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# Clinicopathological and Prognostic Features of Extragastrointestinal Stromal Tumors of the Omentum: A Review

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### Abstract

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal neoplasms of the digestive tract. A small percentage of GISTs form extragastrointestinal masses in the omentum, mesenteries, retroperitoneum, and undefined abdominal sites. These tumors have been labelled as "extra-gastrointestinal stromal tumors" (EGISTs). By definition, extragastrointestinal stromal tumors display no connection to the walls of the gastrointestinal tubular organs. They are usually located in the omentum or in the mesentery and account for 5%-10% of all GISTs. Omental EGISTs seem to display overlapping morphological and phenotypic similarities with GISTs found elsewhere, however, their clinical, radiological and histological features are not yet widely known. This review focuses on the most relevant clinicopathological issues regarding the diagnosis and clinical behaviour of extragastrointestinal stromal tumors presenting in the omentum.

### Keywords

Extragastrointestinal stromal tumor, Omentum, GIST, Risk factor, Prognostic factor

## Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the digestive tract, accounting for 0.1%-3% of all gastrointestinal malignancies. GISTs occur primarily in older patients and show no gender difference in incidence, which is estimated in 5000-10000 new cases per year [1]. These tumors are thought to originate from the interstitial cells of Cajal, which are the pacemaker cells regulating gastrointestinal peristalsis and share with these cells the expression of the protein tyrosine kinase KIT (CD117), detected by immunohistochemistry. The vast majority of GISTs, display mutually exclusive KIT or platelet-derived growth factor alpha (PDGFRA) mutations [2]. The KIT mutation, most often in exon 11, results in constitutive activation of the KIT receptor, which is thought to promote proliferation and/or decrease apoptosis [2]. The most frequently affected gastrointestinal organs are the stomach (60%), small intestine (30%), duodenum (5%), rectum and colon (4%) and the esophagus (< 1%) [3]. A small subgroup of GISTs originates from outside the gastrointestinal tract or may become detached from the digestive tract during their development. These neoplasms are referred as extragastrointestinal stromal tumors (EGIST).

By definition, EGISTs display no connection to the walls or serosal surfaces of GI tubular organs and account for 5%-10% of all GISTs [4]. Approximately 80% are located in extra gastrointestinal abdominal wall structures including omentum or mesentery. The retroperitoneum, soft tissues of the abdominal cavity, liver and pancreas represent rare sites of occurrence [5]. EGISTs display morphological and phenotypic similarities with GISTS and are thought to develop from the detachment of a primary intra-abdominal tumor or from independent mesenchymal cell growth of the mesentery, omentum and retroperitoneum [6]. Their histogenesis, evolutionary potential and the therapeutic possibilities, however, are

**Table 1:** Clinicopathological features of reported cases of omental gastrointestinal stromal tumors.

| Reference | N.of cases | Median age (y) | Sex | | Median tumor size (range) | Histology | | | Mitotic count/50 HPF (range) | Kit IHC | | Risk | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | m | f | | Spindle | Epithelioid | Mixed | | + | - | high | low |
| Miettinen [6] | 95 | 60 years (range: 27 to 88 y) | 49 | 46 | 15 cm (3.5-33 cm) | 1 | 10 | 10 | 8 (0-16) | 65 | 5 | 9 | 86 |
| Yamamoto [2] | 5 | 57 years (range: 41 to 69 y) | 3 | 2 | 18,3 (8.5-33cm) | / | 5 | / | 4 (0-18) | / | 5 | 2 | 3 |
| Zhu J [11] | 4 | 46 years (range: 40 to 60 y) | 1 | 3 | > 10 cm | 4 | | | / | 4 | | / | |
| Fan Feng [25] | 99 | 60 years (range: 22 to 99 y) | 55 | 38 | 13 cm (0.7-40 cm) | 42 | 29 | 16 | / | 49 | | 88 | 11 |
| Patnayak [30] | 2 | 36 years (range: 22 to 50 y) | 2 | | 24 cm (20-29 cm) | 2 | | | 12 (10-15) | 2 | | 2 | |
| Trombatore [14] | 1 | 69 | x | | 7 cm | | x | | < 5/50 HPF | x | | | x |
| Todoroki [31] | 1 | 69 | x | | 20 cm | | | x | 2/50 HPF | x | | | x |
| Tarchouli [28] | 1 | 61 | x | | 34 cm | x | | | 6/50 HPF | x | | x | |
| AIHARA [32] | 1 | 22 | x | | 3 cm | x | | | 4/50 HPF | x | | | x |
| Mouaqit [27] | 1 | 63 | x | | 21 cm | | x | | 2/50 | x | | | x |
| Franzini [33] | 1 | 74 | x | | 33 cm | | x | | 1/50 | x | | | x |
| Fagkrezos [34] | 1 | 63 | x | | 16 cm | | | x | 5/50 | x | | | x |
| Dedemadi [26] | 1 | 68 | x | | 15 cm | x | | | 1/50 | x | | | x |
| Divakaran [35] | 1 | 58 | | x | 9 cm | x | | | 4/10 HPF | x | | | x |
| Suzuki [36] | 1 | 65 | x | | 13 cm | x | | | 8/50 HPF | x | | x | |

N: Number; HPF: High power fields; IHC: Immunohistochemistry.

not completely defined to date. This review focuses on the most relevant clinico-pathological, prognostic and molecular features regarding EGISTs presenting in the omentum. A comprehensive literature review of all the reported cases of omental EGISTs is provided (Table 1).

## Etiology

The origin of primary omental EGISTS is still uncertain; however these tumors display morphological and phenotypic similarities with conventional GISTS. Therefore, many authors believe that omental and mesenteric GISTs originate from a primary gastric or intestinal tumor. These tumors, for unknown reasons, may become detached from the gastrointestinal wall during their development [6].

In addition, recent studies have emphasised the presence of multipotential mesenchymal stem cells in the mesentery, omentum and retroperitoneum showing histological and immunohistochemical features overlapping to those of the interstitial cells of Cajal [7]. Accordingly, a subgroup of EGISTs may arise from independent mesenchymal stem cell growth. The largest series of omental GISTs is provided by Miettinen, et al. who reported the clinicopathological features of 95 GISTs presenting with omental masses [6]. The author emphasised the clinico-pathological and prognostic differences between solitary omental EGISTs and multiple omental EGISTs. In this

regard solitary tumors displayed better prognosis when compared to multiple tumors. Solitary omental EGISTs usually display a gastric GIST-like histology and a low biologic aggressiveness with long patient survival suggesting a close relationship with gastric GISTs. In contrast, the clinicopathological and biological features of multiple omental EGISTs seem to be more closely related to small intestinal GISTs.

## Clinical Presentation

Omental EGISTs occur predominantly in adults, with a mean age of between 50 and 60 years [4,8,9]. Sporadic cases affect children and adolescents. Also, there is no difference in incidence between lesser and greater omentum. The clinical onset of these neoplasms is non-specific and depends mostly on the tumor size and location. The most common presenting complaint is an abdominal mass; however the majority of omental EGISTs are diagnosed incidentally during investigations for unrelated medical conditions. In addition, the anatomic location and the development outside the gastrointestinal tract explain why these neoplasms can remain clinically silent for a long time despite large tumor size. Hence most omental EGISTs cases are diagnosed at a late stage, leading to a difficult surgical management of the patients and thereby resulting in worse clinical outcomes.

## Radiologic Features

The preoperative diagnosis of omental EGISTs is often difficult. These neoplasms present usually as large masses with solid and cystic components and without an air-fluid level, however their imaging features are variable depending on the size and aggressiveness [10].

CT and MRI provide useful informations in identifying the location and extent of EGISTs. In addition, radiological characteristics, such as a large tumor size, il-defined borders, tumor vessels and distant metastasis, are useful to predict the malignant behaviour of EGISTs [11]. Large tumors usually show a peripheral enhancement pattern, due to central necrosis, cysts or haemorrhagic areas [12]. Haemorrhage is a frequent finding on CT and MRI acquisitions. It could be observed on CT as small and ill-defined hyper dense areas [13]. MRI exam show hyperintense areas on T1-weighted acquisitions, and hypointense areas on T2-weighted sequences. CT-angiography or MRI-angiography is useful tools to study the vascularization of the tumor which is an important feature to be considered to better investigate the origin of EGIST [14]. The angiographic evidence of some feeding vessels arising from the left gastric artery, associated with a poor blood supply from the hepatic arteries, could be probably a crucial sign suggesting an omental primitive tumor.

## Pathologic Features

Histologically, EGISTs range from hypocellular to densely cellular lesions and are composed of a population of spindle cells or epithelioid cells. Usually one pattern predominates; although about 10% of cases consist of a mixture of these two morphologies [8]. The epithelial type is more frequently observed in the stomach and omentum. GISTs arising from small bowel and rectum usually display spindle cell morphology [15]. Epithelioid GISTs usually display a sheet-like or nested growth pattern whereas GISTs with spindle cell morphology are always arranged in fascicles. All GISTs subtypes display a hyalinized or myxoid stroma with occasional calcifications. Prominent deposits of collagen, the so called skeinoid fibers, are another histologic feature usually encountered in GISTs with small intestinal morphology [16]. Most tumors display a mild to moderate mitotic activity and cytologic pleomorphism. Increased mitotic count and atypical mitotic figures are rare and when present suggest the presence of a high-grade or dedifferentiated GIST [9]. Immunohistochemical and molecular characteristics of EGISTs are similar to GISTs. The majority of both show positive staining for CD117 antibody and harbour mutually exclusive gain-of-function KIT or platelet-derived growth factor receptor-alpha (PDGFRA) mutations [17]. Approximately 15% of GISTs are neg-ative for mutations in KIT and PDGFRA. Recent studies of these so-called wild-type GISTs have uncovered a number of other oncogenic drivers, including mutations in neurofibromatosis type I, RAS genes, BRAF, and subunits of the succinate dehydrogenase complex [18]. Another recent immune histochemical marker, DOG1 (discovered on GIST-1), is expressed in GISTs irrespective of KIT or PDGFRA mutation status [19]. Along with CD117, CD 34 is also expressed by majority of the EGISTs. Approximately 5% of tumors with clinical and morphological features of GIST do not express KIT protein by immunohistochemistry and Western blot evaluations. These cases should be differentiated from false negative immunohistochemical results, including fixation artifacts, very small biopsies from tumors in which KIT staining is focal in distribution and rare cases that lose KIT expression perhaps following Imatinib mesylate therapy [20]. Several studies suggest that kit-negative GISTs show clinical, pathological and genetic differences form Kit-positive GISTs. Most of these tumors harbour platelet-derived growth factor receptor alpha (PDGFRA) mutations, but rare cases have shown KIT mutations despite the absence of immunohistochemical KIT protein expression [21].

## Differential Diagnosis

The differential diagnosis between omental EGISTs and other intra-abdominal tumors is broad and depends mostly on the morphology and location of the tumor. EGISTs with a spindle cell morphology show overlapping radiologic and histological features with other spindle cell neoplasms, including smooth muscle neoplasms, nerve sheath tumors, inflammatory myofibroblastic tumors (IMTs), and intra abdominal fibromatoses (desmoid tumors). EGISTs with epithelioid morphology must be distinguished from neuroendocrine tumors, melanoma, PEComa and metastatic carcinoma [11].

## Treatment and Prognosis

Many criteria have been proposed in order to distinguish benign from malignant GISTs, or at least to predict the metastatic potential of these neoplasms. The most reliable parameters for risk stratification of GISTs according to Miettinen, et al. Fletcher's classification and UICC classification are based on mitotic index, tumor size and location [16,22]. But none of these classifications include the EGISTs. Based on several large studies, the Armed Forces Institute of Pathology (AFIP) proposed to classify those GISTs that develop in other anatomic locations, including omental EGISTs, according to the criteria for jejunum/ileum [23]. In addition, Joensuu has proposed a further risk stratification of GISTS into either gastric or non-gastric tumors in order to emphasise that gastric tumors carry a better prognosis. Resection margins and

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tumor rupture seem to be additional prognostic factors for EGISTs [24]. However, the literature studies regarding the prognosis of EGISTs are still limited. Most studies suggest that the prognosis of EGISTs is less favourable compared to GISTs [25]. This is partly true because the origin of the tumor outside the gastro-intestinal tract may result in a delay of the presentation of clinical symptoms, and explains why most EGISTs cases are diagnosed at a late stage. Furthermore, Miettinen, et al. emphasised the clinicopathological and prognostic differences between solitary and multiple omental GISTs. The author suggested that multiple omental GISTs carry a malignant behaviour, and further prognostication by histologic parameters seems to have limited relevance in these cases [6]. These tumors display clinical and histologic features similar to small intestinal GISTs and probably represent advanced, metastatic GISTs dislodged or extending into the omentum from an inconspicuous gastro-intestinal attachment.

Given the rarity of omental EGISTs, no specific treatment data from clinical trials are available; hence their clinical and surgical management follows the guidelines of classical GISTs [26]. Complete surgical resection with negative microscopic margins remains the standard treatment for localized omental EGISTs [27]. The administration of Imatinib (STI-571), a tyrosine kinase inhibitor, is considered the treatment of choice for metastatic and unresectable EGISTs [28]. Adjuvant therapy with Imatinib is also recommended as after a complete surgical resection of high-risk GISTs in order to prevent recurrences or metastatic disease [29].

## Conclusion

EGISTs arising in the omentum are very rare mesenchymal neoplasms most often diagnosed incidentally during investigations for unrelated medical conditions. The distinction between solitary and multiple omental GISTs seems to have important clinicopathological and prognostic implications. Because of the rarity of these neoplasms, their management strategy as well as their risk stratification criteria are not well defined, and still follow the guidelines used for classical GISTs. Further and more detailed studies are necessary for better understanding these neoplasms.

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