GIST 201: The Pathology of GIST: 10th Anniversary GIST Summit (GSI)

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Saturday 22 September 2018
Disclosures

• Research Support / Consulting
  – AstraZeneca / Medimmune
  – BMS
  – Novartis
  – Roche / Genentech
  – Merck
  – GlaxoSmithKline
  – Myriad
  – Oncothyreon
  – Life Tech
  – Illumina
  – GE Healthcare
  – Beta-Cat
  – ArcherDX
GIST Pathology: Lecture Overview

1. What information should be in my pathology report?

2. Why is this information there?

3. What is the evidence that the information is useful?
What happens to my tumor in pathology?
Tumor sample is received from the OR and logged into computer.

Tumor is examined by a pathologist.
Tumor is sampled and placed in plastic cassettes for further processing. Tumor is also given to cytogenetics, tumor bank, molecular diagnosis and electron microscopy when appropriate.
The tissue blocks are fixed in formalin and then loaded on a tissue processor overnight.
Tissue processing is done overnight and utilizes graded treatments of formalin, ethanol, xylene and paraffin.
Blocks are retrieved from the tissue processor.
The tissue fragments are embedded in a paraffin mold and cooled – resulting in a tissue block.
The paraffin-embedded blocks are loaded and cut using a microtome.
Tissue paraffin ribbons are placed in a warm waterbath and then picked up on glass slides.
The unstained slides can be used for H&E, special stains, immuno-histochemistry, molecular studies, etc.
Most slides are H&E (hemotoxlin & eosin) stained, given coverslips, organized and delivered to the proper pathologist.
Additional unstained slides can be cut at a later time.
After final diagnosis, both slides and the paraffin blocks from which they are cut are cataloged and stored for future use.
What information should be in my pathology report?
Protocol for the Examination of Specimens From Patients With Gastrointestinal Stromal Tumor (GIST)

Based on AJCC/UICC TNM, 7th edition
Protocol web posting date: June 2012

Procedures
• Biopsy
• Resection

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GASTROINTESTINAL STROMAL TUMOR (GIST): Resection

Select a single response unless otherwise indicated.

Procedure
___ Excisional biopsy
___ Resection
      Specify type (e.g., partial gastrectomy): __________
___ Metastasectomy
___ Other (specify): _________________________
___ Not specified

Tumor Site
Specify (if known): _________________________
___ Not specified

Tumor Size
Greatest dimension: ___ cm
+ Additional dimensions: ___ x ___ cm
___ Cannot be determined (see “Comment”)

Tumor Focality
___ Unifocal
___ Multifocal
      Specify number of tumors: ______
      Specify size of tumors: _____________

GIST Subtype
___ Spindle cell
___ Epithelioid
___ Mixed
___ Other (specify): ______________________
Mitotic Rate
Specify: ___ /50 HPF

Note: The required total count of mitoses is per 5 mm² on the glass slide section. With the use of older model microscopes, 50 HPF is equivalent to 5 mm². Most modern microscopes with wider 40X lenses/fields require only 20 HPF to embrace 5 mm². If necessary please measure field of view to accurately determine actual number of fields required to be counted on individual microscopes to count 5 mm².

+ Necrosis
+ ___ Not identified
+ ___ Present
  + Extent: ___%
+ ___ Cannot be determined
Risk Assessment (Note C)

___ None
___ Very low risk
___ Low risk
___ Intermediate risk
___ High risk
___ Overtly malignant/metastatic
___ Cannot be determined

Margins

___ Cannot be assessed
___ Negative for GIST
   Distance of tumor from closest margin: ___ mm or ___ cm
___ Margin(s) positive for GIST
   Specify margin(s): __________________

Pathologic Staging (pTNM) (Note G)

TNM Descriptors (required only if applicable) (select all that apply)
___ m (multiple)
___ r (recurrent)
___ y (posttreatment)

Primary Tumor (pT)

___ pTX: Primary tumor cannot be assessed
___ pT0: No evidence for primary tumor
___ pT1: Tumor 2 cm or less
___ pT2: Tumor more than 2 cm but not more than 5 cm
___ pT3: Tumor more than 5 cm but not more than 10 cm
___ pT4: Tumor more than 10 cm in greatest dimension

Regional Lymph Nodes (pN) (Note D)

___ Not applicable
___ pN0: No regional lymph node metastasis
___ pN1: Regional lymph node metastasis

Distant Metastasis (pM) (Note D)

___ Not applicable
___ pM1: Distant metastasis
   + Specify site(s), if known: __________________

+ Additional Pathologic Findings
+ Specify: __________________
Ancillary Studies (select all that apply) (Note E)

**Immunohistochemical Studies**
- ___ KIT (CD117)
  - ___ Positive
  - ___ Negative
- ___ Others (specify): ______________________
- ___ Not performed

**Molecular Genetic Studies (eg, KIT or PDGFRA mutational analysis)**
- ___ Submitted for analysis; results pending
- ___ Performed, see separate report: ______________________
- ___ Performed
  - Specify method(s) and results: ______________________
- ___ Not performed

**Preresection Treatment (select all that apply)**
- ___ No therapy
- ___ Previous biopsy or surgery
  - Specify: ______________________
- ___ Systemic therapy performed
  - Specify type: ______________________
- ___ Therapy performed, type not specified
- ___ Unknown

**+ Treatment Effect (Note F)**
- + Specify percentage of viable tumor: ___%

**+ Comment(s)**
Getting the diagnosis right
Case 1

Female, aged 40, with 25 cm mass involving the small bowel.
Case 2

Male, aged 38, with 10 mm polyp at 10 cm in rectum.
Case 3
Male, aged 36, with 17 cm gastric wall mass.
Case 5

Female, aged 29, with 10 cm gastric wall mass.
<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>KIT</th>
<th>CD34</th>
<th>Ker</th>
<th>SMA</th>
<th>DES</th>
<th>S-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIST</td>
<td>+</td>
<td>+(70%)</td>
<td>-</td>
<td>+(40%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+(sar)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Melanoma</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Leiomyoma</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Schwannoma</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Fibromatosis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Immunohistochemical Profile of GISTs (Circa 1997 and prior)

CD34 +ve (70%)
SMA +ve (30-40%)
Desmin –ve
S-100 protein –ve
Keratin –ve

Courtesy of Brian Rubin, U. Washington
Gastrointestinal Stromal Tumor

- Arise from the interstitial cells of Cajal (ICC)
- ICC have a “pacemaker” function and are important in coordinating peristalsis

Hornick & Lazar. GSI website: Understanding Your Pathology Report for GIST
**Immunohistochemical Profile of GIST**

<table>
<thead>
<tr>
<th>H&amp;E</th>
<th>CD117 (KIT)</th>
<th>CD34</th>
<th>Smooth muscle actin</th>
<th>S100 protein</th>
<th>Desmin</th>
<th>Pan-keratin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>95%</td>
<td>70%</td>
<td>30%</td>
<td>5%</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

- **KIT (CD117) +ve (95%)**
- **CD34 +ve (70%)**
- **SMA +ve (30-40%)**
- **Desmin –ve**
- **S-100 protein –ve**
- **Keratin –ve**
The many faces of GIST
Clinical Characteristics of GIST

Wide age range – peak in 5th-7th decade

M = F

Small lesions = “incidentalomas”

Presenting symptoms include:
abdominal pain,
gastrointestinal bleeding,
early satiety,
symptoms referable to a mass
Exon 11
V559_V560del

6 bp del?  
TT GT

gag gag ata act

(V559-V560del)
Exon 9
A502_Y503dup
Detection of SNV in KIT Exon 10,
KIT immunoreactivity in GIST
KIT-negative GIST
Gastric GISTs with Distinctive Histology (Multinodular/Plexiform)

- Pediatric GISTs
  Female predominance (peak 2\textsuperscript{nd} decade)
  Indolent, but late metastases common
  Molecular genetic basis unknown

Carney Triad
  Gastric GIST, pulmonary chondroma, paraganglioma
  Molecular genetic basis unknown

Carney-Stratakis Syndrome
  Gastric GIST and paraganglioma
  Germline mutations in succinate dehydrogenase subunit genes (\textit{SDHA, SDHB, SDHC, or SDHD})
GIST with Distinctive Histology

- Multinodular/plexiform growth pattern
- Epithelioid or mixed morphology
- “Pediatric-type” or “type 2” GISTs
- Loss of SDHB staining by IHC
- Lymph node metastases common
- Distant metastases common – clinically indolent
- Current risk assessment criteria do not reliably predict behavior
- No response to imatinib
11-year-old female

Courtesy of Jason Hornick, BWH/Harvard, Boston, MA
Pediatric-type GIST in an Adult

49-year-old female

Courtesy of Jason Hornick, BWH/Harvard, Boston, MA
“Wild-type” gastric GIST
Risk assessment in GIST
GIST – Prognostic Factors

- **Size**
- **Mitotic Rate**
- **Anatomic Location**
  - Pleomorphism
  - Cellularity
  - Necrosis
  - Mucosal Invasion
- Proliferation Markers (Ki-67, Mib-1, PCNA, etc)
- DNA Flow Cytometry
- Image Analysis
- Nuclear Organizer Regions

Problem – Small GISTs without mitoses can metastasize!
### NIH Consensus Risk Assessment

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Size</th>
<th>Mitotic Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low Risk</td>
<td>&lt; 2 cm</td>
<td>&lt; 5/50 HPF</td>
</tr>
<tr>
<td>Low Risk</td>
<td>2-5 cm</td>
<td>&lt; 5/50 HPF</td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>&lt; 5 cm</td>
<td>6-10/50 HPF</td>
</tr>
<tr>
<td></td>
<td>5-10 cm</td>
<td>&lt; 5/50 HPF</td>
</tr>
<tr>
<td>High Risk</td>
<td>&gt; 5 cm</td>
<td>&gt; 5/50 HPF</td>
</tr>
</tbody>
</table>

Fletcher et al., Hum Pathol, 2002
GIST: Sites of Involvement

- **Stomach**: 60%
- **Small intestine**: 25%
- **Esophagus**: 8%
- **Rectum**: 5%
- **Other (colon, mesentery, retroperitoneum)**: 2%
- **Omentum, mesentery, pelvis and retroperitoneum = EGIST (<1%)**

Hornick & Lazar. GSI website: Understanding Your Pathology Report for GIST.
### 2007/2010/2014 NCCN GIST Risk Assessment Guidelines***

<table>
<thead>
<tr>
<th>Tumor Parameters</th>
<th>Size</th>
<th>Gastric</th>
<th>Duodenum</th>
<th>Jejunum/Ileum</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mitotic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 2 cm</td>
<td></td>
<td>None (0%)</td>
<td>None (0%)</td>
<td>None (0%)</td>
<td>None (0%)</td>
</tr>
<tr>
<td><strong>Index</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 2 ≤ 5 cm</td>
<td></td>
<td>Very low (1.9%)</td>
<td>Low (8.3%)</td>
<td>Low (4.3%)</td>
<td>Low (8.5%)</td>
</tr>
<tr>
<td>≤ 5 per 50 hpf</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 5 ≤ 10 cm</td>
<td></td>
<td>Low (3.6%)</td>
<td>(Insuff. data)</td>
<td>Moderate (24%)</td>
<td>(Insuff. data)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 10 cm</td>
<td></td>
<td>Moderate (10%)</td>
<td>High (34%)</td>
<td>High (52%)</td>
<td>High (57%)</td>
</tr>
<tr>
<td><strong>Mitotic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 2 cm</td>
<td></td>
<td>None*</td>
<td>(Insuff. data)</td>
<td>High*</td>
<td>High (54%)</td>
</tr>
<tr>
<td><strong>Index</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 2 ≤ 5 cm</td>
<td></td>
<td>Moderate (16%)</td>
<td>High (50%)</td>
<td>High (73%)</td>
<td>High (52%)</td>
</tr>
<tr>
<td>&gt; 5 per 50 hpf</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 5 ≤ 10 cm</td>
<td></td>
<td>High (55%)</td>
<td>(Insuff. data)</td>
<td>High (85%)</td>
<td>(Insuff. data)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 10 cm</td>
<td></td>
<td>High (86%)</td>
<td>High (86%)</td>
<td>High (90%)</td>
<td>High (71%)</td>
</tr>
</tbody>
</table>

***Modified from Miettinen & Lasota, *Semin Diagn Pathol*, 2006 by Dr. Chris Corless, OHSU
Data based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal and 111 rectal GIST
GIST - Gross Appearance

Courtesy of Brian Rubin, Cleveland Clinic

<table>
<thead>
<tr>
<th>Tumor Parameters</th>
<th>Risk of Progressive</th>
<th>Disease# (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Size</td>
<td>Gastric</td>
</tr>
<tr>
<td><strong>Mitotic</strong></td>
<td>≤ 2 cm</td>
<td>None (0%)</td>
</tr>
<tr>
<td><strong>Index</strong></td>
<td>&gt; 2 ≤ 5 cm</td>
<td>Very low (1.9%)</td>
</tr>
<tr>
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<tr>
<td></td>
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</tr>
<tr>
<td><strong>Mitotic</strong></td>
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<td>None*</td>
</tr>
<tr>
<td><strong>Index</strong></td>
<td>&gt; 2 ≤ 5 cm</td>
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<tr>
<td><strong>&gt; 5 per 50 hpf</strong></td>
<td>&gt; 5 ≤ 10 cm</td>
<td>High (55%)</td>
</tr>
<tr>
<td></td>
<td>&gt; 10 cm</td>
<td>High (86%)</td>
</tr>
</tbody>
</table>

***Modified from Miettinen & Lasota, Semin Diagn Pathol, 2006 by Dr. Chris Corless, OHSU. Data based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal and 111 rectal GIST.**
GIST - Recurrence-Free Survival Following Surgical Treatment of Primary GIST

- Recurrence-free survival is predicted by tumor size and mitotic index

FNCLCC Grading

• All three numbers are summated to determine degree of differentiation

Grade 1 : 2-3
Grade 2 : 4-5
Grade 3 : 6-8

• Proven to correlated well with survival

• **Mitotic Count.** In the most mitotically active area, ten successive high-power fields (at 400x magnification=0.1734 mm²) using a 40x objective.
  1. 0-9 mitoses per 10 HPFs
  2. 10-19 mitoses per 10 HPFs
  3. >20 mitoses per 10 HPFs

• **Tumor necrosis.** Evaluated on gross examination and validated with histological sections
  0 No tumor necrosis
  1. <50% tumor necrosis
  2. >50% tumor necrosis

• **Degree of Differentiation.** 1-3
Genomic complexity and prognosis

Possible approaches

• (Histological grading)

• Risk assessment +:
  – Array-CGH
  – Carter signature
  – Next generation Sequencing
Spectrum of KIT Exon 11 Mutations

The recommendations for adjuvant imatinib therapy by integration of the risk assessment (based on modified NIH classification) and tumor genotype [KIT ex. 9 p.A502_Y503dup, KIT ex. 11 (KITdel-inc557/558 and other), and PDGFRA ex. 18 (p.D842V and other)] in ...

* Metastatic/locally advanced GIST with KIT ex. 9 mutations respond better to 800 mg imatinib daily (compared with the standard 400 mg). Therefore, increased dose may be considered in the adjuvant setting.

Chromosomal complexity and prognosis

97 chromosomes and more than 50 translocations

Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)
CINSARC: GO analysis of the 67 significant genes

CINSARC is a signature related to chromosome management and mitosis control associated with genome complexity.

Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)
Chromosomal instability signature
Carter et al Nat Genet 2002

- Computational method for evaluating aneuploidy
- Analysis of genes differentially expressed according to the level of aneuploidy
- Aneuploidy is a consequence of chromosomal instability (CIN)
- CIN70 signature predicts survival in several types of cancers
- No prediction in French series of sarcomas

Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)
CINSARC: arrayCGH analysis and correlation with FNCLCC grading

« Arm » Profile

« Rearranged » Profile

Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)
Molecular grading in sarcomas

3 tests to compare the expression profiles of tumors classified according to:

- **CGH**: 86 genes
- **Grade**: 73 genes
- **Carter**: 39 genes

**GO analysis:**
To identify the underlying pathways
Selection of genes involved in the most significantly overrepresented pathways (p<10^{-5})

- 37 genes
- 18 genes
- 39 genes

67 genes

Chibon et al, Nat Med 2010; 16: 781-7

Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)
CINSARC: Prognostic signature?

Prognostic value of CINSARC:
Metastasis free survival

Cohort 1

Cohort 2

Multivariate analysis

CINSARC is an independent prognostic factor

Courtesy of J-M Coindre & F Chibon,
Bordeaux, France (Fresch Sarcoma Group)
CINSARC and GIST

In-silico study of 32 GISTs
(Yamaguchi et al 2008)

n=32
p=0.003

Metastasis-free survival

In-silico study of 32 GISTs
(Yamaguchi et al 2008)

n=16

Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)
GIST (n=42)

LMS (n=30)
<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>10</th>
<th>14</th>
<th>15</th>
<th>22</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIS 1:</td>
<td>-1p distal, -22q</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GIS 2:</td>
<td>-1p distal, -22q, -14q</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>GIS 3:</td>
<td>-1p, -22q, -14q, -15q</td>
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<td></td>
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<td></td>
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<tr>
<td>GIS 4:</td>
<td>-1p, -22q, -14q, -15q, -10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Genomic Index (GI) is a prognostic factor in GIST...

\[ GI = \frac{\text{Alt}^2}{n} \]

\[ n = 66 \]
\[ p = 8.9 \times 10^{-10} \]

\[ \text{DFS} \]

\[ \text{GI}<10 \]
\[ \text{GI}>10 \]

Genomic Index (GI) is a prognostic factor in GIST...

- Frozen tissue is rarely available
- Method applicable on paraffin tissue
- Genomic Index (GI) on CGH

Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)
GIST and molecular signature


Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)
More Data

82 intermediate-risk (AFIP) GISTS Array CGH from FFPE blocks

- Leuven (M Debiec-Rychter)
- Köln (E Wardelmann)
- Warsaw (P Rutkowski)
- Treviso (AP Dei Tos)
- French Sarcoma Group

Treatment can cause big changes.
Treatment effect

Pre-Imatinib  Post-Imatinib (8 weeks therapy)
Case No. 22 - Marked Effect – 7 days pre-op (exon 11)
Case No. 12 - Marked Effect – 5 days pre-op (exon 11)
Case 8. - Moderate Effect – 3 days pre-op (exon 11)
Case 11. - Moderate Effect – 5 days pre-op (exon 11)
Case 20. Minimal Effect – 5 days pre-op (exon 11)
Long term Imatinib Tx
Long term Imatinib Tx
Thanks!
Acknowledgements

• Brian Rubin, Cleveland Clinic.
• Jason Hornick, Brigham & Women’s Hospital/Harvard
• Jean-Michel Coindre & Frederic Chibon, Bordeaux, France (French Sarcoma Group)
• Michael Heinrich & Chris Corless, University of Oregon.
• Jon Trent, University of Miami.
• Many Fine Colleagues at UTMDACC.