GIST 201: Why Pathology & Your Pathologist Matter

GSI Patient Summit Saturday 13 September 2014

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GIST Pathology: Lecture Overview

1. What happens to my tumor in pathology?
2. What information is in my pathology report?
3. Why is this information there?
4. 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 is 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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For the Members of the Cancer Committee, College of American Pathologists

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GASTROINTESTINAL STROMAL TUMOR (GIST): Resection

Select a single response unless otherwise indicated.

Procedure
____ Excisional biopsy
____ Resection
   Specify type (eg, 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
Histologic Grade (Note B)
- Gx: Grade cannot be assessed
- G1: Low grade; mitotic rate ≤5/50 HPF
- G2: High grade; mitotic rate >5/50 HPF

Risk Assessment (Note C)
- None
- Very low risk
- Low risk
- Intermediate risk
- High risk
- Overly 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)
- 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 37, with 13 cm gastric wall mass.
SMA
Des
panK
S-100 p
KIT
Case 4

Male, aged 36, with 17 cm gastric wall mass.
Case 5
Female, aged 29, with 10 cm gastric wall mass.
# Immunohistochemical Scheme

<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**

- KIT (CD117) +ve (95%)
- CD34 +ve (70%)
- SMA +ve (30-40%)
- Desmin −ve
- S-100 protein −ve
- Keratin −ve

The many faces of GIST.
Exon 11
V559_V560del
Exon 9
A502_Y503dup

A502_Y503 dup
Detection of SNV in KIT Exon 10, currently not covered by Sanger
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}, \textit{SDHB}, \textit{SDHC}, or \textit{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
Pediatric-type GIST in an Adult

49-year-old female

Courtesy of Jason Hornick, BWH/Harvard, Boston, MA
Metastatic pediatric-type GIST
SDHB

KIT exon 11-mutant GIST
SDHB

"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>
<tr>
<td></td>
<td>&gt; 10 cm</td>
<td>Any Mitotic Rate</td>
</tr>
<tr>
<td></td>
<td>Any Size</td>
<td>&gt; 10/50 HPF</td>
</tr>
</tbody>
</table>

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

- Rectum (5%)
- Esophagus (2%)
  Other (colon, mesentery, retroperitoneum)
- Other (colon, mesentery, retroperitoneum)
- Small intestine (8%)
- Stomach (60%)
- Small intestine (25%)

Omentum, mesentery, pelvis and retroperitoneum = EGIST (<1%)

Hornick & Lazar. GSI website: Understanding Your Pathology Report for GIST.

<table>
<thead>
<tr>
<th>Tumor Parameters</th>
<th>Risk of Progressive Disease# (%)</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size</strong></td>
<td><strong>Gastric</strong></td>
<td><strong>Duodenum</strong></td>
</tr>
<tr>
<td><strong>Mitotic</strong></td>
<td>≤ 2 cm</td>
<td>None (0%)</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 ≤ 5 cm</td>
<td>Very low (1.9%)</td>
</tr>
<tr>
<td></td>
<td>≤ 5 per 50 hpf</td>
<td>Low (3.6%)</td>
</tr>
<tr>
<td></td>
<td>&gt; 10 cm</td>
<td>Moderate (10%)</td>
</tr>
<tr>
<td><strong>Mitotic</strong></td>
<td>≤ 2 cm</td>
<td>None*</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 ≤ 5 cm</td>
<td>Moderate (16%)</td>
</tr>
<tr>
<td></td>
<td>&gt; 5 per 50 hpf</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 cases 2007/2010/2014 NCCN GIST Risk Assessment Guidelines***

Miettinen et al. 2005 and 2006
# 2007/2010/2014 NCCN GIST Risk Assessment Guidelines***

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<th>Tumor Parameters</th>
<th>Risk of Progressive</th>
<th>Disease# (%)</th>
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<tbody>
<tr>
<td></td>
<td>Size</td>
<td>Gastric</td>
</tr>
<tr>
<td>Mitotic</td>
<td>≤ 2 cm</td>
<td>None (0%)</td>
</tr>
<tr>
<td>Index</td>
<td>&gt; 2 ≤ 5 cm</td>
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***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 correlate 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
GIST - Overall Survival by Risk Group

Risk Groups
- Normal pop.
- Very low
- Low
- Intermediate
- High
- Overtly malignant

Years since diagnosis

Estimated proportion surviving

Kindblom. at: http://www.asco.org
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
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)
Results

- **Minimal effect**: 11/25 (44%)
- **Moderate effect**: 10/25 (40%)
- **Marked effect**: 4/25 (16%)

No moderate or marked changes seen in control cases (p<0.0009)
Minimal and Moderate effects were seen across all durations of therapy.

Marked effect appeared to be a late finding peaking at 5 days.

Histological Effect by Pre-Imatinib Day

- **Minimal**
- **Moderate**
- **Marked**

Cases

<table>
<thead>
<tr>
<th>Duration</th>
<th>Minimal</th>
<th>Moderate</th>
<th>Marked</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 days</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Histological Effect by Pre-Imatinib Day

- Minimal
- Moderate
- Marked

p<0.37
Long term Imatinib Tx
Long term Imatinib Tx
CINSARC : GO analysis of the 67 significant genes

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

- 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.
- Colleagues at UTMDACC.
What is new and exciting in GIST pathology?
Chromosomal complexity and prognosis

97 chromosomes and more than 50 translocations

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

• Which genes / pathways are related to the chromosomal complexity?

• Is there a link between chromosomal complexity and prognosis?
Chromosomal instability signature
Carter et al Nat Genet 2002

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

Arm

Rearranged

Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)
Genomic complexity and prognosis

Possible approaches

• Histological grading
• Array CGH
• Carter signature

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

3 t 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})

- CGH: 37 genes
- Grade: 18 genes
- Carter: 39 genes

67 genes

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

Complexity INdex In SARComas CINSARC

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

Prognostic value of CINSARC:
Metastasis free survival

Multivariate analysis

CINSARC is an independent prognostic factor

Cohort 1

Cohort 2

Cohort 1

n=127
p=5 x10^{-4}

n=83

n=100

n=183
p=1 x10^{-7}

Cohort 2

n=85

n=42

n=127
p=5 x10^{-4}

Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)
GIST - Overall Survival by Risk Group

Estimated proportion surviving

Years since diagnosis

Risk Groups

Normal pop.

Intermediate

High

Overtly malignant

Very low

Low

Kindblom. at: http://www.asco.org
CINSARC and GIST

*In-silico* study of 32 GISTs

(Yamaguchi *et al* 2008)

*Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)*
GIS 1:
-1p distal, -22q

GIS 2:
-1p distal, -22q, -14q

GIS 3:
-1p, -22q, -14q, -15q

GIS 4:
-1p, -22q, -14q, -15q, -10
Normal tissue → GIS 1 → GIS 2 → GIS 3 → GIS 4

-22q → -15q

-1p distal → -14q → -1p proximal → -10

$p = 0.006$

GIS1 & GIS2
GIS3 & GIS4

0 20 40 60 80 100
**GIST and molecular signature**


- 67 patients (Leuven + Bordeaux)
- Localised GIST
- No adjuvant treatment
- Frozen tissue from primary
- Miettinen classification
- Follow-up

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

AURKA is a prognostic factor in GIST

- Low AURKA
- High AURKA

Yamagushi et al JCO 2008

Bergonié + Leuven

Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)
AURKA – top ranked gene in CINSARC

- Gene maps to chromosome 20q13
- Mitotic centrosomal protein kinase
- Control of chromosome segregation
- Overexpression induces centrosome duplication/distribution abnormalities and aneuploidy
- Overexpression associated with poor prognosis in several cancers

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

- *AURKA* is overexpressed in aggressive GIST
- No amplification of *AURKA*
- Deletion of p16 (*CDKN2A*) or *RB1*
- Likely causal events leading to increase *AURKA* and CINSARC gene expression, chromosomal instability and complexity, and finally to metastasis

Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)
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)
**Intermediate GIST and array-CGH**

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

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

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