Original Article

Surgical treatment of gastrointestinal stromal tumors of the duodenum: a literature review

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Background: Gastrointestinal stromal tumors (GIST) are the most frequent mesenchymal tumours in the digestive tract. The duodenal GIST (dGIST) is the rarest subtype, representing only 4–5% of all GIST, but up to 21% of the resected ones. The diagnostic and therapeutic management of dGIST may be difficult due to the rarity of this tumor, its anatomical location, and the clinical behavior that often mimic a variety of conditions; moreover, there is lack of consent for their treatment. This study has evaluated the scientific literature to provide consensus on the diagnosis of dGIST and to outline possible options for surgical treatment.

Methods: An extensive research has been carried out on the electronic databases MEDLINE, Scopus, EMBASE and Cochrane to identify all clinical trials that report an event or case series of dGIST.

Results: Eighty-six studies that met the inclusion criteria were identified with five hundred forty-nine patients with dGIST: twenty-seven patients were treated with pancreatoduodenectomy and ninety-six with only local resection (segmental/wedge resections); in four hundred twenty-six patients it is not possible identify the type of treatment performed (pancreatoduodenectomy or segmental/wedge resections).

Conclusions: dGISTs are a very rare subset of GISTs. They may be asymptomatic or may involve symptoms of upper GI bleeding and abdominal pain at presentation. Because of the misleading clinical presentation the differential diagnosis may be difficult. Tumours smaller than 2 cm have a low biological aggressiveness and can be followed annually by endoscopic ultrasound. The biggest ones should undergo radical surgical resection (R0). In dGIST there is no uniformly adopted surgical strategy because of the low incidence, lack of experience, and the complex anatomy of the duodenum. Therefore, individually tailored surgical approach is recommended. R0 resection with 1–2 cm clear margin is required. Lymph node dissection is not recommended due to the low incidence of lymphatic metastases. Tumor rupture should be avoided.

Keywords: Duodenal gastrointestinal stromal tumor (dGIST); surgery

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Introduction

Gastrointestinal stromal tumours (GIST) are the most common type of mesenchymal tumours found in the gastrointestinal tract (1). For years, GISTs have been defined as smooth gastrointestinal muscle tumors and have been called under various names and often misdiagnosed as leiomyomas, schwannomas and sarcomas (2). Currently, the distinctive feature of GIST is the mutation in the *c-kit* protooncogene leading to gain-of-function and subsequent cell proliferation (3-5). GISTs are rare, with relative annual incidence of 14.5 per million and prevalence of 129 per million (6). GIST may occur anywhere in the digestive tract, but are more frequently located in the stomach (60–70%) and midgut (25%) and less often in colon and rectum (5–10%) (7). Extravisceral GIST occurs in less than 10% of patients, most frequently in mesentery, intrabdominal, pelvis and retroperitoneal space (7). Duodenal GISTs (dGIST) represent only 4–5% of all GISTs, but accounted for 6–21% of surgical resected ones (8-10). The complex anatomy of the duodeno-pancreatic region can make their diagnosis and treatment extremely challenging. Anatomical closeness to noble structures (i.e., to the head of the pancreas, kidney and biliary structures) can lead to misdiagnosis and inappropriate management (11). Additionally, several factors complicate the management of dGISTs such as the relative lack of experience, the ambiguous clinical manifestations that often mimic a wide range of clinical conditions, the anatomical complexity and the lack of consensus on treatment.

The publication of solid research findings (3,12) that characterize the pathogenesis and histology of GIST have created a discontinuity in the terminology used to describe this entity. Due to the unclear terminology of scientific literature published before 2000, it is very difficult to analyse and interpret the previous reports, but the researches published since then has significantly increased (4).

Herein, we aimed to perform a state-of-the-art review of available English literature to improve the understanding of dGIST and to outline the best options for surgical treatment.

Methods

Search strategy

Comprehensive research has been conducted to identify all clinical studies that report the occurrence of dGIST. The search was carried out on the electronic databases MEDLINE, Scopus, EMBASE and Cochrane Libraries. The research strategy included all studies published after 2000 and focused on relevant articles using the following keywords: “gist”, “duodenal”, “stromal gastrointestinal cancer”, “surgery” and associated free terms. No language restrictions have been imposed to limit results.

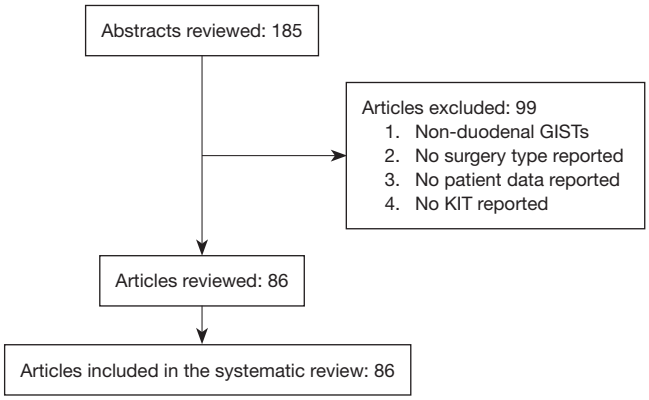

Figure 1 Study selection process.

Inclusion criteria

Studies were selected for consideration in this analysis provided they reported cases with dGIST. In order to select only those studies that certainly dealt with dGIST, only those studies in which the immunohistochemical analysis of the *cKIT* was reported and were positive were included.

Study selection

The inclusion criteria were used to examine the title, abstracts and full texts of the studies obtained from the research results. Two reviewers independently examined all citations on titles and abstracts produced by the search strategy and retrieved all potentially relevant reports. Two other independent readers then screened the full text of the studies to identify the entries that met the inclusion criteria. Any disagreements have been resolved by consensus. Differences in data extraction have been resolved by consensus, with references to the original article.

Results

The initial search produced 185 potentially relevant articles (*Figure 1*, *Tables 1*,*2*,*3*,*4*,*5*) that were suitable for subsequent screening. The titles and abstracts of these articles were screened to determine the relevance and eligibility for inclusion—53 papers were excluded for different reasons:

Table 1 Characteristics of included studies: pancreaticoduodenectomy

Study (year of publication)	Nation	Number of patients with duodenal GIST	Patient (age/gender)	Duodenal portion location	Symptoms and signs at admission
Takahashi 2001 (13)	Japan	1	77; F	Second	Mild anemia
Uchida 2004 (14)	Japan	1	53; F	Extramural	Asymptomatic
Hompes 2004 (15)	Belgium	2	32; F	Second	Right superior abdominal discomfort
			72; F	Second	Hypovolemic shock, melena, pallor, weakness, fatigue, anemia
Kim 2004 (16)	Korea	1	37; F	Second	Weakness, nausea, melena, anemia
Sakakima 2004 (17)	Japan	1	46; F	Second	Epigastralgia, melena, anemia
Sakakura 2006 (18)	Japan	1	37; M	Second	Abdominal discomfort
Ludvigsen 2007 (19)	Denmark	1	41; M	Second	Anemia
Fiore 2009 (20)	Italy	3	49; F	NR	NR
			66; M	NR	NR
			71; M	NR	NR
Hecker 2010 (21)	Germany	1	58	Second	Recurrent episodes of upper abdominal pain, anemia, weight loss, fatigue and fever attacks, upper gastrointestinal bleeding after neoadjuvant imatinib
Frampton 2010 (22)	UK	1	37; F	Second	Right upper quadrant pain, sweating, nausea, hot flushes, palpitations
Wall 2010 (23)	–	1	36; F	–	Diarrhea, bloating, weight loss, lethargy, collapse, melena, hypotension, tachycardia
Machado 2011 (24)	Oman	1	58; M	Second	Melena, weight loss
Morcos 2011 (25)	Jordan	1	38; F	Second	Epigastric discomfort, abdominal pain, anemia
Singh 2012 (26)	India	1	30; M	Second	Mass in the right upper abdomen, abdominal pain
Koontz 2012 (27)	USA	1	36; F	Third	Upper gastrointestinal bleeding, abdominal fullness, early satiety, fatigue, anemia, syncope
Blandamura 2014 (28)	Italy	1	72; M	Third	Increasing vomiting, weight loss
Bormann 2014 (29)	Germany	1	64; F	Second	Slowly increasing pain in right upper abdomen
Kobayashi 2014 (30)	Japan	1	36; M	Second	Loss of consciousness
Parisi 2014 (31)	Italy	1	68	Second	Fatigue, anemia, positive fecal occult blood
Bhambare 2015 (32)	India	1	38; M	Second	Large abdominal lump, abdominal pain
Okasha 2015 (33)	Egypt	1	42; F	Second	Abdominal discomfort, melena, hematemesis
Niikura 2016 (34)	Japan	1	75; M	First	Anemia, melena, hemorrhagic shock
Yamamoto 2016 (35)	Japan	1	81; F	Second	Diarrhea
Tornambe 2017 (36)	Italy	1	69; M	Second	Melena, asthenia, dizziness, severe anemia

NR, information not reported

Table 2 Characteristics of included studies: local resection

Study (year of publication)	Nation	Number of patients with duodenal GIST	Patient (age; gender)	Duodenal portion location	Symptoms and signs at admission
Sawaki 2003 (37)	Japan	1	54; F	First	Asymptomatic
Sakamoto 2003 (38)	Japan	1	31; F	Third	NR
Kurihara 2005 (39)	Japan	1	64; M	Second	Tarry stools, dizziness, and severe anemia
Goh 2005 (40)	Singapore	2	72; F	Second	Epigastralgia, melena, anemia
			69; M	Second and third	Abdominal discomfort
Cavallini 2005 (41)	Italy	1	66; F	Second	Anemia, melena
Vu 2005 (42)	Japan	1	43; M	Third	NR
Towu 2006 (43)	UK	1	7; M	Second and third	Severe upper gastrointestinal bleeding
Kwon 2007 (44)	Korea	1	49; M	Second and third	Asymptomatic
Graham 2007 (45)	UK	1	57; M	Fourth	Melena, anemia
Gupta 2007 (46)	USA	1	63; M	Second and third	Gastrointestinal bleeding
Mohiuddin 2007 (47)	UK	1	56; M	Second	Melena, anemia
Fernández Salazar 2007 (48)	Spain	1	44; M	NR	GI bleeding
Mennigen 2008 (49)	Germany	1	29; M	Third	Acute upper gastrointestinal bleeding
Takahashi 2009 (50)	Japan	1	57; F	First	Bloody stools
Takeuchi 2009 (51)	Japan	1	55; M	Third	Asymptomatic
Seçkin 2009 (52)	Turkey	1	56; M	Third	Melena, anemia
Hirashima 2009 (53)	Japan	1	68; F	NR	Asymptomatic
Mehta 2011 (54)	USA	1	33; F	Third	Melena, dizziness, anemia, hypotension, tachycardia
Chung 2011 (55)	Korea	2	65; M	Third	Abdominal pain
			49; F	Fourth	Upper gastrointestinal bleeding, melena
Cameron 2011 (56)	Germany	1	62; M	Second	NR
Kato 2011 (57)	Japan	1	60; M	Third	NR
Chen 2012 (58)	Australia	1	52; M	NR	Anemia
El-Gendi 2012 (59)	Egypt	12	60; F, n=5, M, n=7	First, n=3	Melena, anemia
				Second n=1	
				Third, n=3	
				Fourth, n=1	
Acar 2013 (60)	Turkey	1	65; F	Third	Abdominal pain
Mouaqit 2013 (61)	Morocco	1	65; F	Second and third	Abdominal pain, anemia
Mokhtare 2013 (62)	Iran	1	2; M	Third	Acute upper gastrointestinal bleeding

Table 2 *(continued)*

Table 2 *(continued)*

Study (year of publication)	Nation	Number of patients with duodenal GIST	Patient (age; gender)	Duodenal portion location	Symptoms and signs at admission
Shaw 2013 (63)	UK	1	61; M	Third and fourth	Hypovolemic shock, upper gastrointestinal bleeding, melaena, hematemesis, temporary loss of consciousness
Ueda 2014 (64)	Japan	1	72; F	Third	Asymptomatic
Hankiewicz-Ziołkowska 2014 (65)	Poland	1	65; F	First	Asymptomatic
Manxhuka-Kerliu 2014 (66)	Kosovo	1	30	Fourth-jejunum	Abdominal pain, nausea, vomiting
Fukuyama 2014 (67)	Japan	1	69; M	Second	Anemia, melena
Borgaonkar 2015 (68)	India	2	52; F	NR	NR
			23; M	NR	NR
Jones 2015 (69)	USA	2	40; F	NR	Epigastric pain, recurrent gastrointestinal bleeding
			29; F	Second	Asymptomatic
Mrak 2015 (70)	Austria	1	68; F	Upper portions	Abdominal pain, melena, hemodynamic instability
Kumar 2015 (71)	India	1	55; F	Second and Third	Epigastric pain
Chung 2015 (72)	Korea	21	59; F, n=9, M, n=12	First, n=7	Incidental finding, abdominal pain, bleeding
				Second, n=5	
				Third, n=5	
				Fourth, n=4	
Graziosi 2015 (73)	Italy	1	51; F	Second	Anemia, melena
Boselli 2016 (74)	Italy	3	75; F	Fourth	Melena, anemia
			82; F	Passage between second and third	Melena, syncope, anemia, hemodynamic instability
			76; M	Passage between second and third	Melena, syncope, anemia, hemodynamic instability
Caruso 2016 (75)	Italy	1	73	Fourth, duodenojejunal junction	Anemia, melena
Jones 2016 (76)	USA	1	71; F	Second	Recurrent GI bleeding
Turculeț 2016 (77)	Romania	1	48; M	Third and Fourth	Melena, asthenia, dizziness, severe anemia
Huo 2016 (78)	China	1	58; F	First	Epigastric abdominal discomfort, diarrhea, recurrent vomiting
Mori 2016 (79)	Japan	1	74; M	Third	NR
Valli 2016 (80)	Switzerland	1	19; F	Second	Fainting, anemia, melena

Table 2 *(continued)*

Table 2 *(continued)*

Study (year of publication)	Nation	Number of patients with duodenal GIST	Patient (age; gender)	Duodenal portion location	Symptoms and signs at admission
Crocetti 2016 (81)	Italy	9	70; F, n=9, M, n=12	NR	Pain, bleeding, dyspepsia
Thillai 2017 (82)	India	1	50; F	Second and third	Abdominal pain
Elston 2017 (83)	Australia	1	29; M	Second	Acute upper gastrointestinal hemorrhage, melena
Vasile2017 (84)	Romania	1	59; F	First and second	Abdominal pain, upper gastrointestinal bleeding (melena), faintness, anemia
Zioni2017 (85)	Israel	1	68; M	Second and third	Upper gastrointestinal bleeding, general weakness, melena, anemia
Perfetti2017 (86)	Italy	1	33; M	Second	Gastrointestinal bleeding, anemia
Hakozaki 2017 (87)	Japan	1	70; F	First	Positive fecal occult blood test

NR, information not reported.

Table 3 Characteristics of included studies: PD and local resections

Study (year of publication)	Nation	Number of patients with duodenal GIST	Patients (age; gender)	Duodenal portion location	Symptoms and sign at admission
Miettinen 2003 (9)	USA	156	56; F, n=71, M, n=85	First, n=10	Anemia, melena, obstruction, acute abdomen
				Second, n=42	
				Third, n=17	
				Second-third, n=7	
				Fourth, n=11	
Relles 2009 (88)	USA	2	43; M	Second	Melena, fatigue, shortness of breath
			31; M	Ligament of Treitz	Solid food dysphagia, abdominal discomfort
Tien 2010 (89)	Taiwan	25	62; F, n=9, M, n=16	3 first	Bleeding, pain, mass
				13 second	
				5 third	
				4 fourth	
Miki 2010 (90)	Japan	6	64; F	Second	Melena
			70; F	Fourth	Abdominal mass
			67; F	First	Asymptomatic
			39; F	First	Melena
			65; M	Second	Anemia
			75; F	Second	Anemia
Yagishita 2011 (91)	Japan	4	62; F	Second	NR
			69; M	First	NR
			76; M	Second	Anemia
			72; M	First	NR

Table 3 *(continued)*

Table 3 *(continued)*

Study (year of publication)	Nation	Number of patients with duodenal GIST	Patients (age; gender)	Duodenal portion location	Symptoms and sign at admission
Liang 2013 (92)	Japan	28	28; F	Second	Melena
			48; F	Second	Asymptomatic
			60; M	Second	Melena
			70; M	Second	Abdominal pain
			71; M	Third	Asymptomatic
			76; F	Second	Melena
			42; F	Second	Melena
			74; M	First	Melena
			53; F	First	Melena
			47; F	Second	Melena
			55; F	Fourth	Melena
			51; M	Second	Melena
			50; M	Second	Hematemesis
			69; F	Third	Abdominal pain
			65; M	Third	Melena
			63; M	Second	Acute abdomen
			44; F	Second	Hematemesis
			57; F	Third	Discomfort
			20; F	Second	Melena
			52; M	Fourth	Abdominal pain
			53; F	Second	Abdominal pain
			71; F	Second	Early satiety
			53; M	First	Early satiety
			50; F	First	Melena
			46; F	Second	Abdominal pain
			55; M	Second	Melena
			51; M	Third	Asymptomatic
			46; F	Second	Melena
Hoeppner 2013 (93)	Germany	9	51; M	Second	Bleeding
			63; M	Third	Bleeding
			52; M	First	Bleeding
			62; F	First	Jaundice
			58; M	First	Abdominal pain
			69; F	Second	Incidental finding
			43; F	Fourth	Bleeding
			75; M	Third	Bleeding
			49; F	Second	Bleeding

Table 3 *(continued)*

Table 3 *(continued)*

Study (year of publication)	Nation	Number of patients with duodenal GIST	Patients (age; gender)	Duodenal portion location	Symptoms and sign at admission
Yang 2013 (94)	China	22	58; F, n=7, M, n=15	First, n=3 Second, n=14 Third-fourth, n=5	Asymptomatic, abdominal discomfort/ pain, melena, weight loss, fatigue, abdominal distension, anorexia, back pain, hematemesis, jaundice, anemia, palpable abdominal mass
Zhou 2013 (95)	China	48	53; F, n=20, M, n=28	First, n=11 Second, n=17 Third, n=6 Fourth, n=2 First-second, n=2 Second-third, n=4	Bleeding, abdominal pain, abdominal discomfort, jaundice
Duffaud 2014 (96)	France	114	57; F, n=55, M, n=59	First, n=8 Second, n=38 Third, n=27 Fourth, n=15	Pain, GI bleeding, anemia, asymptomatic
Ucar 2015 (97)	Turkey	2	65; M	First	Upper gastrointestinal bleeding
			60; M	Second	Ileus, acute abdomen, hemorrhagic pancreatitis
Lv 2017 (98)	China	10	44; F	Third	Abdominal pain
			50; M	Second	Asymptomatic
			43; M	Second	Melena
			50; F	Second and third	Abdominal pain
			60; M	Second	Abdominal discomfort
			44; M	Second	Abdominal discomfort
			50; F	Third	Melena
			44; M	Second and third	Melena
			65; M	Second	Melena
			64; F	Third	Abdominal pain

NR, information not reported.

Table 4 Characteristics of included studies: PD and local resections

Study (year of publication)	Histologic characteristics					
	c-kit	DOG1	CD34	Smooth muscle actin	S100	Desmin
Miettinen 2003 (9)	109	NR	49	38	19	No
Relles 2009(88)	Yes	NR	Yes	NR	No	NR
	Yes	No	Yes	No	No	No
Tien 2010 (89)	25	NR	5	5	4	No

Table 4 *(continued)*

Table 4 *(continued)*

Study (year of publication)	Histologic characteristics					
	c-kit	DOG1	CD34	Smooth muscle actin	S100	Desmin
Miki 2010 (90)	Yes	NR	NR	NR	NR	NR
	Yes	NR	NR	NR	NR	NR
	Yes	NR	NR	NR	NR	NR
	Yes	NR	NR	NR	NR	NR
	Yes	NR	NR	NR	NR	NR
	Yes	NR	NR	NR	NR	NR
Yagishita 2011 (91)	Yes	No	Yes	No	No	NR
	Yes	No	Yes	No	No	NR
	Yes	No	Yes	No	No	NR
	Yes	No	No	No	No	NR
Liang 2013 (92)	Yes	NR	No	Yes	No	No
	Yes	NR	Yes	Yes	No	NR
	Yes	NR	No	Yes	No	NR
	Yes	NR	Yes	Yes	Yes	NR
	Yes	NR	Yes	Yes	No	NR
	Yes	NR	Yes	No	Yes	No
	Yes	NR	No	Yes	Yes	No
	No	NR	Yes	No	No	NR
	Yes	NR	Yes	Yes	Yes	NR
	Yes	NR	No	Yes	Yes	NR
	Yes	NR	Yes	No	Yes	NR
	Yes	NR	Yes	No	Yes	NR
	Yes	NR	Yes	Yes	No	NR
	Yes	NR	Yes	Yes	No	NR
	Yes	NR	Yes	Yes	No	NR
	Yes	NR	Yes	No	Yes	NR
	Yes	NR	Yes	No	Yes	NR
	Yes	NR	Yes	No	No	NR
	Yes	NR	No	Yes	No	No
	Yes	NR	Yes	No	No	No
	Yes	NR	No	Yes	No	NR
	Yes	NR	Yes	No	No	No
	Yes	NR	No	Yes	Yes	No
	Yes	NR	No	Yes	No	No
	Yes	NR	No	Yes	No	NR
	Yes	NR	No	No	Yes	NR
	Yes	NR	Yes	No	No	No
	Yes	NR	Yes	Yes	Yes	NR

Table 4 *(continued)*

Table 4 *(continued)*

Study (year of publication)	Histologic characteristics					
	c-kit	DOG1	CD34	Smooth muscle actin	S100	Desmin
Hoeppner 2013 (93)	Yes	NR	NR	NR	NR	NR
	Yes	NR	NR	NR	NR	NR
	Yes	NR	NR	NR	NR	NR
	Yes	NR	NR	NR	NR	NR
	Yes	NR	NR	NR	NR	NR
	Yes	NR	NR	NR	NR	NR
	Yes	NR	NR	NR	NR	NR
	Yes	NR	NR	NR	NR	NR
	Yes	NR	NR	NR	NR	NR
Yang 2013 (94)	18	NR	17	10	8	No
Zhou 2013 (95)	47	NR	32	NR	5	6
Duffaud 2014 (96)	105	NR	58	NR	NR	NR
Ucar 2015 (97)	Yes	Yes	Yes	NR	NR	NR
	Yes	Yes	Yes	NR	NR	NR
Lv 2017 (98)	Yes	NR	NR	NR	NR	NR
	Yes	NR	NR	NR	NR	NR
	Yes	NR	NR	NR	NR	NR
	Yes	NR	NR	NR	NR	NR
	Yes	NR	NR	NR	NR	NR
	Yes	NR	NR	NR	NR	NR
	Yes	NR	NR	NR	NR	NR
	Yes	NR	NR	NR	NR	NR
	Yes	NR	NR	NR	NR	NR
	Yes	NR	NR	NR	NR	NR

NR, information not reported.

Table 5 Characteristics of included studies: PD and local resections

Study (year of publication)	Tumor extension out duodenum	Type of treatment	Neoadjuvant treatment with Imatinib	Postoperative treatment with Imatinib	Survival (years; months)
Miettinen 2003 (9)	Duodenum	15 enucleation; 48 segmental resection; 21 wedge resection; 21 pancreaticoduodenectomy; 51 NR	NR	NR	NR
Relles 2009 (88)	Duodenum	Pancreaticoduodenectomy	NR	NR	NR
	Duodenum	Local resection	NR	NR	NR
Tien 2010 (89)	Duodenum	9 pancreaticoduodenectomy; 16 local resection	NR	NR	NR

Table 5 *(continued)*

Table 5 *(continued)*

Study (year of publication)	Tumor extension out duodenum	Type of treatment	Neoadjuvant treatment with Imatinib	Postoperative treatment with Imatinib	Survival (years; months)
Miki 2010 (90)	Duodenum	Duodenectomy	NR	No	NR
		Local resection	NR	Yes	NR
		Local resection	NR	No	NR
		Local resection	NR	No	NR
		Local resection	NR	No	NR
		Pancreaticoduodenectomy	NR	No	NR
Yagishita 2011 (91)	Duodenum	Partial duodenectomy	NR	NR	NR
	Duodenum	No treatment	NR	NR	NR
	Duodenum	No treatment	NR	NR	NR
	Duodenum, pancreas	Pancreaticoduodenectomy	NR	NR	NR
Liang 2013 (92)	Duodenum	Segmental resection	No	No	164 m
		Wedge resection		No	146 m
		Pancreaticoduodenectomy		No	61 m
		Pancreaticoduodenectomy		No	35 m
		Segmental resection		No	23 m
		Segmental resection		No	25 m
		Pancreaticoduodenectomy		No	73 m
		Wedge resection		No	61 m
		Segmental resection		No	116 m
		Pancreaticoduodenectomy		No	111 m
		Segmental resection		No	55 m
		Pancreaticoduodenectomy		No	23 m
		Wedge resection		No	102 m
		Pancreaticoduodenectomy		No	NR
		Segmental resection		No	68 m
		Pancreaticoduodenectomy		No	49 m
		Pancreaticoduodenectomy		No	33 m
		Segmental resection		No	57 m
		Segmental resection		No	86 m
		Segmental resection		No	33 m
		Wedge resection		No	40 m
		Segmental resection		No	59 m
		Wedge resection		No	75 m
		Segmental resection		No	73 m
		Segmental resection		Yes	71 m
		Pancreaticoduodenectomy		No	70 m
		Segmental resection		Yes	63 m
		Pancreaticoduodenectomy		No	61 m

Table 5 *(continued)*

Table 5 *(continued)*

Study (year of publication)	Tumor extension out duodenum	Type of treatment	Neoadjuvant treatment with Imatinib	Postoperative treatment with Imatinib	Survival (years; months)
Hoeppner 2013 (93)	Duodenum	Open wedge resection	No	No	6 m
		Open wedge resection	No	Yes	7 m
		Laparoscopic wedge resection	No	No	13 m
		Pancreaticoduodenectomy	No	No	Died at 3 m
		Open wedge resection	No	No	90 m
		Open wedge resection	No	No	111 m
		Segmental resection	No	No	92 m
		Open wedge resection	Yes	No	Died at 37 m
		Tumor resection	Yes	Yes	39 m
Yang 2013 (94)	Duodenum	9 pancreaticoduodenectomy; 13 local resection	No	5	NR
Zhou 2013 (95)	Duodenum	34 local resection; 14 pancreaticoduodenectomy	NR	NR	NR
Duffaud 2014 (96)	Duodenum	82 local resection; 23 pancreaticoduodenectomy	11	20	NR
Ucar 2015 (97)	Duodenum	Local resection	NR	NR	NR
		Pancreaticoduodenectomy	NR	NR	NR
Lv 2017 (98)	Duodenum	Segmental resection	Yes	NR	36 m
		Tumor resection	Yes	NR	50 m
		Radical resection	Yes	NR	44 m
		Segmental resection	Yes	NR	47 m
		Tumor resection	Yes	NR	17 m
		Tumor resection	Yes	NR	36 m
		Segmental resection	Yes	NR	17 m
		Radical resection	Yes	NR	16 m
		Segmental resection	Yes	NR	16 m
		Pancreaticoduodenectomy	Yes	NR	41 m

NR, information not reported.

non-duodenal GISTs, no surgery type reported, and no patient data reported leaving 132 studies for inclusion in the present review. Of them, 46 studies did not report the data about *cKIT* and were excluded thus leaving 86 studies included in the analysis. The patients excluded for non-duodenal GIST were 7,142, those excluded for no surgery type reported were 1,039 and 1,002 patients were excluded because of no *cKIT* reported. The characteristics of the included studies have been summarized in *Tables 1*,*2*,*3*,*4*,*5*. All studies were published between 2001 and 2017. Eighty-two papers with 539 cases reported data on the signs and symptoms at the time of hospital admission, whereas in four studies there were no data. Upon admission, the most common symptoms were GI bleeding and melena, followed by abdominal pain and discomfort. Symptoms of fatigue, fainting, vomiting, and ankle edema were also reported but occurred far less frequently. In the majority of cases dGISTs were located in the second portion of the duodenum. Several cases reported dGIST localization in both the second and third portions of the duodenum.

The included studies summoned a total of 549 patients with dGIST—27 patients treated with pancreatoduodenectomy (PD) (*Table 1*), 96 patients treated with local resection (*Table 2*), and 426 patients treated with either PD or segmental/wedge resections (*Tables 3*,*4*,*5*).

Among patients treated with PD (*Tables 1*,*6*), the majority

Table 6 Characteristics of included studies: pancreaticoduodenectomy

Study (year of publication)	Local tumor extension	Surgical access	Neoadjuvant treatment with imatinib	Postoperative treatment with imatinib	Multivisceral resection	Survival (years, months)
Takahashi 2001 (13)	Duodenum, pancreatic head, gall bladder, gastric antrum, regional lymph nodes	Open	NR	NR	Gastric antrum	NR
Uchida 2004 (14)	Duodenum	Open	No	No	No	NR
Hompes 2004 (15)	Duodenum, pancreas, mesocolon	Open	No	No	Ascending colon	NR
Kim 2004 (16)	Duodenum	Open	No	No	No	5 m
Sakakima 2004 (17)	Duodenum	Open	NR	NR	No	NR
Sakakura 2006 (18)	Duodenum	Open	No	Yes	No	24 m
Ludvigsen 2007 (19)	Duodenum, hilum, liver, right kidney, right hemicolon, right hemipancreas, celiac trunk, inferior vena cava, right renal vein, right renal pelvis	Open	Yes	Yes	Right kidney, adrenal gland	NR
Fiore 2009 (20)	Duodenum	Open	Yes	NR	No	NR
			Yes	NR	No	NR
			Yes	NR	No	NR
Hecker 2010 (21)	Duodenum, pancreas, right flexure of the colon	Open	Yes	Yes	Right hemicolon	NR
Frampton 2010 (22)	Duodenum	Open	NR	NR	No	NR
Wall 2010 (23)	Duodenum	Open	No	No	No	NR
Machado 2011 (24)	Duodenum, right hemicolon	Open	No	Yes	Right hemicolon	2 m
Morcos 2011 (25)	Duodenum	Open	No	No	No	34 m
Singh 2012 (26)	Duodenum	Open	No	Yes	No	NR
Koontz 2012 (27)	Duodenum	Open	Yes	Yes	No	NR
Blandamura 2014 (28)	Duodenum	Open	No	No	No	NR
Bormann 2014 (29)	Duodenum, pancreas	Open	No	No	No	NR
Kobayashi 2014 (30)	Duodenum	Open	No	No	No	18 m
Bhambare 2015 (32)	Duodenum	Open	No	Yes	No	NR
Okasha 2015 (33)	Duodenum	Open	No	No	No	NR
Niikura 2016 (34)	Duodenum	Open	No	Yes	No	6 y
Yamamoto 2016 (35)	Duodenum	Open	No	No	No	NR
Tornambe 2017 (36)	Duodenum	Open	No	No	No	12 m

NR, information not reported.

were females (n=14, 52%; males: n=11, 41%; not reported: n=2, 7%), with a median age of 50 years (*Table 1*). Most patients presented with symptoms of anemia (n=11, 40%), melena (n=8, 27%), fatigue (n=4, 15%), and weight loss (n=4, 15%). However, in 3 patients the information was not reported. For most patients, the dGIST were located in the second portion of the duodenum (first: n=1, 4%; second: n=19, 70%; third: n=1, 4%; not reported: n=5, 18%) (*Table 1*). Four studies (13,19,21,25) reported dGIST tumors that extended beyond the duodenum. All PDs were performed by open procedure. While some patients received imatinib as a neoadjuvant treatment (n=7, 26%), a greater proportion received the treatment post-operatively (n=9, 33%) (*Table 6*). For most patients, no long term survival data were reported (n=21, 75%). Notably, the PD studies reported histological information on KIT, DOG1, or CD34.

Among patients treated with local resection (*Tables 2*,7) there was a slight preponderance of males (n=51, 53%; females: n=45, 47%) with a median age of 57.3 years (*Table 2*). Upon admission, patients most commonly presented with nausea (n=1, 1%), abdominal pain (n=8, 8%), undetermined pain (n=18, 19%), melena (n=20, 21%), dizziness (n=3, 3%), and/or GI bleeding (n=14, 16%). No data on presenting signs and symptoms was available for 7 patients (*Table 2*).

Within this group, most dGIST were located in the second and third portions of the duodenum (first: n=16, 17%; second: n=29, 30%, third: n=32, 33%; fourth: n=12, 12%; not reported: n=7, 7%), with tumors extending beyond the duodenum in four cases. For all local resections reported, surgical access was predominantly achieved by either open (n=89, 92%) or laparoscopic procedure (n=5, 5%). Patients treated with a local resection received less neoadjuvant (n=13, 13%) and post-operative (n=22, 23%) treatment with imatinib (*Table 8*), as compared to patients treated with a pancreaticoduodenectomy (*Table 6*), and four patients underwent multiple visceral resections.

Of the patients whose histological or molecular data were provided (*Table* 7), most tested positive for *cKIT* (n=85, 46%), CD34 (n=48, 26%) and DOG1 (n=20, 11%). A minority of patients tested positive for either smooth muscle actin (n=5, 3%), S100 (n=7, 4%) or desmin (n=1, 1%).

Four hundred twenty-six patients were treated with either PD or segmental/wedge resections. Within this group, there was preponderance of males (n=218, 51%) *vs.* females (n=183, 43%), not reported (n=25, 6%). At the time of admission, patients frequently presented with symptoms of bleeding (n=137, 32%), abdominal pain or discomfort (n=258, 60%) and melena (n=235, 55%). Five patients were asymptomatic (*Tables 3*,*4*,*5*). dGISTs were predominantly located in the second and third portions of the duodenum in this group (first: n=47, 11%; second: n=164, 38%; third: n=83, 19%; fourth: n=41, 9%). In many cases the tumors extended into multiple portions of the duodenum simultaneously. All of these studies reported data on *cKIT* and several studies reported data on CD34 and DOG1.

Within this cohort the most common type of surgical treatment was local resection (n=151, 35%), followed by PD (n=92, 21%) and segmental (n=97, 15%) or wedge resections (n=32, 7%). No data on the type of surgical treatment were available for 51 patients. Within this group of patients, both neoadjuvant and post-operative treatment with imatinib were rarely applied (neoadjuvant treatment: n=23, 5%; adjuvant treatment: n=30, 7%). Most patients received no imatinib treatment prior to surgery (n=160, 38%) or post-operatively (n=149, 35%).

Surgical treatment

There are three main surgical options: pancreatoduodenectomy (PD) (10,24), wedge resection (40,60,63,97) and segmental resection. PD is indicated in the cases with involvement of major duodenal papilla, pancreas or pancreatic duodenal wall and is required in 20–40%. Based on the literature, the following options for surgical reconstruction according to the localization and extent of duodenal resection are available:

First and second duodenal portions:

- wedge resection with primary transverse closure of duodenum (39) or retrocolic Roux-en-Y loop to cover a large defect (97);
- segmental resection, closure of distal stump and duodenojejunostomy by retrocolic Roux-en-Y loop (99);
- segmental resection with antrectomy with side-to-side posterior or Roux-en-Y gastrojejunostomy (55,59);
- subtotal resection with side-to-side duodenojejunostomy (100);
- sleeve resection with gastroduodenostomy (the case with situs inversus totalis) (82);
- ampullectomy with sphincteroplasty (55).

Third and fourth duodenal portions:

- segmental resection with closure of distal stump and side-to-side (93) or end-to-side/end-to-end duodenojejunostomy (62,92);
- segmental resection, end-to-end anastomosis, pylorus closure and gastroenterostomy with/without feeding jejunostomy (77);
- segmental resection, closure of distal stump near leg.

Table 7 Characteristics of included studies: local resection

Study (year of publication)	Histologic characteristics					
	C-kit/CD117	DOG1	CD34/PDGFR-alfa	Smooth muscle actin	S100	Desmin
Sawaki 2003 (37)	Yes	NR	Yes	No	No	No
Sakamoto 2003 (38)	Yes	NR	NR	NR	NR	NR
Kurihara 2005 (39)	Yes	NR	Yes	Yes	No	No
Goh 2005 (40)	Yes	NR	NR	NR	NR	NR
	Yes	NR	NR	NR	NR	NR
Cavallini 2005 (41)	Yes	NR	NR	No	Yes	No
Vu 2005 (42)	Yes	NR	No	Yes	No	No
Towu 2006 (43)	Yes	NR	No	No	NR	NR
Kwon 2007 (44)	Yes	NR	Yes	No	NR	NR
Graham 2007 (45)	Yes	NR	Yes	NR	NR	NR
Gupta 2007 (46)	Yes	NR	NR	No	No	NR
Mohiuddin 2007 (47)	Yes	NR	NR	NR	NR	NR
Fernández Salazar 2007 (48)	Yes	NR	NR	NR	Yes	NR
Menningen 2008 (49)	Yes	NR	Yes	No	No	NR
Takahashi 2009 (50)	Yes	No	Yes	No	Yes	No
Takeuchi 2009 (51)	Yes	NR	Yes	No	No	NR
Seçkin 2009 (52)	Yes	NR	Yes	NR	Yes	NR
Hirashima 2009 (53)	Yes	NR	Yes	NR	No	No
Mehta 2011 (54)	Yes	No	Yes	Yes	No	No
Chung 2011 (55)	Yes	NR	NR	NR	NR	NR
	Yes	NR	NR	NR	NR	NR
Cameron 2011 (56)	Yes	NR	NR	NR	NR	NR
Kato 2011 (57)	Yes	NR	NR	NR	NR	NR
Chen 2012 (58)	Yes	NR	NR	NR	NR	NR
El-Gendi 2012 (59)	12	NR	8	NR	2	No
Acar 2013 (60)	Yes	NR	NR	NR	Yes	NR
Mouaqit 2013 (61)	Yes	NR	Yes	NR	NR	NR
Mokhtare 2013 (62)	Yes	Yes	Yes	NR	NR	NR
Shaw 2013 (63)	Yes	NR	Yes	NR	NR	NR
Ueda 2014 (64)	Yes	NR	Yes	NR	NR	NR
Hankiewics-Ziolkowska 2014 (65)	Yes	NR	Yes	NR	NR	NR
Manxhuka-Kerliu 2014 (66)	Yes	NR	Yes	Yes	No	No

Table 7 *(continued)*

Table 7 *(continued)*

Study (year of publication)	Histologic characteristics					
	C-kit/CD117	DOG1	CD34/PDGFR-alfa	Smooth muscle actin	S100	Desmin
Fukuyama 2014 (67)	Yes	NR	NR	NR	NR	NR
Mrak 2015 (70)	Yes	No	No	No	No	No
Kumar 2015 (71)	Yes	NR	Yes	NR	NR	NR
Chung 2015 (72)	21	NR	14	NR	10	No
Graziosi 2015 (73)	Yes	Yes	NR	NR	NR	NR
Boselli 2016 (74)	Yes	Yes	Yes	No	No	No
	Yes	Yes	No	No	No	No
	No	No	No	No	No	Yes
Caruso 2016 (75)	Yes	No	Yes	No	No	No
Jones 2016 (76)	Yes	NR	Yes	No	No	No
Turculeț 2016 (77)	Yes	Yes	No	Yes	No	NR
Huo 2016 (78)	Yes	No	Yes	No	No	No
Mori 2016 (79)	Yes	Yes	No	No	No	No
Valli 2016 (80)	Yes	Yes	Yes	No	No	No
Crocetti 2016 (81)	Yes	Yes	NR	NR	NR	NR
Thillai 2017 (82)	Yes	No	Yes	No	No	No
Elston 2017 (83)	Yes	Yes	No	No	No	No
Vasile 2017 (84)	Yes	NR	Yes	No	No	NR
Zioni 2017 (85)	Yes	NR	NR	NR	NR	NR
Perfetti 2017 (86)	Yes	Yes	Yes	No	No	No
Hakozaki 2017 (87)	Yes	NR	Yes	NR	No	NR

Table 8 Characteristics of included studies: local resection

Study (year of publication)	Tumor extension out duodenum	Type of surgical access	Neoadjuvant treatment with Imatinib	Postoperative treatment with Imatinib	Multiple visceral resection	Survival (years; months)
Sawaki 2003 (37)	Duodenum	Open	No	Yes	No	NR
Sakamoto 2003 (38)	Duodenum	Open	No	No	No	NR
Kurihara 2005 (39)	Duodenum	Open	No	No	No	NR
Goh 2005 (40)	Duodenum	Open	No	No	No	NR
	Duodenum, transverse mesocolon, small bowel mesentery	Open	No	No	Small bowel resection and transverse colectomy	NR
Cavallini 2005 (41)	Duodenum	Open	No	No	No	4 y

Table 8 *(continued)*

Table 8 *(continued)*

Study (year of publication)	Tumor extension out duodenum	Type of surgical access	Neoadjuvant treatment with Imatinib	Postoperative treatment with Imatinib	Multiple visceral resection	Survival (years; months)
Vu 2005 (42)	Duodenum	Open	NR	NR	NR	NR
Towu 2006 (43)	Duodenum	Open	No	No	No	NR
Kwon 2007 (44)	Duodenum	Open	No	No	No	NR
Graham 2007 (45)	Duodenum	NR	No	Yes	No	NR
Gupta 2007 (46)	Duodenum	Open	No	No	No	NR
Mohiuddin 2007 (47)	Duodenum	Open	No	Yes	No	42 m
Fernández Salazar 2007 (48)	Duodenum	Open	NR	NR	No	NR
Mennigen 2008 (49)	Duodenum	Open	No	No	No	NR
Takahashi 2009 (50)	Duodenum	NR	No	No	No	NR
Takeuchi 2009 (51)	Duodenum	Open	No	No	No	24 m
Seçkin 2009 (52)	Duodenum	Open	NR	NR	No	NR
Hirashima 2009 (53)	Duodenum	Open	No	No	No	NR
Mehta2011 (54)	Duodenum	NR	No	No	No	NR
Chung 2011 (55)	Duodenum	Open	No	No	No	42 m
		Open	No	No	No	13 m
Cameron 2011 (56)	Duodenum	Open	No	Yes	No	10 y
Kato 2011 (57)	Duodenum	Laparoscopic-endoscopic	NR	NR	No	NR
Chen 2012 (58)	Duodenum	Open	NR	NR	No	NR
El-Gendi 2012 (59)	Duodenum	Open	No	10	No	45 m
Acar 2013 (60)	Duodenum	Open	No	No	No	NR
Mouaqit 2013 (61)	Duodenum	Open	No	Yes	No	24 m
Mokhtare 2013 (62)	Duodenum	Open	No	No	No	NR
Shaw 2013 (63)	Duodenum	Open	NR	NR	No	NR
Ueda 2014 (64)	Duodenum	Laparoscopic	No	No	No	NR
Hankiewics-Ziolkowska 2014 (65)	Duodenum	Open	No	No	No	NR
Manxhuka-Kerliu 2014 (66)	Duodenum, jejunum	Open	No	No	No	NR
Fukuyama 2014 (67)	Duodenum	Open	Yes	Yes	No	12 m
Borgaonkar 2015 (68)	Duodenum	Open	NR	2	No	NR
Jones 2015 (69)	Duodenum	Open	Yes	Yes	No	NR
Mrak 2015 (70)	Duodenum	Open	No	Yes	No	NR
Kumar 2015 (71)	Duodenum	Open	No	No	No	6 m

Table 8 *(continued)*

Table 8 *(continued)*

Study (year of publication)	Tumor extension out duodenum	Type of surgical access	Neoadjuvant treatment with Imatinib	Postoperative treatment with Imatinib	Multiple visceral resection	Survival (years; months)
Chung 2015 (72)	Duodenum	19 open, 2 laparoscopic	No	No	No	NR
Graziosi 2015 (73)	Duodenum	Open	No	Yes	No	NR
Boselli 2016 (74)	Duodenum	Open	No	No	No	NR
	Duodenum	Open	No	No	No	NR
	Duodenum	Open	No	No	No	NR
Caruso2016 (75)	Duodenum, jejunum	Open	No	No	No	NR
Jones 2016 (76)	Duodenum	Open	No	No	No	NR
Turculeț 2016 (77)	Duodenum	Open	No	No	No	NR
Huo 2016 (78)	Duodenum	Open	No	No	No	12 m
Mori 2016 (79)	Duodenum	Open	No	No	No	NR
Valli 2016 (80)	Duodenum	Open	Yes	No	No	NR
Crocetti 2016 (81)	NR	Open	Yes	No	No	NR
Thillai 2017 (82)	Duodenum, adherent to ascending colon and Gerota's fascia	Open	No	Yes	No	NR
Elston 2017 (83)	Duodenum	Open	No	No	No	NR
Vasile 2017 (84)	Duodenum	Open	No	Yes	Gastric antrum, distal common bile duct, pancreatic head	24 m
Zioni 2017 (85)	Duodenum	Laparoscopic	No	No	No	1,5 y
Perfetti 2017 (86)	Duodenum	Open	Yes	Yes	No	1,5 y
Hakozaki 2017 (87)	Duodenum	Open	No	No	No	NR

NR, information not reported.

Treitz and end-to-side duodenojejunostomy with first jejunal loop (99);

- ❖ segmental resection with end-to-side or end-to-end duodenojejunostomy to the left of the superior mesenteric vessels (66,72,75) segmental resection, closure of distal stump on the right of superior mesenteric vessels, papilloplasty, end-to-side duodenojejunostomy, transcystic tube and transjejunal tubes draining the main pancreatic duct and decompressing duodenum (38);
- ❖ segmental resection of third and fourth part of duodenum, closure of second portion stump and side-to-end duodenojejunostomy (49);

Discussion

Duodenal GIST is typically seen in individuals between the ages of 60–70 years old. There were few papers reporting an occurrence of dGIST in children and teenagers, all of which manifested with severe bleeding (80,97,101). The median age of the patients with dGIST is 56 years with a slight preponderance of males (54% *vs.* 46%) (1,5).

Risk factors

Most cases are sporadic, whereas familial clustering is reported in only 1.5–4% of the cases (69,102). Familial

GIST is an autosomal dominant condition caused by germline mutations of *cKIT* or PDGFRA and manifests at earlier age. GIST may be part of Carney's triad (gastric GIST, paraganglioma, and pulmonary chondroma) or Carney-Stathakis syndrome, which are caused by germline mutations in SDH (89). It is a well-known fact that von Recklinghausen neurofibromatosis type 1 (NF 1) is associated with an increased risk for GIST. GISTs in NF 1 occur in 6–7%, affect duodenum in 22–31%, and tend to be smaller, multiple and with lower mitotic count and occur at younger age (89,103,104). Hakozaki *et al.* described a case of dGIST and rectal cancer in a patient with NF 1 (87). Malignant carcinoid of ampulla Vateri and bilateral feochromocitoma have been also described with low responses to imatinib (105). Few papers reported extremely rare combination with pancreatic neuroendocrine neoplasia (64) and somatostatinoma in NF 1 (35) and Brunner's gland cysts (78).

Localization

Most dGISTs develop in the second (59–63%) and third portion (22%) of duodenum (55,106), whereas the first and forth are less frequently affected. GIST of ampulla Vateri is extremely rare and according to the review of Kobayashi *et al.* only 12 cases have been described till 2014 (30). In all cases pain, jaundice and melena were the most frequent symptoms. Despite its rarity, this localization requires meticulous differential diagnosis (neuroendocrine tumors, carcinoma, paraganglioma) because usually the radical treatment requires PD (107).

Histopathology and molecular characteristics

Histologically, dGISTs do not differ from other GIST localizations. The most frequently reported pattern was spindle cell (67%), but epithelioid (11%), pleomorphic, mixed (22%), hemangioma-like or hemangiopericytoma-like patterns can also be seen (9,13,55,93,99,101,108-114). Immunohistochemistry staining of the specimens revealed the following distribution of the markers: CD117 (*c-kit*) (92–100%), and less frequently CD34 (54–70%), smooth muscle actin (20–30%), S-100 protein (10–20%), and neurofilament 68 (14%), DOG1 protein (6%) (9,12,65,94,115). Lack of DOG-1 expression was associated with poor prognosis in a recent study with 332 patients (93). The differential diagnosis includes fibromatosis (110), schwannomas, leiomyomas, inflammatory fibroid tumors, solitary fibrous tumor, mesenteric sclerosing fibrotic lesions, sarcomas, metastasis from malignant melanoma, glomus tumors, paragangliomas, ectopic pancreas (65,92,98).

At the molecular level, approximately 96% of GISTs have *cKIT* (CD117) mutation, typically in exon 11, but mutations in exons 9, 13, and 17 may also occur (101). Exon 11 mutations carry a better prognosis and respond well to standard dose (400 mg/dayly) of imatinib (116). Some authors reported worse outcomes in exon 9 mutation (102). Approximately 8% of the cases have PDGRFA mutation, which is mutually exclusive with *cKIT* but is associated with longer relapse-free interval (43,59,116). Some PDGFRA are resistant to imatinib (65). The so-called wild type is observed in 10–15% of the cases and in 90% of children. It is caused by germline mutations in BRAF V600E, RAS family or succinate dehydrogenase subunits (SDH A-D). GISTs in NF1 are usually wild type with possible implication of RAS-MAPK pathway (104,117-119). This subset of GISTs is relatively resistant to the treatment with imatinib. Further large studies are needed to elucidate the individual prognosis according to the mutational status.

Clinical manifestation

Approximately 70% of the cases manifest with symptoms, while 21% are found incidentally and 10% on autopsy (120). Our analysis revealed that in contrast to the other localizations the most frequent manifestation of dGIST is the upper gastrointestinal bleeding, which is in accordance with the literature (21,74,121). Constant/intermittent dull pain/discomfort or abdominal palpable mass are less frequent initial symptoms (10,32,71). Rarely, however, dGISTs may have various initial presentations leading to misdiagnosis. Millonig *et al.* reported extrahepatic cholestasis and Takotsudo cardiomyopathy in a patient with undiagnosed NF1 (122). The extremely rare dGIST of ampulla Vateri can also manifest with jaundice (30). In certain cases, extramural growth may mimic pancreatic head tumor (26,44,84,97), large duodenal cyst (61), bleeding or uncomplicated duodenal diverticula (33, 46). Wall *et al.* reported a rare case with duodenal-jejunal intussusception (23). Lin *et al.* described two cases with bleeding small dGISTs (<2 cm) initially misdiagnosed as hemobilia (123). A case mimicking refractory peptic ulcer treated for 8 years was also described (76), even hypercalcemia due to elevated serum calcitriol in metastatic disease as well (124).

Risk stratification

The recurrence risk and survival outcomes for dGIST are difficult to be determined based solely on the histopathological characteristics. Multiple factors have been proposed as predictive of survival outcomes, including tumor location and size, mitotic rate, kinase mutational status, and incidence of tumor rupture. However, tumor size and mitotic rate are the two most widely accepted risk indicators (125,126).

The Fletcher's and subsequently the modified National Institute of Health classification are the most popular risk classifications (95). Miettinen *et al.*, based on the follow-up of 140 cases with dGIST, proposed a distinct risk stratification of dGIST in which group 1 (<2 cm and <5 mitoses) is considered benign, whereas group 6 (>5 cm and >5 mitoses) carries an extremely poor prognosis with 86% mortality (18/21) within 21 months (9). The overall mortality in their series was 34%. This classification was externally validated by the French Sarcoma group in a series with 114 patients (119). The overall doubling time for dGIST is 17 months in comparison to leiomyoma (231 months). According to the risk group the doubling time is 24, 17 and 4 months in low, intermediate and high risk dGISTs (115).

Generally, there are contradictory results in the literature regarding the prognosis of dGIST in comparison to the other localizations. Certain authors reported worse outcome in comparison to small bowel and gastric GISTs (43), whereas others reported similar prognosis with small bowel localization. The more recent, population-based study of Guller *et al.* reported similar survival in gastric, duodenal and small bowel GISTs in contrast to colonic and extravisceral localizations (127). This finding was corroborated after subgroup analysis of two periods (1998–2004 *vs.* 2005–2011) thus eliminating a possible cofounding factor associated with the implementation of imatinib therapy.

Diagnosis

Although it may be straightforward in most cases, certain considerations should be kept in mind due to their occasionally misleading manifestation (128). Differential diagnosis includes adenocarcinoma, endocrine tumors, benign tumors and rare entities such as intrabdominal fibromatosis (110), ectopic pancreas (129), and Brunner's gland cysts (78).

Because most of dGISTs present with acute bleeding or chronic anemia endoscopic evaluation of upper gastrointestinal tract should be the first step (101). It allows for biopsy and can be also therapeutic. In case of failure, transarterial embolization is a method of choice, either as definitive hemostasis or as a bridging procedure before surgical intervention (39). Occasionally, endoscopy may be misleading, especially in small intramural lesions without mucosal involvement (ulceration or central depression) or located near the papilla Vateri. In such cases of diagnostic uncertainty, endoscopic ultrasound (EUS) is an invaluable modality. Usually dGISTs appears as hypoechoic and well-vascularized lesion. Two small series reported a significant correlation between the presence of intratumoral vessels on contrast-enhanced or color Doppler EUS and the malignant potential of dGISTs (130,131). EUS provides a precise evaluation of the size, border, layer of origin, echogenicity and heterogeneity of the lesions thus facilitating the differential diagnosis (lipomas, hemangiomas, ectopic pancreas, and cysts) and decision-making process (112). Additionally, EUS allows also fine needle or trucut biopsy with 100% specificity and 84% sensitivity (92,112,131,132). Percutaneous biopsy should be avoided when possible because of the risk for tumor spillage and dissemination.

Abdominal US is useful screening tool in the cases with dull pain in upper abdomen, but computed tomography (CT) and magnetic resonance imaging (MRI) are mandatory to make an exact staging and preoperative planning of surgery (107,113). On CT dGISTs appear as well-defined, heterogeneously enhanced, hypervascular mass with prominent feeding arteries and intra- or extramural growth (107,114). In contrast, the ectopic pancreas has intraluminal growth and ill-defined border with enhancement of the overlying mucosa (129). The periampullary pancreatic cancer is usually hypodense on arterial phase with concomitant pancreatic duct dilatation, periampullary neuroendocrine tumors reveal hypervascular enhancement, calcifications, lack of ductal obstruction, central necrosis and cystic degeneration, whereas solid periampullary tumors demonstrate heterogeneous hypoenhancement in both phases (114). Fluorodeoxyglucose positron emission tomography (FDG-PET) is not routine tool but can be useful to monitor the effect from imatinib treatment and follow-up (133,134).

Surgical treatment

The ESMO guideline suggests that tumors under 2 cm has low aggressive behaviour and therefore could be followed

annually by endoscopic ultrasound, "although an evidence-based optimal surveillance policy is lacking" (109). In contrast to the other localizations, in dGIST there is no uniformly adopted surgical strategy because of the low incidence, lack of enough experience, and the complex anatomy of the duodenum. Therefore, individually tailored surgical approach is recommended. In fact, there are three main surgical options: pancreatoduodenectomy (PD), wedge resection and segmental resection.

PD is indicated in the cases with involvement of major duodenal papilla, pancreas or pancreatic duodenal wall and is required in 20–40% (101,135). In some cases, it can be performed successfully in emergency setting due to life-threatening bleeding (10,24,111) even with second-stage pancreatojejunostomy (17). Tien *et al.* found that size >5 cm and preoperative diagnosis of dGIST were more frequently treated by PD (89). In another series, the patients with PD had larger tumor size and higher mitotic count (118). A recent meta-analysis of seven comparative studies confirmed categorically the above-mentioned findings (89).

Imatinib mesylate have played a key role as a neoadjuvant therapy in the management of GISTs (21,122). In locally advanced disease neoadjuvant imatinib may downstage the tumor to allow R0 resection or even an organ preserving intervention (11,122,136-138) despite the risk of bleeding (111). Ludvigsen *et al.* reported a successful PD en-block with right kidney and suprarenal gland (19). Fukuyama *et al.* reported even avoidance of PD after downstaging neoadjuvant therapy with imatinib (67). Recently, successful organ-preserving duodenectomies after neoadjuvant therapy in 9 of 10 cases was reported (92) similarly to other authors (82).

PD is, however, burdened by significant morbidity and longer hospital stay in comparison to local resection, probably due to the "soft" pancreas and small caliber of pancreatic duct (116,118,119). Moreover, several studies reported no significant difference in recurrence rate and disease specific survival between limited resection and pancreatoduodenectomy (55,97,101,104), which is categorically supported from the meta-analysis of Chok *et al.* (122) and the experience of the French Sarcoma Group (119).

R0 resection with 1–2 cm clear margin is sufficient treatment and lymph node dissection is not recommended due to the low incidence of lymphatic metastases (102). There are several options for local resection and surgical reconstruction according to the localization of the tumour. The rupture of GIST during the surgery should be avoided because is associated with nearly 100% risk for recurrence (125). Therefore, the good knowledge of anatomy, gentle handling of the tissues, and careful dissection of duodenal wall from the inferior border of pancreas, meticulous hemostasis and knowing of the possible options for duodenal reconstruction are mandatory for successful outcomes.

Laparoscopic resection is feasible and safe with reported subtotal resection with side-to-side duodenojejunostomy (100) and wedge resection (85,139). Tanaka *et al.* reported eighth cases successful segmental resections of duodenojejunal junction with side-to-side anastomosis comparable with 11 open procedures (140). Some authors reported laparoscopically assisted endoscopic submucosal resection of 20 mm GIST located in the third portion (57).

There are six reported cases of dGIST localized in first and second portion removed by robotic surgery: wedge resection (140-142) and segmental resection with side-to-side duodenojejunostomy (143).

Although in most cases wedge and segmental resections could be relatively straightforward, severe complications may occur such as acute pancreatitis, pancreatic fistula, significant blood loss and anastomotic stenosis (117,118). Delayed gastric emptying treating with gastrojejunostomy and the fearsome anastomotic failure necessitated secondary PD (101) and injury of the mesenteric root managed by total enterectomy have been described in the literature (132). The pitfalls in segmental resections are associated with the superior mesenteric vessels lying on the third portion, adjacent pancreas and the common blood supply, necessity to preserve ampulla Vateri (117,107).

Conclusions

dGIST is a very rare entity. It may be asymptomatic or may involve symptoms of upper GI bleeding and abdominal pain at presentation. Because of the misleading clinical presentation the differential diagnosis may be difficult. Gastrointestinal endoscopy is the most common initial diagnostic procedure while abdominal and thoracic CT scan are mandatory for accurate oncologic staging and surgical planning.

Tumours smaller than 2 cm have a low biological aggressiveness and can be followed annually by endoscopic ultrasound; the biggest tumors should undergo radical surgery (R0) (144). In contrast to the other localizations, dGIST have no uniformly adopted surgical strategy because of the low incidence, lack of experience, and complex anatomy of the duodeno-pancreatic region. Therefore, individually tailored surgical approach is recommended. R0 resection with 1–2 cm clear margin is sufficient treatment

and lymph node dissection is not recommended due to the low incidence of lymphatic metastases. Tumor rupture should be avoided.

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None.

Footnote

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