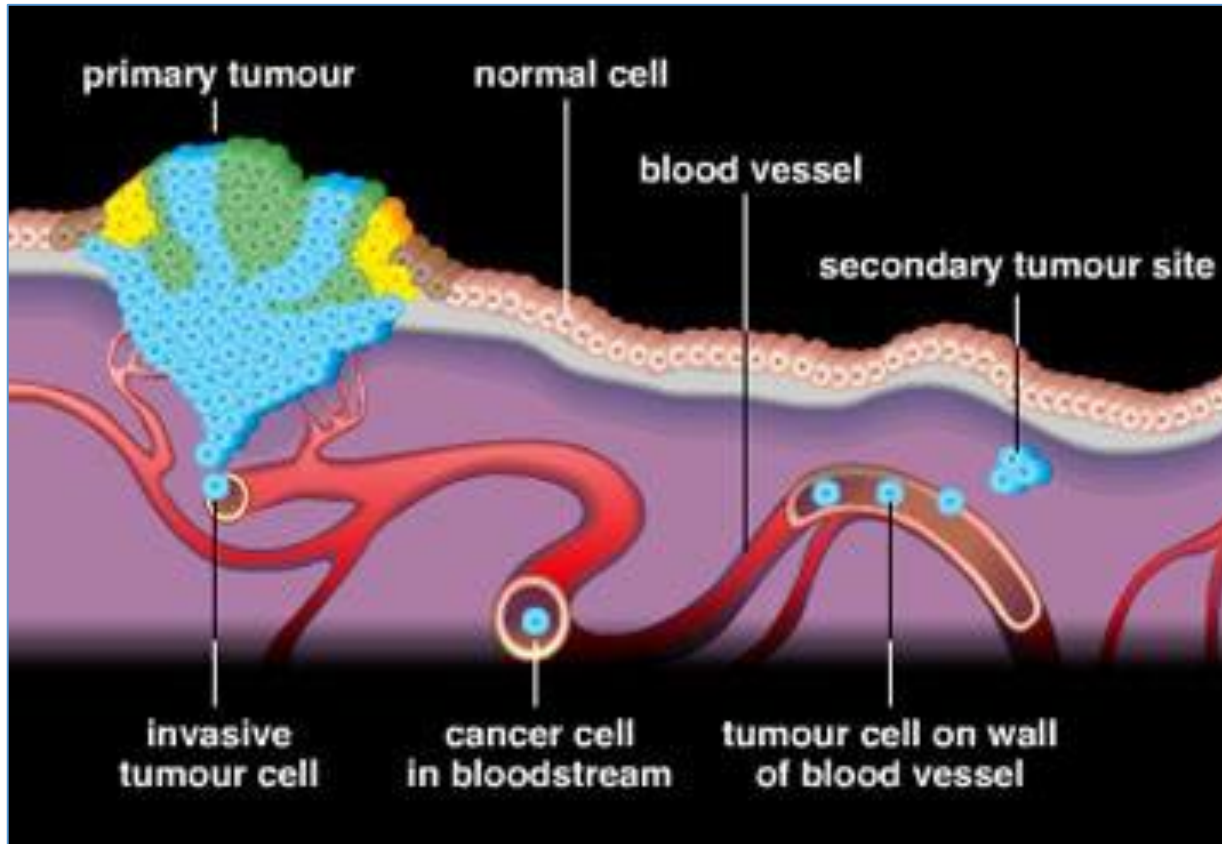


Tumor invasion and metastasis



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Objectives



- Define local invasion and metastases
- Describe the steps in tumor invasion and metastases
- Give examples of different routes of tumor spread
- Apply the knowledge to describe clinical features arising from tumor spread

Invasion and metastasis

Why do we need to know the extent of spread

- For adequate resection
- To decide on treatment modalities
- As it carries lethal consequences

Spread of tumour

2 steps

1. Invasion of the extracellular matrix



2 a. Vascular dissemination



2 b. Homing of tumor cells & colonisation

1. Invasion of the extracellular matrix



Steps of invasion of matrix

4 steps

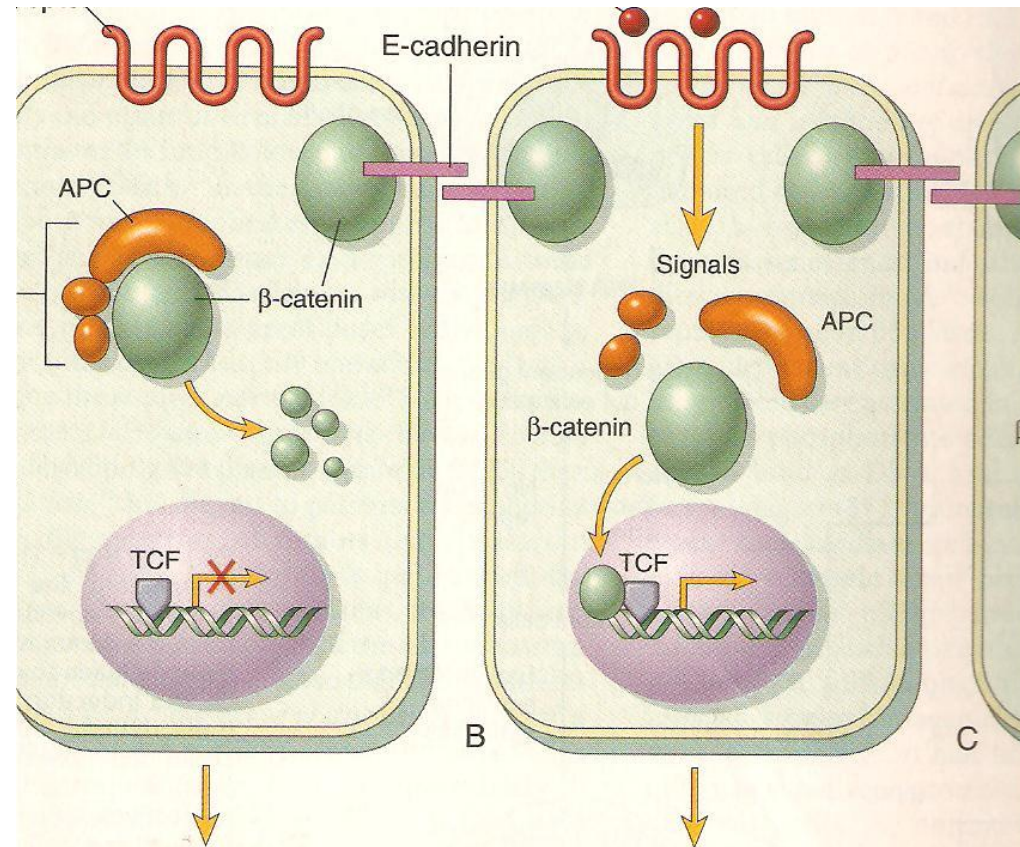
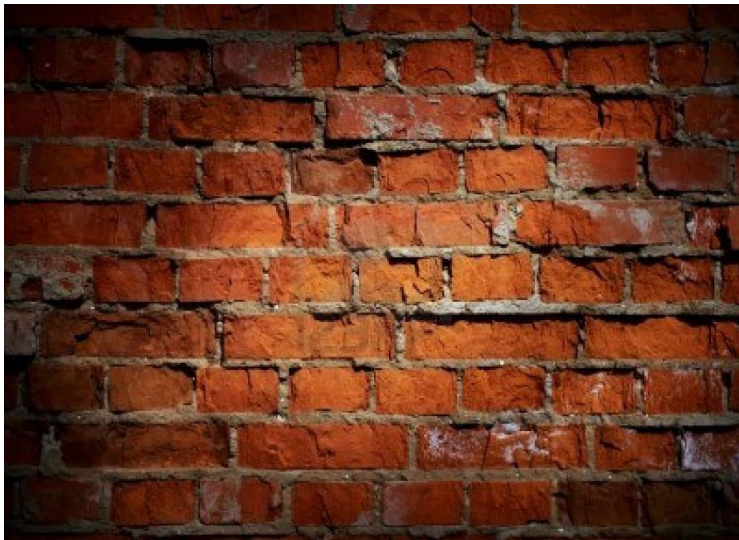
1. Loosening of tumor cells.
2. Degradation of the BM & interstitial connective tissue
3. Attachment to novel ECM components
4. Migration of tumor cells



Step 1. Loosening of tumor cells

Normally cells are adherent to each other by adhesion molecules

eg. E cadherin and beta catenin

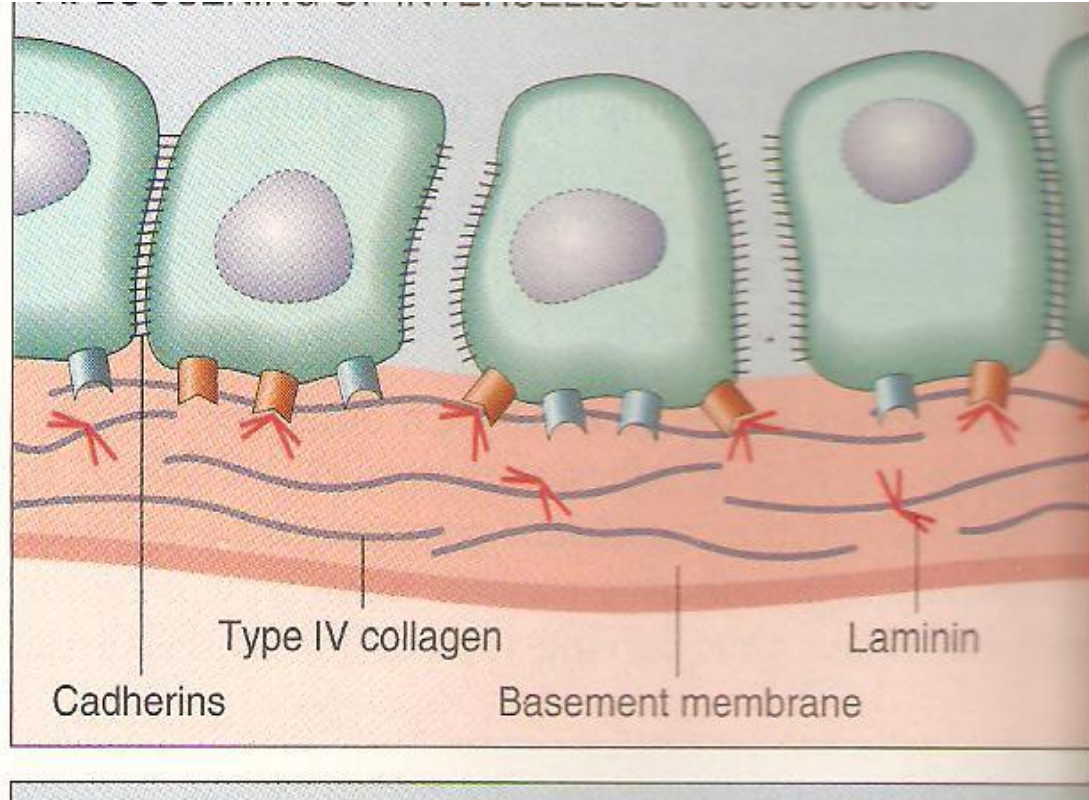


Step 1. Loosening of tumor cells

Downregulation of E
cadherin expression

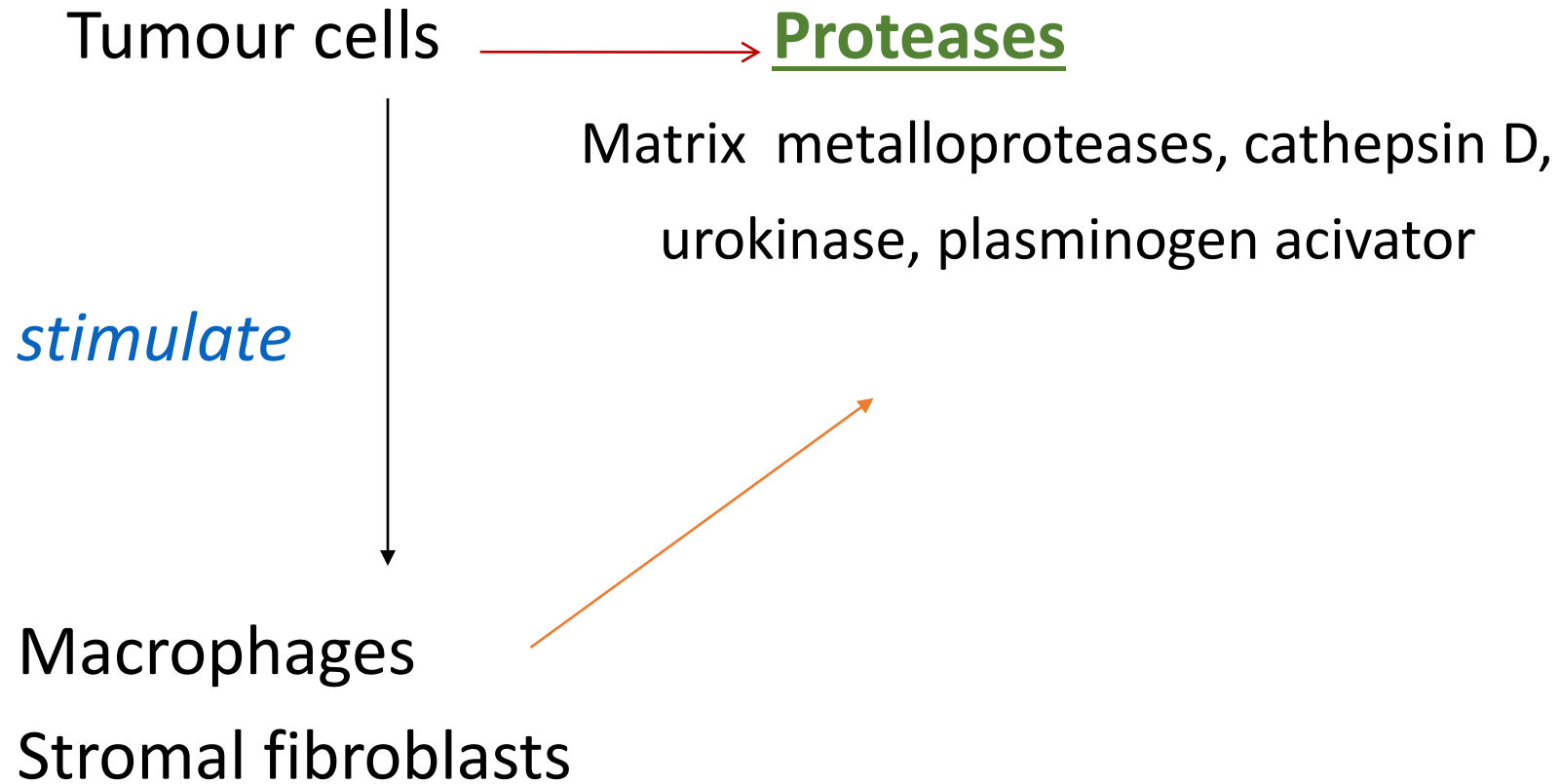


Facilitate detachment



Step 2. Degradation of the BM & interstitial connective tissue

-



Cleavage products of collagen and proteoglycans have-

- Growth promoting activity
 - Angiogenic activity
 - Chemotactic activity –tumour cell migration
-
- Concentration of MMP inhibitors are reduced



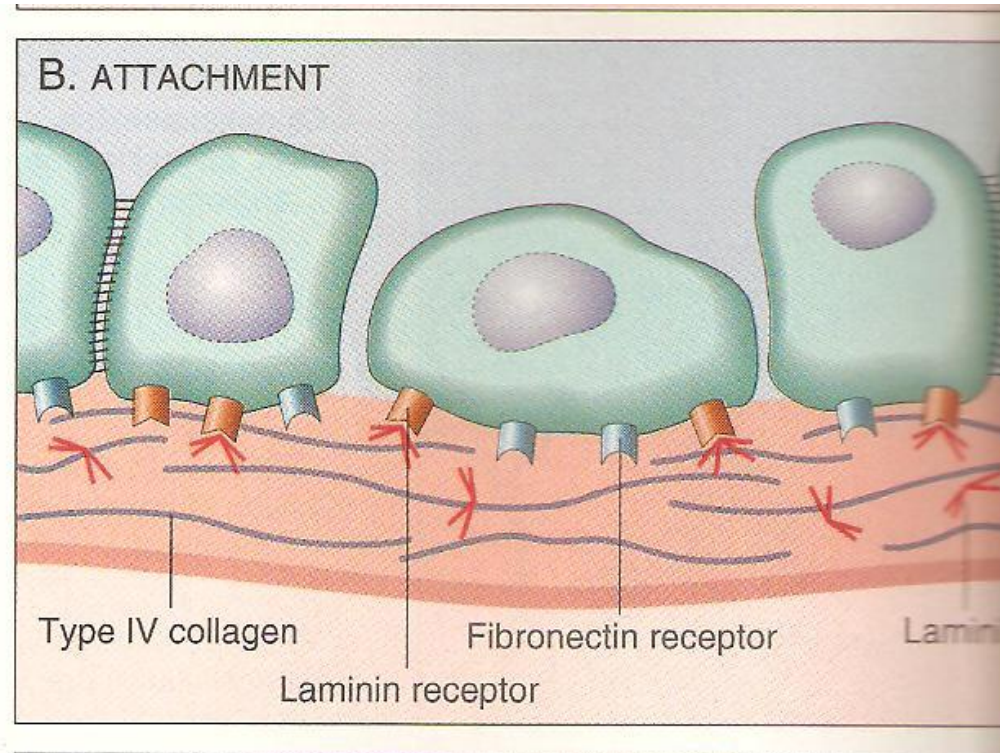
Step 3.Changes in attachment of tumor cells to ECM proteins

Normally basal
receptors for
attachment

Tumor cells –
Receptors
expressed all over
the cell



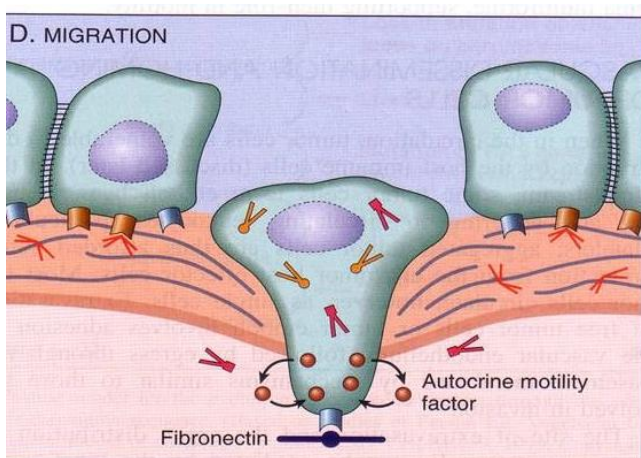
Facilitate
attachment
to matrix proteins



Step 4. Locomotion

Locomotion of tumor cells

- Movement of tumor cells through the matrix
- Multistep process
- Involves tumor cell derived cytokines , cleavage products and growth factors with chemotactic activity



Spread of tumour

Invasion of the matrix

2 a. **Vascular dissemination**

2 b. Homing of tumor cells



2 a.Vascular dissemination

- Tumor cells penetrate the BM of blood vessels and enter the circulation
- Within the circulation host immune mechanisms act against the tumor cells




- Tumor cells form small emboli to evade these immune mechanisms

Homotypic adhesion- adhere to each other

Heterotypic adhesion – Adhere to blood cells with platelets
and form emboli

2 b. Homing of tumor cells

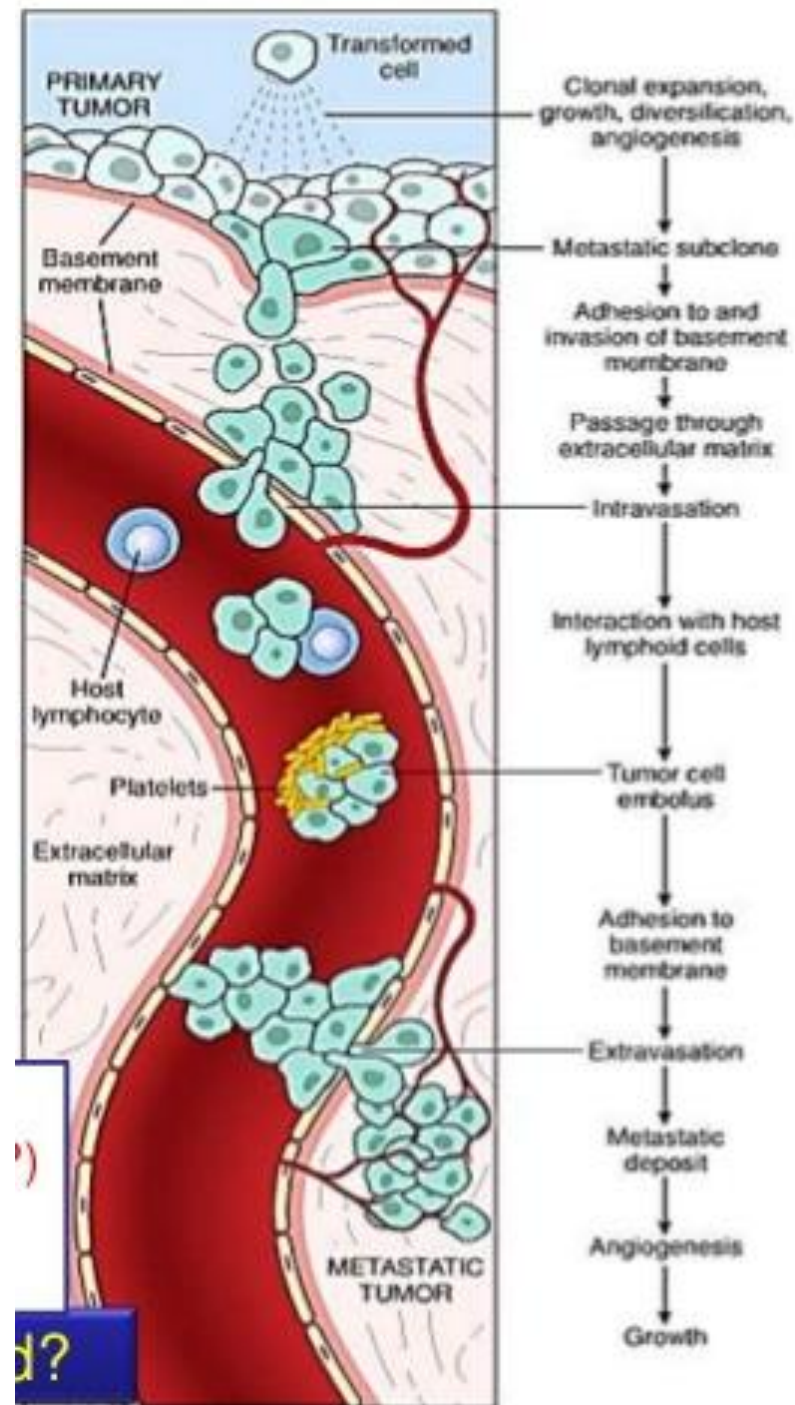
- Usually the tumors metastasize along the natural pathway of drainage
- Some tumors have specific affinity to form metastatic deposits in specific organs(organ tropism)
- Tumor cells express **adhesion molecules**
..........*metastatic deposits form*
- Vascular endothelium of the organ express specific ligands
- Expression of **chemokines** and their receptors
- Colonize

Angiogenesis

Steps of angiogenesis

- Proteolytic digestion of BM of post capillary venules by plasminogen activators and matrix metalloproteinases
 - Migration of cord of endothelial cells
 - Proliferation of endothelial cells
 - Formation of new blood vessels with lumina
-
- VEGF , FGF & Angionectin important in angiogenesis

Steps of invasion and spread



Antitumour effector mechanisms

Cell mediated and humoral immunity

- 1) Cytotoxic T cells (CD8+)
- 2) NK cells (Activated by IL-2)
- 3) Macrophages (Activated by IFN-gamma)
- 4) Antibodies -?

Local invasion

- Infiltration and destruction of the BM & surrounding tissue
- Follow the paths of lowest resistance
- Loose fibrous tissue and adipose tissue easily penetrated
- Fascia , periosteum etc initially resistant to invasion

Metastasis(Distant spread)

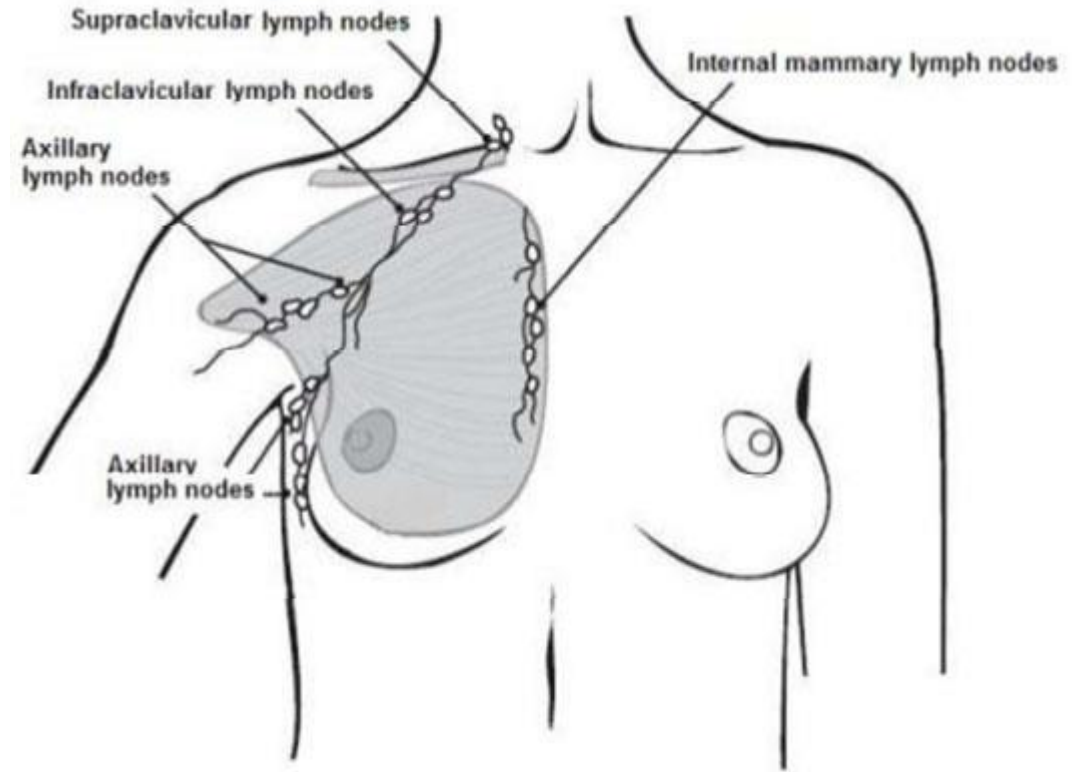
- Spread of tumour resulting in a discontinuous tumour mass.

Routes

- 1)Lymphatic
- 2)Haematogenous
- 3)Others – Trancoelomic spread , via CSF

1) Lymphatic spread

- Carcinoma favor lymphatic spread
- Lymphatic emboli → Lymph node
- Usually to regional node –
Breast CA → axilla
Bronchial CA → Hilar nodes



- Skip metastasis
Due to obliteration of the LN by inflammation/radiation

1)Lymphatic spread cont.

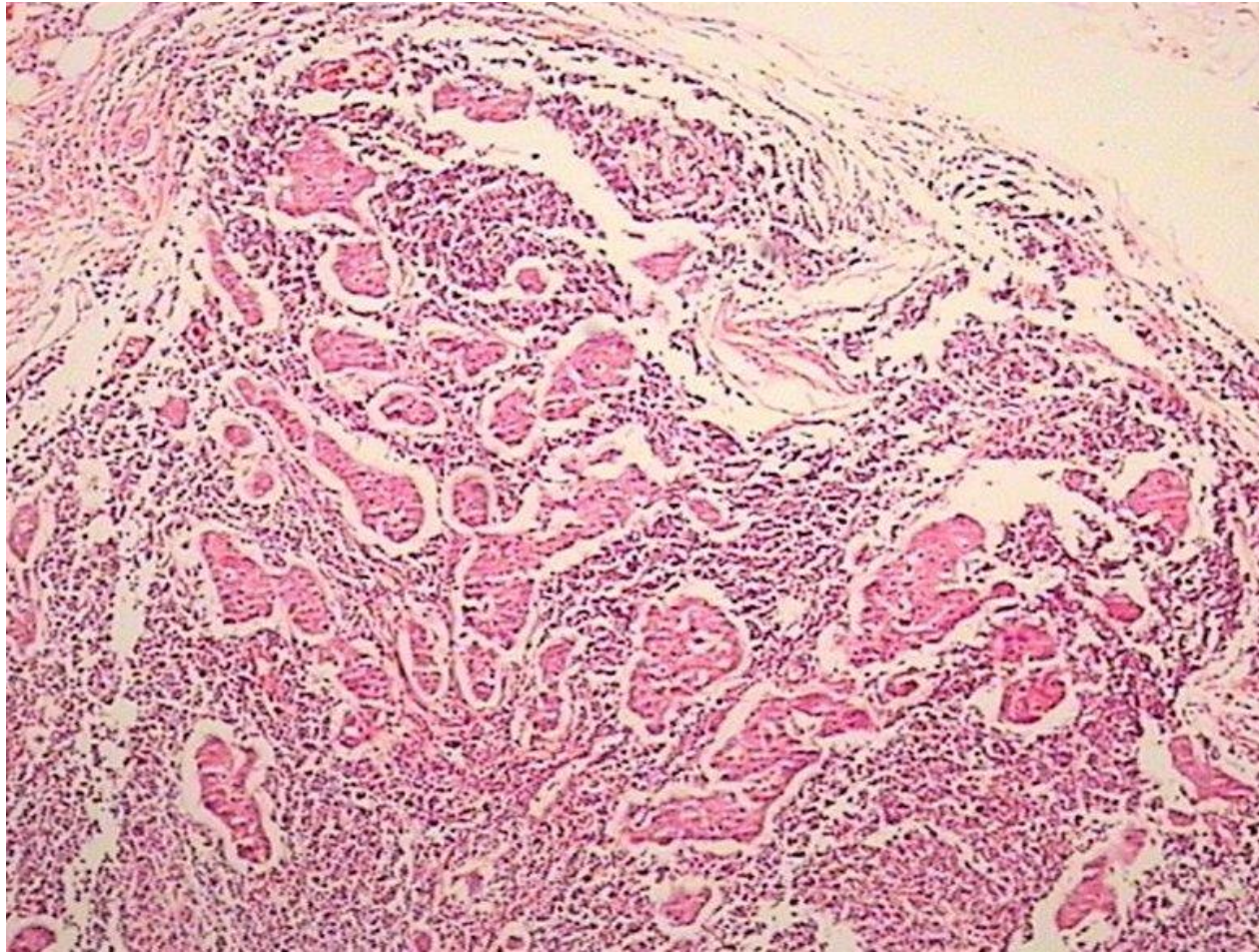
- Virchow's node

Metastatic deposit of the supraclavicular LN
Carcinoma of stomach

- LN enlargement could be reactive as well
- Regional LN – Initial barrier filter
 - Destruction of tumour cells
 - Fertile soil for growth of tumour

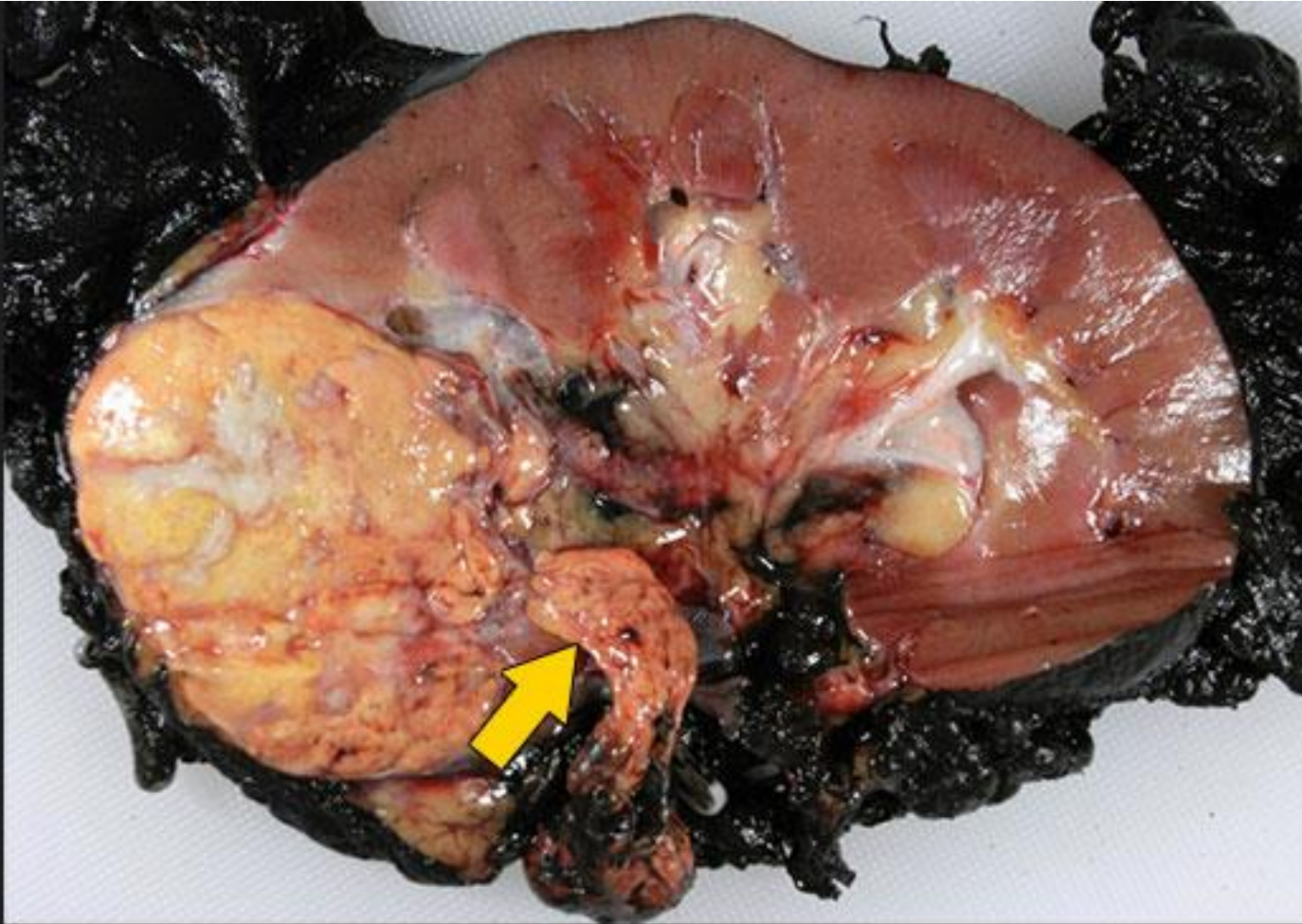


1)Lymphatic spread cont.



2)Haematogenous spread

- Commonest route of spread for sarcomas
- Common sites – lung, liver , bone , brain
- Unfavorable sites – spleen , heart , skeletal muscle.
- Tumor cells permeate capillaries and veins
 - Systemic veins —————>Lung
 - Portal veins —————>Liver



Renal carcinoma spread along the renal vein

2) Haematogenous spread cont.

- Retrograde spread by blood routes
Along the paravertebral venous plexus – Vertebral metastasis in prostate and thyroid CA
- Commonly multiple round nodules
- Some bigger than the primary tumour

Metastatic deposit in the liver



Metastatic deposits in the brain



Lymphovascular invasion

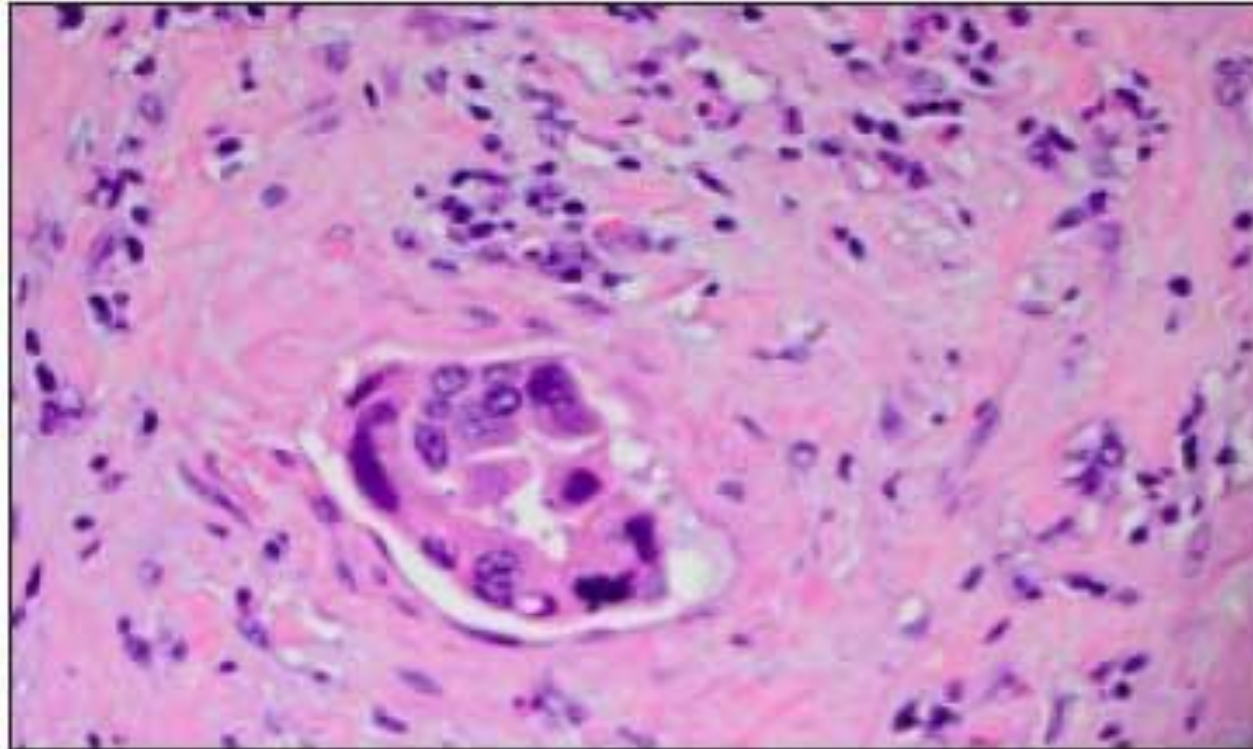


Figure 2: Lymphovascular Invasion Is Evident In the Center of This Pathology Slide.

3) Spread along body cavities and natural passages

A) Transcoelomic spread

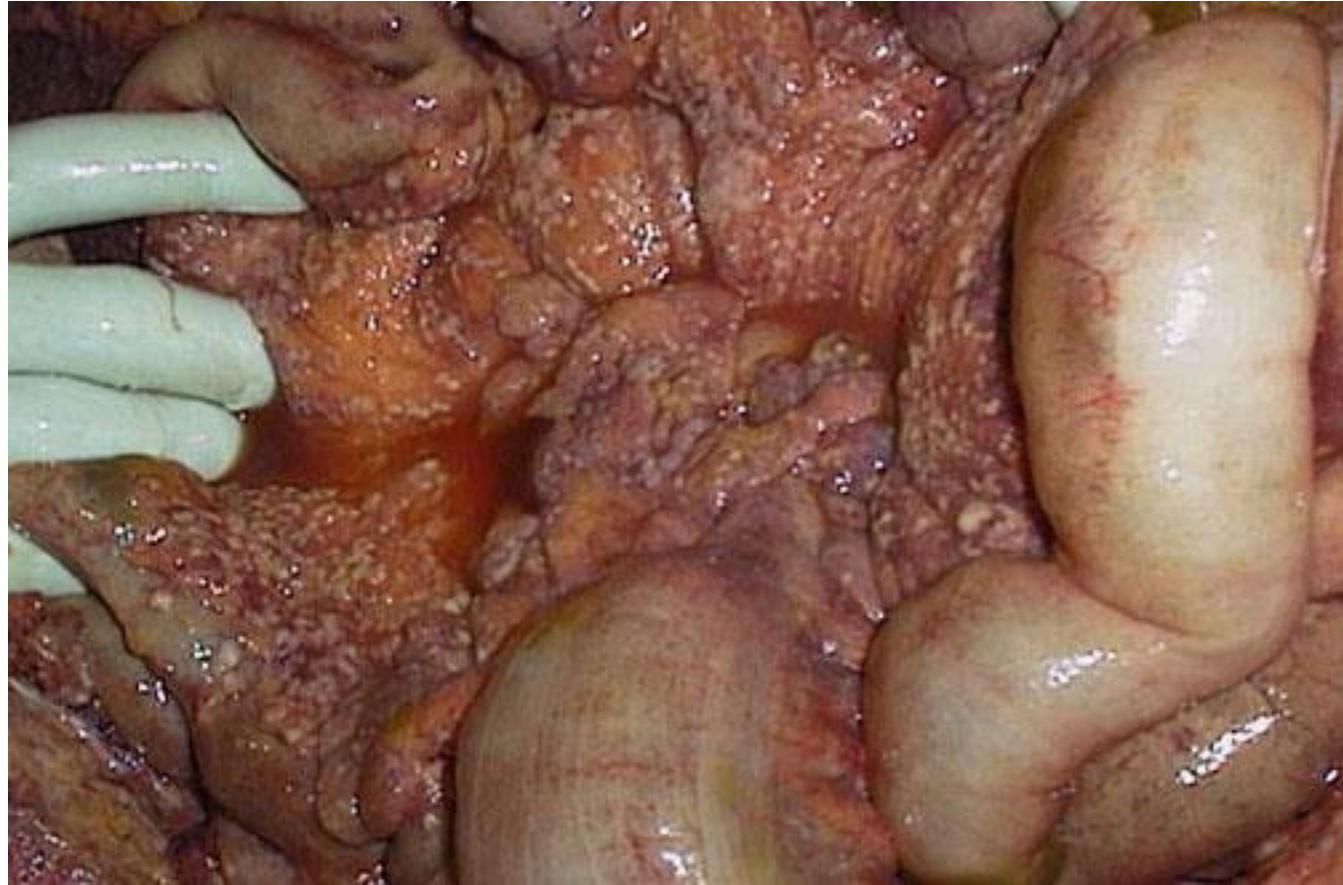
Tumor cells spread via coelomic fluid, Peritoneal , pleural , pericardial cavity

a) Krukenberg tumour- Metastatic deposits in both ovaries from a primary gastric carcinoma



b) Carcinoma of ovary - peritoneal cavity

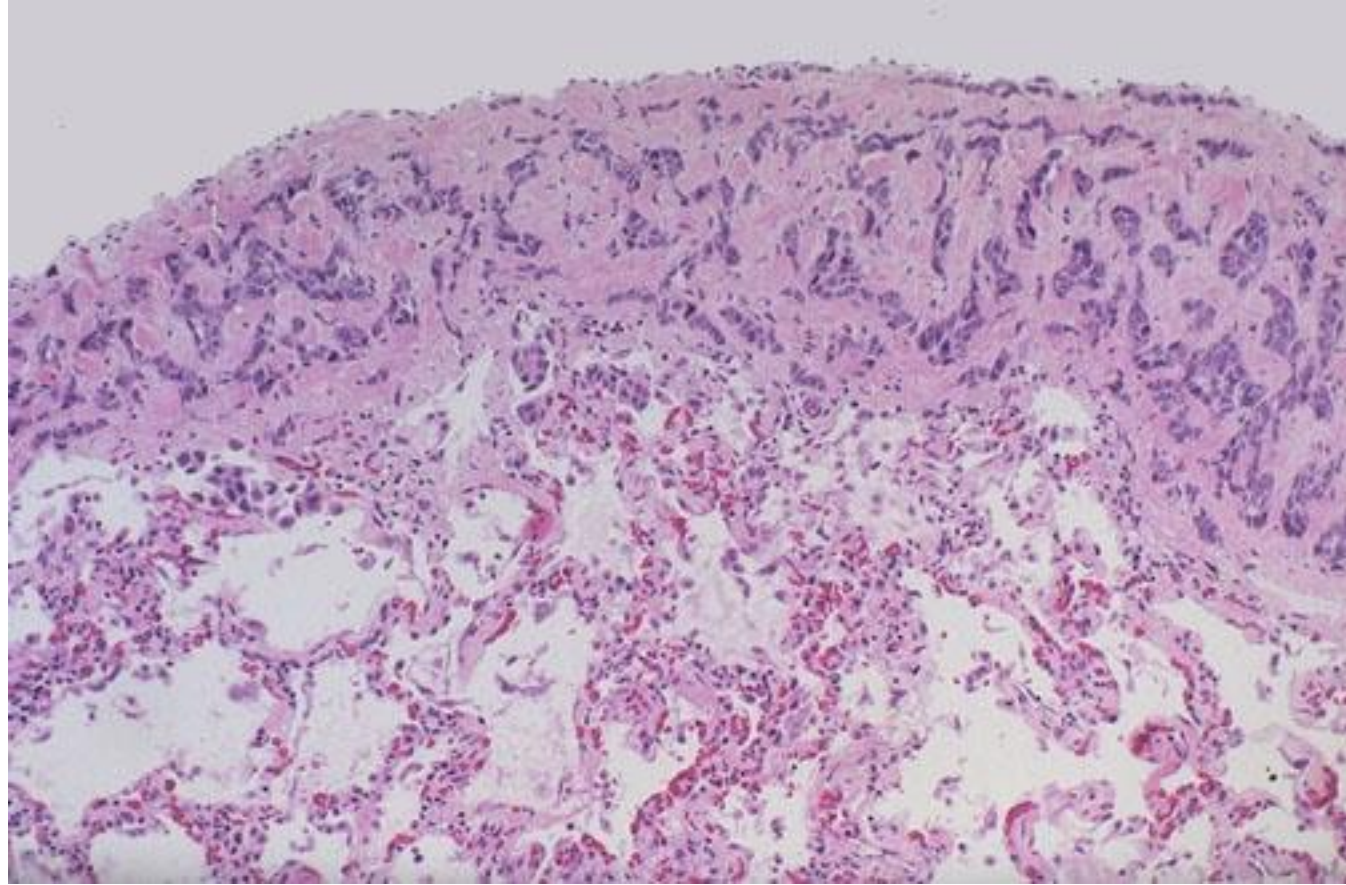
Peritoneal deposits



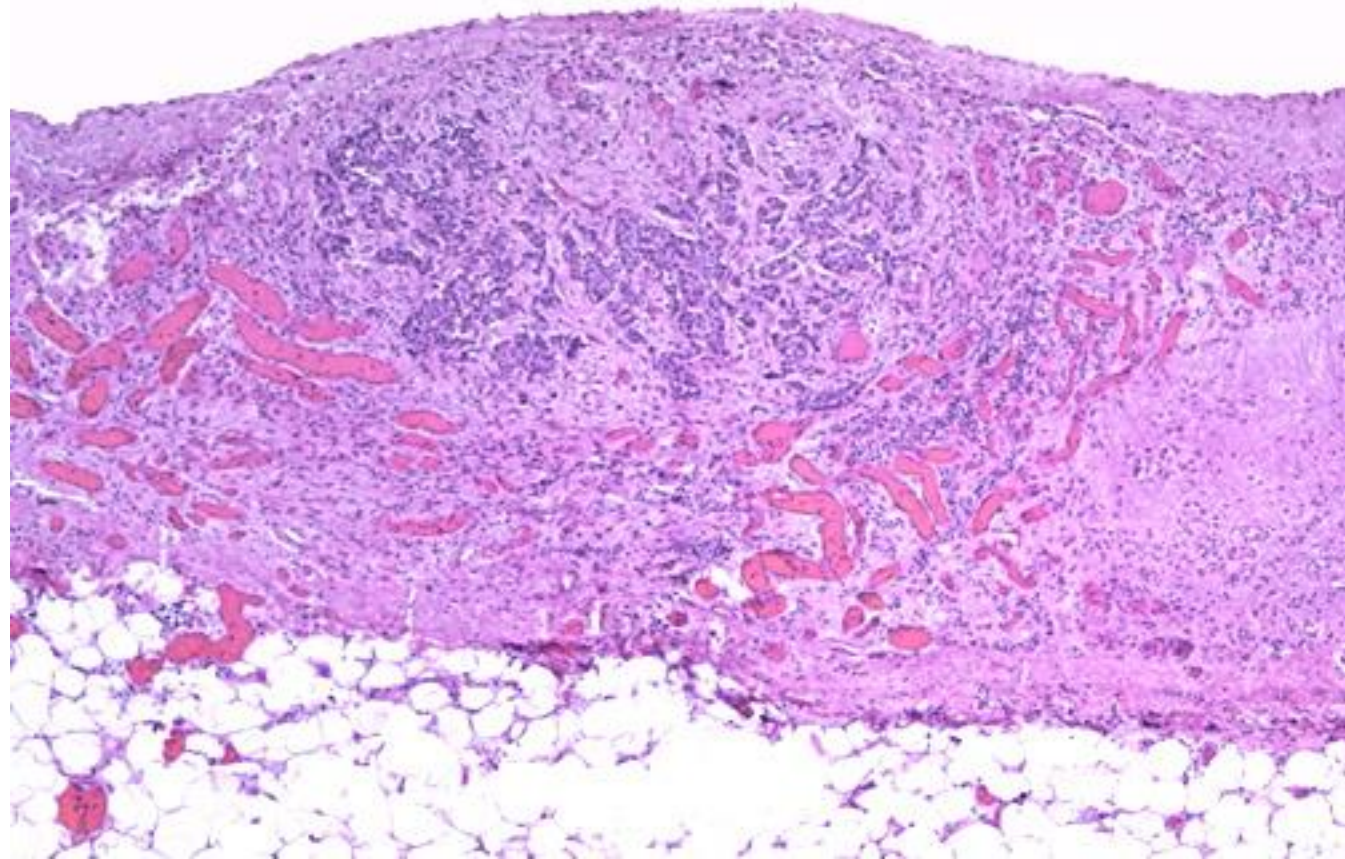
Metastatic ovarian cancer



Metastatic deposits in the pleura



Pericardial deposits



Sister Mary Joseph's nodule



Metastatic cancer of the umbilicus, known as Sister Mary Joseph's nodule, is typically associated with adult cancers of the gastrointestinal tract and ovary. This condition was named for Sister Mary Joseph (1856 –1939), a surgical assistant for Dr. William Mayo, who noted the association between paraumbilical nodules observed during skin preparation for surgery and metastatic intra-abdominal cancer confirmed at surgery

3) Spread along body cavities and natural passages cont.

B) Spread along epithelium lined surfaces

- Endometrial Ca → through fallopian tube → Ovary
- Kidney → through ureter → lower urinary tract

Spread along body cavities and natural passages
cont.

C)Spread via cerebrospinal fluid

- CNS tumors
- Leukaemias-ex:ALL/AML

Host defense against tumors: Tumor immunity

- Describe tumor antigens.
- Describe the antitumor effector mechanisms.

Assignment

- Find out the clinical presentations due to local spread of tumor
- Find the systemic effects/clinical presentations due to systemic spread of tumors

Effects of tumor spread

Local effects-

- 1)mass effect
- 2)Ulceration
- 3)Haemorrhage
- 4)Pain
- 5)Obstruction
- 6)Perforation
- 7)Destruction
- Find out the clinical presentations due to these effects

