Neoplasia –1

Terms

- Neoplasia: “new growth”
- Cancer: a malignant growth
- Tumor: “swelling” - synonym for neoplasia
- Growth: synonym for neoplasia
- Benign: doesn’t invade tissues or metastasize
- Malignant: capable of invasion and metastasis
  - Carcinoma = epithelial cell origin
  - Sarcoma = mesenchymal origin

The confusing terminology of neoplasia

- Long history (2,500 years)
- Irrational nomenclature
- Identifying presumptive tissue of origin a mixture of experience, science (esp. cell markers) and subjectivity/bias
- Tumor: ‘-oma’
  - Most benign tumors have ‘-oma’ suffix
  - Exceptions: lymphoma, melanoma, hepatoma, mesothelioma, seminoma
- Mesenchymal origin:
  - Sarcoma, with prefix to indicate origin - rhabdomyosarcoma
- Epithelial origin:
  - Carcinoma, with prefix to indicate origin – mammary adenocarcinoma
Defining cancer

1. Purposeless: of no use to host*
2. Atypical cells: structurally/functionally abnormal to varying degree
3. Autonomous: escape normal controls of cellular growth
4. Aggressive: may invade and harm host

* If viral in origin, it may be useful to virus to induce neoplastic cells

End-stage neoplasia

Features of neoplasia

- Arise in any tissue with nucleated cells
- Multiple causes:
  - Environmental mutagens
  - Viral agents
  - Physical
- Metabolically similar to healthy cells:
  - Dilemmas in treatment – ‘bystander effects’
- Genetic damage:
  - Usually multiple “hits”
  - Especially genes controlling
    - Cell cycle
    - Growth
    - Apoptosis
US Mortality, 2005

<table>
<thead>
<tr>
<th>Rank</th>
<th>Cause of Death</th>
<th>No. of deaths</th>
<th>% of all deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Heart Diseases</td>
<td>652,091</td>
<td>26.6</td>
</tr>
<tr>
<td>2.</td>
<td>Cancer</td>
<td>559,312</td>
<td>22.8</td>
</tr>
<tr>
<td>3.</td>
<td>Cerebrovascular diseases</td>
<td>143,579</td>
<td>5.9</td>
</tr>
<tr>
<td>4.</td>
<td>Chronic lower respiratory diseases</td>
<td>130,933</td>
<td>5.3</td>
</tr>
<tr>
<td>5.</td>
<td>Accidents (unintentional injuries)</td>
<td>117,809</td>
<td>4.8</td>
</tr>
<tr>
<td>6.</td>
<td>Diabetes mellitus</td>
<td>75,119</td>
<td>3.1</td>
</tr>
<tr>
<td>7.</td>
<td>Alzheimer disease</td>
<td>71,599</td>
<td>2.9</td>
</tr>
<tr>
<td>8.</td>
<td>Influenza &amp; pneumonia</td>
<td>63,001</td>
<td>2.6</td>
</tr>
<tr>
<td>9.</td>
<td>Nephritis</td>
<td>43,901</td>
<td>1.8</td>
</tr>
<tr>
<td>10.</td>
<td>Septicemia</td>
<td>34,136</td>
<td>1.4</td>
</tr>
</tbody>
</table>

2010 Estimated US Cancer Deaths - WOMEN

<table>
<thead>
<tr>
<th>Females</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>71,040</td>
<td>26%</td>
</tr>
<tr>
<td>Breast</td>
<td>36,940</td>
<td>15%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>24,790</td>
<td>9%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>18,020</td>
<td>7%</td>
</tr>
<tr>
<td>Ovary</td>
<td>13,050</td>
<td>5%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>9,500</td>
<td>4%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>9,180</td>
<td>3%</td>
</tr>
<tr>
<td>Uterine Corpus</td>
<td>7,950</td>
<td>3%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>6,190</td>
<td>2%</td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
<td>6,720</td>
<td>2%</td>
</tr>
<tr>
<td>All Sites</td>
<td>270,290</td>
<td>100%</td>
</tr>
</tbody>
</table>

Why so difficult to control?

- Cancer is not one disease
- Multiple causes
- Detected late in biological course
- Altered host cells:
  - Safe targeted treatment difficult
  - Immunological control difficult

CRITERIA for benign mass

- Slow growth
- Usually encapsulated
- Smooth surface
- Local compression
- Usually small
- Not fatal unless:
  - Bleed out
  - Compression of vital organ
  - Growth in confined space
- Cells differentiated
- Cells uniform and resemble each other
- Blood vessels in tumor well formed
- Minimal or no necrosis
- NEVER metastasize
- DNA content usually normal
- Karyotype usually normal
- Normal mitotic figures
2/22/2011

Benign pedunculated lipoma – a sporadic cause of death in horses

Life-threatening benign tumors

Adenoma of pituitary gland
Local effects on:
- Optic nerves
- Hypothalamus
Distant effects on:
- Adrenal glands
- Thyroid glands

More than one road to malignancy:

1. Normal cell \(\rightarrow\) dysplastic \(\rightarrow\) benign \(\rightarrow\) malignant
2. Normal cell \(\rightarrow\) malignant
Criteria for malignant mass

- Metastasis
- Local invasion
- Irregular surface
- Little or no capsule
- May be large with rapid growth
- Often death if untreated
- Less well differentiated than benign neoplasm
- May not resemble tissue of origin

- Pleomorphism
- ↑ mitotic activity
- Vessels numerous/poorly formed
- Necrosis and hemorrhage
- DNA content increased
- Additional chromosomes present
- Karyotypic abnormalities
- Nuclei large and hyperchromatic

F32523 – oral SCC of tongue in adult cat
Features of neoplastic cells

- Lack of differentiation
- Rapid growth
  - Abnormal nuclei and nucleoli; cytoplasmic basophilia
- Atypia
- Loss of cell-specific organelles
- Immortal
  - Telomerase expressed in most tumors
- Loss of anchorage dependence
- Loss of contact inhibition
- Decreased requirement for growth factors

One unequivocal sign of malignancy: METASTASIS

Necrosis and/or ulceration in tumors – an index of probable malignancy
For tumor to be malignant

- Self-sufficient in growth promoting signals
- Insensitive to growth inhibitory signals
- Evades apoptosis
- Defective DNA repair
- Limitless ability to replicate
- Induces sufficient blood supply
- Escapes immune surveillance
- Ability to invade and metastasize

Grading tumors

- Still an infant in veterinary medicine
- For malignant tumors, usually 1 – 3 grade, based on:
  - Atypia and pleomorphism
  - Mitotic numbers
  - Necrosis
  - Nucleolar size
  - Invasion of vessels
  - Also: antigens; location; size; AgNOR
- Clinical staging systems based on size, location and metastasis

Biological classification

- Conventional histopathology:
  - Good lump vs. bad lump
- Antigen markers:
  - E.g., estrogen-receptor (ER)–negative and ER-positive breast cancer
- Microarray-based profiling:
  - Expression level of multiple mRNA transcripts
    - For more refined classification
    - For better resolution of tissue of origin
    - To predict likelihood of metastasis
Staging tumors

Table 1. Clinical stages (TNM) of digital tumors of dogs.

<table>
<thead>
<tr>
<th>T</th>
<th>Primary tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of tumor found</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor &lt; 2 cm in diameter superficially invasive</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor 2-10 cm in diameter minimally invasive</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &lt; 10 cm with invading subcutis</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invading fascia or bone</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>Regional lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No evidence of tumor found</td>
</tr>
<tr>
<td>N1</td>
<td>Metastatic SUVs</td>
</tr>
<tr>
<td>N2</td>
<td>Metastatic left or bilateral</td>
</tr>
<tr>
<td>N3</td>
<td>Metastatic right or contralateral</td>
</tr>
<tr>
<td>N4</td>
<td>No tumor acheived</td>
</tr>
<tr>
<td>N5</td>
<td>Tumor with bone</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M</th>
<th>Distant metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No metastasis found</td>
</tr>
<tr>
<td>M1</td>
<td>Metastatic lesions at specific sites</td>
</tr>
</tbody>
</table>

TNM. Tumor stage, neoplastic tumors staging.
Source: World Health Organization.12

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Tumors have personalities

- Approximately 600 tumors recognized in people (histology)
- Behavior roughly predictable
- Predicting clinical outcome (days to death) an inexact science
- What is histologically malignant in one species may be benign in another

- Cutaneous histiocytoma:
  - Intra-epidermal APC (Langerhans cells)
  - Common in young dogs (<1 year)
  - Benign behavior
  - Regression after several months
  - Viral?
  - More pleomorphic in older dogs

- Extramedullary plasmacytoma:
  - Plasma cells
  - Histology: pleomorphic
  - Behavior: benign
  - Eos. mouth, ears, digits
  - Amyloid deposition
  - Eos. some breeds (cocker, Airedales, Kerry blue, etc)
The structure of tumors

- Neoplastic component:
  - Parenchyma
- “Normal” cell components:
  - Connective tissue stroma and capsule
  - Vascular supply
  - Inflammatory cells

Each component the basis of intensive research for purposes of control

Assessing outcomes in cancer – Kaplan-Meier curves

Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 Mutation