Editorial

Understanding the critical role for surgery in the management of wild-type gastrointestinal stromal tumor (GIST)

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Recently in the *Journal of Clinical Oncology*, Weldon and coworkers from the National Institutes of Health reported a retrospective single institution experience with patient outcomes following the surgical treatment of WT gastrointestinal stromal tumor (GIST). Main outcomes examined was the association of surgery with event free survival (EFS) (1). Overall, the study reported a 1-, 5-, and 10-year EFS of 73%, 24%, and 16% respectively. Tumor biology factors such as metastatic disease [adjusted hazard ratio (AHR) =2.3; confidence interval (CI): 1.0–5.1; P=0.04) and >5 mitoses per 50 high-power fields (AHR =2.5; CI: 1.1–6.0; P=0.03) had a significantly increased hazard of disease progression or recurrence. In contrast, surgical considerations such as microscopic resection margin and type of gastric resection (wedge *vs.* anatomic) were not significantly associated with EFS.

GIST is a neoplasm derived from the interstitial cells of Cajal (2). The cells of Cajal are the pacemaker cells of the gut that produce peristaltic contractions. They are located in the myenteric plexus of the gastrointestinal tract. This explains how GIST can develop anywhere along the gastrointestinal tract, with a propensity for the stomach (50–60%), followed by small intestine (30–35%), colon and rectum (5%), and esophagus (<1%) (3). Overall, one demographic study showed GIST to be affected in 53% men, 72.2% Caucasians, 15.6% African Americans and 9.1% Hispanics (4).

GIST without mutations in KIT or platelet-derived growth factor alpha (PDGFRA) have been commonly classified as KIT/PDGFRA wild type GIST or WT GIST (5). KIT and PDGFRA are both type III tyrosine kinases and in patients who develop GIST mutations appear to be mutually exclusive as either mutation can drive GIST proliferation and lead to malignancy (6). Stem-cell factor or platelet-derived growth factor are the normal ligands for KIT and PDGFRA, respectively; and when bound, kinase domains are activated for receptor dimerization (7). In the setting of patients who develop GIST, approximately 75–80% of GIST have KIT mutations, and this typically affects the juxtamembrane domain encoded by exon 11 resulting in ligand-independent receptor activation. Mutations in the juxtamembrane domain disrupt its normal function of dimerization regulation. KIT mutations can also be observed in the extracellular domain (typically exon 9, approximately 6%) and Kinase I and II domains (exons 13 and 17, approximately 2%) (8). Tumors with KIT exon 9 mutations predominantly originate in small intestines and PDGFRA exon 9 mutations in the stomach. When not mutated, kinsase II domains aid in the activation loop for conformational regulation of the ATP binding pocket of each kinase. Among the patients without KIT mutations, one-third have mutations in PDGFRA in domains similar to those observed in KIT mutations. Any one of these mutations of KIT and PDGFRA will promote oncogenic signaling via the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathway (9).

Although WT GIST represents 10–15% of all cases (10), WT GIST are very common in young patients who develop

GIST. In up to 85% of patients, WT GIST appears to be present in patients 22 years of age or younger (11). WT GIST are known to affect a larger proportion of females as well as almost exclusively arising from the stomach (12,13). WT GIST has been noted to have a more indolent course when compared to KIT/PDGFRA mutated GIST (14,15). For patients with mutations in KIT or PDGFRA, small molecule inhibitors of the mutant KIT and PDGFRA receptor tyrosine kinases, imatinib and sunitinib, have proven to significantly prolong survival in these subset of GIST patients (16-19). For WT GIST patients, first line therapy drug therapy with imatinib is unfortunately less effective (20). As a result, surgery is a critically important facet of treating WT GIST overall (14,21).

Recently, comprehensive molecular analysis has elucidated KIT/PDGFRA WT GIST to be a more complex entity dividing into several different subtypes. 20–40% of WT GIST are characterized to be succinate dehydrogenate ubiquinone complex (SDH)-deficient GIST; more specifically, subunit B (SDHB) protein expression is lost typically due to germ-line and/or somatic loss-of-function mutations in any of the four SDH A, B, C, or D subunits. The remaining WT GIST are not SDH-deficient and are represented by a BRAF V600E mutation (22), neurofibromatosis (NF) type 1 mutation (23), or a *quadruple* WT GIST (24).

Among the patients tested, the NIH Pediatric and Wildtype GIST clinic reported 55% of participants to be SDH deficient and 35% SDH competent without another mutation. Ten percent (5 patients) were SDH competent and with other mutations (NF 1 tumor suppressor gene deficient, BRAF deficient, and CBL deficient). Furthermore, the analysis from Weldon *et al.* demonstrated that EFS was not significantly affected by tumor SDH-competent status (median SDH-deficient EFS, 4.6 years *vs.* SDH-competent, 2.8 years; P=0.10) or germline SDH-competent status (median SDH-deficient EFS, 4.6 years *vs.* SDH-competent, 2.8 years; P=0.20). Although this study represents the largest cohort of SDH deficient (germline SDH deficient, 27 patients; tumor SDH deficient, 23 patients) WT GIST patients to date, it still remains a significantly underpowered study that restricts the ability to definitively identify clinical meaningful determinations associated with the presence of SDH mutations.

For surgical management of WT GIST, Weldon *et al.* reported no association between extent of gastric resection and EFS (log-rank test, P=0.67). Furthermore, repeated resections after initial resection were identified to be significantly associated with decreasing postoperative EFS (P<0.01). Similarly, a difference in outcome of local recurrence was not seen between initial anatomic gastric resection *vs.* non-anatomic gastric resection.

In summary, the NIH Pediatric and Wildtype GIST clinic report a surgical experience with the treatment of WT GIST that demonstrated tumor biology factors to be most important in its treatment in contrast to surgical factors. Nonetheless, surgical resection remains an important component (21,25), likely the key component, in the treatment strategies for this disease. In particular, the role of debulking surgery in metastatic disease in efforts to delay time to drug resistance continues to be studied. WT GIST represents one subtype of GIST that will need specific agents and treatment strategies based on its unique biologic characteristics. More specifically, in spite of cost, KIT and PDGFRA sequencing should be recommended when WT GIST is suspected.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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