Surgery: The Primary Treatment for GIST

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Disclosure

• Investigator-Initiated Trial sponsored by Bristol-Myers Squibb (2017-present)
Principles of Surgery for GIST

1. Multidisciplinary Management
2. No Tumor Rupture
3. 1-2 cm margin
4. Complete Resection:
   • Including adjacent involved organs
Historically classified as:
- leiomyoma
- leiomyosarcoma
- leiomyoblastomas

1998: Hirota and colleagues:
- Interstitial Cells of Cajal
- Pacemaker cells throughout intestine
- cKIT+
What do Surgeon’s think about when evaluating a patient with GIST?

1. Where is the tumor located?
2. Additional organs involved?
3. Bad location?
4. Bad Biology?
5. Approach?
   - Role for laparoscopy
   - ? Role for Observation

Would preoperative imatinib (Gleevec) help?
GISTs-Historical Outcomes

Table 2. PATIENT PRESENTATION IN 200 PATIENTS WITH GASTROINTESTINAL STROMAL TUMOR

<table>
<thead>
<tr>
<th>Presentation</th>
<th>n</th>
<th>Median Survival (months)</th>
<th>Complete Resection</th>
<th>% of Row Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>93</td>
<td>60</td>
<td>80</td>
<td>86</td>
</tr>
<tr>
<td>Metastatic</td>
<td>94</td>
<td>19</td>
<td>28</td>
<td>30</td>
</tr>
<tr>
<td>Metastasis only</td>
<td>51</td>
<td>22</td>
<td>16</td>
<td>31</td>
</tr>
<tr>
<td>Primary tumor + metastasis</td>
<td>26</td>
<td>23</td>
<td>8</td>
<td>31</td>
</tr>
<tr>
<td>Local recurrence + metastasis</td>
<td>17</td>
<td>9</td>
<td>4</td>
<td>24</td>
</tr>
<tr>
<td>Locally recurrent</td>
<td>13</td>
<td>12</td>
<td>6</td>
<td>46</td>
</tr>
</tbody>
</table>
GIST discovery: right place, right time

- Clinical trial in leukemia
- Imatinib (Gleevec)

- Tyrosine kinase inhibitor (TKI)
  - Bcr-Abl
  - cKIT
  - PDGF-R
Imatinib reduces recurrence after surgery

Who should get Imatinib after surgery?

Prognostic Factors - Recurrence

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Stomach</td>
<td>Small/large intestine</td>
</tr>
<tr>
<td>Size</td>
<td>$\leq 5 \text{ cm}$</td>
<td>$&gt; 5 \text{ cm}$</td>
</tr>
<tr>
<td>Mitotic index</td>
<td>$\leq 5/50 \text{ HPF}$</td>
<td>$&gt; 5/50 \text{ HPF}$</td>
</tr>
<tr>
<td>Mutation</td>
<td>PDGFRA</td>
<td>WT</td>
</tr>
<tr>
<td>KIT mutation</td>
<td>Exon 11 duplication/insertion</td>
<td>Exon 11 deletion, Exon 9</td>
</tr>
<tr>
<td>Surgery</td>
<td>R0 resection</td>
<td>R1, tumor rupture</td>
</tr>
</tbody>
</table>
**Gastric vs. non-gastric GIST: Different outcomes**

### Predictors of GIST Biologic Behavior

**Table 1: Gastric GISTs: Proposed Guidelines for Assessing the Malignant Potential**

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>Mitotic Rate</th>
<th>Predicted Biologic Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2 cm</td>
<td>≤5 mitoses/50 HPFs</td>
<td>Metastasis rate: 0%</td>
</tr>
<tr>
<td>&gt;2 cm ≤5 cm</td>
<td>&gt;5 mitoses/50 HPFs</td>
<td>Metastasis rate: 0%*</td>
</tr>
<tr>
<td>&gt;5 cm ≤10 cm</td>
<td>≤5 mitoses/50 HPFs</td>
<td>Metastasis rate: 1.9%</td>
</tr>
<tr>
<td>&gt;10 cm</td>
<td>≥5 mitoses/50 HPFs</td>
<td>Metastasis rate: 16%</td>
</tr>
</tbody>
</table>

GISTs: Gastrointestinal stromal tumors; HPFs: High-power fields; *predictive rate based on tumor category with very small numbers

### Predictors of GIST Biologic Behavior

**Table 2: Non-Gastric GISTs: Proposed Guidelines for Assessing the Malignant Potential**

<table>
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<th>Tumor Size</th>
<th>Mitotic Rate</th>
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<tbody>
<tr>
<td>≤2 cm</td>
<td>≤5 mitoses/50 HPFs</td>
<td>Metastasis rate: 0%</td>
</tr>
<tr>
<td>&gt;2 cm ≤5 cm</td>
<td>&gt;5 mitoses/50 HPFs</td>
<td>Metastasis rate: 50%–54%</td>
</tr>
<tr>
<td>&gt;5 cm ≤10 cm</td>
<td>≤5 mitoses/50 HPFs</td>
<td>Metastasis rate: 1.9%–8.5%</td>
</tr>
<tr>
<td>&gt;10 cm</td>
<td>≥5 mitoses/50 HPFs</td>
<td>Metastasis rate: 50%–73%</td>
</tr>
</tbody>
</table>

GISTs: Gastrointestinal stromal tumors; HPFs: High-power fields
What do Surgeon’s think about when evaluating a patient with GIST?

1. Where is the tumor located?
2. Additional organs involved?
3. Bad location?
4. Bad Biology?
5. Approach?
   • Role for laparoscopy
   • ? Role for Observation
75 yo M Diagnosed with anemia

Biopsy: Exon 11 mutant GIST
75 yo M Diagnosed with anemia

- OR- partial gastrectomy & splenectomy
- Path- 6 x 3.5 cm, < 5% tumor viable, margins negative, 0 mitosis
- Continued adjuvant Gleevec 300 mg/day
- Last F/U 3.5 years → No disease
77yo M Diagnosed with gastric GIST: Bad Location

Needs resection distal stomach due to location

Plan for wedge resection (local excision)

Warning: Surgery Photos

- No need for post-operative imatinib
GIST prior to Therapy

Photo: Kelly Hunt, MD
GIST after Therapy
Preoperative Therapy: Little to lose, lots to gain

• Rationale:
  • Decrease the size of the tumor
  • Decrease the vascularity
  • Diminish extent of resection required

• For locally advanced primary GIST patients receiving preoperative therapy
  • 1% complete response, 73% partial response, 9% stable, 1% progressive disease

Preoperative imatinib is safe

- Randomized Phase II trial
  - 19 patients: preoperative therapy for 3, 5 or 7 days
  - No effects on surgical complications
  - 62% had evidence of radiographic response

- RTOG 0132
  - Multi-institutional study: 53 patients
  - 2 months preoperative imatinib + 2 years post-op
  - No significant effects on surgical complications

How long to treat for localized disease?

- Treat to maximal effect
- ~ 6 months but up to 12 months or longer
- Imaging after 2-3 months and discuss: Med Onc, Surg Onc and patient.
  - Is now the right time for surgery?
  - Will further shrinkage change to extent or approach of surgery?
Laparoscopic resection of GIST-Feasible?

Photo: Chan Raut, MD
Tumor size important for determining approach
Need to get the tumor out!

Trocar size: 0.5 cm-1.2 cm

https://www.ncbi.nlm.nih.gov/books/NBK65959.3/figure/CDR0000062957__234/?report=objectonly
Laparoscopic resection of GIST-Reasonable?

- Review of 11 nonrandomized studies of 765 patients
  - 381: laparoscopy
  - 384 open
- Higher proportion of high-risk tumors and gastrectomies in open group
- Laparoscopy: superior short-term outcomes without compromising oncologic safety
- Best approach: what the surgeon is most comfortable with

Koh et al, Ann Surg Onc 2013
Preoperative imatinib-smaller operation

Needs resection distal stomach due to location

Plan for wedge resection (local excision)
70 yo M with abdominal pain-What to do?

1.5 cm GIST
Why not just take it out?

High-risk features: irregular border, cystic spaces, ulceration, heterogeneity
# PREDICTORS OF GIST BILOGIC BEHAVIOR

Table 1: Gastric GISTs: Proposed Guidelines for Assessing the Malignant Potential

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<td>≤2 cm</td>
<td>≤5 mitoses/50 HPFs</td>
<td>Metastasis rate: 0%</td>
</tr>
<tr>
<td></td>
<td>&gt;5 mitoses/50 HPFs</td>
<td>Metastasis rate: 0%*</td>
</tr>
<tr>
<td>&gt;2 cm ≤5 cm</td>
<td>≤5 mitoses/50 HPFs</td>
<td>Metastasis rate: 1.9%</td>
</tr>
<tr>
<td></td>
<td>&gt;5 mitoses/50 HPFs</td>
<td>Metastasis rate: 16%</td>
</tr>
<tr>
<td>&gt;5 cm ≤10 cm</td>
<td>≤5 mitoses/50 HPFs</td>
<td>Metastasis rate: 3.6%</td>
</tr>
<tr>
<td></td>
<td>&gt;5 mitoses/50 HPFs</td>
<td>Metastasis rate: 55%</td>
</tr>
<tr>
<td>&gt;10 cm</td>
<td>≤5 mitoses/50 HPFs</td>
<td>Metastasis rate: 12%</td>
</tr>
<tr>
<td></td>
<td>&gt;5 mitoses/50 HPFs</td>
<td>Metastasis rate: 86%</td>
</tr>
</tbody>
</table>

GISTs: Gastrointestinal stromal tumors; HPFs: High-power fields; *predicted rate based on tumor category with very small numbers
Summary: Localized Disease

1. Where is the tumor located?
   - Stomach vs. other: different outcomes

2. Need for preoperative imatinib? Treat to maximal response
   - Additional organs involved?
   - Bad location?
   - Approach?
What do Surgeon’s think about when evaluating a patient with GIST?

1. Where is the tumor located?
2. Additional organs involved?
3. Bad location?
4. Bad Biology?
5. Approach?
   • Role for laparoscopy
   • Role for Observation
Treatment of Metastatic GIST: Evolution over time

**Progression-free Survival**

- 400mg/day: 345 patients, 278 failed, median (months) 18
- 800mg/day: 349 patients, 267 failed, median (months) 20

**Overall Survival**

- 400mg/day: 345 patients, 168 deaths, median (months) 55
- 800mg/day: 349 patients, 174 deaths, median (months) 51

Blanke et al, JCO 2008
Surgery for Metastatic GIST: Who is Benefitting?

Surgery for Metastatic GIST: Who is Benefitting?

- Remove all gross disease
- Unable to remove all disease
- OS: ~ 5 years

Bauer et al, Eur J Surg Onc 2014
Identification of preoperative factors associated with improved prognosis in patients with metastatic GIST

- 87 patients
  - Complete resection of metastatic/recurrent GIST
  - Treated with TKI preoperatively

<table>
<thead>
<tr>
<th></th>
<th>Time to Recurrence</th>
<th>GIST-Specific Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Progression</td>
<td>62 months</td>
<td>Not reached</td>
</tr>
<tr>
<td>Progression</td>
<td>8 months</td>
<td>35 months</td>
</tr>
<tr>
<td>Unifocal Disease</td>
<td>41 months</td>
<td>106 months</td>
</tr>
<tr>
<td>Multifocal Disease</td>
<td>15 months</td>
<td>51 months</td>
</tr>
</tbody>
</table>

Roland et al, Eur J Surg Onc 2018
Clinical trial of surgery vs. no surgery for metastatic GIST: failure to enroll

- Randomized trial in China
- Planned to enroll 210 patients
  - Recurrent or metastatic GIST
  - No prior imatinib
  - No progression on imatinib
- Stopped at 41 patients
- Primary Endpoint: Progression-free survival
Clinical trial of surgery vs. no surgery for metastatic GIST: negative b/c low numbers

Du et al, *Eu J Cancer* 2014
Surgery for Metastatic GIST: Who is Benefitting?

- Patient selection is key

How long can we wait to get to this point?

progressing
39yo M Diagnosed with metastatic small bowel GIST

- Gleevec → response but side effects
- Sunitinib → progressed
- 1 year after diagnosis - attempted resection
  - Unresectable, drained
39yo M Diagnosed with metastatic small bowel GIST

- 2 years after diagnosis
- Continue gleevec
39yo M Diagnosed with metastatic small bowel GIST

- 3 years after diagnosis
- Continue gleevec
- Drain removed
39yo M Diagnosed with metastatic small bowel GIST

- 3.5 years after diagnosis
- Surgery referral
- Small bowel resection, GIST removal
- Gleevec indefinitely
Conclusions—Localized GIST

- Wide clinical spectrum based on:
  - Tumor Size
  - Location
  - Mitotic activity
- High risk GISTs require multidisciplinary management
- Preoperative therapy for:
  - Additional organs involved
  - Bad location
  - Approach
Conclusions-Metastatic Disease

- No standard management of recurrent/metastatic GIST
  - Almost always involves initiation of TKI

- Surgery may benefit highly selected patients
  - Response to imatinib
  - Location and number of tumors
  - Long disease-free interval
  - Ability to remove all tumors
Unanswered Questions

• Optimal Duration of imatinib
  • Preoperatively and after surgery
• Ability to measure response
• Better prognostic systems
  • Mutation status