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Review Article

Cervical metastasis of undetermined origin: evaluation and criteria for management

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ABSTRACT

Background: Cervical metastatic cancer of undetermined primary site is described as the presence of metastasis in the cervical lymph node(s) without any identifiable primary site, despite detailed clinical and investigative evaluations. Identification of primary origin is still a big challenge even in the phase of modern diagnostic options. This review was meant to lay open the challenges and offer options of evaluation and managing these cases in a resource limited environment.
Methods: The literature search was carried out to retrieve relevant published articles, books, guidelines. The search was limited to articles in English while unpublished literatures were excluded.
Results: The process of metastasis might begin before the obvious growth of the primary mass, making detection of primary site of a malignant tumour difficult to determine. There is no current worldwide consensus for evaluation and treatment of cervical metastasis of undetermined primary; however, the primary purpose for management should be towards cure along with locoregional control. This is always based on a well-studied natural history of the mucosal squamous cell cancers of the upper aerodigestive tract.
Conclusions: The first step in the work up remains thorough clinical evaluation and the minimum evaluation should include computed tomography scan of the head and neck, core needle biopsy of the metastatic cervical lymph node(s) for histological analysis, panendoscopy and biopsies from suspicious sites in the upper airway. Treatment modalities can be classified into modified radical neck dissection with or without adjuvant radiotherapy, radiotherapy alone, and combination of surgical intervention and chemoradiation.

Keywords: Head and neck, Cervical metastasis, Primary site, Panendoscopy, Chemoradiation

INTRODUCTION

A head and neck metastatic cancer of unknown or undetermined primary site (CUPS), which was previously referred to as the metastasis of unknown origin (MUO), can be defined as the presence of cancer cells or tissue in one or more lymph nodes within the head and neck region (not solely in the supraclavicular region), without an identifiable primary origin.[1] It can be further elaborated as a metastatic tumour whose site of origin remains undetermined or unknown at the time of assessment and decision making, despite detailed history, thorough physical examination, laboratory investigations, and mandatory imaging and endoscopic evaluation.[2-4] In other words, patient should be considered to have CUPS when metastatic cancer is detected at one or more sites and adequate clinical evaluation and thorough investigations failed to define or detect a primary tumor site o- pattern.[5-7]

CUPS is an uncommon clinical syndrome, accounting for approximately 3-5% of all oncologic diagnoses.[2,4,5,8] Various studies from different regions have reported a general incidence of patients with CUPS as 2-15%.[4,8,9] Factors likely to be responsible for the wide ranges includes (but not limited to) the differences in the defining criteria from center to center, different protocols and assessments methods used in different institutions. Another important factor is whether diagnosis was limited to only squamous cell carcinoma (SCC) or other types of cancer like undifferentiated, adenocarcinoma.[9] Calabrese et al reported that the cervical lymph node metastases from occult primary site constitute about 5-10% of all patients with CUPS in the body system and 2-9% of all head and neck cancers (HNCs).[10] Abbruzzese et al and Ofo et al noted that CUPS accounts for about 1-5% of HNCs while Nieder et al also added that 2-4% of the SCC of the head and neck region will present as CUPS.[4,11,12] The most frequent histopathological diagnoses of unknown primary cancers are SCC in 65-76% of cases, followed by undifferentiated carcinoma, adenocarcinoma, and lymphoepithelial carcinoma. The mean age at diagnosis ranged from 55 to 65 years, with a male gender predominance. Level II group of nodes was the most frequently involved, followed by level III, with the N2 stages having apparent prevalence.[7,13,14] The level of the involved lymph nodes most often serves as a pointer into the region of the primary site and may also guide the diagnostic assessment. Unilateral cervical lymphadenopathy was commoner, while bilateral was present in approximately 10% of the patients.[15,16] Identification of primary site in CUPS is still a big challenge; with modern diagnostic options like positron emission tomography/computerized tomography (PET/CT), panendoscopy, tonsillectomy and directed biopsies, only 59.6% of primary tumors are identified.[17]

Studies done in a tertiary centre in North Central of Nigeria have shown a gradual decline in the prevalence of CUPS from 10.1% to 5.6% over a period of 20 years.[18,19] Results from a national survey by the Danish Society also revealed similar finding of a decreased from 2.5 to 1.7% in a 20-year period.[7] This significant decrease in the frequency of CUPS was alluded to improvement in diagnostic modalities which included better endoscopic and imaging assisted investigative measures.[7,19]

There are at least two major hypotheses involved in CUPS biology that have been reported: one suggests that CUPS are heterogeneous group of site-specific tumors which share the properties of the small primary from where they were derived and the other refers to CUPS as a distinct entity with a specific genetic asset.

It is clearly evident that the biological and genetic mystery behind CUPS is enclosed in the molecular mechanisms that speed up distant metastasis so as to confer the primary lesion a status comparable to dormancy.[20]

Cervical lymph nodes are the first structures to receive metastases for many head and neck cancers; however, it is important to note that they can also be involved in metastases from other primary sites including lung, breast and pancreas.[21] For example, SCC of the head and neck has a specific and predictable metastatic pattern to the regional lymph nodes. However, there are cases in which the primary site of origin could not be found even with the most accurate clinical examination, imaging and the usage of flexible/rigid endoscopes.[9] In cases where the morphology, imaging and molecular predictive assays are non-contributory, they could only be correctly described as CUPS.[20] In few other cases, the primary tumor is found after the treatment of the metastatic tumour.[9]

METHODS

We did a literature search for relevant articles in PubMed/Medline, Scopus, Cochrane library, Web of Science and Google scholar as well as relevant books magazines, leaflets and professional body guidelines. The keywords used for the search includes: head and neck cancers, cervical lymph node, metastasis of undetermined/unknown origin, metastatic tumour, primary tumour. The Boolean operators "AND" and "OR" were used to achieve more focused and productive search. We ensured that relevant studies conducted many years ago and the recent ones were captured in the search results.

The search was also restricted to publications written in English but not restricted by date or publication type. Abstracts, conference proceedings, unpublished articles and/or studies with low relevance to the scope of this study were excluded. All downloaded articles were imported into the literature management software: Mendeley Desktop to eliminate duplicated records and for proper referencing.

CLINICAL EVALUATION

There is no universal guideline for evaluation and workup of CUPS currently. Generally, evaluation begins with a full history and physical examination to include flexible fiber optic nasopharyngolaryngoscopy (Figure 1).[22] A painless and unilateral cervical mass is the usual clinical presentation. The site and level of the palpable lymph node(s) may be useful in suggesting or giving insight to the location of the primary tumor site.[15,16] Neck masses presenting with no determined primary site can be solid or cystic, which can either be single or multiple. Bilateral involvement and other symptoms like pain or difficulty in swallowing has been reported in less than 10 per cent of patients presenting with cervical CUPS.[6] Zhuang et al reported that the most frequently involved level of lymph node is level II in 30-50% of cases, followed by levels I and III in 10-20% and levels IV and V (5-10%) metastases to levels I, II, III, V and VI are generally attributed to head and neck cancers, whereas the involvement of level IV is often associated with primaries below the clavicles.[10,16]

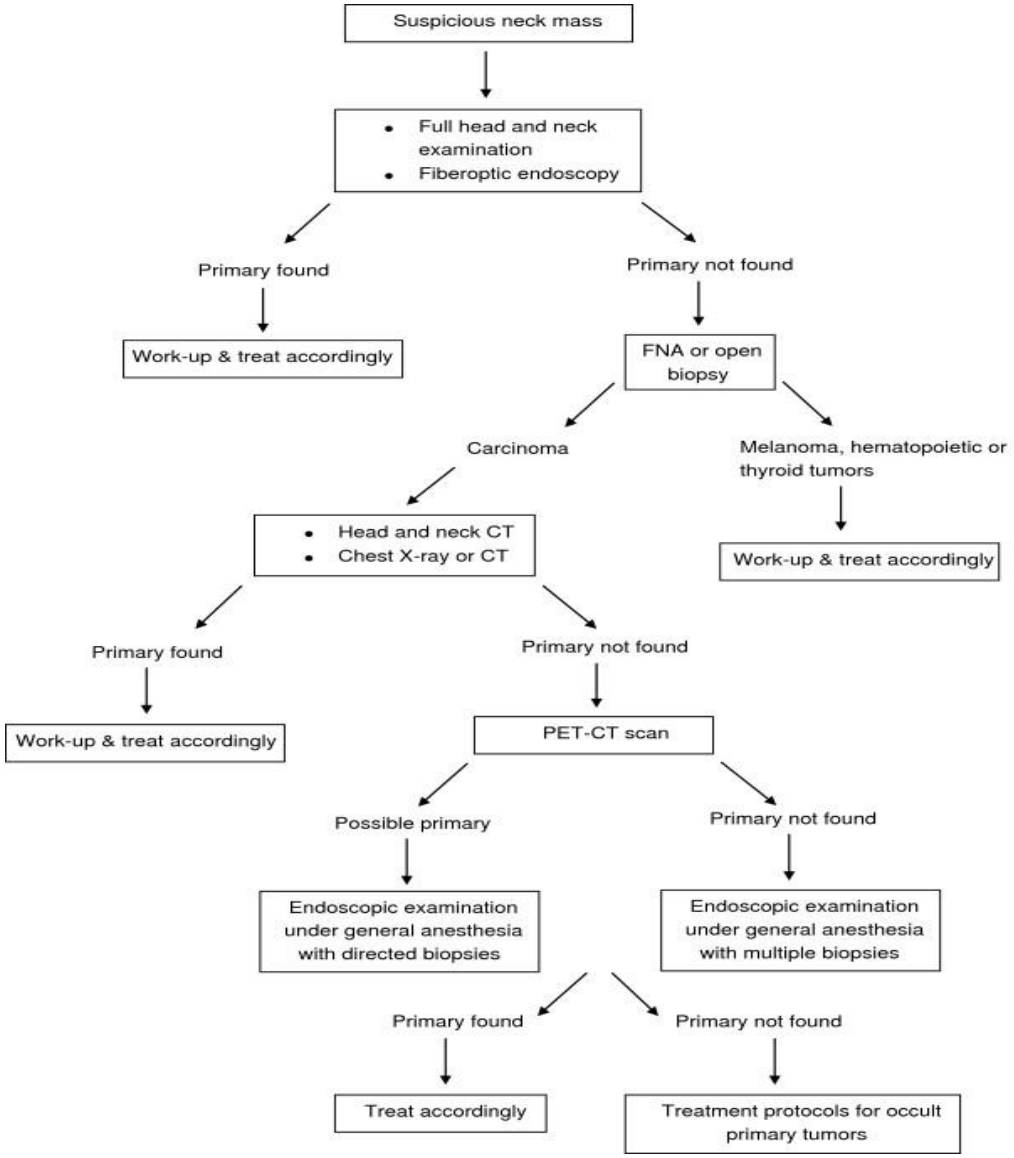

Figure 1: Flow chart for the evaluation of CUPS.[33]

The nasopharynx, tonsil and base of tongue were the most predominant sites mentioned in the literatures as culprits for CUPS.[6,15] Therefore, physical examination of the nasal cavity nasopharynx, oral cavity, oropharynx, larynx and hypopharynx as well as palpation of the floor of the mouth and base of the tongue under direct vision and also with the aid of endoscopes (rigid and flexible) are mandatory for clinical evaluation.[6] The skin and scalp of the head and neck region should also be well examined uncover any significant cutaneous lesion. A complete and careful general and systemic examination should not be left out. A further examination and evaluation in form of panendoscopy should be employed in case of a high suspicion of lesion along with biopsies from all suspicious sites or blindly from the sites of possible origin of the primary.[6,10] Detection of suspicious sites via an endoscopic assessment is based on the evidence of gross structural changes noticed on the mucosal lining. Therefore, the sensitivity of endoscopic detection is limited by the capability of the human eye to visualize any irregularity or granularity. A great majority of the primary malignancies that escape detection may still be confined, in their early stages of growth, to changes that involve molecular rather than structural alterations.[23] If there is no obvious or highly suspicious lesion after proper assessment, then the patient should be regarded as having an 'clinical' unknown primary site of a cervical lymph node metastasis.[6] The clinical N stage at presentation is commonly N2a, N2b or N2c. The authentication of human papilloma virus (HPV)-related squamous carcinoma especially with subclinical primaries in the oropharynx is the presence of cystic malignant metastases in level II. The first echelon lymph node(s) involved can serve as a tracer to the potential origin of the index primary. It is very important to note that patients presenting with supraclavicular lymphadenopathy may present with symptoms and signs not related to the head and neck because of their association with infraclavicular neoplasms like bronchogenic or lung cancer.[6]

When proper clinical assessments including office endoscopy do not reveal a primary, it is expedient to proceed to carrying out a panendoscopy of the upper respiratory and digestive tract under general anaesthesia and biopsy. However, it is advisable to carry this out following the completion of all of the available imaging modalities because any instrumentation and biopsy of these areas prior to image scan would likely trigger mucosal inflammatory process and compromise the accuracy of the subsequent radiological assessments. Another supportive reason is that, imaging may help to identify a suspicious intramucosal lesions that will be targeted for examination under direct vision as well as biopsy of such.[6,24]

During panendoscopy, each of the subsites of the head and neck is usually examined by use of different types of straight and angled telescopes appropriate for each area. The subsites which should be examined closely are the nasal cavities, paranasal sinuses, nasopharynx, oral cavity, hard and soft palates, tongue base, tonsil, posterior pharyngeal wall, vallecula, supraglottis, glottis, subglottis, post-cricoid area, pyriform sinus and proximal oesophagus. Palpation of fossae of Rosenmular, oral cavity and tongue base should also be performed.[6] Whether a clear primary location is identified or not, direct random biopsies from sites at risk of occult primary are typically recommended (Figure 1).[24,25]

Although this is controversial, it could by chance expose unpredictable sites of primary tumours.[25] Again, it is good to note that an open biopsy of the enlarged neck lymph nodes should not be considered prior to the completion of a thorough clinical, radiological and endoscopic search for the primary tumor.[16]

Investigative modalities

The identification of the primary site is very important in optimizing treatment plans, which, in turn may improve the treatment outcome. This goal should be considered ahead of suspecting a metastatic cancer of occult primary. Since the undetermined primary lesion can be located anywhere in the body, a cross-sectional whole-body imaging modality is the proper means to look for the origin of the primary. An ultrasound scan is a fairly fast and easy technique that doesn't use radiation. This is why it is often the first tests done in a case of suspected internal mass.[20]

Furthermore, in trying to determine the site of the primary, the next step to take in the pedigree of the investigative modalities is to establish the presence of metastatic lesions in the cervical lymph node. Fine needle aspiration cytology (FNAC) is a well-established and very useful diagnostic method for metastatic lesions in lymph nodes because of its cheap, simple, rapid and effective diagnostic properties. It is better performed with specificity when carried out under ultrasound guidance with a higher diagnostic accuracy. FNAC can be performed in the clinic, bedside and also in cases where an incisional biopsy is contraindicated. A cytological or histological report confirming malignant cells will automatically initiate the need for further investigations.[6,26] Mustafa et al reported a sensitivity and specificity of 97.37% and 93.75% respectively with an overall diagnostic accuracy of 96.29%.[26] A core needle biopsy (CNB) on the other hand involves the use of a wide 16-gauge needle compared to a 23-gauge needle used in FNAC. Therefore, while only a cytological analysis can be offered on an aspirated sample, conventional histopathological analysis can be performed with a core biopsy material because it allows for better cell identification and assessment of tissue architecture.[27,28] CNB also provides a sufficient amount of specimen for automated immunostaining, immunotyping and molecular/ monoclonal antibodies evaluations.[28,29] With the advantages of CNB over FNAC, it has become part of the diagnostic workup for cervical lymphadenopathy especially when FNAC offers inconclusive reports.[27,29] Allin et al[27] therefore suggested that ultrasound guided CNB can help to reach diagnosis in cases of cervical lymph node enlargement being evaluated for primary site. This can potentially reduce the number of patients being subjected to excisional biopsy of cervical nodes under general anaesthesia especially the elderly and immunocompromised patients. CNB should be taken into account when evaluating the origin of a cervical metastatic tumor with either squamous, thyroid, salivary, breast or bronchial origins. This might be possible from the cell architecture to suggest the potential origin of the index primary site. Cervical lymph nodes with suspected metastasis originating from a papillary thyroid carcinoma (PTC) for example will reveal characteristic cystic changes and calcifications.[30] However, while analyzing the diagnostic role of core needle biopsy in cervical lymphadenopathy, Ryu et al did not totally support CNB as a first-line biopsy method in place of FNAC owning to the possibility of tumor seeding during screening of metastatic cervical lymphadenopathy of undetermined origin.[29] Although, they agree that, in cases where the primary goal is to rule out lymphoma from other disease entities, CNB should be considered first.

Immunohistochemistry and gene sequencing can serve as a guide to identify an occult primary site.[25] More specific investigations such as identification of Epstein-Barr virus (EBV) may be highly correlated with a nasopharyngeal site. Human papilloma virus is a significant aetiological factor in oropharyngeal cancer and so the identification of HPV type 16 and 18 in a lymph node sample would be a strong pointer to an primary site in the oropharynx.[6] In cases where there are adequate tissue available, p16 testing is recommended. And a positive result points more strongly towards a tonsil or base of tongue as primary site (70% of oropharyngeal squamous cell carcinomas are HPV positive).[24] Immunohistochemical stains, like the use of lung or thyroid markers have the potential to exclude specific sites like the lung or thyroid gland respectively.[6]

All patients with cervical lymph node metastasis should have computed tomography (CT) imaging from the vertex

to the root of the neck with inclusion of a chest CT as part of the assessment of a newly diagnosed SCC of the head and neck (Figure 1). CT will help to confirm and assess the extent of the cervical lymphadenopathy, the site of a primary tumour and whether there is a second primary or metastasis in the chest.[6,24] In cases where the cervical lymph nodes involvements were in levels II and III, a magnetic resonance imaging (MRI) should be carried out to examine the oropharynx, and most especially the tongue base, palatine tonsils and retromolar trigone. It could also be argued that all cases of unknown primary sites should have an MRI of the neck up to skull base done.[6] MRI may also add more information to define soft tissue extension for suspected primary tumour sites that were not well defined on CT.[24] The chance for CT, MRI or both to detect the primary site ranges from 9 to 23% and when suspicious findings on imaging are used to guide biopsy, the chance to find the primary tumor rises up to 60%.[31] For lymph nodes located in levels IV and V, additional chest/abdominopelvic CT-scans are recommended.[31]

[18F]-Fluoro-2-deoxyglucose positron emission tomography combined with CT imaging (FDG-PET/CT) scan is the recognized investigative modality of choice in the assessment of an unknown or undetermined primary site.[6,24] [18F]-fluoro-2-deoxyglucose ([18F]-FDG) is the most commonly used radiopharmaceutical due to its preferential uptake by cells with rapid turnover, such as malignant cells.[11] This nuclear medicine scan involves injecting a glucose analogue followed by whole body imaging to identify any distant metastases as well as the extent of spread through the head and neck region.[11] From this perspective, PET scan using the radiotracer ([18F]-FDG is the leading approach since it provides functional and metabolic information with an excellent lesion versus background ratio. According to international nuclear medicine guidelines, determination of an unknown primary site is one of the most appropriate indications for PET scanning.[20,32,33] It can help to identify unexpected subclinical distant metastases which can therefore positively influence the treatment plan and long-term prognosis of patients with cervical CUPS.[33] PET-CT is superior to carrying out CT scanning alone. When combined with CT imaging scan for structural clarity, it plays a very great role in the location and identification of primary sites, even outside of the head and neck region.[9,11,33] FDG-PET-CT is able to detect 37% of primary tumors in patients with CUPS, with both sensitivity and specificity rate of 84% each.[20,34] In another recent study, PET-CT has been reported to have an identification rate of 44%, a sensitivity of 97% and 68% specificity rate.[6] In the United Kingdom National Multidisciplinary Guidelines, PET-CT scan has been recommended for all cases of cervical lymph node metastatic with undetermined primary site.[6]

While Pepper et al agreed that CT scans of the neck, chest, and abdominopelvic region should be prioritized and PET-CT only carried out if the CT scans are not contributory; Krishnamurthy felt that PET-CT scan should be done upfront because it effectively guides the further course of management by picking the primary site and ruling out distant metastasis.[35,36] It is really a useful diagnostic tool when standard radiological work-up showed negative or inconclusive results, however, its major limitation is that tumors less than 1 cm in diameter are not reliably detected and it should also be performed before any invasive procedures, which possibly hamper the evaluation of the scans due to iatrogenic induced tissue alteration.[22,31] It is therefore advisable to perform PET-CT scan before panendoscopy because it allows for targeted biopsy of suspicious lesions in the airway.[11] In cases where clinical evaluation and PET-CT could not point to the primary site, diagnostic rates decrease to about 9-29%.[22]

The general challenges associated with PET imaging and PET agents are associated with training of workforce, cost, availability of radiopharmaceuticals and regulatory issues.[37] Globally, the low and low-middle income countries have the lowest numbers of PET sites and have been particularly identified with barriers like lack of education and lack of trained and qualified staff (clinicians, radiochemists, physicists, and radiopharmacists). These different levels of drawbacks especially in the developing countries limit exposure of patients to the standard evaluation of CUPS.[37]

Treatment options

CUPS is generally difficult to manage because it behaves differently to the primary cancer of the same type and location. The treatment modalities still remain controversial with no worldwide consensus. This is due to the paucity of randomized clinical trials that will compare different treatment options.[16,38] The lines of treatment are currently patterned according to institutional policy and experience based on non-randomized data and outcomes which gave rise to different approaches to treatment.[9,16] The primary aim of the treatment should be curative with locoregional control. This is always based on a well-studied natural history of the mucosal squamous cell cancers of the upper aerodigestive tract.[6] The modalities include the wide-field primary irradiation or chemoradiation (CRT) with or without modified radical neck dissection but most treatment regimens are based on combination therapy.[6,17] Surgical neck dissection or radiotherapy seem to have similar efficacy in the early nodal stages (N1) and can therefore be treated with monotherapy, while more advanced cases (N2, N3) require combination therapy.[10] In a retrospective analysis, Wang et al gathered that surgical neck dissection followed by adjuvant radiotherapy or chemoradiotherapy depending on the nodal staging is the most commonly adopted treatment modality.[38] And the aim is to eradicate the primary tumour and the microscopic neck disease.[6] However, Hainsworth and Weiss submitted that radical neck dissection should be considered in cases where patients had any evidence of residual cancer after a combination of radiotherapy and chemotherapy.[5]

The surgical neck dissections consist of a comprehensive radical or modified radical neck dissection which is either unilaterally or bilaterally based on the findings in the CT and/or MRI scan.[15] Patients presenting with metastasis in a single ipsilateral cervical node that is less than 3cm in widest dimension without extracapsular spread may be treated with surgery alone This should be in the form of a selective neck dissection (SND) but preferably modified radical neck dissection (MRND) with preservation of ipsilateral sternomastoid muscle, internal jugular vein and accessory nerve.[6] However, in cases of extracapsular spread, surgical neck dissection should be combined with adjuvant radiotherapy (Figure 2).[39] Postoperative chemoradiation is preferable to postoperative radiotherapy alone, most especially for pathologically confirmed extracapsular spread. This is also applicable to cases with N2 and N3 disease.[6] Radical neck dissection should also be considered in patients who have features of residual cancer after a complete dose of chemoradiation therapy.[5,39]

Sudoko et al advocated the addition of lingual tonsillectomy (LT) as part of the algorithm of procedures for the identification and surgical management of CUPS.[22] They observed that about 25% of patients who had normal PET-CT results had detection of primary site of CUPS in the lingual tonsils. It was also noticed that the rate of detecting a primary site from the lingual tonsil ranges from 18 to 90%. LT improves unknown primary site detection and carries low risk of complications.[22]

Radiation therapy is a very important tool in the treatment of CUPS. In addition to the involved neck, the field of radiation should include the potential mucosal primaries sites: nasopharynx, base of tongue, tonsillar fossa, and hypopharynx, while sparing the larynx, although the extent of the wide field radiotherapy which entails irradiation of both sides of the neck and upper airway mucosa remains debatable.[5,7,10,15] The reason is because the potential benefit obtainable from this extensive radiotherapy should be weighed against the side effects and adverse effects.[10] Grau et al revealed a significantly low loco-regional failures compared with patients treated with ipsilateral techniques.[7] In all, the diverse treatment modalities to be prescribed should be dependent on the nodal stage, the performance status, and willingness of patients.[15]

The standard fractionated radiotherapy of 1.8–2 Gy per fraction and 5 fractions per week for 6 to 8 weeks, with the total dose of 60–70 Gy to the sites is commonly used in the treatment of CUPS.[40] In cases of postoperative patients, the total dose is dependent on the status of the surgical margins.[9,38] However, and in most cases, 60–66 Gy radiated on the neck dissection site.[39] The major salivary glands, cervical esophagus, brain stem, spinal cord, the obits and the optic nerves are always outlined as dose-limiting structures.

Concurrent chemotherapy is usually administered for patients with more advanced disease stages to improve local control and reduce the risk of distant spread.[38] Neoadjuvant chemotherapy schedule included different combinations of taxanes, 5-flurouracil, and platinum-based drugs while concomitant chemotherapy schedules consisted of cisplatin/carboplatin 100 mg/m^2 with or without 5-fluorouracil (5-FU) at 400 mg/m^2 to be given once per three weeks during the period of radiotherapy. Cetuximab is also being used in case of adjuvant chemotherapy.[15,38,39] Mackenzie et al submitted that the indications for chemotherapy in the management of CUPS should be as for treatment of patients with a detectable head and neck SCCs.[6] However, the regimen to be used should be at the discretion of the treating clinicians.

Follow up

Post treatment of a patient with CUPS, there will be need for regular follow up visits at the multidisciplinary head and neck clinic. They are expected to visit regularly: monthly in the first year then bimonthly in the second year, and quarterly in the third to fifth year.[6,9,15] A prolonged follow up (more than five tears) should be slated for selected patients with suspected possibilities of second tumour or recurrence.[6] The content of follow-ups will include an accurate and thorough physical examination with the aid of flexible nasopharyngeal and laryngeal endoscopes, along with ancillary imaging tests which depends on the clinical presentation at each visit.[9] PET-CT scan at three to four months after treatment is also a useful follow-up strategy for patients treated by chemoradiation therapy.[6]

Prognosis

Patients with neck node metastases from occult head and neck cancer have prognosis similar to other head and neck malignancies.[7] In prognosticating the outcome of CUPS, it could be divided into the favourable and the unfavourable outcome (based on presentation and the stage of the disease) which are in most instances 20% and 80% of cases respectively. In terms of the average survival time, patients in the favorable group have 12 to 36 months while it is only 6 to 7 months for the unfavorable cases. The unfavorable group usually receives palliative therapy due to poor prognosis. For favorable cases, efforts are directed towards cure.[41] Studies have reported survival rate of about 70-80% in the first two years and 25-66% five-year survival rate.[41-43]

Hainsworth and Weiss found a five-year survival rates with combined therapy modality among 60% to 70% of cases when compared with rate found with local or single-modality therapy in 30% to 50% of cases.[5] Prognostic factors include nodal stage at presentation, gender, haemoglobin, tumour differentiation and overall treatment time.[7] Prognosis is significantly better among patients with N1 and N2 when compared with N3 disease. Female gender seems to have better outcome with neck control. Patients with high haemoglobin levels were found to do better on treatment as well.[7] Abu-Shama et al found that the duration between the point of diagnosing CUPS and

the date of recurrence (progression-free survival) or locoregional relapse is a factor of the interval of more than 10 weeks between diagnosis and treatment.[44] The extent and number of the cervical lymph node involvement, supraclavicular nodal involvement and unhealthy lifestyle habits, such as betel nut chewing are other important prognostic factors.[5,15]

CONCLUSION

Metastases are microscopic lesions that emerge far from their primary sites, through haematogenous or lymphatic vessels. The process of metastasis might begin before the obvious growth of the primary mass, making detection of primary site of a malignant tumour difficult to determine. So far, there is no worldwide consensus on the management of CUPS. When encountered, the first step in the work up remains thorough clinical evaluation which involves a full history and physical examination, including flexible fiber optic nasopharyngolaryngoscopy. All patients with confirmed cervical lymph node with metastatic cancer but no apparent primary site should undergo positron emission tomography-computed tomography whole-body scan, panendoscopy and directed biopsies (to include tonsillectomy and tongue base mucosectomy). However, in a resource limited environment like ours, minimum evaluation should include contrast enhancing computed tomography scan of the head and neck region, core needle biopsy of the metastatic cervical lymph node(s) for histological analysis and immunohistochemistry, and contact endoscopy of the upper airway including the nasal cavities, oral cavities and the hypopharyngeal region (Figure 3). Treatment modalities can be classified into modified radical neck dissection alone, MRND with adjuvant radiotherapy, radiotherapy alone, and combined therapy which includes surgical intervention and chemoradiation. Patients should be followed up to a minimum of five years with at least two-monthly in the first two years and three to six months in the subsequent years. While efforts are being put into expanding the ability and proficiency for determining the primary site of a cervical metastatic lymphadenopathy and in turn reduce the prevalence of CUPS especially in the developing countries where patients are easily lost to follow-up during a treatment process, we will suggest a combination regimen of functional neck dissection and platinum based concurrent chemo radiotherapy (Figure 3). There is also a dire need to define a treatment regimen with minimized adverse effects so as to reduce the morbidity associated with treating CUPS.

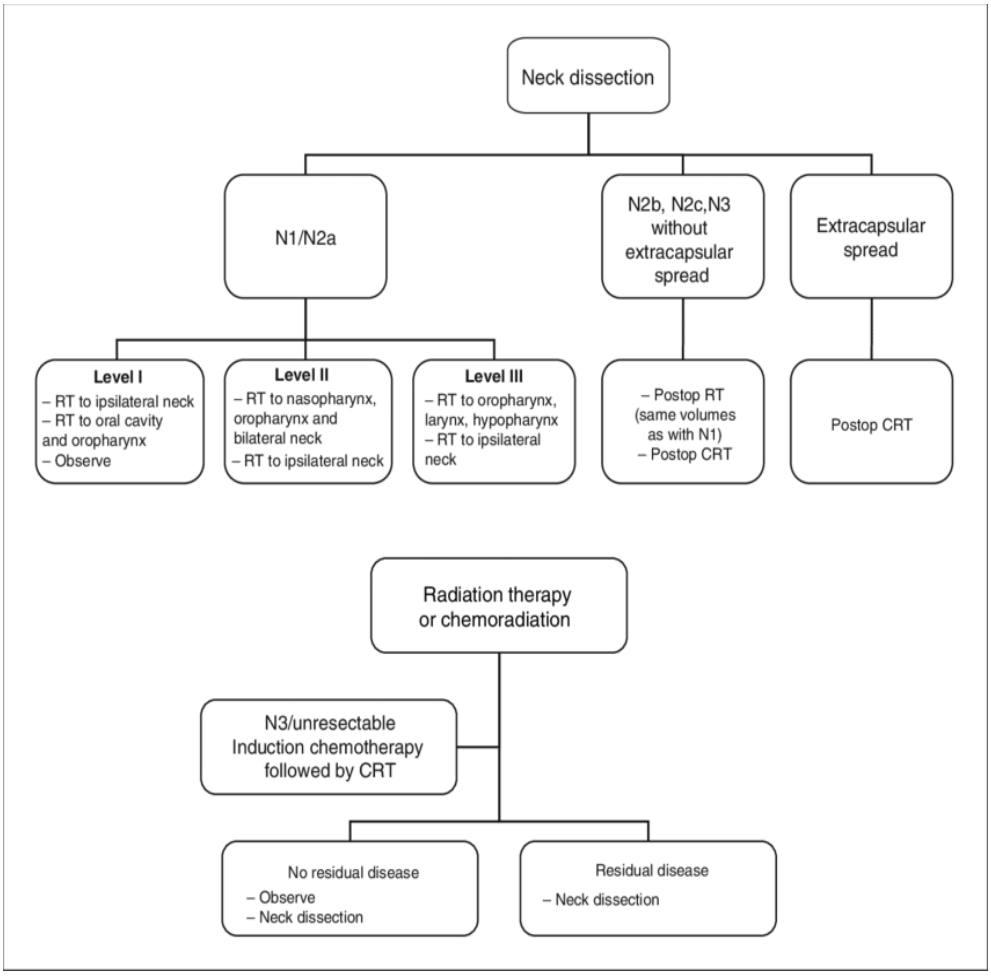

Figure 2: Algorithm for the treatment of CUPS.[39]

NA: fine needle aspiration

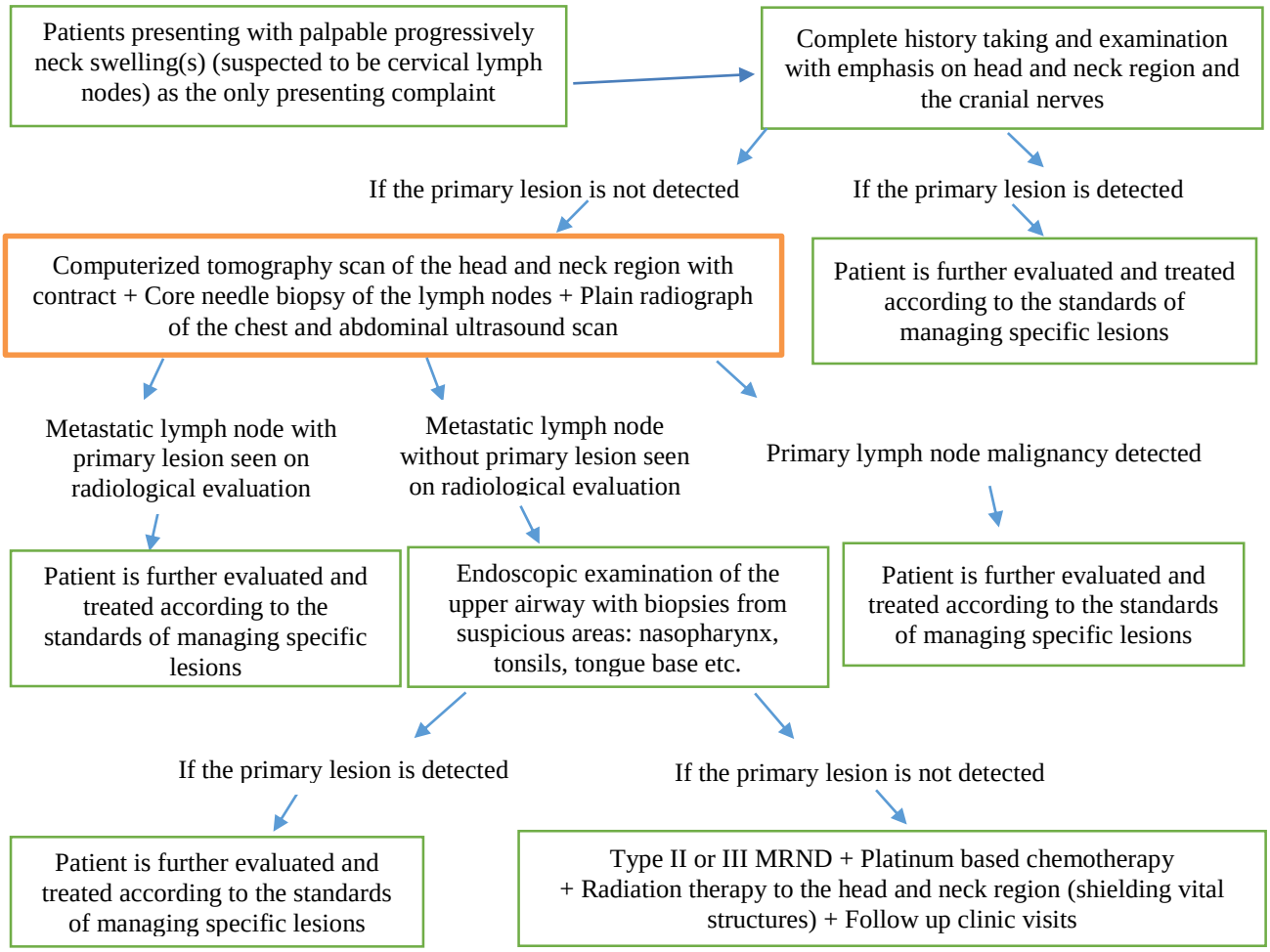

Figure 3: Recommended management outline for CUPS in resource limited environment.

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