

Squamous Cell Carcinoma

Cutaneous epithelial malignancy: mechanisms, morphology and clinical relevance

A pathology teaching lecture

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Learning outcomes

- Explain the UV–DNA damage axis and additional risks for cutaneous SCC.
- Distinguish actinic keratosis, carcinoma in situ and dermal invasion.
- Recognize the morphologic spectrum of invasive squamous differentiation.
- Relate common presentation, metastatic potential and therapy to pathology.

Conceptual framework

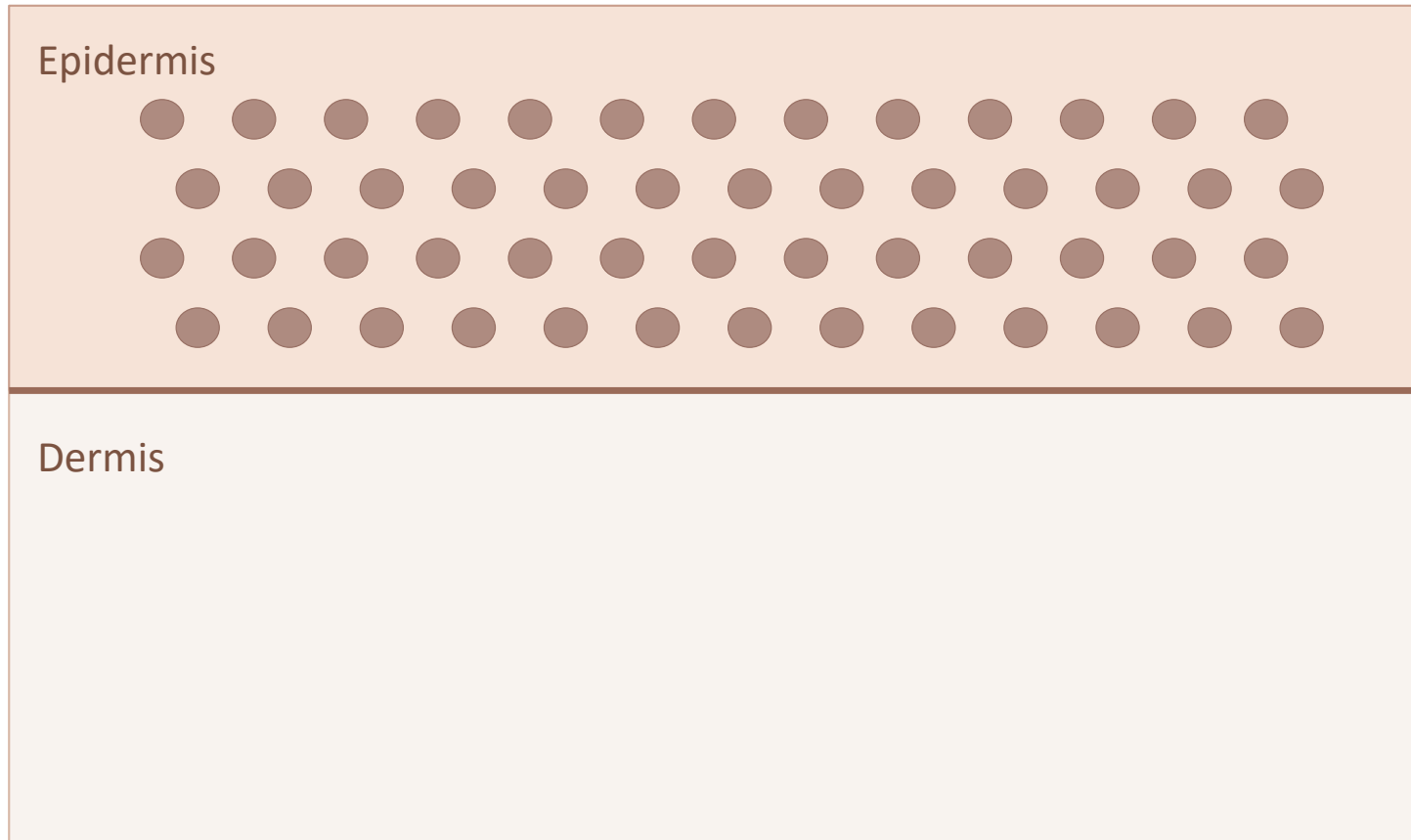
Keratinocyte malignancy in a sun-damaged epithelium

The central diagnostic distinction is atypia confined above the basement membrane versus invasive growth into the dermis.

Where cutaneous SCC fits

- A malignant epithelial tumor of squamous/keratinocytic differentiation.
- Most often arises on chronically sun-exposed skin of older adults.
- Actinic keratosis and SCC in situ occupy the precursor / preinvasive spectrum.
- Invasive SCC crosses the dermoepidermal basement membrane.

The epidermal boundary that defines invasion



Observe

- Epidermis lies above the dermoepidermal junction.
- The basement membrane is the diagnostic boundary.
- Dermal tumor nests establish invasive growth.

Schematic — not a histologic specimen

Relative frequency among cutaneous cancers

- SCC is second to basal cell carcinoma among tumors of sun-exposed skin.
- This comparison refers to cutaneous tumors, not SCC across all organs.
- Early recognition and local excision explain why most lesions remain controllable.

Age, sex and environmental context

- Classically seen in older adults with cumulative sun exposure.
- Most sites show a higher incidence in males than females.
- The lower legs are a stated exception to the usual sex pattern.
- The risk profile reflects exposure, pigmentation and host surveillance.

The importance of anatomic location

- Face, arms and dorsal hands are frequent actinic-damage sites.
- Scalp lesions may be nodular or ulcerated when invasive.
- The lip can develop actinic cheilitis as a related precursor.
- Consider the skin site before generalizing findings from SCC of the oral cavity or lung.

Clinical spectrum: Flat plaque to nodule

- In situ SCC: A sharply demarcated, red, scaling plaque.
- Invasive SCC: Often nodular with variable surface keratin.
- Ulceration can occur as invasive lesions progress.
- Gross appearance suggests but does not establish tissue invasion.

Most tumors are recognized at a local stage

- Invasive SCC is commonly discovered while small and resectable.
- Clinical visibility facilitates early recognition.
- Local excision is usually effective for readily recognized lesions.
- Metastatic disease nevertheless matters because SCC is common.

Etiology and predisposition

UV light, repair failure and impaired immunity

The malignant phenotype results from acquired driver alterations in susceptible keratinocytes.

Three intersecting etiologic domains

Genotoxic exposure

UV radiation is the dominant driver; Ionizing radiation, arsenicals and industrial agents also matter.

Host susceptibility

Light pigmentation, defective nucleotide excision repair and immunosuppression modify risk.

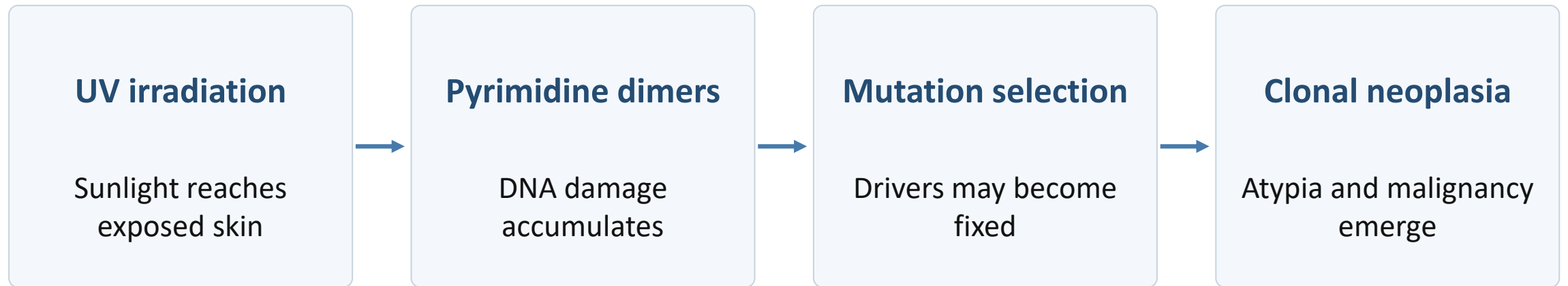
Local tissue milieu

Chronic ulcers, draining osteomyelitis and old burn scars are associated with SCC.

Lifetime UV exposure is the dominant risk

- UV radiation produces DNA damage in epidermal keratinocytes.
- Tumor incidence rises with the degree of lifetime sun exposure.
- Chronic exposure supplies repeated opportunities for driver mutations.
- Lightly pigmented individuals are especially susceptible to actinic change.

UV injury creates mutagenic DNA lesions

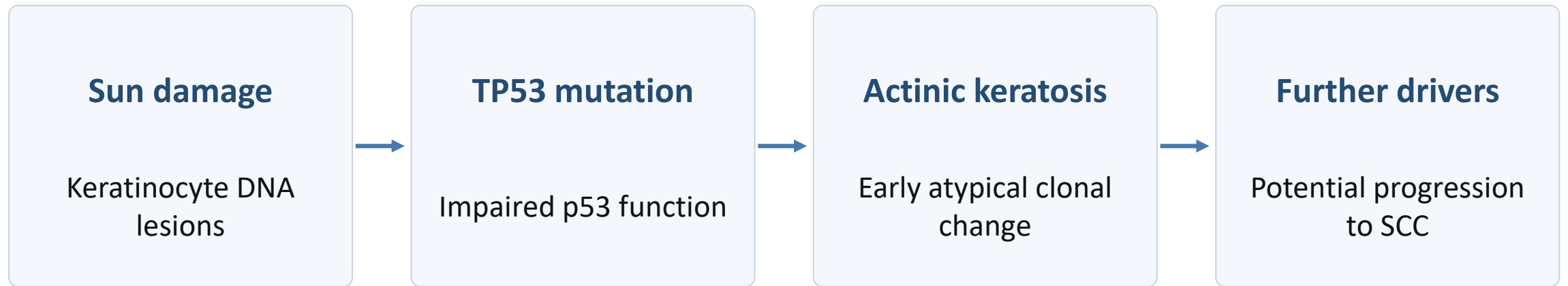


This is a conceptual causal sequence, not a measured rate or a uniquely deterministic pathway.

Why pyrimidine dimers matter

- UV exposure creates lesions involving adjacent pyrimidine bases.
- A subset of TP53 mutations occurs at these damaged sites.
- Their mutational context supports sunlight as an upstream cause.
- Unrepaired lesions increase the opportunity for permanent mutations.

P53 alteration can precede invasive cancer

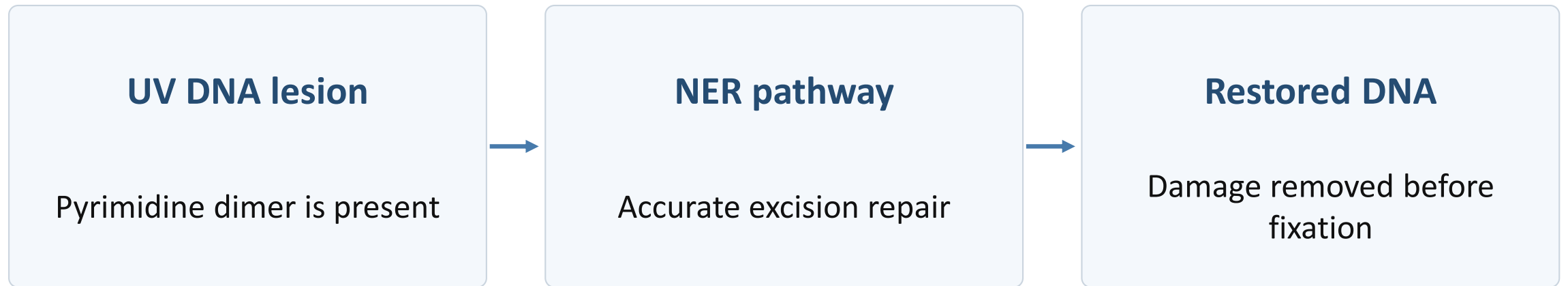


Early p53 dysfunction is suggested by its high prevalence in actinic keratoses.

How to interpret TP53 mutations

- Frequent TP53 mutations have been documented in actinic keratosis.
- Thus p53 dysfunction is an early molecular event, not proof of invasion.
- A TP53 mutation alone does not define SCC morphology.
- Tissue architecture remains decisive for in situ versus invasive classification.

Nucleotide excision repair protects the genome



Failure of this pathway permits mutagenic repair and accumulation of alterations.

Xeroderma pigmentosum is mechanistic evidence

- An inherited disorder involving nucleotide excision repair genes.
- Defective repair of UV-induced pyrimidine dimers increases mutations.
- Error-prone pathways may substitute when accurate repair fails.
- The resulting mutation burden explains pronounced SCC susceptibility.

Multiple drivers cooperate in cutaneous SCC

TP53 dysfunction

Disrupts a major tumor-suppressive response to DNA injury.

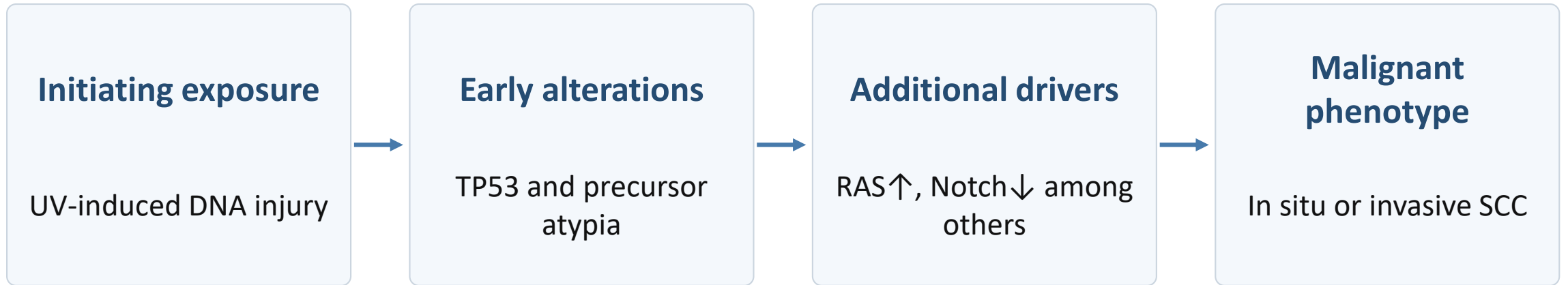
Increased RAS signaling

A contributor that favors keratinocyte transformation.

Reduced Notch signaling

Another common contributor to transformation.

A multistep, not a single-hit, neoplasm



Sequence is a didactic simplification; Source does not define a fixed obligatory mutation order.

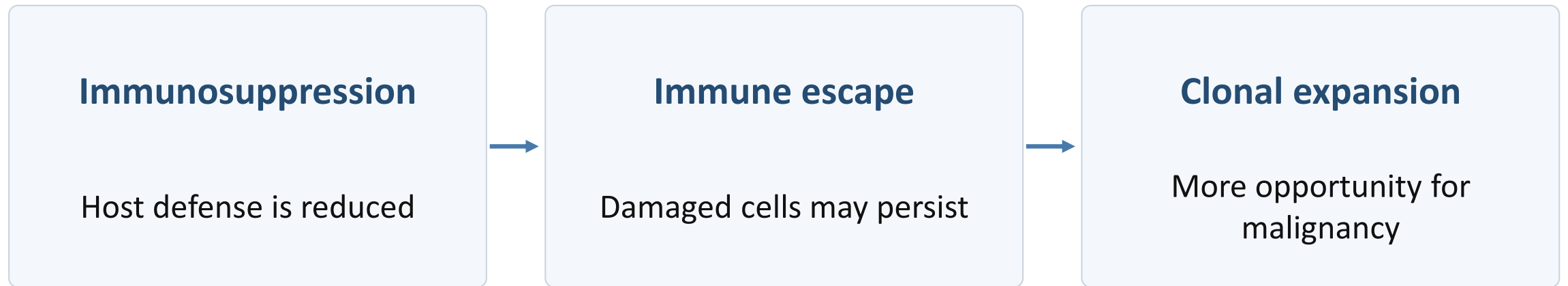
UV exposure also affects local immunity

- Sunlight may transiently impair innate immunity in skin.
- The mechanism is not fully understood.
- Reduced immune elimination may allow damaged keratinocytes to persist.
- This is a possible cooperating mechanism, separate from direct DNA damage.

Immunosuppression: An important association

- Tumor risk is elevated with immunosuppressive states.
- Organ transplantation and chemotherapy are highlighted examples.
- Reduced host surveillance may permit survival of altered keratinocytes.
- Virus susceptibility has been proposed as an additional explanation.

Potential consequences of reduced surveillance



Proposed biologic contribution, not a validated patient-level prediction

HPV: Suspected association versus demonstrated role

General cutaneous SCC

Some cutaneous HPV types have been considered possible contributors; Causality is not established for ordinary SCC in this source.

Epidermodysplasia verruciformis

HPV types 5 and 8 as clearly implicated in SCC arising in this rare inherited condition.

Epidermodysplasia verruciformis

- Rare autosomal recessive disorder.
- Marked susceptibility to cutaneous SCC.
- HPV 5 and HPV 8 are clearly implicated in SCC arising in this context.
- Do not equate this setting with all cutaneous SCC or with mucosal HPV-driven SCC.

Additional carcinogenic exposures

Industrial agents

Tars and oils are associated with cutaneous SCC.

Systemic/toxic agents

Ingested arsenicals are listed among risk factors.

Physical exposure

Ionizing radiation can contribute to keratinocytic malignancy.

Persistent injury and scar-associated SCC

- Chronic ulcers are recognized settings for SCC development.
- Chronic draining osteomyelitis is another listed predisposition.
- Old burn scars are implicated.
- These contexts broaden the assessment beyond sun-exposed skin.

Do not import oral-cavity etiologies into skin SCC

- Tobacco and betel nut chewing specifically for oral SCC.
- They should not be presented as dominant causes of cutaneous SCC.
- Cutaneous and mucosal SCC share squamous differentiation but differ in exposure biology.
- Organ-specific context matters when interpreting risk-factor lists.

Preinvasive disease

From actinic keratosis to full-thickness atypia

Atypia can extend progressively through the epidermis before tumor cells cross its basement membrane.

Actinic keratosis is a key precursor

- Occurs predominantly in chronically sun-damaged skin.
- Is particularly common in lightly pigmented individuals.
- Shows excessive keratin and dysplastic squamous epithelium.
- Some lesions progress toward cutaneous SCC.

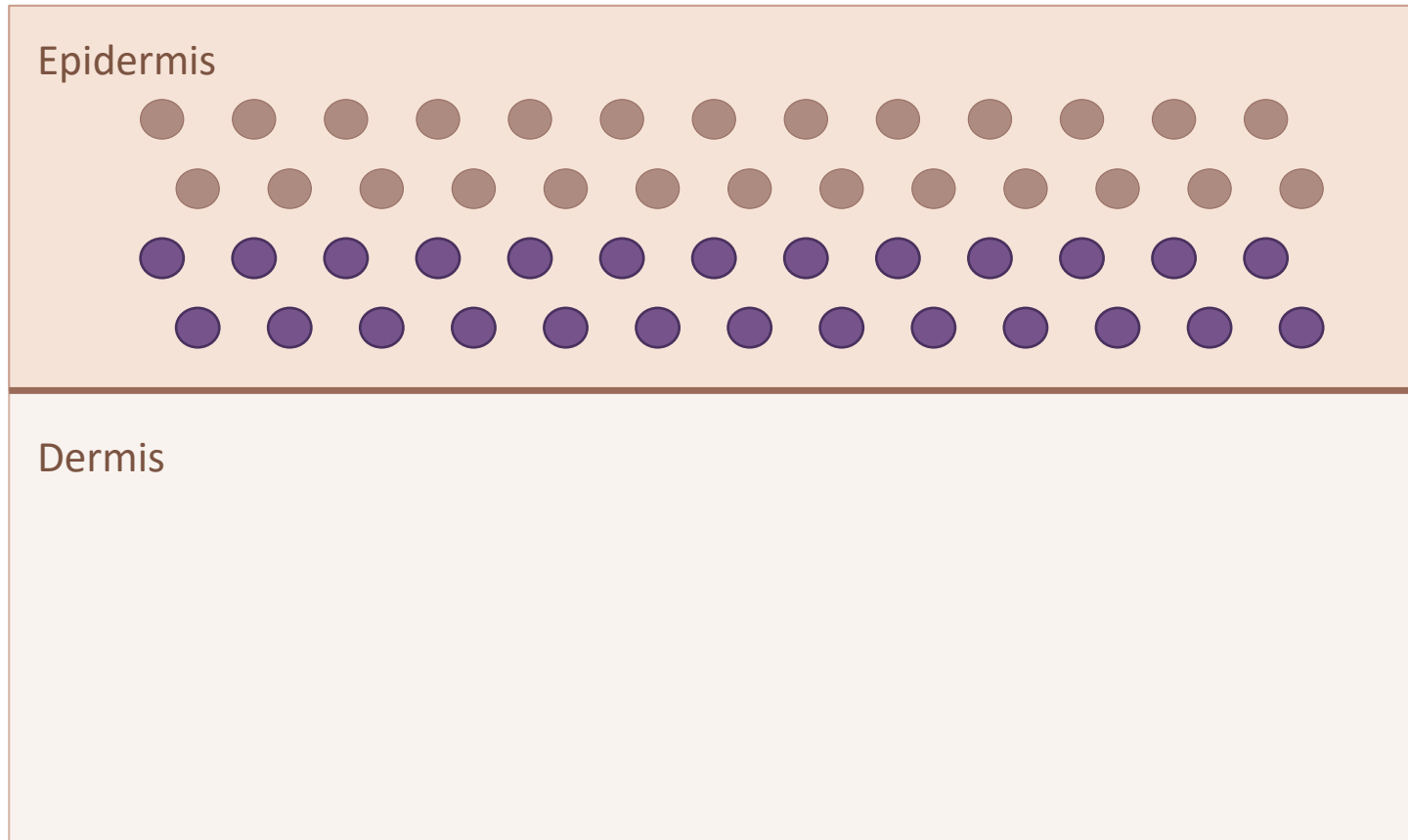
How actinic keratosis appears clinically

- Usually small, often less than 1 cm across.
- Can be tan-brown, red or skin-colored.
- The surface often feels rough or sandpaper-like.
- Marked excess keratin may create a cutaneous horn.

The distribution of actinic keratoses

- Face and exposed arms are frequent sites.
- The dorsal hands are another characteristic location.
- Related sun-damaged changes may occur on the lips.
- A precursor lesion identifies an area that has sustained cumulative exposure.

Actinic keratosis: Lower epidermal atypia



Observe

- Atypical cells mainly occupy basal/lower layers.
- Surface keratinization may be pronounced.
- Basement membrane remains intact.

Schematic — not a histologic specimen

Dyskeratosis and intercellular bridges

- Atypical keratinocytes may acquire eosinophilic/pink cytoplasm.
- This altered keratinization is described as dyskeratosis.
- Intercellular bridges are visible in squamous epithelium.
- This contrasts with basal cell carcinoma, where bridges are not seen.

Hyperkeratosis versus parakeratosis

- Hyperkeratosis: Thickened surface cornified layer.
- Parakeratosis: Nuclei persist in cells of the stratum corneum.
- Both may accompany actinic keratosis.
- Surface change should be read alongside the distribution of cellular atypia.

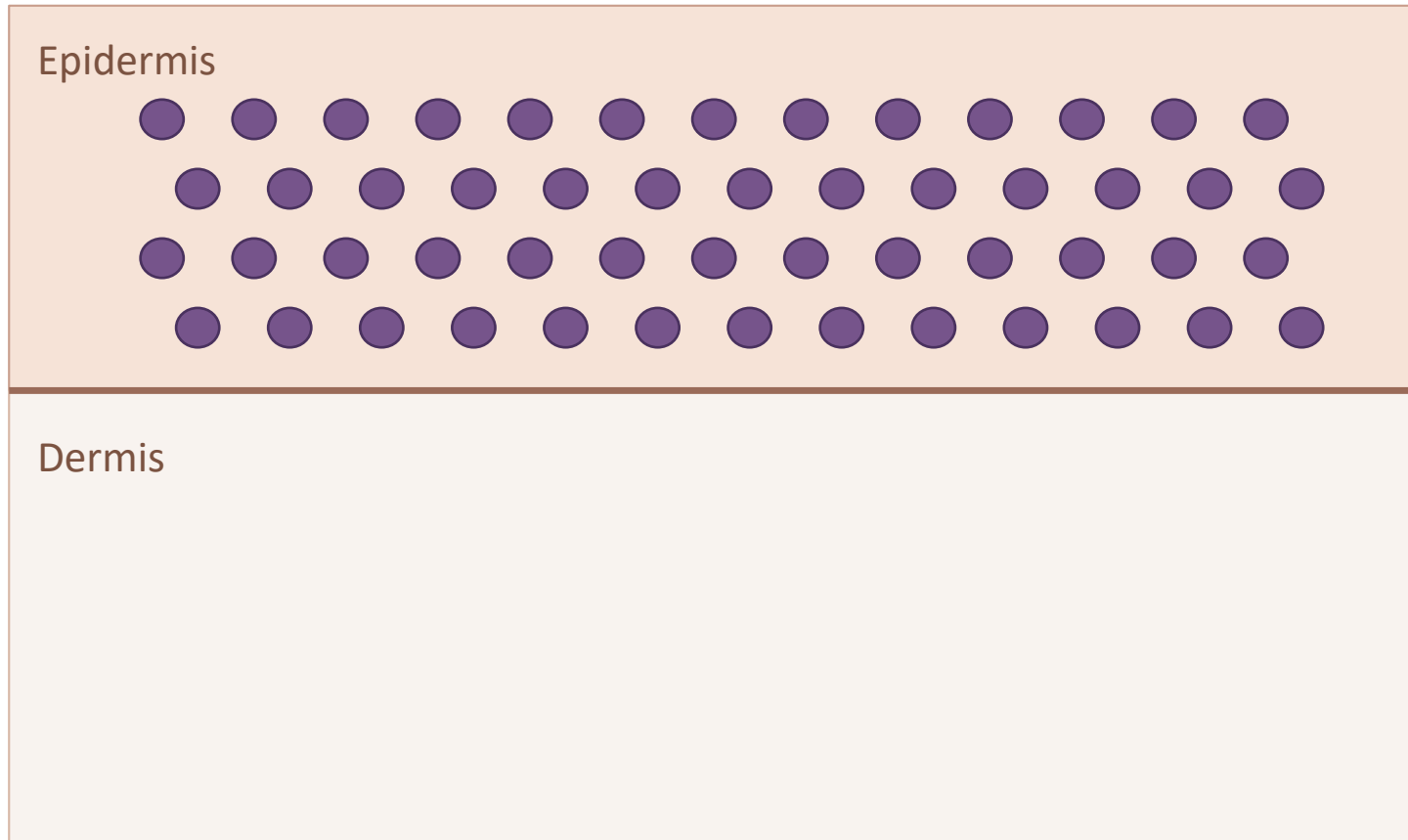
Solar elastosis documents chronic damage

- Superficial dermal elastic material becomes thickened and blue-gray.
- This change as elastosis.
- It is associated with abnormal elastic-fiber production after sun injury.
- Elastosis supports sun damage; It does not independently establish invasion.

Atypia may progress in epidermal extent

- Initial dysplasia affects the lower epidermal layers.
- Progressively severe lesions show greater epithelial thickness involved.
- Full-thickness nuclear atypia signifies carcinoma in situ.
- In situ carcinoma can retain superficial maturation in some lesions.

Carcinoma in situ: Atypia throughout epidermis



Observe

- Atypical nuclei extend through all epidermal levels.
- No tumor nest has crossed into the dermis.
- The boundary remains continuous.

Schematic — not a histologic specimen

Actinic keratosis versus SCC in situ

Actinic keratosis

Cytologic atypia chiefly in basal/lower epidermis; Marked cornification and sun-damage changes often coexist.

Squamous carcinoma in situ

Atypical enlarged, hyperchromatic nuclei involve the full thickness of the epidermis; Still no basement breach.

Clinical presentation of SCC in situ

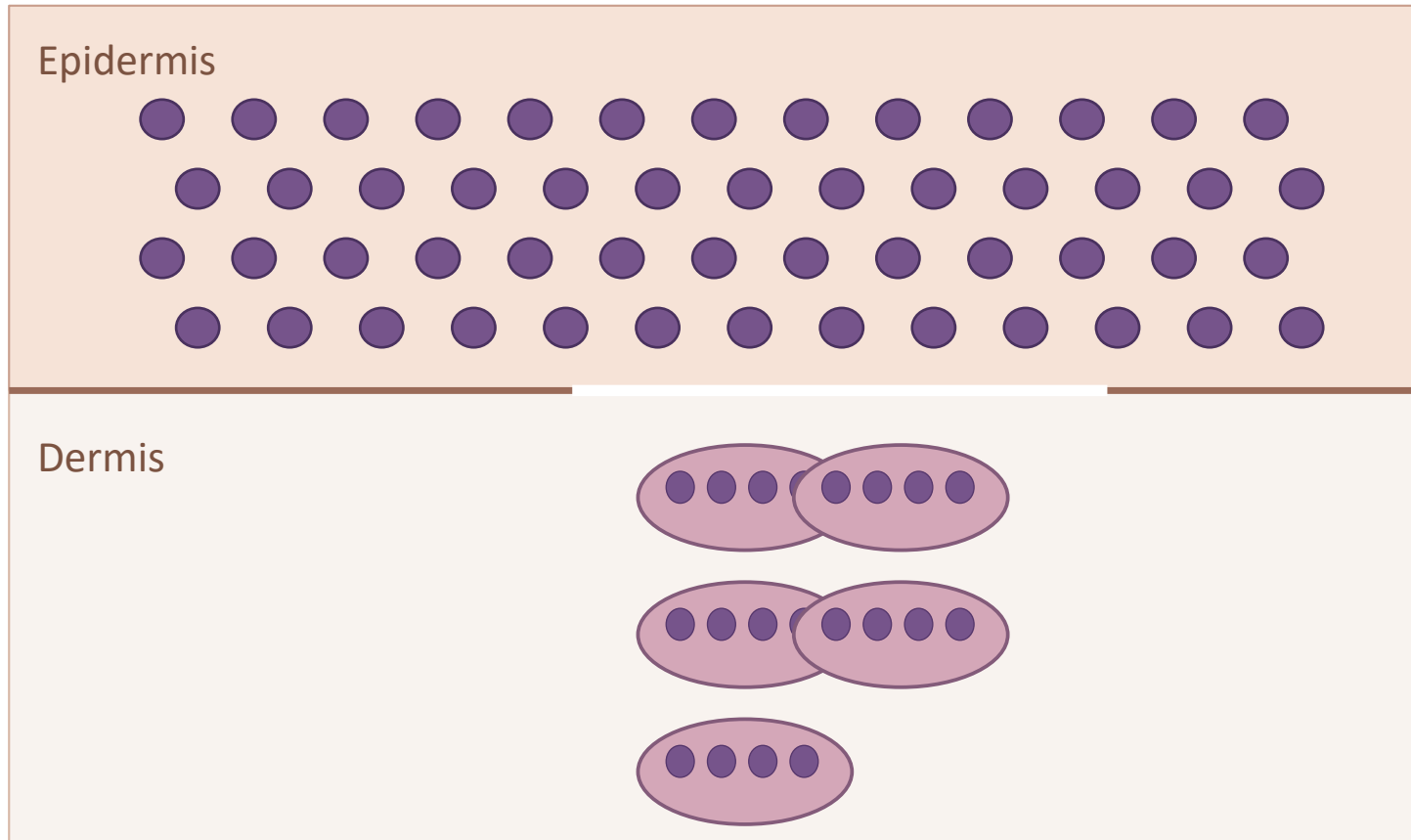
- Typically a sharply defined red scaling plaque.
- Microscopic full-thickness atypia determines the in-situ designation.
- A flat plaque does not alone prove that a lesion is noninvasive.
- Clinical and histopathologic assessments provide complementary information.

Invasive squamous carcinoma

Crossing the basement membrane changes the diagnosis

The defining histologic event is tumor penetration beyond the dermoepidermal junction.

Invasive SCC: Atypical nests within dermis



Observe

- Neoplastic cells cross the basement membrane.
- Tumor forms invasive dermal tongues or nests.
- Dermal location distinguishes invasive from in situ disease.

Schematic — not a histologic specimen

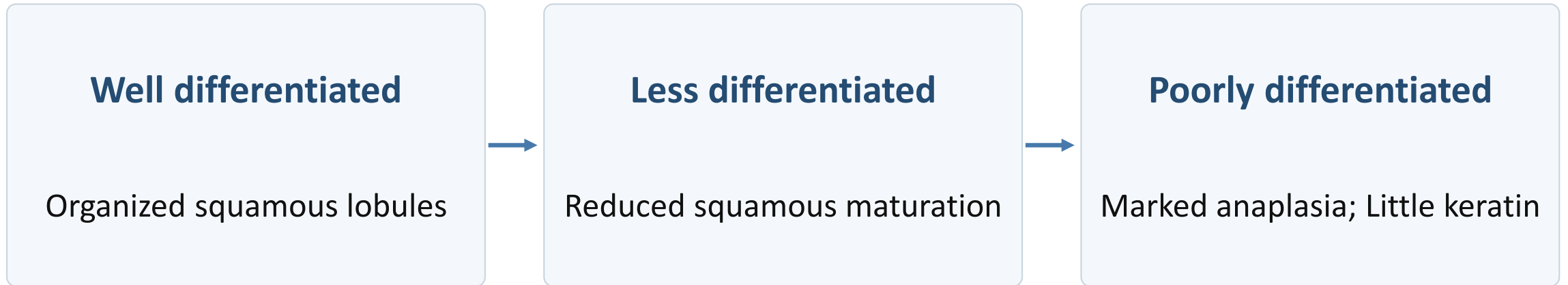
Invasive lesions: Gross morphology

- Invasive SCC often appears as a nodule.
- Variable keratin production produces an irregular hyperkeratotic surface.
- Tumors may ulcerate.
- Gross appearance can suggest an invasive lesion but is not a substitute for histology.

Invasion requires architectural evidence

- Examine the relationship between atypical epithelium and dermis.
- Tongues or nests of malignant squamous cells extend beneath the junction.
- The pattern is different from simple full-thickness intraepidermal atypia.
- The important distinction is basement-membrane transgression.

Squamous differentiation spans a spectrum

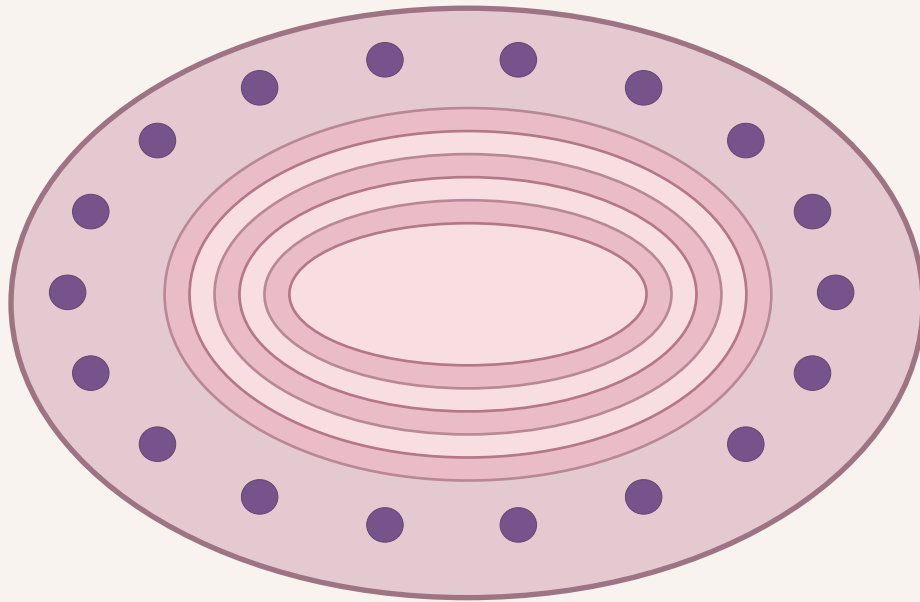


Differentiation describes morphology; It is not the same concept as anatomical stage.

Well-differentiated invasive SCC

- Polygonal malignant squamous cells grow in relatively orderly lobules.
- Substantial areas of keratinization may be present.
- Squamous maturation remains readily recognizable.
- Invasion still defines malignancy even when cells keratinize abundantly.

Keratinization within invasive tumor islands



Schematic — tumor keratinization

Conceptual pattern

In differentiated SCC, polygonal squamous cells may form coherent lobules with conspicuous central keratinization. This graphic does not substitute for an H&E photomicrograph.

Poorly differentiated SCC

- Neoplastic cells may be highly anaplastic.
- Squamous maturation can be minimal or difficult to identify.
- Keratin may be restricted to individual cells (dyskeratosis).
- Recognition of epithelial lineage may then require ancillary stains.

Cytologic hallmarks of invasive SCC

- Enlarged tumor-cell nuclei.
- Irregular or angulated nuclear contours.
- Prominent nucleoli may be visible.
- Interpret cytologic atypia together with infiltrative architecture.

Why keratin immunostains may be needed

- Poor differentiation can obscure overt squamous maturation.
- Immunohistochemical detection of keratins may confirm epithelial identity.
- Robbins does not specify a universal diagnostic keratin panel here.
- IHC supports, rather than replaces, architectural and cytologic interpretation.

Morphology: Three questions at the microscope

Where is atypia?

Basal layer, full epidermis or dermal nests?

Is there keratinization?

Extensive, limited or only isolated dyskeratotic cells?

How atypical are cells?

Assess nuclear enlargement, contour and nucleoli.

Diagnostic comparison across the spectrum

Feature	Actinic keratosis	SCC in situ	Invasive SCC
Main atypia	Lower epidermis	Full epidermis	Dermal tumor nests
Basement membrane	Not transgressed	Not transgressed	Transgressed
Clinical pattern	Rough keratotic area	Red scaly plaque	Often nodule / ulcer
Keratinization	Hyperkeratosis; dyskeratosis	Variable	Variable; may be extensive

SCC and basal cell carcinoma: A focused contrast

Dimension	Cutaneous SCC	Basal cell carcinoma
Frequency	Second most common on sun-exposed skin	Most common invasive cutaneous cancer
Characteristic biology	UV injury; TP53, RAS, Notch alterations	Hedgehog-pathway activation
Differentiation	Squamous; keratinization possible	Basaloid morphology
Metastases	Uncommon but important	Exceptionally uncommon

Clinical findings do not determine invasion

- A thick keratotic lesion may still be predominantly intraepidermal.
- An in-situ carcinoma can look like an ordinary scaly plaque.
- The key decision requires histologic assessment of the junction.
- Do not infer dermal invasion merely from surface hyperkeratosis.

Clinical behavior and management

Most tumors are local; A minority metastasize

The population burden remains consequential despite relatively infrequent nodal spread.

Regional-node metastasis: Context matters

- Fewer than 5% metastasize to regional lymph nodes.
- That figure is a broad textbook estimate, not a patient-specific prognostic score.
- Skin SCC has lower reported nodal metastatic frequency than some mucosal/visceral SCC.
- Do not treat all squamous cancers as having equivalent metastatic behavior.

Why a low proportion still matters

- Cutaneous SCC is common in the population.
- A small metastatic fraction can still yield a substantial disease burden.
- Local disease and metastatic SCC differ greatly in clinical consequences.
- Management decisions must distinguish these disease states.

Local excision is effective for many lesions

- Invasive tumors are often detected while small and resectable.
- Recognizable skin lesions facilitate definitive local treatment.
- Local excision as effective in typical early lesions.
- This teaching point does not specify margins or current surgical protocols.

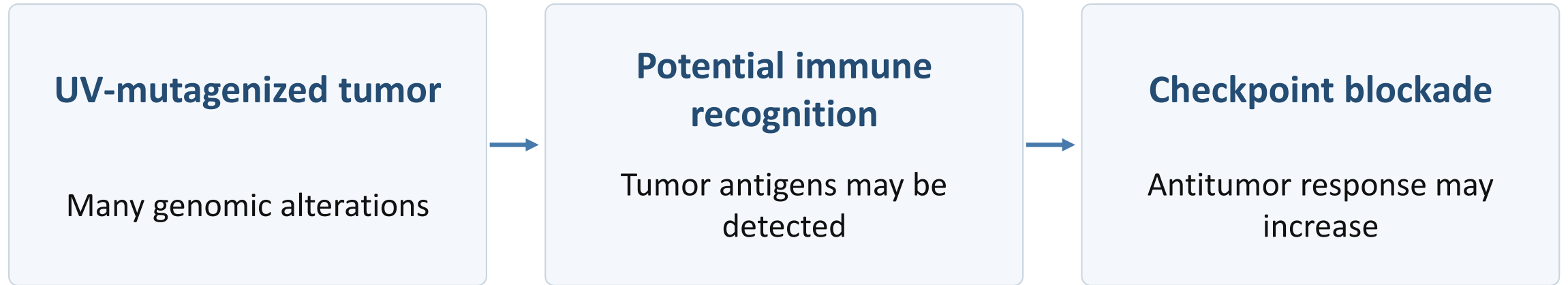
Locoregional metastatic SCC and radiation

- Metastatic cutaneous SCC as generally chemotherapy resistant.
- It describes sensitivity to radiotherapy.
- Radiotherapy is cited for localized metastatic disease.
- Actual modality selection depends on contemporary individualized oncology practice.

High mutation burden supports immunotherapy

- Cutaneous SCC has a very high somatic mutational burden.
- High mutation load is linked to immune checkpoint inhibitor responsiveness.
- Checkpoint inhibitors are often first-line for metastatic disease.
- Specific agents and regimen decisions are intentionally outside this source-limited lecture.

Why checkpoint inhibition can be effective



Mechanism is schematic and not a guarantee of response in any patient.

Application 1: Precursor versus invasion

A chronically sun-exposed area shows a rough, scaly lesion. Histology demonstrates atypical keratinocytes confined chiefly to basal epidermal layers.

What diagnosis best fits the distribution of atypia?

Interpretation: Actinic keratosis; No dermal invasion is described.

Application 2: Recognizing in-situ disease

A sharply outlined red scaly plaque contains enlarged hyperchromatic keratinocytes at all epidermal levels. The basement membrane remains intact.

Which feature makes this carcinoma in situ?

Interpretation: Full-thickness epidermal atypia without basement-membrane transgression.

Application 3: The decisive invasive feature

An epithelial lesion has dermal tongues of atypical polygonal cells beneath the dermoepidermal junction and conspicuous squamous keratinization.

Which architectural finding establishes invasive SCC?

Interpretation: Malignant squamous epithelium within the dermis.

Application 4: Inherited repair defect

A person with a rare inherited defect of nucleotide excision repair develops numerous UV-associated skin cancers.

Which molecular failure explains SCC susceptibility?

Interpretation: Ineffective removal of UV-induced pyrimidine dimers.

Application 5: Interpreting an HPV association

A lecture slide states that HPV types 5 and 8 are proven causal agents in all sporadic cutaneous SCC.

Is this statement justified by Robbins?

Interpretation: No. Clear implication is specified for epidermodysplasia verruciformis.

Synthesis: Recognize three separable layers of evidence

Etiologic evidence

Sun exposure, immunosuppression, repair deficiency and other documented risks.

Pathogenetic evidence

TP53 alteration, RAS and Notch pathway changes, mutational accumulation.

Diagnostic evidence

Extent of epidermal atypia, basement transgression and squamous differentiation.

Final diagnostic synthesis

- First identify the spatial extent of atypical keratinocytes.
- Next determine whether the basement membrane has been crossed.
- Then characterize squamous keratinization and differentiation.
- Use keratin immunostains when severe anaplasia obscures epithelial lineage.

Final biologic and clinical synthesis

- Cumulative UV DNA injury is the dominant initiating context.
- Repair defects, immunosuppression and other exposures modify risk.
- A subset of actinic lesions progresses to in situ or invasive SCC.
- Most lesions are treatable locally; Advanced disease may merit radiotherapy or checkpoint inhibition.

Primary reference and evidence limits

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Chapter 25, The Skin: Actinic Keratosis and Squamous Cell Carcinoma.
- Basal Cell Carcinoma is used only for focused comparative teaching.
- All morphology diagrams are native editable schematics, not clinical images.