

A Comprehensive Approach to the Management of Occult Primary with Secondaries in the Neck Lymph Nodes: A Tertiary Hospital Based Study in Andhra Pradesh

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Abstract

Background: An unknown primary is defined as a squamous cell carcinoma (SCC) presenting in a lymph node or nodes in the neck with no primary index site in the head and neck having been identified.

Aim of the Study: The aim of the study was to analyze the clinical, investigative, and therapeutic results of patients with occult primary with secondaries in the neck lymph nodes.

Materials and Methods: A prospective cross-sectional analytical study on 49 adult patients with malignant neck masses with unknown primary was conducted. Demographic data, clinical symptomatology and clinical examination of the neck masses were completed. Ear, nose, throat examination, video laryngoscopy, nasopharyngoscopy, and clinical staging of the neck lymph nodes were done according to tumor-node-metastasis classification. Fine needle aspiration cytology (FNAC)/ultrasound guided FNAC, core biopsy and/or open biopsy of the lymph nodes were done. Selective neck dissection, modified radical neck dissection was done with or without radiotherapy (RT) or chemotherapy. All the data were analyzed with standard statistical methods.

Observations and Results: A total of 49 adult patients with neck nodal metastases without primary being identified; 32 males and 17 female patients with M:F ratio of 1.88:1. The mean age was 53.42 ± 4.10 years in males and 57.35 ± 3.80 years in females. 16/49 (32.65%) patients were seen in the age group of 50–65 years, 13/49 (26.53%) in 35–50 years age group, 11/49 (22.44%) in 65–80 years age group, and 9/49 (18.36%) in 20–35 years age group. The most common symptom was mass in the neck (100%) followed by pain in 6/49 (12.24%). Overall, symptoms excluding presentation of mass in the neck accounted for <10% in this study. Levels II and III involvement, in this study was 41/49 (83.67%) followed by Level IV 6/49 (12.24%) patients.

Conclusions: Patients with occult primary and secondaries in the neck should be investigated with positron emission tomography-computed tomography scan, magnetic resonance imaging, FNAC, true cut biopsy, to totally rule out the presence of primary site of the malignant tumor in the aerodigestive tract before embarking on the treatment of the nodal metastases. The treatment should include radical surgical treatment of the nodal metastases followed by RT. Adjunct chemotherapy could be added wherever necessary. If total mucosal irradiation is to be considered, then intensity modulated radiation therapy should be used. Follow-up should be same as for the patients with the known primary.

Key words: Cervical metastases, Chemotherapy and radiation, Malignancy, Primary tumor, Squamous cell carcinoma

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INTRODUCTION

Secondaries in the neck lymph nodes may present in three forms; with known primary, with clinically unidentified primary, and with an occult primary.^[1] It is easier to locate the primary tumor in the first two forms, but the investigations and treatment required for the last form are exhaustive and

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economically taxing on both the surgeon and patients.^[2] When all the investigations do not show any evidence of primary, such cases are known as occult primary with secondaries in the neck lymph nodes.^[3] The reasons for the occult primary may be too small primary to detect, possibility of immunological spontaneous regression of primary and inability of the available diagnostic tools to detect the primary.^[4] As part of the assessment, the lymph node should be subjected to ultrasound-guided fine needle aspiration cytology (FNAC) and/or core biopsy under ultrasound guidance. Once the cytological or histological report is confirmed as squamous cell carcinoma, it needs for further investigation.^[5] The advantage of a core biopsy over FNAC cytology is that a clearer histological picture can be determined.^[6] Clinically, these nodes in the neck present with hard to cystic nature, single or multiple, and unilateral or bilateral. Associated symptoms of dysphagia or pain are present only 10% of the patients.^[7] Those nodes which are presented in the supraclavicular area represent a different clinical entity,^[8] due to the potential for association with infraclavicular neoplasms, such as lung cancer. Occult primary with secondaries in the neck constitutes to 5–10% of all the tumors.^[1,2] Squamous cell carcinoma (SCC) is the most common histologic variety in occult primary, followed by adenocarcinoma, undifferentiated carcinoma, and lymphoma, and melanoma.^[9,10] The treatment guidelines differ in malignancies other than squamous cell carcinoma and have varied prognosis.^[11] As squamous cell carcinomas are characterized by locoregional progression and relatively low risk of distant metastases, the priority is given to locoregional control. Therefore, local modalities including surgery and radiotherapy (RT) remain cornerstones of treatment.^[12] However, recently adjuvant chemotherapy after surgery of head and neck SCC with nodal metastases has been stressed.^[13]

Type of Study

This was a prospective, cross-sectional analytical study.

Institute of Study

This study was conducted in R. V. S. Institute of Medical Sciences, Chittoor, Andhra Pradesh.

Period of Study

This study was from March 2016 to –February 2017.

MATERIALS AND METHODS

A prospective cross-sectional analytical study was conducted in R. V. S. Institute of Medical Sciences, Chittoor, Andhra Pradesh, a tertiary teaching hospital in Chittoor over a period of 1 year. 49 adult patients with malignant neck masses with unknown primary attending the Department of Ear, Nose, and Throat (ENT) were included in this study. An ethics committee approval was obtained.

Inclusion Criteria

(1) Patients aged 20–80 years were included. (2) Patients whose primary tumor could not be diagnosed in spite of all the endoscopy, radiological, and isotope scans investigations were included. (3) Patients with all types of histopathological varieties were included.

Exclusion Criteria

(1) Patients aged below 20 years and above 80 years were excluded. (2) Patients with multiple malignancies, distant metastases, and acute systemic diseases were excluded. (3) Patients with immunocompromise diseases were excluded. Demographic data of the patients were obtained in an approved pro forma. Clinical symptomatology and clinical examination of the neck masses were completed in all of them. All the patients were subjected to ENT examination including video laryngoscopy and nasopharyngoscopy. Clinical staging of the neck lymph nodes was done according to tumor, node, metastasis (TNM) classification. FNAC/ultrasound guided FNAC, core biopsy and/or open biopsy of the lymph nodes were done. Treatment was given based on the staging of the disease and discovery and confirmation of the primary site of the tumor. For stage unilateral T0 N1, selective neck dissection (SND) or modified radical neck dissection was done (MRND) without RT or chemotherapy. For bilateral T0 N1, SND or MRN with RT and chemotherapy was considered. For T0 N2 a, b, and c SND or MRND ± contralateral SND or MRND with RT was considered. For T0 N3 radical or type I MRND with RT was considered. Patients included in the RT treatment were having cytological proven squamous cell carcinoma; they were treated with curative intent; had no evidence of any distant metastasis and had not received any previous chemo or RT. Patients who had primarily been treated by surgical modality were not included in this analysis. The median dose given to treat with RT alone was 67 Gy (range, 60–70 Gy) as opposed to a value of 66 Gy (range, 60–70 Gy). RT was given with megavoltage equipment using parallel opposed lateral portals treating head and neck mucosal sites; the main potential primary sites of the nasopharynx, oropharynx, larynx, and hypopharynx, and upper cervical lymph nodes and en face anterior portals treating lower cervical and supraclavicular lymph nodes by once-daily fractionation. Chemo-RT patients were given weekly IV cisplatin in a dose of 35 mg/m² along with radiation. All the patients were followed up for a period of 2 years. All the data were analyzed and tabulated using standard statistical methods.

OBSERVATIONS AND RESULTS

A total of 49 adult patients were included in this study presenting with neck nodal metastases without primary

being identified. There were 32 males and 17 female patients with M:F ratio of 1.88:1. The mean age was 53.42 ± 4.10 years in males and 57.35 ± 3.80 years in females. The youngest patient was aged 28 years and the eldest patient was 77 years. Patients were divided into 4 age groups with an interval of 15 years. 16/49 (32.65%) patients were seen in the age group of 50–65 years, 13/49 (26.53%) in 35–50 years age group, 11/49 (22.44%) in 65–80 years age group, and 9/49 (18.36%) in 20–35 years age group [Table 1]. 27/49 (55.10%) patients had unilateral neck metastases and 22/49 (44.89%) had bilateral neck nodes with occult primary. Single node was seen in 11/49 (22.44%), 26/49 (53.06%) had 2–4 nodes involved, and more than 4 nodes involved in 12/49 (24.48%) patients. 11/49 (22.44%) patients had fixed nodes to deeper structures and 38/49 (77.55%) had no fixity. Skin involvement was observed in 13/49 (26.53%) and none in 36/49 (73.46%) patients. The most common symptom was mass in the neck (100%), followed by pain in 6/49 (12.24%), dysphagia in 6 (12.24%), and hoarseness of voice in 07 (14.28%). Overall symptoms excluding presentation of mass in the neck accounted for <10% in this study. Level II and III involvement, in this study was 41/49 (83.67%) followed by Level IV 6/49 (12.24%) patients. This indicates that the primary site of the malignant tumor could be in the oral cavity, oropharynx, tonsil, posterior pharyngeal wall, or hypopharynx. TNM classification applied to the nodal involvement in the study showed that T0 N2 a, b, and c stages together accounted for 25/49 (51.02%) followed by T0 N1 6/49 (12.24%) and T0 N3 4/49 (8.16%) patients. There were 46/49 smokers among the study group, and 4/49 (9.38%) alcoholics in the study group (9.38%) [Table 1]. Professions in which the patients were engaged, showed that there were manual laborers 21/49 (42.85%) and agricultural laborers 17/49 (34.69%) [Table 1].

FNAC reports and true cut biopsy reports among the study group patients revealed that squamous cell carcinoma was seen in 30/49 (61.22%), anaplastic carcinoma in 9 (18.36%), lymphoma in 2 (4.08%), adenocarcinoma in 03 (6.12%), adenoid cystic carcinoma in 01 (2.04%), sarcoma in 1 (2.04%), and verrucous carcinoma in 3 (6.12%) patients [Table 2]. Human papillomavirus in tissue was identified in 3/49 (6.12%) patients and Epstein Bar virus in 4/49 (8.16%) patients. Radiodiagnosis revealed no primary tumors in computed tomography (CT) scan, magnetic resonance imaging (MRI), or positron emission tomography (PET) CT scan studies in this study.

One year follow-up of the patients following treatment with different combinations of treatment surgery, RT, and chemotherapy; there was recurrence in 3/27 of unilateral neck nodes (2 nodal and 1 lung metastases) and 2/22 of bilateral neck nodes with occult primary (1 with nodal

Table 1: Showing the demographic data and clinical presentation (n=49)

Observations	Male-32	Female-17	Percentage
Age			
20–35 years - 9	06	03	18.36
35–50 years - 13	09	04	26.53
50–65 years - 16	11	05	32.65
65–80 years - 11	06	05	22.44
Unilateral - 27	20	07	55.10
Bilateral - 22	12	10	44.89
Single node - 11	07	04	22.44
2–4 nodes - 26	19	07	53.06
>4 nodes - 12	06	06	24.48
Fixed - 11	07	04	22.44
Not fixed - 38	25	13	77.55
Skin involved - 13	05	08	26.53
Skin not involved - 36	26	09	73.46
Symptoms			
Swelling - 49	32	17	100.00
Pain - 6	0	03	12.24
Dysphagia - 6	03	03	12.24
Nasal stuffiness - 4	03	01	08.61
Hoarseness of voice - 7	05	02	14.28
Levels of involvement			
Level I - 2	01	01	04.08
Level II - 23	1	08	46.93
Level III - 18	11	07	36.73
Level IV - 6	05	01	12.24
Nodal classification (TNM)			
T0 N1-6	04	02	12.24
T0 N2a - 15	09	06	30.61
T0 N2b - 14	09	05	28.57
T0 N2c - 10	07	03	20.40
T0 N3-4	03	01	08.16
Habits			
Smoker - 46	43	03	93.87
Alcoholic - 47	41	06	95.91
Profession			
Manual laborer - 21	15	06	42.85
Agriculture laborer - 17	11	06	34.69
Officegoer - 4	04	00	08.16
Housewife - 7	00	07	14.28

recurrence and 1 lung metastases). All the remaining patients were healthy and without recurrence either at the suspected primary site or nodal recurrences [Tables 3 and 4].

DISCUSSION

Secondaries in the neck lymph nodes with occult primary are not uncommon in India. The prevalence in India is between 5% and 8.5% of the total head and neck malignancies.^[14] Large reported in the world literature quote the frequency is around 3% of the total head and neck cancer cases.^[15,16] These reports are retrospective in nature, but the present study is a prospective one and hence a small sample which includes 49 cases of occult primary patients with secondaries in the neck. In this study, 55.10% patients had unilateral neck metastases and 44.89% had bilateral neck nodes. Single node involvement in 22.44%, 2–4 nodes involved in 53.06%, and

more than 4 nodes involved in 24.48% patients. In all the patients presenting complaint was mass in the neck (100%), followed by pain in 12.24%, dysphagia in 12.24%, and hoarseness of voice in 14.28%. Overall symptoms excluding presentation of mass in the neck accounted for <10% in this study. Level II and III involvement, in this study was 83.67% followed by Level IV 12.24% patients. This indicates that the primary site of the malignant tumor could be in

oral cavity, oropharynx, tonsil, posterior pharyngeal wall, or hypopharynx. T0 N2 a, b, and c stages together accounted for 51.02% patients followed by T0 N1 stage in 12.24% and T0 N3 4/49 in 8.16% patients. Martin and Morfit^[15] quoted that “neck lumps presenting with no discernible primaries can be solid or cystic lesions, which can be solitary or multiple lumps”. The lumps are usually located in Level 2, followed by level 3, with bilateral involvement and other symptoms (i.e., pain and dysphagia) reported in <10%. The clinical N stage at presentation is usually N2a, N2b, and N2c from observations of a large study conducted by them. In the present study, 39/49 (79.59%) patients had N2a, b, and c staging of TNM classification in this study, 6/49 (12.24%) had N1 staging and 4/49 (8.16%) had N3 staging. 27/49 (36.73%) had unilateral neck nodes and 22/49 (28.57%) had bilateral neck nodes. In similar studies by Erkal *et al.*^[17] and Sinnathamby *et al.*,^[18] the frequency of N2 a, b, and c stages was 57% and 16% had bilateral lymph node metastases. The mean age in this study was 53.42 ± 4.10 years in males and 57.35 ± 3.80 years in females. The youngest patient was aged 28 years and the eldest patient was 77 years. This was similar to a study by Shukla *et al.*,^[19] in a study by Beldi *et al.*,^[20] the mean age was 55 years with a range of 55–65 years. In addition, in their study, there was male preponderance in the secondaries of cervical lymph nodes. In this study also there was male preponderance with M:F ratio of 1.88:1. Human papillomavirus (HPV) was observed in 3/49 cases and Epstein–Barr virus in 2/49 patients in this study. Martin and Morfit opined that the presence of cystic malignant metastases in Level 2 is often considered to be a hallmark of HPV-related squamous carcinoma, usually with subclinical primaries in the oropharynx.^[15] Review of literature showed that the most promising results of the occult primary with neck metastases have been achieved with neck dissection followed by comprehensive irradiation whenever feasible^[21,22] from among the proposed treatments available: Neck dissection

Table 2: Showing the FNAC, histopathology, and radiological investigations in the study (n-49)

Observations	Male-32	Female-17	Percentage
FNAC			
Squamous cell carcinoma - 30	18	12	61.22
Anaplastic carcinoma - 9	06	03	18.36
Lymphoma - 2	02	00	04.08
Adenocarcinoma - 3	01	02	06.12
Adenoid cystic carcinoma - 1	01	00	02.04
Sarcoma - 1	01	00	02.04
Verrucous carcinoma - 3	03	00	06.12
Histopathology			
Squamous cell carcinoma - 30	18	12	61.22
Anaplastic carcinoma - 09	06	03	18.36
Lymphoma - 02	02	00	04.08
Adenocarcinoma - 3	01	02	06.12
Adenoid cystic carcinoma - 1	01	0	02.04
Sarcoma - 1	01	00	02.04
Verrucous carcinoma - 3	03	00	06.12
Tissue viral antigen			
Papilloma (HPV 16, 18) - 3	02	01	06.12
Epstein bar virus (EBV) - 4	04	00	08.16
CT Scan - 11			
Negative	06	05	100
MRI - 22			
Negative	17	13	100
PET CT scan - 16			
Negative	08	08	100

FNAC: Fine-needle aspiration cytology, EBV: Epstein–Barr virus, HPV: Human papillomavirus, CT: Computed tomography

Table 3: Showing the treatment schedules given in unilateral neck lymph node malignancies (n-27/49)

Observations	SND-14	MRND-13	RT-12	Chemotherapy-07	Follow up
TON1-6	04	02	00	00	Healthy, no recurrence
T0 N2a - 8	05	03	04	01	Healthy, no recurrence
T0 N2b - 7	04	03	05	03	2 nodal recurrences
T0 N2c - 4	01	03	01	01	Healthy, no recurrence
T0 N3-2	00	02	02	02	1 lung metastases

SND: Selective neck dissection, MRND: Modified radical neck dissection, RT: Radiotherapy

Table 4: Showing the treatment schedules given in bilateral neck lymph node malignancies (n-22/49)

Observations	SND-12	MRND-12	RT-12	Chemotherapy-06	Follow up
T0 N1-00	00	00	00	00	--
T0 N2a - 7	05	05	04	01	Health, no recurrence
T0 N2b - 7	07	04	05	03	Healthy, no recurrence
T0 N2c - 6	00	01	01	01	1 nodal recurrence
T0 N3-2	00	02	02	02	1 lung metastases

SND: Selective neck dissection, MRND: Modified radical neck dissection, RT: Radiotherapy

alone, RT alone, or neck dissection with postoperative RT. Mintzer *et al.*^[23] and Haas *et al.*^[24] from their studies observed that the prognosis of the occult primary with neck metastases is similar to neck metastases with known primary using similar modalities of treatment, i.e., 50% of them survive 5 years period without recurrence. In the present study, all the patients were followed up to 2 years from the completion of the treatment, and the number of patients with recurrence in unilateral neck nodes was 3/27, and from among the bilateral neck nodes was 2/22 (5/49 [10.20%]). The 5 years survival rate reported by Shukla *et al.*^[19] study was 31.6%. Since this study was not conducted for 5 years given the number of recurrences, that is, 10.20% following up of the remaining patients for another 3 years would have given matching figures in this study. Other studies give 5 years survival rates ranging from 22% to 67% for occult primary with neck nodal metastases^[12,25,26] In this study, out of 3/27 unilateral neck nodes with occult primary 2 were nodal recurrences and one lung metastases; among the bilateral neck nodes with occult primary one was nodal and another was lung metastases. This type of recurrences is also recorded in the literature by studies of Fernandez *et al.*^[26] and Sobin *et al.*^[27] whereas Reddy and Marks^[27] observed in their study that the recurrence was common at the primary site and followed by nodal recurrence.

CONCLUSIONS

Patients with occult primary and secondaries in the neck should be investigated with PET CT scan, MRI, FNAC, true cut biopsy, to totally rule out the presence of primary site of the malignant tumor in the aerodigestive tract before embarking on the treatment of the nodal metastases. The treatment should include radical surgical treatment of the nodal metastases followed by RT. Adjunct chemotherapy could be added wherever necessary. If total mucosal irradiation is to be considered, then intensity modulated radiation therapy should be used. Follow-up should be same as for the patients with the known primary.

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