NEOPLASIA
DEFINITIONS AND EXAMPLES

Kenneth Alonso, MD, FACP

Cancer mortality

- Cancer deaths accounted for 23.1% of all deaths in the United States in 2017.
- It is second only to cardiovascular deaths as a major cause of mortality.
- For both men and women, lung cancer was the major cause of cancer death and accounted for 5.1% of all deaths

Major causes of death by cancer

- For men:
- Lung and bronchus cancer
- Percentage of all deaths: 2.7%
- Prostate cancer
- Percentage of all deaths: 1.1%
- Colorectal cancer
- Percentage of all deaths: 1.0%

Major causes of death by cancer

- For women:
- Lung and bronchus cancer
- Percentage of all deaths: 2.4%
- Breast cancer
- Percentage of all deaths: 1.4%
- Colorectal cancer
- Percentage of all deaths: 0.8%

Probability of developing cancer

- 2014-2019 US data based on probability of developing cancer
- 32.8% breast (women, 40+ years of age)
- 11.7% prostate cancer (men, 50+ years of age)
- 6.4% lung cancer
- 4.5% colorectal cancer
- 3.1% uterine cancer
- 3.0% melanoma
- 2.5% bladder

Probability of developing cancer

- 2.3% non-Hodgkin's lymphoma
- 1.7% renal cancer
- 1.6% leukemia
- 1.6% pancreas
- 1.3% ovarian cancer
- 1.3% thyroid cancer
- 1.3% oral cancer

Nomenclature

- Neoplasm means new growth
- a disorder of cell growth that is triggered by a series of [acquired] mutations affecting a single cell and its clonal progeny
- All neoplasms have two basic components:
- Neoplastic cells that constitute the tumor parenchyma
- Reactive stroma composed of connective tissue, blood vessels, and variable numbers of cells of the adaptive and innate immune system.

Nomenclature

- The suffix –oma is generally attached to a noun stem that indicates the origin of the growth
- Fibroma (fibrous tissue)
- Chondroma (cartilaginous tissue)
- Rhabdomyoma (striated muscle)
- Growths that arise from epithelial tissues have may be named for the cell of origin of the growth pattern or microscopic architecture

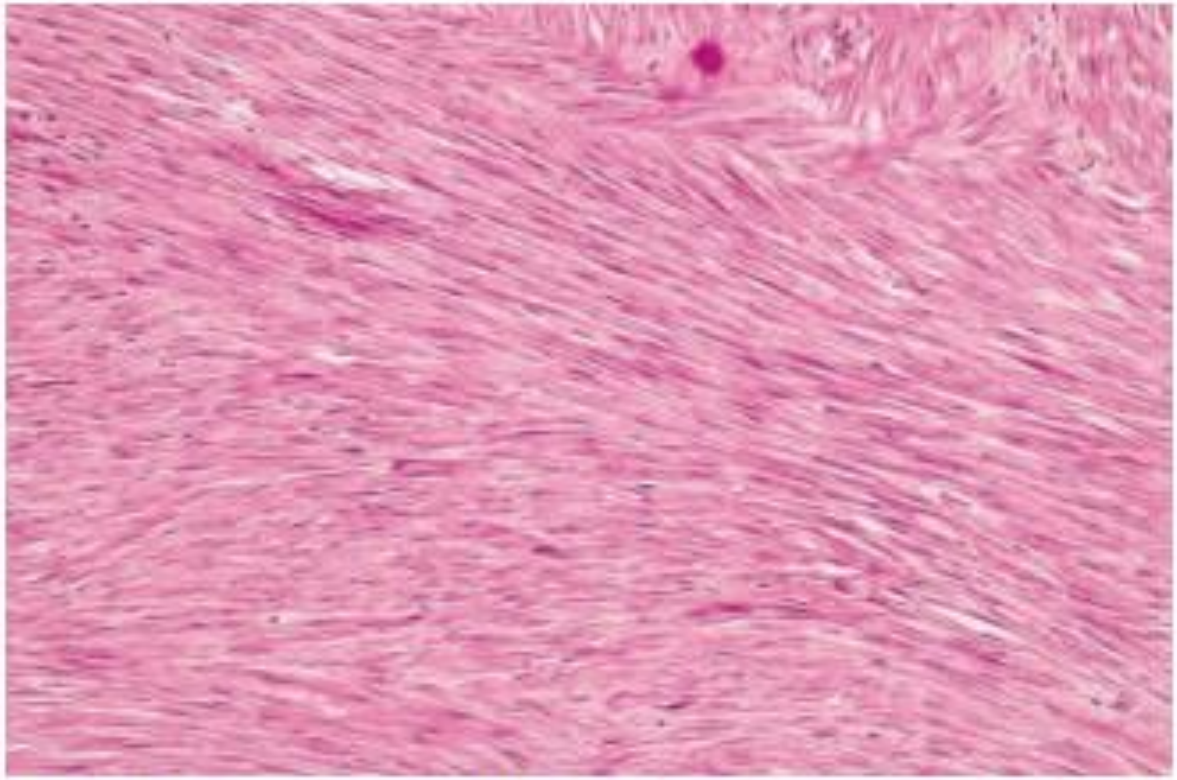


Figure 7-4 Leiomyoma of the uterus. This benign, well-differentiated tumor contains interlacing bundles of neoplastic smooth muscle cells that are virtually identical in appearance to normal smooth muscle cells in the myometrium.

Nomenclature

- Adenoma
- Benign epithelial neoplasm derived from glands
- Although they may not form glandular structures
- A mass that arises from renal tubular cells growing in the form of numerous tightly clustered small glands is termed an adenoma
- A heterogeneous mass of adrenal cortical cells growing as a solid sheet is termed an adenoma
- Benign epithelial neoplasms producing microscopically or macroscopically visible fingerlike or warty projections from epithelial surfaces are referred to as papillomas

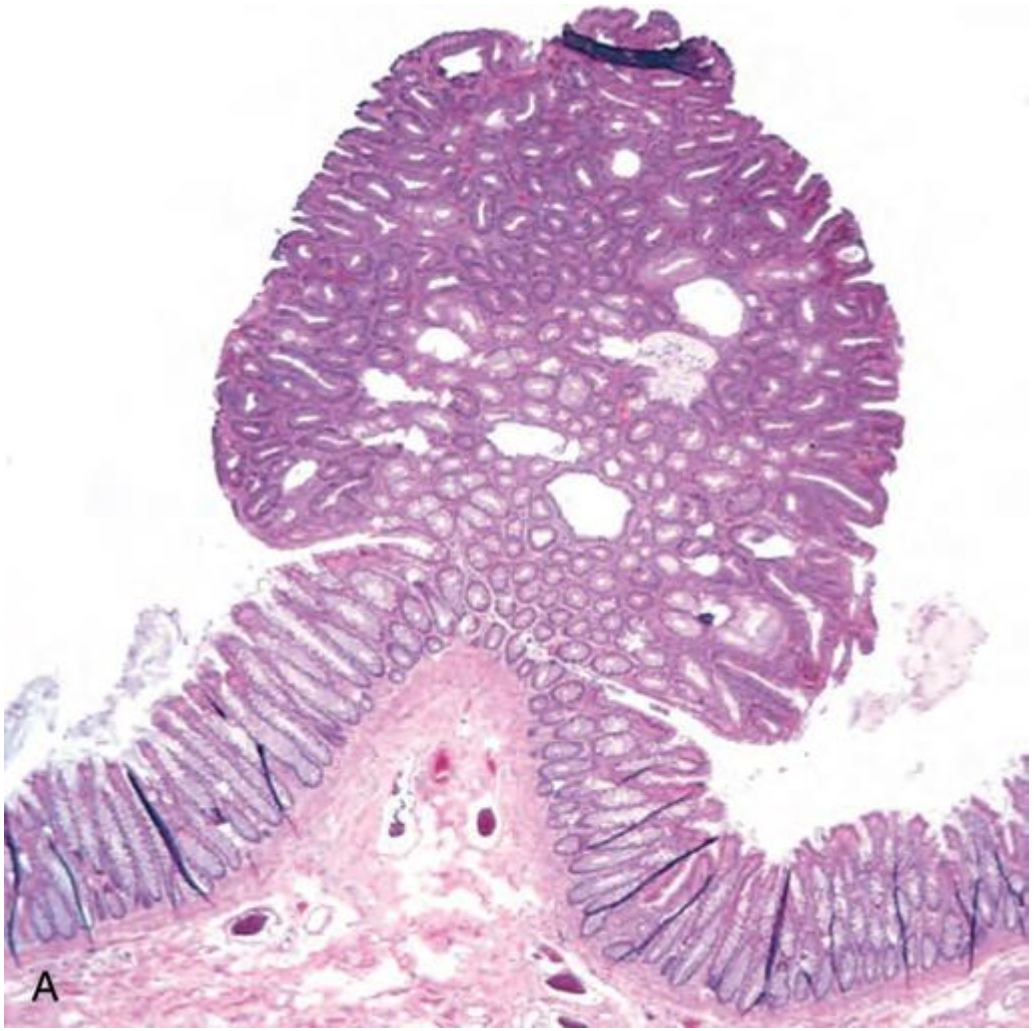
Nomenclature

- Those that form large cystic masses are referred to as cystadenomas.
- Some produce papillary patterns that protrude into cystic spaces and are called papillary
- cystadenomas.
- The cysts are serous if they contain a serum-life fluid
- The cysts are mucinous if they contain mucin

Cystadenoma of the ovary

Nomenclature

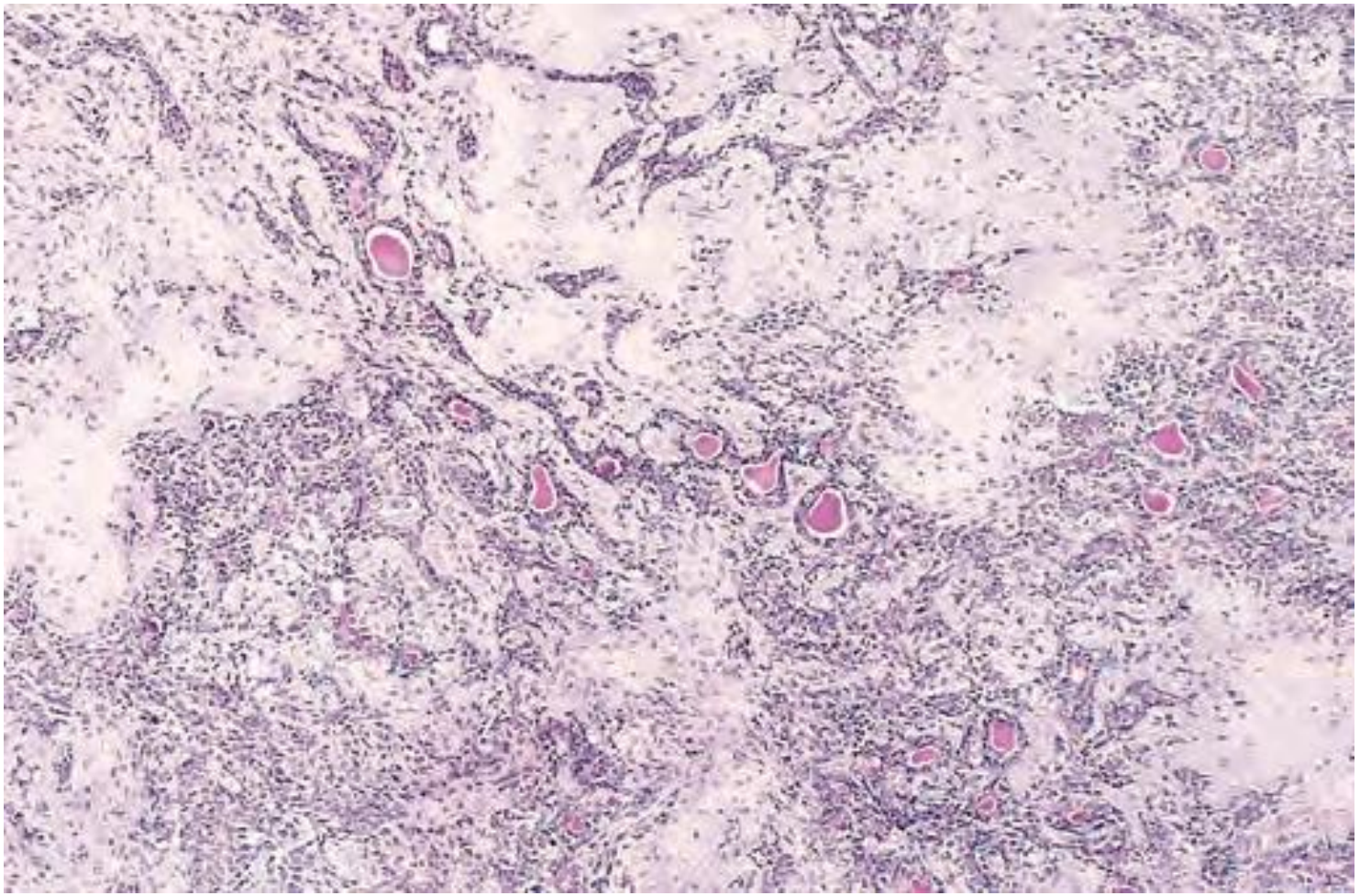
- A macroscopically visible projection above a mucosal surface that projects into a lumen is termed a polyp.
- If the polyp has glandular tissue, it is called an adenomatous polyp



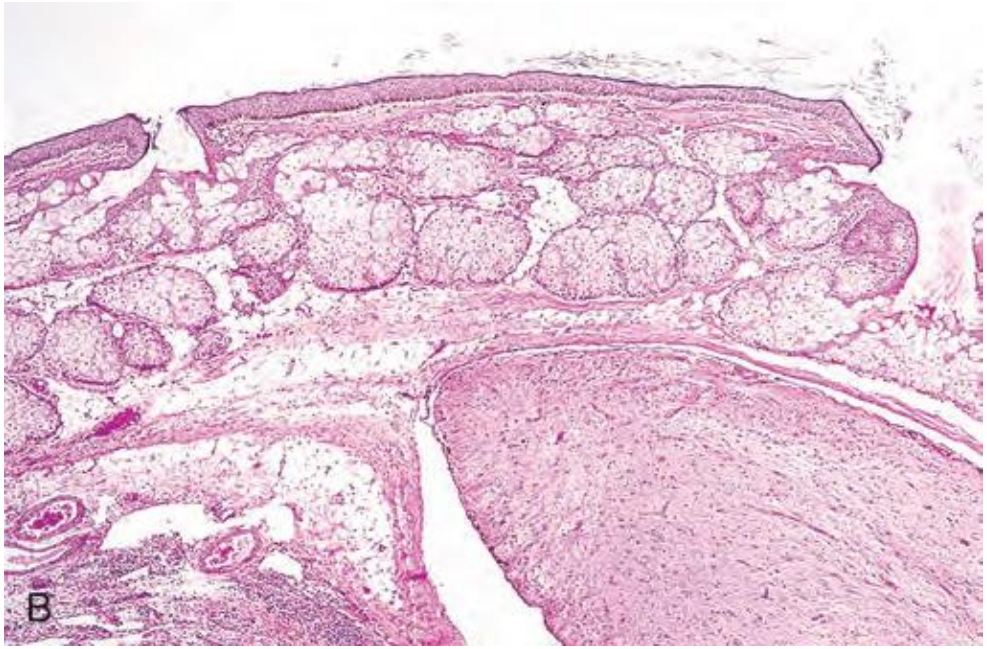
Colonic polyp. A, An Adenomatous (glandular) polyp is projecting into the colonic lumen and is attached to the mucosa by a distinct stalk. B, Gross appearance of several colonic polyps Figure 7-1

Nomenclature

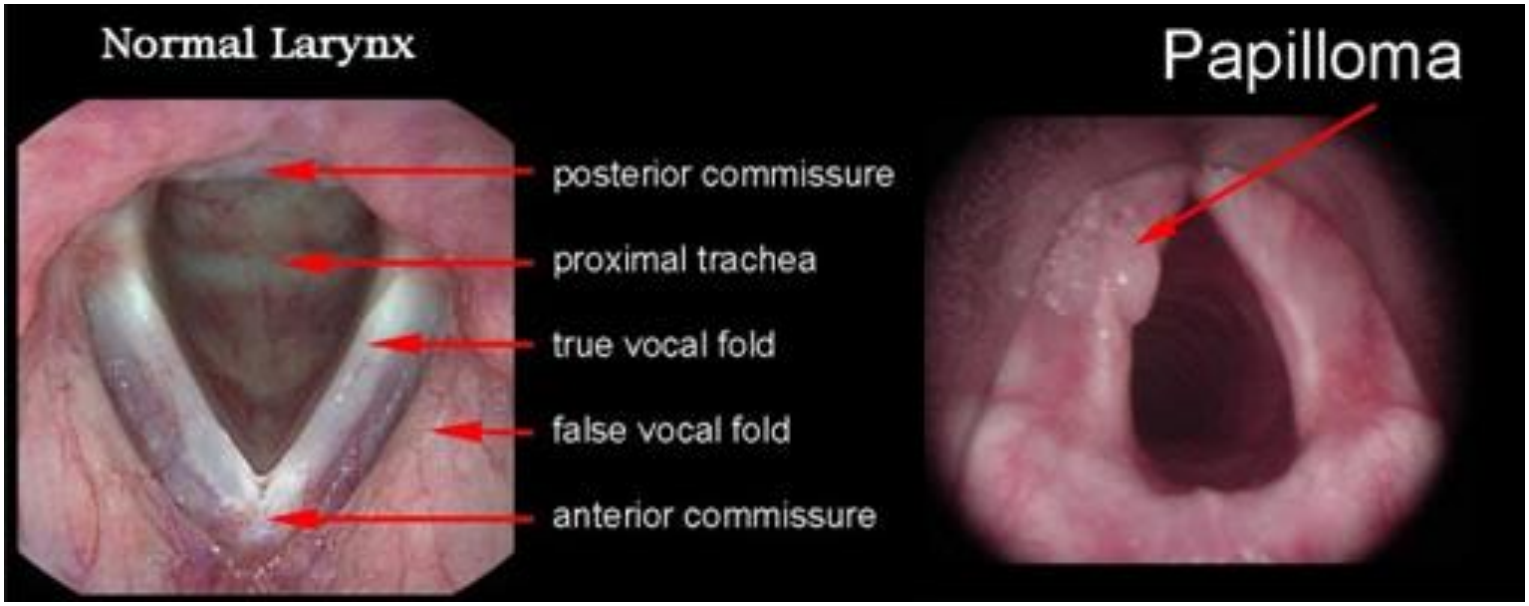
- Mixed tumors arise from a single clone and demonstrate divergent pathways with capabilities of generating epithelial or myoepithelial cells
- Contain epithelial cells and myxoid stroma
- Cartilaginous elements may be identified
- All derived from a single germ layer
- Teratoma
- Originates from totipotential germ cells
- May give rise to neoplasms containing epithelial, mesenchymal, and neural elements
- If immature element present, is malignant



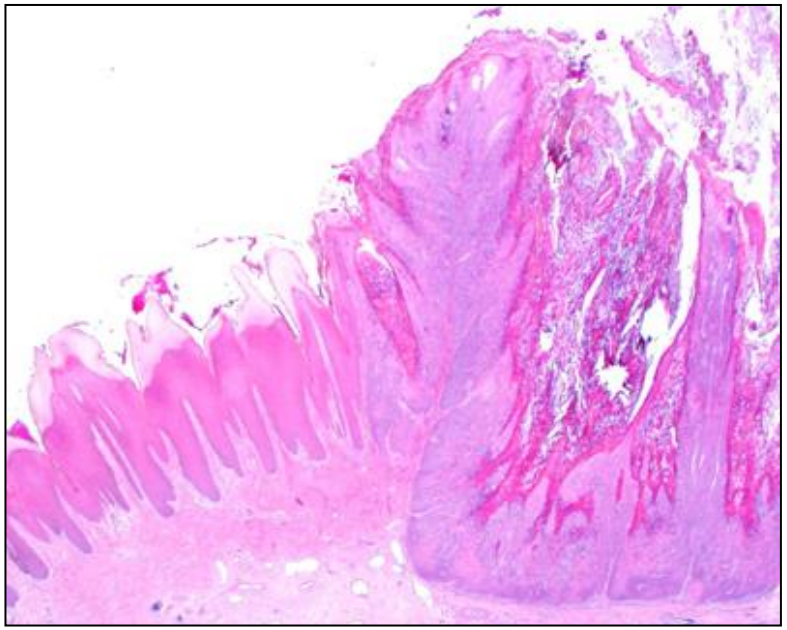
A mixed tumor of the parotid gland that contains epithelial cells forming ducts and myxoid stroma that resemble cartilage. Figure 7-2
(Courtesy Dr. Trace Worrell, University of Texas Southwestern Medical School, Dallas, Texas.)

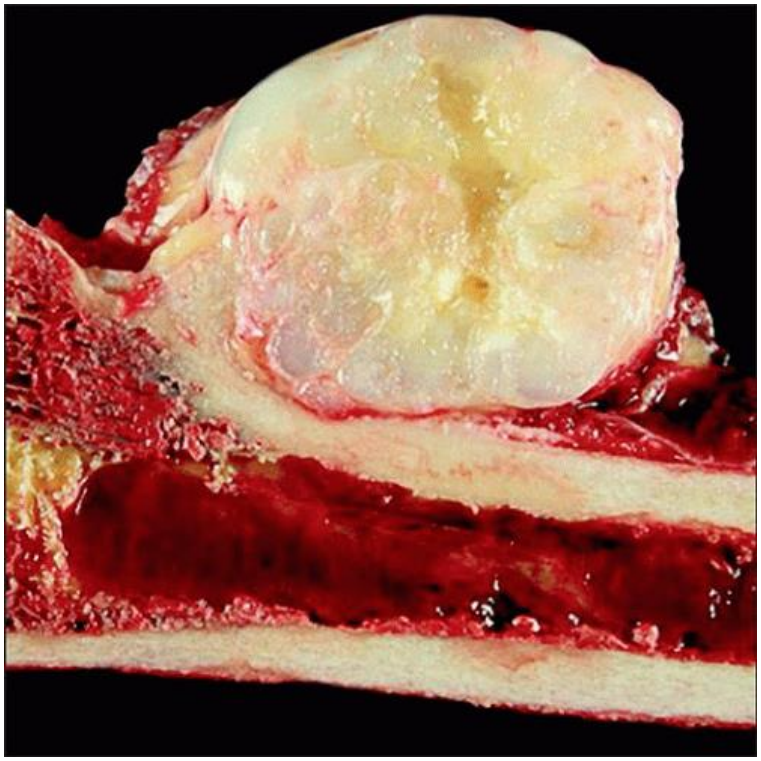


A, Gross appearance of an opened cystic teratoma of the ovary. Note the presence of hair, sebaceous material, and tooth. B, A microscopic view of a similar tumor shows skin, sebaceous glands, fat cells, and a tract of mature neural tissue (arrow). Figure 7-3



- Laryngeal papilloma
- Finger-like off-shoots of lining epithelium are shown in the microscopic slide (right)
- HPV most common cause





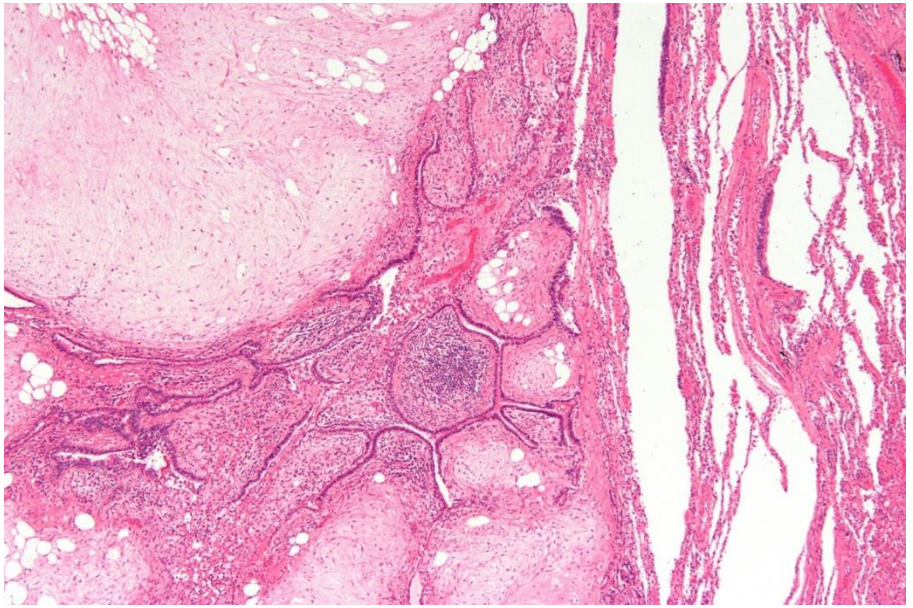
Periosteal chondroma:
A benign tumor
composed of cartilage

Ovarian fibroma: A sex chord stromal tumor composed of dense fibrous tissue. Frequently present with ascites. If effusion preent as well, is a Meig's tumor.

Nomenclature

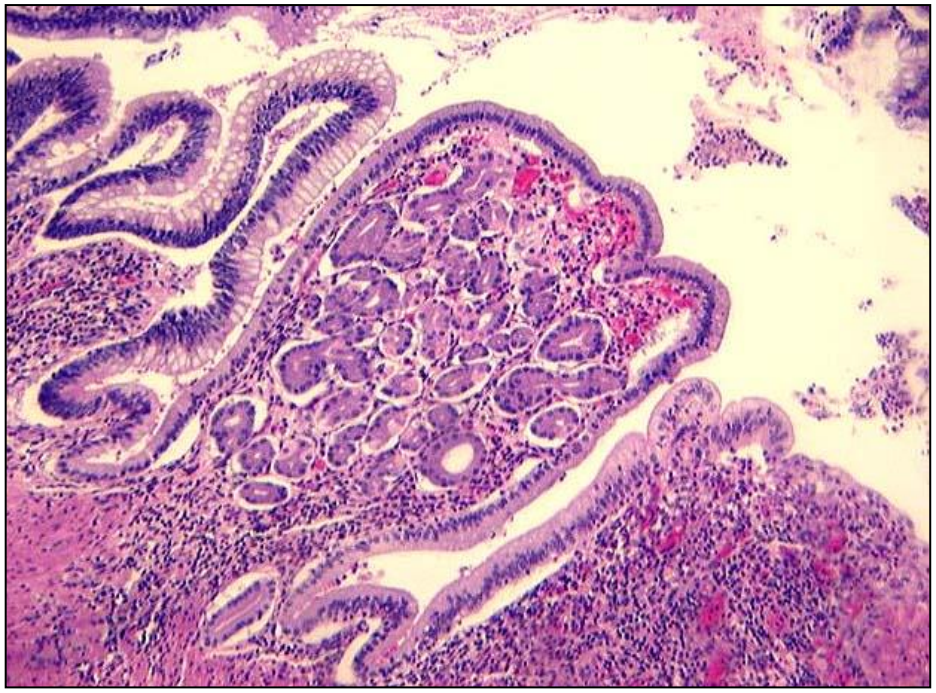
- Hamartomas
- Disorganized but benign masses composed of cells indigenous to the involved site.
- Many have clonal chromosomal aberrations that are acquired through somatic mutations
- Choristoma
- Heterotopic cell rests

Hamartoma



Usually in the young. A well-rounded lesion. To the right is the lesion removed from the lung. It contains cartilage and disorganized bronchi, respiratory epithelium, and vessels.

Choristoma

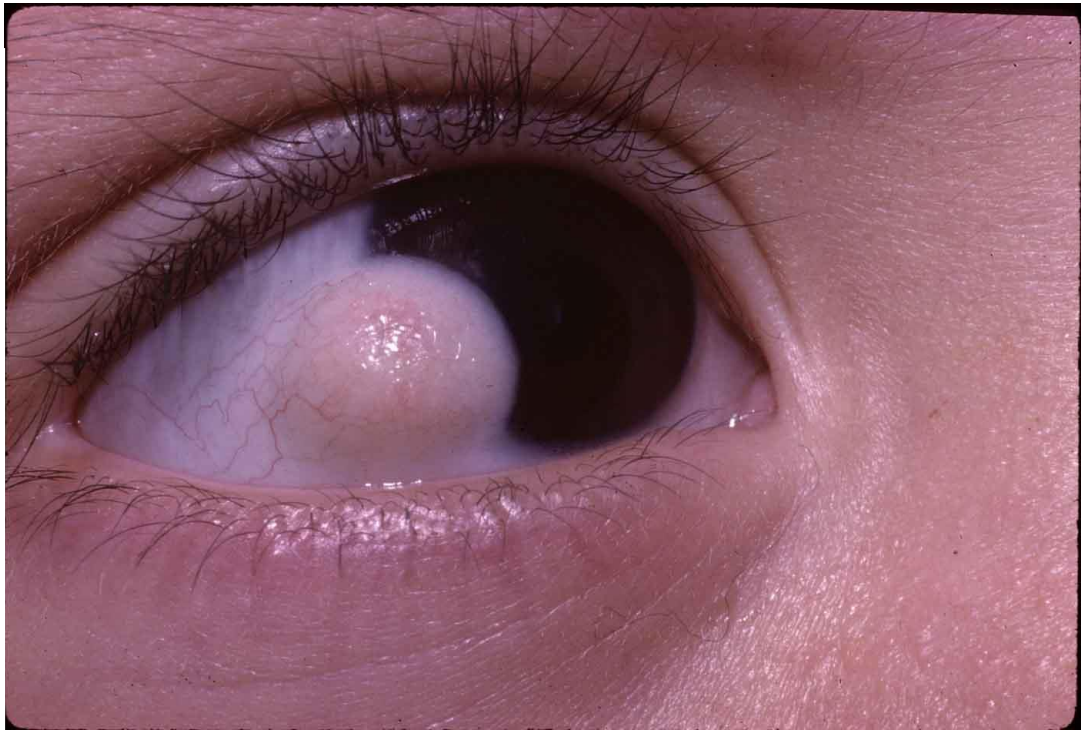


Ectopic gastric epithelium
in a Meckel’s diverticulum

Choristoma

Choristomas are the most common epibulbar and orbital tumors in children.

May have features of a dermoid cyst or dermolipoma (skin & adipose tissue), and include other tissues such as cartilage, bone, and glands



Nomenclature

- Malignant tumors are locally invasive or may spread to distant sites (metastasize)
- Malignant growths are called cancers.
- Sarcoma reflects origin from mesenchymal tissue
- Leukemia reflects origin from white blood cells
- Lymphoma reflects origin from lymphocytes
- Melanoma relfects origin from melanocytes
- Carcinomas arise from epithelial tissues
- Adenocarcinoma if glandular
- Squamous carcinoma if resembles stratified squamous epithelium

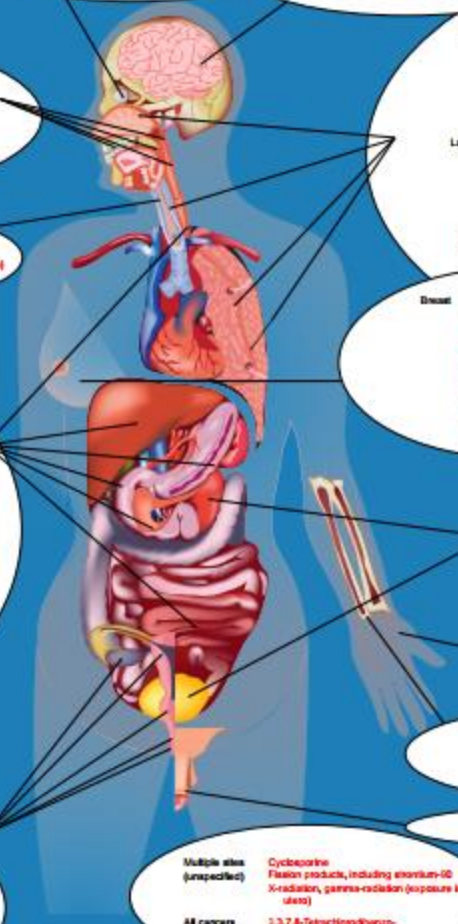
Table 7-1 Nomenclature of Tumors

Tissue of Origin	Benign	Malignant
Composed of one parenchymal cell type		
Tumors of Mesenchymal Origin		
Connective tissue and derivatives	Fibroma Lipoma Chondroma Osteoma	Fibrosarcoma Liposarcoma Chondrosarcoma Osteogenic sarcoma
Vessels and surface coverings		
Blood vessels	Hemangioma	Angiosarcoma
Lymph vessels	Lymphangioma	Lymphangiosarcoma
Mesothelium	Benign fibrous tumor	Mesothelioma
Brain coverings	Meningioma	Invasive meningioma
Blood Cells and Related Cells		
Hematopoietic cells		Leukemias
Lymphoid tissue		Lymphomas
Muscle		
Smooth	Leiomyoma	Leiomyosarcoma
Striated	Rhabdomyoma	Rhabdomyosarcoma
Tumors of Epithelial Origin		
Stratified squamous	Squamous cell papilloma	Squamous cell carcinoma
Basal cells of skin or adnexa		Basal cell carcinoma
Tumors of Epithelial Origin (cont'd)		
Epithelial lining of glands or ducts	Adenoma Papilloma Cystadenoma	Adenocarcinoma Papillary carcinomas Cystadenocarcinoma
Respiratory passages	Bronchial adenoma	Bronchogenic carcinoma
Renal epithelium	Renal tubular adenoma	Renal cell carcinoma
Liver cells	Hepatic adenoma	Hepatocellular carcinoma
Urinary tract epithelium (transitional)	Transitional cell papilloma	Transitional cell carcinoma
Placental epithelium	Hydatidiform mole	Choriocarcinoma
Testicular epithelium (germ cells)		Seminoma Embryonal carcinoma
Tumors of Melanocytes	Nevus	Malignant melanoma
More than one neoplastic cell type—mixed tumors, usually derived from one germ cell layer		
Salivary glands	Pleomorphic adenoma (mixed tumor of salivary origin)	Malignant mixed tumor of salivary gland origin
Renal anlage		Wilms tumor
More than one neoplastic cell type derived from more than one germ cell layer—teratogenous		
Totipotential cells in gonads or in embryonic rests	Mature teratoma, dermoid cyst	Immature teratoma, teratocarcinoma

Human Cancer: Known Causes and Prevention by Organ Site

IARC Monographs on the Identification of Carcinogenic Hazards to Humans and Handbooks of Cancer Prevention

Monographs 1-125, Handbooks 1-17, updated 29 November 2019
Agents classified as carcinogenic to humans (Group 1) (in red)
Interventions with sufficient evidence of a cancer-preventive effect (in green)



Eye
Human immunodeficiency virus type 1
Ultraviolet-emitting tanning devices
Welding

Brain and central nervous system
X-radiation, gamma-radiation
Absence of excess body fatness (meningioma)

Oral cavity
Alcoholic beverages
Betel quid with tobacco
Betel quid without tobacco
Human papillomavirus type 16
Quitting smoking
Smokeless tobacco
Tobacco smoking

Pharynx (oro-, hypo- and/or NOS)
Alcoholic beverages
Betel quid with tobacco
Human papillomavirus type 16
Quitting smoking
Tobacco smoking

Nasopharynx
Epstein–Barr virus
Formaldehyde
Salted fish, Chinese-style
Wood dust

Tonsil
Human papillomavirus type 16

Salivary gland
X-radiation, gamma-radiation

Thyroid
Absence of excess body fatness
Radioiodines, including iodine-131 (exposure during childhood and adolescence)
X-radiation, gamma-radiation

Lung
Aluminium production
Arsenic and inorganic arsenic compounds
Asbestos (all forms)
Beryllium and beryllium compounds
Bis(chloromethyl)ether; chloromethyl methyl ether (technical grade)
Cadmium and cadmium compounds
Chromium (VI) compounds
Coal, indoor emissions from household combustion
Coal gasification
Coal-tar pitch
Coke production
Diesel engine exhausts
Gamma-radiation
Haematite mining (underground)
Iron and steel founding
MOPP (vincristine–prednisone–nitrogen mustard–procarbazine mixture)
Nickel compounds
Outdoor air pollution
Outdoor air pollution, particulate matter in
Painter (occupational exposure as)
Plutonium
Quitting smoking
Radon-222 and its decay products
Rubber production industry
Silica dust, crystalline
Soot
Sulfur mustard
Tobacco smoke, secondhand
Tobacco smoking
Welding fumes
X-radiation

Nasal cavity and paranasal sinus
Isopropyl alcohol manufacture using strong acids
Leather dust
Nickel compounds
Radium-226 and its decay products
Radium-228 and its decay products
Tobacco smoking
Wood dust

Larynx
Acid mists, strong inorganic
Alcoholic beverages
Asbestos (all forms)
Quitting smoking
Tobacco smoking

Pleura or peritoneum (mesothelioma)
Asbestos (all forms)
Erionite
Painter (occupational exposure as)

Stomach
Absence of excess body fatness (gastric cardia)
Helicobacter pylori
Quitting smoking
Rubber production industry
Tobacco smoking
X-radiation, gamma-radiation

Upper aerodigestive tract
Acetaldehyde associated with consumption of alcoholic beverages

Liver (hepatocellular carcinoma)
Absence of excess body fatness
Aflatoxins
Alcoholic beverages
Estrogen–progestogen contraceptives
Hepatitis B virus
Hepatitis C virus
Plutonium
Thorium-232 and its decay products
Tobacco smoking (in smokers and in smokers' children)

Liver (angiosarcoma)
Vinyl chloride

Biliary tract
1,2-Dichloropropane
Clonorchis sinensis
Opisthorchis viverrini

Pancreas
Absence of excess body fatness
Quitting smoking
Smokeless tobacco
Tobacco smoking

Oesophagus
Acetaldehyde associated with consumption of alcoholic beverages
Alcoholic beverages
Absence of excess body fatness (adenocarcinoma)
Betel quid with tobacco
Betel quid without tobacco
Quitting smoking (squamous cell carcinoma)
Smokeless tobacco
Tobacco smoking
X-radiation, gamma-radiation

Gall bladder
Absence of excess body fatness
Thorium-232 and its decay products

Colon and rectum
Alcoholic beverages
Absence of excess body fatness
Physical activity
Processed meat (consumption of)
Screening with gFOBT
Screening with FIT
Screening with sigmoidoscopy
Screening with colonoscopy
Tobacco smoking
X-radiation, gamma-radiation

Anus
Human immunodeficiency virus type 1
Human papillomavirus type 16

Breast
Alcoholic beverages
Absence of excess body fatness (postmenopausal)
Diethylstilbestrol
Estrogen–progestogen contraceptives
Estrogen–progestogen menopausal therapy
Mammography screening (50–74 years)
Physical activity
X-radiation, gamma-radiation

Urinary bladder
Aluminium production
4-Aminobiphenyl
Arsenic and inorganic arsenic compounds
Auramine production
Benzidine
Chlornaphazine
Cyclophosphamide
Magenta production
2-Naphthylamine
Painter (occupational exposure as)
Quitting smoking
Rubber production industry
Schistosoma haematobium
Tobacco smoking
ortho-Toluidine
X-radiation, gamma-radiation

Kidney
Absence of excess body fatness
Quitting smoking
Tobacco smoking
Trichloroethylene
X-radiation, gamma-radiation

Renal pelvis and ureter
Aristolochic acid, plants containing
Phenacetin
Phenacetin, analgesic mixtures containing
Tobacco smoking

Corpus uteri (endometrium)
Absence of excess body fatness
Estrogen menopausal therapy
Estrogen–progestogen menopausal therapy
Tamoxifen

Uterine cervix
Conventional cytology screening (35–64 years)
Diethylstilbestrol (exposure in utero)
Estrogen–progestogen contraceptives
Human papillomavirus testing
Human immunodeficiency virus type 1
Human papillomavirus types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
Quitting smoking
Tobacco smoking

Vagina
Diethylstilbestrol (exposure in utero)
Human papillomavirus type 16

Vulva
Human papillomavirus type 16

Ovary
Absence of excess body fatness
Asbestos (all forms)
Estrogen menopausal therapy
Tobacco smoking

Bone
Plutonium
Radium-224 and its decay products
Radium-226 and its decay products
Radium-228 and its decay products
X-radiation, gamma-radiation

Penis
Human papillomavirus type 16

Leukaemia/lymphoma
Absence of excess body fatness (multiple myeloma)
Azathioprine
Benzene
Busulfan
1,3-Butadiene
Chlorambucil
Cyclophosphamide
Cyclosporine
Epstein–Barr virus
Etoposide with cisplatin and bleomycin
Fission products, including strontium-90
Formaldehyde
Helicobacter pylori
Hepatitis C virus
Human immunodeficiency virus type 1
Human T-cell lymphotropic virus type 1
Kaposi sarcoma herpesvirus
Lindane
Melphalan
MOPP (vincristine–prednisone–nitrogen mustard–procarbazine mixture)
Pentachlorophenol
Phosphorus-32, as phosphate
Rubber production industry
Semustine [1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea, or methyl-CCNU]
Thiotepa
Thorium-232 and its decay products
Tobacco smoking
Treosulfan
X-radiation, gamma-radiation

Multiple sites (unspecified)
Cyclosporine
Fission products, including strontium-90
X-radiation, gamma-radiation (exposure in utero)

All cancers combined
2,3,7,8-Tetrachlorodibenzo-*para*-dioxin

Group 1 agents with less than sufficient evidence in humans
2,3,4,7,8-Pentachlorodibenzofuran
Polychlorinated biphenyls with a WHO TEF ("dioxin-like")
4,4′-Methylenebis(2-chloroaniline) (MOCA)
Alpha- and beta-particle emitters
Areca nut
Aristolochic acid
Benzidine, dyes metabolized to
Benzo[a]pyrene
Ethanol in alcoholic beverages
Ethylene oxide
Etoposide
Ionizing radiation (all types)
Neutron radiation
N-Nitrosonornicotine (NNN) and 4-(*N*-nitroso-methylamino)-1-(3-pyridyl)-1-butanone (NNK)
Ultraviolet radiation

Skin (melanoma)
Polychlorinated biphenyls
Solar radiation
Ultraviolet-emitting tanning devices

Skin (other malignant neoplasms)
Arsenic and inorganic arsenic compounds
Azathioprine
Coal-tar distillation
Coal-tar pitch
Cyclosporine
Methoxsalen plus ultraviolet A
Mineral oils, untreated or mildly treated
Shale oils
Solar radiation
Soot
X-radiation, gamma-radiation

Endothelium (Kaposi sarcoma)
Human immunodeficiency virus type 1
Kaposi sarcoma herpesvirus

International Agency for Research on Cancer

World Health Organization

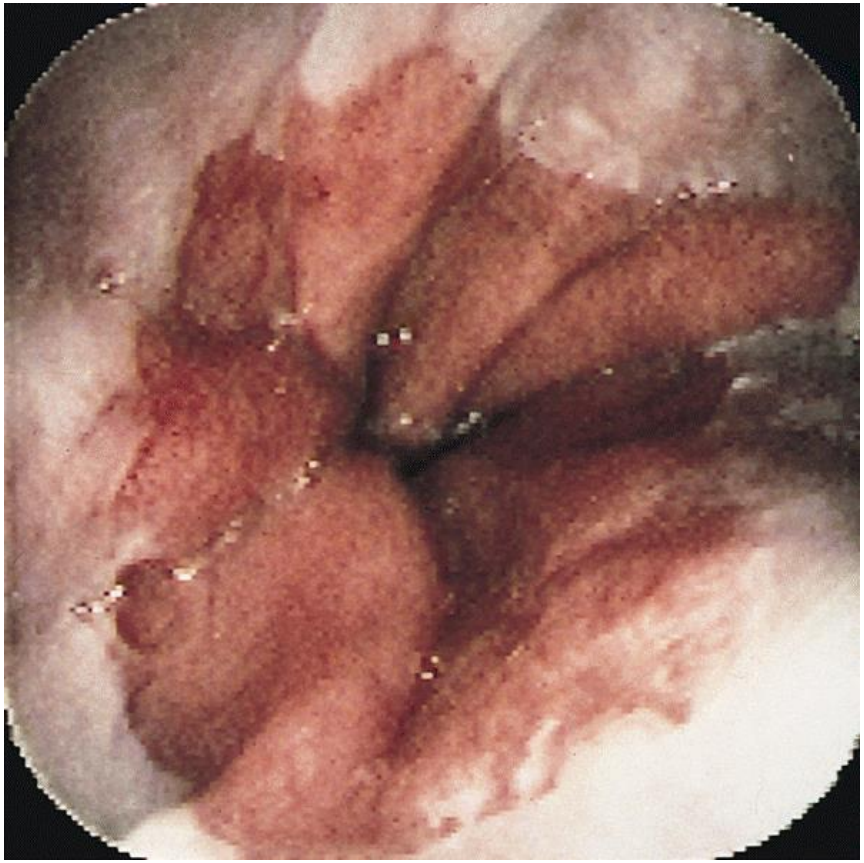
Nomenclature

- Metaplasia is the replacement of one type of cell with another type
- Metaplasia is nearly always found in association with tissue damage, repair, and regeneration.
- Often the replacing cell type is better suited to some alteration in the local environment.

Precursor lesions

- Many precursor lesions arise in the setting of chronic inflammation and can be recognized by the presence of metaplasia:
- Barrett esophagus (gastric and colonic metaplasia of the esophageal mucosa in the setting of gastric reflux)
- Squamous metaplasia of the bronchial mucosa (in response to smoking)
- Squamous metaplasia of the bladder mucosa (in response to schistosoma infection)

Esophago-gastric junction

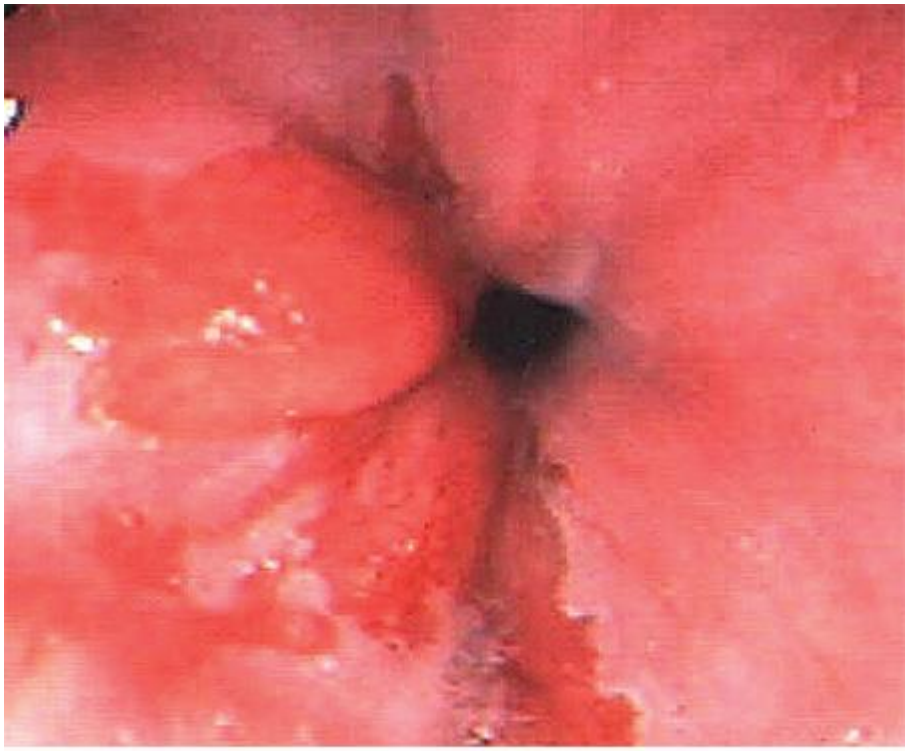


Endoscopic appearance of the z-line (the esophago-gastric junction).

Fig. 2-2

Lewin, KJ, Appelman, HD., “Tumors of the esophagus and stomach.” Atlas of Tumor Pathology, Third Series, Fascicle 18. Armed Forces Institute of Pathology, Washington, DC. 1996.

Barrett esophagus

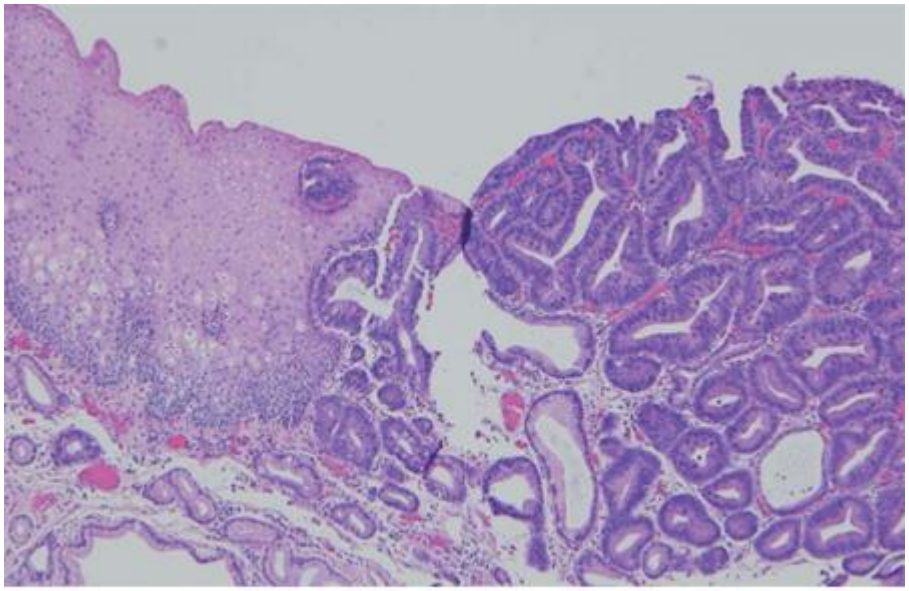


Endoscopic view. Metaplastic change.

(Courtesy of Klaus Monkemuller, MD, UAB, Birmingham, AL)

Fig. 14-16
Accessed 04/01/2010

Barrett esophagus



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Metaplastic change

(*Courtesy of Dr. Stephen May, MD, and Dr. Asif Rashid, MD, UTMDACC, Department of Pathology, Houston, TX*)

Fig.14-17 Accessed 04/01/2010

Precursor lesions

- Colonic metaplasia of the stomach (in the setting of pernicious anemia and chronic atrophic gastritis).
- Noninflammatory hyperplasias.
- Endometrial hyperplasia caused by sustained estrogenic stimulation of the endometrium.
- Leukoplakia, a thickening of squamous epithelium that may occur in the oral cavity or on the penis or vulva and give rise to squamous carcinoma.

Endometrial hyperplasia

Endometrial hyperplasia usually results with conditions of prolonged estrogen excess and can lead to metrorrhagia (uterine bleeding at irregular intervals), menorrhagia (excessive bleeding with menstrual periods), or menometrorrhagia.

https://webpath.med.utah.edu/FEMHTML/FEM019.html Accessed 05/05/2020

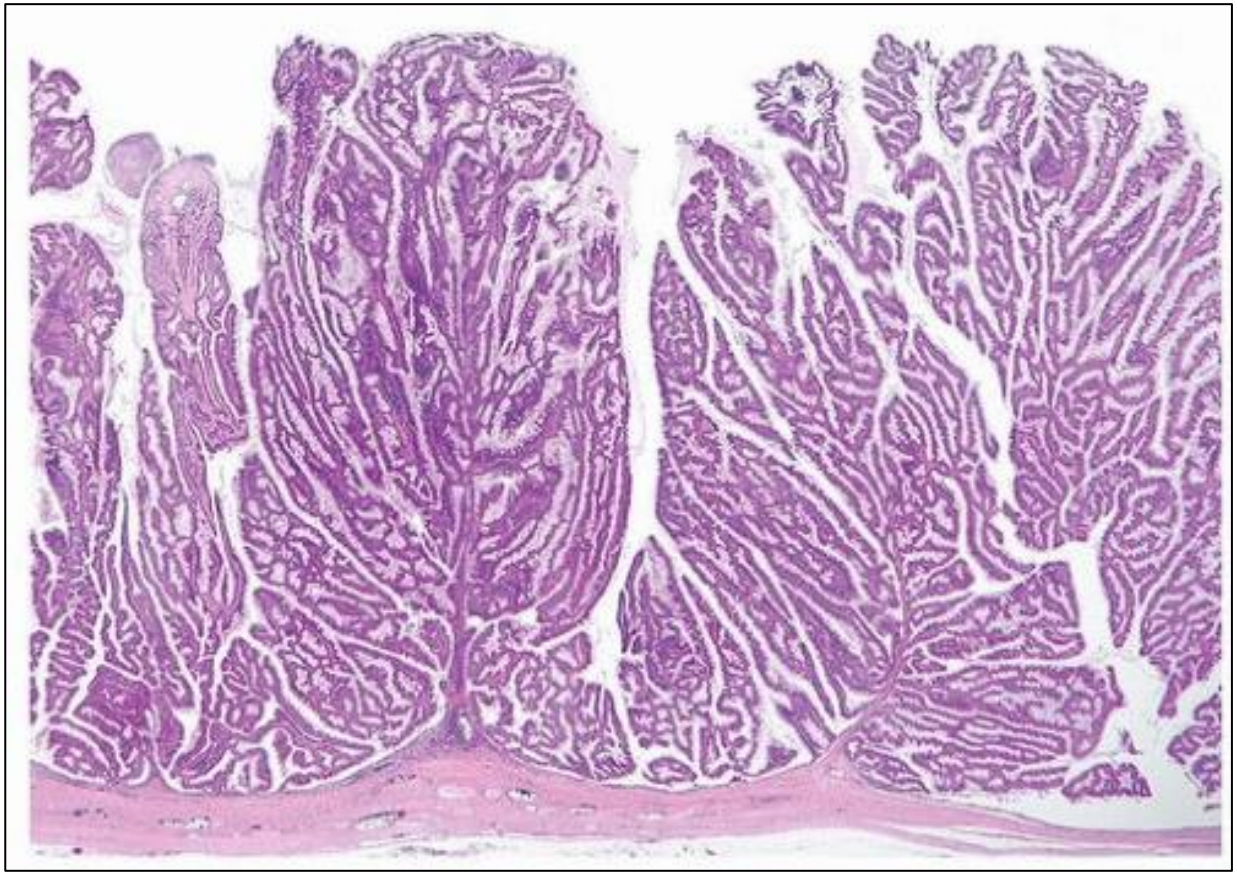
Leukoplakia

https://byebyedoctor.com/wp-content/uploads/2011/05/leukoplakia-2.jpg
Accessed 1/22/2019

Precursor lesions

- Benign neoplasms that are at risk for malignant transformation.
- Villous adenoma (progresses to cancer in 50% of cases)
- May reflect genomic instability
- Immunodeficiency states
- Particularly T-cell impairment

Villous adenoma



Broad based. Pre-malignant. May be secretory.

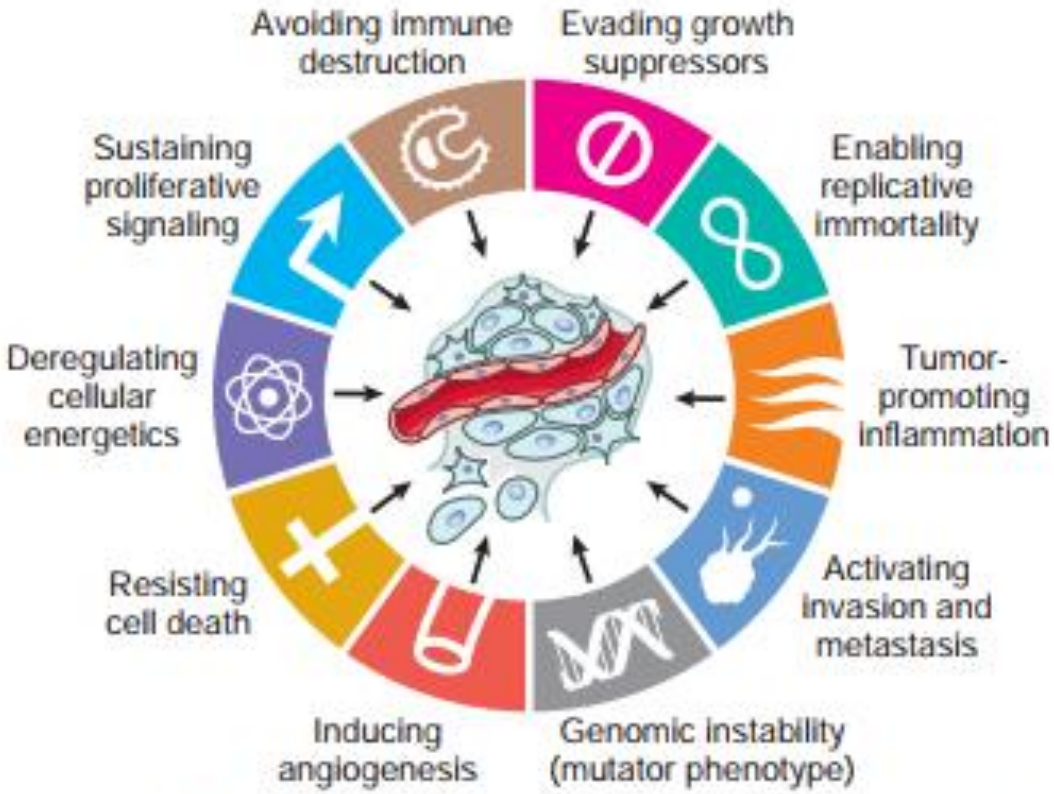


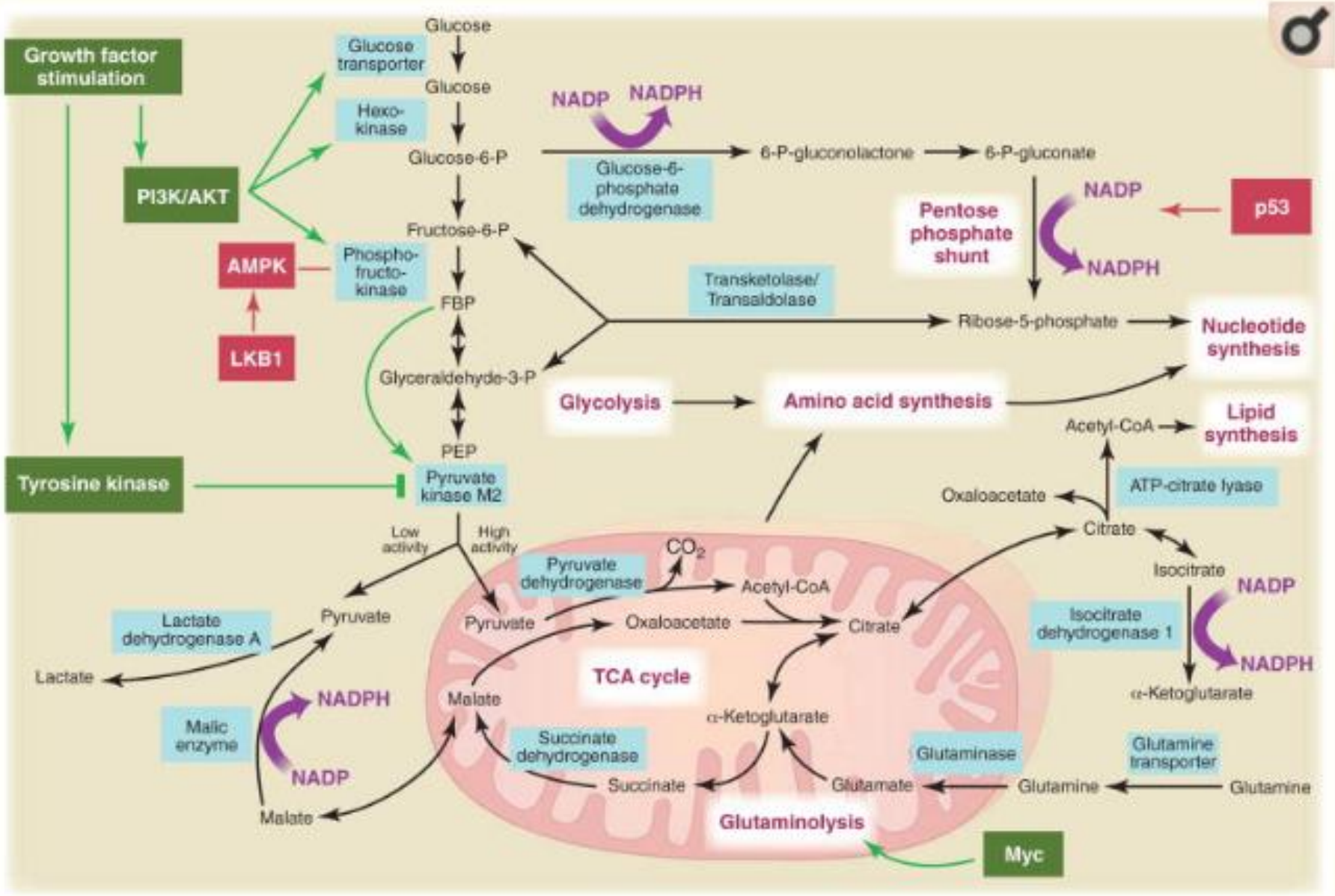
Figure 7-24 Hallmarks of cancer. (Adapted from Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011; 144:646.)

Warburg effect

- In contrast to normal differentiated cells, which rely primarily on mitochondrial oxidative phosphorylation to generate the ATP needed for cellular processes, most cancer cells instead rely on aerobic glycolysis, a phenomenon termed "the Warburg effect.“
- Aerobic glycolysis provides rapidly dividing tumor cells with glutamine and lactate intermediates that are needed for the synthesis of cellular components.
- Fewer reactive oxygen species generated, diminishing apoptosis and promoting metastasis

Warburg effect

- TP53 gene at 17p13.1 promotes mitochondrial oxidation
- KISS1 gene at 1q32.1 inhibits cell migration
- Both inhibit the Warburg effect

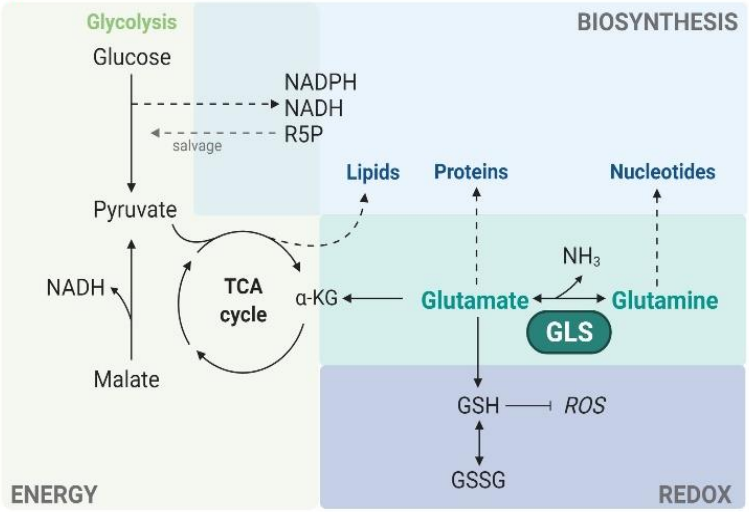


Vander Heiden, MG, Cantley, LC, Thompson, CB, "Understanding the Warburg Effect: The Metabolic Requirements of Cell Proliferation," Science 2009 May 22; 324(5930): 1029–1033. doi: 10.1126/science.1160809

Fig. 3

Glutamine overview

Glutamine metabolism



- Glutamine is an important metabolic fuel that helps rapidly proliferating cells meet the increased energy demands for ATP, and synthetic precursors
- Glutamine → glutamate by glutaminase (GLS)
- Glutamate is converted to the TCA cycle intermediate α-ketoglutarate
- α-KG is a critical metabolite that serves in both ATP production and in replenishing TCA cycle intermediates
- Many cancers are dependent on glutamine for anabolic growth and proliferation

Presented By: Dwight Owen, MD, MSc, FACP
Dwight.owen@osumc.edu

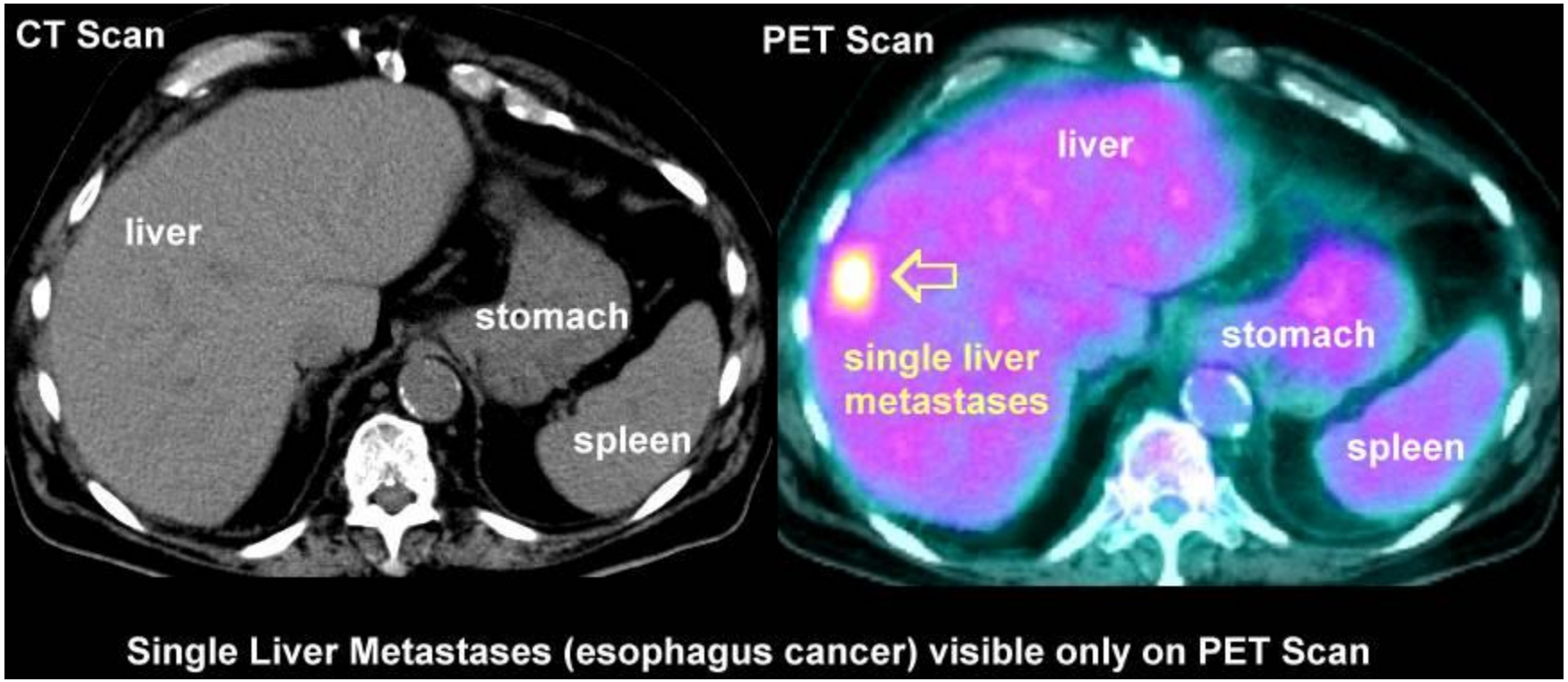
KEAP and STK11 co-mutations associated with lack of benefit to pembrolizumab
Longest benefit of glutamine inhibition noted in melanoma and ASNS low ovarian carcinoma

PET scan

- A PET scan takes advantage of the Warburg effect.
- PET scanning with the tracer labeled ^{18}Fluorodexoyglucose(FDG).
- FDG is a glucose analog that is taken up by glucose-using cells and phosphorylated by hexokinase, whose mitochondrial form is significantly elevated in rapidly growing tumors.
- Metabolic trapping of the radioactive glucose molecule allows the PET scan to be utilized.

PET scan

- FDG localization is identified on the radioisotope scan and is superimposed on a CT scan obtained at the same time for anatomic detail.
- PET scans are useful in staging lymphomas as well as identifying occult metastases in solid cancers.



http://www.aboutcancer.com/liver_met_pet_sah_807.jpg
Accessed 05/05/2020

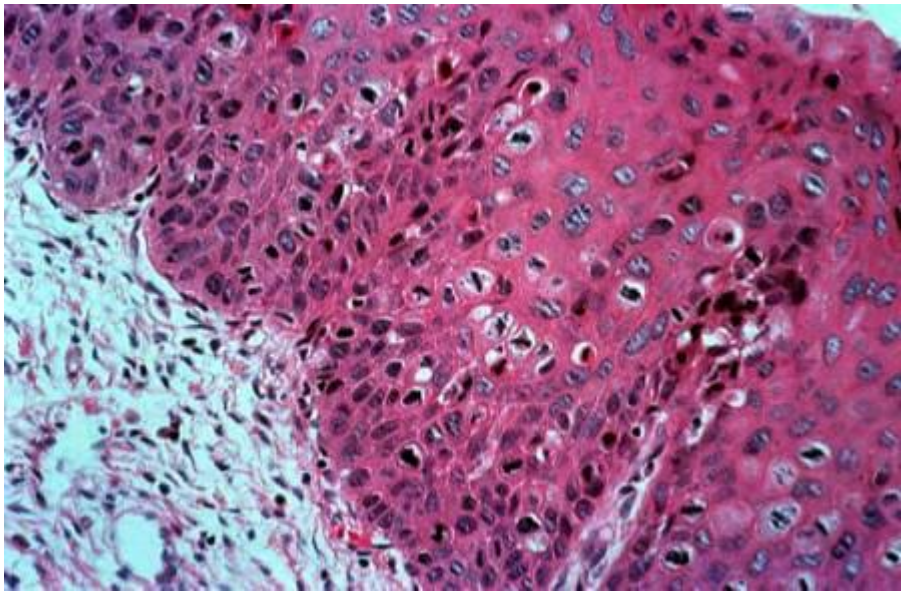
Differentiation

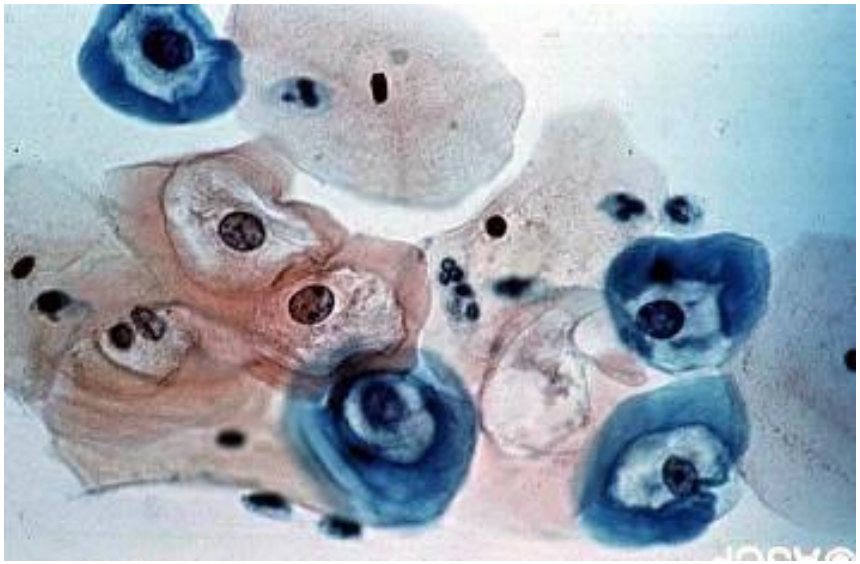
- Differentiation refers to the extent to which neoplastic parenchymal cells resemble the corresponding normal parenchymal cells, both morphologically and functionally
- In hyperplasia, there is an increase in the number of cells in an organ or tissue that appear normal microscopically
- Atypia refers to a structural abnormality noted microscopically in a cell
- It may not necessarily be associated with increased risk of cancer

Dysplasia

- Dysplasia is a precursor of malignancy
- Characterized by a constellation of developmental changes that include a loss in the uniformity of the individual cells as well as a loss in their architectural orientation.
- Dysplastic cells may exhibit considerable pleomorphism (variation) and often contain large hyperchromatic nuclei with a high nuclear-to-cytoplasmic ratio.
- The architecture of the tissue may be disorderly.

- At the right above is a cervical biopsy showing dysplastic change through upper two-thirds of epithelium.
- Koilocytic atypia is present.
- The Pap smear is at the right below. The vacuolization is characteristic of HPV infection. (Koilocytic atypia)





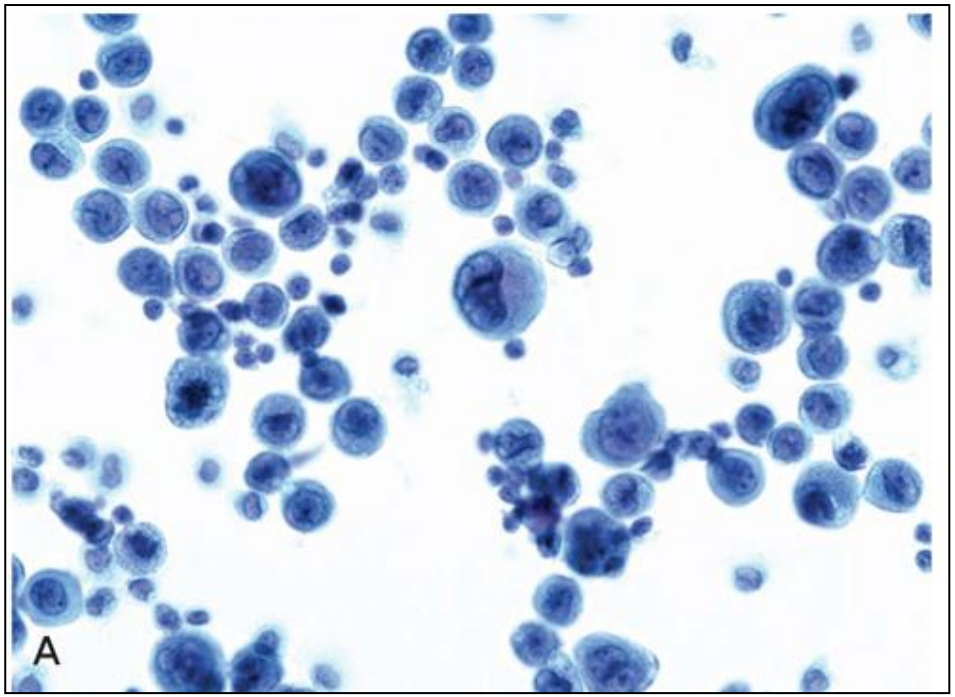
Dysplasia

- When dysplastic changes are marked and involve the full thickness of the epithelium, but the lesion does not penetrate the basement membrane, it is considered a pre-invasive neoplasm and is referred to as carcinoma in situ
- Once the tumor cells breach the basement membrane, the tumor is said to be invasive.

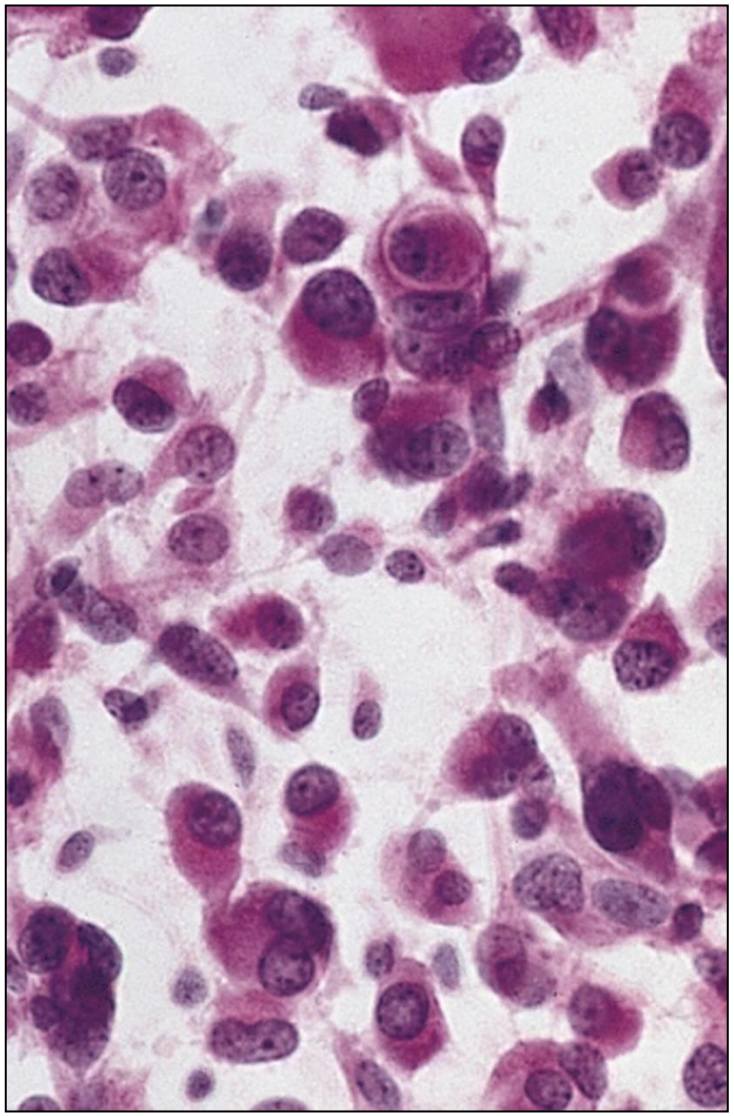
Anaplasia

- Lack of differentiation
- Pleomorphic as there is variation in cell size
- Nuclear atypia
- Nuclei large for size of cell.
- The nuclear shape is variable and often irregular, and the chromatin is often coarsely clumped and distributed along the nuclear membrane, or more darkly stained than normal (hyperchromatic).
- Chromatin clearing (vesicular nuclear chromatin) may also be present.
- Abnormally large nucleoli are also commonly seen.

Pleomorphism

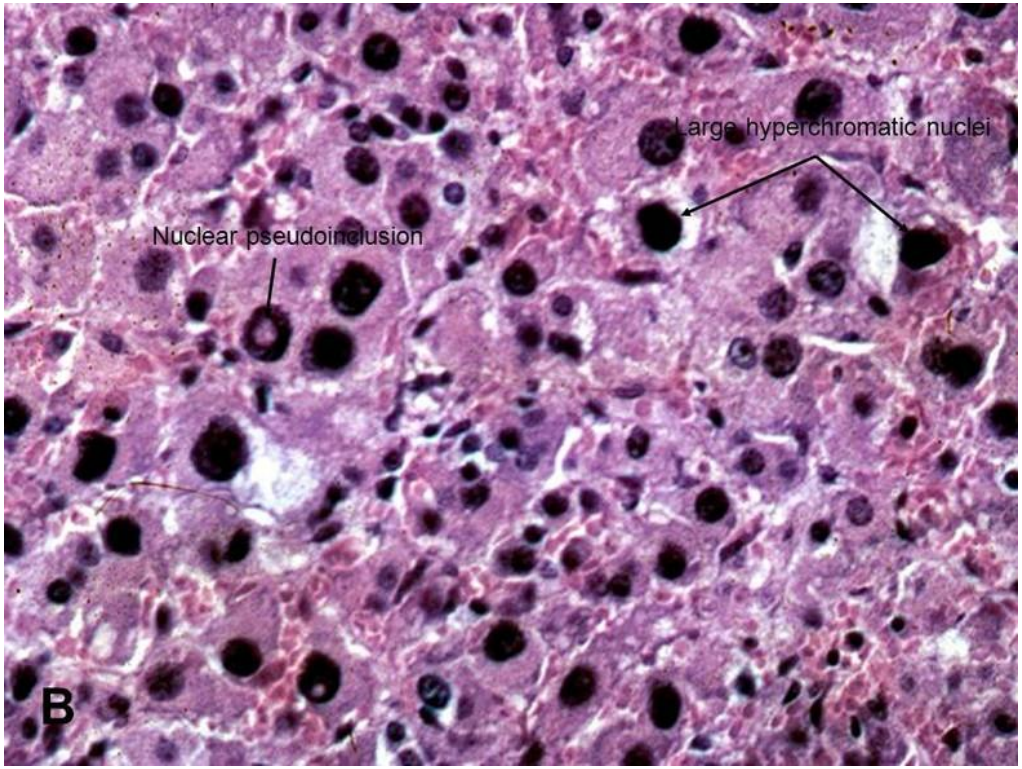


Variation in size and shape. High nuclear to cytoplasmic ratio



Hyperchromatism

Hyperchromatism may be seen in regenerative processes as well



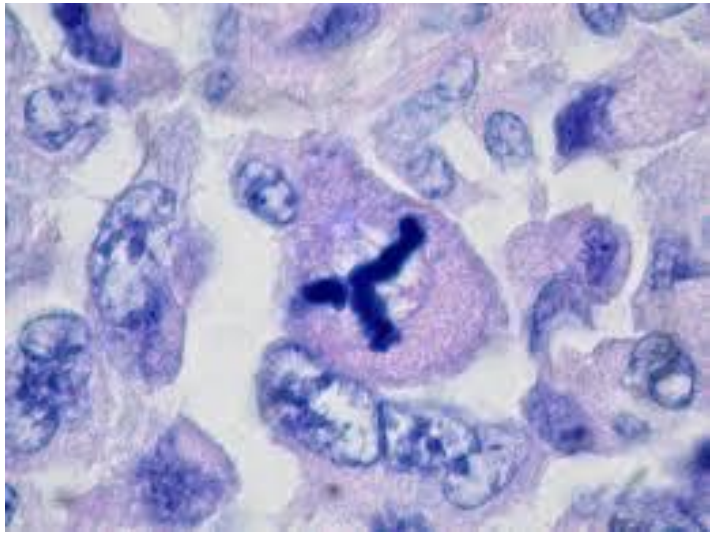
Chromosomal changes

- Chromosomal changes that can be identified microscopically include two mutually exclusive patterns:
- Multiple small extrachromosomal structures called double minutes
- Homogeneous staining regions.
- These derive from the insertion of amplified genes into new chromosomal locations, which may be distant from the normal location of the involved oncogene.
- The affected chromosomal regions lack a normal pattern of light and dark-staining bands

Mitoses

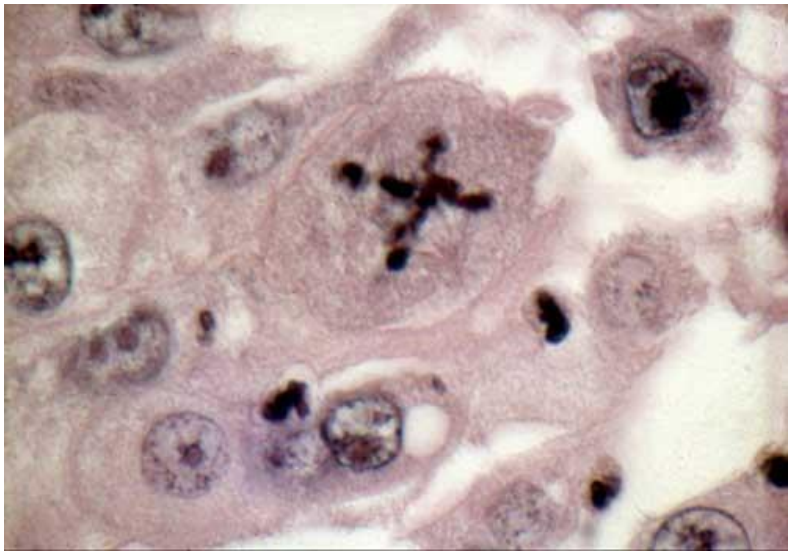
- Mitoses are indicative of proliferation
- Atypical, bizarre mitotic figures, sometimes with tripolar, quadripolar, or multipolar spindles are important morphologic features of malignancy
- Loss of polarity
- In addition to the cytologic abnormalities, the orientation of anaplastic cells is markedly disturbed. Sheets or large masses of tumor cells grow in an anarchic, disorganized fashion.

Mitoses

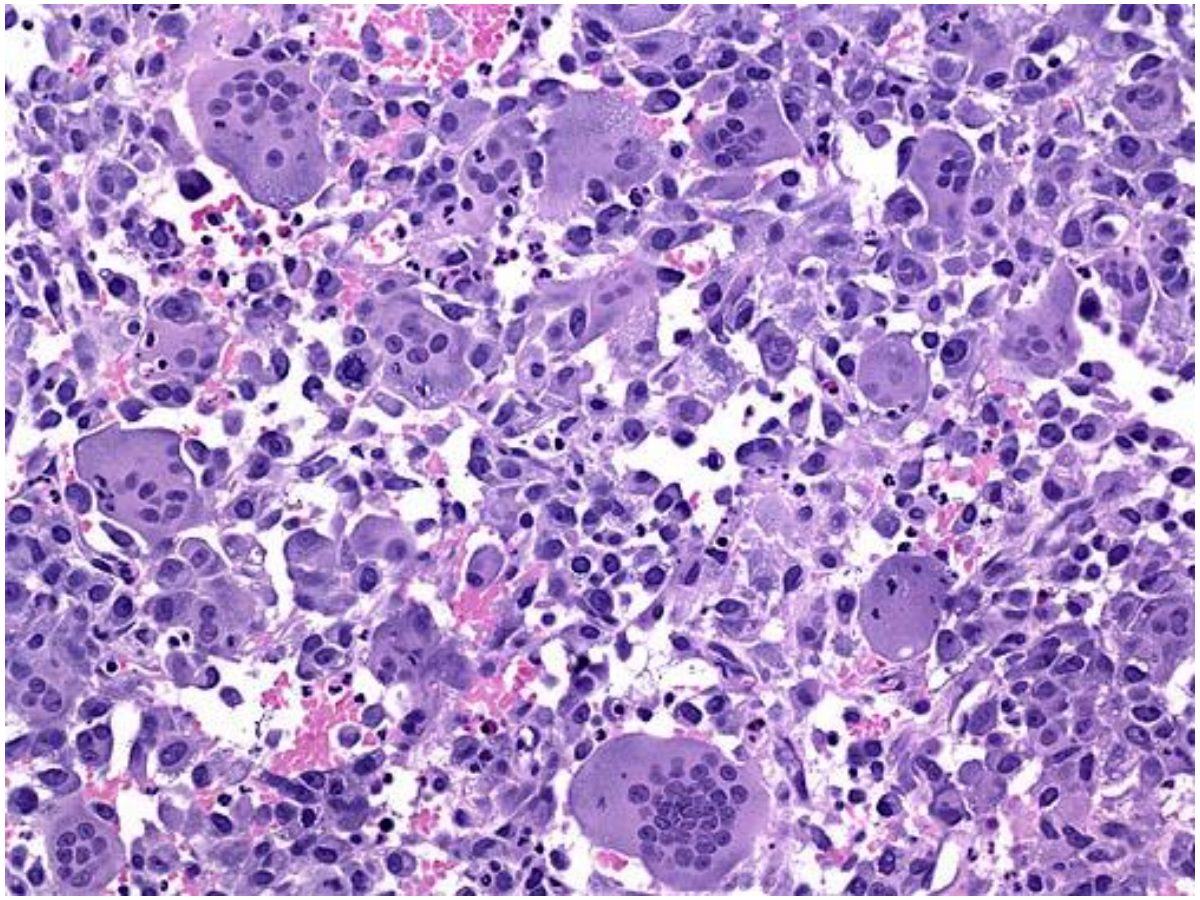


Above: tripolar mitosis

At right: quadripolar mitosis



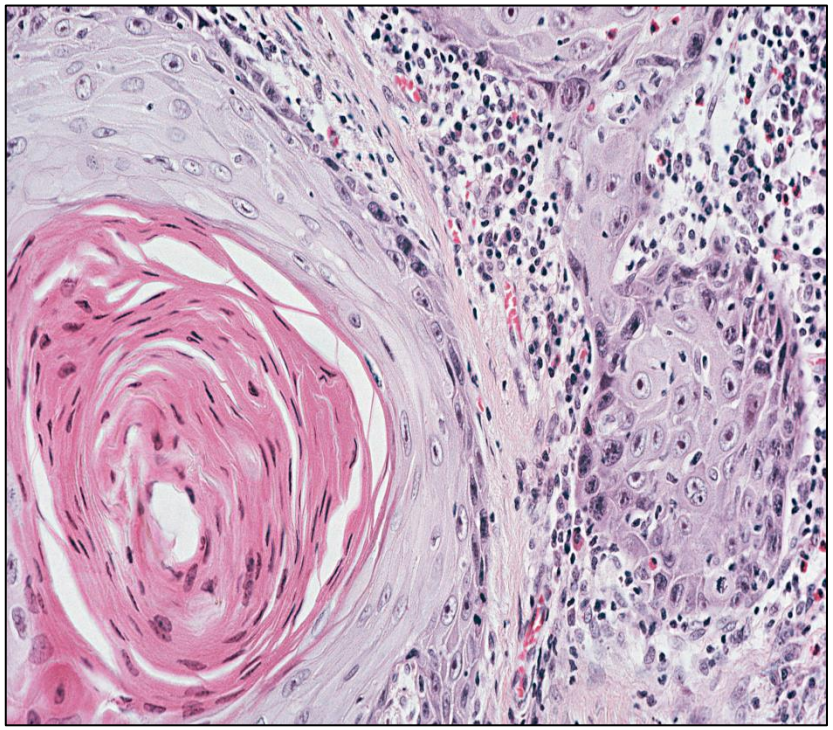
Tumor giant cells



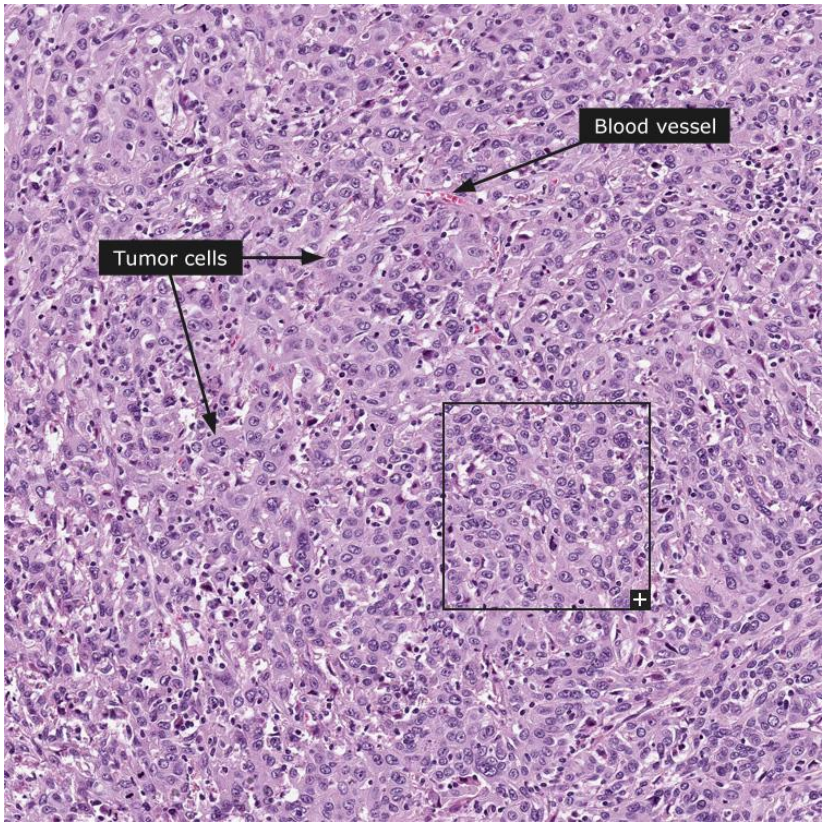
Giant cell tumor of bone.

These are not malignant osteoclasts.

Spectrum of differentiation

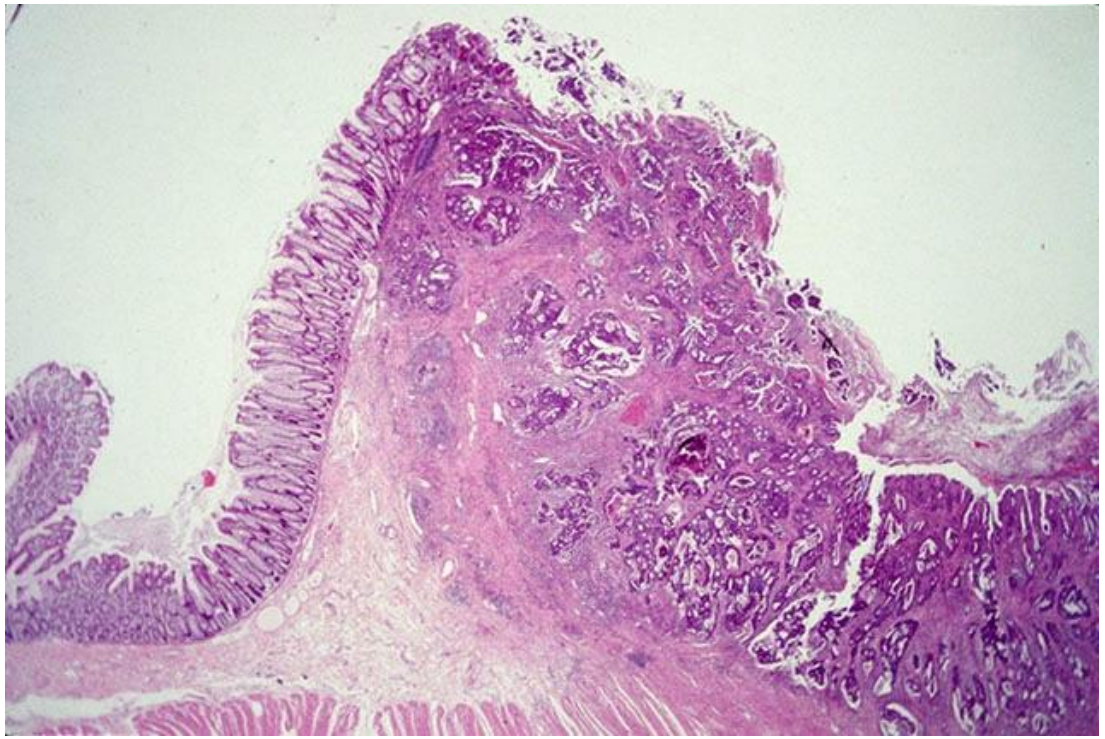


Left: Well-differentiated squamous cell carcinoma. Note keratinization and a squamous pearl.



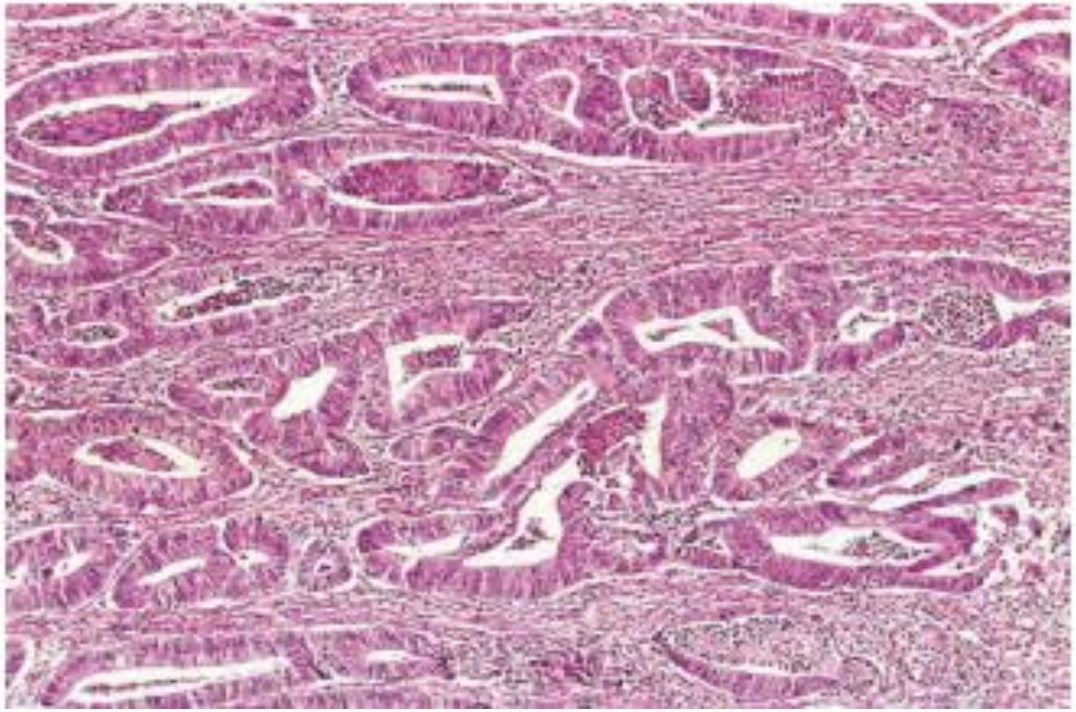
Right: Poorly-differentiated squamous cell carcinoma. Loss of organ outline. No evidence of keratinization.

Well differentiated adenocarcinoma



Compared with the well-formed and normal-looking glands characteristic of a benign tumor, the cancerous glands are irregular in shape and size and do not resemble the normal colonic glands.

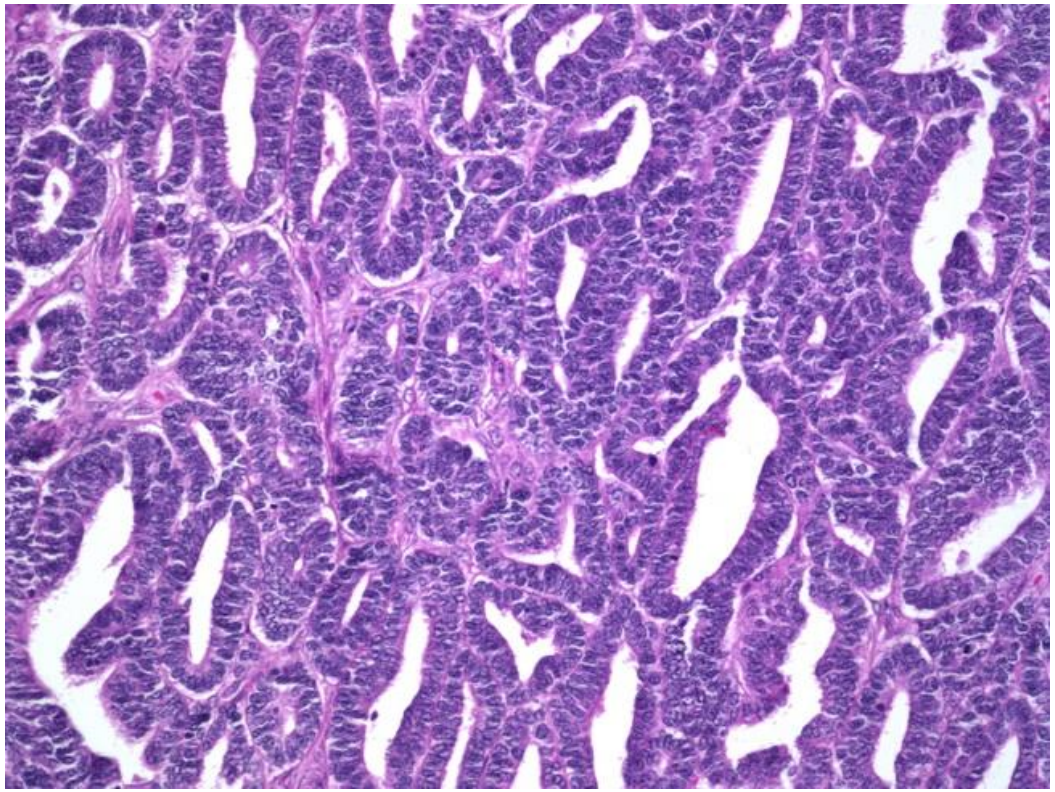
Well differentiated adenocarcinoma



This tumor is considered differentiated because gland formation is seen. The malignant glands have invaded the muscular layer of the colon.

(Courtesy Dr. Trace Worrell,University of Texas Southwestern Medical School, Dallas, Texas.) Figure 7-6

Well differentiated adenocarcinoma



This tumor endometrial adenocarcinoma is considered differentiated because gland formation is seen.

Poorly differentiated rhabdomyosarcoma

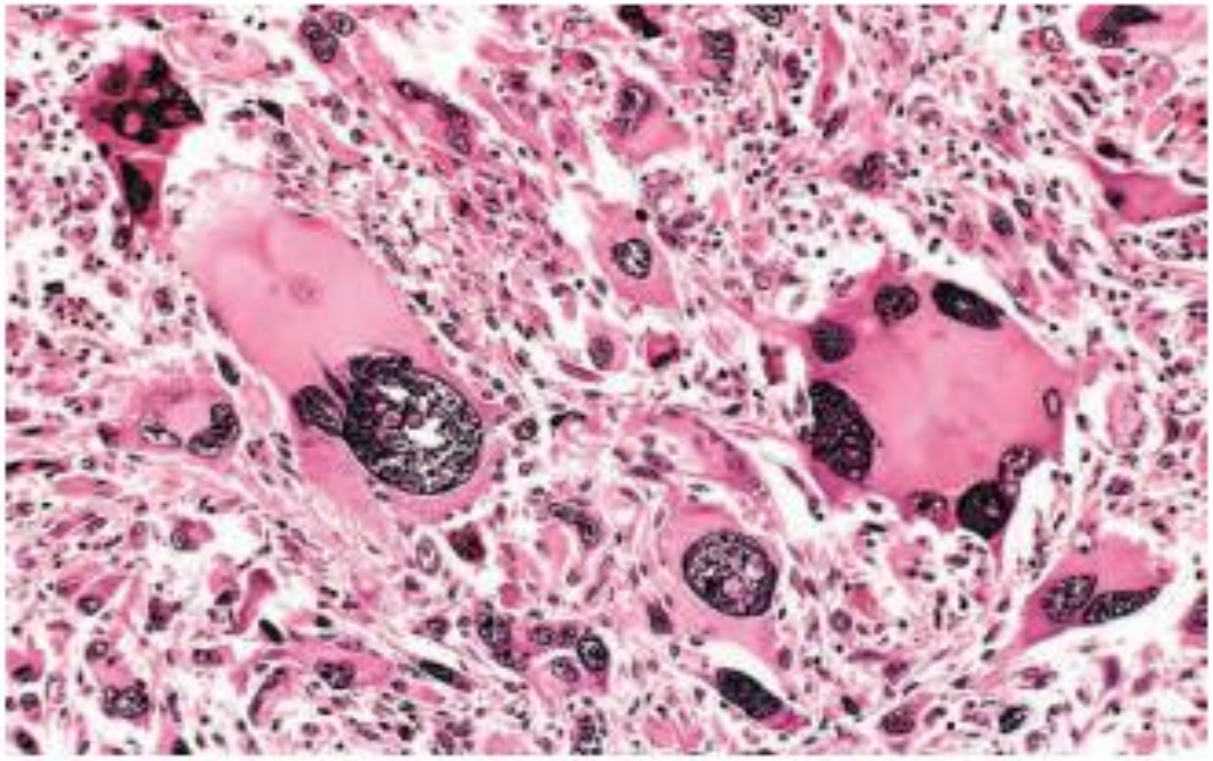
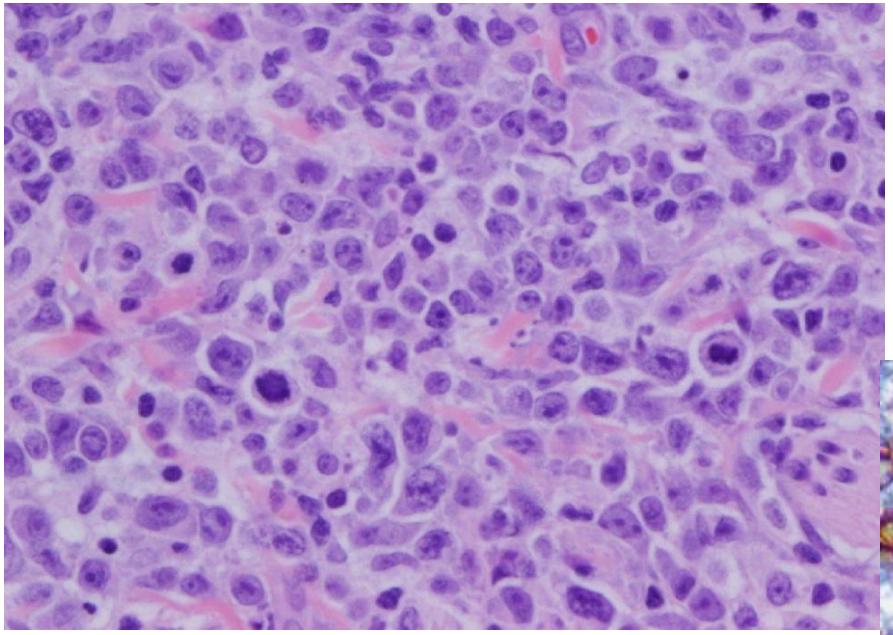
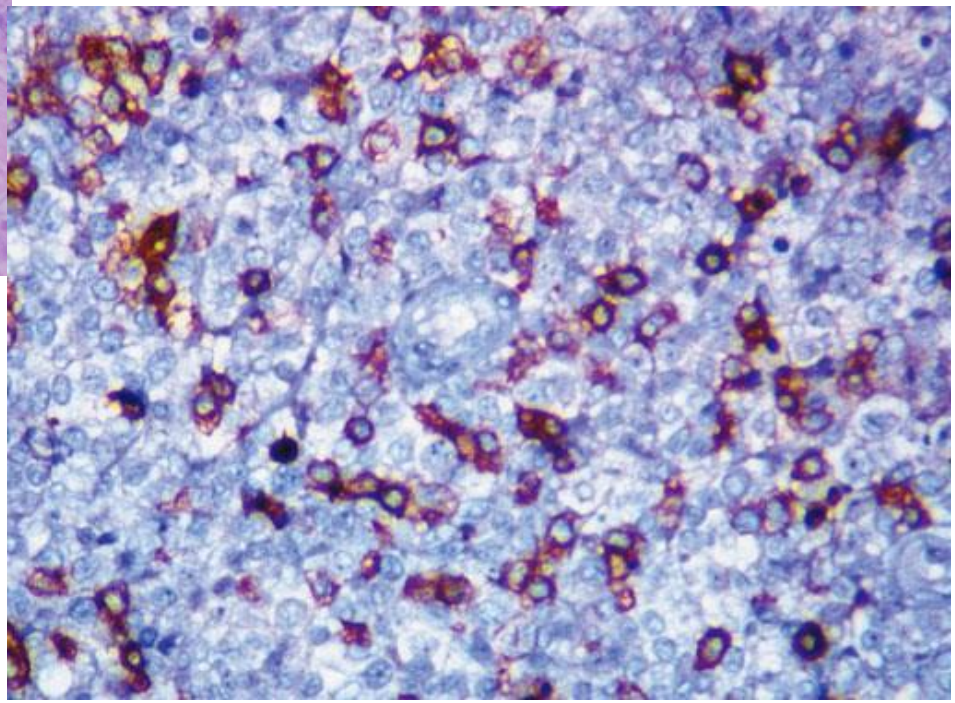


Figure 7-9 Pleomorphic tumor of the skeletal muscle (rhabdomyosarcoma). Note the marked cellular and nuclear pleomorphism, hyperchromatic nuclei, and tumor giant cells. (Courtesy Dr. Trace Worrell, University of Texas Southwestern Medical School, Dallas, Texas.)

Anaplasia or lymphoma



H & E staining of tumor showing anaplastic features



Same tumor stained with CD 30 proves it to be a lymphoma, not an anaplastic carcinoma

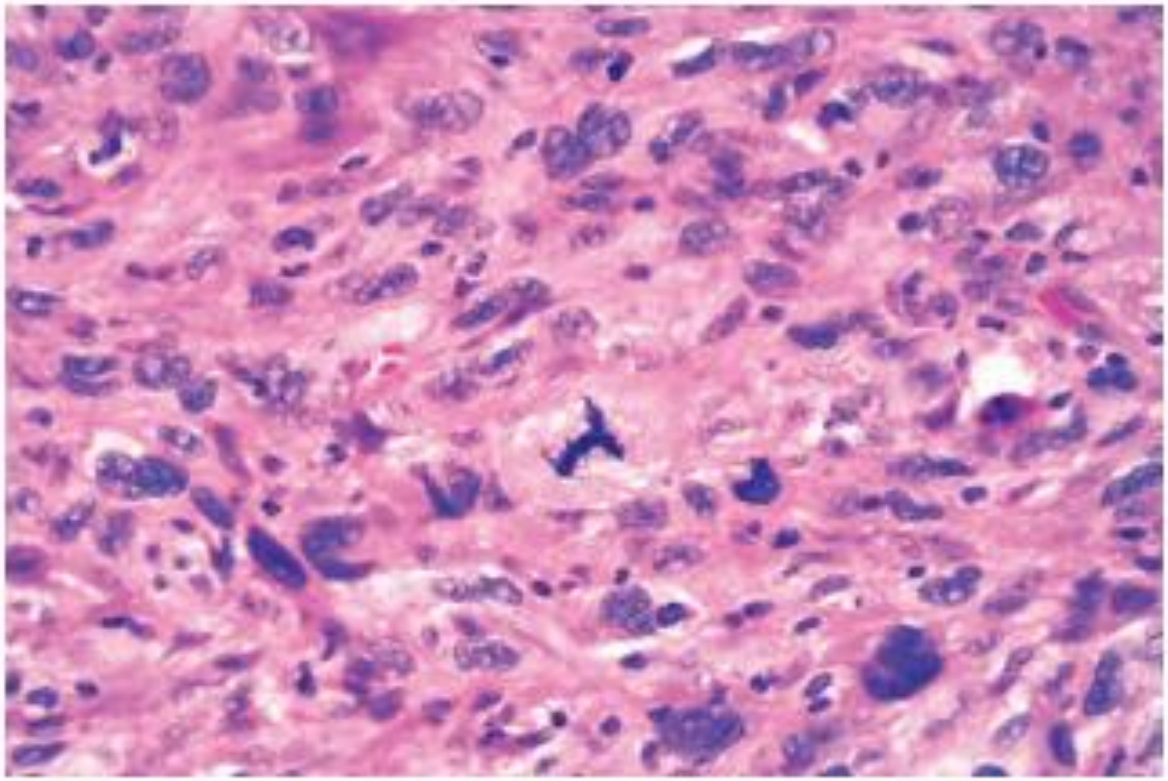


Figure 7-8 Anaplastic tumor showing cellular and nuclear variation in size and shape. The prominent cell in the center field has an abnormal tripolar spindle.

What constitutes invasion

- Benign tumors grow as cohesive expansile masses that remain localized to their site of origin and lack the capacity to infiltrate, invade, or metastasize to distant sites.
- The tumor has not penetrated the basement membrane nor has it entered lymphatics or venules.
- Frequently the benign lesions are encapsulated

Encapsulated lesion

Figure 7-11 Fibroadenoma of the breast. The tan-colored, encapsulated small tumor is sharply demarcated from the whiter breast tissue.

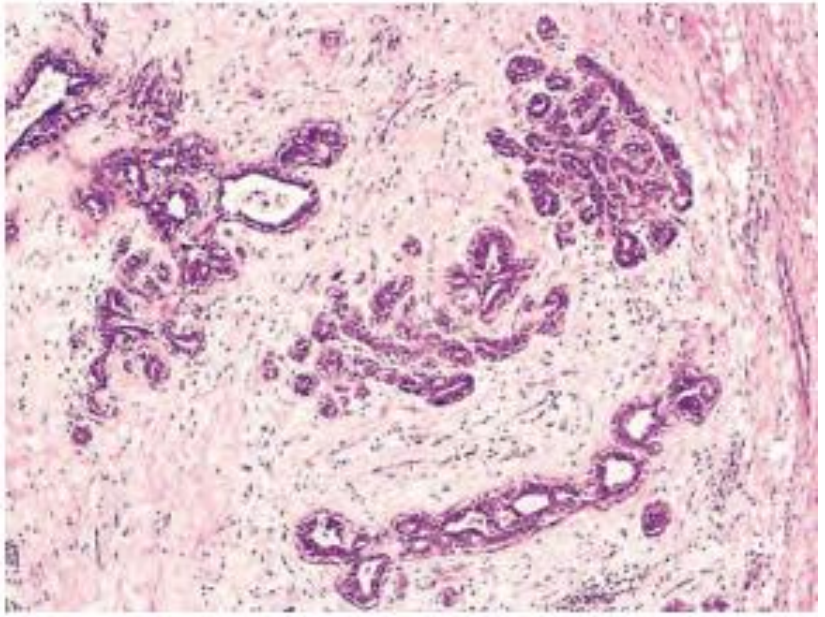
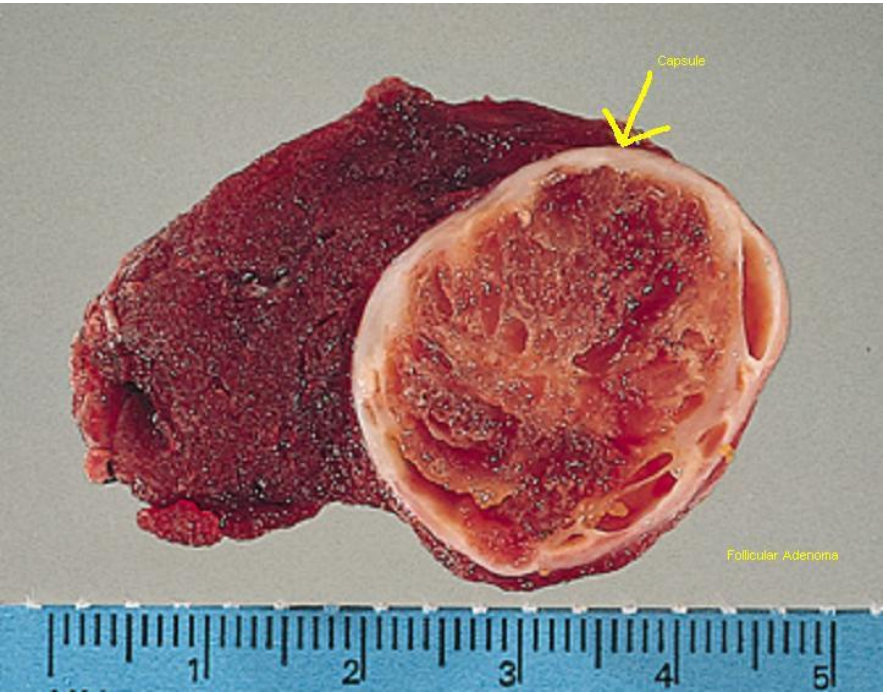


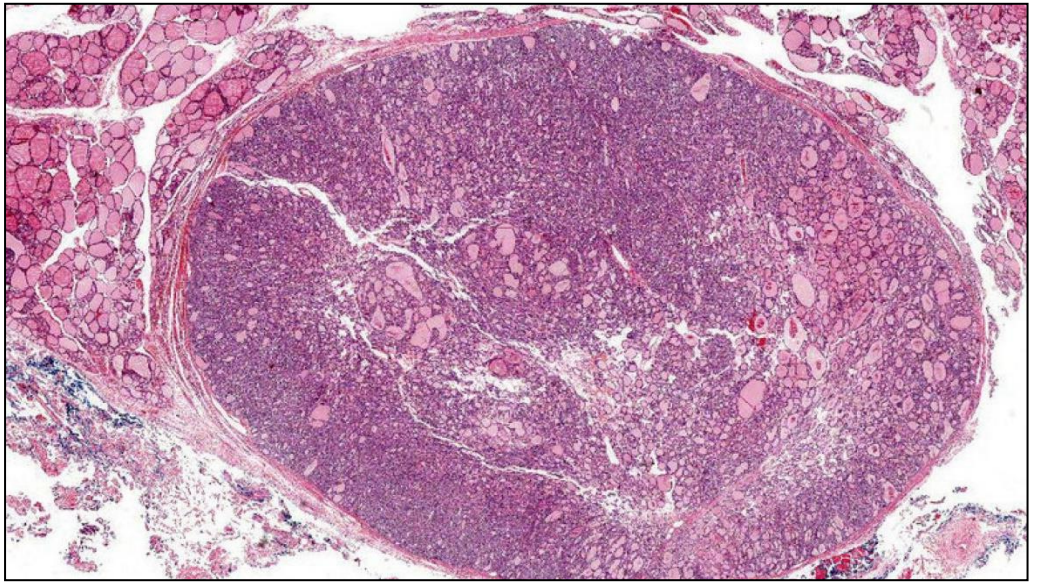
Figure 7-12 Microscopic view of fibroadenoma of the breast

The fibrous capsule (right) delimits the tumor from the surrounding tissue.

(Courtesy Dr. Trace Worrell, University of Texas Southwestern Medical School, Dallas, Texas.)



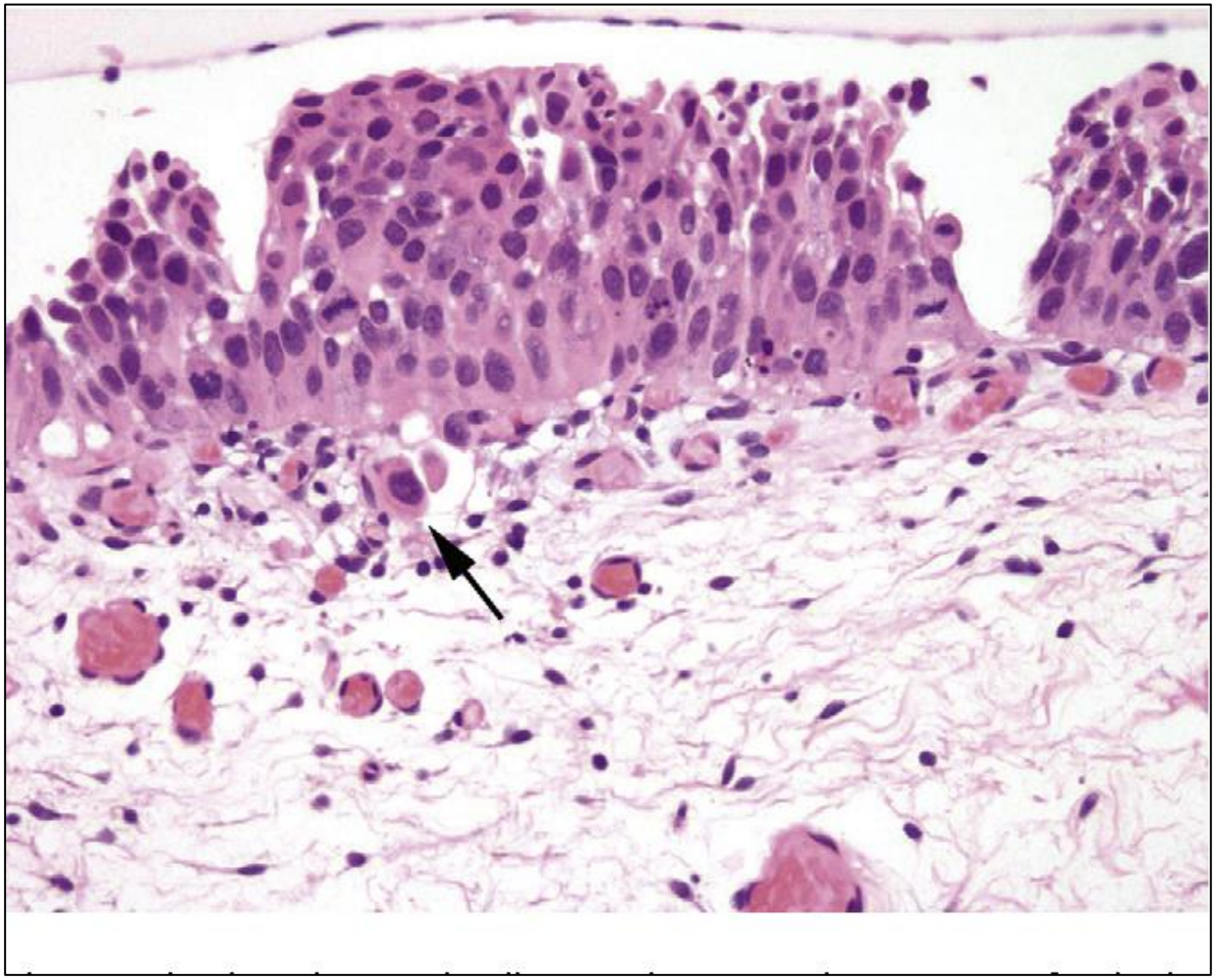
Follicular Adenoma Thyroid
Left: Well demarcated nodule (arrow)
Below: A capsule separates the adenoma from adjacent thyroid tissue. Colloid containing thyroid follicles are within the adenoma. There is no invasion into the surrounding normal thyroid. Both morphology and function are maintained



Local invasion

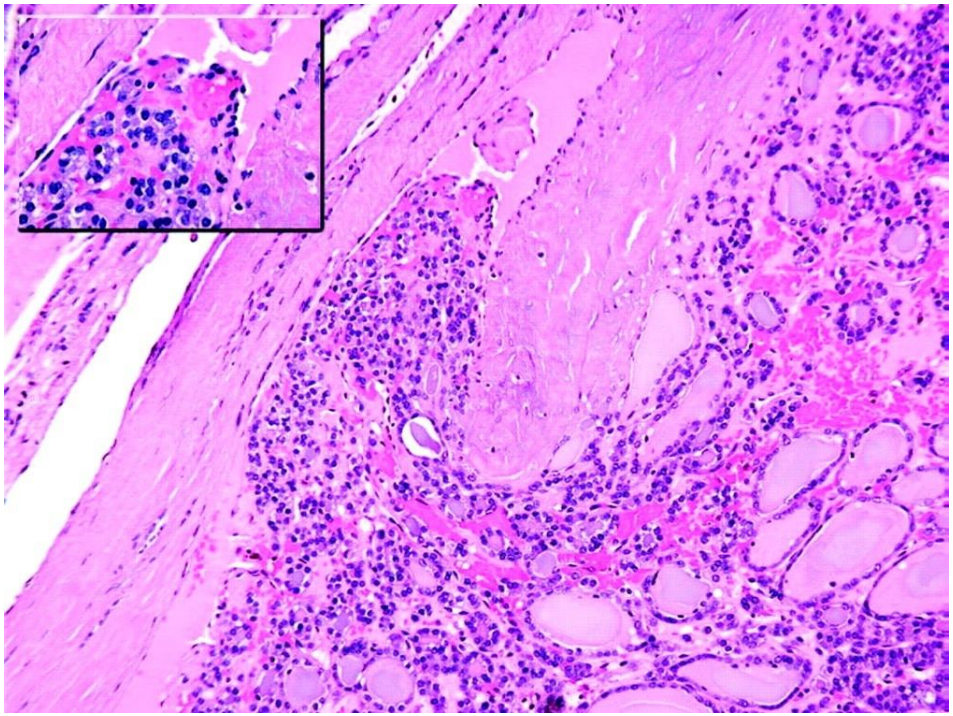
- The growth of cancers is accompanied by progressive infiltration, invasion, and destruction of the surrounding tissue
- Malignant lesions lack capsules and are poorly demarcated from surrounding tissues
- Invasion differentiates benign from malignant lesions

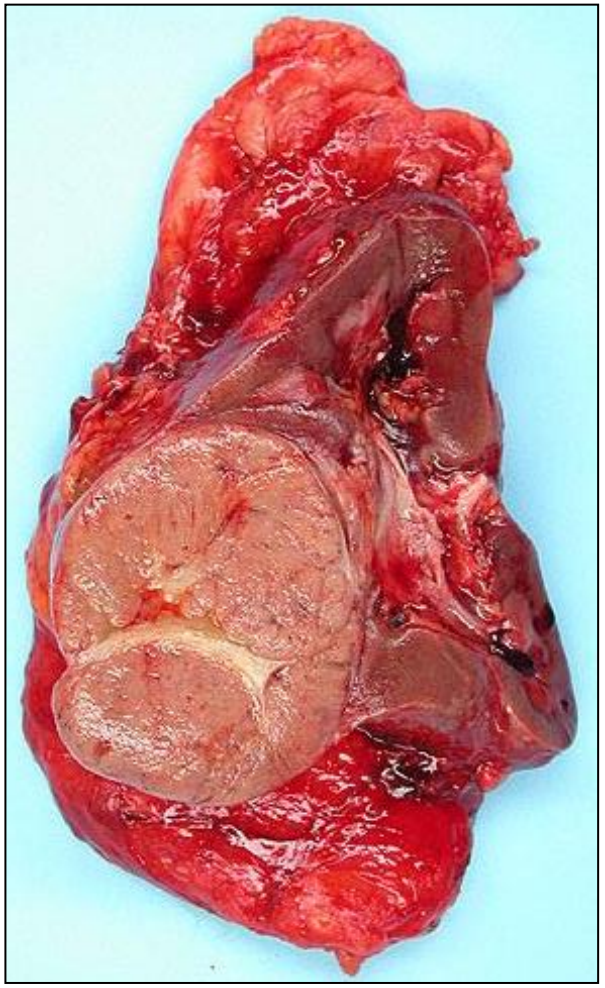
Local invasion



The arrow points to an area of basement membrane loss with invasion from the overlying carcinoma in situ

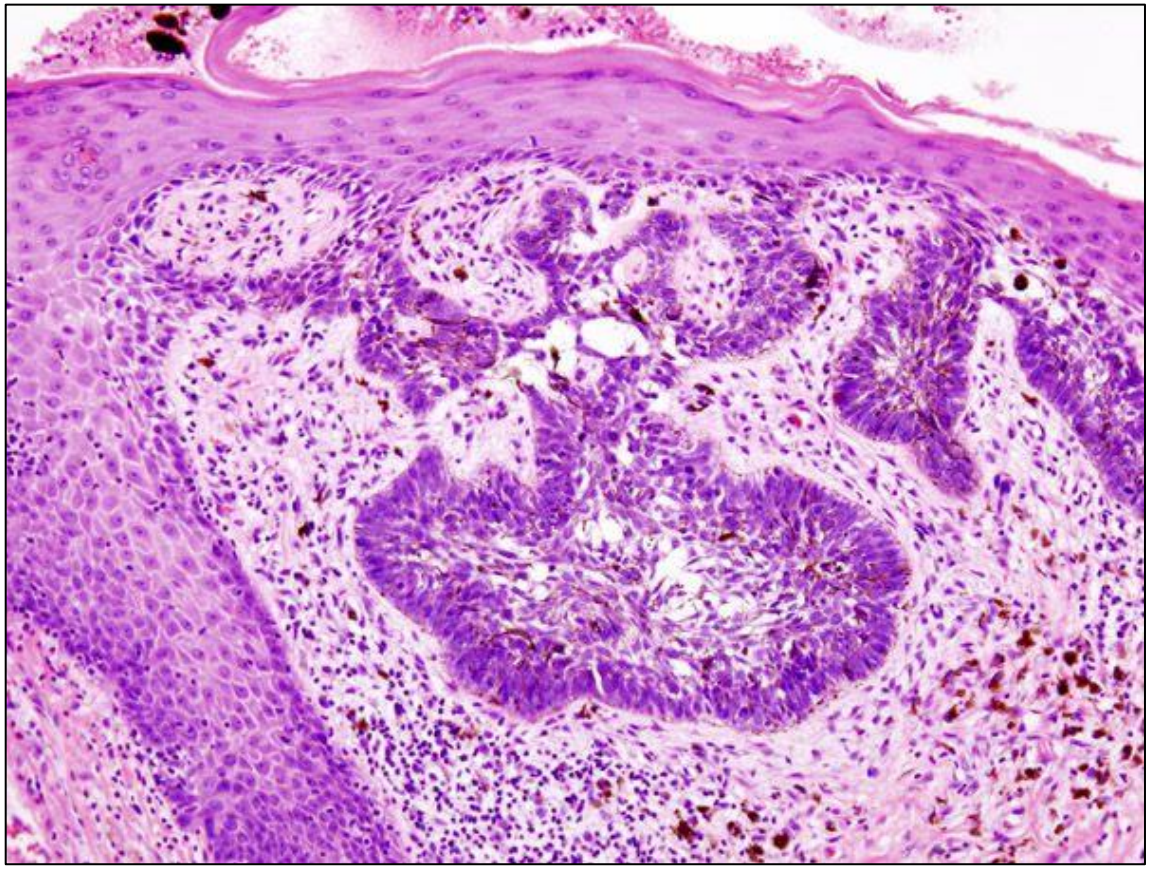
Well demarcated thyroid lesion at left.
Below is the microscopic picture of the lesion. There is a focus of well-differentiated carcinoma that has extended beyond the capsule and into a venule.





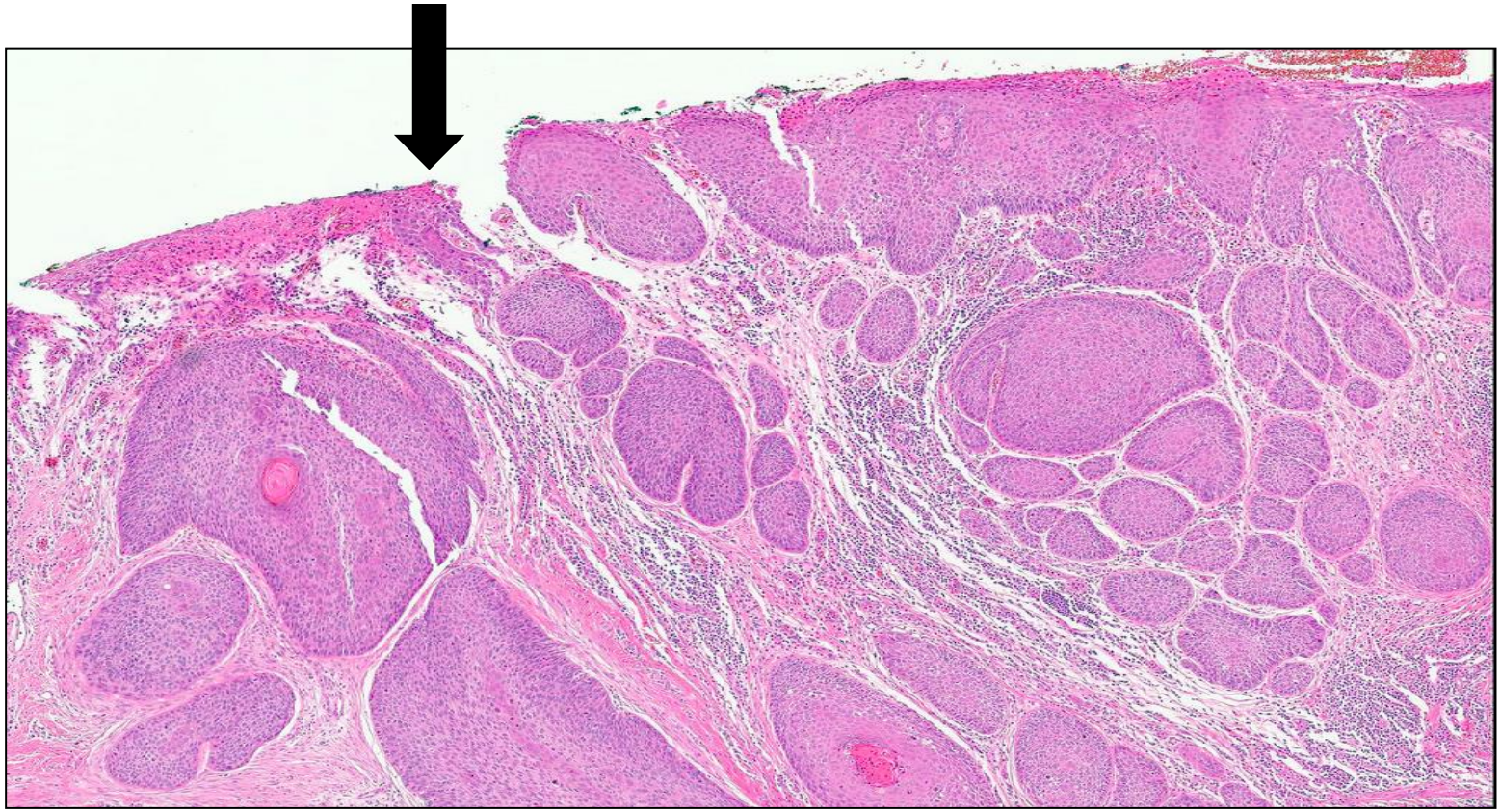
Renal Cell Carcinoma commonly presents with a pseudocapsule and a pushing margin. That it is a psuedocapsule is determined microscopically when tumor is found extending into surrounding tissue.

Local invasion



Basal cell carcinoma. There is downward proliferation of the epithelium. Cells are in palisade around the tumor.

Local invasion



Carcinoma of the cervix. Arrow points to transition between endocervix and ectocervix.

Comedo carcinoma

Nipple discharge

Discharge of cellular debris. May be bloody. Associated with underlying intraductal carcinoma in situ. The central core in the intraductal carcinoma above is the comedo.

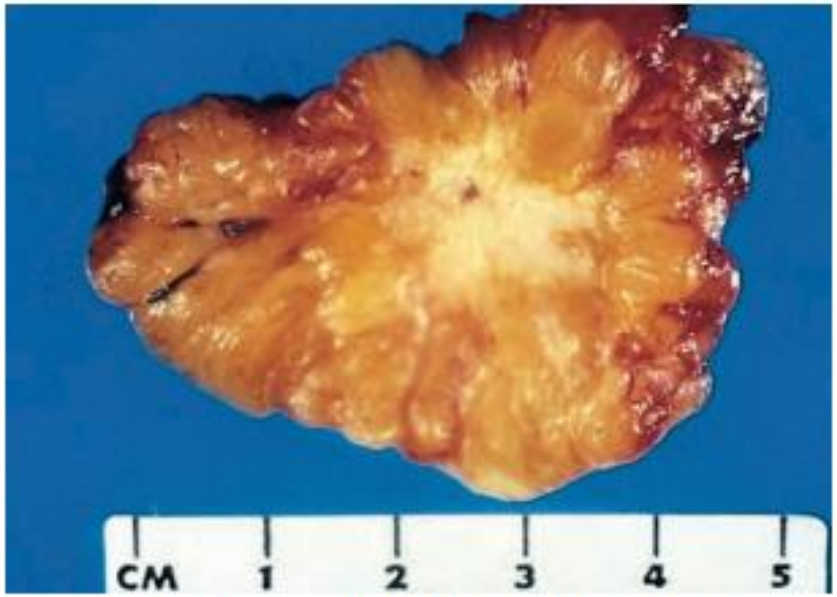


Figure 7-13 Cut section of an invasive ductal carcinoma of the breast. The lesion is retracted, infiltrating the surrounding breast substance, and would be stony hard on palpation. (Courtesy Dr. Trace Worrell, University of Texas Southwestern Medical School, Dallas, Texas.)

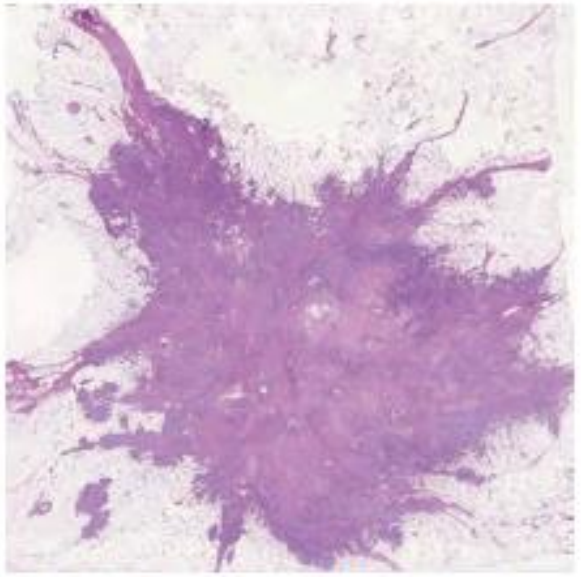
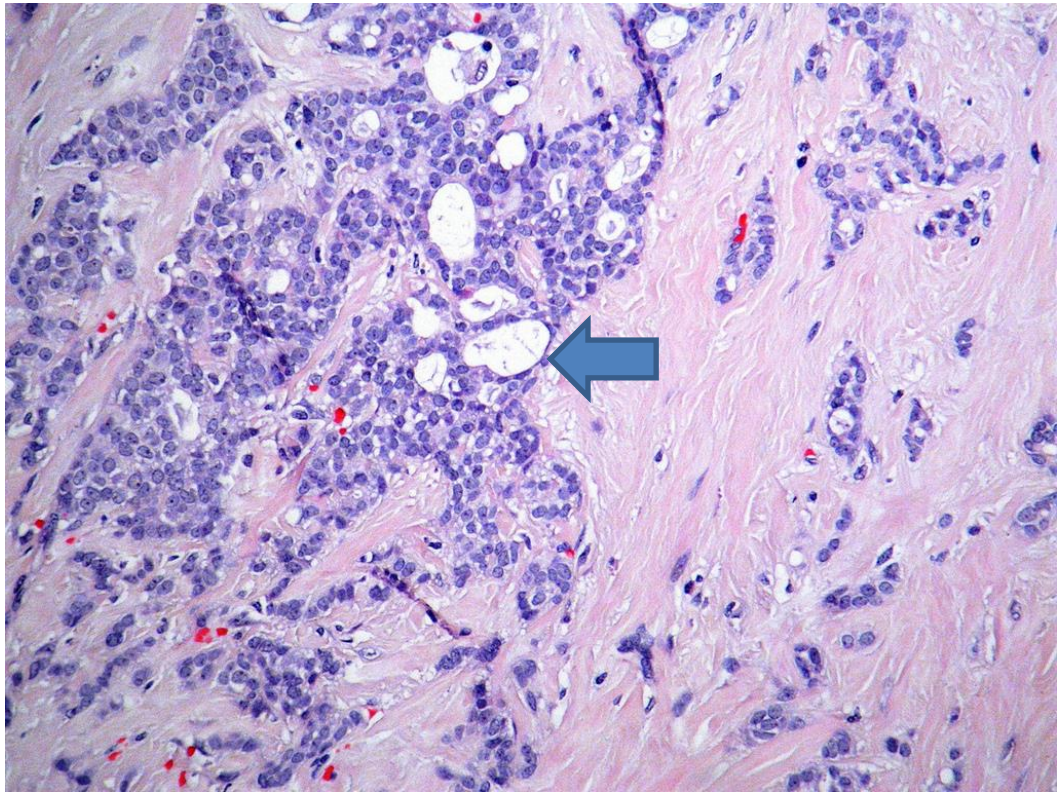
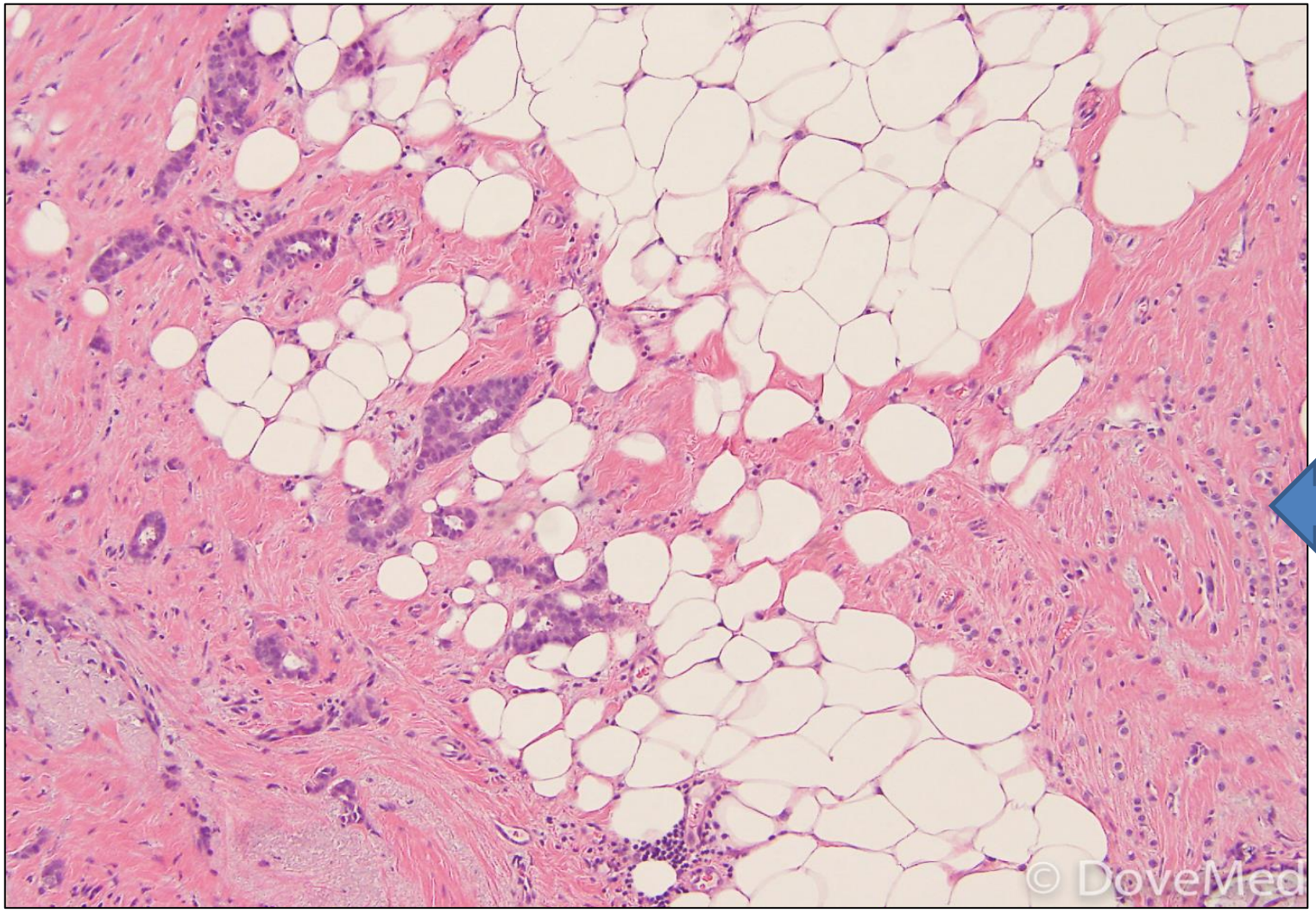


Figure 7-14 Low power microscopic view of invasive breast cancer. Note the irregular infiltrative borders without a well-defined capsule and intense stromal reaction. (Courtesy Dr. Susan Lester, Brigham and Women's Hospital, Boston, Mass.)

Local invasion



Ductal carcinoma of the breast demonstrating cribiform change (arrow) and extension into surrounding (reactive) fibrous tissue.
Cribiform change refers to the “Roman bridge” pattern of proliferation within the duct.



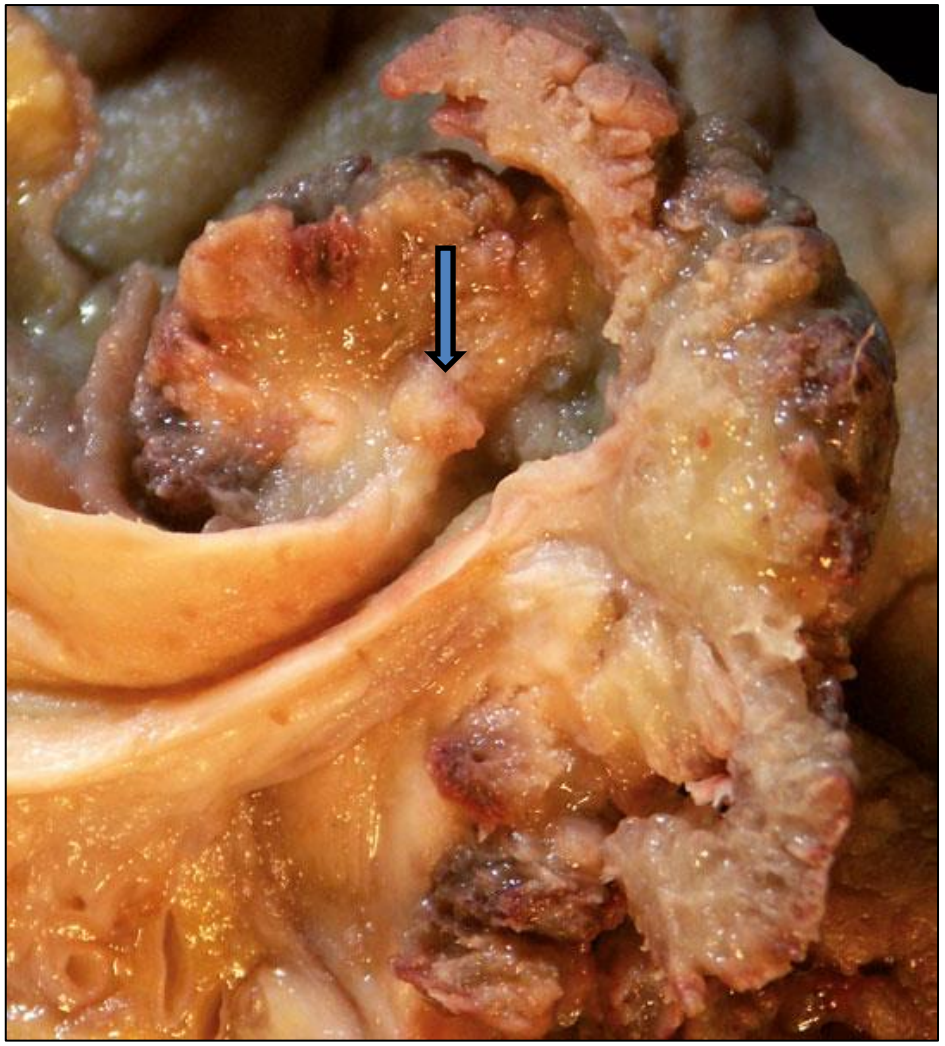
Invasive ductal carcinoma (as single cells in file). The well formed glands are not carcinomatous.

Local invasion

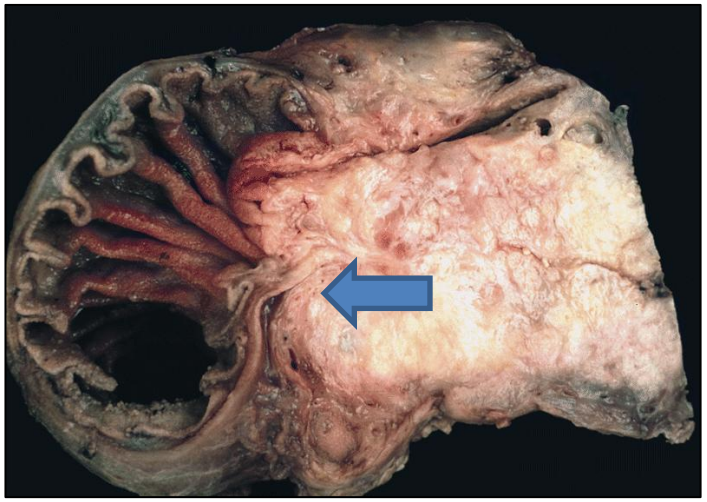
At the upper left is the uterus. To the right is the urinary bladder.

The tumor in the urinary bladder has penetrated the wall and has invaded the vagina.

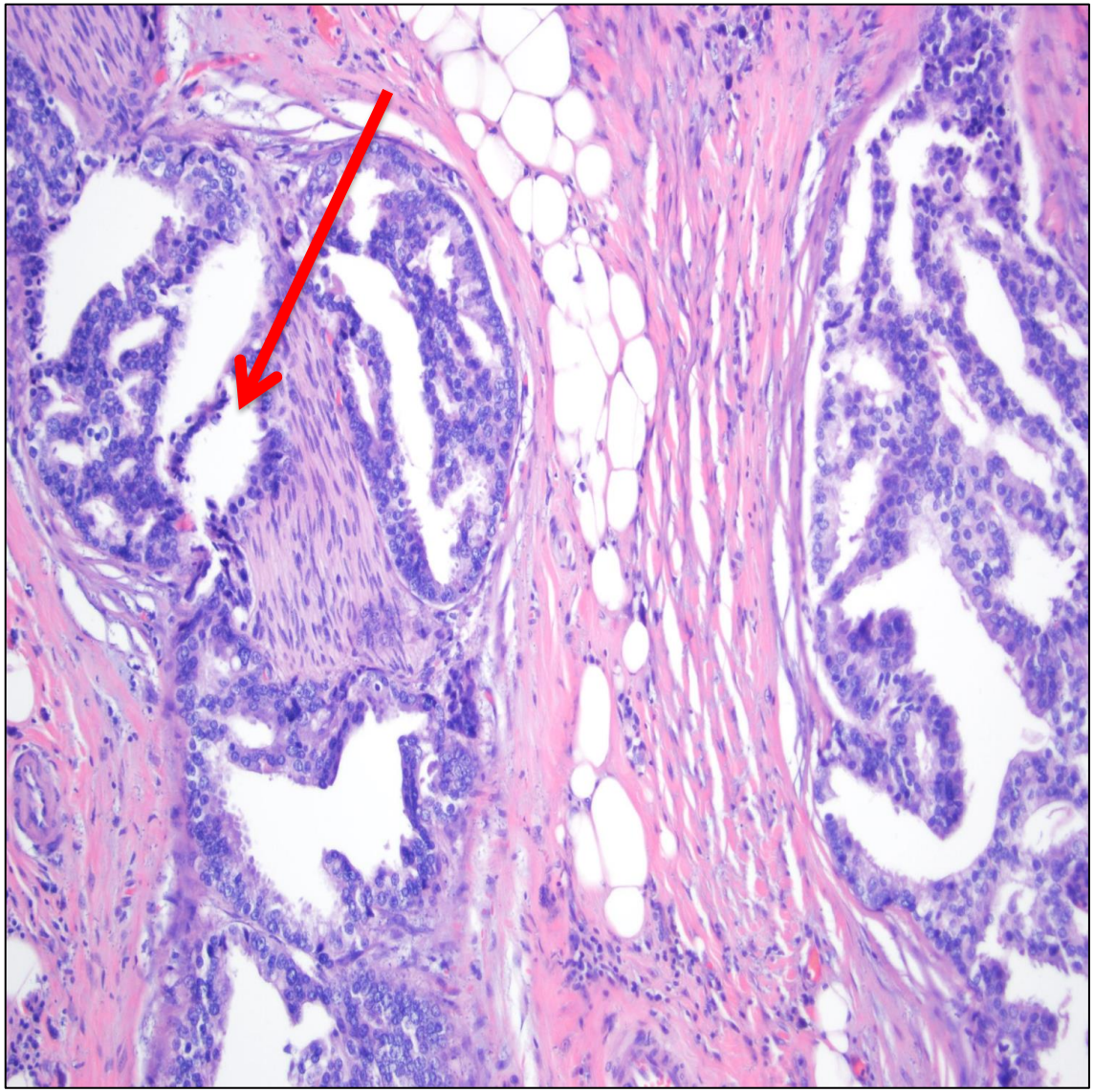
Local invasion



Adenocarcinoma of the head of the pancreas which has penetrated the wall of the duct (arrow). The outlet is obstructed (arrowhead).



Local invasion



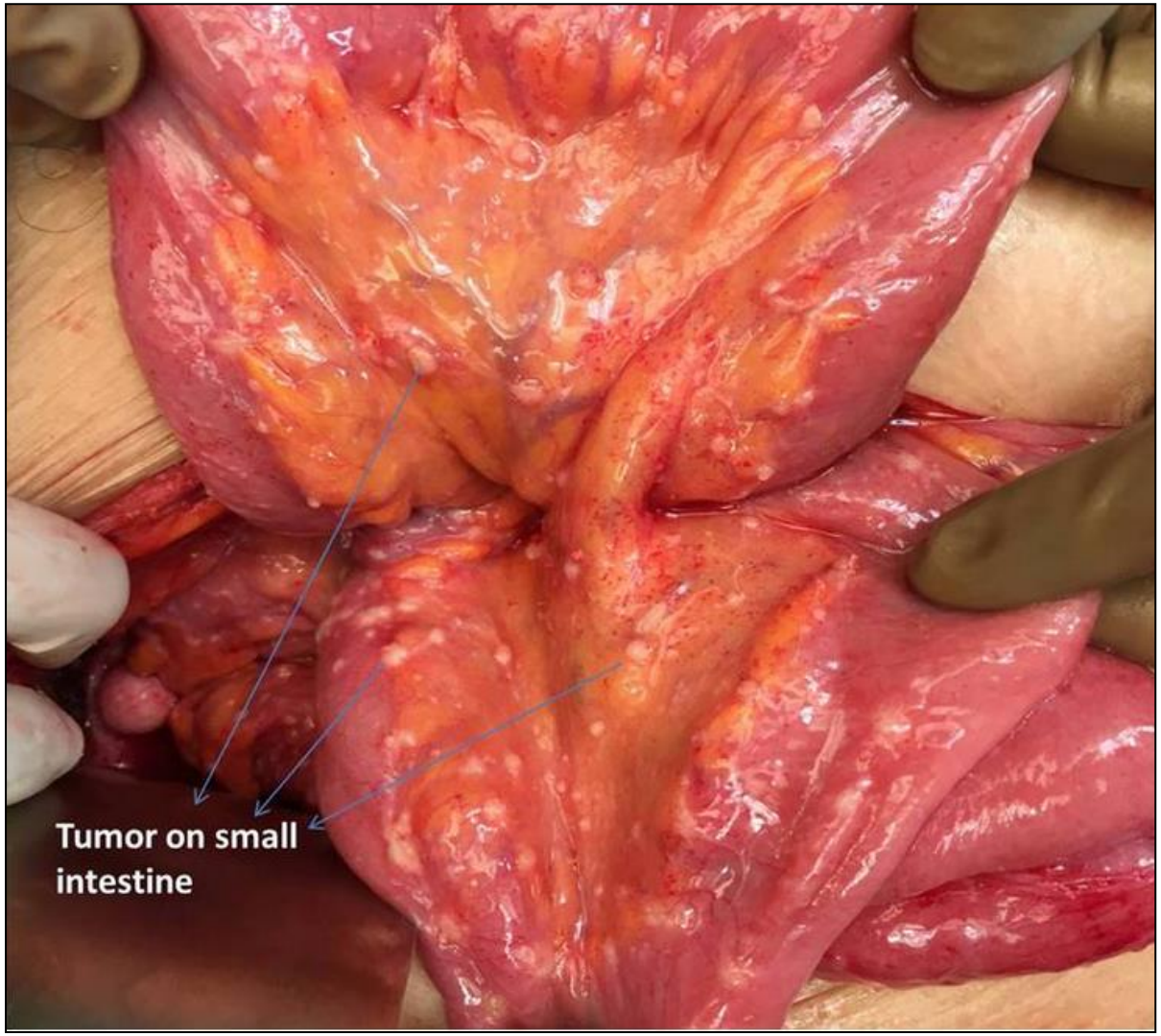
Adenocarcinoma of the prostate. Nerve invasion (arrow). Tumor is present in the nerve sheath.

Metastasis

- Metastasis is defined by the spread of a tumor to sites that are physically discontinuous with the primary tumor
- Benign neoplasms do not metastasize.
- The invasiveness of cancers permits them to penetrate into blood vessels, lymphatics, and body cavities, providing the opportunity for spread.
- Transport through lymphatics is the most common pathway for the initial dissemination of carcinomas
- Sarcomas principally spread by a hematogenous route (usually venous invasion).

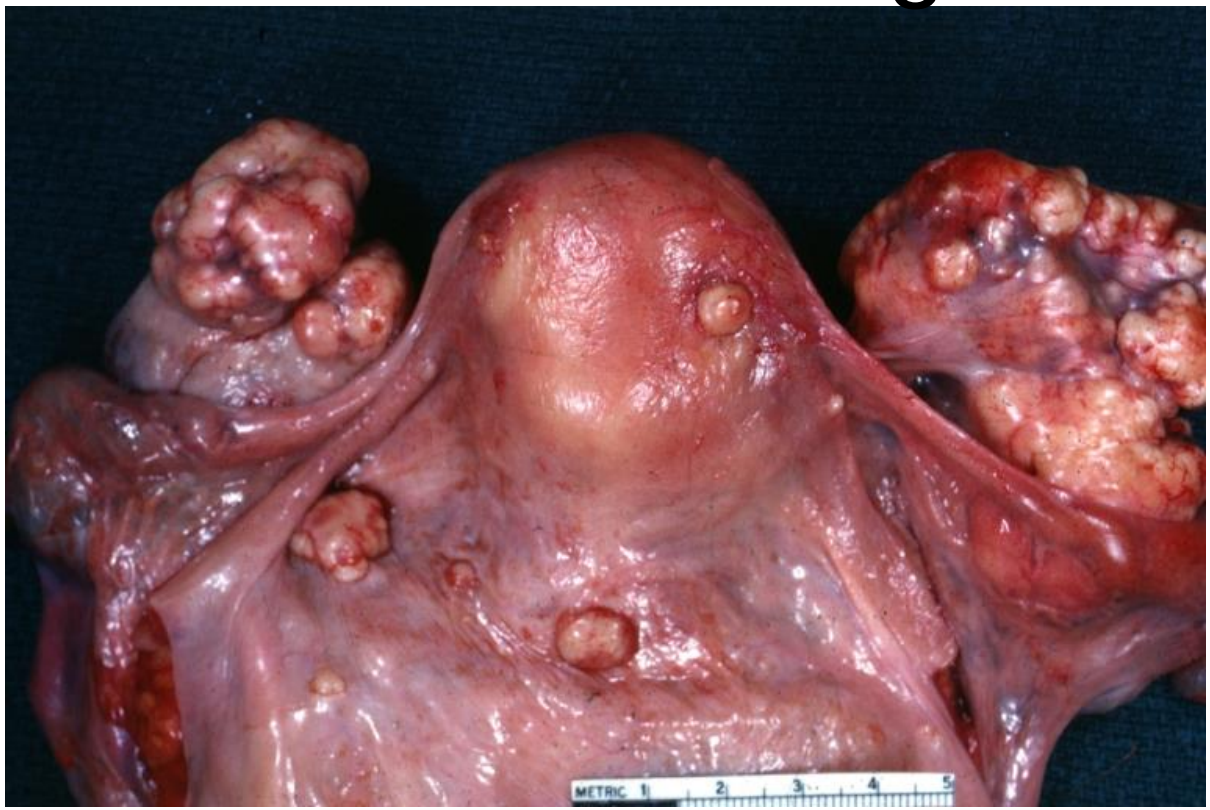
Metastasis

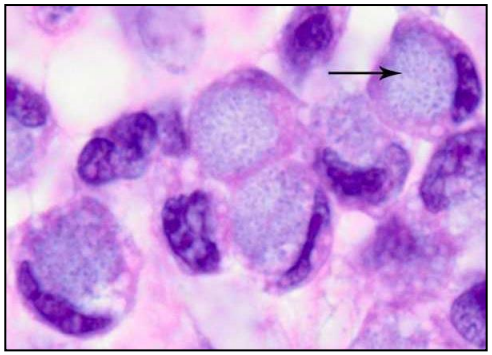
- Seeding of Body Cavities and Surfaces.
- No barriers to spread
- Epithelial ovarian carcinomas frequently spread to the peritoneal cavity, studding the surface with tumor
- Mucus-secreting appendiceal carcinomas or ovarian carcinomas may fill the peritoneal cavity with a gelatinous neoplastic mass referred to as pseudomyxoma peritonei.



Peritoneal spread

Krukenberg tumor





Retrograde lymphatic spread of mucin producing gastric carcinoma in peritoneal cavity. Nodules on surface of ovaries.
At right are signet ring cells characteristic of gastric adenocarcinoma.
Lobular carcinoma of the breast may also metastasize in the same fashion.

Metastasis

- Transport through lymphatics is the most common pathway for the initial dissemination of carcinomas.
- Sarcomas may also use this route.
- Tumors do not contain functional lymphatics, but lymphatic vessels located at the tumor margins are apparently sufficient for the lymphatic spread of tumor cells.
- The pattern of lymphatic spread follows the normal lymphatic drainage of the organ.

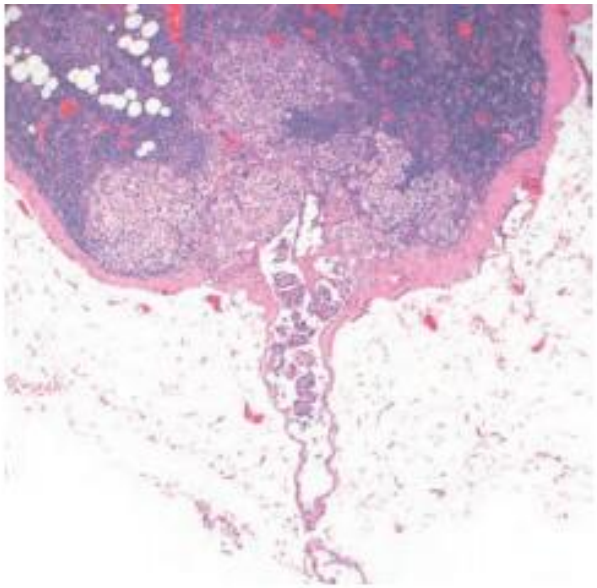
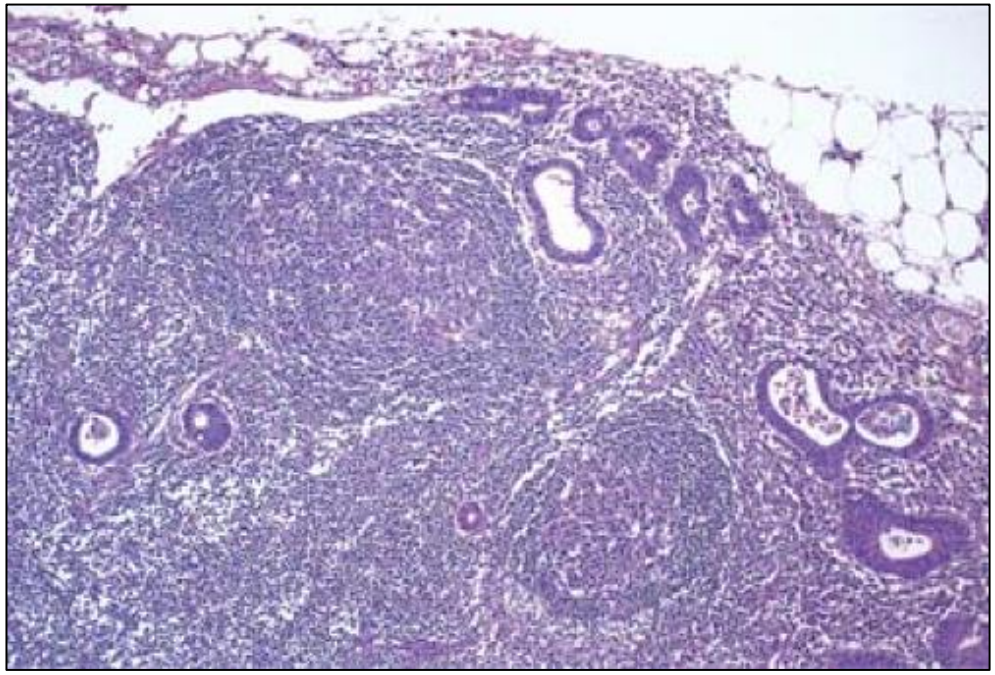


Figure 7-16 Axillary lymph node with metastatic breast carcinoma. Note the aggregates of tumor cells within the substance of the node and the dilated lymphatic channel. (Courtesy Dr. Susan Lester, Brigham and Women's Hospital, Boston, Mass.)

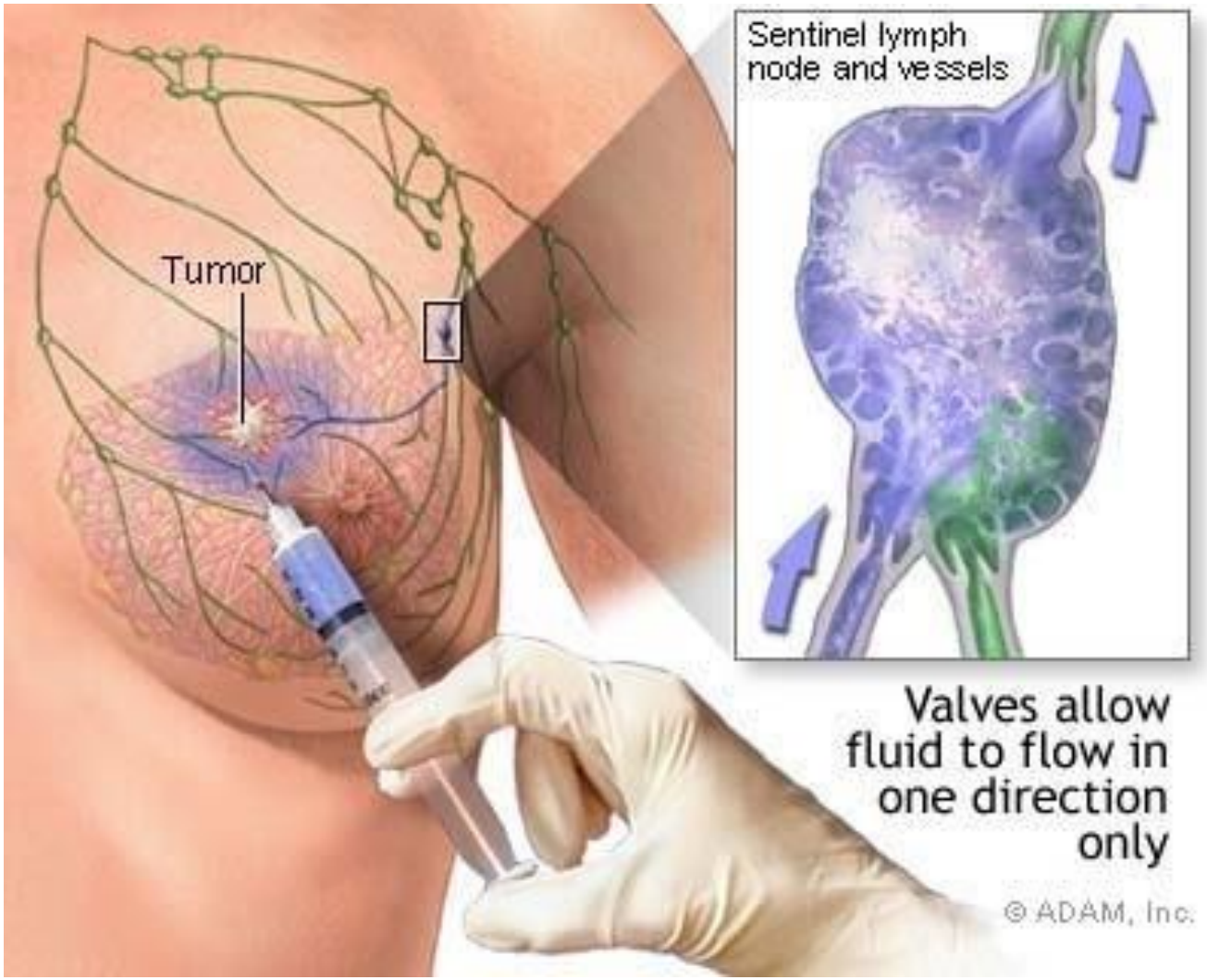


Metastasis

- Because carcinomas of the breast usually arise in the upper outer quadrants, they generally disseminate first to the axillary lymph nodes.
- Cancers of the inner quadrants drain to the nodes along the internal mammary arteries.
- Thereafter, the infraclavicular and supraclavicular nodes may become involved.

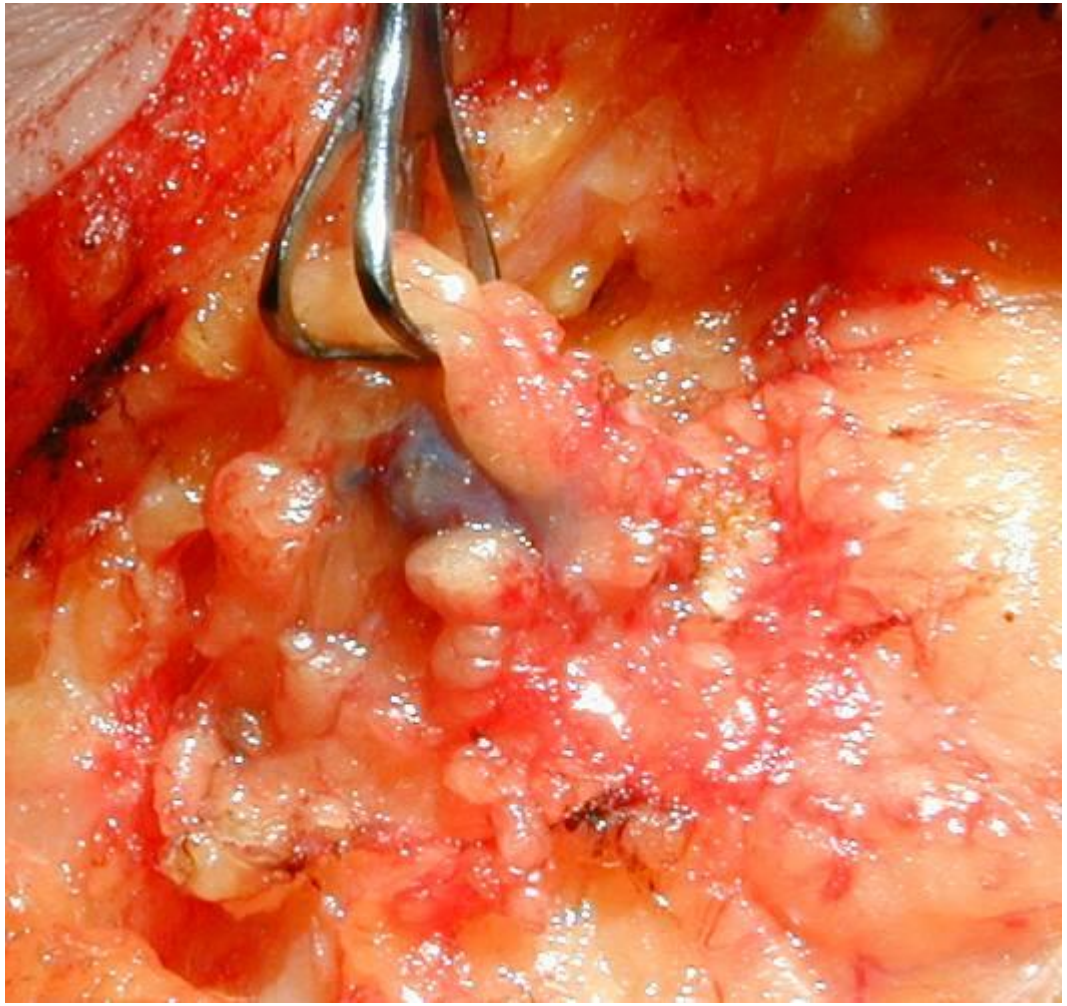
Metastasis

- To avoid the considerable surgical morbidity associated with dissection of a regional lymph node basin, biopsy of a sentinel node is often used to assess the presence or absence of metastatic lesions in the lymph nodes.
- A sentinel lymph node is defined as “the first node in a regional lymphatic basin that receives lymph flow from the primary tumor.”
- This is usually employed for staging in breast and colon cancers as well as melanoma.
- Dye or radioisotope is injected and the involved node is identified at surgery.



99m-Technetium is injected in the tumor and allowed to spread. Prior to surgery a blue dye is also injected. The sentinel node(s) are identified by radioactivity and blue color.

Sentinel node



Metastasis

- Carcinomas of the lung arising in the major respiratory passages metastasize first to the perihilar tracheobronchial and mediastinal nodes.
- Local lymph nodes, however, may be bypassed (skip metastasis) because of venous-lymphatic anastomoses or because lymphatic channels have been obliterated.
- Recall that lymph node enlargement may also reflect reactive hyperplasia as the body mounts an immune response. Tumor infiltrating lymphocytes (TILs) have been sought in such lymph nodes to be expanded and returned to the patient as a means of specific immunotherapy.

Metastasis

- Hematogenous spread is typical of sarcomas but is also seen with carcinomas.
- Arterial spread is uncommon, principally because of thicker walls. It may occur, however, when tumor cells pass through the pulmonary capillary beds or pulmonary arteriovenous shunts or when pulmonary metastases themselves give rise to additional tumor emboli.

Metastasis

- With venous invasion, the cells follow the venous flow draining the site of the organ, and the tumor cells often come to rest in the first capillary bed they encounter.
- The liver and the lungs are most frequently involved in such hematogenous dissemination, because all portal area drainage flows to the liver and all caval blood flows to the lungs.
- Cancers arising in close proximity to the vertebral column often embolize through the paravertebral plexus,
- Carcinomas of the thyroid and prostate frequently metastasize to the vertebral column.

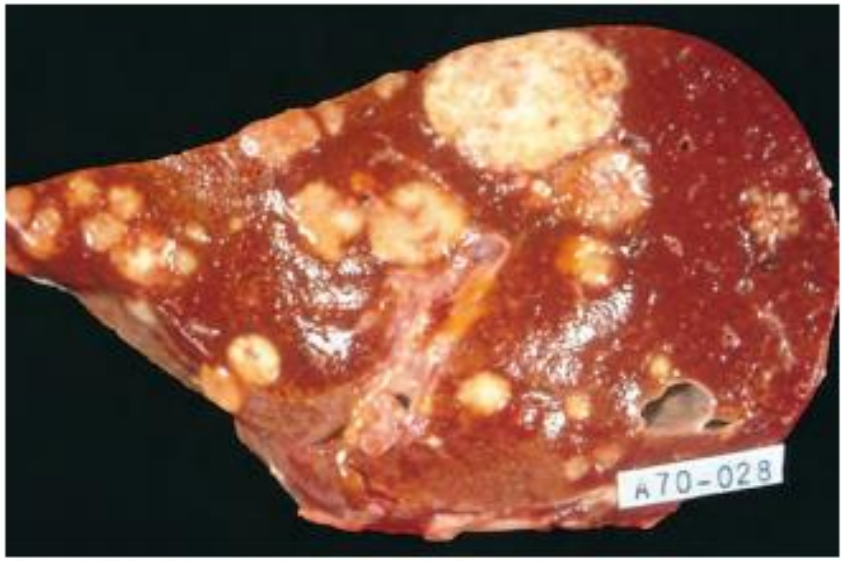


Figure 7-17 A liver studded with metastatic cancer.

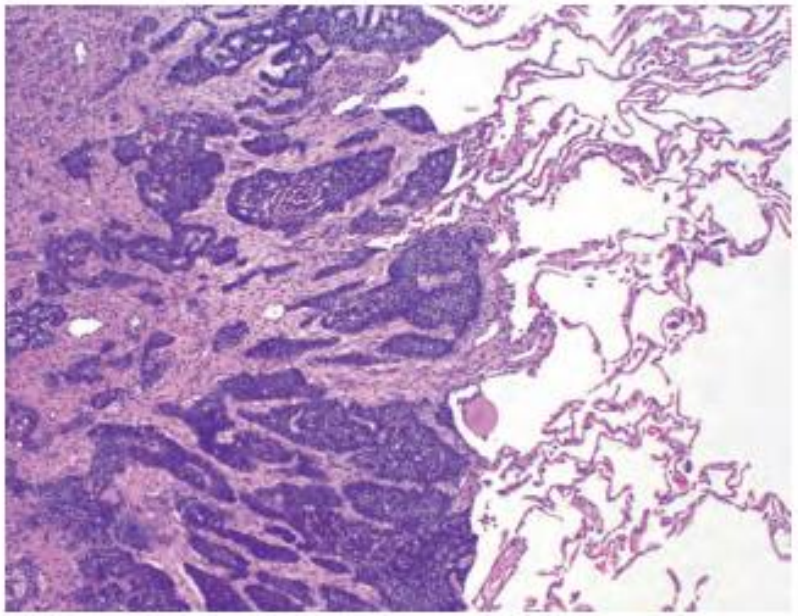


Figure 7-18 Microscopic view of lung metastasis. A colonic adenocarcinoma has formed a metastatic nodule in the lung. (Courtesy Dr. Shuji Ogino, Dana Farber Cancer Institute, Boston, Mass.)

Metastasis

- Renal cell carcinoma often invades the branches of the renal vein and then the renal vein itself, from where it may grow in a snakelike fashion up the inferior vena cava, sometimes reaching the right side of the heart.
- Hepatocellular carcinomas often penetrate portal and hepatic radicles to grow within them into the main venous channels.

Metastasis

- Breast carcinoma preferentially spreads to bone
- Bronchogenic carcinomas tend to involve the adrenals and the brain
- Neuroblastomas spread to the liver and bones.
- Skeletal muscles and the spleen, despite receiving a high percentage of the cardiac output and having large vascular beds, are rarely the site of secondary deposits.

Table 7-2 Comparisons Between Benign and Malignant Tumors

Characteristics	Benign	Malignant
Differentiation/ anaplasia	Well differentiated; structure sometimes typical of tissue of origin	Some lack of differentiation (anaplasia); structure often atypical
Rate of growth	Usually progressive and slow; may come to a standstill or regress; mitotic figures rare and normal	Erratic, may be slow to rapid; mitotic figures may be numerous and abnormal
Local invasion	Usually cohesive, expansile, well-demarcated masses that do not invade or infiltrate surrounding normal tissues	Locally invasive, infiltrating surrounding tissue; sometimes may be misleadingly cohesive and expansile
Metastasis	Absent	Frequent; more likely with large undifferentiated primary tumors

Staging

- Tumors are staged according to agreed upon criteria that reflect prognosis
- Staging reflects tumor size (T), regional lymph node involvement (N), and the presence of metastatic disease (M)