

# Metastasis

Biologic foundations and clinicopathologic interpretation

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# Learning objectives

Define metastasis and distinguish it from contiguous local invasion.

Explain variation in metastatic behavior among malignant tumors.

Relate dissemination routes to anatomy, tumor biology, and examination of regional nodes.

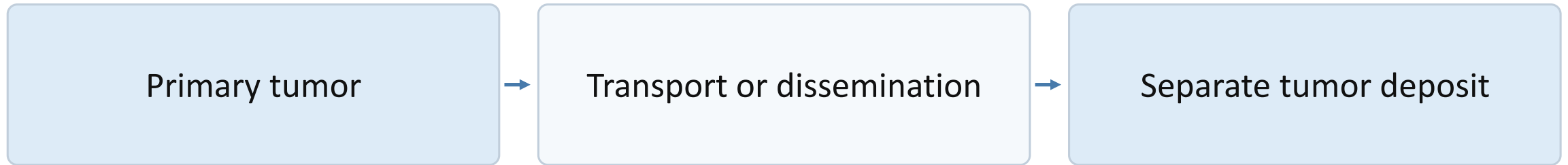
Follow the principal steps from matrix invasion to colonization.

## A precise definition

**Spread of a primary tumor to physically discontinuous sites**

*This finding unequivocally establishes malignant behavior.*

## Discontinuous spread: The essential feature



The secondary focus is not simply direct extension of the primary mass.

Physical separation is the defining spatial distinction.

# Primary tumor and metastatic deposit

## Primary tumor

Original neoplasm at the site of origin.

## Metastatic deposit

Tumor at a physically separate site  
derived from the primary.

*A metastatic focus is malignant even when its morphology is well differentiated.*

# Metastasis is a decisive marker of malignancy

Benign neoplasms lack the capacity to establish true metastases.

The finding is stronger evidence of malignancy than growth rate or apparent circumscription.

An absence of detectable metastases does not establish benignity.

# Invasion and metastasis are distinct properties

## Local invasion

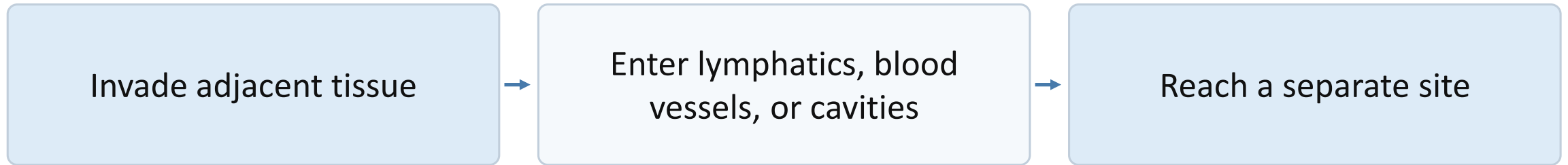
Tumor infiltrates contiguous surrounding tissues.

## Metastasis

Tumor establishes a separate focus at a distant or noncontiguous site.

*A tumor may invade early yet metastasize only rarely.*

# How invasion creates access to dissemination



Invasion creates opportunities for spread; It does not guarantee successful colonization.

## Benign masses usually remain localized

### Benign pattern

Expansile, often circumscribed growth;  
No distant spread.

### Malignant pattern

Infiltration across tissue planes; Possible  
distant deposits.

*A capsule or smooth border alone is not a universal discriminator.*

## Why local invasion matters even without spread

Destruction of adjacent structures can cause morbidity without metastasis.

Infiltrative margins make complete excision more difficult.

Local behavior and metastatic potential require separate assessment.

## Malignant tumors differ in metastatic frequency

Malignant tumors have metastatic potential, but expression of that potential varies widely.

Many carcinomas spread readily; Selected invasive cancers seldom disseminate.

A universal rate or timetable cannot be assigned to “malignancy.”

## Gliomas illustrate an important exception

Glial malignancies within the central nervous system can be highly locally invasive.

Despite invasion, extracranial metastases are uncommon.

Clinical severity can reflect local destruction rather than systemic deposits.

## Basal cell carcinoma illustrates another exception

Basal cell carcinoma is malignant and can invade adjacent tissue.

Distant metastasis is very rare.

Its malignant classification does not depend on frequent systemic spread.

# Why those exceptions matter

## Incorrect inference

“Rarely metastasizes” means the lesion must be benign.

## Correct inference

Invasiveness and metastatic dissemination are biologically separable.

*Do not use a single behavior in isolation to classify a tumor.*

## Hematologic malignancies are a special case

Leukemias and lymphomas derive from cells capable of physiologic circulation.

They often involve multiple anatomic sites at presentation.

Their malignant status does not require the solid-tumor pattern of metastasis.

# Solid tumors versus blood cancers

## Solid tumors

Arise from cells not normally circulating freely; Spread is acquired.

## Leukemia / lymphoma

Arise from lineages naturally trafficking through blood or lymphoid tissues.

*“Disseminated” is not interpreted identically across these tumor classes.*

## Metastatic disease at presentation



≈ 30%

Approximately 30% of solid tumors present with metastatic disease.

*Robbins estimate; Excludes skin cancers other than melanoma.*

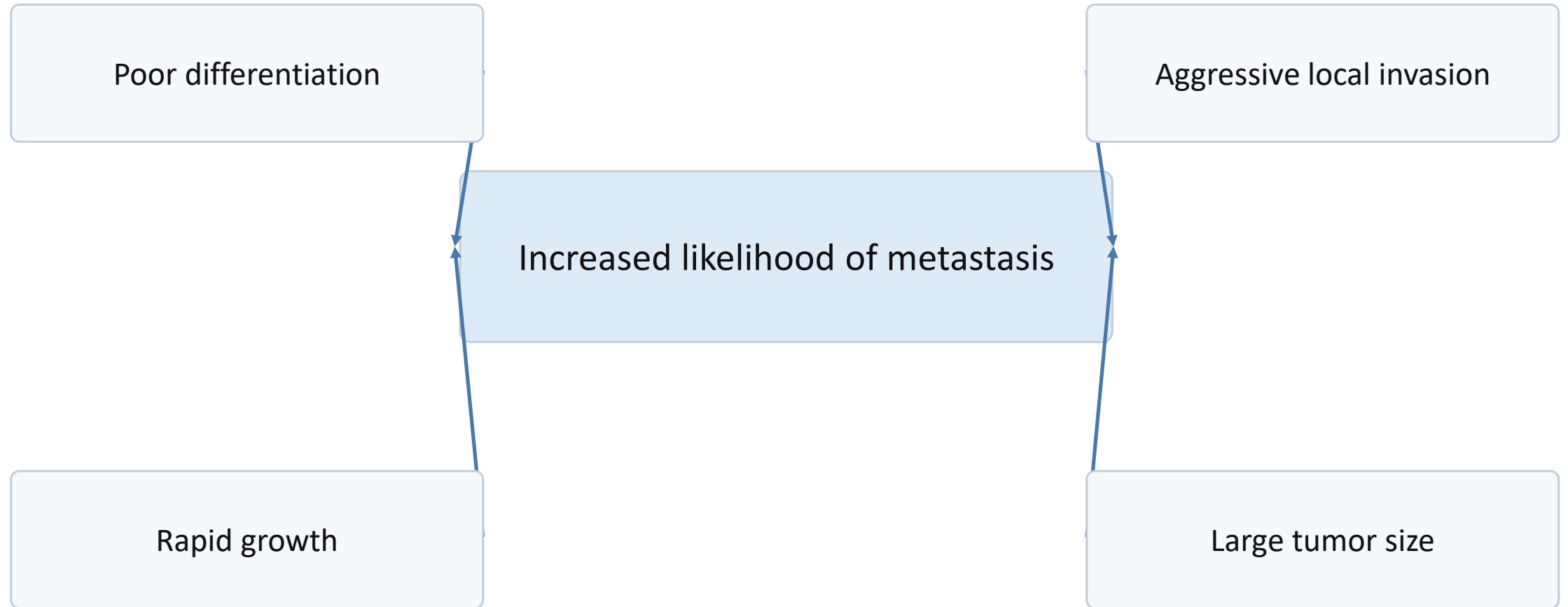
## Interpreting the textbook estimate

The figure describes metastatic disease already present at diagnosis.

It is not the lifetime probability that every solid tumor will metastasize.

The stated exclusion prevents direct application to all cancers combined.

# Features broadly correlated with metastasis



## Poor differentiation: An association

Loss of differentiation commonly accompanies more aggressive tumor biology.

Undifferentiated appearance is a correlate—not proof—of metastatic spread.

Morphology must be interpreted alongside actual stage and observed behavior.

## Aggressive local invasion: An association

Extensive infiltration signals ability to overcome tissue barriers.

Tumors breaching boundaries may gain access to vascular and lymphatic channels.

Invasion provides opportunity; Distant colonization is a further hurdle.

## Rapid growth: An association

Rapidly enlarging malignant tumors more often exhibit aggressive behavior.

Kinetic appearance alone cannot predict whether metastases are present.

Some slow-growing tumors nevertheless develop widespread deposits.

## Large size: An association, not a rule

Increasing primary tumor size often correlates with metastatic likelihood.

Size does not fully capture the tumor's metastatic competence.

A small neoplasm can already have metastasized.

## Small tumors can spread widely

### Primary lesion

Small; Sometimes well differentiated and slow growing.

### Clinical observation

May nevertheless show extensive metastatic deposits.

*Do not equate a reassuring primary appearance with absence of metastasis.*

## Large tumors may remain localized

### Primary lesion

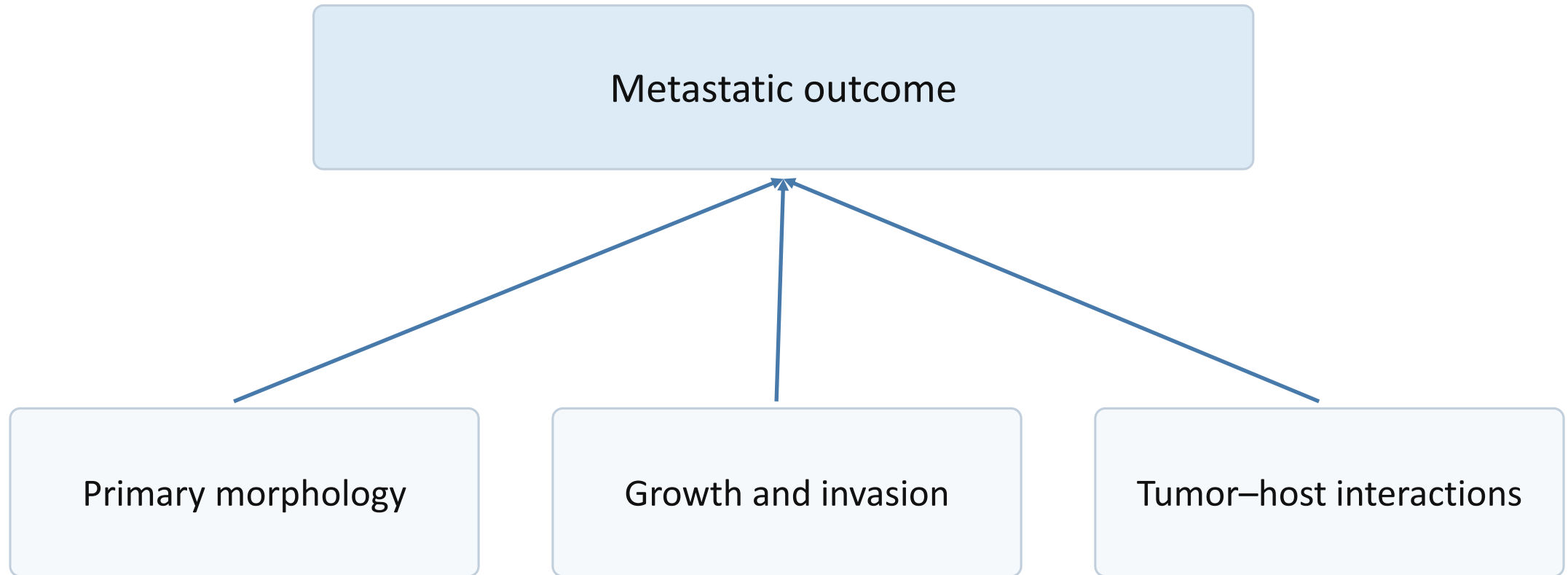
Large and rapidly growing.

### Clinical observation

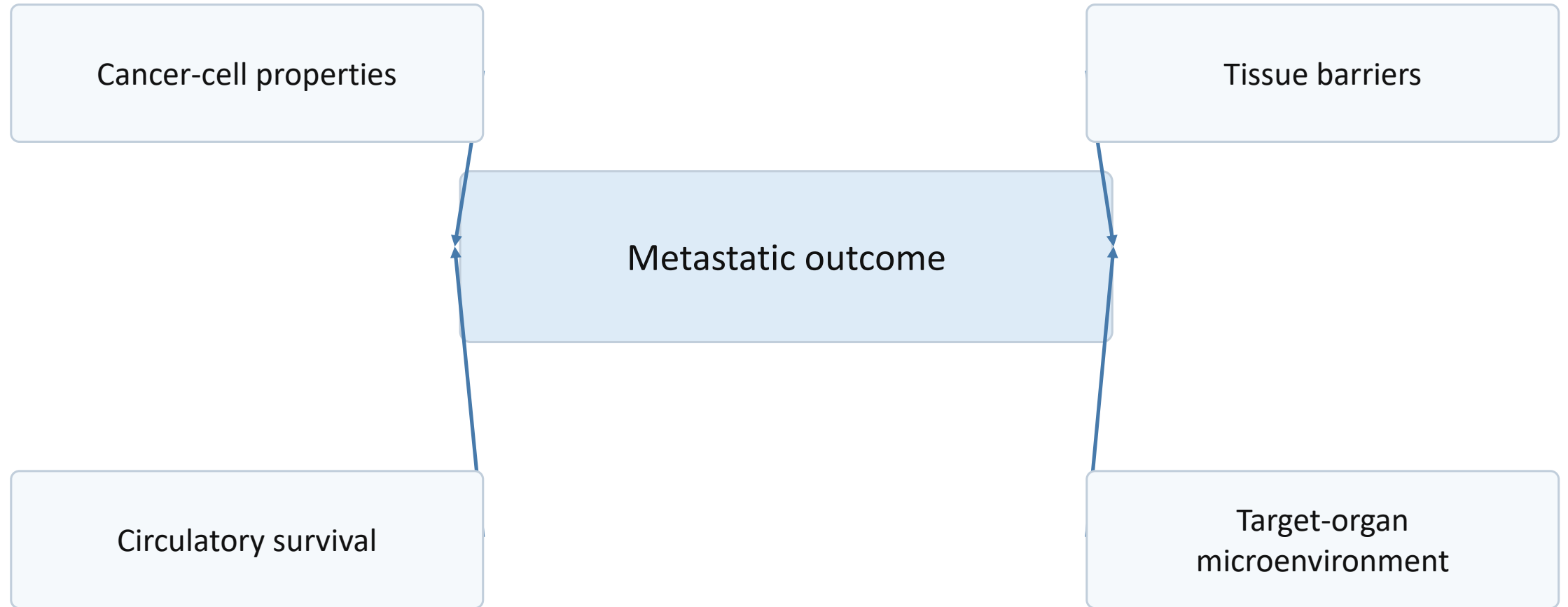
May remain confined to the primary site.

*Metastatic competence cannot be inferred from size alone.*

# No simple metastatic prediction score



# Tumor and host both influence spread



## Why metastasis changes prognosis

Separate deposits indicate disease outside the primary tumor bed.

Complete local excision alone may not eliminate disseminated disease.

Metastatic spread strongly reduces the possibility of cure.

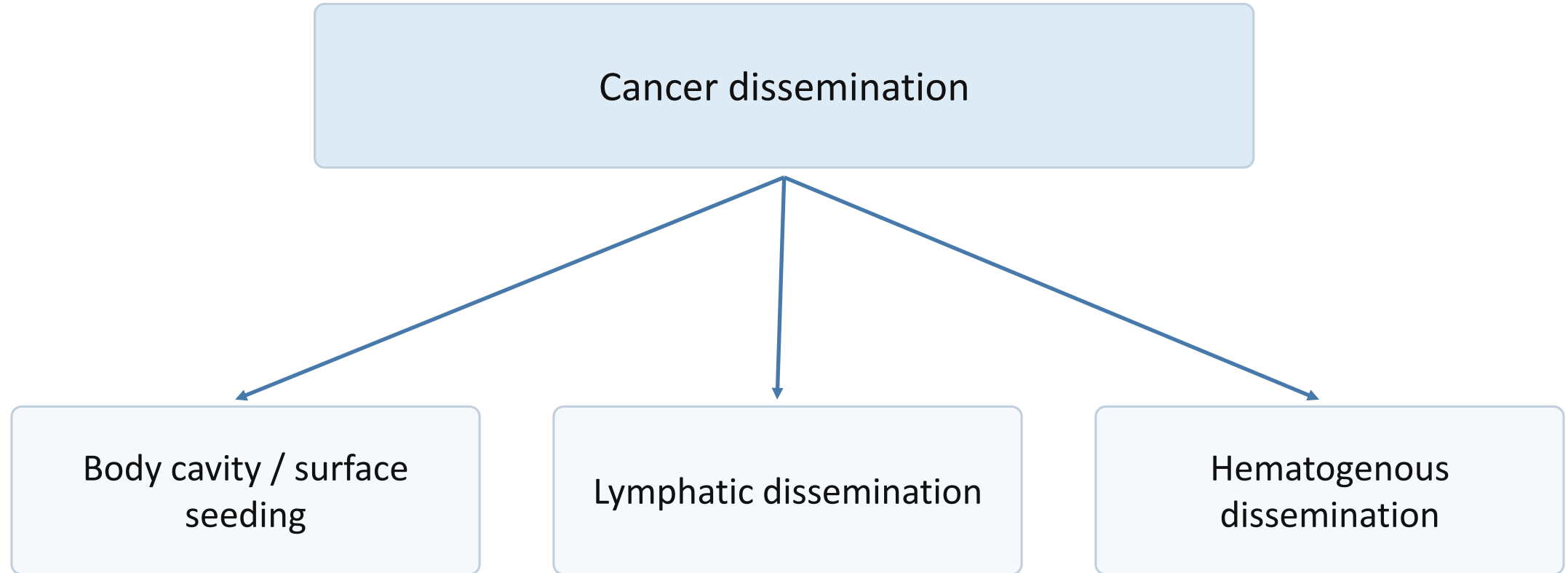
## Metastasis may precede first diagnosis

A clinically apparent primary lesion may already have seeded distant sites.

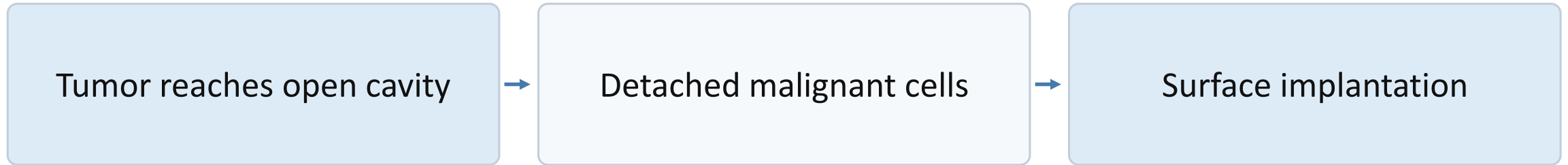
Interventions that only prevent later cell escape may be too late in some patients.

Early detection and systemic disease assessment therefore remain important.

# Three principal routes of dissemination



## Seeding onto open body surfaces



The peritoneal cavity is commonly involved.

Pleura, pericardium, meninges, and joints can also be affected.

## Ovarian carcinoma: Peritoneal seeding

Ovarian carcinomas characteristically disseminate across peritoneal surfaces.

Serosal and omental deposits may produce extensive surface coating.

This is transcoelomic spread rather than a contiguous mass alone.

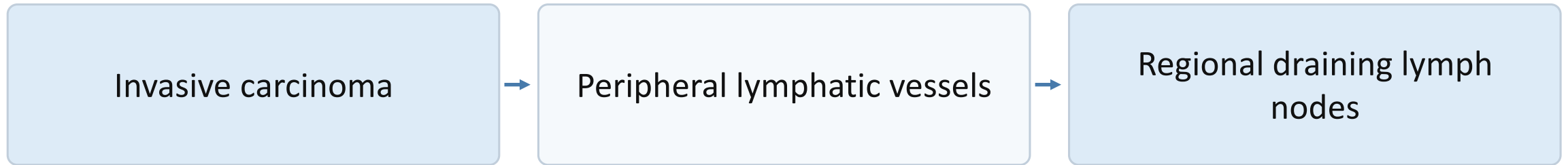
## Pseudomyxoma peritonei: An example

Certain mucin-producing appendiceal or ovarian carcinomas disseminate within the peritoneal cavity.

A gelatinous neoplastic mass can accumulate in the peritoneal space.

Pseudomyxoma peritonei to illustrate surface seeding.

# Lymphatic spread of carcinomas



Most common initial dissemination pathway for carcinomas.

Sarcomas can also use lymphatic dissemination.

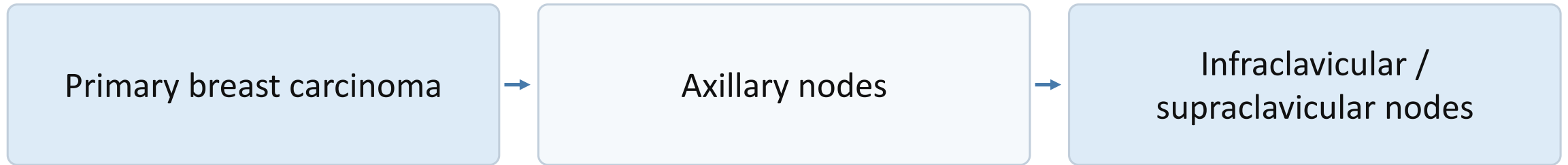
# Lymphatics at invasive tumor margins

Functional lymphatics at the invasive perimeter enable tumor-cell entry.

Those marginal channels from functional vessels within the tumor.

Routes reflect local anatomy and regional drainage.

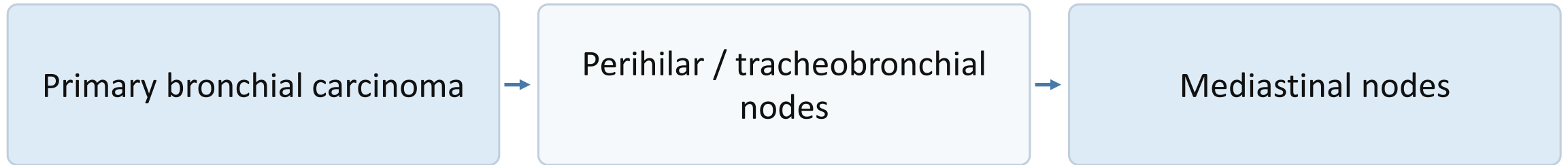
## Breast carcinoma: A drainage example



The described sequence is typical, not inevitable.

Node evaluation has prognostic and therapeutic relevance.

## Lung carcinoma: A drainage example



The anatomical location of the primary shapes expected nodal stations.

# Skip metastasis

## Expected pattern

Sequential spread through an adjacent regional node basin.

## Skip pattern

A more distant node is involved while an expected station is not identified as involved.

*Variable drainage and possibly missed microscopic disease.*

# What is a sentinel lymph node?

**The first node in a regional basin receiving lymphatic drainage from a primary tumor**

*Its evaluation samples an early nodal route of dissemination.*

## Sentinel-node mapping: Rationale



Radiolabeled tracers or dyes can map drainage.

Sampling can reduce the need for extensive regional dissection in selected settings.

## An enlarged regional node is not always metastatic

### **Metastatic involvement**

Malignant tumor cells are found within nodal tissue.

### **Reactive hyperplasia**

Immune stimulation enlarges the node without metastatic tumor.

*Microscopic examination resolves the distinction.*

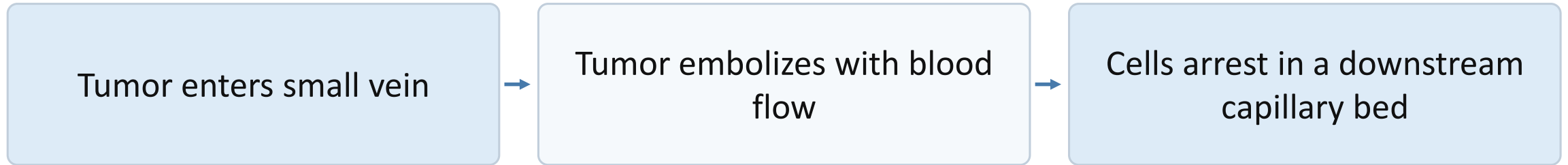
# Hematogenous dissemination

A typical route for sarcomas; Also occurs in carcinomas.

Histologic vascular invasion is an ominous feature.

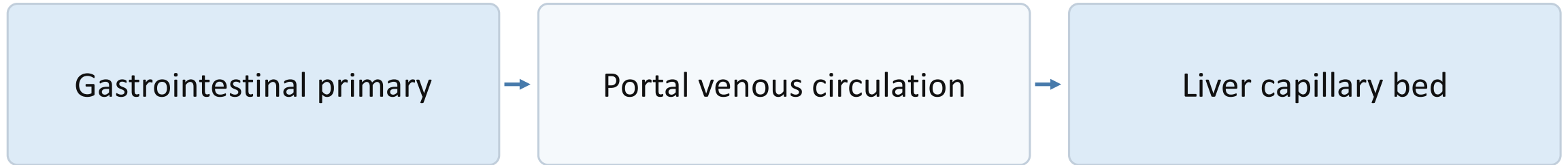
Tumor cells commonly penetrate small veins; Arterial walls are more resistant.

# Why venous invasion is prominent



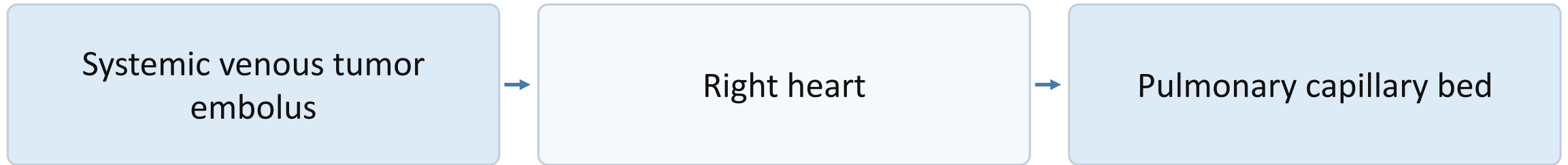
The first capillary filter often influences organ distribution.

## Portal venous drainage predicts liver deposits



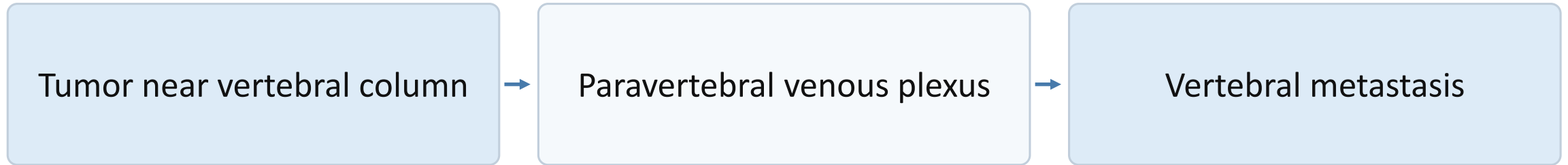
Colon cancer has a strong anatomical pathway for hepatic metastasis.

# Systemic venous drainage predicts lung deposits



Lung is a common site of blood-borne deposits.

## A vertebral route of dissemination



Thyroid and prostate carcinomas as examples.

# Vascular drainage does not explain everything

Metastatic organ patterns can be characteristic of individual cancer types.

Some preferred sites are not predicted by first-pass vascular filtration.

Tumor–endothelial and tumor–tissue interactions also matter.

# Venous extension is not identical to widespread metastasis

## Renal cell carcinoma

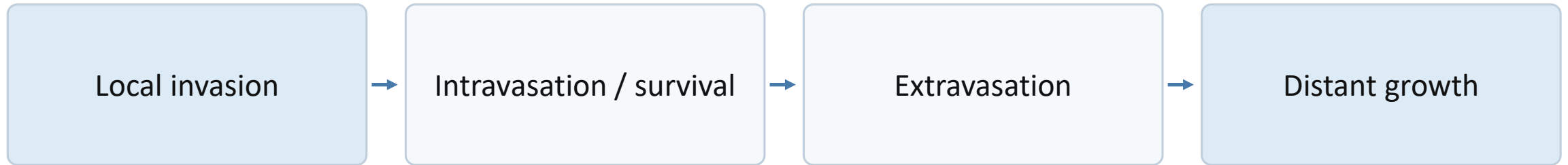
May grow along renal vein into inferior vena cava.

## Hepatocellular carcinoma

May extend into portal or hepatic venous channels.

*Extensive intravascular growth may occur without proportionate distant deposits.*

# The metastatic cascade



A successful metastatic deposit requires completion of multiple distinct steps.

Each step can restrict overall success.

## Matrix barriers are encountered twice

### At the primary site

Cancer traverses epithelial and vascular basement membranes to intravasate.

### At the secondary site

Cancer crosses vessel-associated barriers to invade new tissue.

*Interstitial extracellular matrix lies between these boundaries.*

## Four steps in local extracellular-matrix invasion

1. Reduced cell–cell adhesion



2. Proteolytic remodeling of ECM



3. Attachment to altered ECM



4. Cell migration through matrix

## E-cadherin and epithelial cohesion

E-cadherin mediates homotypic adhesion between epithelial cells.

Reduced adhesion can permit detachment of neoplastic cells.

In selected cancers, mutation or altered expression disrupts E-cadherin function.

# Epithelial–mesenchymal transition: Proposed role

## Epithelial program

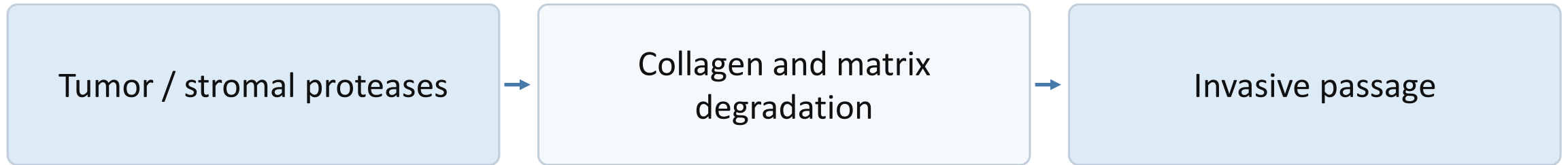
E-cadherin-mediated cohesion and epithelial differentiation markers.

## Mesenchymal-like program

SNAIL / TWIST-associated changes;  
Vimentin and motility-associated features.

*EMT as an implicated mechanism, not a universal prerequisite.*

## Proteases remodel tissue barriers



MMPs, cathepsins, and urokinase plasminogen activator are implicated.

Proteolysis can also liberate matrix-sequestered growth signals.

## Matrix remodeling can amplify invasion

MMP2 and MMP9 cleavage of laminin and type IV collagen exposes new binding sites.

MMP9 can release extracellular-matrix-bound VEGF.

The degraded matrix is not simply a passive gap; It can generate bioactive signals.

# Integrins, attachment, and anoikis

Integrins connect cells to extracellular matrix and transmit survival cues.

Loss of anchorage normally can initiate anoikis, a form of apoptosis.

Tumor cells that resist anoikis can survive detachment and altered matrix attachment.

# Locomotion is an active process

Leading-edge attachment



Actin cytoskeletal contraction

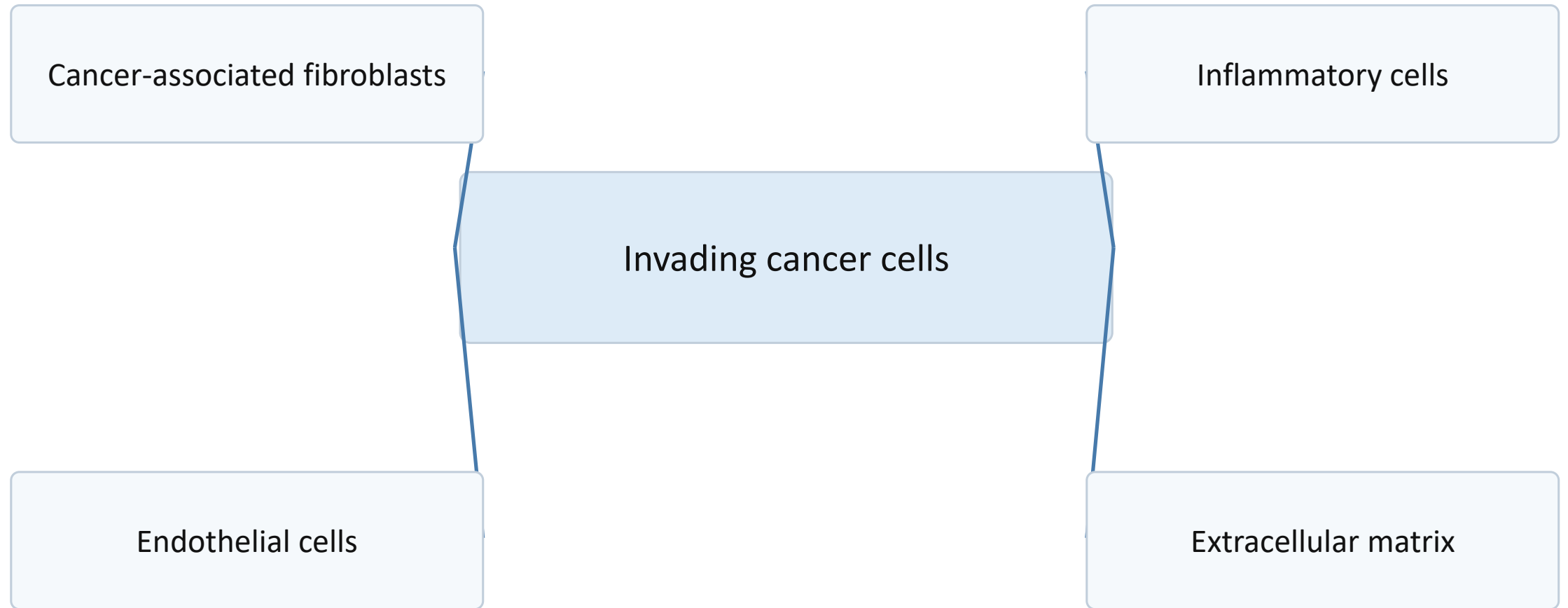


Trailing-edge detachment

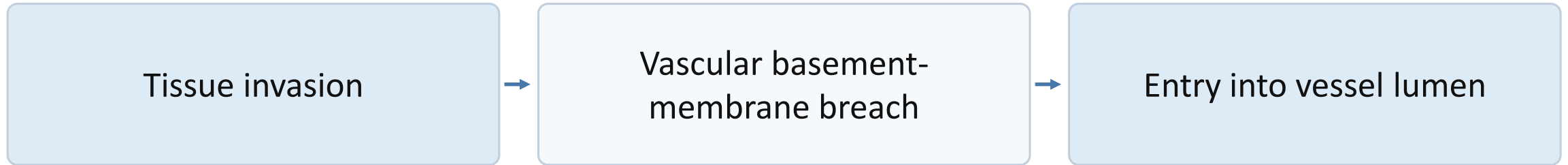
Migration depends on coordinated adhesion, cytoskeletal change, and signaling.

Tumor-derived and stromal motility signals may guide movement.

# Microenvironmental partners in invasion

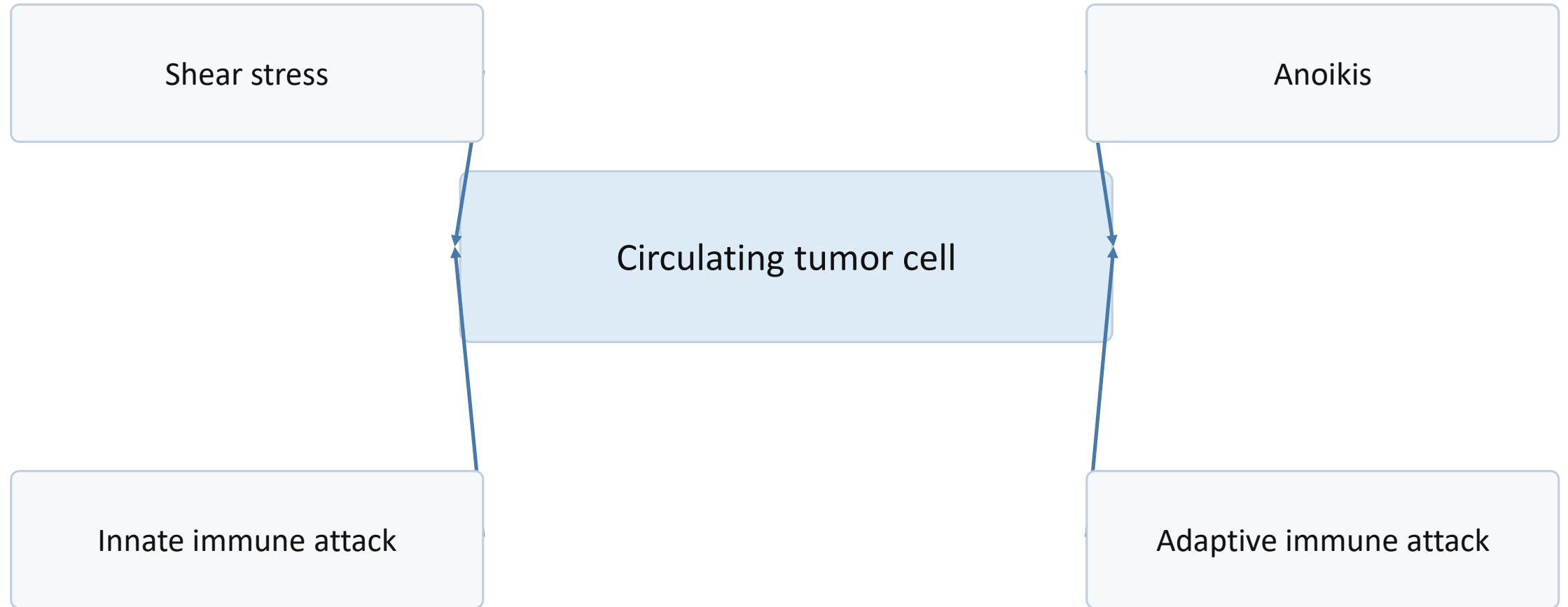


## Intravasation: Entering vascular space



The invasion programme provides physical access to hematogenous spread.

# Survival in blood is a bottleneck



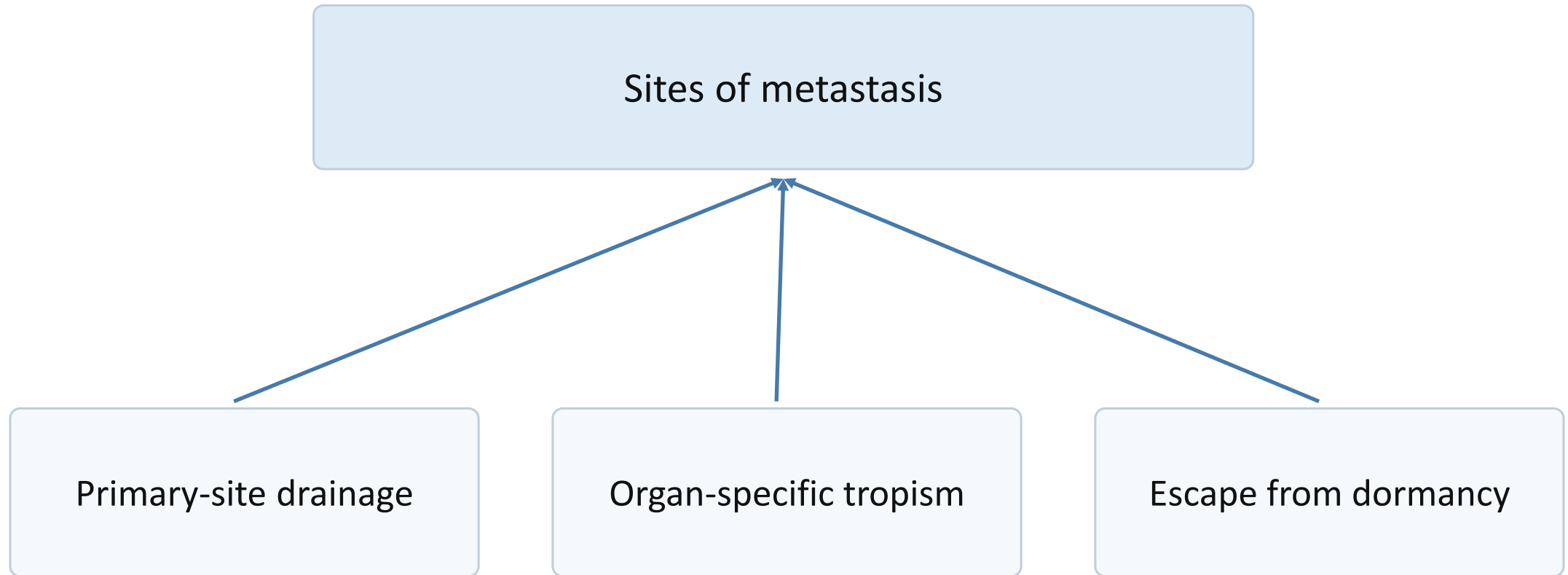
## Clusters may support circulating tumor cells

Evidence favoring multicellular aggregates in metastatic establishment.

Interactions with platelets may help stabilize and protect tumor emboli.

Circulating cells are commoner than successful metastatic colonies.

# Three determinants of distant deposits



## Organ tropism beyond anatomic flow

Some tumors preferentially metastasize to selected organs.

Adhesion molecules and chemokine receptors can contribute to selective homing.

The new organ's microenvironment must also support cancer-cell survival.

# The seed-and-soil concept

## Seed

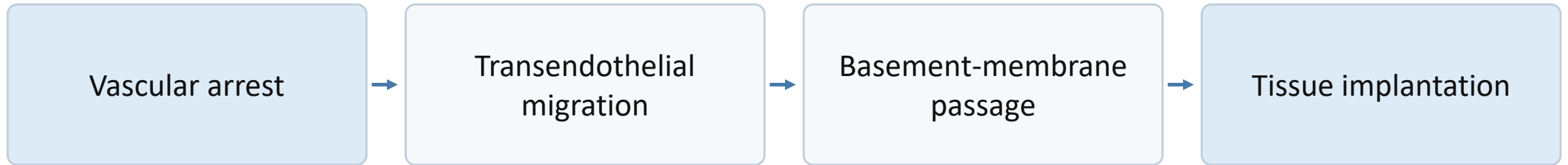
Circulating cancer cells with properties enabling survival and growth.

## Soil

A receptive target-organ stroma and extracellular environment.

*Highly vascular tissues are not uniformly permissive to metastasis.*

## Extravasation at the secondary organ



Adhesion molecules, proteases, and chemokines can contribute.

Mechanisms differ by target-organ endothelium.

# Tumor dormancy: Surviving without expansion

## Microscopic survival

Tumor cells remain at a distant site without a growing clinical lesion.

## Overt metastasis

Colonization progresses to a clinically significant tumor deposit.

*Dormancy is described in melanoma, breast carcinoma, and prostate carcinoma.*

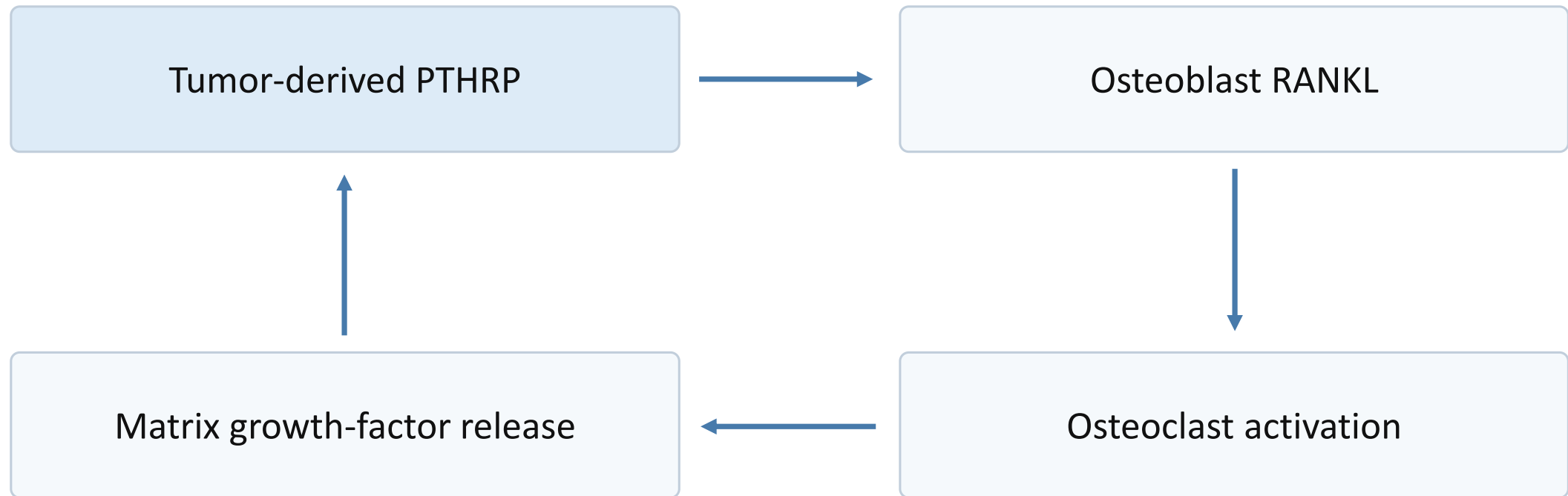
## Metastatic colonization depends on host stroma

Cancer-derived signals can alter resident stromal cells at a secondary site.

The modified stroma can supply matrix and growth factors supporting expansion.

Survival after extravasation is not equivalent to successful outgrowth.

## Bone metastasis: A reciprocal growth circuit



*Released IGF and TGF- $\beta$  can further support tumor growth.*

## Clinical application: An invasive basal cell carcinoma

A skin lesion shows infiltrative malignant basaloid growth. There is no evidence of distant disease.

**Does the absence of metastasis invalidate its classification as malignant?**

No. Basal cell carcinoma can invade locally yet metastasize very rarely.

## Clinical application: A small distant-spreading tumor

A relatively small, well-differentiated primary malignancy is associated with lesions in separate organs.

**Does small size or good differentiation exclude metastasis?**

No. Robbins explicitly describes small, well-differentiated tumors that metastasize widely.

## Clinical application: An enlarged draining node

A carcinoma drains to a palpable enlarged regional lymph node.

**Can enlargement alone establish nodal metastasis?**

No. Reactive hyperplasia is another explanation; Microscopic assessment is needed.

## Five distinctions to retain

| Term                       | Working interpretation                        |
|----------------------------|-----------------------------------------------|
| <b>Metastasis</b>          | Physically discontinuous neoplastic deposit   |
| <b>Local invasion</b>      | Contiguous infiltration at primary site       |
| <b>Lymphatic spread</b>    | Transport through regional lymphatic drainage |
| <b>Hematogenous spread</b> | Transport through blood with vascular arrest  |
| <b>Colonization</b>        | Successful growth at a secondary site         |

## Selected source reading

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. Chapter 7, “Neoplasia.”

Core teaching unit: “Metastasis,” p. 242.

Contextual sections: “Pathways of Spread,” pp. 243–244; “Invasion of Extracellular Matrix,” pp. 274–275; “Vascular Dissemination, Homing, and Colonization,” pp. 275–276.