What’s new with Gastrointestinal Stromal Tumor?
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Bullet Points

- Protein kinase C θ is a new immunohistochemical marker that shows promise in the diagnosis of KIT negative GIST.
- Most sporadic GISTs harbor either KIT or PDGFRA mutations.
- Prognostication in GIST is based upon anatomic site, size, and mitotic rate.
- Targeted therapy with imatinib (first line) and sunitinib (second line) is the current standard of care in GIST treatment.

Clinical Features:

While gastrointestinal stromal tumors (GISTs) were originally thought to be very rare, it is now apparent that they are much more common than previously thought, with as many as 4,500-6,000 new cases in the USA each year. They have an equal sex predilection and although they arise over a wide age range, from pediatric to elderly patients, 75% of GISTs occur in individuals over the age of 50. Overall, the median age is 58 years. GISTs can arise anywhere along the gastrointestinal (GI) tract. Approximately 5% arise within the esophagus, 50% in the stomach, 25% in the small bowel, and 10% in the colon and rectum. Most of the colorectal lesions are found within the rectum. In approximately 10% of patients, GISTs arise outside of the tubal gut, within the mesentery, omentum, retroperitoneum, or pelvis and are known collectively as extra-gastrointestinal stromal tumors (EGISTs).

Presenting symptoms include early satiety, bloating, gastrointestinal bleeding, or fatigue related to anemia. Clinically aggressive GISTs metastasize to the liver or disseminate diffusely throughout the abdomen. GISTs rarely (<<1%) metastasize to lymph nodes or spread outside of the abdomen.

Pathologic Features:

GIST can be identified as incidental lesions at routine endoscopy or in resection specimens that are removed for other reasons (ie-gastric carcinoma). GISTs vary in size from less than 1 cm to very large lesions measuring more than 35 cm. The median size is approximately 5 cm. GISTs are usually centered on the bowel wall but may extend inward towards the mucosa, outwards towards the bowel wall, or have a dumbbell configuration with both mucosal and serosal based masses. They are usually uninodular but may present as multiple/numerous nodules. On cut section, GISTs are usually fleshy and solid but may have central cystic degeneration, hemorrhage, or necrosis.

GISTs can exhibit either epithelioid or spindle cell cytomorphology and mixed spindle cell and epithelioid GISTs are common. Spindle cell GISTs are usually arranged in fascicles while epithelioid lesions may be arranged in nests or sheets. The stroma can be hyalinized or myxoid and blood vessels can be very prominent, mimicking solitary fibrous tumor/hemangiopericytoma. Cytologically, GISTs are monomorphic, with rounded to elongated nuclei with fine chromatin and inconspicuous nucleoli, and abundant pale pink fibrillary cytoplasm. They can also exhibit prominent paranuclear vacuoles, extensive nuclear palisading, and hyaline eosinophilic cytoplasmic structures known as “skenoid” fibers. Mitotic activity is
usually very minimal (<1 mitotic figure/10 HPF). Necrosis can be seen. Pleomorphism is very rare; present in approximately 2% of all GISTs.5

**Immunohistochemical Markers:**
Approximately 95% of GISTs are positive for KIT (CD117), 60-70% are positive for CD34, 30-40% for smooth muscle actin (SMA), 5% are positive for S-100 protein, and 1-2% are positive for desmin or keratin.5 KIT positivity is usually diffuse and strong and can have a cytoplasmic, membranous, or paranuclear “dot-like” distribution. Approximately 5% of GISTs are negative for KIT.5 These are morphologically typical lesions in the proper clinical context that for some inexplicable reason, lack KIT expression.

One potential solution to the problem of KIT negative GISTs is protein kinase C theta (PKC θ), a new immunohistochemical marker for GIST.7 It has the advantage that it is immunoreactive in most cases that are negative for KIT, with PKC θ staining in approximately 77% of KIT negative GISTs.7 PKC θ is relatively specific; it is negative in most cases of other mesenchymal tumors in the differential diagnosis of GIST. PKC θ staining varies in intensity but is usually diffuse. Since its initial publication, the sensitivity and specificity for PKC θ in the differential diagnosis of GIST has been validated in additional studies.8-10

**Differential Diagnosis:**
The main differential diagnosis of conventional GIST includes true smooth muscle tumors (leiomyomas and leiomyosarcomas), schwannoma, inflammatory fibroid polyp, and desmoid fibromatosis.11 Immunohistochemical studies are extremely helpful in sorting out this differential diagnosis. True smooth muscle tumors are positive for smooth muscle actin and desmin and are negative for KIT. Schwannomas are positive for S-100 protein and are negative for KIT. Inflammatory fibroid polyps can be positive for CD34. However, they are negative for KIT and contain inflammatory cells including eosinophils. There is some controversy about whether or not desmoid fibromatosis is positive for KIT. However, based on personal experience, desmoid fibromatosis usually exhibits focal weak to negative staining for KIT. Care should be taken in the use of KIT immunohistochemistry since melanomas, germ cell tumors, angiosarcomas and some carcinomas are also positive for KIT. Fortunately, these lesions can usually be excluded on the basis of their characteristic morphologic features and immunoreactivity for other antibodies that are not positive in GIST.

**Molecular Features involved in tumor initiation:**
KIT is a receptor tyrosine kinase that is involved in the development and maintenance of germ cells, hematopoietic cells, melanocytes, and interstitial cells of Cajal.12 GISTs are believed to arise from interstitial cell of Cajal precursors through activating KIT or platelet derived growth factor receptor A (PDGFRA) gene mutations.13-15 KIT mutations are identified in 85-90% of GISTs. Studies have shown that these mutations result in ligand independent activation of KIT.13 Approximately 3-4% of GISTs have mutations within PDGFRA.15 These mutations are very similar to KIT mutations and also result in ligand independent kinase activation. KIT and PDGFRA mutations are mutually exclusive.

A small number of familial GIST families inherit GISTs with an autosomal dominant pattern of inheritance. These families harbor germline activating KIT or PDGFRA mutations identical to those seen in sporadic (non-familial) GISTs.12,16 Interestingly, all patients that harbor germline activating KIT or PDGFRA mutations develop ICC hyperplasias and GISTs. Recently,
two mouse GIST models have been developed by transgenic "knock-in" technology that harbor germline activating KIT mutations of the type seen in sporadic and familial GISTs. As is seen in humans, mice harboring the activated KIT alleles develop ICC hyperplasia and/or GISTs with 100% penetrance.

GISTs are also found in neurofibromatosis type I (NF1) patients. Up to 7% of NF1 patients harbor GISTs. However, NF1 GISTs do not contain either KIT or PDGFRA mutations, indicating that they have a different pathogenesis. GISTs are also seen in Carney’s triad, which is characterized by the presence of pulmonary chondromas, extra-adrenal paraganglioma and multifocal gastric GIST. This syndrome usually occurs in young females and is also associated with a variety of other neoplasms. GISTs that arise in Carney triad are not associated with KIT or PDGFRA mutations but the genetic lesion in Carney triad has not been identified. Finally, Carney-Stratakis syndrome is a rare and recently described tumor syndrome that is characterized by the presence of multifocal gastric GISTs and paraganglioma. Interestingly, the genetic basis of this disease has already been elucidated and is due to germline mutations in genes coding for succinate dehydrogenase subunits SDHB, SDHC, and SDHD. Of interest, mutations in these genes have also been described in inherited paraganglioma and pheochromocytoma. Mutations in SDHB, SDHC, and SDHD are not identified in Carney triad.

Molecular features involved in tumor progression.

It is taken for granted that KIT or PDGFRA mutation is the initiating event in the pathogenesis of most GISTs. However, not as much is known about the secondary events involved in malignant progression. The accumulated data from cytogenetic and comparative genomic hybridization analysis indicates that losses at chromosomes 14q and 22q are very frequent and not thought to contribute to tumor grade. However, losses at 1p, 9p/9q, 11p, 15q and gains at 5p, 8q, 17q, and 20q are reported more often in high grade/clinically aggressive GISTs. Greater numbers of genetic changes correlate with more aggressive behavior.

Loss of 9p is associated with aggressive/malignant behavior and appears to represent loss of the CDKN2A locus. The CDKN2A locus encodes two distinct tumor suppressor genes, p16(INK4A) and p14(ARF). Loss of both transcripts contributes to the aggressive phenotype.

Precursor Lesions:

Recently, attention has been focused on the identification and characterization of precursor or early GIST-like lesions. Kawanowa and colleagues examined 100 whole stomachs histologically (mean of 130 slides for each stomach !). They identified 50 microscropic GISTs in 35 cases and most were located in the upper stomach. Several stomachs contained multiple lesions. The lesions ranged from 0.2-4 mm (mean 1.5 mm) and were found in the muscularis propria or around the myenteric plexus. They were able to isolate DNA from 25 of the lesions and two of these harbored typical KIT exon 11 mutations (V559D and del 557-561). Agaimy et al. collected grossly visible, but tiny lesions from 98 consecutive autopsies. The lesions, which they termed GIST tumorlets, were detectable in 22.5% of autopsies of patients 50 years of age or older. These lesions arose primarily in the proximal stomach ranged from 1-6mm (3 mm avg) and involved the muscularis propria and myenteric plexus. The cytologic features were similar to larger GISTs. However, 49% showed central dystrophic calcifications, occasionally replacing almost the entire lesion. Genomic DNA was isolated in 24 case and KIT mutations were found in 11 cases (46%) and PDGFRA mutations were found in one case (4%). This same group performed a careful examination of 77 consecutive distal esophageal cancer resection specimens.
and identified microscopic GISTs (called ICC hyperplasias) in 9%. All mutations identified were of the type found in typical GISTs. All cases from both studies were positive for KIT and CD34 and negative for desmin, smooth muscle actin and S100.

These results are astounding and suggest that GISTs are much more common than previously believed. However, it is apparent from these findings that only a miniscule fraction of GISTs progress to become clinically important. Since they are histologically and immunophenotypically similar to clinically relevant GISTs, the precursors likely represent lesions that have undergone tumor initiation, likely through KIT or PDGFRA mutation but have not developed additional genetic factors that allow the lesions to progress. Agaimy and colleagues suggested that the calcifications were evidence of tumor regression in the absence of additional tumor progressive factors. Clearly much more work is necessary to determine the significance of such precursor lesions and their relationship to more clinically important GISTs.

**Prognostic Factors and Risk Stratification:**

The most important prognostic factors are anatomic location, size and mitotic count. However, low mitotic rate and small size does not absolutely guarantee a benign clinical course. Small GISTs with a low mitotic rate have been known to metastasize. This prompted the development of guidelines for defining risk of aggressive behavior based on size and mitotic rate. Central to these guidelines was the idea that all GISTs have potential for aggressive clinical behavior. However, since the original guidelines were issued, much work has been done to revise GIST risk stratification criteria. Recently, new guidelines were issued by the National Comprehensive Cancer Network (NCCN)(Table 1). These guidelines are essentially the same as were recommended by Lasota and Miettinen.

**Table 1 – 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>&lt; 5/50 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>≤ 5/50 hpf</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 hpf</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 hpf</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 hpf</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 hpf</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 hpf</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 hpf</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>

Adapted from Miettinen and Lasota and Demetri et al. 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.
Therapeutic Considerations:

The revelation that most GISTs harbor activating KIT mutations spawned the hypothesis that targeting KIT might be useful in treating GISTs. This was particularly important since prior to the onset of targeted therapy, GISTs did not respond to any known chemotherapy or radiation therapy. However, with the availability of imatinib mesylate (Gleevec®, Glivec®, Novartis), a small molecule inhibitor that binds to the kinase domain of KIT and PDFRA, cooperative group studies were initiated to study the efficacy in GIST. These studies have shown that GIST responds well to imatinib, although the response is dependent on the location of the KIT mutation. Primary resistance is seen predominantly in the setting of KIT and PDGFRA wild-type GISTs as well as the most common PDGFRA mutant. Exon 9 mutant GISTs are less responsive to imatinib, requiring increased dosage for efficacy. Imatinib has largely been studied as salvage therapy for recurrent/metastatic GISTs but ongoing studies are looking at the role of imatinib in the neoadjuvant and adjuvant setting.

Acquired, secondary resistance to imatinib is an emerging problem. The mechanism of resistance is primarily due to acquisition of second site mutations within KIT or PDGFRA that disrupt the interaction with imatinib. It is interesting and scary that many GISTs develop polyclonal resistance. This is characterized by the development of tumor nodules with different secondary mutations that all confer resistance to imatinib. Sunitinib malate (Sutent®, Pfizer) is another small molecule kinase inhibitor that has activity against vascular endothelial growth factor receptor in addition to KIT and PDGFRA. It was approved as second line therapy in 2006 and is currently used in the setting of imatinib treatment failure. Interestingly, sunitinib seems to elicit a better response in KIT mutants which are resistant to imatinib. Clinical trials to evaluate the relative roles of imatinib and sunitinib in the treatment of GISTs of different genotypes are needed. While it is clear that different KIT and PDGFRA genotypes respond differently to imatinib and sunitinib, currently, there is no recommendation to determine the KIT and PDGFRA mutation status at diagnosis. However, as we become more knowledgeable regarding the dependence of response on genotype, this will likely change. It is not difficult to imagine a future where treatment of GIST will be based on tumor genotype.

There is a growing literature on histologic response to imatinib. While changes such as hypercellularity, myxoid stroma, and necrosis have been described, these changes do not appear to correlate reliably with clinical response. While it makes sense to note the histologic appearance of treated GISTs in pathology reports, evaluating treatment response histologically does not play a role in the current management of GIST patients.

Molecular Correlations:

As more GISTs have been analyzed for KIT and PDGFRA mutations, several interesting molecular correlations have emerged. KIT exon 9 duplications of A-502 and Y-503 are found almost exclusively in small bowel GISTs and tend to be clinically aggressive. Furthermore, they are less sensitive to imatinib than exon 11 mutations and may be more susceptible to sunitinib. GISTs with PDGFRA mutations tend to arise in the stomach, have an epithelioid cytomorphology and may have a less aggressive clinical phenotype. KIT exon 11 mutations are heterogeneous and there are three subtypes of exon 11 mutations with prognostic significance. Deletions in the proximal portion of exon 11, especially W-577 and K-558 are associated with aggressive clinical behavior while duplications of the distal portion of exon 11 are associated with a better prognosis. Finally, while most KIT exon 11 mutations are homozygous or
hemizygous, a minority of GISTs harbor homozygous exon 11 KIT mutations and these lesions are associated with a greatly increased risk of aggressive clinical behavior.39

References


What’s new with Gastrointestinal Stromal Tumor

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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
GIST – Anatomic Location

- Stomach - 60%
- Small Bowel – 30%
- Esophagus/Colon/Rectum – 5%
- Extra-gastrointestinal - 1% or less
  - Omentum
  - Mesentery
Spindle Cell GIST
Epithelioid GIST
KIT immunoreactivity in GISTs

Cytoplasmic Pattern

Dot-Like Pattern
KIT immunoreactivity in GISTs

Membranous Pattern
Mast Cells are Positive for KIT
Immunohistochemical Profile of GISTs

- KIT (CD117) +ve (95%)
- CD34 +ve (70%)
- SMA +ve (30-40%)
- Desmin (1-2%)
- S-100 protein (1-2%)
- Keratin (1-2%)
The Interstitial Cells of Cajal

- Innervated network of cells associated with Auerbach’s plexus
- “Pacemaker” function
- Important in coordinating peristalsis
- Express KIT strongly
- GISTs arise from ICC-like cell
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
The KIT Signaling Cascade

Adhesion
Chemotaxis
Proliferation

Apoptosis
Chemotaxis
Proliferation

Proliferation/Apoptosis
KIT negative GIST

- Small percentage of GISTs are negative for KIT by immunohistochemistry
- Medeiros et al. found 25/495 (4%) GISTs KIT -ve
  - Typical of GIST clinically and histologically
  - Majority are gastric (56%) or EGIST (40%)
  - 72% had PDGFRA mutations
    - 12/18 (66%) epithelioid morphology
    - 5/18 (28%) mixed morphology
    - 1/18 (6%) spindle cell morphology
    - 10/18 (56%) gastric
    - 7/18 (39%) EGIST
    - 1/18 (6%) small bowel
- Most KIT negative GISTs are epithelioid gastric or extragastrointestinal GISTs with PDGFRA mutations.

**PDGFRA mutation positive GIST**

- PDGFRA is a type III RTK
- *KIT* and *PDGFRA* mutations are mutually exclusive
- Approximately 7% of all GISTs
- Predilection for gastric and extra-gastrointestinal location
- **Epithelioid cytomorphology**
- Myxoid stroma
- Multinucleated cells
- Rhabdoid cells

Heinrich et al. *Science* 2003;299;708
Lasota et al. *Lab Invest* 2004;84:874
Corless et al. *J Clin Oncol*, 2005;23;5357
Daum et al. *Ann Diagn Pathol*, 2007;11;27
PDGFRA GIST

Binucleate-Multinucleate Cells
PDGFRA GIST

Myxoid Stroma

Paranuclear Vacuoles
KIT faintly positive to negative
**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)**
- Exon 12 (2%)
- Exon 14 (rare)
- Exon 18 (5.5%)

Heinrich M and Corless C – Personal Communication
**KIT and PDGFRA Mutations: Significance**

- *KIT* deletion W557 and K558 associated with worse prognosis
- *KIT* deletions may have worse prognosis than point mutations
- *KIT* 3’ duplications may have better prognosis
- *KIT* exon 9 mutations arise predominantly in small intestine and colon and appear to be more aggressive.

Wardelman et al. *Virchows Arch* 2007; 451:743
KIT and PDGFRA Mutations: Significance

- PDGFRA mutations preferentially occur in gastric and extra-gastrointestinal sites and may be less aggressive – KIT negative by IHC.
- Homozygous/hemizygous KIT mutations more aggressive.
- Mutation type may predict response to TKIs.
- Prognostication based on mutation status not recommended at this point.

Wardelman et al. Virchows Arch 2007; 451:743
Protein Kinase C theta

• Identified by gene expression arrays
• Duensing et al.
  • PKCθ expression in 13/18 (72%) KIT –ve GISTs by IHC
    • 11/13 PDGFRA mutation positive GIST
    • 2/20 leiomyosarcomas
• Commercially available!

Duensing et al. Cancer Res 2004; 64:5127
Motegi et al. Pathology Int. 2005;55:106
Kim et al. Modern Path2006;19:1480
DOG1

- Identified by gene expression arrays
- Sensitive and selective for GIST
- Especially useful for *PDGFRA* mutation positive GIST
- Not commercially available

### DOG1

<table>
<thead>
<tr>
<th>Mutation Status</th>
<th>DOG1</th>
<th>KIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>33/37 (89%)</td>
<td>29/35 (83%)</td>
</tr>
<tr>
<td>KIT</td>
<td>200/218 (92%)</td>
<td>180/221 (81%)</td>
</tr>
<tr>
<td>PDGFRA</td>
<td>23/29 (79%)</td>
<td>3/32 (9%)</td>
</tr>
</tbody>
</table>

935 soft tissue tumors evaluated
1/326 (0.3%) leiomyosarcomas +ve
1/39 (2.5%) synovial sarcomas positive

DOG 1

KI

Courtesy of Dr. Matt van de Rijn
Familial GISTs

- Several families have been identified with affected family members inheriting GISTs with an autosomal pattern of inheritance (KIT and PDGFRA on 4q).

- Affected family members have germline mutations in KIT or PDGFRA that are the same as found in sporadic GISTs.

Other GIST syndromes

• **Neurofibromatosis 1**
  • Loss of function mutations in \( NF1 \) gene (neurofibromin)
  • 7% of NF1 patients have GIST
  • No \( KIT \) or \( PDGFRA \) mutations

• **Carney Triad**
  • Pulmonary chondromas, extra-adrenal paraganglioma and epithelioid gastric GIST
  • Mostly in girls
  • Genetic basis is unknown – No \( KIT \) or \( PDGFRA \) mutations

• **Carney-Stratakis syndrome**
  • Multifocal gastric GISTs and paraganglioma
  • Characterized by mutations in succinate dehydrogenase subunits \( SDHB, SDHC, SDHD \).
  • Same mutations described in paraganglioma and pheochromocytoma
### ? 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 (10%)</td>
<td>Not Done</td>
</tr>
</tbody>
</table>

Incidental Gastric GIST
Incidental Gastric GIST

CD34

SMA

DES

KIT
Incidental Duodenal GIST
Cancer is a multi-step (collaborative) process

Hanahan D & Weinberg RA Cell 100:57-70, 2000
What do we know about tumor progression in human GISTs?

- Evidence from cytogenetics and CGH.
  - Loss of 14q, 22q, 1p, 9p/9q, 11p, 15q
  - Gains of 5p, 8q, 17q, 20q

Wozniak et al. Genes, Chromosomes, Cancer 2007;46:261
Loss of 9p21

- 9p21 harbors the \textit{INK4a/ARF/INK4b} locus also known as \textit{CDKN2a} and \textit{CDKN2b}

- Deleted in a wide spectrum of neoplasms including melanoma, pancreatic adenocarcinoma, GBM, NSCLC, TCC of the bladder

Courtesy of M. Debiec-Rychter
Dedifferentiated GIST

• Abrupt transition from morphologically typical KIT positive GIST to anaplastic KIT negative GIST
• 3M:1F; 23-55 yrs; all were gastric tumors
• One patient with prior exposure to imatinib
• 3 tumors presented with metastasis
• Three tumors were KIT and PDGFRA wild-type
• One tumor had KIT exon 11 deletion in both components
• FISH showed KIT gene copy abnormalities in dedifferentiated areas in three cases
• TP53 mutation in ¼ cases in both components

Antonescu et al. Mod Pathol 2007;11A
Dedifferentiated GIST
Significance of activating *KIT* mutations

Imatinib mesylate

Courtesy of Paul Manley, Novartis Oncology
Imatinib Mesylate Therapy

A

March 3, 2000

B

April 5, 2000

NEJM, 344: 2001
GIST: KIT and PDGFRA Mutations Predict Overall Survival

GIST: Progression Free Survival
*KIT* exon 9 mutations

GIST: Progression Free Survival

*KIT* exon 11 mutations

Imatinib – Primary Resistance

- Patients who never show a true tumor response (or even prolonged stable disease) during the first 6 months of imatinib treatment.
  - *KIT* WT
  - *KIT* exon 9 mutants
  - Most common *PDGFRα* mutant (exon 18 – D842V)

Show phosphorylation of KIT and downstream pathways, both before and during therapy.
Imatinib – Secondary Resistance

• Patients who show a partial remission (or no significant tumor growth for 6 months) and then experience progression.

• Phosphorylation present in pre-treatment specimens but become nearly undetectable during the first several days of therapy. Followed by re-activation of KIT and downstream effectors.
Resistance to Imatinib Mesylate: Recognition of Clonal Evolution

Courtesy of Dr. G.D. Demetri.
V654A, D816H in separate lesions (Patient 15 this report)
D820E, N822K, N822Y in separate lesions (Patient 5 this report)
V654A, N822K in separate lesions (Antonescu et al.)
D816E, D820V, D820E and N822K in separate lesions (Wardleman et al.)
V654A, T670E, Y823D (Wardleman et al.)
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

Heinrich et al. JCO Sept 2006
• Of >150 TKs & STKs profiled—Sunitinib was > 30X selective for class III & V RTKs vs all kinases evaluated & > 100X selective vs. 93% of kinases
• >30X selectivity sufficient in tumor cells & PD models in vivo
• Sunitinib exhibits relevant kinase activity vs. class III & V RTKs & RET
Sunitinib Biologic Activity Demonstrated Utilizing Functional Imaging Modalities

FDG-PET Response in a GIST Patient

- PET Imaging has demonstrated utility in RTK studies, including imatinib FDG-PET (glucose metabolism) & FLT-PET (cell proliferation) demonstrated evidence of sunitinib biologic activity in multiple patient populations
- Potential to demonstrate (predict?) response to therapy prior to CT
GIST – Sunitinib’s Efficacy & Safety Confirmed in Registration Trial

Multicenter Trial Conducted in 56 Sites Worldwide, Imatinib Refractory Patients Randomized to Sunitinib or Placebo (with crossover at PD)

Significant improvements in TTP (> 4-fold) & OS (not reached) observed in patients initially treated with sunitinib versus control. After 1st Interim Analysis—all Patients moved to sunitinib arm—survival benefit likely underestimated
Sunitinib Phase I/II Study
Time to Progression by Original Mutation Status

Treatment Related Changes

• Evaluated in the neoadjuvant setting

• Hypocellularity

• Myxoid Stroma

• Fibrosis

• Necrosis

• Nests/islands of tumors cells virtually always present

• Best to report as percentage of viable tumor
Treatment Related Changes
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>&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>&gt; 2 cm</td>
<td>V-low (1.9%)</td>
<td>Low (8.3%)</td>
<td>Low (4.3%)</td>
<td>Low (8.5%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 5 cm</td>
<td>Low (3.6%)</td>
<td>(Insuff)</td>
<td>Moderate (24%)</td>
<td>(Insuff)</td>
<td></td>
</tr>
<tr>
<td>&gt; 10 cm</td>
<td>Mod (10%)</td>
<td>High (34%)</td>
<td>High (52%)</td>
<td>High (57%)</td>
<td></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>&gt; 2 cm</td>
<td>Mod (16%)</td>
<td>High (50%)</td>
<td>High (73%)</td>
<td>High (52%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 5 cm</td>
<td>High (55%)</td>
<td>(Insuff)</td>
<td>High (85%)</td>
<td>(Insuff)</td>
<td></td>
</tr>
<tr>
<td>&gt; 10 cm</td>
<td>High (86%)</td>
<td>High (86%)</td>
<td>High (90%)</td>
<td>High (71%)</td>
<td></td>
</tr>
</tbody>
</table>

Hpf = high power field; insuff = insufficient data; v-low = very low; mod = moderate
Adapted from Miettinen and Lasota – Semin Diagn Pathol 2006; 23:70.
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
Reporting in GIST

- Size (cm)
- Mitotic Activity (mf/50 hpf)
- Anatomic Location (stomach, duodenum, etc.)
- Risk assessment classification or percentage
- Epithelioid, spindle cell or mixed
- Margins (involved or uninvolved)
- Lymph node status (if sampled)
- Treatment related changes (percentage)