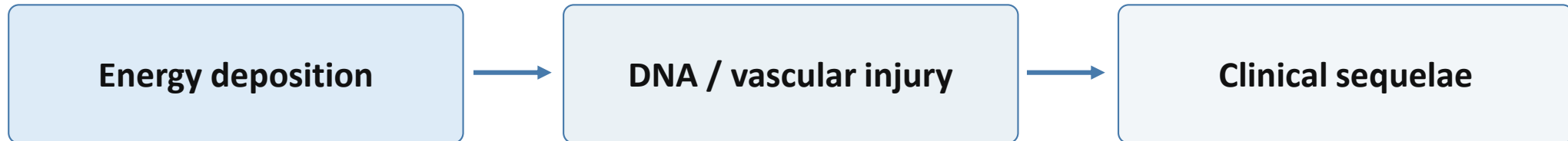


Injury Produced by Ionizing Radiation

From ionization to tissue injury, fibrosis, and carcinogenesis



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Learning objectives

- Distinguish ionizing from nonionizing radiation and describe common radiation types.
- Explain how radiation damages DNA and why proliferating tissues are vulnerable.
- Recognize acute systemic effects, delayed vascular injury, and radiation-induced fibrosis.
- Connect imperfect DNA repair to mutagenesis and later malignancy.

Why ionizing radiation is a pathology problem

- Radiation has indispensable diagnostic and therapeutic applications.
- The same energy deposition can cause tissue loss, chronic scarring, and genetic injury.
- Consequences depend on radiation properties, tissue susceptibility, field size, and timing.
- Pathology includes both direct cellular changes and delayed vascular–stromal remodeling.

Radiation: Energy transferred to matter

- Radiation may travel as waves or energetic particles.

Nonionizing

Ionizing

- Biologic effects depend on whether energy can eject bound electrons.

Insufficient energy to
displace tightly bound
electrons

Can remove electrons
from atoms

- Ionization changes molecular chemistry and can initiate tissue injury.

Different physical interactions; Different biological consequences

Ionizing versus nonionizing energy

- Nonionizing energy is insufficient to remove tightly bound electrons.
- Ionizing radiation liberates electrons from atoms or molecules.
- Do not equate every radiation modality with ionization.

Nonionizing

Insufficient energy to
displace tightly bound
electrons

Ionizing

Can remove electrons
from atoms

*Different physical interactions; Different biological
consequences*

What produces ionizing radiation?

- X-rays and gamma rays are high-energy electromagnetic radiation.

X-rays / γ -rays

High-energy photons

α particles

2 protons + 2 neutrons

- Alpha and beta particles are particulate radiation.

β particles

Electron or positron

Neutrons

Uncharged particles

- High-energy neutrons also cause ionizing injury.

X-rays and gamma rays: Distributed deposition

- Both are high-energy photons capable of ionization.
- They travel farther in tissue than densely ionizing alpha particles in the source comparison.
- At equivalent energy, damage is distributed over a deeper or longer track.
- Medical diagnostic imaging and radiotherapy exploit photon radiation.

Alpha particles: Concentrated tissue injury

- Alpha particles contain two protons and two neutrons.
- They transfer substantial energy across a restricted region.
- The local biologic effect differs from that of sparsely ionizing photons.
- Internal deposition of alpha-emitting material is relevant to radon-associated lung risk.

Beta particles and neutrons

- Beta particles consist of electrons or positrons.
- Neutrons are another type of high-energy ionizing radiation.
- Particle identity influences how physical energy is deposited in tissues.
- Equal absorbed energy does not guarantee equal biological effect.

Spatial pattern of ionization matters

- Dense localized ionization can severely damage a restricted region.
- More distributed deposition may expose deeper tissues.
- Compare both absorbed dose and radiation quality when interpreting effects.

Same incident energy does not imply the same spatial injury pattern

α : Concentrated deposition

X/ γ : More dispersed path

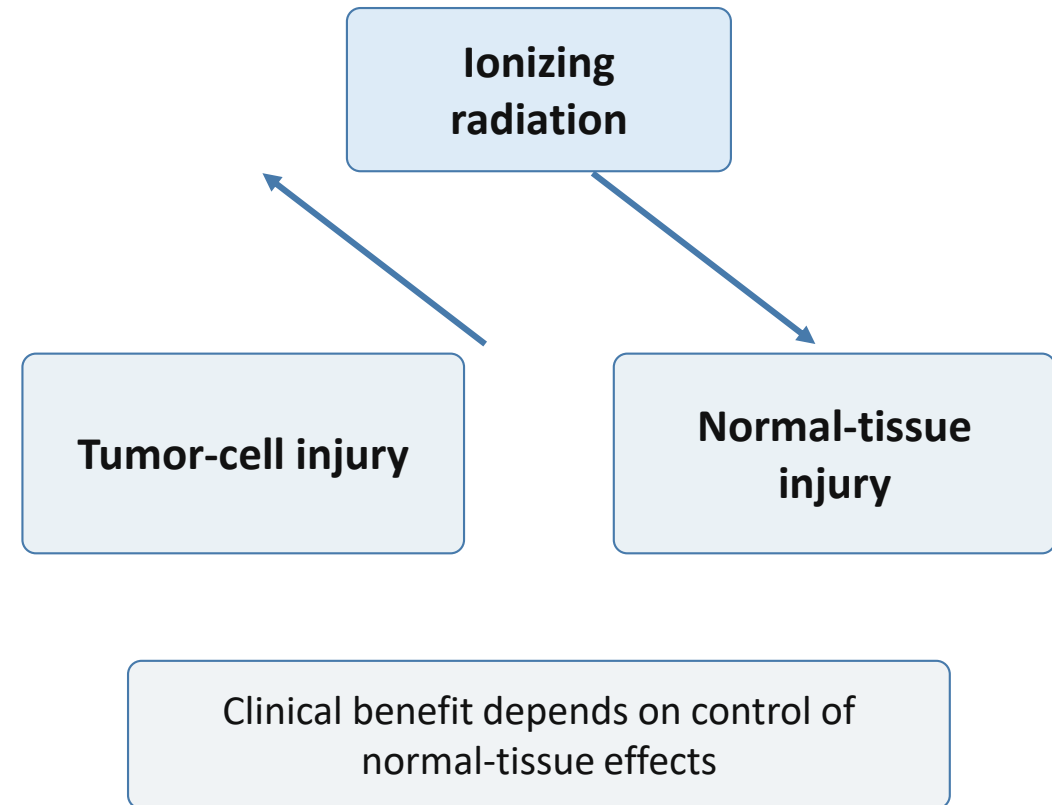


Sources of exposure in medical practice

- Diagnostic imaging exposes tissues to ionizing radiation.
- Cancer radiotherapy deliberately directs radiation at target volumes.
- Diagnostic and therapeutic radioisotopes are additional medical sources.
- Clinical benefit must be interpreted alongside potential acute and late effects.

Radiation is a therapeutic double-edged sword

- Ionizing energy can arrest proliferation and kill target cells.
- Surrounding normal tissues may accumulate acute or delayed lesions.
- Radiotherapy aims for tumor effect with acceptable normal-tissue injury.



Schematic

Three distinct ways to describe a dose

- Source activity, absorbed energy, and biologically weighted dose describe different concepts.
- The units Ci, Gy, and Sv therefore answer different questions.
- Do not substitute one unit for another without specifying the quantity.

Activity

Radionuclide disintegrations

Ci

Absorbed dose

Energy per mass

Gy

Equivalent/effective dose

Biologic weighting

Sv

Curie: Activity of a radioactive source

- The curie (Ci) describes radionuclide disintegrations per second.
- It quantifies activity of a source, not energy absorbed by a target.
- Two sources with the same activity need not deliver the same tissue dose.

Gray: Energy absorbed per tissue mass

- The gray (Gy) measures absorbed radiation dose.
- The unit reflects energy delivered to a mass of irradiated material.
- Absorbed dose is not by itself a complete measure of biologic harm.

Sievert: Biologically weighted radiation dose

- The sievert (Sv) expresses equivalent or effective dose after biological weighting.
- For the same absorbed dose, radiation qualities can produce different injury.
- Interpret Sv in the context of the quantity being reported and exposure geometry.

Radiation units: Diagnostic distinctions

Quantity	Unit	What it represents
Radioactivity	Curie (Ci)	Nuclear disintegration rate
Absorbed dose	Gray (Gy)	Energy absorbed per unit mass
Equivalent / effective dose	Sievert (Sv)	Biologically weighted radiation dose

Radiation weighting and tissue distribution affect interpretation; These are not interchangeable quantities.

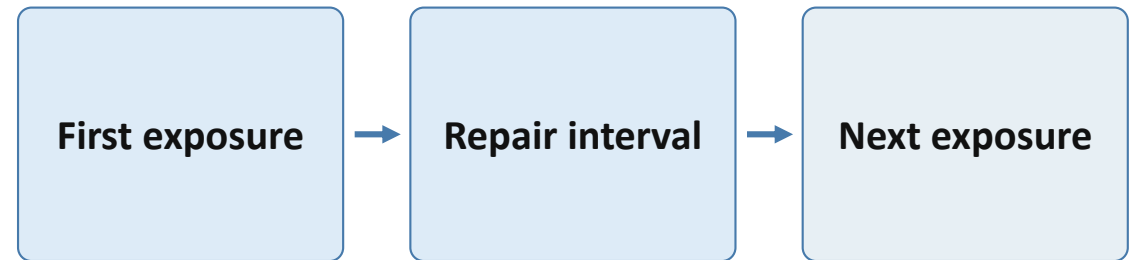
Biologic injury has multiple determinants

- Radiation quality and total absorbed dose influence the primary lesion.
- Dose rate and fractionation determine opportunities for repair.
- Exposed field size controls how much functional tissue is threatened.
- Cell proliferation, oxygenation, and vascular integrity modify outcomes.

Dose fractionation permits partial repair

- Dividing an exposure into fractions permits repair of some sublethal damage.

- Cumulative harm depends on residual injury after each interval.



- Normal-tissue recovery underpins the therapeutic use of fractionation.

Schematic

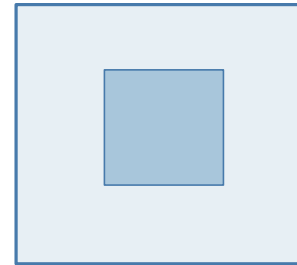
Why fractionated radiotherapy can work

- Tumor and normal cells may differ in capacity for repair and recovery.
- Intervals between treatments allow some normal tissues to recover.
- Tumor killing can accumulate when damage is inadequately repaired.
- Fractionation does not eliminate late toxicity or make irradiation harmless.

Field size modifies the clinical consequence

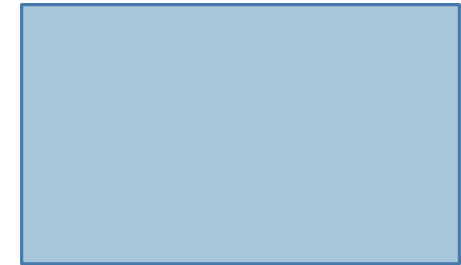
- A restricted field can receive a high dose without exposing the whole body.
- A larger field injures more critical tissues and stem-cell compartments.
- The same nominal dose may have different consequences in focal versus whole-body exposure.

Small field



Local tissue exposure

Large field



More tissues affected

Cell proliferation predicts radiosensitivity

- Ionizing radiation injures DNA needed for successful cell division.

Bone marrow

Rapid turnover

Lymphoid tissue

Highly sensitive

- Rapidly proliferating cell populations express injury early.

GI mucosa

Rapid renewal

- Bone marrow, lymphoid tissue, germ cells, and GI mucosa are vulnerable.

Germinal cells

Proliferative

High-turnover tissue: Why injury appears early

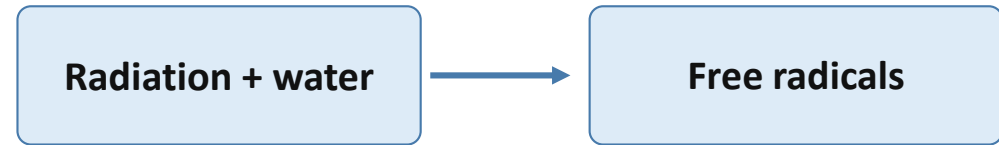
- Stem and progenitor cells are required for continual tissue replacement.
- Their depletion first becomes apparent as short-lived mature cells are lost.
- Damaged proliferative compartments may recover if viable precursors remain.
- Severe depletion prevents tissue reconstitution and prolongs dysfunction.

Quiescent cells are relatively radioresistant

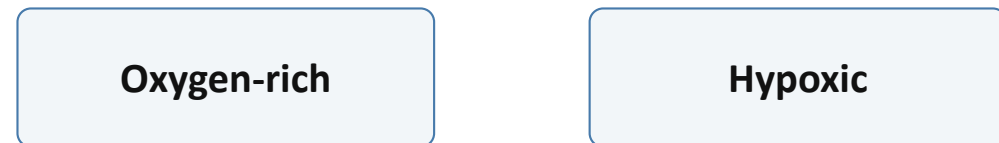
- Nondividing neurons and mature muscle cells are less vulnerable to division-dependent DNA injury.
- Extremely high doses may interfere with essential nuclear functions in such cells.
- Relative cellular resistance does not protect an organ from vascular or stromal injury.

Oxygen modifies free-radical injury

- Radiolysis of water yields reactive species that injure DNA.



- Oxygen enhances the effectiveness of radical-mediated damage.



More effective radical-mediated DNA damage

Reduced sensitivity to indirect damage

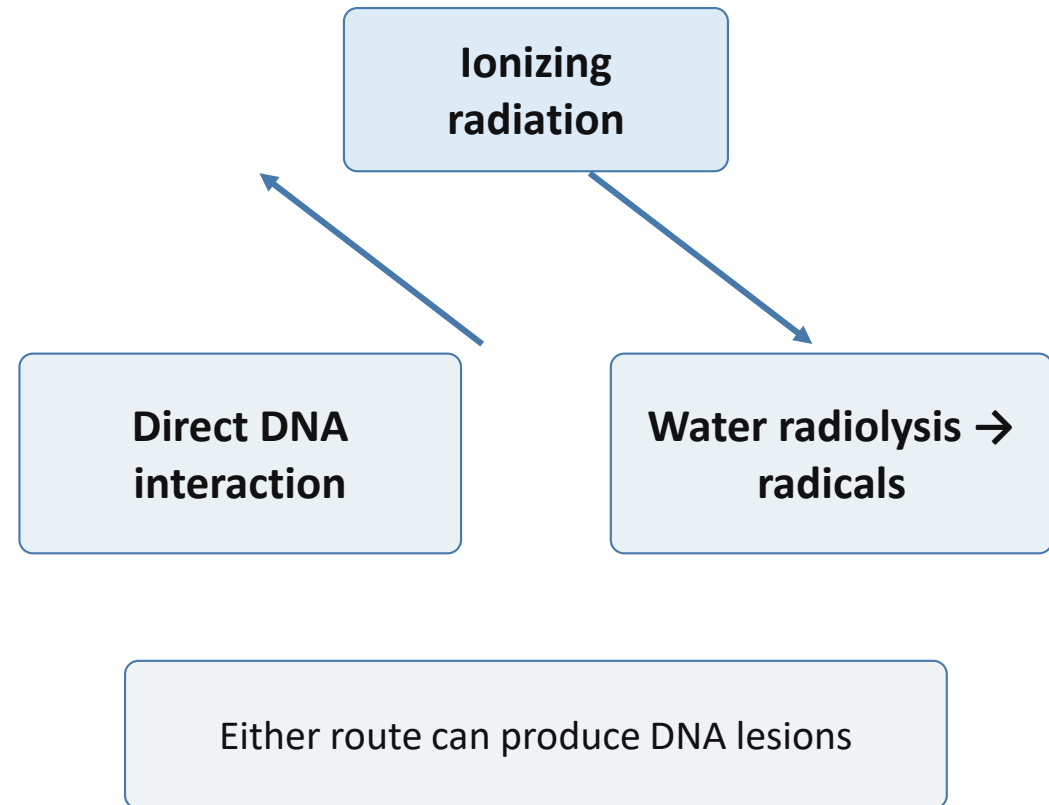
- Hypoxic tissue, including poorly perfused tumor regions, is less sensitive to this pathway.

Hypoxic tumor regions: Mechanistic implication

- Rapid tumor growth can outstrip local vascular supply.
- Low oxygen tension reduces indirect radiation injury.
- Consequently, nonhypoxic tumor areas may respond differently from hypoxic areas.
- Oxygen effect is a biologic modifier, not a substitute for dosimetry.

Two pathways converge on DNA damage

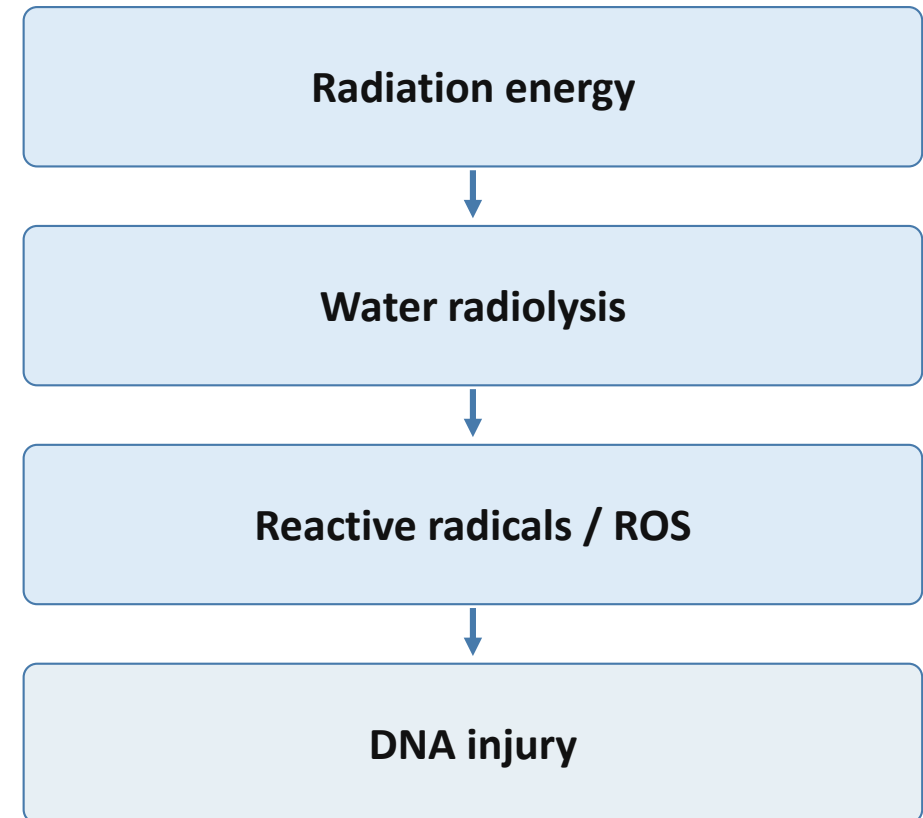
- A direct effect transfers energy to DNA or other macromolecules.
- An indirect effect produces free radicals, particularly from water.
- Free-radical production as a major mechanism.



Schematic

Indirect damage begins with radiolysis

- Biological tissues contain abundant water.
- Radiolysis generates highly reactive chemical intermediates.
- These species can alter DNA even when radiation does not strike the DNA directly.



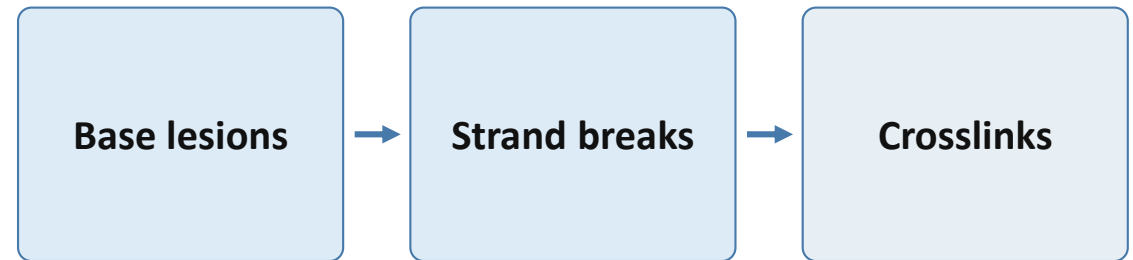
Schematic

DNA injury has several molecular forms

- Reported lesions include base changes, single-strand breaks, and DNA–protein crosslinks.

- Double-strand breaks are particularly consequential for genomic integrity.

- Different lesions differ in repair complexity and consequences.



Schematic

Double-strand breaks: A high-risk lesion

- Both DNA strands are interrupted at or near one genomic location.
- Correct joining requires preserving the original chromosomal organization.
- Misrepair can yield deletions, inversions, translocations, or other aberrations.
- Unrepaired lesions can trigger cell-cycle arrest or cell death.

DNA damage and potential outcomes

Primary injury	Possible outcome	Pathologic implication
Single-base damage	Enzymatic correction or mutation	Sequence-level alteration
Single-strand break	Repair or persistent injury	Genome maintenance stress
Double-strand break	Faithful or aberrant rejoining	Chromosomal rearrangement
DNA–protein crosslink	Impaired DNA processing	Complex molecular injury

Each entry is qualitative: The lesion does not dictate a single inevitable outcome.

Homologous recombination: One DSB repair route

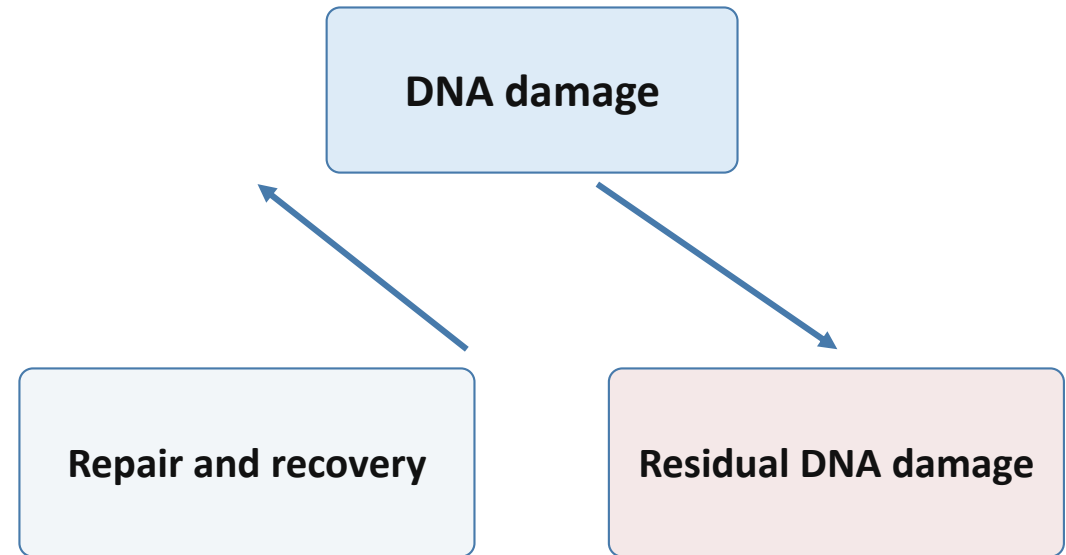
- Homologous recombination is a recognized mammalian repair pathway.
- Repair uses a homologous DNA sequence to guide reconstruction.
- Successful repair can restore sequence integrity.
- Repair fidelity influences whether irradiated cells retain genomic damage.

Nonhomologous end joining: A frequent DSB route

- Nonhomologous end joining (NHEJ) is described as the more common DSB repair pathway.
- The broken DNA ends are reconnected without the same template-based mechanism.
- Joining errors can cause small deletions or duplications.
- Aberrant rejoining can also produce translocations and inversions.

Cell fate follows DNA injury and repair

- Effective repair may preserve viability and tissue reconstitution.
- Persistent injury can inhibit division or induce cell death.
- Aberrant repair may permit survival with unstable genetic information.



The ultimate outcome depends on the lesion and repair fidelity

Cell-cycle checkpoints limit propagation

- Checkpoints can arrest replication of cells carrying DNA breaks.
- Failure to arrest permits chromosomal lesions to persist through cell division.
- Surviving damaged clones may accumulate additional transforming events.
- The transition to cancer can occur after a prolonged latency.

Early and late injury are mechanistically distinct

- Early injury reflects depletion of proliferative cells and acute tissue dysfunction.
- Late injury reflects cumulative vascular damage and stromal fibrosis.
- Carcinogenesis depends on surviving genetically altered cells.
- Latency varies with the tissue, radiation exposure, and lesion.

Whole-body versus localized irradiation

- Large exposed volumes can threaten multiple regenerative organs at once.

Localized

Small treatment field

- Systemic syndromes differ from the injury caused by a focal therapeutic field.

Whole-body

Multiple proliferative organs

- Whole-body radiation effects escalate as exposure increases.

Delayed

Persistent vascular / stromal effects

Total-body radiation: Broad syndrome pattern

Exposure band	Predominant site	Dominant manifestations
0–1 Sv	No dominant site	Little or no acute symptomatology
1–2 Sv	Lymphocytes	Lymphopenia / granulocyte changes
2–10 Sv	Bone marrow	Cytopenias, bleeding, vomiting
10–20 Sv	Small intestine	Diarrhea, fever, fluid/electrolyte loss
>50 Sv	Brain	Ataxia, coma, convulsions

Textbook schematic categories; These bands should not be treated as clinical triage thresholds.

Acute radiation syndromes: Severity progression

- As systemic exposure rises, injury extends beyond isolated circulating lymphocytes.
- Marrow suppression impairs host defense and hemostasis.
- Greater exposures damage gastrointestinal barrier function.
- At extreme exposures, severe central nervous system manifestations occur.

Lymphoid tissues are highly radiosensitive

- Lymphocytes are depleted directly in blood and lymphoid organs.
- High-dose, large-field exposure can produce severe lymphopenia within hours.
- Lymph nodes and spleen may shrink as lymphocytes are lost.
- Regeneration requires survival of competent lymphoid precursors.

Hematopoietic injury unfolds over time

- Different circulating blood cells have different survival times.
- A marrow insult first reduces rapidly renewed populations.
- The temporal pattern of cytopenias reflects cellular turnover and marrow reserve.

Hours



Lymphopenia

Days



Neutropenia

~1 week



Thrombocytopenia

2–3 weeks



Anemia

Neutropenia after marrow irradiation

- A brief rise in the circulating neutrophil count may precede neutropenia.
- Neutropenia becomes apparent within several days.
- Counts may reach their nadir during the second week.
- Recovery can take months after survivable exposure.

Thrombocytopenia after marrow irradiation

- Thrombocytopenia appears around the end of the first week.
- Platelet nadir generally occurs after the granulocyte nadir.
- Low platelets contribute to the hemorrhagic consequences of marrow injury.
- Recovery depends on surviving hematopoietic precursors.

Anemia develops later than other cytopenias

- Red cells circulate much longer than granulocytes or platelets.
- Anemia may become evident after 2–3 weeks.
- It can persist for months while erythropoiesis recovers.
- Timing is a pathophysiologic clue to marrow rather than isolated blood-cell damage.

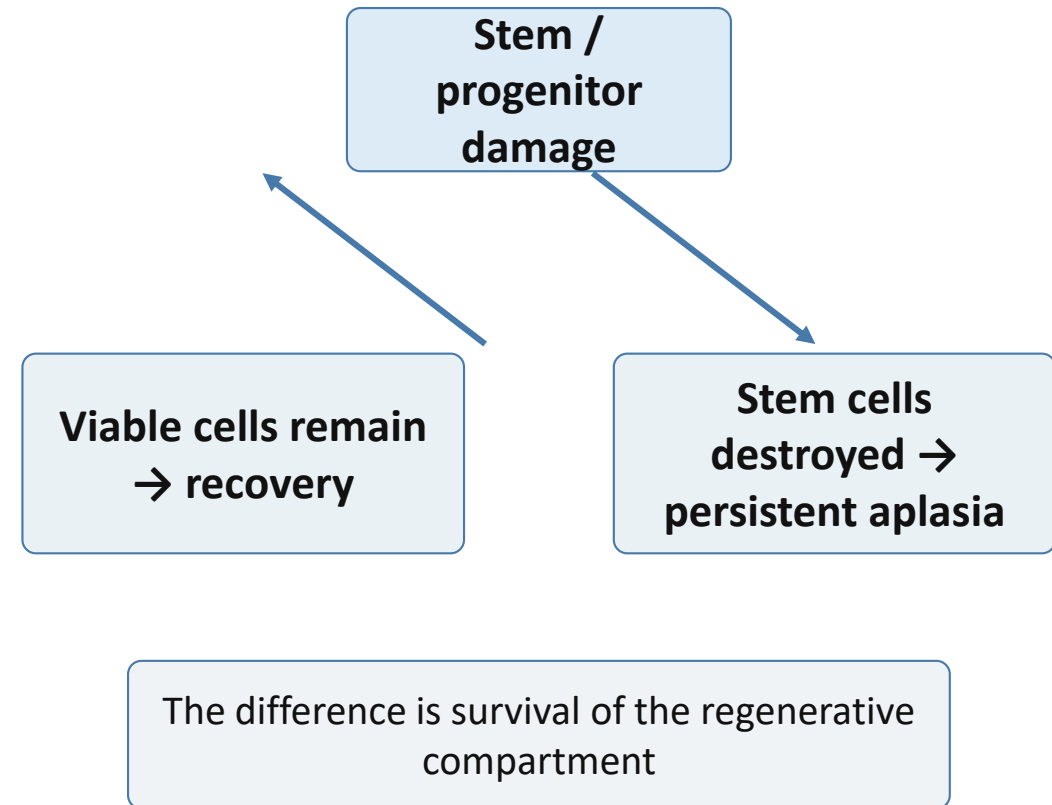
Peripheral blood kinetics after irradiation

Lineage	Typical timing	Explanation
Lymphocytes	Within hours	Direct lymphocyte killing
Granulocytes	Several days; Nadir ~week 2	Rapid turnover
Platelets	From ~week 1; Later nadir	Intermediate survival
Erythrocytes	Anemia after 2–3 weeks	Longer circulating lifespan

Timings are descriptive textbook observations after significant exposure; Individual courses vary.

Marrow aplasia may be reversible or permanent

- Sublethal injury may allow counts to normalize.
- Very high exposure can eliminate hematopoietic stem cells.
- Permanent aplasia is marked by failure of blood-count recovery.



Schematic

Organ-specific acute radiation injury

Tissue	Early manifestation	Biologic basis
Skin	Erythema, edema	Epidermal and vascular response
Gastrointestinal tract	Mucosal damage / ulceration	Crypt-cell loss
Bone marrow	Multilineage cytopenias	Progenitor depletion
Gonads	Germ-cell injury	Highly proliferative cell loss

Qualitative organ patterns summarized, Fig. 9.16 and accompanying text.

Skin: Early and delayed consequences

- Early skin manifestations include erythema and edema.
- Pigment change can evolve over weeks to months.
- Later changes include skin atrophy and increased cancer risk.
- Chronic radiation dermatitis also shows dermal fibrosis and vascular ectasia.

Gastrointestinal tract: Barrier injury

- Renewing gastrointestinal mucosa is susceptible to proliferative-cell damage.
- Early effects include mucosal injury and ulceration.
- Severe whole-body exposure can produce diarrhea and fluid-electrolyte imbalance.
- The wall may become fibrotic late after irradiation.

Gonads: Germ-cell injury

- Spermatogenic cells and ovarian germ cells are radiosensitive.
- Gonadal exposure can cause temporary or permanent impairment of fertility.
- Late tissue atrophy and fibrosis can follow more severe injury.
- Magnitude and reversibility depend on exposure and viable cell reserve.

Lung: Acute and chronic effects

- Radiation-exposed lung may develop edema and acute respiratory injury.
- Interstitial fibrosis may appear over subsequent months or years.
- Late fibrosis impairs tissue architecture in previously irradiated fields.
- Pulmonary toxicity must be understood in relation to exposed lung volume.

Brain: Maturity influences cellular response

- Adult neural parenchymal cells are comparatively resistant to division-dependent killing.
- The developing embryonic nervous system is markedly more vulnerable.
- At extreme whole-body exposures, severe neurologic syndromes occur.
- Relative cellular resistance does not imply complete clinical protection.

Radiation: Chromosomal morphology

- Deletions, translocations, and chromosomal fragmentation may follow injury.
- Mitotic spindle abnormalities can accompany aneuploidy or polyploidy.
- Changes are consequences of genome injury, not specific proof of cancer.

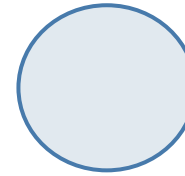


Schematic

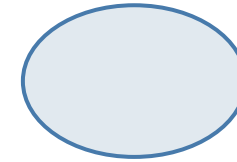
Nuclear changes in surviving irradiated cells

- Nuclear swelling, chromatin clumping, and condensation may occur.
- Pleomorphic or multinucleated giant cells can persist long after exposure.
- Severe injury may produce pyknosis, nuclear lysis, or apoptosis.

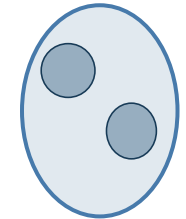
Irradiated surviving cells can show atypical nuclei



Swollen / irregular



Pleomorphic



Multinucleated

Schematic • not diagnostic microscopy

Cytoplasmic morphology of radiation injury

- Cell swelling can accompany nuclear injury.
- Mitochondria and endoplasmic reticulum may show degenerative change.
- Focal plasma-membrane defects can develop.
- Multiple organelle alterations indicate injury is not restricted to DNA.

A diagnostic pitfall: Radiation atypia

- Pleomorphic nuclei and abnormal mitoses may resemble residual malignancy.
- Radiation history and treatment field are essential interpretive context.
- Atypia alone must not be equated with viable recurrent tumor.
- Anatomic architecture and additional histologic evidence remain important.

Radiation effect

Viable malignant tumor

Pleomorphic nuclei and giant cells can mimic malignancy

Integrate history + morphology + viable tumor architecture

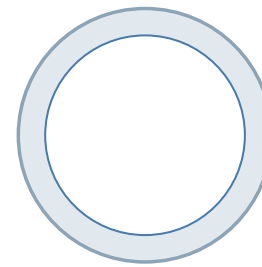
Acute vascular changes after irradiation

- Early vessel changes may consist primarily of dilation.
- Greater injury causes endothelial swelling and vacuolation.
- Severe endothelial damage can lead to wall necrosis or rupture.
- Thrombosis may occur when vascular integrity is disrupted.

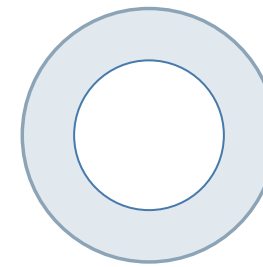
Late vascular remodeling narrows the lumen

- Endothelial proliferation and intimal collagen deposition develop later.
- Hyalinization and thickened intima narrow affected vessels.
- Advanced lesions may obliterate the vascular lumen.
- Chronic flow reduction promotes ischemic parenchymal atrophy.

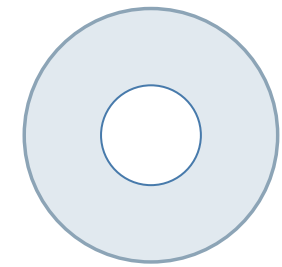
Progressive luminal compromise



Early dilation



Intimal thickening

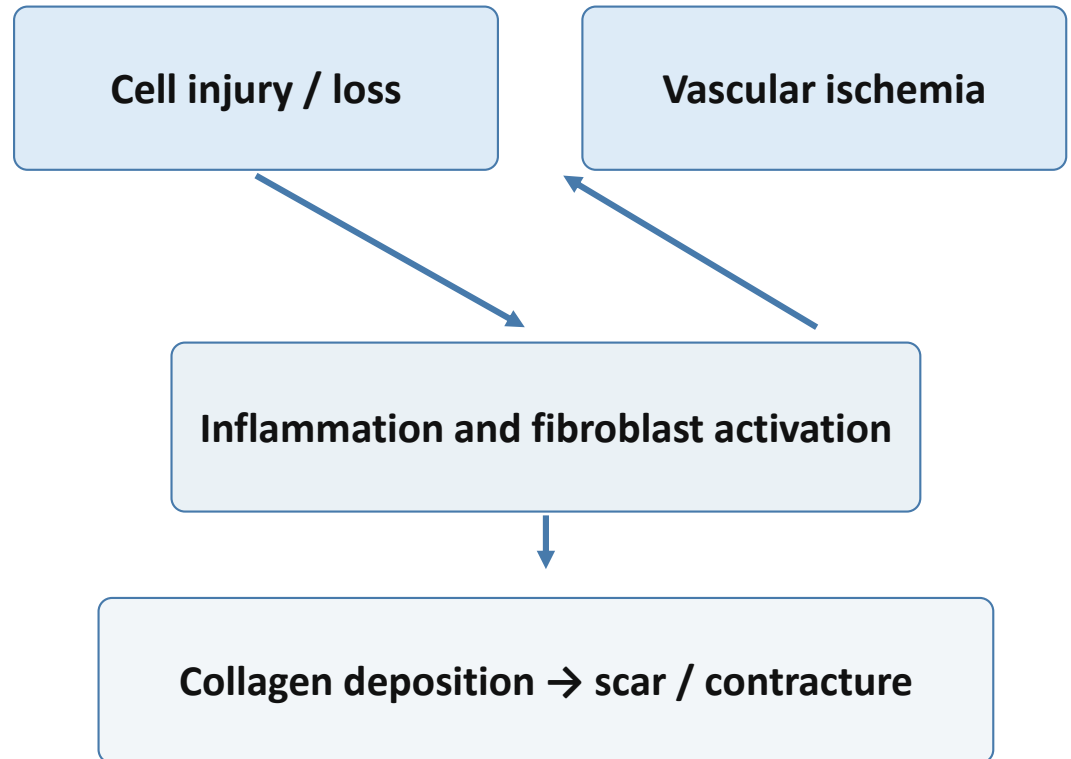


Marked stenosis

Schematic vascular cross-sections

Why radiation produces fibrosis

- Parenchymal-cell loss creates a need for tissue replacement.
- Vascular injury amplifies ischemic cell loss.
- Inflammatory signals and fibroblast activation favor collagen accumulation.
- The final result may be scarring, adhesions, and tissue contraction.



Radiation fibrosis: The time course

- Fibrosis can emerge weeks to months after treatment.
- Later vascular narrowing can continue to impair perfusion.
- Replacement collagen alters elasticity and organ function.
- The scar lies within the irradiated field rather than representing new viable parenchyma.

Common anatomic settings for fibrosis

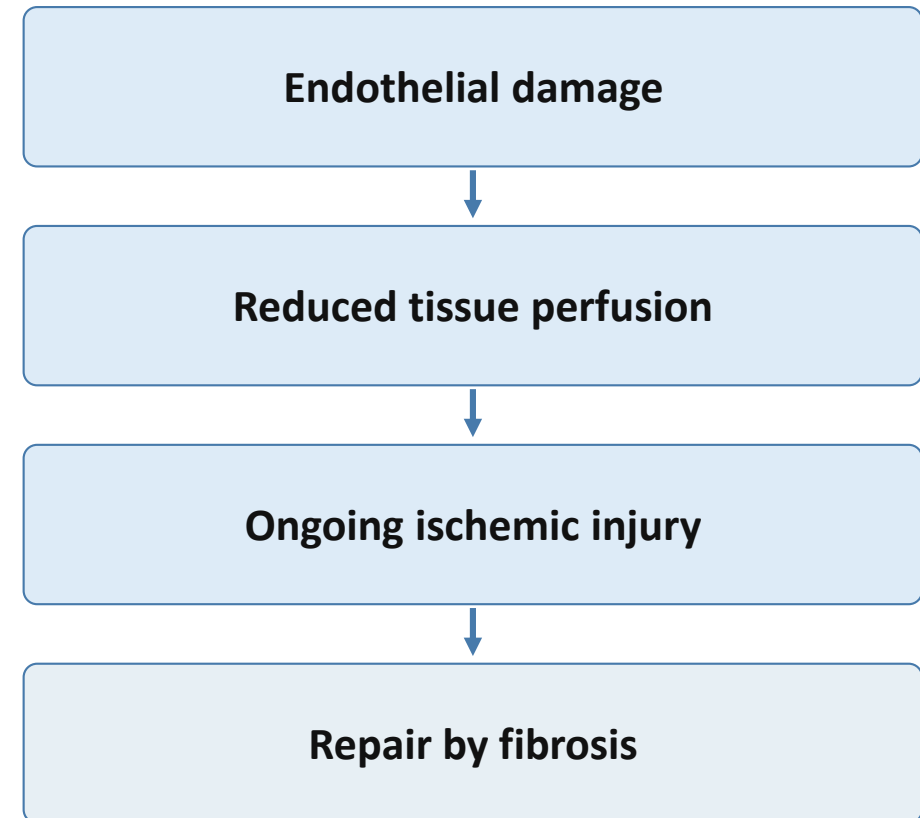
- Lung fibrosis can follow irradiation involving pulmonary parenchyma.
- Salivary gland fibrosis can follow head-and-neck radiotherapy.
- Colorectal and pelvic tissues may scar after treatment of pelvic malignancies.
- Local tissue anatomy governs the eventual functional impairment.

Salivary gland: A field-specific example

- Irradiated gland tissue may lose functional parenchyma.
- Interstitial collagen progressively replaces damaged tissue.
- Arterioles may show fibrointimal thickening and sclerosis.
- The combined parenchymal and vascular damage explains persistent dysfunction.

Vascular injury and impaired tissue repair

- Late radiation lesions may evolve after early cell death subsides.
- Chronic ischemia limits normal regeneration.
- Repair can proceed by scar rather than restoration of specialized tissue.



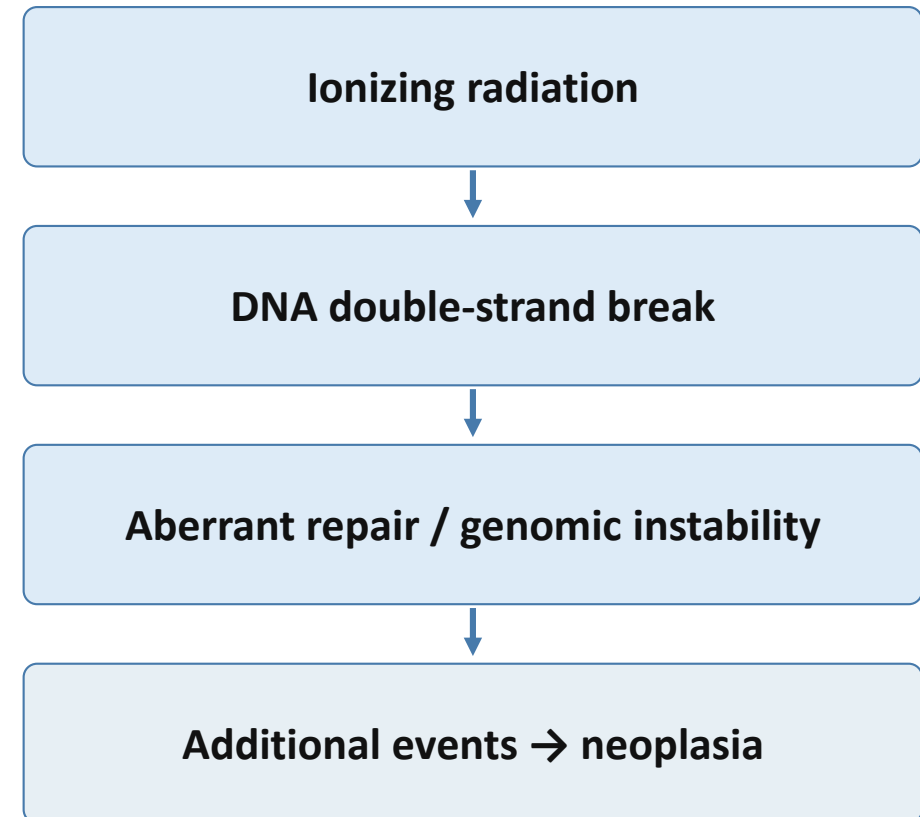
Schematic

Cancer arises from surviving altered cells

- DNA damage alone does not guarantee malignant transformation.
- Incorrect repair can produce persistent chromosomal changes.
- Additional transforming events may accumulate over time.
- Cancer may develop after prolonged latency in a surviving proliferative clone.

Carcinogenesis following radiation exposure

- Mutations arise when DNA injury is misrepaired or persists.
- Checkpoint escape allows genetically abnormal cells to replicate.
- Radiation-related neoplasia is a delayed outcome rather than an acute syndrome.



Schematic

Epidemiologic evidence of radiation-associated cancer

- Atomic-bomb survivor cohorts demonstrate excess leukemias and several solid tumors.
- Chernobyl-associated exposure is linked to thyroid cancer in affected populations.
- Fallout exposures and cancer survivors treated with radiation provide further evidence.
- Risk varies with age, tissue, radiation type, and exposure history.

Low-dose cancer risk is harder to quantify

- Small increments in long-term risk require very large cohorts to detect.
- Dosimetry uncertainties and background cancer incidence complicate inference.
- Stronger evidence at higher doses from greater uncertainty at lower doses.
- A numerical risk estimate should not be inferred from the slide examples alone.

Children: Additional vulnerability to late cancer

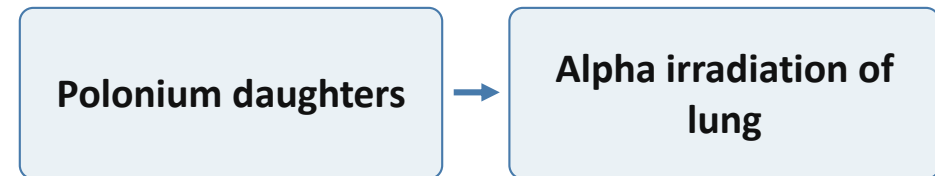
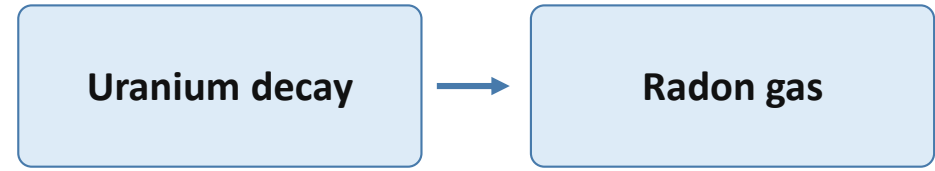
- Children have more dividing cells and longer remaining lifespans.
- Small but measurable risks after repeated pediatric CT exposures.
- Chest irradiation during adolescence has been associated with later breast cancer.
- Clinical imaging still requires balancing justified diagnostic benefit against radiation risk.

Second malignancies after radiotherapy

- Radiotherapy survivors may develop malignancies after long latency.
- Leukemia, myelodysplastic syndrome, and solid second tumors.
- The risk is a late stochastic effect distinct from deterministic tissue fibrosis.
- Interpret a post-treatment lesion in light of prior irradiation and tumor history.

Radon: An internally deposited alpha source

- Radon is generated in the decay chain of uranium.
- Polonium decay products emit alpha particles and can lodge in the lung.
- Chronic inhalation provides a biologically plausible route to lung carcinogenesis.



Chronic inhalational exposure → carcinogenic risk

Radon and concurrent tobacco exposure

- Elevated radon concentrations may occur in occupational or domestic settings.
- Occupational lung cancer risk among exposed miners.
- Household radon is also a health concern, particularly with concurrent smoking.
- The hazard reflects alpha-emitting decay products deposited in respiratory tissue.

Case: Pleomorphic cells after radiotherapy

Clinicopathologic problem

A biopsy from a previously irradiated site contains scattered multinucleated giant cells with bizarre nuclei and dense stromal fibrosis. The requisition asks whether the original cancer has persisted.

Which findings can be caused by irradiation, and what is the diagnostic pitfall?

Case analysis: Separate atypia from viability

- Radiation damage can cause giant cells, nuclear pleomorphism, and abnormal mitoses.
- Fibrosis and chronic vascular alterations support a treatment-affected field.
- These features may mimic malignancy; They do not by themselves establish viable tumor.
- Clinical history and evidence of true residual neoplastic architecture guide interpretation.

Case: Sequential cytopenias after exposure

Clinicopathologic problem

Following substantial whole-body irradiation, a patient develops early lymphopenia, then neutropenia, thrombocytopenia, and later anemia.

Why do the cell counts decline in this sequence?

Case analysis: Turnover drives blood-count timing

- Direct lymphocyte loss can be evident within hours.
- Granulocytes are replaced rapidly, so neutropenia appears within days.
- Platelet counts fall later; The longer-lived erythrocyte pool delays anemia.
- Recovery requires surviving hematopoietic precursors.

Case: Delayed organ injury

Clinicopathologic problem

Months after radiotherapy, an organ within the treated field becomes indurated and less functional. Histology shows subintimal vessel thickening and increased interstitial collagen.

Explain the causal link between vascular change and fibrosis.

Case analysis: Ischemia feeds the fibrotic response

- Endothelial injury initiates intimal thickening and luminal narrowing.
- Impaired perfusion produces chronic parenchymal ischemia.
- Loss of regenerative cells and fibroblast activation increase collagen deposition.
- Organ dysfunction reflects both parenchymal depletion and structural scarring.

Synthesis: Four integrated pathways

- Energy transfer and ionization initiate molecular damage.
- DNA injury preferentially disrupts regenerating tissues and cell division.
- Endothelial injury generates delayed ischemia and fibrosis.
- Misrepaired DNA in surviving cells creates long-term neoplastic potential.

Final integration: Effect, substrate, latency

Effect	Primary substrate	Typical temporal logic
Acute cytopenia	Marrow / lymphoid cells	Early loss of short-lived lineages
Delayed fibrosis	Vessels, stroma, parenchyma	Months–years after injury
Radiation atypia	Irradiated surviving cells	May persist long after exposure
Secondary cancer	Surviving mutant clone	Delayed, often years later

Mechanisms and timing are drawn from the radiation-injury discussion.

Primary reference and scope

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- The radiation-injury discussion covers ionization, dose concepts, tissue sensitivity, morphology, fibrosis, and cancer risk.
- Conceptual schematics in this lecture are original editable drawings, not reproductions of textbook figures.