Surgical Management of GISTs in the Era of TKIs

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THE LIFE RAFT GROUP
MIAMI FL
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Historical Perspective

- Term GIST coined in 1983
- Cells arise from intestinal pacemaker cells (Interstitial cells of Cajal)
- c-kit was identified as a marker of GIST in 1998 resulting in distinguishing these tumors from leiomyosarcomas
GIST: What is it?

- The most common GI mesenchymal tumor
- About 5000/year in USA
- Most express CD34 and c-kit tyrosine kinase (CD117) by IHC
Presentation

- Nonspecific
- 50% bleeding
- SB obstruction
- Rare perforation
- 30-50% present ‘urgently’
Distribution Of GIST And Other GI Mesenchymal Neoplasms

- Found anywhere in the GI tract
- <3% of all GI cancers
- 20% of SB cancers
## 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
Incidence

- Prior to use of c-kit IHC, GIST was misdiagnosed as smooth muscle tumor
- SEER data set after 2000 indicates 82% of all GI mesenchymal tumors and 96% of gastric tumors are GISTS
Pathology

- 70% spindle cell: cf. leiomyosarcoma
- 30% epithelioid: cf. leiomyoblastoma
- CD 34: 70-80%
- c-kit: 95%
- Often PDGFRA
- Actin: 30%
- Rarely desmin or S100
GI mesenchymal tumors: Classification

Hirota S and Isozaki K. Pathology International 2006
Sporadic (90%) and familial (100%) cases show gain of function mutations of the c-kit gene.
- Sporadic: somatic
- Familial: Germ-line

C-kit is a Tyrosine Kinase receptor encoded by the protooncogene c-kit
GIST: Pathogenesis: c-kit

EC domain

TM domain
JM domain
TK-I domain
KI
TK-II domain

Exon 9
Exon 11
Exon 13
Exon 17

Hirota S and Isozaki K. Pathology International 2006
GIST: Pathogenesis: c-kit

- Natural ligand: Stem cell factor (SCF)
- Two wild-type molecules form a dimer by the binding of 2 molecules of SCF

DIMERIZATION

Hirota S and Isozaki K. Pathology International 2006
GIST: Pathogenesis: c-kit

Dimerization

Phosphorylation of intracellular TK

Cell proliferation and differentiation

$2^0$ to IC signaling cascade

RAS/MAP Kinase, PI3k/Akt pathway
mTOR, p70/85S6K
STAT1, STAT3

Rubin BP. Histopathology 2006
Hirota S and Isozaki K. Pathology International 2006
Gain-of-function mutations of \textit{c-kit} protooncogene

Constitutive tyrosine phosphorylation without SCF
GIST: Pathogenesis: c-kit

Normal Switch

Loss of function mutation

Gain of function mutation

Hirota S and Isozaki K. Pathology International 2006
GIST: *c-kit* Mutations

Identified in 85-90% of GISTs

Mutations result in full-length *c-kit* proteins

<table>
<thead>
<tr>
<th>Location of mutation</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exon 9</td>
<td>Duplication of 502-Ala and 503-Try</td>
</tr>
<tr>
<td>Exon 11</td>
<td>Various mutations from 550-Lys to 592-Gy</td>
</tr>
<tr>
<td>Exon 13</td>
<td>Point mutation of 642-Lys to Gu</td>
</tr>
<tr>
<td>Exon 17</td>
<td>Point mutation of 822-San to Lys or His</td>
</tr>
<tr>
<td></td>
<td>No Mutation= Wild Type</td>
</tr>
</tbody>
</table>

Hirota S and Isozaki K. Pathology International 2006
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%
Historical Perspective

- Before 2000, surgery only effective therapy for $1^0$ or $2^0$ disease
- Even today, no cure without surgery
- Radiation, chemotherapy, IORT, intraop hyperthermic chemotherapy ineffective
## GIST – Pre Imatinib

<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 - Presentation

GIST: DFS By Tumor Size

![Graph showing survival rates by tumor size](image)
GIST: Recurrence After Complete Resection

- Recurs in >40% of patients – most will die from disease.
- Predominant site is intra-abdominal
  - Liver: 2/3
  - Local
  - Peritoneal
Challenges
(1) Diagnosis

- H & P - mass, bleeding (GI or peritoneal), obstruction, or perforation
- Endoscopy
- EUS
- CT/MRI
- PET - including response to Rx
Challenges
(2) Criteria For malignancy

- Metastases
- Invasion of adjacent structures
- Size >5 cm (20%<5 cm metastasize)
- Mitotic index: >5 per 50 HPF
- Necrosis
- Ki-67 index >10%
Challenges

(3) 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
Challenges

(4) Local Extension Or Metastases

- Therapy evolving 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 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
Principles In Era Of Imatinib

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
6) 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 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?

SEER data
Benefits of Surgery

- Surgery: curative or palliative intent
- DFS only with surgical resection
- Palliative resection can extend survival
- Optimal extent of surgical resection?
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
## Improved Survival for Gastric Mesenchymal Neoplasms Including GIST after 2000

<table>
<thead>
<tr>
<th></th>
<th>2-Year Survival Pre-2000</th>
<th>Median Survival (Months)</th>
<th>2-Year Survival Post-2000</th>
<th>Median Survival (Months)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>58.88% (n=525)</td>
<td>&gt;35</td>
<td>73.09% (n=307)</td>
<td>&gt;35</td>
<td>0.0031</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized</td>
<td>78.94% (n=302)</td>
<td>&gt;35</td>
<td>88.3% (n=175)</td>
<td>&gt;35</td>
<td>0.0439</td>
</tr>
<tr>
<td>Regional</td>
<td>36.86% (n=86)</td>
<td>17.78</td>
<td>74.58% (n=54)</td>
<td>&gt;35</td>
<td>0.0117</td>
</tr>
<tr>
<td>Distant</td>
<td>16.67% (n=102)</td>
<td>9.14</td>
<td>35.94% (n=58)</td>
<td>13.3</td>
<td>0.0391</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 4.9cm</td>
<td>76.96% (n=80)</td>
<td>&gt;35</td>
<td>89.18% (n=54)</td>
<td>&gt;35</td>
<td>0.1319</td>
</tr>
<tr>
<td>5-9.9cm</td>
<td>68.7% (n=158)</td>
<td>&gt;35</td>
<td>86.39% (n=103)</td>
<td>&gt;35</td>
<td>0.0104</td>
</tr>
<tr>
<td>10-20cm</td>
<td>57.74% (n=155)</td>
<td>33.23</td>
<td>73.72% (n=80)</td>
<td>&gt;35</td>
<td>0.1762</td>
</tr>
<tr>
<td>Greater than 20cm</td>
<td>40% (n=45)</td>
<td>18.83</td>
<td>43.26% (n=20)</td>
<td>12.01</td>
<td>0.3961</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I,II</td>
<td>80.03% (n=143)</td>
<td>&gt;35</td>
<td>87.22% (n=41)</td>
<td>&gt;35</td>
<td>0.5829</td>
</tr>
<tr>
<td>III,IV</td>
<td>38.24% (n=102)</td>
<td>16</td>
<td>52.22% (n=51)</td>
<td>&gt;35</td>
<td>0.1146</td>
</tr>
</tbody>
</table>
Imatininb for Advanced Disease
B2222 trial - ASCO 2006

- Objective response rate - 68%
- Exon 11 response rate - 87%
- No KIT or PDGFRA mutation – 0% response
- Median time to response – 13 weeks
- Median duration of response - 118 weeks
- Median time to failure – 84 weeks
- Median survival – 4.8 years
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 f-up and crossover design
- Need longer f-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

Lancet Onc 2010
Benefit of Surgery After Imatinib For Advanced Disease- f/up 15 mths

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

Brigham, 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 1 vs 3 Yrs
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
Esophageal Primary

- Dysphagia
- GI bleeding
Acute Abdominal Pain
Difficult, or Inoperable?
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
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 loop of Small Bowel
Dilated jejunum and collapsed ileum - no disease in liver
Contrast in massively dilated jejunum with ‘hungry’ distal bowel
Omentectomy and R2 debulking-obstruction was due to internal hernia. Indefinite TKIs.
Rectal GISTs
- 66 yo male with urinary frequency and hard, frequent stools with straining
- Firm, fixed anterior mass 2cm above dentate line
- Transrectal biopsy = GIST
Rectal GIST

- Treated with imatinib 10 months, tumor stable, symptoms resolved
- Transrectal US confirmed location of mass, unable to assess invasion prostate
- PET/CT decreased SUV uptake
- Localized to pelvis
Rectal GIST

- Lower midline incision
- 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?
Who Should Receive Imatinib?

- Neoadjuvant: locally advanced?
- Therapeutic: Unresectable, metastatic, recurrent disease