Editorial

# Therapeutic strategies for wild-type gastrointestinal stromal tumor: is it different from *KIT* or *PDGFRA*-mutated GISTs?

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Gastrointestinal stromal tumor (GIST) is the most common and potentially-malignant mesenchymal tumor in the gastrointestinal tract (1,2). GIST may arise at any age although it is frequently reported around the 60s. GISTs are found most often in the stomach, followed by the small intestine, but GISTs may occur at any sites of the gastrointestinal tract and peritoneal cavity including the colon and esophagus. The proliferation of most GISTs (80% to 90%) is driven by gain-of-function mutations either in the *KIT* or platelet-derived growth factor receptor alpha (*PDGFRA*) gene, which are mutually exclusive. Surgery is the only potentially-curative treatment for primary GIST. Nearly 40% of GIST patients, however, have had disease recurrence even after complete resection (3). Imatinib mesylate (Gleevec, Novartis Pharmaceuticals, Basel, Switzerland) has revolutionized treatment of advanced and recurrent GISTs by inhibiting the KIT and PDGFRA signaling pathways (4).

Wild-type GISTs are usually defined as GISTs which lack mutations both in the *KIT* and *PDGFRA* genes (1,2,4). Thus, wild-type GISTs may have several different driver mutations and may be consisted from heterogeneous entities, such as succinate dehydrogenase (SDH)-deficient GISTs, *BRAF*-mutated GISTs, and neurofibromatosis type I-associated GISTs (NF1-GISTs). Wild-type GISTs may comprise nearly 10% of adult GISTs and may be more commonly found in GISTs affecting children and adolescents. Wild-type GISTs are generally considered to be indolent in clinicopathological features and insensitive to imatinib. However, wild-type GISTs lack details of clinical features, outcomes of surgical and medical treatment.

Recently, Weldon *et al.* have reported surgical outcomes for wild-type GISTs based on their data obtained from the NIH Pediatric and Wild-Type GIST Clinic (5). They have shown that wild-type GISTs is an indolent disease even after relapses with the median event-free survival (EFS) of 2.5 years and that EFS after primary surgery is significantly related to the presence of metastatic disease and high mitosis (>5/50 HPF), whereas negative microscopic resection margins and type of gastric resection had no significant effects. They also suggested that repeated resection was significantly associated with decreased postoperative EFS compared with initial procedures, and indicated that subsequent resections could be performed only to address symptoms such as obstruction or bleeding. This study has the largest database collecting wild type GISTs. The report significantly contributes understanding of current outcomes of wild-type GIST patients after surgery and its prognostic factors, especially those for SDH-deficient GISTs.

The diagnosis of molecular subtypes of wild-type GISTs is often performed as shown *Figure 1* in the clinical practice and research (2,6,7). SDHB-immunostaining discriminates SDH-deficient and SDH-competent GISTs. The former may have either mutation in *SDH* subunits or promoter methylation of the SDH genes (6-8). The latter may consist from NF1-GISTs and the other GISTs with rare driver mutations, such as, mutations in the *BRAF*, *KRAS*, or *CBL* gene (7,9-13) (*Table 1*). Incidence of GISTs is estimated to

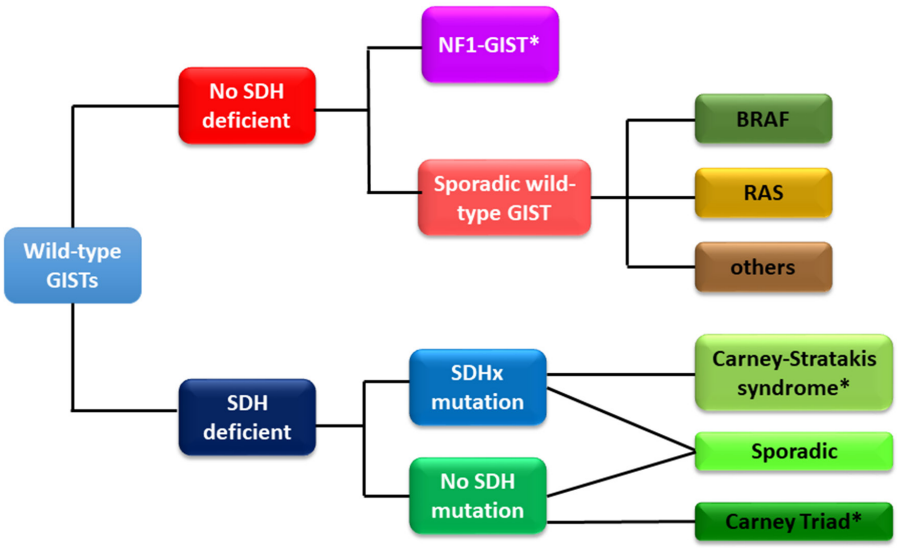


**Figure 1** Diagnostic flow of wild-type GISTs. The clinical and pathological diagnostic flow is shown. *, syndromic GISTs. GIST, gastrointestinal stromal tumor; SDH, succinate dehydrogenase; NF1-GIST, neurofibromatosis type I-associated GISTs.

be 10/million/year and GISTs without mutations in *KIT* and *PDGFRA* may account for 10–15% of total GISTs. However, the precise incidence of each rare subtype is unknown, although SDH-deficient GIST is the most frequent wild-type GIST. Each molecular subtype may have some specific features including location, clinical presentation and pathological characteristics as shown in *Table 1*, though, they are based on small retrospective studies (6-13). Wild-type GISTs consistently express KIT tyrosine kinase, however, KIT and PDGFRA tyrosine kinases are, typically, not activated because the kinases lack auto-activation mechanisms, such as gain-of-function mutations or autocrine-loop. Basic and clinical data indicate that imatinib, a KIT/PDGFRA-targeting agent, is not considered to have antitumor activities for "true" wild-type GISTs (18). Recent small cohort studies and sub-analysis of clinical trials indicate that inhibitors for vascular endothelial growth factor receptor, such as sunitinib, regorafenib, and pazopanib, may have significant activities on SDH-deficient GISTs (16-18). GISTs with typical *BRAF* mutations (V600E) were indicated to be sensitive to BRAF and/or MEK inhibitors (15). Some translational investigations indicate that the proliferation of NF1-GISTs may be potentially controlled by MEK1/2 inhibitors (14). These findings suggest that, in future, medical treatment for wild-type GISTs should be developed depending on their molecular features (18).

The study of Weldon *et al.* (5) predominantly included young adults and pediatric patients, thus, more than half of patients included in the study were SDH-deficient GISTs. From their data, SDH-deficient GISTs had relatively more events (recurrence or progression) after initial surgery than SDH-competent ones, although the statistics are marginal. Each subtype of wild-type GISTs may have individual clinicopathological-features and may show different clinical outcomes (*Table 1*), for example, NF1-GISTs may have multiple tumors and, sometimes, the NF1 patients may have second-primary GISTs, but not recurrent, after initial complete surgery (9). Hence, it may be thought that the study mainly reflected surgical outcomes and prognostic factors of SDH-deficient GISTs and it may not be always true for the other rare molecular-subtype GISTs. The other thing is extent of organ resection. Most GIST guidelines have suggested to consider preservation of organ function at surgical resection from early on, which has strongly encouraged surgeons to avoid anatomic resection and adopt partial or wedge resection when applicable (2,19-21). Accordingly, most anatomic resection, such as distal or total gastrectomy, was probably unavoidable for complete resection due to tumor extent including large tumor size, multiple occurrence, and/or nodular extension, although the authors recommended a limited surgery with wedge resection for wild-type GISTs. They compared surgical outcomes after primary and subsequent operations, and

 

**Table 1** Rare mutated-subtypes of wild-type GISTs

| Alteration | Estimated frequency | Location | Characteristic features | Medical therapy | References |
|---|---|---|---|---|---|
| *NF1* mutation (NF type I-associated) | 1–2% | Small intestine | Mostly indolent and slow growing<br>Multiple focal tumors<br>Spindle cell type<br>KIT-positive<br>Hyperplasia of ICCs | Imatinib-insensitive | (9,14) |
| *BRAF* mutation | <1% | Small intestine; stomach | Spindle cell type<br>KIT-positive<br>VE1-positive | Probably imatinib-insensitive may sensitive to BRAF and MEK inhibitors | (10,15) |
| *RAS* mutation (including KRAS) | Very rare | n.s. | n.s. | Probably imatinib-insensitive | (11) |
| *SDHA*, *SDHB*, *SDHC* or *SDHD* mutation (including Carney-Stratakis syndrome) | 7–5% | Stomach | Children or young adult<br>Relatively female predominant<br>Frequent lymph node metastasis<br>Multiple nodular tumors<br>Epithelioid cell type<br>KIT-positive<br>SDHB-negative | Probably imatinib-insensitive maybe VEGFRI sensitive | (5-8,16,17) |
| Loss of SDHB expression (including Carney Triad) | <1% | Stomach | Children or young adult<br>Female predominant<br>Frequent lymph node metastasis<br>Multiple nodular tumors<br>Epithelioid cell type<br>KIT-positive<br>SDHB-negative | Probably Imatinib-insensitive maybe VEGFRI sensitive | (5-7) |
| Others including *PIK3CA*, *CBL*, *ETV6–NTRK3*, etc. | Very rare | n.s. | n.s. | n.s. | (7,12,13) |

GIST, gastrointestinal stromal tumor; ICCs, interstitial cells of Cajal; VEGFRI, vascular endothelial growth factor receptor inhibitor; n.s., not specified.

found significant difference between them. They have not evaluated treatment with interventional radiology, such as radiofrequency ablation (RFA), cryoablation and/or transarterial embolization (TAE), which are less invasive than surgery but are still required evidence for recurrent or imatinib-resistant GISTs (1,2).

In summary, wild-type GISTs account for 10% to 15% of total GISTs and still lack evidence-based treatment strategies. The several reports including Weldon *et al.* suggest that, compared with *KIT* or *PDGFRA*-mutated GISTs, wild-type GISTs are generally indolent in clinicopathological features and show relatively good prognosis even after recurrence (5-13). Limited resection, taking account of organ-function, is recommended for primary wild-type GIST, and roles of surgery are limited for recurrent disease of wild-type GIST. Weldon *et al.* (5)

 

also indicated that watch-and-wait approach may be applicable for wild-type GISTs when biology is indolent. Wild-type GISTs are heterogeneous entity and consist of several molecular subtypes, including GISTs with mutations in *SDH* genes, those lacking expression of SDH complex without mutations, those associated with NF1, those with mutations in the *BRAF*, *KRAS* or other genes. They are considered to be insensitive to imatinib, and therapeutic agents will be developed based on their molecular features. The work of Weldon *et al.* (5) has opened the evidence-door of surgical treatment for wild-type GIST, and we still need more evidences based on clinical studies and on prospective real-world registry research because it is extremely rare.

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## Footnote

*Conflicts of Interest:* T Nishida has received honoraria for speeches from Novartis, Bayer, Eisai, and Pfizer.

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