ASCO special articles

Diagnosis and Management of Squamous Cell Carcinoma of Unknown Primary in the Head and Neck: ASCO Guideline

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abstract

PURPOSE To provide evidence-based recommendations to practicing physicians and other health care providers on the diagnosis and management of squamous cell carcinoma of unknown primary in the head and neck (SCCUP).

METHODS The American Society of Clinical Oncology convened an Expert Panel of medical oncology, surgery, radiation oncology, radiology, pathology, and 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 2008 through 2019. Outcomes of interest included survival, local and regional disease control, and quality of life. Expert Panel members used available evidence and informal consensus to develop evidence-based guideline recommendations.

RESULTS The literature search identified 100 relevant studies to inform the evidence base for this guideline. Four main clinical questions were addressed, which included subquestions on preoperative evaluations, surgical diagnostic and therapeutic procedures, appropriate pathology techniques, and adjuvant therapy.

RECOMMENDATIONS Evidence-based recommendations were developed to address preoperative evaluation for patients with a neck mass, surgical diagnostic and therapeutic procedures, appropriate treatment options in unilateral versus bilateral SCCUP.

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

In 2019, the American Society of Clinical Oncology (ASCO) published management guidelines on metastatic carcinoma to the neck from a known oral cavity or oropharyngeal primary site.[1] The aim of this subsequent guideline is to provide up-to-date management recommendations for patients with squamous cell carcinoma of unknown primary (SCCUP) in the head and neck based on published literature and expert panel consensus.

Squamous cell carcinoma (SCC) metastatic to cervical lymph nodes from an unknown primary site constitutes < 5% of all head and neck malignancies.[2,3] The workup for SCCUP consists of a thorough medical history, complete head and neck examination including flexible endoscopy, and diagnostic imaging. Cytology and positron emission tomography (PET) imaging may guide intraoperative diagnostic biopsies. For example, when the SCCUP is p16 and human papillomavirus (HPV) positive but with no obvious primary suggestion on exam and imaging, surgical tonsillectomy (palatine and/or lingual) is frequently successful in localizing a primary site.[3] Expert-performed transoral surgery localizes the primary tumor in > 60% of cases.[2-5] The primaries identified are frequently small T1 cancers and at times are successfully removed with negative margins. This guideline aims to define the best evidence for the diagnosis and management of SCCUP.

Management decisions for SCCUP are best decided in the context of a multidisciplinary tumor board and with careful consideration of HPV status, disease burden and distribution in the neck, a patient's overall health and well-being, potential treatment-related toxicity, and rehabilitation potential for functional recovery.

THE BOTTOM LINE

Diagnosis and Management of Squamous Cell Carcinoma of Unknown Primary in the Head and Neck: ASCO Guideline

Guideline Questions

1. What is the appropriate preoperative evaluation for patients with a neck mass suspicious for malignancy?
2. What are the appropriate surgical diagnostic and therapeutic procedures for squamous cell carcinoma of unknown primary (SCCUP)?
3. What are the treatment considerations and appropriate techniques for surgical management of the neck?
4. What are treatment considerations for radiotherapy and systemic therapy in SCCUP?

Target Population

Patients with SCCUP in the head and neck.

Target Audience

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

Methods

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

Preoperative Evaluation

Recommendation 1.1 Patients undergoing evaluation for a neck mass suspicious for SCC should undergo a thorough history and physical examination including fiberoptic laryngoscopy, which may be complemented with advanced visualization techniques, such as narrow-band imaging to facilitate identification of the anatomic location of the primary tumor and to inform potential therapeutic management options (Type of recommendation: informal consensus, benefit outweighs harm; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 1.2 Fine-needle aspiration or core biopsy of a clinically suspicious neck mass should be performed (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.3: High-risk (HR) human papillomavirus (HPV) testing should be done routinely on level II and III SCCUP nodes. Epstein-Barr virus (EBV) testing should be considered on HPV-negative metastases (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: moderate).
Note: HR-HPV testing may be done nonroutinely for SCC metastases at other nodal levels when clinical suspicion is high.

Recommendation 1.4: Contrast-enhanced computed tomography (CECT) of the neck should be the initial test for workup of metastatic cervical lymphadenopathy (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.5:
If a primary is not evident on clinical examination and CECT, positron emission tomography (PET)–CT should be the next diagnostic step (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

Diagnostic and Therapeutic Surgical Procedures

Recommendation 2.1: Patients should undergo a complete operative upper aerodigestive tract evaluation of mucosal sites at risk (oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx), including directed biopsy of any suspicious areas. Random biopsies of nonsuspicious areas have a low yield and should not be performed. Intraoperative advanced visualization techniques may be used to investigate potential primary sites for targeted biopsy (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 2.2: For patients with unilateral lymphadenopathy, if a primary site is not confirmed on initial evaluation, the surgeon should perform ipsilateral palatine tonsillectomy. If palatine tonsillectomy fails to identify a primary, ipsilateral lingual tonsillectomy may be performed. Bilateral palatine tonsillectomy may be considered according to clinical suspicion, at the discretion of the surgeon (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: moderate).

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THE BOTTOM LINE (CONTINUED)

Recommendation 2.3: For patients with bilateral lymphadenopathy, if a primary site is not confirmed on endoscopic examination, the surgeon may perform unilateral lingual tonsillectomy on the side with the greater nodal burden and may perform contralateral lingual tonsillectomy if the ipsilateral procedure fails to identify a primary. Bilateral palatine tonsillectomy after bilateral lingual tonsillectomy should be avoided (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 2.4: For patients in whom the primary tumor is identified during operative upper aerodigestive tract evaluation and definitive surgical management is intended (including neck dissection), clinicians should make every effort to resect the identified primary using transoral techniques to a negative surgical margin (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 2.5: Tissue specimens from suspected primary sites (biopsies, palatine and lingual tonsillectomies) should be entirely submitted for histologic examination. Resection specimens should be anatomically oriented by the surgeon, and margin evaluation should be performed. p16 immunohistochemistry may aid in evaluation of atypical or cauterized tissue for HPV-related SCC (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 2.6: Intraoperative frozen section of biopsies of suspicious primary sites may be performed to confirm the presence of tumor prior to resection. Intraoperative frozen section evaluation of palatine or lingual tonsillectomy specimens should be performed when the primary tumor remains clinically undetected. The tissue should be entirely submitted for frozen section examination. Resection specimens should be anatomically oriented by the surgeon, and margin evaluation should be performed intraoperatively (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

Surgical Considerations

Recommendation 3.1: For unilateral, small-volume neck disease, either definitive surgery or radiotherapy may be offered after multidisciplinary discussion (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 3.2: For small-volume bilateral neck disease with no clinical evidence of extranodal extension, either definitive surgery (with or without adjuvant therapy) or radiotherapy (with or without concurrent chemotherapy) may be offered after multidisciplinary discussion (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 3.3: Large-volume bilateral neck disease and/or gross (macroscopic) extranodal extension (ENE) favor definitive chemoradiotherapy, given the possible increased morbidity of extensive bilateral neck dissection and increased likelihood of trimodality therapy in such cases (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 3.4: When primary surgery is planned, levels IIA, III, and IV should be routinely dissected in cases when an oropharyngeal primary is suspected or confirmed for SCCUP. Additional nodal basins should be considered for dissection depending on the extent of nodal burden (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

Radiotherapy

Recommendation 4.1: Patients receiving radiotherapy or concurrent chemoradiotherapy as primary management of CUP should receive treatment to gross nodal disease, neck regions at risk of containing microscopic disease and the anatomic mucosal regions at risk of harboring the occult primary. Specific volumes treated will depend on the clinicopathologic presentation of the patient after complete workup as outlined in Recommendations 1 and 2. (Type: Evidence based, benefit outweighs harm; Evidence quality: Intermediate; Strength of recommendation: Strong)

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THE BOTTOM LINE (CONTINUED)

Recommendation 4.2: Patients treated with primary radiotherapy for unilateral (American Joint Committee on Cancer [AJCC] 8th N1) HPV-related adenopathy and carcinoma of unknown primary (CUP) should receive treatment to the gross node(s) and with consideration of coverage of putative primary sites in the ipsilateral tonsillar bed, ipsilateral soft palate, and the mucosa of the entire base of tongue, which may be modified based on prior surgical diagnostics (see Recommendation 2.2) at the discretion of the radiation oncologist (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: moderate).
Note: Consideration may be given to including additional areas in the oropharynx in patients for whom a PET scan was not available or who did not undergo a contralateral tonsillectomy because of the low risk of an occult contralateral tonsillar primary. Patients presenting with bilateral (AJCC 8th N2) adenopathy and CUP require bilateral treatment of the oropharyngeal mucosa.

Recommendation 4.3: Patients treated with primary radiotherapy for unilateral (AJCC 8th N1-N2b) HPV-negative nodal disease and SCCUP should receive treatment as to the above (Recommendation 4.2). Patients presenting with bilateral (AJCC 8th N2c) adenopathy and SCCUP should receive bilateral treatment of the oropharyngeal mucosa (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 4.4: In patients presenting with clinical scenarios highly suggestive of an occult cutaneous primary SCC, radiation of mucosal sites should be avoided (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 4.5: In patients with a clinicopathologic presentation highly suggestive of an occult nasopharyngeal primary, the mucosal radiation treatment may be limited to the nasopharynx. Nodal volumes in this scenario should be typical for nasopharyngeal management and include bilateral levels II-V, including retropharyngeal nodes (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 4.6: Patients treated with primary radiotherapy for unilateral involvement of multiple nodes and no clinical and radiologic evidence of ENE should routinely receive bilateral treatment (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 4.7: In addition to anatomic mucosal regions at risk, patients treated with primary radiotherapy for unilateral involvement of a single node and no clinical and radiologic evidence of ENE may consider treatment only to the unilateral involved neck (with the exception of those at risk for a nasopharyngeal primary (Recommendation 4.5) (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 4.8: Patients treated with primary radiotherapy for N3 and/or bilateral nodal involvement and/or clinical and/or radiologic evidence of ENE require bilateral neck treatment (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 4.9: For patients treated with primary radiotherapy, a biologically equivalent dose of 70 Gy over 7 weeks should be delivered to gross nodal disease. The biologically equivalent dose of approximately 50 Gy in 2 Gy fractions or slightly higher should be delivered to mucosal regions at risk of harboring the occult primary site and a biologically equivalent dose of 40 to 50 Gy in 2 Gy fractions electively to clinically and radiographically negative nodal regions at risk for microscopic spread of tumor (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 4.10: Patients receiving radiotherapy or concurrent chemoradiotherapy adjuvant to surgical management of CUP should receive treatment to regions of the neck and mucosa at risk of containing microscopic disease. The need for treatment should be determined by the extent of the surgery performed and pathologic results of the surgery (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 4.11: Patients for whom no primary site is pathologically identified at the time of surgery may benefit from treatment to the anatomic mucosal regions at risk of harboring the occult primary site, as defined in Recommendation 4.1. Nodal volumes requiring treatment are similar to those in Recommendations 4.5-4.7 (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

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THE BOTTOM LINE (CONTINUED)

Recommendation 4.12: Adjuvant radiotherapy should not be administered to patients with a single pathologically positive node without ENE after high-quality neck dissection (definition in ASCO's management of the neck practice guideline) and in whom, after a thorough evaluation, no primary tumor is identified (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 4.13: Adjuvant radiotherapy should be administered to patients with multiple pathologically involved nodes and/or pathologic evidence of ENE (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 4.14: Adjuvant radiation dose to the dissected regions of neck should be the equivalent of 60 Gy to the node levels that harbored gross resected disease and 50 Gy to regions beyond this thought to be at risk for microscopic residual disease. Nodal regions from which nodes were determined to have pathologic ENE may be considered for higher doses of adjuvant radiation, the equivalent of 60 to 66 Gy (Type of recommendation: evidence based; benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: moderate).

Systemic Therapy

Recommendation 4.15: Concurrent administration of cisplatin with definitive radiotherapy should be offered to patients without contraindications to cisplatin chemotherapy and with a suspected mucosal primary HPV/p16-negative SCC in the presence of unresected AJCC 8th N2-N3 nodal disease (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

Recommendation 4.16: Concurrent administration of cisplatin with definitive radiotherapy should be offered to patients without contraindications to cisplatin chemotherapy and with a suspected mucosal primary HPV/p16-positive SCC in the presence of unresected multiple ipsilateral, or bilateral, lymph node involvement or lymph nodes >3 cm in size (Type of recommendation: evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

Recommendation 4.17: Concurrent administration of cisplatin to adjuvant radiotherapy should be offered to patients without contraindications to cisplatin chemotherapy with a suspected mucosal primary SCC and pathologic evidence of ENE (Type of recommendation: evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

Recommendation 4.18: Concurrent administration of cisplatin with definitive radiotherapy should be offered to patients without contraindications to cisplatin chemotherapy and with an Epstein-Barr encoding region–positive stage II-IVA (AJCC 8th) carcinoma of unknown primary (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: high; Strength of recommendations: strong).

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-and-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.

GUIDELINE QUESTIONS

This clinical practice guideline addresses four overarching clinical questions:

1. What is the appropriate preoperative evaluation for patients with a neck mass suspicious for malignancy?
2. What are the appropriate surgical diagnostic and therapeutic procedures for squamous cell carcinoma of unknown primary (SCCUP)?
3. What are the treatment considerations and appropriate techniques for surgical management of the neck?
4. What are treatment considerations for radiotherapy and systemic therapy in SCCUP?

METHODS

Guideline Development Process

This systematic review–based guideline product was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff with health research methodology expertise (Appendix Table A1, online only). The Expert Panel met via teleconference and 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 two 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 guideline, which was then circulated for external review and submitted to *Journal of Clinical Oncology* 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 prior to publication. All funding for the administration of the project was provided by ASCO.

The recommendations were developed using a systematic review (2008-2019) of phase III randomized clinical trials (RCTs), observational studies, and clinical experience. Articles were selected for inclusion in the systematic review of the evidence based on the following criteria:

- Population: Patients with SCCUP in the head and neck
- Intervention of interest included surgical interventions (tonsillectomy, transoral removal of the primary, neck dissection), immunohistochemistry stain, HPV testing, PET/computed tomography (CT)/magnetic resonance imaging (MRI), multimodality treatment, adjuvant therapy and radiotherapy.
- Study designs included were systematic reviews, meta-analyses, RCTs, and prospective and retrospective comparative observational studies.

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, narrative reviews; or (3) published in a non-English language. The guideline recommendations are crafted, in part, using the Guidelines Into Decision Support (GLIDES) methodology and accompanying BRIDGE-Wiz software.[6] In addition, a guideline implementability review is conducted. 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 cochairs 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

Characteristics of Studies Identified in the Literature Search

A total of 100 studies met eligibility criteria and form the evidentiary basis for the guideline recommendations. These included 8 systematic reviews,[7-14] 2 phase II clinical

trials,[15,16] 19 prospective observational studies,[3,17-34] and 71 retrospective studies.[2,4,5,35-102] The identified trials were published between 2008 and 2019 and focused on surgical interventions, immunohistochemistry stain, HPV testing, imaging, multimodality treatment, adjuvant therapy, and radiotherapy. The primary outcomes reported in studies on surgical and therapeutic interventions included primary tumor detection rate, overall survival (OS), locoregional control, as well as progression-free survival (PFS), disease-free survival (DFS), and quality of life, while the studies on imaging reported outcomes on primary tumor detection rate, sensitivity, specificity, and likelihood ratios. Of note, while many of the studies quoted in this paper used the American Joint Committee on Cancer (AJCC) 7th edition, all references to stage in the recommendations in this guideline are based on the current 8th edition of the AJCC staging system.[103] Details on the study characteristics are included in the Data Supplement (online only). The systematic review flow diagram is also shown in Figure 1.

RECOMMENDATIONS

CLINICAL QUESTION 1

What is the appropriate preoperative evaluation for patients with a neck mass suspicious for malignancy?

Recommendation 1.1

Patients undergoing evaluation for a neck mass suspicious for squamous cell carcinoma should undergo a thorough history and physical examination, including fiberoptic laryngoscopy, which may be complemented with advanced visualization techniques, such as narrow-band imaging to facilitate identification of the anatomic location of the primary tumor and to inform potential therapeutic management options (Type of recommendation: informal consensus, benefit outweighs harm; Evidence quality: low; Strength of recommendation: moderate).

Literature review and clinical interpretation. Patients with head and neck cancer usually present with cervical lymph node metastases; despite a detailed diagnostic work up, the primary site will remain unknown in approximately 3% of cases.[2] The difficulties in finding the primary tumors may be explained by their small size as well as the difficult access to anatomic locations that can be missed by physical examinations and/or imaging studies.[4] The presence of a neck mass in adults for over two weeks and without evidence of infection is highly suspicious of malignancy. Diagnostic delays may result in progression of disease with increased morbidity, loss of function, and increased mortality.[7,104] Concerning associated symptoms to acknowledge are dysphagia, odynophagia, ipsilateral otalgia and/or recent hearing loss, hoarseness, oral or pharyngeal ulcers, nasal obstruction and/or epistaxis, and unexplained weight loss, among others.

There are certain characteristics of the targeted physical exam that pose an increased suspicion of malignancy, such as presence of a nontender neck mass with a size $>$ 1.5 cm, fixed to adjacent tissues, and ulceration noted on the overlying skin.[104] Initial physical examination should include evaluation of the patient's voice (hoarseness, "hot-potato" voice), head/face/ears (skin lesions, ulcerations, asymmetry), oral cavity (trismus and/or limited tongue mobility, any ulcers or masses), and pharynx (tonsillar and/or soft palate asymmetry). Bimanual palpation of the floor of the mouth assessing for mass or induration is advised as well. Further fiberoptic examination of the aerodigestive sites should be done, since occult primary tumors may arise from anatomic sites, such as the nasopharynx, base of the tongue, supraglottic larynx, and hypopharynx, which are not otherwise easily assessed.[4,22,65] Narrow-band imaging (NBI) with filtered light is reported to improve the diagnostic accuracy of simple clinic fiberoptic exams with white light due to its ability to identify focal increase vascularization in the superficial mucosa to help targeted biopsies. A 2019 published meta-analysis of 5 studies on diagnostic performance of NBI in SCCUP revealed an overall primary detection rate of 35%.[13] The primary site was revealed in 61 of 169 patients who had otherwise nonlocalized disease after standard diagnostic workup including conventional cross-sectional imaging.

Important information from the social and past medical history are gender (SCCUP is more common in men), age $>$ 40 years, tobacco and alcohol use, lifestyle including sexual history, prior history of head and neck cancer and/or head and neck radiation, immunodeficiency, and socioeconomic status. There are defined racial and geographic populations at risk for nasopharyngeal carcinoma, suggesting causative environmental (ie, Epstein-Barr virus [EBV]) and genetic factors.[105]

Younger patients presenting with a neck mass who are of male gender, with multiple oral sexual partners, with lesser smoking or alcohol consumption, and higher socioeconomic status and level of education may be more likely to have a diagnosis of HPV-positive head and neck cancers, especially oropharyngeal squamous cell carcinoma (OPC). These patients will have a better clinical outcome. A retrospective study by Tribius et al[90] evaluated 63 patients with carcinoma of unknown primary (CUP) and the association of HPV status and smoking history on survival outcomes. Results revealed that 37% had HPV DNA/p16-positive samples and 63% were negative for either/both markers. A high proportion of patients were previous or current smokers (79%); significantly fewer patients with HPV-positive/p16-positive were smokers in comparison with those who were negative for either/both HPV/p16 markers (61% *v* 90%, respectively; $P = .00067$). OS appeared to be superior in patients with $<$ 10 pack-years smoking history and HPV-positive/p16-positive disease. The study concluded that both tobacco smoking history

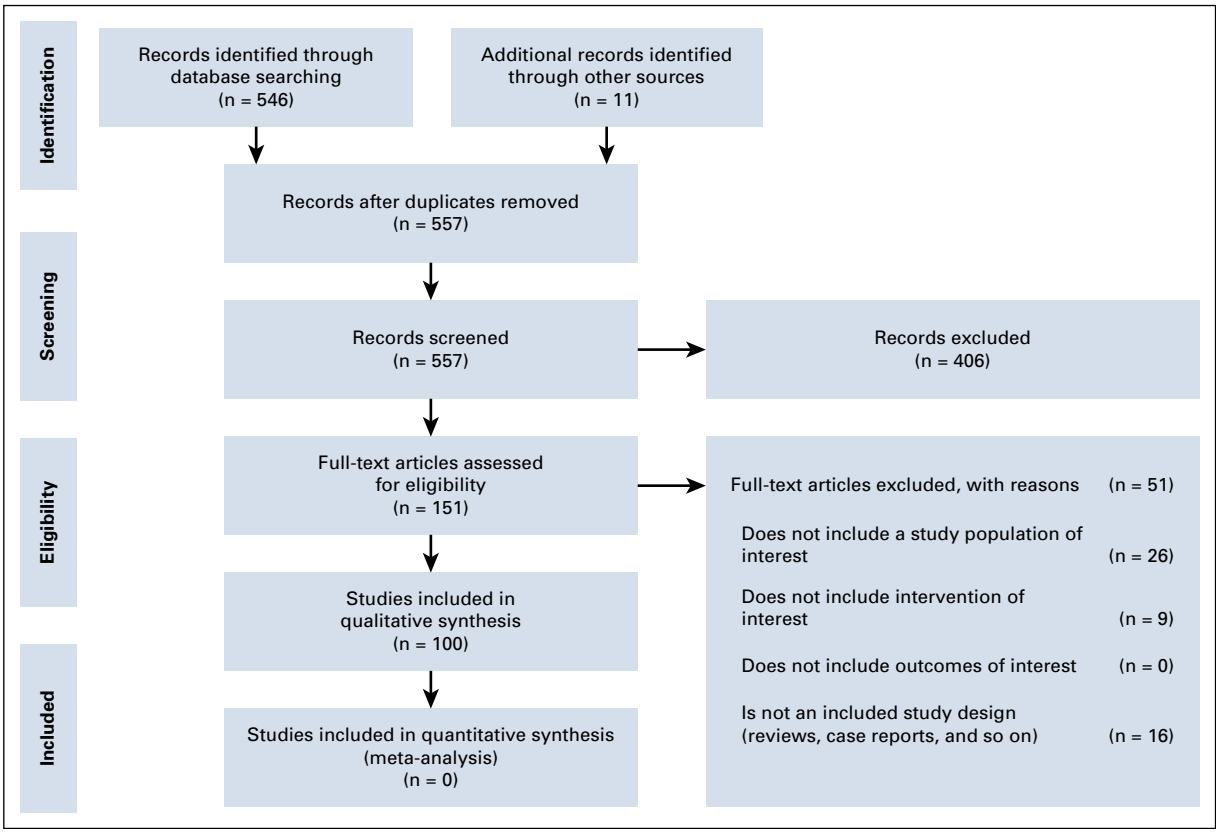

FIG 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of included studies.

along with HPV DNA/p16-posive status should be considered as prognostic factors in patients with CUP.[44,65,90]

Recommendation 1.2

Fine-needle aspiration (FNA) or core biopsy of a clinically suspicious neck mass should be performed (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and clinical interpretation. Biopsy of a neck mass is necessary to establish the diagnosis of SCC prior to treatment. FNA biopsy is most commonly performed, as it is easy, safe, minimally invasive, and cost effective.[106,107] However, a subset of FNAs, especially when taken from cystic nodes, will yield a nondiagnostic result or insufficient material for testing. Core-needle biopsy may be helpful in this setting.[106,108,109] An approach where FNA biopsy is performed with immediate evaluation by a cytopathologist to confirm adequacy followed by a small core biopsy to obtain additional material for high-risk (HR) HPV testing as indicated has been proposed.[108]

Recommendation 1.3

HR-HPV testing should be done routinely on level II and III SCCUP nodes. EBV testing should be considered on HPV-negative metastases (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: moderate).

Note: HR-HPV testing may be done nonroutinely for SCC metastases at other nodal levels when clinical suspicion is high.

Literature review and clinical interpretation. The HR-HPV testing recommendations made here are based on the guidelines for HR-HPV testing in head and neck carcinoma published by the College of American Pathologists and endorsed by ASCO in 2018.[110] Because HPV-associated SCC commonly presents in the neck lymph node, many SCCUP will be HPV positive.[111] Most HPV-positive metastases will ultimately prove to originate from the oropharynx, either palatine tonsils or base of tongue.[19,62] HR-HPV testing of SCCUP is recommended, because it aids in determining the most likely primary site; a p16/HPV-positive result favors oropharyngeal origin. Furthermore, if a primary tumor is subsequently identified in the oropharynx, HR-HPV testing (which is recommended for all OPCs[110]) does not necessarily need to be repeated on the primary tumor, if it has already been performed on the lymph node metastasis. As detailed in the ASCO-endorsed CAP guidelines, routine HR-HPV testing is recommended only for metastases located in neck levels II or III, because these are the lymph node groups involved by the vast majority of HPV-associated OPCs. Nonroutine HR-HPV

testing can be performed on lymph node metastases outside of these lymph node groups when clinical suspicion for an HPV-associated metastasis is high.

According to the guideline, the preferred method for initial HR-HPV testing of tissue specimens (core biopsy or excisions) is p16 immunohistochemistry. p16 immunohistochemistry is a sensitive surrogate marker for HR-HPV.[112-115] In high-prevalence settings, it is also specific. However, p16 lacks specificity in low-prevalence settings, such as when there is a high likelihood of lung or skin cancer, as a significant subset of SCCs from these sites are also p16 positive but HPV unrelated.[44,116,117] In contrast, p16 immunohistochemistry alone is sufficient when the probability of an HPV-associated OPC is high, specifically if the metastasis of unknown primary is located in level II or III lymph node groups and has nonkeratinizing morphology.[118-121] Otherwise, additional HR-HPV specific testing should be performed on p16-positive tumors to exclude a false-positive result. In contrast to the CAP guidelines, ASCO recommended confirmatory HR-HPV specific testing of all p16-positive unknown primary metastases. A negative p16 result does not require additional testing, as p16 is a very sensitive surrogate for HR-HPV. It should be emphasized that this recommendation is for testing performed on tissue (core biopsy or excision specimens) and not FNA biopsies. The ASCO-endorsed CAP guideline does not recommend a specific methodology for HR-HPV testing of FNA samples but does recommend that, whatever method is used, it should be validated.

EBV-associated SCCs are much less common than HPV-associated OPC in the United States, and they infrequently present as an unknown primary in the neck.[122,123] Nevertheless, EBV testing may be considered for SCCUPs that are HPV negative. A positive EBV test result would favor nasopharyngeal or salivary origin but may occasionally be from other head and neck or non–head and neck sites.[122] Epstein-Barr encoding region (EBER) in situ hybridization is the preferred testing method.

Recommendation 1.4

Contrast-enhanced CT of the neck (CECT) should be the initial test for workup of metastatic cervical lymphadenopathy (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and clinical interpretation. CECT is usually the first line of imaging on patients with metastatic cervical lymphadenopathy including CUP. This test is widely available, affordable, reproducible, and easy to perform. In a study by Cianchetti et al,[4] 236 patients were evaluated with lymph node biopsy, and 96% of the patients underwent CECT of the head and neck. In this study, patients who underwent a CECT of the head and neck prior to panendoscopy had a significantly higher rate of detection of a primary site.[4] It is important that imaging be performed prior to endoscopy and biopsy to enhance accuracy in sampling and diagnosis.

Recommendation 1.5

If a primary is not evident on clinical examination and CECT, PET-CT should be the next diagnostic step (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and clinical interpretation. PET-CT has been shown to have utility in detecting a primary tumor but has limitations in terms of both false positive rates and false negative rates. The literature is replete with studies comparing PET or PET-CT with other imaging modalities, such as CECT and MRI.[25,27,32,36,68,79,80] It is important to understand that a step-wise approach to imaging for assessment of metastatic cervical lymphadenopathy will almost always include CECT as the first-line modality, and this along with meticulous clinical history and examination, will identify the majority of primary tumors. If a primary tumor is not evident, PET-CT has added utility especially in directing biopsy, palatine tonsillectomy, or lingual tonsillectomy.[124]

PET-CT scan has demonstrated utility in localizing primary tumors and metastases in patients with CUP.[32] A study by Roh et al[25] reported that PET-CT was more sensitive than CECT for detecting primary tumors (87.5% *v* 43.7%; $P = .016$), but their specificity did not differ (82.1% *v* 89.3%; $P = .500$). PET-CT correctly detected distant metastases in 6 of 6 patients. This study concluded that PET-CT is a useful screening method for primary tumor detection, accurate nodal staging, and detection of distant metastatic disease in patients with CUP.[25]

In a retrospective value analysis by Han et al,[36] 120 patients with CUP were referred for PET-CT. Results revealed that PET-CT was able to detect the primary tumor in 42.5% with a sensitivity, specificity, and accuracy of 91.5%, 85.2%, and 88.3%, respectively. The conclusion was that this imaging modality is both noninvasive and very sensitive, allowing for detection of the primary tumor and cancer staging in a single examination.[36]

Deonarine et al[80] showed that PET-CT detected primary tumor sites in 37.3%, and occult metastases in 54.9%, of cases. Its sensitivity, specificity, and accuracy were 79.2%, 70.4%, and 74.5%, respectively.[80] Another retrospective cohort study by Mani et al[79] included 52 patients. Twenty-seven PET-CT scans suggested a primary site (83% sensitivity, 87% specificity; positive predictive value, 89%; negative predictive value, 80%). In this study, three tongue base tumors were identified and confirmed on panendoscopy; these three cases were undetected by preoperative PET-CT. The authors concluded that intraoperative examinations were necessary despite PET-CT.[79]

To compare the PET-CT with classic endoscopic approach, Barbosa et al,[68] pursued a retrospective study of 89 patients with CUP despite physical exam and CECT or MRI of the head and neck. These patients underwent PET-CT. Primary site detection rate was 32.6%. In patients with metastases in higher cervical levels (II and III; n = 76), 43% had had both PET-CT and endoscopy with biopsies of the upper aerodigestive tract in different sequence, to complete the diagnostic workup in situations when the first test was inconclusive. No statistically significant difference was found between these two methods ($P = .25$).[68] It was not possible in this study to define with evidence which modality should be performed first. Of importance was the study conclusion that up-front negative scans should not obviate performing endoscopies. However, Rudmik et al,[27] in a small prospective comparative study, concluded that PET-CT performed prior to panendoscopy increased the diagnostic yield in patients with CUP.[27] Johansen et al[59] reported retrospective findings for 60 patients with SCCUP investigated with PET-CT either before or after endoscopic biopsies. Primary site detection was described as similar in either group (37% *v* 27%; $P = .43$); however, of 20% false positives, most were observed on patients undergoing PET-CT following endoscopic biopsies. This would suggest for patients with SCCUP presentation, PET-CT is optimally performed following standard imaging and expert physical examination yet prior to any endoscopic biopsies if the primary remains unknown. This permits the dual advantage of guiding biopsies and reducing the false-positive rate.

CLINICAL QUESTION 2

What are the appropriate surgical diagnostic and therapeutic procedures for SCCUP?

Recommendation 2.1

Patients should undergo a complete operative upper aerodigestive tract evaluation of mucosal sites at risk (oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx), including directed biopsy of any suspicious areas. Random biopsies of nonsuspicious areas have a low yield and should not be performed. Intraoperative advanced visualization techniques may be used to investigate potential primary sites for targeted biopsy (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendations: strong).

Recommendation 2.2

For patients with unilateral lymphadenopathy, if a primary site is not confirmed on initial evaluation, the surgeon should perform ipsilateral palatine tonsillectomy. If palatine tonsillectomy fails to identify a primary, ipsilateral lingual tonsillectomy may be performed. Bilateral palatine tonsillectomy may be considered according to clinical suspicion, at the discretion of the surgeon (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and clinical interpretation. There are no randomized trials comparing the outcomes of survival and/or locoregional control between patients who have or have not undergone complete operative upper aerodigestive tract evaluation (UADT), with or without directed biopsy. However, the majority of papers about the history of head and neck CUP reporting have included this intervention, because it represents the most thorough and least invasive method of searching for a primary of origin while preserving patient comfort. The yield of primary site discovery from operative endoscopy with or without biopsy alone, with rare exception,[2] is within the 20% to 30% range.[5,9,59,68] This recommendation is fundamental to the search for a primary and usually precedes definitive treatment of any type.

While thorough operative endoscopy of all mucosal sites within the UADT should be implemented, there is a very low yield from routine biopsy of normal appearing mucosa.[49] This historic practice is no longer recommended. Intraoperative endoscopy with advanced visualization techniques including NBI has been successfully applied for investigating potential primary sites for targeted biopsy (Recommendation 1.1). Once confirmed, it may also assist in defining surgical margins and to achieve a higher rate of initially R0 resections.[34] If the patient has unilateral adenopathy, a thorough operative endoscopy is immediately followed by palatine tonsillectomy, ipsilateral to the metastatic node(s). While there are no randomized trials comparing survival outcomes between patients who have and have not undergone ipsilateral tonsillectomy, the yield for discovery of the primary rises to a 30% to 50% range after ipsilateral tonsillectomy. Importantly, identification of a well-lateralized tonsil primary may allow for ipsilateral-only primary surgery or radiotherapy. Recent reports of these discovery rates have usually been in the context of transoral laser microsurgery (TLM) or transoral robotic surgery (TORS) assisted procedures.[4,19,84,125] If the ipsilateral palatine tonsil is negative on frozen section, attention may be turned to the glosso-tonsillar sulcus and ipsilateral lingual tonsil. Although there is no prospective clinical trial evidence to advocate for this practice, the discovery rates of primaries in the tongue base following a lingual tonsillectomy in retrospective and prospectively assembled observational cohort studies, ranged from 40%[19] to 65%.[91] Meta-analysis of twenty one TLM and TORS studies yielded an overall tongue base discovery rate of the primary in 53% of cases.[11] This same meta-analysis of transoral studies showed an overall discovery rate of 78% using transoral technologies after a negative workup, which would have included physical examination, PET and/or CT imaging, and examination under anesthesia (EUA) with palatine tonsillectomy.[11]

If a primary in the contralateral tonsil is suspected, contralateral tonsillectomy may be considered. However, the presence of a small primary that is lateralized within the palatine tonsil that is contralateral to the known neck

disease implies the tonsil primary is metachronous to the occult primary that has resulted in neck metastasis.[126]

Recommendation 2.3

For patients with bilateral lymphadenopathy, if a primary site is not confirmed on endoscopic examination, the surgeon may perform unilateral lingual tonsillectomy on the side with the greater nodal burden and may perform contralateral lingual tonsillectomy if the ipsilateral procedure fails to identify a primary. Bilateral palatine tonsillectomy after bilateral lingual tonsillectomy should be avoided (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and clinical interpretation. Bilateral adenopathy presenting as an unknown head and neck primary is rare. Subsites in the UADT where a single primary tumor may cause bilateral adenopathy are the oral tongue and floor of mouth, nasopharynx, tongue base, soft palate, posterior oro- and hypopharyngeal walls, supraglottic larynx, and postcricoid area. While contralateral metastasis from a lateralized palatine tonsillar primary is reported, this clinical presentation is very rare.[127,128]

If the putative subsites have been investigated and no primary is identified following the operative endoscopic evaluation (see Recommendation 2.1), a transoral lingual tonsillectomy ipsilateral to the side with greater nodal burden is considered. This recommendation especially pertains to level II and/or level III adenopathy that is most likely to originate from the base of tongue. If frozen section does not reveal a primary, the opposite lingual tonsil may also be removed. A palatine tonsillectomy ipsilateral to the neck with greater nodal burden may be considered, but there is no evidence that bilateral tonsillectomy in this context will result in significantly improved primary tumor yield or survival, plus it may be unnecessarily morbid when performed concurrent with bilateral lingual tonsillectomy.

Large retrospective series employing transoral approaches for both unilateral and bilateral disease have shown excellent success in identifying primary lesion(s). In their prospectively assembled case series, analyzed retrospectively, Karni et al[5] found that the TLM-associated primary discovery rate of 94% strikingly outperformed the (then) standard-of-care discovery rate of 25%, using only clinical and radiologic workup and naked eye endoscopy, with or without palatine tonsillectomy. A similarly high primary discovery rate using TORS alone was documented in multi- and single-center studies.[84,125] Meta-analysis of transoral studies[11] showed a discovery rate of 78% using transoral technologies in the presence of a negative workup, including examination, PET and CT imaging, and EUA with palatine tonsillectomy. A recent study[65] associated primary discovery with improved oncologic outcomes, although it was not controlled for HPV mediation.

Recommendation 2.4

For patients in whom the primary tumor is identified during operative upper aerodigestive tract evaluation and definitive surgical management is intended (including neck dissection), clinicians should make every effort to resect the identified primary using transoral techniques to a negative surgical margin (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and clinical interpretation. There are no randomized trials comparing survival outcomes between different initial treatment strategies for SCCUP. The retrospective data are convincing that it is feasible to routinely obtain clear margins in this scenario. Negative margin rates in excess of 95% are achievable using transoral approaches,[129] especially with early T stages[130] and in transoral surgical series that include unknown primaries.[131] Although based on an unplanned subset analysis selected from trials that did not include HPV status, adjuvant chemoradiotherapy is often recommended for patients treated with primary surgical therapy that results in a positive margin.[132] It is therefore critical that an identified primary tumor treated with primary surgery is resected to a negative margin.

Recommendation 2.5

Tissue specimens from suspected primary sites (biopsies, palatine and lingual tonsillectomies) should be entirely submitted for histologic examination. Resection specimens should be anatomically oriented by the surgeon and margin evaluation should be performed. p16 immunohistochemistry may aid in evaluation of atypical or cauterized tissue for HPV-related squamous cell carcinoma (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 2.6

Intraoperative frozen section of biopsies from suspicious primary sites may be performed to confirm the presence of tumor prior to resection. Intraoperative frozen section evaluation of palatine or lingual tonsillectomy specimens should be performed when the primary tumor remains clinically undetected. The tissue should be entirely submitted for frozen section examination. Resection specimens should be anatomically oriented by the surgeon, and margin evaluation should be performed intraoperatively (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and clinical interpretation. The successful identification of the primary site allows for focused local therapy, either surgical or radiotherapeutic, and eliminates the need for irradiation of the entire oropharynx and/or entire pharyngeal and/or laryngeal mucosa. Careful

pathologic evaluation of the diagnostic surgical specimens is therefore an essential component of this process. By definition, the primary tumor is occult to routine imaging and clinical inspection, and thus tissue specimens from the suspected primary site should be wholly submitted for pathologic examination to maximize the probability of locating the primary tumor. As discussed in Recommendation 2.4, an identified primary tumor is often resected as part of a curative-intent operation, in which case it is essential to obtain negative margins. With this goal in mind, the surgeon should orient the submitted resection specimens to facilitate margin control. If the SCCUP is known to be p16 positive/HPV-related, strong and diffuse p16 expression in atypical or cauterized tissue is strongly suggestive of tumor and may provide critical information to guide patient management.[22,64,65,67]

With modern transoral surgical techniques, the likelihood of unknown primary identification has increased substantially, with recent series reporting success rates ranging from 50% to 90%.[3,19,55,64] Improved diagnostic yields provide an option for immediate therapeutic resection, in which case intraoperative frozen section evaluation is an integral component of the treatment. While frozen section evaluation does not replace formal permanent analysis, it is generally highly accurate[133-135] and can be considered sufficient confirmation of malignancy for the surgeon to move forward with an oncologic resection, if desired.

CLINICAL QUESTION 3

What are the treatment considerations and appropriate techniques for surgical management of the neck?

Recommendation 3.1

For unilateral, small-volume neck disease, either definitive surgery or radiotherapy may be offered after multidisciplinary discussion (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 3.2

For small-volume bilateral neck disease with no clinical evidence of extranodal extension, either definitive surgery (with or without adjuvant therapy) or radiotherapy (with or without concurrent chemotherapy) may be offered after multidisciplinary discussion (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 3.3

Large-volume bilateral neck disease, and/or gross (macroscopic) extranodal extension (ENE) favor definitive chemoradiotherapy, given the possible increased morbidity of extensive bilateral neck dissection and increased likelihood of trimodality therapy in such cases (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 3.4

When primary surgery is planned, levels IIA, III, and IV should be routinely dissected in cases when an oropharyngeal primary is suspected or confirmed for SCCUP. Additional nodal basins should be considered for dissection depending on the extent of nodal burden (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and clinical interpretation. The optimal regional therapy for SCCUP is somewhat controversial, given the absence of randomized data on this question. Moreover, the clear etiologic shift to HPV-driven disease makes older retrospective studies less relevant in a modern cohort. Older retrospective studies have shown mixed results on the preferred neck approach.[17,47,57,60,71] A multiinstitutional retrospective analysis from the University of Florida and Wisconsin showed improved regional control with neck dissection on multivariable analysis,[17] and other retrospective studies have also supported primary neck dissection.[60,71] Conversely, more recent studies using definitive intensity-modulated radiotherapy (IMRT) showed regional control rates in excess of 90%,[47,57,98] and other comparative studies have also shown no statistical difference in regional control or OS between primary surgical and radiation treatment.[7,45] With competing retrospective studies supporting both treatment paradigms, the morbidity profiles of these alternatives take on greater priority. As detailed in both the ASCO neck guideline[1] and this guideline, patients with resected lymph nodes harboring extranodal extension should be offered treatment with adjuvant chemoradiotherapy. Taken together, the current body of evidence suggests that treatment is often driven by the nodal status. Therefore, the nodal stage of patients presenting with SCCUP should be carefully evaluated. The avoidance of trimodality therapy (ie, neck dissection, radiotherapy, and concurrent chemotherapy) is a valuable goal to avoid the combined toxicities of each treatment; thus, individuals whose clinical scenario suggests a high likelihood of requiring postoperative chemoradiotherapy should generally receive definitive radiation management. Careful multidisciplinary consideration is warranted.

As discussed earlier in this guideline, the oropharynx is the most likely site for SCCUP, and thus, for the majority of patients undergoing upfront surgery, neck dissection should follow the traditional nodal drainage patterns from the oropharynx. As detailed in the Management of the Neck in Squamous Cell Carcinoma of the Oral Cavity and Oropharynx: ASCO Clinical Practice Guideline,[1] levels IIA, III, and IV contain the vast majority of nodal metastases from the base of tongue and tonsillar fossa and should be routinely dissected. Other nodal levels containing grossly positive pathologic lymphadenopathy should be dissected, and nodal basins considered to be at high risk for microscopic cancer based on the clinical and/or radiologic burden of disease may be dissected as well.

CLINICAL QUESTION 4

What are treatment considerations for radiation therapy and systemic therapy in SCCUP?

Recommendation 4.1

Patients receiving radiotherapy or concurrent chemoradiotherapy as primary management of CUP should receive treatment to gross nodal disease, neck regions at risk of containing microscopic disease, and the anatomic mucosal regions at risk of harboring the occult primary. Specific volumes treated will depend on the clinicopathologic presentation of the patient after complete workup, as outlined in Recommendations 1 and 2 (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and clinical interpretation. There is a paucity of prospective randomized literature evaluating primary radiotherapy-based approaches for management of patients with SCCUP. Numerous retrospective series describe successful management of SCCUP with radiotherapy with or without the addition of concurrent systemic chemotherapy,[16,17,47,57] with such approaches defined as one option for treatment in NCCN guidelines. Given the retrospective nature of the majority of studies of SCCUP, it is important to take into consideration biases such as patient selection, physician aptitude, and undertreatment in the definitive setting (eg, radiotherapy without concurrent chemotherapy) that may lead to the discrepancy in reported outcomes between series. Furthermore, the increasing incidence of HPV in SCCUP requires consideration when comparing current with historical series. Given the generally favorable outcomes for patients with SCCUP, especially those with HPV/p16–associated disease, judicious use of radiotherapy is required to ensure adequate coverage and appropriate dose to areas harboring gross tumor and those at risk for occult regional metastases to ensure cure and limit acute and long-term toxicities.

There has been a steady evolution of radiotherapy technique coupled with treatment volume reduction over the past several decades, resulting in reduced toxicity without compromising clinical outcomes in the management of patients with SCCUP. Historical standards of care typically recommended coverage of all mucosal surfaces at risk for harboring the occult primary, including the nasopharynx, oropharynx, hypopharynx, and larynx, using 2-dimensional techniques. Treatment of such large volumes to intermediate radiotherapy doses places the patient at risk for the development of long-term toxicities, such as cranial nerve palsies, severe xerostomia, dysphagia, laryngeal dysfunction, hypopharyngeal stricture, and esophageal stenosis. The transition from 2-dimensional to 3-dimensional conformal and eventually IMRT has enabled focused radiation on at-risk mucosal surfaces while decreasing dose to normal tissues. Indeed, the improvement in dose conformity with IMRT has been shown to improve the therapeutic ratio while maintaining favorable clinical outcomes.[16,38,47,57,58,73,86]

In addition to technologic advances, further reduction in toxicity has been enabled by applying data from surgical and pathologic series. Approximately 90% of previously identified unknown primary tumors are located in the oropharynx.[4] Radiotherapy series that have targeted only the mucosa of the oropharynx and avoided the larynx and hypopharynx and nasopharynx (in non-Asian patients) have resulted in excellent primary disease control.[17,93] More recently, the strong association with HPV/p16–associated tumors with the oropharynx has provided additional rationale for targeting only the oropharynx if the metastatic nodal disease is determined to be positive for either marker.

Specific targeting of the contralateral tonsil complex in patients with unilateral cervical adenopathy and an unknown primary may be avoided, given the low propensity of an occult contralateral tonsillar primary as the source of the adenopathy or the presence of bilateral occult tonsillar primaries.[136]

Recommendation 4.2

Patients treated with primary radiotherapy for unilateral (AJCC 8th N1) HPV-related adenopathy and CUP should receive treatment to the gross node(s) and with consideration of coverage of putative primary sites in the ipsilateral tonsillar bed, ipsilateral soft palate, and the mucosa of the entire base of tongue, which may be modified based on prior surgical diagnostics (see Recommendation 2.2) at the discretion of the radiation oncologist (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: moderate).

Note: Consideration may be given to including additional areas in the oropharynx in patients for whom a PET scan was not available or who did not undergo a contralateral tonsillectomy because of the low risk of an occult contralateral tonsillar primary. Patients presenting with bilateral (AJCC 8th N2) adenopathy and CUP require bilateral treatment of the oropharyngeal mucosa.

Recommendation 4.3

Patients treated with primary radiotherapy for unilateral (AJCC 8th N1-N2b) HPV-negative nodal disease and SCCUP should receive treatment as to the above (Recommendation 4.2). Patients presenting with bilateral (AJCC 8th N2c) adenopathy and SCCUP should receive bilateral treatment of the oropharyngeal mucosa (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 4.4

In patients presenting with clinical scenarios highly suggestive of an occult cutaneous primary squamous cell carcinoma, radiation of mucosal sites should be avoided

(Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and clinical interpretation. Surgical series examining patients with established tonsillar primary cancers report rates of a second contralateral tonsillar primary of 3% to 10%.[137,138] Similar low rates (6%-9%) have been described in patients undergoing contralateral tonsillar resections or biopsies for SCCUP.[49,137] Finally, patients undergoing unilateral radiation for known tonsillar cancer have very low rates of recurrence (or metachronous cancers) in the contralateral tonsil (Huang et al, Liu et al).[136,139] While there will remain a low rate of primary emergence in the untreated contralateral tonsil, which should be discussed with the patient, avoiding radiation to this region will facilitate sparing of the contralateral salivary tissue, particularly for those patients not receiving contralateral irradiation.

In the setting of bilateral nodal involvement, bilateral coverage of tonsils is required given the uncertainty of the laterality of the primary. Furthermore, inclusion of bilateral tonsils should be considered in radiotherapy clinical volumes if there is concern of a contralateral synchronous primary on high-resolution imaging or in those patients who did not undergo thorough examination of the contralateral tonsil during their surgical evaluation.

Patients may present with neck metastasis likely to have arisen in an occult cutaneous primary. The importance of recognizing these patients affords the opportunity to avoid irradiating any mucosa and the contralateral neck, and these patients may also avoid mucosal surgical approaches. Such patients will often present with HPV-negative adenopathy, a previous history of multiple skin primaries in the setting of chronic sun exposure, advanced age, male gender, or immunosuppression after organ transplantation. Further, in some instances, these patients will not have risk factors of alcohol and tobacco exposure associated with a mucosal primary. Nodal presentations within the preauricular and parotid regions are far more often associated with an occult cutaneous primary of the face or scalp than pharyngeal mucosa. Despite these considerations there will remain a small possibility that these patients have an occult mucosal primary that may declare itself if untreated; therefore, the Expert Panel recommends a careful discussion of the risks and benefits of avoiding mucosal irradiation with the patient.

Recommendation 4.5

In patients with a clinicopathologic presentation highly suggestive of an occult nasopharyngeal primary, the mucosal radiation treatment may be limited to the nasopharynx. Nodal volumes in this scenario should be typical for nasopharyngeal management and include bilateral levels II-V, including retropharyngeal nodes (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and clinical interpretation. Clinical features at presentation suggestive of an occult nasopharyngeal primary would include extensive retropharyngeal and level V nodal involvement, particularly in the setting of patients originating from endemic regions of Asia and Northern Africa. The highest probability of nasopharyngeal origin, however, requires pathologic association with the detection of tumoral EBV-encoded early RNA (ie, EBER) or elevated serum EBV DNA titers. Such evidence should provide the clinician with enough assurance to limit the mucosal field to the nasopharynx while sparing the remaining pharynx. Delivery of comprehensive bilateral neck irradiation is considered standard of care for this disease.

Recommendation 4.6

Patients treated with primary radiotherapy for unilateral involvement of multiple nodes and no clinical and radiologic evidence of ENE should routinely receive bilateral treatment (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 4.7

In addition to anatomic mucosal regions at risk, patients treated with primary radiotherapy for unilateral involvement of a single node and no clinical and radiologic evidence of ENE may consider treatment only to the unilateral involved neck (with the exception of those at risk for a nasopharyngeal primary [Recommendation 4.5]) (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 4.8

Patients treated with primary radiotherapy for N3 and/or bilateral nodal involvement and/or clinical and/or radiologic evidence of ENE require bilateral neck treatment (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and clinical interpretation. Unlike the volume de-escalation described in Recommendation 4.7, patients with SCCUP presenting with nodes in the lower cervical stations (III and IV) should be considered for treatment of the larynx and hypopharynx, given the marginally higher risk of spread to stations III and IV from these organs. However, given the concern for long-term toxicities with this approach, a discussion with patient discussing the risks and benefits should be undertaken.

Bilateral neck irradiation for SCCUP has been considered standard of care historically, with data in support.[140] However, this approach results in considerable toxicity, including increasing dose to salivary glands, larynx,

pharyngeal constrictors, mandible, hypopharynx, and esophagus. Following high-resolution imaging, ipsilateral-only radiotherapy has been demonstrated to results in very acceptable rates of contralateral failure[46,89,94,96,97,141] and reduced doses to the above-named structures. Therefore, ipsilateral neck irradiation in patients with unilateral disease involving a single node without extranodal extension and preferably in lymph node level II is recommended. In patients with multiple nodes, nodes > 6 cm, level III or IV nodes, and/or clinical or radiologic ENE, prognosis is worse; given higher rates of contralateral involvement, bilateral neck treatment is recommended.

Recommendation 4.9

For patients treated with primary radiotherapy, a biologically equivalent dose of 70 Gy over 7 weeks should be delivered to gross nodal disease. The biologically equivalent dose of approximately 50 Gy in 2 Gy fractions or slightly higher should be delivered to mucosal regions at risk of harboring the occult primary site and a biologically equivalent dose of 40 to 50 Gy in 2 Gy fractions electively to clinically and radiographically negative nodal regions at risk for microscopic spread of tumor (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and clinical interpretation. Radiation doses recommended for the primary management of SCCUP are extrapolated from standard doses recommended for the management of SCC of the head and neck in the curative setting[142] and reflect those in use as control arms in contemporary clinical trials of head and neck SCC. These have evolved empirically and aim to strike a balance between efficacy and toxicity. In the setting of HPV-associated SCC, recent interest has focused on radiation dose de-escalation in the curative setting. NRG HN002 recently demonstrated acceptable 2-year PFS of 91% with dose reduction to 60 Gy for patients with favorable-risk HPV-related OPC when accompanied by concurrent weekly cisplatin.[143] ECOG 1308 reported a 2-year PFS of 96% in a similar population of patients with favorable-risk HPV-related OPC who demonstrated a complete response to induction chemotherapy followed by 54 Gy.[144] These data would suggest the likelihood that a significant radiation dose reduction for patients with CUP is on the horizon; however, it is premature to recommend de-intensification outside of the setting of a clinical trial.[145]

Conversely, there are now compelling higher-level data on treating the elective neck to a lower dose than the standard 50 Gy in 25 fractions. Nevens et al[146] recently performed a randomized study of elective dose de-escalation to the neck, comparing 50 Gy with 40 Gy and finding no significant difference in elective nodal failure between these two dose levels. Moreover, in a retrospective study, Nevens et al[147] described outcomes in 233 patients receiving 40 Gy to elective neck regions for a variety of primary sites, predominantly (90%) HPV negative. With a median follow-up of 26 months, they reported a 2-year actuarial rate of elective volume recurrence of 3.9%, suggesting elective volume dose de-escalation may also be applicable in the HPV-negative setting.[145]

Recommendation 4.10

Patients receiving radiotherapy or concurrent chemoradiotherapy adjuvant to surgical management of CUP should receive treatment to regions of the neck and mucosa at risk of containing microscopic disease. The need for treatment should be determined by the extent of the surgery performed and pathologic results of the surgery (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 4.11

Patients for whom no primary site is pathologically identified at the time of surgery may benefit from treatment to the anatomic mucosal regions at risk of harboring the occult primary site, as defined in Recommendation 4.1. Nodal volumes requiring treatment are similar to those in Recommendations 4.5-4.7 (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and clinical interpretation. There are no randomized trials specifically addressing radiotherapeutic management of SCCUP adjuvant to primary surgical management. The principals of adjuvant radiotherapy for SCCUP are extrapolated from the literature describing the adjuvant management of SCC arising in known mucosal sites.[148] These general principals are based on the estimation of the risk of residual tumor in the surgically managed anatomy at the primary site and neck as well as anatomic regions at risk for harboring microscopic extent of tumor that were not encompassed in the surgical intervention. Such regions may include undissected neck and/or potential primary site direct routes of spread and in the scenario of SCCUP mucosa at risk for harboring an occult primary. Risk estimation in the adjuvant setting is based on the extent, location, and characteristics of malignancy identified pathologically in the surgical specimens along with the knowledge of the specific surgical procedures performed.

In the setting of surgically managed SCCUP for which a primary site is identified, the need for adjuvant therapy to the mucosal anatomy (at the identified primary site) is guided by an estimation of the likelihood of a complete resection (extent and surgical margins). By definition, these patients are no longer considered to have SCCUP and are managed accordingly. Patients for whom a primary site is not identified at the time of surgery remain at risk for progression in an unrecognized primary site. The absolute risk of eventual progression at an untreated primary site is uncertain, with small retrospective series of highly selected

patients describing crude rates varying from 2% to 50% for subsets of SCCUP patients managed with surgery alone.[29,61,74,75,82] Most rates within this risk range would exceed the threshold for adjuvant treatment.

Recommendation 4.12

Adjuvant radiotherapy should not be administered to patients with a single pathologically positive node without ENE after high-quality neck dissection (definition in ASCO's management of the neck practice guideline) and in whom after a thorough evaluation no primary tumor is identified (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 4.13

Adjuvant radiotherapy should be administered to patients with multiple pathologically involved nodes and/or pathologic evidence of ENE (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and clinical interpretation. A recent meta-analysis by Liu et al in 2016[10] described twelve retrospective series including 965 SCCUP patients for whom rates of primary site emergence were described relative to radiotherapy volumes (neck and mucosa *v* neck alone). Crude rates of primary site emergence were 73 (12%) of 608 for neck and mucosa–radiated patients versus 57 (16%) of 357 for the neck-alone radiation group, with a hazard ratio of 0.59 (95% CI, 0.39 to 0.89) in favor of mucosal treatment. It should be recognized that this literature largely predates the routine use of PET and modern surgical procedures; hence, for this cohort of patients, the risk of mucosal progression in the absence of mucosal irradiation may be higher. Garboyes et al[19] reported a retrospective analysis of 64 patients presenting with HPV-related adenopathy in the neck and unknown primary. After ipsilateral lingual and palatine tonsillectomies, the primary remained unknown for 14 patients who subsequently did not receive any adjuvant radiotherapy with subsequent emergence of the primary reported in only one patient (7%). It is reasonable to assume that this risk is lowest in scenarios whereby adjuvant treatment to the neck is not indicated and the patient has had thorough evaluation of the potential primary site(s) with transoral resection of lingual and palatine tonsillar tissue. In such instances of a single pathologically positive node, observation may be considered after careful discussion of the risks and benefits with the patient and taking into account the likelihood of patient's compliance with surveillance by the head and neck oncology team. Outcomes for these patients should ideally be captured within the context of a clinical trial or a prospective database from which outcomes can eventually be reported.

Management of the neck adjuvant to initial surgery for SCCUP will largely parallel that defined for SCC of known primary sites. ASCO guidelines for neck management in SCC of oral cavity and oropharynx have recently been published and reviewed the topic thoroughly.[1] The key elements relevant to SCCUP include the recommendation for avoidance of adjuvant radiotherapy for patients with a single pathologically positive node without ECE for whom a high-quality neck dissection has been performed (defined as dissection of levels II-IV including at least 18 identified nodes).[1] There remains some controversy as to the need for adjuvant radiotherapy with single node involvement for patients with a known primary. This is based on a range of outcomes reported in retrospective series that are heterogeneous with respect to the extent of known primary site risk factors, such as perineural and/or lymphovascular invasion, ENE in the involved node, and quality of neck dissections performed.[1] By definition, these risk factors will not exist in the population described in Recommendation 4.12. Hence, the Expert Panel recommends observation in this setting. Patients for whom more advanced nodal disease is pathologically present in the form of multiple involved nodes and/or ENE have consistently demonstrated worse outcomes and a benefit in locoregional control with the addition of adjuvant radiotherapy.[148]

Recommendation 4.14

Adjuvant radiation dose to the dissected regions of neck should be the equivalent of 60 Gy to the node levels that harbored gross resected disease and 50 Gy to regions beyond this thought to be at risk for microscopic residual disease. Nodal regions from which nodes were determined to have pathologic ENE may be considered for higher doses of adjuvant radiation, the equivalent of 60 to 66 Gy (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and clinical interpretation. Radiation doses delivered in the adjuvant setting for head and neck cancer have evolved empirically with limited randomized data from which to derive a clear dose-response relationship.[148] Standard doses have been defined according to the characteristics of the specific targets for treatment. High-risk regions are identified as primary sites with close or positive surgical margins and/or regions occupied by involved nodes displaying ENE and are recommended to receive a dose equivalent of at least 60 to 66 Gy. Surgically manipulated regions, including those containing gross disease without high-risk pathologic features, are recommended to receive a 60-Gy equivalent; finally, anatomic regions at risk for harboring microscopic tumor that were not encompassed in the surgical intervention (mucosa at risk for harboring occult primary and/or relevant undissected nodal regions) should receive a 50-Gy equivalent. Adjuvant radiation dose de-escalation in the setting of HPV-related SCC is under investigation. In 2019, Ma et al reported the results for 80 patients enrolled in a single-arm, phase II adjuvant de-escalation protocol (ECOG 3311,

ClinicalTrials.gov: NCT01898494) delivering 30 to 36 Gy in 20 bid fractions over 2 weeks with concurrent docetaxel. With a minimum follow-up of 25 months, they observed a 2-year PFS of 91.1% and low toxicity. ECOG 3311 will soon report results of adjuvant radiation dose de-escalation from 60 Gy to 50 Gy in intermediate-risk patients. The results of these studies and others may in the future permit a significant reduction in the adjuvant RT dose for CUP patients presenting with HPV-related adenopathy however at present routine dose reduction should not be used outside of the clinical trial setting.

Recommendation 4.15

Concurrent administration of cisplatin with definitive radiotherapy should be offered to patients without contraindications to cisplatin chemotherapy and with a suspected mucosal primary HPV/p16-negative squamous cell carcinoma in the presence of unresected AJCC 8th N2-N3 nodal disease (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

Recommendation 4.16

Concurrent administration of cisplatin with definitive radiotherapy should be offered to patients without contraindications to cisplatin chemotherapy and with a suspected mucosal primary HPV/p16–positive squamous cell carcinoma in the presence of unresected multiple ipsilateral or bilateral lymph node involvement or lymph nodes >3 cm in size (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

Literature review and clinical interpretation. No randomized controlled data exist to help guide the appropriate use of systemic therapy in the curative-intent treatment of carcinomas of unknown primaries. Prospectively evaluated regimens among locally advanced head and neck mucosal SCCs with known primary generally exclude this uncommon subset. Evidence generated by these studies are often extrapolated to the SCCUP population, which are accepted as biologically similar to their known primary counterparts, and success with such regimens have been reported in various single- or multi-institutional retrospective studies.

Prior to the recognition of the HPV-related OPC subset, the randomized phase III Intergroup study enrolled 295 patients with unresectable, locally advanced oropharynx, oral cavity, larynx, and hypopharynx cancers.[149] This study demonstrated that, compared with radiation alone and multiagent chemotherapy concurrent with split-course radiation, the concurrent administration of cisplatin 100 mg/m^2 on days 1, 22, and 43 of definitive radiation confers an OS and disease-specific survival advantage. Similarly, the 3-arm randomized, phase III trial RTOG 91-11[150] enrolled 547 patients with locally advanced laryngeal primary SCC and demonstrated a superior larynx preservation rate and locoregional control rate with cisplatin 100 mg/m^2 administered every 3 weeks during definitive radiotherapy. Of note, both of these studies also demonstrated significantly increased toxicity when cisplatin was concurrently administered with radiotherapy.

The new AJCC 8th edition has separately staged p16-positive OPC and has included the T0 designation to reflect that unidentified primaries are not uncommon in this subset. Recent randomized, phase III clinical trials exclusive to the distinct p16-positive oropharynx population have been completed. The study RTOG 1016[151] enrolled 987 patients with locally advanced HPV-related SCCs of the oropharynx; patients with AJCC 7th T1N1 were excluded, as were patients with an unidentified primary site. This trial compared bolus cisplatin (100 mg/m^2 dosed on days 1 and 22) concurrent with accelerated radiotherapy versus the same radiation plan with weekly cetuximab, and it was powered to detect an OS difference between the two arms. The DE-ESCALATE[152] study was similarly designed, with notable differences being that (1) patients with AJCC 7th T1N1 were permitted to participate, (2) patients with a $>$ 10 pack-year smoking history were excluded, (3) radiation therapy was administered using standard fractionation, and (4) the primary endpoint examined acute and late toxicities between both regimens. Both studies revealed the superior oncologic outcomes among patients receiving cisplatin and, of particular interest, no significant increase in rates of acute and late toxicities between the two treatment arms. This contrasts with the reports of enhanced toxicity with concurrent chemoradiation in the studies predating the HPV era. Per-patient toxicity (expressed as the T score) was significantly higher in the patients enrolled in RTOG 1016.[151]

Whether patients with AJCC 7th N1 disease (a single lymph node measuring ≤ 3 cm) would benefit from a concurrent cisplatin-based chemoradiation approach is not well defined. AJCC 7th T1N1 disease was not represented in the Intergroup study, was specifically excluded from RTOG 1016, but was allowed in the DE-ESCALATE study.[152] Ongoing de-escalation studies in the HPV-positive SCCs are examining dose-reduced radiation with various systemic therapy agents, and the results are anticipated to shed light on the appropriate treatment of this subset.

There are limited data guiding the selection of an optimal regimen for patients who are deemed cisplatin ineligible. A few large RCTs[153-155] have been completed in which noncisplatin systemic therapy was administered, and all of these studies once again excluded patients without a known primary site. The IMCL1895 study[153] compared definitive radiotherapy versus cetuximab concurrent with radiotherapy among 424 patients with locally advanced oropharynx, hypopharynx, and larynx cancers and demonstrated an OS, PFS, and locoregional control benefit with the cetuximab and radiation combination. The GORTEC 94-01[154] study, conducted in the pre-HPV era, compared definitive radiotherapy versus carboplatin, 5-fluorouracil,

and radiotherapy among 226 patients with locally advanced OPC and demonstrated OS, disease-specific survival and locoregional control benefit in the concurrent chemoradiation arm. Recently, GORTEC 2007-01[155] demonstrated a PFS and locoregional control benefit of a systemic regimen consisting of carboplatin, 5-fluorouracil, and cetuximab with radiotherapy compared with cetuximab and radiotherapy among 406 patients with locally advanced SCCs of the head and neck. Further investigation into the optimal treatment of cisplatin ineligible patients of all head and neck anatomic sites, including SCCUP, is warranted.

Recommendation 4.17

Concurrent administration of cisplatin to adjuvant radiotherapy should be offered to patients without contraindications to cisplatin chemotherapy, with a suspected mucosal primary squamous cell carcinoma and pathologic evidence of ENE (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

Literature review and clinical interpretation. The addition of bolus cisplatin 100 mg/m^2 concurrent to postoperative radiotherapy is well established in mucosal head and neck SCC by two landmark studies, RTOG 9501[156] and EORTC 22931.[157] In a comparative unplanned subset analysis of these contemporaneous studies,[158] survival was improved in patients with high-risk features of positive surgical margins and/or ENE when bolus cisplatin was added to radiotherapy. It should be noted that those studies included only 28% oropharyngeal primary cases combined and predated the HPV era. Prospective data to support use of concurrent cisplatin and radiotherapy in resected nodal disease of SCCUP is lacking, though numerous retrospective studies have demonstrated favorable disease control and survival endpoints with concurrent chemoradiation in patients with SCCUP, both in the definitive and postoperative settings.[15,47,54,56,93] Patients treated with concurrent chemoradiation were largely N2 or higher disease staged or demonstrated pathologic ENE. One retrospective study reported 37 patients who were treated with concurrent cisplatin and bilateral neck radiotherapy following a modified neck dissection.[77] The majority of patients had ≥ N2 disease (92%), and very few patients developed regional recurrence (5%) or distant failure (11%).

Optimal dosing or administration schedule of cisplatin concurrent with adjuvant or definitive radiotherapy remains a matter of debate. In the pre-HPV era, Bachaud et al[159] reported the results of a prospective, randomized study comparing cisplatin given at a fixed dose of 50 mg weekly during postoperative radiotherapy with postoperative radiotherapy alone in 83 patients with resected SCCs of the head and neck and ENE. It is of interest that this study included patients with unknown primary, though the number of patients with SCCUP was not reported. In this study, cisplatin and radiotherapy improved survival without locoregional recurrence, DFS, and OS. A more contemporary prospective randomized trial[160] compared weekly cisplatin (30 mg/m^2) to bolus concurrent with radiotherapy in a primarily postoperatively treated oral cavity patient population in India. This study showed higher toxicity rates with bolus cisplatin administration but improved locoregional control rates. Bolus cisplatin administered with radiotherapy remains the regimen with the most robust supporting prospectively evaluated evidence. In keeping with ASCO's consensus statement in the Management of the Neck in Squamous Cell Carcinoma of the Oral Cavity and Oropharynx,[1] and in agreement with the ASCO-endorsed American Society for Radiation Oncology evidence-based clinical practice guideline on radiotherapy for oropharynx cancer,[142] this guideline maintains that "concurrent weekly cisplatin may be delivered with postoperative radiotherapy to patients who are considered inappropriate for standard high-dose intermittent cisplatin after a careful discussion of patient preferences and the limited evidence supporting this treatment schedule." Ongoing studies in head and neck SCC are employing weekly dosed cisplatin with radiotherapy in both definitive (ClinicalTrials.gov identifiers: NCT02135042, NCT02254278) and postoperative (ClinicalTrials.gov identifiers: NCT01810913, NCT02775812) settings. In addition, a Japanese randomized phase II/III study comparing weekly versus bolus cisplatin concurrent with radiotherapy in the adjuvant setting for head and neck SCC with identified primary sites is ongoing.[161] Further prospective studies evaluating the optimal treatment of CUP are warranted, and the Expert Panel encourages enrollment in such clinical trials when available.

Recommendation 4.18

Concurrent administration of cisplatin with definitive radiotherapy should be offered to patients without contraindications to cisplatin chemotherapy and with an EBER-positive stage II-IVA (AJCC 8th) carcinoma of unknown primary (Type of recommendation: evidence based, benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

Literature review and clinical interpretation. Similar to HPV-related disease and other known primary mucosal SCCs, the treatment of EBER-positive CUP is also extrapolated from studies in nasopharynx cancer. The Intergroup 0099 study established cisplatin plus radiotherapy as the accepted treatment of nasopharyngeal cancer (NPC) given superior survival endpoints over radiotherapy alone.[162] This survival benefit was confirmed by subsequent randomized studies, again favoring platinum-based chemoradiation therapy over radiotherapy alone.[163,164] Alternatives to bolus cisplatin dosing are once again brought into question, and perhaps the most robust data with weekly administration in nasopharyngeal carcinoma are from a randomized phase

III trial comparing 40 mg/m^2 weekly cisplatin to standard bolus dosing, which revealed no significant differences in response rates or 2-year failure-free survival.[165]

The role of further adjuvant chemotherapy following definitive chemoradiotherapy for NPC remains unknown. The Intergroup trial was the first randomized study to demonstrate a survival benefit when adjuvant chemotherapy was added to radiotherapy[162]; however, Chen et al[165] reported no difference in OS or DFS in patients with locally advanced NPC treated with chemoradiotherapy versus chemoradiotherapy followed by adjuvant chemotherapy.[166] An ongoing cooperative group study is utilizing EBV as a biomarker to select for further adjuvant therapy, though patients with EBER-positive CUP are excluded from this trial (CinicalTrials.gov: NCT02135042).

Induction chemotherapy (IC) paradigms are well reported within the NPC literature, though with inconsistencies in outcomes and again a paucity of data in the CUP population. Zhang et al[167] compared induction chemotherapy with gemcitabine and cisplatin followed by cisplatin–radiotherapy versus cisplatin–radiotherapy in locally advanced node-positive NPC and demonstrated significantly improved survival endpoints with the addition of induction chemotherapy.[167] The incidence of grade 3 or higher adverse events was also higher in the IC arm, and it remains unclear which subset of patients with NPC might receive the most benefit with IC to justify the increase in toxicities, which risk compromising curative radiation treatment. The efficacies of adding adjuvant chemotherapy and IC remain uncertain; further investigation into the use of IC or adjuvant chemotherapy, in addition to the inclusion of patients who have EBV-positive CUP into such trials, are areas of ongoing research.

Figures 2 and 3 provide visual interpretations of these recommendations in the management algorithm.

PATIENT AND CLINICIAN COMMUNICATION

Patients with SCCUP and clinicians treating this disease face different challenges. A multidisciplinary team to address the different steps across the diagnosis and treatment trajectory is recommended to ensure a high-quality oncology management of this population. Clinicians who treat SCCUP of the head and neck faces a unique set of communication challenges, given the daunting repercussion to a patient's quality of life as areas such as speech, taste, saliva, chewing, swallowing, lymphatic processes, nerve damage, teeth, facial bone structure, and physical appearance are affected. Patient and family caregivers suffering should be acknowledged with empathy, promoting stronger relationships with them. An individualized discussion among the multidisciplinary team, aligning the goals of treatment with the patient expectations and their families, is critical to optimal modern care.

It is understood that strategies to manage CUP would naturally vary according to the specialist skills, experience, and availability of different technologies and resources in a variety of settings. Given the involvement of multiple physicians and other health care providers, many centers have developed navigators to facilitate processes and minimize the challenge patients face when they first come in contact with large systems. Identifying resources in the community, such as support groups or other willing survivors to share the experiences, could be instrumental in providing information and strategies tailored specifically to a personalized treatment experience.

ASCO has long believed that strong and clear communication between physicians, patients, and families is paramount for delivery of high-quality care. For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[168]

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. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial/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 care of poor quality than other Americans.[169-172] 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 health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

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 (MCCs)—is challenging. Patients with MCCs 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 in which study selection criteria may exclude these patients to avoid potential interaction effects or confounding of results associated with MCCs. 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.

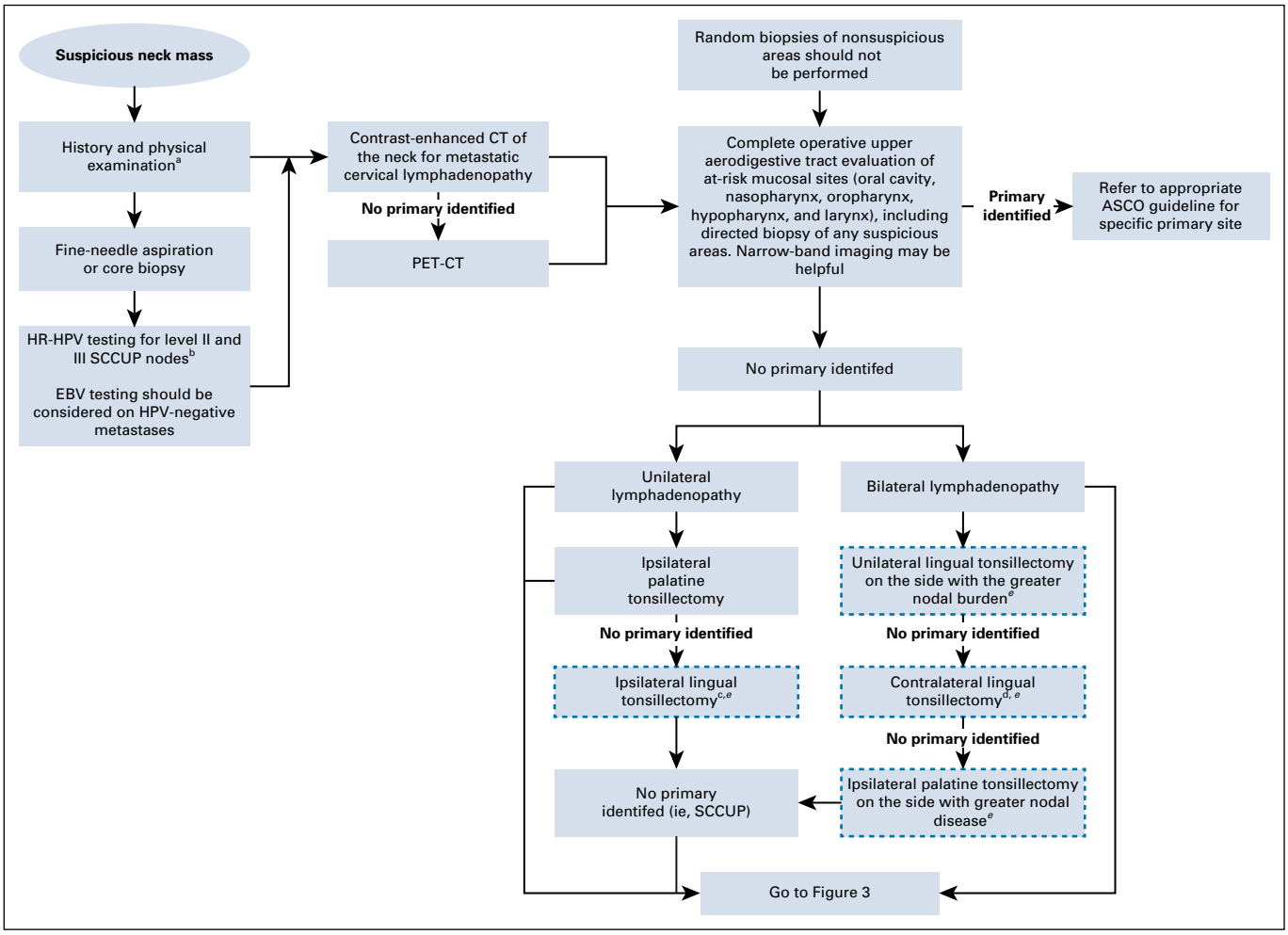

FIG 2. Diagnosis and management algorithm of squamous cell carcinoma of unknown primary (SCCUP) in the head and neck. Boxes with dotted lines indicate that the level of obligation is moderate. ([a]) Includes office endoscopy, which may be complemented by narrow-band imaging. ([b]) High-risk human papillomavirus (HR-HPV) testing may be done nonroutinely for squamous cell carcinoma metastases at other nodal levels when clinical suspicion is high. ([c]) Bilateral palatine tonsillectomy may be considered according to clinical suspicion, at the discretion of the surgeon. ([d]) Bilateral palatine tonsillectomy after bilateral lingual tonsillectomy should be avoided. ([e]) If a primary is identified, refer to appropriate ASCO guideline of primary site. CT, computed tomography; EBV, Epstein-Barr virus; PET, positron emission tomography.

As many patients for whom guideline recommendations apply present with MCCs, 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 the above considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCCs, 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 MCCs.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[173,174] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[175,176]

Discussion of cost can be an important part of shared decision making.[177] 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.[177]

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

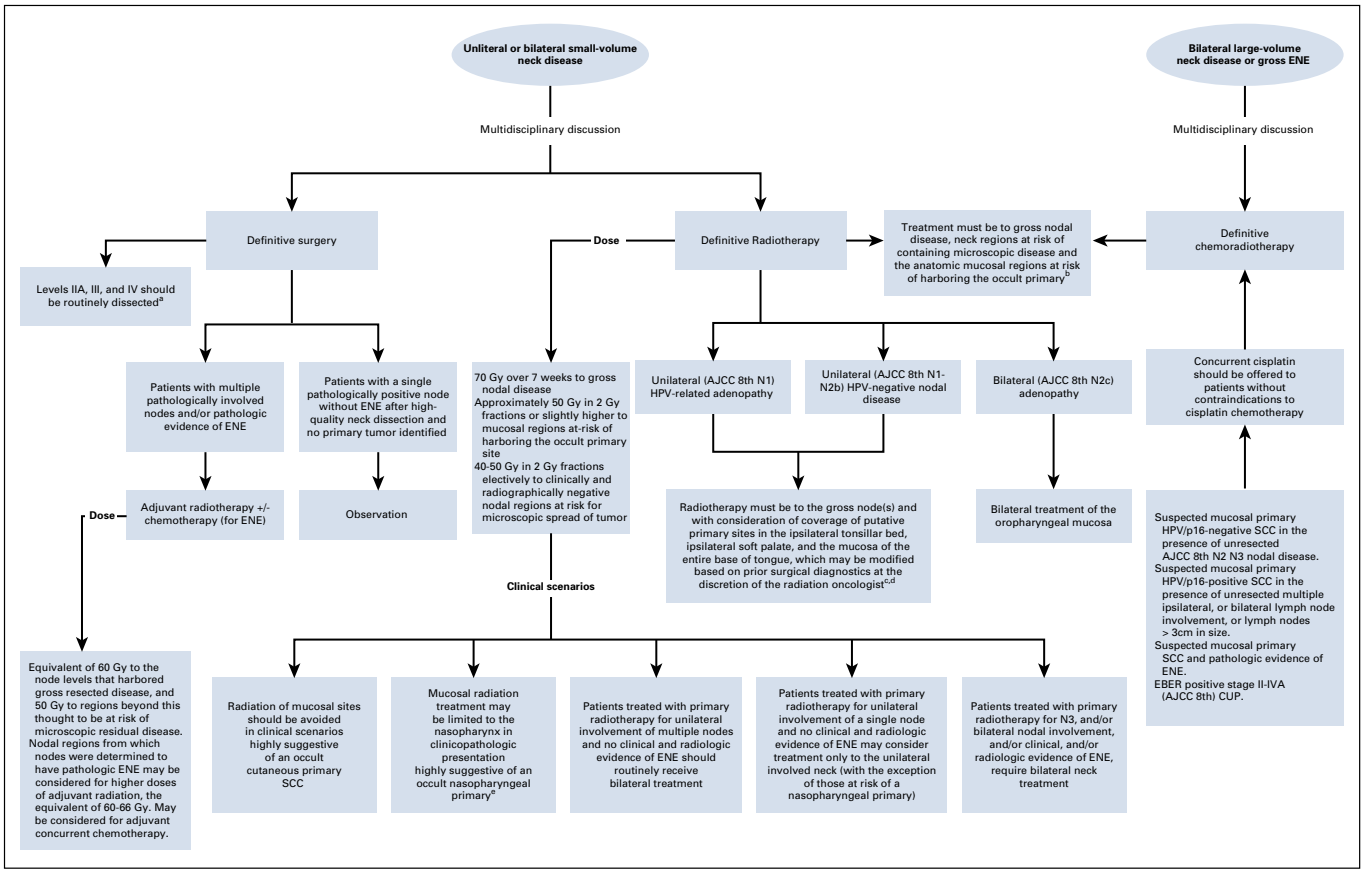

FIG 3. Diagnosis and management algorithm of squamous cell carcinoma (SCC) of unknown primary (SCCUP) in the head and neck. ([a]) Additional nodal basins should be considered for dissection depending on the extent of nodal burden. ([b]) Specific volumes treated will depend on the clinicopathologic presentation of the patient after complete work-up. ([c]) Consideration may be given to including additional areas in the oropharynx in patients for whom a positron emission tomography (PET) scan was not available or who did not undergo a contralateral tonsillectomy because of the low risk of an occult contralateral tonsillar primary. ([d]) Patients presenting with bilateral (American Joint Committee on Cancer [AJCC] 8th N2) adenopathy and CUP require bilateral treatment of the oropharyngeal mucosa. ([e]) Nodal volumes in this scenario should be typical for nasopharyngeal management and include bilateral levels II-V, including retropharyngeal nodes. EBER, EBV-encoded RNA; EBV, Epstein-Barr virus; ENE, extranodal extension; HPV, human papillomavirus.

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.[177]

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-effective analyses that lack contemporary cost data; 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 September 4 through September 23, 2019. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree. See comments," were captured for every proposed recommendation, with 27 written comments received. A total of 75% of the responses either agreed or agreed with suggested modifications to the recommendations, and 25% 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 prior to Clinical Practice Guideline 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 on the guideline panel is to assess the suitability of the recommendations to

implementation in the community setting and to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line 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 web site and most often published in *JCO* and the *JCO Oncology Practice*.

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.

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-and-neck-cancer-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Integration of Palliative Care Into Standard Oncology Practice[178] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[168] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Role of Treatment Deintensification in the Management of p16-Positive Oropharyngeal Cancer[145] (http://ascopubs.org/doi/10.1200/JCO.19.00441)
- Management of the Neck in Squamous Cell Carcinoma of the Oral Cavity and Oropharynx[1] (http://ascopubs.org/doi/10.1200/JCO.18.01921)
- Human Papillomavirus Testing in Head and Neck Carcinomas[110] (http://ascopubs.org/doi/10.1200/JCO.18.00684)

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EDITOR'S NOTE

This American Society of Clinical Oncology (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-and-neck-cancer-guidelines.

EQUAL CONTRIBUTION

E.M. and J.C. were Expert Panel co-chairs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.20.00275.

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Conception and design: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Diagnosis and Management of Squamous Cell Carcinoma of Unknown Primary in the Head and Neck: ASCO Guideline

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APPENDIX

TABLE A1. SCCUP Expert Panel Membership

Name	Affiliation/Institution	Role/Area of Expertise
Ellie Maghami, MD (co-chair)	City of Hope, Duarte, CA	Surgical oncology
James Caudell, MD (co-chair)	Moffitt Cancer Center, Tampa, FL	Radiation oncology
Adriana Alvarez, MD	Cleveland Clinic Foundation, Cleveland, OH	PGIN representative
Rebecca Chernock, MD	Washington University School of Medicine, St Louis, MO	Pathology
Doug Crook	Indianapolis, IN	Patient representative
Umamaheswar Duvvuri, MD	University of Pittsburgh, Pittsburgh, PA	Surgical oncology
Jessica Geiger, MD	Cleveland Clinic, Cleveland OH	Medical oncology
Neil Gross, MD	MD Anderson Cancer Center, Houston, TX	Surgical Oncology
Bruce Haughey, MD	Advent Health Medical Group, Otolaryngology - Head and Neck Surgery, Celebration, FL, University of South Florida (collaborative), Tampa, FL, and University of Auckland, (adjunct) Auckland, New Zealand	Surgical Oncology
Doru Paul, MD	Weill Cornell Medical College, New York, NY	Medical Oncology
Cristina Rodriguez, MD	University of Washington, Seattle, WA	Medical Oncology
David Sher, MD	University of Texas Southwestern, Dallas, TX	Radiation Oncology
Hilda E. Stambuk, MD	Memorial Sloan Kettering Cancer Center, New York, NY	Radiology
John Waldron, MD	Princess Margaret Cancer Centre, Toronto, Ontario, Canada	Radiation Oncology
Matt Witek, MD	University of Wisconsin School of Medicine and Public Health, Madison, WI	Radiation Oncology
Nofisat Ismaila, MD	ASCO, Alexandria, VA	ASCO Practice Guidelines Staff (health research methods)

Abbreviations: PGIN, Practice Guideline Implementation Network; SCCUP, squamous cell carcinoma of unknown primary in the head and neck.