The Pathology of Neoplasia Part II

February 2018

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ASSOCIATE PROFESSOR OF ONCOLOGY PATHOLOGY AND DERMATOLOGY
Clinical goals of cancer pathology

1. Identify presence of cancer
2. Classify cancer
3. Predict biology of cancer and prognosis
4. Identify optimal therapy
5. Evaluate success of treatment
Clinical goals of cancer pathology

1. Identify presence of cancer
   - Tissue biopsy, aspirate, smear
   - Circulating tumor cells or nucleic acid: “liquid biopsy”

2. Classify cancer

3. Predict biology of cancer and prognosis

4. Identify optimal therapy

5. Evaluate success of treatment
Clinical goals of cancer pathology

1. Identify presence of cancer

2. Classify cancer
   - Histology, immunohistochemistry
   - FISH, cytogenetics, mutation profile

3. Predict biology of cancer and prognosis

4. Identify optimal therapy

5. Evaluate success of treatment
Clinical goals of cancer pathology

1. Identify presence of cancer
2. Classify cancer

3. Predict biology of cancer and prognosis
   - Pathologic Grade and Stage
   - Immunohistochemistry biomarkers
   - Genetic evaluation

4. Identify optimal therapy
5. Evaluate success of treatment
Clinical goals of cancer pathology

1. Identify presence of cancer
2. Classify cancer
3. Predict biology of cancer and prognosis
4. Identify optimal therapy
   - Immunohistochemical biomarkers
   - Personalized medicine ("actionable targets")
   - Immune therapy
5. Evaluate success of treatment
Clinical goals of cancer pathology

1. Identify presence of cancer
2. Classify cancer
3. Predict biology of cancer and prognosis
4. Identify optimal therapy
5. Evaluate success of treatment
   - Histology (residual tumor, tumor margins, etc)
   - Molecular testing for residual disease
Clinical goals of cancer pathology

1. Identify presence of cancer
2. Classify cancer
3. Predict biology and prognosis of cancer
4. Identify optimal therapy
5. Evaluate success of treatment
GRADING AND STAGING MALIGNANCY
Grading Malignancy

- Grading is based on cytologic and/or architectural characteristics of the tumor

- Attempts to predict future behavior of a tumor
  - High, Severe or Poor essentially means Bad behavior

- Generic systems for many tumors

  Well → Moderate → Poor → Undifferentiated
  Severe → Moderate → Mild
  High → Low
Grading Malignancy

- Some tumor types have specific, well validated grading systems:
  - Prostate → Gleason Grade
    - Primarily based on tumor architecture
  - Breast → Nottingham Grade
    - Tubule formation, Nuclear features, Mitotic rate
  - Endometrium → FIGO Grade
    - Architecture with nuclear feature modifier
Gleason Grading of Prostate Carcinoma

Figure Taken from Epstein J. et al. Am J Surg Pathol 29(9): 1228 (2005).

**Figure 12.** Schematic diagram of modified Gleason grading system.
Cancer Staging

Staging is a precise method for establishing the type and extent of tumor *at a specific point in time* during the course of the disease. Staging is critical to the modern management of cancer because it allows the clinical team to:

1. Plan treatment
2. Estimate prognosis
3. Group similar patients to evaluate results on treatment protocol studies
4. Facilitate information exchange between institutions
5. Otherwise contribute to the study of cancer
Staging

- Performed according to guidelines published by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC or Union Internationale Contre le Cancer)

- Stage is **NOT** the same thing as grade

- The staging system for each tumor type is different (see example for melanoma)
Staging Melanoma

- **Breslow Depth**: 3.1 mm
- **Ulceration**
### Staging Melanoma (8\textsuperscript{th} AJCC edition)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tr>
<td>Tis</td>
<td>Melanoma in-situ</td>
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<tr>
<td>T1</td>
<td>Melanoma measuring 1.0 mm or less</td>
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<tr>
<td></td>
<td>a] no ulceration, depth &lt; 0.8 mm</td>
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<tr>
<td></td>
<td>b] ulceration or depth 0.8 – 1.1 mm</td>
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<td>Melanoma measuring 1.1 – 2.0 mm</td>
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<td></td>
<td>b] ulceration</td>
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<tr>
<td>T3</td>
<td>Melanoma measuring 2.1 – 4.0 mm</td>
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<td></td>
<td>b] ulceration</td>
</tr>
<tr>
<td>T4</td>
<td>Melanoma measuring &gt; 4.1 mm</td>
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<tr>
<td></td>
<td>a] no ulceration</td>
</tr>
<tr>
<td></td>
<td>b] ulceration</td>
</tr>
</tbody>
</table>
Staging Melanoma

NX  Lymph nodes not assessed
N1  One lymph node positive OR In-transit/satellite metastasis with no positive nodes
N2  Two or three nodes positive OR In-transit/Satellite metastasis and one positive node
N3  Four or more nodes positive OR In-transit/Satellite metastasis AND 2+ nodes positive

M0  No distant metastasis
M1  Distant metastasis
<table>
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<th>Stage Group</th>
<th>T Classification</th>
<th>N Classification</th>
<th>M Classification</th>
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<td>Tis</td>
<td>No</td>
<td>Mo</td>
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<tr>
<td>Stage IA</td>
<td>T1a,T1b</td>
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<td>Mo</td>
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<tr>
<td>IB</td>
<td>T2a</td>
<td>No</td>
<td>Mo</td>
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<tr>
<td>Stage IIA</td>
<td>T2b</td>
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<td>Mo</td>
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<td>Mo</td>
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<tr>
<td>IIB</td>
<td>T3b</td>
<td>No</td>
<td>Mo</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>No</td>
<td>Mo</td>
</tr>
<tr>
<td>IIC</td>
<td>T4b</td>
<td>No</td>
<td>Mo</td>
</tr>
<tr>
<td>Stage IIIA-D</td>
<td>any T</td>
<td>any N+</td>
<td>Mo</td>
</tr>
<tr>
<td>Stage IV</td>
<td>any T</td>
<td>any N+</td>
<td>M1</td>
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</table>
Melanoma Survival by AJCC Stage

Figure taken from Melanoma Molecular Map Project (www.mmmp.org)
ESOPHAGUS

BREAST

National Cancer Institute SEER Data 1998-2001
## Grade and Stage are Different

<table>
<thead>
<tr>
<th>Grade</th>
<th>Stage</th>
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<tbody>
<tr>
<td>- How does it look?</td>
<td>- How much and where?</td>
</tr>
<tr>
<td>- Predict tumor behavior</td>
<td>- Predict prognosis and plan treatment</td>
</tr>
<tr>
<td>- Similar to degree of</td>
<td>- Measure of tumor extent at one time</td>
</tr>
<tr>
<td>differentiation</td>
<td>- Overall stage includes all tumor burden and sites</td>
</tr>
<tr>
<td>- Can vary over time,</td>
<td></td>
</tr>
<tr>
<td>within a tumor, or</td>
<td></td>
</tr>
<tr>
<td>between tumor masses</td>
<td></td>
</tr>
<tr>
<td>and metastases</td>
<td></td>
</tr>
</tbody>
</table>
Grade and Stage are Different

1. LOW GRADE  EARLY STAGE  BETTER
2. HIGH GRADE  EARLY STAGE
3. LOW GRADE  LATE STAGE
4. HIGH GRADE  LATE STAGE  WORSE
ADVANCES in pathology and pathology in research
Clinical goals of cancer pathology

1. Identify presence of cancer
2. Classify cancer
3. Predict biology and prognosis of cancer
4. Identify optimal therapy
5. Evaluate success of treatment
The Changing World of Pathology

- Traditional histopathology merges with molecular and genetic evaluation:
  - Molecular or genetic classification of cancer.
  - Stratify tumor risk, predict behavior
  - Identify primary origin of metastasis (“unknown primary”)
    - Compare tumor genetic profile to profiles from known primaries

- Personalized therapy
  - Use biopsy tissue to plan best treatment
  - OmniSeq multigene platform
  - Immune therapy
## Classifying Myeloid Leukemia – 70’s style

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<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>M0</td>
<td>Undifferentiated acute myeloblastic leukemia</td>
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<tr>
<td>M1</td>
<td>AML with minimal maturation</td>
</tr>
<tr>
<td>M2</td>
<td>AML with maturation</td>
</tr>
<tr>
<td>M3</td>
<td>Acute promyelocytic leukemia (APL)</td>
</tr>
<tr>
<td>M4</td>
<td>Acute myelomonocytic leukemia</td>
</tr>
<tr>
<td>M5</td>
<td>Acute monocytic leukemia</td>
</tr>
<tr>
<td>M6</td>
<td>Acute erythroid leukemia</td>
</tr>
<tr>
<td>M7</td>
<td>Acute megakaryoblastic leukemia</td>
</tr>
</tbody>
</table>
2016 WHO Classification: myeloid neoplasms and acute leukemia.

### Acute myeloid leukemia (AML) and related neoplasms

- **AML with recurrent genetic abnormalities**
  - AML with t(8;21)(q22;q22.1); RUNX1-RUNX1T1
  - AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
  - APL with PML-RARA
  - AML with t(9;11)(p21.3;q32.3); MLLT3-KMT2A
  - AML with t(6;9)(p23;q34.1); DEK-HKMY214
  - AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM
  - AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); RBM15-MKL1

**Provisional entity: AML with BCR-ABL1**

- AML with mutated NPM1
- AML with biallelic mutations of CEBPA
  **Provisional entity: AML with mutated RUNX1**

### Acute leukemias of ambiguous lineage

- **Acute undifferentiated leukemia**
- **Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); BCR-ABL1**
- **MPAL with t(v;11q23.3); KMT2A rearranged**
- **MPAL, B/myeloid, NOS**
- **MPAL, T/myeloid, NOS**

### B-lymphoblastic leukemia/lymphoma

- **B-lymphoblastic leukemia/lymphoma, NOS**
- **B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities**
- **B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2); BCR-ABL1**
- **B-lymphoblastic leukemia/lymphoma with t(v;11q23.3); KMT2A rearranged**
- **B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); ETV6-RUNX1**
- **B-lymphoblastic leukemia/lymphoma with hyperdiploidy**
- **B-lymphoblastic leukemia/lymphoma with hypodiploidy**
- **B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3); IL3-IGH**
- **B-lymphoblastic leukemia/lymphoma with t(1;19)(q23.1;p13.3); TCF3-PBX1**
  **Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1-like**
  **Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21**

### T-lymphoblastic leukemia/lymphoma

- **Provisional entity: Early T-cell precursor lymphoblastic leukemia**
- **Provisional entity: Natural killer (NK) cell lymphoblastic leukemia/lymphoma**
Lung Adenocarcinoma: Driver Mutations

Based on data from:
Ding et al., Nature 455:1069, 2008
And modified from a figure developed by:
Dr. F. Hirsch, University of Colorado
Molecular Classification

- Should we group tumors by genotype or driving mutation/target rather than conventional histology or site of origin?

- *BRAF* V600E mutated tumors:
  - Melanoma
  - Colorectal adenocarcinoma
  - Lung adenocarcinoma
  - Papillary thyroid carcinoma
The facts of life: Finding cutoffs

DISEASE

HOW PATHOLOGISTS SEE DISEASE

HOW SURGEONS WISH WE SAW DISEASE
Melanocytic Tumor of Uncertain Malignant Potential

- Melanocytic lesions in which traditional histological criteria may be insufficient to fully predict biology

- Example:
  - Spitz Nevus
  - Atypical Spitz Nevus
  - Atypical Spitz Tumor ← MELTUMP
  - Spitzoid melanoma
Melanoma
Spitz Nevus (photo from pathologyoutlines.com)
MELANOMAS OF CHILDHOOD *

Sophie Spitz, M.D.
(From the Pathology Laboratories of the Memorial Hospital, New York, N.Y.)

It has become apparent over a period of years that even when a histologic diagnosis of malignant melanoma has been made in children the clinical behavior rarely has been that of a malignant tumor. The disparity in behavior of the melanomas of adults and children, despite the histologic similarity of the lesions occurring in the different age groups, is obviously a matter of fundamental importance and the following questions immediately arise: Does the histologically malignant melanoma of children differ in any structural detail from that of adults? Can the clinical behavior of these lesions be predicted from their histologic structure? What, if any, are the factors known to influence the clinical behavior? Should the melanomas of children be treated any differently from the melanomas of adults?

SUMMARY AND CONCLUSIONS

Of 13 cases of juvenile melanoma in this series, only one (7.7 percent) has had a clinically malignant and fatal course despite the similarity of the juvenile lesions to the malignant melanoma of adults.

The juvenile melanoma may be distinguished histologically from adult melanoma in about one-half the cases by the presence of giant cells in the former which seldom occur in the latter.

There is a precipitous rise in the capacity of melanomas to metastasize after puberty despite the histologic similarity to the usually non-metastasizing juvenile melanoma.
Spitzoid Melanocytic Lesions

- Nevus
- Meltump
- Melanoma
How can we improve our diagnosis?

- Immunohistochemistry – sometimes helpful
- Comparative genomic hybridization
- Fluorescence in-situ hybridization
- Proprietary molecular tests – controversial
CGH and Sequencing

- Conventional melanoma
  - Genomic instability
  - Most have multiple chromosome copy number gains or losses
    - Telomerase reverse transcriptase (TERT) promoter mutations
- Spitz nevi
  - Very rare to have multiple abnormalities
  - Some single abnormalities (gain 11p, gain 7q)
  - BAP1 mutation, HRAS mutation, kinase fusions
Risk Assessment for Atypical Spitzoid Melanocytic Neoplasms Using FISH to Identify Chromosomal Copy Number Aberrations
Spitz Tumor assessment by FISH

- **HIGH RISK – Progression beyond SLN**
  - 9p21 homozygous deletion (*CDKN2A* gene/p16)

- **INTERMEDIATE RISK**
  - 6p25 gain (*RREB1* gene)
  - 11q13 gain (*CCND1* gene)

- **LOW**
  - 6q23 deletion (*MYB* gene)
  - No abnormalities by FISH
Clinical goals of cancer pathology

1. Identify presence of cancer
2. Classify cancer
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4. Identify optimal therapy
5. Evaluate success of treatment
The Future of Pathology

- Traditional histopathology merges with molecular and genetic evaluation:
  - Molecular or genetic classification of cancer.
  - Stratify tumor risk, predict behavior
  - Identify primary origin of metastasis

- Personalized therapy
  - Use biopsy tissue to plan best treatment
  - OmniSeq multigene platform
  - Immune therapy
Lung Adenocarcinoma: Molecular targets

Based on data from:
Ding et al., Nature 455:1069, 2008
And modified from a figure developed by:
Dr. F. Hirsch, University of Colorado
the EGFR Pathway

Basic Algorithm for Handling Lung Cancer Specimens

1. Tumor Biopsy
   - Small Cell
   - Non-small cell
     - Advanced Disease
     - Surgical Candidate
       - Stains to further classify
         - Squamous
           - Biomarkers?
             - Treatment
         - Non-squamous
           - EGFR K-ras EML4/ALK
             - Definitive Classification
               - Prognostic Assessment Molecular? Morphologic?
             - Personalized Treatment
Personalized medicine offers glimpse into the future

By: Henry Davis / News Medical Reporter
Personalized Medicine

- **OmniSeq Comprehensive™**
  - Next gen molecular sequencing of DNA and RNA
  - 144 cancer associated “actionable” genes such as ALK, EGFR, PTEN, KRAS, NRAS, BRAF, etc
  - Detects mutations, translocations/fusions, copy number changes, etc.
<table>
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<th>Mutations (SNVs and Indels)</th>
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<th>Copy Number</th>
<th>RNA-Seq</th>
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<td>Coding Sequence</td>
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<td>Gain</td>
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<td>APC</td>
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<td>GNAQ</td>
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<td>ATM</td>
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<td>M TOR</td>
<td>WT1</td>
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</table>
Immune Therapy: PD-L1 Blockade

A. Absence of immunotherapy

- Mismatch repair deficiency
- Frameshift mutations
- Protein with mutation-associated neoantigen (MANA)
- Tumor cell
- MANA/MHC
- PD-L1
- TCR
- PD-1
- T-cell anergy

PD-L1/PD-1 interaction blocks T-cell activation

B. Presence of anti-PD-1

- Mismatch repair deficiency
- Frameshift mutations
- Protein with mutation-associated neoantigen (MANA)
- Tumor cell
- MANA/MHC
- PD-L1
- Anti-PD-1 antibody
- TCR
- PD-1
- T-cell activation

PD-L1/PD-1 interaction blocked by antibody, freeing T cell to kill tumor cell

© 2016 American Association for Cancer Research
Examples of PD-L1 IHC Staining of NSCLC Samples Using the Clinical Trial Assay

PS <1%
PS 1-49%
PS ≥50%

5x magnification
40x magnification

Brown chromogen: PD-L1 staining.
Blue color: hematoxylin counterstain.
Immune Therapy: PD-L1 Blockade

- Pembrolizumab and Nivolumab FDA approved for certain tumors to block PD-1 and PD-L1 interaction
- Facilitate immune mediated tumor killing

- Melanoma
- Non-small cell lung cancer
- Renal cell carcinoma

- Proof of PD-L1 staining needed prior to drug in some treatment situations (eg: Pembro and NSCLC)
Pathology and Research

- Initiate both basic and translational research
- Tissue procurement and specimen archiving

- Bridge between clinic and research bench
  - Analyze human/animal experimental histology
  - Build and evaluate tissue based experiments
    - example: tissue microarray
  - Provide clinical perspective to scientific groups
Pathology Resource Network (PRN)

The Pathology Resource Network provides human specimens and laboratory services for basic and translational research to further the understanding of the cellular and molecular pathogenesis of human cancers. The overall mission is to facilitate access to human tissue for investigators with IRB approval with an emphasis on translational efforts.

Please use the links to the left to access LIMS services available for this RPCI resource.

Online Dashboard Reports:
- Biopspecimen Inventory
- Procurement Events
- Distribution Summary
- Non Procurement Events
- Daily Procurement Events

Welcome
Account Information
- Human Projects
- Change Shipping Address
- Change Billing Address
Your Samples
- RNA Samples
- DNA Samples
- Other Samples
Order Details
- Project Details
Documents for Request
- Forms & Templates
Contact Us
- Lab Service Support
- LIMS Technical Support
A tally of primary lung adenocarcinomas with genomic DNA banked at RPCI.
Tumor Procurement

Procurement events from one random Friday’s surgical schedule...

Tissue may be distributed FRESH to labs or flash frozen for long term banking.

Procurement group provides QA evaluation of samples.
Pathology and Research

- Initiate both basic and translational research
- Tissue procurement and specimen archiving

- Bridge between clinic and research bench
  - Analyze human/animal experimental histology
  - Build and evaluate tissue based experiments
    - one example: tissue microarray
  - Provide clinical perspective to scientific groups
Tissue Microarray
Pathology: Bringing it all together and describing a new tumor entity

Myolipoma of Soft Tissue
Clinicopathologic Analysis of 34 Cases

Mana Fukushima, MD, Inga-Marie Schaefer, MD, and Christopher D.M. Fletcher, MD, FRCPath
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Site (Side)</th>
<th>Size (cm)</th>
<th>Resection Margins</th>
<th>SMA</th>
<th>Desmin</th>
<th>Caldesmon</th>
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ANED indicates alive with no evidence of disease; DOC, died of other causes; NA, not available.
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FIGURE 1. Myolipoma is usually thinly encapsulated and has a variably fatty or more tan-colored, fleshy cut surface (Image courtesy of Dr Richard Cheney, Roswell Park, NY).
translocation. Recently, Panagopoulos et al\textsuperscript{4} described fusion of the \textit{HMG\textsubscript{A}2} and \textit{C9orf92} genes resulting from a \textit{t}(9;12)(p22;q14) in 1 case of myolipoma. Our data support probable rearrangement of \textit{HMG\textsubscript{A}2} in myolipoma. In addition, 2 cases showed either focal MDM2 positivity or weak CDK4 positivity, which was unconvincing and likely of no significance.

\textbf{FIGURE 4.} Myolipoma—showing diffuse positivity for desmin (A), smooth muscle actin (B), and nuclear positivity for \textit{HMG\textsubscript{A}2} in both smooth muscle cells and adipocytes (C).
Outline

What is Pathology?

What is a Pathology Department?

The pathologist’s “tools”

Pathology Definitions and Concepts

How do we approach a pathology specimen?

A General Classification of Neoplasia.

The ugly histologic face of cancer (recognizing malignancy).

Grading and Staging Malignancy.

The Changing World of Pathology

Pathology and Research
The End

feel free to contact me with questions or comments:

paul.bogner@roswellpark.org