STOWE WEEKEND of HOPE

Welcome to Cancer Biology 101

Jane Lian, PhD  The ‘why’ and ‘how’ on becoming cancer cell, and ‘ways’ to prevention

Nicholas Farina, PhD – Monitoring cancer risk and progression with “Biomarkers”

Andrew Goodwin, MD – Understanding your Biopsy Report

May 3, 2019
What are the risk factors for individuals in developing cancer?

Cancer is caused by factors that can act together or in sequence and accumulate to initiate and promote tumor progression

- Genetic
- Environmental
- External and internal factors

How does the normal cell become a cancer cell?

Multiple insults give rise to the activated cancer cells:

- Benign tumors are local
- Malignant tumors can spread to distal sites

Understanding and overcoming the challenges in treating cancers.

These include:

- Chemo resistance to drugs
- Tailoring radiation therapy to avoid tissue damage
- Optimizing immune therapy
- Using targeted intervention approaches
Part 1. Cancer Develops Over Time, a Disease of Aging

the longer you live, the higher the probability
External Risk Factors
Cancers Attributed to Modifiable Risk Factors

Carcinogens
Viruses

Data from Islami, F. et al., Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States, CA Cancer J Clin. 2018;68:31-54. Credit: American Association for Cancer Research (AACR)
Internal Risk Factors

- Genetic factors (family history)
- Heritable traits in DNA sequence (mutations) or changes in the chromatin organization
- Chronic Inflammation
- Hormones
- Immunosuppression
- Infectious Agents
- Metabolism

Specific Microorganisms (bacteria, fungi, viruses) Influence Cancer
Part 2: The Six Hallmarks of Cancer

A cell biology perspective of cancer cell activities

1. Self-sufficiency in proliferative signals
2. Insensitivity to anti-growth signals
3. Evading cell death (apoptosis)
4. Limitless replicative potential
5. Sustained angiogenesis
6. Metastasis capability

Adopted from Hanahan & Weinberg Cell 2000
What Protects and Causes Normal Cell Transformation to Cancer Cells in Tumors

Remember: Multiple insults (external/internal) give rise to the activated cancer cells

1. **DNA damage**, but repair enzymes go to work; however mutations accumulate

2. A small population of **cancer stem cell arises from mutations**

3. In normal cells, we have genes that function as:

   - **A- tumor suppressors**, but mutations can occur in these protective genes
   - **B- oncogenes (cancer causing genes) in tumor cells** that occurred from mutations and drive tumor growth, progression and metastasis. A most infamous oncogene is C-MYC (regulates cell growth in normal development), but acquires mutations that cause cancer.
Many Different Cell Types in the Tumor Environment Support Cancer

Cancer cells have the “power” to “change”/“reprogram” normal cell activity

1. CAFs / MSCs are attracted to TCs; they exchange signals that makes the CAFs support survival of TCs
2. Signaling between M2 macrophages elicited by the TCs promote blood vessel formation
3. TCs evade being killed by immune cells by recruiting immune cell inhibitors of T and NK cells
Tumor Associated Cell Types Support Tumor Growth

Ongoing Research is targeting these cells for early intervention of cancer

1. **Cancer Stem Cells (CSC)** - a small but terrifying population of mutated normal progenitor cells because they have:
   - hiding places (called niches, e.g. in bone marrow, lung and other tissues);
   - can form a barrier of low oxygen laying dormant until activated by internal signals;
   - the worst is their chemo- and radiation resistant because they divide slowly

2. **Cancer Associated Fibroblasts (CAFs)** - Cancer cells (CCs) send signals to the MSCs/CAFs that cause them to induce tumor growth properties in the primary tumor; CAFs acquire many functions that promote metastasis

3. **M2-Tumor Associated Macrophages (TAMS) and Monocytes** – secrete multiple growth factors that bring in blood vessels

4. **CCs evade the immune cells** – T cells should eliminate cancer cells, but CCs are protected by their hypoxia (low oxygen) environment and they recruit into the tumor anti-immune cells
Cancer Associated Fibroblasts (CAF): Why are they so devastating in promoting tumor progression and metastasis

CAFs have many functional activities that promote tumor progression

- Reprogram metabolism of tumor cells
- Regulate Cancer Stem Cells
- They assist tumor cells in the epithelial-mesenchymal (EMT) transition (a Cloak and Dagger trick for tumor cells to metastasize)

Normal epithelial cells are the inner lining of the glands and some organs

Epithelial tumor cells (ETCs)
Part 3: New Strategies to Beat Cancer

Understanding and overcoming the challenges in treating cancers:
  Chemo resistance to drugs,
  Tailoring radiation therapy to avoid tissue damage

What are we doing?

1. Optimizing immune therapy to kill CCs,
2. Developing Intervention approaches targeted to Cancer Stem Cells, Cancer Associated Fibroblasts and Tumor Associated Macrophages
3. Personalized Treatments
4. Biomarker monitoring for early Intervention (Dr. Farina’s presentation)
How the Immune System Functions at the first Sign of a Cancer Cell

1. Recognition and lysis of stressed cells & stimulation of the other immunocytes
2. Release of tumor antigens (cell death)
3. Presentation of tumor antigens by DC and macrophages
4. Recognition and lysis of tumor cells by CD8 T cells stimulated by CD4 T cells

NATURAL KILLER CELLS (NK)
T-CELLS and cytotoxic lymphocytes

DENDRITIC CELL APC
Tumor Cell Escape from Immuno-suppression

Cancer cells have a way to inhibit NK, T cells and CTLs through cell surface molecules that induce negative controls

**The Bad Cells:**
- Cancer cells and CAFs accumulate M2-TAMs, MDSCs and Treg cells in the tumor environment
- Give rise to immune evasion through clearance or inhibition of CD8+ effector T cells and NK good cells
- MDSC inhibit the antitumor reactivity of T cells and NK cells and convey stem-like properties to cancer cells

**The Good Cells**

CAFs - cancer-associated fibroblasts
M2-TAMs - tumor associated macrophages M2-type
MDSC - myeloid derived tumor suppressor
Treg - regulatory T cells
Discovery of Programmed Death 1 (PD1, a receptor) on T cells and the Ligands PDL-1 and PDL-2 on Tumor Cells

PD-1 is the most important tumor cell inhibitory molecule expressed by T cells to reverse immune evasion.

- **Drugs developed to PDL1** are antibodies that inhibit binding to the PD-1 (RECEPTOR). His allows Cells to kill tumor cells.

- High levels of the ligands PD-L1 and PD-L2 are found cancer associated cells that block PD-1 activity on T-cells, thus allowing the cancer cell to escape immune suppression by T cells. PD-L1 can destroy the T-cell.
CAR T-cell therapy, for chimeric antigen receptor T-cell therapy is being studied in the treatment of some types of cancer.
Strategies to Promote Immunosuppression and Killing of Tumor Cells

**Drugs are Available to Counteract Escaped Immune Defenses**

**Step 1**
Modify Tumor Inflammation

- **Inhibit Innate Immunity**
  VEGF inhibition to prevent blood vessel formation

- **Reprogram Immunity**
  Inhibit the signaling pathways between Cancer cells and Immune ‘bad’ cells

**Step 2**
Induce/Boost T-cell Anti-tumor Immunity

- **Deliver tumor antigen**
  Load Dendritic with antigen to activate T-cells

- **Transfer Immunity**
  by CAR-T cell

- **Combine with Chemo and Radiation**

**Step 3**
Reverse Immune Tolerance

- **Reverse Immunosuppression**
  TGFβ, COX2 inhibitors

- **Block Immune checkpoints**
  Anti-PD1/PD1-1 and Anti CTLA-4 antibodies
Summary of Cancer Biology 101

**Very Bad Cells**
- Cancer cell
- MDSC
- Treg
- TAM
- TAN
- Th17

**Good Cells**
- CD8+ T cell
- NK cell

**Primary Tumor Microenvironment**

**a** Inhibition of antitumor immune response
- TGF-β, IL-10, IDO, PD-L1, B7-H4

**b** Promotion of tumor cell invasion and intravasation
- MMPs, EGF, TNF-α, CXCL12, IL-1, IL-6

**c** Formation of pre-metastatic niche
- IL-6, IL-17, IL-23, G-CSF, TGF-β

**d** Facilitating EMT
- exosomes, TGF-β, IL-1β

**e** Induction of angiogenesis
- ANG2, VEGF-A

**Pre-metastatic niche**
- Extracellular matrix
Many Tools at Hand to Diagnosis and Treat Cancer

Susceptibility, Diagnosis, Activity, Severity, Damage, Response to Therapy

Genomics
DNA Sequencing

Cytology
Pathologist

Epigenetics
Cancer Cell Chromatin Effective Drugs

Proteomics
Proteins promoting cancer Use antibodies

Metabolomics
Bacteria, Virus influencing cancer

Multidimensional understanding of the disease biology

Disease etiology/pathogenesis

Unbiased clinical outcome
Thank you for being here!
Monitoring cancer risk and progression with “Biomarkers”

Nicholas H. Farina, PhD
Department of Biochemistry
University of Vermont
The Hallmarks of Cancer

Source: Hanahan at Weinberg. Cell. 2011
Targeted cancer treatment

- EGFR inhibitors
- Cyclin-dependent kinase inhibitors
- Immune activating anti-CTLA4 MAb
- Telomerase Inhibitors
- Selective anti-inflammatory drugs
- Inhibitors of VEGF signaling
- Inhibitors of HGF/c-Met

- Aerobic glycolysis inhibitors
- Deregulating cellular energetics
- Resisting cell death
- Genome instability & mutation
- Inducing angiogenesis
- Activating invasion & metastasis
- Tumor-promoting inflammation
- Avoiding immune destruction
- Enabling replicative immortality

Hanahan and Weinberg, 2011
How do we know what cancer hallmarks to treat?
Molecular biomarkers identify cancer cell activity

**Biomarker**: *biological marker*; a measurable indicator
Biomarkers inform clinical decision making

Example: Prostate Specific Antigen (PSA) test

<table>
<thead>
<tr>
<th>Patients</th>
<th>Specimen</th>
<th>Determine PSA levels</th>
<th>Result</th>
<th>Clinical Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (50-75)</td>
<td>Blood</td>
<td></td>
<td>≤ 3ng/mL</td>
<td>Continue normal screening</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt; 3ng/mL in repeated tests</td>
<td>Perform biopsy</td>
</tr>
</tbody>
</table>

From http://www.pfizer.ie/personalized_med.cfm
Biomarker discovery: big data approach

The Cancer Genome Atlas

Harmonized Cancer Datasets
Genomic Data Commons Data Portal

Data Portal Summary

Projects
- 45

Primary Sites
- 68

Cases
- 33,549

Files
- 365,463

Genes
- 22,872

Mutations
- 3,142,246

**Example: Biomarker panels for prostate cancer progression**

**mRNA gene expression**

*Pathways tested:* Proliferation, adhesion, motility, cell cycle, immune modulation, androgen signaling

**mRNA gene expression**

*Pathways tested:* Androgen signaling, cell organization, stromal response, proliferation

**mRNA gene expression**

*Pathways tested:* Proliferation

**Quantitative multiplex proteomics**

*Proteins assessed:* DERL1, CUL2, SMAD4, PDSS2, HSPA9, FUS, pS6, YBOX1
Example: Biomarker panels for prostate cancer progression

Prostate “cross-section”

Anterior

4+3

4+5

Tumor sites

3+3

Posterior

Biopsy sites

https://en.wikipedia.org/wiki/Gleason_grading_system

Adapted from Dr. Eric Klein 3/22/17 UVMCC Urology Grand Rounds
Example: Biomarker panels for prostate cancer progression

Prostate “cross-section”

Anterior

Posterior

Biopsy sites

Tumor sites

Tumor A

Tumor B

Tumor C

Tumor D

Tumor E

Tumor F

shared gene(s) expression changes in tumors A-D

Adapted from Dr. Eric Klein 3/22/17 UVMCC Urology Grand Rounds
Liquid biopsy: a non-invasive way to measure biomarker levels
All that from a drop of blood…
Ongoing efforts to discover cancer biomarkers at UVM

Towards personalized medicine
The biomarker potential of circulating microRNA

C-miRNA
The High Risk Breast Program
Established in 2003 at UVMMC

• Goal:
  - Establish a clinical and tissue database of women at increased risk for breast cancer development *(600+ women enrolled to date)*

• Eligibility:
  - Germline mutation in a breast cancer associated gene
  - Strong family history
  - Biopsy showing atypia or lobular neoplasia *(benign breast disease)*
  - History of Hodgkin’s disease and radiation
  - Gail risk of 2%/5 years

• Protocol:
  - History/physical, questions, serum collection *(repeat at 4 and 8 years)*
  - Continue high-risk screening/prevention
  - Yearly follow-up through medical records available
  - Approval for contact for additional research studies

Marie Wood, MD
HRBP Director

Melissa Cuke, MS
HRBP Coordinator
Study design: Discover new biomarkers for long-term breast cancer risk

Serum Collection

At Risk but Cancer-Free

> 6 Months

Cancer Diagnosis

Tumorigenesis

Case: Eventual Breast Cancer Diagnosis
Control: Cancer-Free to Date

Source: Farina NH, et al. Oncotarget (2017) Volume 8(68);112170
Study design: Discover new biomarkers for long-term breast cancer risk

Blood collection and processing → C-miRNA Profiling → Data Processing → Risk Score

- Blood collection and processing
- C-miRNA Profiling
- Data Processing
- Risk Score

Source: Farina NH, et al. Oncotarget (2017) Volume 8(68);112170
A biomarker panel of 6 C-miRNA classifies cases and controls

Control

Case

Source: Farina NH, et al. Oncotarget (2017) Volume 8(68);112170
How can this C-miRNA risk signature be utilized in the clinic?
Improved prediction of individual breast cancer risk

Lisa

- 54 year old female
- Annual mammogram
- Healthy diet and gets regular exercise
- No genetic abnormality
- Sister and aunt with breast cancer diagnosed before 50

Susan

Both high-risk women because of strong family history
Improved prediction of individual breast cancer risk

Source: Farina NH, et al. Oncotarget (2017) Volume 8(68);112170
Prostate cancer risk assessment

*Potential for C-miRNA Biomarkers*

**Modern Approach to Prostate Cancer Screening**

*(MAPS study)*

*Dr. James Wallace and Dr. Scott Perrapato*

- Risk assessed on clinical characteristics using a novel algorithm
  - Family History
  - BRCA mutation
  - Ethnicity
  - Lynch syndrome diagnosis
  - Age
  - Serum PSA level

- Serum collected and banked at enrollment and subsequent follow-up visits

- Health status monitored and risk factors updated
Prostate cancer risk assessment
Potential for C-miRNA Biomarkers

Prostate Cancer Circulating miRNAs for Precision-based Medicine (PROMISE trial)

Dr. Steven Ades
Take home points to remember

**Biomarker**: *biological marker*; a measurable indicator

Reflect disease state

Can be tested in tumor tissue (biopsy) and body fluids (liquid biopsy)

Provide individualized information

Guide screening and treatment strategies
Questions?
Making the Diagnosis in Anatomic Pathology

Andrew Goodwin, MD
Associate Professor of Pathology and Laboratory Medicine
University of Vermont Larner College of Medicine
University of Vermont Medical Center
Pathology Reports- Biopsies

Final Pathologic Diagnosis:

Vocal cord, anterior right, biopsy:
- Squamous papilloma with moderate epithelial dysplasia. See comment.

Comment:
This papilloma reveals moderate dysplasia as indicated by mitotic figures half way in the mucosa and abundant dyskeratotic cells in addition to keratin pearls. Dr. Elhosseiny has been consulted on this case and agrees with the above diagnosis. (Dr. deKay)/mpl.

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Final Pathologic Diagnosis:

A. Brain, cerebellum, tumor, biopsy:
   1. Metastatic adenocarcinoma. See comment.
B. Brain, cerebellum, tumor, biopsy:
   1. Metastatic adenocarcinoma. See comment.

Comment:
Immunohistochemical staining was performed on this case to further characterize the lesion. Positive and negative controls stained appropriately. The immunohistochemical profile supports a primary adenocarcinoma of the lung. (Dr. Ciampa).

<table>
<thead>
<tr>
<th>Block</th>
<th>Antibody (Clone)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>A2</td>
<td>CK7 (OV-TL 12/30, Lab Vision)</td>
<td>Strongly positive.</td>
</tr>
<tr>
<td></td>
<td>CK20 (Ks20.8, Lab Vision)</td>
<td>Negative.</td>
</tr>
<tr>
<td></td>
<td>TTF-1 (SPT24, Vision Biosystem)</td>
<td>Positive.</td>
</tr>
</tbody>
</table>
Final Pathologic Diagnosis:

Cecum and ascending, right hemicolecction:

1. Mucinous adenocarcinoma.
   - Histologic grade: Low-grade (moderately differentiated).
   - Type of polyp in which invasive tumor arose: Sessile serrated adenoma.
   - Tumor site: Cecum.
   - Tumor size: 1.8 x 1.2 x 0.6 cm.
   - Macroscopic tumor perforation: Not identified.
   - Depth of invasion: Subserosa (AJCC: pT3, pN0).
   - Lymph-vascular invasion: Not identified.
   - Perineural invasion: Not identified.
   - Intratumoral lymphocytic response (tumor infiltrating lymphocytes): Moderate.
   - Peritumoral lymphocytic response (Crohn-like response): Moderate.
   - Neoadjuvant treatment effect: Not applicable.
   - Tumor deposits (discontinuous extramural extension): Not identified.
   - Surgical resections margins:
     - Proximal margin: Uninvolved by invasive carcinoma; uninvolved by adenoma.
     - Distal margin: Uninvolved by invasive carcinoma; uninvolved by adenoma.
     - Radial margin: Uninvolved by invasive carcinoma.
     - Distance of invasive carcinoma from closest margins: 9.0 cm from radial margin.

2. Non-neoplastic bowel shows no specific pathologic features.
3. Appendix shows direct involvement by tumor.
4. Lymph nodes, pericolic:
   - 14 lymph nodes negative for malignancy (0/14).
Final Pathologic Diagnosis:

A. Breast, left, partial mastectomy:
   1. Adenocarcinoma, invasive, ductal type, moderately differentiated. See comment.
      - Specimen integrity: Intact.
      - Tumor location: Upper outer quadrant.
      - Tumor position: 3 o'clock.
      - Tumor focality: Single focus of invasive carcinoma.
      - Tumor measures 6.0 mm in greatest dimension (AJCC: pT1b, pN0(sn)).
      - Surgical resection margins positive; invasive tumor present:
          - At posterior margin (A4) (see re-excision below).
          - Extent of margin involvement focal.
          - 5.0 mm from superior margin (A6).
          - 9.0 mm from inferior margin (A6).
          - Lymph vascular invasion is not identified.
   2. Ductal carcinoma in situ (DCIS) not identified.
   3. Lobular carcinoma in situ (LCIS) is not identified.
   4. Skin: Not present.
   5. Nipple: Not present.

B. Lymph node, left axilla, sentinel, count 15891, excision:
   1. One lymph node negative for malignancy (0/1).

C. Breast, left, re-excision of medial posterior margin:
   1. Focal residual invasive ductal carcinoma.
      - Invasive carcinoma present 3.0 mm from new margin of resection.
   2. Ductal carcinoma in situ (DCIS), solid pattern, with central comedo type necrosis, high (III)
      nuclear grade.
      - Area of involvement by DCIS measures 1.5 x 1.4 x 0.8 cm (A6).
      - Surgical resection margins negative; DCIS present:
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   3. Lobular carcinoma in situ (LCIS) is not identified.
   4. Fibrocystic changes including:
      - Adenosis, microcysts, apocrine metaplasia, and interlobular fibrosis.
   5. Microcalcifications associated with DCIS.

D. Lymph node, left axilla, sentinel, count 2003, excision:
   1. One lymph node negative for malignancy (0/1).

E. Lymph node, left axilla, sentinel, count 20062, excision:
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      - Tumor measures 6.0 mm in greatest dimension (AJCC: pT1b, pN0(sn)).
      - Surgical resection margins positive; invasive tumor present:
         - At posterior margin (A4) (see re-resection below).
         - Extent of margin involvement focal.
         - 5.0 mm from superior margin (A5).
         - 9.0 mm from inferior margin (A6).
      - Lymph vascular invasion is not identified.
   2. Ductal carcinoma in situ (DCIS) not identified.
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D. Lymph node, left axilla, sentinel, count 2083, excision:
   1. One lymph node negative for malignancy (0/1).

E. Lymph node, left axilla, sentinel, count 20882, excision:
   1. One lymph node negative for malignancy (0/1).
Objectives

» Define the term neoplasm
» Compare and contrast benign and malignant neoplasms including their behaviors
» Describe the two most common types of malignant neoplasms
» Describe the elements in an anatomic pathology report which are essential for diagnosis, prognosis, and treatment
» Provide additional information describing how to understand your pathology report
Objectives

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Neoplasms

» New growth

- Abnormal mass of tissue
- Growth exceeds surrounding normal tissue
- Uncoordinated compared to surrounding normal tissues
- Persists in the excessive manner after cessation of stimuli which the change
  • Non-reversible
Neoplasm

» New growth

» Clonal
  – Population of cells arising from a single cell which incurred genetic change (stimuli)

» Derangement of normal growth control mechanisms

» Balance of cell death and cell division is abnormal
Neoplasm

» Additional terms used to describe neoplasms
  – Tumor
  – Cancer
» These are often clinical terms
Tumor

• Originally applied to swelling caused by inflammation
  – Rubor
  – Calor
  – Dolor
  – TUMOR
  – Functio laesa

• In the current practice of medicine
  – Tumor = Neoplasm
    • Does not specify benign vs. malignant
Cancer

» The commonly used term for **malignant** neoplasms

» The literal definition...
  – **Cancer** is Latin for crab
  – “Adheres to any part it seizes upon in an obstinate manner”
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Neoplasm- Benign vs. Malignant

**Benign**
- Remains local
- Does NOT invade adjacent tissues
- Cannot spread
- Cured by removal
- Patient generally survives
- *Well-differentiated*

**Malignant**
- Invades and destroys adjacent structures
- Can spread to other sites
- May or may not be treatable
- Often causes death (if left untreated)
- Variable *differentiation*
Uterus

Benign Neoplasm

Malignant Neoplasm

BENIGN (Leiomyoma)
- Small
- Well demarcated
- Slow growing
- Noninvasive
- Nonmetastatic
- Well differentiated

MALIGNANT (Leiomyosarcoma)
- Large
- Poorly demarcated
- Rapidly growing with hemorrhage and necrosis
- Locally invasive
- Metastatic
- Poorly differentiated

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Uterus

Benign Neoplasm-Leiomyoma(s)
Breast Tissue - Benign vs. Malignant

Benign - Fibroadenoma

Malignant - Invasive adenocarcinoma
Neoplasm- Behaviors

» **Benign**
  - Predictable behavior
  - Indolent

» **Malignant**
  - Often predictable behavior
  - Variably Aggressive

» **Uncertain Malignant Potential**
  - Unpredictable behavior
  - Cannot be classified by histologic features
  - Treatment may vary
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Nomenclature for Neoplasms

» Carcinoma
» Sarcoma
» Lymphoma/Leukemia
» Melanoma
» Germ Cell
» Totipotential cells
  – More than one cell type
Basic Nomenclature Rules

If termed **carcinoma**
   – Describing a **malignant** epithelial neoplasm
     • Squamous cell carcinoma
     • Adeno**carcinoma**
       – **Adeno**- indicates epithelium originating from glandular epithelium
         » Breast
         » Lung
         » Endometrial
         » Colonic
Basic Nomenclature Rules

If termed sarcoma

- Describing a malignant mesenchymal neoplasm
  - Leiomyosarcoma
  - Rhabdomyosarcoma
  - Fibrosarcoma
  - Osteosarcoma
  - Liposarcoma
Objectives

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» Compare and contrast benign and malignant neoplasms including their behaviors
» Describe the two most common types of malignant neoplasms
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Terms for **Malignant** Neoplasms

» In-situ vs. Invasive

» Primary vs. Metastatic

» Tumor differentiation
Malignant Neoplasm

• **In-situ**
  – Does **not** invade the basement membrane
  – Considered pre-invasive cancer
  – **No** capability to metastasize

• **Invasive**
  – Tumor cells **breach the basement membrane**
  – Grows **into** surrounding tissue
  – Now tumor cells have access to vasculature
    • Ability to **metastasize**
In-situ and Invasive Malignant Neoplasm

Carcinoma in-situ

Invasive carcinoma
Access to Vessels

• **Carcinoma in-situ**
  – Not invasive
  – Cannot access the vasculature
  – Cannot spread

• Once a tumor is **invasive**
  – Access to vessels
  – Metastatic spread
Primary vs. Metastatic

• **Primary**
  – Tumor arising at the site of origin
    • *Carcinoma* of the breast arising in the breast
• **Metastatic**
  – Spread of tumor to distant sites
    • Lymphatic
    • Hematogenous
    • Seeding body cavity
  – Invasive *carcinoma* of the breast spreading to lung
• **Direct extension**
  – Neoplasm invades into adjacent organ
    • Prostate *carcinoma* invading into adjacent bladder
Differentiation- All Grown Up?

- Process by which a less specialized cell becomes a more specialized cell
- Extent to which the neoplastic cells resemble comparable normal cells
  - Morphologic and functional
- **Well-differentiated**
  - Tumor resembles identifiable tissue types
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Gross Examination and Microscopic Features of Neoplasm
Neoplasm Circumscription

Benign

Malignant
Liver section with single subcapsular neoplasm.

Smooth, circumscribed border.

Diagnosis: Hepatic adenoma
Circumscription of Malignant Neoplasm

Liver section with single large neoplasm with irregular circumscription

Diagnosis: Hepatocellular carcinoma
Microscopic Features

• Features appreciated in tissue sections
  – Biopsy or resection specimens
  – Tissue is fixed in formalin, paraffin embedded, 5 micron section cut, and H&E stains are performed

• Look for architectural and cytologic (cellular) features to confirm the diagnosis

• Compare to surrounding, NON-neoplastic tissues
Circumscription

• Irregular border
• Finger or claw-like infiltration into surrounding normal tissues
  – Caner=crab
  – Insinuates the surround normal tissues
    • Does not simply move tissue aside
• Destroys adjacent structures
• **Benign** neoplasms
  – Smooth and circumscribed border
Breast Tissue - Benign vs. Malignant

Benign - Fibroadenoma

Malignant - Invasive adenocarcinoma
Circumscription

Irregular border of invasion - Malignant

Smooth border - Benign

Irregular border of invasion - Malignant
Adenocarcinoma, invasive ductal, no special type

Loss of normal breast architecture

Desmoplastic stromal response

Normal
Cytologic Features of Neoplasms

» What are the cellular features of neoplasms
  – Disturbed polarity/loss of cohesiveness
  – Pleomorphism
  – Increased nuclear-to-cytoplasmic ratio
  – Irregular nuclear membranes
  – Chromatin clumping
  – Hyperchromasia
  – Abnormal mitoses
Polarity- Cytologic Sample

Normal colonic epithelium with uniform arrangement

Adenocarcinoma with loss of uniform cellular arrangement
Squamous cell carcinoma showing variation in size and shape of cells and nuclei
Cytologic Features - Abnormal Mitoses

Benign

Rare number of mitoses

Malignant

Marked increase in number of mitoses

Malignant

Atypical appearing tripolar mitotic figure
Abnormal Mitoses

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Differentiation- Revisited

• Term used to further classify malignant neoplasms

• **Prognosis**
  – Well-differentiated neoplasms have better prognosis compared to poorly-differentiated

• **Treatment**
  – Determines the modality to treat malignancy
    • Adenocarcinoma vs. small cell carcinoma of the lung
Grade the Tumor

» **Grade** communicates important information about the tumor

- Degree of differentiation
- Degree of cytologic atypia
- Proliferative nature (via mitoses)
Grade the Tumor

» Different tumor types using different grading systems
  – Breast cancer
    • Nottingham Combined Histologic Grade
  – Prostate cancer
    • Gleason Grade
  – Endometrial
    • FIGO Grade
<table>
<thead>
<tr>
<th>Tubule formation</th>
<th>Nuclear pleomorphism</th>
<th>Mitotic count</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 &gt; 75% tubules</td>
<td>1 Small regular nuclei, 1-1.5 X RBC</td>
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</tr>
<tr>
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Five distinct glandular patterns are identified and shown in order of increasing lack of differentiation. More than one pattern may be present in a surgical specimen; the pathologist identifies the two predominant ones and adds them to yield a final Gleason grade (e.g., $3 + 4 = \text{grade 7}$). Reproduced with the permission of the publisher.
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Lymphatic Drainage of the Breast

**Sentinel lymph node** is the first node in a regional lymphatic basin receiving lymph from primary tumor.
Stage the Patient

» **Stage** describes the extent or severity of a patient’s cancer based on extent of the primary tumor and amount metastasis disease

» Based on a T, N, M classification
  - **T**= Tumor
    - Size of tumor/extent into surrounding tissue
  - **N**= Lymph node
    - Spread to lymph node
  - **M**= Metastatic disease
    - Extent or number of metastases
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How to Read Your Pathology Report

To diagnose diseases such as cancer, a sample of tissue called a biopsy is taken from a patient and examined by a pathologist to determine if cancer is present.

A pathologist is a medical doctor who specializes in the diagnosis and classification of diseases by looking at tissue or cells under a microscope and by interpreting medical laboratory tests.

The pathologist is also the doctor who examines specimens removed during surgery (resections) for conditions such as cancer, to determine whether a tumor is benign or cancerous, and if cancerous, the exact cell type, grade, and stage of the tumor.

In some cases, the pathologist also performs molecular biomarker analysis and reports genetic alterations that may guide targeted therapy for a specific cancer.

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Your Surgical Pathology Report

Surgical pathology reports vary somewhat regarding the information they contain. However, each report will document the significant details that affect the management of your diagnosed condition or disease process.

2 Patient Identifiers and Clinical Information

To ensure that the report is about you and your specimen, each pathology report contains your patient identifiers—specific information that relates directly to you and includes your name, birth date, and hospital or medical record number. In addition, your pathologist’s name and signature and the laboratory’s name and address will appear on the report.

The container in which your specimen is sent to the laboratory also is labeled with your patient identifiers and matched to your medical record to ensure that the specimen is from you. After the specimen arrives in the laboratory and is processed and after the final pathology report is prepared, these identifiers are checked repeatedly to ensure the correct information is provided to your medical team.

How to Read Your Pathology Report (continued)

2 Gross Description

The gross description describes how the specimen looks to the “naked eye” and details what portions of the specimen selected are examined under the microscope. It includes the size, color, number of tissue samples, and, when appropriate, weight of the specimen. A gross description of a small biopsy specimen is typically short. However, a more complex specimen, such as a cancer resection specimen, will have a more detailed description.

The pathologist uses his or her training and experience to select areas of the specimen that should be sampled for microscopic examination or special studies. Usually, if there are multiple tissues or organs in the specimen, each is described and sampled. Even for a single organ, different portions of the organ are often selected for microscopic examination, including areas that look abnormal as well as those that look normal to the naked eye. Each of these samples is used to make a microscope slide and will be listed in your pathology report.

For a specimen that contains cancer, the pathologist uses specific guidelines when examining the specimen and sampling it for microscopic slides. These vary depending on the location and type of the cancer.

3 Microscopic Description

The microscopic section details how the specimen looks under the microscope and how it compares with normal cells. It also describes if the cancer has invaded nearby tissues. Pathologists always perform the microscopic evaluation of a specimen, even if the final pathology report does not include a written description.

Using specially equipped microscopes and permanent inks applied to specimens, the pathologist can provide detailed and precise measurements, which are valuable because tumor cells may be present beyond what the naked eye can see. Able to measure distances as small as one-tenth of a millimeter, the pathologist can determine if the tumor has been completely removed and how far the tumor is from the margin of the surgically excised tissue. This information helps guide future treatment.

The microscopic description is then used, along with the gross description, to help the reader understand the impact of the disease on the patient’s health.

4 Diagnosis Section

The diagnosis section provides the final pathology diagnosis that is established after thorough examination of the specimen. The diagnosis is also used to document the results of special studies that may have been used to reach the diagnosis and exclude other diagnoses.

5 Synoptic Report

In cancer resection cases, there will be a synoptic special case summary or synoptic report. The synoptic report lists all of the most important findings in the case, summarized as one concise table. The specific items listed in this summary are those that a panel of cancer experts has determined to be essential to cancer treatment. All this information helps determine which additional treatments or testing, if any, are needed, and helps predict how the patient will do over time (outcome). Pathology staging information is also provided in the synoptic report. Staging information details how extensive the tumor is and if it has spread beyond the organ in which it originated. This information directly affects subsequent treatment and helps to predict prognosis.

Comment Section

Sometimes there are diseases that are subtle and difficult to diagnose, or the disease process is considered controversial or unclear. Many pathologists tend to use the comment section to explain these types of issues and recommend possible additional testing.

https://www.cap.org/member-resources/patient-education/how-to-read-your-pathology-report
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