Neoplasia 6

CARCINOGENIC AGENTS

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ETIOLOGY OF CANCER: CARCINOGENIC AGENTS

- Carcinogenic agents inflict genetic damage, which lies at the heart of carcinogenesis.

- Three classes of carcinogenic agents have been identified:
- (1) Chemicals.
- (2) Radiant energy.
- (3) Microbial products.

1.MAJOR TYPES OF CHEMICAL CARCINOGENS:

A. Direct-Acting Agents:

Direct-acting agents require no metabolic conversion to become carcinogenic. e.g., alkylating agents).

Alkylating Agents: Direct, used in chemotherapy of cancer - may induce Leukemia

B. Indirect-Acting Agents :

- Polycyclic Hydrocarbons: Indirect & very strong - include benzopyrene in cigarette smoke → CA Lung

- Aromatic Amines & Azo dyes: Indirect -Rubber & Food Industry e.g. β-naphthylamine → Bladder CA

Another important examples of indirect-acting carcinogens.

- **Aflatoxin B1 from Aspergillus with hepatocellular carcinoma .**
- **Nitrites used as food preservatives are suspected to be carcinogenic. cause Gastric & Colon CA…etc.**

Mode of action of chemical Carcinogens

- Chemical carcinogens contain highly reactive electrophile groups that combine to DNA, RNA or protein producing mutations

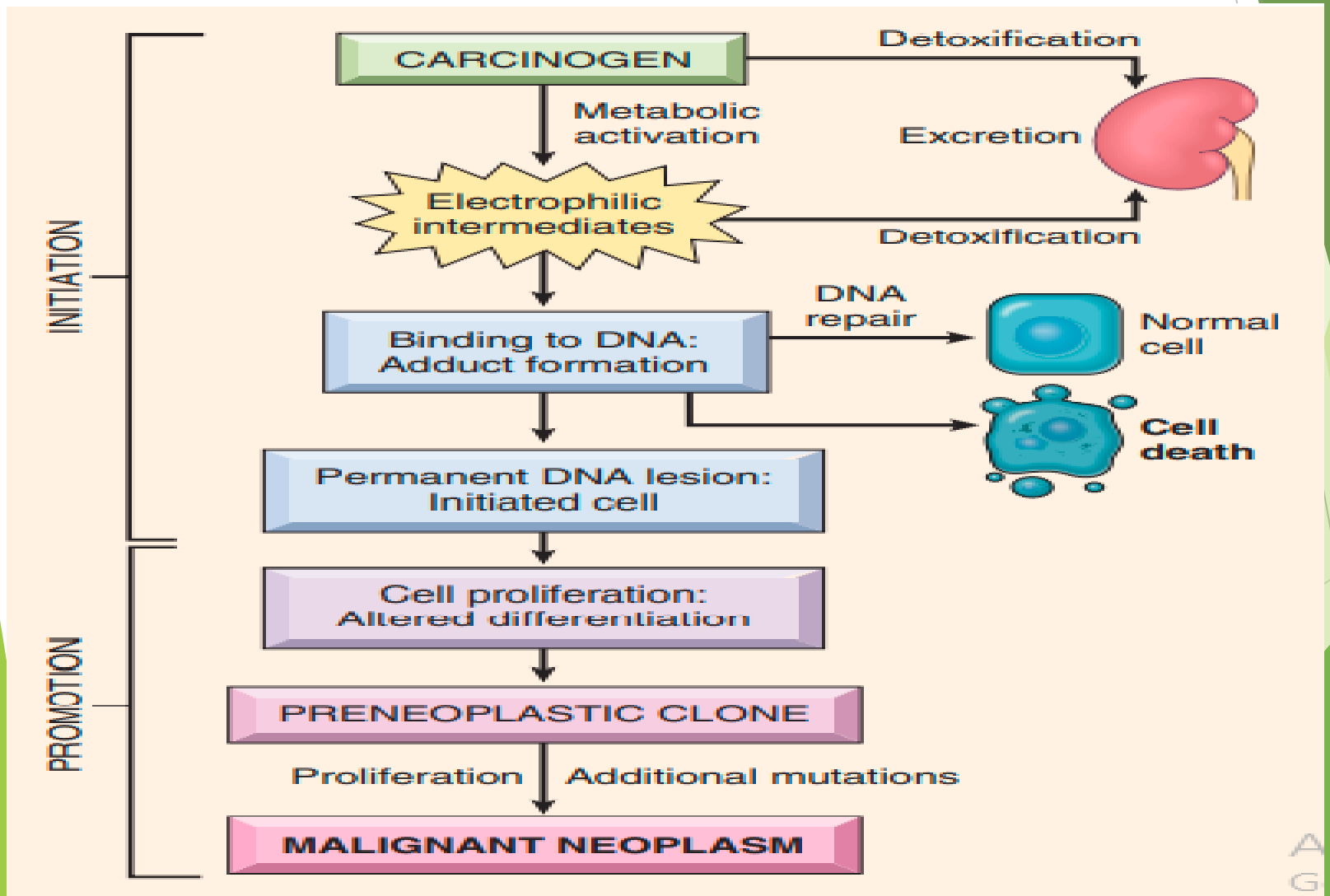
- Genes commonly affected are RAS & TP53

  May be very specific ’Signature Mutation ’, e.g. Aflatoxin-induced TP53 mutation.

- Some strong chemicals act as Initiator & Promoter e.g. polycyclic hydrocarbon.

Mechanisms of Action of Chemical Carcinogens

- Most chemical carcinogens are mutagenic.



2. Radiation Carcinogenesis

- Radiation, whatever its source (UV rays of sunlight, radiographs, nuclear fission, radionuclides), is an established carcinogen.

- Biologically, doublestranded DNA breaks seem to be the most important form of DNA damage caused by radiation

2. Radiation Carcinogenesis

- **U-V light:**
- **- Effect depends on intensity of exposure & quantity of melanin**
- **- Production of pyrimidine dimers in DNA overwhelms nucleotide excision repair pathway → Failed repair → Skin Cancer, including:**
- ***Squamous Cell CA , *Basal Cell CA &**
- ***Melanoma**

2. Radiation Carcinogenesis

- A follow-up study of survivors of Hiroshima and Nagasaki disclosed a markedly increased incidence of leukemia, thyroid, breast, colon, and lung carcinomas.

- Therapeutic irradiation of the head and neck can give rise to papillary thyroid cancers years later.

3. Viral and Microbial Oncogenesis

- **Many DNA and RNA viruses have proved to be oncogenic and its include:**

- **A. Oncogenic RNA Viruses.**
- **B. Oncogenic DNA Viruses.**
- **c. Helicobacter pylori.**

A. Oncogenic RNA Viruses:

- Human T-cell leukemia virus type 1 (HTLV-1).
- It cause adult T-cell leukemia/lymphoma (ATLL) .
- HTLV-1 has tropism for CD4+ T cells, and hence this subset of T cells is the major target for neoplastic transformation.
- Leukemia develops in only 3% to 5% of the infected individuals, typically after a long latent period of 40 to 60 years

B. Oncogenic DNA Viruses

- Five DNA viruses are strongly associated with human cancer:
- HPV.
- Epstein-Barr virus (EBV).
- Kaposi sarcoma herpes virus [HHV-8]).
- Polyoma virus called Merkel cell virus.
- Hepatitis B virus (HBV)

1. Human Papilloma virus(HPV)

- They are subdivided into:
- low-risk HPVs (type 6,11):
  - cause genital warts have, it low malignant potential

- high-risk HPVs (types 16 and 18):
  - cause squamous cell carcinoma of the cervix and anogenital region and oropharyngeal cancers.

2. Epstein-Barr Virus

- EBV, a member of the herpesvirus family, was the first virus linked to a human tumor, Burkitt lymphoma.

- EBV is implicated in the pathogenesis of :
  - lymphomas in immunosuppressed patients.
  - Hodgkin lymphoma.
  - uncommon T-cell and NK-cell tumors
  - nasopharyngeal carcinoma
  - a subset of gastric carcinoma.

pathogenesis

- EBV uses the complement receptor CD21
- to attach to and infect B cells
- That leads to polyclonal B cell proliferation
- generation of immortal B lymphoblastoid cell lines

3. Hepatitis B and Hepatitis C Viruses

- **The epidemiologic evidence linking chronic HBV and hepatitis C virus (HCV) infection with hepatocellular carcinoma is strong .**

- **The dominant effect seems to be immunologically mediated chronic inflammation with hepatocyte death, leading to regeneration and genomic damage.**

4. Helicobacter pylori

- H. pylori infection is implicated in the genesis of both gastric adenocarcinomas and gastric lymphomas (MALT lymphoma).
- The scenario for the development of gastric adenocarcinoma is involves increased epithelial cell proliferation on a background of chronic inflammation.

H.Pylori

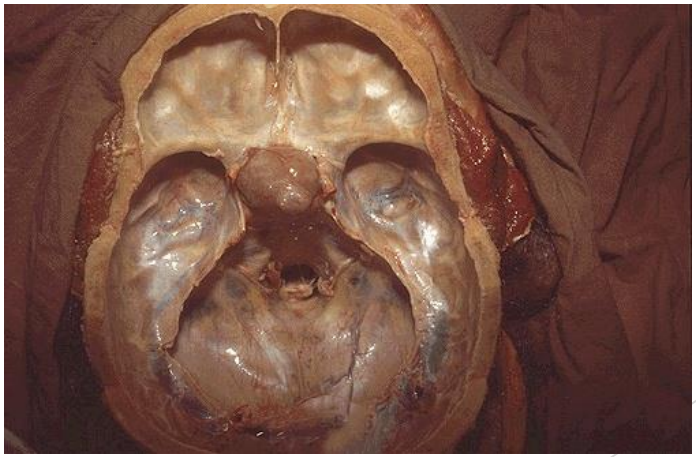
- Although the immune system generally is thought to be protective, recent work has demonstrated that in the setting of unresolved chronic inflammation, as occurs in viral hepatitis or chronic gastritis caused by H. pylori , the immune response may become maladaptive, promoting tumorigenesis.

CLINICAL ASPECTS OF NEOPLASIA

- The importance of neoplasms ultimately lies in their effects on patients.
- 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

- 1. location:
- 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.



- 2. Signs and symptoms related to hormone production , e.g;
- Neoplasm arising in the beta cells of the pancreatic islets of Langerhans can produce hyperinsulinism.

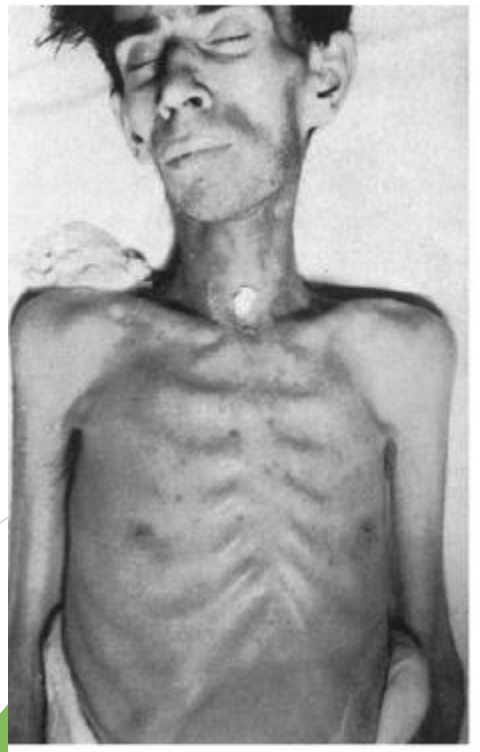
- 3. A tumor may ulcerate through a surface, with consequent bleeding or secondary infection.

Cancer Cachexia

- Many cancer patients suffer progressive loss of body fat and lean body mass, accompanied by profound weakness, anorexia, and anemia—a condition referred to as **cachexia**.

- current evidence indicates that cachexia results from the action of soluble factors such as cytokines produced by the tumor and the host, rather than reduced food intake

- In patients with cancer, calorie expenditure remains high, and basal metabolic rate is increased, despite reduced food intake.
- It is suspected that TNF produced by macrophages mediate cachexia



Paraneoplastic Syndromes

- Symptom complexes that occur in patients with cancer and that cannot be readily explained by local or distant spread of the tumor or by the elaboration of hormones indigenous to the tissue of origin of the tumor.

- The neoplasms most often associated with Paraneoplastic Syndromes are:
  - lung .
  - breast cancers .
  - hematologic malignancies

- The most common paraneoplastic syndromes are :
- Hypercalcemia.
- Cushing syndrome.
- Nonbacterial thrombotic endocarditis.

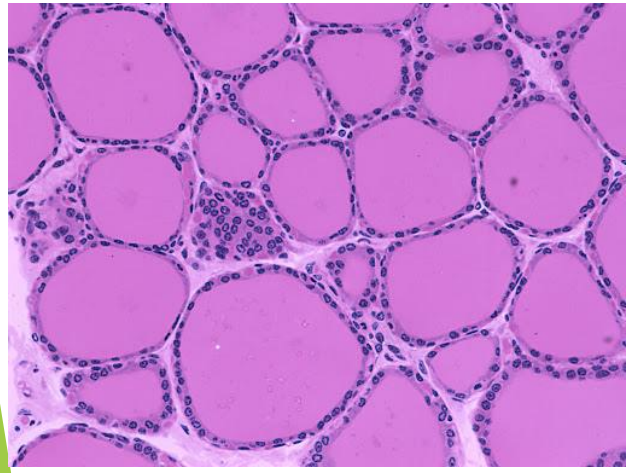
Table 6.6 Paraneoplastic Syndromes

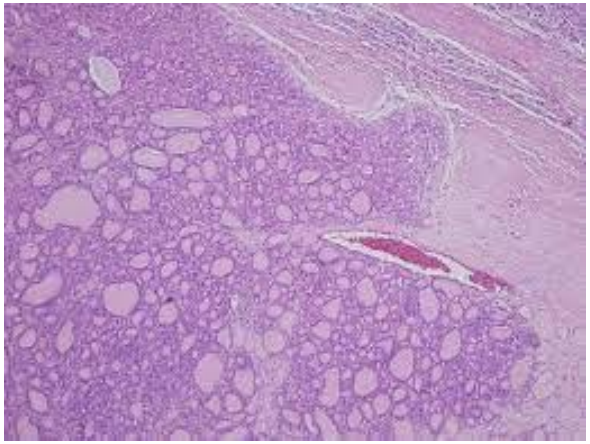
Clinical Syndrome	Major Forms of Neoplasia	Causal Mechanism(s)/Agent(s)
Endocrinopathies		
Cushing syndrome	Small cell carcinoma of lung Pancreatic carcinoma Neural tumors	ACTH or ACTH-like substance
Syndrome of inappropriate anti-diuretic hormone secretion	Small cell carcinoma of lung; intracranial neoplasms	Anti-diuretic hormone or atrial natriuretic hormones
Hypercalcemia	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	Insulin or insulin-like substance
Polycythemia	Renal carcinoma Cerebellar hemangioma Hepatocellular carcinoma	Erythropoietin

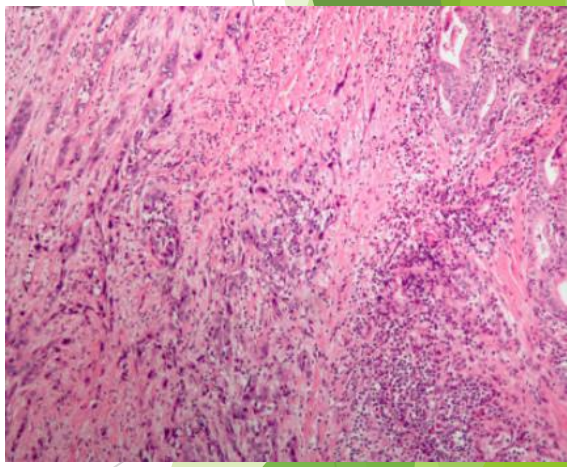
Grading and Staging of Cancer

- Systems have been developed to express, the level of differentiation, or grade, and extent of spread of a cancer within the patient, or stage, as parameters of the clinical gravity of the disease and clinical aggressiveness .

- Grading of a cancer is based on the degree of differentiation of the tumor cells, and generally range from two categories (low grade and high grade).







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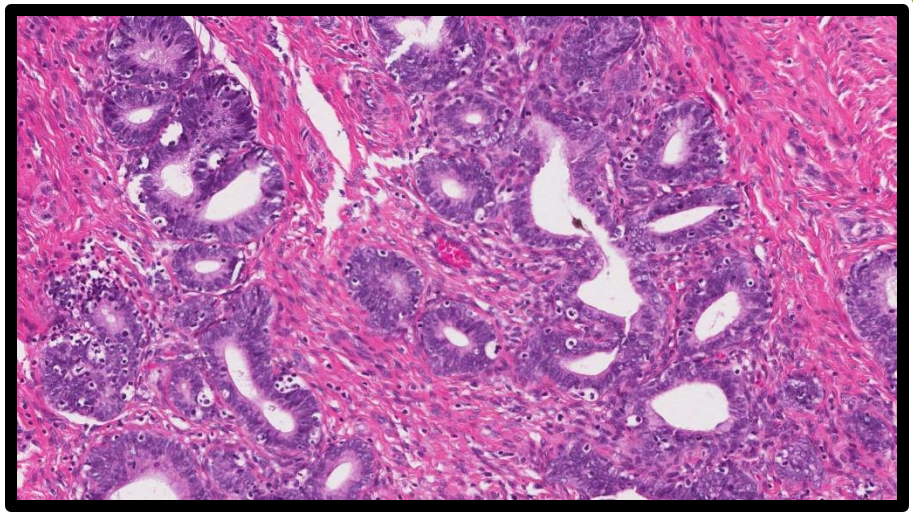
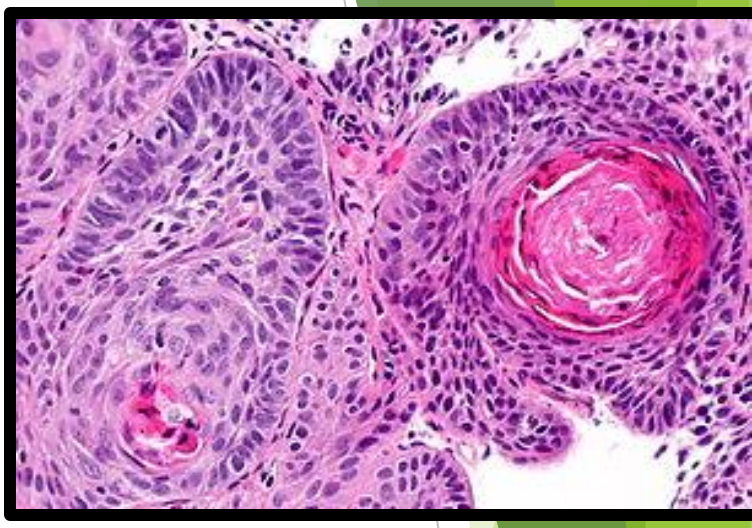
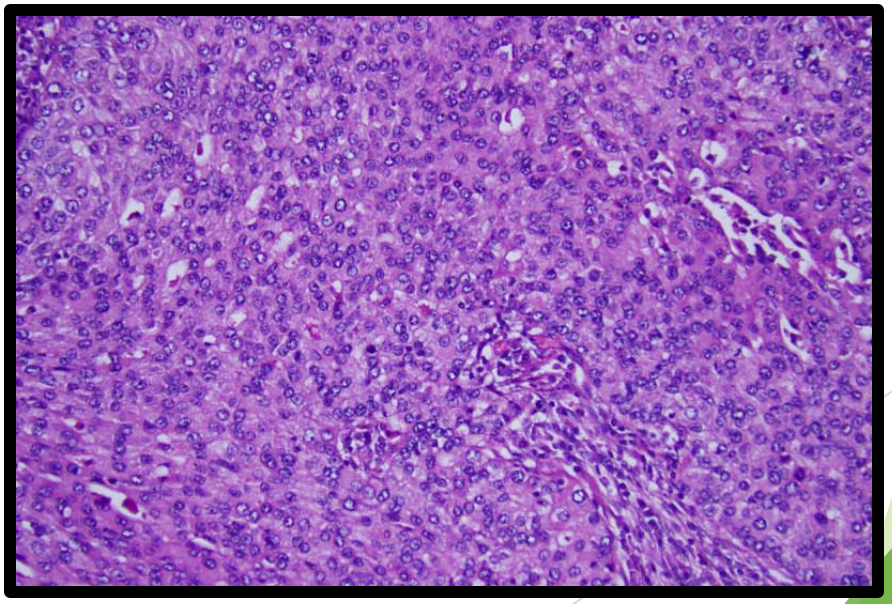
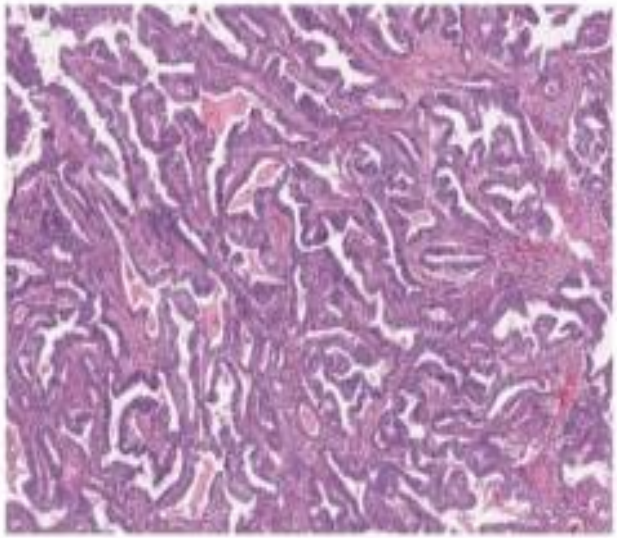
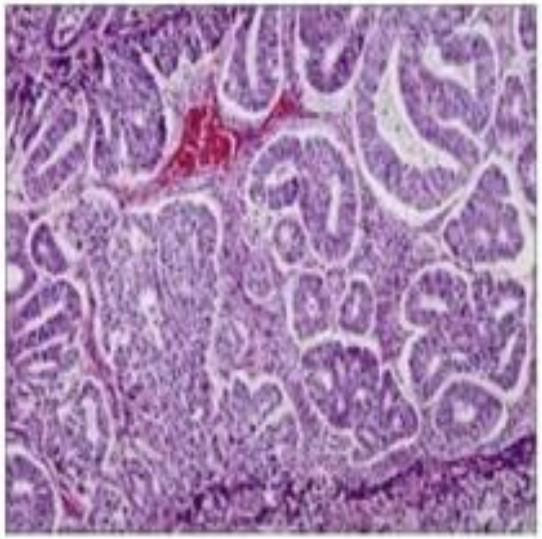
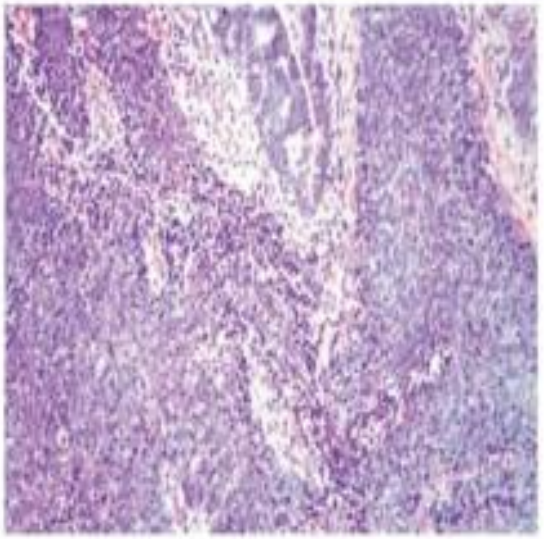




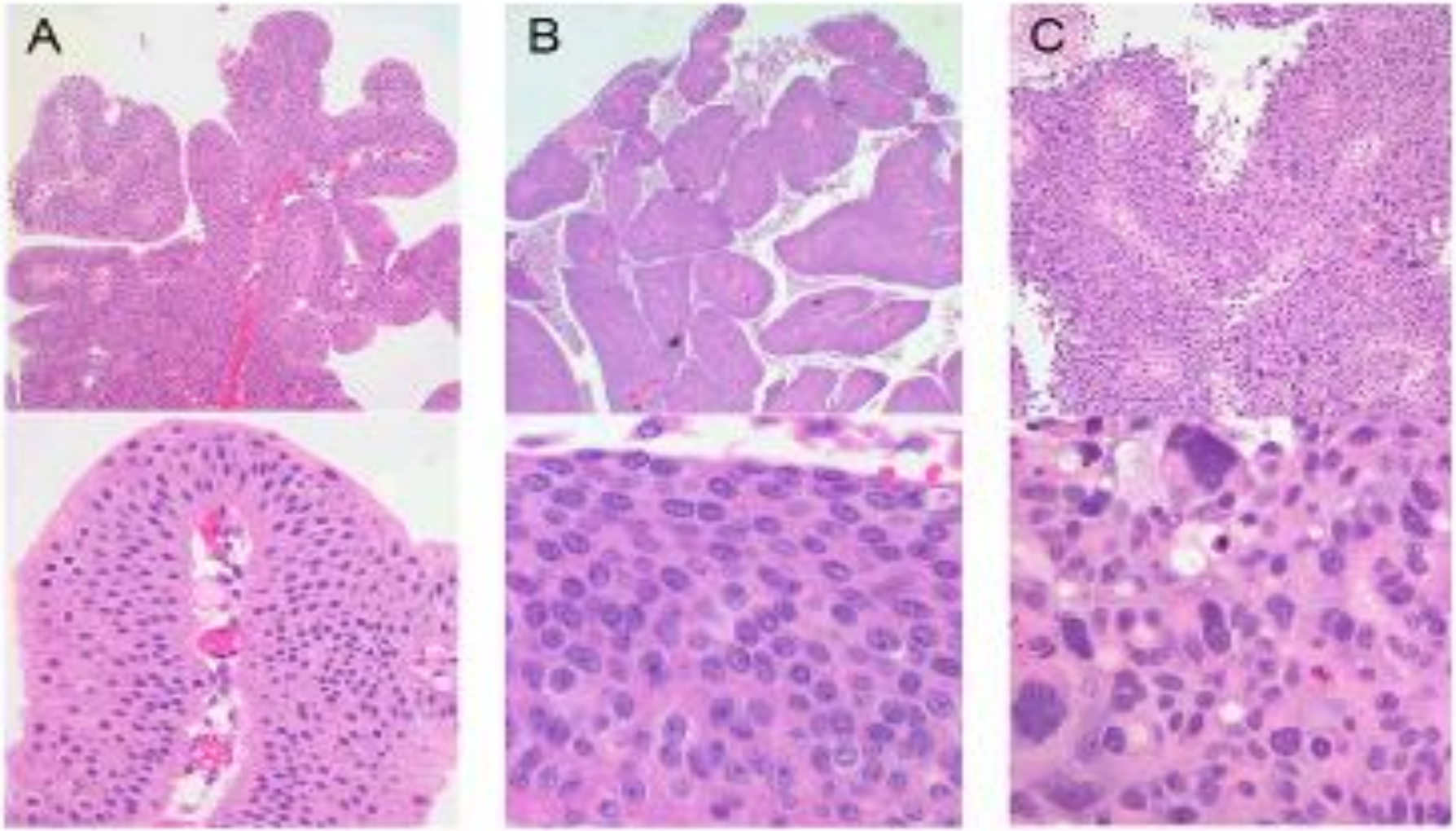


Endometrial CA grade

Well differentiated / **grade 1**	Moderately differentiated / **grade 2**	Poorly differentiated/ **grade 3**
		
Well formed glands	Well formed glands with solid sheets (<50%)	glands with solid sheets (>50%)

@VijayPatho

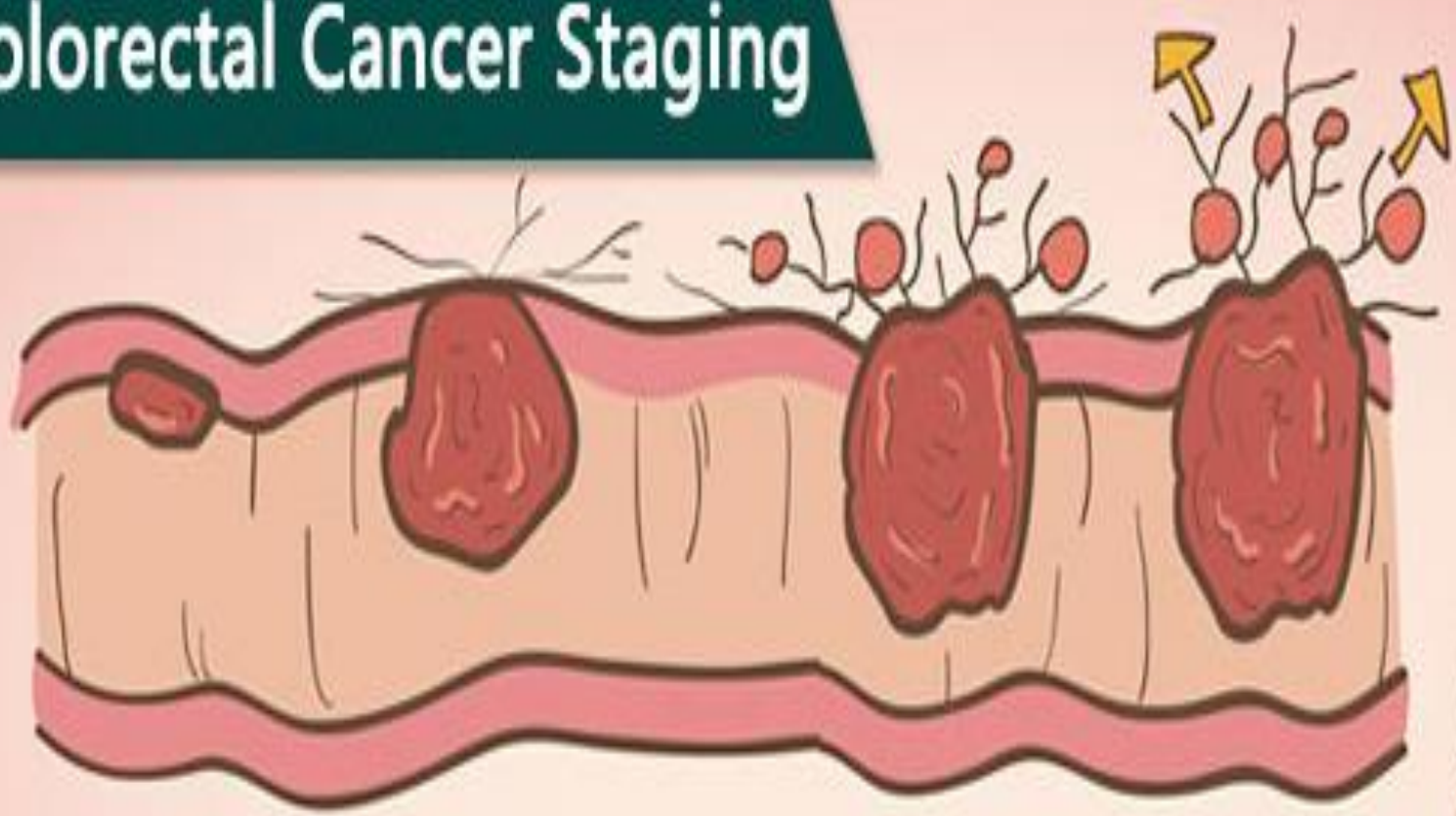
Urothelial carcinoma grade



- The major staging system currently in use is the American Joint Committee on Cancer Staging, TNM system
- The staging of solid cancers is based on:
- the size of the primary lesion (T for primary tumor)
- its extent of spread to regional lymph nodes(N for regional lymph node).
- presence or absence of blood borne metastases (M for metastases).

Assignment of TNM Scores	Description of Score
T stage, tumor size and invasiveness	
T1	≤ 1.0 cm
T2	> 1–4.0 cm
T3	> 4.0 cm, limited to thyroid
T4	Any size tumor with extrathyroidal invasion
N stage, lymph node metastasis	
N0	None
N1	Present
M stage, distant metastasis	
M0	None
M1	Present

Colorectal Cancer Staging



Stage I

the cancer has invaded the submucosa.

Stage II

invaded nearby tissues or organs.

Stage III

spread to nearby lymph nodes

Stage IV

spread to distant organs.

CANCER DIAGNOSIS

GENERAL OUTLINE:

- **History & clinical examination**

  - Symptoms: What the health care worker learns from talking to the patient.
  - Signs: Physical examination of patient

    e.g. A mass may be palpable or visible, fever…etc.

- **Radiographic techniques**
  - X ray
  - CT scan
  - MRI
  - Ultrasound
  - Nuclear Medicine (Radioisotope scan)
- **Laboratory tests:**
  - General such as blood picture, stool for occult blood, blood sugar…….etc
  - Special techniques

Morphological Methods:

A- Cytological Methods:

- Study of cells:
  - Smear.
  - FNA, Brush, Fluid tapping…etc

  Papanicolaou stain (Pap) often used.

  False(+), False (-)

- Advise biopsy, even sometimes if (+)

Normal Pap smear of Cervix

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Normal Pap smear of Cervix

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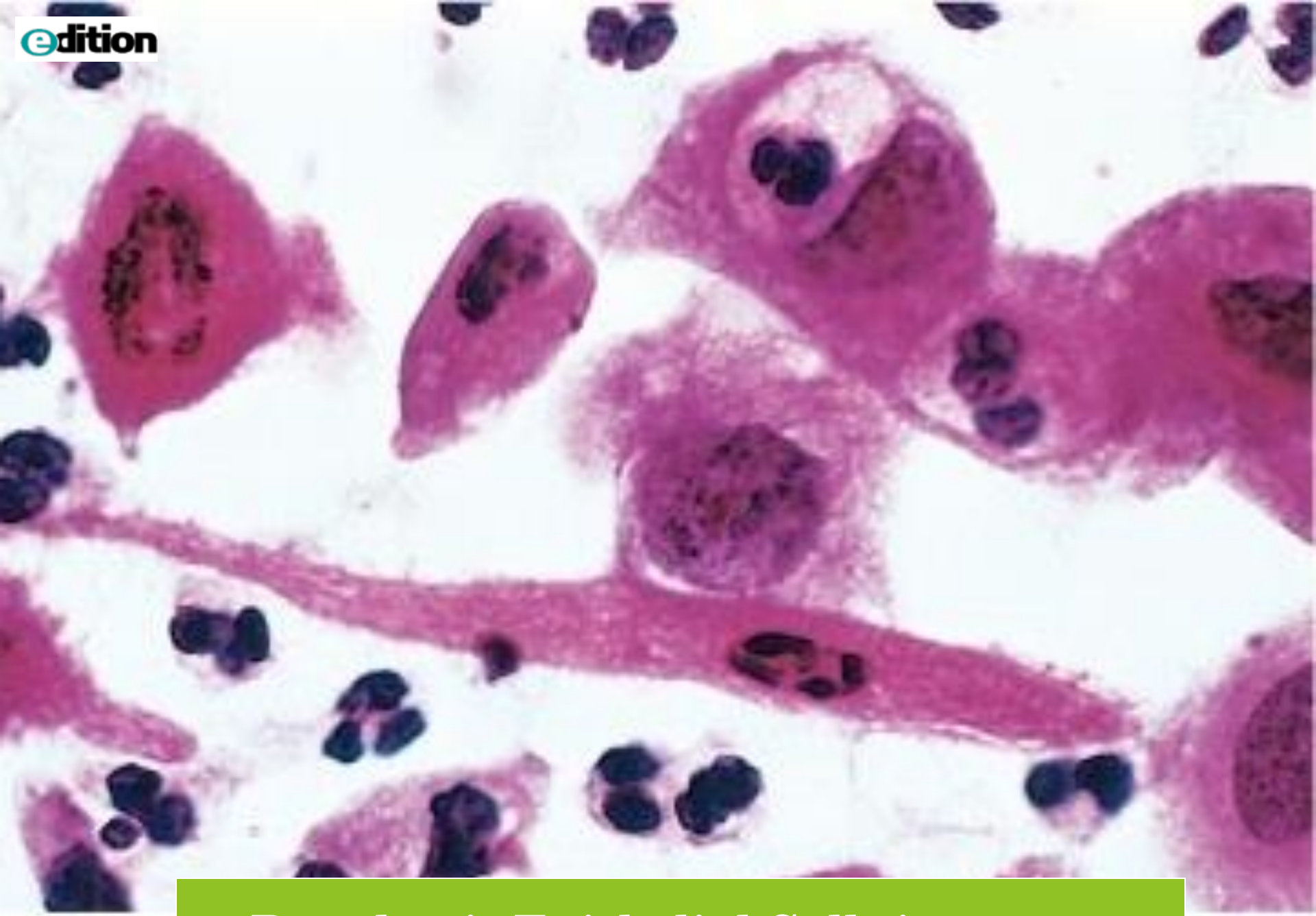
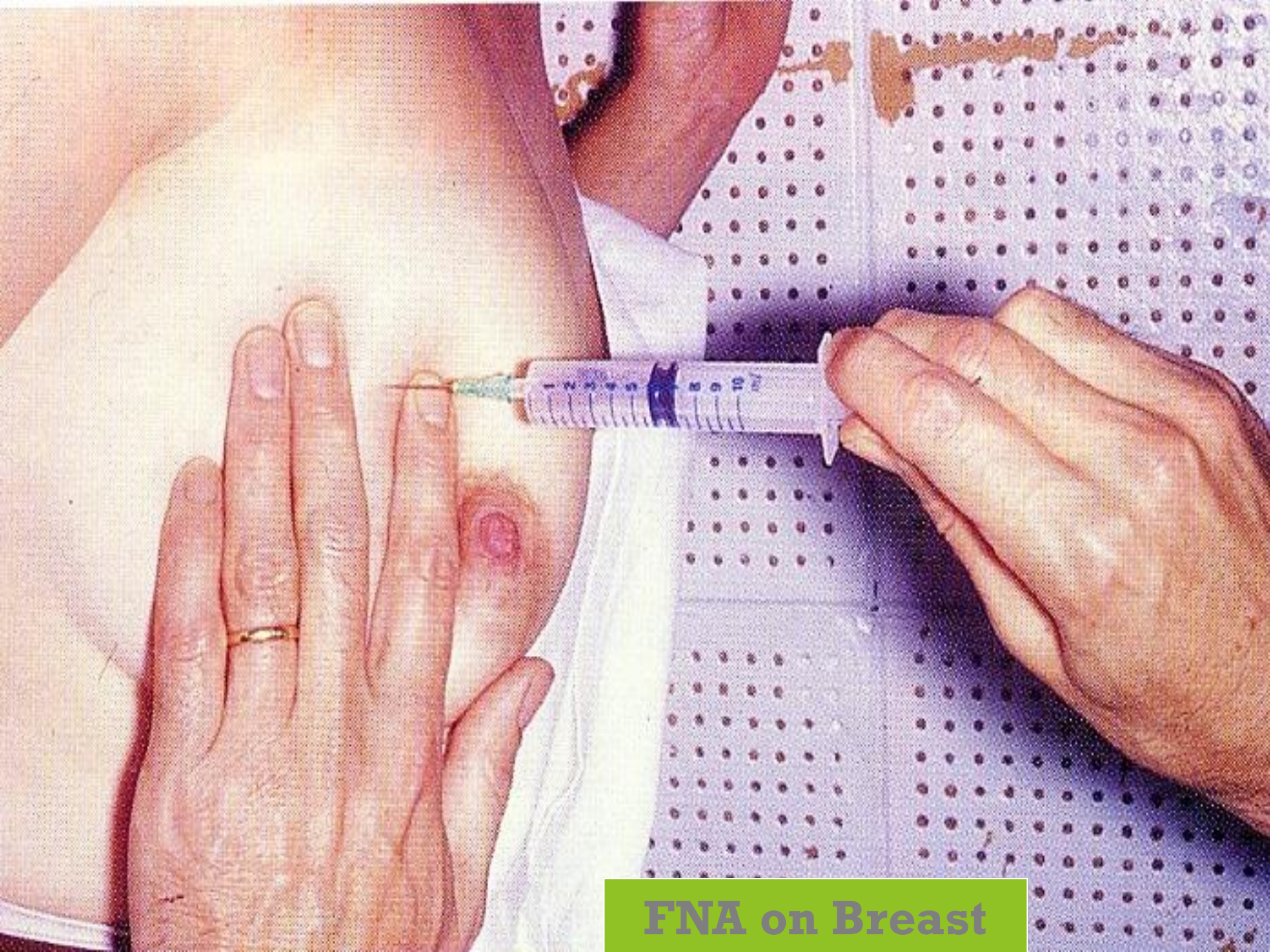


Dysplastic Epithelial Cells in smear



FNA on Breast

B- HISTOLOGICAL METHODS:

- Biopsy of tissue:

  Needle & core biopsy, Endoscopic Biopsy, or open surgical biopsy

- Frozen Section (Rapid technique)

- Paraffin Section (36-48 hrs. or longer)

- H&E, Special histochemical stains e.g.

  (PAS, CONGO RED, PERL's iron stains) or by IMMUNOHISTOCHEMICAL Methods

C- Immunohistochemistry:

Staining by use of monoclonal AB directed against various components in cell: May help in **diagnosis of undifferentiated cancers** or help in **identifying source of a metastatic tumor.**

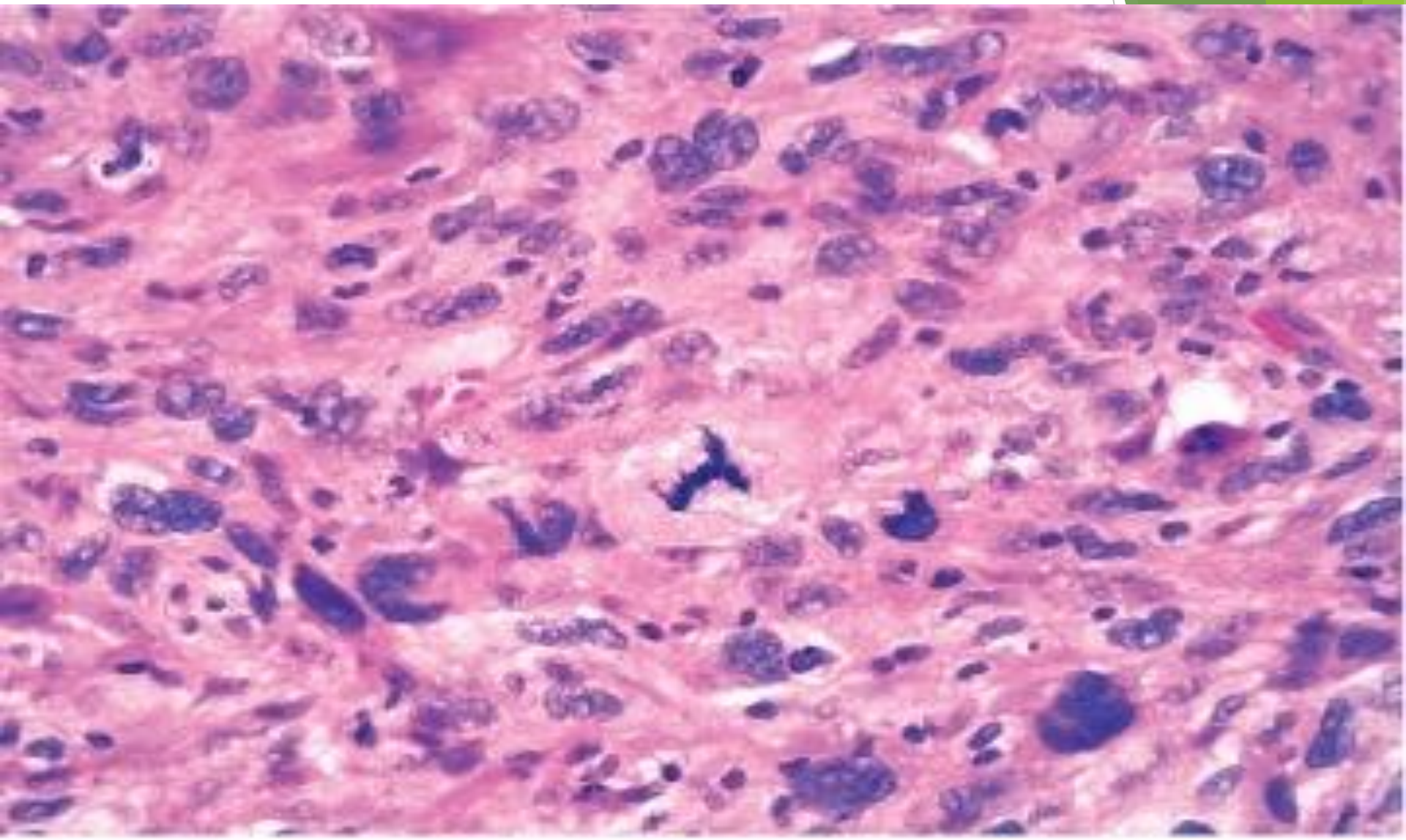
- Cytokeratin→ Carcinoma
  - Different groups of cytokeratins indicate origin of the carcinoma e.g. CK 7, CK20….etc

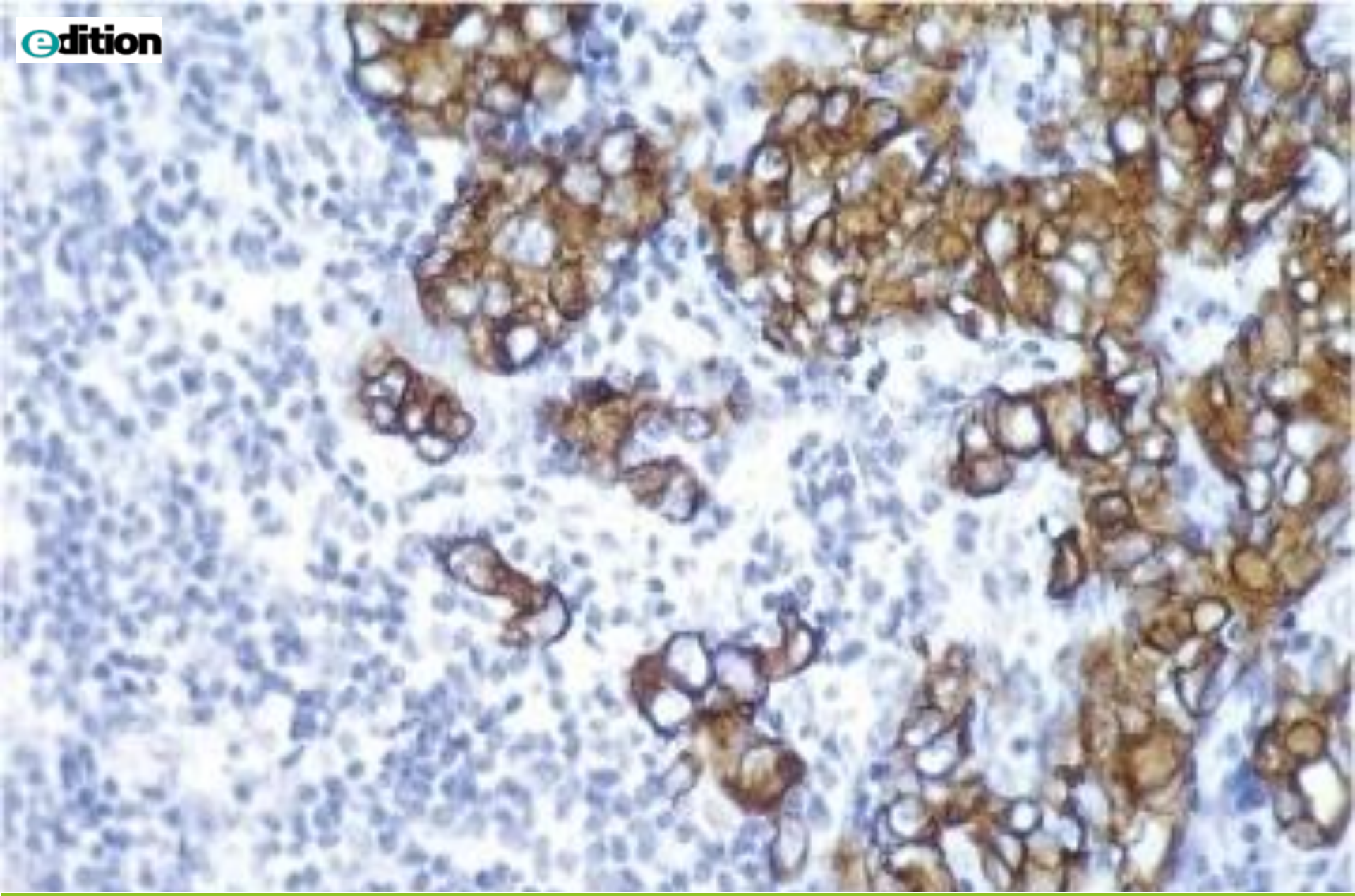
Leukocyte Common Antigen → Lymphoma

S 100→ Neural tissue, melanocytic lesions

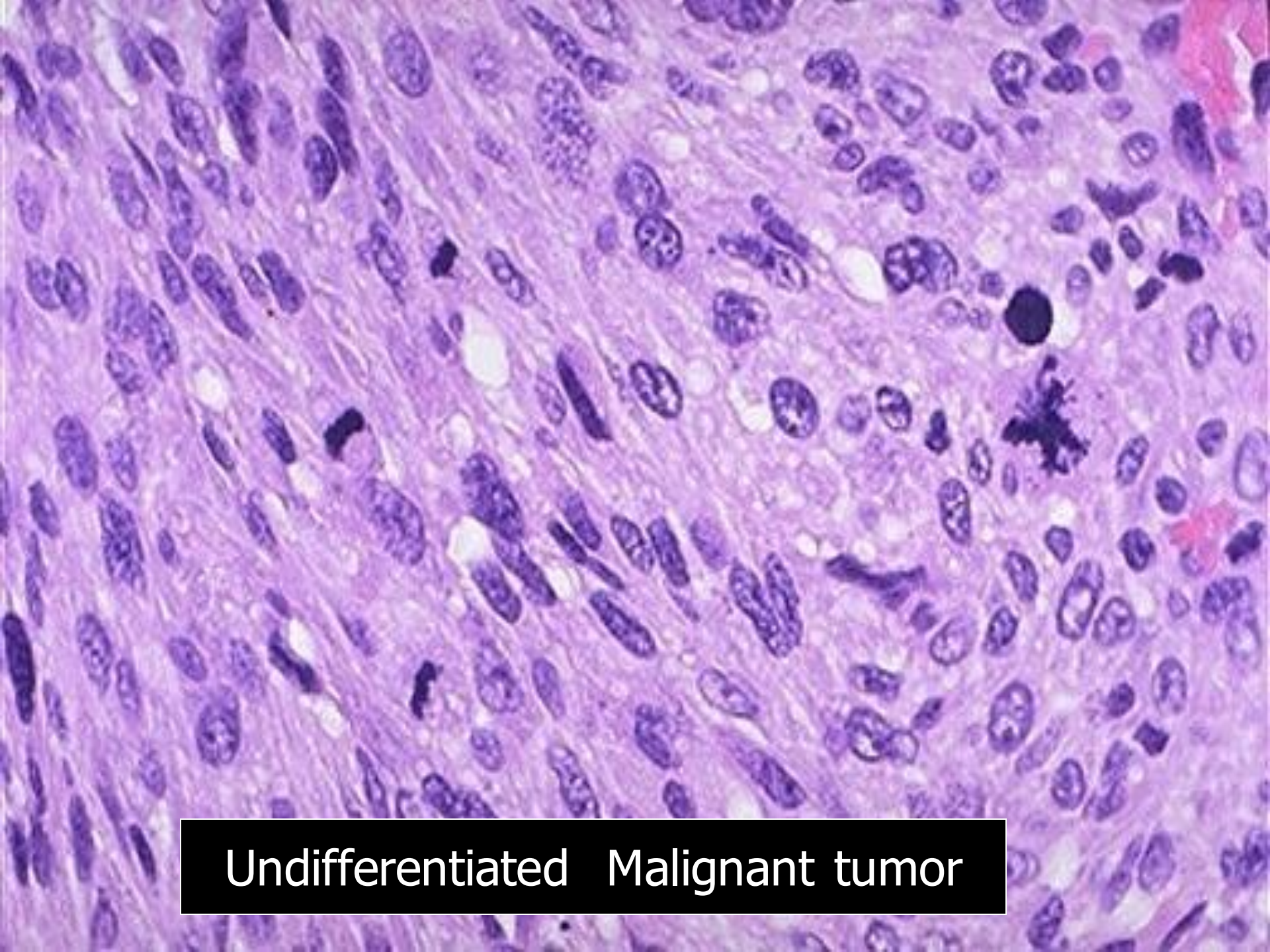
Vimentin, Desmin → Sarcoma

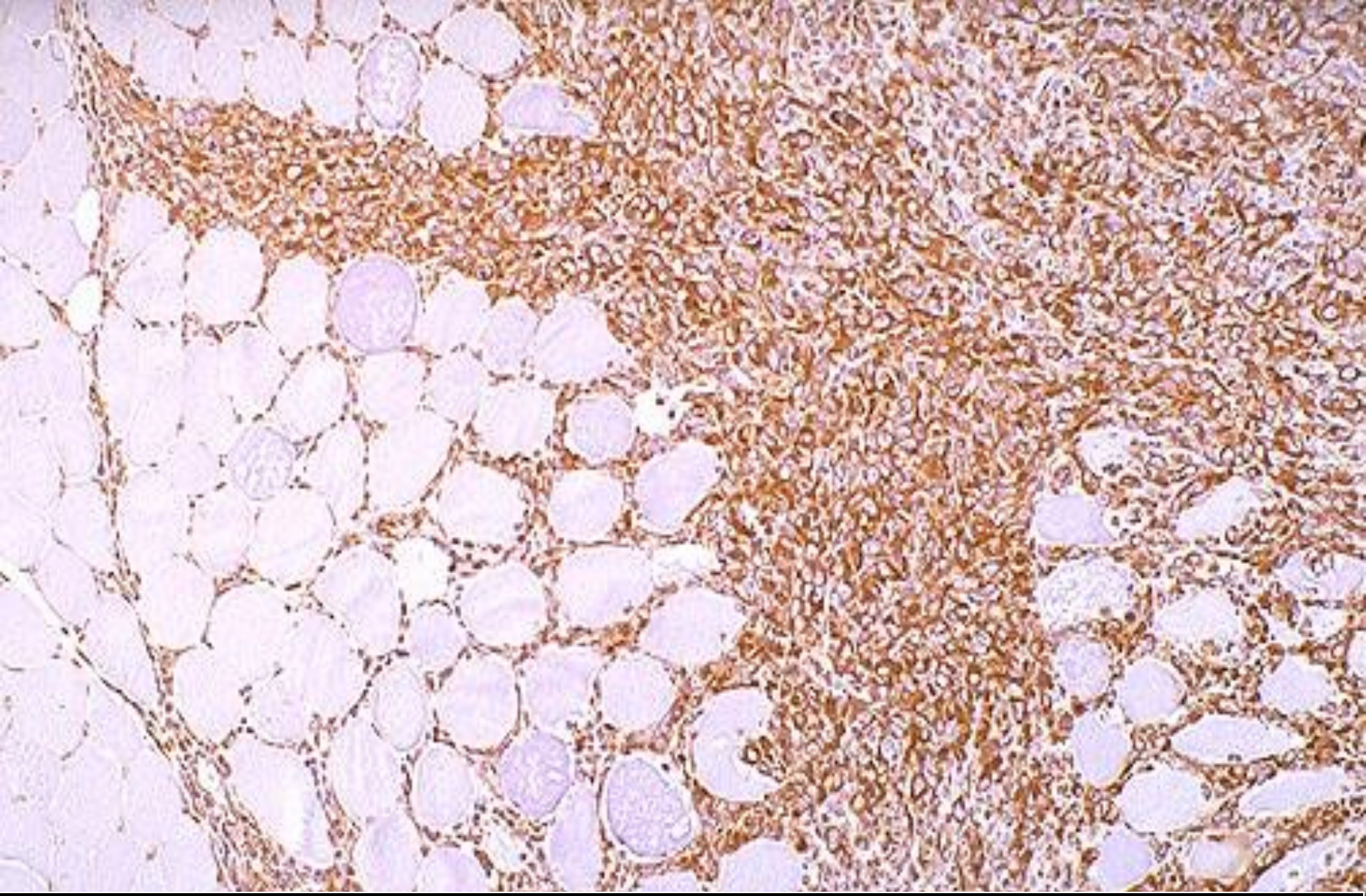
UNDIFFERENTIATED TUMOR





Cytokeratin for epithelial cells indicating Carcinoma


Undifferentiated Malignant tumor



Vimentin Positive for connective tissue indicating Sarcoma

D- ELECTRON MICROSCOPY:

- For recognition of intracellular structures e.g. desmosomes, or neurosecretory granules….etc.
- Not considered a practical tool for diagnosis.

Laboratory Diagnosis of Cancer

- **Tumor Markers:**
- Biochemical assays for tumor-associated enzymes, hormones, and other tumor markers in the blood cannot be utilized for definitive diagnosis of cancer; however, they are used as:
- screening tests.
- monitoring the response to therapy
- detecting disease recurrence.

examples

- **PSA**, used to screen for prostatic adenocarcinoma.
- **CEA** which is elaborated by carcinomas of the colon, pancreas, stomach, and breast.
- **AFP** which is produced by hepatocellular carcinomas.

Molecular Diagnosis

- An increasing number of molecular techniques are being used for the diagnosis of tumors and for predicting their behavior.

- 1. Diagnosis of malignancy:
- E.g PCR-based detection of BCR-ABL transcripts can confirm the diagnosis of chronic myeloid leukemia .

Molecular Diagnosis

- 2. Prognosis and behavior:
- Certain genetic alterations are associated with a poor prognosis, e.g HER2 and NMYC, expression breast cancers and neuroblastomas, respectively.

- 3. Diagnosis of hereditary predisposition to cancer, e.g BRCA1

EARLY DIAGNOSIS OF CANCER:

This is very important as many cancers are curable if they are diagnosed early.

- Specific symptoms should be followed up

e.g. Abnormal bleeding

Change of voice

Change in a nevus

Abnormal lump in breast

An ulcer that does not heal……etc.

- Specific procedures:

  - Self examination of the breast
  - Mammography.
  - Serial Pap smears for the cervix
  - Serial sputum cytology in smokers
  - Serial urine cytology in some cases,
    e.g. bilharziasis, workers in rubber
- Screening for genetic mutations in familial cancers.

Good Luck