Diagnosis and Treatment of Abdominal Extra-Gastrointestinal Stromal Tumors

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Abstract

Background: To investigate the clinicopathological features and treatment outcome of abdominal extra-gastrointestinal stromal tumors (EGISTs). **Methods:** The clinicopathological data and follow-up results of 22 patients with abdominal EGISTs proved by pathology were reviewed retrospectively. **Results:** The main symptoms were abdominal mass in 14 cases, abdominal distention and pain in 6, detected by healthy screening in one, spontaneous rupture of tumor and intra-abdominal hemorrhage in one. The tumor locations were retroperitoneum in 11 cases, mesentery in 6, and greater momentum in 3, liver in one and pancreas in one, and the tumor size <5cm in one case, 5-10cm in 9 and >10cm in 12. The immunochemistry stain revealed that the positive rate of CD117 was 95.5%, CD34 36.4%, DOG-1 13.6%, SMA 4.5%, and S-100 protein 4.5%. The resection rate was 81.8% (18/22 cases), including tumor resection in 16, an irregular hepatectomy in one, a distal pancreatectomy in one, and simple laparotomy with biopsy in 4. The radicality of operation was R0 resection in 14 cases, R1 resection in 2 and R2 resection in 2. Eleven cases (50.0%) in this group received imatinib adjuvant treatment, including administration greater than 1 year in 6 cases, and greater than 3 years in 5. The 1, 3, 5-year overall survival rates in the study were 88.9% (16/18 cases), 72.2% (13/18), and 55.6% (10/21), respectively. Among them, 72.7% (8/11), 45.5% (5/11) and 45.5% (5/11) were for retroperitoneal tumors, respectively; and 100.0% (6/6), 100.0% (6/6) and 66.7% (4/6) for mesentery EGIST, respectively. **Conclusions:** Abdominal EGISTs have a high potential of malignancy, the surgery is the choice of the treatment, and the postoperative adjuvant treatment with imatinib may improve the survival rate of high-risk cases. [Key words] Extra-gastrointestinal stromal tumor; Abdomen; Surgical treatment; Imatinib

Background

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors originating from the interstitial cells of Cajal in the gastrointestinal tract, with KIT or PDGFR α (platelet-derived growth factor receptor alpha) activation mutations [1-4]. The most common localization is the stomach (50-60%), followed by small bowel (20-30%), rectum (10%) and esophagus (5%) [1-2].

Tumors that originate from outside of the gastrointestinal tract, which show no connection to the wall or the peritoneal surface of the gastrointestinal tract, are defined as extra-gastrointestinal stromal tumor (EGIST) [5]. It is reported that EGISTs constitute only 5%-10% of GISTs cases, and most EGISTs are derived from the mesentery, omentum, and retroperitoneum [4-10], and other unusual primary anatomic locations of EGISTs have also been reported, including the liver, pancreas, mediastinum and gall bladder [5-15]. Though EGISTs exhibit similar histological features and immunohistochemistry to GISTs, they are a unique entity, which require distinction from GISTs [11]. For example, EGISTs possess a higher malignant potential and risk of recurrence following surgery, and exhibit a worse prognosis by comparison with GISTs in the alimentary tract [1,5,8-10]. In view of the unclear clinicopathological behavior and treatment of EGISTs, further study is necessary [2-4]. The data of 22 cases of abdominal EGISTs were respectively analyzed for the purpose of improving diagnosis and treatment level.

Methods

1. Patient characteristics

22 patients with abdominal EGISTs were treated at the First Affiliated Hospital of Wenzhou Medical University, Jiangxi Cancer Hospital and Henan Cancer Hospital, China from January 2000 to December 2016, who underwent surgery and were proven histopathologically and immunohistologically. They included 13 males and 9 females; the median age on diagnosis was 60.3 years, ranging from 25 to 74 years old.

The following patients were included in this study: ①patients who were pathologically diagnosed as having abdominal EGISTs preoperatively or postoperatively; ②the location, the extent and the size of tumor were determined by preoperative endoscopic ultrasonography (EUS) and/or abdominal computerized tomography (CT) examination; ③and patients without other malignant tumors. Patients who refused surgical intervention were excluded.

This study was conducted according to Wenzhou Medical University ethics guidelines and was approved by the institutional review board in each institution. Written informed consents were obtained from the patients for the publication of this report and any accompanying medical records.

2. Pathological diagnosis and classification for malignant potential

Two pathologists who were blinded to the data reviewed all the specimens; if their initial diagnoses differed, the pathologists would reassess the specimens and discuss their findings to reach the consensus. The diagnostic criteria of abdominal EGIST were as following [1-2]: ①gastrointestinal stromal tumor diagnosed by histopathology; ②the tumor location was abdominal tissues except gut (including esophagus, stomach, duodenum, small bowel and colorectum); ③the entire histopathological data.

Tumor risk category was comprehensively defined by tumor size, cellular heteromorphism, mitotic index, and ki-67 protein expression, based on the suggestion of the consensus of the National Institutes of Health (NIH) workshop[2]. Tumors of <5cm with slight heteromorphism, mitotic index <5 mitoses/50 high-power fields (HPF) and ki-67 index< 10% were classified into the low-risk group; Those of >5-10cm with medium heteromorphism, mitotic index >5 mitoses/50HPF and ki-67 index< 10% were classified into the intermediate risk group; A tumor of >10cm with high heteromorphism, mitotic index >10 mitoses/5 HPF and ki-67 index< 30% were classified into the high risk group.

3. Postoperative follow-up

Patients were scheduled for follow-up with abdominal CT scanning and/or endoscopy according to risk classification, every 3 months during the first two years and every 12 months thereafter. Follow-up was completed by either chart review or telephone interview in December 2016.

4. Statistical analysis

Statistical analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA). The different characteristics were compared between the groups using a Chi-square test or Fisher's exact test for categorical variables and using a Student's t-test for continuous variables. $P < 0.05$ was considered as statistically significant.

Results

1. The clinicopathological features of EGISTs

The median age of 22 cases with abdominal EGIST was 60.3 years old (ranging from 25 years to 74 years). The main clinical presentations were abdominal mass in 14 cases, abdominal distention and pain in 6, detected by healthy screening in one, spontaneous rupture of tumor associated with intra-abdominal hemorrhage in one. No hematoemesis, melena and intestinal obstruction symptoms were found in this group. Synchronous liver metastasis was in one case at the time of diagnosis.

Ultrasound examination was performed in all cases, and it revealed retroperitoneal solid and liquid tumor in 11, abdominal occupying lesion in 8, greater omentum in 1 and liver tumor and pancreas in one each. Abdominal CT scanning revealed abdominal tumor in 13 cases, mesentery mass in 4, greater omental mass in 3, liver tumor in one, and pancreatic tumor in one. Twelve of 22 cases underwent magnetic resonance imaging (MRI) study and revealed abdominal and retroperitoneal tumor in 16, mesentery mass in 2, greater omental mass in 1, liver tumor and pancreatic tumor in one each.

All patients underwent endoscopy to rule out the tumor arising from gastrointestinal tract.

2. Histopathological findings and risk classification

The primary tumors were retroperitoneum in 11 cases, mesentery in 6, and greater momentum in 3, liver and pancreas in one each. The median tumor size was 8.6cm in diameter (ranging from 4.0 to 22.0cm), including tumor size <5 cm in two cases, among 5 to 10cm in 6 and >10 cm in 14. The smallest tumor located at lesser omentum, and largest tumor located at retroperitoneum.

Histopathological examination of the specimen showed a well circumscribed lobulated mass with surrounding fibrous capsule and pushing borders made up of proliferation of epithelioid cells. On microscopy, the tumor cells were spindle, oval or round in shape, sometimes signet-ring like cells could be observed with a clear cytoplasm. Seven cases (31.8%, 7/22) displayed spindle cell morphology, 14 (63.6%, 14/22) displayed epithelioid morphology and 1 displayed mixed morphology (4.5%, 1/22).

The mitotic index of 16 cases exceeded 5/50 high power field (HPF) (16/22, 72.7%). According to NIH risk classification, one (4.5%, 1/22) were low risk, 6 (27.3%, 6/22) were intermediate risk, and 15 (68.2%, 15/22) were high risk.

3. Immunohistochemical staining

Immunohistochemical analysis showed diffusely strong CD117 positivity for both cytoplasmic and membranous components and focal positivity for S100, and CD117 positivity was detected in 21 cases (95.5%, 21/22), CD34 positivity was detected in 8 (36.4%, 8/22), DOG-1 positivity was detected in 3 (13.6%, 3/22), smooth muscle actin (SMA) protein positivity in 1 (4.5%, 1/22), S-100 protein positivity in 1 (4.5%, 1/22) and desmin negative. Desmin and neuron specific enolase (NSE) are used for differential diagnosis.

4. Surgical outcomes

All EGISTs underwent laparotomy, including elective surgery in 21 cases, and emergent surgery in 1 because of tumor rupture associated with intra-abdominal hemorrhage. The resection rate was 81.8% (18/22 cases), and the surgical procedure was removal of tumor in 16 (once case with removal of primary tumor and liver metastasis), an irregular hepatectomy in one, a distal pancreatectomy in one, and simple laparotomy with biopsy in 4 due to tumor invasion of major vessels, and lymph node metastasis. The radicality of operation was R0 resection in 14 cases, R1 resection in 2, and R2 resection in 2.

5. Oncological results

The follow-up data was available for 18 cases, and 4 lost to follow-up, including 3 cases arising from retroperitoneum and one originating from liver. The median follow-up was 18.5 months, ranging (6-163 months). The 1, 3, 5-year survival rates of all abdominal EGISTs were 88.9% (16/18 cases), 72.2% (13/18), and 55.6% (10/21), respectively. Among them, the 1, 3, 5-year survival rate of 11 retroperitoneal tumors were 72.3% (8/11), 45.5% (5/11) and 45.5% (5/11), respectively; and 100.0% (6/6), 100.0% (6/6) and 66.7% (4/6) for 6 cases with mesentery EGIST, respectively. Once omental EGIST case with follow-up data survived more than 5-years, and the pancreatic EGIST case survived more than three year, the other two abdominal EGIST only treated with laparotomy died within 1 year after operation (Figure 1).

6. Adjuvant treatment with imatinib after surgery

Information of adjuvant imatinib therapy were recorded in 11 patients (50.0%), and they underwent adjuvant therapy with imatinib 400mg qd by mouth, six of the 11 patients had taken imatinib more than 1 year, and five had taken imatinib more than 3 year.

The main side-effects were hand-foot syndrome in 5 cases, liver dysfunction in 3, most of them were grade 1 or 2, and only one with pelvic EGIST complicated with grade IV side-effect and had to discontinue using the agent.

Conclusions

The so-called extra-gastrointestinal stromal tumors (EGISTs) are rarely reported group of tumors that arise outside the gut but histologically and immunohistochemically similar to GISTs, which are caused by

KIT or PDGFR α mutations [1,5,9-11]. EGISTs are very rare tumors accounting only the 5-7% of all GISTs, and it can arise from omentum, mesentery and retroperitoneum, very rarely it can originate from pancreas, liver, ovary, prostate gland and so forth [7,8-10]. GISTs are typically solitary neoplasms, mainly originating in stomach (60%), small intestine (30%), rectum (5%), and esophagus (5%). By immunohistochemistry, most GISTs are positive for DOG1 (found on GISTs) and KIT (CD117), and often also for CD34. These stains are helpful in the differential diagnosis of morphologically similar intraabdominal lesions [9-16].

1. The clinical features of EGIST

The clinical presentation of abdominal EGIST varies greatly due to anatomic location and tumor size, usually the abdominal mass with pain, and abdominal tumor with rupture are the most common findings, rarely present as gastrointestinal obstruction and hemorrhage[2,5-7,9-14]. Sometimes, EGISTs are discovered incidentally during a work up for an unrelated condition [2,5-7]. Feng et al [12] collected 93 cases of omental GIST reported in English literature, the most common symptom was abdominal pain (25/51, 49.0%), followed by abdominal mass (10/51, 19.6%) and abdominal distension (8/51,15.7%). Yi et al[17] analyzed the clinicopathologic features of 51 EGIST patients in South Korea, the most common site was the mesentery (n=15), followed by the retroperitoneum (n=13) and omentum (n=8). The median tumor size was 9.0 cm (range: 2.6-30.0 cm) and the median mitotic rate was 5.0/50HPF. In this study, the main clinical presentations were abdominal mass in 14 cases, abdominal distention and pain in 6, detected by healthy screening in one, spontaneous rupture of tumor and intra-abdominal hemorrhage in one, and synchronous liver metastasis was in one case at the time of diagnosis, which is similar to the literature report [2-3,4-16]. Also, our study revealed that the tumor size was 6.8cm (ranging from 4.0cm to 22.0cm), including 2 cases with tumor <5cm in diameter, 6 with tumor size between 5 to 10cm, 14 with tumor> 10cm, this results suggested the most EGISTs were very advanced disease at diagnosis, difficult to diagnose in early stage.

2. Histopathological behavior

The diagnosis of EGIST is established based on the morphology and immunophenotyping[1-2]. In this study, the specimen showed a well circumscribed lobulated mass with surrounding fibrous capsule appearance, and the tumor cells were spindle, oval or round in shape, sometimes signet-ring like cells could be observed with a clear cytoplasm on microscopic observation. Moreover, the histopathological types included spindle cell morphology in 7 cases (31.6%), epithelioid morphology in 14 (63.6%) and mixed morphology in 1(4.5%). Those changes in this study revealed that the histopathologic changes and types in EGISTs were similar to those in GISTs, they were in accordance with the description by Reith et al [9].

In 95% of EGIST cases, the CD117 protein exhibits a strong, diffuse positive immunohistochemical reaction, and 60-70% of EGISTs were CD34-positive[2-4]. Feng et al[12] reported the positive rates of CD117, CD34 and DOG-1 were 84.5%, 83.7% and 88.9%, respectively. An immunochemical study of EGIST from Reith et al [9], revealed that the tumors expressed CD117 (100%), CD34 (50%), NSE (44%), SMA

(26%), desmin (4%), and S-100 protein (4%). Miettinen et al[10] reported the immunochemical study of omental GIST was as following: these tumors were KIT positive 38/41, CD34 positive 20/33. Immunohistochemical stain in this study showed diffusely strong CD117 positivity for both cytoplasmic and membranous components, and the positive rate of CD117 was 95.5% (21/22), CD34 positivity 36.4% (8/22), DOG-1 positivity 13.6% (3/22), SMA positivity 4.5% (1/22) S-100 positivity 4.5% (1/22). These results suggest EGIST has a similar immunochemistry with GIST.

The risk of malignant behavior of E-GISTs ranges from very low to high based on mitotic rate and size and also on location. Generally, tumors larger than 5cm with more than 5 mitoses per 50 HPFs are considered to be high-risk and EGISTs of retroperitoneum are more aggressive[3,4,9]. In this study, the mitotic index of 16 cases exceeded 5/50 HPF (72.7%). According to NIH risk classification, 1 tumor (4.5%) were low risk, 6 (27.3%) were intermediate risk, and 15 (68.2%) were high risk. These results suggest most EGISTs are high risky and aggressive group of stromal tumors with a malignant potential and a high rate of recurrence.

3. Surgical treatment of EGIST

Surgical removal is the gold standard treatment and the only known curative therapy for non-metastatic GISTs and it is important to achieve a complete removal of the mass when “en block” with the contiguous tissues is possible [2,5-8,18-19]. Following this principle, complete surgical resection with negative margins (R0 resection) is the choice of therapy, and lymph node dissection is not a routine standard practice, because diffuse intraabdominal spread and liver metastasis are the common spread pattern of tumor ways, whereas lymph node metastases are extremely rare [4-9]. Moreover, laparoscopic resection is not being suggested routinely owing to its easy rupture of tumor before or during surgery, which can cause abdominal dissemination and affect the prognosis of EGIST patients. In our study, the resection rate was 81.8% (18/22 cases), and the surgical procedure was removal of tumor in 16 (once case with removal of primary tumor and liver metastasis), an irregular hepatectomy in one, a distal pancreatectomy in one, and simple laparotomy with biopsy in 2 due to tumor invasion of major vessels, and lymph node metastasis. The radicality of operation was R0 resection in 14 cases, R1 resection in 2, and R2 resection in 2.

4. Imatinib mesylate treatment

Imatinib mesylate, which is an inhibitor of the tyrosine kinase activity of C-Kit, has been effective in treatment of GISTs, and neoadjuvant and adjuvant therapy with imatinib has been shown to reduce the risk of recurrence and improve the survival[18-25]. Dimofte et al[20] reported that a case of a primary epithelioid EGIST of the greater omentum treating with surgery following Imatinib mesylate, was disease free at two-year follow-up. Yi et al[17] reported that 31 of 51 patients with an EGIST had undergone surgery, and 10 had unresectable disease and accepted palliative imatinib treatment, which resulted in 22.7 mo of progression-free survival. In this study, 11 cases (35.5%) underwent adjuvant therapy with imatinib 400mg qd by mouth, 10 of them had taken imatinib more than 1 year, 4 had taken imatinib more than 3 years.

5. Survival and recurrence

Compared with GISTs, EGISTs are considered to exhibit a worse prognosis, because EGISTs are commonly accompanied by certain adverse prognostic factors, such as larger tumors, late detection and distant or lymph node metastases[1-2,4-9,11,13-16, 21]. The estimated 5- and 15-year recurrence-free survival rates for GISTs treated with surgery alone are 70.5 and 59.9%, respectively[2,4-9]. Feng et al[12]summarized 93 cases of omental GISTs, the 1-, 3- and 5-year disease-free survival was 90.8%, 86.3% and 86.3%, respectively. Miettinen et al[10] reported the median survival was 129 months (range: 0 to 397 months). Bischof et al[22] collected 158 advanced GIST patients, they found the 3-year recurrence-free survival and overall survival (OS) rates in locally advanced GIST patients (n=87) were 65% and 87%, respectively; whereas those in recurrent/metastatic GIST patients (n=71) were 49% and 82%, respectively. In our study, the 1, 3, 5-year survival rates of all abdominal EGISTs were 88.9% (16/18 cases), 72.2% (13/18), and 55.6% (10/18), respectively. Among them, the 1, 3, 5-year survival rate of 11 retroperitoneal tumors were 72.3% (8/11 cases), 45.5% (5/11) and 45.5% (5/11s), respectively; the 1, 3, 5-year survival rate of 6 cases with mesentery EGIST was 100.0% (6/6), 100.0% (6/6) and 66.7% (4/6), respectively.

Approximately half of patients undergoing macroscopically complete surgical resection will experience disease recurrence within the following 5 years [5,9-15,22-23]. Feng et al[12]summarized 93 cases of omental GIST, and found 7 showed recurrence or metastasis, 6 suffered from GIST related deaths. Li et al[23] analyzed 112 Chinese patients with GIST, they found the 3, 5-year OS rates were 71.4 and 58.6%, respectively, and multivariate analysis showed that tumor size, metastasis, resection margin status, mitotic rate, P53 and adjuvant therapy with imatinib were independent prognostic factors associated with OS. Many of the studies had reported that a tumor size of more than 5 cm and a mitotic count of >5/50 HPF has high tumor-related mortality[1-2,4]. Prognostic factors of recurrence have been investigated for R0 or R1 surgical patients, tumor size, mitosis and tumor location is considered to be significant and independent prognostic factor [22]. In addition, rare tumor rupture has recently been identified as a prognostic factor [24-26].The only features that have proved to be predictive of GIST behavior are tumor size and mitotic rate. In this study, the mitotic index of 16 patients with EGIST exceeded 5/50 HPF (16/22, 72.7%), and most were either NIH intermediate risk (27.3%) or high risk (68.2%).

In conclusion, EGISTs are very rare aggressive tumors with high metastatic potential and a high recurrence rate, though they have similar histological and immunohistochemical features. Complete tumor resection with a microscopic negative margin and the postoperative adjuvant treatment with imatinib are considered the optimal treatment option, and may improve the survival rate of high-risk cases.

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Declarations

Conflict of interest

We have no conflicts of interest to declare.

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Ethical approval

Documented informed consent was obtained from patients.

Author contribution

Study conception and design: Han SL; Data collection and data analysis: Rao HM, Ji SQ and Huang HZ; Analysis and interpretation of data: Zhou F; Writing manuscript: Du Z and Han SL.

Consent

Written informed consent has been already obtained from these patients and we describe about it in our manuscript.

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Tables

Table 1: The histopathological variables of abdominal EGIST

Variables	Cases (%)
Clinical presentation	
Abdominal mass	14(63.6%)
Abdominal distention and pain	6(27.3%)
Detected in healthy screening	1(4.5%)
Spontaneous rupture of tumor associated with intra-abdominal hemorrhage	1(4.5%)
Tumor location	
Retroperitoneum	11(50.0%)
Intestinal mesentery	6(27.3%)
Greater omentum	3(13.6%)
Liver	1(4.5%)
Pancreas	1(4.5%)
Tumor size (diameter)	
<5cm	2(9.1%)
5-10cm	6(27.3%)
>5cm	14(63.6%)
Histology	
Spindle cell morphology	7(31.8%)
Epithelioid morphology	14 (63.6%)
Mixed morphology	1(4.5%)
Mitotic index	
<5/50HPF	6(27.3%)
>5/50HPF	16(72.7%)
NIH risk classification	
Low risk	1(4.5%)
Intermediate risk	6(27.3%)
High risk	15(68.2%)
Immunohistochemical staining	
CD117	21(95.5%)
CD34	8(36.4%)
DOG-1	3(13.6%)
SMA	1(4.5%)
S-100	1(4.5%)

NSE	0
Desmin	0

HPF: high power field; NSE: neuron specific enolase; SMA: smooth muscles actin

Key Message

Though extra-gastrointestinal stromal tumor (EGIST) shares the same histological features and immunophenotype, the clinicopathological behavior and treatment has not been elicited. In this study, the data of 22 patients with abdominal EGIST was reviewed retrospectively. The results suggested that abdominal EGIST had a high malignant potential, surgery and postoperative adjuvant treatment with imatinib might improve the survival rate of high-risk cases.

Figures

Figure 1

The survival of patients with abdominal extra-gastrointestinal stromal tumor: Though the survival of mesentery EGIST seems better than retroperitoneal or total abdominal EGIST, the difference is not significant ($P>0.05$)