Primary Pancreatic GIST- A single centre case series and systematic review of literature

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Abstract

There is evolving literature on similarities and differences between GIST and EGIST. Despite their behavioural similarities, results cannot be generalised to larger population due to lack of evidence. Pancreatic GIST is a rare entity. There are many documented case reports, however long term data is unavailable. Our case series is by far the largest single centre series with long follow up data but with limited number of cases. Survival values cannot be generalised due to limited data. Large case series are required to further understand the disease biology and long term outcomes of pancreatic GIST.

Introduction

Gastrointestinal stromal tumors (GIST) are the most common non epithelial mesenchymal tumors of gastrointestinal tract (GI) with median age being 60–65 years and predominance in male gender[1]. They are believed to be kit mutation driven mesenchymal neoplasm specific to GI tract and can occur at any site where there are interstitial cells of Cajal. The most common site of GIST has been described as stomach. GISTs arising from organs outside GI tract are defined as extragastrointestinal GISTs (EGIST). Though the origin cells of EGIST are not interstitial cells of Cajal but their histology, immunohistochemistry and molecular profiles are similar to GISTs.

We present the largest single centre case series of primary pancreatic GIST so far with review of existing literature.

Materials and Methods

A total of 9 patients were treated at our institute from September 2016- February 2023. Literature search was done for previously published articles from Pubmed, MEDLINE, Google scholar and google database using key words “pancreas and GIST”, “pancreas and gastrointestinal stromal tumor”, “pancreas and extragastrointestinal stromal tumor”. Finally 51 articles including 57 patients were identified. Studies published before February 2023 were included. Clinicopathological data including age, sex, symptoms, location, tumor size, imaging features, surgical intervention, histologic type, mitotic index, immunohistochemical features, mutational status, National Institute of Health (NIH) risk classification, adjuvant imatinib therapy and survival data were recorded.

Data were processed using SPSS 25.0 for windows. Risk factors for survival were identified by univariate analysis. Survival analysis including disease free survival was obtained by Kaplan Meier method for a total of 49 patients for whom complete data of all the variables was available. The p values were considered to be significant at 5% level.

Figure 1 shows the flow chart representation of study selection process

Results

A total of 9 patients of primary pancreatic GIST were treated at our centre from 2016 to 2023. The clinicopathological features are summarised in table 1a. The most common presenting symptom was abdominal pain (n=4). All patients belonged to a median age group of 53 years (28 to 74 years). There were 55% females (n=5) and 45% males(n=4). The most common epicentre was pancreatic head (n=7) with only two patients having tumor epicentre in tail of pancreas. The median tumor size was 6 cm (2- 18 cm). Mitotic index of 5 patients were < 5/50 hpf (high power field) whereas data was not available for 4 patients and 4/8 patients were categorised as high risk as per NIH (National institute of health) risk category. Six patients displayed solid mass on cross-sectional imaging. All patients had spindle morphology on histopathology. Three patients had exon 11 kit mutation on further analysis. Two patients had recurrence with site being liver in both of them.

Review of literature

A total of 57 patients were identified from 51 published articles. Clinicopathological characteristics of all patients have been summarised in table 1b. All patients belonged to a median age group of 55 years (30-84 years). There were 47% females (n=27) and 45% males (n=26). The most common location was pancreatic head/uncinated process (n=35) followed by body/tail (n=18) with one patient having involvement of entire pancreatic tissue. The majority of patients underwent Whipple procedure or distal pancreaticosplenectomy (DPS) as per tumor location. The median tumor size was 7 cm (0.8 to 35 cm). 18 patients had mitotic count >5/50 hpf and 23 patients </=5/50 hpf. While 28 patients were categorised as high risk as per NIH risk stratification, 11 patients belonged to intermediate and 6 patients to low risk category. 50 biopsy samples were positive for CD 117 while 1 was negative and data was not available for 6 patients. CD 34 was positive for 35 patients and negative for 9 patients while data was missing for 13 patients. 26 patients received adjuvant imatinib while 10 patients didnot receive any adjuvant therapy and adjuvant therapy details were not available for 21 patients. 8 patients had recurrence postoperatively and most common site of recurrence was liver (n=5). Spindle histology was found in 39 patients while 6 had mixed and only 1 patient had epitheloid histology and data was missing for 11 patients. Median follow up time was 24 months.

Prognostic factors for DFS according to univariate analysis are summarised in table 2.

The calculated median DFS was 74 months (28.6-119.3, 95% CI) with 5 year DFS being 71.9%. [Figure 2]

Discussion

The most frequent sites in GI tract are stomach (40%-70%) followed by small intestine (20–40%), colon and rectum (5%) and esophagus (< 1%)[1, 2]. The term extragastrointestinal stromal tumors (EGIST) was first used by Reith et al to describe histologically similar stromal tumors arising from soft tissues of abdomen outside the GI tract[3]. EGISTs comprise 5%-10% of all GISTs[2, 4, 5, 6, 7]. The majority of EGISTs arise from small intestinal mesentry, mesocolon,

omentum, retroperitoneum, abdominal wall, liver and pancreas with pancreas comprising less than 5% of it[8, 9, 10]. EGISTs are usually diagnosed in adult age group with predominance in female gender[11]. The pathogenesis is explained by a gain of function mutation in c-KIT gene (90%) or platelet derived growth factor receptor alpha, PDGFRA gene (5–7%) resulting in over expression of their respective receptors and thus leading to cell proliferation[2, 4]. Multiple studies have suggested that they may arise either by extensive extramural growth resulting in loss of contact with muscularis propria of small intestine or as metastasis from a primary tumor[12].

CT (computed tomography) is usually the first modality to evaluate like other GI tumors. In case of tumors arising from pancreas, it may be confused with other solid or cystic tumors of pancreas like adenocarcinoma, pseudocyst, serous or mucinous cystadenoma/cystadenocarcinoma, lymphangioma or neuroendocrine tumors but endoscopic ultrasound guided FNA can provide an adjuct in diagnosis[13]. PET CT (positron emission tomography) can be used in both diagnosis and response assessment to neoadjuvant therapy and is of special help where both CT and MRI (magnetic resonance imaging) are inconclusive[14].

The clinical presentation and symptom severity is determined by the tumor size and its location in the pancreatic tissue. The most common symptoms reported are abdominal pain, weight loss, fatigue, abdominal mass and distension, GI bleeding, anemia and jaundice[5, 15]. In our review, most common symptoms were abdominal pain and weight loss (48.4%) and 18.2% cases were diagnosed incidentally.

Histopathologically, GISTs are classified into spindle cell (70%), epitheloid (20%) or mixed types (10%) of which spindle cell is the most common type[5]. EGISTs have typical immunohistochemical features most common of which is CD 117 (95%) followed by CD 34 (60–70%). In cases with negative staining for CD 117, further testing for PDGFRA is suggested[2]. Additional staining markers of GISTs are heavy caldesmon (80%), SMA (30%-40%), S100 (5%), and desmin (< 5%)[2, 5, 6, 15]. In present review out of histopathological data available for 44 patients, 82% cases had spindle cell morphology while mixed and epitheloid comprising only 18% with spindle cell morphology associated with 2 years DFS of 77% ($p < 0.001$). CD 117 was positive for 98.3% (59 out of 60 patients) and CD 34 in 83% (40 out of 48 patients) which is in accordance with the literature. The characteristic histopathological features are depicted in Fig. 3.

Understanding risk stratification of disease is important for management. Fletcher[16] defined a criteria for defining risk of aggressive behaviour in GISTs based on tumor size and mitotic count. As per criteria, GISTs are classified into very low risk (< 2cm, < 5/50 hpf), low risk (2–5 cm, < 5/50 hpf), intermediate risk (< 5 cm, 6–10/50 hpf; 5–10 cm, < 5/50 hpf), high risk (> 5cm, > 5/50 hpf; >10 cm, any mitotic rate; any size, > 10/50 hpf). This classification aids in neoadjuvant and/or adjuvant treatment selection and planning. In present review, risk stratification was available for 44 patients out of which, 59% patients belonged to high risk category while 41% to intermediate and low risk.

Surgery with microscopically negative margins is the treatment of choice for pancreatic GISTs[2, 5]. Extent of surgery depends on the tumor location. Regional lymph nodal involvement is rare in pancreatic EGISTs and hence routine systematic regional lymph node dissection can be avoided[5, 9].

With the advent of imatinib, c-kit tyrosine kinase inhibitor for GIST management, median overall survival now gets extended upto 5 years with a positive response rate to therapy upto 60–70%[5, 15]. It can be used either as neoadjuvant therapy for downstaging or as adjuvant therapy in case of positive margin, aggressive risk category and poor prognostic features[2, 5]. It can also be used for metastatic or advanced unresectable tumors for downstaging thus making surgical resection feasible and providing better prognosis[5]. In present review, only 18.2% patients received neoadjuvant therapy with Imatinib while details were not known for 12%. At our institute we give neoadjuvant therapy to all patients with locally advanced GIST who might require extensive resection which in our series was given to 7 out of 9 patients.

Conclusion

There is evolving literature on similarities and differences between GIST and EGIST. Despite their behavioural similarities, results cannot be generalised to larger population due to lack of evidence. Pancreatic GIST is a rare entity. There are many documented case reports, however long term data is unavailable. Our case series is by far the largest single centre series with long follow up data but with limited number of cases. Survival values cannot be generalised due to limited data. Large case series are required to further understand the disease biology and long term outcomes of pancreatic GIST.

Declarations

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The authors declare that they have no conflict of interest.

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Vipul Gupta, Amit Chopde. The first draft of the manuscript was written by Vipul Gupta and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

The study is compliant with ethical standards.

Written informed consent was obtained from the patient for the surgery

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Tables

Table 1a: Clinicopathological characteristics of patients treated in our institute

S.No.	Characteristics	n (%)
1.	Age	5 (55)
	</=53	4 (45)
	>53	
2.	Sex	
	Male	4 (45%)
	Female	5 (55%)
3.	Epicentre	
	Head	7 (77)
	Tail	2 (22)
4.	Tumor size	
	</=6	5 (55)
	>6	4 (45)
5.	Histology	
	Spindle	9 (100)
6.	Mitotic index	
	</=5	5 (55)
	>5	0
7.	NIH risk category	
	High	4 (45)
	Low	4 (45)
8.	Neoadjuvant therapy	
	Yes	7 (77)
	No	2 (23)
9.	Adjuvant therapy	
	Yes	7 (77)
	No	1 (11)
10.	Immunohistochemistry	
	CD 117	8 (89)
	CD 34	5 (55)
	DOG 1	9 (100)
11.	Mutational status	
	Wild	2 (22)
	Exon 11	3 (33)
12.	Imaging features	6 (66)
	Solid	3 (33)
	Mixed	

Table 1b Clinicopathological characteristics of 57 patients identified from literature

Reference	Year	Age (years)	Sex	Presentation	Tumor location	Tumor Size (cm)	Histology	NIH risk	Mitotic Count (per 50 hpf)	CD 117	CD 34	S
Beji[17]	2022	53	M	Abdominal pain	Body + Tail	NA	NA	High	NA	+	-	E
Zackria[18]	2022	74	F	Incidental finding	Uncinate	2.9x2.5	Spindle	Intermediate	NA	+	+	N
Uzunoglu[19]	2021	39	M	NA	Head	0.8	Mixed	Intermediate	NA	NA	NA	W c
Dragos[20]	2021	53	F	Malena + weight loss	Head	8x7x5	Spindle	High	>5	+	-	W
Castellon CJ[21]	2020	50	M	Abdominal pain + Weight loss	Head	3.5x2.8x2	Spindle	NA	<5	+	-	L e
Irene Yau[22]	2019	53	M	Malena	Head	2.3x1.5	Spindle	NA	NA	+	NA	N
Tounsi[23]	2018	49	F	Abdominal pain	Head	2.4	NA	NA	<5	+	+	E
Rasool[24]	2018	60	M	Abdominal pain +weight loss	Head	3.5	NA	High	<5	NA	NA	P
Sinan Yol[25]	2018	56	M	Abdominal pain	Head	15	Spindle	NA	<5	+	+	W
SJ Yeo[26]	2018	45	F	Abdominal pain	Head + uncinate	6.5	Spindle	Low	<5	+	+	P
Abderraheman[27]	2017	53	F	Abdominal pain	Head	11.6 × 10.5 × 9	Mixed	High	>5	+	+	W c
Kwon[28]	2017	64	F	Incidental finding	Head	7	Spindle	High	5	+	+	W
Zhang[29]	2016	60	F	Abdominal pain	Head	3.6	Spindle	Low	NA	NA	NA	W
Lei liu[30]	2016	56	F	Incidental	Body	5.7x2.7	Spindle	NA	<5	+	-	N
Elgeidi[31]	2016	30	M	Abdominal pain + weight loss	Tail	1.2x1.1x0.3	Spindle	NA	>5	+	+	D
Aziret[32]	2015	56	M	Abdominal pain	Head	4	NA	High	NA	+	+	W
Joseph[33]	2015	60	M	Abdominal pain	Body + Tail	2.1x1.8x 1.4	Epitheloid	Intermediate	<5	+	+	N
Stanek[34]	2015	55	M	Incidental finding	Uncinate	2×1.7× 1.6	Spindle	High	<5	+	+	T
Hansen[35]	2014	74	F	Malena	NA	12 × 8 × 5	Mixed	High	>5	+	-	E
Ambrosio[36]	2014	72	M	Abdominal pain	Head	1.9x1.4x 1.2	Mixed	Low	>5	+	+	W
		50	F	Abdominal lump	Head	7x4x3	Spindle	Low	<5	+	+	W
		NA	NA	NA	Head	7x5.5x 3.5	Mixed	Intermediate	>5	+	+	W
Tian et al[5]	2014	61	NA	Incidental finding	Tail	6 × 8	Spindle	NA	< 5	+	+	D
		60	M	Incidental finding	Head	6 × 5	Spindle	Intermediate	> 5	+	NA	T
Akbulut[15]	2014	61	F	Weight loss	Head	5x4	Spindle	Low	NA	NA	NA	W
Beltrame[37]	2014	63	F	NA	Uncinate	2.4	NA	High	<5	+	NA	E
Paklina et al[38]	2013	38	F	Abdominal discomfort	Head	9	Spindle	NA	<5	+	NA	N
Serin et al[4]	2013	30	M	Abdominal distension	Tail	13	NA	High	NA	+	NA	D

Soufi et al[10]	2013	39	M	Weight loss + abd pain + constipation	Head	9 × 7 × 5	Spindle	Intermediate	< 5	+	+	W c
Wegge et al[39]	2012	55	M	Haematemesis + haematochezia	Head	4.6 × 4.5 × 4.4	Spindle	High	>5	+	+	W
Babu et al[9]	2012	55	F	Upper abdominal pain	Head	5 × 4 × 3	Spindle	High	>5	+	+	P re
Kim et al[40]	2012	55	M	Abdominal discomfort	Tail	13 × 9 × 8.5	Spindle	Intermediate	>5	+	+	D
Cecka et al[6]	2012	74	F	Abdominal mass	Tail	11 × 8× 4	Spindle	Intermediate	5	+	+	D
Vij et al[11]	2011	35	M	Weight loss + abdominal discomfort	Head	8 × 6	Spindle	High	>5	+	-	W
Meng[41]	2011	42	M	Abdominal lump	Head	10x8x3	Spindle	Intermediate	<5	+	+	N
Rao et al[42]	2011	40	M	Weight loss + abdominal pain + anemia	Head + Body	6.5 × 6	Spindle	High	>5	+	+	W
Yang et al[43]	2011	55	M	Abdominal discomfort	Body + Tail	17.8 × 19.6	Spindle	High	>5	+	+	D
Barros et al[7]	2011	63	F	Abdominal pain + ponderal loss	NA	NA	NA	High	< 5	+	+	N
		81	F	Difficult gastric emptying + ponderal loss	NA	10	NA	High	< 5	+	+	L
Joshi et al[44]	2010	84	M	Weight loss + abdominal distension	Entire pancreatic tissue	34×24×27	Spindle	High	NA	+	+	N
Crisan et al[45]	2010	61	M	Weight loss + fever	Tail + Body	14	Spindle	High	NA	+	+	D
Saif et al[46]	2010	31	M	Weight loss + abdominal pain + anemia	Head	5.6 × 5.1 × 4.2	Spindle	High	>5	+	-	W p
Padhi et al[2]	2010	42	F	Weight loss + abdominal pain	Body + Tail	35×3× 25	Spindle	High	>5	+	+	D h
Harindhanavudhi[47]	2009	63	F	Fatigue + weakness+anemia	Body	16 × 11	Spindle	High	< 5	+	+	C
Trabelsi et al[48]	2009	52	F	Epigastric pain	Head	10.5 × 8 × 3	Spindle	High	>5	+	+	W c
Goh et al[8]	2009	58	M	Incidental finding	Head	9	Spindle	High	> 5	+	NA	W
Showalter et al[49]	2008	72	F	Incidental finding	Tail	7	NA	Intermediate	<5	+	-	D
Yan et al[50]	2008	47	M	Nausea + vomiting	Uncinate	2.4 × 2.1	Spindle	NA	<5	+	NA	N
Ganesh et al[51]	2008	76	F	Weight loss + abdominal pain	Tail + body	NA	Spindle	Intermediate	NA	+	+	N
Daum et al[52]	2005	70	F	Incidental finding	Head	10×8 ×6	Spindle	High	<5	+	-	W
Krska et al[53]	2005	38	F	Abdominal pain	Head + Body	17×12	Spindle	NA	<5	-	+	P
Pauser et al[54]	2005	51	M	Incidental finding	Tail	3	Spindle	NA	NA	+	+	R
		54	F	Abdominal discomfort	Body	2	Spindle	High	NA	+	+	R

Neto et al[55]	2004	67	F	Weight loss + abd pain	Body + Tail	20×19× 12	Mixed	High	>5	+	+	D
Yamaura et al[56]	2004	54	F	Incidental finding	Tail	14×12 ×8	Spindle	Low	NA	+	+	D g
Boyer[57]	2001	52	NA	NA	Head	NA	NA	High	NA	NA	NA	S
		61	NA	NA	Head	NA	NA	NA	NA	NA	NA	P d

Table 2 Univariate analysis for DFS

Characteristic	2 year DFS probability	N	Event N	p-value[1]
Age Code				0.4
<=55	72% (54%, 97%)	31	6	
>55	68% (49%, 96%)	18	6	
Sex				0.14
Male	58% (38%, 89%)	24	8	
Female	83% (67%, 100%)	25	4	
EPICENTRE				0.8
Body/Tail	71% (51%, 100%)	17	4	
Head/uncinate	72% (54%, 94%)	30	8	
TUMOR SIZE CM				0.5
<=7 (Median)	70% (52%, 94%)	25	8	
>7 (Median)	71% (51%, 100%)	22	4	
Histologic Type Code				**<0.001**
Spindle	77% (62%, 95%)	36	8	
Mixed/ Epitheloid	0% (37%, 100%)	8	4	
MITOTIC INDEX				**0.002**
<=5	88% (73%, 100%)	21	2	
>5	14% (2.3%, 83%)	17	8	
NIH Risk Code				**0.013**
Low / Intermediate	100% (100%, 100%)	18	1	
High	52% (33%, 82%)	26	10	
MUTATIONAL STATUS				0.3
Wild	100% (100%, 100%)	2	0	
Exon 9 kit	— (—, —)	2	1	
Exon 11 kit	86% (63%, 100%)	7	2	
Exon 18 kit	— (—, —)	1	1	
ADJUVANT				**0.013**
No	100% (100%, 100%)	13	0	
Yes	53% (35%, 80%)	28	12	
NEOADJUVANT				>0.9
No	66% (50%, 88%)	39	9	
Yes	88% (67%, 100%)	8	3	
Overall	72% (58%, 89%)			

Figures

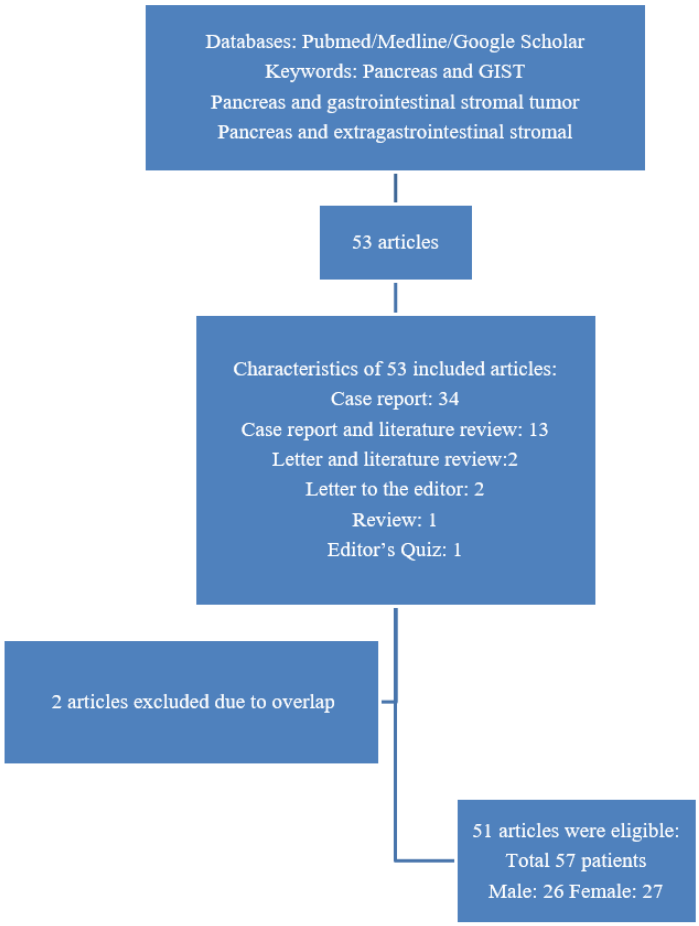

Figure 1

Study Selection Process

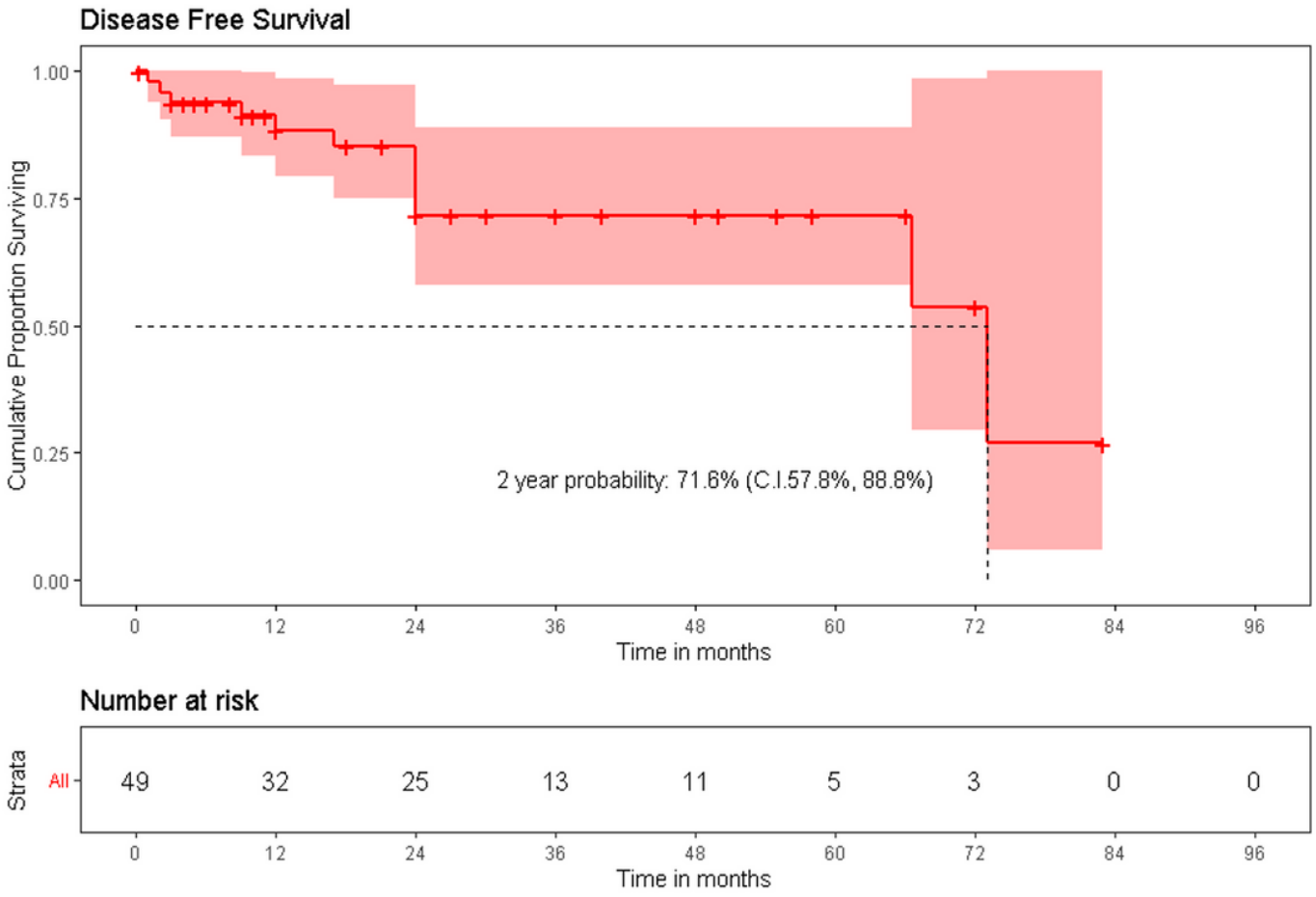

Figure 2

Disease free survival of pancreatic GIST patients

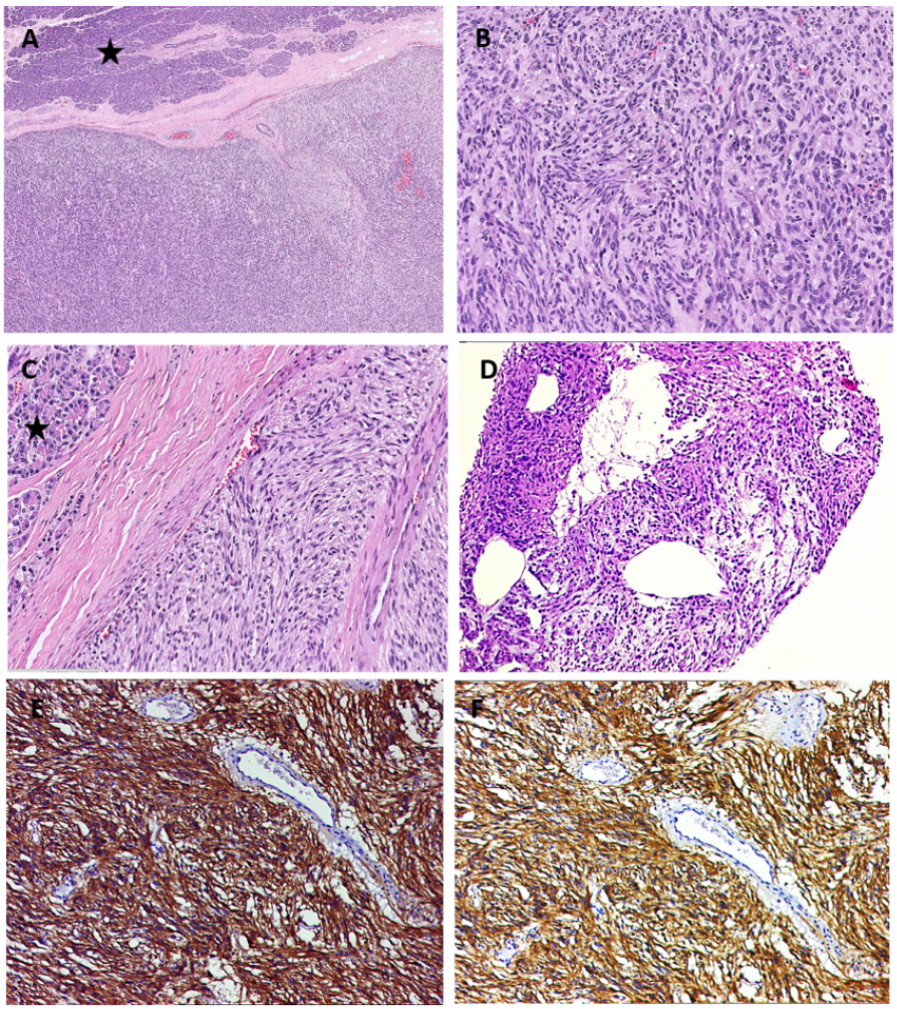

Figure 3

Histopathologic features of pancreatic gastrointestinal stromal tumors (GIST).

A-D) Haematoxylin and eosin stained sections. A) Low magnification reveals a tumor with pushing borders invading pancreatic parenchyma (star). B) Higher magnification shows spindled tumor cells arranged in short fascicles and exhibiting moderate nuclear atypia and low mitosis. C. Tumor is composed of uniform appearing spindle cells in a collagenous stroma; pancreatic tissue is visible at one aspect (star). D. Pancreatic biopsy cores showing a spindle cell GIST with scant myxoid stroma. E-F) Immunohistochemistry stains. E) Immunohistochemistry for CD117 (c-kit) reveals strong and diffuse cytoplasmic positivity in the tumor cells. F) Tumor cells are strongly positive for DOG1 immunohistochemistry