GIST TUMORS

Dr. Kourosh Kazemi
Associate prof. of General & HPB Surgery
Liver transplant surgeon
SHIRAZ/ IRAN
1400
Introduction

- GIST are rare malignancies
- most common sarcoma of the GI tract
- represent only 0.2% of all GI tumors,

- subject of considerable clinical and experimental interest, because of the identification of their activating signal (oncogenic mutation of the c-kit receptor) and

the development of a therapeutic agent that suppresses tumor growth by inhibiting this signal
• Diagnosis of GIST has dramatically increased since 1992, and survival has greatly improved since 2002, when imatinib mesylate was approved by FDA for GIST

GIST-Epidemiology

- Age
  - Can present at any age
  - Median age at diagnosis is 60 years
  - Range 40-80 years
  - Rare in children as a familial syndrome/ part of Carney’s triad
- Sex
  - Equal in males and females
- Race and ethnicity
  - No predilection
GIST-Clinical features

- Generally detected when they become symptomatic
- Nonspecific symptoms,
  - Vague abdominal pain & fullness
  - Early satiety, malaise, fatigue
- Symptoms due to obstruction or bleeding
  - Haematemesis or malena
  - Dysphagia(Esophageal)
  - Obstructive jaundice(duodenal tumor)
  - Features of small bowel obstruction or peritonitis
  - Constipation(colorectal)
GISTs can occur anywhere along the GI tract

Most common in the

- **stomach** (50%)
  - small bowel (25%)
  - Colon (10%),
  - omentum/mesentery (7%)
  - esophagus (5%) are less common primary sites

A few GISTs occur within the abdomen and retroperitoneum
• Liver metastases and/or dissemination within the abdominal cavity are the usual clinical manifestations of malignancy.

• Lymph node metastases are extremely uncommon.
Pathology

- Arise from the interstitial cells of Cajal (ICC),
  - components of the intestinal autonomic nervous system
  - pacemakers regulating intestinal peristalsis
- Tumors are generally centered on the bowel wall but may form polypoid serosal- or mucosal-based masses.

- Ulceration of the mucosa is often associated with GI bleeding.
• Most GISTs show 1 of 3 histologic patterns:
  – predominantly spindle cells (the most common pattern)
  – predominantly epithelioid cells
  – a mixture of both spindle and epithelioid cells
Prognosis

- 2 most important prognostic features of a primary tumor are its **size and mitotic index**

- Small lesions may remain stable for years
CT Scan

- Seen as **solid hyperdense-enhancing mass**

- Critical to determine the anatomic extent of a GIST and to assist with operative planning

- **Ghanem and colleagues** recently reported
  - **Small GIST**
    - Sharp margins
    - Intraluminal growth pattern
    - Homogenous density on both unenhanced and contrast-enhanced scans
CT Scan

- Larger GIST
  - Irregular margins
  - Extragluminal growth patterns
  - Inhomogeneous density

- Radiographic signs for aggressive malignant GIST include **calcification, ulceration, necrosis, cystic areas, fistula formation, metastasis, ascites, and signs of infiltration of local tissues**
Goal of Surgery

Complete gross resection with an intact pseudocapsule and negative microscopic margins
Principles of surgical management

If the disease is metastatic, medical therapy with TKIs is standard treatment and maintained indefinitely.

If a wedge or segmental resection of the involved gastric or intestinal tract.

For open or laparoscopy, the abdomen should be thoroughly explored to identify any previously undetected peritoneal metastatic deposits.

The goal of surgery is R0 excision. R0 or R1 resections are associated with better outcomes than an R2 excision.

Local recurrence after R0 surgery is very unlikely in GISTs.

Tubular or violation of the tumor capsule during surgery are associated with a risk of recurrence, and therefore should be avoided.

Whether or not lymphadenectomy is not routinely required, because lymph nodes are rarely involved (patients) and are thus resected only when they are clinically suspect.
GENERAL SURGICAL PRINCIPLES

• **Type of treatment and surgery depend on:**
  – confidence in the preoperative diagnosis
  – tumor location & size
  – extent of spread
  – clinical presentation (eg, whether there is evidence of tumor obstruction, perforation, or uncontrolled hemorrhage).
**Point 1**

**Preoperative biopsy or (EUS)-guided (FNA)**

- **may not be necessary if:**
  - mesenchymal GI tumor is strongly suspected,
  - it appears to be resectable
  - the patient is otherwise operable.

- **a biopsy is preferred to confirm the diagnosis if:**
  - metastatic disease is suspected or
  - if preoperative imatinib is considered prior to attempted resection
Point 2

- All **GISTs ≥2 cm** in size should be resected. However, there is no consensus on the management of smaller GISTs.
- **Surgical resection is the treatment of choice for potentially resectable tumors.**
- However, initial therapy with imatinib may be preferred if:
  - tumor is borderline resectable
- or
  - if resection would necessitate extensive organ disruption
Point 3

• the goal of surgical treatment is complete gross resection with an intact pseudocapsule
• Segmental resection of the stomach or intestine should be performed with the goal of achieving negative resection margins.
• Wider resection of uninvolved tissue is of no additional benefit. However, peritumoral as opposed to segmental resection should be avoided, as there is a higher risk of local recurrence, particularly with leiomyosarcoma
• Routine lymphadenectomy is unnecessary because nodal metastases are rare
• If involved other organs, in some cases, en bloc resection is necessary because of dense adhesions.
At laparotomy, the abdomen should be thoroughly explored, peritoneal surfaces and liver to exclude metastatic spread. 

- Avoid rupture

The necessity of achieving negative microscopic margins is uncertain with large (>10 cm) GISTs.

The management of a positive margin according to the “Final pathology report is not well defined and depends on whether the surgeon believes the finding accurately reflects the surgical procedure that was undertaken.

Although patients who undergo a microscopically incomplete resection may be at greater risk for a locoregional recurrence, other factors such as tumor grade and size may play a more significant role in determining the risk of recurrence.

The risks and benefits of reexcision versus initiation of imatinib must be carefully considered.
Point 5

- *imatinib* is approved by the FDA in the United States for adjuvant treatment of completely resected GISTs ≥3 cm in size.

- In practice, we risk stratify patients for consideration of adjuvant imatinib. The European regulatory body, the European Medicines Agency, recommended adjuvant imatinib for patients with a resected primary GIST at a significant risk of relapse.

- They specified that patients with very low/low risk GISTs should not get adjuvant imatinib.
PRESENTATION AND MANAGEMENT AT SPECIFIC SITES
Esophagus

- **Endoscopic resection**: all small submucosal tumors has been suggested to establish their benignity.
- A more conservative approach for small asymptomatic lesions that lack features suggesting malignancy is to perform follow-up examinations using endoscopic ultrasound (EUS).
- Follow-up studies consist of repeat EUS at six and 12 months. If no changes occur within one year, the follow-up intervals can be lengthened.
- Surgical removal should be performed if the tumor becomes symptomatic, enlarges to >1 cm, or shows structural changes.
- Snare polypectomy should be reserved for lesions with mucosal elevations that meet the previously described criteria.
- Surgical resection also is indicated in any case in which a malignancy is suspected.
GIST of ESOPHAGUS

- >=2cm
  - Open enblock esophagectomy

- Or GEJ

- Small & confined to wall of distal
  - Local resection if neg margin

- <2cm
  - Controversial
    - ESMO: F/U By EUS
      - Excise if enlarged
    - Canadian: All resected
The stomach is the most frequent site for GISTs.

The majority of soft tissue tumors arising in the stomach are GISTs, followed by leiomyomas.

"Carney's triad":
- young women that includes mainly gastric GISTs, paraganglioma, and pulmonary chondroma.
- GISTs arising in this setting can be relatively indolent even if metastatic, especially in children and young adults.

Carney-Stratakis syndrome:
- A familial syndrome consisting of: multicentric paragangliomas + multifocal GIST tumors with an AD pattern of inheritance in young men and women.
Small intestine

• The small intestine is the **second most frequent site for smooth muscle tumors**.

• Tumors are most commonly found in **the jejunum**, followed by the ileum and then duodenum.

• Surgical treatment for a localized, potentially resectable GIST and a leiomyosarcoma of the small bowel is similar and consists of en bloc segmental resection with tumor-free margins.

• Peritumoral as opposed to segmental resection should be avoided.

• **Mesenteric lymphadenectomy** is neither necessary nor beneficial.

• There is less experience with laparoscopic resection of small bowel GISTs than with gastric GIST.
Small bowel gist

Deodenum

Locally advanced
Near papilla

Local resection

Resection anastomosis
without LND

Jjunum ileum

Neoadj imatinib then local resection, auto Tx, SB Tx

PD
Colon & rectum

• Smooth muscle tumors are uncommon overall in the colon and rectum, and especially rare in the appendix
• In the rectum, the great majority of smooth muscle tumors are GISTs
• standard colectomy based on the blood supply to the bowel
• resection of the adjacent mesentery (and the performance of a TME for rectal GISTs) is not necessary
• Rectal GIST may require extensive surgery to achieve a surgically complete resection. Such cases should be considered for neoadjuvant imatinib to reduce tumor size
• Outcomes with surgery alone are poor
• We prefer initial imatinib for most patients with a rectal GIST, unless the tumor is small and sphincter-preserving surgery is possible upfront.
Rates of progression-free survival for gastrointestinal stromal tumors (GISTs) of the stomach, small intestine, and rectum, grouped by mitotic rate and tumor size

<table>
<thead>
<tr>
<th>Tumor size (cm)</th>
<th>Mitotic rate (HPF): ≤5/50</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gastric</td>
<td>Jejunum/ileum</td>
<td>Duodenum</td>
<td>Rectum</td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>2 to 5</td>
<td>98.1</td>
<td>95.7</td>
<td>91.7</td>
<td>91.5</td>
<td></td>
</tr>
<tr>
<td>5 to 10</td>
<td>96.4</td>
<td>76</td>
<td>66*</td>
<td>43*</td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>88</td>
<td>48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitotic rate (HPF): &gt;5/50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>100Δ</td>
<td>50Δ</td>
<td>–</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>2 to 5</td>
<td>84</td>
<td>27</td>
<td>50</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>5 to 10</td>
<td>45</td>
<td>15</td>
<td>14*</td>
<td>29*</td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>14</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Based on long-term follow-up studies on 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal cancers.
ADJ and NEOADJ imatinib

• **Neo adj : imatinib**
  - patients with an *unresectable* or *borderline resectable* locally advanced tumor
  - a potentially resectable tumor that *requires extensive organ disruption*
  - patients with a GIST arising in the *esophagus, esophagogastric junction, duodenum, or rectum*

• **Adj :**
  - imatinib is approved in the United States for use as adjuvant therapy for any *primary GIST ≥3 cm.*
  - patients *at high risk of recurrence* after complete resection
## Modified NIH risk stratification criteria for GIST with rupture included

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Tumor size (cm)</th>
<th>Mitotic index (per 50 HPFs)</th>
<th>Primary tumor site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low risk</td>
<td>&lt;2.0</td>
<td>≤5</td>
<td>Any</td>
</tr>
<tr>
<td>Low risk</td>
<td>2.1 to 5.0</td>
<td>≤5</td>
<td>Any</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>2.1 to 5.0</td>
<td>&gt;5</td>
<td>Gastric</td>
</tr>
<tr>
<td></td>
<td>&lt;5.0</td>
<td>6 to 10</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>5.1 to 10.0</td>
<td>≤5</td>
<td>Gastric</td>
</tr>
<tr>
<td>High risk</td>
<td>Any</td>
<td>Any</td>
<td>Tumor rupture</td>
</tr>
<tr>
<td></td>
<td>&gt;10 cm</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>Any</td>
<td>&gt;10</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>&gt;5.0</td>
<td>&gt;5</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>2.1 to 5.0</td>
<td>&gt;5</td>
<td>Nongastric</td>
</tr>
<tr>
<td></td>
<td>5.1 to 10.0</td>
<td>≤5</td>
<td>Nongastric</td>
</tr>
</tbody>
</table>

NIH: National Institutes of Health; GIST: gastrointestinal stromal tumor; HPF: high power fields.

Reproduced from: Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol 2008; 39:1411. Table used with the permission of Elsevier Inc. All rights reserved.

Graphic 85938 Version 2.0
Modified NIH risk stratification criteria for GIST with rupture included

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Tumor size (cm)</th>
<th>Mitotic index (per 50 HPFs)</th>
<th>Primary tumor site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low risk</td>
<td>&lt;2.0</td>
<td>≤5</td>
<td>Any</td>
</tr>
<tr>
<td>Low risk</td>
<td>2.1 to 5.0</td>
<td>≤5</td>
<td>Any</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>2.1 to 5.0</td>
<td>&gt;5</td>
<td>Gastric</td>
</tr>
<tr>
<td></td>
<td>&lt;5.0</td>
<td>6 to 10</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>5.1 to 10.0</td>
<td>≤5</td>
<td>Gastric</td>
</tr>
<tr>
<td>High risk</td>
<td>Any</td>
<td>Any</td>
<td>Tumor rupture</td>
</tr>
<tr>
<td></td>
<td>&gt;10 cm</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>Any</td>
<td>&gt;10</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>&gt;5.0</td>
<td>&gt;5</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>2.1 to 5.0</td>
<td>&gt;5</td>
<td>Nongastric</td>
</tr>
<tr>
<td></td>
<td>5.1 to 10.0</td>
<td>≤5</td>
<td>Nongastric</td>
</tr>
</tbody>
</table>

NIH: National Institutes of Health; GIST: gastrointestinal stromal tumor; HPF: high power fields.

Reproduced from: Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol 2008; 39:1411. Table used with the permission of Elsevier Inc. All rights reserved.

Graphic 85938 Version 2.0
ROLE OF SURGERY IN PATIENTS WITH METASTATIC DISEASE

• The **liver and peritoneum** are the most common metastatic sites

• 25 to 30 percent of patients present with recurrent/metastatic disease have potentially resectable disease.

• **(TKIs)** has become the “first-line treatment for metastatic GIST, and need for continued treatment with TKI therapy after surgery to increase OS
Why we should consider surgery in metastatic GIST?

• complete responses to TKI (imatinib) are only rarely achieved. Even tumor masses that appear nonviable by metabolic imaging (eg, with PET scans)
• resistance via additional mutations in the KIT gene. (The median time for resistance: two years)
• The goal of metastasectomy is to remove disease before secondary resistance develops and stop disease progression by eliminating resistant clones.
• 25 to 30 percent of patients who present with recurrent/metastatic disease have potentially resectable disease.
Time of surgery after initiation of imatinib?

• treated for **six to nine months with a TK inhibitor** and then considered for surgery if the disease appears completely grossly resectable

• the median time to best response is 3.5 months

• there is **little incremental tumor shrinkage after nine months**

• **All patients treated with presurgical imatinib should resume TKI therapy postoperatively, typically with the same agent and dose.**
Hepatic resection for liver metastases

- Liver is the site of recurrence in as many as 67 percent of patients with relapsed GIST.
- 5y survival rates from 27 to 34 percent in patients undergoing resection alone.
- Now, for patients with isolated liver metastases, hepatic resection combined with imatinib provides the greatest opportunity for long-term disease control.
- A course of preoperative therapy (three to nine months) is preferred:
  - Reduce the extent of needed surgery
  - Permits the "biologic selection" of the best candidates for surgery
- As an example, in the setting of multiple bilateral lesions (which are common with GIST), a two-staged approach may be needed, with or without portal vein embolization to increase the volume of the future liver remnant prior to hepatic resection.
• An important component of periodic response assessment during neoadjuvant imatinib is the understanding that a response to therapy consists less often of a change in tumor size or diameter, and more often of changes in density (i.e., the development of cystic structures) and vascularity. This renders size-based tumor response criteria such as the Response Evaluation Criteria in Solid Tumors (RECIST) less useful.

• Guidelines from NCCN and ESMO recommend the indefinite administration of imatinib for patients with resected metastases in the liver or peritoneum, even if the resection was complete.
Other local therapy options for liver metastases

- **Hepatic arterial embolization and chemoembolization**
- **Radiofrequency ablation**
  - patients are ineligible because they have multifocal bilobar disease
  - unresectable but isolated liver metastases from GISTs.
  - multifocal disease progression in liver despite use of available systemic therapeutic options
Conclusions

• Surgery is first-line treatment for patients with resectable GISTs
  – Up to 50% patients have recurrence after complete resection
• Tyrosine kinase inhibitor imatinib now standard treatment for unresectable or metastatic or advanced GIST
• Adjuvant Imatinib now standard treatment for high risk GIST
• Neoadjuvant Imatinib for locally advanced GIST