The Role of Surgery in GIST Treatment
Neoadjuvant and Adjuvant Therapy

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Surgical Resection May Be Curative…
Goals of Resection in GIST > 2 cm

- Total gross resection without tumor rupture (including disruption of tumor capsule)
- Negative microscopic margins (R0)
- Lymphadenectomy is not generally indicated because LN metastases are uncommon outside SDH-def GIST and gene fusion GIST
Complete Resection

Not Always Possible

### Factors to Consider

<table>
<thead>
<tr>
<th>Biology</th>
<th>Location &amp; Anatomy</th>
<th>Good</th>
<th>Bad</th>
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<tbody>
<tr>
<td>Good</td>
<td>Good Location</td>
<td>Good Biology</td>
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**Neoadjuvant Therapy?**
Definitions

Neoadjuvant Therapy → Operation → Adjuvant Therapy
NCCN & ESMO Recommendations

**Neoadjuvant Treatment**

1. Marginally resectable disease (i.e., locally advanced or large tumors) where total gross resection may not be feasible
2. Likely positive margins
3. Potential for adjacent organ sparing
4. Opportunity for less extensive operation
5. Potential for safer operation (e.g., less bleeding or lower risk of tumor rupture)
# Studies to Support Safety and Efficacy

<table>
<thead>
<tr>
<th>Trial (phase)</th>
<th>Imatinib dosage and duration</th>
<th>Patients</th>
<th>Outcomes</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG S032/ ACRIN 6665&lt;sup&gt;49&lt;/sup&gt; Phase II, nonrandomized, prospective trial</td>
<td>Neoadjuvant: 600 mg/d for 8–12 wk&lt;br&gt;Adjuvant: 400 mg/d for 2 yrs&lt;br&gt;Follow-up: 3 yr</td>
<td>( N = 63 )&lt;br&gt;(52 analyzable): 30 with primary GIST; 22 with recurrent/metastatic</td>
<td>Primary GIST: 7% PR; 83% SD; 10% unknown&lt;br&gt;Recurrent GIST: 4.5% PR; 91% SD; 4.5% PD&lt;br&gt;2-yr PFS: 83% for primary; 77% for recurrent&lt;br&gt;2-yr OS: 93% for primary; 91% for recurrent</td>
<td>Post-operative toxicities: 29% Gr 3; 16% Gr 4; 4% Gr 5</td>
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<tr>
<td>BFR14 substudy&lt;sup&gt;59&lt;/sup&gt; Phase III, BFR14 database sub-analysis (retrospective)</td>
<td>Median treatment duration prior to surgery: 7.3 mo</td>
<td>( N = 25 ) (9 patients underwent resection) locally advanced GIST without metastases</td>
<td>Median PFS: not reached for resected vs 29.4 mos for non-resected&lt;br&gt;Median OS: Median not reached for resected vs 42.2* months for non-resected</td>
<td>NA</td>
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</table>

Eisenberg and Trent. *Int J Cancer*. 2011.
“Bad” Location

• Gastroesophageal junction
  • Avoid total gastrectomy

“Bad” Location

**Gastroesophageal junction**
- Avoid total gastrectomy

**Duodenum**
- Avoid Whipple(s) operation (pancreaticoduodenectomy)

“Bad” Location

- **Gastroesophageal junction**
  - Avoid total gastrectomy

- **Duodenum**
  - Avoid Whipple(s) operation (pancreaticoduodenectomy)

- **Rectum**
  - Avoid Low Anterior Resection (LAR)
  - Avoid Abdominoperineal Resection (APR)

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Bad Location + Bad Biology
Biology Beats Technique

If Tumors Respond... *Patients Do Better.*

Progression-Free Survival

Overall Survival

Neoadjuvant Therapy Summary

• Neoadjuvant imatinib therapy is generally safe for patients with GIST, but bleeding with response may occur.

• Treatment is usually recommended for 6-9 months to achieve maximal response.

• Treatment may be stopped earlier if additional response will not change conduct or safety of the operation.

• Imatinib may be stopped immediately before an operation and may be restarted once the patient has recovered.

• Tumor mutation analysis may help exclude patients with imatinib-resistant mutations (e.g., PDGFRA D842V) from consideration for neoadjuvant imatinib therapy.

• Currently lacking established safety data for neoadjuvant avapritinib for PDGFRA D842V mutant GIST.
Risk of Recurrence (ROR)

- Resection is the primary treatment for localized GIST
- However, it is not routinely curative despite complete gross resection
  - >50% patients will develop recurrence or metastasis
  - 5-year OS rate is ~50%\(^1,2\)

### ROR Depends on 4 Prognostic Factors

<table>
<thead>
<tr>
<th>Assessment Methodology</th>
<th>Mitotic Rate</th>
<th>Tumor Size</th>
<th>Tumor Site</th>
<th>Tumor Rupture</th>
<th>Peritoneal Dissemination</th>
<th>Mucosal Invasion</th>
<th>Mutational Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fletcher, et al, 2002 (NIH Guidelines)¹</td>
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<td>Huang, et al, 2007²</td>
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<td>Miettinen, et al, 2006³</td>
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<td>Mucciarini, et al, 2007⁴</td>
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<td>Hassan, et al, 2008⁵</td>
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<td>DeMatteo, et al, 2008⁶</td>
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<td>Joensuu, 2008 (Modified NIH)⁷</td>
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<td>Gold, et al, 2009⁸</td>
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<td>Takahashi, et al, 2007⁹</td>
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<td>Singer, et al, 2002¹⁰</td>
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<td>Edge, et al, 2010¹¹</td>
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<td>Joensuu, et al, 2012¹²</td>
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Modified NIH Criteria (Joensuu)

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<tr>
<th>Risk category</th>
<th>Tumor size (cm)</th>
<th>Mitotic index (per 50 HPFs)</th>
<th>Primary tumor site</th>
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</thead>
<tbody>
<tr>
<td>Very low risk</td>
<td>&lt;2.0</td>
<td>≤5</td>
<td>Any</td>
</tr>
<tr>
<td>Low risk</td>
<td>2.1-5.0</td>
<td>≤5</td>
<td>Any</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>2.1-5.0</td>
<td>&gt;5</td>
<td>Gastric</td>
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<tr>
<td></td>
<td>&lt;5.0</td>
<td>6-10</td>
<td>Any</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</td>
<td>Any</td>
<td>Tumor rupture</td>
</tr>
</tbody>
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**Mitotic Index (MI)**
- Mitoses per 50 hpf (old microscopes)
- Mitoses per 20 hpf (new microscopes)
- Mitoses per 5 mm² (standardized)

Tumor rupture is a poor prognostic factor

Definitions

Neoadjuvant Therapy → Operation → Adjuvant Therapy
Adjuvant Imatinib Therapy

- **Total trials = 12**
  - Pilot/retrospective studies (N=2)
  - Phase II (N=7)
  - Phase III (N=3)

- **Duration of therapy**
  - Duration ≤ 1 year (N=5)
  - Duration ≥ 1 year (N=7)

2 Pivotal Trials
Phase III randomized, double-blind, placebo-controlled ACOSOG Z9001

- Multicenter
- 713 patients with KIT-positive GIST of ≥3 cm in size
- Treated with imatinib (359) or placebo (354) for 1 year
- Estimated 1-year RFS rate was significantly higher in the imatinib arm (98%) compared with the placebo arm (83%; [HR], 0.35; \(P < 0.0001\)) >> early termination
- No difference in OS at 4 years of follow-up.
- FDA Approval in 2009 for adjuvant imatinib

Corless et al., *JCO*, 2010.
Adjuvant Imatinib for High ROR

- Phase III RCT
- Scandinavian Sarcoma Group (SSG) XVIII/AIO
- Patients with high risk GIST (modified NIH):
  - Rule of 10s
    - >10 cm
    - MI >10
    - >5 cm + MI >5
    - Tumor rupture


5-year OS
92% (3 yr)
81.7% (1 yr)

Adjuvant Imatinib for 3 years is now the gold standard for high-risk GIST
Optimal Duration of Adjuvant Therapy?

Recurrences begin at 8 months after stopping therapy. Many experts will recommend indefinite imatinib or until recurrence/intolerance

Joensuu et al., JAMA, 2012
Adjuvant Therapy Summary

• Assessing an individual patient’s risk for GIST recurrence is essential, as GIST may recur despite complete gross resection.

• Risk assessment is complex, with 4 factors reported to be predictive of recurrence.

• If a patient is recommended for adjuvant imatinib therapy, mutation profiling should be performed as only KIT and select PDGFRA mutations are imatinib sensitivity.

• Adjuvant imatinib for >3 years is the gold standard for high-risk GIST (modified NIH Criteria) with consideration of 5 years (or even lifelong) therapy, although one may consider tailoring this to intermediate risk patients in select cases.
THANK YOU!

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