Why Pathology & Your Pathologist Matter (or, That Mysterious Doctor You Never Meet)

GSI Patient Summit Saturday 17 September 2016

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 (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

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, FRCPth
  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. Maki, 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, FRCPth†
  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.
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: ______________
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

Preregression 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.
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>
</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></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.
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
Exon 11
V559_V560del
Exon 9
A502_Y503dup

A502_Y503 dup
Detection of SNV in KIT Exon 10,

Patient Sample

Negative
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
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>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%
- **Other (colon, mesentery, retroperitoneum)**: 25%
- **Rectum**: 5%

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

Hornick & Lazar. GSI website: Understanding Your Pathology Report for GIST.
Tumor Parameters
Risk of Progressive Disease

<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>None (0%)</td>
<td>None (0%)</td>
<td>None (0%)</td>
<td>None (0%)</td>
<td></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>
<td></td>
</tr>
<tr>
<td>&gt; 5 per 50 hpf</td>
<td>High (55%)</td>
<td>(Insuff. data)</td>
<td>High (85%)</td>
<td>(Insuff. data)</td>
<td></td>
</tr>
<tr>
<td>&gt; 5 ≤ 10 cm</td>
<td>High (86%)</td>
<td>(Insuff. data)</td>
<td>High (90%)</td>
<td>(Insuff. data)</td>
<td></td>
</tr>
<tr>
<td>&gt; 10 cm</td>
<td>High (86%)</td>
<td>High (86%)</td>
<td>High (90%)</td>
<td>High (71%)</td>
<td></td>
</tr>
</tbody>
</table>

Data based on long-term follow-up of 1055 gastric, 529 small intestinal, 144 duodenal and 111 rectal GIST.


*Miettinen et al. 2005 and 2006*
GIST - Gross Appearance

Courtesy of Brian Rubin, Cleveland Clinic

<table>
<thead>
<tr>
<th>Tumor Parameters</th>
<th>Risk of Progressive Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>Gastric</td>
</tr>
<tr>
<td>Mitotic ≤ 2 cm</td>
<td>None (0%)</td>
</tr>
<tr>
<td>Index &gt; 2 ≤ 5 cm</td>
<td>Very low (1.9%)</td>
</tr>
<tr>
<td>≤ 5 per 50 hpf</td>
<td>&gt; 5 ≤ 10 cm</td>
</tr>
<tr>
<td>&gt; 10 cm</td>
<td>Moderate (10%)</td>
</tr>
<tr>
<td>Mitotic ≤ 2 cm</td>
<td>None*</td>
</tr>
<tr>
<td>Index &gt; 2 ≤ 5 cm</td>
<td>Moderate (16%)</td>
</tr>
<tr>
<td>&gt; 5 per 50 hpf</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

Miettinen et al. 2005 and 2006
**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 vs. months for different tumor sizes and mitotic indices.](image)

*Singer et al. J Clin Oncol. 2002;20:3898*
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)
• Histologic grading +
• Array-CGH
• Carter signature
• Next generation Sequencing

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

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**

<table>
<thead>
<tr>
<th>GO.ID</th>
<th>selection</th>
<th>array</th>
<th>pValue</th>
<th>Z-Score</th>
<th>GO.Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>GO:0000775</td>
<td>10</td>
<td>37</td>
<td>1,06E-14</td>
<td>23,58</td>
<td>chromosome, pericentric region</td>
</tr>
<tr>
<td>GO:0005819</td>
<td>7</td>
<td>14</td>
<td>3,88E-12</td>
<td>27,03</td>
<td>spindle</td>
</tr>
<tr>
<td>GO:0005876</td>
<td>6</td>
<td>12</td>
<td>1,48E-10</td>
<td>25,02</td>
<td>spindle microtubule</td>
</tr>
<tr>
<td>GO:0000776</td>
<td>4</td>
<td>21</td>
<td>5,18E-06</td>
<td>12,73</td>
<td>chromosome</td>
</tr>
<tr>
<td>GO:0005875</td>
<td>6</td>
<td>54</td>
<td>3,42E-07</td>
<td>11,42</td>
<td>microtubule associated complex</td>
</tr>
<tr>
<td>GO:0005874</td>
<td>8</td>
<td>178</td>
<td>2,32E-06</td>
<td>7,88</td>
<td>microtubule</td>
</tr>
<tr>
<td>GO:0000940</td>
<td>2</td>
<td>3</td>
<td>0,0002</td>
<td>10,67</td>
<td>outer kinetochore of condensed chromosome</td>
</tr>
<tr>
<td>GO:0030496</td>
<td>2</td>
<td>7</td>
<td>0,0008</td>
<td>10,84</td>
<td>midbody</td>
</tr>
<tr>
<td>GO:0005657</td>
<td>2</td>
<td>8</td>
<td>0,0010</td>
<td>10,12</td>
<td>replication fork</td>
</tr>
<tr>
<td>GO:0005814</td>
<td>2</td>
<td>9</td>
<td>0,012</td>
<td>9,52</td>
<td>centriole</td>
</tr>
<tr>
<td>GO:0015630</td>
<td>2</td>
<td>13</td>
<td>0,0022</td>
<td>7,84</td>
<td>microtubule cytoskeleton</td>
</tr>
<tr>
<td>GO:0000922</td>
<td>2</td>
<td>16</td>
<td>0,0032</td>
<td>7,02</td>
<td>spindle pole</td>
</tr>
<tr>
<td>GO:0000785</td>
<td>3</td>
<td>75</td>
<td>0,0059</td>
<td>4,47</td>
<td>chromatin</td>
</tr>
<tr>
<td>GO:0000786</td>
<td>2</td>
<td>32</td>
<td>0,0111</td>
<td>4,77</td>
<td>nucleosome</td>
</tr>
<tr>
<td>GO:0001939</td>
<td>1</td>
<td>3</td>
<td>0,0187</td>
<td>8,30</td>
<td>female pronucleus</td>
</tr>
<tr>
<td>GO:0005816</td>
<td>1</td>
<td>3</td>
<td>0,0187</td>
<td>8,30</td>
<td>spindle pole body</td>
</tr>
</tbody>
</table>

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 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 ?
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
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})

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

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

LMS (n=30)
GIS 1:
-1p distal, -22q

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

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

GIS 4:
-1p, -22q, -14q, -15q, -10
**GIST and molecular signature**

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

![Graph showing disease-free survival with p log rank = 5.44e-09](image.png)

Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)
Genomic Index (GI) is a prognostic factor in GIST...

GI = Alt² / n of altered chr.

n = 66
p = 8.9 x 10⁻¹⁰

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)
**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

Cutaneous Melanoma Integrative Analysis

Modified from The Cancer Genome Atlas Pan-Cancer analysis project
Whole Exome Sequencing (WES): Melanoma has the Highest Mutation Rate of Cancers Sequenced to Date

Somatic mutation frequencies observed in exomes from 3,083 tumour–normal pairs.

Broad Institute
Mike Lawrence
Gad Getz
*Nature*, 2013
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

<table>
<thead>
<tr>
<th>Effect</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal</td>
<td>11</td>
</tr>
<tr>
<td>Moderate</td>
<td>8</td>
</tr>
<tr>
<td>Marked</td>
<td>3</td>
</tr>
</tbody>
</table>

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.
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.