal segments where complete excision with wide margins are relatively straightforward procedures, wide resection of DGISTs will almost always entail a pancreaticoduodenectomy (PD), which is massively invasive and technically challenging.

Innovations and breakthroughs

In recent years, a limited resection (LR) of DGISTs demonstrated a comparable outcome to PD in selected cases. However, the optimal surgical approach (LR or PD) for DGISTs is largely unknown, as all the available evidence has been derived from small retrospective series. In addition, scholars have gradually recognized the complexities of DGISTs, and these tumors have been classified separately from other small intestine GISTs into an independent category. Also, a number of papers on DGISTs have been released. Nevertheless, more experiences with long-term oncological observations are required, especially for surgeons.

Applications

This article provides a single center experience of operable cases in China, and

an update on the clinical management of DGISTs.

Terminology

GIST is the most common mesenchymal neoplasm of the gastrointestinal tract. GIST is a primary gastrointestinal disease that can arise anywhere along the digestive tract in adults.

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DGIST represents a subset of small bowel GISTs that requires special consideration given its clinical manifestations, especially for the difficult surgical decisions and poor prognoses. Surgeons can choose the limited resection or pancreaticoduodenectomy for operable DGISTs according to the tumor size, location, proximity to the duodenal papilla, and their technical feasibility, and either of the two approaches leads to an indistinctive oncological prognosis as long as clear surgical margins are achieved. The prognoses of DGISTs are poor, thus a comprehensive treatment is necessary. The authors provided a single center experience of operable cases in China, and reviewed update on the clinical management of DGISTs.

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