MED444
KING SAUD UNIVERSITY

PATHOLOGY TEAMWORK

MED444

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Grading , staging & clinical features of Tumors

OBJECTIVES

- define the host defenses against cancer
- define tumor grade & clinical stage
- define cachexia & its causes
- 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.

Editing file

COLOR INDEX:

MAIN TEXT (BLACK)

FEMALE SLIDES (PINK)

MALE SLIDES (BLUE)

IMPORTANT (RED)

DR'S NOTE (GREEN)

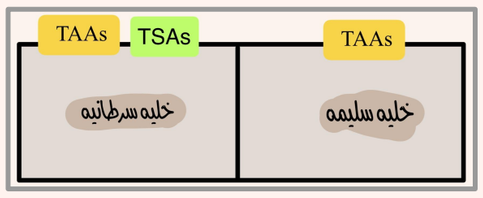
EXTRA INFO (GREY)

Host & Defense Against Tumors

GIRL'S SLIDES
-all page-

tumors antigens

بروتين معينه خاصه ب tumors - زي العلامة على الخلايا يتعرف عليها جهاز المناعة ومن خلالها يا يهجم عليها لكونها تحمل TSA - خليه سرطانيه - او يتعرف عليها كانخلية طبيعية لكونها تحمل فقط TAA-



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

Classes of tumor antigens:

1. **Products of mutated oncogenes and tumor suppressor genes** — Example → **P53** tumor suppressor gene; **RAS** oncogene
2. **Products of amplified genes** — Example → **HER2-NEU**

DR'S NOTE
Commonly in breast cancer

3. **Tumor antigens produced by oncogenic viruses** (viruses can cause tumors) — Example → **HPV, EBV**
4. **Oncofetal antigens:** expressed during embryogenesis but not in normal adult tissues. — Example → **CEA** in colon , **AFP** in liver carcinoma
5. **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. — Example → **PSA** in prostatic carcinoma

DR'S NOTE
بروتين موجود بشكل طبيعي في الدم ولكن بكمية قليله لو صار في العضو (البروستات) آي شي غير طبيعي مثلا تومر او انفلميشن بيزيد البروتين هذا
ف يعتبر organ specific not tumor specific

Antitumor effector mechanisms

Humoral mechanisms:
- Complement system
- Antibodies

Macrophages

Natural killer cells

Cytotoxic T lymphocytes

Clinical Aspects of Neoplasia

Both malignant & benign tumors may cause problems because of:

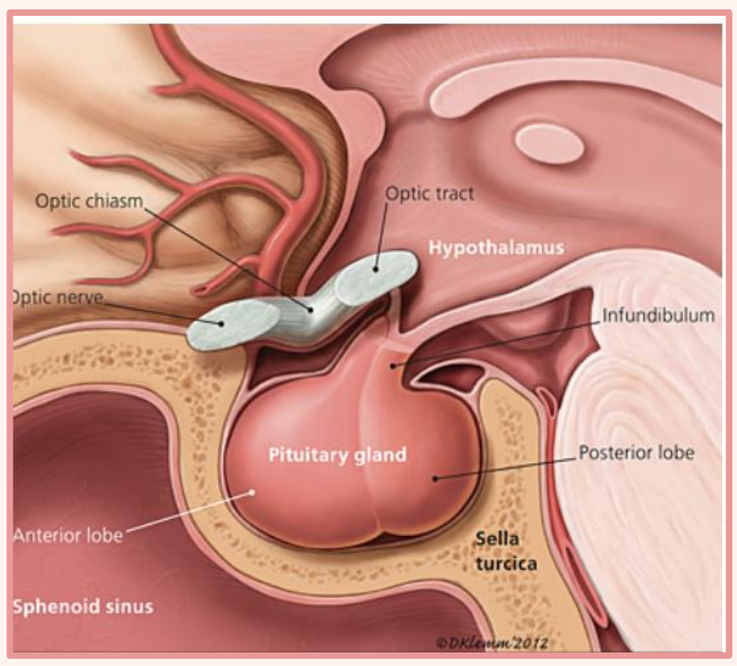
- Cachexia or wasting.
- Symptoms that result from rupture, obstruction or infarction
- Functional activity such as hormone synthesis or the development of paraneoplastic syndromes
- Bleeding, secondary fractures or infections
- Location and impingement on adjacent structures

Location and impingement on adjacent structures

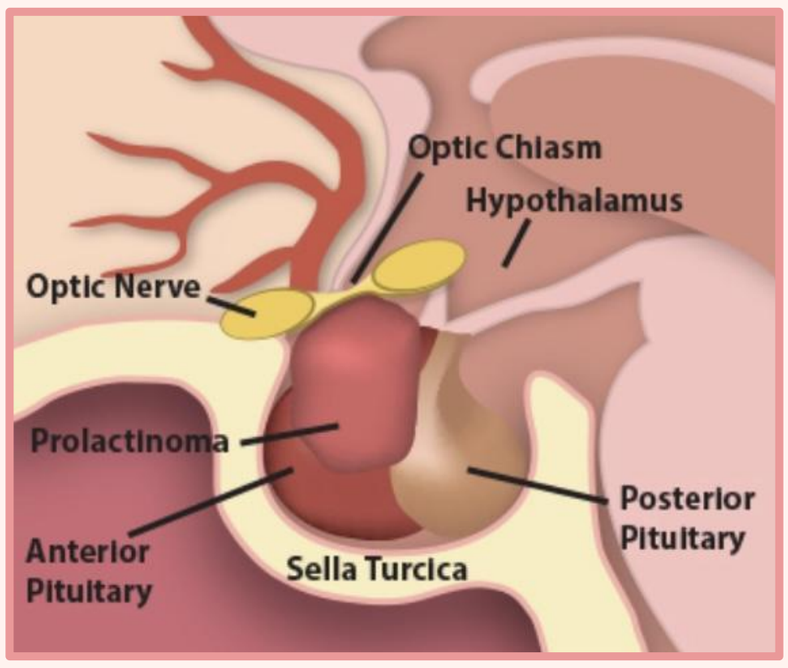
GIRL'S SLIDES

- 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.

Pituitary Gland



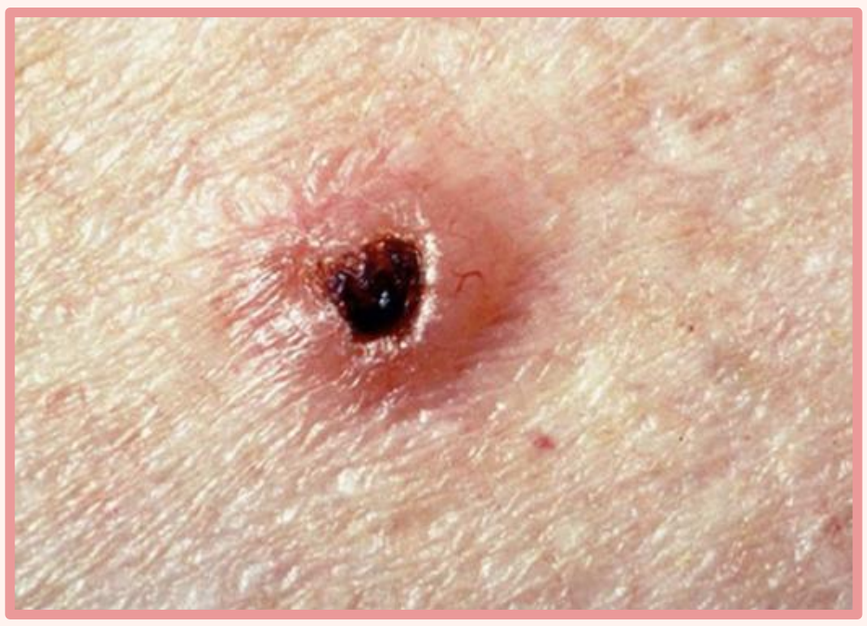
Pituitary Adenoma

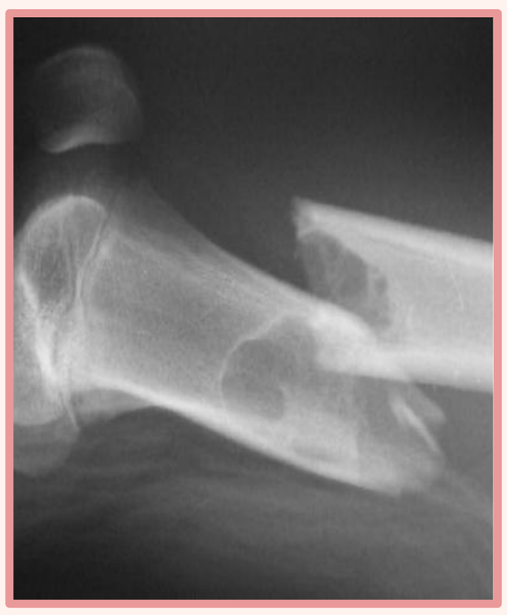


Bleeding,secondary fractures and infection

GIRL'S SLIDES

- A tumor may ulcerate through a surface or adjacent structures causing consequent bleeding or secondary infection or fracture.





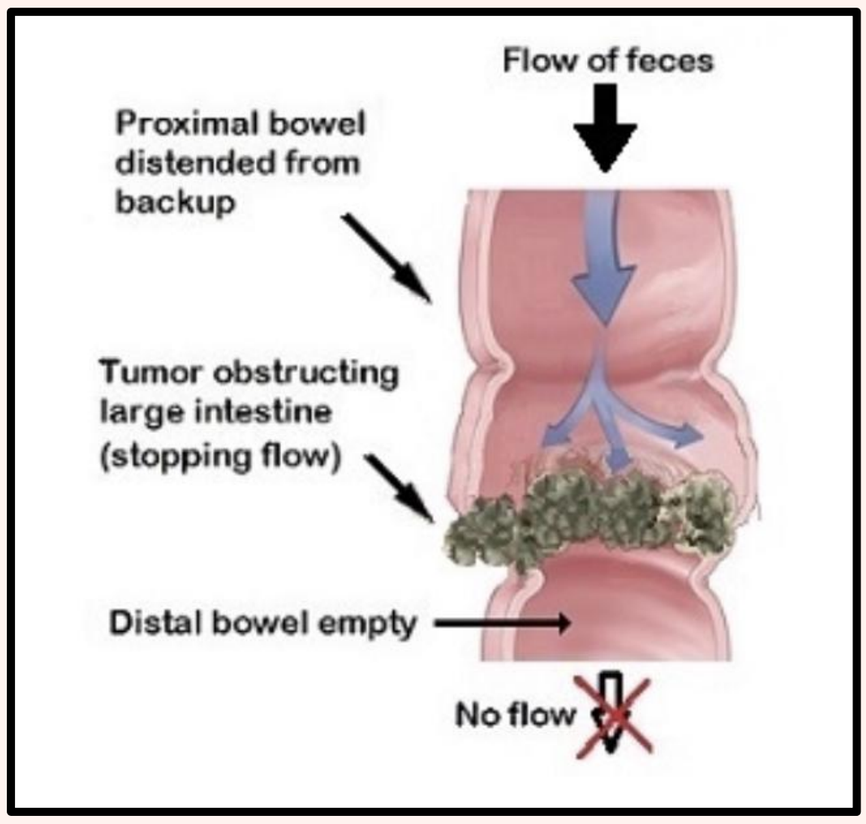
DR'S NOTE

Secondary infection or fracture means:
العظم ضعيف وانكسر بسبب حاجه مفروض ما تسبب كسر للعظم الطبيعي ، ممكن يكون سبب ضعفه هو tumor او infection او osteoporosis

Primary fracture:
العظم طبيعي وصحي وصار له trauma وانكسر

Clinical Aspects of Neoplasia

Symptoms that result from rupture, obstruction or infarction:

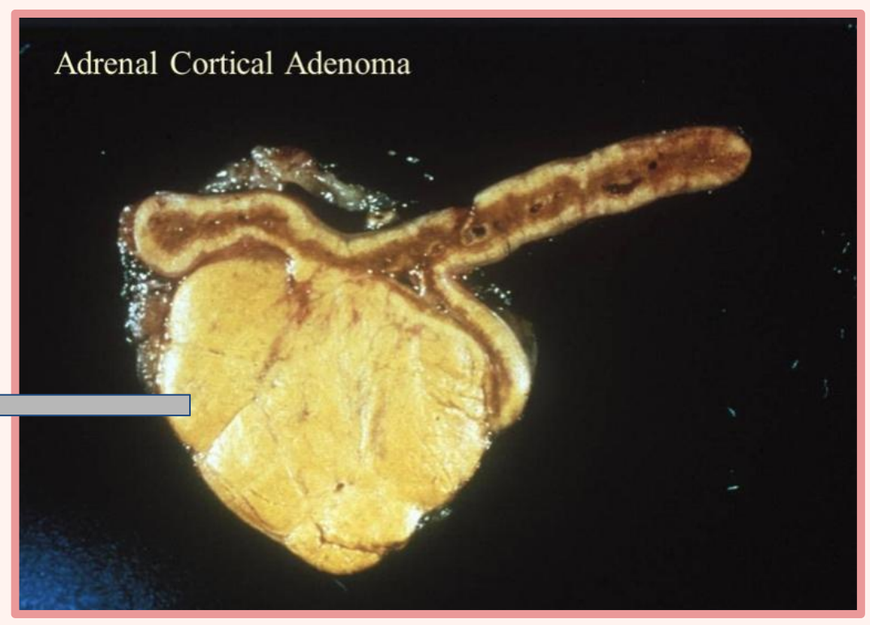


Functional activity such as hormone synthesis or the development of paraneoplastic syndromes

- 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 hyper-insulinism, sometimes fatal.

EXTRA INFO
خلايا بيتا هي الي تفرز الانسولين ف وجود الاورام المذكوره اعلاه تسبب بزياده افراز الانسولين مما يؤدي الى دروب في الشقر

- Some adenomas and carcinomas of the adrenal cortex elaborate corticosteroids that affect the patient (e.g., aldosterone, which induces sodium retention, hypertension, and hypokalemia)



EXTRA INFO
adenoma

- Such hormonal activity is more likely with a well-differentiated benign tumor than with a corresponding carcinoma.

Clinical Aspects of Neoplasia

Paraneoplastic syndromes:

- They are symptoms that occur in cancer patients & cannot be explained
- Paraneoplastic syndromes, defined as systemic symptoms that cannot be explained by tumor spread or by hormones appropriate to the tissue, are caused by the ectopic production and secretion of bioactive substances such as ACTH, PTHrP, or TGF-α.
- They are diverse and are associated with many different tumors.
- They appear in 10% to 15% of patients.
- Clinical recognition is important for several reasons:
- They may represent significant clinical problems & may be lethal.
- They may mimic metastatic disease.
- They may represent the earliest manifestation of an occult neoplasm.
- The most common paraneoplastic syndrome are:

1. Hypercalcemia very common
2. Cushing syndrome
3. Nonbacterial thrombotic endocarditis

- The most often neoplasms associated with these syndromes: Lung and breast cancers and hematologic malignancies

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
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 cancer	Tumor products (mucins that activate clotting)
Nonbacterial thrombotic endocarditis	Advanced cancers	Hypercoagulability
Anemia	Thymoma	Immunologic
Others		
Nephrotic syndrome	Various cancers	Tumor antigens, immune complexes

DR'S NOTE

الجداول ؟ حفظظظظظ

الي عليه خط هذي common مع حقتها clinical syndrome

Cancer cachexia and wasting

Cancer Cachexia

Cachexia defined: as progressive loss of body fat and lean body mass

caused by release of cytokines by the tumor or host

accompanied by profound weakness, anorexia (loss of appetite), 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:

1- Anorexia (reduced calorie intake): TNF suppresses appetite.

2- Increased basal metabolic rate & calorie expenditure.

despite reduced food intake. This is in contrast with the lower metabolic rate that occurs as an adaptive response in starvation.

3- General metabolic disturbance

wasting

- A protein-mobilizing factor called proteolysis-inducing factor, which causes breakdown of skeletal muscle proteins by the ubiquitin-proteosome pathway, has been detected in the serum of cancer patients.
- It is suspected that TNF produced by macrophages in response to tumor cells or by the tumor cells themselves mediates cachexia.

Grading and staging

Grading and Staging of Cancer

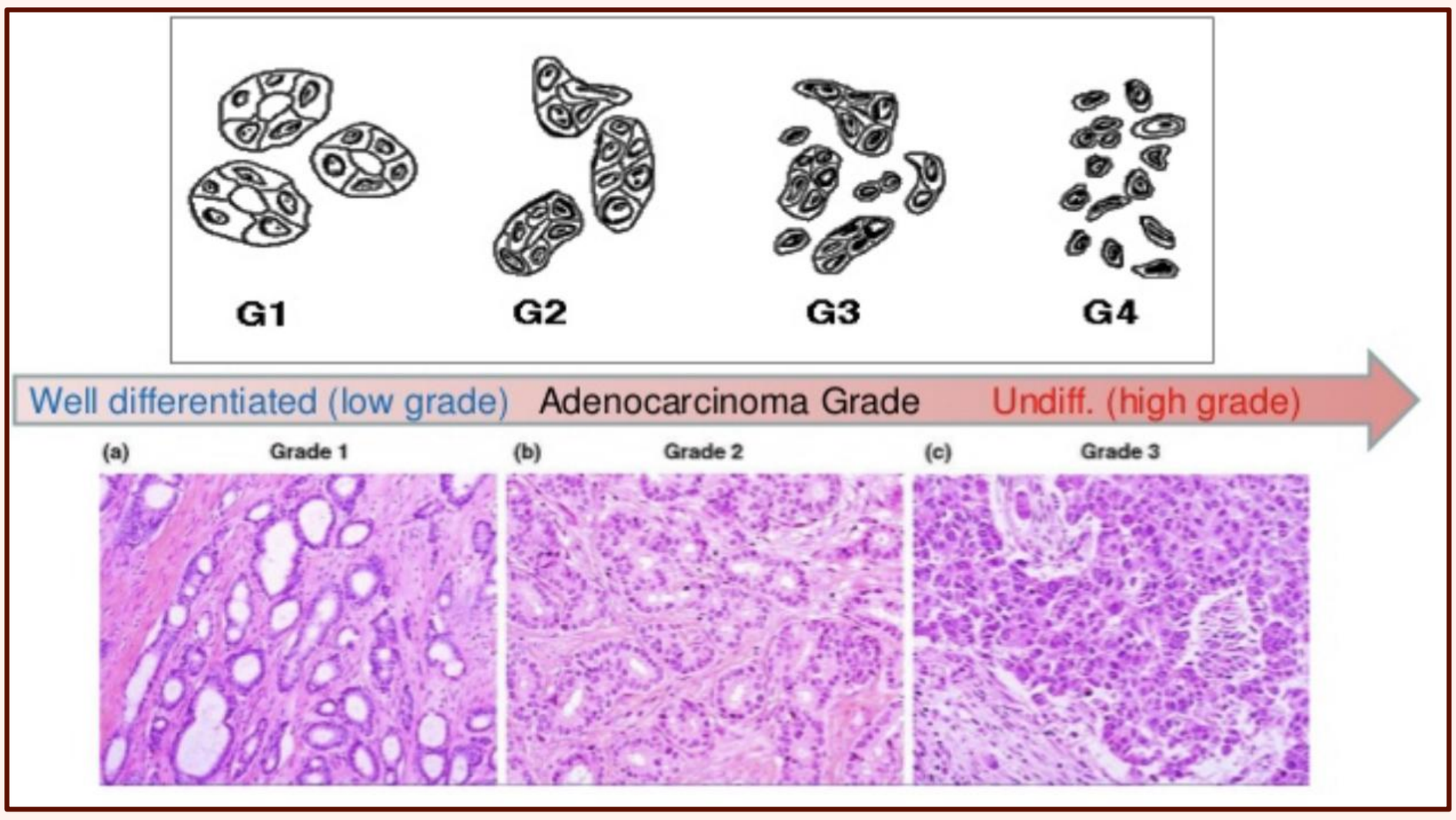
Methods to quantify the probable clinical aggressiveness of a given neoplasm and its apparent extent and spread in the individual patient are necessary for making an accurate prognosis and for comparing end results of various treatment protocols. (grading and staging is only for malignant tumors because benign tumors are very well differentiated)

Grading

It is based on the cytologic differentiation of tumor cells and the number of mitoses within the tumor.

Malignant tumors are classified as:

1. Grade I
Well differentiated
2. Grade II:
Moderately differentiated
3. Grade III : Poorly differentiated
4. Grade IV:
Anaplastic (undifferentiated)



staging

Staging

- Staging of cancers is based on the size of the primary lesion, its extent of spread to regional lymph nodes, and the presence or absence of metastases.
- This assessment usually is based on clinical and radiographic examination
- When compared with grading, staging has proved to be of greater clinical value.

Cont. staging

Two methods of staging are currently in use: the TNM system and the AJC (American Joint Committee) system

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.

AJC SYSTEM

AJC method, the cancers are divided into stages 0 to IV, incorporating the size of primary lesions and the presence of nodal spread and of distant metastases

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

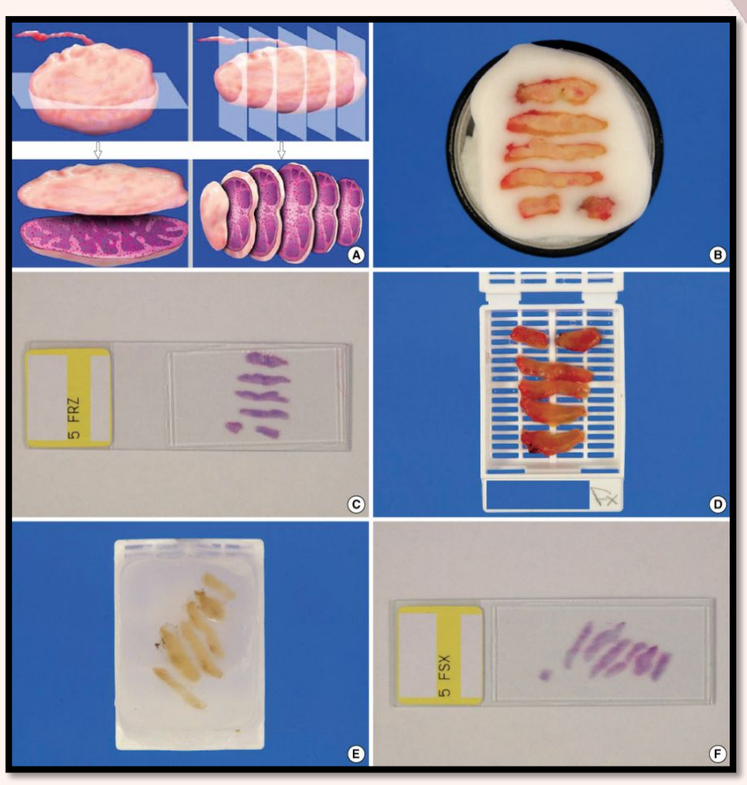
laboratory Diagnosis of cancer

- Laboratory diagnosis of cancer can be achieved by:
  - Morphologic methods (بالشكل)
  - Biochemical assays (تحاليل دم او غيرها)
  - Molecular tests (genetics)

- **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

- **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

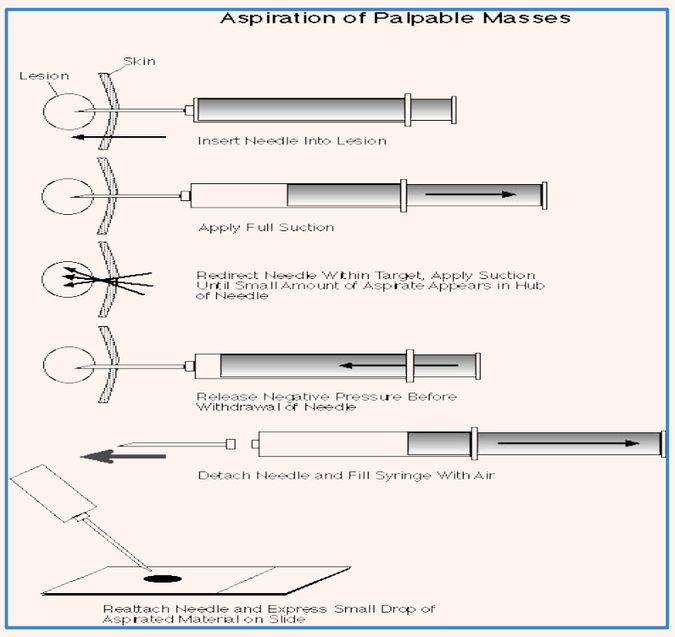
• Several sampling approaches are available, including excision or biopsy, fine-needle aspiration, and cytologic smears , immunohistochemical stains , flow cytometry.

• Requesting ***frozen section*** diagnosis is sometimes desirable, as in determining the nature of a mass lesion or in evaluating the regional lymph nodes in a patient with cancer for metastasis. This method, in which a sample is quick-frozen and sectioned, permits histologic evaluation within minutes .

MALE SLIDES

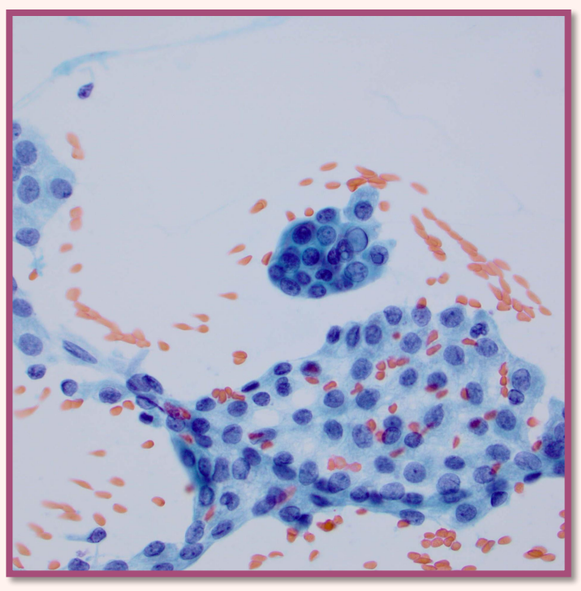
Fine needle aspiration

Fine needle aspiration involves aspiration(شفط) of cells from a mass, followed by cytologic examination of the smear.
-This procedure is used most commonly with readily palpable lesions affecting the breast, thyroid, lymph nodes, and salivary glands. •
-**Modern imaging** techniques permit extension of the method to deeper structures, such as the liver, pancreas, and pelvic lymph nodes.



FNA

FEMALE SLIDES



MALE SLIDES

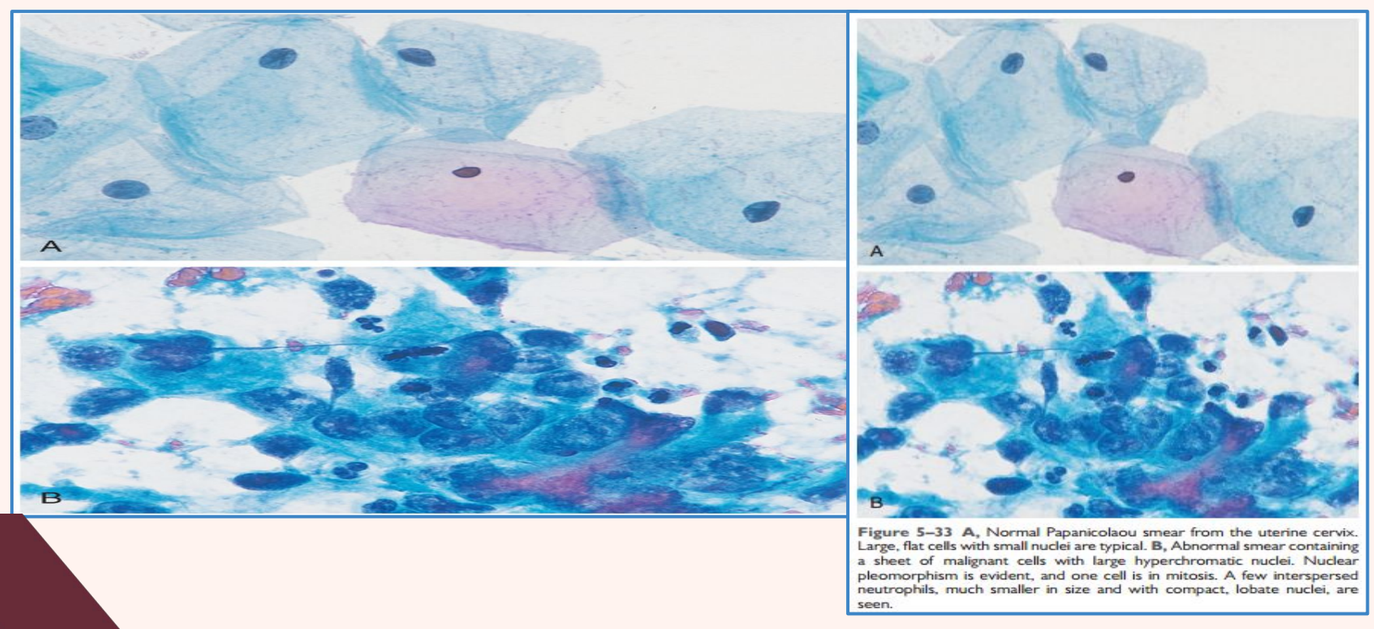


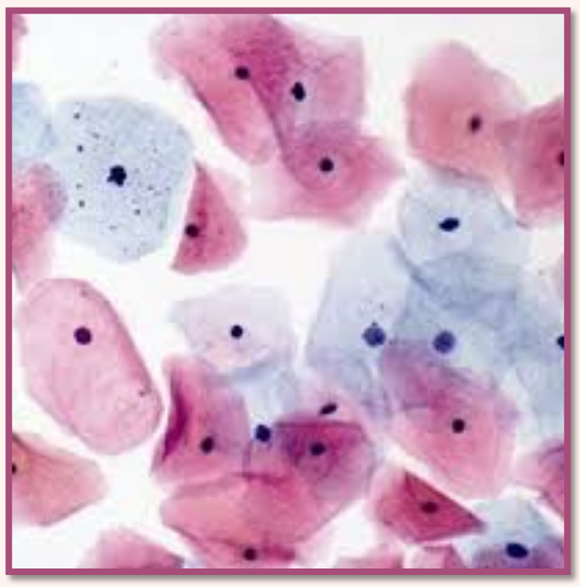
Figure 5–33 A, Normal Papanicolaou smear from the uterine cervix. Large, flat cells with small nuclei are typical. B, Abnormal smear containing a sheet of malignant cells with large hyperchromatic nuclei. Nuclear pleomorphism is evident, and one cell is in mitosis. A few interspersed neutrophils, much smaller in size and with compact, lobate nuclei, are seen.

Cytologic (Papanicolaou) smears

Cytologic (Papanicolaou) smears provide another method for the detection of cancer. Historically, this approach has been used widely for discovery of **carcinoma of the cervix** but now it is used to investigate many other forms of suspected malignancy, such as endometrial carcinoma, bronchogenic carcinoma, bladder and prostate tumors, and gastric carcinomas. Neoplastic cells are less cohesive than others and are therefore shed into fluids or secretions.

FEMALE SLIDES

Pap Smear

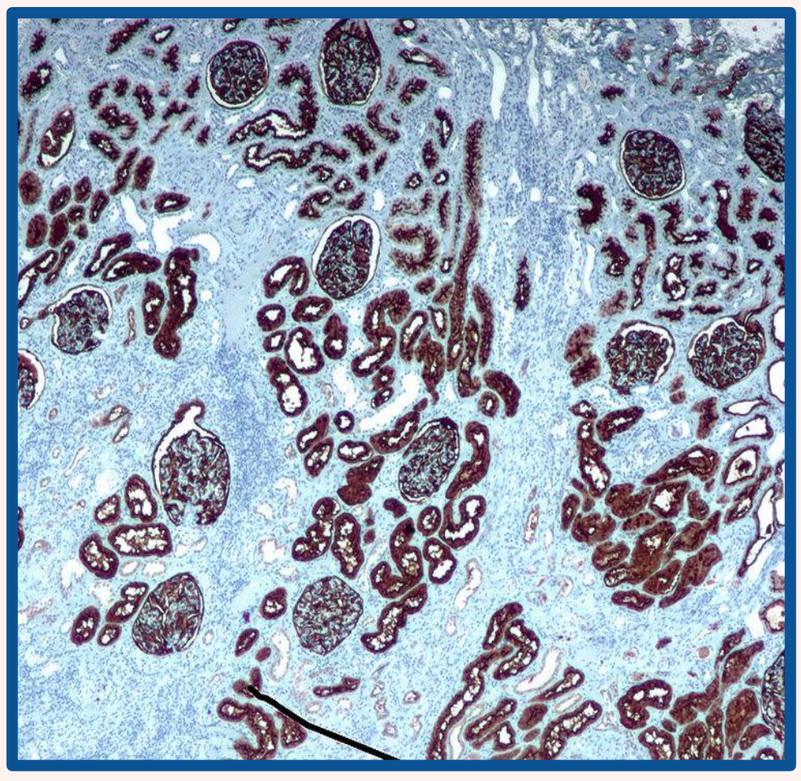


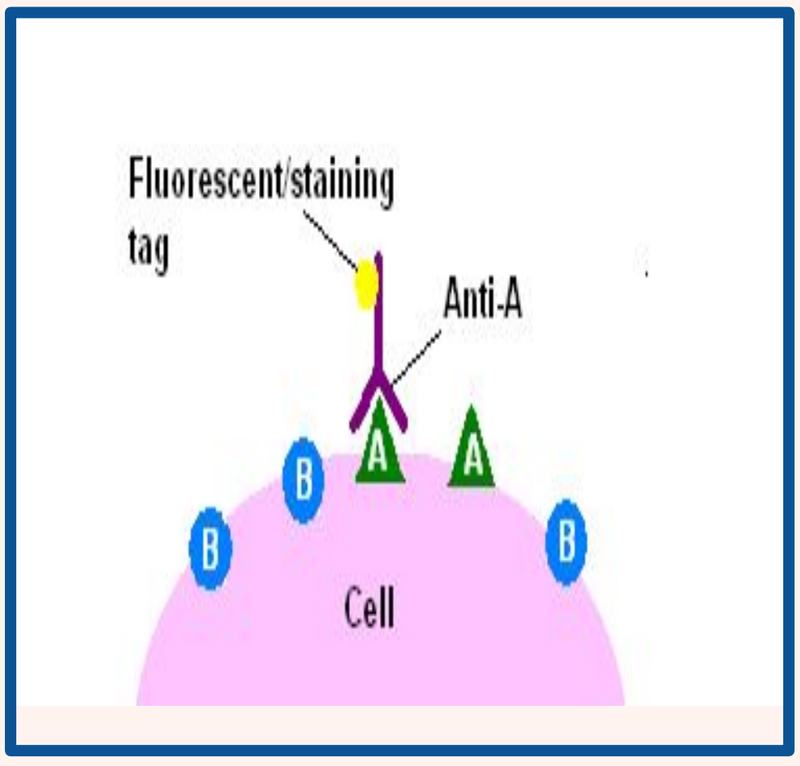
Morphologic Methods

- Immunocytochemistry (stains) offers a powerful adjunct to routine histologic examination.
- Detection of cytokeratin (CK) by specific monoclonal antibodies labeled with **peroxidase points** to a diagnosis of undifferentiated carcinoma rather than large cell lymphoma.
- Detection of prostate-specific antigen (PSA) in metastatic deposits by immunohistochemical staining allows definitive diagnosis of a primary tumor in the prostate.

Immunocytochemistry

MALE SLIDES



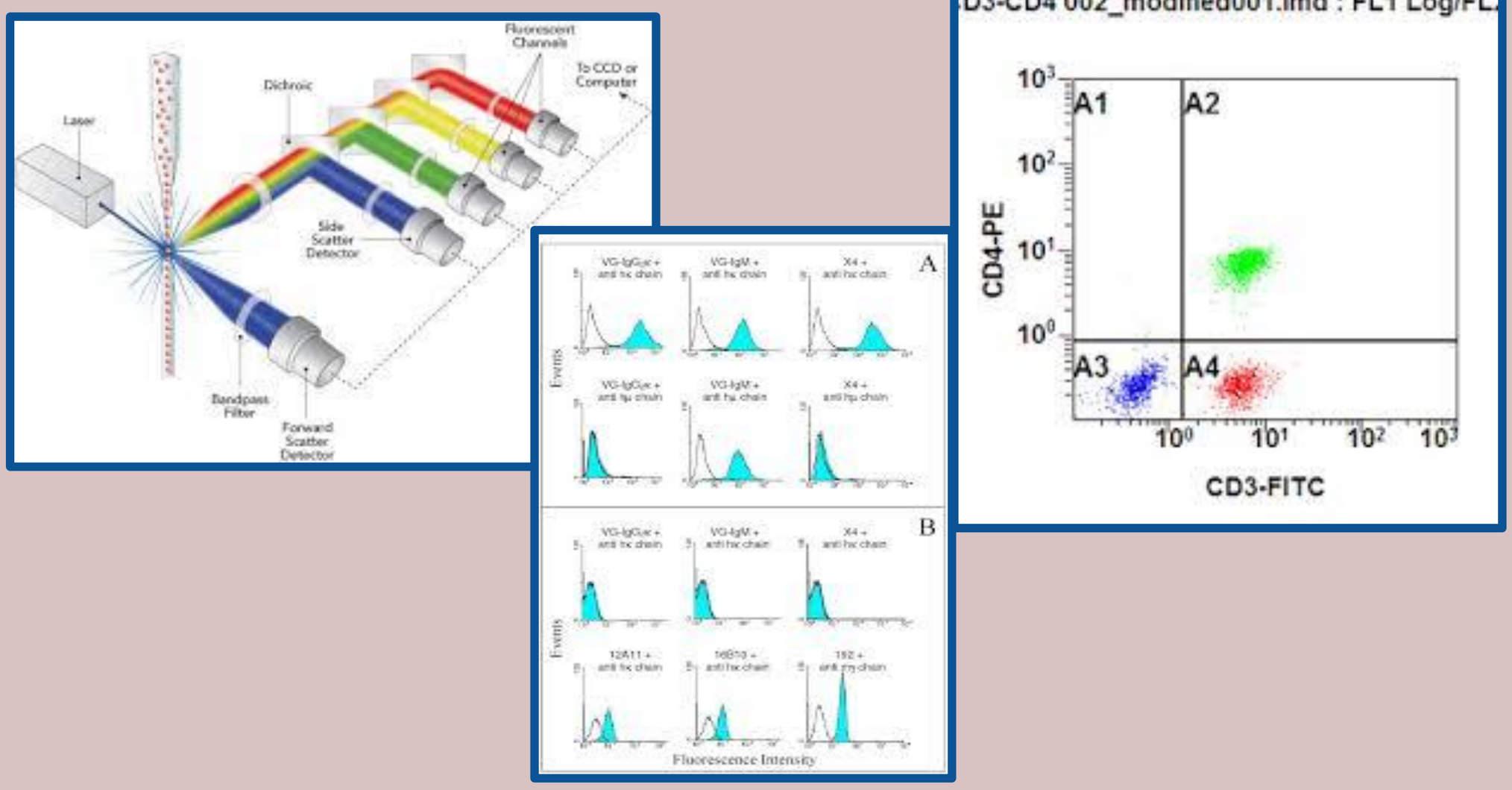


Advanced Methods

• **Flow cytometry** is used routinely in the classification of leukemias and lymphomas. In this method, fluorescent antibodies against cell surface (mainly), cytoplasmic and nuclear, molecules and differentiation antigens are used to obtain the phenotype of malignant cells.

• It is also a powerful diagnostic/follow up tool that has been used in many other non-neoplastic disease

MALE SLIDES



Tumor Markers

- Biochemical assays for tumor-associated enzymes, hormones, and other tumor markers in the blood **cannot be utilized** for definitive diagnosis of Cancer.
  - They are useful for measuring the levels of tumor associated enzymes, hormones, and tumor markers in serum.

- They can be useful **screening tests** and, in some instances, have utility in **quantitating the response** to therapy or detecting disease **recurrence**.
  - Elevated levels may not be diagnostic of cancer e.g. PSA
- PSA, used to screen for **prostatic adenocarcinoma**, may be one of the most frequently and successfully used tumor markers in clinical practice.
- Prostatic carcinoma can be suspected when elevated levels of PSA are found in the blood
- The PSA test suffers from both low sensitivity and low specificity
  - Only few tumor markers are proven to be clinically useful e.g. CEA & AFP.

MALE SLIDES

TABLE 7-12 -- Selected Tumor Markers

HORMONES	
Human chorionic gonadotropin	Trophoblastic tumors, nonseminomatous testicular tumors
Calcitonin	Medullary carcinoma of thyroid
Catecholamine and metabolites	Pheochromocytoma and related tumors
Ectopic hormones	See "Paraneoplastic Syndromes" (Table 7-11)
ONCOFETAL ANTIGENS	
α-Fetoprotein	Liver cell cancer, nonseminomatous germ cell tumors of testis
Carcinoembryonic antigen	Carcinomas of the colon, pancreas, lung, stomach, and heart
ISOENZYMES	
Prostatic acid phosphatase	Prostate cancer
Neuron-specific enolase	Small-cell cancer of lung, neuroblastoma
SPECIFIC PROTEINS	
Immunoglobulins	Multiple myeloma and other gammopathies
Prostate-specific antigen and prostate-specific membrane antigen	Prostate cancer
MUCINS AND OTHER GLYCOPROTEINS	
CA-125	Ovarian cancer
CA-19-9	Colon cancer, pancreatic cancer
CA-15-3	Breast cancer
NEW MOLECULAR MARKERS	
p53, APC, RAS mutants in stool and serum	Colon cancer
p53 and RAS mutants in stool and serum	Pancreatic cancer
p53 and RAS mutants in sputum and serum	Lung cancer
p53 mutants in urine	Bladder cancer

Molecular Diagnosis

A — Diagnosis of malignancy

Because each **T and B** cell exhibits unique rearrangement of its antigen receptor genes, **polymerase chain reaction** (**PCR**)–based detection of T cell receptor or immunoglobulin genes allows distinction between **monoclonal** (**neoplastic**) **and polyclonal** (**reactive**) proliferations. Many **hematopoietic neoplasms**, **as well as a few solid tumors**, are defined by **particular translocations**, so the diagnosis can be made by detection of such translocations. Fluorescence in situ hybridization (**FISH**) **or PCR analysis** can be used to detect translocations.

- **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.

B — Therapeutic decision-making

Therapies that directly target specific mutations are increasingly being developed, and thus detection of such mutations in a tumor can guide the development of targeted therapy, as discussed later.

C — Prognosis and behavior

Certain genetic alterations are associated with a poor prognosis, and thus the presence of these alterations determines the patient's subsequent **therapy**. FISH and PCR methods can be used to detect amplification of oncogenes such as HER2/NEU and N-MYC, which provide prognostic and therapeutic information for breast cancers and neuroblastomas

Molecular design

D

Detection of minimal residual disease

Another emerging use of molecular techniques is for detection of minimal residual disease after Treatment.

E

Diagnosis of hereditary predisposition to cancer

Germline mutation of several tumor suppressor genes, such as BRCA1, increases a patient's risk for development of certain types of cancer. Thus, detection of these mutated alleles may allow the patient and the physician to devise an aggressive screening protocol, as well as an opportunity for prophylactic surgery. In addition, such detection allows genetic counseling of relatives at risk.

F

- **DNA microarray analysis:**

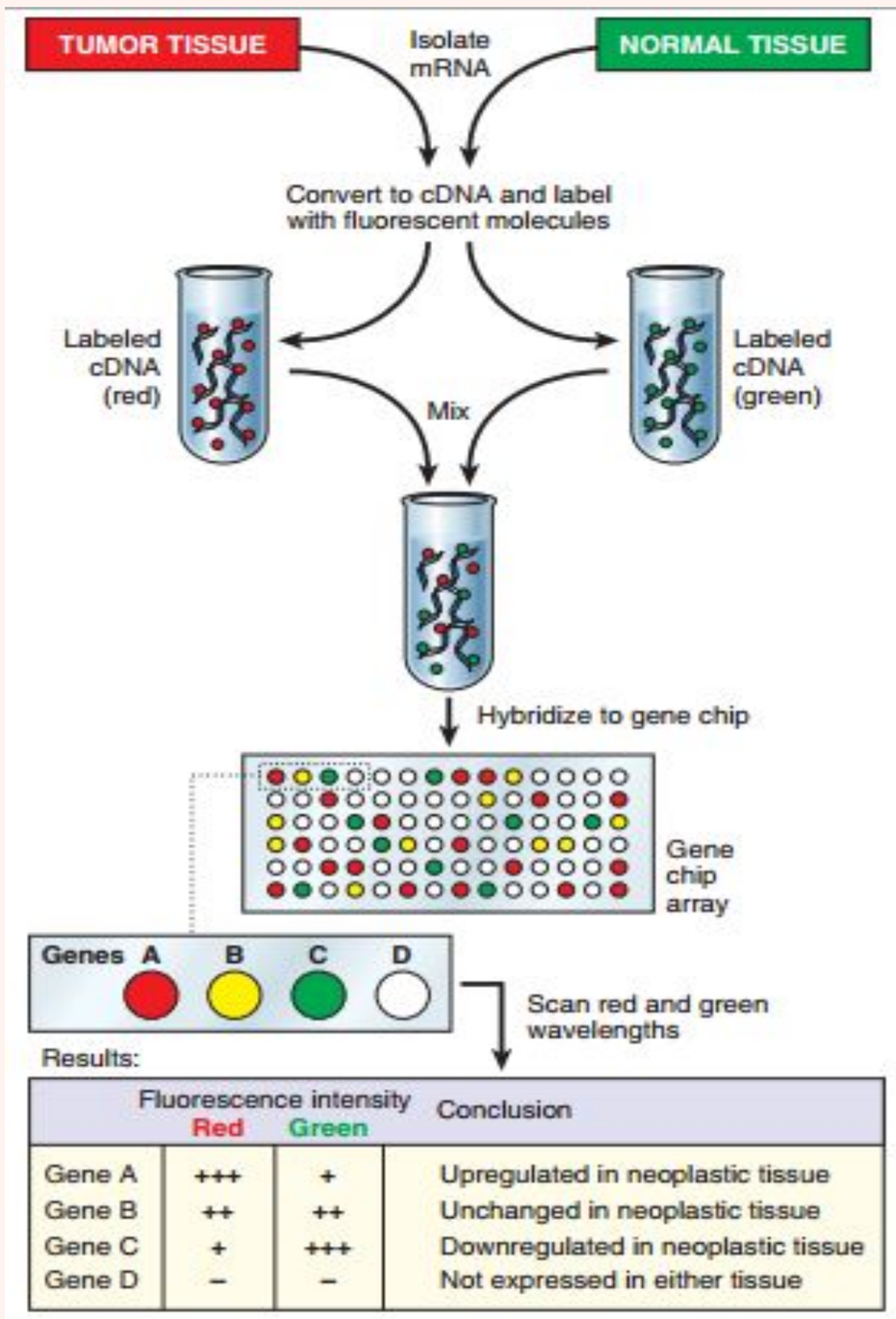
- It evaluates the expression of thousands of genes.
- Different tissues have different patterns of gene expression.
- It is a powerful tool for subcategorizing diseases e.g. lymphomas.
- It confirms the morphologic diagnoses.
- It is useful in illustrating genes involved in certain disease & help plan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

Molecular Profiling of Tumors

Male's SLIDES

- Expression Profiling (Microarray).
- Whole Genome Sequencing (NGS).

Expression Profiling: allows simultaneous measurements of the expression levels of several thousand genes.



	Fluorescence intensity Red	Green	Conclusion
Gene A	+++	+	Upregulated in neoplastic tissue
Gene B	++	++	Unchanged in neoplastic tissue
Gene C	+	+++	Downregulated in neoplastic tissue
Gene D	–	–	Not expressed in either tissue

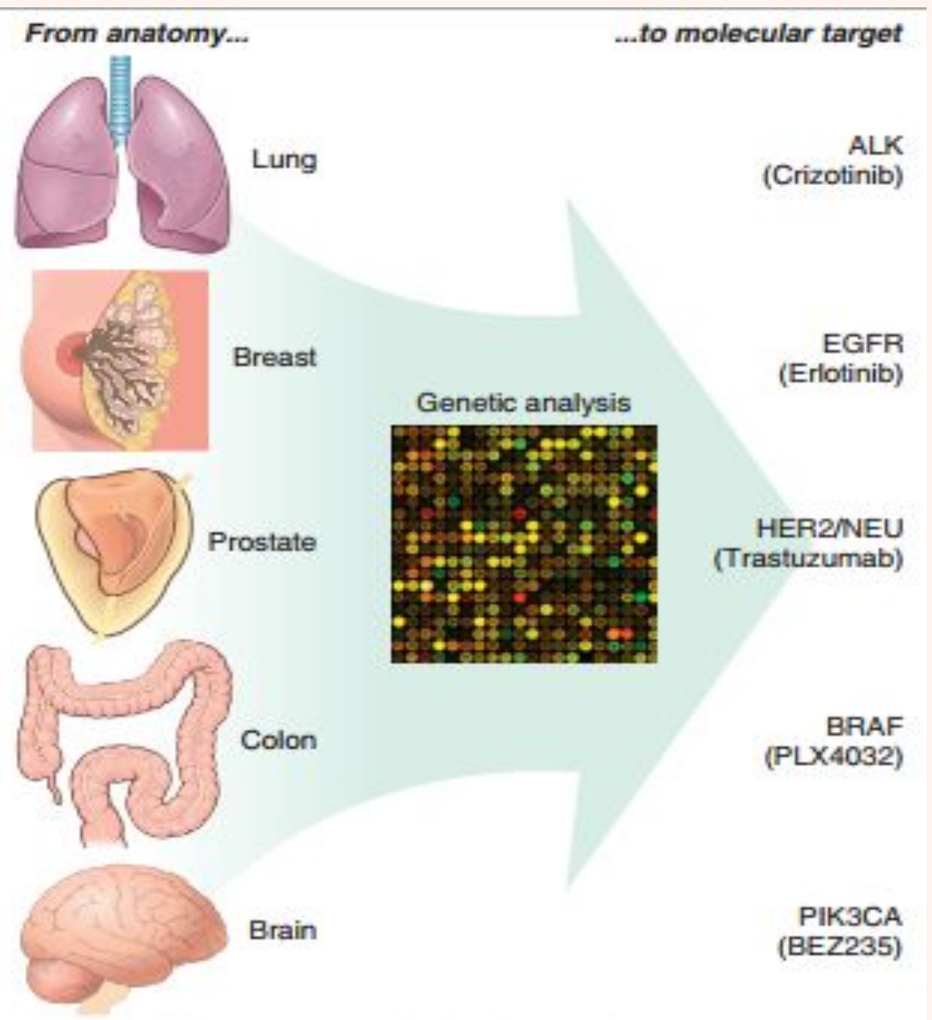


Figure 5–36 A paradigm shift: Classification of cancer according to therapeutic targets rather than cell of origin and morphology.

in the classification and therapy of tumors. Perhaps in the future the diverse group of tumors that bear a common mutation such as BRAF will be classified as BRAF-omas (Fig. 5–34), rather than individual types based on morphology or cell of origin!

Molecular Profiling of Tumors

Male's SLIDES

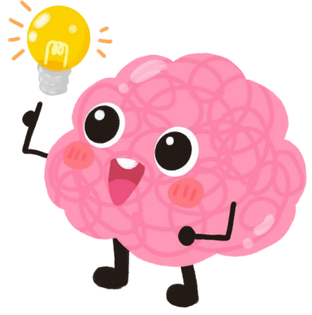
Whole Genome Sequencing:

Sequences of the entire tumor genomes, when compared with the normal genome from the same patient, can reveal all **the somatic alterations** present in a tumor.

It is hoped that identification of all potentially targetable mutations in each individual tumor will refocus the treatment of tumors from the tissue of origin to the molecular lesion, as drugs **that target specific mutations** are developed.

Summary:

- The importance and the differences between **grading and staging**.
- The **clinical effects** of tumors (cancer **cachexia and paraneoplastic** syndromes).
- The different **laboratory methods** used to diagnose tumors and other purposes.



KEYWORDS

Tumor-specific antigens	which are present only on tumor cells and not on any normal cells.
Staging	**Staging of cancers is based on the size of the primary lesion, its extent of spread to regional lymph nodes, and the presence or absence of metastases.**
Cachexia	defined as progressive loss of body fat and lean body mass,
★ Grading	It is based on the cytologic differentiation of tumor cells and the number of mitoses within the tumor.

MCQ

1-a , 2-d , 3-d , 4-c, 5-a

1- Tumor antigens that are present only on tumor cells and not on any normal cells are called:			
A)Tumor-specific antigens	B) Tumor-associated antigens	C)Mutated oncogenes	D)Amplified genes
2- Which of the following is an example of a differentiation antigen expressed by tumors?			
A)P53 tumor suppressor gene	B)CEA in colon carcinomas	C)HPV	D)PSA in prostatic carcinoma
3- Which of the following is NOT an antitumor effector mechanism?			
A)Cytotoxic T lymphocytes	B)Natural killer cells	C)Macrophages	D)Cytokines
4- Paraneoplastic syndromes are caused by ?			
A)Tumor spread	B)Hormones appropriate to the tissue	C)Ectopic production and secretion of bioactive substances	D)Metastatic disease
5- Cachexia is defined as:			
A)Progressive loss of body fat and lean body mass	B)Excessive calorie intake	C)Hypertension and hypokalemia	D)Breakdown of skeletal muscle proteins

MCQ

ج-6 ، ب-7 ، ب-8 ، ب-9

6- Grading of tumors is based on:			
A)Size of the primary lesion	B)Spread to regional lymph nodes	C)Cytologic differentiation of tumor cells and number of mitoses	D)Presence or absence of distant metastases
7-Staging of cancers is based on:			
A)Cytologic examination	B)Clinical and radiographic examination	C)Presence of tumor-specific antigens	D)Immunohisto chemical stains
8- The TNM system is used for:			
A)Grading tumors	B) Staging tumors	C) Diagnosing cancer	D) Assessing host defenses

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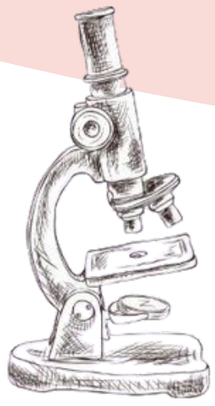

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