Review

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Primary gastrointestinal stromal tumors: Current advances in diagnostic biomarkers, prognostic factors and management of its duodenal location

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Summary **Gastrointestinal stromal tumors (GIST) constitute 1-3% of all gastrointestinal malignancies and is the most common mesenchymal tumor of the gastrointestinal tract. Although GIST were first described in the literature in the year 1941, important advances of kit mutation and tyrosine kinase inhibitors were not made to understand and manage GIST until the last decade. Here current advances in research of possible cellular origin, diagnostic biomarkers and prognostic factors of primary GIST are reviewed, and the management of primary duodenal GIST is focused on due to its specific location. It is possible that personalized assessment and therapy will turn out to be another milestone for primary GIST.**

Keywords: Gastrointestinal stromal tumor, diagnostic biomarker, prognostic factor, primary duodenal GIST

1. Introduction

Gastrointestinal stromal tumors (GIST) contribute about 1-3% of all gastrointestinal malignancies, and is the most common mesenchymal tumor of the gastrointestinal tract. It can also be seen in the omentum, mesentery, and retroperitoneum (*1-3*). GIST was historically classified as smooth muscle, nerve sheath or autonomic nerve tumors (*4-11*); actually GIST were first described by Golden and Stout (*12*) as a set of mesenchymal tumors arising in the bowel wall in 1941, however, until 1983 when Mazur and Clark (*13*) first introduced the term "stromal tumors" for these mesenchymal tumors, the terminology and understanding of GIST were still in chaos. The second milestone for GIST took place in 1998, when Japanese researchers Hirota and his colleagues (*14*) presented that most GIST possessed CD117 (c-kit) mutations that resulted in full-length KIT proteins with ligand-independent activation, and also discovered that most GIST were positive for CD117. The third milestone for GIST was the development of the tyrosine kinase inhibitor imatinib mesylate for advanced GIST by the end of 2000, and for primary GIST in 2009. In 2007, due to the difference in recurrence-free survival (RFS) between groups of imatinib mesylate and the control, a randomized trial (American College of Surgeons Oncology Group (ACOSOG) Z9001) was prematurely terminated and the result promoted Food and Drug Administration (FDA) approval of adjuvant imatinib for primary GIST (*15,16*) (Figure 1).

As GIST can be divided into primary GIST and metastatic or advanced GIST according to the disease stage, GIST can also be divided into esophageal, gastric, duodenal, small intestine, colon GIST *etc*. when considering the location of origin, the present work will focus on recent features for primary GIST, and special focus will be given to the management of primary duodenal GIST, which sometimes is a big challenge for the surgeon.

2. The incidence and possible cellular origin of primary GIST

2.1. *The estimated incidence of primary GIST*

Regarding that the primary definition of "malignant

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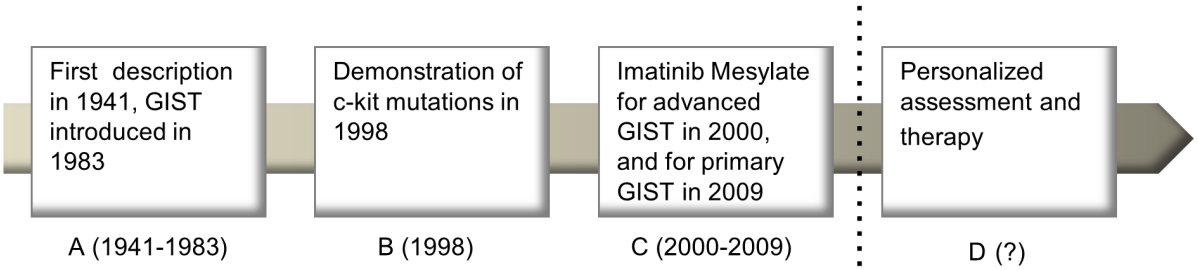

Figure 1. Serial milestones (A-C) of the research history of GIST, and the possible fourth milestone (D) of GIST research in the near future.

GIST" was adopted from criteria in 1990 until it was molecularly assessed in 1998, it was difficult to evaluate the exact epidemiologic data of primary GIST (*17*). The most dependable and exact data of incidence for primary GIST should be from population-based studies that verified all data of all cases of potential GIST (*18-21*), however, there have not been international data for the exact incidence of primary GIST.

According to published data, the estimated incidence of GIST in the United States was approximately 5,000 new cases/year (*8,22*), and that was about 15.91 per million population. The annual incidence of GIST was 13.74 per million population in Taiwan (*21*). In Finland and Sweden the annual incidence of GIST was 10~20 per million population (*1,18*). While the annual incidence of GIST in the Netherlands was 12.7 per million population (*20*) and the incidence of GIST in Iceland was 1.1 per million population (*19*). In HongKong, the annual incidence of GIST before and after the introduction of CD117 was 1.1 per million population and 2.1 per million population respectively (*23*) (Figure 2). The Turkish GIST Working Group (*24*) also reported the national data of 1,160 Turkish cases with a male to female ratio of 1.22 and a mean age of 56.75 years.

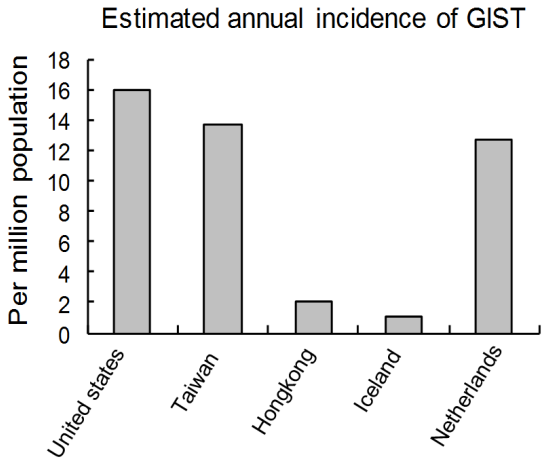

Figure 2. Estimated annual incidence of GIST in different countries and areas according to the literature (*Ref. 1,8,18-24*)**.**

2.2. *The location of primary GIST in the gastrointestinal tract*

GIST contribute 1-3% of all gastrointestinal malignancies, and they are also the most common mesenchymal tumors of the gastrointestinal tract (*1-3*). Although there is a possibility of their ubiquity, it was reported that GIST commonly originated in the stomach (40-60%), small bowel was the second most common site (30-40%), followed by duodenum (about 5%), colon, rectum or appendix (collectively 5-9.3%), and esophagus (2-3%). It was also reported that 12.6% of GIST could arise from omentum-peritoneum, however, GIST were extremely rare in other abdominal locations although they could arise anywhere besides the gastrointestinal tract from the esophagus to the anus (*24-28*).

2.3. *The possible cellular origin of primary GIST*

GIST were historically classified as smooth muscle, nerve sheath or autonomic nerve tumors (*4-11*), and since GIST are the most common mesenchymal tumors of the gastrointestinal tract (*1-3*), there is a trend to conclude that the cellular origin of GIST should be correlated to mesenchymal cells of the gastrointestinal tract. Up until now, is there any exact known origin of primary GIST?

In the year 1995, Huizinga JD *et al*. reported that GIST might be related to the interstitial cells of Cajal (ICC), because lots of gastrointestinal autonomic nerve tumors (a type of GIST before the term GIST were introduced and accepted) were positive for CD34 (*29,30*). Subsequently Kindblom *et al*. and others also proposed that most stromal tumors originate from a mesenchymal stem cell that differentiates toward an ICC phenotype (*31-33*). Actually ICC was first introduced by Cajal SR around 1889, and this type of cell was located in the stroma of the villi, in Auerbach's plexus, deep muscular plexus, circular muscular layer of the intestine, and around the acini and blood vessels of the pancreas, Dogiel subsequently called them ICC. ICC was also known as pacemaker cells and a population of cells in charge of the motility of the gastrointestinal tract (*34*).

In 1998, Kindblom *et al*. (*7*) presented that most GIST were positive for CD117(c-kit) which was first reported by Hirota and colleagues (*14*). Kindblom *et al*. also demonstrated that the ultrastructure and immunophenotype of GIST were similar to that of ICC, which provided stronger evidence for the possible

origin of GIST from ICC or stem cells differentiating to an ICC phenotype. In 2000, Wang Lina *et al*. (*35*) also demonstrated that benign GIST (CD34-negative) were composed of more mature ICC, whereas malignant GIST were composed of dedifferentiated ICC that expressed CD34-positive stem cells.

It seems that the possible cellular origin of primary GIST is ICC or mesenchymal stem cells in the gastrointestinal tract which may subsequently differentiate to a different phenotype and stage of ICC.

3. The diagnostic biomarkers of primary GIST

There is no specified clinical presentation of primary GIST even when the tumor reaches a size larger than 5 cm. When it is a small size, it is asymptomatic; and when the tumor is a large size and symptomatic, the symptoms also vary according to its location and size. The nonspecific symptoms might include abdominal pain, fatigue, dyspepsia, nausea, anorexia, weight loss, fever, obstruction, and chronic or overt GI bleeding. Metastasis can be found 10-15 years post-primary surgery to the lung, bone or liver, however, lymph node metastasis is rare (*36,37*). Sometimes it is very difficult to differentiate GIST from other tumors, such as smooth muscle tumors, schwannomas, desmoid fibromatosis, inflammatory myofibroblastic tumors, inflammatory fibroid polyps, solitary fibrous tumors, synovial sarcomas, follicular dendritic cell sarcomas, glomus tumors, and melanomas (*38*) with clinical presentation and imaging techniques, and then diagnostic biomarkers come to be of huge importance for diagnosis of primary GIST.

Although there is still no serum diagnostic biomarker of primary GIST developed there are some tissue diagnostic biomarkers. As we mentioned before that the second milestone of GIST research is the contribution of Hirota and his colleagues (*14*). They presented that most GIST possessed CD117 mutations that resulted in full-length KIT proteins with ligand-independent activation, they also discovered that most GIST (95%) were positive for the KIT antibody of CD117. This contribution is a breakthough in the diagnosis of GIST. KIT is a member of the type III transmembrane receptor tyrosine kinase family (*39*). 70-80% of GIST possess a *KIT* gene mutation, which were found at exon 11(50-77%), exon 9 (10-18%), exons 13 (1-4%) and exons 17 (1-4%) (*40-46*). All of the above are the first diagnostic biomarkers.

The second diagnostic biomarker is CD34 which is expressed in almost 80% of gastric GIST, 50% of small intestine GIST, and 95% of esophagus and rectum GIST (*47-49*).

The third diagnostic biomarker is the transmembrane protein discovered on GIST1 (DOG1). There are different types of commercial antibodies of DOG1, it is reported that DOG1.1 (Stanford University Medical Center, Stanford, California) and clone K9 DOG1 (Novocastra antibodies, Leica Microsystems, Wetzlar, Germany) were the most applied antibodies. Clone K9 DOG1 was found to be more useful for detecting both KIT-positive and KIT-negative tumors, and tumors with a spindle cell or with an epithelioid morphology. DOG1 is able to detect most CD117-positive GIST and up to 33% of CD117-negative GIST. The sensitivity of DOG1 in detecting GIST varied from 75-100% (*50-52*).

The fourth diagnostic biomarker is a mutation of the platelet-derived growth factor receptor-α (PDGFRA), about 5-7% of GIST present with mutations in the PDGFRA gene in domains similar to those found in the KIT gene. They were mutations in the PDGFRA juxtamembrane domain (encoded by exon 12), the ATP-binding domain (encoded by exon 14) or the activation loop (encoded by exon 18) (*43-45,53*).

The fifth diagnostic biomarker is a combination of the above biomarkers. It was reported that a combination of CD117 and clone K9 DOG1 antibodies can contribute to the diagnosis of 99% of GIST cases (*54*). There will be other combinations of biomarkers for diagnosis of GIST in the future.

4. The prognostic factors of primary GIST

Definitive surgery remains the first option for primary localized GIST that is resectable, and when it came to the third milestone of GIST we presented before, there were gradually adjuvant and neoadjuvant therapy with imatinib or alternative agents for resected and advanced GIST. However, there is an approximately 40-90% recurrence rate after definitive surgery (*54*). Dematteo RP *et al*. (*55*) reported that 127 patients with localized GIST demonstrated a 5-year recurrence-free survival (RFS) rate of 63% after complete resection, they also presented that a tumor size of 10 cm, a mitotic rate of 5/50HPFs, tumor location, and intraperitoneal rupture or bleeding contributed to the postoperative recurrence. Thus prognostic factors become very important for both assessing recurrence risk and the choice of adjuvant and neoadjuvant therapy.

In 2001, The National Institutes of Health (NIH) of the United States convened a GIST Workshop and proposed the NIH consensus classification system (*8*) (Table 1). The NIH classification was based on the lowest level of evidence of consensus opinion, however,

Table 1. NIH classification system for prognosis of primary GIST (2001) (*Ref. 55,56*)

Items	Tumor size in the single largest dimension (cm)	Mitotic count (per 50 HPFs[#])
Very low risk	< 2	< 5
Low	2-5	< 5
Intermediate	< 5	6-10
	5-10	< 5
High	> 5	> 5
	> 10	Any mitotic rate
	Any size	> 10

[#] HPFs: high-power fields.

Table 2. Risk stratification system proposed by Joensuu H. (2008) (*Ref. 56*)

Items	Tumor size in the single largest dimension (cm)	Mitotic count (per 50 HPFs[#])	Primary tumor site
Very low risk	< 2	≤5	Any
Low	2.1-5	≤ 5	Any
Intermediate	2.1-5	> 5	Gstric
	< 5	6-10	Any
	5.1-10	≤ 5	Gstric
High	Any	Any	Tumor rupture
	> 10	Any	Any
	Any	> 10	Any
	> 5	> 5	Any
	2.1-5	> 5	Nongastric
	5.1-10	≤ 5	Nongastric

[#] HPFs: high-power fields.

prognostic factors such as tumor size in the largest dimension and mitotic count included in the system were subsequently proved to be valuable according to the accumulated clinical data evidence. There were four risk categories in the system which were for prognosis rather than for diagnosing whether the tumor was benign or a malignant tumor (*56*).

With the accumulated clinical data evidence, especially data of adjuvant and neoadjuvant therapy with imatinib mesylate, other prognostic factors were proposed besides the NIH consensus classification system. In 2008, Joensuu H proposed a new risk stratification (Table 2) in which tumor rupture and tumor site were added for GIST. The author suggested that the new risk stratification would be useful in selecting adult patients for adjuvant systemic treatments, and identify which patients are most likely to benefit from adjuvant therapy.

Mutation status was also found to be an important prognostic factor for GIST. It was reported that patients with mutation in exon 11 of KIT had a better prognosis when compared to patients with mutation in exon 9 or KIT wild-type when they were treated with imatinib (*57*). Recently, Mazurenko NN (*58*) reported that patients with point mutations and duplication in KIT axon 11 had a better prognosis than those with other KIT mutations, and patients with a PDFGRA mutation had a better prognosis than those with KIT mutations. Watanabe T (*59*) demonstrated that the 2 year recurrence free survival rate of patients who underwent definitive surgery only was lower in patients who had both 557 and 558 codon mutations than those with either 557 or 558 codon mutations.

5. Current advances on management of primary duodenal GIST

Primary duodenal GIST constitute about 5% of GIST in the gastrointestinal tract (*25*), however, primary duodenal GIST contribute 10-30% of all malignant duodenal tumors (*60*). Since definitive surgery is the cornerstone of treatment for primary localized GIST, and lymphnode metastasis is very rare (*61*), segmental duodenal resection with end-to-end anastomosis can be performed on the tumor located in the D1, D3, and D4 segments of the duodenum. However, when the tumor locates in the D2 segment of the duodenum, which sometimes is a big challenge to the surgeon because the D2 segment of the duodenum is a specific location due to the important adjacent anatomical structures (pancreatic head, ampulla of Vater, common bile duct, *etc*.), the surgeon has to decide whether pancreatoduodenectomy or conservative surgery is to be performed for a better outcome. Some researchers argued that conservative surgery was safe and provided similar oncologic outcomes as pancreatoduodenectomy, which should be the choice in patients with GIST in the duodenum that does not involve the pancreatic side of the duodenum (*60*).

In the era of anti tyrosine kinase therapies with imatinib mesylate or other alternative drugs, surgical resection remains to be only considered to be curative, however, duodenal GIST appeared to have the greatest risk of recurrence, when compared to GIST in other locations of the gastrointestinal tract (*62*). It has been confirmed that adjuvant therapy with imatinib mesylate can improve disease-free survival (DFS) and overall survival (OS) of patients (*16,63*). Imatinib mesylate was also recommended to be the neoadjuvant therapy for unresectable tumor, which can decrease the tumor size (*64*).Then there is a new question. Since pancreatoduodenectomy is a complicated procedure with a relatively higher incidence of complications, is it possible for the patient with a large GIST in the D2 segment of the duodenum receive neoadjuvant therapy with imatinib mesylate or other alternative drugs due to imatinib mesylate resistance?

Unfortunately, there are no data of prospective randomized clinical trials focusing on neoadjuvant therapy for large GIST in the D2 segment of the duodenum. Recently in a retrospective multi-center study, Colombo C *et al*. (*65*) reported that neoadjuvant therapy with imatinib mesylate might facilitate surgical resection and increase the chance of preserving normal

biliary and pancreatic anatomy.

6. Prospects for the future

Since 1983 when the term GIST was first introduced, there have been several important advances in GIST research, among which have been discovery of kit mutations and CD117 positive results in GIST as breakthoughs. Recently DeMatteo RP (*66*) proposed a concept of personalized therapy for GIST, we agree with this concept, because there are accumulating research data in biology, such as genetic mutations, and adjuvant or neoadjuvant therapy with systemic medicines, such as tyrosine kinase inhibitors. Personalized assessment and therapy may appear to be the fourth milestone for GIST research (Figure 1). As focusing on primary duodenal GIST, prospective randomized clinical trials are needed for evaluating the outcome of neoadjuvant therapy followed by conservative surgery in patients with a large GIST in the D2 segment of the duodenum.

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