

Radiation-induced fibrosis

Mechanisms, morphology and clinicopathologic consequences

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

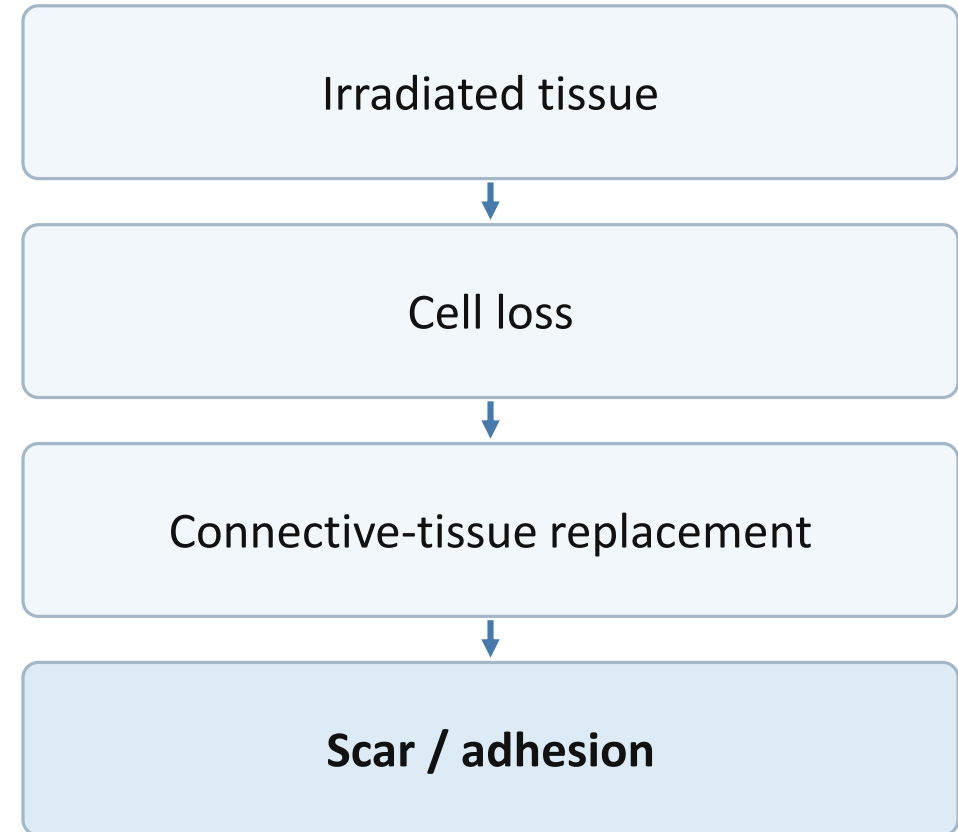
www.abusuraihsakhri.com

Learning objectives

- Connect radiation injury to delayed collagenous scarring.
- Explain vascular injury, stem-cell loss and profibrotic signaling.
- Recognize organ-specific patterns and major diagnostic pitfalls.

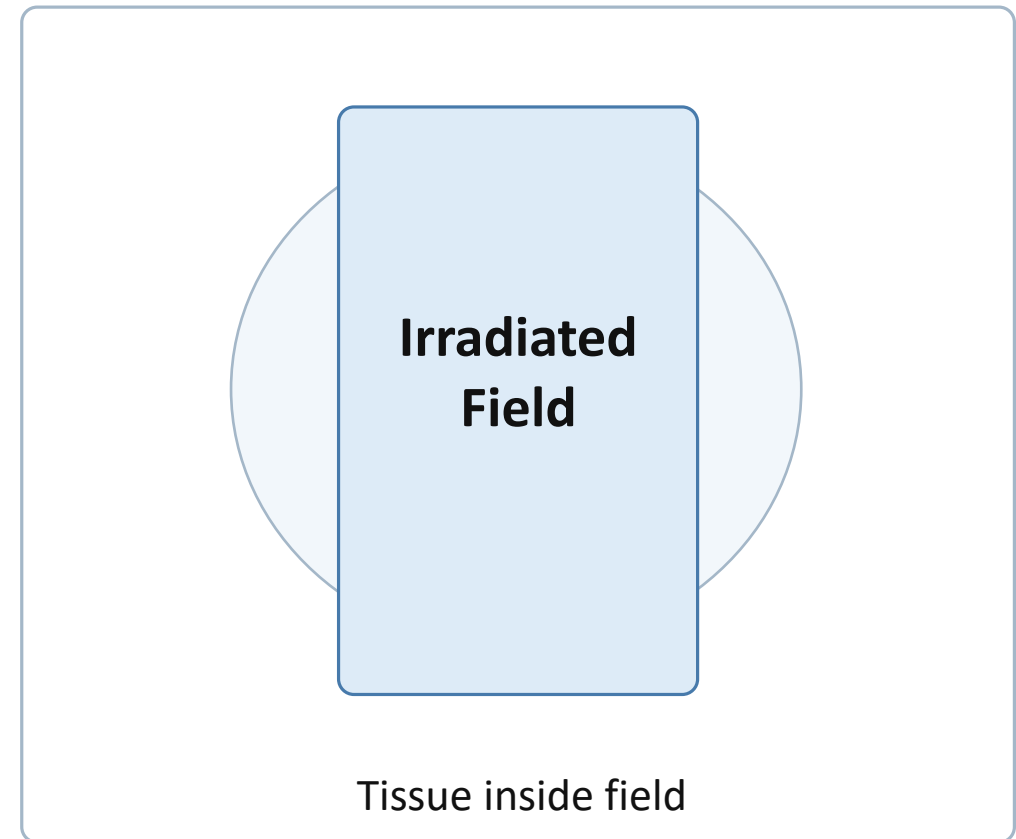
The meaning of “fibrosis” in this topic

- An adverse late tissue response within a previously irradiated field.
- Dead functional cells are replaced by connective tissue.
- The resulting scar may distort structures or create adhesions.



A local complication of cancer radiotherapy

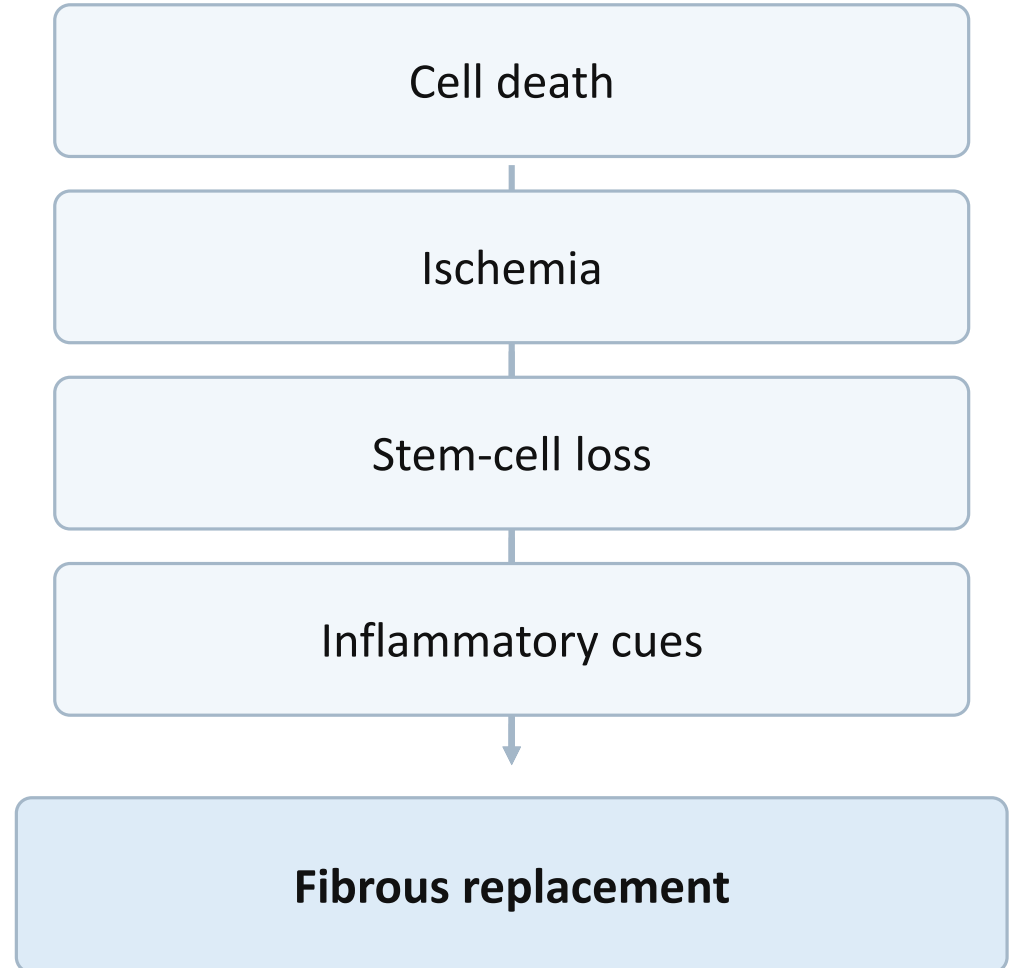
- Therapeutic irradiation targets tumor-bearing tissue.
- Non-neoplastic cells and vessels inside the field may also be injured.
- The same field can show both early damage and delayed fibrosis.



SCHEMATIC — NOT A CLINICAL / HISTOLOGIC SPECIMEN

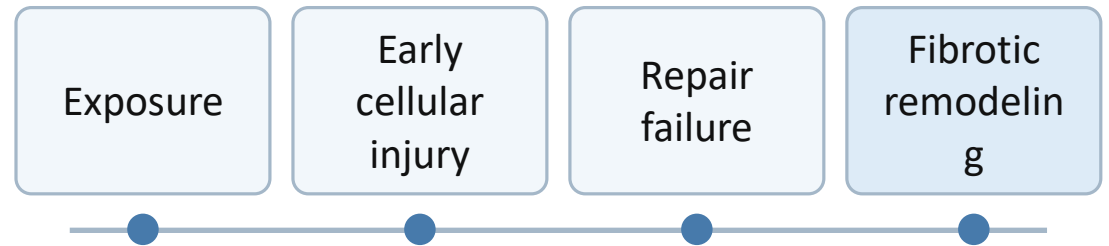
Core mechanistic contributors

- Parenchymal-cell death removes functioning tissue.
- Vascular damage produces chronic ischemic injury.
- Stem-cell depletion limits tissue restitution.
- Inflammatory signals stimulate fibroblasts and matrix synthesis.



Why radiation injury outlasts treatment

- DNA injury may immediately impair vulnerable cells.
- Delayed microvascular remodeling progressively restricts perfusion.
- Incomplete regeneration and continuing matrix deposition reshape tissue.



Ionizing radiation and its cellular targets

- Ionization removes tightly bound electrons from atoms.
- DNA injury occurs through direct events and indirect free radicals.
- Tissue injury depends on which cellular compartments survive.

Direct DNA interaction



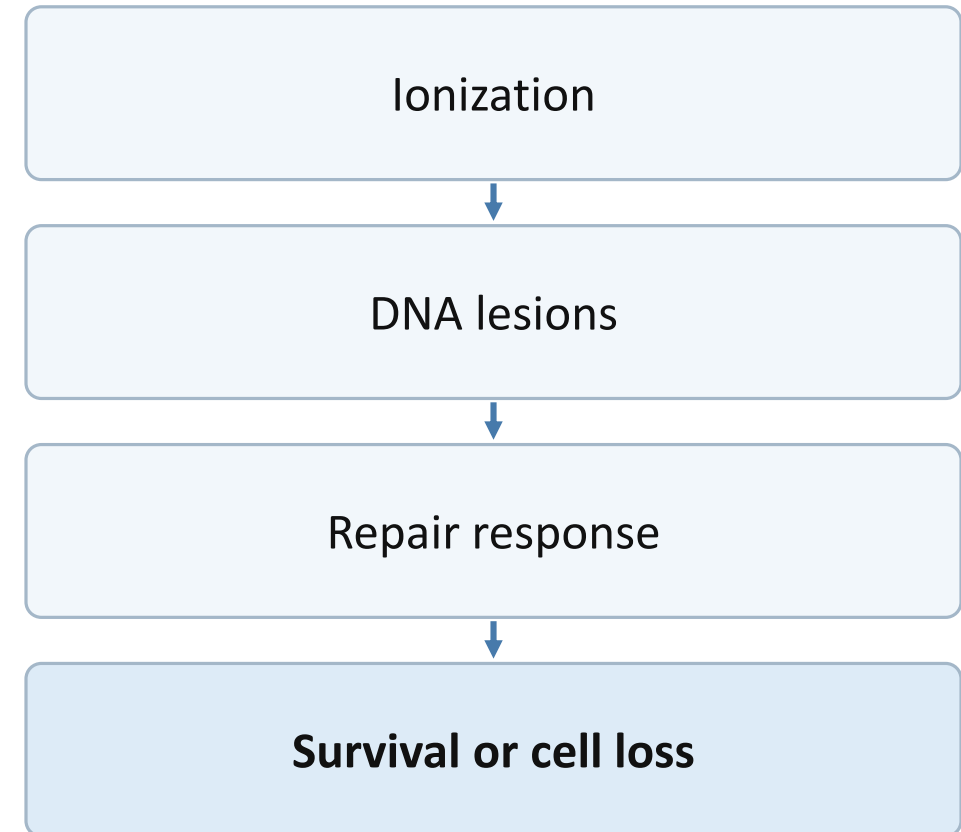
Water radiolysis → radicals



Cellular damage

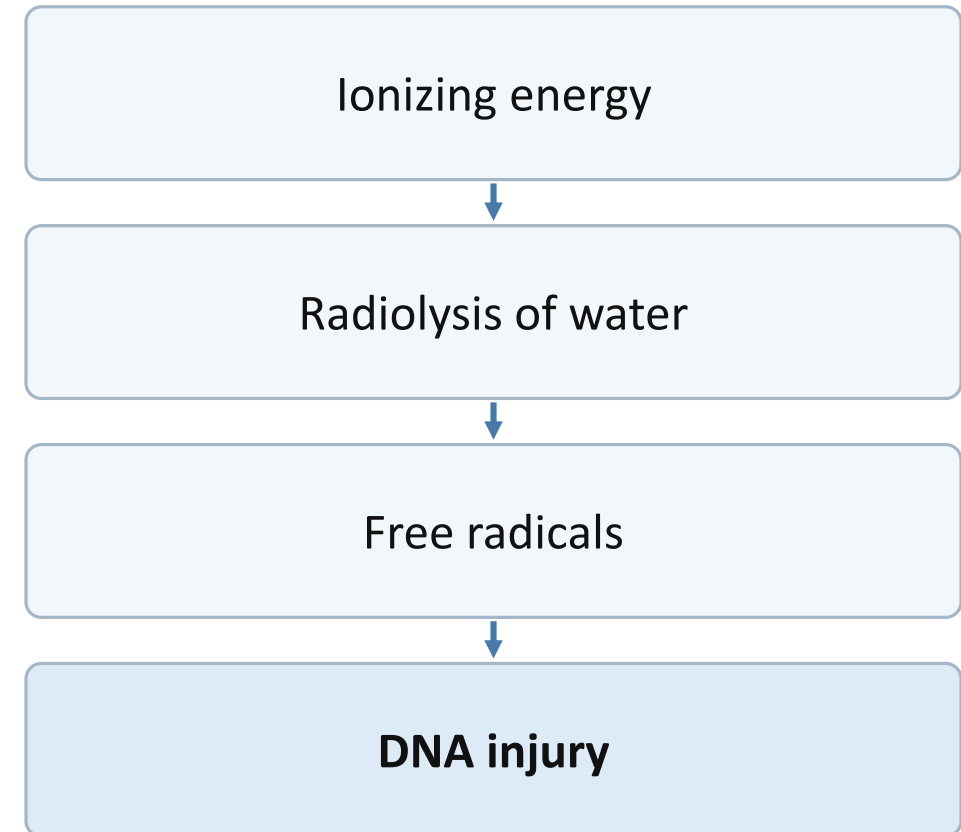
Direct DNA injury

- Ionizing radiation can damage DNA without an intervening radical.
- Double-strand breaks are a particularly important lesion.
- The outcome depends on DNA repair and cell-cycle responses.



Indirect injury through water radiolysis

- Radiolysis of water produces reactive free radicals.
- Radical-mediated DNA damage is a prominent radiation effect.
- This pathway provides a molecular start for tissue injury.



The influence of tissue oxygen

- Oxygen enhances free-radical-mediated radiation injury.
- Poorly oxygenated tissues are generally less radiosensitive.
- Radiobiologic sensitivity cannot be inferred from fibrosis alone.

Well oxygenated

More effective radical-associated injury

Greater radiosensitivity in this mechanism

Poorly oxygenated

Lower radiation sensitivity

Hypoxia changes initial cell injury

DNA damage has several downstream outcomes

- Successful repair allows cells to survive and repopulate tissue.
- Extensive or unrepaired injury can stop division or cause death.
- Fibrosis is a tissue-level outcome of injury and failed restitution.

Survival and reconstitution



Cell death / regeneration failure



Tissue outcome

Why proliferating cells are vulnerable

- DNA replication magnifies the consequences of strand damage.
- Bone marrow, lymphoid tissue and gut mucosa respond early.
- Late fibrosis additionally reflects effects on vessels and stem cells.

Early response

Injury in actively cycling cells

Cell loss during rapid turnover

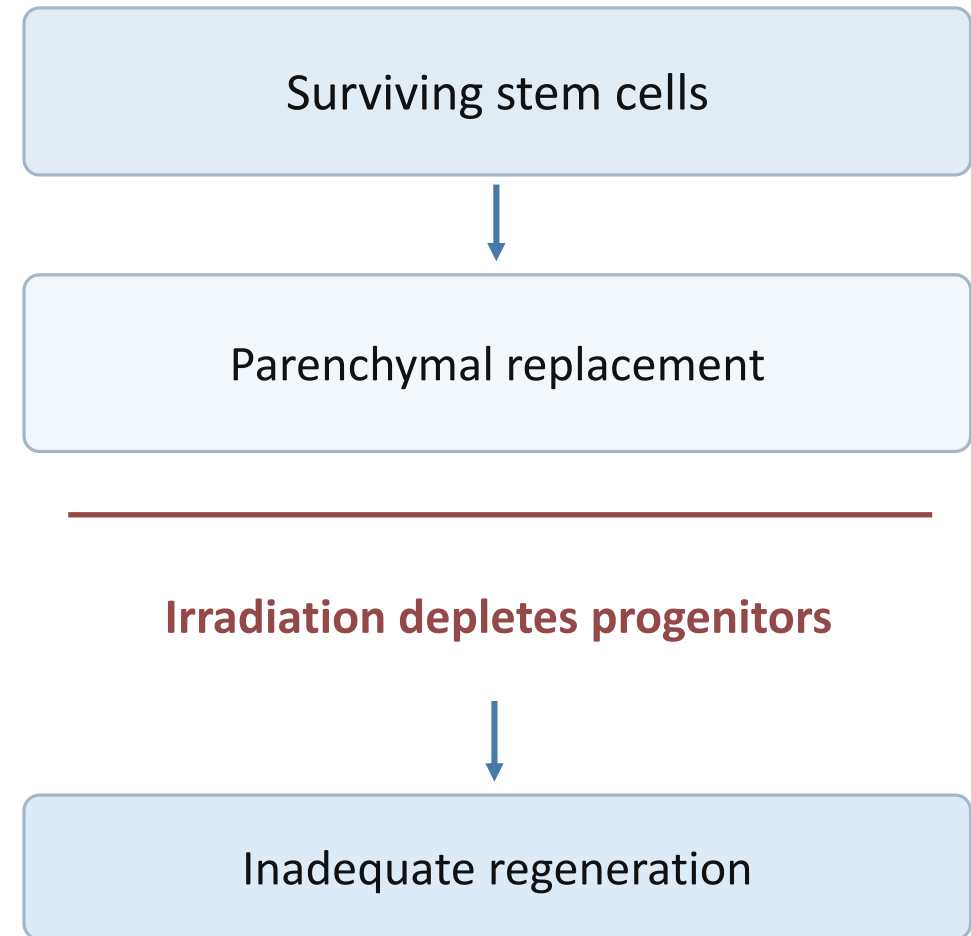
Delayed response

Vascular remodeling

Atrophy and connective-tissue replacement

Regeneration requires a viable cell pool

- Surviving differentiated cells and stem cells support restitution.
- Radiation-mediated stem-cell loss diminishes replacement capacity.
- The greater the regenerative deficit, the more relevant scar repair becomes.



SCHEMATIC — NOT A CLINICAL / HISTOLOGIC SPECIMEN

Structural support also determines repair

- Tissue architecture depends on viable cells and extracellular matrix.
- Damage to support structures makes complete restitution difficult.
- Collagenous repair fills a defect but does not recreate normal parenchyma.

Regeneration

Restores functional cellular components

Requires surviving regenerative capacity

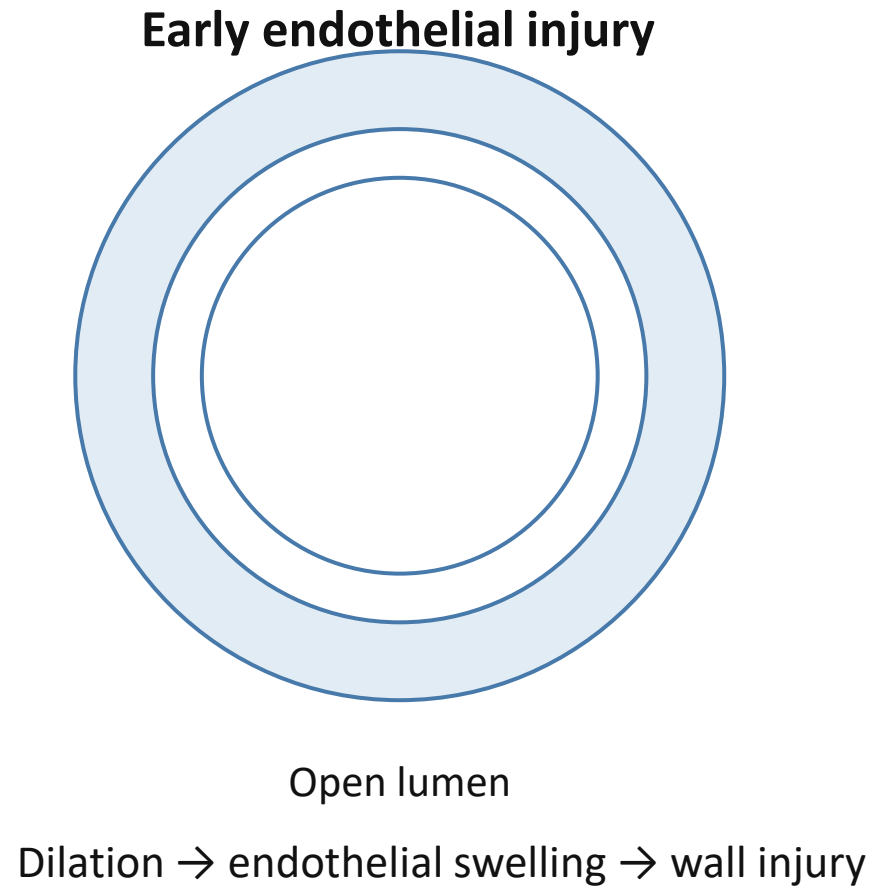
Scarring

Connective tissue substitutes for lost structure

May compromise original function

Early radiation-associated vascular change

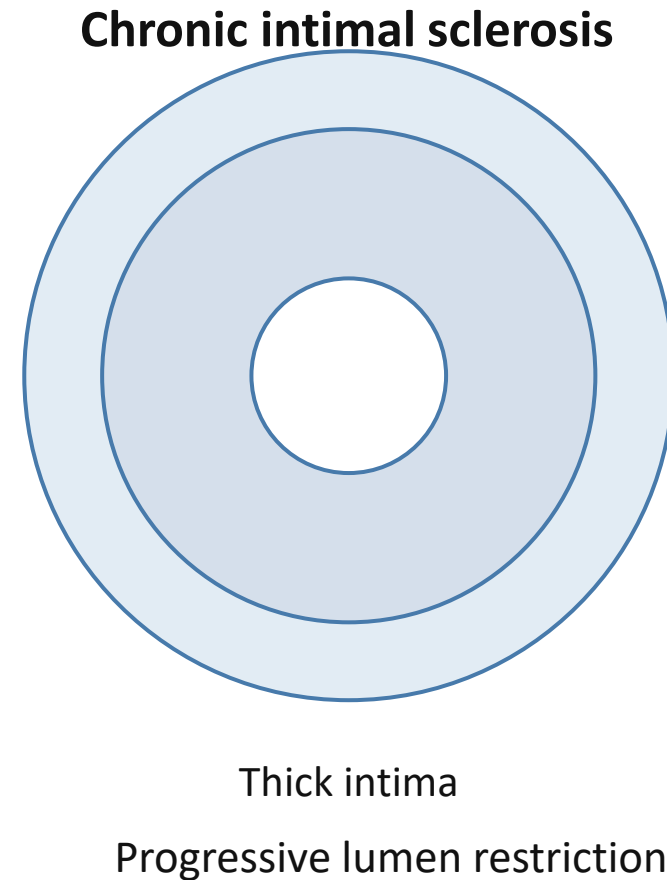
- Vessels may initially show dilation.
- Endothelial swelling, vacuolation and degeneration can follow.
- More severe injury may cause wall necrosis, rupture or thrombosis.



SCHEMATIC — NOT A CLINICAL / HISTOLOGIC SPECIMEN

Late vascular remodeling

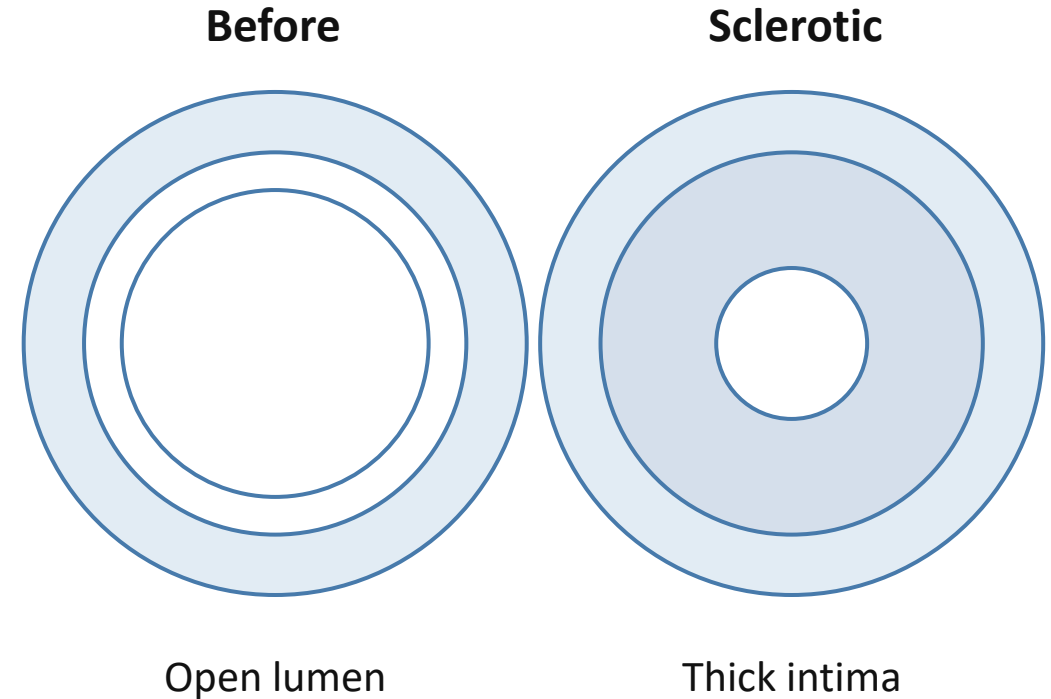
- Endothelial proliferation and intimal collagenous thickening develop.
- Hyalinization narrows small-vessel lumens.
- Marked narrowing or obliteration compromises local perfusion.



SCHEMATIC — NOT A CLINICAL / HISTOLOGIC SPECIMEN

The vascular lumen is the decisive variable

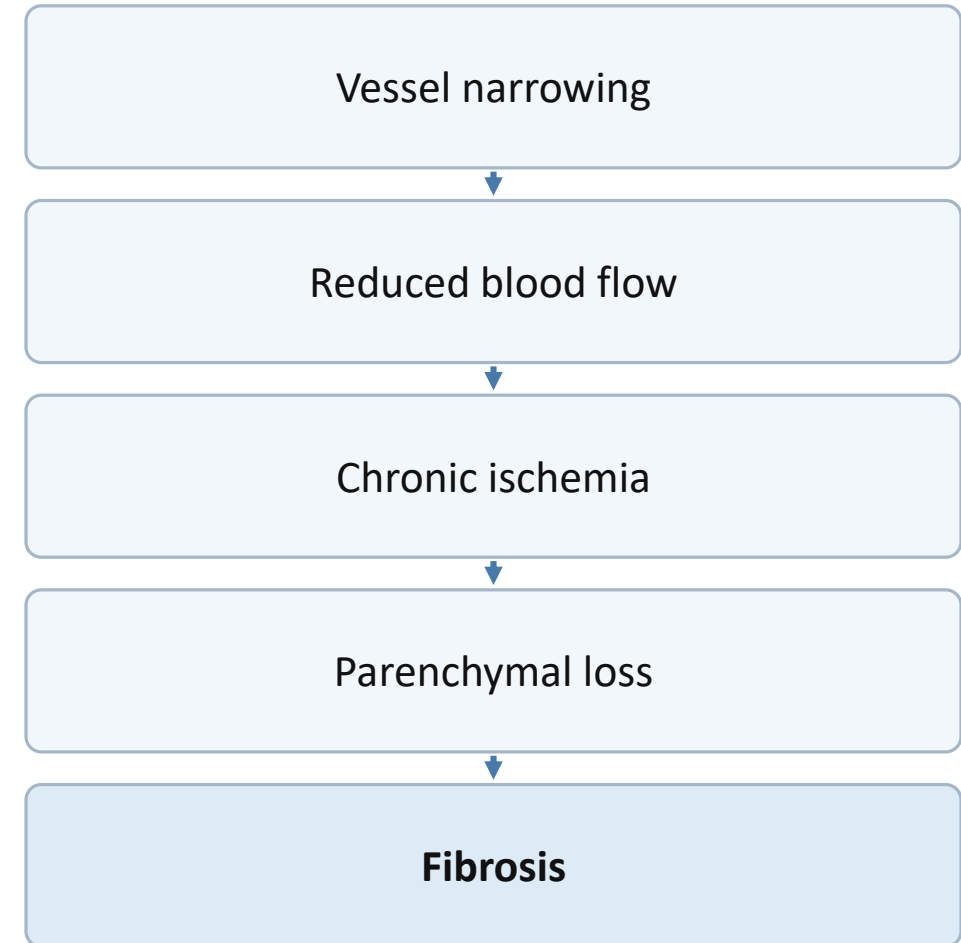
- Intimal collagen accumulates between endothelium and vessel wall.
- The remaining lumen becomes smaller despite a thickened wall.
- Less perfusion increases the vulnerability of irradiated parenchyma.



SCHEMATIC — NOT A CLINICAL / HISTOLOGIC SPECIMEN

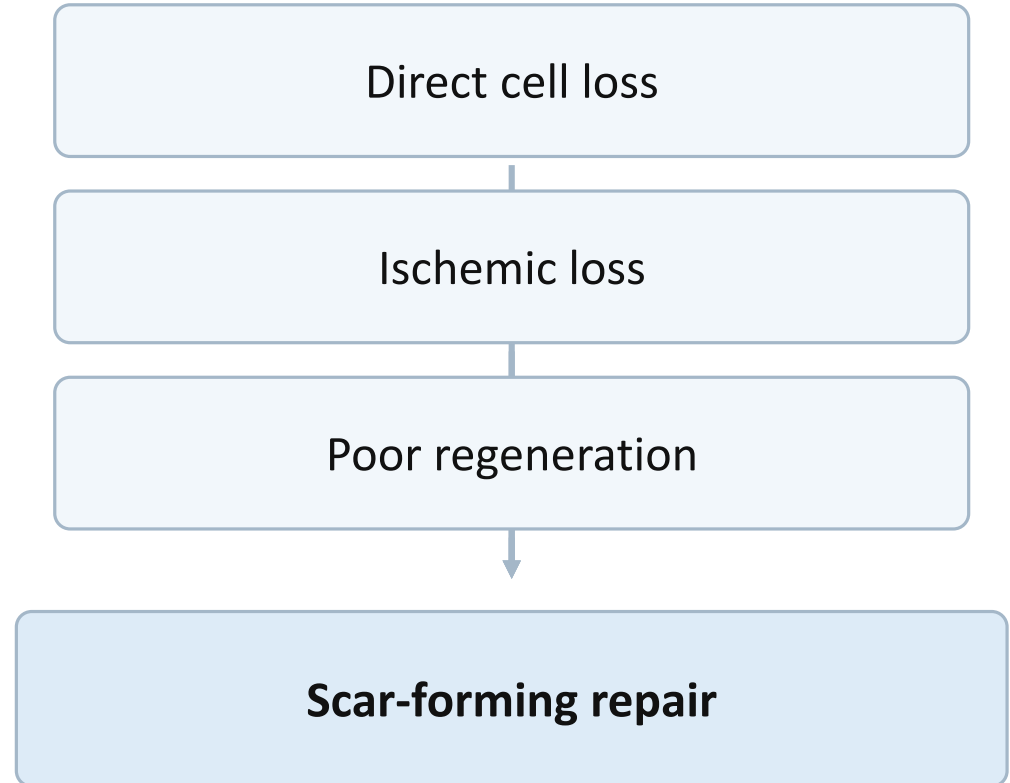
From vessel sclerosis to tissue ischemia

- Vascular lumen loss restricts blood supply.
- Chronic ischemia aggravates parenchymal atrophy and cell death.
- Replacement fibrosis can then accumulate in the affected field.



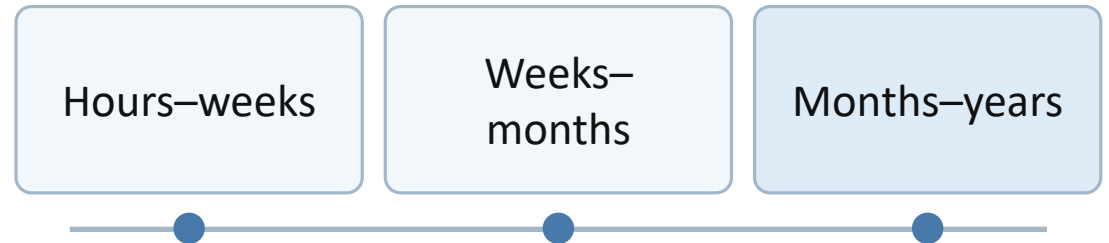
Three injury routes converge

- Direct parenchymal injury reduces cellular mass.
- Microvascular sclerosis produces ischemic cell loss.
- Stem-cell injury blocks effective restitution.



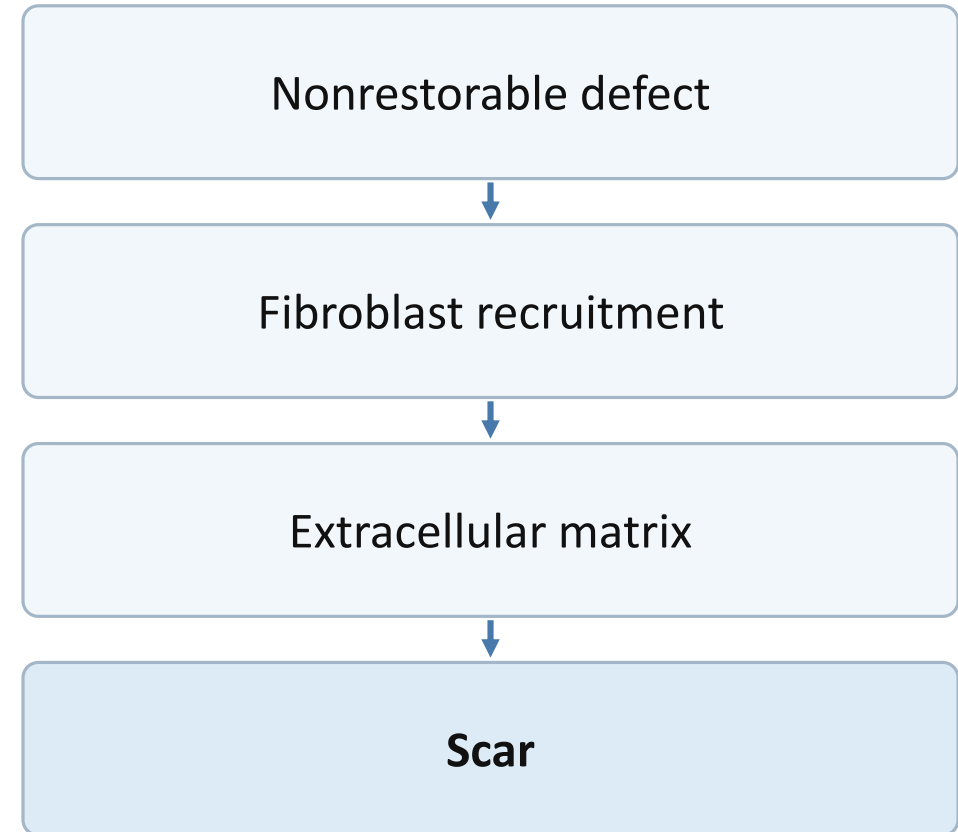
Time course: Early injury versus late injury

- Cellular injury may appear hours to weeks after irradiation.
- Fibrosis can emerge weeks or months after treatment.
- Progressive vascular change and organ scarring may persist for years.



Why scar tissue forms

- Mammalian organs often cannot fully recreate damaged parenchyma.
- Fibroblasts deposit extracellular matrix to stabilize a defect.
- Structural repair is achieved at the expense of original architecture.



Fibrosis is not synonymous with regeneration

- Regeneration replaces lost tissue with appropriate cells.
- Fibrosis replaces tissue with connective tissue.
- The two responses can occur together but have different consequences.

Regeneration

Restitution of
parenchyma

Closer to original tissue
organization

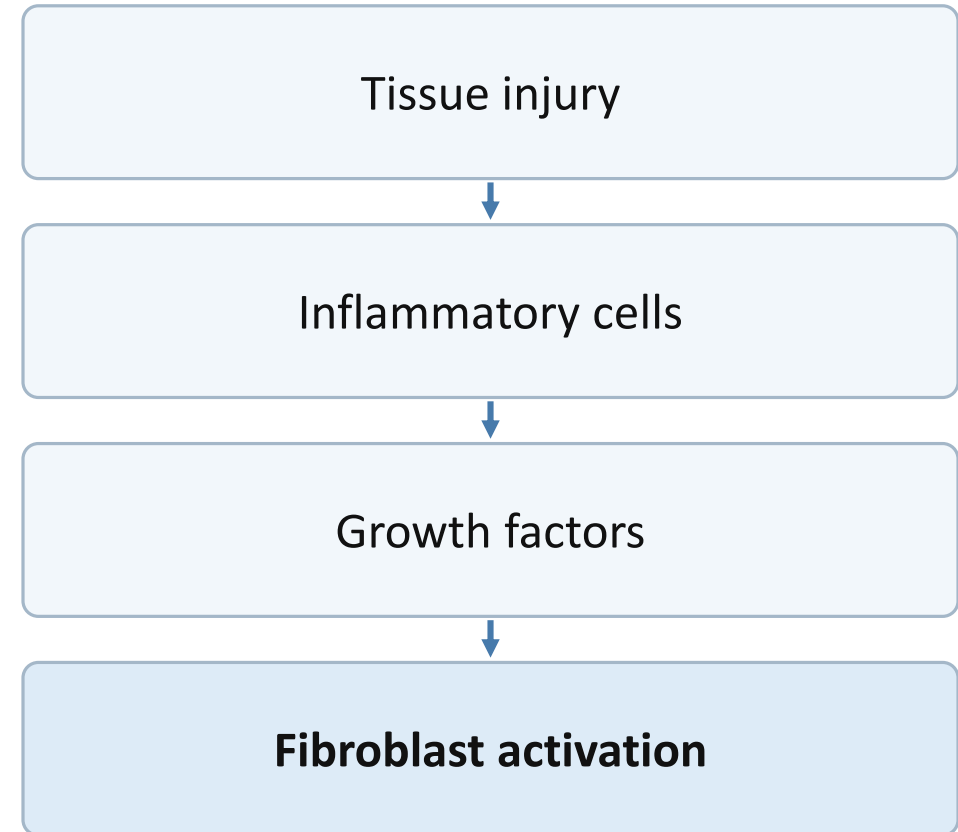
Fibrosis

Collagen-rich
replacement

May create contracture
or impaired function

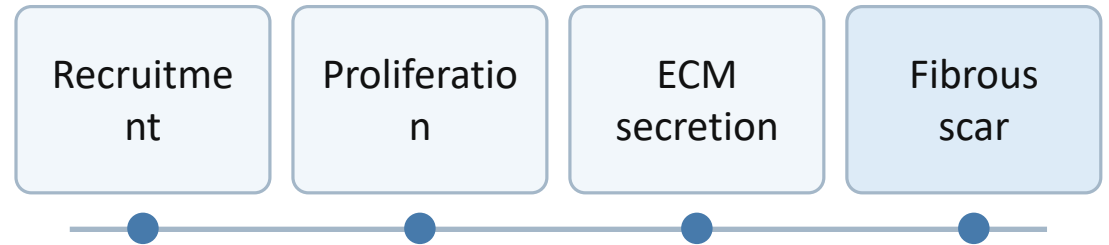
Inflammatory cells recruit fibroblasts

- Injury-associated inflammatory cells generate growth factors.
- Macrophages are major sources of profibrotic mediators.
- These signals promote fibroblast migration, proliferation and activation.



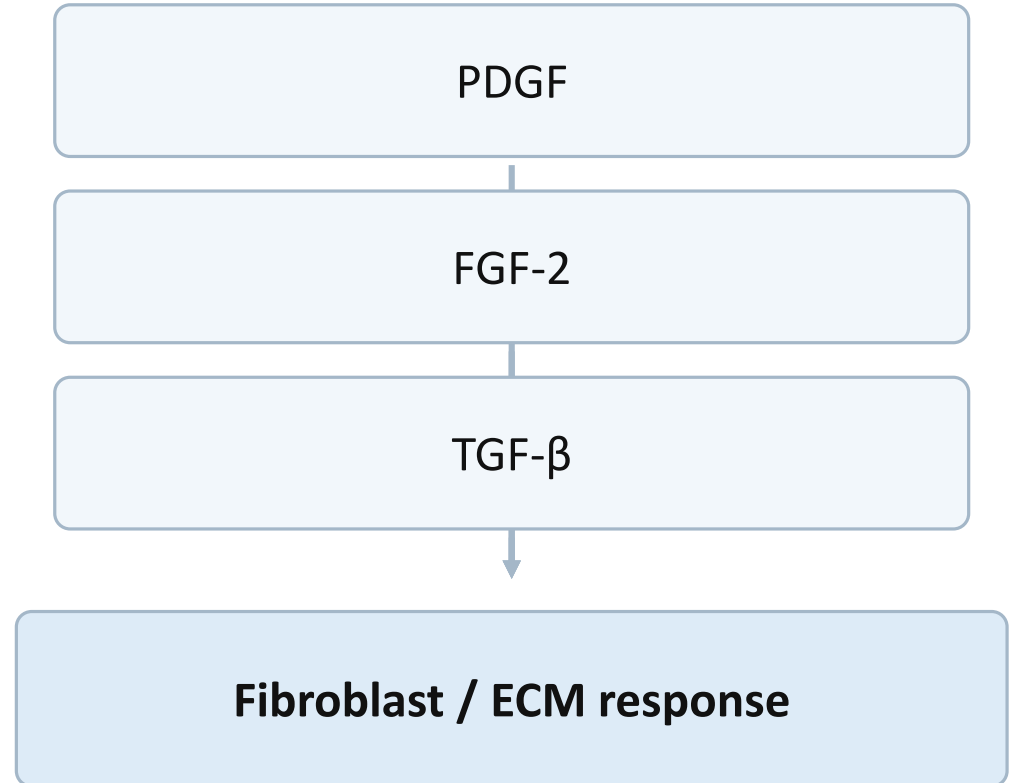
Recruitment precedes matrix production

- Fibroblasts first migrate into the injured site and multiply.
- Activated fibroblasts synthesize collagen and other matrix proteins.
- Accumulation of these products creates the physical scar.



Growth factors organize connective-tissue repair

- PDGF and FGF-2 contribute to fibroblast recruitment and proliferation.
- TGF- β strongly promotes extracellular-matrix deposition.
- The result is a coordinated but potentially excessive repair response.



TGF- β is central to connective-tissue deposition

- Stimulates fibroblast migration and proliferation.
- Increases synthesis of collagen and fibronectin.
- Also reduces extracellular-matrix degradation.

Increased matrix synthesis



Reduced matrix clearance



Matrix accumulation

Matrix accumulation is a balance

- Fibrosis depends on more than collagen production alone.
- Extracellular matrix is simultaneously synthesized and remodeled.
- Disproportionate deposition favors persistent scarring.

Synthesis

Fibroblasts deposit
collagen and fibronectin

TGF- β supports
production

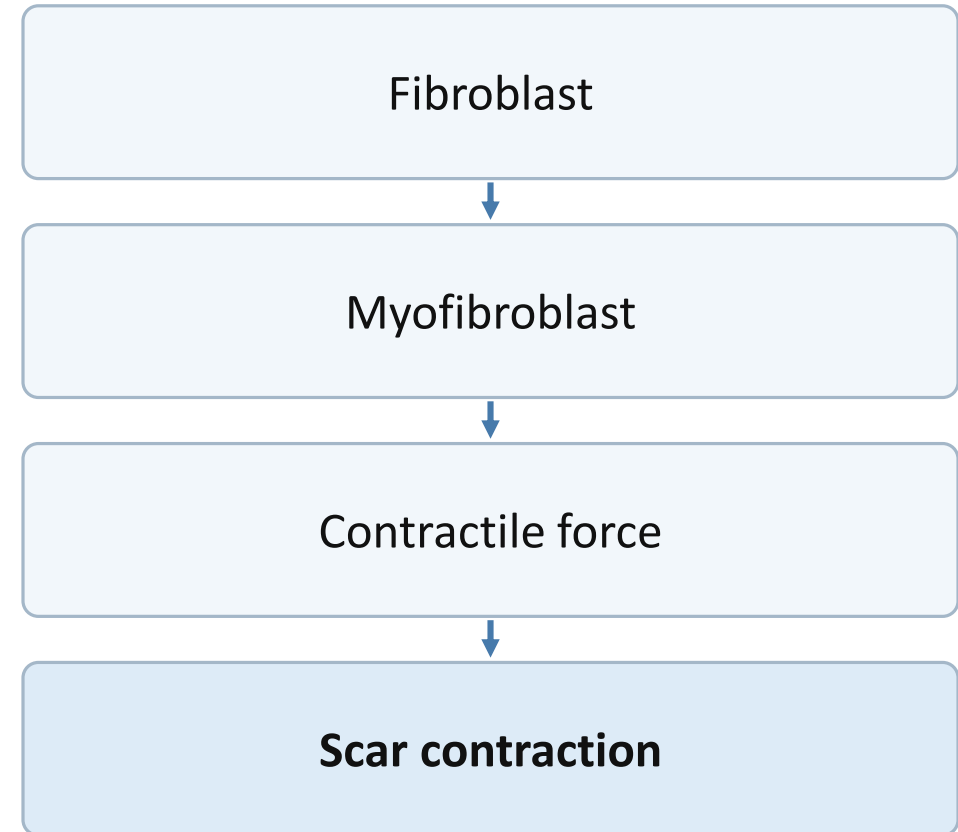
Degradation

Matrix
metalloproteinases
remodel ECM

TIMPs restrain
metalloproteinases

Myofibroblasts generate contraction

- Some fibroblasts acquire actin-rich contractile features.
- These myofibroblasts contribute to wound contraction.
- In fixed anatomic spaces, contraction may distort local structures.



Connective-tissue remodeling persists

- Matrix metalloproteinases degrade selected ECM components.
- Tissue inhibitors of metalloproteinases limit their activity.
- Scar architecture reflects the balance between both systems.

MMP-mediated cleavage



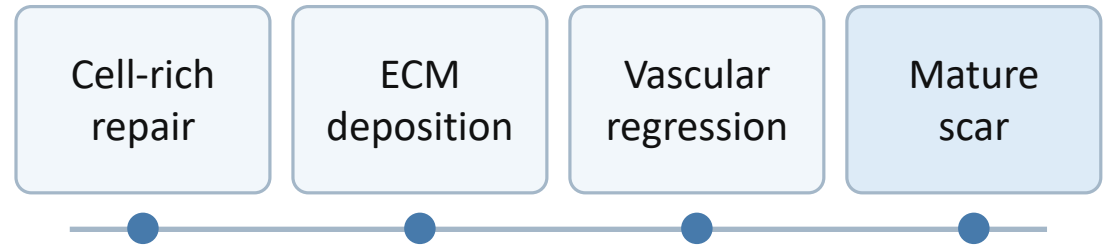
TIMP-mediated inhibition



ECM remodeling balance

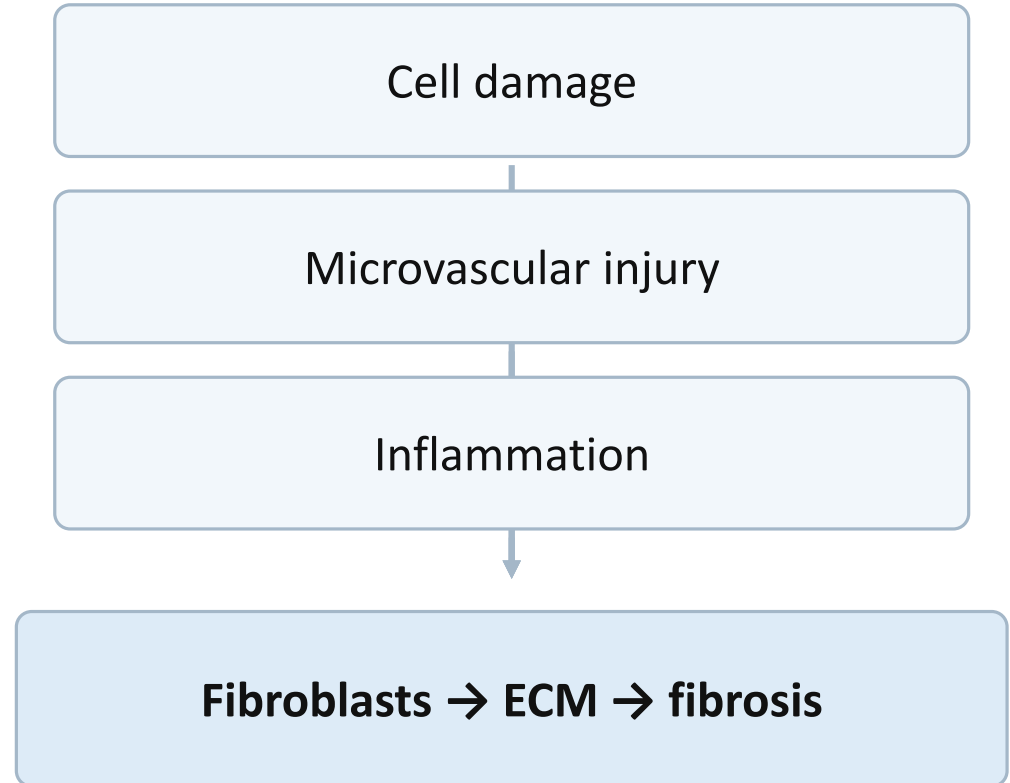
Maturation produces a collagen-rich scar

- Granulation tissue becomes less vascular as healing progresses.
- Collagen persists while the vascular network regresses.
- The resulting dense scar differs from the lost normal tissue.



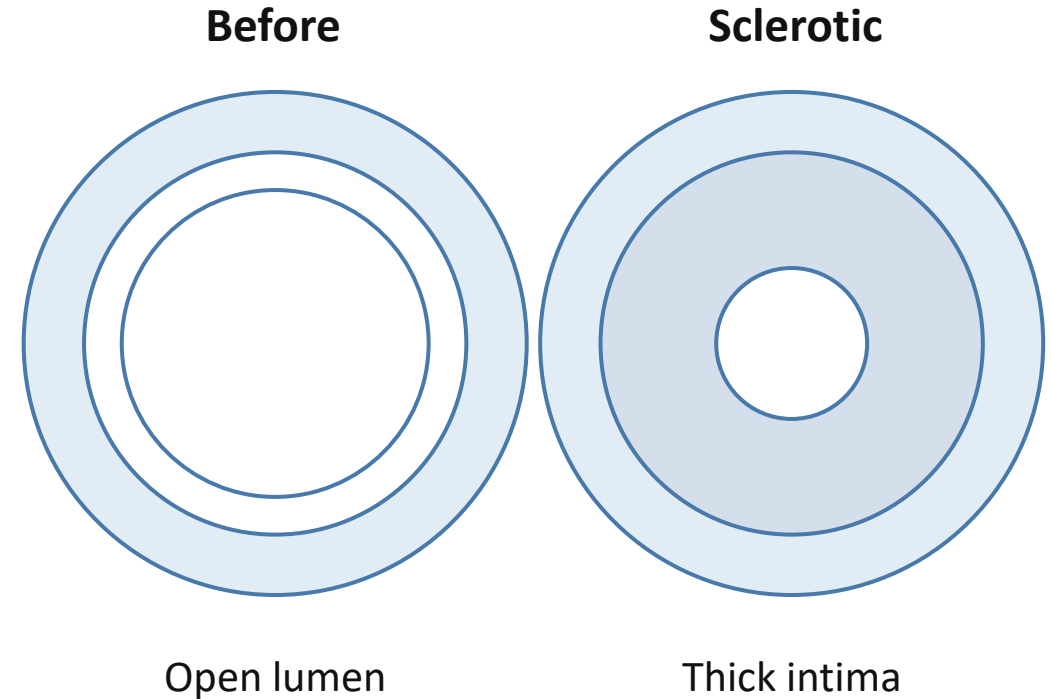
Integrated pathogenesis of radiation fibrosis

- Initial cell and endothelial injury initiate tissue loss.
- Defective regeneration and cytokine signaling shift repair toward scar.
- Collagen accumulation and contraction generate functional injury.



The two major structural hallmarks

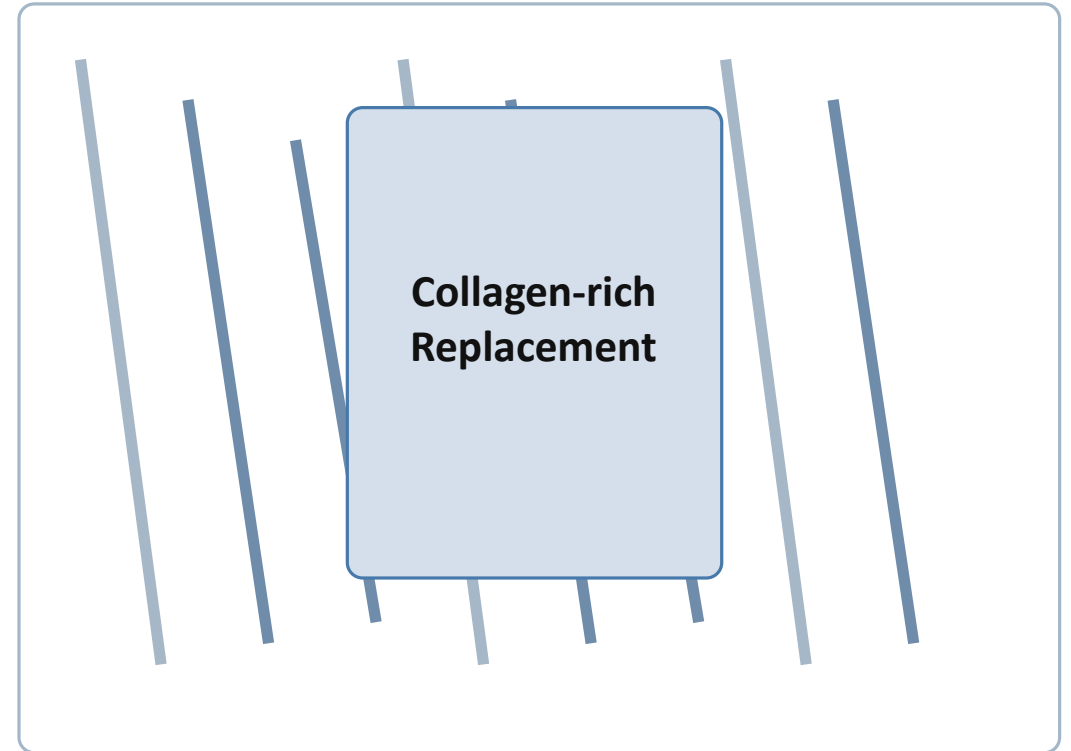
- Thickened, narrowed or obliterated vessels.
- Increased interstitial collagen with loss of normal parenchyma.
- The two alterations reinforce impairment of tissue function.



SCHEMATIC — NOT A CLINICAL / HISTOLOGIC SPECIMEN

Fibrosis changes the geometry of tissues

- Scar tissue fills spaces previously occupied by functioning cells.
- Contraction can pull neighboring structures together.
- Adhesions may develop where surfaces heal through connective tissue.



Schematic tissue remodeling

SCHEMATIC — NOT A CLINICAL / HISTOLOGIC SPECIMEN

Microscopic radiation injury is not only fibrosis

- Radiation may produce pleomorphic or multinucleated giant cells.
- Nuclear swelling, chromatin changes and atypical mitoses can occur.
- These features can resemble neoplastic atypia.

Radiation effect

Nuclear atypia and giant cells

Abnormal mitotic appearances

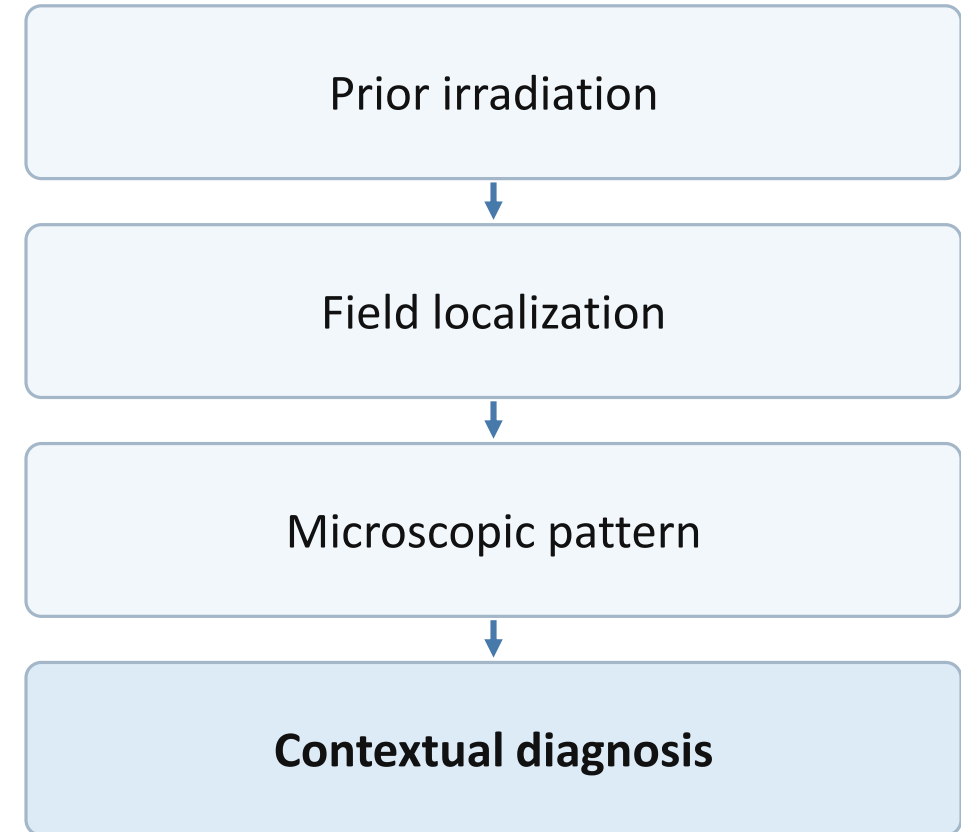
Diagnostic risk

Changes can mimic residual tumor

Clinical treatment history is essential

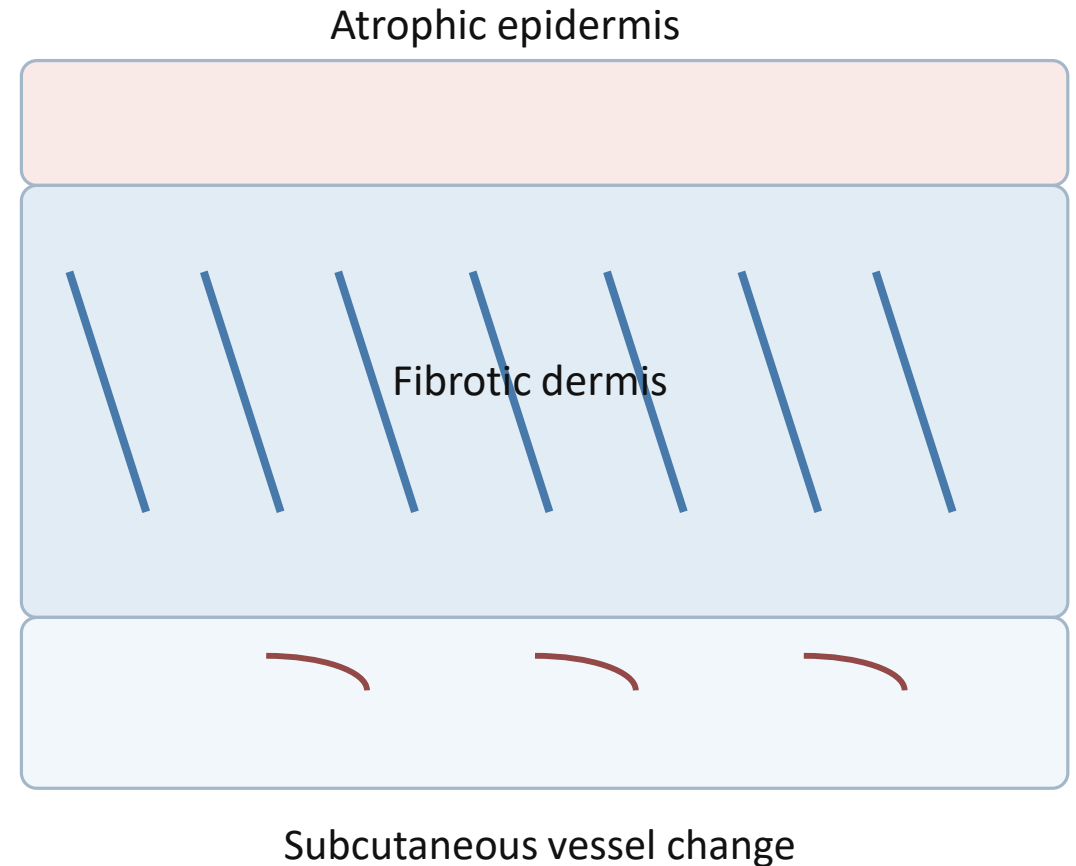
The pathologist must integrate treatment history

- Know whether the sampled tissue lies inside the radiation field.
- Distinguish therapy-related atypia from persistent neoplasia.
- Interpret scar, atypical cells and vascular injury together.



Skin: Chronic radiation dermatitis

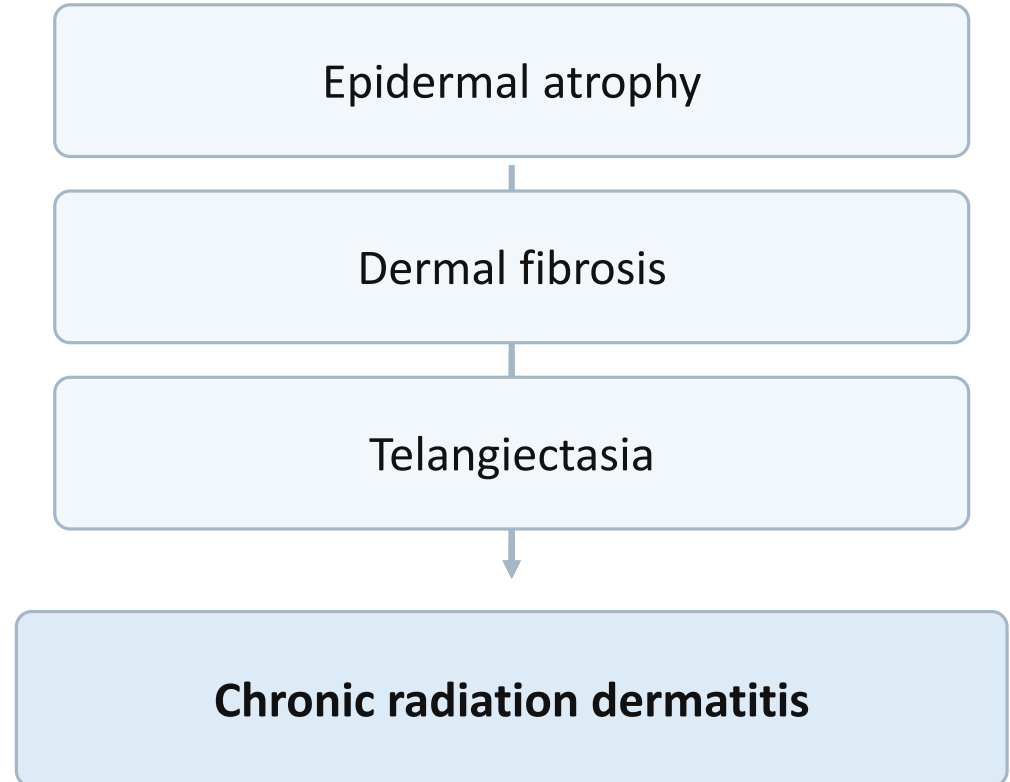
- The textbook illustration describes epidermal atrophy.
- Dermal fibrosis and subcutaneous vascular telangiectasia coexist.
- The triad links epithelial, stromal and vascular damage.



SCHEMATIC — NOT A CLINICAL / HISTOLOGIC SPECIMEN

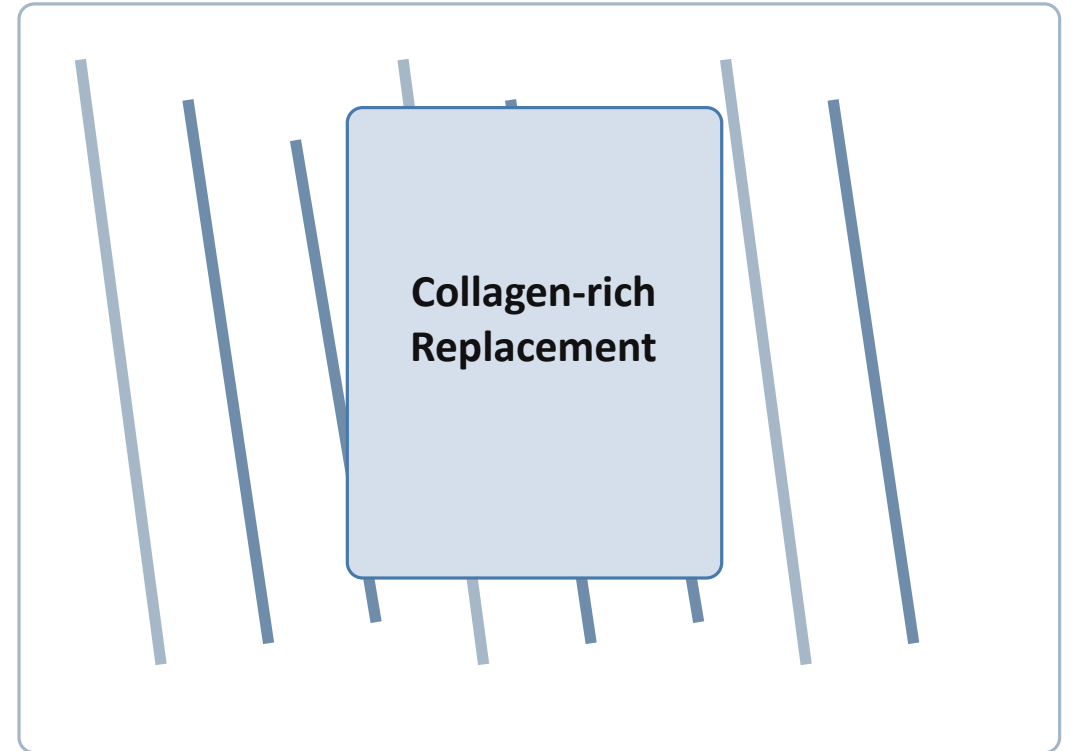
Skin: Why the changes occur together

- Epidermal loss reflects failure of epithelial maintenance.
- Collagen deposition thickens the supporting dermal compartment.
- Vascular abnormalities persist in damaged tissue.



Mediastinum: An example of extensive fibrosis

- Radiotherapy can produce dense fibrous tissue in the mediastinum.
- The Robbins illustration includes a markedly thickened pericardium.
- Tissue planes may be replaced by constricting scar.

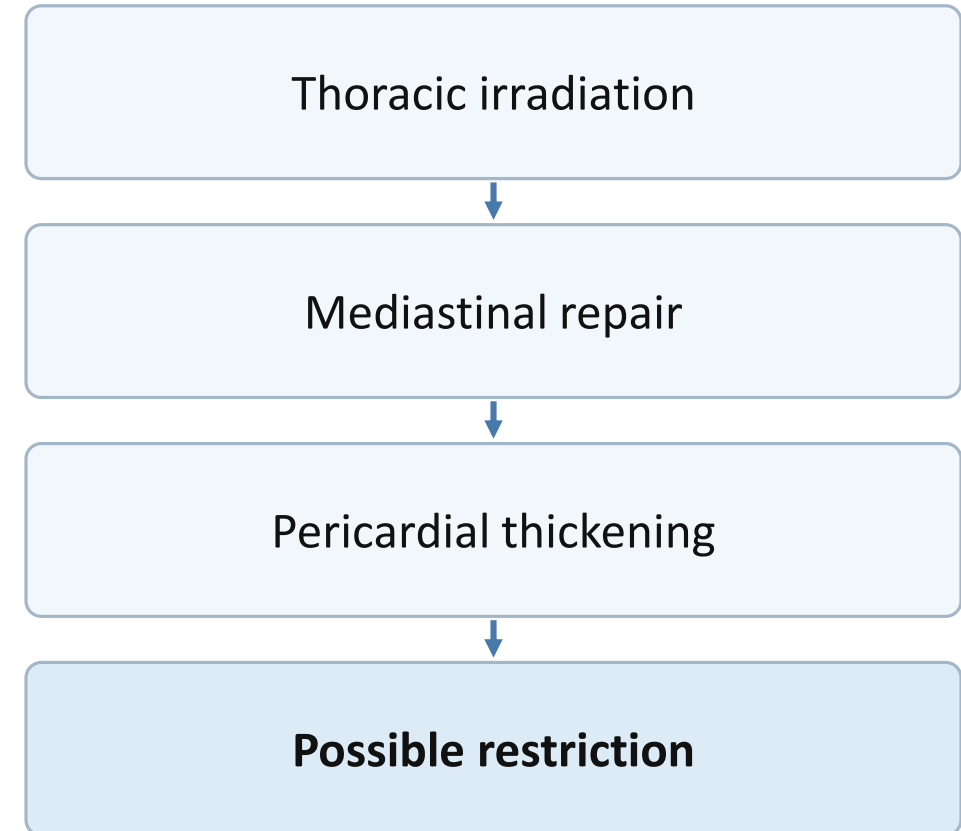


Schematic tissue remodeling

SCHEMATIC — NOT A CLINICAL / HISTOLOGIC SPECIMEN

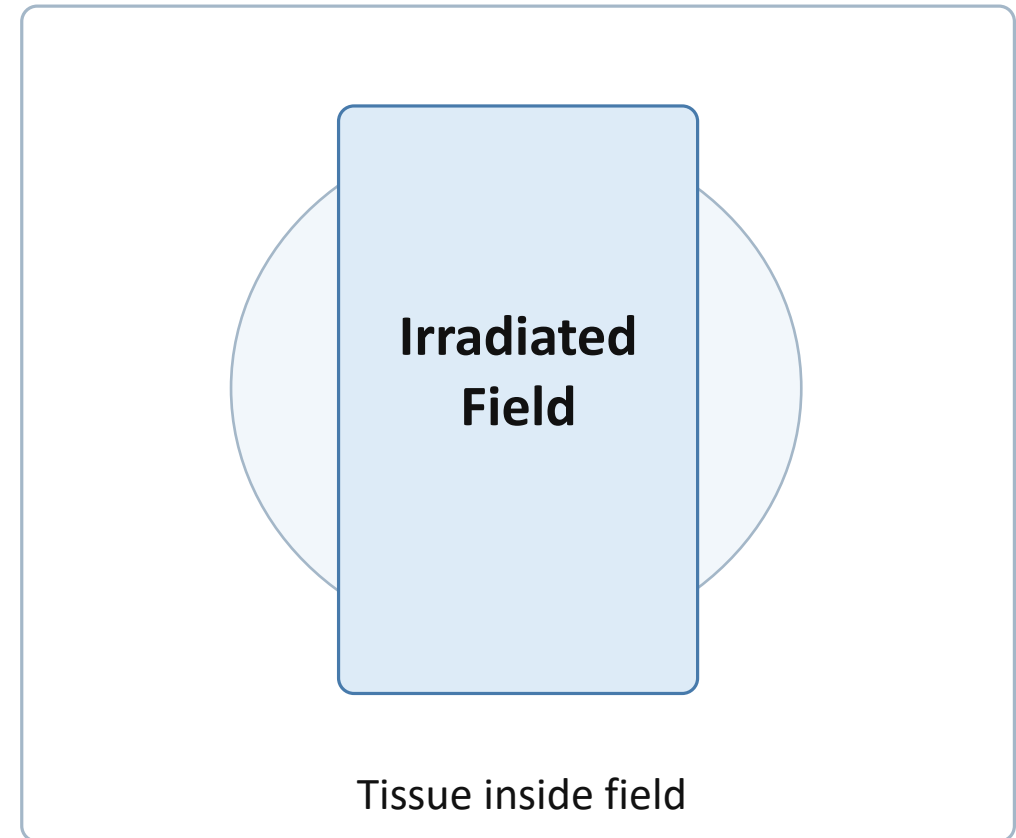
Pericardial thickening is a structural clue

- The mediastinal example places the pericardium within the scarred field.
- Thickening reflects replacement or encasement by fibrous tissue.
- Functional effects require organ-specific clinical evaluation.



Lung: A clinically important radiation target

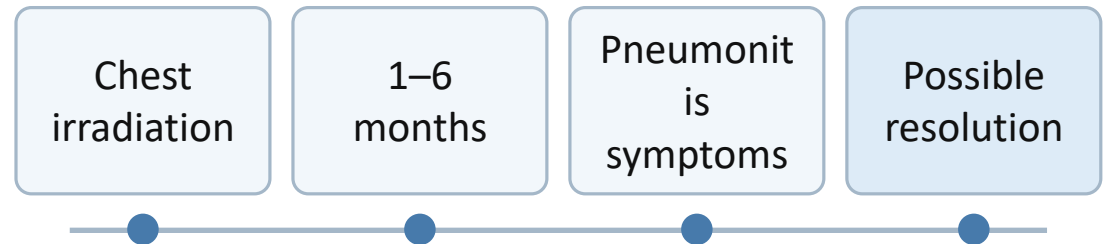
- Thoracic radiotherapy may involve lung, esophageal, breast or mediastinal tumors.
- Injury typically affects lung tissue within the irradiated field.
- Acute pneumonitis and chronic fibrosis are related patterns.



SCHEMATIC — NOT A CLINICAL / HISTOLOGIC SPECIMEN

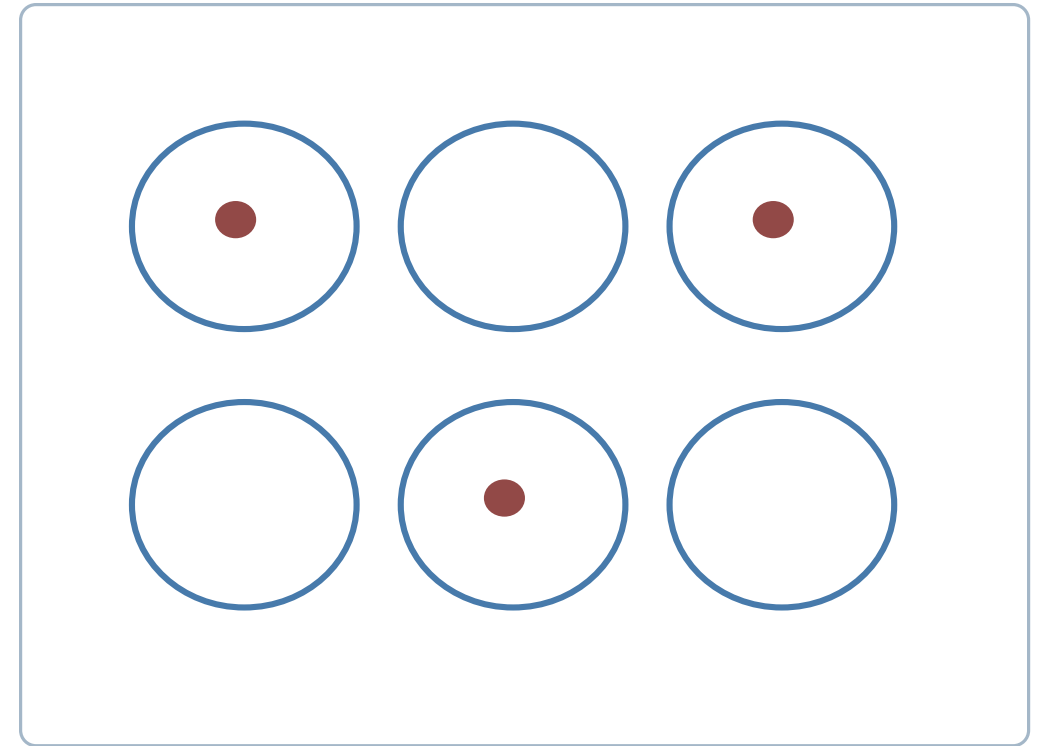
Acute radiation pneumonitis

- Presentation 1–6 months after irradiation.
- Symptoms may include fever, dyspnea and pleural effusion.
- Pulmonary infiltrates are part of the described clinical pattern.



Morphology of the pneumonitis phase

- The described pattern includes diffuse alveolar damage.
- Hyperplastic type II pneumocytes and fibroblasts may be atypical.
- Epithelial atypia and vascular-wall foam cells support radiation effect.



Alveolar wall injury (simplified)

SCHEMATIC — NOT A CLINICAL / HISTOLOGIC SPECIMEN

Some injured lungs progress to fibrosis

- Acute inflammatory lung injury may resolve.
- Other cases evolve into chronic radiation pneumonitis with fibrosis.
- Fibrosis may also arise without a clinically recognized acute phase.

Resolution after pneumonitis



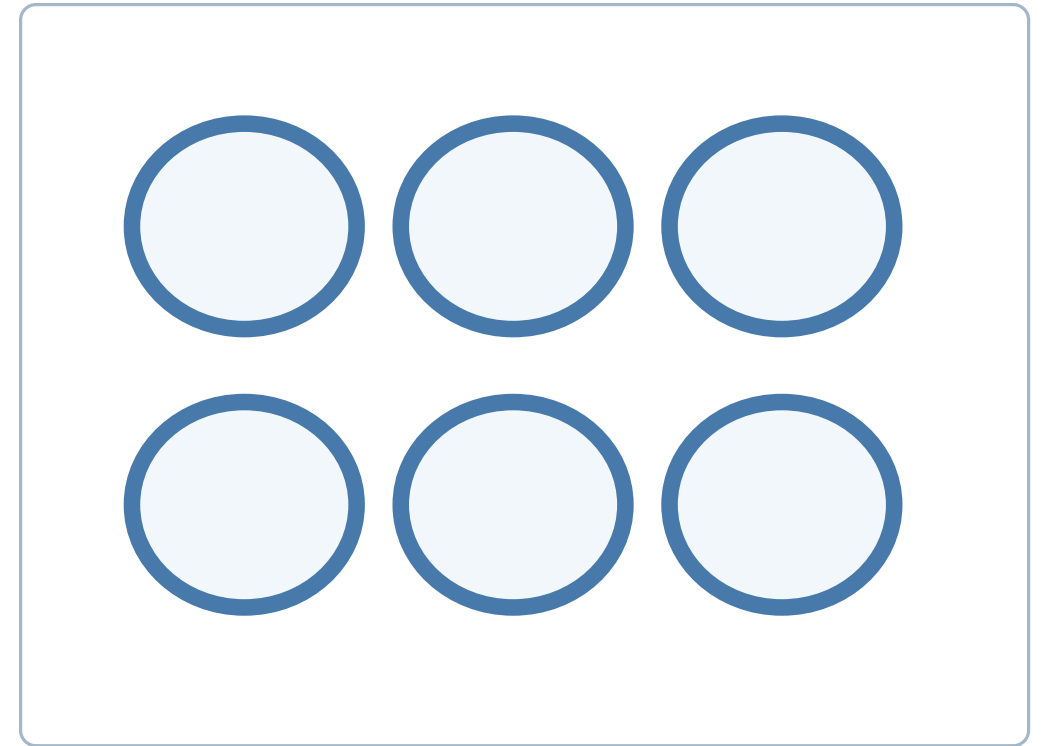
Progression / delayed fibrosis



Different clinical courses

Fibrosis replaces functional alveolar architecture

- Interstitial collagen increases as injury becomes chronic.
- The simplified schematic shows loss of thin gas-exchange septa.
- Reduced compliant lung tissue explains progressive functional limitation.

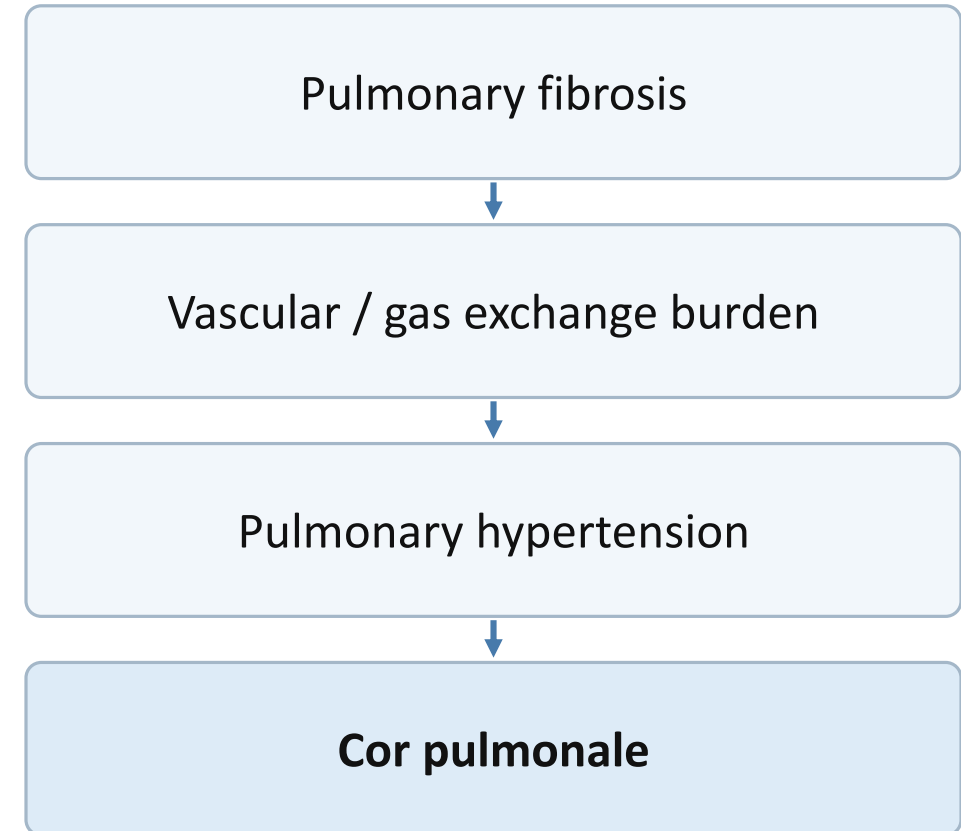


Thickened interstitium; Fewer thin septa

SCHEMATIC — NOT A CLINICAL / HISTOLOGIC SPECIMEN

Severe chronic lung consequences

- Chronic progressive fibrosis may cause cyanosis.
- Pulmonary vascular consequences can include pulmonary hypertension.
- Advanced disease may lead to cor pulmonale.

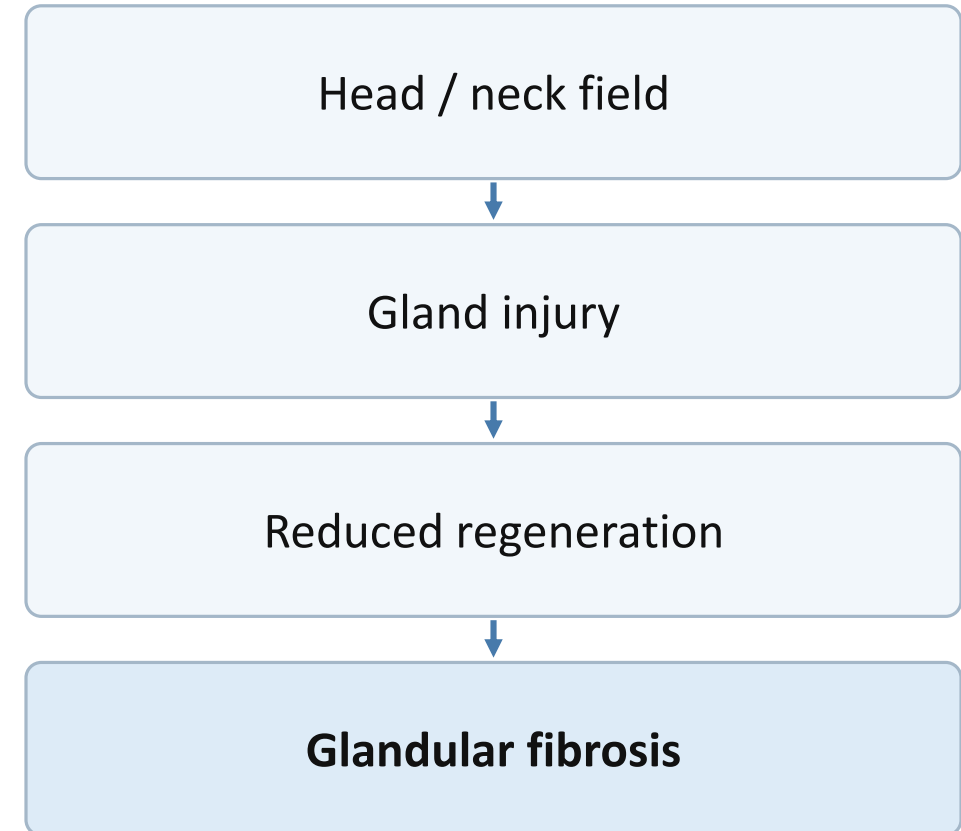


Acute and chronic lung injury differ

Feature	Acute radiation pneumonitis	Chronic radiation fibrosis
Timing	Usually 1–6 months	Delayed / progressive
Dominant process	Inflammatory alveolar injury	Interstitial collagen deposition
Morphology	DAD, type II cell atypia	Architectural scarring
Course	May resolve or progress	May be persistent / progressive

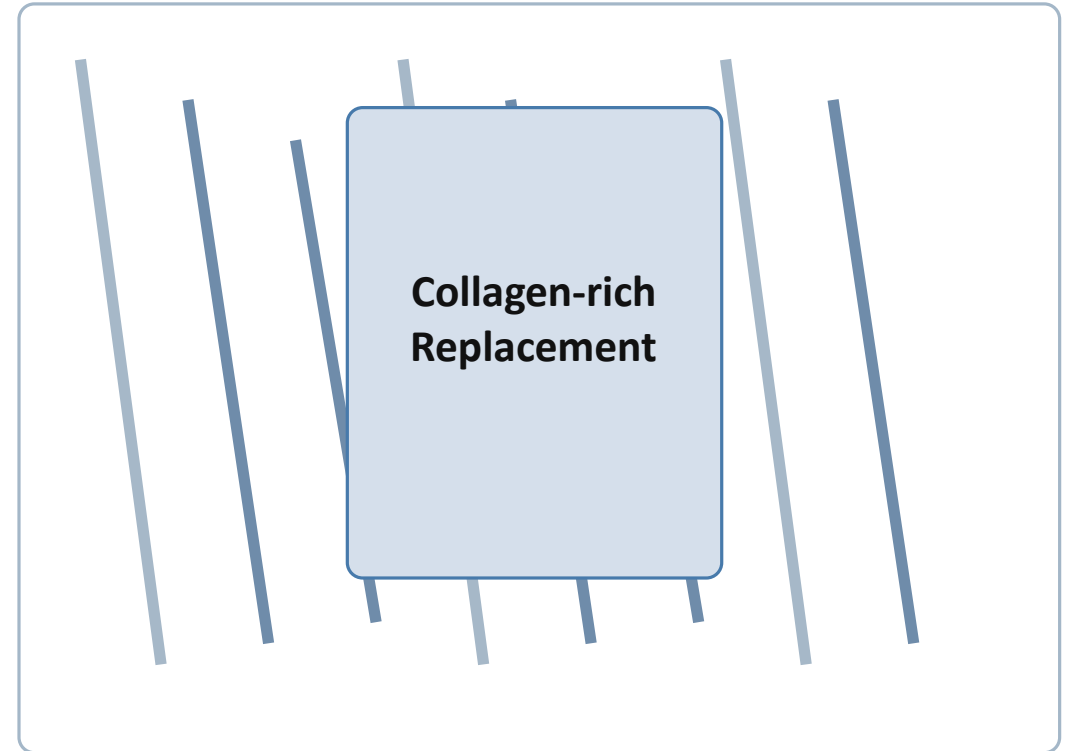
Salivary glands: A recognized site

- Head and neck radiotherapy may include salivary glands.
- Radiation-related fibrosis can follow loss of glandular parenchyma.
- Residual tissue function depends on the surviving compartments.



Colorectal and pelvic irradiation

- Radiotherapy for prostate, rectal or cervical cancer exposes pelvic tissues.
- Fibrotic healing can occur within the irradiated pelvic field.
- Scars and adhesions can alter normal relationships between structures.

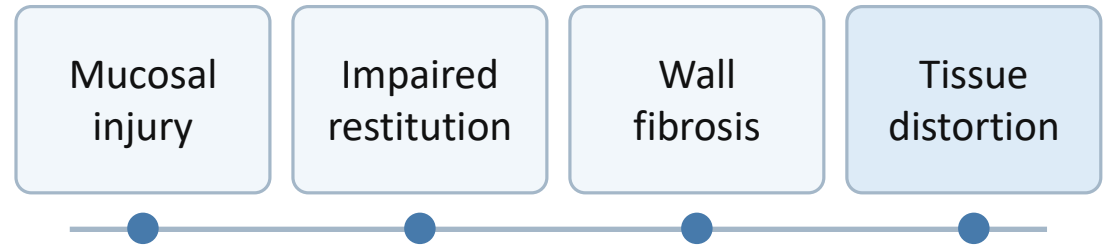


Schematic tissue remodeling

SCHEMATIC — NOT A CLINICAL / HISTOLOGIC SPECIMEN

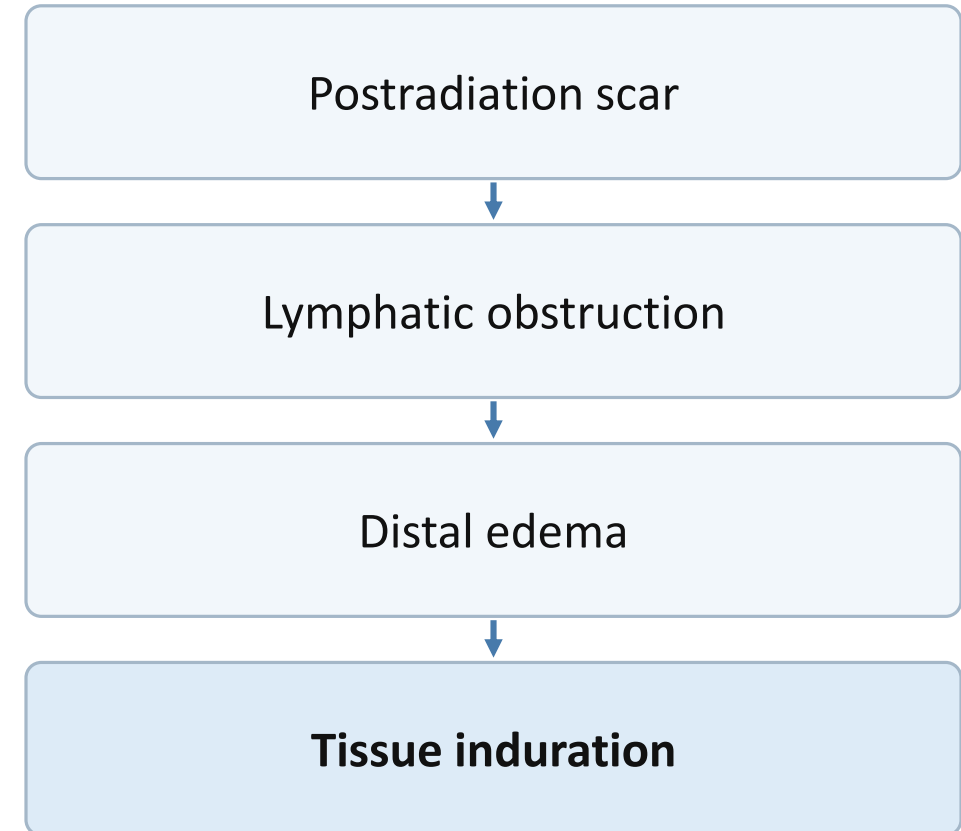
Gastrointestinal wall fibrosis is delayed

- Early intestinal radiation injury primarily involves mucosal cells.
- Late injury may produce fibrosis of the bowel wall.
- This illustrates sequential epithelial loss and stromal replacement.



Obstructed lymphatics can follow irradiation

- Postradiation fibrosis is a listed cause of secondary lymphedema.
- Fibrosis can impair lymphatic drainage through obstructed channels.
- Chronic edema may itself be followed by further ECM deposition.



Organ pattern follows the treated field

Site	Recognized fibrotic change	Context
Lung	Interstitial pulmonary fibrosis	Thoracic radiotherapy
Salivary tissue	Gland fibrosis	Head and neck therapy
Mediastinum	Dense scar; pericardial thickening	Thoracic field
Colorectal / pelvis	Fibrosis; scars and adhesions	Prostate, rectal, cervical therapy

Rate of radiation delivery modifies damage

- Subdividing a total dose permits repair between exposures.
- Fractionation limits injury when surviving normal cells recover.
- Incomplete recovery may still lead to delayed tissue effects.

Single concentrated exposure

Less inter-fraction repair opportunity

Greater immediate injury at comparable context

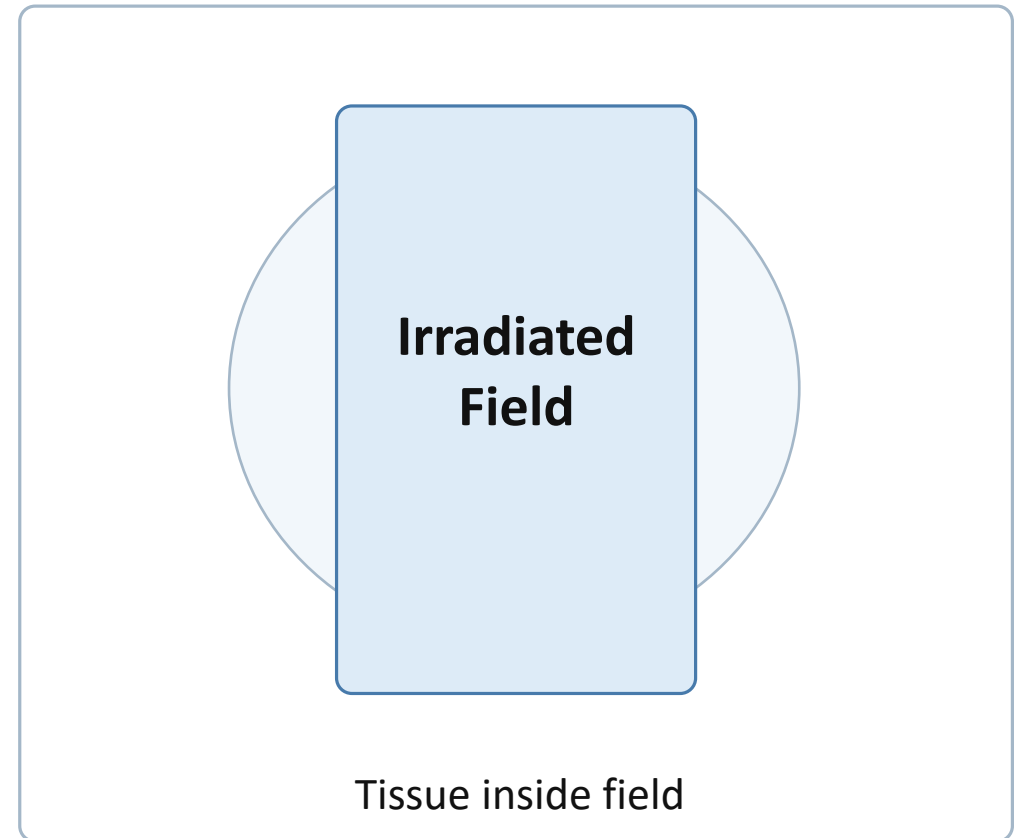
Fractionated course

Intervals allow partial normal-tissue repair

Residual effects may accumulate

Field size changes tissue consequences

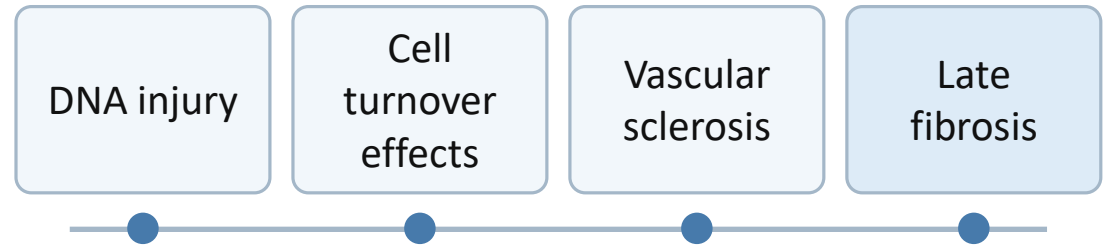
- The irradiated volume is a major determinant of biologic effects.
- Smaller, shielded fields confine injury to less tissue.
- Organ-specific consequences depend on what lies inside the field.



SCHEMATIC — NOT A CLINICAL / HISTOLOGIC SPECIMEN

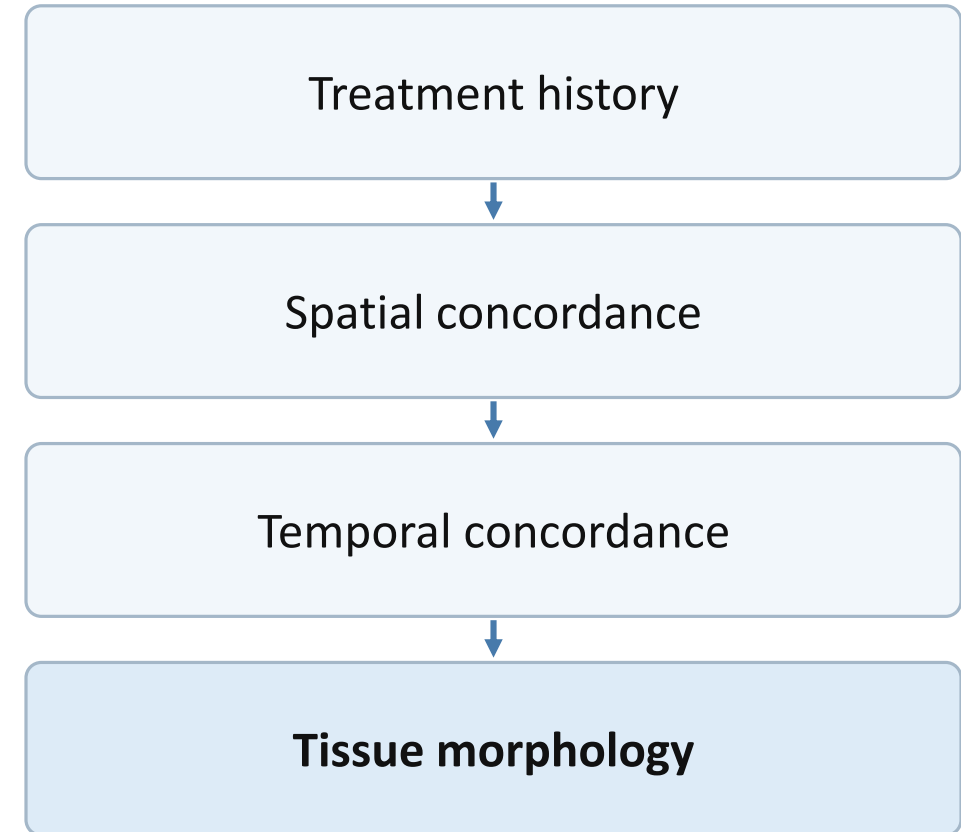
Cell turnover and vascular injury act on different clocks

- Rapidly dividing populations can show early tissue depletion.
- Delayed vascular stenosis can appear months or years later.
- Both mechanisms can contribute to the final fibrotic state.



The field and chronology support recognition

- Confirm a compatible history of radiotherapy.
- Map the abnormality to the treated anatomic territory.
- Combine delayed timing with collagenous and vascular changes.



Morphology must be interpreted as a pattern

- Scar alone is not specific for radiation as the cause.
- Atypical nuclei alone do not prove residual carcinoma.
- Concordant vessel, parenchymal and stromal injury is more informative.

Insufficient alone

Collagen deposition

Radiation-like cytologic atypia

Better interpretation

Treatment field and timing

Vascular + stromal + cell findings

Radiation fibrosis is distinct from carcinogenesis

- Fibrosis follows tissue loss and connective-tissue repair.
- Carcinogenesis results from persisting genomic alterations.
- They are different late consequences of radiation exposure.

Cell death → scarring



Mutation persistence → tumor risk



Distinct late pathways

Case: Dyspnea after thoracic radiotherapy

- A patient develops dyspnea several months after chest irradiation.
- Imaging shows abnormalities predominantly in the irradiated lung.
- Which acute radiation-associated process is suggested?

CLINICAL REASONING

Which mechanism or diagnosis best fits the exposure, timing and tissue findings?

Answer and rationale in presenter notes

Case interpretation: Pneumonitis is not fibrosis

- Acute pneumonitis reflects an inflammatory/alveolar injury phase.
- Some cases resolve; Others progress to chronic fibrosis.
- Do not label every postradiotherapy opacity as established scar.

Pneumonitis

Inflammatory lung injury

Potentially reversible

Fibrotic sequela

Collagenous
architectural
replacement

May be persistent

Case: Thickened tissue after thoracic radiation

- A post-treatment specimen shows fibrous mediastinal tissue.
- The pericardium is markedly thickened.
- Which tissue-level mechanisms explain this pattern?

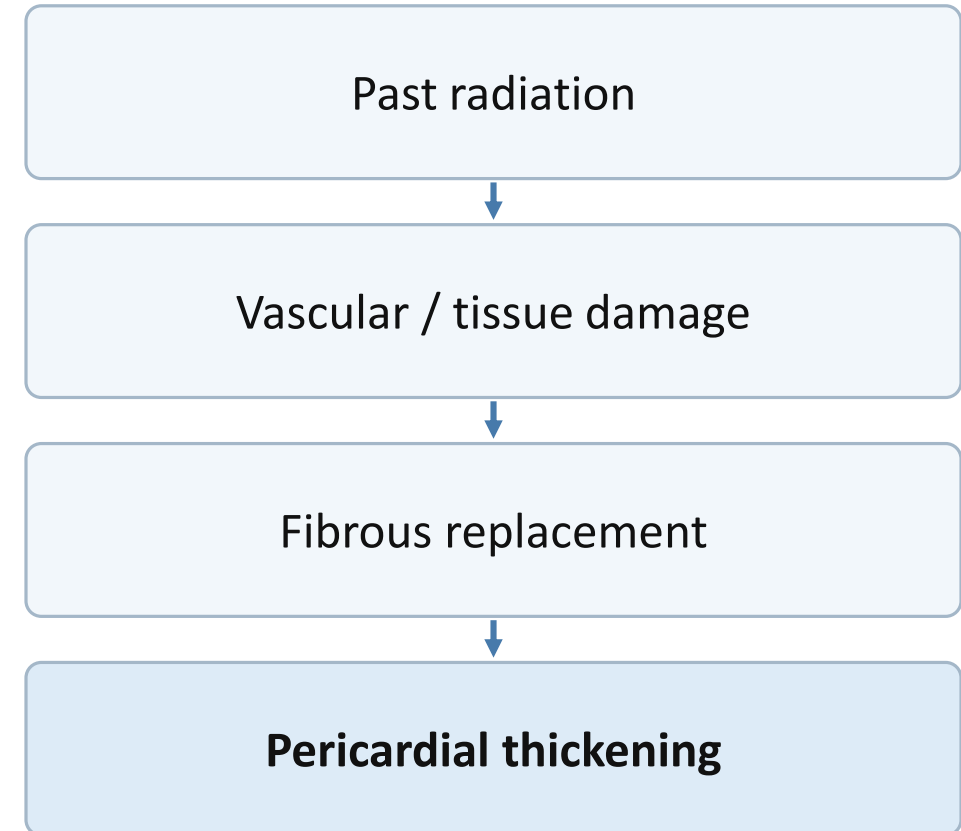
CLINICAL REASONING

Which mechanism or diagnosis best fits the exposure, timing and tissue findings?

Answer and rationale in presenter notes

Case interpretation: Mediastinal fibrosis

- Location within the treated field supports therapy-related injury.
- Vascular sclerosis and collagen deposition account for the scar.
- Any functional consequence should be assessed clinically.



Case: Atypical cells in an irradiated specimen

- A biopsy contains bizarre enlarged and multinucleated cells.
- The tissue was previously treated with ionizing radiation.
- Why is tumor persistence not inferred from atypia alone?

CLINICAL REASONING

Which mechanism or diagnosis best fits the exposure, timing and tissue findings?

Answer and rationale in presenter notes

Case interpretation: Avoid an attribution error

- Recognize radiation-associated cellular atypia as a mimic.
- Search for an adequately supported neoplastic pattern.
- Treatment history changes interpretation of cellular morphology.

Observed atypia

Pleomorphism or giant cells

Unusual nuclear appearances

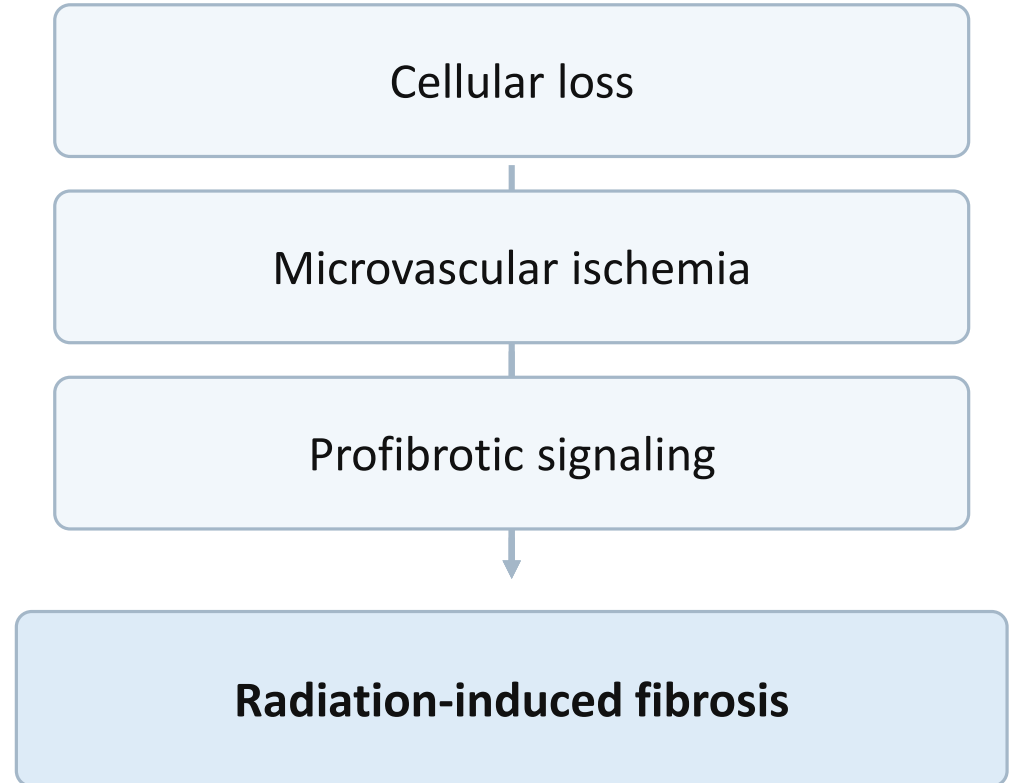
Additional information needed

Prior radiation field and timing

Architecture and other tumor evidence

Synthesis: Tissue injury becomes scar

- Parenchymal loss and blocked regeneration create a defect.
- Damaged vessels sustain ischemia and impair repair.
- Profibrotic signaling promotes fibroblasts, collagen and contraction.



High-yield distinctions

Distinction	Interpretive principle
Fibrosis vs regeneration	ECM replacement vs restoration of tissue-specific cells
Early vs late radiation effects	Cell loss often precedes sclerosis and interstitial scar
Pneumonitis vs lung fibrosis	Acute alveolar injury vs chronic architectural replacement
Radiation atypia vs tumor	Microscopy requires treatment and tissue-context correlation

Final learning check

- What three injury processes promote delayed radiation fibrosis?
- How does TGF- β influence extracellular matrix?
- Why can radiation-related cellular atypia complicate diagnosis?

Selected textbook sources

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026).
- Chapter 9: radiation injury and fibrosis (pp. 390–394).
- Chapter 3: connective-tissue deposition and remodeling (pp. 93–97).
- Chapter 15: radiation-induced lung diseases (p. 634).