



Review Article

Management of neck node with unknown primary - A review

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ABSTRACT

Cancer of unknown primary site (CUP) is an intriguing clinical phenomenon seen in 3-9% of all Head and neck cancers. Neck node metastasis seen around 5-10% of all patients with CUP. Metastasis in upper and middle neck occurs from head and neck cancers. Where as metastasis to lower neck is associated with cancers below the clavicles like thyroid cancer, lung cancer, colon cancer and ovarian cancer. Diagnostic set up consist clinical evaluation, panendoscopy of upper aerodigestive tract, CT & MRI imaging, Biopsies (FNAB, open biopsy), molecular assay from all suspicious site. The optimal therapeutic management of patient with cervical CUP remains controversial due to absence of randomized studies comparing different treatment options. However NCCN has given a established guidelines for management of CUP. The major authors recommend surgical removal of neck disease, followed by post-operative radiotherapy alone or radio-chemotherapy.

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1. Introduction

Cancer of unknown primary site (CUP) is a heterogeneous group of malignancies presenting with lymph node or distant metastasis whose primary tumor is not detected after a thorough clinical head and neck examination. Beside this reasons may be involution or slower growth rate at primary tumor site, due to different genetic alternation in primary or metastasis which cannot be detected during clinical examination. Cervical CUP preferentially affect male patients more than female, aged 55-60 years with a history of alcohol and tobacco abuse which are typical risk factor. However CUP may be seen in younger nonsmoker with HPV (~90% HPV-16) related oropharyngeal cancer, Epstein Bar Virus related nasopharyngeal cancer.¹⁻³ Squamous cell carcinoma compromising about 53-77% of neck node is most common type; followed by adenocarcinoma, undifferentiated carcinoma and other malignancy (examples: lymphoma, melanoma). CUP accounts for 5-10% of all the head and neck tumors, but

recently its number has decreased due to using of advanced diagnostic procedures like triple endoscopy. Treatment is based on non-randomized evidence and institutional policy. Recommendations include surgery or radiotherapy, extensive prophylactic irradiation of all potential mucosal sites and both sites of head and neck, with or without concomitant chemotherapy.^{4,5}

2. Assessment of a patient

Clinical evaluation of head and neck including palpation of all anatomic sub-sites of oral cavity, oropharynx, base of tongue and search for scars in head and neck indicating previous surgery is done. The site of palpable lymph node may be helpful to finding possible primary tumor site. Example: for level IB, involved neck lymphnode is submandibular lymphnode and possible primary site is buccal mucosa, lower alveolus, lateral border of tongue of floor of mouth of ipsilateral side. Family & personal history (previous history of malignancy in head and/or neck; history of previous facial or cervical skin lesion which has disappeared; history of any previous disease).

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FNAB / FNAC (fine needle aspiration biopsy/ cytology) from the neck node is mostly used diagnostic procedure to establish a diagnosis. It's conducted by an experience histopathologist. Repeat FNAB, core or biopsy may be required in case of uncertain or non diagnostic sample.⁵ Computed tomography scan (CT scan) & Magnetic resonance (MRI) of head & neck performed to determined the extent of disease, staging evaluation of lymphnode prior the treatment. If level IV, V lymph node is Involved chest, abdominal, pelvic CT and endoscopic examination (like tracheobronchoscopy, oesophago-gastroscopy, colonoscopy) is recommended. Now PET (positron emission tomography- computed tomography scanning) is mostly used for unknown primary and shown to superior to CT scan alone.⁶

Molecular studies are helpful to understand the etiology & pathology of head & neck tumor. Epstein bar virus genome is found only in nasopharyngeal carcinoma HPV infections is seen in oropharyngeal cancer. When primary is not detectable, an evaluation under general anesthesia (EUA) is required. Biopsies are taken all suspicious and possible primary origin site: base of the tongue, tonsillar fossa, pyriform sinus, nasopharynx on lesion site. Planned neck dissection and open biopsy also performed. The detection rate with use of CT scan is about 15-20% and use of panendoscopy with biopsy is 65%.^{7,8}

3. Management

The optimal therapeutic management of patient with cervical CUP is a controversial due to absence of randomized studies comparing different treatment options. National cancer comprehensive network (NCCN) has given the guidelines for management of CUP. The type of treatment depend on patient age, tumor site, histology and extend of metastatic lymphnode. Major head and neck surgeon recommended surgical removal and followed by comprehensive post operative radiotherapy or chemo-radiation.⁹

3.1. Squamous cell carcinoma

Therapeutic includes surgery (biopsy and neck dissection) and radiotherapy. However optimal extents of surgery and radiotherapy is still controversial.

3.2. Treatment Recommendations

1. ECS: Extra capsular spread
2. SND: Selected Neck Dissection
3. MRND: Modified Neck Dissection

Stage	Surgery	Radiotherapy	Chemotherapy
T0N1 (no ECS)	SND or MRND	No unless for mucosal site	No
T0N1 (ECS)	SND or MRND	Yes-either involved lymphnode or ipsilateral neck and boost to involved lymphnode	Should be considered
T0N2a, N2b, N2c	SND or MRND+_ Contralateral SND or MND	Yes-ipsilateral but bilateral should be considered	Should be considered
T0N3	Radical or Type I MRND	Yes-ipsilateral but bilateral should be considered	Should be considered

3.3. Surgery

3.3.1. RND (Radial Neck Dissection)

Removal of all cervical lymphatics and lymphnodes from level I-V with sacrifice of spinal accessory nerve (SAN), Internal jugular vein (IJV), Sternocleidomastoid muscle (SCM).

3.3.2. MRND (Modified Radial Neck Dissection)

Removal of all cervical lymphatics and lymphnodes with one or more non lymphatic structure – SAN, IJV, SCM.

3.3.3. SND (Selective Neck Dissection)

There are preservation of one or more lymph node that are routinely removed in MRND along with preservation of SAN, IJV, SCM. Removal of lymph node group depends upon pattern of metastasis relative to primary site of tumor. It is generally performed for staging of neck and rarely use as a therapeutic procedure.

3.3.4. Radiotherapy

For N1 disease with extracapsular spread, For N2, N3 disease, initial chemo-radiation with planned neck dissection only for those patients not achieving a clinical or metabolic complete response on post treatment imaging is a valid treatment strategy. The majority patient receive extensive bilateral neck irradiation including head and neck mucosa (pharyngeal axis) as a potential site of primary. The curative radiotherapy dose to mucosa from 50 – 70 Gy and to neck from 59 – 70 Gy. During management of head and neck cancers hyperfractional radiotherapy was used in CUP patients.¹⁰ It's effect is superiority over conventional irradiation. Undifferentiated and the majority of patients receive extensive bilateral neck irradiation including pharyngeal mucosa. According to Large Danish Study, risk of locoregional relapse after bilateral extensive radiotherapy was reduces 2 fold as compared to ipsilateral therapy. A combination chemotherapy- radiotherapy was

proposed by several authors.¹¹

3.3.5. Chemotherapy

Combination of chemotherapy and extensive irradiation was proposed by many authors. According to ESMO (European Society of Medical Oncology), platinum based chemotherapy with radiotherapy is recommended for N3 disease. According to PDQ (American Data Query) both chemotherapy and hyperfractional radiotherapy remain investigational approaches. While the meta-analysis of chemotherapy in head and neck cancer (MACH-NC) failed to demonstrate a significant benefit for the use of induction chemotherapy, many of the historical trials included predated the use of taxanes. Both the EORTC 24971 and TAX 323 studies and the TAX 324 trial found that the addition of docetaxel (T) to cisplatin (P) and 5-FU resulted in improved PFS, OS and response rate and yet lower associated toxicity.^{12,13}

3.4. Recommendations

1. Concomitant chemotherapy with radiation should be considered in patients with an unknown primary.
2. Neo-adjuvant chemotherapy (NACT) can be used in gross ‘unresectable’ disease.

3.5. Poorly differentiated carcinoma

The most frequent possible site of origin is pharynx, particularly nasopharynx. Treatment consists of radiotherapy to the neck and Waldeyer’s ring including the nasopharynx then followed by Neck Dissection. Concomitant chemotherapy is indicated in the case of N2, N3 Nodes

3.6. Adenocarcinoma

Node located at level I – III which is developed of salivary glands tumor. First excisional biopsy done. If clinical, pathological examination cannot identify the site of origin, Neck Dissection (level I – V) with parotidectomy is done and followed by radiotherapy. In the case off possible thyroid origin thyroidectomy with Neck Dissection (II, VI) should be performed.

3.7. Follow up

Follow up schedule should be keep for monitoring the patient who received treatment for Head and Neck CUP. Follow up schedule of individual determined by recurrence, to survey for appearance of primary tumor, development of second primary tumor. During follow up, surgeon should be check patient experience (eg- difficulty during nutritional intake, airway, pain control).

3.8. Recommendations

1. Patients should be followed up at least two months in the first two years and three to six months in the subsequent years
2. Patients should be followed up to a minimum of five years with a prolonged follow-up for selected patient
3. Positron emission tomography–computed tomography scan at three to four months after treatment is a useful follow-up strategy for patients treated by chemotherapy

4. Source of Funding

None.

5. Conflict of Interest

None.

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