Proposed diagnostic algorithm for head and neck squamous cell carcinoma with an occult primary tumor: an evidence-based approach

Review Article

Authors

Diogo Cunha-Cabral
Hospital Pedro Hispano – Unidade Local de Saúde de Matosinhos, Portugal

Pedro Marques Gomes
Hospital Pedro Hispano – Unidade Local de Saúde de Matosinhos, Portugal

José Pedro Pereira
Hospital Pedro Hispano – Unidade Local de Saúde de Matosinhos, Portugal

André Alves Carção
Hospital Pedro Hispano – Unidade Local de Saúde de Matosinhos, Portugal

Nuno Oliveira
Hospital Pedro Hispano – Unidade Local de Saúde de Matosinhos, Portugal

Marta Vilaça
Hospital Pedro Hispano – Unidade Local de Saúde de Matosinhos, Portugal

Gustavo Lopes
Hospital Pedro Hispano – Unidade Local de Saúde de Matosinhos, Portugal

José Ferreira Penêda
Hospital Pedro Hispano – Unidade Local de Saúde de Matosinhos, Portugal

Correspondence:
Diogo Cunha-Cabral
diogo.cabral08@outlook.com

Article received on November 3, 2025.
Accepted for publication on February 16, 2026.

Abstract

Objectives: Creation of a diagnostic algorithm for cases of head and neck squamous cell carcinoma with an unknown primary tumor.
Materials and Methods: A narrative literature review was conducted in PubMed and Scopus in June 2025, focusing on studies addressing the diagnostic approach to head and neck squamous cell carcinoma with an unknown primary tumor.
Results: The proposed protocol begins with viral stratification through p16 and EBER testing on lymph node biopsy specimens, followed by a sequential diagnostic workflow guided by these results, incorporating functional imaging with PET-CT prior to performing biopsies of suspicious sites. In EBER-negative cases, systematic surgical exploration of the upper aerodigestive tract is recommended and, in the absence of suspicious lesions, should be complemented by bilateral palatine tonsillectomy and ipsilateral tongue base mucosectomy. In EBER-positive cases, the diagnostic focus is directed toward the nasopharynx, with magnetic resonance imaging.
Conclusions: Implementing a systematic approach in cases of squamous cell carcinoma presenting as cervical lymph node metastases with an unknown primary may optimize resource utilization and enhance the identification rate of the primary tumor.

Keywords: Head and neck cancer, Squamous cell carcinoma, Occult primary tumor

Introduction

Approximately 50% of patients with head and neck squamous cell carcinoma (SCC) present with metastatic cervical lymphadenopathy at diagnosis, which is often the reason for the initial medical consultation[1]. In such cases, efforts should focus on identifying the primary tumor in order to enable more targeted treatment, thereby increasing the likelihood

of disease control and reducing treatment-related morbidity[2,3]. Furthermore, knowledge of the primary tumor location facilitates post-treatment surveillance [3]. Despite efforts to identify the primary tumor, its location remains unknown in 2% to 5% of cases[4], constituting a diagnosis of head and neck SCC of unknown primary (CUP) [3]. In recent years, there has been an increase in these cases, which may be linked to the increasing incidence of oropharyngeal SCC associated with the human papillomavirus (HPV)[5].

Recently, several studies have been published regarding the role of different ancillary diagnostic tests and procedures in locating the primary tumor in cases of CUP [5]. Although a larger and more diverse amount of diagnostic tools is currently available, their incorrect use can be costly and lead to diagnostic errors and delays[6,7]. Therefore, a systematic diagnostic approach is essential to ensure the effective and efficient use of resources for the patient's benefit. In this paper, we propose a diagnostic algorithm for use in CUP cases.

Materials and Methods

To develop the algorithm, a literature review was conducted in June 2025 on PubMed (Medline) using the following search string: ("Carcinoma, Squamous Cell"[Mesh] OR "squamous cell carcinoma"[tiab]) AND ("Head and Neck Neoplasms"[Mesh] OR "head and neck cancer"[tiab] OR "head and neck neoplasms"[tiab]) AND ("Neoplasms, Unknown Primary"[Mesh] OR "unknown primary"[tiab] OR "occult primary"[tiab]) AND ("Diagnosis"[Mesh] OR diagnosis[tiab] OR "diagnostic algorithm" [tiab] OR "workup"[tiab]). Scopus was also searched for articles using similar terms.

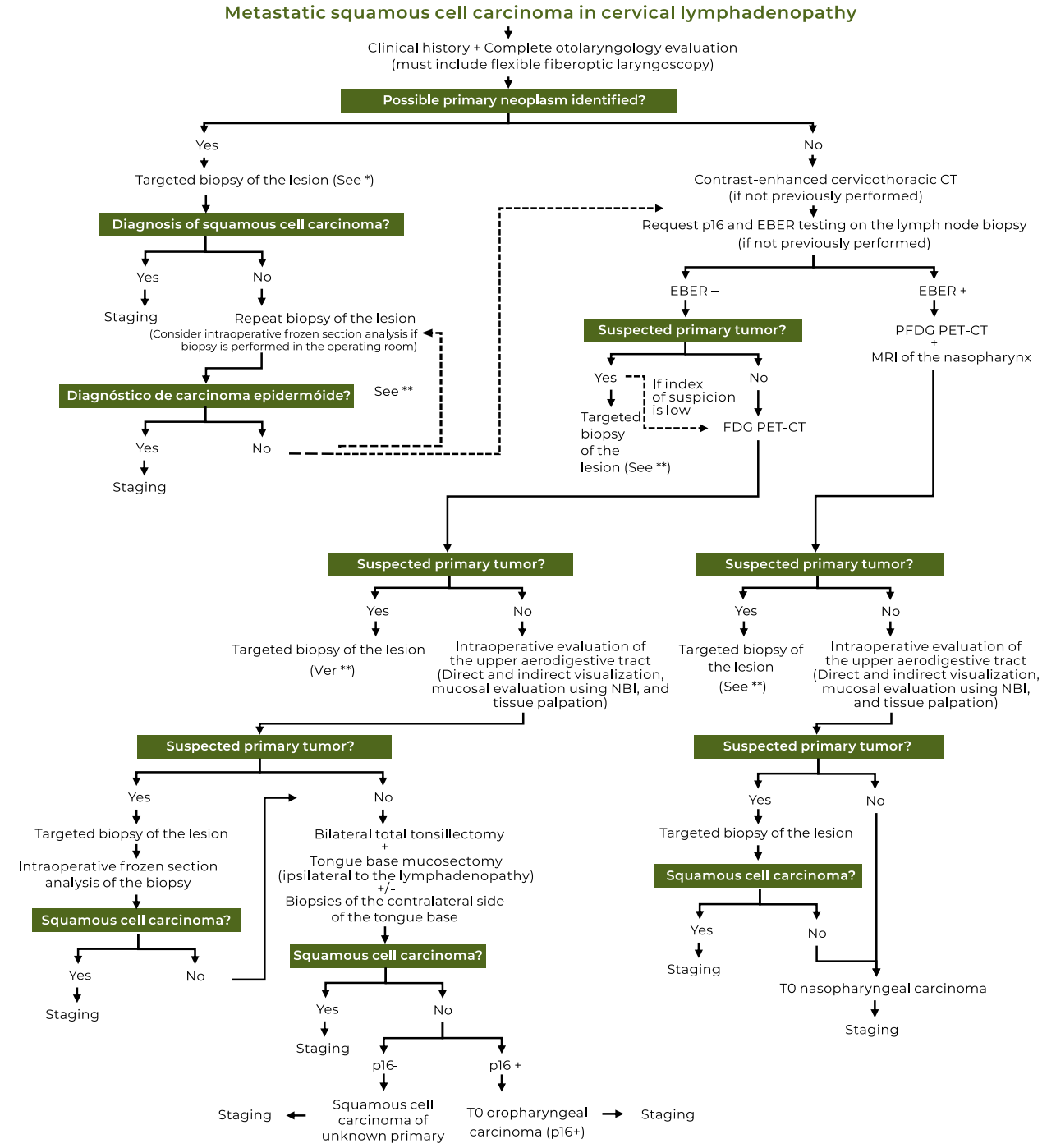
Original studies, systematic reviews, meta-analyses, and consensus recommendations relevant to the diagnostic approach to occult primary tumors of the head and neck in the adult population published in English were included. Isolated case reports and case series with a small number of patients were excluded. No time restriction was applied.

The articles were selected independently by two authors, with any discrepancies resolved by consensus among all the authors. The initial search yielded a total of 576 articles, and following a careful review of the abstracts, 53 articles were selected for inclusion in the analysis. Based on a critical evaluation of these articles, a diagnostic algorithm was developed from scratch by the primary author. After it was reviewed by the other authors, modifications were proposed to be incorporated into it. The final version of the algorithm was decided by a consensus.

Results

Figure 1 presents the proposed diagnostic algorithm for cases of SCC of the head and neck with an unknown primary tumor. Upon diagnosis of SCC in a cervical lymph node, the patient should undergo a complete clinical evaluation by an otolaryngologist. If the primary tumor is not identified at this stage, the case is classified as a CUP, and an initial imaging evaluation should be conducted using cervicothoracic contrast-enhanced computed tomography (CT). Subsequently, systematic testing for viral markers in the lymph node sample is recommended—specifically for p16 protein and EBV-encoded RNA (EBER). This permits for an initial stratification of patients into two main groups: EBER-negative and EBER-positive. In EBER-negative cases, the diagnostic workup proceeds with an 18F-fluorodeoxyglucose positron emission tomography scan combined with computed tomography (PET-CT), ideally before conducting biopsies of any suspicious areas. If no primary lesions are evident, a systematic intraoperative evaluation of the upper aerodigestive tract is indicated, preferably using narrow-band imaging (NBI). If no suspicious lesions are found, the evaluation should be supplemented by a bilateral total tonsillectomy and an ipsilateral tongue base mucosectomy to search for a potential primary tumor in these locations. If the histology of the specimens does not reveal SCC, the initial p16 status should be considered: if negative, the case is classified

Figure 1
Proposed diagnostic algorithm for head and neck squamous cell carcinoma cases of unknown primary origin



* Performance in the operating room depends on the lesion's location and patient cooperation
** Ideally performed in the operating room with intraoperative frozen section analysis

In all biopsies:
-If oropharyngeal lesion – request p16 testing
-If nasopharyngeal lesion – request EBER testing

as a true occult primary tumor; if positive, it is classified as a T0 oropharyngeal carcinoma.

For EBER-positive cases, the diagnostic algorithm focuses primarily on the nasopharynx. In these cases, a PET-CT scan is recommended, along with targeted magnetic resonance imaging (MRI) of the nasopharynx. If the primary tumor is not identified, an intraoperative evaluation of the upper aerodigestive tract is conducted; however, tonsillectomy and tongue base mucosectomy are not required, as a nasopharyngeal origin (T0 nasopharyngeal carcinoma) is presumed.

Discussion

The presented algorithm begins once a diagnosis of SCC in a cervical lymph node has been confirmed via fine-needle aspiration (FNA) or core-needle biopsy (CNB). In this scenario, the patient should undergo an otolaryngology evaluation, which must include a detailed clinical history and a comprehensive physical examination, including flexible fiberoptic laryngoscopy[7]. If no suspicious lesion is identified at this stage, the CUP diagnostic pathway should be followed.

All patients with CUP should undergo an initial imaging evaluation focused on the head and neck. This is typically performed using contrast-enhanced CT, a widely available, fast, and relatively inexpensive imaging modality that can help identify suspicious areas and guide biopsies[3,7]. MRI provides better soft-tissue characterization and is less prone to dental artifacts than CT[8]; however, it requires a longer acquisition time and is more susceptible to motion artifacts (e.g., swallowing and breathing) [9]. Furthermore, MRI may be less accessible and carries higher associated costs.

CT also accurately characterizes the extent of nodal disease and identifies distant metastatic lesions[8]. For this reason, as it may be useful later during the staging phase, we decided to include the thoracic region in the initial imaging evaluation to avoid delays associated with conducting additional imaging studies.

A fundamental step in the diagnostic approach is testing for viral markers in the lymph node biopsy, specifically those associated with high-risk HPV and Epstein-Barr virus (EBV) infections.

High-risk HPV is strongly associated with oropharyngeal SCC, typically leading to a distinct clinical presentation characterized by small primary tumors and advanced nodal disease at diagnosis, often resulting in a CUP diagnosis[10]. Indeed, in the vast majority of cases of high-risk HPV-associated SCC diagnosed in cervical lymphadenopathy with CUP, the primary tumor is subsequently identified in the oropharynx, highlighting the importance of HPV testing in CUP cases[11-13]. Currently, high-risk HPV testing is recommended for nodal metastases at levels II and III, as these are most frequently affected by HPV-associated oropharyngeal SCC[7]; however, cases of cervical nodal metastasis at other levels have also been reported[14]. Therefore, we recommend this evaluation for lymphadenopathy at all cervical levels.

The p16 protein is a sensitive marker for high-risk HPV infection. Its expression can be evaluated via immunohistochemistry in samples collected by FNA or CNB and is frequently used as an initial screening method for high-risk HPV[7]. Despite its high sensitivity, p16 has lower specificity; therefore, additional confirmatory tests, such as HPV DNA testing by PCR, may be recommended[14].

The association between EBV and nasopharyngeal SCC is well-established[15]. EBV is the primary etiological factor for undifferentiated nasopharyngeal SCC, which is the most prevalent subtype in endemic regions[3]. Although Portugal is not considered an endemic area, undifferentiated nasopharyngeal SCC is still the most frequent subtype in that country[16], with an EBV infection detected in approximately 85% of cases[17]. This type of nasopharyngeal SCC typically presents with small primary lesions that may be located in the submucosal areas, which can lead to a diagnosis of CUP[3,16].

EBV can be identified in tissue obtained via FNA or CNB, with EBER *in situ* hybridization being

the most commonly used method[7]. Testing is currently recommended for CUP cases in which p16 testing is negative[7]. Considering the lengthy turnaround times and to prevent delays in diagnosis and treatment, we suggest simultaneous p16 and EBER testing during the initial lymph node biopsy. A positive EBER result strongly suggests that the primary tumor is located in the nasopharynx; however, EBV can also be detected in lymph nodes from other primary tumor sites [18]. Although rare, these cases should be considered during the diagnostic workup for CUP (*vide infra*). Conversely, a negative result does not entirely rule out the possibility of a nasopharyngeal primary tumor[3].

Based on the viral marker results, particularly the EBER results, the algorithm is divided into two branches: EBER-positive CUP cases and EBER-negative CUP cases.

EBER-negative CUP:

Several studies have revealed the importance of positron emission tomography with 18F-fluorodeoxyglucose (PET) in the diagnostic approach to CUP cases[7]. PET identifies tissues with an increased glucose uptake, which typically occurs with malignant tumors. Combining information on the metabolic activity of tissues obtained by PET with the anatomical detail of CT images (PET-CT) increases the ability to identify lesions and assess their nature (benign vs. malignant)[19,20].

PET-CT detects the primary tumor in 24.5% to 42.5% of CUP cases in which physical examination and other imaging methods (CT and/or MRI) were negative[7,21,22]. This diagnostic tool does not have very high sensitivity (79.2% to 91.5%)[22,23], resulting in a high rate of false negatives, especially for small lesions. Therefore, a negative result should not preclude further diagnostic workup to identify the primary tumor. Furthermore, its specificity is not high (70.4% to 87%) [23,24], which can lead to false positives. Some false positives occur due to increased metabolism in previously biopsied tissues. Consequently, whenever possible, if there is a low suspicion regarding a primary tumor location indicated by another diagnostic tool, biopsies should only be performed after the PET-CT scan[25,26].

If PET-CT fails to identify a possible primary lesion, an intraoperative evaluation of the upper aerodigestive tract must be performed. This evaluation should include the nasal cavities, nasopharynx, oral cavity, oropharynx, hypopharynx, larynx, and esophagus. Direct inspection of some of these regions with an endoscope can be advantageous, particularly when using the NBI technique[7]. NBI improves visualization of vascular patterns in both the mucosa and submucosa, helping to identify small lesions that may not be visible with other methods and guiding biopsies[27]. A systematic review and meta-analysis by Di Maio et al. revealed that the use of NBI allowed for the identification of the primary tumor in approximately 35% of CUP cases in which white-light endoscopy and imaging methods (CT and/or MRI) were negative[27]. Considering its ease and speed of use, we indicate its use during the intraoperative evaluation of the upper aerodigestive tract.

If suspicious lesions are found during the intraoperative evaluation of the upper aerodigestive tract, they must be biopsied, and an intraoperative frozen section analysis of the collected samples is recommended.

Several studies have shown that, with the exception of the oropharynx, performing blind biopsies of non-suspicious areas has an extremely low diagnostic yield[18,28], and is therefore not recommended[3,7]. Thus, if no suspicious lesions are identified or if the intraoperative frozen section analysis is negative, the diagnostic approach should proceed with sampling the oropharynx. Indeed, in most CUP cases in which the primary is eventually identified, it is located in the oropharynx. In a sample of 236 CUP cases, Cianchetti et al. identified the primary tumor in the tonsillar fossa in 44.7% of cases and in the base of the tongue in 43.9%[29], which justifies sampling these locations even if no lesions are clinically evident.

Total tonsillectomy yields a higher primary

tumor identification rate than incisional biopsies of the palatine tonsil (29%-39% vs. 3.2%-13%); therefore, it should be the preferred method for obtaining tissue samples from the palatine tonsil[30]. There is no consensus in the literature regarding whether unilateral (ipsilateral to the affected lymph node) or bilateral total tonsillectomy is the ideal procedure. However, previous studies show that bilateral total tonsillectomy allows the identification of synchronous tumors in both tonsils or a primary tumor in the tonsil contralateral to the adenopathy in 10%-23% of cases[30-32]. Considering the acceptable increase in the risk of complications, we have chosen to include bilateral total tonsillectomy in this protocol. Mucosectomy has proven to be an extremely effective method for sampling the base of the tongue, with a 78% primary tumor detection rate in patients whose previous diagnostic workup yielded negative results (physical exam, CT/MRI, PET-CT, and total tonsillectomy)[33]. The procedure involves a complete resection of the mucosa at the base of the tongue ipsilateral to the affected lymph node, extending from the midline to the lateral pharyngeal wall and from the circumvallate papillae to the vallecula, using the tongue's muscular layer as the deep surgical margin[34]. Previous studies show that bilateral mucosectomy enabled the identification of synchronous tumors on both sides of the tongue base in only 0.69% of cases and a primary tumor on the side contralateral to the affected lymph node in 1.85% of CUP cases[33]. Consequently, considering the lack of clear benefits and a possible higher risk of complications such as odynophagia and dysphagia, we decided to include only unilateral mucosectomy of the ipsilateral tongue base in our algorithm. This procedure is implemented during the same operative session as the intraoperative evaluation of the upper aerodigestive tract and bilateral total tonsillectomy; therefore, it does not depend on the tonsils' histological results. A staged approach— performing bilateral total tonsillectomy first and the tongue base mucosectomy in a second surgery—could theoretically reduce surgical morbidity by avoiding tongue base mucosectomy if the primary tumor is found in the tonsils. However, in our experience, conducting both procedures together is generally well-tolerated. It spares the patient from two similar recovery periods in a short timeframe and the associated post-surgery care, risks, and symptoms. Additionally, the combined approach optimizes the use of time and resources. If the histopathological results from the palatine tonsils and the tongue base mucosa ipsilateral to the affected lymph node show no evidence of a primary tumor in these locations, the final diagnosis depends on high-risk HPV (p16) infection markers in the initial lymph node biopsy. In the absence of p16 expression, the case is classified as a true SCC of occult primary tumor. Conversely, p16 positivity strongly indicates an oropharyngeal origin; these cases should be classified as T0 oropharyngeal carcinoma[35], though confirmatory HPV DNA PCR testing is recommended[36]. This diagnostic approach allows for treatment de-escalation, reducing radiotherapy-related morbidity. Some studies show that in these cases, limiting treatment to the cervical region and oropharynx yields good locoregional control and overall survival with lower morbidity[7,37]. However, as evidence remains limited, therapeutic strategies should be determined on a case-by-case basis within a multidisciplinary team.

EBER-positive CUP:

As previously mentioned, EBER positivity is highly suggestive of a primary tumor located in the nasopharynx. In such cases, attention should initially focus on this region.

In these cases, we always indicate performing a PET-CT scan. Beyond its previously mentioned ability to identify suspicious areas, this scan also plays an important role in staging.

Nasopharyngeal MRI has high sensitivity and specificity for detecting nasopharyngeal lesions[38], enabling the identification of small early or submucosal lesions even if they are not endoscopically visible[39]. For this reason,

we decided to include it for all patients with EBER+ CUP. If the physical examination, initial cervicothoracic CT, PET-CT, and MRI do not reveal any suspicious lesions in the nasopharynx, an intraoperative evaluation of the upper aerodigestive tract is recommended, as previously described. Although rare, EBER+ head and neck CUP cases have been identified in locations other than the nasopharynx[40], and these possibilities must be ruled out.

However, tonsillectomy and tongue base mucosectomy are not considered necessary in these cases. Therefore, if no suspicious lesions are identified during intraoperative evaluation of the upper aerodigestive tract, the nasopharynx is presumed to be the site of origin (T0 nasopharyngeal carcinoma).

Conclusion

Cases of head and neck SCC with an unknown primary tumor often pose a diagnostic challenge. Although a wide range of diagnostic tools is currently available, their inappropriate use can lead to contradictory results, delayed diagnosis and treatment, and unnecessary costs. A systematic diagnostic approach in these cases can optimize the use of available resources and contribute to improved patient outcomes.

Conflicts of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

Data Confidentiality

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

Protection of humans and animals

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the 2013 Helsinki Declaration of the World Medical Association.

Privacy policy, informed consent and Ethics Committee Authorization

The authors declare that they have written consent for the use of photographs of patients in this article.

Funding Sources

This work did not receive any contribution, funding or scholarship.

Availability of scientific data

There are no datasets available, publicly related to this work.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used the artificial intelligence platform OpenEvidence for literature research. Following the use of this tool/service, the authors reviewed and edited the content as necessary and assume full responsibility for the content of the publication.

Referências bibliográficas

1. Xing Y, Zhang J, Lin H, Gold KA, Sturgis EM, Garden AS. et al. Relation between the level of lymph node metastasis and survival in locally advanced head and neck squamous cell carcinoma. Cancer. 2016 Feb 15;122(4):534-45. doi: 10.1002/cncr.29780.
2. Hosni A, Dixon PR, Rishi A, Au M, Xu W, Song Y. et al. Radiotherapy characteristics and outcomes for head and neck carcinoma of unknown primary vs T1 base-of-tongue carcinoma. JAMA Otolaryngol Head Neck Surg. 2016 Dec 1;142(12):1208-1215. doi: 10.1001/jamaoto.2016.3083.
3. Manoharan M, Kalman NS, Rabinowits G. Head and neck squamous cell carcinoma of unknown primary: a diagnostic work-up. Oncologist. 2024 Mar 4;29(3):192-199. doi: 10.1093/oncolo/oyad311.
4. Grau C, Johansen LV, Jakobsen J, Geertsen P, Andersen E, Jensen BB. 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 May;55(2):121-9. doi: 10.1016/s0167-8140(00)00172-9.
5. Golusinski P, Di Maio P, Pehlivan B, Colley S, Nankivell P, Kong A. et al. Evidence for the approach to the diagnostic evaluation of squamous cell carcinoma occult primary tumors of the head and neck. Oral Oncol. 2019 Jan:88:145-152. doi: 10.1016/j.oraloncology.2018.11.020.
6. Alzahrani F, Sahovaler A, Mundi N, Rammal A, Fnais N, MacNeil SD. et al. Transoral robotic surgery for the identification of unknown primary head and neck squamous cell carcinomas: its effect on the wait and the weight. Head Neck. 2022 May;44(5):1206-1212. doi: 10.1002/

hed.27023
7. Maghami E, Ismaila N, Alvarez A, Chernock R, Duvvuri U, Geiger J, et al. Diagnosis and management of squamous cell carcinoma of unknown primary in the head and neck: ASCO guideline. J Clin Oncol. 2020 Aug 1;38(22):2570-2596. doi: 10.1200/JCO.20.00275.
8. Masuoka S, Hiyama T, Kuno H, Sekiya K, Sakashita S, Kobayashi T. Imaging approach for cervical lymph node metastases from unknown primary tumor. Radiographics. 2023 Mar;43(3):e220071. doi: 10.1148/rg.220071.
9. Havsteen I, Ohlhues A, Madsen KH, Nybing JD, Christensen H, Christensen A. Are movement artifacts in magnetic resonance imaging a real problem?-A narrative review. Front Neurol. 2017 May 30:8:232. doi: 10.3389/fneur.2017.00232.
10. Motz K, Qualliotine JR, Rettig E, Richmon JD, Eisele DW, Fakhry C. 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 Mar;142(3):223-8. doi: 10.1001/jamaoto.2015.3228.
11. Park JM, Jung CK, Choi YJ, Lee KY, Kang JH, Kim MS. et al. The use of an immunohistochemical diagnostic panel to determine the primary site of cervical lymph node metastases of occult squamous cell carcinoma. Hum Pathol. 2010 Mar;41(3):431-7. doi: 10.1016/j.humpath.2009.09.001.
12. Vent J, Haidle B, Wedemeyer I, Huebbers C, Siefer O, Semrau R. et al. p16 expression in carcinoma of unknown primary: diagnostic indicator and prognostic marker. Head Neck. 2013 Nov;35(11):1521-6. doi: 10.1002/hed.23190.
13. Graboyes EM, Sinha P, Thorstad WL, Rich JT, Haughey BH. Management of human papillomavirus–related unknown primaries of the head and neck with a transoral surgical approach. Head Neck. 2015 Nov;37(11):1603-11. doi: 10.1002/hed.23800.
14. Lewis Jr JS, Beadle B, Bishop JA, Chernock RD, Colasacco C, Kalicanin T. et al. Human papillomavirus testing in head and neck carcinomas: guideline update. Arch Pathol Lab Med. 2025 Jun 1;149(6):e115-e150. doi: 10.5858/arpa.2024-0388-CP.
15. Altekin I, Taş A, Yalcin O, Guven SG, Aslan Z, Adali MK. et al. Frequency of Epstein-Barr virus and human papilloma virus in patients with nasopharyngeal carcinoma. Eur Arch Otorhinolaryngol. 2020 Jul;277(7):2041-2047. doi: 10.1007/s00405-020-05907-x.
16. Eduardo B, Raquel C, Rui M. Nasopharyngeal carcinoma in a south European population: epidemiological data and clinical aspects in Portugal. Eur Arch Otorhinolaryngol. 2010 Oct;267(10):1607-12. doi: 10.1007/s00405-010-1258-3.
17. Breda E, Queirós A, Moniz C, Ferreira V, Palmeira C, Pinto D. Detecção do virus Epstein-Barr no carcionoma indiferenciado da nasofaringe em Portugal-zona Norte. Rev Port ORL. 2001;39:363-8.
18. Bowe CM, Garg M. The role of non-oropharyngeal biopsies in head and neck squamous cell carcinoma of unknown primary: a systematic review. Clin Otolaryngol. 2024 Sep;49(5):531-537. doi: 10.1111/coa.14157.
19. von Schulthess GK, Steinert HC, Hany TF. Integrated PET/CT: current applications and future directions. Radiology. 2006 Feb;238(2):405-22. doi: 10.1148/radiol.2382041977.
20. Yeung HW, Schöder H, Smith A, Gonen M, Larson SM. Clinical value of combined positron emission tomography/computed tomography imaging in the interpretation of 2-deoxy-2-[F-18]fluoro-D-glucose-positron emission tomography studies in cancer patients. Mol Imaging Biol. 2005 May-Jun;7(3):229-35. doi: 10.1007/s11307-005-4113-y.
21. Rusthoven KE, Koshy M, Paulino AC. The role of fluorodeoxyglucose positron emission tomography in cervical lymph node metastases from an unknown primary tumor. Cancer. 2004 Dec 1;101(11):2641-9. doi: 10.1002/cncr.20687.
22. Han A, Xue J, Hu M, Zheng J, Wang X. Clinical value of 18F-FDG PET-CT in detecting primary tumor for patients with carcinoma of unknown primary. Cancer Epidemiol. 2012 Oct;36(5):470-5. doi: 10.1016/j.canep.2012.03.002.
23. Deonarine P, Han S, Poon F, de Wet C. The role of 18F-fluoro-2-deoxyglucose positron emission tomography/computed tomography in the management of patients with carcinoma of unknown primary. Scott Med J. 2013 Aug;58(3):154-162. doi: 10.1177/0036933013496958.
24. Mani N, George MM, Nash L, Anwar B, Homer JJ. Role of 18-Fludeoxyglucose positron emission tomography-computed tomography and subsequent panendoscopy in head and neck squamous cell carcinoma of unknown primary. Laryngoscope. 2016 Jun;126(6):1354-8. doi: 10.1002/lary.25783
25. Rudmik L, Lau HY, Matthews TW, Bosch JD, Kloiber R, Molnar CP. et al. Clinical utility of PET/CT in the evaluation of head and neck squamous cell carcinoma with an unknown primary: a prospective clinical trial. Head Neck. 2011 Jul;33(7):935-40. doi: 10.1002/hed.21566.
26. Johansen J, Buus S, Loft A, Keiding S, Overgaard M, Hansen HS. 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 Apr;30(4):471-8. doi: 10.1002/hed.20734.
27. Di Maio P, Iocca O, De Virgilio A, Giudice M, Pellini R, D'Ascanio L. et al. Narrow band imaging in head and neck unknown primary carcinoma: a systematic review and meta-analysis. Laryngoscope. 2020 Jul;130(7):1692-1700. doi: 10.1002/lary.28350.
28. Tanzler ED, Amdur RJ, Morris CG, Werning JW, Mendenhall WM. Challenging the need for random directed biopsies of the nasopharynx, pyriform sinus, and contralateral tonsil in the workup of unknown primary squamous cell carcinoma of the head and neck. Head Neck. 2016 Apr;38(4):578-81. doi: 10.1002/hed.23931.
29. Cianchetti M, Mancuso AA, Amdur RJ, Werning JW, Kirwan J, Morris CG. et al. Diagnostic evaluation of squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site. Laryngoscope. 2009 Dec;119(12):2348-54. doi: 10.1002/lary.20638.
30. Koch WM, Bhatti N, Williams MF, Eisele DW. Oncologic rationale for bilateral tonsillectomy in head and neck squamous cell carcinoma of unknown primary source. Otolaryngol Head Neck Surg. 2001 Mar;124(3):331-3. doi: 10.1067/mhn.2001.114309.
31. Lindberg R. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer. 1972 Jun;29(6):1446-9. doi: .1002/1097-0142(197206)29:6<1446::aid-

cncr2820290604>3.0.co;2-c.
32. Kothari P, Randhawa PS, Farrell R. Role of tonsillectomy in the search for a squamous cell carcinoma from an unknown primary in the head and neck. Br J Oral Maxillofac Surg. 2008 Jun;46(4):283-7. doi: 10.1016/j.bjoms.2007.11.017.
33. Farooq S, Khandavilli S, Dretzke J, Moore D, Nankivell PC, Sharma N. 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 Apr:91:97-106. doi: 10.1016/j.oraloncology.2019.02.018.
34. Fu TS, Foreman A, Goldstein DP, de Almeida JR. The role of transoral robotic surgery, transoral laser microsurgery, and lingual tonsillectomy in the identification of head and neck squamous cell carcinoma of unknown primary origin: a systematic review. J Otolaryngol Head Neck Surg. 2016 May 4;45(1):28. doi: 10.1186/s40463-016-0142-6.
35. Doescher J, Veit JA, Hoffmann TK. [The 8th edition of the AJCC Cancer Staging Manual: Updates in otorhinolaryngology, head and neck surgery]. HNO. 2017 Dec;65(12):956-961. doi: 10.1007/s00106-017-0391-3.
36. Mehanna H, Taberna M, von Buchwald C, Tous S, Brooks J, Mena M. et al. Prognostic implications of p16 and HPV discordance in oropharyngeal cancer (HNCIG-EPIC-OPC): a multicentre, multinational, individual patient data analysis. Lancet Oncol. 2023 Mar;24(3):239-251. doi: 10.1016/S1470-2045(23)00013-X.
37. Chen AM, Meshman J, Hsu S, Yoshizaki T, Abemayor E, John MS. Oropharynx-directed ipsilateral irradiation for p16-positive squamous cell carcinoma involving the cervical lymph nodes of unknown primary origin. Head Neck. 2018 Feb;40(2):227-232. doi: 10.1002/hed.24906.
38. Gorolay VV, Niles NN, Huo YR, Ahmadi N, Hanneman K, Thompson E. et al. MRI detection of suspected nasopharyngeal carcinoma: a systematic review and meta-analysis. Neuroradiology. 2022 Aug;64(8):1471-1481. doi: 10.1007/s00234-022-02941-w.
39. King AD, Woo JKS, Ai QY, Chan JSM, Lam WKJ, Tse IOL. et al. Complementary roles of MRI and endoscopic examination in the early detection of nasopharyngeal carcinoma. Ann Oncol. 2019 Jun 1;30(6):977-982. doi: 10.1093/annonc/mdz106.
40. Luo WJ, Feng YF, Guo R, Tang LL, Chen L, Zhou GQ. et al. Patterns of EBV-positive cervical lymph node involvement in head and neck cancer and implications for the management of nasopharyngeal carcinoma T0 classification. Oral Oncol. 2019 Apr:91:7-12. doi: 10.1016/j.oraloncology.2019.01.012