Principles of Grading & Staging of Malignant Tumors with Local & Systemic Manifestations

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Objectives

- **Define grading and staging of malignant tumors.**
- **Explain the effect of tumor location and its hormonal products on the patient.**
- **Understand the concept of cancer cachexia and paraneoplastic syndromes.**
- **Know the different laboratory methods of cancer diagnosis and follow up.**

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

- The ***grading*** of a cancer attempts to establish some estimate of its aggressiveness or level of malignancy **based on the cytologic differentiation of tumor cells and the number of mitoses** within the tumor.
- The cancer may be classified as **grade I, II, III, or IV**, in order of increasing anaplasia. Criteria for the individual grades vary with each form of neoplasia and are not detailed here.

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 .
- Two methods of staging are currently in use: the **TNM system** and the **AJC (American Joint Committee) system.**
- ***TNM system***, **T1, T2, T3, and T4** describe the increasing **size** of the primary lesion; **N0, N1, N2, and N3** indicate progressively advancing **node involvement**; and **M0 and M1** reflect the absence and presence, respectively, of **distant metastases**.
- ***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.
- W*hen compared with grading, staging has proved to be of greater clinical value*.

Effects of Tumor on Host

- Both malignant and benign tumors may cause problems because of
  1. Location and impingement on adjacent structures
  2. Functional activity such as hormone synthesis or the development of paraneoplastic syndromes.
  3. Bleeding and infections when the tumor ulcerates through adjacent surfaces.
  4. Symptoms that result from rupture or infarction.
  5. Cachexia or wasting.

Effects of Tumor on Host

- 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.
- Some adenomas and carcinomas of the adrenal cortex elaborate corticosteroids that affect the patient.
- Such hormonal activity is more likely with a well-differentiated benign tumor than with a corresponding carcinoma.

Cancer Cachexia

- ***Cachexia***, defined as progressive loss of body fat and lean body mass, accompanied by profound weakness, anorexia, and anemia, is caused by **release of cytokines by the tumor or host**.

- In patients with cancer, calorie expenditure remains high, and basal metabolic rate is increased, despite reduced food intake. **This is in contrast** with the lower metabolic rate that occurs as an adaptive response in **starvation**.

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.

Paraneoplastic Syndromes

- **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**.
- Clinical **recognition is important** for several reasons:
  1) Such syndromes may represent the earliest manifestation of an occult neoplasm.
  2) In affected patients, the pathologic changes may be associated with significant clinical illness and may even be lethal.
  3) The symptom complex may mimic metastatic disease, thereby confounding treatment.

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 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

ACTH, adrenocorticotropic hormone; IL-1, interleukin-1; TGF-α, transforming growth factor-α; TNF, tumor necrosis factor.

Laboratory Diagnosis of Cancer

- *Morphologic Methods.*
- *Tumor Markers.*
- *Molecular Diagnosis.*

Morphologic Methods

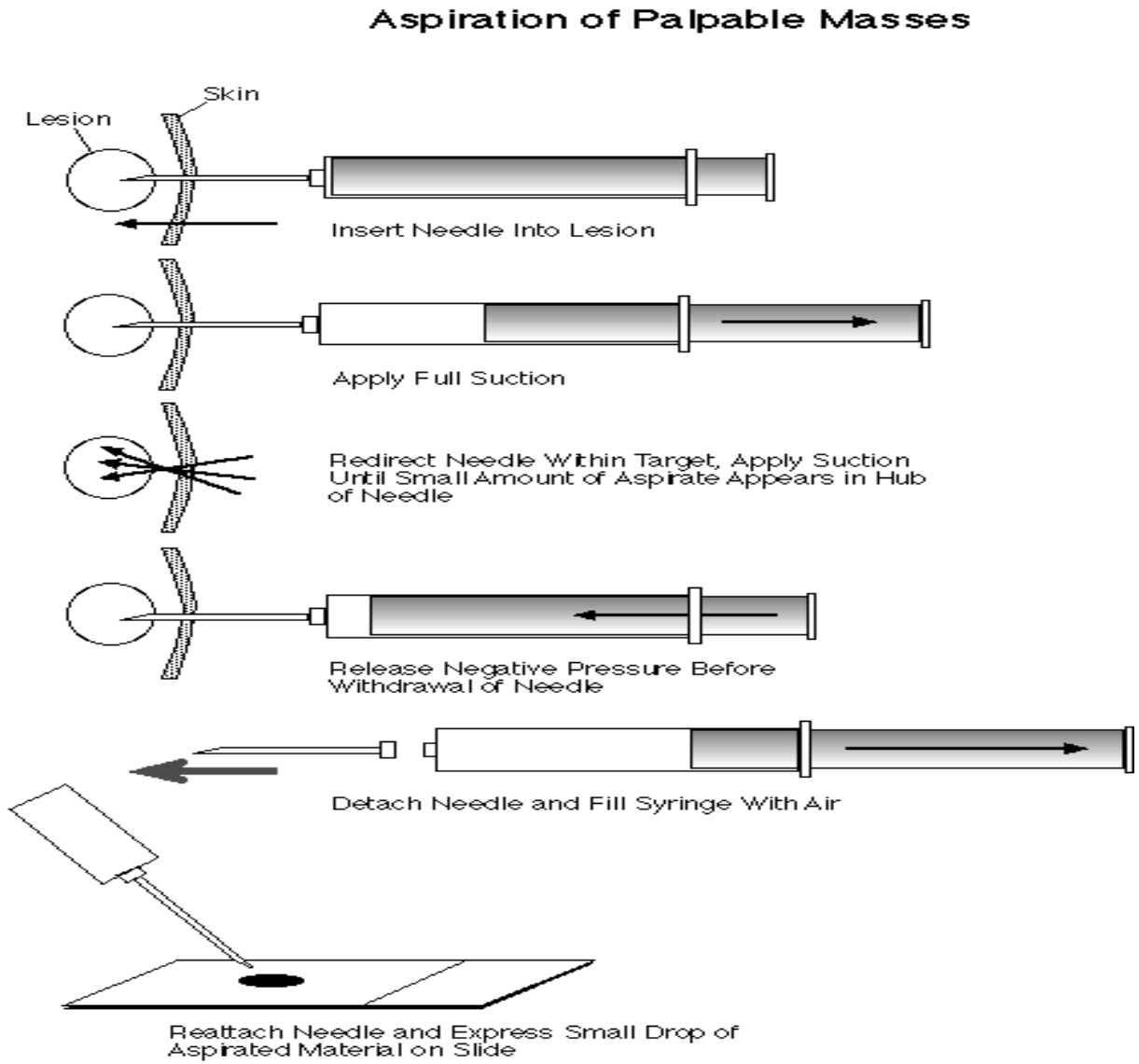
- Several sampling approaches are available, including excision or biopsy, fine-needle aspiration, and cytologic smears.
- Requesting ***frozen section*** diagnosis is sometimes desirable, as in determining the nature of a mass lesion or in evaluating the regional lymph nodes in a patient with cancer for metastasis. This method, in which a sample is quick-frozen and sectioned, permits histologic evaluation within minutes.

Frozen section

Morphologic Methods

- ***Fine needle aspiration*** involves aspiration 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.

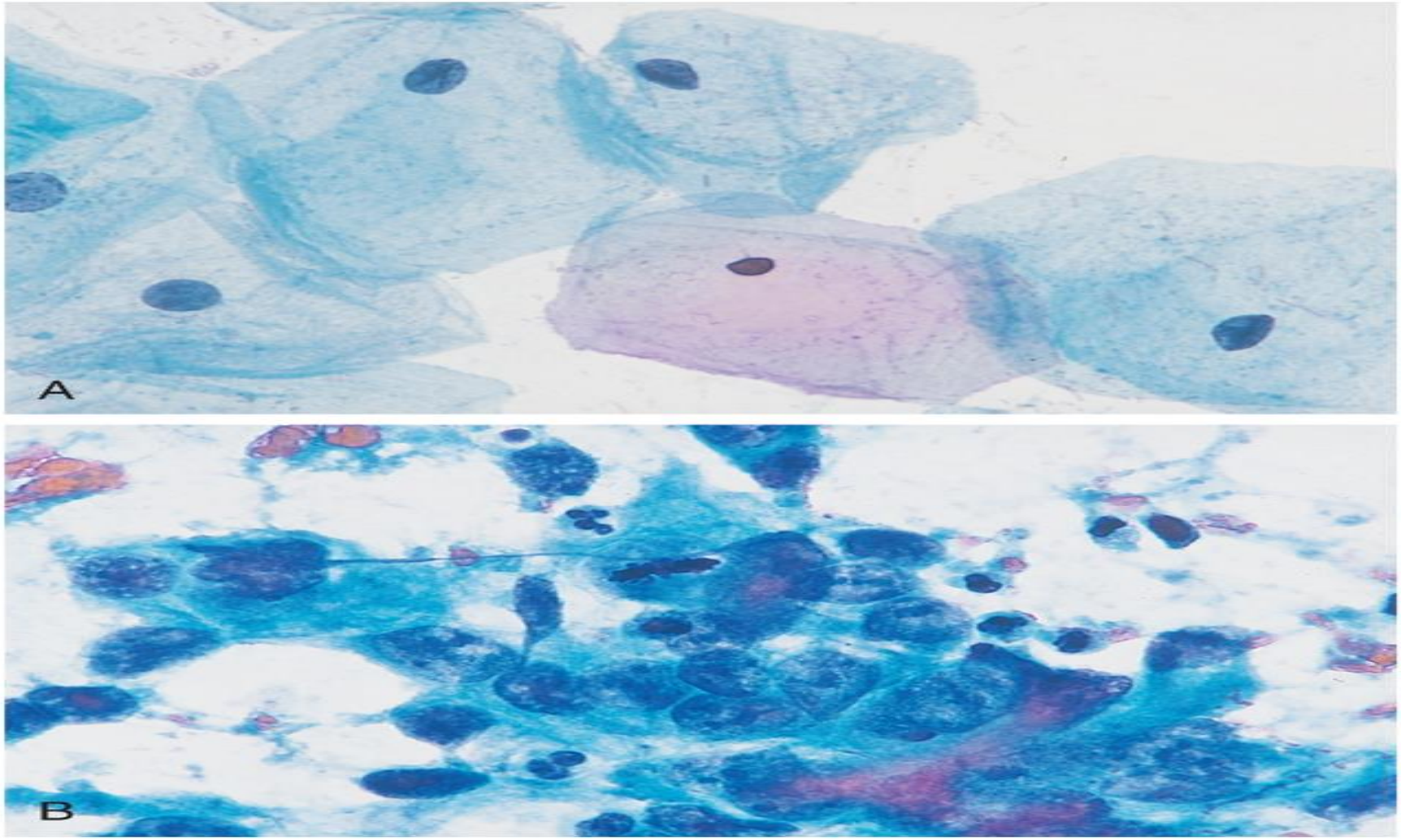
Fine Needle Aspiration



Morphologic Methods

- **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.

Cytological smear



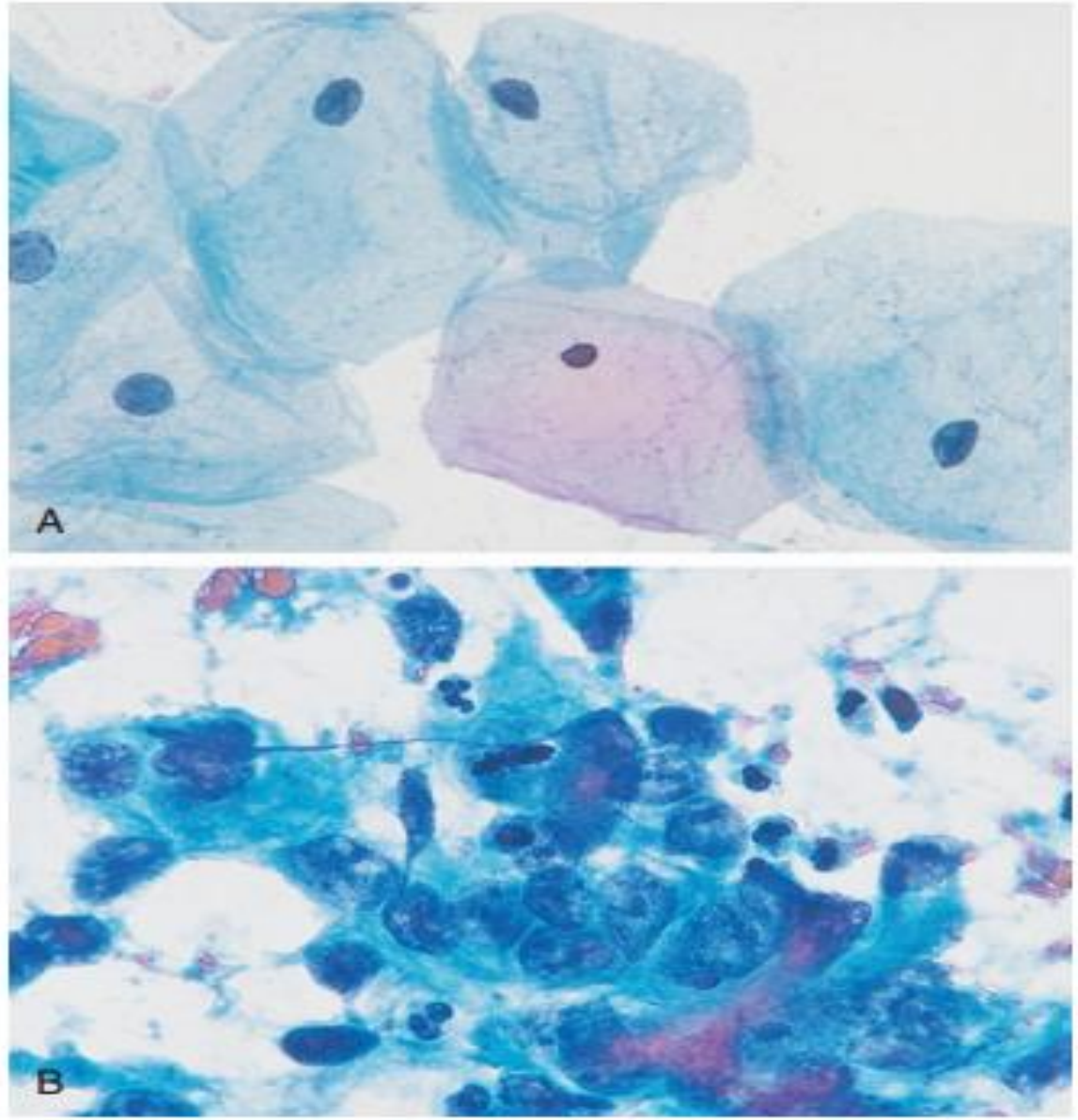
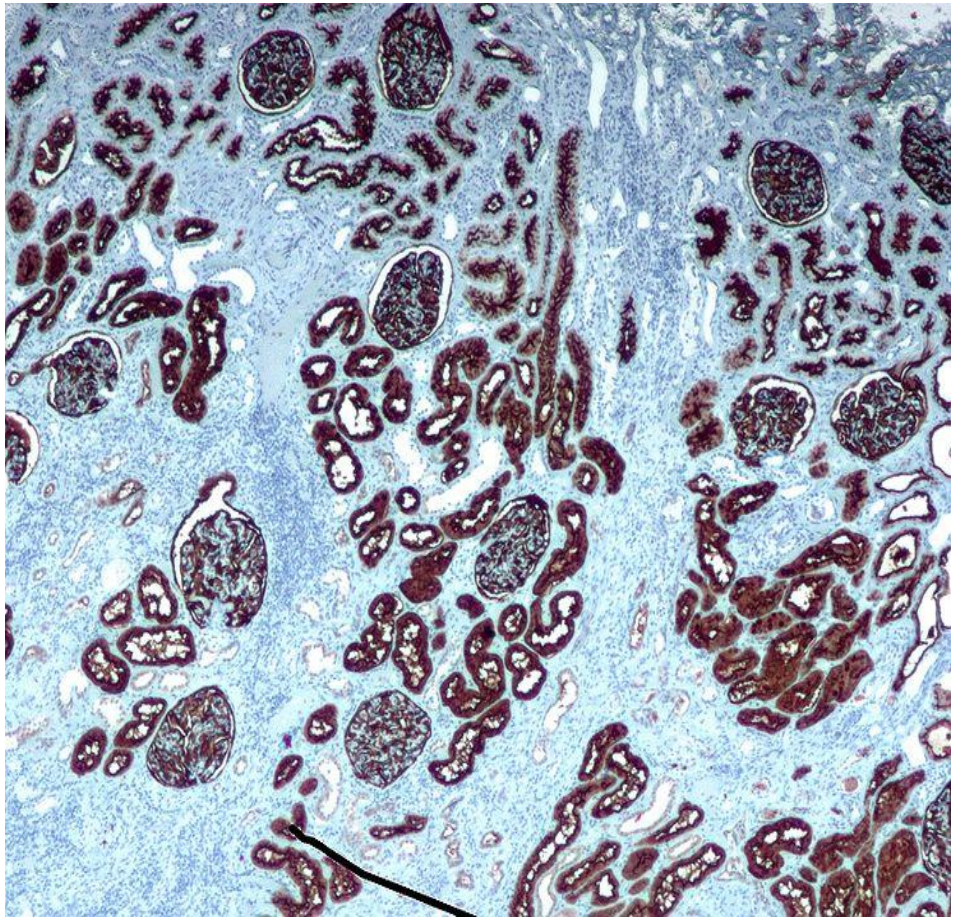


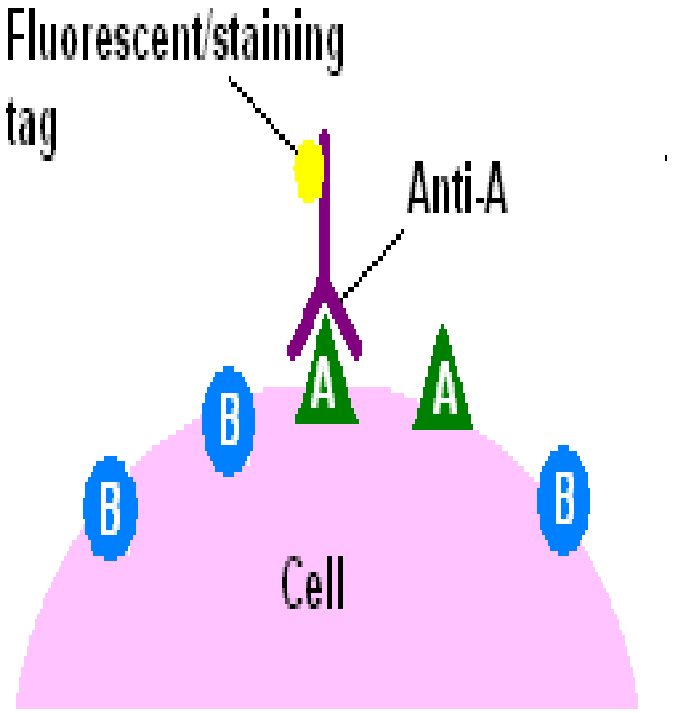
Figure 5–33 **A,** Normal Papanicolaou smear from the uterine cervix. Large, flat cells with small nuclei are typical. **B,** Abnormal smear containing a sheet of malignant cells with large hyperchromatic nuclei. Nuclear pleomorphism is evident, and one cell is in mitosis. A few interspersed neutrophils,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

Morphologic Methods

- **Immunocytochemistry** 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.

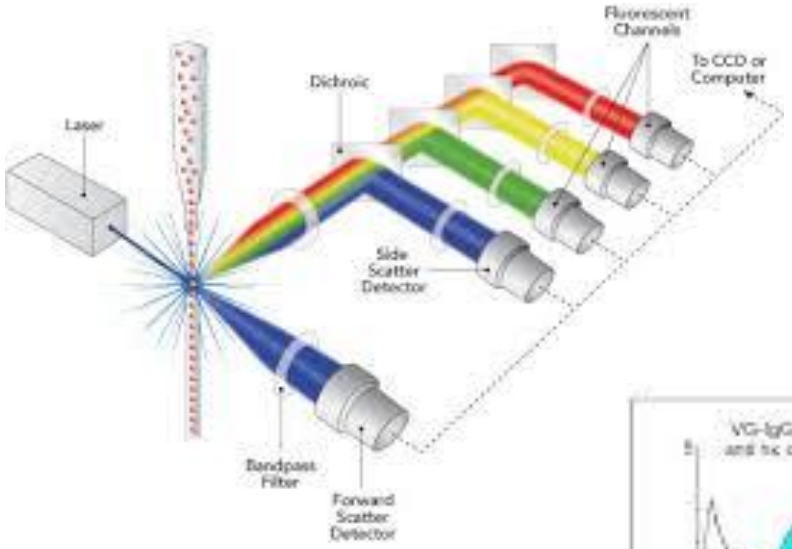
Immunocytochemistry

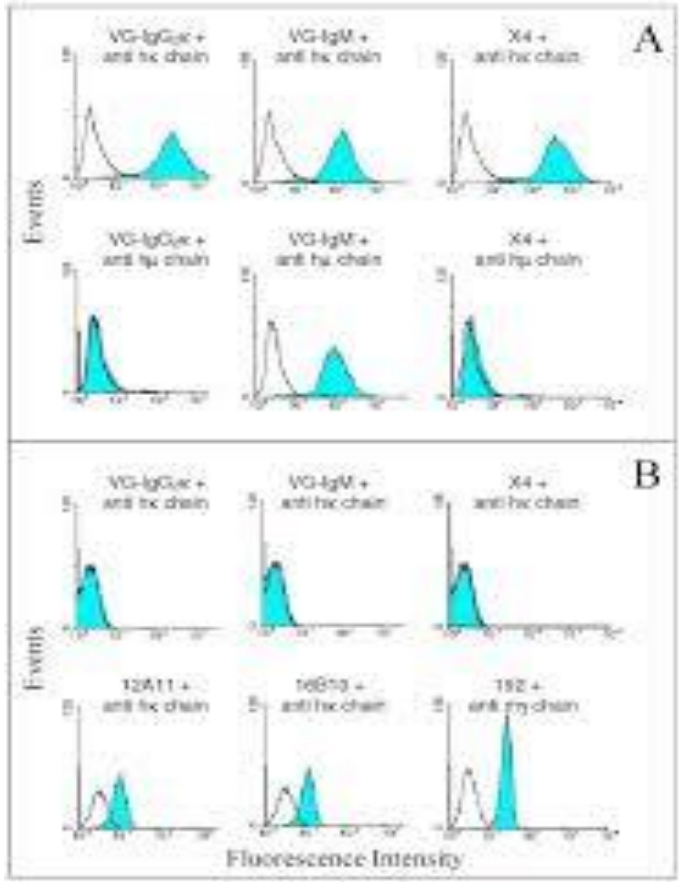


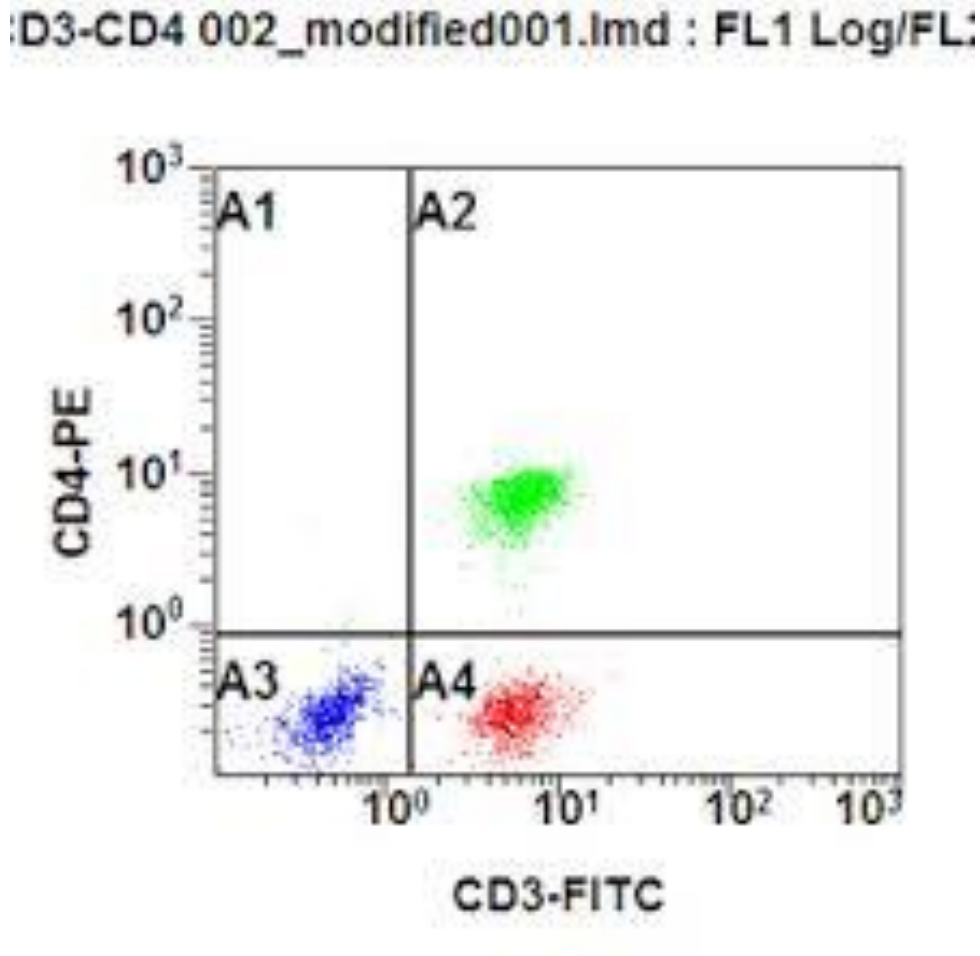


Advanced Methods

- ***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.


Fluorescent Channels
To CCD or Computer
Dichroic
Laser
Side Scatter Detector
Bandpass Filter
Forward Scatter Detector


A
B
Events
Fluorescence Intensity


D3-CD4 002_modified001.lmd : FL1 Log/FL
A1
A2
A3
A4
CD4-PE
CD3-FITC

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 can be useful **screening tests** and in some instances have utility in **quantitating the response** to therapy or detecting disease **recurrence**.
- **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** (How?)

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.

Molecular Diagnosis

- **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.

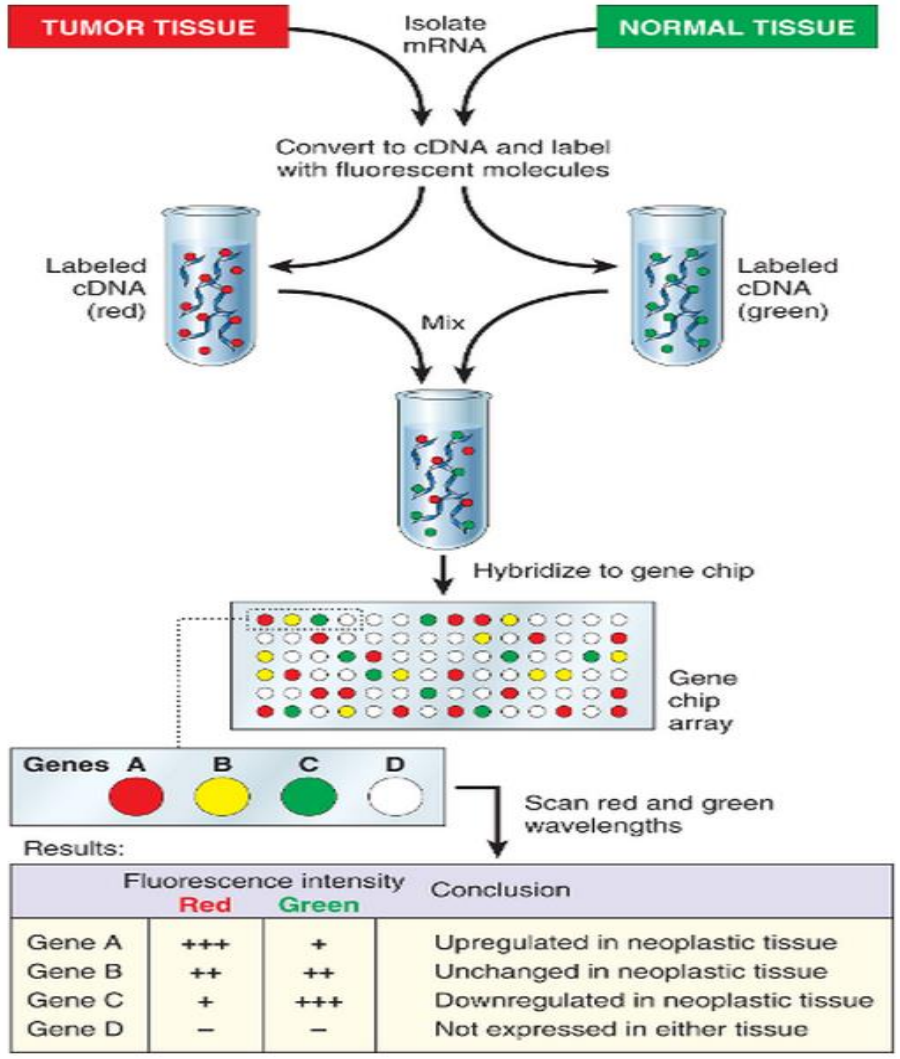
Molecular Diagnosis

- **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.

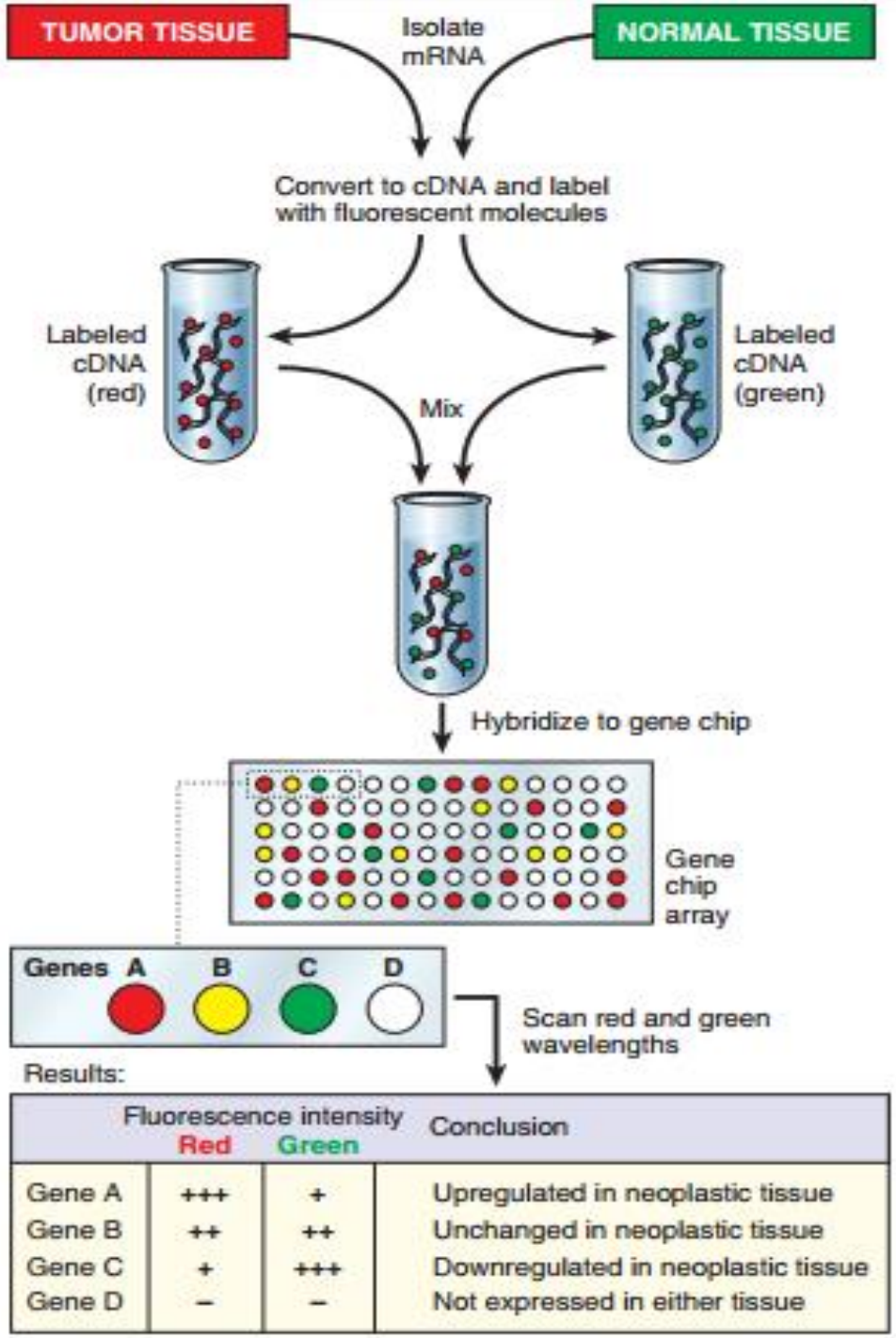
Molecular Profiling of Tumors

- Expression Profiling.
- Whole Genome Sequencing.

- 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



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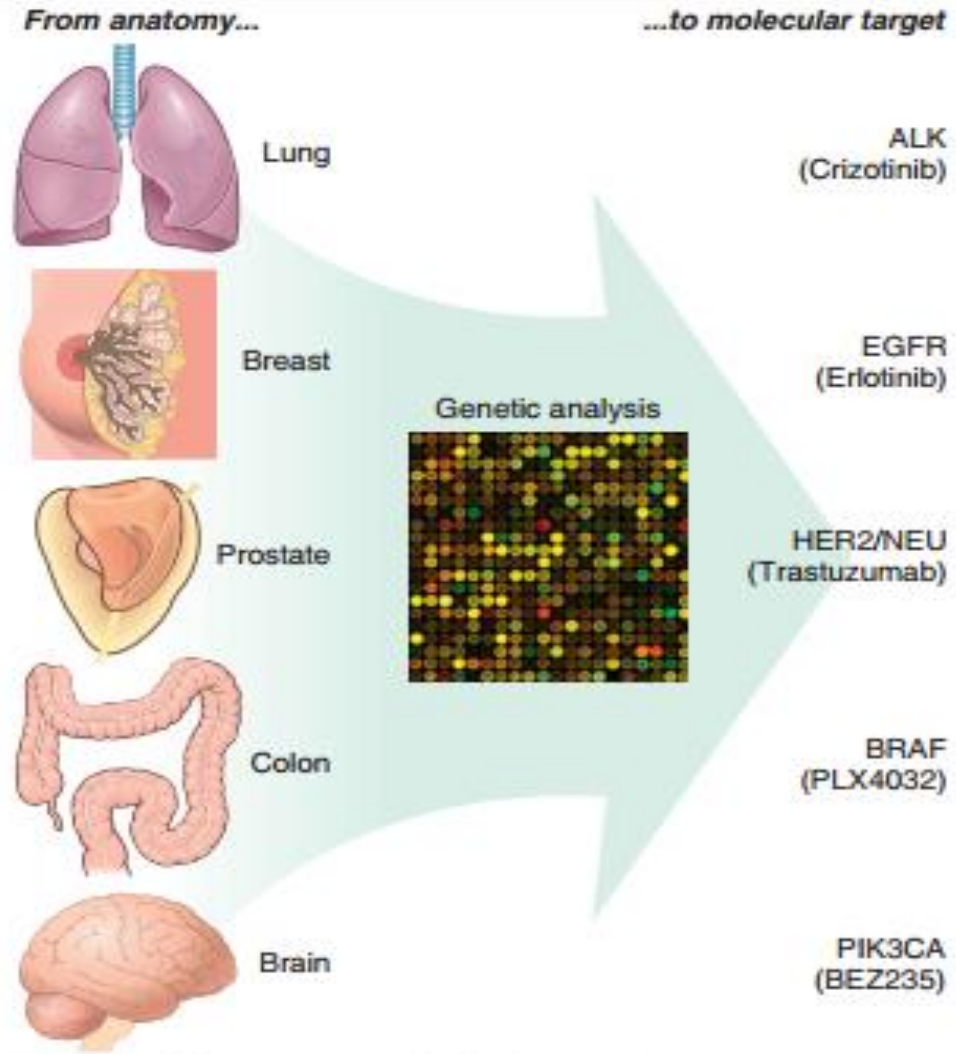

Figure 5–36 A paradigm shift: Classification of cancer according to therapeutic targets rather than cell of origin and morphology.

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!

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.