

# Neoplasia

- **Cell Biology of Cancer**
- **Cancer Genetics**
- **Principles of Cancer Treatment**
- **Tumors of the Liver And Biliary Tract**
- **Bladder and Renal Cell Carcinomas**

# Cell Biology of Cancer

- **Characteristic features**
  1. Autonomous cell growth (neoplasm)
  2. The capacity to invade tissues and metastasize (malignant neoplasm)
- Cancer is a synonym for malignant neoplasm

# Cell Biology of Cancer

## **Metastasis**

- Metastasis is the spread of neoplastic cells from the primary tumor site to distant sites, where new tumors form.
- Two primary pathways of spread
  - Hematogenous
  - Lymphatic

# Cell Biology of Cancer

- **Characteristic features**
  - The >200 discrete cell types in the body are not equally susceptible to developing cancer.
  - Resistant cell types to cancer
    - Cardiac myocytes
    - Sensory receptor cells for light and sound
  - Susceptible cell types to cancer
    - Lung
    - Gastrointestinal epithelial cells

# Neoplasia

- Cancer Is A Genetic Disease
  - Cancer arises because of alterations in DNA (random replication errors, exposure to carcinogens (e.g., radiation), or faulty DNA repair processes)
- Nearly all cancers originate from a single cell
  - multiple cumulative events are required

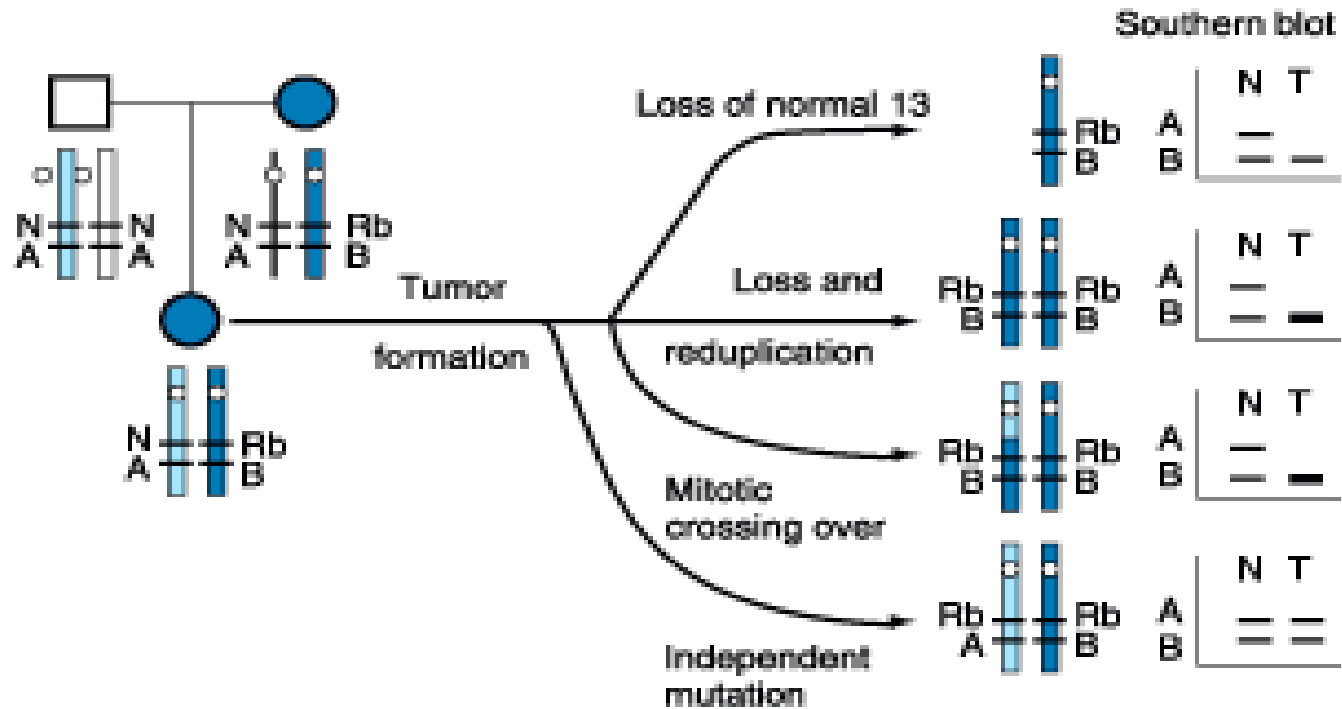
# Neoplasia

- **Boveri hypothesis (1914)**
  - Overactivation of a gene that promotes cell division (**protooncogenes**)
  - Loss of function of a gene that normally restrains growth (**tumor suppressors**)
- DNA repair genes

# Retinoblastoma gene (*RB*)

- The retinoblastoma gene (*RB*) is a paradigm of tumor suppressor genes
- Germline mutation occurs in one allele of the *RB* gene on chromosome 13
- Analysis of the DNA from the tumors invariably shows that the wild-type allele has also been lost by one of several possible mechanisms

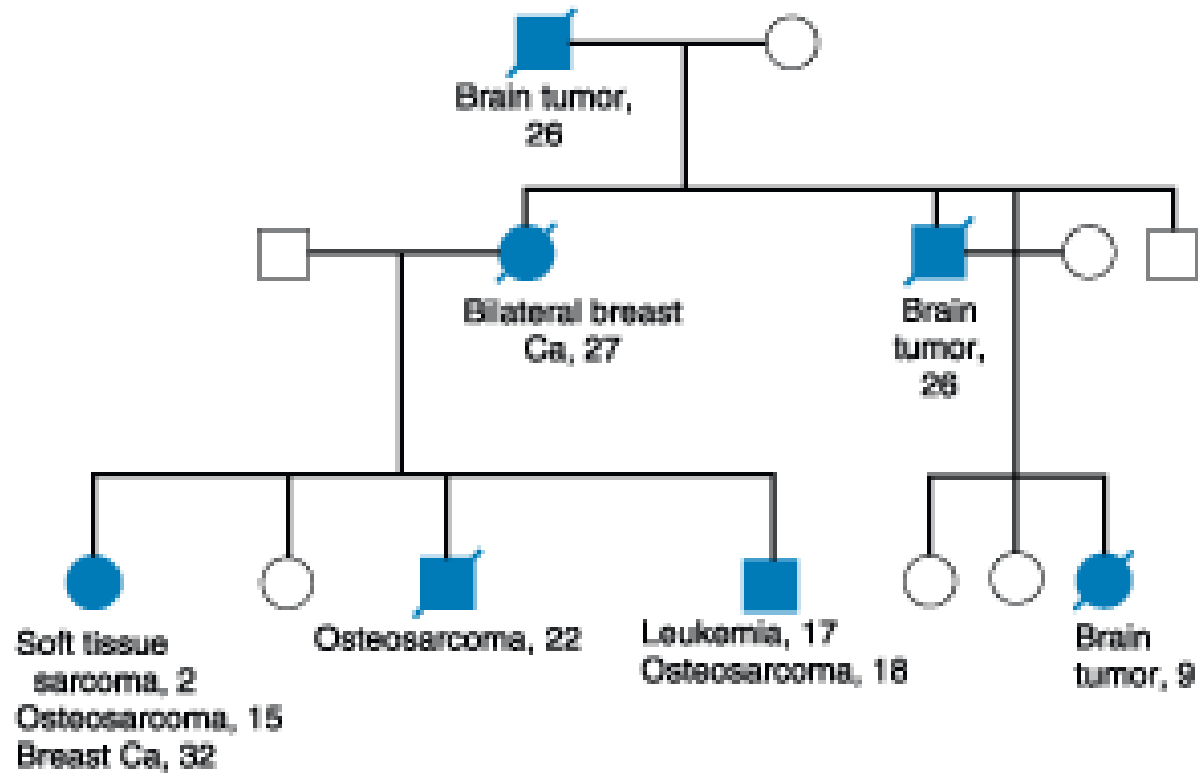
# Retinoblastoma gene (*RB*)



## p53 gene

- Another tumor suppressor gene is the p53 gene on chromosome 17p
- Mutations in p53 are found in nearly half of human tumors
- Germline mutations in p53 have dramatic consequences

# p53 gene



## More Complex Inherited Forms of Cancer

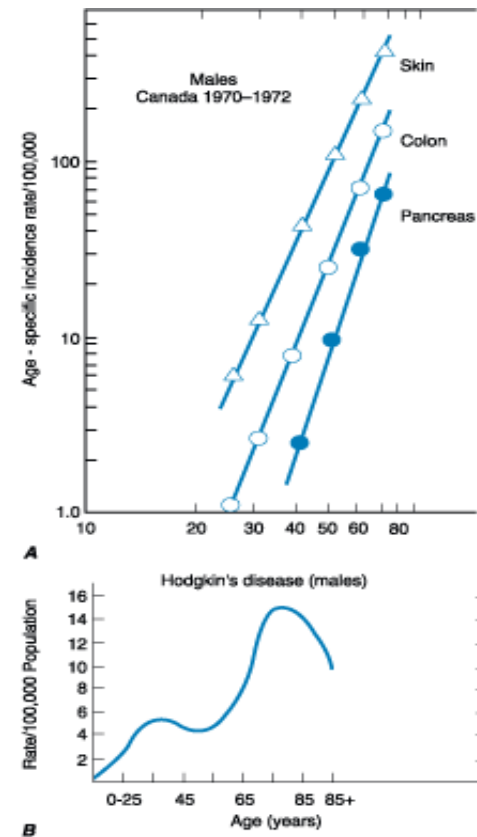
- Most forms of cancer do not follow simple Mendelian patterns of inheritance.
- In many instances (e.g., lung cancer), a strong environmental contribution is involved.
- Usually mutations must occur in several genes to give rise to neoplasia.

# More Complex Inherited Forms of Cancer

- A small subset (5-10%) of breast and ovarian cancers might be caused by susceptibility genes, **BRCA1** and **BRCA2**.
- **BRCA1** is capable producing a high risk (up to 85% lifelong) of breast cancer and also of ovarian cancer (50% lifelong risk).
- **BRCA2**, also confer a high risk of breast cancer (and a somewhat lower risk of ovarian cancer .
- Roughly 1 in 500 women carries a **BRCA1** mutation.
- The frequency of **BRCA2** mutations is about 1 in 1000.

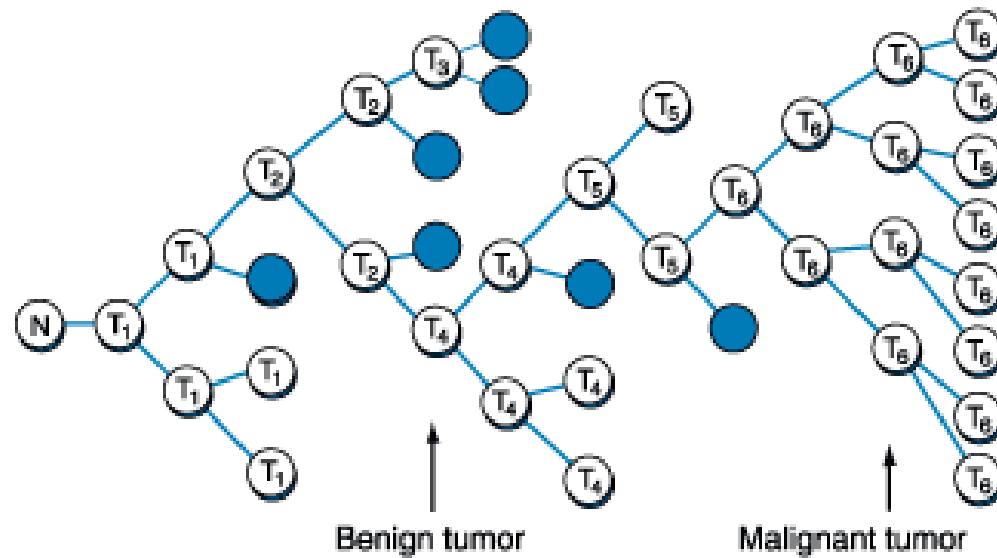
# Acquired Mutations in Cancer

- The overall incidence of cancer increases by age for most malignancies
- For some tumors, the shape of the age-incidence curve suggests heterogeneity in molecular mechanisms

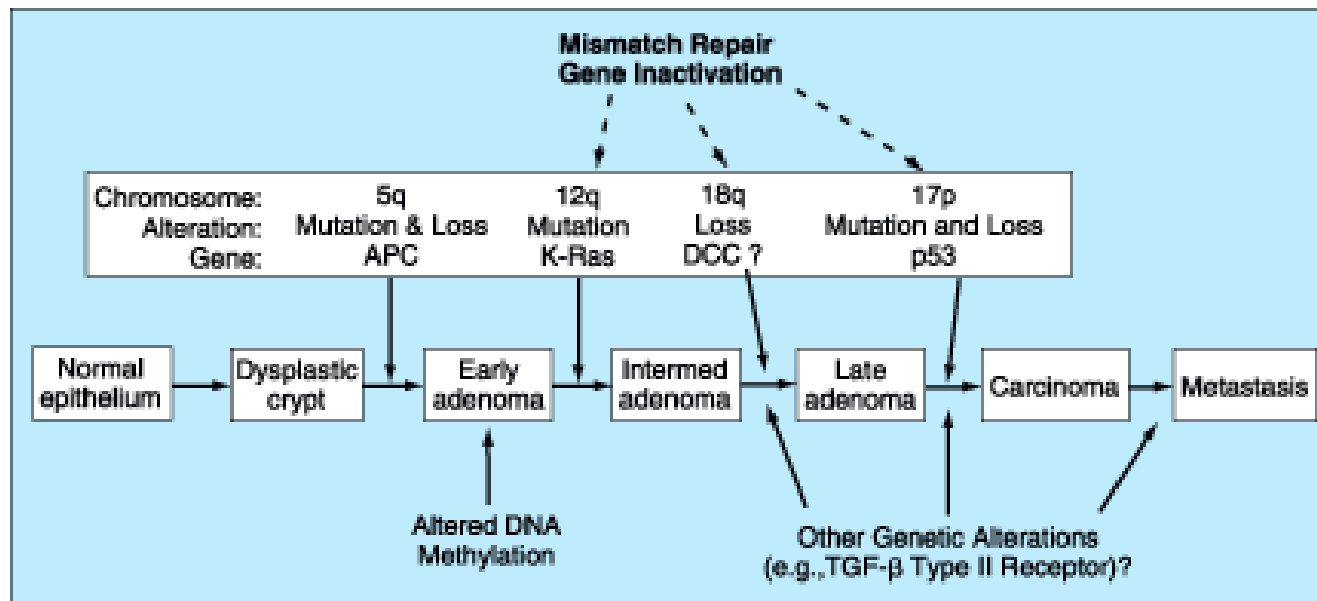


# Acquired Mutations in Cancer

- From 5 to 10 accumulated mutations are thought to be necessary for a cell to move from the normal to the fully malignant phenotype.



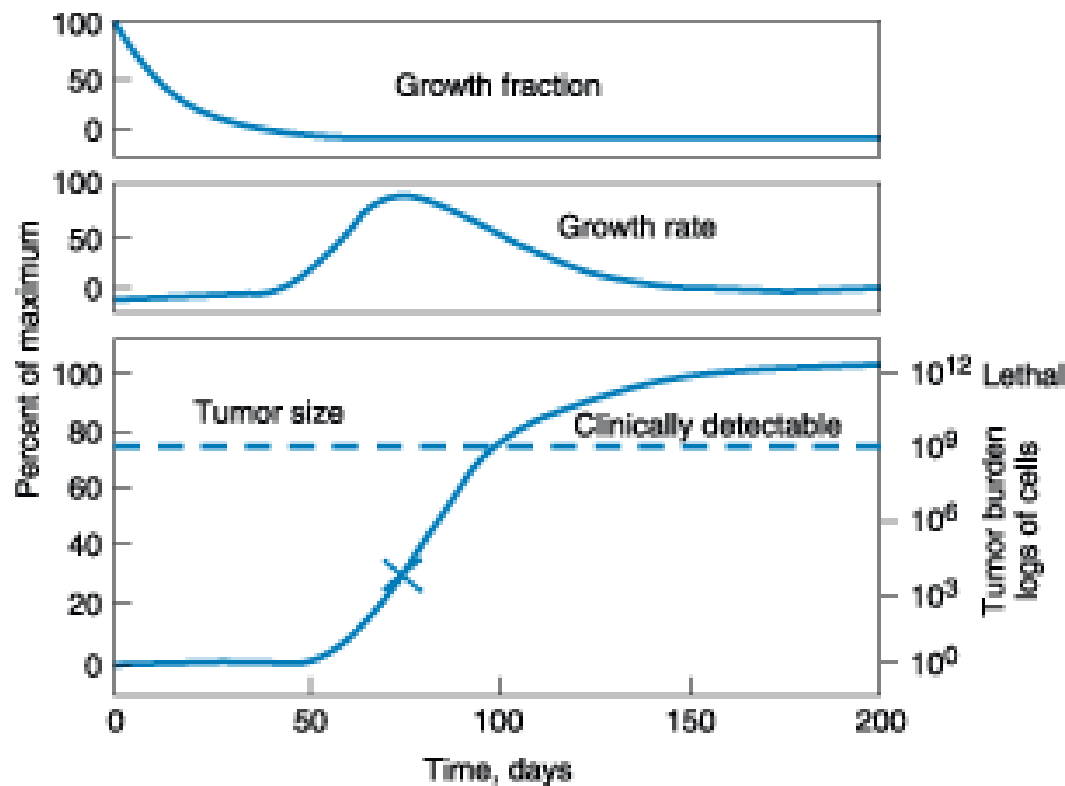
# Acquired Mutations in Cancer



- Progressive somatic mutational steps in the development of colon carcinoma. The accumulation of alterations in a number of different genes results in the progression from normal epithelium through early adenoma to full blown carcinoma.

# Principles of Cancer Treatment

- Gompertzian growth curve



# Growth fraction

- Percent of proliferating cells within a given system
- The growth fraction of a neoplasm starts at 100% with the first transformed cell and declines exponentially over time
- By the time of diagnosis ( $1$  to  $5 \times 10^9$  cells) the growth fraction is usually 1 to 4%.

# Clinical Disease and Tumor Mass

## Number of Cancer Cells

$10^{13} = 10 \text{ kg}$

$10^{12} = 1 \text{ kg}$

$10^{11} = 100 \text{ gm}$

$10^{10} = 10 \text{ gm}$

$10^9 = 1 \text{ gm}$

$10^8 = 100 \text{ mg}$

$10^6 = 1 \text{ mg}$

$10^3 = 1 \text{ mcg}$

$10^0 = 1 \text{ ng}$

## Clinical Event

Death

Severe Metastatic Disease

Advanced Metastases

Regional Spread of Cancer

Clinical Detection (Symptoms)

Subclinical Disease

Subclinical Disease

Carcinoma in situ

Neoplastic Transformation

# Principles of Cancer Treatment

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- Surgery
- Radiation therapy
- Chemotherapy
- Biologic therapy

# Cell Biology of Cancer

- **Staging**

- **TNM classification**

- T = tumor - N = Node - M = metastasis

- **Staging provides information for:**

- Treatment
    - Prognosis

# Principles of Radiation Therapy

- **Physical Properties and Biologic Effects**

- Radiation therapy is a physical form of treatment that damages any tissue in its path.
- Tumor cells seem somewhat more sensitive to the lethal effects of radiation than normal tissues primarily because of differences in ability to repair sublethal DNA and other damage.
- The challenge for radiation treatment planning is to deliver the radiation to the tumor volume with as little normal tissue in the field as possible.

# Principles of Radiation Therapy

- **Delivery ways**

- **Teletherapy**

- The beams of radiation generated at a distance and aimed at the tumor within the patient

- **Brachytherapy**

- Encapsulated sources of radiation implanted directly into or adjacent to tumor tissues

- **Systemic therapy**

- Radionuclides targeted in some fashion to a site of tumor

# Principles of Radiation Therapy

- **Nonparticulate waves**

- **X-rays** and **gamma rays** are the forms of radiation most commonly used to treat cancer. They are both electromagnetic, nonparticulate waves.
- X-rays are generated by linear accelerators; gamma rays are generated from decay of atomic nuclei in radioisotopes such as cobalt and radium.

# Principles of Radiation Therapy

- **Particulate waves**

- Electron beams have a very low tissue penetrance and are used to treat skin conditions such as mycosis fungoides.
- Neutron beams may be somewhat more effective than x-rays in treating salivary gland tumors.

# Principles of Radiation Therapy

- **Influencing Factors (Biological)**

- Hypoxia
- Growth fraction
- Cell cycle time and phase
- Tumor mass

# Principles of Radiation Therapy

## ● Influencing Factors (Radiation)

- Low-energy orthovoltage beams (150 to 400 kV) scatter when they strike the body
  - More damage to adjacent normal tissues
  - Less radiation delivered to the tumor
- Megavoltage radiation (1 MeV) has very low lateral scatter
  - More homogeneous distribution
  - Greater deposit of the energy in the tumor

# Principles of Radiation Therapy

## ● **Influencing Factors (Chemical Agents)**

- Alter DNA stereochemistry
  - e.g., halogenated pyrimidines and cisplatin
- DNA synthesis inhibitor
  - e.g., hydroxyurea
- Thiol depleting compounds
  - e.g., buthionine and sulfoximine

# Principles of Radiation Therapy

- **Radioresistant organs**

- Bone
- Heart
- Skeletal muscle
- Nerves

- **Radiosensitive organs**

- Epiphyseal growth plate of bones in children
- Bone marrow
- Vascular endothelium
- Mucosal lining of the intestinal tract
- Testis
- Ovary

# Principles of Radiation Therapy

## Complications

- Thyroid failure
- Blindness (Cataracts and Retinal damage)
- Salivary glands atrophy
- Myocardial infarction
- Pericarditis
- Lung fibrosis
- Radiation enteritis
- Spinal cord transection
- Development of second solid tumors

# Bladder Carcinomas

- A transitional cell epithelium lines the urinary tract from the renal pelvis to the ureter, urinary bladder, and the proximal two-thirds of the urethra.
- Carcinomas may occur at any point, but generally 90% develop in the bladder, 8% in the renal pelvis, and 2% in the ureter or urethra.

# Bladder Carcinomas

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## **Epidemiology**

- The median age at diagnosis is 65 years.
- Overall, urinary bladder cancer is the fourth most common cancer in men and the ninth in women.

# Bladder Carcinomas

## Risk Factors

- Cigarette smoking
  - Smoking increases the rate of cancer two- to fourfold and the effect may persist for 10 years or longer after smoking is stopped.
- Chronic cyclophosphamide exposure
- Diets rich in meat and fat
- Exposure to *Schistosoma haematobium*

# Bladder Carcinomas

## Pathology

- 90 to 95% of bladder tumors diagnosed are transitional cell tumors.
- Once diagnosed, these tumors exhibit the tendency to recur over time and in new locations in the urothelial tract.
- Growth pattern: in-situ, solid, and papillary

# Bladder Carcinomas

## Pathogenesis

- **Superficial tumors**

- 9q deletions

- **Invasive tumors**

- Deletions of 3p, 5q, 17p, 18q and the *RB* gene locus
- p53 overexpression

# Bladder Carcinomas

## Clinical Presentation

- Hematuria - 80 to 90%
- Irritative symptoms
- Flank pain (ureteral obstruction)

# Bladder Carcinomas

## Diagnosis

- Sonography
- CT scan
- MRI
- Intravenous pyelogram (IVP)
- Cystoscopy

# Bladder Carcinomas

## Staging

|                                 |  | STAGE | TNM | L.Nodes% | 5-YEAR SURVIVAL |
|---------------------------------|--|-------|-----|----------|-----------------|
| Superficial                     |  | 0a    | T1a |          | 90%             |
|                                 |  | 0a    | T1  |          |                 |
| Infiltrating                    |  | I     | T2  | 7-30     | 70%             |
|                                 |  |       | T3a | 25       |                 |
|                                 |  | II    | T3b | 50       | 35-50%          |
| Invasion of adjacent structures |  | IV    | T4  | 70       | 10-20%          |
| Lymph node invasion             |  | IV    | N+  | 100      |                 |
| Distant Extension               |  | IV    | M+  | 100      |                 |
|                                 |  |       |     | 50       |                 |

# Bladder Carcinomas

## Treatment

- Treatments are based on the extent and depth of invasion of the tumor within the primary site and the presence or probability of metastatic spread.

# Tumors of the Liver

- **Benign Liver Tumors**

- Hepatocellular Adenomas
- Focal Nodular Hyperplasia
- Hemangioma

- **Carcinomas of the Liver**

- Hepatocellular Carcinoma
- Hepatoblastoma
- Angiosarcoma

# Hepatocellular Adenomas

## Epidemiology

- Predominantly in women in their third and fourth decades

# Hepatocellular Adenomas

## Pathology

- Microscopically, they consist of normal or slightly atypical hepatocytes.

# Hepatocellular Adenomas

## Clinical Manifestations

- Pain and the presence of a palpable mass
- Intratumor hemorrhage (pain and circulatory collapse)

# Hepatocellular Adenomas

## Diagnosis

- Sonography
- Computed Tomography (CT)
- Magnetic Resonance Imaging (MRI)
- Selective hepatic arteriography
- Radionuclide scans

# Hepatocellular Adenomas

## Management and Treatment

- Imaging surveillance for small tumors
- Surgery for lesion larger than 8 to 10 cm, near the surface, and resectable

# Hepatocellular Carcinoma

## Epidemiology

- Annual incidence in the United States has increased from 1.4/100,000 in the period 1976 to 1980 to 2.4/100,000 in 1991 to 1995
- The incidence peaks in the fifth to sixth decades of life
- Four times more common in men than in women
- Usually arises in a cirrhotic liver
- Incidence of this cancer is about 100-fold higher in individuals with HBV infection than in noninfected controls

# Hepatocellular Carcinoma

## Risk Factors

- Any chronic liver disease
- HBV
- HCV
- Alcoholic liver disease
- $\alpha_1$ -antitrypsin deficiency
- Hemochromatosis
- Tyrosinemia
- Aflatoxin B<sub>1</sub>
- Mycotoxin

# Hepatocellular Carcinoma

## Pathogenesis

- The loss, inactivation, or mutation of the tumor suppressor gene p53
- Hormonal factors may also play a role

# Hepatocellular Carcinoma

- **Clinical Manifestations**

- Cancers of the liver initially may escape clinical recognition because they occur in patients with underlying cirrhosis, and the symptoms and signs may suggest progression of the underlying disease. The most common presenting features are abdominal *pain* with detection of an abdominal mass.

# Hepatocellular Carcinoma

## Diagnosis

- **Imaging procedures**
  - Ultrasound, CT, MRI, hepatic artery angiography, and technetium scans
- AFP levels >500 g/L
- Percutaneous **liver biopsy**

# Hepatocellular Carcinoma

## Treatment

- Surgical resection
  - Liver transplantation
  - Hepatic artery embolization
  - Ultrasound-guided cryoablation
  - Percutaneous alcohol injection
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- The liver cannot tolerate high doses of radiation.
  - The disease is not responsive to chemotherapy.

# Hepatocellular Carcinoma

## Prognosis

- Most patients die within 3 to 6 months of diagnosis
- When hepatocellular carcinoma is detected very early, survival is 1 to 2 years after resection