PET/CT Evaluation of Head and Neck Cancer of Unknown Primary

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The diagnosis of carcinoma of unknown primary in the head and neck is made when there is a metastasis but no primary lesion is identified after physical exam and diagnostic CT or MR imaging. PET/CT is the first step in searching for a primary lesion, followed by more invasive techniques such as endoscopy and surgery. Knowledge of the different tumor histologic types, preferential locations of nodal spread, imaging pitfalls, and other special considerations such as cystic metastases can be helpful in the ultimate identification of primary tumors, which leads to improved overall patient survival.
Semin Ultrasound CT MRI 40:414-423 © 2019 Elsevier Inc. All rights reserved.

Introduction

Definition of CUP

The determination of carcinoma of unknown primary (CUP) in the head and neck (HNCUP) is made when there is a histologically confirmed metastatic lesion (usually within a cervical lymph node) without a primary tumor identified by physical examination and diagnostic CT or MRI.[1,2] The pathophysiology behind why primary malignancies cannot be determined is not clear; however, possible theories include regression of the primary tumor, small lesion size with a slow growth rate, or histologic and genetic differences between the primary tumor and metastasis. Risk factors for HNCUP are the same for squamous cell head and neck cancer including male gender, older age (median 60 years), tobacco and alcohol use, and positive human papilloma virus (HPV) status.[3,4]

Discussion

Epidemiology, Incidence, and Prognosis of HNCUP

Studies have shown that diagnostic CT or MRI can only detect the primary site of disease in 10%-35% of first presentation metastatic cervical lymph node cases.[5,6] Many early studies suggested that FDG-PET/CT has a sensitivity for determining primary site location in 25%-53% of HNCUP.[5-11] More recent studies indicate a higher success rate of PET/CT in the detection of primary lesions from 66% to 87% with up to one-third of the patients undergoing subsequent changes in management strategy after a primary lesion is identified.[2,9,12,13] The increased rate of detection could be attributed to advances in PET/CT scanner technology; however, more large-scale data are needed to confirm these rates. Regardless, PET/CT has been widely accepted as the next step in search for a primary tumor followed by more invasive techniques such as panendoscopy (laryngoscopy, nasal endoscopy, and rigid esophagoscopy), bilateral tonsillectomy, and potential nontargeted radiation if the primary tumor has not been identified with other methods (see Fig 1).

Approximately 3%-14% of patients with palpable metastatic lymph nodes of the head and neck end their extensive work-up with a true diagnosis of CUP.[9,14,15] Newer studies from 2015 have shown the incidence is likely in the lower end of the range (2%-5%) due to advances in imaging technique and transoral surgical methods.[14] Greater than 65% of HNCUP tumors are squamous cell carcinomas (SCCs), followed by adenocarcinomas, undifferentiated tumors, and neuroendocrine tumors.[4] The number of overall HNCUP cases has increased over the past few decades likely related to an increase in HPV related cancers.[16]

The advantages of localizing a primary lesion in any CUP are well established, with vital effects on both treatment planning and prognosis including fewer treatment-related side effects. These benefits substantiate the need for an exhaustive search of a primary site. Several studies have shown that CUPs

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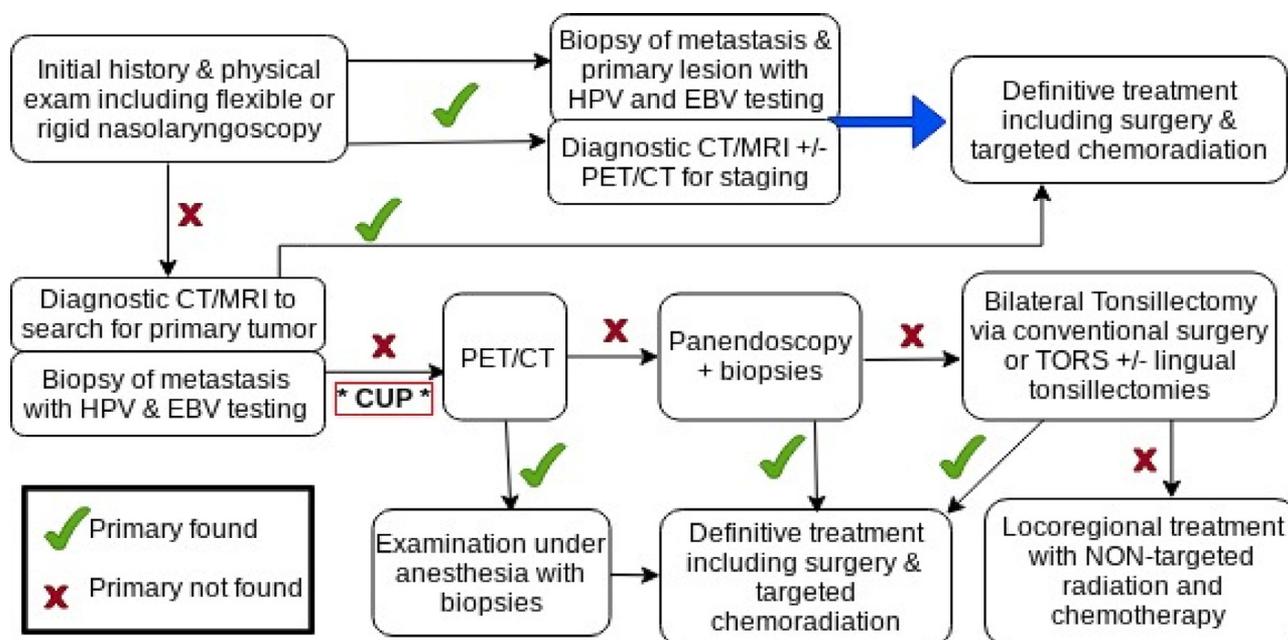
Figure 1 Typical diagnostic timeline and algorithm for evaluating HNCUP.

in general have poor prognosis with patients often having less than 1 year life expectancy.[9] While HNCUPs tend to have better overall survival than other causes of CUP, they do not quite match the curative success rate of known primary tumors of the head and neck. However, prognosis for HNCUP continues to improve with reports of 58% 3-year survival prior to the year 2000 and up to 74% 3-year survival by 2011.[3,16,17] The improved prognosis of HNCUP is partly due to the use of locoregional surgical/treatment strategies and the increasing number of responsive HPV positive tumors.

Typical Clinical Timeline

The initial physical exam includes direct visualization and palpation to localize a lesion. Endoscopic evaluation with both rigid and flexible scopes may also be performed during the initial clinical exam. While there is no international consensus for working up CUP lesions, the American Head and Neck Society and United Kingdom National Multidisciplinary Guidelines committee have developed recommendations[18,19] regarding the typical clinical algorithm for assessing HNCUP (summarized in Fig 1).

When imaging fails to detect a primary lesion, more invasive methods are utilized in a progressive order including panendoscopy with directed biopsies, bilateral palatine tonsillectomy, and possible tongue base mucosectomy (lingual tonsillectomy).[6,20] PET/CT is strongly encouraged prior to endoscopy due to a 50% false positive rate when PET/CT is performed postoperatively.[11,18]

The majority (85%) of cervical metastatic lymph nodes originate from tumors in the head and neck, with 90% of the primary sites of disease ultimately found in the oropharynx (palatine tonsils or base of tongue). For this reason, panendoscopy and tonsillectomies are performed when PET/CT fails to reveal a primary tumor.[5,14,16,21] Other potential primary

sites of HNCUP include the vertex of the scalp, bilateral external auditory meati, nasal vestibule, oral cavity, nasopharynx, hypopharynx, and larynx with extension into the distal esophagus. A step-wise approach for diagnostic evaluation has been supported by results from a few studies in which primary lesions were detected during panendoscopy in 9%-31% of patients who had a negative PET/CT.[10,11] Many centers also advocate for bilateral tonsillectomies as opposed to ipsilateral tonsillectomies due to a possibility of occult contralateral tonsillar tumors which occur in 6%-25% of HNCUP cases.[14,16,22] Bilateral tonsillectomies also reduce false-positive rates on post-treatment follow-up PET/CTs due to lack of confounding physiological uptake.

Some institutions also perform base of tongue mucosal resections in the setting of HPV positive metastases with some success increasing diagnostic yield, although this is not yet widely accepted.[15] A few investigators also reported increased rates of primary tumor detection when using transoral robotic surgery or transoral laser surgery to perform tonsillectomies and base of tongue resections instead of conventional techniques. Detection rates of primary tumor when using transoral robotic surgery varies between 25% and 50% when following a negative PET/CT.[16,22,23]

Typical 18F-FDG PET/CT Protocol

18F-FDG PET/CT imaging takes advantage of the upregulation of GLUT-1 transporters occurring in tumor cells which provides a measurable difference between normal and abnormal tissue for localization of primary sites and extent of disease.[24] Patients generally receive 10-17 mCi of intravenous 18F-FDG and then rest quietly for a period of time prior to scanning.[25,26] Although the European Association of Nuclear Medicine guidelines recommend a 60-minute uptake period, the duration of quiet rest between injection of FDG tracer

and initiation of the scan varies widely ranging from 45 minutes to 90 minutes.[1,24-31] Some studies have shown that about 10 minutes is the optimal image acquisition time because of decreased background noise, increased lesion detection rate, and reduced time in the scanner (thus higher patient turnaround).[29]

Contrast Enhanced CT (CECT) vs Noncontrast CT for PET/CT

Traditionally, most centers use unenhanced CTs for attenuation correction purposes, but routine administration of intravenous contrast for head and neck PET/CT has become more common and takes advantage of the superior performance of diagnostic CECT in detection of small mucosal tumors. Most facilities performing CECT with PET use between 60 mL and 125mL nonionic contrast with a 30−40-second delay before imaging.[5,26,27,32] A few institutions even utilize a split dose of intravenous contrast, one for the dedicated head and neck PET and another for the whole body portion.[5] Although 1 study from 2009 found no significant difference in lesion detection in PET/CT with or without intravenous contrast, this study heavily relied on PET images for diagnosis and used a 90-second delay for the CT portion of the exam which may have affected sensitivity. The advantages of contrast in diagnostic neck CTs is well known with superior lesion detection rate, which argues strongly for use of diagnostic contrast-enhanced neck CTs with PET imaging. The potential disadvantages of intravenous contrast in PET/CT are the potential for errors in attenuation correction (leading to artifacts on PET imaging), potential allergic reaction, and added cost. However, in the setting of HNCUP the advantages of contrast likely greatly outweigh these risks.

Dual Time Point FDG-PET/CT Imaging

Delayed head and neck PET/CT images are commonly obtained after whole body imaging. The benefit of dual time point imaging is the ability to expose the difference in uptake of background tissues (which fades over time) and uptake in tumors (which generally increases over time) leading to theoretical higher sensitivity for detecting malignant lesions. While dual time point PET/CT can be helpful for staging tumors and differentiating between malignant and benign lesions, it has mixed results on accurately predicting prognosis for patients with locally invasive disease. In fact, solitary SUVmax measured in the early phase has previously shown a better prognostic value than the percent change in SUVmax on dual time point imaging.[33]

Dedicated Field of View vs Whole Body PET/CT

Whole body PET/CT has decent resolution and is reportedly up to 100% sensitive for lymph nodes greater than 1 cm but is only 23% sensitive for pathologic nodes smaller than

5 mm.[34] Dedicated PET/CT of the head and neck has shown higher sensitivity for detecting metastatic lymph nodes smaller than 15 mm and particularly in those that are 5-10 mm in size (4-fold increased detection) compared to whole body PET/CT.[25,34]

In 2009, Yankevich et al[26] found that patients with SCC of the head and neck (HNSCC) and no thoracic metastases had such a low incidence of metastases in the head or abdomen that the head and abdominal portions of routine PET/CTs for HNSCC are unnecessary. The investigators proposed that patients with HNSCC should undergo limited neck and chest PET/CT in the absence of suspected thoracic metastases. Unfortunately, this approach would miss about 2% of metastatic lesions leading with subsequent nonideal disease management. The advantages to limited PET/CT scanning is the reduction in overall cost, decreased radiation, and decreased scanner time,[26] but these probably do not outweigh the risks of inadequate tumor staging given the potential impact on overall survival.

Whole body PET/CT is useful in head and neck cancers for accurate staging, reportedly diagnosing metastatic disease in 5%-15% of patients and a synchronous primary tumor (usually lung carcinoma) 1%-8% of the time.[16,27,32] Results of PET/CT imaging alters management decisions in up to 80% of head and neck cancer cases. Some case reports have even shown unusual distant metastases from head and neck primaries including diffuse liver metastases from a nasopharyngeal carcinoma[35] and renal metastasis from adenoid cystic carcinoma of the sinus,[36] which supports the continued practice of whole body PET/CT imaging for head and neck cancers.

FDG-PET/MRI vs Isolated Diffusion Weighted Imaging (DWI) for CUP

DWI has been investigated as a potential replacement for PET/CT imaging in determining the origin of CUP because of its wider availability, lower cost, and lack of ionizing radiation. However, multiple studies confirmed that DWI is inferior to PET/CT for detection of primary tumors. Combining DWI with PET/CT also showed no added benefit, with similar results when comparing PET/MRI vs PET/CT. In places where PET/CT is not available, DWI could be a reasonable alternative because it still has relatively high diagnostic accuracy (81% compared to 94% for PET/CT), but in general is not a good replacement for the standard use of PET/CT in CUP.[37]

Multiple studies have also shown that complete PET/MRI performs with similar sensitivity when compared to PET/CT for the detection of primary sites of disease in HNCUP. For example, 1 study showed a 55% detection rate for both PET/MR and PET/CT.[5] In certain populations, such as pediatric and adolescent patients, PET/MRI is a desirable alternative for cancer work-up and restaging because of its lower dose of ionizing radiation relative to PET/CT. However, PET/MRI is not widely available compared to PET/CT so its use remains limited.

Non-FDG PET-CT Alternative Options for Diagnosing HNCUP

Ultrasound (US)

Transcervical and transoral US have been used to evaluate oropharyngeal cancers with some success. One small study of 10 patients showed that US has a 70% detection rate of primary tumors in patients with HPV positive HNCUP who otherwise had undetectable lesions via flexible larygoscopy and PET/CT, though further investigation is needed to validate these findings.[6] Given the propensity for HPV-positive SCC to originate in the oropharynx, US could be an alternative noninvasive evaluation tool for detection of primary sites, hypothetically leading to higher yield biopsies and more specific treatment strategies.

68Ga-DOTA-TATE PET/CT

For neuroendocrine metastases of unknown origin (NET-CUP), 68Ga-DOTATATE PET/CT scans offer increased sensitivity for the detection of primary tumors. A dual-tracer imaging protocol using 18F-FDG and 68Ga-DOTATATE PET/CT has also been investigated for NET-CUP with some success. The dual-tracer method takes advantage of 68Ga-DOTA-TATE's high sensitivity for low-grade tumors and 18F-FDG PET/CT's sensitivity for intermediate to high-grade tumors. One study reported a sensitivity of about 60% for detection of primary lesions in NET-CUP using both 18F-FDG and 68Ga-DOTATATE tracers.[38] While this sensitivity is similar to 18F-FDG PET/CT alone for CUP in general, neuroendocrine tumors tend to be smaller in size and often occult by 18F-FDG PET/CT. More research is needed to determine the efficacy of 68Ga-DOTATATE specifically for head and neck NET-CUP, but when considering the low incidence of this tumor type, large-scale data collection may be difficult.

C-11 PET/CT

C11-choline PET/CT has shown diagnostic promise for head and neck cancers due to its low level of background activity. It is of particular interest in nasopharyngeal carcinoma cases where background physiological FDG uptake by the adjacent brain and reactive nasopharyngeal lymphoid tissue may be confounders; however, C-11 radiotracer is not routinely used for head and neck cancers due to much higher cost and limited availability, warranting further investigation before widespread use.[39]

18F-MISO PET/CT

18F-MISO PET/CT has also been investigated for use in hypoxia imaging and has been shown to be a potential helpful prognostic tool in head and neck cancer patients: however, these PET/CTs often suffer from increased background noise, poor resolution, higher cost, and prolonged rest time between injection and imaging (up to 3 hours).[30]

Limitations/Pitfalls of 18F-FDG PET/CT for CUP

Interpretation of PET/CT in the head and neck can be challenging since PET has lower spatial resolution and several normal structures take up FDG radiotracer physiologically. For example, tissues in the Waldeyer ring of lymphoid tissue (palatine and lingual tonsils) can take up FDG greater than background mucosa and physiological radiotracer uptake in the brain and tongue muscles could mask adjacent lesions. One meta-analysis reported that PET/CT has a false positive rate of 39% for tonsillar lesions and weak sensitivity in the tongue base, detecting only 80% of mucosal lesions.[20] Another typical source for false-positive findings on 18F-FDG PET/CT is reactive tonsillar hyperplasia or reactive adenopathy which is common in these patient populations.[27,32]

As many as 40% of metastatic lymph nodes measure less than 7 mm in size, which contributes to 18F-FDG PET/CT's poor sensitivity for the detection of these tumors (50%).[32] Using a general size threshold of 1 cm to determine a benign vs malignant lymph node (or lesion) would not be helpful in diagnostic imaging and PET resolution is borderline too low to reliably detect such small lesions. These observations reiterate that treatment decision-making should not be solely based on imaging and patients with mucosal head and neck lesions may benefit from tonsillectomies and neck dissection for more accurate diagnosis and staging.

Reporting post-treatment PET/CT imaging for CUP requires concentration and extra effort on the radiologist's behalf. Review of the patients' medical records is extremely important in these cases to review the original site of disease and confirm prior treatments. Postradiation changes affect the mucosa including diffuse FDG uptake and inflammation that may decrease sensitivity for detecting recurrent disease, as well as potentially result in confounding features such as cartilage necrosis, which should not be mistaken for tumor invasion or recurrence.[32]

Histopathology

Squamous Cell Carcinoma

SCC is by far the most common histologic subtype of head and neck cancer accounting for more than 90% of all head and neck cancers.[40] Likewise, SCC is the most common subtype of CUP in the head and neck and accounts for 1%-10% of all head and neck tumors.[3,6,8,10,41] Some studies have reported good sensitivity of PET/CT for detecting primary tumors in SCC type of HNCUP (up to 73%)[10] which is higher than the sensitivity reported for HNCUP in general (up to 53%). Unfortunately, even after extensive work-up, the primary site still cannot be determined in 27%-60% of SCC cases.[6,10]

HPV and EBV Positive SCC

HPV positive metastases most commonly arise in the oropharynx (usually palatine tonsils) with a much lower percentage found in the nasopharynx. On the contrary, Epstein-Barr Virus (EBV) positive tumors primarily occur in the nasopharynx. Although HPV positive oropharyngeal SCC can be quite small with early advanced nodal disease, they maintain a favorable prognosis. HPV-positive tumor status in oropharyngeal carcinoma is an independent predictor of survival with an 80% decrease in risk of death or disease progression,

even when the primary lesion is unknown.[22] The small size of most primary HPV positive SCC lesions could account for the reported 34% of HPV-related SCC's that are initially worked up as CUP (compared to 5%-10% for general head and neck cancers).[14]

Adenocarcinoma and Undifferentiated Carcinoma

Adenocarcinomas are less common in HNCUP when compared to SCC, but carry a poorer prognosis. Since most of the nonhead and neck primary tumors that metastasize to cervical lymph nodes are adenocarcinomas, it is important to perform whole body diagnostic imaging in these patients in order to exclude a distant primary malignancy yielding metastatic disease to the neck.

Neuroendocrine Carcinoma

Neuroendocrine carcinomas (NECs) are an uncommon source of CUP, accounting for only 5% of CUP tumors in the whole body.[28] Given the relatively rare occurrence of NEC as a source of HNCUP, the clinical utility and effectiveness of PET/CT is not well known. A few studies have indicated limited use for PET/CT in neuroendocrine tumors of the head and neck with results showing relatively low sensitivity (60%) for detection of the primary site of disease. The rate of false-negative PET/CT in head and neck NEC is probably related to the small size of the lesions and poor glucose metabolism in NEC cell types. However, PET/CT can still detect the majority of primary sites of NEC-CUP and is an appropriate diagnostic tool when endoscopy and CT/MR have not revealed a source of CUP. For example, Ying et al[28] described a case of CUP presenting as right-sided cervical adenopathy with an otherwise normal ENT examination and negative diagnostic neck CT and MRI. The F-18 FDG-PET/CT subsequently showed a right laryngeal lesion which was proven to be supraglottic laryngeal NEC at subsequent surgery.

Subsites of Disease for CUP

It is important to consider the subsites of primary disease when evaluating head and neck tumors as each site confers different prognosis, management, and anticipated sites of nodal spread. Knowledge of which tumors tend to metastasize to each nodal level can help a radiologist work backward and converge on more specific areas in the head and neck to find a source of CUP (Table 1). Most metastatic cervical lymph nodes involve Level II (up to 50%), followed by Level I and III (up to 20%), with the majority being unilateral (90%). Metastatic lymph nodes involving levels I-III are usually SCCs with primary sites in the head and neck, whereas level IV-V metastases usually arise from primary lesions located below the clavicles and are more commonly adenocarcinomas.[3,4]

Oral Cavity

Like other regions of the head and neck, SCC is the most common carcinoma of the oral cavity. Most of these lesions arise from the anterior two-thirds of the tongue (40%) with another large percentage noted in the floor of mouth

Table 1 Most Common Metastatic Nodal Distribution Based on Primary Site of Disease

Metastatic Lymph Node Region	Most Common Primary Tumor Sites
Level IA	Oral cavity, face
Level IB	Oral cavity, nasal cavity, face
Level II	Oral cavity, nasal cavity, pharynx, larynx, hypopharynx
Level III	Oral cavity, pharynx, larynx, hypopharynx
Level IV	Oropharynx, larynx, hypopharynx, below clavicles
Level V	Nasopharynx, thyroid, scalp
Level VI	Thyroid, larynx, hypopharynx, below clavicles
Intraparotid	Parotid gland, lateral face and scalp
Supraclavicular	Thyroid, non-H&N primary

(30%).[42] Other locations include the gingiva, buccal mucosa, palate, and retromolar trigone, which are important potential hiding spots to consider for occult lesions. Overall, oral cavity carcinomas have poor prognosis with 5-year survival between 20% and 60% depending on location (worst in the floor of mouth).[42] Diagnostic CECT has a 41%-82% detection rate of primary tumors with increased sensitivity of retromolar lesions up to 94% when utilizing a puffed-check technique during the scan.[42] PET/CT and MR are also useful tools to evaluate the primary lesion (see Fig 2), but PET/CT can have limitations in the oral cavity due to physiological activity in the tongue musculature. The most common diagnostic error is to attribute abnormal mucosal uptake to benign inflammation.
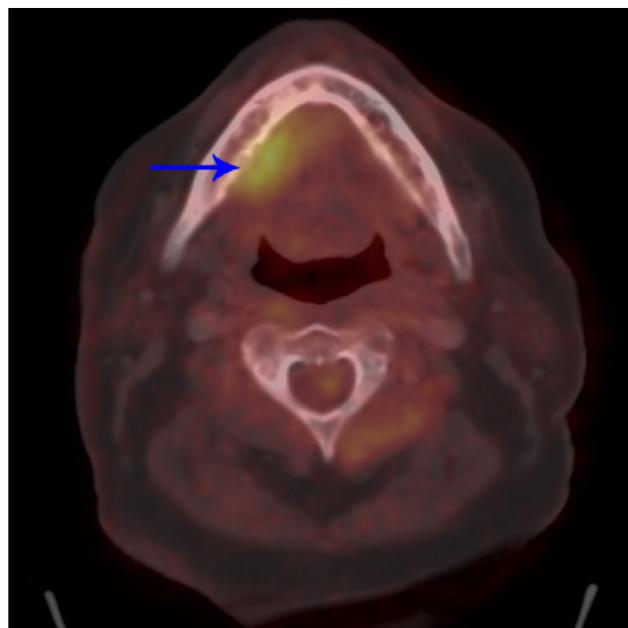

Figure 2 Oral cavity lesion identified on PET/CT: Asymmetric hypermetabolic activity along the right aspect of the oral cavity medial to the mandibular body, identified as a primary site of disease in this patient with a history of CUP.
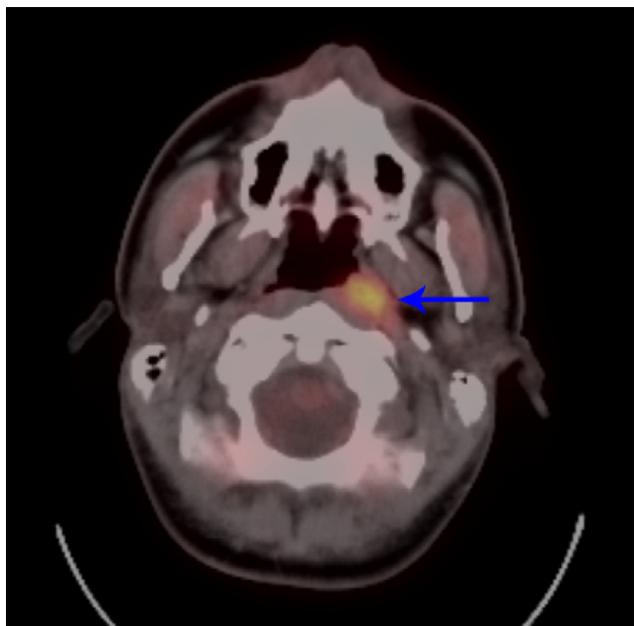
Figure 3 Left nasopharyngeal lesion identified on PET/CT: Patient presented with left neck lymphadenopathy without primary site of disease identified. PET/CT demonstrated asymmetric hypermetabolic activity associated with soft tissue fullness in the left fossa of Rosenmüller consistent with primary site of malignancy.

Nasopharynx and Oropharynx

As mentioned before, the great majority of HNCUP are from primary lesions in the nasopharynx or oropharynx, usually SCC type (see Fig 3). Unfortunately, 56%-76% of tonsillar carcinomas can show minimal or no asymmetry on CT/MRI, making them particularly difficult to identify.[1] It is also important to note that nasopharyngeal primary tumors are 3 times more likely to have distant metastases at presentation than non-nasopharyngeal tumors, which is important for treatment planning and prognosis.

There are conflicting reports regarding the utility of SUVmax comparisons when trying to determine pathologic vs physiological asymmetric tonsillar uptake in patients with HNCUP. In general, studies agree that the SUVmax ratio between tonsils has better accuracy for detection of tonsillar carcinoma rather than a standard threshold SUVmax.[1,7,43] This ratio is determined by taking the SUVmax of the tonsil ipsilateral to the metastatic lymph node(s) divided by the contralateral tonsil SUVmax. Unfortunately, a few studies have showed limited reliability on SUVmax ratio with an overlap in values between normal and neoplastic tonsil tissue.[1] For example, a study by Pencharz et al[1] showed an overlap of SUVmax ratios in both normal tonsillar uptake and pathologic uptake ranging between 0.9 and 1.3:1, so even a symmetric ratio of 1:1 may not exclude tumor. However, the investigators did find that a cutoff SUVmax ratio of >1.6 had 100% specificity and 100% PPV for malignancy, suggesting that values >1.6 could confirm a primary site of CUP. The false negative rate for PET/CT in detecting tonsillar carcinoma is likely attributed to small size of the primary lesions, T1 disease, or HPV positive tumor status, which have been reported to have lower FDG uptake.[1]

Nasal Cavity and Sinuses

Sinonasal tumors are relatively rare, accounting for less than 3% of all mucosal head and neck cancers. The most common types of sinonasal carcinoma are SCC, adenocarcinoma, adenoid cystic carcinoma, and undifferentiated carcinoma (SNUC) with most common locations in the maxillary and ethmoid sinuses. Lymphatic drainage from the nasal cavity and sinuses is variable with pathways to the parapharyngeal, parotid, submandibular, and facial regions. One study found that sinonasal carcinomas more commonly spread to nodal levels II/III but may involve levels I and V depending on primary tumor size and location.[44]

Larynx

Laryngeal cancer is the most common malignancy in the head and neck, accounting for 25% of all primary head and neck tumors. These cancers are predominantly SCC (95%-98%) and if involving the glottic larynx, often present early due to their noticeable effects on phonation. Laryngeal tumors usually involve the glottis (60%-65%) and less commonly the supraglottic (30%-35%) and subglottic regions (5%)[27,32] (see example in Fig 4). Mucosal lesions involving the glottis tend to stay localized for an extended period of time and infrequently have cervical nodal metastases (<10% of the time) due to their limited anatomic access to the lymphatic system relative to other laryngeal subsites. However, when cervical metastases do occur in the setting of glottic or subglottic lesions, they tend to spread to levels IV and VI and the primary site usually shows submucosal and/or paraglottic invasion.[32] The more common supraglottic lesions are more prone to cervical lymph node metastases (25%-75%) and usually occur bilaterally in the level II and III regions.[27]

In one study by Tatar et al,[27] PET/CT showed significantly higher accuracy for staging laryngeal cancers when compared to a combination of diagnostic MRI/CT (89% vs 67%), which implies that patients are correctly staged more often by PET/CT and therefore should translate into more appropriate treatment. Unfortunately, primary laryngeal cancer confers increased risk for a second primary neoplasm (1%-18%) which adds to the diagnostic challenge of HNCUP.[11,45] It is also important to remember non-neoplastic causes of asymmetric laryngeal uptake such as unilateral vocal cord paralysis. Paralyzed cords do not take up FDG and will preferentially be in the apposed position so the contralateral normal cord will falsely appear to have focal radiotracer uptake.

Hypopharynx

The hypopharynx is located between the valleculae and the cricopharyngeus muscle and includes the pyriform sinuses, posterior hypopharyngeal wall, and postcricoid region. The hypopharynx has the same embryologic origin as the supraglottis, therefore it is also highly associated with SCCs (95%) and presents with a similar nodal metastatic distribution to Levels II and III.[32] Most tumors of the hypopharynx occur in the pyriform sinuses (65%) and less commonly in the posterior hypopharyngeal wall (15%) and postcricoid region (25%), which tend to have the worst prognosis. Lesions
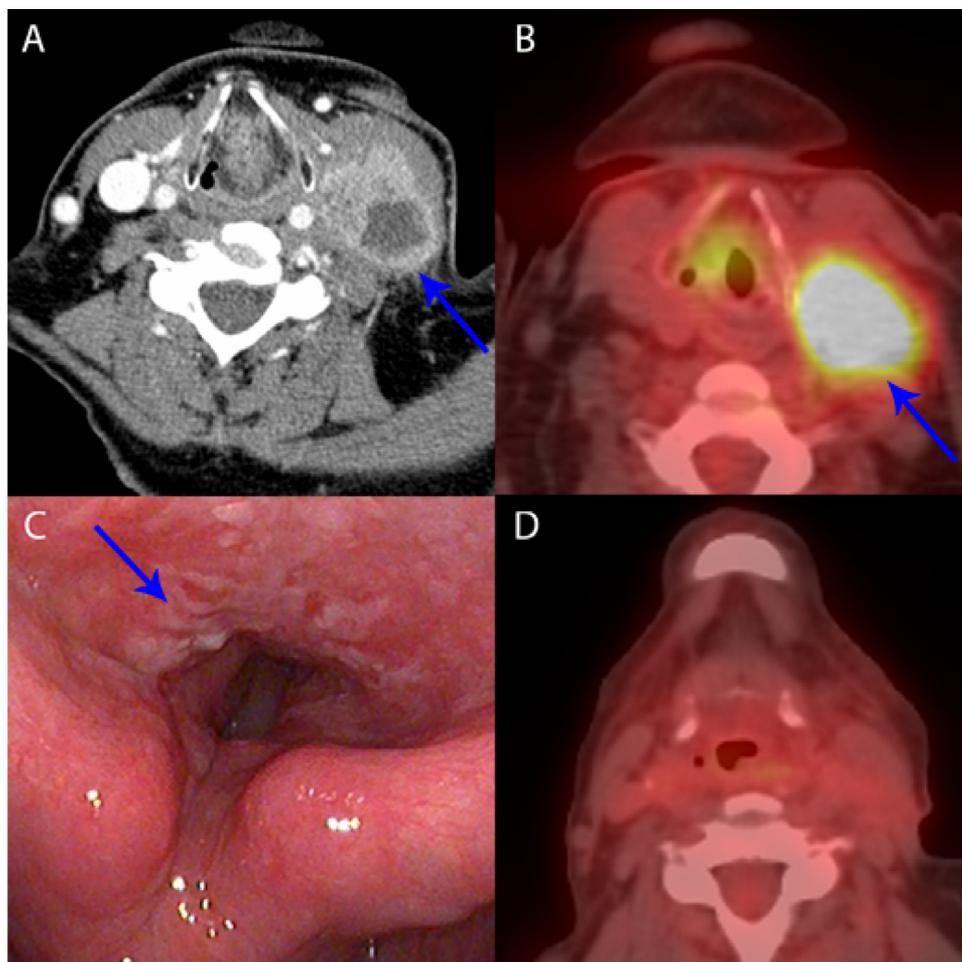
Figure 4 Head and neck carcinoma of unknown primary: Axial contrast enhanced CT soft tissue neck (A) shows a 5 cm necrotic left neck nodal mass which was subsequently biopsied as squamous cell carcinoma. Diagnostic imaging failed to detect a primary lesion. Axial F-18 FDG PET/CT (B) shows prominent hypermetabolic activity within the left neck mass with asymmetric hypermetabolic activity along the right aryepiglottic fold. Flexible laryngoscopy (C) shows leukoplakic thickening of the epiglottic surfaces with biopsy showing dysplasia, presumed epiglottic primary disease site. Post-treatment axial F-18 FDG PET/CT (D) shows marked decrease in metabolic activity at previous site of left neck nodal disease.

originating from the posterior hypopharyngeal wall are often aggressive with invasion of nearby structures and metastases to retropharyngeal lymph nodes, which stratifies these lesions into unresectable category.[32] Hypopharyngeal tumors (like nasopharyngeal lesions) have a higher occurrence of distant metastases at presentation when compared to nonpharyngeal lesions (7% vs 3%) (see Fig 5). In fact, up to 75% of hypopharyngeal cancers have been reported as stage III-IV at presentation.[46]

Special Cases
Benign Lesions
One retrospective review showed that 5.5% of lesions undergoing work-up for suspected metastatic disease of unknown origin were ultimately diagnosed with benign diseases on pathology or advanced imaging. These entities included hemangioma, venolymphatic malformation, schwannoma, neurofibroma, and tuberculosis.[13] While benign masses can present as palpable masses in the neck and may be indeterminate on initial imaging, they rarely lead to a diagnostic dilemma after histologic evaluation and advanced CT/MRI.

Cystic HNCUP vs Branchial Cleft Cyst
While most of the nodal metastases from head and neck cancer are SCC and occur as solid nodal masses, 33%-62% of HNSCC metastases have been reported to be primarily cystic.[21,47] Since head and neck nodal metastases commonly spread to the Level II cervical region, this can be a dangerous source of confusion for radiologists and has led to misdiagnoses because of their close resemblance to branchial cleft cysts (BCC). As many as 21% of solitary cystic nodal metastases were reportedly initially diagnosed as BCCs on CT/MR in the past, especially when the primary site was not easily detected.[21] Pathologists used to have similar difficulty differentiating BCC from cystic metastatic carcinoma because they both have squamous histology, however newer immunohistochemistry testing usually confirms the diagnosis.[14] Extreme
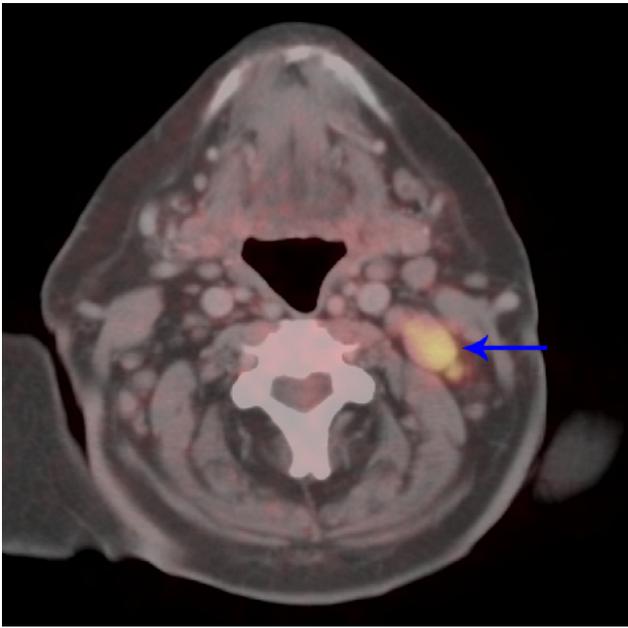
Figure 5 Left level II nodal disease with unknown primary: Patient presented with left neck lymphadenopathy and underwent US-guided biopsy demonstrating SCC. Subsequent work-up including PET/CT demonstrated enlarged, hypermetabolic left level II lymph nodes (maximum SUV 5.2) without primary site of disease identified. Patient underwent panendoscopy and biopsies which revealed a primary lesion of the hypopharynx.

caution must be exerted when making the novel diagnosis of a branchial cleft cyst in an adult, which should be considered a cystic metastasis from SCC (particularly HPV-related) until proven otherwise. Solitary cystic nodal metastasis from papillary thyroid carcinoma (PTC) can cause a similar diagnostic dilemma for radiologists with up to 70% of nodal metastases from PTC having cystic features. The accuracy of fine needle aspiration for diagnosing cystic masses in the neck is relatively poor with a false negative rate of 50%-67%, often making this test unreliable.[48] The cystic portion of necrotic lymph nodes can consume the entire node causing decreased sensitivity of PET/CT for such lesions as well.[47]

It is important to remember that the most common primary tumors to generate cystic nodal metastases in the head and neck are SCC (particularly positive HPV type) and PTC, so careful attention to the thyroid gland and Waldeyer ring is recommended. Incorrectly diagnosing cystic neck masses as benign lesions leads to a delay in diagnosis and therefore worse outcomes with increased mortality.[48] Any adult (young or old) with a new cystic mass in the cervical region should be assumed to have metastatic SCC until proven otherwise. This is especially true now with an increasing number of young adult patients with HPV-positive SCC.

Cervical Nodes as Distant Metastases

Metastatic lymph nodes in the lower cervical chains and supraclavicular regions (Virchow or "signal" node) are often from primary tumors below the clavicles including lung and breast carcinoma.

Melanoma

Melanoma of unknown primary accounts for 2%-8% of all melanomas, with nodal disease representing the majority of these lesions and the parotid gland representing the second most common head and neck site.[49,50] In one study of metastatic melanoma of unknown primary, FDG PET/CT only identified the primary site in 5.3% of patients. This very low sensitivity argues against reliance on PET/CT for localizing primary melanoma lesions.[9]

Thyroid Carcinoma as HNCUP

While PTC often present with metastatic lymph nodes (more than 50% of the time), it is quite uncommon to be a source of HNCUP after diagnostic imaging. One study found that only 4.4% of metastatic thyroid tumors were occult after dedicated imaging and these lesions were all <1 cm in size. Unfortunately, when thyroid carcinoma lymph node metastases have no identifiable primary tumor they are at increased risk for recurrence after radioactive iodine treatment.[14] It is also important to remember that occult thyroid carcinomas can initially present as cystic nodal metastases[14,48] (see Fig 6).

Parotid Lesions as HNCUP

While primary parotid lesions such as adenocarcinoma and adenoid cystic carcinoma could present as a palpable neck mass, they are almost never associated with CUP in cervical lymph nodes.[14] However, metastatic lesions to the parotid can occasionally present as CUP. The majority of metastases to the parotid glands arise from skin lesions of the scalp and face (SCC or melanoma) followed by primary tumors below the clavicles (breast, prostate, etc). In one small study of 23

Figure 6 Cystic papillary thyroid carcinoma metastasis: A young adult patient presented with an enlarged cystic-appearing right level II node with unknown primary site of disease. Diagnostic considerations included HPV-related HNSCC nodal disease vs branchial cleft cyst. Biopsy demonstrated cystic papillary thyroid carcinoma.

patients, 13% of SCC metastases to a parotid lymph node had an unknown primary site.[51]

Future Development

Many have studied the usefulness of metabolic tumor volume and total lesion glycolysis as additional diagnostic and prognostic signifiers in PET/CT imaging of head and neck cancers. Finding optimal thresholds and parameters for these variables will continue to be an area of high interest, especially regarding HNSCC.[46] PET/CT is also being studied to determine microvessel density within head and neck SCCs which correlates with outcomes in HNSCC.[52] Immunohistochemistry and molecular profiling of CUP tumors has also decreased the number of CUP diagnoses and will likely continue to significantly decrease the incidence of HNCUP with future developments. Post-treatment follow-up imaging has also undergone recent changes as well with the development of NI-RADS criteria,[53] which will hopefully provide more uniform interpretations and reduce false-positive rates when using PET/CT for recurrence surveillance.

Conclusion

CUP in the head and neck is a complex diagnosis with many factors for radiologists to consider. When a patient has a cervical metastasis of unknown origin after initial diagnostic imaging they should proceed down the pathway of HNCUP work-up, which usually starts with PET/CT. Unfortunately, PET/CT alone is not sufficient to identify all primary tumors and more invasive measures may be needed, including panendoscopy, tonsillectomies, and sometimes nontargeted locoregional radiation if no primary is found. Radiologists should be familiar with cervical nodal stations and the most common sites of primary disease spread. Since identifying the primary lesion is associated with better overall survival and fewer treatment related complications, it is important to perform an exhaustive search of primary tumors.

Declaration of Competing Interest

None of the above authors have any relevant financial conflicts of interest related to this article.

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