

Mucoepidermoid Carcinoma

Salivary gland pathology · morphology, molecular basis and clinical behavior

A carcinoma with mucous, intermediate and epidermoid differentiation

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Learning objectives

- Recognize the three characteristic epithelial populations and their growth patterns.
- Interpret the CRTC1::MAML2 alteration without overstating its significance.
- Relate morphology and histologic grade to local behavior and prognosis.
- Apply a practical differential diagnosis and reporting framework.

Defining the entity

Primary malignant epithelial neoplasm of a salivary gland

- Combines mucous, intermediate and epidermoid (squamoid) cells.
- Architecture ranges from cystic structures to cords and solid sheets.
- Biologic behavior is heterogeneous: Low-grade and high-grade tumors differ substantially.

Place among salivary gland tumors

Benign lesions

Pleomorphic adenoma and Warthin tumor are important benign reference entities.

Mucoepidermoid carcinoma

Most common primary malignant salivary-gland neoplasm.

Other carcinomas

Adenoid cystic and acinic cell carcinoma provide useful morphologic contrasts.

A salivary gland mass cannot be classified from location alone.

How common is mucoepidermoid carcinoma?

Among all salivary gland tumors

~15%

The proportion cited; Denominator is benign plus malignant tumors.

Among primary malignancies

Most common

The ranking refers to primary malignant salivary-gland tumors.

Anatomic distribution

Parotid gland

60–70%

Most MECs develop in the parotid gland.

Other glands

A substantial contribution to salivary tumors elsewhere, particularly minor salivary glands.

“Most tumors arise in the parotid” ≠ “most parotid tumors are MEC.”

Minor salivary glands are clinically important

- MEC contributes a large fraction of the neoplasms arising outside the parotid.
- A minor-gland site does not exclude a salivary primary.
- Accurate site assignment matters when interpreting resection boundaries and local extension.

Why the name is informative

Muco-

Mucous cells with intracellular and/or luminal mucin.

-epidermoid

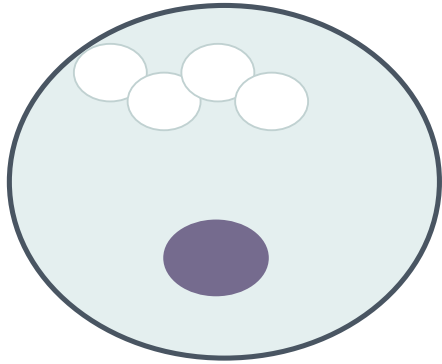
Squamoid epithelial differentiation within the same neoplasm.

Intermediate

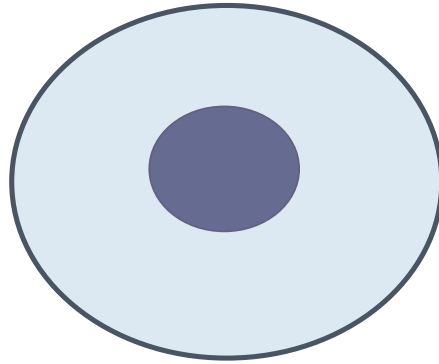
A third, often less distinctive population bridges the recognized appearances.

Cellular heterogeneity is an identification clue, not a grade by itself.

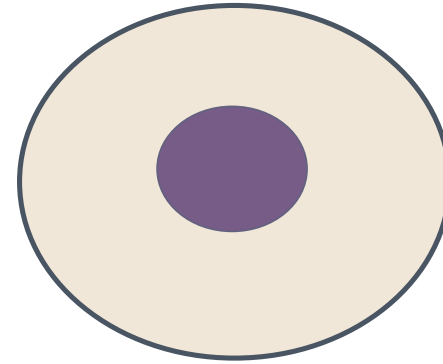
Three epithelial populations



Mucous



Intermediate



Epidermoid / squamoid

Schematic cell forms — concept illustration; Not a photomicrograph.

How the cells contribute to architecture

Mucous cells

Contribute mucin to intracellular vacuoles and lumina



Intermediate cells

Contribute to compact epithelial nests



Epidermoid cells

Produce squamoid areas within mixed structures

Interpret cell type together with architectural pattern and invasion.

A tumor with several growth patterns

Cords

Elongated or branching strands of tumor cells.

Sheets

Broad, densely cellular expanses of tumor.

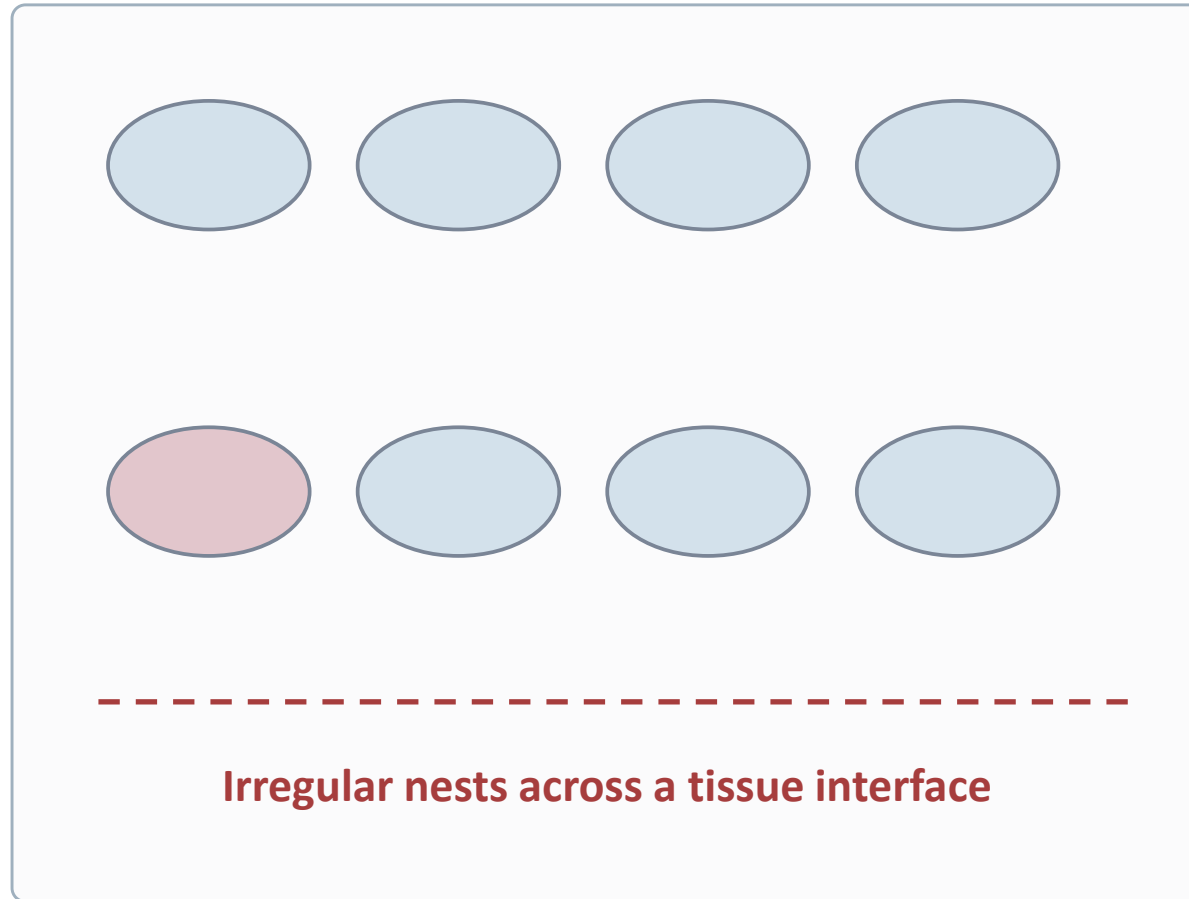
Cystic structures

Luminal spaces may contain mucin and vary in size.

Gross dimensions and appearance

- Reported lesions can reach approximately 8 cm in diameter.
- Typical cut surface: Pale gray-white tissue.
- Small mucin-containing cysts may punctuate the solid component.

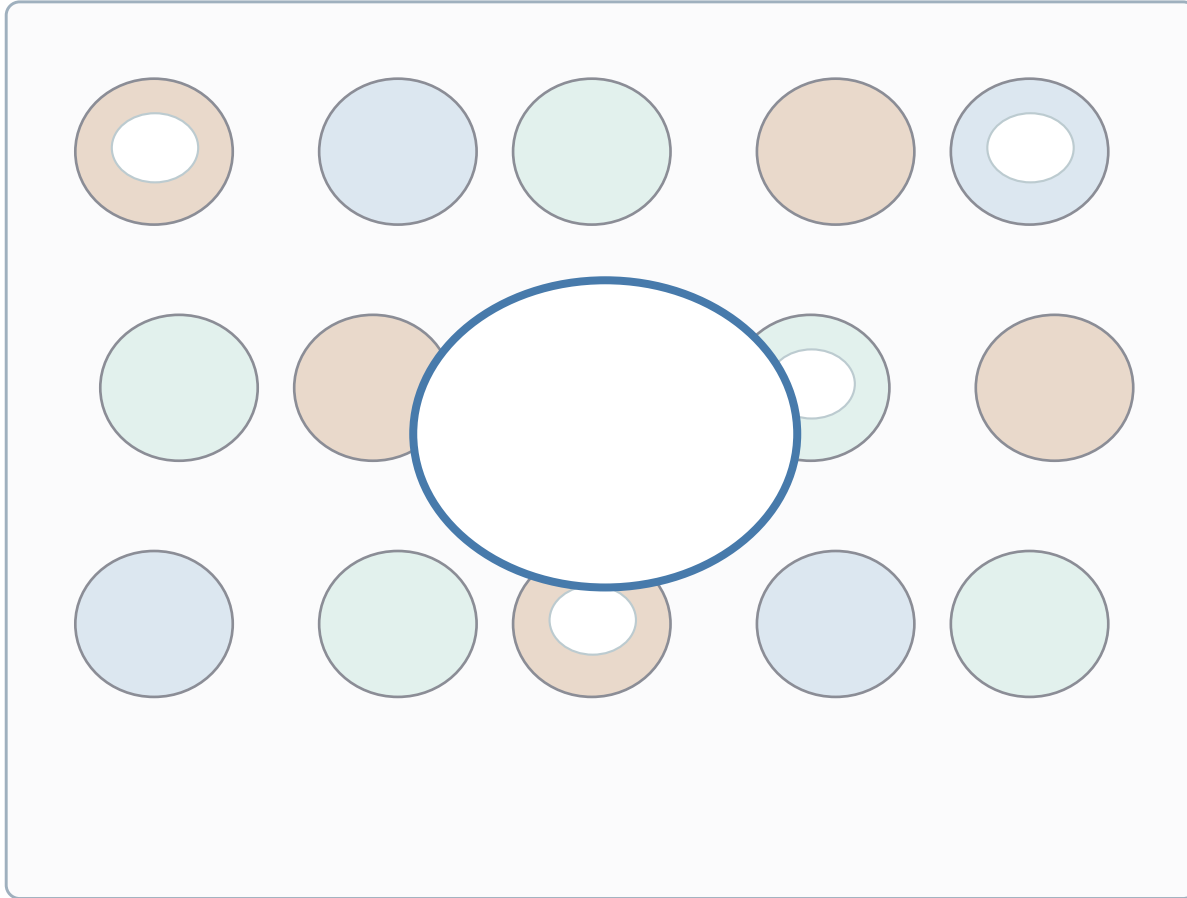
Apparent circumscription can be deceptive



Macroscopic impression

- The lesion may look demarcated.
- A well-defined true capsule is absent.
- Growth may extend into nearby tissue.

What a mucin-filled cyst means

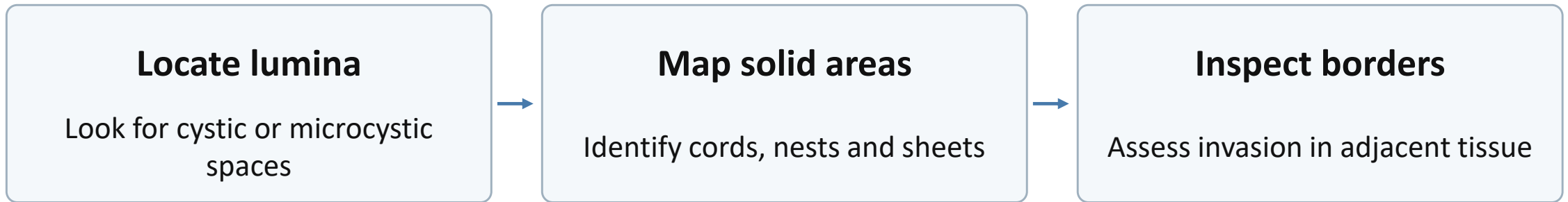


Pathologic connection

- Cystic spaces are a recognized growth configuration.
- Mucin may collect within small lumina.
- Cysts do not imply a benign lesion.

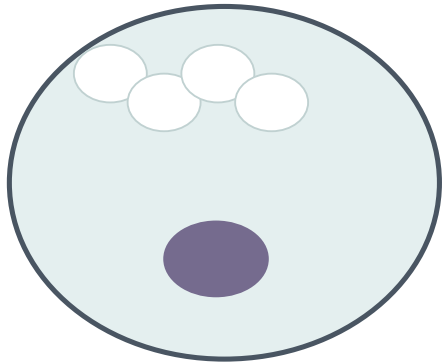
Low-power histology: Diagnostic search pattern

Scan architecture before committing to cytologic interpretation.

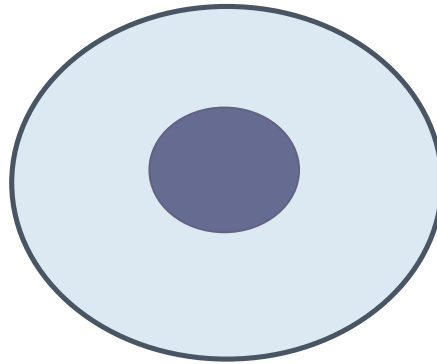


Schematic teaching workflow derived morphology; Not a formal diagnostic algorithm.

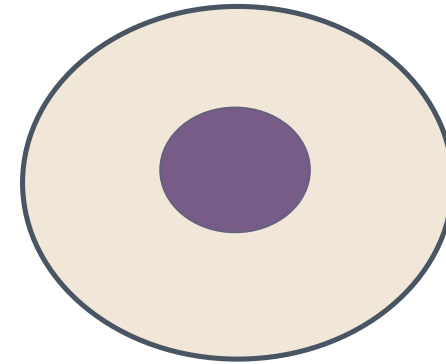
High-power histology: Three-cell survey



Mucous



Intermediate



Epidermoid / squamoid

Survey at least several representative areas; One dominant cell population may obscure the others.

Schematic cell forms — concept illustration; Not a photomicrograph.

Mucous differentiation

- Mucous cells produce the component that gives the tumor its “muco-” designation.
- Intracellular mucin and mucin-bearing lumina may be easier to appreciate than rare isolated mucous cells.
- Mucin positivity supports differentiation; It is not a standalone diagnosis of MEC.

Intermediate-cell differentiation

- Intermediate cells constitute one of the three morphologic populations.
- They can dominate compact portions of the tumor and make the lesion appear monotonous.
- Search for associated mucous and epidermoid differentiation before classifying a predominantly intermediate-cell tumor.

Epidermoid or squamoid differentiation

- Squamoid areas contribute a second identifiable epithelial phenotype.
- The coexistence of mucous and intermediate cells is more informative than squamoid morphology alone.
- A predominantly solid, squamoid carcinoma invites careful differential diagnosis.

Mucin stains: Complementary evidence

H&E

Shows cystic architecture and mucinous cell vacuoles, when sufficiently evident.

Histochemical mucin stain

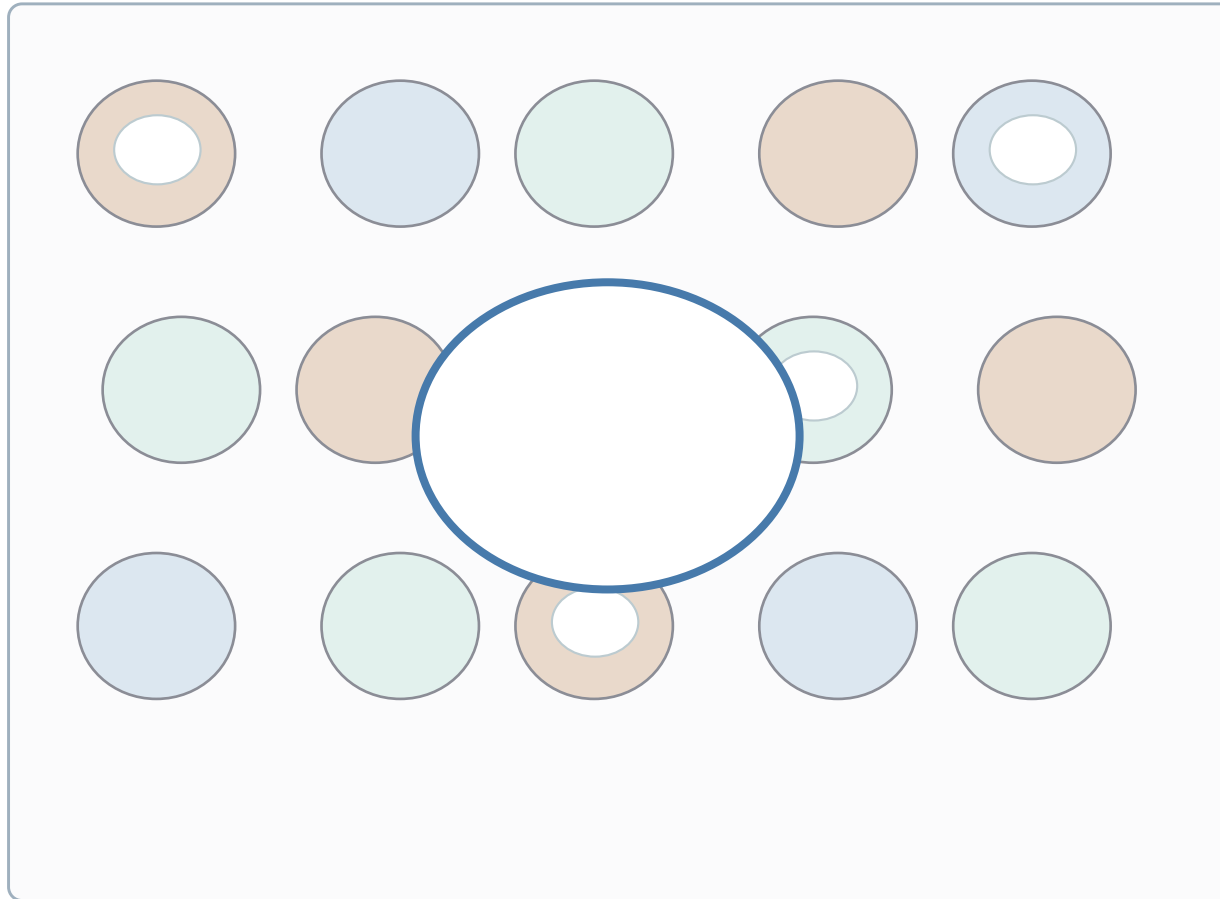
Can highlight intracellular or luminal mucin in equivocal areas.

Interpretation

A supportive phenotypic finding; Retain architectural and cytologic context.

The uploaded chapter provides no image file or mucin-staining protocol; This is ancillary diagnostic context.

Mucin accumulation: A schematic model



Three linked observations

- Mucous epithelial differentiation
- ↓
- Mucin within luminal structures
- ↓
- Grossly appreciable small cysts

Compare three growth configurations

Cords

Linear, branched epithelial groupings; Examine relationships with stroma.

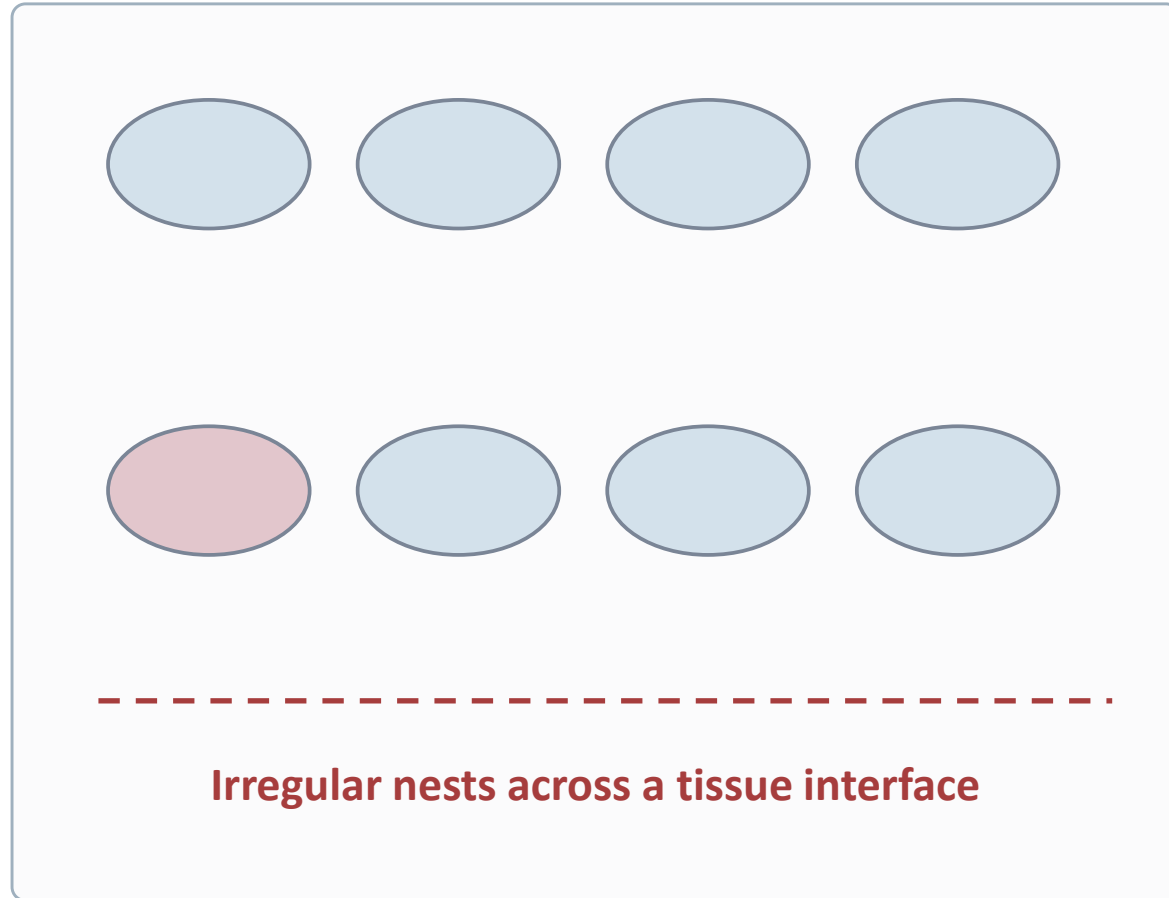
Sheets

Confluent tumor cells with reduced luminal emphasis.

Cysts

Spaces containing mucin and/or lined by mixed tumor cells.

Cords require interface assessment



Read the edge of the lesion

- Cords may approach or infiltrate the surrounding salivary tissue.
- Overall demarcation does not prove encapsulation.
- The interface is critical when evaluating malignant growth.

Sheets alter the visual impression

- Broad sheets can make some MECs appear largely solid.
- At high magnification, cytologic blandness or striking anaplasia may be seen depending on grade.
- Sample cystic and solid regions to avoid interpreting one area as the entire tumor.

Cystic architecture can be prominent

- MEC frequently includes small cystic and microcystic configurations.
- A cyst-rich appearance should prompt a search for the defining cellular mixture.
- A seemingly circumscribed cystic lesion still requires evaluation for infiltrative foci.

Cytologic variability is unusually broad

Relatively bland

Uniform nuclei and limited atypia
may predominate



Intermediate appearance

Cytologic findings vary with tumor
region



Highly anaplastic

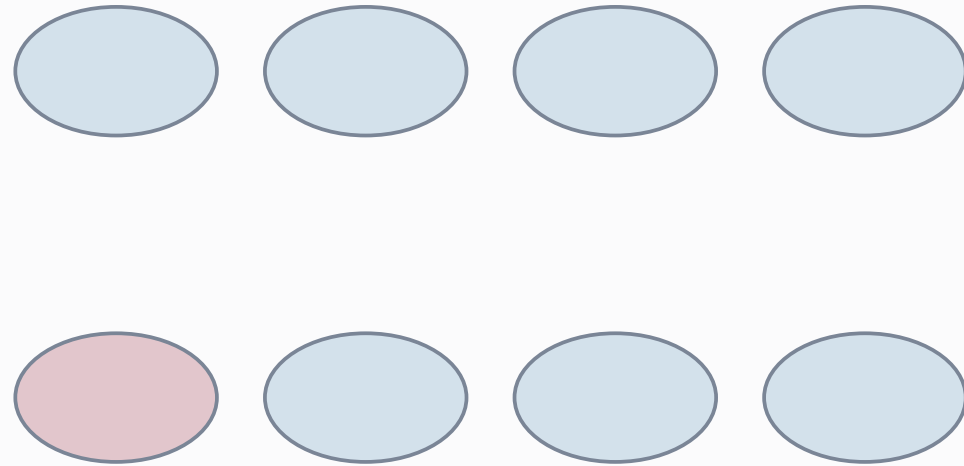
Conspicuously malignant cells may
predominate

Morphologic grade provides the link between appearance and expected behavior.

Bland cells do not establish benignity

- Robbins explicitly describes cytologically bland MECs.
- A malignant neoplasm may be infiltrative despite deceptively mild nuclear atypia.
- Architecture, tumor borders and the recognized cell mixture must be read together.

Infiltration is a decisive morphologic issue



Irregular nests across a tissue interface

Interpret the interface

- No continuous, well-defined capsule.
- Tumor may invade neighboring structures.
- Invasion helps explain the potential for local recurrence.

The molecular hallmark

Recurrent translocation

T(11;19)

Balanced rearrangement involving 11q21 and 19p13.

Resulting fusion

CRTC1::MAML2

A chimeric transcription-related protein identified in more than half of Robbins cases.

Reading the chromosome notation

T(11;19)

A translocation between
chromosomes 11 and 19.

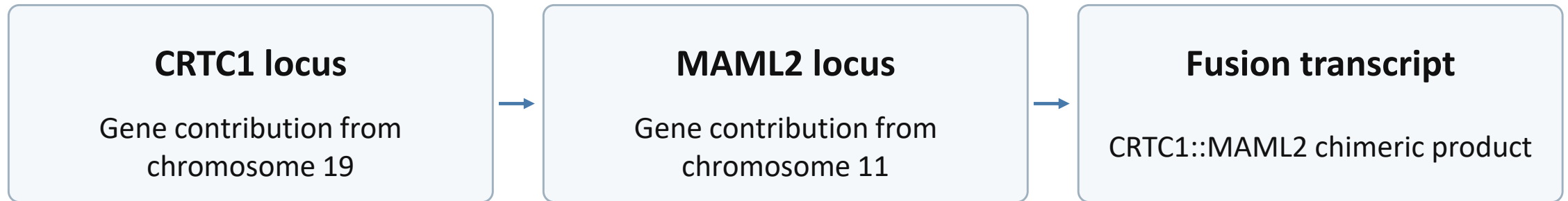
(q21;p13)

Named breakpoints on the
long arm of chromosome 11
and short arm of chromosome
19.

Fusion product

Genomic rearrangement
brings portions of CRTC1 and
MAML2 together.

Fusion formation: Conceptual sequence

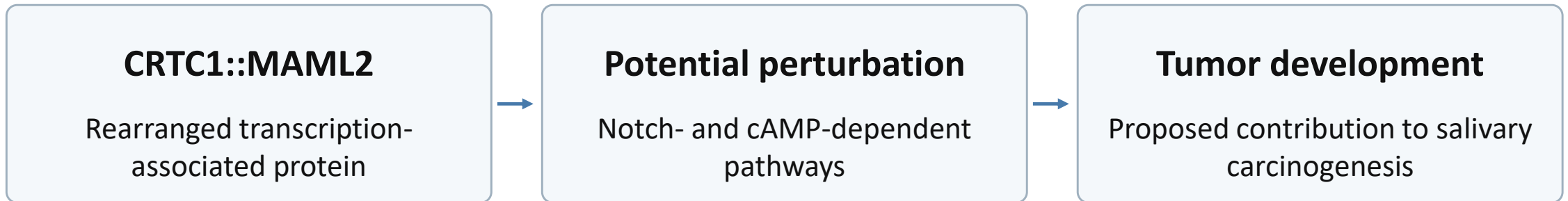


The translocation is recurrent, not universal.

The fusion protein is not normal MAML2

- The incorporated portion of MAML2 cannot interact with Notch signaling components as intact MAML2 does.
- The encoded fusion is therefore functionally distinct from its parent proteins.
- Robbins treats the downstream tumorigenic mechanism as a hypothesis, not a settled linear pathway.

Hypothesized signaling effects



Causal pathway is shown as a hypothesis, consistent with Robbins (“believed”, “possibly”).

What can—and cannot—be inferred

Established observation	Interpretive boundary
CRTC1::MAML2 occurs in many MECs	Not detected in every MEC
Fusion protein is structurally altered	Full downstream mechanism remains uncertain
A recurrent molecular feature exists	Presence alone does not specify grade or stage

An additional fusion is recognized

Classic rearrangement

CRTC1::MAML2 associated with t(11;19).

Alternative rearrangement

CRTC3::MAML2 is an additional recognized fusion partner combination.

These represent related molecular routes; Do not replace morphologic classification.

Molecular testing: Diagnostic role

- MAML2 rearrangement is a desirable diagnostic feature in the WHO 5th-edition framework.
- Molecular assessment can assist when morphology is ambiguous or a variant pattern mimics another entity.
- A negative assay does not, by itself, exclude MEC; Interpret the test within sample and assay limitations.

Avoid overinterpreting fusion status

- Fusion presence has been investigated in relation to histologic type and outcome.
- Morphologic grade and pathologic stage remain clinically important independent domains.
- Avoid a categorical prognostic claim based on the rearrangement alone.

Recognize morphologic variants

Classical pattern

Mixed populations in typical cystic and solid arrangements.

Cytologic variants

Clear/oncocytic and other unusual dominant cytoplasmic appearances.

Stromal or architectural variants

Examples include sclerosing and Warthin-like appearances.

Variant names are supplementary literature context; Not an exhaustive classification list.

Low-grade MEC: Morphologic orientation

- Cystic growth and recognizable mucous differentiation commonly feature in low-grade lesions.
- Cells can be relatively uniform rather than frankly anaplastic.
- Low grade does not mean noninvasive or incapable of recurrence.

High-grade MEC: Morphologic orientation

- A more solid architecture and conspicuous cytologic atypia can predominate.
- High-grade examples may be highly anaplastic and unmistakably malignant.
- Infiltration and the difficulty of complete excision are clinically important.

Intermediate grade: The diagnostic middle

- Robbins recognizes low, intermediate and high histologic grades.
- Intermediate-grade tumors lie between the morphologic extremes.
- Assigning grade requires assessment of the composite specimen, not a single isolated feature.

What grading schemes examine

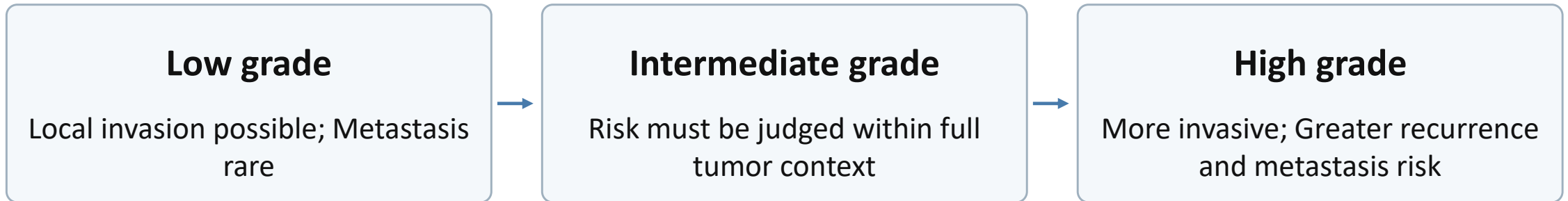
Structural features	Cytologic / activity features
Cystic versus solid growth	Nuclear anaplasia / pleomorphism
Invasive border	Mitotic activity
Perineural or lymphovascular involvement	Tumor necrosis

Feature list is educational; Not a point-based grading formula.

Why grading systems can disagree

- Published MEC grading methods weight architectural and cytologic findings differently.
- The same specimen can receive different grades under different grading algorithms.
- Specify the grading system when using formal scoring criteria and avoid mixing cutoffs across systems.

Grade is linked to clinical course



Grade describes tumor behavior; Stage separately records anatomic extent.

Low-grade outcome data

Local recurrence

~15%

Can recur after treatment despite relatively favorable biology.

Distant metastasis

Rare

Uncommon in low-grade MEC as.

5-year survival

>90%

A textbook summary estimate; Not individualized prognosis.

High-grade outcome data

Recurrence

Up to 30%

Clinically consequential local or regional relapse can occur.

Distant metastasis

30%

Reported in the Robbins high-grade summary.

5-year survival

50%

Substantially below the low-grade figure.

Contrast: Grade and prognosis

Clinical dimension	Low grade	High grade
Local behavior	May invade	Often highly invasive
Recurrence	Approximately 15%	Up to 30%
Distant metastasis	Rare	Approximately 30%
5-year survival	More than 90%	Approximately 50%

Textbook summary figures; These are not patient-specific estimates or matched study cohorts.

Histologic grade is not pathologic stage

Grade

Degree of structural and cellular aggressiveness in a histologic sample.

Stage

Anatomic disease extent using the relevant AJCC framework.

Report both

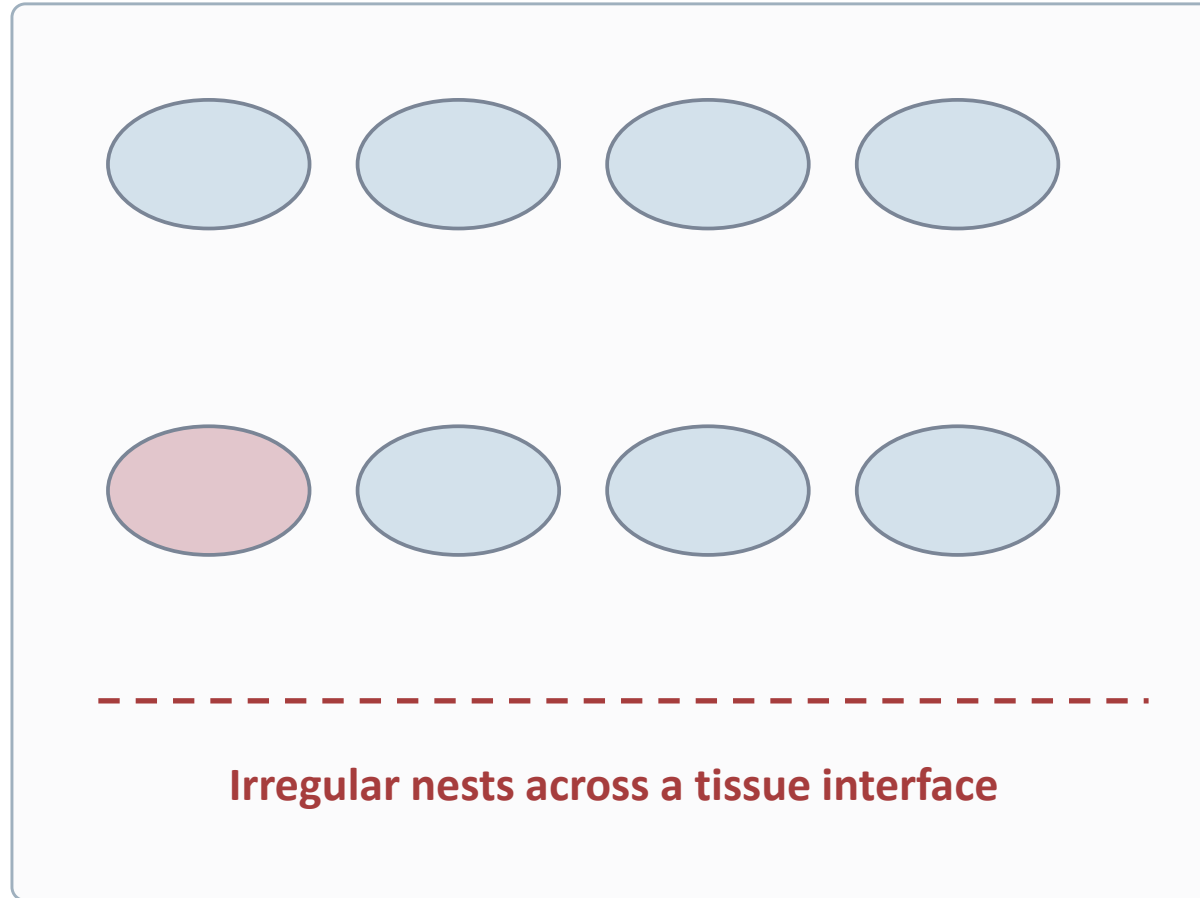
Do not substitute microscopic appearance for anatomic spread—or vice versa.

AJCC Version 9 applies to salivary-gland carcinoma staging from 2026 (CAP/AJCC).

Resection pathology: Key data domains

- Document site and tumor size, histologic type and histologic grade.
- Assess tumor extent, resection margins and relevant invasive features.
- Evaluate regional nodes where submitted and apply current site-specific staging.

The margin problem begins at the border



Pathology questions

- How far does tumor extend?
- Is a true capsule present?
- Does tumor reach an inked margin?

Comparative diagnosis: Pleomorphic adenoma

Property	Mucoepidermoid carcinoma	Pleomorphic adenoma
Nature	Malignant epithelial tumor	Benign mixed tumor
Characteristic elements	Mucous + intermediate + squamoid	Ductal / myoepithelial cells and chondromyxoid stroma
Margins	Often infiltrative, no definite capsule	Usually circumscribed; protrusions possible

Comparative diagnosis: Warthin tumor

Property	Mucoepidermoid carcinoma	Warthin tumor
Behavior	Malignant	Benign
Architecture	Cords / sheets / mucin-containing cysts	Papillary-cystic oncocytic epithelium
Stroma	May be infiltrative	Lymphoid tissue often with follicles
Site	Many salivary sites	Predominantly parotid

Comparative diagnosis: Adenoid cystic carcinoma

Property	Mucoepidermoid	Adenoid cystic
Cellular differentiation	Mucous / intermediate / squamoid	Basal myoepithelial and epithelial
Typical architecture	Cysts and solid areas	Often cribriform / tubular or solid
Characteristic biology	MAML2 rearrangement recurrent	MYB / MYBL1 alteration recurrent
Clinical behavior	Strong grade-related spectrum	Perineural infiltration and late recurrence prominent

Comparative diagnosis: Acinic cell carcinoma

Property	Mucoepidermoid carcinoma	Acinic cell carcinoma
Cell population	Mixed mucous, intermediate, epidermoid	Serous acinar-type cells
Cytoplasm	May include mucin-rich cells	Often granular / zymogen-rich
Patterns	Cords, sheets, cysts	Sheets, microcysts, glands or papillae
Molecular concept	CRTC1::MAML2 in many	NR4A3 alteration recognized (WHO 2022)

When the lesion resembles squamous carcinoma

- A squamoid-dominant MEC may resemble a conventional squamous carcinoma.
- Search for convincing mucous cells and intermediate-cell differentiation.
- Consider MAML2 testing as supportive evidence when morphologic overlap is substantial.

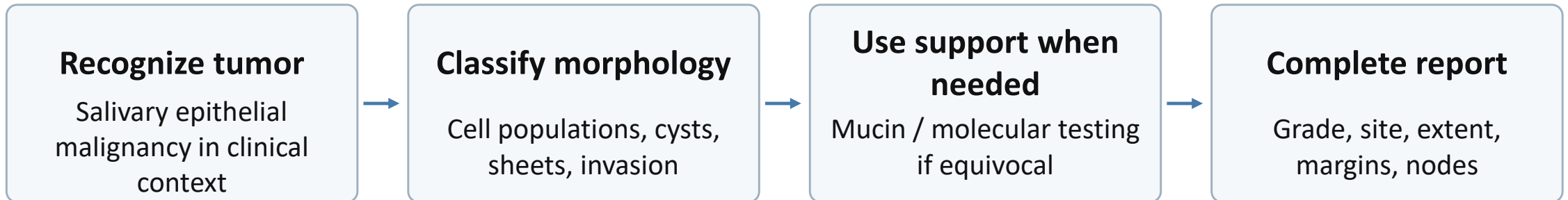
Diagnostic comparison matrix

Clue	MEC	Key contrast
Mucous + squamoid cells	Characteristic mixed differentiation	Usually not the defining pair in pleomorphic adenoma
Chondromyxoid matrix	Not a defining MEC feature	Supports pleomorphic adenoma
Double oncocytic layer + lymphoid stroma	Not typical MEC pattern	Favors Warthin tumor
Cribriform hyaline spaces	Not the defining architecture	Suggests adenoid cystic carcinoma

FNA and limited biopsy: What is knowable?

- Fine-needle aspiration may provide an initial cytologic classification; The Milan system is referenced by the WHO update.
- A core or aspirate samples only part of a heterogeneous neoplasm.
- Full invasive boundaries and definitive grade may be difficult to assess on limited material.

A practical diagnostic workflow



Use this as a teaching framework, not a substitute for local diagnostic protocols.

Case 1: A deceptively bland lesion

A parotid mass contains mucin-bearing cysts and mixed epithelial cells.

- Cells show little cytologic atypia, but irregular nests extend into adjacent salivary tissue.
- Question: Does bland nuclear morphology justify a benign diagnosis?
- Question: Which features should enter the grading discussion?

Case 1: Interpretation

Classification

The combined mucous, intermediate and squamoid cells support MEC.

Evidence of malignancy

Infiltration is not negated by bland nuclei or a cyst-rich appearance.

Next step

Assess the full specimen for histologic grade, margins and extent.

Case 2: A densely cellular salivary malignancy

A salivary-gland resection reveals broad solid sheets and marked nuclear atypia.

- Only focal mucous differentiation is identified on further sampling.
- Question: What diagnosis should enter the differential?
- Question: What is the clinical relevance of a high-grade pattern?

Case 2: Interpretation

Diagnostic consideration

Consider high-grade MEC alongside other high-grade epithelial malignancies.

Grade-related risk

High grade to greater recurrence and distant metastasis.

Workup

Complete sampling and ancillary tests may clarify a morphologically difficult case.

Pattern-recognition exercise

Finding A

Mixed cell types with cystic spaces containing mucin.

Finding B

Infiltrative cords lacking a discrete true capsule.

Finding C

High-grade sheet-like growth with pronounced anaplasia.

Identify: Diagnostic identity, malignant growth pattern, and grade-related feature.

Pattern-recognition: Answers

Finding	Principle	Why it matters
A	Characteristic differentiation	Supports MEC when cell types are documented
B	Invasive interface	Explains why apparent circumscription is misleading
C	High-grade morphology	Raises concern for aggressive behavior

Four recurring diagnostic pitfalls

Cysts → benign

False: Low-grade MEC may appear cystic.

Bland cells → benign

False: Malignant invasion may coexist with bland cytology.

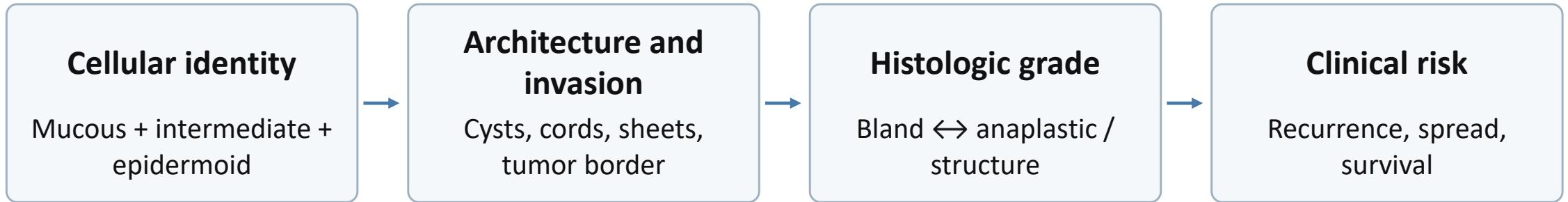
Fusion → grade

False: A molecular feature does not replace histologic grading.

Site → identity

False: Parotid predominance alone cannot classify a tumor.

Integrated clinicopathologic model



Relations summarize source-supported observations; This is not a quantitative prediction tool.

Core concepts to retain

- MEC is the most common primary malignant salivary-gland neoplasm.
- Mixed epithelial differentiation and variable cystic/solid growth define the morphologic concept.
- CRTC1::MAML2 is recurrent, but neither universal nor a substitute for morphology.
- Histologic grade strongly influences recurrence, distant spread and survival.

References and teaching evidence

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