Objectives:

After learning, students should be able to describe and discuss in the topics of…

1. Terminology and classification of neoplastic cells
2. Invasion, metastasis, grading and staging of tumors
3. Cell and molecular biology of neoplastic cells
4. Carcinogenesis
5. Host defense against tumors
6. Cancer epidemiology

Terminology and Classification of Neoplastic cells
The study of tumors is called "oncology" (oncos = tumor, logos = study of).

Neoplasia means "new growth".

Neoplasm often is referred to as a tumor. The study of tumors is called "oncology".

Cancer is the common term for all malignant tumors.

Neoplasm

Mesenchymal tissue

Epithelial tissue

Benign

Malignant

Benign

Malignant

-oma

-sarcoma

-oma

-carcinoma

1. Benign tumor

1.1 Benign tumor of mesenchymal tissue

The suffix "-oma" to the cell of origin

- Fibroblastic cells → Fibroma
- Lipid cells → Lipoma
- Smooth muscle → Leiomyoma

1.2 Benign tumor of epithelial tissue

base on their cells of origin and microscopic architecture

Adenoma (base on origin cell)

- Benign epithelial neoplasm that forms glandular patterns.
- Tumors derived from glands.
Papilloma (base on microscopic architecture)
- Benign neoplasm
- Microscopically visible finger-like projections

Polyp
- Neoplasm produces a macroscopically visible projections above a mucosal surface.
- Polyp preferably is restricted to benign tumor.

2. Malignant tumor

2.1 Malignant tumor of mesenchymal tissue
- They are usually called sarcoma.
- Sarcoma = “fleshy tumor”
  - Fibroblastic cells → Fibrosarcoma
  - Lipid cells → Liposarcoma
  - Smooth muscle → Leiomyosarcoma

2.2 Malignant tumor of epithelial tissue
- They are called carcinoma.
  - Squamous cell carcinoma (Squamous cell type)
  - Adenocarcinoma (Grandular growth pattern)
Teratoma (Dermoid cyst)
- It is made up of variety of parenchymal cell types.
- Arise from totipotential cells
- Is a benign type

Dysplasia
- Is a disordered growth, it often occurs in metaplastic epithelium.
- Remains confined by the basement membrane, it is considered to be a carcinoma in situ.
- Dysplasia does not necessarily progress to cancer.

Inappropriate nomenclature
Some inappropriate nomenclatures but deeply entrenched usages
- Melanoma = CA of melanocyte
- Seminoma = CA of testicular origin
- Hepatoma = CA of hepatocyte
- Lymphoma = CA of lymphoid tissue
- Leukemia = CA of hematopoietic cells

Well differentiated tumors
- Cell is resemble normal morphology of original tissue.
- In general, benign tumors are well differentiated cells.

Differentiation & Anaplasia

Cervical intraepithelial neoplasia, CIN (Robbin, 2005)

FIGURE 7.6 Lacerectomy of the uterus. This benign, well-differentiated tumor contains groups of uniform smooth muscle cells that are visually identical in appearance to normal smooth muscle cells in the myometrium.

FIGURE 7.8 Brain tumor (glioma) of the cerebral. Note the unusual mass (well-differentiated, welldifferentiated glioma). University of Texas Southwestern Medical School, Dallas, TX.)
- Well differentiated adenocarcinoma
  - gland formation
  - irregular in shape and size
- Well differentiated squamous cell carcinoma
  - intercellular bridge
  - keratin pearl

(Robbin, 2005)

Poorly differentiated or undifferentiated tumors

- This anaplasia is marked by a number of morphologic and functional changes, it is a hallmark of malignant transformation.
- Lack of differentiation

(www.springerimages.com)

The characteristics of malignant cells

- Pleomorphism: variation in size and shape
- Hyperchromatic cells are the dark staining of nuclei that contained DNA.
- The nuclei are disproportionately large for the cell (nuclear/cytoplasmic ratio = 1:1).
- Coarsely clumped chromatin
- Increased mitotic figures

(Robbin, 2010)
Invasion and metastasis

**Local invasion**

- Invasion is the most important sole criterion for *malignant tumors*.

**Metastasis**

- The process whereby malignant tumors spread from their *site of origin* to form *other tumors* at *distant sites*.
- Metastasis marks a tumors as *malignant*.
- Common routes of metastasis include *lymphatic channels, blood vessels, and through body cavities*. 

1. Direct seeding of body cavities or surface
   Most often involved is the peritoneal cavity.
2. Lymphatic spread
Most common pathway for carcinoma types.

![Image 1](image1.png)

*(Robbin, 2005)*

3. Hematogenous spread
It is typical of sarcoma but is also used by carcinoma.

![Image 2](image2.png)

*(Robbin, 2005)*

Characteristics of benign and malignant tumors

Grading and staging of neoplasms
Grading of a cancer

- Based on the degree of differentiation of the tumor cells and the number of mitoses
- Presumed correlates of the neoplasm’s aggressiveness

- **Low-grade** = the cancer cells tend to be slow-growing, look quite similar to normal cells (are well differentiated), tend to be less aggressive.

- **Intermediate-grade** = a middle grade

- **High-grade** = the cancer cells tend to be fast growing, look very abnormal (are poorly differentiated), tend to be more aggressive, and are more likely to spread quickly.

The staging of cancer

- 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

- Two major staging systems are currently in use
  - Union Internationale Contre Cancer (UICC)
  - American Joint Committee (AJC)

**TNM system (UICC)**

- **T** - primary tumor ( T1, T2, T3, T4 )
- **N** - regional lymph node involvement ( N0, N1, N2)
- **M** - metastases ( M0, M1 or sometimes M2 )

**AJC method system**

- Stage 0, I , II, III, IV

**TNM classification:**

- **T** - primary tumour has grown locally
- **N** - cancer has spread to the local lymph nodes
- **M** - cancer has spread to other parts of the body

**Stomach cancer**

- **T-1** means the primary tumor is still in the stomach wall. **T-3** means the primary tumor has grown right through the stomach wall and **T-4** means it is invading nearby structures such as the pancreas.

- **N-0** means there is no spread to lymph nodes. **N-1** means that some local lymph nodes are affected. **N-2** means more extensive spread to local lymph nodes.

- **M-0** means there are no metastases. **M-1** means that there are metastases to some other area of the body such as the liver or brain.
Cell and molecular biology for cancer development

**Biology of tumor growth**

- Growth of the transformed cells
- The growth rate of tumors correlated with their level of differentiation.
- Most *malignant tumors* grow rapidly than do *benign tumors*.

**Molecular basis of cancer**

- **Targeted genes**
  - Proto-oncogenes
  - Tumor suppressor genes
  - Genes controlling apoptosis
  - Genes regulating DNA repair
- **Other genes involved**
  - Genes regulating angiogenesis
  - Genes enhancing invasion and metastasis
Oncogenes and cancer

- Protooncogenes = cellular gene that promote normal growth and differentiation.
- Oncogenes = cancer-causing genes
- Oncoproteins are protein products of oncogenes.

- Oncogenes are derived from protooncogene.
- Oncogenes promote autonomous cell growth in cancer, their normal cellular counterparts are protooncogenes.

Tumor suppressor genes

- Insensitivity to growth
- Inhibitory signals
- Tumor suppressor genes: the protein products that apply brakes to cell proliferation.

A misnomer of “tumor suppressor genes”
- regulate cell growth
- not only to prevent tumor formation

Tumor is a lesion resulting from autonomous abnormal growth of cells that persists after the initiating stimulus has been removed.
**Tumor angiogenesis**

- Angiogenesis is a process of tumors stimulate the growth of host blood vessels (neovascularization).
- It formed for supplying nutrients to the tumor.
- Tumor angiogenesis can occur by recruitment of endothelial cell precursors.
Carcinogenesis

1. Initiation stage

- In this stage, DNA is *irreversibly changed* by genotoxic agents.
- DNA damage to a cell most frequently results in cell death, but sometimes DNA mutation creates rapidly dividing cells.
- Most initiating mutations affect *protooncogenes* or *tumor suppressor genes*.

2. Promotion stage

- Promotion can be *an increased expression* of the altered DNA formed in the initiation stage.
- The carcinogen that caused the initiation stage may or may not be the toxin driving the promotion stage.
- Promotion can be stopped through removal of the promoter carcinogen.
3. Progression stage

- Cells rapidly divide, normal tissue is invaded by cancerous cells, metastasis, and cells lose differentiation.
- Progression is an irreversible process.
- In this stage, the cells are not affected by removing the carcinogen.

Host defense against tumors

- Cytotoxic T lymphocytes (CTLs) are the major immune defense mechanism against tumors.

Tumors evade the immune

<table>
<thead>
<tr>
<th>Anti-tumor Immunity</th>
<th>Immune evasion by tumors</th>
<th>T cell recognition of tumor antigen leading to T cell activation</th>
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</thead>
<tbody>
<tr>
<td>Oncogene products: mutated RAS, Bcr/Abl fusion proteins</td>
<td>Various mutant proteins in carcinogen, or radiation, induced animal tumors; various mutated proteins in melanomas</td>
<td>Lack of T cell recognition of tumor</td>
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<tr>
<td>Tumor suppressor gene products: mutated p53 protein</td>
<td>Overexpressed tyrosinase, gp100, MART in melanomas</td>
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<td>Aberrantly expressed; cancer-testis antigens (NAGE, BAGE)</td>
<td>Lack of T cell recognition of tumor</td>
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<td>Human papillomas virus E6, E7 proteins in cervical carcinoma; EBNA proteins in EBV induced lymphoma</td>
<td>Production of immuno-suppressive proteins</td>
<td>Inhibition of T cell activation</td>
</tr>
</tbody>
</table>

(Robbin, 2005)
Cancer epidemiology

Leading cancer in Thailand (mean annual ASR 2010-2012)

Number by Age-group and Sex of All Cancer in Thailand-2011

(www.ncri.go.th/th)

(NCI, 2011)
Inherited predisposition to cancer

<table>
<thead>
<tr>
<th>Inherited Cancer Syndromes (Autosomal Dominant)</th>
<th>Gene</th>
<th>Inherited Predisposition</th>
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<tbody>
<tr>
<td>RB1</td>
<td>Retinoblastoma</td>
<td></td>
</tr>
<tr>
<td>p53</td>
<td>Li-Fraumeni syndrome (various tumors)</td>
<td></td>
</tr>
<tr>
<td>p16INK4A</td>
<td>Melanoma</td>
<td></td>
</tr>
<tr>
<td>APC</td>
<td>Familial adenomatous polyposis/colon cancer</td>
<td></td>
</tr>
<tr>
<td>NF1, NF2</td>
<td>Neurofibromatosis 1 and 2</td>
<td></td>
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<tr>
<td>BRCA1, BRCA2</td>
<td>Breast and ovarian tumors</td>
<td></td>
</tr>
<tr>
<td>MEN1, RET</td>
<td>Multiple endocrine neoplasia 1 and 2</td>
<td></td>
</tr>
<tr>
<td>MLH1, MLH3, MSH6</td>
<td>Hereditary nonpolyposis colon cancer</td>
<td></td>
</tr>
<tr>
<td>PATCH</td>
<td>Nevoid basal cell carcinoma syndrome</td>
<td></td>
</tr>
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</table>

Familial Cancers
Familial clustering of cases, but role of inherited predisposition not clear for each individual
- Breast cancer
- Ovarian cancer
- Pancreatic cancer

Inherited Autosomal Recessive Syndromes of Defective DNA Repair
- Xeroderma pigmentosum
- Ataxia-telangiectasia
- Bloom syndrome
- Fanconi anemia

Non hereditary predisposing conditions

- **Chronic inflammation and cancer**
  Ulcerative colitis, Helicobacter pylori gastritis, viral hepatitis, and chronic pancreatitis

- **Precancerous conditions**
  Solar keratosis of the skin, leukoplakia of the oral cavity, vulva, and penis

References