Neoplasia = the process of new growth.

Neoplasm = the new growth (benign or malignant).

Tumor = historically referred to any swelling; now synonymous with neoplasm.

Oncology = the study of neoplasia.

Oncogenesis = the causation or production of neoplasia.

Cancer = common term for all malignant neoplasms (esp human medicine).
"A tumor is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissue and persists in the same excessive manner after cessation of the stimuli which evoked the change." (Willis, 1952)

"Tumor cells do not necessarily proliferate at a faster rate than their normal counterparts. Tumor growth depends on other factors, such as the growth fraction (proportion of cycling cells) and the rate of cell death. The major determinant of tumor growth is clearly the fact that more cells are produced than die in a given time." (Essential Pathology. Rubin & Farber, 1995)

“the persistence of tumors... results from heritable genetic alterations that are passed down to the progeny of the tumor cells. These genetic changes allow excessive and unregulated proliferation that becomes autonomous (independent of physiologic growth stimuli) although tumors generally remain dependant on the host for their nutrition and blood supply.” (Pathologic Basis of Disease, 2005)
• despite rules & regulations for classifying / naming neoplasms, inconsistencies persist.

• the term for a neoplasm must convey whether it is:
  
  benign or malignant

  mesenchymal versus epithelial origin.

  the suffix -oma is almost always present.

**Mesenchyma** = the part of the embryonic mesoderm, that differentiates into connective tissue, bone, cartilage, muscle and hematopoietic / lymphatic systems.

**Epithelium** = cells that line surfaces or lumina of organs (eg epidermis, gut, lung, kidney) and form glands (eg liver, pancreas, mammary, thyroid, etc)
Benign

1 mesenchymal (structural / connective tissues, vessels):

   lipoma,
   fibroma,
   osteoma,
   chondroma,
   leiomyoma,
   rhabdomyoma,
   hemangioma,
   etc.
Benign epithelial:

i) **non-glandular** epithelial proliferations

- papilloma,
- trichoepithelioma,
- pilomatrixoma, etc.

Esophageal papilloma, bovine. Note finger-like projections from the surface.
Skin papilloma, bovine. In this low power histologic section note the finger-like projections (fronds) from the surface of the mass.
Benign

epithelial:

ii) adenoma:

- cells form recognizable glandular structures: mammary adenoma
  (tubules / acini) pulmonary adenoma
  intestinal adenoma
  renal tubular adenoma

- cells derived from glandular tissue: pituitary adenoma
  (but no tubules/acini) hepatocellular adenoma
  adrenal cortical adenoma
Inflammatory polyps, urinary bladder, dog. Polyps resulting from inflammation & secondary hyperplasia are occasionally observed on mucosal surfaces, such as urinary bladder, nasal sinuses, etc. On gross examination it is sometimes difficult to differentiate hyperplastic from neoplastic (adenomatous) polyps.
Malignant

1. mesenchymal:

   - sarcomas: liposarcoma,
     fibrosarcoma,
     osteosarcoma,
     chondrosarcoma,
     leiomyosarcoma,
     rhabdomyosarcoma,
     hemangiosarcoma, etc.

2. epithelial / parenchymal:

   - carcinoma: squamous cell carcinoma
     (no glandular patterns)
     pituitary carcinoma
     hepatocellular carcinoma
     adrenal cortical carcinoma

   - adenocarcinomas: bronchoalveolar adenocarcinoma
     (glandular patterns)
     mammary adenocarcinoma
     intestinal adenocarcinoma
Inconsistencies:

lymphoma (or lymphosarcoma) = neoplastic disorder (malignant) of lymphoid tissue.

leukemia = malignant neoplasm of blood-forming tissues.

melanoma (or malignant melanoma) = a malignant tumor of melanocytes.

melanocytoma = benign tumor of melanocytes.
Mixed Tumors

- the majority of neoplasms are composed of cells representative of a single germ layer, and a single cell type.
- mixed tumors contain more than one cell type, but all derived from one germ layer.
Mixed Tumors

Mixed Mammary Tumor
- a relatively common mammary tumor of dogs.
- contains both epithelial and mesenchymal elements.
SEM of a mammary gland acinus showing the branching myoepithelial cells occupying grooves between the bases of the secretory cells. (source: Textbook of Histology. 1986.)

Diagram of myoepithelial cells and epithelial cells of a secretory acinus.
Mixed mammary tumor, dog. This slide includes some acinar / tubular structures of variable size & shape lined by a cuboidal epithelium (arrows), a loose mesenchymal tissue containing a relatively small number of elongated fibroblast-like cells (i.e., proliferating myoepithelial type cells) producing abundant fibrous to fibromucinous matrix (stroma). Toward the bottom, there is gradual merging of this loose mesenchymal tissue with cartilage (C) that contains some chondroblasts. Aggregates of inflammatory cells (mainly plasma cells) are at the top left of the slide (*). Based on the anaplasia & abundance of necrosis in other parts of the section, this tumor was considered malignant.
Same case as previous slide (different area). A larger amount of mature cartilaginous tissue (C) is evident and a small amount of osseous tissue (O) is present in this area. This likely represents metaplasia of the mesenchymal myxoid stroma.
Teratomas

- composed of variety of tumor cell types representative of more than one germ layer.
- arise from totipotential embryonic cells (likely PGC’s); primarily found in the gonads.
- these totipotential cells differentiate into various types of tissues.

Ovarian teratoma, equine. Grossly the tumor consists mostly of fibrous-like tissue with several cyst like structures evident. Note the large aggregate of hair in the left part of the mass.
Ovarian teratoma, 7-year-old red-eared slider turtle. This microscopic section shows a wide diversity of tissues, such as cartilage (C), bone (B), stratified squamous epithelium (with some keratinization) (K), mucous epithelium (M), nervous tissue (N), band of melanocytes (arrow).
Higher magnification of previous slide. Cartilage (C), keratin (K) from stratified squamous epithelium, mucous epithelium (M), nervous tissue (N), band of melanocytes (arrow).
Benign vs Malignant Neoplasms

Robbin’s Figure 7-22  Comparison between a benign tumor of the myometrium (leiomyoma) and a malignant tumor of similar origin (leiomyosarcoma).
Benign vs Malignant Neoplasms

**Benign**

- well differentiated cells & architecture that closely resemble the normal counterpart.
- grow as cohesive expansile masses that remain localized to their site of origin.
- grow & expand slowly with compressive atrophy of adjacent parenchymal cells.
- many have a fibrous capsule formed from the surrounding compressed stroma.

Thyroid (follicular cell) adenoma, equine. Note: well demarcated and compression atrophy of adjacent thyroid tissue is evident on histology (right).
Exophytic skin mass – this could be one of a large number of skin tumors, however on palpation it may have a similar texture to fat, making you suspicious of a lipoma.

On cut surface the mass extends into the subcutis and has a similar appearance and texture of subcutaneous fat. This is one tumor skin tumor that you can be pretty sure about the diagnosis from gross examination alone.
To make a definitive diagnosis you have to do histology. In this case the mass consists of lobules of well differentiated adipocytes. Also note how well circumscribed the mass is from the adjacent dermal collagen (arrows). These features confirm your diagnosis of subcutaneous lipoma.

Lipomas, like other benign tumors, tend to be small and slow growing. If left for a long period however, benign tumors can in some cases become quite large. This large mass on the hind limb of a dog is a simple lipoma which was allowed to grow over a long time (not known how long, but I would guess many months or more likely several years).
• exceptions - **cutaneous histiocytoma** is anaplastic, yet benign behavior & regresses.

• some benign neoplasms may have serious, consequences:
  ① tumors of the brain (space-occupying lesions).
  ② some hormone-producing tumors, eg insulinoma, adrenal cortical adenoma.
  ③ pedunculated intraabdominal lipomas may entrap segments of intestines.
Intracranial meningioma, dog. Despite its relatively small size, such a tumor can have serious consequences because of its critical location. Note well circumscribed meningioma compressing a cerebral hemisphere.

Intracranial meningioma, cat. Note meningioma attached to the dura matter with compression of the cerebellum (arrow).
Pedunculated lipoma equine. Although these lipomas are benign, because they are attached by an long narrow stalk (peduncle), they can often wrap around and strangulate segments of bowel (as in above photo).
Benign

- some benign tumors may regress; eg cutaneous papillomas, cutaneous histiocytoma.
- other benign tumors may slowly progress to malignancy eg colonic adenomas.
- some tumors are malignant from the onset, eg oral melanomas.

Colonic adenomatous polyps are relatively common in humans and dogs. If not removed, these can progress to colonic adenocarcinoma.
Malignant

• designation of malignancy indicates an aggressive, life-threatening tumor.

• malignancy is characterized by:

  1. anaplasia
  2. rapid rate of growth
  3. local invasion of tissue
  4. metastasis
• differentiation refers to the extent to which neoplastic cells resemble comparable normal cells.

• lack of differentiation is called anaplasia and characterizes malignancy.

• most cancers likely arise from transformed stem cells that show varying degrees of differentiation.
i) Pleomorphism
   - variation in size and shape of both the cells and their nuclei.

Uterine adenocarcinoma, bovine. The neoplastic cells are highly anaplastic: cellular and nuclear pleomorphism, anisocytosis and anisokaryosis (compare the two cells labelled 1), high nucleus / cytoplasm ratio, large nucleoli (2), binucleated cell (3). The name of this tumor implies it is derived from glandular epithelial cells that normally would form acini. Yet, the cells in this field are so undifferentiated that they have remained as individual cells and show no tendency to form acinar structures.
ii) Abnormal nuclei
- nuclei often large (high N/C ratio)
- chromatin often coarsely clumped and marginalized.
- nucleoli often large and/or multiple.

Fibrosarcoma, cat. The cells show nuclear pleomorphism and marked anisokaryosis, and their nucleoli are often multiple and of different sizes (generally larger than normal)
iii) Mitoses
- increased numbers of mitotic figures.
- abnormal (atypical to bizarre) mitotic figures.

Fibrosarcoma, dog. Several mitotic figures evident. The two marked with large arrows have the chromosomes aligned at the equatorial plane (metaphase plate), the three marked small arrows have the chromosomes at the cellular poles (anaphase / telophase).
iii) Mitoses
    - increased numbers of mitotic figures.
    - abnormal mitotic figures.

Fibrosarcoma, cat. This slide shows two abnormal mitotic figures, in which there is no orderly chromosomal arrangement.
iv) Loss of Polarity
- cells lose their nuclear polarity & grow in an disorganized fashion.

Uterine adenocarcinoma, bovine. Two acini, surrounded by smooth muscle, are present. The neoplastic cells show features of anaplasia including anisokaryosis and particularly, loss of polarity; ie in many cases the nuclei are not in the normal basal location and also the cells tend to pile up on each other instead of forming a single layer of cuboidal epithelium along the basement membrane of the acinus.
v) Other
• tumor giant cells.

Anaplastic tumor of the skeletal muscle (rhabdomyosarcoma). Note the marked cellular and nuclear pleomorphism, hyperchromatic nuclei and tumor giant cells (with large single or multiple nuclei).
Anaplasia

v) Other
  • ischemic necrosis / hemorrhage

Hepatocellular carcinoma, dog. The cut surface of the tumor shows extensive hemorrhage and numerous yellow areas of necrosis (arrows), good indications that the tumor is growing rapidly and is malignant.
Malignant

Anaplasia

• not all features of anaplasia are necessarily seen in a given malignant tumor.

• anaplastic features usually calls for a poor or guarded prognosis.

• some malignant neoplasms are composed of well differentiated cells.

• the whole clinical, morphologic (gross & microscopic) and epidemiologic aspects of each tumor must be evaluated in order to provide an accurate prognosis.
Rate of Growth (Tumor Cell Kinetics)

- growth rates of neoplasms correlates with their level of differentiation / anaplasia.

i) Doubling time of tumor cells

- after clinical detection, doubling times can range from 1–12 months (ave of 2-3 months).

Robbin’s fig 7-12. Biology of tumor growth. Minimal estimates of tumor cell doublings that precede the formation of a clinically detectable tumor mass. By the time a solid tumor is detected, it has already completed a major portion of its life cycle as measured by cell doublings.
ii) Fraction of tumor cells in the replicative pool ("growth fraction")

- Tumors with low growth fraction are more refractory to treatment.

iii) Rate of cell loss from the tumor

- For tumor growth, cell production must exceed cell loss (apoptosis, shedding, etc).

Robbin’s fig 7-13. Schematic representation of tumor growth. As the cell population expands, a progressively higher percentage of tumor cells leaves the replicative pool by reversion to $G_0$, differentiation, and death.
Malignant Local Invasion of Tissue

- cancer growth is characterized by progressive infiltration (invasion) and destruction of surrounding tissues.

Osteosarcoma of the nasal cavity, dog. The neoplasm has invaded the adjacent nasal sinuses and the hard palate (white arrows), and also the calvarium / brain (black arrow)
Osteosarcoma, dog. This tumor originated from the proximal region of the left femur. It has destroyed the femoral head and has extensively invaded the adjacent bone and surrounding soft tissues. Hemorrhages within the neoplastic mass are also consistent with a malignant process.
Malignant  Metastasis  i) Lymphatic spread

Metastatic osteosarcoma, axillary lymph node, dog. Several metastatic foci of osteosarcoma are scattered throughout a local lymph node.
Intestinal adenocarcinoma, dog. The primary tumor is within the intestinal wall (large arrow). The large mass on the right represents confluent metastases (M) of the primary tumor to local lymph nodes. The mesentery in the center of the picture contains several small white nodules (small arrows) which represent additional sites of metastasis of the primary tumor.
Same case as previous slide. Multiple hepatic metastases (via portal blood flow) of an intestinal adenocarcinoma, dog. It is not possible to tell from this picture alone whether these neoplastic masses are metastases from an extrahepatic tumor or from a primary hepatic tumor. Also, hepatic granulomas would not protrude so much above the surface of the liver and hepatic abscesses would have a smoother surface.
Pulmonary metastatic osteosarcoma. Ostosarcomas frequently show early metastasis to the lungs. In fact they have often metastasized to lung by the time the primary tumor has been diagnosed clinically.
ii) Hematogenous spread

Metastatic hemangiosarcoma, brain, dog. Hemangiosarcomas often show widespread metastasis. Lung, heart, liver & brain are frequently involved.
iii) Seeding of Body Cavities and Surfaces ("exfoliation and implantation")

Uterine adenocarcinoma, bovine (above, arrow) with numerous metastatic implants on the mesentery (left). These metastatic sites are the result of numerous individual neoplastic cells that have exfoliated from the surface of the primary tumor and after random movement through the pelvic / peritoneal cavity fluid have implanted on the mesentery and grown into individual tumor masses.
Splenic hemangiosarcoma, dog. The primary tumor is in spleen (large arrow) with numerous tumor implants attached to the omentum or visceral surfaces (a few labeled with small arrows).

iii) Seeding of Body Cavities and Surfaces ("exfoliation and implantation")

Malignant Metastasis
iii) Seeding of Body Cavities and Surfaces ("exfoliation and implantation")

Hemangiosarcoma, dog. Widespread seeding of the abdominal cavity with tumor implants. A few small tumors are also evident in the liver (right, arrows), however these likely occurred by concurrent hematogenous spread.