GRADING, STAGING AND CLINICAL MANIFESTATIONS OF TUMORS

Dr. Maria A. Arafah

Assistant Professor – Department of Pathology

http://fac.ksu.edu.sa/mariaarafah/courses

Objectives

- To define the host defenses against cancer
- To define tumor grade & clinical stage.
- To define cachexia & its causes.
- To define a paraneoplastic syndrome & know examples of tumors associated with endocrinopathies, osseous, vascular and hematologic changes.
- To be familiar with the general principles, value, procedures, and applications of biopsies, exfoliative & aspiration cytology and frozen sections.
- To list examples of tests used to diagnose cancer: immunohistochemistry & flow cytometry.
- To discuss the use of molecular diagnostic testing in the setting of cancer diagnosis & prognosis.

Host Defense Against Tumors

- Tumor antigens:
  - *Tumor-specific antigens,* which are present only on tumor cells and not on any normal cells.
  - *Tumor-associated antigens,* which are present on tumor cells and also on some normal cells.

Host Defense Against Tumors

- Classes of tumor antigens:
  - Products of mutated oncogenes and tumor suppressor genes
    - P53 tumor suppressor gene, RAS oncogene
  - Products of amplified genes
    - HER2-NEU
  - Tumor antigens produced by oncogenic viruses
    - HPV, EBV

Host Defense Against Tumors

- Classes of tumor antigens:
  - Oncofetal antigens: expressed during embryogenesis but not in normal adult tissues.
    - CEA, AFP in colon and liver carcinomas, respectively.
  - Cell type–specific differentiation antigens: Tumors express molecules that normally are present on the cells of origin. These antigens are called *differentiation antigens,* because they are specific for particular lineages or differentiation stages of various cell types.
    - PSA in prostatic carcinoma

Host Defense Against Tumors

- Antitumor effector mechanisms
  - Cytotoxic T lymphocytes
  - Natural killer cells
  - Macrophages
  - Humoral mechanisms:
    - Complement system
    - Antibodies

Clinical Aspects of Neoplasia

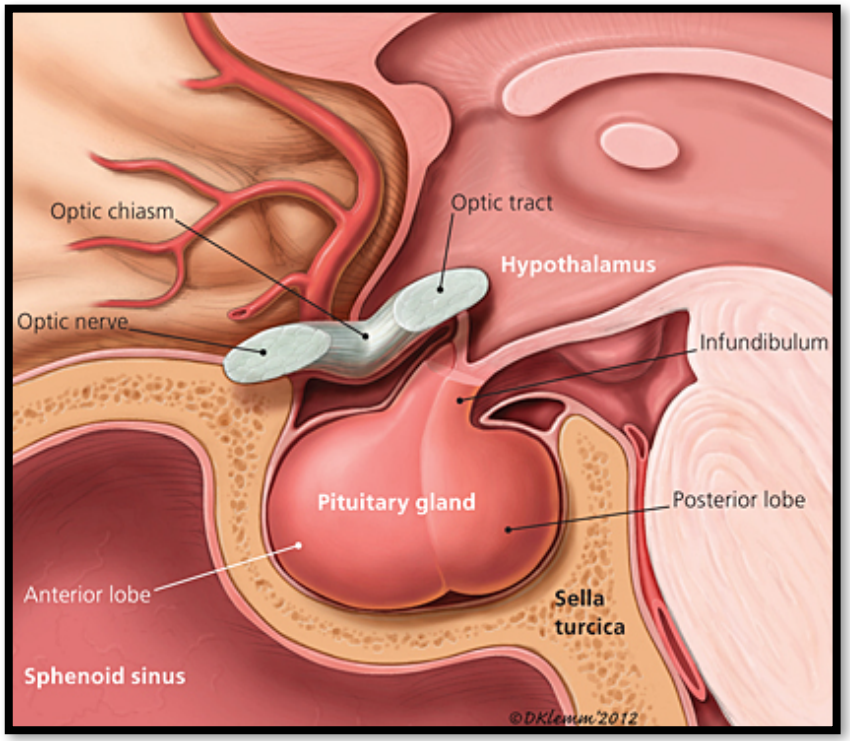
- Both malignant & benign tumors may cause problems because of:
  - Location and impingement on adjacent structures
  - Bleeding, secondary fractures or infections
  - Symptoms that result from rupture, obstruction or infarction
  - Functional activity such as hormone synthesis or the development of paraneoplastic syndromes
  - Cachexia or wasting.

Clinical Aspects of Neoplasia

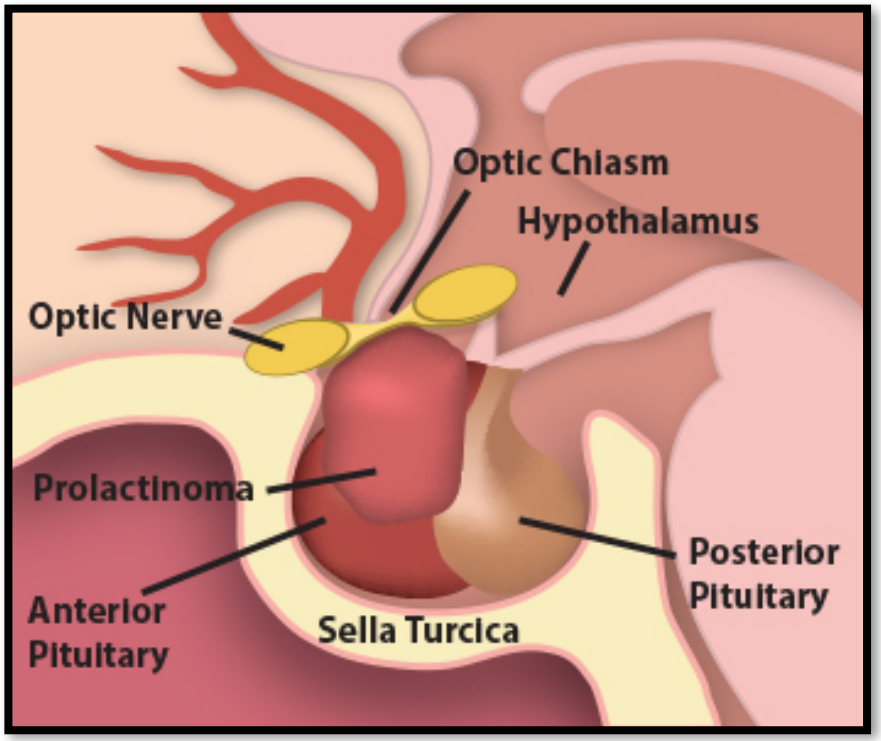
- Location and impingement on adjacent structures:
  - Location is crucial in both benign and malignant tumors.
  - A small (1-cm) pituitary adenoma can compress and destroy the surrounding normal gland, giving rise to hypopituitarism.
  - A 0.5-cm leiomyoma in the wall of the renal artery may encroach on the blood supply, leading to renal ischemia and hypertension.

Clinical Aspects of Neoplasia

Pituitary Gland

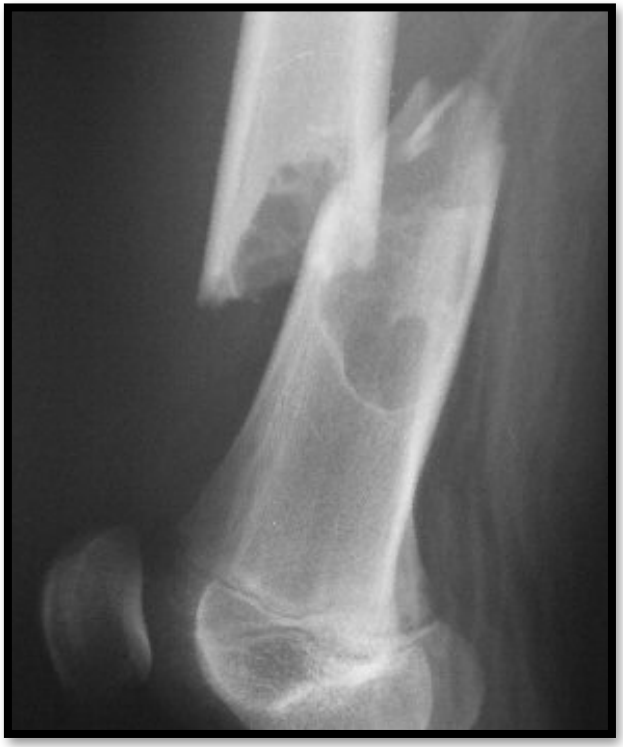


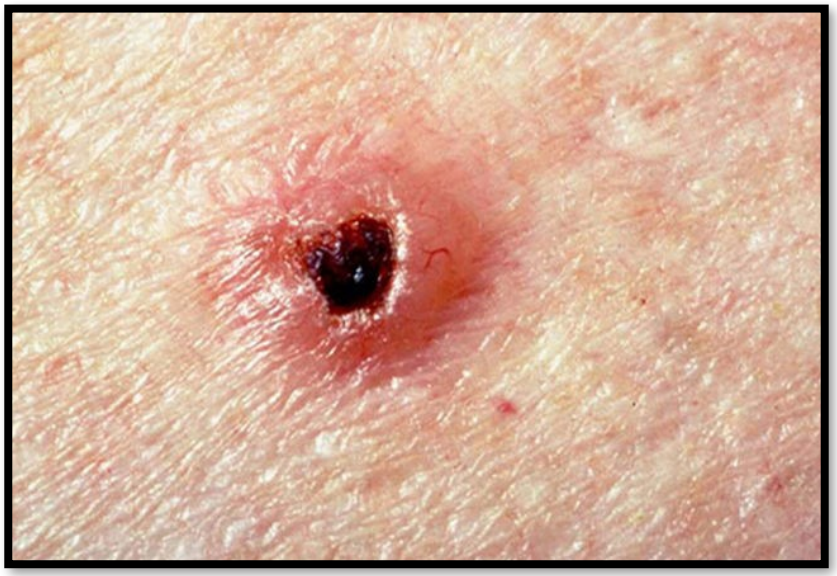
Pituitary Adenoma



Clinical Aspects of Neoplasia

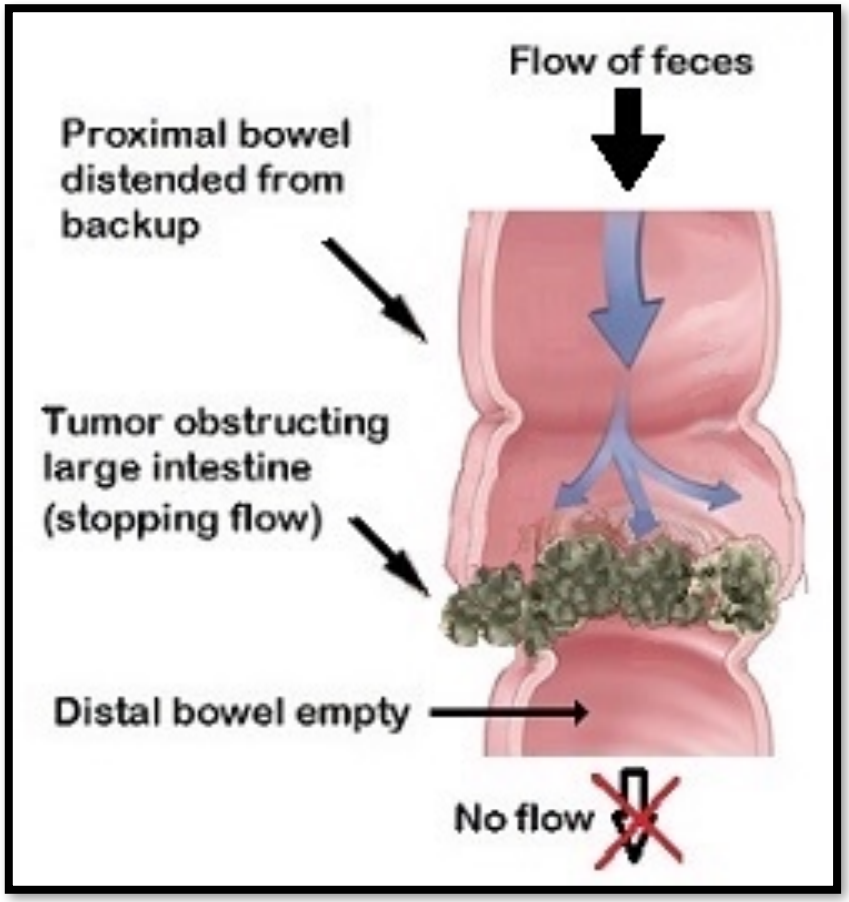
- Bleeding, secondary fractures and infections:
  - A tumor may ulcerate through a surface or adjacent structures causing consequent bleeding or secondary infection or fracture.





Clinical Aspects of Neoplasia

- Symptoms that result from rupture, obstruction or infarction:

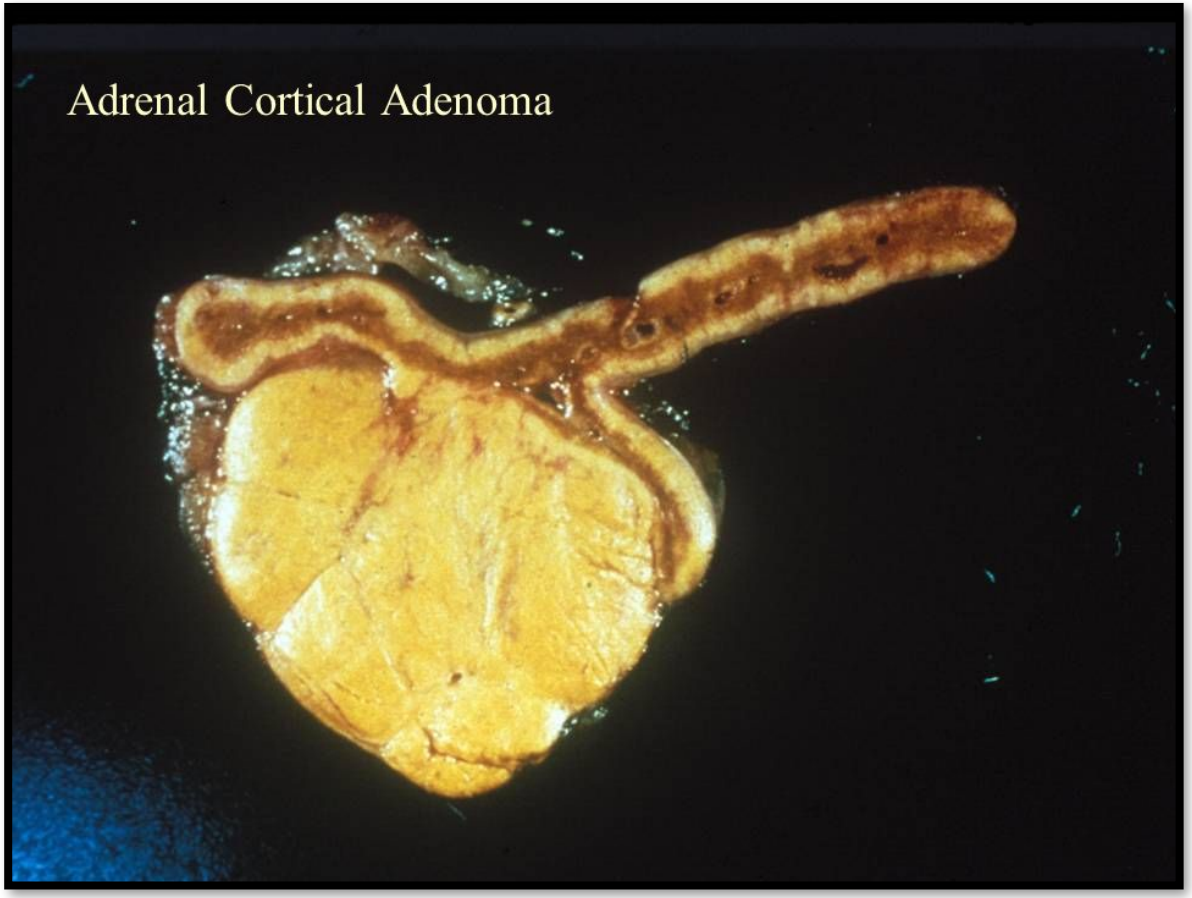


Clinical Aspects of Neoplasia

- Functional activity such as hormone synthesis or the development of paraneoplastic syndromes:
  - Hormone production is seen with benign and malignant neoplasms arising in endocrine glands.
  - Adenomas and carcinomas arising in the beta cells of the pancreatic islets of Langerhans can produce hyperinsulinism, sometimes fatal.
  - Some adenomas and carcinomas of the adrenal cortex elaborate corticosteroids that affect the patient (e.g., aldosterone, which induces sodium retention, hypertension, and hypokalemia).
  - Such hormonal activity is more likely with a well-differentiated benign tumor than with a corresponding carcinoma.

Clinical Aspects of Neoplasia

- Functional activity such as hormone synthesis:



Clinical Aspects of Neoplasia

- Paraneoplastic syndromes:
  - They are symptoms that occur in cancer patients & cannot be explained.
  - They are diverse and are associated with many different tumors.
  - They appear in 10% to 15% of patients.
  - They may represent the earliest manifestation of an occult neoplasm.
  - They may represent significant clinical problems & may be lethal.
  - They may mimic metastatic disease.

Clinical Aspects of Neoplasia

- Paraneoplastic syndromes:
  - The most common paraneoplastic syndrome are:
    - Hypercalcemia
    - Cushing syndrome
    - Nonbacterial thrombotic endocarditis
  - The most often neoplasms associated with these syndromes:
    - Lung and breast cancers and hematologic malignancies

Paraneoplastic Syndromes

Clinical Syndrome	Major Forms of Neoplasia	Causal Mechanism(s)/Agent(s)
Endocrinopathies		
Cushing syndrome	Small cell carcinoma of lung Pancreatic carcinoma Neural tumors	ACTH or ACTH-like substance
Syndrome of inappropriate antidiuretic hormone secretion	Small cell carcinoma of lung; intracranial neoplasms	Antidiuretic hormone or atrial natriuretic hormones
Hypercalcemia	Squamous cell carcinoma of lung Breast carcinoma Renal carcinoma Adult T cell leukemia/lymphoma Ovarian carcinoma	Parathyroid hormone–related protein, TGF-α, TNF, IL-1
Hypoglycemia	Fibrosarcoma Other mesenchymal sarcomas Hepatocellular carcinoma	Insulin or insulin-like substance
Carcinoid syndrome	Bronchial adenoma (carcinoid) Pancreatic carcinoma Gastric carcinoma	Serotonin, bradykinin
Polycythemia	Renal carcinoma Cerebellar hemangioma Hepatocellular carcinoma	Erythropoietin

Paraneoplastic Syndromes

Nerve and Muscle Syndrome		
Myasthenia	Bronchogenic carcinoma, thymoma	Immunologic
Disorders of the central and peripheral nervous systems	Breast carcinoma, teratoma	
Dermatologic Disorders		
Acanthosis nigricans	Gastric carcinoma Lung carcinoma Uterine carcinoma	Immunologic; secretion of epidermal growth factor
Dermatomyositis	Bronchogenic and breast carcinoma	Immunologic
Osseous, Articular, and Soft Tissue Changes		
Hypertrophic osteoarthropathy and clubbing of the fingers	Bronchogenic carcinoma	Unknown
Vascular and Hematologic Changes		
Venous thrombosis (Trousseau phenomenon)	Pancreatic carcinoma Bronchogenic carcinoma Other cancers	Tumor products (mucins that activate clotting)
Nonbacterial thrombotic endocarditis	Advanced cancers	Hypercoagulability
Anemia	Thymoma	Immunologic
Others		
Nephrotic syndrome	Various cancers	Tumor antigens, immune complexes

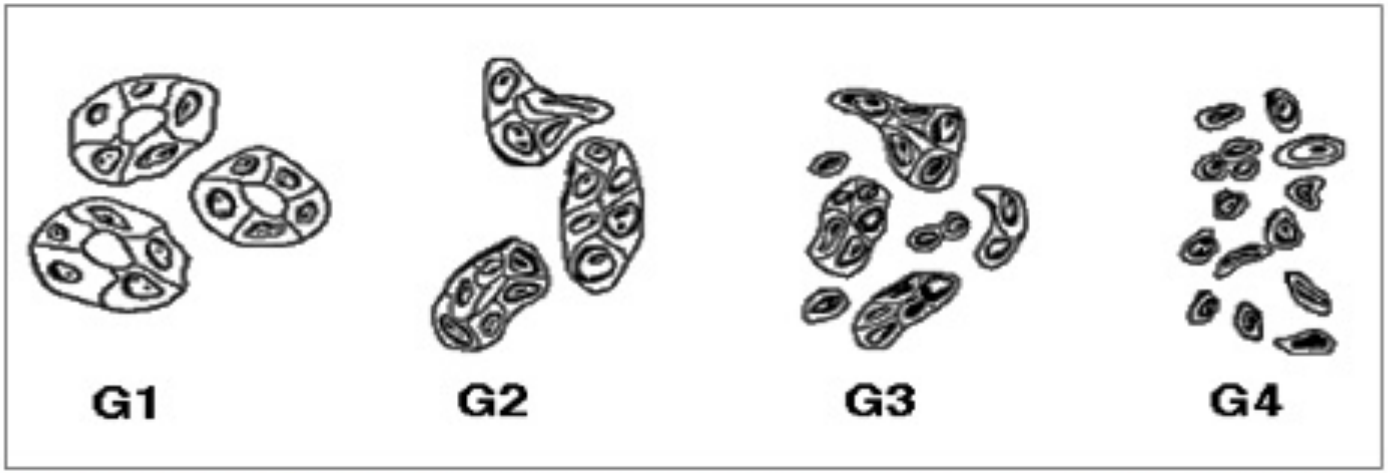
Clinical Aspects of Neoplasia

- Cancer cachexia:
  - It is usually accompanied by weakness, anorexia and anemia.
  - The severity of cachexia is generally correlated with the size and extend of spread of the cancer.
  - The origin of cancer cachexia is multifactorial:
    - Anorexia (reduced calorie intake): *TNF* suppresses appetite.
    - Increased basal metabolic rate & calorie expenditure.
    - General metabolic disturbance

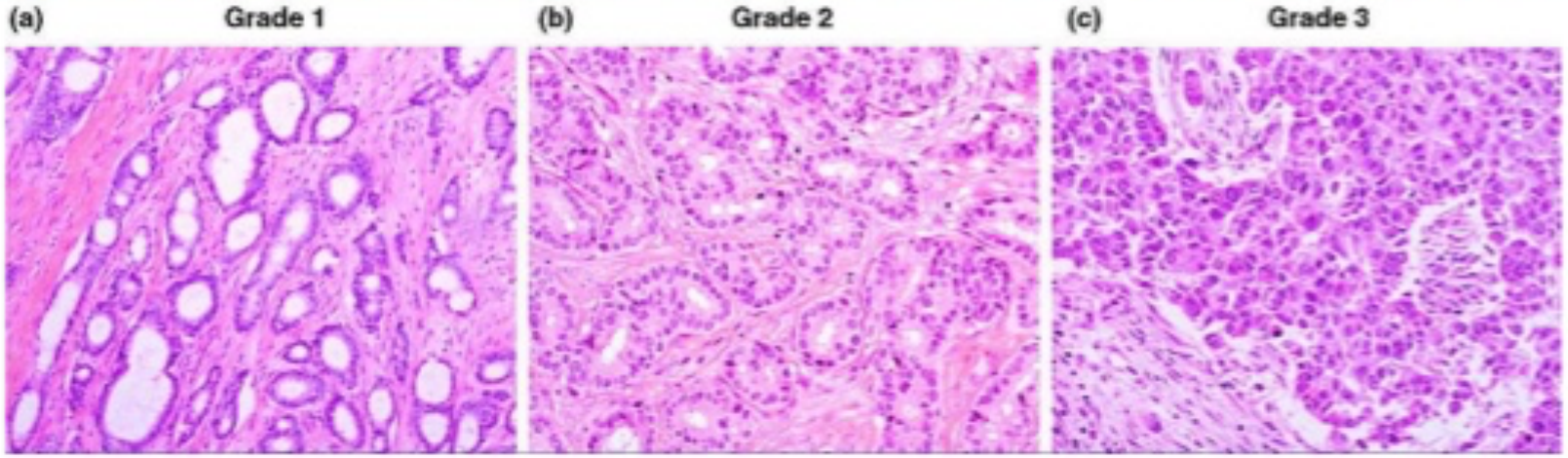
Grading and Staging of Cancer

- Grading:
  - It is based on the cytologic differentiation of tumor cells and the number of mitoses within the tumor.
  - Malignant tumors are classified as:
    - Grade I → well differentiated
    - Grade II → moderately differentiated
    - Grade III → poorly differentiated
    - Grade IV → anaplastic (undifferentiated)

Grading



Well differentiated (low grade) Adenocarcinoma Grade Undiff. (high grade)



Grading and Staging of Cancer

- Staging:
  - Staging is based on the size of the primary lesion, its extent of spread to regional lymph nodes, and the presence or absence of metastases.
  - Two methods of staging are currently in use: the TNM system (*T,* primary tumor; *N,* regional lymph node involvement; *M,* metastases) and the AJC (American Joint Committee) system.

Grading and Staging of Cancer

- Staging:
  - TNM staging system:
    - T0, Tis, T1, T2, T3, and T4 describe the increasing size of the primary lesion
    - N0, N1, N2, and N3 indicate progressively advancing node involvement
    - M0 and M1 reflect the absence and presence, respectively, of distant metastases.

Staging

Stage	Definition
Tis	In situ, non-invasive (confined to epithelium)
T1	Small, minimally invasive within primary organ site
T2	Larger, more invasive within the primary organ site
T3	Larger and/or invasive beyond margins of primary organ site
T4	Very large and/or very invasive, spread to adjacent organs
N0	No lymph node involvement
N1	Regional lymph node involvement
N2	Extensive regional lymph node involvement
N3	More distant lymph node involvement
M0	No distant metastases
M1	Distant metastases present

Laboratory Diagnosis of Cancer

- Laboratory diagnosis of cancer can be achieved by:
  - Morphologic methods
  - Biochemical assays
  - Molecular tests

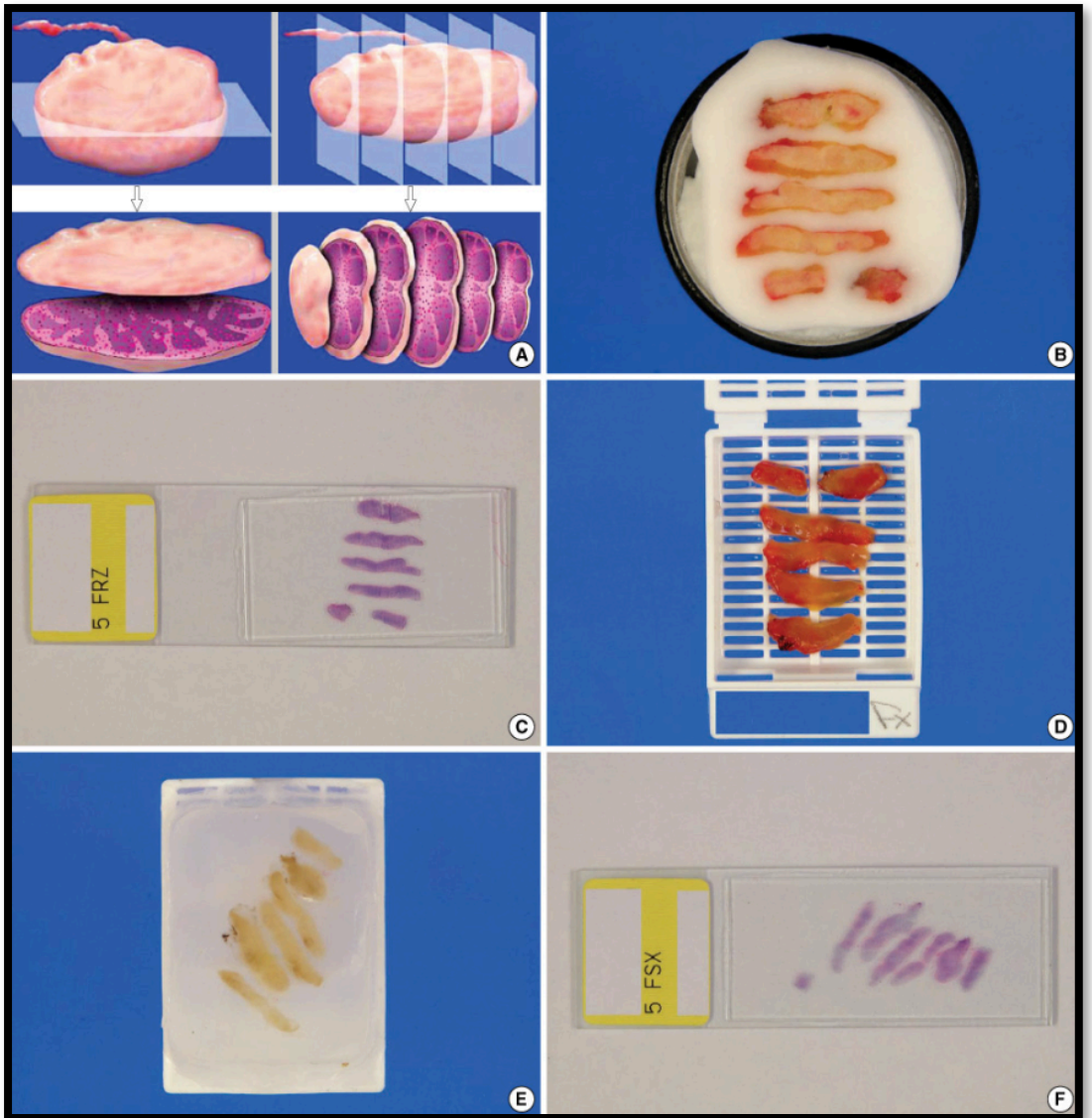
Laboratory Diagnosis of Cancer

- Morphologic methods include microscopic tissue or cellular diagnosis:
  - It is the gold standard for cancer diagnosis.
  - Several sampling approaches are available:
    - Biopsy, excision & frozen section
    - Fine-needle aspiration
    - Cytologic smears
    - Immunohistochemical stains
    - Flow cytometry

Laboratory Diagnosis of Cancer

- Sampling approaches:
  - Biopsies
  - Surgical excisions
  - Frozen section: a method in which a sample is quick-frozen and sectioned, permits histologic evaluation within minutes.

Frozen Section & Histological Sections



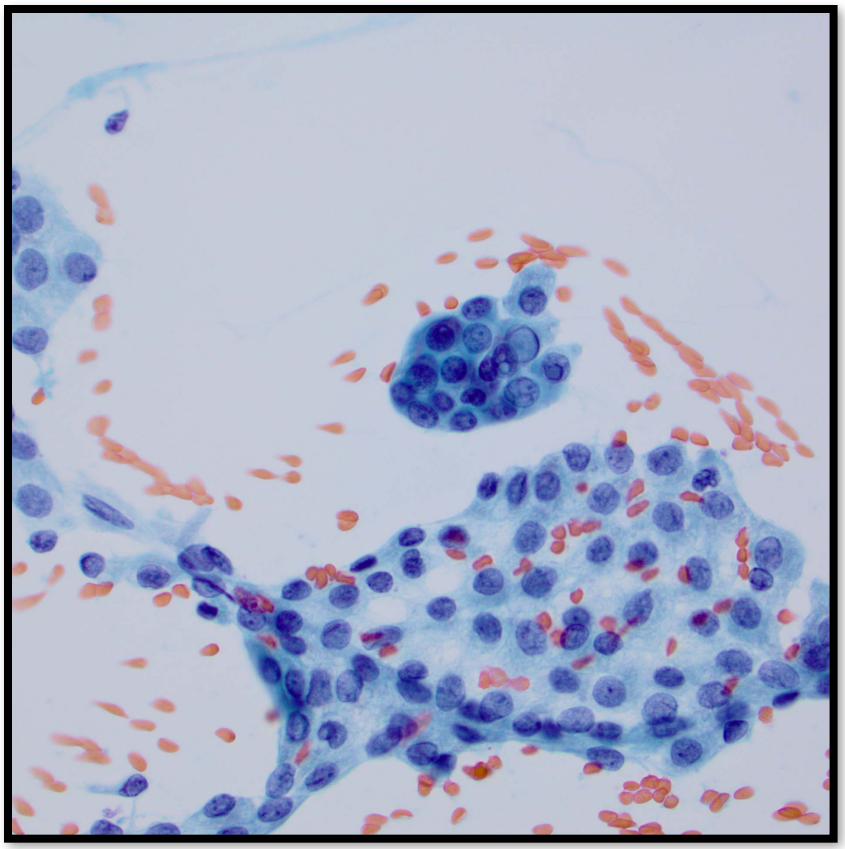
Laboratory Diagnosis of Cancer

- *Fine needle aspiration*: it involves aspiration of cells from a mass, followed by cytologic examination of the smear.

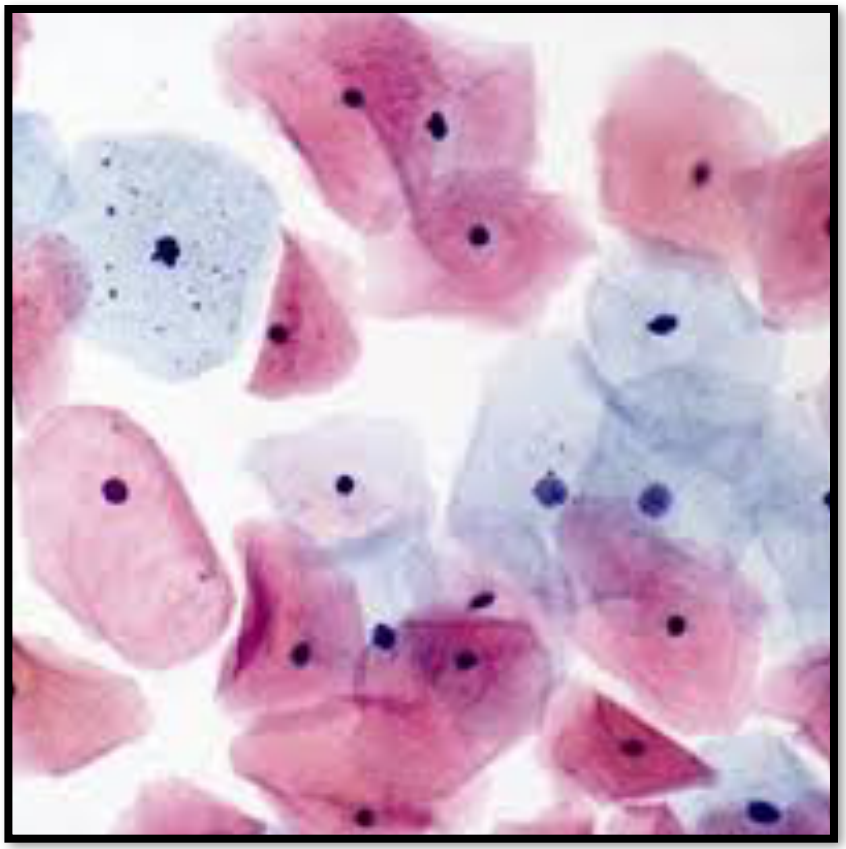
- *Cytologic (Papanicolaou) smears* provide another method for the detection of cancer. Neoplastic cells are less cohesive than others and are therefore shed into fluids or secretions.

Laboratory Diagnosis of Cancer

FNA



Pap Smear



Laboratory Diagnosis of Cancer

- *Immunocytochemistry* offers a powerful adjunct to routine histologic examination.

- *Flow cytometry* is used routinely in the classification of leukemias and lymphomas.

Laboratory Diagnosis of Cancer

- Biochemical assays:
  - They are useful for measuring the levels of tumor associated enzymes, hormones, and tumor markers in serum.
  - They are useful in screening, determining the effectiveness of therapy & detecting tumor recurrences.
  - Elevated levels may not be diagnostic of cancer e.g. PSA.
  - Only few tumor markers are proven to be clinically useful e.g. CEA & AFP.

Laboratory Diagnosis of Cancer

- Molecular tests:
  - Polymerase chain reaction (PCR)
    - PCR is useful for the detection of BCR-ABL transcripts in chronic myeloid leukemia.
  - Fluorescent in situ hybridization (FISH)
    - FISH is useful for detecting chromosomal translocations characteristic of many tumors.
  - Both PCR and FISH can show amplification of oncogenes e.g. HER2-NEU & N-MYC.

Laboratory Diagnosis of Cancer

- Molecular tests:
  - DNA microarray analysis:
    - It evaluates the expression of thousands of genes.
    - Different tissues have different patterns of gene expression.
    - It is a powerful tool for subcategorizing diseases e.g. lymphomas.
    - It confirms the morphologic diagnoses.
    - It is useful in illustrating genes involved in certain disease & help plan possible therapies.

Reference

- Kumar V, Abbas AK, Aster JC. Robbins Basic Pathology. 10th ed. Elsevier; 2018. Philadelphia, PA.

END OF LECTURE

Thank You