Management of Unknown Primary Cancer of the Head and Neck

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Introduction

Head and neck cancer of unknown primary (CUP) often presents as a painless enlarging neck mass alone. A subsequent fine needle aspiration (FNA) frequently confirms malignancy. After a thorough evaluation with no identification of a primary tumor, the designation of CUP is confirmed. This represents about 1–4% of all head and neck cancers [1]. In patients over age 40, any painless, cystic or solid neck mass should be considered cancer until proven otherwise [2]. In the era of high-risk HPV (HR-HPV) associated head and neck cancers, the oropharynx is the most common site of the primary tumor [3]. It is likely that the incidence of CUP is rising along with the rise in HR-HPV associated head and neck cancers [4]. The majority of patients presenting with CUP will have a detectable primary after thorough evaluation. An algorithm for management of CUP has been described in the National Comprehensive Care Network Version 1.2018 guidelines. While the primary tumors in 50–80% of cases presenting as CUP are eventually discovered in the tonsils and base of tongue [5], metastatic nodal disease in the neck also requires consideration of other primary sites beyond the oropharynx, including cutaneous, thyroid, hematologic, thoracic, and rarely abdominal-pelvic sites. The benefit of primary site identification is targeted therapy with reduced morbidity to uninvolved sites, as CUP has become a highly curable disease. For the patients whose diagnosis remains CUP after comprehensive examination and imaging—difficult decisions focus on

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anatomical sites for treatment targeting. Radiotherapy to the nasopharynx, oropharynx, larynx, and hypopharynx for CUP has been supplanted in select HR-HPV associated (or p16 positive) cases by directed therapy towards the oropharynx, and at times the nasopharynx. Advances in radiotherapy such as intensity modulated radiotherapy (IMRT) have further reduced treatment morbidity compared to conventional external beam radiotherapy and 3D conformal techniques. Additionally, molecular testing for HR-HPV, p16 expression, Epstein Barr Virus (EBV), and other biomarkers are important diagnostic aids for localization of primary tumors.

The primary focus of this chapter is to review the contemporary evaluation and management of patients with CUP. The majority of the focus is on head and neck squamous cell carcinoma with unknown primary site, as this presentation has become the most commonly encountered CUP in practice. The role of imaging, diagnostic and therapeutic surgery, and the role of radiotherapy with or without systemic chemotherapy are explored. The balance of functional and oncologic outcomes in the treatment of CUP is reviewed. Because all cited literature was published prior to implementation of the American Joint Commission on Cancer (AJCC) eighth Edition Staging Manual, we continue to refer to TNM staging as defined in the seventh Edition.

Search Strategy

We performed a broad search in Pubmed with keywords (unknown primary head neck) to identify relevant literature available in English, regarding the epidemiology, evaluation, and treatment of CUP (see Table 9.1).

Results

Our focus is primarily on CUP diagnosed by FNA or open biopsy results of a neck mass showing squamous cell or undifferentiated carcinoma, wherein a primary site is not identified after thorough work up. Tables are provided to summarize the more contemporary literature at the time this book's publication, with the results section providing examples of data that substantiate the general approach to CUP. The included studies, mostly with small sample sizes, generally showed good agreement with regards to oncologic and functional outcomes (Table 9.2). While HR-HPV or p16 positive CUP comprise the majority of unknown primaries and are mostly of

Table 9.1 Search strategy (PICO table)

Population	Intervention	Comparison	Outcomes
Patients with head and neck cancer with unknown primary	Endoscopy with mucosal biopsy Definitive transoral surgery Radiation therapy or chemoradiation	Transoral surgery ± radiotherapy ± chemotherapy versus primary radiotherapy ± concurrent chemotherapy	Overall survival Disease-specific survival Locoregional control Quality of life Functional outcomes

Table 9.2 Outcomes based on treatment modality in patients with head and neck squamous carcinoma with unknown primary

	Intervention	Overall survival (years)	Disease specific survival (years)	Locoregional control (years)	Type of study (number of patients)
Mizuta et al. [6]	All	72.5% (3)	80.3% (3)	89.7% (3)	Retrospective cohort study (80)
	ND	71% (3)	81.8% (3)	83% (3)	
	ND → RT/CRT	71.9% (3)	79.5% (3)	91.1% (3)	
	RT/CRT ± ND	83.3% (3)	83.3% (3)	100% (3)	
Balaker et al. [7]	All	48.6% (5)			Systematic review (1726)
	Sx + RT/CRT	59.8% (5)			
	RT/CRT	46.6% (5)			
Argiris et al. [46]	ND → CRT	75% (5)		87% (5)	Retrospective cohort study (25)
Nieder et al. [5]	Bilateral RT Unilateral RT	50% (5) 36.4% (5)		81–91% (5) 48.5–92% (5)	Systematic review (122)
Grau et al. [1]	All	36% (5)	48% (5)	44% (5)	Prospective cohort study (260)
	Sx	65% (5)	76% (5)	29% (5)	
	RT	37% (5)	45% (5)	44% (5)	
	RT + Sx	28% (5)	49% (5)	59% (5)	
Kamal et al. [8]	ND + IMRT	84% (5)		91% (5)	Retrospective cohort study (260)
Wallace et al. [9]	RT ± ND	52% (5)	73% (5)	81–92% (5)	Retrospective cohort study (179)
Aslani et al. [10]	Bx + RT	64.8% (8)		76.3% (5)	Retrospective cohort study (61)
	ND + RT	67.6% (8)		85% (5)	
Demiroz et al. [47]	ND + RT	85.3% (4)		90.9% (4)	Retrospective cohort study (41)
	RT	85.6% (4)		88.8% (4)	
Huo et al. [48]	Mucosal (RT)	79.6% (5)		88.5% (5)	Retrospective cohort study (63)
	Cutaneous (Sx + RT)	66% (5)		91.9% (5)	
Chen et al. [11]	Ipsilateral IMRT ± Sx	92% (2)	87% (2)	91% (2)	Retrospective cohort study (25)
De Ridder et al. [49]	IMRT ± ND/ Chemo	62% (5)	78% (5)	90–100%	Retrospective cohort study (80)
McDowell et al. [50]	Sx ± RT	45% (5)	65% (5)	37% (5)	Retrospective cohort review (105)[a]
Cuaron et al. [51]	All	74.5% (5)		86.4% (5)	Retrospective cohort study (85)
	Sx/RT + Chemo	76% (5)		79.4% (5)	
	Sx/RT − Chemo	74.9% (5)		91% (5)	

Abbreviations: *Sx* surgery, *RT* radiation therapy, *CRT* chemoradiation therapy, *ND* neck dissection, *IMRT* intensity-modulated radiation therapy, *Bx* biopsy

Bolded results indicate statistically significant comparative results

[a]All study patients had squamous cell carcinoma parotid metastases. From this it was inferred that all patients had cutaneous unknown primaries. 105 of 143 patients underwent treatment with curative intent

oropharyngeal origin—less common putative sites including cutaneous malignancies, thyroid malignancies, melanoma, lymphoma, and non-head and neck primaries need to be considered. We do not examine these in depth. We will discuss:

1. Imaging modalities in the evaluation of CUP.
2. Molecular testing.
3. Surgical management of the neck and nodal assessment.
4. The role of transoral surgery for diagnosis and treatment.
5. Role of radiotherapy to the neck and mucosal sites for oncologic treatment.
6. Dysphagia after treatment.

Imaging Modalities in the Evaluation of CUP

A brief overview of diagnostic imaging in CUP focuses on cross-sectional and functional imaging, obtained after thorough in-office head and neck examination [12–14]. Imaging aids identification of the primary site and feasibility of neck dissection. Neck magnetic resonance imaging (MRI) and computed tomography (CT) can increase primary detection rate beyond physical exam by 25–30%, and suspicious imaging findings may double the rate of primary detection over negative imaging studies [13, 15]. If anatomical imaging should fail to suggest a primary site, or if distant metastases are strongly suspected, a skull base-to-mid thigh positron emission tomography fused with computed tomography (PETCT) scan is recommended prior to endoscopic evaluation under general anesthesia [16]. One Review article concluded that PET/CT identified primary sites after negative anatomical Imaging in 25% of patients, [45] and in another small study suspicious PETCT findings doubled primary detection rates during endoscopy, compared to endoscopic without such imaging [17]. PETCT is a valuable complement to transoral surgery (discussed below) in the identification of the primary site in CUP [18, 19].

> As cost and institutional availability allows, PETCT should be obtained as part of the diagnostic work-up for head and neck cancer with unknown primary. It is superior to PET or CT alone, and increases the detection rate of primary lesions, modifying therapy in a significant number of patients (quality of evidence moderate, conditional recommendation).

Molecular Testing

Malignant FNA cytology of a neck mass without a clear primary site should prompt testing for expression of p16 on immunohistochemistry (IHC). It is now well-established that up to 90% of p16 positive FNA samples will test positive for HR-HPV, and the majority are associated with primary oropharyngeal cancers [4, 16, 20, 21]. More rarely p16 positivity may indicate a cutaneous or nasopharyngeal

primary [22–25]. An oropharyngeal primary site is less likely to be the primary candidate when the nodal metastasis is in a lower (levels 3, 4, or 5) or higher (parotid) nodal echelon than level 2, requiring consideration of thyroid, nasopharyngeal, cutaneous, and primary parotid malignancies. Molecular and imaging testing for these are beyond the scope of this chapter.

An FNA with cytopathology should be obtained for all patients with a neck mass and no evidence of a primary lesion. FNA should be sent for cytopathology, and a cell block prepared for p16 IHC staining. Depending upon clinical suspicion, EBV titer, thyroglobulin, calcitonin, PAX8 and or TTF should also be tested. Obtaining adequate sample for a cell block is essential, as IHC has important diagnostic and prognostic value (quality of evidence—high, strong recommendation).

Surgical Management of the Neck and Nodal Assessment

A minority of CUP patients can be cured with neck dissection alone. NCCN guidelines recommend neck dissection for definitive treatment of patients with N1 disease [2]—a solitary metastatic node less than or equal to 3 cm diameter (AJCC seventh Edition). For CUP with N1 disease that is HR-HPV or p16 positive with no extracapsular extension (ECE) on final pathology, observation is considered without adjuvant radiation. However the delineation between N1 and N2a disease may be inconsequential in HR-HPV related cancers—N2a disease (i.e. solitary node greater than 3 cm, less than 6 cm, AJCC seventh Edition) without ECE may also be adequately treated with neck dissection alone. Prognostically, this is recognized in the AJCC eighth Edition for p16 positive tumors. Clinical N stage now designates one or more ipsilateral nodes 6 cm or less in size as N1. Pathologic staging now designates four or fewer metastatic nodes as N1, and greater than four metastatic nodes as N2—without incorporating nodal size into pathologic staging classification.

No prospective comparisons between CUP patients whose management of the neck included surgery, and patients who received radiotherapy or chemoradiotherapy alone, are available to assess the true effect of neck dissection on regional control and survival. One retrospective review of 179 CUP patients reported improved regional control for those patients who underwent neck dissection [9], while no benefit of surgery was observed in another series of 61 patients [10]. In both studies, all patients received radiotherapy as part of their overall treatment. A 2001 systematic review of outcomes in CUP patients reported the highest locoregional control rates were achieved in patients who underwent upfront neck dissection followed by adjuvant radiation to the neck and potential primary sites [5]. The period of interest for the aforementioned studies was largely prior to the recognition of HR-HPV in oropharyngeal cancer. The potential heterogeneity in HR-HPV status of the

analyzed patients may have obscured any oncologic benefit of neck surgery. While HPV data will become more readily available in future studies, even large contemporary studies have significant gaps in reporting of this important predictor. One of the largest recent retrospective studies in CUP by Kamal et al. in 2018 reported their experience with treatment of 260 CUP patients that included IMRT—less than 50% of patients had known HPV or p16 status. This study also saw no increase in overall survival in patients who underwent neck dissection as a component of treatment [8].

Whether neck dissection improves oncologic outcomes in CUP with advanced nodal disease remains unclear—perhaps more importantly, increased nodal burden itself appears associated with worse regional control, overall and disease specific survival [6, 8]. Mizuta et al. [6] reported a retrospective multi-institutional study of 80 patients with CUP, comparing patients treated with neck dissection alone (27 of 80, 33.8%), neck dissection followed by RT or CRT (41 of 80, 51.3%), and radiotherapy followed by neck dissection (12 of 80, 15%)—i.e. all patients underwent neck dissection. For the entire group the 3-year overall survival and disease specific survival were 72.5% and 80.3%, respectively. On multivariate analysis the only predictor of OS, DSS, regional relapse free survival (RFS), and distant metastasis free survival (DMFS) was nodal burden (N1–N2a versus N2b–N3) [6].

Interestingly neither the Kamal et al. [8] or Mizuta et al. [6] studies found ECE to be a significant predictor of any oncologic outcome on multivariate analysis. Minimal ECE (e.g. 1 mm capsular invasion) may not have a prognostic impact in the HR-HPV era, unlike gross ECE or diffuse microscopic ECE [5, 7, 8, 26, 27].

While primary radiotherapy is an option for most CUP patients, surgical management of the neck is considered for low nodal burden, especially in the absence of obvious extracapsular spread. Some of these patients will be able to avoid adjuvant radiotherapy to the neck, and dose de-escalation will likely be an option supported by clinical trials in the near future. Nodal burden remains the greatest prognostic predictor in CUP. The AJCC eighth Edition staging system for HPV/p16 positive oropharyngeal cancers reflects a need to redefine early and advanced disease and investigate safe deintensification of treatment (quality of evidence- moderate, conditional recommendation).

Role of Transoral Surgery for Diagnosis and Oncologic Treatment

If a malignant neck mass FNA tests positive for HR-HPV or p16 expression, an oropharyngeal primary is most likely. Transoral surgery—most commonly either TORS or TLMS—may identify the primary site (Table 9.3). For CUP patients the tongue base and palatine tonsils should be thoroughly evaluated for an occult primary. The surgeon's expertise dictates the actual transoral technique. In the absence of a grossly suspicious palatine tonsillar lesion, tonsillectomy is recommended over simple incisional biopsy. If a frozen section of the ipsilateral tonsil is negative for

Table 9.3 Outcomes of transoral surgery for the evaluation of CUP

Study	Patients	Intervention	Outcome classification	Detection rate after TORS/TLMS	HR-HPV or p16 status	Quality of Evidence
Patel et al. [18]	CUP patients who underwent TORS in search of primary tumor	Imaging (multiple modalities) followed by TORS	Localization of primary tumor site	12 of 15 (80%) of patients with no preoperative physical exam or radiologic suspicion	26 positive of 47 tested; in this study 32 patients had suspicious exam and/or radiologic findings prior to TORS	Moderate quality
Patel et al. [28]	CUP patients who underwent TORS in search of primary tumor	Imaging (multiple modalities) followed by TORS	Localization of primary tumor site	26 of 35 (74%) of patients with no preoperative physical exam or radiologic suspicion	18 positive of 24 tested, no difference in HPV status between detected and undetected	Moderate quality
Kuta et al. [19]	CUP patients who underwent PETCT and TLMS[a] in search of primary tumor	PETCT followed by TLMS[a]	Localization of primary tumor site	25 of 27 (92.6%) of patients with no preoperative physical exam or radiologic suspicion	25 positive of 27 (92.6%)	Moderate quality
Geltzeiler et al. [29]	CUP patients who underwent TORS in search of primary tumor	Direct laryngoscopy and TORS[b]	Localization of primary tumor site	37 of 50 (74%) of TORS patients (excludes 14 additional CUP with primary found on direct laryngoscopy)	48 positive of 50 (96%) who underwent TORS	Moderate quality
Hatten et al. [52]	CUP patients who underwent TORS in search of primary tumor	TORS assisted examination for primary tumor	Localization of primary tumor site	48 of 60 (80%) undergoing TORS surgical protocol. 32 of 59 (54%) had preoperative PET-CT without suspicious findings	55 positive of 60 (92%)	Moderate quality

[a]*TLMS* transoral laser microsurgery

[b]Various TORS techniques were used on an individual patient basis: unilateral, versus bilateral lingual tonsillectomy, bilateral versus ipsilateral palatine tonsillectomy

tumor, a unilateral or bilateral lingual tonsillectomy may reveal the primary. Numerous small retrospective studies of CUP have reported success rates from 50–100% in detection of the primary using transoral surgery beyond palatine tonsillectomy [18, 28–33]. The preoperative evaluation for a primary site amongst these studies reported various positive or negative exam and imaging findings. This in part explains the range of detection rates during transoral surgery. In these cases, presumably the primary is either very small or nonexistent, and either TORS or TLMS can facilitate a more comprehensive biopsy survey than endoscopic random biopsies alone—especially along the lingual tonsillar base of tongue. While all experienced surgeons who employ these techniques recognize the seriousness of bleeding complications, rarely are other adverse events encountered, including long term speech or swallowing impairment. The opportunity to completely excise a small primary may obviate the need for pharyngeal radiation. Similarly the identification of a lateral-positioned primary can reduce the radiation volume to midline and contralateral mucosal sites that otherwise would be considered at-risk. Lastly, a negative TORS or TLMS exploration most likely indicates a small primary, or no primary exists—and with a low probability of long-term complications, this should be a considered a worthwhile confirmation of a true unknown primary that usually portends a good prognosis.

Transoral surgery (TORS or TLMS) should be considered, beyond direct laryngoscopy, to search for, and potentially cure small occult primary lesions. This approach can be combined with neck dissection for clinically N1 patients. In selected patients without adverse features, adjuvant therapy can be avoided (quality of evidence-moderate, conditional recommendation).

Role of Radiotherapy to the Neck and Mucosal Sites

While similar outcomes between neck dissection and primary radiotherapy for early nodal disease have been observed, radiotherapy is indicated for all advanced nodal disease. The planned treatment volume, and dose of radiotherapy delivered is evolving. Historically patients with CUP would receive radiotherapy to bilateral necks and all pharyngeal mucosal levels. Individual case decisions might spare the larynx and/or hypopharynx [34]. While locoregional control was achievable, the technique was not sparing of potentially uninvolved pharyngeal structures.

Numerous retrospective studies have examined treatment outcomes comparing ipsilateral and bilateral neck radiation, sparing low risk mucosal levels—but no prospective data is available. Poor accrual led to closure of a prospective trial EORTC 22205 that was designed to answer these questions. Numerous retrospective studies have included small numbers of patients who received ipsilateral radiotherapy, with low rates of contralateral neck recurrence similar to patients who received bilateral neck radiation [1, 3, 9, 35–42].

The largest retrospective CUP study reporting on 352 patients observed one contralateral neck recurrence in patients treated with ipsilateral radiotherapy (1%), compared to five contralateral recurrences when bilateral necks were radiated (4%) [1]. No HPV data, and limited ECE data was available for detailed description of these patients. Furthermore at most only 38% of patients underwent either neck CT or MRI, or PET scan as part of their diagnostic evaluation. Without anatomical imaging the designation of a true unknown primary may have differed between studies and affected survival analyses.

Mourad et al. reported that sparing the larynx, hypopharynx and nasopharynx does not compromise locoregional control and survival in select patients [35].

Kamal et al. reported treatment of 260 patients with CUP that included IMRT—79% of patients had N2b disease or greater [8]. Radiation to mucosal at-risk sites was administered in 245 of 260 (94%) of patients, and only 4% of patients had emergence of a primary tumor after treatment. Regional control (91%), distant metastasis free survival (94%) and overall survival (84%) were excellent 5 years after treatment. In this study, systemic therapy did not improve these outcomes regardless of nodal stage, either when given concurrently with IMRT, or as a neoadjuvant regiment. While fewer than 50% of the study patients had available HPV or p16 data, presumably the majority had HR-HPV associated cancers—the more favorable biology and response to treatment in these patients compared to other head and neck cancers suggests systemic therapy has a more limited role in treatment.

Dysphagia After Treatment

Dysphagia is a major acute and long-term concern for treatment of CUP. Refinement of radiotherapy volume is critical for acceptable long-term swallow function. While an imperfect metric for severity of dysphagia, gastrostomy tube placement is frequently studied. The majority of patients will have their gastrostomy tube removed in the year following treatment, irrespective of radiated pharyngeal levels and addition of systemic therapy [8]. Even those patients with chronic radiation-associated dysphagia (RAD) are often free from gastrostomy tube dependence [8, 43]. Small studies of patients with CUP treated with radiation have variably reported a minority or no patients with grade 3 (severe) or greater dysphagia and a majority of patients self-reporting that they swallow ‘as well as ever’ 6 months following treatment [11]. Still, another small study observed most patients reporting no difference in pre and post-treatment speech, but worse satisfaction with eating 12 months post-treatment [44].

Recommendations Based on the Data

The evaluation and management of CUP is well described in the NCCN 2018 guidelines based upon available evidence. Additionally, the implementation of the AJCC eighth edition staging system—which contains different stage reporting

guidelines for HPV+ and HPV− tumors, reflects the prognostic importance of HPV or p16 testing. Patients presenting with HPV and/or p16 positive CUP are designated T0, while HPV or p16 negative CUP is not assumed to harbor an oropharyngeal primary.

Based upon the preceding data and historical studies, the following summary of recommendations can be made for the management of CUP patients:

1. Transoral surgery (TORS or TLMS) should be considered, beyond direct laryngoscopy, to search for, and potentially cure small occult primary lesions. This approach can be combined with neck dissection for clinically N1 patients. In selected patients without adverse features, adjuvant radiotherapy can be avoided. More advanced nodal disease requires radiotherapy as a component of treatment. The AJCC eighth Edition staging system for HPV/p16 positive oropharyngeal cancers reflects a need to redefine early and advanced disease and investigate safe deintensification of treatment (quality of evidence—moderate, conditional recommendation).
2. In the study of patients with CUP who have HPV-related disease, ECS has likely included a heterogeneous group ranging from minimal microscopic to gross extranodal extension of disease. Patients with a solitary pathologic node and minimal ECS can be considered for neck dissection and adjuvant radiotherapy without the addition of systemic therapy, although definitive data is not yet available (quality of evidence—moderate, conditional recommendation).
3. Primary radiotherapy with or without chemotherapy is recommended for CUP patients with advanced nodal disease (N2b, N2c, N3, or with gross ECE) [2]. The planning target volume (PTV) for radiotherapy in patients with CUP should be strongly informed by HPV or p16 testing, and EBV testing when clinically suspected. Primary radiotherapy for patients with undetected primaries should include high-risk nodal levels and mucosal sites. With respect to mucosal target volume, HPV or p16 positive CUP patients should receive radiation primarily to the oropharynx and consider inclusion of the nasopharynx, limiting radiation to other pharyngeal levels (quality of evidence—moderate, conditional recommendation).

Personal View of Data in the Management of CUP

There is a wealth of valuable experience in the treatment of patients with CUP as evidenced by the previously cited studies. It is clear that the majority of patients with CUP have HPV-associated disease of likely oropharyngeal origin. As such, we counsel them appropriately that the disease is life threatening, but with appropriate treatment there is a high probability of cure.

Limitations of the cited research are common in retrospective studies. Radiation volume was often only broadly described, and comorbidity status was often unreported. Both of these variables may have a powerful influence on overall survival. Comorbidity status in particular has a significant role in treatment selection.

It is important to convey a balanced perspective on treatment options—primary surgery with or without adjuvant therapy, versus primary radiation-based protocols. Patients rightfully focus on which treatment is the 'right' choice, and there is a great deal of comfort that the clinician can provide by describing the excellent outcomes experienced by most patients—regardless of the treatment protocol employed. Centers with a high volume of transoral surgical experience have the opportunity to both detect primary tumors and fully treat the neck and mucosal disease, when nodal burden is low. This will be a small proportion of CUP patients that can avoid radiotherapy, however this subgroup benefits greatly from the low long-term morbidity of surgery. Conversely, we counsel most patients regarding the excellent oncologic outcomes even if a primary site is not discovered, when primary radiotherapy or chemoradiotherapy is chosen. Future research needs to clearly define and distinguish between HPV positive and negative CUP—the study of planned radiation volumes, success of transoral surgical approaches, and prognostic significance of nodal burden need to be considered within these two subgroups separately.

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