

Ionizing Radiation

DNA damage, carcinogenesis and tissue response

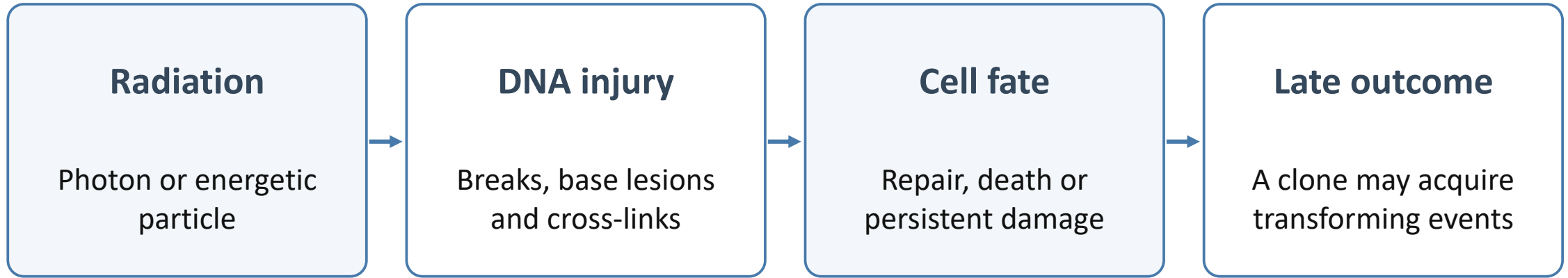
Pathologic mechanisms • Epidemiologic evidence • Clinical interpretation

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Ionizing radiation: Cellular injury to cancer



Carcinogenesis depends on survival and propagation of altered genetic information—not simply the amount of immediate tissue destruction.

Learning outcomes: Molecular pathology

- Recognize the ionizing modalities and the types of DNA lesions they produce.
- Explain direct ionization, radiolysis of water and the modifying effect of oxygen.
- Distinguish accurate DNA repair from mutagenic repair and persistent genomic injury.

Learning outcomes: Clinicopathologic interpretation

- Contrast early cell killing with the delayed emergence of radiation-associated neoplasia.
- Compare radiation-associated leukemias, thyroid cancers and other solid tumors.
- Interpret risk using exposure setting, age, latency, target tissue and clinical context.

Ionizing versus nonionizing radiation

Ionizing radiation

- Sufficient energy to remove tightly bound electrons.
- Initiates cascades of ionization and chemical injury.
- Includes x-rays, gamma rays and energetic particles.

Nonionizing radiation

- Insufficient energy to directly remove tightly bound electrons.
- Can cause molecular excitation or vibration.
- Includes ultraviolet and infrared light comparison.

UV is a carcinogen, but through different characteristic DNA photolesions.

Major forms of ionizing radiation

Electromagnetic

X-rays and gamma rays



Charged particles

Alpha and beta radiation; Protons



Uncharged particles

Energetic neutrons

All listed modalities can be carcinogenic; The spatial pattern of energy deposition is not identical.

X-rays and gamma rays versus alpha particles

X-rays / gamma rays

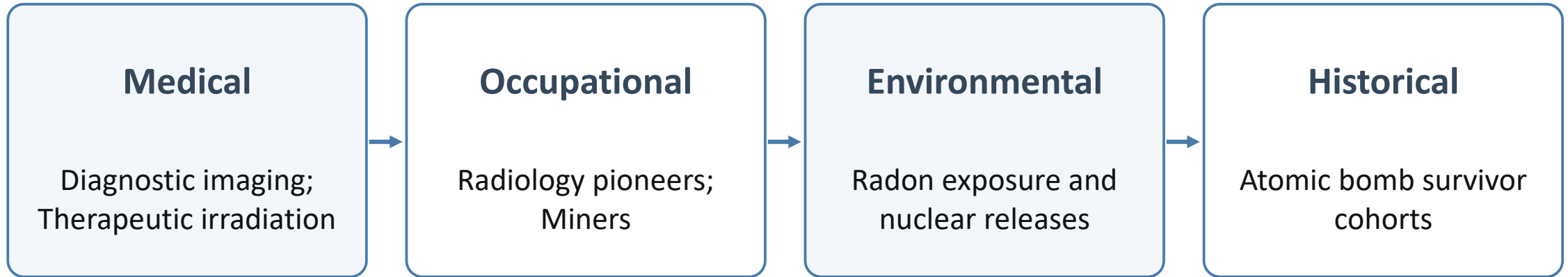
- Penetrating electromagnetic radiation.
- Energy dissipated over a longer tissue path.
- Less localized damage at equal deposited energy.

Alpha particles

- Relatively heavy, charged particles.
- Intense ionization along a restricted track.
- Particularly consequential for locally deposited radionuclide products.

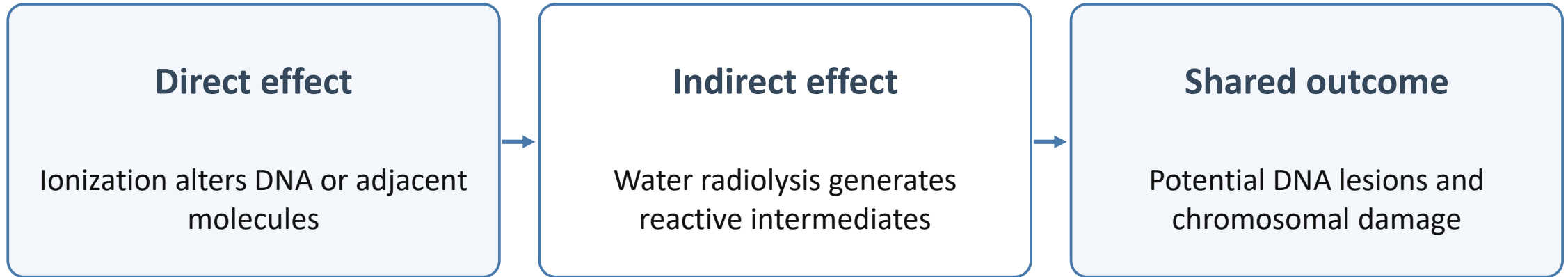
The biologic effect also depends on absorbed dose and exposure geometry.

Exposure contexts in the Robbins discussion



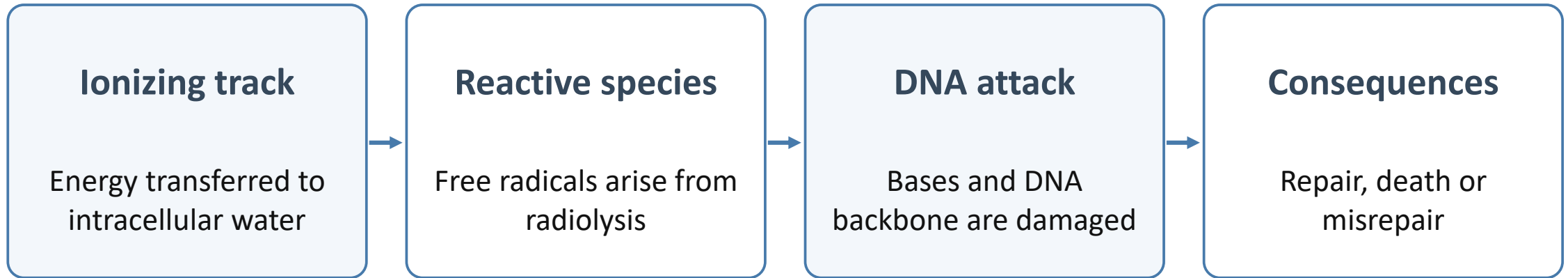
Evidence for carcinogenesis spans distinct exposure patterns, ages, doses and follow-up periods.

Two convergent routes to DNA damage



Indirect free-radical damage as the predominant pathway for DNA injury.

Radiolysis of water and DNA injury



This mechanism explains why the effects are not limited to the atoms directly struck by a photon or particle.

Reactive intermediates: Why oxygen matters

- The free radicals generated by ionized water damage DNA and other cellular constituents.
- Higher oxygenation enhances radiation effects; Tumor hypoxia can decrease radiosensitivity.
- Oxygen modifies the severity of injury, but oxygen tension alone does not determine tumor response.

Irradiated tumor: Oxygenated and hypoxic zones

Better-oxygenated tumor region

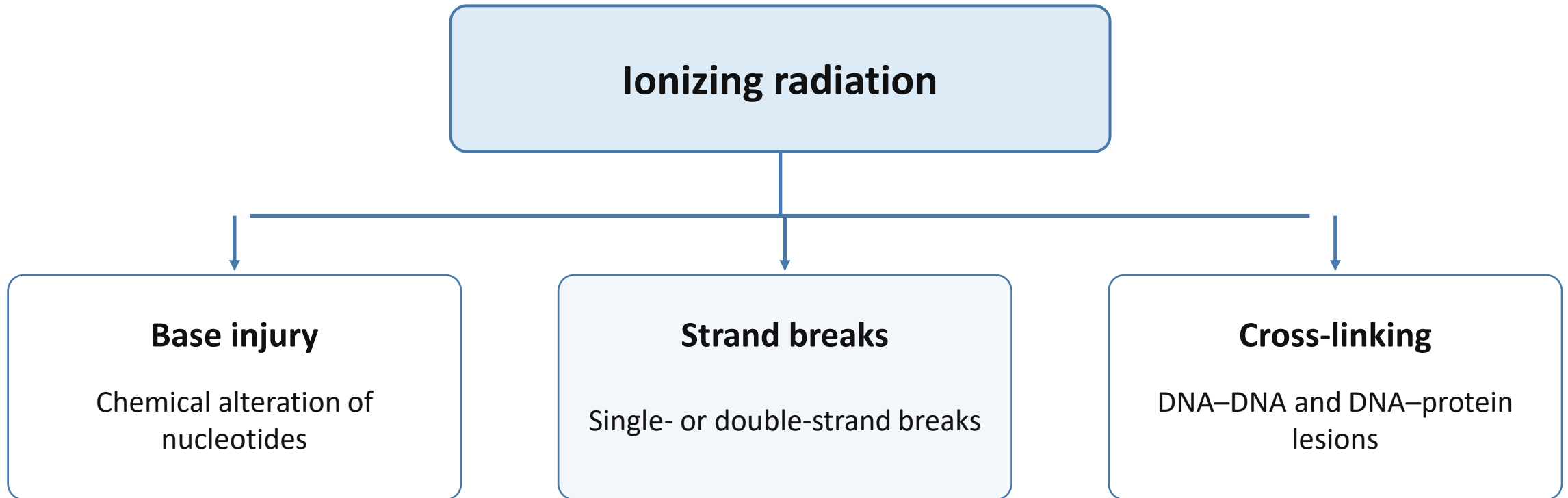
- Greater radiosensitivity associated with oxygen-dependent chemical injury.
- Radiation damage is more likely to translate into lethal lesions.
- Illustrates the oxygen effect.

Poorly oxygenated tumor region

- Hypoxia reduces sensitivity to radiation-induced cell injury.
- Hypoxic regions may persist despite irradiation.
- The tumor microenvironment therefore modifies treatment response.

This is a conceptual comparison, not an imaging or histology finding.

DNA damage has several molecular forms



Multiple lesion classes can coexist within a single irradiated cell.

Single-strand breaks: Injured DNA backbone

- Ionizing energy may break one DNA strand while the complementary strand remains intact.
- Repair systems can use the complementary strand to restore genetic continuity.
- Single-strand lesions nevertheless contribute to the overall burden of radiation injury.

Double-strand breaks: A central lethal lesion

- Both strands of the DNA duplex are interrupted.
- Double-strand breaks are especially consequential because accurate restoration is difficult.
- Incorrect rejoining can leave deletions, inversions or chromosomal translocations.

Misrejoining can create chromosomal rearrangement

Two DNA breaks

Broken ends require rejoining



Aberrant repair

Ends joined in an incorrect configuration



Stable alteration

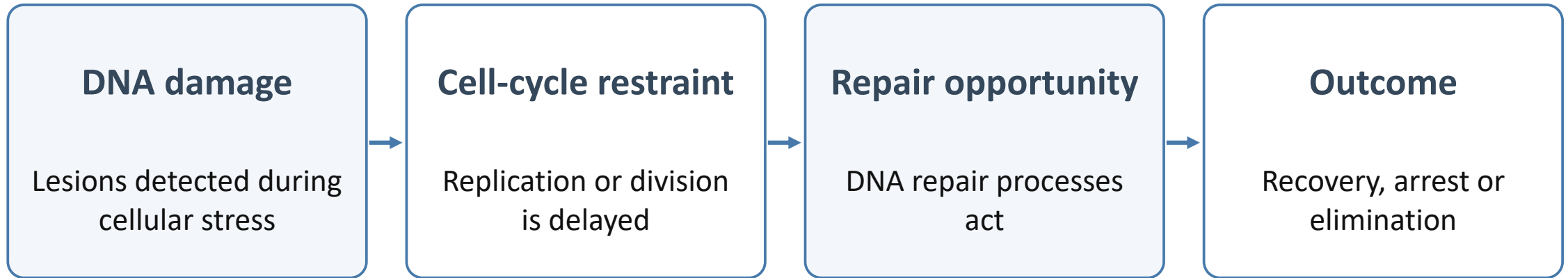
Inversion or translocation may persist

The illustration depicts a class of rearrangements, not a specific cancer-defining translocation.

DNA–protein cross-links: A different obstacle

- Ionizing radiation can cross-link DNA with itself or with proteins.
- Such damage threatens DNA replication and normal genomic function.
- The potential carcinogenic outcome depends on how the surviving cell handles the lesion.

Checkpoint control limits propagation of damage



Failed checkpoint restraint after double-strand breaks to persistence of chromosomal lesions.

Two routes for repairing double-strand breaks

Homologous recombination

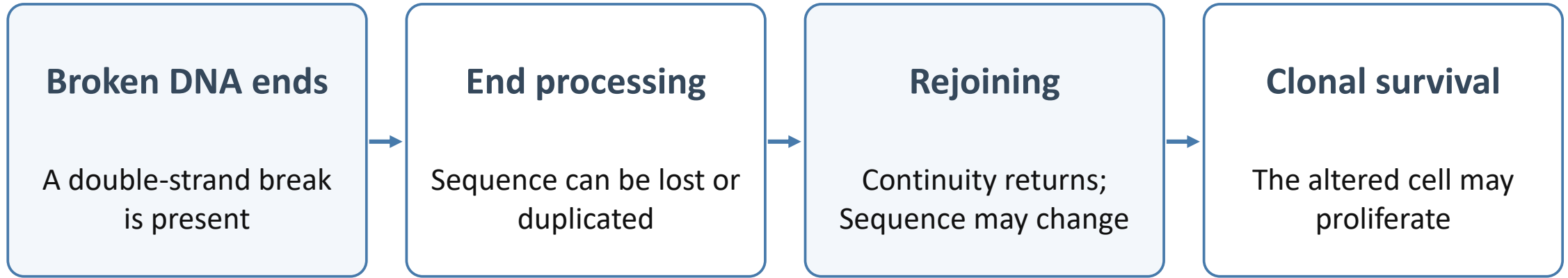
- Uses a homologous sequence to guide reconstitution.
- One of the two repair mechanisms named by Robbins.
- Can provide more faithful sequence restoration.

Nonhomologous end joining (NHEJ)

- Directly rejoins broken DNA ends.
- Described as the commoner route in mammalian cells.
- Can generate small deletions or duplications and rearrangements.

These are alternatives for repairing double-strand breaks; Their accuracy is context dependent.

How NHEJ may generate a mutation

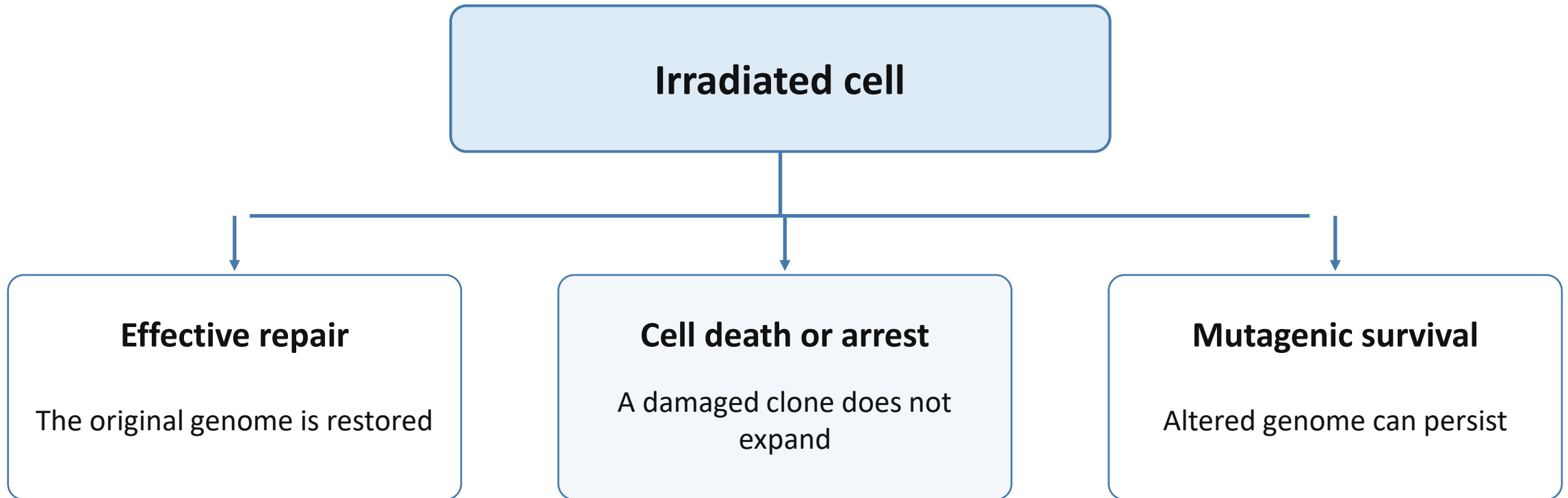


Repair of DNA continuity is not necessarily repair of the original nucleotide sequence.

NHEJ and large-scale genome disruption

- Deletions and duplications among possible NHEJ-related changes.
- Translocations and inversions can occur when breaks are repaired aberrantly.
- These abnormalities constitute plausible substrates for later oncogenic evolution.

DNA damage is not synonymous with cancer

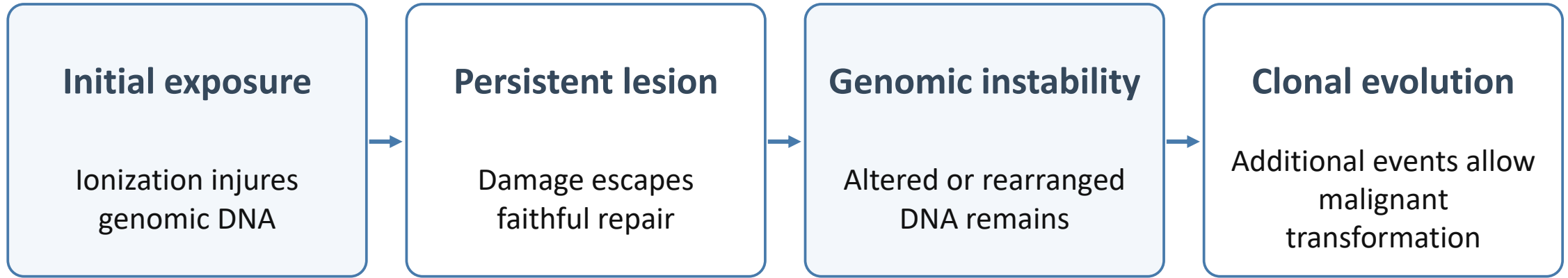


Carcinogenesis requires survival, continued proliferation and further transforming events.

Why a cell that survives matters most

- Massive radiation injury may kill affected cells rather than produce cancer from them.
- A surviving cell with stable, oncogenic genetic damage has malignant potential.
- Late disease reflects persistence and subsequent expansion of a mutated lineage.

A mechanistic model of radiation carcinogenesis



The sequence is a teaching model; No single mutation is presented as sufficient for every cancer.

Genomic instability after ionizing injury

- Radiation can generate DNA breaks and structural chromosome abnormalities.
- Imperfectly repaired lesions may be inherited by daughter cells.
- Subsequent transforming events can make a radiation-associated tumor clinically apparent years later.

Acute injury and delayed neoplastic effects

Early radiation injury

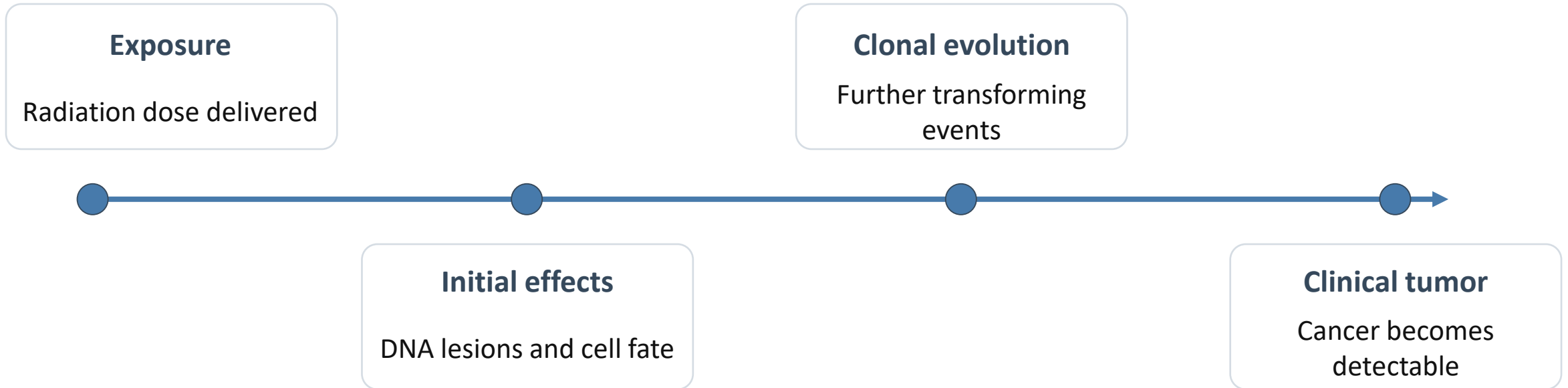
- Dominated by cell damage, impaired proliferation and death.
- Frequently affects rapidly dividing tissues.
- May lead to cytopenias and mucosal injury after high exposures.

Delayed carcinogenesis

- Requires survival of genetically injured cells.
- Mutations and clonal expansion accumulate over time.
- Leukemias and solid tumors may emerge years to decades later.

High acute radiosensitivity does not automatically imply maximal cancer incidence.

Latency separates exposure and cancer manifestation



Latency is variable; The schematic is not drawn to a numerical time scale.

Determinants of biological effect

- Type of ionizing radiation changes the density and distribution of damage.
- Absorbed dose and delivery rate influence cellular repair opportunity.
- Size of irradiated field, tissue proliferation and oxygenation modify outcomes.

Single exposure versus fractionated exposure

Concentrated exposure

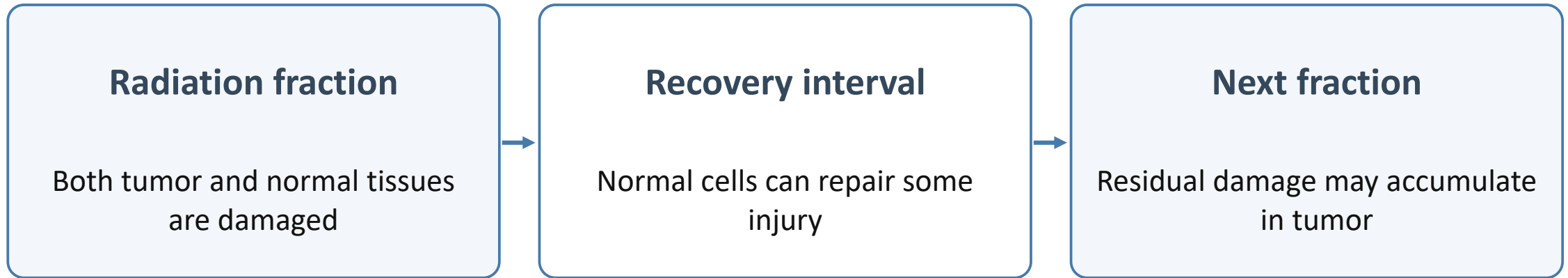
- More injury delivered without substantial time for inter-fraction recovery.
- Can overwhelm the ability of tissues to repair DNA.
- Consequences vary with dose and irradiated volume.

Fractionated exposure

- Separated exposures permit partial repair between fractions.
- Cumulative damage remains when repair is incomplete.
- This differential recovery is used in radiotherapy.

Fractionation changes biological effect; It does not imply that cumulative risk vanishes.

Why fractionation can protect normal tissues



The principle as comparatively faster recovery of many normal cells than tumor cells.

Small-field and large-field exposure

Small, shielded field

- Local irradiation limits the volume exposed.
- Higher local doses may be tolerated.
- Aims to spare uninvolved tissues.

Broad or total-body field

- Large exposed volume recruits multiple sensitive organs.
- Even lower doses may produce severe systemic effects.
- Marrow and intestinal injury are major risks.

Field geometry determines the clinical expression of radiation injury.

Proliferation affects early tissue radiosensitivity

DNA-directed cellular injury

```
graph TD; A[DNA-directed cellular injury] --> B[Highly proliferative<br/>Marrow, gut mucosa and gonads]; A --> C[Intermediate context<br/>Endothelial cells may sustain injury]; A --> D[Nondividing mature cells<br/>Often more resistant to immediate cell killing];
```

Highly proliferative

Marrow, gut mucosa and gonads

Intermediate context

Endothelial cells may sustain injury

Nondividing mature cells

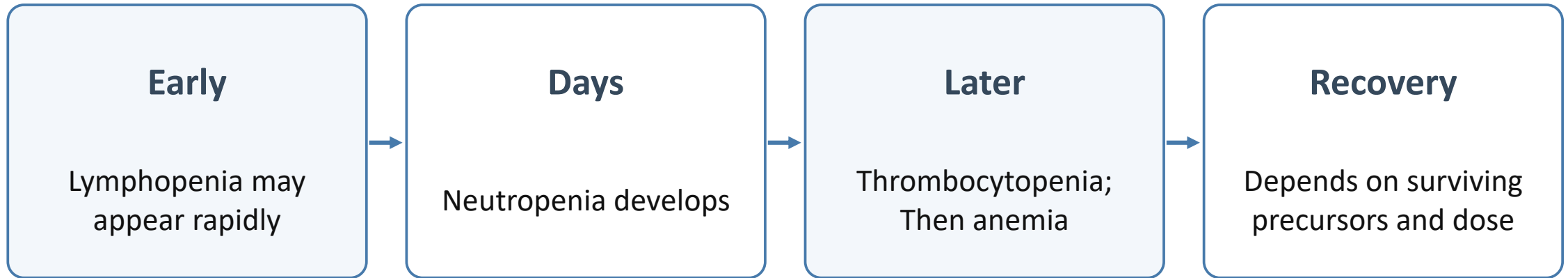
Often more resistant to immediate cell killing

Radiation exposure damages all these compartments, but clinical consequences differ.

Bone marrow: The cost of rapidly dividing cells

- Hematopoietic precursors are sensitive to DNA damage and radiation-induced arrest or death.
- Severe exposure may cause dose-dependent marrow hypoplasia or aplasia.
- Peripheral blood effects develop according to the turnover of each cell population.

The hematologic sequence after marrow irradiation



These are qualitative temporal phases; Actual timing and severity vary with exposure.

Lymphoid tissue is especially radiation-sensitive

- Radiation can directly kill circulating and tissue lymphocytes.
- Severe exposures may shrink lymph nodes and spleen.
- After sublethal injury, surviving precursors can repopulate the lymphoid compartment.

Gastrointestinal mucosa: Early tissue loss

- Crypt epithelial turnover depends on continuous stem and progenitor proliferation.
- Radiation suppresses renewal and may cause mucosal injury and ulceration.
- The severe acute intestinal response must be distinguished from relative resistance to induced gastrointestinal carcinomas described in the neoplasia discussion.

Tissue killing versus tissue transformation

Sensitive to early cell killing

- Lymphoid and bone marrow compartments.
- Rapidly renewing gastrointestinal epithelium.
- Germinal cells and supporting reproductive tissue.

At risk for later cancers

- Myeloid hematopoietic lineages.
- Thyroid tissue, particularly after young-age exposure.
- Breast, lung and salivary tissues in the chapter's hierarchy.

These lists answer different questions and should never be conflated.

Radiation-induced cancer: Comparative tissue vulnerability

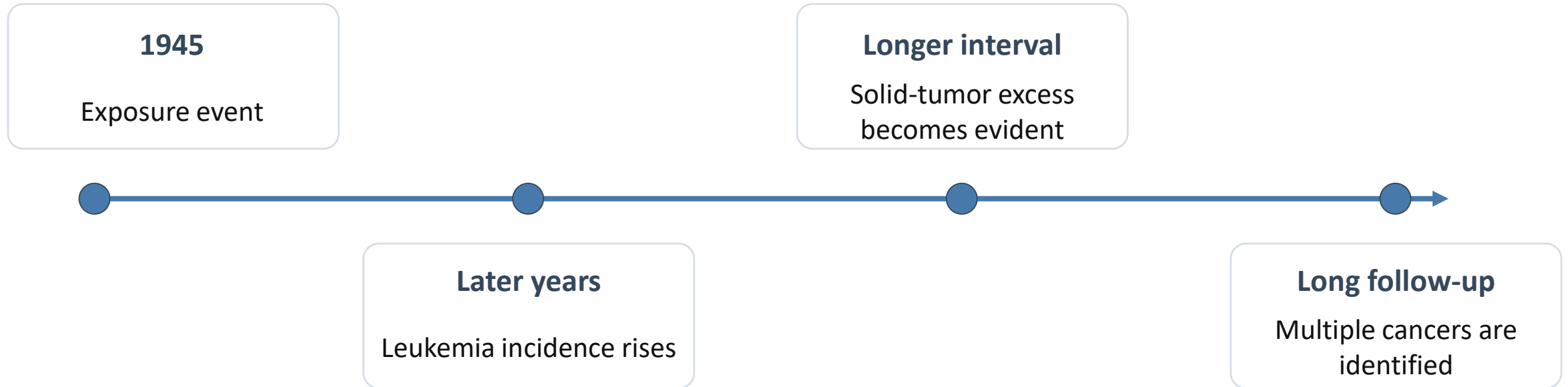
Category	Examples	Interpretation
Prominent	Myeloid leukemia	Important early epidemiologic signal
High in young	Thyroid carcinoma	Strong age dependence
Intermediate	Breast, lung, salivary cancers	Documented solid-tumor associations
Relatively less	Skin and gastrointestinal epithelium	Lower induction tendency in this comparison

This is the textbook's qualitative hierarchy; Not a universal numerical ranking.

Why leukemias are an early signal

- Atomic bomb follow-up found a marked increase in certain forms of leukemia.
- An average latent period of approximately seven years for the early leukemia excess.
- Hematopoietic malignancies therefore supplied an important epidemiologic signal before many solid tumors became apparent.

Atomic bomb survivor follow-up: Two temporal patterns



The timeline demonstrates ordering only; The distance between markers is not proportional to incidence or years.

Solid tumors require prolonged observation

- Longer latent intervals followed the earlier radiation-associated leukemia excess.
- Breast, colon, thyroid and lung carcinomas are examples cited among later tumors.
- Observation lasting decades is needed to capture the full burden of delayed neoplasia.

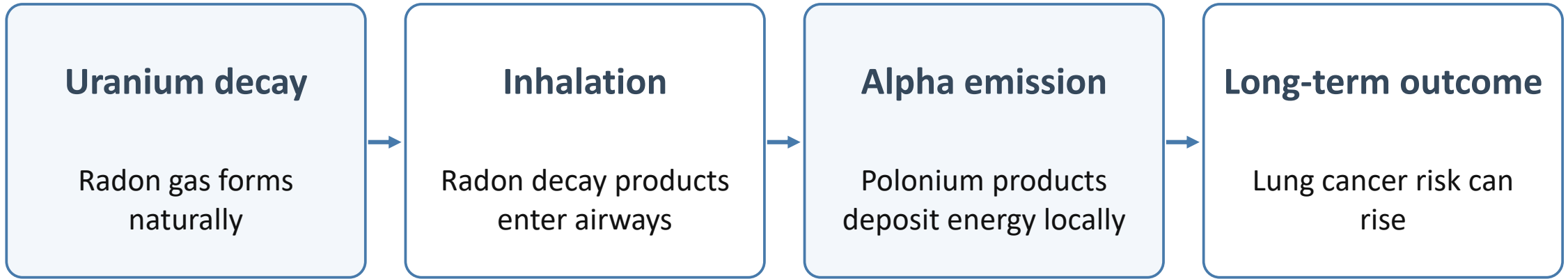
Early radiology workers: An occupational warning

- Pioneers using x-rays had substantial unprotected exposure compared with current practice.
- Skin cancers among early x-ray workers.
- The historical pattern helps establish that medically useful ionizing radiation can also be carcinogenic.

Uranium miners: Radiation and lung carcinoma

- Miners of radioactive elements were observed to have higher rates of lung cancer.
- Historical cohorts showed a tenfold excess in historical European and Rocky Mountain mining cohorts.
- Inhaled radon progeny and alpha emission to the lung exposure pathway.

Radon exposure: From source to lung injury



The mechanism concerns inhaled radioactivity; It is not the same exposure geometry as external x-rays.

Radon daughters and high local ionization

- Robbins specifically names polonium-214 and polonium-218 as relevant radon decay products.
- Their alpha emission delivers dense local energy in tissues where radioactive particles deposit.
- Chronic inhalation is a plausible route to accumulating lung-cell DNA damage.

Residential radon risk: Interpreting context

- Concern about homes with very high radon concentrations.
- The text also raises the possibility that lower household radon contributes to risk, especially with smoking.
- Exposure history and concurrent carcinogenic insults matter when interpreting lung cancer causation.

Atomic bomb survivor studies as causal evidence

- Hiroshima and Nagasaki cohorts were observed after a sudden radiation exposure.
- The subsequent excess of leukemia and multiple solid malignancies supports radiation carcinogenesis.
- Cancer incidence and latency required many years of survivor follow-up.

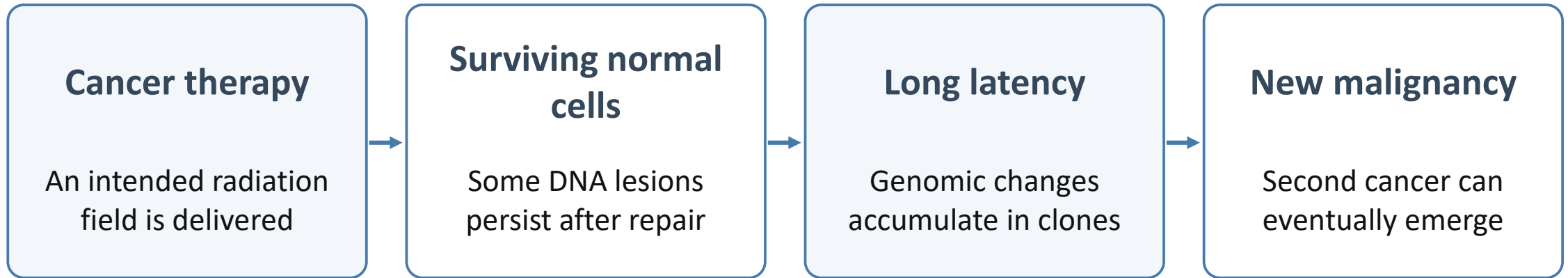
Chernobyl: A thyroid-cancer association

- Thyroid cancers in people exposed during the Chernobyl nuclear accident.
- This evidence complements the age-dependent thyroid susceptibility identified in the neoplasia section.
- Organ-specific exposure and age must be considered before generalizing population risk.

Marshall Islands: Consequences of fallout

- Exposed Marshall Islands populations as a radiation-risk example.
- Reported effects included elevated thyroid cancers and leukemias, among other consequences.
- Nuclear fallout illustrates a complex environmental exposure rather than a single uniform tissue dose.

Second malignancies after therapeutic irradiation



The risk is distinct from local recurrence of the original malignancy.

Second cancers after treatment for Hodgkin lymphoma

- Radiation therapy for Hodgkin lymphoma as an example of later secondary neoplasia.
- Myeloid malignancies, including acute myeloid leukemia and myelodysplastic syndrome, are listed.
- Solid tumors may also occur after sufficient latency; Prior treatment history is a critical interpretive variable.

Adolescent chest irradiation and breast cancer

- Breast cancer risk after chest radiotherapy in adolescent females.
- Susceptibility is age-dependent, with young exposure of particular concern.
- The radiation field and treatment history should be included in cancer risk assessment.

Diagnostic imaging: Illustrative textbook dose examples

Investigation	Textbook dose	Why this is contextual
PA chest radiograph	0.01 mSv	Illustrative low-dose reference
Lateral chest radiograph	0.15 mSv	Different projection and exposure
Chest CT	10 mSv	Illustrative higher-dose modality

Values are those printed in the radiation-injury discussion, not contemporary protocol-specific dose guarantees.

Pediatric CT: Relative and absolute risk

- Studies linking repeated pediatric CT to a measurable excess risk of leukemia and brain tumors.
- It reports roughly a threefold relative risk under certain scan-count comparisons.
- The absolute excess was small; Interpretation must distinguish relative from absolute risk.

Relative risk and absolute excess are not interchangeable

Relative increase

- A ratio compares the rate in exposed and reference groups.
- A threefold association may sound large without baseline context.
- Does not identify an individual child who will develop cancer.

Absolute excess

- Counts extra outcomes against a baseline population rate.
- A small baseline may yield a small number of additional events.
- Needed to place diagnostic benefit and exposure risk in context.

That pediatric imaging risk is small but measurable.

Balancing imaging benefit against carcinogenic risk

- Ionizing imaging is diagnostically valuable and often clinically necessary.
- Repeated or avoidable examinations add to cumulative exposure considerations.
- The textbook's practical emphasis is to minimize unnecessary radiation while preserving appropriate diagnostic care.

Three different ways of describing radiation

Measurement	Unit	Meaning
Radioactivity	Curie (Ci)	Disintegrations from a source
Absorbed dose	Gray (Gy)	Physical energy delivered to tissue mass
Biologic dose	Sievert (Sv)	Radiation-weighted biological impact

Do not confuse emitted activity, absorbed physical dose and biologically weighted dose.

Why physical dose alone is insufficient

- Equal absorbed doses delivered by different radiation types may cause different biological damage.
- Radiation type, tissue distribution and exposure conditions modify the resulting injury.
- The sievert is intended to capture weighting relevant to biologic effect rather than emitted source activity.

Low-dose uncertainty versus established exposure effects

Strongly established at higher doses

- Major accidents and historical exposed cohorts demonstrate cancer excess.
- The textbook considers exposures above 100 mSv clearly consequential.
- Risk can include leukemia and organ-specific solid cancers.

Harder to quantify at lower doses

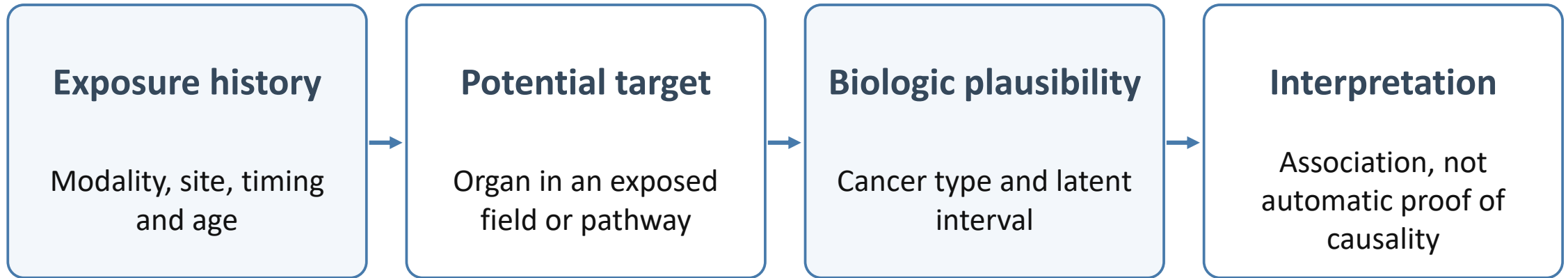
- Small cancer increments are difficult to estimate in limited populations.
- The textbook stresses the very large samples required for low-dose comparisons.
- A weak individual-level signal does not demonstrate absence of risk.

Quantitative risk attribution should not be overstated where statistical power is limited.

Why radiation risk studies need large cohorts

- Cancers also occur spontaneously in people without known ionizing exposure.
- At low doses, any radiation-attributable excess may be small relative to background cancer occurrence.
- Distinguishing signal from random variation therefore requires substantial follow-up and population size.

Clinical assessment of radiation-associated cancer



No routine morphology alone is described as pathognomonic for radiation etiology.

Radiation-induced cellular atypia

- Surviving irradiated cells may have enlarged or pleomorphic nuclei.
- Multinucleated giant cells, chromatin abnormalities and atypical mitoses may be seen.
- Robbins warns that therapy-related atypia can mimic residual malignancy.

Post-treatment radiation atypia versus persistent tumor

Radiation-injured tissue

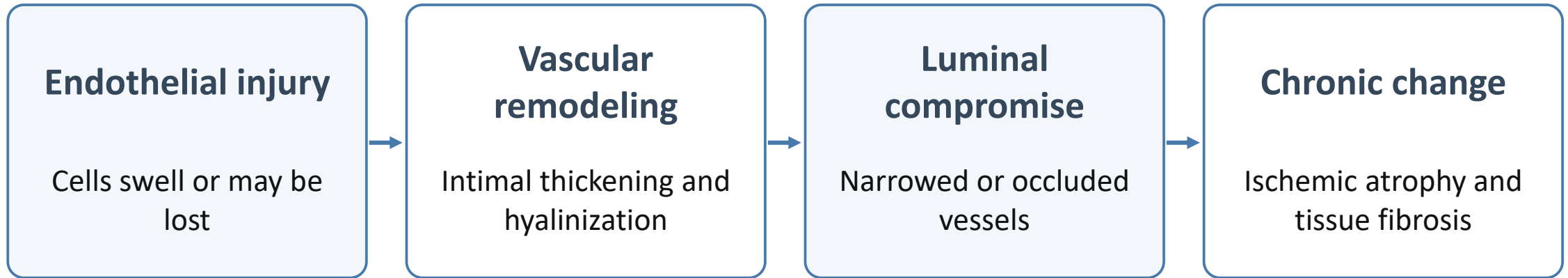
- Can show enlarged, irregular or multinucleate cells.
- Damage may coexist with vascular sclerosis and fibrosis.
- History, timing and architecture are essential to interpretation.

Persistent neoplasm

- Requires an integrated assessment of malignant morphology and context.
- Not established by nuclear atypia alone after treatment.
- Clinical and tissue correlation helps avoid overcalling therapy effect.

No generated specimen is shown; These are conceptual diagnostic distinctions.

Late vascular injury produces ischemic fibrosis



Vascular damage contributes to delayed organ dysfunction after radiotherapy.

Radiation fibrosis: Pathogenesis

- Death of parenchymal cells can lead to replacement by scar tissue.
- Vascular injury causes ischemia and impaired recovery.
- Inflammatory mediators and fibroblast activation amplify collagen deposition.

Radiation fibrosis: Typical tissue settings

- Lung fibrosis is a recognized consequence of radiation treatment.
- Salivary glands may undergo scarring after irradiation for head and neck malignancies.
- Colorectal and pelvic tissue fibrosis can follow treatment for nearby cancers.

Three outcome domains after radiation exposure

Ionizing radiation injury

```
graph TD; A[Ionizing radiation injury] --> B[Acute tissue response<br/>DNA damage, cell death,<br/>cytopenias]; A --> C[Chronic tissue response<br/>Vascular sclerosis and fibrosis]; A --> D[Oncogenic response<br/>Mutagenic survival and delayed<br/>cancer];
```

Acute tissue response

DNA damage, cell death,
cytopenias

Chronic tissue response

Vascular sclerosis and fibrosis

Oncogenic response

Mutagenic survival and delayed
cancer

Exposure conditions, tissue type and time govern which effects predominate.

Clinical reasoning: Child with repeated CT examinations

HYPOTHETICAL TEACHING SCENARIO

A child undergoes several clinically indicated CT examinations over a period of years. The family asks whether the examinations will cause leukemia.

- How should relative and absolute risk be distinguished?
- Why does patient age affect risk interpretation?
- What is the appropriate message about necessary imaging?

Case analysis: Pediatric CT exposure

- Repeated CT can be associated with a small increase in later cancer risk; Risk is not deterministic.
- The textbook's reported relative-risk estimates should not be interpreted as a prediction for one child.
- Indicated imaging benefits must be considered while minimizing avoidable exposure.

Clinical reasoning: New lung cancer in a miner

HYPOTHETICAL TEACHING SCENARIO

A retired uranium miner develops lung carcinoma many years after working underground. The history also includes tobacco exposure.

- Which inhaled radioactive agent and decay products are relevant?
- How does alpha radiation produce local DNA damage?
- Why should causation consider concurrent tobacco exposure?

Case analysis: Mining, radon and smoking

- Inhaled radon decay products can expose lung epithelium to local alpha radiation.
- Historical mining cohorts demonstrate increased lung cancer incidence.
- Coexisting tobacco exposure complicates individual attribution but does not negate radiation-associated risk.

Clinical reasoning: Atypical cells after radiotherapy

HYPOTHETICAL TEACHING SCENARIO

A post-treatment biopsy contains enlarged pleomorphic cells and interstitial fibrosis in a previously irradiated field.

- Can radiation effects imitate malignant cytology?
- Which histologic and clinical features help contextualize atypia?
- Why is nuclear pleomorphism alone insufficient to prove recurrence?

Case analysis: Radiation effect versus recurrence

- Irradiated tissues may contain persistent pleomorphic, multinucleated or abnormal mitotic cells.
- Fibrosis and chronic vascular injury provide supporting evidence of a treatment effect.
- Residual cancer cannot be excluded by these findings alone; Architecture and clinical context remain decisive.

Contrast with ultraviolet carcinogenesis

Ultraviolet radiation

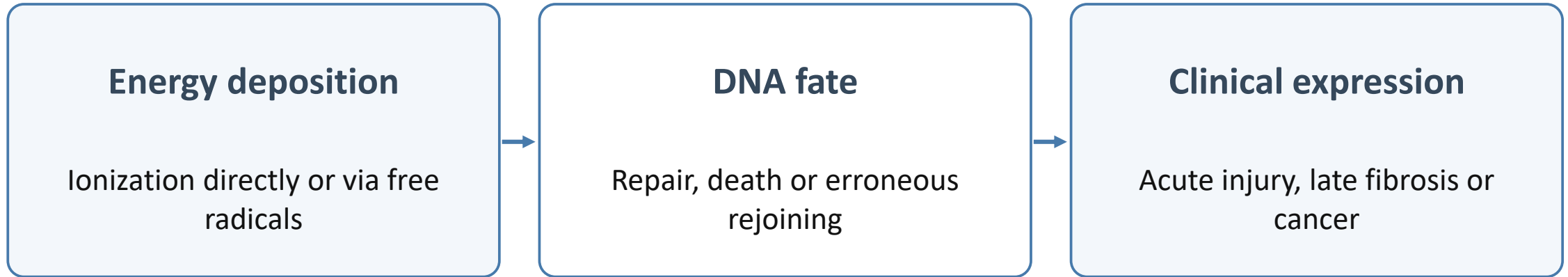
- Characteristic lesion: Pyrimidine dimers.
- Associated primarily with sun-exposed skin tumors.
- Nucleotide-excision repair defects heighten susceptibility.

Ionizing radiation

- Characteristic lesions: Strand breaks and cross-links.
- Associated with hematologic and many organ-based malignancies.
- Double-strand break repair integrity is central.

Both are carcinogenic radiation exposures, but DNA damage signatures differ.

Synthesis: From exposure to pathologic consequence



Mechanism and outcome must always be interpreted with organ, dose, age and latency.

Five pathology principles to retain

- Ionizing radiations are carcinogens because they damage DNA.
- Double-strand breaks and aberrant repair can create durable genomic changes.
- Acute cell death and late tumor incidence are biologically distinct endpoints.
- Age, organ, dose distribution, oxygen and delivery schedule influence effect.
- Late cancers require long follow-up and contextual risk interpretation.

Robbins sources and lecture boundaries

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Neoplasia section: ionizing radiation, DNA injury and long-term carcinogenesis.
- Radiation-injury section: cellular effects, fibrosis, clinical exposures and delayed tumors.
- All illustrations are original editable schematics; no textbook clinical figures are reproduced.