ASCO special articles

Management of Salivary Gland Malignancy: ASCO Guideline

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abstract

PURPOSE To provide evidence-based recommendations for practicing physicians and other healthcare providers on the management of salivary gland malignancy.

METHODS ASCO convened an Expert Panel of medical oncology, surgical oncology, radiation oncology, neuroradiology, pathology, and patient advocacy experts to conduct a literature search, which included systematic reviews, meta-analyses, randomized controlled trials, and prospective and retrospective comparative observational studies published from 2000 through 2020. Outcomes of interest included survival, diagnostic accuracy, disease recurrence, and quality of life. Expert Panel members used available evidence and informal consensus to develop evidence-based guideline recommendations.

RESULTS The literature search identified 293 relevant studies to inform the evidence base for this guideline. Six main clinical questions were addressed, which included subquestions on preoperative evaluations, surgical diagnostic and therapeutic procedures, appropriate radiotherapy techniques, the role of systemic therapy, and follow-up evaluations.

RECOMMENDATIONS When possible, evidence-based recommendations were developed to address the diagnosis and appropriate preoperative evaluations for patients with a salivary gland malignancy, therapeutic procedures, and appropriate treatment options in various salivary gland histologies.

Additional information is available at www.asco.org/head-neck-cancer-guidelines.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Salivary gland malignancies (SGMs) are rare neoplasms accounting for < 1%-5% of all head and neck cancers.[1,2] Given the rarity of the disease, there are limited clinical trial data to help guide therapy, and no formal evidence-based or consensus guidelines have previously been published as far as the Expert Panel was aware. This guideline aims to provide up-to-date management recommendations for patients with SGM based on published literature and Expert Panel consensus.

SGMs encompass a wide spectrum of histologies with a variety of biologic behaviors that prove to be challenging for specialists to diagnose and treat optimally. Definitive surgical management is the mainstay of treatment, and there is good evidence for the efficacy of adjuvant radiotherapy in more advanced cancers.[3-6] The role of systemic therapy concurrently or in the recurrent-metastatic setting is an ongoing question. The behavior of SGMs is dependent upon histology, and thus, appropriate pathologic technique and testing are crucial in proper diagnosis. High-risk or high-grade cancers (Table 1) behave more aggressively, and thus require additional treatment considerations. Therefore, this guideline also aims to define the best evidence for the diagnosis, workup, and management of SGMs.

The intricacies of patient management decisions for SGM are best decided in the context of a multidisciplinary tumor board and with careful consideration of histology, disease burden and distribution, the patient's overall health and comorbidities, potential treatment-related toxicities, and function. It is the Expert Panel's goal that this guideline will provide a framework and the best current evidence for managing the care of patients with SGM from diagnosis to treatment.

GUIDELINE QUESTIONS

This clinical practice guideline addresses six overarching clinical questions: (1) What is the appropriate

THE BOTTOM LINE

Management of Salivary Gland Malignancy: ASCO Guideline

Guideline Question

1. What is the appropriate preoperative evaluation for patients with salivary gland malignancy (SGM)?
2. What are the proper surgical procedures for SGM?
3. What are the treatment considerations and appropriate radiotherapy technique for patients with SGM?
4. What is the role of systemic therapy in the management of SGM?
5. What are the appropriate post-treatment follow-up and evaluation of patients with SGM?
6. What are treatment options in recurrent-metastatic disease for patients with SGM?

Target Population

Patients with SGM.

Target Audience

Medical oncologists, radiologists, radiation oncologists, clinical oncologists, surgeons, nurses, pathologists, oncology pharmacists, caregivers, and patients.

Methods

An Expert Panel was convened to develop clinical practice guideline recommendations based on a systematic review of the medical literature.

Recommendations

Preoperative evaluation

Recommendation 1.1
Providers should perform imaging (neck ultrasound, computed tomography [CT] with intravenous contrast, and/or magnetic resonance imaging [MRI] of the neck and primary site) in patients with a suspicion of a salivary gland cancer (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.2
Providers should perform CT of the neck with intravenous contrast for patients with suspicion of salivary gland cancer and involvement of adjacent bone (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.3
Providers should perform contrast-enhanced MRI with a diffusion sequence of the neck and skull base for patients with suspicion of salivary gland cancer with concern for perineural invasion and/or skull base involvement (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.4
Providers may perform a PET/CT from the skull base to mid-thighs for patients with advanced-stage high-grade salivary gland cancers (Type: evidence based; Evidence quality: low; Strength of recommendation: weak).

Recommendation 1.5
Providers should perform a tissue biopsy (either fine needle aspiration biopsy [FNAB] or core needle biopsy [CNB]) to support distinction of salivary gland cancers from nonmalignant salivary lesions (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.6
Providers may perform CNB if FNAB is inadequate or subsite precludes FNAB such as deep minor salivary glands (Type: evidence based; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 1.7
Pathologists should report risk of malignancy using a risk stratification scheme for salivary FNABs with particular attention to high-grade features (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.8
Pathologists may perform ancillary testing (immunohistochemical or molecular studies) on FNABs and core needle biopsies to support diagnosis and risk of malignancy (Type: evidence based; Evidence quality: low; Strength of recommendation: weak).

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Diagnostic and therapeutic surgical procedures

Recommendation 2.1
Surgeons should offer open surgical excision for histologically confirmed salivary gland malignancies (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 2.2
Surgeons may request intraoperative pathologic examination to support immediate alterations in intraoperative management (extent of resection and neck dissection). Decisions that would result in major harm such as facial nerve resection should not be based on indeterminate preoperative or intraoperative diagnoses alone (Type: evidence based; Evidence quality: low; Strength of recommendation: weak).

Recommendation 2.3
Surgeons may perform partial superficial parotidectomy for appropriately located superficial T1 or T2 low-grade salivary gland cancers (Type: evidence based; Evidence quality: low; Strength of recommendation: weak).

Recommendation 2.4
Because of the risk of intraparotid nodal metastases in high-grade or advanced-stage parotid cancer, surgeons should perform at least a superficial parotidectomy with consideration of a total or subtotal parotidectomy for any high-grade or advanced (T3-T4) parotid cancer (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 2.5
Surgeons should perform facial nerve preservation in patients with intact preoperative facial nerve function when a dissection plane can be created between the tumor and the nerve (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 2.6
Surgeons should perform resection of involved facial nerve branches in patients with impaired facial nerve movement preoperatively or when branches are found to be encased or grossly involved by a confirmed malignancy (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 2.7
Surgeons should offer an elective neck treatment over observation in a clinically negative neck in T3 and T4 tumors and high-grade malignancies (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 2.8
For operative elective neck management of salivary cancers, ipsilateral selective neck dissection should be performed with levels dependent on the primary site. For parotid malignancies, levels may include 2-4 (Type: evidence based; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 2.9
For a cN+ neck, surgeons may perform an ipsilateral neck dissection of involved and at-risk levels and may extend to adjacent levels, up to levels 1-5 (Type: evidence based; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 2.10
In the setting of resectable, recurrent locoregional disease and no distant metastatic disease, regardless of prior treatment type, patients should be offered revision resection and appropriate surgical reconstruction and rehabilitation (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 2.11
In the setting of resectable, recurrent locoregional disease and distant metastatic disease, regardless of prior treatment type, treatment may include palliative revision resection and appropriate surgical reconstruction and rehabilitation, if the metastatic disease is not rapidly progressive or imminently lethal (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 2.12
Patients undergoing revision surgery for recurrent salivary gland cancer should be evaluated for potential adjuvant therapy (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Radiotherapy

Recommendation 3.1
Postoperative radiation therapy (RT) should be offered to all patients with resected adenoid cystic carcinoma (ACC) (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 3.2
Postoperative RT should be offered to patients with tumors with the following features: high-grade tumors, positive margins; perineural invasion; lymph node metastases; lymphatic or vascular invasion; and T3-T4 tumors (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

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Recommendation 3.3
Postoperative RT may be offered to patients with tumors with close margins or intermediate-grade tumors (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: weak).

Recommendation 3.4
In postoperative cases, the high-dose target should cover the salivary gland surgical bed and appropriate nodal levels (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 3.5
In the case of perineural invasion, the associated nerve(s) may be covered with an elective or intermediate dose to the skull base (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Recommendation 3.6
Elective nodal coverage may be offered for T3-T4 primary and high-grade malignancies (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Recommendation 3.7
Radiation should be initiated within 8 weeks of surgery (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Recommendation 3.8
Particle therapy, including proton, neutron, and carbon ion therapy, may be used for patients with SGM; there are no indications for the use of heavy particle therapy over photon or electron therapy (Type: evidence based; Evidence quality: low; Strength of recommendation: weak).

Recommendation 3.9
Elective neck irradiation may be offered to patients with cN0 disease for the following indications: T3-T4 cancers or high-grade malignancies (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 3.10
Radiotherapy should be offered to patients with SGM who are not candidates for surgical resection (because of extent of disease or medical comorbidity) (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).
Note. The high-dose target should cover the gross disease in the salivary gland and any appropriate nodal levels.

Systemic therapy

Recommendation 4.1
In the setting of patients undergoing adjuvant radiotherapy, the addition of concurrent chemotherapy may not be routinely offered outside of a clinical trial (Type: evidence based; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 4.2
In the setting of patients undergoing radiotherapy for nonoperable salivary gland cancer, the addition of concurrent chemotherapy may not be routinely offered outside of a clinical trial (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Recommendation 4.3
In patients with salivary gland tumors expressing androgen receptor (AR) and/or HER2-Neu, adjuvant endocrine or targeted therapy may not be routinely offered outside of a clinical trial (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Follow-up evaluations

Recommendation 5.1
Clinical follow-up with history and physical examination should be completed on a regular basis with decreasing frequency as time elapses from completion of treatment of salivary gland cancer (Type: informal consensus; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 5.2
Post-treatment baseline imaging with contrast CT or MRI (for patients without contraindications) of the primary site and/or positron emission tomography/CT should be obtained 3 months after completion of all treatment (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 5.3
Follow-up surveillance imaging of the primary site (contrast CT or MRI) and the chest CT may be obtained every 6-12 months for the first 2 years after treatment (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

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Recommendation 5.4
Follow-up imaging of the primary site and the chest from years 3-5 should be directed by symptoms and physical examination findings. Yearly follow-up imaging may be offered in cases of high-grade histology or poor prognostic clinicopathologic features (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 5.5
Long-term follow-up (beyond 5 years) with yearly examination should be offered to all patients with salivary gland cancer. Yearly chest CT may be offered especially in patients with high-grade histology or poor prognostic clinicopathologic features (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recurrent-metastatic disease

Recommendation 6.1
Patients presenting with metastatic disease may be evaluated for further treatments such as local ablative treatments or systemic therapy. These options should be discussed with the patient and will depend on the patient and tumor factors (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Recommendation 6.2
In the setting of ACC and/or low-grade tumors with indolent biology with limited metastases (ie, ≤ 5 metastases), local ablative treatments such as surgery (metastatectomy) or stereotactic body radiation therapy may be offered to delay local disease progression (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Recommendation 6.3
Patients may be considered for initiation systemic therapy in the following circumstances: (1) metastatic deposits are symptomatic and not amenable to palliative local therapy, (2) growth has the potential to compromise organ function, or (3) lesions have grown more than 20% in the preceding 6 months (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 6.4
For patients with ACC who are candidates for initiation systemic therapy, a multitargeted tyrosine kinase inhibitor (TKI), such as lenvatinib or sorafenib, may be offered if a clinical trial is not available (Type: evidence based; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 6.5
For patients with nonadenoid cystic salivary gland cancer who are candidates for initiation of systemic therapy, targeted therapy based on tumor molecular alterations (ie, *AR*, *HER2*, and *NTRK*) may be offered if a clinical trial is not available (Type: evidence based; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 6.6
Cytotoxic chemotherapy combinations may be offered to patients with symptomatic disease (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Recommendation 6.7
For patients who are candidates for systemic therapy, checkpoint inhibitors should not be routinely offered at this time except for patients with selected molecular alteration (high tumor mutational burden [TMB], MSI-H) (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Recommendation 6.8
For patients with histologic tumor types with a high prevalence of targetable molecular alterations (ie, *AR* in salivary duct carcinoma and *NTRK3* in secretory carcinoma), confirmatory target-specific testing should be performed (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 6.9
Patients who may be potential candidates for systemic therapy with histologic tumor types with low prevalence of targetable molecular alterations and unknown driver mutation status should be screened using a comprehensive panel for driver mutations; patients with driver mutation–negative tumors may then be offered target-specific testing (ie, *AR* and *NTRK3*) (Type: evidence based; Evidence quality: low; Strength of recommendation: weak).

Additional Resources

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/head-neck-cancer-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

TABLE 1. Stratification of Salivary Gland Carcinomas (Based on WHO 2017)

Low Aggression	High Aggression
Acinic cell carcinoma	Adenoid cystic carcinoma Tubular/cribriform pattern predominant Solid pattern > 30%
(Mammary analogue) Secretory carcinoma	Poorly differentiated carcinoma: neuroendocrine and non-neuroendocrine Undifferentiated carcinoma Large-cell neuroendocrine carcinoma Small-cell neuroendocrine carcinoma
Mucoepidermoid carcinoma Low grade Intermediate grade	Mucoepidermoid carcinoma High grade
Polymorphous adenocarcinoma Classic Cribriform	Polymorphous adenocarcinoma High grade
Epithelial-myoepithelial carcinoma	
(Hyalinizing) Clear cell carcinoma	
Basal cell adenocarcinoma	
Sebaceous adenocarcinoma	Lymphoepithelial carcinoma
Intraductal carcinoma Low grade High grade	(Conventional) Salivary duct carcinoma
Adenocarcinoma, NOS Low grade	Adenocarcinoma, NOS High grade
Myoepithelial carcinoma	
Oncocytic carcinoma	Carcinosarcoma
Carcinoma ex pleomorphic adenoma—risk is determined by type of carcinoma and extent of invasion	

Abbreviation: NOS, not otherwise specified.

preoperative evaluation for patients with SGM? (2) What are the proper surgical procedures for SGM? (3) What are the treatment considerations and appropriate radiotherapy technique for patients with SGM? (4) What is the role for systemic therapy in the management of SGM? (5) What are the appropriate post-treatment follow-up and evaluation of patients with SGM? (6) What are treatment options in recurrent-metastatic disease for patients with SGM?

METHODS

Guideline Development Process

This systematic review (SR)–based guideline product was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise. The Expert Panel met via teleconference and/or webinar and corresponded through e-mail. Based upon the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were sent for an open comment period of 2 weeks allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review and submitted to the *Journal of Clinical Oncology* (*JCO*) for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guidelines Committee before publication. All funding for the administration of the project was provided by ASCO.

The recommendations were developed by using an SR (January 2000-December 2020) of SRs, phase III randomized clinical trials (RCTs), observational studies, and clinical experience. Articles were selected for inclusion in the SR of the evidence based on the following criteria:

- Population: Patients with SGM
- Interventions of interest: Imaging studies (neck computed tomography [CT], positron emission tomography [PET]/CT, magnetic resonance imaging [MRI], neck ultrasound [US]), pathologic evaluations (fine needle aspiration [FNA], core, immunohistochemical [IHC], and molecular testing), surgical interventions (extracapsular dissection, parotidectomy, neck dissection, facial nerve resection, and intraoperative frozen section), systemic therapy, radiotherapy, and multimodality treatment.
- Study designs: SRs, meta-analyses, RCT, and prospective and retrospective comparative observational studies.

Articles were excluded from the SR if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, and narrative reviews; and (3) published in a non-English language. The guideline recommendations are crafted, in part, using the *Guidelines Into Decision Support* methodology and accompanying BRIDGE-Wiz software.[7] In addition, a guideline implementability review was conducted (Data Supplement, online only). Based on the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation.

The ASCO Expert Panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

Guideline Disclaimer

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

A total of 293 studies met eligibility criteria and form the evidentiary basis for the guideline recommendations. These included nine SRs,[8-16] two RCTs,[17,18] and 25 phase II,[19-43] 28 prospective,[44-71] and 229 retrospective studies.[5,72-299] Identified trials focused on preoperative evaluations, surgical diagnostic and therapeutic procedures, radiotherapy techniques, and systemic therapy in SGM. The primary outcomes reported in studies on therapeutic interventions included overall survival (OS), progression-free survival (PFS), relapse-free survival, failure-free survival (FFS), disease-free survival (DFS) as well as distant FFS or control rate, locoregional FFS or control rate, and quality of life. Although many of the studies quoted in this guideline used the American Joint Committee on Cancer 6th or 7th editions, all references to stage in the recommendations in this guideline are based on the current 8th edition of the American Joint Committee on Cancer staging system.[300] Details on the study characteristics are included in the Data Supplement. The SR flow diagram is shown in the Data Supplement.

RECOMMENDATIONS

Clinical Question 1: What Is the Appropriate Preoperative Evaluation for Patients With Salivary Gland Malignancy?

Recommendation 1.1. Providers should perform imaging (neck ultrasound, CT with intravenous [IV] contrast, and/or MRI of the neck and primary site) in patients with a suspicion of a salivary gland cancer (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and clinical interpretation. For any patient, adult or pediatric, cross-sectional imaging with CT or MRI offers localization of a palpable mass to a major salivary gland and allows detection of additional salivary masses or nodal metastases. Imaging has diagnostic limitations, even in distinguishing between benign and malignant tumors; however, cross-sectional imaging may offer further tumor characterization.[64,245,247,298,301] CT and US may also assist in guidance for FNA or biopsy, which provides greater accuracy for pathologic diagnosis.[61,228,239,240,250]

Adult salivary gland masses are most often inflammatory or malignant, whereas pediatric masses may also be congenital lesions such as infantile hemangiomas, vascular malformations, and first branchial cleft cysts of the parotid. Benign tumors are otherwise uncommon in children. Ultrasound, which involves no ionizing radiation and does not require patient immobility, is often a first-line imaging tool in children. US may be used for the initial evaluation of a new mass in adult patients, differentiating extra from intraglandular masses and identifying features that are suspicious for malignancy.[55,57,248] However, US is limited for evaluation of the deep extent of masses or involvement of the skull base, as well as delineation of cranial

nerve involvement.[252] When there is concern for malignancy such as neck adenopathy or cranial nerve dysfunction or full tumor delineation is required for operative planning, contrast-enhanced CT or contrast-enhanced MRI of the glands and neck is recommended. It is not uncommon to use both MRI and CT when planning resection of a malignant salivary gland mass, particularly when there is concern for skull base invasion and/or perineural tumor spread along the large named nerves.

Recommendation 1.2. Providers should perform CT of the neck with IV contrast for patients with suspicion of salivary gland cancer and involvement of adjacent bone (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and clinical interpretation. One of the advantages of CT over MRI and US is the ability to evaluate for erosion of bone that may occur with masses adjacent to the temporal bone, skull base or mandible, or the palate with minor salivary gland tumors.[241,301] To best evaluate such erosion and invasion, bone algorithm images should be processed concurrently with routine soft-tissue algorithm. CT has better delineation also of focal intratumoral calcifications, which are most often seen in benign and malignant mixed tumors.

IV iodinated contrast is recommended for all neck CT scans to increase the conspicuity of the primary lesion, to allow better characterization of necrotic or hypervascular masses, for increased sensitivity of detection of metastatic adenopathy, and to allow evaluation of patency of associated vascular structures.[105]

Recommendation 1.3. Providers should perform contrast-enhanced MRI with a diffusion sequence of the neck and skull base for patients with suspicion of salivary gland cancer with concern for perineural invasion and/or skull base involvement (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and clinical interpretation. MRI allows better delineation of the contours of a mass and offers significantly improved ability to characterize salivary gland masses and is preferred over other imaging modalities if there is concern for intracranial extension.[52,62,224,245,247,253,254] Diffusion-weighted imaging offers additional information that may increase the concern for malignancy.[101,246,251,277] The entire MRI scan should cover both the glands and neck for adenopathy, and IV gadolinium–based contrast agents should routinely be used.

Recommendation 1.4. Providers may perform a PET/CT from the skull base to mid-thighs for patients with advanced-stage high-grade salivary gland cancers (Type: evidence based; Evidence quality: low; Strength of recommendation: weak).

Literature review and clinical interpretation. There is no literature to support the use of fluorodeoxyglucose (FDG)-PET/CT for the initial evaluation of a parotid mass, and PET/CT does not provide the spatial resolution for anatomic detail required in preoperative evaluation. PET/CT may more accurately predict the extent of nodal and distant metastatic disease in high-grade tumors and identify locoregionally recurrent and metastatic disease.[147,170,230] It, therefore, is of value for staging and surveillance in patients with advanced-stage salivary malignancies or those with high metastatic potential.[66] There are numerous caveats with this recommendation including an awareness that some salivary malignancies do not have high FDG uptake and many benign tumors including Warthin and benign mixed tumors are FDG-avid.[145,243]

Recommendation 1.5. Providers should perform a tissue biopsy (either FNAB or CNB) to support distinction of salivary gland cancers from nonmalignant salivary lesions (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Literature review and clinical interpretation. When managing salivary gland masses, it is important to distinguish between infectious or inflammatory lesions, benign or low-grade tumors, and high-grade primary cancers and metastases as the approach to work up and management differs significantly across this spectrum. For inflammatory lymphadenopathy or lymphoma, management would be nonoperative, whereas, for benign or malignant primary salivary tumors, surgical excision is typically recommended. For metastasis to a salivary gland, treatment varies according to the primary site. The use of FNAB is an effective, minimally invasive way to obtain a tissue diagnosis.[53,54,122,124,129,167,171,179,182,217] In an SR, FNAB was found to be accurate in distinguishing malignant from benign lesions with an estimated sensitivity of 80% and a specificity of 97%, although across studies, this varied as widely as 57%-86% and 87%-100% for sensitivity and specificity, respectively.[11-13] Sources for this variation are multifactorial and include the experience of the cytopathologist and variability within several procedural and technical aspects of FNAB workflow.[12] Moreover, this technique has shown a diagnostic accuracy of up to 99% when identifying high-grade salivary cancers, a distinction that can help with preoperative counseling and surgical planning.[194] Lin and Bhattacharyya[198] demonstrated that when a preoperative FNA indicated malignancy, a higher rate of upfront neck dissection (47% *v* 13%, $P = .036$) was performed and there was a higher rate of clear pathologic margins (71% *v* 31%, $P = .027$). This was supported by Eytan et al,[122] who found that the FNA results changed the surgical plan in 19% of patients.

Recommendation 1.6. Providers may perform CNB if FNAB is inadequate or subsite precludes FNAB such as deep

minor salivary glands (Type: evidence based; Evidence quality: low; Strength of recommendation: moderate).

Literature review and clinical interpretation. The use of ultrasound-guided CNB has been shown to have an estimated sensitivity of 94% and specificity of 98%, with only 1.2% of biopsies having an inadequate sample.[11,14] This technique, while slightly more invasive than FNAB and marginally more prone to minor complications (ie, hematoma), is potentially slightly more accurate (particularly regarding sensitivity) and more likely to provide a specific diagnosis.[15,60] It may prove to be beneficial in individuals with nondiagnostic FNAs and/or those where there is a concern for lymphoma. CNB has a lower inadequacy rate (1.2%)[11,12] than FNAB (8%), suggesting its use when FNAB is nondiagnostic. One comparative SR confirms that CNB has statistically fewer nondiagnostic results (relative risk, 0.85; 95% CI, 0.82 to 0.88; $P < .001$) than FNAB.[15] When using a combined approach of performing CNB when FNAB is inadequate, one study[272] reports an improvement in sensitivity while minimizing the exposure to the risks of CNB. CNB is also more likely to yield adequate materials for ancillary testing (ie, lymphoma workup).[213] Literature specifically addressing the performance of CNB (and FNAB), specifically in minor salivary glands, is sparse. Although FNAB may be feasible on a subset of intraoral minor salivary gland and parapharyngeal space neoplasms with comparable performance,[275,299] some tumors are simply not accessible for FNAB. In such scenarios, providers may perform CNB for preoperative diagnosis.

Recommendation 1.7. Pathologists should report risk of malignancy (ROM) using a risk stratification scheme for salivary FNABs with particular attention to high-grade features (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.8. Pathologists may perform ancillary testing (IHC or molecular studies) on FNABs and core needle biopsies to support diagnosis and ROM (Type: evidence based; Evidence quality: low; Strength of recommendation: weak).

Literature review and clinical interpretation. Although the simple distinction of malignant from benign salivary gland tumors can be useful in preoperative management, intrinsic limitations of FNAB (ie, morphologic overlap between benign and malignant entities and lack of architectural elements) ultimately place a ceiling on its performance characteristics in this regard. As with other organ sites,[302] categorical schemes assigning ROM and even risk of high-grade malignancy have recently evolved and show potential for providing more nuanced information for decision making.[303,304] The current standard reporting scheme is the Milan System for Reporting Salivary Gland Cytopathology (MSRSGC).[305]

The MSRSGC consists of the following categories: nondiagnostic, non-neoplastic, atypia of undetermined significance, neoplasm, suspicious for malignancy, and malignant groups. The neoplasm category is generally divided into benign and salivary gland neoplasm of uncertain malignant potential. The malignant category is also subdivided into low grade and high grade. Estimated ROM in recent meta-analysis of more than 16,000 FNAB in 92 studies[16] is summarized in Table 2.

In addition to providing more granular details to inform management decisions, MSRSGC introduces standardization of reporting, which in turn may reduce the variability in FNAB performance across practice settings. Studies on interobserver agreement showed modest agreement overall (kappa: 0.42), although individual categories differ in this respect.[306]

While not extensively vetted, MSRSGC can provide risk of high-grade malignancy as well, thus providing supporting evidence in some scenarios for more aggressive upfront management (Table 3). Limited data indicate that cytopathologists are fairly accurate in subcategorizing low-grade and high-grade malignancies.[157,307]

With the evolution of molecular understanding in salivary gland neoplasms, both FNAB and CNB are amenable to molecular testing for defining alterations, thus providing more accurate ROM in indeterminate categories and in many instances providing a specific diagnosis.[308] Conceptually, this is appealing, but data establishing performance characteristics for testing on FNAB are limited to small series.[309-315]

Clinical Question 2: What Are the Proper Surgical Procedures for SGM?

Recommendation 2.1. Surgeons should offer open surgical excision for histologically confirmed salivary gland malignancies (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

TABLE 2. ROM for Each MSRSGC Category[16]

MSRSGC Category	ROM (%)
Nondiagnostic	17
Non-neoplastic	8
Atypia of undetermined significance	34
Neoplasm, benign	4
Neoplasm, salivary gland neoplasm of uncertain malignant potential	42
Suspicious for malignancy	58
Malignant	91

Abbreviations: MSRSGC, Milan System for Reporting Salivary Gland Cytopathology; ROM, risk of malignancy.

TABLE 3. ROHM for Each MSRSGC Category[69,219,223]

MSRSGC Category	ROHM (%)
Nondiagnostic	5
Non-neoplastic	2
Atypia of undetermined significance	0
Neoplasm, benign	1
Neoplasm, salivary gland neoplasm of uncertain malignant potential	8
Suspicious for malignancy	18
Malignant	71

Abbreviations: MSRSGC, Milan System for Reporting Salivary Gland Cytopathology; ROHM, risk of high-grade malignancy.

Literature review and clinical interpretation. Surgery with adequate free margins for resectable cases is the principal treatment for cancer of the salivary glands in the absence of distant metastases.[316] Unresectable disease has been defined as T4b disease or cervical lymph node metastases invading the carotid artery.[20] The extent of adequate free margin is not well-established because of the absence of prospective randomized trials, the different anatomic sites that these tumors involve, and the diverse histologic types. Furthermore, the presence of the facial nerve for parotid tumors also significantly affects the extent of margin that can be achieved.

Recommendation 2.2. Surgeons may request intraoperative pathologic examination to support immediate alterations in intraoperative management (extent of resection and neck dissection). Decisions that would result in major harm such as facial nerve resection should not be based on indeterminate preoperative or intraoperative diagnoses alone (Type: evidence based; Evidence quality: low; Strength of recommendation: weak).

Literature review and clinical interpretation. A combination of preoperative and intraoperative data is used to guide the surgeon in deciding the amount of gland to remove, how to manage the facial nerve, and removal of parotid and regional nodes. Although the patient's history, examination findings, imaging, and FNA are useful in detecting salivary gland malignancies, there remains some difficulty in diagnosing the exact nature of some salivary gland tumors. Furthermore, false-negative needle aspirates (rates as high as 20%) can be a concern when deciding upon the appropriate operation.[12] Intraoperative frozen sections are a useful adjunct to preoperative examinations in identifying malignant salivary gland pathologies. The accuracy of frozen section is 99% in identifying neoplastic lesions and 96% in identifying non-neoplastic lesions, but they become less accurate when attempting to report the exact tumor type: 90% in benign lesions as opposed to 59% in malignant lesions.[152] In addition to being a useful adjunct in diagnosing malignant tumors, Olsen et al also found that frozen sections can be used to reliably affect intraoperative decision making. With a 98.5% sensitivity and 99% specificity in detecting malignant parotid tumors, they identified only 4 of 220 cases whereby the frozen section diagnosis would have changed the intraoperative decision making if the final pathology report had been known.[317] In general, frozen sections enable the surgeon to alter the operation based on the pathology; however, the surgeon should refrain from making decisions resulting in major harm (such as facial nerve sacrifice) on indeterminate preoperative or intraoperative results alone.

Recommendation 2.3. Surgeons may perform partial superficial parotidectomy for appropriately located superficial T1 or T2 low-grade salivary gland cancers (Type: evidence based; Evidence quality: low; Strength of recommendation: weak)

Literature review and clinical interpretation. Although there are no randomized trials evaluating the extent of surgery for low-grade parotid cancer, the clinical behavior of these tumors is similar to pleomorphic adenomas and other benign salivary neoplasms. In these cancers, the goal is for complete excision, but there is not a need to remove additional parotid tissue containing adjacent lymph nodes because of the low rate of metastatic spread.[318] Because of their location adjacent to the facial nerve, resection of many parotid tumors often results in a close surgical margin (< 5 mm). Despite this, early-stage low- and intermediate-grade parotid cancers have been shown to have excellent disease control when managed with complete surgical resection, even with narrow surgical margins, in the absence of adverse features such as perineural or lymphovascular invasion or pathologic nodal disease.[319-322] Zenga et al[321] demonstrated a 100% locoregional control at a mean follow-up of 74 months in a series of 15 patients with T1-2N0 low- or intermediate-grade mucoepidermoid cancer managed with surgery alone, despite a surgical margin of ≤ 2 mm. Similarly, in a series of 18 patients with early-stage acinic cell carcinomas of the parotid gland without adverse features (pathologic nodal disease, lymphovascular or perineural invasion, or high-grade histology), only one patient experienced a recurrence with a median follow-up of 64 months.[320] In another series by Stodulski et al,[322] 32 low- or intermediate-grade parotid cancers managed with surgery alone with negative (≥ 1 mm) but close (≤ 5 mm) surgical margins, a 5-year DFS of 90.6% was observed. Consequently, in an effort to optimize tumor excision while minimizing the risk to the facial nerve, it is recommended to perform a partial superficial parotidectomy for appropriately located T1 or T2 low-grade salivary cancers. Additional excision of uninvolved parotid parenchyma is not necessary.

Recommendation 2.4. Because of the risk of intraparotid nodal metastases in high-grade or advanced-stage parotid cancer, surgeons should perform at least a superficial parotidectomy with consideration of a total or subtotal

parotidectomy for any high-grade or advanced (T3-T4) parotid cancer (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and clinical interpretation. For advanced (T3-T4) or high-grade parotid cancers, the surgical approach should take into account not only the removal of the primary tumor but also the adjacent at-risk parotid lymph nodes. Although complete parotidectomy is the most definitive approach, more aggressive surgery may result in higher risk to the facial nerve.[126] Much of the literature pertaining to whether a superficial versus a total parotidectomy should be performed also includes metastatic cutaneous lesions involving the gland. In a 2014 publication by Olsen and Moore,[323] 27 patients were found to have deep lobe spread from either parotid cancers or tumors outside the gland. Thom et al[324] found that in their series of 65 patients managed for parotid metastatic lesions of cutaneous origin, 22% had deep lobe involvement. However, although the presence of occult deep lobe spread may exist, there are no data available for parotid cancers, or cutaneous squamous cell carcinoma with metastases to the gland, that more aggressive surgery yields improved survival or locoregional control when adjuvant therapy is used. In addition, in a series of 64 patients who underwent surgery and adjuvant radiation therapy (RT) for metastatic squamous cell carcinoma to the parotid, a 3.7% rate of parotid bed recurrence was observed, with no difference seen based on extent of parotidectomy.[325] Consequently, given that adjuvant RT would be recommended in patients with advanced and/or high-grade parotid cancers (see Recommendation 3.2), it is advised for these patients to receive at least a superficial parotidectomy with removal of additional parotid tissue, when possible if it is deemed to not place the facial nerve at significant increased risk.

Recommendation 2.5. Surgeons should perform facial nerve preservation in patients with intact preoperative facial nerve function when a dissection plane can be created between the tumor and the nerve (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 2.6. Surgeons should perform resection of involved facial nerve branches in patients with impaired facial nerve movement preoperatively or when branches are found to be encased or grossly involved by a confirmed malignancy (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and clinical interpretation. When resecting salivary cancers, achieving negative surgical margins has been shown to improve OS.[326] Moreover, patients with preoperative facial weakness and/or evidence of perineural invasion at the time of resection have been shown to have a worse prognosis.[196,327,328] However, in the context of parotid and submandibular malignancies where preoperative facial nerve is normal, additional margin clearance may constitute resection of facial nerve branches and thus can result in significant morbidity to the patient. Because of obvious ethical reasons, there have been no controlled prospective trials to assess the impact of facial nerve resection on survival and disease control. In early-stage low- and intermediate-grade parotid cancers, complete surgical resection with close margins has been shown to result in excellent disease control, supporting the concept of facial nerve preservation in these patients.[319-322] For advanced and high-grade tumors, it is less clear. In a retrospective series of 107 patients undergoing parotidectomy for parotid cancer, Guntinas-Lichius et al[131] used the following criteria for nerve resection: preoperative nerve weakness confirmed by electromyography believed to be related to the tumor or intraoperative suspicion of tumor infiltration of the nerve. In their study, there was no statistically significant difference in DFS, but there was a trend toward improved 5- and 10-year OS in the total parotidectomy compared with radical parotidectomy, suggesting a possible selection bias. In this series, those in the total parotidectomy group were more likely to have high-grade cancers, and there was a trend toward a higher rate of adjuvant RT in this cohort. In patients with adenoid cystic carcinoma (ACC), the oncologic benefit of nerve resection is also not clear. Iseli et al[282] published a retrospective series of parotid ACCs and evaluated the impact of facial nerve resection and the use of adjuvant radiation on survival and recurrence. In their single-institution group of 75 patients, facial nerve resection did not show statistically improved local control (LC) over facial nerve preservation (10-year LC of 70% and 100% in the facial nerve preservation and the facial nerve resection groups, respectively). There was a trend toward improved 10-year OS in the nerve resection group. In the same study, the use of adjuvant RT did increase LC at 5 years and trended toward better 10-year OS. Therefore, based on the evidence of the importance of clear surgical margins on LC in salivary cancer, as well as the functional and quality-of-life implications of facial nerve sacrifice, it is recommended to resect facial nerve branches only when this will allow for complete margin clearance or when the nerve is grossly infiltrated or encased by malignancy.

Recommendation 2.7. Surgeons should offer an elective neck treatment over observation in a clinically negative neck in T3 and T4 tumors and high-grade malignancies (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and clinical interpretation. In looking at the National Cancer Database, salivary duct carcinoma (SDC), adenocarcinoma not otherwise specified, carcinoma ex pleomorphic adenoma, and mucoepidermoid carcinoma all had over a 20% rate of clinically positive nodal involvement at presentation.[318] In the same study, these high-grade histologies also had the highest rates of occult nodal disease.

Wang et al[329] performed a multivariate analysis on 219 patients in their single-institution study and found that lymph node metastases were predicted by major nerve invasion, histologic grade, lymphovascular invasion, and extracapsular invasion. Currently, there are no data available looking at the impact of elective neck dissection in disease control and survival in instances where adjuvant therapy is given postoperatively. However, Chen et al[102] demonstrated that elective neck irradiation resulted in 100% regional control in 131 patients, compared with a neck recurrence rate of 20% in those where the neck was observed. A similar series by Herman et al[133] demonstrated comparable neck control rates for patients with cN0 high-grade salivary cancers who received either elective neck dissection or elective neck irradiation. Given these findings, it is recommended that cN0 patients with high-grade salivary cancers and those with cT3-T4 at presentation should have elective treatment of their neck with either elective nodal dissection or elective neck irradiation.

Recommendation 2.8. For operative elective neck management of salivary cancers, ipsilateral selective neck dissection should be performed with levels dependent on the primary site. For parotid malignancies, levels may include 2-4 (Type: evidence based; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 2.9. For a cN+ neck, surgeons may perform an ipsilateral neck dissection of involved and at-risk levels and may extend to adjacent levels, up to levels 1-5 (Type: evidence based; Evidence quality: low; Strength of recommendation: moderate).

Literature review and clinical interpretation. When looking at the location of occult cancer spread in cN0 patients with parotid cancer, Ali et al[278] found levels II and III to be the most frequently involved, with level IV being involved in 11% and level I and V being involved in < 7%. In the same series, when patients had evidence of regional metastatic disease preoperatively, levels I to V were positive with 52%, 77%, 73%, 53%, and 40%, respectively. This high rate of level V involvement in cN+ necks was also demonstrated by Lim et al[330] when they found 82% of patients with therapeutic neck dissections having level V disease. As a result, for those who are cN0 with high-grade or T3-T4 primary parotid cancers who are receiving elective neck dissection, levels II-IV should be removed. For those undergoing a therapeutic neck dissection for cN+ disease, an ipsilateral neck dissection of involved and at-risk levels may extend to include levels I-V. For submandibular cancers, because of the risk to the marginal mandibular branch of the facial nerve as well as the lingual and hypoglossal nerve with revision suprahyoid surgery, it is recommended that at least a level I nodal dissection is offered to patients affected by these tumors. Moreover, since occult metastatic diseases are confined to levels I-III in cN0 patients with submandibular cancers,[331] an elective supraomohyoid dissection is recommended for those with high-grade or advanced (T3-T4) tumors undergoing operative neck management.

Recommendation 2.10. In the setting of resectable, recurrent locoregional disease and no distant metastatic disease, regardless of prior treatment type, patients should be offered revision resection and appropriate surgical reconstruction and rehabilitation (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 2.11. In the setting of resectable, recurrent locoregional disease and distant metastatic disease, regardless of prior treatment type, treatment may include palliative revision resection and appropriate surgical reconstruction and rehabilitation, if the metastatic disease is not rapidly progressive or imminently lethal (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 2.12. Patients undergoing revision surgery for recurrent salivary gland cancer should be evaluated for potential adjuvant therapy (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and clinical interpretation. Primary treatment of recurrent salivary gland cancer should begin with revision surgical resection to clear margins. Because such interventions, especially in cases of advanced recurrence and high-grade histology, may carry significant attendant functional and cosmetic morbidity, surgery should be carefully planned with thorough shared patient decision making regarding therapeutic intent, side effects, and potential complications. It is imperative that appropriate and realistic assessment of true resectability is determined before surgery as postsurgical residual disease and positive margins are associated with poor prognosis.[283,332] Degree of surgical resection should be placed in appropriate context, balancing goals of total resection with morbidity. Therefore, greatly extending surgery in one anatomic region to obtain wide margins adds little benefit if another area has inherently close margins, secondary anatomic or morbidity limitations. Similarly, appropriate availability of collaborative surgical services should be planned for necessary otological and skull base resection as well as reconstruction of cranial nerve deficits, craniofacial bone, and soft-tissue anatomy. Comprehensive neck dissection of appropriate levels should be undertaken for all N+ disease. Elective neck dissection of appropriate levels at risk should also be encouraged in the N0 neck in conjunction with revision surgery, although this is frequently required in conjunction with vessels access for appropriate reconstructive surgery.

Surgical efforts at re-resection, with the attendant morbidity, should primarily be considered appropriate after ruling out evidence of metastatic spread, which could significantly limit life expectancy mitigating the potential patient benefit from surgery. Yet, clinical situations often

arise (especially in the setting of ACC) where significantly advanced and morbid locoregional disease occurs in the context of slowly progressive and essentially asymptomatic metastatic disease. If the locoregional disease is technically resectable and with acceptable attendant morbidity, comprehensive surgical resection and reconstruction of locoregional disease can be undertaken to improve or preserve quality of life in the context of metastatic disease, which may not be lethal for years.[284,333]

All patients with recurrent salivary gland cancer should be evaluated in a multidisciplinary setting, whenever possible. If no previous adjuvant treatment was given as part of primary treatment, adjuvant RT should be planned after revision surgery. If previous radiation was completed, selected patients may be eligible for consideration of adjuvant re-irradiation or intraoperative interventions such as intraoperative RT or brachytherapy at selected centers. Similarly, evolving experience with chemoradiation as well as immunotherapy and targeted therapy warrants consideration in the context of clinical trials.

Clinical Question 3: What Are the Treatment Considerations and Appropriate Radiotherapy Technique for Patients With SGM?

Recommendation 3.1. Postoperative RT should be offered to all patients with resected ACC (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and clinical interpretation. ACC is characterized by an infiltrative growth pattern and spread along nerves. Although surgery is the primary treatment for ACC, postoperative radiation has been shown to increase locoregional control.[99,286] The benefit of postoperative RT in ACC has been noted in all stages of disease. Using the National Cancer Database, Lee et al[334] showed that there was an OS benefit in adding adjuvant RT for even early-stage ACC. However, despite achieving locoregional control, many patients with ACC eventually succumb to distant recurrences.[97,118]

Recommendation 3.2. Postoperative RT should be offered to patients with tumors with the following features: high-grade tumors, positive margins; perineural invasion; lymph node metastases; lymphatic or vascular invasion; and T3-4 tumors. (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 3.3. Postoperative RT may be offered to patients with tumors with close margins or intermediate-grade tumors (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: weak).

Literature review and clinical interpretation. There is strong evidence that postoperative RT increases locoregional control for resected tumors with the following adverse features: high-grade tumors, positive margins; perineural invasion; lymph node metastases; lymphatic or vascular invasion; and T3-4 tumors.[139,173,204] Using the SEER registry, Mahmood et al[199] showed that adjuvant RT improved survival of patients with high-grade and locally advanced malignant salivary gland tumors. Another large study of 4,068 patients with malignant salivary gland tumors also showed improved survival associated with the use of adjuvant RT.[201] However, for intermediate-grade tumors and close margins, the data are inconclusive whether postoperative RT is required or not.[319] In 32 patients with low- or intermediate-grade parotid carcinoma and close margins treated with surgery alone, only 3 (9.38%) experienced a local recurrence.[322]

Recommendation 3.4. In postoperative cases, the high-dose target should cover the salivary gland surgical bed and appropriate nodal levels (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and clinical interpretation. Preoperative imaging, operative notes, surgical pathology reports, and any postoperative imaging including CT simulation should be reviewed closely to formulate target volumes for radiotherapy. In general, the salivary gland surgical bed and involved nodal levels should constitute the high-dose target volume. Coverage and appropriate dosing of these areas have been demonstrated to significantly reduce the risk of locoregional recurrence, as noted in Recommendation 3.3. Postoperative radiotherapy when conventionally fractionated should be at least 60 Gy to the high-dose target.[203]

Recommendation 3.5. In the case of perineural invasion, the associated nerve(s) may be covered with an elective or intermediate dose to the skull base (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Literature review and clinical interpretation. Perineural invasion, particularly named nerve invasion that is identified clinically or pathologically, is an intermediate- to high-risk feature for recurrence.[97,118,132,146,203] Coverage of the involved nerve to the base of skull with an elective or intermediate dose (46-54 Gy in 2 Gy fractions) may be reasonable to reduce the risk of retrograde nerve failure toward the base of skull.

Recommendation 3.6. Elective nodal coverage may be offered for T3-4 primary and high-grade malignancies (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Recommendation 3.7. Radiation should be initiated within 8 weeks of surgery (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Recommendation 3.8. Particle therapy, including proton, neutron, and carbon ion therapy, may be used for patients with SGM; there are no indications for use of heavy particle

therapy over photon or electron therapy (Type: evidence based; Evidence quality: low; Strength of recommendation: weak).

Literature review and clinical interpretation. For patients diagnosed with SGM, RT is typically performed using well-established techniques, namely, photon or electron therapy. These techniques are widely available at radiation centers; the majority of studies integrate photon therapy, previously conventional two-dimensional or three-dimensional treatments based on bony landmarks and more recently intensity-modulated radiation therapy (IMRT), which allows for shaping of the beam to the target and minimizing dose to neighboring structures. Particle therapy comprises radiation treatment using other modalities, most commonly neutron, proton, or carbon-ion therapy. These techniques are limited to specialized centers around the world. There has been considerable interest in studying the potential benefit of particle therapy in patients with SGM. There are arguments that the use of these techniques improves conformality, allows an increased dose to be delivered safely, or has a biologic effect benefit (because of high linear energy transfer of neutron and carbon-ion therapy).

There are multiple studies evaluating particle therapy in SGM; the majority are retrospective[120,160,163,165,166,289] or small phase II studies[34] without comparison with photon-based therapy, especially IMRT. These studies suggest that particle therapy may allow further dose escalation, especially if used as a boost, with LC benefit in the treated fields; however, in the absence of comparison with modern photon (IMRT) techniques, there are no clear indications for particle therapy for patients with SGM. Given the potential for toxicity with high-linear energy transfer radiation techniques (neutron and carbon-ion therapy), there have been multiple retrospective studies that monitor patients with SGM for toxicity of treatment; these have not noted increased rates in their follow-up times.[165,166]

In total, these studies suggest that particle therapy may be used for treatment of SGM with acceptable cancer outcomes and toxicity burden; however, without comparative data and the limitation of particle therapy availability, there are no clear indications for the use of particle therapy over photon or electron therapy for patients with SGM.

Recommendation 3.9. Elective neck irradiation may be offered in patients with cN0 disease for the following indications: T3-T4 cancers or high-grade malignancies (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and clinical interpretation. When treating with definitive radiotherapy or postoperative radiotherapy where the neck was not addressed, elective nodal radiation may be helpful in cases of locally advanced (T3-T4) or high-grade malignancies. The risk of microscopic involvement exceeds 12% for parotid gland tumors and 33% for submandibular gland tumors in the presence of these risk features.[203] Elective neck radiation appears to reduce the risk of regional recurrence in high-risk cN0 patients.[97] For patients who have had a neck dissection with positive nodes identified, treating the next nodal echelon at risk with an elective dose may improve regional control.[162] There appears to be a trend toward a regional control benefit with elective neck doses $\geq$ 46 Gy.[203]

Recommendation 3.10. Radiotherapy should be offered to patients with SGM who are not candidates for surgical resection (because of extent of disease or medical comorbidity) (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Note. The high-dose target should cover the gross disease in the salivary gland and any appropriate nodal levels.

Literature review and clinical interpretation. Although the primary recommendation for upfront SGM management is for surgical resection, there is a subset of patients for whom surgery is not feasible. Patients may be deemed to have inoperable cancer based on the extent of disease, the presence of metastatic disease, or underlying medical comorbidities; the proportion deemed inoperable varies based on the study and its inclusion criteria (eg, SGM histology and primary site) but ranges between 7% and 30%.[161,203,286] For those patients who cannot have surgical resection, retrospective series have demonstrated that definitive radiotherapy to a curative dose (approximately 70 Gy or equivalent) provides an LC benefit and a cause-specific survival of approximately 40% at 10 years.[161] Other series suggest similar local and locoregional benefits to definitive RT in the setting of unresectable disease.[286,288] Although these outcomes are inferior to those provided by surgery and radiation in suitable patients, these data suggest that radiation is still beneficial for those patients who cannot be treated with surgery.

Given the small case series examining the role of definitive RT in SGM, there are a variety of practice patterns and techniques used. These encompass the use of particle therapy as primary therapy or as a boost, including neutron,[276] proton,[279] and carbon ion therapy[34,140,160]; there are no prospective data suggesting the benefit of one radiation modality over another in the setting of unresectable disease. Historic case series do show some differences in outcomes; however, these were largely before the integration of IMRT for photon therapy,[163] and more modern comparisons suggest that these differences may be abrogated.[288]

Similarly, the integration of chemotherapy with definitive RT in the treatment of unresectable SGM is unclear. Several case series have used concurrent chemoradiation most typically with platinum-based regimens.[273,279,281,287,288] There is a lack of data on the relative efficacy of concurrent platinum-based regimens in this setting (see the Systemic Therapy section).

For patients who have unresectable disease, the primary disease and gross nodal disease (with margin) should be treated to curative dose (equivalent to 70 Gy in 2-2.12 Gy fractions). Potential routes of spread should be covered based on knowledge of the nodal drainage (for SGM subtypes that spread to nodes) and perineural tracts (for SGM subtypes that spread via nerves) (see the Radiation Therapy section).

Clinical Question 4: What Is the Role for Systemic Therapy in the Management of SGM?

Recommendation 4.1. In the setting of patients undergoing adjuvant radiotherapy, the addition of concurrent chemotherapy may not be routinely offered outside of a clinical trial (Type: evidence based; Evidence quality: low; Strength of recommendation: moderate).

Literature review and clinical interpretation. There are no randomized trials comparing survival outcomes of patients with salivary gland cancer who are candidates to receive postoperative radiation with or without concomitant chemotherapy. Only retrospective analyses have been conducted. Some of them reviewed patients receiving RT or chemoradiation for high-risk features such as high-grade histology, advanced stage, margins, nodal status.[74,81,88,114,127] Few were focusing on resected major salivary cancers[72,80] or just parotid gland primary tumors,[82] and other studies included only specific histotypes such as squamous cell carcinoma,[75] ACC,[81,111] and SDC.[91] Although there are data supporting the role of radiation alone in patients with high-risk features,[199,201] reasons for performing postoperative radiation may differ by type, number of adverse factors, and center practice patterns. It might be postulated that patients, who outside a clinical study, received CT or RT might have been negatively selected concerning their oncological picture and possibly positively selected for age, performance status, and comorbidity.

In this context, interpretation of the results achieved by an intensified postoperative approach is difficult and poorly informative in relation to the therapeutic question.

Among the 10 most relevant studies,[72,74,75,80,81,88,91,111,114,127] only four reported some benefit for the addition of chemotherapy to postoperative RT.[74,75,81,111] Three of these four were studies focusing on specific histotypes: ACC, in which an improvement of LC was found, and squamous cell carcinoma where an OS advantage was observed.[74,75,81]

At least three randomized prospective studies are ongoing (ClinicalTrials.gov identifier: NCT01220583, NCT02776163, and NCT02998385). However, the rarity and complexity of the disease will prevent us from gathering unequivocal results even from randomized studies, although their results will serve to improve the general knowledge of this group of rare, variegated cancers.

Recommendation 4.2. In the setting of patients undergoing radiotherapy for nonoperable salivary gland cancer, the addition of concurrent chemotherapy may not be routinely offered outside of a clinical trial (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Literature review and clinical interpretation. There are no randomized trials or prospective studies comparing survival outcomes of patients with nonoperated salivary gland cancer who would be potential candidates to receive radiation with or without concomitant chemotherapy. Only case series have been reported. The Expert Panel identified four studies on unresected salivary gland cancer[273,279,281,287] and one study that reported a mixed population (17 patients) since some of the patients were operated on after full-dose radiation and concomitant cisplatin-based polychemotherapy. From this study, 23% of unresected salivary gland cancer of mixed histotypes obtained a complete response (CR).[335] Among seven patients with unresected salivary gland cancers with mixed histologies treated with concomitant cisplatin-based chemotherapy and radiation, only two resulted to be free of local failure after 8 months and after 13 years.[273]

Three case series collected unresected ACC for a total of 31 participants.[273,279,281,287] All participants received a cisplatin-based combination with radiation, half of them with protons. Globally, the LC ranged from 44% to 100% with median follow-up periods ranging from 27 to 62 months. Toxicities were in line with what was expected from the combination of chemoradiation. In the nine cases receiving protons,[273] 43% grade 3 local toxicities were reported and one patient with one severe eye disorder that was expected because of the critical vicinity of the eye of the tumor site. It is interesting to note that the combination is associated with some long-term LCs of unresected ACC, whether this is due to full-dose radiation or the association of chemotherapy is unknown.

On this basis, data are insufficient to recommend concurrent chemotherapy in nonresected salivary gland cancers.

Recommendation 4.3. In patients with salivary gland tumors expressing AR and/or HER2-Neu, adjuvant endocrine or targeted therapy may not be routinely offered outside of a clinical trial (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Literature review and clinical interpretation. There are no randomized trials comparing survival outcomes between patients who have or have not undergone adjuvant systemic therapy, and prospective data are lacking. A retrospective cohort study compared the use of adjuvant androgen deprivation therapy (ADT) in 22 patients with high-risk stage IVA AR-positive SDC with a historical control group of 111 patients who did not receive adjuvant ADT.[290] Following tumor resection, patients received adjuvant ADT (bicalutamide [n = 12] or luteinising hormone-releasing

hormone (LHRH) analog [n = 1] or a combination of these [n = 9]) for a median duration of 12 months (range 1-114 months). The median DFS was 33 months in the adjuvant ADT-treated patients and 21 months in the control group; the 3-year DFS was estimated to be 48% and 28% (P = .04). Differences in OS in favor of the ADT-treated patients were only significant after adjusting for confounders in multivariate regression analyses (hazard ratio, 0.064; 95% CI, 0.005 to 0.764; P = .03). No patients stopped therapy because of toxicity.

Retrospective case series have studied adjuvant HER2–targeted therapies in combination with chemotherapy in patients with resected HER2–positive SDC.[259,271] In one study, eight patients with resected stage III or IVA SDC received adjuvant chemoradiation with trastuzumab and five patients remained disease free at 2 years post-completion of therapy.[271] Another study reported on a cohort of 17 patients with resected HER2–positive SDC.[259] Nine patients received adjuvant chemoradiation with trastuzumab. In patients with HER2-positive or neu-positive (IHC 3+) tumors, adjuvant trastuzumab was associated with longer median DFS and OS (DFS, 117 *v* 9 months; P = .02; OS, 74 *v* 43 months; P = .02), with no difference among other HER2/neu (IHC 0-2+) subgroups.

Adjuvant ADT– and HER2–targeted therapies are of interest and warrant further prospective investigation to define the optimal duration, regimen, efficacy, and toxicity before recommendations can be made for adoption into routine practice.

Clinical Question 5: What Are the Appropriate Post-Treatment Follow-up and Evaluation of Patients With SGM?

Recommendation 5.1. Clinical follow-up with history and physical examination should be completed on a regular basis with decreasing frequency as time elapses from completion of treatment of salivary cancer (Type: informal consensus; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and clinical interpretation. Locoregional and distant recurrence at 5 years after completion of treatment can vary widely for salivary gland malignancies. This is due to a diverse range of histologic tumor types with a wide range of clinical behaviors. The likelihood of recurrence also varies based on the pathologic grade and stage of the tumor at diagnosis. Regardless, close and reproducible surveillance is recommended during the post-treatment follow-up period.

Follow-up for salivary gland malignancies broadly follows the current NCCN recommendations for variations of the far more common upper aerodigestive tract squamous cell carcinomas.[336] These guidelines recommend close initial follow-up, which decreases in frequency as the time since initial treatment completion lengthens. Examination time between visits may vary between practitioners, and patients are recommended to undergo surveillance history and physical examination quarterly for the first 2-3 years and then biannually until 5 years out from treatment. Yearly visits are then recommended.

History should center on changes at the primary site and treatment-related side effects. The physical examination should focus on the primary site and lymphatic levels at risk with attention to new mass presentation or new neurological defects such as facial nerve weakness and regional dysesthesia. For patients with minor salivary gland malignancies of the upper aerodigestive tract, fiberoptic endoscopic examination may be warranted. After reaching the five-year mark, patients may be seen on a yearly basis, especially if initially presenting with a higher stage and higher histopathologic grade.[337,338]

Recommendation 5.2. Post-treatment baseline imaging with contrast CT or MRI (for patients without contraindications) of the primary site and/or PET/CT should be obtained 3 months after completion of all treatment (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 5.3. Follow-up surveillance imaging of the primary site (contrast CT or MRI) and the chest CT may be obtained every 6-12 months for the first 2 years after treatment (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 5.4. Follow-up imaging of the primary site and the chest from years 3-5 should be directed by symptoms and physical examination findings. Yearly follow-up imaging may be offered in cases of high-grade histology or poor prognostic clinicopathologic features (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 5.5. Long-term follow-up (beyond 5 years) with yearly examination should be offered in all salivary gland cancer patients. Yearly chest CT may be offered especially in patients with high-grade histology or poor prognostic clinicopathologic features (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Literature review and clinical interpretation. Appropriate follow-up imaging is also recommended during post-treatment surveillance, especially during the early phase. Both CT and MRI are acceptable and directed by factors such as imaging type used in primary staging, accessibility, and examination tolerance. MRI with contrast offers some differentiation of benign and malignant disease, better soft-tissue characterization for differentiation of scar, and recurrence during follow-up and is more sensitive to changes indicative of perineural spread and skull base invasion. Contrast-enhanced CT is significantly cheaper to obtain and allows delineation of bony anatomy. It allows

evaluation of nodal metastatic disease and can be performed concurrently with chest CT scans during the surveillance period. PET/CT is of mixed utility for salivary tumors because of variable avidity of salivary gland pathology.[66,339] Some benign parotid tumors have high avidity, such as benign mixed tumors, whereas malignant tumors such as ACC may not take up FDG. Post-treatment imaging should be considered at 3 months and then yearly for 12-24 months. Yearly imaging may be obtained thereafter in cases of advanced-stage malignancy or high-grade histopathology.

The lungs are a relatively frequent site of salivary tumor metastasis, and surveillance for this is best obtained with chest CT. These should be performed yearly for the initial 2 years of follow-up, which can be extended on a yearly basis. Chest surveillance can extend beyond the 5-year mark as late pulmonary metastases are not uncommon with salivary gland cancers, especially in cases of specific histology, such as ACC. Standard chest X-ray lacks sensitivity and should not be used.

Clinical Question 6: What Are Treatment Options in Recurrent or Metastatic Disease for Patients With SGM?

Recommendation 6.1. Patients presenting with metastatic disease may be evaluated for further treatments such as local ablative treatments or systemic therapy. These options should be discussed with the patient and will depend on the patient and tumor factors (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Literature review and clinical interpretation. In patients with malignant salivary gland tumors, factors such as age, high stage, and adverse pathologic features such as intermediate- or high-grade histology, or nerve invasion increase the risk of distant metastases.[139,340,341] Using data from US National Cancer Institute's SEER program, Ellington et al[341] analyzed cases of ACC of the head and neck reported from 1973 through 2007 and found that 11.57% (317 of 3,026) had distant metastases. Furthermore, despite having metastatic disease, 10% of patients with ACC can survive $>$ 10 years.[342] In a National Cancer database study of 4,431 patients with mucoepidermoid carcinoma of the parotid gland, decreased survival was associated with increasing age, comorbidities, high tumor grade, advanced pathologic group stage, and positive surgical margins.[343] Thus, depending on patient and tumor factors, locoregional and/or systemic treatment options should be discussed.

Recommendation 6.2. In the setting of ACC and/or low-grade tumors with indolent biology with limited metastases (ie, $\leq$ 5 metastases), local ablative treatments such as surgery (metastatectomy) or stereotactic body radiation therapy may be offered to delay local disease progression (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Literature review and clinical interpretation. In a retrospective study of 109 patients with ACC who underwent pulmonary metastasectomy between 1991 and 2014, Girelli et al[344] reported the cumulative survival of 66.8% at 5 years and 40.5% at 10 years. The authors recommended proceeding with metastasectomy when two conditions are met: (1) complete surgical resection is feasible and (2) the time to pulmonary relapse after primary tumor treatment is $>$ 36 months. Similar results have been reported by Locati et al[345] and Bobbio et al.[269] Patients with acinic cell carcinoma metastases have similarly long-term survival after surgical management.[173] In patients with lung metastases where surgical removal is technically difficult because of tumor location or in patients with medical contraindications to surgery, an emerging treatment option is stereotactic ablative body radiotherapy.[10,280,346] In a cohort of 358 patients with oligometastatic disease treated with stereotactic body radiation therapy, Franceschini et al[280] reported that the LC at 6 and 24 months was 94.6% and 78.9% with a median OS of 34.7 months. Similarly, Palma et al[347] reported a 42.3% 5-year survival rate in patients with limited metastatic disease treated to all sites with stereotactic ablative body radiotherapy. From a radiation oncology perspective, the European Society for Radiotherapy and Oncology-American Society for Radiation Oncology consensus definition of oligometastatic disease is one to five metastatic lesions, preferably a controlled primary tumor, and all metastatic sites must be safely treatable.[348]

Recommendation 6.3. Patients may be considered for initiation systemic therapy in the following circumstances: (1) metastatic deposits are symptomatic and not amenable to palliative local therapy, (2) growth has the potential to compromise organ function, or (3) lesions have grown more than 20% in the preceding 6 months (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Literature review and clinical interpretation. Systemic therapy has modest efficacy in metastatic salivary gland tumors. To date, no single-agent or combination therapy has been shown to have a survival advantage. Furthermore, there are no randomized trials comparing treatment with supportive care alone. Few studies investigated any effect on quality of life. Phase II trial of lenvatinib in ACC found that some quality-of-life domains deteriorated over 6 months of therapy because of toxicity.[68]

Because of heterogeneous clinical behavior of salivary gland tumors, it may be difficult to determine when, and if, expected benefit from systemic therapy will outweigh toxicity and resultant effect on quality of life. Therefore, clinicians are encouraged to use clinical judgment and consider initiating treatment in symptomatic patients or those with imminent organ damage because of metastatic burden. Rapid progression of disease as defined by

standard response criteria may be used as a surrogate for impending change in clinical status.

Recommendation 6.4. For patients with ACC who are candidates for initiation systemic therapy, a multitargeted TKI, such as lenvatinib or sorafenib, may be offered if a clinical trial is not available (Type: evidence based; Evidence quality: low; Strength of recommendation: moderate).

Literature review and clinical interpretation. Several clinical trials have demonstrated the activity of multitargeted TKIs in ACC including lenvatinib and sorafenib. Several prospective trials have shown antitumor activity as witnessed by modest rates of disease stabilization (50%-94%) and partial responses (PRs) in some patients (3%-15%), with apparent improvements in clinical outcomes compared with historical controls.[28,30,32,33] Although definitive conclusions are difficult given the lack of a randomized trial,[349] different TKIs studied[21,26,27,29,38,68] and inclusion of non-ACC patients in some studies[27,29,30,33,38] response rates are on par with those seen in multidrug chemotherapy regimens with a more favorable toxicity profile.[22,37,42,89,285]

Recommendation 6.5. For patients with nonadenoid cystic salivary gland cancer who are candidates for initiation of systemic therapy, targeted therapy based on tumor molecular alterations (ie, *AR*, *HER2*, and *NTRK*) may be offered if a clinical trial is not available (Type: evidence based; Evidence quality: low; Strength of recommendation: moderate).

Literature review and clinical interpretation. No randomized trials comparing survival outcomes between different targeted systemic therapy regimens in salivary gland cancer exist.

Patients with secretory carcinomas (SCs) of the salivary glands, harboring NTRK gene fusion without a known acquired resistance mutation, may be offered first-line or subsequent-line NTRK inhibitor therapy rather than chemotherapy, given the high response rates and favorable toxicity profile. In a combined analysis of two phase I and one phase II studies of larotrectinib in patients with advanced NTRK fusion–positive cancers, objective responses were observed in 18 of 20 patients (90%) with NTRK fusion–positive SC of the salivary glands (median duration of response 35 months).[350] In a pooled analysis of two phase I and one phase II trials, seven patients with NTRK fusion–positive SC received entrectinib and 86% had an objective response.[351]

Patients with HER2-positive salivary gland carcinoma may be offered HER2-targeted therapies (trastuzumab plus taxane, pertuzumab plus trastuzumab, or ado-trastuzumab emtansine [T-DM1]) as first-line or subsequent-line therapies. In a single-center, single-arm phase II study of 57 patients with advanced HER2-positive salivary duct cancer, trastuzumab plus docetaxel demonstrated an ORR of 70% and a median PFS of 9 months.[31] Prior systemic therapy for metastatic disease was allowed. Smaller retrospective case series have also demonstrated high response rates with trastuzumab plus paclitaxel or carboplatin in the recurrent-metastatic setting.[259,271] In an open-label phase IIa basket trial, 15 patients with HER2 amplified and/or overexpressed salivary gland tumors received trastuzumab plus pertuzumab and nine objective responses were observed (60% ORR; one CR, eight PR) with a median PFS of 8.6 months.[352] In a phase II basket trial, 10 patients with HER2-amplified salivary gland cancer received T-DM1 and the ORR was 90% including five CRs after prior trastuzumab, pertuzumab, or antiandrogen therapy.[353] Two of three patients with HER2-amplified salivary gland cancer had a PR to first-line T-DM1 in the NCI-MATCH study.[354]

For patients with AR-positive salivary gland cancer, combined androgen blockade (CAB) may be offered in the first- or subsequent-line setting. A single-arm phase II trial of leuprorelin and bicalutamide in 36 patients with AR-positive salivary gland cancer demonstrated an ORR of 42% (including 11% CR) and a median PFS of 8.8 months.[20] Only 14% of patients had prior chemotherapy for recurrent-metastatic disease. Retrospective studies encompassing 72 patients with AR-positive recurrent-metastatic salivary gland cancer have shown an ORR of 18%-67% with first-line ADT either single-agent LHRH analogs or AR antagonist (enzalutamide or bicalutamide), or CAB (LHRH analog plus bicalutamide).[255,291,355] A single-arm phase II study of enzalutamide in 46 patients with AR-positive salivary gland cancer with prior AR-targeted therapies allowed demonstrated two confirmed PR and five unconfirmed PR, and 24 patients had stable disease as best response.[356] Prospective comparison of CAB versus chemotherapy in patients with AR-positive salivary cancer in an ongoing randomized phase II EORTC1206 trial will further determine the efficacy of first- or second-line ADT (ClinicalTrials.gov identifier: NCT01969578).

Other targeted therapies including axitinib,[38] tipifarnib,[259] gefitinib,[27] and lapatinib[357] have demonstrated clinical benefit rather than significant objective responses in small phase II studies, and these remain investigational.

Recommendation 6.6. Cytotoxic chemotherapy combinations may be offered to patients with symptomatic disease (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Literature review and clinical interpretation. Prospective evaluation of cytotoxic regimens in salivary gland cancers has been limited by small patient numbers, inclusion of heterogenous populations with histologic and biologic diversity, and lack of comparisons with supportive care. As a result, there is no high-level evidence that indicates a survival benefit to the use of cytotoxic chemotherapy (or any systemic therapy for that matter) in patients with

metastatic salivary gland cancers. In the majority of these clinical trials, a small proportion of patients do appear to have objective responses to cytotoxic chemotherapy. This suggests a potential for these regimens to reduce tumor burden and consequently, tumor burden–related symptoms in the setting where palliation is the therapeutic goal.

Although modest in activity, single-agent cytotoxic agents have been explored in this disease. An early phase II clinical trial completed in 1987, published by Licitra et al, tested the activity of single agent cisplatin 100 mg/m^2 once every 21 days given for four cycles. The investigators observed an overall response rate of 16% (two ACCs, one mucoepidermoid carcinoma, and one parotid squamous cell carcinoma) with a 7-month median response duration.[37] A more contemporary experience was reported by Gilbert et al, in ECOG1394, a single-arm prospective experience with paclitaxel 200 mg/m^2 given once every 21 days in 50 patients with recurrent-metastatic ACC, adenocarcinomas, and mucoepidermoid carcinomas. The objective responses were observed in eight patients, three mucoepidermoid carcinomas, and eight adenocarcinomas (no objective responses were seen in ACCs). In the entire cohort, the median time to progression was 4 months. Not surprisingly, no objective responses were noted in patients with ACC. The median survival of the entire cohort was 12.5 months, and no differences in time to progression and OS were observed among the three histologic subtypes.[22]

Combination regimens also appear to result in responses in heterogenous populations examined in clinical trials. Airoldi et al reported an overall response rate of 34% in 16 patients with salivary gland malignancies treated with a combination of cisplatin (80 mg/m^2) on day 1 and vinorelbine 25 mg/m^2 on days 1 and 8 of a 21-day cycle. Three patients (19%) achieved a CR, two ACCs, and one undifferentiated carcinoma, with CR durations lasting 6-27 months.[19] A triplet combination of cisplatin, adriamycin, and cyclophosphamide in a phase II trial of 22 patients with diverse histologies was reported by Licitra et al, revealing an overall response rate of 27% (six PRs in three ACCs, one SDC, one mucoepidermoid carcinoma, and one neuroendocrine carcinoma). The median duration of response was 7 months.[37] A trial reported by the NCIC explored the activity of gemcitabine and a platinum agent in a phase II trial of 33 patients with salivary gland malignancies. Gemcitabine was given at 1,000 mg/m^2 once on days 1 and 8 of a 21-day cycle, and cisplatin given at 80 mg/m^2 once on day 2 OR carboplatin at an area under the curve of five given once on day 1. The investigators observed an overall response rate in eight patients (24%); these responses were noted in patients with adenocarcinoma, adenoid cystic, mucoepidermoid, and SDC histologies.[285] Higher response rates in cytotoxic chemotherapy and monoclonal antibody combinations have been demonstrated in biomarker enriched salivary gland cancer populations, such as the HER2 overexpressors, discussed separately in this guideline.

There are well-recognized limitations to the applicability of these single-arm studies in nontrial clinical scenarios, including the inclusion of known biologically more indolent subsets such as ACCs (often without mandating progression before clinical trial enrollment). The well-reproduced observation of responses in a small subset of patients supports the use of these regimens in situations where a fit patient may benefit from symptom control or tumor burden reduction. The panel, however, recommends enrollment in a clinical trial if available.

Recommendation 6.7. For patients who are candidates for systemic therapy, checkpoint inhibitors should not be routinely offered at this time except for patients with selected molecular alteration (high TMB, MSI-H) (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Literature review and clinical interpretation. The prospective experience with the antiPD1 checkpoint inhibitors in salivary gland carcinomas consists of small phase I and II clinical trials, again with heterogenous histologies and variations in design and eligibility. Cohen et al reported the phase Ib KEYNOTE-28 experience using single-agent pembrolizumab 10 mg/kg once every 2 weeks in 38 PDL1 expressing recurrent-metastatic salivary gland carcinomas. This study did not mandate evidence of progression before participation, and the majority of enrolled participants had adenocarcinomas. Among 38 patients enrolled, three had a PR with an overall response rate of 12% with a 3-month median duration of response.[36] Mahmood et al, in a small randomized study of 20 patients with progressing ACC, compared single-agent pembrolizumab (200 mg IV every 21 days) with pembrolizumab with hypofractionated radiation (30 Gy in five fractions) to a site of metastatic disease. No objective responses were noted in either arm, and stable disease was noted in 7 of 10 patients in the pembrolizumab alone arm and 5 of 10 patients in the pembrolizumab and radiation arm.[39]

Combination strategies using the immune checkpoint inhibitors have also been explored in these salivary gland cancers. Rodriguez et al reported a phase I and II experience combining the HDAC inhibitor vorinostat 400 mg given orally five days on and two days off with pembrolizumab 200 mg once during each 21 day cycle among 25 patients with recurrent-metastatic salivary gland cancer with evidence of progression before trial enrollment. Objective responses were noted in 4 (16%) of patients, with a median response duration of 10.5 months.[40] In a single-arm phase II study, Tchekmedyian et al[42] explored the activity of nivolumab 3 mg/kg given once every 2 weeks and ipilimumab 1 mg/kg given once every 6 weeks in 32 patients with progressing ACC.

One confirmed PR and one unconfirmed PR were observed; 15 patients had stable disease as their best response.

Taken together, the currently available prospective data using checkpoint inhibitors among salivary gland cancers have demonstrated low response rates in both unselected and biomarker-enriched populations. Although pembrolizumab carries a primary site agnostic US Food and Drug Administration approval for mismatch repair–deficient tumors, it is important to note that this was based on a nine-patient cohort of noncolorectal cancer patients, none of whom had salivary gland malignancies.[43,358] Similarly, pembrolizumab is approved for TMB high malignancies, among a phase I cohort of 102 patients, 3 (3%) of whom had a salivary gland primary site.[43] With the current available data, this guideline panel does not recommend the routine use of immune checkpoint inhibitors outside of a clinical trial.

Recommendation 6.8. For patients with histologic tumor types with a high prevalence of targetable molecular alterations (ie, *AR* in SDC and *NTRK3* in SC), confirmatory target-specific testing should be performed (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 6.9. Patients who may be potential candidates for systemic therapy with histologic tumor types with low prevalence of targetable molecular alterations and unknown driver mutation status should be screened using a comprehensive panel for patients with driver mutations; driver mutation–negative tumors may then be offered target-specific testing (ie, *AR*, *NTRK3*) (Type: evidence based; Evidence quality: low; Strength of recommendation: weak).

Literature review and clinical interpretation. Numerous, albeit largely retrospective, studies demonstrate that selected targetable molecular alterations have an exceptionally high prevalence in specific histologic types. Most notable among these include AR in SDC and the *ETV6-NTRK3* translocation in SC. AR expression is present in between 80% and 97% of SDCs[78,359,360] and is arguably diagnosis defining with most AR-negative SDC representing other tumor types.[359] From its initial description in salivary gland in 2010 by Skalova et al,[361] the *ETV6-NTRK3* translocation has been linked to the diagnosis of SC. The majority harbor this canonical translocation, with only a small recently described subset (estimated at approximately 3%-5%) showing alternate translocations such as *ETV6-RET*,[362] *ETV6-MET*,[363] and *VIM-RET*,[364] among others. In these scenarios, where a particular diagnosis is linked with a high pretest probability of harboring a targetable alteration, direct and focused testing for this alteration (ie, AR immunohistochemistry and *ETV6-NTRK3* fusion testing by molecular methods) is the most efficient approach.[365]

In other tumor types, the prevalence of targetable molecular alterations is rather low, and routine screening for these targets is thus inefficient. For instance, AR expression is uncommon in non-SDC, ranging from 3% to 15% depending on the staining threshold used to define positivity.[360] NTRK fusions outside of the diagnosis of SC are even rarer and to date, restricted to anecdotal cases.[366] Furthermore, many salivary gland tumor types will still demonstrate nontargetable oncogenic drivers (ie, *MYB-NFIB* and *MYBL1-NFIB* translocations in ACC[367] and *CRTC1/3-MAML2* translocations in mucoepidermoid carcinoma[368]), which are typically mutually exclusive of the aforementioned targetable molecular alterations. In such cases where the patients may be candidates for systemic therapy, a more comprehensive genomic screening (usually next-generation sequencing [NGS]–based) approach may be useful.[365] This serves to identify unanticipated targets of interest (ie, *ALK*[369]) and identify other driver mutations that may be mutually exclusive of the target of interest. Thus, the remaining cases that are driver mutation–negative may potentially represent an enriched population that may benefit most from subsequent screening with target-specific testing if not already adequately represented on an NGS panel.[365]

The Data Supplement provides visual interpretations of these recommendations in the management algorithm.

PATIENT AND CLINICIAN COMMUNICATION

As the advancement of science continues, controversies around old and new practices continue to arise. Improving outcomes requires careful consideration in the continuous balance of literature.

Strategies to manage cancer in the head and neck, oral cavity, and oropharynx naturally vary according to a surgeon's experience and the availability of different technologies. As surgical techniques and the understanding of disease pathogenesis improve, patients are given even more options. However, head and neck cancer clinicians face a unique set of challenges given the potential adverse impacts that many of these treatments have on a patient's quality of life. The clinician needs to consider how treatment might have acute and late toxicities for the patient affecting speech, taste, saliva, chewing, swallowing, lymphatic processes, nerves, teeth, facial bone structure, and physical appearance. The clinician needs to discuss these potential impacts with the patient to balance the most effective treatment with the patient's quality-of-life objectives.

This guideline does not seek to encompass all approaches. Yet, given the rapid pace of scientific complexities, the Expert Panel believes that some basic approaches are clearer than others. A personal discussion among the multidisciplinary team, the patient, and their families is critical for optimal modern care. Many centers have developed navigators to facilitate processes and minimize the challenge that patients

face when they first encounter large systems of physicians and providers. The Expert Panel hopes that centers can help patients and their caregivers identify resources such as targeted support groups or introduction to other survivors to share information and strategies that can improve the patient treatment experience.

ASCO has always believed that strong and clear communication between physicians, patients, caregivers, and families is paramount for delivering the best quality care. For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: ASCO Consensus Guideline.[370]

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care and/or receive fragmented care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial or ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving fragmented care or poor quality care than other Americans.[371-374] Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and healthcare providers should strive to deliver the highest level of cancer care to these vulnerable populations.[375,376]

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCC)—is challenging. Patients with MCC are a complex and heterogeneous population, making it difficult to account for all of the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients to avoid potential interaction effects or confounding of results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

As many patients for whom guideline recommendations apply present with MCC, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCC and highlights the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

In light of these considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCC, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and co-insurance.[377,378] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[379,380]

Discussion of cost can be an important part of shared decision making.[381] Clinicians should discuss with patients the use of less expensive alternatives when it is practical and feasible for treatment of the patient's disease and there are two or more treatment options that are comparable in terms of benefits and harms.[381]

Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[381,382]

As part of the guideline development process, ASCO may opt to search the literature for published cost-effectiveness analyses that might inform the relative value of available treatment options. Excluded from consideration are cost-effectiveness analyses that lack contemporary cost data and agents that are not currently available in either the United States or Canada and/or are industry-sponsored. No cost-effectiveness analyses were identified to inform the topic.

EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from November 16 through November 30,

2020. Response categories of "Agree as written", "Agree with suggested modifications," and "Disagree. See comments" were captured for every proposed recommendation with 25 written comments received from six respondents. Most of the responses received either agreed or agreed with slight modifications to the recommendations, and very few of the responses disagreed. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated before Clinical Practice Guidelines Committee review and approval.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guideline Implementation Network (PGIN) on the panel. The additional role of this PGIN representative in the guideline panel is not only to assess the suitability of the recommendations to implementation in the community setting but also to identify any other barrier to implementation that a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among frontline practitioners and survivors of cancer and caregivers and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO website and most often published in the *Journal of Clinical Oncology*.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

RELATED ASCO GUIDELINES

- Integration of Palliative Care into Standard Oncology Practice[383] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[370] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Role of Treatment Deintensification in the Management of p16+ Oropharyngeal Cancer[384] (http://ascopubs.org/doi/10.1200/JCO.19.00441)
- Management of the Neck in Squamous Cell Carcinoma of the Oral Cavity and Oropharynx[385] (http://ascopubs.org/doi/10.1200/JCO.18.01921)
- Human Papillomavirus Testing in Head and Neck Carcinomas[386] (http://ascopubs.org/doi/10.1200/JCO.18.00684)
- Diagnosis and Management of Squamous Cell Carcinoma of Unknown Primary in the Head and Neck[387] (http://ascopubs.org/doi/10.1200/JCO.20.00275)
- Chemotherapy in Combination with Radiotherapy for Definitive-Intent Treatment of Stage II to IVA Nasopharyngeal Carcinoma[388] (http://ascopubs.org/doi/full/10.1200/JCO.20.03237)

ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/head-neck-cancer-guidelines. Patient information is available at www.cancer.net.

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EDITOR'S NOTE

This ASCO Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/head-neck-cancer-guidelines.

EQUAL CONTRIBUTION

J.L.G. and P.H. were Expert Panel co-chairs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.21.00449.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Management of Salivary Gland Malignancy: ASCO Guideline

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APPENDIX

TABLE A1. Management of Salivary Gland Malignancy Expert Panel

Name	Affiliation/Institution	Role/Area of Expertise
Jessica Geiger, MD (co-chair)	Cleveland Clinic, Cleveland, OH	Medical Oncology
Patrick Ha, MD (co-chair)	University of California San Francisco, San Francisco, CA	Surgical Oncology
Beth Beadle, MD, PhD	Stanford University, Stanford, CA	Radiation Oncology
Jimmy J. Caudell, MD, PhD	Moffitt Cancer Center, Tampa, FL	Radiation Oncology
Nicole Chau, MD	BC Cancer, Vancouver, BC, Canada	Medical Oncology
Daniel Deschler, MD	Massachusetts Eye and Ear Infirmary, Boston, MA	Surgical Oncology
Christine Glastonbury, MBBS	University of California San Francisco, San Francisco, CA	Neuroradiology
Marnie Kaufman	Adenoid Cystic Carcinoma Research Foundation, Needham, MA	Patient Representative
Eric Lamarre, MD	Cleveland Clinic, Cleveland, OH	Surgical Oncology
Harold Y. Lau, MD	University of Calgary, Calgary, AB, Canada	Radiation Oncology
Lisa Licitra, MD	Istituto Nazionale Tumori in Milan and University of Milan, Italy	Medical Oncology
Michael G. Moore, MD	Indiana University School of Medicine, Indianapolis, IN	Surgical Oncology
Cristina Rodriguez, MD	University of Washington, Seattle, WA	Medical Oncology
Anna Roshal, MD	Indiana University Health, Indianapolis, IN	Community Oncology
Raja Seethala, MD	University of Pittsburgh, Pittsburgh, PA	Pathology
Paul Swiecicki, MD	University of Michigan, Ann Arbor, MI	Medical Oncology
Nofisat Ismaila, MD	American Society of Clinical Oncology, Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)