The Surgeon’s Role in Contemporary GIST Surgery
How much is enough?

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DISTRIBUTION OF GIST AND OTHER GI MESENCHYMAL NEOPLASMS

- Stomach  44%
- Small Intestine  32%
- Rectum  10%
- Large intestine  5%
- Other*  9%

* intraabdominal, mesentery, omentum, esophagus, diaphragm
PRESENTATION

• Nonspecific
• 50% bleeding
• SB obstruction
• Rare perforation
• 30-50% present ‘urgently’
GIST: PROGNOSTIC FACTORS
MOST IMPORTANT

- size greater than 5.0 cm
- > five mitoses per 50 HPFs
- Necrosis
- Metastases
- Distal location
- High proliferation index: Ki-67 >10%
## GIST: NIH Risk Assessment

<table>
<thead>
<tr>
<th>Size, mm</th>
<th>Mitotic Index 50 HPF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very Low risk</strong></td>
<td>&lt;20</td>
</tr>
<tr>
<td><strong>Low risk</strong></td>
<td>20-50</td>
</tr>
<tr>
<td><strong>Intermediate Risk</strong></td>
<td>&lt;=50</td>
</tr>
<tr>
<td></td>
<td>50-100</td>
</tr>
<tr>
<td><strong>High Risk</strong></td>
<td>&gt;50</td>
</tr>
<tr>
<td></td>
<td>&gt;100</td>
</tr>
<tr>
<td></td>
<td>Any</td>
</tr>
</tbody>
</table>
HISTORICAL PERSPECTIVE

• Before 2000, surgery only effective therapy for $1^0$ or $2^0$ disease

• Even today, no cure without surgery

• Radiation, chemotherapy, IORT, HIPEC ineffective
<table>
<thead>
<tr>
<th>Author (Institution)</th>
<th>Years</th>
<th>Total Patients</th>
<th>Complete Resection</th>
<th>5-year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bearhs (Mayo)</td>
<td>1950-74</td>
<td>108</td>
<td>52</td>
<td>50</td>
</tr>
<tr>
<td>Shiu (MSKCC)</td>
<td>1949-73</td>
<td>38</td>
<td>20</td>
<td>65</td>
</tr>
<tr>
<td>Parker (MCV)</td>
<td>1951-84</td>
<td>51</td>
<td>30</td>
<td>63</td>
</tr>
<tr>
<td>Pollock (MDACC)</td>
<td>1957-97</td>
<td>191</td>
<td>99</td>
<td>48</td>
</tr>
<tr>
<td>DeMatteo (MSKCC)</td>
<td>1982-98</td>
<td>200</td>
<td>80</td>
<td>54</td>
</tr>
</tbody>
</table>
# GIST: Survival by Presentation

<table>
<thead>
<tr>
<th></th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>60</td>
</tr>
<tr>
<td>Metastatic</td>
<td>19</td>
</tr>
<tr>
<td>Locally Recurrent</td>
<td>12</td>
</tr>
<tr>
<td>Metastasis Only</td>
<td>22</td>
</tr>
<tr>
<td>Primary + mets</td>
<td>23</td>
</tr>
<tr>
<td>Local Recurrence + mets</td>
<td>9</td>
</tr>
</tbody>
</table>

DeMatteo Ann Surg 2000
GIST: RECURRENCE AFTER COMPLETE RESECTION

- Recurs in >40% of patients
- Predominant site is intra-abdominal
  - Liver: 2/3
  - Local
  - Peritoneal
EMERGENCY PRESENTATION

• 1/3 of patients have bleeding, obstruction, or perforation
• GIST found unexpectedly
• Must know principles
• Resect if possible
• Do FS before radical surgery to R/O lymphoma or germ cell tumor
PRINCIPLES IN ERA OF IMATINIB

1) Percutaneous biopsy not routinely recommended unless lesion unresectable or change in diagnosis would alter therapy e.g. lymphoma or germ cell tumor

• EUS with FNA and IHC helpful
GIST: CYTOLOGY

Increasing FNAC performed endoscopically

c-kit +ve
PRINCIPLES OF SURGERY IN ERA OF IMATINIB

2) Main Rx for primary resectable GIST is still surgery:
   - clear margins but not radical
   - en bloc resection of involved organs
   - rupturing tumor worsens prognosis
   - no routine lymphadenectomy
3) Imatinib cannot compensate for inadequate initial surgery:

- get grossly clear margins

- microscopic margins may not impact survival
PRINCIPLES IN ERA OF IMATINIB

4) Locally advanced disease:
   - downstage with imatinib (4-6 months)

5) Unsuspected metastases:
   - usually poor prognosis
   - avoid radical surgery unless can safely get clear margins
PRINCIPLES OF SURGERY IN ERA OF IMATINIB

1. Metastatic primary disease - initially Rx with imatinib
   a. if good global response, consider resection with relapse
   b. if global progression, surgery unhelpful
   c. resect single imatinib-resistant clone
PRINCIPLES OF SURGERY IN ERA OF IMATINIB

7) Recurrent disease (>40% of pts.)
   usually intraabdominal

   • prior to imatinib, 1/3 resectable with median survival of 15 months
   • resect isolated liver met with long disease free interval
   • treat local recurrences initially with imatinib
EVALUATING IMATINIB RESPONSES

• Clinical response
• CT can be misleading - no shrinkage
• PET scan - decreased FDG uptake, and often rapid response
WHAT RESULTS CAN BE ANTICIPATED APPLYING THESE PRINCIPLES?
BENEFITS OF SURGERY

- Surgery: curative or palliative intent
- DFS only with surgical resection
- Palliative resection can extend survival
- Optimal extent of surgical resection?
BENEFITS OF SURGICAL RESECTION

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Median survival (months)</th>
<th>n</th>
<th>5 year survival (%)</th>
<th>No resection</th>
<th>Partial resection</th>
<th>Total resection</th>
<th>Radical resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>No resection</td>
<td>10</td>
<td>317</td>
<td>19.2</td>
<td>p&gt;0.000</td>
<td>p&gt;0.000</td>
<td>p&gt;0.000</td>
<td>p&gt;0.000</td>
</tr>
<tr>
<td>Partial resection</td>
<td>51</td>
<td>258</td>
<td>44.7</td>
<td>p&gt;0.000</td>
<td>p=0.218</td>
<td>p&gt;0.000</td>
<td>p&gt;0.000</td>
</tr>
<tr>
<td>Total resection</td>
<td>68</td>
<td>919</td>
<td>51.6</td>
<td>p&gt;0.000</td>
<td>p=0.218</td>
<td>p&gt;0.000</td>
<td>p&gt;0.000</td>
</tr>
<tr>
<td>Radical resection</td>
<td>32</td>
<td>349</td>
<td>29.3</td>
<td>p&gt;0.000</td>
<td>p=0.010</td>
<td>p&gt;0.000</td>
<td>p&gt;0.000</td>
</tr>
</tbody>
</table>
EFFECTS OF IMATINIB ON SURVIVAL

- FDA approval of Imatinib in 2000
- Improved survival in advanced and metastatic GIST
- Initially unclear how to integrate surgery with imatinib
- Clues from SEER data and trials
IMPROVING OUTCOMES OF PATIENTS FOLLOWING SURGICAL RESECTION: THE IMPACT OF IMATINIB

Perez et al

Total

Cum Survival

Survival time (total # of months)
IMPROVING OUTCOMES OF PATIENTS FOLLOWING SURGICAL RESECTION: THE IMPACT OF IMATINIB

Overall
Partial
Total
Radical

Partial

Cum Survival

Survival time (total # of months)

Perez et al
WHO SHOULD RECEIVE IMATINIB?
ACOSOG Z9001: PHASE III TRIAL

• All R0, >3cm, and c kit positive
• Adjuvant Gleevec for 1 year
• Median follow-up 19.7 months
• Recurrence free survival (RFS)- 98 vs 83%
• RFS regardless of size (esp high risk)

DeMatteo, Lancet 2009
WHO SHOULD RECEIVE IMATINIB?

ACOSOG Z9001: PHASE III TRIAL

- See recurrences 6 months after stopping
- Continue imatinib indefinitely if high risk?
- OS similar due to short follow up and crossover design
- Need longer follow up to show if adjuvant Rx increases cure rate

DeMatteo, Lancet 2009
ONE VS 3 YRS ADJUVANT IMATINIB?
HIGH RISK GISTS (SCANDINAVIA)

RFS at 5 years: 66% vs 48% (HR 0.46)

- OS at 5 years: 92% vs 82% (HR 0.45)
- Benefit in exon 11 > exon 9?
- Is longer treatment justified?

Joensuu JAMA 2012
IMATINIB- HOW LONG?
FRENCH SARCOMA GROUP

- Advanced GIST with 1 year of tumor control
- Continuous Rx arm-26 patients with 31% progression
- Interrupted arm- 32 pts 81% progression at median 6 mths even if had no detectable tumor

JCO 2007
IMATINIB- HOW LONG?
FRENCH SARCOMA GROUP

• 92% again responded to imatinib

• Drug holiday not recommended

JCO 2007
IMATINIB- HOW LONG?

FRENCH SARCOMA GROUP (2)

- Advanced GIST with 5 years of tumor control
- Continuous Rx arm-no progression
- Interrupted arm- 45% progression at 1 yr
- Imatinib does not cure advanced GISTs
BENEFIT OF SURGERY (DEBULKING) AFTER IMATINIB FOR ADVANCED DISEASE - F/UP 12 MTHS

• If stable disease: NED 78%, OS 95%
• Limited progression: NED 25%, OS 88%
• General progression: NED 7%, OS 0%

Raut C, JCO 2006
BENEFIT OF SURGERY AFTER IMATINIB FOR ADVANCED DISEASE (134 PTS KOREA)

- If stable disease: resect residual disease
- Time to progression with resection 88 months vs. 43 months with imatinib alone
- Surgery decreased risk of progression by 3X and risk of death by 5X

Park, ASCO 2013
COST EFFECTIVENESS 3 YEARS ADJUVANT IMATINIB (USA COST) QUALITY ADJUSTED LIFE YEARS

- QALYs 8.53 vs 7.18
- Cost $302K vs $217K
- Cost $62K/QALY

Sanon J Med Econ 2013
INTERESTING CASES?
DYSPEPSIA AND ABDOMINAL DISCOMFORT
ACUTE ABDOMINAL PAIN
PREVIOUS RESECTION, STABLE DISEASE
ON IMATINIB
REPEAT EXPLORATION, R0 RESECTION

GIST arising from Jejunum and attached to distal sigmoid colon
STOMACH, PANCREAS, SPLEEN, ADRENAL, DIAPHRAGM

GIST arising from the back of the stomach—prolonged imatinib
R0 resection-
Partial gastrectomy,
distal pancreas,
spleen, left adrenal
STOMACH, LIVER, SPLEEN, AND TRANSVERSE COLON
EIGHT MONTHS OF IMATINIB
EN BLOC RESECTION OF STOMACH, LEFT LOBE OF LIVER, COLON, SPLEEN
R0 RESECTION-INDEFINITE IMATINIB
GIST INVOLVING LIGAMENT OF TREITZ WITH FISTULIZATION
IMAGES PRIOR TO IMATINIB
IMAGES PRIOR TO IMATINIB
POST IMATINIB/PRE-OP IMAGES
POST IMATINIB/PRE-OP IMAGES
D3, D4, PROXIMAL JEJUNUM
NECROTIC GIST
FISTULA INTO DUODENUM
R0 RESECTION- INDEFINITE IMATINIB
OBSTRUCTED FOR 8 MONTHS ON HYPERALIMENTATION-PREVIOUS RESECTIONS INCLUDING RIGHT HEPATIC LOBECTOMY-FLEW DOWN TO OUR HOSPITAL
METASTATIC GIST BUT NON-MALIGNANT SBO

Don’t give up too soon!
Dilated jejunum and collapsed ileum - no disease in liver
Omentectomy and R2 debulking-obstruction was due to internal hernia

Indefinite TKIs
RECTAL GISTS
SHE REFUSED A COLOSTOMY

GIST arising from Rectum
9 months of imatinib
• 66 yo male with urinary frequency and hard, frequent stools with straining
• Firm, fixed anterior mass 2cm above dentate line
• Transrectal biopsy = GIST
- Localized to pelvis-adherent to prostate and seminal vesicles
- R1 resection on prostate
- Primary repair of rectum
- Indefinite TKIs
WHEN TO GIVE UP ON RECURRENCES?
• 61 yo woman presented with abdominal pain in Haiti, underwent exploration for presumed uterine fibroids
• TAH + BSO performed, resection of 24 x 19 x 12cm “uterine leiomyosarcoma”
• Tumor, recurred, diagnosis revised as GIST
• Multiple tumors on CT with response to imatinib
• Ultimate progression of disease
• Changed from imatinib to sunitinib
• Dramatic decrease in abdominal size in just 1 month, tolerating diet, good energy level, feeling well
• Continue sunitinib repeat imaging in 2-3 months, and re-evaluate for debulking
WHO SHOULD RECEIVE IMATINIB?

- Neoadjuvant: locally advanced?
- Therapeutic: Unresectable, metastatic, recurrent disease
• With new therapeutics, the role of surgery in treatment of GIST need to be continuously and repeatedly evaluated.
THANK YOU / QUESTIONS?