Gastrointestinal Stromal Tumor (1 of 5)

1. Patient presents w/ signs & symptoms suggestive of or an incidental endoscopic finding of a gastrointestinal mass
   - REFER TO SPECIALIST

2. EVALUATION
   Do the history, PE, laboratory tests reveal a potentially resectable tumor?
   - Yes
     - A. Surgery
       - If pre-op reduction of tumor size is beneficial, consider neoadjuvant therapy w/ Imatinib
     - DETERMINE PATHOLOGY RESULT
       - Gastrointestinal Stromal Tumor (GIST)
       - Other Sarcoma
   - No
     - B. Tissue biopsy
       - Is Gastrointestinal stromal tumor confirmed?
         - Yes
           - DETERMINE BASELINE CT &/OR MRI
             - C. Chemotherapy
               - Imatinib
             - D. Follow-up
         - No
           - REFER TO SPECIALIST

POST-OP MANAGEMENT
See next page

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Specific prescribing information may be found in the latest MIMS.
**Gastrointestinal Stromal Tumor (2 of 5)**

**POST-OP MANAGEMENT OF PATIENTS W/ CONFIRMED GIST**

Complete resection w/ pre-op Imatinib

- MAY CONTINUE IMATINIB IF PRE-OP THERAPY SHOWED GOOD RESPONSE
- Follow-up

Complete resection w/o pre-op Imatinib or incomplete Resection

- C Adjuvant chemotherapy
  - Imatinib
- Follow-up

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**1 CLINICAL PRESENTATION**

- Most common mesenchymal tumor originating from the gastrointestinal tract
- Usually occurs in the stomach (60%) or the small intestines (30%)

**Signs & Symptoms of GI tumor**

- Abdominal mass
  - May be an incidental finding on endoscopy
- GI bleeding
- Hemoperitoneum
- Anemia
- GI perforation

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**2 EVALUATION**

**Diagnostic Workup**

- Abdominal/pelvic CT w/ contrast
  - Allows assessment of primary tumor & extent of metastasis; investigation of choice for staging & follow-up
  - For incidentally found mass on endoscopy, CT may be performed if endoscopic ultrasound is not available
  - Initial imaging done for large palpable masses or for patients presenting w/ hemorrhage, abdominal pain or obstruction
  - GIST usually shows an extraluminal mass arising from the digestive tract wall
- MRI
  - Gives better preoperative staging data regarding rectal GISTs
  - May provide tumor localization & relationship w/ adjacent organs
- Positron emission tomography (PET)
  - Provides early neoplastic information
  - Detects metabolic changes within the tumor earlier than the visible changes
  - May be used as part of the pre-operative assessment
  - May also be used to assess responsiveness of the tumor to Imatinib
- Chest x-ray
- Endoscopic ultrasound (EUS)
  - Should be performed first if submucosal mass is an incidental endoscopic finding
  - Important in diagnosis of small masses (<2 cm)
  - Most useful in assessment of masses located in the esophagus, stomach, duodenum & anorectum
  - Potential high-risk features include cystic spaces, echogenic foci, heterogeneity, irregular border, & ulceration
- Endoscopy (if not yet done)
- Mutational analysis
  - Performed when diagnosis is uncertain for mutations involving KIT & PDGFRA genes
    - Testing for these genes is strongly recommended
  - Genotyping must be performed when medical treatment is planned
    - Helps in identifying genotypes that will benefit from Imatinib therapy & the appropriate dose for treatment of KIT exon 9 mutations
    - If KIT or PDGFRA mutations are lacking, consider testing for germline mutations in the succinate dehydrogenase (SDH) genes

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### EVALUATION (CONT’D)

#### Diagnostic Approaches

- For a <2-cm esophagogastric or duodenal nodule, laparoscopic/laparotomic excision is considered for histological diagnosis as endoscopic biopsy may be difficult.
- Rectal or recto-vaginal space nodules are biopsied/excised regardless of tumor size as risk is high for a GIST at this location.
- Laparoscopic/laparotomic excision may be performed for abdominal nodules not amenable to endoscopic assessment.
- Multiple core needle biopsies via EUS guidance for a mass that is likely to have a multi-organ resection.
- For obvious metastases, diagnostic biopsy of the metastases is sufficient & may not need laparotomy.

#### Differential Diagnoses

- Though it is the most common GI mesenchymal tumor, GIST should be differentiated from non-epithelial neoplasms, leiomyoma, leiomyosarcoma, schwannomas & other malignancies of the GI tract.

### SURGERY

- Complete surgical excision is the standard treatment of localized or potentially resectable GIST.
  - Initial management of small GISTs <2 cm w/ high-risk EUS features.
  - Recommended for tumors ≥2 cm, & w/ signs of malignancy & increasing size.
- Wide local resection w/ 1- to 2-cm margin is done for most tumors.
- May consider using laparoscopic approach in tumors located in the anterior wall of the stomach, jejunum & ileum, or the greater curvature.
- Tumors located in the colon may require hemicolectomy while tumors located in the rectum & anus will require abdominoperineal resection of the anus & rectum.
- Surgery may be warranted in unresectable or metastatic GIST if there is limited disease progression unresponsive to Imatinib or a locally advanced previously unresectable tumor which had a good response to Imatinib preoperatively.

#### Preoperative Assessment

- CT scan of the chest & abdomen should be done on all patients.
  - Angiography performed if necessary (ie major vessels occluded by the tumor).
- If large tumors are considered on the right or left upper quadrant of the abdomen, endocrine clearance should be done to exclude adrenal tumors.
- Alpha-fetoprotein & beta-hCG levels should be determined in male patients w/ centrally placed tumors to exclude teratomas.

### BIOPSY

- Morphologic diagnosis from histologic microscopic examination is the standard for diagnosis.
  - Diagnosis of primary GIST is confirmed w/ a biopsy before starting preoperative therapy.
- GISTs are soft and fragile & may cause hemorrhage & increased dissemination.
  - Pseudocapsule should be preserved & tumor spillage avoided.
- EUS-FNA biopsy is preferred over percutaneous biopsy & may be done in GISTs <2 cm.
- Metastatic disease may be confirmed via percutaneous image-guided biopsy.

#### Histopathology summary should include the following:

- **Diagnosis**
  - Tumor type (ie spindle, epithelioid or mixed), mitotic rate.
  - Presence or absence of necrosis, hemorrhage & lymphovascular invasion.
  - Invaded structures.
- **Immunohistochemistry result, KIT expression status**.
- **Margin evaluation**.
- **Prognostic category; prognostic factors include:**
  - Mitotic rate.
  - Tumor size & site.
  - Gastric GISTs <2 cm are usually benign but colonic GISTs <2 cm w/ mitotic activity can recur & metastasize.
  - Small bowel or colonic GISTs have an aggressive behavior compared w/ gastric GISTs.
  - Surgical margin.
  - Tumor rupture (has a highly adverse prognosis).
- **Recommendation on a multidisciplinary team meeting**.
Gastrointestinal Stromal Tumor (4 of 5)

Prior to Therapy

- Assess present disease state for treatment monitoring purpose
- Inform & discuss w/ patient that the tumor cannot be cured, the duration of treatment required by the condition including the course of possible disease progression
- Determine cardiac status
  - Physical activity should not be severely limited
  - No myocardial infarction within the last 2 mth
- Laboratory tests (ie liver function tests, CBC, etc)

Imatinib

- Recommended treatment for GIST that is unresectable &/or metastatic
  - Adjuvant therapy for patients w/ high risk of relapse & for ruptured tumor during surgery
- Increases survival rate in patients w/ metastatic &/or unresectable GIST
- When Imatinib is used pre-op, PET scan should be used to assess response

Discontinuation of Treatment

- Stop Imatinib if intolerable side effects occur & restart once toxicity resolves
- For less severe toxicity, consider decreasing the dose

Sunitinib

- A 2nd-line agent that may be used if intolerance to Imatinib develops, if tumor is Imatinib resistant, or disease progression occurs
- Demonstrated efficacy in terms of progression-free survival on a “4 wk on-2 wk off” regimen

Regorafenib

- A 3rd-line agent for patients unresponsive to both Imatinib & Sunitinib
- Shown to prolong progression-free survival in a prospective placebo-controlled randomized trial

Therapeutic Options

- Eg Dasatinib, Sorafenib, Nilotinib, Pazopanib
- Several studies have shown that these agents possess therapeutic effects for patients w/ GIST resistant to Imatinib & Sunitinib
- Dasatinib may be considered in patients w/ Imatinib-resistant GIST w/ PDGFRA D842V mutation

FOLLOW-UP

- Relapses affect the liver & peritoneum & rarely the bone
  - Risk of relapse is high w/ ruptured tumors
- Evaluate tumor response by checking for tumor shrinkage, tumor density changes on CT scan, & absence of tumor progression
- For GISTs <2 cm w/o high-risk EUS features, consider endoscopic surveillance every 6-12 mth

Post-surgery

Completely Resected Tumors w/ or w/o Pre-op Imatinib

- Clinical evaluation every 3-6 mth x 5 yr, then annually
  - May be less frequent for small tumors (<2 cm)
- Abdominal/Pelvic CT every 3-6 mth x 3-5 yr, then annually

Metastatic Disease or Persistent Gross Residual Disease w/ or w/o Pre-op Imatinib

- Clinical evaluation & abdominal/pelvic CT every 3-6 mth
  - May be less frequent for small tumors (<2 cm)

Management of Disease Progression

Limited Disease Progression

- Continue or increase Imatinib dose as tolerated or may change to Sunitinib & reassess tumor response via PET or CT
- For progressing lesions while continuing Imatinib, consider surgical resection if still feasible, radiofrequency ablation or embolization, or palliative radiation therapy for bone metastases

Systemic Disease Progression

- Increase Imatinib dose as tolerated or may change to Sunitinib & assess response via PET or CT
- If still w/ limited or systemic disease progression, consider Regorafenib, a clinical trial or supportive care

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## Dosage Guidelines

### TARGETED CANCER THERAPY

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Adverse Reactions</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>400 mg/day PO&lt;br&gt;As indicated, may increase to 800 mg/day PO</td>
<td>• CNS effect (headache); GI effects (N/V, diarrhea, abdominal pain); Musculoskeletal effects (arthralgia, muscle spasm &amp; cramps); Dermatologic effects (dermatitis, eczema, rash); Hematologic effects (thrombocytopenia, neutropenia, anemia, fatigue); Other effects (peripheral edema, fluid retention)</td>
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<tr>
<td>Regorafenib</td>
<td>160 mg PO 24 hrly for the 1st 21 days of a 28-day cycle</td>
<td>• GI effects (N/V, diarrhea, mucositis, decreased appetite); Dermatologic effects (palmar-plantar erythrodysesthesia, rash, alopecia); Other effects (hypertension, fatigue, dysphonia, hypocalcemia, hypophosphatemia, anemia, thrombocytopenia, hemorrhage)</td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td>50 mg PO 24 hrly x 4 wk followed by a 2-wk off period to comprise a complete 6-wk cycle</td>
<td>• GI effects (N/V, diarrhea, dyspepsia, stomatitis); Dermatologic effects (palmar-plantar erythrodysesthesia, rash, dry skin, changes in hair color, skin discoloration); Other effects (hypertension, fatigue, anorexia, pulmonary embolism, thrombocytopenia, tumor hemorrhage, febrile neutropenia)</td>
<td></td>
</tr>
</tbody>
</table>

**Adverse Reactions**
- • CNS effect (headache); GI effects (N/V, diarrhea, abdominal pain); Musculoskeletal effects (arthralgia, muscle spasm & cramps); Dermatologic effects (dermatitis, eczema, rash); Hematologic effects (thrombocytopenia, neutropenia, anemia, fatigue); Other effects (peripheral edema, fluid retention)

**Special Instructions**
- • Use w/ caution in patients w/ renal or hepatic impairment, history of CV disease, severe fluid retention
- • Wt, LFT, CBC should be monitored

*All dosage recommendations are for non-pregnant & non-breastfeeding women, & non-elderly adults w/ normal renal & hepatic function unless otherwise stated.*

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*Products listed above may not be mentioned in the disease management chart but have been placed here based on indications listed in regional manufacturers’ product information.*

*Specific prescribing information may be found in the latest MIMS.*

*Please see the end of this section for the reference list.*