Gastrointestinal stromal tumor of the stomach : progresses in diagnosis and treatment

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Abstract

Gastrointestinal stromal tumors (GISTs) are rare mesenchymal smooth muscle neoplasms that can arise anywhere within the gastrointestinal tract. Approximately 60-70% are located in the stomach. Once considered variants of smooth muscle tumors, they are now understood as originating from the interstitial cells of Cajal or their stem cell precursors. The majority of GISTs (approximately 95%) express the CD117 antigen (KIT), a proto-oncogene product ; 85-95% of these neoplasms have mutations in the c-KIT gene ; only 5-7% has mutations in platelet-derived-growth factor α (PDGFRα).

GISTs can be asymptomatic and incidentally found during examination for other pathologies or at autopsy. The most common symptoms of gastric GIST are abdominal pain and bleeding. Diagnostic work up consists of endoscopy with ultrasonography and cross-sectional imaging studies (computed tomography and/or magnetic resonance imaging).

Surgery remains the first-line treatment for localized gastric GISTs. Both open and laparoscopic operations have been shown to reduce recurrence rates and improve long-term survival. The use of small-molecule selective tyrosine kinase receptor inhibitors has revolutionized the treatment of advanced GISTs. (Acta gastroenterol. belg., **2013**, 76, **403-406**).

Key words : GIST, stomach, gastrointestinal stromal tumor, diagnosis, laparotomy, laparoscopy, SILS.

Introduction

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract representing 1-2% of all gastrointestinal malignancies (1,2). The stomach is the site of origin for more than 60-70% of these tumors. Previously these mesenchymal tumors of the gastrointestinal tract (GI) were classified as leiomyoma or leiomyosarcoma. GIST is now understood as a malignancy arising from interstitial cells of Cajal, an intestinal pacemaker cell, or their stem cell precursors (3,4). Hirota *et al*. discovered the presence of a KIT protein and the possibility of kit mutations, which distinguishes GISTs from other similar tumors (5).

Around 95 percent of GISTs express KIT. Approximately 85-95 % of GISTs have KIT gene mutations that lead to constitutive activation of the KIT receptor that has been postulated to play an important role in tumorgenesis (5-10). A subset of GISTs lacking KIT mutations has activating mutations in the related receptor tyrosine kinase (RTK) platelet-derived-growth factor α (PDGFRα) (11,12). And a few GIST do not have an identified driver mutation.

Most gastric GIST appear usually after age of 50, and are composed of uniform spindle cells or epithelioid cells (13). Most cases are sporadic, and affect men slightly more frequently than women (2).

All GISTs have the potential for malignant behavior. The overall prognosis appears to be related to tumor size, mitotic activity, and location along the gastrointestinal tract. Gastric tumors display a less aggressive behavior than some other locations in the gastrointestinal tract (1, 7,14-15).

Complete surgical resection is considered the first-line treatment of choice for locally gastric GISTs without evidence of metastatic spread (1). GIST do not metastasize to regional lymph nodes. As a consequence, routine lymphadenectomy has not been associated with improved oncologic outcomes, which provides additional justification for laparoscopic surgery of gastric GISTs (1,16,17).

This paper summarizes progress in the diagnosis and treatment of gastric GIST.

Diagnostic work-up of Gastric GIST

Some gastric GISTs are incidentally diagnosed during imaging, endoscopy, surgery for other pathologies, or autopsy. If symptomatic, the most common symptoms of gastric GISTs are bleeding, dyspepsia, anorexia and abdominal pain. Other symptoms include nausea, vomiting and weight loss (2).

At *upper endoscopy* a gastric GIST commonly appears as a submucosal mass with normal overlying mucosa. In some cases, the mucosa can be ulcerated or appears inflammatory.

Endoscopic ultrasonography (EUS) is the most accurate method for distinguishing GISTs from other submucosal lesions, typically showing hypoechogenic, homogeneous lesions with well-defined margins (18,19).

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The endosonographic characteristics of the tumor can help to predict benign versus malignant GISTs. Tumor size (diameter > 4 cm), irregular extraluminal border, echogenic foci, cystic spaces greater than 4 mm depth, and heterogeneity predict the malignant potential of GISTs (20).

A definitive diagnosis of GIST can only be made histologically. Endoscopic biopsies usually do not provide enough tissue for a definite diagnosis because the lesion is located beyond the mucosa and thus the grasp of the forceps. Upper endoscopy with EU guided fine needle biopsy is a better diagnostic modality to acquire tissue for diagnosis (21). Percutaneous biopsy is not recommended because of the risk of haemorrhage or rupture of the soft and fragile GIST with higher rates of tumor recurrence and/or intraperitoneal dissemination. Preoperative biopsy is not generally recommended for a lesion that can be resected unless the biopsy results would definitively influence the choice of treatment. Biopsy is mandatory to confirm the diagnosis of GIST if preoperative imatinib (Glivec®) is considered for a large locally-advanced gastric GIST or whenever metastatic disease is suspected (22).

Contrast- enhanced abdominal and pelvic *Computed tomography (CT)* scanning is the standard imaging method in patients with GISTs to evaluate its extension and the presence of metastatic disease. CT scan is widely available, has high patient comfort, and is an economically competitive method (23,24). A CT scan can localize the gastric tumor as a mass enhancing a soft-tissue rim surrounding a necrotic center with a heterogeneous aspect (25). A CT scan is also a very sensitive technique to detect distant metastasis within liver or lungs.

CT scan is better than is Magnetic Resonance Imaging (MRI) at global evaluation of the abdomen, especially for hollow viscera. *MRI* is an acceptable alternative to CT for patients with renal dysfunction or allergy to iodine contrast agents, but is preferred at specific sites, such as rectum and liver. MRI should be applied in cases of potential resection of liver metastases due to higher sensitivity in detecting small liver lesions (2,26).

Positron emission tomography (PET) is a potential additional exam to CT and is particularly indicated in terms of ambiguous CT or MRI results (2,27). Furthermore, PET may be useful in confirming distant metastatic disease and determining the response to neoadjuvant targeted therapy within days to weeks of induction therapy but does not replace CT as the initial imaging modality of choice, or as follow-up method in medically treated advanced disease (28,29).

Observation versus endoscopic resection

The treatment approach varies according to size. Stable submucosal *gastric GISTs < 1 cm* on EUS findings suggestive for a benign lesion may be followed-up conservatively with follow-up visits scheduled every 6-12 months. Resection is advised if lesions become symptomatic, increase in size, or show sonographic features of malignancy (30).

Whether *gastric GISTs between 1 and 2 cm* need to be removed is controversial according to the available literature (31,32). Although the prognosis of gastric GISTs is better than those arising elsewhere in the intestinal tract, some authors recommend resection of these GIST because even lesions < 2 cm in diameter with < 1 mitosis per 10 high power fields (HPFs) occasionally metastasize to the liver, peritoneum or lung (15,33). We also support this thesis, even if the malignant transformation is minimal, but not nul.

Endoscopic resection techniques have been described but remain controversial too, because of the risk of positive margins, tumor spillage, haemorrhage and perforation. Only intragastric GISTs arising from the superficial circular layer or muscularis mucosa are good candidates for removal by submucosal dissection or endoscopic enucleation (34). These procedures are technically demanding and require experience and skill.

Surgical resection of gastric GIST

The standard approach for *gastric GISTs > 2 cm* is surgical excision. Because gastric GIST usually grows out of the primary organ and do not invade the neighboring organs, wide excision is not necessary and wedge resection is a correct procedure from an oncologic point of view (1). Given the rarity of lymphatic dissemination, regional lymphadenectomy is not routinely performed (1,16). Historically, a 1-2 cm margin has been recommended, even though tumor size determines survival (1,35). Standard oncologic principles of tumor resection must be followed. Tumor spilling or haemorrhage should be avoided given their association with high locoregional recurrence rates and/or development of peritoneal metastases.

Standard operations include both “open” and minimally invasive techniques. Wedge or “full-thickness” partial gastrectomy is an effective intervention for tumors located at the anterior wall, along the lesser or greater curvature of the stomach. A limited gastric mobilization around the lesion is sufficient in these cases.

Posteriorly-based gastric GISTs often require a more extensive mobilization of the stomach with ligation of the gastrocolic omentum, the short gastric vessels and the gastrohepatic ligament. Posterior exophytic lesions can be resected with wedge stapling at the pedicle after mobilization of the stomach. Posterior endophytic lesions are treated using transgastric techniques through an anterior longitudinal gastrotomy with eversion of the lesion and dividing its pedicle with a linear stapling device. The anterior gastrotomy is closed with a stapling device or running suture (36).

Anatomic gastrectomy (ie, subtotal or total gastrectomy) is considered for large tumors involving a significant portion of the stomach, or for tumors involving the pylorus or esophagogastric junction.

If the adjacent organs are involved "en bloc resection" should be considered. The vital structures should not be sacrificed if possible (1).

Operative lymphadenectomy is unnecessary because of uncommon lymphatic spread and the role of laparoscopy in GIST surgery had increased in the last decade.

The goals for laparoscopic surgery remain the same as those for open surgery : resection with grossly negative margins, removal of the tumor without rupture, avoidance of tumor manipulation, with respect for the principles of oncology (37). Indications for minimally invasive resections depend on tumor size, position and pattern of growth.

Although the National Comprehensive Cancer Network (NCCN) guidelines recommend laparoscopic resection for gastric GIST up to 5 cm several surgical investigators have reported successful and safe resection of larger GISTs of the stomach (2,38-44). All reports were retrospective series. A formal meta-analysis was not performed given the lack of uniform reporting of outcome data. The available information shows reasonable operative times, acceptable complication rates, and few conversions to open operations. The postoperative length of hospitalization is shorter than for open operations among historical controls. Caution has to be taken in broadly extrapolating these results to all patients with gastric GIST : most series had a potential for selection bias, a relatively short follow up, and most operations were performed by surgeons with considerable experience with these techniques (38-44). Our institutional experience with laparoscopic resection of GIST suggests that laparoscopic techniques are both feasible and effective treatment for tumors up to 11 cm in diameter (45).

It appears that minimally-invasive operations for gastric GIST have been less successful to treat patients with tumors in difficult locations, i.e. the gastroesophageal junction (GEJ) or the pylorus. A laparoscopic intraluminal intragastric surgery technique using three laparoscopic trocars placed separately in the inflated stomach and penetrating both the abdominal wall and the stomach can overcome these limitations (46-51). Single port techniques can also give a solution for these cases (52-53).

Tyrosine kinase inhibitors

Conventional chemo- and radiation therapy are historically ineffective adjuvant treatment for GISTs and do not significantly improve survival in patients with recurrent, metastatic or unresectable primary tumors (54).

The evolution of targeted therapy has dramatically altered outcomes for patients with advanced GIST. Imatinib mesylate is an orally selective molecular inhibitor of cellular tyrosine kinases. First used to treat Philadelphia chromosome-positive chronic myelogeneous leukemia (CML), imatinib inhibits tyrosine receptor kinases KIT and PDGFRA. The usual start dosis of imatinib is 400 mg daily (54).

Imatinib mesylate is used in neoadjuvant setting, in advanced disease, and is also approved for adjuvant treatment of GISTs with a high risk profile for relapse.

Postoperative follow up

National Cancer Comprehensive Network (NCCN) guidelines suggest a strict follow-up schedule after complete resection of gastric GIST : patients should be followed with comprehensive history and physical examinations every 3-6 months for 5 years, then annually. Abdominal/pelvic contrast enhanced CT scans are recommended every 3-6 months, for at least 3 to 5 years postoperatively (2).

Given the risk of renal failure with iodinated contrast and the cumulative ionizing radiation exposure with frequent CT scan, less intensive surveillance programs should be advocated. MRI remains an acceptable alternative for suitable patients and avoids the deleterious radiation exposure associated with serial CT scans. It is reasonable to consider a PET scan one-year after resection to rule out a local or anastomotic recurrence.

It is important in the follow-up of these patients that new lesions should be critically examined and biopsied, as these regulary prove to be a second malignancy rather than a GIST recurrence.

Conclusion

A complete resection remains the most important treatment of primary gastric GIST. Imatinib may improve the clinical outcome of patients with an incompletely resected, metastatic or recurrent gastric GIST or as an adjuvant treatment in high risk patients. Neoadjuvant imatinib should be considered in cases that pose anticipated surgical problems.

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