On the Cutting Edge of GIST: Novel Surgical Approaches

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Associate Professor of Surgery

Where discoveries are delivered.℠
Disclosures

- Investigator-initiated Trial Sponsored by Novartis Pharmaceuticals (2013 – present)
- Investigator-initiated Trial Sponsored by Foundation Medicine (2015 – present)
- Consultant, Sirtex (2015)
- Consultant, Grand Rounds (2015 - present)
- Research funding, Blueprint Medicines (2015)
- Consultant, CARsgen Therapeutics (2017)
ICCs are Submucosal Cells
Submucosal Tumor (SMT) Growth Pattern

Endophytic

Exophytic

SMT DDx: leiomyoma, leiomyosarcoma, schwannoma, pancreatic heterotopia, gastric cavernous hemangioma
Spectrum of Clinical Presentation

Asymptomatic

- Incidentally discovered (median size 3 cm)
Spectrum of Clinical Presentation

- Nausea/vomiting
- Abdominal pain
- Abdominal distension
- Early satiety
Spectrum of Clinical Presentation

- **Bleed**
  - Slow bleeding
    - Anemia
    - Melena
  -acute bleeding
    - Intraluminal erosion
    - Intra-peritoneal rupture
Spectrum of Clinical Presentation

- Acute onset pain
- Fever
- Leukocytosis
Tumor Biology

Push

Left Renal Vein

Rarely Invade
Hematogenous (Not Lymphatic) Spread

Liver Metastases  Peritoneal Metastases

< 1/3 patients have both types of metastases
Nodal and other metastases are rare
Survival in the Era of TKIs

Entire GIST cohort
- 5-year DSS: 79%
- 5-year OS: 65%

5-year OS by Stage
- Localized disease: 77%
- Regional disease: 64%
- Distant metastases: 41%

Ma...Sicklick, *Cancer Epidemiology, Biomarkers & Prevention*. 2015
Surgery is the Primary Treatment

Potentially Curative
Goals of Surgical Treatment

- Total gross resection
- Negative microscopic margins
- Intact pseudocapsule without tumor rupture
- Because LN metastases are uncommon, lymphadenectomy is not generally indicated
Surgical Margins, Not the Technique, Dictate Prognosis

Table 1: Clinicopathological parameters and recurrence-free survival/disease-specific survival of Gastrointestinal Stromal Tumor (GIST) patients.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>RFS (n (%)</th>
<th>Events (n)</th>
<th>HR</th>
<th>95% CI</th>
<th>p Value</th>
<th>DSS (n (%)</th>
<th>Events (n)</th>
<th>HR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wedge/segmental resection</td>
<td>53 (55)</td>
<td>6</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>56 (54)</td>
<td>7</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Enucleation</td>
<td>21 (22)</td>
<td>2</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>22 (21)</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Total/subtotal organ resection</td>
<td>20 (21)</td>
<td>4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>22 (21)</td>
<td>4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>En bloc resection</td>
<td>2 (2)</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>4 (4)</td>
<td>2</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Table 2: Multivariate analysis of prognostic factors of disease-specific survival of GIST patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margin status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R0</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R1</td>
<td>1.54</td>
<td>0.34–7.08</td>
<td>0.57</td>
</tr>
<tr>
<td>R2</td>
<td>5.72</td>
<td>1.44–22.71</td>
<td>0.013</td>
</tr>
</tbody>
</table>

R0 = Complete gross and microscopic resection.
R1 = Complete gross resection and microscopic incomplete resection.
R2 = Incomplete gross resection.

*95% confidence interval for HR.

Gouveia et al., World J Surg. 2008
Tumor Rupture is a Poor Prognostic Factor

Risk of Recurrence: Modified NIH (Joensuu)

<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>≤2.0</td>
<td>≤5</td>
<td>Any site</td>
</tr>
<tr>
<td>Low risk</td>
<td>2.1-5.0</td>
<td>≤5</td>
<td>Any site</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>≤5.0</td>
<td>6-10</td>
<td>Gastric</td>
</tr>
<tr>
<td></td>
<td>5.1-10.0</td>
<td>≤5</td>
<td>Gastric</td>
</tr>
<tr>
<td>High risk</td>
<td>Any size</td>
<td>Any count</td>
<td>Tumor rupture</td>
</tr>
<tr>
<td></td>
<td>&gt;10.0</td>
<td>Any count</td>
<td>Any site</td>
</tr>
<tr>
<td></td>
<td>Any size</td>
<td>&gt;10</td>
<td>Any site</td>
</tr>
<tr>
<td></td>
<td>&gt;5.0</td>
<td>&gt;5</td>
<td>Any site</td>
</tr>
<tr>
<td></td>
<td>≤5.0</td>
<td>&gt;5</td>
<td>Any site</td>
</tr>
<tr>
<td></td>
<td>5.1-10.0</td>
<td>≤5</td>
<td>Nongastric</td>
</tr>
</tbody>
</table>

Tumor Rupture Influences Recurrence-free Survival

Balancing Operative Approach

Cosmesis and Recovery  Oncologic Outcomes
Operative Approach: Means to an End

OPEN PROCEDURE

LAPAROSCOPIC PROCEDURE
Laparoscopic Approach

ADVANTAGES

1. Shorter incision length with lower hernia risk
2. Less pain
3. Shorter length of stay
4. Lower blood loss
5. Decreased ICU admissions
6. No oncologic disadvantages in experienced centers with experience surgeons (i.e., pancreas, liver, gastric, colon cancers)
Lap vs. Open Gastric Resections for GIST

No Difference in Oncologic Outcomes

<table>
<thead>
<tr>
<th>Variables</th>
<th>Surgery type</th>
<th></th>
<th></th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (N = 80)</td>
<td>Lap (N = 40)</td>
<td>Open (N = 40)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>74</td>
<td>37 (93%)</td>
<td>37 (93%)</td>
<td>.91</td>
</tr>
<tr>
<td>Adjuvant (imatinib)</td>
<td>5</td>
<td>3 (60%)</td>
<td>2 (40%)</td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant and adjuvant</td>
<td>1</td>
<td>0 (0%)</td>
<td>1 (100%)</td>
<td></td>
</tr>
<tr>
<td>Margins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gross − micro</td>
<td>79</td>
<td>39 (49%)</td>
<td>40 (50%)</td>
<td></td>
</tr>
<tr>
<td>Gross + micro</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Gross close (&lt;0.1 cm) micro</td>
<td>1</td>
<td>1 (1%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Recurrences, metastatic</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Survival status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive and recurrence free</td>
<td>72</td>
<td>36</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Alive with disease</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Died of other causes</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Died of unknown causes</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Karakousis et al., Ann Surg Onc. 2011
Operative Approach: Questions to Ask

Tumor Factors

• Can total gross resection be achieved safely (for either local, regional or metastatic disease)?

• Is the tumor small enough to be manipulated laparoscopically?

• Is the tumor invading adjacent structures?

• Even if a laparoscopic resection is feasible, how large will the incision be to remove the tumor?
Operative Approach: Questions to Ask

Tumor Factors

- Is tumor rupture a significant concern?
- Is this a primary tumor or a recurrence...will the surgical bed be “stuck”?
- Is there concern for multi-focal disease?
- With preoperative (neoadjuvant) therapy, could tumor shrinkage change the resection, make it safer, or make it easier?
Patient Factors

- Is the patient an appropriate operative candidate… other medical problems?
- Has the patient had prior abdominal operations- laparoscopic or open?
Operative Approach: Questions to Ask

Surgeon Factors

• Is the surgeon skilled at a laparoscopic approach?
• Best approach is what the surgeon is most comfortable with.
## Operative Approaches in GIST

<table>
<thead>
<tr>
<th>Surgical Technique</th>
<th>Advantages</th>
<th>Limitations (Evidence)</th>
<th>Tumor location</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparoscopy</td>
<td>Full-thickness resection of stomach wall; negative margins; minimal risk of dissemination; shorter hospital stay</td>
<td>Small studies (N=4–61)</td>
<td>Stomach; small bowel</td>
<td>Can be technically challenges with larger tumors &gt; 10 cm</td>
</tr>
<tr>
<td>Laparotomy</td>
<td>Better visualization and mobilization of larger tumors or those in technically challenging locations</td>
<td>Small case series; retrospective studies</td>
<td>Any</td>
<td>Longer hospital stay; More blood loss; Longer operation time</td>
</tr>
</tbody>
</table>

What Approach is Appropriate?
How should one approach resecting a GIST close to the GEJ…Open vs. Laparoscopic?
Operative Approaches in GIST

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<th>Limitations (Evidence)</th>
<th>Tumor location</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopy</td>
<td>Minimally invasive; potentially shorter operation time</td>
<td>Small series; retrospective study Limited data on long-term outcomes</td>
<td>Esophagus; stomach; rectum for small lesions (1-3 cm)</td>
<td>Often leaves positive margins with capsular invasion and/or tumor rupture Complications: perforation, pneumothorax (9.4%), and GI bleeding (5%)</td>
</tr>
</tbody>
</table>

Emerging Surgical Approach

Laparoscopy + Endoscopy

Laparo-Endoscopy
## Operative Approaches in GIST

<table>
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<th>Limitations (Evidence)</th>
<th>Tumor location</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparoscopic endoscopy</td>
<td>Monitor endoscopic resection; repair injury/perforation</td>
<td>Case reports and series</td>
<td>Stomach; duodenum</td>
<td>Technically demanding</td>
</tr>
</tbody>
</table>

_Laparoscopic transgastric resection of gastric submucosal tumors_

Juan S. Barajas-Gamboa · Geylor Acosta · Thomas J. Savides · Jason K. Sicklick · Syed M. Abbas · Fehmi · Alisa M. Coker · Shannon Green · Ryan Broderick · Diego F. Nino · Cristina R. Harnsberger · Martin A. Berducci · Bryan J. Sandler · Mark A. Talamini · Garth R. Jacobsen · Santiago Horgan

Laparo-Endoscopic Surgical (LES) Approach

ADVANTAGES

1. Extra working port via the endoscope in order to minimize instrument changes while decreasing the clutter/clashing of additional trocars/instruments
2. Improved ability to visualize remote locations in the abdomen given the endoscope’s flexibility
3. Superior ergonomics when compared to single access laparoscopic surgery
Lessons Learned

• Takes a team approach with coordination between surgeons and gastroenterologists
• Approach reduces the number of trocars
• Avoids large gastric resections for proximal gastric tumors
• Oral extraction is generally safe and feasible for tumors < 3-4 cm in size
Assessment of Intragastric Single-Port Surgery for Gastric Tumors

Felix Krenzien, MD; Johann Pratschke, MD; Ricardo Zorron, MD, PhD

JAMA Surgery  August 2017  Volume 152, Number 8

Figure. Intragastric Single-Port Surgery (IGS)

A  Schematic of IGS

B  Anterior wall of the stomach

C  GIST at the cardia
Limited Metastatic Disease

- Long-term survival in patients in whom surgical complete remission can be achieved.
- Incomplete resection, including debulking surgery does not seem to prolong survival.

Cytoreductive Surgery for Metastatic Gastrointestinal Stromal Tumors Treated With Tyrosine Kinase Inhibitors

A 2-institutional Analysis

Mark Fairweather, MD,*∥ Vinod P. Balachandran, MD,† George Z. Li, MD,* Monica M. Bertagnolli, MD,*∥ Cristina Antonescu, MD,‡ William Tap, MD,¶ Samuel Singer, MD,∥ Ronald P. DeMatteo, MD,‡ and Chandrajit P. Raut, MD, MSc*∥

![Graphs showing survival rates and progression types for different treatments and patient groups.](image-url)
Summary

• Although surgery remains the only potentially curative treatment, patients who undergo complete resection may still experience local recurrence or distant metastases.
• Therapeutic strategies that combine surgical resection and imatinib therapy may represent the best treatment to maximize patient outcomes.
• Selected patients with metastatic disease may be treated with a combination of preoperative imatinib and metastasectomy.
• Surgery in metastatic GIST patients in the absence of MPD on imatinib is associated with outcomes at least comparable with second-line sunitinib and may be considered in select patients.
Future Directions in Surgical Management of GIST?
Approach Surgical Challenges in the Lab

• Diagnosis
  • Can be mistaken for benign gastric submucosal tumors
    • Schwannoma
    • Leiomyoma

• Surgical Treatment
  • R0 resection
  • Cytoreduction of peritoneal and/or liver metastases in highly selected patients

• Response to Tyrosine Kinase Inhibitor Therapy
To develop a technique for using fluorophore-conjugated anti-KIT antibodies delivered intravenously to transgenic GIST-bearing mice for detection of GISTs \textit{in vivo}. 
Metildi, et al. JACS 2012
In Vivo Fluorescent Labeling of GIST
KIT K641E^{+/-} Transgenic Mouse Model of GIST

Provided by B. Rubin, Cleveland Clinic
In Vivo Fluorescent Labeling of GIST

- Multiple translatable surgical applications:
  - Laparoscopic staging
  - Assessment of margin status or residual disease