Grading, Staging & Clinical Features of Tumors

Objectives:

- To define the host defenses against cancer.
- To define tumor grading & 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.

Color Index:
Slides
Important
Male's slides only
Female's slides only
Notes
Extra information

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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.

Classes of tumor antigens:

Products of mutated oncogenes and tumor suppressor gene.	<u>P53</u> tumor suppressor gene, RAS oncogene (normally, doesn't show on staining because levels are low)
Products of amplified genes (normally, every gene has 2 copies. Amplification produce more copies)	HER2-NEU
Tumor antigens produced by oncogenic viruses	HPV, EBV
Oncofetal antigens: expressed during embryogenesis but not in normal adult tissues. (shouldn't be present after birth)	CEA, AFP in colon and liver carcinomas, respectively Extra: CEA: carcinoembryonic antigen, AFP: Alpha-feto protein.
Cell type-specific differentiation antigens: Tumors express molecules that normally are present on the cells of origin. These antigens are called differentiation stages of various cell types.	PSA in prostatic carcinoma. (specific for prostate if we find it in other organs could point to prostatic carcinoma)

AntiTumor effector mechanisms From Female Slides

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

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Clinical Aspects of Neoplasia :
(each point will be explained in details)

✳Both malignant & benign tumors may cause problems because of:

A- **Location and impingement on adjacent structures.** (depends on sensitivity of important structure)

B- **Bleeding, secondary fractures or infections.**

C- **Symptoms that result from rupture, obstruction or infarction**

D- **Cachexia or wasting.**

E- **Functional activity**

Clinical Aspects of Neoplasia :

A- **Location** and impingement on adjacent structures.

(depends on sensitivity of important structure)

✳ 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. (or even infraction)

✳ A 0.5-sm leiomyoma (Benign mesenchymal smooth muscle) in the wall of the renal artery may encroach on the blood supply, leading to renal ischemia and hypertension.

Pituitary Gland
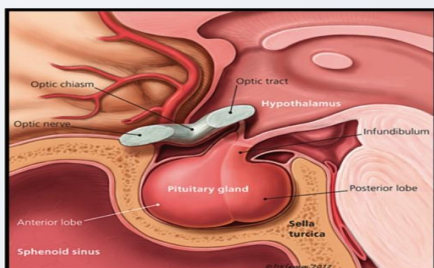
Pituitary Adenoma (benign tumor)
- can produce hormones just like normal
- may cause visual problems if enlarged
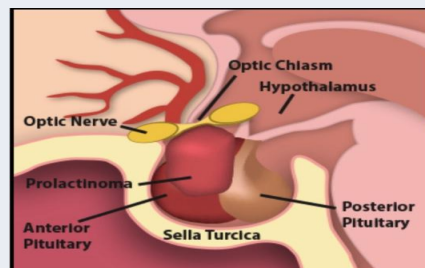
Clinical Aspects of Neoplasia :
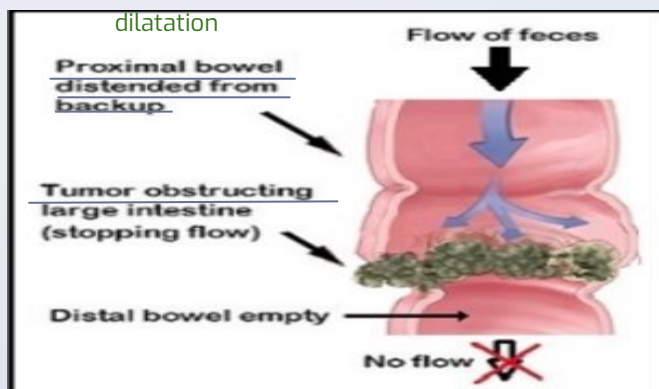
B- **Bleeding, secondary fractures or infections.**

✳ A tumor may ulcerate through a surface or adjacent structures causing consequent bleeding or secondary infection or fracture.
E.g. a tumor metastasized to the bone causing a pathological fracture

Clinical Aspects of Neoplasia :

C- Symptoms that result from rupture, obstruction or infarction

dilatation

Flow of feces

Proximal bowel distended from backup

Tumor obstructing large intestine (stopping flow)

Distal bowel empty

No flow

Clinical Aspects of Neoplasia :

D-Cancer cachexia: (Unknown mechanism)

＊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:

Clinical Aspects of Neoplasia :

E- Functional activity

＊such as <u>hormone synthesis</u> or the development of <u>paraneoplastic syndromes:</u>

(Important)
Important: Hormone production is seen with benign and malignant neoplasms arising in endocrine glands
(hormone production seen in well differentiated malignant To a lesser extent in moderately differentiated)

Adrenal Cortical Adenoma
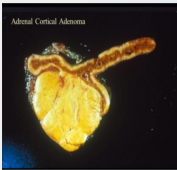
Adenomas and carcinomas arising in the beta cells of the pancreatic islets of langerhans can produce hyperinsulinism
(overproduction, which leads to Hyperglycemia), sometimes fatal

(Important) Important: Some Adenomas and carcinomas of the adrenal cortex elaborate corticosteroides 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.

paraneoplastic syndromes:

(group of symptoms with no explanation)

✳ symptoms that occur in cancer patients & cannot be explained.

✳ diverse and are associated with many different tumors.

✳ appear in 10% to 15% of patients.

✳ may represent the earliest manifestation of an occult neoplasm.

✳ may represent significant clinical problems & may be lethal.

✳ may mimic metastatic disease.

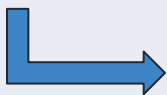|	
✳ The most often neoplasms associated with these syndromes: - Lung and breast cancers - hematologic malignancies	✳ The most common paraneoplastic syndrome are: - Hypercalcemia - Cushing syndrome - Nonbacterial thrombotic endocarditis

important*

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 anti-diuretic hormone secretion (ADH)	Small cell carcinoma of lung; intracranial neoplasms	Anti-diuretic hormone or atrial natriuretic hormones
Hypercalcemia (common)	Squamous cell carcinoma of lung Breast carcinoma Renal carcinoma Adult T cell leukemia/lymphoma	Parathyroid hormone–related protein, TGF-α
Hypoglycemia	Fibrosarcoma Other mesenchymal sarcomas Ovarian carcinoma +Hepatocellular carcinoma (liver)	Insulin or insulin-like substance
Polycythemia	Renal carcinoma Cerebellar hemangioma Hepatocellular carcinoma (lung)	Erythropoietin
Nerve and Muscle Syndrome		
Myasthenia	Bronchogenic carcinoma, thymoma	Immunologic
Disorders of the central and peripheral nervous systems	Breast carcinoma, teratoma	Immunologic
Vascular and Hematologic Changes		
Venous thrombosis (Trousseau phenomenon)	Pancreatic carcinoma Bronchogenic carcinoma Other cancers	Tumor products (mucins that activate clotting)

- "Just Focus on the common"

From Males slide

Paraneoplastic syndromes		
Syndrome	**Mechanism**	**Example**
Cushing's Syndrome	ACTH -like substance	Lung oat cell carcinoma
Hypercalcemia	Parathormone -like substance	Lung squamous cell carcinoma Renal cell carcinoma Breast carcinoma
Hyponatremia	Inappropriate ADH secretion	Lung oat cell carcinoma
Polycythemia	Erythropoietin -like substance	Cerebellar haemangioma Renal cell carcinoma
Trousseau's Syndrome	Hypercoagulable state	Various carcinomas
Hypoglycemia	Insulin -like substance	Various carcinomas and sarcomas
Carcinoid Syndrome	Serotonin, Bradykinin	Metastatic malignant carcinoid tumors

✳ Grading of cancer

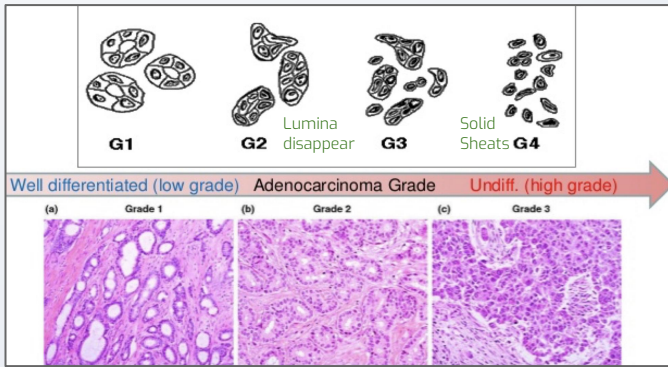| Grading | based on the <u>cytologic</u> differentiation of tumor cells and the number of mitoses within the tumor. (depends on histopathological features of neoplasm) |

| **Grade I** Well Differentiated | **Grade II** Moderately Differentiated | **Grade III** Poorly Differentiated | **Grade IV** Anaplastic (Undifferentiated) |

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

✳ Staging of cancer

| staging | The **most important** prognostic factor. based on the <u>size</u> of the primary lesion its extent of spread to regional <u>lymph nodes</u> and the presence or absence of <u>metastases</u> |

Two methods of staging

AJC (American Joint Committee) system.

TNM system

- *T = primary **T**umor Size,* describe increasing size of primary lesion **(**T0, Tis, T1, T2, T3, T4)
- *N = **Regional Lymph Node involvement,*** indicate progressively advancing node involvement (N0, N1, N2, N3)
- *M = **Metastases,*** reflect absence and presence of distant metastases (M0, M1) respectively (only one that is the same for all organs)

Laboratory Diagnosis of cancer

✳ 1. Morphologic Methods

- Include microscopic tissue or cellular diagnosis
- The gold standard for cancer diagnosis

Available Sampling Approaches

Biopsies

Flow Cytometry
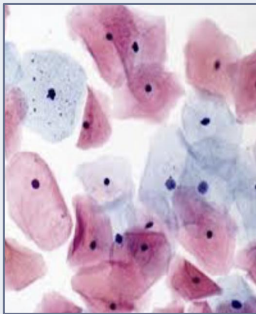used routinely in the classification of leukemias and lymphomas.

Immunocytochemistry stains
offers a powerful adjunct to routine histologic examination.
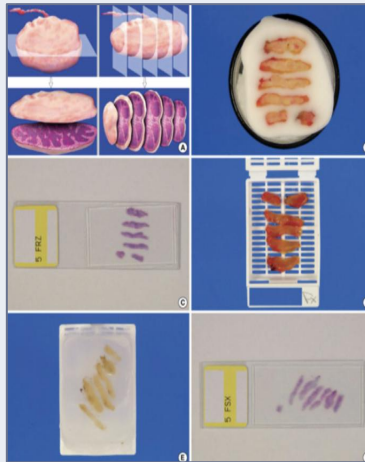
Surgical Excisions

Fine Needle Aspiration
involves aspiration of cells from a mass, followed by cytologic examination of the smear.
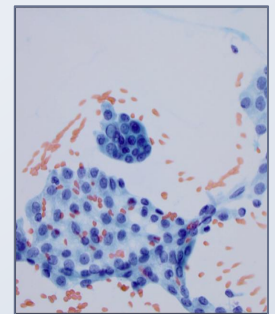
Frozen Section:
a method in which a sample is quick-frozen and sectioned, permits histologic evaluation within minutes.

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.

FNA

Frozen section & histological sections

Pap Smear

Laboratory Diagnosis of cancer cont.

✳ 2. Biochemical Assays ★

- Measure tumor antigens
- Nonspecific for cancer (except Oncofetal antigen), only associated with it

- **Useful In:-**
  - Measuring the levels of tumor associated enzymes, hormones, and tumor markers in serum.
  - Screening, determining the <u>effectiveness</u> of therapy & detecting tumor <u>recurrences</u>.
- Elevated levels may not be diagnostic of cancer e.g. *PSA*
  - ➢ It may also increase in Infection or Infarction of the prostate (Tumor <u>associated</u>).
- Only few tumor markers are proven to be clinically useful E.g. *CEA & AFP*.
  - ➢ Arise only from Tumor cells (Tumor <u>specific</u>)

✳ 3. Molecular tests

- **Polymerase chain reaction (PCR) :**
  - ○ 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.
- **DNA microarray analysis:**
  - Evaluates the expression of thousands of genes.
  - Different tissues have different patterns of gene expression.
  - A powerful tool for sub-categorizing diseases e.g. lymphomas.
  - It confirms the morphologic diagnosis.
  - It is useful in illustrating genes involved in certain disease & help plan possible therapies.

MCQs

1- .... Found only on tumor cells and not on any normal cells.

a- Tumor-associated antigen	B- Tumor-specific antigen	C- Tumor antigen	D- Host defense mechanisms

2- Which one of the following neoplasia forms is associated with cushing syndrome?

A- Renal carcinoma	B- Breast carcinoma	C- Small cell carcinoma of lung	D- bronchogenic carcinoma

3- a method in which a sample is quick-frozen and sectioned , permits histologic evaluation within minutes

A- Biopsies	B- Surgical excisions	C- Frozen section	D- Flow cytometry

4- Only few tumor markers are proven to be clinically useful for example ....

A- CEA	B- PSA	C- PCR	D- FISH

5- Which one of the following is considered as a paraneoplastic syndrome?

A- hyperinsulinism	B- hypercalcemia	C- peptic ulcer	D- Retinoblastoma

6- Which one indicates to more distant lymph node involvement?

A- T4	B- N3	C- M0	D- T3

SAQs

1- The origin of cancer cachexia is multifactorial, mention one of them.
2- how is flow cytometry used?
3- What is type of molecular diagnosis that is useful for detecting chromosomal translocation of tumors?
4- According to TNM system of staging, what is the code that indicate to no distant metastases?

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Editing File