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Abstract:

Metastases to the cervical lymph nodes from a occult primary (CUP) of head and neck squamous carcinomas has been increasing in presentation (HNSCC). Modern diagnostic workup, including clinical evaluation, conventional imaging, FDG-PET/CT and panendoscopy/tonsillectomy enables detection of the primary site in over half of all cases, and is associated with significantly improved survival rates. Recent studies have demonstrated the utility of novel molecular pathology and transoral surgical techniques in improving diagnosis and treatment. We present a new, evidence-based protocol incorporating these novel diagnostic modalities. It aims to identify the site of the primary tumor, and determine the stage of the disease, including extranodal extension. This information can personalise treatment recommendations, rationalise combinations of treatment modalities, and thereby potentially minimise toxicity and improving functional outcomes.

Introduction

The carcinoma of unknown primary in the head and neck (CUP) occurs when a patient presents with clinically-evident cervical lymphadenopathy, but where a primary tumor cannot be identified by thorough medical history, clinical examination and non-invasive and invasive diagnostic workup [1].

The identification of the primary site by modern functional imaging has significantly reduced the prevalence of true CUP [2]. In the past, only about 1-7% of all head and neck cancer patients present with metastases to the lymph nodes as the only clinical evidence of the disease [3-5]. This appears to be is increasing in incidence due to the increasing human papillomavirus-related oropharyngeal cancer [5]. The natural history of the development of CUP remains unclear. Potential reasons for the inability to detect the primary site may include small tumour volume, hidden location (e.g. tonsillar crypt), slow growth rate, and/or possible involution of the primary tumor, thereby hindering its recognition[6, 7].

Several guidelines, consensus statements, and literature reviews have been published describing the diagnostic and therapeutic approach to CUP in the last decade [8-10]. However, recently there has been a considerable amount of new and essential data published on novel diagnostic approaches, including the role of Human papillomavirus (HPV) detection and the utility of transoral minimally-invasive procedures. Our aim here is to present an evidence-based algorithm for the diagnosis and treatment of patients with CUP, that incorporates recent developments.

Objectives:

The principal objectives of the diagnostic evaluation of the patient with CUP are to identify the location of the primary tumor, to reliably determine the histology, to ascertain the extent of locoregional disease (including nodal extranodal extension), and to exclude distant metastases. The other important consideration for the diagnostic workup should be the utilization of the shortest and the least invasive pathway to achieve diagnosis and treatment, with the least morbidity and the highest cost-effectiveness [9].

A retrospective study of 236 patients with an initial presentation of CUP

demonstrated ultimate detection of a primary tumour after investigation in 53% of cases. Approximately 88% of these were oropharyngeal primaries (equally divided between the base of tongue and tonsil). The likelihood of a biopsy-proven primary decreased significantly in patients with no findings on examination and radiology, compared to those with positive findings on both (29% vs. 64% respectively)[11].

Identification of the primary site is crucial as it helps direct therapy and has been reported by some studies to be associated with better prognosis and survival. A matched paired retrospective analysis by Davis (n=22), demonstrated significantly improved survival in patients with CUP where the primary tumour was subsequently identified, compared to those where it was not (HR = 0.125; 95% CI, 0.019–0.822; *P* = .030). This may be in part because lesions that were identified were more likely to be HPV positive[12]. Similarly, Haas et al. reported 100% 3-year survival in the eight patients whose oropharyngeal primary was identified compared to 58.8% for the 34 patients with a persistent "occult primary" (n=34) [13].

TNM staging:

In the American Joint Cancer Commission (AJCC) [14] and Union for International Cancer Control (UICC) 8th Editipn TNM Staging Manual [15], substantial changes have been introduced to the staging of patients with CUP. Previously, CUP cases were categorized as T0, but were not assigned to a specific anatomic subsite. Evidence now shows that that upto 90% of cases initially designated as having actually have virally-assciated (HPV or EBV) cancers Consequently the presence of either Epstein-Barr Virus (EBV) or HPV in metastatic lymph nodes may facilitate identification of an anatomic site of origin [16, 17]. Therefore, at least p16 immunohistochemistry and EBV encoded (EBER) RNA-in situ hybridisation(ISH) are recommended for all cervical lymph nodes with carcinoma of unknown primary site. Thus, one key change from prior editions of the TNM system is the elimination of the T0 category in sites other than the nasopharynx, HPV–associated oropharyngeal cancer, and salivary gland cancers (which can be identified by histology). If no primary lesion can be identified, then the lymph node may have emanated from any mucosal site, so there is no rationale to support retaining the T0 designation outside of the virally associated cancers of the

oropharynx and nasopharynx[18]. In other words, when the presence of EBV RNA is determined by ISH, the patient is staged as per nasopharyngeal cancer, and when p16 positive IHC is present, as per oropharyngeal cancer. In all other scenarios, the clinical and pathological node definitions are as per non-HPV positive oropharyngeal cancers.

Presentation and clinical examination

The majority of CUP patients present to the outpatient clinic with a palpable neck mass. This was the primary reason for consultation in 94% of a series of 352 patients [3] and all subjects of a separate cohort of 167 patients [1]. Other characteristic head and neck cancer symptoms such as dysphagia, pain and weight loss were reported in less than 10% of patients. Demographically, patients with CUP were typically male, between 55-65 years old with a history of chronic tobacco and/or alcohol use [1, 19]. More recently, this pattern appears to have changed with an increase in younger non-smoking patients presenting with human papillomavirus (HPV)-related oropharyngeal cancer [20].

A thorough history should always be taken. This includes eliciting a history of other malignancies, immunosuppression or compromise, sun exposure, skin cancer or removal of skin lesions. This should be followed by clinical examination, which should routinely involve assessment of the entire upper aerodigestive tract, along with neck palpation and flexible nasendoscopy. Physical examination should also include skin examination. The location of the cervical lymph node metastasis may suggest the location of the primary site, due to established patterns of lymphatic drainage in the head and neck. Most commonly, enlarged cervical lymph nodes are identified at level II, followed by level III, with bilateral involvement reported in <10% [1, 3, 19]. This is in keeping with the majority of tumours in CUP patients being from the oropharynx. Bilateral nodal metastases should draw attention to the nasopharynx, base of tongue, hypopharynx and midline structures. Non-oropharyngeal primaries, such as skin or distant metastases from non-head and neck primary, should be suspected in patients with intraparotid lymph nodes or posterior or supraclavicular nodal involvement. The involvement of both upper and lower nodal levels should prompt the physician to exclude distant metastases, which are much more frequent in these patients compared to the patients with involvement of just the upper nodal levels[21]. The median

nodal size is 3.5 to 5 cm[22]. The time interval between first appearance of a cervical mass and diagnosis ranged between 2 and 5 months[1, 3, 23].

Imaging

The choice and sequence of imaging technique is important in the diagnostic workup of CUP. The imaging techniques utilized should be able to identify the primary site, the extent of nodal disease (including extranodal extension), and the presence of distant metastases. Computed tomography (CT) and/or Magnetic Resonance imaging (MRI) with intravenous contrast of the neck and thorax have been the mainstay of diagnostic workup in CUP detection. There appears to be no significant difference in the efficacy of CT and MRI - both have reported detection rates of 9-23% [24-26]. With regards to identifying extracapsular nodal extension, MRI is reported to be marginally superior to CT, with specificities and sensitivities 85% and 84% vs. 77% and 80% respectively [27]. An analysis by the NICE guidelines reported the pooled sensitivity of CT to detect extranodal extension in 4 studies to be lower, at 44% (95 % confidence interval [CI] 30%, 58%) and the specificity as 75% (95% CI 57, 88)[28]. Chai et al. report the negative predictive value of CT for the detection of the extranodal extension to be 49%. Therefore, CT imaging may be considered useful in positively identifying extracapsular extension, but not for convincingly excluding it [29].

There is now a large body of evidence supporting the use of FDG-PET/CT as an effective diagnostic tool for the identification of the site of the primary tumour, when standard imaging techniques are negative. A meta-analysis by Rusthoven et al., which included 302 patients from 16 studies published between 1994 and 2003, demonstrated a primary tumour detection rate by FDG-PET of 24.5% (sensitivity 88.3%; specificity 74.9%; diagnostic accuracy 78.8%)[30]. The highest false-positive rate was seen in the tonsils (39.3%), while the lowest sensitivity rate was seen in the base of the tongue (80.5%). A more recent meta-analysis by Kwee et al. using hybrid FDG-PET/CT included 11 studies published between 2005 and 2007 and comprised 433 patients. Here, the overall primary tumor detection rate, pooled sensitivity, and specificity of FDG-PET/CT/ were

37%, 84% (95% CI 78-88%) and 84% (95% CI 78-89%), respectively [31]. The false positive rate (15%) was again highest for oropharyngeal tumors.

FDG-PET/CT scanning does have some limitations however. The resolution of FDG-PET/CT limits its ability to detect tumors smaller than 5mm. In addition, the basal uptake of FDG in normal lymphoid tissues within Waldeyer's ring and the uptake of FDG by salivary gland tissue limit the value of FDG-PET/CT in identifying small or superficial lesions in these locations. Additionally, FDG-PET/CT is relatively more expensive in comparison to conventional imaging modalities. In a recent study from Denmark, Dale et al. showed that the additional efficacy of FDG-PET/CT in identifying the primary site in patients where it has not been previously identified by clinical examination, flexible endoscopy, and standard cross-sectional imaging was only 7% (95 % CI 2–21 %). Therefore, we believe FDG-PET/CT is ideally indicated only when the primary site has not been identified by clinical examination and conventional imaging [32].

Tissue diagnosis

Fine needle aspiration biopsy (FNA) is currently the most widely used technique for obtaining diagnostic information from metastatic lymph nodes. It is safe, cost-effective and reliable [33]. Excisional biopsy of lymph nodes should be avoided due to the potential local complications (such as hematoma, infection, disruption of fascial planes for subsequent neck disscetion), as well as the theoretical risk of neck recurrence [34]. However, despite certain advantages, FNA has also some drawbacks, especially in the setting of CUP. Cystic nodal metastases are particularly associated with HPV-driven malignancies[35], which are common causes of cup. In patients with cystic metastases, the efficacy of FNA is significantly reduced, with a false negative rate of up to 42% [36]. Furthermore, the differential diagnosis of a metastatic node includes brachial cleft cysts, a necrotic node with abscess formation or tuberculosis, which can sometimes be difficult to differentiate on needle aspiration alone. Sensitivity of this technique therefore may not exceed 50% [37], however performing FNA under ultrasound guidance can improve the sensitivity considerably, up to 80% [35].

Ultrasound-guided core biopsy of the involved lymph nodes can retrieve a more substantial tissue sample, and is also considerably less invasive than an excisional biopsy.

Although core biopsy may not significantly improve the overall sensitivity of diagnosing squamous cell carcinoma in lymph node metastases, it substantially enhances sample adequacy for obtaining a diagnosis. Novoa et al., in a meta-analysis and systematic review (16 studies, N=1267) of core needle biopsies used in the evaluation of head and neck lesions, showed that adequate material for histologic diagnosis and ancillary studies was obtained in 95% of cases [38]. In some centers, a core biopsy routinely follows the FNA to enhance sample accuracy for HPV testing [38, 39]. Furthermore, the risk of potential complications of core biopsy (including tumor seeding and major bleeding) have been proven to be negligible. Due to these advantages, we prefer US-guided core biopsy to US-guided FNA in the diagnostic workup of CUP, but both are valid alternatives.

Since up to 80% of all oropharyngeal tumors can be HPV driven malignancies, the determination of HPV testing in fine needle aspirates and core biopsies has gained relevance to guide the localization of the primary tumor[40]. The preferential distribution of p16 staining in carcinomas of the oropharynx supports the use of p16 staining for discerning the site of tumor origin in those patients presenting with cervical lymph node metastases. Begum et al. identified HPV16 in 10 of 19 metastases from the oropharynx, but in none of 46 metastases from other sites (53% versus 0%; $P < 0.0001$) [41]. p16 expression in nodal metastases was highly correlated with site of tumour origin.

Studies that have addressed HPV testing of cytological samples have primarily tried to adapt tissue-targeted approaches, e.g. p16 immunohistochemistry and HPV in-situ hybridization to cytological specimens[41, 42]. Numerous studies have confirmed the feasibility of p16 immunostaining in fine needle aspirates and biopsies of cervical lymph node metastases [41-43]. Holmes et al. [44] detected p16 staining in the FNA of involved nodes in 71% of the 85 patients with metastatic oropharyngeal squamous cell carcinomas. This is similar to the findings of other authors [41, 45]. In contrast, p16 immunostaining on FNA was only seen in 13% of nodal metastases from non-oropharyngeal sites ($p< 0.001$) [44]. Jakscha et al. found that in their cohort of 54 patients, p16 positivity by immunohistochemistry of FNA cytology correlated with that of excised lymph nodes in every HPV positive case [46]. Of the 17 lymph node metastases that were p16 negative on histology, 15 (88%) were p16-negative on FNA, and two cases were false positive. In a very recent study, Cheol Park et al. compared the diagnostic value of HPV, p16, and EBV in the aspirates from the cervical lymph nodes to FDG-PET/CT in a prospective series of 54

consecutive cases. Overall, primary tumors were identified in 28 (51.9%) of patients. The sensitivity of p16 (85.7%) and accuracy of HPV (85.2%) were higher than those of FDG-PET/CT (42.9% and 68.5% respectively, $p < 0.05$) [47]. It should be noted however that, in most studies, HPV testing of cytological FNA specimens was restricted to the small subset of the overall cases – that subset consisted of case from which sufficient cellular material was available for the construction of cell blocks. For example, Begum et al. reported, that only 20% of the FNA samples were sufficiently cellular for HPV testing [41]. Limited cellularity affecting p16 immunohistochemistry may also produce false negative results [44, 48, 49]. This further supports the superiority of core biopsies over FNA to facilitate HPV testing.

Included in the differential diagnosis of metastatic lesions of the neck (especially those located in levels V, but also levels II-IV), is EBV-related, undifferentiated nasopharyngeal carcinoma, which should also be considered in those patients who have no apparent primary [50, 51]. Nakao et al. evaluated 36 nasopharyngeal cancer patients (30 primary tumour and 6 lymph node metastases) by EBV in-situ hybridization and determined that 60% of primaries and 50% of metastatic cases were associated with EBV. In contrast, among patients with lymph nodes metastases from other head and neck sites (n=13) EBV was not identified in any of the cases [52]. A retrospective analysis of 22 metastatic lymph nodes from CUP patients attempted to determine the localization of the primary tumor by assessment of the HPV and EBV status in the nodes. In all 3 cases where the primary was eventually identified in nasopharynx, the cystic metastases turned out to be EBV positive and HPV negative. Where the primary originated from other anatomical site, 1 case were EBV positive [53]. In other consecutive series of CUP patients, oncogenic viral infections (EBV or HPV) were found in 12 cases (54%). In that series, EBV was detected in 2 cases [50]. Therefore, for non-keratinizing or undifferentiated carcinomas that are p16 negative, EBV in situ hybridization (EBER) should be performed. The combination of undifferentiated morphology and EBV positivity is sufficient evidence to strongly suggest an occult nasopharyngeal primary[54]. In the newly published American Joint Cancer Commission (AJCC) 8th Edition TNM staging Manual [14] and Union for International Cancer Control (UICC)[15], the algorithm for workup of SCC of unknown primary includes HPV and EBV testing. Tumours positive for the viruses are staged according to the respective staging criteria for oropharynx and nasopharynx (see relevant section above).

Panendoscopy with biopsy and tonsillectomy

Regardless of the findings of the above combination of investigations, performing meticulous examination under anesthesia (EUA) and panendocscopy is mandatory in all CUP cases. Where imaging has identified the primary site, EUA allows histological confirmation by diagnostic biopsy. For example, Cianchetti confirmed the findings in 64% of cases where the index tumor had been previously identified by clinical examination and PETCT[11]. When the primary tumor has not been identified despite conventional and FDG-PET/CT imaging, subsequent EUA enabled identification of primary site in approximately 35% of patients[4, 11]. Therefore, a negative FDG-PET/CT does not preclude the need for panendoscopy to detect the primary site. In that situation, EUA should include the examination of nasopharynx, laryngoscopy, pharyngoscopy, and oesophagoscopy. Palpation of accessible subsites is also strongly advocated. Importantly, Miller also demonstrated that the overall risk of subsequent manifestation of a primary tumor of the upper aerodigestive tract in patients that have had a negative FDG-PET/CT and a negative panendoscopy was very low (5.8%), demonstrating the efficacy of this combined approach [4].

Random biopsies are of very low diagnostic value [35]. In contrast, Karni found that undertaking transoral microscopic examination of the base of tongue identified a significantly higher number of primary tumors in the base of tongue compared to rigid EUA (94% vs. 25% respectively) [55]. Therefore, examination of the base of tongue with a 30◦ 4mm endoscope or a microscope, in conjunction with a Feyh-Kastenbauer (FK) retractor, is recommended. The new generation of high and ultra-high definition systems is likely to assist further in this respect.

Narrow band imaging

Narrow band imaging (NBI) identifies abnormal neoangiogenic patterns on the mucosa. Its application in the pre-and intra-operative setting has been recently been shown to be an useful adjunct in the detection of primary lesion. Filauro at al. analyzed the consecutive case series of 29 CUP cases, where the CT and/or MRI and FDG-PET/CT did not reveal the primary lesion. NBI used during panendoscopy identified the primary tumor in 10

patients (34.5%). The sensitivity, specificity, positive and negative predictive values and accuracy were 91%,95%, 91%,91% and 90% respectively[56]. A pooled analysis of 5 studies by the NICE guidance [28] reported a pooled sensitivity and specificity of narrow band imaging as 77% (95 % confidence interval [CI] 50, 92) and 84% (95% CI 68, 93), respectively.

Tonsillectomy

In patients where no primary can be found on EUA, tonsillectomy is indicated. In a cohort of 126 patients with CUP, Walton et al. reported a positive yield in 30% of patients who underwent tonsillectomy. In comparison, in the same study, deep biopsies only identified the malignancy in 3% of cases, reflecting the fact that some tumors are small and located within the tonsillar crypts and so cannot be identified by simple biopsy. While there are no clear recommendations available on performing unilateral or bilateral tonsillectomy, rates of contralateral tumours of up to 10-17% [57, 58], have been reported, suggesting a need for considering bilateral tonsillectomy.

Tongue base mucosectomy

In addition to tonsillectomy, there is now increasing evidence for the role of tongue base mucosectomy for patients whose primary remains undetected after undergoing the protocol described above. During this procedure, the whole of the tongue base mucosa (including the lingual tonsils) is removed en bloc or in two (right and left) sections. Meticulous histopathological examination, with multiple sections, is then undertaken. For example, Patel et al. performed a retrospective, multi-institutional case series, in which data were pooled from the 6 institutions. The primary site was located by transoral robotic surgery (TORS) in 34 of 47 patients (72.3%), of which the primary site was located in the base of tongue for 20 patients (58.8%). In 18 of 47 patients (38.3%), both preoperative radiographic and physical examination failed to suggest a primary site. Of these 18 patients, a tongue base primary as identified in 13 (72.2%) cases after undergoing TORS [59]. Similarly, Byrd reported identifying the primary in 19 (86.4) of the 22 cases of lingual tonsillectomy by TORS [60] . In another study, the average time to return to normal swallowing function was 2.7 days, and there were no major surgical complications [61]. More recently, Winter et al., reported on a retrospective case review from 4 head and neck centers in the United Kingdom, analyzing 35 patients where the primary tumor was not identified during clinical

examination, imaging (including FDG-PET/CT) and bilateral tonsillectomy. The primary tumor site was identified in the tongue base in 53% (n=17) of patients. In 15 (88%) of these patients, the tumor was in the ipsilateral tongue base, while in two cases (12%) the tumor was located in contralateral tongue base[62]. Similar retrospective single-center analyses have been performed by Hatten[63] and Geltzeiler [64], who examined consecutive cohorts of 60 and 64 patients with unknown primary respectively. In the Hatten study, transoral robotic surgery procedures enabled the identification of the primary in 48 (80%) patients, all in the oropharynx. In 28 (50.8%) patients, the index tumor was identified in base of the tongue, while in 18 patients (38%) the primary tumors were in the palatine tonsils. The mean size of the identified mucosal primary lesions was 1.3mm (SD 0.1mm), which is below the resolution of detection by FDG-PET/CT. Geltzeiler reported that the primary tumor was found in 51 (80%) of 64 patients. Of those patients, 14 (22%) were found on EUA alone. Fifty patients underwent further robotic transoral lingual tonsillectomy ± palatine tonsillectomy, with primary tumors identified in 37 (74%) cases. The primary tumor was located in the lingual tonsil in 32 patients (86%) and palatine tonsil in 5 patients (10%, $p<0.001$).

Transoral laser microsurgery appears to be similarly effective. Karni et al.[55] compared transoral laser microsurgery (TLM) with traditional EUA, reporting detection rates of 94% compared to 25% respectively in a series of 30 patients. Nagel et al. reported a detection rate of 86% in a retrospective series of 36 TLM patients, using their algorithm of directed biopsies, frozen section, and lingual tonsillectomy [65].

In a very recent meta-analysis of 552 patients from 21 studies [66], the reported pooled rate of identification of a primary by tongue base mucosectomy was 57%. In patients with a negative conventional imaging, PETCTscanning, EUA and tonsillectomy, the rate of identification by tongue base mucosectomy rose to 78% [66].

The question then arises whether tonsillectomy and transoral mucosectomy should be performed concurrently or sequentially. Byrd et al. showed that the simultaneous tonsillectomy and TORS treatment strategy was associated with lower *direct* hospital costs and physician fees compared to the sequential strategy. However, simultaneous base of the tongue resection and tonsillectomy was associated with significantly more pain. As a result, two of five patients who underwent the simultaneous procedures required longer inpatient stays for pain control due to inability to eat, which resulted in an increased *overall* cost for

the simultaneous strategy. There was also concern about the development of late circumferential stenosis, especially after radiation or concurrent chemoradiation. Overall, analysis of incremental cost savings for sequential and simultaneous EUA and TORS base of tongue resection were $8619 and $5774 respectively per additional primary identified, compared to EUA+ tonsillectomy alone, highlighting not only the cost-effectiveness of lingual tonsillectomy in this indication, but also higher cost-effectiveness of the sequential approach compared to concomitant procedure approach[60]. We therefore, advocate that delayed transoral mucosectomies are undertaken, only when the tumor remains unidentified after EUA and tonsillectomy.

Proposed algorithm for diagnosis and treatment of CUP

Based on the analysis of the above literature review, we propose an evidence-based algorithm for the diagnosis and management of patients presenting with clinical CUP (Fig1). However due to the dearth of high quality prospective or randomised data in the CUP setting, we have relied on data from studies of patients with known head and neck cancer primaries, and extrapolated this to the CUP setting.

Fig. 1 The proposed diagnostic and therapeutic protocol for CUP in head and neck.

For patients who present with a palpable neck mass where the primary tumor is not identified on clinical examination including flexible nasendoscopy (preferably with narrow band imaging), we recommend a CT or MRI scan of the neck, with intravenous contrast and a CT scan of the thorax, depending on institutional availability and waiting lists. Patients should also have an ultrasound-guided core biopsy (preferable to fine needle aspiration biopsy, albeit both are acceptable). Immunohistochemical staining of the biopsy sample for p16 is strongly recommended, and if negative, then EBV insitu hybridization should be undertaken, especially for presentations suggesting naso[haryngeal cancer. If the CT/MRI scan does not identify the primary site, a FDG-PET/CT scan should be requested immediately (preferably by the reporting radiologist) to avoid delay to further management. Requesting a FDG-PET/CT scan as the primary diagnostic modality is a viable alternative, and research on the relative cost-effectiveness of the two approaches is needed.

Subsequent management when the primary lesion is identified:

When imaging identifies the primary lesion, EUA with directed biopsies for histological confirmation should be undertaken. Further management should then follow national and institutional guidelines. In our proposed protocol, further management is then determined by the status of the cervical nodal disease. If imaging detects a single node that is less than 3 cm in size with no extranodal extension and a resectable (T1-T2) primary tumor, we advocate surgical resection of the index tumor along with a neck dissection. Surgery is advocated in this instance due to the relatively low risk (<30%) of having indications for postoperative chemoradiotherapy (extranodal extension or involved resection margins), as demonstrated by Sinha et al [67]. We would strongly recommend a transoral approach, with either robotic or laser resection based on the experience of the surgical team, as transoral surgery has been shown to result in less gastrostomy and tracheostomy rates than open surgery for oropharyngeal cancer, and has been shown to be more cost effective[68]. On the other hand, the Sinha study [67] demonstrated that in a cohort of HPV+ patients undergoing TORS/TLM, 55-60% of patients with multiple nodes had extranodal extension. In that situation, according to current evidence [69], the patient is highly likely to require radiotherapy or chemoradiotherapy, despite surgical resection.

There is some controversy regarding the significance of extranodal extension in HPV+ patients who are treated surgically. Sinha et al showed that extranodal extension may not be an important factor, in a cohort treated with surgery and adjuvant therapy [67] .Furthermore, in a large follow-up study, Haughey et al [70] demonstrated that extranodal extension showed only a trend(HR1.6, 0.98-2.63, p=0.06) towards association with overall survival, with only 100 patients. Importantly, however, they showed that post-operative radiotherapy (HR=0.55, p=0.033) and chemoradiotherapy (HR=0.45, p0.017) were significantly associated with improved survival following transoral surgery for HPV+ oropharyngeal cancer, highlighting the importance of adjuvant therapy in this setting. There are ongoing studies examining whether chemotherapy could be eliminated in patients with low risk HPV+OPC treated surgically and who have extracapsular spread[71, 72]. Till these studies report, management of extranodal extension should remain unchanged out with clinical trials. We therefore advocate in these cases proceeding directly to primary

radiotherapy or chemoradiotherapy, as this approach reduces the risk of the patient receiving triple therapy, with an additional (unnecessary) neck dissection and/or surgical excision of the primary tumor.

Subsequent management when primary lesion is not identified:

In the case that the ultrasound-guided biopsy confirms squamous cancer metastasis to the lymph nodes, but conventional imaging followed by FDG-PET/CT could not identify the site of the primary lesion, we advocate that further management should again be undertaken depending on the number and characteristics of the nodal disease on imaging. In patients with advanced neck disease, with multiple unilateral or bilateral nodal disease or those with extracapsular extension on imaging, but no primary site identified, tonsillectomy and an examination under anesthetic should be performed, along with examination of the tongue base using a 4mm endoscope or a microscope and narrow band imaging, as described above[55, 56]. If that does not identify the tumor, then performing tongue base mucosectomy (preferably as a separate procedure) is advised. If no primary is identified, definitive treatment by chemoradiotherapy should then be considered. Neck dissection is not recommended in this case, except in cases of rapidly progressive neck disease or genuine uncertainty regarding extracapsular spread, because as discussed previously, these patients have a high risk of requiring chemoradiotherapy due to extracapsular spread or involved margins [67]. Where no primary has been identified, panmucosal chemoradiotherapy should be considered. However, if the nodal disease is positive for p16 on core biopsy and negative for EBV, then sparing of the post nasal space and larynx may be undertaken given the fact that a p16 positive primary is highly likely to be oropharyngeal in origin, as demonstrated in the studies of Begum et al.[41] Likewise, if the patient is EBV positive and HPV negative, radiotherapy could be directed to the nasopharynx.

Some clinicians question the need for the tongue base mucosectomy on the basis that identification of a small tongue base primary may not alter management. However, on retrospective review of the Pittsburgh experience of 28 cases treated with TORS for unknown primary, Byrd et al. demonstrated the real economic value of identifying the primary site – with savings of between $5774 and $8619, compared to patients where the primary site was not identified.[60] This is partly because a small number of patients may be spared radiotherapy altogether – 6% in one study [73], and moreover as Byrd study

demonstrates, 10 of the 19 identified primaries resected by TORS had clear margins[60]. In addition to the financial savings, a significant proportion of patients may benefit functionally from receiving radiotherapy to smaller areas of mucosa (in 46% of cases in that study), including sparing the contralateral tonsil, lateral constrictors and nodal structures (reported to take place in 30% of cases in the same study)[73]. The new consensus guidelines for outlining of primary tumours in HNSCC [74] , with tighter delineation of primary tumour Clinical Target Volumes, will likely result in further sparing of mucosa and constrictors. However, the clinical benefits of this approach need to be prospectively assessed and the contouring protocol defined, particularly given the varying use of neck dissection in retrospective series.

When there is a single node measuring less than 3 cm and there is no evidence of extranodal extension, we advocate EUA, bilateral tonsillectomy and neck dissection performed at the same time. If subsequent histology confirms the presence of a tumor in the tonsil and no extracapsular extension is identified, transoral completion (TLM or TORS) of the resection is advocated, if indicated by involved resection margins and is technically feasible. This can then be followed by adjuvant treatment, as determined by the standard indications [69]. If tonsillectomy does not identify the index malignancy, transoral mucosectomy of the tongue base should be undertaken. If this is negative, then close follow-up with no further treatment could be considered, as in this situation the declaration of the primary tumor at a later date is low, reported to be only between 5.8-7%[4].

Research

Finally, it is widely acknowledged that the quality of evidence for the investigation and management of carcinoma of the unknown primary in the head and neck is poor, relying mainly on retrospective case studies, or on better quality data for the management of head and neck cancer with known primaries. There is an urgent need for more trials and prospective studies (see Table 2). Due to the relatively low numbers of cases, multicentre and more likely multi-national co-operative studies are likely to be required.

Conclusion

We propose a streamlined protocol, based on currently available evidence. There is a dearth of evidence for carcinoma of unknown primary, and so, where there is a lack of evidence, we have relied on evidence from studies of patients with identified primary tumours. Trials or well-designed prospective studies are urgently needed to examine the long term efficacy and functional outcomes of different combinations and sequences of investigations and treatment modalities for CUP.

Table1: Sensitivity and specificity of different investigations from meta-analyses studies

Investigation type (reference)	Sensitivity (95 % CI)	Specificity (95 % CI)	Primary detection rate
CT scan for extranodal extension [28]	44% (30%, 58%)	75% (57, 88)	N/A
Narrow band imaging [30]28]	77% (50, 92)	84% (68, 93)	N/A
PET CT [30], [31]	88.3% 84% (78-88%)	74.9% 84% (78-89%)	24.5% 37%
Tongue base mucosectomy [66]	-	-	78%

Key:
confidence interval =CI

Table 2:

Potential research questions:

What is the efficacy and cost-effectiveness of different sequences of investigations to detect the primary site? Especially does starting with conventional imaging better and more cost effective than starting with PET CT?

Does doing a tongue base mucosectomy to identify the site of the primary result in additional, functional quality of life or other benefits in patients who are going to be treated with radical chemoradiotherapy anyway? And is it cost-effective?

Does extranodal extension in patients with HPV+ CUP behave differently to that in patients with HPV-negative CUP?

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An evidence-based approach to the investigation and management of squamous cell carcinoma occult primary tumors of the head and neck.

Abstract:

Metastases to the cervical lymph nodes from a occult primary (CUP) of head and neck squamous carcinomas has been increasing in presentation (HNSCC). Modern diagnostic workup, including clinical evaluation, conventional imaging, FDG-PET/CT and panendoscopy/tonsillectomy enables detection of the primary site in over half of all cases, and is associated with significantly improved survival rates. Recent studies have demonstrated the utility of novel molecular pathology and transoral surgical techniques in improving diagnosis and treatment. We present a new, evidence-based protocol incorporating these novel diagnostic modalities. It aims to identify the site of the primary tumor, and determine the stage of the disease, including extranodal extension. This information can personalise treatment recommendations, rationalise combinations of treatment modalities, and thereby potentially minimise toxicity and improving functional outcomes.

Introduction

The carcinoma of unknown primary in the head and neck (CUP) occurs when a patient presents with clinically-evident cervical lymphadenopathy, but where a primary tumor cannot be identified by thorough medical history, clinical examination and non-invasive and invasive diagnostic workup [1].

The identification of the primary site by modern functional imaging has significantly reduced the prevalence of true CUP [2]. In the past, only about 1-7% of all head and neck cancer patients present with metastases to the lymph nodes as the only clinical evidence of the disease [3-5]. This appears to be is increasing in incidence due to the increasing human papillomavirus-related oropharyngeal cancer [5]. The natural history of the development of CUP remains unclear. Potential reasons for the inability to detect the primary site may include small tumour volume, hidden location (e.g. tonsillar crypt), slow growth rate, and/or possible involution of the primary tumor, thereby hindering its recognition[6, 7].

Several guidelines, consensus statements, and literature reviews have been published describing the diagnostic and therapeutic approach to CUP in the last decade [8-10]. However, recently there has been a considerable amount of new and essential data published on novel diagnostic approaches, including the role of Human papillomavirus (HPV) detection and the utility of transoral minimally-invasive procedures. Our aim here is to present an evidence-based algorithm for the diagnosis and treatment of patients with CUP, that incorporates recent developments.

Objectives:

The principal objectives of the diagnostic evaluation of the patient with CUP are to identify the location of the primary tumor, to reliably determine the histology, to ascertain the extent of locoregional disease (including nodal extranodal extension), and to exclude distant metastases. The other important consideration for the diagnostic workup should be the utilization of the shortest and the least invasive pathway to achieve diagnosis and treatment, with the least morbidity and the highest cost-effectiveness [9].

A retrospective study of 236 patients with an initial presentation of CUP

demonstrated ultimate detection of a primary tumour after investigation in 53% of cases. Approximately 88% of these were oropharyngeal primaries (equally divided between the base of tongue and tonsil). The likelihood of a biopsy-proven primary decreased significantly in patients with no findings on examination and radiology, compared to those with positive findings on both (29% vs. 64% respectively)[11].

Identification of the primary site is crucial as it helps direct therapy and has been reported by some studies to be associated with better prognosis and survival. A matched paired retrospective analysis by Davis (n=22), demonstrated significantly improved survival in patients with CUP where the primary tumour was subsequently identified, compared to those where it was not (HR = 0.125; 95% CI, 0.019–0.822; *P* = .030). This may be in part because lesions that were identified were more likely to be HPV positive[12]. Similarly, Haas et al. reported 100% 3-year survival in the eight patients whose oropharyngeal primary was identified compared to 58.8% for the 34 patients with a persistent "occult primary" (n=34) [13].

TNM staging:

In the American Joint Cancer Commission (AJCC) [14] and Union for International Cancer Control (UICC) 8th Editipn TNM Staging Manual [15], substantial changes have been introduced to the staging of patients with CUP. Previously, CUP cases were categorized as T0, but were not assigned to a specific anatomic subsite. Evidence now shows that that upto 90% of cases initially designated as having actually have virally-assciated (HPV or EBV) cancers Consequently the presence of either Epstein-Barr Virus (EBV) or HPV in metastatic lymph nodes may facilitate identification of an anatomic site of origin [16, 17]. Therefore, at least p16 immunohistochemistry and EBV encoded (EBER) RNA-in situ hybridisation(ISH) are recommended for all cervical lymph nodes with carcinoma of unknown primary site. Thus, one key change from prior editions of the TNM system is the elimination of the T0 category in sites other than the nasopharynx, HPV–associated oropharyngeal cancer, and salivary gland cancers (which can be identified by histology). If no primary lesion can be identified, then the lymph node may have emanated from any mucosal site, so there is no rationale to support retaining the T0 designation outside of the virally associated cancers of the

oropharynx and nasopharynx[18]. In other words, when the presence of EBV RNA is determined by ISH, the patient is staged as per nasopharyngeal cancer, and when p16 positive IHC is present, as per oropharyngeal cancer. In all other scenarios, the clinical and pathological node definitions are as per non-HPV positive oropharyngeal cancers.

Presentation and clinical examination

The majority of CUP patients present to the outpatient clinic with a palpable neck mass. This was the primary reason for consultation in 94% of a series of 352 patients [3] and all subjects of a separate cohort of 167 patients [1]. Other characteristic head and neck cancer symptoms such as dysphagia, pain and weight loss were reported in less than 10% of patients. Demographically, patients with CUP were typically male, between 55-65 years old with a history of chronic tobacco and/or alcohol use [1, 19]. More recently, this pattern appears to have changed with an increase in younger non-smoking patients presenting with human papillomavirus (HPV)-related oropharyngeal cancer [20].

A thorough history should always be taken. This includes eliciting a history of other malignancies, immunosuppression or compromise, sun exposure, skin cancer or removal of skin lesions. This should be followed by clinical examination, which should routinely involve assessment of the entire upper aerodigestive tract, along with neck palpation and flexible nasendoscopy. Physical examination should also include skin examination. The location of the cervical lymph node metastasis may suggest the location of the primary site, due to established patterns of lymphatic drainage in the head and neck. Most commonly, enlarged cervical lymph nodes are identified at level II, followed by level III, with bilateral involvement reported in <10% [1, 3, 19]. This is in keeping with the majority of tumours in CUP patients being from the oropharynx. Bilateral nodal metastases should draw attention to the nasopharynx, base of tongue, hypopharynx and midline structures. Non-oropharyngeal primaries, such as skin or distant metastases from non-head and neck primary, should be suspected in patients with intraparotid lymph nodes or posterior or supraclavicular nodal involvement. The involvement of both upper and lower nodal levels should prompt the physician to exclude distant metastases, which are much more frequent in these patients compared to the patients with involvement of just the upper nodal levels[21]. The median

nodal size is 3.5 to 5 cm[22]. The time interval between first appearance of a cervical mass and diagnosis ranged between 2 and 5 months[1, 3, 23].

Imaging

The choice and sequence of imaging technique is important in the diagnostic workup of CUP. The imaging techniques utilized should be able to identify the primary site, the extent of nodal disease (including extranodal extension), and the presence of distant metastases. Computed tomography (CT) and/or Magnetic Resonance imaging (MRI) with intravenous contrast of the neck and thorax have been the mainstay of diagnostic workup in CUP detection. There appears to be no significant difference in the efficacy of CT and MRI - both have reported detection rates of 9-23% [24-26]. With regards to identifying extracapsular nodal extension, MRI is reported to be marginally superior to CT, with specificities and sensitivities 85% and 84% vs. 77% and 80% respectively [27]. An analysis by the NICE guidelines reported the pooled sensitivity of CT to detect extranodal extension in 4 studies to be lower, at 44% (95 % confidence interval [CI] 30%, 58%) and the specificity as 75% (95% CI 57, 88)[28]. Chai et al. report the negative predictive value of CT for the detection of the extranodal extension to be 49%. Therefore, CT imaging may be considered useful in positively identifying extracapsular extension, but not for convincingly excluding it [29].

There is now a large body of evidence supporting the use of FDG-PET/CT as an effective diagnostic tool for the identification of the site of the primary tumour, when standard imaging techniques are negative. A meta-analysis by Rusthoven et al., which included 302 patients from 16 studies published between 1994 and 2003, demonstrated a primary tumour detection rate by FDG-PET of 24.5% (sensitivity 88.3%; specificity 74.9%; diagnostic accuracy 78.8%)[30]. The highest false-positive rate was seen in the tonsils (39.3%), while the lowest sensitivity rate was seen in the base of the tongue (80.5%). A more recent meta-analysis by Kwee et al. using hybrid FDG-PET/CT included 11 studies published between 2005 and 2007 and comprised 433 patients. Here, the overall primary tumor detection rate, pooled sensitivity, and specificity of FDG-PET/CT/ were

37%, 84% (95% CI 78-88%) and 84% (95% CI 78-89%), respectively [31]. The false positive rate (15%) was again highest for oropharyngeal tumors.

FDG-PET/CT scanning does have some limitations however. The resolution of FDG-PET/CT limits its ability to detect tumors smaller than 5mm. In addition, the basal uptake of FDG in normal lymphoid tissues within Waldeyer's ring and the uptake of FDG by salivary gland tissue limit the value of FDG-PET/CT in identifying small or superficial lesions in these locations. Additionally, FDG-PET/CT is relatively more expensive in comparison to conventional imaging modalities. In a recent study from Denmark, Dale et al. showed that the additional efficacy of FDG-PET/CT in identifying the primary site in patients where it has not been previously identified by clinical examination, flexible endoscopy, and standard cross-sectional imaging was only 7% (95 % CI 2–21 %). Therefore, we believe FDG-PET/CT is ideally indicated only when the primary site has not been identified by clinical examination and conventional imaging [32].

Tissue diagnosis

Fine needle aspiration biopsy (FNA) is currently the most widely used technique for obtaining diagnostic information from metastatic lymph nodes. It is safe, cost-effective and reliable [33]. Excisional biopsy of lymph nodes should be avoided due to the potential local complications (such as hematoma, infection, disruption of fascial planes for subsequent neck disscetion), as well as the theoretical risk of neck recurrence [34]. However, despite certain advantages, FNA has also some drawbacks, especially in the setting of CUP. Cystic nodal metastases are particularly associated with HPV-driven malignancies[35], which are common causes of cup. In patients with cystic metastases, the efficacy of FNA is significantly reduced, with a false negative rate of up to 42% [36]. Furthermore, the differential diagnosis of a metastatic node includes brachial cleft cysts, a necrotic node with abscess formation or tuberculosis, which can sometimes be difficult to differentiate on needle aspiration alone. Sensitivity of this technique therefore may not exceed 50% [37], however performing FNA under ultrasound guidance can improve the sensitivity considerably, up to 80% [35].

Ultrasound-guided core biopsy of the involved lymph nodes can retrieve a more substantial tissue sample, and is also considerably less invasive than an excisional biopsy.

Although core biopsy may not significantly improve the overall sensitivity of diagnosing squamous cell carcinoma in lymph node metastases, it substantially enhances sample adequacy for obtaining a diagnosis. Novoa et al., in a meta-analysis and systematic review (16 studies, N=1267) of core needle biopsies used in the evaluation of head and neck lesions, showed that adequate material for histologic diagnosis and ancillary studies was obtained in 95% of cases [38]. In some centers, a core biopsy routinely follows the FNA to enhance sample accuracy for HPV testing [38, 39]. Furthermore, the risk of potential complications of core biopsy (including tumor seeding and major bleeding) have been proven to be negligible. Due to these advantages, we prefer US-guided core biopsy to US-guided FNA in the diagnostic workup of CUP, but both are valid alternatives.

Since up to 80% of all oropharyngeal tumors can be HPV driven malignancies, the determination of HPV testing in fine needle aspirates and core biopsies has gained relevance to guide the localization of the primary tumor[40]. The preferential distribution of p16 staining in carcinomas of the oropharynx supports the use of p16 staining for discerning the site of tumor origin in those patients presenting with cervical lymph node metastases. Begum et al. identified HPV16 in 10 of 19 metastases from the oropharynx, but in none of 46 metastases from other sites (53% versus 0%; $P < 0.0001$) [41]. p16 expression in nodal metastases was highly correlated with site of tumour origin.

Studies that have addressed HPV testing of cytological samples have primarily tried to adapt tissue-targeted approaches, e.g. p16 immunohistochemistry and HPV in-situ hybridization to cytological specimens[41, 42]. Numerous studies have confirmed the feasibility of p16 immunostaining in fine needle aspirates and biopsies of cervical lymph node metastases [41-43]. Holmes et al. [44] detected p16 staining in the FNA of involved nodes in 71% of the 85 patients with metastatic oropharyngeal squamous cell carcinomas. This is similar to the findings of other authors [41, 45]. In contrast, p16 immunostaining on FNA was only seen in 13% of nodal metastases from non-oropharyngeal sites ($p< 0.001$) [44]. Jakscha et al. found that in their cohort of 54 patients, p16 positivity by immunohistochemistry of FNA cytology correlated with that of excised lymph nodes in every HPV positive case [46]. Of the 17 lymph node metastases that were p16 negative on histology, 15 (88%) were p16-negative on FNA, and two cases were false positive. In a very recent study, Cheol Park et al. compared the diagnostic value of HPV, p16, and EBV in the aspirates from the cervical lymph nodes to FDG-PET/CT in a prospective series of 54

consecutive cases. Overall, primary tumors were identified in 28 (51.9%) of patients. The sensitivity of p16 (85.7%) and accuracy of HPV (85.2%) were higher than those of FDG-PET/CT (42.9% and 68.5% respectively, $p < 0.05$) [47]. It should be noted however that, in most studies, HPV testing of cytological FNA specimens was restricted to the small subset of the overall cases – that subset consisted of case from which sufficient cellular material was available for the construction of cell blocks. For example, Begum et al. reported, that only 20% of the FNA samples were sufficiently cellular for HPV testing [41]. Limited cellularity affecting p16 immunohistochemistry may also produce false negative results [44, 48, 49]. This further supports the superiority of core biopsies over FNA to facilitate HPV testing.

Included in the differential diagnosis of metastatic lesions of the neck (especially those located in levels V, but also levels II-IV), is EBV-related, undifferentiated nasopharyngeal carcinoma, which should also be considered in those patients who have no apparent primary [50, 51]. Nakao et al. evaluated 36 nasopharyngeal cancer patients (30 primary tumour and 6 lymph node metastases) by EBV in-situ hybridization and determined that 60% of primaries and 50% of metastatic cases were associated with EBV. In contrast, among patients with lymph nodes metastases from other head and neck sites (n=13) EBV was not identified in any of the cases [52]. A retrospective analysis of 22 metastatic lymph nodes from CUP patients attempted to determine the localization of the primary tumor by assessment of the HPV and EBV status in the nodes. In all 3 cases where the primary was eventually identified in nasopharynx, the cystic metastases turned out to be EBV positive and HPV negative. Where the primary originated from other anatomical site, 1 case were EBV positive [53]. In other consecutive series of CUP patients, oncogenic viral infections (EBV or HPV) were found in 12 cases (54%). In that series, EBV was detected in 2 cases [50]. Therefore, for non-keratinizing or undifferentiated carcinomas that are p16 negative, EBV in situ hybridization (EBER) should be performed. The combination of undifferentiated morphology and EBV positivity is sufficient evidence to strongly suggest an occult nasopharyngeal primary[54]. In the newly published American Joint Cancer Commission (AJCC) 8th Edition TNM staging Manual [14] and Union for International Cancer Control (UICC)[15], the algorithm for workup of SCC of unknown primary includes HPV and EBV testing. Tumours positive for the viruses are staged according to the respective staging criteria for oropharynx and nasopharynx (see relevant section above).

Panendoscopy with biopsy and tonsillectomy

Regardless of the findings of the above combination of investigations, performing meticulous examination under anesthesia (EUA) and panendocscopy is mandatory in all CUP cases. Where imaging has identified the primary site, EUA allows histological confirmation by diagnostic biopsy. For example, Cianchetti confirmed the findings in 64% of cases where the index tumor had been previously identified by clinical examination and PETCT[11]. When the primary tumor has not been identified despite conventional and FDG-PET/CT imaging, subsequent EUA enabled identification of primary site in approximately 35% of patients[4, 11]. Therefore, a negative FDG-PET/CT does not preclude the need for panendoscopy to detect the primary site. In that situation, EUA should include the examination of nasopharynx, laryngoscopy, pharyngoscopy, and oesophagoscopy. Palpation of accessible subsites is also strongly advocated. Importantly, Miller also demonstrated that the overall risk of subsequent manifestation of a primary tumor of the upper aerodigestive tract in patients that have had a negative FDG-PET/CT and a negative panendoscopy was very low (5.8%), demonstrating the efficacy of this combined approach [4].

Random biopsies are of very low diagnostic value [35]. In contrast, Karni found that undertaking transoral microscopic examination of the base of tongue identified a significantly higher number of primary tumors in the base of tongue compared to rigid EUA (94% vs. 25% respectively) [55]. Therefore, examination of the base of tongue with a 30◦ 4mm endoscope or a microscope, in conjunction with a Feyh-Kastenbauer (FK) retractor, is recommended. The new generation of high and ultra-high definition systems is likely to assist further in this respect.

Narrow band imaging

Narrow band imaging (NBI) identifies abnormal neoangiogenic patterns on the mucosa. Its application in the pre-and intra-operative setting has been recently been shown to be an useful adjunct in the detection of primary lesion. Filauro at al. analyzed the consecutive case series of 29 CUP cases, where the CT and/or MRI and FDG-PET/CT did not reveal the primary lesion. NBI used during panendoscopy identified the primary tumor in 10

patients (34.5%). The sensitivity, specificity, positive and negative predictive values and accuracy were 91%,95%, 91%,91% and 90% respectively[56]. A pooled analysis of 5 studies by the NICE guidance [28] reported a pooled sensitivity and specificity of narrow band imaging as 77% (95 % confidence interval [CI] 50, 92) and 84% (95% CI 68, 93), respectively.

Tonsillectomy

In patients where no primary can be found on EUA, tonsillectomy is indicated. In a cohort of 126 patients with CUP, Walton et al. reported a positive yield in 30% of patients who underwent tonsillectomy. In comparison, in the same study, deep biopsies only identified the malignancy in 3% of cases, reflecting the fact that some tumors are small and located within the tonsillar crypts and so cannot be identified by simple biopsy. While there are no clear recommendations available on performing unilateral or bilateral tonsillectomy, rates of contralateral tumours of up to 10-17% [57, 58], have been reported, suggesting a need for considering bilateral tonsillectomy.

Tongue base mucosectomy

In addition to tonsillectomy, there is now increasing evidence for the role of tongue base mucosectomy for patients whose primary remains undetected after undergoing the protocol described above. During this procedure, the whole of the tongue base mucosa (including the lingual tonsils) is removed en bloc or in two (right and left) sections. Meticulous histopathological examination, with multiple sections, is then undertaken. For example, Patel et al. performed a retrospective, multi-institutional case series, in which data were pooled from the 6 institutions. The primary site was located by transoral robotic surgery (TORS) in 34 of 47 patients (72.3%), of which the primary site was located in the base of tongue for 20 patients (58.8%). In 18 of 47 patients (38.3%), both preoperative radiographic and physical examination failed to suggest a primary site. Of these 18 patients, a tongue base primary as identified in 13 (72.2%) cases after undergoing TORS [59]. Similarly, Byrd reported identifying the primary in 19 (86.4) of the 22 cases of lingual tonsillectomy by TORS [60] . In another study, the average time to return to normal swallowing function was 2.7 days, and there were no major surgical complications [61]. More recently, Winter et al., reported on a retrospective case review from 4 head and neck centers in the United Kingdom, analyzing 35 patients where the primary tumor was not identified during clinical

examination, imaging (including FDG-PET/CT) and bilateral tonsillectomy. The primary tumor site was identified in the tongue base in 53% (n=17) of patients. In 15 (88%) of these patients, the tumor was in the ipsilateral tongue base, while in two cases (12%) the tumor was located in contralateral tongue base[62]. Similar retrospective single-center analyses have been performed by Hatten[63] and Geltzeiler [64], who examined consecutive cohorts of 60 and 64 patients with unknown primary respectively. In the Hatten study, transoral robotic surgery procedures enabled the identification of the primary in 48 (80%) patients, all in the oropharynx. In 28 (50.8%) patients, the index tumor was identified in base of the tongue, while in 18 patients (38%) the primary tumors were in the palatine tonsils. The mean size of the identified mucosal primary lesions was 1.3mm (SD 0.1mm), which is below the resolution of detection by FDG-PET/CT. Geltzeiler reported that the primary tumor was found in 51 (80%) of 64 patients. Of those patients, 14 (22%) were found on EUA alone. Fifty patients underwent further robotic transoral lingual tonsillectomy ± palatine tonsillectomy, with primary tumors identified in 37 (74%) cases. The primary tumor was located in the lingual tonsil in 32 patients (86%) and palatine tonsil in 5 patients (10%, $p<0.001$).

Transoral laser microsurgery appears to be similarly effective. Karni et al.[55] compared transoral laser microsurgery (TLM) with traditional EUA, reporting detection rates of 94% compared to 25% respectively in a series of 30 patients. Nagel et al. reported a detection rate of 86% in a retrospective series of 36 TLM patients, using their algorithm of directed biopsies, frozen section, and lingual tonsillectomy [65].

In a very recent meta-analysis of 552 patients from 21 studies [66], the reported pooled rate of identification of a primary by tongue base mucosectomy was 57%. In patients with a negative conventional imaging, PETCTscanning, EUA and tonsillectomy, the rate of identification by tongue base mucosectomy rose to 78% [66].

The question then arises whether tonsillectomy and transoral mucosectomy should be performed concurrently or sequentially. Byrd et al. showed that the simultaneous tonsillectomy and TORS treatment strategy was associated with lower *direct* hospital costs and physician fees compared to the sequential strategy. However, simultaneous base of the tongue resection and tonsillectomy was associated with significantly more pain. As a result, two of five patients who underwent the simultaneous procedures required longer inpatient stays for pain control due to inability to eat, which resulted in an increased *overall* cost for

the simultaneous strategy. There was also concern about the development of late circumferential stenosis, especially after radiation or concurrent chemoradiation. Overall, analysis of incremental cost savings for sequential and simultaneous EUA and TORS base of tongue resection were $8619 and $5774 respectively per additional primary identified, compared to EUA+ tonsillectomy alone, highlighting not only the cost-effectiveness of lingual tonsillectomy in this indication, but also higher cost-effectiveness of the sequential approach compared to concomitant procedure approach[60]. We therefore, advocate that delayed transoral mucosectomies are undertaken, only when the tumor remains unidentified after EUA and tonsillectomy.

Proposed algorithm for diagnosis and treatment of CUP

Based on the analysis of the above literature review, we propose an evidence-based algorithm for the diagnosis and management of patients presenting with clinical CUP (Fig1). However due to the dearth of high quality prospective or randomised data in the CUP setting, we have relied on data from studies of patients with known head and neck cancer primaries, and extrapolated this to the CUP setting.

Fig. 1 The proposed diagnostic and therapeutic protocol for CUP in head and neck.

For patients who present with a palpable neck mass where the primary tumor is not identified on clinical examination including flexible nasendoscopy (preferably with narrow band imaging), we recommend a CT or MRI scan of the neck, with intravenous contrast and a CT scan of the thorax, depending on institutional availability and waiting lists. Patients should also have an ultrasound-guided core biopsy (preferable to fine needle aspiration biopsy, albeit both are acceptable). Immunohistochemical staining of the biopsy sample for p16 is strongly recommended, and if negative, then EBV insitu hybridization should be undertaken, especially for presentations suggesting naso[haryngeal cancer. If the CT/MRI scan does not identify the primary site, a FDG-PET/CT scan should be requested immediately (preferably by the reporting radiologist) to avoid delay to further management. Requesting a FDG-PET/CT scan as the primary diagnostic modality is a viable alternative, and research on the relative cost-effectiveness of the two approaches is needed.

Subsequent management when the primary lesion is identified:

When imaging identifies the primary lesion, EUA with directed biopsies for histological confirmation should be undertaken. Further management should then follow national and institutional guidelines. In our proposed protocol, further management is then determined by the status of the cervical nodal disease. If imaging detects a single node that is less than 3 cm in size with no extranodal extension and a resectable (T1-T2) primary tumor, we advocate surgical resection of the index tumor along with a neck dissection. Surgery is advocated in this instance due to the relatively low risk (<30%) of having indications for postoperative chemoradiotherapy (extranodal extension or involved resection margins), as demonstrated by Sinha et al [67]. We would strongly recommend a transoral approach, with either robotic or laser resection based on the experience of the surgical team, as transoral surgery has been shown to result in less gastrostomy and tracheostomy rates than open surgery for oropharyngeal cancer, and has been shown to be more cost effective[68]. On the other hand, the Sinha study [67] demonstrated that in a cohort of HPV+ patients undergoing TORS/TLM, 55-60% of patients with multiple nodes had extranodal extension. In that situation, according to current evidence [69], the patient is highly likely to require radiotherapy or chemoradiotherapy, despite surgical resection.

There is some controversy regarding the significance of extranodal extension in HPV+ patients who are treated surgically. Sinha et al showed that extranodal extension may not be an important factor, in a cohort treated with surgery and adjuvant therapy [67] .Furthermore, in a large follow-up study, Haughey et al [70] demonstrated that extranodal extension showed only a trend(HR1.6, 0.98-2.63, p=0.06) towards association with overall survival, with only 100 patients. Importantly, however, they showed that post-operative radiotherapy (HR=0.55, p=0.033) and chemoradiotherapy (HR=0.45, p0.017) were significantly associated with improved survival following transoral surgery for HPV+ oropharyngeal cancer, highlighting the importance of adjuvant therapy in this setting. There are ongoing studies examining whether chemotherapy could be eliminated in patients with low risk HPV+OPC treated surgically and who have extracapsular spread[71, 72]. Till these studies report, management of extranodal extension should remain unchanged out with clinical trials. We therefore advocate in these cases proceeding directly to primary

radiotherapy or chemoradiotherapy, as this approach reduces the risk of the patient receiving triple therapy, with an additional (unnecessary) neck dissection and/or surgical excision of the primary tumor.

Subsequent management when primary lesion is not identified:

In the case that the ultrasound-guided biopsy confirms squamous cancer metastasis to the lymph nodes, but conventional imaging followed by FDG-PET/CT could not identify the site of the primary lesion, we advocate that further management should again be undertaken depending on the number and characteristics of the nodal disease on imaging. In patients with advanced neck disease, with multiple unilateral or bilateral nodal disease or those with extracapsular extension on imaging, but no primary site identified, tonsillectomy and an examination under anesthetic should be performed, along with examination of the tongue base using a 4mm endoscope or a microscope and narrow band imaging, as described above[55, 56]. If that does not identify the tumor, then performing tongue base mucosectomy (preferably as a separate procedure) is advised. If no primary is identified, definitive treatment by chemoradiotherapy should then be considered. Neck dissection is not recommended in this case, except in cases of rapidly progressive neck disease or genuine uncertainty regarding extracapsular spread, because as discussed previously, these patients have a high risk of requiring chemoradiotherapy due to extracapsular spread or involved margins [67]. Where no primary has been identified, panmucosal chemoradiotherapy should be considered. However, if the nodal disease is positive for p16 on core biopsy and negative for EBV, then sparing of the post nasal space and larynx may be undertaken given the fact that a p16 positive primary is highly likely to be oropharyngeal in origin, as demonstrated in the studies of Begum et al.[41] Likewise, if the patient is EBV positive and HPV negative, radiotherapy could be directed to the nasopharynx.

Some clinicians question the need for the tongue base mucosectomy on the basis that identification of a small tongue base primary may not alter management. However, on retrospective review of the Pittsburgh experience of 28 cases treated with TORS for unknown primary, Byrd et al. demonstrated the real economic value of identifying the primary site – with savings of between $5774 and $8619, compared to patients where the primary site was not identified.[60] This is partly because a small number of patients may be spared radiotherapy altogether – 6% in one study [73], and moreover as Byrd study

demonstrates, 10 of the 19 identified primaries resected by TORS had clear margins[60]. In addition to the financial savings, a significant proportion of patients may benefit functionally from receiving radiotherapy to smaller areas of mucosa (in 46% of cases in that study), including sparing the contralateral tonsil, lateral constrictors and nodal structures (reported to take place in 30% of cases in the same study)[73]. The new consensus guidelines for outlining of primary tumours in HNSCC [74] , with tighter delineation of primary tumour Clinical Target Volumes, will likely result in further sparing of mucosa and constrictors. However, the clinical benefits of this approach need to be prospectively assessed and the contouring protocol defined, particularly given the varying use of neck dissection in retrospective series.

When there is a single node measuring less than 3 cm and there is no evidence of extranodal extension, we advocate EUA, bilateral tonsillectomy and neck dissection performed at the same time. If subsequent histology confirms the presence of a tumor in the tonsil and no extracapsular extension is identified, transoral completion (TLM or TORS) of the resection is advocated, if indicated by involved resection margins and is technically feasible. This can then be followed by adjuvant treatment, as determined by the standard indications [69]. If tonsillectomy does not identify the index malignancy, transoral mucosectomy of the tongue base should be undertaken. If this is negative, then close follow-up with no further treatment could be considered, as in this situation the declaration of the primary tumor at a later date is low, reported to be only between 5.8-7%[4].

Research

Finally, it is widely acknowledged that the quality of evidence for the investigation and management of carcinoma of the unknown primary in the head and neck is poor, relying mainly on retrospective case studies, or on better quality data for the management of head and neck cancer with known primaries. There is an urgent need for more trials and prospective studies (see Table 2). Due to the relatively low numbers of cases, multicentre and more likely multi-national co-operative studies are likely to be required.

Conclusion

We propose a streamlined protocol, based on currently available evidence. There is a dearth of evidence for carcinoma of unknown primary, and so, where there is a lack of evidence, we have relied on evidence from studies of patients with identified primary tumours. Trials or well-designed prospective studies are urgently needed to examine the long term efficacy and functional outcomes of different combinations and sequences of investigations and treatment modalities for CUP.

Table1: Sensitivity and specificity of different investigations from meta-analyses studies

Investigation type (reference)	Sensitivity (95 % CI)	Specificity (95 % CI)	Primary detection rate
CT scan for extranodal extension [28]	44% (30%, 58%)	75% (57, 88)	N/A
Narrow band imaging [30]28]	77% (50, 92)	84% (68, 93)	N/A
PET CT [30], [31]	88.3% 84% (78-88%)	74.9% 84% (78-89%)	24.5% 37%
Tongue base mucosectomy [66]	-	-	78%

Key:
confidence interval =CI

Table 2:

Potential research questions:

What is the efficacy and cost-effectiveness of different sequences of investigations to detect the primary site? Especially does starting with conventional imaging better and more cost effective than starting with PET CT?

Does doing a tongue base mucosectomy to identify the site of the primary result in additional, functional quality of life or other benefits in patients who are going to be treated with radical chemoradiotherapy anyway? And is it cost-effective?

Does extranodal extension in patients with HPV+ CUP behave differently to that in patients with HPV-negative CUP?

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Figure 1

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Key

ENE = extranodal extension
RT = radiotherapy
CRT = chemoradiotherapy
ND = neck dissection
TORS = transoral robotic surgery
TLM = transoral laser microsurgery
EUA = examination under anaesthetic
* = indications for CRT are extranodal extension on neck dissections and/or persistent positive margins on resection of primary