GIST 201: Why Pathology & Your Pathologist Matters (or, That Mysterious Doctor You Never Meet)

GSI Patient Summit Saturday 26 September 2014

Alexander Lazar MD/PhD
Director, Sarcoma & Melanoma Molecular Diagnostics
Section of Soft Tissue/Sarcoma Pathology
Faculty, Sarcoma Research Center
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 (hematoxlin & 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

Authors
Brian P. Rubin, MD, PhD, FCAP*
  Departments of Anatomic Pathology and Molecular Genetics, Cleveland Clinic, Lerner Research Institute and Taussig Cancer Center, Cleveland, Ohio
Charles D. Blanke, MD, FACP
  British Columbia Cancer Agency and University of British Columbia, Vancouver British Columbia, Canada
George D. Demetri, MD
  Dana-Farber Cancer Institute, Boston, Massachusetts
Ronald P. Dematteo, MD
  Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York
Christopher D. M. Fletcher, MD, FRCPath
  Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts
John R. Goldblum, MD
  Department of Anatomic Pathology, Cleveland Clinic, Cleveland, Ohio
Jerzy Lasota, MD, PhD
  Department of Soft Tissue Pathology, Armed Forces Institute of Pathology, Washington DC
Alexander J. Lazar, MD PhD, FCAP
  Department of Pathology, Sarcoma Research Center, The University of Texas M. D. Anderson Cancer Center, Houston, Texas
Robert G. Mak, MD, PhD
  Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York
Markku Miettinen, MD, PhD
  Department of Soft Tissue Pathology, Armed Forces Institute of Pathology, Washington DC
Amy Noffsinger, MD
  Department of Pathology, University of Chicago Medical Center, Chicago, Illinois
Mary Kay Washington, MD, PhD, FCAP
  Department of Pathology, Vanderbilt University Medical Center, Nashville, Tennessee
Thomas Krausz, MD, FRCPath†
  Department of Pathology, University of Chicago Medical Center, Chicago, Illinois
For the Members of the Cancer Committee, College of American Pathologists

* Denotes primary author. † Denotes senior author. All other contributing authors are listed alphabetically.
Surgical Pathology Cancer Case Summary

Protocol web posting date: June 2012

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)
- __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:
  - 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

Pre-resection 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: ___%
Getting the diagnosis right
Case 1
Case 2

Male, aged 38, with 10 mm polyp at 10 cm in rectum.
Case 3
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

<table>
<thead>
<tr>
<th></th>
<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>Value</td>
<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.
Exon 11
V559_V560del
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 2nd 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 (*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
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>
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<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**

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

**References:** Miettinen et al. 2005 and 2006

<table>
<thead>
<tr>
<th>Tumor Parameters</th>
<th>Risk of Progressive Disease</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Size</td>
</tr>
<tr>
<td>Mitotic</td>
<td>≤ 2 cm</td>
</tr>
<tr>
<td>Index</td>
<td>&gt; 2 ≤ 5 cm</td>
</tr>
<tr>
<td>≤ 5 per 50 hpf</td>
<td>&gt; 5 ≤ 10 cm</td>
</tr>
<tr>
<td></td>
<td>&gt; 10 cm</td>
</tr>
<tr>
<td>Mitotic</td>
<td>≤ 2 cm</td>
</tr>
<tr>
<td>Index</td>
<td>&gt; 2 ≤ 5 cm</td>
</tr>
<tr>
<td>&gt; 5 per 50 hpf</td>
<td>&gt; 5 ≤ 10 cm</td>
</tr>
<tr>
<td></td>
<td>&gt; 10 cm</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

![Graph showing recurrence-free survival by tumor size and mitotic index](image)

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
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 5\textsuperscript{th}-7\textsuperscript{th} decade

M = F

Small lesions = “incidentalomas”

Presenting symptoms include: abdominal pain, gastrointestinal bleeding, early satiety, symptoms referable to a mass
courtesy of Susan Abraham, UTMDACC, Houston, TX
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%)

Effect of Short Term Imatinib Therapy
• Minimal and Moderate effects were seen across all durations of therapy
• Marked effect appeared to be a late finding peaking at 5 days
Long term Imatinib Tx
Long term Imatinib Tx
What is new and exciting in GIST pathology?
CINSARC : GO analysis of the 67 significant genes

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

• Alain Aurias and Frédéric Chibon
• Sarcomas with a complex genetic profile
• Array-CGH and expression profile analyses
• Which genes / pathways are related to the chromosomal complexity ?
• Is there a link between chromosomal complexity and prognosis ?

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 our 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

Silence of the « Rearranged » Profile

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})

86 genes → 37 genes
73 genes → 18 genes
39 genes → 39 genes

67 genes

Complexity INdex In SARComas CINSARC

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**
- n=100
- n=83
- Probability
- Time in months
- HR = 3.1; 95% CI [1.8 – 5.4]

**Cohort 2**
- n=85
- n=42
- Probability
- Time in months
- HR = 3.1; 95% CI [1.8 – 5.4]

Multivariate analysis

CINSARC is an independent prognostic factor

Coursy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)
CINSARC and GIST
*In-silico* study of 32 GISTs
(Yamaguchi *et al* 2008)

Courtesy of J-M Coindre & F Chibon, Bordeaux, France (French Sarcoma Group)
<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>10</th>
<th>14</th>
<th>15</th>
<th>22</th>
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<tbody>
<tr>
<td>GIS 1:</td>
<td>-1p distal, -22q</td>
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<td>GIS 2:</td>
<td>-1p distal, -22q, -14q</td>
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<td>GIS 3:</td>
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</table>
**GIST and molecular signature**


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

![Disease Free Survival Graph](image)

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


AURKA is a prognostic factor in GIST

[Graph showing Kaplan-Meier survival curves for two groups: Low AURKA and High AURKA. The graph on the left indicates a significant difference with \( p = 9.5 \times 10^{-4} \), \( n = 32 \).]
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 (French 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 (French 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 (French Sarcoma Group)

n = 66
p = 8.9 x 10^{-10}
GIST and molecular signature

Latest 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

Disease-free survival (DFS) by tumor size (A), mitotic count per 50 HPF (B), tumor site (C), and mutational status (D); P < 0.0001 for all.
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.

Thanks!
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