Advances in the Surgical Management of GI Stromal Tumors

GIST Summit
September 14, 2013

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Agenda

- Advances in diagnosis and treatment
- Surgical management of GISTs by anatomic site
- Neoadjuvant therapy
- Laparoscopic resection
- Surgical management of metastatic disease
Gastrointestinal Stromal Tumors

- GISTS are rare neoplasms requiring multidisciplinary management
- Management has been revolutionized with the introduction of tyrosine kinase inhibitors
- Rapid progress from bench to bedside
- Rigorous clinical investigation redefining the standards of care
Background

- Approximately 6000 new cases of GIST diagnosed in US each year
- Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor of the GI tract
- Thought to originate from the interstitial cells of Cajal
- Males and females affected equally
- Mean age of 63 years at diagnosis
Diagnostic Criteria

• Anatomic Site: GI-tract, mesentery, omentum, retroperitoneum

• Appropriate histologic appearance

• CD117 (KIT receptor) immuno-reactivity
Distribution of GIST in the GI Tract

Most common anatomic locations of GISTs.\textsuperscript{4,5,7,8}

- Stomach (50\%-70\%)
- Small intestine (20\%-30\%)
- Colon/rectum (<10\%)
- Retroperitoneum (<5\%)
- Omentum/mesentery/esophagus/other (<5\%)
Gastrointestinal Stromal Tumors
Clinical Presentation

Signs/symptoms related to location of tumor

- GI hemorrhage
- Abdominal mass
- Vague GI pain / discomfort
- Anorexia, weight loss, nausea, anemia
- Surgical emergencies – perforation, bleeding

Often asymptomatic, incidental finding
Establishing Diagnosis

- History and Physical Exam
- Pathologic Assessment
  - About 95% of GISTs are positive for KIT (CD117)
- Radiologic Assessment
  
  CT imaging
  - Mass
  - Absence regional lymph node metastases
  - Metastases: liver, implants
## Prognostic Factors

<table>
<thead>
<tr>
<th>Good prognosis</th>
<th>Poor prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor &lt; 5 cm</td>
<td>Tumor &gt; 10 cm</td>
</tr>
<tr>
<td>Low mitotic rate (&lt; 2 /10 HPF)</td>
<td>High mitotic rate (&gt;5–10 /10 HPF)</td>
</tr>
<tr>
<td>Low proliferation index</td>
<td>Tumor rupture</td>
</tr>
<tr>
<td>Absence of necrosis</td>
<td>High proliferation index</td>
</tr>
<tr>
<td>Gastric tumor</td>
<td>Necrosis</td>
</tr>
<tr>
<td>Age &lt; 40 years</td>
<td>Extraintestinal tumor</td>
</tr>
<tr>
<td>Male gender</td>
<td>Male gender</td>
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</tbody>
</table>
Surgical Principles

- Surgical resection is standard practice for localized GIST
  - Generally no role for radiation
  - GISTs are mostly refractory to standard chemotherapy

- Most recurrences distant rather than local
  - Liver or widespread intra-abdominal disease
  - Recurrence rates are about 50% at 5 years

- Goal of surgery: Achieve complete resection
Surgical Principles

- Aim is to resect the tumor with negative margins
  - Small bowel 2-3 cm segmental resection
  - Stomach 1-2 cm wedge resection
- The pseudocapsule of the tumor should not be violated

Warning:
Slides contain photographs of surgical specimens
Small bowel GIST
Tyrosine kinase inhibitors

- Effective in reducing recurrence after surgery and against metastases
- Considered for treating tumors before surgery (neoadjuvant) when tumors are large or in anatomic sites that could benefit from reduction in tumor size before resection

Demetri G et al., N Engl J Med, 2004
GIST Patient Treated With Imatinib:

CT Scan Results: Decrease in Tumor Volume

June 27
Before Therapy

October 4
After Therapy
GIST Prior to Therapy
GIST After Therapy
Treatment of GIST

- Localized Resectable Disease
  - Surgical Resection
  - Extent of resection dependent on anatomic site

- Locally Advanced Unresectable Disease
  - Gleevec (Imatinib mesylate)
  - Surgical resection of residual disease (if downstaged)
    - (little prospective data to support survival benefit)

- Metastatic Disease
  - Gleevec - FDA approved 2002
  - Possible surgical resection of residual disease
    - (if response)
  - Secondary resistance (median 24 months)
    - – dose escalation, sunitinib or other trials
Esophageal GIST

- Tumors < 2cm that don’t involve adjacent structures can be resected.
- Tumors > 2cm and those close to juncture of stomach may require esophagectomy (through left abdominothoracic incision).
- Large tumors that involve other structures (such as diaphragm) may require imatinib treatment before surgery (neoadjuvant) to reduce the size of the tumor first.
Gastric GIST

- < 2cm tumors may be managed nonoperatively
  - Endoscopic surveillance to monitor growth
- Tumors near esophagus may be surgically removed to avoid more extensive resection
- Tumors > 3cm or with chance of invading other organs such as liver or diaphragm should be considered for neoadjuvant imatinib
- Tumors in mid-body of stomach could be resected laparoscopically
Gastric GIST
GIST of small intestine

- Neoadjuvant imatinib may be considered for duodenal GIST because of proximity to pancreas
- Tumors in jejunum and ileum are often relatively large because of later diagnosis
  - <5 cm possible laparoscopic resection
  - Other organs may be involved and could benefit from neoadjuvant imatinib
Small bowel GIST after therapy
Small bowel GIST involving the mesentery
GIST of colon or rectum

- Tumors < 3cm can be considered for resection
- Tumors that may involve sphincters or other organs could be considered for neoadjuvant imatinib to reduce need for radical resection or colostomy.
Rectal GIST before and after treatment
Neoadjuvant therapy

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

  - 1% complete response, 73% partial response, 9% stable disease, 1% progressive disease
  - Responding patients had a median decrease in tumor volume of 85% (27-99%)
Neoadjuvant Therapy for GIST

Locally Advanced Primary

Metastatic/Recurrent

Potential Benefits

- Decreased tumor size
- Decreased surgical complexity
- In situ measure of drug response

- Assessment of tumor biology
- Early treatment of microscopic distant disease
Neoadjuvant Therapy for GIST

- Randomized phase II trial
  - 19 pts received neoadjuvant imatinib for 3, 5, or 7 days
  - No effects on surgical morbidity
  - Increased tumor apoptosis with increased exposure
  - 62% had evidence of radiographic response

  McAuliffe et al, Ann Surg Onc, 2009

- RTOG 0132
  - Multi-institutional prospective trial of 53 pts
  - 2 months neoadjuvant imatinib + 2 yrs adjuvant therapy
  - No significant effects on surgical morbidity
  - 5 yr PFS: 57% in primary and 30% in metastatic/recurrent
  - 5 yr OS: 77% in primary and 68% in metastatic/recurrent

Laparoscopic Resection for GIST?
Laparoscopic ports
A total of 11 nonrandomized studies reviewed 765 patients: 381 LR and 384 OR.

A higher proportion of high-risk tumors and gastrectomies in the OR compared with LR.

LR results in superior short-term postoperative outcomes without compromising oncological safety and long-term oncological outcomes compared with OR.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Recruitment period</th>
<th>Country</th>
<th>Study design</th>
<th>LR</th>
<th>OR</th>
<th>Conversion</th>
<th>Mean/median size (cm)</th>
<th>Inclusion/exclusion</th>
<th>Study quality scoring scale</th>
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<td>China</td>
<td>Retro</td>
<td>68</td>
<td>88</td>
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<td>Lee15</td>
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<td>2001-2008</td>
<td>Korea</td>
<td>Retro</td>
<td>50</td>
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<td>1</td>
<td>2.9</td>
<td>70% of cases GIST only</td>
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<td>39</td>
<td>1</td>
<td>4.0</td>
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<td>31</td>
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<td>5.0</td>
<td>10 patients with metastatic GIST</td>
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</table>

Study quality based on Newcastle Ottawa Scale with maximum of 4 for selection, 3 for comparability and 2 for outcome.
Tumor size impacts surgical approach
Gastric GIST
Prognostic Factors Determining Outcome after Surgical Resection

- Tumor size
- Mitotic index
- Location
Nomogram for Predicting Recurrence-Free Survival

Prognostic Factors Determining Outcome after Surgical Resection

- Tumor size
- Mitotic index
- Location
- Mutation type: deletion and insertion mutations in \textit{KIT} exon 11 and 9
Is there a role for surgery in patients with metastatic disease?
Favorable Prognostic Factors following GIST Recurrence

- Disease-free interval >20 months from primary tumor resection to recurrence
- Recurrence limited to *either* peritoneal cavity or liver
- Complete resection of metastatic disease

Langer et al., BJS 2003.
Duodenal Mass with Liver Metastases: GIST
Metastatic GIST and response to therapy

**Initial**

**3 months**

Before Gleevec

After Gleevec
Outcomes based on response


Figure 2. Kaplan-Meier curve for disease-specific survival from the time of imatinib onset according to response at the time of selection for surgery ($P < 0.01$).
Future of GIST Therapies

- Recent scientific advances have had a profound impact in patient care
- Molecular mechanisms of drug resistance
- Identification of new targets for therapy
- Development of novel agents
- Addressing subpopulations of GIST progenitor cells and stem cells
Conclusions

• Wide clinical spectrum of GISTs from benign to more malignant tumor behavior which can be predicted based on:
  - tumor size
  - mitotic activity
  - anatomic site

• High risk GISTs have high rate of recurrence requiring multidisciplinary management
Conclusions

• No standard management of recurrent/metastatic GIST

• Important prognostic factors to consider when considering surgical resection of recurrent GIST
  - prior response to Gleevec
  - disease-free interval
  - location and number of tumor(s)
  - symptomatic tumors
  - availability other targeted agents or clinical trials
Future directions

- What is optimal duration of neoadjuvant imatinib treatment?
- Need to be able to measure response
  - Functional imaging
- New prognostic systems needed for risk stratification
  - Consider mutation status and therapy
- What is the optimal duration of adjuvant treatment?
Thank you!