16 ■ CARCINOMA OF UNKNOWN PRIMARY OF THE HEAD AND NECK

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QUICK HIT ■ Head and neck CUP represents ~3% of H&N cancers. Detailed diagnostic workup is required to identify a primary source for malignancy (must include): comprehensive H&P, analysis of the histology and anatomic disease distribution (nodal levels), presence/absence of biomarkers (p16, HPV DNA, EBV DNA) advanced imaging (e.g., contrast-enhanced CT and PET/CT), diagnostic surgical procedures (e.g., palatine tonsillectomy), with further therapy guided by findings. Biopsy showing adenocarcinoma in the low neck should prompt evaluation for a salivary gland tumor, thoracic, gynecologic, or gastrointestinal primary. SCCUPs despite thorough workup are assumed to arise from H&N sites (mucosal or skin) and treated based on the probability of the primary site given anatomic location of nodal involvement and presence/absence of biomarkers. Two broad treatment approaches exist: primary surgery (with risk-adapted adjuvant RT ± chemotherapy) and definitive RT (± chemotherapy) (Table 16.1).

Table 16.1 General Treatment Paradigm for Unknown Primary Presenting as Squamous Carcinoma of H&N Lymph Nodes

	Treatment Options
cT0N1	Option 1: Neck dissection (at least levels II–IV with or without TORS lingual tonsillectomy) • Observation with no additional adverse features • Add postoperative RT (PORT) for pN2/3 (see Chapter 17) • Add chemoRT for extranodal extension (ENE+) Option 2: RT alone
cT0N2-3	Option 1: Definitive chemoRT (favored for bilateral/bulky presentation or radiographic concern for ENE to avoid tri-modality therapy) Option 2: Neck dissection (with or without TORS lingual tonsillectomy) • Add PORT for pN2/3 (see Chapter 17) • Add chemoRT for ENE+

Dose: In 2 Gy/fx, treat gross disease to 66 to 70 Gy, low-risk neck to 54 to 56 Gy, and potential primary sites to 50 to 60 Gy (or a biologically equivalent dose scheme)

EPIDEMIOLOGY: CUP represents 2% to 3% of all newly diagnosed H&N carcinomas. Median age at diagnosis is 50 to 70 years with male predominance (M:F of 4:1). The majority of HNSCCUP in the United States are now HPV associated.[1]

RISK FACTORS: Standard risk factors for H&N cancer apply, as do those of other primaries that spread to cervical lymph nodes.

General: Alcohol, tobacco, betel and areca nuts, Plummer–Vinson syndrome. Oropharyngeal: HPV infection.

Nasopharyngeal: EBV infection, salt-cured foods, occupational smoke/dust exposure. Sinonasal: Nickel, wood dust, leather tanning agents. Cutaneous: UV exposure

ANATOMY: Pattern of nodal involvement on physical exam helps direct further workup toward potential sites of the occult primary.

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Table 16.2 Lymph Node Levels* and Correlation With Possible Primary Site		
Level	**Anatomic Correlation**	**Possible Primary Site**
Ia	Submental	Anterior oral cavity/lower lip
Ib	Submandibular	Oral cavity (upper and lower lip, cheek, nose) and skin (lip, nose, medial canthus)
II	Upper jugular	Oropharynx, hypopharynx, oral cavity, larynx
III	Middle jugular	Oropharynx, larynx, hypopharynx, thyroid
IV	Lower jugular	Larynx, hypopharynx, thyroid, cervical esophagus, trachea
V	Posterior cervical triangle	Nasopharynx, skin of posterior neck, scalp, hypopharynx
VI	Anterior cervical (prelaryngeal (Delphian), pre/paratracheal, tracheoesophageal)	Larynx, thyroid
VII	Lateral retropharyngeal and retrostyloid	Nasopharynx, oropharyngeal wall or soft palate, hypopharynx, paranasal sinuses
Supraclavicular	Medial SCV (IVa) and lateral SCV (Vc)	Thyroid, cervical esophagus, infraclavicular primary (e.g., lung, gastrointestinal or gynecologic)
VIII	Intra/periparotid	Skin

*Cervical LN levels as per Robbins et al.[2]

PATHOLOGY: Most common pathology of HNCUP is SCC. Adenocarcinoma and neuroendocrine carcinomas are less common. Lymphoma, sarcoma, thyroid, melanoma, and germ cell tumors may also be encountered.

CLINICAL PRESENTATION: Classic presentation is unilateral painless neck mass in level II (~50%) ± level III. N1 presentation occurs in ~25%. With the rise of HPV-related cancers, some centers have noted a higher incidence of HNSCCUP,[3] with the hypothesis that HPV-related disease often presents with a small primary tumor,[4] which can be difficult to identify against a background of often irregular-appearing lymphoid tissue.

WORKUP:

Comprehensive H&P: Attention to past history of malignancy (including skin cancers) and risk factors. Exam should include direct inspection of the mucosal surfaces of the upper aerodigestive tract (including flexible nasopharyngolaryngoscopy to visualize surfaces not able to be evaluated on standard exam, that is, nasal cavity, nasopharynx, posterior/inferior oropharynx, larynx, and hypopharynx); digital exam of high-risk sites to evaluate for palpable abnormalities (without a visual correlate) and thorough exam of the skin of the head and neck. Anatomic location of the pathologic lymph node and histology will provide clues as to the primary site (Table 16.2).

Labs: CBC, CMP (thyroglobulin and calcitonin if adenocarcinoma).

Biopsy: FNA of pathologic LN for initial sampling (unless suspicious for lymphoma). If FNA is nondiagnostic, proceed to core needle biopsy. Excisional biopsy is a less favored alternative; if done, ideally with planned neck dissection to follow. Excisional biopsy alone is not recommended due to disruption of tissue planes, which can alter lymphatic drainage (non-oncologic resection). In the current era, testing of viral and other biomarkers from the biopsy specimen is essential in directing the search for a primary tumor (Table 16.3). IHC for p16 protein or another HPV-specific test should be performed on every SCCUP with levels II–III LN involvement ± with other levels as clinically indicated. If p16 is negative, other markers (e.g., EBV) should be performed.

Table 16.3 Pathologic Markers and Correlation With Possible Primary Site	
Marker	**Possible Primary Site**
EBV	Nasopharynx
p16+, HPV ISH+	Oropharynx
p16+, HPV ISH-	Skin[5]
Adenocarcinoma, TTF+	Thyroid, lung

Imaging: CECT is the primary imaging modality for evaluation of cervical lymphadenopathy. PET/CT is the next test of choice if CECT and clinical exam (including scope) are unrevealing for a primary site. MRI not clearly superior to CECT; although it could help guide biopsies if substantial metal artifact, iodine contrast allergy, or if nasopharynx primary is suspected.[6] Imaging should be performed prior to panendoscopy to guide selection of biopsy sites and to avoid uncertainties of interpretation due to false-positive FDG avidity at sites manipulated during endoscopy. PET detection rate of primary tumor is approximately 30% in patients with HNCUP after standard workup.[7]

Procedures: Following PET/CT, next step is EUA w/panendoscopy with directed biopsies of any suspicious areas. With panendoscopy, the primary site is identified in 50% to 65% of patients with suspicious radiographic or physical findings, but only in 15% to 29% of those without.[8,9] Utility of random biopsies in absence of PET/CT or clinical suspicion is very low and no longer recommended.[10] If LN levels I–III are involved, ipsilateral palatine tonsillectomy is still recommended, and increases detection of the primary tumor by about 10-fold as compared to tonsillar biopsy (3% vs. 30%).[11,12] Particularly in the p16+ setting, consider lingual tonsillectomy if palatine tonsillectomy is negative. Meta-analyses of lingual tonsillectomy a.k.a. "tongue base mucosectomy" with transoral approach (via TORS or TLM) demonstrated 78% of patients had a primary site in the BOT after negative comprehensive workup.[13] Palatine and/or lingual tonsillectomies can be unilateral if there is only unilateral lymph node involvement.[10] If bilateral lymph nodes are involved, the primary site is more likely to be in the BOT than the palatine tonsil. Consider unilateral lingual tonsillectomy on the side with greatest nodal burden and contralateral lingual tonsillectomy if frozen sections are negative. Consider unilateral palatine tonsillectomy if lingual tonsillectomy is negative but avoid bilateral palatine tonsillectomy and bilateral lingual tonsillectomy due to morbidity.[10] Tissue specimens taken during diagnostic evaluation ideally are anatomically oriented and margin evaluation performed.

PROGNOSTIC FACTORS: Histology, number of LNs, LN level (upper vs. lower/SCV), KPS, extracapsular extension, and grade among others.

NATURAL HISTORY: Mucosal emergence rates, historically, are low after comprehensive RT. One series suggested rates of 25% after neck dissection alone and rates from 8% to 14% with RT. These rates may be lower in the modern era with improved imaging. Regional failure in neck and distant metastases are more common at 20% to 35%.[14]

STAGING: T-classification for cancer of unknown primary is T0 (not TX, which implies incomplete workup). LN staging for squamous cancers is per standard H&N staging (see Chapter 11 for details). EBV-associated unknown primary follows nasopharyngeal LN staging.

TREATMENT PARADIGM: Initial treatment can follow a paradigm of primary surgery (with risk-adapted adjuvant RT ± CHT as indicated) or primary RT (± CHT as indicated). Results have generally been comparable with either approach, and institutional preference often determines treatment algorithm.[15–17] Treatment strategy should take into account analysis of toxicities of each therapy.[18]

Surgery: For HNSCCUP, NCCN guidelines recommend surgery/neck dissection (preferred) or radiation therapy as primary therapy for N1 disease.[11] With modern staging, outcomes after surgery alone for N1 disease are excellent with 90% control above clavicles.[19] Typically, selective dissection is performed with levels IIA–IV routinely dissected ± other levels based on anatomic location of involved nodes, nodal burden, and suspected primary site.[10] Potential complications of neck dissection include hematoma, seroma, chyle leak, lymphedema, wound infection/dehiscence, fistula, cranial nerve damage (e.g., CN XI), and carotid rupture. The major potential

complication of lingual tonsillectomy is hemorrhage, occurring in 4.9% of patients.[13] After surgery, adjuvant RT ± CHT should be offered based on standard recommendations for HN cancer (see Chapter 17 for details).

Chemotherapy: Concurrent CHT with radiation therapy is recommended for patients with either (a) ENE or residual disease after a neck dissection or (b) cN2–3 disease treated nonoperatively. These concepts are largely extrapolated from major definitive and post-op studies in setting of known H&N primaries (see Chapters 11–15 and 17). There have been small observational studies in setting of unknown primary that have shown good outcomes with chemoRT for patients with N2–N3 nodal disease.[18,20–22] If delivered, CHT dosing strategy is similar to that of other H&N sites, commonly high-dose cisplatin 100 mg/m^2 on days 1, 22, and 43 or cisplatin 40 mg/m^2 weekly. CHT may not be recommended concurrently with adjuvant radiation after resection of LN metastases with high suspicion for a skin primary due to lack of benefit seen on TROG 05.01,[23] though some may still consider concurrently for treatment in the definitive setting.

Radiation

Indications: RT can be employed in either the (a) high-risk postoperative setting or the (b) definitive setting. Following neck dissection, RT indications mimic standard indications for PORT in the head and neck: more than one involved node (N2–3), ENE, or positive margin. In the definitive setting, RT can be delivered alone or with concurrent CHT (e.g., cN2–3; see the preceding text).

Fields: Most commonly, RT is delivered to putative mucosal sites along with bilateral neck, unless skin primary is suspected.

- Primary: Classically, comprehensive RT for likely mucosal primaries included the nasopharynx, oropharynx, and hypopharynx with exclusion of oral cavity and larynx (sites that can be easily visualized). Potential gain w/ comprehensive RT in controlling primary should be weighed against its effects on QOL/toxicity. Target volumes have evolved and are often modified by HPV/EBV status and diagnostic interventions (e.g., palatine or lingual tonsillectomy). Guidelines recommend targeting only oropharynx for HPV+ disease (ipsilateral tonsil ± soft palate and bilateral BOT, modified by prior surgical diagnostic interventions).[10] Consider treating only nasopharynx for EBV+ disease. For HPV– disease in levels II–III, we consider the ipsilateral tonsil, entire base of tongue, ipsilateral Fossa of Rosenmüller, and ipsilateral pyriform sinus to be at risk.
- Neck/lymphatics: Most treat bilateral neck levels II to IV with RP, though other levels (IB, V, RP) should be included as indicated by presumed primary location (e.g., include V and RP with EBV+ presumed nasopharyngeal primary). Unilateral nodal treatment for suspected mucosal primaries is controversial and should be considered only with involvement of a single node (unless concerned for nasopharyngeal primary, in which bilateral coverage is recommended).[10] In the adjuvant setting, putative primary sites are treated as in definitive setting.[10] Omitting putative mucosal sites after comprehensive surgical diagnostics (at least ipsilateral palatine tonsillectomy and high-quality bilateral lingual tonsillectomy) is investigational. Pathologic N1 disease (small, single LN involved without ENE) can be observed.[10]

Dose: As in target delineation, dosing is heterogeneous. An acceptable dose scheme in the definitive setting is 70 Gy/35 fx to gross disease, 56 to 63 Gy/35 fx to mucosal sites at risk, and 56 Gy/35 fx to the uninvolved neck (or a radiobiologic equivalent scheme). Postoperatively, an acceptable dose regimen is 66 Gy in 30 to 33 fx to areas harboring ENE (or gross residual disease), 60 Gy in 30 fx to the postoperative bed and pathologically involved nodal levels, and 54 Gy in 30 fx to the uninvolved neck (or a radiobiologic equivalent scheme).

Toxicity:

- Acute: Mucositis, skin erythema/desquamation, odynophagia, dysphagia, fatigue, aspiration, xerostomia/thickened secretions, taste alterations.
- Late: Xerostomia, taste alteration, fibrosis, trismus, decreased hearing, hypothyroidism, submental lymphedema, dysphagia, esophageal strictures, bone/soft tissue necrosis, secondary malignancy.

EVIDENCE-BASED Q&A

Does association with HPV carry same implications in HNCUP as it does in oropharyngeal cancer?

Yes. HPV-associated HNCUPs have a better prognosis relative to their p16-negative counterparts, independent of nodal status.[24] In one study, 5-year OS was 92% if p16+ vs. 30% if p16–.[1] HPV positivity also leads practitioners to target only likely primary sites (i.e., oropharynx), which may decrease toxicity of treatment.

What is role of transoral lingual tonsillectomy in workup of HNCUP?

Recently, TORS has been used to perform lingual tonsillectomy in search of occult primary and appears to increase the likelihood of detecting a primary site when added to the standard diagnostic algorithm.

Mehta, Pittsburgh (*Laryngoscope* 2013, PMID 23154813): Ten patients with SCCUP underwent transoral robotic base-of-tongue resection (lingual tonsillectomy). In 9 of 10 patients (90%), primary was detected with mean diameter of 0.9 cm.

Patel, Multi-Institution (*JAMA Otolaryngol Head Neck Surg* 2013, PMID 24136446): Retrospective multi-institution series of patients treated with TORS to identify primary site in patients with SCCUP of head and neck. Six institutions enrolled a total of 47 patients. Primary site was found in 72%. Primary was in BOT in 59% and in tonsil in 38%. In 18 patients without suspicious radiographic or examination findings, 72% of primaries were identified with TORS.

Farooq, Meta-analysis (*Oral Oncol* 2019, PMID 30926070): Meta-analysis including 21 studies. In patients with negative exam, conventional imaging, and PET/CT, tongue base mucosectomy identified the primary in 64% of cases, which rose to 78% in patients who also had a negative EUA and tonsillectomy.

Does bilateral neck RT improve outcomes as compared to unilateral treatment?

Unilateral treatment is controversial considering that occult primary tumors presumed to be arising from the oropharynx often reside in the base of tongue, which is a midline structure. Table 16.4 provides a summary of various series investigating unilateral treatment. Although failure rates appear low (approximately 10%), this remains controversial. Of note, many of the historical papers compared ipsilateral RT without mucosal coverage to comprehensive RT. Less controversy exists in the setting of a single LN without clinical or radiologic evidence of ENE, in which case, it is reasonable to consider unilateral neck RT with coverage of putative mucosal sites.[10]

Table 16.4 Studies Investigating Unilateral Neck Treatment

Author	Institution	Year	Ipsilateral LN Treated, N	Contralateral Failure, N (%)	Comment
Carlson et al.[25]	MDACC	1986	13	2 (15.6%)	2D fields, no CT imaging
Colletier et al.[26]	MDACC	1998	14	1 (7.1%)	May overlap with Carlson; unclear if one contralateral failure was in ipsilateral-only-treated patient
Reddy et al.[27]	U Chicago	1997	16	9 (56%)	All nodes treated ipsilaterally with electron beam only; 5 of 9 recurrences were primary and contralateral nodes synchronously

(*continued*)

Table 16.4 Studies Investigating Unilateral Neck Treatment (*continued*)					
Author	**Institution**	**Year**	**Ipsilateral LN Treated, N**	**Contralateral Failure, N (%)**	**Comment**
Grau et al.[28]	Denmark	2000	26	1 (4%)	Patients treated with bilateral RT on study had 2% contralateral failure
Beldi et al.[29]	Milan	2007	33	Not reported	Report worse survival in unilateral patients but many were treated palliatively
Ligey et al.[30]	Dijon	2009	59	6 (10.2%)	Seven primary tumors emerged in unilateral group
Fakhrian et al.[31]	Munich	2012	17	1 (5.9%)	Comprehensive RT not associated with OS/RFS.
Cuaron et al.[32]	MSKCC	2015	6	0 (0%)	Small, but all CT imaging
Perkins et al.[33]	Wash U	2012	21	1 (5%)	All treated post neck dissection
Overall approximate crude rate			172	21 (12.2%)	Excluding Reddy: 12/156 = 7.7%

REFERENCES

1. Keller LM, Galloway TJ, Holdbrook T, et al. p16 status, pathologic and clinical characteristics, biomolecular signature, and long-term outcomes in head and neck squamous cell carcinomas of unknown primary. *Head Neck*. 2014;36(12):1677–1684. doi:10.1002/hed.23514
2. Robbins KT, Clayman G, Levine PA, et al. Neck dissection classification update: revisions proposed by the american head and neck society and the american academy of otolaryngology-head and neck surgery. *Arch Otolaryngol Head Neck Surg*. 2002;128(7):751–758. doi:10.1001/archotol.128.7.751
3. Motz K, Qualliotine JR, Rettig E, et al. Changes in unknown primary squamous cell carcinoma of the head and neck at initial presentation in the era of human papillomavirus. *JAMA Otolaryngol Head Neck Surg*. 2016;142(3):223–228. doi:10.1001/jamaoto.2015.3228
4. Huang SH, Perez-Ordonez B, Liu FF, et al. Atypical clinical behavior of p16-confirmed HPV-related oropharyngeal squamous cell carcinoma treated with radical radiotherapy. *Int J Radiat Oncol Biol Phys*. 2012;82(1):276–283. doi:10.1016/j.ijrobp.2010.08.031
5. McDowell LJ, Young RJ, Johnston ML, et al. p16-positive lymph node metastases from cutaneous head and neck squamous cell carcinoma: no association with high-risk human papillomavirus or prognosis and implications for the workup of the unknown primary. *Cancer*. 2016;122(8):1201–1208. doi:10.1002/cncr.29901
6. Ruhlmann V, Ruhlmann M, Bellendorf A, et al. Hybrid imaging for detection of carcinoma of unknown primary: a preliminary comparison trial of whole body PET/MRI versus PET/CT. *Eur J Radio*. 2016;85(11):1941–1947. doi:10.1016/j.ejrad.2016.08.020
7. Johansen J, Buus S, Loft A, et al. Prospective study of 18FDG-PET in the detection and management of patients with lymph node metastases to the neck from an unknown primary tumor. Results from the DAHANCA-13 study. *Head Neck*. 2008;30(4):471–478. doi:10.1002/hed.20734
8. Cianchetti M, Mancuso AA, Amdur RJ, et al. Diagnostic evaluation of squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site. *Laryngoscope*. 2009;119(12):2348–2354. doi:10.1002/lary.20638
9. Mendenhall WM, Mancuso AA, Parsons JT, et al. Diagnostic evaluation of squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site. *Head Neck*. 1998;20(8):739–744. doi:10.1002/(SICI)1097-0347(199812)20:8<739::AID-HED13>3.0.CO;2-0
10. Maghami E, Ismaila N, Alvarez A, et al. Diagnosis and management of squamous cell carcinoma of unknown primary in the head and neck: ASCO guideline. *J Clin Oncol*. 2020;38(22):2570–2596. doi:10.1200/JCO.20.00275
11. Head and Neck Cancers. NCCN Clinical Practice Guidelines in Oncology. 2020; Version 2.2020 — June 9, 2020.
12. Waltonen JD, Ozer E, Schuller DE, Agrawal A. Tonsillectomy vs. deep tonsil biopsies in detecting occult tonsil tumors. *Laryngoscope*. 2009;119(1):102–106. doi:10.1002/lary.20017

13. Farooq S, Khandavilli S, Dretzke J, et al. Transoral tongue base mucosectomy for the identification of the primary site in the work-up of cancers of unknown origin: systematic review and meta-analysis. *Oral Oncol*. 2019;91:97–106. doi:10.1016/j.oraloncology.2019.02.018
14. Nieder C, Ang KK. Cervical lymph node metastases from occult squamous cell carcinoma. *Curr Treat Options Oncol*. 2002;3(1):33–40. doi:10.1007/s11864-002-0039-7
15. Demiroz C, Vainshtein JM, Koukourakis GV, et al. Head and neck squamous cell carcinoma of unknown primary: neck dissection and radiotherapy or definitive radiotherapy. *Head Neck*. 2014;36(11):1589–1595. doi:10.1002/hed.23479
16. Christiansen H, Hermann RM, Martin A, et al. Neck lymph node metastases from an unknown primary tumor retrospective study and review of literature. *Strahlenther Onkol*. 2005;181(6):355–362. doi:10.1007/s00066-005-1338-2
17. Balaker AE, Abemayor E, Elashoff D, St John MA. Cancer of unknown primary: does treatment modality make a difference? *Laryngoscope*. 2012;122(6):1279–1282. doi:10.1002/lary.22424
18. Chen AM, Farwell DG, Lau DH, et al. Radiation therapy in the management of head-and-neck cancer of unknown primary origin: how does the addition of concurrent chemotherapy affect the therapeutic ratio? *Int J Radiat Oncol Biol Phys*. 2011;81(2):346–352. doi:10.1016/j.ijrobp.2010.06.031
19. Galloway TJ, Ridge JA. Management of squamous cancer metastatic to cervical nodes with an unknown primary site. *J Clin Oncol*. 2015;33(29):3328–3337. doi:10.1200/JCO.2015.61.0063
20. Sher DJ, Balboni TA, Haddad RI, et al. Efficacy and toxicity of chemoradiotherapy using intensity-modulated radiotherapy for unknown primary of head and neck. *Int J Radiat Oncol Biol Phys*. 2011;80(5):1405–1411. doi:10.1016/j.ijrobp.2010.04.029
21. Argiris A, Smith SM, Stenson K, et al. Concurrent chemoradiotherapy for N2 or N3 squamous cell carcinoma of the head and neck from an occult primary. *Ann Oncol*. 2003;14(8):1306–1311. doi:10.1093/annonc/mdg330
22. Shehadeh NJ, Ensley JF, Kucuk O, et al. Benefit of postoperative chemoradiotherapy for patients with unknown primary squamous cell carcinoma of the head and neck. *Head Neck*. 2006;28(12):1090–1098. doi:10.1002/hed.20470
23. Porceddu SV, Bressel M, Poulsen MG, et al. Postoperative concurrent chemoradiotherapy versus postoperative radiotherapy in high-risk cutaneous squamous cell carcinoma of the head and neck: the Randomized Phase III TROG 05.01 Trial. *J Clin Oncol*. 2018;36(13):1275–1283. doi:10.1200/JCO.2017.77.0941
24. Dixon JG, Bognar BA, Keyserling TC, et al. Teaching women's health skills: confidence, attitudes and practice patterns of academic generalist physician. *J Gen Intern Med*. 2003;18(6):411–418. doi:10.1046/j.1525-1497.2003.10511.x
25. Carlson LS, Fletcher GH, Oswald MJ. Guidelines for radiotherapeutic techniques for cervical metastases from an unknown primary. *Int J Radiat Oncol Biol Phys*. 1986;12(12):2101–2110. doi:10.1016/0360-3016(86)90008-8
26. Colletier PJ, Garden AS, Morrison WH, et al. Postoperative radiation for squamous cell carcinoma metastatic to cervical lymph nodes from an unknown primary site: outcomes and patterns of failure. *Head Neck*. 1998;20(8):674–681. doi:10.1002/(SICI)1097-0347(199812)20:8<674::AID-HED3>3.0.CO;2-H
27. Reddy SP, Marks JE. Metastatic carcinoma in the cervical lymph nodes from an unknown primary site: results of bilateral neck plus mucosal irradiation vs. ipsilateral neck irradiation. *Int J Radiat Oncol Biol Phys*. 1997;37(4):797–802. doi:10.1016/S0360-3016(97)00025-4
28. Grau C, Johansen LV, Jakobsen J, et al. Cervical lymph node metastases from unknown primary tumours: results from a national survey by the Danish Society for Head and Neck Oncology. *Radiother Oncol*. 2000;55(2):121–129. doi:10.1016/S0167-8140(00)00172-9
29. Beldi D, Jereczek-Fossa BA, D'Onofrio A, et al. Role of radiotherapy in the treatment of cervical lymph node metastases from an unknown primary site: retrospective analysis of 113 patients. *Int J Radiat Oncol Biol Phys*. 2007;69(4):1051–1058. doi:10.1016/j.ijrobp.2007.04.039
30. Ligey A, Gentil J, Crehange G, et al. Impact of target volumes and radiation technique on loco-regional control and survival for patients with unilateral cervical lymph node metastases from an unknown primary. *Radiother Oncol*. 2009;93(3):483–487. doi:10.1016/j.radonc.2009.08.027
31. Fakhrian K, Thamm R, Knapp S, et al. Radio(chemo)therapy in the management of squamous cell carcinoma of cervical lymph nodes from an unknown primary site: a retrospective analysis. *Strahlenther Onkol*. 2012;188(1):56–61. doi:10.1007/s00066-011-0017-8
32. Cuaron J, Rao S, Wolden S, et al. Patterns of failure in patients with head and neck carcinoma of unknown primary treated with radiation therapy. *Head Neck*. 2016;38 Suppl 1:E426–E431. doi:10.1002/hed.24013
33. Perkins SM, Spencer CR, Chernock RD, et al. Radiotherapeutic management of cervical lymph node metastases from an unknown primary site. *Arch Otolaryngol Head Neck Surg*. 2012;138(7):656–661. doi:10.1001/archoto.2012.1110