Invasion
And
Metastasis

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Biology of tumor growth

The natural history of malignant tumors can be divided into four phase:

A. Transformation
B. Growth of transformation cells
C. Local invasion
D. Distant metastases

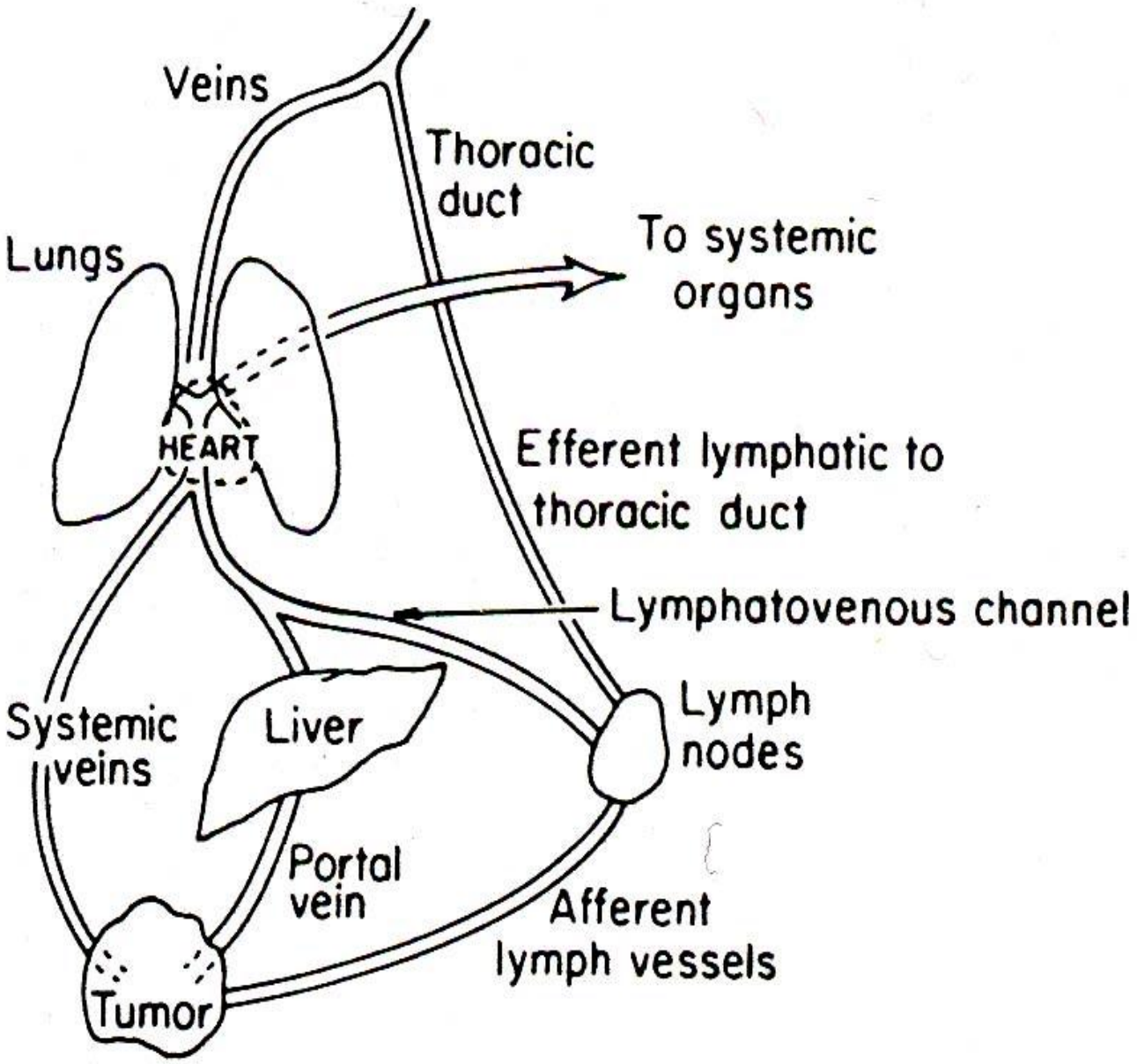
Spread of Cancer

- Local Invasion (direct extension)
- Metastasis (spread at a distance)
  - Lymphatic (via lymph vessels and nodes)
  - Hematogenous (via blood vessels)
  - Body Cavity Seeding (pleural and peritoneal)

Routes of tumor spread

- Hematogenous (bloodstream)
  - sarcomas

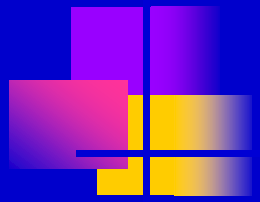
- Lymphatic (lymph nodes)
  - Carcinomas
    : Breast cancer, lung cancer


Veins
Thoracic duct
To systemic organs
Lungs
HEART
Efferent lymphatic to thoracic duct
Lymphatovenous channel
Systemic veins
Liver
Lymph nodes
Portal vein
Afferent lymph vessels
Tumor

Colon CA: Metastasis to Liver

from Robbins

Biology of tumor growth

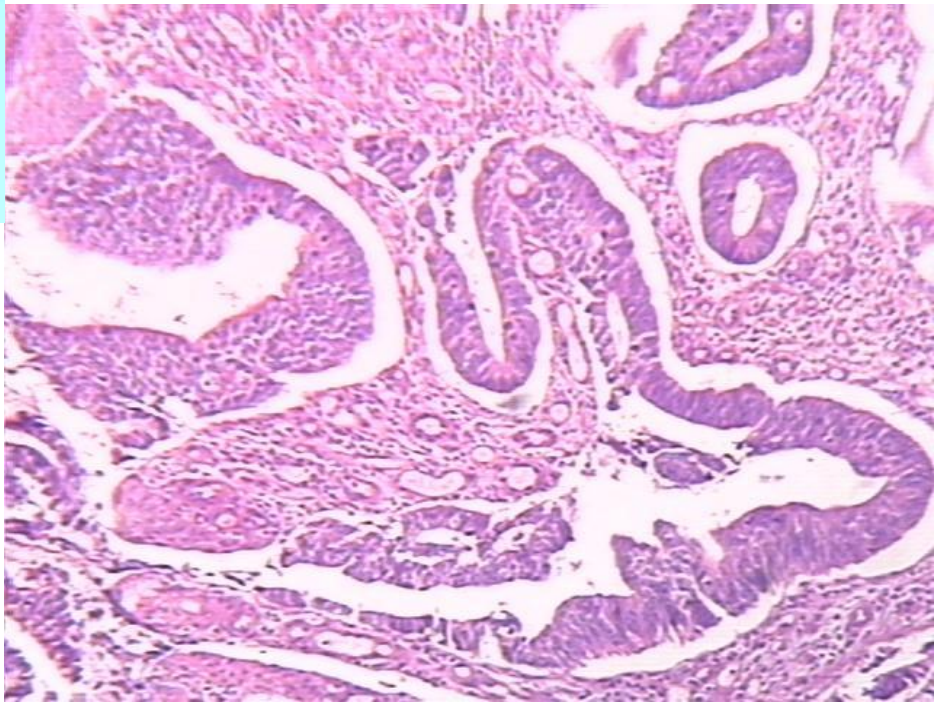


1. Local invasion

2. Distant metastases

1. Local Invasion

a. Progressive infiltration, invasion, and destruction of the surrounding tissue
b. Ill-defined and non-encapsuled
c. The particular growth pattern of malignant tumors
d. Be surgically enucleated difficultly



Invasive growth pattern

Mechanisms of invasion and metastasis

Invasion of the extracellular metastasis

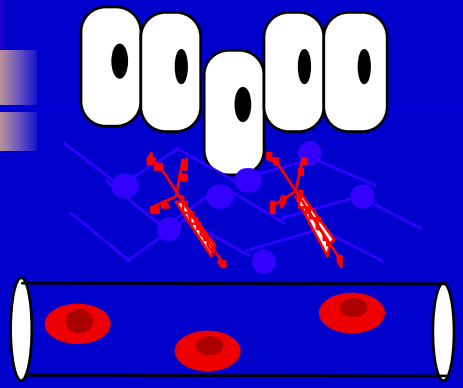
a. Loosening up of tumor cells from each other: E-adhering expression is reduced

b. Attachment to matrix components: cancer cells have many more receptors of lamina and fibronectin.

c. Degradation of extra cellular matrix: Tumor cells can secrete proteolytic enzymes or induce host cells to elaborate proteases.

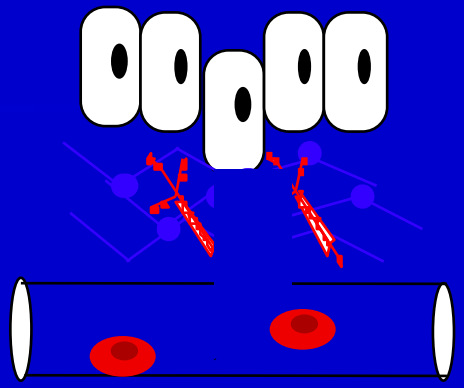
The three steps of invasion

1



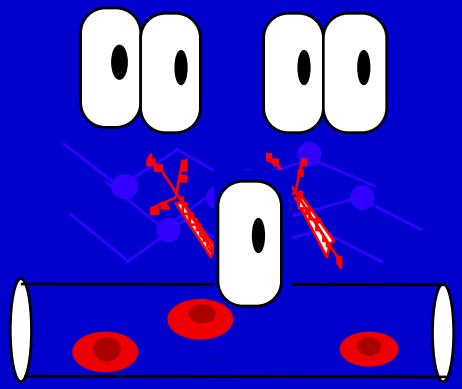
Matrix attachment

2



Matrix degradation

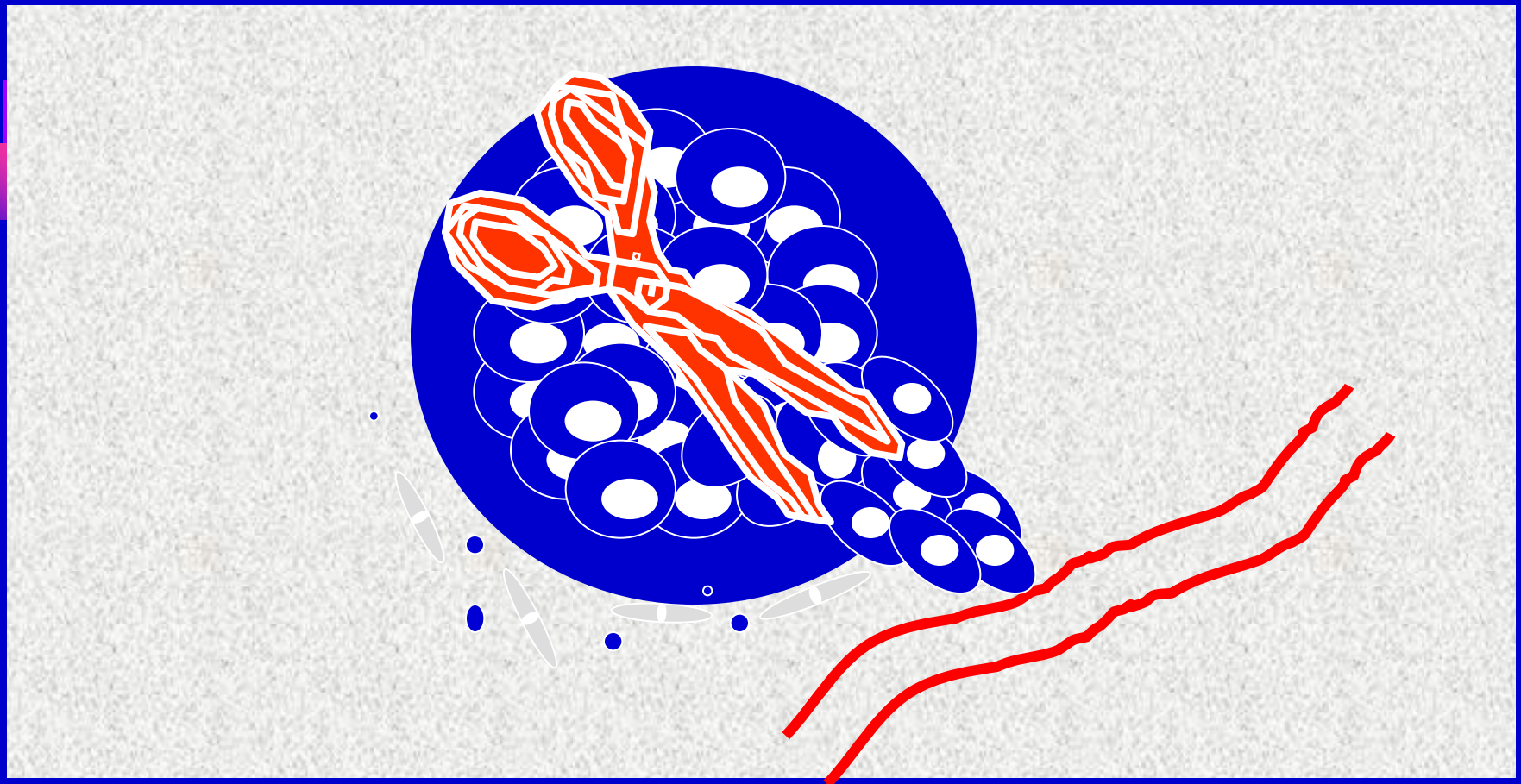
3



Locomotion

Liotta, LA. Tumor invasion and metastasis-role of the extracellular matrix. Cancer Res 46: (1986)

Matrix degradation by proteinases



Metalloproteinases (MMPs)
Serine proteinases (plasmin, uPA)
Cysteine proteinase (Cathepsin B,L)
Aspartyl proteinases (Cathepsin D)
Threonine proteinases
(not extracellular)

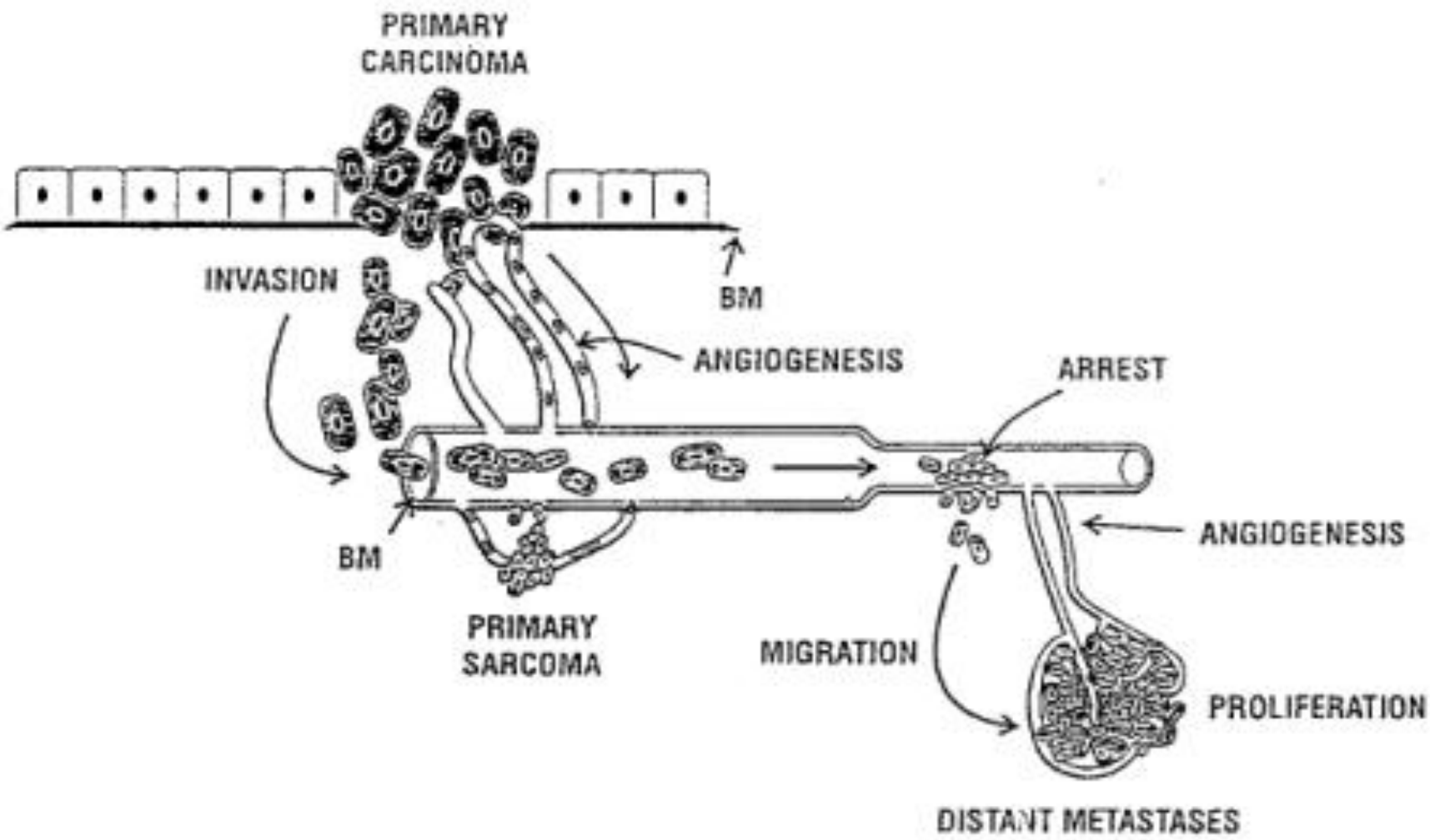
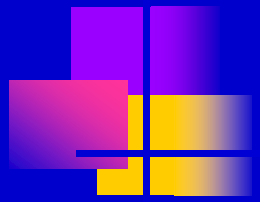


Figure 9.3. A model of the major steps of metastasis. Anchorage-independent growth of epithelial cells results in the formation of a primary carcinoma. The tumor induces the growth of blood vessels into the tumor by angiogenesis. Some cells separate from the primary tumor, invade through the basement membrane, enter the vasculature, and eventually arrest in capillaries, where they extravasate out of the blood vessels into the underlying connective tissue at the metastatic site; there, further cell growth and angiogenesis results in the formation of metastatic tumor growth. Angiogenesis may not be as critical for the invasion and metastasis of sarcomas, as these tumors arise in the stroma in close vicinity to blood vessels. The activity of a variety of adhesion molecules has been implicated in most of the steps in this metastatic cascade.

Biology of tumor growth

1. Local invasion

2. Distant metastases



Metastasis

Definition:

development of secondary implants discontinuous with the primary tumor, possibly in remote tissue.

Why do metastases establish where they do?

- Mechanical/Anatomical hypothesis - Ewing

First capillary bed reached: cells trapped in small vessels

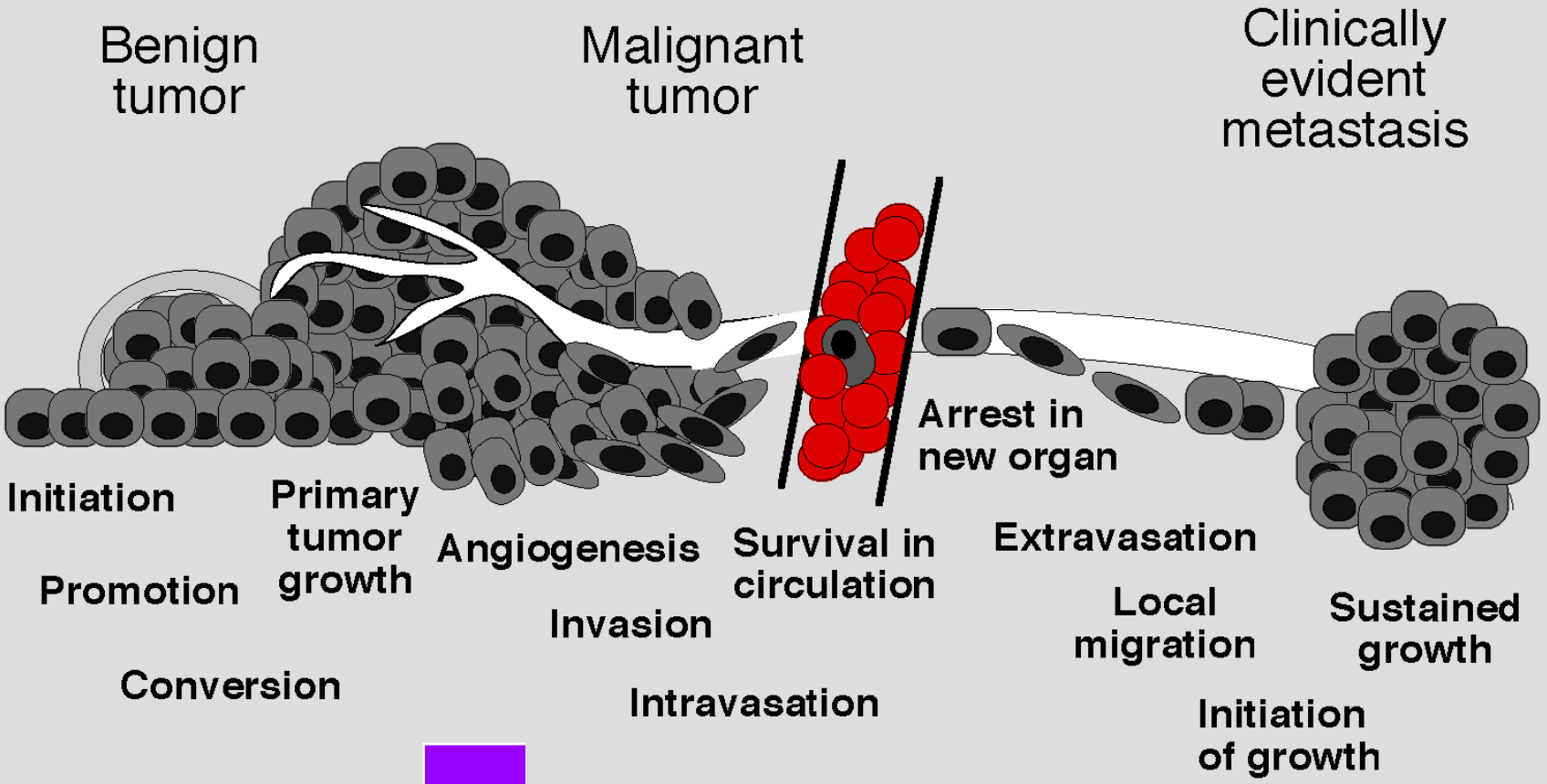
- "Seed and soil" hypothesis - Paget

Importance of microenvironment

"When a plant goes to seed,
its seeds are carried in all directions;
but they can grow only if they fall on congenial soil."

Stephen Paget, Lancet 1:571, 1889

TUMOR PROGRESSION



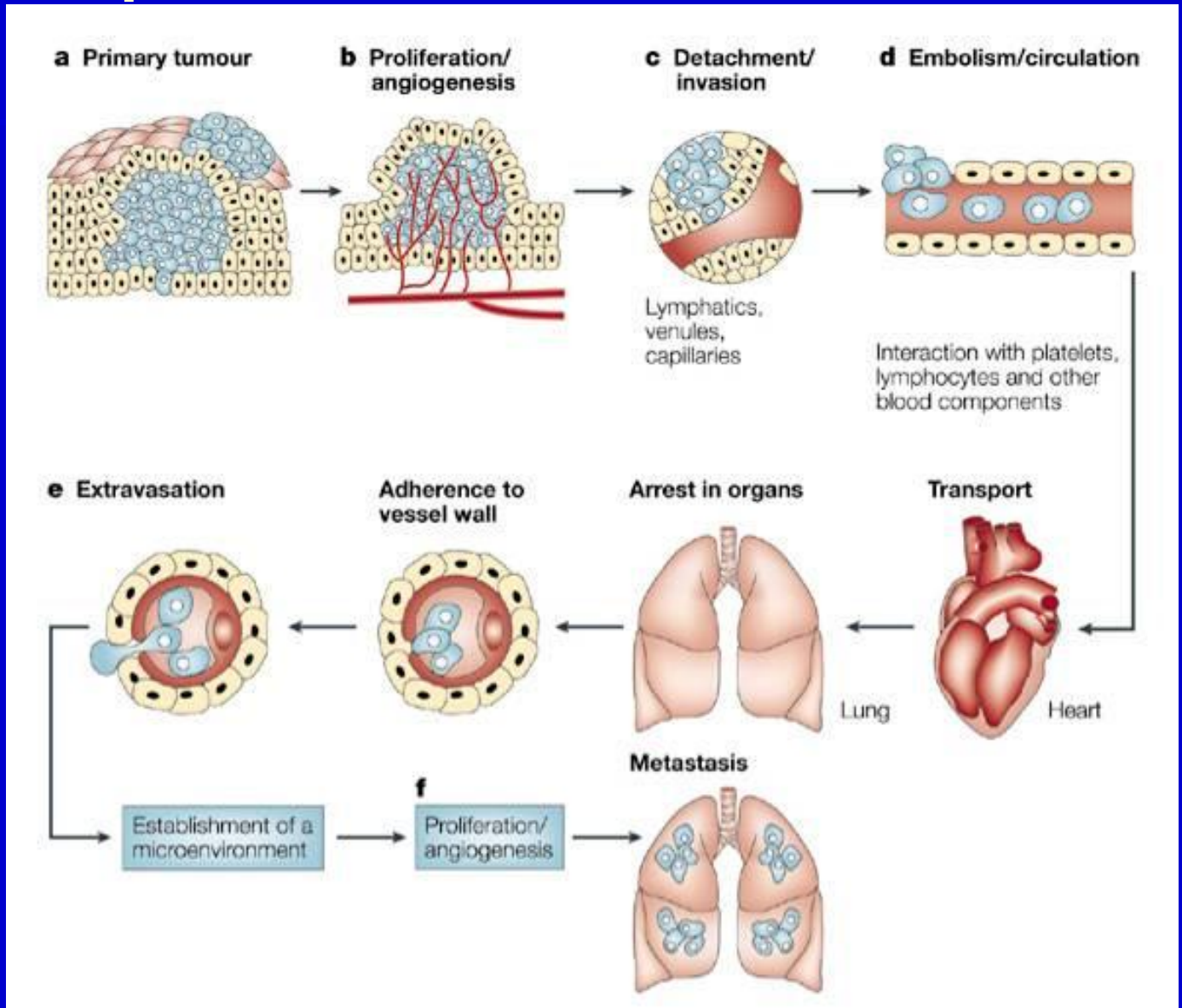
The Clinical Problem

- 30% of patients present with overt metastases
- 30-40% appear clinically free of metastases, but occult lesions appear later
- 30% do not metastasize and can be cured by eradicating primary tumor

- Variation in tumor types :

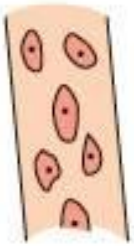
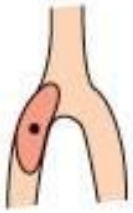
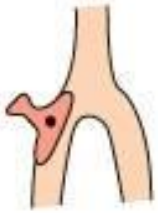
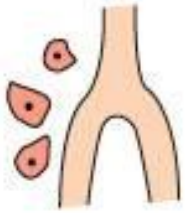
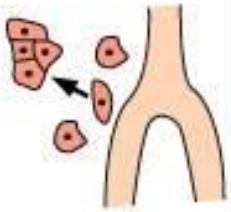
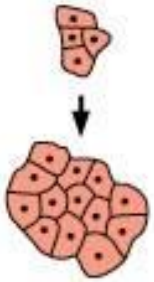
  - Melanoma can metastasize when very small
  - Colon and breast adenocarcinomas have a greater tendency to metastasize as get larger
  - Basal cell carcinomas of the skin rarely metastasize

Steps to Metastatic Disease



Fidler, 2003

Rate Limiting Steps?

escape from parent tissue	travel through circulation			colonization of remote site		
entry into blood-stream or lymphatic vessel	survival in the circulation	arrest in capillary or other small vessel	exit into remote tissue or organ	survival of cells in foreign tissue	initial growth of cells in foreign tissue	persistence of growth
						
DIFFICULT	EASY			DIFFICULT		

from Alberts MBoC

Route of Metastasis

1. Lymphatic Metastasis
2. Hematogenous Metastasis
3. Implantation Metastasis

Route of Metastasis

1. Lymphatic Metastasis
2. Hematogenous Metastasis
3. Implantation Metastasis

① Lymphatic metastasis

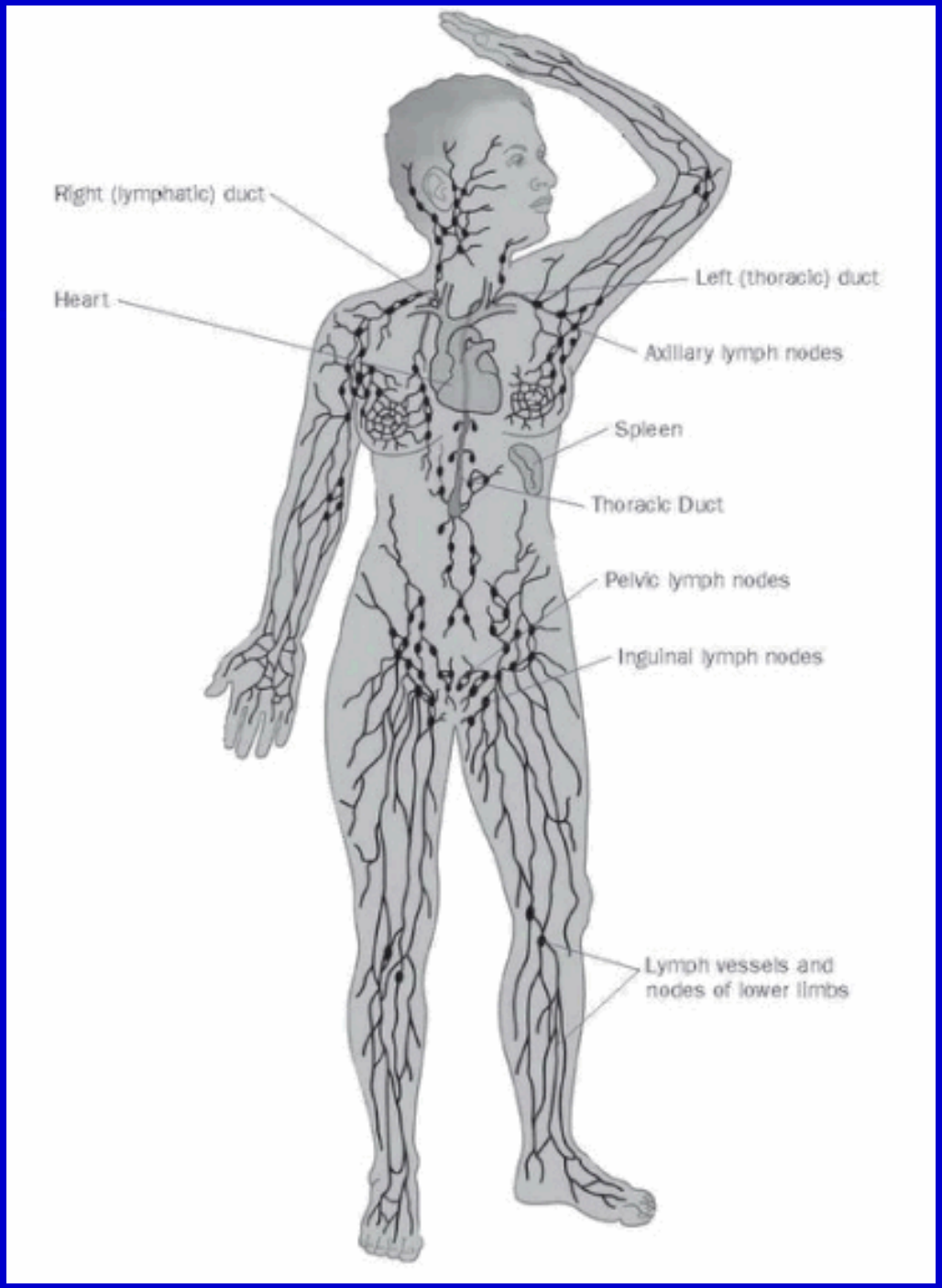
a. This is the most common pathway for initial dissemination of carcinoma.

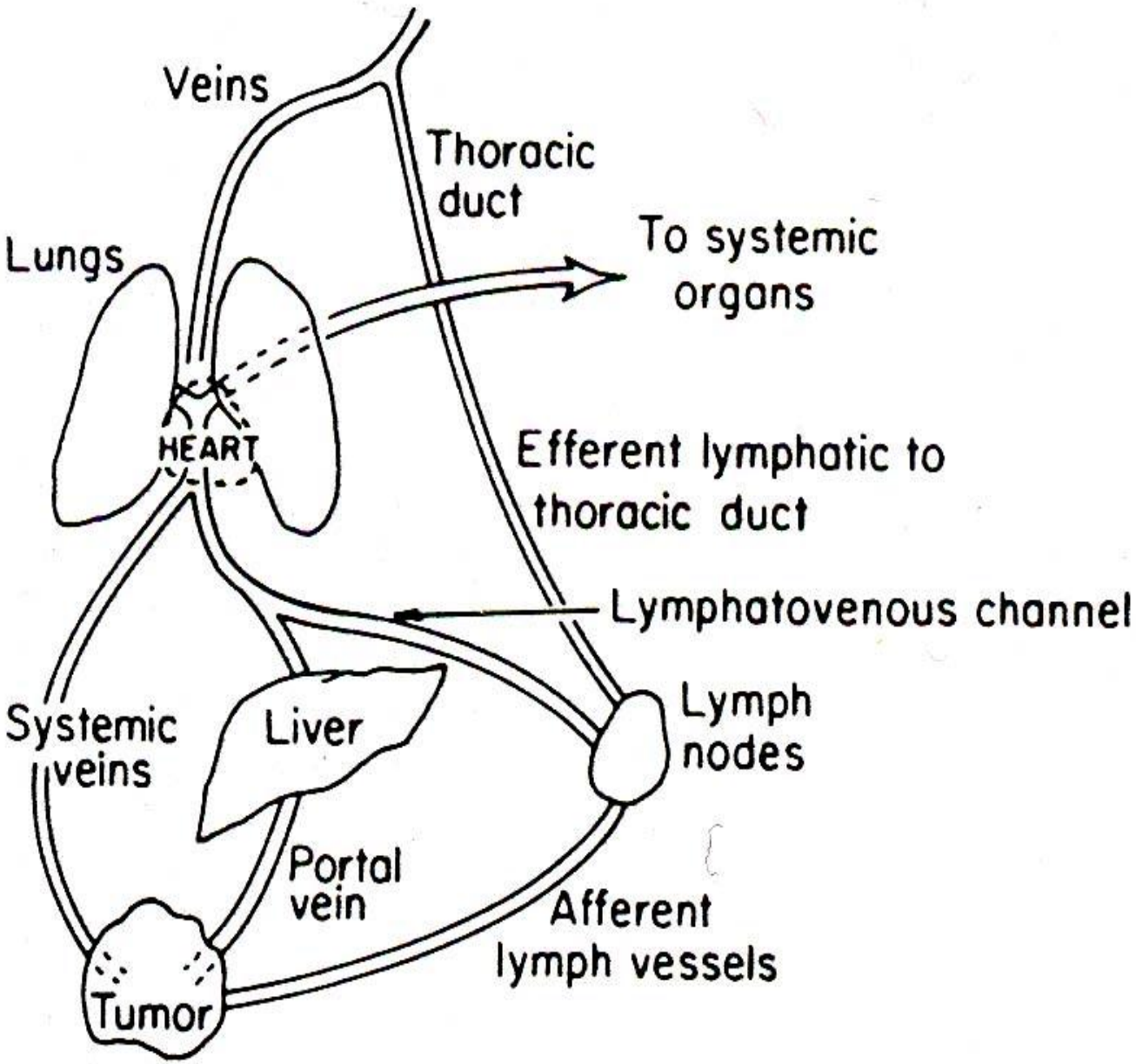
b. Tumor cells gain access to an afferent lymphatic channel and carried to the regional lymph nodes.

In lymph nodes, initially tumor cell are confined to the subcapsular sinus; with the time, the architecture of the nodes may be entirely destroyed and replaced by tumor.

c. Through the efferent lymphatic channels tumor may still be carried to distanced lymph rode, and enter the bloodstream by the way of the thoracic duct finally.

d. Destruction of the capsule or infiltration to neighboring lymph nodes eventually causes these nodes to become firm, enlarged and matted together.


Right (lymphatic) duct
Heart
Left (thoracic) duct
Axillary lymph nodes
Spleen
Thoracic Duct
Pelvic lymph nodes
Inguinal lymph nodes
Lymph vessels and nodes of lower limbs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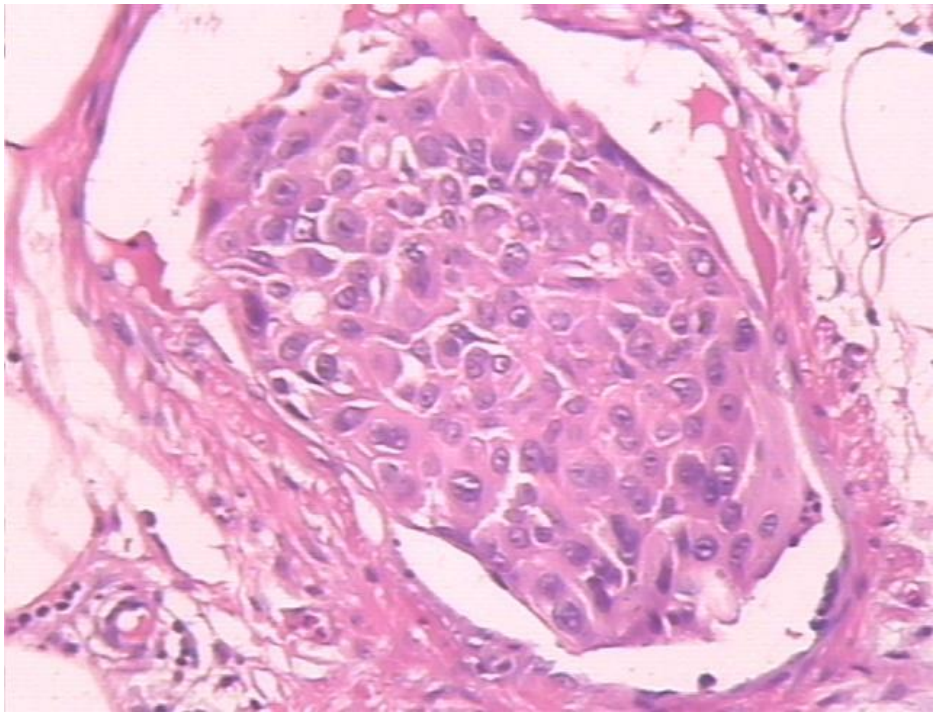
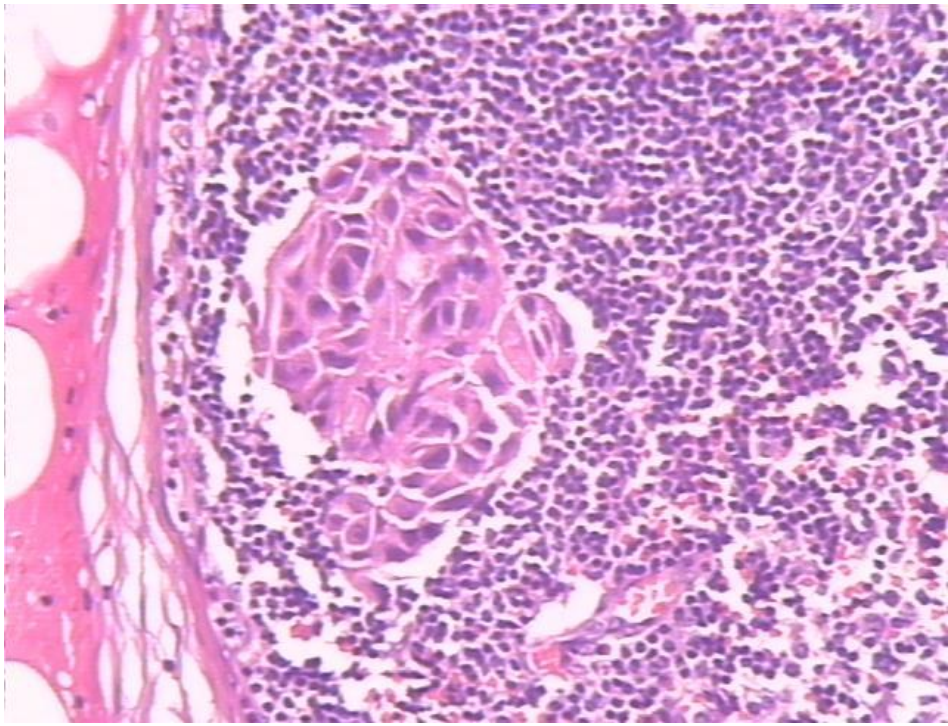
Tumor





Lymphatic metastasis

Route of Metastasis

1. Lymphatic Metastasis
2. Hematogenous Metastasis
3. Implantation Metastasis

Route of Metastasis

1. Lymphatic Metastasis
2. Hematogenous Metastasis
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② Hematogenous metastasis

a. This pathway is typical of sarcoma but is also used by carcinoma

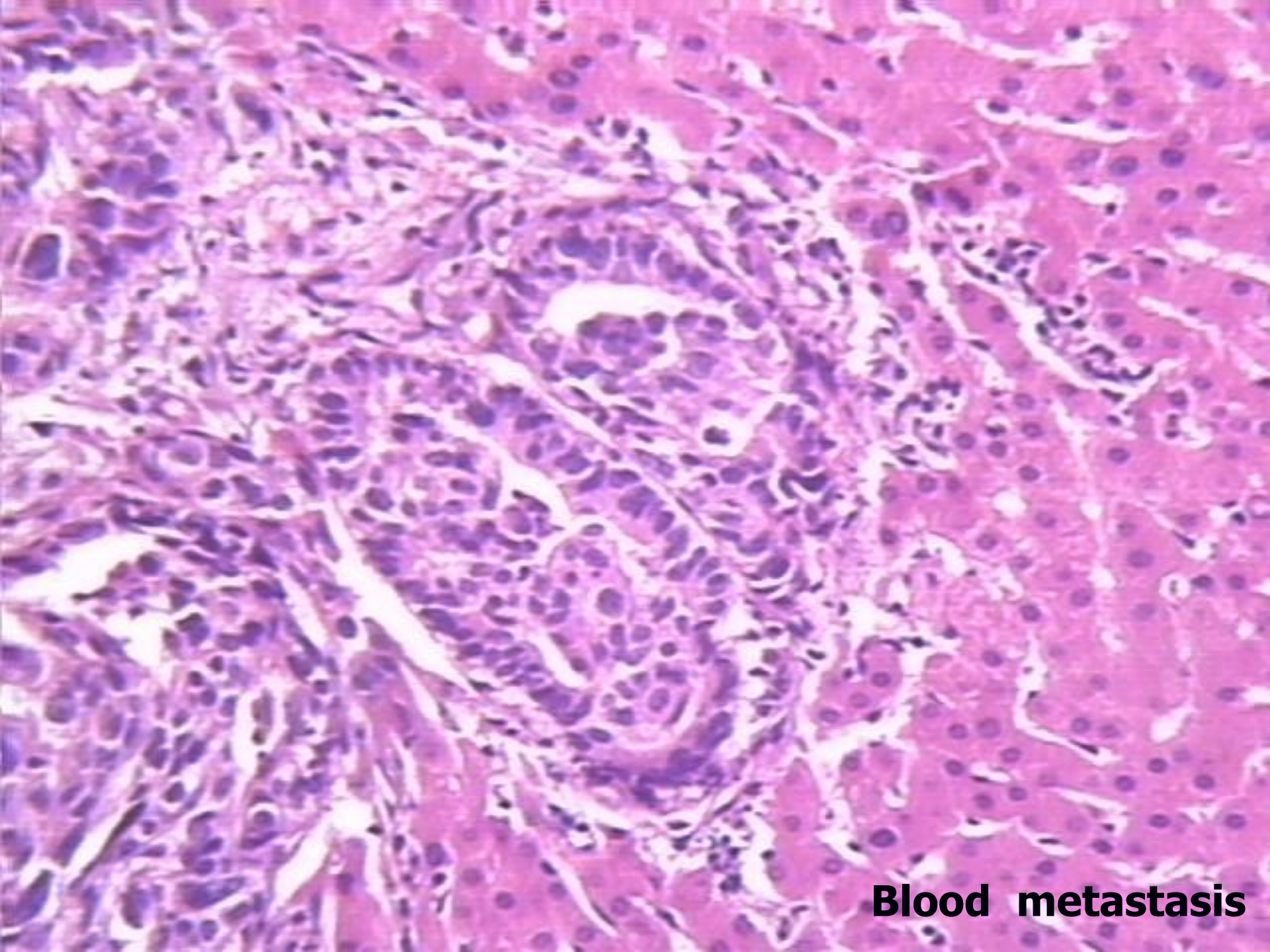
b. **Process:** tumor cells →small blood vessels→ tumor emboli→ distant parts→ adheres to the endothelium of the vessel→ invasive the wall of the vessel→ proliferate in the adjacent tissue→ establish a new metastatic tumor.

c. follow the direction of blood flow. Tumors entering the superior or inferior vena cava will be carried to the lungs tumors entering the portal system will metastasize to the liver.

d. Some cancers have preferential sites for metastases, lung cancer metastasize to the brain,

Prostate cancer frequently metastasize to the bones.

e. Morphologic features of metastasis tumors multiple, circle, scatter


Blood metastasis

Invasion-Metastasis Cascade Adapted from Fidler, Nat. Rev. Cancer 3: 453-458, 2003

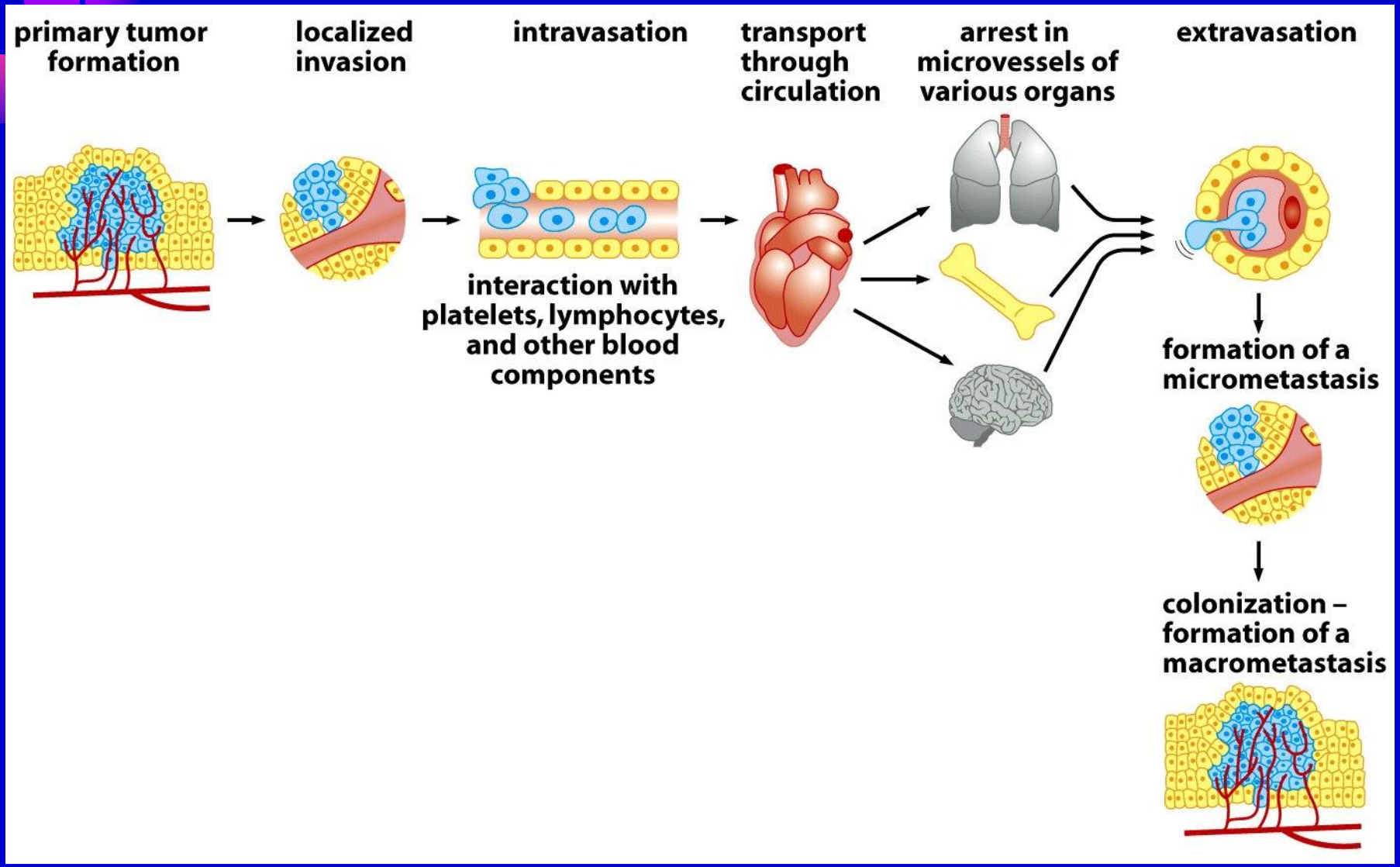
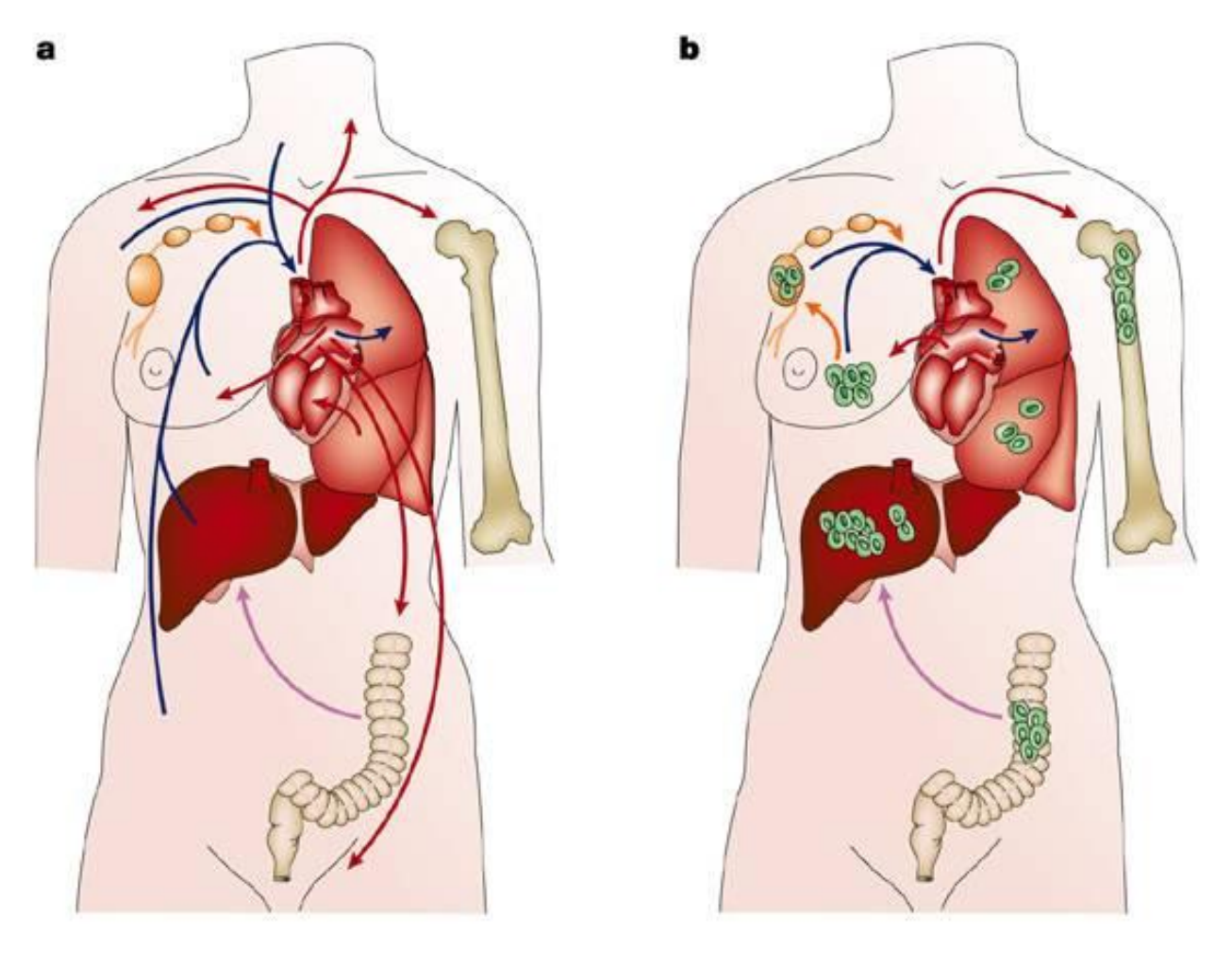


Figure 14.4 *The Biology of Cancer* (© Garland Science 2007) p. 591

Vascular Routes of Cancer Spread

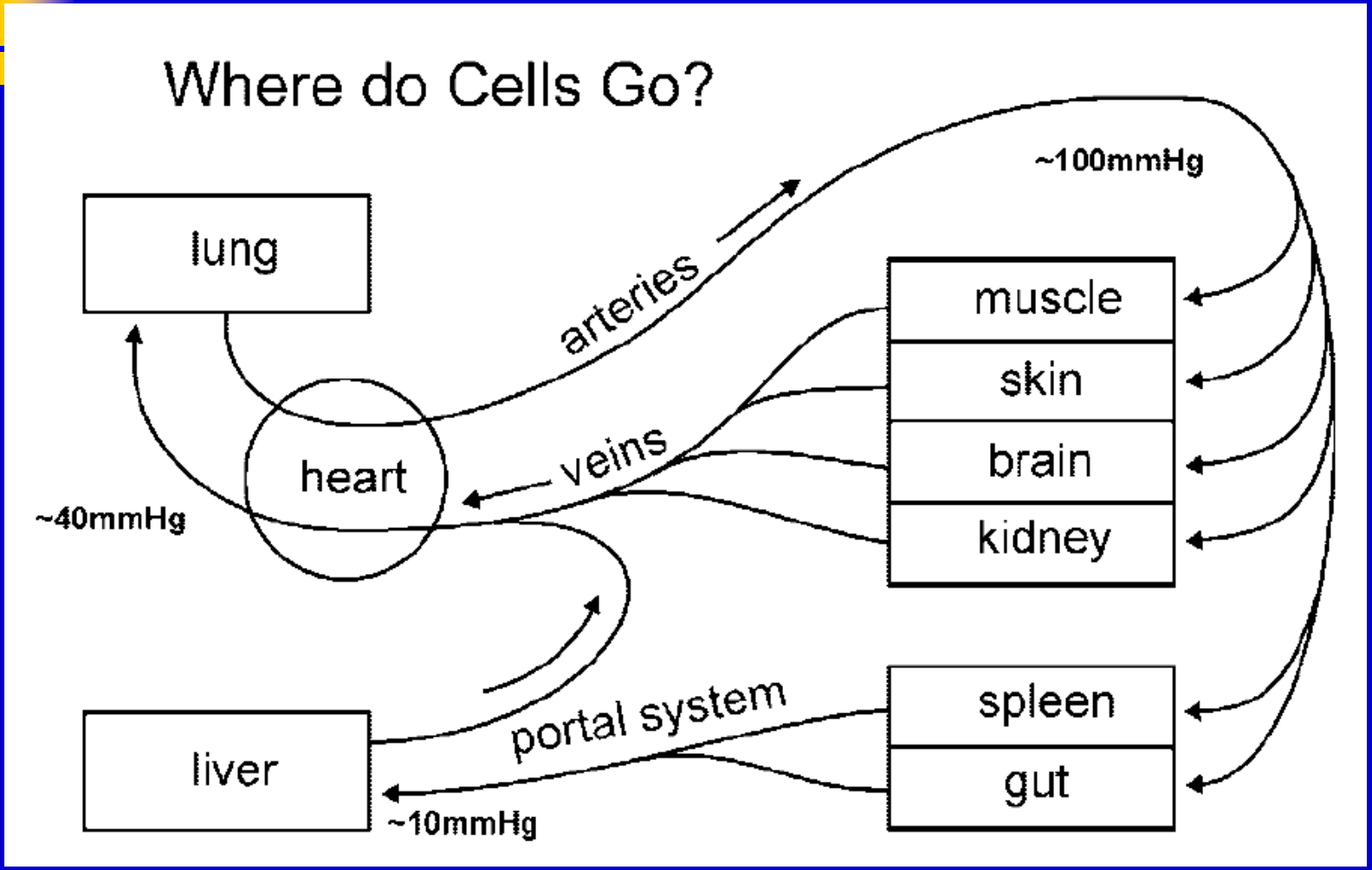


Red = arterial
Blue = venous; Purple = portal
Yellow = lymphatic

Breast vs Colon CA

Chambers, et al, 2002

Hematogenous Spread



MacDonald, et al, 2002

Weiss, 1992

Organ site preference for metastasis

Breast adenocarcinoma	Bone, brain, adrenal
Prostate adenocarcinoma	Bone
Lung: SCLC	Bone, brain, liver
Melanoma - cutaneous	Brain, liver, colon
Thyroid adenocarcinoma	Bone
Kidney clear cell carcinoma	Bone, liver, thyroid
Testis carcinoma	Liver
Bladder carcinoma	Brain
Neuroblastoma	Liver, adrenal
Colon cancer	Liver

Metastasis is not a random event!

Primary Tumors and Preferred Sites of Metastatic Spread

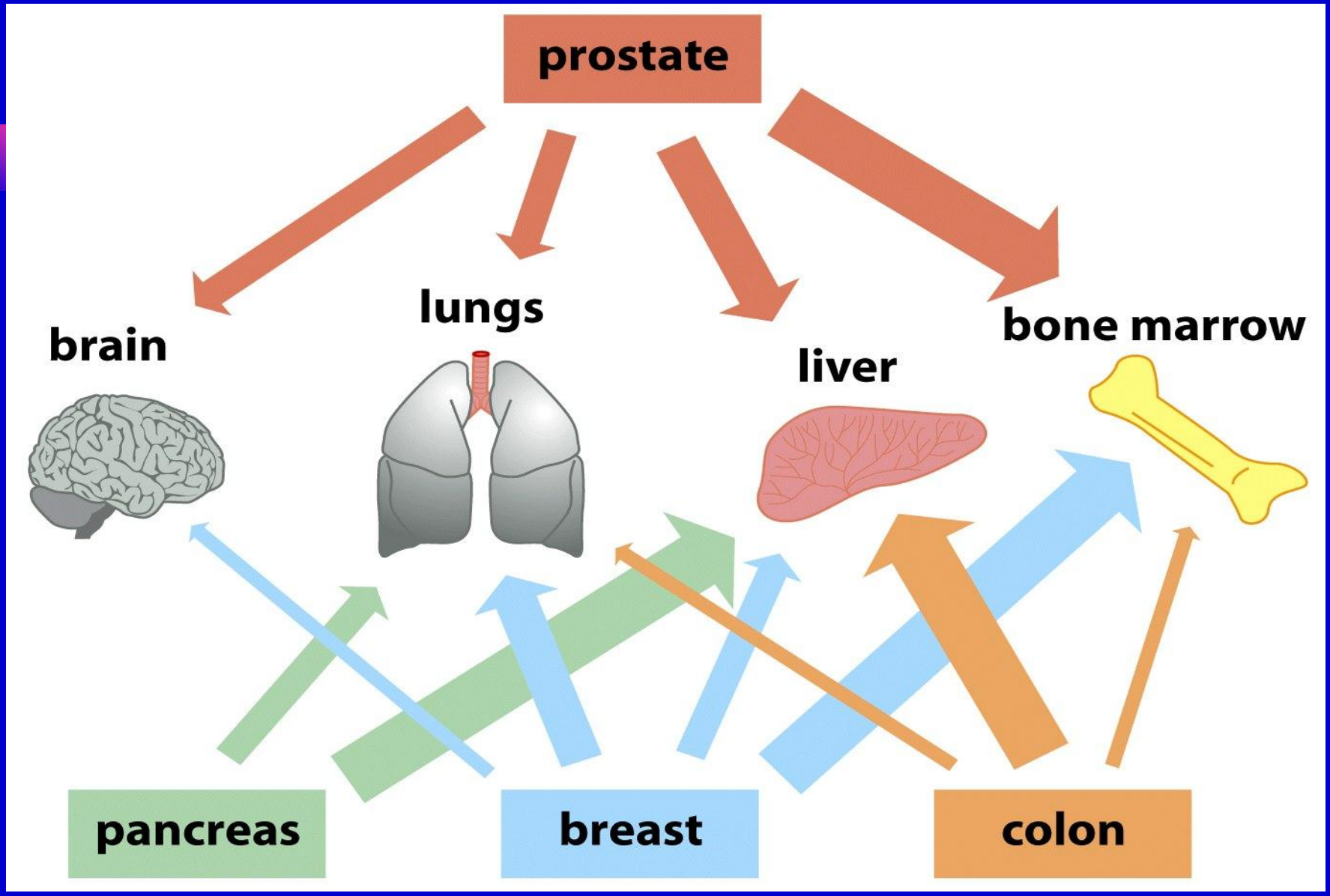


Figure 14.42 *The Biology of Cancer* (© Garland Science 2007)

p. 635

Factors Contributing to Metastatic Spread

1. Metastasis-Associated Up-regulated Genes

2. Host Responses (not necessarily immunological)
   - Inflammatory responses Clot Formation
   - Cytokine and Growth Factor Production

3. Tumor Responses
   - Tumor-induced immune suppression

4. Possible Facilitation of Metastasis by Treatment

- **Diagnostic and surgical manipulation**
- **X-ray Damage**
- **Immune suppression**

  by Drug Treatment

  by Surgery and Anesthesia

  by Stress Hormones

Factors Hindering Metastatic Spread

1. **Metastasis-Suppressor Genes:**

e.g. TIMP: Tissue Inhibitor of Metalloproteinases or RhoGD1-2: Down-regulates Rho – Stimulator of Actin Polymerization

2. **Responses**

- **Activated Macrophages**
- **Natural Killer Cells**
- **Cytotoxic Lymphocytes**

3. **Hydrodynamic Effects in Host circulation**

4. **Failure to Recognize and Arrest at Secondary Site**

Presence of Micrometastases and Clinical Prognosis: Breast Cancer

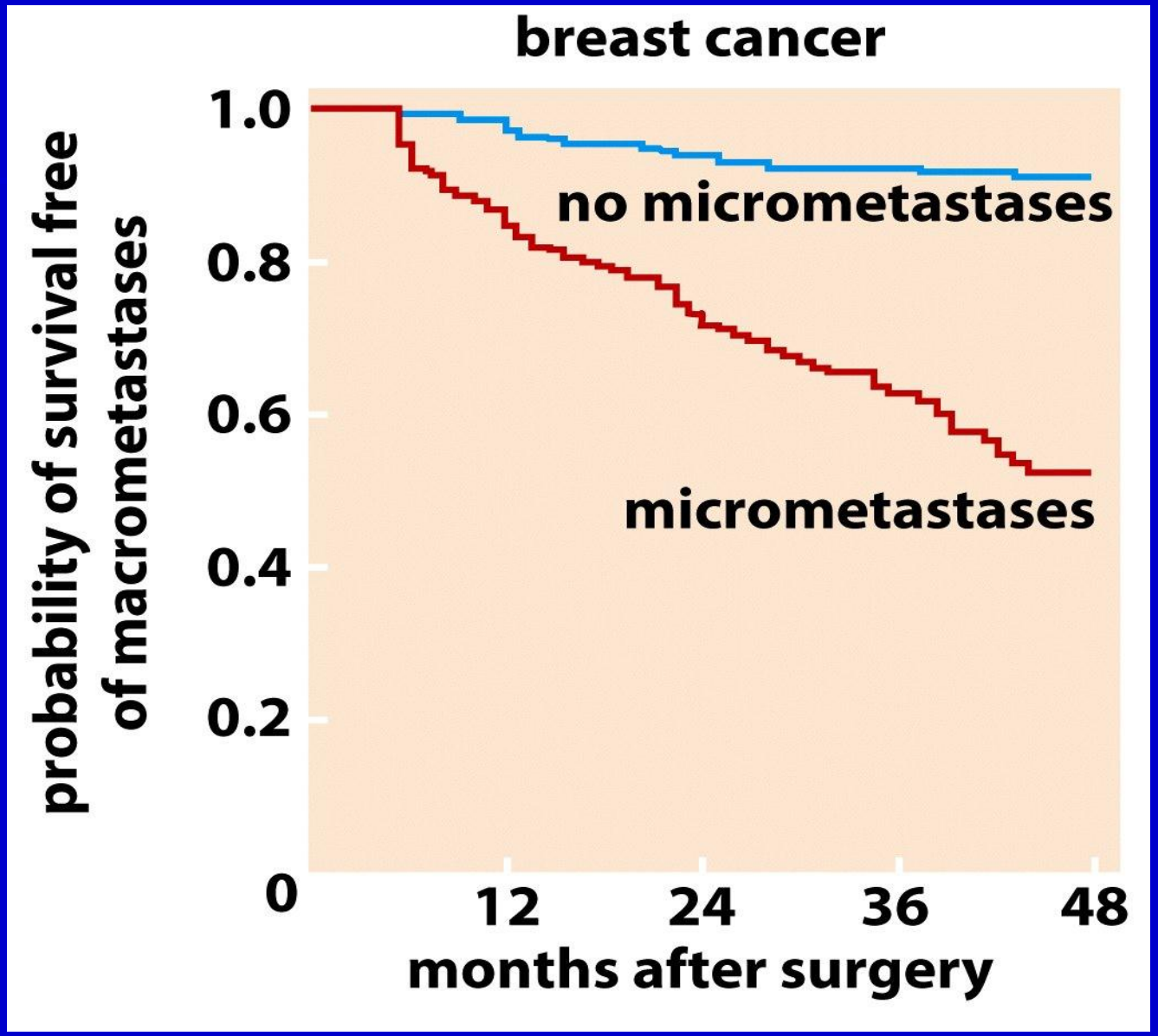


Figure 14.50a *The Biology of Cancer* (© Garland Science 2007)

Presence of Micrometastases and Clinical Prognosis: Colon Cancer

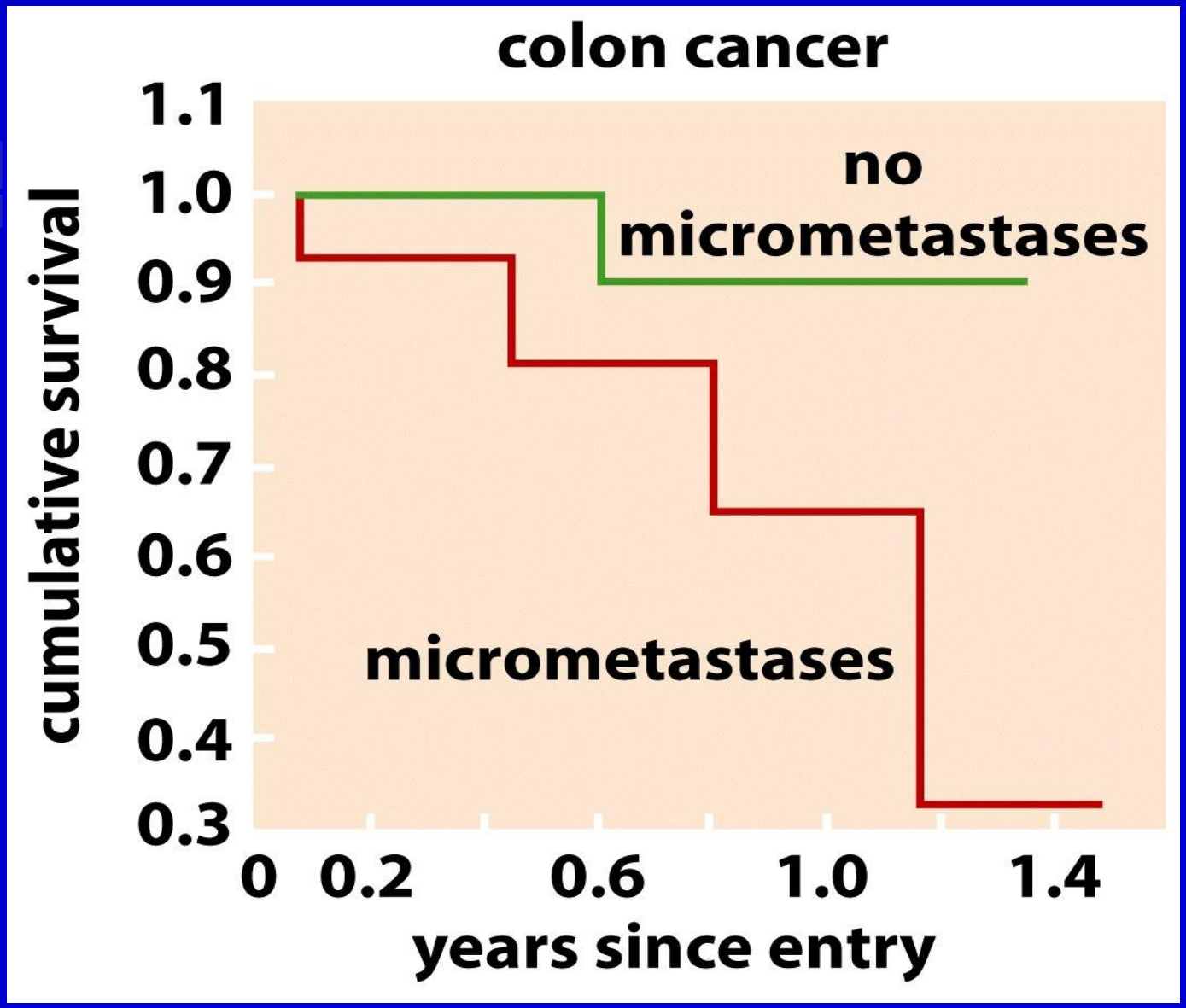
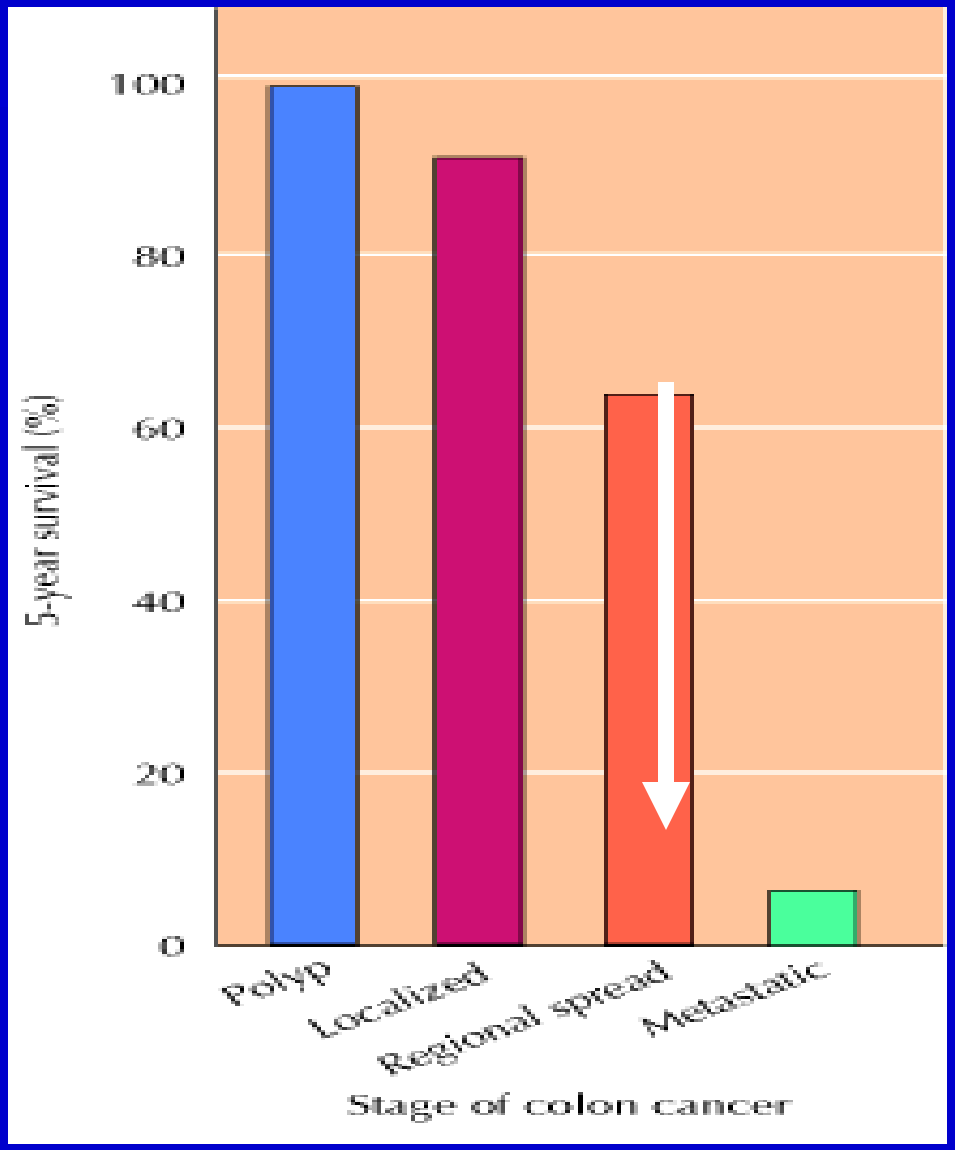


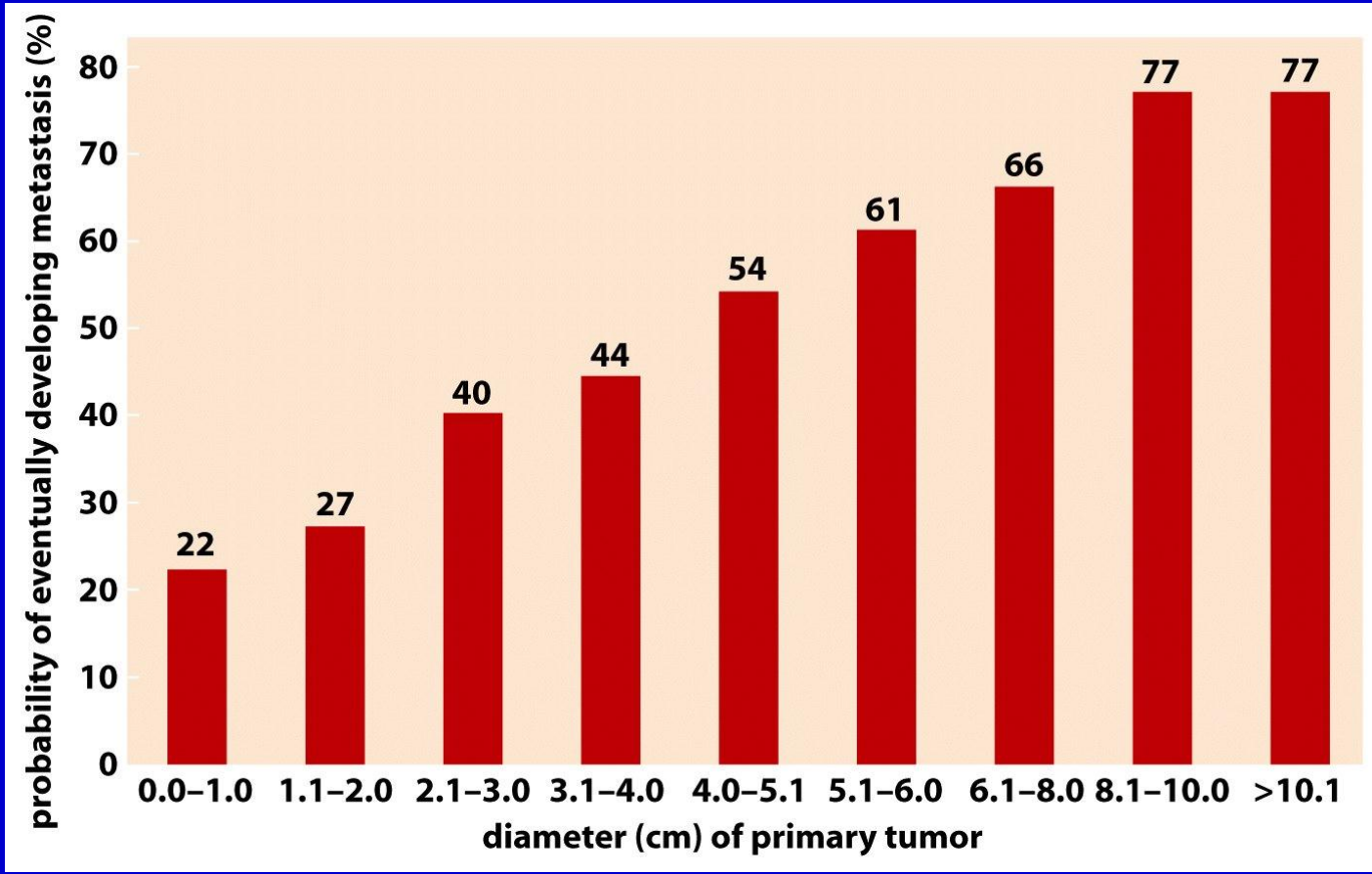
Figure 14.50b *The Biology of Cancer* (© Garland Science 2007)

Colon Cancer: Five Year Survival



from Cooper

The slide below shows a relationship between the size of the primary tumor and the risk of metastases.



Secondary Metastatic Growth

Growth at site of secondary arrest

- **Protection by fibrin clot?**

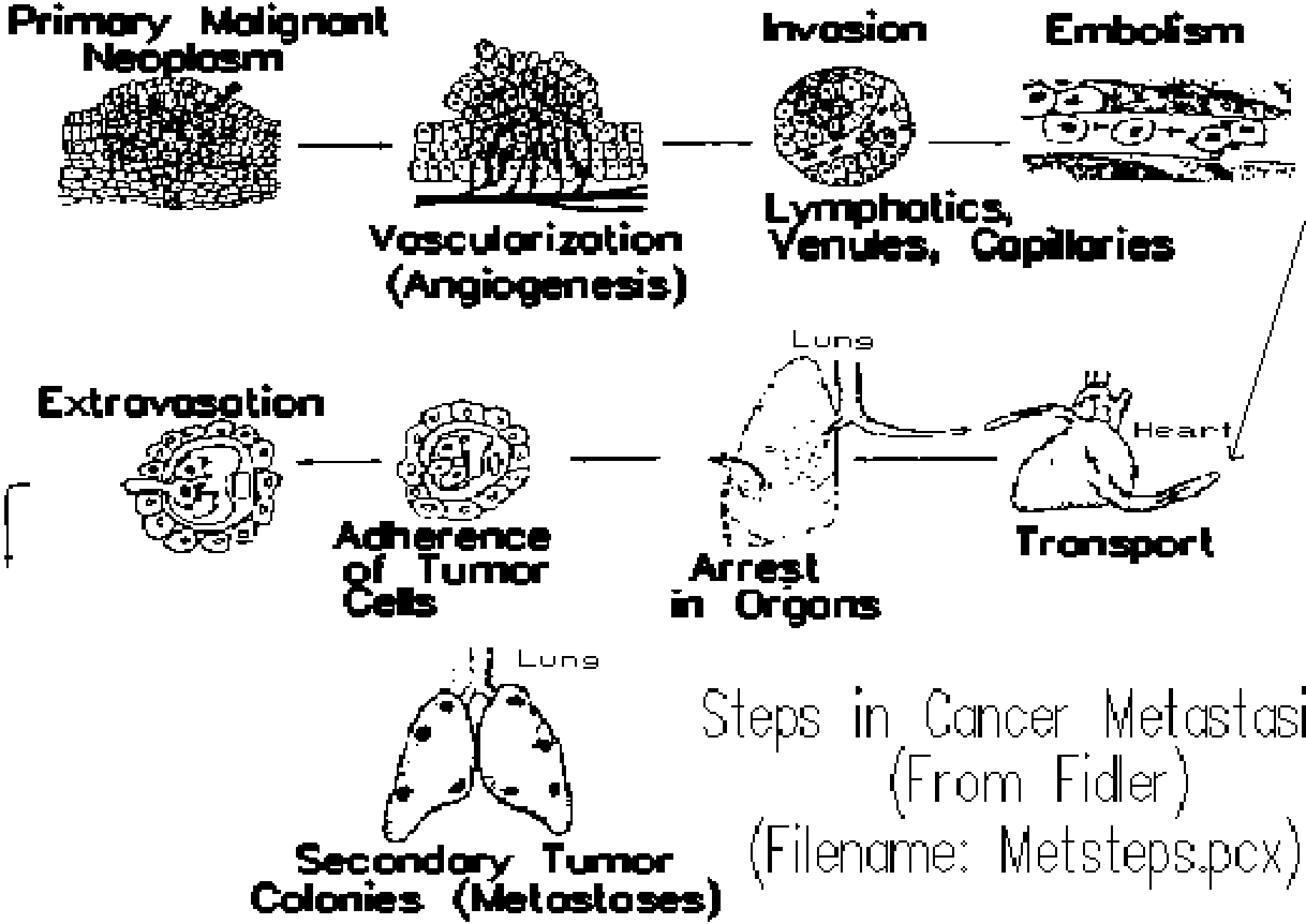
Secondary Invasion

- **Out of vasculature into target tissue**
- **Active**
- **Passive**

Growth of Metastatic Nodules

- **Angiogenesis**
- **Invasion into metastatic organ site**

Potential for Tertiary Invasion



Steps in Cancer Metastasis
(From Fidler)
(Filename: Metsteps.pcx)

Route of Metastasis

1. Lymphatic Metastasis
2. Hematogenous Metastasis
3. Implantation Metastasis

Route of Metastasis

1. Lymphatic Metastasis
2. Hematogenous Metastasis
3. Implantation Metastasis

③ Implantation metastasis

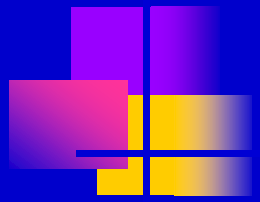
a. Tumor cells seed the surface of body cavities

b. Most often involved is the peritoneal cavity

c. But also may affect pleural, pericardial, subarachnoid, and joint space.

Krukenberg Tumor

- **Krukenberg tumor** refers to a malignancy in the ovary that metastasized from a primary site, classically the gastrointestinal tract (implantation metastasis), although it can arise in other tissues such as the breast



DIAGNOSIS

Diagnosis of Metastasis

- Anamnesis
- Physical Diagnosis
- Lab
- Imaging (X ray, Ultrasound, CT scan ,MRI, PET scan, Scintigraphy)

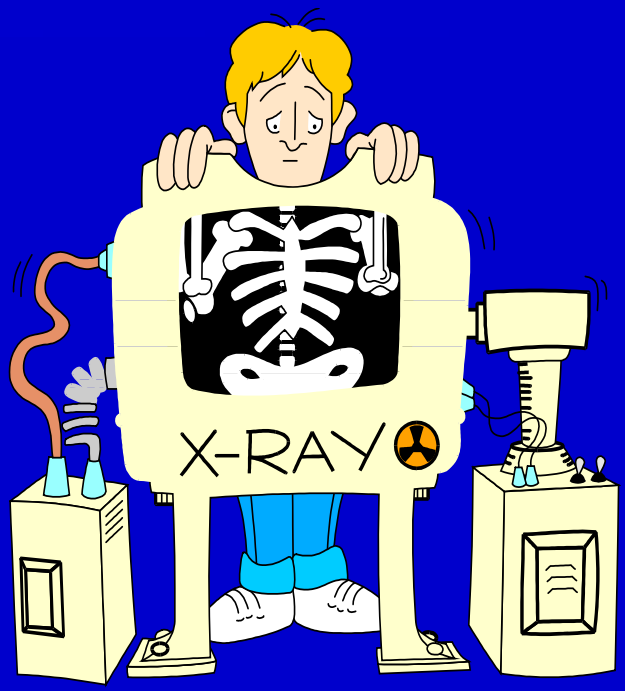
Symptom

- Lung Metastasis
  - Nagging cough, dyspnea (bulky metastasis). Pleural effusion
- Liver Metastasis
  - Dyspepsia syndrome
  - Pain at epigastric
  - Hepatomegali

- Bone metastasis
  - Bone pain, Pathologic fracture
- Brain metastasis
  - Severe headache
  - Vertigo
  - Nausea and vomit

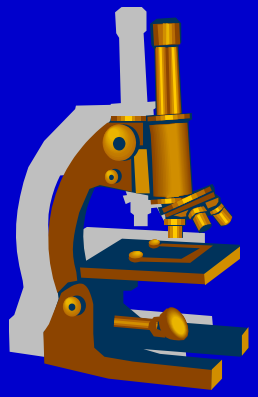
Clinical Finding

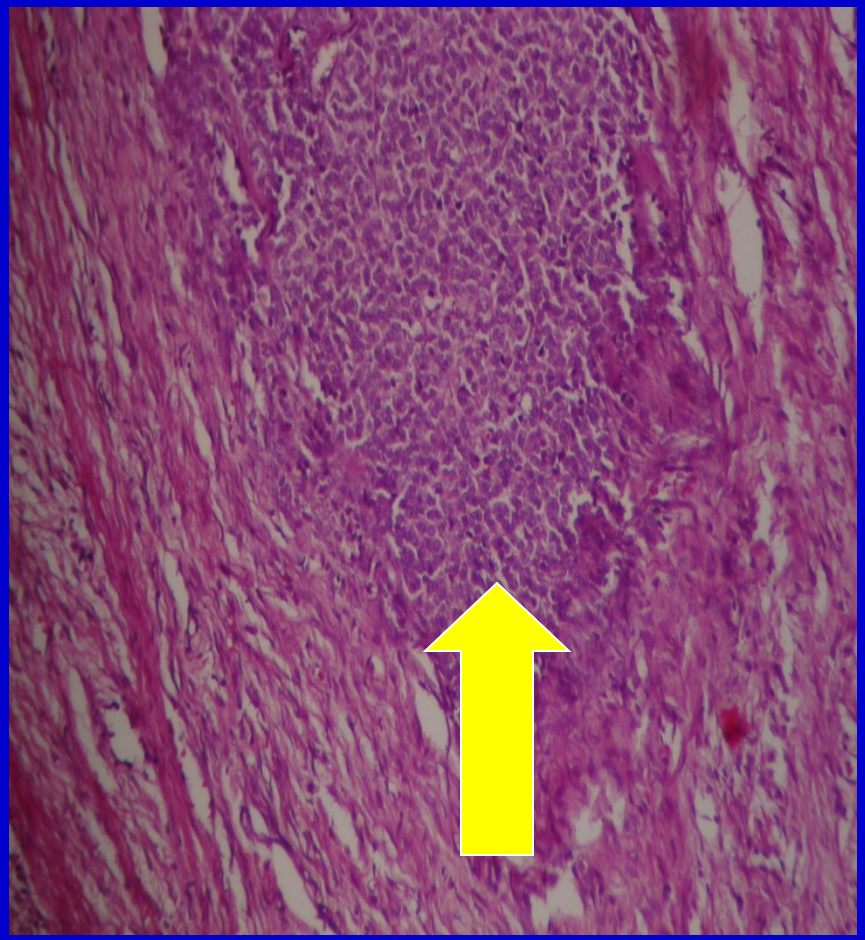
- Lymphadenopathy
- Ascites fluid
- Pleural Effusion
- Hepatic nodule
- Pathologic fracture
- Krukenberg tumor



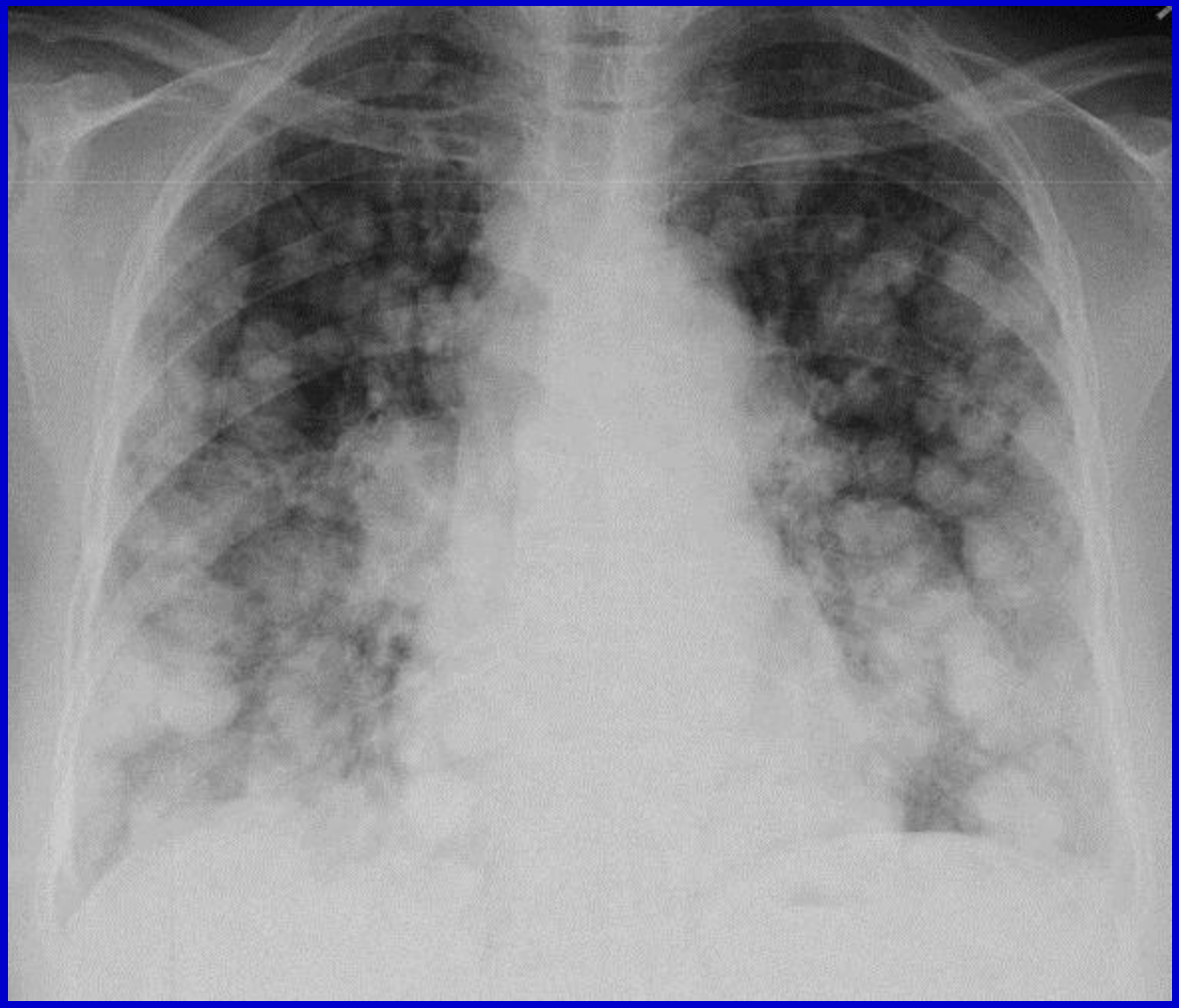
Imaging

- Chest X Ray
- USG
- Bone scan
- CT Scan
- MRI
- Cytology
- Pathology





Coin Lession
(Lung Metastasis by Chest X Ray)



Metastatic Nodule in Lung (CT Scan)

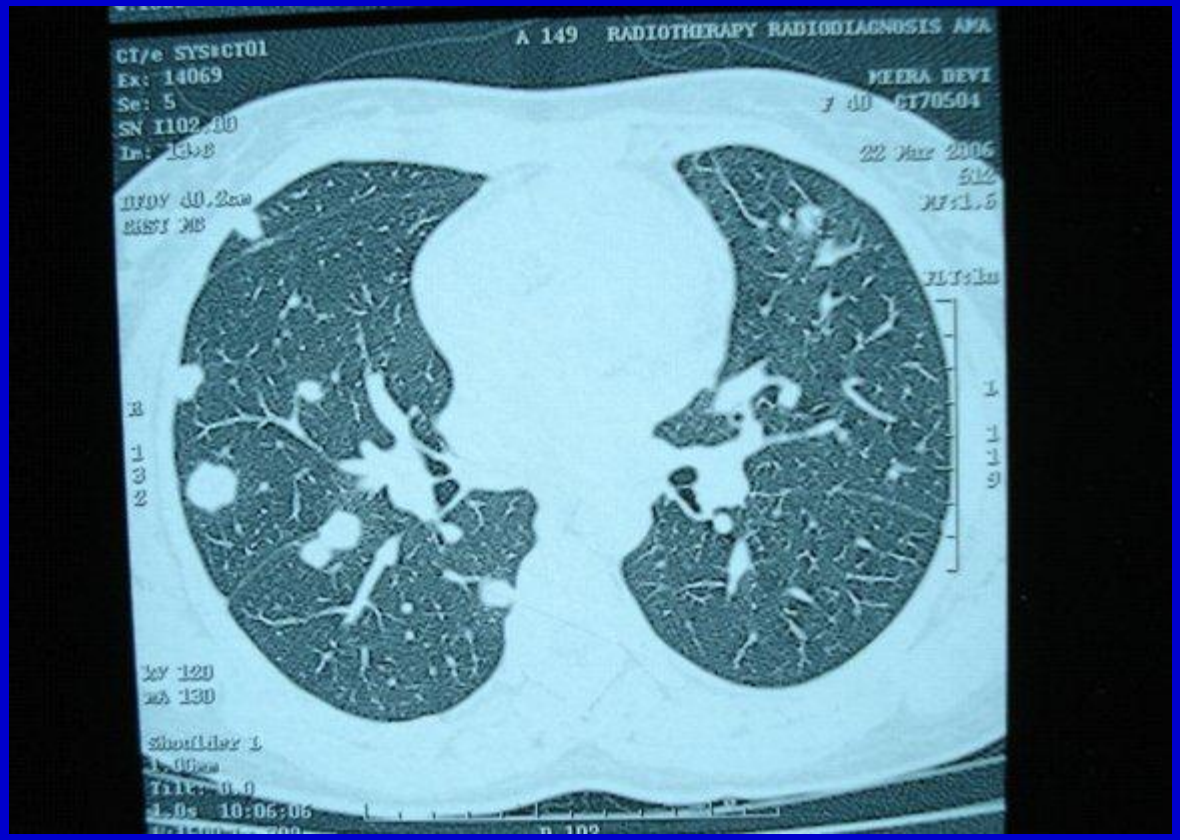


Fig. 2.2b and c

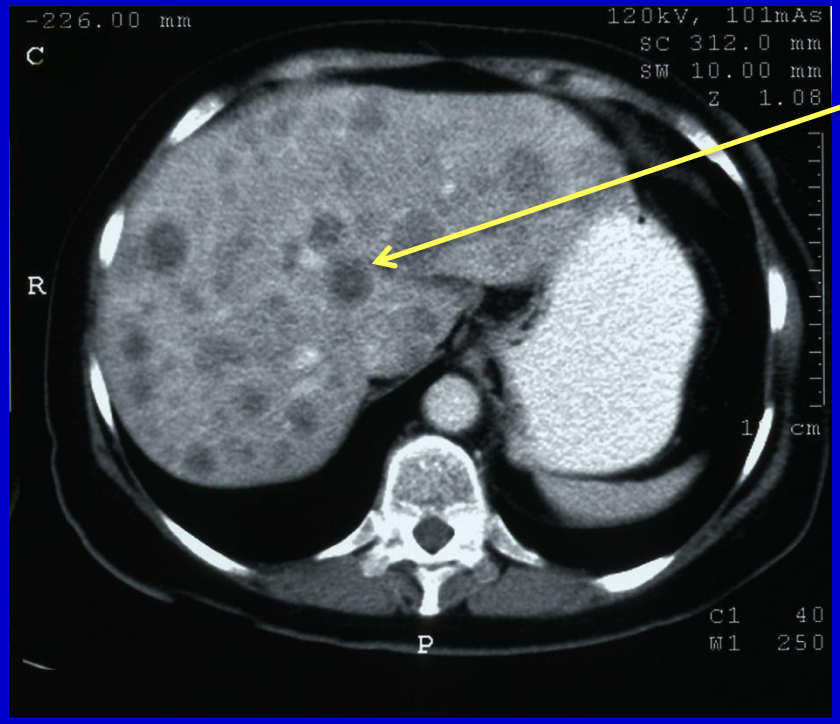
Weinberg

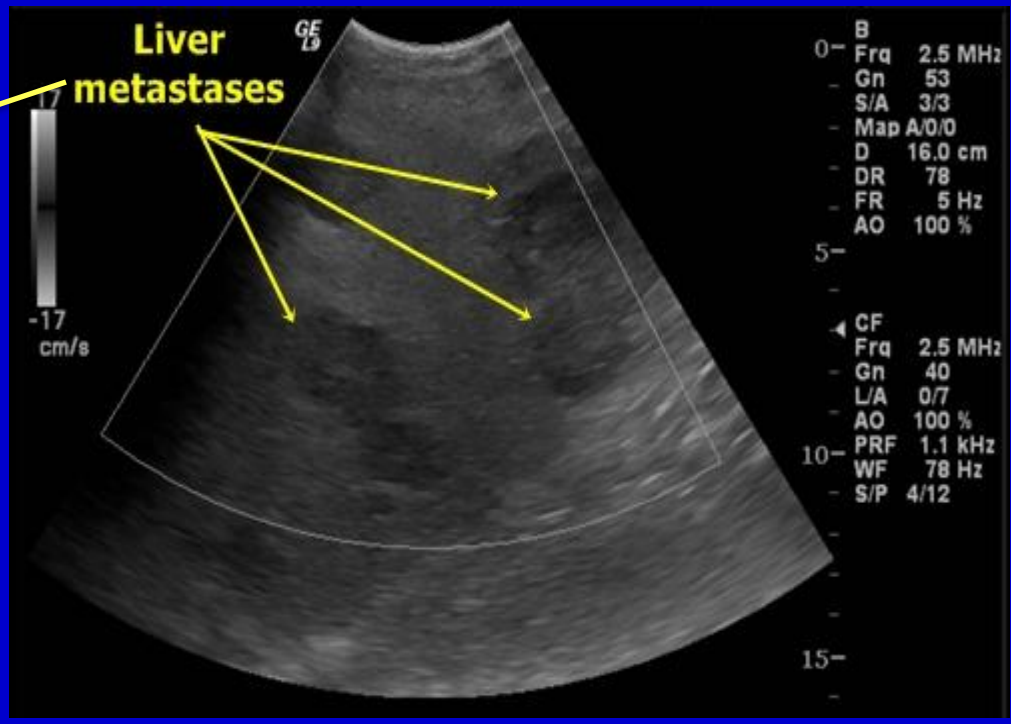
p. 27

Colon Carcinoma Metastatic to Liver

Breast Carcinoma Metastatic to Brain

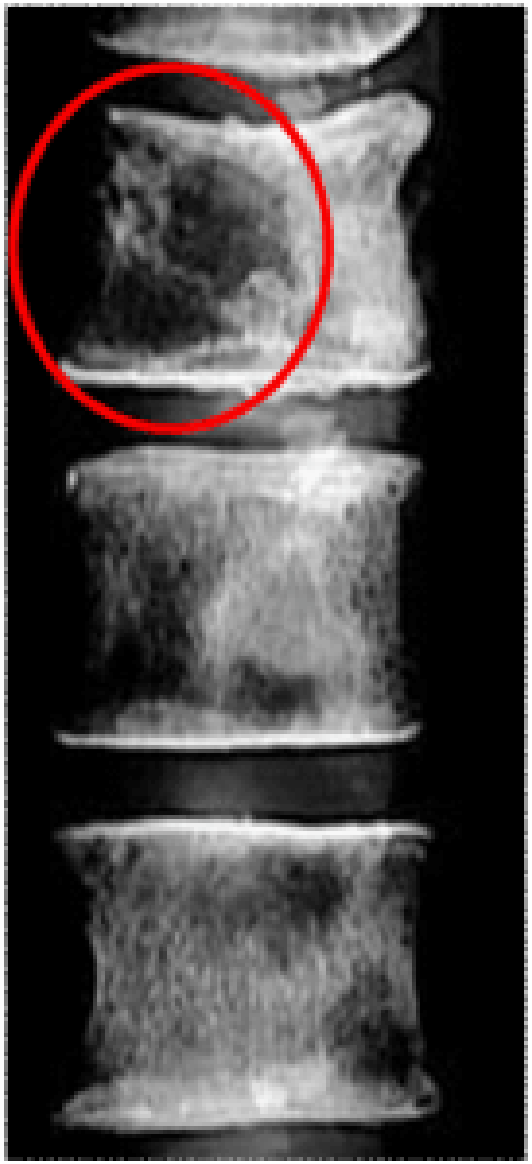
Liver CT scan vs Liver Ultrasound



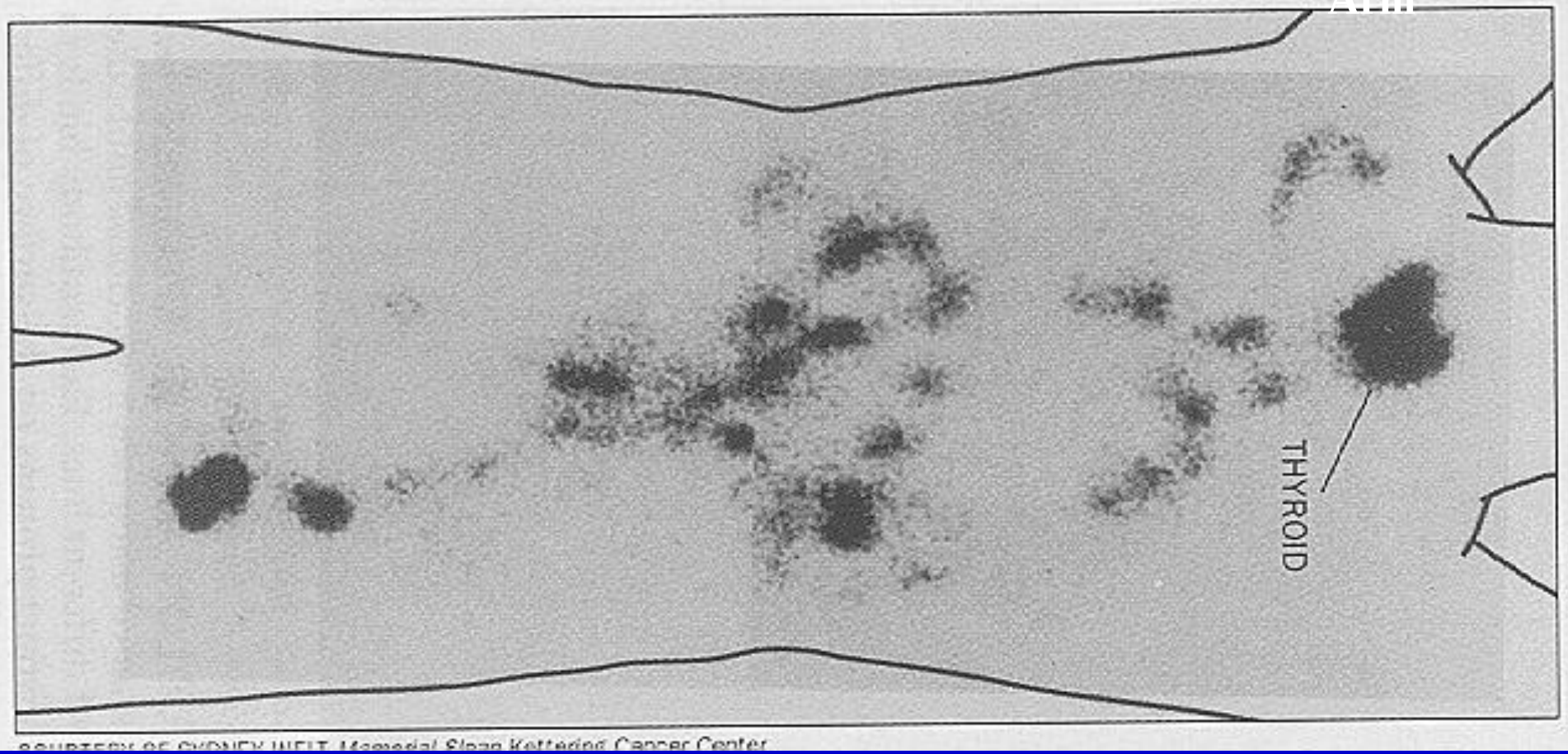


Osteoblastic lesion commonly found in prostate cancer

Osteolytic lesion and weakened bone commonly found in MM and breast cancer

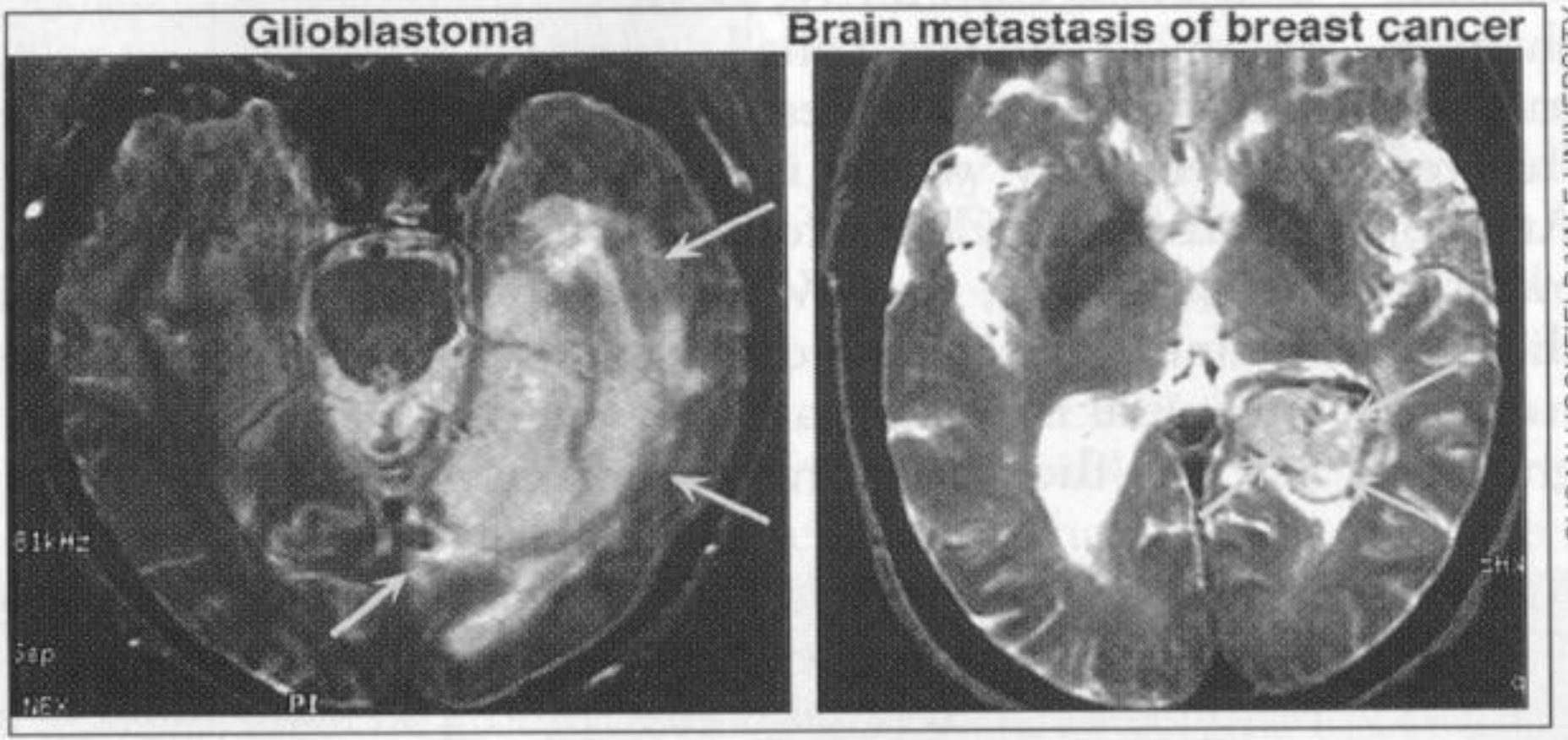


Imaging on Metastatic Colon Carcinoma with Radioactive-Iodine



COURTESY OF SYDNEY WEIT, Memorial Sloan Kettering Cancer Center

Primary Glioblastoma Compared to Breast Carcinoma Metastasis to the Brain



Invasion. Cells fan out into healthy tissue from the border of a human glioma *(left)*. A breast cancer tumor that has metastasized to the brain shows no such invasiveness *(right)*.

MetnGlio

Metastatic non-Hodgkins Lymphoma

CT Scan and PET Scan (positron emission tomography) of incorporated radioactively-labelled deoxyfluoroglucose.

(Brain activity is normal, abdominal active is pathological)

Figure 14.1 *The Biology of Cancer* (© Garland Science 2007). P. 588

Prognosis

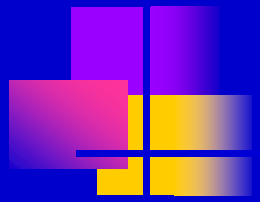
- Lung / Liver metastasis : 8-12 months
- Brain metastasis : 6 months
- Bone metastasis : 2-4 years

Treatment

- Paliative treatment
- Relieve of symptom : pain, dyspneu,severe headache,dyspepsia etc
- Risk and benefit of treatment
- Usually : chemotherapy / hormonal /radiotherapy
- Surgery : depent on situation

Prevention of Metastasis

- Early Diagnosis
- Prompt and Accurate Treatment
- Depend of cancer type



Thank You