

Basal Cell Carcinoma

Mechanisms · clinical morphology · histopathology

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Why basal cell carcinoma matters

- The most common invasive human cancer; Extremely frequent in routine dermatopathology.
- Usually slow growing and treatable by local excision when recognized early.
- Biologically distinctive because its central oncogenic driver is Hedgehog pathway activation.
- The principal threat is local destruction; Distant spread is exceptionally uncommon.

Learning objectives

- Explain exposure-related and inherited susceptibility to basal cell carcinoma.
- Trace PTCH, SHH, SMO and GLI1 signaling in normal and neoplastic settings.
- Distinguish nodular, superficial, pigmented and ulcerated clinical presentations.
- Recognize basaloid nests, peripheral palisading and stromal clefts in tissue sections.
- Connect molecular pathogenesis with the rationale for targeted treatment.

The dual identity: Common yet locally aggressive

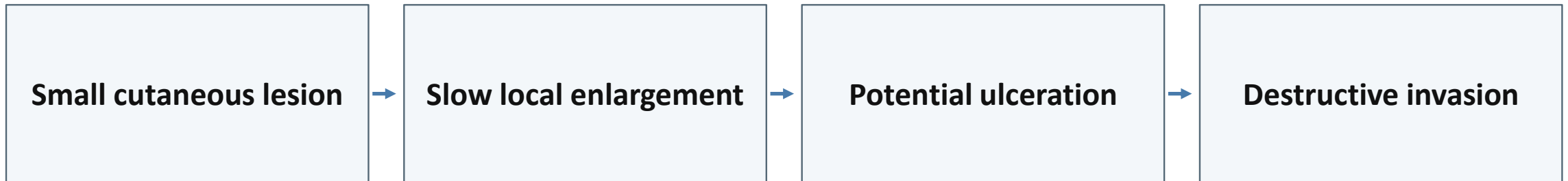
Common clinical course

- Slow evolution in most patients
- Early recognition allows local cure
- Metastasis is rare

Uncommon advanced course

- Progressive invasion can damage contiguous structures
- Facial soft tissues, bone or sinuses may be involved
- Distant disease occurs only exceptionally

Natural history depends on detection



- Many lesions are recognized while limited and resectable.
- Prolonged neglect permits continued local extension rather than rapid dissemination.
- The distinction between low metastatic potential and local invasion is crucial.

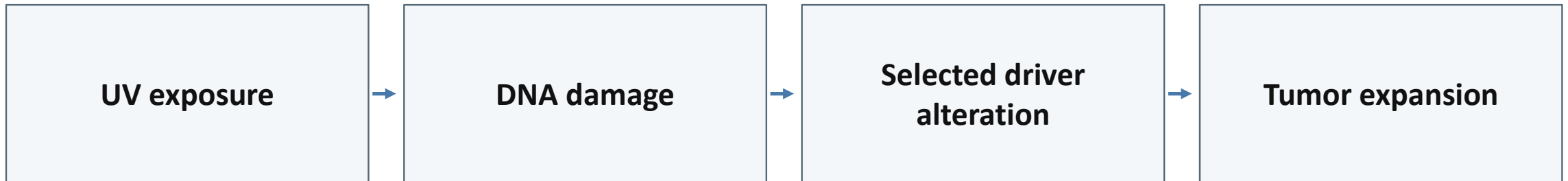
Metastasis is not the dominant hazard

- BCC rarely metastasizes, even though it is an invasive malignancy.
- Local tissue invasion explains the potential for clinically important morbidity.
- Risk is not captured by the metastasis rate alone: The affected anatomical site matters.
- Source emphasis: Most cancers are cured locally; Only a small minority behave destructively.

Who develops basal cell carcinoma?

- Classically occurs on sun-exposed skin in older, lightly pigmented adults.
- Longstanding cumulative ultraviolet exposure contributes to disease risk.
- Inherited defective DNA repair increases susceptibility to skin carcinoma.
- Immunosuppression is another recognized risk context.

Ultraviolet exposure and tumor formation



- UV-induced DNA injury can create acquired driver mutations.
- Loss of PTCH function removes a normal brake on growth signaling.
- Not every exposed keratinocyte becomes malignant; Other biological constraints remain.

Exposure and host vulnerability

Exposure component

- Sun-exposed cutaneous sites
- A UV mutational signature is found in many BCC drivers
- Lifetime exposure is important

Host component

- Reduced immune surveillance in immunosuppressed people
- Defective DNA repair in xeroderma pigmentosum
- Inherited PTCH defect in Gorlin syndrome

Immunosuppression changes susceptibility

- BCC incidence is increased in immunosuppressed individuals.
- The association is shared with cutaneous squamous cell carcinoma.
- Immunosuppression is a risk modifier, not the defining molecular driver of BCC.
- Interpret a suspicious lesion using morphology rather than immunosuppressive status alone.

Xeroderma pigmentosum: Defective repair

- Xeroderma pigmentosum is a disorder of nucleotide excision DNA repair.
- Defective handling of UV-induced DNA lesions predisposes to skin malignancies.
- Its relevance to BCC is the broader link between DNA damage and acquired driver mutations.
- This is a distinct genetic route from inherited PTCH dysfunction in Gorlin syndrome.

BCC and cutaneous SCC: Shared context

Feature	Basal cell carcinoma	Cutaneous squamous cell carcinoma
Major exposure	Sun exposure	Sun exposure
Molecular emphasis	Hedgehog/PTCH–SMO–GLI	UV-associated multiple drivers, including TP53
Typical morphology	Basaloid nests with palisading	Atypical squamous cells with keratinization
Clinical pattern	Very rare spread; local invasion	Regional spread occurs in a minority

Risk interpretation exercise

A longstanding sun-exposed facial lesion develops in an older patient receiving immunosuppressive therapy. Which factors are relevant?

Teaching interpretation

- UV exposure and immunosuppression both contribute to risk.
- Age, site and pigmentation provide clinical context but not a tissue diagnosis.
- A biopsy or excision requires histologic pattern assessment for definitive classification.

Gorlin syndrome identifies a driver

- Nevroid basal cell carcinoma syndrome (NBCCS) is also called Gorlin syndrome.
- It is an autosomal dominant inherited predisposition to multiple BCCs.
- Tumors may appear before age 20 years, unlike the usual sporadic presentation.
- Investigation of NBCCS clarified the PTCH tumor-suppressor role.

Gorlin syndrome is multisystem

- Multiple cutaneous basal cell carcinomas are a defining tumor manifestation.
- Associated neoplasms include medulloblastomas and ovarian fibromas.
- Odontogenic keratocysts and palmoplantar pits are important clues.
- Certain skeletal or other developmental abnormalities may also be present.

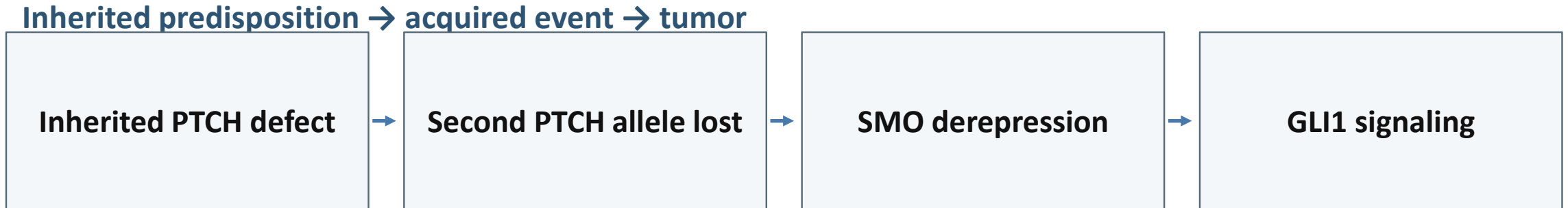
NBCCS: Classify the manifestations

Category	Manifestations in the Robbins discussion
Skin	Multiple basal cell carcinomas; palmoplantar pits
Jaw	Odontogenic keratocysts
Other tumors	Medulloblastoma; ovarian fibroma
Development	Selected skeletal and other developmental anomalies

Autosomal dominant risk is not tumor certainty

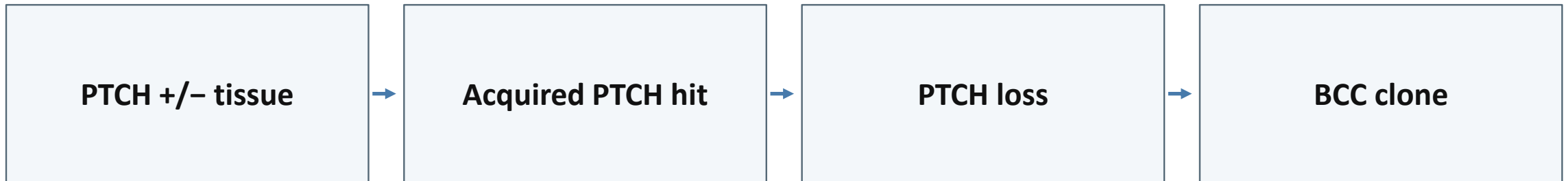
- An individual with NBCCS inherits one nonfunctional PTCH allele.
- The remaining functional allele provides a normal suppressor copy initially.
- Somatic inactivation of that allele enables tumor development in a clone.
- Inherited susceptibility therefore differs from a fully transformed cell state.

PTCH is a two-hit tumor suppressor



- The germline change creates a predisposed tissue field.
- Acquisition of the second hit produces local loss of tumor-suppressor activity.
- This framework explains why separate tumors can arise in one predisposed person.

Ultraviolet light can supply the second hit



- In NBCCS, the second PTCH allele can be inactivated by an acquired mutation.
- UV exposure is specifically identified as a frequent mutagenic source.
- The oncogenic consequence is constitutive Hedgehog signaling in affected cells.

Why rare syndromes explain common tumors

- Inherited syndromes amplify one lesion mechanism enough to make it discoverable.
- Identification of PTCH in NBCCS provided a route to study sporadic BCC.
- Loss of PTCH activity is not confined to inherited cases.
- Disease mechanism—not simply pedigree—therefore guides therapeutic development.

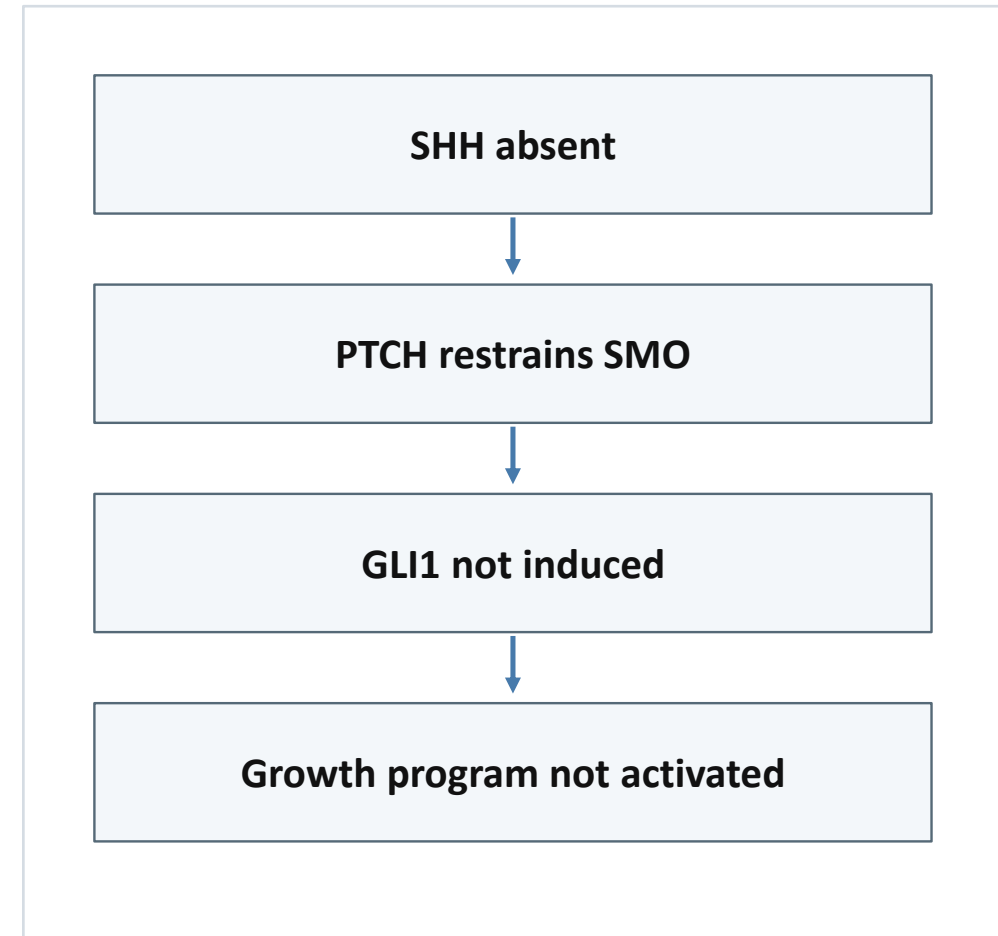
Hedgehog signaling has normal functions

- The SHH–PTCH–SMO pathway regulates embryonic patterning and development.
- Robbins specifically emphasizes polarity and central nervous system development.
- The pathway also participates in hair follicle formation and growth.
- Its normal developmental role explains why constitutive signaling can affect both neoplasia and patterning.

Hedgehog signaling: Ligand absent

Mechanistic explanation

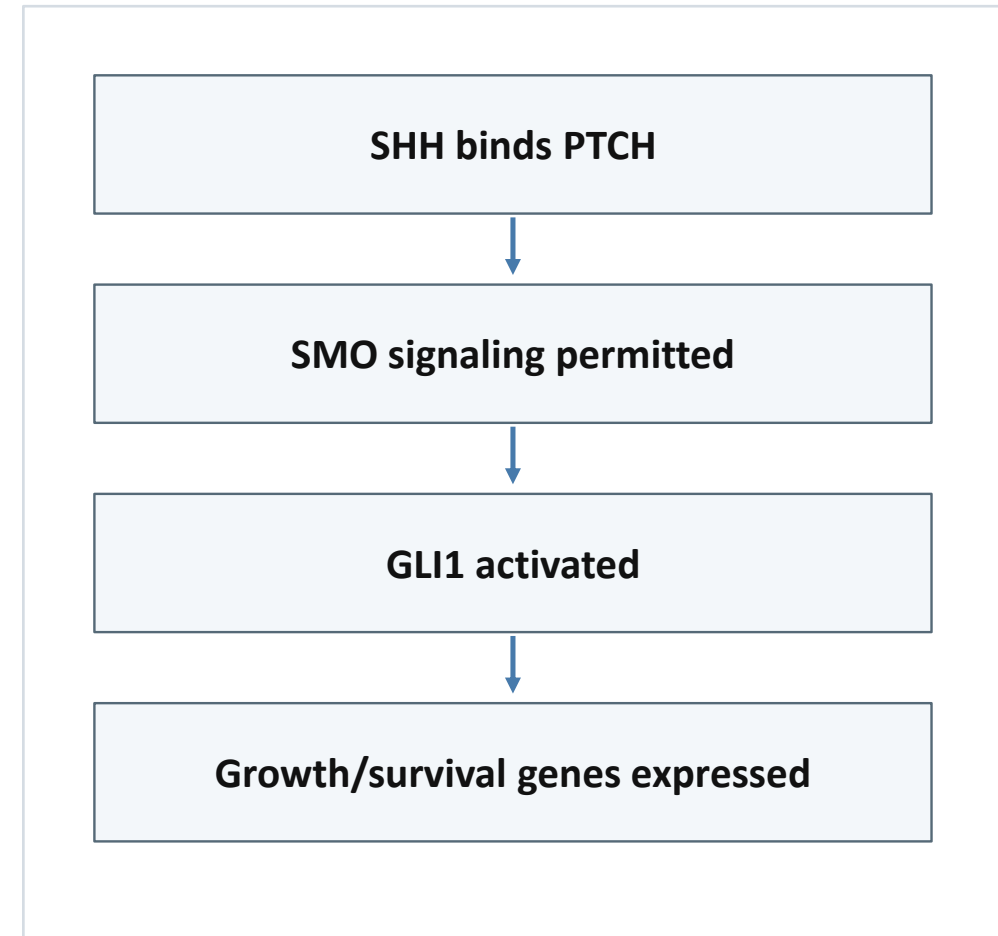
- Without sonic hedgehog ligand, PTCH suppresses SMO activity.
- GLI1-dependent transcription is not pathologically stimulated.
- PTCH is therefore a negative regulator of the pathway.



Hedgehog signaling: Ligand present

Mechanistic explanation

- SHH binding to PTCH relieves inhibition of SMO.
- SMO activates downstream signaling culminating in GLI1 activation.
- GLI1 promotes transcriptional programs supporting growth and survival.



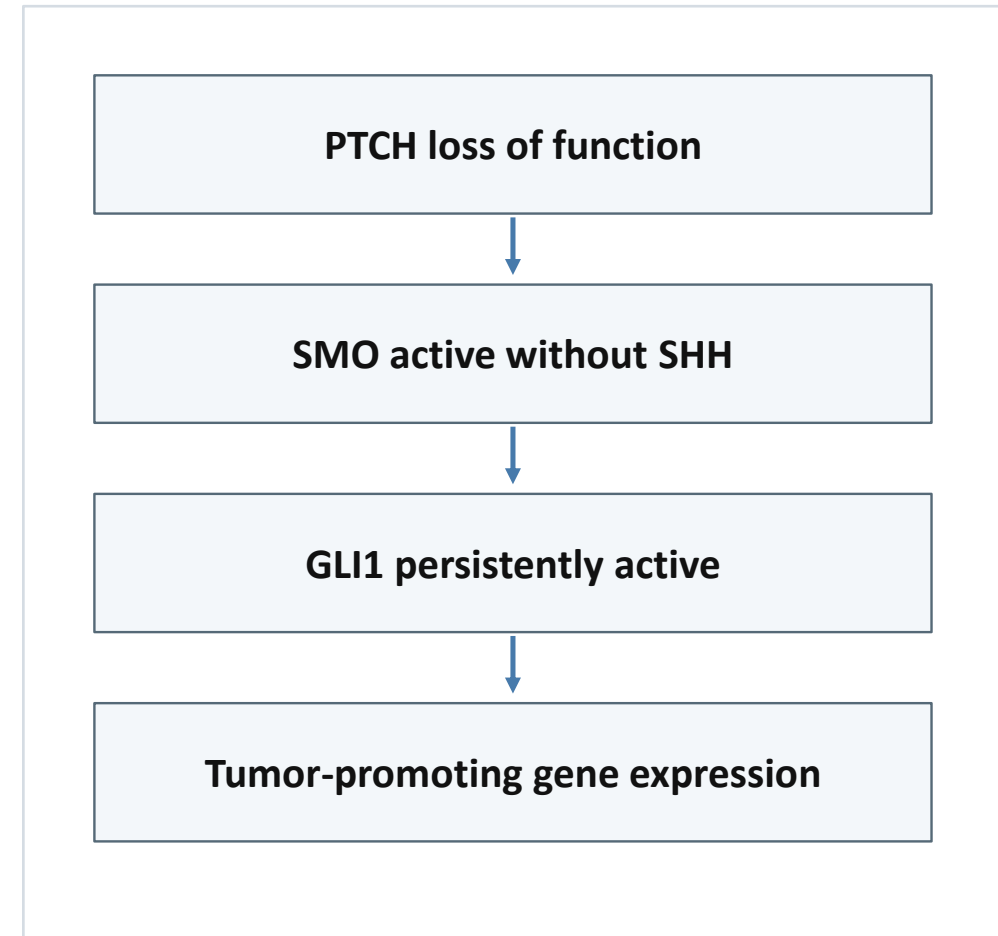
Normal pathway: Off versus on

Regulatory element	SHH absent	SHH present
PTCH–SMO relationship	PTCH inhibits SMO	SHH binding relieves inhibition
SMO signal	Suppressed	Active
GLI1 output	Not induced by SHH	Activated
Biologic context	Regulated baseline state	Ligand-dependent developmental signaling

Mutant PTCH removes the brake

Mechanistic explanation

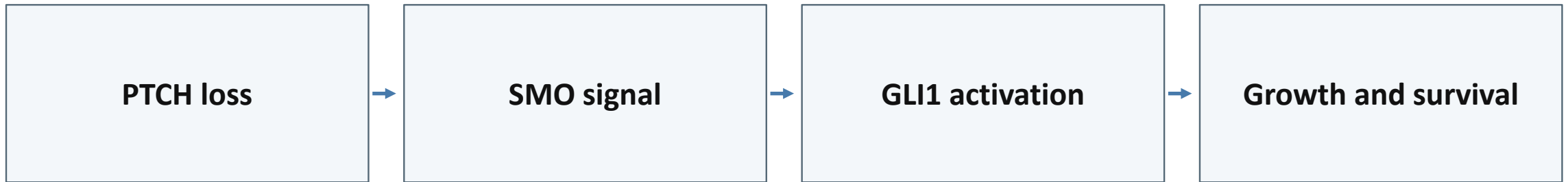
- PTCH loss of function prevents normal restraint of SMO.
- SMO can signal without SHH ligand binding.
- GLI1 is constitutively activated in the neoplastic clone.
- The pathway becomes ligand independent.



SMO mutation offers another entry point

- The Robbins figure describes oncogenic mutations in PTCH and, less often, SMO.
- The common functional endpoint is inappropriate SMO activity.
- Upstream genetic events may differ while downstream GLI signaling converges.
- The distinction matters for identifying the regulatory site of pathway activation.

GLI1 links signaling to tumor behavior



- SMO activity engages downstream transcriptional regulation.
- GLI1 increases expression of genes that support tumor-cell growth and survival.
- Constitutive signaling can sustain the basal-cell carcinoma growth program.

Physiologic versus oncogenic signaling

Physiologic Hedgehog signal

- Depends on SHH binding
- PTCH regulation remains intact
- Supports controlled development and homeostasis

Oncogenic Hedgehog signal

- May operate without ligand
- PTCH dysfunction or activating SMO change
- Persistent GLI-dependent expression

Inherited and sporadic BCC converge

Aspect	Inherited NBCCS-associated BCC	Sporadic BCC
Starting state	Germline PTCH loss-of-function allele	No inherited PTCH defect required
Acquired changes	Second PTCH allele inactivated	Somatic Hedgehog-activating mutations
Shared biology	SMO–GLI1 activation	SMO–GLI1 activation
Clinical tendency	Often multiple, potentially early lesions	Usually occurs in older sun-exposed persons

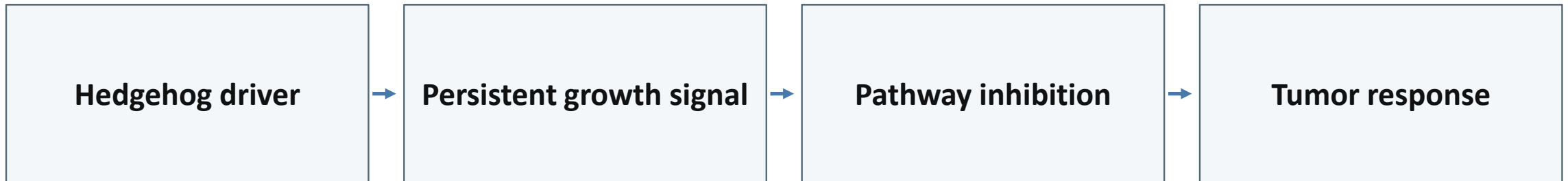
A UV signature exists in PTCH mutations

- PTCH loss-of-function mutations occur commonly in sporadic BCC.
- That about one-third are C→T transitions.
- This substitution pattern is a classic signature of UV-associated DNA damage.
- Mutation type supports etiologic inference but does not replace pathologic diagnosis.

Genetic associations need correct interpretation

- PTCH is a negative regulator and tumor suppressor—not an oncogene activated by overexpression.
- Mutant PTCH can activate the pathway through loss of normal inhibition.
- SMO is a positive signaling component; Activating changes can produce a similar endpoint.
- GLI1 is a downstream transcriptional effector rather than the original germline lesion.

The molecular therapeutic rationale



- The driver pathway is functionally activated at the level of SMO/GLI signaling.
- Hedgehog pathway inhibitors were developed from this causal understanding.
- Targeting a disease dependency is different from merely treating surface ulceration.

Molecular logic predicts clinical relevance

- Most BCCs remain suitable for local treatment; Systemic targeting is not the default.
- Locally advanced or metastatic disease creates a need for nonlocal therapy.
- The Robbins discussion identifies Hedgehog inhibitors and immune checkpoint inhibitors as options.
- Treatment selection and eligibility require patient-specific clinical assessment beyond this pathology scope.

The classic pearly papule

Clinical interpretation

- Typical BCC may appear as a small pearly or translucent papule.
- The appearance reflects a characteristic surface phenotype, not a definitive histologic finding.
- Examination should note the lesion contour, vessels, pigmentation and ulceration.

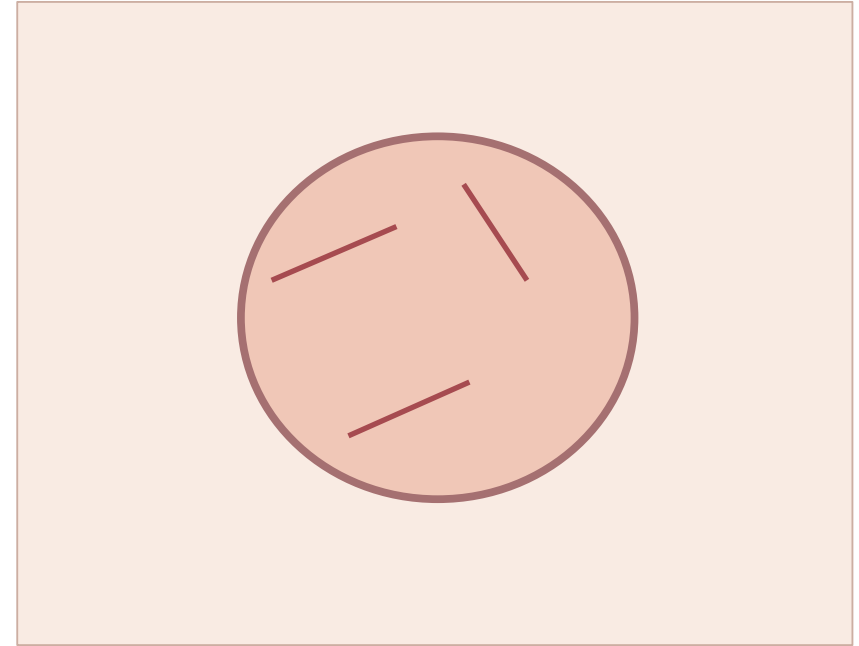


Clinical morphology schematic

Telangiectasia supports suspicion

Clinical interpretation

- Prominent dilated superficial blood vessels may be visible over a papule.
- These are described as subepidermal telangiectasias in the text.
- Their presence supports clinical recognition in an appropriate lesion and setting.



Clinical morphology schematic

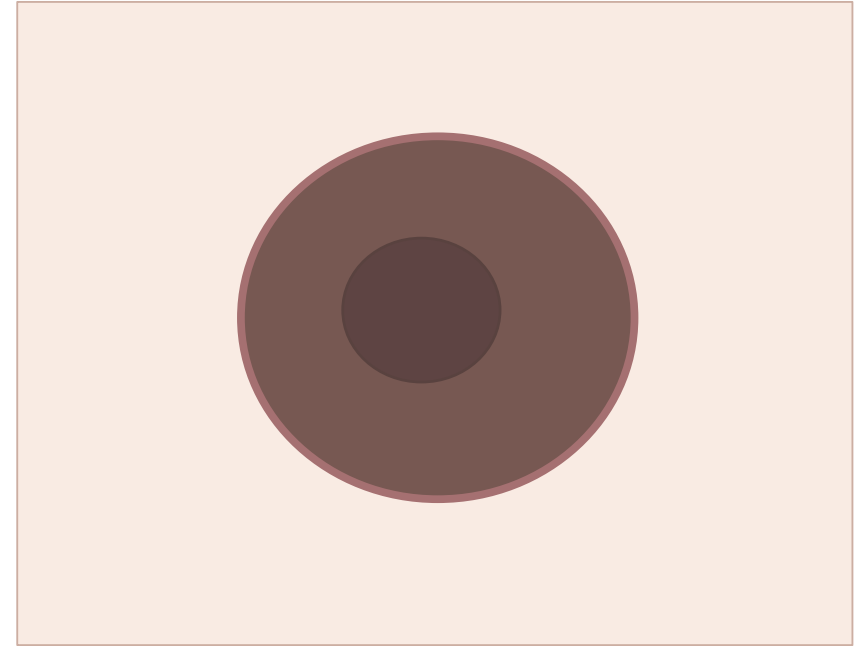
Skin pigmentation alters clinical appearance

- Pearly change and telangiectasia can be less apparent in more highly pigmented skin.
- Failure to see the textbook appearance does not exclude BCC.
- Clinical descriptions need to accommodate a range of skin pigmentation.
- Histologic confirmation remains applicable regardless of surface appearance.

Pigmented basal cell carcinoma

Clinical interpretation

- Some BCC lesions contain melanin pigment.
- Such lesions can resemble a melanocytic nevus or melanoma on inspection.
- Pigmentation alone does not establish a melanocytic tumor diagnosis.
- Recognize the need for histologic distinction.

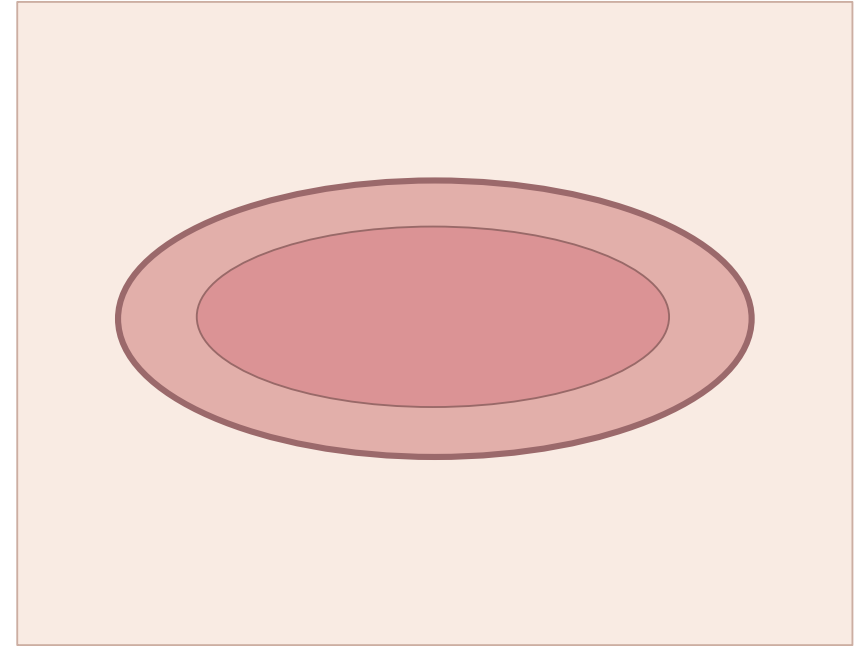


Clinical morphology schematic

Superficial BCC is often plaque-like

Clinical interpretation

- Superficial BCC may appear as an erythematous plaque.
- Some superficial lesions are pigmented.
- A flat plaque can be mistaken for a different cutaneous lesion, including melanoma.
- Its architecture is often multifocal and near the surface.



Clinical morphology schematic

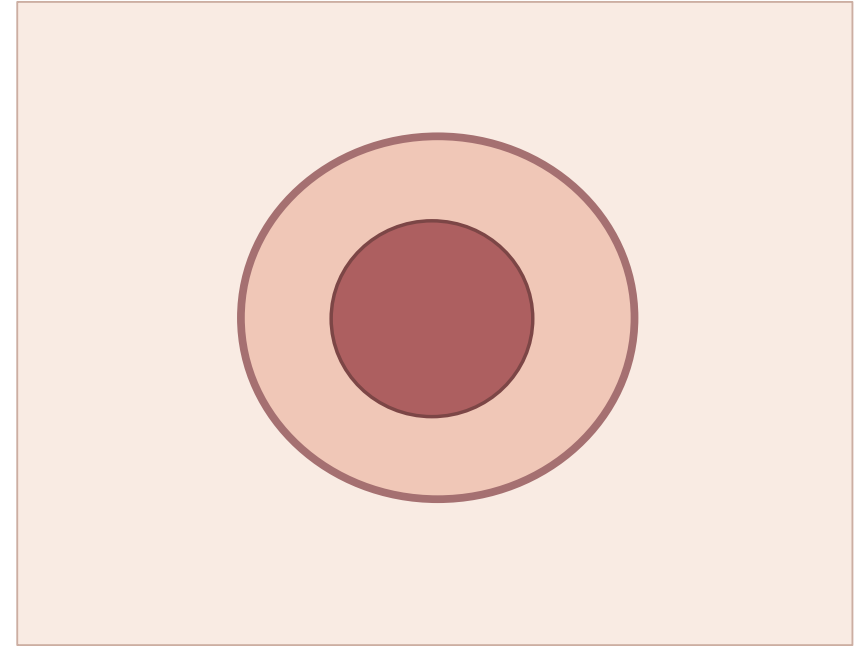
Nodular and superficial patterns

Feature	Nodular BCC	Superficial BCC
Clinical appearance	Pearly or translucent papule/nodule	Erythematous or pigmented plaque
Growth geometry	Islands and cords may extend deeply into dermis	Multifocal growth arising from epidermis
Key recognition	Surface vessels, possible ulceration	Potential resemblance to other plaques

Ulceration in advanced disease

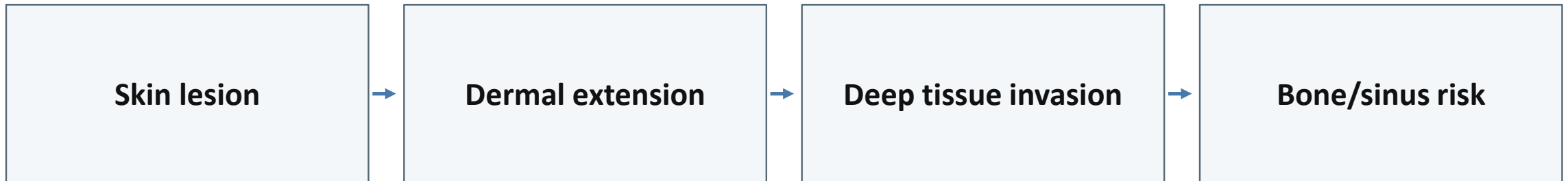
Clinical interpretation

- Older, neglected lesions can ulcerate.
- The traditional term “rodent ulcer” reflects the destructive local behavior.
- Ulceration is a clue to disease progression but is not exclusive to BCC.
- Assessment must address depth and contiguous tissue involvement.



Clinical morphology schematic

Local extension can threaten anatomy



- BCC spreads predominantly by direct local growth.
- The source describes invasion into bone and facial sinuses after prolonged neglect.
- This route explains severe morbidity without requiring distant metastasis.

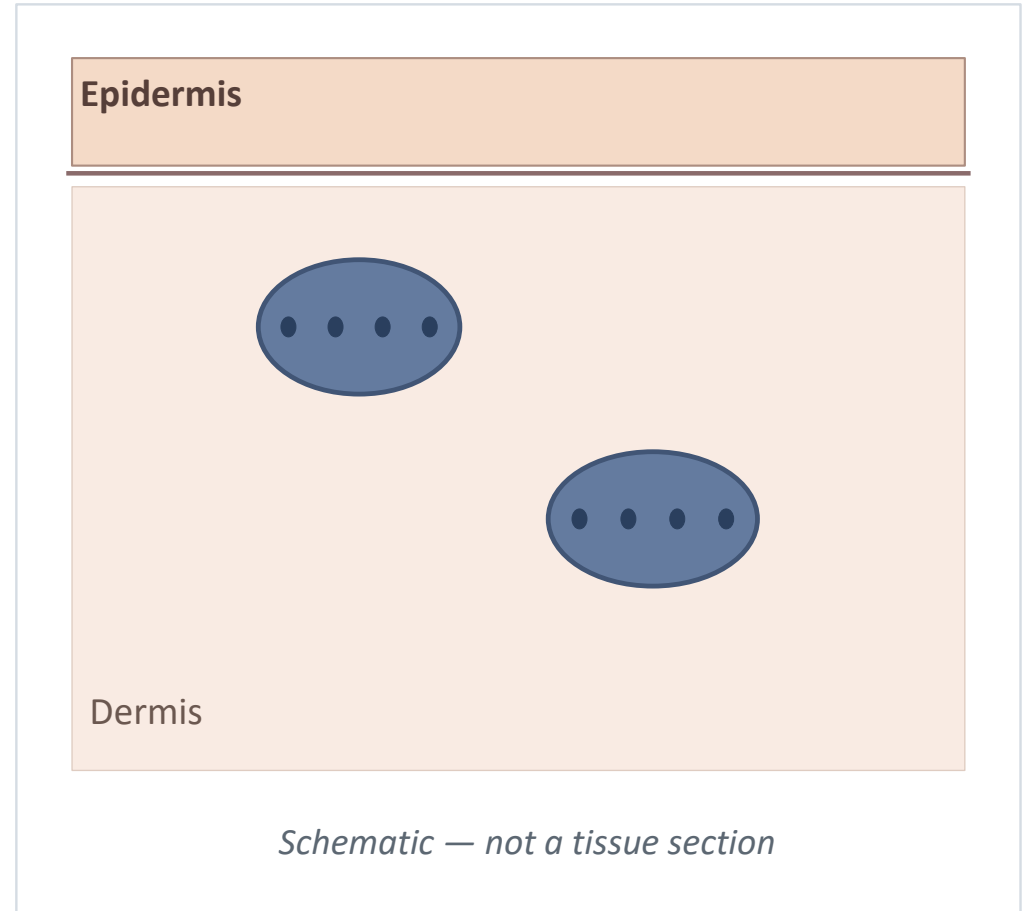
Clinical patterns: Useful distinctions

Pattern	Typical surface description	Potential clinical problem
Nodular	Pearly papule; telangiectasia	Progressive depth and ulceration
Pigmented	Darkly pigmented papule or plaque	May mimic a melanocytic lesion
Superficial	Erythematous ± pigmented plaque	May resemble non-BCC plaques
Neglected lesion	Ulcerated, locally destructive growth	Deep invasion of adjacent tissue

Histologic origin: Skin, not mucosa

Histologic interpretation

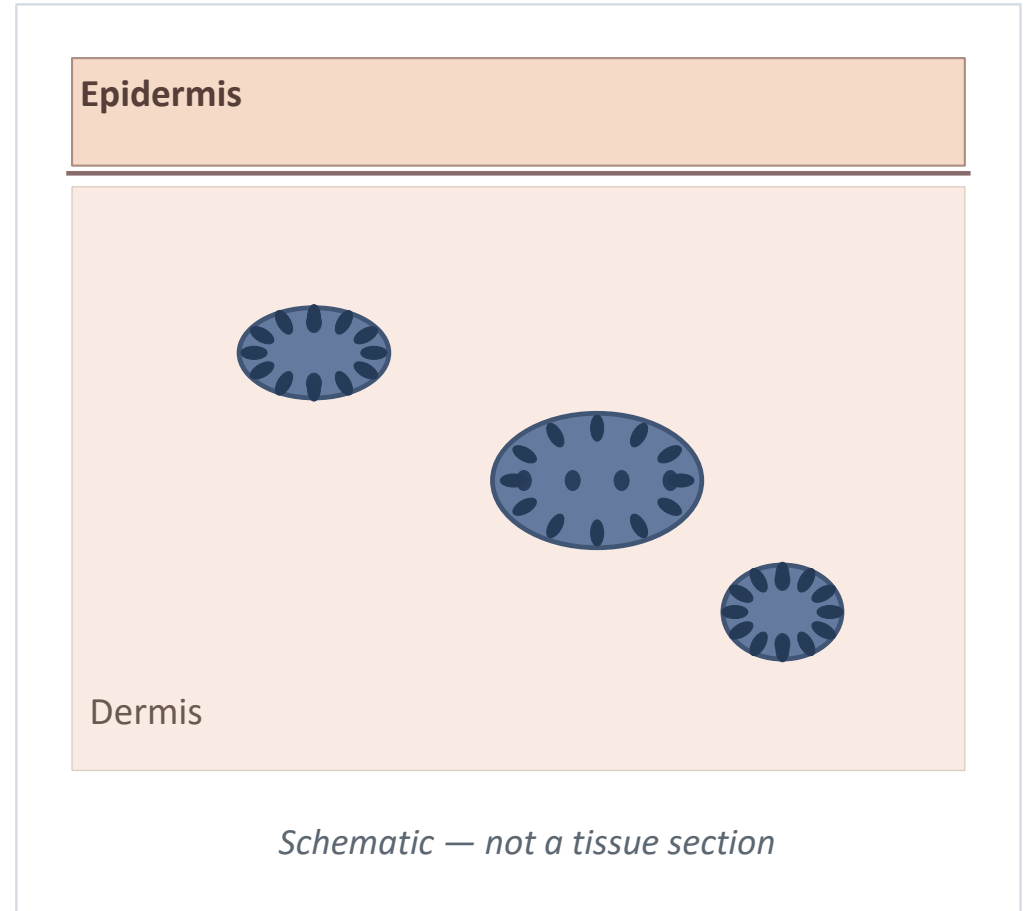
- Tumors arise from epidermis or follicular epithelium.
- The proliferating cells resemble the epidermal basal cell population.
- BCC is defined here as a cutaneous tumor and does not occur on mucosal surfaces.



Basaloid differentiation is central

Histologic interpretation

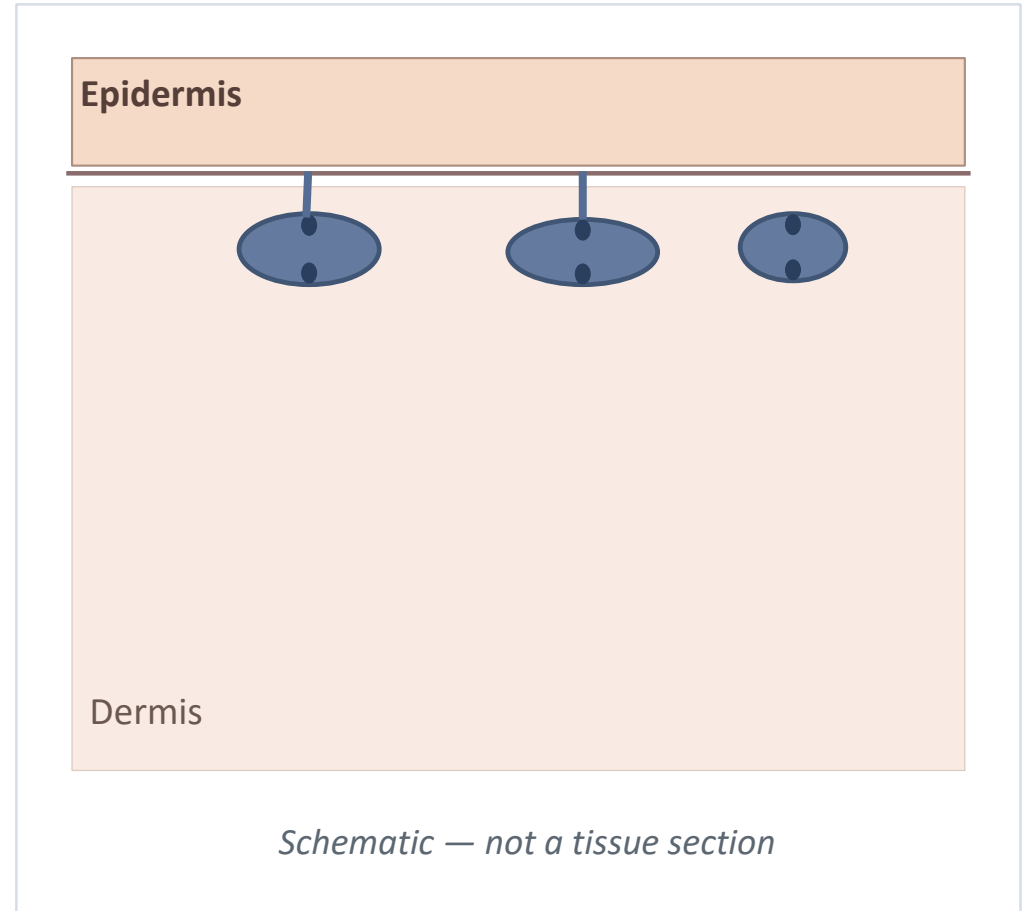
- Neoplastic cells resemble those of the normal basal epidermal layer.
- Tumor cells tend to be relatively uniform and basophilic.
- Architectural arrangement and the tumor–stroma interface are important clues.



Multifocal superficial histologic growth

Histologic interpretation

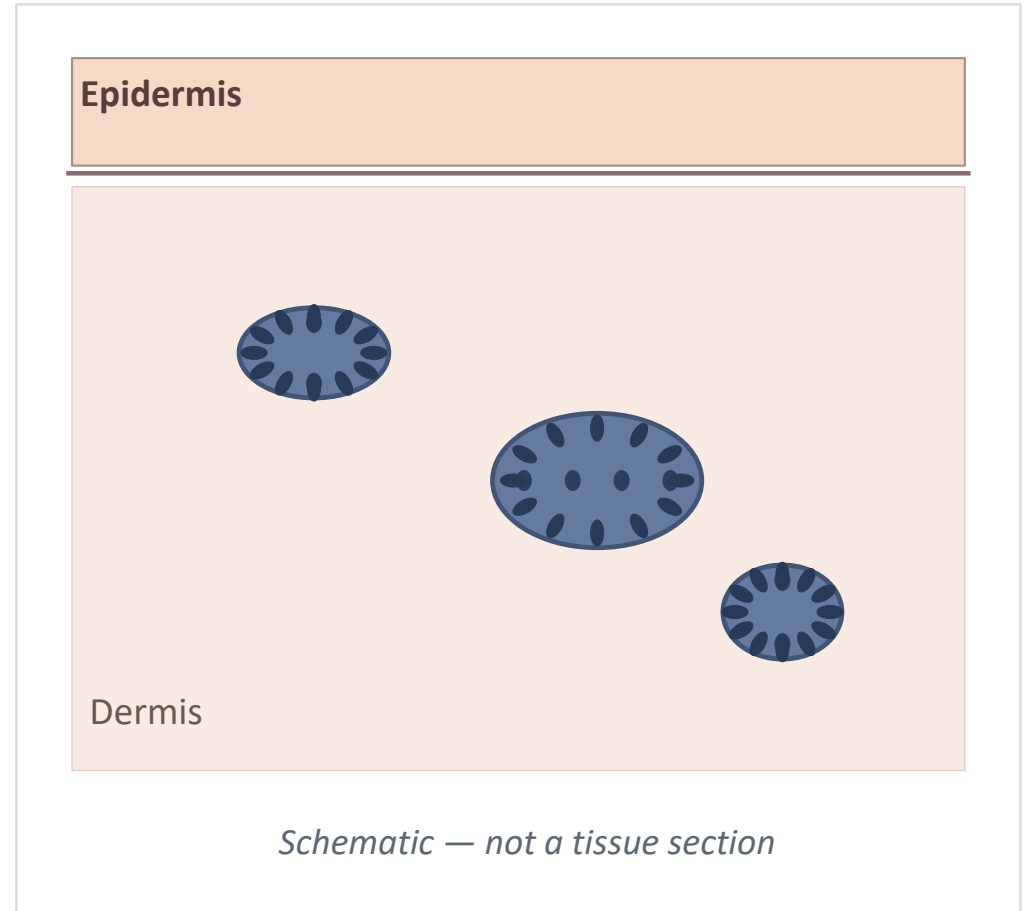
- Superficial BCC can arise as separate foci from the epidermis.
- The involved surface may cover several square centimeters.
- The key concept is lateral multifocality rather than a single deep nodule.



Nodular BCC invades the dermis

Histologic interpretation

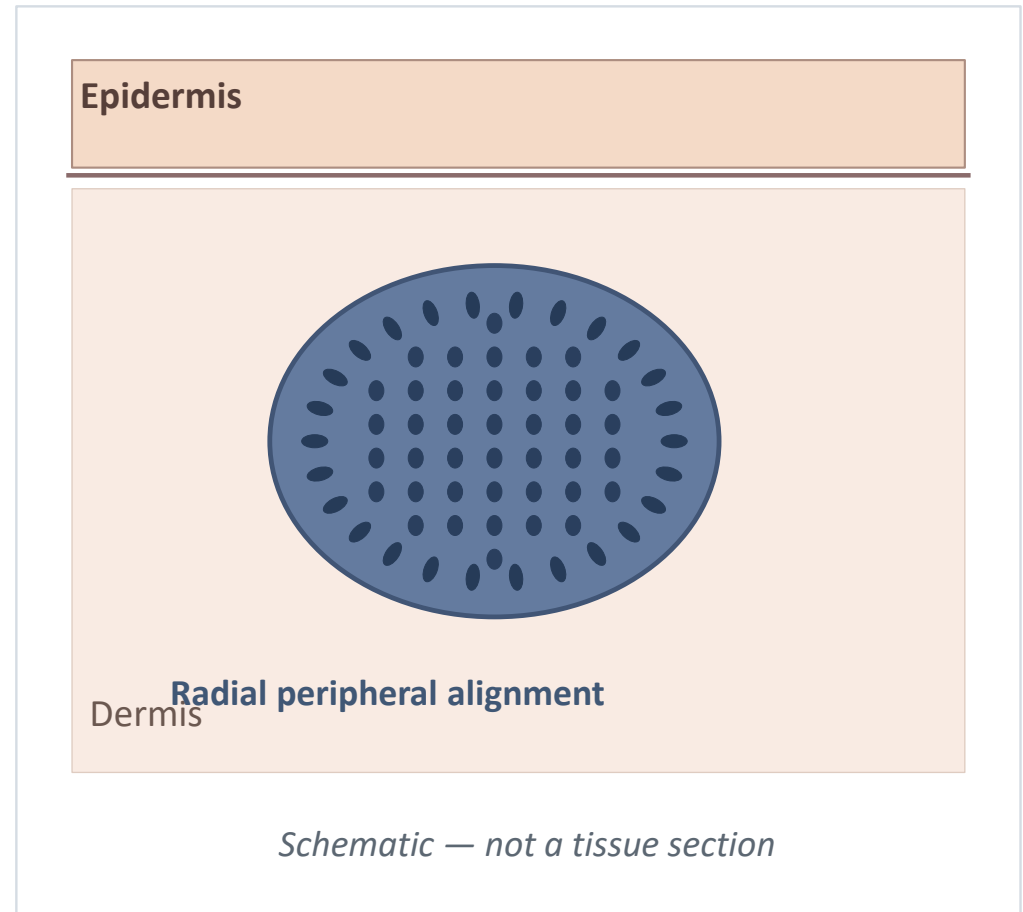
- Nodular tumors grow downward as cords or islands of basaloid cells.
- The nests may extend to different depths within the dermis.
- Their growth pattern contrasts with flat, multifocal superficial lesions.



Basophilia and nuclear appearance

Histologic interpretation

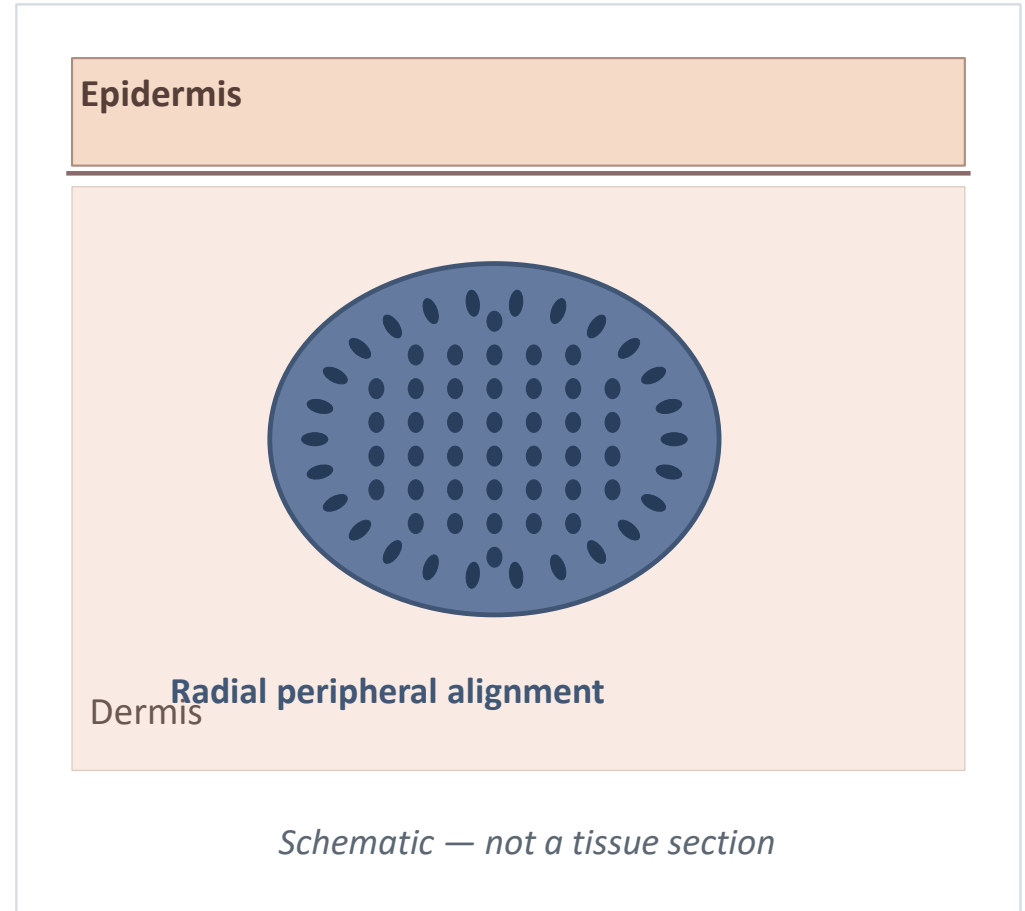
- Tumor islands are variably basophilic on conventional histology.
- Nuclei are described as hyperchromatic.
- The overall basaloid cytomorphology is interpreted together with architecture.



Peripheral palisading: The rim clue

Histologic interpretation

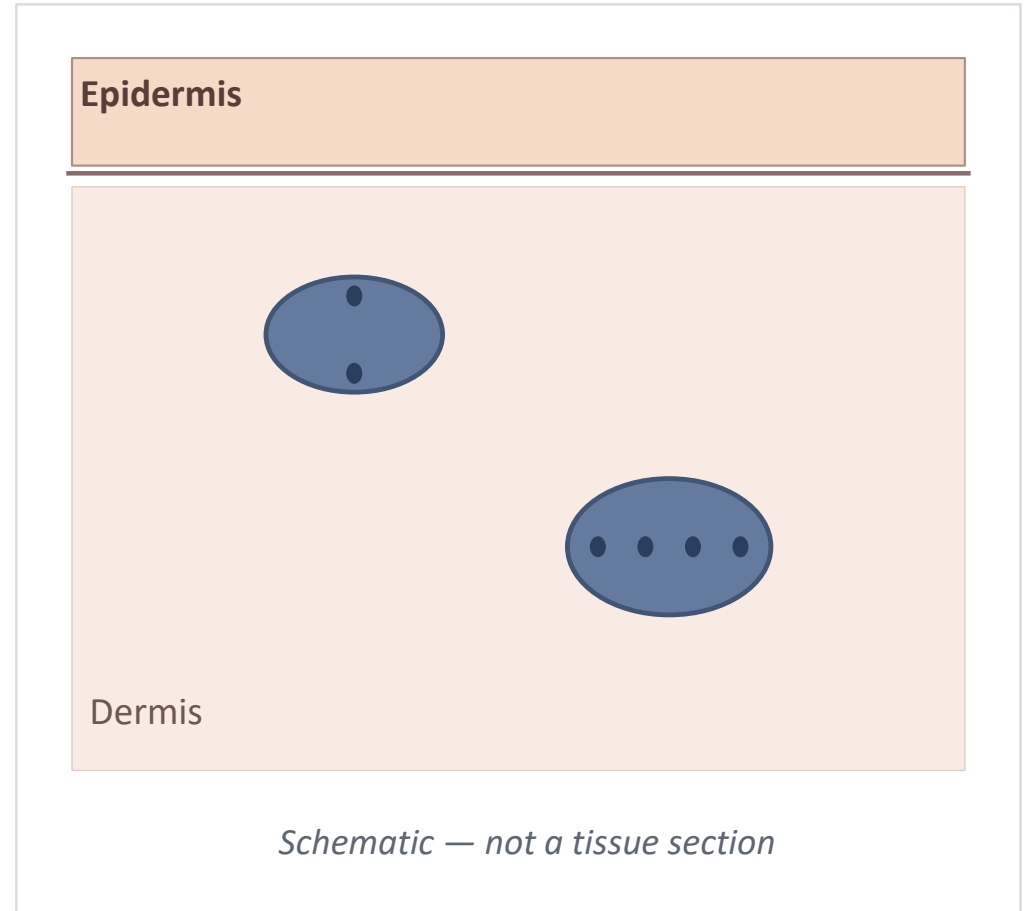
- Cells at the edges of tumor nests may align radially.
- Their long axes are arranged roughly parallel around the tumor perimeter.
- This peripheral nuclear arrangement is termed palisading.



The tumor has a stromal context

Histologic interpretation

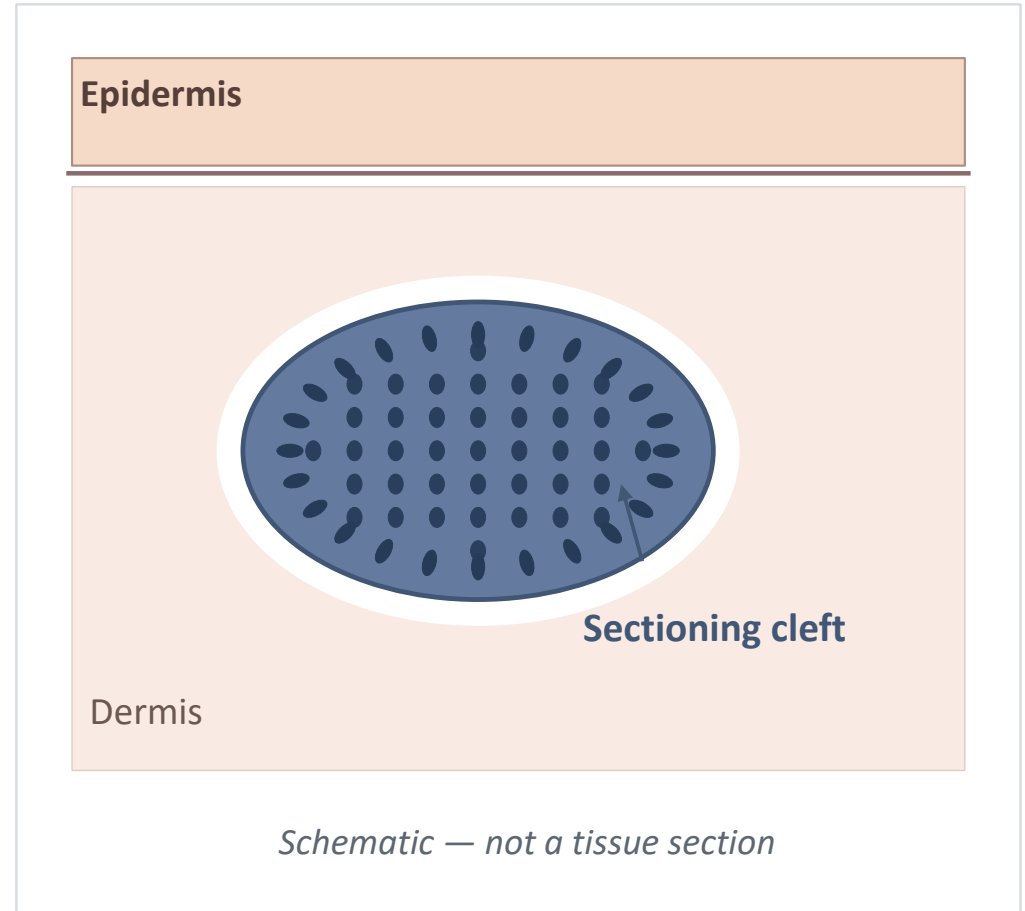
- The source describes tumor islands within a mucinous extracellular matrix.
- Many fibroblasts and lymphocytes can surround the basaloid nests.
- Tumor–stroma relationships contribute to recognizing BCC.



Retracted stroma creates clefts

Histologic interpretation

- In tissue sections, a clear space often separates tumor nests from adjacent stroma.
- This is a sectioning artifact rather than an anatomic cavity in vivo.
- Stromal retraction is diagnostically helpful but should be interpreted in context.



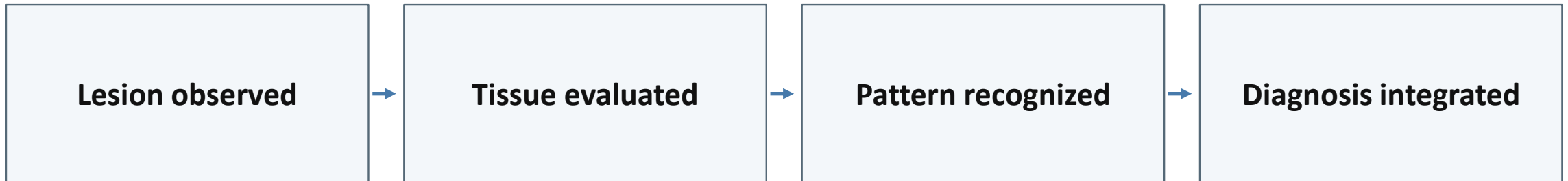
BCC versus trichoepithelioma

Question	BCC interpretation	Why comparison matters
Basaloid islands present?	Yes, commonly	Appendage tumors may also be basaloid
Tumor–stroma cleft?	Frequently conspicuous artifact	Helps favor BCC in the appropriate context
Can one feature decide?	No; integrate multiple features	Morphology requires contextual interpretation

BCC versus SCC: Morphology

Histologic feature	Basal cell carcinoma	Squamous cell carcinoma
Cell type	Relatively uniform basaloid cells	Atypical squamous cells
Architecture	Dermal nests or superficial multifocal growth	Infiltrating squamous tongues/lobules
Peripheral palisading	Characteristic pattern	Not a defining feature
Keratinization/intercellular bridges	Intercellular bridges not evident	Squamous differentiation may be evident

Clinical suspicion and tissue morphology



- The clinical lesion establishes the need to evaluate a cutaneous neoplasm.
- Tumor architecture, basaloid cytology and stromal interface support BCC classification.
- A pigmented or superficial appearance requires attention to relevant mimics.

Histology exercise: A clefted island

A skin section shows dermal nests of small basophilic cells, peripheral palisading, and separation from stroma. What is favored?

Teaching interpretation

- The combination strongly favors basal cell carcinoma.
- Palisading and retraction are complementary architectural clues.
- If the tumor is basaloid, relevant follicular appendage tumors remain considerations.

Clinical exercise: Pearly nasal nodule

A slowly enlarging, pearly sun-exposed facial nodule contains visible fine vessels. What is the leading diagnostic consideration?

Teaching interpretation

- Basal cell carcinoma is strongly suggested by the clinical morphology.
- The lesion still requires appropriate clinical-pathologic confirmation.
- Recognition while limited is important because most lesions are cured locally.

Clinical exercise: A pigmented plaque

A flat pigmented erythematous plaque is clinically suspicious for melanoma. Which BCC pattern can produce this presentation?

Teaching interpretation

- Superficial or pigmented BCC is within the differential.
- The clinical impression alone cannot distinguish epithelial from melanocytic tumors.
- Histology clarifies the lineage and tumor architecture.

Syndromic exercise: Multiple early BCCs

A young patient presents with multiple BCCs, jaw keratocysts and palmoplantar pits. Which genetic syndrome should be considered?

Teaching interpretation

- Nevroid basal cell carcinoma syndrome (Gorlin syndrome).
- Autosomal dominant PTCH-related predisposition explains the phenotype.
- A second acquired PTCH hit can drive the individual tumors.

Advanced case: Neglected facial tumor

A longstanding ulcerated facial lesion infiltrates adjacent deep structures. Why is the presentation dangerous even without distant metastasis?

Teaching interpretation

- Local destruction is the dominant hazard of most advanced BCC.
- The source documents possible invasion of facial sinuses or bone after prolonged neglect.
- Advanced disease warrants assessment beyond simple surface morphology.

Local treatment is usually curative

- The great majority of BCCs are identified early.
- Local excision cures most patients discussion.
- Treatment decisions depend on the extent and clinical context of the tumor.
- The source does not provide detailed surgical margin or risk-stratification rules.

When the disease is locally advanced

- A rare subset of BCC cannot be managed as a straightforward small cutaneous lesion.
- Hedgehog pathway inhibitors may be effective in advanced disease.
- Immune checkpoint inhibitors are another therapy.
- These statements describe treatment classes, not an up-to-date clinical sequencing guideline.

Connect mutation to therapy



- PTCH inactivation makes SMO–GLI signaling ligand independent.
- Therapeutic Hedgehog inhibition targets this pathway dependency.
- Mechanism-guided therapy illustrates how inherited cancer genetics can inform treatment.

Four linked dimensions of BCC

Dimension	Core teaching point
Risk	Sun exposure, pigmentation, age, immunity, DNA repair, inherited susceptibility
Driver	PTCH/SMO aberration produces GLI1-dependent Hedgehog signaling
Recognition	Pearly/telangiectatic, pigmented or superficial plaque presentations
Microscopy	Basaloid islands, peripheral palisading, stromal retraction
Clinical outcome	Usually cured locally; rarely deeply destructive or metastatic

Avoid four common interpretation errors

- Rare metastasis does not mean that BCC cannot invade or cause severe damage.
- A pigmented lesion is not necessarily melanocytic, and a superficial plaque need not be SCC.
- An inherited PTCH mutation establishes predisposition—not immediate malignant transformation.
- A histologic retraction cleft is a diagnostic artifact, not a true intratumoral lumen.

Core conclusions for pathology practice

- BCC is a locally invasive skin carcinoma commonly related to UV-associated damage.
- The dominant molecular lesion creates constitutive Hedgehog signaling through SMO and GLI1.
- Recognize the spectrum from classic pearly nodules to superficial and pigmented lesions.
- Histology integrates basaloid cell islands, peripheral palisading and stromal clefting.
- Early local treatment is typically successful; Advanced lesions can be profoundly destructive.

Primary reading and figure references

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- The Skin: basal cell carcinoma section.
- Conceptual reference: normal and oncogenic Hedgehog signaling.
- Morphologic reference: clinical and histologic basal cell carcinoma patterns.