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

Maghami et al.
Introduction

- In 2019, 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.

- 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.

- 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 ASCO Clinical Practice Guidelines Committee guideline process includes:

- a systematic literature review by ASCO guidelines staff
- an expert panel provides critical review and evidence interpretation to inform guideline recommendations
- final guideline approval by ASCO CPGC

The full ASCO Guideline methodology manual can be found at:

www.asco.org/guideline-methodology
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?
Target Population and Audience

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.
Summary of 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 SCC should undergo a thorough history and physical examination including fiberoptic laryngoscopy, which may be complemented with advanced visualization techniques, narrow-band imaging to facilitate identification of the anatomic location of the primary tumor and to inform potential therapeutic management options. (Type: Informal consensus, benefit outweighs harm; Evidence quality: Low; Strength of recommendation: Moderate)
Summary of Recommendations

**Recommendation 1.2**

Fine-needle aspiration or core biopsy of a clinically suspicious neck mass should be performed. (Type: 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: 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.*
Summary of Recommendations

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

CLINICAL QUESTION 2

What are the appropriate surgical diagnostic and therapeutic procedures for squamous cell carcinoma of unknown primary (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: Evidence based, benefit outweighs harm; Evidence quality: Intermediate; Strength of recommendation: Strong)
Summary of Recommendations

**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: Evidence based, benefit outweighs harm; Evidence quality: Intermediate; Strength of recommendation: Moderate)

**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: Evidence based, benefit outweighs harm; Evidence quality: Intermediate; Strength of recommendation: Moderate)
Summary of Recommendations

**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: 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: Evidence based, benefit outweighs harm; Evidence quality: Intermediate; Strength of recommendation: Strong)
Summary of Recommendations

**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: Evidence based, benefit outweighs harm; Evidence quality: Intermediate; Strength of recommendation: Strong)
Summary of Recommendations

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: 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: Evidence based, benefit outweighs harm; Evidence quality: Intermediate; Strength of recommendation: Moderate)
Summary of Recommendations

**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: 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: Evidence based, benefit outweighs harm; Evidence quality: Intermediate; Strength of recommendation: Strong)
Summary of Recommendations

CLINICAL QUESTION 4
What are treatment considerations for radiotherapy 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: Evidence based, benefit outweighs harm; Evidence quality: Intermediate; Strength of recommendation: Strong)
Summary of Recommendations

**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: 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.
Summary of Recommendations

**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: 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: Evidence based, benefit outweighs harm; Evidence quality: Intermediate; Strength of recommendation: Moderate)
Summary of Recommendations

**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: 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: Evidence based, benefit outweighs harm; Evidence quality: Intermediate; Strength of recommendation: Strong)
Summary of Recommendations

**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: 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: Evidence based, benefit outweighs harm; Evidence quality: Intermediate; Strength of recommendation: Strong)
Summary of Recommendations

**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: 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: Evidence based, benefit outweighs harm; Evidence quality: Intermediate; Strength of recommendation: Strong)
Summary of Recommendations

**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: Evidence based, benefit outweighs harm; Evidence quality: Intermediate; Strength of recommendation: Strong)

**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: Evidence based, benefit outweighs harm; Evidence quality: Intermediate; Strength of recommendation: Strong)
Summary of Recommendations

**Recommendation 4.13**

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

**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: 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: Evidence based, benefit outweighs harm; Evidence quality: High; Strength of recommendation: Strong)
Summary of Recommendations

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: 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: Evidence based, benefit outweighs harm; Evidence quality: High; Strength of recommendation: Strong)
Patient and Clinician Communication

- 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.

- 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.

- 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.
Additional Resources

More information, including a Data Supplement, 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
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