Prognostication in GIST
A New Paradigm

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GIST

- Most common mesenchymal tumor of the GI tract.
- 0.2% of all GI Tumors; 80% of GI sarcomas.
- Up to 5000 new cases/year in USA.
- Annual incidence of 7-19 cases/million.
GIST – Anatomic Location

- Stomach - 60%
- Small Bowel – 30%
- Esophagus/Colon/Rectum – 5%
- Extragastrointestinal - 1% or less
  - Omentum
  - Mesentery
KIT immunoreactivity in GISTs

Cytoplasmic Pattern

Dot-Like Pattern
KIT immunoreactivity in GISTs

Membranous Pattern
KIT and PDGFRA Mutations in 950 GISTs

Overall Mutation Frequency: 86%

KIT (78.5%)
  - Exon 9 (9%)
  - Exon 11 (67%)
  - Exon 13 (1%)
  - Exon 17 (1%)

PDGFRA (7.5% total)
  - (35% of KIT-WT)
  - Exon 12 (2%)
  - Exon 14 (rare)
  - Exon 18 (5.5%)

Heinrich M and Corless C – Personal Communication
What is KIT?

- Type III receptor tyrosine kinase
- Located on chromosome 4q
- Involved in the proliferation and maintenance of:
  - germ cells
  - hematopoietic cells (mast cells)
  - melanocytes
  - interstitial cells of Cajal
Prognosis in GIST

• GIST as a paradigm for personalized medicine.

• Areas of importance
  • To determine who should receive follow-up for patients with resectable localized disease.
  • To determine who should receive adjuvant therapy for patients with resectable localized disease.
  • To determine the type of targeted therapy for treatment of metastatic disease.
Prognostic Biomarkers in GIST
Mitotic Rate

- High mitotic rate associated with more aggressive clinical behavior in many studies.
- Mitotic rate of $\geq 5/50$ HPFs had a hazard ratio of 14.6 ($p < 0.001$) in univariate and multivariate analysis in study by DeMatteo and colleagues.

Influence of mitotic activity on behavior

Hazard Ratio 14.6
(6.5-32.4)

P<0.0001 by
Univariate and
multivariate analysis

Influence of tumor size on behavior

Hazard Ratio 2.5
(1.3-4.8)

P=0.0004 by Univariate and P=.007 by multivariate analysis

Influence of tumor location on behavior

P=0.0004 by Univariate and P=.009 by multivariate analysis

Other prognostic biomarkers

- Ki67
- S-100
- CD44
- Multiple growth factors
- BCL-2
- p53
- COX-2
- p16\textsuperscript{INK4A}
- p14\textsuperscript{ARF}
- Midkine
- Several cyclins
- Rb
- MDM2
- HIF-1 alpha
- c-MYC
- DNA ploidy
- Cytogenetic complexity
- Telomerase activity
- Microvessel density
- Lack of KIT expression
- Type of \textit{KIT} mutation

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Tumor size in greatest dimension</th>
<th>Mitotic count (per 50 HPFs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low</td>
<td>&lt;2 cm</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Low</td>
<td>2-5 cm</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&gt;5 cm</td>
<td>6-10</td>
</tr>
<tr>
<td></td>
<td>5-10 cm</td>
<td>&lt;5</td>
</tr>
<tr>
<td>High</td>
<td>&gt;5 cm</td>
<td>&gt;5</td>
</tr>
<tr>
<td></td>
<td>&gt;10 cm</td>
<td>Any mitotic rate</td>
</tr>
<tr>
<td></td>
<td>Any size</td>
<td>&gt;10</td>
</tr>
</tbody>
</table>

Risk stratification by Fletcher Criteria of 259 GIST patients

<table>
<thead>
<tr>
<th>Mitotic Index</th>
<th>Size</th>
<th>Gastric</th>
<th>Duodenum</th>
<th>Jejunum/Ileum</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 per 50 hpf</td>
<td>&lt; 2 cm</td>
<td>None (0%)</td>
<td>None (0%)</td>
<td>None (0%)</td>
<td>None (0%)</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 ≤ 5 cm</td>
<td>V-low (1.9%)</td>
<td>Low (8.3%)</td>
<td>Low (4.3%)</td>
<td>Low (8.5%)</td>
</tr>
<tr>
<td></td>
<td>&gt; 5 ≤ 10 cm</td>
<td>Low (3.6%)</td>
<td>(Insuff)</td>
<td>Moderate (24%)</td>
<td>(Insuff)</td>
</tr>
<tr>
<td></td>
<td>&gt; 10 cm</td>
<td>Mod (10%)</td>
<td>High (34%)</td>
<td>High (52%)</td>
<td>High (57%)</td>
</tr>
<tr>
<td>&gt; 5 per 50 hpf</td>
<td>&lt; 2 cm</td>
<td>None±</td>
<td>(Insuff)</td>
<td>High±</td>
<td>High (54%)</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 ≤ 5 cm</td>
<td>Mod (16%)</td>
<td>High (50%)</td>
<td>High (73%)</td>
<td>High (52%)</td>
</tr>
<tr>
<td></td>
<td>&gt; 5 ≤ 10 cm</td>
<td>High (55%)</td>
<td>(Insuff)</td>
<td>High (85%)</td>
<td>(Insuff)</td>
</tr>
<tr>
<td></td>
<td>&gt; 10 cm</td>
<td>High (86%)</td>
<td>High (86%)</td>
<td>High (90%)</td>
<td>High (71%)</td>
</tr>
</tbody>
</table>

Hpf = high power field; insuff = insufficient data; v-low = very low; mod = moderate
Data are based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal GISTs.
*Defined as metastasis or tumor-related death
+Denotes small number of cases

Adapted from Miettinen and Lasota – Semin Diagn Pathol 2006; 23:70.
Significant Differences between Fletcher-NIH and Miettinen Criteria

- NIH-Fletcher appeared to overestimate the risk of GIST $\leq 2$ cm with $\leq 5$ mitotic figures per 50 HPFs.
- NIH-Fletcher appeared to overestimate the risk of large gastric GIST.
## ? Precursor Lesions

<table>
<thead>
<tr>
<th>Study</th>
<th>Site</th>
<th>Size</th>
<th>Prevalence</th>
<th>Mut. Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agaimy and Wunsch¹ (Sporadic Cajal cell hyperplasia)</td>
<td>Esophagus (Mean 8 sections)</td>
<td>0.4-1 mm (mean 0.7 mm)</td>
<td>7 of 77 (9.1%)</td>
<td>Not done</td>
</tr>
<tr>
<td>Kawanowa et al.² (microscopic GISTs)</td>
<td>Proximal – upper stomach. (mean 130 slides)</td>
<td>0.2-0.4 mm (mean 1.5 mm)</td>
<td>50 GISTs in 35 of 100 stomachs (35%)</td>
<td>KIT mutations 2/25 (8%)</td>
</tr>
<tr>
<td>Agaimy et al.³ Gastric Sclerosing Stromal Tumors (GIST tumorlets)</td>
<td>Stomach – cardia, fundus or proximal body</td>
<td>1-10 mm (mean 4mm)</td>
<td>22.5% of autopsy stomachs</td>
<td>KIT mutations 11/24 (46%) PDGFRA mutations 1/24 (4%)</td>
</tr>
<tr>
<td>Abraham et al.⁴ “Seedling” GISTs</td>
<td>44% - gastric 50% - esophageal Mean 30 sections</td>
<td>0.2-0.3 mm (mean 1.3 mm)</td>
<td>18 GISTs in 15 of 150 esoph-gastrectomy specimens</td>
<td>Not Done</td>
</tr>
</tbody>
</table>

Incidental Gastric GIST
Incidental Gastric GIST

CD34

SMA

DES

KIT
The Future of Risk Stratification

• Nomogram – “a graphical interface for a statistical model using variables with additive prognostic importance to predict precisely a patient outcome”

GIST nomogram

Points

Size (cm)

Mitotic index

Site

Total points

Probability of 2-year RFS

Probability of 5-year RFS

GIST Nomogram

- Marginal improvement over Miettinen criteria.
- However – still some problems.
  - 88% 5-year recurrence-free survival for 7 cm gastric GIST with 4/50 HPFs
  - 18% 5-year recurrence-free survival for 7 cm gastric GIST with 5/50 HPFs

Targeting activating *KIT* mutations with small-molecule tyrosine kinase inhibitors

**Imatinib mesylate**

![Imatinib mesylate structure](image)

*Courtesy of Paul Manley, Novartis Oncology*
Imatinib Mesylate Therapy

March 3, 2000  April 5, 2000

Joensuu H et al. NEJM 2001; 344:1052
Who should be followed clinically?

- GIST $\leq 2$ cm with $\leq 5$ mits/50HPFs do not need follow-up.
- Very low to low risk categories range from 1.9%-8.5%.
- Intermediate to high-risk GIST require follow-up.
Adjuvant Imatinib prolongs recurrence free survival

Who should receive adjuvant therapy?

- No guidelines issued by FDA for who should receive therapy or for how long.
- ? High-risk GIST?
Tyrosine Kinase Inhibitors for Treatment of Metastatic GIST

- Two large phase III studies
  - progression-free survival of approximately 20 months
  - median overall survival of 50 months
Primary Imatinib Resistance

- Seen in at least 10% of GIST
- Those tumors that progress within 3-6 months of initiating therapy.
  - \( KIT\) WT
  - \( KIT\) exon 9 mutants
  - Most common \( PDGFRA\) mutant (exon 18 – D842V)

GIST: KIT and PDGFRA Mutations Predict Overall Survival in Patients Treated with Imatinib

GIST: Progression Free Survival

KIT exon 9 Mutations Treated with Imatinib

Progression-free and overall survival of patients treated with imatinib depends on genotype.
Should we treat according to KIT/PDGFRA Genotype?

- Imatinib and Sunitinib appear to have different efficacies in GIST of different genotype.
- *KIT* exon 9 mutants may respond better to imatinib 800 mg/d or sunitinib.
- *KIT* WT may respond better to sunitinib.
- Current recommendations are imatinib 400mg/d followed by imatinib 800mg/d followed by sunitinib.

Demetri GD et al. *JNCCN* 2007; 5 Suppl 2:S1
Imatinib – Delayed Resistance

- Characterized by patients who show partial response or at least stable disease and then go on to develop disease progression.
- Usually happens within 2 yrs of initiation of therapy.
- Most common mechanism is intra-allelic, second site \( KIT \) mutations in regions that encode the ATP binding domain or activation loop of KIT.
- Two of the most common mutations, V654A and T670I sensitive to imatinib.
Resistance to Imatinib Mesylate: Recognition of Clonal Evolution

Courtesy of Dr. G.D. Demetri.
Variety of secondary mutations in a single patient

Exon 9 mutant

Exon 9 / N822K
Exon 9 / D820E
Exon 9 / N822Y
Exon 9 / D820G
Exon 9 / V654A
Exon 9 / N822H

Courtesy of Dr. Jonathan Fletcher
Location and biochemical properties of secondary KIT kinase mutations in TKI-resistant GIST

Summary

- Important biomarkers for risk stratification include mitotic rate, tumor size and anatomic location.
- Provides information to determine who should have clinical follow-up and adjuvant imatinib.
- KIT/PDGFRA mutation status predicts response to imatinib/sunitinib.
- Provides theoretical basis for determining who should receive imatinib/sunitinib.
Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the intestinal tract with as many as 4,500-6000 new cases in the USA each year (1) and an annual incidence of 7-19 cases per million (2-4). GISTs may arise anywhere along the gastrointestinal tract but are most common in the stomach (60%) and small bowel (30%) (1). They also arise rarely in extragastrointestinal locations such as the omentum and mesentery (5). Approximately 85% of GIST harbor activating mutations in KIT, a receptor tyrosine kinase. Another 5-7% have activating mutations in a related receptor tyrosine kinase, platelet-derived growth factor receptor A (PDGFRA) (1, 6-7). KIT and PDGFRA mutations are mutually exclusive. Importantly, GIST is a paradigm for oncogene addiction, whereby a tumor is significantly dependent on a single oncogenic protein; KIT or PDGFRA in the case of GIST (8). Small-molecule inhibitors such as imatinib mesylate (Gleevec; Novartis Pharmaceuticals) and sunitinib malate (Sutent; Pfizer) inhibit KIT, leading to inhibition of proliferation and clinically, to partial response or stable disease (9-10). Thus, imatinib and sunitinib are targeted therapies that target an oncogenic protein (KIT).

Determining prognosis in GIST is particularly important in the context of effective targeted therapies. GIST is an important paradigm for personalized medicine. There are three major areas of potential importance in which prognosis may play an important role: 1. to determine who should receive follow-up for patients with resectable localized disease 2. to determine who should receive adjuvant therapy for patients with resectable localized disease and 3. to determine the type of targeted therapy for treatment of metastatic disease.

Risk Stratification

Numerous studies have shown that mitotic rate is by far the most important prognostic biomarker in GIST (11). Higher mitotic rate is associated with more aggressive clinical behavior. In a recent study of 127 GIST by DeMatteo and colleagues, they found that a mitotic rate ≥ 5/50 HPFs had a hazard ratio of 14.6 with a p-value of <0.001 in both univariate and multivariate analyses (12). While not nearly as strongly predictive as mitotic rate, tumor size is also an important prognostic biomarker with independent predictive value by univariate and multivariate analysis across many studies (11). Larger size predicts more aggressive biological behavior at all sites. Finally, tumor location also has independent prognostic significance (11). The most important point regarding site is that gastric GIST have a favorable prognosis as compared with GIST that occur elsewhere.
Other prognostic factors including: tumor necrosis, cellular atypia, expression of Ki67, S-100, CD44, multiple growth factors, bcl-2, p53, COX-2, p16^{INK4a}, p14^{ARF}, midkine, several cyclins, Rb, MDM2, HIF-1α, c-MYC, DNA ploidy, cytogenetic complexity, telomerase activity, microvessel density, and lack of KIT expression have all been assessed for prognostic significance in small series of GIST and some look promising. However, at this point, none have made their way into commonly used risk stratification schemes.

In April of 2001, the National Institutes of Health convened a consensus conference on GIST, which gave rise to the NIH-Fletcher criteria, which used size and mitotic rates to predict GIST behavior (Table 1)(13). Note that since GIST typically have low mitotic rates, the mitotic rate is based on 50 HPF. Subsequently, these criteria were validated in several large retrospective studies and performed well (see excellent review by Joensuu for summary)(11).

Table 1 – NIH consensus classification of Primary GIST by Mitotic Index and Size

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Tumor size in greatest dimension</th>
<th>Mitotic count (per 50 HPFs)</th>
</tr>
</thead>
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<tr>
<td>Very Low</td>
<td>&lt;2 cm</td>
<td>≤5</td>
</tr>
<tr>
<td>Low</td>
<td>2-5 cm</td>
<td>≤5</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&lt; 5 cm</td>
<td>6-10</td>
</tr>
<tr>
<td></td>
<td>5-10 cm</td>
<td>≤5</td>
</tr>
<tr>
<td>High</td>
<td>&gt;5 cm</td>
<td>&gt;5</td>
</tr>
<tr>
<td></td>
<td>&gt;10 cm</td>
<td>Any mitotic rate</td>
</tr>
<tr>
<td></td>
<td>Any size</td>
<td>&gt;10</td>
</tr>
</tbody>
</table>

More recently, Miettinen and Lasota developed criteria for risk stratification based on mitotic rate, size, and anatomic site (Table 2)(14). The criteria were developed based on long-term follow-up from 1055 gastric GIST (15), 629 GIST of the jejunum and ileum (16), 144 duodenal GIST (17), and 111 rectal GIST (18). These criteria have been adopted by the AJCC Cancer Staging Manual and College of American Pathologists Guidelines for reporting on GIST (19-20). One main difference between the NIH-Fletcher criteria and the Miettinen criteria is that the NIH-Fletcher criteria appeared to overestimate the risk of the very low risk category which essentially has no risk for aggressive behavior. In addition to the data from Miettinen’s group showing that GIST <2 cm with ≤5 mitotic figures per 50 HPFs had no metastatic potential, recent work has shown that sub-centimeter GIST are very common (21-23). In one study by Kawanowa and colleagues, they found that 35% of gastrectomy specimens contained at least one sub-centimeter GIST (23). The other main difference between the NIH-Fletcher criteria and the Miettinen criteria is that the NIH-Fletcher criteria appeared to overestimate the risk of large gastric GIST. Miettinen found that intestinal GIST >10 cm with ≤5 mitotic figures per 50 HPFs had a metastatic rate of 52% and intestinal GIST measuring 2-5 cm with mitotic figures 5 per 50 HPFs had a metastatic rate of 73%, much higher than the corresponding gastric GIST with metastatic rates of 11% and 16% (15-16).
Table 2 – Risk Stratification of Primary GIST by Mitotic Index, Size and Site

<table>
<thead>
<tr>
<th>Mitotic Index</th>
<th>Size</th>
<th>Gastric</th>
<th>Duodenum</th>
<th>Jejunum/Ileum</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 5/50 HPFs</td>
<td>≤ 2 cm</td>
<td>None (0%)</td>
<td>None (0%)</td>
<td>None (0%)</td>
<td>None (0%)</td>
</tr>
<tr>
<td>≤ 5/50 HPFs</td>
<td>&gt; 2 ≤ 5 cm</td>
<td>Very low (1.9%)</td>
<td>Low (8.3%)</td>
<td>Low (4.3%)</td>
<td>Low (8.5%)</td>
</tr>
<tr>
<td>≤ 5/50 HPFs</td>
<td>&gt; 5 ≤ 10 cm</td>
<td>Low (3.6%)</td>
<td>Insufficient data</td>
<td>Moderate (24%)</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>≤ 5/50 HPFs</td>
<td>&gt; 10 cm</td>
<td>Moderate (10%)</td>
<td>High (34%)</td>
<td>High (52%)</td>
<td>High (57%)</td>
</tr>
<tr>
<td>&gt; 5/50 HPFs</td>
<td>≤ 2 cm</td>
<td>None – small number of cases</td>
<td>Insufficient data</td>
<td>High – small number of cases</td>
<td>High (54%)</td>
</tr>
<tr>
<td>&gt; 5/50 HPFs</td>
<td>&gt; 2 ≤ 5 cm</td>
<td>Moderate (16%)</td>
<td>High (50%)</td>
<td>High (73%)</td>
<td>High (52%)</td>
</tr>
<tr>
<td>&gt; 5/50 HPFs</td>
<td>&gt; 5 ≤ 10 cm</td>
<td>High (55%)</td>
<td>Insufficient data</td>
<td>High (85%)</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>&gt; 5/50 HPFs</td>
<td>&gt; 10 cm</td>
<td>High (86%)</td>
<td>High (86%)</td>
<td>High (90%)</td>
<td>High (71%)</td>
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</table>

Adapted from Miettinen and Lasota (14). Data are based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal and 111 rectal GISTs.

* Defined as metastasis or tumor-related death.

Are there ways of improving risk criteria for GIST? There have already been several suggestions that look interesting. For instance, DeMatteo and colleagues have proposed the use of a nomogram (“a graphical interface for a statistical model using variables with additive prognostic importance to predict precisely a patient outcome”), which is based on anatomic location, tumor size, and mitotic rate (24). Risk scores associated with each prognostic biomarker are added together and the 2-year and 5-year recurrence-free survival can be read from the nomogram. In comparison with the Miettinen criteria, the nomogram performed marginally better. However, as pointed out by Joensuu, there are problems with the nomogram, which is based on the same three prognostic biomarkers as the Miettinen criteria (11). For instance, the nomogram predicts about 88% 5-year recurrence-free survival for a patient with a 7 cm gastric GIST with four mitotic figures per 50 HPFs, but only 18% recurrence-free survival for a similar case with five mitotic figures per 50 HPFs (11).

**Risk stratification to determine need for follow-up**

Assessing risk of aggressive behavior of primary GIST is useful for determining who should be followed-up clinically. Based on the Miettinen criteria, it is easy to argue that
patients with GIST at all locations that are completely resected and measure ≤2 cm with ≤5 mitotic figures per 50 HPFs, do not have to be followed. However, it is not clear cut for the very low or low risk categories with probabilities of metastasis ranging from 1.9% - 8.5%. Currently these decisions are being made by oncologists and their patients, who determine the mode and length for follow-up. Given the cost of follow-up and potential for radiation damage from repeated abdominal CT scans, this is not a trivial issue.

**Risk-stratification in the adjuvant setting**

Based on its success in treating patients in the metastatic setting, clinical trials were conducted to evaluate imatinib in the adjuvant setting. In a pivotal, large, randomized, double-blind, placebo-controlled trial, with 400mg/d of imatinib for 12 months, there was a marked improvement in 1 year recurrence-free survival compared with placebo (97% versus 83%; p <0.00001) (25). These results led to FDA approval for usage of imatinib in the adjuvant setting for GIST. Unfortunately, no guidelines were given for either which risk categories should receive adjuvant imatinib or for the duration of treatment. Most experts agree that high-risk GIST should receive adjuvant imatinib but the duration is problematic and other risk categories are less clear (26). Again, deciding who should and should not receive adjuvant imatinib is important, especially considering a cost of approximately twenty thousand dollars per year, only for imatinib, not to mention all of the ancillary costs from blood tests, doctor visits and so forth.

**Prediction of therapeutic response in the metastatic setting**

Currently, both imatinib (first line) and sunitinib (second line) are approved for use in treating metastatic GIST. Extensive analysis in phase I, II, and III trials revealed that imatinib is very useful in the treatment of metastatic GIST. Patients in two large phase III studies achieved progression-free survival of approximately 20 months and a median overall survival of 50 months in either the 400 mg/day or 800 mg/day arms of the studies (27-28). Molecular analysis revealed that response to imatinib corresponds to genotype (29-30). **Primary imatinib resistance**, which is seen in at least 10% of GIST patients, is defined as those tumors that progress within 3 to 6 months of initiating therapy. While in general, GIST with KIT exon 11 mutations (the most common mutations) respond well to imatinib, GIST that are likely to have primary resistance are those that are KIT and PDGFRA wild-type, those that have a KIT exon 9 mutation, and those that have the most common PDGFRA mutation, D842V (29). KIT exon 9 mutant GIST appear to respond to the higher dose of imatinib (800mg/day) (30). Sunitinib has been shown to be effective in stabilizing a subset of patients who were intolerant of or exhibited primary resistance to imatinib (10). A phase III, placebo-controlled trial in patients who were either intolerant or resistant to imatinib showed a median progression free survival of 24.1 weeks in the treatment arm versus 6 weeks in the placebo arm (10). Interestingly, KIT and PDGFRA sequence analysis revealed that KIT and PDGFRA wild-type and KIT exon 9 mutants were more likely to respond to sunitinib than KIT exon 11 mutants (31). In other words, imatinib and sunitinib appear to be most effective in treating GIST with different genotypes and genotype appears to predict response. This suggests that patients should be stratified by genotype in terms of whether or not they receive imatinib or sunitinib and
the dose but this remains to be examined prospectively in a carefully controlled clinical trial. Furthermore, an argument can be made to give imatinib at 800mg/day to patients with KIT exon 9 mutations (30). At the current time, imatinib is FDA approved as the first line therapy for recurrent/metastatic GIST while sunitinib is used in those patients who are intolerant of or progress on imatinib at the higher dose of 800 mg/day (26).

**Delayed imatinib resistance**, is characterized by patients who show partial response or at least stable disease and then go on to develop disease progression. This usually happens within 2 years of treatment. KIT gene sequence analysis has revealed that delayed (also known as acquired or secondary) imatinib resistance is due to secondary intra-allelic, second site KIT mutations in regions that encode the ATP binding domain (encoded by exons 13 or 14) or the activation loop of KIT (encoded by exons 17 or 18) in about 50% to 66% of cases (Fig. 1) (32-33). One of the more interesting aspects of delayed resistance is that it is characterized by actively proliferating nodules that appear to grow out as individual clones from tumors (33). Gene sequence analysis reveals that each clone appears to be unrelated as they frequently contain different secondary mutations. Luckily, two of the more common delayed resistance mutations, V654A and T670I are sensitive to sunitinib (Fig. 1 from (34)) (31). Currently, KIT and PDGFRA gene sequence of tumors from patients with delayed imatinib resistance does not play a role in determining therapy.

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**Fig. 1 – Location of secondary KIT mutations in imatinib or sunitinib resistant GIST**

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**Bibliography**