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AHNS Series: Do you know your guidelines? Guideline recommendations for head and neck cancer of unknown primary site

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Abstract

This article reviews the clinical practice guidelines for head and neck oncology focusing on the management of head and neck cancers of unknown primary (CUP). The primary purpose of this series is to raise awareness of the current guidelines in head and neck oncology by reviewing the recommendations and the evidence supporting such recommendations, particularly those published by the National Comprehensive Cancer Network (NCCN). We review the importance of a thorough history and physical examination, the impact of the American Joint Committee on Cancer (AJCC) eighth edition changes and the importance of immunohistochemistry, the timing and type of imaging, the role of panendoscopy and tonsillectomy (palatine and lingual), and the role of surgery, radiation, and chemotherapy in the primary management of these tumors.

KEY WORDS

cancer, education, guidelines, head and neck surgery, unknown primary

1 | INTRODUCTION

The following article adds to the series being published periodically in *Head & Neck* through an initiative by the American Head and Neck Society's (AHNS) Education Committee. Here, we review clinical practice guidelines for head and neck oncology, in this issue, focusing on the management of head and neck cancers of unknown primary (CUP). The primary purpose of this series is to raise awareness of the current guidelines in head and neck oncology by reviewing the recommendations and the evidence supporting such recommendations, particularly those published by the National Comprehensive Cancer Network (NCCN). The ultimate goal of this series is to improve adherence to guidelines and improve patient outcomes.

Head and neck CUP origin comprises approximately 2%-5% of all head and neck cancers, although the true incidence

is probably lower with advances in surgical visualization and radiological imaging to identify the primary site.¹⁻³ There has been a recent rise in CUP likely related to the increase in human papillomavirus (HPV)-associated oropharyngeal cancers.⁴ All CUP are considered in the occult primary management pathway in the NCCN guidelines, as many of these cancers convert from being CUP to having a known and discoverable primary site. Identifying the primary site is of the utmost importance to help select the best treatment while decreasing treatment-related morbidity and mortality.

The NCCN guidelines are developed by a group of experts in the field based on their views of currently accepted approaches to treatment through a series of statements of evidence and consensus. These guidelines are particularly useful for cancers, such as CUP, in which there is no level 1 evidence. Nonetheless, the guidelines also recommend making

treatment decisions based on the individual clinical circumstances and independent medical judgment allowing for personalization of care.

In this article, we discuss the diagnostic and treatment approaches for patients with an occult primary, which is a cervical node with CUP source, while reviewing the rationale and evidence for these decisions.

1.1 | First steps — Thorough history and physical examination

It is common for patients to present with a chief complaint of a neck mass, and, in those over the age of 40 years, this often leads to the diagnosis of a metastatic cancer. A thorough history and physical examination in this population, as recommended by the NCCN guidelines, will often identify a primary tumor site in >90% of cases.^{3,5} The medical history should include assessment of risk factors (tobacco or alcohol use), previous malignancy (as those with a prior head and neck cancer in the antecedent 5-year period may have a regional recurrence), and any history of skin lesions/cancers. A thorough physical examination should include fiber-optic nasolaryngoscopy with visualization of the nasopharynx, oropharynx, larynx, and hypopharynx. Palpation of the tonsils and tongue base adds additional information to fiber-optic examination and should always be performed in this population. During fiber-optic examination, a variety of maneuvers can assist in visualizing folded mucosal layers.^{6,7} Asking the patient to pull out their tongue can allow for better visualization of the tongue base and vallecula, whereas asking the patient to puff out their cheeks allows better visualization of the pyriform sinuses. Neither of these maneuvers is as good as visualization during direct endoscopy in the operating room but they are certainly worthwhile maneuvers that can improve yield of the in-office physical examination.

1.2 | Second step — Biopsy; impact of American Joint Committee on Cancer eighth edition update

Fine-needle aspiration (FNA) biopsy is a critical step in the assessment of occult primary tumors of the neck after history and physical examination. Core biopsy or open biopsy should be avoided as these can interfere or change subsequent management and increases the risk of tumor seeding along the biopsy tract. To improve the yield of the FNA, ultrasound guidance can be utilized particularly for partially cystic lymph nodes in which accessing the solid component is of critical importance. Having access to an onsite pathology technician with cytopathologist at the time of the biopsy can help confirm adequacy of the sample but this is not always readily available at most institutions.⁸ Routine

assessment for p16 and Epstein-Barr virus can and should be performed on FNA specimens.

Open biopsy before definitive neck dissection should be avoided because of the risk of tumor spillage, challenging revision surgery secondary to disruption of fascial planes, and, above all, increased risk of local recurrence and distant metastases.⁹ If an open biopsy is required, the patient should be prepared for definitive management at the time of that procedure, including a formal neck dissection. At the time of the open biopsy, the incision should be planned in a position that would make extension of the incision for a formal neck dissection possible and frozen section biopsy can be performed, which if positive for squamous cell carcinoma should lead to a formal neck dissection to better prognosticate the neck.¹⁰

Unknown primary cancers were not previously staged in the American Joint Committee on Cancer (AJCC) seventh edition. However, it is included in the newest edition.¹¹ The new staging of CUP requires p16 immunohistochemical stains as a surrogate for HPV-associated oropharyngeal cancers, and Epstein-Barr virus-encoded RNA (EBER), which is associated with nasopharyngeal cancer. Therefore, the FNA or open biopsy/neck dissection specimen should be checked for p16 and EBER. Calcitonin can also be checked if medullary thyroid cancer is suspected. Thyroid-transcription factor can also be tested to distinguish between lung squamous cell carcinoma for which it is positive versus head and neck squamous cell carcinoma for which it is usually negative. These advanced immunohistochemical tests can help guide future endoscopy, increasing the likelihood of finding the primary tumor site.

The recent changes in the AJCC have not yet impacted the NCCN guidelines as it relates to the management of unknown primary and oropharyngeal cancer p16 status. It is quite likely that future editions of the NCCN guidelines will reflect differences in the prognosis of these 2 different groups of cancers (p16-positive vs negative), particularly as further deescalation trials are completed. The remainder of this review will be based on the NCCN recommendations based on the seventh edition of the AJCC nodal classification. For completeness, however, we do include a brief update on the staging changes as it demonstrates the importance of p16 and EBER testing.

Unknown primary cancers, which are p16-positive, are staged as T0 and the N classification is based on the oropharyngeal clinical and pathologic groupings (Tables 1 and 2). For patients with p16-positive CUP with information limited to clinical staging, the N classification dictates the overall stage (cN1 classification I; cN2 classification II; and cN3 classification III). Similarly, for those with pathologic staging, the N classification dictates the overall stage (cN1 classification I and cN2 classification II). If the EBER is positive, the patients are staged as T0 and the N classification is based on the nasopharyngeal nodal groupings. If the node is EBER

TABLE 1 p16-positive unknown primary and oropharynx clinical nodal staging

N classification	N criteria
cN1	One or more ipsilateral lymph nodes, none larger than 6 cm
cN2	Contralateral or bilateral lymph nodes, none larger than 6 cm
cN3	Lymph node(s) larger than 6 cm

Abbreviation: cN, clinical N classification.

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and p16-negative, the patients are staged as T0 and the nodal classification is designated in the cervical nodes chapter, which requires assignment of extranodal extension (ENE; Table 3). Updated staging will be implemented in January 2018.

1.3 | Type and timing of imaging

If the FNA demonstrates a carcinoma and no primary site has been found on physical examination, imaging studies should be pursued before operative endoscopy with biopsy. Conventional imaging, including CT and/or MRI, should be pursued first. However, positron emission tomography with CT fusion (PET-CT) is recommended in all patients if conventional imaging does not identify the primary site, as it can often detect occult tumors >1 cm in size.

A number of excellent reviews on the topic of PET-CT in the management of CUP have demonstrated its utility. Yoo et al¹² performed a thorough systematic review of the literature in 2012 to make recommendations on this topic in the context of a universal healthcare system. The high cost of a PET-CT necessitated strong evidence to recommend this imaging modality in this healthcare context.¹² This excellent

TABLE 2 The p16-positive unknown primary and oropharynx pathologic nodal staging

N classification	N criteria
pN1	Metastasis in 4 or fewer nodes
pN2	Metastasis in >4 lymph nodes

Abbreviation: pN, pathological N classification.

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review highlights 3 landmark studies. The first, published in 2007, summarizes 2 systematic reviews, each with 8 primary studies, and an additional 2 primary studies, demonstrating that PET was able to detect the primary site in patients with CUP, in 30% of those missed by conventional imaging.¹³ A subsequent single institution study comparing PET-CT to contrast-enhanced CT alone found a much higher rate of detecting the primary tumor site with PET-CT.¹⁴ Last, a Canadian prospective clinical trial demonstrated that patients with cervical metastases from CUP benefited from PET-CT before endoscopy and biopsy with higher detection rates secondary to more directed biopsies.¹⁵ Furthermore, this treatment approach has been demonstrated to be cost-effective, particularly for N1 and N2 disease.¹⁶

Overall, PET-CT has a sensitivity of 43%-88%, specificity of 33%-88%, and a detection rate of 15%-50% in the management of CUP (Table 4).¹⁷⁻²² A recent systematic review of 7 studies (246 patients) demonstrates an overall sensitivity of 44% and specificity of 97%.²³

Completing this imaging modality before diagnostic endoscopy (nasopharyngoscopy, direct laryngoscopy, esophagoscopy, and bronchoscopy) is of the utmost importance, as highlighted by the NCCN guidelines. Manipulation of the tissues in the upper aerodigestive tract specifically with biopsy may lead to false-positive results on the PET-CT from inflammation at the biopsy site, thereby decreasing the diagnostic yield of the PET-CT. Furthermore, having these results before operative endoscopy allows the surgeon to focus on particular high-risk sites, as identified on the PET-CT for biopsy.¹⁹ The introduction of PET-CT has improved detection rates with 1 study demonstrating preintroduction and postintroduction of PET-CT detection rates of 40.5% and 59.6%, respectively ($P = .02$).¹⁹

An additional benefit of PET-CT imaging is the detection of previously undiagnosed distant metastases in 11% of cases and regional disease in 15% of cases.¹⁷

In addition to all of the aforementioned head and neck imaging, the NCCN guidelines also recommend imaging the chest, abdomen, and pelvis with CT (or PET-CT) in those patients with level IV and low level V metastatic nodes on presentation, as these sites can harbor the primary site.¹⁰

1.4 | Panendoscopy and directed biopsy (include levels of neck as algorithm)

The NCCN guidelines make recommendations regarding endoscopy and directed biopsies based on the levels of the neck involved. For those patients with a level IV or low level V metastatic node, in addition to the aforementioned imaging recommendations, the guidelines recommend examination under anesthesia, including direct laryngoscopy, esophagoscopy, and bronchoscopy.¹⁰ On the other hand, for patients with levels I, II, III, or high level V nodes, the guidelines

TABLE 3 The p16-negative and Epstein-Barr virus-encoded RNA-negative unknown primary clinical and pathological nodal staging

N classification	N criteria
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE-negative
N2a	Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE-negative
N2b	Metastasis in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE-negative
N3b	Metastasis in any node(s) and clinically overt ENE-positive

Abbreviation: ENE: extranodal extension.

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recommend examination of the larynx and nasopharynx through nasolaryngoscopy, inspection and palpation of the oral cavity and oropharynx, examination under anesthesia with biopsies of areas of clinical concern, and finally a tonsillectomy with or without lingual tonsillectomy if a primary is not identified on the previous steps.¹⁰ The different approaches based on nodal level are directly related to the primary site association with nodal levels. Most (74%) CUP are from the oropharyngeal subsite, specifically the tonsils and base of tongue, and, therefore, increased attention should be paid to these subsites on endoscopy.¹⁹ Palpation of these subsites, a maneuver not well tolerated by all patients in the clinic, provides important additional tactile information and increases the likelihood of identifying a primary in the high yield subsites.

The NCCN guidelines do not make specific recommendations on sidedness of the tonsillectomy and in which cases a lingual tonsillectomy is indicated. The literature clearly identifies that at the very least a tonsillectomy is superior to deep tonsil biopsies, increasing the likelihood of finding a primary in the tonsils by 30%, likely due to the crypt architecture of the tonsils making some of these cancers not visible on physical examination.^{24–26} A contralateral tonsillectomy identifies the primary tumor in 15%–25% of cases (Table 5)^{27–29} and,

therefore, if a patient has tonsillar tissue present, bilateral tonsillectomies increases the detection rate.^{27–29} This is reasonable given the minimal additional morbidity of bilateral tonsillectomy to unilateral tonsillectomy. Furthermore, performing a unilateral tonsillectomy may produce confusion and raise anxiety on follow-up examination in this patient population.

Blind biopsies of the nasopharynx, pyriform sinus, and hypopharynx, in the absence of suspicious clinical or radiographic findings, is no longer indicated in the NCCN guidelines because of the low incidence of cancers at these subsites.

However, management of the base of tongue is more controversial. The NCCN guidelines offer the option of performing a lingual tonsillectomy while not specifying whether this can be performed unilaterally or bilaterally. A formal lingual tonsillectomy, defined as a resection of the base of tongue tissue in the muscular layer as the deep plane of dissection, from midline of the tongue to the lateral pharyngeal wall and from the circumvallate papillae to the vallecula, has increased in popularity due to advances in operative techniques that include improved visualization and instrumentation with transoral laser microsurgery and transoral robotic surgery. One study demonstrated a 90% tumor identification (mean diameter 0.9 cm) with transoral robotic base of tongue

TABLE 4 Scoping review of positron emission tomography-CT detection rates in cancers of unknown primary

Study	Sample size	Sensitivity	Specificity	Detection rate
Rusthoven et al ¹⁷	302	88%	75%	25%
Yaylali et al ¹⁸	50	88%	33%	50%
Waltonen et al ¹⁹	52	43%	72%	15%
Lee et al ²⁰	56	69%	88%	50%
Karapolat and Kumanlioglu ²¹	20	87%	83%	35%
Majchrzak et al ²²	41	69%	86%	17%

TABLE 5 Rate of contralateral or bilateral tonsillar disease in cancers of unknown primary

Study	Sample size	Study type	Rate of contralateral or bilateral tonsil disease
Koch et al ²⁷	16	Single institution	25% (12.5% bilateral and 12.5% contralateral)
Kothari et al ²⁸	22	Single institution	23%
Fu et al ²⁹	139	Systematic review	15%

resection when PET-CT, formal endoscopy, and bilateral tonsillectomy were all negative for malignancy in patients with CUP.³⁰ Similarly, Graboyes et al³¹ demonstrated an 89% detection rate using this approach in the p16-positive population. A systematic review on the additional benefit of formal lingual tonsillectomy in the assessment of patients with CUP, which included a total of 8 studies and 139 patients, demonstrated a detection rate of 56% when lingual tonsillectomy was performed.²⁹ This is likely because PET-CT misses subcentimetric tumors and the average tumor size identified in this review was just over 1 cm.²⁹ It is, therefore, not surprising that the most recent NCCN guidelines no longer recommend random base of tongue biopsies as the likelihood of identifying these subcentimetric tumors with this approach is low. Therefore, a unilateral lingual tonsillectomy is indicated at the time of tonsillectomy when no primary can be identified. Some have advocated for a bilateral lingual tonsillectomy, as 6% of the contralateral lingual tonsillectomy specimens were positive for carcinoma²⁹; however, this does carry an increased risk in addition to the additional rare complication of oropharyngeal stenosis with a nearly circumferential mucosal raw surface.³²

In the next section of the article, we review the accepted NCCN treatment algorithm for CUP when the primary site is not identified focusing on the unique role of surgery, radiation, and systematic therapy. The NCCN guidelines provide clear recommendations regarding each therapy and are far more prescriptive than for most other head and neck cancer subsites.

1.5 | The role of surgery (neck dissection) — N1 disease

Primary surgery (neck dissection) is preferred over radiotherapy for patients with N1 disease (a single lymph node <3 cm in size) based on the seventh AJCC classification.¹⁰ There are 2 main reasons for this clear preference in primary treatment: (1) neck dissection provides important prognostic information that can help determine important adjuvant treatment; and (2) because surgery provides the best chance of regional disease control without missing a significant number of primary tumors.

Extracapsular extension (ECE), the most important pathologic predictor for the use of systematic therapy, is not

accurately diagnosed on contrast-enhanced neck CT by expert neuroradiologists, making surgery the primary and best method of diagnosing ECE.³³ Neck dissection often identifies more extensive disease upstaging approximately one third of patients with more than 1 lymph node or ECE in the clinically N1 presentation.⁵

Comparing surgery and radiotherapy alone, surgery is cheaper, faster, and has less morbidity particularly as it relates to swallowing dysfunction. There is some evidence that surgery alone (neck dissection) in patients with N1 disease followed by observation is reasonable and this is listed as a treatment option by the NCCN guidelines when there is no ECE.¹⁰ However, historic evidence demonstrates that patients receiving surgery alone have a higher rate of tumor discovery in the posttreatment period than if they had received radiotherapy (with or without neck dissection)² and, therefore, most patients with N1 unknown primary tumors without ECE post-neck dissection are treated with adjuvant radiotherapy, which is also listed as a treatment option in this group by the NCCN guidelines.³⁴

1.6 | The role of radiation

Primary radiotherapy (with chemotherapy) is the main treatment used for unknown primary cancers of the head and neck because it addresses mucosal surfaces at the same time as the regional neck disease and has been shown to decrease the rate of primary tumor discovery in the posttreatment period. Therefore, the NCCN guidelines recommends postoperative radiotherapy for patients with N2/N3 disease (without ECE) and also suggests “considering” systemic therapy.¹⁰ It should be noted, however, that there have been no trials comparing neck dissection followed by radiotherapy versus concurrent chemoradiotherapy in patients with greater than or equal to N2 CUP.

When radiotherapy is used, treatment volumes include bilateral mucosal surfaces and both sides of the neck. This is associated with improved disease-free survival, lower primary tumor discovery, and contralateral neck disease recurrence when compared with patients treated with unilateral radiotherapy to the neck and mucosal surfaces.^{35,36}

The NCCN guidelines recommend 70 Gy dosing for the primary nodal disease levels, 50 Gy to the lower-risk neck sites (contralateral neck and uninvolved levels, including the

retropharyngeal nodes), and 60-66 Gy for at-risk mucosal sites.¹⁰ Historically, patients would receive radiation to the nasopharynx, oropharynx, larynx, and hypopharynx in addition to the bilateral sides of the neck. This is associated with significant morbidity with an average of 60-66 Gy to all sites, despite advanced intensity-modulated radiotherapy technology. In the era of oropharyngeal-associated HPV disease, some have advocated only radiating the oropharynx and bilateral sides of the neck with inclusion of the retropharyngeal nodes, particularly for those patients with HPV-positive tumors.³⁷ Although this approach is discussed by the NCCN guidelines, which suggests that treatment volume should be determined by the nodal levels involved, tumor size and HPV/Epstein-Barr virus status, there is very little literature on this approach compared to the conventional treatment approach. The NCCN guidelines clarify that if HPV status is to be used to change treatment volumes, this should only be performed in the context of a clinical trial. One study, with a small sample size ($n = 17$), demonstrated that larynx and hypopharynx-sparing radiotherapy in the management of CUP is safe with comparable survival and recurrence outcomes while providing a lower toxicity profile.³⁸ As the lower treatment volume approach is increasingly used by some centers, retrospective data will be available in the coming years to compare these 2 approaches, although due to the relative rarity of CUP this will take many years. A collaborative multi-institutional trial should be considered to answer this question, as suggested by the NCCN.

1.7 | Chemotherapy (N2, N3, and any extracapsular extension)

Chemotherapy is indicated for patients with ECE, as demonstrated by the landmark Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer 2004 studies, which were studied in combination by Cooper et al³⁹ Bernier et al^{40,41} in 2004 and 2005. These studies highlight the importance of the prognostic information afforded by a neck dissection for patients who would otherwise receive radiotherapy alone without systemic therapy (N1 disease).³⁹⁻⁴¹ The NCCN recommends chemoradiotherapy when ECE is present, although it should be noted that there are no randomized trials demonstrating this treatment approaches' utility or superiority over radiotherapy alone in the CUP population. Furthermore, systematic therapy can be considered in addition to radiotherapy in the postoperative setting for patients with N2/N3 disease without ECE. Functional outcome data are not available for this particular subgroup of patients; however, outcomes are directly related to tissue toxicity depending on the field and dose of radiation, the number of modalities used as primary treatment and cumulative, and the type of radiotherapy used. There are similar survival outcomes among patients with T1 base of

tongue cancers and patients with CUP demonstrating that, if the primary is found, a lower dose with narrower field may impact functional outcomes, although this has not been specifically studied.⁴²


1.8 | Follow-up and surveillance

Follow-up posttreatment is the same for CUP and other head and neck cancers; every 1-3 months in the first year, every 2 to 6 months in the second year, and every 4-8 months in the third year. A posttreatment scan within 6 months of treatment can also be used to assess treatment response regardless of the treatment modality used.¹⁰ In situations in which there is an inadequate response in the neck from a nonsurgical approach with persistence of a neck mass, a PET-CT scan can be used with an excellent negative predictive value.¹² This approach, in patients treated nonsurgically with advanced neck disease, has been demonstrated to be more cost-effective with similar survival compared to a planned neck dissection in the posttreatment period.⁴³⁻⁴⁵

2 | CONCLUSION

The incidence of CUP is increasing but with advances in immunohistochemical staining, imaging, and intraoperative visualization of high-risk subsites has increased the likelihood of identifying the primary site. The PET-CT scans are indicated for CUP before surgical endoscopy and biopsies. In those patients in whom the primary site is not identified, bilateral tonsillectomy with lingual tonsillectomy is indicated. Neck dissection is recommended for N1 disease. For \geq N2 disease without ECE, the NCCN recommends radiotherapy with the option of considering systemic therapy. For patients with ECE, systemic therapy is indicated.

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