Extragastrointestinal Stromal Tumor (EGIST): A 16-Year Experience of 13 Cases Diagnosed at a Single Center

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
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Background: Gastrointestinal stromal tumor (GISTs) rarely occurs outside the GI tract as extragastrointestinal stromal tumor (EGIST). The aim of this study was to review the clinical presentation, diagnosis, and outcome of EGIST at a single center.

Material/Methods: The study was a retrospective study performed at Istanbul University Hospital in a 16-year period and included patients with a histopathological diagnosis of EGIST confirmed to arise outside the GI tract. The patients' available medical records included patient demographics, imaging and surgical data, and diagnostic histopathology reports. Cases of EGIST underwent follow-up for several years and the medical files of patients were well maintained.

Results: Thirteen cases of EGIST included six women and seven men, with a mean age of 59.6 years (range, 33–83 years). Eleven patients had EGISTs located in the intra-abdominal cavity, one patient's tumor was in the retroperitoneum, and in the jejunal mesentery in one patient. The mean diameter of the EGISTs was 15.6 cm (range, 4–30 cm). Immunohistochemistry showed that all cases were negative for desmin, with positive immunostaining for CD34 (n=6), smooth muscle actin (SMA) (n=3), and Ki67 (n=6), without specific diagnostic markers. Following surgical resection, tumor recurrence occurred in three patients, and metastasis in two patients. The mean overall survival (OS) was 45.66 months (56.44 months for women; 32.57 months for men); the 5-year survival rate of our patients was 38%.

Conclusions: EGIST presented with a large tumor size at diagnosis, was mainly intra-abdominal, and had a low mean patient survival time with no specific diagnostic tissue immunomarkers.

MeSH Keywords: Abdominal Neoplasms • Gastrointestinal Stromal Tumors • Gastrointestinal Tract

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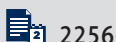
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Background

Extragastrointestinal stromal tumor (EGIST) is defined as a gastrointestinal stromal tumor (GIST) that develops outside of the gastrointestinal (GI) tract. GIST, although rare, is the most common primary mesenchymal neoplasm that originates from the GI tract and accounts for up to 1% of all GI tumors [1]. EGIST was first described in 1999, by Miettinen et al. [2]. EGIST accounts for 10% of all GISTs [3]. The main distinction between GIST and EGIST is the site of origin of the primary tumor, as GIST occurs throughout the GI tract, from the esophagus to the anus, whereas EGIST is a tumor without any connection with the intestinal wall and are reported in the retroperitoneum, mesentery, and omentum [4].

There have been many published studies on clinical and pathological features of GISTs, and several factors have been reported as being related to the degree of aggressive behavior and prognosis of GISTs, such as *c-KIT* mutation status, patient age [5], gender [6], mitotic index [1], tumor size [7], metastasis, recurrence [8], and other properties of the tumor [9].

Although most cases of EGIST are considered to be malignant, there have been limited published studies on the incidence, pathogenesis, prognosis, prognostic biomarkers and tumor genotypes. Currently, the malignant potential of EGIST is determined by evaluating parameters such as tumor size, mitotic rate, and the presence of tumor necrosis, which are factors that are also used in the evaluation of GIST [10]. However, it is still unclear whether the approach to the evaluation of GIST can reasonably be applied to EGIST, as there is some evidence that patients with EGIST have a lower age of onset, a larger tumor size, and poorer prognosis compared with patients with GIST [11].

At this time, it is important to continue to report the clinical observations regarding patients with EGIST to contribute to the further understanding of these tumors. There have been several individual case reports and small case series reported in the literature, but the number of cases has been limited [12,13].

The aim of this study was to review the clinical presentation, diagnosis, and outcome of EGIST at a single center. To our knowledge, this is the first case series of EGIST from Turkey, and the study conveys the findings of a 16-year experience of cases of EGIST, from one of Turkey's leading hospitals located in Istanbul, the largest city in Turkey.

Material and Methods

Patients studied

A retrospective clinical study was undertaken to evaluate all patients who were diagnosed with extragastrointestinal stromal tumor (EGIST) in Istanbul University Hospital, Department of General Surgery, in a 16-year period from January 2000 to December 2015. All patients included in the study underwent surgery with tumor resection. The diagnosis of EGIST was made by the pathologists in the same hospital using light microscopy and immunohistochemistry analysis of tissue samples obtained from the surgical resection specimens.

Thirteen patients were included in the study with a histopathological diagnosis of EGIST confirmed to arise outside the GI tract. Available medical records included patient demographics, imaging and surgical data, and diagnostic histopathology reports. Cases of EGIST underwent follow-up for several years and the medical files of patients were well maintained. In this retrospective review of patient medical records, all patients provided clinical informed consent for diagnostic and surgical procedures.

Data collection

All tissue samples obtained from EGIST patients during surgery were investigated by pathologists in the same center. Patient follow-up data were collected from the medical files. All relevant patient data including age at presentation, gender, clinical findings at presentation, tumor properties, and treatment variables were recorded.

Histopathology and immunohistochemistry

Tissue samples were processed by routine clinical laboratory methods, being fixed in 10% formaldehyde and embedded in paraffin wax. Tissue sections were cut, using a microtome, at 5 μm thickness, placed onto glass slides, and the sections were stained with hematoxylin and eosin (H&E) and examined under the light microscope.

Immunohistochemistry was performed using a panel of primary antibodies to CD117 (c-kit), CD34, SMA, S100, and desmin. Tissue sections were de-de-waxed and dehydrated through xylene (10 min) and graded alcohols (5 min each). Antigen retrieval was performed using trypsinization (for desmin) or using a pressure cooker (for the remaining antibodies), and sections were incubated in 100 μl of casein for 5 min to prevent non-specific antibody binding.

Tissue sections of EGIST were then incubated for 60 minutes with the primary antibody solution (diluted according to manufacturer's recommendation). The secondary antibody incubation included a solution of 1: 100 3,3'-diaminobenzidine (DAB), which was performed for 30 minutes, according to manufacturer recommendation. Counterstaining of the tissue section was done by incubation for one minute using Meyers' hematoxylin, washing the section and mounting with a coverslip.

All immunostained tissue section were then evaluated by experienced pathologists, with the immunohistochemistry findings recorded in the patient notes.

Visual microscopic quantification of immunostaining in the EGIST tissue sections for each antibody used was performed by calculating the percentage of immunostained cells (brown being positive staining). Tumors were then grouped as negative (<10% positive tumor cells), or positive (≥10% positive tumor cells).

Results

Clinical characteristics of patients with extragastrointestinal stromal tumors (EGIST)

Thirteen cases of extragastrointestinal stromal tumors (EGIST) included six women and seven men, with a mean age of 59.6 years (range, 33–83 years). Eleven patients had EGIST located in the intra-abdominal cavity, one patient's tumor was in the retroperitoneum, one patient's tumor was in the jejunal mesentery. The mean diameter of the EGISTs was 15.6 cm (range, 4–30 cm).

Histopathology and immunohistochemistry

Tumor classification was based on the Armed Forces Institute of Pathology (AFIP) criteria (Miettinen's criteria), most of the patients (n=9) were classified as high-risk; three patients were intermediate risk; and one patient was in the low-risk group. Immunohistochemistry showed that all cases were negative for desmin, with positive immunostaining for CD34 (n=6), smooth muscle actin (SMA) (n=3), S100 (n=1), and Ki67 (n=6), without specific diagnostic markers.

Clinical outcome and patient survival

Tumor recurrence occurred in three patients, and tumor metastasis occurred in two patients with EGIST. The metastases were to the omentum (n=1) and the liver (n=1). The mean overall survival (OS) for the patients with EGIST in this study was 45.66 months; 56.44 months for women and 32.57 months for men. The 5-year survival rate of patients with EGIST in this study was 38%. Table 1 summarizes the characteristics of the 13 patients with EGIST in this study.

Discussion

The findings of previously published studies on extragastrointestinal stromal tumors (EGIST) have led authors to believe that these tumors are histologically and immunohistochemically similar tumors, with features that are also similar to those found in gastrointestinal stromal tumors (GIST), including the expression of c-KIT and PDGFR-α gene mutations [4,14,15] (Song Zheng, Huang, Tao, & Pan, 2011). The similar findings from previous studies have supported the assumption that GIST and EGIST arise from similar cells. Further evidence to support the common cell of origin of GIST and EGIST include the finding that omental EGIST has been shown to have similar histological features as gastric GIST [2]. Omental EGIST, mesenteric EGIST, and gastric GIST have been shown to have a better prognosis compared with intestinal GIST [16,17]. Also, in a study that hypothesized that there was no difference between EGIST and GIST, the patient records from 14 cases of EGIST were re-evaluated, and most of the cases (11/14) were reclassified as GIST [18]. Although other authors have argued that there is no difference between EGIST and GIST [19], EGIST is a separate tumor group in current classification systems.

In the present study, 5-year survival rate was found as 38%, which was lower than previous studies. For example, Zhou et al. reported a 48.9% 5-year survival rate for EGIST [11]. Zheng et al. reported a 60.9% 5-year survival rate for EGIST [14]. In the present study, mean overall survival (OS) time of our patients was 45.7 months. Barros et al. reported an average OS of 26.4 months in their study of nine patients [20]. In previous studies, the identification of factors associated with prognosis was not possible because the number of EGIST cases were too few. In a retrospective clinical study by Zhou et al., although tumor site, tumor size, and tumor cell nuclear pleomorphism were determined as significant prognostic factors in 22 cases of EGIST, these investigators could not find any associations with survival time in multivariate analyses [11]. Zheng et al., in their retrospective review study of 42 patients with EGIST, showed that mitotic index was an independent factor associated with recurrence-free survival times, using multivariate analysis [21]. Survival analysis from a 22 case study showed that the mitotic count and Ki-67 labeling index were associated with patient survival time [14]. Similarly, Yi et al. found an association between mitotic rate and patient survival time [22]. Also, in a key study in this field, Reith and colleagues highlighted that mitotic index and necrosis were predictive factors for survival time for patients with EGIST [4]. In a multicenter study; tumor size, mitotic rate, necrosis and histologic type were found to be significant predictors of survival in 28 patients with EGIST [10].

The conflicts between studies in terms of risk factors, patient prognosis, and survival in EGIST may be due to various causes including: low sample size, which will affect statistical significance; the varying time intervals between studies, which may have led to differences in diagnosis and management; and the difference in opinions regarding the status of GIST and EGIST, leading to different classification of similar tumors. It is clear that further studies on the pathogenesis, behavior,

Table 1. Clinical characteristics of 13 patients with extragastrointestinal stromal tumor (EGIST) and the immunohistochemical findings.

No	Age	Gender	Location	Clinic	Tumor size (cm)	Risk Score	Rec.	Met.	c-kit	Histologic type	s 100	Ki-67	SMA	CD34	Mitotic index	Lymph node	OS (m)
1	33	F	Jejunum sac	AP	22	High	–	M (L)	100	Mixed	–	60	–	–	35/50	–	49
2	53	M	Intra-abdominal	AP	4	Intermediate	+	NM	100	Spindle	–	10	–	–	4/50	–	72
3	71	F	Intra-abdominal	E	15	High	+	NM	90	Mixed	–	3	50	100	2/50	–	11 (d)
4	47	M	Retroperitoneal	AP	24	High	–	NM	100	Spindle	–	7	–	100	4/50	–	70
5	56	F	Intra-abdominal	AP	19	High	–	NM	100	Mixed	–	20	–	100	37/50	–	82
6	72	F	Intra-abdominal	B	5	Intermediate	–	NM	100	Mixed	–	2	–	–	0/50	–	62 (d)
7	51	M	Intra-abdominal	B	26	High	–	NM	50	Spindle	–	11	–	–	6/50	–	8 (d)
8	58	M	Intra-abdominal	AP	24	High	–	M (O)	50	Mixed	–	7	–	50	38/50	–	22 (d)
9	83	M	Intra-abdominal	AP	6	Intermediate	–	NM	50	Mixed	–	1	–	–	1/50	–	22 (d)
10	65	M	Intra-abdominal	E	26	High	+	NM	100	Mixed	–	12	10	50	20/50	–	21 (d)
11	39	F	Intra-abdominal	E	5	Low	–	NM	50	Spindle	10	8	10	–	0/50	–	84
12	72	F	Intra-abdominal	AP	16	High	–	NM	50	Mixed	–	8	–	–	0/50	–	21 (d)
13	75	M	Intra-abdominal	E	30	High	–	NM	100	Mixed	–	12	–	40	21/50	–	11 (d)

F – Female; M – Male; AP – abdominal pain; B – bleeding; E – detected during examination; Rec – recurrence, (+) – positive; (–) – negative; Met – metastasis; M – metastasic; NM – non-metastatic; L – liver; 0 – omentum; D – desmin; S100 – Ki-67; SMA – smooth muscle antigen; OS(m) – overall survival (months); (d) – death due to disease.

and molecular biology of EGIST are needed before evidence-based diagnostic or prognostic recommendations can be made.

Review of the current published literature on EGIST has shown that these tumors arise more frequently in the intra-abdominal cavity and retroperitoneum. Also, cases of EGIST have been reported in unusual locations, including the pancreas, prostate, and abdominal wall [23]. In the present study, 84.6% (11/13) of cases of EGIST were located in the intra-abdominal cavity. Similarly, in other studies, the most common anatomic location of the tumor was in the intra-abdominal cavity, including the mesentery or omentum in 78.6% [10], 83.3% [4], 56.4% [15] 76.0% [14], and 63.6% [11]. In the same previous studies, the second most common site for EGIST was the retroperitoneum in 10.7% [10], 16.7% [4], 43.6% [15] 24.0% [14], and 36.4% [11]. Except for one study [21], the intra-abdominal cavity was previously reported as the most common primary site, and the retroperitoneum as the second most primary site for EGIST [22,24–26]. In this study of 13 cases, one case of EGIST was found in the jejunal mesentery, which is a rare primary site for EGIST, on review of the previously published literature.

In previous studies, EGIST has been reported to occur typically in older patients. The mean age of the patients in the present study was 59.6 years. This finding is supported by previous studies, which have reported a mean age of 58 years [4,10,19] and 59 years [14,27]. In other studies, the median age has been reported as 45.5 years [11] and 51 years [22]; the mean age has been reported as 45.8 years [26], 50.6 years [28], 50.1 years [24], and 56 years [29].

Tumor size has been determined by previous studies as a risk factor that affects the survival of EGIST patients, as most of the cases were not detected until the tumor size reached 10 cm., and most cases presented with a mean or median tumor size greater than 10 cm [4,10,14,19,21,24–29]. There has been no case of EGIST in which a tumor smaller than 2 cm

in diameter was detected, and there are very few studies in which a tumor smaller than 5 cm was reported. Late diagnosis of EGIST may be due to their anatomical location and non-specific, late-onset symptoms.

Although almost two decades have passed since the initial identification of EGISTs by Miettinen et al. [2], there is still a lack of sufficiently large and/or detailed studies which aim to clarify the characteristics, differentiation, and prognosis of these tumors. This study, combined with with other recent studies, may provide further information to address this knowledge gap. The strengths of this study were that a large number of parameters were included in the diagnosis and follow-up of cases of EGIST, combined with an extensive review of the literature, and a long follow-up period for the patients in the study, including the use of well-maintained medical records. However, the study had limitations, which included the use of patient medical records, as changes in diagnostic methods, approach, and management during this long study period of 16 years may have resulted in changes in approach to diagnosis and management. This study limitation is found in most long-term studies. A further study limitation was the low number of patients studied, as there were only 13 diagnoses of EGIST within the 16-year study period in our center. These study limitations would have prevented advanced survival analysis evaluation. Also, this study did not include comorbidity data analysis, which was a study limitation.

Conclusions

In this retrospective clinical review of 13 patients diagnosed with extragastrointestinal stromal tumors (EGIST) during a 16-year period at a single center, EGIST presented with a large tumor size at diagnosis was mainly intra-abdominal, and had a low mean patient survival time, with no specific diagnostic tissue immunomarkers. The low incidence of GIST, and the even lower incidence of EGIST indicate that large-scale, multi-center, controlled studies are needed to determine the prognostic factors and survival characteristics for EGIST.

Conflict of interest

None.

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