Gastrointestinal Stromal Tumors

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GISTs

• 6,500 new cases in the US
• Most common sarcoma of the GI tract
• Micro-GISTs may be present in 10-25%
• Familial GISTs rare (Carney-Stratakis syndrome)

• Interstitial cell of Cajal (ICC) origin within the muscularis layer
• Gain of function mutation in oncogenic tyrosine kinase along with ETV1 transcription factor activation
  ✓ KIT (75%) or PDGFRa (10%)
  ✓ ‘Wild-type’ GISTs mutations: SDH, BRAF, NF1
GISTs
Clinical Presentation

Median patient age 60 yrs
Slight male predominance

Most common sites:
  - Stomach 60%
  - Small intestine 30% (jejenum, ileum, duodenum)
  - Rectum 5%
  - Esophagus < 5%
  - Colon <1%

- Average tumor size 5 cm (range 0.5 – 30 cm)
- Incidental finding on imaging, endoscopy, or exploration
- Symptoms arise from space occupation or organ displacement
- Bleeding from mucosal erosion (25%)
- Tumor rupture leading to peritoneal dissemination
- Liver metastasis at presentation (< 10%)
GISTs: Work-up

**Contrast-enhanced CT**

- **Enhancing tumors**
  - Heterogeneous from tumor necrosis or haemorrhage
  - Adjacent organ abutment (liver, spleen, pancreas)

- **Exophytic**
- **Endophytic**
- **Mixed/Dumbbell**

**MRI**
- Duodenal or Rectal primary sites

**PET-CT**
- Monitor response to TKIs, multifocal metastases
GISTs: Diagnosis

EUS-guided FNA for cytology
- 90% sensitive
- Mitotic index not available
- c-kit mutation analysis if planning neoadjuvant therapy

Spindle cell neoplasm
Immunohistochemistry
- KIT+ 95% GISTs
- DOG1+ in KIT- GISTS 95%

Avoid percutaneous biopsy

CD117 staining for KIT+ GIST
### Tumor Parameters

<table>
<thead>
<tr>
<th>Mitotic Index</th>
<th>Size</th>
<th>Stomach</th>
<th>Duod</th>
<th>Jejunum or Ileum</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 5 per 50 hpf</td>
<td>&lt; 2cm</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>&gt; 2 ≤ 5cm</td>
<td>very low (1.9%)</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td>&gt; 5 ≤ 10cm</td>
<td>low (3.6%)</td>
<td>insuff data</td>
<td>moderate (24%)</td>
<td>insuff data</td>
<td></td>
</tr>
<tr>
<td>&gt; 10cm</td>
<td>moderate (10%)</td>
<td>high (34%)</td>
<td>high (52%)</td>
<td>high (57%)</td>
<td></td>
</tr>
</tbody>
</table>

| > 5 per 50 hpf | < 2cm    | none    | insuff data | high | high (54%) |
| > 2 ≤ 5cm   | moderate (16%) | high (50%) | high (73%) | high (52%) |
| > 5 ≤ 10cm  | high (55%) | insuff data | high (85%) | insuff data |
| > 10cm      | high (86%) | high (86%) | high (90%) | high (71%) |

Data based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal GISTs.

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### Poor Prognostic Variables

- Size > 5 cm
- MI > 5/50 hpf
- Non-gastric site
- Metastases
- Tumor rupture

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KIT Genotype Predicts Progression-free Survival

Emile et al. *Gastroenterology*, 2006; 131:976-86
### Relationship between GIST site and KIT genotype

<table>
<thead>
<tr>
<th>Site</th>
<th>Total</th>
<th>WT</th>
<th>KIT Exon 9</th>
<th>KIT Exon 11</th>
<th>KIT Exon 17</th>
<th>PDGFRA Exon 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>74</td>
<td>17 (23%)</td>
<td>-</td>
<td>49 (66%)</td>
<td>-</td>
<td>8 (11%)</td>
</tr>
<tr>
<td>Small bowel</td>
<td>35</td>
<td>7 (20%)</td>
<td>3 (9%)</td>
<td>24 (69%)</td>
<td>1 (3%)</td>
<td>-</td>
</tr>
<tr>
<td>Colon/rectum</td>
<td>14</td>
<td>4 (29%)</td>
<td>1 (7%)</td>
<td>9 (64%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>1 (25%)</td>
<td>-</td>
<td>3 (75%)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### Relationship between site and KIT exon 11 mutations

<table>
<thead>
<tr>
<th>Site</th>
<th>Total</th>
<th>No KIT Exon 11 Mutation</th>
<th>Del557or8</th>
<th>Other Deletion</th>
<th>Insertion</th>
<th>Point Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>74</td>
<td>25 (34%)</td>
<td>18 (24%)</td>
<td>5 (7%)</td>
<td>9 (12%)</td>
<td>17 (23%)</td>
</tr>
<tr>
<td>Small bowel</td>
<td>35</td>
<td>11 (31%)</td>
<td>8 (23%)</td>
<td>11 (31%)</td>
<td>1 (3%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Colon/rectum</td>
<td>14</td>
<td>5 (36%)</td>
<td>8 (57%)</td>
<td>1 (6%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>1 (25%)</td>
<td>1 (25%)</td>
<td>1 (25%)</td>
<td>1 (25%)</td>
<td>1 (25%)</td>
</tr>
</tbody>
</table>
KIT Genotype Predicts Imatinib Response

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Percentage of cases</th>
<th>Imatinib response</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIT exon 11 mutation</td>
<td>70%</td>
<td>85%</td>
</tr>
<tr>
<td>KIT exon 9 mutation</td>
<td>15%</td>
<td>45%</td>
</tr>
<tr>
<td>KIT exon 13 mutation</td>
<td>&lt;5%</td>
<td>Some (few cases)</td>
</tr>
<tr>
<td>KIT exon 17 mutation</td>
<td>&lt;5%</td>
<td>Some (few cases)</td>
</tr>
<tr>
<td>PDGFRA D842V mutation</td>
<td>4%</td>
<td>None</td>
</tr>
<tr>
<td>PDGFRA other mutations</td>
<td>1%</td>
<td>Some (few cases)</td>
</tr>
<tr>
<td>No KIT or PDGFRA mutation</td>
<td>5%-10%</td>
<td>Little</td>
</tr>
</tbody>
</table>

Diagram: Extracellular domain, Transmembrane domain, Juxtamembrane domain, Kinase domain, TK1 Domain exons 13, 14, TK2 Domain exon 17.
A 62 year-old patient presents with upper abdominal pain, dyspnea with recumbency, and early satiety. A complete blood count reveals microcytic anemia. A small 2 mm ulcer is found along the greater curvature of the stomach during upper endoscopy. Biopsies of the ulcer margin show benign gastric mucosa. A CT scan of the abdomen reveals a solitary 12 cm tumor in the LUQ.

Biopsy?
Management of Primary GISTs

Site-specific considerations
- Peri-ampullary duodenum
- GE junction
- Low rectum

Primary GIST
Easily resectable?

No
- Neoadjuvant imatinib
- Surveillance

Yes
- Surgical resection
- *Adjuvant imatinib

3-6 mos
Duodenal GISTs

Neoadjuvant imatinib for tumor downsizing

D2 duodenum: may permit duodenal excision without need for PD

D3/4 duodenum: adjacent organ involvement (colon, pancreas, mesentery)

Technical considerations:

D2 duodenum:
- Tumor excision w duodenorrhaphy (or RenY drainage)
- Pancreatioduodenectomy

D3/4 duodenum:
- Segmental resection w primary anastomosis
- Tumor excision (1 cm margin) w duodenorrhaphy
Rectal GISTs

Neoadjuvant imatinib for tumor downsizing

Sphincter-preservation
• Transabdominal excision
• Transanal excision
• Transacral excision

6 mos imatinib
NEoadjuvant imatinib for tumor downsizing for endophytic tumors, occasionally exophytic tumors

- Rarely involves esophagus
- Lumen narrowing concerns with posterior tumors
- Avoids esophagogastrectomy
- Adjacent organ involvement for exophytic tumors (pancreas, spleen, colon)
Open technique for excision of GE Junction GIST
Nomogram for predicting 2- and 5-yr survival after resection of primary GISTs

https://www.mskcc.org/nomograms/gastrointestinal/stromal-tumor
Survival after resection of patients with primary GIST > 3 cm randomized to 1 year of adjuvant imatinib v. placebo

Metastatic GISTs

Synchronous or Metachronous
Liver, peritoneum, lung, bone, CNS

- Complete staging w CT, repeat imaging 6 weeks after start date
- KIT mutation analysis prior to targeted therapy with TKI
- Median time to imatinib resistance for exon 11 kit mutation: ~24 mos
Management of Recurrent or Metastatic GISTs

- **Recurrent or Metastatic GIST**
  - **Imatinib**
    - Partial response, stable disease, or focal resistance
      - Surgery
      - Ablation
      - Hepatic artery embolization
      - Chronic imatinib
    - Progression
      - Sunitinib
      - Regorafenib
      - Other TKIs
      - Clinical trials
Gastrointestinal Stromal Tumors

- Most common sites are the stomach and small intestine with activating mutations of KIT or PDGFRa
- Disease varies from indolent micro-GISTs to high-risk tumors with synchronous metastases
- Oncologic surgery involves grossly clear margins, no touch techniques to avoid tumor rupture
- Consider neoadjuvant imatinib for non-metastatic GISTs involving the duodenum, rectum, and GEJ
- Consider neoadjuvant imatinib for locally advanced tumors with adjacent organ invasion in order to decrease operative bleeding and magnitude of resection
- Adjuvant imatinib (3 yrs) and monitoring for high-risk GISTs

48th Annual Postgraduate Course in General Surgery
26 April 2019, Charleston, SC
SDH Mutations in Patients With Wild-Type GIST

- Patients with GIST and wild-type KIT and/or wild-type PDGFR can have germline mutations in succinate dehydrogenase
  - SDH–ubiquinone complex II catalyses oxidation of succinate to fumarate in the Krebs cycle (ie, part of the respiratory chain)
  - SDH mutations result in loss of SDH expression (Carney-Stratakis syndrome) and can lead to GIST and increased risk of paraganglioma
  - Pathogenic SDH mutations and lack of complex II activity may be a central oncogenic mechanism in wild-type GIST
