European Review for Medical and Pharmacological Sciences 2014; 18: 3076-3085

Gastrointestinal stromal tumors: current translational research and management modalities

R.-X. HUANG, P. XIANG, C. HUANG[1]

Digestive Endoscopy Center, Affiliated Huadong Hospital, Fudan University, Shanghai, P.R. China
[1]Department of General Surgery, Affiliated First People's Hospital, Shanghai Jiao Tong University, Shanghai, P.R. China

R.-X. Huang, P. Xiang, and *C. Huang* contributed equally

Abstract. – Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract. In recent years, detection of these subepithelial lesions has improved due to advances in endoscopic imaging techniques. Furthermore, developments in immunohistochemical technologies, allowing for reliable differentiation of GISTs from other subepithelial tumors, have improved the understanding of these lesions significantly. Alongside the emergence of these new technologies, clinical management of GISTs has progressed greatly in the last decade. However, major controversies still exist in various aspects of GIST management, such as diagnosis, treatment, and prognosis. This review article provides the current overview of the research status in the management of GISTs.

Key Words:
GIST, Endoscopy, Surgery, Targeted therapy.

Introduction

Although rare, gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms, accounting for 1-2% of all neoplasms of the digestive tract[1]. Initially, GISTs were recognized as distinct entities that contained both smooth muscle and neural features[2]. In 1998, Hirota et al[3] discovered the *c-kit* proto-oncogene and KIT, a tyrosine kinase receptor that plays a role in GISTs. This greatly revolutionized the ability to differentiate these lesions from other mesenchymal, myogenic, and neurogenic subepithelial tumors. Subsequently, similarities between GIST cells and cells of Cajal in the intestinal wall led to the hypothesis that GISTs originate from the stem cell precursors of Cajal cells, which regulate gastrointestinal motility by generating spontaneous electrical slow waves in the digestive tract[4,5]. Although many controversies concerning GISTs still exist, increased knowledge of their molecular biology, morphology, and biological cause; invention of new radiological, endoscopic, and surgical instruments; and advances in operative techniques in recent years, have led to major developments in their management with respect to diagnosis, treatment, and prognosis.

Epidemiology

GISTs may arise almost anywhere along the gastrointestinal tract, but the most common site of occurrence is the stomach (50-70%), followed by the small intestine (25-35%), the colon and rectum (5%-10%), and the esophagus (<5%). Metastatic disease may be found intraparenchymally within the liver and along the peritoneal, serosal, and omental surfaces of the abdominal cavity. Metastases in the lung, bone, and other soft tissue sites are rare and are generally only seen in late stages of the disease[6]. In terms of diagnosis, these lesions most commonly occur in patients with a median age of 60, with equal distribution between men and women. Several population-based studies suggested that the clinically relevant incidence of GISTs is 6.5 to 14.5 per million, with a median age at diagnosis of 63-66 years[7-10].

Pathogenesis

In 1998, Sarlomo Rikala M et al[11] established the KIT protein (CD117) in GIST cells using immunohistochemical methods. The cellular KIT protein is a transmembrane cytokine receptor with an intracellular region that functions as a tyrosine kinase. Subsequently, researchers found that the KIT protein is coded through the *c-kit* proto-oncogene, which is well documented in humans. Human *c-kit* is located on the long arm of chromosome 4, consisting of 21 exons[12]. KIT

Corresponding Author: Chen Huang, MD; e-mail: richard-hc@hotmail.com

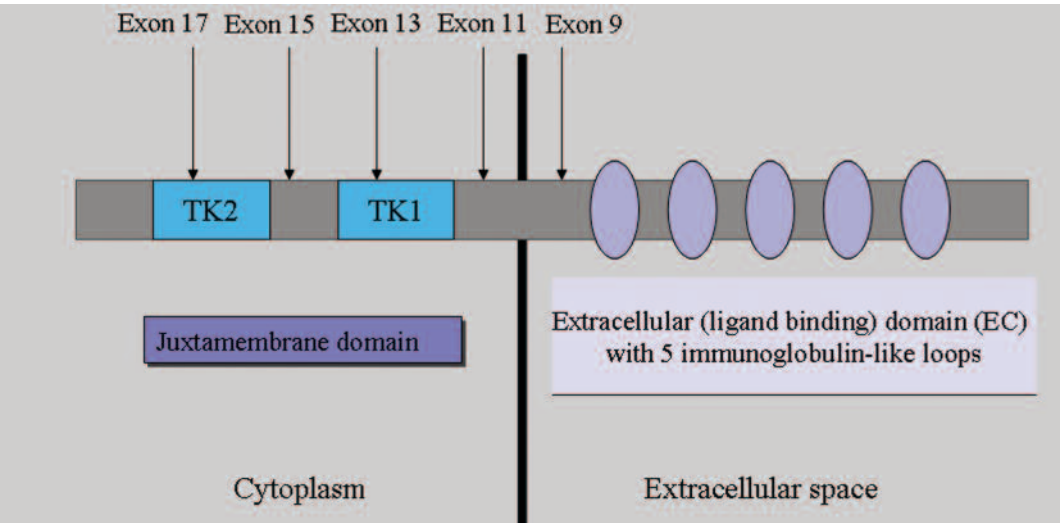

Figure 1. KIT structure and localization of common KIT mutations.

consists of an extracellular (EC) domain with 5 immunoglobulin-like loops, a transmembrane region, and a cytoplasmic domain with a juxtamembrane (JM) region and a split tyrosine kinase (TK) domain. The latter is divided into an adenosine triphosphate (ATP)-binding region (TK1) and a phosphotransferase region (TK2), by a hydrophilic kinase insert (KI)[13] (Figure 1). Normally, KIT is activated by stem cell factor. Ligand binding to the EC domain results in the dimerization of receptors and phosphorylation of tyrosine in the cytoplasmic TK domains. This leads to a phosphorylation cascade and activation of signal transduction pathways including Ras/MAP kinase, Rac/Rho-JNK, PI3K/AKT, and SFK/STAT signaling networks[14]. Approximately 95% of GISTs express the KIT receptor TK, and approximately 80% of GISTs have *c-kit* gene mutations that lead to constitutive activation of the KIT receptor[6]. These mutations can be divided into 2 categories based on their location: mutations of the receptor regulatory domain (EC and JM) and mutations of the enzymatic domain (TK1 and TK2)[15]. Most involve the JM domain (exon 11) and consist mainly of deletions or point mutations. Mutations in the JM domain affect KIT's autoregulatory function and promote spontaneous kinase activation[16]. Heinrich et al[17] reported that primary *c-kit* mutations are observed most commonly in exons 11 (67%) and 9 (18%), and less commonly in exons 13 (< 2%) and 17 (< 2%). In 2003, Heinrich et al[18] found an activation mutation for another proto-oncogene, named *platelet-derived growth factor receptor alpha* (*PDGFRα*), which is also located on the long arm of chromosome 4 close to *c-kit*. This encodes a related receptor, TK PDGFRα, and was observed in approximately 30% of *c-kit*-negative GISTs. Grover et al[6] indicated that primary *PDGFRα* mutations were found in exons 12 and 18. These mutations changed the activation loop and, when activated, PDGFRα triggers the same signaling pathways as KIT, giving rise to GISTs. Another gene *DOG1* (*Discovered On GIST1*) has been found to be overexpressed in most GISTs. DOG1, a monoclonal antibody against a chloride channel protein expressed by GISTs, is immunoreactive in 95% of GISTs, irrespective of their mutation status, i.e., in unusual GIST subgroups that lack *c-kit* or *PDGFRα* mutations[19,20]. Overall, DOG1 exhibits high sensitivity and specificity and is considered an easier stain for histopathological interpretation than CD117. Hence, it has become a very promising new marker for GISTs[21-23]. In the latest publication of Hwang et al[24], the authors demonstrated that DOG1 is a more sensitive and robust marker than KIT on GIST cell blocks, and is a useful marker in the diagnosis of GISTs in cytological specimens.

Assessment of Malignant Potential

The clinical behavior of GISTs can vary widely, making it difficult to discern aggressive lesions from nonaggressive tumors based on clinical and histological features. Approximately 10-30% of GISTs are regarded as clinically malignant; therefore, all GISTs have malignant potential and no

GIST can truly be considered benign[25,26]. In 2008, in an attempt to predict and assess the malignant potential of GISTs, Joensuu[27] proposed a method for risk stratification of patients diagnosed with GISTs, and this methods was favored by many (Table I). Although researchers have attempted to improve the accuracy of assessment of the malignant potential of GISTs, a reliable set of histopathological criteria based on nonsurgical specimens does not currently exist.

Clinical Presentation

Population-based studies have reported that approximately 70% of GISTs are clinically symptomatic, 20% are incidentally discovered during surgery, and 10% are identified at autopsy[28,29]. However, these estimates are probably attributable to case-finding bias as many more small asymptomatic GISTs go unrecognized. Of those with symptoms, the majority (53%) presented with gastrointestinal bleeding. Overt gastrointestinal bleeding was noted in 34% of patients, whereas anemia with suspected occult gastrointestinal bleeding was noted in 19% of patients[30]. Other presenting symptoms were abdominal pain (32%) and the presence of a palpable mass (13%). Rare symptoms that were specific for the site of involvement included dysphagia for esophageal GISTs and obstruction or perforation for colonic GISTs. A significant number of GISTs are asymptomatic and are incidentally discovered on imaging, during endoscopic examination for other reasons, after surgical resection or at autopsy. Although the incidence of asymptomatic subepithelial masses identified during endoscopy is unclear, such lesions are increasingly being recognized with heightened awareness and improved endoscopic imaging.

Clinical Diagnostics

Clinical diagnoses of GISTs are generally based on imaging and endoscopic examination techniques.

Imaging

Contrast-enhanced computed tomography (CT) might be useful in detecting tumors that are 2 cm or larger, particularly for extraluminal tumors or tumors with calcifications, necrosis, or substantial vascularization[31]. In addition, CT scanning plays an important role in the detection and monitoring of post-treatment metastasis regression[32]. Positron Emission Tomography (PET) scans are generally only used to evaluate lesions showing ambiguity on CT scanning (for example, to confirm a GIST via high ^{18}F-fluorodeoxyglucose (FDG) uptake)[6]. Kamiyama et al[33] found a significant correlation between the FDG uptake and both the Ki67 index and the mitotic index in GISTs, indicating that FDG uptake is a predictor of the malignant potential of a GIST.

Light Endoscopy

During general light endoscopy, most subepithelial lesions present as a bulge in the gastrointestinal tract, with smooth, intact, normal overlying mucosa. Light endoscopy can assess the subepithelial lesions for estimated size, mucosal appearance, and pulsation[34]. Probing of the lesion with closed biopsy forceps is often performed and can provide additional information regarding mobility and consistency. However, the accurate diagnosis of GISTs with light endoscopy alone is poor. In the study of Hwang et al[35], the diagnostic specificity for light endoscopy was only 64%.

Table I. Malignancy Risk Stratification of Patients Diagnosed with GISTs.

Risk category	Tumor diameter (cm)	Mitotic index (per 50 HPFs)	Primary tumor site
Very low risk	< 2.0	≤ 5	Any
Low risk	2.1–5.0	≤ 5	Any
Intermediate risk	2.1–5.0	> 5	Gastric
	< 5.0	6–10	Any
	5.1–10.0	≤ 5	Gastric
High risk	Any	Any	Tumor rupture
	> 10.0	Any	Any
	Any	> 10	Any
	> 5.0	> 5	Any
	2.1–5.0	> 5	Non-gastric
	5.1–10.0	≤ 5	Non-gastric

EUS

Endoscopic ultrasonography (EUS) can provide valuable information about submucosal lesions with regard to tumor size, wall layer of origin or extramural origin, echogenicity, vascularity, and appearance of the tumor margins. GISTs arise from the fourth sonographic layer, which correlates with the muscularis propria. GISTs are typically hypoechoic, homogeneous lesions with a smooth, rounded appearance. Hunt et al[36] used the criteria of submucosal tumors larger than 4 cm and those with ulcerations or cystic spaces for the diagnosis of GISTs with EUS, concluding the sensitivity was 64.7% and specificity was 91.7%. Brand et al[37] reported a sensitivity and specificity of 95% and 72%, respectively for an EUS-based diagnosis of GISTs, by using the simple criterion of any hypoechoic lesion not originating from the submucosa. Conversely, other researchers have demonstrated that the diagnostic accuracy of EUS alone was subject to inter-observer variability and have reported it to be as low as 48%, with the conclusion that the diagnostic accuracy heavily depended upon the experience of the endoscopist[35].

EUS-FNA

As tissue acquisition and immunohistochemical analysis is required to confirm the diagnosis of GISTs, EUS-guided fine-needle biopsy has emerged as a preferred method for sampling lesions[34,38]. EUS-guided fine-needle aspiration (EUS-FNA) is the most commonly practiced method for obtaining tissue from subepithelial lesions. Immunohistochemical staining for KIT receptor (CD117) has been routinely performed for lesions arising from the fourth wall layer(1). Many studies have demonstrated the superiority of EUS-FNA for diagnosing GISTs with high sensitivity (up to 95%) and satisfactory diagnostic accuracy (up to 60%)[39-41]. However, other studies have suggested a much lower rate of sensitivity (58%) and specificity (8%) with EUS-FNA of GISTs[42]. EUS-FNA does have its limitations. Inadequate tissue acquisition may occur in up to 33.3% of samples[43], which may result in the inability to determine malignant potential. Mitotic count cannot be routinely calculated with cytology specimens and a reliable set of histopathological criteria for malignancy does not yet exist. Although there is still controversy surrounding the best management strategy for diagnosing GISTs, most experts still recommend performing EUS-FNA for suspected lesions.

EUS-CNB

EUS-guided core needle biopsy (EUS-CNB) has been proposed as an alternative to EUS-FNA. This uses a 19-gauge core needle to obtain a core of tissue rather than a cluster of cells. Therefore, EUS-CNB has the potential advantage of obtaining more tissue for performing immunohistochemical staining as well as the ability to calculate the mitotic rate. Several studies reported that EUS-CNB had a higher diagnostic accuracy than EUS-FNA[44-46]. However, other studies did not demonstrate a difference in the diagnostic yield between EUS-FNA and EUS-CNB[47,48]. Moreover, EUS-CNB has also been associated with higher rates of complications, such as bleeding, and technical difficulties, as the spring-loaded cutting sheath of the core needle is limited by the angulation of the echoendoscope, meaning its use is limited to lesions in the esophagus, stomach, and rectum[44,48,49].

Laparoscopic or Open Biopsy

In lesions that are not amenable to endoscopic biopsy, a laparoscopic or open biopsy may be necessary. However, transperitoneal biopsy is associated with the risk of hemorrhage, perforation and peritoneal seeding. Thus, laparoscopic or open biopsy is not generally recommended[6].

Treatment of Primary Localized GISTs

Along with obtaining more knowledge about GISTs and improving the operative instruments and techniques, various methods have been adopted to improve the treatment of primary localized GISTs. Although recognized guidance and regulation of the treatment of GISTs are still absent, substantial developments have been made in this respect during recent years.

Endoscopic Surveillance

The American Gastroenterological Association recommends removal of all GISTs with a diameter ≥ 3 cm, as well as tumors with a < 3-cm diameter with concerning endosonographic features (for example, an irregular border, presence of cystic spaces, echogenic foci, or heterogeneity)[34]. The European Society for Medical Oncology recommends removal of all GISTs > 2 cm in diameter[50]. However, the management of incidentally discovered small GISTs of less than 2-cm diameter remains controversial. Nowadays, most experts advocate EUS surveillance for incidentally discovered small (< 2-cm diameter)

asymptomatic GISTs. Guidelines for the period of EUS surveillance have not yet been established[6,25].

Traditional Open Surgery

Traditional open surgery is the first-line treatment and the only treatment approach that might lead to full remission in patients with a primary localized GIST larger than 2 cm in diameter[26]. Unlike carcinomas, GISTs exhibit distinct features, in particular, an absence of metastases within locoregional lymph nodes. Therefore, operations requiring extended lymph node dissection, typically designed for carcinomas such as gastrectomy with extended lymph node dissection; Whipple's procedure; and total mesorectum excision, are inappropriate for treating GISTs originating from the stomach, duodenum, and rectum, respectively[51]. Instead, limited wedge or segmental resections are the correct operative choices[25,51].

Laparoscopic Surgery

Laparoscopic wedge resection, which is less invasive than traditional open surgery, has demonstrated promising results with regard to efficacy, safety profile, and length of hospitalization[52,53]. To date, most of the available data on laparoscopic resection are limited to gastric GISTs, while outcomes following laparoscopic resection of GISTs at other sites are still unknown[6]. NCCN Guidelines suggest that laparoscopic wedge resection may be used for tumors ≤ 5 cm in diameter[38]. However, with the improvement of surgical techniques, Jeong et al[54] indicated that laparoscopic surgery for gastric GISTs is also safe and feasible even in large (> 5-cm diameter) tumors.

Endoscopic Resection

As endoscopic devices and techniques have been developed, some researchers have considered endoscopic resection of GISTs. Multiple small case series have demonstrated adequate endoscopic resection of small GISTs using various techniques, including endoscopic submucosal dissection (ESD), band ligation, and endoscopic enucleation[54-57]. Liu et al[58] reported that endoscopic muscularis dissection of GISTs localized in the esophagus and stomach appears to be a feasible and minimally invasive treatment. Although there is a higher risk of perforation than with ESD, perforations have become manageable endoscopically. Zhou et al[59] reported successful endoscopic full-thickness resection without laparoscopic assistance for gastric submucosal tumors originating from the muscularis propria. However, it is still doubtful whether full-thickness suturing for gastrostomy closure with a conventional loop clip is safe enough, as the clip can only hold the mucosal surface. Thus, development of a full-thickness suturing device for a flexible endoscope is essential. Jeong et al[54] specified that although endoscopic resection showed good results with no recurrence, until the suitability for oncological principles and the long-term safety of this approach were clarified, this approach should be limited to select cases with a high operative risk or a need for preservation of organ function.

Laparoscopic and Endoscopic Cooperative Surgery

As judging the location of GISTs is often difficult under laparoscopic examination alone and suture techniques are still immature for endoscopic resections at present, laparoscopic and endoscopic cooperative surgery (LECS) may be an alternative choice. Mori et al[60] and Tsujimoto et al[61] both demonstrated the feasibility and satisfactory surgical outcome for gastric GISTs after LECS.

Targeted Therapy

The discovery of the orally available imatinib mesylate (Gleevec, Novartis, Basel, Switzerland) is a key breakthrough that has revolutionized the management of GISTs. Imatinib mesylate inhibits the TK domains of various receptors, including wild-type and mutant forms of KIT (CD117) and some mutant forms of PDGFRα, except for the mutation in exon 18 D842V[62-66]. Duffaud et al[67] indicated that preoperative treatment with imatinib might reduce the primary tumor to a size small enough to be removed surgically. Eisenberg et al[68] also evaluated the safety and feasibility of imatinib as a neoadjuvant agent and found that the neoadjuvant imatinib is a well-tolerated and feasible treatment option. Other studies have investigated the effects of adjuvant therapy with imatinib following resection of primary localized GISTs and, according to these studies, adjuvant therapy of imatinib extends the recurrence-free period[69]. Although the optimal duration of adjuvant therapy remains uncertain, it does appear that 3 years is better than 1[69]. Patients with advanced GISTs who progress on or are intolerant of the first-line imatinib therapy usually start the second-line sunitinib malate (Sutent, Pfizer Inc., New York, USA) therapy. Tumors with sec-

ondary mutations (new mutations acquired after imatinib exposure, resulting in imatinib intolerance) involving KIT exons 13 or 14 are especially sensitive to sunitinib. Sunitinib targets KIT, PDGFRα, PDGFRβ, several vascular endothelial growth factor receptors (VEGFR1, VEGFR2, and VEGFR3), the ret proto-oncogene receptor, and Fms-like tyrosine kinase-3 receptor (Flt3)[6,26]. To deal with GISTs resistant to both imatinib and sunitinib, more clinical trials involving novel drugs such as nilotinib, sorafenib, and crenolanib, targeting the inhibition of other signaling pathways, are currently underway[6,70-72].

Treatment of Locally Advanced, Metastatic, Recurrent GISTs

Imatinib is approved by the Food and Drugs Administration (FDA) as the first-line therapy for patients with advanced GISTs, in order to improve progression-free survival rates and overall survival rates. Once imatinib therapy is instituted for metastatic or recurrent GISTs, most researchers suggest treatment should be continued. In studies, patients with responsive or stable disease who discontinued imatinib therapy after 1, 3, and 5 years had a much higher rate of disease progression than did those who continued with therapy[73,74]. Reichardt et al[75] indicated that standard therapy for locally advanced or metastatic GISTs was imatinib at a dose of 400 mg/day, while patients with mutations in KIT at exon 9 should be treated with 800 mg imatinib/day, since they profited from a significantly longer progression-free survival. However, it is also important to note that there were very few true complete remissions from medical therapy alone. Thus, along with the effective targeted therapy, cytoreductive surgery has been pursued in patients with metastatic or recurrent GISTs[6,26].

The figure below shows the summarized strategy for GIST therapy (Figure 2).

Prediction of Recurrence of GISTs

Due to the malignant potential of GISTs it is important to be able to predict the possibility of recurrence after surgical or endoscopic resection of the primary localized GIST. Several researchers have evaluated the recurrence predicting factors of GISTs. Kim et al[76] demonstrated that after resections of gastric GISTs of diameters ≤ 5 cm, high mitotic index (>10 per 50 High Power Fields) and abnormally high levels of p53 expression were predictive factors of recurrence. Interestingly the authors indicated that a positive microscopic resection margin was not associated

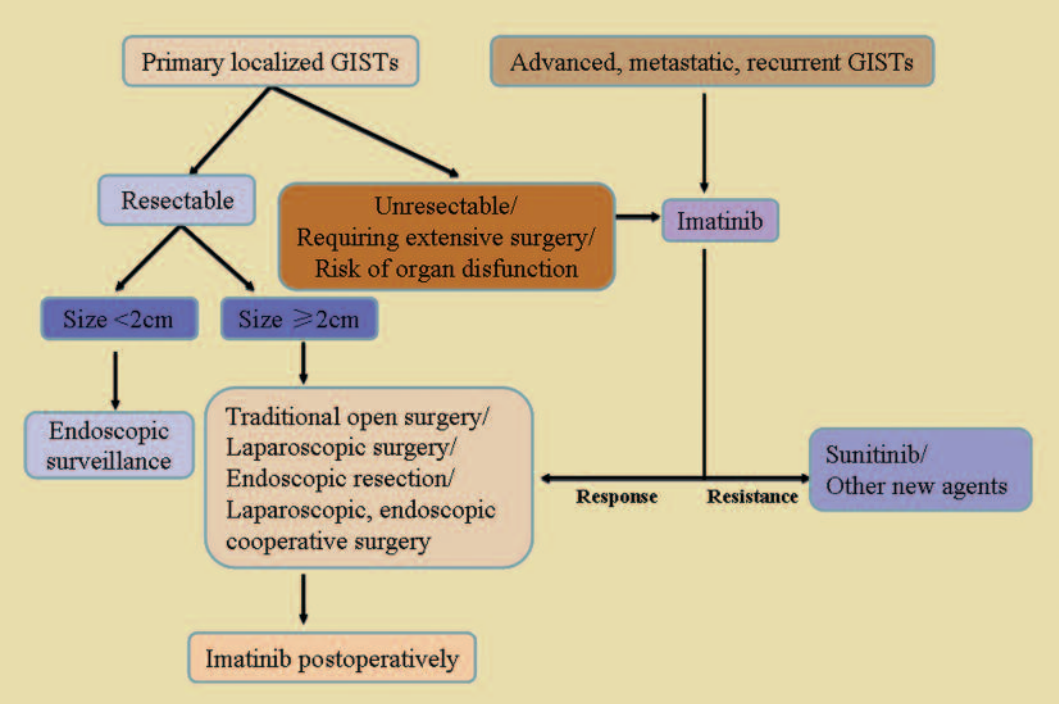

Figure 2. Strategy of GISTs therapy.

with recurrence. A multicentric, prospective analysis in a much larger population should be carried out in the near future to confirm the predictors of recurrence for GISTs.

Conclusions

Over the past decade, increased knowledge of the pathogenesis of GISTs has led to improved understanding of these lesions and the ability to readily identify and differentiate GISTs from other submucosal tumors. EUS-FNA is considered as the preferable and feasible option for confirming the diagnosis of GISTs. EUS-CNB is also a promising method for their diagnosis. Although surgical resection is the first-line treatment, and the only method that might lead to full remission in patients with primary GIST, various new techniques for endoscopic resections are emerging. Many researchers demonstrated satisfactory results with endoscopic resections, but more studies should take place to confirm the prognosis of endoscopic therapy. Last but not the least, targeted therapy represented by imatinib and sunitinib has clearly improved the survival rates in patients with primary, metastatic, or recurrent GISTs. As various novel techniques are persistently improving the management of GISTs it is expected that both individual risk assessment and therapy for each lesion may be provided to each patient someday.

Acknowledgements

The work is supported in part by grants 81101844 and 81210108027 (to C. Huang) from the National Natural Science Foundation of China and grant 2012040 and 13PJD024 (to C. Huang) from Shanghai Municipal Human Resources and Social Security Bureau.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Chandrasekhara V, Ginsberg GG. Endoscopic management of gastrointestinal stromal tumors. Curr Gastroenterol Rep 2011; 13: 532-539.
2) Mazur MT, Clark HB. Gastric stromal tumors: reappraisal of histogenesis. Am J Surg Pathol 1983; 7: 507-519.
3) Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, Kawano K, Hanada M, Kurata A, Takeda M, Muhammad Tunio G, Matsuzawa Y, Kanakura Y, Shinomura Y, Kitamura Y. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998; 279: 577-580.
4) Sircar K, Hewlett BR, Huizinga JD, Chorneyko K, Berezin I, Riddell RH. Intestinal cells of Cajal as precursors of gastrointestinal stromal tumors. Am J Surg Pathol 1999; 23: 377-389.
5) Kindblom LG, Remotti HE, Aldenborg F, Meis-Kindblom JM. Gastrointestinal pacemarker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the intestinal cells of Cajal. Am J Pathol 1998; 152: 1259-1269.
6) Grover S, Ashley SW, Raut CP. Small intestine gastrointestinal stromal tumors. Curr Opin Gastroenterol 2012; 28: 113-123.
7) Cassier PA, Ducimetiere F, Lurkin A, Ranchère-Vince D, Scoazec JY, Bringuier PP, Decouvelaere AV, Méeus P, Cellier D, Blay JY, Ray-Coquard I. A prospective epidemiological study of new incident GISTs during two consecutive years in Rhone Alpes region: incidence and molecular distribution of GIST in a European region. Br J Cancer 2010; 103: 165-170.
8) Mucciarini C, Rossi G, Bertolini F, Valli R, Cirilli C, Rashid I, Marcheselli L, Luppi G, Federico M. Incidence and clinicopathologic features of gastrointestinal stromal tumors: a population-based study. BMC Cancer 2007; 7: 230.
9) Rubió J, Marcos-Gragera R, Ortiz MR, Miró J, Vilardell L, Gironès J, Hernandez-Yagüe X, Codina-Cazador A, Bernadó L, Izquierdo A, Colomer R. Population-based incidence and survival of gastrointestinal stromal tumours (GIST) in Girona, Spain. Eur J Cancer 2007; 43: 144-148.
10) Steigen SE, Eide TJ, Wasag B, Lasota J, Miettinen M. Mutations in gastrointestinal stromal tumors: a population-based study from Northern Norway. APMIS 2007; 115: 289-298.
11) Sarlomo Rikala M, Kovatich AJ, Barusevicius A and Miettinen M: CD117: a sensitive marker for gastrointestinal stromal tumors that is more specific than CD34. Mod Pathol 1998; 11: 728-734.
12) Yarden Y, Kuang WJ, Yang-Feng T, Coussens L, Munemitsu S, Dull TJ, Chen E, Schlessinger J, Francke U, Ullrich A. Human proto-oncogene c-kit: a new cell surface receptor tyrosine kinase for an unidentified ligand. EMBO J 1987; 6: 3341-3351.
13) Bayraktar UD, Bayraktar S, Rocha-Lima CM. Molecular basis and management of gastrointestinal stromal tumors. World J Gastroenterol 2010; 16: 2726-2734.
14) Fletcher JA. Role of KIT and platelet-derived growth factor receptors as oncoproteins. Semin Oncol 2004; 31: 4-11.

15) Longley BJ, Reguera MJ, Ma Y. Classes of c-KIT activating mutations: proposed mechanisms of action and implications for disease classification and therapy. Leuk Res 2001; 25: 571-576.

16) Chan PM, Ilangumaran S, La Rose J, Chakrabartty A, Rottapel R. Autoinhibition of the kit receptor tyrosine kinase by the cytosolic juxtamembrane region. Mol Cell Biol 2003; 23: 3067-3078.

17) Heinrich MC, Corless CL, Demetri GD, Blanke CD, von Mehren M, Joensuu H, McGreevey LS, Chen CJ, Van den Abbeele AD, Druker BJ, Kiese B, Eisenberg B, Roberts PJ, Singer S, Fletcher CD, Silberman S, Dimitrijevic S, Fletcher JA. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 2003; 21: 4342-4349.

18) Heinrich MC, Corless CL, Duensing A, McGreevey L, Chen CJ, Joseph N, Singer S, Griffith DJ, Haley A, Town A, Demetri GD, Fletcher CD, Fletcher JA. PDGFRA activating mutations in gastrointestinal stromal tumors. Science 2003; 299: 708-710.

19) Espinosa I, Lee CH, Kim MK, Rouse BT, Subramanian S, Montgomery K, Varma S, Corless CL, Heinrich MC, Smith KS, Wang Z, Rubin B, Nielsen TO, Seitz RS, Ross DT, West RB, Cleary ML, van de Rijn M. A novel monoclonal antibody against DOG1 is a sensitive and specific marker for gastrointestinal stromal tumors. Am J Surg Pathol 2008; 32: 210-218.

20) Lopes LF, West RB, Bacchi LM, van de Rijn M, Bacchi CE. DOG1 for the diagnosis of gastrointestinal stromal tumor (GIST): comparison between 2 different antibodies. Appl Immunohistochem Mol Morphol 2010; 18: 333-337.

21) Lee CH, Liang CW, Espinosa I. The utility of discovered on gastrointestinal stromal tumor 1 (DOG1) antibody in surgical pathology-the GIST of it. Adv Anat Pathol 2010; 17: 222-232.

22) Novelli M, Rossi S, Rodriguez-Justo M, Taniere P, Seddon B, Toffolatti L, Sartor C, Hogendoorn PC, Sciot R, Van Glabbeke M, Verweij J, Blay JY, Hohenberger P, Flanagan A, Dei Tos AP. DOG1 and CD117 are the antibodies of choice in the diagnosis of gastrointestinal stromal tumours. Histopathology 2010; 57: 259-270.

23) Ho MY, Blanke CD. Gastrointestinal stromal tumors: disease and treatment update. Gastroenterology 2011; 140: 1372-1376.

24) Hwang DG, Qian XH, Hornick JL. DOG1 antibody is a highly sensitive and specific marker for gastrointestinal stromal tumors in cytology cell blocks. Am J Clin Pathol 2011; 135: 448-453.

25) Sepe PS, Brugge WR. A guide for the diagnosis and management of gastrointestinal stromal cell tumors. Nat Rev Gastroenterol Hepatol 2009; 6: 363-371.

26) Paral J, Slaninka I, Kalabova H, Hadzi-Nikolov D. Gastrointestinal stromal tumors: Review on morphology, molecular pathology, diagnositics, prognosis and treatment options. Acta Gastroenterol Belg 2010; 73: 349-359.

27) Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol 2008; 39: 1411-1419.

28) Nilsson B, Bümming P, Meis-Kindblom JM, Odén A, Dortok A, Gustavsson B, Sablinska K, Kindblom LG. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era–a population-based study in western Sweden. Cancer 2005; 103: 821-829.

29) Tryggvason G, Gíslason HG, Magnússon MK, Jónasson JG. Gastrointestinal stromal tumors in Iceland, 1990-2003: the icelandic GIST study, a population-based incidence and pathologic risk stratification study. Int J Cancer 2005; 117: 289-293.

30) Tryggvason G, Kristmundsson T, Orvar K, Jónasson JG, Magnússon MK, Gíslason HG: Clinical study on gastrointestinal stromal tumors (GIST) in Iceland, 1990-2003. Dig Dis Sci 2007; 52: 2249-2253.

31) Da Ronch T, Modesto A, Bazzocchi M. Gastrointestinal stromal tumor: spiral computed tomography features and pathologic correlation. Radiol Med 2006; 111: 661-673.

32) Van den Abbeele AD. The lessons of GIST-PET and PET/CT: a new paradigm for imaging. Oncologist 2008; 13(Suppl 2): 8-13.

33) Kamiyama Y, Aihara R, Nakabayashi T, Mochiki E, Asao T, Kuwano H, Oriuchi N, Endo K. 18F-fluorodeoxyglucose positron emission tomography: useful technique for predicting malignant potential of gastrointestinal stromal tumors. World J Surg 2005; 29: 1429-1435.

34) Hwang JH, Rulyak SD, Kimmey MB, American Gastroenterological Association Institute. American Gastroenterological Association Institute technical review on the management of gastric subepithelial masses. Gastroenterology 2006; 130: 2217-2228.

35) Hwang JH, Saunders MD, Rulyak SJ, Shaw S, Nietsch H, Kimmey MB. A prospective study comparing endoscopy and EUS in the evaluation of GI subepithelial masses. Gastrointest Endosc 2005; 62: 202-208.

36) Hunt GC, Rader AE, Faigel DO. A comparison of EUS features between CD-117 positive GI stromal tumors and CD-117 negative GI spindle cell tumors. Gastrointest Endosc 2003; 57: 469-474.

37) Brand B, Oesterhelweg L, Binmoeller KF, Sriram PV, Bohnacker S, Seewald S, De Weerth A, Soehendra N. Impact of endoscopic ultrasound for evaluation of submucosal lesions in gastrointestinal tract. Dig Liver Dis 2002; 34: 290-297.

38) Demetri GD, Benjamin RS, Blanke CD, Blay JY, Casali P, Choi H, Corless CL, Debiec-Rychter M, DeMatteo RP, Ettinger DS, Fisher GA, Fletcher CD, Gronchi A, Hohenberger P, Hughes M, Joensuu H, Judson I, Le Cesne A, Maki RG, Morse M, Pappo AS, Pisters PW, Raut CP, Reichardt P, Tyler DS, Van den Abbeele AD, von Mehren M, Wayne JD, Zalcberg J and NCCN Task Force. NCCN Task Force report:

management of patients with gastrointestinal stromal tumor (GIST)-update of the NCCN clinical practice guidelines. J Natl Compr Canc Netw 2007; 5(Suppl 2): S1-S29.

39) Ando N, Goto H, Niwa Y, Hirooka Y, Ohmiya N, Nagasaka T, Hayakawa T. The diagnosis of GI stromal tumors with EUS-guided fine needle aspiration with immunohistochemical analysis. Gastrointest Endosc 2002; 55: 37-43.

40) Sepe PS, Moparty B, Pitman MB, Saltzman JR, Brugge WR. EUS-guided FNA for the diagnosis of GI stromal cell tumors: sensitivity and cytologic yield. Gastrointest Endosc 2009; 70: 254-261.

41) Mekky MA, Yamao K, Sawaki A, Mizuno N, Hara K, Nafeh MA, Osman AM, Koshikawa T, Yatabe Y, Bhatia V. Diagnostic utility of EUSguided FNA in patients with gastric submucosal tumors. Gastrointest Endosc 2010; 71: 913-919.

42) Philipper M, Hollerbach S, Gabbert HE, Heikaus S, Böcking A, Pomjanski N, Neuhaus H, Frieling T, Schumacher B. Prospective comparison of endoscopic ultrasound-guided fine-needle aspiration and surgical histology in upper gastrointestinal submucosal tumors. Endoscopy 2010; 42: 300-305.

43) Rodriguez SA, Faigel DO. Endoscopic diagnosis of gastrointestinal stromal cell tumors. Curr Opin Gastroenterol 2007; 23: 539-543.

44) Levy MJ, Wiersema MJ. EUS-guided Trucut biopsy. Gastrointest Endosc 2005; 62: 417-426.

45) Levy MJ, Jondal ML, Clain J, Clain J, Wiersema MJ. Preliminary experience with an EUS-guided trucut biopsy needle compared with EUS-guided FNA. Gastrointest Endosc 2003; 57: 101-106.

46) Ginès A, Wiersema MJ, Clain JE, Pochron NL, Rajan E, Levy MJ. Prospective study of a Trucut needle for performing EUS-guided biopsy with EUS-guided FNA rescue. Gastrointest Endosc 2003; 62: 597-601.

47) Fernández-Esparrach G, Sendino O, Solé M, Pellisé M, Colomo L, Pardo A, Martínez-Pallí G, Argüello L, Bordas JM, Llach J, Ginès A. Endoscopic ultrasound-guided fine-needle aspiration and trucut biopsy in the diagnosis of gastric stromal tumors: a randomized crossover study. Endoscopy 2010; 42: 292-299.

48) Varadarajulu S, Fraig M, Schmulewitz N, Roberts S, Wildi S, Hawes RH, Hoffman BJ, Wallace MB. Comparison of EUS-guided 19-gauge Trucut needle biopsy with EUS-guided fine-needle aspiration. Endoscopy 2004; 36: 397-401.

49) PolkowskiM, GerkeW, Jarosz D, Nasierowska-Guttmejer A, Rutkowski P, Nowecki ZI, Ruka W, Regula J, Butruk E. Diagnostic yield and safety of endoscopic ultrasound-guided trucut biopsy in patients with gastric submucosal tumors: a prospective study. Endoscopy 2009; 41: 329-334.

50) Casali, PG, Jost L, Reichardt P, Schlemmer M, Blay JY, ESMO Guidelines Working Group. Gastrointestinal stromal tumors: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2008; 19(Suppl 2): ii35-ii38.

51) Gervaz P, Huber O, Morel P. Surgical management of gastrointestinal stromal tumours. Br J Surg 2009; 96: 567-578.

52) Catena F, Di Battista M, Fusaroli P, Ansaloni L, Di Scioscio V, Santini D, Pantaleo M, Biasco G, Caletti G, Pinna A. Laparoscopic treatment of gastric GIST: report of 21 cases and literature's review. J Gastrointest Surg 2008; 12: 561-568.

53) Huguet KL, Rush RM Jr, Tessier DJ, Schlinkert RT, Hinder RA, Grinberg GG, Kendrick ML, Harold KL. Laparoscopic gastric gastrointestinal stromal tumor resection: the Mayo clinic experience. Arch Surg 2008; 143: 587-590.

54) Jeong IH, Kim JH, Lee SR, Kim JH, Hwang JC, Shin SJ, Lee KM, Hur H, Han SU. Minimally invasive treatment of gastric gastrointestinal stromal tumors: laparoscopic and endoscopic approach. Surg Laparosc Endosc Percutan Tech 2012; 22: 244-250.

55) Huang WH, Feng CL, Lai HC, Yu CJ, Chou JW, Peng CY, Yang MD, Chiang IP. Endoscopic ligation and resection for the treatment of small EUS-suspected gastric GI stromal tumors. Gastrointest Endosc 2010; 71: 1076-1081.

56) Lee IL, Lin PY, Tung SY, Shen CH, Wei KL, Wu CS. Endoscopic submucosal dissection for the treatment of intraluminal gastric subepithelial tumors originating from the muscularis propria layer. Endoscopy 2006; 38: 1024-1028.

57) Katoh T, Itoh Y, Mohri T, Suzuki H. Endoscopic enucleation of gastrointestinal stromal tumors of the stomach: report of five cases. World J Gastroenterol 2008; 14: 2609-2611.

58) Liu BR, Song JT, Qu B, Wen JF, Yin JB, Liu W. Endoscopic muscularis dissection for upper gastrointestinal subepithelial tumors originating from the muscularis propria. Surg Endosc 2012; 26: 3141-3148.

59) Zhou PH, Yao LQ, Qin XY, Cai MY, Xu MD, Zhong YS, Chen WF, Zhang YQ, Qin WZ, Hu JW, Liu JZ. Endoscopic full-thickness resection without laparoscopic assistance for gastric submucosal tumors originated from the muscularis propria. Surg Endosc 2011; 25: 2926-2931.

60) Mori H, Kobara1 H, Kobayashi M, Muramatsu A, Nomura T, Hagiike M, Izuishi K, Suzuki Y, Masaki T. Establishment of pure NOTES procedure using a conventional flexible endoscope: review of six cases of gastric gastrointestinal stromal tumors. Endoscopy 2011; 43: 631-634.

61) Tsujimoto H, Yaguchi Y, Kumano I, Takahata R, Ono S, Hase K. Successful gastric submucosal tumor resection using laparoscopic and endoscopic cooperative surgery. World J Surg 2012; 36: 327-330.

62) Buchdunger E, Cioffi CL, Law N, Stover D, Ohno-Jones S, Druker BJ, Lydon NB. Abl protein-tyrosine kinase inhibitor STI571 inhibits in vitro signal transduction mediated by c-kit and platelet derived growth factor receptors. J Pharmacol Exp Ther 2000; 295: 139-145.

63) Heinrich MC, Griffith DJ, Druker BJ, Wait CL, Ott KA, Zigler AJ. Inhibition of c-kit receptor tyrosine kinase activity by STI 571, a selective tyrosine kinase inhibitor. Blood 2000; 96: 925-932.

64) Corless CL, Schroeder A, Griffith D, Town A, McGreevey L, Harrell P, Shiraga S, Bainbridge T, Morich J, Heinrich MC. PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. J Clin Oncol 2005; 23: 5357-5364.

65) Hirota S, Ohashi A, Nishida T, Isozaki K, Kinoshita K, Shinomura Y, Kitamura Y. Gain-of-function mutations of platelet-derived growth factor receptor alpha gene in gastrointestinal stromal tumors. Gastroenterology 2003; 125: 660-667.

66) Debiec-Rychter M, Cools J, Dumez H, Sciot R, Stul M, Mentens N, Vranckx H, Wasag B, Prenen H, Roesel J, Hagemeijer A, Van Oosterom A, Marynen P. Mechanisms of resistance to imatinib mesylate in gastrointestinal stromal tumors and activity of the PKC412 inhibitor against imatinib-resistant mutants: Gastroenterology 2005; 128: 270-279.

67) Duffaud F, Le Cesne A. Imatinib in the treatment of solid tumors. Target Oncol 2009; 4: 45-56.

68) Eisenberg BL, Harris J, Blanke CD, Demetri GD, Heinrich MC, Watson JC, Hoffman JP, Okuno S, Kane JM, von Mehren M. Phase II trial of neoadjuvant/adjuvant imatinib mesylate (IM) for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumor (GIST): early results of RTOG 0132/ACRIN 6665. J Surg Oncol 2009; 99: 42-47.

69) Dematteo RP, Ballman KV, Antonescu CR, Maki RG, Pisters PW, Demetri GD, Blackstein ME, Blanke CD, von Mehren M, Brennan MF, Patel S, McCarter MD, Polikoff JA,Tan BR, Owzar K. Adjuvant imatinib mesylate after resection of localized, primary gastrointestinal stromal tumor: a randomized, double-blind, placebo-controlled trail. Lancet 2009; 373: 1097-1104.

70) Heinrich MC, Marino-Enriquez A, Presnell A, Donsky RS, Griffith DJ, Mckinley A, Patterson J, Taguchi T, Liang CW, Fletcher JA. Sorafenib inhibits many kinase mutations associated with drug-resistant gastrointestinal stromal tumors. Mol Cancer Ther 2012; 11: 1770-1780.

71) Cauchi C, Somaiah N, Engstrom PF, Litwin S, Lopez M, Lee J, Davey M, Bove B, von Mehren M. Evaluation of nilotinib in advanced GIST previously treated with imatinib and sunitinib. Cancer Chemother Pharmacol 2012; 69: 977-982.

72) Heinrich MC, Griffith D, McKinley A, Patterson J, Presnell A, Ramachandran A,Debiec-Rychter M. Crenolanib inhibits the drug-resistant PDGFRA D842V mutation associated with imatinib-resistant gastrointestinal stromal tumors. Clin Cancer Res 2012; 18: 4375-4384.

73) Blay JY, Le Cesne A, Ray-Coquard I, Bui B, Duffaud F, Delbaldo C, Adenis A, Viens P, Rios M, Bompas E, Cupissol D, Guillemet C, Kerbrat P, Fayette J, Chabaud S, Berthaud P, Perol D. Prospective multicentric randomized phase III study of imatinib in patients with advanced gastrointestinal stromal tumors comparing interruption versus continuation of treatment beyond 1 year: the French Sarcoma Group. J Clin Oncol 2007; 25: 1107-1113.

74) Le Cesne A, Ray-Coquard I, Bui BN, Adenis A, Rios M, Bertucci F, Duffaud F, Chevreau C, Cupissol D, Cioffi A, Emile JF, Chabaud S, Pérol D, Blay JY, French Sarcoma Group. Discontinuation of imatinib in patients with advanced gastrointestinal stromal tumours after 3 years of treatment: an open-label multicentre randomised phase 3 trial. Lancet Oncol 2010; 11: 942-949.

75) Reichardt P, Reichardt A. Gastrointestinal stromal tumour (GIST): current standards in multimodal management. Zentralbl Chir 2011; 136: 359-363.

76) Kim MY, Park YS, Choi KD, Lee JH, Choi KS, Kim DH, Song HJ, Lee GH, Jung HY, Kim JH, Yun SC, Kim KC, Yook JH, Oh ST, Kim BS, Ryu MH, Kang YK. Predictors of recurrence after resection of small gastric gastrointestinal stromal tumors of 5cm or less. J Clin Gastroenterol 2012; 46: 130-137.