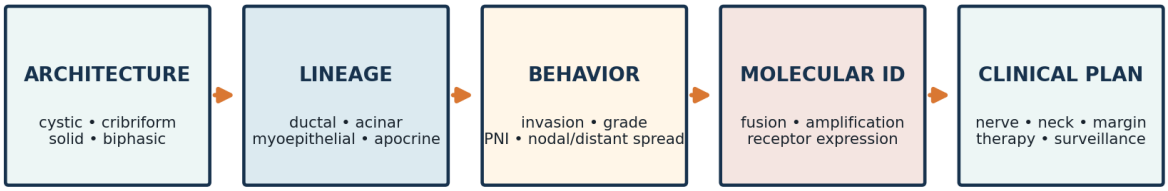
SALIVARY GLAND NEOPLASMS

VOLUME III

Malignant Neoplasms

Histologic identity, molecular biology, patterns of spread, and the findings that change treatment

A malignant salivary diagnosis is a biologic model, not merely a name



The resident's job is to translate morphology into patterns of spread and operation-changing risk.

Figure 1. Original synthesis. Malignant salivary pathology becomes clinically useful only after entity, biologic tier, extent, and actionable biology are integrated.

THE CENTRAL QUESTION | What pattern of failure should this tumor be expected to produce - along nerves, into cervical nodes, through the bloodstream, or by local infiltration - and what must the first treatment plan anticipate?

A first-principles guide for otolaryngology residents • Prepared July 2026

CHAPTER 0

Orientation

Malignant salivary tumors should be learned as biologic families, not as an alphabetical list of rare names.

A malignant salivary diagnosis must do more than label a specimen. It should predict the structures at risk, the likely routes of spread, the value and limitations of neck treatment, the time horizon of recurrence, and whether a molecular result can confirm the diagnosis or open a systemic-treatment option. Those predictions differ sharply among tumors that may look similarly bland in a small biopsy.

This volume therefore begins with a shared pathology language and then follows the major malignant entities from morphology to molecular identity to clinical behavior. Detailed parotidectomy technique, facial-nerve reconstruction, neck-dissection strategy, postoperative radiation, and surveillance protocols are developed in Volumes IV and V. Here, management appears only when it explains why the diagnosis matters before the patient reaches the operating room or tumor board.

Learning Objectives

- Read a malignant salivary pathology report in four coordinates: entity, biologic tier, anatomic extent, and actionable biology.
- Recognize the defining architecture and cell populations of the major carcinomas, including mucoepidermoid, adenoid cystic, acinic cell, secretory, salivary duct, carcinoma ex pleomorphic adenoma, and polymorphous adenocarcinoma.
- Explain why tumor-specific grade, high-grade transformation, perineural invasion, lymphovascular invasion, margin status, and nodal disease convey different information.
- Associate characteristic molecular alterations with the correct diagnostic and therapeutic use - without treating a fusion as a substitute for morphology.
- Predict whether a tumor is primarily nerve-seeking, node-seeking, hematogenously metastatic, locally infiltrative, or biologically indolent with a long recurrence horizon.
- Recognize common mimics, especially metastatic cutaneous squamous carcinoma, metastatic renal cell carcinoma, lymphoma, and high-grade transformation in another salivary primary.

Contents

HOW TO USE THIS VOLUME | On the first pass, follow each tumor from low-power pattern to spread pattern. On the second pass, cover the molecular and immunophenotypic tables and reconstruct them. On the third pass, work the cases by asking what the diagnosis changes about nerve, neck, margin, systemic staging, and follow-up.

CHAPTER 1

A Practical Language for Malignant Salivary Pathology

The useful diagnosis is not one word. It is a structured claim about identity, behavior, extent, and uncertainty.

Salivary carcinomas are unusually diverse because a small set of epithelial programs can be recombined into many architectures. A tumor may be ductal and myoepithelial, mucous and squamoid, acinar and secretory, or apocrine and high grade. Cytologic blandness does not guarantee benignity, and striking atypia does not identify the parent tumor. The first step is therefore to separate four questions that are often collapsed into one.

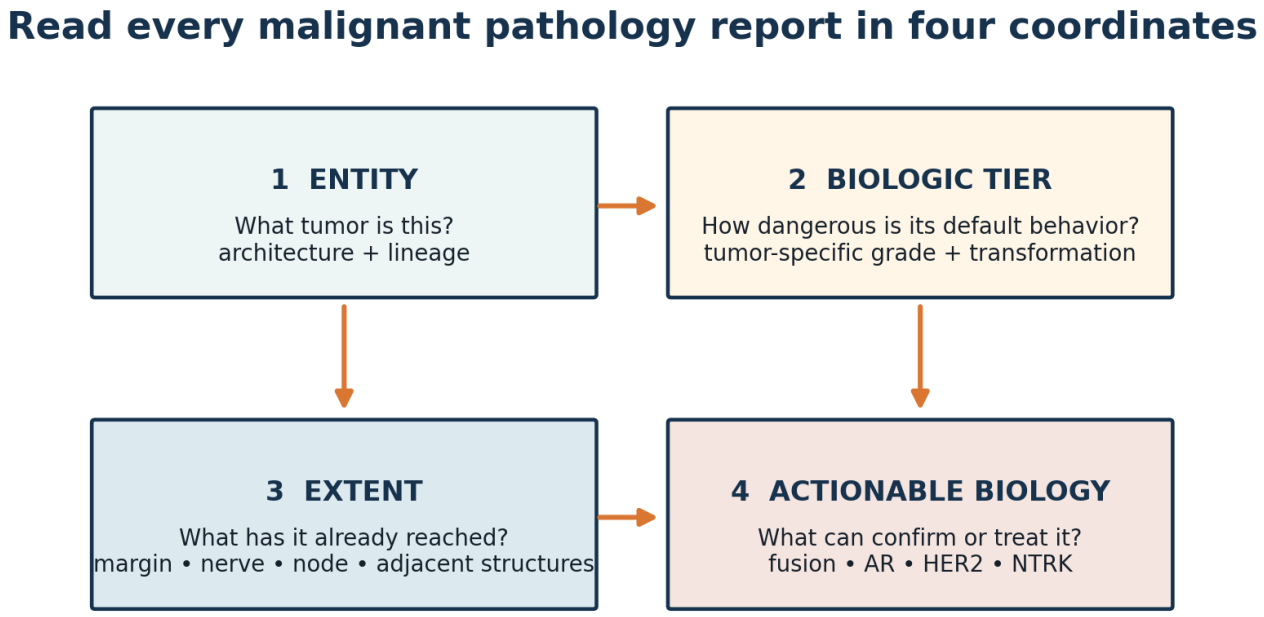


Figure 2. Original synthesis. A malignant diagnosis is most useful when identity, biologic tier, extent, and actionable biology are reported separately.

1.1 Entity: what tumor is this?

Entity is established by the combination of architecture, cell phenotype, interface, immunophenotype, and - when needed - a defining molecular alteration. Architecture is disproportionately important. Mucoepidermoid carcinoma requires the appropriate mixture of mucous, intermediate, and epidermoid cells. Adenoid cystic carcinoma is a dual-cell basaloid tumor with true ducts and pseudocystic spaces. Secretory carcinoma is not diagnosed merely because S100 is positive; the microcystic or papillary architecture and fusion context must fit.

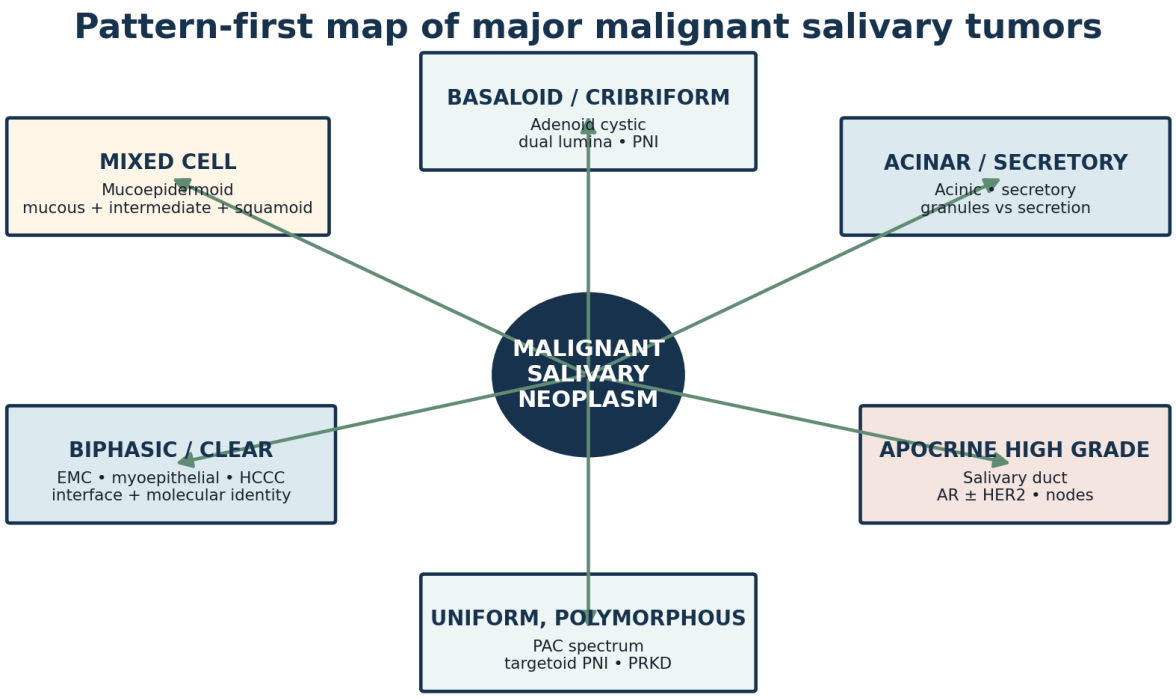


Figure 3. Original synthesis. A pattern-first map narrows the malignant differential before individual stains are interpreted.

1.2 Biologic tier: grade is tumor specific

"Low grade" and "high grade" are not universal morphologic recipes. Mucoepidermoid carcinoma has formal grading systems. Adenoid cystic carcinoma is often risk-stratified by solid growth and transformation. Acinic cell and epithelial-myoepithelial carcinomas are usually considered low grade unless adverse morphology or high-grade transformation is present. Salivary duct carcinoma is high grade by identity. The pathology report should name the grading system when one is used because different mucoepidermoid systems may assign different grades to the same tumor.[1-4]

FIRST PRINCIPLE | Grade describes the aggressiveness of a recognized entity. It cannot rescue an uncertain diagnosis. A "high-grade carcinoma" with no lineage is a starting point for additional work, not an endpoint.

1.3 Extent: the tumor-normal interface and routes of spread

The malignant interface may be obvious, subtly multinodular, or impossible to evaluate in an FNA. Pathologists should report destructive invasion, extraparenchymal extension when applicable, perineural and lymphovascular invasion, margin status, nodal metastasis, and extranodal extension. The surgeon should interpret these findings in context. Microscopic perineural invasion in a small unnamed nerve is not identical to radiographic spread along a named nerve to the skull base, but both reveal a biologic preference that influences treatment fields and surveillance.

Table 1. Adverse findings answer different questions and should not be blended into a single vague risk label.

Finding	What it proves	What it does not prove
Perineural invasion	Tumor is tracking around or through a nerve; supports local aggressiveness and nerve-pathway risk.	It does not by itself define gross named-nerve spread or require sacrifice of an otherwise functioning uninvolved nerve.
Lymphovascular invasion	A route into regional or systemic circulation is present.	It does not equal established nodal or distant metastasis.
Positive margin	Tumor reaches the inked resection edge.	It does not describe how much residual tumor remains or whether re-resection is anatomically feasible.
High-grade transformation	A conventional tumor contains an abrupt poorly	It is not synonymous with ordinary tumor-specific

Finding	What it proves	What it does not prove
	differentiated component.	high grade.
Fusion or amplification	May confirm lineage or reveal a target.	It does not replace stage, margin status, or adverse morphology.

1.4 Molecular testing: three legitimate uses

1. Diagnostic confirmation: resolving a morphologic differential, such as secretory versus acinic cell carcinoma.
2. Classification refinement: defining a molecularly coherent entity or subgroup, such as EWSR1::ATF1 clear cell carcinoma.
3. Therapeutic selection: identifying a target such as an NTRK fusion or HER2 amplification in advanced disease.

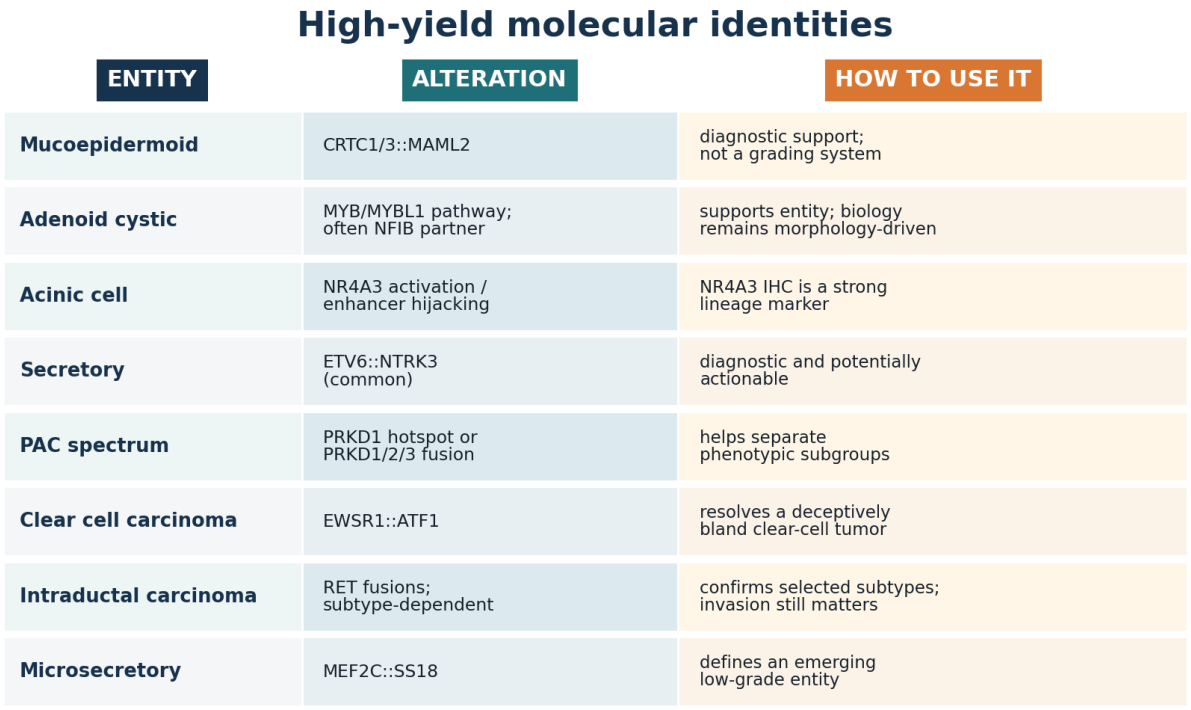


Figure 4. Original synthesis. The same molecular result may serve a diagnostic, classificatory, or therapeutic purpose; the report should make the intended use explicit.

1.5 The report the resident needs

Table 2. A pathology report is a communication tool for treatment planning, not merely a taxonomic exercise.

Required domain	Questions for the pathology report
Identity	Is a specific entity established? If not, what is the narrowed differential and what limits certainty?
Biologic tier	Is the tumor graded? Which system? Is high-grade transformation present?
Extent	Tumor size, extraparenchymal or adjacent-structure invasion, PNI, LVI, margins, nodes, ENE.
Actionable biology	Was testing performed for AR, HER2, NTRK, or another target? Is the result validated and clinically interpretable?
Specimen context	Primary resection, limited biopsy, FNA, core, recurrent tumor, or metastasis? Was the interface adequately sampled?

Chapter Synthesis

- Start with architecture and lineage; use ancillary studies to resolve a specific question.
- Separate entity, grade, extent, and actionable biology.

- Cytologic blandness is compatible with malignancy in several salivary tumors.
- The tumor-normal interface and route of spread often determine the clinical meaning of the diagnosis.

CHAPTER 2

Mucoepidermoid Carcinoma

The common malignant salivary tumor whose name is simple but whose grade and mimics require discipline.

OPENING CASE | A 34-year-old has a painless 1.6-cm parotid mass. FNA is predominantly cystic with rare mucinous cells and is interpreted as a low-grade salivary neoplasm. The resection shows mucous, intermediate, and epidermoid cells in a largely cystic tumor with MAML2 rearrangement. The clinically important result is not merely "MEC": it is a low-grade, completely excised MEC without adverse features.

2.1 The defining cell mixture

Mucoepidermoid carcinoma (MEC) is built from mucous cells, intermediate cells, and epidermoid or squamoid cells in variable proportions. Low-grade tumors are often macrocystic and mucin rich. Higher-grade tumors become more solid, with a greater intermediate-cell component, cytologic atypia, necrosis, mitotic activity, and infiltrative growth. True keratinization is usually limited; a carcinoma composed almost entirely of overtly keratinizing squamous cells should trigger a search for another diagnosis or metastatic cutaneous disease.[1,2]

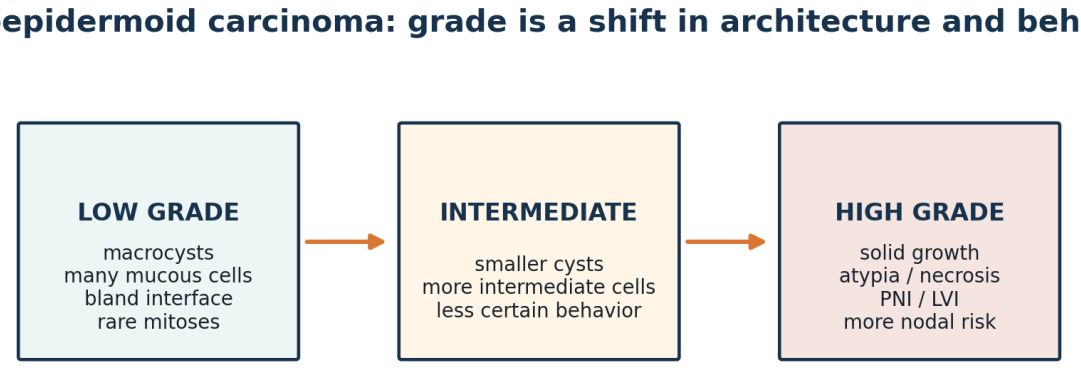


Figure 5. Original synthesis. MEC grade reflects a coordinated change in architecture, cytology, and invasive behavior.

2.2 Why grading is difficult

The AFIP and Brandwein systems weight features differently. Cystic proportion, neural invasion, necrosis, mitoses, anaplasia, and pattern of invasion may all contribute. Intermediate-grade assignment is especially vulnerable to disagreement. The resident should therefore look for the named grading system and should not assume that "intermediate" carries identical meaning across institutions or studies. When the grade seems discordant with the clinical or imaging picture, pathology review is appropriate before definitive treatment is fixed.[1]

Table 3. Grade is a continuum of coordinated features, not the number of mucous cells alone.

Low-grade tendency	High-grade tendency
Prominent macrocysts	Predominantly solid architecture
Many mature mucous cells	Intermediate/squamoid cells dominate
Minimal atypia and mitotic activity	Pleomorphism, brisk mitoses, necrosis
Pushing or limited invasion	Destructive invasion, PNI, LVI
Lower regional and distant risk	Greater nodal, local, and distant risk

2.3 MAML2: highly useful, commonly overused

Most conventional low- and intermediate-grade MECs harbor CRTC1::MAML2 or CRTC3::MAML2. Demonstration of a MAML2 rearrangement can support the diagnosis when the architecture and cell mixture fit, particularly in a cystic or unusual lesion. Fusion-positive tumors often have favorable biology, but MAML2 is not a grading system and cannot neutralize frank high-grade morphology, advanced stage, or incomplete resection. Conversely, absence of MAML2 does not automatically exclude MEC; it should prompt careful review for mimics and for whether the tumor actually contains the defining cell populations.[1,2]

2.4 Important mimics

Mimic	Why it overlaps	Clue against MEC
Warthin tumor / metaplastic Warthin	Cysts, oncocytes, lymphoid stroma, squamous or mucous metaplasia.	Orderly bilayered oncocytic lining and no infiltrative intermediate-cell population; MAML2 context may help.
Squamous cell carcinoma	Epidermoid cells and high-grade morphology.	No convincing mucous/intermediate component; assess skin, upper aerodigestive tract, and intraparotid nodal disease.
Clear cell carcinoma	Clear cells and p63/p40 positivity.	Hyalinized stroma and EWSR1::ATF1; lacks characteristic mucous cell mixture.
Secretory carcinoma	Cystic architecture and secretions.	S100/mammaglobin phenotype and ETV6-related fusion; lacks epidermoid population.
Necrotizing sialometaplasia	Squamous metaplasia and mucous glands in a minor-gland site.	Lobular preservation, ischemic context, and reparative evolution rather than neoplastic proliferation.

2.5 Clinical behavior and operation-changing implications

Low-grade MEC often behaves as a local surgical disease, but site and stage still matter. High-grade MEC more closely resembles other aggressive salivary carcinomas: cervical nodal evaluation becomes important, wider local planning may be required, and postoperative radiation is frequently considered when adverse features are present. Facial weakness, skin fixation, bone invasion, or radiographic nodes should never be reconciled away by a limited sample labeled “low grade.” That discordance demands additional tissue or expert review.

BOARD TRAP | A cystic salivary lesion with scant diagnostic cells can produce a false-negative FNA. “Cyst contents” is not a benign diagnosis when the mass persists.

Chapter Synthesis

- MEC requires mucous, intermediate, and epidermoid cells in an appropriate architecture.
- State the grading system; intermediate-grade classification is not perfectly reproducible.
- MAML2 supports identity and often favorable biology but does not override morphology or stage.
- High-grade MEC has greater nodal and systemic risk than low-grade MEC.

CHAPTER 3

Adenoid Cystic Carcinoma

A deceptively uniform basaloid tumor whose defining clinical behaviors are perineural spread and late hematogenous metastasis.

OPENING CASE | A patient with a small submucosal palatal mass reports months of deep pain and new numbness. Biopsy shows a cribriform dual-cell carcinoma. The mass is not “early” simply because it is small: the symptom localizes the biologic problem to a nerve pathway that must be mapped to the skull base.

3.1 Architecture: true ducts and false spaces

Adenoid cystic carcinoma (AdCC) contains luminal ductal cells and abluminal myoepithelial or basal-type cells. Tubular areas show small true ducts. Cribriform areas create a sieve-like pattern with both true lumina and pseudocystic spaces containing basement-membrane-like material. Solid areas lose much of the classic architecture and carry worse prognosis. Tumors often mix patterns, so the report should describe the solid component rather than forcing the entire tumor into one box.[3,4]

Table 4. AdCC architecture is a prognostic variable, not just a pattern-recognition exercise.

Pattern	Low-power appearance	Clinical meaning
Tubular	Small ducts with an inner luminal and outer abluminal layer.	Generally the most differentiated pattern.
Cribriform	“Swiss cheese” nests with pseudocysts and hyaline material.	Classic pattern; intermediate biologic risk.
Solid	Sheets or nests of basaloid cells with fewer spaces.	Adverse; grading systems use presence or proportion of solid growth.
High-grade transformation	Abrupt anaplastic component, necrosis, brisk mitoses, loss of dual-cell architecture.	Markedly more aggressive, with increased nodal and distant risk.

3.2 Perineural invasion versus perineural spread

Microscopic perineural invasion is common and may be clinically silent. Perineural spread refers to macroscopic or radiographically detectable extension along a named nerve, often with pain, paresthesia, weakness, denervation change, or skull-base foraminal enhancement. The distinction matters because the treatment volume and resection plan follow the nerve pathway, not merely the visible glandular mass. Trigeminal routes through the palate and masticator space, and facial-nerve routes from the parotid toward the stylomastoid foramen and facial canal, are especially important.

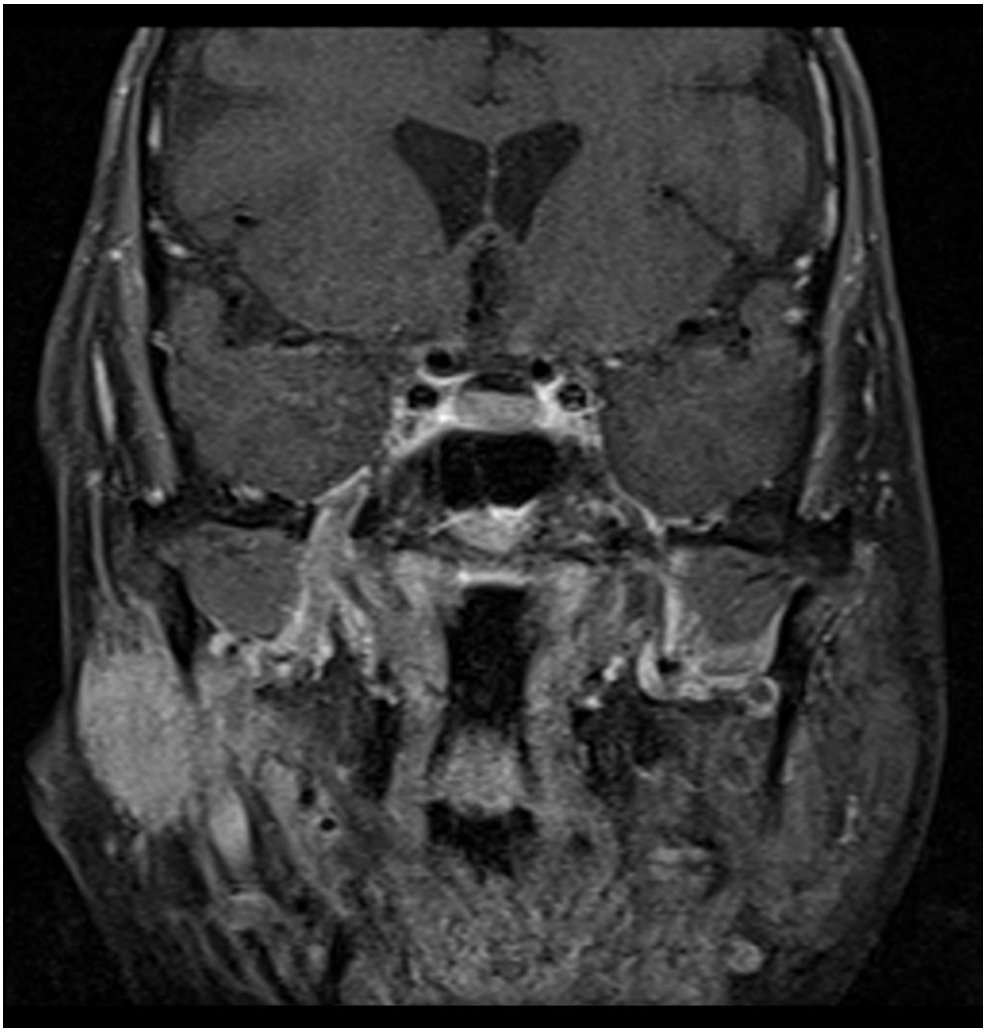


Figure 6. Coronal fat-suppressed postcontrast T1 MRI demonstrating a parotid adenoid cystic carcinoma with perineural spread along a trigeminal pathway. Jto410, CC BY-SA 3.0, via Wikimedia Commons.

CLINICAL PEARL | Pain out of proportion to mass size, palatal or facial numbness, weakness, masticator denervation, or foraminal enhancement should trigger dedicated contrast-enhanced MRI of the complete nerve pathway.

3.3 The long natural history

AdCC often grows slowly enough to create false reassurance, yet it can recur locally or metastasize years after apparently successful therapy. Hematogenous metastasis, particularly to lung, is more characteristic than early cervical nodal spread. Pulmonary metastases may remain indolent for a prolonged interval, so the presence of metastasis and the tempo of metastatic disease are separate clinical facts. Long-term survival curves continue to decline, making ten- and fifteen-year follow-up more informative than a five-year snapshot.[3-5]

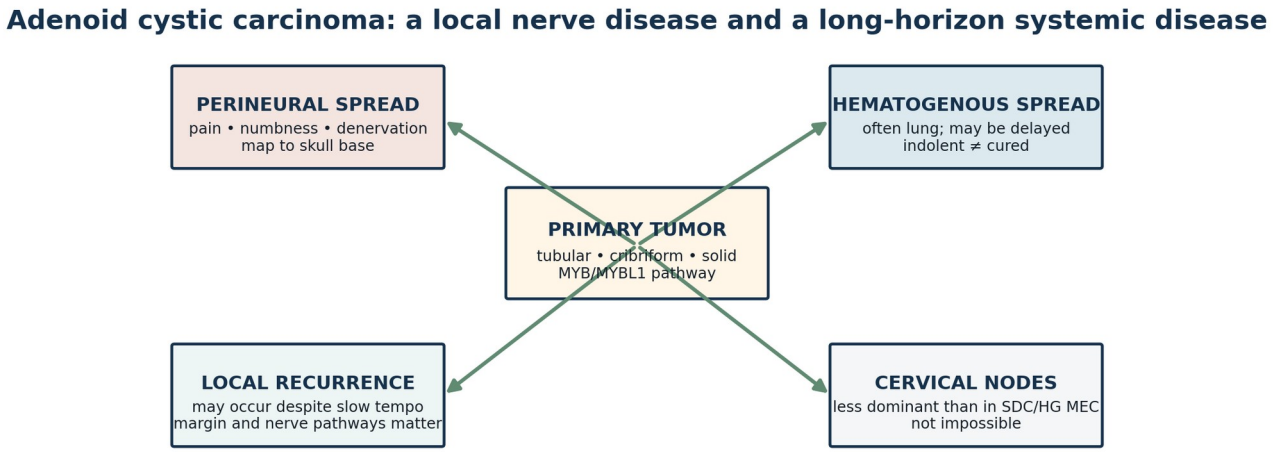


Figure 7. Original synthesis. AdCC combines nerve-seeking local behavior with a long-horizon risk of hematogenous metastasis.

3.4 Molecular biology

Many AdCCs activate the MYB or MYBL1 transcriptional program, frequently through rearrangements involving NFIB. These alterations can support diagnosis but are not required in every case and do not replace architecture. Additional genomic changes, including NOTCH-pathway alterations in some aggressive tumors, are biologically important but are not yet a single routine grading assay. The practical message is that the classic phenotype remains morphology first, with molecular testing used to resolve difficult cases or guide trials.

3.5 Surgical and boards implications

- A functioning nerve is not sacrificed solely because microscopic PNI is possible; gross involvement, preoperative dysfunction, imaging, and achievable margins guide the nerve plan.
- A clinically negative neck is not treated identically to salivary duct carcinoma because occult nodal risk is usually lower; site, T category, solid/HGT features, and institutional practice still matter.
- Postoperative radiation decisions are heavily influenced by PNI, margins, advanced T category, and named-nerve pathways.
- Surveillance must remain long term and should include the chest because late pulmonary metastasis is characteristic.

BOARD TRAP | “Slow growing” does not mean benign or curable by narrow excision. AdCC is the classic salivary carcinoma in which tempo understates long-term risk.

Chapter Synthesis

- Recognize dual-cell tubular/cribriform architecture and quantify adverse solid growth.

- Differentiate microscopic PNI from clinically or radiographically evident named-nerve spread.
- Expect late local and pulmonary failure, often after an initially indolent course.
- Use MYB/MYBL1-pathway testing as support, not as a substitute for morphology.

CHAPTER 4

Acinic Cell Carcinoma

A generally low-grade parotid carcinoma whose broad morphology and occasional transformation make lineage confirmation essential.

OPENING CASE | A 46-year-old has a slowly enlarging parotid mass. Core biopsy shows a microcystic tumor with granular cytoplasm. The diagnostic problem is not whether it looks "low grade"; it is whether the cells demonstrate true serous acinar differentiation or instead represent secretory carcinoma, metastatic renal cell carcinoma, or another clear/granular neoplasm.

4.1 Serous acinar differentiation

Acinic cell carcinoma (AciCC) recapitulates serous acinar cells. Classic cells contain basophilic or amphophilic cytoplasmic zymogen granules that are PAS positive and diastase resistant. Some tumors are dominated by intercalated-duct-like, vacuolated, clear, or nonspecific cells, and the diagnostic granules may be focal. Architectural patterns include solid, microcystic, papillary-cystic, and follicular forms. Because these patterns can coexist, low-power recognition plus lineage markers is more reliable than any single high-power field.[6-8]

4.2 NR4A3 and the modern diagnostic framework

Recurrent enhancer hijacking activates NR4A3 in most conventional AciCCs. Nuclear NR4A3 immunohistochemistry is therefore a powerful marker of acinar differentiation and is especially useful in morphologically ambiguous tumors. DOG1 and SOX10 may support the diagnosis but are less specific. A panel matters: a granular parotid tumor that is NR4A3 negative and diffusely S100/mammaglobin positive should raise secretory carcinoma, while PAX8 and renal markers raise metastatic renal cell carcinoma.

4.3 Behavior: low grade does not mean zero risk

Many AciCCs are cured by complete surgery, yet local recurrence and distant metastasis occur, sometimes after a prolonged interval. Adverse findings include infiltrative margins, necrosis, increased mitotic activity, prominent stromal fibrosis at the invasive front, lymphovascular or perineural invasion, nodal disease, and high-grade transformation. Proposed grading systems are promising but are not universally standardized; the report should describe the actual adverse features rather than relying on an unexplained label.[6]

Table 5. The diagnostic and prognostic information in AciCC comes from different features.

Finding	Interpretation
Zymogen granules / PAS-D positivity	Supports serous acinar differentiation; may be focal.
Nuclear NR4A3	Strong modern support for AciCC lineage.
Papillary-cystic change	Can be prominent and should not be mistaken automatically for a different tumor.
Tumor-associated lymphoid stroma	May occur, particularly in some microcystic tumors.
Necrosis, brisk mitoses, infiltrative front	Adverse biology; look carefully for transformation.
Abrupt high-grade component	High-grade transformation; report separately and treat as a major risk modifier.

4.4 High-grade transformation

In transformed AciCC, a conventional low-grade component abuts an abrupt high-grade carcinoma with solid growth, necrosis, pleomorphism, and increased proliferation. The transformed component may lose obvious acinar morphology and some lineage markers. Extensive sampling is therefore essential: a biopsy that captures only the high-grade area may be called poorly differentiated carcinoma unless the parent tumor is found. Transformation substantially increases regional and distant metastatic risk.

BOARD TRAP | The historical term “acinic cell adenocarcinoma” is obsolete. Acinic cell carcinoma is malignant even when cytologically bland.

Chapter Synthesis

- AciCC is defined by serous acinar differentiation, not by one architecture.
- Nuclear NR4A3 is a high-value lineage marker.
- Describe adverse morphology explicitly because grading is not fully standardized.
- Search for and report high-grade transformation; it changes the clinical disease.

CHAPTER 5

Secretory Carcinoma

A molecularly defined carcinoma that resembles breast secretory carcinoma and must be separated from acinic cell carcinoma.

5.1 The phenotype

Secretory carcinoma typically forms microcysts, tubules, papillae, or cribriform structures filled with eosinophilic secretory material. Cells have eosinophilic or vacuolated cytoplasm and relatively uniform nuclei. The tumor is usually S100, mammaglobin, and GATA3 positive and often SOX10 positive. It generally lacks the convincing zymogen granules and nuclear NR4A3 expression expected in AciCC.[9]

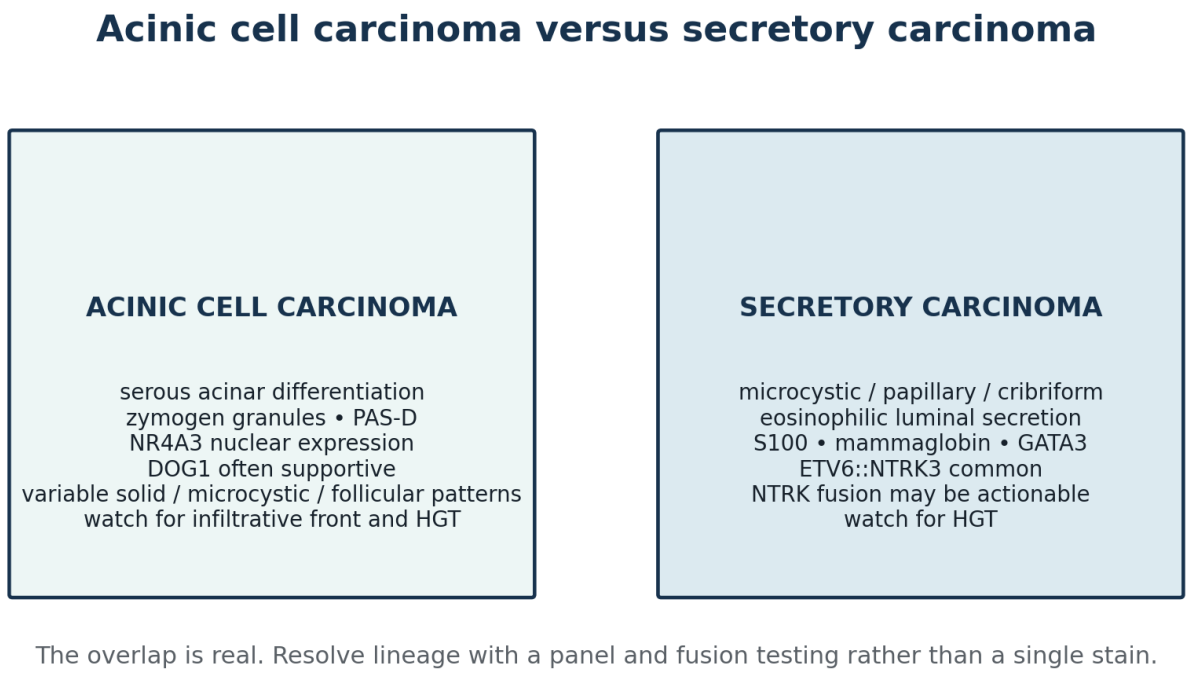


Figure 8. Original synthesis. AciCC and secretory carcinoma overlap morphologically; lineage and fusion testing resolve the difficult cases.

5.2 ETV6::NTRK3 and diagnostic certainty

Most secretory carcinomas harbor an ETV6::NTRK3 fusion, although alternative ETV6 partners and other kinase fusions occur. Fusion confirmation is especially valuable when morphology or immunophenotype is incomplete, when pan-TRK staining is equivocal, or when targeted therapy is being considered. Pan-TRK immunohistochemistry is a screening tool rather than definitive fusion proof because staining pattern and performance vary by fusion and assay.

5.3 Natural history and high-grade transformation

Most secretory carcinomas behave as low- to intermediate-grade tumors, but cervical nodal and distant metastases are documented. High-grade transformation produces an abrupt solid, pleomorphic, mitotically active component and is associated with aggressive behavior. The presence of an NTRK fusion does not guarantee indolence; it establishes lineage and may provide a therapeutic target in unresectable or metastatic disease.

5.4 Why the distinction from AciCC matters

Table 6. Use a convergent panel; no single immunostain should carry the entire diagnosis.

Feature	Acinic cell carcinoma	Secretory carcinoma
Cytoplasm	Basophilic/amphophilic; zymogen granules may be focal.	Eosinophilic/vacuolated with luminal secretion.
Architecture	Solid, microcystic, follicular, papillary-cystic.	Microcystic, tubular, papillary, cribriform.
NR4A3	Usually nuclear positive.	Generally negative.
S100 / mammaglobin	Usually not the diffuse paired phenotype.	Typically diffuse positive.
DOG1	Often supportive.	Usually negative or limited.
Molecular alteration	NR4A3 activation.	ETV6::NTRK3 or related kinase fusion.
Advanced-disease implication	No single defining target in routine practice.	NTRK fusion may confer sensitivity to TRK inhibition.

OPERATING-ROOM RELEVANCE | The immediate operation may be similar for a localized AciCC and secretory carcinoma, but the diagnosis changes pathology review, prognostic counseling, molecular documentation, and options if the disease becomes unresectable or metastatic.

Chapter Synthesis

- Secretory carcinoma combines a characteristic secretory phenotype with an ETV6-related kinase fusion.
- Differentiate it from AciCC with morphology, NR4A3/DOG1, S100/mammaglobin, and fusion testing.
- NTRK testing may be both diagnostic and therapeutic.
- High-grade transformation overrides the usual indolent expectation.

CHAPTER 6

Salivary Duct Carcinoma

An aggressive apocrine carcinoma in which AR and HER2 testing are integral to the diagnosis and future treatment options.

OPENING CASE | A 67-year-old man presents with a rapidly enlarging parotid mass, facial weakness, and level II adenopathy. Core biopsy shows a high-grade cribriform carcinoma with comedonecrosis and strong nuclear AR staining. This is a node-seeking, high-grade disease until proven otherwise; the workup and operation cannot be planned like a bland salivary neoplasm.

6.1 Morphology: the breast ductal analogy

Salivary duct carcinoma (SDC) resembles high-grade apocrine ductal carcinoma of the breast. It forms cribriform, solid, papillary, and duct-like structures with comedonecrosis. Cells have abundant eosinophilic cytoplasm, prominent nucleoli, and apocrine snouts may be visible. Invasion, lymphovascular permeation, perineural invasion, and nodal metastasis are common. SDC may arise de novo or as the malignant component of carcinoma ex pleomorphic adenoma.[10-12]

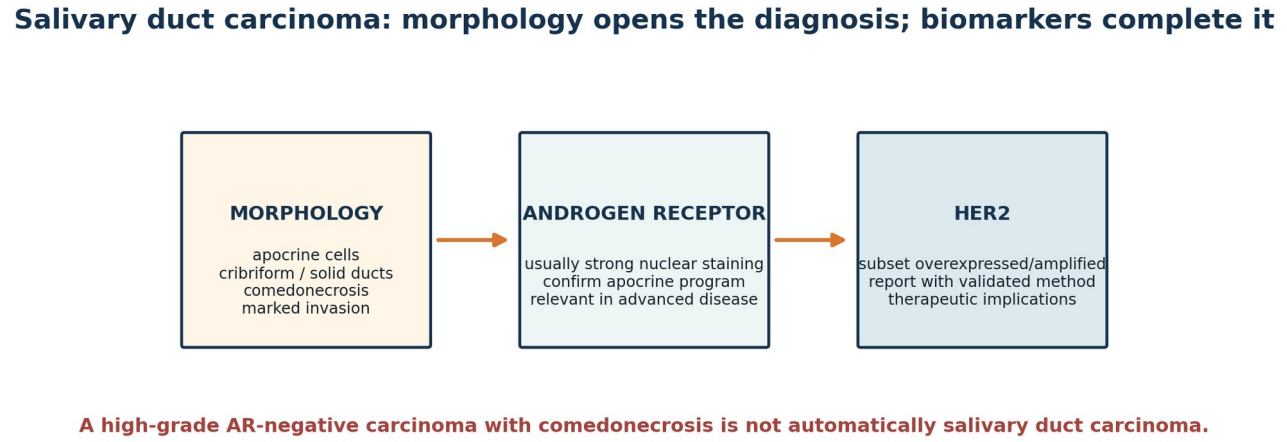


Figure 9. Original synthesis. AR and HER2 are not optional decorative stains in SDC; they complete the diagnostic and therapeutic profile.

6.2 Androgen receptor

Most conventional SDCs show strong, diffuse nuclear androgen-receptor expression. AR confirms the apocrine program and helps distinguish SDC from other high-grade salivary carcinomas that may show comedonecrosis after transformation. Heterogeneity and loss of staining can occur, especially in transformed or metastatic components. An AR-negative high-grade carcinoma should therefore be sampled extensively and reconsidered before the SDC label is accepted.

6.3 HER2 and additional alterations

A substantial subset of SDC overexpresses and/or amplifies HER2. Reporting should use a validated method and, where appropriate, confirm equivocal immunohistochemistry with in situ hybridization. AR and HER2 status are clinically important because androgen-deprivation and HER2-directed strategies may be used in recurrent or metastatic disease. HRAS, PIK3CA, and other pathway alterations occur and may support trial selection, but they do not replace the core AR/HER2 assessment.

6.4 Clinical behavior

SDC is high grade by identity. Patients often present with advanced local disease, facial weakness, and cervical adenopathy. Regional and distant failure can occur early. The clinically negative neck is approached with a lower threshold for elective treatment than in classic AdCC or low-grade AciCC, and postoperative radiation is commonly indicated after resection because of grade, stage, nodal disease, PNI/LVI, or margin risk. Detailed algorithms are deferred, but the pathology should immediately trigger comprehensive staging and multidisciplinary planning.

Table 7. The SDC report should be built for tumor-board decisions and future systemic therapy.

Question	Required answer
Is the morphology truly apocrine SDC?	Conventional high-grade ductal/cribriform architecture, comedonecrosis, apocrine cytology, and AR support.
Is it de novo or ex pleomorphic adenoma?	Search for residual PA, hyalinized scar-like precursor, and PLAG1/HMGA2 context.
Is HER2 positive?	Report validated IHC/ISH result and heterogeneity.
Has it reached nodes?	Document number, size, levels, and extranodal extension.
Is the facial nerve involved?	Correlate preoperative function and imaging with operative/pathologic findings.

BOARD TRAP | Comedonecrosis is not specific for SDC. High-grade transformation in AdCC, AciCC, epithelial-myoepithelial carcinoma, or myoepithelial carcinoma can mimic it.

Chapter Synthesis

- SDC is a high-grade apocrine carcinoma with strong regional and distant metastatic potential.
- Strong nuclear AR is characteristic; HER2 is positive in a clinically important subset.
- Determine whether the tumor is de novo or arises ex pleomorphic adenoma.
- An AR-negative comedonecrotic carcinoma requires additional sampling and a broader differential.

CHAPTER 7

Carcinoma ex Pleomorphic Adenoma

A malignant transformation diagnosis that is incomplete until the carcinoma subtype and depth of invasion are reported.

OPENING CASE | A patient reports rapid growth and pain in a parotid mass present for fifteen years. Imaging shows an irregular mass with nodal disease. Resection reveals salivary duct carcinoma arising within a hyalinized pleomorphic adenoma. The biologic driver is the carcinoma, but the precursor explains the history and may influence molecular interpretation.

7.1 Recognizing the precursor

Carcinoma ex pleomorphic adenoma (CXPA) requires a malignant epithelial or myoepithelial neoplasm arising in a preexisting pleomorphic adenoma. Residual PA may be obvious, tiny, extensively hyalinized, or represented mainly by a scar-like nodule with calcification. The malignant component is most often salivary duct carcinoma but may be myoepithelial carcinoma, adenocarcinoma, epithelial-myoepithelial carcinoma, or another phenotype. The report should name that component because its biology and biomarkers shape treatment.[13,14]

7.2 Intracapsular, minimally invasive, and widely invasive

The traditional WHO framework divides CXPA into intracapsular disease, minimally invasive disease extending no more than 1.5 mm beyond the PA capsule, and widely invasive disease extending farther. The cutoff has limitations because capsules are irregular and studies have used different thresholds. A high-quality report therefore includes the actual measured invasion in millimeters, not merely the category, and integrates malignant subtype, grade, PNI/LVI, margins, nodes, and stage.

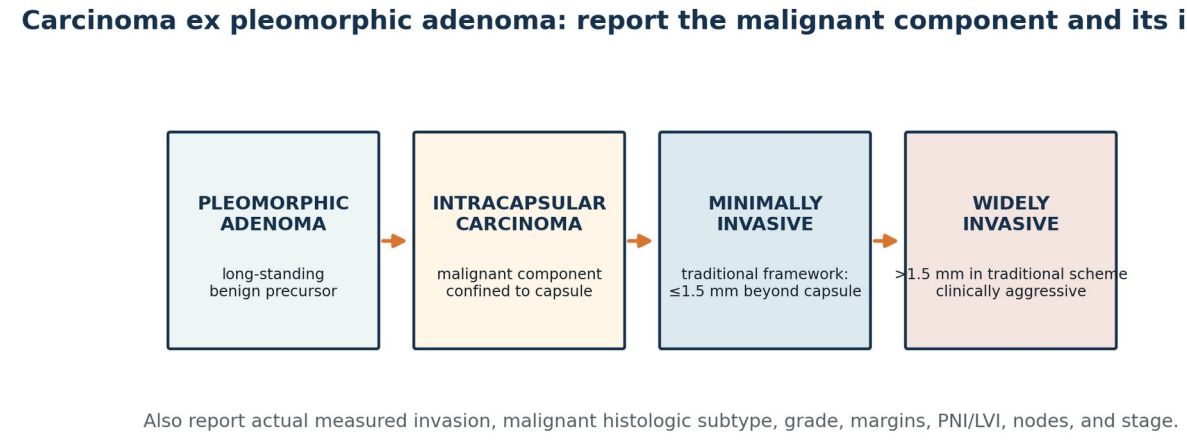


Figure 10. Original synthesis. The ex-PA label must be paired with malignant subtype and measured invasion.

7.3 Molecular support

PLAG1 and HMGA2 alterations are characteristic of the pleomorphic adenoma lineage and may persist in CXPA. They can support origin from PA when the residual precursor is scant, but a positive result does not establish the invasive category or the carcinoma phenotype. TP53, HER2, and other alterations may accumulate during malignant progression, particularly in salivary duct carcinoma ex PA.

7.4 Clinical clues and diagnostic traps

Table 8. History can raise suspicion, but CXPA remains a pathologic diagnosis.

Clue	Interpretation
Long-standing mass with recent rapid growth	Classic history, but absence does not exclude CXPA.
New pain, fixation, facial weakness, skin change	Suggests invasive malignant transformation and mandates oncologic imaging.
Carcinoma adjacent to hyalinized nodule	Sample extensively for residual PA and consider lineage studies.
High-grade carcinoma in a recurrent “PA” bed	Review prior slides and operative history; recurrent PA can be multinodular and carcinoma may be focal.
No demonstrable PA or molecular support	Do not force ex-PA solely because the patient recalls a long-standing lump.

BOARD TRAP | “Carcinoma ex pleomorphic adenoma” is not a single histology. A report that omits the malignant component is clinically incomplete.

Chapter Synthesis

- Find and name the malignant component.
- Report actual invasion and the traditional intracapsular/minimal/wide category.
- PLAG1/HMGA2 can support PA lineage but do not grade or stage the carcinoma.
- Rapid change in a long-standing PA is a red flag, not proof.

CHAPTER 8

Polymorphous Adenocarcinoma Spectrum

Bland cytology plus architectural diversity - with a cribriform phenotype that deserves particular attention to the neck.

8.1 The paradox: uniform cells, polymorphous architecture

Polymorphous adenocarcinoma (PAC) usually arises in minor salivary glands, especially the palate. The cells are strikingly uniform, but the architecture changes from tubular to trabecular, papillary, cribriform, fascicular, and targetoid patterns. Infiltration and perineural growth establish malignancy. Targetoid arrangement around nerves is classic. Because the nuclei resemble one another across patterns, the diagnosis becomes easier when the resident deliberately separates cytology from architecture.[15,16]

8.2 Classic PAC and the cribriform phenotype

Classic PAC is generally indolent but can recur locally and rarely metastasize. Tumors with prominent cribriform, glomeruloid, or papillary architecture - historically called cribriform adenocarcinoma of salivary gland - often arise at the tongue base or oropharynx and show a greater tendency for cervical nodal metastasis. Current classification treats these lesions within a molecular and morphologic spectrum, but terminology continues to evolve. The practical point is stable: the pathology report should flag the cribriform/tongue-base phenotype because it changes regional-risk thinking.

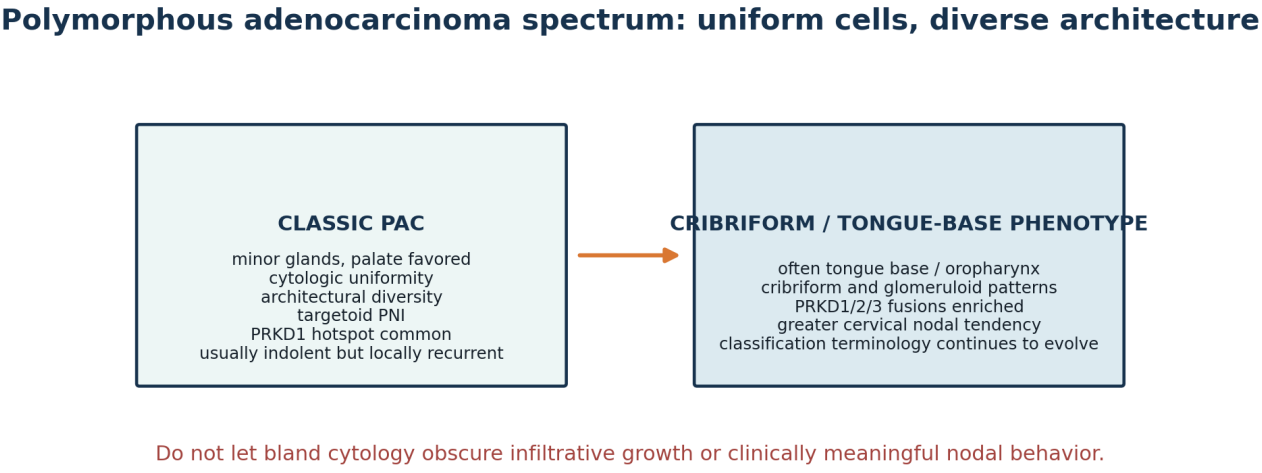


Figure 11. Original synthesis. The cribriform/tongue-base phenotype has greater nodal relevance than classic palatal PAC.

8.3 PRKD alterations

A recurrent PRKD1 hotspot mutation is enriched in classic PAC, while PRKD1, PRKD2, or PRKD3 fusions are more common in cribriform-spectrum tumors. These alterations support the biologic continuum and can help in difficult cases. They do not remove the need to describe site, architecture, invasion, PNI, nodal status, and any high-grade transformation.

8.4 Differential diagnosis

Mimic	Distinguishing approach
Adenoid cystic carcinoma	AdCC has a more basaloid dual-cell phenotype, true ducts and pseudocysts, MYB/MYBL1 pathway, and often darker angular nuclei.
Pleomorphic adenoma	PA is circumscribed and matrix-rich; PAC is infiltrative with targetoid PNI and lacks classic chondromyxoid stroma.
Secretory carcinoma	Secretory phenotype, S100/mammaglobin and ETV6-related fusion; architecture may overlap but targetoid pattern is less characteristic.
Epithelial-myoepithelial carcinoma	Biphasic ductal units with conspicuous outer clear myoepithelial cells.
Metastatic papillary thyroid carcinoma	PAX8/TTF1/thyroglobulin context and thyroid-type nuclei; clinical correlation essential.

CLINICAL PEARL | A bland cribriform minor-gland tumor at the tongue base should prompt deliberate nodal assessment. Bland cytology does not equal negligible regional risk.

Chapter Synthesis

- PAC combines cytologic uniformity with architectural diversity and infiltrative/targetoid growth.
- Classic palatal PAC is usually indolent but can recur.
- Cribriform/tongue-base tumors have greater nodal tendency.
- PRKD alterations support the spectrum but do not replace morphology or site.

CHAPTER 9

Biphasic and Myoepithelial Carcinomas

Tumors in which bland cells and preserved differentiation make the invasive interface more important than atypia.

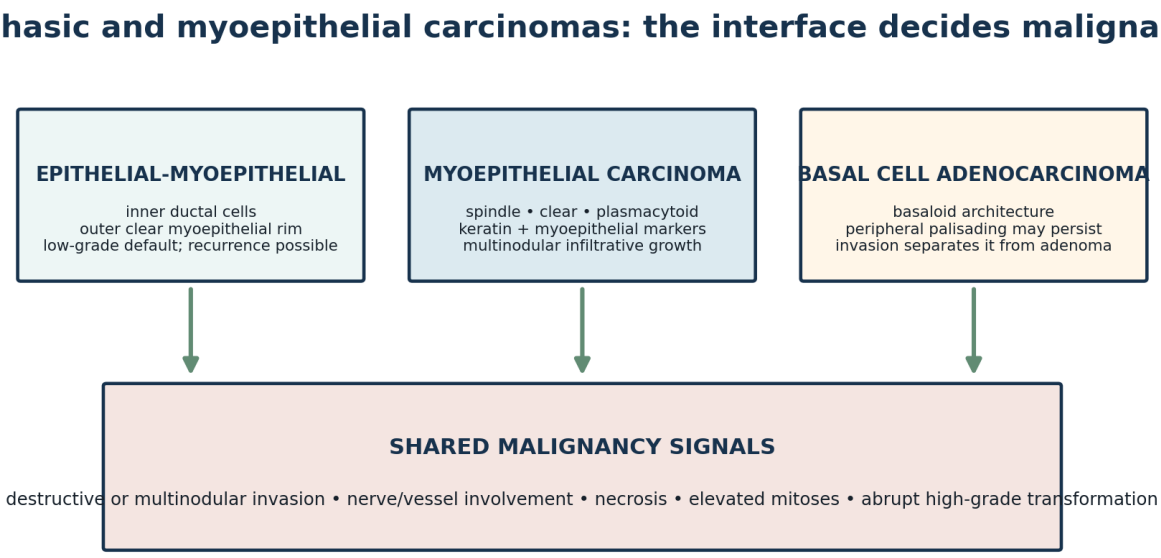


Figure 12. Original synthesis. In biphasic and myoepithelial tumors, invasion is often the decisive evidence of malignancy.

9.1 Epithelial-myoepithelial carcinoma

Epithelial-myoepithelial carcinoma (EMC) forms ducts with an inner eosinophilic epithelial layer and an outer clear myoepithelial layer. It is generally low grade but infiltrative, with a meaningful risk of local recurrence and occasional nodal or distant metastasis. The outer layer may be prominent, attenuated, or focally lost, and the tumor can show oncocytic, apocrine, sebaceous, or double-clear variants. High-grade transformation may arise in either component and markedly worsens behavior.[17,18]

9.2 Myoepithelial carcinoma

Myoepithelial carcinoma is one of the most morphologically variable salivary tumors. Cells may be spindle, epithelioid, plasmacytoid, clear, or stellate, arranged in solid, reticular, or multinodular patterns within hyalinized or myxoid stroma. The immunophenotype should demonstrate epithelial differentiation plus myoepithelial markers, but no single marker is both perfectly sensitive and specific. Destructive or multinodular infiltration separates carcinoma from myoepithelioma; cytologic atypia may be minimal. Some tumors arise ex pleomorphic adenoma and share PLAG1 or HMGA2 abnormalities.[19,20]

9.3 Basal cell adenocarcinoma

Basal cell adenocarcinoma resembles basal cell adenoma cytologically and architecturally. Peripheral palisading and basaloid nests may persist. The difference is invasion: destructive growth into salivary parenchyma, fat, muscle, nerve, or vessel. A limited biopsy may therefore be unable to make the distinction. Basal cell adenocarcinoma is usually low grade but can recur and occasionally metastasize.

Table 9. Cytology alone is insufficient in the biphasic/basaloid family.

Entity	Defining architecture	Malignancy signal	Typical behavior
Epithelial-myoepithelial carcinoma	Inner ductal cells + outer clear myoepithelial layer.	Infiltration, PNI/LVI, transformation.	Low-grade default; local recurrence is important.
Myoepithelial carcinoma	Monomorphic or mixed myoepithelial cell	Destructive or multinodular	Wide spectrum from

Entity	Defining architecture	Malignancy signal	Typical behavior
	shapes in solid/reticular/multinodular pattern.	infiltration; necrosis/mitoses/HGT.	indolent to aggressive.
Basal cell adenocarcinoma	Basaloid nests/trabeculae, often palisaded.	Invasion beyond a circumscribed border.	Usually low grade; recurrence > distant spread.
Carcinoma ex PA with myoepithelial phenotype	Malignant myoepithelial component plus residual PA.	Invasion depth and transformed morphology.	Depends strongly on extent and grade.

BOARD TRAP | A core biopsy showing "basal cell neoplasm" may be an honest limit of the specimen. The adenoma-versus-adenocarcinoma distinction often requires the excisional interface.

Chapter Synthesis

- EMC is a biphasic ductal carcinoma with generally low-grade but recurrent behavior.
- Myoepithelial carcinoma is defined by lineage plus invasion, not by one cell shape.
- Basal cell adenocarcinoma may be cytologically indistinguishable from adenoma on a limited sample.
- High-grade transformation is a major adverse modifier across the group.

CHAPTER 10

Clear-Cell, Intraductal, and Emerging Low-Grade Entities

Rare tumors are best retained as compact clinicopathologic packages: site, pattern, defining alteration, and malignant mimic.

10.1 Hyalinizing clear cell carcinoma

Clear cell carcinoma, often called hyalinizing clear cell carcinoma, usually arises in oral minor salivary glands. It consists of cords, nests, and trabeculae of glycogen-rich clear cells in a hyalinized stroma. p63 and p40 are often positive, which can create confusion with mucoepidermoid or squamous carcinoma. EWSR1::ATF1 establishes the diagnosis in the appropriate morphology. Most tumors are low grade, but perineural invasion, local recurrence, nodal metastasis, and rare high-grade transformation are documented.[21-23]

10.2 Intraductal carcinoma

Intraductal carcinoma is characterized by a neoplastic epithelial proliferation confined, at least predominantly, within ducts surrounded by a continuous myoepithelial rim. Intercalated-duct-type tumors are often S100/SOX10 positive and frequently harbor RET fusions. Apocrine intraductal carcinomas may express AR and HER2, while oncocytic variants have additional molecular diversity. Although many are indolent, invasive foci occur; the pathologist must sample the interface and document whether the myoepithelial boundary is preserved.[24-26]

10.3 Microsecretory adenocarcinoma

Microsecretory adenocarcinoma is an emerging low-grade minor-gland carcinoma composed of infiltrative microcysts and small tubules with basophilic luminal secretion and bland cells. It is defined by MEF2C::SS18. The subtle infiltration can be mistaken for a benign ductal proliferation or chronic inflammatory process. The key is to recognize an unencapsulated, permeative gland-forming lesion and use molecular confirmation when needed.[27]

10.4 Sclerosing microcystic adenocarcinoma

Sclerosing microcystic adenocarcinoma is a low-grade infiltrative carcinoma of minor salivary sites, composed of small ducts and microcysts in dense sclerotic stroma, often with perineural invasion. It resembles cutaneous microcystic adnexal carcinoma and can also be confused with sclerosing sialometaplasia. Surface connection, site, deep infiltration, and the complete clinicopathologic context are essential.[28,29]

Table 10. Compact profiles for rare but boards-relevant malignant entities.

Entity	Favored setting	Defining package	Principal trap
Clear cell carcinoma	Oral minor glands	Clear glycogen-rich cells + hyalinized stroma + EWSR1::ATF1.	p63/p40 positivity misread as SCC or MEC.
Intraductal carcinoma	Parotid predominance	Intraductal epithelial proliferation with myoepithelial rim; RET and subtype-specific alterations.	Assuming all cases are noninvasive without extensive interface sampling.
Microsecretory adenocarcinoma	Oral minor glands	Bland microcysts/tubules, basophilic secretion, MEF2C::SS18.	Benign ductal or inflammatory process.
Sclerosing microcystic adenocarcinoma	Minor glands, often oral	Deep infiltrative microcysts in sclerosis, frequent PNI.	Sclerosing sialometaplasia or cutaneous adnexal carcinoma.

RESIDENT TAKEAWAY | For a rare low-grade carcinoma, retain four anchors: favored site, low-power architecture, defining molecular alteration, and the mimic that would lead to the wrong operation.

Chapter Synthesis

- Hyalinizing clear cell carcinoma is an EWSR1::ATF1 tumor, usually of oral minor glands.
- Intraductal carcinoma requires proof of the myoepithelial boundary and careful search for invasion.
- Microsecretory and sclerosing microcystic adenocarcinomas are subtle infiltrative minor-gland tumors.
- Rare does not mean clinically irrelevant; a defining alteration may prevent a major diagnostic error.

CHAPTER 11

High-Grade Transformation and Difficult Mimics

When a familiar salivary tumor abruptly loses its differentiation, the parent component becomes the key to diagnosis.

11.1 What high-grade transformation means

High-grade transformation is an abrupt transition from a conventional salivary carcinoma into a poorly differentiated or anaplastic component. It has been described in AciCC, AdCC, EMC, secretory carcinoma, PAC, myoepithelial carcinoma, and other entities. The transformed area shows solid growth, necrosis, prominent atypia, brisk mitotic activity, and often loss of the parent tumor's immunophenotype. This is distinct from gradual progression within an ordinary grading system and is associated with substantially increased nodal, distant, and mortality risk.[30,31]

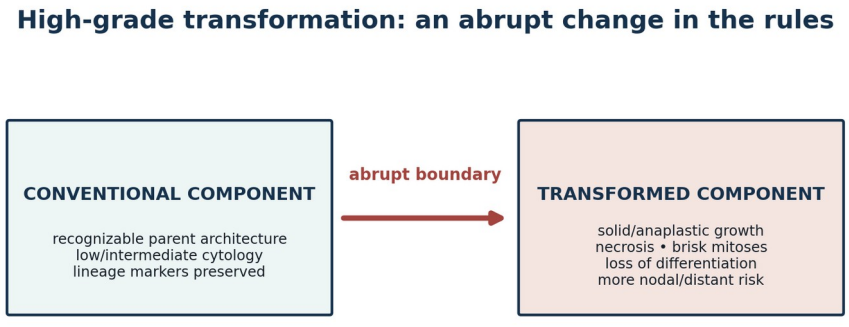


Figure 13. Original synthesis. High-grade transformation creates a second biologic component that must be sampled, named, and reported.

11.2 Why limited biopsy fails

A core that samples only the transformed component may yield “poorly differentiated carcinoma,” “adenocarcinoma NOS,” or even “salivary duct carcinoma” if comedonecrosis is present. Conversely, a small sample of only the conventional component may understate the disease. Imaging-guided sampling should target solid or rapidly growing regions, and the resection specimen requires extensive sampling of heterogeneous areas. Comparison with prior pathology is particularly valuable in a recurrent tumor.

11.3 Adenocarcinoma NOS as a diagnosis of exclusion

Modern molecular classification has reduced the appropriate use of adenocarcinoma, not otherwise specified. Before accepting NOS, the pathologist should exclude secretory carcinoma, salivary duct carcinoma, clear cell carcinoma, intraductal carcinoma, metastatic adenocarcinoma, and a transformed component of another salivary tumor. NOS remains legitimate when a true salivary adenocarcinoma lacks defining morphology or molecular identity, but it should not be used as a substitute for incomplete workup.

11.4 Non-salivary malignancy in a salivary gland

Table 11. The parotid contains lymph nodes; a malignant parotid-region mass is not automatically a primary salivary carcinoma.

Diagnosis to exclude	Clinical clue	Pathology / ancillary clue
Metastatic cutaneous SCC to intraparotid node	Prior scalp, temple, auricular, or facial skin cancer; parotid-tail or multifocal nodal disease.	Nodal architecture, keratinizing SCC; no convincing primary salivary precursor. HPV/UV signatures may help in selected cases.
Metastatic melanoma	Skin history, pigmented lesion, multiple nodes.	SOX10/S100/Melan-A context; morphology can be epithelioid or spindle.
Lymphoma	Autoimmune disease, bilateral or diffuse gland enlargement, systemic nodes.	Flow cytometry and hematolymphoid markers; avoid relying on epithelial FNA algorithms.
Metastatic renal cell carcinoma	Hypervascular clear-cell lesion, renal history or occult renal mass.	PAX8/CAIX/renal markers; rich sinusoidal vasculature.
Metastatic thyroid carcinoma	Thyroid lesion or cervical nodal pattern.	Thyroglobulin, TTF1, PAX8; nuclear features and clinical imaging.
Direct extension / metastasis from upper aerodigestive SCC	Mucosal symptoms or primary lesion.	Anatomic continuity or HPV/EBV-associated context depending site.

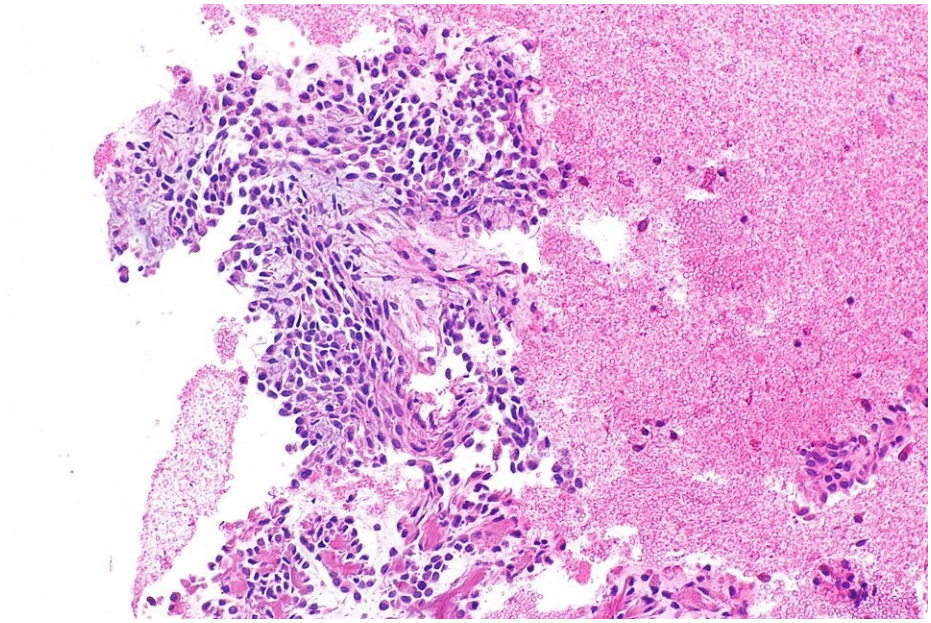


Figure 14. Cell-block preparation from FNA of pleomorphic adenoma. Librepath, CC BY-SA 3.0, via Wikimedia Commons. Cytology can identify cells and matrix, but it cannot reliably assess the complete invasive interface or exclude an unsampled transformed component.

BOARD TRAP | Primary squamous cell carcinoma of a salivary gland is exceptionally uncommon. Exclude metastatic cutaneous SCC, a mucosal primary, and high-grade MEC before using that diagnosis.

Chapter Synthesis

- HGT is an abrupt biologic shift, not merely “a high grade” within the parent tumor.
- Sample heterogeneous tumors extensively and compare with prior pathology.
- Use adenocarcinoma NOS only after modern entities and metastases are excluded.
- Remember intraparotid lymph nodes: metastatic cutaneous SCC is a common malignant parotid-region problem.

CHAPTER 12

Integrated Reasoning, Pathology Reports, and Boards Review

The final skill is to convert a tumor name into a pattern of failure and a defensible treatment-planning question.

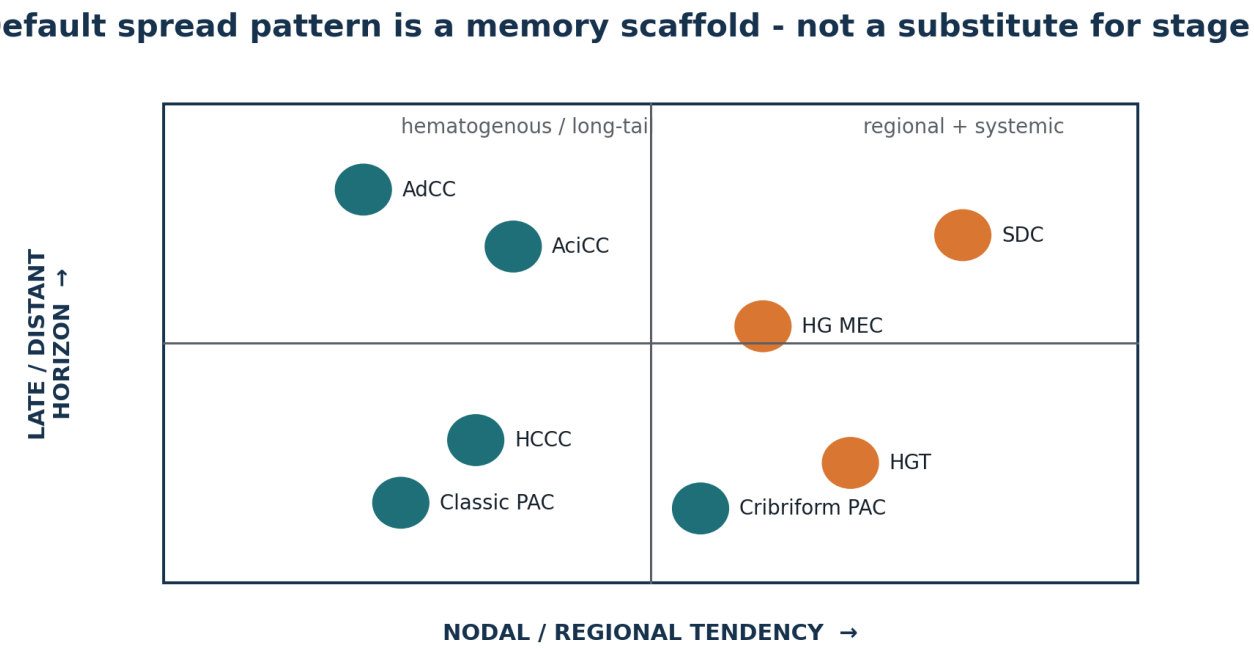


Figure 15. Original synthesis. Default spread patterns help organize memory, but actual stage and adverse features remain decisive.

12.1 A five-step read of any malignant report

1. Confirm the specimen and certainty: FNA, core, resection, recurrence, or metastasis; definitive entity versus favored diagnosis.
2. Name the biologic family: mucous/squamoid, basaloid/cribriform, acinar/secretory, apocrine high grade, polymorphous, biphasic, or clear-cell.
3. Extract risk modifiers: tumor-specific grade, solid component, HGT, PNI, LVI, margins, nodes, ENE, and adjacent-structure invasion.
4. Translate to a failure pattern: local/nerve, cervical nodes, hematogenous spread, or long-horizon recurrence.
5. Identify operation- or therapy-changing uncertainty: need for skull-base MRI, neck staging, expert pathology review, molecular confirmation, or biomarker testing.

12.2 Clinical vignettes

Case 1: The painful palatal mass

A 52-year-old has a 2-cm hard-palate submucosal mass, deep pain, and V2 numbness. Biopsy shows cribriform AdCC. The key next step is not simply wide local excision. MRI should map the complete trigeminal pathway toward the pterygopalatine fossa, foramen rotundum, and skull base. The symptom is evidence about extent.

Case 2: The cystic parotid carcinoma

A 29-year-old has a cystic parotid lesion with scant mucous and intermediate cells on FNA. MAML2 rearrangement is present. This supports MEC, but the operation and neck plan still depend on grade, imaging, facial-nerve function, and stage. A fusion does not make a large infiltrative tumor low risk.

Case 3: The "acinic" tumor with diffuse S100

A parotid tumor is microcystic, S100 and mammaglobin positive, and NR4A3 negative. Secretory carcinoma is favored and ETV6/NTRK testing is appropriate. The distinction establishes a molecularly defined entity and may matter greatly if the tumor later becomes unresectable or metastatic.

Case 4: The long-standing mass that changed

A parotid lump present for twelve years enlarges rapidly and produces facial weakness. Imaging shows an irregular tumor and nodes. The team should plan for carcinoma ex PA or another high-grade carcinoma, obtain adequate tissue, stage the neck and chest, counsel regarding possible facial-nerve sacrifice/reconstruction, and avoid an unplanned limited excision.

Case 5: The bland tongue-base cribriform tumor

A minor-gland tumor at the tongue base has uniform cells, cribriform architecture, PRKD fusion, and a metastatic level II node. This fits the cribriform PAC-spectrum phenotype. The bland cells should not distract from the site-specific nodal behavior.

12.3 High-yield comparison

Table 12. The core malignant salivary tumor map.

Entity	Defining pattern / marker	Default clinical memory	Classic board trap
Mucoepidermoid	Mucous + intermediate + epidermoid; MAML2 often.	Grade-dependent; high grade more nodal/systemic.	MAML2 is not a grading system.
Adenoid cystic	Dual-cell tubular/cribriform; MYB/MYBL1 pathway.	Nerve-seeking; late lung metastasis.	Slow growth mistaken for low risk.
Acinic cell	Serous acinar differentiation; NR4A3.	Usually low grade, long horizon; HGT possible.	Confused with secretory carcinoma.
Secretory	S100/mammaglobin; ETV6::NTRK3.	Usually low/intermediate; targetable fusion.	Pan-TRK alone treated as definitive.
Salivary duct	Apocrine high-grade; AR, HER2 subset.	Node-seeking and aggressive.	Any comedonecrotic tumor called SDC.
CXPA	Carcinoma arising in PA; PLAG1/HMGA2 support.	Depends on carcinoma subtype and invasion.	Ex-PA reported without malignant subtype.
PAC spectrum	Uniform cells, diverse/cribriform patterns; PRKD.	Classic indolent; cribriform tongue-base more nodal.	Bland cytology mistaken for benignity.
Clear cell carcinoma	Hyalinized clear-cell cords; EWSR1::ATF1.	Generally low grade; PNI possible.	p63 positivity mistaken for SCC.
EMC / myoepithelial	Biphasic or myoepithelial lineage + invasion.	Local recurrence; spectrum of aggressiveness.	Limited biopsy cannot assess interface.

12.4 Boards-style rapid recall

Table 13. High-yield recall should attach a feature to a biologic consequence.

Prompt	Best answer
Most characteristic salivary carcinoma for perineural spread and late lung	Adenoid cystic carcinoma.

Prompt	Best answer
metastasis	
Fusion-associated carcinoma with mucous, intermediate, and epidermoid cells	Mucoepidermoid carcinoma; CRTC1/3::MAML2.
Parotid carcinoma with zymogen granules and nuclear NR4A3	Acinic cell carcinoma.
S100/mammaglobin-positive tumor with ETV6::NTRK3	Secretory carcinoma.
High-grade apocrine carcinoma with AR and possible HER2 amplification	Salivary duct carcinoma.
Rapid growth in a decades-old pleomorphic adenoma	Carcinoma ex pleomorphic adenoma until proven otherwise.
Bland palatal carcinoma with targetoid PNI and PRKD alteration	Polymorphous adenocarcinoma.
Clear-cell minor-gland carcinoma with hyalinized stroma and EWSR1::ATF1	Hyalinizing clear cell carcinoma.
Inner ductal and outer clear myoepithelial layers	Epithelial-myoepithelial carcinoma.
Abrupt anaplastic area arising in an otherwise recognizable low-grade carcinoma	High-grade transformation.

FINAL RESIDENT TAKEAWAY | Do not memorize salivary carcinomas as isolated names. For every entity, retain one low-power pattern, one molecular anchor, one dominant route of failure, and one diagnostic trap. That four-part package is durable enough for clinic, the operating room, tumor board, and boards.

CHAPTER APPENDIX

Consolidation, References, and Figure Credits

A compact review sheet and the evidence base used for this volume.

One-Page Malignant Salivary Framework

Question	Resident answer
What is it?	Entity established by architecture + lineage ± molecular confirmation.
How aggressive is its default biology?	Tumor-specific grade, solid component, or identity-defined high grade.
Has the biology changed?	Look for high-grade transformation and heterogeneity.
Where has it spread?	Local structures, named nerves, lymphovascular spaces, nodes/ENE, distant sites.
What will fail first?	Local/nerve, nodal/regional, hematogenous, or delayed recurrence.
What must be tested?	MAML2, MYB/MYBL1, NR4A3, ETV6/NTRK, AR/HER2, PRKD, EWSR1, RET as morphology dictates.
What uncertainty changes treatment?	Discordant biopsy, unsampled interface, possible metastasis, unclear grade, or missing biomarker.

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- All original diagrams are educational abstractions and are not substitutes for review of complete histologic slides, current WHO criteria, CAP protocols, or institutional pathology consultation.

EDUCATIONAL SCOPE | This study guide is designed for resident education. Classification, staging, biomarker interpretation, and treatment recommendations should be checked against the current WHO classification, AJCC manual, CAP protocol, and institutional multidisciplinary practice.