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# Gastrointestinal Stromal Tumors: A Focus on Diagnosis and Management

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**Abstract** Gastrointestinal stromal tumors (GISTs) are rare tumors of the gastrointestinal (GI) tract that usually start in very early forms of special cells found in the wall of the GI tract, called the interstitial cells of Cajal (ICCs). Symptoms are usually variable, depending on tumor size and location, but many patients are asymptomatic. Most gastrointestinal stromal tumors (GISTs) occur in the stomach or small intestine. These tumors might not cause any symptoms unless they are in a certain location or grow to a certain size. Small tumors might not cause any symptoms and may be found accidentally when the physician is looking for another problem. These tumors are often benign. The main treatment for GIST that hasn't spread is usually surgery to remove all of the tumors. The above mentioned topics, as well as classification, causes, clinical presentation, diagnosis and prognosis of GISTs were discussed in this review.

***Keywords:*** *gastrointestinal, stroma, tumor, diagnosis, management*

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## 1. Introduction

Gastrointestinal stromal tumors (GISTs) are not common disease, and the exact number of people diagnosed with these tumors each year is not known. Until the late 1990s, not much was known about these tumors, so many of them ended up being classified as other kinds of GI cancers [1]. Current estimates for the total number of GIST cases each year in the United States range from about 4,000 to about 5,000. These tumors can start anywhere in the GI tract, but they occur most often in the stomach (about 60%) or the small intestine (about 30%). Most of the rest are found in the esophagus, colon, and rectum. A small number develop in the abdomen outside the GI tract. Most people diagnosed with GIST are older than 50, but these tumors can occur in people at any age. They are slightly more common in men [2].

Cancer starts when cells in the body begin to grow out of control. Cells in nearly any part of the body can become cancer, and can spread to other areas of the body [3]. Gastrointestinal stromal tumors start in the digestive system. Gastrointestinal stromal tumors (GISTs) are uncommon tumors of the GI tract. These tumors start in very early forms of special cells found in the wall of the GI tract, called the interstitial cells of Cajal (ICCs). ICCs are cells of the autonomic nervous system, the part of the nervous system that regulates body processes such as digesting food. ICCs are sometimes called the "pacemakers" of the GI tract because they signal the muscles in the digestive system to contract to move food and liquid through the GI tract [4]. More than half of GISTs start in the stomach. Most of the others start in the small intestine, but GISTs can start anywhere along the GI tract. A small number of GISTs start outside the GI tract in nearby areas such as the omentum (an apron-like layer of fatty tissue that hangs over the organs in the abdomen) or the peritoneum (the layer of tissue that lines the organs and walls of the abdomen). Not all GISTs are cancerous. Some are benign (not cancerous) and don't grow into other areas or spread to other parts of the body. Doctors have ways to find out whether a GIST is benign or cancerous [5].

## 2. Classification of GISTs

GISTs are usually classified according to the site of origin of the primary tumor [6]. GISTs that start in the stomach or the omentum are classified into four main stages under which there are subdivisions. In stage IA, the tumor is not larger than 5 cm in diameter (T1 or T2), not spread to the nearby lymph nodes (N0) or distant sites (M0) with low mitotic rate. *In stage IB, t*he tumor is larger than 5 cm but not larger than 10 cm in diameter (T3), not spread to nearby lymph nodes (N0) or distant sites (M0) with low mitotic rate. In stage IIA, the tumor is no larger than 5 cm in diameter (T1 or T2). The tumor has not spread to nearby lymph nodes (N0) or distant sites (M0) with high mitotic rate. In stage IIB, the tumor is larger than 10 cm in diameter (T4), not spread to the nearby

lymph nodes (N0) or distant sites (M0) with low mitotic rate. In *stage IIIA, t*he tumor is larger than 5 cm but not larger than 10 cm in diameter (T3), not spread to nearby lymph nodes (N0) or distant sites (M0) with high mitotic rate. In *stage IIIB, t*he tumor is larger than 10 cm in diameter (T4), not spread to the nearby lymph nodes (N0) or distant sites (M0) with high mitotic rate. In stage IVA, the tumor can be of any size (any T), has spread to the nearby lymph nodes (N1) but not spread to distant sites (M0). The tumor can have any mitotic rate. In stage IVB, the tumor can be of any size (any T) and it may or may not have spread to the nearby lymph nodes (any N). The tumor has spread to distant sites, such as the liver or the lungs (M1) and may have any mitotic rate [7].

GISTs that start in the small intestine, esophagus, colon, rectum, or peritoneum are more likely to grow quickly than GISTs that start in the stomach [7]. They are classified into four stages. In stage I, the tumor is no larger than 5 cm in diameter (T1 or T2), not spread to nearby lymph nodes (N0) or distant sites (M0) with low mitotic rate. In stage II, the tumor is larger than 5 cm but not larger than 10 cm in diameter (T3). The tumor has not spread to nearby lymph nodes (N0) or distant sites (M0) with low mitotic rate. In stage IIIA, the tumor is no larger than 2 cm in diameter (T1), has not spread to nearby lymph nodes (N0) or distant sites (M0) with high mitotic rate. In stage IIIA, the tumor is larger than 10 cm in diameter (T4), has not spread to nearby lymph nodes (N0) or distant sites (M0) with low mitotic rate. In stage IIIB, the tumor is larger than 2 cm in diameter (T2 to T4), has not spread to the nearby lymph nodes (N0) or distant sites (M0) with high mitotic rate. In stage IVA, the tumor can be any size (any T) and the tumor has spread to nearby lymph nodes (N1). It has not spread to distant sites (M0). The tumor can have any mitotic rate. In stage IVB, the tumor can be any size (any T) and it may or may not have spread to the nearby lymph nodes (any N). The tumor has spread to distant sites, and may have any mitotic rate [8].

## 3. Etiology of GISTs

The interstitial cells of Cajal (ICCs) form a complex cellular network within the muscular wall of the GIT where they function as a pacemaker system controlling gut motility. Expression of the c-kit proto-oncogene is essential for the slow wave activity of ICCs and for the development of the ICC system [9]. Although not limited to this cell type, c-kit expression is widely recognized as a molecular marker of ICCs. The c-kit receptor encodes a tyrosine kinase that is dimerized and activated upon ligand stimulation, leading to autophosphorylation as well as phosphorylation of a number of signal transduction molecules. Ultimately, this process results in cellular responses such as cell division, actin reorganization, and chemotaxis [10].

Mutant c-kit tyrosine kinase receptors are activated in the absence of its ligand, the stem cell factor. Naturally occurring mutations in the receptor gene, as well as in that of its ligand cause defects in migration, differentiation and proliferation of stem cells. Also, stable transfection of the mutant c-kit cDNAs into murine lymphoid cells induces malignant transformation [10]. In GISTs, KIT mutations cause constitutive oncogenic signaling in the absence of their ligands leading to alterations in cell cycle, protein translation, apoptosis and metabolism [11].

## 4. Clinical Presentation of GIST

Symptoms of GISTs usually depend on tumor size and location, but many and location, but many patients are asymptomatic **[1]**. Clinical symptoms associated with GIST include abdominal pain, fatigue, dysphagia, satiety, and obstruction. Tumors in the stomach or small bowel commonly present with either chronic GI bleeding (causing anemia) or acute GI bleeding (caused by erosion through the gastric or bowel mucosa) or rupture into the abdominal cavity causing life-threatening intraperitoneal hemorrhage [4]. In the esophagus or rectum, the first manifestations may be obstruction, dysphagia, or altered bowel habits. At laparotomy, intra-abdominal malignant tumors are often cystic and hemorrhagic. In general, mucosal ulceration is considered a sign of malignancy [12]. Previously, a population-based study revealed that approximately 70% of GISTs were associated with clinical symptoms, 20% were detected incidentally during surgery for other reasons and 10% were detected at autopsy. The median tumor size in each of these categories was 8.9, 2.7, and 3.4 cm, respectively. The vast majority of initially symptomatic patients had marked clinical improvement, including hemorrhage, abdominal pain and abnormal electrolytes [5]. The clinical signs and symptoms are related to the presence of a mass or bleeding. However, as it is mentioned above, 10% remain asymptomatic, because of their small size and they are diagnosed incidentally. Finally, GIST patients may present with metastasis in surgical scars [13].

## 5. Diagnosis of GIST

Most GISTs occur in the stomach or small intestine. These tumors might not cause any symptoms unless they are in a certain location or grow to a certain size. Small tumors might not cause any symptoms and may be found accidentally when the doctor is looking for some other problem. These tumors are often benign. Epidemiology of GIST is incompletely known. Three studies that used up-to-date diagnostic criteria found the annual incidence of GIST to be 14.5 per million in south-west Sweden, 11 per million in Iceland, and 12.7 per million in the Netherlands [12]. Approximately 10% of cases were detected at autopsy in these series, and 20% at endoscopy, imaging of the abdomen, or at surgery for other conditions. GISTs vary in malignancy potential ranging from small, incidentally detected tumors with excellent outcome to aggressive sarcomas. The proportion of overtly malignant or high-risk GISTs is 20–35% of all GISTs [12,14] suggesting that the annual incidence of GISTs with a high malignancy potential is about 5 per million.

### 5.1. Medical History and Physical Examination

If there is a reason to suspect that you may have a GIST or other type of GI tumor , the doctor will use imaging

tests or endoscopy exams to help find out if it is cancer or something else. If it is a GIST, further tests will be done to help determine the extent stage of the cancer [15].

### 5.2. Barium x-rays

Barium x-rays are not used as much today as in the past. In many cases they are being replaced by endoscopy – where the doctor actually looks into your colon or stomach with your colon or stomach with a narrow fiber-optic scope. For these tests, a chalky solution containing barium is used to coat the inner lining of the esophagus, stomach, and intestines [1]. This makes abnormalities of the lining easier to see on x-ray. These tests are sometimes used to diagnose GI tumors, but they can miss some small intestine tumors. If the colon is being examined, you might need to take laxatives and/or enemas to clean out the bowel the night before or the morning of the exam [16].

### 5.3. Computed Tomography (CT) Scan

CT scan is an X-ray test that produces detailed, cross-sectional images of your body. CT scans can be useful in patients with GISTs to find the location and size of a tumor, as well as to see if it has spread into the abdomen or the liver. In some cases, CT scans can also be used to guide a biopsy needle precisely into a suspected cancer. However, this can be risky if the tumor might be a GIST because of the risk of bleeding and a possible increased risk of tumor spread, so these types of biopsies are usually done only if the result might affect the decision on treatment [17].

### 5.4. Magnetic Resonance Imaging (MRI) Scan

MRI scans use radio waves and strong magnets instead of x-rays. The energy from the radio waves is absorbed and then released in a pattern formed by the type of tissue and by certain diseases. MRI scans can be useful in people with GISTs to help find the extent of cancer in the abdomen, but usually CT scans are enough. MRIs can also be used to look for cancer that has come back (recurrence) or spread (metastasis) to distant organs, particularly in the brain or spine [18].

### 5.5. Positron Emission Tomography (PET) Scan

For a PET scan, a radioactive substance is injected into the blood. The amount of radioactivity used is very low. Because cancer cells in the body grow quickly, they absorb large amounts of the radioactive sugar. PET scan images are not finely detailed like CT or MRI images, but a PET scan can look for possible areas of cancer spread in all areas of the body at once. PET scans can be useful for looking at GISTs, especially if the results of CT or MRI scans aren't clear. This test also can be used to look for possible areas of cancer spread to help determine if surgery is an option [19]. PET scans can also be helpful in finding out if a drug treatment is working, as they can give an answer quicker than CT or MRI scans. The scan is usually obtained about 4 weeks after starting the medicine. If the drug is working, the tumor will stop taking up the radioactive sugar. If the tumor still takes up the sugar, your doctor may decide to change your drug treatment [18].

### 5.6. Gastrointestinal Endoscopy

A flexible lighted tube (endoscope) with a tiny video camera on the end into the body should be used to detect GISTs. The camera sends pictures to a video screen, so that the doctor can clearly see any masses (tumors) in the lining of the digestive tract. If abnormal areas are found, small pieces can be biopsied through the endoscope. GIST tumors are often below the mucosa of the GI tract. This makes them harder to see with endoscopy than more common GI tract tumors, which typically start in the mucosa. The doctor may see only a bulge under the normally smooth surface if a GIST is present. GISTs that are below the mucosa are also harder to biopsy through the endoscope. This is one reason only about half of GISTs are diagnosed before surgery [20].

### 5.7. Biopsy

Even if a mass is found on an imaging test such as a barium x-ray or CT scan, these tests cannot tell if the mass is a GIST, some other type of tumor, or some other condition like an infection. The only way to know what it is for sure is to remove cells from the abnormal area by biopsy. The cells are then examined by a pathologist. GISTs are often fragile tumors that tend to break apart and bleed easily. If the doctor suspects a tumor may be a GIST, biopsies must be done carefully and are usually done only if they will help determine treatment options, because of concerns the biopsy might cause bleeding or possibly increase the risk of cancer spreading [21].

### 5.8. Blood Tests

There are no blood tests that can tell if a person has a GIST. These tumors do not release any known substances in the blood that can be used to diagnose a GIST or to measure its response to treatment. However, blood tests can sometimes point to a possible tumor or to its spread. For example, a complete blood count can tell if you have a low red blood cell count. Some people with GIST may become anemic because of bleeding from the tumor. Abnormal liver function tests may mean that the GIST has spread to your liver. Blood tests are also done to check your overall health before you have surgery or while you get other treatments such as targeted therapy [1].

## 6. Complications of GIST

Large-sized tumors GISTs may cause obstruction, hemorrhage of the GIT, perforation of bowel or inward collapse of the intestine resulting in torsion of bowel wall. Complications are also dependent on the site and severity of the tumor. It is easier to treat the primary tumor, but if metastasis occurs, the treatment can be very challenging. Frequently, metastasis of the tumor occurs in the liver and

peritoneum. High risk of tumor recurrence after surgery had been reported in aggressive tumors. Damage of vital nerves, blood vessels, and surrounding structures may occur during surgery. Surgery-related post-surgical infections, ulceration, lung and heart related complications may occur. Side effects from chemotherapy and radiation therapy can also occur [22].

# 7. Treatment of GIST

## 7.1. Surgery

The main treatment for GIST that hasn't spread is usually surgery. The goal of the surgery is to remove the entire tumor. The tumor should be removed en-bloc, with a clear margin. The pseudocapsule should be removed and not penetrated. Therefore, a wedge resection (stomach) or segmental resection (intestine) is required. If neighboring structures are involved, en-bloc resection should still be contemplated [23].

## 7.2. Ablation and Embolization

Treatments such as ablation and embolization are often used to treat cancers that start in the liver, but they can also be used to treat areas of cancer spread in the liver. This technique may provide palliation in patients with GIST metastatic to the liver. Due to the vascular nature of GIST, occluding the supplying artery may be effective. There has been more interest in chemoembolization, which allows increased local drug delivery, but reduced systemic effects due to high first pass metabolism in the liver [24]. Ablation can be used to destroy tumors in the liver caused by the spread of gastrointestinal stromal tumor (GIST). This technique can be used if there are a few small tumors in the liver. There are several types of ablation including radiofrequency ablation, ethanol ablation, microwave thermotherapy and cryosurgery [25]. Embolization is a procedure that injects substances to try to block or reduce the blood flow to cancer cells in the liver. Embolization does reduce some of the blood supply to the normal liver tissue, so it may not be a good option for some patients whose liver has been damaged by diseases such as hepatitis or cirrhosis [26].

## 7.3. Targeted Therapy

Some drugs are able to target the gene changes in gastrointestinal stromal tumor (GIST) cells that have been found in recent years. These drugs work differently from standard chemotherapy drugs. Targeted drugs are very helpful in treating GISTs, while standard chemo drugs are usually not effective. Imatinib is a small molecule tyrosine kinase inhibitor with activity against ABL, BCR-ABL, KIT, PDGFRA, PDGFRB, ARG and possibly CSFlR [27]. Its structure mimics ATP and it binds competitively to the ATP binding sites of the target kinases. Two important findings suggested that imatinib might be effective against gastrointestinal stromal tumours. The first was that imatinib could inhibit the kinase activity of both wild-type and mutant KIT. The second was that it inhibited the growth of a gastrointestinal stromal tumor cell line containing a KIT gene mutation [28].

## 7.4. Chemotherapy

Chemotherapy is the use of drugs to treat cancer. Often, these drugs are injected into a vein or given by mouth. They enter the bloodstream and reach throughout the body, making this treatment potentially useful for cancers that have spread beyond the organ they started in. The role of chemotherapy in management of GISTs is minimal as most cases are resistant to the traditional chemotherapeutic agents [1,29].

## 7.5. Radiation Therapy

Radiation therapy has little role to play in the management of GIST. Most tumors are not amenable to treatment because of their location and close proximity to vital organs. GISTs are thought to be relatively radio-resistant. Nevertheless, radiotherapy can be successfully used in patients with advanced disease to control bleeding or other troublesome symptoms [30].

# 8. Prognosis of GISTs

The prognosis of a patient with primary GIST depends on tumor size, location, and cellular division. The effect of the anatomical location on prognosis is debatable. In one study, anatomical location was found to be a prognostic factor independent from age, mitotic index and tumor size. In another, the anatomic placement of the GIST was found to have an effect on the expression of CD34 and smooth muscle actin [31]. Recently a mutation in exon 9 of c-kit was found in small intestinal GISTs and this was related to an increase in tumor aggressiveness. However, in most studies it is reported that tumor size and mitotic index were the most important prognostic factors, that recurrence and death were more common in the patients in the high-risk group, and that these patients needed additional treatment. Generally, patients with tumors that are 10 cm or greater in size have a high chance of developing tumor recurrence. Meanwhile, those with tumors less than 2 cm are more likely to be cured by surgical resection. Patients with tumors between 2 and 10 cm have an intermediate risk of having the tumor come back after surgery [32]. The location of a primary GIST is also thought to influence outcome. Patients with stomach GIST fare better than those with small intestine GIST. The rate of cellular division (known as mitotic rate) of GIST is determined by examining the tumor under a microscope. Patients with a mitotic rate of 5 or greater per 50 high power microscopic fields have a higher chance of tumor recurrence after removal of a primary GIST. Another important factor in predicting outcome is the presence of tumor metastasis at the time of diagnosis of a primary GIST; these patients have a worse prognosis [33].

# 9. Conclusion

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. The etiology is still not fully determined, but increased expression of the c-kit proto-oncogene may be an important predisposing factor. Classification of GISTs

depends on the primary site of origin of the tumor and the presence of distant metastasis. Most cases of GISTs are asymptomatic and they are discovered accidentally on routine clinical examination. Diagnosis usually needs a combination between imaging techniques, endoscopy and biopsy. Lines of treatment include surgical removal of the tumor, ablation, chemoembolization, radiation therapy and targeted therapy. Prognosis of GISTs largely depends on the location of the primary tumor and the presence of tumor spread at the time of diagnosis.

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