Neoplasia

Fatima Obeidat, MD
Assistant Professor of Neuropathology
- *Neoplasia* literally means "new growth"
- Neoplastic cells are *transformed* because they continue to replicate, independent of normal regulatory influences.
- Neoplasms enjoy a certain degree of autonomy and tend to increase in size; Their autonomy is not complete, some neoplasms require endocrine support, and depend on the host for their nutrition and blood supply.
- A neoplasm is referred to as a tumor and study of tumors is called oncology (oncos, "tumor," and logos, "study of").

- The neoplasms are divided into benign and malignant
I. Benign tumors

a. its microscopic and gross characteristics are considered to be relatively innocent,

b. it will remain localized and amenable to local surgical removal; the patient generally survives
II. Malignant tumors are collectively referred to as **cancers**

a. Implies that the lesion can invade adjacent structures

b. Spread to distant sites (metastasize) to cause death

Note: Not all cancers pursue a deadly course, the most aggressive may be curable but the term constitutes a red flag
The tumor has two basic components:

1. Parenchyma, made up of transformed or neoplastic cells
   - It determines its biologic behavior, and
   - Is this component from which the tumor derives its name

2. The supporting, host-derived, non-neoplastic stroma,
   - Made up of connective tissue, blood vessels, and
   - Is crucial to the growth of the neoplasm, since it carries the blood supply and provides support for the growth of parenchymal cells
Nomenclature

1. Benign Tumors of mesenchymal tissues

- In general, are designated by attaching the suffix -oma to the cell type from which the tumor arises.

a. A benign tumor of fibrous tissue is a fibroma;

b. A benign cartilaginous tumor is a chondroma

c. A benign tumor of bone is called osteoma
2. Benign epithelial tumors are classified either:
   a. on the basis of their microscopic pattern
   b. Or on the basis of their macroscopic pattern.
   c. Others are classified by their cells of origin
I. **Adenoma**:

- Is applied to benign epithelial neoplasm producing gland patterns and to neoplasms derived from glands but not necessarily forming glands

a. A benign epithelial neoplasm arising from renal tubule, cells and growing in glandlike patterns called adenoma

b. A mass of benign epithelial cells that produces no glandular patterns but has its origin in the adrenal cortex
Colonic polyp
II. Papillomas:
- Are benign epithelial neoplasms, growing on any surface, that produce microscopic or macroscopic finger-like fronds

III. A polyp:
- A mass that projects above a mucosal surface, as in the gut, to form a macroscopically visible structure and although this term commonly is used for benign tumors, some malignant tumors may grow as polyps,

IV. Cystadenomas
- Are hollow cystic masses that typically arise in the ovary
Colonic polyp
Colonic polyp
Ovarian cystadenoma
The nomenclature of malignant tumors

I. Malignant neoplasms arising in "solid" mesenchymal tissues or its derivatives are called sarcomas,
   a. A cancer of fibrous tissue origin is a fibrosarcoma,
   b. Cancer of chondrocytes is a chondrosarcoma

II. Whereas those arising from the mesenchymal cells of the blood are called leukemias or lymphomas.
III. While the epithelia are derived from all three germ cell layers, malignant neoplasms of epithelial cells are called *carcinomas* regardless of the tissue of origin.

a. Thus, a malignant neoplasm arising in the renal tubular epithelium (mesoderm) is a carcinoma,

b. As are the cancers arising in the skin (ectoderm)

c. and lining epithelium of the gut (endoderm).
Carcinomas are subdivided further.

a. Carcinomas that grow in glands are *adenocarcinomas*

b. Those that produce squamous cells are called *squamous cell carcinomas*.

- Sometimes the tissue or organ of origin can be identified, as in the designation of renal cell adenocarcinoma.
Adenocarcinoma
Well differentiated squamous cell carcinoma
The transformed cells in a neoplasm, resemble each other, as though all had been derived from a single progenitor, consistent with the monoclonal origin of tumors.

In some instances, however, the tumor cells undergo divergent differentiation, creating so-called mixed tumors.
1. *Mixed tumor of salivary gland:*
- (pleomorphic adenoma:)
- It has epithelial components dispersed throughout a fibromyxoid stroma with islands of cartilage or bone.

2. *Fibroadenoma of the female breast:*
- This benign tumor contains a mixture of ductal elements (adenoma) embedded in a loose fibrous tissue (fibroma).
Benign mixed tumor of the parotid
Fibroadenoma of the breast
Teratoma:-
- Is a special type of mixed tumor that contains recognizable mature or immature tissues representative of more than one germ cell layer.
- Originate from **totipotential** germ cells such as those normally present in the ovary and testis.
- Teratomas they may give rise to neoplasms that have bone, epithelium, muscle, nerve, and other tissues.
Teratoma
Some glaring inconsistencies may be noted.

a. Lymphoma: malignant tumor of lymphocytes

b. **Mesothelioma**: malignant tumor of mesothelium

c. Melanoma: malignant tumor of melanocytes

d. Seminoma: malignant tumor of germ cells in testis.

e. Astrocytoma: malignant tumor in brain.
Hamartoma: Is a mass of disorganized tissue indigenous to the particular site and examples include:

- Lung hamartoma is a mass composed of disorganized islands of cartilage, bronchi, and blood vessels

- Hamartomas have traditionally been considered congenital but genetic studies suggest a neoplastic origin
Hamartoma
Choristoma

- Called heterotopia

- Means presence of normal tissue in another tissue and is a congenital anomaly.

- For example, a small nodule of normally organized pancreatic tissue may be found in the submucosa of the stomach, duodenum, or small intestine
CHARACTERISTICS OF BENIGN AND MALIGNANT NEOPLASMS
- In general, benign tumors are genetically "simple," harboring fewer mutations than cancers, and genetically stable, changing little in genotype over time.

- In practice, the determination of benign versus malignant is made with remarkable accuracy using long-established clinical and anatomic criteria, but some neoplasms defy easy characterization but certain features may indicate innocence, and others may indicate malignancy.
I. Differentiation and anaplasia

- Differentiations is seen only in the parenchymal cells and refers to the extent to which tumor cells resemble their normal forebears morphologically and functionally.

A. Benign neoplasms: Are composed of well-differentiated cells that closely resemble their normal counterparts.

- A chondroma is made up of mature cartilage cells that synthesize their usual cartilaginous matrix—evidence of morphologic and functional differentiation.

- In benign tumors, mitoses are rare and are of normal configuration.
B. Malignant neoplasms: can be well differentiated or completely undifferentiated.

- For example, well-differentiated carcinomas of the thyroid may contain normal-appearing follicles, such tumors may be difficult to distinguish from benign proliferations.

**Note:** The stroma carrying the blood supply is crucial to the growth of tumors but does not aid in the separation of benign from malignant ones and the amount of stroma does determine, however, the consistency of a neoplasm

**Desmoplasia:** Production of abundant amount of stroma by some cancers and these tumors called scirrhouss tumors
Invasive ductal carcinoma of breast showing desmoplasia
Adenocarcinoma with desmoplasia
**Anaplastic tumors**: Are malignant neoplasms that are composed of un-differentiated cells.

- Lack of differentiation, or anaplasia, literally means “backward formation”-implying dedifferentiation, or loss of the structural and functional differentiation of normal cells.

- But some cancers arise from stem cells; therefore, failure of differentiation, rather than de-differentiation of specialized cells, accounts for their undifferentiated state.

- In some cases, dedifferentiation of apparently mature cells does occur during carcinogenesis.
- Anaplastic cells display
  a. Marked *pleomorphism* (i.e., variation in size and shape)
  b. The *nuclei are extremely hyperchromatic* (dark-staining)
  c. An increased nuclear-to-cytoplasmic ratio that may approach 1:1 instead of the normal 1:4 or 1:6
  d. Prominent nucleoli and giant cells.
  e. Mitoses often are numerous and distinctly atypical; tripolar or quadripolar mitotic figures
  f. Fail to develop recognizable patterns of orientation to one another (they lose normal polarity), they may grow in
Anaplastic malignant tumor
Anaplastic tumor cells with abnormal mitoses
sheets, with total loss of glandular or squamous architecture

- The more differentiated the tumor cell, the more it retains the functional capabilities of its normal counterparts.

  a. Benign neoplasms and even well-differentiated cancers of endocrine glands frequently elaborate the hormones characteristic of their origin.

  b. Well-differentiated squamous cell carcinomas produce keratin
Note: In other instances, unanticipated functions emerge.

- Some cancers may elaborate fetal proteins not produced by comparable cells in the adult
- Cancers of nonendocrine origin may produce so-called ectopic hormones For example, certain lung carcinomas may produce adrenocorticotropic hormone (ACTH), parathyroid hormone-like hormone,. 
- Despite exceptions, the more rapidly growing and the more anaplastic a tumor, the less likely it is to have specialized functional activity.
**Dysplasia**, disorderly but non-neoplastic proliferation.

- Dysplasia is encountered principally in epithelial lesions.
- It is a *loss in the uniformity of individual cells and in their architectural orientation*.

Dysplastic cells exhibit

a. considerable pleomorphism with hyperchromatic nuclei.

b. Mitotic figures are more abundant than usual and appear in abnormal locations within the epithelium, for example in dysplastic stratified squamous epithelium. Mitoses may be seen at all levels and even in surface cells.
• Carcinoma insitu-cervix
c. There is considerable architectural anarchy. For example, the usual progressive maturation of tall cells in the basal layer to flattened squames on the surface may be lost and replaced by a disordered of dark basal-appearing cells.

- When dysplastic changes involve the entire thickness of the epithelium, the lesion is referred to as **carcinoma in situ**, a preinvasive stage of cancer.

- The term *dysplasia* is not synonymous with cancer;

- *Mild to moderate dysplasias sometimes regress completely, particularly if inciting causes are removed*.
II. Rate of Growth:
- Most benign tumors grow slowly, and most cancers grow much faster but there are exceptions.
- Some benign tumors grow more rapidly than some cancers, for example, the rate of growth of leiomyomas (benign smooth muscle tumors) of the uterus is influenced by estrogens levels, they may increase rapidly in size during pregnancy and then cease growing after menopause.
- Adequacy of blood supply may affect the growth rate of benign tumors, for example, pituitary adenoma locked in the sella turcica may shrink suddenly because they
undergo a wave of necrosis as progressive enlargement compresses their blood supply.

- Despite these caveats, it is true that most benign tumors increase in size slowly over months to years.

- The rate of growth of malignant tumors usually correlates inversely with their level of differentiation. In other words, poorly differentiated tumors tend to grow more rapidly than do well-differentiated tumors.

- However, there is wide variation in the rate of growth. Some grow slowly for years and then enter a phase of rapid growth signifying the emergence
Uterus-leiomyomas
of an aggressive subclone of transformed cells.

- Others grow relatively slowly and steadily;
- Despite these rarities, most cancers progressively enlarge over time, some slowly, others rapidly,
- Rapidly growing malignant tumors often contain central areas of ischemic necrosis, because the tumor blood supply, derived from the host, fails to keep pace with the oxygen needs of the expanding mass of cells.
III. INVASION

- A benign neoplasm remains localized at its site of origin. It does not have the capacity to infiltrate or invade.

- For example, as adenomas slowly expand, most develop an enclosing fibrous capsule separating them from the host tissue and this capsule probably is derived from the stroma of the host tissue and the stroma of the tumor.

• Note: Not all benign neoplasms are encapsulated.

- For example, the leiomyoma of the uterus is discretely demarcated from the surrounding smooth muscle by a zone of compressed myometrium, but there is no well-
developed capsule but has a well-defined cleavage plane

- Some benign vascular neoplasms of the dermis are neither encapsulated nor discretely defined; therefore, the lack of a capsule does not mean that a tumor is malignant

Cancers:

- Grow by progressive infiltration, invasion, destruction, and penetration of the surrounding tissue and do not develop well-defined capsules.

- There are occasional instances in which a slowly growing malignant tumor deceptively appears to be encapsulated...
but microscopic examination usually reveals tiny crablike feet penetrate the margin and infiltrate adjacent structures.

- The infiltrative growth pattern makes it necessary to remove a wide margin of surrounding normal tissue when surgical excision of a malignant tumor is attempted and pathologists carefully examine the margins of resected tumors to ensure that they are devoid of cancer cells (clean margins)

- **Next to the development of metastases, local invasiveness is the most reliable feature that distinguishes malignant from benign tumors.**
IV. Metastasis

- Are secondary implants of a tumor that are discontinuous with the primary tumor and located in remote tissues

- More than any other attribute, the property of metastasis identifies a neoplasm as malignant.

- Not all cancers have equivalent ability to metastasize,
  a. Basal cell carcinomas of the skin and most primary central nervous system, rarely metastasize.
  b. At the other extreme are osteosarcomas which usually have metastasized to the lungs at the time of initial discovery
- Approximately 30% of patients with newly diagnosed solid tumors (excluding skin cancers other than melanomas) present with clinically evident metastases.

- In general, the more anaplastic and the larger the tumor, the more likely is metastatic spread, but as with most rules, there are exceptions; small cancers have been known to metastasize, conversely, some large may not.

- Dissemination may preclude the possibility of curing the disease, so obviously, short of prevention of cancer, no achievement would confer greater benefit on patients than the prevention of metastases.
Metastatic adenocarcinoma in lymph node
Malignant neoplasms disseminate by one of three pathways

1. **Spread by seeding**: Occurs when neoplasms invade a natural body cavity and it is characteristic of
   a. Ovarian cancers which often cover the peritoneal surfaces
   b. Medulloblastoma of the cerebellum may be carried by the cerebrospinal fluid to reimplant on the meninges

2. **Lymphatic spread** is more typical of carcinomas, whereas **hematogenous spread** is favored by sarcomas

- There are numerous interconnections, between the
lymphatic and vascular systems, so all forms of cancer may disseminate through either or both systems

**Note:**
- The pattern of lymph node involvement depends principally on the site of the primary neoplasm and the natural pathways of local lymphatic drainage.

--. Carcinoma of the breast usually arises in the upper outer quadrant and first spreads to the axillary nodes

- A "sentinel lymph node" is the first regional lymph node that receives lymph flow from a primary tumor and can be identified by injection of blue dyes near the primary tumor
- Biopsy of sentinel lymph nodes allows determination of the extent of tumor spread and can be used to plan treatment

**Note,**

- Although enlargement of nodes near a primary tumor should arouse concern for metastatic spread, it does not always imply cancerous involvement: the necrotic products of the tumor evoke immunologic responses in the nodes, such as proliferation of sinus histiocytosis; Thus, histopathologic verification of tumor within an enlarged lymph node is required.
3- **Hematogenous** spread is the favored pathway for sarcomas, but carcinomas use it as well
- arteries are penetrated less readily than are veins.

a- With venous invasion, malignant cells follow the venous flow draining the site of the neoplasm
- Since all portal area drainage flows to the liver, and all caval blood flows to the lungs, **the liver and lungs are the most frequently involved sites in hematogenous spread**

b- Cancers arising near the vertebral column such as prostate carcinoma often embolize through the **paravertebral plexus**
- Some carcinomas may grow within veins, renal cell carcinoma may invade the renal vein to grow in a snake-like fashion up the inferior vena cava, and may reach the right side of the heart and such intravenous growth may not be accompanied by widespread dissemination.

- Many observations suggest that the anatomic localization of a neoplasm and its venous drainage cannot wholly explain the systemic distributions of metastases. For example: Lung carcinomas tend to involve the adrenals.

- Note: Skeletal muscles, although rich in capillaries, are rarely the site of secondary deposits.
EPIDEMIOLOGY:

- Contribute to knowledge about the origin of cancer.
- The concept that cigarette smoking is associated with lung cancer arose primarily from epidemiologic studies.
- A comparison of the incidence rates for colon cancer and dietary patterns in the Western world and in Africa led to the recognition that dietary fat and fiber content may figure importantly in the causation of this cancer.
- Causes of cancer can be known from epidemiologic studies that relate particular environmental, racial and cultural influences to the occurrence of specific neoplasms.
Cancer Incidence

-- Over several decades, the death rates for many forms of cancer have changed. There was significant increase in the overall cancer death rate among men that was attributable largely to lung cancer, but this has finally begun to drop.

- By contrast, the overall death rate among women has fallen slightly, mostly as a result of the decline in death rates for cancers of the cervix, stomach, and large bowel.
The declining death rate from cervical cancer is related to widespread use of cytologic smear studies for early detection of this tumor and its precursor lesions.

The development of the human papillomavirus (HPV) vaccine may eliminate this cancer in the coming years.

The causes of decline in death rates for cancers of the stomach are obscure; but might be due to decreasing exposure to dietary carcinogens.

There is a striking climb in the rate of lung cancer in women, which was an uncommon form of neoplasia in this sex.
Geographic and Environmental Variables:

- Many advances in understanding the molecular pathogenesis of cancer have been made by analyzing hereditary cancers, it is fair to state that environmental factors are the predominant cause of the most common sporadic cancers.

- Death rates from breast cancer are about five times higher in the United States than in Japan and conversely, the death rate for stomach carcinoma is about seven times higher in Japan than in the US.

- Liver cell carcinoma is relatively infrequent in the US but
is the most lethal cancer among many African populations

- Nearly all the evidence indicates that these geographic differences are environmental rather than genetic in origin.

- The carcinogens lurk in environment, in food, and in personal practices and the most distressing environmental influences, in terms of prevention are those incurred in personal practices, such as cigarette smoking and chronic alcohol consumption.

- The risk of cervical cancer is linked to age at first intercourse and the number of sex partners (pointing to a causal role for transmission of the oncogenic virus HPV).
**Age:** In general, the frequency of cancer increases with age and Most cancer deaths occur between ages 55 and 75;
- The rising incidence with age may be explained
  a. by the accumulation of somatic mutations associated with the emergence of malignant tumors 
b. The decline in immune competence with ageing.
- Cancer causes slightly more than 10% of all deaths among children younger than 15 years and the major lethal cancers in children are leukemias, tumors of the central nervous system, lymphomas, and soft tissue and bone sarcomas.
Heredity:-

Hereditary forms of cancer are divided into three categories:

1. Autosomal Dominant Cancer Syndromes:
   a. Are cancers in which inheritance of a single mutant gene greatly increases the risk of developing a tumor.
   b. The predisposition to these tumors shows an autosomal dominant pattern of inheritance.

Example: Retinoblastoma in which 40% are familial and inherited mutations in a tumor suppressor gene (RB) are responsible for the development of this tumor in families.
- Carriers of this gene have a 10,000-fold increased risk of developing retinoblastoma

c. The Tumors in this category may be bilateral: patients with familial retinoblastoma develop bilateral tumors,

- And they also have a greatly increased risk of developing a second cancer, particularly osteosarcoma

d. Tumors are associated with a specific marker phenotype.

1. In Familial polyposis coli syndrome, there may be multiple colonic polyps (benign tumors) in the colon

2. Many endocrine tumors in multiple endocrine neoplasia syndromes
II. Autosomal Recessive Syndromes of Defective DNA Repair

- A group of rare autosomal recessive disorders collectively characterized by chromosomal or DNA instability and high rates of certain cancers.

--One of the best-studied is xeroderma pigmentosum, in which DNA repair is defective.
3. Familial Cancers of Uncertain Inheritance

- All the common types of sporadic cancers were reported to occur in familial forms where the inheritance pattern is unclear: examples are carcinomas of colon, breast, ovary.

- Features that characterize familial cancers include:
  
  a. Early age at onset, and might be multiple or bilateral
  b. Tumors arising in two or more close relatives of the case
  c. Are not associated with specific marker phenotypes,

- In contrast with the familial polyposis coli, familial colonic cancers do not arise in preexisting benign polyps.
In general, siblings have a relative risk between 2 and 5% to 10% of all human cancers.

NOTE: no more than 5% to 10% of all human cancers fall into one of the three aforementioned categories.

- What can be said about the influence of heredity in the large preponderance of malignant tumors?
- There is emerging evidence that the influence of hereditary factors is subtle and sometimes indirect: The genotype may influence the likelihood of developing environmentally induced cancers; For example, polymorphisms in drug-metabolizing enzymes confer genetic predisposition to lung cancer in people who smoke cigarettes.
Acquired Preneoplastic Lesions:

- Are referred to as *preneoplastic lesions* or "precancers".
- These designations are unfortunate because they imply inevitability, but although such lesions increase the likelihood of malignancy, but most do not progress to cancer.
- In many instances, precursor lesions arise in the setting of chronic injury or inflammation, which may increase the likelihood of malignancy by stimulating continuing regeneration or by exposing cells to byproducts of inflammation, both of which can lead to somatic mutations.
Many precursor lesions possess some of the genetic lesions found in their associated cancers.

Clinically, these precursor lesions are important to recognize, because their removal or reversal may prevent the development of a cancer and Examples include:

1. Squamous dysplasia of the bronchial mucosa, seen in habitual smokers—a risk factor for lung cancer
2. Endometrial hyperplasia and dysplasia, seen in women risk factor for endometrial carcinoma
3. Villous adenomas of the colon, associated with a high risk of colon adenocarcinoma
"What is the risk of malignant change in a benign neoplasm?"-or, stated differently, "Are benign tumors precancerous?"

- In general the answer is no, but there are exceptions, and perhaps it is better to say that each type of benign tumor is associated with a particular level of risk, ranging from high to virtually nonexistent.

- For example, villous adenomas of the colon as they enlarge can undergo malignant transformation in 50% of cases; and malignant change is extremely rare in leiomyomomas of the uterus.
THE MOLECULAR BASIS OF CANCER

- Nonlethal genetic damage lies at the heart of carcinogenesis and such genetic damage (or mutation):
  a. may be acquired by environmental agents, such as chemicals, radiation, or viruses,
  b. or it may be inherited in the germ line.

- The genetic hypothesis implies that a tumor results from the clonal expansion of a single progenitor cell that has incurred genetic damage (i.e., tumors are monoclonal).
Four classes of normal regulatory genes are the principal targets of genetic damage

a. Growth-promoting proto-oncogenes

b. Growth-inhibiting tumor suppressor genes

c. Genes that regulate (i.e., apoptosis),

d. Genes involved in DNA repair

- Oncogenes: Are genes that induce a transformed phenotype when expressed in cells and most oncogenes are mutated or over expressed versions of normal cellular genes called proto-oncogenes
- They are considered dominant because mutation of a single allele can lead to cellular transformation

**Tumor suppressor genes**:

- Are genes that normally prevent uncontrolled growth and, when mutated, allow the transformed phenotype to develop.

  a. Usually both normal alleles of tumor suppressor genes must be damaged for transformation to occur

  b. Tumor suppressor genes are usefully placed into two general groups, "governors" and "guardians"
1- "Governors" Such as RB, where it smutation leads to transformation by removing an important brake on cellular proliferation.

2- Guardian" genes are responsible for sensing genomic damage and some of these genes initiate "damage control response and this response leads to the cessation of proliferation or, if the damage is too great to be repaired, the induction of apoptosis

a. TP53, the so-called "guardian of the genome,“
b. Genes are involved in repairing specific kinds of DNA damage
Mutation of TP53 does not directly transform cells, and loss of guardian function has no direct effect on cellular proliferation or apoptosis.

Instead, loss of the guardian genes permits the acquisition of mutations in oncogenes and tumor suppressor genes that can lead to cancer development and this increase in mutation rate is often referred to as a mutator phenotype.

Note: Genes that regulate apoptosis and DNA repair may act like proto-oncogenes (loss of one copy is sufficient) or tumor suppressor genes (loss of both copies).
- Carcinogenesis is a multistep process resulting from the accumulation of multiple genetic alterations that collectively give rise to the transformed phenotype.

- Many cancers arise from non-neoplastic precursor lesions, which already possess some of the mutations needed to establish a full-blown cancer.

- Malignant neoplasms have several phenotypes such as excessive growth, local invasiveness, and metastasis.

- And over a period of time, many tumors become more aggressive and acquire greater malignant potential.
This phenomenon is referred to as tumor progression and is not represented simply by an increase in tumor size. Increasing malignancy is acquired in incremental fashion. At the molecular level, tumor progression are most likely to result from multiple mutations that accumulate in different cells, generating subclones with different characteristics such as ability to invade, metastatic ability, hormonal responsiveness, and susceptibility to antineoplastic drugs. Some of the mutations may be lethal; others may spur cell growth by affecting proto-oncogenes or suppressor genes.
Thus even though most malignant tumors are monoclonal in origin, by the time they become clinically evident their constituent cells may be extremely heterogeneous.

During progression, tumor cells are subjected to immune and nonimmune selection pressures. For example, cells that are highly antigenic are destroyed by host defenses, whereas those with reduced growth factor requirements are positively selected.
When tumors recur after chemotherapy, the recurrent tumor is always resistant to the drug regimen if it is given again and this acquired resistance, is a manifestation of selection, as subclones that by chance bear mutations imparting drug resistance survive.

Thus, genetic evolution and selection can explain two of the most pernicious properties of cancers: the tendency for cancers to become

1) more aggressive and
2) less responsive to therapy over time