

Malignant Lesions of Interlobular Stroma

Breast stromal pathology, with emphasis on angiosarcoma

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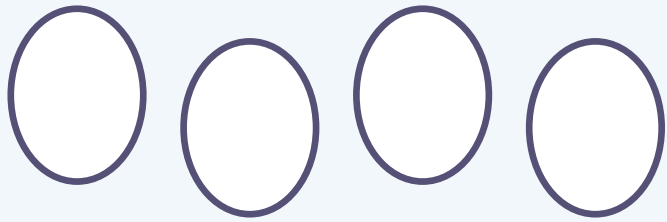
Learning objectives

Diagnose the problem by tissue compartment, vascular lineage, and clinical setting.

- Distinguish intralobular biphasic tumours from purely stromal lesions.
- Contrast primary and secondary breast angiosarcomas.
- Recognize the histologic and endothelial-marker patterns.
- Use MYC testing appropriately and identify major mimics.

Two stromal compartments of the breast

Intralobular stroma



Gland-associated,
Cellular specialized stroma



Interlobular stroma



Connective tissue between
Lobules and ducts

Stromal tumours: The two anatomical groups

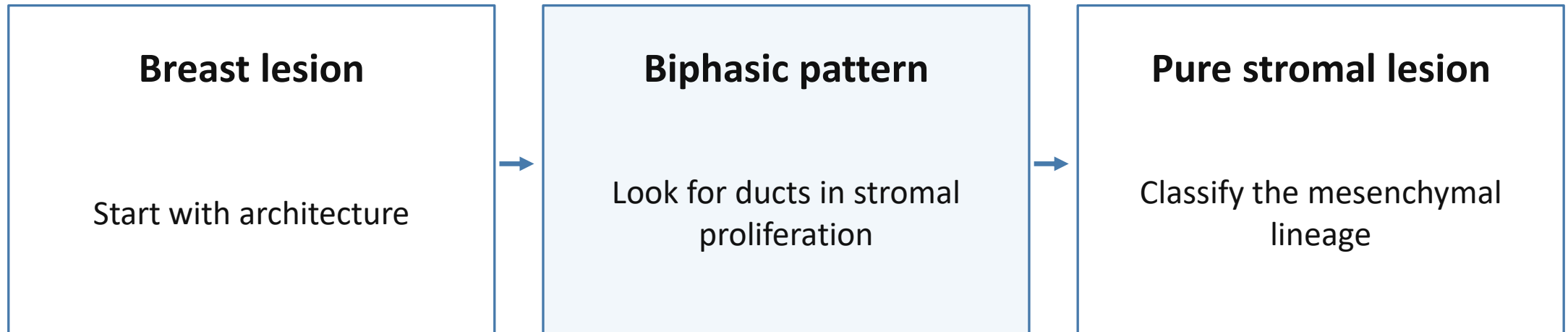
Intralobular

- Fibroadenoma and phyllodes tumour
- Biphasic: Neoplastic stroma plus entrapped non-neoplastic epithelium
- Architecture commonly incorporates ducts

Interlobular

- Mesenchymal lesions analogous to those at other body sites
- No required accompanying epithelial component
- Includes lipoma, fibromatosis, and angiosarcoma

Separating epithelial and stromal components



Phyllodes tumour belongs to intralobular stroma even when its stromal component is malignant.

Interlobular tumour spectrum

Behaviour	Examples	Key distinguishing point
Benign	Lipoma; Myofibroblastoma	Adipocytic or myofibroblastic lesions
Locally aggressive	Fibromatosis	Infiltrative but non-metastasizing
Malignant	Angiosarcoma	Malignant endothelial neoplasm; Poor prognosis

Cell lineage determines the diagnostic route

Mesenchymal breast lesion

Identify the proliferating cell population



Vascular endothelial lineage

Irregular blood-filled channels; Endothelial IHC



Angiosarcoma

Malignant endothelial growth; Infiltrative architecture

What is angiosarcoma?

A malignant tumour showing vascular endothelial differentiation.

- In breast, it is the most frequent sarcoma discussed under interlobular-stromal malignancy.
- It may arise without prior breast therapy or develop after radiation / chronic lymphedema.
- Its appearance ranges from recognizable vascular channels to high-grade solid growth.

Rarity in the breast

< 0.05%

Robbins: Angiosarcoma among all breast malignancies; Exceedingly uncommon.

Primary and secondary disease are distinct clinical contexts

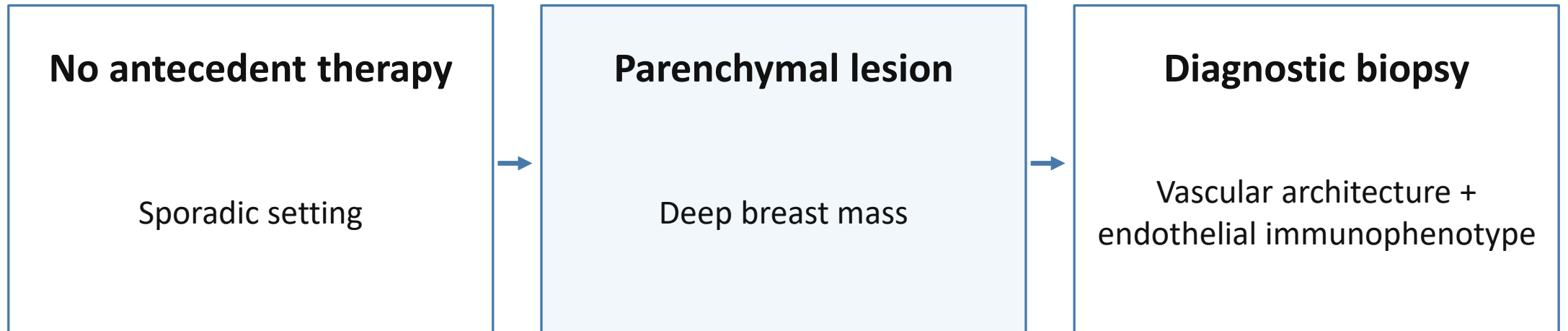
Primary (sporadic)

- No prior radiation required
- Often a parenchymal mass
- Usually presents at a younger age

Secondary (therapy-associated)

- Occurs after breast cancer treatment
- Typically affects dermis and subcutis
- Prior irradiation or chronic lymphedema is important

Primary angiosarcoma: Typical clinical sequence



Age profile in primary disease

Mean age: 35 years

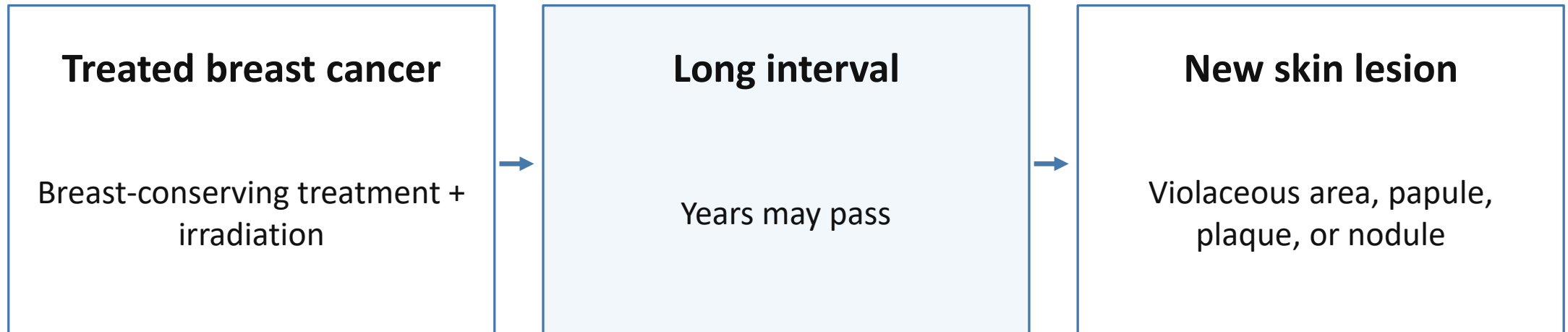
Sporadic breast angiosarcoma mainly in young females.

Primary angiosarcoma: Presentation

A parenchymal mass may be the first clue.

- Reported cases may present as a palpable, sometimes enlarging breast mass.
- Mammography may be nonspecific in young patients with dense breast tissue.
- A bland-appearing vascular core biopsy does not automatically indicate a benign lesion.

Radiation-associated angiosarcoma: Path to recognition

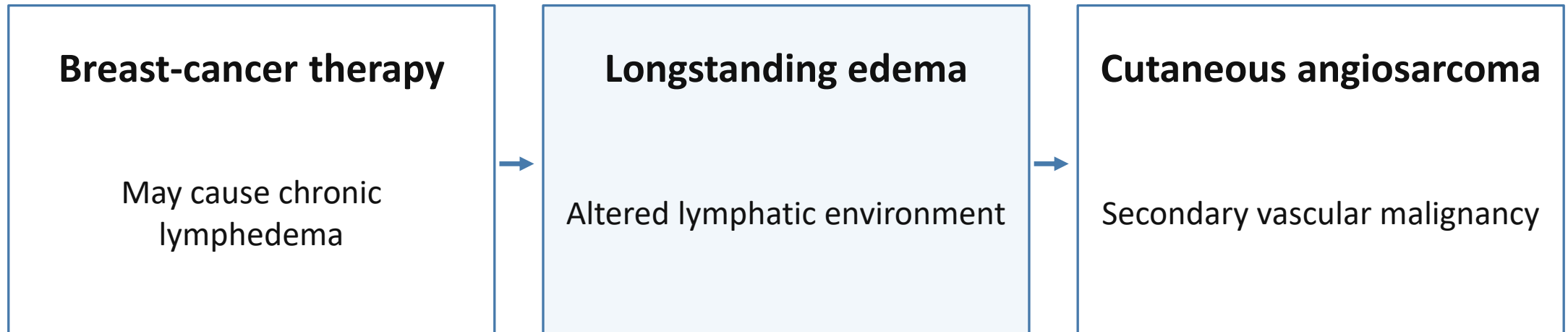


Post-treatment anatomy directs clinical suspicion

The irradiated skin is often the first affected tissue.

- Secondary lesions typically begin in dermis and subcutis rather than deep parenchyma.
- Discoloration or a skin plaque can be the primary presentation without a dominant breast mass.
- A new skin change in the radiation field requires clinicopathologic attention.

Lymphedema-associated disease (Stewart–Treves)



Stewart–Treves is a clinical association, not a histologic subtype defined by one stain.

Latency after radiotherapy

5–10 years

Robbins: Most radiation-associated breast angiosarcomas are diagnosed in this interval.

Absolute risk after breast irradiation

~0.3%

Textbook estimate; Estimates vary across populations and studies.

Cutaneous warning patterns after radiation

Bruise-like patch

A violaceous or erythematous discoloured area.

Raised papule / plaque

May be multifocal in an irradiated field.

Nodular lesion

Can indicate progressively bulky disease.

Subtle early disease

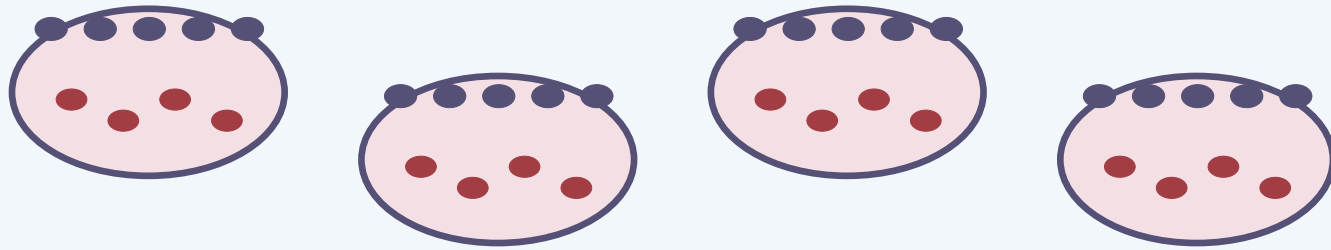
Skin changes can resemble benign post-therapy effects.

Gross and macroscopic features

Vascular nature helps explain hemorrhagic appearance.

- Lesions may be red-purple and poorly circumscribed.
- Cut surfaces can be hemorrhagic, friable, or contain blood-filled spaces.
- Gross appearance alone cannot determine grade or distinguish the main vascular mimics.

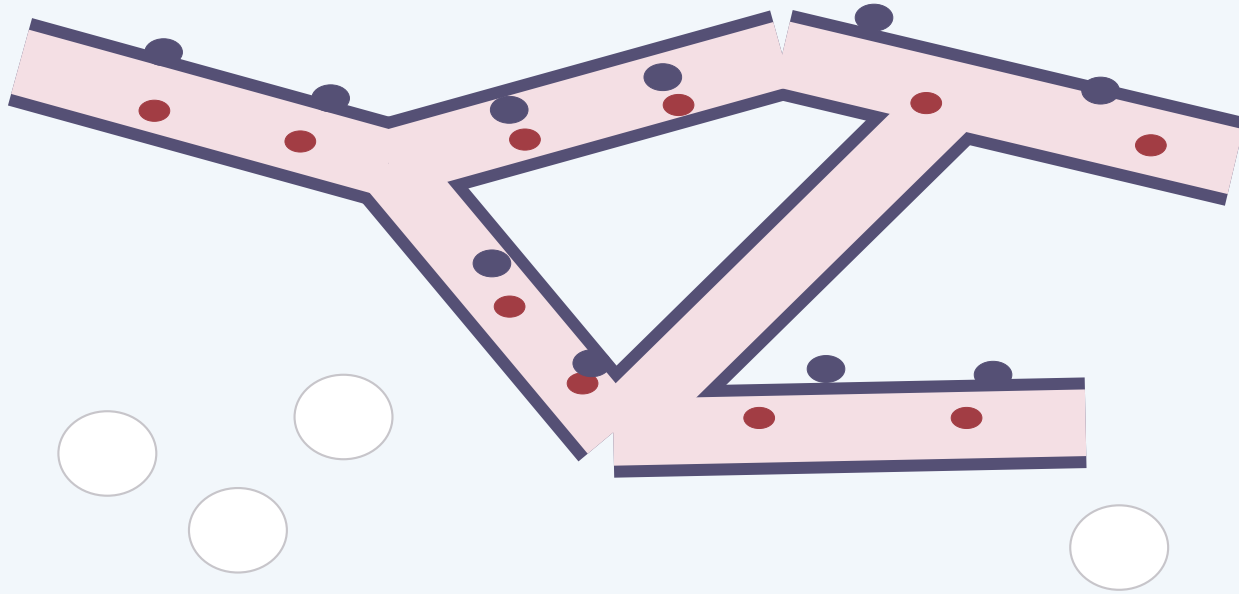
The underlying vasoformative architecture



Conceptual schematic — not a histologic specimen

- Recognizable channels
- Irregular vasoformation
- Invasive growth still matters

Anastomosing vascular channels dissect tissue



Conceptual schematic — not a histologic specimen

- Branching and anastomosis
- Stromal and fat infiltration
- Endothelial lining is abnormal

Endothelial atypia: What the pathologist assesses

Nuclear change

Hyperchromasia, pleomorphism and conspicuous nucleoli.

Growth organisation

Single layers versus stratified endothelial cells.

Mitotic activity

Proliferation supports malignancy in context.

Infiltrative pattern

Dissection through breast stroma and fat is a major clue.

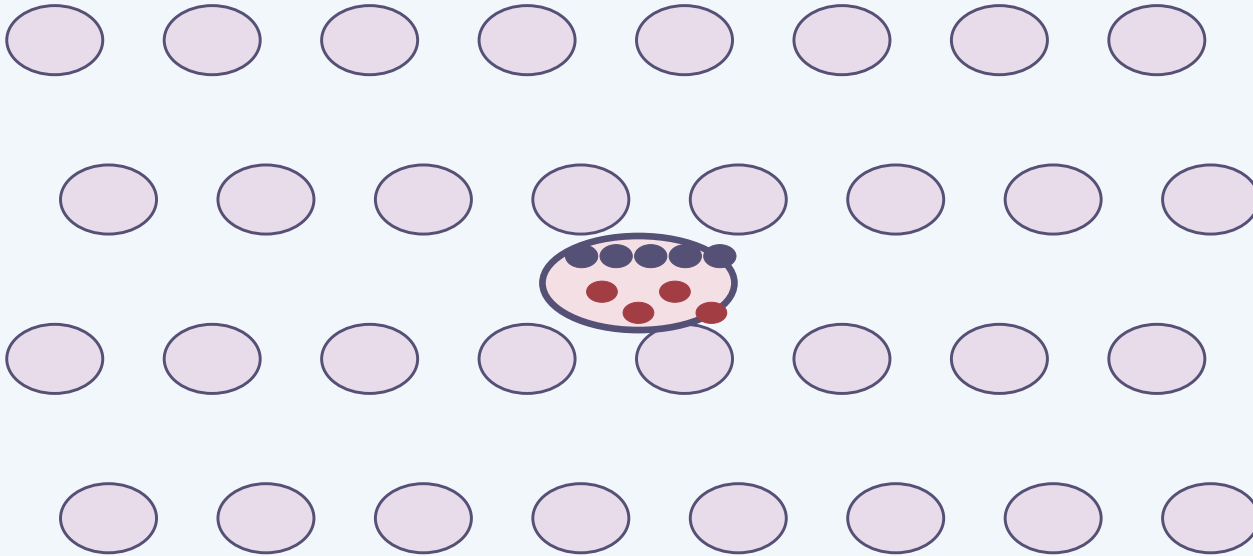
Tufting and endothelial multilayering



Conceptual schematic — not a histologic specimen

- Intermediate morphology
- Endothelial stratification
- Tufting and nuclear atypia

High-grade angiosarcoma can appear solid



Conceptual schematic — not a histologic specimen

- Poorly differentiated
- Solid or spindle-cell growth
- Endothelial IHC may be essential

A spectrum of endothelial differentiation

Well-formed channels

- Irregular lumina remain recognizable
- May show only modest cytologic atypia
- Deep infiltration remains critical

Intermediate architecture

- Layering and tufting become conspicuous
- Increasing atypia and mitotic activity
- Both vascular and solid areas may coexist

Poorly differentiated

- Sheets of epithelioid or spindle cells
- Blood lakes, hemorrhage and necrosis
- Endothelial IHC is often decisive

Features that favour aggressive biology

Tissue invasion

Growth penetrates adjacent stroma or adipose tissue.

Cellular atypia

Pleomorphism beyond a reactive endothelial response.

Mitotic figures

Cell division may be numerous in high-grade areas.

Necrosis or blood lakes

Often encountered in less differentiated tumours.

Primary versus secondary: Morphologic tendency

Primary angiosarcoma

- Broader morphologic spectrum
- Low-, intermediate-, and high-grade differentiation
- Often centred in breast parenchyma

Radiation-associated

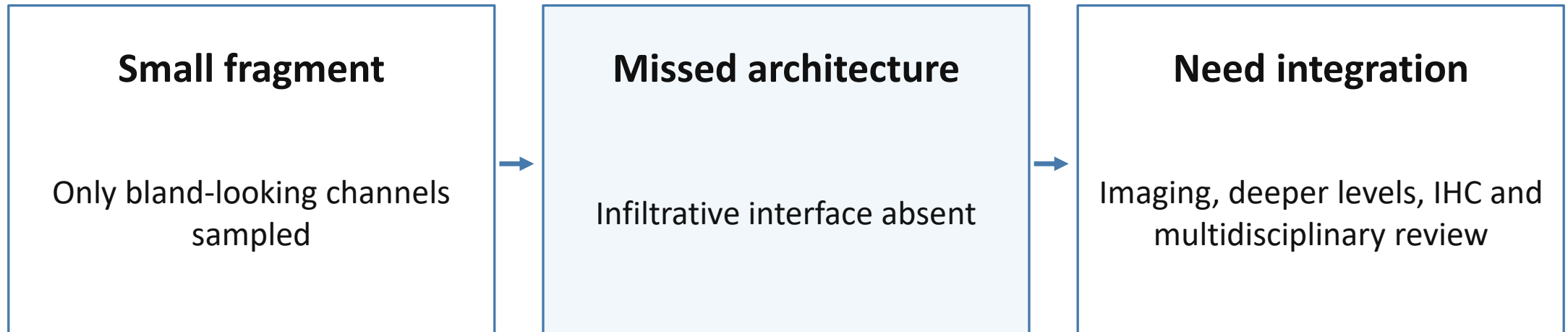
- Often high-grade and multifocal
- Dermal / subcutaneous distribution
- Prominent solid, spindle, or hemorrhagic foci

Secondary lesions may be multicentric

Sample beyond the dominant visible focus.

- Small lesions or peripheral regions may look less atypical than the main tumour.
- Diffuse cutaneous involvement may exceed the area visible clinically.
- Patchy vasoformation requires thoughtful tissue sampling.

Core-biopsy pitfall in primary angiosarcoma

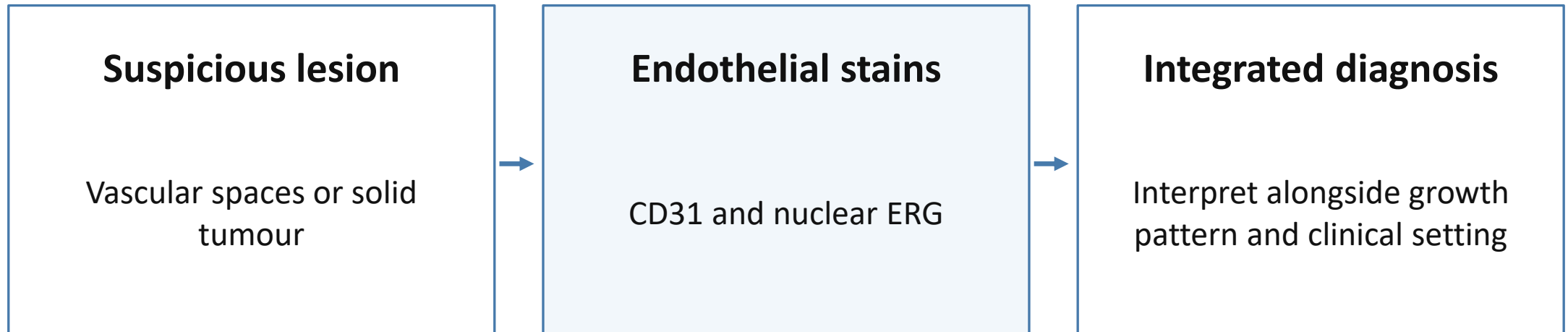


A low-grade-looking vascular core is not proof of benignity.

Features to report in a vascular biopsy

Feature	Diagnostic meaning
Infiltrative interface	Evaluate dissection of native stroma or fat
Vasoformation	Describe anomalous anastomosing channels
Endothelial atypia	Note distribution and degree
Cellularity / mitoses	Document foci of increased proliferation
Solid / necrotic foci	May indicate high-grade component

Immunophenotype: Establish endothelial differentiation



Marker positivity is supportive; It is not sufficient to establish malignancy.

CD31: An endothelial-lineage marker

Membranous and cytoplasmic CD31 helps identify tumour endothelial cells.

- Useful in vasoformative and poorly differentiated areas.
- Interpret distribution and morphology rather than staining alone.
- A confirmed endothelial phenotype does not distinguish benign from malignant vascular growth.

ERG: A nuclear endothelial marker

ERG complements CD31 in difficult lesions.

- Nuclear labelling helps localize the neoplastic endothelial population.
- Particularly helpful when vasoformation is subtle.
- A panel and morphologic review remain necessary; ERG is not a malignancy-specific stain.

Auxiliary endothelial markers and their limits

CD34

- Can highlight vascular differentiation
- Sensitivity varies by tumour area and grade
- Not specific to angiosarcoma

FLI1 / factor VIII

- Can support endothelial lineage
- May be used with CD31 and ERG
- No single stain substitutes for morphology

Cytokeratin is not an absolute exclusion test

A subset of angiosarcomas may express cytokeratin.

- Solid/epithelioid angiosarcoma can mimic carcinoma.
- A broad epithelial panel may be positive in a minority of cases.
- Endothelial markers and the spatial growth pattern resolve the differential.

Diagnostic IHC: Clinical question versus interpretation

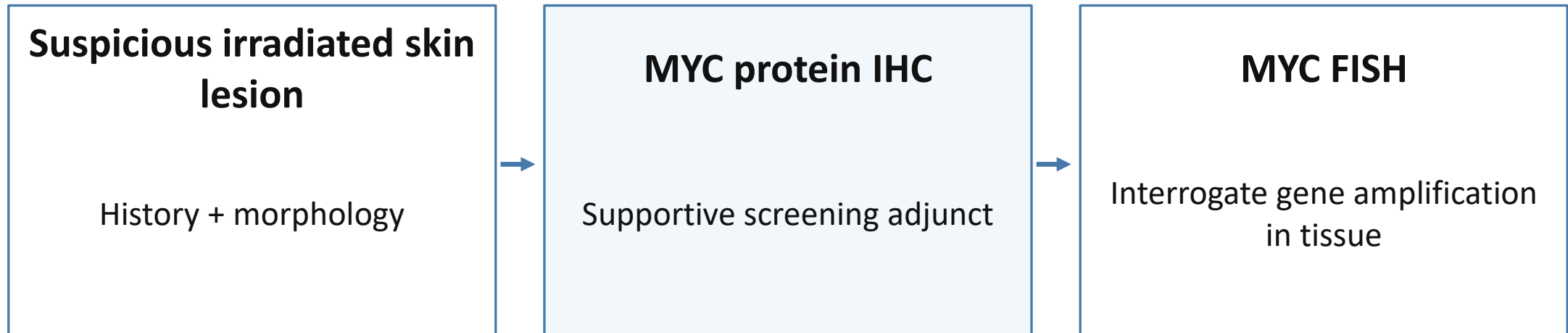
Marker / method	Main use	Important limitation
CD31; ERG	Confirm endothelial differentiation	Also mark non-malignant endothelium
CD34; FLI1	Additional vascular support	Not diagnostic in isolation
Pan-cytokeratin	Assess epithelial differentiation	Some angiosarcomas express keratin
MYC IHC / FISH	Support radiation-associated disease	Negative result does not exclude all cases

Secondary angiosarcoma: Hallmark alteration

MYC amplification

High-level MYC amplification in >90% of secondary cases.

How MYC amplification may be demonstrated



MYC amplification supports the diagnostic context but does not replace histologic assessment.

MYC: The crucial interpretive nuance

High-level amplification is strongly associated with secondary angiosarcoma.

- Use the result as diagnostic support in a lesion arising after radiation or lymphedema.
- Strong diffuse MYC IHC is more convincing than isolated weak staining.
- Primary tumours may show variable MYC expression; Clinical history is essential.

A MYC-negative sample cannot rule out angiosarcoma

Morphology and sampling can override a negative ancillary result.

- Not all secondary cases show the classic amplified profile in every published series.
- Biopsy may undersample heterogeneous or invasive components.
- Reassess tumour extent and degree of atypia if clinical concern persists.

Postradiation atypical vascular lesion (AVL)

Typical setting

- Arises in irradiated breast skin
- Can appear as a small vascular proliferation
- May mimic an early angiosarcoma

Reasons for caution

- Limited biopsy may miss infiltrative tumour
- Cytologic atypia may overlap
- MYC supports, but does not replace, morphology

AVL versus radiation-associated angiosarcoma

Criterion	Atypical vascular lesion	Angiosarcoma
Depth	Usually superficial dermal	May infiltrate deeply / subcutis
Atypia	Limited or focal	More pronounced, possibly variable
Growth	More restricted architecture	Infiltrative / anastomosing channels
MYC status	Usually no amplification	Frequently amplified

Primary versus secondary breast angiosarcoma

Domain	Primary	Secondary
Typical patient	Younger; No prior therapy	Older; Breast therapy / lymphedema
Usual focus	Breast parenchyma	Skin and subcutaneous tissues
Morphology	Variable differentiation	Often high-grade and multifocal
Molecular clue	No characteristic MYC amplification pattern	Frequent high-level MYC amplification

Malignant phyllodes versus breast angiosarcoma

Diagnostic domain	Malignant phyllodes	Angiosarcoma
Compartment	Intralobular	Interlobular
Epithelial component	Present, possibly focally sampled	No intrinsic biphasic epithelium
Stromal pattern	Leaf-like fibroepithelial lesion	Vasoformative endothelial lesion
Diagnostic strategy	Extensive search for epithelial clefts	Vascular morphology + endothelial IHC

Other interlobular lesions are not angiosarcoma

Fibromatosis

- Clonal fibroblast–myofibroblast proliferation
- May infiltrate muscle
- Locally aggressive but does not metastasize

Myofibroblastoma

- Myofibroblastic interlobular tumour
- Not a vascular endothelial neoplasm
- Can occur in either sex

Lipoma

- Mature adipocytic lesion
- Can be palpable or radiologically apparent
- Vascular atypia is not the defining pattern

Angiosarcoma versus epithelial carcinoma

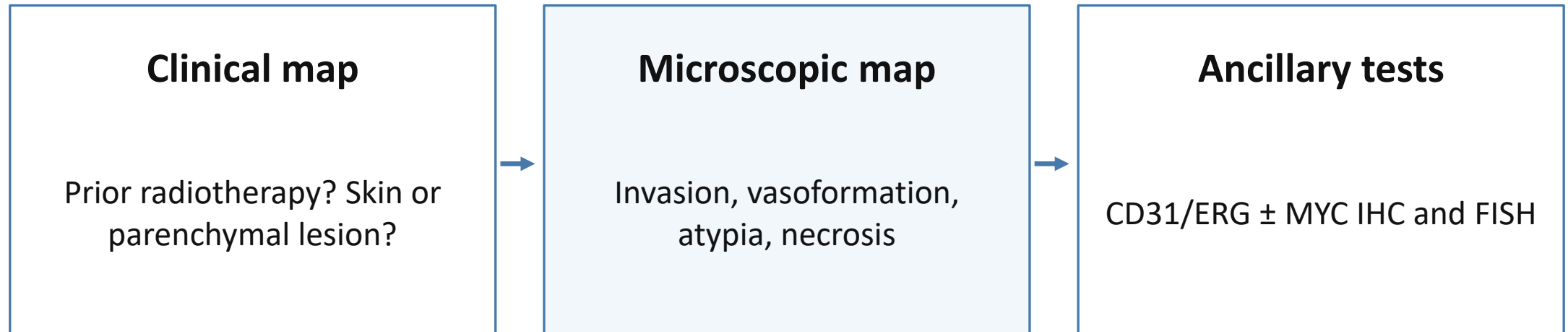
Consider carcinoma when

- Definitive ductal/glandular epithelial architecture
- Epithelial immunophenotype dominates
- No convincing malignant endothelial network

Consider angiosarcoma when

- Dissecting, atypical blood-filled spaces
- Tumour cells express CD31 / nuclear ERG
- Skin lesion follows irradiation or lymphedema

Practical diagnostic workflow



Expert review and sampling adequacy remain crucial when stains and morphology are discordant.

Imaging findings: Supportive, not pathognomonic

Imaging determines site and extent; Histology establishes the diagnosis.

- Primary lesions may be mammographically nonspecific or occult.
- Radiation-associated lesions can manifest as skin thickening and abnormal enhancement.
- Ultrasound or magnetic resonance imaging may help target suspicious tissue for biopsy.

Why diagnosis may be delayed

Low prior probability

Angiosarcoma accounts for a tiny fraction of breast malignancies.

Post-therapy mimic

Discoloration can resemble bruising or radiation skin change.

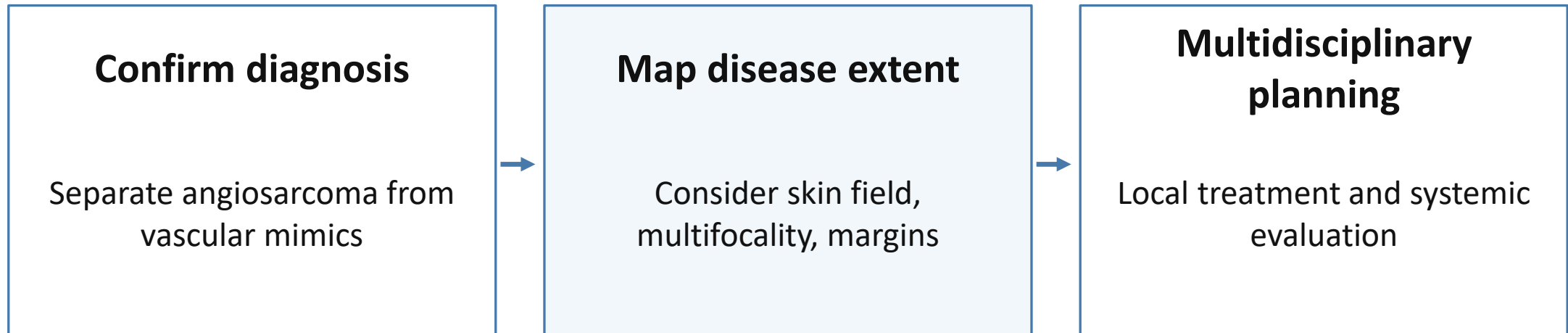
Heterogeneous histology

A small fragment may sample only mild-looking vasoformation.

Disparate tests

Negative/weak MYC or focal cytokeratin requires contextual review.

Pathology informs clinical management



Treatment choice is individualized; This lecture emphasizes pathology rather than prescribing a regimen.

Local recurrence is a central clinical problem

Secondary angiosarcoma often demonstrates diffuse cutaneous spread.

- Multifocal or microscopic peripheral extension complicates complete excision.
- Negative margins and careful assessment of distribution are clinically important.
- Published recurrence estimates vary substantially because series are small and heterogeneous.

Distant spread and prognosis

Angiosarcoma has aggressive malignant potential.

- Hematogenous spread is an important metastatic route.
- Pulmonary metastases are reported; Atypical metastatic sites also occur.
- Prognostic assessment requires disease extent and the full clinical context.

Case 1: A young patient with a vascular mass

A 34-year-old woman has a growing deep breast mass; No previous breast irradiation.

Clinical–pathological information

- Core biopsy contains irregular blood-filled spaces.
- Channels dissect between native ducts and adipose tissue.
- Tumour cells express CD31 and nuclear ERG.

Which feature most strongly supports angiosarcoma?

Case 1: Interpret the infiltrative interface

The key clue is dissection through native breast tissue.

- Unusual anastomosing channels invading adipose tissue support a malignant vascular process.
- CD31 / ERG substantiate endothelial differentiation.
- Absence of radiation history favours a primary clinical context, not benignity.

Case 2: A skin plaque years after radiotherapy

A 70-year-old woman develops expanding violaceous patches in a previously irradiated breast.

Clinical–pathological information

- Radiotherapy was administered 7 years earlier.
- Dermal biopsy shows atypical endothelial channels with tufting.
- High-level MYC amplification is found by FISH.

Which diagnosis best integrates the findings?

Case 2: Radiation-associated angiosarcoma

Prior irradiation, dermal distribution, and MYC amplification converge.

- A 5–10 year latency fits the textbook pattern.
- The skin-centred appearance matches the usual secondary presentation.
- MYC amplification is strong ancillary support for secondary angiosarcoma.

Case 3: Small postradiation vascular proliferation

A small superficial vascular papule is biopsied from irradiated breast skin.

Clinical–pathological information

- Mild endothelial atypia without unequivocal deep invasion.
- MYC immunostaining is negative.
- The biopsy is shallow and fragmented.

What is the most defensible next interpretation?

Case 3: Do not overcall or exclude malignancy

Atypical vascular lesion remains possible, but sampling limits are real.

- MYC negativity supports AVL in the correct architecture; It cannot independently rule out angiosarcoma.
- Reassess depth, infiltrative edges and clinical enlargement.
- Additional tissue or expert consultation may be needed for persistent suspicion.

Diagnostic synthesis

Domain	Primary angiosarcoma	Secondary angiosarcoma
Topography	Often parenchymal	Often cutaneous
Clinical association	Sporadic; Younger patients	Radiation / lymphedema; Older patients
Histological hallmark	Infiltrative malignant endothelial growth	Same lineage, often high-grade
Useful tests	CD31 / ERG	CD31 / ERG; MYC testing
Most important pitfall	Bland vascular areas on core biopsy	Misclassification as AVL or benign skin change

Four principles to carry into practice

A vascular lesion must be classified by site, invasion, cytology and clinical context.

- Interlobular stromal malignancy is rare; Angiosarcoma is the key entity.
- Primary parenchymal and secondary cutaneous disease are distinct settings.
- CD31/ERG support endothelial lineage; MYC aids secondary/AVL distinction.
- No stain substitutes for adequate sampling and evaluation of infiltrative growth.

Selected source readings

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