SALIVARY GLAND NEOPLASMS

VOLUME V

Adjuvant Therapy, Recurrent Disease, and Surveillance

From final pathology to radiation, salvage, systemic therapy, and lifelong follow-up

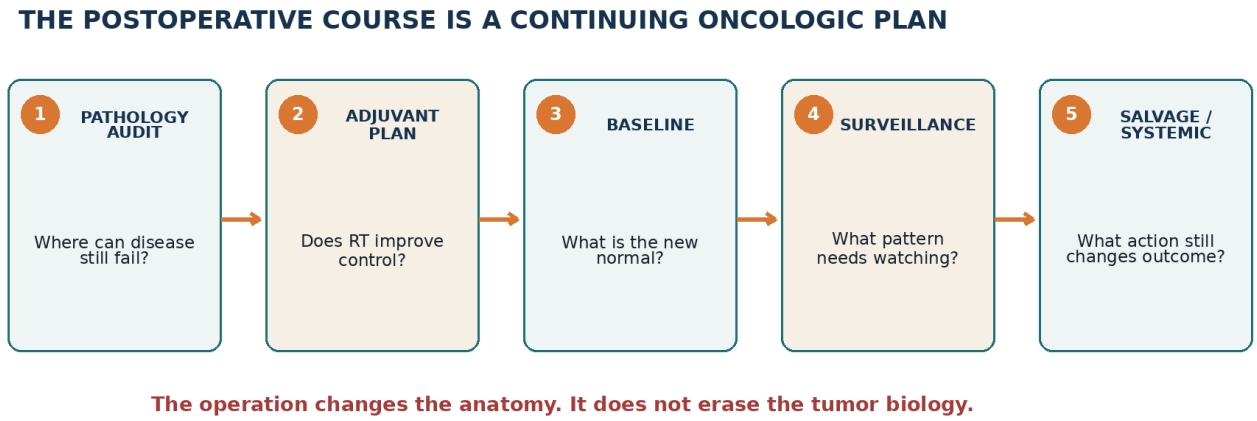

Figure 1. Original synthesis. The postoperative course remains an active oncologic plan: pathology defines failure risk, adjuvant treatment modifies that risk, surveillance establishes the trajectory, and recurrence is re-staged before treatment.

THE CENTRAL QUESTION | After the operation, which failure pattern is most likely - and what treatment, surveillance, or systemic strategy can meaningfully change it?

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

CHAPTER 0

Orientation

Salivary cancer follow-up is not a generic head-and-neck template. It must be adapted to surgical anatomy, histology, nerve pathways, metastatic tempo, and molecular targets.

The operation ends with an altered anatomy and a pathology report. The resident's next task is to convert those two records into a forecast: where could microscopic disease remain, how likely is it to matter, and what intervention has enough evidence to justify its morbidity? This forecast drives postoperative radiation, target design, the decision not to add chemotherapy routinely, the intensity of surveillance, and the timing of salvage or systemic treatment.

Salivary malignancies make this difficult because "recurrence" can mean very different things. A high-grade salivary duct carcinoma may develop rapidly progressive nodal and visceral disease. Adenoid cystic carcinoma may remain controlled locally yet produce slowly enlarging pulmonary metastases many years later. Secretory carcinoma may be transformed from a rare chemotherapy-resistant diagnosis into a highly targetable disease when an NTRK fusion is demonstrated. The useful framework is therefore not simply local versus distant; it is site of failure, biologic tempo, symptoms, resectability, and actionable biology.

Learning objectives

- Interpret final pathology as a map of local-bed, perineural, regional, and distant failure risk.
- Identify strong and discretionary indications for postoperative radiation and explain how operative anatomy shapes target volumes.
- Explain why concurrent chemotherapy is not routinely added to postoperative or definitive radiation outside a clinical trial.
- Build a workup and treatment sequence for unresectable, locally recurrent, regional, oligometastatic, and widely metastatic disease.
- Distinguish when observation, local ablative therapy, cytotoxic chemotherapy, targeted therapy, or a clinical trial is appropriate.
- Use AR, HER2, NTRK, and broader molecular testing to guide advanced-disease treatment without overinterpreting small studies.
- Design surveillance that respects both early recurrence risk and the late natural history of adenoid cystic and other salivary cancers.
- Integrate xerostomia, dental care, facial function, vision, swallowing, hearing, fibrosis, lymphedema, pain, and psychosocial recovery into long-term care.

Contents

EVIDENCE NOTE | The principal management anchors are the ASCO guideline and ESMO-EURACAN guideline. Many systemic data come from small, single-arm studies because individual histologies are rare. Response rates should guide discussion, not be treated as direct cross-trial comparisons.

CHAPTER 1

The Final Pathology Conference

The pathology report is not merely a diagnosis. It is the handoff from resection to risk-adapted postoperative care.

A salivary pathology report should be read beside the preoperative imaging, operative note, specimen orientation, and nerve map. A “negative margin” is more useful when the surgeon and pathologist agree which surface faced the facial nerve, skull base, mucosa, skin, or deep parapharyngeal space. Perineural invasion is more actionable when the involved nerve caliber and clinical pathway are understood. A positive intraparotid node means something different from an isolated low-grade primary with no regional risk. Multidisciplinary review is therefore not ceremonial: it reconstructs the disease in three dimensions after the specimen has been divided into slides.

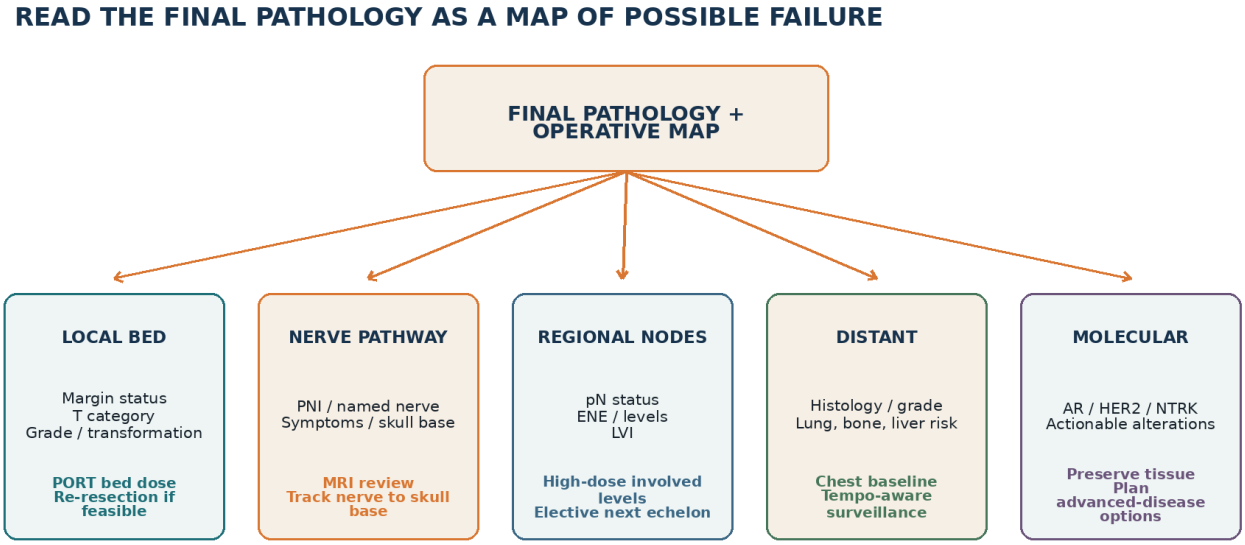

Figure 2. Original synthesis. Final pathology should be converted into a failure map that links adverse features to local-bed, nerve-pathway, nodal, distant, and molecular decisions.

1.1 The minimum postoperative data set

Domain	Resident questions	Management consequence
Histology and grade	Is the entity definitive? Is there high-grade transformation or a high-grade component?	Changes PORT strength, nodal/distant risk, molecular testing, and surveillance intensity.
Primary and extent	Exact site, size, extraparenchymal or adjacent-structure extension, T category?	Defines the surgical bed and likelihood of residual microscopic disease.
Margins	Positive, close, or widely clear? Which mapped margin? Can it be re-resected?	Positive margin strongly supports PORT; a focal accessible margin may justify revision before RT.
Neural disease	Microscopic PNI, large/named nerve involvement, symptoms, or gross nerve invasion?	Determines MRI review, nerve-pathway target, skull-base coverage, and surveillance signs.
Lymphovascular and nodal	LVI, number/size of nodes, intraparotid nodes, levels, extranodal extension?	Defines nodal high-dose volumes and next-echelon elective coverage.
Molecular phenotype	AR, HER2, NTRK fusion, or other alteration relevant to the entity?	Usually does not replace local therapy, but preserves options for recurrent/metastatic disease.

1.2 Re-resection before radiation

A positive margin is not automatically solved by radiation. If the involved margin is anatomically identifiable and can be cleared with acceptable morbidity, re-resection should be discussed. The decision depends on whether the positive

edge represents an avoidable residual focus or an intentionally close boundary at a critical structure, whether additional surgery would delay adjuvant therapy, and whether a wider resection meaningfully improves the probability of control. Revision surgery for recurrent disease also warrants renewed evaluation for adjuvant treatment.[1]

BOARD PEARL | A “close” margin is not a universal numeric diagnosis across salivary sites. Interpret the measured distance together with histology, growth pattern, anatomic barrier, specimen handling, and whether the margin is a true patient-side margin.

1.3 Pathology features as spatial instructions

Adenoid cystic carcinoma and other tumors with neural tropism require attention to the named nerve pathway even when the main specimen margin is negative. Nodal metastasis requires more than treating the primary bed; involved levels and the next echelon at risk must be integrated into the plan. High-grade transformation implies that the aggressive component, not the indolent parent label, should drive regional and distant risk assessment. Conversely, an early low-grade carcinoma that was removed with a clearly mapped negative margin may be appropriately observed rather than irradiated reflexively.

CHAPTER SYNTHESIS

- Review pathology beside imaging, operative anatomy, and specimen orientation.
- Margins, grade, PNI, LVI, T category, and nodal disease predict different spatial patterns of failure.
- Re-resection remains preferable when a positive margin can be safely and meaningfully cleared.
- Molecular testing preserves future options but does not substitute for adequate local-regional therapy.

CHAPTER 2

Postoperative Radiation Therapy

PORT is a risk-reduction treatment directed at microscopic disease; its indication and volume should be explicit.

Surgery is the primary treatment for resectable salivary-gland carcinoma, but local-regional control is threatened by infiltrative histology, high grade, advanced local extent, neural spread, nodal disease, lymphovascular invasion, and inadequate margins. ASCO recommends PORT for all resected adenoid cystic carcinomas and for high-grade tumors, positive margins, perineural invasion, nodal metastases, lymphatic or vascular invasion, and T3-T4 disease. PORT may also be considered for close margins and intermediate-grade tumors, where the evidence is less certain.[1]

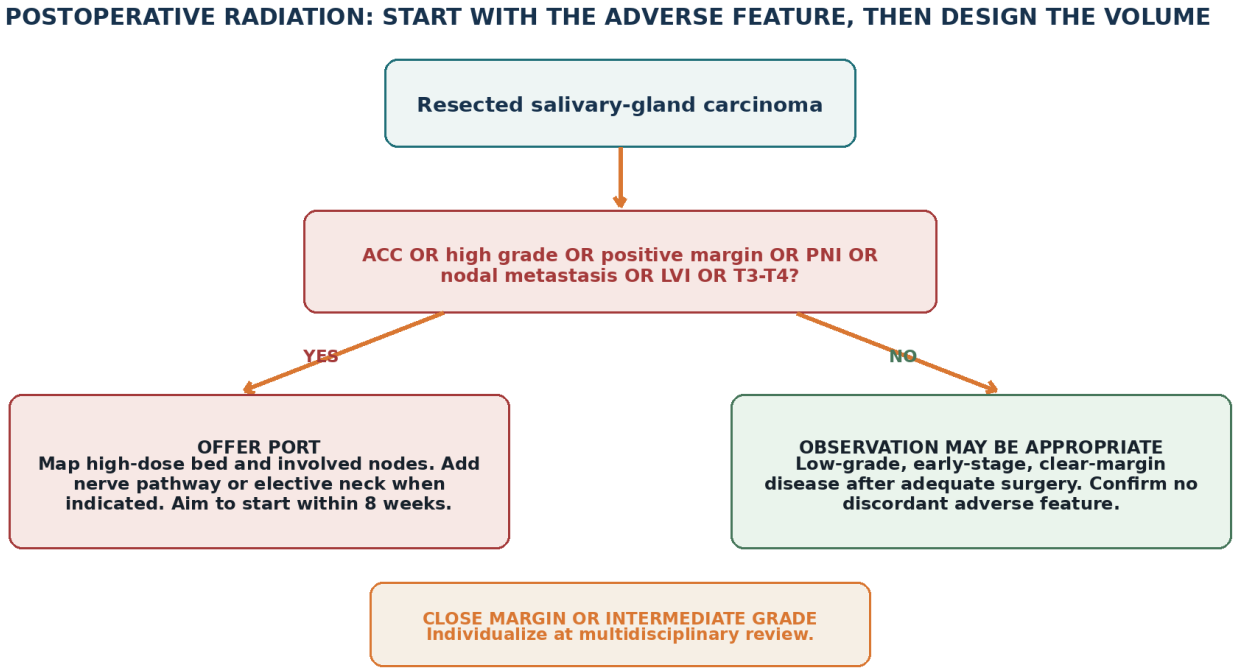

Figure 3. Original synthesis based on ASCO guidance. The strongest PORT indications are adverse biologic or anatomic features; low-risk observation still requires confidence in diagnosis, margin mapping, and surgical adequacy.

2.1 Strong versus individualized indications

Feature	PORT stance	Why it matters
Adenoid cystic carcinoma	Offer PORT after resection across stages.	Infiltrative and perineural biology creates microscopic local risk even in small primaries.
High-grade histology or high-grade transformation	Offer PORT.	Higher local, nodal, and distant recurrence risk.
Positive margin	Offer PORT; evaluate re-resection first when feasible.	Gross or microscopic residual disease is a dominant local-risk feature.
Perineural invasion	Offer PORT.	Failure can occur along the nerve beyond the apparent primary bed.
Pathologic nodal metastasis	Offer PORT to appropriate bed and nodal levels.	Regional recurrence risk persists despite dissection, especially with multiple nodes or ENE.
Lymphatic or vascular invasion	Offer PORT.	Marker of dissemination beyond the gross tumor.
T3-T4 disease	Offer PORT.	Large size or extraparenchymal/adjacent-structure extension increases microscopic residual risk.
Close margin / intermediate grade	Individualize.	Evidence is less definitive; anatomy and other adverse features determine the balance.
T1-T2 low-grade, clear margin, no adverse feature	Observation is often appropriate.	RT morbidity may exceed the incremental control benefit after adequate surgery.

2.2 Timing and postoperative readiness

ASCO recommends initiating postoperative radiation within 8 weeks of surgery.[1] This is a planning deadline, not a reason to irradiate an unhealed wound. The interval should be used actively: finalize pathology, obtain dental evaluation when oral cavity or mandible will receive dose, secure nutrition and swallowing support, document hearing when cochlear dose or ototoxic therapy is relevant, manage infection or fistula, and complete simulation. Delays caused by preventable referral or dental logistics should not be normalized.

2.3 Expected benefit and limits

PORT is most consistently supported for improved local-regional control. The magnitude of overall-survival benefit is harder to define because salivary histologies are heterogeneous, distant failure may dominate, and retrospective series are confounded by selection. Residents should therefore avoid two opposite errors: treating PORT as optional simply because randomized evidence is sparse, or promising that PORT eliminates the late metastatic risk of adenoid cystic or high-grade disease.

COUNSELING LANGUAGE | "Radiation is being recommended because the pathology shows a meaningful risk that microscopic disease remains in the bed, nerve pathway, or nodes. Its main purpose is to improve local-regional control; it cannot remove all future risk of distant metastasis."

2.4 Elective neck irradiation

When the cN0 neck was not surgically treated, elective nodal irradiation may be offered for T3-T4 cancers or high-grade malignancies. After a positive neck dissection, the high-dose volume includes involved levels and the elective volume may cover the next echelon at risk. The exact levels depend on the primary site, prior dissection, and nodal distribution rather than a one-size-fits-all parotid template.[1]

CHAPTER SYNTHESIS

- Offer PORT for ACC and for high grade, positive margin, PNI, nodal disease, LVI, and T3-T4 tumors.
- Close margins and intermediate grade require individualized multidisciplinary judgment.
- Plan actively so RT can begin within 8 weeks without compromising wound, dental, nutritional, or functional readiness.
- PORT improves local-regional control but does not erase histology-specific distant risk.

CHAPTER 3

Radiation Target Design and Toxicity

The target is a reconstructed anatomic story: surgical bed, residual-risk interfaces, nerve pathways, and nodal echelons.

A good radiation plan begins before the operation is forgotten. The radiation oncologist needs the preoperative imaging, operative report, specimen map, pathology, and postoperative anatomy. A generic preauricular volume can miss a deep-lobe margin, a stylomastoid-foramen pathway, a palatal nerve toward the pterygopalatine fossa, or a nodal basin that was not dissected. Conversely, indiscriminate expansion increases cochlear, brainstem, temporal-lobe, mandible, oral-cavity, and swallowing dose.

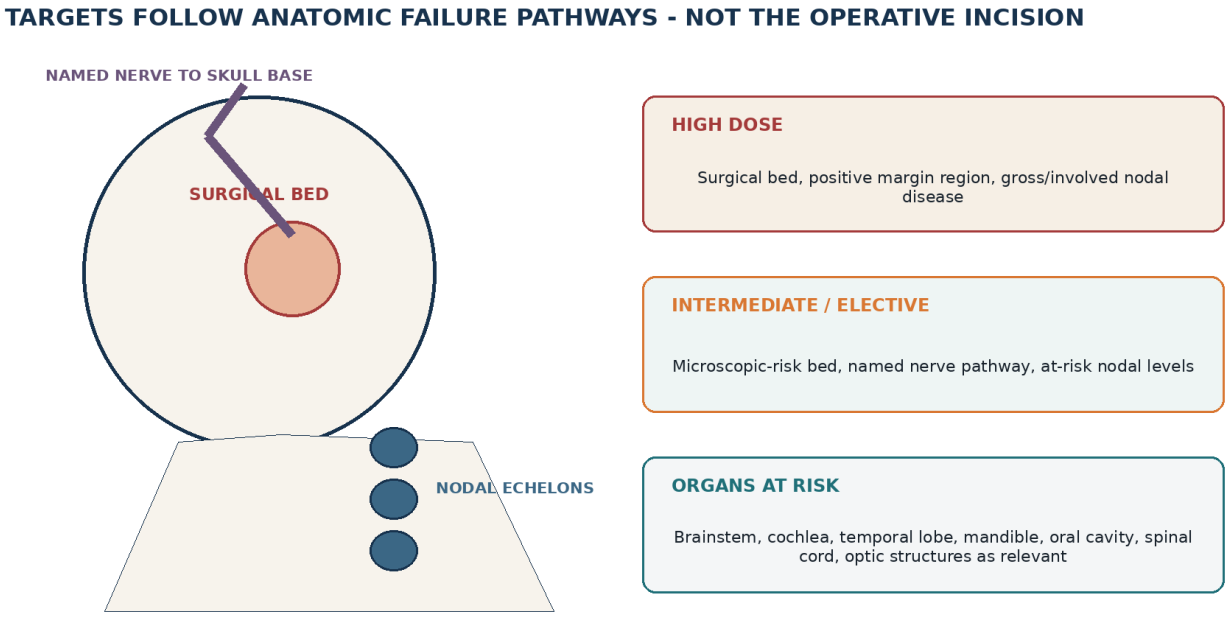

Figure 4. Original synthesis. High-dose and elective targets follow the surgical bed, neural routes, and nodal echelons while respecting adjacent organs at risk.

3.1 High-dose and elective targets

ASCO recommends that the postoperative high-dose target cover the salivary-gland surgical bed and appropriate nodal levels. Conventionally fractionated high-dose postoperative treatment is generally at least 60 Gy, with dose escalation or a residual-disease strategy determined by margin and gross disease. Elective or intermediate-dose volumes cover microscopic-risk regions rather than every tissue encountered during exposure.[1]

Risk pattern	Volume concept	Resident contribution
Positive or close primary margin	Map the specific anatomic surface and any re-resection; avoid an unhelpful label such as “deep.”	Orient specimen and name the patient-side interface in the operative note.
Perineural invasion	Cover the associated nerve toward the relevant skull-base foramen when indicated.	Document symptoms, sacrificed branches, proximal/distal margins, and nerve course.
Pathologic nodes	High dose to involved levels/bed; elective dose to at-risk adjacent echelons.	Separate nodal levels and intraparotid nodes; record ENE suspicion and violated nodal disease.
Minor-gland primary	Target follows the mucosal-site resection and site-specific neural/lymphatic anatomy.	Provide exact subsite, bone involvement, mucosal margins, and reconstruction boundaries.
Gross residual/unresectable disease	Definitive-dose gross target plus appropriate neural and nodal routes.	Clarify what is truly unresectable or intentionally residual versus postoperative change.

3.2 Perineural invasion versus perineural spread

Microscopic PNI is a pathology finding; clinical or radiographic perineural spread is a disease distribution. The latter may produce pain, numbness, weakness, foraminal enlargement, denervation change, or enhancement along a named nerve. Both can justify nerve-pathway coverage, but gross spread requires a more extensive high-risk map. Review MRI with neuroradiology rather than relying on the word “PNI” alone.

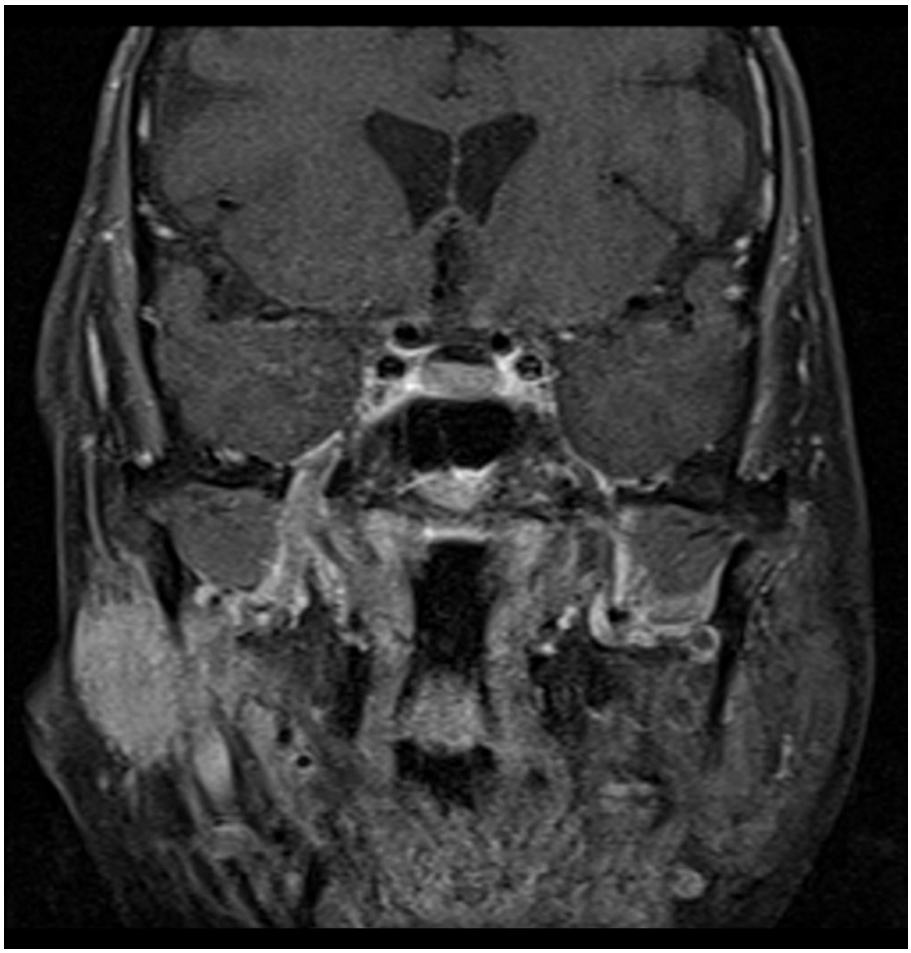

Figure 5. MRI example of perineural tumor spread along the facial nerve. Jto410, CC BY-SA 3.0, via Wikimedia Commons. Named-nerve disease should be followed toward the appropriate skull-base corridor rather than treated as a focal gland-bed finding.

3.3 Particle therapy in context

Photon IMRT remains widely used. Proton, neutron, and carbon-ion therapy may be considered in selected salivary cancers, particularly difficult skull-base or adenoid cystic presentations, but ASCO found no established indication that requires heavy-particle therapy over photon or electron treatment. ESMO notes potential advantages of particle therapy in selected unresectable skull-base/ACC cases while emphasizing limited availability and nonrandomized evidence.[1,2] The practical question is dosimetric and clinical: can a modality achieve adequate target coverage while reducing meaningful normal-tissue dose?

3.4 Acute and late toxicity

Time	Common toxicity	Prevention / management priorities
During RT	Dermatitis, mucositis, taste loss, xerostomia, fatigue, odynophagia, nausea, weight loss.	Skin/oral care, analgesia, nutrition, swallow exercise, hydration, treatment adherence.
Early months	Persistent xerostomia, thick secretions, trismus, dysphagia, lymphedema, neuropathic pain.	Dental prevention, jaw stretching, SLP, lymphedema therapy, pain-directed treatment.
Late	Dental caries/osteoradionecrosis risk, fibrosis, trismus, cranial neuropathy, hearing loss, temporal-lobe or brainstem injury depending on field.	Lifelong fluoride/dental care, dose-aware hearing follow-up, rehabilitation, MRI for new neurologic symptoms.

Reirradiation setting	Soft-tissue necrosis, carotid blowout, cranial neuropathy, bone injury, severe fibrosis.	Composite-dose review, strict selection, experienced multidisciplinary planning, frank counseling.

RESIDENT TAKEAWAY | The radiation consultation is better when the surgeon provides a spatial operative report: tumor interface, nerve course, true margins, nodal levels, reconstruction, and any intentional residual disease.

CHAPTER SYNTHESIS

- Target volumes are reconstructed from preoperative imaging, operative anatomy, specimen orientation, and pathology.
- Named-nerve risk may require coverage to the skull base; microscopic PNI and gross perineural spread are not interchangeable.
- Particle therapy is a selected modality choice, not a universal salivary-cancer requirement.
- Functional preparation and toxicity prevention begin before simulation and continue lifelong.

CHAPTER 4

Unresectable Disease and the Role of Chemotherapy

Definitive radiation is standard local treatment when surgery is not feasible; concurrent systemic therapy remains unproven.

4.1 What “unresectable” should mean

Unresectability may reflect encasement or extension that prevents a complete operation, unacceptable neurologic or vascular morbidity, a field in which reconstruction cannot produce a safe result, or medical comorbidity that makes surgery prohibitive. It should not be used loosely for a difficult but potentially curable skull-base or parapharyngeal case without review at an experienced multidisciplinary center. Distant metastases also do not automatically make the primary irrelevant; symptomatic or threatening local disease may still warrant definitive or palliative treatment.

4.2 Definitive radiation

For patients who cannot undergo resection, ASCO recommends radiotherapy, with the gross primary and appropriate nodal disease treated to a curative dose. ESMO describes conventional photon treatment to approximately 70 Gy in many centers and notes selected particle approaches for skull-base and adenoid cystic disease.[1,2] Neural tracts and elective nodal regions are included according to histology and anatomic risk.

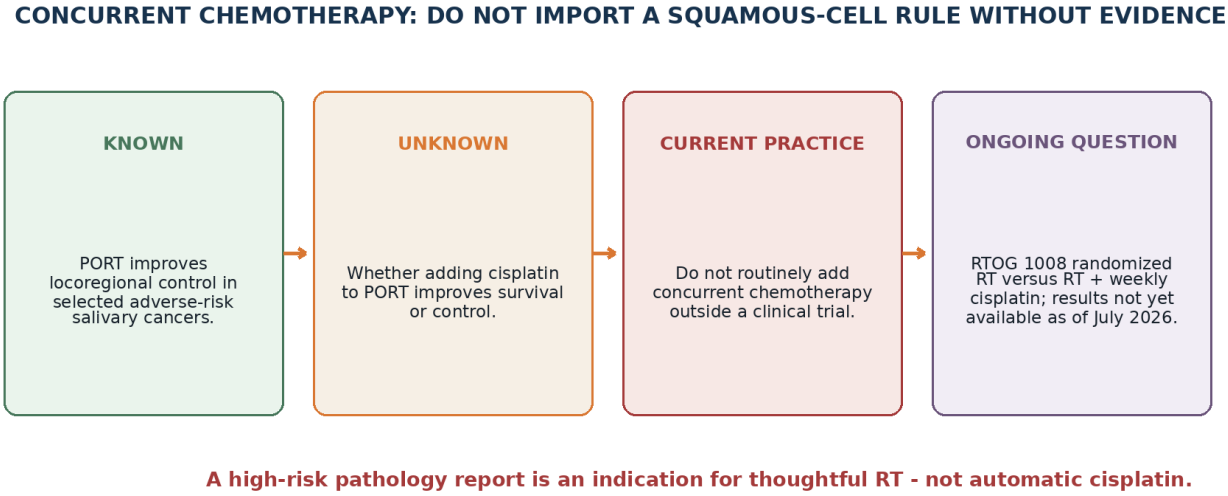

Figure 6. Original synthesis. High-risk pathology supports PORT, but the addition of concurrent cisplatin remains an unresolved question rather than an imported squamous-cell standard.

4.3 Why cisplatin is not routine

ASCO recommends that concurrent chemotherapy not be routinely added to adjuvant radiation or to radiation for nonoperable salivary cancer outside a clinical trial.[1] The biologic rationale and extrapolation from mucosal squamous carcinoma are not sufficient. Salivary cancers are a collection of distinct diseases, and retrospective comparisons are vulnerable to selection bias. RTOG 1008 randomizes resected high-risk patients to radiation alone versus radiation with weekly cisplatin; the trial completed accrual with 252 patients, but its primary completion is estimated for October 2026 and results are not yet available as of this guide.[3]

Situation	Current stance	Reason
Resected high-risk disease receiving PORT	Do not routinely add concurrent chemotherapy outside a trial.	No mature randomized evidence of benefit; increased acute toxicity is expected.
Unresectable disease receiving definitive RT	Do not routinely add concurrent chemotherapy outside a trial.	Evidence consists mainly of small case series and extrapolation.
Adjuvant AR- or HER2-directed therapy after complete local treatment	Not routine outside a trial.	Activity in metastatic disease does not prove adjuvant benefit.
Gross recurrent/metastatic disease	Use histology- and biomarker-directed systemic therapy when treatment is indicated.	Here the drug is treating measurable disease, not unproven microscopic risk.

BOARD TRAP | Positive margins and extranodal extension mandate concurrent cisplatin in mucosal squamous carcinoma, but that rule should not be automatically transferred to salivary-gland carcinoma.

CHAPTER SYNTHESIS

- Definitive RT is appropriate for functionally or medically unresectable salivary cancer.
- Approximately 70 Gy-equivalent gross-disease treatment is commonly used in curative definitive plans.
- Concurrent chemotherapy is not routine in adjuvant or definitive salivary RT outside a trial.
- RTOG 1008 addresses this question, but results were not available as of July 2026.

CHAPTER 5

Locoregional Recurrence and Salvage

Recurrence should trigger a new diagnostic and anatomic workup, not a reflex declaration of incurability.

A new mass, pain syndrome, cranial neuropathy, skin lesion, or imaging abnormality after salivary treatment may represent recurrence, radiation change, denervation, infection, a second primary, or nodal metastasis from another source. Tissue confirmation is valuable when feasible, particularly if the result will determine a morbid salvage operation or systemic therapy. The original pathology should be re-reviewed when the recurrence behaves unexpectedly.

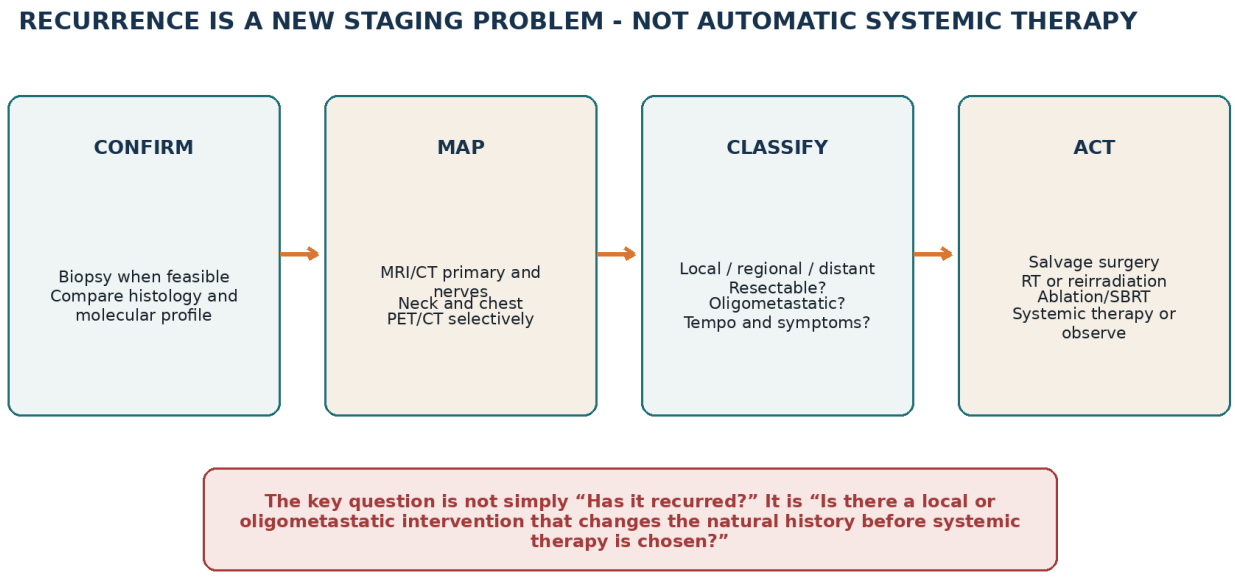

Figure 7. Original synthesis. Recurrent disease is confirmed, mapped, classified by resectability and tempo, and then treated with the most effective local or systemic strategy.

5.1 Restaging the recurrence

- MRI with contrast for local bed, skull base, and perineural pathways when neural or deep-space disease is possible.
- Contrast CT for bone, nodal, thoracic, or urgent anatomic definition; chest CT is essential because lung metastases may coexist.
- PET/CT selectively for high-grade disease, an unclear extent of recurrence, or a search for additional sites that would change salvage intent.
- Biopsy of the safest informative site, with preservation of tissue for AR, HER2, NTRK, and broader sequencing when advanced-disease therapy may be needed.
- Review prior RT plan and cumulative doses before proposing reirradiation.

5.2 Salvage surgery

Surgery offers the clearest chance of durable control for isolated, resectable locoregional recurrence, especially after a long disease-free interval and when complete resection is achievable. The operation may be more extensive than the original because scar obscures planes and recurrence may track along a nerve or reconstructive interface. The team should reassess facial and lower cranial nerve reconstruction, skull-base access, carotid involvement, wound coverage, and the possibility of postoperative or reirradiation. ASCO recommends evaluating patients undergoing revision surgery for recurrent salivary cancer for potential adjuvant therapy.[1]

5.3 Reirradiation and focal local therapy

Reirradiation may be appropriate for unresectable recurrence or after salvage surgery in carefully selected high-risk patients. Selection depends on the prior field and dose, interval, target size, proximity to carotid, mandible, brainstem, temporal lobe, optic structures, and the probability that local control will translate into meaningful benefit. Stereotactic or hypofractionated techniques can be useful for selected focal recurrences or oligometastases, but the label “SBRT” does not eliminate cumulative normal-tissue risk.

Recurrence pattern	Potential strategy	Features favoring benefit
Isolated resectable primary-bed recurrence	Salvage resection +/- adjuvant or reirradiation.	Long interval, complete resection feasible, no uncontrolled distant disease, reconstructable defect.
Named-nerve/skull-base recurrence	Specialty skull-base review; surgery and/or definitive/reirradiation.	Limited proximal extent, acceptable cranial-nerve cost, targetable volume.
Isolated nodal recurrence	Therapeutic neck surgery if feasible, often followed by RT/reirradiation based on prior treatment and pathology.	Resectable levels, no carotid encasement, limited distant burden.
Small unresectable focal recurrence	Definitive RT, reirradiation, or stereotactic approach in selected patients.	Small volume, safe geometry, meaningful control horizon.
Diffuse locoregional plus distant progression	Palliative local treatment plus systemic strategy.	Symptoms or organ threat define the urgent target; curative salvage is unlikely.

CLINICAL PEARL | New facial weakness, numbness, trismus, or deep pain after treatment should be treated as recurrent perineural or skull-base disease until an adequate evaluation proves otherwise.

CHAPTER SYNTHESIS

- Confirm and re-stage recurrence with attention to neural pathways and distant disease.
- Complete salvage resection can be durable in selected isolated recurrences.
- Reirradiation requires cumulative-dose and normal-tissue analysis at an experienced center.
- Symptom-directed local therapy remains valuable even when systemic disease is present.

CHAPTER 6

Distant Metastases: Observe, Ablate, or Treat

The presence of metastasis does not determine its urgency; histology, distribution, growth rate, symptoms, and organ threat do.

The lung is the dominant metastatic site for adenoid cystic carcinoma and several other salivary malignancies, but the clinical trajectory varies from years of indolent pulmonary disease to rapidly progressive liver, bone, brain, or multisite involvement. Starting systemic therapy solely because a scan shows small stable lung nodules can expose the patient to toxicity without improving symptoms or survival. Delaying therapy in rapidly progressive salivary duct carcinoma can be equally harmful.

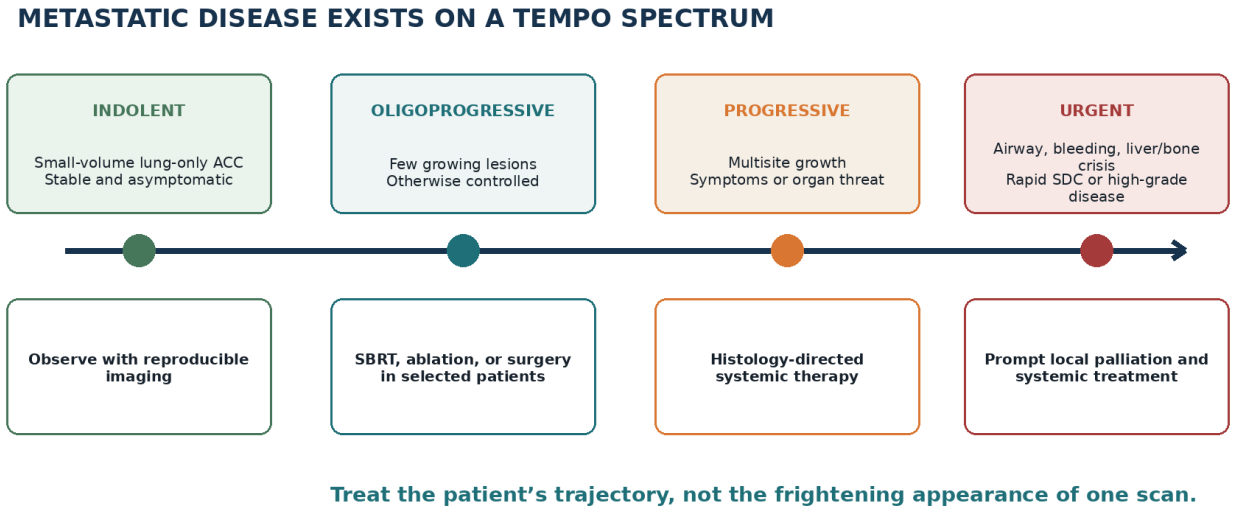

Figure 8. Original synthesis. Metastatic salivary cancer is managed along a spectrum from observation through focal therapy to urgent systemic treatment.

6.1 When observation is reasonable

ESMO supports a watch-and-wait strategy for selected patients with adenoid cystic carcinoma who have lung-only metastases, low burden, no symptoms, and stable disease. The strategy requires reproducible measurements and an explicit trigger for intervention; it is not abandonment. Short-interval imaging may be used initially to establish growth kinetics, after which the interval can be lengthened if the trajectory is convincingly indolent.[2]

6.2 Oligometastatic and oligoprogressive disease

Surgery, stereotactic radiation, or ablation can be considered for selected limited metastases, particularly after a long disease-free interval and when all active disease can be treated. In ACC, retrospective metastasectomy data suggest the best outcomes in patients with a disease-free interval longer than approximately 36 months and complete resection. [2] Local therapy is also useful for a single painful bone lesion or a few progressing sites while a systemic therapy continues to control the remainder.

6.3 Triggers to start systemic treatment

Trigger	Why it matters
Consistent radiographic progression	Confirms that disease is active rather than merely present.
Symptoms or declining function	Treatment has a patient-centered target: pain, dyspnea, neurologic deficit, bleeding, or fatigue.
Liver, bone, CNS, or other organ-threatening distribution	Lower threshold because consequences of progression are less forgiving than small pulmonary nodules.
Rapid high-grade or salivary duct carcinoma behavior	Delays can permit abrupt loss of control; test AR/HER2 early.
No feasible local-control option	Systemic therapy becomes the main disease-modifying strategy.
Trial eligibility window	Performance status and measurable progression may create an opportunity that is lost after further decline.

6.4 Palliative care is concurrent care

Palliative medicine should be integrated when symptoms, treatment burden, or prognostic uncertainty become substantial. It is not limited to end-of-life care. Pain control, airway and bleeding planning, nutrition, fatigue, mood, caregiver burden, and advance-care preferences often improve the patient's ability to receive disease-directed treatment and to decide when treatment is no longer worthwhile.

CHAPTER SYNTHESIS

- Metastatic urgency is determined by tempo, symptoms, distribution, and organ threat.
- Observation is legitimate for selected stable lung-only ACC when triggers for treatment are defined.
- Local ablative therapy may control oligometastatic or oligoprogressive disease in carefully selected patients.
- Palliative care should run alongside, not after, disease-directed treatment.

CHAPTER 7

A Systemic-Therapy Framework

The treatment name should come after the histology, biomarker, clinical trajectory, and therapeutic goal are clear.

The term “salivary gland cancer” is too broad to select a drug. Advanced treatment should begin with pathology review and sufficient tissue. Salivary duct carcinoma and carcinoma ex pleomorphic adenoma may be driven by androgen receptor or HER2. Secretory carcinoma is commonly defined by an NTRK fusion. Adenoid cystic carcinoma has a distinct natural history and modest response to most cytotoxic therapies, with VEGFR-directed multikinase inhibitors producing disease stabilization and occasional responses. Other tumors may harbor rare fusions or mutations that are actionable in a clinical trial or through a tissue-agnostic approval.

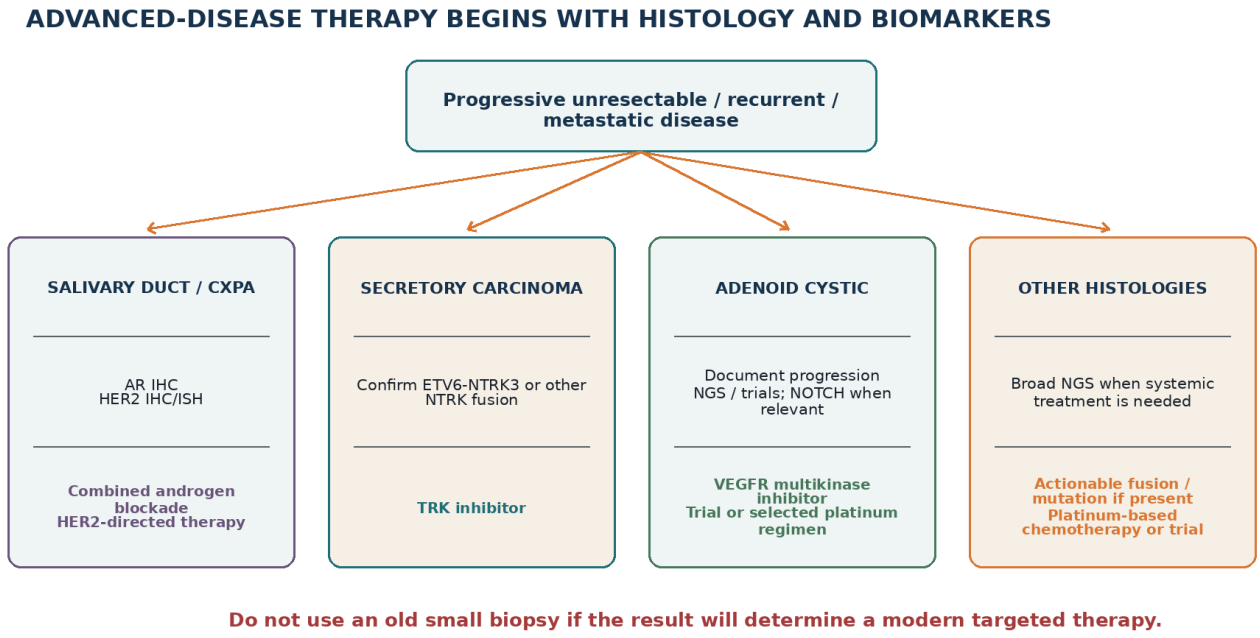

Figure 9. Original synthesis. In advanced salivary cancer, histology determines the first biomarker questions and the most plausible treatment family.

7.1 Before ordering systemic therapy

1. Confirm that systemic treatment is actually indicated: measurable progression, symptoms, organ threat, or no useful local option.
2. Review the original and recurrent pathology; high-grade transformation or a metastatic mimic can change the diagnosis.
3. Obtain AR and HER2 testing for salivary duct carcinoma and related high-grade adenocarcinomas; confirm NTRK fusion in secretory carcinoma.
4. Use broad next-generation sequencing when no standard biomarker explains the disease and treatment is needed; include RNA-based fusion detection when relevant.
5. Define the treatment goal: tumor shrinkage, symptom relief, disease stabilization, bridge to local therapy, or trial access.
6. Assess comorbidity and toxicity: cardiac function for HER2 therapy, pulmonary risk with antibody-drug conjugates, blood pressure/proteinuria for VEGFR inhibitors, and hormonal effects with androgen blockade.

7.2 Molecular testing: common errors

Error	Why it fails	Better approach
Assuming secretory morphology proves an NTRK fusion	Mimics exist and treatment depends on a real fusion.	Confirm with an appropriate fusion assay.
Using HER2 1+ or equivocal staining as if it were HER2-amplified SDC	Evidence and guideline criteria are strongest for IHC 3+ or amplification/ISH positivity.	Report method and level of positivity; discuss therapy in context.
Calling any AR staining “AR-driven”	Clinical studies often enrich for strong/diffuse expression; thresholds vary.	Document percent and intensity and use disease-specific expertise.
Relying on old decalcified or tiny FNA material	False negatives and incomplete profiling may result.	Re-biopsy a safe active lesion when the result will change therapy.
Ordering DNA-only testing for a fusion-driven entity	Some fusions are missed depending on panel design and introns.	Use RNA sequencing or validated fusion testing when appropriate.
Treating a molecular result without considering tempo	A target does not force immediate therapy in stable asymptomatic disease.	Integrate the alteration with clinical need and local options.

TUMOR-BOARD QUESTION | “What result would make us choose a different drug?” If the answer is unclear, the testing or therapy plan is not yet sufficiently specific.

CHAPTER SYNTHESIS

- Advanced therapy is selected by histology, biomarker, tempo, and treatment goal.
- Re-biopsy or re-review pathology when old material is inadequate for a high-impact treatment decision.
- RNA-based testing may be necessary for fusion-driven tumors.
- Actionable biology informs drug choice but does not determine when treatment must begin.

CHAPTER 8

Histology-Directed Systemic Therapy

The evidence is strongest when a biologically selected population is paired with a matched treatment.

8.1 Salivary duct carcinoma and carcinoma ex pleomorphic adenoma

Recurrent/metastatic salivary duct carcinoma is often clinically aggressive and should be profiled early. ESMO recommends prompt systemic treatment when disease is active, with AR-directed therapy considered for strongly AR-positive tumors and HER2-directed therapy for HER2 IHC 3+ or amplified disease.[2] In a prospective phase II study of combined androgen blockade with leuprorelin and bicalutamide, the objective response rate was 41.7%, clinical benefit rate 75%, and median progression-free survival 8.8 months.[5] Enzalutamide monotherapy produced only 4.3% confirmed responses, illustrating that all androgen-pathway regimens are not equivalent.[10]

For HER2-positive salivary duct carcinoma, trastuzumab plus docetaxel produced a 70.2% response rate in a 57-patient phase II study, with median PFS 8.9 months.[4] A pooled phase I analysis of trastuzumab deruxtecan in 17 HER2-expressing salivary cancers reported a 58.8% response rate and median PFS 20.5 months, but drug-related interstitial lung disease occurred in 29.4%, including grade 3 disease.[7] These results are compelling but arise from small, selected cohorts and require expertise in sequencing and toxicity.

8.2 Secretory carcinoma and NTRK fusion

Secretory carcinoma is the clearest precision-oncology success in salivary cancer. In 24 patients with TRK fusion-positive salivary cancers treated with larotrectinib, all carried ETV6-NTRK3; the objective response rate was 92%, including 13% complete responses, and the 24-month PFS rate was 78%.[6] This degree of activity justifies confirming the fusion in advanced disease rather than accepting a purely morphologic label.

8.3 Adenoid cystic carcinoma

Systemic therapy for ACC should generally be reserved for documented progression, symptoms, or threatening distribution. Cytotoxic response rates are modest. Multikinase VEGFR inhibitors can slow disease and occasionally shrink tumors. In a phase II lenvatinib study of 33 progressive R/M ACC patients, 15.6% had a confirmed partial response and 75% stable disease; dose modification and discontinuation for toxicity were common.[8] Axitinib, apatinib, and combinations with immunotherapy have also shown signals, but no therapy has established an overall-survival benefit.[2,9] Clinical trials, including strategies directed at NOTCH-activated disease, remain important.

8.4 Other salivary carcinomas

For other progressive salivary carcinomas without a matched target, platinum-based chemotherapy is a reasonable palliative option. Carboplatin-paclitaxel is commonly used, and cisplatin-based combinations such as CAP have historical activity. The expected benefit depends strongly on histology and the need for shrinkage. Broader genomic profiling may uncover rare RET, BRAF, ALK, or other alterations, but evidence may be limited to tissue-agnostic approvals, small series, or case reports.

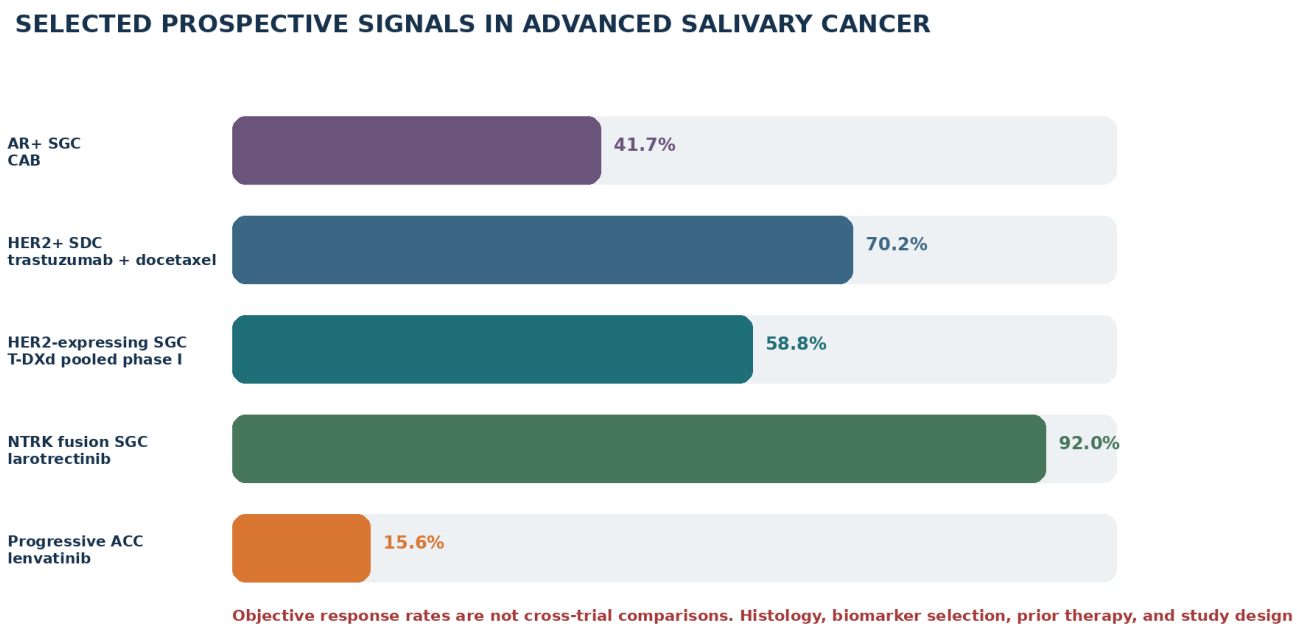

Figure 10. Original chart using selected prospective studies.[4-8] Response rates are shown for orientation only and must not be compared directly across different histologies, biomarkers, and study designs.

8.5 Immunotherapy

Checkpoint inhibitors produce durable responses in a small minority of unselected salivary cancers, but response rates are generally low. Immunotherapy is most defensible in a clinical trial or when a tumor has an established tissue-agnostic biomarker such as MSI-high, mismatch-repair deficiency, or high tumor mutational burden. PD-L1 expression alone is not a reliably strong salivary-cancer selector. Combining VEGFR inhibition and checkpoint blockade remains investigational.

Disease / biomarker	Preferred discussion	Important toxicity / caveat
AR-positive SDC / related adenocarcinoma	Combined androgen blockade; regimen and sequence individualized.	Hot flashes, sexual/metabolic effects, bone health, hepatic effects; monotherapy data are less compelling.
HER2 IHC3+ or amplified SDC	Trastuzumab-taxane, T-DM1, T-DXd or trial depending on line and access.	Cardiac monitoring; cytopenia; T-DXd interstitial lung disease requires immediate recognition.
NTRK fusion secretory carcinoma	Larotrectinib or entrectinib.	Confirm fusion; watch hepatic, neurologic, and drug-interaction issues.
Progressive ACC	VEGFR multikinase inhibitor, selected platinum regimen, or trial.	Hypertension, proteinuria, bleeding, mucosal/oral toxicity; stable disease can be meaningful.
No target / other histology	Platinum-taxane or other histology-directed chemotherapy; trial.	Goal is palliation or shrinkage, not presumed cure.
Tissue-agnostic biomarker	Appropriate matched FDA-approved therapy or trial.	Evidence may not be salivary-specific; confirm assay quality and clinical need.

BOARD PEARL | AR- and HER2-directed treatments have an established role in advanced biomarker-selected salivary duct carcinoma, but neither is routine adjuvant therapy after complete resection and PORT.

CHAPTER SYNTHESIS

- Combined androgen blockade and HER2-directed therapy have meaningful activity in selected SDC.
- NTRK fusion-positive secretory carcinoma is highly responsive to TRK inhibition.
- VEGFR inhibitors in ACC often produce stabilization with occasional responses and meaningful toxicity.
- Unselected immunotherapy response is low; use trials or established tissue-agnostic biomarkers.

CHAPTER 9

Surveillance and Detection of Late Failure

A surveillance plan should be reproducible enough to establish trajectory and long enough to respect salivary tumor biology.

Surveillance has three purposes: detect a recurrence that can still be treated, distinguish treatment effects from new disease, and manage late functional toxicity. There is no single evidence-based schedule for every histology. ASCO recommends regular history and examination with decreasing frequency, a post-treatment baseline study at approximately 3 months, primary-site and chest imaging every 6-12 months during the first 2 years, risk- and symptom-directed imaging during years 3-5, and yearly long-term examination beyond 5 years.[1]

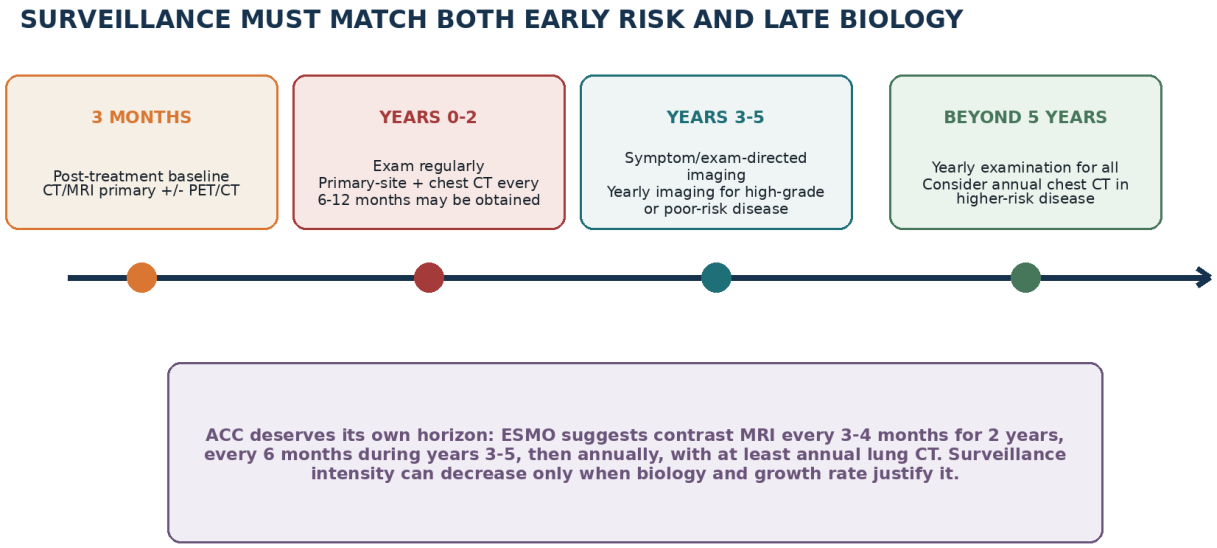

Figure 11. Original synthesis based on ASCO and ESMO guidance. Surveillance becomes less frequent with time for many cancers, but long-term examination and histology-specific chest/neural imaging remain important.

9.1 What the visit should detect

Domain	Ask / examine	Concerning change
Primary bed	New mass, skin change, wound breakdown, deep pain, trismus, mucosal lesion.	Progressive focal finding rather than stable postoperative asymmetry.
Cranial nerves	Facial movement, facial sensation, tongue, palate, voice, shoulder as relevant.	New weakness, numbness, neuralgia, dysphonia, or denervation symptoms.
Neck	Palpate parotid bed and nodal levels; inspect scalp, auricle, face when cutaneous metastasis was relevant.	New firm node or intraparotid mass.
Chest / systemic	Cough, dyspnea, bone pain, weight loss, neurologic symptoms.	New symptom in a histology with late distant risk.
Treatment toxicity	Dry mouth, dental disease, swallow, eye closure, hearing, lymphedema, pain, mood.	Functional decline that is treatable even without recurrence.

9.2 Imaging choices

Contrast MRI is particularly useful for deep soft tissue, skull base, denervation, and perineural recurrence. CT is efficient for bone, nodal evaluation, and pairing primary-site imaging with chest surveillance. PET/CT can be useful for selected high-grade or unclear recurrences but is not a universal routine surveillance test. Imaging should be compared with the post-treatment baseline and, whenever possible, performed with a consistent protocol so that growth kinetics are interpretable.

9.3 ACC-specific horizon

ESMO suggests contrast head-and-neck MRI every 3-4 months for the first 2 years after ACC treatment, every 6 months from years 3-5, and annually thereafter, together with at least annual lung CT.[2] This is more intensive and prolonged than many generic head-and-neck schedules because ACC can recur along nerve pathways and metastasize late. The schedule remains adjustable for age, treatment burden, previous findings, and disease tempo.

9.4 Surveillance after known metastatic disease

Imaging frequency should answer a decision. Patients with active R/M disease are often scanned two to four times per year, but a lower frequency may be reasonable for very slow growth. Short intervals are useful when establishing tempo, starting a new treatment, or watching an organ-threatening site. Repeated scans that cannot change management should be reconsidered rather than continued automatically.

PATIENT COUNSELING | "You are not 'done' at five years. The visit frequency can fall, but some salivary cancers recur late, so yearly follow-up and a plan for chest imaging remain important."

CHAPTER SYNTHESIS

- Obtain a post-treatment baseline at about 3 months and use it for longitudinal comparison.
- Primary-site and chest imaging is most intensive during the first 2 years, then becomes risk-directed.
- ACC requires prolonged MRI and chest surveillance because local neural and pulmonary failures can be late.
- Surveillance visits must also detect and treat functional toxicity.

CHAPTER 10

Survivorship and Rehabilitation

Cancer control is incomplete when the patient is left with preventable visual, dental, swallowing, hearing, or facial disability.

Salivary cancer survivorship often combines surgical and radiation effects in the same anatomic system. A radical parotidectomy may produce facial paralysis and exposure risk; radiation may add xerostomia, fibrosis, trismus, dental disease, and hearing loss. Skull-base or minor-gland treatment may affect multiple cranial nerves and swallowing. These consequences should be anticipated during treatment planning and followed with the same seriousness as imaging.

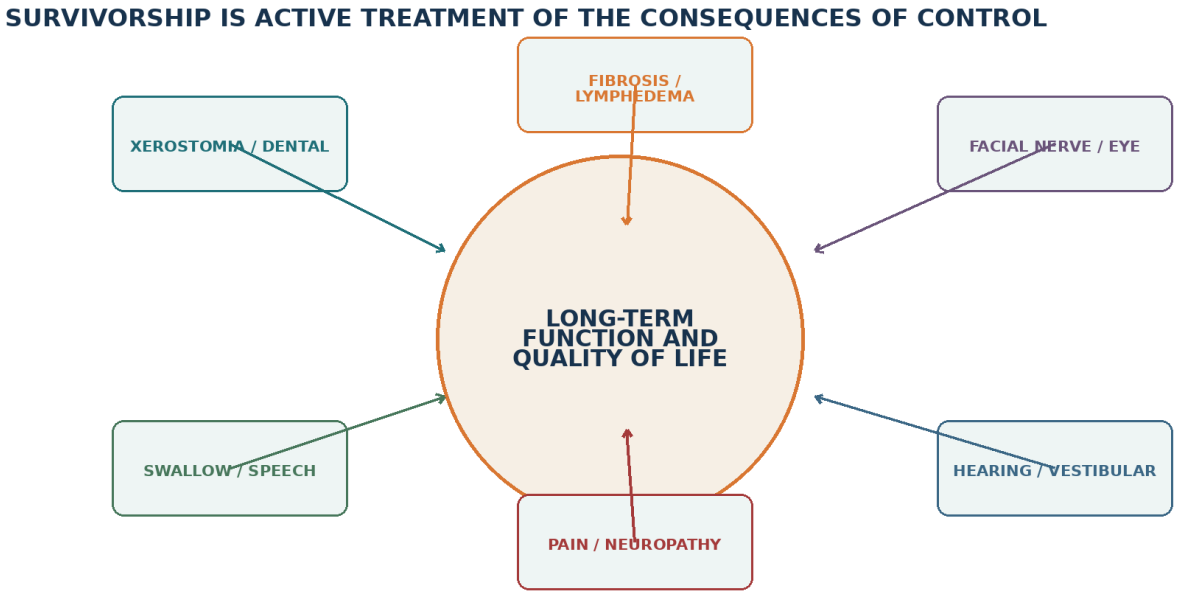

Figure 12. Original synthesis. Long-term care is an active rehabilitation program spanning oral health, swallowing, facial function, vision, hearing, pain, fibrosis, and lymphedema.

10.1 Xerostomia and dental prevention

Baseline dental evaluation is required when teeth and mandible will receive clinically meaningful dose. Lifelong fluoride, meticulous hygiene, frequent dental follow-up, diet counseling, saliva substitutes, and selected sialogogues reduce caries and infection. Extractions after radiation require dose review and coordination because osteoradionecrosis risk is not captured by elapsed time alone. The patient should know that dry mouth is a chronic medical condition, not merely an inconvenience.

10.2 Swallow, trismus, fibrosis, and lymphedema

Speech-language pathology should begin before or during treatment for patients at meaningful risk of dysphagia. Maintaining oral intake and swallowing exercises when safe can limit disuse. Jaw range-of-motion exercises are more effective before severe trismus is established. Neck and facial lymphedema may impair contour, comfort, and swallowing and can respond to specialized therapy. Progressive fibrosis or new dysphagia years later warrants evaluation for both late toxicity and recurrence.

10.3 Facial nerve and eye

Patients with postoperative facial weakness require repeated assessment of corneal protection, static tone, synkinesis, and candidacy for nerve transfer, eyelid weight, canthoplasty, sling, chemodenervation, or neuromuscular retraining. A clear cornea today does not eliminate future exposure risk as tone changes. The treatment record should state what nerve reconstruction was performed and the expected time course of reinnervation.

10.4 Hearing, vestibular function, and neuropathy

Cochlear dose, skull-base targets, prior ear surgery, and ototoxic systemic therapy determine hearing risk. Baseline and interval audiometry should be used when a change would alter rehabilitation. New imbalance may reflect vestibular injury, neuropathy, medication, or recurrence. Neuropathic facial or skull-base pain deserves directed treatment but also renewed oncologic evaluation when it is new or progressive.

Problem	Core surveillance	Common interventions
Xerostomia / dental	Caries, mucosal health, exposed bone, fluoride adherence.	Fluoride, hygiene, saliva support, sialogogue when appropriate, coordinated dental procedures.
Dysphagia / trismus	Weight, diet, aspiration symptoms, jaw opening.	SLP, exercises, nutrition, instrumental swallow study, jaw-mobility program.
Facial weakness / eye	Closure, Bell phenomenon, corneal symptoms, resting tone, synkinesis.	Lubrication, moisture chamber, eyelid/static procedures, nerve transfer, facial therapy.
Hearing / vestibular	Audiogram when at risk, tinnitus, imbalance, falls.	Hearing aid or implant evaluation, vestibular rehabilitation, medication review.
Fibrosis / lymphedema	Neck range, edema, skin change, functional restriction.	Specialized therapy, exercise, compression/manual techniques, rule out recurrence.
Pain / psychosocial	Neuropathic pattern, sleep, mood, work, caregiver strain.	Multimodal pain care, counseling, social work, palliative medicine when appropriate.

CHAPTER SYNTHESIS

- Long-term functional care is a core component of oncologic treatment.
- Dental and swallowing prevention should begin before radiation toxicity is established.
- Facial paralysis requires longitudinal eye protection, reanimation assessment, and rehabilitation.
- New late neurologic or pain symptoms must be evaluated for recurrence as well as treatment toxicity.

CHAPTER 11

Integrated Clinical Cases and Boards Review

The correct answer follows from failure pattern, tempo, resectability, and biomarker - not from memorizing a single treatment name.

Case 1: Small ACC with clear margins

A 42-year-old undergoes complete excision of a 1.4-cm minor-salivary ACC of the hard palate. Margins are negative, no nodes are involved, and there is focal microscopic PNI. Should the patient be observed because the tumor is small?

ANSWER | No. ASCO recommends postoperative radiation for all resected ACC. The target should be designed from the palatal bed and the relevant neural pathway; small size and a negative margin do not erase infiltrative and neural biology.

Case 2: Low-grade early parotid carcinoma

A 55-year-old has a 1.8-cm low-grade acinic cell carcinoma removed with an intact specimen and a clearly mapped negative margin. The facial nerve is intact, there is no LVI or PNI, and the neck is negative. Is PORT mandatory?

ANSWER | No. Observation is reasonable after adequate surgery for early low-grade disease without adverse features. Confirm that the diagnosis, grade, margin, and extent are genuinely secure rather than inferred from a limited sample.

Case 3: Positive margin and nodal disease

A high-grade salivary duct carcinoma has a focally positive deep margin and two level II nodes with extranodal extension. The patient is HER2-amplified. Should trastuzumab replace radiation or be added adjuvantly?

ANSWER | No. Re-resection should be considered if the mapped margin can be safely cleared; otherwise PORT is strongly indicated to the bed and appropriate nodal levels. HER2-directed therapy is active in measurable advanced disease but is not routine adjuvant therapy outside a trial. Concurrent cisplatin is also not automatically standard in salivary carcinoma.

Case 4: Stable pulmonary ACC metastases

Eight years after ACC treatment, a patient has six bilateral lung nodules measuring 4-9 mm. They have changed minimally over 18 months, the patient is asymptomatic, and there is no locoregional disease. Must systemic therapy start?

ANSWER | No. Continued active surveillance is reasonable. Establish reproducible growth kinetics and define triggers such as consistent progression, symptoms, organ threat, or a local-treatment opportunity. The presence of metastasis alone is not an indication for toxic therapy in indolent ACC.

Case 5: Progressive AR-positive SDC

A patient develops rapidly enlarging pulmonary and hepatic metastases from salivary duct carcinoma. Tumor cells show strong diffuse AR expression and are HER2-negative. What principle should guide treatment?

ANSWER | This is active, threatening disease and should be treated promptly. Combined androgen blockade has prospective activity and is more strongly supported than enzalutamide monotherapy. Clinical trial and chemotherapy options remain relevant based on response need and access.

Case 6: Secretory carcinoma with NTRK fusion

A patient with unresectable recurrent secretory carcinoma has a confirmed ETV6-NTRK3 fusion. What is the preferred systemic concept?

ANSWER | Use a TRK inhibitor such as larotrectinib or entrectinib. This is a biomarker-defined setting with unusually high response rates; confirm the fusion rather than treating solely from morphology.

Case 7: New facial numbness after RT

Three years after surgery and PORT for adenoid cystic carcinoma, the patient reports progressive cheek numbness and deep facial pain. The parotid bed is flat and the neck examination is normal. What is the next step?

ANSWER | Urgently evaluate for perineural recurrence with contrast MRI along the relevant trigeminal pathway and skull base. A normal superficial examination does not exclude neural disease.

Boards-style consolidation

Prompt	Best principle
Resected ACC, any stage	Offer PORT.
High grade, positive margin, PNI, nodal metastasis, LVI, T3-T4	Offer PORT.
Close margin or intermediate grade alone	Individualize.
Start of PORT	Aim within 8 weeks after surgery while completing wound/dental/functional preparation.
PNI	Consider elective/intermediate nerve-path coverage to skull base.
Concurrent cisplatin with PORT	Not routine outside a trial.
Unresectable local disease	Definitive RT; systemic radiosensitization remains unproven.
Stable asymptomatic lung-only ACC metastases	Observation can be appropriate.
AR-positive progressive SDC	Consider combined androgen blockade.
HER2 IHC3+/amplified SDC	Consider HER2-directed therapy.
NTRK fusion secretory carcinoma	TRK inhibitor.
Surveillance beyond 5 years	Yearly exam for all; consider ongoing chest imaging based on risk.

CHAPTER 12

Resident Workflow and One-Page Synthesis

A reproducible checklist protects against omission when histology and treatment pathways are rare.

Postoperative tumor-board card

Question	Write the answer
What was resected?	Primary site, T category, adjacent structures, nerves, neck levels, reconstruction.
What is the final biology?	Histology, grade, high-grade transformation, molecular phenotype.
Where is residual risk?	Positive/close mapped margin, PNI/named nerve, LVI, nodes/ENE, intentional residual disease.
Is PORT indicated?	ACC; high grade; positive margin; PNI; nodal disease; LVI; T3-T4; individualized close/intermediate grade.
What must be targeted?	Bed, mapped margin, involved nodes, next echelon, nerve to skull base, gross residual disease.
Can RT begin by 8 weeks?	Wound, dental, nutrition, SLP, hearing, simulation, referrals.
What is the baseline?	Post-treatment CT/MRI or PET/CT at approximately 3 months; chest baseline.
What is the surveillance horizon?	Histology, grade, neural risk, chest risk, late-recurrence plan.
What tissue is preserved for recurrence?	AR, HER2, NTRK, NGS/RNA fusion testing as relevant.
What function requires follow-up?	Eye/facial nerve, dental/xerostomia, swallow, hearing, lymphedema, pain, psychosocial health.

The five decisions to say out loud

1. Failure map: local bed, nerve, nodes, distant, molecular.
2. Adjuvant choice: observation, re-resection, PORT, or trial - and why.
3. Target map: exact bed, margin, nerve pathway, and nodal levels.
4. Surveillance plan: baseline, first two years, years three to five, and beyond five years.
5. Recurrence plan: what finding would trigger biopsy, salvage, local ablation, systemic therapy, or a trial.

FINAL RESIDENT TAKEAWAY | Do not let a rare histology make the plan vague. Every case can still be organized by anatomy, failure pattern, tempo, resectability, and actionable biology.

References

1. Geiger JL, Ismaila N, Beadle B, et al. Management of Salivary Gland Malignancy: ASCO Guideline. J Clin Oncol. 2021;39:1909-1941. doi:10.1200/JCO.21.00449.
2. van Herpen C, Vander Poorten V, Skalova A, et al. Salivary gland cancer: ESMO-EURACAN Clinical Practice Guideline for diagnosis, treatment and follow-up. ESMO Open. 2022;7:100602. Corrigendum published 2023.
3. NRG Oncology/RTOG 1008. Radiation Therapy With or Without Chemotherapy in Resected High-Risk Malignant Salivary Gland Tumors. ClinicalTrials.gov NCT01220583. Record updated 2026; results not available at preparation of this guide.
4. Takahashi H, Tada Y, Saotome T, et al. Phase II Trial of Trastuzumab and Docetaxel in HER2-Positive Salivary Duct Carcinoma. J Clin Oncol. 2019;37:125-134.
5. Fushimi C, Tada Y, Takahashi H, et al. Prospective Phase II Study of Combined Androgen Blockade in AR-Positive Metastatic or Unresectable Salivary Gland Carcinoma. Ann Oncol. 2018;29:979-984.
6. Le X, Bauman JE, et al. Larotrectinib Treatment for Patients With TRK Fusion-Positive Salivary Gland Cancers. Oncologist. 2022;27:e779-e788.
7. Takahashi S, Bando H, Kinoshita I, et al. Trastuzumab Deruxtecan in HER2-Expressing Salivary Gland Carcinoma: Pooled Analysis of Two Phase I Studies. Jpn J Clin Oncol. 2024;54:434-443.
8. Tchekmedyian V, Sherman EJ, Dunn L, et al. Phase II Study of Lenvatinib in Progressive, Recurrent or Metastatic Adenoid Cystic Carcinoma. J Clin Oncol. 2019;37:1529-1537.

References continued

9. Ho AL, Dunn L, Sherman EJ, et al. A Phase II Study of Axitinib in Patients With Incurable Adenoid Cystic Carcinoma. Ann Oncol. 2016;27:1902-1908.

10. Ho AL, Foster NR, Zoroufy AJ, et al. Phase II Study of Enzalutamide for AR-Positive Salivary Gland Cancers (Alliance A091404). J Clin Oncol. 2022;40:4240-4249.

Final Resident Framework

After treatment, keep five decisions explicit so a rare histology never produces a vague plan.

1. **FAILURE MAP**
   Local bed, nerve pathway, nodes, distant disease, and actionable biology.

2. **ADJUVANT CHOICE**
   Observation, re-resection, postoperative radiation, or clinical trial - and why.

3. **TARGET MAP**
   Exact surgical bed, mapped margin, named nerve route, and nodal levels.

4. **SURVEILLANCE PLAN**
   Baseline study, first 2 years, years 3-5, and the long-term horizon.

5. **RECURRENCE PLAN**
   Define what would trigger biopsy, salvage, ablation, systemic therapy, or a trial.

Figure credits

- Figures 1-4 and 6-12 are original educational syntheses created for this guide from the cited guidelines and studies.
- Figure 5 uses an open-license MRI example of facial-nerve perineural tumor spread by Jto410, CC BY-SA 3.0, via Wikimedia Commons.
- All clinical algorithms are educational summaries and do not replace multidisciplinary review, institutional protocols, or current drug labeling.

EDUCATIONAL USE	This guide supports resident education and multidisciplinary discussion. It does not replace current guidelines, institutional protocols, drug labeling, or patient-specific judgment.