Introduction to NEOPLASIA
(Part 1)

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DUMC

Today: Vocab
Later: Epidemiology and Molecular Biology of Cancer followed by immunology and treatment of cancers
NEOPLASIA

Today’s Goals and Objectives

1. Define neoplasm
2. Define benign and malignant
3. Differentiate benign from malignant neoplasms based on histologic appearance
4. Explain how neoplasms are named and infer properties of a neoplasm from its name
5. Explain what grade is, and how it impacts prognosis
1. What is a Neoplasm?

• NEOPLASM = “New growth”

• Synonym: TUMOR = “swelling”
  – Originally used for inflammation, but now used as synonym for neoplasm

• Oncology = the study of tumors (Greek “oncos” = tumor)
NEOPLASM
Definition

“A neoplasm is an abnormal mass of tissue which exceeds and is uncoordinated with that of the normal tissues, and persists in the same excessive manner after the cessation of the stimuli which evoked the change.”

Sir Rupert Willis, 1952
Two Fundamental Features of Neoplasms

1. Unregulated growth
2. Clonal genetic defects

Subject of later lecture

Neoplasia III (Dr. Yan)
Mount Sacagawea, Montana
2. What Do “Benign” and “Malignant” Mean?

The fundamental difference for tumors arising from most tissues is the ability to metastasize - see next slide. Brain tumors are the notable exception to this rule. Glioblastomas are malignant but they do not metastasize.
Malignant Neoplasm “CANCER”

- Metastasis = Malignant.
- Metastasis: spread to distant, non-contiguous site
  - Lymphatic metastases (nodes)
  - Hematogenous metastases (lung, liver, bone, brain)
  - Implantation in body cavities
- Fatal if untreated
Lymph Node Metastasis

Cancer

Normal

Dark blue is the normal small lymphocytes
Hematogenous Metastases

white nodules are foci of metastatic cancer

Green because of the bile backup due to tumor blocking the bile excretion

Breast cancer metastases in liver

Courtesy PEIR digital library
Hematogenous Metastases

Breast cancer metastases in vertebra

pale areas are cancer in bone marrow

Courtesy PEIR digital library
Peritoneal Metastases

Ovarian Cancer

Omentum covered with thousands of nodules - common way ovarian cancer likes to spread
Benign Neoplasms

• Do not metastasize
• In general, do not result in death of the patient
  – Location, location, location!
  – Secretory products can be lethal (e.g. endocrine tumors)
  unless in a bad location
From a practical standpoint, benign neoplasms often can be cured by simple surgical excision while malignant neoplasms often cannot be cured by surgery alone.
Benign vs. Malignant

Malignant neoplasms have the potential for metastasis

<table>
<thead>
<tr>
<th></th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Distant Metastases?</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Life-threatening</strong></td>
<td>No (usually)</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Benign vs. Malignant

<table>
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<tr>
<th>Distant Metastases?</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
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<tbody>
<tr>
<td>No</td>
<td></td>
<td>Yes</td>
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Definition correct but clinically not helpful…do you want to wait for your patient to develop metastatic disease before you start treatment for cancer? 

The answer here is no
Cham Museum, Danang, Viet Nam
3. How can we tell if a neoplasm is malignant BEFORE it metastasizes?

Histopathology!
Histologic Features Distinguishing Benign vs. Malignant

Three big things to look at:

a) Borders
b) Growth rate
c) Anaplasia

Anaplasia - lack of differentiation

Is this cancer or not?

Courtesy PEIR digital library
Benign Neoplasms

- Encapsulated (pushing borders)
  - Do not invade locally
- Slow growth
- Mild anaplasia (well differentiated)
Breast, fibroadenoma

Pushing Borders

tumor with sharp circumscribed borders
Pushing Borders

sharp interface - pushing duct to the side

not invading the duct

Breast, fibroadenoma
Malignant Neoplasms

- Local Invasion
  - Infiltrative borders
  - “Stellate” or “spiculated”

Can be seen on x-rays and pathologically. Malignant tumors are fixed to adjacent structures, not mobile. This can be palpated on physical exam if the tumor is large.
Local Invasion

Pale tumor sending fingers throughout the vessels and into the pleural space of the lung - infiltrative growth pattern.
Local Invasion

Breast cancer

spiculated/stellate architecture
Malignant Neoplasms

• Local Invasion

• Rapid growth rate
  – Histology: Mitotic figures numerous
  – Not unique to malignancies, many normal tissues grow rapidly (GI mucosa, endometrium, bone marrow)

Can be seen clinically too - something that has grown over several weeks or months
Mitotic Figures in Cancer

Breast, malignant phyllodes tumor

Arrows pointing to mitoses Frequently talked about how many mitoses are seen on a high power field (40x field microscope). This allows the pathologist to tell the clinician how badly the tumor is likely to behave.
Malignant Neoplasms

• Local Invasion
• Rapid growth rate
• Anaplasia
ANAPLASIA

“Lack of Differentiation”

• “Differentiation” is the extent to which neoplastic cells resemble normal tissues, both morphologically and functionally
  – Well-differentiated: closely resembles tissue of origin
  – Poorly-differentiated: unspecialized, little resemblance to tissue of origin

Anaplastic cells are poorly differentiated
ANAPLASIA
“Lack of Differentiation”

– Anaplastic skeletal muscle cells make little actin and myosin (lose cross striations)
– Anaplastic colonic epithelial cells make little or no mucin
– Anaplastic glandular cells make only few glands
Benign: No Anaplasia

Note microscopic similarity to normal smooth muscle

Uterus, leiomyoma

Tumor that has no anaplasia - histologically looks almost exactly the same as normal smooth muscle cells.
Normal

Neoplastic glands still resemble normal endometrial gland

pinker glands are neoplastic ones - still look similar to normal though
Cancer: Moderate Anaplasia

Normal Skin

Squamous cell carcinoma

Neoplastic squamous cells still make abundant keratin (arrows)

The cancer side is more disorganized than the left side, but still making keratin (pink whirls).
Severe Anaplasia

Can't even recognize the breast histologically - no glands, only solid cord of cells

Normal

Breast Cancer: No gland formation
Severe Anaplasia

Normal Colon Cancer

No resemblance to normal

Sheets of unrecognizable cells - doesn't even look like an epithelium
ANAPLASIA: Abnormal Nuclei

- High ratio of nucleus to cytoplasm
- Nuclear hyperchromasia.
- Clumped chromatin.
- Prominent nucleoli.

“Blue is BAD”

Known as the N/C ratio

first impression of looking at a neoplasm under the microscope is blueness.

Does this correlate with the rate of growth?
A: Cells that are dividing rapidly have less cytoplasm, nuclear hyperchromasia is from replicating DNA so it’s all related. Anaplastic cells may have multiple copies of chromosomes and therefore more DNA.
ANAPLASIA:

Other Nuclear Features

- **Pleomorphism**
  - Variation in size and shape
  - Nuclear and cytoplasmic
  - Tumor giant cells
- Frequent and sometimes abnormal mitoses

In normal tissues, the cells are relatively uniform
Mild Anaplasia: Nuclei

Remember--blue is bad!

Normal Colon

Adenoma

Still making glands, but a little bluer, lost some mucin, a little darker and a little larger than normal

Benign neoplasm of the colon
Severe Anaplasia: Nuclei

Nuclear pleomorphism, tumor giant cells, tripolar mitosis

Mercedes Benz sign - cell dividing three ways (almost always a sign of malignancy)
Histologic Diagnosis Of Malignancy

There is no single parameter (other than metastasis) which always allows recognition of a malignant neoplasm microscopically. However, the presence of severe anaplasia and a pattern of invasiveness are the criteria which are most generally useful.
There is gray area with neoplasms. Can have tumors that metastasize 1/10 or 1/1000 times. You have to recognize lesions that are intermediate in their biology.
Quick Review: Which of these is malignant?
Quick Review:
Which of these is malignant?

Malignant (infiltrative borders)

Breast cancer: infiltrative stellate borders

Benign (pushing borders)

smooth, pushing rounded borders
Quick Review: Which of these thyroid tumors is malignant?
Quick Review:
Which of these thyroid tumors is malignant?

Malignant (severe anaplasia!)

Benign (no anaplasia!)

Upper left is super anaplastic. Big giant nuclei, very pleomorphic.
Duke University, North Carolina
4. How do we name neoplasms?
Nomenclature

Neoplasms are composed of proliferating neoplastic cells but also contain non-neoplastic supportive stroma of connective tissue and blood vessels.

Ignore the supporting stroma - only look at the clonally neoplastic cells for nomenclature
Nomenclature

Tumors are named according to the neoplastic component

(Cell type) + (modifier to indicate benign/malignant) + (site of origin)
Benign Neoplasms: Nomenclature

- Benign tumors are often designated by the suffix - "oma".
- Prefix designates the cell of origin
# Benign Mesenchymal Neoplasms

<table>
<thead>
<tr>
<th>CELL TYPE</th>
<th>BENIGN TUMOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat</td>
<td>Lipoma</td>
</tr>
<tr>
<td>Smooth muscle</td>
<td>Leiomyoma</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>Rhabdomyoma</td>
</tr>
<tr>
<td>Fibrous tissue</td>
<td>Fibroma</td>
</tr>
<tr>
<td>Blood vessel</td>
<td>Hemangioma</td>
</tr>
<tr>
<td>Cartilage</td>
<td>Chondroma</td>
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</tbody>
</table>
Benign Epithelial Neoplasms

- **ADENOMA**: benign neoplasm derived from glandular epithelium
- **CYSTADENOMA**: benign epithelial neoplasm with cystic or fluid-filled cavity
- **PAPILLOMA**: benign epithelial neoplasm producing finger-like or papillary projections (think sea anemone)
Interior of tumor

Papillary growth inside cyst

papilloma - can see little fingers growing in the cyst
Examples of benign neoplasms

- Leiomyoma of the uterus
- Chondroma of the femur
- Adenoma of the colon
- Cystadenoma of the ovary
- Papilloma of the larynx
Malignant Neoplasms: Nomenclature

CARCINOMA: arising from epithelial tissue

ADENOCARCINOMA: arising from glandular epithelium

SARCOMA: arising from mesenchymal tissue
Malignant Neoplasms
Nomenclature

LYMPHOMA = arising from lymphoid tissue
LEUKEMIA = arising from blood or bone marrow elements
...Then add site of origin:

Examples of malignant neoplasms

- Leiomyosarcoma of the uterus
- Chondrosarcoma of the femur
- Adenocarcinoma of the colon
- Squamous cell carcinoma of the larynx
### Summary:
#### Neoplasm Nomenclature

<table>
<thead>
<tr>
<th>Origin</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibroblasts</td>
<td>Fibroma</td>
<td>Fibrosarcoma</td>
</tr>
<tr>
<td>Glands</td>
<td>Adenoma</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Smooth muscle</td>
<td>Leiomyoma</td>
<td>Leiomyosarcoma</td>
</tr>
<tr>
<td>Squamous</td>
<td>Squamous papilloma</td>
<td>Squamous cell carcinoma</td>
</tr>
</tbody>
</table>
# Summary: Neoplasm Nomenclature

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytes</td>
<td>(?)</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Granulocytes</td>
<td>(?)</td>
<td>Leukemia</td>
</tr>
<tr>
<td>3 germ cell layers</td>
<td>Teratoma</td>
<td>Teratocarcinoma</td>
</tr>
<tr>
<td>GI wall</td>
<td>GI stromal tumor</td>
<td>GI stromal tumor</td>
</tr>
</tbody>
</table>

- **Lymphocytes**
  - Benign: (?)
  - Malignant: Lymphoma
    - **No real benign tumor because once lymphs proliferate in bloodstream, they go everywhere**

- **Granulocytes**
  - Benign: (?)
  - Malignant: Leukemia

- **3 germ cell layers**
  - Benign: Teratoma
  - Malignant: Teratocarcinoma

- **GI wall**
  - Benign: GI stromal tumor
  - Malignant: GI stromal tumor

- **GI wall**
  - Benign: GI stromal tumor
  - Malignant: GI stromal tumor

- **GI wall**
  - Benign: GI stromal tumor
  - Malignant: GI stromal tumor
Exceptions

• Many “-omas” are malignant
  – Lymphoma
  – Hepatoma
  – Seminoma
  – Melanoma

  lymphocytes
  liver cells
  Seminiferous Tubules
  Should be called “melanosarcoma” but it’s not. Tumor of melanocytes
Exceptions

- Some “carcinomas” or “sarcomas” are benign
  - Basal cell carcinoma of skin
  - Cystosarcoma phyllodes of breast
  - Well differentiated liposarcoma of skin

Most common cancer, but it almost never metastasizes

Point: If you're not sure about whether something is malignant or benign - look it up.
Name that tumor!
Tumor #1 – Liver

How would you describe the liver? Irregular borders, nodules everywhere. Could be necrotic in the center.
Tumor #1 – Liver

Mitoses

this is bad

Where is it coming from? Bile ducts.
Tumor #1

- **Dx:** Adenocarcinoma of the bile duct
- **Malignant features**
  - Infiltrative borders, many mitoses
  - Gland forming neoplasm
- **aka “Cholangiocarcinoma”**
Tumor #2-Adrenal

How would you describe the border of this tumor? Pushing border

answer in two slides

Courtesy Healthcentral.org
Tumor #2-Adrenal

Minimal anaplasia - resembles normal adrenal

No mitoses or pleomorphisms
Tumor #2

- **Dx:** Adenoma of the Adrenal Cortex
- **Benign features**
  - Pushing, circumscribed borders, no mitoses or anaplasia
5. What is Grade?
Grading Of Cancer

Grade: A histologic parameter quantitating the degree of differentiation of the cancer cells.

capture the anaplasticity of the tumor. Grade is a way to describe (quantify) how anaplastic the tumor cells are.
Differentiation

- Well-differentiated ("low grade") tumors resemble mature normal cells of the tissue of origin.
- Poorly differentiated ("high grade") tumors show little resemblance to the tissue of origin.
Grading of Cancer

- Many tumors graded according to a three-tiered scheme: well, moderately, and poorly differentiated (grade 1, 2, 3).
- Grading systems vary by different tumor type.
Importance of Grade

Many tumors show a range of differentiation from low grade to high grade. For those that do...

Grade predicts behavior
(for many common malignancies)

Predicts response to chemotherapy, how they will metastasize, etc.
## Grade and Prognosis

**Breast Cancer**

<table>
<thead>
<tr>
<th>Grade</th>
<th>5 yr survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
</tr>
</tbody>
</table>

Can base your treatment strategy based on the grade.
Grading Of Cancer

• Limitations:
  – Many tumors are of intermediate differentiation
  – There is sampling error with small biopsies
  – Grading is based on subjective light microscopic interpretation
Factors that would influence whether a surgical resection would be curative include:

A. Whether it is benign or malignant
B. Location of the neoplasm
C. Cell type of the neoplasm
D. Degree of anaplasia of the neoplasm
E. All of the above
Factors that might influence whether surgery for a neoplasm will be curative include:

A. Whether the neoplasm is benign or malignant
B. Location of the neoplasm
C. Cell type of the neoplasm
D. Degree of anaplasia of the neoplasm
E. All of the above
Q: Some tumor types are class associated? i.e. GBM (glioblastoma multiforme - which is a common, aggressive brain tumor) have a grade and a class
GBM is always Grade 4. Staging is not applied to GBM because they do not metastasize (More detail after Spring Break)
A: Every tumor has its own grading scheme, but what we have learned is how most tumors are graded.

Q: Is there a range of differentiation in the same tumor?
A: Yes, within one tumor if there is a range, you use the worst looking area. It is assumed that this area will be the most aggressive area.

Q: If you perform a surgery on a benign tumor, will it convert it to a malignant one?
A: Usually no. The only potential problem is that some benign neoplasms don't spread distantly but spread locally so if you do a bad job taking it out, you can spread benign neoplasms locally but you don't convert it to a malignancy.
Sometimes a pathologist (horrors) may make a mistake an call a malignant tumor benign. There are many reasons for this which include sampling error and communication difficulties.
Take home lesson - develop a good working relationship with your pathologist.