NEOPLASIA

Neoplasia: Cancer Facts and Figures

- Recently there has been a decline in cancer mortality but the problem is still mammoth
- With many forms of malignancy, most notably the leukemias and lymphomas, there are now dramatic improvements in the 5 year survival rates
- Today a greater proportion of cancers are being cured or arrested than ever before

Neoplasia: Definitions

- NEOPLASIA literally means “new growth”
- The new growth is called a NEOPLASM
- The term tumor was originally applied to the swelling caused by inflammation; now TUMOR is equated with neoplasm
- ONCOLOGY is the study of tumors or neoplasms (Greek oncos means tumor)
- Cancer (Latin for crab) is the common term for ALL MALIGNANT tumors
- A NEOPLASM is an “abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after cessation of the stimuli which evoked the change” (Willis, 1952)

Neoplasia: Nomenclature

- All tumors, benign and malignant, have two basic components:
  - 1) proliferating neoplastic cells that constitute their PARENCHYMA
  - 2) SUPPORTIVE STROMA made up of connective tissue and blood vessels
- It is the parenchyma of the tumor that largely determines its biologic behavior and is the component from which the neoplasm derives its name
- On occasions the parenchymal cells of a tumor stimulate the formation of abundant collagenous stroma which is referred to as DESMOPLASIA

Benign Tumor Nomenclature

- In general, benign tumors are designated by attaching the suffix -OMA to the cell of origin
- Tumors of mesenchymal cells generally follow this rule

- For example, a benign tumor arising from fibroblastic cells is called a FIBROMA
- A OSTEOMA is a benign tumor of osteoblasts, while a benign cartilaginous tumor is called a CHONDROMA
- The terminology of benign epithelial tumors is more complex with some being classified based on the cells of origin while others are classified by microscopic architecture and still others on their macroscopic patterns
- ADENOMA is the term applied to the benign epithelial neoplasm that forms a glandular pattern or to a tumor arising from glands but not reproducing glandular patterns
- Benign epithelial neoplasms producing microscopically or macroscopically visible finger-like or warty projections from epithelial surfaces are referred to as PAPILLOMAS
- Tumors forming large cystic masses in organs such as the ovary are called CYSTADENOMAS
- When a benign, or malignant, neoplasm produces a macroscopically visible projection above a MUCOSAL surface and projects into a lumen, as in the GI tract, it is termed a POLYP
- It is preferred that the term polyp be used only with benign tumors as malignant polyps are better called polypoid cancers

Malignant Tumor Nomenclature

- Malignant tumors arising in mesenchymal tissue are usually called SARCOMAS (Greek sar means fleshy)
- A malignant tumor arising from fibroblastic cells would be called a FIBROSARCOMA while one developing from osteoblastic cells would be termed an OSTEOSARCOMA
- Malignant neoplasms of epithelial origin arising from any of the three germ layers are called CARCINOMAS
- Carcinomas can be further qualified: One with a glandular growth pattern microscopically is termed an ADENOCARCINOMA
    - A malignant tumor producing recognizable squamous cells arising in any

Malignant Tumor Nomenclature
(Continued)

- Epithelium of the body is termed a SQUAMOUS CELL CARCINOMA
- Not infrequently, a cancer is composed of undifferentiated cells and must be

designated as a poorly differentiated or undifferentiated malignant tumor

- The parenchymal cells in a neoplasm usually more or less resemble each other
- Occasionally the stem cell may undergo divergent differentiation, creating the so-called mixed tumor, example: mixed tumor of salivary gland origin
- However, these mixed tumors are composed of cells representative of a single germ layer

Tumor Nomenclature

- In contrast, the TERATOMA is made up of a variety of parenchymal cell types representative of MORE than one germ and usually all three germ layers

Inconsistent, Inappropriate and Confusing Nomenclature

- A malignant tumor of melanocytes has for years been called a MELANOMA when it is better termed a MELANOCARCINOMA
- A HAMARTOMA is a malformation (not a neoplasm) that presents as a mass of disorganized tissue indigenous to a particular site; example: nodule in lung containing cartilage, bronchi, blood vessels

Inconsistent, Inappropriate and Confusing Nomenclature

- Another misnomer is the CHORISTOMA, which is a congenital anomaly composed of a heterotopic rest of cells; example: pancreatic tissue found in the submucosa of the stomach

CHARACTERISTICS OF BENIGN AND MALIGNANT TUMORS

Differences Between Benign and Malignant Tumors

- These can be discussed under the headings:
  - 1) Differentiation and Anaplasia
  - 2) Rate of Growth

- 3) Local Invasion
- 4) Metastasis

Differentiation and Anaplasia

- DIFFERENTIATION refers to the extent to which parenchymal cells resemble comparable normal cells, both morphologically and functionally
- WELL-DIFFERENTIATED tumors are composed of cells resembling the mature normal cells of the tissue of origin of the neoplasm
- POORLY OR UNDIFFERENTIATED tumors have primitive-appearing, unspecialized cells
- In general, BENIGN tumors are WELL-DIFFERENTIATED
- In contrast, MALIGNANT tumors range from WELL-DIFFERENTIATED to UNDIFFERENTIATED
- Malignant neoplasms composed of undifferentiated cells are said to be ANAPLASTIC; lack of differentiation or ANAPLASIA is considered a hallmark of malignant transformation
- Anaplasia literally means "to form backward"; however lack of differentiation is not the consequence of dedifferentiation
- Anaplasia is marked by a number of morphologic and functional changes which include:
  - 1) PLEOMORPHISM: variation of size and shape of the cells and their nuclei
  - 2)Nuclei contain an abundance of DNA are are extremely dark staining which is termed HYPERCHROMATISM
  - 3) Anaplastic tumors usually possess large NUMBERS of mitoses

The presence of mitoses does not necessarily indicate that a tumor is malignant or th

Differentiation and Anaplasia

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- at the tissue is neoplastic
- 4) More important as a morphologic feature of malignant neoplasia is the presence of ATYPICAL, BIZARRE mitotic figures

Other features of anaplasia include:

- 5) TUMOR GIANT CELLS
- 6) ORIENTATION of anaplastic cells is markedly disturbed

- Generally, the more rapidly growing and the more anaplastic a tumor, the less likely it is that there will be specialized functional activity. The cells in benign tumors are almost always well differentiated and resemble their normal cells of origin; the cells in cancer are more or less differentiated but some loss of differentiation is always present

Rate of Growth

- Generally most BENIGN tumors grow SLOWLY over a period of years, whereas most CANCERS grow RAPIDLY, sometimes at an erratic pace
- In general, the growth rate of tumors correlates with their level of differentiation and thus most malignant tumors grow more rapidly than do benign ones

Local Invasion

- Nearly all benign tumors grow as cohesive expansile masses that remain localized
- Because benign tumors typically grow slowly, they usually develop a rim of compressed connective tissue, which may be called a fibrous capsule
- The growth of malignant tumors is accompanied by progressive infiltration, invasion and destruction of surrounding tissue leaving them poorly demarcated
- Next to the development of metastases, invasiveness is the most reliable feature that differentiates malignant from benign tumors

Metastasis

- METASTASES are tumor implants that are DISCONTINUOUS with the primary tumor
- Metastasis unequivocally marks a tumor as malignant because benign neoplasms do not metastasize
- With few exceptions, all cancers can metastasize; malignant glial cell tumors and basal cell carcinomas rarely metastasize
- In general, the more aggressive, the more rapidly growing and the larger the primary neoplasm, the greater the likelihood it has or will metastasize
- Approximately 30% of the newly diagnosed patients with solid tumors

(excluding most skin tumors) present with metastases

Metastasis: Pathways of Spread

- Dissemination of cancers may occur through one of three pathways:
  - 1) direct seeding of body cavities or surfaces
  - 2) lymphatic spread
  - 3) hematogenous spread
- Seeding of Body Cavities and Surfaces: may occur whenever a malignant tumor penetrates into a natural “open field”
- The peritoneal cavity is most often involved but pleural, pericardial, subarachnoid and joint spaces may be affected
- Lymphatic spread is the most common pathway for the initial dissemination of carcinomas but sarcomas may use this route
- The pattern of lymph node involvement follows the natural routes of drainage
- Nodal enlargement in proximity to a cancer does not necessarily mean dissemination of the primary tumor
- Hematogenous spread is typical of sarcomas but carcinomas may also use this route
- The liver and lungs are most frequently involved secondarily in such hematogenous dissemination
- Veins are more easily invaded by tumors and certain cancers, such as renal cell carcinomas have a propensity for them

Clinical Features of Tumors

- Tumors are essentially parasites with some only causing mischief while others are catastrophic
- ALL tumors, even benign ones, can cause morbidity and mortality
- Every new growth requires careful appraisal lest it be cancerous; with a few exceptions, all masses require anatomic evaluation
- The following will be discussed under this heading:
  - 1) the effects of a tumor on the host
  - 2) the grading and clinical staging of cancer
  - 3) the laboratory diagnosis of tumors

Effects of Tumor on Host

- Certainly cancers are for more threatening than benign tumors but both types can cause problems because of:
  - 1) location and impingement on adjacent structures
  - 2) functional activity such as hormone synthesis
  - 3) bleeding and secondary infections when they ulcerate
  - 4) initiation of acute symptoms caused by either rupture or infarction

Effects of Tumor on Host: Local and Hormonal Effects

- Location of a tumor may be critical as for example a pituitary adenoma. While this tumor is benign and even though a particular one may not produce hormone, a pituitary adenoma can destroy the remaining gland and cause serious endocrinopathy; benign and malignant tumors of the gut may cause obstruction

Local and Hormonal Effects

- Neoplasms arising in endocrine glands may produce manifestations by elaboration of hormones
- The erosive destructive growth of cancers or the expansile pressure of a benign tumor on any surface may cause ulcerations, secondary infections and bleeding

Effects of Tumor on Host: Cancer Cachexia

- Cancer patients commonly suffer progressive loss of body fat and lean body mass accompanied by profound weakness, anorexia and anemia. This wasting syndrome is termed CACHEXIA
- The causes of cachexia are obscure but cachexia is NOT caused by the nutritional demands of the neoplasm

Cancer Cachexia

- Current evidence indicates that cachexia results from the action of soluble factors such as cytokines (TNF-alpha and IL-1) either produced by the tumor or the host

- Reduced food intake alone is not sufficient to explain the cachexia of malignancy

Effects of Tumor on Host: Paraneoplastic Syndromes

- Symptom complexes in cancer patients that cannot readily be explained, either by the local or distant spread of the tumor or by the elaboration of hormones indigenous to the tissue from which the tumor arose, are known as PARANEOPLASTIC SYNDROMES

Paraneoplastic Syndromes

- Paraneoplastic syndromes are important for three reasons:
  - 1) they may represent the earliest manifestation of an occult tumor
  - 2) they may represent significant clinical problems and may even be lethal
  - 3) they may mimic metastatic disease and therefore confound treatment

Endocrinopathies
Nerve and Muscle Syndromes
Dermatologic Disorders
Vascular and Hematologic Changes
Other Paraneoplastic Syndromes

Grading and Staging of Tumors

- Comparison of the end results of various forms of cancer treatment, particularly between clinics, requires some degree of comparability of neoplasms being assayed
- To this end, systems have been derived to express these results
- To accomplish this goal, at least in semiquantitative terms, the level of

differentiation, or GRADE, and the extent of spread of a cancer within the patient, or STAGE, serve as parameters of the clinical gravity of the disease

- GRADING of a cancer is based on the degree of differentiation of the tumor cells and the number of mitoses within the tumor as presumed correlates of the neoplasm's aggressiveness
- Cancers are classified as grades I to IV with increasing anaplasia
- Criteria for the individual grades vary with each form of neoplasia; some of these will be discussed later and in other courses
- In general, and with few exceptions, grading of cancers has proven to be of less clinical value than has staging
- The STAGING of cancers is based on the size of the primary lesion, its extent of spread to regional lymph nodes, and the presence or absence of blood-borne metastases
- There are two major staging systems: 1) Union International Contre Cancer (UICC) and 2) American Joint Committee (AJC) on Cancer Staging
- The UICC uses the TMN system
- T for primary tumor: T0 (in situ); T1 to T4 with increasing size
- N for regional lymph node involvement: NO(none); N1 to N3 denotes involvement of an increasing number and range of nodes
- M for metastases: MO(none); M1 and M2 indicates the presence of mets and number

Grading and Staging of Tumors
(Continued)

- The AJC employs a different nomenclature and divides all cancer into stages 0 to IV, incorporating within each of these stages the size of the primary lesion as well as the presence of nodal spread and distant metastases
- The use of these systems will be described later in consideration of specific tumors

Laboratory Diagnosis of Cancer

- Every year the approach to laboratory diagnosis of cancer becomes more complex, more sophisticated and more specialized
- Importance of Clinician in diagnosis: 1) clinical data; 2) adequate, representative and properly preserved specimen
- Sampling approaches for histologic and cytologic methods: 1) excision or biopsy; 2) fine-needle aspiration; and 3) cytologic smears

- Immunocytochemistry: Availability of specific monoclonal antibodies has greatly facilitated the identification of cell products or surface markers
- The utility of immunohistochemistry includes:
- 1) Categorization of undifferentiated malignant tumors; ex. keratin in tumors of epithelial origin
- 2) Categorization of leukemias and lymphomas; ex. classification of T and B cell tumors
- 3) Determination of site of origin of metastatic tumors; ex. prostate-specific antigen in a tumor
- 4) Detection of molecules that have prognostic or therapeutic significance; ex. detection of hormone (estrogen and/or progesterone) receptors in breast cancer cells

Molecular Diagnosis

- 1) Diagnosis of malignant tumors; ex. molecular techniques used in differentiating benign (polyclonal) proliferations of T or B cells from malignant (monoclonal) proliferations
- 2) Prognosis of malignant neoplasms; ex. N-myc gene and deletions of 1p bode poorly for patients with neuroblastoma

3) Detection of minimal residual disease; ex. PCR-based amplification

Molecular Diagnosis

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- gives a measure of residual leukemia cells in treated pts. with chronic myeloid leukemia
- 4) Diagnosis of hereditary predisposition to cancer; ex. germ line mutation in cancer-suppressor genes is associated with an extremely high risk of developing specific cancers

Flow Cytometry

- Flow cytometry can rapidly and quantitatively measure several individual cell characteristics, such as membrane antigens and DNA content of tumor cells
- Cell surface antigens can be used for classification; ex. leukemias/lymphomas
- Relationship between DNA content and prognosis; ex. aneuploidy-poorer prognosis

Tumor Markers

- Tumor markers are biochemical indicators of the presence of a tumor
- Tumor markers include: cell surface antigens, cytoplasmic proteins, enzymes and hormones
- Example: Carcinoembryonic antigen (CEA) is found in carcinomas of colon, pancreas, lung, stomach and breast
- CEA assays lack both specificity and the sensitivity required for the detection of early cancers
- Alpha-fetoprotein (AFP) is associated with liver cell cancer and nonseminomatous germ cell tumors of the testis
- AFP can be seen in non-neoplastic conditions such as cirrhosis and hepatitis

SUPPLEMENTAL TABLES
Paraneoplastic Syndromes (Endocrinopathies)
Paraneoplastic Syndromes (Endocrinopathies)
Paraneoplastic Syndromes (Endocrinopathies)
Paraneoplastic Syndromes (Nerve and Muscle Syndromes)
Paraneoplastic Syndromes (Dermatologic Disorders)
Paraneoplastic Syndromes (Osseous, Articular, Soft Tissue Change)
Paraneoplastic Syndromes (Vascular/Hematologic Changes)

Paraneoplastic Syndromes
Comparison Between Benign and Malignant Tumors
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TUMOR MARKERS
(Hormones)
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(Oncofetal Antigens)
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(Isoenzymes)
TUMOR MARKERS
(Specific Proteins)
TUMOR MARKERS
(Mucins & Other Glycoproteins)
OCCUPATIONAL CANCERS
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