

Merkel cell carcinoma

An aggressive cutaneous neuroendocrine carcinoma

- Core mechanisms: polyomavirus-associated oncogenesis and ultraviolet DNA injury.
- Clinical priority: recognize rapid growth, nodal risk, and the need for biopsy.

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Learning objectives

- Distinguish the virus-associated and UV-driven molecular pathways.
- Recognize the clinical and microscopic phenotype of MCC.
- Select and interpret a discriminating immunohistochemical panel.
- Relate primary tumor pathology to regional-node staging and reporting.
- Explain why immune therapy has transformed advanced disease management.

Definition and biological identity

A rare, high-grade neuroendocrine carcinoma arising in the skin

- Epithelial and neuroendocrine features coexist.
- Rapid growth and early regional spread distinguish it from many other cutaneous carcinomas.

Where MCC sits among cutaneous tumors

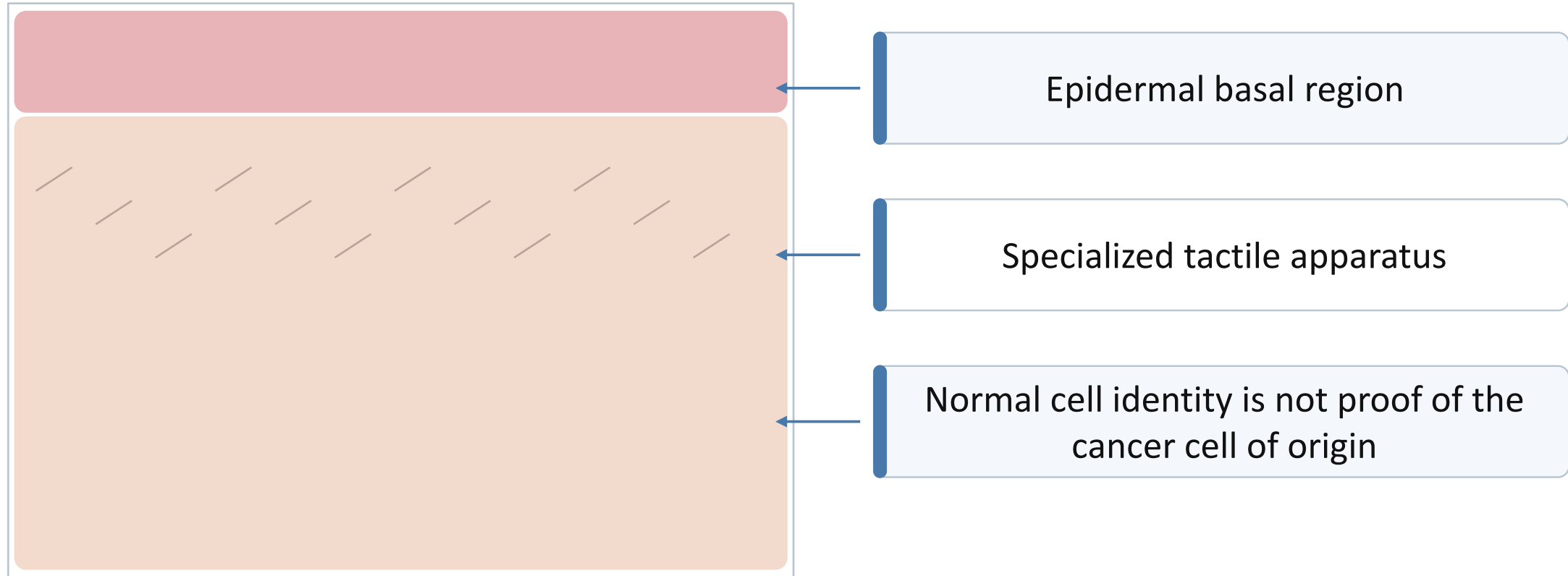
Keratinocyte carcinomas

- Basal cell carcinoma: Usually local invasion.
- Squamous cell carcinoma: Invasive squamous differentiation.
- UV exposure is an important shared context.

Merkel cell carcinoma

- Cutaneous neuroendocrine carcinoma.
- Morphology resembles a high-grade small-cell neoplasm.
- Early nodal dissemination is a major clinical concern.

Normal Merkel cells: Functional context

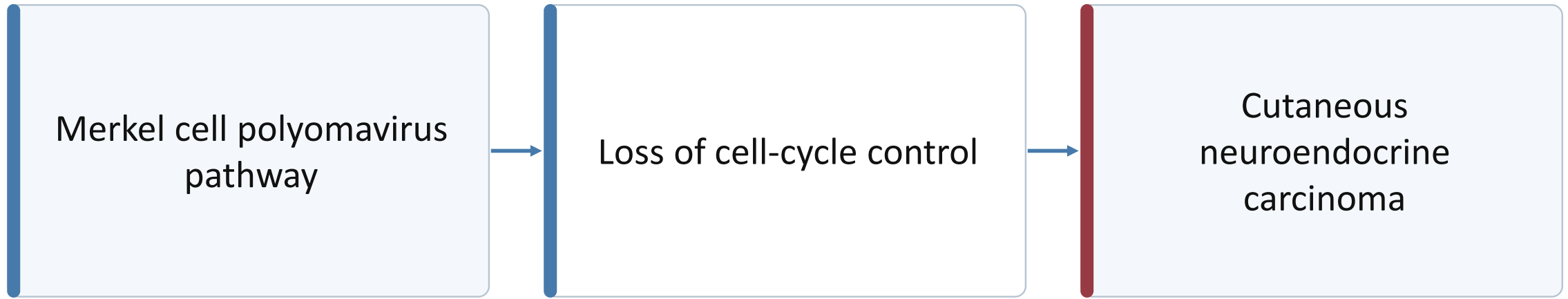


Schematic — not a histologic specimen

Cell of origin remains an active question

- Merkel cells are specialized epithelial cells involved in light-touch sensation.
- They also exhibit neuroendocrine characteristics.
- The tumor is conventionally named for its phenotypic resemblance.
- A definitive origin from mature Merkel cells is not established for every molecular subtype.

Two pathways converge on one tumor phenotype



An alternative UV-driven route creates many somatic DNA alterations rather than viral oncogene dependence.

Risk contexts are clinically distinct

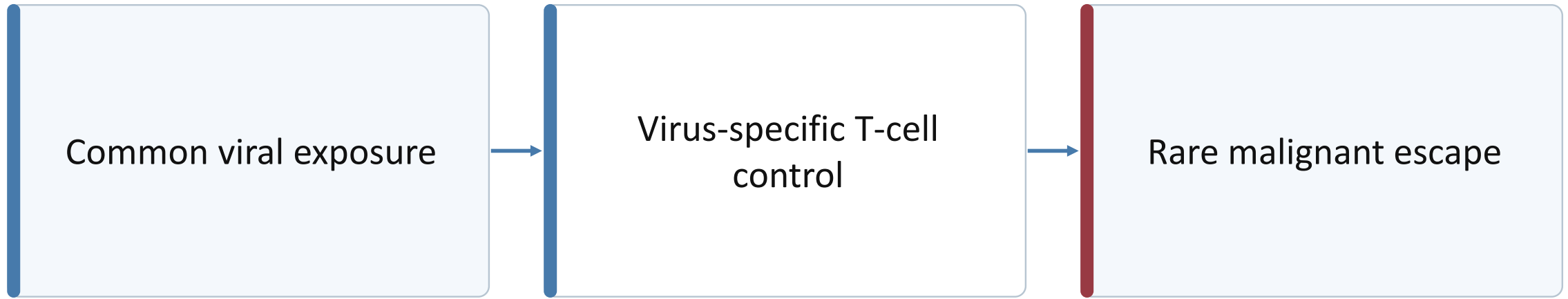
Chronic immunosuppression

- Solid-organ transplantation.
- HIV/AIDS and other impaired immune surveillance.
- Virus-associated pathogenesis is especially relevant.

Chronic UV-exposure phenotype

- Older patients.
- Lightly pigmented, photodamaged skin.
- Virus-negative tumors often carry a strong UV mutational signature.

Immune surveillance is central to MCC biology



Common infection does not imply that carcinoma is common; Host immune control is a key barrier.

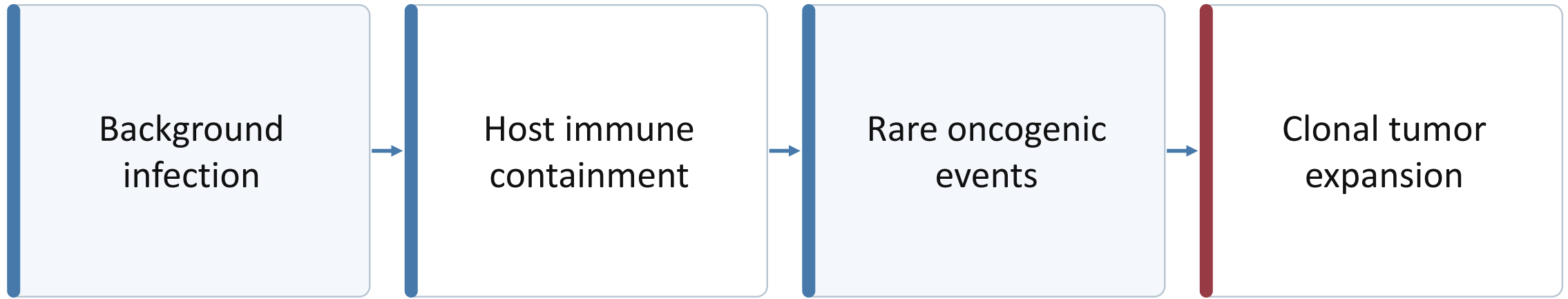
Why UV exposure matters

- Ultraviolet light produces a characteristic DNA damage pattern.
- Older, sun-exposed individuals form a major clinical risk group.
- Virus-negative tumors typically exhibit a high somatic mutation burden.
- UV exposure is a risk context—not a requirement for every patient.

Merkel cell polyomavirus (MCPyV)

- A member of the polyomavirus family.
- Frequently encountered infection; MCC develops in only a small minority of exposed people.
- Tumor-associated viral sequences may become integrated in the cancer genome.
- The virus-associated tumor is biologically distinct from UV-driven MCC.

Infection is not equivalent to transformation



The presence of virus in normal skin is not sufficient to diagnose Merkel cell carcinoma.

Clonal viral integration: The key observation

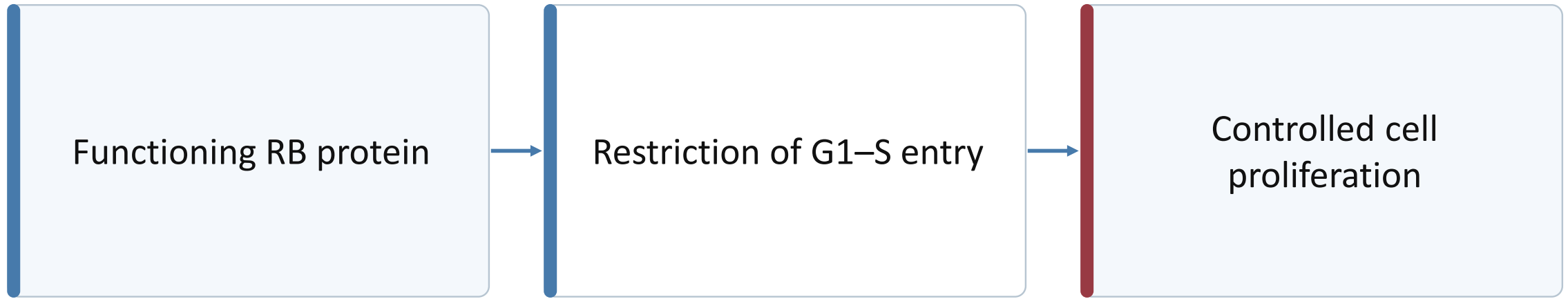


Integrated viral DNA within the cancer genome supports a causal role in virus-associated tumors.

Viral oncoproteins perturb host regulation

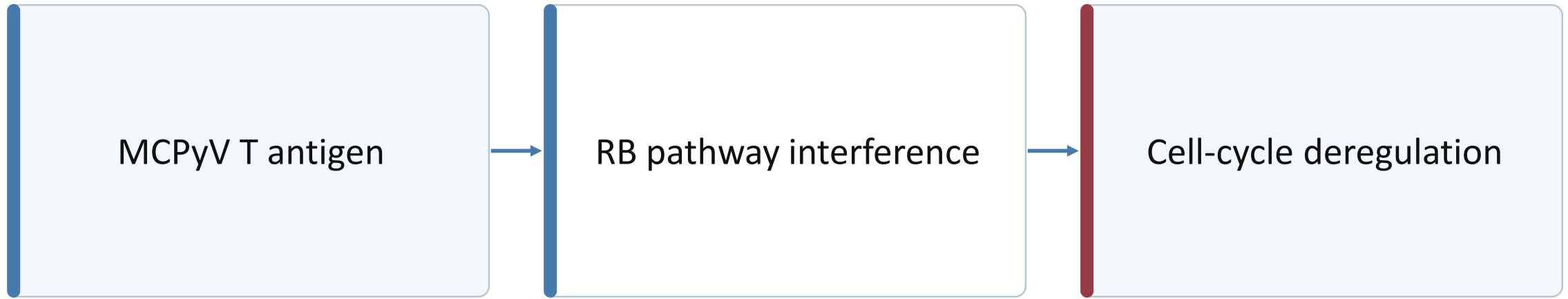
- Viral T-antigen programs interfere with cellular tumor-suppressive controls.
- Retinoblastoma pathway disruption is a central functional event.
- The textbook also discusses altered p53, PP2A, and MYC-related functions.
- These interactions are not identical to inactivating mutations in every named gene.

Retinoblastoma gate: Normal function



RB pathway dysfunction weakens normal control over cell-cycle progression.

Viral pathway: Functional RB suppression



This mechanism differs from genomic loss of RB1 in UV-driven tumors, even when the end effect overlaps.

Additional host signaling interactions

Host regulator	Teaching relevance
RB	Central G1–S restriction checkpoint affected by viral oncoproteins.
P53	Tumor-suppressive stress-response network discussed in viral transformation.
PP2A	Phosphatase with tumor-suppressive activity; A reported interaction target.
MYC	Growth-related oncoprotein network discussed in the Robbins passage.

Why widespread MCPyV is not widespread MCC

- Exposure is common by adulthood account.
- MCC requires additional tumor-promoting events and a permissive host setting.
- MCPyV-specific T cells plausibly suppress virus-driven tumor emergence.
- Immunosuppression can compromise this protective layer.

The typical virus-positive genome

Integrated viral DNA with comparatively few acquired somatic mutations

- Often near-diploid' description.
- Low mutation burden does not imply biologic indolence or absent metastatic risk.

Virus-associated tumor as a dependency model



Conceptual model; Exact protein dependencies vary with experimental system and tumor biology.

Virus-negative MCC: A separate oncogenic route

Ultraviolet mutagenesis can drive MCC without integrated oncogenic MCPyV

- A high mutational burden and UV signature characterize this subtype.
- Neuroendocrine appearance alone does not establish viral status.

UV DNA injury accumulates with time

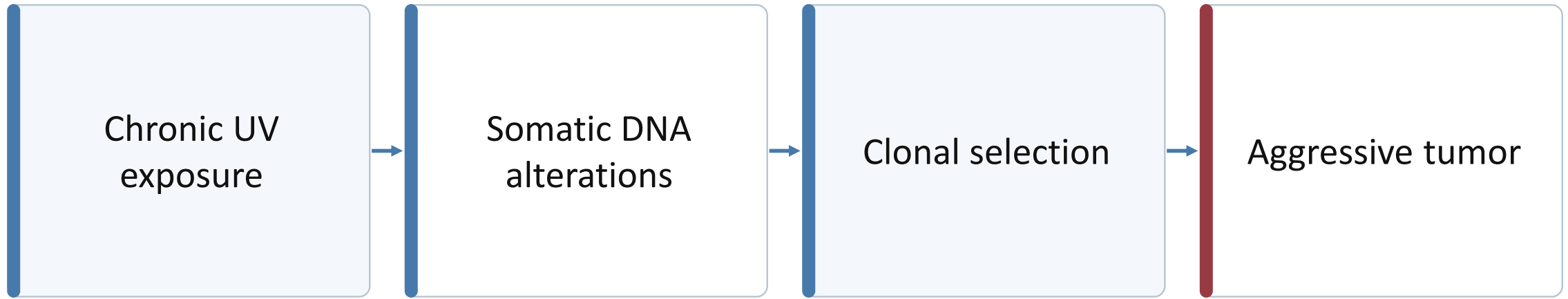


Diagram illustrates an etiologic sequence, not a claim that every UV-damaged keratinocyte becomes MCC.

RB1 and TP53 abnormalities in UV-driven MCC

- RB1 loss of function is commonly acquired in virus-negative tumors.
- TP53 loss of function is also frequent.
- These are tumor-cell genetic lesions, unlike functional suppression by virus-encoded proteins.
- The two processes converge on weakened proliferation and stress-response control.

Copy-number complexity distinguishes the UV route

Virus-associated MCC

- Generally low somatic mutational load.
- Often relatively stable or diploid genome.
- Integrated viral DNA and viral antigens.

UV-driven MCC

- Abundant UV-signature substitutions.
- Numerous copy-number gains and losses.
- Common RB1 and TP53 inactivation.

The pathways can converge morphologically

A shared high-grade neuroendocrine phenotype can arise from different molecular causes

- Routine H&E alone does not reliably assign etiologic subtype.
- Use clinical setting and validated ancillary assays; Do not infer viral status from morphology alone.

Comparison: Molecular and clinical context

Feature	MCPyV-associated	UV-driven
Typical host context	Impaired immunity common	Older, sun-damaged skin
Driver	Viral oncogene program	Somatic UV mutagenesis
Mutation burden	Relatively low	Relatively high
RB pathway	Functional interference	Frequent RB1 alteration
TP53	Usually not heavily mutated	Frequently mutated
Genomic copy changes	Often fewer	Often numerous

Interpret molecular subtype without overclaiming

- Viral detection is helpful but technical methods and sensitivity differ.
- Subtypes cannot be reliably assigned using patient age or location alone.
- Mutation burden is not a direct substitute for a complete diagnostic work-up.
- Molecular differences inform biology; Treatment choices require clinical staging and guidelines.

The classic clinical presentation

A rapidly enlarging, usually painless cutaneous nodule

- Erythematous to violaceous coloration may occur.
- Clinical appearance is nonspecific; Tissue diagnosis is decisive.

AEIOU: A clinical recognition aid

Letter	Clinical association
A	Asymptomatic lesion
E	Expanding rapidly
I	Immunosuppression
O	Older age
U	UV-exposed skin site

Mnemonic aids suspicion but is neither a diagnostic rule nor a substitute for biopsy.

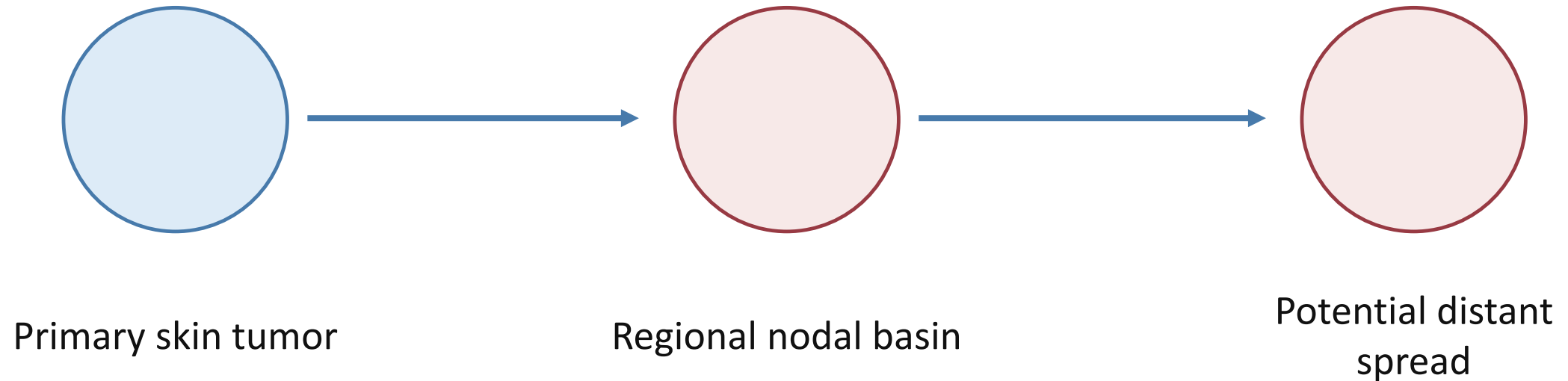
Distribution and examination

- Often affects sun-exposed skin: Head and neck and extremities.
- Examine the complete skin surface for a potential primary.
- Inspect for local satellites or in-transit disease.
- Palpate the draining nodal basin; Nodes may be occult.

Why small appearance does not imply low risk

- MCC can disseminate through regional lymphatics early.
- The risk of microscopic nodal involvement is clinically relevant even without palpable nodes.
- Size is informative for stage and risk but does not replace nodal assessment.

From skin primary to regional disease

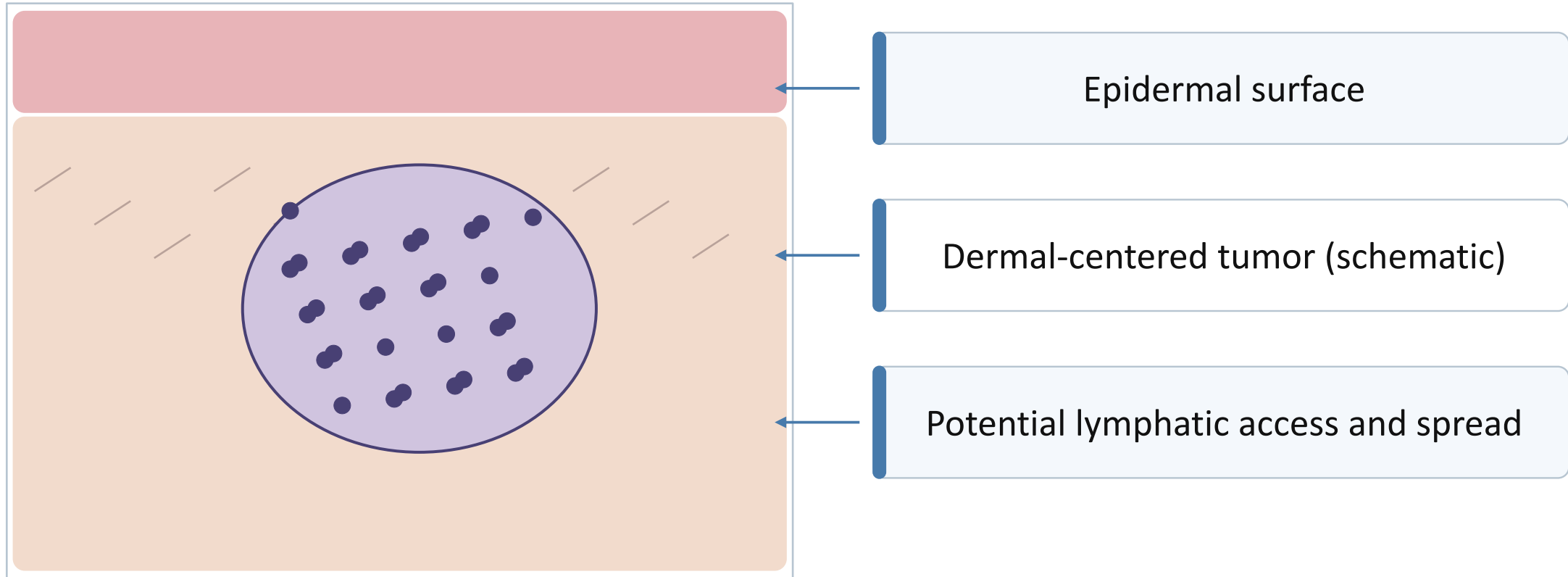


Lymphatic metastasis is a major practical consequence of aggressive MCC biology.

What the clinician must communicate to pathology

- Site, duration, recent growth rate, and lesion size.
- Prior skin cancer or possible extracutaneous neuroendocrine malignancy.
- History of transplantation, HIV, or other immune compromise.
- Whether sampled tissue is the primary skin lesion or a regional node.

MCC arises within the cutaneous compartment



Schematic — not a histologic specimen

High-grade neuroendocrine morphology

- Microscopically resembles an aggressive neuroendocrine carcinoma.
- Typical appearance is a dermal “small round blue cell” tumor.
- Crowded cells, little cytoplasm, and brisk proliferation raise suspicion.
- A tissue section and IHC are essential for lineage assignment.

Nuclear features: What to look for

- High nuclear-to-cytoplasmic ratio.
- Round to oval nuclei with fine neuroendocrine-type chromatin.
- Nuclear molding and numerous mitoses may be seen.
- Necrosis and apoptosis underscore high-grade behavior.

Histologic architecture is not pathognomonic

- Diffuse sheets, nests, and trabecular arrangements are described.
- An overlying epidermis may be relatively uninvolved.
- Architecture overlaps other cutaneous or metastatic small-cell neoplasms.
- Interpret the growth pattern together with immunophenotype.

Proliferation and cell death: Aggressive phenotype

Histologic observations

- Frequent mitotic figures.
- Apoptotic fragments and necrosis.
- Potential lymphovascular invasion.

Clinicopathologic implication

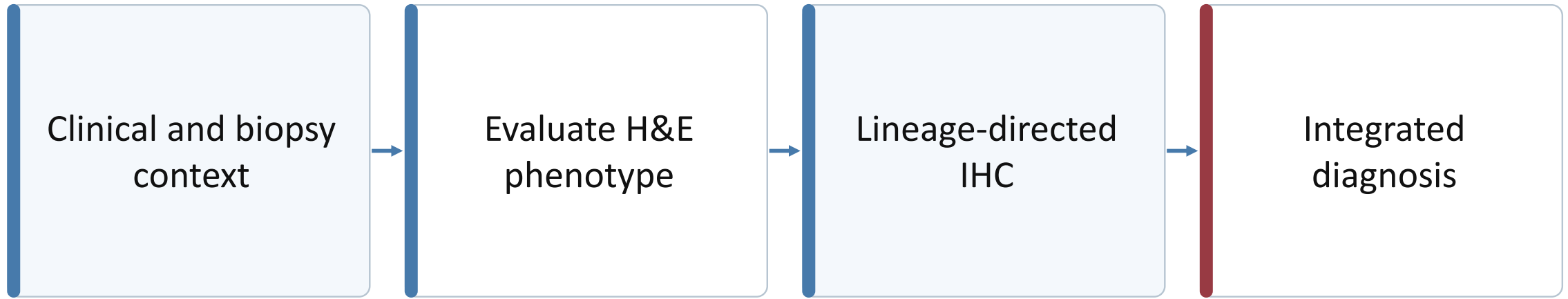
- Rapidly enlarging lesion.
- Propensity for early regional spread.
- Risk stratification requires stage and other features.

Small blue cell appearance is a starting point

**A “small blue cell tumor” is a morphologic category—
not a final diagnosis**

- Neuroendocrine carcinoma, lymphoma, melanoma and other entities may overlap.
- Lineage-defining IHC resolves most common differentials.

Diagnostic workflow: Morphology to classification

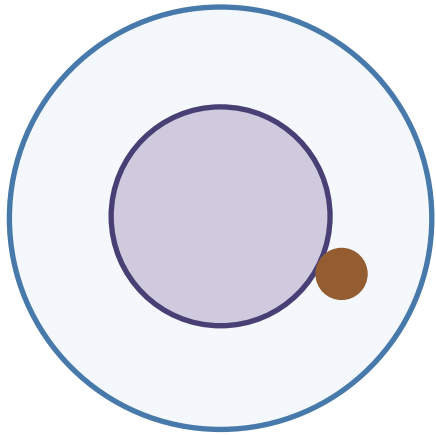


No single immunostain should be interpreted in isolation.

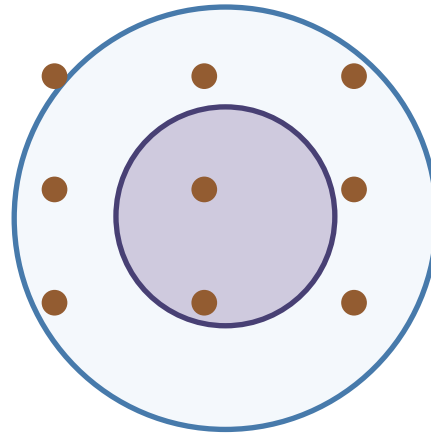
Why cytokeratins matter

- Cytokeratin expression establishes epithelial differentiation.
- CK20 is a particularly useful MCC-associated marker.
- A classic perinuclear dot-like pattern is a key diagnostic clue.
- A negative CK20 result does not exclude all MCC cases.

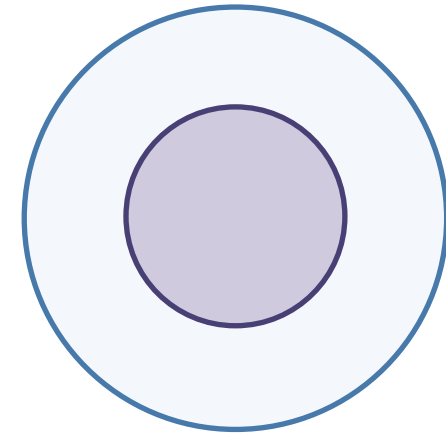
CK20: Interpret the localization pattern



**CK20 perinuclear
dot**



**Neuroendocrine
marker**



TTF-1 usually absent

Schematic marker localization only — not a patient IHC image.

Neuroendocrine markers support the phenotype

- Synaptophysin and chromogranin support neuroendocrine differentiation.
- CD56 and INSM1 may provide further supporting evidence.
- The marker combination matters more than a single positive stain.
- Other neuroendocrine carcinomas may share this expression profile.

MCC versus metastatic pulmonary small-cell carcinoma

Favor cutaneous MCC

- Characteristic CK20 dot positivity.
- TTF-1 usually negative.
- Compatible skin-centered clinical presentation.

Favor pulmonary origin

- TTF-1 often positive.
- CK20 usually negative.
- Correlate with imaging and clinical history.

Exceptions exist: A full panel and clinical evaluation remain mandatory.

Exclude melanoma and lymphoid malignancy

Melanoma lineage

- SOX10 and other melanocytic markers support melanoma.
- Usually lacks epithelial cytokeratin profile of MCC.
- Can be amelanotic and mimic MCC.

Lymphoid lineage

- CD45 and subtype markers support hematolymphoid origin.
- Diffuse blue-cell infiltrates can be deceptive.
- An epithelial/neuroendocrine signature redirects toward MCC.

Practical immunohistochemistry comparison

Marker	MCC typical	Small-cell lung CA	Melanoma	Lymphoma
CK20	+; Dot-like	Usually –	–	–
TTF-1	Usually –	Often +	–	–
Synaptophysin	Often +	Often +	Usually –	Usually –
SOX10	Usually –	Usually –	Often +	Usually –
CD45	–	–	–	Often +

“Typical” patterns have exceptions; Use the clinical context and a panel, not an isolated stain.

Interpreting CK20-negative suspected MCC

- CK20 negativity is not sufficient to rule out MCC.
- Revisit H&E and add broad cytokeratin and neuroendocrine markers.
- Neurofilament and other supportive markers may be informative.
- Exclude cutaneous metastasis of a visceral small-cell carcinoma.

Viral large-T antigen testing

- Large-T antigen IHC can provide evidence of MCPyV-associated tumor biology.
- It is not a universal positive marker across all MCCs.
- Virus-negative MCC retains the diagnosis when morphology and phenotype support it.
- A molecular classification assay does not replace an adequate differential panel.

MCC and basal cell carcinoma may overlap

Basal cell carcinoma

- Basaloid nests, peripheral palisading.
- Stromal clefting often present.
- Characteristic Hedgehog pathway context.

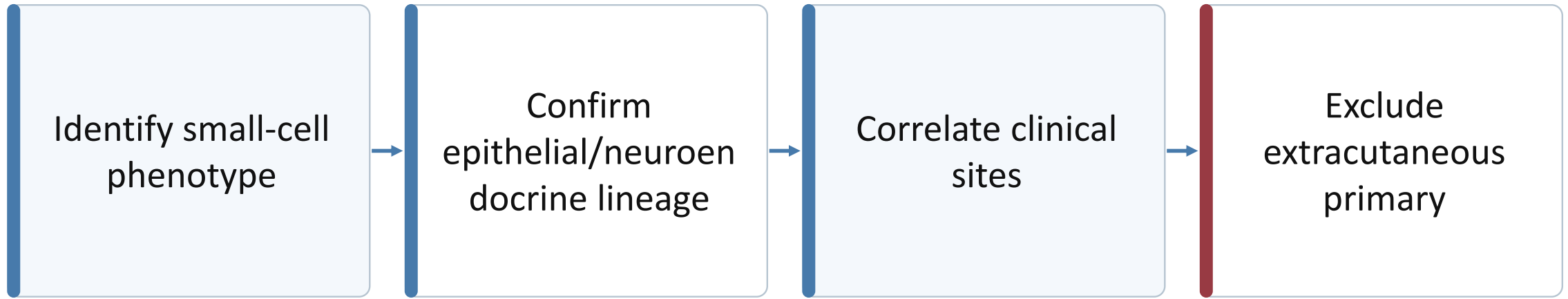
Merkel cell carcinoma

- High-grade neuroendocrine cytology.
- CK20 dot and neuroendocrine IHC support diagnosis.
- Aggressive lymph-node metastatic potential.

Small biopsy pitfalls

- Limited superficial samples may underrepresent tumor architecture.
- Crush artifact can compromise nuclear evaluation.
- Metastatic small-cell carcinoma may resemble a primary MCC.
- A targeted but sufficiently broad IHC panel prevents premature closure.

Primary MCC or metastasis to skin?

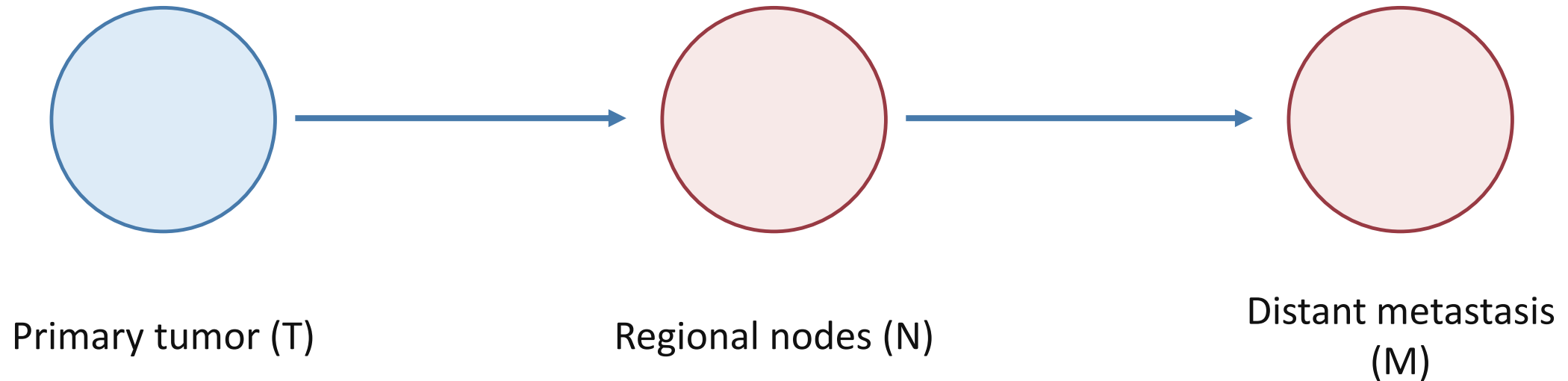


TTF-1 and CK20 help orient the investigation but are not absolute site-of-origin tests.

Why regional nodal staging changes interpretation

- Occult lymph-node metastasis may be present despite clinically negative nodes.
- Sentinel lymph node biopsy provides pathologic staging information.
- Micrometastases may require keratin immunohistochemistry to identify.
- Staging must combine primary-tumor, nodal, and distant-disease evidence.

Staging assessment: The basic compartments



Use the institutionally applicable current TNM system; Do not mix AJCC8 with UICC TNM9.

Current staging references require edition control

- ICCR's January 2026 second-edition dataset incorporates UICC TNM9.
- ESMO–EURACAN 2024 uses the eighth-edition UICC framework.
- Stage boundaries and terminology should always be tied to the specific edition.
- This lecture emphasizes T/N/M concepts rather than transplanting older tables into a newer framework.

Imaging complements pathology

- Assess the draining nodal basin and potential distant spread.
- Guideline-directed CT or FDG-PET/CT may be indicated at initial staging.
- Imaging does not replace histologic nodal staging when this is clinically appropriate.
- A multidisciplinary pathway integrates examination, pathology, and imaging.

MCC resection report: Essential questions

Reporting domain	Question to answer
Tumor identity	Is the sampled lesion primary cutaneous MCC?
Location and extent	Where is the tumor, and how far does it extend?
Size and dimensions	What are the measured tumor dimensions?
Margins	Is invasive tumor present at a resection margin?
Lymphovascular invasion	Is involvement observed?
Associated findings	Is there relevant morphologic diversity or other pathology?
Regional nodes	Are nodes submitted and what is their involvement?

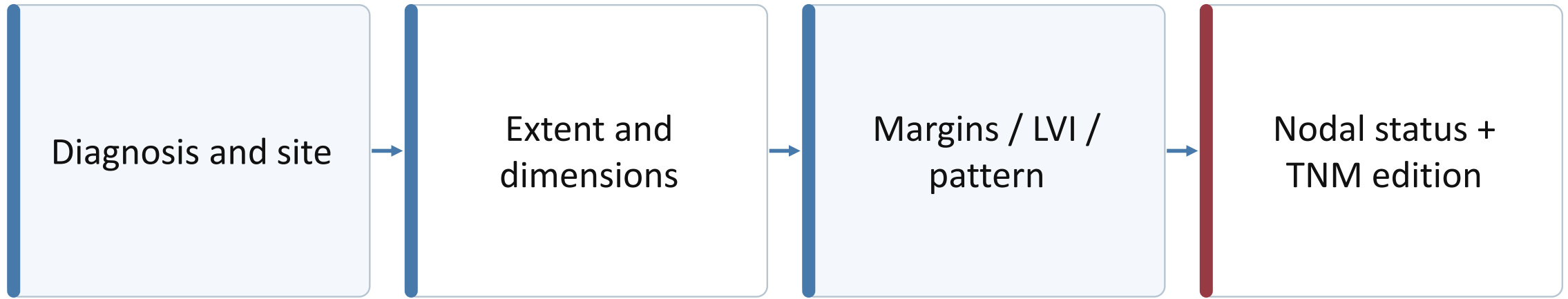
ICCR reporting has a defined specimen scope

- The 2026 ICCR dataset is designed for primary cutaneous MCC excision specimens with tumor.
- Partial superficial biopsies and cytology do not require the same complete synoptic elements.
- A re-excision with no residual carcinoma should say so.
- Prior diagnostic material may contribute when the final excision contains only part of the lesion.

Pathologic risk assessment: What adds value

- Extent of primary disease and nodal status dominate staging.
- Tumor dimensions and invasion beyond the dermis can matter clinically.
- Lymphovascular invasion and infiltrative pattern have been associated with outcomes in studies.
- Do not convert retrospective prognostic associations into deterministic predictions.

A structured sign-out logic



Example of report organization, not a fabricated patient report.

Radiosensitivity does not guarantee cure

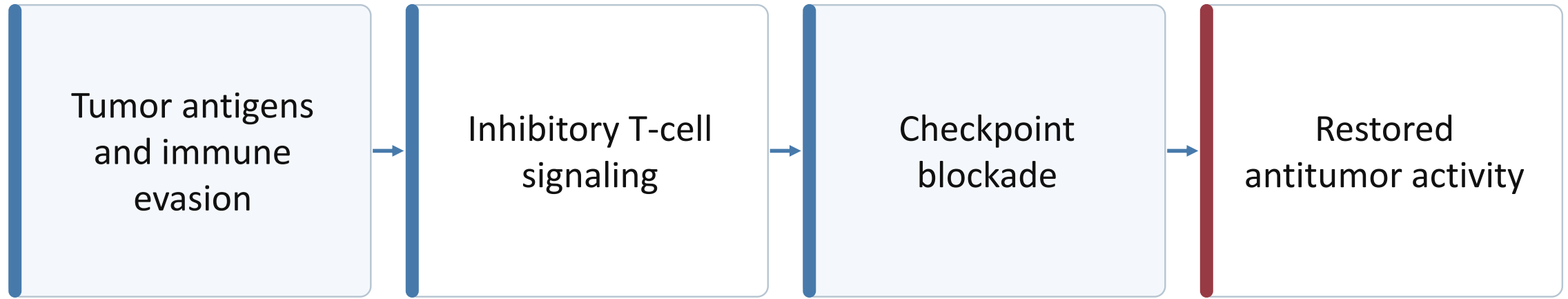
Tumor response

- MCC is highly responsive to radiotherapy.
- Chemotherapy can produce tumor regression.
- Local control remains clinically important.

Why relapse occurs

- Regional and distant spread may be present.
- Systemic relapse can occur despite response.
- Durability differs across treatment modalities.

Immune checkpoint therapy: Biological rationale



The clinical response is variable; Blockade does not ensure immune eradication in every patient.

Checkpoint inhibition changed advanced MCC care

- Some patients with unresectable or metastatic disease achieve durable responses.
- The clinical benefit can extend beyond conventional chemotherapy durability.
- The textbook specifically highlights responses in UV-driven, mutation-rich disease.
- Therapeutic sensitivity is not restricted to one molecular subtype.

What PD-L1 does—and does not—tell us

- PD-L1 expression reflects aspects of tumor–immune interaction.
- It should not be treated as a universal binary gatekeeper for immune therapy.
- Prognostic and predictive performance of candidate biomarkers remains imperfect.
- Treatment decisions depend on disease stage and contemporary clinical guidance.

Immunosuppression affects both risk and management

- Impaired host immunity is a major susceptibility context.
- Immune function also modulates antitumor responses.
- Transplant and other immunosuppressed patients require individualized multidisciplinary decisions.
- Oncologic benefit must be weighed against immune-mediated complications.

Follow-up aims to detect early recurrence

- Skin and regional nodal examination are central to surveillance.
- Evaluate new rapidly growing lesions or nodal abnormalities promptly.
- The schedule and imaging strategy should follow current risk-adapted clinical guidance.
- A negative prior examination does not exclude subsequent dissemination.

Case exercise: Immunosuppressed patient

A transplant recipient develops a quickly enlarging, painless dermal nodule. Biopsy shows a high-grade small-cell neuroendocrine carcinoma; MCPyV large-T antigen is detected.

Which oncogenic pathway is most directly supported?

Case interpretation: Viral oncogenesis

- Virus-associated MCC is strongly supported by viral large-T antigen detection.
- Immune suppression is a relevant host context.
- Expected biology includes viral oncogene activity and relatively low mutation burden.
- Regional nodal assessment remains necessary regardless of viral status.

Case exercise: An older sun-exposed patient

An older patient presents with a rapidly expanding forearm nodule. Histology shows cutaneous neuroendocrine carcinoma. Sequencing reveals a prominent UV mutational signature with RB1 and TP53 alterations.

Which pathogenetic route is favored, and why?

Case interpretation: UV-driven oncogenesis

- The UV signature and RB1/TP53 alterations favor virus-negative MCC.
- The clinical context supports but does not independently prove the route.
- Aggressive histology can overlap with virus-positive disease.
- Immunophenotypic work-up and nodal staging remain essential.

Case exercise: Small-cell carcinoma in a node

A regional lymph node contains small-cell carcinoma. CK20 has a dot-like pattern; Synaptophysin is positive, TTF-1 is negative, and no skin primary is immediately evident.

What is the most important next diagnostic interpretation?

Case interpretation: A possible occult primary

- The immunophenotype supports MCC in the appropriate setting.
- Examine the entire skin and investigate alternative primary sites.
- MCC may present with involved nodes and an occult or regressed skin primary.
- Document the evidence and uncertainty; Do not invent a primary site.

Synthesis: What determines diagnosis and risk?

Question	Evidence used
What tumor is present?	H&E morphology + epithelial/neuroendocrine IHC.
Is it primary cutaneous?	Skin examination, distribution and alternate-site assessment.
What pathway drove it?	Viral assay or validated molecular findings.
How far has it spread?	Primary features, nodal sampling and imaging.
How should it be reported?	Current ICCR dataset with specified TNM edition.
What informs treatment?	Stage, host immunity and multidisciplinary guidance.

Final principles

- MCC is uncommon but clinically aggressive: A rapidly growing nodule warrants biopsy.
- Virus-associated and UV-driven routes converge on neuroendocrine carcinoma.
- CK20 dot-like staining is a useful clue; Exceptions demand a panel.
- Regional nodal disease drives much of clinical staging and risk assessment.
- Pathology, current staging terminology, and systemic therapy decisions must remain integrated.

Selected references

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